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

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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:

**Literature review**

**Recruitment of expert members**

**Development and rating of risk factors:**
- PR: predisposing risk, odds-ratio evaluation
- ER: exposing risk, 5 point scale evaluation

**Development of patient cases and rating of appropriateness of prophylaxis:**
- medical patients
- surgical patients

**2 expert meetings (medical and surgical panel):**
- Finalisation of PR factors
- Modification of ER factors
- Discussion and reworking of appropriateness evaluation
- Creation of DecisionMatrix™ model

**Post meeting:**
- Finalisation and evaluation of ER factors
- Finalisation of appropriateness evaluation
- Validation of DecisionMatrix™ model using 2 sets of 54 patient cases

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.