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Risk Factors for Bleeding Events with Enoxaparin, Dabigatran and Fondaparinux in Hospitalized Patients with Varying Levels of Renal Impairment

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Abstract

Background: Anticoagulants with renal elimination may accumulate in patients with renal impairment and potentially increase the risk of bleeding. Limited data are available to elucidate the potential bleeding risk present in patients with moderate renal impairment defined as creatinine clearance of 30-50 mL/min.

Objective: To evaluate potential risk factors for bleeding over various renal function ranges in patients on enoxaparin, fondaparinux, or dabigatran.

Methods: Retrospective chart review from 2010 until 2011 identified patients who incurred a bleeding episode on therapeutic dosed enoxaparin, dabigatran, or fondaparinux stratified according to renal function and presence of pre-defined potential risk factors for bleeding. Bleeding episodes identified using UHC Safety Intelligence, a self-reporting database used to identify safety improvement opportunities.

Results: A total of 27 (2.16%) bleeding episodes were identified, 20 occurring during enoxaparin pharmacotherapy and 7 during treatment with dabigatran. There were no fondaparinux bleeds identified. Patients with normal renal function, moderate renal impairment and severe renal impairment incurred 9, 12 and 6 bleeds, respectively.

Conclusion: A similar number of patients incurred bleeding episodes on enoxaparin in the normal renal function group and moderate renal impairment group. Patients experiencing bleeding episodes in the enoxaparin group with moderate renal impairment were of advanced age and female. Enoxaparin bleeding episodes were noted in patients with hypertension in all renal function ranges. Patients who bled on dabigatran had some degree of renal impairment and were of advanced age. Concomitant p-glycoprotein inhibitor use was observed in patients with bleeding episodes on dabigatran in patients with renal impairment.

Keywords: Anticoagulation; Medication safety; Low-molecular-weight heparin; Bleeding; Dabigatran

Introduction

Low Molecular Weight Heparins (LMWH) such as enoxaparin, factor Xa inhibitors such as fondaparinux and Direct Oral Anticoagulants (DOACs) such as dabigatran are anticoagulants with predictable pharmacokinetic properties that do not require routine monitoring of laboratory chemistries. Despite this advantage, these agents accumulate in the presence of renal insufficiency and may precipitate or potentiate bleeding episodes [1,2]. The majority of enoxaparin studies have excluded patients with renal dysfunction [3-6]. Thus recommendations for renal dosing adjustments have been derived largely from pharmacokinetic data and retrospective studies. Much of this data postulates that patients with a Creatinine Clearance (CrCl) less than 30 ml/min achieve supratherapeutic anti-factor Xa levels due to enoxaparin accumulation [7,8]. However, elevated anti-factor Xa levels may not correlate with an increased bleeding risk [9]. Nevertheless, a post hoc analysis of two major clinical trials revealed an increase in hemorrhagic events in patients with CrCl less than 30 ml/min [10]. Dabigatran, an oral direct thrombin inhibitor, is predominantly excreted in the urine with approximately 80% of the drug being excreted in its active form via the kidneys [11]. Landmark clinical trials including RE-LY12 and RE-COVER13 excluded patients with severe renal insufficiency and thus dosing recommendations in that range have been made using pharmacokinetic data. In addition, there are no widely available sensitive and reliable laboratory parameters to measure the degree of anticoagulation with dabigatran. Dabigatran's drug label recommends that renal function should be assessed before starting dabigatran and annually in elderly patients (age>75 years) or in patients with mild-to-moderate renal impairment defined as CrCl 30-50 ml/min. The renal clearance of fondaparinux is significant as well; approximately, 77% of the active drug is excreted through urine and with a half-life ranging from 17-21 h in healthy volunteers, accumulation in renal impairment is expected [12]. Although, fondaparinux is contraindicated with a CrCl ≤ 30 ml/min,

no dose adjustment is recommended for patients with a CrCl of 30-50 ml/min.

Anecdotal observations as well as pharmacodynamic data suggest that patients with moderate renal impairment (CrCl 30-50 ml/min) may be at an increased risk for bleeding events. A 2005 study by Bazinet et al. showed significantly supratherapeutic anti Xa levels in patients receiving enoxaparin with moderate renal impairment compared to the normal renal function group (CrCl ≥ 50 ml/min) [13]. Another study by Hulot et al. showed 31% decrease in enoxaparin clearance in patients whose CrCl was between 30 and 50 ml/min compared to 17% decrease in the CrCl 50-80 ml/min group [14]. Furthermore, another post-hoc analysis by Fox et al. noted an increased rate of major and minor bleeding in patients with CrCl of 30-60 ml/min compared to those with greater clearance being treated with enoxaparin for ST-segment elevated myocardial infarction [15]. Moreover, a study by Green et al. suggested that enoxaparin accumulation occurs after steady state is achieved in patients with CrCl ≤ 80 ml/min. This accumulation is especially prominent in the moderate renal impairment range; hence, the authors recommend an empiric dose adjustment based on pharmacokinetic and pharmacodynamic data [16]. However, the package insert only recommends dose reduction at a CrCl<30 ml/min. Simulation pharmacokinetic studies looking at dabigatran have noted a steady state C_{max} at a CrCl of 40-60 ml/min that is nearly doubled that of patients with normal renal function (CrCl>90 ml/min) [2]. Indeed, one particular simulation study cited a maximum Ecarin Clotting Time (ECT) and activated Partial Thromboplastin Time (apTT) to be greater in patients with moderate renal impairment compared to those with normal kidney function [11]. Unfortunately, the major dabigatran trials did not include sub group analysis data on bleeding rates in moderate renal impairment patients [17,18]. However, post marketing data revealed that co-administration of dabigatran with P-glycoprotein (P-gp) inhibitors such as ketoconazole or dronedarone approximately double dabigatran levels. Therefore, it is recommended that a dose reduction be made in dabigatran to 75 mg twice daily for patients with moderate renal impairment (CrCl 30-50 mL/min) who are also on these concomitant medications [19]. As part of a quality assurance, we sought to evaluate patients who experienced bleeding episodes on enoxaparin, dabigatran, or fondaparinux to assess the frequency of events and characterize potential risk factors for bleedings over various renal function ranges. The oral factor Xa inhibitors, apixaban, rivaroxaban and edoxaban were not included during this time period as they were not on hospital formulary at the time of this study (Table 1).

Drug	CrCl (mL/min) >30	CrCl (mL/min) 15-30	CrCl (mL/min) <15
Enoxaparin	1 mg/kg q12h or 1.5 mg/kg q24h	1 mg/kg q24h	-
Dabigatran	150 mg q12h	75 mg q12h	Contraindicated

Table 1: Standard therapeutic dosing recommendations.

Methods

Design: We performed a retrospective chart review from January 2010 to January 2011 to evaluate risk factors associated with bleeding events in patients receiving enoxaparin or dabigatran with varying levels of renal impairment. Approval from the New York University institutional review board was obtained. Patients were included if they were greater than 18 years of age and experienced a bleeding episode while on therapeutic enoxaparin or dabigatran. Patients were excluded if they received less than 4 doses of study drug. Patients were identified using pharmacy analytics software, ICD-9 codes and UHC patient safety intelligence reports, a voluntary adverse event reporting system.

Outcomes: The primary endpoint was the number of bleeding episodes with enoxaparin or dabigatran according to renal function. Bleeding severity was divided into major or non-major bleeding. Severity of bleeding was defined based on the categorization utilized by the Einstein group (Table 2) [20].

Major Bleed	Non-major Bleed
Decrease in hemoglobin ≥2 g/dL	Medical intervention performed
Intracranial bleed	Study drug interrupted or discontinued
Intraspinal bleed	Epistaxis
Intraocular bleed	Spontaneous gingival bleeding
Pericardial bleed	Spontaneous macroscopic hematuria
Intraarticular bleed	Melena/hematemesis
Retroperitoneal bleed	Rectal blood loss if > a few spots
Intramuscular bleed	Hemoptysis
Fatal bleed	Intramuscular hematoma
Admission to ICU as direct result of bleed	Subcutaneous hematoma

Table 2: Einstein bleeding severity.

The secondary outcome was the distribution of several proposed risk factors in patients experiencing bleeding episodes over varying renal function ranges (Table 3). Potential risk factors were selected based on previously identified bleeding risk factors with anticoagulant use [21].

Proposed Risk Factors for Bleeding
Age
Sex
BMI
Duration of therapy
Congestive heart failure
Hypertension
Diabetes mellitus
Malignancy
Intensive care unit
Concomitant medications

Table 3: Proposed risk factors for bleeding.

Statistics: Descriptive statistical analysis was performed using SPSS version 18.0.

Results

In total, there were 1090 patients encounter with more than 4 therapeutic dosed enoxaparin administrations, 134 patients encounter with more than 4 dabigatran administrations and 24 patients encounter with more than 4 fondaparinux administrations identified. Twenty-seven bleeding episodes (2.16%) of total population receiving these anticoagulants were identified through the safety reporting system during the study period. Twenty bleeding episodes (1.6%) occurred on enoxaparin while 7 bleeds (0.56%) occurred on dabigatran. Fondaparinux related bleeding episodes were not identified. Out of the 27 bleeds, patients in the normal renal function range experienced 9 (33%) total bleeding episodes, 8 of which were in the enoxaparin group. Twelve (45%) total bleeding episodes were identified in patients with moderate renal impairment, 9 of which were in the enoxaparin group. Patients who incurred bleeding episodes with severe renal impairment were identified 6 times (22%); these were split equally between the enoxaparin and dabigatran groups (Figure 1 and Table 4).

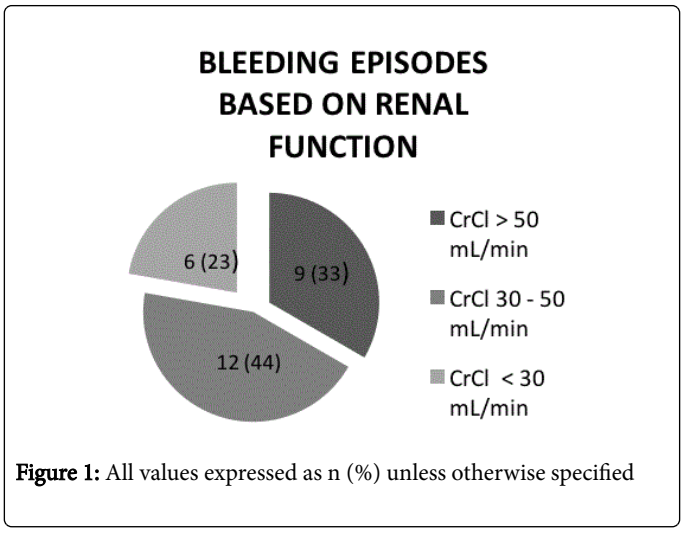

Figure 1: All values expressed as n (%) unless otherwise specified

Drug n=27	CrCl>50 mL/min	CrCl 30-50 mL/min	CrCl<30 mL/min
Enoxaparin	8/20 (44)	9/20 (50)	3/20 (6)
Dabigatran	1/7 (14)	3/7 (43)	3/7 (43)
All values expressed as n (%) unless otherwise specified			

Table 4: Bleedings episodes based on drug and renal function.

Sixteen of 20 patients who experienced bleeding episodes on enoxaparin received 1 mg/kg q12h dosing, 3 received 1.5 mg/kg q24h and only 1 of 3 patients in the severe renal impairment group received the appropriate 1 mg/kg q24h dosing adjustment. Of the 7 dabigatran-related episodes, 4 patients received 150 mg q12h and 3 received the adjusted 75 mg/kg q12h dosing regimen. Regarding the severity of the 27 bleeding episodes, 17 (63%) bleeds were categorized as major bleeds (12 in the enoxaparin group and 5 in the dabigatran group (Figure 2).

The mean age in this study was 74 years and 59% of patients were female. In patients who experienced bleeding episodes on enoxaparin, a larger percentage of patients were seen with moderate or severe renal impairment, 78% and 100% for moderate and severe, respectively.

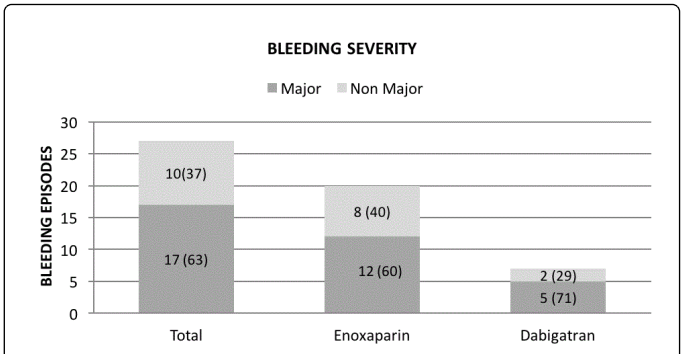

Figure 2: All values expressed as n (%) unless otherwise specified.

The mean Body Mass Index (BMI) for enoxaparin related bleeding episodes was 29.8, 29.5 and 35.7 in the normal renal function, moderate impairment and severe impairment groups, respectively. In dabigatran-related bleeding episodes, the mean BMI was 27.5, 24.9 and 27 in the normal renal function, moderate impairment and severe impairment groups, respectively. Baseline hypertension was present in 16 of 27 patients experiencing enoxaparin related bleeding episodes (63% in the normal renal function and moderate impairment group and 67% in the severe renal impairment group). Hypertension was also seen in 4 of 7 dabigatran-related bleeding episodes.

Variable	n=27	Co-morbidities	n=27
Mean age, years ± SD	74 ± 13.8	Hypertension	16 (59)
Female	16 (59)	Malignancy	11 (40)
Mean BMI ± SD	30.3 ± 6.2	Diabetes mellitus	7 (26)
≥10 Days of therapy	13 (48)	Congestive heart failure	7 (26)
Enoxaparin bleeding episodes	20	Liver disease	2 (7)
1 mg/kg q12h	16 (80)	Intensive care unit	5 (19)
1.5 mg/kg q24h	3 (15)	Concomitant medications	
1 mg/kg q24	1 (5)	Aspirin	6 (22)
Venous Thromboembolism (VTE)	14 (70)	Warfarin*	7 (35)
Atrial fibrillation	4 (20)	Median INR (range)	2.7 (1.2-3.6)
Valve replacement	2 (10)	NSAID	1 (4)
Dabigatran bleeding episodes	7	Dronedarone†	2 (29)
150 mg q12h	4 (57)	Amiodarone†	1 (14)
75 mg q12h	3 (43)	-	-
Atrial fibrillation	7 (100)	-	-
All values expressed as n (%) unless otherwise specified, * Data for enoxaparin only, † Data for dabigatran only			

Table 5: Patient demographics.

Concomitant warfarin use was seen in 7 (35%) of the enoxaparin patients where enoxaparin was used as bridge therapy. The median INR was 2.7 (range: 1.2-3.6). Concurrent aspirin use was identified in 6 (22%) total patients. Dabigatran-related bleeding episodes were identified with the concomitant p-glycoprotein inhibitors dronedarone or amiodarone in 3 of 7 cases (43%). Other agents that may predispose patients to bleeding episodes were not observed (Table 5).

Discussion

Our results identified that patients with moderate renal impairment were most likely to present with a bleeding episode, which was the presenting renal function range for 45% of our patients. Patients with any form of renal impairment made up 65% of all presenting bleeding episodes. Additionally, we noted that the majority of presenting bleeding episodes was classified as major bleeds based on the EINSTEIN criteria [19]. This held true for both enoxaparin and dabigatran bleeds. However, given the nature of ICD-9 codes and the patient safety intelligence reports, there may have been a predisposition to detect major as opposed to non-major bleeding episodes. We were not able to identify any bleeding episodes occurring with fondaparinux pharmacotherapy, likely due to the infrequent use at our institution. We observed a similar rate of bleeding episodes for patients on enoxaparin in both the normal renal function group (n=8) and the moderate renal impairment group (n=9). We initially hypothesized that patients with moderate renal impairment may experience an appreciable degree of anticoagulant accumulation, leading to an increased risk of bleeding. Although, previous data has implicated that bioaccumulation of enoxaparin is seen in patients whose CrCl is in the 30-50 ml/min range, this may not be clinically significant in all patients [13]. However, a retrospective review of Veterans affairs data by Decarolis did indeed find an increased bleeding risk in patients with moderate renal impairment compared to those with normal renal function [21].

Variable	CrCl >50 mL/min n=8	CrCl 30-50 mL/min n=9	CrCl <30 mL/min n=3
Mean age, years ± SD	67 ± 18	77 ± 12	73 ± 4
Female	2 (25)	7 (78)	3 (100)
Mean BMI ± SD	29.8 ± 5.2	29.5 ± 6.5	35.7 ± 7.1
≥10 days of therapy	5 (63)	3 (33)	1 (33)
Hypertension	5 (63)	5 (63)	2 (67)
Malignancy	5 (63)	3 (33)	2 (67)
Diabetes mellitus	2 (25)	3 (33)	1 (33)
Congestive heart failure	1 (13)	3 (33)	1 (33)
Warfarin	3 (38)	3 (33)	1 (33)
Aspirin	1 (13)	3 (33)	0 (0)
NSAID	0 (0)	0 (0)	1 (33)
All values expressed as n (%) unless otherwise specified			

Table 6: Enoxaparin bleeding episodes.

We attempted to discern if potential risk factors for bleeding may be present in a significant portion of patients in the moderate renal impairment group. Hypertension, which was identified as a risk factor in the literature was present in 67% of patients in both the normal renal function and moderate impairment group. Interestingly, patients presenting with bleeding episodes with moderate renal impairment were more likely to be female (78%) and greater than 75 years of age. While advanced age was previously recognized as a potential risk factor, gender has not been implicated [22]. Of note, the mean BMI for all enoxaparin patients was 31.7, classifying these patients as obese. This is an interesting finding as enoxaparin's volume of distribution is approximately 5 L similar to that of total body plasma, lending credence to the controversial subject of using an adjusted body weight to dose enoxaparin in obese patients [23]. We were only able to identify 3 bleeding episodes in patients with severe renal impairment. There are several possible explanations for this finding. Firstly, the recommend dose adjustment for patients in this renal function range may be sufficient at eliminating the potential for enoxaparin accumulation. Additionally, there may be a general consensus to avoid enoxaparin as the anticoagulant agent of choice in patients with severe renal impairment when possible thus leading to decreased overall exposure of patients in this renal function range to enoxaparin. An interesting finding is that 7 total enoxaparin patients (35%) incurred bleeding episodes while being bridged to warfarin with a median INR at the time of the bleed of 2.7 (range 1.2-3.6). Two of these patients were receiving anticoagulation for atrial fibrillation and the other for a mechanical valve. All 3 of these bleeding episodes were major bleeds. This highlights the importance of weighing the risk vs benefit for deciding which patients on warfarin should be on 'bridge' therapy with enoxaparin while off warfarin (Table 6).

Variable	CrCl>50 mL/min n=1	CrCl 30-50 mL/min n=3	CrCl<30 mL/min n=3
Mean age, years ± SD	72 ± NA	82 ± 2.6	87 ± 11.7
Female	1 (100)	1 (33)	2 (67)
Mean BMI ± SD	27.5 ± NA	24.9 ± 2.25	27.0 ± 4.80
≥ 10 days of therapy	1 (100)	2 (67)	3 (100)
Hypertension	1 (100)	0 (0)	3 (100)
Malignancy	0 (0)	1 (33)	0 (25)
Diabetes mellitus	0 (0)	1 (33)	0 (0)
Congestive heart failure	0 (0)	1 (33)	1 (33)
Warfarin	0 (0)	2 (67)	0 (0)
Aspirin	0 (0)	0 (0)	1 (33)
NSAID	72 ± NA	82 ± 2.6	87 ± 11.7
All values expressed as n (%) unless otherwise specified			

Table 7: Dabigatran bleeding episodes.

We only identified 7 dabigatran bleeds as the drug was newly added to the formulary during this time period and may not have been chosen in patients with renal impairment. Only one dabigatran-related

bleed was identified in a patient with normal renal function. The remaining 6 bleeding episodes were evenly divided between patients with moderate renal impairment and severe renal impairment. Given that dabigatran is 80% renally cleared as unchanged drug and the recommended dose reduction to 75 mg is derived from pharmacokinetic data, this finding is not entirely surprising [11]. Additionally, 5 of 7 dabigatran-related bleeding episodes were categorized as major bleeds. Dabigatran patients identified were also more likely to be of advanced age with a mean age of 82 and 87 years in the moderate and severe renal impairment group, respectively. Additionally, dabigatran-related bleeding episodes were seen in patients with lower BMIs than those seen in enoxaparin patients. Finally, Permeability Glycoprotein (P-gp) inhibitors, specifically dronedarone and amiodarone were seen as concomitant therapy in 3 of 7 bleeding episodes. Two of these patients were in the moderate impairment group and one in the severe impairment group. Given that dabigatran is a P-gp substrate and these two agents are often prescribed in patients with atrial fibrillation, this is a concerning finding and echoes an FDA statement recommending dose adjustment of dabigatran for patients with moderate renal impairment receiving concurrent pharmacotherapy with P-gp inhibitors (Table 7).

This study possessed several limitations, including the retrospective design and small sample size. The small overall number of bleeding episodes identified affected the overall robustness of the study, particularly in patients receiving dabigatran and fondaparinux. However, this may be due to the propensity to avoid renally cleared anticoagulants in patients at risk for bleeding. Finally, due to the intrinsic predisposition of ICD-9 codes and the patient safety intelligence reporting system to identify major bleeding episodes; our bleeding severity data may have been disproportionally skewed.

Conclusion

In conclusion, anticoagulants that rely on renal clearance may accumulate in moderate renal impairment in addition to severe impairment. Although, we noted more bleeding episodes in the moderate impairment group, this was not seen when looking at the enoxaparin group specifically. A greater percentage of bleeding episodes identified were of major severity, particularly in the dabigatran group. Our study highlights that major bleeds are more likely to be self-reported than minor bleeds. The majority of dabigatran bleeding episodes occurred in patients with some degree of renal impairment and of advanced age. Our investigation further supports the clinical significance of bioaccumulation of renally cleared anticoagulants in patients with moderate renal impairment. Our investigation should be considered a hypothesis-generating study for future analysis of the clinical significance of drug accumulation in patients with moderate renal impairment on all anticoagulants with renal clearance, including all of the DOACs.

References

1. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE (2009) Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 43: 1064-1083.
2. Trocóniz IF, Tillmann C, Liesenfeld KH, Schäfer HG, Stangier J (2007) Population pharmacokinetic analysis of the new oral thrombin inhibitor dabigatran etexilate (BIBR 1048) in patients undergoing primary elective total hip replacement surgery. J Clin Pharmacol 47: 371-382.
3. Cohen M, Blaber R, Demers C, Gurfinkel EP, Langer A, et al. (1997) The essence trial: efficacy and safety of subcutaneous enoxaparin in unstable angina and non-q-wave MI: a double-blind, randomized, parallel-group, multicenter study comparing enoxaparin and intravenous unfractionated heparin: methods and design. J Thromb Thrombolysis 4: 271-274.
4. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, et al. (1999) Enoxaparin prevents death and cardiac ischemic events in unstable angina/non–q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 100: 1593-1601.
5. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, et al. (2004) Enoxaparin vs unfractionated heparin in high-risk patients with non–ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy. JAMA 292: 45-54.
6. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, et al. (2002) Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 134: 191-202.
7. Chow SL, Zammit K, West K, Dannenhoffer M, Lopez-Candales A (2003) Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. J Clin Pharmacol 43: 586-590.
8. Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, et al. (2002) Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. Thromb Res 105: 225-231.
9. Montalescot G, Collet JP, Tanguy ML, Ankri A, Payot L, et al. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. Circulation 110: 392-398.
10. Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, et al. (2003) Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J 146: 33-41.
11. Stangier J (2008) Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 47: 285-295.
12. Donat F, Duret JP, Santoni A, Cariou R, Necciari J, et al. (2002) The pharmacokinetics of fondaparinux sodium in healthy volunteers. Clin Pharmacokinet 41: 1-9.
13. Bazinet A, Almanric K, Brunet C, Turcotte I, Martineau J, et al. (2005) Dosage of enoxaparin among obese and renal impairment patients. Thromb Res 116: 41-50.
14. Hulot JS, Montalescot G, Lechat P, Collet JP, Ankri A, et al. (2005) Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. Clin Pharmacol Ther 77: 542-552.
15. Fox KA, Antman EM, Montalescot G, Agewall S, SomaRaju B, et al. (2007) The impact of renal dysfunction on outcomes in the extract-TIMI 25 trial. J Am Coll Cardiol 49: 2249-2255.
16. Green B, Greenwood M, Saltissi D, Westhuyzen J, Kluver L, et al. (2005) Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. Br J Clin Pharmacol 59: 281-290.
17. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361: 1139-1151.
18. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, et al. (2009) Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 361: 2342- 2352.
19. Nutescu E, Chuatrisorn I, Hellenbart E (2011) Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. J Thromb Thrombolysis 31: 326-343.
20. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365: 883-891.

21. Hughes M, Lip GYH (2007) Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. QJM 100: 599-607.

22. Decarolis DD, Thorson JG, Clairmont MA, Leuthner AM, Rector TS, et al. (2012) Enoxaparin outcomes in patients with moderate renal impairment. Arch Intern Med 172: 1713-1718.

23. Lovenox [package insert] (2010) Laval, Quebec: sanofi-aventis Canada Inc.