# Safety of dalteparin for the prophylaxis of venous thromboembolism in elderly medical patients with renal insufficiency: a pilot study

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The aim of this prospective cohort study was to determine the incidence of dalteparin bioaccumulation (measured using anti-Xa levels), and bleeding during thromboprophylaxis in elderly patients with renal failure who were admitted to hospital with an acute medical illness. Patients who met the criteria for being at high thromboembolic risk received dalteparin 5,000 IU subcutaneously once daily while the other patients (low risk) received 2,500 IU daily. Thromboprophylaxis was administered for at least 6 days. Anti-Xa activity was determined before the first dalteparin dose and again on day 6, 4 hours after the administration of the dalteparin dose. Bleeding was assessed daily. Compression ultrasonography was performed to identify any deep vein thromboses. There was no evidence of bioaccumulation on day 6 of therapy, irrespective of renal function. No episodes of major bleeding or venous thromboembolism occurred. Larger, randomized studies are warranted to confirm the safety of dalteparin in this patient population.

Key words: low molecular weight heparin, venous thromboembolism prophylaxis, renal failure, acute medical illness.

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The *American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy* strongly recommends the use of either low-dose unfractionated heparin or low-molecular-weight heparins (LMWH) for the prevention of venous thromboembolism in medical patients.[1] Although there is no evidence that LMWH provide either superior antithrombotic efficacy or improved safety when compared with low-dose unfractionated heparin,[2,3] LMWH are being used with increasing frequency because of their being easier to use.[4] Nevertheless, LMWH should be administered with care in medical patients who suffer from renal insufficiency since there is the risk of bioaccumulation[5] and bleeding.[6] Most medical hospital admissions involve elderly patients, who are the population at highest risk of having renal failure.[7] They are, however, usually excluded from randomized studies of prophylaxis against thromboembolism. Consequently studies specifically examining the safety of multiple thromboprophylactic doses of LMWH in this patient population of patients are required.[8]

The aim of this study was to assess anti-Xa activity, and the rate of bleeding complications in elderly patients with renal failure who had received multiple thromboprophylactic doses of dalteparin during the course of a hospital admission for an acute medical illness.

## Design and Methods

Eligible patients were patients aged 65 years or older admitted with an acute medical illness requiring immobilization for at least 3 days and who had a serum creatinine ≥1.2 mg/dL (females), or ≥1.4 mg/dL (males). Patients with a history of active peptic ulcer disease, hemorrhagic stroke, a platelet count <100,000/mL, baseline coagulopathy (INR>1.7), were chronically anticoagulated with warfarin, on LMWH at the time of admission or had a known hypersensitivity to LMWH were excluded. The study was approved by the local ethics committee. All patients were informed of the procedures and agreed to participate in the study. All patients were treated for a minimum of 6 days with dalteparin administered by subcutaneous injection once daily in the morning. The dose of dalteparin was determined according to a pre-specified stratification of risk. Patients aged 75 years or older, those who had active cancer and those who had a previous history of venous thromboembolism were considered at high risk, and received 5,000 IU daily. All other patients were considered at low risk, and received 2,500 IU daily. The individual characteristics and the clinical conditions included in our risk stratification protocol have been recognized as risk factors in population studies,[9] and have become inclusion criteria in clinical trials on thromboprophylaxis in medical patients.[10,11] We preferred our protocol to two

recently proposed but not yet validated scores,[12,13] because its simplicity of use. Anti-Xa activity was measured on venous blood samples drawn on day 1, immediately before the first injection of dalteparin and again on day 6, 4 hours after the injection of dalteparin.[4] According to the recommendations of the College of American Pathologists,[14] plasma anti-Xa activity was measured using a chromogenic assay (Spectrolyse® Heparin Xa, Biopool, Trinity Biotech, Ireland), and was expressed in IU/mL. Serum creatinine levels were measured on day 1 and on day 6, and creatinine clearance was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation.[15] This was preferred to the Cockcroft and Gault formula, as we hypothesized that reliable weights would be difficult to obtain in elderly, bedridden patients. Patients were divided into three groups according to their estimated creatinine clearance values:[16] those with mild (creatinine clearance of 60-89 mL/min), moderate (creatinine clearance 30-59 mL/min) and severe renal failure (creatinine clearance <30 mL/min).

A bleeding assessment was completed at baseline using the Outpatient Bleeding Risk Index,[17] defining the patient's bleeding risk as low, intermediate, or high. Drugs that affect bleeding risk were also documented. During the patient's hospital admission, bleeding events were recorded daily. Bleeding events in hospital were classified as minor or major using the Warfarin Optimized Outpatient Follow-up Study Classification.[18]

A complete compression ultrasound examination was done on day 1 and a second scan was scheduled on day 6, unless the patient had a clinically suspected thrombotic event before that date. A diagnosis of deep vein thrombosis (DVT) was made if there was absent flow in an incompressible venous segment.[19] Compression ultrasonography was used to diagnose DVT since (i) it is a non-invasive technique and in many countries has almost completely replaced contrast venography in clinical practice; (ii) it has been used to assess efficacy in clinical studies of thromboprophylaxis in medical patients;[11] and (iii) it has been shown to be a promising alternative to venography for the diagnosis of asymptomatic DVT in studies of thromboprophylaxis.[20]

The primary study end-point was the level of anti-Xa activity on day 6. Secondary end-points were the occurrence of hemorrhage during the period in hospital, objectively confirmed symptomatic (limb pain and swelling) DVT, and objectively confirmed asymptomatic DVT.

### Statistical analysis

Continuous variables are presented as means±standard deviation, while categorical data are presented as frequencies. The ANOVA test or Student's T-test was used to compare continuous data, and the $\chi^2$ test (or Fisher's exact test in the case of insufficient cell frequency) was used for categorical data. A two-sided $p$ value ≤0.05 was considered statistically significant. Statistical analyses were performed using the SPSS/PC release 11.0.0. (19 September 2001) software program (SPSS Inc., Chicago, IL, USA).

**Table 1. Clinical characteristics of the study population.**

| *Total number of patients* | *115* |
|---|---|
| Mean age (y) | 83±8 |
| Gender | |
| male | 59 (51.3%) |
| female | 55 (48.7%) |
| Reasons for admission | |
| pulmonary edema | 33 (28.7%) |
| acute respiratory disease (including pneumonia) | 6 (5.2%) |
| stroke | 5 (4.3%) |
| acute infectious disease | 36 (31.3%) |
| cancer | 10 (8.7%) |
| acute rheumatic disease | 4 (3.5%) |
| other | 26 (22.6%) |
| Risk stratification for thromboembolism | |
| high | 93 (81%) |
| low | 22 (19%) |
| Bleeding risk index | |
| intermediate | 103 (89.6%) |
| high | 12 (10.4%) |

## Results and Discussion

The study was carried out between March 2004 and June 2005 in the Cardiovascular Medicine Unit of the Civic Hospital, Modena, Italy. During the enrollment period, 1,841 patients were admitted to the unit, and 115 patients (59 males and 56 females, mean age 83±8 years) met the study inclusion criteria. Only 6.2% of the eligible patients were enrolled. The principal reasons for exclusion were age less than 65 years, absence of renal failure, prior indication for anticoagulation, anticipated need for anticoagulation, and expected hospitalization of less than 3 days. The clinical characteristics of the patients are presented in Table 1. Three patients, two females and one male, died in hospital from causes related to their diseases but unrelated to LMWH prophylaxis.

There were no major bleeding events; no symptomatic thromboembolic events and no asymptomatic DVT were recorded (95% confidence interval 0 to 2.5%).

Of the 115 patients, three (2.7%) had minor hemorrhages (95% confidence interval 0.6 to 6.7%). These three patients were a 93-year old male with minor epistaxis, who was admitted for pneumonia, had moderate renal failure (creatinine clearance 51 mL/min), a high risk score for thromboembolism, and an intermediate bleeding risk score; an 89-year old female with minor rectal bleeding, who was admitted for pulmonary edema, had moderate renal failure (creatinine clearance 32 mL/min), a high risk score for thromboembolism, and an intermediate bleeding risk score (and received ticlopidine 250 mg *bid* in addition to dalteparin); and an 88-year old male with minor hematuria, who was admitted for pulmonary edema, had moderate renal failure (creatinine clearance 34 mL/min), a high risk score for thromboembolism and an intermediate bleeding risk score. All three patients were receiving dal-

**Table 2.** Anti-Xa activity levels on day 6, and renal failure.

| | *Mild renal failure* | *Moderate renal failure* | *Severe renal failure* | *p* |
|---|---|---|---|---|
| Number of patients | 12 | 73 | 24 | 0.72 |
| Anti-Xa activity levels (IU/mL) | 0.030±0.086 | 0.033±0.075 | 0.048±0.084 | |

*Three patients died, and three bled before day 6.*

**Table 3.** Gender difference in anti-Xa activity levels on day 6, age, renal failure, and dalteparin dose.

| | *Male n=56* | *Female n=53* | *p** |
|---|---|---|---|
| anti-Xa activity levels (IU/mL) | 0.01±0.04 | 0.06±0.09 | 0.001 |
| Age (years) | 81±7 | 84±7 | 0.03 |
| Renal failure | | | |
| mild | 8 (14.3%) | 4 (7.5%) | |
| moderate | 41 (73.2%) | 32 (60.4%) | 0.03 |
| severe | 7 (12.5%) | 17(32.1%) | |
| Dalteparin dose 5000 IU | 44 (78.6%) | 50 (94.3%) | 0.02 |

**T-test and $\chi^2$ test.*

teparin 5000 IU daily, and in all three cases anti-Xa activity was undetectable at the time of the bleed.

As expected, anti-Xa levels before the first dose of dalteparin were undetectable. There was also no relationship between the degree of renal impairment and the peak anti-Xa heparin level on day 6 (Table 2). No patient had a day 6 anti-Xa activity of more than 0.5 IU/mL. Correlation analysis did not reveal any association between creatinine clearance and anti-Xa levels (Pearson's correlation -0.092, $p$=0.341).

Logistic regression analysis was performed to determine which variables predicted the anti-Xa activity levels on day 6. In the final model, gender was the only significant variable (β=0.309, $p$=0.001). Thus, female patients had higher anti-Xa activity levels, were older, had more severe renal failure, and more frequently received the higher dose of dalteparin (Table 3).

This pilot study suggests that clinically important bioaccumulation of dalteparin does not occur after 6 days of treatment at prophylactic doses, even in frail medical female patients with a high frequency of significantly impaired renal function. Our study is the first to carefully examine anti-Xa activity levels and the likelihood of bleeding complications using dalteparin in prophylactic doses in elderly patients with impaired renal function, particularly patients with severe renal failure who are often excluded from thromboprophylaxis studies.

Since there is a risk of bioaccumulation, the ACCP Consensus Conference recommends unfractionated heparin over LMWH if therapeutic anticoagulation is required by patients with severe renal insufficiency.[4] However, the risk of bioaccumulation associated with using prophylactic doses of LMWH in such patients is unknown. In one study an increase of anti-Xa activity levels was observed during thromboprophylaxis with enoxaparin, although the levels measured were not clearly associated with an increase of bleeding.[21] To our knowledge no previously published studies have addressed this issue in medically ill patients treated with dalteparin.[11] Our results are likely to be valid and generalizable. We enrolled a well-defined population, administered prophylaxis according to a predefined risk stratification, assessed outcomes in all patients while in-hospital and all patients had complete follow-up.

The principal limitation of the study is the small number of enrolled patients. Despite this, there were no major bleeding or thromboembolic events among 115 patients, and it is likely that the risks of major bleeding and thrombosis in such patients are low. Our protocol for the assessment of a patient's risk of thrombosis, though novel and not yet validated, appears to be highly effective and should be tested in future prospective studies.

We conclude that dalteparin thromboprophylaxis in elderly patients admitted with an acute medical illness who have renal impairment is associated with a low risk of both bioaccumulation and bleeding. Larger studies are required to validate our observations.

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