The role of primary thromboprophylaxis in people with cancer: A systematic review and meta-analysis

Fiona Anne Dewar (150083580)[1], Dr Kathryn Musgrave[1,2], Dr John Hanley[2] , Professor John Simpson[1,3]

1. Translational and Clinical Research Institute, Newcastle University
2. Department of Haematology, Newcastle Upon Tyne Hospitals NHS Trust
3. Department of Respiratory Medicine, Newcastle Upon Tyne Hospitals NHS Trust

1. Introduction

- Patients with cancer are at an increased risk of venous thromboembolism (VTE). Many patients are unaware of this risk and of preventative measures despite VTE being a leading cause of death in this population[1].
- The hypercoagulable state in malignancy arises due to higher levels of circulating tissue factor, a potent initiator of coagulation. Furthermore, direct damage by cytotoxic chemotherapy agents, disrupts the endogenous fibrinolytic activity of the vascular endothelium[1].
- In the United Kingdom the widespread use of primary thromboprophylaxis, with parenteral or oral anticoagulant agents, is not recommended for patients with cancer receiving systemic chemotherapy[2].
- This standpoint is due to concern that the population benefit from treatment does not outweigh the potential risk of bleeding events.

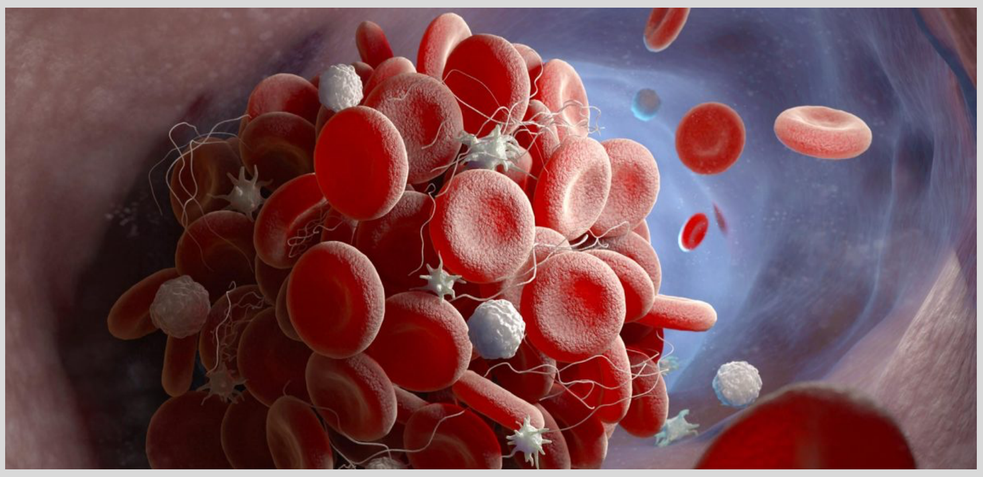

***Image 1**: A computer generated image of a fibrin thrombus[3].*

2. Aims and Hypothesis

- This project aimed, through systematic review and meta-analysis of the available evidence, to provide an accurate and reliable summary estimate of the efficacy and safety of primary thromboprophylaxis in patients with cancer receiving chemotherapy.
- In doing so, it aimed to evaluate the current clinical recommendations for the prevention of VTE in malignancy, whilst facilitating patient-clinician discussions and raising awareness of Cancer Associated Thrombosis (CAT).
- The underlying hypothesis of the project was that prophylactic anticoagulation reduces rates of VTE, without an increase in major bleeding, in this population and setting.

3. Methods

- The scope and research question were established through discussion with clinical haematologists.
- The study inclusion criteria were defined as randomised control trials (RCTs) with the following characteristics:

1. **Participants**- adults with a confirmed diagnosis of malignancy, receiving systemic chemotherapy.
2. **Intervention**- one of low molecular weight heparin (LMWH), ultra-LMWH (u-LMWH) or a direct oral anticoagulant (DOAC).
3. **Comparator**- placebo or chemotherapy only (observation).
4. **Outcomes**- summary data on one or both of VTE and major bleeding.

- Ovid's Medline(R), Embase, Clinicaltrials.gov, Cochrane's CENTRAL database and the ISRCTN register were searched without date restriction up to the 2nd June 2020.
- Initial screening of studies by title and abstract was followed by data extraction from relevant full texts.
- The risk of bias in individual studies was assessed and summarised using Cochrane's RoB2 tool.
- Quantitative synthesis was performed using RevMan5® software. Summary effect estimates were generated for the outcomes of VTE and major bleeding.

4. Results

***Table 1**: A summary of results. The summary effect estimate is generated by combining outcome data from individual studies, which gives a more precise estimate of the true population effect (see Figure 1). Heterogeneity indicates the variation between studies arising from clinical and statistical differences. There is moderate heterogeneity present under the VTE outcome. An alpha level of 0.05 denoted statistical significance. The numbers needed to treat and harm (NNT & NNH) are estimates of the number of individuals required to receive the intervention in order to observe a desirable or adverse outcome respectively.*

Outcome	Number of participants	Summary effect estimate	Heterogeneity	Significance	Epidemiological Measures
Venous Thromboembolism	Intervention n= 3927 Comparator n=3448	OR 0.39 [95% CI 0.27, 0.56]	41%	P= <0.00001	NNT= 27
Major Bleed	Intervention n= 3860 Comparator n= 3385	OR 1.39 [95% CI 0.96, 2.04]	0%	P= 0.08	NNH= 200

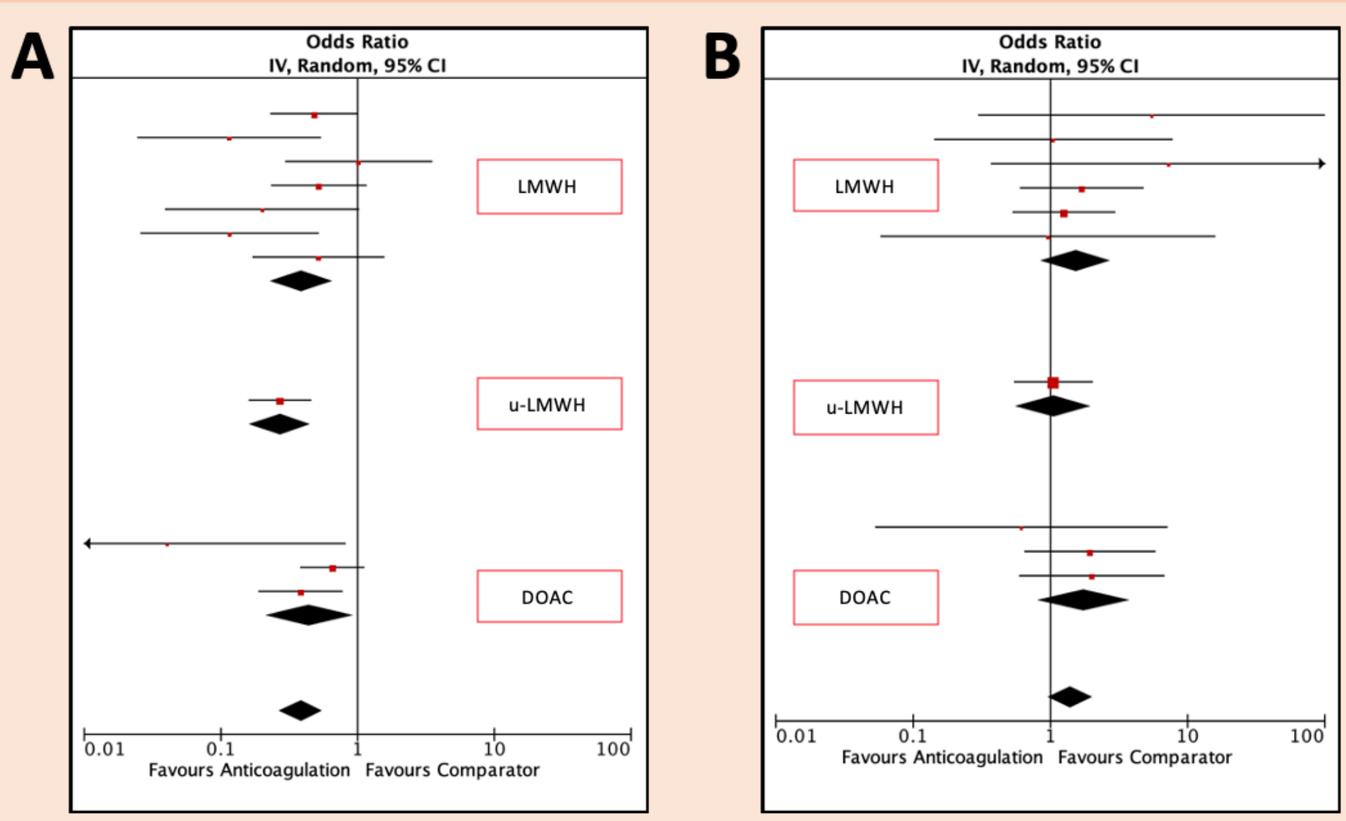

***Figure 1:** Forest plots showing the results of the meta-analysis of RCTs included in this review. The point estimates of individual studies included under each subgroup are shown. The comparator across all subgroups was placebo or observation only. The overall effect estimate is represented by the bottom-most diamond.*
***A) Venous Thromboembolism:** 11 RCTs were included, pooling of their results generated an overall effect estimate of OR= 0.39 [0.27, 0.56 I^2 41% P= <0.00001].*
***B) Major Bleeding:** 10 RCTs were included, pooling of their results generated an overall effect estimate of OR=1.39 [0.96, 2.04 I^2 0% P=0.08].*

5. Conclusions

- Primary thromboprophylaxis reduces the occurrence of venous thromboembolic events in ambulatory patients with cancer receiving chemotherapy.
- There was no significant increase in major bleeding events with prophylactic anticoagulation in this study population.

6. Discussion

- Primary thromboprophylaxis has the potential to improve the disease course and outcomes of patients with cancer. However, the number needed to treat remains high, limiting its widespread recommendation.
- The treatment benefit was greater in higher risk patients, such as those with late stage pancreatic cancer receiving chemotherapy agents known to predispose to VTE events.
- A validated risk stratification tool exists, yet its positive predictive value is low so future work may be focused around improving this. Potentially, through the development of biomarkers.

References and Acknowledgements

1. Al-Samkari, H, et al. *Adv Cell Gene Ther*. 2020; 3:e73. https://doi.org/10.1002/acg2.73
2. NICE. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism 2018
3. European Cancer Patient Coalition: https://ecpc.org/tool-box/cancer-associated-thrombosis-cat/

With thanks to Dr Kim Pearce for her statistical expertise.