

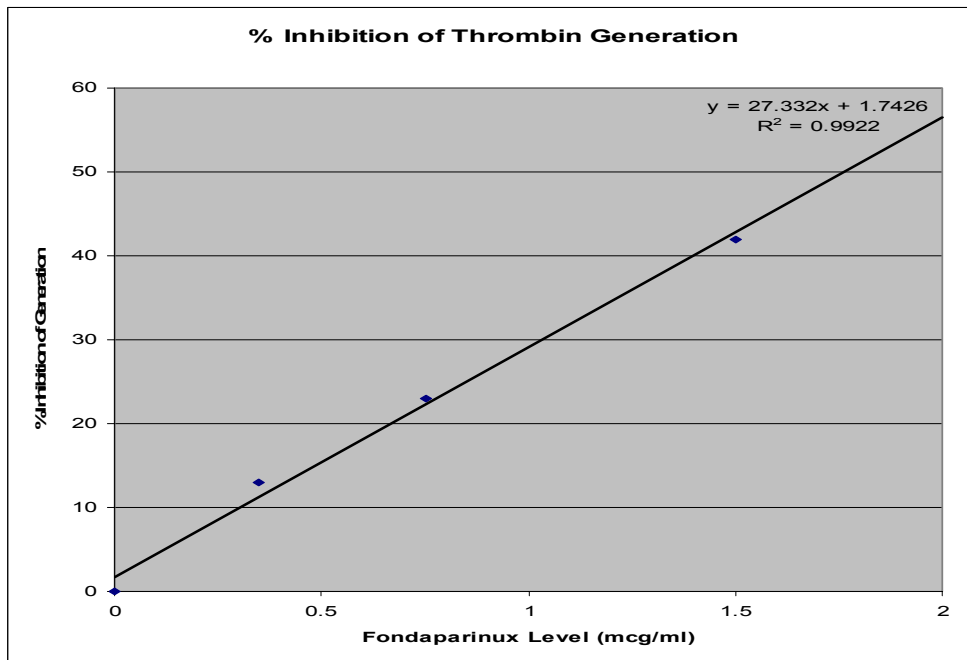
Bon Secours Richmond  
Pharmacy & Therapeutics Committees  
Arixtra (fondaparinux sodium)  
11/2006

**Recommendations:**

- Fondaparinux (Arixtra®) was approved by MEC not to be added to formulary in 9/2002 due to bleeding concerns and lack of reversibility. It is recommended for inclusion at this time and will be restricted to hematologists for patients who have or have had heparin induced thrombocytopenia or who are allergic to LMWH. Pharmacy will automatically adjust the dose of fondaparinux, when ordered for DVT/PE treatment, based on the patient's renal function and lean body weight.
  - Pharmacy will determine the patient's creatinine clearance and lean body weight before dispensing fondaparinux.
  - Patients will not receive fondaparinux unless a recent serum creatinine has been determined and the calculated creatinine clearance is  $\geq 30$  ml/min.
  - Fondaparinux prophylaxis should not be given to patients weighing  $< 50$  kg following orthopedic surgery.
  - Fondaparinux is contraindicated in patients with bacterial endocarditis
  - Patients receiving fondaparinux will have a serum creatinine and BUN determined every other day during therapy.
  - Fondaparinux Anti Xa levels will be drawn on all patients.

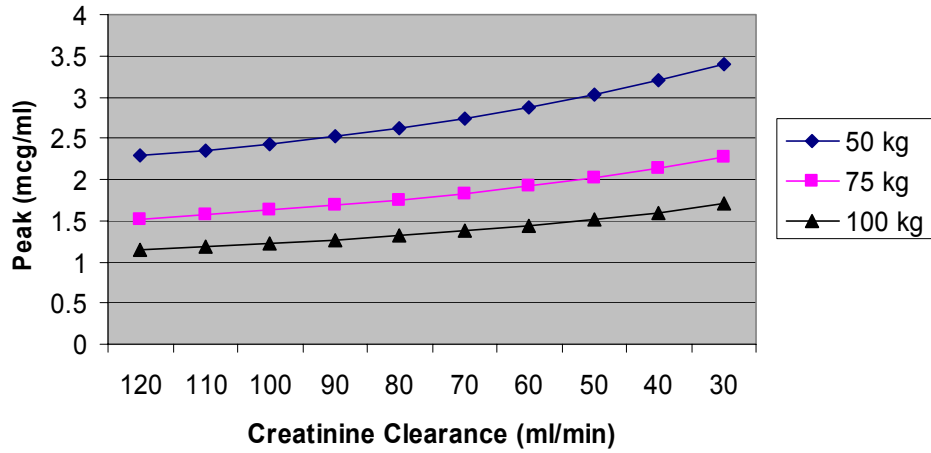
**Rationale for Recommendations**

- Inhibition of thrombin generation, within fondaparinux's therapeutic range ( $< 2$ mcg/ml), is directly correlated with the serum level of fondaparinux, see graphic below.
- Major determinants of fondaparinux serum levels are lean body weight and renal function.
  - Fondaparinux's major route of elimination is renal.
  - Seventy-seven percent of the dose is renally eliminated unchanged.
  - The half-life ranges from 17 hours in young patients to 40 hours in renal failure.
  - The dose of fondaparinux should be adjusted for both renal function and lean body weight to minimize the risk of bleeding while maintaining efficacy for therapeutic indications.
- Use of the package insert dosing would lead to wide variation of levels depending on the patient's weight and renal function (see graphics below) and increase the risk of major bleeding.
  - 7.5 mg for patients 50-100 kg with renal function of 30-120 ml/min as recommended by the manufacturer would result in the following levels:
    - Peaks 1.14-3.3 mcg/ml, troughs 0.45-2 mcg/ml

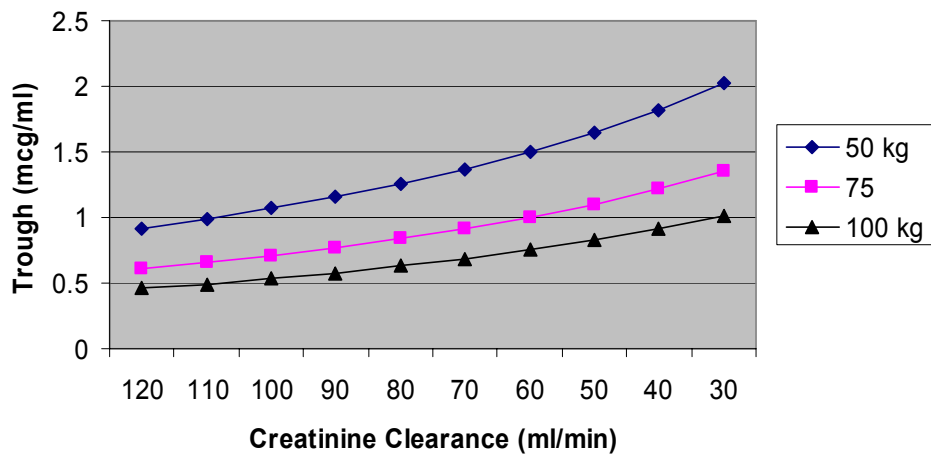


Graphic Adapted from Arixtra Product Monograph

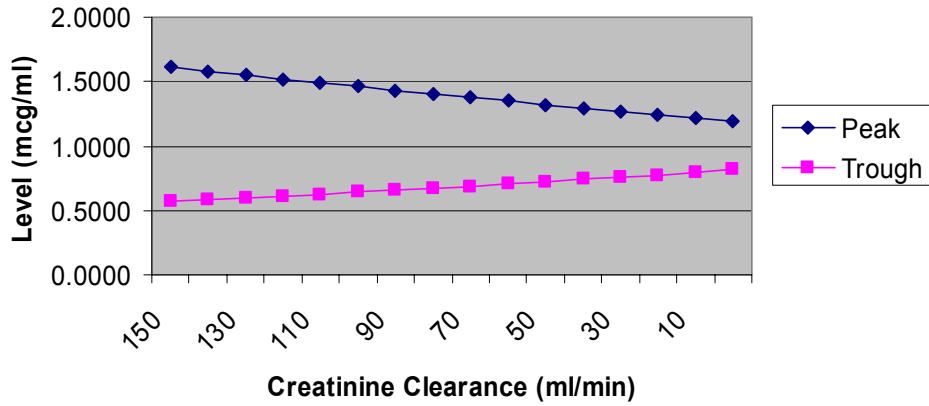
**Peak Serum Levels for Arixtra 7.5 mg Daily**



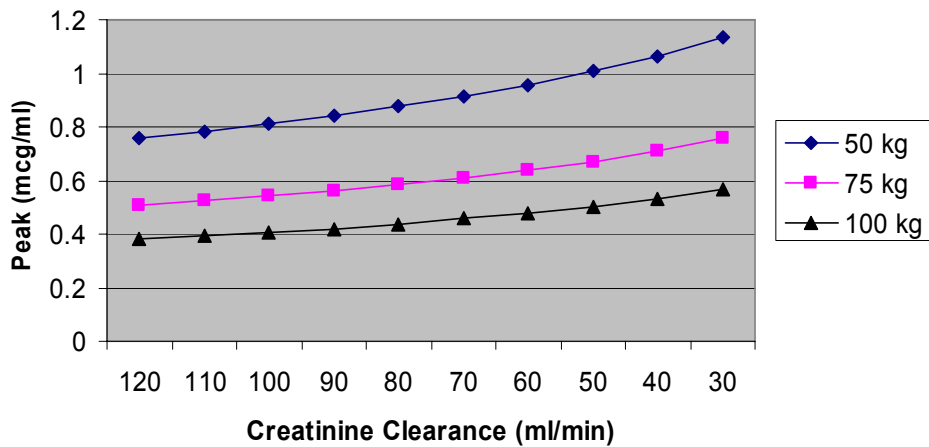
**Trough Serum Levels for Arixtra 7.5 mg Daily**



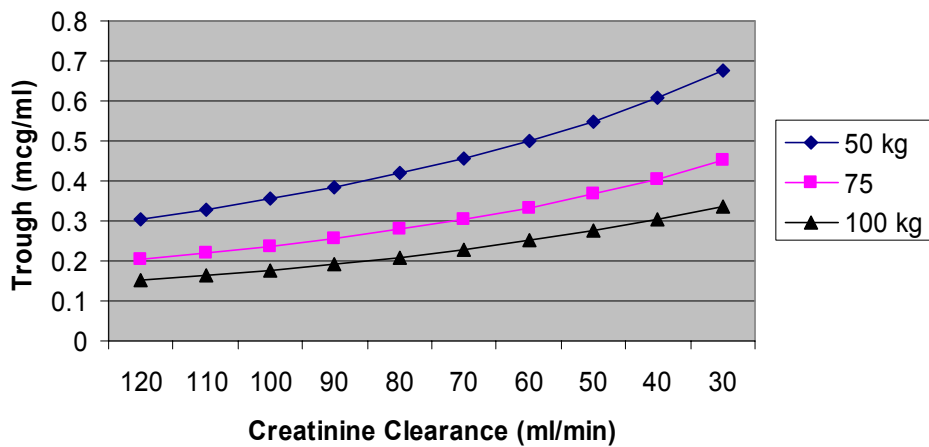
### Arixtra Dosing Using Lean Body Weight and Creatinine Clearance



### Arixtra 2.5 mg Daily For Prophylaxis



### Arixtra 2.5 mg Daily For Prophylaxis



- The rate of major bleeding is related to renal function, weight, and age of patient.

		<b>Degree of Renal Impairment Creatinine Clearance</b>			
		Severe < 30 ml/min	Moderate 30-50 ml/min	Mild 50-80 ml/min	Normal > 80 ml/min
<b>Indication</b>	<b>Daily Dose mg</b>	<b>Incidence of Major Bleeding</b>			
Orthopedic Surgery Prophylaxis	2.5	4.8%	3.8%	2.4%	1.6%
Abdominal Surgery Prophylaxis	2.5	7.1%	6.7%	3.6%	2.1%
Treatment of DVT/PE	5-10	7.3%	2.2%	1.6%	0.4%

- The risk of major bleeding associated with Fondaparinux sodium increased with age: 1.8% (23/1253) in patients <65 years, 2.2% (24/1111) in those 65 to 74 years, and 2.7% (33/1227) in those 75 years and older.
- Patients weighing < 50 kg (clearance decreased by 30% compared to higher weight patients) demonstrated major bleeding in 5.4% versus 2.1% in patients weighing greater than 50 kg
- Protamine is not effective in reversing the effects of fondaparinux. *Fondaparinux continues to have pharmacologic effects until it is excreted from the body.***
  - Fondaparinux has a high affinity for the antithrombin molecule and binds rapidly. When fondaparinux binds to antithrombin III it forms a complex and causes a conformational change in the antithrombin molecule, increasing antithrombin III's activity with Factor Xa by 300 times, and decreases thrombin generation without affecting circulating thrombin. Fondaparinux is not consumed in the inactivation of factor Xa, but is released from antithrombin III once the antithrombin III-fondaparinux complex has bound to and inactivated factor Xa. The company suggests using fresh frozen plasma, blood replacement, and surgical hemostasis to control bleeding (personal communication with company).
  - Recombinant factor VIIa in doses of 90 mcg/kg may be used to temporarily reverse the effects of fondaparinux. Factor VIIa when complexed with tissue factor can activate coagulation Factor X to Xa. The duration of action is short and may last from 2 to 6 hours. The cost of one dose for a 70 kg patient is \$6888. (Bijsterveld NR, Circulation 2002;106:2550-2554).

<b>Bon Secours Richmond</b>	
<b>Use of Reversal Agents In Patient's Receiving Enoxaparin Prior 12 Months</b>	
<b>Medical Patients N=5003</b>	
Protamine	3/5003
FFP	64/5003
Factor VIIa	3/5003
<b>Medical Patients With Discharge Diagnosis of Bleeding N=5003</b>	
Protamine	0/5003
FFP	14/5003
Factor VIIa	0/5003
<b>Medical &amp; Surgical Patient With Discharge Diagnosis of Bleeding N=7406</b>	
Protamine	15/7406
FFP	49/7406
Factor VIIa	2/7406

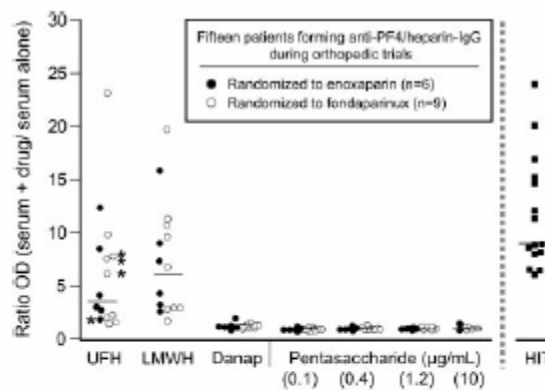
- Fondaparinux causes generation of anti-PF4/heparin antibodies at a similar frequency as patients treated with enoxaparin. Seroconversion rates over time are similar for enoxaparin and fondaparinux. Antibodies reacted equally well in vitro against PF4/UFH and PF4/LMWH, and sometimes weakly against PF4/danaparoid, none reacted against PF4/fondaparinux. Antibodies generated during treatment with fondaparinux are otherwise indistinguishable in their biologic characteristics from those generated during treatment with heparin, therefore patients receiving fondaparinux could develop acute HIT if UFH or LMWH is subsequently given. (Warkentin TE, Blood 2005;106:3791-3796)

**Table 2. Categorical analysis of anti-PF4/heparin antibody seroconversion events**

Study and study drug	No. patients	Group 1, no. (%) <sup>*</sup>	P	Group 2, no. (%) <sup>†</sup>	P	Combined, no. (%)	P
<b>Knee (PENTAMAKS)<sup>14</sup></b>			> .999		.07		.13
Enoxaparin	365	5 (1.4)		14 (3.8)		19 (5.2)	
Fondaparinux	388	5 (1.3)		6 (1.5)		11 (2.8)	
<b>Hip (PENTATHLON)<sup>15</sup></b>			.37		> .999		.55
Enoxaparin	984	1 (0.1)		10 (1.0)		11 (1.1)	
Fondaparinux	989	4 (0.4)		11 (1.1)		15 (1.5)	

<sup>\*</sup>Group 1 defined as formation of anti-PF4/heparin antibodies of IgG class from a negative baseline. Four patients in group 1 tested positive for heparin-dependent platelet-activating antibodies in the serotonin release assay (knee study: 1 in enoxaparin group, 2 in fondaparinux group; hip study: 1 in fondaparinux group).

<sup>†</sup>Group 2 consisted of all non-group 1 patients who had evidence for an immune response, including the formation of IgM or IgA or both (but not IgG) anti-PF4/heparin antibodies or who had a positive test at baseline, but subsequently developed at least a 2-fold increase in reactivity in the EIA (by change in OD).



**Figure 2.** Ratio of antibody binding to PF4/polysaccharide complexes compared to PF4 alone by fluid-phase EIA. Results of fluid-phase EIA testing for sera from 15 patients who formed anti-PF4/heparin-IgG antibodies (detected using solid-phase EIA) while receiving enoxaparin (n = 6, ●) or fondaparinux (n = 9, ○). The data are expressed as ratios of binding to PF4 in the presence of polysaccharide (UFH, 0.6 IU/mL; LMWH, 0.5 anti-Xa U/mL; danaparoid, 0.1 anti-Xa U/mL; and fondaparinux, 0.1, 0.4, 1.2, and 10.0 µg/mL) over the baseline (buffer). Horizontal bars indicate medians. \* indicate the 4 samples that tested positive (in the presence of UFH) in the platelet activation assay. For comparison, results are also shown for 15 patients with clinical HIT (■). Statistically significant increases in reactivity (null hypothesis, mean ratio of OD [presence of drug]/OD [presence of buffer] = 1) for the 15 sera obtained from patients in the orthopedic trials were observed for UFH (P = .003), LMWH (P < .001), danaparoid (P = .002), but not with fondaparinux at any concentration (P > .05). Whereas 14 of 15 sera from patients in the orthopedic trials exhibited more than 2-fold greater reactivity than baseline against PF4/LMWH, none reacted similarly against PF4/fondaparinux (P < .001 by the McNemar test, 2-tailed).

- One abstract and one study failed to demonstrate cross-reactivity of fondaparinux to antibodies to heparin-platelet Factor-4 complexes from patients with type II heparin-induced thrombocytopenia. No studies have been done with Arixtra in patients with HIT per the manufacturer. There are case reports of fondaparinux being successfully used in patients with heparin induced thrombocytopenia as a treatment and prophylaxis. Fondaparinux should be discontinued if the platelet count falls below 100,000 per mm<sup>3</sup> during its use. Moderate thrombocytopenia (platelet count 50,000 -100,000/mm<sup>3</sup>) occurred at a rate or 2.9% and severe (<50,000 /mm<sup>3</sup>) at a rate of 0.2% during clinical trials.
- HIT occurs in less than 1% of patients receiving enoxaparin (Blood 2005;106:a3791-3796)

- Pharmacy Dosing of fondaparinux
  - The elimination rate of fondaparinux ( $\text{hour}^{-1}$ ) =  $0.0002 * \text{creatinine clearance (ml/min)} + 0.0175$ , per package insert information
    - Treatment doses required to maintain the same 12 hour post dose plasma concentration for patients of varying weights and renal function may be calculated using the equation below. Resulting serum levels are the same as a 75 kg patient with normal renal function receiving 7.5 mg per day. See graphic above and tables below.
      - Maintenance Dose (mg/kg of lean body weight) =  $0.0005 * \text{creatinine clearance (ml/min)} + 0.0414$ , maximum daily dose 10 mg
        - Expected 12 hour post dose level 1, peak and trough vary depending on renal function
      - Initial (loading) dose: due to the long time to steady state levels with fondaparinux an initial dose of 0.15 mg per kg of lean body weight is recommended, with a maximum dose of 10 mg.

Time To Draw Level Post Dose (hours) 12.0  
Goal Level 12 hours Post Dose 1.0 mcg/ml

Fondaparinux Daily Dosing Chart Based On Lean Body Weight & Creatinine Clearance

Creatinine Clearance (ml/min)	150	140	130	120	110	100	90	80	70	60	50	40	30
K (hours-1)	0.0475	0.0455	0.0435	0.0415	0.0395	0.0375	0.0355	0.0335	0.0315	0.0295	0.0275	0.0255	0.0235
T1/2 (Hours)	14.6	15.2	15.9	16.7	17.5	18.5	19.5	20.7	22.0	23.5	25.2	27.2	29.5
Dose mg/kg of Lean Body Weight	0.115	0.110	0.105	0.100	0.095	0.090	0.085	0.080	0.075	0.071	0.066	0.061	0.056
50	5.625	5.625	5.000	5.000	5.000	4.375	4.375	3.750	3.750	3.750	3.125	3.125	2.500
55	6.250	6.250	5.625	5.625	5.000	5.000	4.375	4.375	4.375	3.750	3.750	3.125	3.125
60	6.875	6.875	6.250	6.250	5.625	5.625	5.000	5.000	4.375	4.375	3.750	3.750	3.125
65	7.500	6.875	6.875	6.250	6.250	5.625	5.625	5.000	5.000	4.375	4.375	3.750	3.750
70	8.125	7.500	7.500	6.875	6.875	6.250	6.250	5.625	5.000	5.000	4.375	4.375	3.750
75	8.750	8.125	8.125	7.500	6.875	6.875	6.250	6.250	5.625	5.000	5.000	4.375	4.375
80	9.375	8.750	8.125	8.125	7.500	7.500	6.875	6.250	6.250	5.625	5.000	5.000	4.375
85	10.000	9.375	8.750	8.750	8.125	7.500	7.500	6.875	6.250	6.250	5.625	5.000	5.000
90	10.625	10.000	9.375	8.750	8.750	8.125	7.500	7.500	6.875	6.250	5.625	5.625	5.000
95	11.250	10.625	10.000	9.375	8.750	8.750	8.125	7.500	6.875	6.875	6.250	5.625	5.625
100	11.250	11.250	10.625	10.000	9.375	8.750	8.750	8.125	7.500	6.875	6.875	6.250	5.625
Lean Body Weight (kg)	<b>Rounded Dose (mg), to nearest 0.625 mg</b>												

## Findings:

- Fondaparinux is a synthetic pentasaccharide with specific anti-Factor Xa activity. The molecule is a copy of the antithrombin III binding area of heparin. It has a high affinity for the antithrombin molecule and can bind to antithrombin III rapidly. When fondaparinux binds to antithrombin III it forms a complex and causes a conformational change in the antithrombin molecule, increasing antithrombin III's activity with Factor Xa by 300 times, and decreases thrombin generation without affecting circulating thrombin. Fondaparinux is dependent on antithrombin III for its anticoagulant effect. Fondaparinux is not consumed in the inactivation of factor Xa, but is released from antithrombin III once antithrombin III-fondaparinux complex has bound to factor Xa. The lack of impact on circulating thrombin levels is because the small molecular size of fondaparinux allows it to bind to Factor Xa but not bind to the thrombin molecule unlike heparin. It has no antifactor IIa activity and does not effect aPTT or INR.
- When fondaparinux binds to the antithrombin it causes a conformational change that potentiates the activity of antithrombin against Factor Xa by a factor of about 300. The activity of fondaparinux is also influenced by endogenous antithrombin levels. At low antithrombin levels, fondaparinux activity is reduced.
- Heparin-induced thrombocytopenia type II occurs when heparin binds to platelet factor 4 to form a highly immunogenic complex that can lead to the development of antibodies. The antibodies bind to the platelet's surface and stimulate aggregation.
- Fondaparinux has been studied in 4823 patients, all studies excluded patients with creatinine > 2 mg/dl.
- A dose ranging study using 0.75, 1.5, 3, 6 and 8 mg of fondaparinux SC in patients with total hip replacement demonstrated a clear dose effect relationship with minimal VTE/major bleeding combination events at less than 3 mg. VTE events decreased & major bleeding increased with increasing doses.
- Clinical studies comparing fondaparinux 2.5 mg qd SC versus enoxaparin 30 mg SC q12H in hip fracture, elective hip replacement and knee replacement show a significant difference in the rate of VTE and all DVT. The rates of proximal DVT and symptomatic PE were not significantly different. In these studies fondaparinux was given on average 6 hours post surgery and enoxaparin 21 hours post surgery which may have influenced the outcomes in all but one of the studies.
- The first dose should be given 6-8 hours after surgery when hemostasis has been established.
- Patients should be monitored closely for bleeding for 2-8 days (3-5 half-lives), after discontinuation of therapy due to fondaparinux's very long half-life and duration of anticoagulant effect.

	Fondaparinux 2.5 mg SC qd	Enoxaparin 30 mg SC Q12h
<b>Hip Replacement Surgery</b>		
	N = 1128	N=1129
Mean Time to first dose	6 hours	20 hours
VTE	6.1% (48/787)	8.3% (66/797) NS
All DVT	5.6% (44/784)	8.2% (65/796) P < 0.005
Proximal DVT	1.7% (14/816)	1.2% (10/830) NS
Symptomatic PE	0.4% (6/1126)	0.1% (1/1128) NS
<b>Knee Replacement Surgery</b>	N=517	N=517
VTE	12.5% (45/361)	27.8% (101/363) P < 0.001
All DVT	12.5% (45/361)	27.1% (98/361) P < 0.001
Proximal DVT	2.4% (9/368)	5.4% (20/372) NS
Symptomatic PE	0.2% (1/517)	0.8% (4/517) NS

VTE is composite of documented DVT and/or documented symptomatic PE

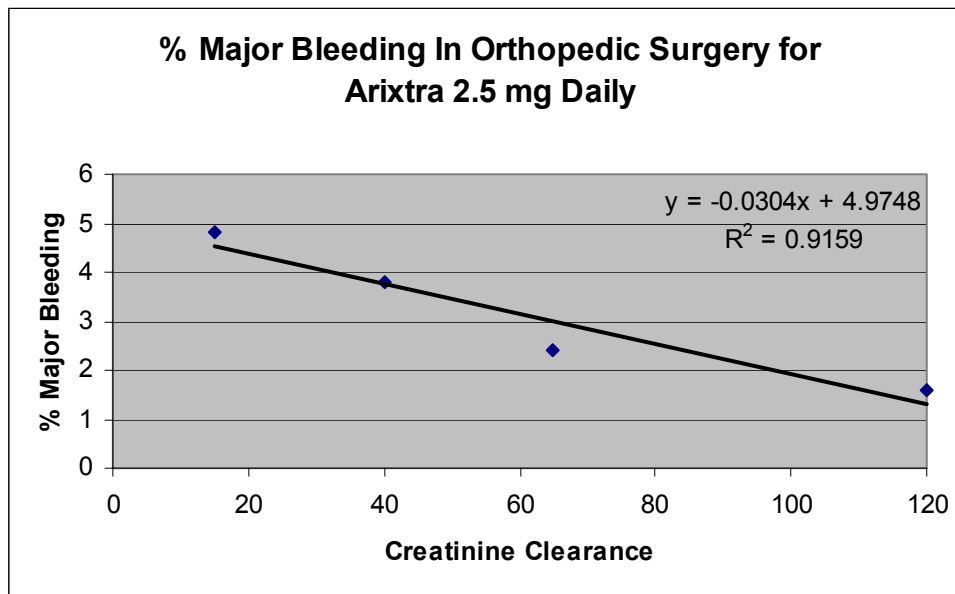
<b>Major Bleeding Episodes Following Hip Fracture, Hip Replacement, and Knee Replacement Surgeries</b>		
Indications	Fondaparinux 2.5mg SC Once daily	LMWH or Enoxaparin
Hip Fracture	18/831 (2.2%)	19/842 (2.3%)
Hip Replacement	67/2268 (3.0%)	55/2597 (2.1%)
Knee Replacement	11/517 (2.1%)	1/517 (0.2%) p = 0.0061
Major Bleeding Across Studies	<b>2.7% (96/3616)</b>	<b>1.9% (75/3956)</b>

Major bleeding was defined as clinically over bleeding that was (1) fatal, (2) bleeding at critical site, (3) re-operation at operative site, (4) bleeding index >= 2

- Currently, there is no FDA-approved agent for specifically reversing the anticoagulant effects of fondaparinux.
- The package insert does not describe how to treat hemorrhage secondary to fondaparinux other than discontinuing the medication. Information from the company suggests using fresh frozen plasma, blood replacement, and surgical hemostasis

(*persona communication*). In preliminary studies, fondaparinux has been demonstrated to be resistant to neutralization with Protamine sulfate.

- A study of healthy male volunteers investigated the neutralization of the anticoagulant effect of fondaparinux by recombinant activated factor VIIa (rVIIa). Sixteen subjects were randomized to one of three treatment groups: 8 subjects received 10 mg SC injection of fondaparinux followed by IV bolus injections of rVIIa (90 ug/kg), 4 received 10 mg SC injection of fondaparinux followed by IV bolus injection of placebo, and 4 received placebo followed by rVIIa. The results of this study demonstrated that the administration of recombinant factor VIIa is able to PARTIALLY reverse the inhibition of thrombin generation in fondaparinux-treated healthy subjects for 2-6 hours at a cost of \$6888.
- Renal Impairment:
  - Fondaparinux is substantially excreted by the kidney, and the risks of adverse effects are higher with renal impairment.
  - Only one study of 20 patients with renal impairment has been published. This study found a half-life of 29 hours in patients with creatinine clearance 31-60 ml/min, and 72 hours for creatinine clearance of 10-30 ml/min. Faaij RA. The influence of renal function on the pharmacokinetics and pharmacodynamic of the novel antithrombotic agent ORG31540/SR90107A. Br J Clin Pharmacol 1997;45:221P-12P
  - Patients with serum creatinine > 2 mg/dl were excluded from clinical studies.



- Fondaparinux should be discontinued immediately in patients who develop severe renal impairment (creatinine clearance < 30 ml/min) or labile renal function while on therapy. The anticoagulant effect lasts for 2-4 days in normal renal function, and is expected to last 5-10 days with clcr < 30 ml/min
- Pharmacokinetics of fondaparinux has not been studied in hepatic impairment.
- Contraindications
  - Patients with creatinine clearance < 30 ml/min and should be used with caution in patients with creatinine clearance 30-50 ml.
  - Body weight < 50 kg (total body clearance is decreased approximately 30%) in orthopedic surgery
  - Bacterial endocarditis
  - Thrombocytopenia associated with antiplatelet antibody in the presence of fondaparinux
- Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use:
  - This drug carries a box warning, "when epidural/spinal anesthesia or spinal puncture is employed, patients anticoagulated with Arixtra for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis".
  - The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as NSAIDs, platelet inhibitors, or other anticoagulants.
- Monitoring of Anti-Xa: assays must be calibrated to fondaparinux.
- Side effects
  - Fondaparinux should be discontinued if the platelet count falls below 100,000 per mm<sup>3</sup>.

- Thrombocytopenia non-immune-mediated (type I)
  - Moderate 2.9%
  - Severe (<50,000 mm<sup>3</sup>) 0.2%

<b>Fondaparinux Data from the Package Insert</b>	
Bioavailability SC	100%
Half Life versus renal function	15.3 hours (young males) k=0.045275 17-21 hours (age ≤ 75 years)
Creatinine Clearance > 80 ml/min	Young 17 hours k= 0.04077 Elderly 21 hours k= 0.033
50-80 ml/min	20.4 hours k=0.033956
30-50 ml/min	25.5 hours k=0.027165
< 30 ml/min	34 hours k=0.020374
Clearance	25% decrease in patients < 50 kg
Creatinine Clearance > 80 ml/min	
50-80 ml/min	25% decrease
30-50 ml/min	40% decrease
<30 ml/min	55% decrease
Duration of anticoagulant effect after drug discontinuation.	
Creatinine Clearance > 80 ml/min	2-4 days
50-80 ml/min	4-5 days
30-50 ml/min	5-6 days
< 30 ml/min	6-8 days
Volume of Distribution	7-11 liters
Protein Binding	94% Highly protein bound to ATIII at levels below 2 mg/l
% Excreted Unchanged	64-77%
Time to Peak SC	2 hours
Molecular Weight	1728
Anti-Xa IU/mg	666

<b>Pharmacokinetics of Fondaparinux and other Anticoagulants</b>							
<b>Parameter</b>	<b>Fondaparinux</b>	<b>Enoxaparin</b>	<b>Dalteparin</b>	<b>Lepirudin</b>	<b>Argatroban</b>	<b>Danaparoid</b>	<b>UFH</b>
Bioavailability	100%	92%	87%	NA	NA	100%	20-30%
Absorption	Rapid	Rapid	Rapid	Rapid	Rapid	slow	Rapid
Elimination	1° renal	1° renal	1° renal	1° renal	1° biliary	1° renal	1° renal
Half-life	17-21 hours	4 hours	3 hours	1.3 hours	0.5 hours	Factor Xa = 24.5 h Factor IIa = 4.3 h	1-2 hours

**FDA Approved Indications: DVT Prophylaxis & Treatment**

<b>Enoxaparin</b>	<b>Fondaparinux</b>
Prophylaxis in Abdominal surgery	Prophylaxis in Abdominal surgery
	Prophylaxis in hip fracture surgery
Prophylaxis in hip replacement surgery	Prophylaxis in hip replacement surgery
Prophylaxis in knee replacement surgery	Prophylaxis in knee replacement surgery
Prophylaxis in medical patients at risk of thromboembolic complications	
Treatment of ischemic complications of unstable angina and non-Q-wave MI	
Treatment of acute DVT with or without PE when administered in conjunction with warfarin	Treatment of acute DVT with or without PE when administered in conjunction with warfarin

**Cost Analysis:**

Lovenox 30 mg q12h cost \$23.51 per day versus \$28.98 for Arixtra 2.5 mg/0.5ml prefilled syringe.