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Thrombophilia ad dies vitae

Cohn, D.M.

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Chapter I

General introduction and outline of the thesis

General introduction

Venous thromboembolism (VTE) is a frequently occurring disease in Western societies, with an annual incidence of 2-3 per 1000 inhabitants.^{1,3} Its clinical spectrum ranges from deep venous thrombosis of the leg to potentially fatal pulmonary embolism.

Even though anticoagulant therapy is highly effective, treatment success is counterbalanced by a 15% annual risk of bleeding, and a 3% annual risk of major bleeding (such as intracranial or gastrointestinal bleeding).⁴ After discontinuation of anticoagulant therapy, the risk of recurrence following the initial event is as high as 17-30% after 7-8 years.^{5,6}

In addition, approximately half of the patients with deep venous thrombosis develop post thrombotic complaints in the leg.⁷

It has been known for many decades that several exogenous factors increase the risk of VTE. These factors include major trauma, prolonged immobilization, surgery, use of oral contraceptives or hormonal replacement therapy, pregnancy, puerperium, cancer and chemotherapy. In addition to these exogenous risk factors, several endogenous conditions are known to be associated with an increased risk of VTE which are denoted as “thrombophilia”.

The term thrombophilia was introduced in 1965 by Olav Egeberg, when he reported a Norwegian family with a remarkable thrombotic tendency due to antithrombin deficiency.⁸ In 1982 and 1984, protein C and protein S deficiency were identified as new hereditary risk factors for VTE.^{9,10} Deficiencies in antithrombin, protein C or protein S are rare in the general population and in patients with VTE.¹¹ It wasn't until the mid-1990s when more common risk factors for VTE were identified, such as factor V Leiden and the prothrombin G20210A mutation.^{12,13}

Factor V Leiden is a gain-of-function mutation that leads to resistance of activated clotting factor V through inactivation by activated protein C.¹⁴ Besides VTE, carriers are also at a slightly increased risk of spontaneous or recurrent miscarriages.¹⁵ Despite these obvious disadvantages, the point mutation -which occurred about 21,000 - 34,000 years ago-¹⁶ has a high prevalence of approximately 4 to 7% in Caucasians.¹⁷ It has long been speculated that the high population frequency of factor V Leiden reflects some sort of evolutionary benefit for carriers.¹⁸⁻²³

Thrombophilia also comprises acquired conditions, of which the antiphospholipid syndrome is the most established. Antiphospholipid syndrome is a disorder, which causes arterial and/or venous thrombosis, as well as pregnancy-related complications such as

miscarriage or preterm delivery. The syndrome occurs due to the autoimmune production of antibodies against plasma proteins that bind to negatively charged phospholipids.

In approximately half of all patients with VTE, a thrombophilic defect can be demonstrated.²⁴ Moreover, one or more exogenous risk factors can be demonstrated in circa 50% of all patients with VTE (the remaining episodes being denoted as “unprovoked”). This implies that in about 25% of patients with VTE no obvious cause can be found. It is therefore likely that other, yet unidentified risk factors are to be discovered.

During the past decade, the associations between various thrombophilic defects and VTE have been clearly established. Nevertheless, several issues remain unresolved. These include the clinical relevance of testing for thrombophilia, the identification of new risk factors for VTE and aspects of thrombophilia related to reproduction. These issues will be addressed in this thesis.

Outline of the Thesis

Originally, the main focus of this thesis was planned to be assessment of the efficacy of testing patients with a first VTE for thrombophilia. For this purpose, we initiated the NOSTRADAMUS (Necessity Of Screening for Thrombophilia At Diagnosis of venous thromboembolism to Assess Most Unresolved issues) trial. This randomized controlled, multicentre trial was the ideal instrument to demonstrate the benefits, if any, of testing for thrombophilia. However, due to a low inclusion rate which was primarily the result of competition with industry initiated intervention studies, this trial was terminated prematurely.²⁵

Nevertheless, we were able to perform several other studies focussing on consequences of testing for thrombophilia and, in addition, on clinical and psychological aspects of VTE. The results of these studies are presented in the first part of the thesis. Chapter 2 reviews the associations between thrombophilia and risk of VTE. In addition, the implications of testing for thrombophilia are highlighted. Whether the risk of recurrent VTE could be reduced by testing patients with a first VTE for thrombophilia (by adjusting therapy or taking preventive measures), is assessed by a systematic review of the available evidence in chapter 3. In Chapter 4, the published research on psychological effects of testing for thrombophilia is systematically reviewed and critically appraised. Even though quality of life is increasingly being conceptualized as the central outcome of health care, instruments

Chapter 1

to specifically measure quality of life following pulmonary embolism are lacking. We therefore created the “Pulmonary Embolism Quality of Life” (PEmb-QoL) questionnaire. The development and validation analyses of this questionnaire are presented in chapters 5 and 6.

The second part of this thesis addresses a search of new risk factors for VTE. Chapter 7 describes a case-control study in which the association between elevated blood glucose levels and the occurrence of deep venous thrombosis is investigated. Chapter 8 elaborates on the risk of VTE and elevated glucose levels. In this study, the pre- and postsurgical glucose levels in 12,383 patients who underwent knee or hip surgery are related to the incidence of (a)symptomatic VTE. Whether an association is present between single nucleotide polymorphisms of the gene encoding for endothelial lipase and VTE is discussed in Chapter 9.

The third part of the thesis describes reproductive aspects of venous thromboembolism and thrombophilia. Chapter 10 addresses the issue of safety of thromboprophylaxis in pregnant women. Even though low-molecular-weight heparins have shown to be safe for the fetus throughout pregnancy, the associated bleeding risk for the mother with high (therapeutic) doses remains unknown. In this chapter, the risk of peripartum blood loss in 83 women who used therapeutic doses of low-molecular-weight heparin during pregnancy is presented and compared to the risk in pregnant women who did not receive thromboprophylaxis. The rate of successful pregnancy outcomes in couples with recurrent miscarriage due to antiphospholipid syndrome of the women is presented in chapter 11. Whether increased male fertility can account for the high population frequency of factor V Leiden is described in chapter 12.

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