

Prevention and Treatment of Venous Thromboembolism: New Strategies and Guidelines for Improving Patient Outcomes

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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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VTE Incidence

Incidence:¹

- 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

Annual number at risk for VTE: US hospitals:²

- 7.7 million medical service inpatients
- 4.3 million surgical service inpatients
- 2/3 of VTE cases and deaths are hospital-acquired¹

1. Heit J, et al. *Blood*. 2005;106:Abstract 910.

2. Anderson FA Jr, et al. *Am J Hematol*. 2007;82:777-782.

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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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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		
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		
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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Independent Risk Factors for First Lifetime Definite VTE Within Olmsted County

RISK FACTOR ^a	AR ^b	95% CI
Hospitalization or nursing home	58.8	53.4-64.2
Hospitalization with surgery	23.8	20.3-27.3
Hospitalization without surgery	21.5	17.3-25.6
Nursing home	13.3	9.9-16.8
Active malignant neoplasm	18.0	13.4-22.6
Trauma	12.0	9.0-14.9
Congestive heart failure	9.5	3.3-15.8
Prior central venous catheter or pacemaker	9.1	5.7-12.6
Neurological disease with extremity paresis	6.9	3.5-10.2
Prior superficial vein thrombosis	5.4	3.0-7.7

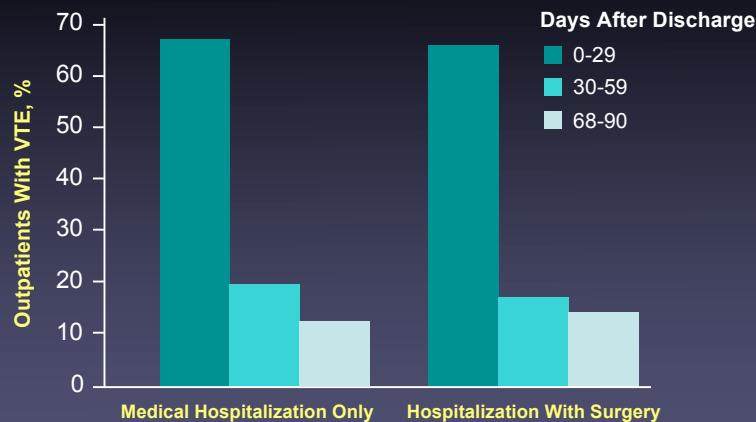
^aAll 8 risk factors together accounted for 74% of all observed VTE cases.

^bAll values are given as percentages. AR = attributable risk. Adjusted for age, sex, year, and terms in final model.

Adapted with permission from Heit JA, et al. *Arch Intern Med.* 2002;162:1245-1248.

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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 on any of 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
- Complete measure specifications available spring 2009

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

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Recommendations for Prophylaxis in Medical Patients

ACCP 2008 Guidelines

- In acutely ill medical patients who have been admitted to the hospital with:
 - congestive heart failure or severe respiratory disease
 - Or who are confined to bed and have ≥ 1 additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease
 - LMWH (Grade 1A; IUA: enoxaparin 40 mg qd or dalteparin 5000 qd)
 - Low-dose UFH (Grade 1A; IUA: 5000 IU tid)
 - Fondaparinux (Grade 1A)*

* Fondaparinux is not approved by the FDA for prophylaxis in medical patients.

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

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Primary Efficacy End Points: Implications for Clinical Practice

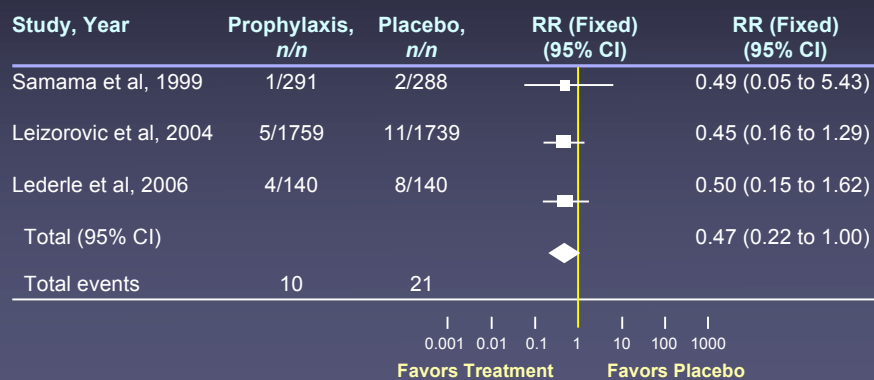
Trial	VTE	RRR	# Needed to Treat
MEDENOX ¹	Distal and proximal venographic DVT + symptomatic VTE + fatal PE	63%	10
PREVENT ²	Compression ultrasonographic DVT + symptomatic VTE + fatal PE	45%	45
ARTEMIS ³	Distal and proximal venographic DVT + symptomatic VTE + fatal PE	47%	20

1. Samama MM, et al. *N Engl J Med.* 1999;341:793-800.
2. Leizorovicz A, et al. *Circulation.* 2004;110:874-879.
3. Cohen AT, et al. *BMJ.* 2006;332:325-329.

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VTE Prophylaxis: 19,958 Medical Patients/9 Studies (Meta-analysis)

- 62% reduction in fatal PE
- 57% reduction in fatal or nonfatal PE
- 53% reduction in symptomatic DVT

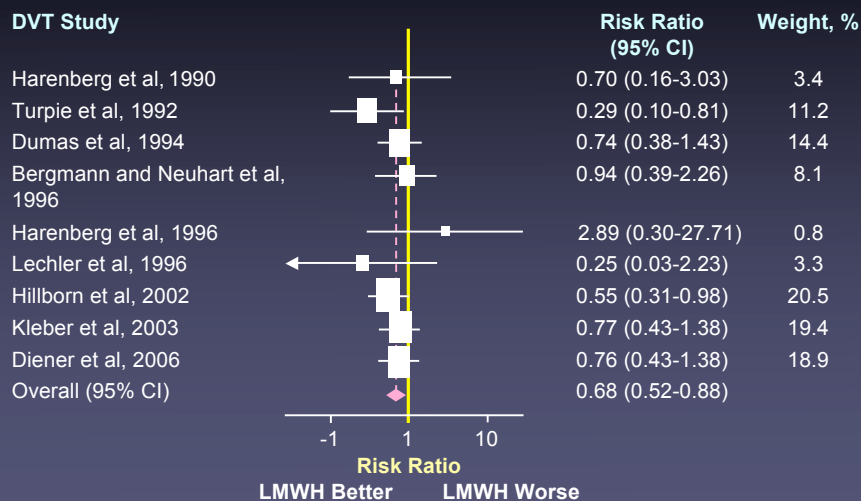


Reprinted with permission from Dentali F, et al. *Ann Intern Med.* 2007;146:278-288.

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VTE Prophylaxis: LMWH vs UFH

Meta-analysis of 36 trials of LMWH or UFH



Reprinted with permission from Wein L, et al. *Arch Intern Med.* 2007;167:1476-1486.

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EXCLAIM: Extended-duration Enoxaparin Prophylaxis in High-risk Medical Patients

End points	Extended prophylaxis n=2013 (%)	Placebo n=2027 (%)	RR reduction (%)	P value
VTE events	2.8	4.9	44	.001
Symptomatic	0.3	1.1	73	.004
No symptoms	2.5	3.7	34	.032

NNT = 46 patients to avoid one VTE event.

NNT = 224 to result in one major bleeding event.

Hull RD, et al. Abstract presented at: ISTH, July 8-11, 2007, Geneva, Switzerland.

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Despite Evidence – Medical Patients at Risk Remain Unprotected

ENDORSE¹

	Medical	Surgical
No. of patients	37,356	30,827
At risk for VTE	42%	64%
Receiving ACCP Tx	40%	59%

IMPROVE²

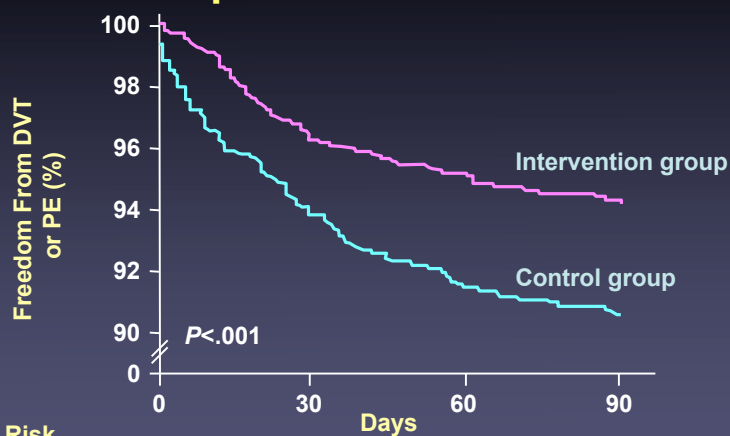
	United States	Other Countries
No. of patients	3,410	11,746
VTE prophylaxis	1852 (54%)	5788 (49%)
LMWH	476 (14%)	4657 (40%)
UFH	717 (21%)	1014 (9%)

1. Cohen AT, et al. Presented at: ISTH, July 8-11, 2007; Geneva, Switzerland.

2. Tapson VF, et al. *Chest*. 2007;132:936-945.

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Electronic Alerts to Prevent VTE in Hospitalized Patients



No. at Risk

Intervention group	1255	977	900	853
Control group	1251	976	893	839

$P < .001$ by the log-rank test for the comparison of the outcome between groups at 90 days.

Reprinted with permission from Kucher N, et al. *N Engl J Med*. 2005;352:969-977.

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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)
- Patients with multiple risk factors who are thought to be at high risk: LMWH, LDUH 3 times/day, or fondaparinux with GCS and/or IPC (Grade 1C)

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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	

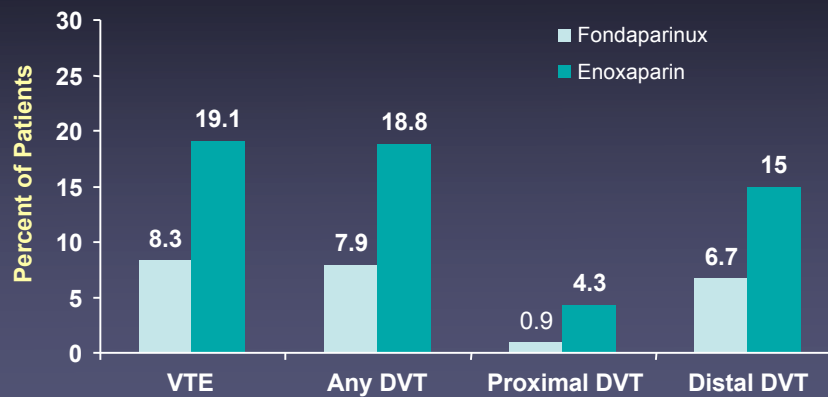
FIT = foot impulse technology.

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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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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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)
- In patients with particularly high thrombosis risk, combine mechanical and pharmacologic method (GCS and/or IPC; post-op LMWH or LDUH) (Grade 2B)

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

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Treatment Strategies for VTE

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2008 ACCP Recommendations: Initial Treatment of VTE

SC LMWH	1A
IV UFH	1A
(Monitored SC UFH	1A)
(Fixed dose unmonitored SC UFH *	1A)
SC fondaparinux *	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 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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Outpatient VTE Protocol Clinical Exclusionary Criteria

Based on compendium of RCTs and observational studies

Absolute

- Active bleeding or positive stool guaiac
- Thrombocytopenia <100K
- Major surgery/trauma or CVA <2 weeks
- Phlegmasia
- Symptomatic PE
- Severe renal dysfunction
- Recent GI bleeding
- Hypertensive emergency
- History of heparin sensitivity or HIT
- Active or major comorbid illness

Relative

- History of familial bleeding disorder
- Morbid obesity
- Iliofemoral DVT
- Pregnancy
- Underlying liver disorder
- Aged >75 yrs
- Acquired or congenital hypercoagulable state

CVA = cerebrovascular accident.

Spyropoulos AC. *Am J Manag Care*. 2000;6:S1034-S1044.

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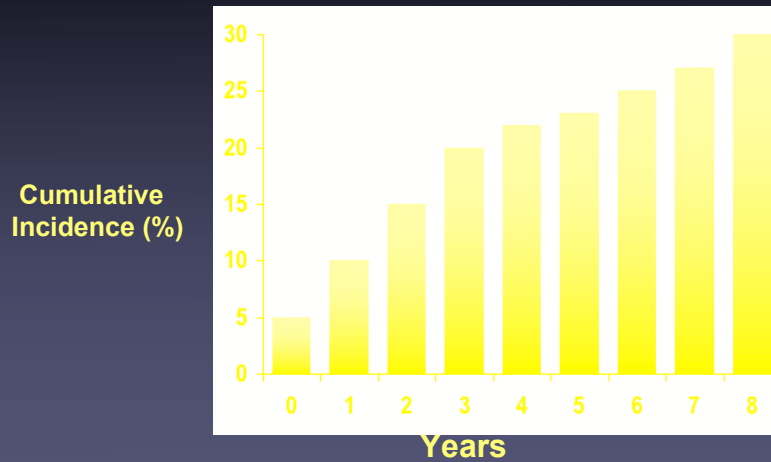
ACCP 2008 Recommendations: Renal Impairment

- 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

Thrombolysis in Management of PE

- American College of Emergency Physicians 2003 Clinical Policy Statement: PE in patients who are hemodynamically unstable are candidates for fibrinolytic therapy
- Risk factors include:
 - Systemic hypotension
 - Congestive heart failure
 - Previous history of a large PE
 - Hypoxia
 - Pulmonary hypertension
- Patients with *massive* PE should be considered candidates for fibrinolytic therapy, unless contraindicated

Recurrent Venous Thrombosis is Common Following a First Episode of Unprovoked Symptomatic DVT



Prandoni et al, *Ann Intern Med* 1996;125:1-7

Factors Influencing Duration of Anticoagulation Following Unprovoked VTE

- Recurrent VTE
 - Risk (% / year) ~10% (5-15%)
 - Consequences (case fatality) 0.2-0.4%
 - Bleeding
 - Risk (% / year) ~1-2%
 - Consequences (case fatality) 0.2%
- ⇒ A recurrent VTE rate of <5% per year is considered "acceptable" (risk of anticoagulation > benefit).

Duration of anticoagulation

- First episode
 - If 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]
- Second episode
 - Long-term warfarin [Grade 1A]

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Risk of Recurrent Venous Thrombosis in Patients with Thrombophilia

- Heterozygosity for Factor V Leiden (FVL) or Prothrombin (PT) G20210A do not increase risk.
- Higher in heterozygotes with both FVL and PT G20210A (retrospective studies); probably higher in homozygotes with FVL
- Antithrombin, Protein C, Protein S Deficiency
 - High in selected kindreds with strong clinical penetrance (retrospective studies)
 - Little data in unselected patients .
- Unprovoked event in association with persistent LA
⇒ **higher than average** risk for recurrent thrombosis
⇒ long-term anticoagulation indicated

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SUMMARY

Thrombophilia and Recurrent VTE (JAMA 2005)

Prothrombotic abnormalities do **not** appear to play an important role in the risk of a recurrent thrombotic event. Clinical factors (e.g., unprovoked vs provoked, active cancer) are generally more important than laboratory abnormalities in determining the risk of recurrence and the need for prolonged anticoagulation therapy (> 3-6 months).

ACCP 2008 (Chest 2008; 133:454S-545S)

The presence of hereditary thrombophilia has **not** been used as a major factor to guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies suggests that these factors are not major determinants of the risk of recurrence.

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Criteria for Long-Term Oral Anticoagulation in Patients with Venous Thrombosis: Individualize

- **Resolution of triggering risk factor**
- Sites and severity of thrombosis
- Bleeding risk
- Identification of a prothrombotic defect coupled with family's thrombotic history
- **PATIENT PREFERENCE** (role of lifestyle and occupation)

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Guidelines on Duration of Anticoagulant Therapy

- First event with reversible or time limited risk factor
 - 3 months at INR 2-3
- Unprovoked VTE, first or second event
 - 3-6 months at INR 2-3, then consider indefinite anticoagulation at INR 2-3 weighing recurrence versus bleeding risk and patient preference
- Special Situations requiring indefinite anticoagulation
 - First unprovoked event in association with
 - Active cancer (consider chronic LMWH)
 - Antiphospholipid antibody syndrome
 - Antithrombin deficiency or multiple genetic defects
 - ? deficiencies of protein C or protein S

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Guidelines on Anticoagulant Therapy

RISK CLASSIFICATION

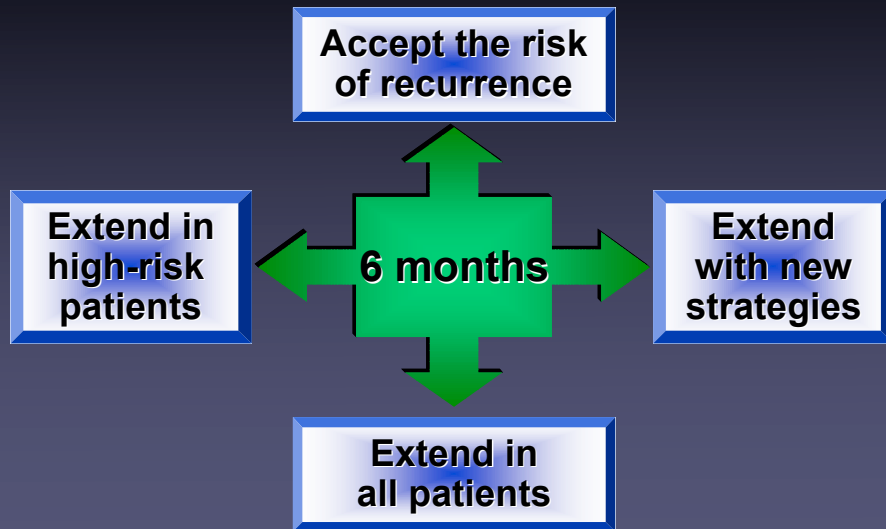
- Moderate-risk
 - 1 event with a stimulus
 - Asymptomatic

MANAGEMENT

Vigorous prophylaxis
in high-risk settings

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After Initial Anticoagulation



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Recurrent VTE in patients with a first unprovoked VTE according to whether D-dimer levels were higher or lower after stopping treatment

Study (D-dimer assay)	D-dimer Level (ng/mL)	Recurrent VTE rate (/100 pt-yr)	Hazard Ratio (95% CI)
Palareti 2003 (Vidas)	≤ 500	4.8	2.43 (1.18-4.61)
	> 500	11.4	
Eichinger 2003 (Asserachrom)	< 250	2.4	0.4 (0.2-0.8)
	≥ 250	5.0	
Shrivastava 2006 (Liatest)	< 500	2.9	3.2 (1.3-8.0)
	≥ 500	10.9	
Palareti 2006 (Simplify)	Negative	4.4	2.49 (1.35-4.59)
	Positive	10.9	

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Should D-dimer be used in practice to risk stratify patients after a 1st unprovoked VTE?

Potential Limitations

Less useful in older patients in Palareti Study (N Eng J Med 2006)

- a) Post-hoc analysis \geq age 65: Hazard ratio for recurrence 1.62 (95% CI, 0.76-3.46)
- b) 74% of subjects with an elevated D-dimer level were \geq 65 (need for age-specific cutoff points).
- c) Patients \geq age 65 with normal D-dimer levels had a higher recurrence rate than younger patients (6.3% vs 2.9%/year, respectively).

Baglin et al (JTH 2008) was unable to confirm the utility of D-dimer in risk stratification.

BMJ 2007; 334:674-681: "Further large, well designed studies are needed to establish the optimum duration of anticoagulation in various subgroups, including more studies of the place of D-dimer testing in determining duration."

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Questions and Answers

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