Title:
Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

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Journal title:
The New England Journal of Medicine

Date, issue, pages of publication:
29th March 2020; 382:1599-607

Digital object identifier:
10.1056/NEJMoa1915103

Introduction, Aims and Design:
This randomised, controlled, open-label, non-inferiority trial aimed to demonstrate that apixaban is non-inferior to low molecular weight heparin (LMWH) in treating proximal DVT/PE in cancer patients. Adjudication of the outcomes was blinded to reduce bias associated with the open-label design. The primary efficacy outcome was recurrent venous thromboembolism (VTE) and the primary safety outcome was major bleeding.

Methods:
1170 patients were randomised to either oral apixaban or subcutaneous dalteparin and followed for 6 months. Patients were eligible if they had newly, objectively diagnosed PE/proximal DVT and active cancer/cancer within the past 2 years. There were several exclusion criteria; including age ≤18, ECOG performance status III/IV and life expectancy ≤6 months.

Results:
Recurrent VTE occurred in 32/576 (5.6%) in the apixaban group and 46/579 (7.9%) in the dalteparin group (HR 0.63, 95% CI 0.37-1.07, P<0.001 for non-inferiority). 3.8% in the apixaban group and 4% in the dalteparin group experienced major bleeding (HR 0.82, 95% CI 0.4-1.69, P=0.6).

Conclusions:
Apixaban is non-inferior to dalteparin in the treatment of cancer-associated VTE and both have a similar risk of major bleeding.

Limitations:
The authors recognise several limitations, not least the open-label design. In order to limit the bias this introduced there was blinded adjudication of the trial outcomes. However, this still has potential for bias and ideally the trial would have been double-blinded with a subcutaneous placebo and oral placebo for the respective groups. Patients with acute leukaemia and primary/secondary intracerebral malignancy were ineligible for inclusion and so the authors recognise that their data cannot be extrapolated to these patients. A limitation not

acknowledged by the authors is that the study was industry-funded, which has been shown to be associated with bias in favour of the funder's product (i.e. apixaban)[1]. The study also excluded patients with ECOG status of ≥III. This group likely accounts for a significant proportion of cancer patients with VTE, and owing to their exclusion we do not have any data on the use of apixaban for these patients.

Applicability:

Long-term daily subcutaneous injections have a significant quality of life impact on patients and a safe efficacious oral alternative is likely to result in a shift from LMWH towards apixaban in cancer patients with VTE. Edoxaban[2] and rivaroxaban[3] have been shown to be non-inferior to LMWH in these patients in preventing recurrent VTE, but were associated with increased risk of bleeding. Therefore apixaban appears to have the advantage and is likely to be the DOAC-of-choice in cancer-associated VTE. However, without head-to-head comparison among DOACs it is difficult to conclude one is superior than the others.

Future Direction:

Notably, this study only followed patients for 6 months and there is currently no data on treating these patients with apixaban for longer. Consequently, further trials are required to determine the efficacy and safety of longer-term apixaban. A post-hoc analysis showed that the efficacy of apixaban appeared to decrease in older patients. These patients, and perhaps frailer patients (ECOG ≥ III), may be the focus of future studies to further elucidate the efficacy of apixaban in this group. Apixaban is the HSE's DOAC-of-choice and has been found by the National Centre for Pharmacoeconomics (NCPE) to be cost-effective in non-valvular AF[4] and post-hip/knee replacement[5]. This study may form the basis for the assessment of apixaban's cost-effectiveness by the NCPE for this indication. I envisage that apixaban will be added to international guidelines (ESC, ISTH, NCCN) for the treatment of cancer-associated VTE, as have edoxaban and rivaroxaban already.

References:

1. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003;326:1167-70.
2. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-24.
3. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36:2017-23.
4. National Centre for Pharmacoeconomics (2013). Cost Effectiveness of Apixaban (Eliquis®) for the Prevention of Stroke and Systemic Embolism in People with Non-Valvular Atrial Fibrillation.
5. National Centre for Pharmacoeconomics (2012). Cost Effectiveness of Apixaban (Eliquis®) for the Prevention of Venous Thromboembolic Events in Adult Patients who have Undergone Elective Total Hip Replacement or Total Knee Replacement.