CONTROVERSIES IN ANTICOAGULATION & THROMBOSIS
WORKSHOP

Society of Hospital Medicine
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VTE Prophylaxis: EBM to QI

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Case 1: 33 y/o woman post C-section

- VTE Risk Factors: no VTE history, post-partum, c-section, immobile, obesity (260lbs), long anesthesia time (2hr 45 min)
- For VTE prophylaxis, you would recommend:
  - A. Elastic Stockings
  - B. SCDs
  - C. UFH
  - D. LMWH
  - E. Multi-modal

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ACCP Guidelines:

- *"It has been recommended that graduated compression stockings be used during and after c-section in patients considered to be at "moderate risk" of VTE and that LMWH or UFH prophylaxis be added in those thought to be at "high risk."*
- Post-op SCDs ordered, but NO record if used

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Timeline

- 1345: 24hr post-op acute SOB/CP
  - BP 63/30 pulse rapid/thready, skin cold/clammy
  - Drowsy, O2 sat 73-74% RA, 87% on 10L
- 1415: MD eval, 2u PRBC, "consider CXR, CT if necessary to r/o PE", "transfer to L&D if necessary" 66/45, HR 112
- 1845: CT-bilateral massive PE into segmental arteries
- 1950: Enoxaparin 120mg "stat"
- 2050: Enoxaparin given
- 2200: Called MICU for transfer
- 0100: Recurrent hypotension 60/40, HR 150s
- 0145: Code blue, intubated, transfer to MICU, tPA ordered
- 0230: Defib, atropine, dobutamine, tPA infused
- 0300: Time of death

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Learning Points

- Order sets are a high value exercise
- Must have *high degree of suspicion* for acute hypotension, SOB, CP post-op
- Must order tests quickly and follow-up on results promptly
  - IF you cannot, *consider* empiric treatment
- Massive PE should be treated with tPA
  - Sub-massive PE should *consider* tPA

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Risk Factors for Thrombosis

Medical Conditions	Hypercoagulable States
MI	**APC Resistance (Factor V Leiden)**5%
CHF	**20210A Prothrombin (Factor II)**
Renal Failure	Anti-thrombin III Deficiency
Stroke	Protein C & S Deficiency
Estrogens (esp OCPs)	Dysfibrinogenemia
Nephrotic Syndrome	Plasminogen Activator Deficiency
Femoral Vein catheter	Antiphospolipid Antibodies and Lupus antocoagulant
Inflamatory Bowel Dz	Hyperhomocystinemia
Pregnancy	Heparin Induced Thrombocytopenia
General Risk Factors	Polycythemia Vera (myeloproliferative disorders)
Obesity (BMI>?)	Hyperviscosity syndromes
Prior VTE	
Malignancy	
Age ≥ 40 (esp >65)	
Immobility/Paralysis	***Risk Factors Are Additive, if not Multiplicative***
Varicose veins	

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Prophylaxis in Medical Patients

- 65 yo male with Wegener's Granulomatosis
  - Non-ambulatory
  - Cavitary lung lesions
- DVT prophylaxis?

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Principles of DVT Prophylaxis

- EBM: Supports VTE prophylaxis
- Need reason why patient DOESN'T need prophylaxis
  - "Meet in the hall test"
  - Practical for the patient and condition
- Order sets make the default to give prophylaxis

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Developing/Adopting a Protocol

Why a protocol?

- *"The key concept is routine. Doing a complex activity the same way each time is the best way to make sure that nothing is left out. In the hospital, protocols serve that purpose. They standardize and structure care delivered by a group of providers."*
  - SHM VTE Collaborative

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STANDARDIZATION Enhances Our Ability To Recognize DIVERSITY.

DIVERSITY Provides the Opportunity to Identify Problems with the STANDARD

STANDARDIZATION and DIVERSITY Complement and Strengthen the Other.

Indeed, They Create Each Other.

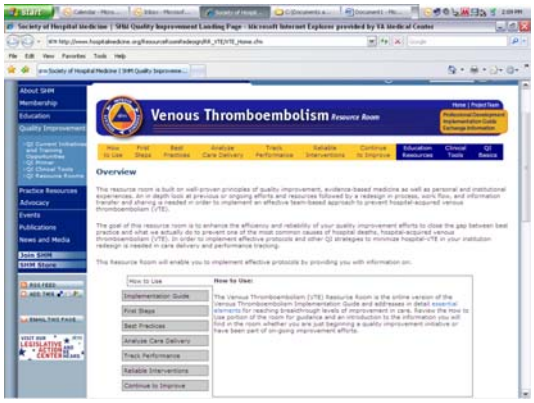
Terry Clemmer MD, LDS Hospital

VA Risk Assessment CPRS Order Set

- Goal: Create Universal EBM Order Set for all Inpatient Wards
  - Collaboration:
    - Hospitalists, Hematology, Surgery, Orthopedics, Neurology, Pharmacy and Informatics
  - Mentorship:
    - Society of Hospital Medicine
  - Lead by VA Hospitalist Field Advisory Committee (FAC)

VHA VTE Risk Assessment & Prophylaxis Initiative

- **Goal:** provide the most convenient and efficient method for VTE assessment and prophylaxis to ensure the highest quality of care for hospitalized veterans.
- **2008 JCAHO Patient Safety Goals**:
  - VTE risk assessment/prophylaxis within 24 hours of hospital admission
  - VTE risk assessment/prophylaxis within 24 hours of transfer to the ICU
- **Surgical Care Improvement Project (SCIP) VTE Performance Measures**:
  - Recommended VTE prophylaxis ordered during admission
  - Recommended VTE prophylaxis within 24 hours prior to surgical incision time to 24 hours after surgery end time.



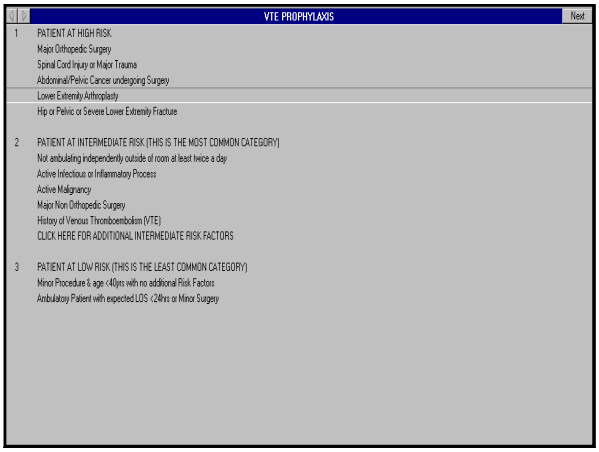
Keep it Simple – A "3 bucket" model example

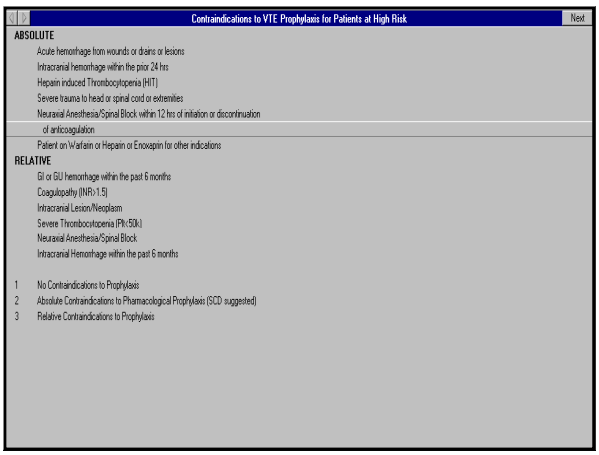
Low	Mod-High	Very High
Ambulatory with no other risk factors. Same day or minor surgery. **24hr observation**	**Everybody Else**	**Elective LE arthroplasty** **Hip/pelvic fx** **Acute SCI w/ paresis** **Multiple major trauma** **Abd / pelvic CA surgery**
Early ambulation	**UFH 5000 units q 8 h (5000 units q 12 h if > 75 or weight <50 kg)** **Enoxaparin 40 q day** **CONSIDER IPCs**	**Enoxaparin 30 mg q 12 h** **or** **Enoxaparin 40 q day** **or** **Fondaparinux 2.5 mg q day** **or** **Warfarin INR 2-3** **PLUS IPCs**

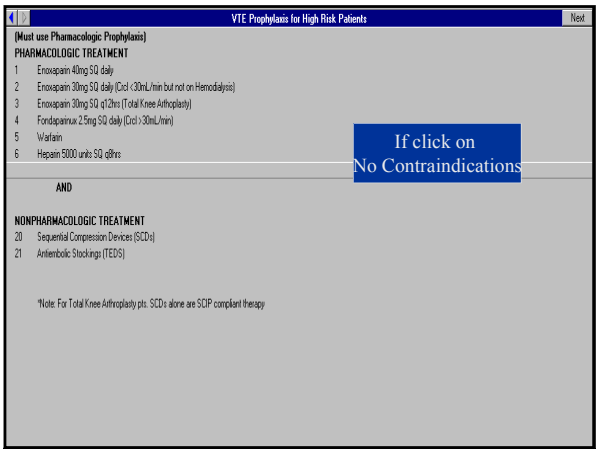
IPC needed if contraindication to AC exists

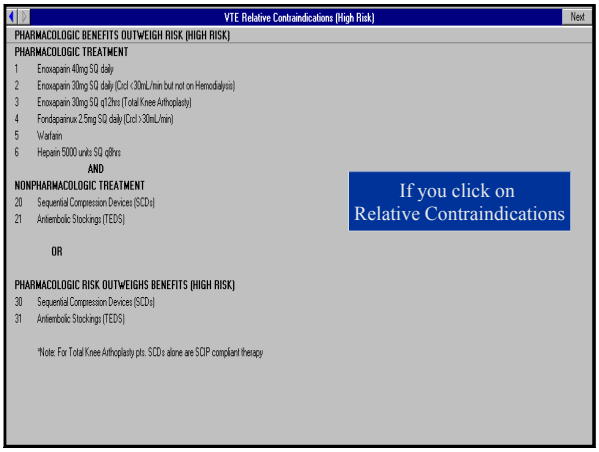
~7 Mousclicks

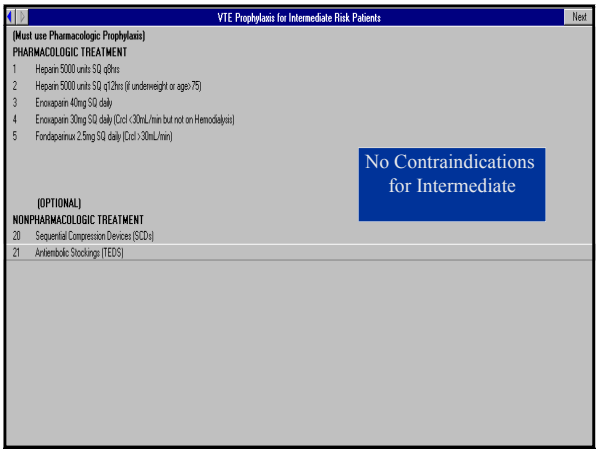
1. Select High/Intermediate/Low Risk Group
2. Educate patient order (automatic)
3. Contraindications (No/Yes/Relative)
4. Select prophylaxis drug/device
5. Accept order for drug/device
6. If additional prophylactic method needed
7. Click “Done”

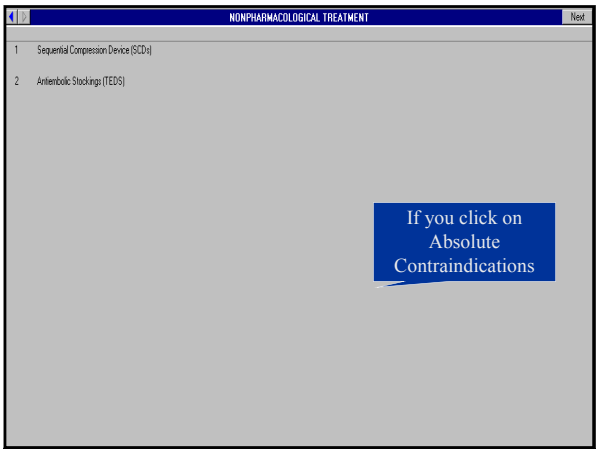





VTE Prophylaxis for High Risk Patients
Next
(Must use Pharmacologic Prophylaxis)
PHARMACOLOGIC TREATMENT
1 Enoxaparin 40mg SQ daily
2 Enoxaparin 30mg SQ daily (Crcl <30mL/min but not on Hemodialysis)
3 Enoxaparin 30mg SQ q12hrs (Total Knee Arthoplasty)
4 Fondaparinux 2.5mg SQ daily (Crcl >30mL/min)
5 Warfarin
6 Heparin 5000 units SQ q8hrs
AND
NONPHARMACOLOGIC TREATMENT
20 Sequential Compression Devices (SCDs)
21 Antiembolic Stockings (TEDS)
*Note: For Total Knee Arthroplasty pts. SCDs alone are SCIP compliant therapy
If click on
No Contraindications


VTE Relative Contraindications (High Risk)
Next
PHARMACOLOGIC BENEFITS OUTWEIGH RISK (HIGH RISK)
PHARMACOLOGIC TREATMENT
1 Enoxaparin 40mg SQ daily
2 Enoxaparin 30mg SQ daily (Crcl <30mL/min but not on Hemodialysis)
3 Enoxaparin 30mg SQ q12hrs (Total Knee Arthoplasty)
4 Fondaparinux 2.5mg SQ daily (Crcl >30mL/min)
5 Warfarin
6 Heparin 5000 units SQ q8hrs
AND
NONPHARMACOLOGIC TREATMENT
20 Sequential Compression Devices (SCDs)
21 Antiembolic Stockings (TEDS)
OR
PHARMACOLOGIC RISK OUTWEIGHS BENEFITS (HIGH RISK)
30 Sequential Compression Devices (SCDs)
31 Antiembolic Stockings (TEDS)
*Note: For Total Knee Arthroplasty pts. SCDs alone are SCIP compliant therapy
If you click on
Relative Contraindications


VTE Prophylaxis for Intermediate Risk Patients
Next
(Must use Pharmacologic Prophylaxis)
PHARMACOLOGIC TREATMENT
1 Heparin 5000 units SQ q8hrs
2 Heparin 5000 units SQ q12hrs (if underweight or age>75)
3 Enoxaparin 40mg SQ daily
4 Enoxaparin 30mg SQ daily (Crcl <30mL/min but not on Hemodialysis)
5 Fondaparinux 2.5mg SQ daily (Crcl >30mL/min)
(OPTIONAL)
NONPHARMACOLOGIC TREATMENT
20 Sequential Compression Devices (SCDs)
21 Antiembolic Stockings (TEDS)
No Contraindications
for Intermediate



Hierarchy of Reliability

Level		Predicted Prophylaxis Rate
1	No protocol* ("State of Nature")	40%
2	Decision support exists but not linked to order writing, or prompts within orders but no decision support	50%
3	**Protocol well-integrated (into orders at point-of-care)**	65-85%
4	Protocol enhanced (by other QI and high reliability strategies)	90%
5	**Oversights identified and addressed in real time**	95+%

*** Protocol = standardized decision support, nested within an order set, i.e. what/when**

Prophylaxis Cost

Method	~Cost (5 days)
Enoxaparin (40mg)	$75
Fondaparinux	$75
SQ Heparin TID	$25
Warfarin (with INR)	$50
IPC/Foot Pump	$175
Elastic Stockings	$5

Bottom Line: Not enormous differences

Summary: VTE Prophylaxis

- If you don't have a protocol for VTE prophylaxis, adopt/develop one.
- If you do have one, perform a real-time audit to see how you are doing.
- Pharmacologic prophylaxis is cost-effective
  - LMWH > Fondaparinux > UFH
- Non-pharmacologic prophylaxis as default when pharmacologic contraindicated
- Next: Direct Thrombin Inhibitor Dabigatran

Thrombophilia Work-up in 2010

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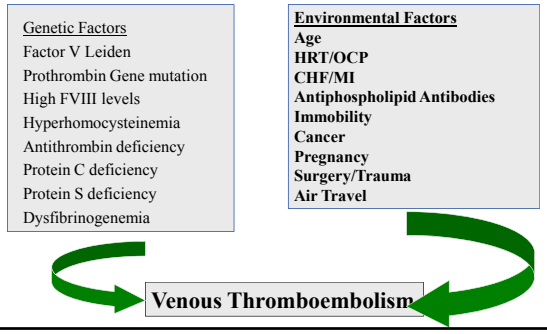
Disclosures

- Consultant
  - Sanofi-Aventis, Astra-Zeneca, Boehringer Ingelheim, Canyon Pharmaceuticals
- Research and Grant Support
  - Astra-Zeneca
- Board Member
  - SPAQI, Anticoagulation Forum

Gene-environment interactions in Thrombotic Disease



Question 1

- When is it appropriate to consider a Thrombophilia or hypercoagulable workup and what should the evaluation consist of?

Why Test?

- Controversial, no randomized clinical trial to date
- Prospective and retrospective studies are inconsistent
- Reasons for Testing:
  - Guidance for thromboprophylaxis in future
  - Duration of treatment
  - Explain cause for thrombosis
  - Counseling about future risk of VTE
- Reasons against Testing:
  - No change in management
  - Risk of misinterpretation of test
  - Risk of higher Insurance premium
  - Issues of paternity if inheritance is inconsistent

Why Test?

- Importance of testing weighed differently by health care providers and patients
- Thrombophilia testing is very prevalent and sometimes indiscriminant
- Evidence that most prothrombotic abnormalities do not appear to increase the risk of recurrence
- Hypercoagulability testing may be cost-effective in patients with idiopathic VTE

Which one of the following patients should NOT be tested?

1. 35-year-old male who develops a calf vein DVT after a 12-hr car drive
2. 65-year-old male with an idiopathic DVT
3. 28-year-old female with recurrent spontaneous abortions
4. 24-year-old female with a very severe headache and MRV shows cerebral venous thrombosis
5. 50-year-old male with lung cancer and now an extensive RLE DVT

Who should be Tested?

- First unexplained VTE before Age 45
- Recurrent episode of VTE
- Patients with VTE who have clear evidence of a first degree relative with VTE
- Patients with visceral (mesenteric, hepatic or portal) vein and cerebral vein thrombosis
- Women with VTE on Oral Contraceptives

Who should be Tested?

History of a stillbirth fetus and contemplating another pregnancy

History of three or more unexplained spontaneous abortions and contemplating another pregnancy

Patient and or physician are looking for an improved understanding for the VTE

Family is seeking identification of other affected relatives

When to test?

Many experts recommend waiting until the end of planned warfarin therapy (3-6 months after episode of VTE)

Transition to LMWH for 2 weeks

Then perform tests

Warfarin interferes with assays of protein C and S levels

Acute thrombosis itself can reduce the levels of antithrombin and increase the levels of factor VIII.

The PCR based assays for Factor V Leiden, prothrombin gene mutation and the ELISA for anti-phospholipid antibodies can however be performed on both heparin and warfarin therapy.

What Tests?

- Factor V Leiden mutation
- G20210A Prothrombin Gene mutation
- Functional assay of Antithrombin
- Functional assay of protein C
- Immunologic assays of total and free Protein S
- Factor VIII
- Lupus anticoagulant assay
- Anti-beta-2-glycoprotein-I IgG and IgM antibodies
- Enzyme–linked immunosorbent assay (ELISA) for antiphospholipid antibodies IgG and IgM
- Fasting total plasma homocysteine levels

Question 2

- What is prevalence of some of these conditions and associated risk of developing an initial VTE?

Prevalence of Thrombophilic States in Patients with Initial Venous Thromboembolism

Thrombophilia	Controls, %	Patients, %
Antithrombin III deficiency	<1	
Protein C deficiency	<1	2.5-5
Protein S deficiency	Uncertain	
FVL, heterozygous	2-10	20
FVL, homozygous	1.5	2
Prothrombin G20210A	1-3	9
Homocystinemia	5-10	18
Antiphospholipid syndrome	1-7	13
Elevated factor VIII	10	20-45
Elevated factor IX	10	18-26
Elevated factor XI	10	18
Elevated fibrinogen	10	18

FVL =factor V Leiden. Dalen et al. Am J Med 2008;121:458-463

Relative Risk of Initial Venous Thromboembolism

Condition	Relative Risk
Oral contraceptive use	2-4
Hyperhomocysteinemia	2.5
FVL, heterozygous	3-10
FVL, heterozygous + HRT	15
FVL, heterozygous + OCA	30-40
FVL, heterozygous + pregnancy	35
FVL, homozygous	79
FVL, homozygous + OCA	100
Prothrombin G20210A mutation	1-5
Prothrombin G20210A + FVL	6-10
Prothrombin G20210A + OCA	16
Protein C or S or ATIII Deficiency + OCA	9.7

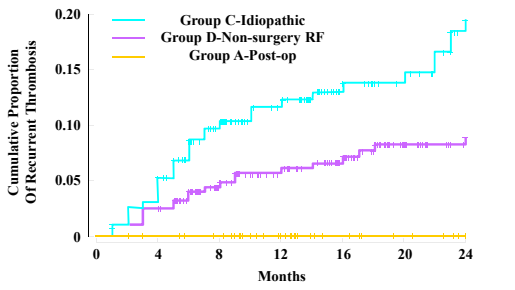
FVL=factor V Leiden mutation; HRT=hormone replacement therapy; OCA =oral contraceptive agent; ATIII=antithrombin III deficiency. Dalen et al. Am J Med 2008;121:458-463

Question 3

What is the duration of anticoagulant therapy in patients with venous thromboembolism and thrombophilias?

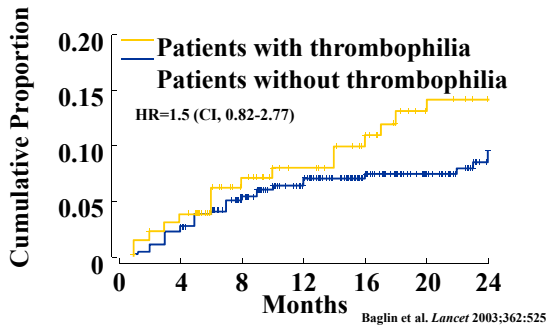
Which patients with thrombophilia require lifelong anticoagulation?

Recurrent Thrombosis After Cessation of Anticoagulant Therapy



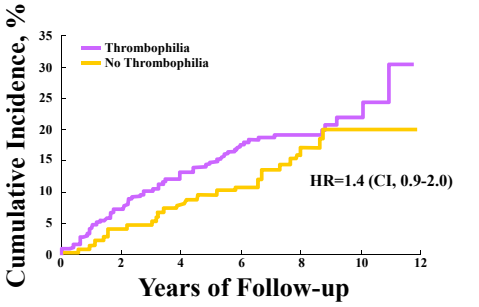
Baglin et al. Lancet, 2003;362:525

Recurrent Thrombosis in Patients With and Without Thrombophilia



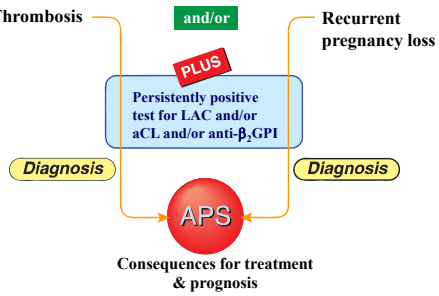
Baglin et al. *Lancet* 2003;362:525

Leiden Thrombophilia Study: Cumulative Incidence of Recurrent VTE



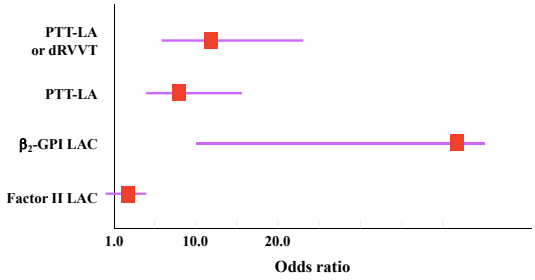
Christiansen et al. JAMA 2005;293:2352-2361

The Updated Classification Criteria for APS



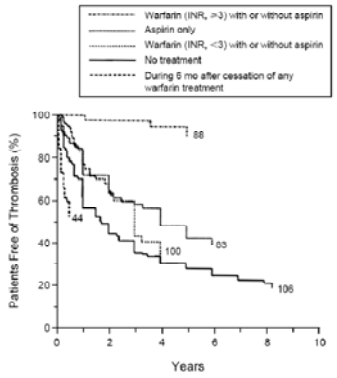
Giannakopoulos et al. Blood. 2009;113:985-994

β_2GPI-dependent LAC Strongly Associated With Thrombosis, Compared With Factor II (Prothrombin)-dependent LAC



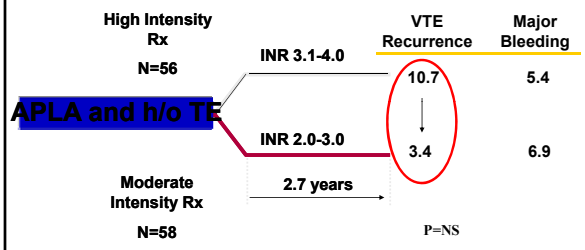
Giannakopoulos et al. Blood. 2009;113:985-994

Risk of Recurrence in APLA is High



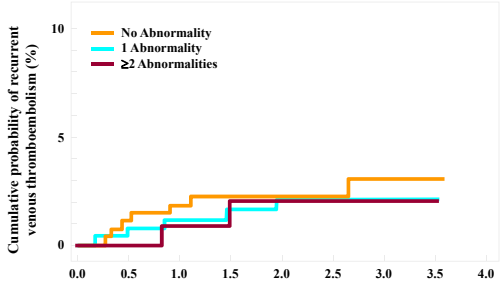
Khamashta et al. N Engl J Med 1995;332:993-997

Rate of Recurrence in APLA
High-Intensity Vs. Moderate Intensity



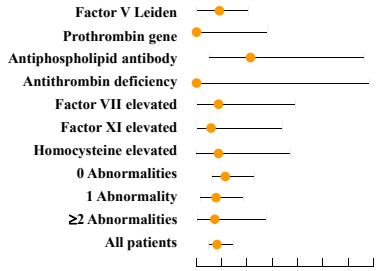
Crowther et al. *N Engl J Med.* 2003;349:1133-1138.

Probability of Recurrent VTE in Patients With Idiopathic VTE



Kearon et al. Blood. 2008;112:4432-4436

Absolute Rates of Recurrent VTE In Patients According to the Type or Number of Thrombophilic Defects



Kearon et al. Blood. 2008;112:4432-4436

Incidence of Recurrent Venous Thromboembolism

Patient Group	Recurrence of VTE per Year
Total group	**2.6%**
With 1 thrombophilia	**2.5%**
Initial VTE provoked	**1.8%**
Initial VTE idiopathic	**3.3%**
Idiopathic with thrombophilia	**3.4%**
Idiopathic without thrombophilia	**3.2%**

VTE = venous thromboembolism. Data from Christiansen et al.[7] Total group = 474 patients with a first episode of VTE.

Dalen et al. Am J Med 2008;121:458-463

Risk of Recurrent VTE after stopping Anticoagulant Therapy

Variable	Relative Risk	Recurrence Yr 1
Cancer	~ 3	~20%
APS	2-4	>20%

Adapted from Kearon et al. Circulation 2004;110(I):I10-I18

ACCP Guidelines

- Treatment of unprovoked first deep venous thromboembolism: For patients with unprovoked DVT, they recommend treatment with a VKA for at least 3 months *(Grade 1A)* and then evaluation of the evaluated for the risks to benefits of indefinite therapy *(Grade 1C)*
- For patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, they recommend long-term treatment *(Grade 1A)*

Kearon et al. Chest, 2008; 133 (Supplement): 454S

ACCP Guidelines

- Treatment of a first episode of DVT secondary to a transient (reversible) risk factor: they recommend treatment with a VKA for 3 months over treatment for shorter periods *(Grade 1A)*

Kearon et al. Chest, 2008; 133 (Supplement): 454S

Suggested Duration of Warfarin Therapy in Patients with Venous Thromboembolism Without Routine Thrombophilia Screening

Clinical Status	Recommended Duration of Warfarin Therapy
Initial VTE with reversible risk factors	3 mo
Initial VTE, idiopathic	1 y
VTE with cancer	Indefinite*
VTE with antiphospholipid syndrome	Indefinite†
≥2 VTE episodes	Indefinite

VTE = venous thromboembolism.
*Or until cancer resolved.
†Or until condition resolved.

Dalen et al. Am J Med 2008;121:458-463

Elevated D-dimer levels predict recurrence in Idiopathic VTE: Meta-analysis

Study	Elevated D-dimer n/N	Normal D-dimer n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Eichinger 2003	63/401	16/209		41.67	2.25 [1.26, 4.00]
Palareti 2003	23/139	10/143		19.33	2.64 [1.21, 5.77]
Palareti 2006	18/120	24/385		22.78	2.65 [1.39, 5.08]
Baglin 2006	21/91	8/51		16.22	1.89 [0.74, 4.80]
Total (95% CI)	751	788		100.00	2.36 [1.65, 3.36]

Total events: 125 (Elevated D-dimer), 57 (Normal D-dimer)
Test for heterogeneity: $\chi^2 = 0.45$, df = 3 (P=0.93), $I^2 = 0\%$
Test for overall effect: $Z = 4.75$ (P <0.00001)

0.1 0.2 0.5 1 2 5 10

Rates of VTE =17% in Elevated D-Dimer group vs. 7% in nl D-Dimer group

Bruinstroop E et al. J Thromb Haemost 2009; 7: 611–8.

Annual Risk and Likelihood Ratios for Recurrent VTE Based on D-Dimer levels after Therapy

D-Dimer Concentration	Number of Studies (n)	Follow-up (person-y)	Recurrent VTE	Pooled annualized risk (95% CI)	LR
Positive	7 (907)	2,462	18%	8.9% (5.8 to 12)	1.5
Negative	7 (981)	2,040	7.5%	3.5% (2.7 to 4.3)	0.6

Verhovsek et al. Ann Intern Med 2008;149:481-90

Conclusions

- The presence of thrombophilia other than antiphospholipid antibody syndrome has minor impact on the rate of recurrent VTE
- Idiopathic VTE is a better predictor of recurrence than the presence of thrombophilia
- There are few indications for thrombophilia testing in practice

Upper Extremity DVT

Case Presentation

36 year old male s/p total colectomy for ulcerative colitis requiring total parenteral nutrition for poor nutritional intake postoperatively develops a right upper extremity DVT secondary to a PICC line. His oral intake is improving and the catheter is still functional.

Management

1. Should you remove the catheter?

2. How long would you treat him?
   1. 3 months?
   2. 6 months?
   3. Indefinitely?

3. Would you consider thrombolysis?

Epidemiology of UEDVT

- 1-4% of all DVTs
- Majority are provoked: 75-80% of cases
- Increasing incidence due to increased use of indwelling catheters
- Complications:
  - PE
  - Recurrence
  - Post-thrombotic syndrome

Should you remove the catheter?

- 74 consecutive eligible patients with active cancer and CVC-associated UEDVT
- Primary efficacy endpoint: rate of central line failure
- All treated with LMWH for 5 days with warfarin transition
  - Treated minimum of 3 months
  - Followed at 7, 28 and 90 days after enrollment
- No lines failed due to the clot
- No patients experienced recurrence or PE
- 3 (4.7%) major hemorrhage

Kovacs M, et al. Journal of Thrombosis and Haemostasis. 2007; 5: 1650-3.

Treatment Duration

- Treatment duration very similar to ACCP guidelines for LE DVT
- Minimum treatment course is 3 months
- Use similar clinical reasoning for duration as in LE DVT
  - Provoked: Minimum of 3 months
  - Unprovoked, single event: 6 months to 1 year
    - Consider indefinite treatment in patients with active cancer
  - Unprovoked, recurrent event: Indefinite

What about thrombolysis?

- 95 consecutive inpatients with subclavian-axillary vein thrombosis
- Retrospective study
  - Followed for median of 40 months
  - Outcomes: rate of PTS and venous recanalization
- Treatment regimens
  - Urokinase thrombolysis + oral anticoagulation (n=33)
  - Oral anticoagulation alone (n=62)
- 29 (88%) of thrombolytic treatments successful and 7 (21%) with bleeding complications

Sabeti S et al. Thromb Res. 2002; 108: 279-85.

What about thrombolysis?

Variable	Lysis + VKA (n=33) N (%)	VKA alone (n=62) N (%)	P-value
Recurrent VTE	2 (6.1)	5 (8.1)	0.9
Major bleed	5 (15.2)	0 (0)	<0.0001
PTS	3 (9.1)	6 (9.7)	0.3

Thrombolysis improves patency and clot resolution over oral anticoagulation alone

Recurrence rate in this study was nonsignificant

High bleeding rate in the thrombolysis group

Poor evidence to date to support routine use

Sabeti S et al. Thromb Res. 2002; 108: 279-85.

Clinical Factors: UEDVT RIETE Registry Data

Clinical Characteristics	UEDVT(N=512) N (%)	LE DVT(N=11,052) N (%)	OR (95% CI)
Immobility >=4d	70 (14)	2808 (25)	0.47 (0.36-0.60)
Prior VTE	36 (7.0)	1898 (17)	0.36 (0.26-0.51)
Cancer	196 (38)	2226 (20)	2.46 (2.04-2.95)
Symptomatic PE*	46 (9.0)	3186 (29)	0.24 (0.18-0.33)
Recurrent DVT*	12 (2.3)	183 (1.7)	1.43 (0.79-2.57)
Recurrent PE*	9 (1.8)	128 (1.2)	1.53 (0.77-3.02)

Munoz F, et al. CHEST 2008; 133: 143-148

Clinical Factors: UEDVT Results of a Prospective Registry

- Prospective US DVT Registry
- 5451 consecutive pts with acute DVT
- 592 (10.9%) with UEDVT
  - 324 (54.7%) CVC-associated: adjusted OR 9.7 (95% CI 7.8-12.2)
  - 78 (13.2%) with cancer
  - 18 (3%) had confirmed PE

Joffe H, et al. Circulation. 2004; 110: 1605-11.

UEDVT and Risk of PE

- Prospective study
- 30 consecutive patients with UEDVT
  - 20 (66.7%) CVC-associated
  - 10 (33.3%) non-CVC associated
- 29/30 underwent VQ scan within 48 hours
- 5 (16.7%) had a PE
  - All in patients with CVC-associated UEDVT
  - One patient symptomatic

Monreal M, et al. CHEST. 1991; 99: 280-83.

UEDVT and Recurrence

- 53 consecutive patients with first UEDVT
  - 6 (11.3%) CVC-associated
  - 6 (11.3%) had concurrent PE
- Treated for at least 3 months with warfarin
- Followed for up to 5 years
- 3 (5.7%) developed recurrent DVT: 2 ipsilateral arm and 1 lower extremity
- Cumulative incidence of recurrence:
  - 2.0% at 1 year
  - 4.2% at 2 years
  - 7.7% at 5 years

Prandoni P et al. BMJ. 2004; 329: 484-85.

Pharmacologic Therapy

- Guidelines similar to treatment for lower extremity DVT
- Initial treatment with therapeutic LMWH, UFH, fondaparinux
- Transition to warfarin with goal INR 2.0-3.0
  - Need to overlap with parenteral anticoagulant for at least 5 days or until INR>=2.0 for 2 consecutive days

ACCP Guidelines 2008; Chest 2008; 133: 454S-545S.

Conclusion

Rising incidence of UEDVT likely related to increased use of central venous catheters

Higher rate of PE than previously thought

Routine removal of catheters not necessary when catheter still functional and needed

Routine use of thrombolytics not recommended

Duration of therapy and treatment regimen very similar to lower extremtity DVT

Alpesh Amin, MD, MBA
Professor of Medicine
Executive Director, Hospitalist Program
University of California, Irvine

Case Presentation

26 y/o white male presents to the emergency department with lower GI Bleed & right lower extremity swelling. Patient has history of Chron's Disease with exacerbation of his disease. Patients blood pressure is stable and hematocrit is stable.

Right lower extremity doppler ultrasound is positive for DVT

Question #1

- What is the incidence of VTE in patients with IBD?

A)1 %

B) 5%

C) 10%

D)20%

Question #2

- What is the treatment for this patients DVT?

A) UFH

B) Aspirin

C) IVC Filter

D) LMWH

E) Monitor

Case Continues

- Patient returns 1 month later with recurrence of right lower extremity swelling which had resolved prior to last hospital discharge. No evidence of GI bleed and hematocrit is stable. The IVC filter is in place.

Question #3

- What is your next step in management of this patient?

A) Monitor & do nothing, patient has an IVC filter

B) Remove the IVC filter, it is contributing to the hypercoagulable state of this patient

C) Treat with anticoagulants at therapeutic levels and monitor for bleeding

Inferior Vena Cava Filters (IVC) Facts

Permanent or retrievables

Reduces, but does not eliminate the risk of symptomatic PE (<5%)

Increase risk of symptomatic DVT in patients with filters[1]

No difference in mortality in one randomized study of patients with DVT[1]

Decousus H, et *al. N Engl J Med*. 1998; 338: 409.

Indications for IVC Filter

Proximal vein thrombosis or PE with contraindications to anticoagulation

Recurrent events on adequate anticoagulation

Chronic recurrent VTE with pulmonary hypertension

Snow V, et al. *Ann Intern Med.* 2007;146:204-210.

1.13 Vena Caval Filters for the Initial Treatment of DVT

1.13.1. For patients with DVT, we recommend against the routine use of a vena cava filter in addition to anticoagulants (Grade 1A)

1.13.2. For patients with acute proximal DVT, if anticoagulant therapy is not possible because of the risk of bleeding, we recommend placement of an inferior vena cava (IVC) filter (Grade 1C)

Kearon, C, et al. *Chest.* 2008

1.13 (cont)

- 1.13.3. For patients with acute DVT who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C)

Kearon, C, et al. *Chest.* 2008

4.6 Vena Caval Filters for the Initial Treatment of PE

4.6.1. For most patients with PE, we recommend against the routine use of a vena caval filter in addition to anticoagulants (Grade 1A)

4.6.2. In patients with acute PE, if anticoagulant therapy is not possible because of risk of bleeding, we recommend placement of an IVC filter (Grade 1C)

Kearon, C, et al. *Chest*. 2008

4.6 Cont.

- 4.6.3. For patients with acute PE who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C)

Kearon, C, et al. *Chest*. 2008

Outpatient Treatment of Pulmonary Embolism

David Lovinger, MD, FHM
NorthShore University HealthSystem and The University of Chicago

Case

67 yo M with sudden onset of pleuritic CP and dyspnea.

Recent hospitalization for cellulitis exacerbation (within 30 d).

CXR is clear

PE protocol CT shows segmental PE in LLL

PMH: HTN, Hyperlipidemia

VS: 98.2, 105, 145/80, 92%/RA

Pt is alert

PEx is benign, except for 1+ RLE edema.

WBC 6.2

Hgb 14.2

SCr 0.9

Does this patient need to be hospitalized?

- A) Yes, pt is high risk and should stay in the hospital until INR is therapeutic
- B) Yes, brief overnight hospitalization and discharge on enoxaparin and warfarin, if stable.
- C) Probably, as there is no compelling data regarding outpatient Rx of PE.
- D) No, pt is low risk and can be discharged on enoxaparin and warfarin.

Objective

- Learn about risk stratification for patients with pulmonary embolism.

LOS and Mortality in Patients with Pulmonary Embolism[1]

PE is a serious medical condition, with substantial morbidity and mortality.

Optimal length of stay unclear in era when all LOS is decreasing.

Which patients need admission and which can be treated safely as an outpatient?

1. Aujesky D, Stone RA, Kim S, Crick EJ, Fine MJ. Length of Hospital Stay and Postdischage Mortality in Patients with Pulmonary Embolism. Arch Int Med. 2008; 168(7), 706-712.

Methods

Retrospective cohort study

15,531 patients

Administrative and clinical data

Inclusion criteria

- Primary dx = PE, or
- Secondary dx = PE and primary dx c/w PE (SOB, resp failure, syncope, cardiac arrest, etc)

Patients with only a secondary dx of PE or transferred from another facility were excluded

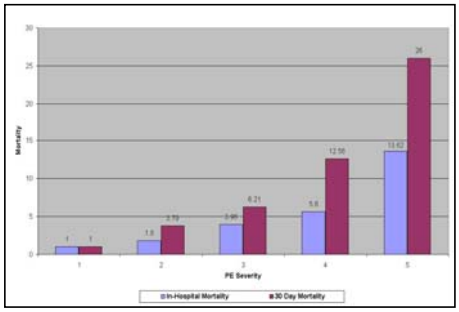
Community acquired PE

Pulmonary Embolism Severity Index (PESI)

- Risk stratification into 5 groups based on score
  - Class I $\leq$ 65
  - Class II 66-85
  - Class III 86-105
  - Class IV 106-125
  - Class V $\geq$ 126
- Patterned on the PSI score, groups 3 and above should be hospitalized.

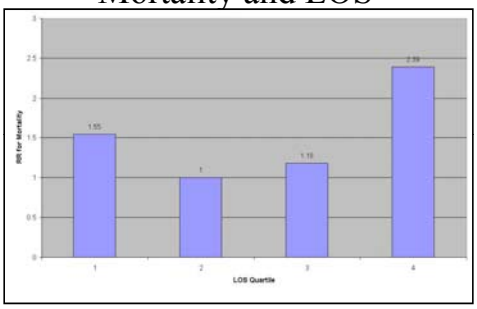
- Age in years
- Male gender (10)
- Cancer (30)
- CHF (10)
- Lung Dz (10)
- Pulse $\geq$ 110 (20)
- SBP < 100 (30)
- Resp $\geq$ 30 (20)
- Altered mental status (60)
- SaO2 < 90% (20)

Mortality and PESI Score[1]



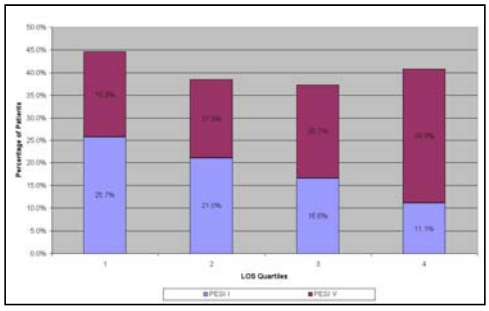
[1]Aujesky D, Obrosky S, Stone RA, Auble TE, Arnaud P, Cornuz, Roy P, Fine MJ. Derivation and Validation of a Prognostic Model for Pulmonary Embolism. Am J Respir Crit Care Med. 2005; 172, 1041-1046.

Mortality and LOS



LOS Quartile: Q1 ≤ 4d; Q2 = 5-6d; Q3 = 7-8d; Q4 > 8d

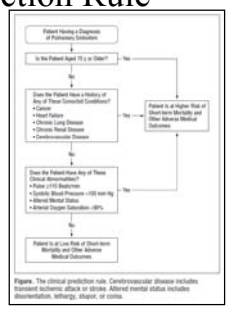
PESI Score and LOS Quartile



Simple Prediction Rule

Simple clinical decision rule incorporating PESI score.

Retrospectively derived and validated (*not* a clinical trial).



1. Aujesky D, Obrosky S, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. A Prediction Rule to Identify Low-Risk Patients with Pulmonary Embolism. Arch Int Med. 2006; 166(2), 169-175.

ACCP 2008

No randomized trials on inpatient vs outpatient rx.

For DVT, recommendations are for treatment "…as an outpatient if possible, or as an inpatient if necessary."

Otherwise relatively silent on this issue.

Case, Cont'd

PESI score is 77 (points for age and male gender), and therefore Class 2.

Pt is also low risk according to simplified clinical prediction rule.

For all outpatient Rx, patient needs to have sufficient capacity to inject medications and have reliable follow-up.

Outpatient treatment options include (all Grade 1A):

- Enoxaparin, 1 mg/kg SC q12
- UFH, 250 units/kg SC bid, dose-adjusted by PTT
- UFH, 333 units/kg SC, followed by 250 Units/kg bid, not dose-adjusted.
- Fondaparinux, weight-based dosing.

Does this patient need to be hospitalized?

- A) Yes, pt is high risk and should stay in the hospital until INR is therapeutic
- B) Yes, brief overnight hospitalization and discharge on enoxaparin and warfarin, if stable.
- C) Probably, as there is no compelling data regarding outpatient Rx of PE.
- **D) No, pt is low risk and can be discharged on enoxaparin and warfarin.**

Conclusions

Outpatient treatment of PE can be safe.

Proper risk-stratification and case selection is important

PESI has the best evidence currently, though the simple prediction rule appears equally compelling

Regardless of treatment setting, treatment with VKA and close follow-up are essential.

Perioperative Management of Patients on Oral Anticoagulation

Society of Hospital Medicine
April 9, 2010

Andrew Dunn, MD, FACP
Professor of Medicine
Director, Hospitalist Service
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Mount Sinai Medical Center
New York, NY

CASE

You are seeing a 60 year-old male with a history of hypertension, CHF (EF=44%), and a mechanical aortic valve (bileaflet) replacement. The patient has had no history of TIA/stroke or bleeding.

The patient will undergo elective major abdominal surgery.

Which bridging regimen would you select?

1. No bridging
2. Prophylaxis-dose pre-op and post-op (UFH or LMWH)
3. Full-dose pre-op bridging (UFH or LMWH) and no or proph-dose post-op
4. Full-dose pre-op and "careful" full-dose post-op bridging (UFH or LMWH)

WHETHER TO BRIDGE
Decision-analysis

The patient is a 60 year-old hypertensive individual with AVR undergoing major abdominal surgery.

Baseline assumptions:

Annual stroke rate off ac	4%
Anticoagulation efficacy	75%
Increase in major bleed by ac	3%
Postop major bleed mortality	3%

Stroke consequences and utilities	Mild	21%,	utility 0.76
	Moderate	9%,	utility 0.39
	Severe	40%,	utility 0.07
	Fatal	30%	utility 0.0

Dunn AS. *Medical Decision Making*. 2005;25:387-97.

WHETHER TO BRIDGE
Decision-analysis

The patient is a 60 year-old hypertensive individual with AVR undergoing major abdominal surgery.

A minimalist strategy yields slightly greater QALE than an aggressive strategy (11.028 vs 11.025 years).

RESULT: TOSS-UP

RESULT: NO BENEFIT FROM BRIDGING

The Surgical Milieu

- Decreased levels of Antithrombin III and TPA
  - ✓ Obvious and dramatic increase in risk of VTE
  - ✓ Controversial impact on risk of arterial thromboembolism
- Rebound hypercoagulability after discontinuation of OAC
  - ✓ Increase in F_{1+2}, TAT complexes, FPA, D-dimers
  - ✓ Increase in Factor VIII

Poller L, et al. *Lancet.* 1964;2:62-4.
Genewein U, et al. *Br J Haem.* 1996;92:479-85.

Consensus?????

Survey of internists, cardiologists, cardiac surgeons, and other specialties.

Based on 4 scenarios of patients with varying degrees of TE and bleeding risk.

Douketis JD. *Can J Cardiol.* 2000;16:326-30.
Douketis JD, et al. *Chest.* 1999;116:1240-6.

Atrial Fibrillation - 70 yo male undergoing hernia repair

Full-dose bridging
17-20%

MVR - Mitral Valves, Plus afib and stroke

Full-dose bridging
91-97%

For Aortic Valves, NO H/O AFIB or STROKE

Full-dose bridging
64-84%

Douketis JD. *Can J Cardiol.* 2000;16:326-30.
Douketis JD, et al. *Chest.* 1999;116:1240-6.

Consensus?
A Pattern Emerges

Lowest risk patients: **Non-aggressive management**

Highest risk patients: **Aggressive management**

Everyone in between:

Literature Review

Systematic Review of the Literature on Bridging Therapy

1868 patients from 30 different reports

Thromboembolism	29/1868 (1.5%)
Stroke/TIA	11/1868 (0.6%)

Dunn AS, Turpie AGG. *Arch Intern Med.* 2003;163:901-8.

Systematic Review of the Literature on Bridging Therapy

LIMITATIONS

- No randomized controlled trials
- Typically no duration of follow-up stated
- Inconsistent or undescribed definitions of events
- Results not always reported by anticoagulation strategy

LMWH as Bridging Anticoagulation:

Assessment of a Standardized Periprocedural Anticoagulation Regimen

Prospective registry: MHV or Afib or embolic stroke
N=650

Preoperative period:

When INR <2.5: Dalteparin 100 IU/kg SC BID

Last preop dose at least 12 hours prior to the procedure

Postoperative period:

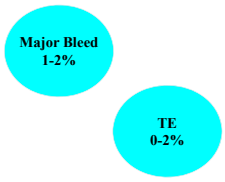
Nonhigh risk:	Dalteparin 100 IU/kg SC BID the day following procedure Dalteparin delayed if inadequate hemostasis Warfarin the evening of procedure
High risk:	No dalteparin Warfarin the evening following the procedure

Douketis JD. *Arch Intern Med.* 2004;164:1319-26.

LMWH as Bridging Anticoagulation RESULTS

High Risk Procedure (n=108)

Major bleed	2 (1.9%)
TE	0 (0%)
TE (possible)	2 (1.9%)
Death	2 (1.9%)



Non-High Risk Procedure (n=542)

Major bleed	4 (0.7%)
TE	2 (0.4%)
Stroke/TIA	1 (0.2%)
Peripheral	1 (0.2%)

Douketis JD. *Arch Intern Med.* 2004;164:1319-26.

PROSPECT

PROSpective Perioperative Enoxaparin Cohort Trial

Atrial fibrillation or prior VTE who require bridging

Hold warfarin 5 days prior to procedure
Start enoxaparin (1.5 mg/kg SC QD) 3 days prior to procedure
No enoxaparin the am of procedure
Restart warfarin the evening of procedure
Restart enoxaparin 12-24 hours after procedure
D/c enoxaparin when INR therapeutic

Dunn AS. *J Thromb Haem.* 2007 In press.

PROSPECT

Thromboembolic Events

Afib

Arterial emboli	4/176 (2.3%)
CVA/TIA	2 (1.1%)
PAT	2 (1.1%)

VTE

DVT/PE	1/96 (1.0%)

PROSPECT

Results

Major Bleeding 9/260 (3.5%)

	Major Bleeding
Invasive procedures	1/145 (1%)
Minor surgery	0/68 (0%)
Major surgery	8/40 (20%)

Bariatric Surgery

Risk of major bleeding

- 1700 patients undergoing bariatric surgery
- 21 patients on OAT received full-dose bridging ac
- Post-op ac started 24 hours after surgery

➢ Major bleeding 3/21 (14%)

➢ Historical controls: 20/450 (4%)

Mourelo R. *Obes Surg.* 2008;18:167-70.

Back to the patient….

60 year-old male with htn, and mechanical aortic valve, undergoing major abd surgery.

Risk of stroke, without ac:
Annual 8%
Over 1 week 0.15%
Higher if hypercoagulable state proven

Increased risk of major postop bleeding, with bridging ac:

UNKNOWN, possibly as high as 10-20%

Back to our patient Part II

Risk of stroke, without ac:

Mathematically over 1 week 0.15%
Based on studies could be: 1% ←

If reduced 75% by ac, then rate is reduced to 0.25%

The absolute benefit is 0.75%

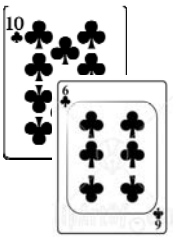
Need to treat 133 patients to prevent 1 stroke/TIA

If major bleeding is increased 10%, then will cause 13 major bleeds

You get what you pay for: Major bleeding leads to withholding ac and to increased risk of stroke/TIA

Hitting on 16

DEALER



YOU

VTE

45 year-old female with a history of ulcerative colitis.

Total colectomy 2 years ago, which was complicated by a PE in the post-operative period. The patient was treated with warfarin uneventfully for 6 months. The patient subsequently developed a spontaneous DVT 8 months ago and has been on warfarin since that time.

The patient is now scheduled for an ileoanal anastamosis.

45 year-old female with a history of ulcerative colitis, PE 2 years ago and DVT 8 months ago. Scheduled for an ileoanal anastamosis.

Risk of VTE, without ac:

- Annual 10-15%
- Over 1 week 0.29%
- Increased up to 100-fold due to hypercoagulable state

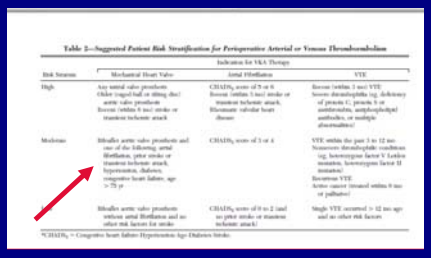
Increased risk of major postop bleeding, with full-dose bridging ac:

- HIGH, possibly as high as 10-20%

EFFICACY OF ANTICOAGULATION VTE Patients

Treatment-dose:	80-90% effective
Prophylaxis-dose	66-75% effective

ACCP GUIDELINE



Douketis J, Berger P, Dunn A, et al. *Chest*. 2008;133:299S-339S.

ACCP GUIDELINE

Low-risk: No bridging.
(example: VTE >12 months)

Intermediate-risk: Bridge with therapeutic dose SC LMWH or IV heparin or prophylaxis-dose LMWH
(example: recurrent VTE)

High-risk: bridge with therapeutic-dose IV UFH or SC LMWH
(example: VTE within 3 months)

Douketis J, Berger P, Dunn A, et al. *Chest*. 2008;133:299S-339S.

APPROACH

RISK (Annual risk without ac)	EXAMPLES	STRATEGY
Low	• 1 prior VTE >12 months ago • Afib with 0-2 stroke risk factors • Mechanical bileaflet AVR	No bridging
Moderate	• VTE 3-12 months ago • Recurrent VTE • Bileaflet AVR + risk factor • Afib with 3-4 risk factors	Bridging possibly beneficial, especially for minor surgery. If bridging chosen for major surgery, consider post-operative proph-dose, particularly for VTE patients.
High	• VTE within 3 months • VTE severe thrombophilia • Afib CHADS 5-6 or CVA • Mechanical mitral valve • Older type AVR	Bridge with full-dose anticoagulation. For high bleed risk procedures, delay full-dose and monitor carefully for post-operative bleeding.