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The management of patients on long-term oral anticoagulant therapy undergoing surgery

Francesco Baudo, Gianni Mostarda, Marco Boniardi, Massimo Finzi, Giuseppe Grassi, Enrica Morra

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table of contents

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Foreword

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Unfractionated heparin was the antithrombotic agent of choice for the prophylaxis and treatment of venous thromboembolism and is also indicated in the treatment of patients with acute coronary syndromes. However, unfractionated heparin has some limitations such as the need for close monitoring of its anticoagulant effect. Low molecular weight fractions (LMWF) prepared from standard commercial-grade heparin have similar antithrombotic activity and safety. Because of their efficacy and safety, LMWF have largely replaced unfractionated heparin in clinical practice and can be used in the out-patient setting. In this *Old and New Heparins* symposium the clinical application of these agents will be discussed by experts in different medical fields. These colleagues, because of their wide clinical experience, will update on us on the problems that we may encounter in our clinical practice.

Dr. Francesco Baudo
Dr.ssa Enrica Morra

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Perspectives on antithrombotic agents: from unfractionated heparin to new antithrombotics

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Unfractionated heparin (UFH) has been the antithrombotic agent of choice for the prevention and treatment of venous thromboembolism (VTE) for a long time. UFH is also widely used for the treatment of patients with acute coronary syndromes. However, UFH has some limitations such as the need for parenteral administration and close monitoring of its anticoagulant effect. UFH is also associated with bleeding, heparin-induced thrombocytopenia and osteoporosis. Low molecular weight heparins (LMWHs) are produced by the depolymerization of UFH. LMWHs have pharmacological advantages over UFH: a better bioavailability after subcutaneous administration, a longer plasma half-life and a more predictable anticoagulant effect. These improved features allow once or twice daily subcutaneous injection of weight-adjusted doses of LMWHs without requiring laboratory monitoring in patients with VTE or unstable angina. A number of new antithrombotic agents are currently under development. These include direct antithrombins and factor Xa inhibitors. The results of the main clinical trials with LMWHs as well as those of the studies with the new antithrombotic agents will be reviewed in this article.

Key words: unfractionated heparin, low molecular weight heparins, venous thromboembolism, acute coronary syndromes, direct antithrombins, pentasaccharide.

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Unfractionated heparin (UFH) has, for long time, been the anticoagulant agent of choice for the prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). UFH has also been extensively evaluated in the management of arterial thrombosis, in patients with acute myocardial infarction to speed-up thrombolysis or to prevent mural ventricular thrombosis, in patients with unstable angina and in patients undergoing vascular surgery and percutaneous transluminal coronary angioplasty (PTCA) to prevent acute arterial thrombosis. UFH has some pharmacological limitations mainly related to its non-specific binding to plasma proteins (fibrinogen, factor VIII, vitronectin and fibronectin), endothelial cells and macrophages. This binding complicates the clearance of UFH, reduces UFH bioavailability, and is responsible for the marked inter-individual variation in the dose-anticoagulant response. UFH also has biophysical limitations due to the inhability of the heparin/antithrombin complex to inactivate factor Xa in the prothrombinase complex. Moreover, UFH is not able to inactivate thrombin when this is bound to fibrin or to exposed subendothelial matrix. Subcutaneous injection of UFH at low doses is associated with low bioavailability and a short half-life. Moreover, UFH may cause heparin-induced thrombocytopenia (HIT), a disease that is often complicated by arterial and/or venous thrombosis (HITT) and has a severe prognosis.

Low molecular weight heparins (LMWHs) are derivatives of UFH, produced by its depolymerization. LMWHs are composed by mixtures of saccharide chains with a mean molecular weight close to 5,000 Daltons. Approximately one third of the heparin chains contain the pentasaccharide sequence that constitutes the heparin-binding site to antithrombin. LMWHs bind less avidly to plasma proteins and endothelial cells than UFH. They have an almost complete bioavailability after subcutaneous administration of low doses, a more linear relationship between dose and anticoagulant effect and a longer plasma half-life than UFH. Finally, HIT is less commonly associated with the use of LMWHs.

LMWHs in the prevention of post-operative venous thromboembolism

General surgery

Without prophylaxis, patients undergoing general surgery have a 19% incidence of venographically-detected DVT. The incidence of proximal DVT (popliteal or more proximal veins) is 6-7%; the incidence of clinically overt PE and fatal PE is 1.6 and 0.9%, respectively.[1] The most extensively investigated anticoagulants are low doses of UFH (5,000 IU every 8 or 12 hours) (LDUFH) and LMWHs. A pooled analysis of 29 trials including more than 8,000 patients randomized to LDUFH (started 2 hours before surgery) or placebo showed that LDUFH reduces the incidence of DVT from 25 to 8%. Data from a meta-analysis[2] and large clinical trials indicate that LDUFH also reduces the occurrence of fatal PE.[3] LMWHs were compared with LDUFH in a series of studies and several meta-analyses. Enoxaparin was investigated in five trials on the prevention of VTE after general surgery. Samama *et al.* compared enoxaparin 20, 40 and 60 mg given once daily with LDUFH every 8 hours.[4] DVT was diagnosed by a fibrinogen uptake test (FUT) confirmed by venography. The incidence of DVT was 3.8, 2.8 and 2.9% in patients receiving enoxaparin at doses of 20, 40 and 60 mg and 7.8, 2.7 and 3.8% in LDUFH patients (p=ns). Dalteparin given at a dose of 2,500 to 5,000 anti-Xa IU once daily showed a similar efficacy and safety to LDUFH, while the 7,500 anti Xa IU dose of dalteparin was associated with an increased incidence of bleeding. Three studies compared nadroparin (2,850 anti-Xa IU) with LDUFH in the prevention of VTE in general surgery.[5-7] Two studies showed the superiority of nadroparin over LDUFH.[5,6] DVT was assessed by FUT and confirmed by venography. In the third study the incidence of DVT, assessed by Doppler ultrasound and plethysmography, confirmed by venography, was low in both treatment groups.[7] Nadroparin was not associated with an increase in bleeding. Reviparin sodium was investigated in a large multicenter trial at a dose of 1,750 anti-Xa IU, and showed a similar efficacy to LDUFH every 12 hours but a lower incidence of bleeding.[8]

Therefore, LMWHs are at least as effective as LDUFH in the prevention of VTE in general surgery patients. The overall incidence of DVT with LMWHs is 6%. LMWHs have the advantage of their once daily administration. Bleeding complications are related to the dose of LMWHs. Indeed, doses of LMWHs higher than 3,400 anti-Xa IU/day are associated with a higher incidence of bleeding complications than LDUFH, whereas doses lower than 3,400 IU/day are associated with a lower incidence of bleeding than that associated with LDUFH.

Cancer surgery

The incidence of DVT diagnosed by bilateral venography in patients undergoing surgery for cancer without prophylaxis is 29%. Patients treated with LDUFH have a 13.7% incidence of DVT. Enoxaparin at a dose of 40 mg once daily was compared with LDUFH every 8 hours in patients undergoing elective abdominal or pelvic surgery for cancer in a large, randomized double-blind venography study.[9] The incidence of DVT was 14.7% in the enoxaparin group and 18.2% in the LDUFH group (p=ns). No difference was observed in terms of bleeding episodes. The results of the ENOXACAN II study have been recently published.[10] This was a randomized, double-blind, venography study evaluating the efficacy and safety of post-discharge prophylaxis with enoxaparin in cancer surgery patients. After an open phase with in-hospital prophylaxis of enoxaparin (40 mg once daily for a week), patients were randomized to 3 weeks of prophylaxis with enoxaparin (40 mg once daily) or to placebo. Patients underwent bilateral venography at the end of the double-blind period. Prolonged prophylaxis with enoxaparin was associated with a significant reduction in the incidence of VTE. The incidence of DVT was 4.8% in patients randomized to enoxaparin and 12% in placebo-treated patients. Moreover, the incidence of proximal DVT was 0.6 and 1.8%, respectively. No increase in major bleeding was associated with prolonged enoxaparin prophylaxis.

Major orthopedic surgery

Patients undergoing major orthopedic surgery (elective total hip replacement, elective total knee replacement or surgery for hip fracture) have a particularly high risk of post-operative VTE.

Patients undergoing total hip replacement (THR) have a high incidence of postoperative VTE despite prophylaxis. Mechanical methods have a moderate efficacy, making pharmacological prophylaxis necessary. The use of aspirin is associated with a 56% incidence of venographic DVT and is not recommended for the prevention of VTE in these patients. LDUFH are not adequately effective in preventing VTE in THR patients. The most effective anticoagulant regimens in the prevention of VTE in these patients are adjusted dose UFH[11] or oral anticoagulants[12] and LMWHs. Adjusted dose UFH or oral anticoagulants are both effective but require strict laboratory monitoring. Two meta-analyses indicate that LMWHs are more effective

than LDUFH in patients undergoing elective THR.[13,14] Moreover, several randomized trials showed that LMWHs are at least as safe and effective as adjusted dose UFH or oral anticoagulants in the prevention of VTE in this setting.[15-17]

The incidence of venographically-detected DVT in patients undergoing elective total knee replacement (TKR) without prophylaxis is close to 60%; approximately 25% of these DVT are proximal. LDUFH and aspirin are barely effective in these patients. A meta-analysis of randomized controlled clinical trials showed that LMWHs are more effective than LDUFH and oral anticoagulants.[18] The efficacy and safety of LMWHs in the prevention of VTE after TKR were investigated in several randomized, controlled clinical trials evaluating enoxaparin, ardeparin, tinzaparin and nadroparin.[17,19-26] Prophylaxis started post-operatively except in two trials and was continued for 4-14 days. DVT was diagnosed by bilateral venography assessed by experts unaware of treatment allocation. LMWHs showed a higher efficacy than oral anticoagulants, however the main difference was confined to isolated distal DVT. The incidence of overall DVT in patients treated with LMWHs was 30%.

The incidence of overall DVT without prophylaxis in patients undergoing surgery for hip fracture is close to 50%. About half of the DVT are proximal; moreover these patients have a high risk of PE. The incidence of DVT with LDUFH was 27%; few trials investigated LMWHs in this setting.[27-29] Dalteparin, 2,500 anti-Xa IU once daily, was compared with LDUFH every 8 hours in 90 patients undergoing surgery for hip fracture; this dose of dalteparin was less effective than LDUFH.[27] Dalteparin 5,000 anti-Xa IU was compared with placebo showing a moderate efficacy (DVT 30 and 58%, respectively).[28] A trial compared enoxaparin at 20 and 40 mg doses, showing that 40 mg once daily was more effective than the 20 mg dose with no increase in bleeding.[29] A meta-analysis of clinical trials on VTE prevention with LDUFH, LMWHs and mechanical methods, in patients undergoing surgery for hip fracture showed that LMWHs and LDUFH have a similar efficacy.[30] A recent trial compared enoxaparin, dalteparin and danaparoid in patients with hip fracture.[31] This randomized trial enrolled 197 patients. Prophylaxis was given for 9-11 days and then bilateral venography was performed. The results indicated no difference between enoxaparin, dalteparin and danaparoid.

The optimal duration of prophylaxis of VTE after major orthopedic surgery has been largely debated. There are several data showing a clear reduction of venographic DVT associated with prolonged (3 weeks after discharge) out-of-hospital prophylaxis with enoxaparin and dalteparin after elective THR. However, the clinical relevance of an asymptomatic venographic DVT is not clear. Indeed, data from recently reported overviews indicate that prolonged prophylaxis with LMWHs or LDUFH is associated with a significant reduction of symptomatic VTE (1.3 vs 3.3%).[32] These results have been confirmed by a recent overview of randomized trials evaluating prolonged out-of-hospital prophylaxis with LMWHs after THR.[33]

Elective neurosurgery

Patients undergoing elective neurosurgery have a high incidence of VTE; on the other hand, clinicians are frightened of bleeding, especially intracranial. For this reason, the most investigated prophylactic methods are elastic stockings and intermittent pneumatic compression (IPC). IPC was associated with a reduction of the incidence of DVT from 23 to 6%. LMWHs were investigated in two large randomized clinical trials. In the first trial, post-operative nadroparin associated with elastic stockings was associated with a non-significant reduction of DVT (26.3, vs 18.7%, p=ns).[34] Nadroparin use caused an increase of bleeding (2.3 vs 0.8%). In the second trial, enoxaparin, 40 mg once daily, started after surgery, associated with elastic stockings was compared with elastic stockings alone. Enoxaparin reduced the incidence of DVT from 32.6 to 16.9% and the incidence of proximal DVT from 13.2 to 5.4% without an increase in bleeding.[35]

LMWHs in the initial treatment of venous thromboembolism

Until recently, the standard initial treatment for VTE has been a course of 5 to 10 days of intravenous UFH followed by at least 3 months of oral anticoagulants. Following the promising results of the initial studies, LMWHs were investigated in two large randomized trials. These studies showed that subcutaneous LMWHs, at weight-adjusted doses, were at least as effective as intravenous UFH.[36,37] The results of the early meta-analyses assessing the efficacy of LMWHs in comparison with UFH in the treatment of VTE suggested that LMWHs are more effective and safer than UFH.[38,39] More recently, an updated meta-analysis comparing the efficacy and safety of UFH and LMWHs was published.[40] Thirteen studies were included in the analysis.[36,37,41-51] The results of the comparison between LMWHs and UFH did not show significant differences in the incidence of recurrent VTE, PE, and major bleeding.

However, the reduction in mortality in patients treated with LMWHs already observed in previous analyses, was confirmed. This meta-analysis also assessed the potential differences in efficacy and safety among various LMWHs. No difference in efficacy among dalteparin, enoxaparin, tinzaparin, reviparin and nadroparin was observed. A lower incidence of major bleeding was found in patients treated with nadroparin as compared with UFH.

LMWHs in the treatment of acute coronary syndromes

Aspirin and intravenous UFH have been the recommended treatment for patients with acute coronary syndromes for a long time.[52] However, the limitations of UFH led to the investigation of new agents such as LMWHs and direct thrombin inhibitors.[53] Five large clinical trials investigated three LMWHs (dalteparin, enoxaparin, and nadroparin) in patients with acute coronary syndromes without ST elevation.[54]

In the FRISC trial, 1,506 patients were randomized to dalteparin or placebo within 72 hours from the onset of symptoms.[55] Dalteparin-treated patients received a twice daily injection of 120 U/kg in the acute phase (6 days) and were then randomized to dalteparin 7,500 IU once daily or placebo in the chronic phase (until day 45). At day 6 the incidence of the composite end-point death, myocardial infarction and urgent revascularization was significantly lower in dalteparin treated patients 5.4% vs 10.3% (p=0.005). This difference remained significant at day 40 (p=0.005).

The FRIC study compared dalteparin (120 IU/kg twice daily) with UFH (5,000 IU intravenous bolus followed by 1,000 IU/hour for 48 hours and then by two daily injection of 12,500 IU) until day 6 in patients with unstable angina within 72 hours from symptom onset.[56] From day 7 to 45, all patients were randomized to dalteparin (once daily dose of 7,500 IU) or placebo. Dalteparin showed a similar efficacy to UFH in reducing the incidence of the combined end-point, death, myocardial infarction and recurrent angina.

The FRAXIS study investigated nadroparin in 3,468 patients with unstable angina within 48 hours from symptoms' onset. Patients were randomized to UFH for 6 days (intravenous bolus of 5,000 IU followed by continuous infusion at doses adjusted by the aPTT) or to 6 days of nadroparin (bolus of 86 IU anti-Xa/kg followed by twice daily subcutaneous injections of 86 IU anti-Xa/kg) or to 14 days of nadroparin at the same dose regimen.[57] At day 6 the incidence of the combined end-point of cardiac death, myocardial infarction, and refractory or recurrent angina was similar in the three groups. Patients treated with 14 days of nadroparin had a higher incidence of bleeding complications.

The ESSENCE study enrolled 3,171 patients with unstable angina within 24 hours from symptoms' onset.[58] Patients were randomized to 2-8 days' treatment with subcutaneous enoxaparin (1 mg/kg every 12 hours) or to intravenous UFH (5,000 IU bolus followed by an infusion at an aPTT target of 55 to 85 seconds). Follow-up was performed at 30 days and at one year. Enoxaparin was more effective than UFH; the combined end-point death, myocardial infarction and recurrent angina at day 14 occurred in 16.6% and in 19.8% of patients, respectively (p=0.02). At day 30, the incidence of the end-point was 19.8 and 23.3% (p=0.02). No increase in major bleeding was observed.

In the TIMI 11B trial,[59] patients treated with enoxaparin received an initial bolus of 30 mg followed by enoxaparin, 1 mg/kg twice daily for 3-8 days. After day 8, enoxaparin dose was reduced to 40 mg/twice daily for patients with a body weight less than 65 kg and to 60 mg/twice daily for patients over 65 kg. Subcutaneous enoxaparin was continued until day 43. At day 14, enoxaparin was associated with a 15% reduction of the combined end-point, death, myocardial infarction and urgent revascularization in comparison with the incidence of the same end-point in patients treated with UFH (14.2 vs 16.7%, p=0.03). At day 43, this difference was no longer statistically significant.

The meta-analysis of the ESSENCE and TIMI 11B trials showed the superiority of enoxaparin versus UFH. Enoxaparin was associated with a 20% reduction of the composite end-point at day 2, 8, 14 and 43 in comparison to UFH without an increase in major bleeding.[60] The results of the one-year follow-up of the ESSENCE study confirmed the superiority of enoxaparin over UFH concerning death, myocardial infarction or residual angina (p=0.022). In conclusion, the results of large randomized clinical trials in acute coronary syndromes indicate that enoxaparin is more effective than UFH, without increasing bleeding. Dalteparin and nadroparin showed an efficacy similar to UFH in this clinical setting. Enoxaparin was recently investigated as an adjunct to thrombolytic therapy in patients affected by acute Q-wave myocardial infarction.[61] The ASSENT III was a randomized, open trial conducted in 6,095 patients with acute myocardial infarction. Patients were randomized, to three regimens: full-dose tenecteplase and enoxaparin for a maximum of 7 days (enoxaparin group; n=2,040), full-dose

tenecteplase with weight-adjusted UFH for 48 hours (UFH group; n=2,038), or half-dose tenecteplase with weight-adjusted UFH and a 12-hour infusion of abciximab, a platelet glycoprotein IIb/IIIa inhibitor (abciximab group; n =2,017). The cumulative primary efficacy end-point was 30-day mortality, in-hospital reinfarction, and in-hospital refractory ischemia. Enoxaparin (11.4% vs 15.4%; p=0.0002) and abciximab plus UFH (11.1% vs 15.4%; p<0.0001) were more effective than UFH. Considering its ease of administration, tenecteplase plus enoxaparin seems an attractive alternative reperfusion regimen.

New antithrombotic agents

The limitations of UFH and LMWHs promoted the development of new antithrombotic agents that could potentially overcome the shortcomings. New antithrombotic agents have specific targets at different levels of the coagulation cascade. In this article, the agents in more advanced phase of clinical investigation will be briefly reviewed.

New antithrombotic agents can be classified in three main categories: direct thrombin (factor IIa) inhibitors, inhibitors of factor Xa, inhibitors of the factor VIIa/tissue factor (TF) complex.

Direct thrombin inhibitors

Human thrombin is a serine protease composed of an A *light* chain (39 amino acids) and a B *heavy* chain of 259 amino acids linked by a disulphide bridge. Thrombin converts fibrinogen to fibrin. Thrombin also activates factor V, factor VIII, thrombomodulin and factor XIII. Moreover, thrombin is a potent platelet agonist. Based on these considerations, thrombin is a crucial target for the development of new antithrombotic agents. Direct antithrombins inhibit thrombin without a plasma cofactor and inhibit both free and fibrin-bound thrombin.[62] Moreover, since direct antithrombins do not bind to plasma proteins, they have a more linear and predictable anticoagulant effect than UFH. Another advantage of direct antithrombins is that their use is not associated to HIT. The most investigated direct antithrombins are hirudin, its synthetic fragment hirulog and the low molecular weight inhibitors of the thrombin active site such as melagatran and its oral prodrug ximelagatran.

Hirudins. Hirudin, a 65-amino acid polypeptide produced by the salivary glands of a medicinal leech (*Hirudo medicinalis*) is the most potent known natural anticoagulant and is now produced through DNA recombinant technology.[63] Hirudin is a specific thrombin inhibitor that acts through the generation of an almost irreversible stoichiometric complex (1:1) with thrombin. It blocks both the active site and the fibrinogen recognition site of thrombin. Hirudin is cleared by the kidneys, and has a plasma half-life of 40 min after intravenous administration and of 120 min after subcutaneous injection.

Desirudin (CGP39393) was investigated in large randomized trials on VTE prevention after THR.[64] In the first trial, 1,119 patients undergoing elective THR were randomized to twice daily subcutaneous injection of desirudin at 10, 15 or 20 mg, or to UFH 5,000 IU three times daily. The incidence of DVT was 23.9, 18.9 and 18.2% in patients treated with desirudin and 34.2% in patients treated with UFH. The rate of proximal DVT in patients treated with the 3 regimens of desirudin was 8.5, 3.1 and 2.4%, respectively. The incidence of proximal DVT in patients treated with UFH was 19.6%. A subsequent trial compared the twice daily injections of 15 mg desirudin with UFH (5,000 IU every 8 hours) in 445 patients undergoing THR. The incidence of DVT was 7.5% in the desirudin group and 23.2% in the UFH group (p <0.0001). The incidence of proximal DVT was 3.4% in the desirudin group and 16.4% in the UFH group (p<0.0001). Desirudin was more effective than enoxaparin in the prevention of VTE after THR in a large, randomized, double blind, clinical trial. Patients (n = 2,079) were assigned to twice daily injection of 15 mg of desirudin, starting 30 minutes before surgery, or to enoxaparin 40 once daily, started the evening before surgery. Prophylaxis was continued for 8-12 days. Patients treated with desirudin had an 18.4% incidence of DVT, while enoxaparin-treated patients had an incidence of DVT of 25.5% (p=0.001). The rate of proximal DVT was 4.5% in the desirudin group and 7.5% in the enoxaparin group (p=0.01). The safety profiles of desirudin and enoxaparin were similar. Therefore desirudin is highly effective in the prophylaxis of DVT in patients undergoing THR and has an acceptable safety profile.

The other form of recombinant hirudin, lepirudin (HBW023) was evaluated in the treatment of VTE in a multicenter, randomized, dose-finding trial. This trial compared 3 doses of lepirudin (0.75, 1.25 and 2 mg/kg twice daily) given subcutaneously with the standard UFH regimen.[65] The 0.75 and 1.25 mg/kg doses of lepirudin were at least as effective as intravenous UFH and were not associated with increased bleeding; by contrast, the 2 mg/kg lepirudin dose was associated with a 3% rate of major bleeding.

The GUSTO IIb study was a prospective, double-blind, randomized comparison of 72 hours' therapy with UFH or desirudin in 12,142 patients with

acute coronary syndromes.[66] Patients without ST elevation were randomized to UFH (5,000 IU bolus followed by 1,000 IU/hour infusion, target aPTT 60 to 90 seconds) or to desirudin (0.1 mg/kg bolus followed by a 0.1 mg/kg/hour infusion). The primary composite end-point was death or non-fatal myocardial infarction at 30 days. The incidence of this end-point was 8.3% in patients treated with desirudin and 9.1% in UFH treated patients (p=ns). Desirudin was associated with a higher incidence of intracranial bleeds (0.2 and 0.02%; p= ns) and with a slight increase in severe or moderate bleeding. However, desirudin was associated with a reduction in mortality and in the incidence of myocardial infarction during the first 24 hours over UFH (1.3 vs 2.1%; p=0.001).

Lepirudin was investigated in OASIS 2, an international, large-scale, randomized, double-blind trial conducted in patients with acute coronary syndromes without ST elevation.[67] This trial compared a 72-hour infusion of lepirudin (n=5,083), bolus of 0.4 mg/kg followed by an infusion of 0.15 mg/kg/hour, with UFH (n=5,058). The incidence of the primary end-point of cardiovascular death or new myocardial infarction at 7 days was lower in the lepirudin group than in UFH group, but this difference was not statistically significant. The incidence of the secondary end-point cardiovascular death, myocardial infarction or refractory angina, was significantly lower in lepirudin-treated patients (5.6 vs 6.7%; p=0.012). Patients treated with lepirudin had a higher incidence of major bleeding (1.2 vs 0.7%; p=0.01). However, the rate of potentially fatal bleeding and strokes was similar.

In the GUSTO IIa study, patients with myocardial infarction were randomized to UFH, 5,000 IU bolus followed by infusion at a target aPTT from 60 to 90 seconds, or to desirudin: 0.6 mg/kg bolus followed by 0.2 mg/kg/hour infusion.[68] Patients with ST elevation were randomized to streptokinase or rt-PA. The trial was prematurely interrupted because of the high incidence of intracranial bleeding in both groups. Patients receiving thrombolytic therapy had a 1.8% incidence of hemorrhagic strokes, while this event occurred in only 0.3% of the patients not exposed to thrombolytics (p<0.001). The TIMI 9A trial was a randomized comparison of UFH and desirudin in patients with myocardial infarction treated with streptokinase or rt-PA.[69] The doses of UFH and desirudin were the same as those in the GUSTO IIa study. The TIMI 9A trial was also prematurely discontinued because of the high incidence of major bleeding.

In the HIT III trial, patients with myocardial infarction receiving rt-PA were randomized to UFH (70 IU/kg bolus followed by 15 IU/kg/hour infusion) or to lepirudin (0.4 mg/kg bolus followed by 0.15 mg/kg/hour infusion).[70] Given the high rate of intracranial bleeding in the lepirudin group, this study was prematurely terminated. The incidence of major bleeding was 6.8% in the lepirudin-treated patients and 1.9% in UFH-treated patients.

Given the high rate of intracranial bleeding observed in the GUSTO IIa and TIMI 9A, lower doses of hirudin were tested in subsequent studies.

In the TIMI 9B study, 3,002 patients with acute coronary syndromes were randomized to UFH at the doses of the GUSTO I trial or to a lower dose of desirudin (0.1 mg/kg bolus followed by 0.1 mg/kg/hour infusion).[71] No difference in death or myocardial infarction was observed between the two treatment groups. Intracranial bleeding occurred in 0.7% of UFH-treated patients and in 0.4% of patients assigned to desirudin. The incidence of other bleeding episodes was about 5% in both groups.

The GUSTO IIb trial investigated reduced doses of desirudin and UFH as an adjunct to thrombolytics (70% of patients received rt-PA and 30% streptokinase) in patients with myocardial infarction. Desirudin was given as intravenous bolus of 0.1 mg/kg followed by a 0.1 mg/kg/hour infusion for 3-5 days. UFH was given as 5,000 IU bolus followed by 1,000 IU/hour infusion (aPTT target 60-85 seconds). The primary outcome was death or non-fatal myocardial infarction or early reinfarction. The incidence of the primary end-point in patients receiving hirudin was 9.9% whereas in patients treated with UFH it was 11.3% (p = ns). The incidence of death or myocardial infarction at 24 and 48 hours was reduced in patients with ST elevation treated with desirudin. There was no difference in the incidence of major bleeding in patients with ST segment elevation, but minor bleeding was more frequent in patients receiving desirudin. The benefit of desirudin over UFH observed in the first 48 hours was partially lost at 30 days. The results of the meta-analysis of the GUSTO IIb and TIMI 9B trials indicate that desirudin is associated with a significant (p=0.024) reduction in reinfarction rate at 30 days.[72] The relative risk reduction (RRR) is 14% (95% confidence interval 0.75-0.98).

Desirudin was compared with UFH after elective PTCA for unstable angina in the HELVETICA study, a multicenter, randomized, double-blind trial.[73] Patients (n = 1,141) were assigned to UFH (bolus of 10,000 IU followed by a 24-hour infusion and subcutaneous placebo twice daily for 3 days; n=382), or to one of two different desirudin regimens: a

bolus of 40 mg followed by a 24 hour-infusion followed by subcutaneous placebo twice daily for 3 days (n=381), or to the same initial regimen of desirudin followed by subcutaneous twice daily administration of 40 mg of desirudin for 3 days (n= 378). The primary end-point was event-free survival after 7 months. Secondary end-points were cardiac events during the first 96 hours, bleeding episodes and other drug-related side-effects and the angiographic assessment of coronary luminal diameter at the 6-month follow-up. The event-free survival rate was similar among the three groups: 67.3% in the UFH group, 63.5% in the group receiving intravenous desirudin alone, and 68.0% in the group randomized to intravenous plus subcutaneous desirudin. Desirudin markedly reduced early cardiac events (p= 0.023). By contrast, the mean minimal luminal diameters at the 6-month angiographic follow-up were similar among the three groups.

Desirudin was investigated in HIT, an immune condition that is often associated with thromboembolic complications.[74] Direct antithrombins have no structural analogy with UFH and do not cross-react with HIT antibody, therefore are an ideal agent for patients for HIT. The results of two prospective trials investigating lepirudin in patients with documented HIT type II have been reported.[75,76] In the first trial, patients were treated with one of 4 doses of lepirudin.[75] Patients with HIT and thrombosis (HITT) received a 0.4 mg/kg bolus followed by an infusion of 0.15 mg/kg/hour; patients with HITT treated with thrombolytics received a bolus of 0.2 mg/kg followed by 0.1 mg/kg/hour. Patients without thrombosis were treated with lepirudin at 0.1 mg/kg/hour, whereas patients undergoing cardiopulmonary bypass[4] received a bolus of lepirudin of 0.25 mg/kg and then boluses of 5 mg as needed. Laboratory evaluation criteria were an increase of the platelet count of more than 30% until 100,000 mm^3 and an aPTT ratio between 1.5 to 3 with no more than 2 dose adjustments. Platelet count rose rapidly in the 88.7% of the patients affected by HIT treated with lepirudin. The combined clinical end-point was death, amputations, and new thromboembolic complications. Results were compared with those from a historical cohort of 120 patients affected by documented HIT. The primary combined end-point incidence was lower in the lepirudin-treated patients at days 7 and 35 (9.9% vs 23% and 25.4% vs 52%; p = 0.014). The incidence of bleeding was similar.

In the second study, 112 patients with confirmed HIT were treated with lepirudin at 3 different doses (treatment of HITT 0.4 mg/kg bolus followed by 0.15 mg/kg/hour infusion, treatment of HITT in conjunction with thrombolytics 0.2 mg/kg and 0.1 mg/kg/hour infusion, patients without thrombosis 0.1 mg/kg/hour infusion).[76] The incidence of the primary combined end-point of death, limb amputation and new thromboembolic event at day 35 was 30.4% while it was 52.0% in the historical control group. In this study, the difference was not statistically significant. There was an increase in the incidence of bleeding with respect to that in the historical control group (44.6 vs 27.2%; p=0.0001) however; there was not an increase in transfusions. Lepirudin was also investigated in 57 patients with HIT undergoing cardiopulmonary bypass;[77] 95% of patients had a favorable clinical outcome. Based on these results, the clinical use of hirudin in patients affected by HIT has been approved in the United States and in Europe.

Hirulog. Hirulog is a synthetic, bivalent antithrombin agent. Hirulog was developed by connecting hirugen, through a tetraglycine linker, to a peptide specific for the inhibition of the catalytic site of thrombin. Hirugen is a synthetic dodecapeptide composed of the carboxy-terminal region of hirudin, which blocks the interaction of thrombin with fibrinogen. Hirulog was investigated in the prevention of VTE after major orthopedic surgery in a dose-finding study in 222 patients.[78] Prophylaxis with subcutaneous hirulog started post-operatively and was continued until day 11. The dose varied from 0.3 mg/kg/12 hours to 1.0 mg/kg/8 hours. The lowest incidence of DVT (17%) and of proximal DVT (2%) was observed in patients treated with the highest dose of hirulog (1.0 mg/kg every 8 hours). Bleeding was observed in less than 5% of the patients. These results suggest that 1.0 mg/kg of hirulog given subcutaneously three-times daily is effective and safe for the prophylaxis of VTE in major orthopedic surgery patients when given post-operatively.

A randomized, double-blind, dose-finding trial investigated hirulog in 410 patients with unstable angina.[79] Patients received 3 days of continuous hirulog infusion at four different doses: 0.02 (n = 160), 0.25 (n = 81), 0.5 (n = 88), and 1.0 (n = 81) mg/kg/hour. The primary combined end-point was death, non-fatal myocardial infarction, rapid clinical deterioration, or recurrent ischemic pain at rest associated with ECG changes during 72 hours. The rate of the primary end-point was similar among the four groups. There was a dose-related reduction in the incidence of the secondary end-point (death or non-fatal myocardial infarction through hospi-

tal discharge): 10% in patients receiving the lowest dose of hirulog and 3.2% in patients treated with the 3 highest regimens of hirulog (p=0.008). Only 2 patients had major bleeding. These results prompted further hirulog evaluation.

The results of the HERO 2 trial have been recently reported.[80] The HERO 2 was a randomized, open-label, assessor-blind trial comparing hirulog with UFH in patients undergoing fibrinolysis with streptokinase for acute myocardial infarction with ST elevation. Patients (n=17,073) were randomized to hirulog (intravenous bolus followed by 48 hour infusion) or to UFH, together with a 1.5 million unit dose of streptokinase. The primary end-point was 30-day mortality. Secondary end-points included reinfarction within 96 hours and bleeding. Analysis was by intention-to-treat. Mortality at day 30 was 10.8% the hirulog group and 10.9% in the UFH group (p=ns). There were significantly fewer reinfarctions within 96 hours in the hirulog group (p=0.001). Severe bleeding and intracerebral bleeding were similar in both groups. The incidence of moderate and mild bleeding was higher in the hirulog group. Hirulog did not reduce mortality compared to UFH, but did reduce the rate of adjudicated reinfarction within 96 hours by 30%. Bivalirudin seems to have a potential role as a new anticoagulant option in patients with acute myocardial infarction treated with streptokinase. Hirulog was investigated in a large, double-blind, randomized clinical trial in patients undergoing PTCA for unstable or post-infarction angina.[81] Patients (n = 4,098) were treated with UFH or hirulog immediately before PTCA. Hirulog infusion was continued for 24 hours. The primary composite end-point was in-hospital death, myocardial infarction, abrupt coronary occlusion, or rapid clinical deterioration from cardiac origin. The incidence of the primary end-point was similar in the two groups (11.4 and 12.2%, respectively). However, hirulog was associated with a lower incidence of bleeding (3.8 vs 9.8%; p<0.001). The cumulative rate of death, myocardial infarction, and repeated revascularization during the 6 months following angioplasty was similar (20.5 versus 25.1%). Hirulog appears to be at least as effective as UFH in patients undergoing PTCA for unstable angina, showing a better safety profile.

Low molecular weight active site inhibitors. Several low molecular weight active site thrombin inhibitors have been recently synthesized. These agents are competitive inhibitors that bind thrombin in a non-covalent manner. Argatroban, a synthetic derivative of arginine is the precursor of these agents. Argatroban has a short half-life, and requires continuous intravenous administration. Argatroban has been successfully investigated in a wide cohort of patients affected by HIT and has been recently approved for this indication.

Melagatran, together with its oral prodrug (ximelagatran) is the most extensively investigated of these agents. Melagatran is a synthetic antithrombin that acts as a competitive and reversible inhibitor of the thrombin active site. Melagatran is administered by parenteral route, has a predictable anticoagulant activity and does not require laboratory monitoring. Ximelagatran has a reasonable gastrointestinal absorption and must be converted to melagatran to exert its antithrombotic activity.[82] Ximelagatran has a half-life of 3 hours and is administered every 12 hours. Melagatran and ximelagatran were initially investigated in the prevention of VTE in major orthopedic surgery in the METHRO I trial.[83] After the promising results of this trial a large phase IIb dose finding study (METHRO II) compared melagatran (started immediately before surgery) and ximelagatran, with dalteparin (5,000 IU anti Xa) in about 1,900 patients undergoing major orthopedic surgery.[84] Patients were subdivided into 5 treatment groups. Doses ranged from 1 mg of melagatran every 12 hours followed by 8 mg of ximelagatran every 12 hours to 3 mg every 12 hours of melagatran followed by 24 mg of ximelagatran every 12 hours. The incidence of DVT in the group treated with the highest doses of melagatran and ximelagatran was 15.1%. The incidence of DVT in the dalteparin group was 28.2%. Thus, the dose of 3 mg melagatran followed by 24 mg of ximelagatran every 12 hours reduced the incidence of DVT by 47% in comparison to dalteparin. This dose also reduced the incidence of proximal DVT by half (3% vs 7%). The results obtained with the highest regimen of melagatran and ximelagatran were more evident in patients undergoing THR (incidence of DVT 12% and 25%, respectively) than in patients undergoing TKR (DVT incidence of 21% and 32%, respectively). The highest doses of melagatran and ximelagatran were associated with a moderate increase in major bleeding with respect to dalteparin.

METHRO III was a randomized, double-blind, double-dummy, parallel-group study in patients undergoing THR or TKR comparing the efficacy and safety of subcutaneous melagatran 3 mg started 4-12 h after surgery, followed by oral ximelagatran 24 mg twice daily, with subcutaneous enoxaparin 40 mg once daily started the evening before surgery.[85] Both treatments were continued for 8-11 days. Efficacy was evaluated by DVT assessed by bilateral

venography on the final day of treatment, and clinically suspected and verified DVT and PE during treatment. Of 2,788 patients, 2,268 (81.3%) had an evaluable venogram. The VTE rate was 31% and 27% in the melagatran plus ximelagatran and in the enoxaparin groups, respectively. The rate of proximal DVT or PE was 5.7% in the melagatran plus ximelagatran group and 6.2% in the enoxaparin group. Total bleeding was similar in the two groups. In a *post-hoc* analysis, the possible effect of timing of the first post-operative dose was evaluated; the population was divided by the median time of the first post-operative dose. The time interval between surgery and the first dose of anticoagulant was found to be crucial to ensure optimal efficacy.

The pharmacokinetic features of ximelagatran are rapid absorption and conversion to melagatran, reasonable bioavailability, low dose-time variability, bioavailability independent of food intake, predictable anticoagulant activity and good tolerability. These features make ximelagatran an attractive antithrombotic agent for the long-term treatment of both venous and arterial thromboembolism. On these bases, ximelagatran is currently under investigation in large, multicenter, international, randomized trials in the treatment of VTE and in the prevention of thromboembolic complications in patients with chronic atrial fibrillation.

Factor Xa inhibitors

Direct inhibitors of factor Xa. Direct factor Xa inhibitors bind to factor Xa and block all its activities. These agents include natural inhibitors of factor Xa such as the tick anticoagulant peptide (TAP) and antistasin. Based on the promising results of TAP in experimental animal models, a series of low molecular weight inhibitors that act against the active site of factor Xa have been recently synthesized. Some of these inhibitors of factor Xa, such as DX 9095a have been recently investigated in phase II trials in patients affected by unstable angina.

Indirect inhibitors of factor Xa. Pentasaccharide is a selective factor-Xa inhibitor composed of five saccharide units and is the smallest heparin-based molecule (molecular weight of 1,728 Daltons) that retains antithrombotic activity. Pentasaccharide has a plasma half-life of about 14 hours after intravenous or subcutaneous administration and has a complete bioavailability after subcutaneous injection. The peak concentration is reached in 1-3 hours. Pentasaccharide is excreted mainly through the urine.

The most clinically relevant data have been obtained in the prevention of VTE after major orthopedic surgery. The PENTATHLON study was a large (933 patients) phase IIB dose-finding trial in the prophylaxis of VTE after elective THR.[86] The dose ascending regimens of pentasaccharide were 0.75 mg, 1.5, 3, 6 and 8 mg, given once daily; the comparator was enoxaparin 30 mg started 12 hours after surgery and then given twice daily. The diagnosis of DVT was made with bilateral venography performed at day 5-10. A clear dose-response effect was observed for the first 3 groups of patients. The incidence of DVT was 11.8% in the 0.75 mg group, 6.7% in the 1.5 mg group and 1.7% in the group treated with 3 mg. The 6 and 8 mg groups were discontinued because of the high incidence of bleeding. The incidence of DVT in the enoxaparin group was 9.4%. Therefore, the 3 mg dose of pentasaccharide led to a highly significant reduction in the incidence of DVT with respect to enoxaparin (p=0.009, RRR of 81%) without a significant increase in major bleeding (4.5% vs 3.5%).

A dose-finding trial was also conducted in patients undergoing elective TKR: the PENTATAK study. The doses of pentasaccharide were the same as those adopted in the PENTATHLON study. The incidence of DVT was 40% in the 0.75 mg group, 30% in the 1.5 mg group and 15% in the 3 mg group. There was a clear dose-effect from the 0.75 to the 3 mg dose. Again, the 6 and 8 mg doses were associated with excessive bleeding. On the bases of the results of these trials, the dose chosen for phase III trials was 2.5 mg.

This dose was investigated in a very large phase III trial program in major orthopedic surgery enrolling 7,344 patients in four trials in patients undergoing elective THR (EPHESUS in Europe and PENTATHLON 2000 in North America), elective TKR (PENTAMAKS in North America) and surgery for hip fracture (PENTHIFRA in Europe). In the EPHESUS trial 2,200 patients undergoing elective THR were randomized to pentasaccharide 2.5 mg once daily starting at least 6 hours after surgery or to enoxaparin 40 mg once daily starting the evening before surgery.[87] The incidence of DVT was 4.1% in the pentasaccharide group and 9.2% in the enoxaparin group with a RRR of 56%; the incidence of proximal DVT was 0.7 and 2.5%, respectively. The incidence of major bleeding was 8.0 and 6.2%.

The efficacy of pentasaccharide in patients undergoing THR was confirmed by the results of the PENTATHLON 2000 study.[88] In this trial, 2,200 patients were randomized to pentasaccharide 2.5 mg at least 6 hours after surgery or to enoxaparin 30 mg twice daily starting at least 12 hours after surgery. The incidence of DVT was 6.2% in the pen-

tasaccharide group and 8.3% in the enoxaparin group, RRR=25%; there was no difference in proximal DVT. The incidence of major bleeding was also similar, being 3% and 3.2%, respectively.

The results of the PENTAMAKS study showed the superiority of pentasaccharide (2.5 mg/die once daily starting at least 6 hours after surgery) over enoxaparin (30 mg twice daily starting at least 12 hours after surgery) in 1,000 patients undergoing elective TKR.[89] The incidence of DVT was 12.5% and 27.8%, respectively with a RRR of 55%. Proximal DVT occurred in 2.4% of patients treated with pentasaccharide and in 5.4% of enoxaparin-treated patients. The incidence of major bleeding was 4.5% and 3.9%, respectively.

In the PENTHIFRA trial, 1,700 patients undergoing surgery for hip fracture were randomized to pentasaccharide 2.5 mg once daily starting at least 6 hours after surgery or to enoxaparin 40 mg once daily starting the evening before surgery.[90] The incidence of VTE was 8.3% in the pentasaccharide group and 19.1% in the enoxaparin group, RRR 56%; the incidence of proximal DVT was 0.9 and 4.1%. There was an increase in major bleeding events in pentasaccharide-treated patients (6.3 vs. 4.4%).

The results of these four large trials have been summarized in an overview analysis. The overall analysis showed a 50% RRR for VTE over enoxaparin. The incidence of PE and death until day 11 was similar in the two groups. The overall safety analysis indicated a higher incidence of major bleeding in the pentasaccharide group (2.3 vs. 1.4%) that was not statistically significant. The results of these trials represent a great step forward for the prophylaxis of VTE after major orthopedic surgery.

Pentasaccharide was investigated in a randomized, parallel group, phase IIb comparison trial with dalteparin in the treatment of patients affected by proximal DVT. The primary outcome measure was a change in the thrombus mass and improvement of the basal lung scan repeated at day 7. The results were similar across treatment groups (pentasaccharide once daily 5 mg, 7.5 mg, 10 mg or dalteparin 100 IU/kg twice daily).[91] Moreover the incidence of symptomatic VTE recurrence was 2.4% in the 334 patients treated with pentasaccharide and 5% in the 119 dalteparin-treated patients: pentasaccharide was not associated with an increase of major bleeding at any dose. On the basis of these results pentasaccharide is being tested in large trials in patients affected by VTE. Pentasaccharide has recently been investigated as an adjuvant to thrombolytic therapy in patients affected by acute myocardial infarction.[92] Patients (n=333) with ST elevation were treated with aspirin and alteplase and randomized to UFH, given intravenously during 48 to 72 h, or to a low, medium or high dose of pentasaccharide, administered once daily for 5 to 7 days, intravenously on the first day, then subcutaneously. Coronary angiography was performed at 90 min and on days 5 to 7. TIMI flow grade 3 rates at 90 min were similar in the four treatment groups. Among patients with TIMI 3 flow at 90 min who did not undergo a coronary intervention (n=155), a trend towards less reocclusion of the infarct-related vessel on days 5 to 7 was observed with pentasaccharide: 0.9% vs 7.0% with UFH (p=0.065). The incidence of the primary safety end-point of intracranial bleeding and transfusion requirement was identical for the pentasaccharide and UFH groups (7.1%). In this study, pentasaccharide together with alteplase was as safe and as effective as UFH in restoring coronary artery patency.

Inhibitors of the factor VIIa/tissue factor pathway

The coagulation cascade starts at the level of the factor VIIa/tissue factor (TF) complex. Renewed consideration of this element has prompted the evaluation of the strategy that blocks coagulation at this level. Two inhibitors of the factor VIIa/TF complex are included in this class of compounds: tissue factor pathway inhibitor (TFPI) and the nematode anticoagulant protein c2 (NAPc2).

TFPI is a naturally occurring coagulation inhibitor that blocks thrombin generation through two steps. TFPI initially binds to factor Xa and inactivates factor Xa, and then the TFPI bound to factor Xa forms a complex with factor VIIa and inactivates it. This process of inactivation of factor VIIa intervenes within the factor VIIa/TF complex. TFPI has a short plasma half-life and is usually administered by continuous intravenous infusion. TFPI is undergoing clinical investigation in patients affected by severe sepsis in order to treat disseminated intravascular coagulation, which is common in such patients.

NAPc2 is derived from an intestinal nematode (*Ankylostoma caninum*), NAPc2 acts by binding to a non-catalytic site located on factor X or on factor Xa and by inhibition of factor VIIa within the factor VIIa/TF complex. NAPc2 is administered subcutaneously, and has an antithrombotic activity that lasts for about 50 hours. NAPc2 has been recently evaluated in a phase IIa study in patients undergoing elective TKR. NAPc2 was given intravenously at dose-ascending regimens from 1.5

µg/kg to 5 µg/kg, prophylaxis was started postoperatively and then the injections were given on alternative days (days 1, 3, 5 and 7). At the end of treatment, patients underwent unilateral venography. The primary safety end-point was the incidence of major bleeding. Of the 293 patients studied, 251 were included in the efficacy analysis. The results showed that the 3 µg/kg dose administered within 1 hour after surgery was associated with the lowest incidence of DVT (12.2%) and with an acceptable rate of major bleeding. These results are comparable with those of the currently adopted prophylactic methods in patients undergoing TKR.[93]

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Heparins in Medicine I

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Heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is an immune-mediated reaction that generally occurs 5 to 14 days after initiation of heparin therapy. It is characterized by a severe decline in platelet count (by >50%) in association with a new thrombo-embolic complication. HIT should be differentiated from a non-immune form of heparin-associated thrombocytopenia, characterized by an early-onset (usually within 48 hours), mild thrombocytopenia (rarely <100,000/mm^3) that often resolves completely without clinical adverse effects, even with continuation of heparin therapy. In recent years, new insights into the pathogenesis of HIT and thrombosis have emerged and new forms of treatment have been introduced. The goal of this review is to summarize these new developments from the perspective of clinical practice.

Pathogenesis

HIT is mediated by an antibody that causes platelet activation in the presence of heparin.[1] The antigenic target of this antibody is a multimolecular complex formed by platelet factor 4 (PF4) and heparin. The antibody reacts with a cryptic epitope on PF4 that emerges only after the protein binds to heparin. The antibody-PF4-heparin complex then binds to platelets via platelet Fcγ receptors (FcγRIIA). Cross-linking of Fcγ receptors results in platelet activation, thromboxane synthesis, release of platelet granules and platelet aggregation, ultimately leading to thrombosis. Recently, it has been shown that transgenic mice expressing both human PF4 and human FcγRIIA injected with a murine anti-human PF4/heparin-specific monoclonal antibody develop severe thrombocytopenia and disseminated thrombosis after exposure to heparin.[2] This is an animal model of HIT that recapitulates the pathogenesis of the disease process in humans.

The HIT antibody causes platelet activation in the presence not only of heparin, but of other mucopolysaccharides as well. Generation of the antigen and induction of HIT antibody appear to depend on the molecular weight of the oligosaccharide. In a clinical trial of patients undergoing hip replacement surgery, Warkentin *et al.*[3] found significantly fewer HIT antibodies in patients receiving low molecular weight heparin (LMWH) than in those receiving unfractionated heparin (UFH) (2% vs. 8%, respectively). Theoretically, a very small LMWH preparation (eg. pentasaccharide) will not cause HIT. This assumption is supported by the results of a clinical trial in patients given pentasaccharide for prevention of deep vein thrombosis after hip replacement: these patients showed no cases of clinically relevant HIT.[4]

Clinical and laboratory diagnosis

The clinical diagnosis of HIT is usually made on the following criteria:[5] a) a fall in platelet count >50% of basal, typically occurring after 5 to 10 days of heparin use. Importantly, HIT can begin more rapidly (within 2 to 18 hours after the start of heparin) in patients who have already received heparin within the previous 100 days;[6] b) exclusion of other causes of thrombocytopenia; c) possible contemporaneous occurrence of a new thromboembolic complication; d) resolution of thrombocytopenia after cessation of heparin; this last criterion, however, can only be applied retrospectively.

Whenever possible, the clinical suspicion of HIT should be confirmed with a specific laboratory test. Two types of tests are available: functional assays and immunoassays. Unfortunately, neither type of assay is 100% reliable for the diagnosis of HIT. The functional assays measure heparin-like dependent platelet activation by the HIT antibody *in vitro* and include, among others, the heparin-induced platelet activation assay and the platelet aggregation test.[7,8] There are important quality control issues using functional assays to test for HIT, such

as careful selection of platelet donors and use of appropriate controls, since platelet reactivity to Fcγ-receptor-mediated activation is highly variable. These technical problems make functional assays difficult to standardize, particularly in non-specialized laboratories.

ELISAs for laboratory diagnosis of HIT are now commercially available. These assays measure antibodies that bind to PF4-heparin complexes absorbed onto the wells of microtiter plates and generally have a satisfactory sensitivity and reproducibility.[7,8] Nevertheless, occasional patients with HIT antibodies of specificity other than PF4 (e.g. anti-IL-8)[9] are not picked up by immunoassays. One reasonable approach is to use the ELISA as a screening test, and reserve the functional assay for samples with negative results but a strong clinical suspicion of HIT.

Thrombosis and other clinical sequelae of HIT

Both venous and arterial thrombosis may complicate HIT. Although arterial thrombosis has been historically associated with HIT, venous thrombosis is a more likely outcome. In a review of 127 patients with serologically confirmed HIT, deep venous thrombosis and pulmonary embolism were the more frequently reported events.[10] Other unusual venous thrombotic complications of HIT have been described, such as warfarin-induced venous limb gangrene, cerebral sinus thrombosis and adrenal hemorrhagic infarction secondary to adrenal vein thrombosis. Arterial thrombosis most commonly involves the large arteries of the lower limbs, leading to acute ischemia. Other complications that involve arteries in HIT include acute cerebrovascular accidents and myocardial infarction.

Other unusual complications of HIT include skin lesions and acute systemic reactions.[11] Skin lesions appear either as erythematous plaques or frank necrosis of the skin at heparin injection sites. These lesions begin after 5 or more days of heparin use and their occurrence is strongly associated with the formation of heparin-dependent, platelet-activating antibodies. Heparin should be withdrawn immediately and the patient carefully followed to ascertain the eventual occurrence of thrombotic complications. Acute systemic reactions are rare clinical syndromes that begin 5 to 30 min after administration of an intravenous heparin bolus to a sensitized patient. The most common signs and symptoms include fever/chills, hypertension and tachycardia. An abrupt decrease in the platelet count invariably accompanies these reactions which are likely caused by acute *in vivo* platelet activation and associated release of inflammatory mediators. Because continued use of heparin has been associated with fatal outcomes in such patients, it is important that these reactions be recognized promptly by physicians as a manifestation of HIT.

Treatment of isolated HIT

Discontinuation of heparin therapy has long been the cornerstone of management of HIT, but this alone is not enough even for patients with isolated thrombocytopenia. The risk of thrombosis is 10% at 2 days, 40% at 7 days and 50% at 30 days despite stopping heparin.[11,12] In 16 patients with apparently isolated HIT, compression ultrasonography or contrast venography showed a deep vein thrombosis in 8 cases (all but one proximal).[13] Subclinical thrombosis early during the course of HIT may account for the high prevalence of subsequent clinical thromboembolism among patients managed solely by withdrawal of heparin. Given the unfavorable natural history of isolated HIT and the efficacy and safety of alternative anticoagulation in patients with HIT and thrombosis (see below), administration of another rapidly acting anticoagulant in patients with isolated HIT is recommended until an adequate platelet count is restored.[14]

Treatment of HIT with thrombosis (HIT-T)

The major treatment options for patients with HIT-T include danaparoid, recombinant hirudin and argatroban.[14] This is because these treatments appeared to be effective based on comparative studies, whereas reports on other drugs for HIT treatment are based on uncontrolled case series.

Danaparoid. Danaparoid is a mixture of anticoagulant glycosaminoglycans (predominatly low-sulfated heparan sulfate and dermatan sulfate) which differ from UFH and LMWH in the structure of the glycosaminoglycan backbone. This explains the low-risk of immunologic cross-reactivity to this drug in patients with HIT antibodies (less than 5%). Danaparoid's antithrombotic activity is mediated primarily via antithrombin III inhibition of factor Xa and is monitored by chromogenic antifactor Xa assay. This is a potential disadvantage because this test may not be readily available. However, most patients achieve therapeutic levels with standard dosing (eg. i.v. bolus of 2400 anti-Xa U, followed by continuous infusion of 200 U/hour). Monitoring to ensure maintenance of appropriate anti-Xa levels (0.5-0.8 U/mL) is recommended only for very small or large patients, those with renal failure and those with life- or limb-threatening HIT. There is considerable experience with the use of danaparoid in

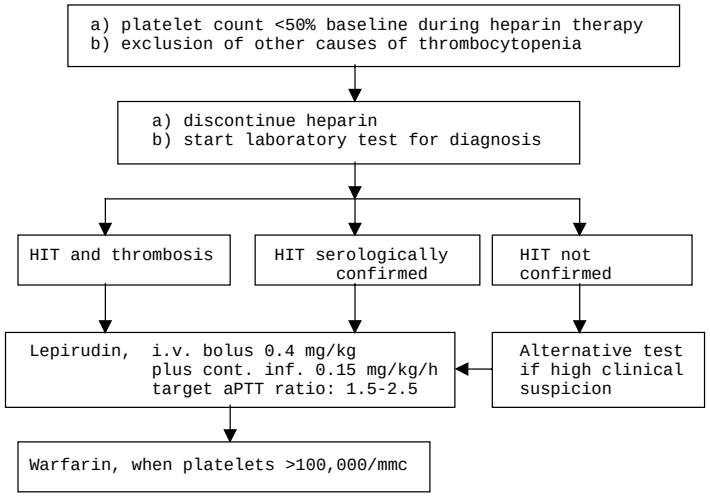

Figure 1. Summary of diagnostic and therapeutic approach to HIT.

HIT-T,[15] included a randomized open-label clinical trial.[16] This study compared danaparoid vs. dextran 70 in 42 patients and showed a complete clinical recovery in 56% of thromboembolic events after danaparoid vs.14% after dextran (OR 10.53, 95% CI 1.6-71.4; *p*=0.02). There was no major bleeding with either treatment. Despite these favorable results, the use of danaparoid in the USA has been largely supplanted by the introduction of two FDA-approved drugs (see below) for use in patients with HIT-T. Danaparoid is currently not available in Italy.

Hirudin. Recombinant hirudin (lepirudin) is a direct inhibitor of thrombin that acts independently of co-factors such as antithrombin or heparin co-factor II. Potential advantages of this drug include its lack of immunologic cross-reactivity with HIT antibodies and the possibility of monitoring its anticoagulant effect readily using the activated partial thromboplastin time (aPTT). Lepirudin is given as a slow i.v. bolus, 0.4 mg/kg, followed by a continuous infusion at 0.15 mg/kg per hour, with dose adjustments to maintain the aPTT between 1.5-2.5 times baseline. In a recent meta-analysis,[12] two prospective cohort studies of lepirudin vs. historical controls for the treatment of HIT-T were evaluated. The primary end-point (combined incidence of death, new thromboembolic events and limb amputation) occurred in 22% of lepirudin-treated patients (CI 14-29%) vs. 48% of controls (CI 33-62%, *p*=0.004). However, bleeding events requiring transfusion were significantly more frequent in patients taking lepirudin than in historical patients (19%, CI 12-26% vs. 7%, CI 1-13%, *p*=0.02). Lepirudin was also compared directly with danaparoid in a retrospective, questionnaire-based, clinical study.[17] The cumulative risk of the combined end-point, as above defined, was similar in both treatment groups (lepirudin 18.5%, CI 13-25% vs. danaparoid 21.5%, CI 14-29%, *p*=0.526), whereas major bleeding occurred in 10.4% (CI 6-16%) of lepirudin-treated patients and 2.5% (CI 0.5-7%, *p*=0.009) of danaparoid-treated patients. These data indicate that lepirudin is highly effective in the treatment of patients with HIT-T but that the risk of bleeding should be carefully considered. Lepirudin is currently approved for this indication in both the United States and countries of the European Union, including Italy.

Argatroban. Argatroban is a synthetic direct and selective inhibitor of thrombin recently approved by the FDA for use in HIT-T. Treatment is initiated at a dose of 2 µg/kg/min and then adjusted to prolong the aPTT 1.5-3 times baseline (maximum 100 sec). Outcomes in 160 patients with HIT who were

treated with argatroban were compared with those in 147 historical controls, and outcomes in 144 patients with HIT-T were compared with those in 46 historical controls.[18] Patients with HIT treated with argatroban had a significant reduction in new thromboses at 37 days (8.1% vs. 22.4%, $p<0.001$). The reduction in thrombosis in patients with HIT-T was more limited (19.4% vs 34.8%, $p=0.044$). Bleeding events were similar between the two groups. Unlike danaparoid and lepirudin, argatroban is excreted normally in patients with renal failure. Therefore, this drug may be particularly useful as an anticoagulant for hemodialysis patients with HIT[19] or other HIT patients with impaired renal function. Argatroban is not available in Italy to date.

Other treatments. In a limited, but interesting, study in Italy, five patients with thromboembolic diseases who developed HIT were treated with dermatan sulfate, a selective thrombin inhititor acting through heparin co-factor II.[20] In four patients, the platelet count increased rapidly after heparin had been discontinued and dermatan sulfate started. None of the patients showed thrombus extension, hemorrhagic complications or other adverse effects. Further clinical experience with this drug in HIT is warranted.

Warfarin alone, LMWH and platelet transfusions are contraindicated in the acute phase of HIT.[14] Warfarin should be given together with a drug that reduces thrombin generation, such as danaparoid, lepirudin or argatroban, until the platelet count has recovered. Warfarin can then be continued alone. A flow-chart summarizing current recommendations for the diagnosis and therapy of HIT is shown in Figure 1.

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Heparins in Medicine I

session I - Chairmen: E. Morra, F. Rodeghiero

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Prophylaxis of venous thromboembolism in medical patients

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Venous thromboembolism (VTE) is a common complication among hospitalized patients, with relevant clinical and economic consequences. Pulmonary embolism (PE) is still considered the most common preventable cause of mortality in hospital patients; it causes or contributes to approximately 10% of all in-hospital deaths. More than 75% of cases of fatal PE occur in non-surgical settings.[1] However, in contrast to surgical patients, prevention of VTE has been less well studied in hospitalized medical patients. Although the majority of trials in medical patients are of small size, there are already sufficient data available to make recommendations about prophylaxis for some non-surgical groups of patients.

For many years, the investigation of VTE prophylaxis in medical patients has languished compared to that in surgical patients, with the exceptions of stroke and myocardial infarction. Reasons for this are the underestimation of risk of VTE in medical patients and the failure of conventional low-dose unfractionated heparin (UFH) and mechanical prophylaxis in some studies. A recent Consensus Conference[2] underlined the urgent need to design new clinical trials concerning the prophylaxis of VTE in medical patients in order to establish more sound and evidence-based recommendations in this setting.

Myocardial infarction

Patients with myocardial infarction who do not receive antithrombotic drugs have an incidence of deep vein thrombosis (DVT) higher than 20%.

From the available data, low dose UFH (5,000 IU every 8 or 12 hours) and full anticoagulation with heparin and oral anticoagulants (warfarin) reduce the incidence of VTE in patients with acute myocardial infarction.[3] However, the current aggressive management of myocardial infarction with thrombolytics, unfractionated heparin, low-molecular weight heparins (LMWH), antiplatelet agents, or combinations of these drugs has made the prevention of DVT a secondary aim in these patients, because they have reduced the incidence of symptomatic DVT.

Stroke

In stroke patients the incidence of DVT in the paretic or paralyzed lower extremity is higher than 50%. About 5% of early deaths following stroke are attributed to PE. Both low-dose UFH and LMWH were shown to be effective in the prevention of DVT.[4,5] To date, at least nine randomized trials have evaluated low-dose UFH or LMWH in acute stroke patients. Two recent trials have directly compared LMWH (enoxaparin 4,000 IU once a day) to low-dose UFH (5,000 IU every 8 hours) using routine contrast venography as the primary outcome.[6,7] Both studies found that LMWH provided greater protection than low-dose UFH without increasing the risk of bleeding.

Few data are available in patients with hemorrhagic stroke. However, the incidence of VTE seems to be similar to that of patients with ischemic stroke. In the fear of worsening of the hemorrhagic lesion with the use of anticoagulant drugs, the use of mechanical prophylaxis, i.e. elastic stockings, intermittent pneumatic compression of the calf or the *foot-pump*, should be considered as standard prophylactic measures.

It should be emphasized that in the published studies prophylaxis was applied for short periods of time (ten to fourteen days). However, many patients with stroke have co-morbid conditions such as paralysis, bed rest, atrial fibrillation, congestive heart failure: in these patients a prolongation of prophylaxis should be considered.

Medical patients

Excluding those with myocardial infarction or

ischemic stroke, medical patients remain a heterogeneous group of patients with a large variety of diseases such as congestive heart failure, chronic obstructive pulmonary disease, infections, cancer, immunological disorders. Moreover, the age of these patients is distributed over a wide range.

The risk of VTE in medical hospitalized patients has been underestimated for a long time. A recent meta-analysis[8] compared the efficacy and safety of low-dose UFH and LMWH in VTE prophylaxis in medical patients. Compared to placebo, both drugs were effective in reducing VTE. No significant differences in the incidence of VTE were detected between the groups treated with either one of drugs, while the use of LMWH was associated with a 50% reduction in the incidence of bleeding if compared with UFH. It should be emphasized that most studies included in the meta-analysis used low doses of LMWH, such as those commonly used in the prophylaxis of low-risk surgical patients. However, recent studies have shown that the thrombotic risk in medical hospitalized patients is similar to that of medium-high risk surgical patients. As a matter of fact, a recent double-blind, placebo-controlled, randomized study by Samama *et al.*[9] confirmed, using venography (in most patients) or color-coded Doppler ultrasonography findings as the primary end-point, the efficacy and the safety of LMWH in primary prophylaxis of DVT in medical patients. The cumulative incidence of DVT was 14.9% in patients who received placebo, 15% in those treated with 2,000 IU and 5.5% in those receiving 4,000 IU of enoxaparin. The higher dose of LMWH was effective in the prevention of DVT if compared to placebo, while the lower dose did not have a significantly different effect from placebo. No differences in safety (hemorrhagic risk and thrombocytopenia) were observed among the three groups.

From the available data, the American College of Chest Physicians suggested the following guidelines for the prophylaxis of VTE in medical patients:[10]

- *acute myocardial infarction*: prophylactic or therapeutic anticoagulant therapy with subcutaneous low-dose UFH or intravenous heparin (grade 1A recommendation);
- *ischemic stroke*: for patients with ischemic stroke and impaired mobility, routine use of low-dose UFH, LMWH (grade 1A recommendation); if anticoagulant prophylaxis is contraindicated, mechanical prophylaxis with elastic stockings or intermittent pneumatic compression of the calf (grade 1C recommendation);
- *other medical conditions*: in general, medical patients with risk factors for VTE (including cancer, bedrest, heart failure, severe lung disease), LDUFH or LWMH (grade 1A recommendation).

No available studies have addressed the issue of the optimal duration of prophylaxis in medical patients. Recent trials in orthopedic and oncologic surgery showed that VTE could be a late event and that 7 to 10 days of pharmacologic prophylaxis may not be sufficient to provide adequate protection. The availability of new, very active drugs in the prophylaxis of VTE will probably boost future research on this topic.

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session I - Chairmen: E. Morra, F. Rodeghiero

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Treatment of venous thromboembolism in hospital and at home

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The main aims of treating acute deep vein thrombosis (DVT) are to prevent the size of the thrombus from increasing, to lower the risk of pulmonary embolism (PE) and DVT recurrence and, finally, to minimize the long-term effects associated with post-thrombotic syndrome. The treatment is usually based on immediate anticoagulation via the administration of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) followed by long-term treatment with oral anticoagulants. Other possible forms of therapy include, in selected cases, the administration of thrombolytic agents or the fitting of caval filters.

Anticoagulation

It has been shown that proper and immediate anticoagulation lowers the risk of recurrence of venous thromboembolism (VTE) by about 80%,[1] while the risk of fatal PE is reduced by up to 0.4%.[2] Some authors,[3] albeit not all,[4] have also observed that the right levels of anticoagulation with heparin must be used from the very beginning of treatment to avoid the development of a condition predisposing the subject to a higher rate of VTE recurrence. Proper anticoagulation levels must be achieved as rapidly as possible since it has been observed that the rate of VTE recurrence increases (23% versus 4-6%) if adequate therapeutic levels are achieved only after 24 hours.[5]

Proper anticoagulation treatment involves the administration of correct doses of heparin (either UFH or LMWH) along with simultaneous administration of an oral anticoagulant for at least 4-5 days; heparin treatment can be discontinued after at least 5 days and after 2 consecutive days with an International Normalized Ratio (INR) > 2.0.[6] Oral anticoagulation therapy (OAT) must then be continued, with a therapeutic range of 2.0-3.0 INR, for at least 3 months, even if the optimal duration of therapy is still a subject of debate and it is reasonable to suppose that it should be correlated to the specific risk factors present in each patient and to the actual nature of the thrombotic event (idiopathic or secondary to transient or permanent risk factors). That initial heparin treatment is crucial was shown in a recent study[7] that recorded a higher incidence of VTE when initial anticoagulation involved merely the administration of oral anticoagulants.

Limits of UFH in the treatment of VTE

UFH has a tendency to bind non-specifically with blood and endothelial cells, and especially with various plasma proteins, some of which are proteins of the acute phase that often increase when an acute thrombotic process is under way.[8] UFH bound in this way is no longer active for anticoagulant purposes. This pharmacokinetic consideration explains why anticoagulant response to UFH administration is so hard to predict and why the dose needed for proper anticoagulation levels varies so much from subject to subject and within the same subject at different times. UFH cannot, in fact, be administered at standard doses and it is crucial that the anticoagulant effect be assessed in the laboratory with a view to regulating doses in the best way possible. It is usually accepted that plasma levels of heparin between 0.2 and 0.4 IU/mL (titrated by protamine sulphate) are needed to offset the thrombotic process effectively.[9] However, from a practical therapeutic point of view, the test routinely used for monitoring treatment with UFH is the activated partial thromboplastin time (aPTT), an overall coagulation test influenced by a series of factors besides heparin. It has been shown that an aPTT ratio level < 1.5 (rela-

tionship between the aPTT of the subject treated and that of the normal control) is associated with a higher risk of thromboembolic recurrence (20-25%).[10] *Vice versa*, an aPTT > 2.5 is associated with a higher risk of hemorrhage. For these reasons the administration of UFH, either by continuous infusion or subcutaneous injection, must be regulated by using a nomogram that regulates the amount of UFH administered on the basis of serially obtained aPTT values.[11,12]

Other important limitations in the use of UFH are linked to the possible onset of clinically relevant complications, notably heparin-induced thrombocytopenia (HIT) and osteoporosis. HIT can cause serious vascular complications, venous and especially arterial (acute limb ischemia, myocardial infarction, stroke), in a high percentage of affected patients (> 20%). HIT usually appears 5-15 days after the beginning of heparin treatment but it may occur earlier if there has been previous contact with heparin. Its incidence varies greatly depending on the case histories and was reported to be about 3% in patients enrolled in a recent study.[13] Bone fractures caused by osteoporosis associated with heparin treatment were observed in 2-3% of patients treated with UFH for over 3 months.[14]

There are practical and organizational limitations to the treatment of VTE via UFH infusion. It is a procedure that is a potential source of a whole series of possible errors tied to: preparation of the heparin solution to be infused, aPTT monitoring and subsequent regulation of the dose to be administered.[15] In a recent study anticoagulation levels were found to be either excessive or insufficient in over 60% of patients within the first 24 hours of treatment.[16]

LMWH: characteristics and advantages for the treatment of VTE

LMWHs are derived from UFH using techniques of chemical or enzymatic depolymerization. Fragments are obtained that are about a third the size of UFH, with a mean molecular weight of 4,000-6,000 Daltons. They are different products both as regards molecular weight and anticoagulant activity. The composition of the different commercial LMWHs varies. All of them contain the pentasaccharide, which is indispensable for binding with antithrombin III and via this with factor Xa, so all LMWHs have an anti-Xa effect. LMWHs also contain a series of saccharide units whose number varies. If the total number of saccharide units (including pentasaccharide) is equal to or above 18 the molecule may bind to the thrombin and produce a direct anticoagulant effect (anti-IIa effect). Commercial products differ since they contain 25-50% molecules with an anti-IIa effect, while the remaining molecules contain less than 18 units and cannot bind to the thrombin (they have only an anti-Xa effect). Hence, while UFH has an anti-Xa-anti-IIa ratio of 1:1, commercial LMWHs have different ratios ranging from 4:1 to 2:1 depending on the distribution of the molecular weight of the component molecules.

Compared to UFH, LMWHs have the following advantages: 1) their non-specific binding with plasma proteins, blood and endothelial cells is much less and so the anticoagulant effect *vis-à-vis* dose administered is easier to predict and individual variability less; 2) the half-life is greater and bioavailability after subcutaneous administration much higher; 3) the incidence of HIT[13] and osteoporosis is much less. A key advantage for DVT treatment is that laboratory monitoring to regulate the indicated dose is not needed since the dose is calculated according to the patient's weight and administered subcutaneously twice or even just once a day.

A large number of level I studies and meta-analyses have compared the efficacy and safety of using LMWH rather than UFH to treat DVT.[17-25] All these studies concluded that LMWH are at least as effective as UFH. Some authors also reported a lower risk of major hemorrhage, VTE recurrence and even a reduction in mortality.[26]

The fact that it is not necessary to perform laboratory tests to monitor and regulate treatment, together with the easy administration route (subcutaneously twice or even once a day) are crucial aspects in the use of LMWH that have made it possible to treat many patients with acute DVT, and also with PE, at home.

Laboratory control of LMWH treatment

It is well known that LMWH is administered in units per kilogram of body weight and not on the basis of its effect in a laboratory test. This means that for this type of heparin therapy no laboratory control is called for.[27] Laboratory tests, essentially chromogenic tests measuring inhibition of factor Xa, are recommended only in selected conditions: a) in patients with severe renal insufficiency; b) in patients weighing less than 50 kg or more than 120 kg; c) during prolonged use of low molecular weight heparin (over 7-10 days).

Control of platelet number

Two types of platelet count reduction associated with heparin administration are recognized: 1) type 1 thrombocytopenia is an acute phenomenon

of moderate entity caused by platelet aggregation; the condition is normally not very marked, often transitory and does not involve the discontinuation of heparin treatment; 2) type II thrombocytopenia, called *heparin-induced thrombocytopenia* (HIT), is a clinically very important complication which often appears after at least 7-10 days of treatment and may cause the onset of serious thrombotic side effects, especially arterial.[13] The process involves the appearance of antibodies (IgG) against the heparin-platelet factor 4 (PF4) complex, which activate platelets via binding of the IgG-heparin-PF4 complex to platelet receptors. It is well known that the risk of HIT can be greatly reduced by using LMWH.[13] However, once this complication has set in there is a high likelihood of crossed immunization with LMWH. It should, therefore, be borne in mind that once HIT has appeared, the use of LMWH is not only not to be recommended but is indeed contraindicated (probability of crossed reactions > 90% *in vitro*, with a risk of clinical therapeutic failure estimated in the range of 25 and 50%).[28] It is good practice, therefore, to control the platelet count during heparin treatment, especially if prolonged. A basal control is normally carried out every 4-7 days. Since therapeutic response varies according to the type of thrombocytopenia, it is also indispensable to be able to perform a specific test to identify anti-PF4 antibodies.[29]

Hospital treatment

DVT (with or without pulmonary embolism) is treated either in hospital or at home by administering proper doses of heparin in conjunction with oral anticoagulants that should be taken for at least 3-6 months. Heparin administration should last at least 5 days and may be discontinued after at least 2 consecutive days with INR > 2.0. The choice between UFH and LMWH in hospital is conditioned by certain factors that it is well to keep in mind. As already mentioned, the use of UFH requires continuous intravenous infusion and frequent laboratory controls. Overall this treatment is somewhat difficult and prone to errors that may lead to clinically significant complications. *Vice versa*, subcutaneous administration and the use of fixed doses correlated to body weight, with no need for laboratory controls, make LMWH extremely simple to use. The latter are therefore the preferred choice except in certain specific conditions in which UFH still needs to be used, notably: a) in patients who present with clinically serious pulmonary embolism, and b) in patients in whom the use of LMWH is contraindicated (patients with renal insufficiency, obese subjects, pregnant women close to delivery, conditions in which surgery or invasive techniques are indicated).

Table 1. Conditions that exclude or contraindicate treatment at home.

House is a long way from hospital
Symptoms of pulmonary embolism
Active bleeding or known hemorrhagic disease
Intracranial hemorrhage within previous 2 months
Serious renal insufficiency
Serious hepatic disease (baseline PT < 50%)
Thrombocytopenia (< 100,000)
Obesity > 120 Kg
Phlegmasia, and/or severe limb pain
Important associated disease requiring acute therapy
Gastro-duodenal ulcer in acute phase (last 4 weeks)
Invasive tests or short-term surgical intervention
Caval (and/or iliac) thrombosis
Unreliability of the patient or inability to apply treatment (elderly on their own, drug dependence, psychiatric cases, alcoholics, if not looked after by family)
Very poor living and housing conditions
Terminal state or very poor general health (unless expressly requested by patient/relations)
Diabetes
Uncontrolled arterial hypertension (>200/110 mmHg)

Treatment at home

The use of low molecular weight heparin instead of UFH in the early phase of DVT treatment has brought with it a series of major advantages and has made it possible to treat patients at home rather than in hospital. Treatment at home for patients with DVT can be either immediate or after a short initial period of hospitalization (24-48 hours, instead of the current average of 7-9 days). The progress made in the number of therapeutic options available can be extremely advantageous both for patients and health authorities since fewer days are needed in hospital with subsequent significant savings. It has been calculated that, compared to hospital treatment with heparin infusion, home treatment with LMWH can generate savings of about 50-60%.[30-32] Less time spent in hospital lowers the risk of iatrogenic complications and is generally welcomed by patients, significantly improving the quality of life.[23]

The initial phase of DVT treatment is not risk free, there being a possibility of thromboembolic (symptomatic PE), or hemorrhagic (as a result of the actual anticoagulant therapy) complications. Clinical studies[22-24] comparing the efficacy and safety of subcutaneously administered LMWH in the early phase of DVT with those of standard continuous

UFH infusion showed that the former are at least just as effective (thromboembolic recurrence 6.1% versus 7.5%, respectively) and safe (major bleeding: 1.3% versus 1.5%) as the latter. These studies also showed that the rate of complications was the same whether the LMWH treatment was given in hospital or at home.

It should, however, be borne in mind that side effects cannot be excluded in the first days of treatment at home. While such effects can occur in equal measure in hospital or at home, it cannot be denied that there is a greater psychological impact (if not clinical consequence) in the latter case. For this reason, it is indispensable that the patient be guaranteed maximum therapeutic effectiveness and safety as well as the best life conditions. To ensure the best results from treatment at home co-ordinated action is called for from health workers operating inside and outside the hospital. First and foremost, cases need to be selected carefully (see Table 1) with guarantees provided regarding proper monitoring and necessary home and hospital-related nursing services, especially regarding oral anticoagulation treatment monitoring. If these conditions are not met, treatment at home may be harmful to the patient: treatment may be inadequately applied, short-term (higher thromboembolic risks) and long-term (post-thrombotic syndrome) therapeutic results may worsen, patients may have to travel for crucial laboratory and clinical controls to the cost and discomfort of the patient and relatives.

Criteria for proper home treatment

a) Careful selection of patients who can be treated at home is a crucial prerequisite (see Table 1).
b) Patients (or relatives) should be instructed on how to self-administer LMWH subcutaneously.
c) Oral anticoagulant treatment (OAT) and its monitoring should be explained carefully.
d) The daily LMWH and OAT doses should be indicated clearly together with the place and the day for the next INR control.
e) During the day the patient must wear class II elastic stockings, must walk and must not stay too long in bed.
f) The patient should be contacted telephonically or by a home visit by a nurse to make sure that the correct therapeutic standard for DVT treatment is being respected, and in particular that LMWH are being correctly administered subcutaneously twice a day (in other countries mono-administration is already available) at the right body weight dosage set by each manufacturer and that oral anticoagulants are being taken at the prescribed dose and with the necessary periodic INR testing.
g) The clinical conditions of the affected limb and other general conditions need to be monitored to evaluate the possible onset of complications.
h) An institutional point of reference should be established so that if complications are suspected the general practitioner can refer the patient for urgent examination when necessary via a privileged and direct channel.
i) The patient must carry out all necessary/scheduled clinical controls, monitor OAT and take all the measures aimed at lowering the risk of post-thrombotic syndrome. After DVT, damage to the deep-perforating vein valvular systems often elicits signs and symptoms of chronic venous insufficiency due to so-called post-thrombotic syndrome (edema, skin discoloration, venous dilatation especially in peri-malleolar areas, risk of trophic skin lesions). To reduce the incidence of these complications it is important to convince the patient to use an elastic stocking for a long period of time (usually over two years) and to undertake adequate walking activity.

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Heparins in Medicine II

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Low molecular weight heparin in the treatment of acute myocardial infarction

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The treatment of unstable angina/non-ST elevated active myocardial infarction (UA/NSTAMI) has changed in the last few years due to the availability of new drugs which have overcome the limited capabilities of aspirin, heparin and first-generation fibrinolytic agents. With the addition of new antithrombotic agents, such as low molecular weight heparins and glycoprotein GPIIbIIIa antagonists, the modern approach to acute coronary syndromes seems to be more effective and less hazardous. Low molecular weight heparins (LMWH) in particular represent a step forward in the management of acute coronary syndromes. They show advantages from pharmacodynamic and pharmacokinetic points of view (Table 1). In particular, LMWH have a direct anti-Xa activity, have greater bioavailability, are conveniently administered by subcutaneous (SC) injection, exhibit a more predictable dose-response, cause less activation of platelets, and are less likely to be associated with thrombocytopenia. There is considerable evidence that LMWH are either equivalent or superior to unfractionated heparin (UFH) in UA/NSTAMI. The *FRagmin in Unstable Coronary Artery Disease* (FRIC)[1] and *FRAXiparine in Ischemic Syndrome* (FRAXIS)[2] trials demonstrated comparable clinical safety and efficacy of dalteparin or nadroparin, respectively, to UFH. The *Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events* (ESSENCE)[3] and *Thrombolysis in Myocardial Infarction* (TIMI) 11B[4] trials, and a prespecified meta-analysis thereof[6] demonstrated a consistent risk reduction associated with enoxaparin when compared with UFH for the pharmacotherapy of UA/NSTAMI. In the meta-analysis, the risk of death/myocardial infarction/urgent revascularization at 8 days was reduced by 21% with enoxaparin, and this relative benefit was maintained at 43 days and 1 year.[6]

Despite the promising results from the use of LMWH in non-ST-elevation acute coronary syndromes, its use in the setting of acute myocardial infarction (AMI) is still debated. In this review we will discuss the role of LMWH in acute myocardial infarction, taking into consideration the rationale and the available results.

Rationale

Plaque rupture with subsequent occlusive thrombus formation is the pathophysiologic process leading to AMI. Coronary occlusion leads to the interruption of blood flow, with a resultant inadequate supply of oxygen available to the tissues, and subsequent myocardial cell death and necrosis. The goals of therapy in myocardial infarction are, therefore, to open the occluded coronary artery as soon as possible, to keep it open, to limit myocardial injury and to preserve ventricular function and vessel homeostasis. The occluded vessel may be opened by fibrinolytic therapy and/or coronary angioplasty. To keep the vessel open various adjunctive antithrombotic therapies have been developed, including heparin and LMWH. Keeping the culprit vessel open and reducing the likelihood of new thrombotic events is of paramount importance once an occluded vessel has been opened. In patients treated with thrombolytic therapy, lysis of the thrombus exposes clot blood thrombin and activates a number of coagulation factors, thus paradoxically creating a locally prothrombotic *milieu*. In patients treated with percutaneous interventional modalities, the devices employed (balloon and stents) can further injure the already damaged vessel wall, again resulting in an increased risk of re-developing

Table 1. Comparison between UFH and LMWH treatments.

	UFH	*LMWH*
Mean molecular weight	15.000	5.000
Anti Xa:IIa	1:1	2-4:1
TFPI release	+	++
Binding to plasma proteins and cells	avid	weak
Half-life	1h	2-4 h
Bioavailability after s.c. injection	30%	>90%
Dose-effect	poor	fair
Direct platelet effects	++	+
HIT	++	+
Neutralization by PF4	++	+
Neutralization by protamine	++	+
Neutralization by heparinase	++	+
Increase in vascular permeability	++	+
Osteoporosis	++	+
Cost	Inexpensive	Expensive

thrombus at the original site of the injury. The already discussed advantage of LMWH over heparin may be particularly beneficial in the setting of AMI in which time is critical, rapidly reliable anticoagulation is important, and bleeding risk should be minimized. Thus, more efficacy in blocking the generation of new thrombin may have direct clinical consequences.

Available results

There have been seven major trials that have looked at the use of LMWHs in the treatment of patients with AMI.

The FRAMI (*Fragmin in Acute Myocardial Infarction*) study[7] examined the efficacy and safety of dalteparin in the prevention of arterial thromboembolism in patients with an acute anterior myocardial infarction. The study randomized 776 patients to dalteparin (n=388; 150 IU/kg q 12 during hospitalization) or placebo. Streptokinase was administered to 91.5% of the patients. The primary end-point was the composite of thrombus formation (echocardiographically diagnosed) and in-hospital arterial embolism. In the 517 patients with evaluable echocardiographic recordings, primary end-point events occurred in 59 of the placebo group (21.9%) and in 35 (14.2%) of the dalteparin group. The overall risk of thrombus formation was reduced by 47% (p=0.02) by dalteparin. There were no differences in the incidence of arterial embolism, reinfarction or mortality but there was a higher risk of major (2.9% vs 0.3%) and minor (14.8 vs 1.8%) hemorrhage with dalteparin.

The BIOMACS trial was a pilot study evaluating the use of dalteparin as an adjunct to streptokinase (SK) in patients with AMI.[8] A total of 101 patients treated with SK were treated with dalteparin (100 IU/kg prior to SK; 120 IU/kg after 12 h) or placebo. Continuous echocardiogram monitoring was performed, serum myoglobin was checked at baseline and after 90 minutes and angiography was performed after 20-28 h to evaluate TIMI flow grade in the infarct-related artery. Normal TIMI flow (grade III) tended to be more frequently present in the dalteparin group (68% vs 51%) although the difference was not statistically significant. Dalteparin had no effect on non-invasive indicators of early reperfusion: in fact, there was no difference in the regression of ST segment elevation at 120 min or myoglobin increase at 90 minute. In patients with signs of early reperfusion (based on the increase in myoglobin levels at 90 minutes) there was a significantly higher rate of normal TIMI flow in the dalteparin group (74% vs 46%; p=0.04). Ischemic episodes from 6-24 h after the start of therapy were also significantly less frequent in the dalteparin group. The overall incidence of bleeding was low, not allowing a statistically meaningful comparison. Reinfarctions were more frequent in the dalteparin group. There was no difference in mortality or revascularization.

The HART II trial[9] randomized 400 AMI patients treated with accelerated recombinant tissue plasminogen activator to either enoxaparin (30 mg intravenous bolus, 1 mg/kg subcutaneously every q 12h) or UFH (5,000 U bolus, infusion 15 U kg/h adjusted to an aPTT ratio of 2-2.5). The primary end-point was non inferiority of enoxaparin vs UFH with regard to patency, evaluated by coronary angiography at 90 minutes following the initiation of recombinant tissue plasminogen activator (rt-PA), and repeated at 5-7 days. At 90 min, 80.1% of the enoxaparin group achieved TIMI II/III flow (52.9% TIMI III) versus 75% (47.6% TIMI III) of the UFH group. These differences were not statistically significant but confirmed the non-inferiority hypothesis. At follow-up angiography, reocclusion tended to occur less frequently in the enoxaparin group. Intracranial hemorrhage occurred in two patients (1 in each group). Major hemorrhages occurred in 3.6% of the enoxaparin group and 3% of the UFH group. In-hospital and 30-day mortality were not different between groups.

The AMI-SK trial[10] evaluated the utility of enoxaparin in conjunction with SK in the setting of AMI. A total of 496 patients with AMI were treated with SK and aspirin within 12 h of the onset of symptoms and randomized to enoxaparin (30 mg intravenous-

ly followed by 1 mg/kg subcutaneously q 12 h for 5-8 days) or placebo. The primary efficacy end-point was patency (TIMI II/III flow) of the infarct-related artery by coronary angiography at 5-10 days. Secondary end-points were ST-segment resolution and clinical outcomes of death, re-infarction and angina at 30 days. Adjunctive enoxaparin significantly improved infarct-related coronary artery patency (TIMI II/III flow 87.6% vs 71.7%). The composite end-point of death, reinfarction and angina at 30 days was also significantly reduced with enoxaparin (13.3 vs 21%), with no significant increase in the incidence of major bleeding (4.8% with enoxaparin vs 2.8% with placebo).

In the ASSENT-Plus trial,[11] 439 patients with AMI were treated with rt-PA and randomized to dalteparin (120 IU/kg q12 for 4-7 days) or intravenous UFH (bolus 5,000 U, infusion 1,000 U/h titrated to an activated partial thromboplastin time of 50-75 s; infusion continued for 48 hours). Coronary angiography was performed prior to discharge and clinical outcome evaluated at 30 days. The primary end-point was the incidence of TIMI III flow at follow-up. There was no difference in the end-points but TIMI 0/II (13.4 vs 24.4%) and the incidence of angiographically visible thrombus (27.9 vs 42%) were lower in the dalteparin group.

In the ASSENT III study 6,095 patients with AMI within the previous 6 h were randomized to full-dose tenecteplase (TNK), or full-dose tenecteplase and enoxaparin for up to 7 days or half-dose TNK plus abciximab. The primary end-point was the composite of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia. This end-point was reduced in both the enoxaparin group (11.4% vs 15.4%) and the group treated with half-dose TNK and abciximab (11.1% vs 15.4). The primary composite safety and efficacy end-point (primary end-point plus in-hospital intracranial hemorrhage or in-hospital major bleeding) was also significantly reduced in both enoxaparin groups (13.7% vs 17%). Even at 48 h there was significant efficacy benefit in the enoxaparin group (6.1% with TNK plus enoxaparin, 5.2% with half-dose TNK plus abciximab and 8.8% with TNK plus UFH) and safety and efficacy benefit (8.1% vs 8.2% and 10.3%, respectively). There was no significant difference in 30-day mortality (5.5 vs 6.5 vs 5.9%, respectively), but significant reductions were found in both in-hospital re-infarction (2.6 vs 2.8 and 4.2% respectively) and in-hospital refractory ischemia (4.5, 3.1 and 6.4%, respectively). In terms of the safety end-points, there was no significant difference in intracranial hemorrhage (0.88 va 0.94 and 0.93%, respectively), and slight, but significant increases in major bleeding events (3.04 vs 4.32 and 2.16%, respectively). Thus, in patients with AMI, both TNK plus enoxaparin and half-dose TNK plus abciximab are significantly superior to TNK and standard UFH. There are slight increases in major bleeding, but the overall rate of major bleeding was low.

In the ENTIRE/TIMI 23 trial[13] the patients are being randomized to standard dose TNK with UFH, standard dose TNK with enoxaparin, half-dose TNK with abciximab and reduced dose UFH, and half-dose TNK with reduced dose enoxaparin. The primary end-point is TIMI III flow at 60 min assessed by angiography. Preliminary results show that there are no significant differences in TIMI flow grade between groups at 60 min. Major bleeding complications have been slightly lower with enoxaparin in patients receiving half-dose TNK (5.6 vs 7.8%) and generally lower in patients receiving full-dose TNK (1.9 vs 1.4% with UFH). Looking at indirect markers of reperfusion, complete ST segment resolution at 60 min is not significantly different in the groups.

The TETAMI trial[13] is an ongoing study examining pharmacologic therapy in AMI patients not eligible for reperfusion therapy with fibrinolytics. The patients will receive either enoxaparin alone, enoxaparin plus tirofiban, UFH alone, or UFH plus tirofiban. This trial addresses an important problem related to the vast majority of patients whose treatment until now has lacked major improvement. The issue is even more important because these patients have the worst prognosis and even a slight improvement of their prognosis could save a substantial number of lives.

Conclusions

LMWH appear to provide substantial added benefit over UFH in AMI patients receiving later generation thrombolytic therapy and could constitute the standard of care. This may not apply to patients treated with streptokinase, in which the standard of care is no additional heparin at all. In these patients the addition of anticoagulant therapy may result in an increase in bleeding complications. A still unexplored issue relates to primary percutaneous transluminal coronary angioplasty especially in association with GPIIbIIIa inhibitors, but trials on this issue are pending. Another important field of application could be in patients not eligible for reperfusion therapy, who represent the majority of patients presenting with AMI and those with the worst prognosis.

A final problem is related to potential differences

that may exist between the individual LMWH. There are structural differences between the compounds that may be manifested as clinical differences. In the absence of true head-to-head comparison, it should be highlighted that most data are available for enoxaparin and dalteparin.

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Heparins in Medicine II

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Heparin during pregnancy

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Unfractionated heparin has been used for years for the prevention and treatment of venous thromboembolism during pregnancy and in pregnant women with prosthetic heart valves. Studies on the pathogenesis of the antiphospholipid syndrome have also shown that heparin can prevent pregnancy loss in some autoimmune conditions. Low-molecular-weight heparin may largely replace unfractionated heparin, based on an equal efficacy and safety profile and pharmacokinetic advantages. Several lines of evidence suggest that hereditary thrombophilias are associated with pregnancy loss and other obstetric complications. These pregnancies should be closely followed by multidisciplinary teams, in order to deal with the complex interplay of potential obstetric, hematologic, cardiovascular, neonatal and rheumatological problems.

Pregnancy as a thrombophilic predisposing factor

Normal pregnancy involves changes in hemostatic factors that contribute to a hypercoagulable state. These include raised plasma levels of fibrinogen and factor VIII, acquired functional resistance to activated protein C (APCR), a decrease in protein S, increases in plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2 (PAI-2), and platelet activation.[1-4] Additional factors increasing the risk of venous thromboembolism (VTE) during pregnancy include obstruction of venous return by the enlarging uterus and venous atonia as a result of female hormones.[5] Interestingly, inherited thrombophilias may confer benefits during pregnancy: for example the factor V Leiden mutation has been associated with a reduced risk of intrapartum bleeding complications, giving carriers a possible survival advantage.[6]

The risk of VTE in pregnancy is 0.05-1.8%, six times greater than in the non-pregnant state, and pulmonary embolism (PE) remains the most common cause of maternal death[4] during pregnancy. Maternal deep venous thrombosis (DVT) is more common in the left leg (accounting for about 85% of leg thromboses).[4-7] DVT and PE are mostly observed in the third trimester and in the postpartum period. The form of delivery is an important risk factor for VTE: the incidence of clinical DVT is estimated at 0.08-1.2% after vaginal delivery, rising to 2.2-3.0% with caesarian section. Emergency caesarean section is associated with the highest risk.

Hereditary and acquired thrombophilias during pregnancy

Pregnancy is an independent risk factor for the development of VTE and this risk is increased by the presence of thrombophilia. Several inherited molecular risk factors for VTE are now recognized. Besides well known but very rare genetic defects such as protein C, protein S and antithrombin (AT-III) deficiencies, more recently identified abnormalities include a mutation in the gene encoding factor V (factor V Leiden) associated with resistance to activated protein C (present in 3-7% of the general population); the prothrombin gene mutation (G20210A) associated with elevated plasma factor II levels (present in about 2-5% of healthy individuals); and hyperhomocysteinemia frequently associated with homozygosity for the thermolabile variant in the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) (present in about 8-10% of healthy individuals).[4]

Abbreviations used in text. VTE: venous thromboembolism; PE: pulmonary embolism, DVT: deep venous thrombosis; MTHFR: methylenetetrahydrofolate reductase, APS: antiphospholipid antibodies syndrome, aPL: antiphospholipid antibodies, RPL: recurrent pregnancy loss, IUGR: intrauterine growth retardation; UFH: unfractioned heparin, LMWH: low-molecular-weight heparin, ACCP: American College of Chest Physicians, ASA: aspirin, HIT: heparin induced thrombocytopenia.

Antiphospholipid antibodies syndrome (APS) is a cause of VTE and obstetric complications. Besides recurrent pregnancy loss (RPL), pre-eclampsia, intrauterine growth retardation (IUGR), *abruptio placentae* and stillbirth have also been described in association with APS.[8] Antiphospholipid antibodies (aPL) may induce thrombotic changes in decidual microvessels, possibly also interfering with the function of placental annexin V;[9] they may also have a direct negative effect on the trophoblast.[10]

Besides APS, an association with RPL is now recognized for maternal congenital thrombophilias. For instance, Brenner and colleagues examined a group of 76 women with RPL of no apparent cause: significantly more women with RPL (49%) had some form of thrombophilia (particularly factor V Leiden) than in the control group (21%).[11,12] The *European Prospective Cohort on Thrombophilia* (EPCOT) analyzed the risk of fetal loss in a cohort of 571 women with a variety of known inherited thrombophilias. The study reported odds ratios of 3.6 for stillbirths and 1.3 for miscarriages. Women with factor V Leiden had odds ratios of 2.0 for stillbirth and 0.9 for miscarriages.[13] Martinelli *et al.* found that both factor V and prothrombin mutations were associated with an approximate tripling of the risk of late fetal loss.[14] Other studies have confirmed the potential role of prothrombin mutation in RPL.[11] Hereditary thrombophilias have also been associated with pre-eclampsia, IUGR and *abruptio placentae*[15,16] as have polymorphisms of PAI-I[4] and hyperhomocysteinemia.[17-19] The effect of this last might be partially masked by the increased use of folic acid during pregnancy.

In conclusion, congenital or acquired thrombophilia increases the thrombotic risk in the mother and is a cause of placental insufficiency with fetal death, obstetric complications and prematurity.

Heparin during pregnancy: *conventional* use

Unfractioned heparin (UFH) and low-molecular-weight heparin (LMWH) are the anticoagulants of choice for the prophylaxis and treatment of VTE during pregnancy.[7] Large clinical trials in non-pregnant patients indicate that LMWHs are at least as effective and safe as UFH for patients with VTE.[20,21]

As regards the prophylaxis of VTE, women can be classified as follows: 1) single episode of VTE associated with a transient risk factor; 2) single idiopathic episode of VTE in a patient not receiving long-term anticoagulation therapy; 3) single episode of VTE in a woman with thrombophilia (confirmed laboratory abnormality), not receiving long-term anticoagulation therapy; 4) no prior VTE in a woman with thrombophilia (confirmed laboratory abnormality); 5) multiple (two or more) episodes of VTE and/or long-term anticoagulation therapy.[7] These are broad categories, and the risk must be assessed individually for each patient. Current studies recommend two general approaches for pregnant women with previous VTE: 1) active prophylaxis, usually with LMWH once daily (e.g. dalteparin 5,000 U, enoxaparin 40 mg, nadroparin 0.4 mL); 2) close clinical surveillance.[7]

In order to obtain a reliable estimate of the true incidence of recurrent VTE, Brill-Edwards and Ginsberg completed a prospective study of 125 pregnant women with a single previous episode of VTE.[22] Antepartum heparin was withheld, and anticoagulants (usually warfarin with an initial short course of UFH or LMWH) were given in the postpartum period for 4 to 6 weeks. The antepartum recurrence rate was 2.4%. Blood tests were done in 95 patients to identify thrombophilia. There were no recurrences in the 44 patients who did not have thrombophilia but had had a previous episode of thrombosis associated with a temporary risk factor. Patients with abnormal test results and/or a previous episode of idiopathic (unprovoked) thrombosis had an antepartum recurrence rate of 5.9%. These results suggest that the absolute risk of antepartum recurrent VTE in women without thrombophilia, in whom a previous episode of thrombosis was associated with a temporary risk factor, is low and antepartum heparin prophylaxis is not routinely justified in these cases.

As regards the treatment of VTE during pregnancy, *American College of Chest Physicians* (ACCP) guidelines recommend LMWH adjusted to body weight during pregnancy (e.g. dalteparin 200 U/kg/day or enoxaparin 1 mg/kg every 12 hours or nadroparin 0.1 mL/10 kg every 12 hours) or full dose intravenous UFH for 5-10 days followed by maintenance subcutaneous heparin twice daily, adjusted so as to prolong the activated partial thromboplastin time (aPTT) into the therapeutic range.[7] Heparin is given until term, and discontinued 6-24 hours before delivery. Warfarin is recommended in the puerperium, with an optimal duration of *post-partum* therapy of 4-6 weeks.

The management of pregnant women with prosthetic heart valves is difficult because of the lack of reliable data on the efficacy and safety of antithrombotic therapy during pregnancy. In general, oral anticoagulants are more active than UFH for prophylaxis. However, at between 6 and 12 weeks' gestation warfarin increases the risk of

embryopathy; substituting oral anticoagulants with UFH adjusted to the aPTT or LMWH adjusted to body weight in this period reduces the fetal risk. This is the only situation in which the use of warfarin is accepted during pregnancy according to ACCP guidelines.[7]

Heparin during pregnancy: *non-conventional* use

Obstetric complications of APS are not only due to vessel thrombosis. De Simone *et al.* demonstrated that, *in vitro*, aPL can bind to the trophoblast, inhibiting syncytium formation and human chorionic gonadotropin (HCG) production.[10] Adding LMWH to the experimental model eliminated the action of aPL, as if heparin were able to protect placental formation.[23,24] These data are in agreement with those of Rai *et al.* who showed the efficacy in preventing first trimester miscarriages of adding LMWH to low-dose aspirin (ASA).[25] ACCP guidelines recommend low dose ASA plus UFH or LMWH in pregnant APS women, based on a few randomized trials.[25,26] With this therapy the rate of live births increases from 20% to 70%, which is similar to the expected pregnancy outcome in the general population.[25-27] Since many of these women are at risk of VTE, antithrombotic therapy should be continued in the postpartum even though the optimal regimen has not yet been established (ASA, heparin, warfarin?).

In the light of experience in acquired thrombophilia, heparin should also be considered in women with hereditary thrombophilia, particularly those with a history of obstetric complications. Women with RPL should be screened for thrombophilia, especially if they have had one or more second- and third-trimester losses. Observational studies have confirmed that UFH or LMWH does improve the outcome of pregnancy in thrombophilic women;[12,28-33] however, randomized, prospective, controlled trials are still needed to confirm this.

ACCP guidelines[7] and Eldor's review[4] suggest therapy with LMWH plus ASA in women with congenital thrombophilia. Similarly, hyperhomocysteinemia should always be managed with folic acid supplementation in the pre-gestational period and during pregnancy.[32] This therapy could be recommended to all women planning pregnancy, in view of its protection against spina bifida.

Dosage and kinetics

Heparinoids are safe for the fetus because they do not cross the placenta; they are not secreted in the breast milk so they can also be given safely to nursing mothers.[7] As the pregnancy progresses, and most women gain weight, the volume of distribution of LMWH changes. Therefore two options are available. The first is simply to change the dose in proportion to the weight change. The second is to test anti-factor Xa weekly 4 hours after the morning dose, and adjust the dose to achieve an anti-Xa level of approximately 0.5-1.2 U/mL.[7] These options have led some authors to report that LMWH needs are doubled around 20 weeks of gestation.[33]

Side effects

Approximately 3% of patients receiving UFH develop heparin-induced thrombocytopenia (HIT), frequently complicated by an extension of existing VTE or new arterial thrombosis. HIT should be suspected when the platelet count falls to < $100x10^9$/L or < 50% of the baseline value 5 to 15 days after starting heparin therapy, or sooner if the patient has had a previous, recent exposure to heparin.[7] The use of LMWH during pregnancy causes less HIT than UFH;[34] in one study of 486 pregnant women treated with LMWH, no cases of HIT were observed.[35]

Osteoporosis is a well known complication of heparin therapy. Symptomatic vertebral fractures have been reported in 2-3% of the patient population.[7] Studies using animal models of heparin-induced osteoporosis suggest that LMWHs cause less osteoporosis than UFH.[7] Bone mineral density in pregnant women receiving LMWHs was assessed in three studies using dual-photon ray absorptiometry of the hip and the lumbar spine. In the first study[36] in 28 pregnancies, subclinical osteoporosis was found in approximately one third of the women but reversed spontaneously in all cases after delivery. In a second study[37] bone densities were comparable in nine *post-partum* women treated with low doses of LMWH from the first trimester onward and in age-matched non-pregnant women. In a third study[35] bone density was measured before starting and upon completion of therapy in 43 women treated with low-dose LMWH throughout pregnancy; no decrease in bone density was found.

It is worth noting that pregnancy is already associated with a tendency to osteoporosis which is worsened by concomitant steroid therapy. We suggest giving these patients calcium from the beginning of pregnancy, adding vitamin D from the second trimester. The safety of LMWH during pregnancy was amply described in a systematic review in 1999.[35]

Our experience

We report the pregnancy outcome of 21 women with inherited or acquired thrombophilia treated with ASA and/or LMWH (nadroparin) (Table 1). Twenty-five pregnancies in 11 women with positive aPL or primary or secondary APS and 10 women with genetic risk factors responsible for thrombophilia were prospectively followed. Among the APS patients, one had primary APS, 4 secondary APS and 6 had a connective tissue disorder with positive aPL and/or lupus anticoagulant (LAC). Reasons for inherited thrombophilia were: 5 heterozygous factor V Leiden mutation, 5 heterozygous prothrombin gene mutation, 2 APCR, and 1 homozygous factor V Leiden. Six patients had combined factors.

Our treatment protocol was as follows (Table 2): if only laboratory abnormalities, no therapy, but ASA in acquired thrombophilia. In the case of APS, ASA + nadroparin 0.4-0.6 mL/day s.c. In the case of inherited thrombophilia plus previous clinical events: nadroparin. The treatment was started from a positive gravindex. Nadroparin was continued in all the patients in the puerperium.

Patients with acquired thrombophilic factors (primary or secondary APS or positivity for aPL and/or LAC) experienced 14 pregnancies: 12 ended with normal delivery and 2 with early spontaneous abortion. LMWH associated with ASA was prescribed in 6 successful pregnancies and ASA alone in the other 6 successful pregnancies and in the 2 early miscarriages. Adverse fetal outcomes were 1 premature membrane rupture and 1 chromosomal malformation.

Table 1. Prophylaxis and pregnancy outcome in women with congenital or acquired thrombophilia: our experience.

Thrombophilia	*No. pregnancies*	*Prophylaxis*	*Pregnancy outcome*
Acquired	14	Only ASA Or ASA +LMWH + steroids if SLE	Livebirth: 12 Miscarriage: 2 Prematurity (<34 wk): 1
Congenital	11	Nadroparin 0.4-0.6 mL/day or enoxaparin 40 mg 2 only ASA 1 no therapy	Livebirth: 11 Miscarriage: 0 Prematurity (>34 wk): 1

Patients with congenital thrombophilia had 11 pregnancies, all ending with a normal delivery except for one case of mild prematurity (35 weeks). LMWH plus ASA was prescribed in seven cases (4 nadroparin 0.4 mL/daily, 1 nadroparin 0.6 mL/daily and 2 enoxaparin 40 mg daily) and ASA alone in 2 cases; 2 cases were given no drug.

Our experience confirms that LMWH seems safe for the mother and the fetus and is, therefore, the first choice anticoagulant during pregnancy. Its effectiveness in reducing fetal loss rate and preventing thromboembolic events in women with APS is proven but its utility in patients with inher-

Table 2. Thrombophilia and pregnancy: prospective study of prophylaxis of maternal and fetal complications with LMWH (nadroparin).

History of obstetric complications and/or thrombotic events

Diagnosis of thrombophilia	*Congenital positive*	*Acquired positive*	*Negative*
Prophylaxis	LMWH*°	LMWH*° + ASA	Previous VTE: LMWH* Previous obstetric complications: LMWH (no evidence; discuss with the patient). ASA, if an autoimmune disease is present

**0.4 mL/day, monitoring placental blood flow + biochemistry; 0.4.mL x 2/day if placental blood flow and/or biochemistry abnormal and in cases with history of APS (from week 16-20); °0.4 mL x 2/day if multiple combined defects, homozygosis, lack of ATIII. No history of obstetric complications and/or VTE.*

Diagnosis of of thrombophilia	*Congenital positive*	*Acquired positive*
Prophylaxis	1. no exception: ATIII, homozygosis combined defects	1. low aPL titer: ASA Positive LAC and/or moderate/high aPL titer: LMWH* + ASA (no evidence: discuss with the patient)

**0.4 mL/day, monitoring placental blood flow + biochemistry; 0.4.mL x 2/day if placental blood flow and/or biochemistry abnormal. LMWH: start from positive gravindex; single dose at 10 a.m and double dose at 10 a.m and 10 p.m; discontinue heparin therapy 24 hours before delivery; discontinue heparin 12 hours before an epidural anesthesia; continue heparin until 4 – 6 weeks after delivery; bone mineral density before pregnancy and after delivery. ASA dosage: 100 mg/day; start from positive gravindex; discontinue at 38 weeks or at least 2 weeks before delivery; if history of APS, decide at the time, in the light of the clinical situation. Folic acid: 15 mg/day before and throughout pregnancy. Monitoring: every month placental blood flows, platelet count, assays of D-dimer and prothrombin fragments $_{1+2}$.*

ited thrombophilia has not yet been established; however, a history of obstetric complications or thrombotic events suggests the need for prophylactic anticoagulant treatment. Randomized studies are needed to answer this question.

Conclusions

Since they are safe for the fetus, heparinoids (LMWH or UFH) are the anticoagulant of choice during pregnancy. They are indicated for the prevention and treatment of VTE and of systemic embolism in patients with mechanical heart valves. They have been employed, often in combination with ASA, for the prevention of pregnancy loss in women with APS. The optimum management of pregnant women with congenital thrombophilia and prior pregnancy loss is still not clear but trials are in progress. The risk of osteoporosis and HIT is less frequent with LMWH than UFH and that is why LMWH will largely replace UFH. To obtain the best outcomes, thrombophilic women with high risk pregnancies must be managed by a multidisciplinary team (obstetrician, hematologist, rheumatologist, neonatologists, etc.) with ample experience in this field.

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Heparins in Medicine II

Heparins and tumors

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After a brief review on the epidemiology of venous thromboembolism in neoplastic patients, we will review the available data on the effectiveness of unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) for the prevention and treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with cancer. Treatment with LMWHs has been associated with a reduced mortality not due to a reduction of the deaths directly caused by PE. This exciting perspective will also be reviewed. The mechanism responsible for this beneficial effect has not been yet been clarified, however, the hemostatic system plays a major role in the development and metastasis of tumors. Conceivably, inhibition of hemostasis might well be a way to inhibit tumor growth.

DVT and PE epidemiology patients with tumors

The association between tumor and thromboembolism has known since 1865,[1] when Professor Trousseau held his famous lesson on *Phlegmasia alba dolens* in neoplastic patients at the Hotel-Dieu in Paris. Up to 11% of neoplastic patients show clinical evidence of DVT or PE. A higher incidence, reaching 50% of cases, was found in *post-mortem* examination of patients with cancer of the head or tail of pancreas.[3] A particularly high association was also found in cases with cancer of the ovary, stomach, prostate or lung.[4]

In recent years, the association between thrombosis and tumors has been revisited in well-defined clinical circumstances. Examples include DVT or PE as the presenting symptom of neoplasia or as a marker of an increased risk of developing a tumor in the short- or medium-term; the increased risk of DVT or PE after surgery; upper limb DVT secondary to central venous catheter (CVC) and DVT during chemotherapy. All these aspects will be addressed in this review.

Venous thrombosis as the presenting symptom of cancer or as a marker of increased risk of cancer development

Several investigations (reviewed in [5]) have shown an association between primary venous thrombosis and coincidental or subsequent tumor diagnosis. Although conflicting results have also been reported, this issue received renewed interest after an article by Prandoni *et al.* published in 1992. This study included 250 consecutive patients with symptomatic venographically confirmed DVT. At the time the DVT was diagnosed, a tumor was found in 3.5% (5/153) of patients with primary thrombosis, whereas neoplasia was not found in the remaining patients with thrombosis secondary to known risk factors. A diagnostic bias for this high incidence of tumors in patients with idiopathic DVT was ruled out by the results of several studies (reviewed in [7]) which compared the incidence of tumor in cases with idiopathic versus secondary DVT, or in cases with suspected but unconfirmed DVT versus those with DVT subsequently confirmed by an objective investigation. These studies showed that in secondary DVT or in suspected but unconfirmed DVT the incidence of neoplasia during the observational follow-up ranged from 1 to 4%, whereas a higher percentage, ranging from 2.5 to 34%, was observed in idiopathic DVT or in cases confirmed by objective methods.

Recently, two population-based studies, conducted in Sweden[8] and in Denmark[5] have been published. These studies were based on several thousands of patients with a discharge diagnosis of DVT or PE during the last decades. Discharge data derived from national registries of hospital discharged diagnosis were matched with data derived from tumor national registries. These studies confirmed the results of clinical studies showing a standardized incidence risk of malignant tumor ranging from 3 to 4.4 during the first 6-12 months after a diagnosis of thromboembolism. The standardized incidence risk reached 6.7 in patients

aged less than 65 in the Swedish study. The highest association with thrombosis was found in patients with ovarian, pancreatic, liver, lung, kidney, brain or esophageal cancer and Hodgkin's and non-Hodgkin's lymphoma. As expected, an exceedingly high incidence was also found in patients with polycythemia vera, in which thrombosis is part of the natural history of the disease.

These data allow the important role that LMWH could represent in tumor patients to be appreciated, especially if some studies, showing a survival advantage in tumor patients treated with these agents, receive confirmation by large ongoing prospective studies. At the moment, however, there is not sufficient evidence to suggest a specific screening for occult neoplasia in patients presenting with idiopathic DVT. In clinical practice, it seems more than appropriate to rely on a patient's history and physical examination, chest radiography and routine chemistry, as indicated by the age and sex of the patient.

Risk factors for DVT in patients with tumors

Generic risk factors, such as prolonged immobilization or venous stasis due to direct tumor compression, are particularly important in these patients who already have a higher thrombotic risk. However, specific attention should be paid to surgery, chemotherapy and a CVC.

After surgery, the risk of DVT in patients with tumor is almost double that in patients without a tumor.[9] A seven times higher risk for PE has been reported.[10] The incidence of DVT and PE after abdominal surgery, based on studies in which sensitive and objective diagnostic methods were used, was evaluated by an extensive literature review made by the American College of Chest Physicians,[11] In neoplastic patients not receiving antithrombotic prophylaxis a particularly high incidence of distal (40-80%) and proximal (10-20%) DVT was documented, with an incidence of fatal PE in 1-5% of cases.

Limited studies are available concerning the incidence of thromboembolism during or after chemotherapy. These studies have been done particularly in patients with breast cancer. This tumor has not been associated with thrombosis in the above-mentioned epidemiological studies. In particular, Pritchard *et al*.[12] studied 703 post-menopausal women with stage II breast cancer treated with tamoxifen or with tamoxifen and chemotherapy. During follow-up, up to 14% of the women treated with tamoxifen and chemotherapy developed DVT, often requiring hospitalization. An even higher incidence, up to 18%, was documented in women with more advanced breast cancer treated with 5 drug polychemotherapy. Thrombosis usually occurs during active chemotherapy, as shown by Levine *et al.*[14] in a study in which two groups of patients received chemotherapy for either 12 or 36 weeks. No thrombosis was diagnosed in the first group after chemotherapy was stopped, whereas thrombotic episodes continued to occur during the additional treatment period in the second group.

Venographic studies have documented a surprisingly high incidence of subclavian vein thrombosis in patients with advanced cancer after chemotherapy infusion through a CVC, justifying prophylactic interventions (as we will discuss later), especially if one considers that, although rarely, PE could originate from this district.

Clinical use of UFH and LMWH in neoplastic patients

A comprehensive perspective demands that the role in prevention and treatment of oral anticoagulation and physical methods, such as pneumatic intermittent compression (PIC) of the legs, graded pressure elastic stockings or electric calf stimulation, be also briefly mentioned in this section.

Prevention of DVT and PE after surgery

The results of the main studies can be summarized on the basis of some recent review articles.[7,10,16]

Physical methods

Physical methods as the sole preventative method significantly reduce DVT in patients with tumor (18.6 vs. 21%). However, none of the very few studies available has been specifically designed for neoplastic patients. The limited data derived from these studies[16] have been included in a meta-analysis[17] without producing any conclusive evidence. Furthermore, no data are available to suggest any efficacy of physical methods in reducing PE deaths.

Low dose UFH administered subcutaneously (calcium heparin)

Among 29 controlled studies in patients undergoing abdominal surgery (excluding gynecologic surgery) included in a meta-analysis, Clagett and Reisch[17] were able to identify 10 studies in which the results obtained in neoplastic patients were separately analyzed. The rate of DVT reduced by more than 50% in cases treated with UFH, from 30% in controls to 13% in those treated. The best dosage remains undetermined and some studies suggest that a higher or more frequent adminis-

tration of UFH may be required when patients with a tumor, compared with patients without neoplastic disease, undergo surgical interventions. On the basis of available studies, the common practice is to administer 5,000 units of UFH 2 hours before surgery, followed by the same dose repeated at 8 or 12 hour intervals for 7 to 10 days. There is evidence that at this dosage UFH is effective in reducing deaths due to PE, as shown by the results of the International Multicenter Trial.[18] In this study, 4,121 patients undergoing a surgical procedure were randomized between an untreated control group and a group treated with UFH. Among the 23% patients subjected to oncologic surgery, fatal PE was reduced from 1.6% in untreated to 0.4% in treated cases.

Safety of UFH in neurosurgery is not sufficiently proved by clinical studies. In pelvic surgery for gynecologic tumors, a series of clinical randomized trials conducted by Clarke-Pearson *et al*.[16] showed that maximum efficacy is obtained by administering 5,000 units of UFH every 8 hours. Administration should start from the time of hospital admission and be maintained for at least 5 days after surgery. Similar results were obtained using PIC.

LMWH

In comparison to UFH, LMWH show favorable pharmacokinetic and pharmacological characteristics. Indeed, a single daily administration is sufficient for an effective antithrombotic protection, without major risk of osteoporosis or heparin-induced thrombocytopenia. Moreover, in general terms, the data available in the setting of DVT prevention after abdominal surgery show similar efficacy usually with a reduced hemorrhagic risk.[19] In the case of neoplastic patients, at least 5 prospective trials including 30-60% cases with tumor have shown a similar efficacy of LMWH in comparison to UFH.[16] Similar results were obtained from studies in which neoplastic cases were considered separately.[16] DVT occurred in 4-15% of cases treated with UFH vs. 2-8% of those treated with different LMWHs including nadroparin, enoxaparin, certoparin, dalteparin and ORG 10172 heparinoid (Orgaran, a mixture of dermatan and heparan sulphate).

A higher incidence of DVT was found in neoplastic patients than in patients without a malignancy, irrespectively of the use of UFH or LMWH. LMWH was generally administered at a dosage twice that used for standard prophylaxis and similar to the dosage employed for orthopedic surgery. Recently, Bergqvist *et al.*[20] have compared 2,500 to 5,000 anti-factor Xa units of LMWH, showing that the higher dose was more effective in preventing DVT (14.9 vs. 8.5%) although at the expense of an hemorrhagic risk twice that with the lower dose. A recent double-blind, randomized trial in neoplastic patients[21] compared the efficacy of 40 mg enoxaparin administered once a day, starting 2 hours before surgery, with standard prophylaxis with UFH administered every 8 hours. A total of 1,115 patients were enrolled and in 631 DVT was assessed using venography. DVT was diagnosed in 18.2% of those treated with UFH vs. 14.7% of those treated with enoxaparin, a not statistically significant difference. Similarly no differences were found in bleeding risk or survival at 1 and 3 months of follow-up.

A double-blind, prospective trial tested the efficacy of nadroparin plus graded pressure elastic stockings in a group of neurosurgical patients (83% had a cerebral tumor). In this study[22] the addition of LMWH resulted in a 29% reduction of DVT incidence (26 vs. 19%) at the cost of a higher incidence of minor bleedings and an alarming increase of major hemorrhages (2.5 vs. 0.8%).

Dermatan sulphate

Dermatan sulphate (DS) is a glycosoaminoglycan that selectively inhibits thrombin through heparin cofactor II. Unlike LMWH, DS also inhibits fibrin-bound thrombin. Furthermore, at least in mouse studies, this agent seems devoid of significant bleeding effect. On the basis of these premises and some promising results obtained in the prevention of DVT in general and orthopedic surgery, an open-label, prospective, controlled study was carried out in Italy.[23] A total of 842 patients undergoing elective oncologic surgery were randomized to receive either 600 mg DS i.m./day starting two days before surgery followed by 300 mg day or to 5,000 units of UFH s.c. every 8 hours starting 2 hours before surgery. Both treatments were maintained for at least 7 days or until the patient was sufficiently ambulant. Venography was available for 521 patients. In cases treated with DS, DVT (almost invariably distal) was diagnosed in 40/267 (15%) vs. 56/254 (22%) in those treated with UFH, showing a significant reduction (32.7%) of the relative risk. Unfortunately, bleeding episodes were similarly distributed in the two groups (around 7%, with 3% of severe hemorrhages). These results clearly deserve confirmation from double-blind, prospective studies.

Chemotherapy

Because of its risk of osteoporosis and secondary thrombocytopenia, UFH is not the best choice for the long-term prophylaxis usually required in patients undergoing chemotherapy for cancer. Similarly, mechanical devices are not of practical use in this setting. LMWHs would offer significant advantages but, unfortunately, these agents have not been properly assessed in these patients. The only available data derive from a study by Levine *et al*.[24] on the use of oral anticoagulants. In this prospective, double-blind study women with stage IV breast cancer were randomized to receive either low dose warfarin (INR 1.3–1.9) or no treatment. Venous thrombosis occurred in 4.4% of women not treated in comparison to in 0.7% of those treated with warfarin, a significant reduction in the incidence of DVT during chemotherapy of 85%. Overall survival was similar in the two groups.

Central venous catheter

Two randomized studies have shown that low intensity oral anticoagulation (OA) is effective in reducing the incidence of DVT due to a CVC.[25,26] Similarly, daily s.c. administration of 2,500 units dalteparin for 90 days was found to be highly effective in the prevention of venographically proven DVT of the upper limb in patients with cancer and a CVC (62% in untreated vs. 6% in treated).[27]

Prevention in other risk conditions

Prophylaxis with mechanical devices or with low doses of UFH or LMWH is always advised whenever a patient affected by tumor is confined to bed or is undergoing even minor surgery.[28]

Treatment and secondary prevention of DVT

When DVT occurs in a patient with a neoplastic disease the immediate approach is similar to that used for most other patients. Therapeutic doses of UFH are administered i.v. for a minimum of 5 days, followed by OA with a target INR between 2 and 3. OA is preferably started within the first 24 hours of heparin treatment. Heparin should be promptly stopped when the desired INR has been maintained for at least 2 days, provided that a minimum of 5 days' treatment has been given. This short treatment with heparin will avoid the risk of heparin-induced thrombocytopenia.

UFH should be given by continuous i.v. infusion. After a bolus injection of 5,000 units, the infusion rate should be adjusted in order to obtain an activated partial thromboplastin time (APTT) between 1.5 and 2 times the control APTT. The average daily dosage is around 30,000 units. An apparent resistance to heparin occurs in some patients due to greatly increased factor VIII or fibrinogen levels. In these case doses higher than 40,000 units/day could be required and the relationship between the level of circulating heparin and APTT prolongation is not always maintained. Measuring heparin with chromogenic anti-factor Xa activity is suggested for these difficult situations.

On the basis of many recently published randomized studies, LMWH could be used in place of UFH. In this case the dose of LMWH should be much higher than that used in the prophylactic setting and one must strictly adhere to the suggestions of the manufacturer. No laboratory monitoring is usually required; moreover the treatment can be prolonged for more than 5 days, due to the very low incidence of heparin-induced thrombocytopenia with these agents. Patients with active tumors remain at risk of DVT and PE and the incidence of recurrences is higher,[29] thus OA should be maintained for a long period of time. A low-intermediate INR around 2 is suggested in these cases after the first months of treatment, especially for patients at higher risk of bleeding.

In case of recurrence during OA, resumption of UFH or preferably LMWH at a therapeutic dosage is suggested for a few days, during which OA intensity is increased in order to obtain an INR level between 3. and 4.5. Especially in patients with a short life-expectancy, we prefer to switch immediately to full doses of LMWH. Caval filter insertion should be considered in case of failure of anticoagulant treatment or in the presence of an exceedingly high risk of bleeding. For the reader interested in a comprehensive review concerning the treatment of thromboembolism in cancer patients the paper by Levine and Lee[30] is suggested.

Anticoagulation and survival in patients with cancer

Sensitive methods show that in cases of active cancer the hemostatic system is almost invariably activated. This activation depends on the many procoagulant activities possessed by neoplastic cells.[31] The activation represents a potentially dangerous and fatal prethrombotic state and seems intrinsically linked to the growth, invasiveness, and metastatic activity of neoplastic cells involved in the angiogenetic process which is required for tumor development. At the end of the 1970s several clinical studies were done in order to assess the role of anticoagulation in slowing tumor progres-

sion and prolonging survival of affected patients. These studies were favored by much exciting and encouraging *in vitro* evidence and many experiments in the mouse that showed an anti-tumor effect of warfarin, heparin and its derivatives or anti-platelets agents. Unfortunately, at the moment, these studies, that we shall briefly review here, do not allow any definitive conclusions to be drawn, despite showing some favorable trends in reducing tumor mortality. Furthermore the beneficial effects, if any, cannot be specifically attributed to the anticoagulant effect or to some, as yet, unknown *cytostatic* properties of the anticoagulant agents employed.

Oral anticoagulation

Setting apart some anecdotal reports, it was the *Veteran's Administration Cooperative Trial*[32] that first explored, in a systematic way, the possibility that anticoagulant therapy could favorably influence the survival of patients with cancer. A survival advantage in comparison to controls treated with chemotherapy only was found in patients treated with both chemotherapy and warfarin. The benefit was evident only for patients with small cell lung cancer. To explain these results the attractive hypothesis was offered that warfarin is able to inhibit the procoagulant activity of the neoplastic cells, which is required for tumor growth and metastasis. Unfortunately, these exciting results were not confirmed by two subsequent studies in which the addition of warfarin treatment to the chemotherapy protocol failed to show any advantage in patients with advanced breast cancer and in patients with small cell lung cancer at a limited stage.[24-33]

However, a recent study by Schulman and Lindmarker[34] has again raised the possibility that OA is able to interfere with tumor development. These authors revisited a study conducted 9 years previusoly in which the optimal duration of OA was assessed in a group of 897 patients with DVT (6 weeks vs. 6 months, with an advantage for the longer period). DVT incidence was analyzed during the follow-up. A similar incidence of new cancers was found during the first year, irrespective of the duration of warfarin treatment, with a standardized incidence risk of 3.4. Surprisingly, during a median follow-up of 8.1 years, cancer developed in 15.8% of those treated for 6 weeks in comparison to in 10.3% of those treated for 6 months. This difference became significant 2 years after the beginning of the treatment, suggesting that OA was able to slow the progression of subclinical cancer. This reduced cancer incidence was not associated with a reduced cancer mortality. Due to the lack of biological plausibility, the lack of confirmation by other studies and some methodological biases[35] this study has not suggested any change in clinical practice. Clearly further studies should be planned.

Heparins

At variance with the contradictory results of clinical trials based on OA, more consistent results are offered by several controlled clinical studies in which LMWHs were used for the treatment of DVT and showed a favorable effect on reducing cancer-related mortality. In contrast, on the basis of a systematic review of available pertinent studies,[36] no evidence of reduced cancer mortality was found after treatment with UFH.

Before reviewing the principal studies, it seems appropriate to emphasize that the knowledge that heparin and its derivatives possess several biological and pharmacological activities, independently of their anticoagulant action carried out through antithrombin or heparin cofactor II, dates back several decades. In particular, we are indebted to Zacharsky and his group for reviewing the several activities potentially important for cancer development. This author repeatedly suggested the need for appropriate clinical trials in this setting.[3-38] We are still lacking this sort of studies. Indeed, all available data are indirect and derive from sub-analyses of neoplastic patients included in studies in which the primary end-point was the comparative efficacy of UFH and LMWH in the initial treatment of DVT or PE.

Within this context two recent prospective studies are of particular interest since they have clearly demonstrated a lower mortality in patients treated with LMWH than in those treated with UFH.[39,40] As subsequently shown by Green *et al.,* by putting together the results of these two studies,[41] the survival advantage in those treated with LMWH was due to a remarkable reduction of cancer-related mortality: 21/67 (31%) in those treated with UFH vs. 7/62 (11%) in those treated with LMWH (p = 0.005). This beneficial effect of LMWH was confirmed by a subsequent meta-analysis of several similar studies, including the two mentioned above.[42,43]

More recently, a more exhaustive formal meta-analysis of all available randomized studies comparing UFH vs. LMWH in the treatment of venous thromboembolism was conducted, by performing a sub-analysis of the data on the survival of neoplastic patients included in the different studies.[44]

To be included the studies had to have no evident methodological biases, sufficient robustness and a minimum follow-up of 3 months after randomization. Nine studies out of 22 potentially available were retained. These trials comprised a total of 3,581 patients with venous thromboembolism of whom 629 (17.6%) were affected by some form of tumor. Of these latter cases, 306 were treated with LMWH and 323 with UFH for 5 to 10 days and OA thereafter for a minimum of 3 months. Among the 629 patients with cancer, 117 (LMWH = 46, UFH = 71) died within 3 months. The three-month mortality odds ratio was 0.61 (90% C.I. 0.40-0.93) in favor of those treated with LMWH. This figure, yielding a crude mortality reduction of 40%, was subsequently adjusted for confounding factors in at least some of the studies. Adjusting for sex, age and primary tumor site, on the basis of 3 studies[39,45,46] did not significantly reduce the odds ratio value (0.75). Similarly, in the only available study including a sufficiently high number of patients,[47] the odds ratio value was estimated to be 0.39, after adjusting for stage at the time of randomization, histology, metastasis sites, type of treatment and duration of disease. However this value did not reach statistical significance due to the limited number of available cases.

In conclusion, initial treatment with LMWH of patients with tumor and venous thromboembolism is definitely associated with an improved survival. This effect is independent of the type of tumor and is not limited to small cell lung cancer, as first demonstrated by the pioneering *Veteran's Administration Cooperative Trial*.[32] As shown by a close examination of the different studies, this beneficial effect is not linked to a proportional reduction in the death rate due to PE or bleeding complications (occurring at very similar rates in those treated with either UFH or LMWH). On the other hand it does not seem sensible to claim an unfavorable effect of UFH on survival probability. However, one has to be cautious in drawing final conclusions, especially considering that none of these studies was specifically designed to test the effect of heparin on cancer-related mortality and that the follow-up is invariably too short.

From a biological perspective it remains hard to understand how a short treatment with LMWH, no longer than 5 to 10 days, could produce such remarkable effects. For the moment, the great interest in the ongoing clinical trials testing this hypothesis specifically is more than justified. The elucidation of the potential but as yet unknown *antitumor mechanism* of LMWHs and their derivatives could represent a major step forward. In animal studies, but not in humans, both UFH and LMWH are able to inhibit experimental metastasis; however it cannot be excluded that only LMWHs possess a potent anti-angiogenetic effect.

Conclusions

The still mysterious interweaving between tumors and thrombosis will continue to stimulate a wide interest in clinicians and researchers devoted to the understanding of cancer biology and pathogenesis of thrombosis. New horizons, well beyond those of the direct control of thrombosis, seem at hand with the use of LMWH. However, for the moment, the main task facing physicians in charge of patients with active cancer is to be aware of all available data, in order to offer their patients the best prevention and treatment. UFH, LMWHs and OA all have their place in the most appropriate treatment, when the fascinating aspects addressed in this paper are fully considered in the single patient. For a more complete review of this issue, the interested reader is referred to a special issue of Thrombosis and Research (Vol. 102, N. 6, June 2001).

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Prevention of venous thromboembolism in surgical patients

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Risk factors for venous thromboembolism (VTE) include commonly encountered clinical situations such as advanced age, prolonged immobility, previous thromboembolism, cancer, trauma, and obesity. Each factor might contribute to the development of venous thrombosis by means of one or more of the pathogenic mechanisms classically described by Virchow (hypercoagulability, vessel damage and venous stasis). Major surgery is a 'complete' risk factor involving all three mechanisms due to (i) release of tissue thromboplastin into the circulation, (ii) direct damage to the vessel wall and (iii) post-surgical immobility.

The fact that many risk factors are often present at the same time in a given patient makes it difficult to calculate the exact risk for VTE; a semiquantitative assessment appears more appropriate. The following is a schematic approach to classify post-surgical thromboembolic risk:[1]

- *Low-risk patients* are those under 40 years old with no clinical risk factors who undergo minor surgery.
- *Moderate-risk patients* are those less than 40 years of age who undergo major surgery or have risk factors.
- *High-risk patients* are those who undergo minor surgery but are over 60 years old or have other risk factors, as well as patients who undergo major surgery at more than 40 years of age or have other risk factors.
- *Very high-risk patients* are those over 40 year olds who undergo major surgery and have additional risk factors such as previous VTE, cancer or thrombophilia. Patients undergoing major orthopedic surgery or those with major trauma or spinal cord injury also belong to this category.

If no antithrombotic prophylaxis is administered, fatal pulmonary embolism occurs at a rate ranging from 0.2% in low-risk patients to 2-3% in very high-risk patients (Figure 1).

From these data it is clear that a more aggressive prevention approach should be used as the patient's thromboembolic risk increases. Thus, while prompt restoration of physical mobility might be sufficient for low-risk patients, different combined strategies might be necessary for very high-risk patients. In this last group, low molecular weight heparin should be used at a higher dosage (i.e. 0.4 mL/die enoxaparin or 0.2-0.3 x 2 mL/die nadroparin) with the additional use of elastic stockings or intermittent pneumatic compression after surgery. Recently discovered antithrombotic agents appear promising in the prevention of VTE in very high-risk patients. A large phase II trial (1,916 patients) evaluated the oral antithrombin agent H376/95 (Astra-Zeneca) in combination with subcutaneous melagatran, which is the active form of the investigational compound, in the prevention of VTE after total hip or total knee replacement surgery. The total incidence of VTE and proximal deep vein thrombosis (DVT) documented with the highest dose of the investigational combination (3 mg melagatran/24 mg H376/95) tested was 15.1% compared with 28.2% in subjects treated with dalteparin sodium, a low-molecular weight heparin (*data presented at the International Congress on Thrombosis in Porto, Portugal, 2001*). Overall, the treatment groups and the dalteparin patients did not differ statistically in terms of increased bleeding. Phase III trials of HP376/95 are currently under way. Another interesting compound, Org31540/SR90107A, is a synthetic pentasaccharide whose risk-benefit ratio for the prevention of VTE appears to be significantly better than that of low-molecular weight heparin after total hip replacement.[2]

Patients undergoing neurosurgery deserve special consideration as their thromboembolic risk is very high; in these patients, hemorrhagic complications could compromise the benefit of surgery or even result in permanent neurologic defects or death. In

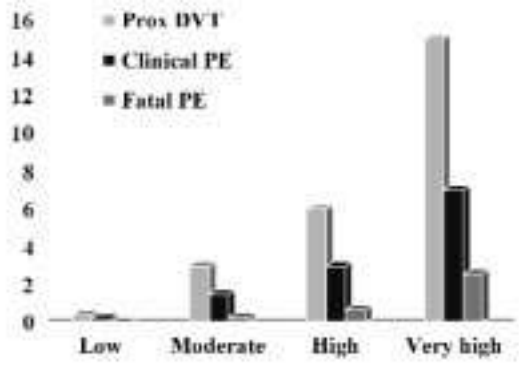

Figure 1. Frequency (%) of thromboembolic events according to risk profile in patients who underwent surgery in the absence of thromboprophylaxis.

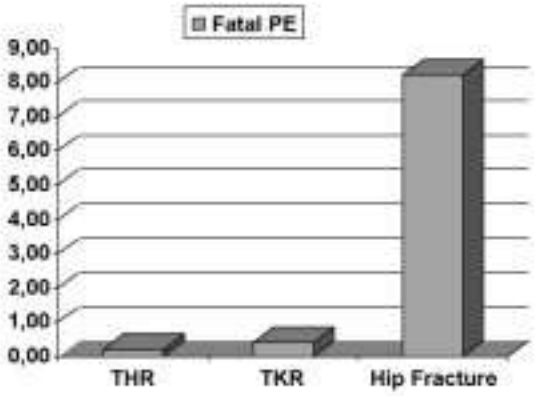

Figure 2. Frequency (%) of fatal PE following orthopedic surgery for total hip replacement (THR), total knee replacement (TKR) or after hip fracture in the absence of antithrombotic prophylaxis.

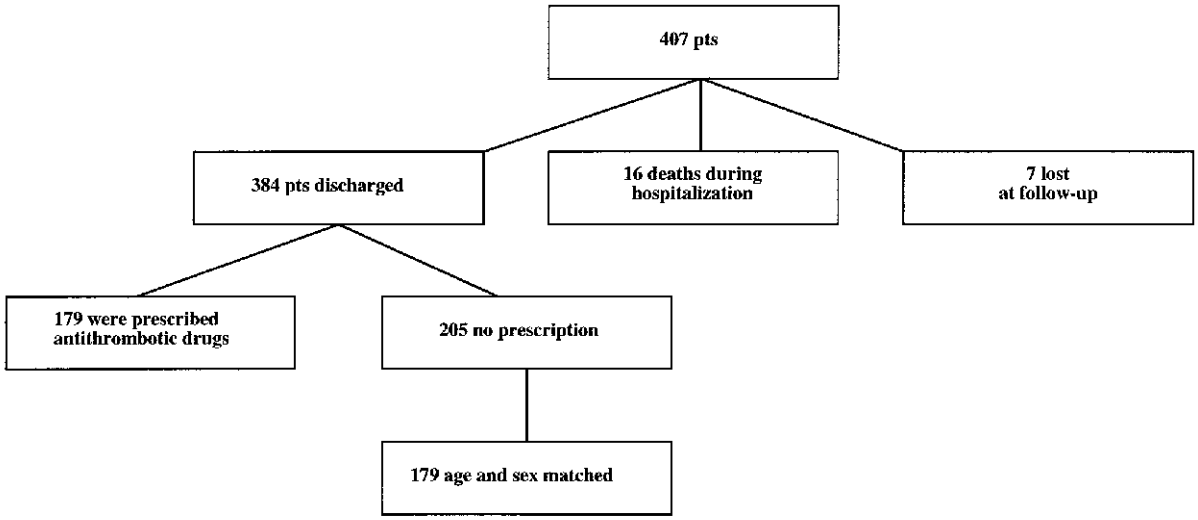

Figure 3. Patients hospitalized for hip fracture in a public health unit (USL 16) of the Veneto region during 1999. Patients continuing antithrombotic treatment after discharge were compared with an age- and sex-matched group of patients who received antithrombotic treatment during hospitalization only.

this clinical setting good results have been obtained by applying elastic stockings or intermittent pneumatic compression. In one recent study the combined use of elastic stockings and post-surgery administration of low-molecular weight heparin was revealed to be superior to the use of elastic stockings alone.[3]

Orthopedic surgery generally exposes patients to a very high risk of VTE. However, while fatal PE occurs at a rate of less than 1% after total hip replacement or total knee replacement, it rises to around 8% after the urgent surgery that follows a hip fracture (Figure 2).

The optimal duration of VTE prophylaxis after orthopedic surgery is a major, still unresolved issue. While treatment for a minimum of 7-10 days is

recommended by experts, prolongation to 3- 4 weeks after discharge appears promising.

We recently addressed this issue by evaluating patients with hip fracture admitted to the hospitals in our area during 1999.[4] As shown in Figure 3, we evaluated a total of 407 patients, 16 of whom died during hospitalization and 7 of whom were lost to follow up. Of the remaining 384 patients, less than 50% were treated with antithrombotic agents after discharge, which generally occurred after 15 days of hospitalization. Treated patients showed a high mortality rate in the three months following discharge in comparison to a group of age- and sex-matched untreated patients. These data suggest that prolongation of antithrombotic treatment beyond the period of hospitalization might be beneficial in such patients. This hypothesis must, however, be confirmed in a randomized clinical trial.

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The management of patients on long-term oral anticoagulant therapy undergoing surgery

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The perioperative management of patients on long-term treatment with oral anticoagulants (OAT) is an ever increasing issue in clinical practice because of the number of patients on OAT requiring surgery.

The more frequent indications for long-term treatment with OAT are atrial fibrillation, prosthetic mechanical heart valves and prophylaxis for thromboembolic disease.[1,2] When surgery is carried out, either in an emergency or electively, the problem arises of balancing the thromboembolic risk with the bleeding risk. The issue is unsettled. No prospective, controlled studies have been published.

The risk of thromboembolic recurrence following discontinuation of OAT was analyzed by Kearon *et al.*[3] The rate of recurrence is highest within one month after proximal deep vein thrombosis (DVT) and declines in the following two months (overall 50%). Continuation of therapy decreases the risk by 80%. The rate of recurrence after recurrent DVT, embolism occurring with atrial fibrillation (AF) and acute arterial thromboembolism is 15%. Non-valvular AF and mechanical heart valve entail a risk below 10%. A fatal event or severe neurological damage are reported in over 60% of the patients with arterial thromboembolism.[3] OAT decreases the risk by 66-75% in all these circumstances.

In the clinical conditions reported above, the risk of thromboembolism is 100-fold higher with surgery: the risk of surgical bleeding with the anticoagulant treatment must be balanced against the thromboembolic risk related to its discontinuation. The data retrieved in the literature are scanty, retrospective and refer mostly to surgery in patients with a prosthetic heart valve. The retrospective study by Katholi in patients with mitral valve prosthesis undergoing surgery confirms that discontinuation of OAT carries an increased risk of thromboembolism; the risk is reduced by continuing treatment but there is a concomitant increase of bleeding.[4] In a subsequent prospective study the authors followed a different policy; in the low risk aortic-valve cases, OAT was discontinued, surgery performed with a compatible INR and therapy resumed two days after surgery; in the high-risk mitral valve prosthesis patients, OAT was discontinued and heparin was administered. The two modalities were safe and effective.[5] On the other hand, Thinker did not observe thromboembolic complications on discontinuation of therapy in a retrospective study of 155 patients.[6] The majority of surgical bleeding complications with anticoagulant treatment are uneventful. Furthermore only a minority (3%) of the major bleeding episodes are fatal. The thromboembolic risk prevails over the bleeding risk.[3] The management of patients on long-term OAT requiring surgery can be outlined from the available information. A comprehensive clinical evaluation of the thromboembolic and hemorrhagic risks is essential: a) the thromboembolic risk inherent to the thromboembolic diseases for which the patient was initially treated; b) the thromboembolic risk inherent to co-morbidity (e.g. neoplasia, heart disease, hypertension, recurrent thrombosis) and other factors such as prolonged bedrest.[7] Major surgery and surgery on particular organs (central nervous system, prostate) carry a higher risk of hemorrhage. Surgical details and anticoagulant treatment in relation to bleeding should be discussed with the surgeon. More than one factor may be associated in the same patient with a cumulative effect.[8]

Table 1. Perioperative treatment of patients on long term OAT.^

Procedures	***Arterial thromboembolic risk*** *Mechanical heart valves* *Non-valvular atrial fibrillation* *Dilated cardiomyopathy*	***Venous thromboembolic risk*** *Previous deep vein thrombosis* *Pulmonary embolism*
Minor surgery	OAT discontinuation Surgery with INR < 1.5 LMWH* from 12 hours after surgery OAT as soon as clinically possible	OAT discontinuation Surgery with INR < 1.5 OAT at the usual doses from the day of surgery
Major surgery	OAT discontinuation, replaced by LMWH* with INR <2.0 Surgery with INR <1.5 LMWH* discontinuation 12 hours before surgery LMWH* from 12 hours after surgery OAT as soon as clinically possible	OAT discontinuation Surgery with INR < 1.5 LMWH* from 12 hours after surgery OAT as soon as clinically possible

*^OAT = oral anticoagulant therapy; *LMWH (body weight adjusted doses): 60 U/kg b.i.d.*

The therapeutic options are discontinuation of OAT to target an INR value less than 2.0 at the time of surgery and its resumption as soon as clinically possible or replacement of OAT with heparin during the perioperative period.[9-12] Subcutaneous low molecular weight heparins (LMWH) are currently used. The advantages of these are a better bioavailability, a more reproducible dose-response curve, their longer half-life and the possibility of carrying out the therapy without laboratory control.[13] An additional advantage is that the patient can be managed as an out-patient. Three recent cohort studies in patients on OAT undergoing surgery or invasive procedures demonstrated that therapy with LMWH is safe, effective and cost-effective.[14-16]

The following criteria are applied in patients on OAT undergoing elective surgery at Niguarda Hospital (Table 1).

Patients with increased arterial thromboembolic risk

Major surgery. OAT discontinued 3-5 days prior to surgery and replaced by nadroparin (60 U/kg s.c. bid) at an INR value less than 2. Nadroparin discontinued the evening before surgery and resumed 12-24 hours after surgery. OAT restarted as soon as clinically possible after surgery. Nadroparin discontinued when the INR is within the therapeutic range for two consecutive days. Vitamin K is not given.

Minor surgery or invasive procedure. OAT discontinued 3-5 days prior to surgery, the procedure carried out with INR<1.5. Nadroparin is started 12-24 hours after surgery associated with OAT and discontinued when the INR is within the therapeutic range for two consecutive days.

Table 2. Anticoagulant treatment and laboratory data in the perioperative period (mean values and SD).

Time of surgery	*Hb g/dL*	*OAT*		*Nadroparin*	
		day	*INR*	*day*	*Dose anti Xa U/kg*
Before	14 (2.5)	Stop –6.6 (2.8)	2.04	Start –5.4 (0.7)	60 x 2
During	14 (1.7)	–	1,18	Stop –12 h	–
After	13.2 (3.7)	Start + 4.5 (5.6)	---	Start 12-24 hours Stop +8.6 (5.6)	60 x 2

Patients with venous thromboembolic risk

Major surgery. OAT discontinued 3-5 days prior to surgery; procedure carried out with INR<1.5, Nadroparin administered 12-24 hrs after surgery associated with OAT. Nadroparin discontinued when the INR is within the therapeutic range for two consecutive days.

Minor surgery, cutaneous or abdominal biopsy, endoscopy, endo-ocular surgery or cataract with topical anesthesia. OAT discontinued 3-5 days prior to surgery; procedure carried out with INR <1.5. OAT at the usual dose restarted the day of surgery

We present data on 34 patients (26 males and 8 females), with a median age of 71 years (range 47-83) undergoing elective major surgery.

Indications for OAT were atrial fibrillation (17 patients), mechanical heart valve prosthesis (9 patients), DVT/pulmonary embolism (9 patients), mitral valve disease with atrial fibrillation (6

patients), congenital cardiopathy (1 patient), and atrial thrombus (1 patient). More than one indication for OAT were present in 9 patients. Pre-existent risk factors, such as acute inflammatory disease (1), neoplasia (7) bed rest > 3 days (3), central venous catheter (1) were associated in 12 patients.

Type of surgery: herniotomy (14 patients), cholecystectomy (6), ileum resection (4), hemicolectomy (3), gastrectomy (3), thyroidectomy (1), mastectomy (1), jejunostomy (1), and hemorrhoidectomy (1).

Results

The anticoagulant treatment and the relevant laboratory data are reported in Table 2. The median post-operative follow-up and the median duration of surgery were 33 days (range 22-50) and 95 minutes (range 40-210), respectively. The mean duration of heparinization was 13.4 days (SD 7.1). No thrombotic events were observed. Three major bleeding episodes occurred (1 in gastrectomy carried out because of pancreatic neoplasia with extensive gastric involvement, 2 in laparoscopic cholecystectomies) and there were 2 minor bleeding episodes (herniotomy). Bleeding occurred during or in the 24 hours after surgery with PT INR values between 1.1 and 1.35 in the absence of heparin treatment.

Our management of patients on long-term oral anticoagulants undergoing surgery follows the outlines published in the literature. Although the number of patients is small, the results suggest that this program, carried out after a complete clinical evaluation of the patients, is adequate for the control of thrombotic and hemorrhagic complications.

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Heparins in Surgery

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Low molecular weight heparins and central neuraxial blocks

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The efficacy and safety of low molecular weight heparins (LMWHs) as post-operative venous thromboembolism prophylaxis has already been demonstrated in many large clinical trials involving more than 200,000 patients. LMWHs are today the reference drugs for the prevention of post-operative venous thromboembolism.[1,2] Central neuraxial blocks (CNB) (subarachnoid anesthesia, epidural anesthesia) are widely used to perform many surgical procedures in several surgical settings (general, orthopedic, gynecologic and urologic surgery). As a matter of fact, spinal or epidural anesthesia, alone or in conjunction with general anesthesia, the so called *blended* anesthesia, might have consistent advantages over general anesthesia alone. Decreased blood loss, rate of venous thrombosis, and rate of graft thrombosis in peripheral vascular surgery are among the major reported benefits for the patients. In addition, the use of subarachnoid or epidural catheters to control post-operative pain may attenuate cardio-respiratory complications and many of the pathophysiologic changes associated with surgery.[3] However this optimistic perspective has in some sense to be tempered. As a matter of fact reports of spinal hematoma occurring after spinal or epidural anesthesia, even if rare, have raised some concerns about the safety of performing CNB in patients treated with LMWHs.[4,5] In a recent letter dealing with CNB and LMWHs, Horlocker stated that "*...we can no longer conclude that spinal bleeding is a rare complication in patients receiving LMWH while undergoing spinal or epidural anesthesia*".[4]

In the present paper, after a short review of the pharmacology of LMWHs, we will focus on the hemorrhagic complications following spinal and epidural anesthesia in patients receiving antithrombotic prophylaxis with LMWHs, specifically addressing the problems of epidemiology of hemorrhagic complications and major risk factors. More recent guidelines to minimize the risk of spinal hematomas in patients undergoing regional anesthesia under some types of anticoagulant-based prophylaxis (anticoagulant, antithrombotic) will also be provided.

Low molecular weight heparins[1,5,6,7]

Heparins (unfractionated heparin, UFH) and heparin derivatives (such as LMWH) are polydisperse heterogeneous mixtures of sulphated polysaccharide chains belonging to the glycosaminoglycan family naturally present in the granules of mast cells of several mammalian tissues.[6] Commercially available heparins are now extracted from porcine mucosa only. The mean molecular weight of UFH is 5,000–30,000 Daltons. UFH acts as an anticoagulant by binding and catalyzing the action of antithrombin (AT) on factor Xa and IIa (thrombin-Thr); the heparin-AT complex inhibits several procoagulant serine proteases, such as factors IIa, IXa, Xa, XIa, and XIIa. Heparin catalytic activity is dependent on both polysaccharide chain length and a specific pentasaccharide sequence within the heparin molecule; this sequence is a high-affinity site for AT. Thirty percent of the UFH molecules contain this pentasaccharide sequence and can catalyze AT; in order to catalyze AT inhibition of factor IIa efficiently, a heparin molecule must contain both the pentasaccharide high-affinity sequence and a chain length of at least 13 additional sugars. In contrast, the pentasaccharide high-affinity sequence is needed to catalyze AT inhibition of factor Xa.[5]

The chemical structure of LMWHs is related to that of the parent drug heparin (UFH). LMWHs are

derived from UFH by chemical or enzymatic depolymerization; fragments are approximately 1/3 the size of the parent molecule. LMWHs have a mean molecular weight ranging between 4,000 to 6,000 Daltons and a polysaccharide chain length of 13–22 sugars. Nadroparin (MW 4,500) and enoxaparin (MW 4,200) are the two most extensively prescribed LMWHs in Italy nowadays.

Depolymerization of UFH into low molecular weight fragments yields five major changes in its action, mainly due to the reduced binding of LMWHs to proteins or cells (Table 1):[1,5]

1. inactivation of factor IIa is reduced (reduced binding capacity), but ability to inactivate factor Xa is completely retained. A reduced affinity for von Willebrand factor is also evident, possibly contributing to the lower bleeding tendency compared to that produced by equivalent anticoagulant doses of UFH;
2. non-specific protein binding is reduced and this contributes to the excellent bioavailability (90%) after subcutaneous administration. The dose-response relationship is highly predictable when given on a weight-adjusted basis. When given in prophylactic doses, LMWHs do not prolong aPTT beyond the upper normal limits, making neither laboratory monitoring nor dose adjustment necessary;
3. binding to macrophages and endothelial cells is reduced: plasma half-life is increased (4–6 hours) and elimination is mainly via the renal route (non-saturable mechanism). Plasma half-life is longer in patients with renal failure but recommendations for reduced dosage in renal failure patients are not available as yet;
4. binding to platelets and PF4 is reduced, possibly explaining the reduced rate of heparin-induced thrombocytopenia (HIT);
5. the rate of binding to osteoblasts is possibly reduced, leading to a reduced rate of osteoporotic lesions.

LMWHs have a dose-dependent predictable antithrombotic effect that it can be accurately assessed by measuring the anti-Xa activity. Six hours after the last dose, the target therapeutic level to prevent venous thrombosis should be in the range of 0.1-0.2 anti-Xa U/mL (rarely is this assessment performed in everyday practice, but it could be advisable in selected cases). Peak anti-Xa activity occurs 3 to 4 hours after a subcutaneous injection and 12 hour anti-Xa levels are approximately 50% of peak levels. Thus, the plasma half-life of LMWHs is approximately 2 to 4 times longer than that of UFH.

Table 1. Depolymerization of UFH into low molecular weight fragments yields five major changes in its action, mainly due to the reduced binding of LMWHs to proteins or cells (from ref. 1, modified).

Reduced binding to:	*Biological effect*	*Effects*
Thrombin	Reduced anti-IIa/anti-Xa ratio (1:2–1:4)	Unknown
Proteins	More predictable dose-response relationship (anticoagulant effect)	Anticoagulant monitoring not needed
Macrophages and endothelial cells	Renal clearance prevalent (longer half-life in renal failure)	Longer plasma half life Once daily subcutaneous administration effective
Platelets and Platelet factor 4	Reduced incidence of heparin dependent antibody	Reduced incidence of HIT
Osteoblasts	Reduced activation	Less chance of osteopenia

The anticoagulant effect of LMWHs is partially reversed by protamine sulphate (1 mg for 100 anti-Xa U LMWHs; anti IIa activity is completely reversed, anti-Xa only partially).[5,7] LMWHs produce their major anticoagulant effects by activating AT; the activation is mediated by the high-affinity pentasaccharide, present in less than 1/3 of the molecules. To form the ternary complex H-AT–Thr a minimum chain length of 18 sugars (including the pentasaccharide sequence) is needed: less than 25-50% of the polysaccharide containing-LMWH molecules above this critical length are able to inactivate factor IIa. In contrast, all LMWHs containing the high affinity pentasaccharide catalyze factor Xa inactivation. The anti-Xa to anti-IIa ratio (anti-Xa/IIa) for LMWHs is thus 4:1 to 2:1, whereas the anti Xa/IIa ratio for UFH, which contains at least 18 saccharide units, is 1:1.[4,6] However, as stressed by Tryba,[11] it must also be considered that several studies have suggested that LMWHs have effects on the fibrinolytic pathway, platelet function and fibrinogen binding. As a matter of fact, according to Bacher *et al.*,[23] LMWHs exhibit a dose-dependent lytic activity which can be compared to clinically effective doses of urokinase, an activity not present in UFH.[23] This profibrinolytic activity of LMWHs could be a result of tPA release, which is much higher in patients receiving LMWHs than in patients being treated with UFH.[11,23] Moreover, binding of fibrinogen to platelets is significantly lower in the presence of LMWHs and endothelial platelet adhesion in the presence of endothelial damage is also reduced. In this setting, the combined effect of platelet inhibition, reduced fibrino-

gen binding and profibrinolytic activity associated with LMWHs may result in an increased risk of bleeding in case of vascular lesions while performing central neuraxial blocks (needle placement, catheter positioning or removal).

In general surgical patients, once daily administration of LMWHs by subcutaneous injection has been associated with a reduced rate of cardiovascular mortality when compared with placebo; it was slightly more effective than UFH (5,000 IU twice or three times daily) in preventing postoperative venous thrombosis without any difference in bleeding.[1] In major orthopedic surgery, the prevalence of deep venous thrombosis (detected by venograms) ranges from 50 (total hip replacement, THR) to 80% (total knee replacement, TKR).[5] LMWHs provide safe and effective prophylaxis against venous thromboembolism in both THR and TKR (incidence of thrombosis reduced by 60–70% vs control group), without major differences in bleeding complications.[1] It has to be underlined, however, that the efficacy varies according to the surgical procedure. LMWHs were consistently more effective than other methods of thromboprophylaxis when administered to patients undergoing TKR surgery.[5]

Regional anesthesia, anticoagulation and hemorrhagic complications

Spontaneous spinal hematomas with or without the presence of anticoagulant or antiplatelets drugs have already been reported and they are of special interest for the anesthesiologist. Spinal hematoma resulting in permanent paraplegia is a rare but feared complication of spinal or epidural anesthesia. Spinal cord compression associated with spinal bleeding may be caused by vascular trauma from needle or catheter placement into the subarachnoid or epidural space: it may cause cord ischemia, rapidly evolving towards irreversible paraplegia.[9,10] Neoplastic diseases or pre-existing vascular abnormalities are sometimes associated pathologies. Bleeding is more frequent in the epidural space because of the presence of a dilated venous plexus, but it can occur in the subarachnoid, subtotal or extradural spaces; in this setting arteries may be the major bleeding source.[8,9] Although spinal or epidural needle trauma can cause spinal bleeding even in the absence of coagulation disorders, the risk of clinically significant hematoma is extremely rare in this setting; in contrast, it seems much more common in the presence of hemostatic abnormalities or in patients receiving anticoagulant drugs after the neuraxial block.[11]

The typical presentation of the development of a spinal hematoma is a severe localized or radiating back pain with lower limb weakness progressing to flaccid paralysis, numbness and paresthesia progressing to sensory loss, and sphincter disturbances (urinary retention, bowel incontinence). It may occur within hours (10-14 hours) or even days (8-10) or weeks (2-3) after the neuraxial block.[10–12] Painless hematoma is however possible, as the onset of cord compression and its related symptoms may take days. The first complaint is usually muscle weakness (46%), followed by back pain (38%) and sensory deficits. Early workup of a suspected spinal hematoma should include prompt neurosurgical consultation, confirmation of the diagnosis by MRI (CT scan is much less specific and sensitive), urgent decompression laminectomy and hematoma evacuation. Surgery should be performed within 8-12 hours after the onset of symptoms to maximize neurologic outcome (mortality less than 30%, complete neurologic recovery in 20-40% of the cases).[10] Neurologic recovery is unlikely if surgery is postponed more than 8-12 hours.[5,9,10] Strict neurologic monitoring for early signs of cord compression is mandatory in the early post-operative period.

The incidence of neurologic dysfunction resulting from hemorrhagic complications after CNB is unknown; according to the available literature, the incidence could be estimated between 1:150,000 after an epidural technique and 1:220,000 after spinal anesthesia.[8-11] Very similar figures were proposed in a recent report from the *Swedish Patient Injury Claims Department*. Reviewing the neurologic complications after CNB between 1997 and 1999, the incidence of spinal hematoma was 1/30,000 after epidural anesthesia and 1/200,000 after spinal anesthesia.[12]

A more exhaustive and larger review dealing with regional anesthesia and hemorrhagic complications was proposed by Vandermeulen *et al.* This included studies published from 1904 to 1994.[13] They found 61 cases of spinal hematoma associated with spinal (15 cases) or epidural anesthesia (46 cases, 32 with indwelling catheters). Hemostatic abnormalities were present in 42 cases (68%). Among these patients, 70% (30/42) had received intravenous or subcutaneous heparin (26 patients) or LMWH (4 patients) in the perioperative period, and 12 patients had evidence of hemostatic disorders (thrombocytopenia, coagulation abnormalities) or were treated with antiplatelet medications, oral anticoagulants, thrombolytics or dextran 70 imme-

diately before or early after the CNB. Complicated needle or catheter placement was reported in 30 patients (15 patients *difficult* placement; 15 patients bloody tap). Thus, in almost 90% of the cases (53/61) either hemostatic abnormalities or technical problems were reported.

Both catheter removal and its timing seem to be critical points. As a matter of fact, among the 32 patients who experienced bleeding complications after epidural catheter placement, 15 had a spinal hematoma immediately after removal of the catheter. Thus, according to the available literature, critical factors in the development of spinal bleeding appear to be catheter removal and patients' hemostatic profile at the time of catheter removal.[5,12]

Significant risk factors associated with spinal hematoma while performing CNB seem to be the following:[27]

1. anatomic abnormalities of the spinal cord or vertebral column;
2. impaired hemostasis (associated pathologies, pharmacological manipulation);
3. technical problems (difficult needle/catheter placement; bloody taps);

Thus, the point to be addressed is the safety of performing a CNB in patients receiving anticoagulant medications before or after the surgical procedure.

Intravenous and subcutaneous heparin

The safety of systemic administration of heparin after CNB was evaluated by Rao *et al.*[14] in a cohort of 4,015 patients undergoing peripheral vascular surgery under continuous epidural anesthesia (3,164) or spinal block (847). Exclusion criteria were pre-existing coagulation abnormalities, thrombocytopenia, and pre-operative anticoagulation therapy. In the case of a bloody tap (4 cases) surgery was postponed to the next day and patients were given general anesthesia. Intravenous heparin was always administered 50 to 60 minutes after catheter placement in dosages able to maintain an activated clotting time (ACT) twice the baseline value (average heparin dosage 2,500 U; mean ACT 170 seconds). The heparin dose was repeated every 6 hours throughout the period of anticoagulation therapy. Catheters were removed the next day, 1 hour before the administration of the maintenance dose of heparin. No patient developed signs or symptoms of spinal cord compression in spite of catheter placement followed by systemic heparinization. Close monitoring of heparin activity and proper timing of catheter placement and removal were considered crucial for the safety of the procedure. No neurologic sequelae were reported by Baron *et al.* in a study involving 912 patients undergoing peripheral vascular surgery under continuous epidural anesthesia and transient intraoperative anticoagulation (heparin: 70 U/kg bolus followed by 15 U/kg/h, infusion; ACT longer than 100 seconds).[15] The catheters were removed immediately after surgery.

Epidural analgesia after cardiac surgery is a relatively new and challanging clinical setting.

In 1997 Chaney *et al.* reviewed the literature addressing the problem of post-operative epidural anesthesia and analgesia in cardiac surgery, in which patients are fully anticoagulated during cardiopulmonary bypass (300-400 IU/kg; 20,000-30,000 IU for a 70 kg patient). The review included 15 studies dealing with intrathecal opioids (771 patients) and 13 studies including 417 patients under epidural analgesia. In none of these reports was an epidural hematoma found as a post-operative complication. It must be underlined that catheters were placed the night before surgery and as long before heparinization as possible; catheter removal was performed after normalization of the hemostatic profile.[3,16]

Low-dose subcutaneous UFH has been administered for years for thromboprophylaxis in major thoracoabdominal surgical procedures. Reviewing more than 5,000 cases, no spinal hematomas were reported in patients who had received subcutaneous UFH and undergone spinal or epidural blocks. It seems possible that, in spite of the widespread use of CNB, spinal hematoma associated with this procedure after low dose UFH is as an extremely rare event. It should, however, be emphasized that the risk can be increased in debilitated patients, after prolonged therapy or in the presence of other anticoagulants.[10,17]

LMWHs and CNB

LMWHs were introduced in Europe for thromboprophylaxis both in surgical and medical settings in the late eighties.[11] In two reviews, Bergqvist *et al.* examined the association between CNB and LMWH administration.[18] They identified more than 9,000 patients in 19 studies who safely received spinal or epidural blocks under LMWH prophylaxis. In the same paper the authors noted that pharmaceutical companies estimated that several million patients had received LMWH association with CNB, and only one case of spinal hematoma had been reported. Even if these results led the authors to

conclude that the combination of CNB and LMWHs appeared safe, the accompanying editorial raised caution and concerns on this statement.

The trauma associated with intrathecal catheter (22G) positioning was prospectively investigated monitoring erythrocyte counts in cerebrospinal fluid (CSF) in 66 patients undergoing vascular, urologic or orthopedic surgery under continuous spinal anesthesia.[19] Enoxaparin was administered to orthopedic patients (2,000–4,000 IU) whereas vascular patients received i.v. heparin intra-operatively (100 IU/kg); urologic patients, receiving no anticoagulants or antiplatelets in the perioperative period, served as controls. Seventeen patients (10 treated, 7 controls) had more than $100x10^6$/L erythrocytes and macroscopically blood-tinged CSF, but no patient had signs or symptoms of spinal hematoma. The following conclusions were drawn: intrathecal catheter placement has to be weighed against the risk of spinal bleeding; perioperative administration of UFH and LMWH was not associated with an increased risk of spinal hemorrhage in the presence of continuous spinal anesthesia.[19] Extensive and safe clinical practice in Europe suggested that there was not an increased risk of bleeding in patients receiving neuraxial anesthesia while under LMWHs. Practice guidelines for safe performance of neuraxial blocks associated with LMWHs were proposed by Tryba in 1993 and 1997; the estimate of spinal bleeding associated with enoxaparin was reported to be in the range of 1:2,250,000.[11] Practice guidelines proposed by Tryba[11] recommended needle and catheter placement to be delayed for at least 10–12 hours after the last dose of LMWH. Similarly, catheters should be removed at least 10 to 12 hours after the last LMWH dose; subsequent dosing should be delayed for at least 2 hours after catheter removal. However, the release in May 1993 of enoxaparin in US/Canada for surgical thromboprophylaxis was associated with an increased rate of spinal hematoma in patients who underwent surgical procedures in the presence of LMWH thromboprophylaxis.[10,20] In correspondence with the FDA[20] on the subject of spinal and epidural hematoma and LMWH, Wysowski *et al.*[20] reported on 43 patients who had, from 1993 to 1998, spinal hematoma or bleeding complications after administration of enoxaparin (the only approved LMWH in US). Twenty-eight patients underwent urgent decompression, 16 had permanent neurologic damage; 36 of the 43 patients had CNB for surgery and received enoxaparin for deep venous thromboprophylaxis at the recommended dose of 30 mg every 12 hours (in two cases the dosage was exceeded). Placement of epidural catheter was reported in 26 cases (72%); in 15 patients catheters were left in place and 6 patients developed bleeding after catheter removal; 16 of the 43 patients had concomitant medications known to increase the risk of bleeding. Higher dosage, epidural catheters, altered hemostasis before administration of LMWH, and administration of medications able to increase bleeding (anticoagulants, antiplatelets) were considered risk factors.[20] The last systematic review performed in 1998 included 52 cases of epidural hematomas associated with CNB and LMWHs: 12 cases were reported in Europe and 40 in the USA. Among them, 34 were associated with epidural catheter placement, and 14 with spinal attempts.

In the latest review of the safety profile of enoxaparin (Lovenox, Aventis) performed by the FDA, there were 80 cases of spinal hematoma after CNB in patients under enoxaparin prophylaxis (MedWatch, FDA Safety, Jan 2002). Of the 12 European cases, 6 were associated with medications able to alter platelet function and 5 with difficult or bloody placement. In contrast, 26 of the 40 cases from the USA were associated with epidural (10 after removal of the catheter) and 10 with spinal anesthetics (among these cases, 3 were receiving antiplatelet medications, 1 i.v. heparin during surgery after LMWH administration and 6 were administered LMWH on the day of surgery).[3] According to Horlocker, in patients undergoing orthopedic surgery in USA, the frequency of spinal hematoma associated with LMWH could be 1:1,000 to 1:10,000 regional anesthetics.[8] In a recent study by Schroeder, the incidence of spinal hematoma after enoxaparin would be 1:3,100 after epidural anesthetics and 1:41,000 after spinal anesthetics.[21]

The comparison of the European and US data highlights a striking difference in bleeding incidences. According to Tryba[11] and Horlocker,[10] the only apparent explanation for the higher incidence of bleeding in the US experience is the higher daily dosage of enoxaparin: 30 mg twice daily in USA, 20 to 40 mg once daily in Europe. However the timing of the administration seems to be relevant too. The first dose in Europe is usually administered the night before surgery (at least 10-12 hours before surgery) or 12 hours after surgery without major changes in cardiovascular complications. This dosage schedule results in a similar thromboembolic efficacy to that of a dosage schedule starting the morning of surgery.[11] The US schedule may lead to a much higher anticoagulant activity (peak activity) while performing the invasive procedures (needle and/or catheter placement).[5,10,11]

Conclusions

Under what conditions is it safe to perform an epidural or spinal anesthesia in patients who are or will be anticoagulated? This seems to be a question that has no clear-cut answer as yet.

Perhaps regional anesthesia can be safely performed in patients receiving anticoagulants (and particularly LMWHs) if appropriate peri-operative precautions, strict post-operative neurologic surveillance and prompt diagnostic work-up in the case of complications are followed and performed. Knowledge of pharmacology of the various anticoagulant agents and their interactions (able to increase the risk of spinal bleeding) are critical points in designing the safest and most effective anesthetic plan in this setting. Everyday practice should follow available scientific data, good quality clinical practice and last but not least, an evaluation of risk-benefit ratio for every single patient: the risk of spinal hematoma outweighs the potential benefits of CNB.

Guidelines and recommendations on performing CNB in the presence of anticoagulant medications (ASRA Consensus Conference, 1998; Horlocker, 1998; Tryba, 1997)

The decision to perform a CNB on a patient receiving anticoagulants (oral medications, standard heparin and LMWH) or antiplatelet medications must always be made weighing the benefits of the regional anesthesia in a specific patient against the small but definite risk of spinal bleeding. As a matter of fact the risk of spinal hematoma outweighs the potential benefits of central neuraxial blocking in patients:[8]

— who have known coagulopathies;
— who suffer from significant thrombocytopenia;
— who have had thrombolytic therapy within the previous 24 hours;
— who are fully anticoagulated.

Needle and catheter placement should be as atraumatic as possible. Small gauge needles and minimal catheter insertion distances (3-4 cm) should avoid major trauma to epidural or subarachnoidal vessels.[22] Common to CNB performed in any patient under anticoagulation is *careful monitoring of the neurologic status* for the first 24–48 hours after the block (in selected cases even for 96 hours) in order to avoid delay both in the diagnostic workup of spinal bleeding and in its rapid surgical decompression. The same recommendations are proposed for catheter removal (longer monitoring in the case of oral anticoagulants). Short-acting local anesthetics should be used in patients at risk of spinal hematoma, to allow immediate neurologic evaluation in the post-operative period.

Table 2. Recommended time intervals and laboratory tests for UFH, LMWHs and oral anticoagulants that should be considered for patients with CNB *(Tryba, 1998, modified)*.

	Hours before the block	*Hours after block (to give heparin)*	*Lab tests*
Standard heparin (low dose)	4 h	1 h	Platelets (> 5 dd)
Standard heparin (high dose)	4 h	1-2 h	APTT,ACT, PLT
LMWH (low dose)	10-12 h	4-8 h	Platelets (> 5 dd)
Coumadin	Several days	After catheter removal	PT, INR

Oral anticoagulants

(Keyser Enneking and Benzon; Reg Anesthesia and Pain Med, vol 23, 140-5, 1998).

Few data exist on the risk of spinal hematoma in patients with epidural catheters while under oral anticoagulants (OA). CNB should not be performed in fully anticoagulated patients. The optimal duration of having a catheter in place and the timing of its removal are still controversial. After having evaluated the proper (and/or mandatory) indication for CNB in patients on OA, the ASRA Consensus Conference panel gave the following recommendations for this setting:

1. patients on chronic OA: therapy must be stopped and INR measured before the start of a CNB. Regional anesthetic must be started only after normalization of INR;
2. heparin and antiplatelet medications (including NSAIDs) may increase the risk of bleeding if concomitantly administered (and INR is not influenced);
3. for patients who had an initial OA dose before surgery, INR must be checked prior to the CNB if the first dose has been given 24 h earlier or a second dose has been administered;
4. patients receiving low-dose OA during epidural analgesia should have their INR monitored daily and checked before catheter removal if initial doses of OA were given 36 hours or more previously;
5. OA dosage should be decreased before removing an epidural catheter. Neurologic monitoring should be continued for 24-48 hours after catheter removal and if the INR was longer than 1.5 at the time of catheter removal;
6. an INR>3 should prompt a reduction/withholding of the OA in patients with epidural catheters;

7. no recommendation is available for removal of the catheters in patients with therapeutic levels of OA.

Antiplatelets drugs

(Urmey and Rowlingson, Reg Anesthesia and Pain Med, 1998, 23:146-51)

1. Antiplatelet drugs (AD) alone do not represent an additional risk for the development of spinal hematoma in patients undergoing CNB. The same opinion was expressed concerning NSAIDs.
2. No data are available on the combination of AD and NSAIDs.
3. There is an increased risk of spinal bleeding if AD or NSAIDs are given in conjunction with LMWH, AO, or UFH (1/4 of the cases of spinal hematoma were associated with LMWH and antiplatelet agents).

Fibrinolytics

(Rosenqvist RW, Brown DL, Reg Anesthesia and Pain Med, 1998, 23:152-6)

1. Patients who have received fibrinolytics within 24 hours are at extremely high risk of *adverse neurologic bleeding* in the case of CNB.
2. Two cases of spinal hematoma in patients who had epidural catheters concomitantly with arterial thrombolysis (femoral artery) were reported. CNB are strongly discouraged in this setting.(*...patients receiving fibrinolytic and thrombolytic agents should be cautioned against receiving spinal or epidural anesthetics except in highly unusual circumstances...*).
3. No data are available to outline the length of time neuraxial blocks should be avoided after discontinuation of these drugs (original contraindications to thrombolytic drugs suggested avoidance of these drugs within 10 days of puncture of non-compressible vessels).
4. In case of CNB in this setting neurologic monitoring must be very strict, for an appropriate time and with a very short interval between checks (even every 2 hours). In the case of catheter infusion the infusion should be limited to drugs minimizing sensory or motor block.
5. No recommendations are available for catheter removal. Measurements of fibrinogen could be helpful.

Standard heparin (UFH)

Liu SS and Mulroy MF, Reg Anesthesia and Pain Med 23:157-63, 1998; Tryba M, Reg Anesthesia and Pain Med, vol 23, 178-82, 1998.

1. Administration of subcutaneous (sc) UFH alone (5,000 IU) does not seem to increase the risk of bleeding in CNB (unless very prolonged utilization). Blocks are safer if performed 4 hours after UFH administration. In the case of CNB performed before UFH administration, it seems safer to delay sc UFH administration by at least 1 hour.[11]
2. Therapeutic dosages of UFH are associated with an increased risk of bleeding; in this setting no neuraxial block or catheter removal should be performed.
3. i.v. UFH (up to 5,000 IU) is not considered an absolute contraindication; careful post-operative neurologic observation is, of course, mandatory in this setting.
4. i.v. UFH should be administered at least 1 hour after the block (single shot/catheter placement).
5. The heparin dosage should be adjusted in order to avoid aPTT (or ACT) longer than twice the normal value.
6. In case of catheter removal, this procedure should be performed:
   a) at least 1 hour before the subsequent i.v. heparin dose.
   b) 2 to 4 hours after the last i.v. UFH administration.
7. If systemic anticoagulation is begun with a catheter in place, it is recommended that catheter removal is postponed for 2 to 4 hours (see above) following infusion discontinuation. Prior reassessment of coagulation profile is advisable.
8. Appropriate neurologic monitoring in the postoperative period (early detection of motor blockade) is recommended.
9. The use of a minimal concentration of local anesthetics to enhance the detection of spinal hematoma should be considered.
10. In the case of a difficult, bloody or traumatic procedure (bloody tap) the risk of spinal hematoma is increased and cancellation of surgery, although not mandatory, should be considered (some authors suggest a 24-hour postponement of surgery and general anesthesia). Otherwise (decision to proceed), the surgeon should be aware of the risk and strict neurologic and hemostatic monitoring are warranted for 48 hours. In this particular setting European guidelines (*Tryba, 1998*) are more conservative: in the case of a bloody tap, surgery should be postponed for at least 12 hours and catheters inserted the night before surgery.
11. Low dose i.v. UFH (2,000 IU) is effective in preventing thromboembolic complications in high risk orthopedic surgery, does not result in

altered hemostasis and should not be considered as a contraindication to central neuraxial block (*Tryba, 1998*).
12. Prolonged therapeutic anticoagulation, particularly if combined with other anticoagulants or antiplatelet drugs, appears to increase the risk of spinal hematoma.
13. It must be stressed again that concurrent medications able to affect the hemostatic profile may increase the risk of bleeding complications for patients receiving standard heparin (OA, AD, NSAIDs, LMWHs).

LMWHs

There are two different clinical perspectives in the USA and in Europe concerning LMWH thromboprophylaxis. In the USA enoxaparin is given at higher dosages (30 mg twice a day) than in Europe (40 mg every 24 hours).

The following recommendations were proposed by the panel in order to minimize the risk of spinal hematoma; complete elimination of the risk seems to be impossible. Both ASRA recommendations and those of the *German Society of Anesthesiologists* are presented.

LMWHs–1

Horlocker TT, Wedel D. Reg Anesthesia and Pain Med, vol 23, 164-77.

1. Monitoring anti-X level is not recommended (not predictive of the risk of bleeding).
2. Patients receiving LMWH can be assumed as having altered coagulation.
3. The risk of spinal hematoma is increased if LMWHs are used together with antiplatelets, anticoagulants, dextran.
4. The presence of blood during needle and catheter placement does not necessitate postponement of surgery. In this setting LMWH should be delayed for 24 hours post-operatively. Traumatic needle placement may increase the risk of spinal hematoma: this must be discussed with the surgeon.
5. In patients receiving pre-operative administration of LMWH, the safest neuraxial technique seems to be single dose spinal anesthetic. The first dose should preceed the central neuraxial block by at least 10-12 hours (night before surgery). In patients receiving higher doses of LMWHs (1 mg/kg twice daily), a longer delay (24 hours) is recommended.
6. It is mandatory to make the anesthesiologist aware of any change of this schedule: administration of LMWH 2-4 hours before the block has the highest incidence of bleeding complications (general surgery).
7. Patients with post-operative initiation of LMWH thromboprophylaxis may safely undergo CNB and/or catheter placement. LMWH should be started 24 hours after surgery and only in the presence of adequate hemostasis. Epidural catheters must be removed before initiation of LMWH thromboprophylaxis. In the case of a continuous technique, the epidural catheter should be left in place overnight and removed the following day. The first dose of LMWH after catheter removal should be delayed for at least 2 hours.[5]
8. The time of catheter removal is of critical importance. Catheter removal should be delayed for at least 10-12 hours after a dose of LMWH. A true normalization of the patient's coagulation profile could be achieved by not administering the evening dose of LMWH and removing the catheter the following morning (24 hours after the last LMWH dose). Subsequent dosing should not occur for at least 2 hours after catheter removal.
9. The coagulation profile could be considered normalized 24 hours after the last LMWH dose.

LMWHs–2

Tryba M, Reg Anesthesia and Pain Med, vol 23, 178-82, 1998.

1. Experience from a study performed in a high-risk population (subjects undergoing total hip replacement) suggested that higher dosage of LMWH (30 mg twice daily) only influenced the risk of wound hematomas but did not decrease the risk of thrombotic complications. In contrast, enoxaparin < 40 mg daily is not associated with an increased risk of spinal bleeding provided that the following recommendations are implemented: a) the interval between LMWH administration and the neuraxial block is >10-12 hours; b) the next LMWH dose is given not earlier than 4-8 hours after the puncture (interval of 8-12 hours until plasma peak concentrations occur); c) epidural catheters are removed at least 12 hours after the last dose of LMWH.
2. Limited data suggest that available LMWHs do not differ significantly in their risk of provoking spinal hematoma.
3. Dextrans seem to increase the risk of spinal bleeding when associated with LMWHs.
4. In patients scheduled for neuraxial block, thromboprophylaxis must be started the night

before surgery and continued the night of the day of surgery (24 hours after the first dose). This schedule yields a similar thromboembolic prophylaxis efficacy as a dosage starting on the morning of surgery.

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