Clinical Research Report

Enoxaparin 20 mg for thromboprophylaxis in severe renal impairment

Lamis R. Karaoui1, Samah Tawil2, Pascale Salameh3 and Nibal Chamoun4

Abstract

Objective: This study was performed to evaluate the efficacy of daily subcutaneous enoxaparin 20 mg in patients with renal failure.

Methods: This retrospective cohort study included nonsurgical patients aged ≥18 years with a creatinine clearance rate of <30 mL/minute who were prescribed enoxaparin 20 mg subcutaneously (SC) daily for ≥3 days. The main outcome measures were the occurrence of a venous thromboembolic event (VTE) and bleeding events.

Results: One hundred sixty patients were identified. VTE occurred in 9 patients (5.6%), and bleeding events occurred in 37 (23.1%). Multivariable analysis showed that an age of >75 years was significantly associated with an increased risk of bleeding, while a creatinine clearance rate of 15 to 29 mL/minute was significantly associated with a lower risk of bleeding.

Conclusion: In patients with renal failure, enoxaparin 20 mg SC daily resulted in a 5.6% incidence of VTE, which is similar to the previously published acceptable incidence of VTE in patients with normal renal function receiving enoxaparin 40 mg SC daily. The incidence of major bleeding events was 10%, which is lower than that previously published in the literature.

Keywords

Enoxaparin, renal failure, thromboprophylaxis, bleeding, thrombosis, venous thromboembolism

Date received: 15 March 2018; accepted: 20 August 2018
Introduction

Thromboembolic disorders are associated with increased mortality and morbidity among hospitalized patients with limited mobility. For thromboprophylaxis, low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) because they require less monitoring of the platelet count and anti-Xa level. However, uncertainties still surround the use of LMWH in patients with severe renal insufficiency. In observational studies, patients with renal insufficiency receiving LMWH developed more bleeding than did patients without renal impairment. Furthermore, patients with advanced kidney disease are already more susceptible to bleeding from uremia-related platelet dysfunction.

More specifically, enoxaparin may bioaccumulate in patients with renal failure, leading to an increased anticoagulant response. In published clinical trials, the evidence regarding thromboprophylactic enoxaparin use in patients with renal impairment and the bleeding risk in such patients does not seem unanimous. In patients with a creatinine clearance (CrCl) rate of ≥30 mL/minute, enoxaparin 40 mg is usually recommended to prevent venous thromboembolism (VTE).

Enoxaparin dose adjustment is commonly recommended for thromboprophylaxis in patients with severe renal insufficiency (CrCl of <30 mL/minute); however, the exact dose reduction varies among different countries and practice guidelines. The American College of Chest Physicians (ACCP) guidelines and enoxaparin US labeling recommend 30 mg subcutaneously (SC) daily for deep vein thrombosis (DVT) prophylaxis in abdominal surgery, in hip or knee replacement, and in medical patients during acute illness when the CrCl rate is <30 mL/minute. Canadian labeling recommends enoxaparin 20 to 30 mg SC daily for prophylaxis in abdominal or colorectal surgery and in medical patients during acute illness. British labeling recommends enoxaparin 20 mg SC daily in patients with severe renal impairment. Moreover, the Food and Drug Administration has not approved enoxaparin for use in patients undergoing dialysis but has approved it for the prevention of thrombosis of the dialysis circuit. In Lebanon, enoxaparin is available in prefilled syringes of 20, 40, and 60 mg in the Lebanese market. Unlike in the US market, the 30mg syringe is not available. Moreover, different medical associations and countries may adopt different enoxaparin dosing protocols in patients with renal failure, and prescribers tend to reflect the practices predominant in the institutions where they completed their medical specialty training.

Previous studies involving older patients compared enoxaparin 20 mg with UFH and reported equal efficacy and safety for DVT prophylaxis in medical patients without renal impairment for a period of 10 days. Robert-Ebadi et al. suggested a 50% reduction of the LMWH dose and anti-Xa monitoring during prolonged treatment to detect accumulation in patients of advanced age with a CrCl rate of <30 mL/minute. This is not evidence-based but depends on an assessment of the risks of drug accumulation and bleeding.

To date, the efficacy and safety of reduced-dose enoxaparin (20 mg) have not been thoroughly evaluated for the prevention of VTE in patients with severe renal insufficiency. In fact, large dose-finding trials have not been conducted, and contemporary studies either excluded patients with renal failure or did not specify whether such patients were recruited.
knowledge, no randomized controlled trial has been performed to compare the standard prophylactic renal-adjusted enoxaparin dose (30 mg) with a reduced dose (20 mg) in patients with severe renal insufficiency, defined as a CrCl rate of <30 mL/minute. Therefore, limited data exist on the preference of one dose over the other in patients with renal impairment.\textsuperscript{15,20,21} Similarly, studies conducted in the Middle East and in Lebanon are lacking. This pilot study reports the initial findings of the efficacy and safety of enoxaparin at 20 mg daily for DVT prophylaxis in hospitalized patients with renal impairment with or without hemodialysis. The study was completed in accordance with the hospital’s ethics code and approved by the hospital’s institutional review board. Because this was a retrospective cohort study with a comprehensive chart review, patient consent was not required per the institutional review board.

**Patients and methods**

This pilot retrospective cohort study was conducted in a tertiary care teaching hospital in Lebanon. A comprehensive chart review was conducted for all patients admitted to the hospital from November 2009 to November 2010 and prescribed enoxaparin 20 mg SC daily for DVT prophylaxis. Participants were included in this study if they were aged ≥18 years and had renal impairment defined as a CrCl rate of <30 mL/minute. Patients were included if they were undergoing intermittent hemodialysis, required DVT prophylaxis based on the ACCP guidelines,\textsuperscript{8} or were hospitalized for ≥3 days (Table 1). Intermittent hemodialysis was defined as hemodialysis performed three times per week according to hospital practice. Patients undergoing therapeutic full-dose anticoagulation and pregnant or breast-feeding women were excluded. The CrCl rate was estimated using the Cockcroft–Gault equation: \([[(140 - \text{age}) \times \text{actual body weight}} / \text{(serum creatinine \times 72)}]\) if female, \(\times 0.85\). In calculating the CrCl, the patient’s actual body

| Table 1. Baseline characteristics. |
|-----------------------------------|
| Characteristic                  | N = 160 patients |
| Age, years                      | 77.22 ± 9.36    |
| Male sex                        | 99 (61.9)       |
| Body weight, kg                 | 71.07 ± 12.8    |
| CrCl rate                        |                 |
| \(15 < \text{CrCl} < 29 \text{ mL/minute}\) | 123 (76.9)     |
| \(\text{CrCl} < 15 \text{ mL/minute}\)   | 37 (23.1)      |
| Intermittent hemodialysis        | 54 (33.8)       |
| Platelet count                   | 228,076 ± 100,228 |
| Potassium level, mEq/L           | 4.49 ± 0.54     |

| Comorbidities                  |
|--------------------------------|
| Hypertension                   | 126 (78.8)     |
| History of venous thrombembolism | 5 (3.1)       |
| Coronary artery disease        | 88 (55.0)      |
| Congestive heart failure       | 52 (32.5)      |
| Atrial fibrillation             | 14 (8.8)       |
| Diabetes                       | 68 (42.5)      |

| Concomitant medications        |
|--------------------------------|
| Antithrombotic therapy         | 121 (75.6)     |
| Aspirin                        | 106 (66.3)     |
| Beta-blocker                   | 95 (59.4)      |
| ACEI/ARB                       | 86 (53.8)      |
| Clopidogrel                     | 71 (44.4)      |
| Steroids                       | 57 (35.6)      |
| Amiodarone                     | 23 (14.4)      |
| Heparin                        | 15 (9.4)       |
| Other antiplatelets             | 15 (9.3)       |
| Spironolactone                 | 5 (3.1)        |
| Digoxin                        | 7 (4.4)        |
| NSAIDs                          | 3 (1.9)        |
| Potassium supplement            | 2 (1.3)        |

| Chief complaint               |
|-------------------------------|
| Respiratory failure           | 91 (56.9)      |
| Congestive heart failure      | 49 (30.6)      |
| Diabetes mellitus             | 53 (33.1)      |
| Atrial fibrillation            | 17 (10.6)      |
| Other                          | 5 (3.1)        |

Data are presented as mean ± standard deviation or n (%). CrCl, creatinine clearance; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.
weight was used if their actual body weight was less than their ideal body weight (IBW). The patient’s adjusted body weight was used if their actual body weight was 20% greater than their IBW. Adjusted body weight was calculated as follows: \(\text{IBW} + 0.4 \times \left(\frac{\text{actual body weight}}{\text{IBW}}\right)^2\).

Each patient’s risk of developing VTE was calculated by the authors according to the Padua prediction score, taking into account active cancer, previous VTE, reduced mobility, any already known thrombophilic conditions, recent trauma and/or surgery, age of >70 years, heart and/or respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity (body mass index of \(\geq 30\) kg/m\(^2\)), and ongoing hormonal treatment. Patients were classified as having a high (Padua prediction score of \(\geq 4\)) or low (Padua prediction score of <4) risk of VTE.

Baseline characteristics were obtained from the patients’ charts and computerized hospital databases. Data collection sheets were used to record the patients’ demographics, including body weight, serum creatinine level, duration of hospitalization, and concurrent medications used including antithrombotic therapy; the patients’ daily laboratory values (platelet count, hemoglobin, hematocrit, potassium) and Doppler ultrasonography findings for detection of thrombosis; the incidence of VTE, including both DVT and pulmonary embolism (PE) according to the documentation in the medical record; and bleeding events and the use of blood products, including packed red blood cells, platelets, or fresh frozen plasma.

The co-primary endpoints were the occurrence of VTE and bleeding events throughout the duration of the hospital stay. VTE was defined as DVT, PE, or both at any point of the hospital stay. VTE events were defined as clinically suspected DVTs further diagnosed by Duplex ultrasonography of the legs and clinically suspected PE as confirmed by computed tomography angiography, according to the documentation in the medical record. Bleeding events included both minor and major hemorrhage. Hemorrhage was classified as major if bleeding was overt and was associated with the need for transfusion of two or more units of packed red cells or fresh frozen plasma or with a decrease in the hemoglobin concentration of \(\geq 2.0\) g/dL from baseline or if bleeding was retroperitoneal, intracranial, or fatal. Hemorrhage was defined as minor if it was overt but did not meet the other criteria for major hemorrhage.

The secondary endpoints were overall mortality, thrombocytopenia, hyperkalemia, and injection site reaction. Thrombocytopenia was defined as a platelet count of <150,000/mm\(^3\); it was considered severe if the platelet count was <50,000/mm\(^3\). Hyperkalemia was defined as a potassium level of >5.4 mEq/L. Drug–drug interactions were screened and recorded for all patients to detect those associated with bleeding, hyperkalemia, or thrombocytopenia based on Micromedex Healthcare Series volume 165.

**Data analysis**

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The mean and standard deviation are used to describe continuous variables, while frequency and percentage are used to describe multinomial and dichotomous variables. The chi-square test was used to compare percentages between groups, provided that the expected counts would be higher than 5; if not, Fisher’s exact test was used. Multivariable analyses were also conducted using forward stepwise likelihood ratio logistic regressions. Any VTE, bleeding, thrombocytopenia, or mortality was used as dependent variables. Variables with a
p-value of $\leq 0.2$ in the bivariate analysis were included in the initial model. A p-value of $<0.05$ was considered statistically significant. No formal power calculation was conducted.

**Results**

The sample population comprised 160 non-surgical patients (61.9% male, 38.1% female) with a mean age of 77 years, mean body mass index of 26.71 kg/m$^2$, mean serum creatinine level of 3.77 mg/dL and median CrCl of 19.705 mL/minute. Most patients were admitted to the internal medicine wards [127/160 (79.38%)], whereas 33/160 (20.62%) were admitted to the intensive care unit. Other baseline characteristics, including the medical history and concomitant medical therapy, are shown in Table 1.

The median duration of hospitalization was 10 days. One hundred fifty patients (93.8%) had a Padua score of $>4$ and were classified as being at high risk for developing VTE, warranting thromboprophylaxis.8,23 Patients received VTE prophylaxis for the following reasons: immobility in 156 (97.5%), previous VTE/PE in 5 (3.1%), myocardial infarction/congestive heart failure/stroke in 53 (33.1%), rheumatic fever/infectious disease in 51 (31.9%), cancer or immunosuppression in 11 (6.9%), age of $>75$ years in 118 (73.8%), and other indications in 5 (3.1%). Enoxaparin was administered post-hemodialysis in 47/54 patients (87.0%) for VTE prophylaxis.

**Venous thromboembolism**

Among all 160 patients, 9 (5.6%) developed VTE, all of which were due to DVT during hospitalization. Venous Doppler was performed in 14 patients (8.8%); however, DVT was only confirmed in 9 patients. VTEs occurred at a mean of 0.96 days post-admission (standard deviation, 3.34). Multivariable analysis showed that a history of DVT was associated with an increased risk of VTE [odds ratio (OR), 32.57; $p = 0.007$] (Table 2).

**Bleeding**

Bleeding occurred in 37/160 patients (23.1%) and comprised 10.0% (16/160) major and 13.1% (21/160) minor bleeding events. Bleeding occurred at a mean of 1.01 days post-admission (standard deviation, 2.57). Bleeding events were characterized as occult blood in the stool in 19 (11.8%) patients, bruising in 1 (0.6%), gastrointestinal bleeding in 3 (1.9%), and other bleeding sites including the knee, nose, eye, hematoma, and hemorrhagic stroke in 6 (3.7%). Bleeding was more common in patients undergoing hemodialysis and in those with a CrCl of $<15$ mL/minute. Bleeding occurred in 35.2% (19/54) of patients undergoing hemodialysis versus 17.9% (18/106) of patients not undergoing hemodialysis ($p = 0.010$). Bleeding occurred in 22/123 (40.5%) patients with a CrCl of $<15$ mL/minute vs. 22/123 (17.9%) patients with a CrCl of 15 to 29 mL/minute ($p = 0.004$). Furthermore, the incidence of bleeding increased in patients who received heparin during hemodialysis [53.3% (8/15)] in addition to enoxaparin 20 mg daily as compared with patients not undergoing hemodialysis [20.0% (29/145), $p = 0.007$].

The number of antithrombotic therapies did not affect the incidence of bleeding. There was no statistically significant difference in the incidence of bleeding regardless of whether patients received concurrent antithrombotic therapy: patients on triple, dual, single, and no antithrombotic therapy had a bleeding incidence of 33.3% (5/15), 22.6% (12/53), 20.1% (11/53), and 23.1% (9/39), respectively. Bleeding was more common in patients with thrombocytopenia [18/40 (45.0%)] than in those without thrombocytopenia [19/120 (15.8%), $p < 0.001$]. Furthermore, the incidence of
bleeding increased with lower platelet counts: the incidence was 100% (2/2) among patients with platelet counts of <50,000, 25% (1/4) among those with platelet counts of 50,000 to 100,000, and 22.2% (34/153) among those with platelet counts of >100,000 (p = 0.030). Thirty-three patients (20.6%) patients received packed red blood cells, and seven patients (4.4%) needed fresh frozen plasma. Multivariable analysis showed that an age of >75 years was associated with an increased risk of bleeding (OR, 3.95; p = 0.031), while better renal function (defined as a CrCl of 15 to 29 mL/minute) was associated with a lower risk of bleeding (OR, 0.18; p = 0.003) (Table 2). Furthermore, higher mean hemoglobin and potassium hemoglobin levels were associated with a lower risk of bleeding.

Hyperkalemia occurred in 39 patients (24.4%). Forty patients (25.0%) developed thrombocytopenia. Concomitant steroid use was associated with a higher risk of thrombocytopenia, whereas higher platelet counts on admission were associated with a lower risk of thrombocytopenia (OR, 3.69; p = 0.004) (Table 2).

---

**Table 2.** Multivariable forward analyses of thrombosis, bleeding, mortality, and thrombocytopenia occurrence by logistic regression.

| Dependent variable | Independent variables | OR [95% CI]; p-value |
|--------------------|-----------------------|----------------------|
| VTE¹                | HTN                   | 0.041 [0.005–0.354]; 0.004 |
|                    | DVT                   | 32.57 [2.624–404.357]; 0.007 |
| Any bleeding event²| CrCl of 15 to 29 mL/minute | 0.18 [0.055–0.561]; 0.003 |
|                    | Age of >75 years      | 3.95 [1.134–13.734]; 0.031 |
|                    | Hemoglobin            | 0.44 [0.28–0.692]; <0.001 |
|                    | Potassium             | 0.21 [0.080–0.558]; 0.002 |
| Thrombocytopenia occurrence³ | Immobility          | 0.04 [0.003–0.422]; 0.035 |
|                    | Steroid intake        | 3.69 [1.528–8.902]; <0.004 |
|                    | Platelets on admission| 0.98 [0.97–0.99]; <0.001 |
| Mortality⁴         | Thrombocytopenia occurrence | 20.43 [5.829–71.614]; <0.001 |
|                    | Heparin intake        | 13.26 [3.306–57.925]; 0.001 |
|                    | ACEI/ARB intake²      | 0.23 [0.069–0.749]; 0.015 |

OR, odds ratio; CI, confidence interval; DVT, deep vein thrombosis; HTN, hypertension; VTE, venous thromboembolism; MI, myocardial infarction; CHF, congestive heart failure; CrCl, creatinine clearance; Afib, atrial fibrillation; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker

¹Variables with a p-value of ≤0.2 in the bivariate analysis were included in the initial model. These variables were a medical history of DVT, medical history of HTN, hyperkalemia, history of VTE, hospitalization for MI/CHF/stroke, hospitalization for a rheumatic or infectious disease, history of trauma or surgery within the past 2 weeks, immobility, immunosuppression or cancer, and Padua score of ≥4

²Variables with a p-value of ≤0.2 in the bivariate analysis were included in the initial model. These variables were a CrCl of 15 to 29 mL/minute, CrCl of <15 mL/minute, hemodialysis, heparin use, age of >75 years, thrombocytopenia, HTN, Afib, hospitalization for MI/CHF/stroke, hospitalization for rheumatic or infectious disease, mean hemoglobin, male sex, and degree of thrombocytopenia

³Variables with a p-value of ≤0.2 in the bivariate analysis were included in the initial model. These variables were the mean platelet count, hyperkalemia, immobility, medical history of CHF, medical history of DVT, and use of steroids/beta-blockers/heparin for DVT

⁴Variables with a p-value of ≤0.2 in the bivariate analysis were included in the initial model. These variables were a CrCl of 15 to 29 mL/minute, CrCl of <15 mL/minute, hemodialysis, heparin use, age of >75 years, thrombocytopenia, hyperkalemia, medical history of CHF, medical history of DVT, hospitalization for rheumatic or infectious disease, Padua score of ≥4, male sex, and use of aspirin, amiodarone, digoxin, beta-blocker, ACEI/ARB, or steroids.
Mortality
Mortality occurred in 24 (15%) patients. Bivariate analysis indicated that hemodialysis, concomitant heparin or steroid use, hyperkalemia, congestive heart failure, and/or rheumatic disease were associated with an increased incidence of death. Patients undergoing hemodialysis had a 25.9% (14/54) incidence of mortality as compared with 9.4% (10/106) among patients not undergoing hemodialysis (p = 0.006). Patients receiving heparin had a 16/145 (11%) incidence of mortality as compared with those who did not receive heparin [8/15 (53.3%)]. Patients on steroid therapy had a 26.3% (15/57) risk of death compared with 8.7% (9/103) in patients who were not on steroid therapy (p = 0.003). Mortality was more common in patients with hyperkalemia [25.6% (10/39) vs. 11.6% (14/121), p = 0.032] and in patients with congestive heart failure [23.1% (12/52) vs. 11.1% (12/108), p = 0.047], and the only VTE risk factor associated with an increased risk of death was rheumatologic or infectious disease [11% (12/109) vs. 23.5% (12/51), p = 0.016]. Furthermore, multivariable analysis showed that patients on concomitant heparin and those with thrombocytopenia had a higher risk of mortality (OR, 13.26; p = 0.001 and OR, 20.43; p < 0.001, respectively). Conversely, patients on beta-blockers and angiotensin-converting enzyme inhibitors had a lower risk of mortality (Table 2).

Discussion
The 5.6% incidence of VTE found in our study is similar to the incidence of VTE reported by Bergmann and Neuhart, who found that enoxaparin 20 mg daily was as effective and well-tolerated as UFH 5000 IU twice daily in the prevention of VTE in bedridden elderly inpatients presenting with acute medical illness. Conversely, in comparison to the MEDENOX trial, which excluded patients with a serum creatinine level of >1.7 g/dL as opposed to our patient population, VTE occurred in 5.5% and 15.0% of patients receiving enoxaparin at 40 mg and 20 mg SC daily, respectively. Therefore, the rates of VTE in our study are similar to the previously published acceptable incidence of VTE in patients with normal renal function receiving enoxaparin 40 mg SC daily.

Our 10% incidence of major bleeding with enoxaparin 20 mg SC daily is lower than that reported in previous studies. Elsaid and Collins reported that the rates of major bleeding in hospitalized patients with a CrCl of <30 mL/minute undergoing treatment with enoxaparin 30 mg SC daily and UFH 5000 units three times daily were 18.87% (10/53) and 4.08% (2/49), respectively. Furthermore, they reported an increased relative risk of bleeding with enoxaparin versus UFH (4.68; 95% confidence interval, 1.06–20.59). The 23.1% incidence of bleeding on enoxaparin 20 mg daily is higher than that reported by Samama et al. [11.7% (41/351)] in patients without renal impairment receiving enoxaparin 20 mg.

Although the bivariate analysis showed that hemodialysis was associated with bleeding, the multivariable analysis did not confirm this finding. A recent study of patients undergoing chronic maintenance dialysis demonstrated that thromboprophylactic doses of enoxaparin were not associated with a higher bleeding risk in comparison with UFH (risk ratio, 0.98; 95% confidence interval, 0.78–1.23).

The finding that age was associated with an increased risk of bleeding is consistent with the risk factors identified by the IMPROVE bleeding risk score. The bivariate analysis showed a significantly increased occurrence of bleeding in patients undergoing hemodialysis and
concurrently receiving UFH. Although the reason for concurrent UFH administration was not explicitly stated in the medical charts, it was most likely for intradialytic use. However, our multivariable analysis that controlled for other confounders did not confirm that concurrent heparin use during hemodialysis is a risk factor for bleeding. Surprisingly, a higher number of antithrombotic therapy agents was not associated with a higher bleeding occurrence, possibly because of the low sample size.

Patients on concomitant heparin therapy and those with thrombocytopenia were at a higher risk of mortality. When compared with LMWH, initial therapy with UFH was associated with a higher mortality rate and higher rate of fatal PE in patients with a CrCl rate of >60 mL/minute or <30 mL/minute, but not in those with a CrCl of 30 to 60 mL/minute. The association of thrombocytopenia and a higher risk of mortality in the intensive care unit was recently reported in critically ill patients undergoing continuous renal replacement therapy.

Limitations of this study include the retrospective data collection, which necessitated reliance only on evaluation of clinical progress notes, laboratory test results, and other documentation. The small sample size and lack of power calculation may have decreased the possibility of detecting some patient risk factors. Furthermore, the incidence of bleeding and VTE were dependent on the accuracy and extent of documentation in the medical record. The incidence of major bleeding may be slightly overreported in this study. This is because the number of blood transfusions was not collected; therefore, any patient who had received blood products in addition to having an overt bleed was considered to have had a major bleed. Some residual confounding may also have been present despite our efforts to control for differences in risk factors via multivariable regression. Furthermore, the lack of power calculation may have decreased the possibility of detecting some patient risk factors.

Conclusion
The incidences of VTE and bleeding after receiving enoxaparin 20 mg for thromboprophylaxis in patients with severe renal impairment were 5.6% and 23.1%, respectively. Our findings warrant further evaluation in prospective trials comparing the efficacy and safety of enoxaparin 20 mg versus other thromboprophylactic regimens such as enoxaparin 30 mg once daily or heparin 5000 units SC three times daily in patients with severe renal insufficiency.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD
Nibal Chamoun http://orcid.org/0000-0002-0987-296X

References
1. Heit JA, Silverstein MD, Mohr DN, et al., Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000; 160: 809–815.
2. Lim W, Dentali F, Eikelboom JW, et al., Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. Ann Intern Med 2006; 144: 673–684.
3. Atiq F, van den Bemt PM, Leebeek FW, et al. A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in
patients with renal insufficiency. *Eur J Clin Pharmacol* 2015; 71: 921–929.

4. Crowther M and Lim W. Low molecular weight heparin and bleeding in patients with chronic renal failure. *Curr Opin Pulm Med* 2007; 13: 409–413.

5. Gerlach AT, Pickworth KK, Seth SK, et al., Enoxaparin and bleeding complications: a review in patients with and without renal insufficiency. *Pharmaco therapy* 2000; 20: 771–775.

6. Garcia DA, Baglin TP, Weitz JI, et al., Parenteral anticoagulants: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. *Chest* 2012; 141(2 Suppl): e24S–e43S.

7. Gould MK, Dembitzer AD, Doyle RL, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999; 130: 800–809.

8. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* 2012; 141(2 Suppl): e195S–e226S.

9. Sanderink GJ, Guimart CG, Ozoux ML, et al. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res* 2002; 105: 225–231.

10. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001; 119(1 Suppl): 64S–94S.

11. Enoxaparin monograph. Lexi-Comp, I.L.-D.L.-C., Inc.; November 20, 2015.

12. 2011, Sanofi aventis, summary of product characteristics, Clexane. http://www.sanofi-aventis.co.uk/products/Clexane_SPC.pdf

13. Kilminster S, Zukas M, Quinton N, et al. Preparedness is not enough: understanding transitions as critically intensive learning periods. *Med Educ* 2011; 45: 1006–1015. doi:10.1111/j.1365-2923.2011.04048.x.

14. Hirsh J, Bauer KA, Donati MB, et al. Parenteral anticoagulants: American college of chest physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133(6 Suppl): 141S–159S.

15. Siddiqui MA and Wagstaff AJ. Enoxaparin: a review of its use as thromboprophylaxis in acutely ill, nonsurgical patients. *Drugs* 2005; 65: 1025–1036.

16. Schmid P, Fischer AG and Wuillemin WA. Low-molecular-weight heparin in patients with renal insufficiency. *Swiss Med Wkly* 2009; 139: 438–452.

17. Bergmann JF and Neuhart E. 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. The enoxaparin in medicine study group. *Thromb Haemost* 1996; 76: 529–534.

18. Gouin-Thibault I, Siguret V and Pautas E. A need for evidence-based clinical practice guidelines for the use of heparins in the elderly. *Clin Interv Aging* 2010; 5: 119–121.

19. Robert-Ebadi H, Le Gal G and Righini M. Use of anticoagulants in elderly patients: practical recommendations. *Clin Interv Aging* 2009; 4: 165–177.

20. Shavit L, Lifschitz M, Lee S, et al. Use of enoxaparin to diminish the incidence of vascular access stenosis/thrombosis in chronic hemodialysis patients. *Int Urol Nephrol* 2011; 43: 499–505.

21. Stratta P, Karvela E, Canavese C, et al. Structure-activity relationships of low molecular weight heparins expose to the risk of achieving inappropriate targets in patients with renal impairment. *Curr Med Chem* 2009; 16: 3028–3040.

22. Cockcroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.

23. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the padua prediction score. *J Thromb Haemost* 2010; 8: 2450–2457.

24. Schulman S, Kearon C and Subcommittee on Control of Anticoagulation of the
Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.

25. 2015 Truven Health Analytics Inc. MICROMEDEX® Healthcare Series Vol. 165.

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

27. Elsaid KA and Collins CM. Initiative to improve thromboprophylactic enoxaparin exposure in hospitalized patients with renal impairment. *Am J Health Syst Pharm* 2012; 69: 390–396.

28. Chan KE, Thadhani RI and Maddux FW. No difference in bleeding risk between subcutaneous enoxaparin and heparin for thromboprophylaxis in end-stage renal disease. *Kidney Int* 2013; 84: 555–561.

29. Hostler DC, Marx ES, Moores LK, et al. Validation of the International Medical Prevention Registry on Venous Thromboembolism Bleeding Risk Score. *Chest* 2016; 149: 372–379. doi: 10.1378/chest.14-2842.

30. Trujillo-Santos J, Schellong S, Falga C, et al. Low-molecular-weight or unfractionated heparin in venous thromboembolism: the influence of renal function. *Am J Med* 2013; 126: 425–434 e1.

31. Guru PK, Singh TD, Akhoundi A, et al. Association of thrombocytopenia and mortality in critically ill patients on continuous renal replacement therapy. *Nephron* 2016; 133: 175–182.