Risk stratification of outpatient management in acute venous thromboembolism

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General introduction and outline

Thrombosis is the formation of a blood clot that obstructs the blood flow through the circulatory system. Rudolf Virchow described this process in the 19th century. Factors in his triad predisposing for the formation of venous thrombosis include: blood stasis, changes in the vessel wall and hypercoagulability. Venous thromboembolism (VTE), mainly consisting of acute pulmonary embolism (PE) and deep-vein thrombosis (DVT), refers to a blood clot in the pulmonary arteries and to the veins of the lower and upper extremities. The burden of VTE constitutes a major global health issue and it represents the third leading cause of vascular disease with nearly 10 million annual cases worldwide.[1] In the past two decades the incidence of VTE has been increased due to a number of reasons. First, because of increasing numbers of patients longer surviving severe diseases such as cancer. Second due to the more advancing age of the overall population and last due to earlier diagnosis due to the availability of more accurate diagnostic imaging modalities.[1,2]

The treatment of patients with thromboembolic disease, and especially acute PE, was historically exclusively provided in a hospital based setting, mainly because of the necessity of parenteral anticoagulation. However, with the introduction of low-molecular-weight heparins (LMWHs) and, more recently, direct oral anticoagulants (DOACs), the option of early hospital discharge or even complete home treatment has emerged. Home treatment or outpatient management has become widely accepted and practiced for the diagnosis DVT in the 90ties of last century.[3,4] Meanwhile, although there has been a trend toward treating more patients with low-risk PE at home in the last decade, the majority of PE patients are still being hospitalized for the initiation of anticoagulant treatment.[5-11]

The first part of this thesis focuses on the outpatient management of acute VTE and especially on optimizing the risk stratification of patients with acute PE. This latter is crucial for selecting patients who can be treated safely at home. An overview of current risk stratification strategies for this purpose is presented in **Chapter 2**. Moreover, the great variety of admission duration throughout Europe is described, demonstrating that the decision to choose for home treatment or hospitalization is not solely based on patient characteristics and risk stratification, but also greatly depends on locoregional preferences as well as the organization of outpatient care by general practitioners and/or outpatient clinics.

In several large trials, the safety and feasibility of home treatment in selected patients with PE has been shown. However, the optimal method for selecting relevant patients for home treatment is still being debated. According to the European Society of Cardiology guidelines (ESC guidelines), this identification process should start with calculating the Pulmonary Embolism Severity Index (PESI) score or its simplified version (sPESI).[12] Both have been shown to appropriately predict the 30-day rate of adverse events in patients with acute PE. However, the decision for home treatment is not only confined to risk of 30-day outcome measures. An alternative risk stratification tool are the Hestia criteria. These latter contain eleven pragmatic parameters of both risk of mortality and bleeding, but also of hypoxemia and pain requiring intravenous analgesia. It has been suggested that risk stratification could be further improved

by combining clinical decision scores such as sPESI and Hestia with cardiac biomarkers.[13-16] In **Chapter 3**, a post-hoc analysis of the Vesta study is described in which the added prognostic value of high-sensitive troponin T measurements on top of the Hestia criteria is investigated.

Besides combining biomarkers and risk stratification tools, imaging biomarkers may also be used for identifying patients with a good prognosis. For instance, CT parameters such as a higher degree of embolus load, higher RV/LV diameter ratio and presence of contrast reflux to the inferior vena cava have been associated with more severe PE. The precise role of measures of RV overload in normotensive PE patients as a tool to identify low-risk patients eligible for home treatment is however debated. According to the current ESC guidelines, all PE patients with signs of RV overload are to be hospitalized.[17] According to the Hestia criteria, formal assessment of RV function is not required to select candidates for home treatment. This contrast in both strategies regarding the explicit value of RV overload in the risk stratification is addressed in the next two chapters. In **Chapter 4**, the incidence of RV dilatation and centrally located PE is described in patients treated at home based on the application of the Hestia clinical decision rule alone. In this way we aimed to investigate the additional prognostic value of RV dilatation on clinical outcome of patients treated at home after application of the Hestia criteria. In **Chapter 5** we aimed to evaluate reasons for hospitalization according to the Hestia criteria, and specifically to explore the reasons for the application of the subjective Hestia criterion. Application of this latter criterion could indeed involve measures of the RV function. To do so, we scrutinized medical charts of PE patients who were hospitalized to identify the exact reasons for hospitalization, and particularly, the impact of hemodynamic parameters and RV/LV diameter ratio on that decision.

The second part of this thesis focuses on current patterns of home treatment and the safety of anticoagulant treatment of PE. Results of outpatient management in the Netherlands are described in **Chapter 6**. In this chapter, we also compare PE-related readmissions between patients treated at home and in hospital. For certain patient populations, the decision to treat patients at home is complicated. One of those settings is cancer-associated PE, where patients have a particular high risk of recurrent VTE but also of major bleeding. According to the simplified PE severity index, all patients with cancer are categorized as high-risk for adverse events and death, implicating that all should be initially hospitalized. However, initial hospitalization of cancer patients with PE will likely not prevent cancer-associated mortality. Moreover, the psychosocial advantages and quality-of life considerations of home treatment in those patients are particularly relevant. In **Chapter 7** we aimed to provide an overview of Dutch clinical practice of home treatment in patients with cancer-associated VTE, and report its outcomes.

In **Chapter 8** the effectiveness and safety of apixaban in practice-based conditions is evaluated in patients with acute PE who were mostly treated at home. Large Phase 3 trials have already shown comparable efficacy of DOACs and vitamin K antagonists in patients with VTE, with less major bleeding events in patients with DOAC treatment. As phase 3 trials have strict in- and exclusion criteria both efficacy and bleeding rates may be underestimated. Evaluation of

the DOACs using practice based data sources in those treated at home is needed to provide a better insight into their effectiveness and safety. Lastly, the aim of **Chapter 9** was to quantify the economic impact of home treatment. It has been suggested that home treatment of PE is associated with significant cost savings which would be a further advantage on top of higher patient satisfaction and the prevention of hospital overcrowding. In this chapter an accurate estimation of cost savings per patient treated at home is described.

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