Perspectives on antithrombotic agents: from unfractionated heparin to new antithrombotics

GIANCARLO AGNELLI, FRANCESCO SONAGLIA
Division of Internal and Cardiovascular Medicine, Department of Internal Medicine, University of Perugia, Italy

Background and Objectives. 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.

Evidence and Information Sources. Low molecular weight heparins (LMWHs) are produced by the depolymerization of UFH. LMWHs have pharmacologic 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.

Perspectives. 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.

© 2002, Ferrata Storti Foundation

Key words: unfractionated heparin, low molecular weight heparins, venous thromboembolism, acute coronary syndromes, direct antithrombins, pentasaccharide.
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. 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 and large clinical trials indicate that LDUFH also reduces the occurrence of fatal PE. 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. 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. Two studies showed the superiority of nadroparin over LDUFH. 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.

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.

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. 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. 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 post-operative VTE despite prophylaxis. Mechanical methods have a moderate efficacy, making pharmacologic 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 or oral anticoagulants 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. 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. 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. 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. 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. 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. Dalteparin 5,000 anti-Xa IU was compared with placebo showing a moderate efficacy (DVT 30 and 58%, respectively). 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. 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. A recent trial compared enoxaparin, dalteparin and danaparoid in patients with hip fracture. 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 greatly 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%). These results have been confirmed by a recent overview of randomized trials evaluating prolonged out-of-hospital prophylaxis with LMWHs after THR.

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). 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.

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. 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. More recently, an updated meta-analysis comparing the efficacy and safety of UFH and LMWHs was published. Thirteen studies were included in the analysis. 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. However, the limitations of UFH led to the investigation of new agents such as LMWHs and direct thrombin inhibitors. Five large clinical trials investigated three LMWHs (dalteparin, enoxaparin, and nadroparin) in patients with acute coronary syndromes without ST elevation.

In the FRISC trial, 1,506 patients were randomized to dalteparin or placebo within 72 hours from the onset of symptoms. 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. 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. 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. 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, 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. 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. 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. 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. 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. 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. 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
In the GUSTO IIa study, patients with myocardial infarction were randomized to UFH (5,000 IU bolus followed by a 24-hour infusion of lepirudin, 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 the UFH group, but this difference was not statistically significant. The incidence of the secondary end-point of cardiovascular death, myocardial infarction or refractory angina, was significantly lower in lepirudin-treated patients than in UFH-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 a 24-hour infusion at a target aPTT from 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=0.024). 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=0.003).

Lepirudin was investigated in OASIS 2, an international, large-scale, randomized, double-blind trial conducted in patients with acute coronary syndromes without ST elevation. 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 the UFH group, but this difference was not statistically significant. The incidence of the secondary end-point of 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 a 24-hour infusion at a target aPTT from 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=0.024). 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=0.003).
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. 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. In the first trial, patients were treated with one of 4 doses of lepirudin. 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 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). 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; 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 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. 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. 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-
Hirulog was investigated in a potential role as a new anticoagulant option in patients with acute myocardial infarction treated within 96 hours by 30%. Bivalirudin seems to have but did reduce the rate of adjudicated reinfarction Hirulog did not reduce mortality compared to UFH, and mild bleeding was higher in the hirulog group. Similar in both groups. The incidence of moderate 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=0.001). 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. 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 produg (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. 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. 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. 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. 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, such as DX 9095a, 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. The dose of pentasaccharide was 3.0 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 patients undergoing elective TKR 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 TKR 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. 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. 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-
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). 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. 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

References


New perspectives on antithrombotic agents


85. Eriksson BI, Ögren M, Agnelli G. The oral direct thrombin inhibitor ximelagatran (formerly H 376/95) and its subcutaneous form melagatran compared with enoxaparin as thromboprophylaxis after total hip or total knee replacement. Thromb Haemost 2001 Suppl 1638a [abstract].


