Retrospective Evaluation of Delayed Administration of Fondaparinux in Providing Comparable Safety and Efficacy Outcomes in Patients Undergoing Elective Arthroplasty.

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Presented
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OBJECTIVE

- Discuss the key components of research/evidence-based practice (EBP)
  - Prophylaxis for venous thromboembolism
    - Arthroplasty
      - Consensus Guidelines
      - New Study Data
- Understand the research question
  - Can a delayed ‘dose’ provide the same level of effectiveness and safety, as other ‘standard’ strategies?
- Facilitate research to assess results and implications for clinical practice at Lehigh Valley Hospital

Venous Thromboembolism (VTE)

- Deep venous thrombosis (DVT)
- Pulmonary embolism (PE)
  - PE is the most frequent cause of death following total joint arthroplasty
- Post-thrombotic syndrome (PTS)

Clinical Risk Factors For VTE

- History of VTE
- Age ≥ 40 years old
- Obesity
- Prolonged immobility
- Pregnancy/childbirth
- Genetic predisposition to hematologic abnormalities
- Trauma
- Other: malignancy, coronary syndromes (e.g., unstable angina)
- Major surgery (e.g., total joint arthroplasty)

Anderson FA, Wheeler HB Venous Thromboembolism: risk factors and prophylaxis. Clin Chest Med 1995;16 (2) 235-251.

DVT and PE: Significant Concerns

- PE and DVT account for 250,000 hospitalizations each year
- 3rd most common cardiovascular disease
- PE is often clinically silent:
  - 50% asymptomatic PE in symptomatic proximal DVT
  - Up to 30% in calf DVT

J AM Col Cardiol 2000; 36:970-1062

Current Options for VTE prophylaxis

- Mechanical prophylaxis
- Pharmacologic anticoagulant therapy

Recommended DVT/VTE Prophylaxis

Risk group	Recommended prophylaxis
Hip replacement	Warfarin, LMWH, fondaparinux
Knee replacement	Warfarin, LMWH, IPC, fondaparinux (Arixtra)
Hip fracture	Warfarin, LMWH, fondaparinux
Major trauma	LMWH, IPC
Abdominal surgery	UFH, LMWH, IPC, warfarin, ES
Medical patients	UFH, LMWH, ES

IPC-Intermittent Pneumatic Compression
SCD - Sequential Compression Devices
ES-Elastic stocking
LMWH-Low Molecular Weight Heparin

Geerts et al Chest 2004

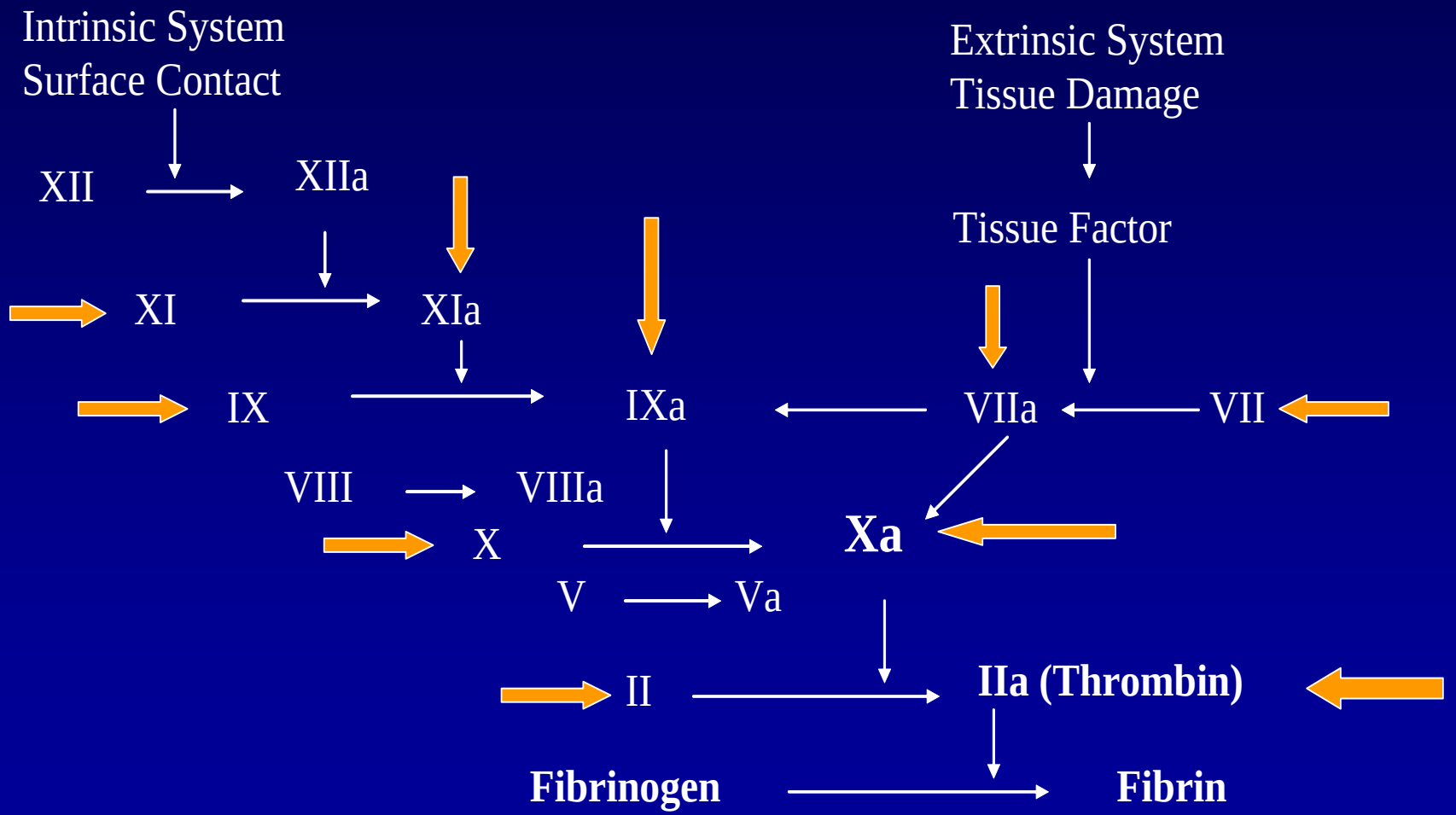
Mechanical Prophylaxis

- Intermittent pneumatic compression (IPC)
- Pneumatic plantar compression (foot pump)
- Advantages
  - Local anti-stasis effects
  - Systemic humoral effects
  - No increase in bleeding risk
- Disadvantages
  - Patient intolerance
  - Compliance difficulties
  - Impractical posthospital discharge application

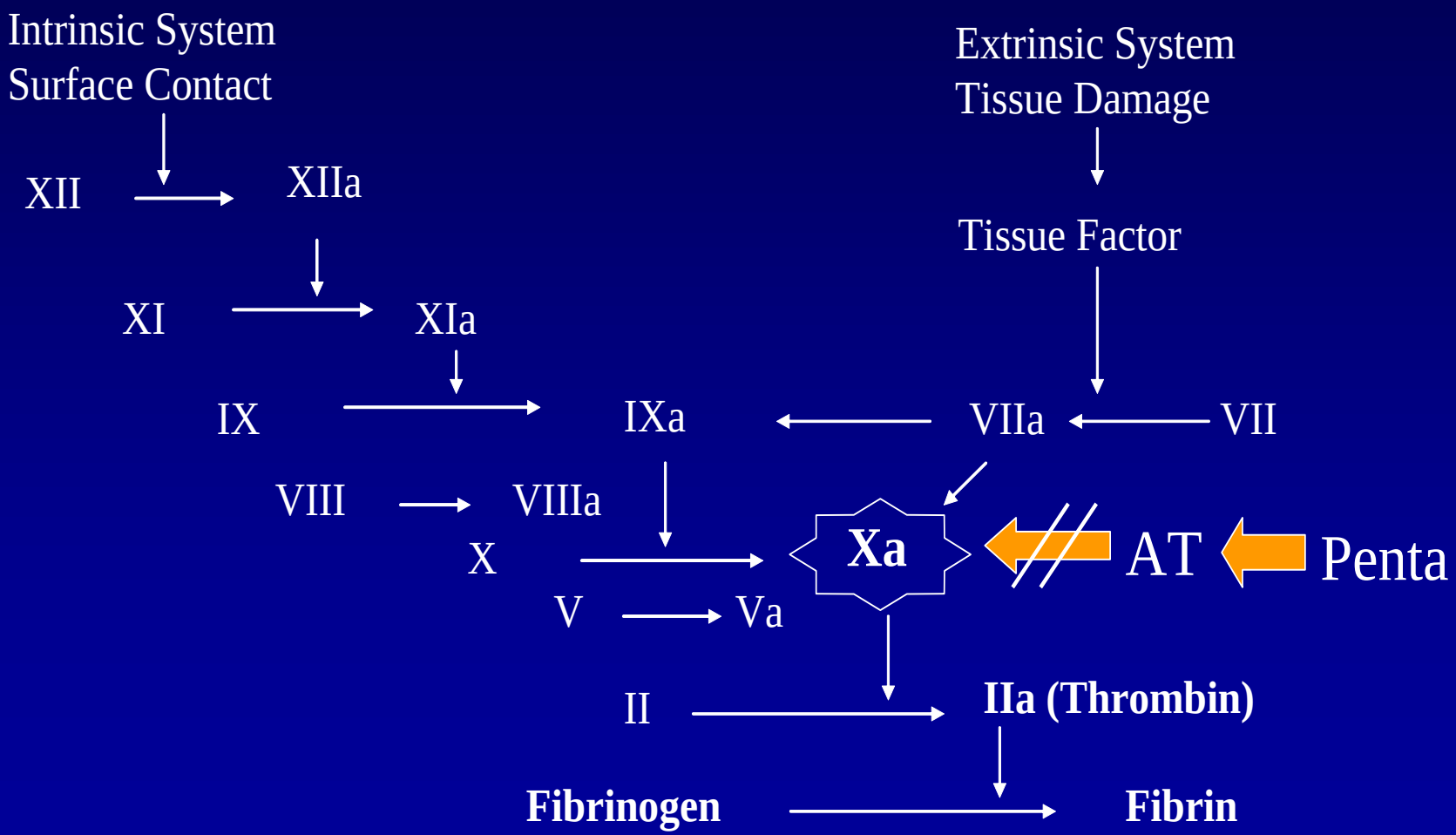
Pharmacologic Anticoagulation

- Oral
  - Warfarin
- Parenteral
  - Unfractionated heparin (UFH)
  - Low-molecular-weight heparins (LMWHs)
- Novel anticoagulation therapies
  - Thrombin inhibitors (lepirudin and others in development)
  - Factor Xa inhibitors (fondaparinux)

Points of Intervention in Clotting Cascade



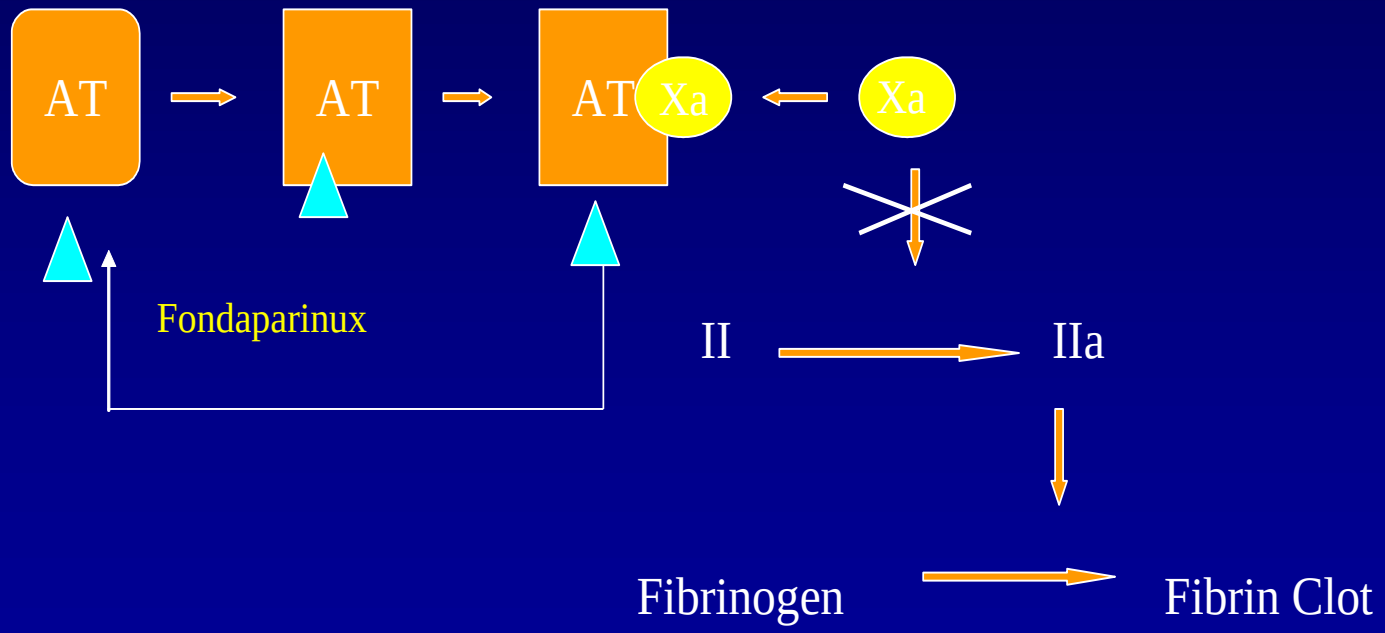
Fondaparinux



Amplification Loop

Fibrinogen

Targeted Mechanism of Action



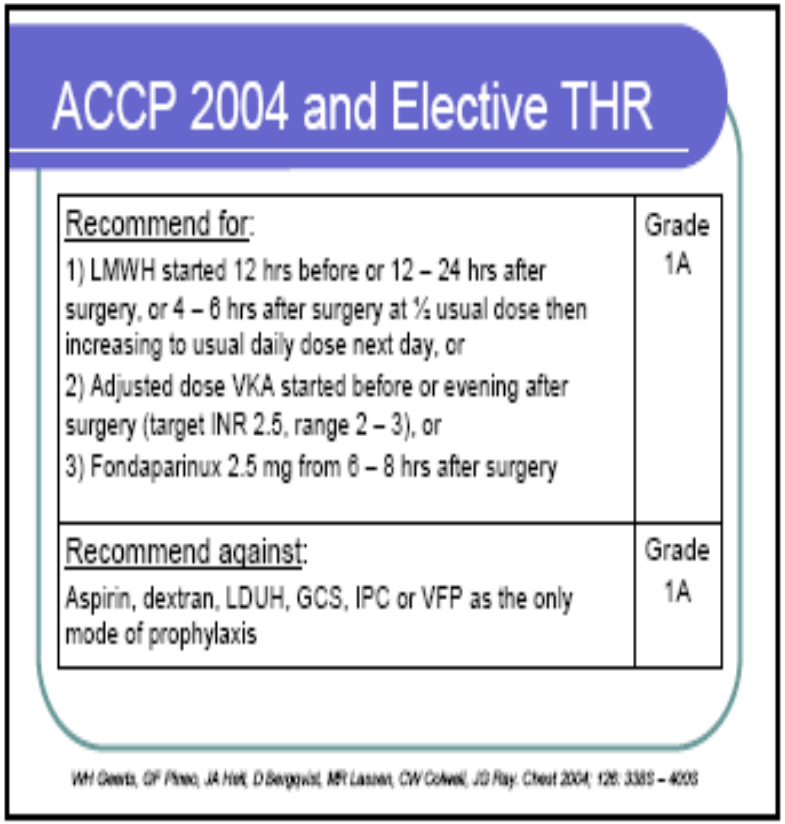
Fondaparinux Advantages

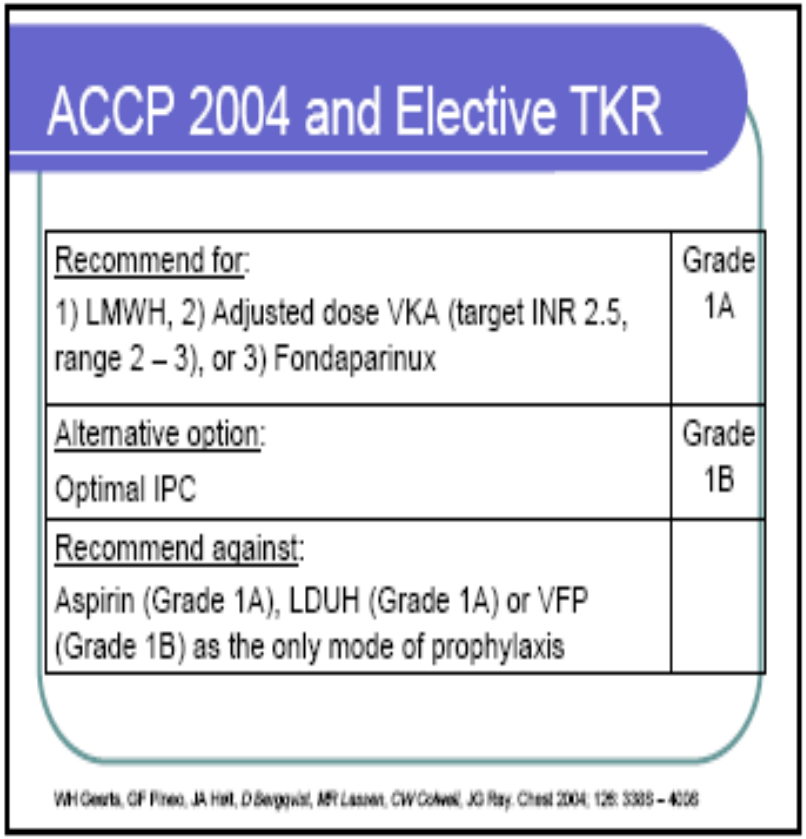
-Specific inhibition of factor Xa via antithrombin
-Highly selective for its target
-100% bioavailability
-Effective and safe
-Total chemical synthesis

Pre-Study Evidence-Based Observations

- Numerous studies and the 7th ACCP Guidelines recommend various VTE (venous thromboembolism) prophylaxis regimens around arthroplasty procedures
  - No definitive answers
- 5 recent published trials suggest fondaparinux is at least equally effective to enoxaparin for VTE prophylaxis after arthroplasty-dosed approximately 6 hours after surgery
- The Pentamaks trial suggests possibly more bleeding
  - Timing of dose may play a part in bleeding risk

2004 ACCP Guidelines-VTE Prophylaxis





Geerts, WH; Pineo, GF; Heit, JA et al.
[The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-based Guidelines]

Volume 126(3) Supplement, September 2004, pp 338S-400S

PENTHIFRA

Table 1. Efficacy of ARIXTRA Injection in the Peri-operative Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Endpoint	Peri-operative Prophylaxis (Day 1 to Day 7 ± 2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily[1]	**Enoxaparin Sodium 40 mg SC once daily[1,2]**
All Treated Hip Fracture Surgery Patients	N = 831	N = 840
All Evaluable[3] Hip Fracture Surgery Patients		
VTE[4]	52/626 8.3%[5] (6.3, 10.8)[6]	119/624 19.1% (16.1, 22.4)
All DVT	49/624 7.9%[5] (5.9, 10.2)	117/623 18.8% (15.8, 22.1)
Proximal DVT	6/650 0.9%[5] (0.3, 2.0)	28/646 4.3% (2.9, 6.2)
Symptomatic PE	3/831 0.4%[7] (0.1, 1.1)	3/840 0.4% (0.1, 1.0)

[1] ARIXTRA was initiated after surgery in 88% of patients (mean 6 hours) and enoxaparin sodium was initiated after surgery in 74% of patients (mean 18 hours).
[2] Not approved for use in patients undergoing hip fracture surgery.
[3] Evaluable patients were those who were treated and underwent the appropriate surgery (i.e., hip fracture surgery of the upper third of the femur), with an adequate efficacy assessment up to Day 11.
[4] VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.
[5] p value <0.001.
[6] Numbers in parentheses indicate 95% confidence interval.
[7] p value: NS.

79% Reduction In Proximal DVT

PENTHIFRA PLUS

Table 2. Efficacy of ARIXTRA Injection in the Extended Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Endpoint	Extended Prophylaxis (Day 8 to Day 28 ± 2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	**Placebo SC once daily**
All Randomized Treated Hip Fracture Surgery Patients	N = 326	N = 330
All Randomized Evaluable Hip Fracture Surgery Patients[1]		
VTE[2]	3/208 1.4%[3] (0.3, 4.2)[4]	77/220 35.0% (28.7, 41.7)
All DVT	3/208 1.4%[3] (0.3, 4.2)	74/218 33.9% (27.7, 40.6)
Proximal DVT	2/221 0.9%[3] (0.1, 3.2)	35/222 15.8% (11.2, 21.2)
Symptomatic VTE (all)	1/326 0.3%[5] (0.0, 1.7)	9/330 2.7% (1.3, 5.1)
Symptomatic PE	0/326 0.0%[6] (0.0, 1.1)	3/330 0.9% (0.2, 2.6)

[1] Evaluable patients were those who were treated in the post-randomization period, with an adequate efficacy assessment for up to 24 days following randomization.

[2] VTE was a composite of documented DVT and/or documented symptomatic PE reported for up to 24 days following randomization.

[3] p value <0.001.

[4] Number in parentheses indicates 95% confidence interval.

[5] p value = 0.021.

[6] p value = NS.

94.3% Reduction In Proximal DVT

PENTATHALON and EPHESUS

Table 3. Efficacy of ARIXTRA Injection in the Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

Endpoint	Study 1		Study 2	
	Fondaparinux Sodium 2.5 mg SC once daily[1]	Enoxaparin Sodium 30 mg SC every 12 hr[3]	Fondaparinux Sodium 2.5 mg SC once daily[2]	Enoxaparin Sodium 40 mg SC once daily[4]
All Treated Hip Replacement Surgery Patients	N = 1,126	N = 1,128	N = 1,129	N = 1,123
All Evaluable[5] Hip Replacement Surgery Patients				
VTE[6]	48/787 6.1%[7] (4.5, 8.0)[8]	66/797 8.3% (6.5, 10.4)	37/908 4.1%[10] (2.9, 5.6)	85/919 9.2% (7.5, 11.3)
All DVT	44/784 5.6%[9] (4.1, 7.5)	65/796 8.2% (6.4, 10.3)	36/908 4.0%[10] (2.8, 5.4)	83/918 9.0% (7.3, 11.1)
Proximal DVT	14/816 1.7%[7] (0.9, 2.9)	10/830 1.2% (0.6, 2.2)	6/922 0.7%[11] (0.2, 1.4)	23/927 2.5% (1.6, 3.7)
Symptomatic PE	5/1,126 0.4%[7] (0.1, 1.0)	1/1,128 0.1% (0.0, 0.5)	2/1,129 0.2%[7] (0.0, 0.6)	2/1,123 0.2% (0.0, 0.6)

[1] In Study 1, ARIXTRA was initiated after surgery in 92% of patients (mean 6.5 hours).
[2] In Study 2, ARIXTRA was initiated after surgery in 86% of patients (mean 6.25 hours).
[3] In Study 1, enoxaparin sodium was initiated after surgery in 97% of patients (mean 20.25 hours).
[4] In Study 2, enoxaparin sodium was initiated before surgery in 78% of patients. The first postoperative dose was given a mean of 13 hours after surgery.
[5] Evaluable patients were those who were treated and underwent the appropriate surgery (i.e., hip replacement surgery), with an adequate efficacy assessment up to Day 11.
[6] VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.
[7] p value versus enoxaparin sodium: NS.
[8] Numbers in parentheses indicates 95% confidence interval.
[9] p value versus enoxaparin sodium in study 1: <0.05.
[10] p value versus enoxaparin sodium in study 2: <0.001.
[11] p value versus enoxaparin sodium in study 2: <0.01.

72% Reduction
In Proximal DVT
Rate
EPHESUS

PENTAMAKS

Table 4. Efficacy of ARIXTRA Injection in the Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

Endpoint	Fondaparinux Sodium 2.5 mg SC once daily[1]	Enoxaparin Sodium 30 mg SC every 12 hours[2]
All Treated Knee Replacement Surgery Patients	N = 517	N = 517
All Evaluable[3] Knee Replacement Surgery Patients		
VTE[4]	45/361 12.5%[5] (9.2, 16.3)[6]	101/363 27.8% (23.3, 32.7)
All DVT	45/361 12.5%[5] (9.2, 16.3)	98/361 27.1% (22.6, 32.0)
Proximal DVT	9/368 2.4%[7] (1.1, 4.6)	20/372 5.4% (3.3, 8.2)
Symptomatic PE	1/517 0.2%[7] (0.0, 1.1)	4/517 0.8% (0.2, 2.0)

1 Patients randomized to ARIXTRA 2.5 mg received the first injection 6 ± 2 hours after surgery providing that hemostasis had been achieved.

2 Patients randomized to enoxaparin sodium received the first injection at 21 ± 2 hours after surgery closure providing that hemostasis had been achieved.

3 Evaluable patients were those who were treated and underwent the appropriate surgery (i.e. knee replacement surgery), with an adequate efficacy assessment up to Day 11.

4 VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.

5 p value <0.001.

6 Numbers in parentheses indicates 95% confidence interval.

7 p value: NS.

55.5% Reduction in Proximal DVT

Bleeding Across Trials

Table 8. Major Bleeding Episodes[1] in Randomized, Controlled, Hip Fracture, Hip Replacement, and Knee Replacement Surgery Studies

	Peri-Operative Prophylaxis (Day 1 to Day 7 ± 1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28 ± 2 post-surgery)	
Indications	**Fondaparinux Sodium 2.5 mg SC once daily**	**Enoxaparin Sodium[2, 3] SC once daily**	**Fondaparinux Sodium 2.5 mg SC once daily**	**Placebo SC once daily**
Hip Fracture	18/831 (2.2%)	19/842 (2.3%)	8/327 (2.4 %)[4]	2/329 (0.6 %)
Hip Replacement	67/2,268 (3.0%)	55/2,597 (2.1%)	—	—
Knee Replacement	11/517 (2.1%)[5]	1/517 (0.2%)	—	—

[1] Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g. intracranial, retroperitoneal, intra-ocular, pericardial, spinal, or into adrenal gland), (3) associated with re-operation at operative site, or (4) with a bleeding index (BI) ≥2 calculated as [number of whole blood or packed red blood cell units transfused + [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dL) values].

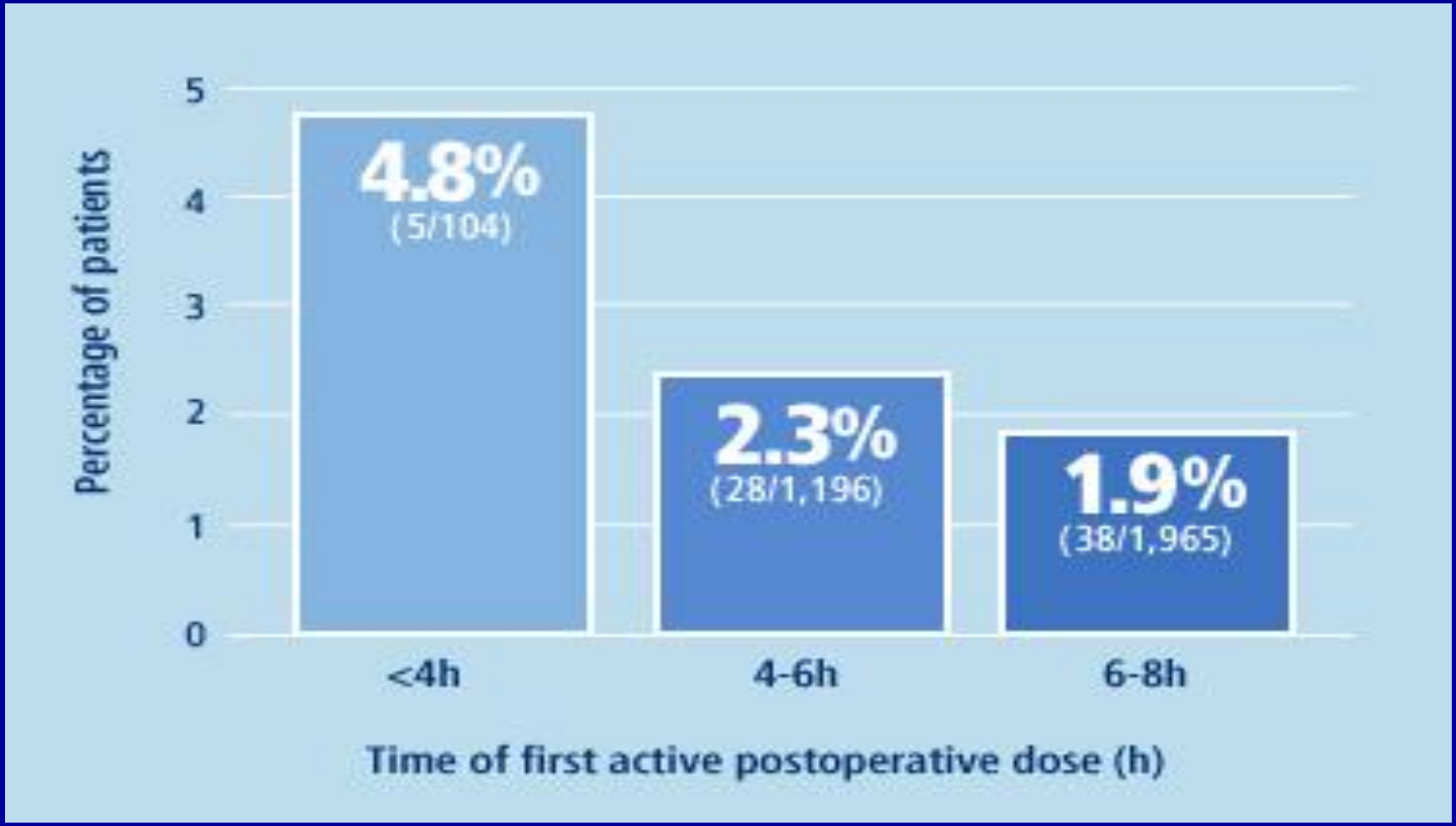
[2] Enoxaparin sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

[3] Not approved for use in patients undergoing hip fracture surgery .

[4] During noncomparative, unblinded, peri-operative prophylaxis, major bleeding was reported in 22/737 (3.0%) patients. Fifteen (15) of these 22 patients continued to receive ARIXTRA in extended prophylaxis. After randomization, 4/327 (1.2%) patients experienced major bleeding for the first time.

[5] p value versus enoxaparin sodium: <0.01, 95% confidence interval: (1.1%, 3.3%) in group receiving ARIXTRA versus (0.0%, 1.1%) in enoxaparin sodium group.

Incidence of Major Bleeding* With ARIXTRA Therapy by Time of First Active Postoperative Dose in Perioperative Prophylaxis Clinical Studies. (N=3,265)



Study Question

- “Would a ‘delayed’ dose of fondaparinux given 18-24 hours post procedure provide the same level of efficacy and safety, as the use of standard warfarin and enoxaparin regimens?”

WHY is VTE prophylaxis IMPORTANT in arthroplasty??

Implications for Clinical Practice

Orthopedic Procedures on the Rise

- An increase in the number of orthopedic procedures is due to:
  - Increased life expectancy
  - Growing population of older individuals
- Total knee replacement: 266,000/year in the US
- Total hip replacement: 168,000/year in the US

Paiement GD, Mendelsohn C. The risk of venous thromboembolism in the orthopedic patient: epidemiological and physiological data. *Orthopedics*. 1997;20(suppl):7-9.
AAOS Web site. Available at: http://orthoinfo.aaos.org/booklet/bookview.cfm?Thread_ID=2&topcategory=Hip. Accessed June 12, 2001.
AAOS Web site. Available at: http://orthoinfo.aaos.org/booklet/bookviacfm?Thread_ID=2&topcategory=knee. Accessed June 12, 2001.

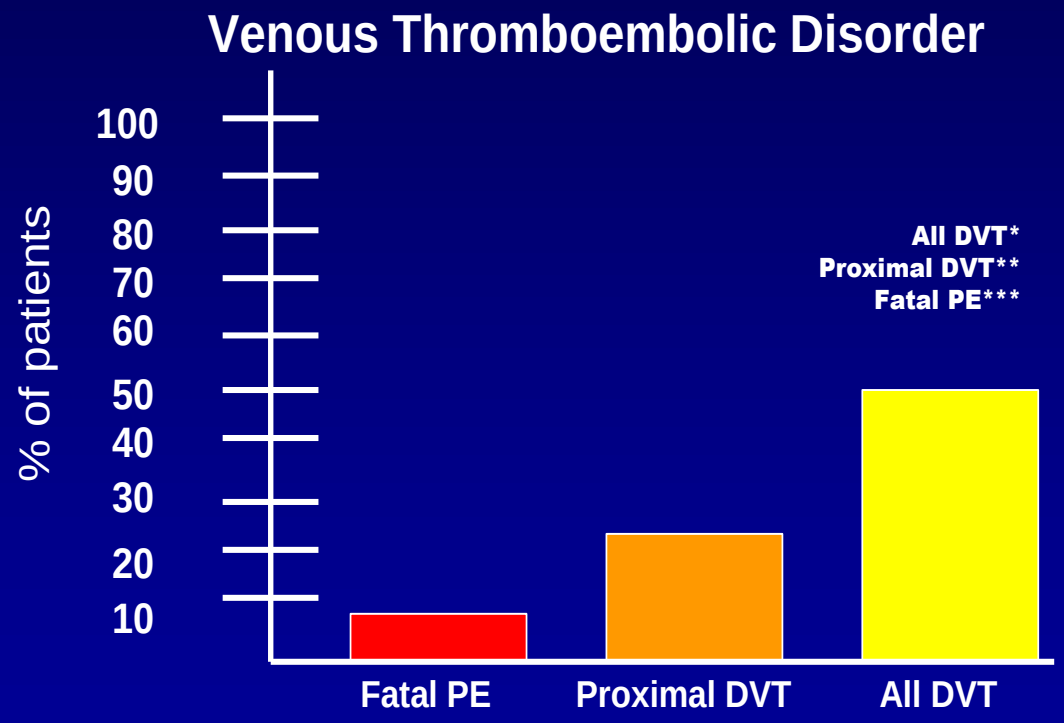
Risk for DVT/VTE

Surgery/condition Risk of all DVT if untreated

General Surgery THR	25% 54%
TKR Neurosurgery	64% 28%
Trauma Acute spinal cord injury	30-60% 80%
Ischemic stroke Medical conditions	55% 16%

Geerts et al; Chest 2001, 2004

The Importance of VTE Prophylaxis in Hip Arthroplasty



* Diagnosed by routine enography and ±10%
** Diagnosed by routine enography and ±5%
*** Diagnosed during routine autopsy

Adapted from Paiement GD and Mendelsohn C. The risk of venous thromboembolism in the orthopedic patient: epidemiological and physiological data. *Orthopedics*. 1997;20 (suppl):7.

Design of Study

- Retrospective review
- Comparison of ‘consecutive’ non-emergent arthroplasty cases
  - Potential flaws
    - cannot perfectly match for co-morbidities
    - similar surgical expertise assumed
    - similar post-surgical care assumed
    - only single center evaluation
    - patient follow-up at other centers could not be accounted for

Methods

¤ Consecutive records of all elective major orthopedic procedures related to total knee and hip replacements
-data from first 6 months of 2004

¤ Comparative groups
-n=185; received fondaparinux
-n=550; received other ‘standard’ VTE prophylaxis regimens

¤ Electronic chart review by Pharmacists to collect pre-selected outcomes

¤ Patient outcomes reviewed
- all cause 30 day readmissions, bleeding
- all cause 30 day readmissions, VTE event
- any in- hospital mortality
- in-hospital VTE events

RESULTS—Similar demographics

Table 1: Patient Demographics

	Study Group	***Standard Group***
	(n=185) <%>	***(n=550) <%>***
Male	***67 <36.2>***	***211 <38.4>***
Female	***118 <63.8>***	***339 <61.6>***
LOS median (days)	***3.0***	***3.1***
LOS mean (days)	***3.55***	***3.67***
Age mean (years)	***65.1***	***64.7***
Hip replacement	***76 <41.1>***	***221 <40.2>***
Knee replacement	***109 <58.9>***	***329 <59.8>***

Outcome Events with Statistical Analysis

Outcome Events	*Fondaparinux*	*Standard Care*	*p-value**
30 day readmission – all cause	*8/185 4.3%*	*15/550 2.7%*	*0.328*
30 day readmission – bleeding	*2/185 1.2*	*3/550 0.5*	*0.604*
30 day readmission - VTE	*0/185 0%*	*1/550 0.2%*	*1.00*
In-hospital mortality	*1/185 0.5%*	*0/550 0%*	*0.252*
In-hospital VTE	*1/185 0.5%*	*7/550 1.3%*	*0.687*

**Fisher's Exact test: There is no difference between the groups for p value> 0.05*

Conclusions

- Patients at Lehigh Valley Hospital were provided with similar levels of safe and effective VTE prophylaxis after non-emergent arthroplasty procedures regardless of the strategy utilized to augment post operative care.
- These results have been confirmed by a multi-center study---FLEXTRA.