The Treatment of Deep Vein Thrombosis in the Pelvis and Leg

Viola Hach-Wunderle, Markus Dux, Anja Hoffmann,
Florian Präve, Max Zegelman, Wolfgang Hach

SUMMARY

Introduction: Deep vein thrombosis is associated with a risk of pulmonary embolism and post thrombotic syndrome (PTS).

Methods: Selective literature review with special reference to the American College of Chest Physicians' current guidelines and the German S2 interdisciplinary guideline.

Results and discussion: The most important therapeutic measure is prompt and adequate anticoagulation with heparin or fondaparinux. Thrombolysis or thrombectomy is only indicated in highly selected severe cases. The risk of PTS can be reduced by immediate ongoing treatment with compression stockings. Prevention of relapse is achieved using vitamin K antagonists with a target INR of 2.0 to 3.0. The duration of anticoagulation should be tailored to the localisation and etiology of the thrombosis, from at least three months to indefinite treatment. The ongoing risk of bleeding secondary to anticoagulation should be re-evaluated at regular intervals as a cost-benefit analysis. New anticoagulants for acute and long term treatment will soon be available for clinical use.

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Gefäßzentrum am Krankenhaus Nordwest, Frankfurt a. M.:
Prof. Dr. med. Hach-Wunderle, Prof. Dr. med. Dux, Prof. Dr. med. Zegelman
Praxis für Innere Medizin und Gefäßkrankheiten, Frankfurt a. M.:
Prof. Dr. med. Hach-Wunderle, Anja Hoffmann, Dr. med. Präve,
Prof. Dr. med. Hach

Deep vein thrombosis is one of the more common illnesses of modern times, with an incidence of 100 to 200 cases per 100 000 persons per year (1, 2). Its correlation with advanced age is particularly noteworthy in view of the aging of the population. The annual incidence of a first venous thromboembolic illness in children up to 15 years of age is low, at fewer than five cases per 100 000 persons per year, but the corresponding figure for persons over age 80 is 450 to 600 cases per 100 000 persons per year (3). The mortality within one month of diagnosis is about 6% for patients with deep vein thrombosis and 12% for patients with pulmonary embolism (3); thus, this disease is of major socioeconomic importance. The major tasks facing the medical profession include improvement in the prophylactic management of patients at risk and the immediate diagnosis and appropriate medical and physical treatment of the condition when it arises.

In this review article, the authors summarize the available study data on the subject and present them in a manner oriented toward everyday medical practice, while also taking the current national and international guidelines into consideration.

Immediate treatment: pharmacotherapy and physical measures

The most important therapeutic step when acute venous thromboembolism has been diagnosed is immediate and adequate anticoagulation (4, 5). In the only randomized study on the subject, published in 1960, it was found that, among a total of 73 patients with symptomatic pulmonary embolism, 53% of the non-anticoagulated patients had recurrent emboli, half of them with a fatal outcome, while there was not a single recurrent embolism among the patients treated with unfractionated heparin and a vitamin K antagonist (6).

Initiation of treatment

Anticoagulation should be begun as soon as deep vein thrombosis is suspected.

TABLE 1

Initial anticoagulation in acute venous thrombosis*¹

Active substance	Dose	Frequency (subcutaneous)
Low-molecular-weight heparins		
Certoparin	8000 A-Xa-IU	b.i.d.
Enoxaparin	1.0 mg/kg BW	b.i.d.
Nadroparin	90 A-Xa-IU/kg BW 180 A-Xa-IU/kg BW	b.i.d. q.d.
Reviparin	0.5–0.9 mL according to body weight 0.6 mL (if body weight >60 kg) (= 10307 A-Xa-IU)	b.i.d. q.d.
Tinzaparin	175 A-Xa-IU/kg BW	q.d.
Pentasaccharide		
Fondaparinux	7.5 mg 5 mg if body weight < 50 kg 10 mg if body weight > 100 kg	q.d.

*¹ Medications that were approved for this indication in Germany as of December 2007, modified after (5).
A-Xa-IU, anti-factor Xa international units; BW, body weight.
In addition to these agents, the intravenous or subcutaneous use of unfractionated heparin is approved for the treatment of venous thrombosis.
For the treatment of pulmonary embolism, tinzaparin and fondaparinux are explicitly approved; enoxaparin is approved for venous thrombosis with or without pulmonary embolism.
Before beginning treatment with any of these agents, see the manufacturer's instructions for use!

These findings yielded a "number needed to treat" (NNT) of 3.8 (95% confidence interval 2.2 to 15.3) for the prevention of fatal pulmonary embolism, 4.1 (2.2 to 23.0) for the prevention of non-fatal pulmonary embolism, and 2.0 (1.4 to 3.6) for the prevention of any pulmonary embolism, fatal or non-fatal. This was a breakthrough for the treatment of venous thromboembolic disease with heparin.

Alongside anticoagulation, compression therapy and the maintenance of mobility are also important (5). Today, these can be performed in the outpatient setting in most cases. These measures help prevent pulmonary embolism as well as progression of the thrombosis. Under certain conditions, thrombolysis or thrombectomy can be considered, with the goal of preventing a severe post-thrombotic syndrome by removing the thrombus as completely as possible.

Initial anticoagulation: heparin or fondaparinux

As long as there is no contraindication, anticoagulation should be begun as soon as deep vein thrombosis

is suspected, in a therapeutic dose calculated according to the patient's weight. The available drugs include low-molecular-weight heparins (LMWH), unfractionated heparin (UFH), and the pentasaccharide fondaparinux (*table 1*).

Acute deep vein thrombosis is usually treated with heparin. Unfractionated heparin with a molecular weight from 3000 to 30 000 daltons (average value, 15 000 daltons) and low-molecular-weight heparins with molecular weights ranging from 3000 to 7000 daltons have been approved for this purpose. Heparins form a complex with antithrombin that inhibits coagulation factor Xa and thrombin; the degree of inhibition depends on the molecular weight of the drug and corresponds to a 1:1 ratio with UFH and a 1.5:1 to 4.5:1 ratio with LMWH (*diagram 1*).

Low-molecular-weight heparins are now the agents of first choice because of their ease of use, high bioavailability, and low complication rate. Many randomized, controlled studies have shown them to be at least as safe, and at least as effective, as unfractionated heparin (7). They are injected subcutaneously in pre-packaged individual doses, adapted according to body weight, either once or twice daily depending on the drug (*table 1*). No routine checking of their anticoagulant effect is required in most cases, but special attention should be paid to this in patients with an abnormal body weight, pregnant women, or patients with renal insufficiency. In these special situations, the anticoagulant effect is usually monitored with an anti-factor Xa test, which should be performed 3 to 4 hours after subcutaneous injection. If low-molecular-weight heparin is given once daily, the target range for this test is 0.6 to 1.3 IU/mL; if it is given twice daily, the target range is 0.4 to 0.8 IU/mL. As a further safety precaution, the manufacturer's instructions for the use of the drug should be followed. The accumulation of different LMWH preparations in patients with renal insufficiency varies as a function of the preparations' molecular weight (*diagram 2*).

Unfractionated heparin is given first by bolus injection and then by subcutaneous injection or intravenous infusion in a dose adapted to the patient's weight (*table 1*). Laboratory testing of the anticoagulant effect, as measured by the activated partial thromboplastin time (APTT), is obligatory; prolongation of the initial value by a factor of 1.5 to 2.5 is the target. Unfractionated heparin does not accumulate to the same extent as low-molecular-weight heparins in patients

Regular checking of the platelet count
should be performed until the end of the third week of treatment with heparin because of the risk of type II HIT.

Laboratory testing

Low-molecular-weight heparin does not require any routine laboratory testing, but unfractionated heparin does in all cases.

DIAGRAM 2

The risk of accumulation of low-molecular-weight heparins in patients with renal insufficiency as a function of their molecular weight (after Alban 2006)

streptokinase, as well as in a number of observational studies with various different thrombolytic agents (13), the technique was found to be markedly superior to anticoagulation alone, with respect to both the acute success of treatment and the long-term recanalization rate 6 or 12 months afterward. The current data suggest that the patients who stand to benefit the most from this procedure are those with an acute thrombosis of the iliofemoral veins, rather than those with an occlusion of the femoro-popliteal circulation. The rate of major hemorrhage varies widely from study to study, ranging from 0% to 13%. Larger, randomized, controlled studies are needed to determine the place of this technique in the overall therapeutic strategy for acute deep vein thrombosis.

In the past, thrombectomy was often performed in cases of acute pelvic vein thrombosis. It was found, however, that this approach provided no clear advantage over anticoagulation alone with respect to the prevention of a post-thrombotic syndrome. In any case, there are still no randomized, controlled studies directly comparing the two treatment measures. The current state of knowledge implies that thrombectomy should only be considered in special situations, such as the following:

- in descending thrombosis, with simultaneous surgical elimination of the source of external venous compression preventing flow,
- in phlebitis of the great or small saphenous vein with a thrombus protruding into the deep vein, or
- in the rare entity of phlegmasia cerulea dolens, with impending gangrene of the leg (14).

A floating thrombus is not an indication for surgery.

Compression and active ambulatory exercise therapy

Position-dependent pain and swelling are among the typical manifestations of severe deep vein thrombosis in the leg. These problems regress within a few days after the application of compression dressings with short- or middle-stretch bandages. A compression stocking is used if the thrombosis does not cause severe pain (or no longer causes severe pain) and is not associated with marked swelling. As a rule, a class II stocking with 23 to 32 mmHg of pressure at the heel is used. The length of the stocking is usually initially determined by the site of the thrombosis: a stocking up to the groin (length A–G) is used in cases of thigh or pelvic vein thrombosis, a stocking up to the knee (length A–D) in cases of calf vein thrombosis. A calf compression stocking (A–D) usually suffices for long-term treatment in most cases regardless of the original site of the thrombosis.

A post-thrombotic syndrome (PTS) of greater or lesser severity develops after 20% to 50% of cases of deep vein thrombosis of the leg. PTS can be treated or prevented with appropriate compression therapy. In two randomized trials, the immediate and consistent wearing of a calf-compression stocking in acute deep vein thrombosis of the leg (independently of the site of thrombosis) was found to yield significantly better results after two years of follow-up than treatment without compression. The incidence of severe post-thrombotic changes was reduced to 11% at five years, compared to 23% without compression, in the trial by Brandjes et al. (15) and to 3% at two years, compared to 11% without compression, in the trial by Prandoni et al. (16). If compression therapy is not begun until one year after the acute thrombosis, it has no advantage over treatment without compression with regard to the prevention of post-thrombotic syndrome (17). The duration of compression is based on the findings of phlebological follow-up examinations. If venous dysfunction persists, with a tendency toward edema, then continuing compression is recommended; otherwise, the current data suggest that compression can be discontinued after a maximum of two years.

Active exercise therapy in patients with acute venous thrombosis, performed simultaneously with compression therapy and adequate anticoagulation, has a beneficial effect on pain and swelling in the affected limb. The patient is instructed to perform walking exercises several times a day, until the point that these become painful. Conversely, strict bed rest

Thrombectomy

should be considered in cases of descending pelvic vein thrombosis, progressive saphenous phlebitis, and phlegmasia cerulea dolens.

Compression

Consistent wearing of a class II calf-compression stocking after venous thrombosis significantly lowers the probability of post-thrombotic syndrome.

is a major risk factor for the development and progression of thrombosis. Among 357 patients who were put to bed rest for five days while being anticoagulated with heparin, 26% developed phlebographically confirmed progression of their deep vein thrombosis, compared to only 1% of patients put to bed rest for one to two days (18). Immobilization should accordingly be limited to cases where it is absolutely necessary, e.g., certain traumatic injuries and postoperative situations, and severe systemic illnesses. Early mobilization in bed, e.g., with breathing exercises, active physical therapy, and a "bed bicycle," would seem to be advisable in parallel with anticoagulation.

Over the past decade, ambulatory treatment for deep vein thrombosis has become increasingly popular. This was possible only after clinical trials revealed that anticoagulation by the subcutaneous injection of low-molecular-weight heparin at home is just as safe and just as effective as the intravenous infusion of unfractionated heparin in the hospital (19, 20).

Later randomized, controlled studies showed that bed rest does not prevent symptomatic pulmonary embolism (21, 22). A further study documented the benefit of immediate compression treatment with respect to regression of symptoms (23) and thereby provided the breakthrough for ambulatory treatment of deep vein thrombosis of the leg and pelvis. Today, 80% to 90% of all patients with acute deep vein thrombosis qualify for ambulatory treatment.

The prerequisites for ambulatory treatment are the following:

- After a thorough explanation of this form of treatment, the patient must give informed consent and be compliant with the proposed treatment.
- The patient should have neither a bleeding tendency nor any serious accompanying illnesses.
- The treatment center should have a large experience in treating this condition and a physician must be available around the clock.
- The type of thrombosis (e.g. floating thrombus) and its localization (e.g. pelvic vein thrombosis) are of secondary importance for the decision to treat in the outpatient setting.

A brief period of inpatient observation may, however, be justified if there is a fear that complications might develop that would be difficult to control out of the hospital, e.g., fulminant pulmonary embolism.

Inferior vena cava filters

Interruption of blood flow in the inferior vena cava with various filter systems has been used for more than 30 years to reduce the risk of pulmonary embolism in patients with proximal deep vein thrombosis of the leg. In a randomized, controlled trial, the insertion of an inferior vena cava filter in addition to standard anticoagulation was found to reduce the frequency of both early and late pulmonary emboli (< 12 days and within 8 years, respectively) to a significant extent, but not to reduce mortality, and the number of subsequent leg vein thromboses was significantly higher after filter implantation (24). Therefore, the current indication for the implantation of an inferior vena cava filter is a high risk of pulmonary embolism in a patient for whom anticoagulation is contraindicated, or else recurrent pulmonary embolism despite adequate anticoagulation.

Transient inferior vena cava filters can be used instead of permanent ones, but there are still no studies that clearly demonstrate their benefit.

Long-term therapeutic anticoagulation

The necessity of pharmacological long-term anticoagulation after acute deep vein thrombosis is evident from the results of randomized clinical trials. These trials have revealed the following:

- In patients with distal deep vein thrombosis, the therapeutic administration of unfractionated heparin for only a few days was associated with progression or recurrence of the thrombosis in 20% of cases (25).
- Long-term prophylactic administration of unfractionated heparin instead of anticoagulation led to a 47% recurrence rate (e1).
- Oral anticoagulation for a short time (six weeks) was associated with significantly more symptomatic recurrences than an oral anticoagulation for a long time (six months): the recurrence rates were 9.5% and 0.4%, respectively (e2).

Vitamin K antagonists (VKA) are the drugs of choice for the prevention of recurrent thromboses. In selected patients, low-molecular-weight heparins can also be used, primarily in patients with cancer or in those for whom vitamin K antagonists are contraindicated.

Standard medication: vitamin K antagonists

As long as no invasive diagnostic or therapeutic measures are planned and there are no other contraindications,

Outpatient treatment

Under optimal conditions, 80% to 90% of patients with venous thromboses acquired out of the hospital can be treated in the outpatient setting.

Indications for the implantation of a vena cava filter:

- High risk of pulmonary embolism in a patient for whom anticoagulation is contraindicated
- Recurrent pulmonary embolism despite adequate anticoagulation

TABLE 2

The recommended duration of secondary prophylaxis with vitamin K antagonists after proximal and/or distal deep vein thrombosis (DVT) depending on risk profile*1

Type of thrombosis	Duration of prophylactic treatment
First thrombosis – with a transient risk factor (e.g. surgery or trauma)	At least 3 months
First thrombosis – idiopathic	At least 6 to 12 months (possibly indefinitely)
First thrombosis – in mild thrombophilia (e.g. heterozygous FV or Pro mutation)	6 to 12 months
First thrombosis – in combined thrombophilia (e.g. heterozygous FV and Pro mutations)	At least 12 months (possibly indefinitely)
First thrombosis – in severe thrombophilia (e.g. antiphospholipid Ab syndrome)	At least 12 months (possibly indefinitely)
First thrombosis – in active malignant disease	Indefinitely
Recurrent thromboses (2 or more documented DVT's)	Indefinitely

*1 Modified after the ACCP guidelines (4) and the German interdisciplinary S2 guidelines (5).
FV = factor V; Pro = prothrombin.

NB: There is still controversy about the significance of other types of thrombotic tendency (thrombophilia), including antithrombin, protein C, and protein S deficiencies, homocysteinemia, and factor VIII elevation, with regard to their severity and therapeutic consequences after thrombotic events!

secondary prophylaxis with a vitamin K antagonist is begun immediately after the diagnosis of deep vein thrombosis between day 1 and day 3. Heparin or fondaparinux is given simultaneously in a dose adapted to the patient's body weight and discontinued only when the effectiveness of anticoagulation with the vitamin K antagonist is stable within the desired target range. Usually, an International Normalized Ratio (INR) above 2.0 for two to three days is desired before heparin or fondaparinux is discontinued. The phase of parallel anticoagulation with two anticoagulant substances usually lasts five to seven days. Anticoagulation with a vitamin K antagonist alone without accompanying heparinization is dangerous and contraindicated, because it takes hours or days for the antithrombotic protective action to set in as the levels of the vitamin-K-dependent coagulation factors slowly drop.

In Germany, the most commonly used vitamin K antagonist is phenprocoumon (half-life 105 to 144

hours), while warfarin (half-life 36 to 42 hours) is most commonly used in the English-speaking countries. If the patient is to undergo invasive procedures in the foreseeable future that will require a switch to intravenous anticoagulation, warfarin should be used in preference to phenprocoumon because of its shorter half-life. The therapeutic range of the INR for both drugs is 2.0 to 3.0.

The duration of anticoagulation with vitamin K antagonists should be chosen in consideration of the patient's individual risk of recurrent thrombosis on the one hand and of hemorrhage on the other. After a first thrombosis, anticoagulation is maintained for 3 to 12 months at a conventional dose (INR 2.0 to 3.0) (table 2 [4]). Any continuation of anticoagulation beyond this time is done on an individual basis.

High risk of recurrence

Potential indications for indefinitely continued anticoagulation include active malignant disease, recurrent thromboembolism, and certain thrombophilic diatheses in the presence of a thromboembolic event that has already occurred (4). After a first idiopathic thrombosis, anticoagulation is usually given for at least 6 to 12 months, and indefinitely in some cases. Long-term anticoagulation should always be considered when one or more permanent risk factors are present, such as certain thrombophilic coagulation disorders, post-thrombotic residual changes in the veins, and persistent elevation of the D-dimer concentration in the blood. In terms of a risk/benefit analysis, it can be assumed that patients with an idiopathic thrombosis and a permanent risk factor stand to benefit more from permanent anticoagulation than those with a secondary ("triggered") thrombosis.

Permanent risk factors

There are hardly any validated methods in the literature for determining the degree of severity of a clotting diathesis. The authors consider the following situations to pose a high risk of thrombosis: congenital antithrombin or protein C deficiency, a homozygous factor V mutation, persistent antiphospholipid syndrome, and certain combined defects, e.g., a heterozygous factor V mutation together with a heterozygous prothrombin mutation. Patients with post-thrombotic residual changes in the venous circulation are presumed to have a two- to three-fold elevation of the risk of recurrence compared to patients with a normal

Vitamin K antagonists

As long as there is no contraindication, oral anticoagulation with vitamin K antagonists is begun as soon as the diagnosis of venous thrombosis is confirmed.

Oral anticoagulation

The initiation of oral anticoagulation with vitamin K antagonists without parallel heparinization is contraindicated.

venous status, regardless of whether the initial thrombosis was idiopathic or triggered (e3). Persistent elevation of the D-dimer concentration in the blood after at least three months of oral anticoagulation for a first thrombosis is also associated with an elevated risk of recurrent thrombosis (e4, e5).

Low risk of recurrence

The risk of recurrence is considered to be low in cases of secondary thrombosis triggered by a transient risk factor such as surgery or trauma. Anticoagulation is usually given only for three months in such cases.

Heterozygous mutations of factor V and prothrombin are among the more common thrombophilic coagulopathies. In the authors' view, and according to the relevant literature, the presence of one of these defects does not affect the decision to provide anticoagulation for a longer period after an initial thrombosis (4, 5, e6) (table 2).

The risk of hemorrhage

If anticoagulation is to be given for an indefinite period of time, then the risk of recurrent thrombosis should be weighed against the risk of hemorrhage in yearly intervals. The risk of hemorrhage under treatment with vitamin K antagonists is affected by individual factors including comorbidity and medications as well as by the age of the patient. It is also a function of the duration and intensity of anticoagulation. In randomized trials, the incidence of severe hemorrhage under conventionally dosed oral anticoagulation (INR 2.0 to 3.0) was significantly lower in the first three months of treatment (0.4 events per 100 patient-years) than after treatment for 12 months or more (1.5 events per 100 patient-years) (13).

In view of these findings, one should consider lowering the intensity of anticoagulation (to a target INR of 1.5 to 2.0) in certain patients for whom long-term anticoagulation is indicated but who also have an elevated risk of hemorrhage (e7). If this is done, the risk of hemorrhage will be lowered, but at the cost of a higher risk of recurrent thrombosis (13).

Alternative medical treatment: low-molecular-weight heparins instead of vitamin K antagonists

If oral anticoagulation is contraindicated or inadequate, low-molecular-weight heparins are the next alternative to be considered. Patients for whom this is a relevant consideration include those with a high risk

of hemorrhage (such as patients with gastrointestinal ulcers) or those who have already sustained a severe hemorrhage (e.g. retroperitoneal or intracranial), as well as those who are especially at risk for recurrent thrombosis, such as cancer patients. Moreover, patients for whom oral anticoagulation is difficult to monitor, or whose compliance with oral anticoagulation is inadequate, may benefit from a switch to a low-molecular-weight heparin. Treatment with low-molecular-weight heparins can be given from the start even if it can be foreseen that the anticoagulation will have to be interrupted multiple times for planned invasive procedures (for more information on the bridging of anticoagulation for invasive procedures, see reference [e8]).

Various types of low-molecular-weight heparin have been found to be just as effective as vitamin K antagonists with respect to the prevention of recurrent thrombosis, while having a comparable or lower rate of hemorrhagic complications (4, 13). This is particularly true when a full therapeutic dose of low-molecular-weight heparin is used, but also when half of the therapeutic dose is given. A prophylactic dose can be considered for patients with an elevated risk of hemorrhage.

Cancer patients with thromboembolic disease, in particular, stand to benefit from treatment with low-molecular-weight heparins rather than vitamin K antagonists. The trial of Lee et al., which involved the largest number of patients, revealed that treatment with the low-molecular-weight heparin dalteparin for one month at the full therapeutic dose, and then for five months at three-quarters of the therapeutic dose, was superior with respect to the rate of recurrent thromboses and did not elevate the risk of hemorrhage or death (e9). The demonstration that anticoagulation with various low-molecular-weight heparins is more effective than anticoagulation with vitamin K antagonists in cancer patients led to a recommendation that low-molecular-weight heparins should be given for at least three to six months in acute deep vein thrombosis (4).

Future medications: new substances

New anticoagulant substances are currently being evaluated for use in acute and long-term therapy for deep vein thrombosis (diagram 1). New types of factor Xa inhibitor include idraparinux (given subcutaneously once per week), rivaroxaban (p.o.), and apixaban (p.o.). Thrombin inhibition is the mechanism of action of

INR

In general, an INR between 2.0 and 3.0 is the target value for oral anticoagulation.

The decisive factors for the duration of oral anticoagulation are:

- the site of the thrombosis
- the patient's individual risk of recurrent thrombosis and of hemorrhage

dabigatran (p.o.). These substances are under study in large-scale clinical trials (e10).

Conclusion

The treatment of deep vein thrombosis in the leg and pelvis has undergone a radical transformation in the past decade, mainly because of the development of new anticoagulant drugs. Continuing research in the field will probably soon yield new knowledge with immediate therapeutic implications.

Conflict of interest statement

Professor Hach-Wunderle received lecture honoraria and consulting fees from Sanofi-Aventis and GlaxoSmithKline as well as financial support from Medi Bayreuth, Juzo, and Sanofi-Aventis. Dr. Präve received lecture honoraria from Sanofi-Aventis and GlaxoSmithKline. The remaining authors state that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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Corresponding author

Prof. Dr. med. Viola Hach-Wunderle
Krankenhaus Nordwest
Gefäßzentrum – Sektion Angiologie
Steinbacher Hohl 2–26
60488 Frankfurt am Main, Germany
Hach-Wunderle@t-online.de

Patients with cancer

Cancer patients with venous thrombosis benefit from a longer treatment with low-molecular-weight heparin, rather than with vitamin K antagonists.

Future medications

Newer antithrombotic agents will be introduced very soon as alternatives to treatment with vitamin K antagonists.

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For e-references please refer to:
www.aerzteblatt-international.de/ref0108

A case report is available at:
www.aerzteblatt-international.de/cme/article08m01

Further Information

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The solutions to the following questions will be published in Volume 9/2008. The CME unit "Involuntary Weight Loss in Elderly People" (Volume 49/2007) can be accessed until the 18th January. For Volume 5/2008 we plan to offer the topic "Diagnosis and Management of Upper Gastrointestinal Bleeding".

Solutions to the CME questionnaire in Volume 45/2007:

Kreis M: The Differential Diagnosis of Right Lower Quadrant Pain: 1/d, 2/d, 3/c, 4/a, 5/c, 6/c, 7/d, 8/e, 9/c, 10/c

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

A 29-year-old woman complains of pain in the left calf one week after a flight in an airplane. Duplex sonography reveals an isolated thrombosis of the fibular vein. Which of the following measures is appropriate?

- a) Low-molecular-weight heparin subcutaneously in a therapeutic dose
- b) Oral anticoagulation for 12 months
- c) Compression stocking of class II A–G (stocking up to the groin) around the clock
- d) Bed rest for two days in view of the danger of pulmonary embolism
- e) First follow-up examination in 2 to 3 weeks

Question 2

Which of the following is a genetic risk factor for venous thrombosis?

- a) Trisomy 21
- b) BRCA-1
- c) Phenylketonuria
- d) Hyperfibrinogenemia
- e) Factor V mutation

Question 3

The target range for the International Normalized Ratio (INR) in oral anticoagulation for venous thrombosis of the leg and pelvis is usually

- a) 1.5 to 2.0
- b) 2.0 to 3.0
- c) 2.5 to 3.5
- d) 3.0 to 3.5
- e) 3.5 to 4.0

Question 4

A 59-year-old patient had an idiopathic proximal leg vein thrombosis three years ago and was then orally anticoagulated for one year. An idiopathic proximal thrombosis is now found in the other leg. Which of the following statements is correct?

- a) Tumor screening is unnecessary.
- b) Oral anticoagulation should be given for a long period of time.
- c) The target INR value is 1.0 to 1.5.
- d) Hospitalization is absolutely necessary.
- e) Compression therapy should be given only if the leg is swollen.

Question 5

What laboratory test can be used for monitoring of treatment with low-molecular-weight heparin?

- a) INR and Quick test
- b) D-dimer test
- c) Russell viper venom test
- d) Anti-factor Xa activity
- e) Activated partial thromboplastin time (APTT)

Question 6

Which of the following patients does not need to be admitted to the hospital?

- a) A patient with venous thrombosis and shortness of breath
- b) A patient with venous thrombosis and marked renal insufficiency

- c) A patient with venous thrombosis and severe upper abdominal symptoms
- d) A patient with venous thrombosis and no other complaints
- e) A patient with venous thrombosis and severe alcoholism

Question 7

When should thrombolysis be considered for a patient with venous thrombosis of the leg and pelvis?

- a) In all cases of extensive thrombosis
- b) In all cases of thromboses that are more than 10 days old
- c) In a young patient with an extensive thrombosis (calf, thigh, and pelvic venous thrombosis) that is estimated to be less than 7 days old
- d) In all cases of proximal thrombosis
- e) If the thrombosis is of the "floating" type

Question 8

Which of the following statements about the treatment of venous thrombosis with low-molecular-weight heparins (LMWH) is correct?

- a) LMWH are not indicated for cancer patients with venous thrombosis.
- b) Heparin-induced type II thrombocytopenia is less likely to occur with LMWH than with unfractionated heparin, but the platelet count should nonetheless be checked regularly during the first three weeks of treatment.
- c) LMWH should not be given if the patient is simultaneously suffering from pulmonary embolism.
- d) LMWH have less favorable pharmacological properties than unfractionated heparin.
- e) LMWH are effective only when given intravenously.

Question 9

Which of the following statements about the duration of oral anticoagulation is correct?

- a) If the risk is only transient (e.g. surgery, trauma), it can usually be limited to 1 month.
- b) For idiopathic thromboses, it should generally be 3 months.
- c) It depends on the risk/benefit profile in the individual case.
- d) Oral anticoagulation should be given indefinitely for patients with a distal thrombosis who have a heterozygous factor V mutation.
- e) The recommended duration of oral anticoagulation is independent of the individual patient's risk of bleeding.

Question 10

Which patients should be tested for anti-factor Xa activity while undergoing treatment with low-molecular-weight heparin?

- a) All patients
- b) Patients with extensive thromboses
- c) All patients treated in the ambulatory setting
- d) Patients with abnormal body weight, pregnant women, and patients with renal insufficiency
- e) Patients with distal thromboses

CASE

Treatment of Deep Vein Thrombosis in the Pelvis and Leg

Viola Hach-Wunderle, Markus Dux, Anja Hoffmann, Florian Präve, Max Zegelman, Wolfgang Hach

Case

Deep Vein Thrombosis of the Leg

A 60-year-old woman came to the doctor's office because of phlebitis. The inflammatory reaction was in the region of a previously diagnosed varicose dilatation of the trunk of the right great saphenous vein. After crossectomy and partial resection of the vessel, the patient was free of symptoms.

Two years later, the right leg became acutely swollen and painful (*figure*). Color-coded duplex sonography revealed a proximal deep venous thrombosis. Anticoagulation was immediately begun with a subcutaneous injection of a low-molecular-weight heparin (LMWH) in a dose adjusted to the patient's body weight. At the same time, a compressive bandage was applied over the entire leg, up to the groin, and treatment with phenprocoumon was initiated. Once the INR value was above 2.0 for two consecutive days, heparinization was discontinued. After the leg became less swollen, a class II compression stocking extending to the groin (A–G) was fitted. A search for possible causes of the thrombosis revealed that the patient had carcinoma of the ovary. Shortly thereafter, the tumor was resected and chemotherapy was begun. The patient tolerated chemotherapeutic medication poorly, however, with the result that this treatment was stopped and the patient declined any further care by the oncologist. Oral anticoagulation was continued for one year with a target INR value of 2.0 to 3.0.

Eight months after oral anticoagulation was discontinued, the patient complained of pain in the left calf. Sonography revealed a distal deep venous thrombosis and a circumscribed thrombophlebitis. She was treated once again with LMWH in a dose adjusted to her body weight. Long-term therapy with LMWH was planned but had to be terminated and replaced by oral anticoagulation because of local pain at the injection sites. The oral anticoagulant that was given this time was acenocoumarin, because the patient had suffered from marked hair loss under the previous treatment with phenprocoumon (*diagram*). It proved to be difficult to find the proper dose of acenocoumarin, and the measured coagulation values fluctuated widely.

Figure: Proximal deep venous thrombosis of the right leg

Two months later, the patient was found to have bilateral pelvic vein thrombosis. The INR at this time was 1.7. A higher dose of oral anticoagulant was given. The target range for INR was set at 2.5 to 3.0, and it was decided that LMWH would be given in addition whenever the INR dropped below 2.5. A recurrence of the ovarian carcinoma was also diagnosed and chemotherapy was begun a second time.

After a further five months, the venous thrombosis progressed into the inferior vena cava, and ultimately the left subclavian vein also became occluded with thrombus. Anticoagulation was switched to LMWH, given at a dose that was transiently even higher than the normal, body-weight-adjusted dose. By this time,

however, the patient had become cachectic and could not tolerate subcutaneous injections for more than a short time because of local pain at the injection sites. Once again, anticoagulation was switched to acenocoumarin, with a higher INR target range of 3.0 to 3.5. The tumor progressed relentlessly and embolized into the pulmonary arteries. The patient suffered from severe dyspnea and leg pain. She died five months later of tumor-related cachexia.

Diagnosis

Recurrent venous thromboembolism in the setting of progressive ovarian carcinoma.

Basic considerations regarding tumor-related thrombosis

- Venous thrombosis may be associated with neoplastic illness. Tumors are found in approximately 5% of cases of venous thrombosis; for idiopathic thromboses, this figure rises to 15%.
- Other features arousing suspicion of an underlying tumor include thromboses in multiple vessels ("polytopic thromboses"), recurrent pulmonary embolism, migratory thrombophlebitis, and thrombotic events despite adequate anticoagulation.

- The basic diagnostic algorithm for the detection of primary tumors includes the following tests, according to the German interdisciplinary S2 guidelines on the diagnosis and treatment of venous thrombosis of the leg and pelvis and of pulmonary embolism (2005): history, physical examination, laboratory testing, chest x-ray, abdominal ultrasonography, and urological/gynecological screening, including a test for occult blood in the stool.
- Patients with venous thromboembolism and neoplastic illness often benefit from long-term treatment with low-molecular-weight heparin (LMWH) rather than oral anticoagulation, not only with respect to progressive thrombosis in the setting of tumor progression, but also with respect to the risk of hemorrhage.
- The long-term use of LMWH by patients with neoplastic diseases and thrombosis can also be problematic, however, because of both local and systemic side effects and because of the high cost of treatment. The risks and benefits must be weighed individually for each patient.

DIAGRAM

Coumarin derivatives