

Prevention, Diagnosis, and Treatment of Venous Thromboembolism

A Systematic Review

SBU Board of Directors and Advisory Committee

Secretariat

EGON JONSSON,
Executive Director

SBU Board of Directors

KJELL ASPLUND
Norrland University
Hospital (Chair)

THOMAS IHRE
The Swedish Society of
Medicine

OLLE STENDAHL
(Ex) Medical Research
Council

EVA FERNVALL MARKSTEDT
The Swedish Association of
Health Professionals

TORE LÖWSTEDT
Federation of Swedish
County Councils

ULLA ÅHS
The Swedish Association of
Local Authorities

BERNHARD GREWIN
Swedish Medical Association

NINA REHNQVIST-AHLBERG
National Board of Health
and Welfare

MARIE ÅSBERG
The Karolinska Institute

MADELEINE ROHLIN
Faculty of Dentistry, Malmö

Advisory Committee

PETER ASPELIN
Huddinge University
Hospital (Chair)

CECILIA BJÖRKELUND
Vasa Hospital, Gothenburg

ANDERS LINDGREN
Ministry of Health and
Social Affairs

HANS-OLOV ADAMI
The Karolinska Institute

ANN-KATHRINE GRANÉRUS
Linköping University
Hospital

DAG LUNDBERG
Lund University Hospital

BJÖRN BEERMANN
Medical Products Agency

KERSTIN HAGENFELDT
Karolinska University
Hospital

MÅNS ROSÉN
National Board of Health
and Welfare

DAVID BERGQVIST
Uppsala University Hospital

ANNA-KARIN HOLM
School of Dentistry, Umeå

LIL TRÄSKMAN-BENDZ
Lund University Hospital

BIRGITTA BERNSPÅNG
Umeå University

BENGT JÖNSSON
Stockholm School of
Economics

GIGGI UDÉN
Malmö University

Summary and Conclusions of the SBU Report on:

Prevention, Diagnosis, and Treatment of Venous Thromboembolism

A Systematic Review

September 2002

Report prepared by:

David Bergqvist (Chair)

Paul Blomqvist

Mats Eliasson

(Project Coordinator)

Bengt Eriksson

Henry Eriksson

Margareta Hellgren-Wängdahl

Lars Holmberg

Jan-Håkan Jansson

Tomas Lindahl

Christina Lindholm

Karl-Gösta Ljungström

Klas Måre

Ulf Nyman

Carl-Gustav Olsson

Stefan Rosfors

Sam Schulman

Åsa Svensson (Project Assistant)

Manuscript reviewed by:

Ulrich Abildgaard

Torbjörn Andersson

Hjördis Björvell

Björn Lindgren

Thomas Mätzsch

English translation by:

Ron Gustafson

Report: Prevention, Diagnosis, and Treatment of Venous Thromboembolism

*Type: Systematic review • ISBN: 91-87890-73-3, 91-87890-79-8 and
91-87890-80-1 • Report number: 158/I, 158/II, and 158/III*

Publishing year: 2002

Conclusions by SBU

- ❑ *Venous thrombosis (the formation, development, or existence of a blood clot in a vein) is common and carries a substantial risk for long-term suffering or death*

Deep vein thromboses that break away from the vein, flow to the lungs, and block circulation (pulmonary emboli) cause over 1 000 deaths annually in Sweden and are the single most common cause of death during pregnancy and in surgical intervention where prophylaxis is not used. The risk for this disorder increases with age. At higher ages it is more common in men; at younger ages it is more common in women. Annually, over 11 000 people are hospitalized for venous thrombosis or pulmonary embolism, and approximately 40 000 patients visit a physician in ambulatory care. In a longer perspective, many people are affected by leg swelling, varicose veins, and slowly healing leg ulcers (conditions not addressed in this report). An SBU survey of practice in Sweden largely confirms that the methods used in the Swedish health services to prevent, diagnose, and treat venous thrombosis have well-documented effects. However, there has been a shift toward using methods that are inadequately assessed, particularly in the field of diagnostics. This highlights the need for early assessment of methods that are finding their way into routine clinical practice.

- ❑ *Venous thrombosis can be prevented to some extent, mainly by treatment with anticoagulants (blood thinning agents) in conjunction with surgical intervention*

However, a triggering cause cannot be found in one of five people affected. Hence, venous thrombosis is difficult to prevent in all cases. The benefits of familial investigation for suspected genetic predisposition to blood clots has been insufficiently studied.

- ❑ *Venous or pulmonary blood clots are often suspected in cases of leg swelling or sudden respiratory distress, but diagnosis is complicated*
The routine diagnostic methods have been complicated, painful, or not accessible around-the-clock. Hence, diagnostics have been less than optimal. New methods that are gentler for the patient and accessible at nearly all hospitals can adequately confirm or exclude the presence of blood clots.
- ❑ *Venous thrombosis can be treated with good effects, and the risks for new blood clots are reduced through secondary prophylaxis*
Treatment with anticoagulants is associated with higher risks for serious hemorrhage. Therefore, health services must maintain a high level of expertise and be well organized to monitor and manage treatment. The patient must be well informed and should be able to actively participate in treatment.
- ❑ *Preventing venous thrombosis*
 - Several drugs are available that prevent blood clots in conjunction with surgical intervention, but the value of these drugs for nonsurgical conditions is unclear.
 - The scientific evidence strongly suggests that low molecular weight heparin can replace unfractionated heparin in preventing and treating blood clots.
 - The preventive effect of acetylsalicylic acid is small, and the benefits of compression stockings and calf muscle pumping vary with the clinical situation.
 - Patients with cancer need more intensive preventive interventions over a longer period.
 - Physicians or midwives should determine the risk for venous thrombosis during pregnancy and prior to treatment involving estrogen, eg, contraceptive pills or following menopause.
 - It is essential to develop better methods to predict the risks for thrombosis from surgical intervention so those at greater or lower risk can be identified for differential prophylaxis.
 - It is essential to study the effects of nonpharmacological methods in patients at higher risk for hemorrhage.

❑ *Diagnosing venous thrombosis and pulmonary embolism*

- Several methods can be used to reliably diagnose or exclude the presence of venous thrombosis in the legs and lungs.
- The presence of treatment-demanding blood clots can be excluded in outpatients by combining the assessment of clinical probability with measurement of D-dimer in blood tests.
- Thorough ultrasonic examination of the leg and a CT scan of the pulmonary vessels usually provide sufficient diagnostic reliability – which strongly supports the use of these methods in clinical practice.
- It is essential to test models in Sweden that include different diagnostic methods to demonstrate which models are the most reliable and the most cost-effective.

❑ *Treating venous thrombosis and pulmonary embolism*

- In treating acute cases, low molecular weight heparin is at least as effective as unfractionated heparin. The risk for hemorrhage is lower and management is simpler, which facilitates outpatient treatment.
- Longer-term secondary prophylaxis with warfarin reduces the risk for relapse, but several years of treatment also increases the risk for severe hemorrhage.
- Acute anticoagulant treatment saves lives in cases of pulmonary embolism with circulatory shock.
- The new coagulation inhibiting tablets should be assessed as quickly as possible, as they may be able to reduce the need for blood test monitoring.

❑ *Investigating the risks for and causes of venous thrombosis and pulmonary embolism*

- Extensive investigation to determine genetic coagulation disorders is meaningful only in patients who are young, who have experienced previous thrombosis, or who have close relatives with thrombosis.

- It is not meaningful to conduct extensive investigations of patients with venous thrombosis to find possible underlying cancer.
 - It is essential to develop more cost-effective methods to investigate genetic predisposition for thrombosis.
- ❑ *Health care organization*
- Currently, the most important task is to educate health care staff to enhance the quality of coagulant treatment that takes place over longer periods in hospitals or outpatient clinics.
 - After training, some patients can measure, monitor, and adjust the dose in their own anticoagulant treatment with good results and a small risk for hemorrhage. It is essential that the health services in Sweden develop this type of care.
 - All health care staff should be well informed concerning the special risks and complications that are associated with anti-coagulant treatment.
 - It is important for health care staff to be aware of the patient groups at risk for developing venous thromboembolism, and when it is necessary to start preventive treatment. It is important that staff in both the health services and the municipal care services are able to recognize the symptoms of venous thrombosis and pulmonary embolism.
 - The simpler application of low molecular weight heparins allow shorter care times or outpatient management, leading to positive economic effects.



SBU Summary and Conclusions

Introduction

The unique ability of blood to coagulate and thereby stop a hemorrhage and initiate wound healing is essential for our survival. Every day, numerous small injuries to the blood vessels heal in a continuously ongoing repair process.

More than 50 different substances in the blood and tissues are active in this process. Some have the purpose of stimulating the blood to coagulate when we are injured. Others prevent the blood from coagulating in the vessels and dissolve blood that may have already coagulated.

If this sensitive balance between stimulating and inhibiting substances is disturbed, the consequences can be directly life-threatening. Coagulated blood in the vessels can form a clot (thrombus) that obstructs circulation or, in the worst-case scenario, stops circulation. If, however, the clot dissolving substances dominate, dangerous internal hemorrhaging can occur.

Venous thromboembolism is a general name covering diseases caused by thrombosis in the veins, the blood vessels that carry blood to the heart. Approximately three fourths of all blood in the body is found in the veins. Each year, approximately 8 000 individuals in Sweden are diagnosed with *deep vein thrombosis* (blood clots in deeply situated veins). The clots often are found in a vein in the calf or thigh where the blood flows slowly on its way to the heart. One end of the clot is attached to the vascular wall, while the loose end can move freely in the blood stream and can continually build up, in some cases reaching several decimeters in length.

Deep vein thrombosis is a serious and feared disease because of the risk that the free end of the clot can break loose. These emboli

can then follow the blood stream, the venous return flow, through the heart and out into the lungs where the clot becomes lodged, partially or completely blocking circulation and causing the oxygenation of the blood to deteriorate. *Pulmonary embolism* (a blood clot in the lungs) can be a life-threatening condition. It is diagnosed in nearly 4 000 individuals annually in Sweden alone and causes approximately 1 000 deaths (diagnosis verified by autopsy). But the statistics are incomplete – increasingly fewer autopsies are performed, and therefore the cause-of-death registry (based on death certificates) no longer provides complete figures on mortality from pulmonary embolism.

If a thrombus in the leg is not dissolved, either naturally or by medical treatment, blood flow is obstructed, the valves in the veins are destroyed, the pressure in the veins increases, and finally, fluid is forced out through the vascular walls, and the leg swells. With age, the skin becomes thinner and the risk increases for slowly healing leg ulcers in the lower legs. Nearly half of all patients with symptoms of deep vein thrombosis are affected by this type of “post-thrombotic syndrome”, which involves major suffering for the individual and requires extensive health care resources.

Given this background, it is extremely important to prevent deep vein thrombosis. It is necessary to establish a correct diagnosis as early as possible and begin treatment to prevent the clot from growing and possibly breaking free.

When the risk for venous thrombosis is elevated, eg, in conjunction with surgical intervention, preventive treatment is necessary.

Risk groups and risk factors

The most common underlying and precipitating factors in deep vein thrombosis are:

- Increasing age. The risk increases from age 40 years and onward. At higher ages, more men than women are affected. Up until 40–50 years of age, more women are affected than men.
- Inactivity, reduced mobility. Long-term bed rest from severe illness, eg, stroke or extended infections. Long periods of sitting

still, eg, during lengthy air travel.

- Trauma. With hip fracture, for example, blood clots are a complication that appears in more than every second case.
- Surgical intervention lasting longer than 30 minutes. In major orthopedic surgery without preventive treatment, the risk for venous thrombosis is 40–70 percent. In gynecological surgery, general abdominal surgery, and neurosurgery, the rate is lower, 15–25 percent.
- Coagulation disorders; often congenital deficiency of certain coagulation inhibitors. Occurs in up to 30 percent of the cases, and is often an underlying cause, even if other factors precipitate the thrombosis itself.
- Close relatives with thrombotic diseases; often, but not always, caused by well-defined genetic deficiencies in coagulation inhibitors.
- Estrogen treatment following menopause and the use of oral contraceptives increases the risk, but from a very low level, and therefore the absolute number of affected individuals is small.
- Pregnancy and the time closely following delivery.
- Previous thrombotic disease. After completed treatment the risk for relapse is elevated for decades.
- Certain types of cancer.
- Severe obesity.

Symptoms

The symptom profile for venous thromboembolism is diffuse and difficult to interpret. For example, in patients with symptoms of deep vein thrombosis, approximately one patient in two also has pulmonary embolism without symptoms.

The first signs of deep vein thrombosis are usually swelling and pain in the leg. In pulmonary embolism, chest pain and respiratory distress are the dominant symptoms, but the variations can be extreme, ie, from no symptoms at all to sudden death.

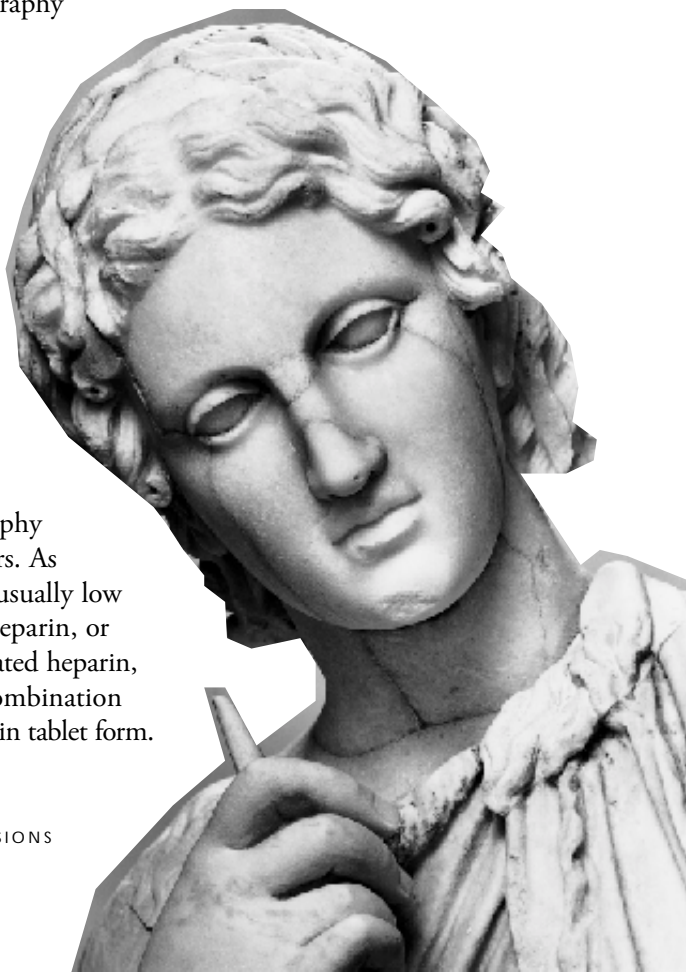
The entire process, from the first clot formation in a vein to a fatal pulmonary emboli, may extend over weeks or months, but in

some cases, eg, in conjunction with surgery, it may be a matter of hours. One patient in ten with symptoms of pulmonary embolism dies within one hour following the onset of symptoms, and these patients seldom or never receive treatment.

Unfortunately, it is not uncommon that a patient who has undergone surgery, without any symptoms of blood clot formation in the legs, is effected by a severe, at times lethal, pulmonary embolism several days after returning home from the hospital.

Practice

A questionnaire survey of practice in Sweden shows that most Swedish hospitals have some type of clinical protocol or guidelines for managing venous thromboembolism. Phlebography has been the most common method used to establish the diagnosis of venous thrombosis. In diagnosing pulmonary embolism, radioisotope scanning has dominated during regular working hours and computed tomography during on-call hours. As regards treatment, usually low molecular weight heparin, or possibly unfractionated heparin, has been used in combination with anticoagulants in tablet form.



Thrombolysis (clot dissolving treatment) is used in exceptional cases. Awareness about the importance of prophylaxis is relatively widespread, particularly in reference to low molecular weight heparin.

Costs to society

Annually, over 11 000 people receive hospital care for pulmonary embolism, deep vein thrombosis, or both. The number of physician visits in outpatient care is estimated at approximately 40 000 per year.

In 1999, the costs to society for diseases caused by venous thromboembolism were estimated to exceed 0.5 billion SEK. Three fourths were direct costs for inpatient care, acute outpatient care, physician visits for followup treatment, drugs, etc. Other direct costs include possible expenditures for municipal health services and social services. Early retirement accounted for the greatest share of the indirect costs, followed by the increasing cost of sick leave.

Project Design

The project has reviewed the methods available in Sweden for the prevention, diagnosis, and treatment of venous thrombosis in the lower extremities and pulmonary embolism in adults. The project did not address studies concerning children, or late complications such as post-thrombotic syndrome with accompanying leg ulcers or chronic pulmonary embolism. The report does not include a systematic review of the effects of preventive interventions based on screening of individuals having inherited forms of thromboembolism. Likewise, the report does not include a review of preventive measures such as interventions against risk factors like overweight or inactivity. (The SBU report on obesity, Report No. 160, addresses the interventions against overweight. The SBU report on hormone replacement therapy, Report No. 159, addresses the elevated risk for blood clots in conjunction with estrogen treatment.)

The report has been prepared by a Project Group of 16 members. The literature search covers all studies published through the summer of 2001. In the Medline database alone, approximately 50 000 studies were found on venous thromboembolism.

The group selected the studies of high scientific quality. The selection has focused on randomized controlled studies, ie, studies where the patients are randomly assigned to different types of treatment to analyze which treatment yields the best results. To assess diagnostic methods, it was necessary to conduct an independent comparison with a known reference method.

The following questions provided the main focus for the work of the Project Group:

- How great is the problem of venous thromboembolism?
- What are the costs to society for the disease?
- Are any groups at particular risk for developing venous thromboembolism?
- What methods should be used to diagnose the disease?
- Are there preventive methods that have better effects than others, and when should they be used?
- How can venous thromboembolism best be treated, and for how long?
- How cost-effective are the various methods of prevention, diagnosis, and treatment?

Synthesizing and Grading the Evidence

Approximately 1 300 scientific studies met the requirements for high scientific quality. Men and women were equally well represented in these studies. The studies were reviewed, evaluated, and synthesized to develop conclusions based on the following 4-grade scale:

Grade 1 – Strong scientific evidence (for the conclusions)

Grade 2 – Moderate scientific evidence

Grade 3 – Weak scientific evidence

Grade 4 – Insufficient evidence, including consensus of experts or completely lacking scientific base

Although the grading process does not necessarily yield the absolute truth, the conclusions that receive grade 1 should yield more concrete information than those receiving grade 3 or grade 4. It is important to note that a conclusion based on grade 4 evidence does not mean that a particular method has no effect, but that the scientific basis for assessment is insufficient. On the other hand, a conclusion on the lack of effect may receive a grade of 1, 2 or 3.

Results of the Literature Review

Prevention

Preventing venous thrombosis is extremely important, considering the suffering and risks to the individual that accompany the disease. It is not possible to identify the risk groups and risk factors with precision so that effective prophylaxis can be given.

The risk for thrombosis increases substantially in conjunction with surgical intervention, mainly orthopedic surgery in the legs and pelvis and in abdominal surgery, particularly for cancer. Some risk for thrombosis is even found in laparoscopic surgery where the time spent in surgery is often longer than in traditional surgery and where patients are often placed in a position that allows blood to collect in the legs.

To prevent the formation of thrombosis, but also to treat manifest thrombosis, injections of anticoagulants (earlier often erroneously referred to as “blood thinning agents”) are often administered in the form of heparin, which reduces the ability of the blood to coagulate and also inhibits inflammation. Heparin is a substance found in the body and is produced as a drug in various forms with somewhat different pharmacological characteristics.

The original form, unfractionated heparin, is administered by repeated injections in prophylaxis and intravenously in treatment. The latter requires hospitalization for careful monitoring accompanied by continual sample testing and dose adjustment. Newer variants, low molecular weight heparins, differ from unfractionated

heparin in several ways. A single injection per day is sufficient due to better uptake in the circulation and a longer acting effect. Also, it is not necessary to check the effects by laboratory testing, and the risks for side effects are fewer. Combined, these characteristics mean that treatment can be carried out largely on an outpatient basis.

Anticoagulants are routinely administered during and following surgery. To some extent, this is also the case for some medical conditions such as acute myocardial infarction and acute ischemic stroke (blood clots in the brain).

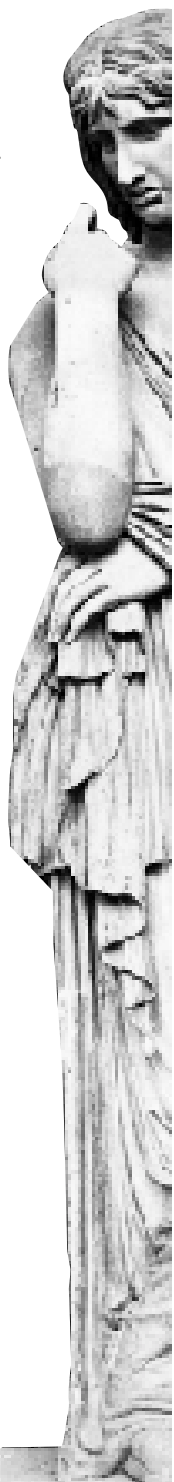
The simplest way to reduce the risk for blood clots following surgery is otherwise to activate the patient as quickly as possible. Sitting and lying increases the risk for clots. This is also why passengers on longer flights are encouraged to get up and walk around intermittently and move their feet and legs while they sit. The following briefly describes the most important conclusions on prophylaxis presented in the report.

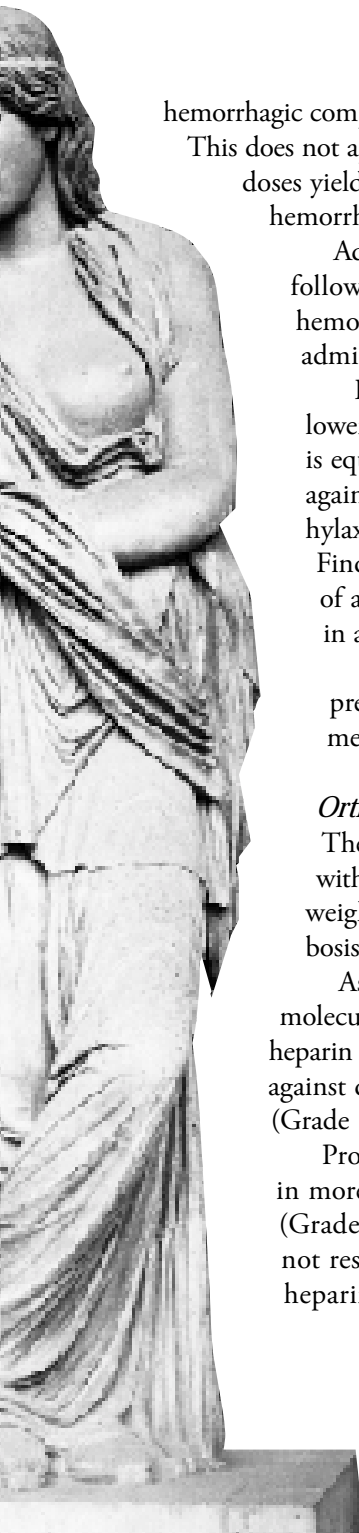
General surgery, gynecology, urology, thoracic surgery, vascular surgery, and neurosurgery

There is strong scientific evidence that prophylaxis with unfractionated heparin in low doses reduces the risk for deep vein thrombosis in asymptomatic patients and the risk for all types of pulmonary embolism (Grade 1) and that it reduces mortality in conjunction with surgery (Grade 2).

As prophylaxis against venous thromboembolism, low molecular weight heparin is equal to unfractionated heparin (Grade 1). The risk for pulmonary embolism is lower from prophylaxis with low molecular weight heparin than with unfractionated heparin (Grade 2).

Prophylaxis with unfractionated heparin increases the risk for hemorrhage in conjunction with surgery (Grade 1). Prophylactic doses of low molecular weight heparin at the higher interval yield more, and at the lower interval yield fewer,





hemorrhagic complications than unfractionated heparin (Grade 2).

This does not apply to cancer surgery where higher prophylactic doses yield better effects without increasing the risk for hemorrhage (Grade 2).

Administration of low molecular weight heparin following the conclusion of surgery yields fewer hemorrhagic complications and is otherwise equal to administering it prior to surgery (Grade 3).

Dextran, a blood replacement agent which, lowers the capacity for blood platelets to coagulate, is equal to unfractionated heparin as prophylaxis against pulmonary embolism, but is inferior as prophylaxis for deep vein thrombosis (Grade 1).

Findings are inconsistent concerning the potential of acetylsalicylic acid to prevent venous thrombosis in asymptomatic patients during surgery (Grade 3).

The evidence is insufficient to evaluate compression stockings and calf muscle pumping as means to prevent pulmonary embolism (Grade 4).

Orthopedic surgery

There is strong scientific evidence that prophylaxis with unfractionated heparin and with low molecular weight heparin reduces the risk for deep vein thrombosis and the risk for pulmonary embolism (Grade 1).

As prophylaxis against pulmonary embolism, low molecular weight heparin is superior to unfractionated heparin (Grade 1). It also has better effects as prophylaxis against deep vein thrombosis in asymptomatic patients (Grade 1).

Prophylaxis with unfractionated heparin results in more hemorrhagic complications than placebo (Grade 2), but low molecular weight heparin does not result in more hemorrhages than unfractionated heparin (Grade 1).

Longer-term treatment with low molecular weight heparin following hospitalization further reduces the risk for deep vein thrombosis and pulmonary embolism (Grade 2).

Dextran is equal to low molecular weight heparin in prophylaxis against pulmonary embolism (Grade 2).

Acetylsalicylic acid administered for preventive purposes does not reduce the risk for venous thromboembolism in orthopedic surgery (Grade 3).

Calf muscle pumping reduces the risk for deep vein thrombosis in asymptomatic patients (Grade 2). However, graded compression stockings do not reduce the risk (Grade 2).

Acute myocardial infarction

Studies from the 1970s and 1980s showed that unfractionated heparin in low doses reduced mortality and the risk for pulmonary embolism, but increased the risk for serious hemorrhage. Since that time, the management of patients with acute myocardial infarction has changed radically. Currently, most are mobilized even after the first day and are treated with acetylsalicylic acid along with clot dissolving agents or low molecular weight heparin. Evidence is lacking to assess the effects of heparin agents in modern intensive coronary care units (Grade 4).

Stroke

Neither unfractionated nor low molecular weight heparin reduces mortality from acute stroke resulting from reduced blood circulation, ie, ischemic stroke (Grade 1). Both agents can reduce the risk for deep vein thrombosis in asymptomatic patients (Grade 2). However, the doses needed to reduce the risk for pulmonary embolism are so high that the risk for serious hemorrhage increases to the same extent (Grade 3).

Other medical conditions

Unfractionated heparin does not reduce the risk for fatal pulmonary embolism (Grade 2) and neither low molecular weight heparin nor

unfractionated heparin reduces mortality in severely ill internal medicine patients (Grade 3).

Both heparin agents reduce the risk for venous thromboembolism in asymptomatic, severely ill internal medicine patients (Grade 1). However, the scientific evidence is insufficient for assessing whether they have an effect on deep vein thrombosis in symptomatic patients (Grade 4).

Health economic aspects

There is limited scientific evidence that prophylaxis with low molecular weight heparin leads to a lower cost per prevented blood clot than prophylaxis with unfractionated heparin (Grade 3).

The evidence is insufficient for determining whether extended prophylaxis following surgery can result in lower costs (Grade 4).

Diagnosis

The diagnostic arsenal for identifying deep vein thrombosis and/or pulmonary embolism is large and varied, from simple lab scans to sophisticated diagnostic imaging. Nevertheless, a firm diagnosis cannot always be established. At times, it may be sufficient to exclude the possibility of venous thromboembolism with a reasonable certainty, and thereby avoid treatment, since treatment always carries a risk for hemorrhagic complications.

The clinical profile, as revealed by the medical history, clinical findings, routine tests, chest x-rays, ECG, etc, is valuable for raising suspicions, but insufficient to confirm or exclude the presence of a blood clot in a vein. Clinical judgement must be reinforced with methods that literally aim at creating the clearest possible image of the vessel and vascular changes.

Phlebography, x-ray examination of one or more veins following the injection of a contrast agent, was introduced in the 1920s and remains the method with which all other tests and methods for diagnosing deep vein thrombosis are compared. Phlebography has few risks and side effects and can be performed at all radiology departments.

Ultrasound provides a good image of blood flow in the veins and is a gentler procedure than phlebography; the examination requires neither puncture of the blood vessel nor contrast agents. Many hospitals in Sweden do not have trained staff on duty around the clock to perform reliable ultrasound examinations.

Pulmonary angiography, contrast x-ray examination that shows the circulation in the lungs, is a reference method for acute pulmonary embolism. The risk for serious complications is low, but proficiency requires considerable practice through a high volume of procedures, which is not the case at most hospitals in Sweden.

Lung scanning, isotope studies using injected, radioactive trace elements, can indirectly reveal pulmonary emboli, but the same findings also appear in several other disease states. Somewhat over one half of the acute care hospitals in Sweden do not have the equipment for lung scanning, and furthermore it is only performed during regular office hours.

A special method of computed tomography scanning, spiral CT, is a radiological method used to image thin slices or cross-sections of the body. It is easy to read, gentle for the patient, and the equipment is available at university hospitals, county hospitals, and most county district hospitals in Sweden. The method is rapid – using spiral CT equipment, the lungs can be scanned in 10–30 seconds.

D-dimer is a fibrin breakdown product found in blood clots, and hence is an indirect indicator of blood clots. D-dimer can be measured in several different ways, with varying reliability, and analyses of the tests are “user-dependent”. Consequently, diagnostic performance of the method is better at a hospital laboratory with few, but experienced, examiners than at an emergency room where several different people with varying degrees of proficiency perform the analysis. In several European countries, D-dimer screening is routinely used to exclude the presence of blood clots as early as possible, thereby reducing both examination costs and unmotivated treatment.

Assessing diagnostic methods requires a standard, or reference, method for comparison. This method must be able to accurately identify a disease with greatest scientifically documented reliability, and is traditionally used to establish a diagnosis.

Phlebography is the reference method for deep vein thrombosis, and pulmonary angiography is the reference method for pulmonary embolism. The summary below describes the report's most important conclusions on diagnostics.



Clinical assessment

Isolated symptoms or findings during an examination of the patient (chest x-ray, ECG, or routine tests) are insufficient for confirming or excluding the presence of deep vein thrombosis or pulmonary embolism (Grade 1).

Score-based diagnostics (checklists, etc) can be used to make a preliminary judgement concerning the probability for disease in patients at an emergency department, but are insufficient to confirm or exclude the presence of deep vein thrombosis or pulmonary embolism (Grade 1). Simple categorization of clinical probability into “low certainty”, “moderate certainty”, or “high certainty” is valuable in interpreting other diagnostic methods.

Venous thrombosis

Measuring D-dimer, with a slightly elevated concentration as a decision limit, contributes only toward excluding – but not confirming – venous thrombosis (Grade 1).

Many inpatients, elderly patients, and patients with cancer, infections, or other serious diseases have elevated D-dimer levels from causes other than venous thromboembolism. Therefore, measuring D-dimer is seldom beneficial for excluding venous thrombosis or pulmonary embolism in these groups (Grade 1).

When clinical probability is low, a negative D-dimer can, with high certainty, exclude treatment-demanding venous thrombosis in outpatients (Grade 2).

Ultrasound examination, that also images the veins of the lower leg, has equally high diagnostic certainty as phlebography (Grade 1). If the clinical probability is low, and a routine ultrasound examination (down to and including the upper part of the calf) does not show clot formation, the risk for pulmonary embolism or later diagnosed blood clots is low (Grade 2).

Pulmonary embolism

Measuring D-dimer contributes only to excluding – but not confirming – pulmonary embolism (Grade 1).

For reasons similar to those in venous thrombosis, it is seldom possible to use D-dimer to exclude pulmonary embolism in severely ill patients (Grade 1).

If clinical probability is low, a negative D-dimer can, with high certainty, exclude treatment-demanding pulmonary embolism in outpatients (Grade 2).

A normal lung scan excludes, with reasonable certainty, clinically relevant pulmonary embolism (Grade 3).

In more than 90 percent of the cases, patients actually have pulmonary embolism when both clinical judgement and lung scanning indicate a high probability (Grade 1). Likewise, more than 90 percent do not have pulmonary embolism when both clinical judgement and lung scanning indicate a low probability (Grade 1).

Different evaluators of lung scans reach different conclusions, mainly when it concerns categories other than normal or high probability for pulmonary embolism (Grade 2). These “middle” categories can represent a substantial share of the examinations, and thereby the diagnosis in some patients can be neither excluded nor confirmed (Grade 1).

Spiral CT scanning can directly reveal pulmonary embolism with the same diagnostic certainty as a lung scan where the probability is judged to be high (Grade 1). Spiral CT scanning yields low certainty in revealing clots in smaller blood vessels (Grade 1). Nevertheless, a normal CT scan excludes, with high probability, clinically relevant pulmonary embolism (Grade 2). The risk for pulmonary embolism following a diagnosis that excludes its presence is equally as low as the risk following negative pulmonary angiography (Grade 2). However, this conclusion is not verified in severely ill patients or in patients with limited cardiovascular function (Grade 4).

Agreement among different evaluators concerning spiral CT scanning exams is “good” to “very good” (Grade 1), better than for pulmonary scanning and comparable to pulmonary angiography (Grade 2).

Economic aspects

There is no scientific evidence on which to assess whether a particular method or diagnostic strategy is more cost-effective than another in diagnosing blood clots in veins or in pulmonary circulation (Grade 4).



Treatment

In nine of ten cases, pulmonary embolism starts with a blood clot in the leg. Consequently, eliminating the risk for pulmonary embolism is the main purpose behind all treatment of deep vein thrombosis.

To prevent a thrombus from becoming larger, initial treatment involves injection of anticoagulants, ie, unfractionated heparin or low molecular weight heparin. In the acute stage, treatment is also initiated using anticoagulants in tablet form. Currently in Sweden, only one such agent is registered, a vitamin K antagonist with warfarin as the active substance. The effects of warfarin are highly individual. To establish the correct dose and minimize the risk for hemorrhage, repeated testing is required with intervals of several days or weeks. Patients must be well informed and be able to take an active role in treatment. It is particularly important that patients be aware of how the effects of warfarin can be influenced by other drugs and even certain foods.

Medication with warfarin continues up to one-half year or longer in most cases.

A person with suspected pulmonary embolism must be quickly transported to the hospital and treated with anticoagulants. Patients severely affected with pulmonary embolism and in shock are treated the same day with thrombolytic (clot-dissolving) drugs, an advanced treatment with risk for hemorrhage.

The risk for severe side effects renders treatment for venous thromboembolism complicated. If the anticoagulant dose is too low, there is a risk that thrombosis continues to develop. If the dose is too high, the risk for hemorrhage increases, possibly leading to a fatal cerebral hemorrhage. Presented below is a summary of the report's most important conclusions about treatment.

Acute anticoagulant treatment

The risk for new thrombosis declines if treatment is initiated with unfractionated heparin compared to treatment only with anticoa-

gulgants in tablet form (Grade 2). In patients with deep vein thrombosis, low molecular weight heparin has an equally good effect as unfractionated heparin in reducing the risk for relapse (Grade 1). In treating pulmonary embolism, low molecular weight heparin is equally as effective as unfractionated heparin in reducing the risk for relapse (Grade 2). However, this effect has not been confirmed for massive pulmonary embolism.

Outpatient treatment of deep vein thrombosis with low molecular weight heparin is equivalent to treatment in hospital with unfractionated heparin as regards the risk for new blood clots, pulmonary embolism, severe hemorrhaging, and death (Grade 2).

Low molecular weight heparin is superior to unfractionated heparin in treating proximal deep vein thrombosis (blood clots in the thigh or pelvis) as concerns mortality, relapse, or severe hemorrhage (Grade 2). Generally, the risk for hemorrhage is less in treatment with low molecular weight heparin than with unfractionated heparin (Grade 2).

Treatment with a single daily injection, rather than two, of low molecular weight heparin yields equally favorable effects in venous thrombosis (Grade 1) and pulmonary embolism (Grade 3).

There is no evidence upon which to compare the effects and safety of different types of low molecular weight heparin (Grade 4).

Secondary prophylaxis with vitamin K antagonists

Since it takes 4–5 days before vitamin K antagonists take effect, they are not used in emergency treatment of deep vein thrombosis or pulmonary embolism, where heparins are standard treatment. Rather, they are used as secondary prophylaxis to reduce the risk for relapse following thrombosis (Grade 1). There is no distinguishable difference if secondary prophylaxis is started immediately or delayed (Grade 1).

A higher initial treatment dose and daily checkups and followup shorten the care time for inpatients while maintaining safety and effects (Grade 3).

A longer period of secondary prophylaxis (maximum six months)

yields fewer relapses than treatment for shorter periods and is equally safe in patients experiencing the first thrombosis or pulmonary embolism (Grade 1). If thrombosis is limited to the lower leg and the underlying cause (eg, casting) is excluded, six weeks of treatment yields an effect equivalent to that from longer-term treatment (Grade 3). With a renewed vein thrombosis, treatment for 6–12 months provides good protection, but substantially longer treatment duration substantially increases the risk for hemorrhage (Grade 3).

If patients, after training and with support from a specialty clinic, carry out their own testing and dosing, secondary prophylaxis with anticoagulants in tablet form (warfarin) is equally safe as that delivered by a specialized clinic (Grade 2).

Secondary prophylaxis with low molecular weight heparin

Secondary prophylaxis 3–6 months with low molecular weight heparin yields the same effect as warfarin in terms of risk for relapse during the treatment episode and within one year following the first blood clot (Grade 2). The treatment methods are also equivalent in terms of the hemorrhage risk during the treatment period, (Grade 3). Secondary prophylaxis by injection may be advantageous when it is uncertain if the patients themselves can participate in treatment, making it difficult to monitor the effects of warfarin.

Thrombolysis (clot-dissolving treatment)

Treatment with clot dissolving agents or thrombolytic drugs (of the same type given routinely for certain types of myocardial infarction) always involves a risk for hemorrhage that is greater with heparin treatment. Hence, the benefits of treatment must be carefully weighed against the risks.

Thrombolysis for pulmonary embolism with circulatory shock reduces mortality compared to heparin treatment alone (Grade 3). There is some evidence that clot-dissolving treatment for deep vein thrombosis reduces the development of post-thrombotic syndrome (Grade 3).

Thrombolysis leads to more hemorrhagic complications than treatment with heparin in deep vein thrombosis (Grade 1) and pulmonary embolism (Grade 2).

Vena cava filter

The scientific documentation concerning the value of various types of filters in the large vena cavis (ie, vena cava filter) to prevent pulmonary embolism is insufficient (Grade 4). The filters do not reduce mortality nor the risk for relapse compared to treatment with unfractionated heparin (Grade 3), and can eventually lead to deep vein thrombosis (Grade 3).

Health economic aspects

Treatment of venous thrombosis with low molecular weight heparin yields lower costs per patient than treatment with unfractionated heparin (Grade 2). There is no scientific evidence to show whether costs are lower to treat and followup patients with blood clots at a specialty clinic than at a general clinic in a hospital or primary care center (Grade 4).

Pregnancy

The characteristics of blood coagulation change in conjunction with pregnancy. Several substances that stimulate coagulation increase while substances that inhibit coagulation decrease. One pregnant woman in one thousand is affected by venous thrombosis, and pulmonary embolism is one of the most common causes of death related to pregnancy. Cesarean sections increase the risk for thrombosis. Since the 1970s, when early mobilization of postpartum mothers was introduced, the number of fatal pulmonary embolism cases has declined, most likely because of increased mobilization and greater use of thromboprophylaxis.

Earlier thrombosis and genetic or acquired predisposition for developing venous thrombosis carries an increased risk (Grade 2). For those previously affected, the risk for relapse during pregnancy is



lower if there is no genetic predisposition and previous thrombosis was related to transient risk factors, eg, trauma (Grade 2).

There are favorable opportunities to establish a reliable diagnosis of venous thrombosis or pulmonary embolism in the mother without harming the fetus through radiation or contrast agents, but this requires a careful approach. Ultrasound examination and magnetic resonance imaging (MRI) involve no radiation, but even phlebography and spiral CT scanning can be used. Since the levels of D-dimer are elevated during pregnancy, measuring this parameter is not helpful in excluding venous thrombosis or pulmonary embolism.

In contrast to warfarin, unfractionated or low molecular weight heparin do not pass the placenta (Grade 2) and do not cause deformity or have other negative effects on the child (Grade 2).

The scientific evidence for comparing prophylaxis and treatment with unfractionated and low molecular weight heparin is insufficient (Grade 4). In practice, low molecular weight heparin during pregnancy is preferred since it is easier to use and carries a lower risk for osteoporosis than does unfractionated heparin.

Cancer

Cancer is common in patients with venous thromboembolism. Since a cancer diagnosis is preceded by a vein thrombosis in some cases, researchers have discussed whether it is important to start searching for possible cancer (eg, screening) when a blood clot is diagnosed. However, the scientific evidence is insufficient for assessing the benefit of broad screening for cancer in patients with venous thromboembolism (Grade 4). Research has not shown whether the discovery of cancer through this type of examination would influence the patient's prognosis or survival.

In cancer surgery, higher doses of heparins and low molecular weight heparin to prevent venous thrombosis may be required (Grade 3), and prolonged prophylaxis following surgery yields better protection (Grade 3).

If needed, secondary prophylaxis can be given using low

molecular weight heparin instead of warfarin (Grade 3). This may be a practical solution in patients with cancer.

Care

The literature search reveals major gaps in research concerning specific care interventions for deep vein thrombosis and pulmonary embolism.

Early mobilization and mobility training are routine following surgery and serious disease, but the evidence is insufficient for scientifically assessing whether this prevents venous thromboembolism (Grade 4).

Patients with blood clots in the knee, thigh, or pelvis (proximal vein thrombosis) experience less discomfort from leg swelling and pain if they are upright and walk with compression than if they remain in bed (Grade 2). With deep vein thrombosis, early mobilization and compression treatment does not result in more pulmonary embolism than strict bed rest (Grade 3).

Investigating underlying biochemical causes

There are many, mainly genetic, disorders that can lead to increased risk for blood clots. An important issue is the extent to which the patient with blood clots should be investigated considering these underlying causes. The value of broad investigations has been questioned. To date, most coagulation centers have chosen to investigate thrombosis patients when the probability of finding a disorder is high, ie, patients younger than 50 years, patients that have experienced thrombosis previously, and cases where thrombotic disease is found among relatives.



Reports *Published by SBU*

Prevention, Diagnosis, and Treatment of
Venous Thromboembolism, Volumes I, II and III (2002)
Obesity – Problems and Interventions (2002), no 160
Hormone Replacement Therapy (2002), no 159
Tobacco and Oral Health (2002), no 157

Treatment of Alcohol and Drug Abuse – An Evidence-Based Review
(2001), 156/I and 156/II
Chemotherapy for Cancer – A Critical Review of the Literature,
Volumes I and II (2001), no 155/1 and 155/2

Need to Assess Dental Care (2000), no 152
Placebo in Health Care (2000), no 154
Mild Head Injury–In-hospital Observation or Computed Tomography?
(2000), no 153
Asthma and COPD (chronic obstructive pulmonary disease) (2000), no 151
Dyspepsia (2000), no 150
Back Pain, Neck Pain (2000), no 145
In Vitro Fertilization (IVF) (2000), no 147
Evidence-Based Nursing – Treatment of People with Schizophrenia (2000), no 4
Evidence Based Treatment of Urinary Incontinence (2000), no 143
Alert – New Methods in Medicine (2000), no 148

Evidence-Based Nursing in Treatment of People with Depression (1999), no 3
Evidence-Based Physiotherapy for Patients with Low-Back Pain (1999), no 102
Evidence-Based Physiotherapy for Patients with Neck Pain (1999), no 101
Advanced Home Health Care and Home Rehabilitation
– Reviewing the Scientific Evidence on Costs and Effects (1999), no 146
The Patient–Doctor Relationship and the Art of Medicine
– An Evidence-Based Review (1999), no 144
Prognostic Methods in Acute Coronary Artery Disease (1999), no 142

Evidence-Based Nursing – Radiotherapy in Patients with Cancer (1998), no 1
Routine Ultrasound Examination During Pregnancy (1998) no 139
Chest Pain: Surgery, Balloon Dilation, Drugs (1998)
Smoking Cessation Methods (1998)
Surgical Treatment of Rheumatic Diseases, Volumes 1 and 2 (1998)

The Economy in Sweden and the Health Care Sector II (1997)
Preventing Disease – with Antioxidants, Volumes 1 and 2 (1997)
Community Intervention Programs to Prevent Cardiovascular Disease (1997)
Treatment with Neuroleptics, Volumes 1 and 2 (1997)
Longer Life and Better Health – A Report on Prevention (1997)

Estrogen Treatment (1996)
Critical Issues in Radiotherapy (1996)
Radiotherapy for Cancer, Volumes 1 and 2 (1996)

Bone Density Measurement (1995)
Mass Screening for Prostate Cancer (1995)
Hysterectomy – Ratings of Appropriateness... (1995)
Benefits and Costs of New Medical Methods in Sweden 1960–1992 (1995)
The Economy in Sweden and the Health Care Sector (1995)

Nursing Care – The Need for Assessment (1994)
Moderately Elevated Blood Pressure (1994)
Traffic Accidents (1994)
CABG and PTCA. A Literature Review... (1994)

Literature Searching and Evidence Interpretation... (1993)
Diabetic Retinopathy – Importance of Early Detection (1993)
Genetic Diagnosis by PCR (1993)

Psychiatry – The Need for Assessment (1992)
Stroke (1992)
Magnetic Resonance Imaging, MRI (1992)
PTCA – Percutaneous Transluminal Coronary Angioplasty (1992)
Critical Medical Analysis (1992)
Prioritization and Rationing in Health Care – Trends in the USA (1992)

Surgery for Epilepsy (1991)
Bone Marrow Transplantation (1991)
Back Pain: Causes, Diagnosis, and Treatment (1991)

Lithotripsy of Kidney Stones and Gallstones (1990)
Vascular Surgery for Arteriosclerosis in the Legs (1990)
Gastrosocopy – In the Diagnosis of Dyspepsia (1990)
The Problem of Back Pain – Conference Report (1990)

Medical Technologies in Need of Assessment (1989)
Bone Anchored Implants in the Head and Neck Region (1989)
Preoperative Routines (1989)
Evaluating Medical Technology and the Efficacy of Health Care (1989)

To Order SBU Reports

The reports listed above can be ordered via the Internet at www.sbu.se, by phone (+46 8 412 32 00), by fax (+46 8 411 32 60), or by returning the order form.

SBU Evaluates Health Care Technology

The Swedish Government has given SBU the following responsibilities:

- SBU shall evaluate the methods used in health care by systematically and critically reviewing the scientific evidence in the field.
- SBU's assessments shall cover the medical aspects and the ethical, social, and economic consequences of disseminating and applying medical and dental technologies.
- SBU's assessments shall be compiled, presented, and disseminated in such a way that all affected parties have access to the information.
- SBU shall contribute, through informational and educational initiatives, toward ensuring that the knowledge gained is used to rationally utilize available resources in health care.
- SBU shall draw on national and international experience and research findings in the field and shall serve as a focal point for health technology assessment in Sweden. This effort shall be managed in a way that secures success and respect for the organization, both domestically and internationally.

Prevention, Diagnosis, and Treatment of Venous Thromboembolism

This report reviews the scientific evidence on Venous Thromboembolism. It is one in a series of scientific reports published by SBU (The Swedish Council on Technology Assessment in Health Care).

An SBU report is an impartial work, based on a systematic and critical review of the complete body of scientific literature on the topic studied. A group of leading experts and researchers develops the report, a process that usually takes several years to complete.

The Summary and Conclusions are endorsed by the SBU Board of Directors and the SBU Advisory Committee.