

Post-Surgical Anticoagulation Management: Risk Management

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North American Thrombosis Forum (NATF, www.NATFonline.org)

MISSION STATEMENT: The goal of the North American Thrombosis Forum is to focus on unmet needs and issues related to thrombosis and cardiovascular diseases such as deep vein thrombosis, pulmonary embolism, myocardial infarction, peripheral arterial occlusive disease, and stroke. NATF's five areas of major focus are:

- 1) Basic translational research
- 2) Clinical research, especially diagnosis and therapy
- 3) Prevention and education
- 4) Public policy
- 5) Advocacy

NATF's vision is to improve patient care, outcomes, and public health by utilizing a multi-disciplinary approach to advance thrombosis research and education. NATF's legacy will be the improvement of patient care, outcomes, and public health by supporting thrombosis-related programs, such as novel research projects, innovative educational programs, public policy initiatives, regulatory issues and advocacy. NATF also seeks to broaden training opportunities for physicians, scientists, and other health professionals.



Learning Objectives

After participating in this activity, participants should be able to:

- Identify the epidemiology and impact of VTE
- Analyze risk factors associated with VTE, including comorbid conditions that can affect VTE prevention and treatment
- Assess current and emerging anticoagulant treatments and the clinical evidence that supports their use
- Evaluate the updated ACCP guidelines for VTE prevention and management
- Implement strategies for meeting standards set by the Joint Commission/National Quality Forum

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Incidence of VTE in the United States

- ~900,000 PEs and DVTs in the USA in 2002
- Estimated 296,000 PE deaths
 - 7% treated unsuccessfully, 34% sudden and fatal, and 59% undetected
- More Americans die each year from PE than from breast cancer, AIDS, and highway fatalities combined
- 2/3 of VTE cases and deaths are hospital-acquired
 - 7.7 million medical service inpatients
 - 4.3 million surgical service inpatients
- VTE is the most common preventable cause of hospital death and disability

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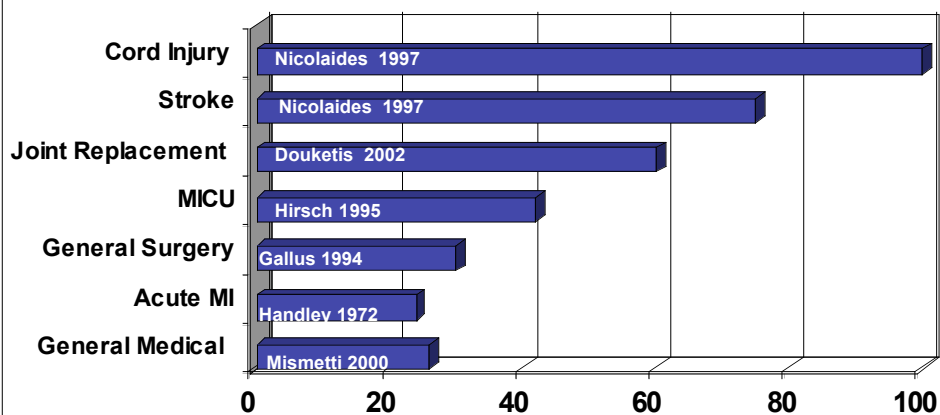
Risk Factors for VTE

- Surgery
- Trauma (major or lower limbs)
- Cancer and/or its treatment
- Previous VTE
- Increasing age
- Pregnancy and postpartum
- Estrogen therapy or estrogen containing oral contraceptives
- Inherited or acquired thrombophilia
- Immobility/Paresis
- Acute medical illnesses
- Inflammatory bowel disease
- Nephrotic syndrome
- Myeloproliferative disorders
- Obesity
- Central Venous catheters

Geerts WH, et al. *Chest*. 2008;133:381S-453S.

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DVT Incidence absent prophylaxis



Geerts WH. *Chest*. 2008;133:381S-453S

Levels of Thromboembolism Risk and ACCP Recommendations for Prophylaxis in Hospital Patients^a

Levels of Risk	Approximate DVT Risk Without Thromboprophylaxis % ^b	Suggested Thromboprophylaxis Options
Low risk		
Minor surgery in mobile patients	< 10	No specific thromboprophylaxis
Medical patients who are fully mobile		Early, "aggressive" ambulation
Moderate risk		
Most general, open gynecologic, or urology surgery patients	10-40	LMWH (at recommended doses), LDUH bid or tid, fondaparinux
Medical patients, bed rest or sick		Mechanical thromboprophylaxis
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis
High risk		
Hip or knee arthroplasty, HFS	40-80	LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2-3)
Major trauma, SCI		Mechanical thromboprophylaxis ^c
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis ^c

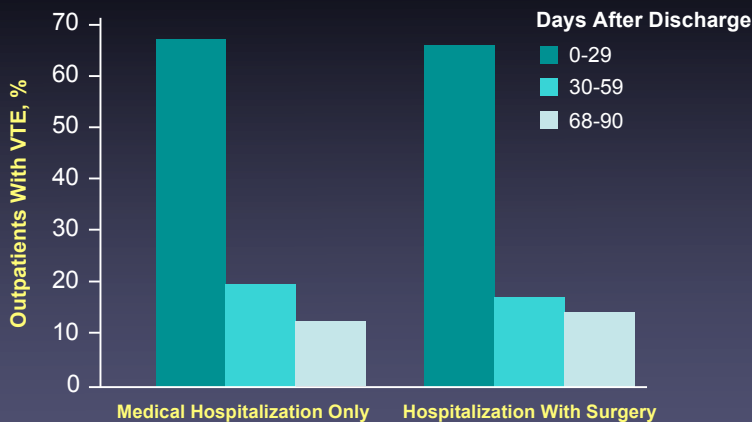
^aDescriptive terms purposely left undefined to allow individual clinician interpretation. ^bRates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis. ^cMechanical thromboprophylaxis includes IPC or VFP and/or GCS; consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases.

HFS = hip fracture surgery; IPC = intermittent pneumatic compression; GCS = graduated compression stockings; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; SCI = spinal cord injury; VFP = venous foot pump.

Reprinted with permission from Geerts WH, et al. *Chest*. 2008;133:381S-453S.

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Outpatient and Inpatient VTE Are Linked



- 74% of VTEs present in outpatients
- 23% of outpatient VTE patients have had recent surgery; 37% recently hospitalized
- Only 43% had received VTE prophylaxis

Reprinted with permission from Spencer FA, et al. *Arch Intern Med*. 2007;167:1471-1475.

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The Importance of DVT Prophylaxis in Patients With Cancer

- VTE is one of the leading causes of death in cancer patients, occurring in 4% to 20% of patients
- Hospitalized patients with cancer and cancer patients receiving active therapy are at high risk for VTE
 - Cancer increased the risk of VTE 4.1-fold
 - Chemotherapy increased the risk 6.5-fold
- Major risk factors include older age, comorbid conditions, recent surgery or hospitalization, active chemotherapy or hormonal therapy
- All hospitalized cancer patients should be considered for prophylaxis

Lyman GH, et al. *J Clin Oncol*. 2007;25:5490-5505.

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Position Statements

Appropriate VTE prophylaxis is required in patients at risk

- Agency for Healthcare Research and Quality, 2001

Utilize clinically appropriate measures to prevent DVT/PE

- The National Quality Forum, 2003

The use of proven and effective DVT prevention methods could save many lives of many patients

- JCAHO, 2004

For every general hospital, we recommend that a formal, active strategy that addresses the prevention of VTE be developed

- ACCP, 2008

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Surgical Care Improvement Project

- Partnership between multiple organizations
 - American Academy of Orthopedic Surgeons, American Hospital Association, American College of Surgeons, JCAHO, AHRQ, CDC, VA, others
 - SCIP set a national goal to reduce preventable surgical morbidity and mortality by 25% by 2010
- Identify best practices (Class I recommendations)
- Hospitals can report in 4 major areas
 - Surgical site infections
 - Cardiovascular events
 - Respiratory complications
 - VTE (including DVT and PE)

Joint Commission/NQF Draft VTE Measures for 2009

- 6 VTE measures endorsed by the NQF in May 2008
 - VTE prophylaxis
 - ICU VTE prophylaxis
 - VTE patients with anticoagulation overlap therapy
 - VTE patients UFH dosages/platelet count monitoring by protocol (or nomogram)
 - VTE discharge instructions
 - Incidence of potentially preventable VTE
- Measures will be available for data collection and reporting for discharges beginning autumn 2009

2008 ACCP Guidelines for Antithrombotic and Thrombolytic Therapy

- The American College of Chest Physicians (ACCP) has successfully provided high-quality clinical practice guidelines for over 20 years.¹
- Extensive review of literature for management of thromboembolic disorders²
- Grading system has been revised for the purposes of consistency and comparison with other guidelines³
 - Less confusion compared with other recommendations
 - This grading system is used by many organizations:
 - American College of Physicians
 - American Thoracic Society
 - World Health Organization
- Clinicians are most interested in the best course of action when considering a treatment, therefore the strength of the recommendation is integrated into the grading system³

1. Baumann MH, Gutterman DD. *Chest*. 2006;129:10-12.
2. Hirsh et al. *Chest*. 2008;133:71S-109S.
3. Guyatt GH et al. *Chest*. 2008;123S-131S.

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ACCP Grades of Recommendation

Strength of recommendation is determined by considering the benefit vs the harm and the quality of evidence

Grade 1: Strong recommendation indicating that benefits outweigh the harms, burdens, or costs

Grade 2: Weaker recommendation, less certainty of benefits

Grade A: Quality, randomized, controlled trials with unbiased results

Grade B: Randomized, controlled trials with inconsistent results, poor study design, and/or biased results

Grade C: Low-quality evidence or observational studies

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Strategies and Current Guidelines for Primary Prevention of VTE/PE in Surgical Patients

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ACCP 2008 Recommendations: General Surgery

- Low-risk patients, minor procedure, no additional risk factors: recommend against specific thromboprophylaxis other than early and frequent ambulation (Grade 1A)
- Moderate-risk patients, major procedure for benign disease: LMWH, LDUH, or fondaparinux (Grade 1A)
- Higher-risk patients, major procedure for cancer: LMWH, LDUH 3 times/day, or fondaparinux (Grade 1A)

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ACCP 2008 Recommendations: General Surgery (cont)

- Patients with high risk of bleeding: GCS or IPC (Grade 1A); pharmacologic therapy substituted or added to mechanical thromboprophylaxis once high bleeding risk decreases (Grade 1C)
- For patients undergoing major general surgery, continue thromboprophylaxis until discharge (Grade 1A)
- Selected high-risk patients, including some who have undergone major cancer surgery or have had VTE previously, continue thromboprophylaxis after discharge; consider LMWH for up to 28 days

Geerts WH, et al. *Chest*. 2008;133:381S-453S.

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Enoxaparin vs UFH: VTE Prophylaxis in Colorectal Surgery

Occurrence of VTE

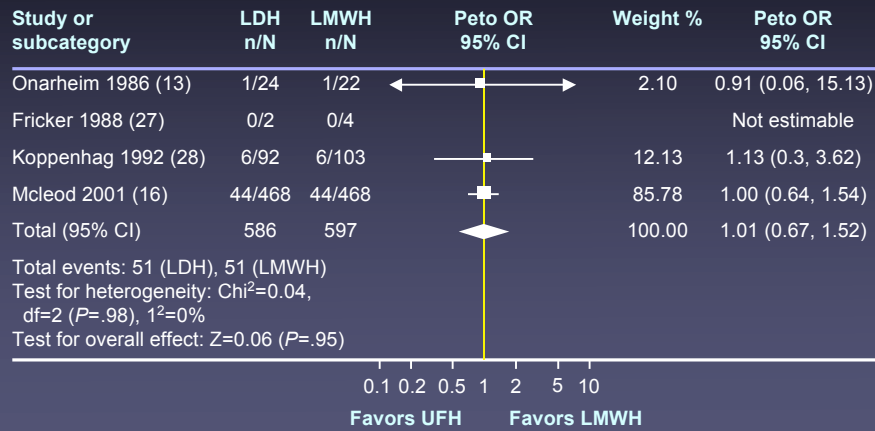
Event, n (%)	UFH (n=468)	Enoxaparin (n=468)
Total VTE	44 (9.4)	44 (9.4)
Symptomatic VTE	3 (0.06)	2 (0.04)
Proximal DVT	12 (2.6)	13 (2.8)
Symptomatic PE	0	1 (0.02)
Major bleeding ^a	10 (1.5)	18 (2.7)

^aBleeding results were based on the intent-to-treat population of 1,349 patients (643 UFH, 653 enoxaparin). Differences between treatment groups were not significant.

McLeod RS, et al. *Ann Surg*. 2001;233:438-444.

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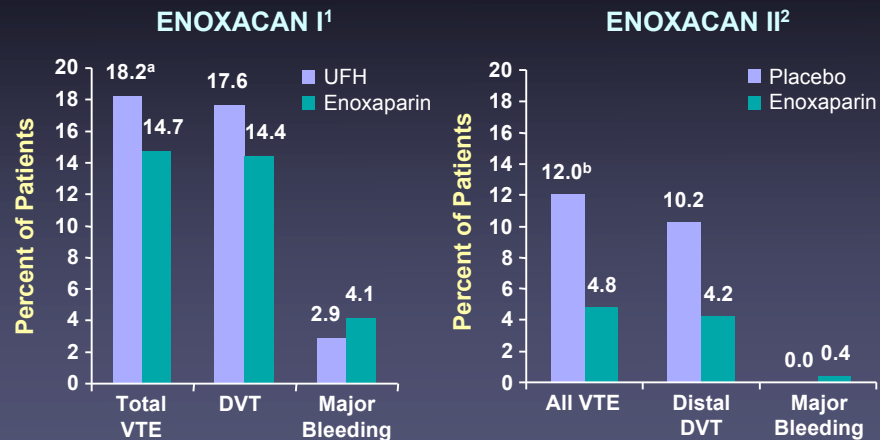
Meta-analysis: UFH vs LMWH in Colorectal Surgery



Reprinted with permission from Borly L, et al. *Colorectal Dis.* 2005;7:122-127.

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Efficacy of LMWH in Patients Undergoing Cancer Surgery – ENOXACAN Results



^a95% CI -9.2-2.3; ^b $P=.02$.

1. ENOXACAN Study Group. *Br J Surg.* 1997;84:1099-1103.

2. Bergqvist D, et al. *N Engl J Med.* 2002;346:975-980.

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VTE After Orthopedic Surgery^{1,2}

- VTE is common after major orthopedic surgery
- DVT occurs in 60% in the absence of prophylaxis
- Incidence of asymptomatic DVT 2-fold higher after total knee arthroplasty (TKA) compared with total hip arthroplasty (THA)
- Despite prophylaxis with LMWHs or warfarin, 15% to 30% still develop DVT

1. Heit JA, et al. *Arch Intern Med.* 2001;161:2215-2221.
 2. Douketis JA, et al. *Arch Intern Med.* 2002;162:1465-1471.

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Guidelines for Prophylaxis in Orthopedic Patients

	ACCP ¹	IUA ²	AAOS ³
Total hip replacement	LMWH, fondaparinux, warfarin	LMWH, fondaparinux, warfarin, IPC or FIT	Aspirin, LMWH, fondaparinux, warfarin
Total knee replacement	LMWH, fondaparinux, warfarin	LMWH or warfarin	Aspirin, LMWH, fondaparinux, warfarin
Arthroscopic knee surgery	LMWH for higher-risk patients	LMWH or IPC if contraindications to LMWH	
Multiple trauma	LMWH or IPC	LMWH or IPC if contraindications to LMWH	

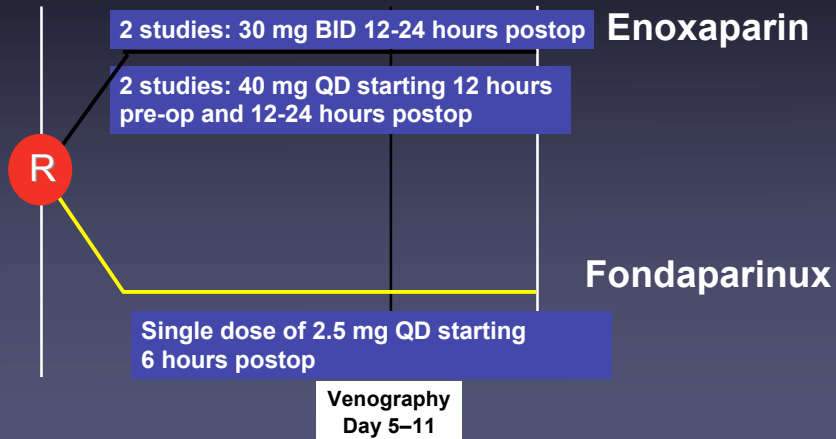
FIT = foot impulse technology.

1. Geerts WH, et al. *Chest.* 2008;133:381S-453S.
 2. International Union of Angiology. *Int Angiol.* 2006;25:101-161.
 3. American Academy of Orthopaedic Surgeons Clinical Guideline, 2007. Available at: <http://www.aaos.org/research/guidelines/guide.asp>. Accessed July 29, 2008.

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Phase III Studies in THR, TKR, and HFS

Double-blind treatment for 7 ± 2 days



Indirect Factor Xa inhibition: effective in VTE prevention after orthopedic surgery

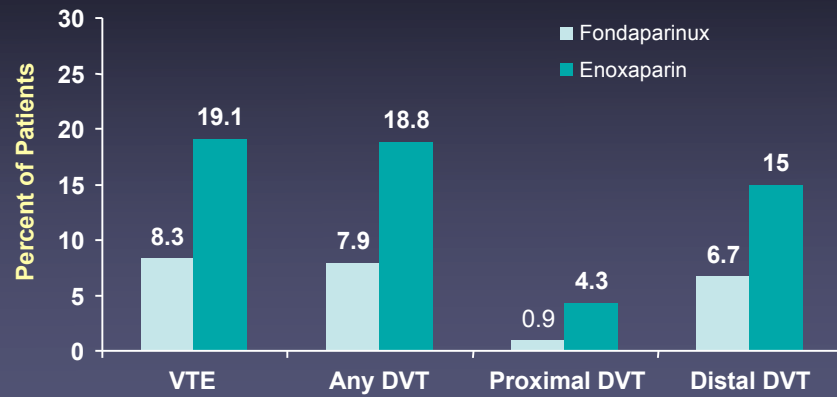
Trial	Fondaparinux	LMWH	RR
VTE prevention in elective hip replacement ¹	4%	9%	56%
VTE prevention in elective hip replacement ²	6%	8%	25%
VTE prevention in hip fracture ³	8%	19%	56%
VTE prevention in elective knee replacement ⁴	13%	28%	55%
Total	7%	14%	50%

1. EPHEBUS
2. PENTATHLON

3. PENTHIFRA
4. PENTAMAKS

VTE Prevention After Hip Fracture Surgery

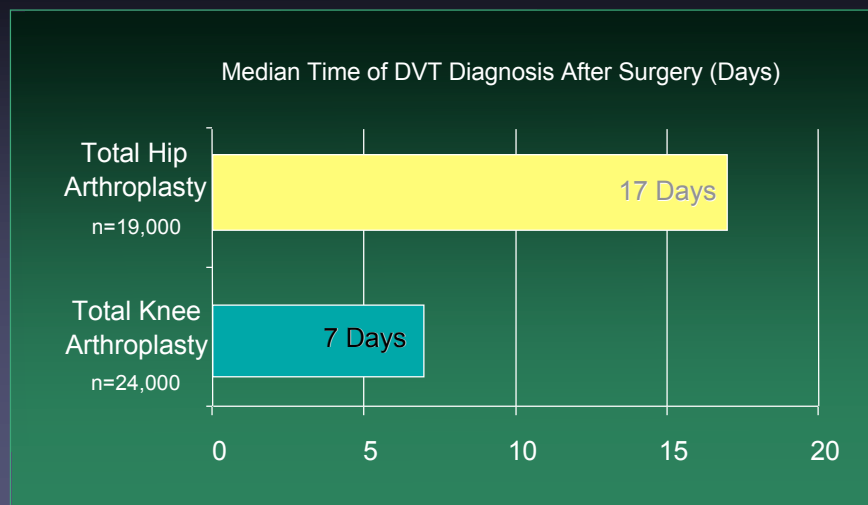
Incidence of VTE by Day 11



$P < .001$ for all fondaparinux vs enoxaparin comparisons.
Eriksson BI, et al. *N Engl J Med.* 2001;345:1298-1304.

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When are VTE Occurring?



White et al. *Arch Intern Med.* 1998;158:1525-1531.

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Extended Thromboprophylaxis Reduces the Incidence of VTE

Total Hip Replacement	No. of Patients	DVT In-hospital Rx	DVT Extended LMWH
Bergqvist et al, 1996 ¹	223	37%	18%
Planes et al, 1996 ²	173	19%	7%
Dahl et al, 1997 ³	218	32%	19%

1. Bergqvist D, et al. *New Engl J Med.* 1996;335:696-700.

2. Planes A, et al. *Lancet.* 1996;348:224-228.

3. Dahl OE, et al. *Thromb Haemost.* 1997;77:26-31.

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Extended Thromboprophylaxis Reduces the Incidence of VTE

Hip Fracture Surgery	No. of Patients	DVT In-hospital Rx Fondaparinux	DVT Extended Fondaparinux
Eriksson et al, 2003 ¹	428	35%	1.4%

Eriksson et al, 2001²

In PENTHIFRA trial, the incidence of VTE at day 11 was 8.3%.

1. Eriksson BI, et al. *Arch Intern Med.* 2003;163:1337-1342.

2. Eriksson BI, et al. *New Engl J Med.* 2001;345:1298-1304.

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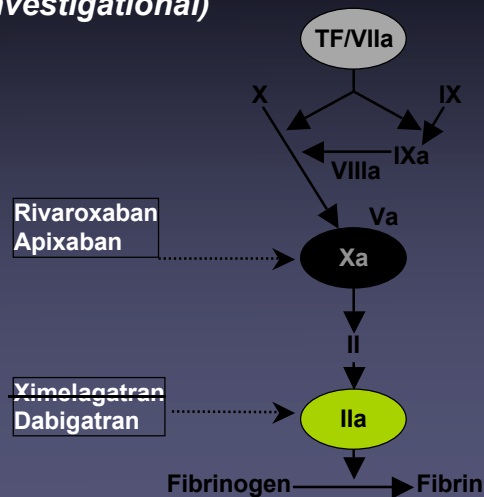
Trials with fondaparinux in the prevention of VTE following major orthopedic surgery clearly established **factor Xa** as an excellent antithrombotic target.

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Targeted Oral Anticoagulants

Adapted from Weitz & Bates, *J Thromb Haemost* 2005

(investigational)



Characteristics:

- No food or drug interactions
- Rapid onset of action
- Half-life ~6-18 hours
- Wide therapeutic window
- Predictable anticoagulant response
⇒ no monitoring required
- No unexpected toxicities (e.g., hepatotoxicity)

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Rivaroxaban: phase III program in orthopedic thromboprophylaxis

Rivaroxaban 10 mg once daily post-op was compared with enoxaparin 40 mg SC 12 hours pre-op/40 mg qd post-op or 30 mg q12h post-op after major orthopedic surgery in >12,000 patients

Study		Duration of rivaroxaban therapy	Duration of enoxaparin therapy
RECORD1	Total hip replacement	5 weeks	5 weeks
RECORD2	Total hip replacement	5 weeks	10–14 days, followed by placebo
RECORD3	Total knee replacement	10–14 days	10–14 days
RECORD4	Total knee replacement	10–14 days	10–14 days

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Comparison of Rivaroxaban vs Enoxaparin As Thromboprophylaxis After Total Hip or Knee Replacement

Endpoint	Rivaroxaban (10 mg)	Enoxaparin (40 mg/30 mg bid*)	P-value
<u>Efficacy (%)</u>	DVT, non fatal PE and all-cause mortality		
RECORD 1	1.1%	3.7%	<0.001
RECORD 2	2.0%	9.3%	<0.001
RECORD 3	9.6%	18.9%	<0.001
RECORD 4	6.9%	10.1%*	0.012
<u>Safety (%)</u>	Major Bleeding		
RECORD 1	0.3%	0.1%	
RECORD 2	0.1%	0.1%	
RECORD 3	0.6%	0.5%	
RECORD 4	0.7%	0.3%*	

Eriksson, NEJM 2007; Kakkar, Lancet 2007
Lassen, NEJM 2007; Turpie, EFORT 2008 32

Clinical Development Programs of Direct Factor Xa and Thrombin Inhibitors

	Phase II	Phase III
VTE prevention in hospitalized medically ill patients		Ongoing
Stroke prevention in atrial fibrillation		Ongoing
VTE treatment and secondary prevention of recurrent VTE	Completed	Ongoing
Secondary prevention of acute coronary syndromes (ACS)	Ongoing	

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ACCP 2008 Recommendations: Neurosurgery

- Routine use of prophylaxis in all patients undergoing major neurosurgery (Grade 1A)
 - Optimal use of IPC (Grade 1A)
 - Acceptable alternatives to IPC: post-op LMWH (Grade 2A) or LDUH (Grade 2B)

Treatment Strategies for VTE

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2008 ACCP Recommendations: Initial Treatment of VTE

SC LMWH	1A
IV UFH	1A
SC fondaparinux *	1A
(Monitored SC UFH	1A)
(Fixed dose unmonitored SC UFH *	1A)

LMWH generally preferred over IV UFH (outpt tx) *

UFH preferred over LMWH in severe renal failure *

* New addition to 2008 guidelines

ACCP = American College of Chest Physicians; SC = subcutaneous; LMWH = low-molecular-weight heparin;

IV = intravenous; UFH = unfractionated heparin.

Kearon C, et al. *Chest*. 2008;133(6 Suppl):454S-545S.

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2008 ACCP Recommendations: Initial Treatment of VTE

Warfarin

Start on same day as UFH/LMWH/fondaparinux

Goal INR 2.5 (2.0 – 3.0)

Discontinue UFH/LMWH/fondaparinux after overlap of 5 days
and when INR is >2.0 for 24 hours

Systematic follow-up of oral anticoagulant therapy

Kearon C, et al. *Chest*. 2008;133(6 Suppl):454S-545S. Ansell J, et al. *Chest*. 2008;133(6 Suppl):160S-198S.

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ACCP 2008 Recommendations: Renal Impairment

- Consider renal function when making decisions about the use and/or dose of LMWH, fondaparinux, and other antithrombotic drugs cleared by the kidneys (Grade 1A)
 - Particularly important in elderly patients, patients with diabetes mellitus, those at high risk for bleeding
- Depending on circumstances, options include (Grade 1B):
 - Avoid anticoagulants that bioaccumulate in the presence of renal impairment (preference for UFH)
 - Use a lower dose of the agent
 - Monitor the drug level or its anticoagulant effect

Geerts WH, et al. *Chest*. 2008;133:381S-453S.

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Duration of anticoagulation

- First episode
 - DVT/PE secondary to a transient (or reversible) risk factor
→ 3 months warfarin therapy [Grade 1A]
 - If unprovoked proximal DVT/PE and no bleeding risk factors and good anticoagulant management available → long-term warfarin [Grade 1A]
 - If unprovoked proximal DVT/PE in association with APLS
→ higher risk for recurrent thrombosis → long-term warfarin
 - If unprovoked proximal DVT/PE in association with active cancer
→ consider chronic LMWH [Grade 1A]
- Second episode
 - Long-term warfarin [Grade 1A]

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Questions and Answers

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