Venous thrombosis - a patient's view

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Contents

"Grau, teurer Freund, ist alle Theorie,
Und grün des Lebens goldner Baum."
(Johann Wolfgang von Goethe, uit 'Faust')

Chapter 1

General introduction

Venous thrombosis

Venous thrombosis poses a challenge to doctors of all disciplines. It is a common complication among hospital inpatients and contributes to longer hospital stays, morbidity, and mortality. Venous thrombosis has an estimated annual incidence in western countries of 1-2 in 1000 persons (1;2). It is the result of the formation of a blood clot in a vein. This clot (the thrombus) blocks the flow of blood in the affected vein, which can cause pain, swelling, redness, and tenderness of the skin. Venous thrombosis can take place in any section of the venous system but the most common manifestation is in the veins of the legs. Pulmonary embolism occurs when a piece of the clot breaks off and travels to the lungs. Fatal pulmonary embolism occurs in 1-5% of patients with venous thrombosis (3).

Approximately 20 to 50% of patients with symptomatic venous thrombosis develop the postthrombotic syndrome, which consists of chronic discomfort in the affected leg or arm and is characterized by swelling and pain, and occasionally varicose veins and leg ulceration (4;5).

The treatment of choice for venous thrombosis is with oral anticoagulant therapy. To maximize efficacy of treatment, and to minimize bleeding complications, frequent measurement of the International Normalized Ratio (INR) is necessary. Techniques for the self-management of this type of treatment have been developed and were found to improve quality of life of patients (6;7).

Venous thrombosis is a multicausal disease, caused by both genetic and environmental risk factors (8). Environmental risk factors for venous thrombosis include obesity, pregnancy and child-birth, the use of oral contraceptives, surgery, and prolonged immobility, for instance after surgery or during a long flight. A risk factor can be detected in about two-thirds of first-time episodes of venous thrombosis (9). A genetic abnormality predisposing to venous thrombosis by affecting blood coagulation is called thrombophilia and can be detected in about 50% of patients with a first spontaneous thrombosis (10).

Thrombophilia

The number of inherited disorders and risk factors that can be detected through genetic testing is increasing rapidly, and genetic testing is becoming a common component of routine medical care. Genetic testing is often applied to detect personal susceptibility to disease, in the belief that awareness of genetic risk will enhance informed medical decision making and have an impact on changing health behaviour (11).

Until recently, an abnormality affecting coagulation could only be pinpointed in a small minority of patients with venous thrombosis. Recently, progress has been made with the identification of several genetic factors that predispose to venous thrombosis

(12). Among the genetic risk factors that have been discovered so far are Factor V Leiden, protein C-, protein S-, and antithrombin deficiency (8). Individuals with inherited thrombophilia have a 16 times increased risk of venous thrombosis compared with a normal population (relative risk 15.7 (95% CI 9.2-26.8)) (13). Note that this risk was observed in individuals who carry thrombophilic defects ánd come from pedigrees with a clear thrombophilic phenotype: individuals with similar defects but without a strong family history appear to have a lower risk, indicative of multiple defects co-segregating in families (14,15). In addition, as the placental vessels depend on the normal balance of coagulation mechanisms, women with familial thrombophilia are at increased risk of fetal loss (16;17).

A debate has been going on about whether widespread thrombophilia testing is beneficial in terms of better prevention and management of venous thrombosis (18;19). Generally, it is believed such widespread testing is not justified because it is not cost-effective (20). However, some argue that screening of patients at a very high risk of venous thrombosis is likely to be useful because it may improve clinical outcome through changes in the duration or intensity of therapy (21). In addition, it is believed that family screening of individuals with a close relative with thrombophilia may help to optimise prophylactic treatment of asymptomatic carriers in high-risk situations (i.e. during surgery or pregnancy). However, to date, there are no data supporting this view (22). Furthermore, the possible psychological consequences of genetic testing for thrombophilia have only received limited attention in the scientific literature. As in similar conditions such as hypercholesterolemia, attention should be paid to the psychological impact of testing for thrombophilia (23). Supporters of thrombophilia screening have stated that testing appears to reduce anxiety about the thrombotic risk (24). A statement like this should be taken with caution until confirmed by formal research, which is currently not available.

However, research has indicated that carriership of a genetic deficit may influence daily life, since it can cause considerable distress, especially in vulnerable individuals (25). Possible negative effects of a positive test result include anxiety and depression following the test, worry about the future and about the possibility of passing the genetic defect on to children. Furthermore, positive test results might cause stigmatization, problems with insurance, and they can interfere with medical decision making. Therefore, the psychological impact of thrombophilia screening deserves wider attention in thrombophilia research and in the debate about the pros and cons of screening.

Quality of life

The World Health Organization definition of health is: 'A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'(26). Based on this definition, quality of life (QOL) in relation to health may be defined as 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by

the patient.' The domains that contribute to this effect are physical, psychological, and social functioning (26;27).

Whereas until about two decades ago, clinical and laboratory measurements were the only indicators of illness, recently, the patient's own view on his or her health has become increasingly important in clinical care and research. Nowadays, quality of life is frequently used in research as an addition to more traditional clinical outcome measures, and large clinical trials have shown that it is responsive to important clinical changes (28).

Researchers have developed a large number of self-report measurements to assess patients' own views on their functioning and quality of life (29). Instruments used to measure quality of life can be classified into generic instruments and disease-specific instruments. Generic instruments allow comparisons across populations of patients with different diseases, whereas disease-specific instruments are sensitive to key dimensions of quality of life that are impaired by specific diseases. An advantage of disease-specific instruments is that they increase acceptability of the questionnaire to the patient by including only relevant dimensions. A recommended research approach for assessing quality of life is the combination of generic and disease-specific instruments in order to combine the advantages of both methods (30;31).

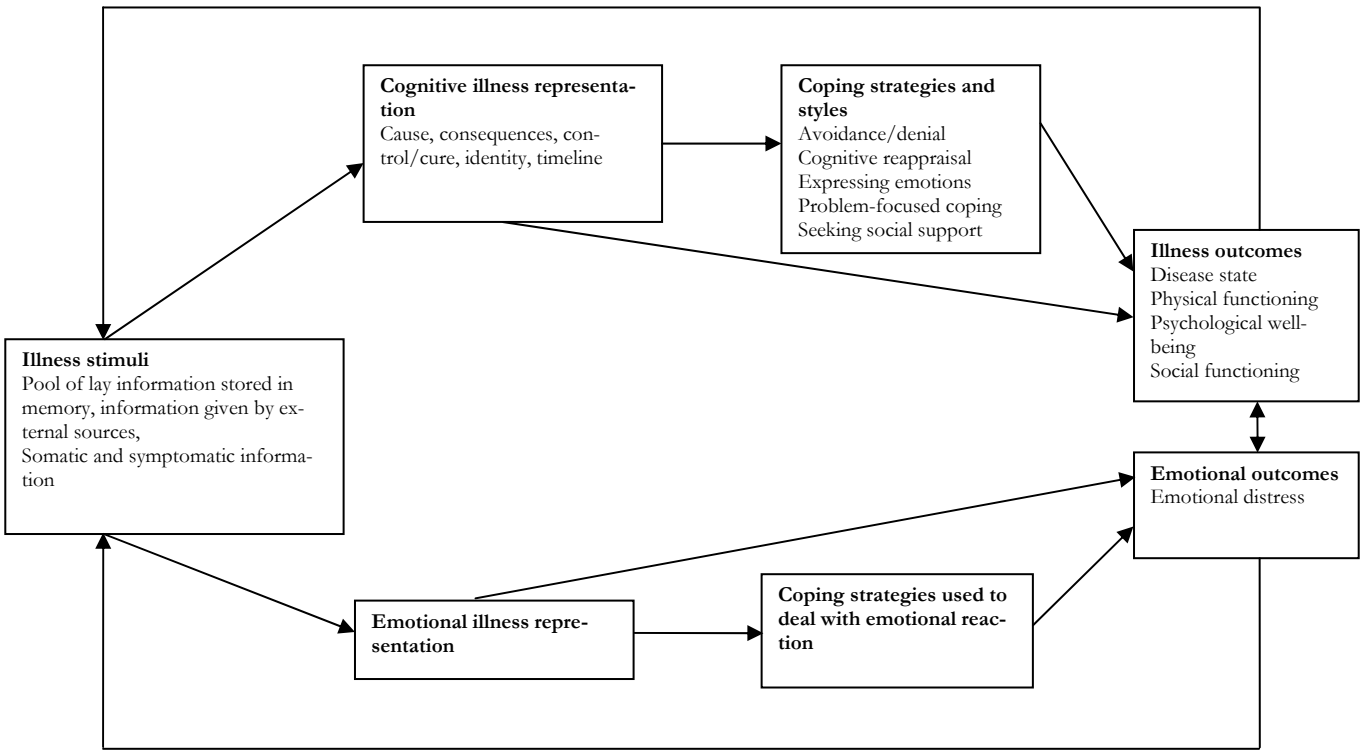
Venous thrombosis is a cardiovascular disease. Quality of life in a diverse array of cardiovascular diseases has been the focus of many studies over the past decades (32-35). However, until some years ago, quality of life in patients with venous thrombosis was an area that did not get much attention in the literature. This is remarkable, because patients with venous thrombosis have to deal with an illness that is possibly fatal, might have serious chronic consequences, and might return. In case of underlying thrombophilia, the effects can also extend to family members. Furthermore, symptomatology and treatment of venous thrombosis are not in any way comparable to other cardiovascular diseases, such as myocardial infarction or stroke. Therefore, it is highly relevant to study the quality of life of this category of patients. One woman in our studies described her first experience with venous thrombosis as follows: *'I couldn't do much (the first three months after venous thrombosis). The first month I could barely walk. I literally went from independent to infirm. From being a young woman with lots of plans for the future, I felt myself robbed of my health.'*

More recently, several researchers have focused on quality of life in this specific group of patients. Several reports by Kahn and colleagues have focused on quality of life after venous thrombosis, especially in the presence of the postthrombotic syndrome, and have found that at first, QOL is impaired in patients with venous thrombosis, but usually improves in the first four months after venous thrombosis. However, in about one third of patients, QOL remains poorer than population norms, especially in patients that suffer from the postthrombotic syndrome (36-38). Similar results were found by Locadia and colleagues, who assessed the impact of the duration of anticoagulant treatment after venous thrombosis on quality of life (39). Apart from the finding that quality of life in patients with venous thrombosis improved over time, this study also showed that quality of life was not related to treatment duration.

Illness perceptions

Quality of life in patients with a chronic illness has been studied extensively, and research has shown that the level of disability as experienced by the patient can not be explained by mere biomedical variables. Therefore, research on quality of life has focused on other factors that influence the perceived impact of the illness. The patient's own perceptions of an illness were found to play an important role in explaining quality of life. Leventhal's Common-Sense Model (CSM) of health and illness behaviour (see Figure 1) is a model that describes a system with two parallel pathways that interact when a patient adapts to an illness or health threat (40;41). Components of the first pathway are the cognitive representations of an illness. Those representations (also called illness perceptions) include five key attributes: the label and symptoms that patients associate with their illness (identity), and their beliefs about the etiology (cause), the outcome (consequences), the duration (timeline) and the controllability (cure/control) of the illness (40;42). The second pathway involves the emotional response to an illness. Together, these illness perceptions can lead to a diverse array of health outcomes, possibly through coping behaviours.

Figure 1. Common-Sense Model of Illness representations (adapted from Hagger & Orbell, 2003)



Several assessment tools of illness perceptions have been developed over the years, including interviews and a number of questionnaires (43;44). The Illness Perceptions Questionnaire (IPQ) and its revised version, the Illness Perceptions Questionnaire-Revised (IPQ-R) are the most widely used examples (45;46).

Quality of life factors represent important outcome components of the Common-Sense Model. The influence of illness perceptions on the quality of life of patients with a chronic disease has been investigated in a number of studies. These studies have provided support for the hypothesis that a strong illness identity (the attribution of many symptoms to an illness), as well as a belief in a long duration and serious consequences of an illness have a negative effect on the well-being of patients (47;48).

Illness perceptions in patients with cardiovascular diseases have been studied to some extent (49-51), but to date, no studies have assessed the illness perceptions and their influence on outcome in patients with venous thrombosis.

Psychological consequences of genetic testing

Informing people of their genetic susceptibility to a disease may motivate them to change their behaviour to reduce their risk (52;53). However, carriership of a genetic deficit may also influence daily life, since it may cause considerable distress, especially in vulnerable individuals (25). Possible negative effects of a positive test result include anxiety and depression following the test, worry about the future and about the possibility of passing the genetic defect on to children, especially in highly anxious individuals (54). Furthermore, positive test results might cause stigmatization, problems with insurance, and they may interfere with medical decision making. Some even argue that family and kinship become medicalized as a result of the current emphasis on medical genetics (55).

As mentioned above, the possible psychological consequences of genetic testing for thrombophilia have not been studied before. In addition to the general psychological distress following a genetic test, it is important to study perceived risk about developing venous thrombosis in thrombophilic individuals. Perceived risk of disease is the expectancy of an individual of developing a specific disease at some point in his or her life. Perceived risk has been identified as a motivator for health behaviour in several studies. In the area of cancer screening, risk perceptions have been found to be often inaccurate perceptions of the actual risk of cancer (56). Moreover, risk perceptions have been found to be positively associated with screening intentions, and preventive behaviour such as breast self-examinations (57;58). Inaccurate perceptions of risk tend to persist even after genetic counselling (59). These inaccurate perceptions of disease risk could have a negative effect on well-being and preventive behaviour. A growing body of research indicates that disease-related worry also plays a motivational role in promoting health behaviour, with an effect that is sometimes even stronger than the effect of risk perception (60;61).

Improved understanding of how individuals estimate their personal disease risk

and what factors influence their disease related worry, is critical in understanding the relationship between risk perception, worry, and health behaviour. Perceptions of health risks such as a genetic risk factor predisposing to an illness are based on perceptions of the target illness, and so the construction of risk perception must be consistent with the theoretical understanding of illness representations. In this light, the Common-Sense Model of illness representation can be useful in understanding risk perceptions and worry about disease in patients at a genetic risk for a disease (62-66). Although the CSM has primarily been applied to understanding outcome in patients who are physically ill, it is likely that illness perceptions are also important predictors of the response to health threats in healthy individuals, such as a genetic predisposition to an illness (67). In families with a history of venous thrombosis, it is likely that genetically predisposed but asymptomatic family members have witnessed episodes of venous thrombosis in their close relatives. This experience, together with the information patients have received from medical caregivers and have gathered themselves (e.g. through the internet), might have generated illness perceptions about thrombosis, which in turn can guide the reaction to this health treat.

Aims of the studies described in this thesis

Since 1985 a large North-American family (n~800) with protein C deficiency due to the 3363C mutation has been studied (IPCI: International Protein C Investigation) (68). It is likely that this mutation was introduced in North America by a couple of French settlers who established themselves in 1669 near Québec City (69). A family of this size is ideal to study the psychological aspects of genetic testing for thrombophilia. Collaboration between the Department of Clinical Epidemiology (LUMC), the Unit of Psychology (LUMC) and the Department of Pathology of the University of Vermont (VT, USA) was established. This collaboration resulted in several studies on quality of life in patients with venous thrombosis and the psychological impact of thrombophilia testing, of which the results are described in this thesis.

The first aim of this thesis was to study the quality of life of patients with venous thrombosis and to examine the role of illness perceptions in explaining the quality of life of these patients. The second aim of this study was to study the psychological consequences of genetic testing for thrombophilia, using the Common-Sense Model as a theoretical framework. As mentioned above, the Common-Sense Model can prove to be a useful model in explaining a diverse array of outcomes in individuals that are at risk of a disease. With our research we hope to contribute to the knowledge of how we can apply the Common-Sense Model to an 'at risk' population and how we can place perceptions of disease risk in this theoretical model.

Outline of this thesis

The thesis is divided into two parts. Part 1, consisting of chapters 2, 3, and 4, focuses on the first aim of the thesis and describes the quality of life and illness perceptions of patients with venous thrombosis.

Chapter 2 presents an overview of the existing literature about quality of life in chronic venous diseases.

Chapter 3 presents the results of a study that was conducted at the thrombosis clinic of the University of Vermont in Burlington (VT, USA). The chapter focuses on the measurement of quality of life in patients with a history of venous thrombosis. The aim of this study was to examine the impact of venous thrombosis on quality of life in a well-defined population of patients with venous thrombosis by using both a generic and a newly developed disease-specific measure and to study the relationship between quality of life, the presence of symptoms, and the presence of the postthrombotic syndrome.

Chapter 4 is based on the same study as chapter 3. This chapter describes illness perceptions in patients with venous thrombosis, and examines their role in the quality of life of these patients.

The second part of this thesis deals with the second aim. This part consists of chapters 5 and 6, and focuses on the psychological consequences of genetic testing for thrombophilia.

Chapter 5 describes the results of a study in a large family with a high incidence of heritable protein C deficiency and venous thrombosis (IPCI: International Protein C Investigation). The aim of this chapter was to explore the attitudes of protein C deficient individuals about genetic testing and to establish the correlates of risk perception, trait anxiety, and thrombosis-related worry in these attitudes.

Chapter 6 focuses on the illness perceptions about venous thrombosis in patients with a genetic predisposition to the disease. Participants in this study were adult thrombophilic individuals who were enrolled in the European Cohort on Thrombophilia (EPCOT) study in the Netherlands. The aim of this study was to use the Common-Sense Model as a theoretical framework to predict risk perception and worry about venous thrombosis.

The thesis concludes with a general discussion. The major results of the studies described in this thesis, their strengths and limitations, and suggestions for further research will be discussed.

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Part 1

Quality of life and illness perceptions in patients with venous thrombosis

Chapter 2

Quality of life in venous disease

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Summary

Quality of life (QOL) can be defined as 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient.' Studies on the impact of chronic venous disease on quality of life are scarce compared to quality of life research in other diseases.

The purpose of this paper was to describe instruments that assess quality of life in patients with chronic venous disease and to review the literature on this topic. A computer search of the MedLine database was performed to identify papers, and the bibliographies of relevant articles were reviewed to obtain additional papers. Papers were included if they described the development or use of a quality of life instrument for patients with chronic venous disease.

A total of 25 papers were identified that fit the inclusion criteria. The studies described in the papers used six different generic instruments and ten disease specific instruments. Quality of life in chronic venous disease was assessed in 12 studies. Six studies compared different types of treatment for chronic venous disease where QOL was an outcome measure.

Despite the wide variety of measures used, results indicate that quality of life of patients with chronic venous disease is affected in the physical domain mostly with regard to pain, physical functioning and mobility, and that they suffer from negative emotional reactions and social isolation. We feel that QOL should be a standard measure in future studies in patients with chronic venous disease, preferably with a combination of generic and disease specific measures.

Introduction

Quality of life (QOL) can be defined as 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient' (1). These functional effects are usually operationalized as (limitations in) physical, psychological and social functioning. Quality of life is increasingly seen as an important outcome measure in diagnostic and treatment studies because of the publication of several large clinical trials showing that quality of life as an outcome measure is responsive to important clinical changes (2). In addition to relieving clinical symptoms and prolonging survival, a primary objective of any health care intervention should be the enhancement of the well-being of the patient (3).

Chronic venous disease may affect several aspects of quality of life. It also requires medical care. Treatment often involves hospital admission and invariably treatment with anticoagulants, which may also have an impact on quality of life.

There have been numerous studies on the etiology, diagnosis, and management of chronic venous disease and about the cost-effectiveness of treatment, but few have ex-

amined the impact of chronic venous disease on quality of life. Studies on chronic venous disease and quality of life are also scarce compared to quality of life research in other diseases.

Instruments used to measure quality of life can be classified into generic instruments and disease-specific instruments. Generic instruments allow comparison across populations of patients with different diseases, whereas disease specific instruments are sensitive to key dimensions of quality of life that are impaired by specific diseases. Therefore, combining generic and disease specific instruments is a preferred strategy in examining quality of life (4).

The purpose of this paper is to describe instruments that have been used to assess quality of life in patients with chronic venous disease, and to review the literature regarding the impact of chronic venous disease on quality of life.

Method

A computer search of the MedLine database from 1966 to February 2003 was performed to identify relevant papers. The following entries were used: (venous thrombosis) and (quality of life). In addition, we reviewed the bibliographies of relevant articles to obtain additional papers. Papers were selected if they met the following inclusion criteria: they were written in the English, French or German language and they had to describe the development or use of a quality of life instrument in venous thrombosis or treatment of venous thrombosis. Because the search specific for 'venous thrombosis' yielded only few results, papers about other chronic venous diseases, such as varicose veins and leg ulceration, were included.

Results

A total of 25 papers fitted the inclusion criteria of describing the development, validation or use of a quality of life measure in patients with chronic venous disease. Twenty-three papers were in the English language, two papers were written in German. Table 1 presents a summary of the 25 papers classified according to the sample that was investigated. The first part of this section will describe two categories of instruments for assessing QOL in chronic venous disease: generic instruments and disease-specific instruments. In the next part of this section the studies assessing QOL in chronic venous disease will be discussed, classified according to the diagnostic category of patients that was investigated.

Table 1: Studies on quality of life in patients with chronic venous disease (N=25)

Author & Year	Objective	Sample	Method used to assess QOL
		Venous disease	
Augustin, 1997 (30)	To develop and validate a QOL questionnaire for CVI patients	246 patients with Chronic venous insufficiency	Freiburger Questionnaire of QOL in venous diseases (FLQA)
Franks, 1992 (28)	To test the accuracy and usefulness of a questionnaire to assess risk factors and symptoms of venous disease	114 patients with venous disease and 114 healthy controls	QOL questionnaire for patients with venous disease and Symptom Rating Test (SRT)
Klyscz, 1998 (31) (German)	To determine QOL in CVI with the Tübingen questionnaire for measuring QOL in patients with CVI (TLQ-CVI)	142 patients with CVI	Tübingen questionnaire for measuring QOL in patients with CVI (TLQ-CVI)
Lamping, 1998 (33;34)	Development and psychometric evaluation of a questionnaire to assess quality of life and symptoms in patients with chronic venous disease of the leg	615 patients with chronic venous disease in Belgium, France, Canada and Italy	VEINES-QOL
Launois, 1996 (32)	To construct and validate a QOL questionnaire in chronic lower limb venous insufficiency	2001 patients with CVI	CIVIQ
		Venous thrombosis	
Beyth, 1995 (19)	To assess long-term outcomes in patients with acute deep-vein thrombosis	124 patients with deep vein thrombosis	Interview with symptoms and SF-36 items
Kahn, 2002 (11)	To compare generic and disease specific QOL instruments in patients with and without PTS after DVT and to examine whether QOL correlates with severity of PTS	41 subjects with venous thrombosis, 19 with and 22 without PTS	SF-36, VEINES QOL
Mathias, 1999 (35)	To test the psychometric properties of a health-related QOL measure	111 patients with deep vein thrombosis	QOL questionnaire for patients with DVT
Ziegler, 2001 (37)	To investigate the impact of the extent of DVT and recurrent thrombotic events in accordance to other presumed prognostic factors for long term outcome after first DVT	161 patients with post-thrombotic syndrome	CIVIQ (modified)
		Venous leg ulceration	
Charles, 1995 (38)	To ascertain the physical, psychological and social effects of living with a leg ulcer	4 patients with chronic venous leg ulcers	Interview
Franks, 1994 (27)	To investigate QOL in patients with leg ulcers	185 patients with leg ulcers	Symptom Rating Test, adapted version of QOL questionnaire from Franks et al. [28]
Franks, 2001 (21)	To determine the validity of the NHP in patients with venous ulceration	383 patients with venous ulceration	Nottingham Health Profile (NHP)
Hyland, 1986 (36)	To assess QOL in leg ulcer patients	50 patients with leg ulcers	QOL questionnaire for patients with leg ulcers

Table 1, continued

Author & Year	Objective	Sample	Method used to assess QOL
Lindholm, 1993 (22)	To assess the influence of chronic leg ulcers on six areas of daily life	125 patients with chronic leg ulcers	Nottingham Health Profile
Phillips, 1994 (39)	To assess the financial, social and psychological implications of leg ulcers	73 patients with chronic leg ulcers	Interview
Smith, 2000 (12)	To validate the Charing Cross venous ulcer questionnaire	98 patients with venous ulcers	SF-36 and the Charing Cross venous ulcer questionnaire
Walters, 1999 (13)	To compare four QOL instruments for use in patients with venous leg ulcers	233 patients with venous leg ulcers	SF-36, EQ, SF-MPQ, FAI
		Varicose veins	
Garratt, 1993 (14)	To develop an outcome measure for patients with varicose veins	281 patients with varicose veins and 542 healthy controls	SF-36 and QOL questionnaire for patients with varicose veins
Kurz, 2001 (15)	To assess the impact of varicose veins on QOL and self-reported symptoms	1054 patients with varicose veins, 259 controls without varicose veins	SF-36, VEINES QOL
		Comparing treatment	
Comerota, 2000 (18)	To evaluate whether catheter-directed thrombolysis for DVT will improve QOL compared to standard anticoagulation	68 patients treated with catheter-directed thrombolysis and 30 patients treated with anticoagulation alone	Questionnaire with SF-12 and disease-targeted scales including health distress, stigma, health interference, physical functioning, symptoms
Frank, 1998 (40) (German)	To compare ambulant with hospital treatment of acute DVT	14 ambulant and 13 hospital treated patients with deep vein thrombosis	Questionnaire with items about perception of pain and well being (Visual Analogue Scale), treatment satisfaction and absence from work
Gänger, 1989 (41)	To compare functional long-term results of surgically and medically treated patients with DVT and to compare QOL in both groups	24 surgically and 25 medically treated patients with DVT	Standardised interview with items about physical ability, disability, well-being, pain, satisfaction with treatment
Koopman, 1996 (17)	To compare treatment for venous thrombosis with intravenous unfractionated heparin in a hospital setting with low-molecular weight heparin administered at home	198 patients receiving intravenous standard heparin and 202 patients receiving low-molecular weight heparin	SF-20, Rotterdam Symptom Checklist with specific items for venous thrombosis and VAS for coping and overall QOL
Kulinna, 1999 (42)	To examine the effect of self-monitoring the International Normalized Ratio (INR) on quality of life	100 patients on oral anticoagulation	Disease specific QOL questionnaire
O'Brien, 1999 (16)	To evaluate cost-effectiveness of out-patient treatment with low-molecular weight heparin for DVT	151 patients receiving standard heparin and 149 patients receiving low-molecular weight heparin	SF-36

Legend Table 1
CIVIQ: Chronic Lower Limb Venous Insufficiency Questionnaire
CVI: Chronic venous insufficiency
DVT : Deep vein thrombosis
EQ: Euro-QOL
FAI: Frenchay Activities Index
PTS: Postthrombotic syndrome
QOL: Quality of life
SF-36: Short Form-36
SF-20: Short Form-20
SF-12: Short Form-12
SF-MPQ: McGill Short Form Pain Questionnaire
VAS: Visual Analogue Scale

Review of available instruments

The generic and disease specific instruments used in the reviewed studies will be described and their reliability and validity will be discussed. An instrument is reliable when it consistently produces the same results when applied to the same subjects when there is no evidence of change (5). One way to assess reliability is to determine the internal-consistency reliability coefficient, which reflects the degree of relatedness between the individual items that make up a scale (6). The items should all measure the same concept, and therefore should be correlated with each other. A measure of overall internal-consistency reliability is Cronbach's alpha (7). Cronbach's alpha is a function of the number of test items and the average inter-correlation among the items. Alpha coefficients ranges in value from 0 to 1. In general, for comparing groups, a reliability coefficient or Cronbach's alpha higher than 0.70 is acceptable (8).

Validity is concerned with whether the indicator actually measures the underlying attribute or not. Validity of a quality of life measure is usually determined by examining correlations between conceptually related measures and by studying associations between the measure and various clinical characteristics (6).

Generic QOL instruments

The generic instruments used in the reviewed studies are depicted in Table 2. The most widely used generic instrument to measure quality of life is the Short Form 36 (SF-36) (9).The SF-36 consists of 36 items spread over 8 dimensions, plus a single item giving information on change in health over the past year.

Table 2: Generic QOL instruments

First author & Year	Instrument	Measured dimensions of QOL
Holbrook, 1983 (25)	Frenchay Activities Index (FAI)	Physical: domestic chores, leisure/work, outdoor activities
Hunt, 1986 (20)	Nottingham Health Profile (NHP)	Physical: physical mobility, pain Psychological: emotional reaction Social: social isolation Other: sleep, energy
Kellner, 1973 (26)	Symptom Rating Test (SRT)	Psychological: depression, anxiety, cognitive function, hostility
Melzack, 1987 (24)	McGill Short Form Pain Questionnaire (SF-MPQ)	Physical: pain
The EuroQol group, 1990 (23)	EurQol (EQ)	Physical: mobility, self care, usual activities, pain Psychological: anxiety
Ware, 1993 (9)	Short Form 36 (SF-36)	Physical: physical functioning, role limitations physical, bodily pain Psychological: role limitations emotional, general mental health, energy/vitality Social: social functioning Other: general health perceptions

Legend: for abbreviations, see Table 1

A major advantage of the SF-36 is its extensive application in several disease conditions and extensive validation in several populations. A paper about quality of life measurement found that the SF-36 was the most widely evaluated measure, over 10% of the 3921 reviewed reports used it (10). The original version of the SF-36 was used in six of the reviewed studies (11-16), two studies used modified versions, the SF-20 (17) and the SF-12 (18), and another study used items of the SF-36 in a standardized interview (19).

The Nottingham Health Profile is another generic QOL instrument (20). It includes 38 items covering six domains. It has been used extensively in outcome studies in several clinical areas such as cardiovascular and rheumatological diseases. The NHP was used in two studies on patients with leg ulceration (21;22).

The EuroQol (EQ) (23), McGill Short Form Pain Questionnaire (SF-MPQ) (24), and Frenchay Activities Index (FAI) (25) are all generic QOL measures and were evaluated together with the SF-36 for use in patients with venous leg ulcers in a study by Walters et al. (13). The EQ consists of 5 dimensions, which measure physical and psychological status. The SF-MPQ is a quantitative measure of pain and the FAI measures activities that reflect level of independence.

The Symptom Rating Test (SRT) measures psychological state, such as depression and anxiety, and was developed as an outcome measure for drug trials (26). Franks and

colleagues used it as a quality of life instrument in two studies with patients with venous disease and leg ulcers (27;28).

The answer to the question: 'which questionnaire should we use?' depends entirely on the research question under study. There is no 'gold standard' for assessing quality of life and therefore no simple answer (29). However, we feel that for the purpose of assessing quality of life in patients with chronic venous disease, an instrument that measures quality of life on the of domains of physical, psychological and social functioning is most appropriate as patients seem to have an impairment in all three domains. This means that the NHP and SF-36 are both good choices.

Disease specific instruments

Ten disease specific questionnaires were found that have been designed to measure QOL in specific groups of patients with chronic venous disease. Table 3 lists the QOL dimensions assessed by the various questionnaires. This section will discuss the instruments classified by the diagnostic category of patients they were developed for.

Instruments for venous disease

Augustin et al. describe the development and validation of a 83-item German disease-specific questionnaire on QOL in patients with chronic venous insufficiency (CVI): The Freiburger Questionnaire of QOL in venous diseases (FLQA) (30). Generally high internal consistency ($\alpha > 0.70$ in all subscales) and high correlations with the NHP provide evidence for the reliability and validity of the scale.

Franks et al. (28) designed a 36-item questionnaire to determine risk factors, quality of life, and use of health resources in patients with venous disease. This instrument contained the Symptom Rating Test and questions about symptoms and daily activities. Reliability and validity of this instrument have not been evaluated.

Another questionnaire that is only available in German was developed by Klyscz et al. (31) for measuring QOL in patients with CVI. This questionnaire meets the requirements of psychometric standards (i.e. adequate reliability and validity) and has proven its use in clinical settings by distinguishing between Stage I/II and Stage III CVI patients with respect to parameters such as 'leg complaints' and 'day-to-day' fears and worries.

Table 3: Disease specific QOL instruments

First author & Year	Instrument & Population	Dimensions
	Venous disease	
Augustin, 1997 (30)	The Freiburger Questionnaire of QOL in venous diseases (FLQA) (German)	Physical: physical complaints, everyday life Psychological: emotional status Social: social life Other: therapy, satisfaction, occupation
Franks, 1992 (27)	Health questionnaire for venous disease	Physical: symptoms, daily activities Psychological: Symptom rating test
Klyscz, 1998 (31)	The Tübingen questionnaire for chronic venous insufficiency (TLQ-CVI) (German)	Physical: physical condition, functional status Psychological: psychological wellbeing Social: social repercussions Other: general health and QOL
Lamping, 1998 (33;34)	VEINES-QOL (for chronic vascular disorders of the leg)	Physical: symptoms, limitations in daily activities Psychological: psychological impact Other: changes in the past year, time of day of highest symptom severity
Launois, 1996 (32)	CIVIQ (for chronic venous insufficiency)	Physical: pain, physical functioning Psychological: psychological functioning Social: social functioning
	Venous thrombosis	
Mathias, 1999 (35)	Health-related quality of life questionnaire for deep vein thrombosis	Physical: physical health (SF-12) Psychological: mental health (SF-12) Other: energy/vitality, health distress, disease interference, Health Utilities Index: emotion, cognition, self-care, pain, vision, hearing, speech, ambulation, dexterity
	Venous leg ulceration	
Franks, 1994 (21)	Health questionnaire for leg ulcers	Physical: symptoms, daily activities Psychological: Symptom rating test
Hyland, 1986 (36)	Self-report QOL questionnaire for patients with leg ulcers	Physical: functional limitations Psychological: dysphoric mood Other: treatment
Smith, 2000 (12)	Charing Cross venous ulcer questionnaire	Physical: domestic activities Psychological: emotional status Social: social functioning Other: cosmetic appearance
	Varicose veins	
Garratt, 1993 (14)	Clinical varicose veins questionnaire	Physical: symptoms, pain, interference with daily activities and work Other: treatment, concern about appearance

Legend: for abbreviations, see Table 1

Launois et al. constructed the 20-item Chronic Lower Limb Venous Insufficiency Questionnaire (CIVIQ) (32). The CIVIQ was validated in a large study sample of 2001 patients and each dimension showed to have good internal consistency and reproducibility.

The VEINES-QOL, developed by Lamping et al., is a 26-item questionnaire designed for use in patients with chronic vascular disorders of the leg. Four language versions (English, French, French Canadian and Italian) have been developed and each version has been evaluated and the results confirmed its reliability and validity (15;33;34).
As previously stated, the decision of which questionnaire to use depends on the research questions of a study. The CIVIQ and the VEINES-QOL may be good choices for assessing QOL in English speaking people with venous diseases, because they are short, well validated and cover most important issues. For German speaking patients, the FLQA would be an appropriate choice.

Instruments for venous thrombosis

Only one questionnaire was specifically designed for use in patients with venous thrombosis. Mathias et al. developed a health-related quality of life measure for patients with deep vein thrombosis (35). The questionnaire items were derived from the Health Utilities Index and the SF-12. New items were developed that were specific for DVT. The internal consistency was good, with Cronbach's α values ranging form 0.69 to 0.95, but not all items showed good variability.

Instruments for venous leg ulceration

For use in patients with leg ulcers, Franks et al. adapted their questionnaire to fit the specific problems of patients with leg ulcers, such as pain and interference with daily activities (27). The validity and reliability of this instrument have not been evaluated.
Two QOL questionnaires have been specifically developed for patients with leg ulcers. The questionnaire by Hyland et al. consists of the following sections: issues central to the experience of the ulcer, and a list of 29 QOL items (36). This questionnaire has not been formally evaluated regarding validity, but there was some evidence for reliability based on inter-item correlations in a study with a sample of 50 patients.

Another 32-item QOL questionnaire for patients with venous ulcers was developed by Smith et al. (12) The questionnaire showed good internal consistency ($\alpha = 0.93$) and test-retest analysis ($r = 0.84$). Validity was demonstrated by high correlations of the questionnaire with all eight domains of the SF-36.

The questionnaire by Smith et al. seems to be the best choice for evaluating QOL in patients with leg ulcers because it covers all aspects of quality of life and has good validity and internal consistency.

Instruments for varicose veins

A 15-item questionnaire for patients with varicose veins was developed by Garratt et al. (14). It has shown a high correlation with the SF-36 and a good internal consistency, and therefore there is some evidence of its reliability and validity.

Review of clinical study results

In this section the studies that conducted quality of life measurement in patients with chronic venous disease and related conditions are reviewed. The studies are presented according to the diagnostic category of patients under investigation.

Quality of life in patients with venous disease

In a study of 114 patients with venous disease matched with 114 healthy control subjects, quality of life was measured with self-reported symptoms and the Symptom Rating Test (28). More cases than controls reported a history of symptoms of venous disease like leg swelling, cramps, itching, restlessness and pain. There were no differences between the two groups in the areas of the SRT, such as depression, anxiety or hostility.

Quality of life in patients with venous thrombosis

Four studies examined QOL in patients with venous thrombosis; three studies used a combination of disease-specific and generic measures (11;19;35), and one study used only a disease-specific measure (37).

A longitudinal study of venous disorders followed 124 patients with deep vein thrombosis 6 to 8 years after thrombosis was diagnosed (19). A 75 item interview was applied, containing items about symptoms and treatment and 19 items from the SF-36. At follow up (6-8 years after diagnosis) 52 patients were interviewed of whom 42% still reported pain, swelling, or discoloration of the leg. The symptoms were rated as mildly or moderately severe. On the SF-36, symptomatic patients had lower perceptions of their health, lower levels of physical functioning and more severe role limitations due to physical health compared to non-symptomatic patients.

A recent study by Kahn and colleagues assessed 41 patients with previous deep vein thrombosis, of whom 19 had postthrombotic syndrome (PTS) (11). They measured quality of life with the SF-36 and the VEINES-QOL. It was found that postthrombotic syndrome had a significant impact on quality of life measured by the disease-specific VEINES-QOL. No differences between patients with and without PTS in quality of life measured by the SF-36 were observed.

Mathias and colleagues studied 111 patients with deep vein thrombosis who had received treatment with urokinase or standard heparin for DVT at least 6 months prior to identification (35). Three groups were distinguished; those with no symptoms, moderate symptoms, and severe symptoms, as determined by a physician at baseline measurement. The group with no symptoms reported better functioning on nearly every scale of the questionnaire compared to the group with moderate symptoms. The group with moderate symptoms reported better functioning compared to the group with severe symptoms. The only significant differences between those two groups were found on stigma and overall symptoms, borderline differences were found on health distress and physical functioning.

Ziegler et al. investigated 161 patients who had been treated for deep vein thrombosis (37). Of these patients, 82% suffered from post-thrombotic syndrome. A modified version of the CIVIQ with questions about pain was completed by 56 patients. No limitation was reported by 29% of patients, 25% were only mildly impaired in their quality of life and 46% of patients evaluated their restriction in QOL as moderate. Estimated impairment of quality of life was associated with the clinical severity of the postthrombotic syndrome. Separate analyses on the four dimensions of the CIVIQ were not reported.

Quality of life in patients with venous leg ulceration

Five studies assessed QOL in patients with leg ulcers; disease-specific measures were used in four studies (27;36;38;39), and one study used a generic QOL measure (22).

Charles interviewed four patients with leg ulcers (38). Open-ended interviews were used. The interviews demonstrated that patients with chronic leg ulcers suffered negative effects in the physical, psychological and social areas of their lives.

Franks et al. interviewed 185 leg ulcer patients who visited a community leg ulcer clinic (27). The patients were interviewed at their first visit to the clinic and after 12 weeks of treatment. Symptom Rating Test scores at 12 weeks showed reductions in anxiety, depression, hostility and changes in cognition compared with baseline scores. Interference with daily activities also decreased, but the effect on 'general health' did not.

Fifty leg ulcer patients completed a QOL questionnaire in a study by Hyland et al. (36). Approximately one-third of patients in this sample reported substantial functional limitations and negative emotions because of their ulcer. A remarkable result was that self-care behavior was unrelated to level of pain or quality of life.

In the study by Lindholm and colleagues, the NHP was used to assess quality of life in 125 chronic leg ulcer patients (22). Compared to population norms, leg ulcer patients showed poorer QOL especially with regard to pain, social isolation, emotional reactions and physical mobility. Men with leg ulcers showed poorer QOL than women with leg ulcers.

Phillips et al. conducted standardized interviews with 73 patients with chronic leg ulcers (39). Most patients suffered from moderate to severe symptoms, especially pain.

81% believed that the ulcer adversely affected their mobility. For the working patients, leg ulcers were correlated with time lost from work, job loss and adverse effects on finances. Of all patients, 68% reported that the ulcer had a negative emotional impact on their lives.

Quality of life in patients with varicose veins

Our search yielded two descriptive studies of quality of life in patients with varicose veins, both of which used a combination of disease-specific and generic measures.

A questionnaire survey of 281 varicose veins patients and 542 control subjects was conducted by Garratt et al. (14). The perceived health of patients with varicose veins measured on the SF-36 was lower than that of the control sample.

A cross-sectional population based study assessed 1054 patients with varicose veins and 259 control subjects (15). Patients with varicose veins had lower scores on the SF-36 physical and mental health dimensions compared to population norms. The scores on the physical dimension decreased according to the increasing severity of the concomitant disease, with lowest scores found in patients with varicose veins and an active ulcer. However, no differences were found between patients with varicose veins alone and control subjects. Thus, results indicate that impairment of QOL in patients with varicose veins is associated with underlying venous disease, rather than with varicose veins alone.

Quality of life in patients with different types of treatment

Six studies examined the effect of different kinds of treatment on quality of life in patients with venous thrombosis; two studies used both disease specific and generic instruments (17;18), one study applied only a generic measure (16), and the other three studies used only a disease specific instrument (40-42). One study examined the effect of surgery compared to standard anticoagulation as treatment for DVT and found that patients treated with surgery had better quality of life after treatment, reported less symptoms and had better functioning (41). This study was not randomized so the results should be interpreted with some caution. Comerota et al. found that patients with iliofemoral DVT treated with catheter-directed thrombolysis had better functioning and well-being, compared with patients treated with anticoagulation alone (18). This study was not randomized either, so future randomized trials to confirm the results of the two studies mentioned above are needed.

Frank et al. (40), Koopman et al. (17), and O'Brien et al. (16) compared the effect of outpatient treatment with hospital treatment of acute DVT on QOL. Koopman et al. studied 198 patients who were treated with standard heparin in the hospital and 202 patients who received low-molecular weight heparin at home (17). Quality of life improved in both groups after treatment, but physical activity and social functioning were better in the low-molecular weight heparin group. Frank et al. on the other hand, found that in

their group of patients with in-hospital treatment (N = 13) well-being was higher than in the outpatients (N = 14) (40). O'Brien assessed quality of life in 151 patients receiving standard heparin and 149 patients receiving low-molecular weight heparin and found significant results only in the domain of social functioning, which was better in patients receiving low-molecular weight heparin (16). This result is consistent with that of Koopman et al.(17)

Kulinna et al. examined the effect of self-monitoring the INR in 100 patients on anticoagulant medication and found that this treatment regime improved quality of life, in particular with respect to independence and organization of vacation and spare time (42).

Discussion

A number of findings stand out when reviewing the topic of quality of life in patients with chronic venous disease. First, the number of empirical studies is low compared to the number of studies on quality of life in patients with other diseases: a review of the literature about QOL in patients with lung cancer between 1970 and 1995 revealed 151 papers (43), whereas our search only yielded 25 papers. Secondly, the use of a wide range of instruments in the reviewed studies indicates a lack of consensus concerning the best way to measure QOL in the area of chronic venous disease. Thirdly, despite the short tradition in assessing QOL in chronic venous disease, it appears that the studies reviewed here have identified some major areas of QOL affected by chronic venous disease. In summary, patients with venous thrombosis report pain and impairment of their physical functioning. They also report low health perceptions and high health distress. Impairment of QOL appears to be related to symptom severity and the presence of the postthrombotic syndrome. Patients with venous leg ulceration report impairment of their physical functioning and mobility and suffer from negative emotions and social isolation. Patients with varicose veins reported a lower health perception than a control sample but real impairment of QOL in patients with varicose veins seems to be associated with underlying venous disease.

Improvement of QOL after treatment in patients receiving low-molecular weight heparin appears to be similar to the QOL improvement of patients receiving in-patient treatment with standard heparin in the hospital.

The majority of studies applied generic quality of life measures, in particular the Short-Form 36, which provides the possibility to characterize patients with venous thrombotic disease in comparison with other clinical samples and the healthy population. However, in the study by Kahn et al. (11), the SF-36 could not detect any differences between patients with and without PTS whereas the VEINES-QOL did detect some differences. This might indicate that a generic measure might not be sensitive to any specific effects of PTS. Of the disease specific measures used in the reviewed studies, only

few have been adequately validated in large groups of patients. In most of these instruments the social dimension has been neglected or only partially captured. Because we feel that this is an important issue, we recommend the use of an instrument that assesses this domain as well and is well validated, such as the CIVIQ (32).

A potential limitation of this review is that we might have missed some publications due to our search strategy. However, to our knowledge, we have been thorough in our search for papers.

A potential limitation of the reviewed studies is that most of the reported studies are questionnaire-surveys. There are recognized limitations in questionnaire studies including patients with low literacy skills or poor eyesight who might not be able to complete them, and that long and demanding questionnaires might reduce compliance. In addition, most of the used questionnaires have not been formally evaluated for reliability and validity. Further, responses on questionnaires that were administered retrospectively could suffer from a response bias.

Given the impact of chronic venous disease on quality of life as described in this review, we feel that QOL should be a standard measure in future studies on clinical work in patients with chronic venous disease. A preferred approach in these studies would be a combination of generic and disease specific measures to allow the results to be compared to other samples and to detect key dimensions of quality of life impaired by chronic venous disease. The European Organization for Research and Treatment of Cancer (EORTC) took the initiative to develop a quality of life instrument for patients with cancer, the QLQ-C30, which is validated in 43 languages and used in more than 3000 studies worldwide. It would be an exciting idea for the future if a similar disease specific instrument was developed for patients with venous thrombotic disease and applied as a standard measure in all clinical studies. Until that day, a combination of well-validated generic and disease specific measures, for instance the SF-36 and VEINES-QOL or CIVIQ, would be the preferred approach.

Second, there should be a focus on longitudinal research about the long-term effect of chronic venous disease on quality of life and on the effect of chronic venous disease on the well being of the partners of the affected individual. In clinical work on patients who use anticoagulation, there should be more attention to the negative effects of this treatment on the quality of life of patients, for instance, the fear of hemorrhage and the burden of regular hospital visits. Eventually, intervention studies to improve the quality of life of patients with venous thrombotic disease could be conducted.

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Chapter 3

The impact of venous thrombosis on quality of life

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Summary

Quality of life (QOL) is increasingly seen as an important outcome in clinical care. Etiology, diagnosis, and management of venous thrombosis have been studied extensively, but only few studies have examined the impact of venous thrombosis on quality of life. The purpose of this study was to examine the impact of venous thrombosis on quality of life in a well-defined population of patients with venous thrombosis, by using both a generic and a disease-specific quality of life measure. A total of 45 patients from the thrombosis clinic of the University of Vermont in Burlington, VT, returned a mailed questionnaire including the Short-Form 36 (SF-36) and a disease-specific quality of life questionnaire (VT-QOL) about the problems faced by patients with venous thrombosis.

The sample consisted of 13 men (28.9%) and 32 women (71.1%). The mean age was 44.1 years, with a range from 21 to 80 years. Compared with population norms of a general U.S. population that were adjusted for age and sex (N= 2,463), venous thrombosis patients scored significantly lower ($p < 0.05$) on all subscales of the SF-36. Patients with the postthrombotic syndrome appeared to have more impairment in their quality of life as measured by both the SF-36 and the disease-specific questionnaire. All correlations between the SF-36 subscales and the subscales of the VT-QOL were significant, most of them on a $p < 0.01$ level. Given the impact of venous thrombosis and the postthrombotic syndrome on quality of life, assessment of QOL should be included in future studies on the outcomes of venous thrombosis.

Introduction

Whereas until about two decades ago, clinical and laboratory measurements were the only indicators of illness, recently, the patient's own view on his or her health has become increasingly important in clinical care and research. Researchers have developed a great number of self-report measurements to assess patients' own views on their functioning and quality of life (1). Several large clinical trials have shown that quality of life as an outcome measure is responsive to important clinical changes and therefore it is increasingly seen as an important outcome measure in diagnostic and treatment studies (2). The World Health Organization definition of health is: 'A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (3). Based on this definition, quality of life in relation to health, may be defined as 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient.' The domains that contribute to this effect are physical, psychological, and social functioning (3;4).

The annual incidence of diagnosed venous thrombosis in western countries is 1 per 1000 persons (5;6). In about 20% of patients, venous thrombosis extends proximally, and of those patients, 1-5% develop fatal pulmonary embolism (7). The postthrombotic

syndrome (PTS) is a chronic condition consisting of leg pain, edema, venous ectasia, skin induration and ulceration and is estimated to occur in up to 50% of patients after an episode of venous thrombosis (8;9).

Etiology, diagnosis, and management of venous thrombosis have been studied extensively but only a few studies have examined the impact of venous thrombosis on quality of life. Assessment of quality of life in conditions like venous thrombosis may provide important information on the burden of an illness that is not normally captured by traditional measures of morbidity (10).

A review on the subject of quality of life in patients with chronic venous diseases identified a total of 25 papers (11), of which 4 dealt with the assessment of QOL in venous thrombosis (12-15). These studies indicate that patients with venous thrombosis report pain and impairment of their physical functioning. They also found that patients have low perceptions of their general health and high health distress. Impairment of QOL appears to be related to symptom severity and the presence of the postthrombotic syndrome.

Instruments used to measure quality of life can be classified into generic instruments and disease-specific instruments. Generic instruments allow comparison across populations of patients with different diseases, whereas disease-specific instruments are sensitive to key dimensions of quality of life that are impaired by specific diseases. An advantage of disease-specific instruments is that they increase acceptability of the questionnaire to the patient by including only relevant dimensions. A recommended research approach for assessing quality of life is the combination of generic and disease-specific instruments in order to combine the advantages of both methods (16-18). Of the studies assessing QOL in patients with venous thrombosis mentioned above, only one study used both a generic and a disease-specific instrument to measure quality of life (13). However, the authors failed to observe differences in the SF-36 scores between patients with and patients without the postthrombotic syndrome.

The aim of this study was to examine the impact of venous thrombosis on quality of life in a well-defined population of patients with venous thrombosis by using both a generic and a newly developed disease-specific measure. The aim of the present study was to study the relationship between quality of life, the presence of symptoms, and the presence of the postthrombotic syndrome. An additional aim was to test the disease-specific questionnaire for a larger investigation.

Materials and methods

Participants

Patients seen by one of the authors (MC) at the thrombosis clinic of the University of Vermont were considered for participation. Their charts were reviewed for eligibility and

the presence of postthrombotic syndrome. Individuals under age 18 or who had comorbid disease were excluded from the study. A total of 86 eligible patients were selected to participate in the study. Of the selected patients, 3 refused, 2 were deceased and 16 could not be reached. Following a telephone call by a research nurse 65 patients (75.6%) gave their consent to participate. The investigators contacted those 65 individuals by phone, and sent out the questionnaire and consent forms by mail. Non-responders received a reminder questionnaire. The research protocol was approved by the local institutional review board of the University of Vermont.

Measures

Demographic and illness related variables

The questionnaire included the following: age, sex, marital status, employment status, number of episodes of thrombosis, location of thromboses, time elapsed since last thrombosis and a list of 11 symptoms that can be related to the postthrombotic syndrome. Patient charts were also reviewed to classify the presence of the postthrombotic syndrome as determined by a physician (MC).

Quality of life

As a generic quality of life instrument, the Short-Form 36 (SF-36) was used (19). The SF-36 is the most widely used and evaluated generic instrument to measure quality of life (20). The SF-36 is a measure which assesses functional, psychological and social status. It consists of 36 items spread over 8 dimensions, plus a single item giving information on change in health over the past year. In addition to the 8 subscales, 2 summary scores can be calculated: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). A major advantage of the SF-36 is its extensive application in several disease conditions and excellent psychometric characteristics. The SF-36 has population norms available against which the results of this study will be compared (21).

As a disease-specific measure, a quality of life questionnaire developed by the authors was used (see Appendix for sample items). The Venous Thrombosis-Quality of Life questionnaire (VT-QOL) was based on interviews held with thrombosis patients and previous QOL research in venous thrombosis (14;22;23). The final instrument consisted of questions assessing quality of life in the dimensions physical functioning (7 items, α = 0.96), social functioning (6 items, α = 0.94), general mental health (6 items, α = 0.94) and thrombosis repercussions (6 items, α = 0.88). We chose this approach because according to the existing literature about QOL measurement in patients with venous thrombosis, to accurately measure quality of life, it is imperative to focus on physical, emotional and social functioning (24). All items were rated on a 5-point Likert scale. It is possible to calculate subscores on all subscales with a range of 0 to 100 where 0 indicates worst possible

quality of life and 100 indicates best possible quality of life. This is in line with the scoring of the SF-36. Additional questions were asked about the perceived severity of thrombosis, overall restriction in daily activities, and perceived pain.

Statistical methods

All data were entered and analyzed using SPSS 11.0. Means were calculated for all SF-36 subscales and compared to U.S. population norms adjusted for age and sex, by means of t-tests. Patients were grouped in three different ways: patients with and without PTS, patients with and without a recent event (<2 years ago), and patients with 1, 2 or multiple events of venous thrombosis. To compare scores between groups, analysis of covariance (ANCOVA) was used and analyses were adjusted for age and sex. Simple univariate correlations were used to detect relationships between subscales of the SF-36 and the thrombosis-specific questionnaire. For all statistical tests, a P-value of 0.05 or less was considered significant.

Results

Sample characteristics

A total of 45 out of 65 patients (69%) returned the questionnaire. The sample consisted of 13 men (28.9%) and 32 women (71.1%). The mean age was 44.1 years, with a range from 21 to 80 years. A total of 13 subjects were unemployed (28.9%), of whom 6 were unemployed due to disability (13.3%). Non-responders were more likely to be male and were slightly younger than responders. No differences were seen between the two groups regarding the type of thrombosis the patients had experienced.

In the participant group, the number of patients with a recent thrombotic event, i.e. after 2000, was slightly lower. Respondents experienced between 1 and 8 thrombotic events, with a median of 2 episodes. All 45 respondents experienced their most recent thrombosis event between 1997 and 2002 with a median elapsed time of 2 years; 38% had their most recent thrombosis event after 2000.

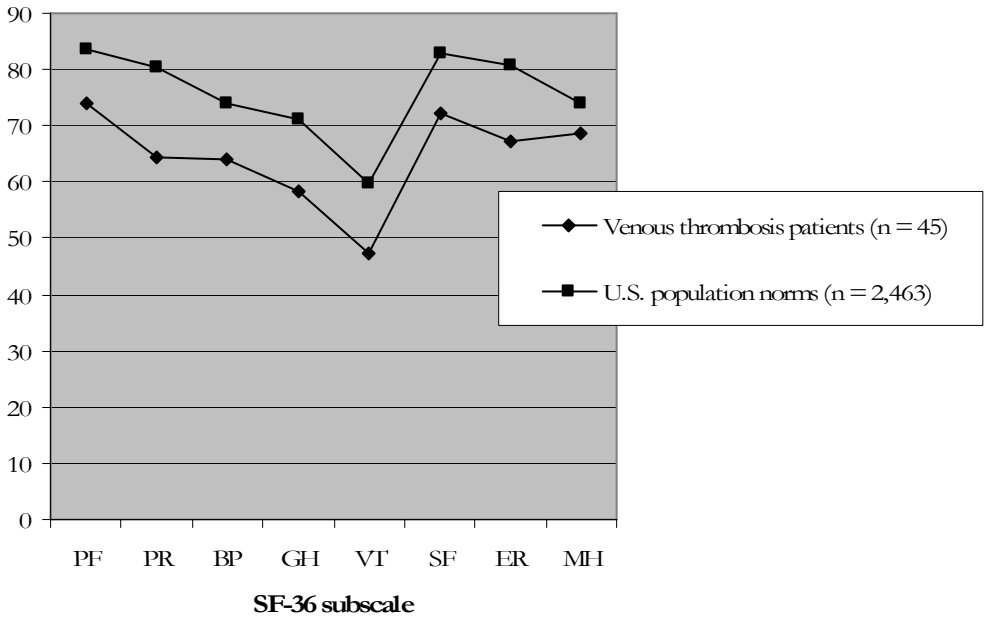
From chart review it was concluded that 20 subjects (44%) had no long-term physical effects from their venous thrombosis and 25 (56%) had mild or severe post-thrombotic syndrome. There were no significant differences in the presence of the post-thrombotic syndrome with respect to age, sex, number of venous thromboses and time elapsed since the last episode. Patients with PTS as diagnosed by a physician had a significantly higher number of self-reported symptoms compared to patients without PTS (3.4 vs. 1.4, $p<0.01$).

Quality of life

Short-Form 36

Because our sample was composed of a higher proportion of women and was older than the group used for the general U.S. population norms (N= 2,463) (21), the U.S. population norms were adjusted by weighting the norms with the age and sex distribution in our sample. The venous thrombosis patients scored significantly lower on all subscales of the SF-36 (see Figure 1). The scores on the Mental Health subscale are significantly lower at the $p < 0.05$ level, all others at the $p < 0.01$ level.

Figure 1. Mean scores of venous thrombosis patients on the SF-36 compared to an U.S. population sample



Legend:
PF: Physical functioning
PR: Physical role limitations
BP: Bodily pain
GH: General health perceptions
VT: Vitality
SF: Social functioning
ER: Emotional role limitations
MH: Mental health

Table 1. Mean SF-36 subscale- and summary scores, for patients with and without a recent event, patients with and without the post-thrombotic syndrome (PTS) and patients with 1, 2 or more events.

	US population norms (n = 2,463)	Venous thrombosis patients (n = 45)	Time since last event		Presence of PTS		Number of thrombotic events		
			0-1 yr (n=17)	> 2 yr (n=28)	PTS (n=25)	No PTS (n=20)	1 (n = 21)	2 (n=15)	>3 (n=9)
Physical Functioning	83.6	73.9	80.6	69.9	64.2	86.1	84.6	62.9	67.2
Physical Role limitations	80.3	64.4	58.8	67.9	58.0	72.5	78.6	55.0	47.2
Bodily Pain	74.0	64.0	61.6	65.4	56.0	74.0	75.2	54.7	53.1
General Health perceptions	71.2	58.3	59.6	57.5	55.0	62.4	60.9	58.2	52.1
Vitality	59.9	47.4	44.4	49.3	43.5	52.0	52.1	40.4	47.2
Social Functioning	82.8	72.2	69.1	74.1	67.0	78.8	77.4	66.7	69.4
Emotional Role limitations	80.8	67.4	56.9	73.8	58.7	78.3	76.2	55.6	66.7
Mental Health	74.1	68.7	71.1	67.3	63.8	74.6	69.7	66.6	69.8
Physical Health component	50.0	44.2	45.2	43.6	41.0	48.1	49.1	40.1	39.1
Mental Health component	50.0	45.8	44.3	46.9	43.8	48.2	46.4	43.8	47.5

Table 1 lists the means of the SF-36 subscales and summary scores for the three different groupings, namely: patients with a recent event and those with an event longer ago, patients with 1, 2 or multiple events, and patients with PTS and without PTS. To determine significant differences between the groups, analyses of covariance were performed for the two summary scores. All analyses were adjusted for age and sex.

The presence of PTS was associated with lower SF-36 summary scores, indicating a worse quality of life for patients with PTS. However, only the difference in mean scores on the Physical Component Summary reached statistical significance {PCS: $F(1,39) = 4.42$, $p < 0.05$, MCS: $F(1,39) = 1.35$, $p = .25$}.

There is no significant relationship in quality of life scores between patients with a recent event and those without a recent event, when adjusted for PTS, although the Physical Component Summary is slightly lower for patients without a recent event and the Mental Component Summary is somewhat higher for this group {PCS: $F(4, 38) = 1.29$, $p = .29$, MCS: $F(4, 38) = 1.14$, $p = .35$}.

The number of thrombotic events the patients had experienced was divided into three groups (1, 2, or more than 2 events). A negative trend was observed between number of thrombotic events and Physical Component Summary. These mean scores were not found to be significantly different when adjusted for PTS {$F(5, 37) = .863$, $p = .52$}.

Table 2. Mean scores, standard deviations and Cronbach alpha's on the venous-thrombosis quality of life questionnaire (VT-QOL) and correlations with SF-36 subscales for the venous thrombosis patient sample (N = 45)

			SF-36 subscales							
Subscales VT- QOL (range)	**Mean (Sd)**	**Cron-bach's alpha**	**PF**	**PR**	**BP**	**GH**	**VT**	**SF**	**ER**	**MH**
Physical Functioning (0-100)	76.4 (28.5)	0.96	.85**	.66**	.65**	.40**	.47**	.46**	.49**	.38*
Social Functioning (0-100)	83.6 (22.5)	0.92	.77**	.69**	.58**	.32*	.45**	.50**	.61**	.50**
General Mental Health (0-100)	75.0 (26.3)	0.94	.70**	.65**	.66**	.68**	.87**	.78**	.76**	.84**
Thrombosis Repercussions (0-100)	72.7 (24.9)	0.87	.51**	.51**	.51**	.44**	.52**	.54**	.49**	.61**
Pain (1-6)	2.1 (1.3)		-.38*	-.39*	-.54**	-.27	-.11	-.24	-.17	-.17
Perceived severity (1-5)	3.5 (1.3)		-.05	.12	.24	-.03	.06	.03	-.07	-.12
Restriction (1-3)	1.5 (0.5)		-.62**	-.51**	-.46**	-.44**	-.32*	-.31*	-.42**	-.30

* $P < 0.05$
** $P < 0.01$

Legend Table 2

PF: Physical functioning
PR: Physical role limitations
BP: Bodily pain
GH: General health perceptions
VT: Vitality
SF: Social functioning
ER: Emotional role limitations
MH: Mental health

Venous thrombosis- quality of life questionnaire (VT-QOL)

Mean scores, standard deviations and Cronbach alpha's on the disease-specific questionnaire (N = 45) are shown in Table 2, along with correlations between the subscales of this disease specific measure and the subscales of the SF-36. Cronbach alpha's for all subscales are high (0.87-0.96), indicating a good internal consistency of the subscales. There were strong correlations of scores of the VT-QOL and SF-36 scores. In addition, pain and restriction in daily activities were significantly correlated with most subscales, especially physical functioning, physical role limitations and bodily pain. Perceived severity did not correlate significantly with any of the SF-36 subscales.

To determine significant differences on the VT-QOL between the groupings (patients with and without PTS, patients with and without a recent event and patients with 1, 2, or multiple events), analyses of covariance were performed for all subscales. All analyses were adjusted for age and sex. Mean scores are listed in Table 3.

Patients with PTS have significantly lower scores on most VT-QOL than subjects without PTS, except for general mental health, perceived severity and restriction in daily activities {physical functioning: $F(3, 39) = 3.43$, $p < 0.05$; thrombosis repercussions: $F(3,39) = 3.42$, $p < 0.05$; social functioning: $F(3,39) = 2.98$, $p < 0.05$; pain: $F(3,39) = 2.87$, $p < 0.05$}.

Patients with a recent event have significantly lower scores on the physical functioning and pain subscales of the VT-QOL, after adjusting for PTS {physical functioning: $F(4,36) = 2.92$, $p < 0.05$; pain: $F(4,36) = 2.67$, $p < 0.05$} The other subscales did not reach statistical difference. A significant negative trend in scores was observed between number of thrombotic events and scores on the physical limitations {$F(5,37) = 2.83$, $p < 0.05$} and thrombosis repercussions subscales {$F(5,37) = 2.86$, $p < 0.05$}. This negative trend was less obvious in the other subscales. A positive trend in scores could be observed in pain and restriction in daily activities (meaning that patients with more thrombotic events experience more pain and are more restricted in their daily life) but these trends failed to reach statistical significance.

Table 3. Mean scores on the VT-QOL, for patients with and without a recent event, patients with and without the postthrombotic syndrome (PTS), and patients with 1, 2 or more events

	All patients (n=45)	Time since last event		Presence of PTS		Number of thrombotic events		
		0-1 yr (n=17)	> 2 yr (n=28)	PTS (n=25)	No PTS (n=20)	1 (n = 21)	2 (n=15)	>3 (n=9)
Physical Functioning	76.4	83.6	71.4	66.6	88.2	88.7	70.5	61.5
Social Functioning	72.7	87.3	81.3	76.6	92.5	89.9	77.8	80.1
General Mental Health	83.6	75.2	74.8	67.2	84.4	81.3	69.2	70.8
Thrombosis Repercussions	75.0	75.0	71.3	63.7	83.5	83.8	66.7	58.3
Pain	2.1	1.7	2.3	1.6	2.5	1.8	2.0	2.7
Perceived severity	3.4	3.4	3.5	3.4	3.4	3.6	3.3	3.4
Restriction	1.5	1.4	1.5	1.6	1.3	1.3	1.5	1.7

Discussion

The results of this study indicate that the quality of life of patients with venous thrombosis is impaired in all domains. This impairment encompasses physical, social and psychological domains. Compared to a general U.S. population sample, venous thrombosis patients scored significantly lower on all subscales of the SF-36 after adjusting the population norms for the age and sex distribution in the sample. The subjects in our study had their last thrombotic event a median of 2 years ago, which indicates that even after some years, quality of life of patients with venous thrombosis is still impaired.

Given our results on both the SF-36 and thrombosis-specific instrument we can also conclude that quality of life impairment is related to the presence of self-reported symptoms and the presence of the postthrombotic syndrome as reported by a physician. Both findings are consistent with earlier research (12-15). From our results on the VT-QOL can also be concluded that the quality of life of venous thrombosis patients is more impaired after multiple events. A study by Kahn and colleagues (13) found that the post-thrombotic syndrome had a significant impact on quality of life as measured by the disease-specific measure VEINES-QOL but no differences were observed in the SF-36 scores. In our study however, we did detect significant differences ($p < 0.05$) in the Physical Health Component score between subjects with and subjects without the post-thrombotic syndrome. On our venous thrombosis-quality of life questionnaire, those differences were even more obvious and were found across almost all dimensions. A reason for this could be that most patients in our study had experienced more than one thrombotic event, whereas in the study by Kahn et al., patients with recurrent venous thrombosis were excluded. Accordingly the patients in our study might have had more severe manifestations of PTS.

The disease-specific QOL measure that we used in this study, the VT-QOL, was developed by our group and has not been formally evaluated for reliability and validity before, because the present study was the first study to use and validate this questionnaire. However, the good internal consistency and high correlations with the SF-36 subscales in this study give encouraging evidence for its reliability and validity and its future use. Its advantage to the SF-36 is the fact that it seems to be more sensitive to the specific problems venous thrombosis patients are facing, which can be concluded from its ability to detect differences between patients with and patients without PTS. Furthermore, unlike the SF-36, the instrument was able to discriminate between patients with one or multiple events and patients with or without a recent event.

When interpreting the results of this study, some limitations should be taken into consideration. We excluded patients with comorbid conditions such as cancer to avoid confounding by conditions that could affect quality of life in other ways. This could limit the generalizability of our study, but it is unlikely that it has affected the major conclusions. Non-responders were more likely to have experienced a recent thrombotic event,

which might have influenced the results, although time since last event was not found to be significantly associated with QOL. Presence of PTS is best determined for research purposes by a known scale such as the CEAP classification (25). In our study, however, presence of PTS was determined by a single clinician at different points in time prior to the QOL assessment. The strong correlation between the classification of PTS by the clinician and the self-reported symptoms at the time of QOL determination suggests minimal impact of this possible confounding factor. Use of a single observer probably minimized the possibility of misclassification of PTS.

Given the observed impact of venous thrombosis and the postthrombotic syndrome on quality of life, assessment of QOL should be included in future studies on the outcomes of venous thrombosis, preferably with a disease-specific measure like the VT-QOL. Venous thrombosis is a multi-causal disease that is caused by both genetic and environmental factors (26). Future studies might also assess the impact of genetic testing for thrombophilia on quality of life. For clinical care, our results indicate that health care givers should be sensitive about the impact of venous thrombosis on the well-being of their patients.

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Appendix

Sample items of the venous thrombosis- quality of life questionnaire (VT-QOL):

During the past 4 weeks, to what extent did your thrombosis problem limit you while doing the following activities? (please circle the number corresponding to the right answer)

	Not limited at all	A little limited	Moderately limited	Very limited	Impossible to do so
Physical functioning					
Finding a comfortable position to sleep	1	2	3	4	5
Standing for a long time	1	2	3	4	5
Social functioning					
Social or leisure activities in which you are standing for long periods (e.g. parties, weddings, shopping etc.)	1	2	3	4	5
Social or leisure activities in which you are sitting for long periods (e.g. going to the cinema or theatre)	1	2	3	4	5
	Not at all	A little	Moderately	A lot	Absolutely
General mental health					
I feel on edge	1	2	3	4	5
I feel I am a burden to others	1	2	3	4	5
Thrombosis repercussions					
I am frustrated about my thrombosis	1	2	3	4	5
I am worried about my future because of my thrombosis	1	2	3	4	5

Chapter 4

Illness perceptions and outcome in patients with venous thrombosis

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Abstract

Objective: The aim of this study was to examine how illness perceptions influence the quality of life of patients with venous thrombosis, a medical condition that has had hardly been subject of psychosocial research.
Methods: Forty-five patients with a history of venous thrombosis from the University of Vermont in Burlington, VT, USA, filled out a mailed questionnaire containing the Short-Form 36 (SF-36) and the Illness Perception Questionnaire-Revised (IPQ-R).
Results: Quality of life of these patients was impaired compared to general population norms. Regression analyses showed that scores on the IPQ-R subscales, especially time-line acute/chronic, personal control and identity, and the cause 'heredity' were able to explain a significant amount of variance in quality of life scores after controlling for ill-ness-related variables.
Conclusion: QOL impairment in patients with venous thrombosis can be explained by illness perceptions. Further research could investigate the role of illness perceptions in patients with a genetic vulnerability to venous thrombosis, and the effects of psychoso-cial intervention methods on quality of life in patients with venous thrombosis.

Introduction

Venous thrombosis is the result of the formation of a blood clot in a vein. This clot is called a thrombus and blocks the flow of blood in the affected vein. The symptoms of venous thrombosis include pain, swelling, redness, and tenderness of the skin. Venous thrombosis is most common in the veins of the legs, but it can also occur in other veins. It is a common complication among hospital inpatients and contributes to longer hospi-tal stays, morbidity, and mortality. The annual incidence of diagnosed venous thrombosis in western countries is 1 in 1000 persons (1). Venous thrombosis of the lower limb usu-ally starts in the veins of the calf. In about 10-20% of patients, the venous thrombosis extends above the knee. Fatal pulmonary embolism occurs in 1-5% of patients with ve-nous thrombosis (2). Between 20 and 50% of patients with symptomatic venous throm-bosis develop the postthrombotic syndrome (PTS), which consists of chronic discomfort in the affected leg or arm and is characterized by swelling and pain, and occasionally vari-cose veins and leg ulceration (3). Venous thrombosis is a multi-causal disease, caused by both genetic and environmental risk factors (4).
Quality of life in relation to health (QOL), may be defined as 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient' (5). The domains that contribute to this effect are physical, psychological, and social functioning. Until recently, quality of life in patients with venous thrombosis was an unstudied area. Studies have now indicated that patients with venous thrombosis suffer from impaired

physical functioning and have low perceptions of their health. On average, QOL improves in the first four months after venous thrombosis, but in about one third of patients, QOL remains poorer than population norms, especially in patients who have the postthrombotic syndrome (6-9).

Quality of life in patients with chronic illness has been studied extensively, and research has shown that the level of disability as experienced by the patient can not always be explained merely by biomedical variables. Therefore, research on quality of life has focussed on other factors that could potentially influence the perceived impact of the illness. The patient's own perceptions of an illness were found to play an important role in explaining quality of life. Leventhal's Common Sense Model (CSM) of health and illness behaviour is a model that describes a system with two parallel pathways that interact when a patient adapts to an illness or health threat (10;11). Components of the first pathway are the cognitive representations of an illness. Those representations (also called illness perceptions) include five key attributes: the label and symptoms that patients associate with their illness (identity), and their beliefs about the etiology (cause), the outcome (consequences), the duration (timeline) and the controllability (cure/control) of the illness (10;12). The second pathway involves the emotional response to an illness. Together, these illness perceptions can lead to a diverse array of health outcomes, possibly through coping behaviours. Quality of life factors can represent important outcome components of the Common Sense Model. The influence of the illness perceptions on the quality of life of patients with a chronic disease has been investigated in a number of studies. These studies have provided support for the hypothesis that a strong illness identity (the attribution of many symptoms to an illness), as well as a belief in a long duration and serious consequences of an illness have a negative effect on the well-being of patients (13;14).

Most previous studies using the CSM have only investigated the cognitive components of patient's perceptions, largely overlooking the emotional component (15;16). To solve this, in the revised version of the Illness Perception Questionnaire (IPQ-R), which was used in this study, a subscale was added to assess emotional responses, such as anxiety and anger, generated by an illness (16). The revised version of the IPQ also incorporates a new subscale called 'illness coherence'. This subscale was added to assess the extent to which the illness 'makes sense' to the patient.

Illness perceptions in patients with cardiovascular diseases have been studied to some extent, but none of these studies dealt with venous diseases (14). Examining patients with venous thrombosis from a biopsychosocial perspective is highly relevant, because these patients not only have to deal with the consequences of their illness, but also with the self-management of their anticoagulation treatment. A better understanding of the patient's perceptions of their illness may help in improving compliance to long-term treatment. In addition, many patients who have suffered from venous thrombosis, have a genetic coagulation disorder which predisposes to thrombosis. As in similar conditions

such as hypercholesterolemia, attention should be paid to the psychological impact of testing for these disorders (17).

The aim of this cross-sectional study was to describe the cognitive and emotional illness perceptions that patients with venous thrombosis form about their illness and to examine their role in outcome, in this case, quality of life.

Method

Procedure

Patients with a history of venous thrombosis seen by one of the authors (MC) at the thrombosis clinic of the University of Vermont in Burlington (VT, USA) were considered for participation. All patients had been referred for evaluation and management of venous thrombosis. Eligibility was assessed through chart review, and individuals under the age of 18 or who had comorbid disease were excluded from the study. A total of 86 patients were selected to participate. Of the selected patients, 2 patients were deceased, 16 patients could not be reached and 3 patients refused to participate. A research nurse obtained verbal consent to participate from 65 patients (75.6%). The investigators contacted those 65 individuals by phone, and sent out the questionnaire and consent forms by mail. Non-responders received a reminder questionnaire. The research protocol was approved by the local institutional review board of the University of Vermont.

Measures

Demographic and illness related variables

The questionnaire included the demographic variables age, sex, marital status, and employment status. The number of thrombotic events, the presence of the postthrombotic syndrome and the time (in years) elapsed since last the last thrombotic event were included as illness related variables. The presence of PTS was specifically evaluated in the clinic and recorded through chart-review.

Quality of Life

The Short-Form 36 (SF-36) was used to measure quality of life (18). The SF-36 is the most widely used generic QOL instrument assessing physical, psychological and social functioning (19). It consists of 36 items spread over the dimensions of physical functioning, physical role limitations, bodily pain, general health perceptions, vitality, social functioning, emotional role limitations and mental health. Major advantages of the SF-36 are

its extensive application in several disease conditions and its excellent psychometric characteristics.

Illness perceptions

To measure illness perceptions, the revised version of the Illness Perception Questionnaire (IPQ-R) was used, which is a measure based on the CSM (16). In the IPQ-R, the identity scale consists of 14 general symptoms and asks patients to state whether or not they have experienced a particular symptom since the beginning of their illness and whether they believe this symptom is related to their illness. The number of illness-related symptoms forms the identity subscale (possible range 0-14). In the following section, the timeline acute/chronic, timeline cyclical, consequences, personal control, treatment control, illness coherence and emotional representations subscales are rated on a 5-point Likert type scale. The total number of items in this section is 38. To calculate scores for each subscale, scores of the items in each subscale were added and the total was divided by the number of items in the subscale (possible subscale range 1-5). The last section presents the causal dimension, consisting of 18 separate items rated on the same 5-point Likert scale. An open ended question at the end of the causes section asks patients to list any other causes that are important to them.

Results

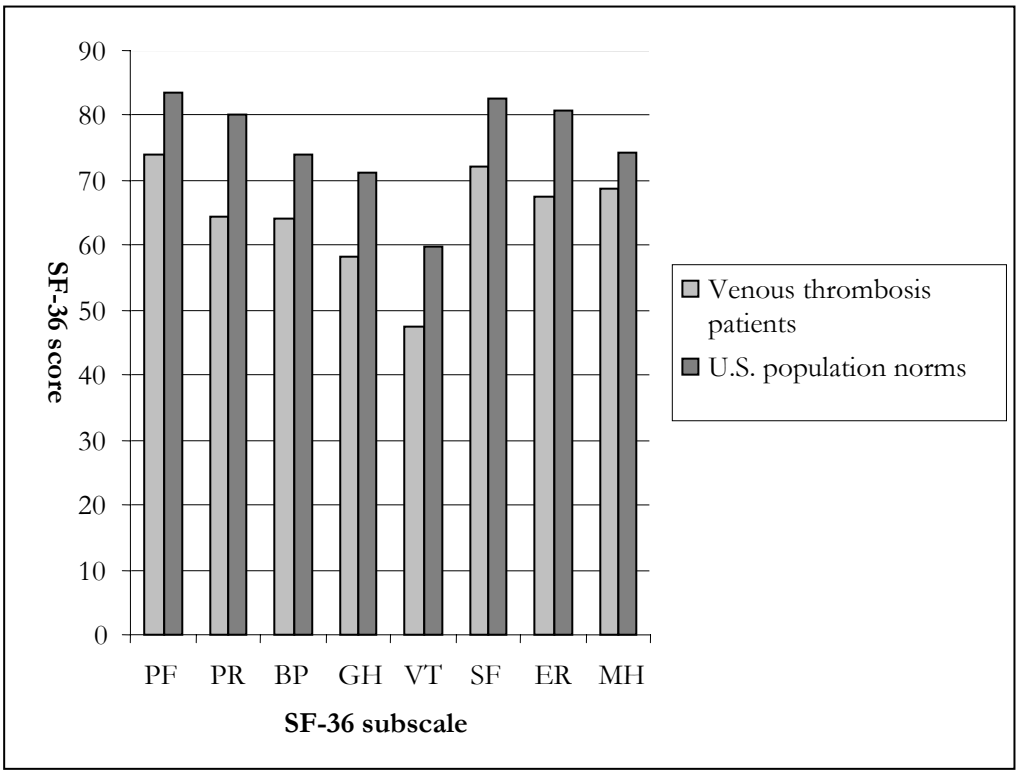
Patient characteristics

Forty-five of the 65 questionnaires sent out were returned (69%). The patient sample consisted of 13 men (29%) and 32 women (71%). The mean age was 44 years, with a range from 21 to 80 years. The subjects had experienced between 1 and 8 thrombotic events with a median of 2 events. Their last thrombotic event had occurred between 1997 and 2002 with a median elapsed time since the last event of 2 years. Twenty-five subjects (56%) had mild or severe PTS and 20 subjects (44%) did not have PTS.
The characteristics of the patients that returned the questionnaire (N=45) were compared to the characteristics of the patients that refused to participate (N=3) or that did not return the questionnaire (N=20). Non-responders were more often men (54%), and slightly younger than responders (mean age 39 years). The number of patients with a recent event (after 2000) was slightly lower in the participant group (38% vs. 46% in the non-participant group).

Quality of Life

Compared to population norms of a general U.S. population (N=2,463) (18), the group of venous thrombosis patients scored significantly lower on all subscales of the SF-36 (see Figure 1). To adjust for the higher proportion of women and older people in our sample, we adjusted the U.S. population norms by weighting the norms with the age and sex distribution in our sample (8). Significance was assessed by means of t-tests and differences in scores were found to be significant for all subscales ($p < 0.05$).

Figure 1. Mean scores of venous thrombosis patients (N = 45) and norms of a U.S. population sample (N = 2,463)



Legend:
PF: Physical functioning
PR: Physical role limitations
BP: Bodily pain
GH: General health perceptions
VT: Vitality
SF: Social functioning
ER: Emotional role limitations
MH: Mental health

Illness perceptions

Means, standard deviations and intercorrelations between the IPQ-R subscales are depicted in Table 1. The reliability of all subscales, was satisfactory (all Cronbach α's > 0.76). Patients attributed a mean of 2.29 out of 14 symptoms of the identity subscale to their venous thrombosis. Most subjects (44%) reported no symptoms at all, 40% reported between 1 and 3 symptoms, and 16% reported that 6 or more symptoms were related to venous thrombosis. The symptom that was attributed to venous thrombosis most often was pain (46%), followed by fatigue (18%), breathlessness (13%) and sleep difficulties (13%).

On all other subscales, mean scores were between 2.49 and 3.40 (see Table 1). Respondents believed that their illness would be prolonged and that their symptoms were not cyclical. They believed in some personal and treatment control over their illness, and had a moderately coherent view of their illness. The emotional impact of their illness was also moderate.

The perceived causes of venous thrombosis reported most frequently by the participants (participants agreed or strongly agreed with the cause) were 'Hereditary-it runs in my family' (38%), while 40% thought the occurrence of thrombosis represented 'chance or bad luck'. In the open-ended question, 20% of participants mentioned hormone replacement therapy or oral contraceptives as a cause, and 28% mentioned bed rest, immobilization or surgery as a cause.

To detect relationships among the illness perceptions, Pearson correlations between the subscales were computed (see Table 1). These correlations show that patients with a strong illness identity (those who attribute more symptoms to venous thrombosis) believed in a longer duration of their illness, more serious consequences, less control of treatment and had stronger representations of emotional distress. A belief in a longer duration of the illness (patients with a higher score on timeline acute/chronic) was related to a belief in more serious consequences, less treatment control and stronger representations of emotional distress. Patients who reported that the symptoms of their illness were cyclical reported less illness coherence and stronger representations of emotional distress. Also, strong representations of emotional distress were correlated with lower illness coherence, less treatment control and had a strong relationship with the perception of more serious consequences.

A significant correlation ($r = 0.31$, $p < 0.05$) was found between the number of thrombotic episodes a respondent had, and the score on the consequences subscale. The number of years since the last thrombotic event did not correlate significantly with any of the subscales.

Table 1. Means, SD's and Pearson correlations between the illness perceptions subscales (IPQ-R)

IPQ-R subscale (**mean,** SD)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1 = Illness identity (**2.29**, 3.34)		.33*	-.20	.50**	-.14	-.32*	.05	.45**
2 = Timeline acute/chronic (**3.39**, 0.97)			.34*	.37*	.29	-.48**	.04	.45**
3 = Timeline cyclical (**2.48**, 0.91)				.38*	-.02	-.15	-.36*	.41**
4 = Consequences (**3.16**, 0.82)					.15	-.27	-.15	.62**
5 = Personal control (**3.39**, 0.74)						.27	-.01	.13
6 = Treatment control (**3.29**, 0.72)							-.03	-.39*
7 = Illness coherence (**3.36**, 0.99)								-.32*
8 = Emotional represen-tations (**2.94**, 0.89)								

* $p < .05$, ** $p < .01$

Older respondents had a lower illness identity than younger patients ($r = -.42$, $p < 0.01$), meaning that they attributed fewer symptoms to venous thrombosis. There were no significant differences between men and women with respect to the illness perception subscales. Patients with PTS attributed more symptoms to their illness, believed in a longer timeline and had a lower understanding of their illness. However, the statistical significance of these differences was only marginal with a $p < 0.1$ level.

Illness perceptions and quality of life

Pearson correlations were computed between the illness perceptions and the subscales of the SF-36 (See Table 2). Illness identity, timeline acute/chronic and consequences had a negative correlation with most subscales of the SF-36. This indicates that patients who attributed more symptoms to venous thrombosis, who saw their illness as more chronic or perceived more serious consequences of their illness, had a lower quality of life scores. Patients who saw their illness as uncontrollable by themselves (personal control) scored significantly lower on the mental health and emotional role limitations. To examine the role of illness perceptions on the quality of life of patients with venous thrombosis, a series of stepwise regression analyses was conducted with the eight SF-36 subscale scores as dependent variables. Because of the small sample, an initial series of stepwise regression analyses was conducted to examine which illness related and demographic variables (age, sex, number of thrombotic episodes, time elapsed since the last event and presence of PTS) contributed significantly to the explanation of variance in SF-36 scores. Only the presence of PTS and the number of thrombotic episodes were found to contribute significantly to the equation in some of the SF-36 subscales (physical functioning, and pain).

Table 2. Pearson correlations between the illness perceptions subscales (IPQ-R) and SF-36 subscales

	SF-36 subscales							
IPQ-R Subscales	**PF**	**PR**	**BP**	**GH**	**VT**	**SF**	**ER**	**MH**
Illness identity	-.30	-.38*	-.24	-.35*	-.38*	-.32*	-.33*	-.31
Timeline acute/chronic	-.43**	-.41**	-.41**	-.46**	-.39*	-.33*	-.33*	-.36*
Timeline cyclical	-.29	-.21	-.24	-.08	-.10	-.20	-.16	-.16
Consequences	-.34*	-.32*	-.21	-.31*	-.28	-.28	-.36*	-.33*
Personal control	.15	.14	.26	.08	.32	.31	.34*	.34*
Treatment control	.28	.31*	.33*	.20	.31	.22	.24	.19
Illness coherence	.11	.00	-.05	-.13	-.24	-.14	.00	-.11
Emotional representations	-.29	-.32	-.11	-.06	-.19	-.10	-.23	-.25

* $p < .05$

** $p < .01$

Legend: For SF-36 subscales: see Figure 1

In the second series of analyses (see Table 3), presence of PTS and number of thrombotic episodes were entered in step 1 to control for possible confounding effects of these factors, and illness perceptions were entered in step 2, using the forward stepwise procedure. In addition, the causes for venous thrombosis that were mentioned most often by the participants (hereditary and chance or bad luck) were entered stepwise in step 2 as well. Results of these analyses indicate that the presence of PTS and the number of thrombotic episodes explained a modest amount of variance in SF-36 scores. In scores on the subscale bodily pain, they contributed the most to the regression equation (12%), but this contribution was not significant. Of the IPQ-R, the subscales timeline acute/chronic, personal control and, to a lesser extent, identity and the cause "heredity" were the strongest predictors of quality of life as measured by the subscales of the SF-36. The IPQ-R subscales had the strongest contribution to the variance of the mental health subscale. On this subscale, the IPQ-R subscales personal control, timeline, and the cause hereditary accounted for 41% of explained variance. Also on the subscales vitality, bodily pain, and emotional role limitations, the IPQ-R subscales were good predictors, contributing 36%, 35% and 32% to the explained variance, respectively.

Table 3. Stepwise regression analyses with SF-36 scores as dependent variables and illness perceptions as predictors

Presence of the postthrombotic syndrome and number of thrombotic episodes were forced into step 1, illness perceptions were entered stepwise in step 2. The adjusted R square was used to control for the number of variables entered. The table presents the variables in the final model.

Criterion	Variable	B	Change R^2 adj.
Physical functioning	No. of episodes	-.08	.07
	Presence of PTS	-.22	
	Timeline	-.43**	.09
	Personal control	.31*	.08
Physical role limitations	No. of episodes	-.17	.01
	Presence of PTS	.01	
	Identity	-.41*	.13
Bodily pain	No. of episodes	-.17	.12
	Presence of PTS	-.22	
	Personal control	.43**	.08
	Timeline	-.42**	.14
General health perceptions	No. of episodes	-.10	.00
	Presence of PTS	-.00	
	Timeline	-.43**	.15
Vitality	No. of episodes	.08	-.04
	Presence of PTS	-.00	
	Identity	-.31*	.12
	Personal control	.48***	.13
	Timeline	-.44**	.15
Social functioning	No. of episodes	.07	-.02
	Presence of PTS	-.15	
	Personal control	.45**	.09
	Timeline	-.44**	.15

Table 3, continued

Criterion	Variable	B	Change R^2 adj.
Emotional role limitations	No. of episodes	.05	-.02
	Presence of PTS	-.06	
	Personal control	.49***	.16
	Timeline	-.36*	.07
	Identity	-.31**	.07
Mental health	No. of episodes	.21	-.01
	Presence of PTS	-.15	
	Cause: hereditary	-.33*	.14
	Personal control	.50***	.14
	Timeline	-.42**	.13

* $p < .05$, ** $p < .01$, *** $p < .001$, PTS = postthrombotic syndrome, Timeline = timeline acute/chronic

Discussion

In this study, patients with venous thrombosis from a thrombosis clinic in Vermont, USA, had an impaired quality of life on all subscales of the SF-36 as compared to a general U.S. population. Most patients did not attribute many symptoms to their illness as measured by the identity subscale of the IPQ-R. An explanation for this may be that the symptoms in the identity subscale are not symptoms that are commonly associated with venous thrombosis, which is a condition characterized by pain, swelling, redness and tenderness of the affected body-part, of which pain is the only symptom that is incorporated in the identity subscale. The venous thrombosis patients in this sample believed that their illness would be prolonged and that their symptoms were not cyclical. These beliefs are consistent with medical evidence that in most people, acute complaints of venous thrombosis will disappear over time.

Compared to a sample of patients with atrial fibrillation (a heart-condition that gives an increased chance of stroke, and can result in symptoms like breathlessness, palpitations and fatigue) (20), our sample of venous thrombosis patients believed their illness to be more serious and of longer duration. Beliefs about the curability of the illness were similar in the two groups.

The perceived causes reported most frequently by the participants were 'Heredi-

tary-it runs in my family' and 'chance or bad luck'. The explanation to the perception of a hereditary cause could be that many people who develop venous thrombosis have a genetic coagulation disorder (21). The fact that many people attributed their venous thrombosis to chance could be due to the fact that venous thrombosis is a multi-causal disease, caused by both genetic and environmental risk factors (4), and thus occurs in a wide range of clinical and life circumstances. In future research on illness perceptions in patients with venous thrombosis, causes that are specific to venous thrombosis should be added to the causal dimension of the IPQ-R. For instance the use of oral contraception, surgery, and immobilization could be included, as these causes are mentioned often in the open ended question about the causes, and are known risk factors for venous thrombosis (22).

We hypothesized that patients with PTS would attribute more symptoms to their illness and would believe in a longer duration and more serious consequences than patients without PTS. We found marginal support ($p < 0.10$) for the first two hypotheses only. Another unpredicted difference we found was that patients with PTS have a less coherent view of their illness. Possibly this is because the patients expected their symptoms to disappear after some time and became confused when the complaints persisted.

The patterns of correlations seen among the illness perceptions subscales are consistent with those reported by earlier research using the IPQ, which studied patients with myocardial infarction (23), multiple sclerosis (24) and irritable bowel syndrome (25). A sample of patients with an acute illness, myocardial infarction (MI) (23), also showed a significant correlation between the number of symptoms attributed to their disease and the seriousness of the disease. However, in our sample of venous thrombosis patients, this correlation was stronger than in the sample of MI patients (.50 vs .26). This could be due to the fact that in general, these venous thrombosis patients attributed less symptoms to their illness (mean 2.29 vs. mean 7.8 in the MI sample), or because the patients experienced venous thrombosis an average of 2 years prior to the survey. Patients who still experience multiple symptoms 2 years after their last event, perceive the consequences of their illness as more severe. This same effect was noted again in the sample of patients with irritable bowel syndrome (IBS) (25). One difference in results was found: in our sample the timeline and treatment control subscales were negatively correlated while a positive association was found in the IBS sample. This is probably due to the fact that patients with a chronic condition such as IBS learn to deal with their illness after some time, whereas patients with venous thrombosis expect their symptoms to disappear over time.

Regression analyses showed that illness perceptions were able to explain a significant amount of variance in quality of life scores. We hypothesized that belief in a longer duration and more serious consequences would be the best predictors of quality of life, and that patients with a low understanding or high emotional representations would experience a more impaired quality of life. However, the dimensions that explained most of

the variance were timeline acute/chronic, personal control, identity and the heredity cause. Unexpectedly, the subscales illness coherence and emotional representations did not correlate significantly with any of the SF-36 subscales, nor did they contribute to the regression equations. Since patients with PTS scored lower on the illness coherence subscale, and patients with PTS had lower QOL scores in all domains, the fact that illness coherence does not seem to play a role in the explanation of QOL in these patients, is noteworthy. It indicates that for these patients, not having a coherent understanding of their illness does not impact on their quality of life. It is interesting to note that the "heredity" cause explained a significant amount of variance in the mental health subscale. This gives an indication that a known or suspected genetic risk factor for venous thrombosis might have a negative impact on psychological well-being.

The main limitations of this study are the small sample size and the fact that the sample was taken from only one thrombosis clinic in the Northeastern USA. Patients were referred and generally had genetic testing performed, so we could not analyze the influence of genetic testing on results. This makes it difficult to generalize our findings to other thrombosis patients so results of this study should be replicated with other and larger venous thrombosis populations. Another limitation is the cross-sectional nature of the study, which makes it harder to be confident about the interpretation of the explanation of variance in quality of life by the illness perception components.

Our study indicates that the three domains of quality of life can help to define the outcome component of the Common Sense Model. Further research using the IPQ-R should focus primarily on the contribution of the new subscales since this study does not give an indication for their significant effects on quality of life in patients with venous thrombosis, but they might influence other outcomes that were not within the scope of this study. Further research on illness perceptions in venous thrombosis patients should adopt a longitudinal design to assure the causal direction of the effects, in which illness perceptions are measured at baseline and outcome is measured on a subsequent occasion. Also, there should be research on the psychological impact of a genetic vulnerability for venous thrombosis, since this study gives an indication that this might influence quality of life. And finally, an intervention study, like that of Petrie and colleagues (26), could be conducted to investigate the impact of a short intervention focused on changing illness perceptions on the well-being of patients with venous thrombosis. For clinical care specifically, our results suggest that health care providers might improve the quality of life of these patients by addressing the illness perceptions of patients. This would specifically be more useful for patients with PTS, since this is a group that seems to be more vulnerable than patients without PTS. In these patients, dealing with duration beliefs and treatment and self-management issues seems to be most advantageous. A biopsychosocial perspective could help patients with venous thrombosis by making both health care professionals and family members of patients more aware of the impact of venous thrombosis on daily life and the role that illness perceptions play in quality of life. Furthermore, it could

play a role in assisting these patients to adjust to the self-management of their anticoagulation treatment (27).

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Part 2

Genetic testing for thrombophilia

Chapter 5

Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency

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Summary

Background: Little research has been done regarding the psychological consequences of knowing that one is at an increased risk for venous thrombosis.
Objectives: The aim of this study was to explore attitudes towards genetic testing for protein C deficiency.
Methods: Questionnaires about genetic testing attitudes, dispositional anxiety, risk perception, and thrombosis-related worry, were completed by 168 asymptomatic members of a North-American kindred with a high prevalence of heritable protein C deficiency conferring a high life-time risk of venous thrombosis. A total of 76 subjects (45%) had not been tested for protein C deficiency before participating in our study whereas the other 92 subjects (55%) had been tested prior to filling in the questionnaire, of whom 34 people had protein C deficiency, while 58 did not.
Results: Family members with protein C deficiency perceived a higher risk of suffering venous thrombosis and scored higher on thrombosis-related worry than family members without protein C deficiency. Participants who had not been tested did not report excessive thrombosis-related worry. Participants with protein C deficiency reported a belief in the psychological and health benefits of testing, and felt they experienced low psychological distress following the genetic test. High psychological distress following the test was related to dispositional anxiety and thrombosis-related worry. Participants without protein C deficiency were relieved after finding out they did not have the deficiency.
Conclusion: There seem to be few negative psychological consequences of knowing that one is at an increased risk for venous thrombosis, except in vulnerable individuals.

Background

The number of inherited disorders and risk factors that can be detected through genetic testing is increasing rapidly, and genetic testing is becoming a common component of routine medical care. Recently, genetic testing is being applied to detect personal susceptibility to disease, in the belief that awareness of genetic risk will enhance informed medical decision making and have an impact on changing health behaviour (1).

Quality of life in patients with venous thrombosis is impaired compared to a healthy population, especially in the presence of the postthrombotic syndrome. This impairment encompasses the physical, social and psychological domains of quality of life (2;3). Venous thrombosis is a multi-causal disease caused by both genetic and acquired risk factors (4;5). Examples of acquired risk factors are older age, the use of oral contraceptives, hormone replacement therapy, pregnancy, and immobilization. The discovery of genetic risk factors for venous thrombosis, and the widespread clinical application of genetic screening, has engendered a debate regarding the pros and cons of thrombophilia

testing (6;7). Generally, it is believed that widespread screening for thrombophilia is not justified because it is not cost-effective. However, some believe screening of patients at a high risk of venous thrombosis is likely to be useful because it may improve clinical outcome through changes in the appropriate use and duration of therapy. It is reasoned that family screening of individuals with a close relative with thrombophilia can help to optimize prophylactic treatment of asymptomatic carriers in high-risk situations (i.e. during surgery or pregnancy in which they would normally not receive treatment)(8). To date, there are no data supporting this view. Opponents of widespread screening have pointed out that it may lead to psychological distress. However, little research has focused on the psychological consequences of knowing that one is at an increased risk for venous thrombosis. This is notable because carriership of a genetic deficit may influence daily life, since it can cause considerable distress. Research on the psychological influence of genetic testing has focused mainly on single gene conditions such as Huntington's disease and on hereditary cancers. Findings suggest that individuals undergoing predictive genetic testing do not experience considerable long-term psychological distress (9;10). However, individuals with a high predisposition to depression or anxiety may be more vulnerable to adverse effects (1;11). Possible negative effects of a positive test result include anxiety and depression following the test, worry about the future and about the possibility of passing the genetic defect on to children. Furthermore, positive test results might cause stigmatization, problems with insurance, and they can interfere with medical decision making. To our knowledge only three previous publications have dealt with the subject of the social and psychological impact of awareness of carriership of thrombophilia. The first study investigated women's reactions to awareness of activated protein C (APC) resistance carriership in 270 women (12). In this study, women were asked to answer questions about the way their knowledge of APC resistance has affected them, in a yes/no format. The study concluded that most women were pleased with having been informed of their status. The majority of women (84%) found that their awareness of APC resistance might be an advantage in the event of future operations or accidents, and 69% reported that their lives were unaffected by the knowledge of APC resistance. However, 27% of the women reported that they had become more worried, and 10% was afraid to get pregnant again. The second study, by Hellmann and colleagues, used a questionnaire with a Likert-scale to examine patient experience of genetic testing for factor V Leiden (FVL) in 110 patients and found that 43% of the patients experienced increased worry (13). In addition, they reported that patients indicated concern with the lack of available information about FVL. The discrepancy in the reported worry rates of these two studies might be explained by the difference in methodology between the two studies. A Likert scale allows participants to be more specific in their responses, rather than having to choose between two endpoints in a yes/no format.

The third study on this subject explored the psychological and social aspects of asymptomatic carriership of the factor V Leiden mutation in a qualitative study. After

interviewing 17 individuals, the authors concluded that carriership of FVL has the potential to influence daily life by inducing concerns, stigmatization and problems with insurance eligibility (14).

The results of these three studies need to be replicated and clarified in more structured studies which assess the psychological impact of genetic testing for thrombophilia and factors that might influence this impact.

Protein C is a vitamin K dependent protein that, upon activation to activated protein C (APC) inhibits thrombus formation by inactivating the coagulation factors Va and VIIIa. Deficiency of protein C was one of the first genetic risk factors associated with hereditary thrombophilia (15). The lifetime risk for venous thrombosis in protein C deficient individuals is about 10-fold increased compared to the normal population (16). Protein C deficiency is caused by a wide variety of mutations in the protein C gene. The present study investigates a large kindred of French-Canadian descent with protein C deficiency caused by a 3363 C insertion mutation (17).

The aim of this study was to explore the attitudes of protein C deficient individuals about genetic testing and to assess their perception of their thrombotic risk and their thrombosis-related worry. Furthermore, we tried to establish the role of trait anxiety in these attitudes to test the hypothesis that, as in earlier research on predictive genetic testing, individuals with a higher psychological vulnerability experience more psychological distress following the genetic test. Age and sex differences were assessed because older age and female hormones are risk factors for venous thrombosis. In addition, we assessed the knowledge of participants about the other risk factors for venous thrombosis, and the relationship of this knowledge with risk perceptions, thrombosis-related worry and attitudes about genetic testing.

Method

Participants

The ascertainment and evaluation of the family members participating in this study was described previously (18). Members of the kindred were contacted by phone by one of the investigators (SN) and an appointment was made to meet with the investigators. At this appointment, several questionnaires were completed. All participating subjects gave informed consent. The study protocol was approved by the Human Experimentation Committee of the University of Vermont College of Medicine, Burlington (VT, USA). Inclusion criteria stipulated that participants had to be over age 18, and physically and mentally capable of completing the questionnaire. Participants were divided into three groups: participants who had not been tested before (group 1), participants with protein C deficiency (group 2), and participants without protein C deficiency (group 3). Most of

the participants who were tested before (group 2 and 3), were tested in a previous study (18).

Measurements

All participants

Risk perception: Perceived risk of venous thrombosis was assessed with two items
1. How likely do you think it is that, at some point in your life, you will get thrombosis?
2. How vulnerable do you think you are to getting thrombosis at some point in your life?
Each item was rated on a 7 point Likert scale ranging from 1 (*not at all*) to 7 (*almost certain or extremely*) and summed to generate risk perception scores.
Worry: Worry about venous thrombosis was assessed with two items: 1. To what extent are you worried about getting thrombosis? 2. To what extent are you concerned about getting thrombosis? Each item was rated on a 7 point Likert scale ranging from 1 (*not at all*) to 7 (*extremely*) and summed to generate worry scores.
Trait anxiety: As a measure of dispositional anxiety the trait form of the State-Trait Anxiety Inventory (STAI) (form Y-2) was included (19). This is a 20-item questionnaire that measures relatively stable individual differences in anxiety proneness. All items are rated on a scale from 1 (*not at all*) to 4 (*very much so).*
Knowledge about risk factors for venous thrombosis: To assess the knowledge of participants about the acquired risk factors for venous thrombosis, a scale with 8 items was used, on which participants had to rate on a 5 point Likert scale (ranging from strongly disagree to strongly agree) whether they believed this risk factor could cause venous thrombosis or not. The scale consisted of the following items: pregnancy or child birth, birth control pills, bed rest, lack of exercise, sitting for long periods, surgery, aging, accident or injury. To calculate a score for the knowledge about risk factors for venous thrombosis, we assigned one point to each item that participant agreed or strongly agreed with, and points were added (possible score range 0-8).

Group 1: Participants who had not been tested before, and group 2: Protein C deficient participants

Attitudes about testing: To assess the attitudes about getting a genetic test for protein C deficiency in both family members that have been tested positive for protein C deficiency and family members that had not been tested before, attitude scales were adapted from a study by Cameron and colleagues, in which the same attitude scales were being applied to assess beliefs about testing for breast cancer susceptibility (20). Both groups completed a similar set of the following items, appropriate to their status. For group 2, items referred to how individuals felt about the genetic test result now, rather than how they felt when they had just received the results.

Health benefits beliefs were assessed with a set of five items (e.g. Knowing whether I have protein C deficiency or not would give me more control over my health; Knowing that I have protein C deficiency gave me more control over my health). These items were all rated on a Likert-scale ranging from 0 (*strongly disagree*) to 6 (*strongly agree*) and summed to generate health benefits beliefs scores.

Psychological benefits beliefs were assessed with four items (e.g. The test would reduce the anxiety of not knowing one's genetic background; The test reduced the anxiety of not knowing my genetic background). These items were all rated on a Likert-scale ranging from 0 (*strongly disagree*) to 6 (*strongly agree*) and summed to generate psychological benefits beliefs scores.

Psychological distress beliefs were assessed with five items (e.g. Knowing that I have protein C deficiency would seriously harm my self-image; Knowing that I have protein C deficiency seriously harmed my self-image). These items were all rated on a Likert-scale ranging from 0 (*strongly disagree*) to 6 (*strongly agree*) and summed to generate psychological distress beliefs scores.

Furthermore, participants who had not been tested before (group 1) filled in two items about their interest in getting a genetic test and their beliefs in the likelihood of receiving a positive test result.

Testing interest: Interest about getting the genetic test for protein C deficiency was assessed with one item: How interested are you in getting a genetic test for protein C deficiency? This item was rated on a 7 point Likert-scale ranging from 1 (*not at all interested*) to 7 (*extremely interested*).

Likelihood of having protein C deficiency: With one item, the belief in the likelihood of receiving a positive test result was assessed: If you would be tested, how likely do you think it is that you have protein C deficiency? This item was rated on a 7 point Likert-scale ranging from 1 (*not at all*) to 7 (*almost certain*).

Group 3: Participants without protein C deficiency

Three additional items were added for participants who tested negative for protein C deficiency. All items were rated on a 7 point Likert-scale ranging from 1 (*not at all*) to 7 (*extremely*).

Relief: One item assessed the amount of relief the participants felt after finding out they did not have protein C deficiency: Did you feel relieved after finding out you do not have protein C deficiency?

Guilt: One item assessed whether participants felt guilty about not having protein C deficiency: If other people in your family have protein C deficiency, did you feel guilty after finding out you do not have it?

Likelihood of having protein C deficiency if tested again: One item assessed the false or correct beliefs of participants about the likelihood of getting a positive test result if they would be tested again: If you would be tested again, how likely do you think it is that you have protein C deficiency?

Results

Demographic variables

A total of 265 family members were invited to participate in the study. Of the non-responders, 30 (11.3%) refused to participate, 22 (8.3%) did not show up at their scheduled appointment, and 15 (5.7%) could not participate due to other reasons such as illness. A questionnaire was eventually filled out by 198 (74.7%) family members. Questionnaires of 24 participants who had already suffered from venous thrombosis were removed from the present analyses because the aim of this paper was to study attitudes about genetic testing in trombophilic individuals without a history of venous thrombosis.

A further 6 questionnaires were removed because of incomplete data. The remaining database consisted of 168 participants. The mean age of the participants was 44.4 (SD 14.2) years with a range from 18 to 76 years. The sample consisted of 73 men (43%) and 95 women (57%). Of all participants 92 subjects (55%) had been tested for protein C deficiency in a previous study (18), and 76 subjects (45%) had not been tested before and thus did not know their status when they completed the questionnaires. Of the tested participants, 34 people had protein C deficiency, and 58 participants had tested negative.

Table 1: Intercorrelations, means, and standard deviations, for group 1: participants that had not been tested for protein C deficiency (N=76)

Measure	Risk perception	Worry	Trait anxiety	Health benefits beliefs	Psychological benefits beliefs	Psychological distress	Testing interest	Likelihood of having PC def.
Risk perception	-	-	-	-	-	-	-	-
Worry	.51*	-	-	-	-	-	-	-
Trait anxiety	-.11	-.01	-	-	-	-	-	-
Health benefits Beliefs	.21	.30	-.08	-	-	-	-	-
Psychological benefits beliefs	.11	.20	.13	.79*	-	-	-	-
Psychological Distress	-.13	-.10	.37*	.00	.19	-	-	-
Testing interest	.20	.38*	-.09	.59*	.46*	-.13	-	-
Likelihood of having PC def	.40*	.50*	-.04	.35*	.41*	.01	.43*	-
Mean	3.9	3.4	36.3	20.6	15.1	7.5	4.6	2.6
SD	2.4	1.9	9.6	7.6	6.1	8.4	2.4	1.6
Range	2-14	2-14	20-80	0-30	0-24	0-30	1-7	1-7

*$p < 0.01$

Table 2: Intercorrelations, means, and standard deviations for group 2: participants with protein C deficiency (N=34)

Measure	Risk perception	Worry	Trait anxiety	Health benefits beliefs	Psychological benefits beliefs	Psychological distress
Risk perception	-	-	-	-	-	-
Worry	.70*	-	-	-	-	-
Trait anxiety	.01	.28	-	-	-	-
Health benefits beliefs	.26	.19	-.11	-	-	-
Psychological benefits beliefs	.04	.21	.19	.60*	-	-
Psychological distress	.13	.52*	.61*	-.05	.30	-
Mean	5.4	5.5	32.9	19.4	14.3	5.3
SD	2.9	2.7	9.0	5.8	5.3	6.9
Range	2-14	2-14	20-80	0-30	0-24	0-30

* $p < 0.01$

Table 3: Intercorrelations, means, and standard deviations for group 3: participants without protein C deficiency (N=58)

Measure	Risk perception	Worry	Trait anxiety	Relief	Guilty	Genetic retest
Risk perception	-	-	-	-	-	-
Worry	.62*	-	-	-	-	-
Trait anxiety	-.11	.10	-	-	-	-
Relief	-.05	.07	.07	-	-	-
Guilty	-.08	.06	-.02	.12	-	-
Genetic retest	.33	.28	.00	-.02	.14	-
Mean	3.2	3.2	32.5	5.4	1.8	1.7
SD	1.7	1.8	9.4	1.9	1.4	.8
Range	2-14	2-14	20-80	1-7	1-7	1-7

* $p < 0.01$

Descriptive analyses

In further analyses, a distinction was made between the three groups of participants: participants who had not been tested (group 1), participants with protein C deficiency, and participants without protein C deficiency. Internal consistency of all attitudes scales was satisfactory (Cronbach's alpha's > .70) and the items that form the risk perception and worry scores were highly correlated (r = .90 and r = .87). To test for age differences, a median split of the sample was made (median = 45). To protect against inflation of type 1 error from multiple correlations and other statistical tests we used $p < 0.01$ as our critical value for all statistical tests.

Group 1: Participants who had not been tested before (n = 76)

Table 1 presents means, standard deviations and intercorrelations among all measures, for participants that had not been tested for protein C deficiency. Means for risk perception and thrombosis-related worry were 3.9 and 3.4 on scales ranging from 2-14, indicating that participants did not think it is very likely that they would ever get venous thrombosis or worry a lot about it. Mean scores on beliefs in the health benefits and psychological benefits of testing were 20.6 and 15.1 on scales ranging from 0-30 and 0-24, whereas the belief in psychological distress following the genetic test was 7.5 on a scale ranging from 0-30. This indicates that beliefs about the positive consequences of getting a genetic test were stronger than beliefs about the negative consequences of the test. For the benefits of testing, the item with the highest mean scores was 'I should get tested for the sake of my family and loved ones' (mean 4.7), indicating that deciding to have a genetic test for protein C deficiency is primarily a matter of concern for the family. The item with the lowest mean score was 'The test results would help me in making decisions about whether and when to have children' (mean 0.7). The mean score on the trait form of the STAI was 36.3 (SD 9.6). Participants were quite interested in getting a genetic test for protein C deficiency (mean 4.6 on a scale ranging from 1-7) and did not think it was very likely that they would have protein C deficiency (mean 2.6 on a scale from 1-7). Risk perception and worry were correlated ($r = .51$, $p < 0.01$). Higher trait anxiety was related to a higher belief in psychological distress following the test ($r = .37$, $p < 0.01$), but not to a higher interest in getting the test, or a higher belief that one will have protein C deficiency. Beliefs in higher health and psychological benefits of testing were correlated with more interest in getting the genetic test ($r = .59$ and .46, $p < 0.01$) and a belief that one will have protein C deficiency ($r = .35$ and .41, $p < 0.01$). Older participants had higher scores on thrombosis-related worry than younger participants ($p < 0.01$). No sex differences could be detected.

Group 2: Participants with protein C deficiency (n = 34)

Table 2 presents means, standard deviations and intercorrelations among all measures, for participants who previously have been tested positive for protein C deficiency. Risk perception and thrombosis-related worry were higher than risk perception and worry scores for participants who had not been tested (means 5.4 and 5.5 on scales ranging from 2-14). Beliefs in the health benefits, psychological benefits and psychological distress following the test were marginally lower than the beliefs of participants who had not been tested (means 19.4 and 14.3 and 5.3 on scales ranging from 0-30, 0-24 and 0-30). For the health and psychological benefits of testing, the item with the highest mean score was again 'I got tested for the sake of my family and loved ones' (mean 4.6 on a scale ranging from 1 to 7). Furthermore, the item with the lowest mean score was again 'The test results helped me in making decisions about whether and when to have children' (mean 1.6 on a scale ranging from 1-7). The mean score on the trait form of the STAI was 32.9 (SD 9.0). Risk perception and worry were correlated ($r = .70$, $p < 0.01$). Beliefs in health benefits and psychological benefits following the genetic test, were also related ($r = .60$, $p < 0.01$). Both thrombosis-related worry and trait anxiety were correlated with psychological distress following the genetic test ($r = .52$ and $r = .61$, $p < 0.01$). There were no sex or age differences for any of the measures.

Group 3: Participants without protein C deficiency (n = 58)

Table 3 presents intercorrelations among all measures, means and standard deviations, for patients who had been tested negative for protein C deficiency. In this group, risk perception and thrombosis-related worry were lower than in the other groups and correlated as well (means 3.2 and 3.2 on scales ranging from 2-14, $r = .62$, $p < 0.01$). The mean score on the trait from of the STAI was 32.5 (SD 9.4). More than half of the participants (61%) reported that they felt relieved after finding out that they did not have protein C deficiency and the majority (81%) did not feel guilty when other family members were tested positive. Furthermore, most participants (87%) correctly assumed that a second test would still be negative. A higher risk perception or worry about getting thrombosis was associated with a higher belief that a second test would give a positive result ($r = .33$ and .28), but these results did not reach statistical difference. There were no sex or age differences for any of the measures.

Between-group differences

T-tests and ANOVAs with Scheffé's post hoc tests were used to test for differences between the three groups on the various measures. Scores for risk perception and worry were found to be significantly higher (ANOVA: $F = 9.4$, $p < 0.001$ and $F = 15.8$, $p <$

0.001) for the group with protein C deficiency compared to the group without protein C deficiency and those who had not been tested before (see Figs. 1 and 2). Surprisingly, scores on the trait form of the STAI scores were highest for the group who did not know their protein C status (See Figure 3), but this effect did not reach statistical significance (ANOVA: $F = 3.2$, $p = 0.45$).

T-tests demonstrate that for attitudes about genetic testing, individuals who had not been tested and individuals with known protein C deficiency did not differ significantly on any of the measures of psychological distress, psychological benefits and health benefits of receiving a genetic test result.

Figure 1: means for risk perception with 95% confidence intervals for means

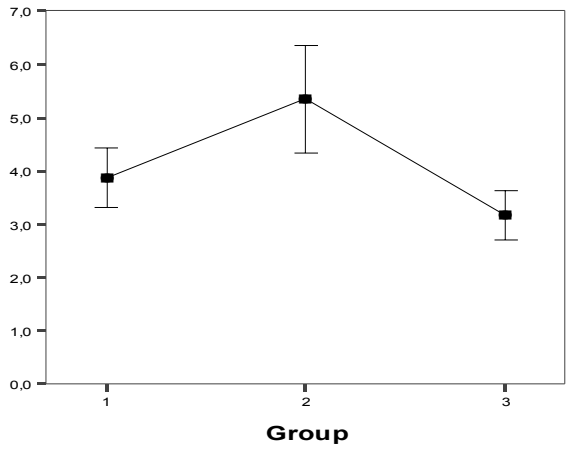


Figure 2: means for thrombosis-related worry with 95% confidence intervals for means

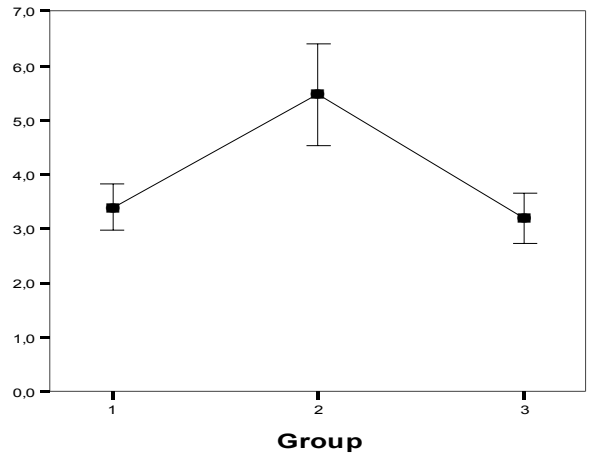
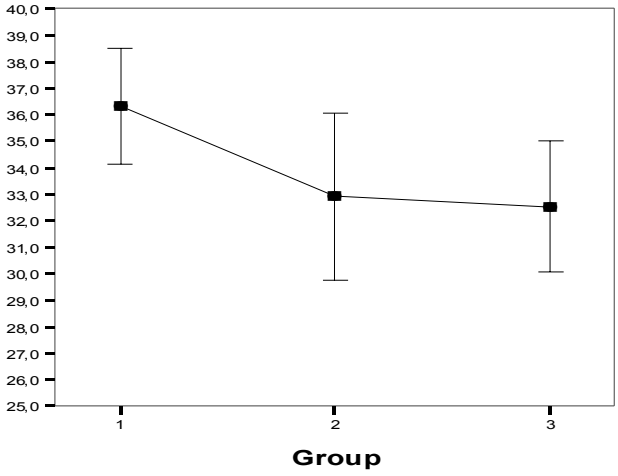


Figure 3: means for trait anxiety with 95% confidence intervals for means



Legend Figure 1, 2, and 3:
Group 1: Participants who had not been tested before
Group 2: Participants with protein C deficiency
Group 3: Participants without protein C deficiency

Knowledge about other risk factors for venous thrombosis

The risk factors that were believed to be most likely to cause venous thrombosis by the participants in our sample were lack of exercise (50% agreed or strongly agreed with the risk factor), aging (49% agreed or strongly agreed with the risk factor) and surgery (45% agreed or strongly agreed with the risk factor). No differences could be detected between the three groups or for younger and older participants. Women were more likely than men to agree with the risk factor birth control pills ($t = -4.53$, $p < 0.001$).

To assess whether knowledge about the risk factors for venous thrombosis was related to perceptions of risk, thrombosis-related worry and attitudes about genetic testing, we calculated correlations between the total knowledge scores and the other measures. The only significant correlation was found in the group that had not been tested between the knowledge and thrombosis-related worry scores ($r = .33$, $p < 0.01$).

Discussion

The results of this family study indicate that asymptomatic individuals with a family history of venous thrombosis perceive the psychological and health benefits of getting a genetic test for protein C deficiency as higher than the psychological distress following the test. Interestingly, it seems that attitudes about getting the genetic test did not differ significantly between the group with protein C deficiency and the group that had not yet been tested. This indicates that the expectations of the participants about getting the genetic test were realistic in terms of their expectations about the potential health and psychosocial benefits of testing as well as the psychological distress a positive test result might cause. However, it is possible that significant differences could not be detected because of the relatively small number of participants in each group. Furthermore, since participants were not recently tested, it is possible that adverse psychological effects have arisen directly after receiving the test result but that individuals have adapted to their condition over the years, by giving the psychological effects of their condition a different meaning. This effect, which has been applied to some extent in quality of life research, is called response shift (21;22). Therefore, these results should be taken with some caution.

For participants who had been tested positive for protein C deficiency, trait anxiety was highly correlated to psychological distress following the genetic test. As the same relationship can be noted for participants who had not been tested before, it seems that in general there are few adverse psychological effects of receiving a positive test result for protein C deficiency, but that certain vulnerable individuals, with a high predisposition to anxiety, might experience considerable distress following the positive test result. This is in line with the findings of Lindqvist and colleagues (12), who found that most APC resistant women reported that their lives were unaffected by the knowledge of being APC resistant, but that about a quarter of the women became more worried after getting the test. Additionally, this effect has been found in earlier research on predictive genetic testing (11). In this light it is also notable that a high score on trait anxiety does not predict interest in getting the genetic test or a higher belief in having protein C deficiency among the individuals who have not been tested before. This suggests that a high dispositional anxiety does not necessarily motivate one to have a genetic test performed or to believe they have a high likelihood of having an abnormal result. It is interesting to note that worry rather than risk perception was the only measure that correlates with the attitudes about the genetic test and interest in getting the genetic test. These findings are consistent with earlier research by Cameron and colleagues (20) and suggest that it is not the perception of risk that motivates people to take a genetic test, but the disease-specific worry people experience. Since the lifetime risk for venous thrombosis in protein C deficient individuals is 50%, even the protein C deficient participants in this study slightly underestimate their risk for venous thrombosis. These relatively low risk perceptions

could be due to people's tendency to underestimate their own risk, also called 'optimistic bias' (23).

Another interesting finding is that knowledge of risk factors for venous thrombosis does not differ between the three groups. However, only for the group that has not been tested, knowledge about the other risk factors for venous thrombosis is related to worry about venous thrombosis. This indicates that without knowing whether one has protein C deficiency or not, knowledge of other risk factors for venous thrombosis increases worry and that this knowledge does not influence worry in participants who have already been tested.

This study describes the results for the asymptomatic family members of one kindred only. It is possible that patients who have experienced an episode of venous thrombosis might react differently to getting a positive test result for protein C deficiency or another form of thrombophilia. Protein C deficiency is a disorder characterized by a tenfold increased risk of developing venous thrombosis and many family members have experienced the episodes of venous thrombosis in a close relative. This likely explains the fact that many family members consider getting tested as very important for their family. Patients with a different family history of venous thrombosis may express different emotional reactions to the knowledge of having thrombophilia. This study was not randomized, so there is a possibility that participants who decided to get tested differed from the other participants. In addition, because this is a family study in which most of the participants had already been tested previously (mostly around 10 years ago for the benefits of an earlier study), it was not possible to assess the reactions to the test, directly after receiving the test result. As discussed earlier, it is possible that adverse psychological effects have arisen directly after receiving the test result but that individuals have adapted to their condition over the years due a response shift. This effect has been noted in earlier research on hereditary cancer as well (9;24), and should be acknowledged in further research on the psychological consequences of genetic testing for thrombophilia.

Taking the limitations of this study and their possible effect on the outcome of this study into account, we can conclude by saying that there do not seem to be many long-term negative psychological consequences of genetic testing for thrombophilia as measured by thrombosis-related worry and psychological distress following the test results. However, the short-term effects of testing deserve more attention in future studies. Future studies should investigate a more diverse group of thrombophilia patients with variation in risk factors. Ideally such a study would have a randomized longitudinal design, with measurements of psychological distress immediately after receiving the test result and at a specified later time point, to investigate whether the duration and intensity of the perceived emotional impact of the test changes over time. In addition, it would be useful to include measures about state anxiety or depression following the genetic test result. From a clinical perspective, this study indicates that genetic testing for protein C deficiency does not have many adverse psychological effects in the long term. However,

it is also important to note non-tested individuals from a high-risk family do not worry excessively about developing venous thrombosis. To make a fully informed choice about genetic testing for thrombophilia, it is important that physicians inform patients in great detail about the other risk factors for venous thrombosis and the lack of treatment for thrombophilia.

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Chapter 6

Using the Common-Sense Model to predict risk perception and disease-related worry in individuals at increased risk for venous thrombosis

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Abstract

This study applied the Common-Sense Model (CSM) to predict risk perception and disease-related worry in 174 individuals with a genetic predisposition to venous thrombosis (thrombophilia). Participants completed an adapted version of the Illness Perception Questionnaire-revised (IPQ-R) and measures assessing risk perception and worry. Regression analyses revealed that illness perceptions were only modest predictors of risk perception but better predictors of worry, suggesting that illness perceptions are more linked with affect after genetic screening rather than cognitive appraisals of disease risk. Further research should refine the IPQ-R in populations at risk of a disease and examine the value of the CSM in explaining the relationship between risk perception, worry, and health behavior.

Introduction

Perceived risk of disease is the expectancy of an individual of getting a specific disease at some point in his or her life, and its role as a determinant of health behavior is well established. In the area of cancer screening, risk perceptions have been found to be positively associated with screening intentions and protective behavior such as breast self-examinations (1;2). Inaccurate perceptions of risk are commonly held by individuals at risk of a disease, and they tend to persist even after genetic counseling (3). These inaccurate perceptions of disease risk could have a negative effect on well-being and preventive behavior. A growing body of research indicates that disease-related worry also plays a motivational role in promoting health behavior, and that its associations with behavior are sometimes even stronger than the associations of risk perception (4-7). Although risk perception and disease-related worry tend to be correlated (4), it appears that they can have distinctive influences on health behavior.

Relatively little research has examined how individuals formulate their appraisals of disease risk and what factors influence their disease-related worry. Perceptions of health risk are fundamentally based on perceptions of the target illness, and so our understanding of the construction of risk perceptions can be informed by the theoretical understanding of illness representations. In this light, the Common-Sense Model of illness representation and self-regulation (CSM) can be useful in understanding risk perceptions and worry about disease in individuals at a genetic risk for a disease (8-11). The CSM can provide a theoretical framework in understanding the meaning of risk by focusing on the health threat that individuals perceive they are at risk of experiencing (12;13). The model describes a system with two parallel pathways of self-regulatory processes that operate when a patient confronts a health threat. Components of the first pathway include the cognitive representation of an illness, which includes five representational at-

tributes: the label and symptoms that individuals associate with the illness (identity), beliefs about the etiology (cause), expected outcomes (consequences), beliefs about the duration (timeline) and the expected controllability (cure/control) of the illness (11;14). The second pathway of the model involves the regulation of emotional reactions to a health threat, such as worry and distress; these emotions are shaped by the representational attributes. Perceived risk and worry about health threats are reflected in these two pathways, respectively. The information represented in each of the domains of illness representations may influence perceptions of disease risk and worry about the disease (12).

The CSM has been applied primarily in studies aimed at understanding psychological responses in patients who are physically ill. Studies investigating the influence of illness perceptions on outcome in patients with a chronic illness have provided support for the hypothesis that a strong illness identity (the attribution of many symptoms to an illness), as well as beliefs in a long duration and serious consequences have a negative effect on the well being of patients (15;16). Yet it is likely that illness perceptions are also important predictors of responses to health threats in healthy individuals, such as those with a genetic predisposition to an illness (17). In families with a history of a certain disease, it is likely that genetically predisposed but asymptomatic family members have witnessed episodes of the disease in their close relatives. These experiences, together with the information received from medical caregivers and gathered by themselves (e.g., through the Internet), may provide the basis for perceptions about the disease which, in turn, guide their risk perceptions and worry about this health threat.

Only few empirical studies have applied the CSM to study the impact of illness perceptions in a population at an increased risk of a disease. A study by Rees and colleagues, assessed the relationship between illness perceptions and distress in women at an increased risk of breast cancer and found a modest relationship between cancer worry and the subscales assessing identity, acute/chronic timeline, and consequences beliefs (18). Kelly and colleagues used the Common-Sense Model in a qualitative study to understand cancer risk perceptions in individuals testing for BRCA1/2 mutations (19). The findings suggested that individuals based their risk perceptions on beliefs regarding the causes of cancer (such as a family history of breast cancer), control or cure of cancer through health behaviors or surgery, and the timeline for developing cancer. In this paper, we used the CSM as the theoretical framework for an assessment of risk perceptions and thrombosis-related worry in a population of individuals with a genetic predisposition to venous thrombosis. This population has received little attention in research on risk perceptions and genetic testing.

In the past several years, several genetic factors that predispose to venous thrombosis have been identified (20-23). Venous thrombosis is a multi-causal disease that is characterized by the formation of a blood clot (thrombus) in a vein, which blocks the blood flow from the affected body part. Symptoms of a venous thrombosis in the deep veins of the legs include pain, swelling, redness and tenderness of the skin. The major

complication, pulmonary embolism, which may be life-threatening, happens when a part of the clot embolises to the lungs. Chronic impairment of the venous outflow of the leg, the postthrombotic syndrome, may cause severe disability. The annual incidence of diagnosed venous thrombosis, including pulmonary embolism, is 1-3 in 1000 individuals (24). Quality of life in individuals with venous thrombosis is impaired relative to that of the general population, especially in the presence of the postthrombotic syndrome. This impairment encompasses physical, social and psychological domains of quality of life (25-27).

Thrombophilia is an increased tendency to develop venous thrombosis, often due to a genetic defect. Among the genetic risk factors that have been discovered so far are factor V Leiden, protein C, protein S, and antithrombin deficiency (20-23;28). Individuals from families with inherited thrombophilia have a 10-20 times increased risk of venous thrombosis compared with a normal population (relative risk 15.7, 95% CI 9.2-26.8) (29). A combination of defects is associated with the greatest risk of venous thrombosis. For the single defects, the lowest risk is associated with Factor V Leiden and the highest risk with antithrombin deficiency (29-31). Although it is possible to treat individuals at a risk of venous thrombosis with prophylactic anticoagulant treatment, this treatment itself encompasses a risk of complications such as bleeding (32;33). Therefore, debate continues about whether widespread thrombophilia testing is beneficial in terms of improved prevention and management of thrombosis, as the benefit of treatment should be weighed against the risk of severe haemorrhage (34;35). Individuals with thrombophilia face uncertainty regarding if and when venous thrombosis will develop, and if and how they can prevent this.

Literature about the possible emotional consequences of genetic testing for thrombophilia is scarce and emotional consequences have not been taken into account in the debate on the usefulness of thrombophilia screening. As in similar conditions such as hypercholesterolemia, it is important to pay attention to the psychological impact of testing for thrombophilia (36). To our knowledge only three publications have evaluated the social and psychological impact of awareness of carriership of thrombophilia (37-39). These studies indicated that individuals who tested positive for thrombophilia were faced with increased worry about developing thrombosis, stigmatization, and problems with insurance eligibility.

The primary objectives of the current study were to examine the representations of venous thrombosis developed by thrombophilic individuals, and to assess the associations of these representations with perceptions of the likelihood of getting thrombosis and thrombosis worry. We predicted that past experience of venous thrombosis would be associated with perceptions of greater likelihood of experiencing venous thrombosis in the future. Furthermore, it was predicted that older individuals without a personal history of venous thrombosis would perceive venous thrombosis to be less likely than younger individuals, based on the reasoning that if it was likely to occur, then they would

have experienced it by this point in their lives. Both of these associations would suggest 'logical' appraisals of perceived likelihood. Yet likelihood perceptions can also be influenced by 'nonrational' influences. Specifically, we expect that the more one has strong consequences beliefs (which are more likely than weak consequence beliefs to involve vivid, graphic, easily imagined scenarios of suffering) and high coherence beliefs (i.e., a clear, developed, coherent representation of the illness), the greater the perceived likelihood of venous thrombosis. These effects would reflect the use of the availability and simulation heuristics (40;41). Thus, we hypothesized that 'consequences' and 'coherence' beliefs would have strong associations with risk perception. Furthermore, theoretically, all of the IPQ-R subscales should be associated with disease-related worry for people who know they are at a genetic risk for a disease (12). In line with the findings of Rees et al. (18), we expect that participants with strong 'identity' and 'consequences' beliefs (those who perceive venous thrombosis as having more symptoms and more serious consequences) will have higher levels of thrombosis worry.

Method

Participants and procedure

Participants in this study were adult thrombophilic individuals who were enrolled in the European Cohort on Thrombophilia (EPCOT) study in the Netherlands between 1994 and 1997 and followed until 2001 (42;43). Included were all registered probands (first of a family in whom thrombophilia was detected) with a deficiency of antithrombin, protein C, protein S or factor V Leiden, and their registered relatives with thrombophilia. Participants in this study had to be over 18 years old and capable of completing a questionnaire. Data were collected in 2004 by mailed questionnaires. Non-responders received a reminder questionnaire about 2 months after the initial questionnaires were sent out. All participants signed an informed consent form to use previously collected medical data for this study.

Measures

Demographic and illness related variables. Demographic and illness-related variables of all participants were collected and included age, gender, thrombosis history (dates, location of the thrombosis), and details about the type of thrombophilia (protein C deficiency, protein S deficiency, antithrombin deficiency, Factor V Leiden or a combination of Factor V Leiden and other defects).

Illness perceptions. To measure illness perceptions, the revised version of the Illness Perception Questionnaire (IPQ-R) was used, which is a measure based on the CSM (44). The

original Illness Perception Questionnaire (IPQ) was designed to assess the five attributes of illness representations: identity, timeline, consequences, control and cause (45). In the revised version, a subscale was added to assess emotional representations, such as anxiety and anger, generated by an illness. The IPQ-R also incorporates a subscale called 'illness coherence'. This subscale was added to assess the extent to which the illness makes sense to the patient. Furthermore, it includes a measure of how much one believes an illness fluctuates or comes and goes over time ('cyclical timeline'), and it has separated the 'cure/control' subscale into 'personal control' and 'treatment control' subscales.

The questionnaire was adapted for use in a population with thrombophilia so that both participants *with* a history of thrombosis and participants *without* a history of thrombosis could complete the same set of questions. The identity scale consisted of 14 general symptoms and asked participants to state whether they believe this symptom is related to venous thrombosis; scores reflect the number of illness-related symptoms. The items for the acute/chronic timeline, cyclical timeline, consequences, personal control, treatment control, illness coherence and emotional representations subscales were rated on a 5-point Likert type scale ranging from *strongly disagree* to *strongly agree*. All items were adapted for use in a population that is genetically predisposed to venous thrombosis, but does not necessarily have a personal experience with the illness. For instance 'My illness will last a short time' was replaced by 'Venous thrombosis lasts a short time'. The total number of items in this section is 37. Scores were the mean rating for each subscale. The last section presented the causal dimension, consisting of 24 items rated on the same 5-point Likert scale ranging from *strongly disagree* to *strongly agree*. Six causes that are specific risk factors for venous thrombosis (such as the use of the oral contraceptives and prolonged bed-rest) were added to the original 18 causes from the IPQ-R. An open-ended question asked individuals to list any other causes that are important to them.

Risk perception. Perceived risk of venous thrombosis was assessed with two items that were adapted from Cameron & Diefenbach (4) (r=.74): 1. How likely do you think it is that, at some point in your life, you will get thrombosis? 2. How vulnerable do you think you are to getting thrombosis at some point in your life? Each item was rated on a 7 point Likert scale ranging from 1 (*not at all*) to 7 (*almost certain or extremely*). To calculate a score for risk perception, ratings on both items were added (range 2-14).

Thrombosis worry. Worry about venous thrombosis was assessed with two items (r=.90) (4): 1. To what extent are you worried about getting thrombosis? 2. To what extent are you concerned about getting thrombosis? Each item was rated on a 7 point Likert scale ranging from 1 (*not at all*) to 7 (*extremely*). These ratings were summed to generate a thrombosis-related worry score (range 2-14).

Statistical analysis

All data were entered and analyzed using SPSS 11.5. Means and standard deviations were calculated for all measures. Internal consistency of the subscales of the IPQ-R was established by calculating Cronbach's alpha coefficients. To compare differences in scores between participants with and without a history of venous thrombosis, *t* tests and 95% confidence intervals were used. To detect differences in scores between participants with different types of thrombophilia analyses of covariance (ANCOVA) were used. Pearson correlations were calculated to detect relationships between the subscales of the IPQ-R, thrombosis worry and perceived risk. To assess the independent associations of the illness perceptions with perceived risk and thrombosis worry scores, regression analyses were performed. In these analyses, demographic and disease-related variables (age, thrombosis-history, and type of thrombophilia) were entered in step 1 and illness perceptions were entered in step 2.

Results

Demographic variables

Questionnaires were sent to 251 individuals. A total of 196 out of 251 individuals (78%) returned the questionnaire. Twelve questionnaires were incomplete, and were therefore not included in the analyses. Furthermore, 10 participants had suffered only from superficial thrombophlebitis. Since this group will potentially have different perceptions of venous thrombosis, but is too small for quantitative analyses, we removed these participants from the present analyses. The remaining database consisted of 174 participants, of whom 95 (55%) had suffered from venous thrombosis. More than half (52%) of these participants had experienced one thrombotic episode, 24% had experienced two episodes and another 24% had experienced 3 or more episodes of venous thrombosis. The remaining 79 participants (45%) did not have a history of venous thrombosis. The sample consisted of 94 women (54%) and 80 men (46%). Ages were between 26 and 87 years of age, with a mean of 53 years. Within the sample 62 participants (35.6%) had the factor V Leiden mutation, 53 participants (30.5%) had protein C deficiency, 26 participants (14.9%) had antithrombin deficiency, 20 participants (11.5%) had protein S deficiency and 13 participants (7.5%) had factor V Leiden in combination with one of the other defects.

Of the 55 non-responders, 6 individuals had moved house and could not be reached, 4 were deceased and 3 were incapable of completing the questionnaire due to illness. Non-responders were slightly younger than responders (48 vs. 53 years). Non-

responders did not differ from responders with respect to gender, type of thrombophilia or history of venous thrombosis.

Illness perceptions

Table 1 presents means and 95% confidence intervals for the means on the subscales of the IPQ-R. Intercorrelations between the subscales of the IPQ-R and Cronbach's alphas are depicted in Table 2. The internal consistencies of the acute/chronic timeline, consequences, illness coherence, personal control and emotional representation subscales were satisfactory, ranging from .68 to .80. The cyclical timeline subscale originally had a Cronbach's alpha of 0.61. After removing item 31 ('Venous thrombosis is very unpredictable'), the internal consistency improved to .69. The low internal consistency of the treatment control subscale (.47) could not be improved by item reduction, so it was decided to leave this subscale out the further analyses.

Table 1 Means and 95% confidence intervals for means on the subscales of the IPQ-R, for participants with and without a history of venous thrombosis, and all participants

IPQ-R subscale	Thrombosis history (N= 95)	No thrombosis history (N=79)	All participants (N = 174)
Identity	4.3 (3.8-4.9)	3.6 (3.1-4.1)	4.0 (3.6-4.4)
Timeline acute/chronic	3.4 (3.2-3.6)	3.3 (3.1-3.4)	3.3 (3.2-3.5)
Consequences	3.1 (3.0-3.3)	3.2 (3.0-3.2)	3.1 (3.0-3.2)
Personal control	3.2 (3.0-3.3)	3.2 (3.1-3.3)	3.2 (3.1-3.3)
Illness coherence	3.7 (3.5-3.8)	3.3 (3.2-3.5)	3.5 (3.4-3.6)
Timeline cyclical	2.9 (2.6-2.9)	2.9 (2.7-3.0)	3.0 (2.7-2.9)
Emotional representations	2.6 (2.4-2.7)	2.5 (2.4-2.6)	2.5 (2.4-2.6)

On the identity subscale, participants attributed a mean of 4.0 symptoms to venous thrombosis. The symptoms that were mentioned most often were pain (87% of individuals reported that this symptom was associated with venous thrombosis), fatigue (65%), breathlessness (51%), and loss of strength (43%). A series of *t* tests was used to detect differences in illness perceptions between participants with and without a history of venous thrombosis. No differences on the subscale identity were detected between participants with and without a history of venous thrombosis. On the other subscales, a significant difference between individuals with and without a history of venous thrombosis could be detected only on the illness coherence subscale (mean 3.7 vs. 3.3, $p < 0.01$, 95% CI of the difference (0.1, 0.6)). This suggests that individuals who have a personal experience with venous thrombosis feel they have a better understanding of the disease.

In terms of perceived causes of venous thrombosis, the causes that were reported most often (the ones with the greatest proportions of participants who agreed or strongly agreed) were heredity (96%), immobilization (92%), surgery (90%), bed rest (85%), and lack of exercise (84%). On the open-ended question, the most frequent answers fell into the categories of heredity (67%), immobilization (59%), and surgery/accident (40%).

Analysis of covariance revealed that differences between groups with different types of thrombophilia could be detected only on the subscale personal control, after controlling for thrombosis history ($F(5,174) = 2.96$, $p < 0.05$), which was due to a differences in scores of participants with antithrombin deficiency and factor V Leiden.

Table 2 Pearson correlations between the IPQ-R subscales, risk perception, and thrombosis worry

	Identity	Timeline acute/chronic	Consequences	Personal control	Illness coherence	Timeline cyclical	Emotional representations	Risk perception	Worry
Identity	-	.16*	.26**	.04	-16*	.18*	.29**	.15*	.25**
Timeline acute/chronic		-	.14	.03	-.12	.24**	-.02	.07	.06
Consequences			-	-.02	-.23**	.33**	.49**	.11	.31**
Personal control				-	.10	.07	-.14	.00	-.07
Illness coherence					-	-.37**	-.41**	.20*	.09*
Timeline cyclical						-	.22**	-.04	.10
Emotional representations							-	.13	.53**
Risk perception								-	.55**
Worry									-
Cronbach's alpha		.80	.68	.73	.75	.69	.85		

* $p < 0.05$

** $p < 0.01$

Thrombosis worry and risk perception

T-tests revealed that participants with a history of venous thrombosis had a significantly higher perception of their risk of getting venous thrombosis again (10.6 vs. 8.1, $p < .001$, 95% CI of the difference (1.6, 3.4)), and were significantly more worried about getting venous thrombosis again (8.0 vs. 6.2, $p < .01$, 95% CI of the difference (0.8, 2.9)) than participants without a history of venous thrombosis. Analyses of covariance revealed that, after controlling for age, thrombosis history was still a significant predictor of risk perception and worry scores (risk perception: $F(2,168) = 33.64$, $p < 0.001$, 95% CI of the difference (1.6, 3.4); worry: $F(2,168) = 11,41$, $p < 0.001$, 95% CI of the difference (0.8, 2.9)).

Risk perception and worry scores for the different types of thrombophilia are depicted in Figures 1 and 2. As can been seen in these figures, participants with antithrombin deficiency had higher scores on both perceived risk and thrombosis worry. Analyses of covariance revealed that, after controlling for the effect of thrombosis history and age, type of thrombophilia was still a significant predictor of perceived risk; $F(4,168) = 2.78$, $p < 0.05$. Scheffé's post-hoc tests revealed that this effect was mainly due to a difference in mean scores between antithrombin deficiency and Factor V Leiden. Scores for worry did not differ significantly between the different types of thrombophilia; $F(4,168) = 0.55$, $p = .70$.

Figure 1: Mean scores and 95% confidence intervals for means on risk perception for the different types of thrombophilia

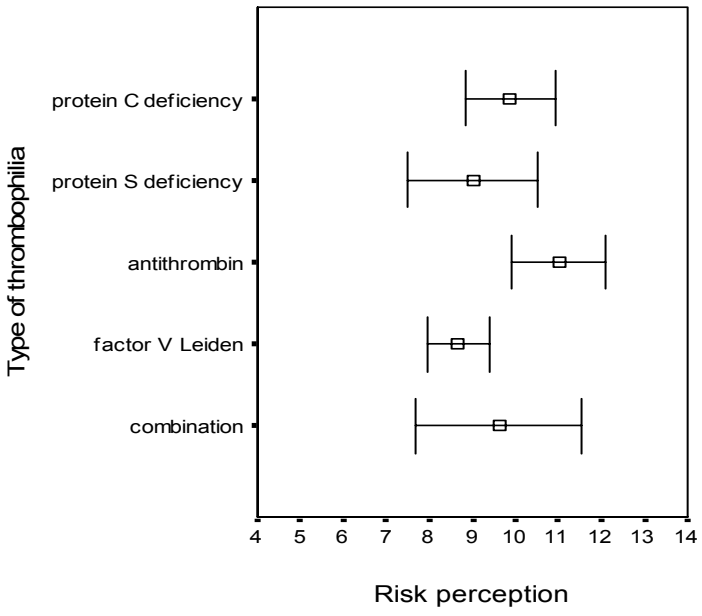
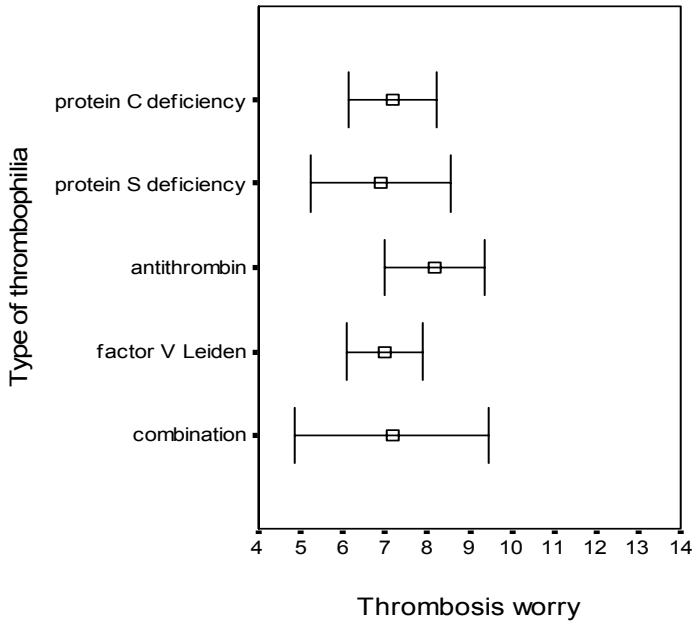


Figure 2: Mean scores and 95% confidence intervals for means on thrombosis worry for the different types of thrombophilia



Associations between illness perceptions, perceived risk, and thrombosis worry

Table 2 shows correlations between the illness perceptions, perceived risk, and thrombosis worry scores. The attribution of more symptoms to venous thrombosis was related to a belief in a longer timeline, more serious consequences, a stronger belief in a cyclical timeline, stronger emotional representations and a less coherent understanding of the disease. A belief in a longer duration was related to a stronger belief that the illness comes and goes over time. A belief in more serious consequences of venous thrombosis was related to a less coherent understanding of the disease, a stronger belief in a cyclical timeline and stronger emotional representations. A more coherent understanding of venous thrombosis was related to weaker emotional representations and a weaker belief in the cyclical timeline of venous thrombosis.

Perceived risk was positively related to illness identity and illness coherence. Thrombosis worry was also related to the attribution of more symptoms to venous thrombosis, as well as a belief in more serious consequences, a less coherent understanding of the disease, and stronger emotional representations. Risk perception and worry were positively correlated with each other ($r = .55$).

Regression analyses

Two-stage regression analyses were performed to assess the independent associations of the illness perceptions with perceived risk and thrombosis worry (see Table 3). Because the emotional representations subscale was highly correlated with thrombosis worry, it was decided to leave this subscale out of the regression analysis to avoid colinearity.

Results of the regression analysis of perceived risk revealed that the demographic and illness-related variables explained 19% of variance, whereas the illness perceptions explained 5%. The full model was significant, $p < 0.001$. Both younger age and a positive history of venous thrombosis were strong predictors of perceived risk scores. The IPQ-R subscale that contributed most to the regression equation was illness coherence .

For thrombosis worry, demographic and illness-related variables accounted for 7% of the variance whereas the illness perceptions explained 12% of the variance. The significance of the total model was $p < 0.001$. Of the demographic and illness-related variables, only a history of venous thrombosis contributed significantly to the regression equation. Beliefs in more symptoms and more serious consequences of venous thrombosis were the most important predictors of thrombosis worry.

Table 3. Two-stage regression analyses testing the value of the illness perceptions in predicting risk perception and thrombosis worry

Dependent variable		Predictors	Regression coefficients		t
			Unstandardized B (95% CI)	**Standardized Beta**	
Risk perception	Step 1				
		Age	-.04 (-.08, -.01)	-.20	-2.73**
		Type of thrombophilia	-.08 (-.42, .25)	-.04	-.47
		Thrombosis history	2.29 (1.28, 3.29)	.42	5.66***
		ΔR^2 = 19			
		F = 12.64* **			
	Step 2				
		Identity	.09 (-.11, .29)	.07	.87
		Timeline	.27 (-.29, .83)	.07	.95
		Consequences	.42 (-.42, 1.26)	.08	.99
		Personal control	-.15 (-.89, .59)	-.03	-.39
		Illness coherence	.73 (-.03, 1.49)	.16	1.90*
		Timeline cyclical	-.05 (-.78, .67)	-.01	-.13
		Emotional representations	.51 (-.25, 1.27)	.12	1.32
		ΔR^2 = .05			
		F = 4.78* **			
Thrombosis-related worry	Step 1				
		Age	-.01 (-.05, .03)	.01	.16
		Type of thrombophilia	.10 (-.28, .48)	.04	.51
		Thrombosis history	1.98 (.87, 3.01)	.27	3.39**
		ΔR^2 = .07			
		F = 4.10 **			
	Step 2				
		Identity	.22 (.00, .44)	.15	2.0*
		Timeline	-.08 (-.70, .54)	-.02	-.25
		Consequences	1.39 (.54, 2.24)	.25	3.23**
		Personal control	-.27 (-1.09, .55)	-.05	-.65
		Illness coherence	-.36 (-1.15, .43)	-.07	-.89
		Timeline cyclical	.05 (-.75, .85)	.01	.12
		ΔR^2 = .12			
		F = 4.21* **			

Note: The IPQ-R dimension emotional representations was not entered into the regression analysis for thrombosis-related worry because of a high correlation with thrombosis-related worry, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Discussion

In this study, the Common-Sense Model (CSM) was used to explore the nature of the cognitive representations of venous thrombosis formed by thrombophilic individuals, and to evaluate how these representations are associated with risk perceptions and thrombosis worry. Perceived risk and thrombosis worry were found to be significantly higher for participants with a history of venous thrombosis than for individuals without a history of venous thrombosis. Furthermore, perceived risk and worry scores were higher for participants with antithrombin deficiency than for participants with any of the other thrombophilias. After controlling for thrombosis history and age, analyses of covariance revealed that this group difference in perceived risk was still present. This group difference reveals realistic perceptions, because individuals with antithrombin deficiency appear to have the greatest venous thrombotic risk of all the single thrombophilias (30;31). This finding indicates that knowledge of thrombophilic individuals about their risk of venous thrombosis is generally good. On the other hand, individuals with a combination of factor V Leiden and other defects do not have higher perceptions of their thrombotic risk than individuals with single defects even though biomedical evidence indicates that combined defects pose the greatest thrombotic risk (29).

Few differences in illness perceptions were identified between individuals with a history of venous thrombosis and individuals without a history of venous thrombosis. The only statistically significant difference in scores was on the illness coherence subscale. In general, it appears that asymptomatic individuals have realistic expectations about the experience of having venous thrombosis. However, despite their realistic beliefs about venous thrombosis, they tend to score lower on illness coherence, indicating that thrombophilic individuals without a history of venous thrombosis do not feel that they have a coherent understanding of the illness. More information about venous thrombosis could help to strengthen their knowledge about the illness to make them feel more confident in understanding the illness. The causes of venous thrombosis that were endorsed most frequently by the participants were heredity, immobilization, and surgery, which is in line with the view of venous thrombosis as a multicausal disease that is caused by both genetic and environmental risk factors (46).

We hypothesized that perceived risk would be associated with 'consequences' and 'illness coherence' beliefs, as well as with younger age and a history of venous thrombosis. The findings partially support these hypotheses. First, correlational patterns revealed that perceived risk was positively associated with illness coherence, but it was not correlated with consequence beliefs. Unexpectedly, perceived risk was associated with higher identity scores, indicating that those who associated venous thrombosis with a greater number of symptoms tended to have higher risk perceptions. The results of the regression analyses indicate that illness perceptions only have a modest contribution in accounting for the variance in perceived risk scores, with illness coherence as the only sig-

nificant predictor. As expected, younger age and a history of venous thrombosis were predictors of perceived risk scores.

We predicted that worry would be associated with all IPQ-R subscales, with the strongest associations for the identity and consequences subscales. Worry was indeed found to be significantly associated with identity and consequences. Regression analyses revealed that illness perceptions could account for a greater amount of variance in thrombosis worry scores than risk perception scores Also, as predicted, identity and consequences were both modest but significant predictors of worry. Demographic and illness-related variables explained only a modest amount of variance in thrombosis worry scores with thrombosis history being the only significant predictor. These results indicate that the cognitive components of illness representations have a stronger association with illness-related affect, rather than with more reasoned, cognitive appraisals of disease risk. Other variables, such as a personal history of venous thrombosis, seem to be better predictors of risk perception.

This is one of the first studies that uses the Illness Perception Questionnaire-Revised to assess the illness perceptions of individuals at risk of a disease. The treatment control subscale showed a low internal reliability ($\alpha = .47$) that could not be improved by item reduction, and it was therefore removed from subsequent analyses. This might give an indication that thrombophilic individuals do not have a clear understanding of the treatment of venous thrombosis. Some other subscales showed only moderate internal consistency, such as the illness coherence subscale. Rees and colleagues (18) encountered similar difficulties regarding the internal consistency of some of the subscales. A further issue is that the emotional representations subscale was highly correlated to thrombosis worry. Although thrombosis worry reflects persistent concern about developing the disease and the emotional representations subscale reflects the affective response to venous thrombosis, it seems that in the present form, the scales are not differentiated enough from each other. Furthermore, the control subscales of the IPQ-R measure control over the recovery of venous thrombosis. In populations at risk of a disease, beliefs about control over the prevention of a disease are probably more relevant. With the original wording of the IPQ-R, it appears to be difficult to capture the illness perceptions of individuals at risk of a disease. Further research should aim at refining the subscales so that they adequately capture illness perceptions in at-risk populations. The development of a new version of the IPQ-R, specifically for individuals 'at risk', could be a possible outcome.

Non-responders were slightly younger than responders in this study, which may have biased the results. Since younger people perceived their risk for venous thrombosis as higher than did older people, the perceived risk means observed in the present study are likely to be somewhat tempered. Another limitation is the cross-sectional nature of the study, which precludes definitive interpretations of the directionality of the influences among perceived risk, worry, and illness perception components.

Further research, preferably with a longitudinal design, and measurements of illness perceptions, risk perceptions, worry, and health behavior before and after genetic counseling, could help to clarify the exact nature of the value of the CSM in explaining the regulation of illness risks. A better understanding of the processes involved in how individuals form their risk perceptions and worry about a health threat could help clinicians in predicting which individuals may exhibit high levels of distress or hold misconceptions about the magnitude of their risk. These insights also could help to increase understanding of the factors that are involved in health behaviors to reduce the risk of a disease.

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Chapter 7

General discussion

Introduction

Venous thrombosis is the result of the formation of a blood clot in a vein. It is a common disease with an incidence of 1-2 in 1000 persons a year. The most common manifestation of venous thrombosis is in the veins of the legs and symptoms include pain, swelling, redness and tenderness of the skin (1;2). When a piece of the clot breaks off and results in pulmonary embolism, it may be fatal (3). Furthermore, patients have up to 50% chance of developing chronic problems, i.e., the postthrombotic syndrome (4). In about 50% of patients with venous thrombosis, a predisposing genetic abnormality can be detected. This predisposition is called thrombophilia (5). Because patients with venous thrombosis have to deal with an illness that is possibly fatal, might have serious chronic consequences, and might return, it is highly relevant to study the quality of life (QOL) of this category of patients. The impact of venous thrombosis on the quality of life of patients has not gained much attention in the scientific literature. In addition, the possible psychological consequences of genetic testing for thrombophilia have only received limited attention in the scientific literature. This is surprising because research has indicated that carriership of a genetic deficit may influence daily life, since it can cause considerable distress, especially in vulnerable individuals (6).

Research of the Unit of Psychology of the Leiden University Medical Centre, has focused on Leventhal's Common-Sense Model of health and illness behaviour (CSM) (7). This model describes a system with two parallel pathways that interact when a patient adapts to an illness or health threat and can be useful in explaining outcome, such as quality of life, in patients with a chronic illness (7;8). Key elements of this model are the illness representations, or illness perceptions. The illness perceptions include five key attributes: the label and symptoms that patients associate with their illness (identity), and their beliefs about the etiology (cause), the outcome (consequences), the duration (timeline) and the controllability (cure/control) of the illness. Research on the Common-Sense Model conducted at the Unit of Psychology has resulted in several journal articles on the impact of illness perceptions and outcome in patients with a diverse array of illnesses, such as Huntington's disease (9), rheumatoid arthritis, chronic obstructive pulmonary disease, psoriasis (10;11), head- and neck cancer (12), and several book chapters (13-15).

Because perceptions of health risks such as a genetic risk factor predisposing to an illness are also based on perceptions of the target illness, in this case venous thrombosis, it is likely that the Common-Sense Model will prove to be a useful model in explaining outcome in individuals who are at risk of a certain illness (16).

Collaboration between the Department of Clinical Epidemiology (LUMC), the Unit of Psychology (LUMC) and the Department of Pathology of the University of Vermont (VT, USA) resulted in several studies on quality of life in patients with venous thrombosis and the psychological impact of thrombophilia testing, of which the results are described in this thesis.

The studies described in this thesis had two main aims:
1) To study the quality of life of patients with venous thrombosis and to examine the role of illness perceptions in explaining the quality of life of these patients.
2) To assess the psychological consequences of genetic testing for thrombophilia, using the Common-Sense Model as a theoretical framework.

Quality of life in patients with venous thrombosis

The first aim of this thesis, to study the quality of life of patients with venous thrombosis and to examine the role of illness perceptions in explaining the quality of life of these patients, was addressed in chapters 2, 3 and 4.

Chapter 2 describes a literature review that aimed to describe studies that assessed quality of life in patients with chronic venous disease. A computer search of the Medline database from 1996 to February 2003 was performed to identify relevant papers. In addition, the bibliographies of relevant papers were reviewed. Papers were selected if they were written in English, French, or German and described the development or use of a quality of life instrument in patients with venous disease or treatment of venous disease. A total of 25 papers were identified, of which only 4 specifically dealt with the assessment of quality of life in patients with venous thrombosis (17-20). One of these studies used only a disease-specific measure of quality of life (20), whereas the other three studies used a combination of disease-specific and generic measures. Main results of these four studies indicate that patients with venous thrombosis are impaired in all domains of quality of life. They are impaired in their physical functioning and report pain. They have low perceptions of their general health and experience health distress. Impairment of QOL seems to be related to symptom severity and the presence of the post-thrombotic syndrome. Furthermore, 6 studies examined the effect of different types of treatment for venous thrombosis on the quality of life of patients (21-26). The other studies reviewed in chapter 2 dealt with quality of life assessment in patients with chronic venous insufficiency (5 studies), venous leg ulceration (8 studies), and varicose veins (2 studies).

In the two years since we published our review, the subject of quality of life in patients with venous thrombosis has fortunately gained more attention in the scientific literature. The group of Kahn and colleagues published a number of studies on this subject (27-29). To assess quality of life, these studies used both the widely used generic measure Short Form-36 (SF-36)(30) and the VEINES-QOL. The VEINES-QOL is a 26-item disease specific questionnaire that measures venous symptoms, limitations in daily activities and psychological disease impact. The major results of these studies indicate that on average, QOL is impaired in patients with venous thrombosis compared to a general population and improves in the first 4 months following venous thrombosis, but

that average QOL remains poorer than population norms. Furthermore, patients with the postthrombotic syndrome reported lower quality of life scores than patients without the postthrombotic syndrome, especially on the VEINES-QOL.

In addition, the subject of quality of life in patients on anticoagulant therapy, which is the treatment of choice after venous thrombosis, has also gained more attention. Locadia et al. published two papers in which quality of life, health state evaluations, and treatment preferences of patients treated with vitamin K antagonists after suffering from venous thrombosis were assessed (31;32). Results of these papers indicate that quality of life in patients with venous thrombosis was not related to treatment duration and that there is substantial variability in health state valuations and treatment preferences in patients with venous thrombosis. Furthermore, Gadisseur et al. assessed quality of life of patients using oral anticoagulants and found that self-management of treatment had a positive effect on quality of life versus management by specialized anticoagulation clinics (33).

In chapter 3, we examined the quality of life of patients with venous thrombosis in a well-defined population, using both a generic measure, the SF-36, and a newly developed disease-specific measure, the VT-QOL. The latter instrument was developed for this research and based on interviews held with patients with venous thrombosis and on previous quality of life research in this patient population (19;34;35). The VT-QOL assesses quality of life on the dimensions physical functioning, social functioning, general mental health, and thrombosis repercussions. The questionnaires were filled out by 45 individuals who had experienced one or more episodes of venous thrombosis. Although the subjects had had their last thrombotic event a median of two years ago, the results of this study indicated that an impaired quality of life could still be detected on both measures. Compared to a general U.S. population sample, the patients in our sample scored significantly lower on all subscales of the SF-36, after adjusting the population norms for the age and sex distribution in the sample. QOL appeared to be related to self-reported symptoms and the presence of the postthrombotic syndrome on both measures. The VT-QOL was more sensitive than the SF-36 in detecting differences between patients with and without the postthrombotic syndrome. These results are consistent with those of Kahn et al., as described above (28;36). We believe that with the VT-QOL, a reliable and valid measure to assess quality of life in patients with venous thrombosis has been developed, which is more sensitive to the specific problems this group of patients experiences, than general measures such as the SF-36.

In this study, the presence of the postthrombotic syndrome was evaluated by chart review. The presence of the postthrombotic syndrome was determined by a clinician at different points in time prior to QOL assessment. Ideally, presence of the postthrombotic syndrome should be determined at the time of quality of life assessment, by a known scale such as the CEAP classification (36;37). However, since the postthrombotic syndrome was assessed by the same clinician in every patient, the possibility of inter-rater

variability was excluded and possible misclassification was minimized. In addition, we found a strong correlation between the classification of the postthrombotic syndrome and self-reported symptoms, which suggests that our method for assessing the post-thrombotic syndrome in this study was still sufficiently reliable.

Although the sample size of this study was rather small, we may still conclude that venous thrombosis has many negative consequences for the quality of life of patients. The study described in chapter 3, along with other research in the field, has now indicated that even several years after the initial episode of venous thrombosis many patients still remain impaired in their quality of life because of persisting symptoms, both in their daily physical functioning and in their social and psychological functioning. This is especially true for patients diagnosed with the postthrombotic syndrome and patients who report several symptoms

Explaining quality of life in patients with venous thrombosis

As found in chapters 2 and 3, even some years after the initial event, quality of life of patients with venous thrombosis may remain poorer than that of a general population, especially in the presence of the postthrombotic syndrome. Since quality of life can not be explained by biomedical variables only, and research has shown that the patients' own perceptions play an important role in explaining quality of life, we aimed to assess how illness perceptions influence the quality of life of patients with venous thrombosis. The results of this study are described in chapter 4. A total of 45 patients with a history of venous thrombosis filled out the SF-36 to measure quality of life, and the Illness Perception Questionnaire-Revised (IPQ-R) (38) to measure illness perceptions. Patients in our sample believed that their illness would be prolonged and that their symptoms were not cyclical. They mostly attributed their venous thrombosis to bad luck or hereditary factors. These attributions are consistent with medical evidence that venous thrombosis is often hereditary (39), but also a multicausal disease, often caused by interplay between genetic and environmental risk factors, making it hard to pinpoint an exact cause in many patients (40). A series of regression analyses, in which we controlled for the presence of the postthrombotic syndrome and the number of thrombotic episodes experienced by the patient, showed that the IPQ-R subscales timeline acute/chronic, personal control, illness identity and the cause 'heredity' were the best predictors of quality of life scores. This is in line with earlier research using the original Illness Perception Questionnaire and hypotheses derived from the Common-Sense Model, suggesting that individuals who perceive their illness as chronic, as having more symptoms, more serious consequences, and perceive less control over their illness, will have less adaptive outcomes, such as impaired quality of life (41).

The subscales that are new in the revised version of the Illness Perception Questionnaire, namely illness coherence and emotional representations, did not contribute to the regression equations. Especially since patients with the postthrombotic syndrome had lower scores on illness coherence as well as on all subscales of the SF-36, the fact that illness coherence does not seem to play a role in the explanation of quality of life, is noteworthy. In this patient group, having an illness of which patients seem to have a limited understanding, does not appear to affect their quality of life. Recent studies by Scharloo et al., and Llewellyn et al., assessing quality of life and illness perceptions in patients with head and neck cancer, found that the emotional representations subscale was a good predictor of emotional functioning (12;42), so it is interesting that in our study this subscale does not have an effect.

Many studies using the IPQ or IPQ-R also incorporate measures of coping, because one of the premises of the Common-Sense Model is that the relationship between illness perceptions and outcome is mediated through coping procedures. However, several studies that have attempted to examine this hypothesis in a number of chronic diseases, have failed to find proof for the hypotheses. Those studies found a significant impact of illness perceptions on outcome, with no or only very small additive impacts of coping behaviours (10;43;44). Therefore, we chose not to include a measure of coping in our study.

When we first started this study, the IPQ-R was not adapted for use in a population of patients with venous thrombosis. The authors of the original papers in which the IPQ and IPQ-R are first described, encourage researchers to adapt the questionnaire to their specific patient population and research setting (38;45). In our study, patients attributed only few of the symptoms in the identity subscale to the illness. Many of the symptoms in the original subscale are not symptoms that are commonly experienced by patients with venous thrombosis. Therefore, in further research symptoms that characterize venous thrombosis, such as swelling, redness and tenderness of skin of the affected body part, should be added to this subscale. This would greatly improve the suitability of this subscale in patients with venous thrombosis. Furthermore, causes that are specific for venous thrombosis should be added to the causal dimension. For instance, known risk factors such as the use of oral contraception, pregnancy/childbirth, surgery and immobilization are a few of the possible additions to this subscale (46).

Chapter 4 gives an indication that besides the presence of the postthrombotic syndrome there are psychological factors that may help to explain quality of life in patients with venous thrombosis. A belief in a longer duration of venous thrombosis, a lower belief in personal control over venous thrombosis, and the attribution of more symptoms to venous thrombosis, have a negative impact on the quality of life of patients.

Psychological implications of genetic testing for thrombophilia

The second aim of the studies described in this thesis was to study the psychological consequences of genetic testing for thrombophilia, using the Common-Sense Model as a theoretical framework and was addressed in chapters 5 and 6.

In chapter 5, the attitudes toward genetic testing for heritable thrombophilia in a large family with a high incidence of protein C deficiency were explored. The questionnaire consisted of items about risk perception, thrombosis worry, beliefs in the health benefits and psychological benefits of testing, and beliefs in psychological distress after testing, derived from research about the consequences of testing for hereditary breast cancer genes by Cameron & Diefenbach (47). Furthermore, knowledge about other risk factors for venous thrombosis was assessed and all participants filled out the trait form of the State-Trait Anxiety Inventory (STAI) as a measure of dispositional anxiety (48). Interest in getting a genetic test for protein C deficiency was assessed in participants who had not been tested for protein C deficiency before. The questionnaires were filled out by a total of 168 participants of whom 76 participants had not been tested for protein C deficiency before, 34 participants who had been tested previously and were found to have protein C deficiency, and 58 participants who were found not to have protein C deficiency when they had been tested. None of the participants had previously experienced venous thrombosis. The main results of this study indicated that the psychological and health benefits of testing are perceived as higher than the psychological distress following the test by both participants that had not been tested before and participants with protein C deficiency. These results are comparable to research on genetic testing in similar conditions, such as familial hypercholesterolemia, which found that learning that one has familial hypercholesterolemia alters perceptions of control over getting coronary heart disease, but does not increase anxiety and depression (49). Trait anxiety was related to (a belief in) more psychological distress following the test result. Furthermore, it seems that increased worry about venous thrombosis was the only variable related to both the attitudes about genetic testing for thrombophilia and genetic testing interest. Perceived risk for venous thrombosis was not associated with any of the attitudes measures or with testing interest. This is a notable finding, since perceived risk has been regarded as a key motivator for health behaviour in a number of theories, such as the health belief model (50) and the precaution adoption process (51). In recent years, however, a growing body of research has indicated that disease-related worry plays a stronger motivational role in promoting health behaviours than perceived risk of disease, and our work supports that line of research (52-54).

Limitations of this study lie mainly in the fact that it was an cross-sectional family study. Participants who had been tested previously, were invited to do so in a previous study. Therefore there is a slight possibility for a selection bias. On the other hand, complete randomization in genetic testing studies is complicated because of ethical considera-

tions. The previous study in which participants had been tested was performed a while ago (54) and because of that it was not possible to assess the reactions to the test directly after receiving the test result. It is possible that adverse psychological effects have arisen directly after receiving the test results but that individuals have adapted to their condition over the years. This phenomenon is called response shift and has been noted in earlier research on hereditary cancers (55-57). Another possible factor that can bias results in this study is the fact that the family members in this study have been involved with medical research for a number of years. Additionally, they might have witnessed each others' experiences with thrombophilia testing and venous thrombosis and it is likely that they have discussed these issues with each other. Therefore, they might be better informed and have different perceptions on venous thrombosis and thrombophilia testing than individuals who do not have these experiences.

Despite these limitations, we believe that the results of the study described in chapter 5, that is amongst the first to describe the impact of genetic thrombophilia testing, indicate that in general there are few long-term negative psychological consequences of testing for thrombophilia, except in individuals who are vulnerable to high levels of anxiety. By most individuals, getting a genetic test is regarded as beneficial for both their health and their psychological well-being.

Using the Common-Sense Model to predict outcome after genetic testing for thrombophilia

In chapter 6 the Common-Sense Model of illness representation (7;8) was applied to predict risk perception and worry in individuals with a genetic predisposition to venous thrombosis. Participants from the European Cohort on Thrombophilia (EPCOT) (58-60) filled out a set of questionnaires. An adapted version of the IPQ-R was used to assess beliefs of thrombophilic individuals about venous thrombosis. In this version of the IPQ-R, the wording of the items was changed to make it applicable to individuals at risk of a disease, and some risk factors that are specific to venous thrombosis were added to the "causes" subscale. In addition, risk perception and thrombosis worry were assessed. A total of 174 participants completed the questionnaire, of whom 95 (55%) had suffered from venous thrombosis. We found that individuals with a history of venous thrombosis and individuals without a history of venous thrombosis had similar perceptions of the disease. Regression analyses revealed that only the IPQ-R subscale illness coherence was significantly related to risk perception scores. Young age and a history of venous thrombosis appeared to be better predictors of perceived risk of getting venous thrombosis than illness perceptions. For thrombosis worry, the subscales consequences and illness identity were significant predictors. These results indicate that the cognitive components of illness representations have a stronger association with illness-related affect, than with

more reasoned, cognitive appraisals of disease risk. Other variables, such as a personal history of venous thrombosis, seem to be better predictors of perceived risk than illness perceptions.

When we compare these results with the only other published quantitative study that used the Common-Sense Model as a theoretical framework to assess psychological impact of genetic testing, the relationship we found between thrombosis worry and the subscales identity and consequences is in line with findings by Rees and colleagues who found similar results in a sample of women at increased risk for breast cancer (61).

This study was amongst the first that used the Illness Perception Questionnaire-Revised to describe the illness perceptions of individuals at risk of a disease, which may be regarded as both a strength and a limitation of this study. For instance, no associations between control beliefs and risk perception or thrombosis worry were identified in our study. This was surprising since associations between control beliefs and adaptation to illness have been clearly demonstrated in several patient populations (10;62). It is likely that beliefs concerning personal control *over risk*, such as ability to prevent venous thrombosis are more important in this population than control *over the disease* as assessed by the IPQ-R.

Furthermore, the treatment control subscale showed a low internal reliability (α = .47) that could not be improved by item reduction, and it was therefore removed from subsequent analyses. Some other subscales showed only moderate internal reliability, such as the illness coherence subscale. Rees and colleagues (61) encountered similar difficulties regarding the internal reliability of some of the subscales. A further issue is that the subscale emotional representations was highly correlated to thrombosis worry, and it was therefore left out of subsequent analyses. With the original wording of the IPQ-R, it appears to be difficult to capture the illness perceptions of individuals at risk of a disease.

With a closer look at the combined results of chapters 5 and 6 and adopting a Common-Sense Model approach, we can note the following: asymptomatic individuals from families with a high risk of disease develop representations of the disease through information provided by health care providers, family members, and the experiences of the disease in family members. This supports the premise of the Common-Sense Model - that illness perceptions are derived not only from direct somatic or symptomatic experience but also from information available in the external social environment (63). A background from a high-risk family or carriership of a genetic abnormality predisposing to a disease is sufficient stimulus to evoke representations of the disease. These illness representations, particularly illness identity, perceived consequences and illness coherence, have an impact on perceived risk of the target disease and, more strongly and importantly, on disease-related worry. In turn, disease-related worry has an impact on interest in getting a genetic test, and beliefs about the possible distress that may occur after testing. The results reported in this thesis have shown how the Common-Sense Model can act as a useful framework to enhance understanding of how psychological factors influ-

ence psychological response to risk of disease and how this psychological response can influence health behaviour.

Implications for clinical practice

From the studies described in this thesis it becomes clear that the effects of venous thrombosis on the life of patients should not be underestimated. After the initial anticoagulant treatment of three to six months, symptoms of venous thrombosis are supposed to disappear, but our research along with other research in the field has now indicated that even several years after the initial episode of venous thrombosis, many patients still remain impaired in their quality of life because of persisting symptoms, both in their daily, physical functioning, and in their social and psychological functioning. It is imperative that health care providers prove sensitive to the problems patients experience in daily life, especially if they are diagnosed with the postthrombotic syndrome. Patients who experience many difficulties when trying to deal with the negative consequences of their illness, could be referred to a health psychologist who could further assist patients in adapting to their illness. Furthermore, our research also indicates that not only biomedical variables contribute to the quality of life of patients with venous thrombosis, but that illness perceptions also play a role. Especially beliefs in the duration of the disease, as well as beliefs about the self-management of venous thrombosis seem to play an important role in the quality of life of these patients. If intervention studies can prove the positive impact of changing illness perceptions on quality of life in these patients, health care providers could aim at addressing perceptions about the duration of their illness and the possible management of venous thrombosis, in order to improve quality of life.

Confronted with decisions about whether to test patients for thrombophilia or not, we may conclude from the results of our study that genetic testing for thrombophilia does not seem to have many adverse psychological consequences in the long term. On the contrary, many members of high risk families feel that knowing whether they have thrombophilia or not will have high health benefits and psychological benefits. We also found that for many patients from these families, getting tested is important for the benefits of their family and children. However, we should note that most non-tested individuals from high-risk families do not worry excessively about their risk for venous thrombosis, so performing a genetic test in order to reduce worry about venous thrombosis is often not necessary. The research described in this thesis has also pinpointed some of the psychological factors that should be taken into account when deciding whether or not an individual patient is eligible for thrombophilia testing. Our results indicate that certain vulnerable individuals with a high predisposition to anxiety might experience considerable distress following the (positive) test result. Furthermore, thrombophilic individuals who believe that venous thrombosis has many symptoms and who be-

lieve in serious consequences of the illness, might experience increased thrombosis worry. Illness beliefs and disease worry should be explicitly assessed in consultations. Patients should be able to make a fully informed choice. Clinicians should inform patients in great detail about advantages and disadvantages of testing, as well as about the meaning of a positive test result. Furthermore, as Marteau & Croyle suggest, the initial offer of a test should be separated in time from the blood sample being taken, to allow patients to make a decision. Test results should be explained and support should be offered to tested patients and their relatives (64).

Further research

From the studies presented in this thesis we may infer some directions for future research on the topics of quality of life in patients with venous thrombosis and psychological impact of genetic testing for thrombophilia. In addition, we can make some recommendations about the direction further research about the Common-Sense Model should take.

First of all, longitudinal research is needed on illness perceptions in patients with venous thrombosis to assure the causal direction of the effects we found in our study, in which illness perceptions are measured at baseline and outcome is measured on a subsequent occasion. Preferably this research would have a large sample size and a population of patients who have recently had their first episode of venous thrombosis, in order to make it possible to follow the changes in quality of life over time. Preferably a disease-specific quality of life measure, such as the VT-QOL, is used to assess quality of life in future studies because disease-specific measures are more sensitive to specific problems patients with venous thrombosis are experiencing. It would also be interesting to assess whether illness perceptions predict other outcomes, such as biomedical variables such as persisting symptoms after 3 months, or return to work. Further research on illness perceptions on quality of life in patients with venous thrombosis should also incorporate a measure of coping. It is likely that patients with venous thrombosis have developed different coping styles to deal with their illness, which were not assessed in the studies described in this thesis. Although previous research has failed to confirm the premise of the Common-Sense Model that the relationship between illness perceptions and outcome is mediated through coping procedures, formal longitudinal research is still needed to prove the rejection of this premise.

In addition, an intervention study, like that of Petrie and colleagues (65) could be conducted to investigate the impact of a short intervention focused on changing illness perceptions on the well-being of patients with venous thrombosis. Such an intervention should focus primarily on beliefs in the duration of the disease, as well as on beliefs about the controllability and curability of venous thrombosis, since these are the illness

perceptions that seem to have the greatest influence on quality of life in patients with venous thrombosis.

Regarding the psychological consequences of genetic testing for thrombophilia, future research should focus more on the short-term effects of testing, since the studies described in this thesis only focussed on the long-term effects. Such a study should investigate a diverse group of thrombophilia patients with variation in risk factors. Ideally, it would have a randomized longitudinal design, with measurements of psychological distress immediately after receiving the test result and at a specified later time point, to investigate whether the duration and intensity of the perceived emotional impact of the test changes over time. In addition, it would be useful to include measures about state anxiety and depression following the genetic test result. This research could also help to clarify the exact nature of the predictive value of the Common-Sense Model in explaining outcome in individuals at risk of a disease.

Our study showed that there are a number of methodological problems that arise when attempting to capture illness perceptions of individuals 'at risk' of a certain disease with the original version of the IPQ-R. Further research should aim at refining the subscales so that they adequately capture illness perceptions in this specific population. The development of a new version of the IPQ-R, specifically for patients 'at risk', could be a possible outcome. In addition, the Common-Sense Model needs to be expanded to encompass beliefs regarding control over risk when applied to individuals at risk of disease. Perceptions of personal control over prevention of the target disease, as well as beliefs regarding the efficacy of prophylactic treatment need to be explored as well.

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Summary

Venous thrombosis is the result of the formation of a blood clot in a vein. The most common manifestation is in the veins of the legs, but in can also occur in other body parts. The clot blocks the flow of blood in the affected body part, which can cause pain, swelling, redness, and tenderness of the skin. In some cases a piece of the clot breaks off and travels to the lungs, where it can cause a (possibly fatal) pulmonary embolism. Up to 50% of all patients with venous thrombosis develop chronic problems. This is called the postthrombotic syndrome. Venous thrombosis has an annual incidence of 1-2 in 1000 persons.

Venous thrombosis is a multicausal disease, caused by both genetic and environmental risk factors. Environmental risk factors for venous thrombosis include the use of oral contraceptives ('the Pill'), obesity, surgery, and prolonged immobility, for instance during a long flight. Genetic risk factors are inherited abnormalities affecting blood coagulation (thrombophilia), such as factor V Leiden and protein C deficiency. Individuals with inherited thrombophilia have a 16 times increased risk of venous thrombosis compared with a normal population. A genetic test can be performed to detect thrombophilia.

Quality of life in relation to health is the subjective effect of illness and its consequent therapy upon a patient. Quality of life is increasingly seen as an important outcome measure in scientific research. The impact of venous thrombosis on quality of life has not gained much attention in the scientific literature. This is remarkable, because venous thrombosis is a potentially fatal illness that often has chronic consequences. Therefore, venous thrombosis will probably have a large impact on the quality of life of patients.

Research has indicated that an increased risk of disease, such as thrombophilia, may influence daily life. Knowing that one has an increased risk of a disease, may increase disease worry. This justifies research about the psychological impact of genetic testing for thrombophilia. The psychological consequences of genetic testing for thrombophilia have only received limited attention in the scientific literature.

Research has shown that quality of life in chronic patients can not be explained by mere biomedical variables. In explaining health outcomes, such as quality of life, Leventhal's Common-Sense Model (CSM) can be a useful model. The model describes how a patient processes information about his illness through a cognitive and emotional pathway, and develops illness perceptions. Furthermore, the model describes how these illness perceptions can influence health outcomes, such as quality of life. Illness perceptions include five components: the symptoms that patients associate with their illness (identity), their beliefs about the etiology (cause), the outcome (consequences), the duration (timeline) and the controllability (cure/control) of the illness. Earlier research found that illness perceptions play an important role in explaining quality of life in chronic patients. One of the premises of the Common-Sense Model is that illness perceptions are derived not only from direct somatic or symptomatic experience but also from information available in the external social environment.

Therefore it is likely that the Common-Sense Model will prove to be a useful model in explaining outcome in individuals who are at risk of a certain illness.

Since 1985 a large North-American family (n~800) with protein C deficiency has been the subject of many studies (IPCI: International Protein C Investigation). A family of this size is ideal to study the psychological aspects of genetic testing for thrombophilia. Collaboration between the Department of Clinical Epidemiology (LUMC), the Unit of Psychology (LUMC) and the Department of Pathology of the University of Vermont (VT, USA) was established. This collaboration resulted in several studies on quality of life in patients with venous thrombosis and the psychological impact of thrombophilia testing, of which the results are described in this thesis.

The studies described in this thesis had two main aims:
1) To study the quality of life of patients with venous thrombosis and to examine the role of illness perceptions in explaining the quality of life of these patients.
2) To assess the psychological consequences of genetic testing for thrombophilia, using the Common-Sense Model as a theoretical framework.

The first aim of this thesis was addressed in chapters 2, 3, and 4. Chapter 2 describes a literature review that discusses all papers about quality of life in patients with venous thrombosis and other venous diseases that were published between 1996 and 2003. A total of 25 papers were identified, of which only 4 specifically dealt with the assessment of quality of life in patients with venous thrombosis. Main results of these studies indicate that patients with venous thrombosis are impaired in their physical, social, and psychological functioning, and that this impairment is related to the severity of the post-thrombotic syndrome. Other studies dealt with quality of life assessment in patients with other venous diseases, such as chronic venous insufficiency, venous leg ulceration, and varicose veins. The remaining articles examined the effect of different types of treatment for venous thrombosis on quality of life.

Chapter 3 describes the results of a study in which quality of life in 45 patients with venous thrombosis was assessed. Quality of life was assessed with a generic measure, the SF-36, and a newly developed disease-specific measure, the VT-QOL. The VT-QOL was developed specifically for use in this patient population. Most patients in this study had their last thrombotic event some years ago. The results of this study indicated that the patients were still impaired in their daily functioning. They also experienced social and psychological impairment as a result of their venous thrombosis. Quality of life was related to self-reported symptoms and the presence of the postthrombotic syndrome. Furthermore, the VT-QOL appeared to be more sensitive to the specific problems patients with venous thrombosis are facing, than the SF-36.
Chapter 4 describes the illness perceptions of the same group of 45 patients and assesses how these perceptions relate to the quality of life of the patients. Illness perceptions were

assessed using the Illness Perception Questionnaire-Revised (IPQ-R) and quality of life was assessed with the SF-36. Patients in this study believed that their illness would be prolonged and that their symptoms were not cyclical. They mostly attributed their venous thrombosis to bad luck or hereditary factors. The illness perceptions 'timeline' (the belief that the illness will have a long duration), 'personal control' (the belief in less personal control over the illness), 'identity' (the attribution of more symptoms to the illness) and the cause 'heredity' were the best predictors of quality of life scores.

Results of the studies described above show that the effect of venous thrombosis on quality of life should not be underestimated, even some years after the venous thrombosis. Furthermore, results give an indication that besides the presence of the post-thrombotic syndrome, illness perceptions may help to explain quality of life in patients with venous thrombosis.

Chapters 5 and 6, which together form part 2 of this thesis, address the second aim of this thesis. The study described in chapter 5 explored the attitudes toward genetic testing for heritable thrombophilia in the family with a high incidence of protein C deficiency described above. The questionnaire used in this study consisted of items about the beliefs in the psychological and health benefits of testing, beliefs in psychological distress after testing, risk perception, and thrombosis worry. Furthermore, knowledge about other risk factors for venous thrombosis, dispositional anxiety, and interest in getting a genetic test in non-tested individuals were assessed. Three groups of participants filled out the questionnaires. The total sample consisted of 168 family members of whom 76 had not been tested for protein C deficiency before. 92 participants had been tested previously, of whom 34 participants had protein C deficiency, and 58 participants did not have protein C deficiency. None of the participants had ever experienced venous thrombosis. The main conclusion of this study is that the psychological and health benefits of testing are perceived as higher than the psychological distress following the test. Perceived risk for venous thrombosis was not associated with any of the attitudes towards the test or with interest in getting a genetic test. Worry about venous thrombosis and dispositional anxiety were related to psychological distress following the test result and in interest in getting tested. This indicates that certain vulnerable individuals (with higher levels of dispositional anxiety) experience more negative consequences of receiving a positive test result for thrombophilia.

In chapter 6 the Common-Sense Model was applied to predict risk perception and worry in individuals with a genetic predisposition to venous thrombosis. A total of 174 participants with thrombophilia completed a questionnaire, consisting of the IPQ-R and items about risk perception and thrombosis worry. 55% of the participants had suffered from venous thrombosis. Results of this study show that individuals with and without a history of venous thrombosis had similar perceptions of the disease. Young age and a history of venous thrombosis appeared to be related to perceived risk of getting

venous thrombosis. Illness perceptions had only limited influence on risk perception. Thrombosis worry could be better explained by illness perceptions than risk perception. Perceptions about the symptoms related to venous thrombosis (identity) and the consequences of venous thrombosis (consequences) were the strongest predictors of thrombosis worry. These results support the premise of the Common-Sense Model - that illness perceptions are derived not only from direct somatic or symptomatic experience but also from information available in the external social environment.

This part of the thesis shows that genetic testing for thrombophilia does not have many adverse psychological consequences. However, certain vulnerable individuals may still experience considerable worry about getting venous thrombosis. Furthermore, results indicate that the Common-Sense Model can act as a useful framework to enhance understanding of how factors contribute to influence psychological response to risk of disease.

In chapter 7, the main results of the studies in this thesis are summarized and discussed. In addition, some recommendations for clinical practice and further research are given in this chapter.

Samenvatting

Veneuze trombose is een ziekte die ontstaat door de vorming van een bloedstolsel in een ader. Veneuze trombose komt meestal voor in de benen, maar kan ook in andere lichaamsdelen voorkomen. Het stolsel blokkeert de bloedtoevoer in het betreffende lichaamsdeel, waardoor het lichaamsdeel pijn doet, gevoelig is, en er rood en gezwollen uit ziet. In sommige gevallen breekt een stukje van het stolsel af, en komt het vast te zitten in de longen, waar het een (mogelijk fatale) longembolie veroorzaakt. Tot 50% van alle patiënten met veneuze trombose blijft chronische klachten houden. Dit wordt het posttrombotisch syndroom genoemd. Veneuze trombose komt jaarlijks bij 1-2 op de 1000 mensen voor.

Veneuze trombose kan door verworven en genetische risicofactoren worden veroorzaakt. Verworven risicofactoren voor veneuze trombose zijn onder andere het gebruik van orale anticonceptie ('de pil'), overgewicht, chirurgie, en langdurig stilzitten, bijvoorbeeld tijdens een lange vlucht. Genetische risicofactoren zijn aangeboren afwijkingen in de bloedstolling (stollingsafwijkingen), zoals factor V Leiden en proteïne C deficiëntie. Mensen met een stollingsafwijking hebben een 16 maal verhoogd risico op veneuze trombose ten opzichte van de normale bevolking. Een genetische test kan worden uitgevoerd om een stollingsafwijking vast te stellen.

Kwaliteit van leven in relatie tot gezondheid is het subjectieve effect van een ziekte en de behandeling op de patiënt. Kwaliteit van leven is een belangrijke uitkomstmaat in veel wetenschappelijk onderzoek. De invloed van veneuze trombose op het leven van de patiënt is weinig onderzocht. Dit is opmerkelijk, aangezien veneuze trombose een potentieel dodelijke ziekte is die vaak chronische consequenties met zich meebrengt. Veneuze trombose zal daarom waarschijnlijk een grote invloed hebben op de kwaliteit van leven van de patiënt.

Uit onderzoek is gebleken dat een verhoogd risico op een ziekte, zoals bij een stollingsafwijking het geval is, van invloed kan zijn op het dagelijkse leven. Kennis van een verhoogd ziekterisico kan bezorgdheid over het krijgen van de ziekte veroorzaken. Dit rechtvaardigt onderzoek naar de psychologische invloed van het testen van stollingsafwijkingen. De psychologische gevolgen van het testen op stollingsafwijkingen hebben echter tot op heden in de wetenschappelijke literatuur nauwelijks aandacht gekregen.

Onderzoek heeft uitgewezen dat kwaliteit van leven bij chronisch zieke patiënten niet alleen door medische variabelen kan worden verklaard. Bij het verklaren van ziekteuitkomsten, zoals kwaliteit van leven, kan Leventhal's 'Common-Sense Model' (CSM) een bruikbaar model zijn. Het model beschrijft hoe een patiënt via cognitieve en emotionele mechanismen informatie over zijn ziekte verwerkt en ziektepercepties ontwikkelt. Vervolgens geeft het model aan hoe deze ziektepercepties klinische uitkomsten, zoals kwaliteit van leven, beïnvloeden. De ziektepercepties bestaan uit 5 componenten: percepties over de klachten die bij de ziekte horen (identiteit), de duur van de ziekte (tijdsduur), de gevolgen van de ziekte (consequenties), de oorzaken van de ziekte (oorzaken) en de behandelbaarheid of beheersbaarheid van de ziekte (genezing/beheersing). Eerder on-

derzoek wijst uit dat kwaliteit van leven van chronisch zieke patiënten in hoge mate wordt bepaald door hun ziektepercepties. Een van de vooronderstellingen van het Common-Sense Model is dat ziektepercepties niet alleen door directe of symptomatische ervaringen worden gevormd, maar ook door informatie uit de sociale omgeving. Het is daarom waarschijnlijk dat het Common-Sense Model ook een nuttig model zal zijn voor het verklaren van uitkomsten bij patiënten met een verhoogd risico op een ziekte.

Sinds 1985 is een grote Noord-Amerikaanse familie (n~800) met proteïne C deficiëntie het onderwerp van diverse studies geweest (IPCI: International Protein C Investigation). Zo'n familie is een ideale onderzoekspopulatie om de psychologische gevolgen van het testen op stollingsafwijkingen te bestuderen. Een samenwerking tussen de afdelingen Medische Psychologie en Klinische Epidemiologie, LUMC, en de Universiteit van Vermont (VT, USA) werd aangegaan. Dit heeft geresulteerd in diverse studies naar de kwaliteit van leven van patiënten met veneuze trombose, en de psychologische gevolgen van het testen op stollingsafwijkingen. De resultaten van deze studies staan in dit proefschrift beschreven.

De studies in dit proefschrift hadden twee doelen:
1. Het bestuderen van de kwaliteit van leven van patiënten met veneuze trombose. Hierbij wordt de rol van ziektepercepties in de verklaring van de kwaliteit van leven van deze patiënten meegenomen.
2. Het bestuderen van de psychologische invloed van het testen op stollingsafwijkingen, waarbij het Common-Sense Model als theoretisch kader wordt gebruikt.

Deel 1 van het proefschrift, hoofdstukken 2, 3, en 4, behandelt het eerste doel. Hoofdstuk 2 beschrijft een literatuuronderzoek waarin alle artikelen worden besproken die tussen 1996 en 2003 over kwaliteit van leven bij patiënten met veneuze trombose en andere veneuze ziekten zijn gepubliceerd. Vijfentwintig artikelen werden gevonden, waarvan slechts vier artikelen specifiek onderzoek over de kwaliteit van leven van patiënten met veneuze trombose bespraken. Deze studies vonden dat patiënten met veneuze trombose zowel in hun fysiek, sociaal, als mentaal functioneren beperkt zijn, en dat deze beperking samenhangt met de ernst van het posttrombotisch syndroom. Andere artikelen behandelden studies over kwaliteit van leven van patiënten met andere veneuze ziekten, zoals spataderen, open wonden en flebitis. De overige artikelen bespraken de invloed van verschillende behandelvormen voor veneuze trombose op kwaliteit van leven.

In hoofdstuk 3 worden de resultaten van een onderzoek beschreven waarin de kwaliteit van leven van 45 patiënten met veneuze trombose met een generieke vragenlijst (de SF-36), en een ziekte-specifieke vragenlijst (VT-QOL) werd gemeten. De VT-QOL werd speciaal voor deze groep patiënten ontwikkeld. De laatste keer dat de patiënten veneuze trombose hadden was in veel gevallen al enige jaren geleden. De resultaten van deze studie wezen uit dat de patiënten in dit onderzoek nog steeds beperkt waren in hun

dagelijks functioneren. Zij ondervonden ook sociale en psychologische nadelen van de doorgemaakte trombose. Vooral patiënten met het posttrombotisch syndroom, en patiënten die zelf aangaven nog steeds veel lichamelijke klachten te hebben, hadden een lagere kwaliteit van leven vergeleken met populatienormen. Tevens bleek de VT-QOL beter geschikt dan de SF-36 om de specifieke problemen waar trombosepatiënten mee te maken hebben te detecteren.

Hoofdstuk 4 beschrijft de ziektepercepties van dezelfde groep van 45 patiënten en kijkt hoe deze percepties samenhangen met de kwaliteit van leven van de patiënten. Ziektepercepties werden met de Illness Perception Questionnaire-Revised (IPQ-R) gemeten, en kwaliteit van leven werd door middel van de SF-36 bepaald. Patiënten in dit onderzoek geloofden dat hun ziekte lang zou duren en geloofden niet dat de symptomen van hun ziekte cyclisch waren. De oorzaak van hun ziekte schreven zij vooral aan pech en genetische factoren toe. De ziektepercepties 'tijdslijn' (het idee dat de ziekte langer zal duren), 'beheersing' (het ervaren van minder controle over de ziekte), 'identiteit' (het toeschrijven van meer symptomen aan de ziekte) en 'genetische oorzaak' (het toeschrijven van de ziekte aan genetische factoren) hingen samen met een slechtere kwaliteit van leven.

Bovenstaand beschreven onderzoeken laten zien dat het effect van veneuze trombose op de kwaliteit van leven van patiënten met veneuze trombose ook enige jaren na het doormaken van de trombose niet onderschat moet worden. Verder blijkt dat naast het posttrombotisch syndroom ook ziektepercepties de kwaliteit van leven van patiënten met veneuze trombose bepalen.

Hoofdstukken 5 en 6, die samen deel 2 van dit proefschrift vormen, gaan in op het tweede doel van dit proefschrift. De studie beschreven in hoofdstuk 5 onderzocht de attitudes ten opzichte van genetisch testen voor stollingsafwijkingen in de eerder beschreven familie met een hoge incidentie van proteïne C deficiëntie. De daarbij gebruikte vragenlijst bestond uit vragen over gezondheids- en psychologisch voordeel van testen, psychologisch lijden na het testen, en vragen over risicoperceptie en bezorgdheid over het krijgen van trombose. Verder werden de kennis over de oorzaken van veneuze trombose, de interesse van niet-geteste familieleden in het krijgen van een test, en de dispositionele angst van de deelnemers bepaald. Drie groepen familieleden vulden de vragenlijsten in. De totale onderzoekspopulatie bestond uit 168 familieleden. 76 deelnemers waren niet eerder getest op proteïne C deficiëntie. 92 deelnemers waren wel getest, waarvan 34 positief en 58 negatief waren voor proteïne C deficiëntie. Geen van de deelnemers had ooit veneuze trombose gehad. De belangrijkste conclusie van dit onderzoek is dat de deelnemers de gezondheids- en psychologische voordelen van het genetisch testen zwaarder lieten wegen dan de nadelen (psychologisch leed). Risicoperceptie bleek niet gerelateerd te zijn aan attitudes ten opzichte van de test of aan interesse in het ondergaan van een test. Wel bleken bezorgdheid voor het krijgen van trombose en dispositionele angst te

relateren aan psychologisch leed en aan de interesse om getest te worden. Dit geeft aan dat individuen met een bepaalde kwetsbaarheid (zoals dispositionele angst) meer nadelen van genetisch testen voor stollingsafwijkingen ondervinden.

In hoofdstuk 6 wordt het Common-Sense Model toegepast om risicoperceptie en bezorgdheid over trombose bij mensen met een stollingsafwijking te verklaren. Een groep van 174 deelnemers met een stollingsafwijking vulde een vragenlijst in, bestaande uit de IPQ-R, en aangevuld met vragen over risicoperceptie en bezorgdheid. Van alle deelnemers had 55% trombose gehad. De resultaten van dit onderzoek laten zien dat de ziektepercepties van de deelnemers met of zonder een trombosegeschiedenis niet van elkaar verschilden. Verder bleken vooral een lagere leeftijd en een trombosegeschiedenis van invloed te zijn op risicoperceptie. Ziektepercepties droegen weinig bij aan het verklaren van risicoperceptie. Bezorgdheid over het krijgen van trombose was beter te verklaren door ziektepercepties dan risicoperceptie. De percepties over de klachten bij trombose (identiteit) en over de gevolgen van trombose (consequenties) waren de sterkste voorspellers. Deze resultaten ondersteunen de vooronderstelling van het Common-Sense Model, dat ziektepercepties niet alleen ontstaan via persoonlijke ervaring met de ziekte, maar ook via informatie uit de omgeving, zoals bij het hebben van een genetisch verhoogd risico het geval is.

Dit deel van het proefschrift laat zien dat het testen op stollingafwijkingen weinig negatieve gevolgen heeft. Desondanks kunnen bepaalde kwetsbare individuen veel bezorgdheid over het krijgen van trombose ervaren. Verder bleek het Common-Sense Model nuttig bij het verkrijgen van inzicht op de verschillende factoren die de psychologische invloed van een verhoogd ziekterisico beïnvloeden.

In hoofdstuk 7 worden de belangrijkste resultaten van de studies uit dit proefschrift samengevat en bediscussieerd. Ook worden in dit hoofdstuk aanbevelingen voor de klinische praktijk en vervolgonderzoek gedaan.

Dankwoord en Curriculum Vitae

Dankwoord

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Curriculum Vitae

Inez van Korlaar werd op 29 augustus 1978 te 's Hertogenbosch geboren. Nadat zij in 1996 haar VWO diploma aan het Jeroen Bosch College in 's Hertogenbosch behaalde, begon zij datzelfde jaar aan een studie Gezondheidswetenschappen aan de Universiteit Maastricht. Tijdens haar studie volgde Inez keuzeonderwijs aan de University of Linköping in Zweden. Daarnaast voltooide zij een onderzoeksstage bij de Pain Research Unit in het Sydney Children's Hospital in Australië. In 2001 behaalde zij haar doctoraal diploma met als afstudeerrichting Geestelijke Gezondheidkunde. In december van datzelfde jaar trad Inez in dienst als promovenda bij de afdeling Medische Psychologie van het Leids Universitair Medisch Centrum. Aldaar heeft zij onder leiding van Prof. dr. A. A. Kaptein (Medische Psychologie) en Prof. dr. F. R. Rosendaal (Klinische Epidemiologie en Hematologie) het promotieonderzoek uitgevoerd dat in dit proefschrift beschreven staat. Tijdens haar promotieonderzoek werkte zij enige tijd op de afdeling Pathologie van de University of Vermont (Burlington, USA) onder leiding van Prof. dr. E.G. Bovill.