How to Approach the Inpatient with Clotting

Steven Fein, MD, MPH

What I’m Going to Tell You

- Who is a clotter? Who is a bleeder?
- Preventing DVT/PE in hospitalized patients.
- What caused my patient’s DVT/PE?
- How to treat my patient with DVT/PE.
- How to prevent another episode of DVT/PE.

Hospital-based hematology

- Hematology is a fundamental inpatient hospital specialty
- Many patients present with heme conditions
- Many life-threatening conditions require hematology experts
- Hospitals have grown accustomed to having limited access or no access to hematologists

When to request an inpatient heme consult

- Bleeding and transfusion concerns, transfusion refusal
- Anemia: iron deficiency, AIHA, sickle cell disease
- Clotting: DVT/PE, HIT, stroke, anticoagulants
- Abnormal blood counts: ITP, aplastic anemia, polycythemia
- Heme malignancy: leukemia, lymphoma, multiple myeloma
- Rare hematology disorders, mystery cases

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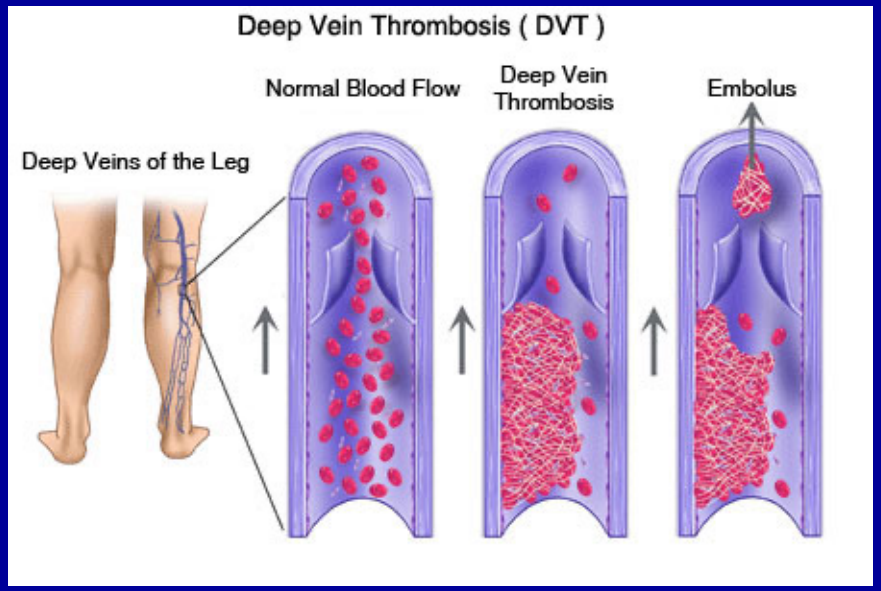
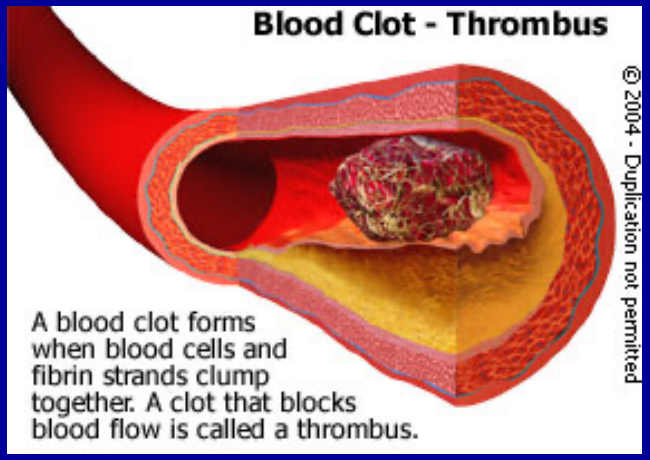
Who is a Clotter?
Who is a Bleeder?

Clotters	Bleeders
Middle aged people 50-75yo -prior clot: stroke/TIA, DVT/PE -definable clotting disorders -cancer -chronic inflammatory states ***Disability and early mortality***	Older people >75yo -prior bleeding -liver dysfunction -anticoagulants -"wine with dinner" ***Longevity***

What is DVT?


Deep Vein Thrombosis (DVT)
Normal Blood Flow
Deep Vein Thrombosis
Embolus
Deep Veins of the Leg


Blood Clot - Thrombus
A blood clot forms when blood cells and fibrin strands clump together. A clot that blocks blood flow is called a thrombus.
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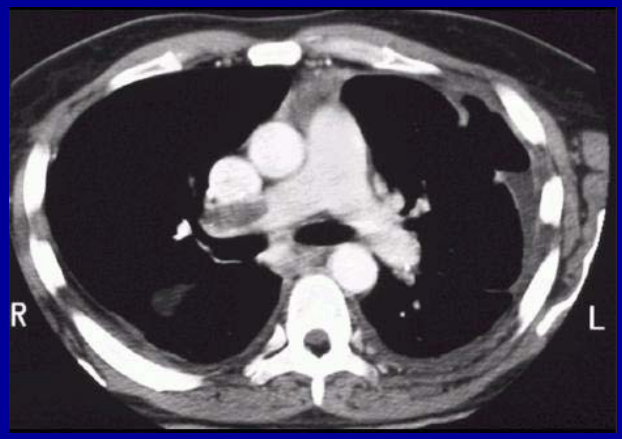
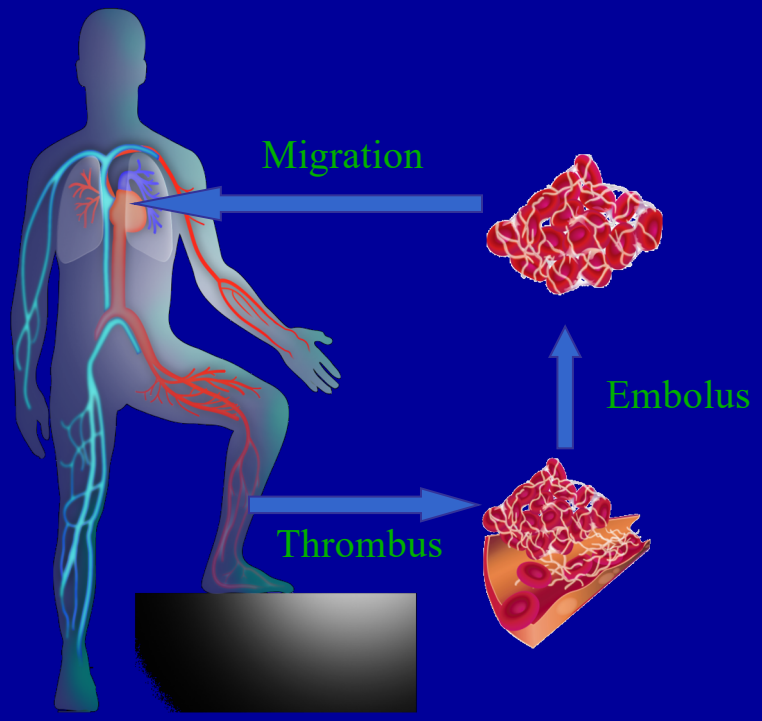
What is Pulmonary Embolism?



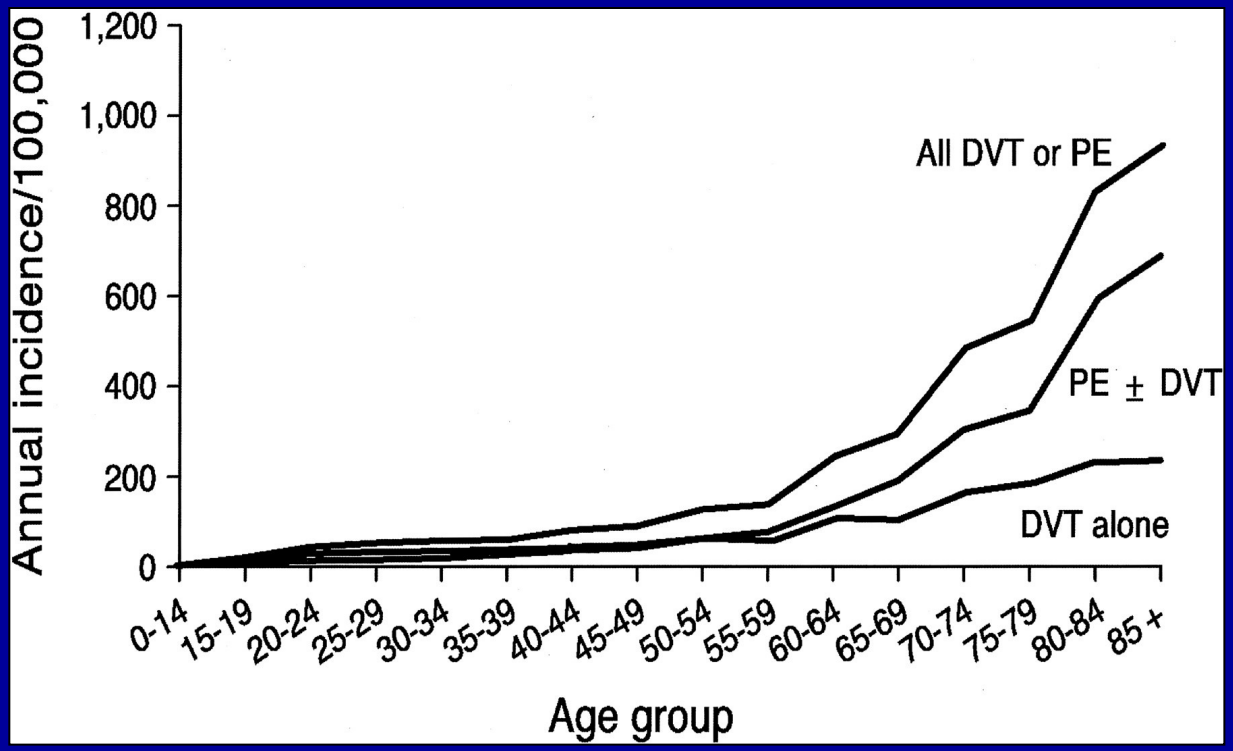
DVT/PE: A Single Entity

50% of patients with proximal DVT of the leg have asymptomatic PE

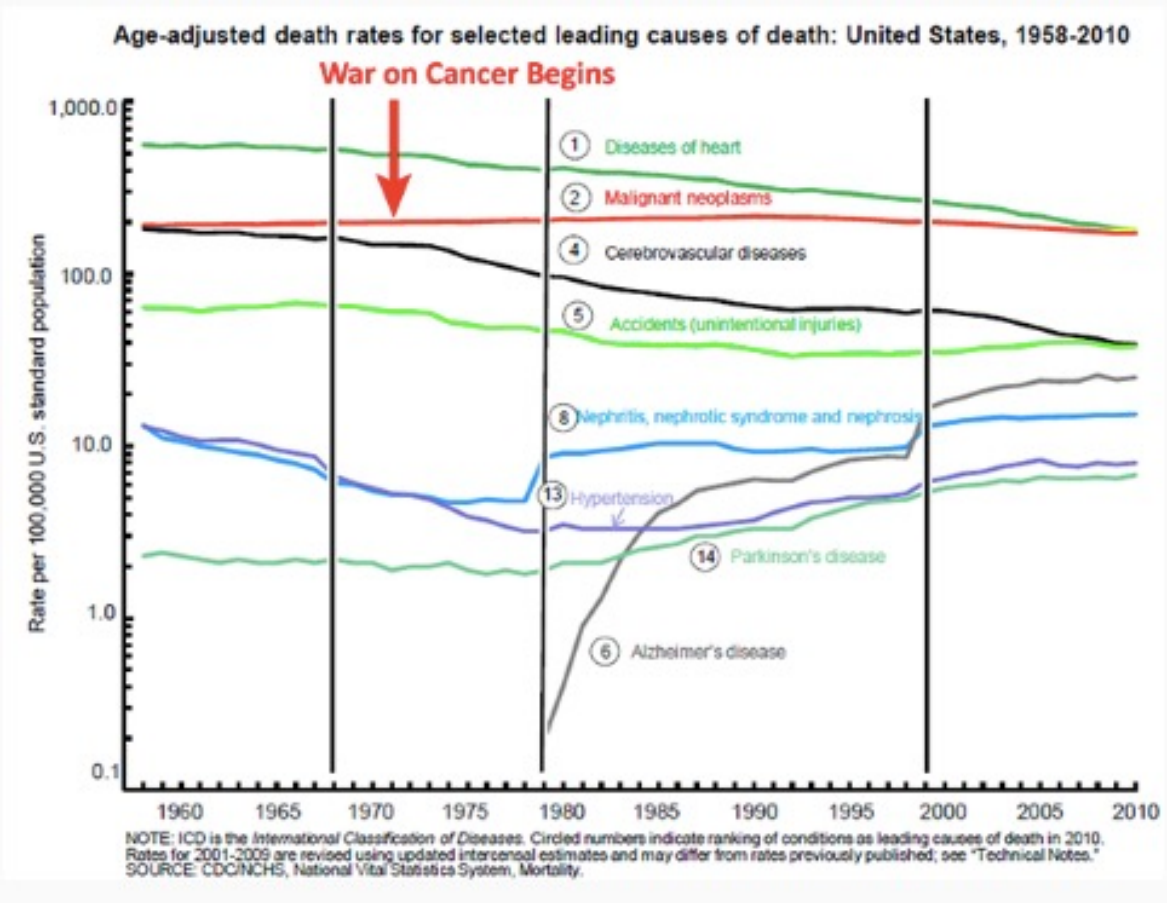
If PE proven→ 80% have DVT



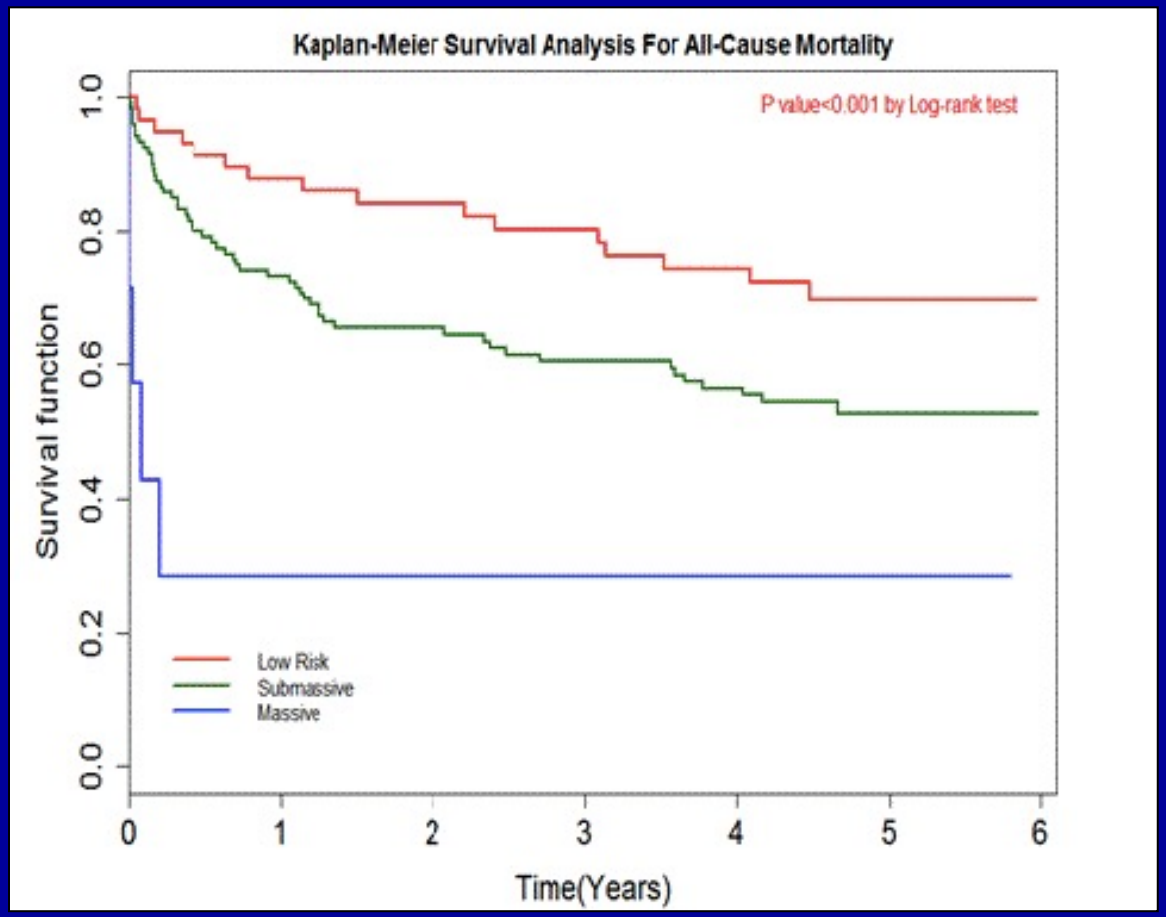
DVT/PE is Common in Age>50



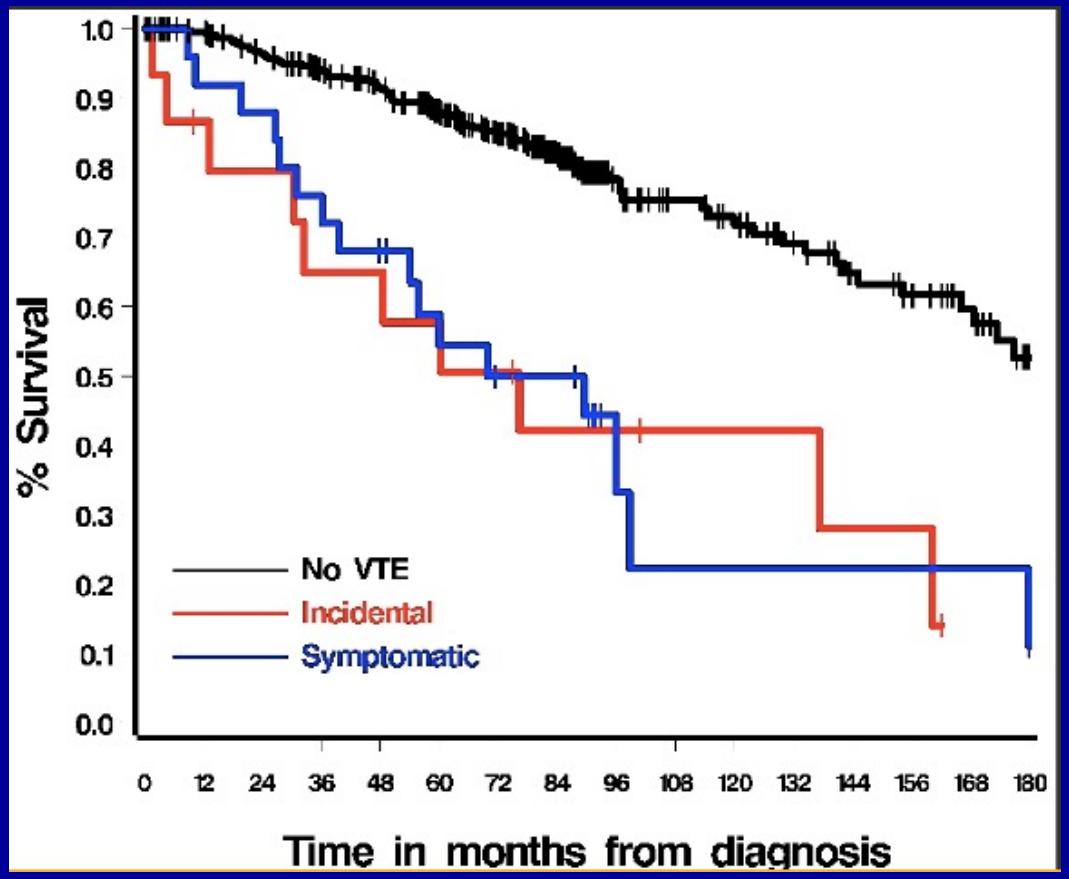
CAD and Stroke are Killers



DVT/PE Predicts Mortality



Cancer Clotters have Shorter Lives than Cancer Patients Without Clotting



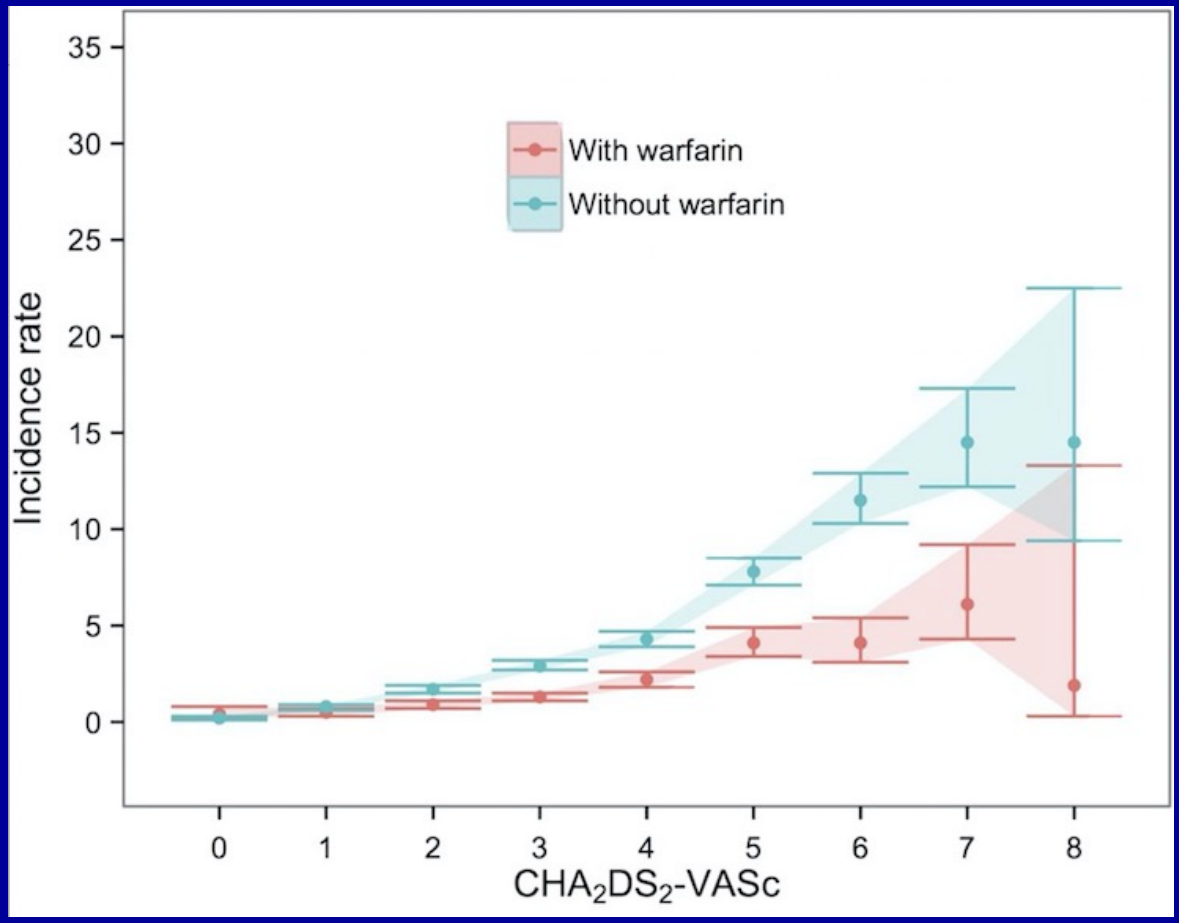
How to Prevent DVT/PE/Stroke

- 50 million Americans take aspirin daily.
- 6 million Americans take anticoagulants daily.
- Identify clotters and prescribe anticoagulants.
  - Identify those at risk of DVT/PE
    - Age>50, cancer patients, prior clotters, hospitalized patients
  - Identify those at risk of stroke: CHA_2DS_2-VASc>1
    - Those who have known CAD, PVD, or prior TIA/stroke
- Prescribe anticoagulants whenever benefit>risk.

Clot Prevention Goals

- Preventing stroke in atrial fibrillation patients.
- Preventing second stroke in prior stroke/TIA patients.
- Preventing DVT/PE after surgery.
- Preventing DVT/PE in non-surgical patients.
- Treating and preventing DVT/PE in clotters.

Anticoagulants Prevent Stroke



Anticoagulants Risky in Bleeders

HAS-BLED

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age > 65)	1
D	Drugs or Alcohol	1 or 2
Maximum Score		9

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Why Does DVT Matter?

- Associated with pulmonary embolism (50%).
- Post-thrombotic syndrome (30%).
- Recurrent DVT (30% long-term recurrence).
- Mortality.

Why Post-op DVT/PE Prevention is Important

Table. 11 Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis

Level of Risk Examples	Calf DVT,%	Proximal DVT,%	Clinical PE,%	Fatal PE,%
Low risk Minor surgery in patients <40 yrs with no additional risk factors	2	0 - 4	0.2	0.002
Moderate risk Minor surgery in patients with additional risk factors; non major surgery in patient aged 40-60 yrs with no additional risk factors ; major surgery in patients <40 yrs with no additional risk factors	10 - 20	2 - 4	1 - 2	0.1 - 0.4
High risk Non major surgery in patients >60 yrs or with additional risk factors; major surgery in patients >40 yrs or with additional risk factors	20 - 40	4 - 8	4 - 8	0.4 - 1.0
Highest risk Major surgery in patients >40 yrs plus prior VTE, cancer, or knee arthoplasty, hip fracture surgery ; major trauma ; spinal cord injury	40 - 80	10 - 20	10 - 20	0.2 - 5

Noninvasive DVT Prevention

INTERMITTENT PNEUMATIC COMPRESSION

Evidence: Limited

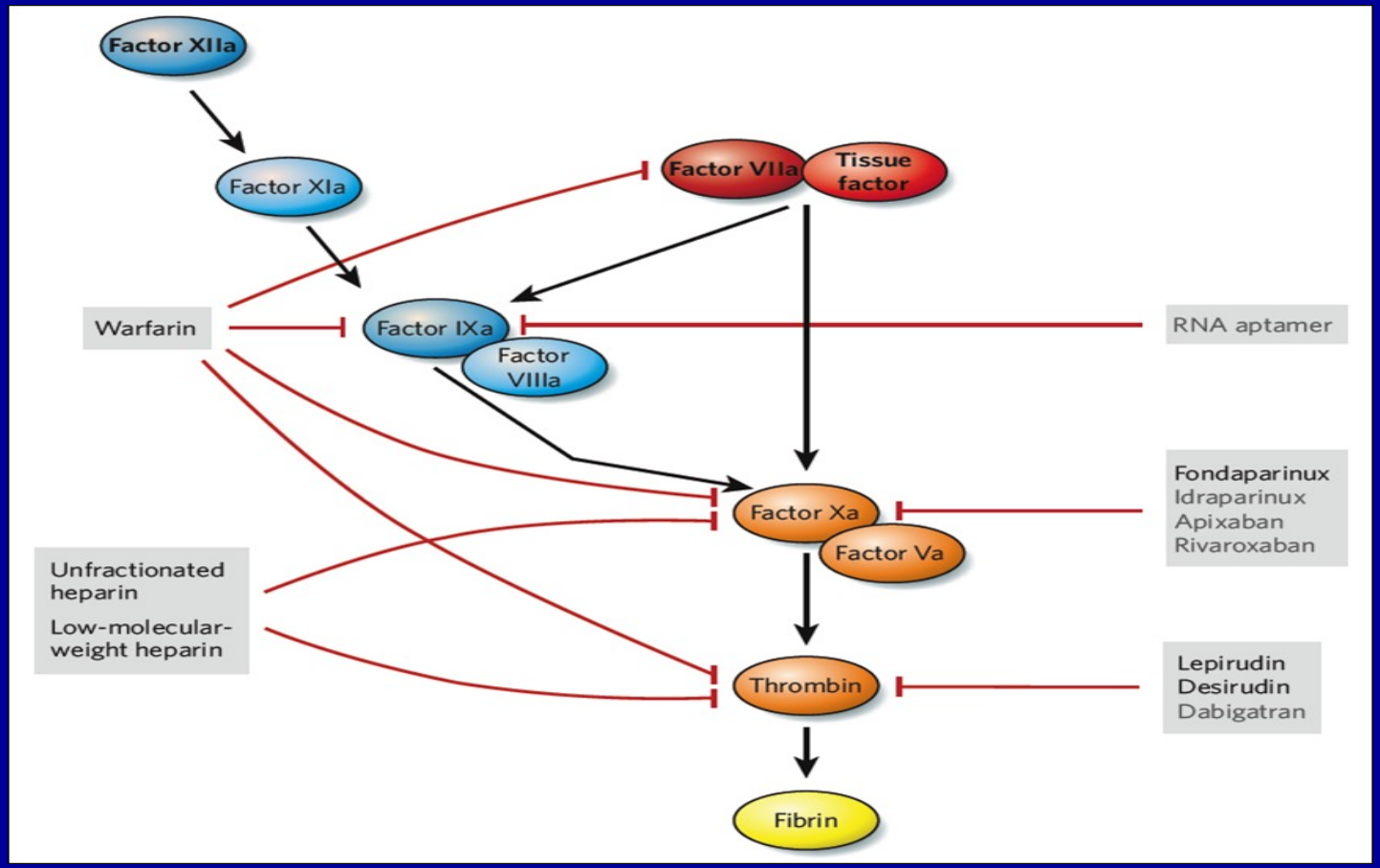
Compliance: Poor

Cost: $56.00 per day
equipment rental

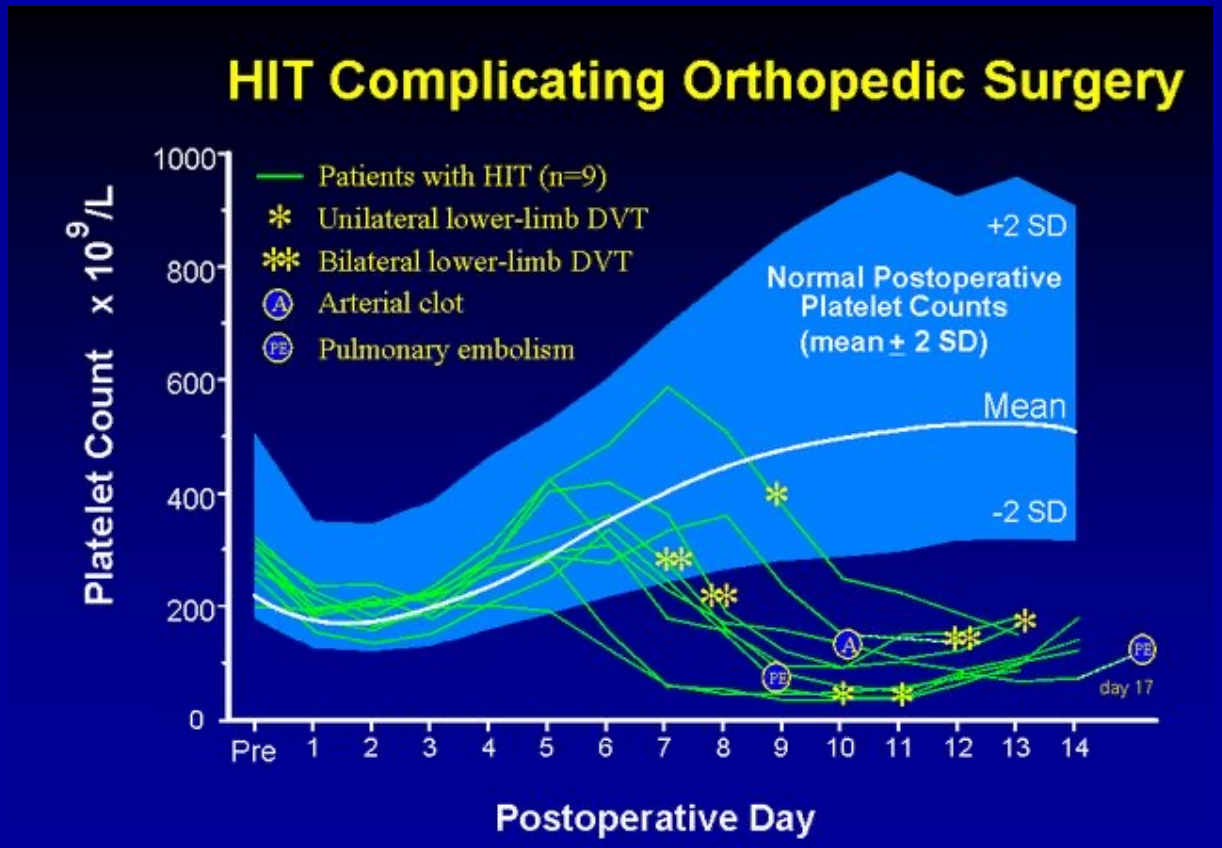
Bleeding risk: NONE

30

How Anticoagulants Work



Heparin Sometimes Causes HIT



Warkentin et al. *N Engl J Med* 1995;332:1330-5

Fondaparinux for Post-op DVT/PE Prevention

FONDAPARINUX COMPARED WITH ENOXAPARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER ELECTIVE MAJOR KNEE SURGERY

Event	Fondaparinux Once Daily		Enoxaparin Twice Daily	
	no. with events/ total no.	percent (95% CI)	no. with events/ total no.	percent (95% CI)
Venous thromboembolism (primary outcome)	45/361	12.5 (9.2 to 16.3)	101/363	27.8 (23.3 to 32.7)
Any deep-vein thrombosis¶	45/361	12.5 (9.2 to 16.3)	98/361	27.1 (22.6 to 32.0)
Any proximal deep-vein thrombosis‖	9/368	2.4 (1.1 to 4.6)	20/372	5.4 (3.3 to 8.2)
Distal deep-vein thrombosis only‖	35/372	9.4 (6.6 to 12.8)	78/366	21.3 (17.2 to 25.9)
Symptomatic venous thromboembolism**	3/517	0.6 (0.1 to 1.7)	7/517	1.4 (0.5 to 2.8)
Symptomatic deep-vein thrombosis	3/517	0.6	4/517	0.8
Nonfatal pulmonary embolism	1/517	0.2	4/517	0.8
Fatal pulmonary embolism	0/517		0/517	

The New England Journal of Medicine

NOAC for DVT/PE Prevention After Knee Replacement

Rivaroxaban efficacy story

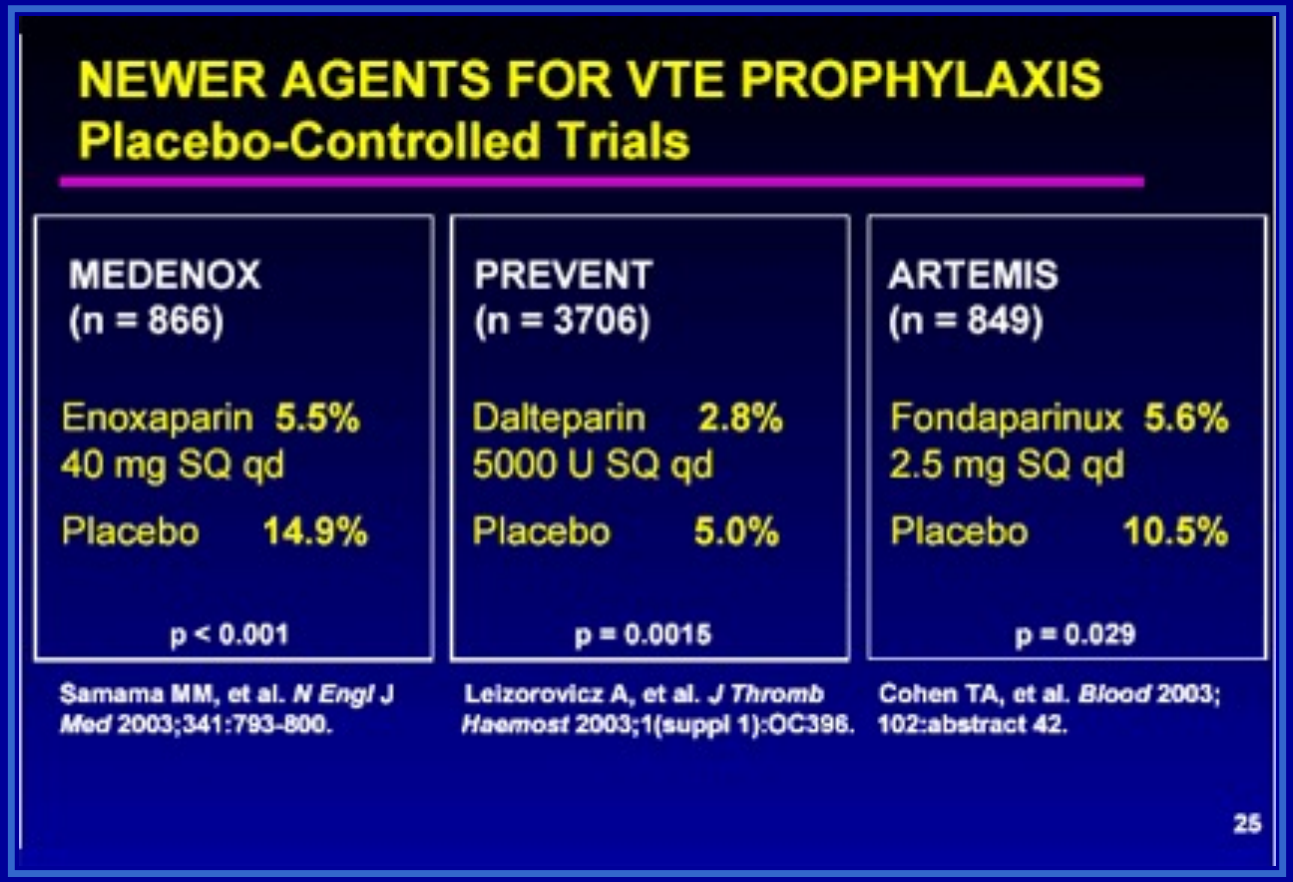
Event	Rivaroxaban (N=1220)		Enoxaparin (N=1239)	
	No. with events/ total no.	% (95% CI)	No. with events/ total no.	% (95% CI)
Up to day 17				
Primary efficacy outcome†	79/824	9.6 (7.7 to 11.8)	166/878	18.9 (16.4 to 21.7)
Death	0/824	0.0 (0.0 to 0.5)	2/878	0.2 (0.0 to 0.8)
Pulmonary embolism	0/824	0.0 (0.0 to 0.3)	4/878	0.5 (0.1 to 1.2)
Deep-vein thrombosis	79/824	9.6 (7.7 to 11.8)	160/878	18.2 (15.7 to 20.9)
Proximal	9/824	1.1 (0.5 to 2.1)	20/878	2.3 (1.4 to 3.5)
Distal	70/824	8.5 (6.7 to 10.6)	140/878	15.9 (13.6 to 18.5)
Major venous thromboembolism (modified intention-to-treat population)‡	9/908	1.0 (0.5 to 1.9)	24/925	2.6 (1.7 to 3.8)

Apixaban efficacy story

	Apixaban (N=1596)		Enoxaparin (N=1588)	
	no. (%)	*95% CI*	*no. (%)*	*95% CI*
Adjudicated major or clinically relevant nonmajor bleeding events	46 (2.9)	2.2–3.8	68 (4.3)	3.4–5.4
All bleeding events	85 (5.3)	4.3–6.6	108 (6.8)	5.7–8.2
Minor bleeding events	39 (2.4)		40 (2.5)	

The New England Journal of Medicine

Anticoagulants for DVT/PE Prevention in Non-surgical Patients



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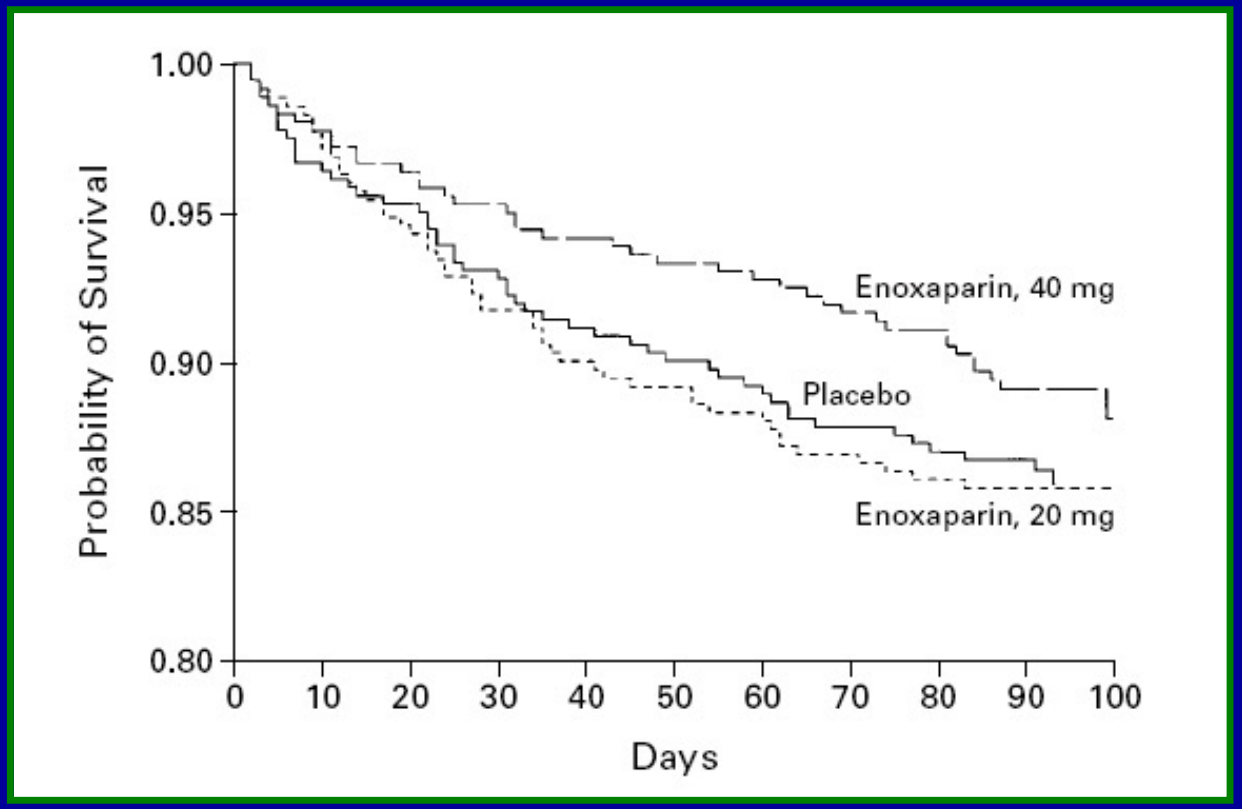

A COMPARISON OF ENOXAPARIN WITH PLACEBO FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN ACUTELY ILL MEDICAL PATIENTS

The New England Journal of Medicine

My Recommendations for Inpatient DVT/PE Prevention

- Do risk assessment: age, cancer, prior clotting.
- Weigh benefit vs. risk for anticoagulants.
- Use NOAC for post-op orthopedic prevention.
- Injection anticoagulants in other hospital patients.
  - Fondaparinux 2.5mg daily if age<75 and nl creat.
  - Enoxaparin 40mg daily if age<75 and procedures.
  - Enoxaparin 30mg daily if age>75 or abnormal creat.
  - Heparin 5000U q12h if ESRD

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What Caused My Patient's DVT/PE?

INDEPENDENT RISK FACTORS FOR VTE IN MEDICALLY ILL PATIENTS

Univariate analysis of *PREDEFINED RISK FACTORS* in 575 MEDENOX pts who received placebo or inadequate prophylaxis (enoxaparin 20 mg qd)

	RR	p
Sex	1.17	0.5
Age > 75	*1.79*	*0.007*
Cancer	*1.59*	*0.07*
Previous VTE	*1.67*	*0.08*
Obesity	0.94	0.91
Varicose veins	1.45	0.10
Hormone therapy	0.51	0.70
Chronic respiratory disease	0.63	0.03
Chronic heart failure	0.79	0.35

Alikhan R, et al. *Arch Intern Med* 2004;164:963-968.

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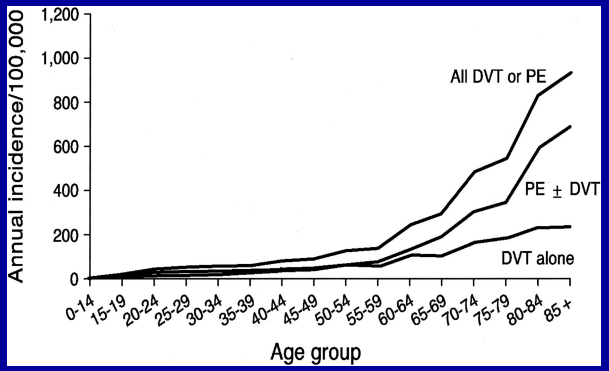

What is a Hypercoagulable State?

- Factor V Leiden mutation
- Prothrombin mutation
- PC/PS/AT deficiency
- Sickle cell disease
- Lupus AC/APLA
- Homocysteine
- Myeloproliferatice d/o
- Lymphoproliferative d/o
- PNH

Clinical features

- Recent heparin exposure (HIT)
- Recent surgery or injury
- Prior clotting
- h/o MI, CAD, stroke, DVT, PE
- h/o “vascular disease”
- Lack of easy bleeding
- Estrogen or pregnancy or OCP
- Cancer
- Platelet count irrelevant
- low plts maybe more clotty

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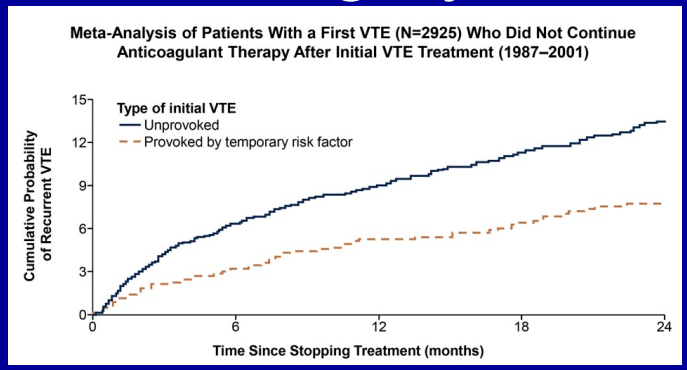
What Caused my Patient's DVT/PE? Practical Perspective

- "Unprovoked"
  - You're a clotter.
  - We don't really know why you clotted.
  - Nothing you could have done to predict or prevent it.
  - Clot mutation testing.
- "Provoked"
  - Trauma
  - Surgery



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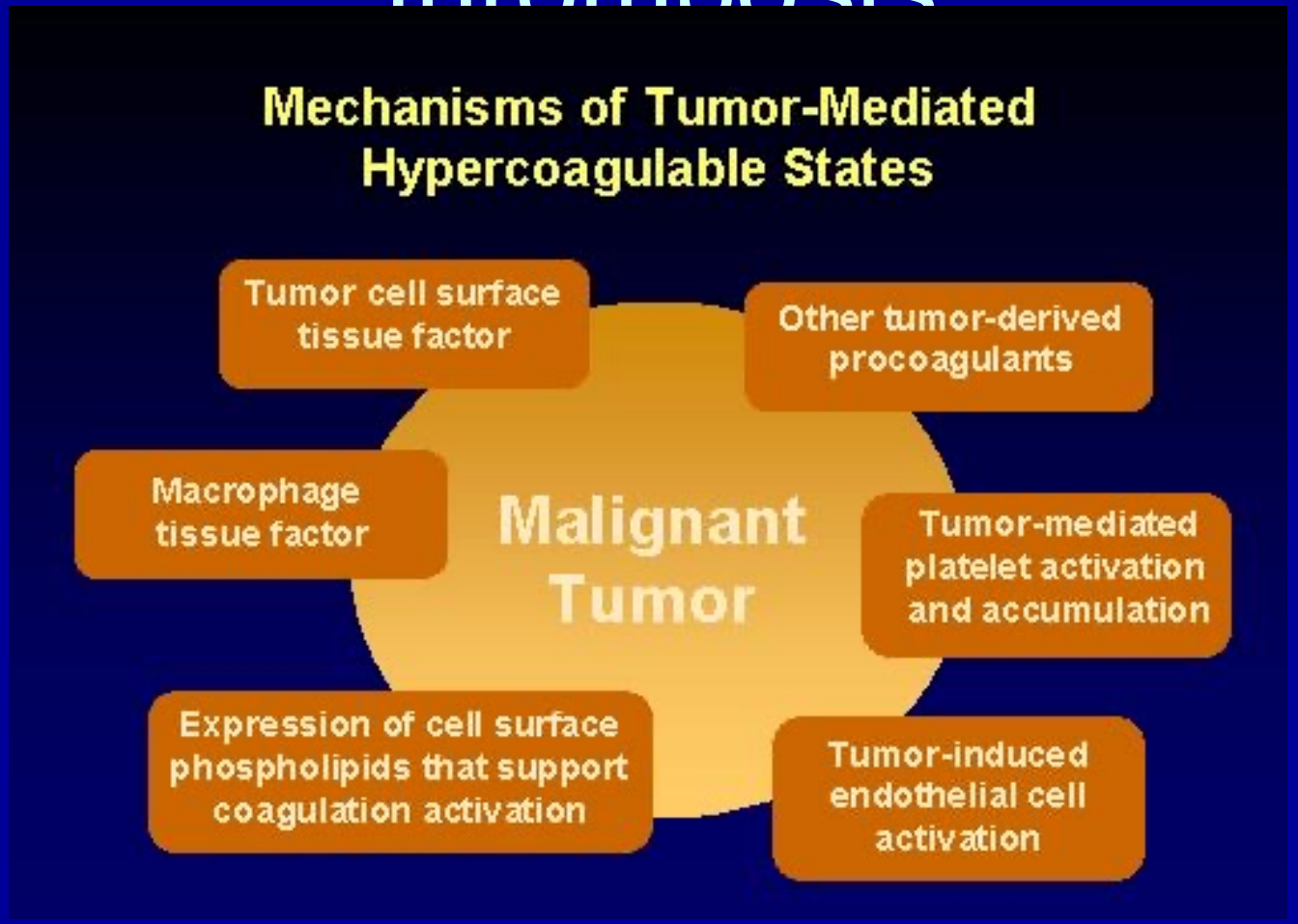
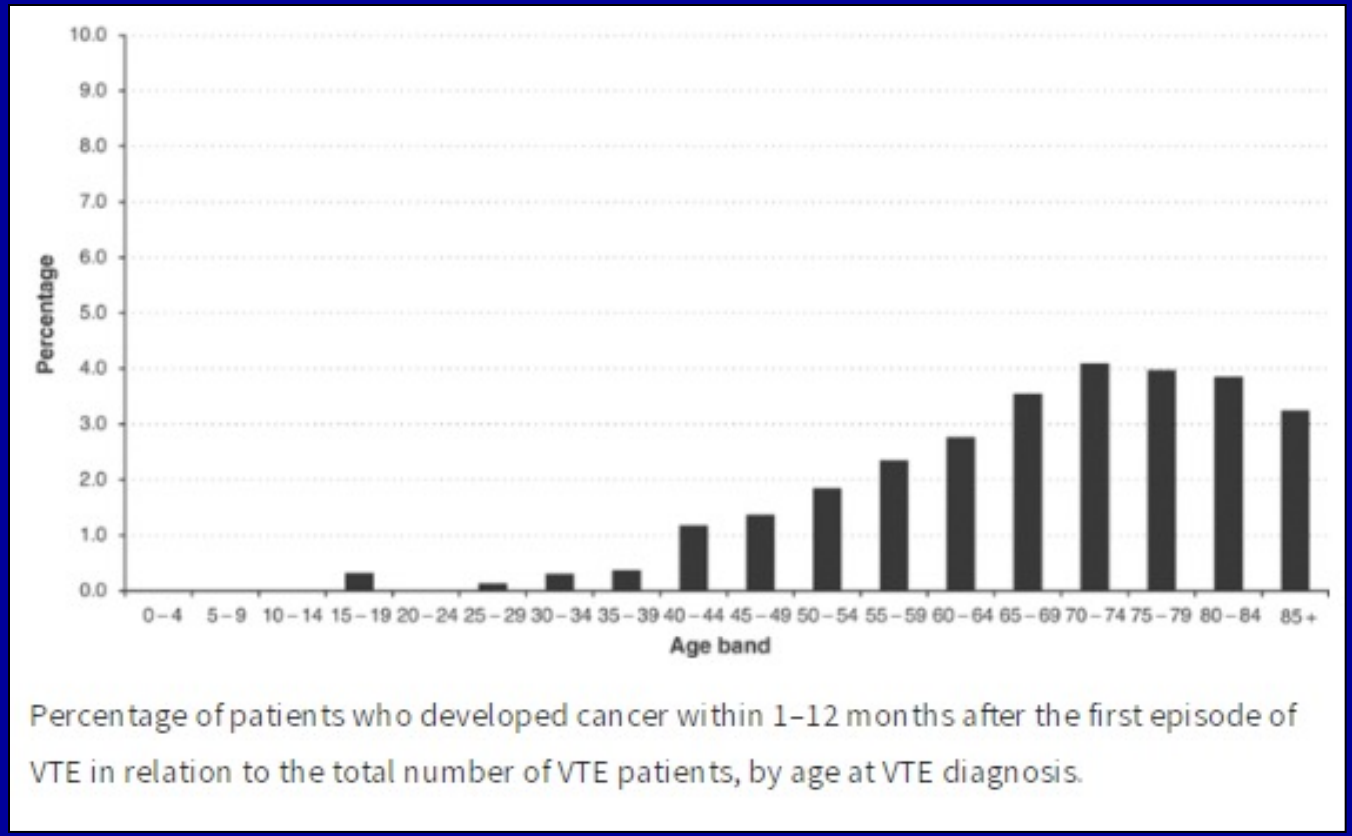
Malignancy assoc with thrombosis



Finding Cancer After DVT/PE



Percentage of patients who developed cancer within 1–12 months after the first episode of VTE in relation to the total number of VTE patients, by age at VTE diagnosis.

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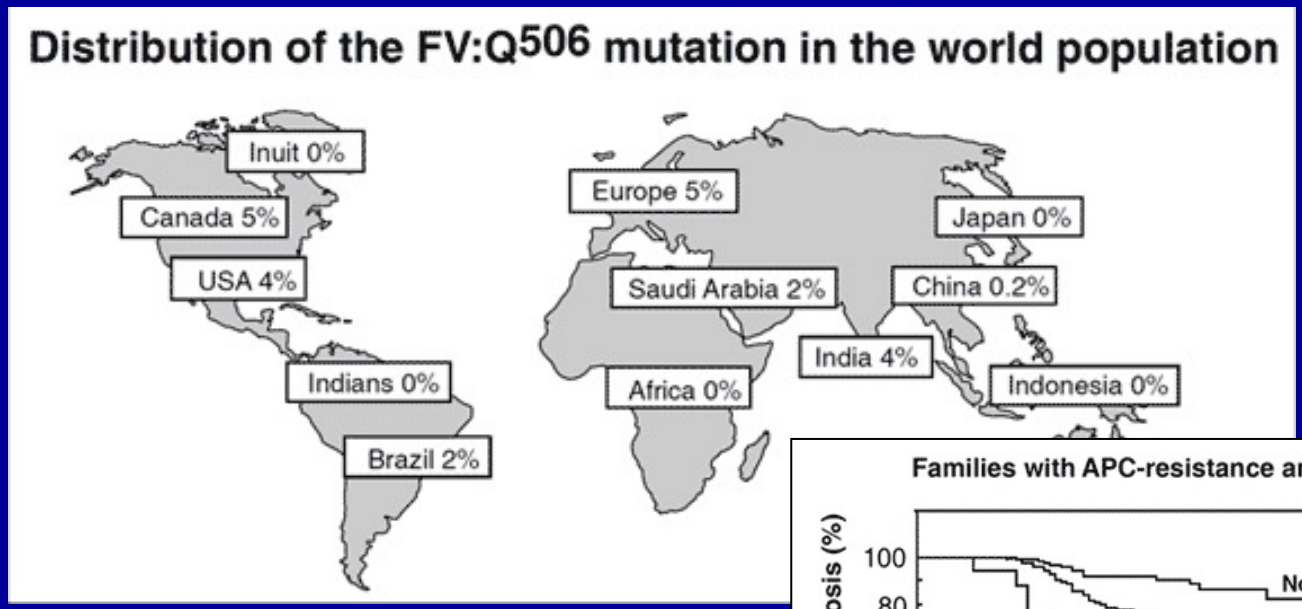
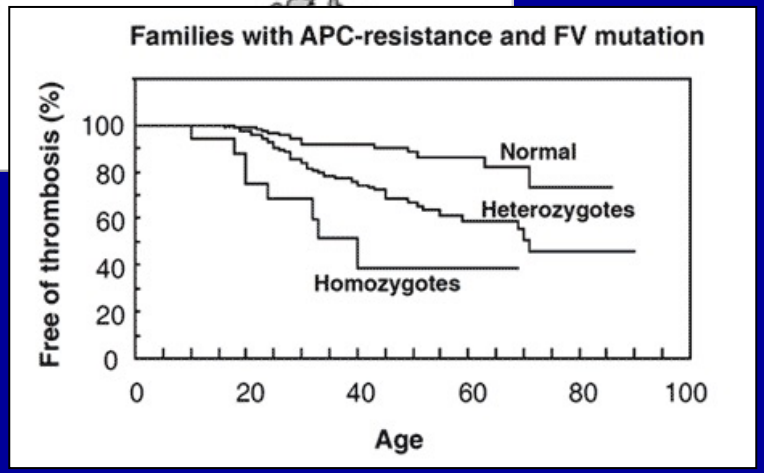
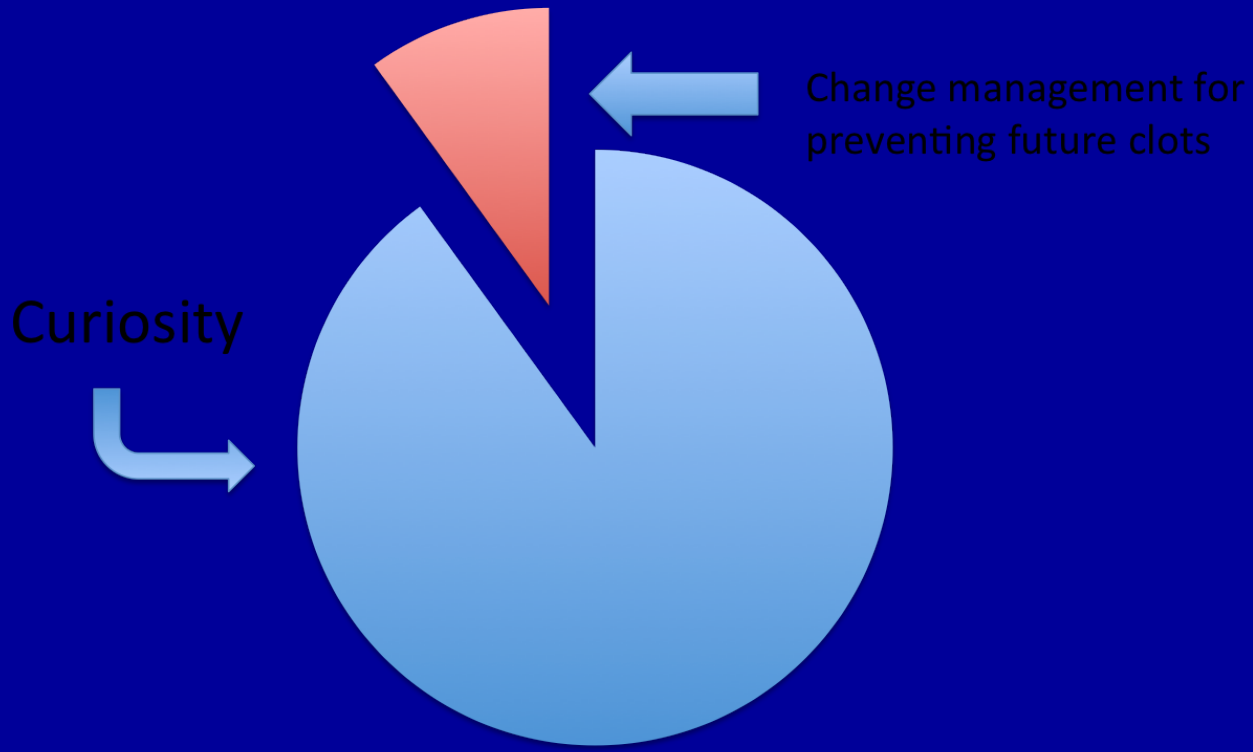
Factor V Leiden Mutation





Clot Mutation Testing



Clot Mutation Testing

PROS

- May identify one of the reasons for clotting.
- Resolve anxiety about why.
- Identify/counsel family members.
- Maybe change management.

CONS

- Infrequent to find patient whose management changes.
- Cause anxiety about future.
- Maybe overaggressive

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CONS

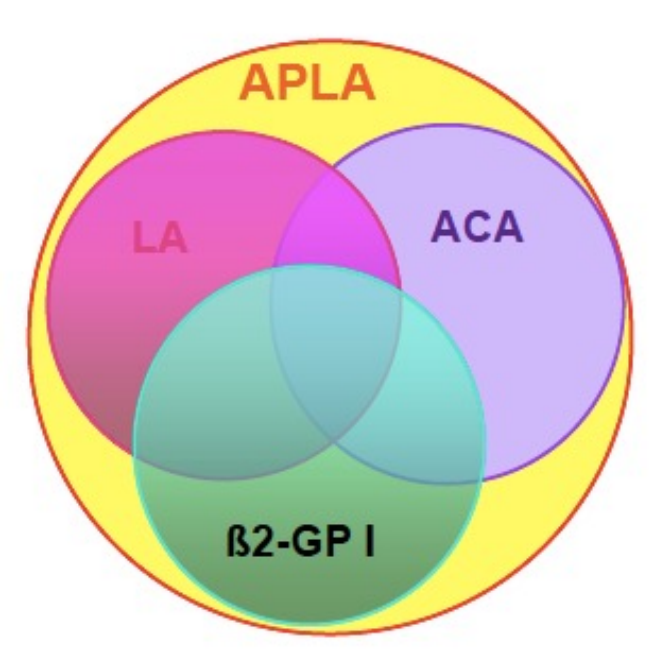
- Infrequent to find patient whose management changes.
- Cause anxiety about future.
- Maybe overaggressive management for patient and family.
- No evidence of benefit for family (primary prev).

My Recommendations for Clot Mutation Testing

- Factor V Leiden and Prothrombin Mutations
  - Test Hispanic & European descent <60-year-old.
  - Test those with family history of clotting.
  - Test those who have repeat clotting events.
  - African Americans need sickle testing, not FVL/PT mutation
  - This testing can be done any time-can be outpatient, but sometimes

    it makes sense to do inpatient testing

Lupus Anticoagulant Testing



Autoimmune Clotting Tendency
Arterial or Venous
Risk of Stroke or recurrent DVT/PE
Risk of Miscarriage

Antibody tests (ELISA)
- Cardiolipin Antibody
- B2-GP1 Antibody

Functional tests
- Lupus Anticoagulant
- Anti-phospholipid Ab

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My Recommendations for Investigating the Cause of Clots

- Factor V Leiden & Prothrombin Mutations
  - Test Hispanic & European descent <60 years old.
  - Test those with family history of clotting.
  - Test those who have repeat clotting events.
- Hemoglobin Electrophoresis
  - Test all African American clotters for sickle trait.
- Look for Cancer Based on Age and Symptoms
- Look for HIT for Those With Recent Heparin
- Explain to patients that they have a clotting tendency, cause unknown

What I’m going to tell you

- Who is a clotter and who is a bleeder?
- Preventing DVT/PE in hospitalized patients.
- What caused my patient’s DVT/PE?
- How to treat my patient with DVT/PE.
- How to prevent another episode of DVT/PE.

How to Treat my Patient With DVT/PE

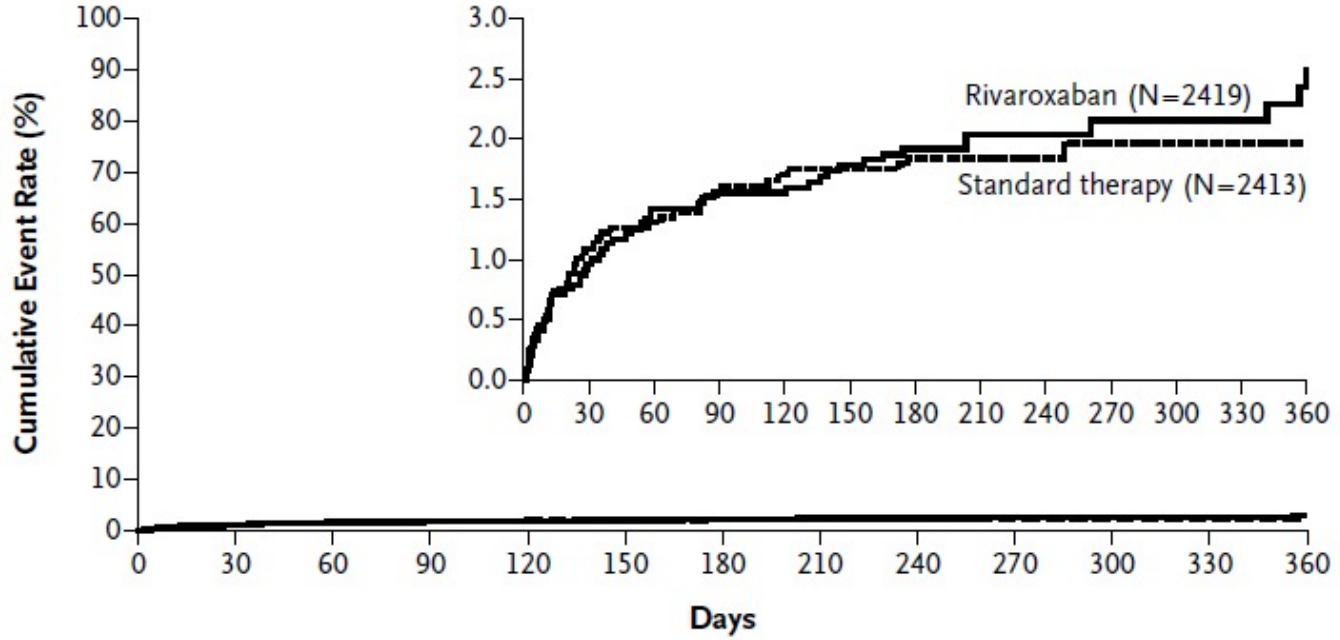
- Which anticoagulant to prescribe
- Need for thrombolysis for DVT or PE?
- Discharge from ER or admit to hospital?
- Stay in bed or walk?
- Leg stockings/TED hose/ACE wraps?
- Need for telemetry?
- Need for IVC filter placement?
- Distal DVT.
- Superficial venous thrombosis.
- When to discharge DVT/PE patients from hospital.

“Initiation” parenteral

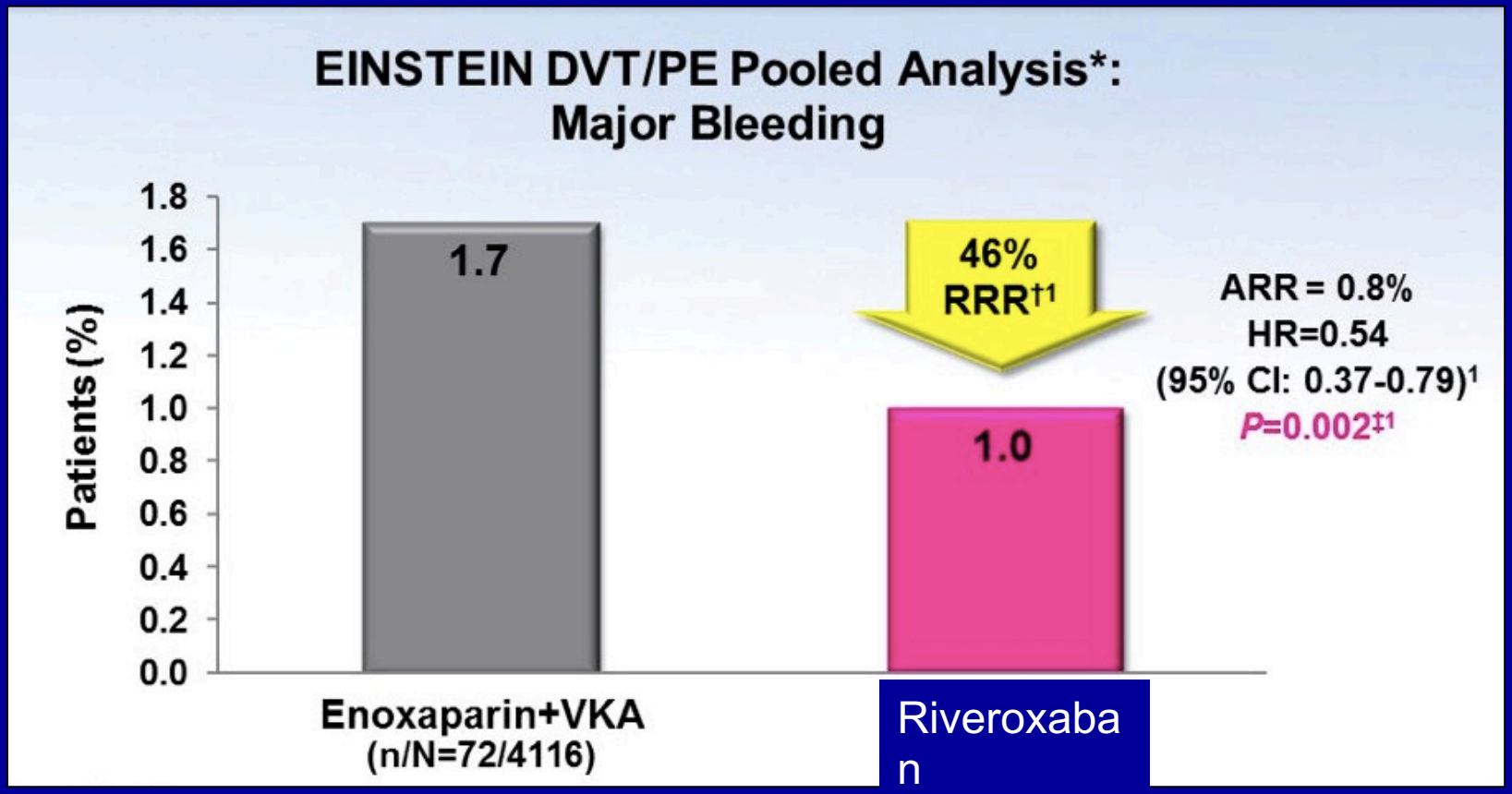
Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The NEW ENGLAND JOURNAL of MEDICINE
APRIL 5, 2012

Primary Efficacy



No. at Risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Standard therapy	2413	2316	2295	2273	2155	2146	2050	835	787	772	746	722	675


EINSTEIN DVT/PE Pooled Analysis*:
Major Bleeding
Patients (%)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.7
1.0
46%
RRR†1
ARR = 0.8%
HR=0.54
(95% CI: 0.37-0.79)1
P=0.002‡1
Enoxaparin+VKA
(n/N=72/4116)
Riveroxaban

Oral NOAC initiation

- Rivaroxaban 15mg po bid x 21 days,
  followed by 20mg po daily OR
- Apixaban 10mg po bid x 7 days,
  followed by 5mg po bid

- If Enoxaparin or Fondaparinux is used >3 days, then consider custom dosing plan for NOAC.

How to Treat my Patient With DVT/PE

- Which anticoagulant to prescribe
- Need for thrombolysis for DVT or PE?
- Discharge from ER or admit to hospital?
- Stay in bed or walk?
- Leg stockings/TED hose/ACE wraps?
- Need for telemetry?
- Need for IVC filter placement?
- Distal DVT.
- Superficial venous thrombosis.
- When to discharge DVT/PE patients from hospital.

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My Recommendations for Treating Patients With DVT/PE

- Initiation: Enoxaparin preferred over IV heparin.
- Consider daily Enox for age>75 or abn creat.
- Consider Fondaparinux for weight>120kg.
- IV heparin only for CKD/ESRD patients.
- Argatroban or Fondaparinux if HIT is suspected.
- Transition to “oral NOAC initiation” when patient is ready for discharge.
- If no improvement after 2-3 days, consider lysis.

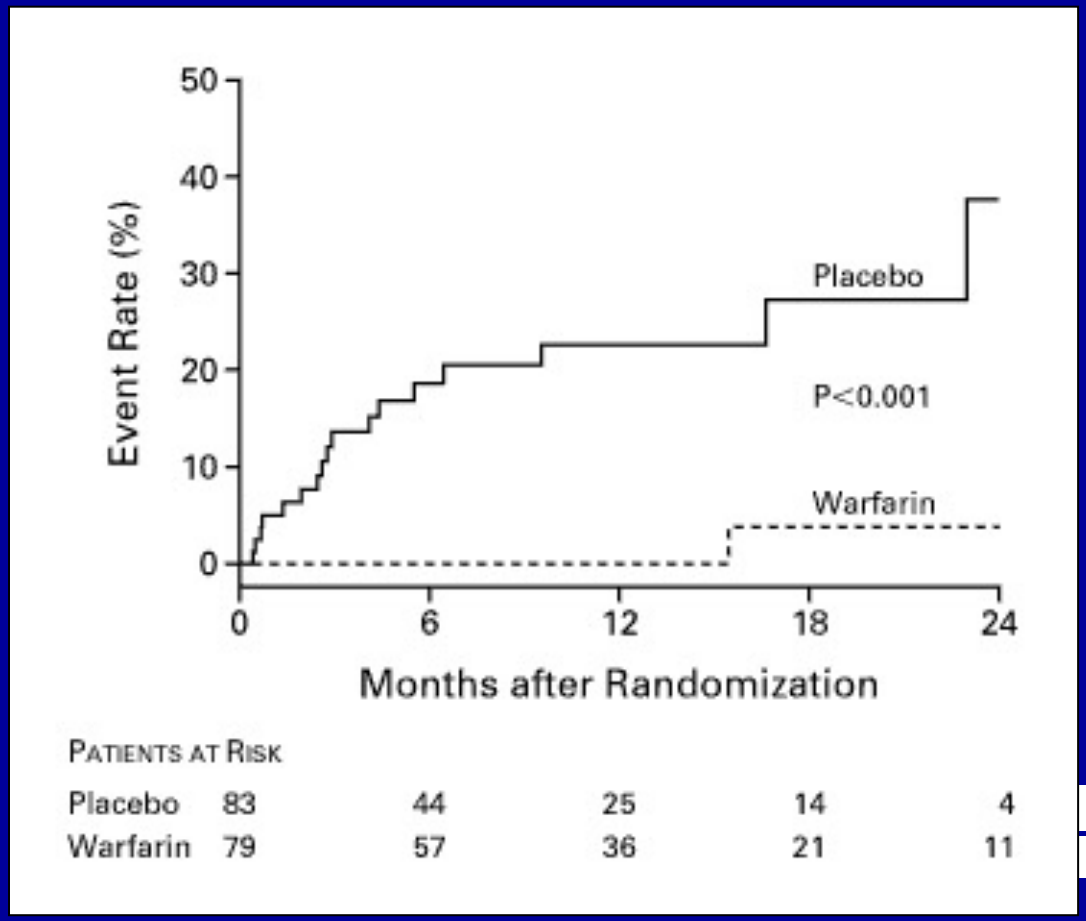
What I’m Going to Tell You

- Who is a clotter and who is a bleeder?
- Preventing DVT/PE in hospitalized patients.
- What caused my patient’s DVT/PE?
- How to treat my patient with DVT/PE.
- How to prevent another episode of DVT/PE.

How to Prevent Another Episode of DVT/PE

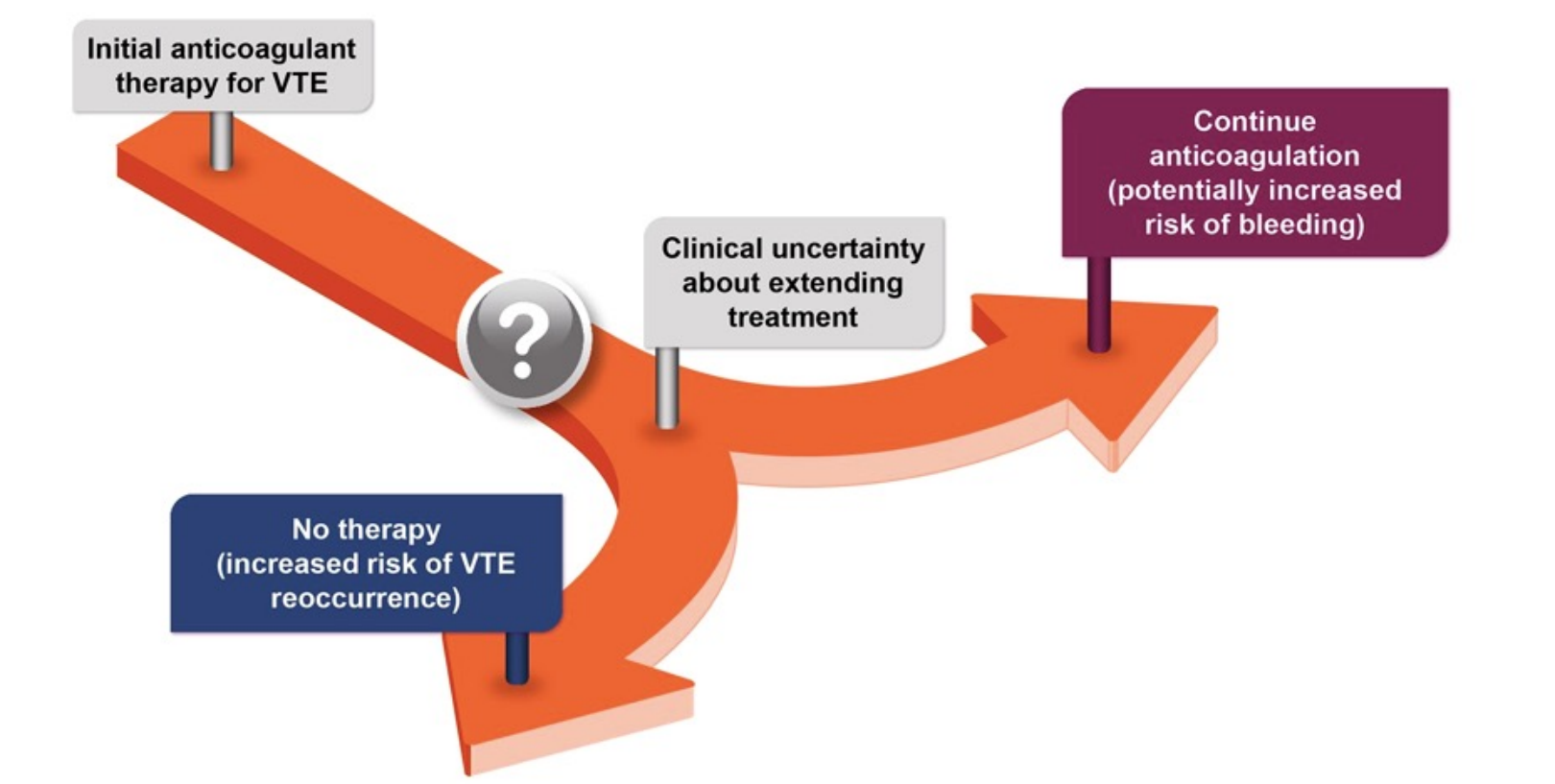
- Transition to maintenance NOAC or aspirin.
- Follow-up appointment to discuss duration of treatment.
- Planning surgical procedures for clotters.
- Pregnant clotters and planning future pregnancy.
- Is it OK for clotters to resume OCP?
- Long flights or long drives for clotters.

Warfarin for Secondary DVT Prevention

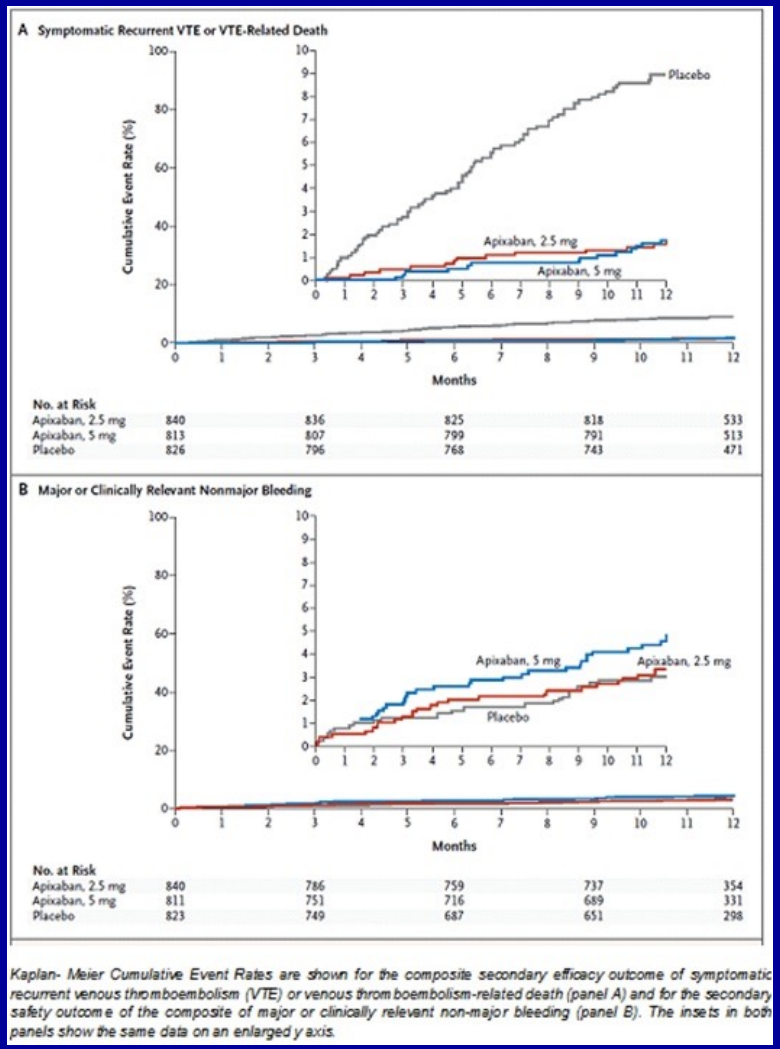


The New England Journal of Medicine
MARCH 25, 1999

Deciding Benefit/Risk for Maintenance Anticoag



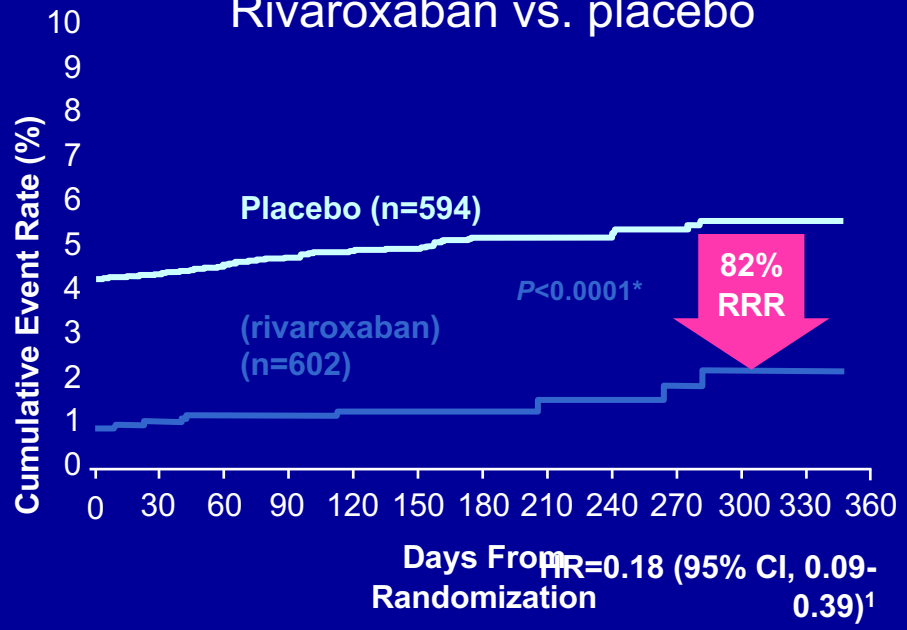
Apixaban for DVT/PE Maintenance



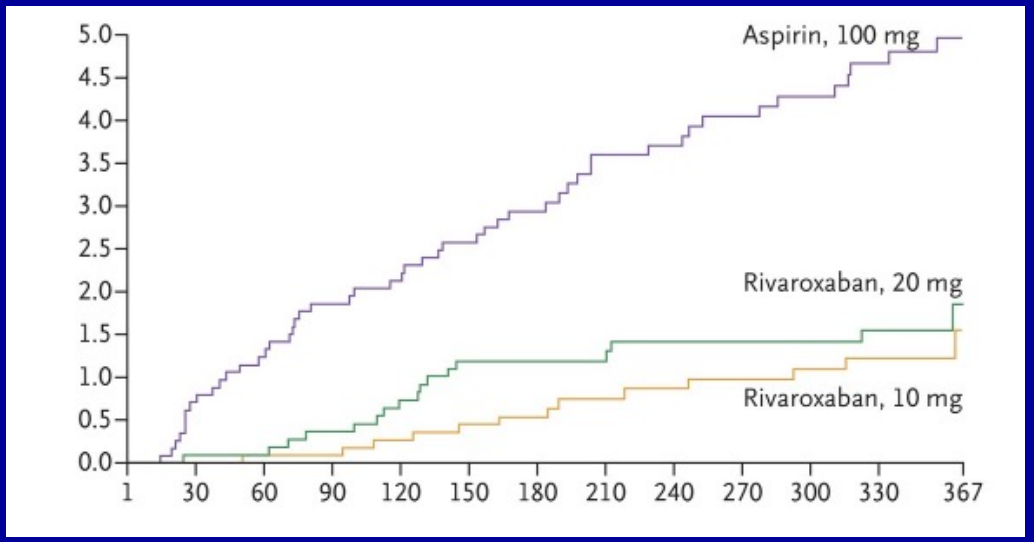
Kaplan- Meier Cumulative Event Rates are shown for the composite secondary efficacy outcome of symptomatic recurrent venous thromboembolism (VTE) or venous thromboembolism-related death (panel A) and for the secondary safety outcome of the composite of major or clinically relevant non-major bleeding (panel B). The insets in both panels show the same data on an enlarged y axis.

Rivaroxaban for DVT/PE Maintenance

Rivaroxaban vs. placebo



Rivaroxaban vs. aspirin



How to Choose Which NOAC to Prescribe to Clotters

- Risk/benefit assessment: age, prior bleeding.
- Apixaban for CKD/ESRD patients.
- Low dose Apixaban for “bleedy” patients.
- Rivaroxaban for those who prefer daily dosing.
- Warfarin causes more major bleeding than NOAC.

How to Prevent Another Episode of DVT/PE

- Transition to maintenance NOAC or aspirin.
- Follow-up appt to discuss duration of treatment.
- Planning surgical procedures for clotters
- Pregnant clotters and planning future pregnancy.
- Is it OK for clotters to resume OCP?
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Maintenance Anticoagulants

How Long To Treat DVT?

Indication	8th ACCP Guideline
First episode of VTE secondary to a transient risk factor	3 months
First episode of idiopathic (unprovoked) VTE	At 3 months, if favorable Risk:Benefit ratio, consider long-term treatment.
Other (recurrent, active cancer, etc.)	Long term.

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My Recommendations for DVT/PE Maintenance

- Weigh benefit vs. risk for low dose anticoagulants.
- Involve the patient's goals, activities, and willingness to risk recurrent clotting vs. bleeding.
- Plan "one year at a time" instead of trying to commit the patient to "lifetime" treatment.
- Remember that, in general, more anticoagulation is better than less because clotting causes more morbidity and mortality.

What I Have Discussed

- Clotting (stroke/DVT/PE) is common.
- Clotting is associated with early mortality.
- Age is the most important predictor of clotting tendency.
- Clot mutation testing may be worthwhile for some patients.
- Consider HIT testing after recent heparin exposure.
- NOAC medications are standard treatments for DVT/PE.
- Long term maintenance NOAC may be appropriate.