

# Post thrombotic syndrome, exploring aspects of pathophysiology and personalized management

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## **Valorization**



Deep vein thrombosis (DVT) of the leg occurs in 1 to 2 per 1000 persons per year.<sup>1-3</sup> After DVT, twenty to fifty percent of patients develop post thrombotic syndrome (PTS).<sup>4,5</sup> PTS has a significant influence on quality of life of patients.<sup>6</sup> In addition, costs of PTS, both healthcare costs and costs due to productivity loss, are substantial.<sup>7</sup> This thesis is separated in two parts: pathophysiology and personalized management of PTS. Therefore, the valorization of the results will also be described in two parts.

In the first part of this thesis the pathophysiology of PTS is studied. Various biomarkers and laboratory measurements were studied in patients with PTS. Biomarkers can be used for diagnostic and prognostic purposes. Biomarkers could contribute to identifying those patients at risk of PTS. Biomarkers together with clinical risk factors could potentially be translated into a risk prediction score, which can be used to individualize management strategies.

In addition, research into the pathophysiology of disease contributes to the understanding of the disease, and may contribute to the development of new therapies. New therapies can potentially decrease the incidence of PTS and decrease the disease burden of PTS.

The results of the studies described in this thesis have added new findings to the existing body of evidence, and although it did not result in the concrete development of new therapies or risk prediction tools yet, this data can be the basis for further study on both subjects. More research is therefore needed. Future studies on the pathophysiology of PTS should include substantial numbers of patients and follow-up of these patients for longer periods of time.

The second part of this thesis is about personalized management of PTS. Currently all patients are advised to wear elastic compression stockings (ECS) for a total period of two years after DVT, to prevent PTS. Probably, not all patients will need ECS therapy for two years, and a shorter duration of therapy might be safe in a subset of patients.<sup>8</sup> Individually tailored duration of ECS therapy is a promising new therapeutic strategy that might save substantial costs and increase patients' well-being. In the Netherlands, individually tailored duration of ECS therapy could induce cost savings of over € 10 million each year. In addition, individually tailored ECS therapy might contribute to patients' well-being, as ECS therapy is considered very unpleasant by most patients.

In this thesis we compared two methods of sample size estimation for non-inferiority trials: the frequentist approach and the decision theory approach. In the decision theory approach both effects and costs are taken into account, and aspects of patient preferences can also be included. In addition, the value of research for society is taken into account in the decision theory approach, as the potential cost savings of a new therapy are compared to the costs of performing the trial. Therefore, the decision theory approach of sample size estimation might be a tool to prioritize research activities, in order to invest these financial resources wisely. Based on the findings of

this thesis we recommend grant providers to demand the inclusion of a sample size estimation according to the decision theory approach in applications of grants for non-inferiority trials. Such implementation does need a more widespread knowledge and knowhow of the decision theory approach and decision modelling, not only for scientists that write the grant applications, but also for the experts that judge the grant applications. Besides knowhow, it would require early modelling; asking researchers to develop decision models in advance to grant applications. The development of open source reference models for distinct disease areas might help to overcome this issue.

A successful clinical trial does not always lead to an improvement in management of disease. The eventual success of management of disease depends, among other factors, on patient behaviour, as compliance and adherence to therapy determines effectiveness of therapies to a large extent. In this thesis, we studied the characteristics of ECS therapy that affect the preferences of patients after DVT and the trade-offs patients make between perceived benefits and burden of ECS therapy. PTS risk reduction was the most important determinant of preference, followed by the ability to put on and take off the ECS independently. These insights can be used by physicians to tailor counselling to improve compliance to therapy. Furthermore, based on this study we can make the recommendation that put-on aids for ECS should be made (economically) available to patients. These put-on aids can enable patients to keep their highly valued independence, which could increase compliance. In addition, costs of home care could be reduced. In general, assessment of patients' preferences should be included, when studying management of disease in clinical trials. Involving patients might increase success of clinical trials and contribute to the eventual implementation of new therapies.

## References

1. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;151: 933-8.
2. Cogo A, Lensing AW, Prandoni P, Hirsh J. Distribution of thrombosis in patients with symptomatic deep vein thrombosis. Implications for simplifying the diagnostic process with compression ultrasound. *Arch Intern Med* 1993;153:2777-80.
3. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *J Intern Med* 1992;232:155-60.
4. Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; 349:759-62.
5. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, Tormene D, Mosena L, Pagnan A, Girolami A. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004;141:249-56.
6. Kahn SR, Shbaklo H, Lamping DL, Holcroft CA, Shrier I, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, Desjardins L, Johri M, Ginsberg JS. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost* 2008;6:1105-12.
7. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis* 2009;28:465-76.
8. Ten Cate-Hoek AJ, Ten Cate H, Tordoir J, Hamulyak K, Prins MH. Individually tailored duration of elastic compression therapy in relation to incidence of the postthrombotic syndrome. *J Vasc Surg* 2010;52:132-8.