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Warfarin is not the anticoagulant of choice for malignancy associated venous thromboembolism

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In a recent article of the *Internal Medical Journal* Hepburn-Brown et al published a detailed review of the diagnosis and management of acute pulmonary embolism (aPE) [1]. The review focused on the diagnosis, pathophysiology and acute management of aPE, while maintenance treatment was covered in brief. Direct oral anticoagulants (DOACs), and the vitamin K antagonist (VKA) warfarin are suggested as the "recommended anticoagulants" for ongoing treatment following aPE in all situations, including in the presence of a provoked irreversible aPE in the setting of malignancy (*Internal Medicine Journal* 2019; 49 (1); 23 table 3). Low molecular weight heparin (LWMH) was not presented as a recommended option.

The setting of cancer associated thrombosis (CAT) represents a special situation. The use of VKAs are acknowledged as an option for the management of cancer associated thrombosis in available guidelines (as discussed in [1] and elsewhere [2]). The use of VKAs is dependent on the clinical stability of the patient as well as consistency of dietary intake and stable gut function (including the absence of nausea, vomiting and altered bowel habit). These factors may change over short periods of time in patients with active malignancy making the use of VKAs in the ambulatory setting complicated, and stretching the available resources of cancer services. Failure to maintain the target International Normalised Ratio (INR) with VKAs

may either expose the patient to excessive risk of bleeding or inadequate protection against VTE.

The largest study to compare LWMH to warfarin was the CLOT trial [3]. The study found a significantly lower rate of recurrent VTE with the LWMH fragmin compared to warfarin over a six month period (hazard ratio 0.48; 95% confidence interval [CI] 0.30 – 0.77, p=0.002) with no difference in rates of major bleeding. A recent Cochrane meta-analysis found a significant reduction in the rates of VTE for LWMH compared with warfarin amongst 1781 participants over five randomised controlled trials (Relative Risk 0.58, 95% CI 0.43 – 0.77, moderate level of evidence) with no differences in the rates of all-cause mortality, major or minor bleeding [4]. More recent studies have compared the DOACs edoxaban and rivaroxaban to LWMH [5, 6]. Edoxaban demonstrated non-inferiority while rivaroxaban demonstrated superiority to LWMH with regards to recurrent VTE events, however in both cases endpoints relating to bleeding were more common with the experimental DOAC [5, 6].

We note that in routine care of the cancer patient with VTE and aPE compromises may have to be made to balance the risk of further thrombosis as compared to the risk of bleeding. On the basis of currently available evidence LMWHs and DOACs are preferred over warfarin for systemic anticoagulation in the setting of malignancy associated VTE.

1. Hepburn-Brown, M., J. Darvall, and G. Hammerschlag, *Acute pulmonary embolism: a concise review of diagnosis and management.* Intern Med J, 2019. **49**(1): p. 15-27.

2. National Comprehensive Cancer Network. *Cancer-Associated Venous Thromboembolic Disease*. 2018 Accessed 15/02/2019; Available from: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf
3. Lee, A.Y., 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**(2): p. 146-53.
4. Kahale, L.A., et al., *Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer.* Cochrane Database Syst Rev, 2018. **6**: p. CD006650.
5. Raskob, G.E., et al., *Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism.* N Engl J Med, 2018. **378**(7): p. 615-624.
6. Young, A.M., 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**(20): p. 2017-2023.

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