Thromboprophylaxis in temporary lower limb immobilization: extrapolate with care

Czuprynska, J.; Nemeth, B.; Roberts, L.N.; Cannegieter, S.C.; Arya, R.

Received: 14 November 2019 | Accepted: 16 November 2019

DOI: 10.1111/jth.14709

jth

Thromboprophylaxis in temporary lower limb immobilization: Extrapolate with care

We read with great interest the systematic review and network analysis of pharmacological thromboprophylaxis to prevent venous thromboembolism (VTE) in patients with temporary lower limb immobilization after injury by Horner et al.[1] We would like to thank the authors for attempting to delve deeper and estimate the effectiveness of thromboprophylaxis in this setting, with a focus on symptomatic events, particularly as this continues to be a controversial area with little consensus and conflicting guidelines. However, we suggest the major limitations of this study necessitate careful interpretation of the authors' conclusions.

An earlier systematic review demonstrated that the efficacy of thromboprophylaxis in preventing asymptomatic deep vein thrombosis (DVT) and symptomatic VTE is not consistent[2] meaning that the efficacy for prevention of *asymptomatic* DVT should not be extrapolated to *symptomatic* VTE. Although the authors attempted to determine the potential effect of thromboprophylaxis on reducing *symptomatic* DVT, only 2 of the 13 studies included in the analysis had symptomatic VTE as a primary outcome, with all others routinely performing venography or compression ultrasonography. The attempt to retrospectively draw out and collate an estimated number of "symptomatic" events from a collection of small, heterogeneous studies with primary outcomes of VTE detected on scheduled imaging, is unreliable in evaluating the effect of low-molecular weight heparin (LMWH) on symptomatic VTE. This is strengthened by the finding that, in two studies, *symptomatic* DVT rates were as high as 5.5%[3]and 6.4%[4] in the control group, whilst this risk is estimated to be "only" 2.0% (95% confidence interval [CI] 1.3-2.7) without the use of thromboprophylaxis.[5]

When symptomatic VTE *was* used as the primary outcome, LMWH did not appear to reduce the risk.[6,7] Prophylactic LMWH during the full period of immobilization due to casting was not effective in preventing symptomatic events.[6] Furthermore, following isolated lower leg fractures requiring surgery, which would be expected to be a higher risk group for VTE, 2 weeks of LMWH failed to demonstrate a difference for a composite primary outcome of symptomatic VTE and asymptomatic proximal DVT on Doppler ultrasound.[7]

The effect observed by Horner et al is likely to be overestimated, difficult to meaningfully interpret, and the large dataset used is not likely to be as methodologically robust as described. Additionally, the authors quite rightly state that the low event rates and heterogeneity between studies mean that the findings of the effect based on thromboprophylactic agent used (using separate network meta-analysis) should be treated with caution—we suggest that this caution should be extended to the wider findings of the study. The authors also underline the limited applicability of the results of the primary studies as most studies excluded patients at highest VTE risk, eg, those with previous VTE or cancer.

We argue then that the efficacy of thromboprophylaxis (using standard prophylactic doses of anticoagulants) in reducing *symptomatic* VTE in lower limb immobilization after injury appears to be minimal and there is limited evidence to support the routine use of thromboprophylaxis in this setting. While the absolute risk of symptomatic VTE in this patient group is low, further research is needed in order to define a population who may benefit from thromboprophylaxis and, moreover, to determine the optimal thromboprophylaxis strategy required.

CONFLICTS OF INTEREST

JC has no relevant disclosures but has received speaker fees from Bayer and Sanofi and a travel grant from Mitsubishi. BN and SCC have none to declare. LNR has no relevant disclosures but has received travel grants from Sanofi and Bayer, speaker fees from Bayer, and an investigator-initiated research grant from Sanofi. RA has received honoraria from Bayer, Pfizer, Sanofi, and Medtronic and research grants from Bayer and Medtronic.

AUTHOR CONTRIBUTIONS

JC wrote the first draft. BN, LNR, SCC, and RA all critically appraised the manuscript and all authors have read and approved the final version for submission.

Julia Czuprynska[1]
Banne Nemeth[2]
Lara N. Roberts[1]
Suzanne C. Cannegieter[2]
Roopen Arya[1]

[1]*King's College Hospital, London, UK*
[2]*Leiden University Medical Center, Leiden, The Netherlands*

Correspondence
Julia Czuprynska, King's College Hospital, London, UK.
Email: juliaczuprynska@nhs.net

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 16 November 2019

ORCID

Julia Czuprynska https://orcid.org/0000-0003-4315-3704
Banne Nemeth https://orcid.org/0000-0002-1214-5923
Lara N. Roberts https://orcid.org/0000-0003-3871-8491

LINKED CONTENT

See also Horner D, Stevens JW, Pandor A, et al. Pharmacological thromboprophylaxis to prevent venous thromboembolism in patients with temporary lower limb immobilization after injury: systematic review and network meta-analysis. *J Thromb Haemost*. 2020; 422–38. https ://doi.org/10.1111/jth.14666 and Horner D, Stevens JW, Pandor A, et al. Reply to Thromboprophylaxis in temporary lower limb immobilization: Extrapolate with care. *J Thromb Haemost*. 2020; 519–20. https://doi.org/10.1111/jth.14708

REFERENCES

1. Horner D, Stevens JW, Pandor A, et al. Pharmacological thromboprophylaxis to prevent venous thromboembolism in patients with temporary lower limb immobilization after injury: systematic review and network meta-analysis. *J Thromb Haemost*. 2020;18(2):422–438.
2. Chan NC, Stehouwer AC, Hirsh J, et al. Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials. *Thromb Haemost*. 2015;114(5):1049-1057.
3. Lapidus LJ, Rosfors S, Ponzer S, et al. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. *J Orthop Trauma*. 2007;21(1):52-57.
4. Lapidus LJ, Ponzer S, Elvin A, et al. Prolonged thromboprophylaxis with dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. *Acta Orthop*. 2007;78(4):528-535.
5. Nemeth B, Cannegieter SC. Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: from a population-based approach to individualized therapy. *Thromb Res*. 2019;174:62-75.
6. van Adrichem RA, Nemeth B, Algra A, et al. Thromboprophylaxis after knee arthroscopy and lower-leg casting. *N Engl J Med*. 2017;376(6):515-525.
7. Selby R, Geerts WH, Kreder HJ, et al. A double-blind, randomized controlled trial of the prevention of clinically important venous thromboembolism after isolated lower leg fractures. *J Orthop Trauma*. 2015;29(5):224-230.

Received: 4 December 2019 | Accepted: 10 December 2019

DOI: 10.1111/jth.14708

Reply to Thromboprophylaxis in temporary lower limb immobilization: Extrapolate with care

We thank Dr. Czuprynska et al for their interest in our work. The authors highlight the key points of our paper and also draw attention to several of the described limitations, which indeed limit the validity of the evidence base. We wish to respond to several points made in the letter.

First, Czuprynska et al suggest the attempt to retrospectively identify symptomatic cases within trials is unreliable and offer examples of variable symptomatic deep vein thrombosis rates within previous studies to support their point. The issue of outcome validity is a recognized limitation to any secondary research; we have highlighted this in both the Methods and Discussion sections. In an attempt to mitigate, we reported symptomatic outcomes as objectively described within trial publications, contacted trial authors to gain further clinical information when relevant, and reported our classification of symptomatic disease transparently. As such, we believe our work represents an accurate summation of the totality of the evidence, accepting these limitations in methodology. In addition, we present results data for seven different classifications of venous thromboembolism (VTE) outcome; this allows readers to see the relative risk impact of prophylaxis on variable definitions of disease.

Second, we suggest that baseline risks in any study vary according to study characteristics and sampling variation; it is the relative treatment effect that is assumed to be constant on a suitable scale, and transportable across populations. In an exploratory analysis we found no evidence to suggest a relationship between the population baseline risk and population treatment effect on the analysis scale.[1]

Last, the authors mention the exclusion of patients at highest risk of VTE as limiting the applicability of the results of primary studies. We acknowledge this limitation, but suggest that exclusion of these patients would be unlikely to impact any relative treatment effect for the reasons detailed above. However, any relative treatment effect would be more likely to impact *absolute risk* within a pragmatic real-world population including such patients, where baseline risk would be higher.

Nevertheless, we agree with Czuprynska et al that the absolute benefit on the risk scale may not always be clinically meaningful, and that the effectiveness and cost-effectiveness on the absolute risk scale depend on the baseline risk in a target population. We highlight this in point 4 of the Essentials, noting that individualized prophylaxis for those at higher baseline risk may be an optimal strategy. We

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 10 December 2019