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Editorial

Low-molecular weight heparin or direct oral anticoagulants for the treatment of cancer associated thrombosis. Are we at the crossroad?

In this issue of Thrombosis Research, Li et al. report a meta-analysis of the two trials comparing low-molecular weight heparin (LMWH) with direct oral anticoagulant (DOAC) treatment for patients with cancer-associated thrombosis (CAT) [1–3]. The two trials pointing in the same direction by showing a better efficacy but a higher risk of bleeding in patients who received the DOAC, the results of the meta-analysis are not unexpected and reinforce the results of the two trials. The results of DOACs for the treatment of CAT were also reported in a series of cohort studies but these latter studies were not included in the formal meta-analysis reported by Li et al. because these studies are subject to a major risk of bias due to differences in the patients receiving LMWH and DOAC.

The two randomized controlled trials include the Hokusai VTE cancer study reported by Raskob et al. and the SELECT-D study reported by Young et al. [2,3]. The Hokusai VTE cancer study was an open-label, noninferiority trial that randomized 1050 patients with cancer and acute symptomatic or incidental venous thromboembolism (VTE) to LMWH for at least 5 days followed by oral edoxaban 60 mg once daily or dalteparin 200 IU/kg daily, for one month followed by 150 IU/kg daily [2]. Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent VTE or major bleeding during 12 months after randomization. Select-D was a prospective, randomized, open label, pilot trial that randomized 406 patients with cancer and acute symptomatic or incidental VTE to the same regimen of dalteparin or rivaroxaban given as 15 mg twice daily for 3 weeks followed by 20 mg once daily, for 6 months in total [3]. Patients were followed for six months and the main outcome was recurrent VTE. According to the meta-analysis reported by Li et al., DOACS were associated with a reduction in the risk of recurrent VTE (Risk Ratio [RR]: 0.65; 95% Confidence Interval [CI], 0.42 to 1.01) and a higher risk of major bleeding (RR 1.74; 95% CI, 1.05 to 2.88) and of clinically relevant non-major bleeding at six months (RR 2.31; 95% CI, 0.85 to 6.28) [1].

Some features of the two trials may deserve discussion. First, the two studies are open-label and although the outcome events were centrally adjudicated (after the study was completed in the Select-D study), some of the differences observed between the two treatments may be related to a different reporting of events by the investigators in the two treatment arms. Of note, this was also the case for the studies comparing LMWH to vitamin K antagonists (VKA) and this was the reason why the recommendation in favor of LMWH was downgraded to IIC in the last issue of the American College of Chest Physicians guidelines [4]. Second, the treatment duration was longer with the DOAC in the Hokusai VTE cancer study and interestingly, the difference in efficacy became apparent only after day 90 [2]. Major bleeds occurred significantly more often in patients with gastrointestinal cancer receiving edoxaban in the Hokusai VTE cancer study, whereas, patients with cancer of the esophagus or gastroesophageal junction were excluded from enrollment in the Select-D trial after the data safety monitoring board reported a non-significant difference in major bleeding in these patients.

1. What lessons can be learned from these trials?

First, LMWH and DOAC appear to have about the same rate of combined efficacy and safety outcomes in patients with CAT, this was observed in the Hokusai VTE cancer study using a combined outcome as the main study outcome [2]. Second, both trials and the meta-analysis indicate that the DOACS were more effective than LMWH for the prevention of recurrent VTE. Noteworthy, this difference was mainly due to a difference in deep vein thrombosis and not to pulmonary embolism. Conversely, the difference in major bleeds was mainly due to the bleeds which were not considered to be a clinical emergency in the Hokusai VTE cancer study [2]. Third, patients with gastrointestinal tumors appear to be at higher-risk of bleeding when receiving a DOAC than patients with other cancer types, whereas, according to a post-hoc analysis of the Hokusai VTE cancer study, no increase in major bleeding was observed among patients with other cancer types [5]. Fourth, although LMWHs are probably more effective than VKA and DOACs more effective than LMWHs, reducing the risk of recurrent VTE at six months from 10 to 16% when using VKA to 4–6.5% when using DOACs; neither LMWHs nor DOACs are safer than LMWH overlapped and followed by VKA and the high risk of bleeding in the cancer population is the main remaining issue to be addressed in this population.

2. What are the remaining questions?

2.1. Are these results applicable to all DOACs?

Although considered as a single class of anticoagulants, the four DOACs have different pharmacologic properties and in the landmark trials comparing these compounds to the traditional approach of LMWH overlapped and followed by VKA, some DOACs demonstrated a significantly lower risk of major bleeding, whereas others did not appear to be safer than the reference treatment [6]. Although no direct comparison is available, the results observed with edoxaban and rivaroxaban may not be reproduced with apixaban and dabigatran. More studies will appear soon with rivaroxaban and the large Caravaggio trial is currently assessing the efficacy and safety of apixaban in patients with CAT [7].

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2.2. Should physicians offer different treatments to different patients?

With one treatment being more effective but associated with an increase in the risk of bleeding, physicians may be tempted to propose a DOAC in patients with a high risk of recurrent VTE and LMWH to the patients with a high risk of bleeding. Such an approach is currently limited by the lack of validated tools for estimating these risks. In the Hokusai VTE cancer study, the risk of major bleeding did not increase significantly with the number of bleeding risk factors [2]. In the CATCH study, the risk of clinically relevant bleeding increased with age > 75 years and intracranial malignancy [8]. In the RIETE registry, patients with immobility, metastases, recent bleeding, or with creatinine clearance < 30 ml/min, had an increased incidence of major bleeding [9].

Stage IV pancreatic cancer, brain cancer, myeloproliferative or myelodysplastic disorders, ovarian cancer, stage IV cancer (non-pancreatic), lung cancer, neurological disease with leg paresis, and cancer stage progression have been identified as independent predictors of VTE recurrence [10]. In the CATCH study, high levels of tissue factor, cancer-associated venous compression and hepatobiliary cancer were associated with recurrent VTE during anticoagulant treatment [11]. The Ottawa score for estimating the risk of recurrent VTE is calculated as follows: +1 point for being a woman, +1 point for lung cancer, +1 point for prior VTE, −1 point for breast cancer and −1 point for localized cancer without metastasis [12]. The probability of VTE recurrence is low if the score is less or equal to −1, intermediate if the score is equal to 0, and high if the score is ≥1. This score has been validated in an independent cohort study and may serve as a guide to identify patients at high risk of recurrence who may benefit from a DOAC.

Conclusion

Pending the results of the ongoing trials comparing other DOACs with LMWH, patients with CAT and a perceived high-risk of recurrent VTE or those who do not tolerate subcutaneous injections, may represent good candidates for receiving a DOAC as opposed to a LMWH, provided they do not have gastrointestinal cancers or a high perceived risk of bleeding. Although, risk of recurrent VTE and bleeding have been identified in patients with CAT, formal and validated tools for estimating the bleeding risk are needed to individualize the anticoagulant treatment in these difficult to treat patients.

Disclosures

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