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Strategies for Diagnosing Deep Vein Thrombosis

-a Cost Effectiveness Analysis

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Abstract

Economic evaluations are used in the health care sector to help decision makers allocate resources. The objective of this study is to evaluate the cost effectiveness of a new diagnostic algorithm of deep vein thrombosis. Patients with suspected deep vein thrombosis are common at emergency departments, although few actually have the disease. The new diagnostic algorithm combines a pre-test probability score and a D-dimer test, avoiding costly diagnostic imaging. The strategy is compared to "the old algorithm", which involves diagnostic imaging, and an alternative implementation of the new algorithm. The analysis is made from health care budget perspective, as well as a societal perspective. A cost effectiveness analysis was performed using a decision model. The same effectiveness was assumed for the different strategies. A decision tree was generated, incorporating the different strategies. A data material comprising 357 patients was obtained from a previous study made in seven hospitals in southern Sweden. The total cost of the new algorithm is estimated to €403 per patient, compared to the old and the alternative implementation of the new algorithm which are estimated to €576 and €419 respectively. Thus, the new algorithm is the most cost effective strategy and implies great savings potential not only for the health care sector, but also to society as a whole.

Keywords: Cost Effectiveness, Decision Analysis, Deep Vein Thrombosis, Diagnostic strategy.

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1. Introduction

Patients with suspected deep vein thrombosis (DVT) are common at emergency departments, even though the number of patients that have the disease is relatively small, about 40% (NBHW p. 137, 2004). There are different options available for physicians when determining a diagnosis. This cost effectiveness study compares three different strategies in diagnosing deep vein thrombosis. Until recently, DVT was diagnosed solely with diagnostic imaging, a strategy here referred to as the old strategy. These techniques are costly as well as time consuming. Diagnostic imaging cost up to €460 (Södra Regionvårdsnämnden p. 154) and takes up to 7 hours at the emergency department (Elf 2008a). During the last decade a new diagnostic strategy has been developed to diagnose DVT in a safe and inexpensive way. Such strategy, here referred to as the new diagnostic algorithm, combines a probability score and a D-dimer test. A large number of studies, in different settings, have shown that low clinical probability and a negative D-dimer test safely out rule suspected DVT (Andersson et al. 2000, Wells et al. 2003, Fancher et al. 2004, Wells et al. 2006, Ljungqvist et al 2008, etc). A patients' probability of having DVT is normally estimated by Wells score, a pre-test probability score. The level of D-dimer is measured trough a simple blood sample. The cost of a D-dimer test is about €16 (Södra Regionvårdsnämnden p. 113). Such strategy obviates the need for further diagnostic testing among a large number of patients. This strategy has been implemented faster in many European countries in comparison to Sweden (SBU p. 26, 2002). Some Swedish hospitals have implemented a strategy involving a D-dimer test and Wells score, but the strategy has been implemented in an alternative way; the D-dimer test includes all patients, before the probability score.

The new algorithm does imply large potential cost savings of the health care budget. Savings that are increasingly important as the the Swedish health care system is facing higher expenses due to an ageing population and more expensive technology.

1.1 Main Objective

The purpose of this research paper is to investigate the potential cost saving of the new diagnostic strategy of deep vein thrombosis. The main question is: "Is a strategy combining Wells score and D-dimer cost effective when diagnosing deep vein thrombosis?" Three different strategies are compared: 1) the new algorithm including a pre-test probability score and D-dimer test, 2) the old algorithm, including diagnostic imaging of all patients, and 3) an alternative implementation of the new algorithm. The comparison is investigated from the perspective of the health care sector and from a societal perspective.

1.2 Outline of the Study

Chapter 2 will give the reader an introduction to the different methods used to diagnose DVT. A brief literature study of previous research made about the new algorithm and a description of the material used in this research paper is also presented. Chapter 3 will explain the method used in this study and the different strategies compared will be presented in detail. The result of the research is described in chapter 4. The last chapter of the study consists of a discussion of results, policy implications and suggestions for further research in the field.

2. Background

This chapter will further introduce the reader to the nature of deep vein thrombosis (DVT) and how to diagnose it, as scholars in economics might not be familiar with the disease. This chapter also gives a brief overview of previous studies made in the field of cost effectiveness in diagnosing DVT and of the material upon which this study is based on.

2.1 Diagnosing Deep Vein Thrombosis

Deep vein thrombosis arises when a blood cloth, "thrombus", forms by coagulated blood in a deep vein. It most commonly occurs in the veins of the lower leg, sometimes of the thigh, although it can occur in other parts of the body. There are a number of reasons that makes diagnosing DVT a challenge to physicians. Firstly, the symptoms of the disease are non-specific and difficult to interpret. The affected extremity is most often painful, swollen and with enlarged superficial veins; symptoms that are diffuse and can occur in many other diseases as well. Secondly, a false diagnosis can have serious consequences. A false negative diagnosis can have fatal results if the clot dislodges and travel to the lungs; known as pulmonary embolism, or put the patient at risk for later complications, known as post-phlebitic syndrome. Furthermore, there is also a possibility of a false positive diagnosis, followed by unnecessary treatment and complications of those treatments.

The diagnostic praxis varies between regions as well as between individual physicians. Contrast venography has traditionally been the most common way of diagnosing DVT, and is still often referred to as the “gold standard”. Contrast venography is an invasive method that includes a small but significant risk of complications. It can be painful and is associated with allergic reactions and other side effects (Wells et. al. p. 1326, 1995). In many countries ultrasonography has therefore replaced venography to some extent. In many Swedish hospitals competent staff is not available 24 hours a day to use diagnostic imaging. Physicians may sometimes be forced to send a patient home with treatments over night, and to wait with diagnostic testing until the next day (Ljungqvist et al. p. 287, 2008). Furthermore both of these diagnostic strategies are expensive and time-consuming for both patients and highly skilled hospital staff at the emergency departments. In an estimation made by Elf (2008a) at the emergency department at Lund University, the total time a patient with suspected DVT spends at the hospital when undergoing diagnostic imaging, is about 7 hours.

D-dimer is a break-down product of the protein fibrin that develops when the cloth is formed. The high level of D-dimer is elevated in DVT, but also in a number of other conditions, such as infection, cancer, pregnancy and after surgery. The D-dimer test has a high sensitivity, but a low specificity[1]. Hence, a negative D-dimer can be used to exclude DVT in low risk patients, while a positive D-dimer never can be used to confirm the diagnosis. The D-dimer test is therefore combined with a "pre test" probability score; the probability before sequent testing. Wells score (Table 1) is now the most well known and most widely used prediction score for DVT (Kelly p. 1890, 2003). A swollen leg, tenderness, cancer, etc. increase the probability of DVT whereas an alternative diagnosis as likely or more likely than DVT, decreases the probability of DVT. A standardized probability score is preferred, since an empirical judgment of a patients probability based on a physician's clinical experience, depends highly on the observer (NBHW, p.22, 2004).

Table 1. Wells score

1. Active cancer - 1 point
2. Paresis, paralysis, or recent plaster or immobilization of lower limbs - 1 point
3. Bedridden > 3 days, or major surgery < 4 weeks - 1 point
4. Localized tenderness - 1 point
5. Entire leg swollen - 1 point
6. Calf swelling > 3 cm compared with asymptomatic leg - 1 point
7. Pittingoedema - 1 point
8. Collateral superficial veins - 1 point
9. Alternative diagnosis as likely or greater than DVT- Subtract 2 points

High probability: 3 or more points
Intermediate probability: 1-2 points
Low probability: 0 or less points

Source: Elf et al. 2008

The D-dimer test, in combination with Wells score, has gained wide acceptance in diagnosing DVT as it can exclude every third patient suspected of having the disease (Righini et al. p.

[1]Sensitivity measures the proportion of actual positives which are correctly identified as such, and specificity measures the proportion of negatives which are correctly identified. Hence, high sensitivity means few false negatives and a high specificity means few false positives. There is often a trade off between the two measures.

1059, 2008). The test has been used in many European countries, but Sweden has been pending (SBU p. 26, 2002). The D-dimer test is inexpensive, about €16 (Södra Regionvårdsnämnden p. 113), and simple to use. There are strong reasons to believe that the new strategy is cost saving, because of the small number of people that actually has DVT out of the large group of people with suspected DVT.

2.2 Previous Research

During the last decade several other clinical studies and meta analysis of studies have shown that a combination of low clinical probability and a normal D-dimer result safely excludes DVT (Andersson et al. 2000, Wells et al. 2003, Fancher et al. 2004, Wells et al. 2006, Ljungqvist et al. 2008, Elf et al. 2008, etc).

In 2004 the Swedish National Board of Health and Welfare (NBHW) published guidelines on diagnosing venous thromboembolism[2]. The board stated that a negative D-dimer test among patients with low probability can exclude DVT (NBHW, p. 114, 2004). The guidelines were based upon a SBU-report made in 2002, and other studies made after the SBU publication. When the new guidelines were published, contrast venography was still the dominating method of diagnosing DVT in Sweden (NBHW, p. 137, 2004). Neither SBU nor NBHW have yet published any further research about how the guidelines may have changed the praxis at emergency departments in Swedish hospitals.

When the SBU report was published in 2002, only three studies dealing with the health economic aspects of diagnosing DVT were found to be relevant in a Swedish clinical setting. The report concludes that not enough research had been done to certify whether a certain diagnostic method, or combination of methods, was more cost effective (SBU p. 321, 2002). Ever since, several cost effectiveness studies have been made. One example compared 18 different strategies for diagnosing DVT to identify the most cost effective strategy for the UK National Health Service (Goodacre et al. 2006). The study consisted of a decision analysis model that included costs and outcomes, valued as quality adjusted life years (QALYs). The optimal and most cost effective strategy was to exclude patients with low Wells score and negative D-dimer from further testing, and to limit ultrasonography to patients with high Wells score or positive D-dimer. The strategies that involved radiological testing for all

[2]Venous thromboembolism (VTE) is the collective term for deep vein thrombosis and pulmonary embolism.

patients were considered unlikely to be cost effective (Goodacre et al. p 384, 2006). Whether an intervention was cost effective was determined by a particular threshold value of willingness to pay per QALY. The threshold for willingness to pay recommended by the National Institute for Clinical Excellence, used in this study was £20 000 per QALY (Goodacre et al. p 381, 2006)

Although several studies concerning the cost effectiveness of the new algorithm have been made internationally, number of reasons makes this study unique. The prevalence of DVT is suspected to be higher in Scandinavia than in other countries (Elf et al. 2008), and few studies of low probability score and D-dimer test have been done in Scandinavian countries. Furthermore, the costs of the health care systems and of different procedures differ in different parts of the world. Therefore, it is important to investigate this strategy in particular settings, in this case Skåne and Sweden.

2.3 Material

This paper is based on a study, *"Clinical probability assessment and D-dimer determination in patients with suspected deep vein thrombosis, a prospective multicenter management study",* published in 2008 by J.L. Elf, K. Strandberg, C. Nilsson and P.J. Svensson. The study was made between December 2003 and December 2005, and investigated the reliability of a pre-test probability score followed by a D-dimer test to exclude DVT. 357 patients with suspected DVT at emergency departments were included in the study. The study concludes that Wells score and D-dimer safely rules out DVT in about 30% of outpatients with suspected DVT (Elf et al. 2008). Although the Swedish study can be considered limited due to a limited sample, the number of other studies which reach the same conclusion supports the implication of a safe strategy.

This research paper is also based on estimations published in the guidelines of the Swedish National Board of Health and Welfare (NBHW s. 143, 2004). This paper can be considered a replication study to a certain extent. The guidelines compares cost estimations of a strategy combining a pre-test score and D-dimer, to the cost of a strategy involving diagnostic imaging.

3. Method

Economic evaluations, dealing with costs and benefits of different strategies, can help decision makers within the health care sector to allocate recourses in an optimal way. When adopting the appropriate diagnostic strategy for deep vein thrombosis (DVT), we have to decide how much we, as a society, are willing to pay to achieve health gains, and take into consideration whether recourses could be better spent elsewhere. This section will discuss the importance of economic evaluation and further explain the method used in this study.

3.1 Perspective

There are three different perspectives when making an economic evaluation. The *"welfarist"* perspective is consistent with economic theory, from which economic evaluations gives the same result as a free market would. With an *"extrawelfarist"* perspective, the economic evaluation aim to optimize the recourses of the health sector budget, comparing the costs with the health gains. The *"decision maker"* perspective takes on a broader societal perspective, including a wider range of costs and consequences. (Drummond p.17-18, 2005)

This analysis is made from a "decision maker" perspective, aiming to optimize the resources of the health care sector as well as the whole society.

3.2 Why make an Economic Evaluation?

Sweden is quite well known for its generously publicly financed health care system. Citizens get health care based of need - not based on ability to pay. Based on economic theory, one could argue that public intervention is justified when we regard health care as a common good. Health care is not a public good, as consumption of health care is private. It does however have some public good characteristics since positive externalities arises from health care. These would be undersupplied by the competitive market, as the price does not reflect the entire cost (Folland et al. p. 411, 2007). An illustrative example of a positive externalities in health care, are the gains that arises to the society from public vaccination programs. Such support the argument of government intervention. Nevertheless, recourses are scare and priorities have to be made. How much resources are we, as a society, willing to devote to improve health gains or to always make an accurate diagnosis? A number of procedures can be done when diagnosing DVT, but there is a decreasing rate of return on additional information. So where do we set the limit?

What health care institutions can provide technically is increasing, as new technology is developed. The population in Sweden is however ageing, and a shrinking tax base is to finance the health care. Therefore, health economics and economic evaluations are increasing in importance in today's public sector. Economic evaluations have increased rapidly the last decades. Economic evaluation has been defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (Drummond et al. p. 9, 2005). Hence, when making a full economic evaluation in health care, the difference in costs has to be compared to the difference in consequences. Decision makers are not only concerned with the cost of a health program, but obviously also the outcome.

3.3 A Cost Effectiveness Study

There are several ways to make an economic evaluation, depending on the measurement used when evaluating the consequence. This study measures the effect of diagnostic strategies as the number of cases of DVT detected, and is therefore to be considered a cost effectiveness evaluation. In this research paper, all strategies are assumed to have the same effectiveness, which is supported by the literature. A study made by Wells (2003) concludes that a combination of a standardized clinical judgment of low probability and a negative D-dimer test is as accurate as ultrasonography to exclude DVT (Wells et al. p. 1227, 2003). Based on expert opinion (Svensson 2008, Elf 2008b), the risk of a false diagnosis is considered the same for all strategies. This assumption is done despite the fact that the data material from the study made by Elf et al. (2008) contained one false negative result, meaning that one person got the diagnose healthy although the patient had DVT. This case was a distal DVT[3] , and the

[3]Proximal DVT is generally defined as above the knee and distal DVT refers to below the knee.

reason why it was not detected is explained by the D-dimer tests' lower sensitivity for distal, rather than proximal DVT. A proximal carries a greater risk of propagating into pulmonary embolism than a distal DVT and therefore a missed distal DVT is not as potentially serious as a missed proximal (Goodacre et al p. 524, 2005).

As the effectiveness of the different strategies is the same, all cases of DVT are assumed to be detected. Therefore, quality adjusted life years, due to a false negative diagnosis or over treatment, have not been calculated in this study.

3.4 Decision Analysis Model

Choosing an appropriate diagnostic strategy requires consideration of the risks and benefits involved, but also the costs of the different options. To investigate the three different strategies in this paper, a decision tree model has been developed to address the different strategies.

The theoretical foundation of decision analysis can be found in statistical decision theory (Drummond et al. p. 277, 2005). The method has been used widely in the fields of business and engineering, as it provides a framework for decision making under conditions of uncertainty. It is also becoming common in health care systems, especially when deciding whether to adopt a new health technology, such as pharmaceuticals. Decision analysis becomes a useful tool as it brings together evidence, probabilities and costs, from a range of different sources (Drummond et al. p.278, 2005). The decision tree is one of the most widely used methods for decision models in economic evaluation. In this paper the decision tree is used to illustrate the different diagnostic strategies compared. The square boxes illustrate decision nodes that represent a decision in the model. The circles are the chance nodes, illustrating the different possible pathways as results of the prior decisions, and defining the uncertainties in the strategy. The probabilities of these events are conditional probabilities, as they only relate to those patients who have experienced the previous event. A number of mutually exclusive pathways are determined in this way, where a given patient can follow only one of these paths. The probability of each pathway is calculated by multiplying the probabilities, resulting in the probability summing to 1 for each strategy. Each pathway is also associated with a cost. The expected cost for each diagnostic strategy is calculated as the sum of the costs weighted by the probabilities of events for the particular pathways for that strategy.

3.5 Strategies compared

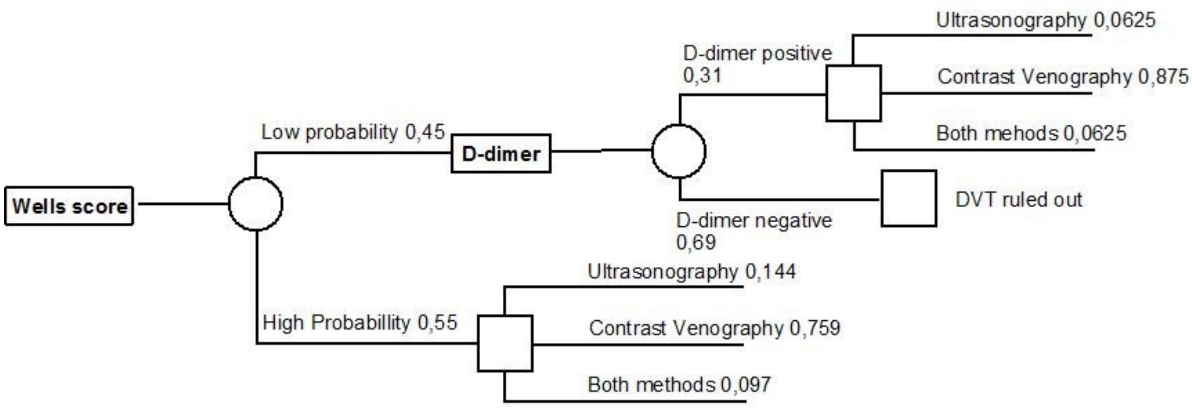
3.5.1 New Diagnostic Algorithm

The algorithm investigated by Elf et al. (2008), a combined strategy of a Wells score followed by a D-dimer test, is here referred to as the new diagnostic algorithm. The algorithm is based on Bayes' theorem which states that the probability that a patient has a disease is based on the pretest probability before the test, and the accuracy of the test.

In the data material, the patients are divided into low, intermediate and high risk groups according to Wells score. In this study, the division is only made between low and high risk, as the diagnostic strategy for the intermediate and high risk groups are the same.

In the study made by Elf et al. (2008) 11 patients who had a low probability and a negative D-dimer, still underwent diagnostic imaging based on the physician's clinical judgment. These patients are excluded from this analysis as physicians are assumed to follow the algorithm. Consistently, the patient who had a positive D-dimer but was ruled out for DVT in the data, is excluded from this study.

Figure 1. New Diagnostic Algorithm

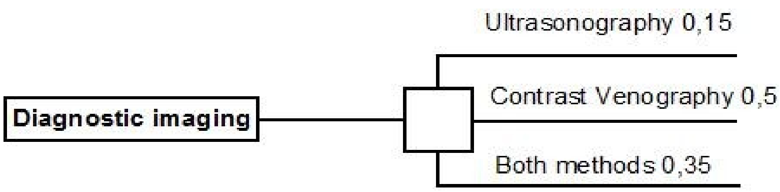


3.5.2 Old Diagnostic Algorithm

The old praxis of diagnosing DVT is to use diagnostic imaging for all patients, without distinguishing between low- and high probability groups. This strategy is not likely to be cost effective due to the small number of people that actually has DVT out of the large group of people with suspected DVT, the large costs of contrast venography and ultrasonography, and the long waiting times. The reason that some patients undergo both types of imaging is based on the understanding that ultrasonography is not enough to exclude the possibility of distal DVT or that the venography examination is technically suboptimal.

The distribution between the different methods of diagnostic imaging are estimates made in the SBU-report about hospital practice of diagnosing DVT before D-dimer and Wells score was an option.

Figure 2. Old Diagnostic Algorithm



3.5.3 Alternative Implementation of New Algorithm

An increasing number of hospitals in Europe has implemented the new diagnostic algorithm over the last decade. There are reports that indicate that some emergency departments have implemented the new algorithm in an alternative way.

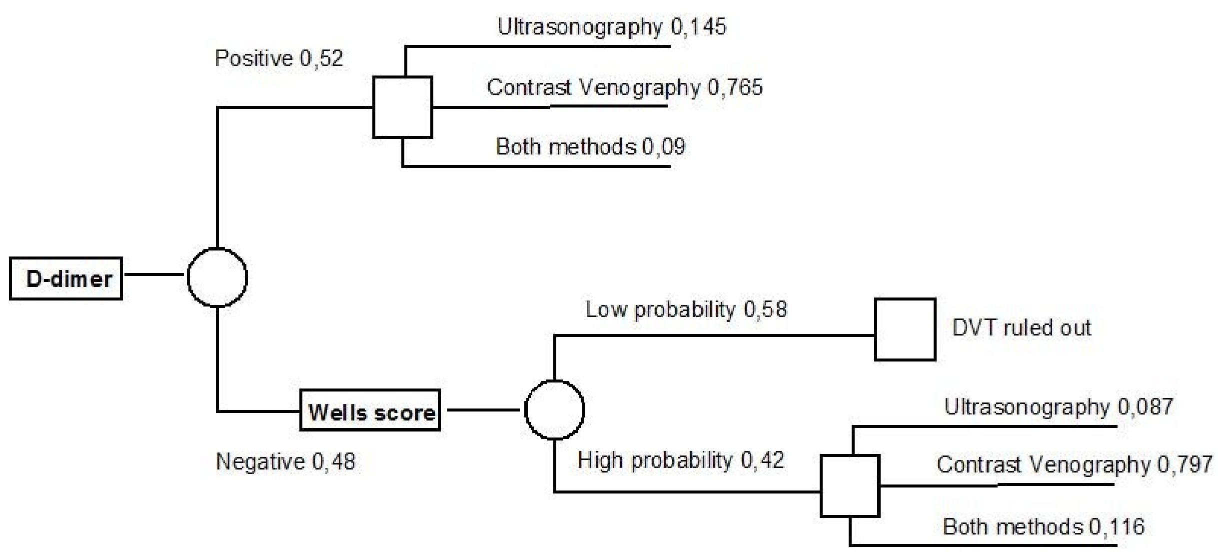
The consequences of what is called "alternative implementation of new algorithm" differ from the new algorithm in two ways. In the alternative algorithm the D-dimer test is taken by the nurse as the patient arrives to the emergency department, before the patients meets the physician. Wells score is not used until after the blood sample. The result of this strategy is that all patients, both low probability patients as well as high probability patients, take a D-dimer test. This procedure differ from the new algorithm, where the level of D-dimer is only examined in low probability patients. This is naturally an increase in the direct cost. Since the D-dimer results are ready when the patient meets the physician, the algorithm is time saving for the patient and the hospital, and is therefore a decrease in indirect cost.

The other consequence of the alternative implementation is that a greater number of patients are likely to be included in the group of suspected DVT. A negative D-dimer reduces the probability of DVT substantially, thus a negative D-dimer can out rule DVT in a safe way. On the other hand, a positive D-dimer does only increase the risk for DVT marginally since a positive D-dimer can depend on many other factors. The positive predictive value is therefore useless since there are many false positives, while the negative predictive value is accurate. However, some physicians seem to believe that a positive D-dimer does increase the risk for DVT (Elf 2008b). Therefore, a larger number of patients are placed in the group of "suspected DVT" even though some cases of a positive D-dimer could be the result of an infection in the leg or a sprained ankle (Elf 2008b).

Since data of this strategy is not available, the effects of a larger number of patients included in the suspected DVT group could not be included in the analysis. Thus, the costs for an alternative implementation of the new algorithm are underestimated in these calculations, as a larger share of the patients would be tested further with diagnostic imaging.

There are no reports on to what extent this strategy is used in Swedish hospitals.

Figure 3. Alternative Implementation of New Algorithm



3.6 Estimation of Costs

The costs included in this study are the costs affecting the health care budget, and the cost imposed on the society as a whole. The direct costs are health care costs, such as the costs for personnel and equipment. Indirect costs occur when patients spend time at the hospital instead of working, or as a loss of leisure time. Such cost is also important to include as productivity gains give rise to tax revenue, it also affects the health care budget. Table 2 presents a list of all direct costs used in the analysis.

Table 2. Valuation of Direct Cost (EUR 2008)

Method	**Cost**	**Source**
D-dimer	€ 16	Södra Regionvårdsnämnden p. 113, 2008
Ultrasonography	€ 157	Södra Regionvårdsnämnden p. 148, 2008
Contrast Venography	€ 461	Södra Regionvårdsnämnden p. 154, 2008

All costs are reported in Euro currency value of 2008[4]

To ensure that the prices of the methods used in the analysis reflect the direct costs of the strategies, prices between health care regions are used. These "out regional costs" reflects all overhead costs; including time, nurses and physicians spend with the patients.

The different strategies result in different times of waiting at the emergency department shown in table 3 below. This results in different indirect costs for each strategy. As market values are absent, the indirect cost of waiting time was estimated by using values for loss of production or loss of leisure time. Such costs are difficult to estimate and different health economic evaluations use different approaches on how to do so. The human capital approach estimates productivity changes by using gross earnings, including employment costs such as social fees. The alternative, the friction cost approach, estimates the productivity changes depend on the time that organizations need to restore the initial production level, which differ substantially between different types of work. In this analysis there is only a very short period of time each patient is absent from work. Therefore, the difference between the approaches

[4] 1 EUR = 9,6055 SEK, average exchange rate 2008 (Swedish National Bank 01/01/09).

becomes less important. There are however, a number of concerns to take into account when including productivity changes in an economic evaluation. For example, by including productivity loss, one assumes that the community loses employed labour. However, it might be the case that pools of unemployed labour fill the gap vacated by patients visiting the hospital. For a short-term absence, as in this case, the worker may compensate losses of production later, or by colleagues. Moreover, the value of the production loss is likely to be lower than the average wage. As most categories of work include more and less important tasks, it is the less important ones that are likely to be left behind because of short-time absence. (Drummond p. 84-85, 2005)

Patients are left with substantially different waiting times depending on what strategy is used. Since the most obvious benefit for the patients is the reduced waiting time, a valuation of time is a substantial part of this study.

Table 3. Average Waiting Time

Algorithm	**Waiting time**	**Source**
New Algorithm (Low prob. + Negative D-dimer)	3h 50 min	Elf 2008a
New Algorithm (Positive D-dimer / High prob.)	8h	
Old Algorithm	7h	Elf 2008a
Alternative Algorithm (Negative D-dimer + Low prob.)	2h 50 min	Elf 2008a
Alternative Algorithm (Positive D-dimer)	7h	

For patients who are in working age, the productivity loss is estimated by using the gross average wage in Sweden 2007 (Statistics Sweden a), inflated to 2008 price level by using consumer price index from Statistics Sweden (Statistics Sweden b). Additional costs of employment are included by assuming a social fee of 38,8% (Ekonomifakta 2009). For patients who are assumed to be retired or unemployed, the indirect cost is calculated as cost of lost leisure time. Patients in the data who are over 65 years old are assumed to be retired. One way to estimate the cost of lost leisure time used in many health economic evaluations is to use estimations made by the transportation sector. In a report from 2007, the estimations of waiting time made by the Swedish road administration varied from a value of € 1 to €27, depending on the total time of waiting and the mean of transportation (Vägverket p. 30, 2008). Another way to estimate leisure time, which is used in this paper, is to assume a 35% value of the average gross wage. This method has been used in previous economic evaluations of health care in Sweden (See for example Johannesson 1996, Claesson et al. 2000, Kobelt et al. 2005).

Table 4. Valuation of Indirect Cost (EUR 2008)

Patient group	**Productivity loss/ Loss of leisure time**	**Source**
Working age (52%)	€ 22 /hour	Statistics Sweden (a)[5]
Retired (43,4%)	€ 7,7 /hour	(Estimation)
Unemployed (4,6%)[6],	€ 7,7 /hour	(Estimation)

All costs are reported in Euro currency value of 2008[7]

The indirect cost of patients' waiting time at the primary care, before coming to the emergency department, is not included since it is assumed to be the same for all strategies. The time family members spend accompanying a patient, known as informal care, is not included in the analysis. This may result in underestimated indirect costs.

3.7 Probability of Events

Probabilities have an important role in decision analysis. Probabilities are the measured frequency of an event in a sample or a population. In a decision tree, the probabilities are used to calculate the expected cost of each strategy. In this analysis the probabilities for the new and the alternative diagnostic algorithm are based upon a clinical trial in study (Elf et al. 2008) and the probabilities for the old diagnostic algorithm are based on approximates made in the guidelines of the Swedish National Board of Health and Welfare (NBHW p. 143, 2004).

The risk of getting DVT increases with age. Therefore the probabilities are age specific; elderly are more likely to have high probability and a positive D-dimer than working and unemployed. This has been acknowledged when estimating the probabilities of the different

[5]The average monthly wage is converted to hourly wage by assuming 8 hours working day and 22 working days per month.
[6]The Swedish "AKU" measure from 2007 is used here (Statistics Sweden, p.14 2007) as it includes the age group 16-64. That is to be distinguished from the ILO measurement used in EU since 2007, which includes the age group 15-74.
[7] 1 EUR = 9,6055 SEK, average exchange rate 2008 (Swedish National Bank 01/01/09).

strategies, as it affects the indirect cost. The age specific probabilities are shown in Table 5 below.

Table 5. Patient Specific Probabilities

Algorithm/Patient Group	**Retired** (43,4%)	**Unemployed** (4,6%)	**Working** (52%)	**Source**
New diagnostic Algorithm				
Low Wells score + Negative D-dimer*	0,239	0,361	0,361	Elf et al. (2008)
Low Wells score + Positive D-dimer*	0,147	0,129	0,129	Elf et al. (2008)
High Wells score	0,613	0,510	0,510	Elf et al. (2008)
Old diagnostic Algorithm				
Diagnostic imaging	1	1	1	NBHW (2004)
Alternative Algorithm				
Negative D-dimer ** + Low Wells score	0,18	0,354	0,354	Elf et al. (2008)
Positive D-dimer**	0,82	0,646	0,646	Elf et al. (2008)

*D-dimer at Emergency department
**D-dimer at Coagulation Laboratory

The study made by Elf et al. (2008) did not include D-dimer tests in high probability patients at the emergency department. The blood samples were saved and analyzed at a coagulation laboratory, after the initial study was made. The probabilities for the alternative implementation of the new algorithm are based on the D-dimer tests made at the coagulation laboratory.

3.8 Dealing with Uncertainties

As the parameters of probabilities are estimated from sampled data, the parameters will represent the particular sample. Whether this sample is a representative selection is still a matter of uncertainty. Because of the uncertainties and variabilities some parameters are to be further scrutinized in a sensitivity analysis. A sensitivity analysis varies certain input variables and assesses how this affects the result of the model. Since only one parameter is varied at a time, it fails to describe the complete picture of uncertainty. A sensitivity analysis does however give an important indication of the significance of particular parameters.

When making a sensitivity analysis it is important to justify how the plausible range is chosen, by reviewing previous literature in the field or consulting expert opinion (Drummond p. 42 2005). The result of the D-dimer analysis can differ between different types of D-dimer tests for individual patients, as the test is not standardized (Neale et al. 2004 p. 663). The result of Wells score can also differ to a certain extent due to the judgment of individual physicians. The D-dimer and Wells score will therefore be varied according to the estimated made by the National Board of Health and Welfare(NBHW p. 139, 143, 2004). Therefore, 80% of the patients with low probability are assumed to have a negative D-dimer to see what impact the D-dimer has on the result. Moreover, 35% of the patients are assumed low probability patients to see what impart that has on the result.

There is a problem of variability, since some input variables may vary systematically in different locations. The time of waiting can differ substantially between hospitals. It also depends on whether it is a weekday or a weekend, and what time of the day a patient enters the emergency department (Elf 2008a). To my knowledge, there is however no other available sources of waiting times than the estimates made by Elf at Lund University Hospital (2008a). Therefore, this variabel will not be used in the sensitivity analysis.

4. Results

In this chapter, the result tables will be presented. The costs are presented from a health care budget perspective and from a societal perspective. The total cost for Skåne and Sweden are also estimated by enlarging the cost to the regional and the national level. The incidence of deep vein thrombosis (DVT) in Sweden is about 1,6 per 1000 inhabitants (Nordström et al. p. 155, 1992). The research about the number of suspected deep vein thrombosis is limited. In this analysis, actual cases are assumed to be 40% of suspected cases, as it is the estimate used by the Swedish National Board of Health and Welfare (NBHW p. 147, 2005). Expert opinion does however indicate that actual cases could be as little as 20% (Svensson 2008). With today's population[8], the number of suspected cases would reach approximately 37 000 patients in Sweden and approximately 4 800 cases in Skåne[9] every year. Costs may vary within a country, which may affect the optimal diagnostic strategy. The local costs should be implemented to make a full evaluation of the national costs. In Sweden costs vary marginally. The costs in Skåne are used to estimate the national expenditure, as these were the data available.

4.1 Heath Care Budget Perspective

The result of a health care budget perspective is presented in terms of direct cost.

Table 6. Direct Cost

Direct Cost (EUR) Prices 2008

	New Algorithm	Old Algorithm	Alternative Algorithm
Average cost/patient	311	471	333
Direct cost Skåne	1494000	2257000	1598000
Direct cost Sweden	11517000	17407000	12324000

For detailed calculations see appendix A

[8] In October 2008 the Swedish population was approximately 9 250 000 inhabitants (Statistics Sweden c)

[9] In 2007 the population i Skåne was approximately 1 200 000 (Statistics Sweden d)

It is obvious that the old algorithm is not cost effective in the results presented above. The new algorithm is the most cost effective of the three optional strategies, reaching an estimated direct average cost of €311 per patient, compared to the old and the alternative implementation of the new algorithm, which are estimated to €471 and €333 respectively.

Looking at the national expenditure, the new algorithm reaches approximately €11 million, compared to the old and the alternative algorithms, which are estimated to €17 and €12 respectively. An implementation of the new algorithm would hence save almost €6 million per year in direct costs compared to the old algorithm.

4.2 Societal Perspective

The societal perspective also includes indirect costs, estimated by including loss of production for patients in working age and loss of leisure time for patients who are assumed to be retired or unemployed.

Table 7. Indirect Cost

Indirect Cost (EUR)Prices 2008

	New Algorithm	Old Algorithm	Alternative Algorithm
Average cost/patient	92	106	86
Indirect cost Skåne	439000	506000	411000
Indirect cost Sweden	3387000	3905000	3170000

For detailed calculations, see appendix B

The indirect cost, calculated as productivity loss and loss of leisure time, is least prominent in the alternative implementation of the new algorithm. The alternative algorithm is estimated to €86 per patient and approximately €3,2 million for Sweden. This is because the waiting time is shorter, as the D-dimer test is performed while the patient waits to see the physician. The old algorithm is most expensive due to the long waiting time for diagnostic imaging, where the cost for one patient is estimated to €106.

Table 8. Total Cost to Society

Total Cost (EUR) Prices 2008	New Algorithm	Old Algorithm	Alternative Algorithm
Average cost/patient	403	576	419
Total cost Skåne	1933000	2764000	2009000
Total Cost Sweden	14905000	21312000	15493000

Total cost is the sum of direct cost, and the indirect cost. Results above show that the new algorithm of diagnosing DVT, summing up to a total cost of approximately €15 million in Sweden, is the least expensive strategy. The difference from the old algorithm, which is estimated to about €21 million, is evident; resulting in a difference of more than €6 million every year. The gap between the new algorithm and the alternative implementation of the new algorithm is estimated to approximately €600 000 on the national level. Only looking at Skåne, the cost savings are over €800 000 each year comparing the new and old algorithm. The direct cost represents the greatest part of the total cost for all strategies.

4.3 Sensitivity Analysis

A sensitivity analysis was carried out to deal with some degree of uncertainty in the new diagnostic algorithm. In the table below, we can see what impact the D-dimer estimation of the guidelines has on the direct cost. In the guidelines made by the Swedish National Board of Health and Welfare, 80% of the patients with low probability estimated to have a negative D-dimer. The probabilities of D-dimer in the study made by Elf et al. (2008) could therefore underestimate the total number of patients with a negative D-dimer.

Table 9. Direct Cost using different D-dimer Results

Direct cost (EUR) Prices 2008 Negative D-dimer 80%	New Algorithm
Average cost/patient	289
Direct cost Skåne	1389000
Direct Cost Sweden	4283000

Using the estimate of the guidelines, would make the new algorithm even more cost effective. It is apparent that the direct cost is sensitive to the level of negative D-dimer results.

The proportion of low and high risk patients could vary in different municipalities due to demographic components etc. In the previously published guidelines, 50% of the patients were assumed to have low probability, which is fairly in accordance with the data used in this analysis where low probability and high probability patients were 45% and 55% respectively. Nevertheless, an assumption of 35% was also presented in the guidelines, to see what impact it would have on potential savings.

Table 10. Direct Cost using different share of Low Probability Patients

Direct cost (EUR) Prices 2008
Low Probability 35%

	New Algorithm
Average cost/patient	338
Diect cost Skåne	1622000
Direct cost Sweden	12508000

In accordance with the guidelines, the assumption that only 35% of the patients are estimated to have low probability in Wells score is made in Table.5 above. Evidently, the result is also sensitive to the number of patients that are scored as high or low probability of having DVT prior to the D-dimer test. If only 35% are assumed low probability patients, the new algorithm is not as cost effective as before. However, the difference to the old algorithm is still large; approximately €338 per patient on average for the new strategy compared to €471 for the old strategy. Hence, the saving potential to the health care sector is still large.

5. Discussion

The results shows that the new diagnostic algorithm is most cost effective to diagnose deep vein thrombosis (DVT) of the algorithms compared in this study, under the assumption that all algorithms have the same effectiveness. The new algorithm, involving Wells score and a D-dimer test, has an estimated total cost of €403 per patient, compared to €576 for the old algorithm. The reduction of cost is due to the opportunity to exclude low probability patients from diagnostic imaging, which is costly and time-consuming. Furthermore, there is another benefit of the new algorithm, mentioned earlier, that cannot be measured in monetary terms. The convenience of a non invasive strategy for low probability patients means that fewer patients has to go through contrast venography, associated with a small but significant risk of complications. The new algorithm is also more cost effective than the alternative implementation of the new algorithm, which is estimated to €419 per patient.

The result can be considered generalizable to other settings to a certain extent. Even though costs differ between countries and regions, the difference in cost is so evident that the new algorithm is likely to be cost effective compared to the old algorithm in other settings as well. Studies in other settings, such as the one made by Goodacre et al. (2006) reach the same conclusion; a diagnostic strategy involving Wells score and D-dimer is more cost effective than diagnostic imaging. Moreover, as the prevalence is assumed to be higher in Scandinavia than in other countries, the new algorithm can be assumed even more cost saving in other settings, as fewer patients have to attend costly diagnostic imaging.

However, the alternative implementation could be more cost effective in another setting, if the indirect costs were to constitute a higher proportion of the total cost. Saving one hour waiting time for patients and hospitals could result in a less expensive strategy, even though a greater number of patients take a D-dimer test compared to the new algorithm.

Procedures differ between hospitals when patients enter emergency departments and the waiting times differ substantially. The estimated time of waiting in this analysis could be overestimated since Lund University hospital, where the estimates were made, has longer waiting times than many other hospitals (Elf 2008b). That would indicate that expected cost of the old strategy is overestimated, since the old algorithm would be less expensive if the waiting times were to be shorter. On the other hand, the indirect cost could be underestimated, which would make the old algorithm more expensive. Informal care is not included, which indicates an underestimation of the indirect costs.

As this paper is based on a clinical study, it is important to consider whether the trial reflects what would happen in regular practice. One uncertainty concerns the distribution between contrast venography and ultrasonography. There are reasons to believe that the hospitals where the study was made use contrast venography more frequently than what is common practice in Sweden (Elf 2008b). This has to be taken into account when comparing and making conclusions about the different strategies. Since contrast venography is the most expensive of the methods in diagnostic imaging, the new algorithm is likely to be even more cost effective compared to the old algorithm, if contrast venography is used to a lesser extent.

Another uncertainty that should be acknowledged is the fact that the D-dimer analyses differ between the new and the alternative algorithms. The D-dimer analyze is from the same clinical trial and the same patient group, but since the new algorithm is based on D-dimer results from the tests analyzed at the emergency department, and the alternative algorithm is based on results from D-dimer analysis from a coagulation laboratory, results can differ between individual patients. The diagnostic performance is better in a laboratory, with highly skilled personnel, than in an emergency department, with less experienced staff (SBU, p. 26, 2002).

Because of uncertainty regarding the D-dimer analysis and proportion of low and high probability patient groups, a sensitivity analysis was carried out. The new algorithm would be even more cost effective if 80% of the patients had negative D-dimer, instead of 69%. The direct cost of the new algorithm would be €289 instead of €311 per patient. If the number of patients with low probability would be 35% instead of 45%, the new algorithm would cost €338 per patient. Thus, the result is sensitive to the number of patients in the population who has negative D-dimer as well as low probability.

One weakness of this study that should not be omitted, is the fact that the different strategies are assumed to have the same accuracy and therefore the same risks of a misdiagnosis. While investigating different approaches on how to diagnose a disease, one important part is evidently to analyze the effectiveness of the different diagnostic methods. More detailed research about the effectiveness of the different strategies is therefore desirable.

Implementing this new diagnostic algorithm for patients with suspected DVT implies great cost savings for the health care sector in Skåne and in Sweden, as well as from a societal point of view. The differences between strategies become more obvious, when enlarged to the regional and the national level. The national expenditure could decrease with €6 million per year, moving from the old to the new algorithm. Only in Skåne, the region could save €800 000 per year. The findings of this research support the implementation of what has here been called the new diagnostic algorithm in diagnosing DVT. This implies a policy change in Swedish health care praxis, with the result of resources being spent more efficiently. Although several studies have shown the benefits of implementing the new algorithm, there still seem to be reluctance among physicians to adopt the new strategy. One reason for this hesitation could be due to the lack of standardization of D-dimer assays (Elf et al. p. 2, 2008). There are a number of different types of D-dimer tests, and since they are not standardized and often read manually, they may differ in their result (Andersson et al. p. 229, 2000).

Although this study does not alone constitute the basis to which upon health care decision makers should base their decisions, this evaluation does however provide important information that increases the understanding of the usefulness of a combined strategy of Wells score and D-dimer.

6. References

Claesson, L., Gosman-Hedstrom, G., Johannesson, M., Fagerberg, B., and Blomstrand, C. (2000), "Resource Utilization and Costs of Stroke Unit Care Integrated in a Care Continuum: A 1-Year Controlled, Prospective, Randomized Study in Elderly Patients: The Goteborg 70+ Stroke Study", *Stroke - the Journal of American Heart Association* Vol 31, Issue 11, pages 2569-2577.

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B., Stoddart, G. L.(2005), *Methods for the Economic Evaluation of Health Care Programmes.* Third edition. Oxford University Press: Oxford.

Ekonomifakta (2009), "Sociala avgifter". Downloaded 2/07/09 from http://www.ekonomifakta.se/sv/Fakta/Arbetsmarknad/Arbetsgivaravgift/

Elf, J.L., Strandberg, K., Nilsson C.,and Svensson, P.J. (2008), "Clinical probability assessment and D-dimer determination in patients with suspected deep vein thrombosis, a prospective multicenter management study", *Thrombosis Research,* May 29.

Fancher, T.L., White, R.H.,Kravitz, R.L. (2004), "Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review", *British Medical Journal,* Vol. 329, Issue 821.

Folland, S., Goodman, A. C., Stano, M. (2007), *The Economics of Health and Health Care*. Fifth edition; Pearson Education, Upper Saddle River

Lind, M., Jansson, J.H. (2006), "ABC om Djup ventrombos" *Läkartidningen* Vol. 103, Issue 13, pages 1031-1034

Goodacre et al. (2006), "How should we diagnose suspected deep vein thrombosis?"

Quarterly Journal of Medicine, Vol. 99, Issue 9, pages 377-388.

Goodacre, S., Sampson, F.C., Sutton, A.J., Mason, S., Morris, F. (2005), "Variation in the diagnostic performance of D-dimer for suspected deep vein thrombosis", *Quarterly Journal of Medicine* Vol. 98, Issue 7, pages 513-527.

Johannesson M. (1996) *Theory and Methods of Economic Evaluation of Health Care.* Dordrecht: Kluwer Academic Publishers

Kobelt, G., Lindgren, P., Lindroth, Y., Jacobson L. and Eberhardt, K. (2005) "Modelling the effect of function and disease activity on costs and quality of life in rheumatoid arthritis", *Rheumatology,* Vol. 44 Issue 9, pages 1169-1175.

NBHW (2004), *Socialstyrelsens riktlinjer för vård av blodpropp/venös tromboembolism,* Stockholm: Elanders Gotab. Downloaded 12/14/2008 from http://www.socialstyrelsen.se/Publicerat/2004/8510/2004-102-3.htm

Neale, D., Tovery, C., Vali, A., Myers, K., Obiako, M., Ramkumar, V., and Hafiz, A. (2004), “Evaluation of the Simplify D-dimer assay as a screening test for the diagnosis of deep vein thrombosis in an emergency department”, *Emergency Medical Journal,* Issue 21, pages 663-666

Nordström M, Lindblad B, Bergqvist D, Kjellström T (1992). “A prospective study of the incidence of deep-vein thrombosis within a defined urban population”, *Journal of Internal Medicine* Vol. 232, Issue 2, pages 155-160.

Righini, M., Perrier, A., De Moerloose, P., and Bounameaux, H. (2008), ”D-dimer for venous thromboembolism diagnosis: 20 years later”, *Journal of Thrombosis and Haemostasis,* Vol. 6, Issue 7, pages 1059-1071.

SBU - Statens beredning för medicinsk utvärdering (2002), *Blodpropp - förebyggande, diagnostik o behandling av venös tromboembolism*. Downloaded 12/16/2008 from http://www.sbu.se/upload/Publikationer/Content0/1/blodpropp_2002/blodproppfull.html

Statistics Sweden (a), “Genomsnittlig månadslön efter sektor 1992-2007”, downloaded 01/13/2009 from http://www.scb.se/templates/tableOrChart____149087.asp

Statistics Sweden (b), “Konsumentprisindex (1980=100), fastställda tal”, downloaded 01/13/2009 from http://www.scb.se/templates/tableOrChart____33847.asp

Statistics Sweden (c), “Snabba siffror” downloaded 01/02/2009 http://www.scb.se/

Statistics Sweden (d), “Folkmängd i riket, län och kommuner efter kön och ålder 31/12/2007”, downloaded 01/02/2009 from http://www.scb.se/templates/tableOrChart____159277.asp

Statistics Sweden (2007), *”Labour Force Survey 2007”* Downloaded 12/09/2008 from http://www.scb.se/templates/PlanerPublicerat/ViewInfo.aspx?publobjid=7033 &lang=EN

Swedish National Bank, (01/01/2009). Downloaded 01/01/2009 from http://www.riksbank.se/ templates/stat.aspx?id=16749

Södra Regionvårdsnämnden, (2008). ”Regionala priser och ersättningar för Södra sjukvårdsregionen 2008”

Vägverkets samhällsekonomiska kalkylvärden 2008:67 (2008), downloaded 01/01/2009 from http://publikationswebbutik.vv.se/shopping/ShowItem____3618.aspx

Wells, P.S., Hirsh J., Anderson D.R., Lensing A.W., Foster G., Kearon C., Weitz J., D'Ovidio R., Cogo A., Prandoni P. (1995), “Accuracy of clinical assessment of deep-vein thrombosis”, *The Lancet*, Vol. 345, Issue 8961, pages 1326-1330.

Wells P.S., Anderson D.R., Rodger, M., Forgie, M, Kearon, C., Dreyer, J., Forgie, M., Kearon, C., Dreyer, J., Kovacs, G., Mitchell, M., Lewandowski, B., and Kovacs, M.J. (2003), “Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis”, *New England Journal of Medicine* Vol. 349, Issue 13, pages 1227-1235.

Wells P.S.,Owen C., Doucette S., Fergusson D., Tran H. (2006), “Does This Patient Have Deep Vein Thrombosis?” *The Journal of the American Medical Association”,* Vol. 295, Issue 2, pages 199-207.

Interviews and E-mail correspondence

Svensson, Peter, (2008). Department for Coagulation Disorders, Lund University, University Hospital, Malmö, Sweden

Elf, Johan (2008a). "Födesschema/ process för patient med misstänkt DVT på akutmottagningen" Not published.

Elf, Johan, (2008b). Department of Emergency Medicine, Lund University, Lund University Hospital, Sweden

Appendix

A. Direct Costs

New Algorithm	Wells score	Wells (p)	D-dimer	D-dimer (p)	Method	Method (p)	∏ (p)	Cost	cost*(∏p)	Cost New Strategy
	Low	0,445	Positive	0,308	Ultrasonography	0,0625	0,009	172,51	1,48	**311,34**
					Venography	0,8750	0,120	477,23	57,31	
					Both Methods	0,0625	0,009	665,56	5,71	
			Negative	0,692			0,308	15,82	4,88	
	High	0,555			Ultrasonography	0,144	0,08	156,68	12,48	
					Venography	0,759	0,42	465,81	196,08	
					Both Methods	0,097	0,05	618,08	33,4	

Old Algorithm	Method	Method (p)	∏ (p)	Cost	Cost*(∏p)	Cost New Strategy
	Ultrasonography	0,15	0,15	156,68	23,5	**470,53**
	Venography	0,5	0,5	461,4	230,7	
	Both Methods	0,35	0,35	618,08	216,33	

Alternative Implementation of New Algorithm	D-dimer	D-dimer (p)	Wells score	Wells (p)	Method	Method (p)	∏ (p)	Cost	cost*(∏p)	Cost Alternative Strategy
	Positive	0,52			Ultrasonography	0,145	0,075	172,51	12,97	**333,11**
					Venography	0,765	0,398	477,23	189,86	
					Both Methods	0,090	0,047	665,56	31,27	
	Negative	0,48	Low	0,58			0,280	15,824	4,428	
			High	0,42	Ultrasonography	0,087	0,017	172,51	3,00	
					Venography	0,797	0,160	477,23	76,13	
					Both Methods	0,116	0,023	665,56	15,45	

B. Indirect Costs

New Algorithm	Group	Group(p)	Diagnostic Method	Method (p)	∏ (p)	Waiting time (h)	Cost production loss/h Cost of lost leisure /h	Cost*h	cost*∏ (p)	Cost New Strategy
	Retired	0,434	Low p + neg D-dimer	0,239	0,104	3,83	5,69	21,79	2,26	66,45
			Low p+ pos d-Dimer	0,147	0,064	8	5,69	45,48	2,9	
			High probability	0,613	0,266	7	5,69	39,8	10,59	
	Unemployed	0,046	Low p + neg D-dimer	0,361	0,017	3,83	5,69	21,79	0,36	
			Low p+ pos d-Dimer	0,129	0,006	8	5,69	45,48	0,27	
			High probability	0,510	0,023	7	5,69	39,8	0,93	
	Working	0,520	Low p + neg D-dimer	0,361	0,188	3,83	15,79	60,53	11,36	
			Low p+ pos d-Dimer	0,129	0,067	8	15,79	126,33	8,46	
			High probability	0,510	0,265	7	15,79	110,54	29,3	
					0,999					

Old Algorithm	Group	Group(p)	Diagnostic Method	Method (p)	∏ (p)	Waiting time (h)	Cost production loss/h Cost production loss/h	Cost*h	cost*∏ (p)	Cost Old Strategy
	Retired	0,434	Diagnostic Imaging	1	0,434	7	5,69	39,8	17,28	76,57
	Unemployed	0,046	Diagnostic Imaging	1	0,046	7	5,69	39,8	1,83	
	Working	0,520	Diagnostic Imaging	1	0,520	7	15,79	110,54	57,46	

Alternative Implementation of New Algorithm	Group	Group(p)	Diagnostic Method	Method (p)	∏ (p)	Waiting time (h)	Cost production loss/h Cost of lost leisure /h	Cost*h	cost*∏ (p)	Cost Alternative Strategy
	Retired	0,434	Neg D-dimer+ Low p	0,18	0,08	2,83	5,69	16,11	1,29	62,19
			High probability	0,82	0,35	7	5,69	39,8	14,1	
	Unemployed	0,046	Neg D-dimer+ Low p	0,354	0,02	2,83	5,69	16,11	0,26	
			High probability	0,646	0,03	7	5,69	39,8	1,18	
	Working	0,520	Neg D-dimer+ Low p	0,354	0,18	2,83	15,79	44,74	8,23	
			High probability	0,646	0,34	7	15,79	110,54	37,14	