Prevention and treatment of venous thromboembolism in the elderly patient

Enrico Tincani[1]
Mark A Crowther[2]
Fabrizio Turrini[1]
Domenico Prisco[3]

[1]Unità Operativa di Medicina Interna Cardiovascolare, Nuovo Ospedale Civile di Modena S.Agostino-Estense, Modena, Italy; [2]McMaster University, St. Joseph's Hospital and McMaster University, Hamilton, Canada;[3] Dipartimento di Area Critica Medico Chirurgica, Universita' di Firenze, Florence, Italy

Abstract: Venous thromboembolism (VTE) is a common complication among hospitalized patients. Pharmacological thromboprophylaxis has emerged as the cornerstone for VTE prevention. As trials on thromboprophylaxis in medical patients have proven the efficacy of both low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH), all acutely medical ill patients should be considered for pharmacological thromboprophylaxis. Unlike in the surgical setting where the risk of associated VTE attributable to surgery is well recognized, and where widespread use of pharmacological thromboprophylaxis and early mobilization has resulted in significant reductions in the risk of VTE, appropriate VTE prophylaxis is under-used in medical patients. Many reasons for this under-use have been identified, including low perceived risk of VTE in medical patients, absence of optimal tools for risk assessment, heterogeneity of patients and their diseases, and fear of bleeding complications. A consistent group among hospitalized medical patients is composed of elderly patients with impaired renal function, a condition potentially associated with bleeding. How these patients should be managed is discussed in this review. Particular attention is devoted to LMWHs and fondaparinux and to measures to improve the safety and the efficacy of their use.

Keywords: venous thromboembolism, elderly patient, fondaparinux

Thromboembolism among hospitalized medical patients: an underestimated problem?

Venous thromboembolism (VTE), a potentially life-threatening disease which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication among hospitalized patients. Its incidence in medical patients may be as high as 20% in selected high-risk medical patients who are not receiving prophylaxis (Geerts et al 2004). Unlike in the surgical setting where the risk of associated DVT attributable to surgery is well recognized, and where widespread use of pharmacological thromboprophylaxis and early mobilization has resulted in significant reductions in the risk of VTE (Geerts et al 2004), appropriate VTE prophylaxis is under-utilized in medical patients.

PE is proven by autopsy studies in about 10% of all in-hospital deaths (Alikan et al 2004). About 80% of these cases occurred in patient older than 60 years, and most such patients had not undergone surgery (Goldhaber et al 1982). In addition to the morbidity and mortality associated with inappropriate lack of use of thromboprophylaxis, a delay in the recognition and treatment of DVT or PE will increase both the morbidity and mortality attributable to these disorders. Nonetheless prompt diagnosis of acute VTE can be difficult. Autopsy studies have proved that DVT can lead to PE without any warning symptoms (Lindblad et al 1991). Furthermore, clinical symptoms, when present, are often misleading: in a review of 67 cases of fatal PE,

Correspondence: Enrico Tincani
Unità Operativa Medicina Interna Cardiovascolare, Nuovo Ospedale Civile S.Agostino-Estense, Via Giardini 1355, Modena, 41100, Italy
Tel +39 0593 961101
Fax +39 0599 61419
Email e.tincani@ausl.mo.it

© 2007 Dove Medical Press Limited. All rights reserved

the diagnosis of PE was made in only 45% of cases before death (Pineda et al 2001).

Evidence for pharmacological prophylaxis

Compared with surgical studies, trials of thromboprophylaxis in medical patients often have smaller sample sizes and other methodological limitations. Nevertheless, both low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH) appear to reduce the incidence of DVT in hospitalized, elderly patients. Their efficacy compared with placebo has been confirmed in systematic reviews (Mismetti et al 2000; Imberti and Prisco 2005) and large studies.

The MEDENOX trial (Samama et al 1999) was a randomized, double-blind study was designed to evaluate the efficacy and safety of enoxaparin versus placebo in medical patients older than 40 years, expected to stay in hospital for at least 6 days (Table). Patients were excluded if they had a serum creatinine level above 1.7 mg/dL. Patients were randomly assigned to receive 40 mg of enoxaparin, 20 mg of enoxaparin, or placebo subcutaneously once daily for 6–14 days. About half of the enrolled patients were elderly. The primary efficacy outcome, the composite of distal and proximal asymptomatic DVT detected by routine venography, symptomatic VTE, and fatal PE up to day 14, was 5.5% in the group that received 40 mg of enoxaparin compared with 14.9% in the placebo group, a significant difference. There was no significant difference in the incidence of VTE between the group that received 20 mg of enoxaparin (15.0%) and the placebo group. The incidence of major bleeding during the study did not differ significantly between the placebo group and either enoxaparin groups. Mortality rates at day 90 were similar.

The PREVENT study (Leizorovicz et al 2004), a randomized, double-blind, placebo-controlled study, was designed to evaluate the efficacy and safety of dalteparin versus placebo in medical patients older than 40 years, expected to stay in hospital for at least 4 days, and not immobilized for more than 3 days (Table 1). Patients were randomly assigned to receive 5000 IU of dalteparin or placebo subcutaneously once daily for 14 days. The primary efficacy outcome, the composite of proximal asymptomatic DVT detected by routine ultrasonography, symptomatic VTE, fatal PE, and sudden death up to day 21, was to 2.7% in the dalteparin group compared with 4.96% in the placebo group, a significant difference. The incidence of major bleeding during the study was low and similar in both groups (0.49% vs 0.16%, respectively). Mortality rates at day 90 were similar. Patients were excluded if they had a serum creatinine level above 2.0 mg/dL. Age more than of 75 years was present in 33% of patients.

In contrast to MEDENOX, which largely evaluated the impact of thromboprophylaxis on venographically detected and largely asymptomatic distal DVT, in PREVENT the major component of the composite efficacy outcome was asymptomatic proximal DVT assessed by systematic screening with compression ultrasound. Compression ultrasonography is a non-invasive, highly sensitive technique for the diagnosis of symptomatic proximal DVT, and in many countries is now the technique of first choice for the diagnosis of DVT in clinical practice (Bressollette et al 2001; Zierler 2004; Blann and Lip 2006).

Guidelines adherence

Based on this body of evidence the panel of experts of The Seventh Consensus Conference on Antithrombotic Therapy of the American College of Chest Physicians (ACCP) recommends "prophylaxis with LDUH or LMWHs in acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease" (Geerts et al 2004). Only UFH, enoxaparin, and dalteparin are approved for venous thromboprophylaxis in most jurisdictions.

In spite of the evidence for the benefits of thromboprophylaxis in medically ill patients, data indicate an underuse of thromboprophylaxis in these patients. In a 1-year historical cohort study (Arnold et al 2001), 253 cases of acute VTE were objectively diagnosed. In 44 out 65 (67.7%) cases of VTE for which thromboprophylaxis had been indicated, inadequate prophylaxis was administered. The main reason for inadequacy was most often the omission of thromboprophylaxis. The DVT FREE study (Goldhaber et al 2004) is a prospective multicenter registry of patients with ultrasound-confirmed acute DVT. Of the 2726 patients who had their DVT diagnosed while in the hospital, only 1147 (42%) received prophylaxis within 30 days before diagnosis. Non-surgical patients were much less likely to receive prophylaxis compared with surgical patients. RIETE is a Spanish registry of consecutively enrolled patients with objectively confirmed, symptomatic acute VTE (Monreal et al 2004). This study demonstrated underuse of thromboprophylaxis in acutely medical ill patients; only 28% of medical patients with DVT had received thromboprophylaxis,

Table 1 The main features and results of the three most important randomized trials on pharmacological prophylaxis in medical patients

	MEDENOX	PREVENT	ARTEMIS
Eligibility criteria			
Age	≥40	≥40	≥60
Bed rest	≥6 days	≥4 days	≥4 days
Disease	Acute heart failure; Acute respiratory illness; or Infection; Bone/joint, Inflamed bowel plus	Acute heart failure; Acute respiratory illness; or Infection; Bone/joint, Inflamed bowel plus	Acute heart failure; acute or chronic lung disease, acute infectious or inflammatory disease
VTE risk	≥1 (>75 y, cancer, previous VTE, obesity, varicose veins, hormones, chronic heart or lung failure)	≥1 (>75 y, cancer, previous VTE, obesity, varicose veins, hormones, chronic heart or lung failure)	
Treatments			
	Enoxaparin 40 mg Enoxaparin 20 mg Placebo	Dalteparin 5000 UI Placebo	Fondaparinux 2.5 mg Placebo
End points			
At Day	14	21	15
	Venographic distal or proximal DVT	Proximal ultrasonographic DVT	Venographic distal or proximal DVT
plus	Symptomatic VTE	Symptomatic VTE	Symptomatic VTE
plus	Fatal PE	Fatal PE and sudden death	Fatal PE
Safety	Major bleeding Death at day 90	Major bleeding Death at day 90	Major bleeding Death at day 90
Results			
	Enoxaparin 40 mg 5.5% Placebo 14.9% p = 0.001	Dalteparin 2.7% Placebo 4.96% p = 0.0015	Fondaparinux 5.6% Placebo 10.5 % p = 0.029

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

compared with 67% of surgical patients. Many reasons for this under-use have been identified, including low perceived risk of VTE in medical patients, absence of optimal tools for risk assessment, heterogeneity of patients and their diseases, and fear of bleeding complications (Kakkar et al 2004).

Unfractionated heparin and low-molecular-weight heparins

LMWHs are being used with increasing frequency for medical thromboprophylaxis (Hirsh and Raschke 2004) despite a lack of evidence that they provide either superior antithrombotic efficacy or improved safety when compared with low-dose UFH (Mismetti et al 2000; Alikan and Cohen 2003). The UFH in current clinical use is a polydispersed unmodified heparin, with molecular weight ranging from 3000 to 30,000 Da and a mean molecular weight of approximately 15,000 Da. Most of the limitations of unfractionated heparin (such as unpredictable anticoagulant response, heparin resistance, heparin-induced thrombocytopenia, and osteopenia) are explained, at least in part, by its charge mediated non-specific binding to cell surfaces and plasma proteins. LMWHs are fragments derived from controlled enzymatic or chemical depolymerization of heparin. LMWH molecules weigh about one third of UFH, usually in the range of 4000–5000 Da (every molecule is made of about 15 monosaccharide units). Because the process of heparin depolymerization is controlled, different heparin fragments with specific pharmacokinetic and anticoagulant properties can be produced. Fragments derived from heparin depolymerization have lower binding affinity for cells and proteins, the key property that explains all anticoagulant, pharmacokinetic, and biological characteristic of LMWHs.

Fondaparinux

Fondaparinux is a synthetic highly sulfated pentasaccharide which has a sequence derived from the minimal antithrombin binding region of heparin. Fondaparinux binds to antithrombin with high affinity in a 1:1 stoichiometric and reversible manner (Olson et al 1992). It does not bind to other plasma proteins, blood cells, or platelet factor 4, making the risk of heparin-induced thrombocytopenia very low (Warkentin et al 2005).

In some jurisdictions, fondaparinux has been approved for the prophylaxis of DVT in patients undergoing various procedures including hip fracture surgery (often with extended or out of hospital administration), hip replacement surgery, knee replacement surgery, and high risk patients undergoing abdominal surgery. Fondaparinux has also been approved in Europe for the prophylaxis of DVT in medical patients, and for the treatment of both acute DVT and acute pulmonary embolism when administered in conjunction with warfarin sodium in the hospital (European Medicines Agency 2007).

Use of fondaparinux is supported by an impressive development program. The MATISSE DVT trial (Buller et al 2004a), a randomized double-blind trial, compared the efficacy and safety of fondaparinux with that of enoxaparin followed by 3 months of vitamin K antagonist (target INR 2.0–3.0) in the initial treatment of DVT. Patients were randomly assigned to receive either fondaparinux as a single subcutaneous daily injection of 5 mg if body weight was <50 kg, 7.5 mg if body weight was 50–100 kg, and 10 mg if body weight was >100 kg, or enoxaparin as a twice-daily subcutaneous injection of 1 mg/kg. Both medications were administered for at least 5 days and until vitamin K antagonists induced an international normalized ratio (INR) >2.0. The primary efficacy outcome, the 3-month incidence of symptomatic recurrent VTE, was 3.9% in the fondaparinux group compared with 4.1% in the enoxaparin group, a non-significant difference. The incidences of major bleeding during the initial treatment period (1.1% vs 1.2%), deaths at 3 months (3.8% vs 3.0%), and thrombocytopenia (0.6% in each group) were also similar. Patients were excluded if they had a serum creatinine level above 2.0 mg/dL. The mean age was less than 65 years in both groups.

The Matisse PE trial (Buller et al 2003), a randomized open-label trial, compared the efficacy and safety of fondaparinux in the initial treatment of PE with that of unfractionated heparin followed by 3 months of vitamin K antagonist (target INR 2.0–3.0). Patients were randomly assigned to receive either fondaparinux as a single subcutaneous daily injection of 5 mg if body weight was <50 kg, 7.5 mg if body weight was 50–100 kg, 10 mg if body weight was >100 kg without monitoring, or a continuous IV infusion of unfractionated heparin to achieve an a PTT ratio of 1.5–2.5. Both medications were given for at least 5 days and until the use of a vitamin K antagonist resulted in an INR >2.0. The incidence of recurrent VTE was 3.8% in the fondaparinux group compared with 5.0% in the unfractionated heparin group, a non-significant difference. The incidences of major bleeding (2.0% vs 2.4%), deaths (5.2% vs 4.4%), and thrombocytopenia (0.9% vs 1.2%) were also similar. Patients were excluded if they had a serum creatinine level above 2.0 mg/dL. The mean age was less than 65 years in both groups.

The recommended dose of fondaparinux for postoperative thromboprophylaxis is 2.5 mg administered by subcutaneous injection once daily to be initiated 6–8 hours after surgery. Administration before 6 hours after surgery has been associated with an increased risk of major bleeding. The usual duration of administration is 5–9 days. In patients undergoing hip fracture surgery extended prophylaxis for up to 24 additional days is recommended.

Special population: elderly patients with impaired renal function

Increasing age is a significant risk factor for VTE. The Worcester DVT study (Anderson 1991) found that annual incidence of DVT increased exponentially with age from 17 per 100,000 persons/year for those between the ages of 40 and 49 to 232 per 100,000 persons/year for those between the ages of 70 and 79. The Longitudinal Investigation of Thromboembolism Etiology (Tsai et al 2002), based on a general US adult population, found an increasing incidence of first VTE with age, with a hazard ratio of 1.7 (95% confidence interval [CI]: 1.5–2.0) for every decade of life after age 55 years. Age is also a risk factor for increased risk of death in patients with PE; the mortality due to PE during hospital stay is 21% in patients older than 65 years and may be as low as 2% in patients younger than 40 years (White 2003). Immobilization as in chronically bedridden nursing home residents (Heit et al 2000; Gatt et al 2004) and immobilization associated with an acute illness are recognized relevant risk factors for the development of DVT in elderly patients even before hospital admission. In a prospective study (Oger et al 2002) of 234 consecutive medical patients who underwent venous compression ultrasonography within 48 hours of admission, the prevalence of asymptomatic DVT was 17.8% in patients older than 80 years and 0% in patients younger than 55 years.

In addition to a higher risk of hospitalization, elderly patients frequently harbour unsuspected renal failure

(El Nahas 2005). Data describing the safety and efficacy of LMWHs in patients with renal failure are inconsistent. The ACCP panel of experts' recommendations are vague: "for each of the antithrombotic agents, we recommend that clinicians consider the manufacturer's suggested dosing guidelines. We recommend consideration of renal impairment when deciding on doses of LMWH, fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients and those who are at high risk for bleeding" (Geerts et al 2004).

Impaired renal function is an important risk factor for bleeding during anticoagulation treatment (Levine et al 2004). Assessing the elderly for renal failure is problematic since the creatinine level may be misleading, as total creatinine decreases with age as muscle mass decreases. Often, a serum creatinine level within the normal range erroneously classifies elderly patients as having a normal renal function. The frequent overestimation of renal function could be avoided by estimating the creatinine clearance (CrCl) using equations such as the Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) (Stevens et al 2006). Though the MDRD equation has many advantages (height or weight are not needed for calculation), it has not been validated in people older than 70 years. Some of the studies that compared the two equations in this patient population have shown that the MDRD equation may underestimate the CrCl in elderly patients (Pedone et al 2006). Nonetheless, these results are not conclusive (Verhave et al 2005), and their clinical significance is uncertain in the absence of data about clinical outcomes that would derive from the use of the MDRD equation. However, when CrCl is properly evaluated by these equations, about 60% of critical medical patients aged over 70 years will have some degree of renal impairment (Clase et al 2002). As they are cleared by the kidneys, the main potential limitation of LMWH is the potential risk of bioaccumulation and bleeding when administered to patients with renal failure (Nagge et al 2002). However, there is emerging evidence that different LMWHs have different risks of bioaccumulation as LMWHs with the higher molecular weight are expected to be cleared mostly through the reticulo-endothelial system; it is also not clear which value of CrCl is a threshold below which there is a risk of bioaccumulation (Nagge et al 2002; Lim et al 2005).

Elderly patients with renal failure have been systematically excluded from most large randomized clinical trials on thrombosis prophylaxis and VTE treatment, as advanced age, age-related renal function impairment, and polypharmacy are potentially associated with bleeding. It is therefore important to design clinical trials for each anticoagulant with the aim of examining the safety of multiple injections in elderly patients with varying severity of renal failure.

Tinzaparin

Tinzaparin has an average molecular weight of 5500–7500 Da, and the following properties (Tinzaparin prescribing information 2006) – onset of action: 2–3 hours, distribution: 3–5 L, half-life elimination: 3–4 hours, metabolism: partially metabolized by desulphation and depolymerization, bioavailability: 87%, time to peak: 4–5 hours, excretion: urine, anti-Xa to anti-IIa activity ratio, 1.9.

There is evidence that therapeutic doses of tinzaparin have a favorable safety profile in elderly patients even with renal failure.

A prospective study (Siguret et al 2000) evaluated whether tinzaparin accumulated in patients older than 70 years of age. Thirty patients (mean age 87 years) suffering from acute thromboembolic disorders were treated with a body-weight dose of tinzaparin (175 anti-Xa IU/Kg) once daily over 10 days. Patients with a CrCl lower than 20 mL/min were excluded. The mean anti-Xa activity measured 5 hours after the second injection of tinzaparin did not significantly vary from day 2 to day 10. No correlation was observed between anti-Xa activity and CrCl. None of the patients developed heparin-induced thrombocytopenia and no major bleeding occurred.

The safety profile of tinzaparin in very elderly patients whose CrCl was above 20 mL/min, and requiring full anticoagulation, was evaluated in another prospective study (Pautas et al 2002). Two-hundred patients, mean age 85 years, mean creatinine clearance 51.2 ± 22.9 mL/min, were treated with a body-weight dose of tinzaparin (175 anti-Xa IU/Kg) once daily up to 30 days. Plasma anti-Xa activity levels were regularly measured throughout the treatment period. Three major bleeding episodes (1.5%) were reported. Heparin-induced thrombocytopenia was confirmed in two patients (1%). No correlation was found between anti-Xa activity and CrCl or age.

These findings suggest that the larger molecular size and increased charge of tinzaparin make it less likely to accumulate than other LMWHs in patients with mild-to-moderate renal insufficiency (CrCl >30 mL/min).

The manufacturer of tinzaparin does not recommend any dose adjustment in elderly renally impaired patients (Tinzaparin prescribing information 2006).

In cases of serious bleeding or large overdose, protamine sulfate (1% solution) can be given by slow IV infusion at a

dose of 1 mg protamine for every 100 anti-Xa IU of tinzaparin given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of tinzaparin may be administered if the aPTT measured 2–4 hours after the first infusion remains prolonged. Even with the additional dose of protamine, the aPTT may remain more prolonged than would usually be found following administration of protamine to reverse unfractionated heparin. Protamine does not completely neutralize tinzaparin sodium anti-Xa activity (maximum about 60%).

Dalteparin

Dalteparin has an average molecular weight of 4000–6000 Da, and the following properties (Dalteparin prescribing information 2006): onset of action: 1–2 hours, duration: >12 hours, half-life elimination (route dependent): 2–5 hours, time to peak, serum: 4 hours, anti-Xa to anti-IIa activity ratio, 2.5.

Studies of dalteparin in patients with old age or with renal failure are few and all recently published (Kucher et al 2005; Shprecher et al 2005; Tincani et al 2006). Available data suggest that administration of repeated prophylactic doses of dalteparin in patients with renal failure is not associated with accumulation and dose reduction is not needed.

There are less data to guide therapeutic doses of dalteparin in patients with renal impairment. A small study (Shprecher et al 2005) did not find any difference in anti -Xa activity in eleven patients with renal failure with respect to 11 patients with normal renal function, after subcutaneous induction of anticoagulation with doses of 100 IU/kg every 12 hours.

In a prospective single-center cohort study conducted in an intensive care unit (Rabbat et al 2005), 19 patients aged 62.7 ± 13.2 years with an APACHE II score of 23.5 ± 9.4, and a creatinine clearance 30 mL/min or higher, were enrolled. Each patient received 5000 IU dalteparin subcutaneously each day for thromboprophylaxis. Peak anti-Xa levels, measured 4 hours post dalteparin dose on 113 occasions, showed no evidence of bioaccumulation of dalteparin.

In a retrospective, post-hoc analysis of PREVENT data (Kucher et al 2005), dalteparin was shown to be both effective and safe for thromboprophylaxis in hospitalized patients 75 years or older compared with placebo. The use of dalteparin reduced VTE events by 52%, and was not associated with an increase of major hemorrhage rates (1.1% in the dateparin group vs 0.7% in the placebo group, respectively, $p = 0.12$). Unfortunately patients with a serum creatinine level above 2.0 mg/dL were excluded, and CrCl was not directly measured.

The results of a prospective, cohort study (Tincani et al 2006) have shown that dalteparin thromboprophylaxis, in patients aged 65 years or older, admitted with an acute medical illness requiring immobilization for at least 3 days, who have renal impairment is associated with a low risk of both bioaccumulation and bleeding. The study enrolled 115 consecutive patients with a mean age of 83 years, who had a serum creatinine ≥1.2 mg/dL (females), or ≥1.4 mg/dL (males). Ninety-three patients judged to be at high thromboembolic risk (patients older than 75 years, with active cancer or previous venous thromboembolism) received dalteparin 5000 IU daily; the other 22, considered at low risk, received 2500 IU daily. Dalteparin was given for 6 days. Anti-Xa activity was determined on day 1, before the first dalteparin dose, and on day 6, 4 hours after its administration. A complete compression ultrasound examination of leg veins was performed at admission and at discharge. The primary study end point was the anti-Xa activity levels at day 6. Secondary end points were: the occurrence of hemorrhage during the in-hospital stay, objectively confirmed symptomatic (limb pain and swelling) DVT, and objectively confirmed asymptomatic DVT. There were no major bleeding events, no symptomatic thromboembolic events, and no asymptomatic DVT was recorded (95% CI 0%–2.5%). Of the 115 patients, 3 (2.7%) had minor hemorrhage (95% CI 0.6%–6.7%). In all 3 cases anti-Xa activity was undetectable at the time of the bleed. There were no cases of VTE. There was also no relationship between the degree of renal impairment and the peak anti-Xa heparin level at day 6. As a small number of patients were enrolled, these preliminary data need to be validated by larger trials.

The manufacturer of dalteparin does not provide any information about dose adjustment in elderly or renally impaired patients.

In cases of serious bleeding or large overdose, protamine sulfate (1% solution) can be given by slow IV infusion at a dose of 1 mg protamine for every 100 anti-Xa IU of dalteparin given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of dalteparin may be administered if the aPTT measured 2–4 hours after the first infusion remains prolonged. Even with the additional dose of protamine, the aPTT may remain more prolonged than would usually be found following administration of protamine to reverse unfractionated heparin. In all cases, protamine does not completely neutralize dalteparin anti-Xa activity (maximum about 60%–75%) (Crowther et al 2002).

Enoxaparin

Enoxaparin has an average molecular weight of 4500 Da, and the following properties (Enoxaparin prescribing information

2006) – onset of action: 3–5 hours, duration: ~12 hours, half-life elimination: 4.5–7 hours, excretion: urine, anti-Xa to anti-IIa activity ratio, 3.6.

To our knowledge, the safety and efficacy of enoxaparin in elderly medical patients has been evaluated in only one study.

The Enoxaparin in Medicine Study Group (Bergmann and Neuhart 1996), in a randomized, double-blind study, compared the efficacy and safety of enoxaparin 20 mg versus UHF 5000 IU twice daily in 442 bedridden patients aged 65 years or more, suffering from an acute medical illness, and not immobilized for more than 4 days. Both treatments were given for 10 days by subcutaneous injections. The studied population was at a moderate risk for VTE. The primary efficacy outcome, the composite of DVT detected by daily fibrinogen uptake test, and clinical PE, was 4.8% in the enoxaparin group compared with 4.6% in the UHF group, a non-significant difference. The incidence of major bleeding during the study was low and similar in both groups (0.9% vs 1.8%, respectively). Patients were excluded if they had a serum creatinine level above 2.0 mg/dL. The mean age was 83 years.

Several studies have evaluated the safety administration of enoxaparin in patients with renal failure at therapeutic, adjusted, and prophylactic doses. A recent meta-analysis (Lim et al 2006) showed that in case of CrCl <30 mL/min, enoxaparin administered at: (a) standard therapeutic-dose is associated with supratherapeutic anti-Xa levels, and with a 2- to 3-fold increased risk for major bleeding; (b) adjusted-dose is associated to therapeutic anti-Xa levels without an increased risk for major bleeding to be confirmed by further trials; (c) prophylactic-dose may bio accumulate.

The manufacturer of enoxaparin recommends, in patients with CrCl <30 mL/min, a reduced dose of 30 mg once daily for DVT prophylaxis, and of 1 mg/kg once daily for VTE treatment.

In cases of serious bleeding or large overdose, protamine sulfate (1% solution) can be given by slow IV infusion at a dose of 1 mg protamine for every 1 mg of enoxaparin, if enoxaparin was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin may be administered if enoxaparin was administered more than 8 hours previous to the protamine administration. A second infusion of 0.5 mg protamine sulfate per 1 mg of enoxaparin may be administered if the aPTT measured 2–4 hours after the first infusion remains prolonged. After 12 hours of the enoxaparin injection, protamine administration may not be required. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found following administration of heparin. In all cases, protamine does not completely neutralize enoxaparin anti-Xa activity (maximum about 60%) (Crowther et al 2002).

Fondaparinux

Fondaparinux has a molecular weight of 1728 Da, and the following properties (Fondaparinux prescribing information 2006): 100% bioavailability after subcutaneous injection, with peak serum concentrations reached approximately 3 hours post-dose. Its half-life of 17 hours allows once daily dosing. Fondaparinux does not prolong the activated partial thromboplastin time (aPTT), prothrombin time, or bleeding time. As PT and aPTT are insensitive measures of fondaparinux activity, antifactor Xa activity of fondaparinux can be measured by the assay if fondaparinux is used as the calibrator. Most of an administered dose of fondaparinux is cleared by the kidney, and excreted unchanged in the urine, with an elimination half-life of 17–21 hours. Clearance of this drug is reduced in subjects with reduced CrCl. The clearance of fondaparinux is approximately 25% lower in patients with mild renal impairment (CrCl 50–80 mL/min), approximately 40% lower in patients with moderate renal impairment (CrCl 30–50 mL/min), and approximately 55% lower in patients with severe renal impairment (CrCl <30 mL/min) compared with patients with normal renal function. Fondaparinux elimination is prolonged in patients older than 75 years. In this group of patients, the clearance is approximately 25% lower compared with patients younger than 65 years. Clearance of fondaparinux is decreased by approximately 30% in patients weighing less than 50 kg.

Fondaparinux has been studied for the prevention of VTE in elderly patients with acute medical illnesses.

The ARTEMIS trial (Cohen et al 2006), a randomized, double-blind study, was designed to evaluate the efficacy and safety of fondaparinux with that of placebo in preventing VTE in medical patients 60 years of age considered to be at moderate risk for VTE (Table). Patients were randomly assigned to receive either fondaparinux as a single subcutaneous daily injection of 2.5 mg, or placebo. Both medications were administered within 48 hours of hospital admission and for a total of 6–14 days. The primary efficacy outcome, the composite of asymptomatic DVT detected by routine venography and symptomatic VTE up to day 15, was 5.6% in the fondaparinux group compared with 10.5% in the placebo group, a significant difference. The incidence of major bleeding during the study was 0.2% in both groups. Patients were excluded if they had a serum creatinine level

above 2.0 mg/dL. The mean age was 75 years in both groups. In this study fondaparinux reduced the rate of venographically proven asymptomatic distal DVT. The importance of this observation is, however, called into question since the clinical relevance of distal asymptomatic DVT is uncertain, as documented by a recent review (Righini et al 2006), and by a retrospective, post-hoc analysis of PREVENT data (Vaitkus et al 2005). This analysis was conducted to compare the mortality rates in patients with asymptomatic proximal DVT, asymptomatic distal DVT, or no DVT. Mortality rates among patients with asymptomatic proximal DVT were 13.75%, compared with 3.39% for patients with asymptomatic distal DVT and 1.92% for those without DVT.

Further studies comparing fondaparinux with UFH or LMWHs are awaited.

The manufacturer warns (a) not to use fondaparinux in patients with CrCl <30 mL/min, and in patients with body weight <50 kg; (b) to prescribe fondaparinux with caution in patients with moderate renal impairment (CrCl 30–50 mL/min) and in patients older than 75 years.

Periodic assessment of renal function is recommended, and fondaparinux should be discontinued immediately in patients who develop severe renal failure while on therapy. Fondaparinux is not inactivated by protamine and no antidote is known.

Monitoring patients treated with LMWHs

None of the pivotal trials in which LMWHs were administered at prophylactic or therapeutic doses used routine anti-Xa heparin levels to monitor the LMWH and no clinical trials have clearly correlated the results of anti-Xa heparin monitoring with clinical outcomes. Nevertheless, experts suggest that monitoring the anticoagulant effect of LMWH might detect bioaccumulation thus improving the safety of LMWHs in selected populations.

Since LMWHs cause mild and unpredictable prolongation of the aPTT this test is inappropriate for monitoring their anticoagulant effect. If such monitoring is warranted, the only recommended test is a chromogenic anti-Xa activity assay test (Laposata et al 1998).

Because the aim of laboratory monitoring is to detect a possible bioaccumulation after multiple doses, the first blood sample should be obtained at the third or fourth day of treatment if LMWHs are administered twice daily, and at the second or third day, in case of a single daily injection.

As most of the trials did not adjust LMWHs doses according to anti-Xa activity, the level of anticoagulation that is most desirable for effective thromboprophylaxis or treatment is unknown. Good examples are provided by the trials in which an adjusted-dose of enoxaparin was used *with therapeutic intent* in patients with acute coronary syndrome and with a CrCl ≤30 mL/min (Collet et al 2003; Montalescot et al 2004). The dose adjustment was made when needed, aiming for a peak anti-Xa activity level between 0.5 and 1.0 IU/mL. The reduced dose was not associated with an increased rate of major bleeding, but the trade-off was an increased rate of myocardial infarction and of early mortality, in particular in case of anti-Xa activity lower than <0.5 IU/mL.

Clinical management of elderly patients with renal failure

Today, the optimal way to use LMWHs in elderly patients hospitalized for an acute medical illness who are at increased risk of VTE and who have renal impairment is unsolved.

Before examining the measures to be adopted to minimize the risk for anticoagulant-related bleeding complications in this population of patients preliminary considerations are necessary.

First of all, UFH remains the parenteral anticoagulant of choice in the treatment of patients with renal failure, at high risk of bleeding, and in whom rapid reversal of anticoagulation may be required (Buller et al 2004). Unlike LMWHs, UFH has a short half-life after intravenous injection (1–2 hours), can be reversed by protamine sulfate, and the clearance is not dependent on renal excretion.

Second, we do not recommend routine monitoring of anti-Xa activity to detect accumulation.

Third, we recommend caution in using simple adjustments in the dose of LMWH based on an estimated creatinine clearance since the impact of these adjustments on therapeutic effect is unknown.

Measures to improve the safety of LMWHs may include, on patient's hospital admission:

1. assessment of the bleeding risk (Beyth et al 1998), to identify patients in whom closer clinical surveillance may be warranted;
2. avoidance of drugs that affect the bleeding risk;
3. estimation of CrCl. The Modification of Diet in Renal Disease Study equation may be preferred to the Cockcroft and Gault formula, as reliable weights are difficult to obtain in elderly, bedridden patients;
4. selection of LMWHs that are less likely to accumulate when CrCl is reduced. The following options seem safe and effective: weight-adjusted doses of tinzaparin and possibly dalteparin for the treatment of VTE; a dose of

5000 IU once daily of dalteparin, of 5000 IU twice daily of UFH (monitoring platelets count), and of 30 mg once daily of enoxaparin for venous thromboprophylaxis.

For the initial treatment of VTE, vitamin K antagonist (VKA) therapy is started with LMWHs or UFH on the first treatment day. The dose of VKA is adjusted to maintain the international normalized ratio between 2.0 and 3.0. LMWHs or UFH are continued for at least 5 days and until the international normalized ratio is greater than 2.0, for 2 consecutive days. The duration of VKA treatment should be determined according to the ACCP recommendations (Buller et al 2004).

The optimal duration of the venous thromboprophylxis is not known for either chronically bedridden patients and for patients discharged from the hospital after an acute medical illness. Whether extended prophylaxis is warranted, and if so at what intensity and for what period, are unkown. This last issue has been evaluated by the investigators of the EXCLAIM study (NIH 2006), whose results should be soon available.

References

Alikhan R, Cohen AT. 2003. A safety analysis of thromboprophylaxis in acute medical illness. *Thromb Haemost*, 89:590–1.

Alikan R, Peters F, Wilmott R, Cohen AT. 2004. Fatal pulmonary embolism in hospitalized patients: a necroscopy review? *J Clin Pathol*, 57:1254–7.

Anderson FA, Wheeler HB, Goldberg RJ, et al. 1991. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med*, 151:933–8.

Arnold DM, Kahn SR, Shrier I. 2001. Missed Opportunities for Prevention of Venous Thromboembolism. An Evaluation of the Use of Thromboprophylaxis Guidelines. *Chest*, 120:1964–71.

Bergmann JF, Neuhart E. 1996. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. *Thromb Haemost*, 76:529–34.

Beyth RJ, Quinn LM, Landefeld CS. 1998. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*, 105:91–9.

Blann DB, Lip GYH. 2006. Clinical review: Venous thromboembolism. *BMJ*, 332:215–19.

Bressollette L, Nonent M, Oger E, et al. 2001. Diagnostic accuracy of compression ultrasonography for the detection of asymptomatic deep venous thrombosis in medical patients-the TADEUS project. *Thromb Haemost*, 86:529–33.

Buller HR, Agnelli G, Hull RD, et al. 2004b. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Antithrombotic Therapy for Venous Thromboembolic Disease. *Chest*, 126:401S–28S.

Buller HR, Davidson BL, Decousus H, et al. 2004a. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*, 140:867–73.

Buller HR, Davidson BL, Decousus H, et al. 2003. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*, 349:1695–702.

Clase C, Garg A, Kiberd B. 2002. Estimating the prevalence of low glomerular filtration rate requires attention to the creatinine calibration assay. *J Am Soc Nephrol*, 13:1338–49.

Cohen AT, Davidson BL, Gallus AS, et al. 2006. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomized placebo controlled trial. *Br Med J*, 332:325–9.

Collet JP, Montalescot G, Fine E, et al. 2003. Enoxaparin in unstable angina patients who would have been excluded from randomized pivotal trials. *J Am Coll Cardiol*, 41:8–14.

Crowther MA, Berry LR, Monagle PT, et al. 2002. Mechanism responsible for the failure of protamine to inactivate low-molecular-weight heparin. *Br J Haematol*, 116:178–86.

Dalteparin Prescribing information. 2006. Accessed 3 November 2006. URL: http://www.fragmin.com/professional/default.asp

El Nahas AM, Bello AK. 2005. Chronic kidney disease: the global challenge. *Lancet*, 365:331–40.

Enoxaparin Prescribing information. 2006. Accessed 3 November 2006. URL: http://www.lovenox.com/consumer/default.aspx

European Medicines Agency. 2007. Accessed February 10, 2007. URL: http://www.emea.europa.eu/humandocs/Humans/EPAR/arixtra/arixtra.htm

Fondaparinux Prescribing information. 2006. Accessed 2 November 2006. URL: http://www.arixtra.com/index.htm

Gatt ME, Paltiel O, Bursztyn M. 2004. Is prolonged immobilization a risk factor for symptomatic venous thromboembolism in elderly bedridden patients? Results of a historical-cohort study. *Thromb Haemost*, 91:538–43.

Geerts WH, Pineo GF, John A, et al. 2004. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Prevention of Venous Thromboembolism. *Chest*, 126:338S–400S.

Goldhaber SZ, Hennekens CH, Evans DA, et al. 1982. Factors associated with correct antemortem diagnosis of major pulmonary embolism. *Am J Med*,73:822–826.

Goldhaber SZ, Tapson VF. 2004. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol*, 93:259–62.

Heit JA, Silverstein MD, Mohr DN, et al. 2000. Risk factors for deep vein thrombosis and pulmonary embolism – a population-based case-control study. *Arch Intern Med*, 160:809–15.

Hirsh J, Raschke R. 2004. The Seventh ACCP Conference on Antithrombotic and ThrombolyticTherapy. Heparin and Low-Molecular-Weight Heparin. *Chest*, 126:188S–203S.

Imberti D, Prisco D. 2005. Venous thromboembolism prophylaxis in medical patients: Future perspective. *Thromb Res*, 116:365–75.

Kakkar AK, Davidson BL, Haas SK. The Investigators Against Thromboembolism (INATE) Core Group. 2004. Compliance with recommended prophylaxis for venous thromboembolism: improving the use and rate of uptake of clinical practice guidelines. *J Thromb Haemost*, 2:221–7.

Kucher N, Leizorovicz A, Vaitkus PT, et al; for the PREVENT Medical Thromboprophylaxis Study Group. 2005. Efficacy and Safety of Fixed Low-Dose Dalteparin in Preventing Venous Thromboembolism Among Obese or Elderly Hospitalized Patients. A Subgroup Analysis of the PREVENT Trial. *Arch Intern Med*, 165:341–5.

Laposata M, Green D, Van Cott EM, et al. 1998. College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulant Therapy: the clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med*, 122:799–807.

Levine MN, Raskob G, Beyth RJ, et al. 2004. The Seventh ACCP Conference on Antithrombotic and ThrombolyticTherapy. Hemorrhagic Complications of Anticoagulant Treatment. *Chest*, 126:287S-310S.

Leizorovicz A, Cohen AT, Turpie AGG, et al; for PREVENT Medical Thromboprophylaxis Study Group. 2004. Randomized, Placebo-Controlled Trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients. *Circulation*, 110:874–9.

Lim W, Al Saleh K, Douketis JD. 2005. Low-molecular-weight heparins for the treatment of acute coronary syndrome and venous thromboembolism in patients with chronic renal insufficiency. *Thromb Res*, 118:409–16.

Lim W, Dentali F, Eikelboom JW, et al. 2006. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*, 144:673–84.

Lindblad B, Sternby NH, Bergqvist D. 1991. Incidence of venous thromboembolism verified by necropsy over 30 years. *Br Med J*, 302:709–711.

Mismetti P, Laporte-Simitsidis S, Tardy B, et al. 2000. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost*, 83:14–19.

Monreal M, Kakkar AK, Caprini JA, et al. 2004. The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients. Findings from the RIETE registry. *J Thromb Haemost*, 2:1892–8.

Montalescot G, Collet JP, Tanguy ML, et al. 2004. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. *Circulation*, 110:392–8.

Nagge J, Crowther M, Hirsh J. 2002. Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med*, 162:2605–9.

NIH 2006. Accessed 5 December 2006. URL: http://www.clinicaltrials.gov/ct/show/NCT00077753.

Oger E, Bressollette L, Nonent M, et al. 2002. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. *Thromb Haemost*, 88:592–7.

Olson ST, Bjork I, Sheffer R, et al. 1992. Role of the antithrombin-binding pentasaccharide in heparin acceleration of antithrombin-proteinase reactions. Resolution of the antithrombin conformational change contribution to heparin rate enhancement. *J Biol Chem*, 267:12528–38.

Pautas E, Gouin I, Bellot O, et al. 2002. Safety profile of tinzaparin administered once daily at a standard curative dose in two hundred very elderly patients. *Drug Saf,* 25:725–33.

Pedone C, Corsonello A, Incalzi RA. 2006. Estimating renal function in older people: a comparison of three formulas. Age Ageing, 2:121–6.

Pineda LA, Hathwar VS, Grant BJ. 2001. Clinical suspicion of fatal pulmonary embolism. *Chest*, 120:791–795.

Rabbat CG, Cook DJ, Crowther MA, et al. 2005. Dalteparin thromboprophylaxis for critically ill medical-surgical patients with renal insufficiency. *J Crit Care*, 20:357–63.

Righini M, Paris S, Le Gal G, et al. 2006 Clinical relevance of distal deep vein thrombosis Review of literature data. *Thromb Haemost*, 95:56–64.

Samama MM, Cohen AT, Darmon JY, et al; for the Prophylaxis in Medical Patients with Enoxaparin Study Group. 1999. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med*, 341:793–800.

Shprecher AR, Cheng-Lai A, Madsen EM, et al. 2005. Peak antifactor Xa activity produced by dalteparin treatment in patients with renal impairment compared with controls. *Pharmacotherapy*, 25:817–22.

Siguret V, Pautas E, Février M, et al. 2000. Elderly patients treated with tinzaparin (Innohep®) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. *Thromb Haemost*, 84:800–4.

Stevens LA, Coresh J, Green T, et al. 2006. Assessing kidney function – Measured and estimated glomerular filtration rate. *N Engl J Med*, 354:2473–83.

Tincani E, Mannucci C, Casolari B, et al. 2006. Safety of dalteparin for the prophylaxis of venous thromboembolism in elderly medical patients with renal insufficiency: a pilot study. *Haematologica*, 91:976–9.

Tinzaparin prescribing information. 2006. Accessed 3 November 2006. URL: http://www.innohepusa.com/corporateweb/innohepus/home.nsf/Content/Home-Healthcare

Tsai AW, Cushman M, Rosamond WD, et al. 2002. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med*, 162:1182–9.

Vaitkus PT, Leizorovicz A, Cohen AT, et al. 2005. Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. *Thromb Haemost*, 93:76–9.

Verhave JC, Fesler P, Ribstein J, et al. 2005. Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. *Am J Kidney Dis*, 2:233–41.

Warkentin TE, Cook RJ, Marder VJ, et al. 2005. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. *Blood*, 106:3791–6.

White RH. 2003. The epidemiology of venous thromboembolism. *Circulation*,107 (Suppl 1):14–18.

Zierler BK. Ultrasonography and diagnosis of venous thromboembolism. 2004. *Circulation*, 109:I-9–I-14.

Appendix

To write this review we performed searches of the Medline electronic database to identify English-language studies on venous thromboembolism management in the elderly medical patient. Randomized controlled trials, observational studies, and prospective or retrospective cohort studies were eligible for the study. The references of the retrieved studies were reviewed for additional studies. The terms used were: deep vein thrombosis prevention or prophylaxis, venous thromboembolism prevention or management, and elderly or geriatric patients. The search was completed on 31 October 2006.