Edoxaban did not differ from dalteparin for treatment of cancer-associated venous thromboembolism

Question

In patients with cancer who have acute symptomatic or asymptomatic (incidental) venous thromboembolism (VTE), is treatment with edoxaban similar to low-molecular-weight heparin for recurrent VTE and major bleeding?

The study

Who? The study included 1046 patients who had cancer that was active or had been diagnosed within the previous 2 years. Patients were included if they had lower limb deep vein thrombosis (DVT) or pulmonary embolism (PE) in segmental or proximal pulmonary arteries and required anticoagulation for at least 6 months.

What? The study compared edoxaban after 5 days of therapeutic low-molecular-weight heparin (LMWH) with dalteparin.

Edoxaban	vs	Dalteparin
Any therapeutic dose LMWH **for 5 days** followed by edoxaban (Lixiana or Savaysa), 60 mg, for 6-12 months. Edoxaban, 30 mg, was used for patients who had reduced renal function, low body weight, or were taking medications that interfere with drug clearance (e.g., P-glycoprotein inhibitors).		Dalteparin, 200 IU/kg, for 30 days followed by 150 IU/kg for 6-12 months.

What the researchers found

Patients in the edoxaban **and dalteparin groups did not differ for the combined outcome of recurrent** VTE **or** major bleeding**.**

3 more patients out of 100 taking edoxaban **had** major bleeding **compared with dalteparin.**

The bottom line

In patients with cancer-associated VTE, edoxaban was similar to dalteparin for combined major bleeding or recurrent VTE. There was a trend toward less recurrent VTE in the edoxaban group, but this group also experienced more major bleeds.

Summary of findings

Edoxaban **vs dalteparin in patients who have cancer-associated** VTE

Outcomes	Rate of events with edoxaban	Rate of events with dalteparin	Absolute effect of edoxaban at 1 year
Recurrent VTE or major bleeding	12.8%	13.5%	No effect*
Recurrent VTE	7.9%	11.3%	No effect*
Recurrent DVT	3.6%	6.7%	No effect*
Recurrent PE	5.2%	5.3%	No effect*
Major bleeding	6.9%	4.0%	About 3 more patients out of 100 had major bleeding
Clinically relevant non-major bleeding	14.6%	11.1%	No effect*
Death from any cause	39.5%	36.6%	No effect*

Outcomes	Rate of events with edoxaban	Rate of events with dalteparin	Absolute effect of edoxaban at 1 year

*Although the rates for the 2 groups look different, the differences were not statistically significant—this means that the difference could simply be due to chance rather than due to the different treatments.

This Evidence Summary is based on the following article:

Raskob GE, van Es N, Verhamme P, et al. ***Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism.*** *N Engl J Med. 2018; 378(7):615-24. PubMed (https://www.ncbi.nlm.nih.gov/pubmed/29231094?dopt=Abstract)*

Why was this study so important?

Largely due to the results of the CLOT trial,[1] the use of LMWH has been the standard of care for treating cancer-associated thrombosis for several years. However, not surprisingly, patients do not like having to inject themselves daily or twice daily for 6 months or longer. When newer direct oral anticoagulants came on the market, there was great interest in finding out if they were as good as LMWH at protecting patients from VTE while avoiding the need for injections.

The multinational Hokusai VTE Cancer trial described above enrolled patients with various types of cancer to compare edoxaban (a new direct oral anticoagulant) and dalteparin (LMWH) for recurrent VTE and bleeding . Edoxaban had slightly lower rates of recurrent thrombosis but at the price of slightly more bleeding events. Bleeding occurred more frequently in patients with gastrointestinal cancers, which suggests that patients with these types of malignancies may not be ideal candidates for direct oral anticoagulants.

It is important to note that LMWH dose was capped at 18,000 units (even when the weight-based dose for the patient should have been higher), and there was a protocolized decrease in dose with platelets less than 100 x 10^9/L (not typical for clinical practice but consistent with the CLOT trial protocol[1]). Also, we do not know if the results with edoxaban can be extapolated to the other direct oral anticoagulants that are currently available. However, the Hokusai Trial does show that at least some cancer patients may be able to take a pill instead of a needle.

Doctor, I have cancer. Can I take a pill instead of a needle to treat my DVT **or** PE**?**

According to the Hokusai trial, taking a new pill (edoxaban) after 5 days of needles is as safe as using injections (dalteparin) on a daily basis for treating DVT or PE due to cancer. While this is good news, pills may not be the best choice for all patients. For example, if you vomit frequently, pills may not absorb properly, which could put you at risk for forming new blood clots. Also, some drugs, including some chemotherapy drugs, interact with the new pill, which means it would be safer to use the needles because they do not interact with other drugs. Lastly, the pills may not be covered by all insurance plans. Your individual case will need to be carefully reviewed before changing your anticoagulant treatment.

[1]Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146-53.

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Glossary

anticoagulant	medications that prevent blood clots from forming or travelling (aka blood thinner)
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deep vein thrombosis (DVT)	formation of a blood clot within a vein deep within the leg
direct oral anticoagulant	anticoagulant pill that does not require blood tests to monitor the effect (aka novel oral anticoagulant, NOAC); examples include apixaban, dabigatran, edoxaban, rivaroxaban

direct oral anticoagulants	anticoagulant pill that does not require blood tests to monitor the effect (aka novel oral anticoagulant, NOAC); examples include apixaban, dabigatran, edoxaban, rivaroxaban
DVT	formation of a blood clot within a vein deep within the leg
edoxaban	Lixiana® (aka DOAC)
gastrointestinal	related to the stomach and the intestines (bowels)
heparin	anticoagulant given by intravenous infusion or by injection under the skin
LMWH	anticoagulant given by injection under the skin (e.g. Fragmin®, Lovenox®, Innohep®) (aka LMWH)
major bleeding	serious bleeding (e.g. requiring a visit to the doctor or hospital, an invasive test to find the source of bleeding or a blood transfusion)
PE	blood clot(s) that cause obstruction of blood vessels within the lungs (pulmonary artery), after travelling from veins, most commonly within the leg or arm or pelvis
pulmonary embolism (PE)	blood clot(s) that cause obstruction of blood vessels within the lungs (pulmonary artery), after travelling from veins, most commonly within the leg or arm or pelvis
venous thromboembolism	the collective term referring to blood clots within the veins, most commonly deep vein thrombosis and pulmonary embolism
venous thromboembolism (VTE)	the collective term referring to blood clots within the veins, most commonly deep vein thrombosis and pulmonary embolism
VTE	venous thromboembolims; collective term referring to blood clots within the veins