VESSELS ARTICLE

Prevention of Venous Thromboembolism

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Abstract

Venous thromboembolism is the most common cause of preventable death among hospitalised patients. Systematic prophylaxis with antithrombotic agents in patients at risk for venous thromboembolism is the most effective approach to reduce morbidity and mortality. Despite this evidence, antithrombotic prophylaxis is still underused, due to the underestimation of incidence of venous thromboembolism and to the unjustified fear of bleeding complications. Both the characteristics of the individual patient and the clinical setting contribute to the definition of the risk for venous thromboembolism. Patient-related risk factors include clinical and molecular abnormalities. The grade of risk for venous thromboembolism is defined better by the clinical setting than by the patient characteristics. Prophylactic studies have been extensively carried out in surgical patients and, only more recently, in medical patients. Prophylactic methods include pharmacological agents, such as heparin, low molecular weight heparins, warfarin, and hirudin, as well as mechanical methods such as compression stockings and intermittent pneumatic compression.

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Key Words: Venous thromboembolism; Deep vein thrombosis; Pulmonary embolism; Heparin; Low molecular weight heparin; Warfarin

Venous thromboembolism includes two clinical manifestations: deep vein thrombosis and pulmonary embolism. Venous thromboembolism is a leading cause of death and morbidity among hospitalised patients. It has been estimated that 100,000 patients die from pulmonary embolism each year in the United States [1]. A fatal pulmonary embolism can be the initial clinical presentation of postoperative venous thromboembolism in patients with asymptomatic deep vein thrombosis and this makes it inappropriate to rely on early diagnosis and treatment. In addition, non-invasive tests have a low sensitivity in the screening of deep vein thrombosis in asymptomatic patients [2,3]. For these reasons, systematic prophylaxis for venous thromboembolism in patients at risk is the most effective strategy to reduce morbidity and mortality. Despite this evidence, pharmacological prophylaxis is still underused [4,5] due to the unjustified belief that the incidence of venous thromboembolism is not sufficiently high and due to the overestimation of the incidence of bleeding side effects from anticoagulants. With respect to the incidence of venous thromboembolism, it should be taken into account that without prophylaxis the incidence of fatal pulmonary embolism is about 0.5% in low-risk patients, 1.5% in elective hip surgery patients, and it approaches 5% in patients undergoing surgery for hip fracture [6]. With respect to the fear of bleeding, a number of clinical studies have demonstrated that prophylaxis with anticoagulants is associated with a higher incidence of surgically related minor bleedings and wound haematomas [7]. However, in these studies no sta-
Table 1. Clinical risk factors for venous thromboembolism

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Previous venous thromboembolism</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
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<tr>
<td>Prolonged immobility</td>
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<tr>
<td>Paralysis</td>
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<tr>
<td>Major medical illness (i.e., stroke, myocardial infarction)</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Estrogen use</td>
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The risk for venous thromboembolism is determined by the patient characteristics, including both clinical and molecular abnormalities, and by the clinical setting. Clinical risk factors include a previous episode of venous thromboembolism, cancer, age greater than 70 years, prolonged bed rest, lower limb paralysis, obesity, severe medical illness (i.e., myocardial infarction and stroke), and use of oral contraceptives (Table 1). Molecular risk factors are inherited or acquired abnormalities of the haemostatic mechanisms that are responsible for a thrombophilic state. Inherited abnormalities include antithrombin III, protein C or protein S deficiencies, activated protein C resistance (factor VR506Q mutation), hyperhomocysteinemia, and prothrombin mutation G20210A. Acquired abnormalities include the occurrence of lupus anticoagulant and the antiphospholipid syndrome. The clinical settings associated with a high incidence of venous thromboembolism are major orthopaedic surgery, including elective hip and knee replacement and hip fracture, surgery for cancer, neurosurgery, acute spinal cord injury, and trauma. Medical conditions such as myocardial infarction, stroke, and burns also indicate high risk for venous thromboembolism. The grade of risk for venous thromboembolism is defined better by the clinical setting than by the patient characteristics. The stratification of patients in classes of risk is shown in Table 2.

Prophylactic methods include pharmacological agents that act by interfering with coagulation and mechanical methods that accelerate venous outflow: among the first category are unfractionated heparin (UH), low molecular weight heparins (LMWH), warfarin, and hirudin; among the second category, compression elastic stockings (ES) and intermittent pneumatic compression (IPC). The adjusted-dose unfractionated heparin regimen consists of preoperative low dose unfractionated heparin (LDUH), followed by postoperative dose adjustment to maintain the activated partial thrombin time in the upper range of normal values. LMWH are derivatives of UH produced by its depolymerisation that have a longer half-life and a better bioavailability after subcutaneous administration than UH. LMWH can be administered at fixed doses without laboratory monitoring and are associated with a lower incidence of heparin-induced thrombocytopenia than UH [11]. Oral anticoagulants are started preoperatively [International Normalised Ratio (INR) about 1.5 before surgery] and then the targeted INR is 2 to 3 in the postoperative period [12]. The alternative is to start oral anticoagulants in the perioperative period to reach an INR of 2.0 to 2.5 within 4 or 5 days [13]. Adjusted-dose UH or oral anticoagulants require laboratory monitoring. Hirudin originally produced by a medicinal leech is now obtained through DNA recombinant technology.

In this article, the evidence about pharmacological and mechanical thromboprophylaxis in the different clinical settings will be reviewed.

1. General Surgery

The incidence of venous thromboembolic events in patients undergoing general surgery without prophylaxis was calculated by pooling the events observed in control patients included in 54 clinical trials on different methods of prophylaxis [14]. An incidence of deep vein thrombosis of 25% was found when deep vein thrombosis was assessed by the radioactive fibrinogen uptake test; this incidence was only slightly reduced to 19% in the studies where the results of the radioactive fibrinogen
Table 2. Stratification of patients in classes of risk for venous thromboembolism

<table>
<thead>
<tr>
<th>Patients younger than 40 years</th>
<th>Moderate risk</th>
<th>High risk</th>
<th>Highest risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated surgery (i.e., hysterectomy)</td>
<td>Any (major or minor surgery in patients 40–60 years and no other risk factors)</td>
<td>Major surgery in patients &gt;60 years and no other risk factors</td>
<td>Major surgery &gt;40 years and previous VTE, or cancer or hypercoagulable state</td>
</tr>
<tr>
<td>Minimal immobility</td>
<td>Major surgery in patients &lt;40 years with no other risk factors</td>
<td>Major surgery in patients 40–60 years and other risk factors</td>
<td>Major orthopaedic surgery</td>
</tr>
<tr>
<td>Minor surgery in patients with risk factors</td>
<td>Patients with myocardial ischemia and medical patients with risk factors</td>
<td>Elective neurosurgery</td>
<td>Multiple trauma or acute spinal cord injury</td>
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Modified from Clagett et al. [14].

uptake test were confirmed by venography. The incidence of proximal deep vein thrombosis (involving the popliteal vein or more proximal venous segments) in patients not receiving prophylaxis was 6 to 7%, while the incidences of clinically overt pulmonary embolism and fatal pulmonary embolism were found to be 1.6 and 0.9%, respectively [14]. The incidence of pulmonary embolism was probably underestimated because most patients in the trials were treated with anticoagulants when the fibrinogen uptake test became abnormal.

In general surgery, the most extensively investigated anticoagulant regimens are LDUH (5000 IU every 8–12 hours, starting 2 hours before surgery) and LMWH given at different doses in most of the cases 2 hours before surgery [7–10,15]. An analysis of 29 trials including more than 8000 patients randomised to LDUH or control showed that LDUH, given in the majority of the patients for 7 days, reduced the incidence of deep vein thrombosis from 25 to 8%. Two meta-analyses [9,16] and three large studies [17–19] indicated that LDUH reduces the incidence of proximal deep vein thrombosis, clinically overt pulmonary embolism, and fatal pulmonary embolism. LMWH have been compared with LDUH in a number of clinical trials and meta-analyses. Considering these studies all together, it could be concluded that LMWH and LDUH are equally effective in the prevention of venous thromboembolism in general surgery with the advantage of the single administration for the LMWH.

The issue of bleeding complications is more controversial because in some studies fewer wound haematomas and bleeding complications were observed with LMWH while other studies showed the opposite. The discrepancy appears to be correlated with the doses of the LMWH. It was found that doses of LMWH higher than 3400 anti-Xa IU/daily were associated with a higher incidence of bleeding complications than LDUH [10]. In contrast, LMWH doses lower than 3400 anti-Xa IU/daily are still equivalent to LDUH but produce less bleeding. Reviparin sodium, 1750 anti Xa IU once daily, has been shown to be effective but tolerated significantly better than conventional prophylaxis with LDUH in general abdominal surgery [20]. Oral anticoagulants have been investigated in general surgery patients either as low fixed dose (1 mg/daily) [21] or as low-intensity warfarin regimen [12]. Warfarin is effective, but because it requires laboratory monitoring it is not widely adopted. Dextran, a 40000 to 70000 dalton polysaccharide, is not as effective as LDUH and LMWH in the prevention of proximal deep vein thrombosis in
general surgery patients [16,22]; however, dextran reduces the incidence of pulmonary embolism to the same extent as LDUH [16].

The meta-analysis of the Antiplatelet Trialists Collaboration indicated that antiplatelet agents reduce the incidence of deep vein thrombosis and pulmonary embolism by 37 and 71%, respectively, in comparison to controls [23]. However, these data must be interpreted cautiously since most individual trials showed no significant benefit of aspirin. IPC showed a similar efficacy to LDUH in reducing the incidence of deep vein thrombosis in patients undergoing general surgery, but its use is limited by its inconvenience [14]. It is unknown whether IPC prevents pulmonary embolism. Similar considerations concerning deep vein thrombosis and pulmonary embolism respectively apply to ES [24].

The use of ES alone should be restricted to a low-risk population. The combination of ES with LDUH in patients at high risk for venous thromboembolism may provide additional benefit with respect to LDUH alone [25,26].

An appropriate strategy for the prevention of venous thromboembolism in individual general surgery patients should take into account the risk for venous thromboembolism and the potential benefits of the various agents. In patients at low risk, no specific prophylaxis other than early mobilisation is recommended. In moderate-risk patients, LDUH every 12 hours, LMWH once daily (<3400 anti-Xa IU), or ES would be sufficient. In patients at higher risk, LDUH given every 8 hours and LMWH are the strategies of choice. The addition of ES to any of these methods provide additional protection. In very high-risk patients, the combination of pharmacological and physical methods provides an excellent protection. Higher daily doses of LMWH (>3400 anti-Xa IU) and perioperative warfarin would also be appropriate.

2. General Surgery in Cancer Patients

In patients undergoing general surgery for cancer without prophylaxis, a 29% incidence of venography-detected deep vein thrombosis has been observed. Patients without malignancy had a 19% incidence of deep vein thrombosis [14].

The beneficial effect observed in the meta-analysis comparing LDUH and controls in general surgery was also observed in trials including patients with cancer. A comparison between the LMWH certoparin (3000 anti Xa IU once daily) and LDUH (three times daily) in a study of limited sample size including patients with gynaecological malignancies showed the two regimens had a similar efficacy [27]. Enoxaparin (40 mg once daily) has been compared with LDUH (three times daily) in patients undergoing curative abdominal or pelvic surgery for malignancy in a large venography study. The incidence of deep vein thrombosis was 14.7% in the enoxaparin group and 18.2% in the LDUH group (p = 0.03). There was no significant difference in the incidence of bleedings was observed. Similar results were obtained by danaparoid in a LDUH-controlled study [29]. Dermatan sulphate, a selective thrombin inhibitor acting through heparin cofactor II, was compared with LDUH for the prophylaxis of venous thromboembolism in patients undergoing surgery for cancer [30]. Patients were randomised to dermatan sulphate (600 mg intramuscularly starting 2 days before surgery, then reduced after surgery to 300 mg once a day) or to LDUH (every 8 hours). Treatment was continued up to seventh postoperative day or until adequate mobilisation. Of the 842 patients randomised, 521 had an adequate venography and/or a confirmed pulmonary embolism. The incidence of venous thromboembolism was 15% in patients receiving dermatan sulphate and 22% in the LDUH group (p = 0.03). There was no significant difference in bleeding complications. IPC has a limited efficacy in patients undergoing surgery for cancer [16].

3. Major Orthopaedic Surgery

Major orthopaedic surgery includes elective hip and knee replacement and surgery for hip fracture. Patients undergoing major orthopaedic surgery have a high incidence of postoperative venous thromboembolism. The high incidence of venous thromboembolism in these conditions makes primary prophylaxis mandatory.

3.1. Elective Hip Replacement

The incidence of venous thromboembolic events in patients undergoing elective hip replacement
without prophylaxis was calculated by pooling the events observed in control patients included in 13 clinical trials on different methods of prophylaxis [14]. An incidence of deep vein thrombosis (proximal and distal thrombosis) of 51% was found when deep vein thrombosis was assessed by venography. Approximately 50% of the thrombosis were proximal. Two different meta-analyses showed that LDUH [9] and aspirin [23] are more effective than placebo in the prevention of venous thromboembolism in patients undergoing total hip replacement; however, both regimens are relatively ineffective when compared with other regimen of prophylaxis and cannot be recommended for this indication. The prophylactic methods of choice in the prevention of venous thromboembolism in hip replacement are adjusted-dose UH [31], LMWH, oral anticoagulants, and recombinant hirudin. Concerning the relative value of these prophylactic strategies, it should be noted that hirudin is not available in all countries and that adjusted-dose UH is rarely used because of its impracticality. Oral anticoagulants are adopted most often by orthopaedic surgeons in North America, while LMWH are the reference strategy in Europe. Two meta-analyses indicated that LMWH are more effective than LDUH in patients undergoing elective hip replacement [8,32]. Moreover, several randomised trials showed that LMWH are at least as effective and safe as adjusted-dose UH or oral anticoagulants [33–35].

Two LMWH, reviparin and enoxaparin, have been shown to be equivalent with respect to the total incidence of proximal deep vein thrombosis; there was less bruising and fewer haematomas in patients receiving reviparin as compared with patients receiving enoxaparin [36]. The results of three randomised double-blind clinical trials indicated that hirudin, given subcutaneously at the dose of 15 mg twice a day, was more effective than LDUH (three times daily) [37,38] and enoxaparin, 40 mg once daily [39], with no difference in bleedings. It was shown that 1.0 mg/kg of hirulog, a 20 aminoacid synthetic analogue of hirudin, given subcutaneously three times a day is effective and safe [40]. Promising results have been obtained with danaparoid, a complex mixture of heparan sulfate, dermatan sulfate, and condroitin sulfate [41].

Compared with general anaesthesia, regional anaesthesia has been shown to be associated with a lower incidence of venous thromboembolism after elective hip replacement [42]. The incidence of venous thromboembolism in patients receiving regional anaesthesia without any pharmacological prophylaxis remains high and it warrants additional pharmacological prophylaxis. IPC and ES alone are not adequately effective.

### 3.2. Elective Knee Replacement

The incidence of venous thromboembolic events in patients undergoing elective knee replacement without prophylaxis was calculated by pooling the events observed in control patients included in four clinical trials on different methods of prophylaxis [14]. An average incidence of deep vein thrombosis (proximal and distal thrombosis) of 61% was found when deep vein thrombosis was assessed by venography. Approximately 25% of the thrombosis were proximal. LDUH [43] and aspirin [44] have a moderate efficacy in the prevention of venous thromboembolism in patients undergoing elective knee surgery. LMWH and oral anticoagulants are the prophylactic methods of choice in the prevention of venous thromboembolism in these patients. However, these prophylactic regimens are less effective in knee surgery than in hip surgery; the difference is mainly due to their relative inefficacy in reducing the incidence of distal deep vein thrombosis. Several trials compared LMWH vs. adjusted-dose warfarin in patients undergoing elective knee surgery using venography to measure the end point. Overall, LMWH were found to be more effective than oral anticoagulants. However, the incidence of venography-detected deep vein thrombosis among patients receiving LMWH remained high, ranging from 25 to 45% [45–47]. Moreover, in some trials LMWH failed to reduce the rate of proximal deep vein thrombosis in comparison to warfarin [47,48]. In the comparative studies, it was shown that LMWH caused more surgical site bleeding and wound haematomas than warfarin.

Several trials showed the efficacy of IPC in patients undergoing knee replacement [49,50]. However, the use of IPC is limited by patient intolerance and by the difficulties in continuing prophylaxis after hospital discharge. ES have shown to be barely effective in patients undergoing knee replacement [51]. In patients at particularly high risk
of venous thromboembolism, the combination of IPC with an LMWH or warfarin should be considered.

3.3. Surgery for Hip Fracture

The incidence of venous thromboembolic events in patients undergoing surgery for hip fracture without prophylaxis was calculated by pooling the events observed in control patients included in nine clinical trials on different methods of prophylaxis [14]. An average incidence of deep vein thrombosis of 51% was found when deep vein thrombosis was assessed by venography. Approximately 50% of the thrombosis were proximal, as is the case for elective hip surgery. The prevention of venous thromboembolism in patients with hip fracture is problematic and it is due to the advanced age of the majority of patients and the recent trauma that increases the risk of bleeding. None of the pharmacological prophylaxis regimens are ideal or universally accepted. Two small trials showed a 27% incidence of deep vein thrombosis in patients treated with LDUH [48, 52]. The pooled results of five trials with LMWH and five trials with low-intensity oral anticoagulants (INR 1.2–1.5) showed a similar incidence of deep vein thrombosis compared to patients treated with LDUH. LMWH and oral anticoagulants are the most extensively evaluated prophylactic regimens in patients undergoing surgery for hip fracture. This circumstance, more than the efficacy, makes LMWH and oral anticoagulants the recommended strategies in this clinical setting. There are no well-conducted trials with mechanical methods (IPC or ES). However, it is conceivable that whenever possible, hip fracture patients should be treated with LMWH or low-intensity oral anticoagulants in combination with IPC or ES.

3.4. Optimal Duration of Prophylaxis after Major Orthopaedic Surgery

The optimal duration of the prophylaxis for venous thromboembolism after major orthopaedic surgery is still undefined. Three randomised clinical trials showed a marked reduction of venography-detected deep vein thrombosis in patients receiving 1 month of anticoagulant prophylaxis after elective hip replacement [53–55]. Overall, the incidence of deep vein thrombosis was reduced from 19–26% to 7–12%. However, the clinical relevance of asymptomatic deep vein thrombosis is unclear. Our group has made an overview in patients having undergone major orthopaedic surgery. It was found that patients receiving in-hospital pharmacological prophylaxis for 8 to 12 days and discharged with a negative venography had a low incidence of clinically overt venous thromboembolic events (1.27%) [56]. Similar findings have been also found in patients discharged from the hospital without any screening for deep vein thrombosis. Large-scale, double-blind, placebo-controlled clinical trials, having as an end point clinically overt venous thromboembolism, will define the safety and the cost-effectiveness of a 1-month regimen of anticoagulant prophylaxis. Prolonged prophylaxis with either LMWH or adjusted-dose warfarin (INR 2–3) can be adopted in patients with additional risk factors such as leg paralysis, malignancy, or previous episode(s) of venous thromboembolism.

4. Elective Neurosurgery

Venous thromboembolism is a common adverse event after neurosurgery. Studies performed in the 1970s and early 1980s, using radioactive fibrinogen uptake test for the diagnosis of deep vein thrombosis, found an incidence of thrombosis ranging between 19 and 50% in control patients. More recently these findings have been confirmed by venography studies that showed an incidence of deep vein thrombosis ranging between 24 and 33% in patients who wore compression stockings but who did not receive any pharmacological prophylaxis. Neurosurgeons are particularly concerned about potential bleeding complications, in particular intracranial bleeding, related to antithrombotic prophylaxis. Therefore, physical methods (IPC and ES) have been initially preferred to anticoagulant agents. IPC appeared highly effective, showing a reduction of the incidence of deep vein thrombosis from 23 to 6% in comparison to placebo in combined trials where radioactive fibrinogen uptake test was used for the diagnosis of deep vein thrombosis [14]. Although comparable rates of deep vein thrombosis have been found in patients receiving ES alone and those receiving the combination of ES and IPC, concerns about the efficacy of ES alone have been raised by recent studies including
high-risk patients such as those undergoing neuro-
surgery for a brain tumour [57,58].

LMWH were investigated in two randomised
trials [57,58]. In the first trial comparing nadroparin
(given postoperatively) plus ES vs. ES alone [57],
nadroparin reduced the incidence of deep vein
thrombosis from 26.3 to 18.7%. The incidence of
proximal deep vein thrombosis was reduced from
11.5 to 6.9%, respectively. Nadroparin was associ-
ated with an increase in the incidence of major
bleedings (0.8 and 2.3%). In the second study, en-
oxaparin (40 mg once daily), started within 24
hours of surgery in association with ES, was com-
pared with ES alone [58]. Enoxaparin reduced the
incidence of deep vein thrombosis from 32.6 to
16.9% and of proximal deep vein thrombosis from
13.2 to 5.4% without an excess of bleeding complica-
tions. In conclusion, LMWH and IPC are both
effective prophylactic methods and their combina-
tion can be considered for patients at particularly
high risk.

5. Acute Spinal Cord Injury

In patients with acute spinal cord injury, an inci-
dence of clinically overt deep vein thrombosis and
pulmonary embolism of 14.5 and 4.6%, respec-
tively, was found in a multicenter review including
a large number of patients [59]. LDUH has been
compared with adjusted-dose UH and with the
LMWH ardeparin in two different trials. These
studies indicate that LDUH is less effective than
adjusted-dose UH and ardeparin [60]. Enoxaparin
has been found to be more effective than adjusted
dose UH (activated partial prothrombin time up
to 10 seconds the normal value) in reducing the
rate of fatal pulmonary embolism (PE) in a study
with a reduced sample size [61]. There is no evi-
dence for the efficacy of IPC in this clinical con-
dition.

6. Trauma

Trauma patients (multiple trauma patients in par-
ticular) are at high risk for venous thromboembo-
lism as confirmed by a large cohort prospective
trial. This study found a 58% incidence of venogra-
phy-detected deep vein thrombosis (18% proxi-
mal) in 349 major trauma patients [62]. Advanced
age, surgery, fracture of the lower limbs, spinal
cord injury, and blood transfusions were associated
with an increased risk of deep vein thrombosis.
A randomised venography trial compared LDUH
(twice daily) with enoxaparin (30 mg twice daily)
starting 36 hours after trauma [63]. Enoxaparin
reduced the incidence of deep vein thrombosis
from 44 to 31% ($p=0.01$). Proximal deep vein
thrombosis was reduced from 15 to 6% ($p=0.01$).
A slight increase in the incidence of major bleeding
was observed in the enoxaparin group (2.9 and
0.6%, respectively). There are no convincing data
supporting the efficacy of IPC or ES in major
trauma patients.

7. Burns

There are few data concerning the incidence of
deep vein thrombosis and pulmonary embolism
in burn patients. The incidence of symptomatic
pulmonary embolism in 1439 burn patients not re-
ceiving prophylaxis was 0.4% [64]. In burn patients
with central venous catheter, the incidence of
upper limb venous thrombosis was found to be
20% [65]. There is not sufficient evidence to sup-
port routine prophylaxis in burn patients; this
should be performed in patients presenting addi-
tional risk factors such as a central venous catheter.

8. Medical Conditions

The prevention of venous thromboembolism in
hospitalised medical patients has been less exten-
sively studied than in surgical patients. Patients
with myocardial infarction and stroke are the most
extensively evaluated among medical patients.

8.1. Myocardial Infarction

Without pharmacological prophylaxis, the inci-
dence of venous thromboembolism in patients with
acute myocardial infarction is about 24% [14]. UH
and oral anticoagulants have been investigated in
open trials where the diagnosis of deep vein throm-
bosis was based on clinical symptoms. UH (10000
U subcutaneously) followed by oral anticoagulants
(targeted INR 2–3) was investigated in a large,
randomised controlled clinical trial in comparison with patients receiving no antithrombotic prophylaxis [66]. The incidence of deep vein thrombosis was 0.2% in the treated group and 2.6% in the controls. However, there was a significant increase in bleeding complications in treated patients (2.6 and 1.2%, respectively). Four clinical trials assessed the benefit of LDUH (5000 IU every 8 to 12 hours or 7500 IU every 12 hours) in comparison with no prophylaxis. The pooled incidence of deep vein thrombosis was 7% in patients treated with LDUH and 24% in the controls [14]. Two trials with reduced sample size investigated high-dose intravenous UH (40000 IU/24 hours). Deep vein thrombosis occurred in three patients (4%): no significant increase in bleeding complications was observed [67,68]. ES were investigated in 80 patients aged over 70 years with acute myocardial infarction [69]. Patients wore ES only in one leg. In the legs wearing ES, no deep vein thrombosis occurred, whereas the incidence of deep vein thrombosis (assessed by radioactive fibrinogen uptake test) was 10% in the control legs ($p=0.003$). In conclusion, LDUH and full-dose UH are effective in reducing the incidence of venous thromboembolism in patients with myocardial infarction. ES and IPC can be used when heparin is contraindicated.

8.2. Ischemic Stroke

Without prophylaxis, the incidence of deep vein thrombosis in patients with ischemic stroke is about 60% [23]. Fatal pulmonary embolism occurs in 1 to 2% of patients. IPC reduced the incidence of deep vein thrombosis assessed by ultrasonography in patients with acute ischemic stroke. LDUH was associated with a significant reduction in deep vein thrombosis in a preliminary trial where no significant increase in major bleedings was observed [70]. In a larger trial the incidence of deep vein thrombosis (assessed by radioactive fibrinogen uptake test) was 22.1% in patients receiving LDUH and 73% in the control group [71]. There was no increase in major bleedings. The LMWH dalteparin was studied in two small trials with contrasting results [72,73]. Danaparoid was investigated for the prophylaxis of venous thromboembolism in patients with acute stroke [74]. Fifty patients were treated with an intravenous bolus of 1000 anti-Xa IU of danaparoid followed by the subcutaneous injection of 750 anti-Xa IU every 12 hours, while 25 patients received placebo. The incidence of deep vein thrombosis was 4% in patients treated with danaparoid and 28% in the placebo group. Danaparoid did not cause a significant increase in major bleedings. A randomised double-blind trial compared danaparoid (750 anti Xa IU every 12 hours) with LDUH in 87 ischemic stroke patients with a paralyzed limb [75]. Deep vein thrombosis occurred in the 8.9% of the patients treated with danaparoid and in 31% of the patients treated with LDUH ($p=0.001$). A subsequent study comparing danaparoid, 1250 anti-Xa IU once daily, with twice daily LDUH did not confirm the superiority of danaparoid [76].

Two large trials have evaluated the therapeutic use of UH, aspirin [77], and danaparoid [78] in patients with acute ischemic stroke. The International Stroke Trial showed a significant reduction in fatal and nonfatal pulmonary embolism in patients treated with UH (5000 or 12500 IU). The incidence was 0.8% in patients receiving heparin and 0.5% in the controls. There was no difference in the incidence of pulmonary embolism among the two heparin groups; however, the higher dose of UH was associated with an increase in bleeding complications. Aspirin did not reduce the incidence of pulmonary embolism [77].

In the Trial of Organon in Acute Stroke Treatment (TOAST), patients receiving full doses of danaparoid (plasma anti-Xa, range 0.6–0.8 IU/mL) had no deep vein thrombosis or pulmonary embolism, whereas the control group had a 0.4% incidence of venous thromboembolism [78]. In conclusion, LDUH and danaparoid are the recommended agents for the prophylaxis of venous thromboembolism in patients with acute ischemic stroke, while there is still limited evidence supporting the use of LMWH. IPC and ES can be an alternative in patients with contraindications to anticoagulants.

8.3. Other Medical Conditions

There are relatively few data on the epidemiology of venous thromboembolism in medical patients other than those affected by stroke or myocardial infarction. A review of these studies reported a 20% incidence of deep vein thrombosis assessed by radioactive fibrinogen uptake test [79]. LDUH
(every 8 hours) was investigated in 100 patients with congestive heart failure, chest infection, or both [80]. The incidence of deep vein thrombosis was 4% in patients treated with LDUH and 26% in the control group \((p=0.01)\). There was no increase in major bleedings. In a subsequent trial, 263 medical patients aged over 65 were randomised to enoxaparin (60 mg once daily) or placebo [81]. Enoxaparin led to a statistically significant reduction in the incidence of venous thromboembolism (3.0 and 9.1%, respectively, \(p=0.03\)). No increase in major bleeding complications was reported. The results of a randomised double-blind clinical trial have been recently reported [82]. Patients (1102) aged over 40 were randomised to the once daily injection of two different doses of enoxaparin (20 or 40 mg) or placebo for 6 to 14 days. The primary end point was venography-detected deep vein thrombosis and objectively confirmed symptomatic pulmonary embolism. Patients assigned to placebo or 20 mg of enoxaparin had a similar incidence of deep vein thrombosis and venous thromboembolism. On the other hand, patients receiving 40 mg of enoxaparin showed a significant reduction in the incidence of venous thromboembolism. In these patients, the rate of venous thromboembolism was 5.5% compared to the 14.9% of the control group \((p=0.0002)\). The incidence of deep vein thrombosis was reduced from 14.2 to 5.5% \((p=0.0004)\); the rate of proximal deep vein thrombosis was reduced from 4.9 to 1.7% \((p=0.04)\). There was no statistically significant difference in the safety outcomes among the three groups.

The efficacies of LMWH and LDUH (every 8 hours) were compared in a preliminary clinical trial [83]. The diagnosis of deep vein thrombosis was made with impedance plethysmography and duplex ultrasonography. The incidence of deep vein thrombosis was 4.5 and 3.6%, respectively, a difference that is not statistically significant. Three multicenter randomised clinical trials investigated the efficacy and safety of LMWH vs. LDUH for the prophylaxis of venous thromboembolism in patients with acute medical illness [84–86]. The first trial compared the once-daily injection of 20 mg of enoxaparin with a twice-daily injection of LDUH. There was no difference in the incidence of venous thromboembolism (4.8 and 4.6%, respectively) or major bleeding complications [84]. The second trial compared the once-daily injection of nadroparin (3600 anti Xa IU) with LDUH (every 8 hours) [85]. No significant difference in the incidence of clinically overt deep vein thrombosis and or pulmonary embolism and asymptomatic proximal deep vein thrombosis detected by ultrasonography or major bleedings was observed. The third trial (PRINCE study) enrolled 665 patients, 451 of whom were included in the efficacy analysis [86]. Patients were subdivided into a group with severe respiratory disease (PRINCE I) and a group with severe heart failure (PRINCE II). All patients were randomised to enoxaparin 40 mg once daily or LDUH (every 8 hours). The primary end point was deep vein thrombosis, detected by fibrin monomer and D-dimer and confirmed by venography, and objectively confirmed symptomatic pulmonary embolism. The incidence of venous thromboembolism in the overall population treated with enoxaparin was 8.4 and 10.4% in the overall LDUH group \((p=0.01)\).

Patients with cancer have an increased risk for venous thromboembolism. In a properly performed study 311 women with metastatic breast cancer receiving chemotherapy were randomised to very low dose warfarin (1 mg daily for 6 weeks and then INR 1.3–1.9) or placebo [87]. Warfarin was associated with a statistically significant reduction in venous thromboembolic events.

Two randomised trials demonstrated the efficacy of 1 mg/daily treatment of warfarin and of once daily 2500 anti-Xa IU of a LMWH (dalteparin) in reducing the incidence of upper deep vein thrombosis in cancer patients with indwelling central venous catheters [88,89].

References

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