Thrombophilia ad dies vitae

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Summary

Thrombophilia, which is the common term for a tendency towards excessive venous clot formation, is the focus of this thesis. Chapter 1 constitutes a short introduction on venous thromboembolism (VTE) and thrombophilia. The remaining chapters are classified into three parts. The first part (chapters 2-6) discusses clinical and psychological aspects of VTE and thrombophilia, the second part (chapters 7-9) addresses the search for new thrombophilic factors and the third part (chapters 10-12) focuses on reproductive aspects of VTE and thrombophilia.

Part I: clinical and psychological aspects of VTE and thrombophilia

Chapter 2 reviews the various thrombophilic factors (antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden, prothrombin G20210A mutation, high levels of clotting factor VIII and antiphospholipid syndrome) and their association with VTE. Furthermore, the potential advantages of testing for thrombophilia are discussed, as well as the disadvantages of testing. In addition, an outline of the NOSTRADAMUS (Necessity Of Screening for ThRombophilia At Diagnosis of venous thromboembolism to Assess Most Unresolved iSsues) study is presented. This study was designed to assess whether testing for thrombophilia and prolonging treatment duration is beneficial in terms of clinical outcomes (the composite endpoint of recurrent VTE and bleeding risk), quality of life and costs. Unfortunately, this study was terminated early. This chapter concludes with the various reasons for the early termination of the NOSTRADAMUS study.

In chapter 3, the available evidence for testing for thrombophilia after VTE is systematically reviewed. We investigated whether testing for thrombophilia leads to reduction of the risk of recurrent VTE by adjusting therapy or taking preventive measures. The Cochrane Peripheral Vascular Diseases Group trials register (last searched 22 April 2008), MEDLINE, EMBASE, and the CENTRAL database (last searched 2008, Issue 2), and reference lists were searched for relevant papers. However, no trials were identified and, therefore, the conclusion of this chapter is that randomized controlled trials are urgently needed to address this issue.

Chapter 4 investigates the extent of psychological impact of testing for thrombophilia, such as fear, depression and worry, which is a potential disadvantage of testing for thrombophilia. Studies that determined the nature and extent of psychological impact following testing for thrombophilia were systematically reviewed. We searched the

MEDLINE database (1966 to February 2008), the EMBASE database (1985 to 2008, week 5) and the PsychInfo database (1806 to February 2008) for relevant trials that focused on the psychological impact of testing for thrombophilia, without language restrictions. In addition, bibliographies of relevant articles were scanned for additional articles. Six studies fulfilled the eligibility criteria, but pooling of the data was not possible since these studies varied tremendously in methodology. These six studies reported few negative results, but most assessments were limited to the short term or lacked methodological accuracy. Therefore, no valid conclusions can be drawn about the psychological impact of genetic testing in patients based on the current available literature.

Chapters 5 and 6 address the development and validation of the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire. Quality of life has become a key component of medical care and an important outcome measure of clinical trials. Indeed, several questionnaires have been developed and validated to specifically assess quality of life following deep venous thrombosis. However, no questionnaires exist to measure quality of life following pulmonary embolism. Therefore, we created the PEmb-QoL questionnaire, by determining relevant social, physical and emotional complaints by interviewing 10 patients with severe lingering symptoms following pulmonary embolism. Subsequent to the creation, the PEmb-QoL questionnaire was distributed together with the Short Form-36 (SF-36) questionnaire twice among 90 consecutive subjects with a history of objectively confirmed acute PE. Internal consistency was adequate (Cronbach's α 0.62 to 0.94), as well as test-retest reliability (intra-class correlation coefficients: 0.78 to 0.94). Furthermore, correlation between the PEmb-QoL questionnaire and the SF-36 questionnaire supported convergent validity. These data indicate that the PEmb-QoL questionnaire is a reliable instrument to specifically assess QoL following PE, which is helpful in the identification of patients with decreased QoL following acute PE.

Part II: identification of new thrombophilic factors

Chapter 7 reports a case-control study among 188 patients with confirmed venous thrombosis (including calf vein thrombosis and superficial thrombophlebitis) and 370 controls with suspected venous thrombosis but in whom the diagnosis was excluded. Glucose levels were measured upon presentation and divided into quartiles based on the distribution in the controls and binary regression analyses were performed to assess whether high glucose levels were associated with venous thrombosis. When adjusted for

body mass index, a known history of diabetes mellitus, age, sex, ethnicity and whether known risk factors for deep venous thrombosis were present, the OR for deep venous thrombosis in the 2nd, 3rd and 4th quartile of glucose levels compared to the 1st quartile was 1.59 (95% CI 0.89 to 2.85), 2.04 (95 % CI 1.15 to 3.62) and 2.21 (95% CI 1.20 to 4.05), respectively, *P* for trend=0.001. These data support the assumption that increased glucose levels measured at presentation are associated with venous thrombosis, but a causal role needs to be investigated in future studies.

Chapter 8 elaborates on the association between hyperglycaemia and VTE. A post-hoc analysis of four phase III clinical trials in 6890 patients undergoing elective total hip and 5493 patients undergoing total knee replacement was performed. Glucose levels were measured at day 0 (admission) and day 1 (after surgery) and categorized into quartiles, based on the distribution in the respective cohorts. Glucose levels measured at day 1 were associated with both symptomatic VTE and total VTE (the composite of symptomatic VTE, asymptomatic deep venous thrombosis and all cause mortality) in patients undergoing hip surgery, adjusted OR highest versus lowest quartile 2.6 (95%CI 1.0 to 6.6) and 2.0 (95%CI 1.3 to 3.1), respectively. However, no association between hyperglycaemia and VTE following knee replacement was observed, which is likely due to the surgical procedure.

Chapter 9 describes the results of two case-control studies (the EPIC-Norfolk study and the ACT study) in which an association between 5 tag single nucleotide polymorphisms in the endothelial lipase gene (*LIPG*) and lipid parameters, coronary artery disease and VTE was investigated. In EPIC-Norfolk, we found that the minor allele of one SNP, rs2000813 (p.T111I), was associated with moderately higher HDL-C and apolipoprotein A-I levels, higher HDL particle number and larger HDL size. No variants were associated with risk of coronary artery disease, but 3 variants were associated with DVT risk OR 0.60 (95%CI 0.43 to 0.84); OR 2.04 (95%CI 1.4 to 2.98) and OR 1.67 (95%CI 1.18 to 2.38) per minor allele for rs2000813, rs6507931 and rs2097055 respectively, p<0.005 for each single nucleotide polymorphism. However, the association between *LIPG* single nucleotide polymorphisms and DVT risk could not be replicated in the ACT study. In conclusion, these data support a modest association between the *LIPG* rs2000813 variant and parameters of HDL metabolism, but no association between common genetic variants in *LIPG* and coronary artery disease or DVT.

Part III: reproductive aspects of VTE and thrombophilia

Chapter 10 reports the results of a cohort study that investigated whether the use of therapeutic doses of low-molecular-weight heparin (LMWH) during pregnancy is associated with an increased risk of post-partum haemorrhage (defined as blood loss exceeding 500mL following vaginal delivery or over 1000mL following caesarean section). We compared the bleeding risk in 83 pregnant women who received therapeutic doses of low-molecular-weight heparin to the risk in 523 pregnant women who did not receive anticoagulant treatment. The risk of post partum haemorrhage after vaginal delivery was 12% in LMWH users and 21% in non-users (RR 0.6; 95%CI 0.3 to 1.2). After caesarean section, PPH risk was 9% (2/22) in LMWH users and 4% (2/51) in non-users (RR 2.3; 0.3 to 17). Median amount of blood loss in vaginal deliveries was 200mL in LMWH users and 300mL in non-users, (difference 100mL; 41 to 159). In caesarean sections the median blood loss did not differ between LMWH users and non-users (425 and 400mL respectively, difference 25mL; -133 to 183). In emergency caesarean sections this was higher in LMWH users than in non-users (450 and 200mL respectively, difference 250mL; 9 to 491). These data suggest that therapeutic doses of LMWH are relative safe for pregnant women who deliver in the hospital setting of optimal obstetric care. An increased risk of bleeding appears to occur in the setting of emergency caesarean section, but more research is needed.

Chapter 11 details the prognosis of a subsequent pregnancy in 176 women with antiphospholipid syndrome (APS) and recurrent miscarriage and 517 women with unexplained recurrent miscarriage. A total of 122/176 women with APS had a subsequent live birth (69%) compared to 324/517 women with unexplained recurrent miscarriage (63%); OR 1.3 (95%CI 0.9 to 1.9). No differences were found for birth weight, gestational age and intra-uterine growth restriction between these two groups. Following stratification for therapy, 53/67 of women with APS who had received aspirin and heparin during their pregnancy had a live birth (79%), compared to 64/104 women with APS who received aspirin only (62%); adjusted OR 2.7 (95%CI 1.3 to 5.8) and compared to 204/305 of women with unexplained miscarriage who received no treatment (67%); adjusted OR 2.2 (95%CI 1.1 to 4.2). In conclusion, the live birth rate between women with recurrent miscarriage and APS and women with unexplained recurrent miscarriage is comparable. In women with APS, combined use of aspirin and heparin appears associated with a higher live birth rate as

compared to women with APS who are treated with aspirin only and as compared to women with unexplained recurrent miscarriage without treatment.

Chapter 12 reports high sperm counts as a possible explanation for the high population frequency of factor V Leiden. A pilot study in 19 men with factor V Leiden showed increased sperm concentration and total sperm counts in the 19 factor V Leiden carriers as compared to men from the general population. For confirmation, we performed a cohort study among 37 factor V Leiden carriers and 921 non-carriers. Factor V Leiden carriers had higher total sperm counts and total motile sperm counts than non-carriers: 236 $x10^6$ (95% CI 158 to 292 $x10^6$) versus 163 $x10^6$ (95% CI 147 to 178 $x10^6$) and 81 $x10^6$ (95% CI 54 to 105 $x10^6$) versus 52 $x10^6$ (95% CI 48 to 57 $x10^6$), respectively. These results provide a possible explanation for the high prevalence of factor V Leiden among Caucasians. To our knowledge, this is the first study that indicates that an increased prevalence of a genotype is controlled by *increased* sperm counts.