Review

New developments in the treatment of deep venous thrombosis

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Abstract

An initial course of standard heparin (SH) or low-molecular-weight heparins (LMWH) is regarded as the treatment of choice for patients with deep venous thrombosis (DVT). LMWH have better bioavailability after subcutaneous administration, have a longer half-life, and show higher and more predictable anticoagulant activity. As a result they can be given subcutaneously and without laboratory control, using a dose that is determined by bodyweight. Because of these multiple advantages of LMWH they will replace SH in the future and subsequently home treatment with LMWH of selected patients seems feasible. The currently accepted approach is to start with SH or LMWH therapy combined with oral anticoagulant therapy (OAT) at the time of diagnosis. The course of SH or LMWH should continue for at least 5 days, provided that international normalized ratio (INR) is in the therapeutic range on 2 consecutive days. OAT should be continued for at least 3 months to prolong the prothrombin time to an INR of 2–3. When oral anticoagulants are either contraindicated or inconvenient, SH or LMWH can be used at the middosing interval. The role of anti-platelet treatment is not yet established and should be compared with coumarin therapy in the future.

Keywords: Deep venous thrombosis; Low-molecular-weight heparin; Heparin; Oral anticoagulants

1. Introduction

Deep venous thrombosis (DVT) is a potentially fatal disorder if untreated. The aims of treating patients with DVT are prevention of death from pulmonary embolism, reduction of morbidity caused by thrombus extension and prevention of the post-thrombotic syndrome (PTS). Prior to the late 1930s, patients with DVT were treated with bedrest alone. Heparin became available in a clinically usable form in 1935. Dicoumarol became available in 1940. The last two decades the approach to the diagnosis of DVT has changed radically and new developments of treatment have occurred [1]. Since accurate diagnostic tools for detection of DVT, like venography, compression ultrasound and plethysmography became available, it has been possible to perform randomized clinical trials to evaluate the various approaches for prevention and treatment of venous
thrombosis [2]. These trials have resolved some of the uncertainties that a clinician confronts in selecting appropriate anticoagulant therapy. Furthermore, new therapeutic agents, like low-molecular-weight heparins, have been introduced and improved dosage regimens have been developed for established drugs.

In the following the current literature dealing with the initial and long-term treatment of DVT is reviewed. Although in practice heparin and oral anticoagulants are administered together, they will be discussed separately.

2. Initial treatment

2.1. Standard unfractionated heparin (SH)

SH has generally been considered the antithrombotic drug of choice for the initial treatment of DVT because of its immediate anticoagulant effect [3]. This approach has been supported by a randomized double-blind study by Brandjes et al. [4]: the efficacy and safety of continuous intravenous SH plus acenocoumarol were compared to treatment with acenocoumarol alone in the initial treatment of proximal DVT. This study was terminated prematurely because of an excessive number of symptomatic thrombotic events in the group that received acenocoumarol alone (20% as compared with 6.7% in the group that received both).

SH acts mainly by binding to and enhancing the effect of antithrombin III, which results in a rapid inhibition of a number of serine proteinases, notably thrombin (factor IIa), factor IXa and factor Xa [5,6]. When administered intravenously as a bolus, SH has an effective concentration-dependent half-life of about $1\frac{1}{2}$ hours.

When SH is given in therapeutic doses, its anticoagulant effect must be monitored and if necessary the dosage should be adjusted, because of a wide interindividual variability in pharmacodynamics. Clinically effective treatment depends on the intensity of the SH anticoagulant effect as measured by daily laboratory tests, like activated partial thromboplastin time (APTT) or heparin level. APTT is the most commonly used laboratory test to monitor SH therapy, although it is not specific for heparin. APTT is sensitive to the inhibitory effects of SH on thrombin, factor Xa and factor IXa. In clinical practice SH is adjusted to maintain the APTT response between an (empirically stated) therapeutic range—i.e., 1.5 and 2.5 times the control value, which is equivalent to a heparin level of 0.2 to 0.4 U/ml by protamine titration [7,8]. For this purpose a nomogram has been developed which results in achieving a therapeutic APTT at 24 and 48 h in a large proportion of patients and in reduced periods of inadequate anticoagulation during SH therapy [9]. It should be noted that the different commercial APTT reagents vary in their responsiveness to SH, so this nomogram is not applicable to all APTT systems but should be adapted by the local laboratory [10].

For this reason some hospitals monitor heparin level by a chromogenic substrate assay according to Teien [11] instead of APTT. This assay allows an accurate reading within a rather broad range, in contrast to APTT, the reproducibility of which decreases with increasing clotting times [12,13]. Also the chromogenic assay is more specific for the heparin level. To demonstrate the value of this chromogenic assay in monitoring heparin therapy, it should be compared to APTT. These studies have not yet been performed.

Prospective trials have indicated that failure to exceed the lower limit of the therapeutic range is associated with an unacceptably high rate of recurrent venous thromboembolism [14,15]. Hull et al. observed that the relative risk of recurrent venous thrombotic events was 15 times higher in patients in whom the APTT remained subtherapeutic during the first 24 h or more of SH therapy than in those patients with a therapeutic APTT [14]. Basu et al. observed that the relative risk of recurrent thrombotic events was 7 times higher in patients in whom APTT was less than 50 s for 2 consecutive days than in patients with therapeutic APTT results [15]. The relationship between bleeding complications and 'excessive' APTT is not clear. One study even demonstrated no association between APTT above the therapeutic range and bleeding [16].

A rapid therapeutic effect of SH is achieved by commencing with a loading dose of 5000 U as an intravenous bolus followed by continuous infusion of 1000–1250 U/h. APTT should be performed at approximately 6 h after the bolus and the SH dose adjusted to the result obtained. In case APTT is
subtherapeutic, it should be repeated 6 h after increasing the SH dose to optimize the therapy.

A controversial issue in the treatment of DVT is the optimal mode of SH administration. SH is not absorbed after oral administration and therefore should be given by intravenous injection, intermittent or continuous. Intramuscular injection can produce large haematoma and should be avoided. A randomized comparison showed that continuous intravenous SH infusion is safer than intermittent intravenous SH injections, because the latter was associated with more bleeding complications, whereas both showed similar efficacy in preventing recurrent thrombosis [17]. The disadvantages of continuous SH infusion include hospitalization, prolonged immobilization and a possible increase in the cost of treatment.

These disadvantages might be overcome if SH could be administered effectively and safely using the subcutaneous route. Studies comparing intravenous to subcutaneous administration are contradictory. A meta-analysis of the most important studies indicated that unfractionated SH administered subcutaneously twice daily is more effective and at least as safe as continuous intravenous SH administration [18]. This is in contrast to a trial performed by Hull et al. in which subcutaneous SH resulted in a higher frequency of recurrent thrombosis [19].

2.2. Low molecular weight heparins (LMWH)

LMWH are an important new class of anticoagulants which have revolutionized the standard care of DVT [20]. LMWH are fragments of heparin, produced by either chemical or enzymatic depolymerization. The mean molecular weight is 4000–5000 Da (the molecular weight of heparin is 25 000 Da).

In pharmacokinetic studies it was shown that the peak anti-Xa and anti-IIa activity appeared after 3 h and that the effect was sustained for at least 12 h and gradually disappeared by 24 h. The intra-individual variation between two administrations was small [21]. The comparing resorption as calculated from anti-Xa activity over an ascending dosage range of several LMWH was linear [22]. Most studies showed a relatively more anti-Xa than anti-IIa activity [23,24]. It should be noted that these studies used low doses of LMWH [25,26]. Recently Agnelli et al. assessed anti-IIa activity with a more sensitive assay. They compared the relative half-lives of prophylactic and therapeutic doses of LMWH by assessing both anti-IIa and anti-Xa activity. In contrast to the other studies, which reported a low half-life of the anti-IIa activity, they found that a high and sustained plasma anti-IIa activity was achieved when LMWH were administered in therapeutic doses used in contemporary trials with only a moderate prolongation of the APTT [27].

LMWH have a number of advantages over SH: because there is less protein binding of LMWH [28], they have a more predictable anticoagulant response when administered in fixed doses, so the dose only has to be adjusted to the patient’s bodyweight. Also LMWH have a longer plasma half-life [29,30] and a more favourable antithrombotic to haemorrhagic risk ratio; they maintain their antithrombotic effect probably through anti-Xa activity but cause less clinical bleeding by a reduced action on the APTT and overall clotting [28,31,32]. These properties might allow LMWH to be administered once daily without laboratory monitoring. The final advantage is early mobilization, because the patient is not hindered by an infusion pump.

LMWH administered in a fixed dose by subcutaneous injection have been compared with dose-adjusted SH administered by continuous infusion in several studies. In these studies two different outcome assessments were used. First, the change in thrombus size was assessed by repeating venography at the end of the course of treatment [33–37]: LMWH were as effective as SH. Second, most studies used the occurrence of the symptomatic recurrent DVT as end-point; there was a strong trend for LMWH to be more effective and safer than SH [38–41]. Two meta-analyses of these trials found similar trends indicating improved efficacy and safety with LMWH [42,43]. It is uncertain if the favorable outcomes of treatment with different LMWH can be extrapolated to all other types of LMWH [24,42,44]. Also it is not certain whether there is bioequivalence between all products. As a consequence similar studies with different types of LMWH should be performed. Finally it should be noted that only a few studies used a once-daily regimen of LMWH [39,41,45], the other studies twice daily. Currently LMWH once versus twice daily are being compared. Table 1 shows the different LMWH that are currently registered for treatment of DVT in the Netherlands.
Table 1
LMWH that are registered for treatment of DVT in the Netherlands

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Company</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparine</td>
<td>Fragmin</td>
<td>Pharmacia</td>
<td>200 IU/kg</td>
</tr>
<tr>
<td>Enoxaparine</td>
<td>Clexane</td>
<td>Rhône-Poulenc Rorer</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Nadroparine</td>
<td>Fraxiparine</td>
<td>Sanofi</td>
<td>225 IU/kg</td>
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LMWH = low-molecular-weight heparin; DVT = deep venous thrombosis.

In conclusion, LMWH seem promising for the initial treatment of DVT and are about to replace intravenous heparin treatment [20]. Recently evidence has been provided that in the future patients with DVT might even be treated with LMWH at home [46,47]. Both studies compared treatment with SH (administered in the hospital intravenously) to LMWH. The studies allowed outpatients taking LMWH to go home immediately and hospitalized patients taking LMWH to be discharged early. Endpoints of the studies were recurrent DVT, major bleeding, quality of life and costs. Levine et al. treated 253 patients with SH and 247 patients with LMWH (1 mg enoxaparin per kg body weight subcutaneously twice daily) [46]. Recurrent DVT occurred in respectively 6.7 and 5.3%, major bleeding in 1 and 2%. Koopman et al. treated 198 patients with SH and 202 patients with LMWH (nadroparine-Ca, dose adjusted to body weight) [47]. Recurrent DVT occurred in respectively 8.7 and 6.9%, major bleeding in 2 and 0.5%. In this study improvements in quality of life were similar in both groups, the LMWH recipients even having better physical and social function. Both studies showed a similar frequency of recurrent thromboembolic events and bleeding complications. In conclusion treatment with LMWH at home seems feasible, effective and safe [46–48]. This change from hospital to community care might overlook two important achievements of recent years. First objective diagnostic testing should be performed in every patient to avoid under- or overtreatment. Secondly, each patient should get size-to-fit compression stockings to prevent the post-thrombotic syndrome.

2.3. Duration of initial treatment

A consensus about the optimal duration of initial treatment in patients with DVT has not been achieved. According to the conventional approach SH was given for 10 days and oral anticoagulant therapy was started on days 5 to 10 to ensure an overlap period of 4 to 5 days before heparin was discontinued. The rationale for this regimen was based on observation in animals [49,50]; subsequent clinical trials have demonstrated its effectiveness.

Two randomized studies in patients with proximal DVT have demonstrated that a short course of SH therapy (4 to 5 days) is associated with a recurrence rate and bleeding complications similar to a longer course (9 to 10 days) [14,51]. Such a short course reduces the length of hospital stay, which offers a substantial financial benefit and may possibly reduce the incidence of heparin-induced thrombocytopenia or hospital acquired infections.

In most countries a short course of SH or LMWH is currently regarded as the standard initial treatment. Provided the international normalized ratio (INR) is in the therapeutic range on 2 consecutive days, SH or LMWH can be discontinued after 5 days. The question is whether in the case of extensive thrombosis (e.g., iliac vein thrombosis) 5 days of SH therapy is also enough; in most trials patients with extensive DVT are excluded.

2.4. Side-effects

The major side-effect of heparin therapy is bleeding. Maintaining the APTT within the therapeutic range does not guarantee protection from bleeding complications. In the case of bleeding, withdrawal of heparin is usually sufficient because it is cleared rapidly from the plasma with an average half-life of 90 min. If bleeding continues, protamine sulphate infusion will neutralize the heparin effect (1 mg protamine neutralizes approximately 150 units of heparin). The risk of bleeding is increased with an increased heparin dose, but also other factors such as recent surgery, trauma, peptic ulcer, malignancy or an haemostatic abnormality are important. Most trials comparing SH to LMWH suggest that LMWH
cause fewer bleeding complications [20,39–41]. This is probably due to a lower anti-IIa/anti-Xa ratio of LMWH than of SH.

Another side-effect of SH or LMWH is thrombocytopenia, an allergic reaction [5,38]. It typically appears 5 or more days after the start of therapy. The thrombocytopenia is caused by heparin-dependent IgG antibodies that activate platelets through their Fc receptors [52]. Paradoxically, thrombotic complications develop in some patients with heparin-induced thrombocytopenia, possibly because of in vivo platelet activation [53]. With these patients the use of danaparoid (a combination of heparan sulphate and dermatan sulphate) should be considered [5,54]. It has been demonstrated that thrombocytopenia occurs less in patients treated with LMWH [55]. Other adverse reactions including osteoporosis, alopecia, local skin necrosis from hypersensitivity and anaphylactic shock are rare.

3. Thrombolysis

In DVT thrombolysis is suggested to prevent post-thrombotic symptoms if complete lysis could be achieved before valve destruction and recurrent venous thromboembolic events have occurred. Several trials have evaluated thrombolytic therapy. Most of them were not able to demonstrate a lower incidence of the post-thrombotic syndrome [56–60]. It was generally accepted that early thrombolysis improves valve function. However, a contentious issue is whether thrombolysis will also decrease the long-term manifestations of PTS. As this has not so far been supported by experimental clinical trials, and because of a high incidence of major bleeding (2.9 times higher than in SH therapy) the use of thrombolysis can not be propagated as routine treatment [57–61]. At present this kind of treatment should be restricted to severe cases of DVT like phlegmasia cerulea dolens.

4. Vena cava filter

The main reason for placing a vena caval filter is the existence of a contraindication or a severe complication of anticoagulation or recurrent pulmonary embolism despite anticoagulation [8,62,63]. No data are available comparing the effect of these filters to standard anticoagulant treatment, so the exact indications are unknown.

5. Long-term treatment

5.1. Oral anticoagulant treatment (OAT)

After the initial treatment period with heparin there is an obvious need for long-term intensive anticoagulant treatment [64]. The rationale for OAT is to prevent recurrent thromboembolic episodes and possibly to assist the physiological resolution of the thrombus. Coumarin derivatives, such as warfarin, acenocoumarol and fenprocoumon are the oral anticoagulants of choice [8,65]. An unacceptably high recurrence rate occurred if no, too short or too low intensity secondary prophylaxis was used [66,67].

Coumarin derivatives are competitive vitamin K antagonists and are well absorbed from the gastrointestinal tract. They inhibit the vitamin-K-dependent carboxylation of coagulant factors II, VII, IX and X [49,50] and also of proteins C and S [66].

Coumarin therapy can be commenced on the same day as heparin therapy with a maintenance dose or with a small loading dose which is approximately twice the average maintenance dose. Larger loading has no advantage over the smaller loading dose and is potentially dangerous, mainly in patients with protein C deficiency (skin necrosis).

In the past prothrombin time (PT) was the most important laboratory test to monitor coumarin therapy. Because the PT was difficult to standardize a calibration model was adopted in 1982 converting the PT ratio observed with the local thromboplastin into an international normalized ratio (INR). It should be noted that there is a wide interlaboratory variation in the accuracy of INR determinations [68]. INR monitoring is usually performed daily during heparin therapy until a stable level is achieved, thereafter it may be performed less frequently. It was recently demonstrated that it is more difficult to sustain a therapeutic INR in patients with a malignancy. More frequent monitoring may be needed in these cases to achieve a low complication rate [69]. Computer-adjusted dose schemes have also been devised for the
ontrol of short- and long-term therapy [70]. Evidence from recent studies indicates that an effective level of anticoagulation in DVT is reflected by an NR of 2.0 to 3.0. It was demonstrated by Hull et al. that it is safe to use a less intense dosage regimen; it was associated with a low frequency of recurrent DVT (2%) and a reduced risk of haemorrhage [67]. A more intense range, that might be indicated for example in patients with recurrent DVT or thrombosis at an abnormal location (vena cava, portal vein), corresponds to an INR of 2.5 to 3.5.

5.2. Low-dose SH or LMWH subcutaneously

In patients who are at risk of developing bleeding, LMWH subcutaneously may be an acceptable alternative to coumarin [71–73]. Hull et al. compared warfarin sodium versus low-dose SH in the long-term treatment of DVT. They found adjusted-dose warfarin sodium more effective than low-dose subcutaneous heparin in preventing recurrent DVT, but its use was accompanied by a significant risk of bleeding [72]. In the study by Pini et al. LMWH were compared with conventional warfarin for 3 months [74]. In this period the recurrence rate was not significantly different in the two groups. However, there was a significant reduction of bleeding complications in the LMWH group.

Comparison of LMWH with coumarin merits confirmation in subsequent studies. To date, secondary thromboprophylaxis with subcutaneous heparin has not shown advantages over oral anticoagulant therapy, particularly in view of the higher costs, the need for administration by injection and the risk of osteoporosis.

5.3. Duration of secondary prophylaxis

Despite investigation in a number of studies over the last few decades, the optimal duration of OAT is still a matter of debate. For most patients it is recommended to be continued for 3 months [8,75]. This approach is supported by 2 studies by Hull et al. who demonstrated low rates of recurrent thrombosis in patients with proximal DVT who received 3 months of OAT [67,71]. Because it is important to minimize the negative side-effects without increasing the recurrence rate, shorter durations of OAT have been evaluated. The results are inconclusive [76–78]. Levine et al. compared 4 weeks with 3 months of coumarin in patients who had a normal impedance plethysmograph (IPG) after 4 weeks. Even after normalization of the IPG 8.6% of the placebo group developed recurrent thrombosis versus 0.9% of the warfarin group. They conclude that even after normalization of the IPG the rate of recurrent DVT after stopping OAT after 4 weeks is high [79].

Schulman et al. compared 6 weeks treatment with 6 months treatment in a large multicentre trial [78]. This study demonstrated a benefit of prolonged anticoagulation in the 6-month group, although the long-term outcome for all patients was discouraging since there was no difference in the incidence of recurrent events in the two groups during 24 months of follow-up after the initial episode.

The duration of OAT should be tailored to the individual patient [80]. The most important factor for continuing OAT is the existence of risk factors, such as inherited thrombophilias, malignancies, mechanical obstruction or prolonged immobilization. In these cases OAT should be continued for a longer time. More detailed information on this subject is not available because there have been no trials published comparing a different duration of OAT in these groups of patients.

5.4. Side-effects of oral anticoagulants

The most important adverse effect of oral anticoagulants is bleeding; it may be mild, such as epistaxis or purpura, or more serious like cerebral haemorrhage, retroperitoneal bleeding, large haematomas or gastrointestinal bleeding. The risk of bleeding is directly linked to the intensity of the anticoagulant effect: less intensive therapy reduces bleeding complications without loss of clinical benefit when INR is above 2 [67].

Coumarin effects can be reversed within 24 h by large doses of parenteral vitamin K. The serious and life-threatening bleeding requires urgent and immediate correction of INR with prothrombin complex after coumarins are stopped.

Another complication associated with the coumarins is hepatitis. Finally, thrombosis in the microcirculation, causing skin necrosis, may occur. This complication occasionally occurs in the first
weeks of therapy and has been associated with protein C deficiency and malignancy. The best way to avoid it is to commence with a small loading dose.

5.5. Anti-platelet treatment

Anti-platelet treatment, like acetylsalicylic acid, dipyridamole and epoprostenol, inhibits platelet aggregation by affecting the balance between prostacyclin and thromboxane A₂. These kinds of drugs are registered for secondary prevention of arterial thrombosis (e.g., after myocardial infarction, stroke or bypass surgery). It has been shown that long-term anti-platelet therapy is feasible and that among patients at high risk of occlusive vascular disease, it reduces the risk of vascular death, myocardial infarction, stroke and other vascular occlusion. Previously, it had generally been concluded that anti-platelet prophylaxis had little or no effect on venous thrombosis or pulmonary embolism. Recently an overview of trials comparing subcutaneous heparin with anti-platelet therapy in thromboprophylactic studies in surgical patients has shown that anti-platelet therapy (usually studied for only about 1 to 3 weeks) substantially reduced the incidence of pulmonary embolism [81,82].

Since anti-platelet therapy seems effective in preventing arterial vascular disease and DVT after surgery, one could assume that this therapy might also be useful in the long-term treatment of DVT, instead of coumarin. Trials comparing these two treatments have not been published yet. Advantages would be that it is a practicable therapy without the use of laboratory monitoring and perhaps with fewer bleeding complications (as in thromboprophylaxis the risk of bleeding complications seemed to be relatively small) [81]. At present, anti-platelet therapy should not be recommended for long-term treatment of DVT until controlled, randomized studies comparing coumarins with antiplatelets have been performed.

6. Pregnancy

The well-known coagulopathy of pregnancy is characterized by an increased concentration of circulating clotting factors, more rapid turnover of platelets and reduced activity of the fibrinolytic system [83]. DVT of the lower extremity during pregnancy is infrequent, but pulmonary embolism remains an important cause of maternal mortality. Coumarin derivatives and fibrinolytic agents are considered to be hazardous in pregnancy. Coumarins cross the placenta and may cause spontaneous abortion and specific embryopathies if given in the first trimester of pregnancy. This risk is said to be greatest between the 6th and 9th week of gestation [84]. There is also concern that they may cause fetal bleeding during and after delivery [85]. The anticoagulant effect on the fetus is more pronounced than in the mother because the immature fetal liver produces only low levels of vitamin-K-dependent clotting factors and the maternal procoagulant factors do not cross the placental barrier due to their large molecular size [83].

Nevertheless, pregnant women with DVT should receive long-term anticoagulation. This is best accomplished with heparin or LMWH. A review of the published experience of the utilization of LMWH in obstetrics and gynaecology revealed that LMWH do not cross the placenta in any trimester and there is no evidence of any mutagenic and teratogenic effect of these drugs [86–88]. When long-term treatment is required, patients should be educated to administer heparin or LMWH by subcutaneous injections to themselves.

When the patient begins labour, heparin or LMWH should be withheld. Following delivery, subcutaneous heparin or LMWH should be started again in the same dose or a coumarin derivative should be given orally for 4 to 6 weeks postpartum.

7. Summary

An initial course of heparin or LMWH is regarded as the treatment of choice for patients with DVT. SH acts as an immediate inhibitor of several steps of the intrinsic coagulation pathway. It should be given intravenously with loading and maintenance doses to consistently prolong the APTT to between 1.5- and 2.5-fold the control value or heparin level between 0.2 and 0.4 U/ml. LMWH have better bioavailability after subcutaneous administration, have a longer half-life, and show higher and more predictable anti-
anticoagulant activity, probably because there is less nonspecific binding to plasma proteins. As a result they can be given subcutaneously and without laboratory control, using a dose that is determined by weight. Also, because the constraints of continuous infusion are lacking, early mobilization is possible. Because of these multiple advantages of MWH they will replace SH in the future and home treatment with LMWH of selected patients then seems feasible.

The currently accepted approach is to start with H or LMWH therapy and oral anticoagulant therapy together at the time of diagnosis. The course of H or LMWH must take at least 5 days, provided that INR is in the therapeutic range on 2 consecutive days. This short-course regimen cannot yet be recommended for patients with more extensive disease like iliac vein DVT, so this should be evaluated with weight. OAT should be continued for at least 3 months to prolong the prothrombin time to an INR of 2–3. However, the optimal duration as well as the optimal intensity still have to be determined. When oral anticoagulants are either contraindicated or inconvenient, SH or LMWH can be used at the mid-dosing interval. The role of anti-platelet treatment is not yet established and should be compared with coumarin therapy in the future.

References


