# Venous Thromboembolic Disease

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**@bloodman**

GENERAL HEMATOLOGY
OHSU

# DISCLOSURE



**Relevant Financial Relationship(s)**

**Speaker Bureau - None**

**Consultant/Research – none**

**Author - UpToDate (Iron)**

# Goals!

- Diagnosis of venous thromboembolic disease
- Immediate non-anticoagulation theray
- Anticoagulation options

# Venous Thromboembolic Disease

- 3rd cause of cardiovascular death after MI and strokes
- Incidence of PE is ~ 1:1000

# Why We Diagnose VTE

- To find patients who will benefit from anticoagulation to prevent *future* thrombosis

# Sequential Approach

- Much work done over past 15 years to find ways to avoid imagining everyone
  - Prediction rules
  - D-dimers

# Prediction Rules

- Quantitating gestalt
- Several rules very well studied
- Well's Rule performs the best (DVT)
  - Very reproducible
  - Easiest to do
  - Several variations

# DVT

- Well criteria
  - Validated prediction rule
- If unlikely probability
  - Obtain D-dimer
- If DD high then imaginee

# Pre-test Probability - DVT

**Clinical characteristics (Well's criteria):**

| | |
|---|---|
| • Active cancer | 1 |
| • Paralysis or plaster immobilization | 1 |
| • Bedridden ≥ 3 d; major surgery in 3 mo | 1 |
| • Entire leg swollen | 1 |
| • Calf swelling > 3cm | 1 |
| • Pitting edema in affected leg | 1 |
| • Collateral non-varicose superficial veins | 1 |
| • Localized tenderness along deep veins | 1 |
| • Previous DVT | 1 |
| • Alternative dx more likely | -2 |

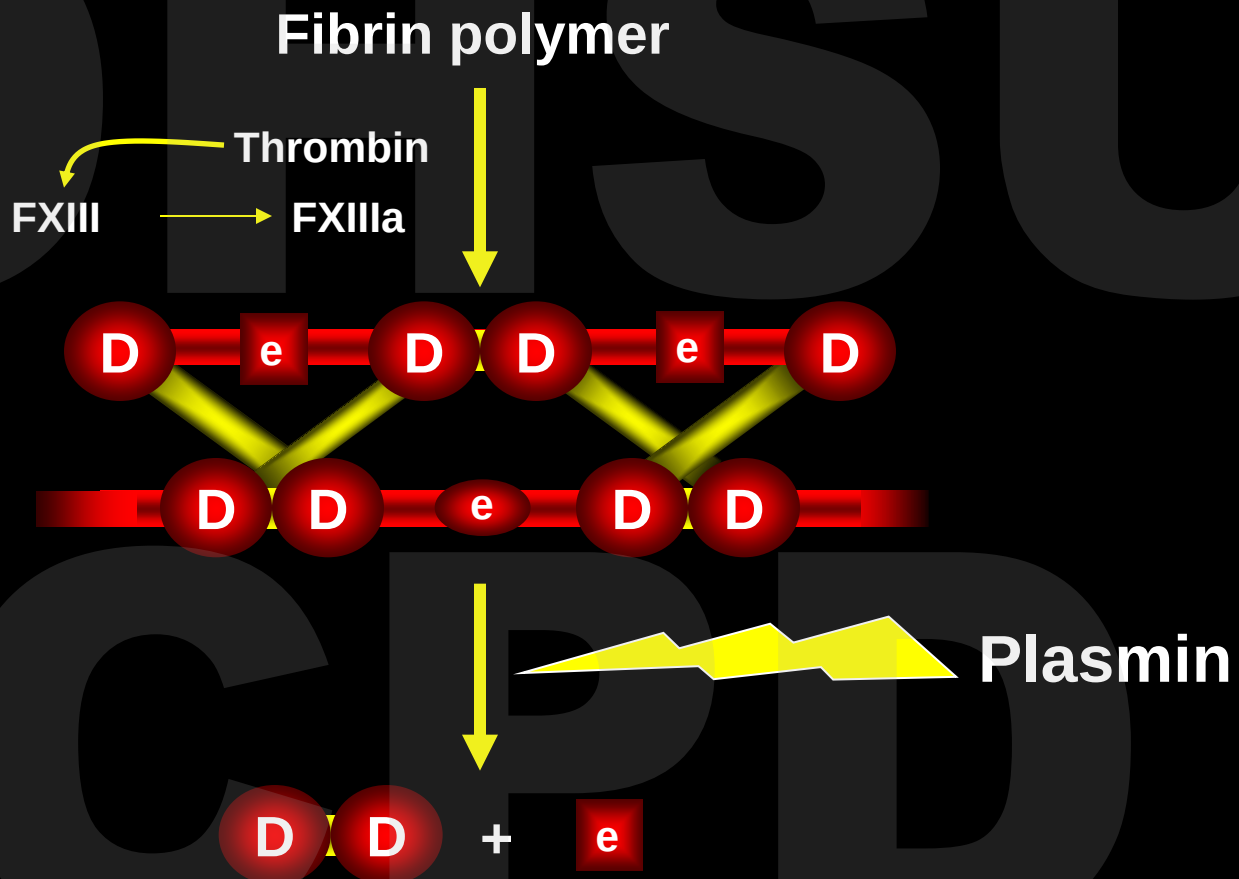
- score < 2: DVT unlikely
- score ≥ 2: DVT likely

[Wells PS. NEJM 2003;349:1227-35]

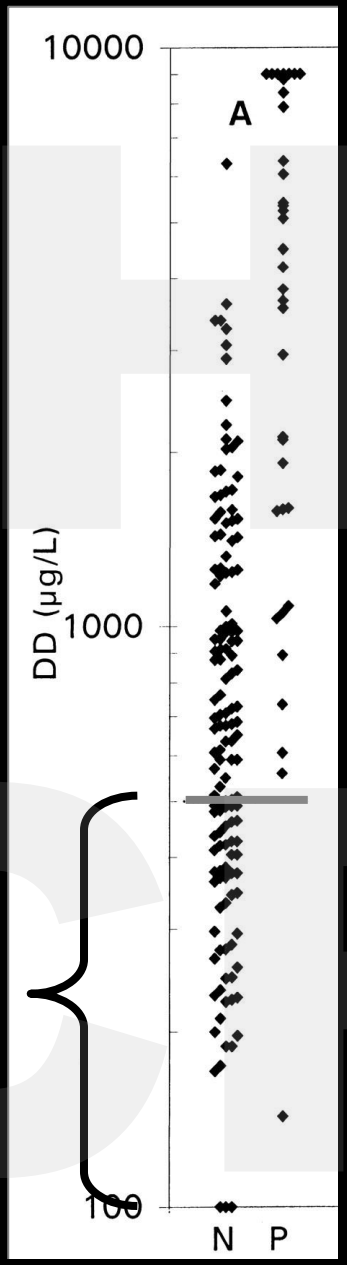
# D Dimer

- Breakdown product of fibrin clot
- Higher levels marker of acute thrombosis
- Sensitive but NOT specific!!

# D-Dimer Formation




DIAGNOSTICA STAGO

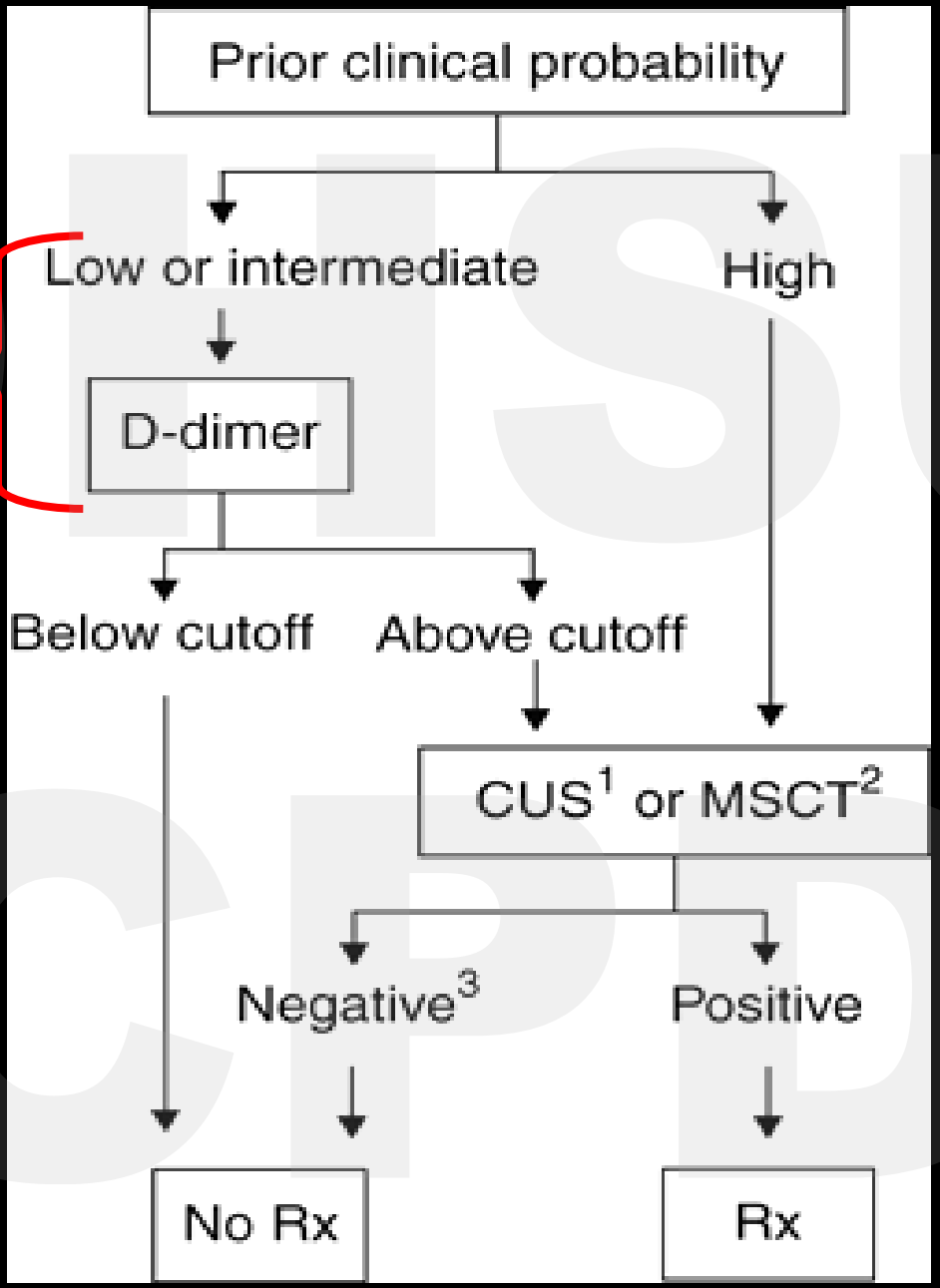



Need to work-up for thrombosis

No need to work-up for thrombosis

Clinical Chemistry 57:1256-1262, 2011

**> 50-80% of patients will be in this pathway**



# Making the D-Dimer Better

- Changing cutoffs
  - Elderly
    - Cut-off = age x 10 (650 for me)
  - > 1000 for low probability patients
- Decreased need for imaging in 20-30% more patients

# High D-Dimer No Clot

- No further work-up needed
- Can be elevated by:
  - Age
  - Pregnancy
  - Exercise
  - Normal people

# Bottom Line

- Use of prediction rules can triage patients for D-dimers
- Can decrease the number of patients undergoing imaging

# PE's

- Only 5-10% of CTA show thrombosis
- Protocol can reduce number of CTA by up to 30-40%
- First step if low suspicion use PERC rule

# PERC Criteria (PE)

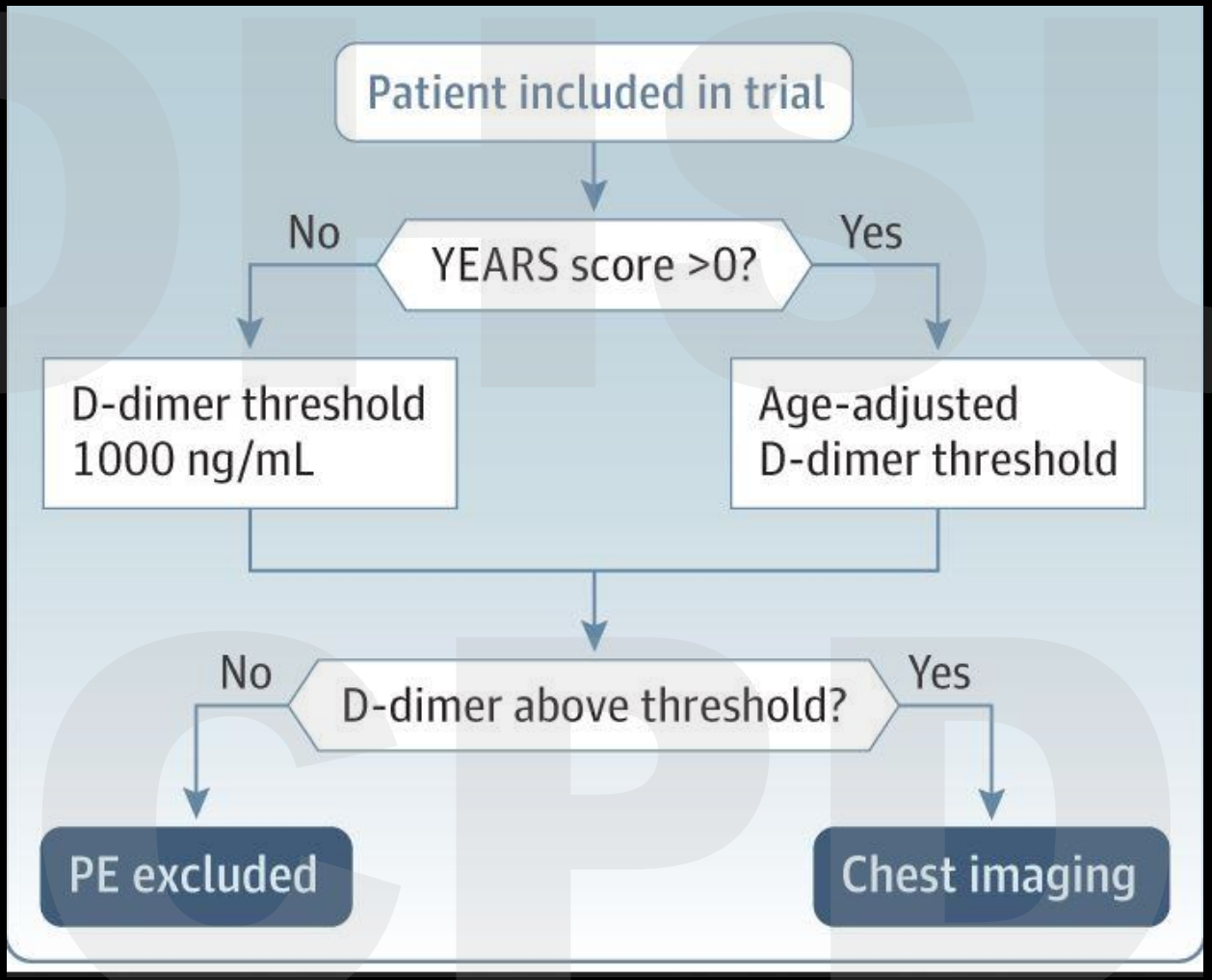
**If the patient has all 8 of these criteria:**

1. **< 50 years of age**
2. **Pulse < 100,**
3. **Pulse oximetry > 94%,**
4. **No unilateral leg swelling,**
5. **No hemoptysis**
6. **No recent surgery**
7. **No oral hormone use.**
8. **No history of DVT or PE**

***Cerebus paribus* their chance of PE is < 1%**

# Prediction Rules

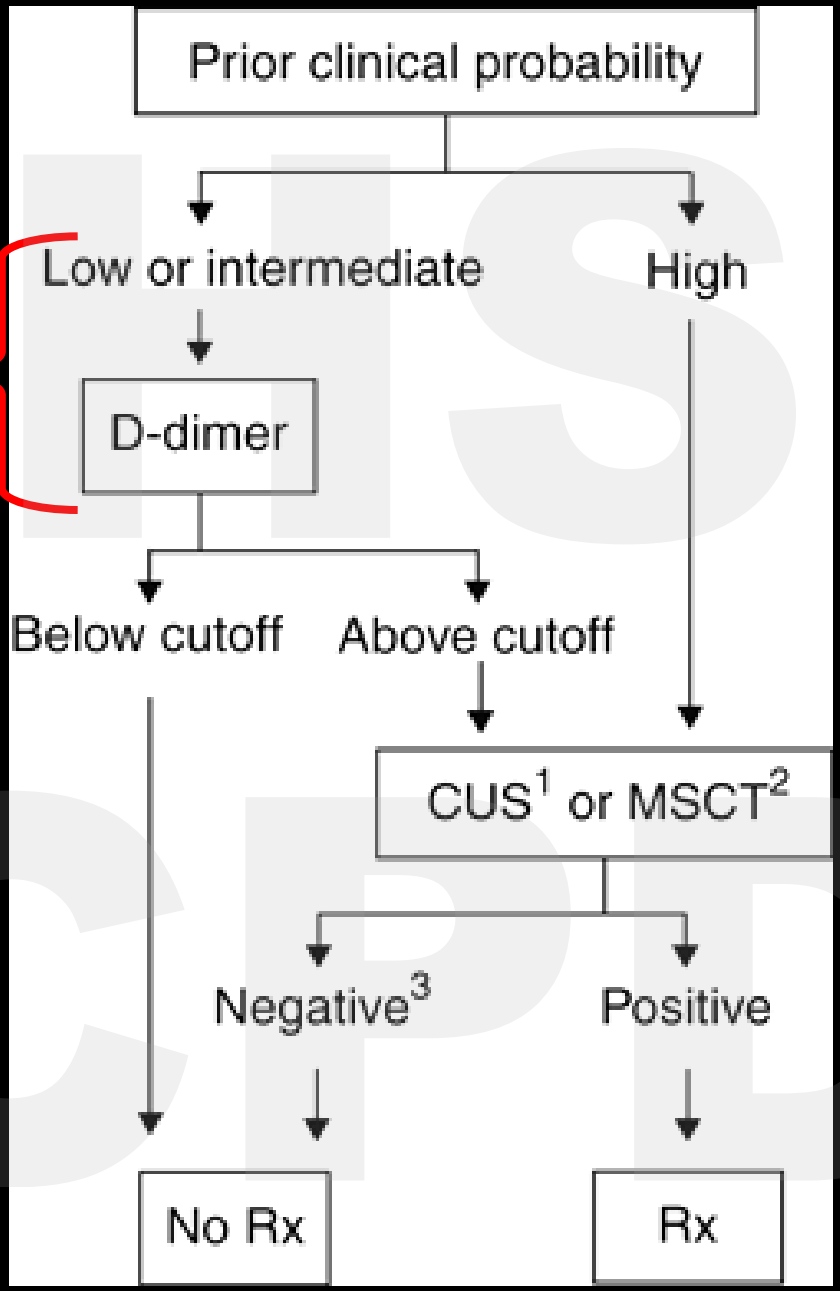
- YEARS criteria most frequently used
  - If 1 or more present then more rigorous D-dimer cut-off
    1. Clinical DVT
    2. Hemoptysis
    3. PE most likely


Patient included in trial
No
YEARS score >0?
Yes
D-dimer threshold
1000 ng/mL
Age-adjusted
D-dimer threshold
No
D-dimer above threshold?
Yes
PE excluded
Chest imaging

# PE: Diagnosis

- Many patients receiving inappropriate CT scans putting them at risk of cancer and renal disease
- Sequential approach
  - PERC
  - Pretest Probability
  - D-dimer
  - CTA

**> 90% of patients will be in this pathway**



# All Venous Thromboembolism Should Be Treated

# Subsegmental PE

- Increasingly found with CT scans
  - 5-15% of all PE
- Controversial
  - Retrospective data suggest benign
  - Prospective studies same natural history as more proximal PE

# Subsegmental PE

- Prospective management trial of not treating low risk SSPE is not safe
- Current data suggests same natural history of more proximal PE and needs to be treated as such
- RCT underway

# Calf Vein Thrombosis

- High risk of progression
  - Up to 10% progression
  - PE rate 2-3%
- Treatment reduced recurrence by 50-60%
- 12 weeks therapy for most patients

# Acute Treatment of DVT/PE

- Bed rest
- Inferior Vena Cava Filter
- Thrombolytic Therapy
- Home therapy
- Post-thrombotic syndrome

# Is Bedrest Useful in DVT Patients?

- At eight trials (N= 5700) compared bedrest with activity
- No trial showed a difference in PE or thrombosis
- One study showed decreased pain and swelling with activity
- Management
  - Activity: as tolerated
  - Trial of elastic stockings knee-high 30-40 mmHg

# Exercise: Key Therapy

- Less post-thrombotic syndrome in more active patients
- Less bleeding in anticoagulated patients
- Encourage activity!

# Inferior Vena Cava Filters

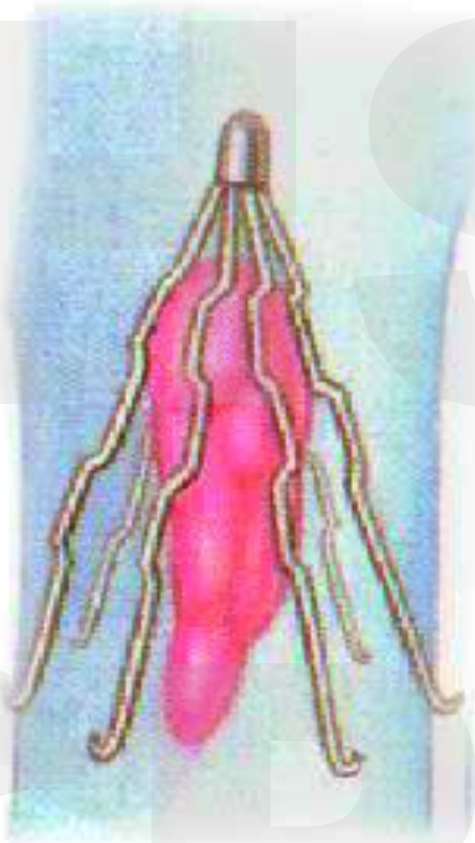
- Overused and under studied!

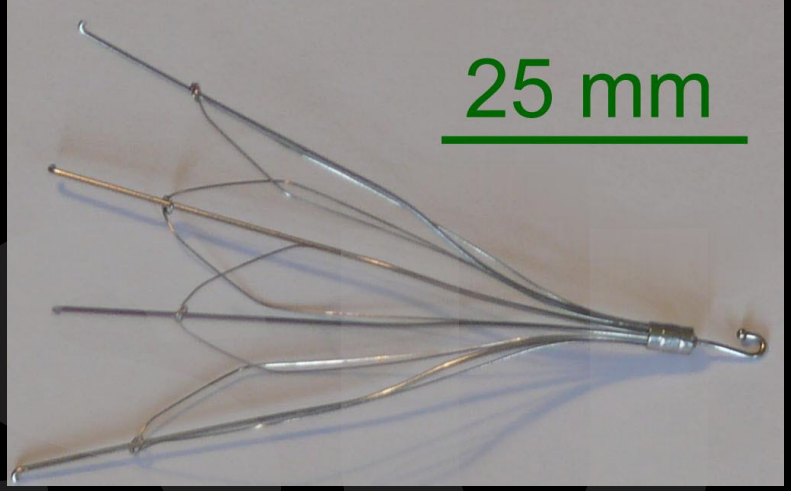
# Filters

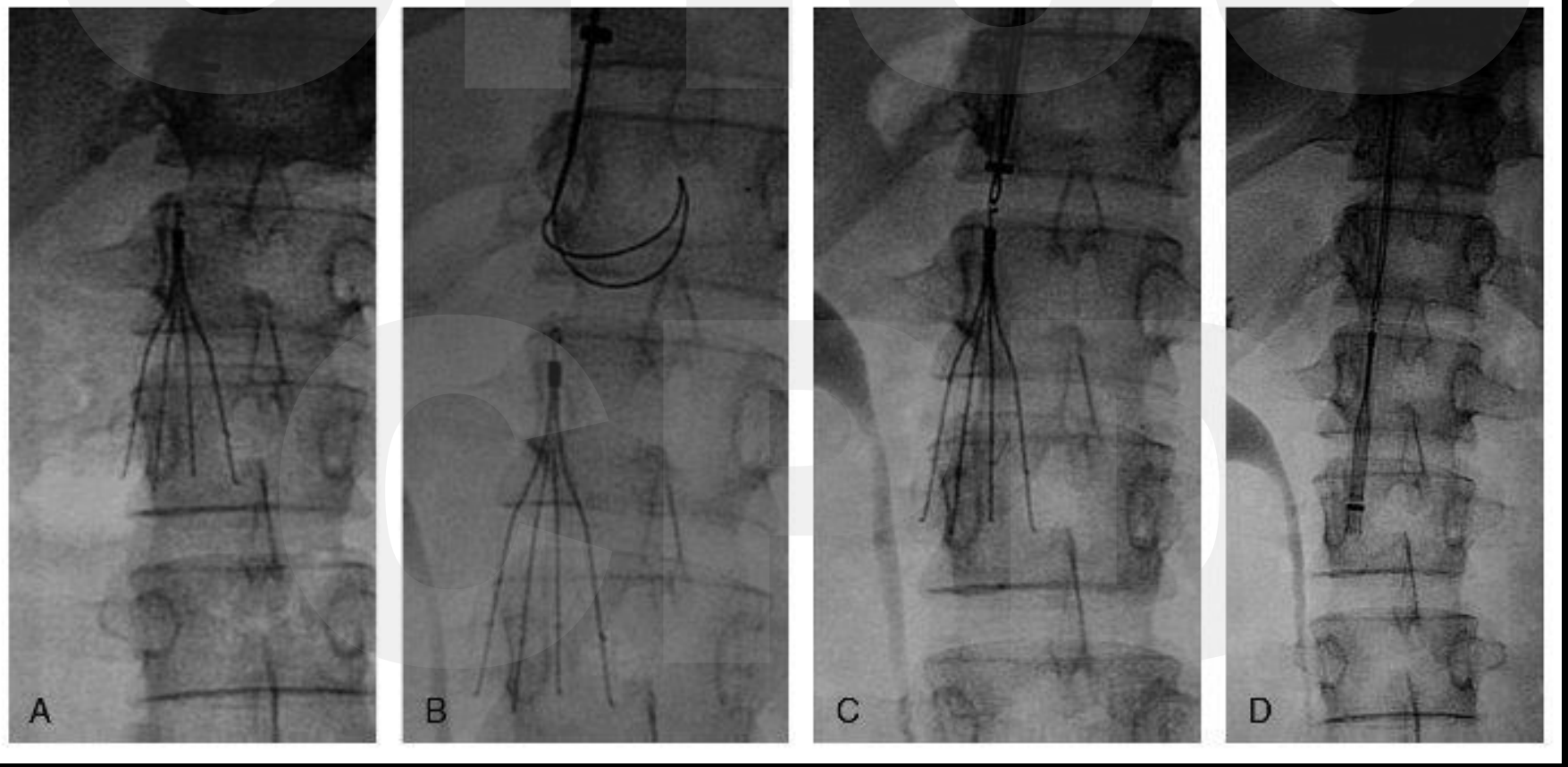
- Only 3 RCT
- No influence on mortality in anticoagulated patients
  - Only one study showed reduction in PE
- ~1-2% fatal PE rate in IVC filters patients in ICU studies
- Raises risk of future DVT with long term use (~2x)

# IVC Filters

- Cohort study of patients unable to be anticoagulated
- Adjusted for “Immortal time bias”
- HR death = 1.18 (1.13-1.22)
- Need RCT
- JAMA Open 2018 018;1(3):e180452.






Arch Bronconeumol. 2011;47:17-24

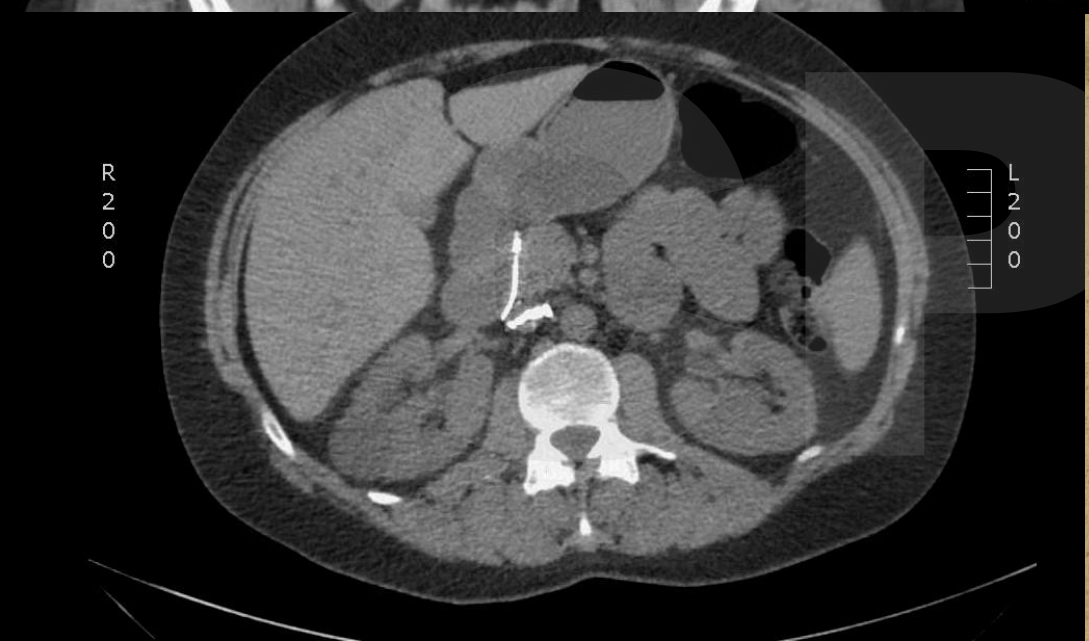
# Retrievable Filters: Panacea or Pandemic?

- Rapid acceptance of retrievable filters
- Caveats
  - 10-20% cannot be removed
  - > 50% aren't removed
  - Limited clinical studies
  - Limited long term follow-up

# Retrievable Filters

- Need system in place to retrieve
- Reports of retrieval many years out
- Can retrieve while anticoagulated
- Strut factures from non-removed filters increasing issue


P
3
2
5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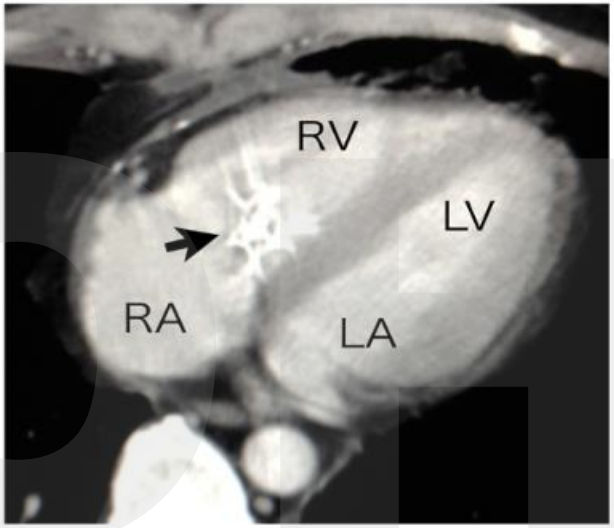
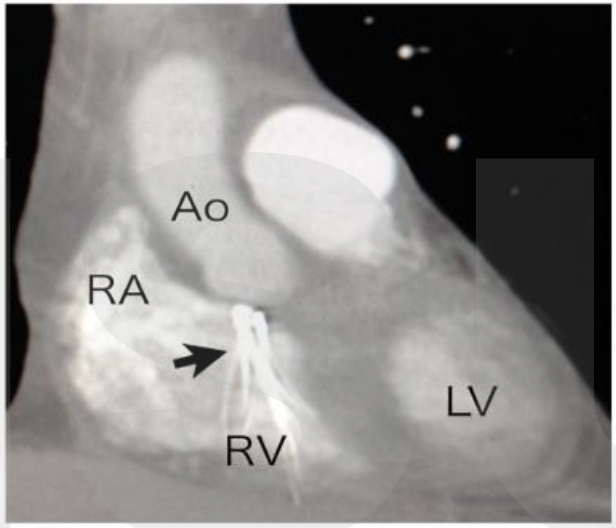
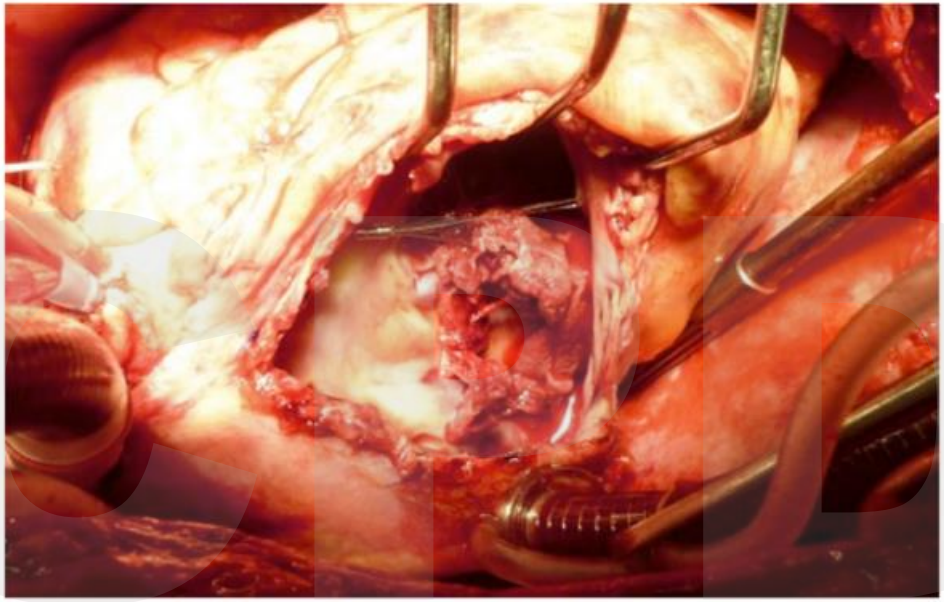



A B

A



Ryomoto et al., J Vasc Med Surg 2013, 1:4

# IVC Filters

- Still should be used with caution
- Indications
  - Large DVT and temporary contraindication to anticoagulation
  - **NOT** indicated for PE prophylaxis
- Patients must be warned that "retrievable" filter may be permanent
- Will RAISE the risk of DVT!
- Need to anticoagulate as soon as feasible

# 2019 Trauma Trial

- N = 240 trauma patients with contraindication to anticoagulation
- No difference in PE in filter vs no filter group

- N Engl J Med 2019; 381:328-337


CT ABDOME


CT ABDOM

# Reasons NOT to Put in a Filter

- Pulmonary embolism:
  - 1st week of anticoagulation
  - Despite warfarin
- Deep venous thrombosis:
  - With free floating thrombus
  - Extension of DVT
  - Despite warfarin
  - In cancer patients

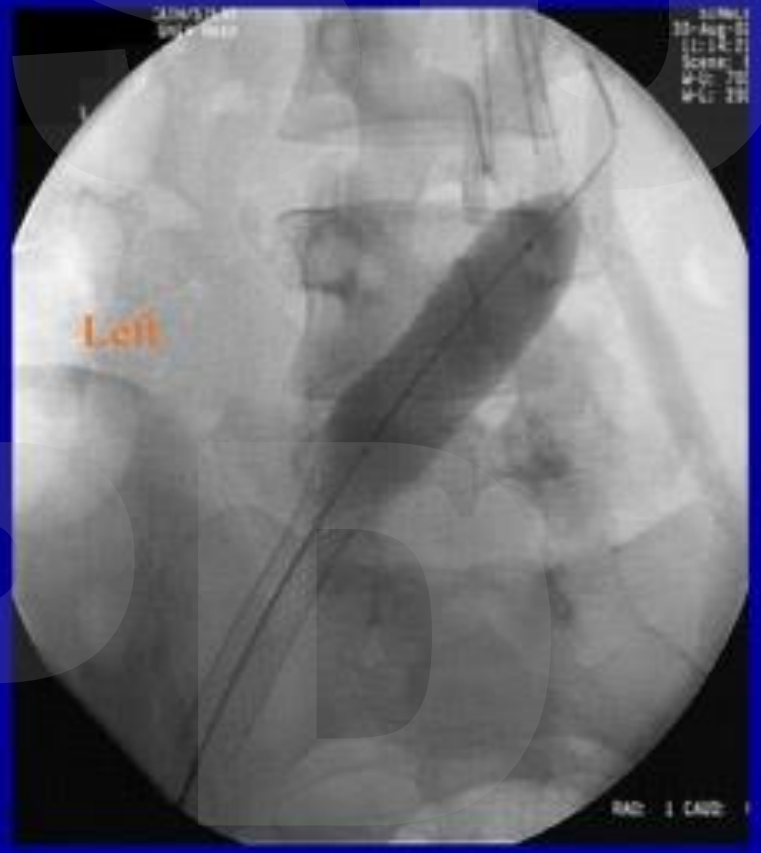
Curr Opin Hem 2009 Sep;16(5):402-6

# IVC Filters: Just Say No!

# Thrombolytic Therapy: DVT

- Catheter directed
  - Promising early trials
- Dramatic increase in use
  - Femoral or Iliac DVT
  - Venoplasty/stenting

# Stent deployment and balloon dilatation

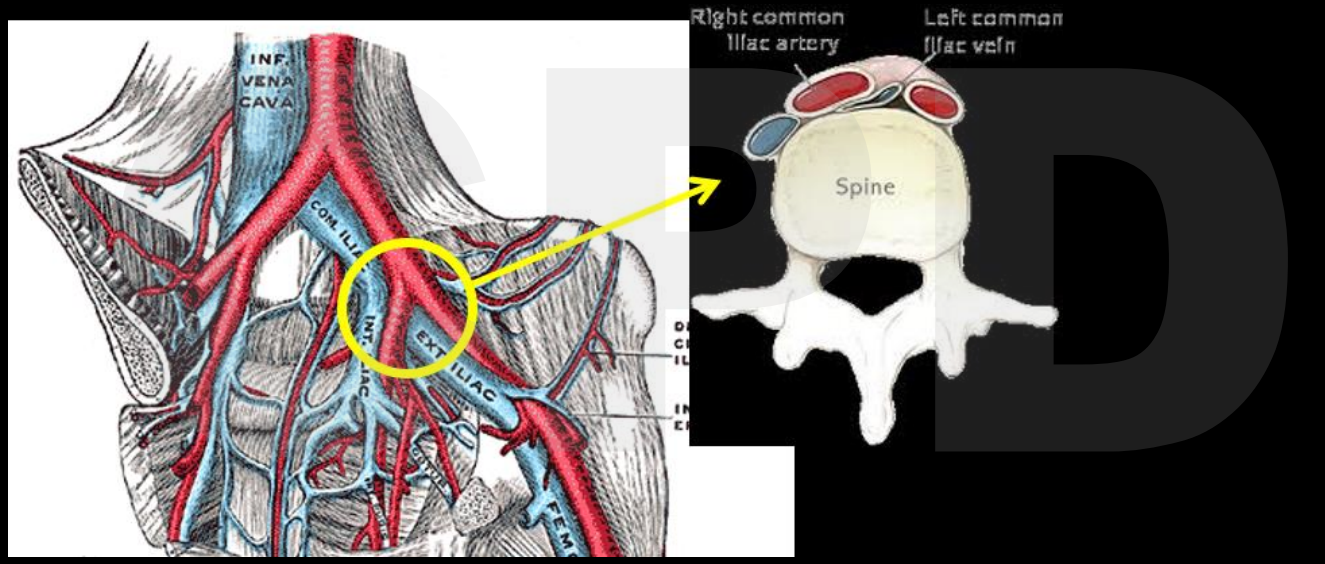



# ATTRACT Trial

- RCT of CDT vs anticoagulation in proximal DVT
- N = 692
- NO difference in post-thrombotic syndrome or quality of life
- NEJM 377:2240, 2017

# Catheter Directed Thrombolytic Therapy

- Current indications
  - Phlegmasia cerulea dolens
  - Disabling venous claudication
  - Severe May-Thurner syndrome



# Thrombolytic Therapy: PE

**There is no clinical utility in thrombolytic therapy for the vast majority of patients with pulmonary embolism**

# PEITHO

- Large 1000 patient RCT of heparin vs thrombolytic for “high-risk” patients
  - + Troponin
  - + R heart strain
  - Normal BP
- N Engl J Med 2014; 370:1402-1411

| PE-related early MORTALITY RISK | | RISK MARKERS | | | Potential treatment implications |
|---|---|---|---|---|---|
| | | CLINICAL (Shock or hypotension) | RV Dysfunction | Myocardial injury | |
| HIGH > 15% | | + | (+)* | (+)* | Thrombolysis or Embolectomy |
| NON HIGH | Intermediate 3 - 15% | − | + | + | Thrombolysis? |
| | | | + | − | Hospital Admission |
| | | | − | + | |
| | Low <1% | − | − | − | Early discharge or home treatment |

# Results

| | Lytics (506) | Placebo(499) |
|---|---|---|
| Death or “collapse” | 13 (2.6%) | 28 (5.6%) |
| Death | 6 (1.2%) | 9 (1.8%) |
| Major Bleeding | 32 (6.3%) | 6 (1.5%) |
| ICH | 12 (2.4%) | 1(0.2%) |

**Long term: NO benefit in symptoms, RV dysfunction or development of pulmonary hypertension**

JACC: 2017 Mar 28;69(12):1536-1544

# JTH Meta-Analysis

- Look at trials specifically for submassive PE
- No benefit for lysis
- 1.7% ICH vs 0.1%

# Thrombolytic Therapy: PE

- Large RCT shows **no** benefit in PE
- Use should be restricted to patient with refractory hypotension
  - Two studies show **doubling** risk of death with thrombolytic therapy when used in normotensive patients
- Screen carefully for bleeding risks

# Lytics for PE: Does it Even Make Sense?

- Two modes of death with PE
  - Sudden death
  - Die of underlying disease
    - High mortality over the next weeks/months but cancer, CHF etc..

# PE: Catheters

- Increased use of catheter based thrombolytic therapy for PE
- Only 1 small RCT
- No long term data
- Severe bleeding 1-6%
- Ongoings RCT

# Thrombolytics: PE

- Hypotensive shock
  - Fluids
  - Systemic or catheter directed lytics
- No shock but big clot
  - LMWH and observation
- All others
  - DOAC/LMWH

# PERT Consortium Handbook of PE 2024

| | Mortality | Acute recurrent VTE | Late recurrent VTE | Complications |
|---|---|---|---|---|
| Lensing et al. (1995) | Favors LMWH | | Favors LMWH | Favors LMWH |
| Siragusa et al. (1996) | Favors LMWH | Favors LMWH | Favors LMWH | Favors LMWH |
| Gould et al. (1999) | Favors LMWH | | Nonsignificant | Favors LMWH |
| Dolovich et al. (2000) | Favors LMWH | | Nonsignificant | Nonsignificant |
| Quinlan et al. (2004) | | Nonsignificant | Nonsignificant | Nonsignificant |
| Castellucci et al. (2014) | | | Favors LMWH | Nonsignificant |
| Robertson and Jones (2017) | Nonsignificant | Favors LMWH | Favors LMWH | Favors LMWH |

**Low molecular weight heparin is preferred due to an increasing body of evidence suggesting lower rates of thromboembolism recurrence and lower rates of hemorrhagic events in patients treated with low molecular weight heparin compared to unfractionated heparin**

# LMWH

- Can be used before procedures
- Can be used patients with renal issues
- No issues in pregnancy

# Can PE be Treated as Outpatients?

- Increasing incidence of “mild” PE
- Key is systems in place for home therapy of thrombosis
  - Compliance with medication
  - Close follow-up

# Pulmonary Embolism Severity Index (PESI)

- Points are assigned as follows:
  - 1 for each year of age
  - 10 for male sex
  - 20 for HR>110 beats/min
  - 10 for heart failure
  - 30 for malignancy
  - 10 for chronic lung disease
  - 30 for SBP<100
  - 20 for RR>30
  - 20 for temp <36 degrees C
  - 60 for AMS
  - 20 for PaO2<90%

# PESI score

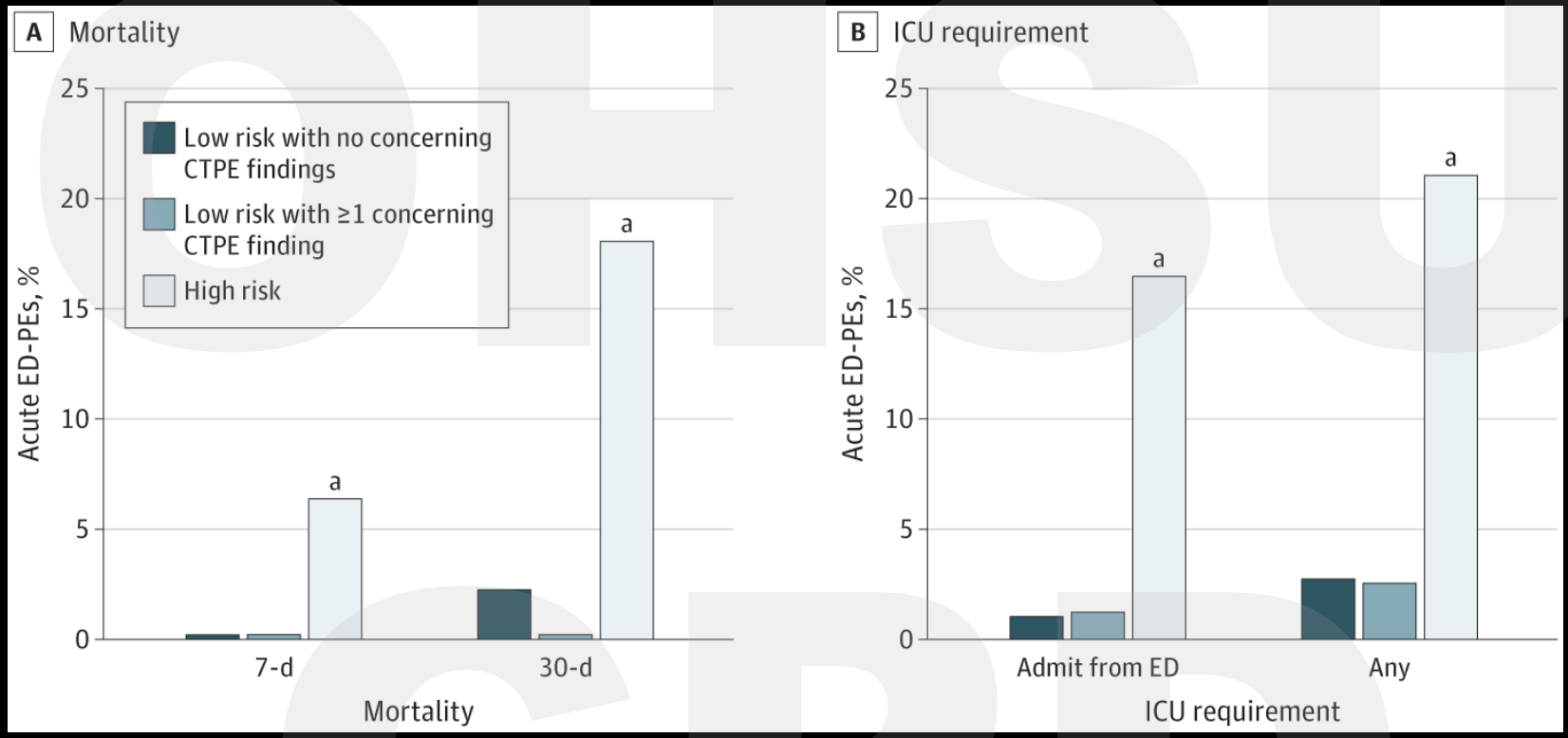
- Class I <65
- Class II 66-85

Low Risk

- Class III 86-105
- Class IV 106-125
- Class V >125
- 30 day mortality increases with each class
- Class V has a 25 fold higher risk of post-discharge death than Class I

# Look At Patient Not At Scan

- CT descriptions of PE as “saddle PE” have no prognostic implications
  - Outcomes same as non-saddle PE
- Need to assess patient’s physiology – PESI etc..




JAMA Netw Open. 2023;6(5):e2311455.

# Clinical Trials

- 4 RCTs
  - Inpatient vs outpatient
  - Low risk patients
- No difference in death, bleeding, or recurrent thrombosis
- Bad outcomes < 1.0%

# Outpatient Therapy

- PESI ≤ 85
  - No hypoxia, SBP < 100, recent bleeding, plts < 70,000, comorbidities or recurrent DVT
- Good social support
- Expected to be compliant


B
POSITIVE

# Post PE PTSD

- High incidence of physiological issues after PE
- More common in younger patients
- Why?
  - First major sickness
  - Can be fatal
  - Sudden and dramatic diagnosis

# Don’t Say..

- “Time Bomb”
- “Lung full of clots”
- “May have died if came in later”
- “People often die from this”

- Reassure patients this is a very treatable issue

# Antithrombotic Therapy

# Anticoagulants: 1991

- Aspirin
- Warfarin
- Heparin

# Anticoagulants: 2024

- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor
- Aggrenox
- Heparin
- Enoxaparin
- Tinzaparin
- Dalteparin
- Fondaparinux
- Abciximab
- Tirofiban
- Eptifibatide
- Lepirudin
- Argatroban
- Bivalirudin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Vorapaxar
- Osocimab
- Milvexian
- Abelacimab
- Asundexian

# Warfarin!

- Still most commonly used anticoagulant
  - 2,200,000 warfarin
  - 4,000,000 apixaban
  - 1,700,000 rivaroxaban
- Been around for > 50 years
- Still a tricky drug to use

# DOACS

- No monitoring
- No food interactions
- Rare drug interactions
- Safer!!!

# DOACs

- Robust randomized trial data for all DOACs
- Now recommend by guidelines first line over warfarin
- Irreversibility = Myth
  - Less need to reverse
  - No difference in bleeding outcomes in multiple studies

# DOAC in VTE

- Recurrent VTE: 0.90 (0.77-1.06)
- Major bleeding: 0.74 (0.59-0.85)
- ICH: 0.37 (0.21-0.68)
- Fatal bleeding: 0.36 (0.15-0.84)

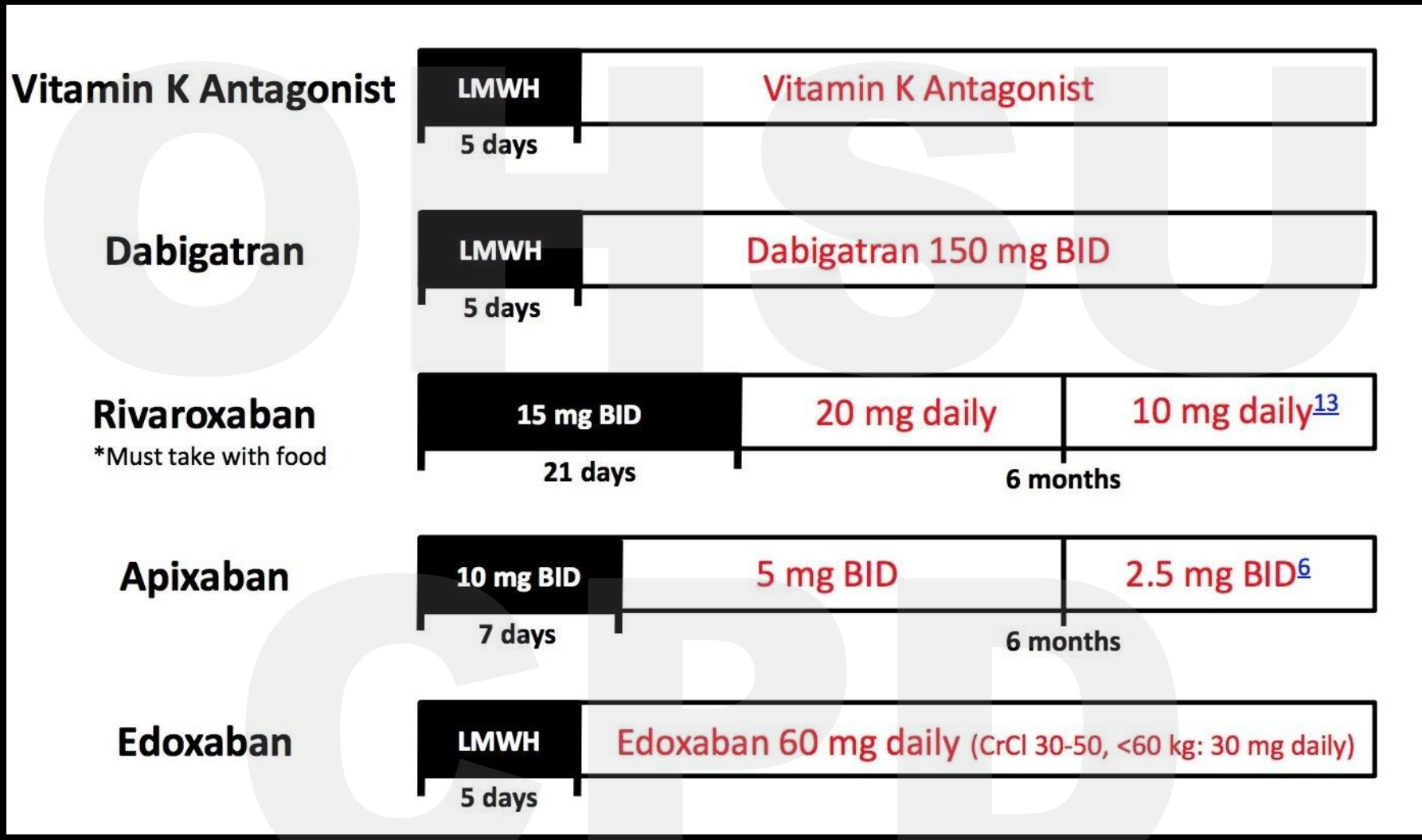
Blood 2014;124(12):1968-75

Eur J Vasc Endovasc Surg. 2014 Nov;48(5):565-575.

# Venous Thrombosis

| Drug | Heparin First? | Thrombosis | Bleeding |
|---|---|---|---|
| Apixaban | No* | Equal | Safer |
| Dabigatran | Yes | Equal | Equal |
| Edoxaban | Yes | Equal | Safer |
| Rivaroxaban | No* | Equal | Safer |

*Apixaban 10mg bid x 7 days then 5mg BID
*Rivaroxaban 15mg bid x 21 days then 20mg daily


Vitamin K Antagonist
LMWH
5 days
Vitamin K Antagonist
Dabigatran
LMWH
5 days
Dabigatran 150 mg BID
Rivaroxaban
*Must take with food
15 mg BID
21 days
20 mg daily
6 months
10 mg daily[13]
Apixaban
10 mg BID
7 days
5 mg BID
6 months
2.5 mg BID[6]
Edoxaban
LMWH
5 days
Edoxaban 60 mg daily (CrCl 30-50, <60 kg: 30 mg daily)

# Renal Disease – OK!

- Data show no difference – perhaps safer – compared to warfarin even in dialysis patients
- Apixaban 5 mg bid most data
  - If > 80 years or < 60kg 2.5 mg bid

# Obesity – Sort of OK!

- Use weight NOT BMI
- Atrial fibrillation
  - < 150kg
- Thrombosis
  - "Guidelines": no limit (!?)
  - Acute < 150 kg
  - Chronic < 200 kg

# Cancer

- DOACs more effective than LMWH
- Apixaban not associated with GI bleeding

# DOAC in Cancer Patients

- DOAC used in majority of patients
- 4 RCT showing equivalence/superiority with LMWH
  - GI bleeding concern with GI tumors
    - Rivaroxaban/edoxaban
  - Apixaban maybe prefer in patients at risk of GI bleeding
- ASCO Guidelines

# Costs!

- BIG issue!
- Warfarin: $4/month
- DOACs: $6-800/month
- Make sure patient can get meds filled!

# Warfarin

- Good
  - Cheap!
  - Used over 60 years
  - Compliance
  - Mandatory for valves and bad APLA
- Bad
  - Incredible food and drug interactions
  - Need for close monitoring
  - Compliance


KILL RATS!
STOP
THIS ROBBER
WITH THE NEW
TESTED AND
RECOMMENDED
Rat Killers
made with WARFARIN*
CLEANS YOUR FARM OF RATS AND MICE
THE NEW ANSWER TO YOUR RAT PROBLEM!
RAX POWDER
KILLS RATS AND MICE
J. B. PENICK & COMPANY
PRENTISS & COMPANY, INC

# Apixaban

- Good
  - Safest drug
  - Best in renal/liver disease
  - No monitoring
- Bad
  - BID drug
  - Expensive!!!

# Rivaroxaban

- Good
  - Safer than warfarin
  - Once a day drug
- Bad
  - Slight higher rates of bleeding
  - Need to take with food
  - Costs!


Tell me the truth...I'm...I'm ready
to hear it.


THERE IS A NEW CLASS OF ANTICOAGULANTS

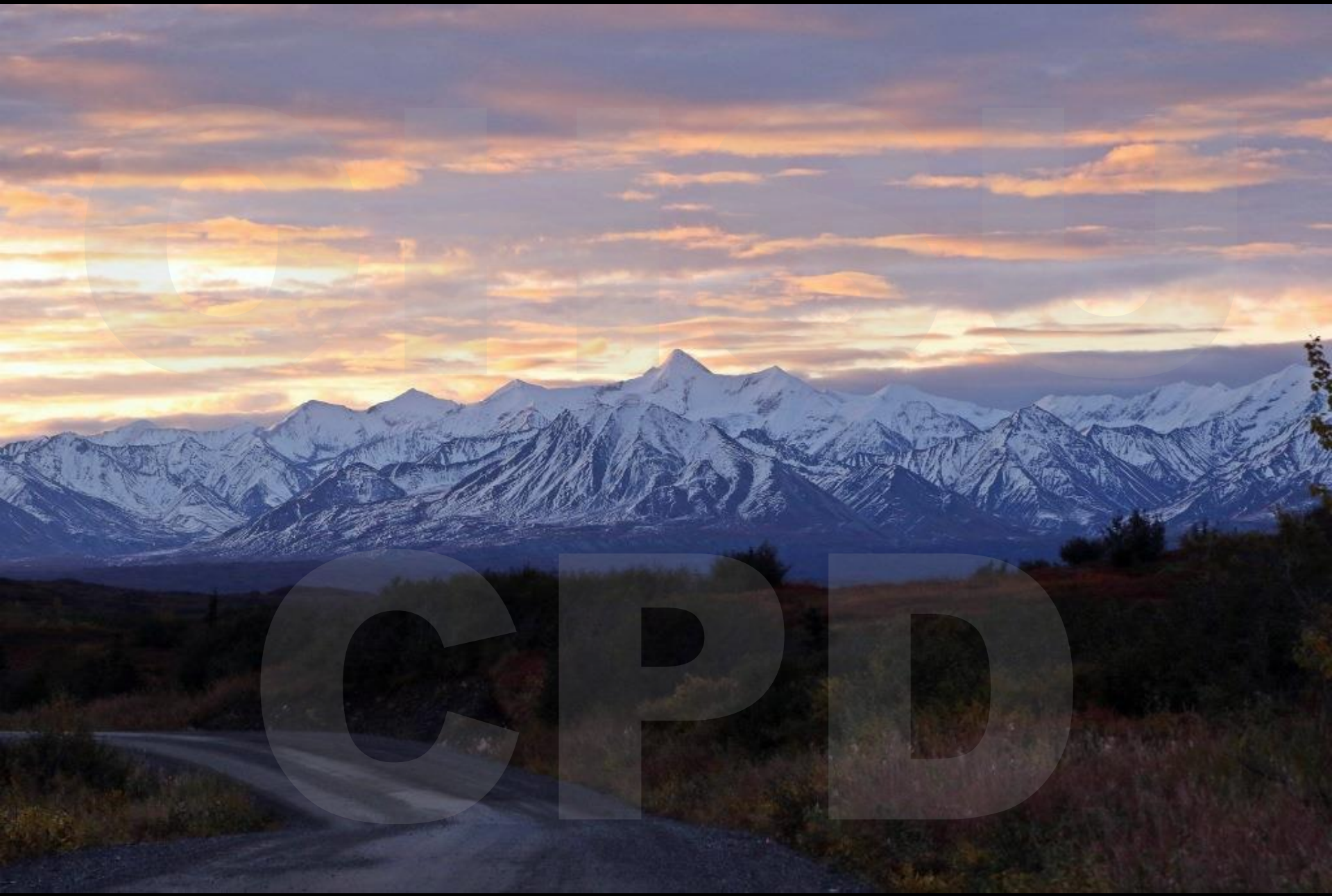

imgflip.com

# The Future!!

- Inhibitors of factor 11 being developed
- Less bleeding
- Some can be dose once a month!

# Goals!

- Diagnosis of venous thromboembolic disease
- Immediate non-anticoagulation theray
- Anticoagulation options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