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Preventing Venous Thromboembolism: Prophylactic Options for Patients at Different Risk Levels

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Preface

Evidence is scarce in many fields of medicine, and the evidence that does exist is often either disputed or of limited relevance for the treatment of specific patient conditions. Nevertheless, physicians need to make treatment decisions on a daily basis, attempting to deliver the best possible treatment to patients in need of care. In the case of prophylaxis of venous thromboembolism (VTE), not only are the treatment options not agreed upon, but a key determinant of appropriate care—the risk posed to individual patients—is difficult to assess.

This report describes the efforts of an international project team to quantify the level of risk posed by different VTE risk factors and, at the same time, to assess the appropriateness of 11 prophylactic treatment options for several medical conditions and surgical interventions. The project made use of a variety of group-based risk assessment tools and the RAND/UCLA Appropriateness Method, all on the basis of a review of the scientific literature on the aetiology of VTE.

The report is of interest to people concerned with the prevention of VTE, as well as scholars and others who are interested in medical decision making, including risk assessment, appropriateness of care, and the use of expert panels to develop quantitative judgements. The main product of the project is a *DecisionMatrix*™ in the form of a CD ROM, available through Sanofi-Synthelabo, which is useful for physicians who must decide whether or not to provide prophylaxis for the prevention of VTE for their patients, and to decide which prophylactic therapy and for how long it should be given.

The background data supporting this report are available upon request to EVIDIS or RAND Europe. These data include preliminary ratings rounds, extended exploratory analyses, and instructions provided to participants.

This project was conducted as a collaborative effort by a core taskforce consisting of a group of experts (see Chapter 2 for their names), EVIDIS from France, RAND Europe from the Netherlands and Sanofi-Synthelabo Group. The taskforce was chaired by Prof. M.M. Samama (Paris, France). Of the authors, Kahan, de Vries and

van Beusekom are from RAND Europe, Cornelis is from EVIDIS, and Wietlisbach is from the Centre Hospitalier Universitaire de Vaud, Lausanne, Switzerland.

The scientific authors of this study note here for the record that the study was sponsored by Sanofi-Synthelabo, but that the potential benefits of Sanofi-Synthelabo products compared to their competitors were never a criterion in any of the analyses, and that the results have not been subject to approval by Sanofi-Synthelabo.

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Executive summary

Background and objectives

Venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality for many patients. Thromboprophylaxis may be effective in preventing these venous thromboembolic events. Whether or not to apply thromboprophylaxis and what sort is a decision that is based upon numerous factors, for which there often does not exist a consensus within the treatment community. There is a need for a consolidation of evidence and experience to create basic guidelines for practitioners and priorities for near-term clinical and pharmacological research.

The orientation adopted in the present study, consistent with the weight of the scientific community investigating thromboprophylaxis, is that the risk a patient incurs is the critical factor in clinical decision-making. This risk may be grouped into those factors based on the patient's individual characteristics ("predisposing risk factors") and those factors based on the medical condition or surgical intervention the patient might undergo ("exposing risk factors"). For purposes of making a clinical decision, these two groups of risk factors must be combined into an overall risk, which then provides a major key in determining whether and what sort of prophylaxis for preventing VTE is appropriate. No risk assessment model currently available has achieved uniform acceptance for individualised patient profiling of VTE risk. This study aims to create such a model and link it to the appropriateness of various prophylactic options.

This report describes the methods used and the results obtained in answering the following four questions:

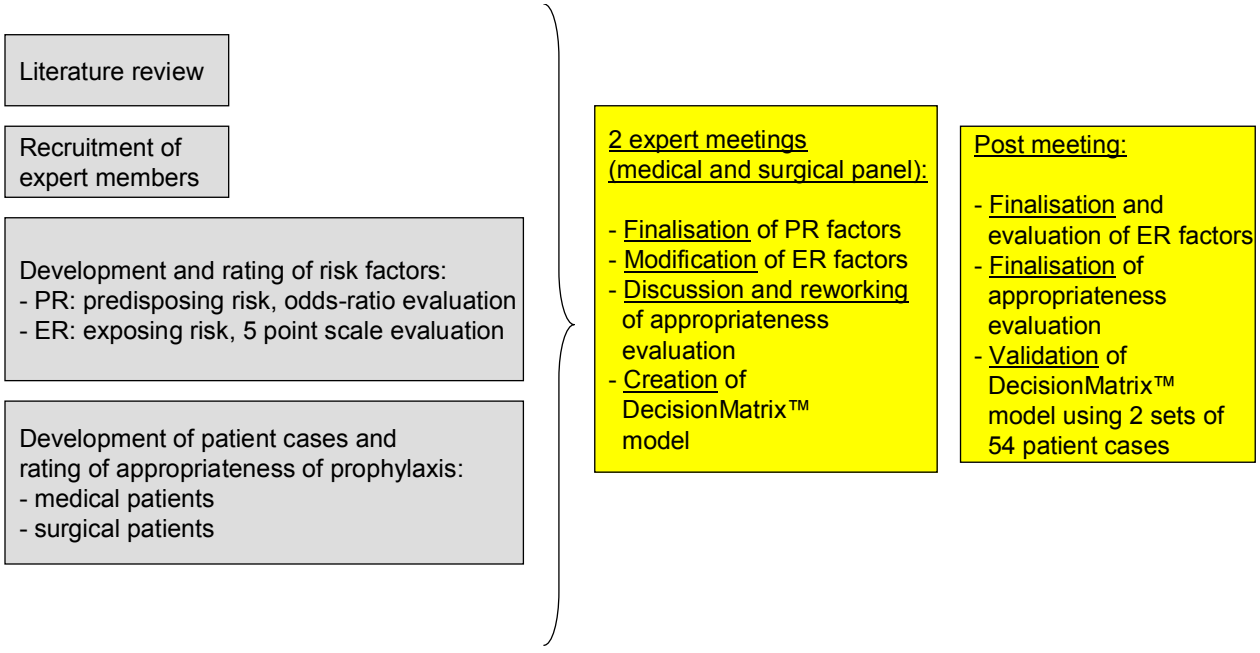
- How severe is the predisposing risk of VTE for different patient characteristics?
- How severe is the exposing risk of VTE for different medical conditions and surgical interventions?
- How may these two separate risk assessments be combined to provide an overall assessment of risk?

- For which patients do the expected benefits of each of a variety of prophylactic treatments available outweigh the possible risks?

Answering these questions allowed us to develop a tool that may be used by the typical health care provider faced with deciding whether or not to employ prophylaxis to prevent VTE, and if so, what type of prophylaxis, in what dosage and for what duration.

Methods

This study was conducted by a structured sequence of tasks. It was accomplished by forming two international panels of experts, one medical and one surgical, and using these panels directly—through their own efforts on the major tasks of the study—and indirectly—through using their good services to recruit their colleagues for specific tasks of the study. The different steps are outlined in the following schema:



PR: predisposing risk; ER: exposing risk

The methods used in the study were the following:

- We conducted a literature review of the state of knowledge on risk factors of VTE and the effects of various prophylaxis regimens available. This literature review served as the basis for all of the subsequent tasks.

- We recruited two international panels of experts on the prevention of VTE, one medical and one surgical. These panels provided expert opinion in light of the literature review, on the estimation of risk and appropriateness of treatment.
- We developed and administered a scale to assess the degree of predisposing risk presented by medical or surgical patients. The development was done by an iterative rating of odds-ratios (compared to a "base case" of a patient with none of the predisposing risks).
- We developed and administered a set of 5-point Likert-type scales to assess the degree of exposing risk possessed by a patient presenting with a medical condition or for a urological, gynaecological or general surgical procedure. These surgical conditions were chosen due to their uncertainty regarding the level of risk. The development was done first by the expert panels (separately for medical and surgical exposing risk) and then by "snowball" referral by the panel to their colleagues.
- Based upon the consensus of meetings held separately by the medical and surgical panels, we constructed a formula that converts both types of predisposing risk and exposing risk into a unique 4-level (low, moderate, high, very high) categorisation of patient risk of VTE.
- We developed two sets of simulated patient descriptions ("cases") that systematically varied the degrees of predisposing and exposing risk. These cases—one set of medical conditions and one set of general surgical interventions, were assessed holistically for the risk of VTE of these simulated patients. The holistic risk was compared to the risk calculated by the formula in order to test the validity of the formula.
- We developed and administered two RAND/UCLA Appropriateness Method instruments for eleven different prophylactic alternatives (including no prophylaxis). One instrument was used with the medical panel and one with the surgical panel. Both panels rated the following alternatives:
    - no prophylaxis
    - acetyl salicylic acid (ASA) used at prophylactic doses
    - graduated compression stockings alone
    - vitamin K antagonist, such as warfarin
    - unfractionated heparin (UFH)

- low molecular weight heparins (LMWH) (classified related to equivalent labelling):
  - enoxaparin 20 mg or dalteparin 2500 IU
  - enoxaparin 40 mg or dalteparin 5000 IU
  - nadroparin 0.3 ml
  - nadroparin body weight adjusted
- combined UFH or LMWH and compression stockings
- prolonged prophylaxis up to 6 weeks

- We refined our measurement tools in order to end with validated, reliable measures of overall risk and appropriateness.

Results

The methods produced robust results to construct the desired guidelines tool.

Predisposing risk. Although we originally envisaged a single measure of predisposing risk that would be applicable to all patients, the study showed that predisposing risk is better considered in two categories. Therefore, we separated the predisposing risk into two separate scores termed "general predisposing risk" and "inherent major predisposing risk", with each score using a heuristically-developed method of combining different non-independent predisposing risks that are present in a single patient. These scores were further simplified by setting cut-off scores separately for surgical and medical patients that divided general predisposing risk into "high" and "low" categories and divided inherent major predisposing risk into "high", "moderate" and "low" categories.

Exposing risk. The panel of medical experts was able to rate in a consistent manner the exposing risk for the conditions we presented to them. The panel of surgical experts expressed discomfort rating surgical conditions outside their own speciality. Therefore, we expanded the group of raters by asking the experts to recruit colleagues within the needed specialities. These separate groups of general surgeons, urologists and gynaecologists rated in a consistent manner exposing risks for the procedures they perform, all on the 5-point Likert-type scale.

Overall risk measure. During the meetings of the two expert panels, a matrix that expressed a formula for integrating the two predisposing risk scales and the exposing risk scale into a unique 4-level measure of overall risk was constructed. The validity of this measure was tested by comparing the formula's prediction of overall risk with that produced for two sets of 54 constructed patient cases (one medical and one general surgical). The formula agreed with the experts in about 70 percent of the cases; the disagreements were always only one level different from the expert judgements, and were much more likely to overstate than to understate the risk. This result therefore is in absolute concordance with the high standards in the healthcare field.

Appropriateness. We assessed the appropriateness of prophylaxis using a recognised method. The results regarding appropriateness, over both the medical and surgical panels, may be summarised as follows:

- If there really is any risk, then "no treatment" is appropriate. And, correspondingly, any other treatment is inappropriate.
- For surgical patients, compression stockings alone are acceptable (essentially in combination with UFH and LMWH), but for medical patients they are not.
- Surgical patients with either low or moderate overall risk should be given low dosages of LMWH as much as possible, shifting to high dosages only if the risk increases. For medical patients, higher dosages of heparin were more generally appropriate.
- Unfractionated heparin was generally viewed as inappropriate for surgical patients. For medical patients, the benefit of unfractionated heparin outweighed the risks, but greater benefit was provided by LMWH.
- Acetyl salicylic acid and vitamin K antagonists were generally not viewed as appropriate by either panel.
- Prolonged prophylaxis was considered appropriate for medical and surgical patients with a very high overall risk but its use was considered uncertain for those with a high overall risk.

Conclusion

This study examined the measurement of predisposing risk, exposing risk, and the appropriateness of various forms of prophylaxis for the prevention of VTE that might

accompany medical or surgical treatment. The primary objective of the study was the development of measurement techniques to aid the clinical practitioner. Along the way, we learned a number of useful pieces of information.

- The literature regarding prophylaxis of VTE is extensive, but still rudimentary. There is a need for more scientific evidence on the degree of risk posed by both general and inherent predisposing factors, and for further detail on exposing risk for different procedures.
- The risk of VTE is real, in the sense that the chances of VTE are overall not slight, and the general awareness of this risk by the typical practitioner is not as high as is needed to ensure the best quality care. Part of this lack of general awareness results from the lack of scientific evidence, as mentioned above, and is partly due to a lack of consensus in the expert community regarding the degree of risk.
- There is a consensus, at least amongst the two panels we assembled, that prophylaxis is appropriate whenever the risk is higher than low or insignificant. This statement, going back to our definition of "appropriate" means that the potential benefits of prophylaxis outweigh their potential harms, without considering the economic costs of the treatment.
- Given that one should engage in prophylaxis, there was a consensus that low molecular weight heparin is the preferred treatment, although for some situations, unfractionated heparin provides equivalent or nearly equivalent benefit. Other treatments, including acetyl salicylic acid, vitamin K antagonists and compression stockings in the absence of medication, were not viewed as providing good benefit-to-harm ratios.

As stated above, the primary purpose of this project was the development of a decision aid. The measures of risk and the appropriateness ratings were combined into a tool in the form of a *DecisionMatrix*™ for the appropriateness of prophylaxis of VTE. This decision aid provides, in a user-friendly form, the results of a uniform and systematic compilation of both the scientific evidence and the consensus of opinion among the leading experts in the field of VTE prevention. The contents of the *DecisionMatrix*™ are the results of an expert panel process based upon a comprehensive review of the literature and should in no case replace the advice of health professionals taking into account different national regulations regarding

prescribing. *DecisionMatrix™,* in the form of a CD ROM, is available as a public service by Sanofi-Synthelabo.

Table of contents

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Chapter 1: Introduction

1.1. Background and objectives

Venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality for a wide group of patients in many different medical conditions or surgical treatments. Thromboprophylaxis may be effective in preventing these venous thromboembolic events (Geerts, et al., 2001).

Whether or not to apply thromboprophylaxis and what type is a decision based upon numerous factors, for which there often does not exist a consensus within the medical community. This lack of consensus is based in part on a lack of basic scientific evidence. But even the evidence that does exist is not well-disseminated to the practitioner community. There is a need for a consolidation of evidence and experience to create basic guidelines for practitioners and priorities for near-term clinical and pharmacological research.

The orientation adopted in the present study, consistent with the weight of current evidence, is that the risk a patient incurs is the critical factor in clinical decision-making concerning prophylaxis. A patient's individual thromboembolic risk is influenced by numerous factors, which may be grouped into those based on the patient's individual characteristics ("predisposing risk factors") and those based on the medical condition or surgical intervention the patient might undergo ("exposing risk factors"). These two groups of risk factors must be combined into an overall assessment of risk, which in turn is key in determining whether and what sort of prophylaxis for preventing VTE is appropriate. A number of risk assessment models have been developed to construct instruments that stratify patients into risk groups—typically either three (low/moderate/high) or four (low/moderate/high/very high) in number (Nicolaides, et al., 2001; Geerts, et al., 2001). However, no risk assessment model currently available has achieved uniform acceptance for individualised patient profiling of VTE risk. This study aims to create such a model and link it to the appropriateness of various prophylaxis options.

The overall goals of this study are

(1) to create a validated risk assessment instrument to categorise the degree of risk of VTE for patients with a variety of medical conditions or undergoing surgical treatments and
(2) to determine whether or not it is appropriate to employ prophylaxis, and, if so, what kind, what dosage of medications, and for what duration.

Both the risk assessment model and the determination of appropriateness are intended to be employed in a decision aid tool to be used as part of a judgement by physicians as to whether and what type of prophylaxis of VTE to give their patients and for how long. The decision tool developed in this project, called the *DecisionMatrix™ for Prophylaxis of VTE* has resulted from a uniform and systematic compilation of both the scientific evidence and the consensus of opinion among the leading experts in the field of VTE prevention.

In order to reach these goals and to create the decision aid, we developed and validated ways to answer the following four questions:

(1) How severe is the predisposing risk of VTE for different patient characteristics?
(2) How severe is the exposing risk of VTE for different medical conditions and surgical interventions?
(3) How may these two separate risk assessments be combined to provide an overall assessment of risk?
(4) For which patients do the expected benefits of prophylactic treatment outweigh the possible risks?

1.2. Overview of this report

The next chapter provides a description of the methods we used to address the four questions posed immediately above. A key feature of these methods was the use of two international panels of medical and surgical experts in VTE, who provided both quantitative and qualitative expressions of their opinions in a two-iteration series of measurements preceded and followed by an open discussion. In chapter three we describe and analyse the results of the study. This chapter is somewhat detailed, and assumes at least a moderate background in statistics and/or medicine. In chapter four, we conclude by answering the research questions and give recommendations for implementation of the results in the form of the *DecisionMatrix™* and guidelines for appropriate prophylactic care.

Chapter 2: Approach and methodology

2.1. Overview of methodologies

In this study, we used a combination of quantitative and qualitative methods. Basically, our approach consisted of three parts:

- We assembled a taskforce to study the problem and structure the research project.
- We obtained a review of the scientific literature on prophylaxis of VTE.
- We recruited two multinational panels of experts on prophylaxis, one for medical conditions and the other for general surgical, urological and gynaecological surgical procedures.
- We developed measures of predisposing and exposing risk, based upon the literature review and the expertise of the taskforce, which were iteratively rated and revised by the two panels. The first round of rating was done by the panel at home. Each panel then met to discuss the ratings and individually re-rate. Finally, further ratings were obtained in some cases when the panellists returned home.
- In conjunction with the development of the risk assessment measures, we constructed and fielded an assessment of the appropriateness of 11 different prophylaxis treatments of VTE, using the RAND/UCLA appropriateness method. Like with the risk assessment measures, this was done iteratively with the panel, including a first round at home, a second round immediately following a group meeting and discussion, and some further ratings upon returning home.
- All of the risk assessment and appropriateness ratings were analysed. The risk assessments were integrated into a unique 4-level measure of risk that was validated by holistic ratings of simulated patient cases done by an expanded group based upon the original two panels.

Thus, the overall research method can be characterised by the following three steps:

(1) asking the experts to express their opinion through a series of quantitative ratings provided on written questionnaires,

(2) discussing these ratings in a group discussion and then

(3) asking the experts for a second and sometimes a third series of ratings, in case of disagreement, on the same issues. The specific form of the

second ratings instruments could be and indeed was modified as a result of the group discussions.

This approach was followed for all four research questions, in order to obtain independent series of ratings for predisposing risk, exposing risk, overall risk and appropriateness. The advantage of having two rounds of ratings separated by a group discussion is that things that might not have been completely clear to the expert raters in the first round can be clarified during the group discussion. In addition to clarifying misunderstandings and different interpretations, the group discussion provides a means for the experts to attempt to convince each other by providing reasons for their opinions. Finally, but not least importantly, the group discussion provides an opportunity for the experts to recommend adjustments as well as additions or deletions to the instruments they rated in the first round. Within the philosophy of this methodological approach, the first round of ratings serves principally the purpose of making both expert raters and researchers familiar with the method and the data that will be obtained by it, while the second round produces the data analysed to achieve the research objectives.

In our analysis of the obtained data, we used a four-step approach to integrate all the different ratings into a unique instrument that could be used in constructing the *DecisionMatrix*™ for the appropriateness of prophylaxis of VTE. These three steps are:

1. The construction of measures of predisposing and exposing risk. One measure to estimate the magnitude of a comprehensive set of predisposing risks was built. Another pair of measures to estimate the magnitude of the exposing risk for a more delimited set of medical conditions and surgical interventions were built. The predisposing risk was assessed by asking experts to estimate the odds-ratio for each item in a list of predisposing risks against a "base patient" having none of the predisposing risks in the list. The exposing risk was assessed by rating the degree of risk for separate lists of medical conditions and surgical interventions on a 1-5 Likert-type scale. Both the medical and surgical lists were anchored by well-defined respective treatments with strong agreement concerning the degree of risk.

2. The calculation of the overall risk by integrating the predisposing and exposing risk measures. As we will show in chapter 3, the predisposing risk was separated into two subgroups: inherent major predisposing risks (personal

and family histories of VTE and critical blood factors predisposing for thrombosis) and other more general predisposing risks. The inherent major predisposing risks (three levels of risk), general predisposing risks (two levels of risk) and exposing risks (three levels of risk) were cast into a three-dimensional matrix, where each cell of the matrix yielded an overall risk assessment that was one of four values: low, moderate, high or very high.

3. The risk assessment provided by integration of the three types of risk was validated by constructing cases of hypothetical patients that spanned the range of possible risks, and asking an enlarged panel of experts to give a holistic rating of the risk posed for each patient case. These holistic ratings were compared to the ratings given by the integrated risk assessment.

4. The determination of the appropriateness of eleven different prophylactic treatments for individual patients. A list of patient descriptions (which we term "indications" but are sometimes referred to as "cases") were constructed by combining the four overall levels of risk with other clinical conditions that might influence whether and which prophylaxis to use. For each of these indications, the panel was asked to assess the relative benefit-to-harm degree for the individual patient described by the indication of 11 different prophylaxis treatments, ranging from "no prophylaxis" to extensive use of anti-thrombotic medications. This assessment was made on a scale of 1 (the expected harms greatly outweigh the expected benefits) to 9 (the expected benefits greatly outweigh the expected harms). The group's median judgement for each indication and treatment combination was screened for whether the group disagreed (defined formally) or not, and then classified as "appropriate," "uncertain" or "inappropriate" for the treatment under review. When the group disagreed, the indication was deemed "uncertain" no matter what the value of the median. In such cases the method can not make a statement favouring or not favouring the treatment and the decision is left to the individual physician who may wish to consider this treatment.

Before engaging in the ratings tasks, the panellists were provided with a review of the recent clinical literature on prophylaxis of VTE that provided a comprehensive overview of independent risk factors for VTE.

The key to the entire process were the two international panels of experts, who were recruited from their home areas by regional representatives of Sanofi-

Synthelabo. Tables 2.1a and 2.1b show the names, countries and specialisation of these doctors.

Table 2.1a. List of experts who participated in the surgical panel.

Name	**Country**	**Specialisation**
Arcelus JI	Spain	Surgery
Dahl OE	Norway	Surgery
Ganzon MSV	Philippines	Cardiology/ Vascular Surgery
Nurmohamed MT	The Netherlands	Surgery
Pantanawitz D	South Africa	Surgery
Park SY	South Korea	Haematology
Perez-Requejo JL	Venezuela	Haematology
Ramacciotti E	Brazil	Vascular Surgery
Souidan T	Egypt	Surgery
Tombal B	Belgium	Urological Surgery
Tripathi R	India	Surgery
Zakhariev T	Bulgaria	Surgery

Table 2.1b. List of experts who participated in the medical panel.

Name	**Country**	**Specialisation**
Ankri A	France	Haematology
Bouslama K	Tunisia	Internal medicine
Gherasim L	Romania	Internal medicine
Haas S	Germany	Internal medicine
Londono Trujillo D[1]	Colombia	Pneumology
Monreal M	Spain	Haematology
Pachenko EP	Russia	Cardiology/ Thrombology
Taher A	Lebanon	Haematology-Oncology
Tomkowski W	Poland	Internal medicine

[1] Due to a personal emergency, Dr. Londono Trujillo was not able to attend the two-day meeting, but he did complete the second-round ratings following telephone discussions.

Additional participants for the validation phase are listed in table 2.2.

Table 2.2. List of experts who participated in the validation phase.

Name	Country
Buchmuller-Cordien A	France
Guillot-Rivron K	France
Eikelboom J	Australia
Beltran	Philippines
Kesteven P	UK
Lef A Levin	Norway
Lodeiro	Venezuela
Khalil I	Lebanon
Veerman DP	The Netherlands
Constandache F	Romania
Fernandez AA	Venezuela
Arias J	Spain

2.2. Predisposing risk factors

The predisposing risk is the pre-existing clinical risk of the patient, i.e., the risk before he/she is admitted to the hospital; this risk is independent of the surgical procedure or medical condition for which he/she is admitted to hospital. The evaluation of this risk was performed using an odds-ratio (OR) measure. An odds-ratio is a statement of the difference in degree of risk of a phenomenon for two different situations, and represents this difference in terms of the multiplicative ratio between the situations. Therefore, the odds-ratio for situation A compared to situation B will be 1.00 if the risks are the same, less than 1.00 if situation A has the lesser risk, and greater than 1.00 if situation A has the greater risk.

Members of both the surgical and medical panels were asked in a rating form to determine the odds-ratio for 61 possible predisposing risk factors. The final lists of items are in Tables 3.1 and 3.2. The list was constructed by the task force group, based on the findings of the literature review and clinical expertise. Before fielding this instrument to the panels, five hospital interns completed a draft version of the rating form in order to test the comprehensibility and feasibility of the questionnaire.

For each separate item, the panel members were asked to assign an odds-ratio representing the risk of that particular patient characteristic or clinical situation, compared to a normal female person younger than 40, in a normal situation

without that particular characteristic. The odds-ratio for this "standard patient" is by definition 1.00. If the expert believes that a certain patient characteristic leads to a risk of VTE twice as high as the risk for the standard patient, he would give it a value of 2.00. If the characteristic would lead to a risk of VTE nine-and-one-third times as high as the standard patient, he would give an odds-ratio of 9.33. Tables 2.3 and 2.4 provide simplified examples of odds-ratio ratings to show how the questionnaire was constructed.

Table 2.3. Example 1

General patient characteristics	Definition	Odds-ratio
Sex	Male (compared to female)	1.10
Obesity	BMI > 30 kg/m^2	2.50
Family history of VTE	in first degree, parents or siblings	16.00

In the first column of both examples, the general patient characteristics are listed. Here, we show for purposes of example only three items: sex, obesity, and family history of VTE. Each is defined in the second column. Finally, in the last column, which was blank in the actual odds-ratio form, are hypothetical estimations of odds-ratios that might be provided. In example 1, the rater believes that being male represents a risk of 1.10 times versus female, having a Body Mass Index (BMI) over 30 represents 2.50 times as much risk of VTE as not being obese, and that having a family history of VTE represents 16 times the degree of risk of VTE as having no family history of VTE.

Table 2.4. Example 2

General patient characteristics	Definition	Odds-ratio
Sex	Male (compared to female)	0.85
Obesity	BMI > 30 kg/m^2	2.75
Family history of VTE	in first degree, parents or siblings	25.00

In case a certain predisposing risk would lower the risk of VTE, panel members could give an odds-ratio between zero and one (for example 0.5 means half the risk of VTE, compared to a normal person). In Example 2, the rater disagrees with the rater in Example 1 about whether males or females have higher risk. This rater believes that being male represents a risk of only 0.85 times as much as being female. While the direction of risk for obesity and family history of VTE are the same for this rater as for the rater in Example 1, the figures differ slightly for obesity but to a large degree for family history of VTE.

In case the expert believed that there were additional predisposing risk factors related to VTE, these could be added, together with definitions and odds-ratios, at

the end of the questionnaire. Few raters took advantage of this opportunity, and any such instances were discussed at the meeting.

For each OR we defined an (arbitrary) cut-off point, which would serve as a trigger for extensive discussion of that predisposing risk with the experts during the panel meeting. The following three measures were used:

1. Differences between ratings given by the surgical and medical panels. In most cases, there was agreement on predisposing risk between the experts in the medical panel and those in the surgical panel. For example, having a previous history of VTE classified as "proximal with or without distal DVT", was rated 6.16 on average by the surgical panel and 6.31 by the medical. However, in some cases there was much less agreement. For example, primary antiphospholipid syndrome (without another autoimmune disease) was rated 5.76 by the surgical panel compared to 9.14 by the medical panel. Whenever the average ratings of the two panels differed by more than a ratio of 1.00:1.50, we flagged that item for discussion.

2. *Spread of ratings among all panellists*. We also looked separately for each risk factor at the amount of agreement in both panels combined, by dividing the standard deviation by the geometric mean for all panellists. For example, the standard deviation of the predisposing risk related to being male is 1.18, which is large compared to the obtained mean value of 1.11. The cut-off point we used here for flagging an item was 1.00. Thus, all rated predisposing risks with a standard deviation equal to or higher than the geometric mean were presented to the panels for discussion.

3. *Comparison of highest and lowest given ratings*. Finally we calculated a measure of dispersion by dividing the rating of the 4^{th} highest individual in the combined panels by the 4^{th} lowest one. The reason for taking the 4^{th} highest/lowest was to exclude the outliers and therefore get a measure of general dispersion. Comparison ratios higher than 2.50 were flagged for discussion. For example, if the 4^{th} highest respondent gave an odds-ratio of 20.00, then if the 4^{th} lowest respondent gave a rating of 8.00 or less, that item would be flagged for discussion.

During the panel meetings, the panel members discussed and revised the list of predisposing risks, and then provided odds-ratios for the revised list. (This list is

presented in Chapter 3, Tables 3.1 and 3.2). In addition to the odds-ratios, the panel members were also asked to indicate the level of evidence they based their ratings upon. Panel members could indicate the following evidence levels:

A = randomised clinical trial or other strong evidence

B = weaker scientific evidence

C = consensus conference or promulgated guidelines

D = personal experience of the rater or colleagues.

The goal was explicitly not to ask what evidence exists – this was already clarified in the literature review. By giving the evidence base of their rating, the panel members could indicate what level of evidence they currently consider most useful for the specific predisposing risk factor. The evidence levels may also provide additional information to the researchers on reasons for disagreement among the panel members.

2.3. Exposing risk factors

The exposing risk is the risk incurred by the surgical procedure or the medical condition causing a patient to be admitted to hospital with the subsequent treatment received. The evaluation of this risk was assessed by ratings on a 5-point Likert-type scale from 1 (insignificant risk) to 5 (high risk). Exposing risk was defined as the added risk resulting from the intervention or treatment. The ratings were anchored by three relatively well established[2] reference points for the surgical and medical panels, respectively, as shown in Table 2.5.

Table 2.5. Definitions of exposing risk in medical and surgical panels

	Medical panel	Surgical panel
1 = Insignificant risk	Young patient with acute asthma	Diagnostic laparoscopy
2 = Minor risk	Condition between the ones rated 1 and 3	Condition between the ones rated 1 and 3
3 = Moderate risk	Heart failure, stages NYHA III or IV	Vaginal hysterectomy (non-cancerous situation)
4 = Substantial risk	Condition between the ones rated 3 and 5	Condition between the ones rated 3 and 5
5 = High risk	Acute stroke (with paralysis)	Repair of hip fracture

In the first round of ratings, exposing risk was assessed by the surgical panel for three different types of surgery:

- general surgery (42 items)
- gynaecological surgery (50 items)
- urological surgery (52 items)

[2] As established by the medical experts in the Task force.

For the medical panel, 25 different types of medical conditions were assessed.

The medical panel discussed exposing risk, made some modifications to the instrument, and then re-rated the exposing risk. The final items used are in Chapter 3, Table 3.3.

During the panel meeting, the surgical group also modified the exposing risk instrument, but expressed discomfort and lack of confidence in rating interventions outside of their own specialities. Therefore, instead of re-rating the indications by the surgical panel, the pool of experts was enlarged by asking both panels to identify and give the exposing risk instrument (modified during the panel discussion) to colleagues with the relevant surgical speciality (gynaecological/urological/general). This resulted in exposing risk being rated by a different groups (11 gynaecologists, 13 urologists and 16 general surgeons/anaesthetists) who rated the three separate instruments, respectively (shown in Tables 3.4, 3.5 and 3.6). Each of the original surgical panel members was in his or her own speciality rating group.

2.3. Overall risk measure

During the meetings of the two expert panels, a matrix that expressed a formula for integrating the two predisposing risk scales and the exposing risk scale into a unique 4-level measure of overall risk was constructed, based upon a consensus revealed during the discussions. The relationship between the three risk factors results in a three-dimensional measure which is presented in chapter 3.

2.4. Validation by cases

A set of patient descriptions (which we call here "cases") was constructed by taking the predisposing and exposing risk rating forms and checking off which overall risk was present. At the panel meetings, the participants were asked to give their holistic ratings of the risk faced by each case on a four-point scale of low/moderate/high/very high risk. The results of the preliminary validation did not meet the expectations - the correlation with integrated ratings was below average, the full range of possible risks was not represented, and there were inconsistencies in the patient descriptions. Therefore, this data set was reworked.

In its place, a more comprehensive set of patient cases was constructed for medical and surgical instances. For the surgical cases, only general surgical interventions were validated; it was assumed that if one type of surgical intervention worked, others would also work. The format of the cases was changed from check lists to a standard format narrative. A total of 54 medical cases and 54 general surgical cases were holistically rated as low/moderate/high/very high overall risk of VTE by 16 medical and 21 surgical specialists, respectively, again recruited by the panel members.

The following are some examples:

Medical cases:

Acute medical condition
Septicaemia
Global patient characteristics
Man, aged between 60-74 yr
Non-O blood group
Smoker
History and blood factors
Previous history of proximal saphenous superficial venous thrombosis
Recent clinical conditions (<3 months)
Recent myocardial infarction
Chronic clinical conditions
NYHA I heart failure

Acute medical condition
Psychiatric disorder
Global patient characteristics
Man, aged between 60-74 yr
Non-O blood group
History and blood factors
Factor II mutation, heterozygote
Recent clinical conditions (<3 months)
Recent major surgery with complications
Chronic clinical conditions
NYHA III heart failure
Locally advanced prostate cancer treated with radiotherapy

Surgical cases:

Surgical intervention
Laparoscopic cholecystectomy
Global patient characteristics
Man, aged between 40-59 yr
BMI >30 kg/m2
History and blood factors
Family history of VTE
Recent clinical situations (<3 months)
No recent clinical event
Chronic clinical situations
Confinement to bed or chair >3 days (not wheelchair- or bed bound)

Surgical intervention
Complicated appendicectomy
Global patient characteristics
Woman, aged between 40-59 yr
OCP (oral contraceptive pill)
History and blood factors
None
Recent clinical situations (<3 months)
Recent major surgery with complications
Chronic clinical situations
Breast cancer treated with lumpectomy and hormonal therapy
COPD
Lower limb swelling

2.5. The RAND/UCLA Appropriateness Method

The RAND/UCLA Appropriateness Method (RAM) was developed by RAND and the University of California Los Angeles (UCLA). In the method, the concept of appropriateness refers to the relative weight of the benefits and harms of a medical or surgical intervention. An appropriate procedure is one in which "the expected health benefit (e.g. increased life expectancy, relief of pain) exceeds the expected negative consequences (e.g. mortality, morbidity, anxiety) by a sufficiently wide margin that the procedure is worth doing, exclusive of cost" (Brook, et al., 1986; Fitch, et al., 2001). In this project experts were asked to rate the appropriateness of prophylaxis of VTE for 11 treatment choices for a number of patient cases (indications). These indications were constructed on a combination of various patient characteristics, including general predisposing risk, individual and family history of thrombosis and other parameters relevant for the choice of prophylaxis.

The RAM was implemented according to the following steps.

Step 1. A thorough literature review identified, summarised, and synthesised the relevant scientific literature relating to the risk factors of VTE and the benefits and harms of prophylaxis of VTE. The goal of the literature review was to gain insight into the existing knowledge and to provide a common basis of understanding for the discussions later in the project.

Step 2. Based upon the evidence presented in the literature review and the expert opinions of the project taskforce members, a set of relevant patient characteristics was created: general patient characteristics (including recent and chronic clinical events) and inherent major predisposing risks. In addition to this, other interventional characteristics germane to the decision regarding prophylaxis were enumerated. The combination of patient characteristics and prophylactic treatment options (including no prophylaxis) resulted in what is termed an indications matrix.

Two indications matrices were constructed, one for surgical interventions and one for medical conditions. They were presented to their respective panels. For both matrices, the list of prophylactic options consisted of the following eleven possibilities:

- no prophylaxis
- Acetyl salicylic acid (ASA) used at prophylactic VTE doses
- graduated compression stockings alone
- Vitamin K antagonists, such as warfarin
- Unfractionated heparin (UFH)
- The following low-molecular weight heparins (LMWH) (classified related to equivalent labelling):
    - enoxaparin 20 mg/dalteparin 2500 IU
    - enoxaparin 40 mg/dalteparin 5000 IU
    - nadroparin 0.3 ml
    - nadroparin body-weight adjusted (BWA), which is 0.4 – 0.6 ml
- Combined UFH or LMWH and compression stockings
- Prolonged prophylaxis: as long as the exposing risk persists, for a maximum of six weeks.

The surgical panel rated the appropriateness of these treatment options for all combinations of the following patient characteristics:

- Patients with low, moderate, high or very high overall risk
- History of VTE, as part of the predisposing risk calculation: None, suspected or confirmed
- Anaesthesia: local, regional or general

The medical panel rated the appropriateness of the same treatment options for each of the combination of patient characteristics described below:

- Patients with low, moderate, high or very high overall risk
- History of VTE, as part of the predisposing risk calculation: None, confirmed history with triggering events, confirmed history without triggering events
- Indwelling venous catheter: with or without

Step 3. The two panels were recruited. Tables 2.1 and 2.2 (above) provide the names and specialities of the panellists. Prior to the meeting, the panel members were sent the literature review and the indications matrix and were asked to rate the appropriateness of the procedure for each indication on a 9-point scale, where 1 = very inappropriate and 9 = very appropriate. A middle rating of 5 can mean either that the risks and benefits are about equal or that there is insufficient basis for making a judgement. The decision is left to the individual physician who may wish to consider this treatment. In the first round, the panel members individually rated the risk factors and the appropriateness for prophylaxis. This first round was made without interaction amongst the panel members and was performed at home. The panel members were given four weeks to complete the indications matrix, as well as the scorings lists for predisposing and exposing risk. Two experienced researchers called the panellists during this period to discuss the procedures and answer any questions that arose.

Step 4. Each panel was convened for a two-day meeting in Paris, held in mid-April, 2002. The ratings of each expert were tabulated and prepared for feedback to the panellists. Each panellist received individualised feedback showing for each indication the group's distribution of the ratings, as well as his or her own original rating. The panels discussed the ratings, paying particular attention to the

indications where there was wide variation among experts in their appropriateness ratings, with two tasks in mind. First, the panels considered whether or not the list of indications required revision. Both panels chose to revise their sets of indications, resulting in the structures provided below in Chapter 3. Mostly these revisions were simplifications of the original structures, as some distinctions made there were not considered important for prophylaxis. No changes were made to the 11 prophylactic treatments by either panel.

Step 5. After the discussions, each panellist in both panels privately re-rated the indications (2^{nd} round of ratings). It is important to note that the panels were not required to come to a consensus on their judgements of appropriateness, but only to discuss differences of opinion and then individually to re-rate. Thus, the method may be characterised as "consensus detecting" rather than "consensus forcing". The two-round process is designed to sort out whether discrepant ratings are due to real clinical disagreement over the use of the procedure ("real" disagreement) or to fatigue or misunderstanding ("artifactual" disagreement).

The measures of appropriateness were analysed by statistical protocols that include agreement and disagreement within the panel. First of all, the median and standard deviation of all scores were analysed. Then a CART analysis was performed on the data.

CART method:

For each expert panel (surgical and medical), a classification tree-pruning technique was used to develop a simplified decision algorithm - based on patient characteristics - helping the physician to adopt an appropriate treatment option and to discard those considered as inappropriate or uncertain. This technique belongs to the classification and regression tree (CART) methods implemented on the SPLUS statistical software. Application of CART methods to panel appropriateness ratings and their advantages over logistic regression models have been shown in Wietlisbach, et al. (1999).

The classification tree technique was applied to the expert panel ratings over all combinations of clinical indications and treatment options. It consists first of successively splitting this whole set into increasingly homogeneous subsets, separating as far as possible the indication-treatment combinations rated as appropriate (A) by the panel from those rated inappropriate or uncertain (I or U). Each split is conditioned by an optimal cut-off in the levels of a single factor and the process is continued as long as it is feasible or statistically significant. In the

second stage, an optimal stepwise pruning method, similar to the tree building process, allows the simplification of the tree by successively clipping away the less meaningful branches. At each step, the indications are assigned to the predominant appropriateness class (A/I/U) in the terminal subgroup to which they belong and the overall correct classification rate is calculated. The pruning process is stopped when this rate exceeds a given threshold which was set to 5% in this instance.

The following factors were used in the classification tree process:

1. All the factors defining the clinical indications (i.e. patient risk level, history of VTE and use of indwelling venous catheter for the medical panel; patient risk level, history of VTE and type of anaesthesia for the surgical panel).
2. A set of variables defining the treatment options (i.e. eleven indicator variables for the different options, two indicator variables for the use of enoxaparin, dalteparin and nadroparin respectively, and a variable specifying the treatment option number which ranges from 1 - no prophylaxis - to 11 - prolonged prophylaxis).

The classification trees resulting from the splitting and pruning processes were re-expressed in summary statements and in cross-tabulations showing the appropriateness status (A/I/U) of the treatment options for the different classes of clinical indications.

Chapter 3 Results

3.1. Introduction

In the following sections we present the results of this study. The results can be categorised in five areas:

1. predisposing risk
2. exposing risk
3. combining these two risk measures to obtain an overall patient risk
4. validation of the overall risk measure by cases
5. appropriateness

In Sections 3.2 and 3.3 we present the results related to predisposing and exposing risk. After this we combine, in Section 3.4, both of these risks by means of an algorithm into a unique overall risk level. Then, in Section 3.5 we discuss a validation of this overall risk measure. In the final Section 3.6, we present the results of the appropriateness study.

3.2. Predisposing risks

Tables 3.1 and 3.2 give the aggregate levels of the ratings of risk (stated as odds-ratios) given by the panellists. In the first column of each table, the general patient characteristics are listed. For each characteristic (such as sex, age or smoking), a brief definition of the risk category is provided; raters were given more complete definitions. The first entry in each table is the base case against which all other entries were compared. For each risk category, the tables provide the geometric mean of the ratings, separately for each panel and combined over panels. The geometric mean is a better measure than the more often used arithmetic mean for odds-ratios because combining multiple odds-ratios is done by multiplication rather than addition. The geometric mean, which is the average product (that is the n^{th} root of the product of the n items), is the more mathematically correct measure of central tendency in this instance. Dispersion of ratings is shown by the standard deviation of the ratings, again separately by panel and combined over panels.

Although the original intention of the project was to construct a single predisposing risk measure, it became apparent in the two panel meetings that there were two types of predisposing risk groups that should be considered

separately. The first type, shown in Table 3.1, is the general risk that "comes with the patient." These are a combination of general characteristics (e.g. gender, age, blood group), recent clinical conditions that happened in the past 3 months (e.g. MI, prolonged travel) and chronic clinical conditions (e.g. cancer, venous insufficiency). The second type is a reflection of the inherent susceptibility of the patient to VTE; some people are highly susceptible and some people are not. These factors were clustered into a group of predisposing risks that we labelled "inherent major predisposing risk" of VTE. The indicators for this susceptibility, shown in Table 3.2, are whether there is a personal history of VTE, a familial history of VTE, or one of several blood factors and genetic markers. The presence of one or more of these indicators immediately puts a patient at higher risk, all other predisposing and exposing risks remaining equal. We will come back to this in section 3.4, where we combine other predisposing risk, exposing risk and these factors of 'inherent major predisposing risk' into a unique overall risk measure.

Table 3.1. Aggregate odds-ratios for general predisposing risk given by the panellists ($N_{surgical}$=12, $N_{medical}$=9)
(Mean=Geometric Mean, SD=Standard Deviation)

General Patient Characteristics	All panellists		Surgical panel		Medical panel	
	Mean	SD	Mean	SD	Mean	SD
Normal female person younger than 40	1.00		1.00		1.00	
Sex						
Male (compared to female)	1.11	1.18	1.08	1.18	1.16	1.19
Age						
40-59 yr (compared to <40)	1.67	1.28	1.66	1.28	1.68	1.31
60-74 yr (compared to <40)	2.91	1.47	2.73	1.50	3.18	1.43
over 75 yr (compared to <40)	4.11	1.48	3.56	1.45	4.97	1.43
Blood group						
Non-O group	1.63	1.43	1.70	1.52	1.54	1.32
Obesity						
BMI > 30 kg/m2	2.17	1.38	2.13	1.50	2.23	1.19
Smoking						
>15 cigarettes per day	1.57	1.59	1.47	1.73	1.71	1.39
Oral contraceptive pill (OCP)						
Combined oestrogen / progesterone treatment	2.95	1.29	2.83	1.24	3.11	1.36
Hormone replacement therapy (HRT)						
Combined oestrogen/ progesterone menopausal treatment	2.96	1.26	3.09	1.24	2.79	1.29
Specific drug use						
With protective effect as Statins, ASA	0.70	1.52	0.66	1.67	0.77	1.28

Recent clinical conditions (less than 3 months)	All panellists		Surgical panel		Medical panel	
	Mean	SD	Mean	SD	Mean	SD
Recent major surgery						
With complications	5.10	1.63	5.62	1.65	4.48	1.60
Without complications	2.95	1.72	3.01	1.78	2.86	1.69
Recent myocardial infarction						
Within last 3 months	3.71	1.54	4.15	1.25	3.20	1.81
Recent ischaemic stroke						
Within last 3 months, without paralysis	3.69	1.66	4.15	1.39	3.15	1.94
Prolonged travel						
More than 6 hours	1.60	1.47	1.60	1.44	1.59	1.53
Dehydration						
Severe dehydration as defined by 10% weight loss	2.05	1.42	1.92	1.42	2.24	1.42
Increased haematocrit						
>45% for women; >50% for men	2.03	1.39	1.91	1.53	2.20	1.16
Hyperviscosity						
Increased blood viscosity[3]	2.39	1.33	2.35	1.33	2.43	1.36

[3] *Defined as: "Normal relative serum viscosity ranges from 1.4-1.8 units; symptoms usually are not seen at viscosities of less than 4 units, and the hyperviscosity syndrome typically requires a viscosity greater than 4 units"*

Chronic clinical conditions	All panellists		Surgical panel		Medical panel	
	Mean	SD	Mean	SD	Mean	SD
Malignancy						
Local stage (compared to no malignancy)	2.61	1.61	2.66	1.67	2.55	1.57
Locally advanced stage (compared to no malignancy)	3.69	1.65	4.14	1.78	3.17	1.44
Metastatic cancer (compared to no malignancy)	5.48	1.48	5.88	1.57	5.00	1.33
Additional risk if specific type is pancreatic, gastrointestinal, ovarian, prostatic, pulmonary, malignant glioma (compared to no malignancy)	6.03	1.74	6.23	1.63	5.76	1.94
Additional risk if treated with radiotherapy (compared to no malignancy)	5.05	1.85	6.13	1.67	3.90	1.96
Additional risk if treated with chemotherapy (compared to no malignancy)	5.60	1.61	5.99	1.46	5.12	1.81
Additional risk if treated with hormonal therapy (compared to no malignancy)	5.88	1.65	6.74	1.44	4.91	1.85
Heart failure						
NYHA I or II[4]	1.86	1.53	2.07	1.58	1.62	1.43
NYHA III or IV[5]	5.08	1.73	5.00	1.89	5.19	1.56
Chronic respiratory disease						
Chronic obstructive pulmonary disease or emphysema	1.74	1.53	1.80	1.60	1.68	1.47
Nephrotic syndrome						
Syndrome of proteinuria, hypoalbuminaemia of <20g/L	1.86	1.52	1.78	1.59	1.97	1.46
Acute severe illness						
With hospitalisation	4.85	1.58	5.08	1.51	4.55	1.69
Systemic sepsis (septicaemia)	6.69	1.59	6.57	1.54	6.86	1.71
Immobilisation						
Confinement to bed or (wheel) chair > 3 days (wheelchair- or bed bound)	3.89	1.75	4.29	1.83	3.49	1.68
Confinement to bed or (wheel) chair > 3 days (not wheelchair- or bed bound)	3.29	1.77	3.37	1.90	3.22	1.69
Lower limb paralysis (hemiplegia / paraplegia / neurological disease)	5.70	1.63	5.91	1.83	5.45	1.38
Inflammatory bowel disease (IBD)						
Crohn's disease and ulcerative colitis	2.87	1.43	2.91	1.51	2.80	1.35
Venous insufficiency						
Varicose veins, prominence of superficial veins on standing	2.20	1.42	2.15	1.34	2.28	1.54
Lower limb swelling, discomfort	2.24	1.46	2.18	1.37	2.32	1.60
Ulceration of skin	3.01	1.35	2.99	1.37	3.04	1.35
Lower limb arteriopathy						
Intermittent claudication	1.41	1.37	1.29	1.42	1.59	1.26
Diabetes						
Includes both type 1 and type 2, any aetiology	1.32	1.31	1.28	1.31	1.36	1.32

[4] *NYHA I defined as: "asymptomatic (no limitation in physical activity despite presence of heart disease)". NYHA II defined as: "mild (slight limitation in physical activity)"*

[5] *NYHA III defined as: "moderate (more marked limitation of activity which interferes with work)". NYHA IV defined as "severe (unable to carry out any physical activity without symptoms)"*

Table 3.2. Aggregate odds-ratios for inherent major predisposing risk given by the panellists ($N_{surgical}$=12, $N_{medical}$=9)

(Mean=Geometric Mean, SD=Standard Deviation)

Inherent major predisposing risk	All panellists		Surgical panel		Medical panel	
	Mean	SD	Mean	SD	Mean	SD
Antiphospholipid Syndrome						
Primary, without another autoimmune disease (e.g. systemic lupus erythematosus (SLE))	7.17	1.50	5.76	1.45	9.14	1.33
Secondary with SLE with LA (lupus anticoagulant) (with anticardiolipin antibodies (aCL))	4.95	1.61	4.70	1.66	5.18	1.60
Secondary with SLE without LA (with aCL)	3.09	1.78	3.24	1.54	2.97	2.03
Secondary, with other autoimmune disease or due to drugs	3.11	1.76	3.96	1.64	2.51	1.76
Myeloproliferative disorders						
Including polycythaemia vera, essential thrombocytosis	3.10	1.33	3.01	1.29	3.23	1.40
Hyperhomocysteinaemia						
Fasting homocysteine plasma levels above 40 µmol/L in women; 18 µmol/L in men	2.36	1.42	2.39	1.59	2.32	1.12
Antithrombin deficiency						
Heterozygote	7.89	2.08	6.62	1.92	9.96	2.22
Protein C deficiency						
Heterozygote	4.65	1.67	4.13	1.68	5.45	1.62
Protein S deficiency						
Heterozygote	3.98	1.59	3.7	1.67	4.36	1.5
Factor V Leiden mutation						
Heterozygote	4.08	1.67	3.58	1.83	4.86	1.37
Factor II mutation						
Heterozygote	2.97	1.47	2.78	1.55	3.24	1.36
Factor V or II mutation						
Homozygote	8.82	2.78	8.03	2.93	10.00	2.72
More than one factor (of the previous 6)	11.18	2.17	9.50	2.44	14.28	1.68
Previous history of VTE						
Proximal saphenous / superficial venous thrombosis	3.33	1.33	3.66	1.30	2.94	1.31
Proximal with or without distal DVT	6.22	1.45	6.16	1.46	6.31	1.47
Distal DVT only	4.07	1.47	4.21	1.45	3.89	1.51
Pulmonary embolism	8.65	1.45	9.79	1.41	7.33	1.44
Additional risk caused by clinical idiopathic	6.86	1.87	7.42	1.72	6.24	2.09
Family history of VTE						
In first degree, parents or siblings	3.85	1.45	4.07	1.62	3.58	1.12

3.3 Exposing risks

Exposing risk is divided into medical exposing risk and surgical exposing risk. Surgical exposing risk was investigated for three surgical groups: general, gynaecological, and urological. It was considered that for these surgical indications the highest need of risk-evaluation exists, whereas for example in the majority of orthopaedic surgical interventions a high/very high risk level is

agreed. The results reported here for the medical exposing risk as well as for the surgical exposing risk are the final ones (as explained in Section 2.3).

Table 3.3 shows an overview of the ratings given for different medical exposing risks. These ratings are the average scores on a 5-point Likert-type scale of exposing risk defined as follows:

1 = insignificant risk: young patient with acute asthma
2 = minor risk: condition between ones rated 1 and 3
3 = moderate risk: heart failure, stages NYHA III or IV
4 = substantial risk: condition between ones rated 3 and 5
5 = high risk: acute ischaemic stroke (with paralysis)

Table 3.3. Aggregate ratings for medical exposing risk given by the panellists (N=9)
(Mean=Arithmetic Mean, SD=Standard Deviation)

Exposing risk	Mean	SD
Acute ischaemic stroke (standard)	5.00	-
Acute spinal cord injury	4.78	0.44
Other general medical patient in ICU with mechanical ventilation	4.33	0.71
Active malignant disease requiring treatment	4.22	0.83
Septicaemia	3.89	0.78
Acute myocardial infarction	3.33	0.50
Other general medical patient in ICU without mechanical ventilation	3.33	0.50
Pulmonary oedema	3.33	0.80
Acute severe infections	3.22	1.09
Acute exacerbation of COPD (Chronic Obstructive Pulmonary Disease)	3.01	1.15
Heart Failure, stage NYHA III or IV (standard)	3.00	-
Acute IBD (Inflammatory Bowel Disease)	2.89	0.33
Ischaemic stroke without paralysis	2.89	1.05
Patient with shock	2.78	0.67
Acute exacerbation of lung disease other than COPD	2.63	1.17
Other general medical patient with acute severe disease	2.56	0.73
Acute exacerbation of chronic renal failure	2.67	0.75
Bone marrow transplantation	2.44	0.53
Acute renal failure without haemodialysis	2.42	0.72
Acute exacerbation of rheumatological disorders	2.22	0.67
Infective endocarditis	2.22	0.83
Pneumonia	2.19	1.28
Decompensated liver cirrhosis	1.67	0.71
Psychiatric disorder	1.67	0.71
Acute asthma (standard)	1.00	-

Like the predisposing risks, the exposing risks were discussed extensively during the expert meeting between the first and second round of ratings. As a result of these discussions the original list of 10 medical exposing risks was expanded to

the above listed 25 factors, presented here in rank order from highest to lowest rated risk.

Tables 3.4-3.6 show the ratings for the surgical exposing risks. These ratings were given according to the following suggested points:

1 = insignificant risk: diagnostic laparoscopy
2 = minor risk: condition between ones rated 1 and 3
3 = moderate risk: vaginal hysterectomy (non-cancerous situation)
4 = substantial risk: condition between ones rated 3 and 5
5 = high risk: repair of hip fracture

Table 3.4. Aggregate ratings for general surgical exposing risk given by the panellists (N=16)
(Mean=Arithmetic Mean, SD=Standard Deviation)

Exposing risk – General surgery	Mean	SD
Pelvic cavity		
Laparoscopy for exploration	1.38	0.62
Liver		
Tumourectomy for cancerous disease	3.81	0.75
Resection for hepatic metastases	4.00	0.85
Segmentectomy (unilateral) for cancerous disease	3.63	0.89
Segmentectomy (bilateral) for cancerous disease	3.94	0.77
Hepatectomy for cancerous disease	4.19	0.83
Segmentectomy for non-cancerous disease, such as biliary duct cyst	2.75	0.77
Hepatectomy for non-cancerous disease, benign tumour	2.81	0.75
Gallbladder		
Open cholecystectomy	2.19	0.75
Laparoscopic cholecystectomy	1.69	0.70
Thyroid		
Thyroidectomy for cancerous disease	1.94	0.93
Thyroidectomy for non-cancerous disease	1.31	0.48
Oesophagus		
Oesophageal surgery for cancerous disease	3.81	0.91
Oesophageal surgery for non-cancerous disease	2.94	0.93
Repair of oesophageal stenosis for cancerous disease	3.19	0.91
Stomach		
Gastric surgery for cancerous disease	3.88	0.72
Gastric surgery for non-cancerous disease	2.69	0.70
Gastroplasty for non-cancerous disease	2.69	1.08
Gastro - duodenal surgery for cancerous disease	3.73	0.59
Gastro - duodenal surgery for non-cancerous disease	2.87	0.52
Small intestine		
Small intestine surgery for cancerous disease	3.56	0.73
Small intestine surgery for non-cancerous disease (such as inflammatory diseases)	2.94	0.68
Small intestine surgery for non-cancerous disease (such as ischaemic bowel)	3.25	0.77
Small intestine occlusion	2.79	0.89

Exposing risk - General surgery	Mean	SD
Large intestine		
Colorectal surgery for cancerous disease	4.13	0.62
Colorectal surgery for non-cancerous inflammatory disease (such as IBD)	3.31	0.48
Colorectal surgery for non-cancerous disease (such as diverticulitis)	2.94	0.68
Adrenal glands		
Adrenal surgery for cancerous disease	3.92	0.79
Adrenal surgery for non-cancerous disease	2.56	0.85
Pancreas		
Pancreatic surgery for cancerous disease	4.25	0.68
Pancreatic surgery for non-cancerous disease	3.19	0.66
Spleen		
Splenectomy for cancerous disease	3.75	0.77
Splenectomy for non-cancerous disease (such as haematological patients)	3.06	0.85
Appendix		
Simple appendicectomy	1.50	0.82
Complicated appendicectomy	2.56	0.73
Hernia		
Inguinal hernia -- open	1.56	0.51
Inguinal hernia -- laparoscopic	1.40	0.51
Hiatal / crural hernia -- open	1.94	0.93
Hiatal / crural hernia -- laparoscopic	1.63	0.72
Other		
Proctologic surgery: haemorrhoid fistulae, abscess, prolapsed rectum	1.38	0.62
Liposuction	1.94	0.85
Abdominal wall surgery other than liposuction	1.81	0.75

Table 3.5. Aggregate ratings for gynaecological surgical exposing risk given by the panellists (N=11)

(Mean=Arithmetic Mean, SD=Standard Deviation)

Exposing risk - gynaecological surgery	Mean	SD
Breast		
Lumpectomy with axillary node dissection for cancerous disease	2.82	0.75
Lumpectomy for non-cancerous disease (adenoma, galactophoria, microcalcification, abscess)	1.55	0.69
Mastectomy for non-cancerous disease	2.09	0.94
Mastectomy for cancerous disease	2.82	1.08
Mastectomy with axillary node dissection for cancerous disease	3.27	1.01
Mastectomy with axillary node dissection for cancerous disease and reconstitution	3.45	0.93
Plastic surgery	1.78	0.67
Uterus		
Laparoscopy for diagnosis	1.45	0.82
Hysteroscopy, with curettage, resection	1.82	0.75
Hysteroscopy, without curettage	1.36	0.67
Hysterectomy with oophorectomy for cancerous disease, vaginal	3.82	0.60
Hysterectomy without oophorectomy for cancerous disease, vaginal	3.55	0.82
Hysterectomy with oophorectomy for non-cancerous disease, laparoscopic	3.09	0.83
Hysterectomy without oophorectomy for non-cancerous disease, laparoscopic	3.00	0.89
Hysterectomy with oophorectomy for non-cancerous disease, abdominal	3.27	0.79
Hysterectomy without oophorectomy for non-cancerous disease, abdominal	3.27	0.65
Hysterectomy with oophorectomy for non-cancerous disease, vaginal	3.00	0.89

Exposing risk - gynaecological surgery	Mean	SD
Hysterectomy without oophorectomy for non-cancerous disease, vaginal (standard)	3.00	-
Myomectomy, abdominal	2.91	0.94
Myomectomy, vaginal	2.18	0.40
In vitro fertilisation	1.45	0.69
Ovaries		
Oophorectomy for cancerous disease, abdominal	4.00	0.45
Oophorectomy for cancerous disease, laparoscopic	3.55	0.52
Oophorectomy and omentectomy for cancerous disease, abdominal	4.18	0.75
Oophorectomy and omentectomy for cancerous disease, laparoscopic	3.64	0.50
Oophorectomy for non-cancerous disease, abdominal	3.09	0.54
Oophorectomy for non-cancerous disease, laparoscopic	2.64	0.67
Fallopian tubes		
Salpingectomy, abdominal	2.55	0.69
Salpingectomy, laparoscopic	1.82	0.60
Salpingotomy, abdominal	2.45	0.89
Salpingotomy, laparoscopic	1.50	0.87
Salpingoplasty, abdominal	2.27	1.03
Salpingoplasty, laparoscopic	1.39	0.89
Salpingorrhaphy, abdominal	2.09	0.94
Salpingorrhaphy, laparoscopic	1.73	0.65
Ovaries and Fallopian tubes		
Adenexectomy for cancerous disease, vaginal	3.36	0.67
Adenexectomy for non-cancerous disease, vaginal	2.45	0.69
Adenexectomy for non-cancerous disease, abdominal	2.73	0.90
Adenexectomy for non-cancerous disease, laparoscopic	2.45	0.82
Uterus, ovaries and Fallopian tubes		
Hysterosalpingo-oophorectomy for cancerous disease, vaginal	3.73	0.65
Hysterosalpingo-oophorectomy for non-cancerous disease, vaginal	2.73	0.65
Hysterosalpingo-oophorectomy for non-cancerous disease, abdominal	3.27	0.90
Hysterosalpingo-oophorectomy for non-cancerous disease, laparoscopic	2.73	0.65
Vulva and/or vagina		
Bartholin's cystectomy	1.40	0.97
Vulvectomy, complete	2.00	0.89
Vulvectomy, partial	1.91	1.14
Birth by Caesarean section		
Caesarean section -- emergency	2.80	0.79
Caesarean section -- elective	2.40	0.52
Termination of pregnancy	1.90	0.57

Table 3.6. Aggregate ratings for urological surgical exposing risk given by the panellists (N=13)

(Mean=Arithmetic Mean, SD=Standard Deviation)

Exposing risk - urological surgery	Mean	SD
Prostate		
Radical prostatectomy for cancer	4.31	0.63
Radical prostatectomy for cancer, laparoscopic	3.69	0.85
Open adenomectomy (Millin -Freyer)	3.25	0.62
Prostate biopsy, transrectal	1.54	0.66
Bladder		
Cystostomy	1.38	0.65
Cystotomy for bladder lithiasis	1.69	0.75
Transvesical diverticulectomy	1.85	0.80
Enterocystoplasty	2.46	1.05
Psoas-hitch	2.00	1.00
Cystectomy for non-cancerous disease + uretero-ileostomy	3.15	0.90
Cystectomy for non-cancerous disease + neo-bladder	3.38	0.77
Cystectomy for cancer + uretero-ileostomy	4.23	0.73
Cystectomy for cancer + neo-bladder	4.31	0.63
Ureter		
Ureterotomy for lithiasis	1.38	0.51
Ureterostomy	1.31	0.48
Transuretero or ureterostomy for urethral obstruction	1.62	0.65
Pyeloplasty for pyelo-ureteral junction syndrome	2.15	0.90
Transvesical ureteral re-implantation	2.08	0.76
Kidney		
Nephrostomy for lithiasis	1.77	0.73
Nephrectomy (simple) for non cancerous disease	2.69	0.63
Nephrectomy (simple) for non cancerous disease, laparoscopic	2.46	0.88
Nephrectomy enlarged for cancer	4.15	0.69
Nephrectomy enlarged for cancer, laparoscopic	3.69	0.85
Nephrectomy + lymph node dissection	3.85	0.90
Nephrectomy by thoraco-phreno-laparotomy	3.85	1.07
Nephrectomy enlarged + cavoplasty or cavotomy	4.62	0.51
Kidney transplant	3.62	0.65
Urethra		
Hypospadias repair, distal	1.15	0.38
Hypospadias repair, proximal	1.23	0.60
Urethrostomy	1.25	0.45
Urethral stricture, distal	1.15	0.38
Testis and scrotum		
Orchidectomy, pulpectomy, scrotal	1.69	0.75
Orchidectomy inguinal for cancer	2.46	1.13
Retroperitoneal lymph node dissection.	3.23	0.93
Circumcision	1.08	0.28
Spermatocoele	1.08	0.28
Epididymectomy	1.15	0.38

Exposing risk - urological surgery	Mean	SD
Endoscopy - percutaneous		
Cystoscopy	1.00	0.00
Cystoscopy + ureteral catheterisation	1.08	0.28
Transurethral resection of the Prostate, TURP	2.08	0.49
Transurethral resection of bladder Tumour (1 cm - superficial)	2.23	1.01
Transurethral resection of bladder Tumour (5 cm - invasive)	3.08	0.67
Ureteroscopy	1.17	0.39
Nephrostomy (percutaneous) - drainage	1.31	0.48
Nephrostomy (percutaneous) - interventional - urolithiasis	1.46	0.52
Nephrostomy (percutaneous) - interventional - tumour	2.08	0.76
Extracorporeal shock wave lithotripsy	1.31	0.63
Incontinence		
TVT (tension-free vaginal tape) for stress incontinence	1.31	0.63
Burch procedure for stress incontinence, vaginal	2.00	0.82
Burch procedure for stress incontinence, laparoscopy	1.92	1.00
Transvesical sling	2.08	0.79
Artificial sphincter	2.25	1.06

3.4 Combining predisposing and exposing risk into an overall risk measure

The two measures of predisposing risk and the measure of exposing risk were combined to construct an overall assessment of the risk of VTE. In order to accomplish this, first the multiplicity of predisposing risk factors for single patients had to be considered, and then the combination of risk developed.

The first issue is the combination of different predisposing risks. Unlike the single exposing risk that defines why a patient is a candidate for VTE; patients can have multiple predisposing risks. We treat general predisposing risks (Table 3.1) and inherent major predisposing risks (Table 3.2) separately, but in the same way. Considering general predisposing risks, the typical patient will have *J* predisposing risks. Were we to assume that there is no interaction among the separate risks; the total amount of predisposing risk is given by[6]:

$$Odds_{tot} = \prod_{j=1}^{J} odds_j \qquad (1)$$

where $Odds_1 \ldots Odds_J$ are the odds-ratios for the *J* separate predisposing risks present in the patient and $Odds_{tot}$ is the odds-ratio for having all *J* predisposing

[6] $\prod$ refers to taking the Product of all the items, just as the more familiar $\sum$ calls for a Sum

risk factors compared to having none of them However, predisposing risks are not independent, either epidemiologically or in theory; instead, they are generally positively correlated with each other (that is, problems come in clusters). This means that equation (1) will be an overestimate of the overall predisposing risk because of double-counting of related risks. The preliminary estimates of the predisposing risk, calculated using equation (1) in test cases showed unreasonably large values. The technically correct way to revise equation (1) would require knowledge of the correlations amongst all of the predisposing risks for each distinct patient subpopulation – clearly an unattainable goal. As an alternative, we have adopted a heuristic of looking "midway" between the product of the risks of equation (1) and the geometric mean of the risks, calculated by

$$Odds_{gm} = \sqrt[J]{\prod odds_j} = \exp\left[\sum \ln odds_j / J\right] \qquad (2)$$

By taking less than the full value of *J* (as always, the number of risks present) as the averaging factor, we allow for the marginal contribution of multiple risks. The resulting number is no longer properly an odds-ratio, but behaves just like one and may be used as an indication of degree of predisposing risk. This calculation is given as:

$$R_p = \exp\left[\sum_{j=1}^{J} \ln odds_j / \sqrt{J}\right] \qquad (3),$$

where the square root of *J* has the property of acting as a balancing factor. This strictly rule-of-thumb measure of risk that resulted from datamining of the odds-ratios for predisposing risks appeared to successfully enable us to convert the predisposing risk odds-ratios for individual risks to an overall categorisation of low vs. high predisposing risk.

Because the aim of the study is to develop a *simple* risk measure, we divide R_p into two categories of predisposing risk: low and high. The cut-off point used, based on calibration against holistic measures of risk, was 8.5 for medical cases and 5 for surgical cases. The difference can be explained by the fact that the presence of general predisposing factors provides a greater risk for surgical patients than for medical patients.

As has been described in section 3.2, we made a distinction between predisposing risk and *major inherent* predisposing risk. For the calculation of major inherent predisposing risk, we used the same approach as for the predisposing risk. That means, major inherent predisposing risk is given by:

$$R_m = \exp\left[\sum_{k=1}^{K} \ln odds_k / \sqrt{K}\right] \qquad (4),$$

with *K* as the number of major inherent predisposing risks present. We categorised R_m in three categories (low, moderate and high) with the following preliminary cut-off points, based on a calibration against a limited set of cases (see section on validation):

$$\text{low} < 3 \leq \text{moderate} \leq 8.5 < \text{high}$$

For exposing risk, we assume that in general a patient will not be exposed to more than one exposing risk, as defined in the lists of section 3.3. Examining situations where a patient is exposed to more than one medical or surgical exposing risk, were considered beyond the scope of this study. It is however realised that the many medical patients have multiple risks factors on admission. As a result, we define the total exposing risk as the arithmetic mean of the ratings given by raters 1…u, for the single risk to which a patient is exposed. The exposing risk is also translated to a simple measure, categorised into the three categories of exposing risk: low, moderate and high, with cut-off points determined by the labelling of the five ratings. Thus, exposing risks with a rating between 1.0 and 2.0 were labelled low, the ones between 2.0 and 4.0 were labelled moderate, and exposing risks with a rating between 4.0 and 5.0 were labelled high.

The classification given above leads to 2 x 3 x 3 combinations of predisposing and exposing risks, as is shown in the risk matrix, Table 3.7. Each cell in this table represents a combination of general predisposing, major inherent predisposing and exposing risk, together with a resulting statement on *overall* risk of VTE. Overall risk is categorised in four categories: Low (**L**), Moderate (**M**), High (**H**) and Very High (**VH**). The matrix was developed during the panel sessions and represents a consensus of both panels.

Table 3.7. Risk matrix for VTE

(**L**=Low, **M**=Moderate, **H**=High, **VH**=Very High overall risk for VTE)

	Exposing risk		
	Low	Moderate	High
Inherent major predisposing risk			
Low	Low gen. pre. risk: **L** High gen. pre. risk: **M**	Low gen. pre. risk: **M** High gen. pre. risk: **H**	Low gen. pre. risk: **H** High gen. pre. risk: **VH**
Moderate	Low gen. pre. risk: **M** High gen. pre. risk: **H**	Low gen. pre. risk: **H** High gen. pre. risk: **VH**	Low gen. pre. risk: **VH** High gen. pre. risk: **VH**
High	Low gen. pre. risk: **H** High gen. pre. risk: **VH**	Low gen. pre. risk : **VH** High gen. pre. risk: **VH**	Low gen. pre. risk: **VH** High gen. pre. risk: **VH**

The matrix can be explained by a simple step rule. If all three risk levels are low (the top left-hand corner of the matrix), then the overall risk assessment is also low. Moving one step in any dimension (that is, changing exposing risk from low to moderate, changing inherent major predisposing risk from low to moderate, or changing general predisposing risk from low to high) changes the overall risk from low to moderate. Moving two steps, either both in the same dimension (for example from low to high exposing risk) or one in each of two dimensions (for example, from low to high general predisposing risk and from low to moderate inherent major predisposing risk) changes the overall risk from low to high. And moving three or more steps, in any combination of dimensions, produces an overall risk of very high.

3.5 Validation of the overall risk measure using clinical cases

In this section we discuss a test of the validity of the risk matrix described in 3.4. In order to be able to do this, we developed two series of 54 clinical cases (patients with specific predisposing and exposing risk of VTE)[7]. One set was for medical patients and one set was for general surgical patients. The cases systematically varied the degree of general predisposing, inherent major

[7] Only results of final validation are shown here

predisposing and exposing risk, so that there would be representation of all four levels of the overall risk. We used the matrix in Table 3.7 to assign each case a risk level of low, moderate, high, or very high. Independently, the two sets of cases were sent to the medical and surgical panellists and requested that they and their colleagues rate each case holistically on the same scale of low, moderate, high and very high overall risk of VTE.

For both the medical and surgical panels, the holistic judgements were close to those obtained using Table 3.7.

Medical case validation was based on 54 cases evaluated by 16 raters, so presenting about 864 ratings. The matrix estimation was compared with the median of the experts' ratings for each case.

Medical patient cases

Table 3.8. Comparison of DecisionMatrix™ and raters for medical cases

		DecisionMatrix™ estimation					DecisionMatrix™ estimation		
		L	M	H	VH		higher	same	lower
	L	1	0	0	0	1	25.9%	66.7%	7.4%
expert	M	0	9	5	0	14			
rating	H	0	3	16	9	28			
	VH	0	0	1	10	11			
		1	12	22	19	54			

Overall risk: L= low; M = moderate; H= high; VH= very high

The DecisionMatrix™ estimation compared to the median of all ratings per case, gave an overall agreement in about 70% of the cases. Very few cases were underestimated by the matrix; about 26% or 14 cases were overestimated by the matrix compared with the expert ratings. 9 out of the 14 overestimated cases appeared to have a rating of very high compared with the high by the expert rating.

General surgery patient cases:

General surgery case validation was based on 54 cases made by 21 raters, so presenting about 1134 ratings. The matrix estimation was compared with the median of the experts' ratings per case.

Table 3.9. Comparison of DecisionMatrix™ and raters for surgical cases

		DecisionMatrix™ estimation					DecisionMatrix™ estimation		
		L	M	H	VH		higher	same	lower
expert rating	L	3	2	0	0	5	27.8%	64.8%	7.4%
	M	0	9	3	0	12			
	H	0	2	14	10	26			
	VH	0	0	2	9	11			
		3	13	19	19	54			

Overall risk: L= low; M = moderate; H= high; VH= very high

The DecisionMatrix™ estimation compared with the median of all ratings per case, gave an overall agreement of nearly 65%. Very few cases were underestimated by the matrix; about 28% or 15 cases were overestimated by the matrix compared with the expert ratings. 10 out of the 15 overestimated cases appeared to have a rating of very high compared with the high by the expert rating.

These results are comparable with reliabilities obtained in other research in the health services field.

3.6 Appropriateness Ratings

In this section the results of the second round of appropriateness ratings are presented. Following some general remarks concerning the degree of agreement in the panels, the results from the panels are analysed separately. The analysis focuses on the appropriateness of the different treatments, but also on the appropriateness ratings per patient type. Finally, the results of the two panels are compared and the main common denominators and differences discussed.

3.6.1. Degree of agreement

The first analysis of an appropriateness study is the extent of agreement amongst the panel members. The RAM is an instrument designed to detect consensus, not to create it, and it is important to ascertain whether there is a consensus. The method defines "disagreement" in a concrete, measurable manner (Fitch K et al., 2001) and each indication can be assessed as to whether or not the panel members disagreed about its appropriateness. Using this measure, the 209 indications rated by the 9-member medical panel yielded 21 indications for which there was disagreement and 188 for which there was not (agreement or

indeterminate). Correspondingly, the 396 indications rated by the 12-member surgical panel produced 22 instances of disagreement and 374 where the panel members did agree. The disagreement rates of 10 percent and 6 percent, respectively, are within the range that is typical for RAM studies and represents good clinical expertise.

In the medical panel, disagreements occurred between the benefits and harms of unfractionated heparin (UFH) for patients with moderate risk and on the value of vitamin K antagonists for some patients with high and very high risk. In the surgical panel, disagreements concerned the low dosages of LMWH (enoxaparin 20 mg/dalteparin 2500 IU and nadroparin at 0.3 ml). Examining the patterns of appropriateness, this disagreement appears to have been concentrated on the benefits and harms of the low dosages in instances when the higher dosages of the same treatments were largely regarded as appropriate. Some surgical panel members believed that the lower dosages as well as the higher dosages could be of benefit, while others believed that only the higher dosages were beneficial for the patient indications rated.

Where there was no disagreement, the median score of the panel was used to ascertain the appropriateness of the indication. A median of 1-3 denoted that the treatment was inappropriate for the indication, a median of 7-9 meant that the indication was appropriate, and a median of 4-6 was interpreted as saying that the treatment's appropriateness was uncertain—that is, the method can not make a statement favouring or not favouring the treatment. When there was disagreement, the median rating of the panel was ignored and the indication was deemed to be of uncertain appropriateness[8].

3.6.2. Medical panel findings

Findings by patient categorisation:

In order to examine factors driving the median panel ratings and therefore the distribution of inappropriate, uncertain and appropriate ratings of indications, we utilised a CART analysis (see section 2.5)**.**

Table 3.10 presents the median appropriateness ratings for each of the 11 different treatment options in terms of the optimal branching rules among the

[8] Almost all indications with disagreement have medians in the 4-6 range, so the consequences of this decision rule are minor.

factors used to build the indication structure. The first thing we see in this table is that there is no entry for whether or not the patient has an indwelling central venous catheter. This means that the distinction was not important for the panellists in their determination of the appropriateness rating. The first row of the table shows that an indication of low risk strictly determines appropriateness ratings; the option of no treatment "none" receives the maximum possible rating and all other treatments receive the lowest possible rating. In other words, when the overall risk is low, prophylaxis is not indicated.

Table 3.10 Median appropriateness ratings in CART summary table

medical patient profile		**prophylactic options**										
Overall risk	**Including history of VTE**	Nil	ASA	GCS	VKA	UFH	enox 20 mg/ dalt 2500 IU	enox 40 mg/ dalt 5000 IU	nadr 0.3 ml	nadr bwa	UFH/ LMWH +stoc	PP
low	**either**	9.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
mod	**no**	1.0	1.0	4.0	3.0	7.0	5.0	7.5	5.5	7.5	4.5	5.0
mod	**yes**	1.0	1.0	5.0	4.0	6.0	2.0	8.5	4.0	9.0	8.0	5.0
high	**either**	1.0	1.0	5.5	5.0	8.0	1.0	9.0	2.0	9.0	9.0	5.0
very high	**either**	1.0	1.0	5.0	6.0	7.0	1.0	9.0	1.5	9.0	9.0	7.0

Nil: no prophylaxis; ASA = acetyl salicylic acid therapy; GCS = graduated compression stockings; VKA = vitamin K antagonists; enox = enoxaparin; dalt = dalteparin; nadr = nadroparin; bwa = bodyweight adjusted; UFH/LMWH + stoc. = UFH/LMWH associated with compression stockings; PP = prolonged prophylaxis with a maximum of 6 weeks

Optimal pruned classification tree with 12 terminal nodes

Overall classification error = 7/264 = 3%

The next row shows that the appropriateness of care for patients at moderate risk depends on whether that risk includes a history of VTE or not. When there is no history of VTE, the benefit-to-harm ratio of lower dosages of LMWH (enoxaparin 20 mg /dalteparin 2500 IU, nadroparin 0.3 ml) is higher than when there is a history of VTE. All of these treatments were rated uncertain except for enoxaparin 20 mg/dalteparin 2500 IU, which was inappropriate. In addition, the additional use of stockings for the patients with history of VTE is seen as appropriate. With both types of VTE history, no treatment and acetyl salicylic acid are inappropriate, and stockings alone, vitamin K antagonists and prolonged prophylaxis are considered uncertain. There was disagreement about UFH and

prolonged prophylaxis: 4 experts consider this highly inappropriate for this patient, 4 didn't know or consider the benefits equal to the harms.

For high and very high risk patients, the VTE history is no longer important (most of these patients will have some history), and more intensive treatment is appropriate. No prophylaxis and ASA were unanimously considered very inappropriate. The ratings were uncertain concerning the possible role of vitamin K antagonists. For both groups, UFH was considered appropriate. Enoxaparin/dalteparin and nadroparin at low dosages were inappropriate, but were highly appropriate (median rating = 9) at high dosages. Combined UFH or LMWH and compression stockings were also considered appropriate as well. The ratings were uncertain regarding prolonged prophylaxis for high risk patients, however for very high risk patients prophylaxis for up to 6 weeks was considered highly appropriate.

Findings by treatment option in the medical panel

- **No prophylaxis** was only considered a treatment option if a patient is at low risk of VTE. For all other patients, the medical experts gave it an appropriateness rating of 1: highly inappropriate.
- **Acetyl salicylic acid** was considered inappropriate in all cases.
- **Graduated compression stockings** alone are generally inappropriate or uncertain. In combination with UFH or LMWH, however, they are appropriate for patients with moderate and VTE history, high and very high risk.
- The panellists agreed that **unfractionated heparin** (UFH) alone was appropriate for patients with high or very high risk, inappropriate for patients with low risk but no agreement exists concerning the moderate risk patients.
- **Vitamin K antagonists** are inappropriate in low risk patients and in moderate risk patients without a history of VTE. In all other cases, the panel considered it indeterminate, for the patients with high and very high risk they disagreed, with all possible scores represented amongst the panellists.
- For low risk patients, **LMWHs** in any dosage were considered inappropriate. For all other overall risk categories**, LMWHs** in higher dosages were considered appropriate. **LMWHs** at lower dosages were considered inappropriate for patients with high or very high overall risk. For patients with moderate overall risk with no history of VTE, the use of low dose **LMWHs** was uncertain. For patients with moderate overall risk with a history of VTE, **enoxaparin/dalteparin** at a low dosage was inappropriate, while nadroparin 0.3 ml was uncertain.

- **Prolonged prophylaxis** (defined as beyond hospital discharge) was considered inappropriate for patients at low risk while uncertain for moderate and high risk patients. For the very high risk patients it was considered appropriate.

3.6.3. Surgical panel findings

Apart from the overall risk, the surgeons rated the appropriateness of the eleven prophylactic options for patients with no history of VTE, a suspected or a confirmed history of VTE who were due to undergo general, regional or local anaesthesia. Originally, the indications matrix only distinguished between no history of VTE and history of VTE, but the panel decided that the decision on prophylaxis might be different if a VTE has not been diagnosed, although it is suspected that the patient might have had one. The results of the panel ratings are given in Table 3.11 below. It was decided that if analysis showed that no difference existed in the ratings among the different types of VTE history or anaesthesia, then these would be collapsed and grouped with the word 'either'.

Findings by patient categorisation:

General findings: There was a large dispersion in the ratings, and not all results are subject to clear-cut interpretations. For low risk patients receiving local anaesthesia, all treatment options are inappropriate except for stockings used alone. The low dosages of LMWH are at the low end of the uncertain range. For patients undergoing general or regional anaesthesia, low dosages of LMWH had a better benefit-to-harm ratio, but never cross the boundary to being considered appropriate.

Table 3.11 Median appropriateness ratings for the surgical panel

surgical patient profile			prophylactic options										
overall risk	including VTE hist	anaest	Nil	ASA	GCS	VKA	UFH	enox 20 mg dalt 2500 IU	enox 40 mg dalt 5000 IU	nadr 0.3 ml	nadr bwa	UFH/ LMWH +stock	PP
low	-	local	3.0	1.0	9.0	1.0	2.0	4.0	2.0	4.0	2.0	3.0	1.0
low	-	gen/ reg	3.0	1.0	8.0	1.0	4.5	6.5	2.0	6.0	2.0	4.0	1.0
mod	either	local	2.0	1.0	5.0	1.0	5.0	5.0	2.0	5.0	2.0	6.0	1.0
mod	no,sus	gen/ reg	1.5	1.0	3.0	1.0	6.5	8.5	3.5	8.5	2.5	5.5	1.5
mod	conf.	gen/ reg	1.0	1.0	2.0	1.0	7.0	7.0	8.0	7.5	5.0	7.5	2.0
high	either	either	1.0	1.0	1.0	2.0	7.0	5.0	8.0	5.0	8.0	9.0	6.0
v.high	either	either	1.0	1.0	1.0	3.0	7.0	1.0	9.0	1.0	9.0	9.0	8.0

Nil: no prophylaxis; ASA = acetyl salicylic acid therapy; GCS = graduated compression stockings; VKA = vitamin K antagonists; enox = enoxaparin; dalt = dalteparin; nadr = nadroparin; bwa = bodyweight adjusted; UFH/LMWH + stoc. = UFH/LMWH associated with compression stockings; PP = prolonged prophylaxis with a maximum of 6 weeks

classification tree analysis (CART method)

optimal pruned classification tree with 17 terminal nodes

overall classification error = 23/396= 6%

For anything greater than low risk, the use of graduated compression stockings alone was generally considered inappropriate — this is probably because stockings are fairly standard in the operating theatre and are more often used in association with UFH or LMWH post-surgery. LMWH are clearly the treatment of choice, but the choice of type and dosage of LMWH demonstrate a complicated pattern. At moderate levels of risk without a confirmed history of VTE, under local anaesthesia, administration of heparin (UFH or LMWH) was uncertain; changing to regional or general anaesthesia, the appropriate choice was LMWH. With moderate risk, regional or general anaesthesia, and a confirmed history of VTE, stockings, UFH and LMWH are all considered appropriate. Higher dosage enoxaparin/dalteparin and nadroparin 0.3ml was also considered appropriate in this setting; one interpretation here is that the lower-dosage nadroparin might be viewed as more efficacious for these patients, and a shift to higher dosage is not recommended. For high and very risk patients, the most appropriate treatment was considered to be high-dosage LMWH with or without stockings. Prolonged

prophylaxis was appropriate for the very high risk patients, but uncertain for the high risk patients.

Findings by treatment option for surgical patients

- **No prophylaxis** was never considered appropriate – even if the overall risk is low.
- **Acetyl salicylic acid** was never considered appropriate.
- **Graduated compression stockings** alone are appropriate for patients with low risk, but the panel was not certain about patients with moderate risk and local anaesthesia. Compression stockings alone are inappropriate for moderate risk with general or regional anaesthesia, high or very high risk patients. In combination with UFH or LMWH, however, they are appropriate for patients with moderate, confirmed history and general or regional anaesthesia, high and very high risk.
- **Vitamin K antagonists** were never considered appropriate.
- **Unfractionated heparin** was considered appropriate for patients with moderate risk with confirmed VTE history under general or regional anaesthesia. It was also considered appropriate for all patients with high or very high risk, mostly with a median of 7.
- **Enoxaparin 20 mg/dalteparin 2500 IU** was only considered appropriate (median 7 – 8.5) for patients with moderate risk under general or regional anaesthesia. There was a lot of disagreement concerning this treatment, especially where it involved the use of local anaesthesia (in this case this regimen is uncertain).
- **Enoxaparin 40 mg/dalteparin 5000 IU** was considered appropriate for patients with moderate overall risk and confirmed history of VTE under regional or general anaesthesia and for all patients with high or very high risk of thrombosis.
- **Nadroparin 0.3 ml** was considered appropriate for patients with moderate overall risk under general or regional anaesthesia. It was inappropriate for patients with very high risk (inadequate dosage). For other indications, it was considered uncertain.
- **Nadroparin bwa** was considered highly appropriate for all patients with high or very high risk.
- **Combined UFH or LMWH and compression stockings** were considered appropriate for:
    - Patients with moderate risk, confirmed VTE history under general or regional anaesthesia

- All patients with high or very high risk

- **Prolonged prophylaxis** was considered highly appropriate for those patients with very high risk and considered uncertain for patients with high risk.

General findings for both the surgical and the medical panel

If there really is no risk, then "no treatment" was considered appropriate. And, correspondingly, any other treatment was inappropriate. If there is even a moderate risk, then doing nothing was not considered appropriate, however what to do depends on the seriousness of the risk.

The surgical and medical panels differed on their use of stockings. The surgical panel considered that stockings were acceptable, by themselves if the heparin (UFH or LMWH) were not appropriate or useful in combination with the heparin (UFH or LMWH) if the medication was appropriate. The medical panel on the other hand didn't consider stockings without medication to be a good idea, and didn't believe they would add much further value when heparin is used. Surgeons, compared to medical physicians, are more used to the general use of stockings.

The dosages of LMWH recommended differed according to the speciality. The surgical panel suggested prescribing the low dosages for several moderate risk groups, only moving to high dosage when the risk was high or very high. The medical panel found high dosages appropriate for patients at overall moderate risk.

Panellists almost never distinguished between competing brands of LMWH. Sometimes, the low dosage nadroparin was preferred to the low dosage of the other therapies, and sometimes low dosage nadroparin might be used when a higher dosage of the other was indicated. These differences probably reflect the different "labelling" or officially approved usages that derive from the original clinical studies of the drugs.

The surgical panel saw little value in the use of UFH. The medical panel saw greater benefit in its use, although this was less compared to the preferred LMWH. Overall, LMWH is seen as providing greater benefit to patients.

Acetyl salicylic acid was not considered relevant to the problem, since the panel considered it inappropriate for any type of patient. Vitamin K antagonists were only considered appropriate in certain very high risk medical patients. For all other patient groups it is considered inappropriate.

Chapter 4: Conclusions

This study developed an overall measurement of individual patient VTE risk, as well as providing the appropriateness of various forms of prophylactic therapy accompanying various medical or surgical conditions. The primary objective of the study was the development of measurement techniques to aid the clinical practitioner. Along the way, we learned a number of useful pieces of information.

- The literature on prophylaxis of VTE is extensive, although still rudimentary. There is a need for greater scientific evidence concerning the degree predisposing risk factors, and for further detail on exposing risk for different procedures.
- The risk of VTE is real, in the sense that the chances of VTE are overall not slight. However often the general awareness of this risk by the typical practitioner is not as high as is needed to ensure the best quality care.
- There is a consensus, at least amongst the two panels we assembled, that prophylaxis was appropriate whenever the risk is higher than insignificant. This statement, going back to our definition of "appropriate" means that the potential benefits of prophylaxis outweigh their potential harms, without considering the economic costs of the treatment.
- Given that one should engage in prophylaxis, there was a consensus that low molecular weight heparin is a preferred treatment option, although for some situations, unfractionated heparin provides equivalent or nearly equivalent benefit. Other treatments, including acetyl salicylic acid, vitamin K antagonists and compression stockings in the absence of medication, were not viewed as providing good benefit-to-harm ratios.
- There was a consensus in recommending prolonged prophylaxis for very high risk patients in both medical and surgical conditions.

This study has employed a variety of methods to develop a tool that may be used by the typical health care provider faced with deciding whether or not to employ prophylaxis to prevent VTE, and if so, what type of prophylaxis, in what dosage and for what duration. This was accomplished by forming two international panels of experts, one medical and one surgical, and using these panels directly—through their own efforts on the major tasks of the study—and indirectly—through using their good services to recruit their colleagues validation and

classification of certain aspects of the study. The methods used in the study were the following:

- A literature review of the state of knowledge on risk factors of VTE and the effects of various prophylaxis regimens available.
- Development and administration of a scale to assess the degree of predisposing risk presented by medical or surgical patients. The development was performed by an iterative rating of odds-ratios (compared to a "base case" of a patient with none of the predisposing risks) by the two expert panels. Analytic steps included separating the predisposing risk into two separate scores termed "general predisposing risk" and "inherent major predisposing risk", and creating a heuristic formula that dealt with multiple predisposing risks present in a single patient.
- Development and administration of a scale to assess the degree of exposing risk possessed by a patient presenting with a medical condition or for a urological, gynaecological or general surgical procedure. The development was performed initially by the expert panels (separately for medical and surgical exposing risk) and then by "snowball" referral by the panel to their colleagues. The ratings were performed on a 5-point Likert-type scale anchored by common conditions with consensually agreed-upon degrees of risk.
- Development and administration of two sets of simulated patient descriptions ("cases") that systematically varied the degrees of predisposing and exposing risk. These cases—one set of medical conditions and one set of general surgical interventions were assessed holistically by the enlarged medical panel and the enlarged general surgical panel, respectively.
- Development of an overall risk of VTE assessment combining the two separate scores for predisposing risk and the score of exposing risk. The structure of the combination algorithm (cast in the form of a risk matrix) was a function of the three different types of risk and was agreed upon by both the medical and surgical panel. The explicit cut-off points for the risk matrix were the result of analysing the holistic ratings and determining the optimal cut-offs to maximise concordance between the statement of the risk matrix and the median holistic judgement of the experts.
- Administration of two RAND/UCLA Appropriateness Method instruments for eleven different prophylaxis alternatives (including no prophylaxis

and prolonged prophylaxis). One instrument was used with the medical panel and one with the surgical panel.

The study produced results for each of the methods that were of robust validity to construct the desired guidelines tool. As a consequence, the tool has been promulgated in the form of a *DecisionMatrix*™ for the appropriateness of prophylaxis of VTE. The contents of the DecisionMatrix™ are the results of an expert panel process based upon a comprehensive review of the literature and should in no case replace the advice of health professionals taking into account different national regulations regarding prescribing. This tool, in the form of a CD ROM, is available as a public service by Sanofi-Synthelabo.

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