# Update on Venous Thromboembolism: Focus on Direct Oral Anticoagulants

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# Learning Objectives

1. Assess the efficacy and safety of DOACs compared to LMWH for the management of cancer-associated thrombosis
2. Discuss use of DOACs in obese patients with VTE
3. Review data on catheter-directed lysis in proximal LE DVT
4. Discuss DOAC reversal agents for life threatening bleeding
5. Determine if an age-appropriate D-dimer cutoff can be used to minimize unnecessary CT-PE imaging
6. Highlight special scenarios in anticoagulation for VTE
   - Incidental subsegmental PE
   - Catheter related thrombosis
   - Anticoagulation in setting of thrombocytopenia
   - Perioperative management of AC

# Case 1: DOACS for cancer-associated VTE

- Mr. K is an African-American man with newly diagnosed pancreatic cancer. He is on his 2$^{nd}$ cycle of systemic chemotherapy.
- He now presents with LLE swelling and is diagnosed with a LLE proximal vein DVT.
- There are no contraindications for anticoagulation
- He cannot afford LMWH.
- He has asks about alternative anticoagulation options, preferably an oral medication?

# Comparative properties of OAC

| | Warfarin | Dabigatran (Pradaxa) | Rivaroxaban (Xarelto) | Apixaban (Eliquis) | Edoxaban (Sayvasa) |
|---|---|---|---|---|---|
| **Target** | F2,7,9,10 | Thrombin | Factor Xa | Factor Xa | Factor Xa |
| **Peak Effect(h)** | 72-96 | 2 – 3 | 2 – 4 | 1-3 | 1-2 |
| **Half-life (h)** | 40 | 12 – 14 | 5 – 13 | 9 – 14 | 6-11 |
| **Dosing Frequency** | QD | BID | QD | BID | QD |
| **Clearance** | Cytochrome P450 2C9 | 80% Renal 20% Biliary | 66% Renal 33% Biliary | 25% Renal 75% Biliary | 34% Renal 66% Biliary |

Harder & Graff. EJCP 2013; 69: 1617.

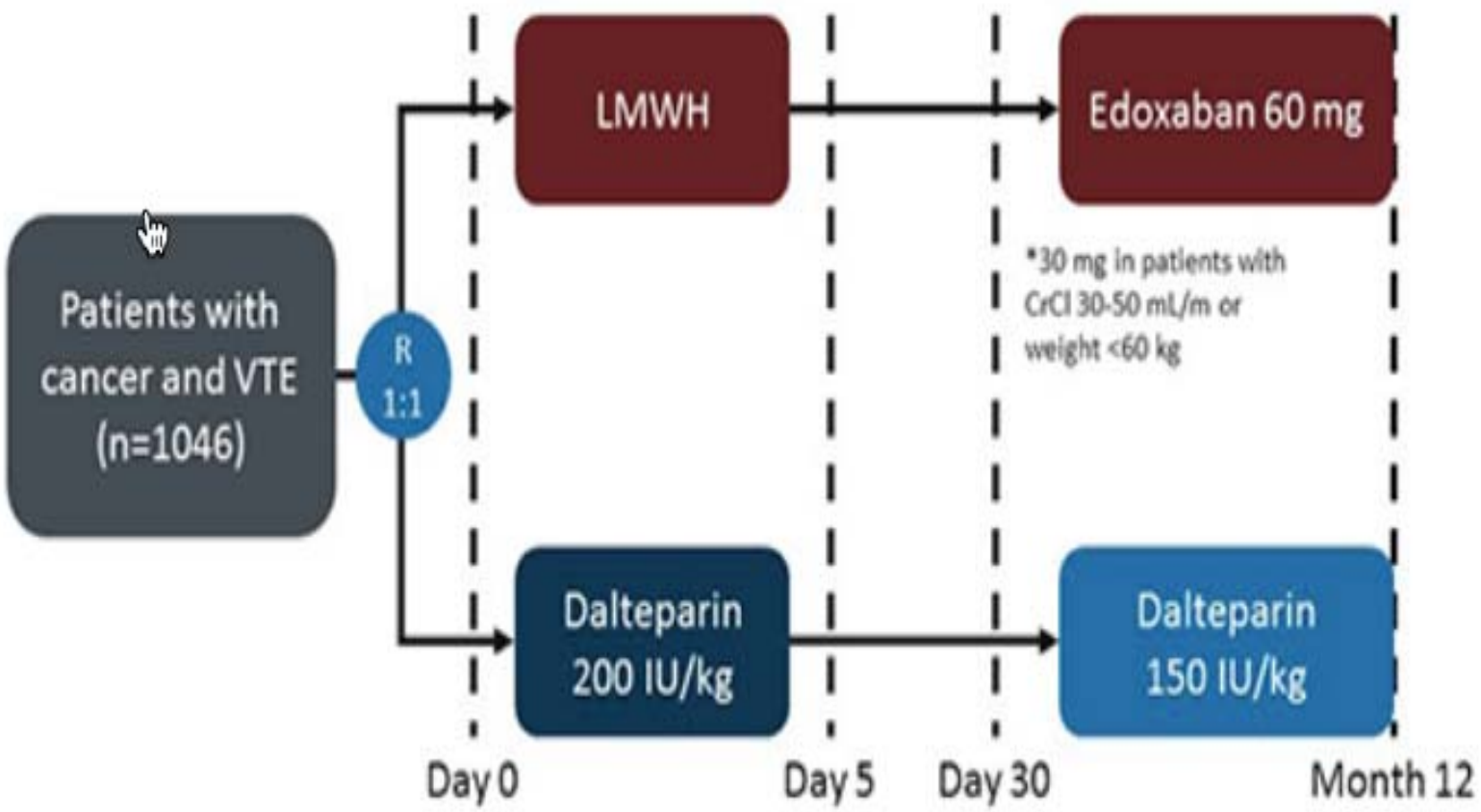
# DOAC FDA approved indications (as of May 2017)

| | Dabigatran (Pradaxa) | Rivaroxaban (Xarelto) | Apixaban (Eiquis) | Edoxaban (Sayvasa0 |
|---|---|---|---|---|
| VTE prophylaxis (THA,TKA) | ✓ | ✓ | ✓ | X |
| Atrial fibrillation | ✓ | ✓ | ✓ | ✓ |
| VTE treatment | ✓ | ✓ | ✓ | ✓ |

Rivaroxaban (Xarelto®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf
Apixaban (Eliquis®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf
Edoxaban (Savaysa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf
Dabigatran (Pradaxa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf

# Hokusai VTE - Cancer Study Design

- Open-label, noninferiority RCT
- Acute symptomatic or incidental VTE
- 58% sympotmatic VTE, 53% metastatic disease

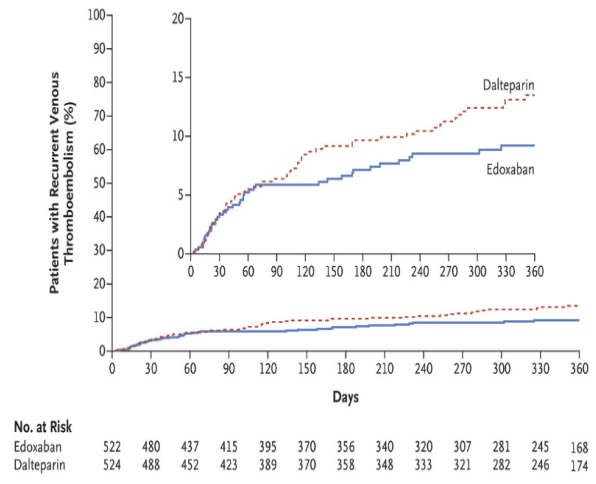



Raskob et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1711948.

# Results

## Recurrent VTE

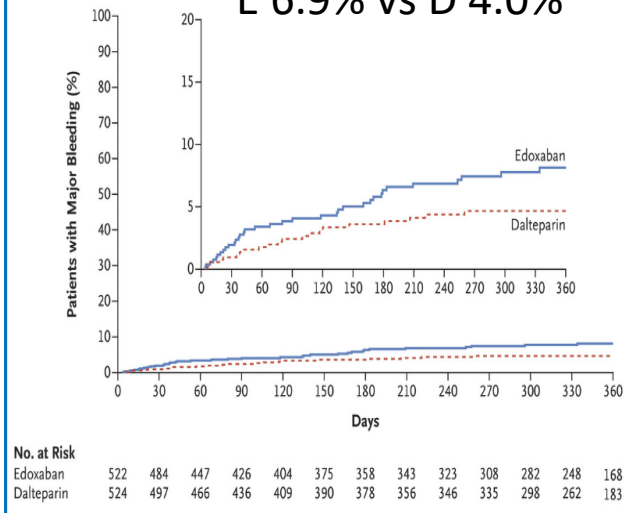
E 7.9% vs D 11.3%




**HR 0.71 (0.48 – 1.06)**
**p = 0.09**

## Major Bleeding

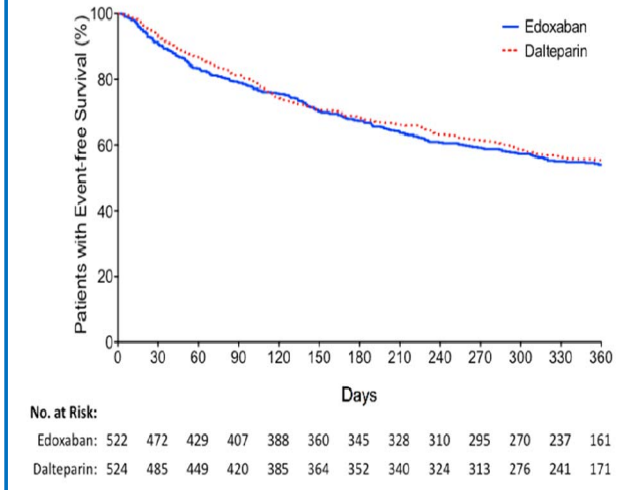
E 6.9% vs D 4.0%




**HR 1.77 (1.03 – 3.04)**
**p = 0.04**

## Event-free Survival

E 55.0% vs D 56.5%




**HR 0.93 (0.77 – 1.11)**
**p= NS**

Raskob et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1711948.

# Major bleeding and severity

| | Edoxaban (N = 522) | Dalteparin (N = 524) | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Major bleeding** | **36 (6.9%)** | **21 (4.0%)** | **1.77 (1.03 – 3.04)** |
| Fatal | 0 | 2 | |
| ICH | 2 | 4 | |
| Upper GI | 17 | 3 | |
| Lower GI | 3 | 3 | |

Raskob et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1711948.

# SELECT-D Trial

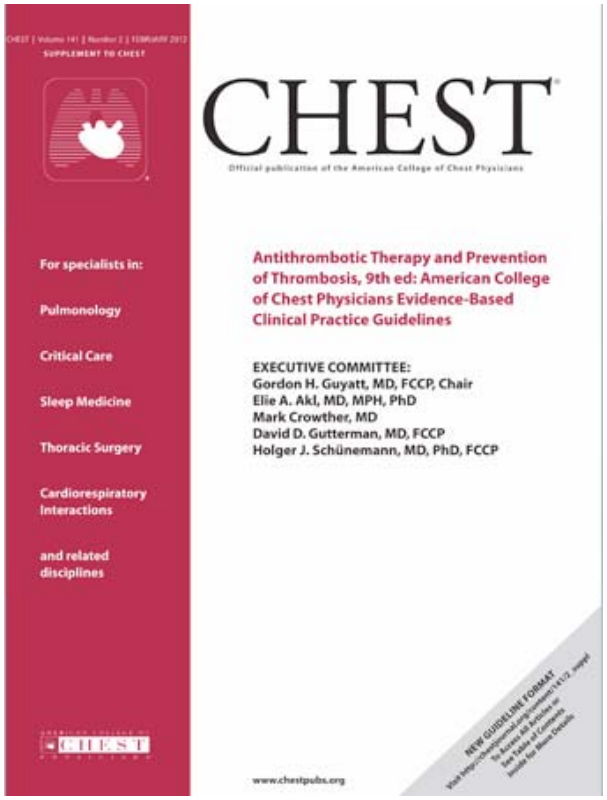
- Open-label, noninferiority RCT in cancer patients with acute VTE
- Dalteparin vs. **Rivaroxaban** x 6 months

| | Rivaroxaban (N = 203) | Dalteparin (N = 203) | Significant ? |
|---|---|---|---|
| Recurrent VTE | 8 (4%) | 18 (9%) | Yes |
| Major bleeding* | 11 (5%) | 6 (3%) | Not SS |
| CRNMB | 25 (12%) | 6 (3%) | Yes |
| All bleeding events | 36 (17%) | 12 (6%) | Yes |

- *1 fatal bleeding event in each arm
- Most major bleeding events were GIB; no CNS bleeds
- Most CRNMBs were gastrointestinal or urological

Young et al JCO 2018; 36: 217-223

# ACCP 2016: VTE Treatment




In non-cancer patients with VTE, as long-term (first 3 months) anticoagulant therapy, we suggest

- DOAC over VKA (Grade 2B)
- VKA over LMWH (Grade 2C)

In cancer patients with VTE, as long-term therapy we we suggest:

•LMWH over VKA (Grade 2B) or DOAC (Grade 2C)

**Await ASH 2019 VTE Guidelines in Cancer**

Kearon Chest 2016

# Case 2: DOACS in obese patients

- Mr. K has a BMI of 36.

*Are DOACs effective and safe in him?*

# Background

- Minimal clinical data exist on the use of DOACs in obese patients.
  - 12-30% of patients in DOAC VTE trials were obese, none morbidly obese

- ISTH guidelines recommend against empiric use of DOACs in patients > 120 kg

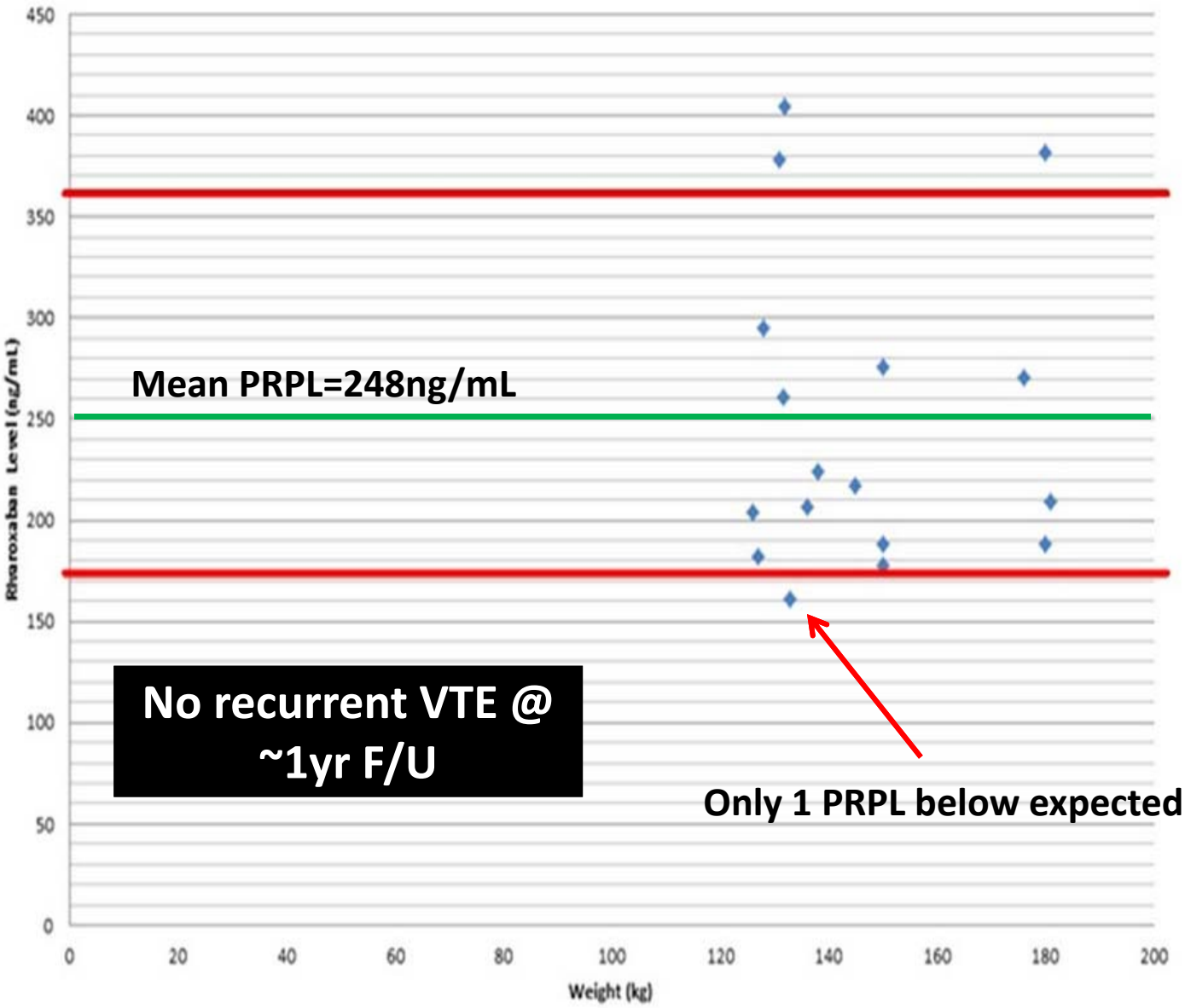
Martin et al. *J Thromb Haemost*. 2016.

# DOACs in Obese

- Retrospective review 2014-2017
- Patients ≥ 120 kg on Rivaroxaban 20 mg daily for treatment or secondary prevention of VTE
- Patients had at least one Peak Rivaroxaban Plasma Level (PRPL) 2-4hrs after ingestion
- Primary objectives: PRPL compared to reference range PRPL in non-obese patients
- Secondary objective: VTE complications while on rivaroxaban
- 17 patients included: Mean weight 146kg, Mean F/U 312 days

Abdulrehman et al. ASH Annual Meeting 2017 abstract #1112; Buller et al. Blood 2008.

# Results: PRPLP compared to reference range




based on reference range in non-obese from prior PK studies

Abdulrehman et al. ASH Annual Meeting 2017 abstract #1112; Buller et al. Blood 2008.

# Safety and Efficacy of DOACS based on BMI

- Single center retrospective review
- Patients on any DOAC for afib or VTE
- Followed for 6 months in VTE group
- Efficacy and safety assessed as a function of BMI
- 76 patients with VTE; 48% BMI >30; 10% >45
- No relationship between major bleeds or recurrent VTE across all BMI groups.
- Reduced CRNMB in BMI >45 taking rivaroxaban

Doucette et al Blood 2017 130:3715.

# Summary of DOACS in Obese

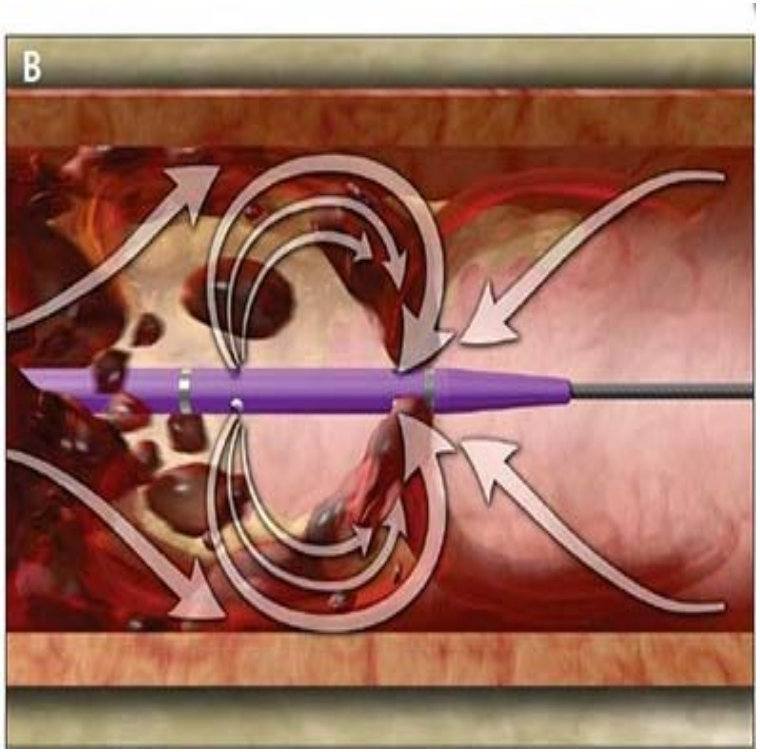
- Peak plasma levels of rivaroxaban appear to be similar to levels in non-obese
- Low quality data suggest similar efficacy (prevention of VTE recurrence) and safety (major bleeding) of DOACs in obese compared to non-obese
- Requires further rigorous evaluation in prospective trials

# Case 3: Proximal vein DVT

- Mrs. V is a 42 year-old who presents with a symptomatic acute iliofemoral DVT. Her leg is swollen, painful, and red but there are no signs of compartment syndrome or limb gangrene.
- She wants to know what options in addition to anticoagulation can help relieve her symptoms and prevent long term complications of DVT?

# Background

- Post-thrombotic syndrome (PTS) develops within 2 years in 50% of patients with proximal LE DVT
- Major cause of chronic symptoms, disability, and impaired QoL
- Pharmacomechanical catheter-directed thrombolysis (CDT) is delivery of a fibrinolytic drug into the thrombus with concomitant thrombus aspiration or maceration.
- CDT goal is to diminish thrombus burden, thereby reducing PTS while minimizing bleeding

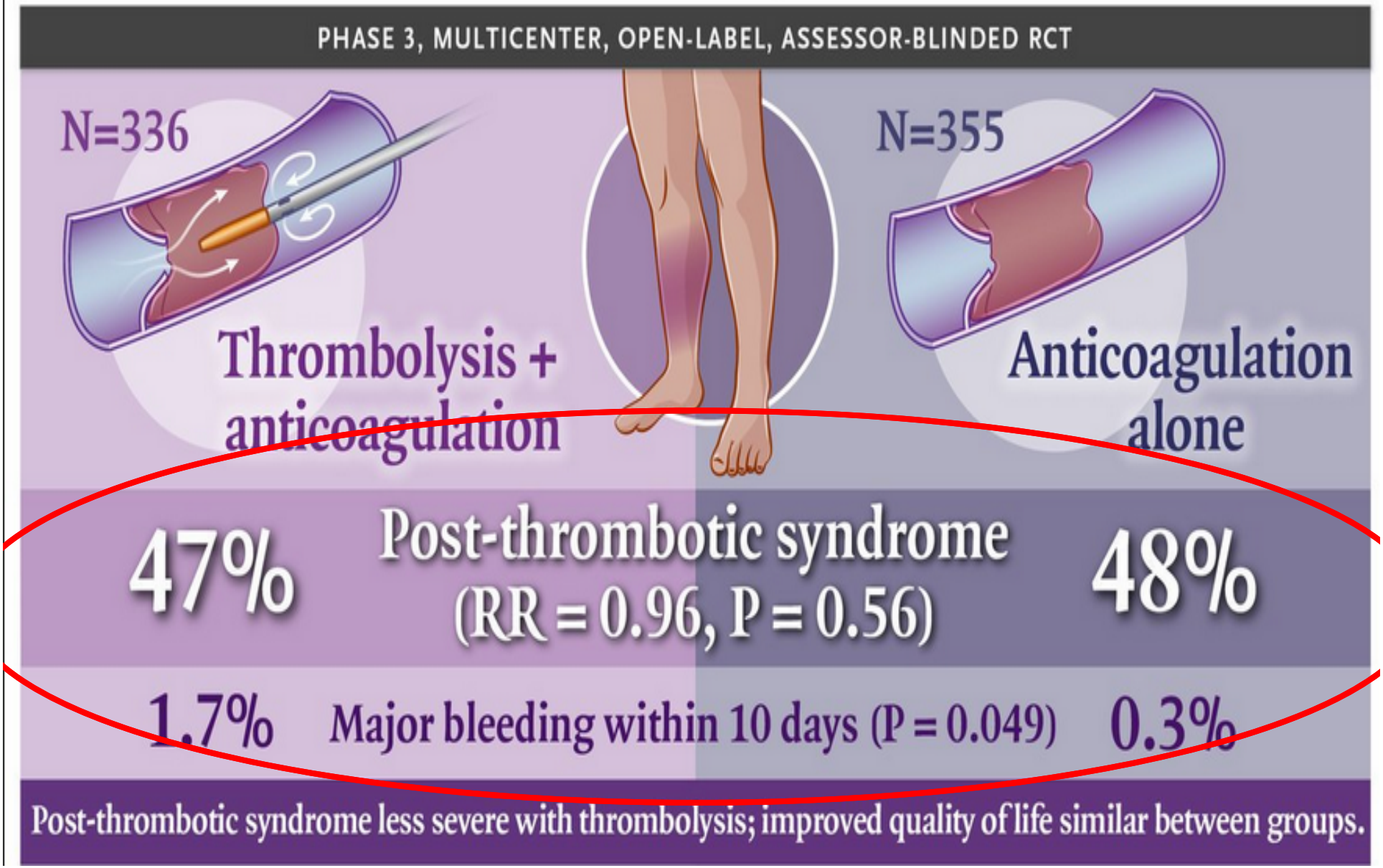


# ATTRACT Study

- Phase III, open label, assessor blinded RCT
- Symptomatic proximal DVT involving the femoral, common femoral, or iliac vein
- Excluded patients with symptoms >14 days, high bleeding risk, active cancer, known PTS
- Pharmacomechanical CDT vs. no procedure
- **All patients** received anticoagulation and compression stockings
- Primary outcome: Post-thrombotic syndrome
- Secondary outcomes
  - Major bleeding, QoL, recurrent VTE, death
- Followed for 2 years

Vedantham et al. N Engl J Med 2017;377:2240-52.

# Catheter-Directed Thrombolysis for Proximal DVT




**No difference in recurrent VTE or QOL at 2 years**

# Case 4:
# Life-threatening bleeding on anti-Xa OAC

Mr. S is a 52 year-old man with a prior history of VTE suffers an abdominal injury with suspected critical bleeding after a MVA. His last dose of rivaroxaban was this this morning.

You send him for a stat abdominal CT which confirms a large retroperitoneal hematoma.

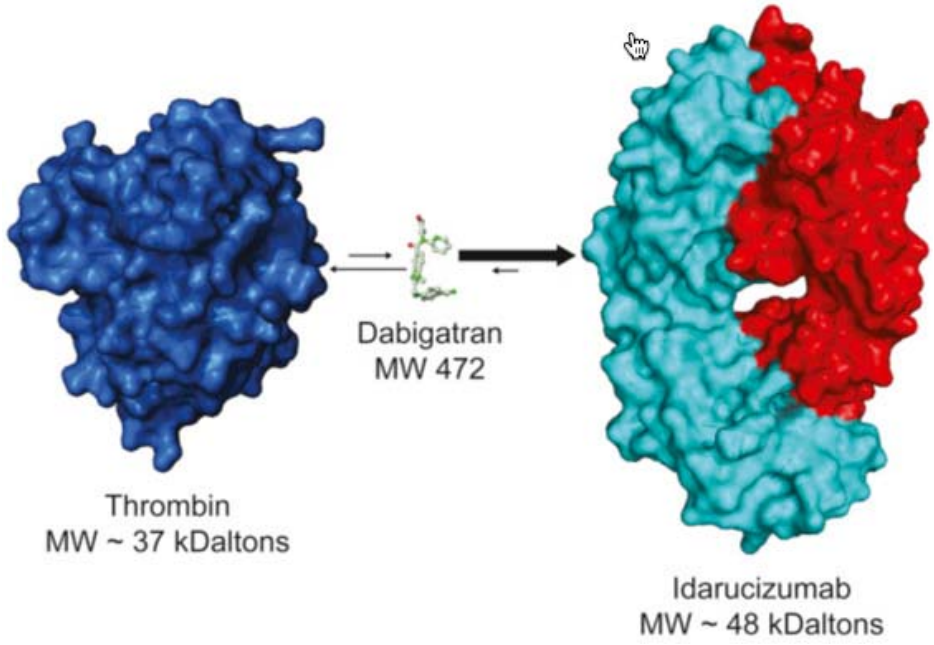
In addition to trauma surgery consultation you recommend ????

# Major Bleeding on DOACS

- Less common than with warfarin
- Less severe than with warfarin (decreased ICH by 30-70%)
- Drugs have shorter t ½ than warfarin (fast on/fast off)
- But…when it does occur…
- Psychologically unsettling for the clinician
- Why?
  - Can't measure
  - Cant' reverse….until NOW!

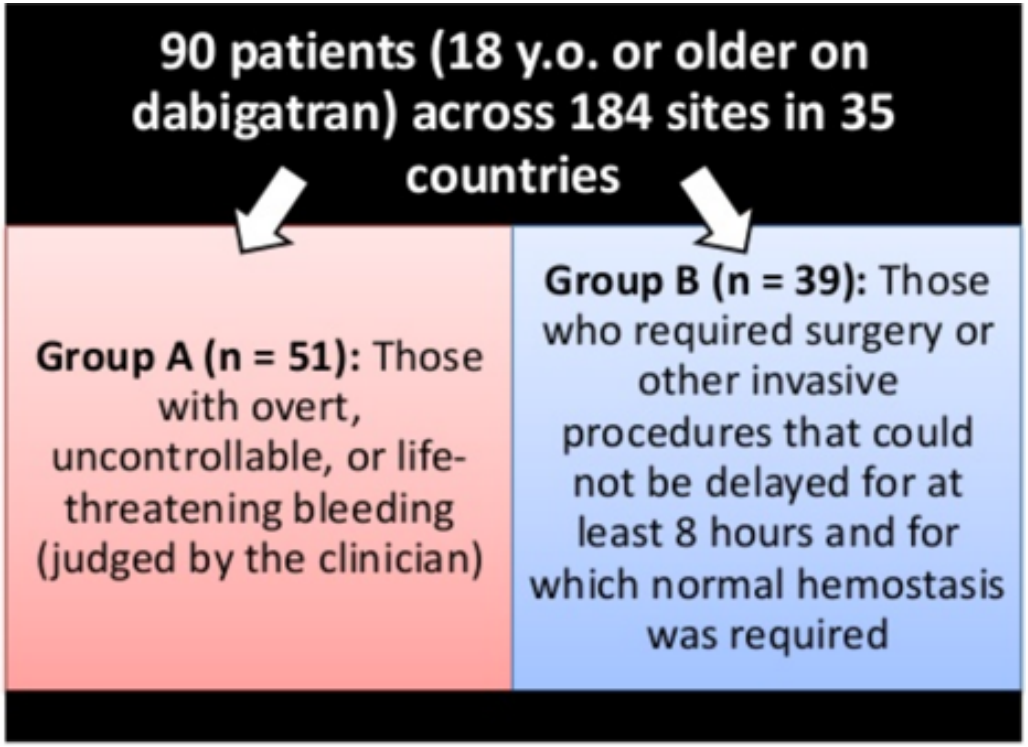
# Idarucizumab

- Humanized mouse monoclonal-Ab
- True reversal agent
- Binds dabigatran with high affinity (350x high than thrombin) and neutralizes anticoagulant activity
- Rapidly cleared by kidney WITH bound dabiagtran
- FDA approved Oct 2015



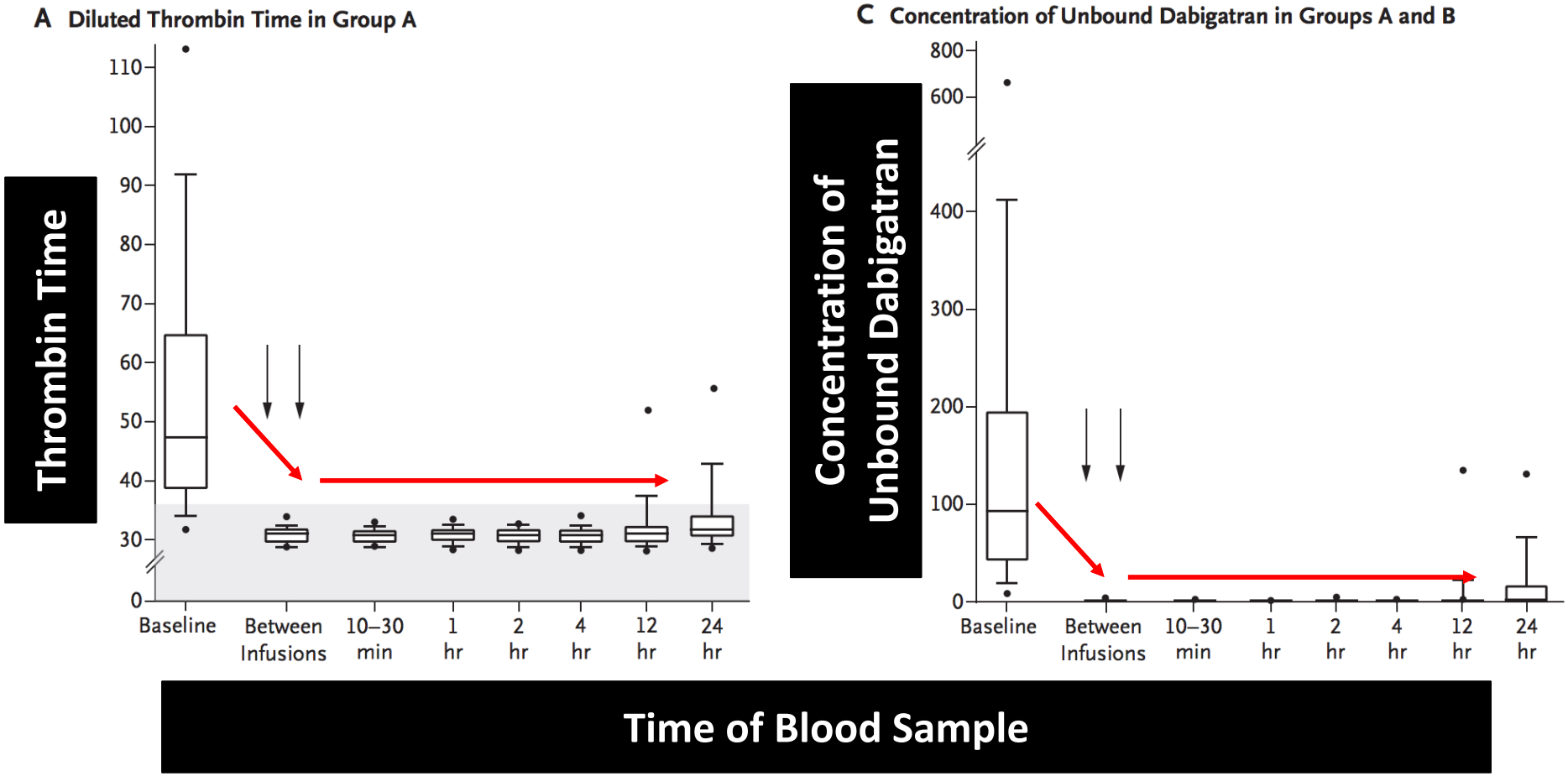
# REVERSE-AD

**Updated in 2017 with full cohort n=503 patients**




- 5 g of intravenous idarucizumab (2 boluses of 2.5gm <15mins apart)
- Primary outcome: % reversal of anticoagulant effect
- Secondary outcome: Clinical resolution of bleeding or periprocedural hemostasis
- Majority on Dabigatran for atrial fibrillation

Pollack et al NEJM 2017; 377:431-441

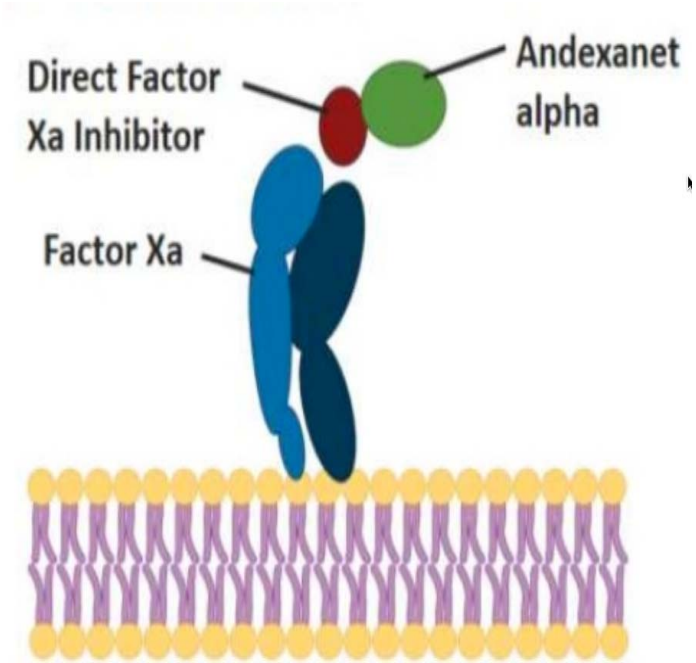



- 67% bleeding cessation within 24hrs, most within 2.5hrs
- In group B--93% had normal intraoperative hemostasis.

Pollack et al NEJM 2017; 377:431-441

# Andexanet Alpha for Acute Major Bleeding Associated with Factor Xa Inhibitors: ANNEXA-4

- Recombinant human FXa decoy.
- Binds with high affinity to anti-Xa DOAC, blocking inhibition of FXa.
- Prospective, open-label single arm study
- 67 patients with acute major bleed within 18hrs of a factor Xa inhibitor ingestion
  - Bolus of andexanet alpha followed by 2 hour continuous infusion
  - Evaluated changes in anti-Xa activity and hemostatic efficacy

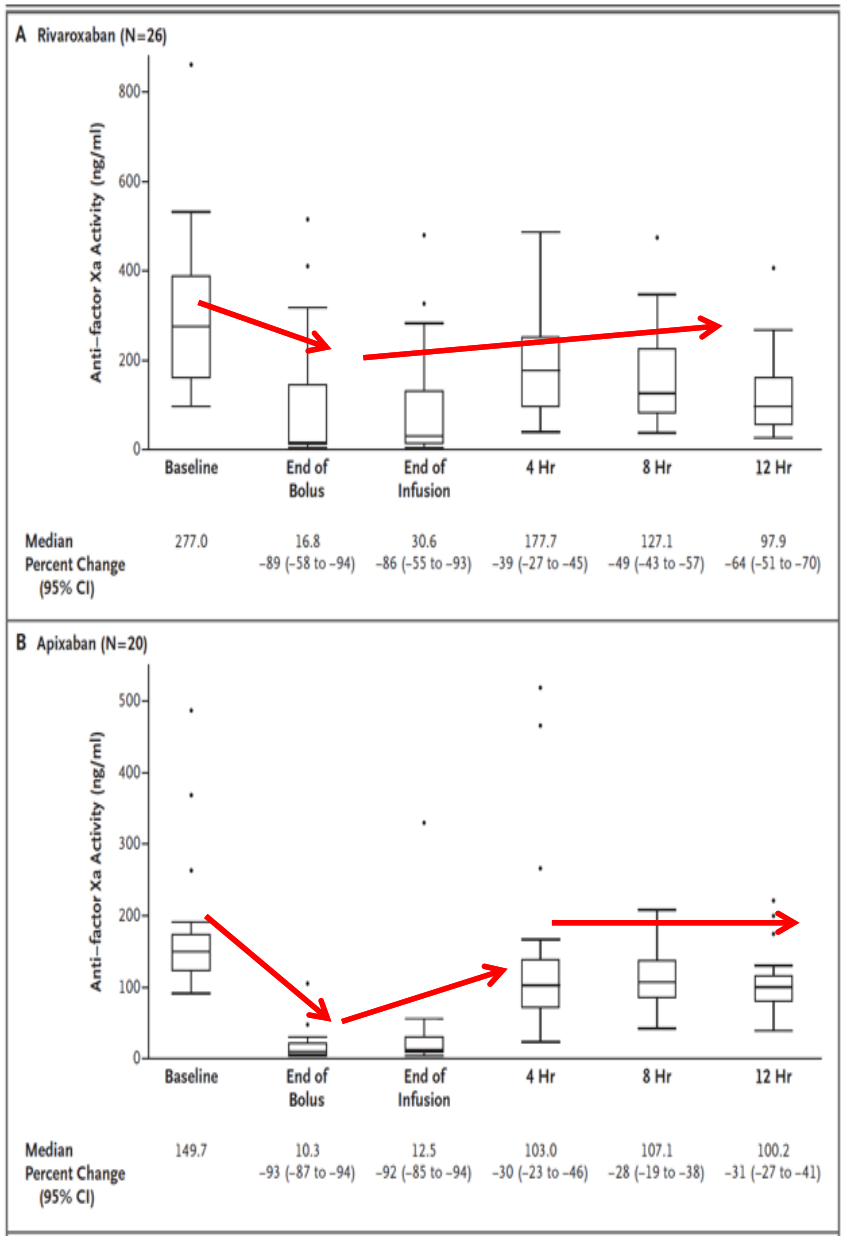



Connolly SJ et al. N Engl J Med 2016;375:1131-1141.

# Interim Results

Median decrease of 93% after bolus and 30% 4 hours after infusion

Median decrease of 89% after bolus and 39% 4 hours after infusion




Anti-Xa activity

**Apixaban**

**Rivaroxaban**

Connolly SJ et al. N Engl J Med 2016;375:1131-1141.

# Cautions and Implications

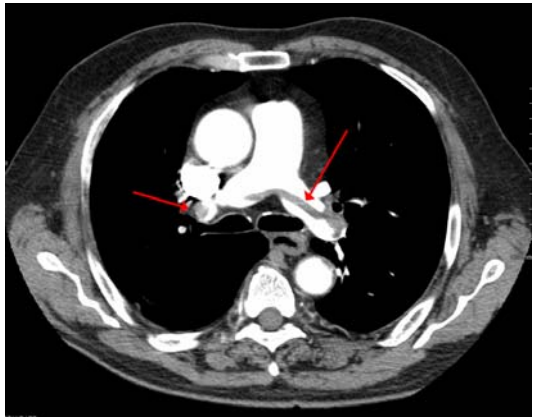
- **Cautions**
  - Preliminary report of a larger ongoing study
  - Single-group cohort study with no placebo comparison arm
  - Optimal dosing of andexanet alpha remains unknown.
  - Cost of andexanet alpha ($50,000/dose)
  - Strict protocols will need to be developed at the institution level, to ensure use only with life-threatening bleeding or the need for emergent surgery

Connolly SJ et al. N Engl J Med 2016;375:1131-1141.

# Case 5: Diagnosis of PE

You are called to the ED to see a 76 year-old obese man who presents with cough and 5 days of shortness of breath.

Pulse oximetry and vitals are normal. Labs and CXR are unremarkable.



The ED attending asks your opinion about assessing for pulmonary embolism.

You recommend ???

# Background

- Imaging with either CT angiogram or V/Q scans is necessary to definitively diagnose a pulmonary embolism (PE).
- PE is only found in 15-25% of CT-angiograms performed for this indication.
- PE is thought to be unlikely with a Wells score $\leq$ 4 and a fixed D-dimer $\leq$ 500 ug/L
  - Imaging and treatment can be withheld.
- An age-adjusted D-dimer (age x 10 ug/L for age > 50 years) has been validated in small studies to exclude PE.
- Using an age-adjusted D-dimer cutoff may decrease the number of unnecessary imaging studies

# Methods

- Individualized-patient data meta-analysis included 7628 patients with clinically suspected PE from 6 large prospective studies using of the Wells rule and D-dimer testing to guide management of PE.
  - 1 used age-adjusted D-dimer, 5 used fixed D-dimer
- **Efficiency**= Patients in whom imaging (and anticoagulation) withheld based on "PE-unlikely":
  - Wells score ≤ 4 AND negative fixed OR
  - Wells score ≤ 4 AND negative age-adjusted D-dimer*
- **Failure**= Patient in whom AC was withheld but subsequently developed symptomatic VTE (F/U 3 months).

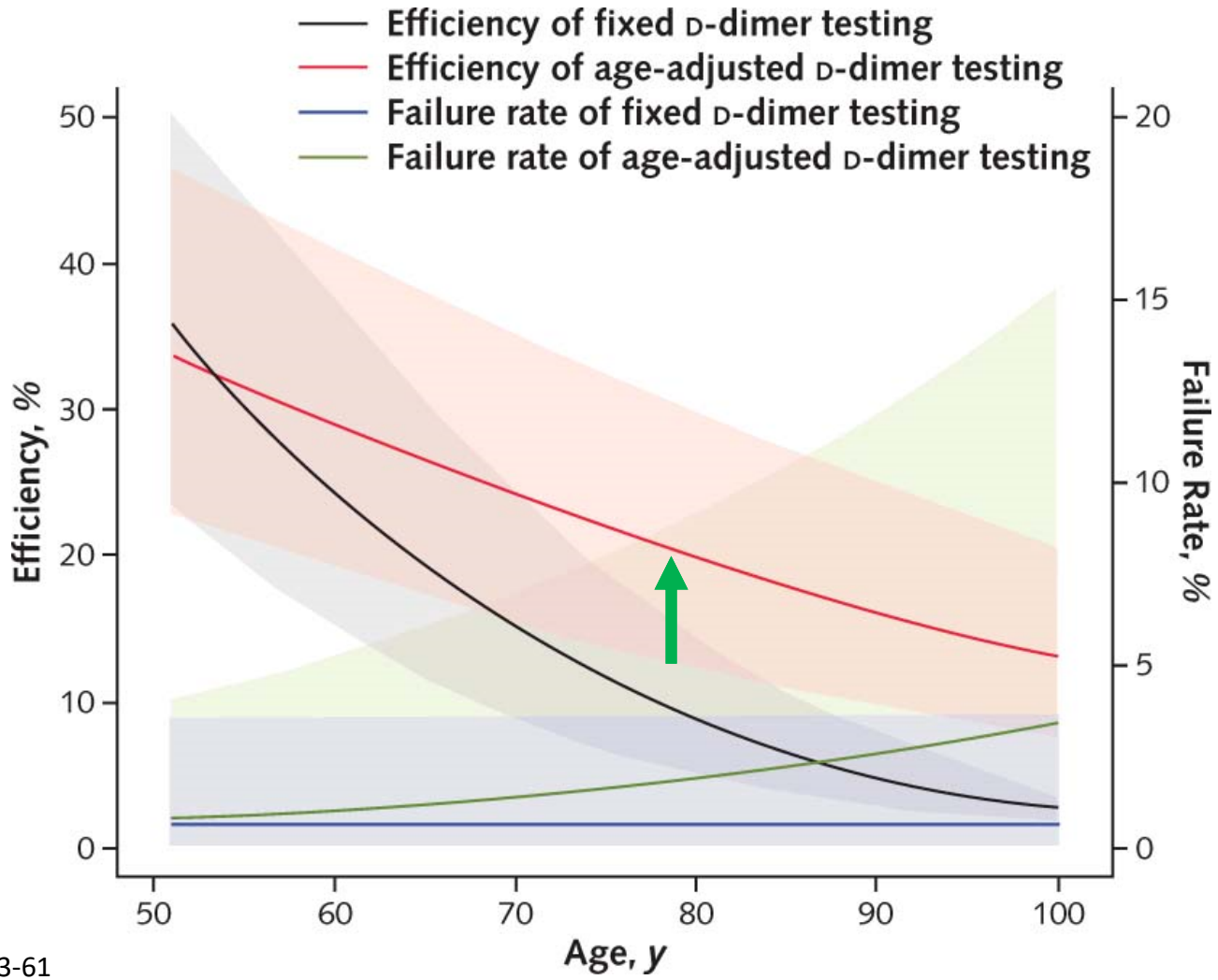
***Fixed cut-off D-dimer→≤500 ug/L**
**Age-adjusted D-dimer cutoff→ ≤ age x10 ug/L in patients aged > 50 year**

van Es N et al. Ann Intern Med. 2016:165:253-61

# Efficiency increased and failure rates remained low with use of an age-adjusted versus fixed D-dimer

Overall efficiency increased from 28% to 33% with use of an age-adjusted D-dimer

- An extra 5% of patients were spared imaging
- Failure rate remained below 3%




van Es N et al. Ann Intern Med. 2016:165:253-61

# Cautions and Implications

- Cautions
  - Results are based in part on post-hoc analysis as the age adjusted D-dimer was only prospectively evaluated in a single study.
  - Efficiency and failure rates were calculated from individual studies which may have led to overestimation.
  - Considerable heterogeneity between studies was noted.
  - D-dimer assays were not standardized between studies.

- Implications
  - Age-adjusted D-dimer in conjunction with a low probability Wells score leads to an increased number of patients in whom imaging can be withheld.
  - There is no added cost with use of an age-adjusted D-dimer.
  - Age adjusted D-dimer should be incorporated into future diagnostic PE algorithms.

# SPECIAL SCENARIOS

# Case 6: Incidental Subsegmental PE (ISSPE)

A 32 year old female with Stage IIE B cell lymphoma undergoes a surveillance CT after 3 cycles of chemotherapy. CT shows partial response to treatment but also detects an incidental sub-segmental PE. She is asymptomatic. Labs are normal.

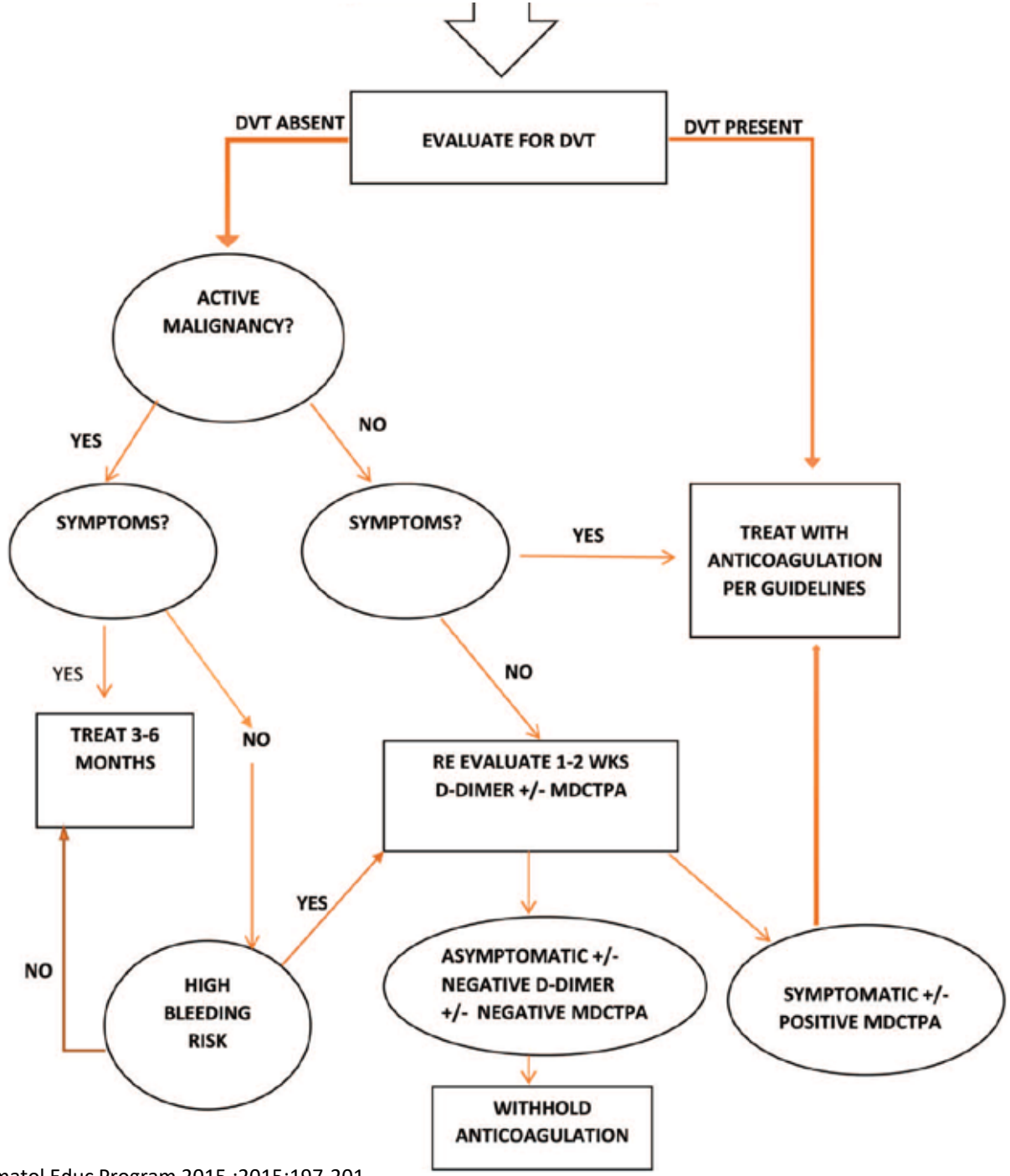
You recommend:

1. Observe and re-image in 6-8 weeks
2. Obtain DUS and only if positive initiate LMWH
3. Obtain DUS and even if negative initiate LMWH
4. Start IV UFH

# ISSPE in Cancer Patients

- Evidence of thrombosis detected on imaging studies performed for other indications.
- Up to half of all PE in cancer patients may be incidentally detected
  - Distribution no different than symptomatic PE
  - Many have unrecognized symptoms
  - No prospective data on outcomes of IPE in cancer
  - Retrospective data- recurrent VTE and bleeding on AC comparable to symptomatic PE
- The majority of providers treat cancer patients with incidental VTE with anticoagulation.
- Unfortunately, cancer patients are higher risk for bleeding complications on anticoagulation.

Moore JCO 2011;29:3466-3473
Franklin Post Grad Med J 2011;87)1033):746-749




O'Connell Hematology Am Soc Hematol Educ Program 2015 ;2015:197-201

# Case 6:
# Catheter-related thrombosis

A 40-year-old man with infective endocarditis is receiving IV antibiotics through a PICC line. He now complains of RUE pain and swelling. He has no history of VTE. The PICC line is functioning. On physical examination, the right arm and hand are swollen and tender.

Compression ultrasonography reveals right axillary vein DVT

Labs: PLT 130,000/µL, Cr 0.9 mg/dL

He needs 4 more weeks of IV antibiotics

Which of the following should you recommend?

(A) Remove the PICC and forgo anticoagulation

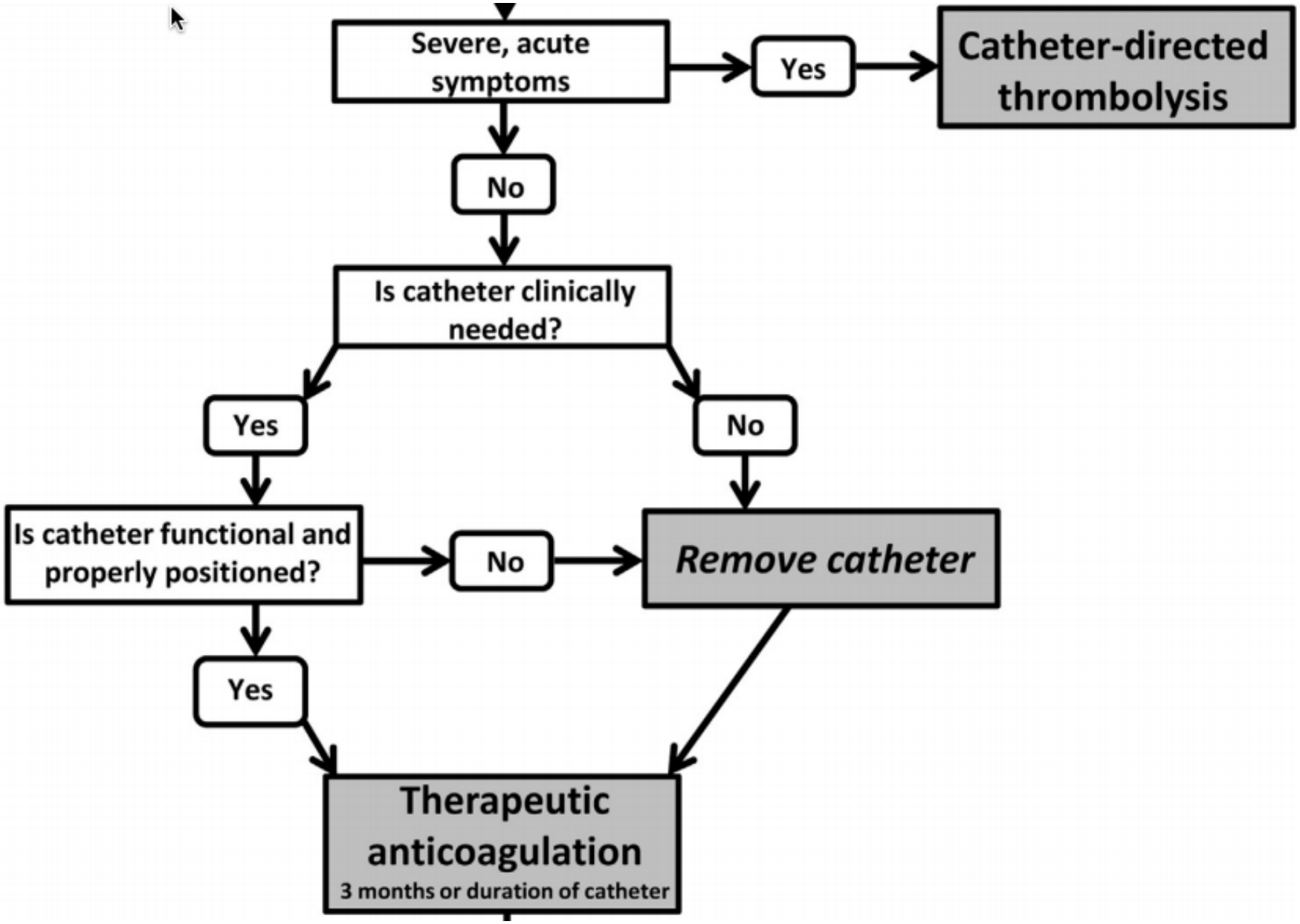
(B) Leave the PICC in place and start warfarin

(C) Leave the PICC in place and start parenteral AC or DOAC

(D) Remove the PICC line and start parenteral AC or DOAC

| Device-related factors | Patient-related factors | Treatment-related factors |
|---|---|---|
| Multiple insertion attempts | Malignancy (metastatic > localized) | Ongoing cancer therapy<br>• Chest radiation therapy<br>• Bolus chemotherapy infusions<br>• Antiangiogenic or platinum therapy |
| Catheter insertion site (femoral>jugular>subclavian) | Recent trauma/surgery/immobilization within 30 days | Erythrocyte stimulating agents |
| Large catheter size to vein diameter ratio | History of VTE | Parenteral nutrition |
| CVT subtype (PICC >centrally inserted catheter >implanted port) | End-stage renal disease | |
| Improper catheter position (not at atriocaval junction) | Systemic or catheter infection | |
| Multiple lumens and larger catheter size | Older age | |
| CVAD material (polyethylene or polyvinylchloride > silicone or polyurethane) | Critically ill patients | |
| Previous CVAD | Inherited thrombophilia | |

Rajasekhar A et al. Blood. 2017;129(20):727-2736.




Crawford et al. J Vasc Surg Venous Lymphat Disorders 2016; 4(3):375-9

# Case 7:
# Anticoagulation with Thrombocytopenia

42 year-old man with metastatic pancreatic cancer receiving systemic chemotherapy presents with LLE swelling. A compression ultrasound reveals an acute L popliteal DVT. He has no personal or FMhx of VTE. No recent UFH/LMWH exposure.

Labs: Hb 9.5g/dL, PLT 30,000/µL, Cr normal, LDH/haptoglobin normal.

Peripheral smear- decreased # PLT, no schistocytes

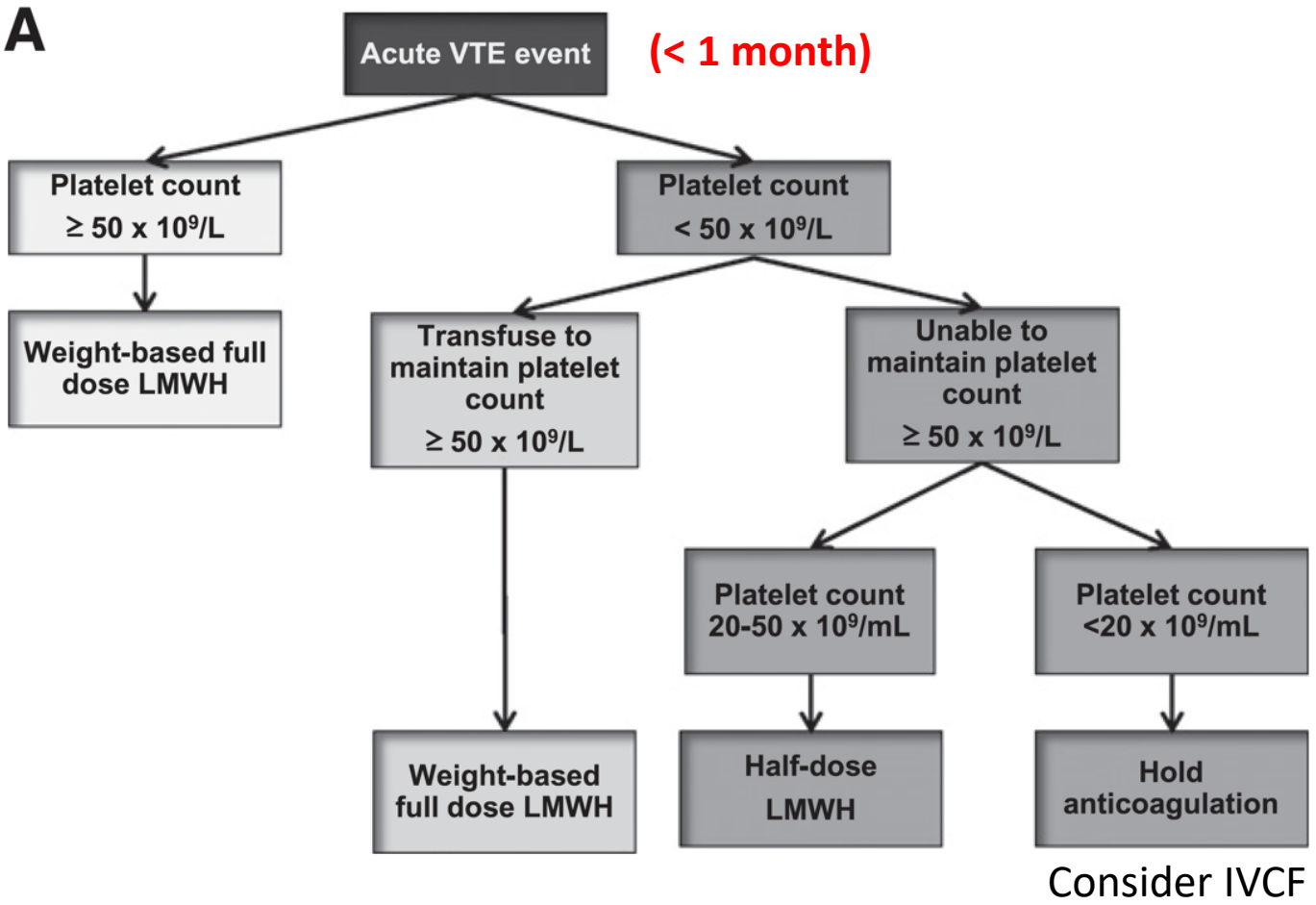
# Anticoagulation in Setting of Thrombocytopenia

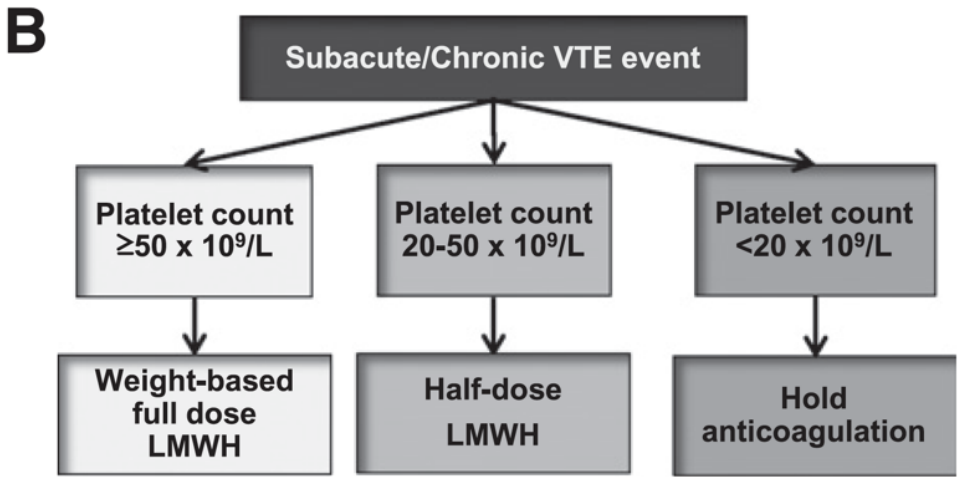
- Assess possible etiology:
  - Ex. HIT, TTP, ITP, or chemotherapy effect
- Transient or permanent?
- Expected nadir?
- Presence of other risk factors for bleeding such as advanced age or renal insufficiency.

# Thrombocytopenia and Anticoagulation

- MSKCC implemented policy in 2011
  - LMWH full dose if PLT >50K
  - LMWH ½ dose if PLT 25-50K
  - Hold LMWH PLT <25K
- Retrospective analysis 101 patients
  - 95% required modified dose (c/w 95% adherence to policy)
  - No recurrent VTE when LMWH held/reduced
  - 1 trauma associated bleed when PLT 28K

Miao ASH 2015 abstract # 429




Lee Blood 2013;122:2310-2317

# Case 8:
# Perioperative management of AC

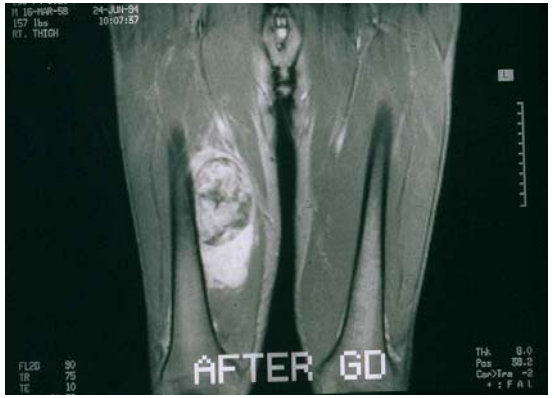
A 78 year-old male is on apixaban for unprovoked VTE 1 year ago. Needs semi-elective resection of a complex thigh mass. CrCl 50 ml/min. No other medications. Surgery thought to be of high bleeding risk due to vascular involvement

What if patient was undergoing port placement?

What if CrCL<30 ml/min?

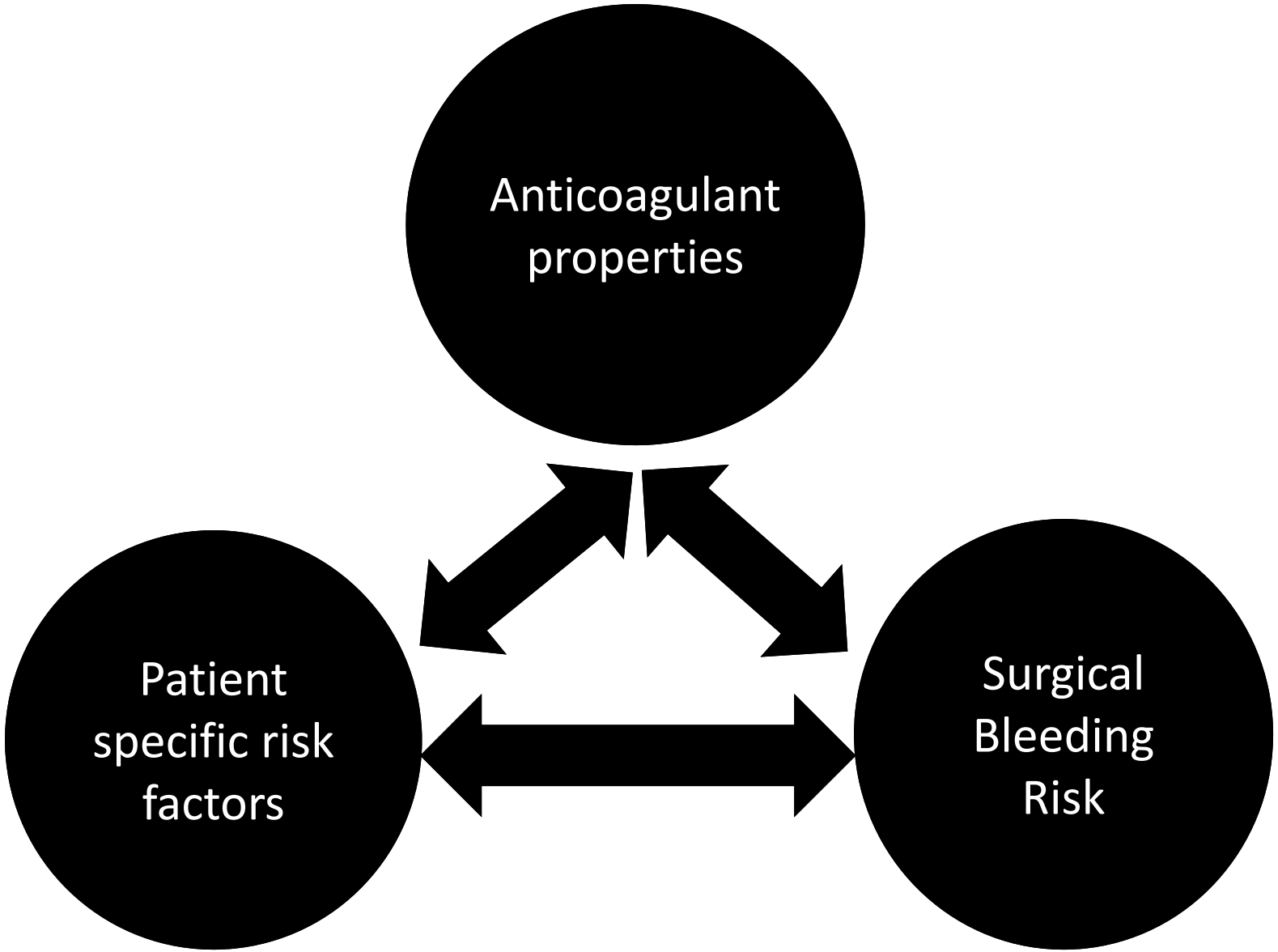
What if having teeth extracted?

What if lumbar puncture?




How long would you recommend holding Apixaban for each scenario? When would you restart?

# Factors to consider



# LOW Bleeding Risk Procedures- Do NOT require AC interruption

- Central venous catheter removal
- Dental procedures
  - Extraction of 1–2 teeth
  - Periodontal surgery
  - Incision of abscess
  - Implant positioning
- Endoscopy without surgery
- Ophthalmology
  - Cataract or glaucoma intervention
- Superficial surgery
  - Abscess incision
  - Small dermatology excisions

# LOW Bleeding Risk Procedures- REQUIRE Interruption of AC

Abdominal hernia repair

Abdominal hysterectomy

Carpal tunnel repair

Cholecystectomy

Dental procedures

Extraction of 3 or more teeth

Dilatation and curettage

Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)

Endoscopy with biopsy or tissue removal

Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endosonography without fine-needle aspiration

Hemorrhoidal surgery

Hydrocele repair

Non-coronary angiography bronchoscopy ± biopsy

Ophthalmology

Non-cataract eye surgery

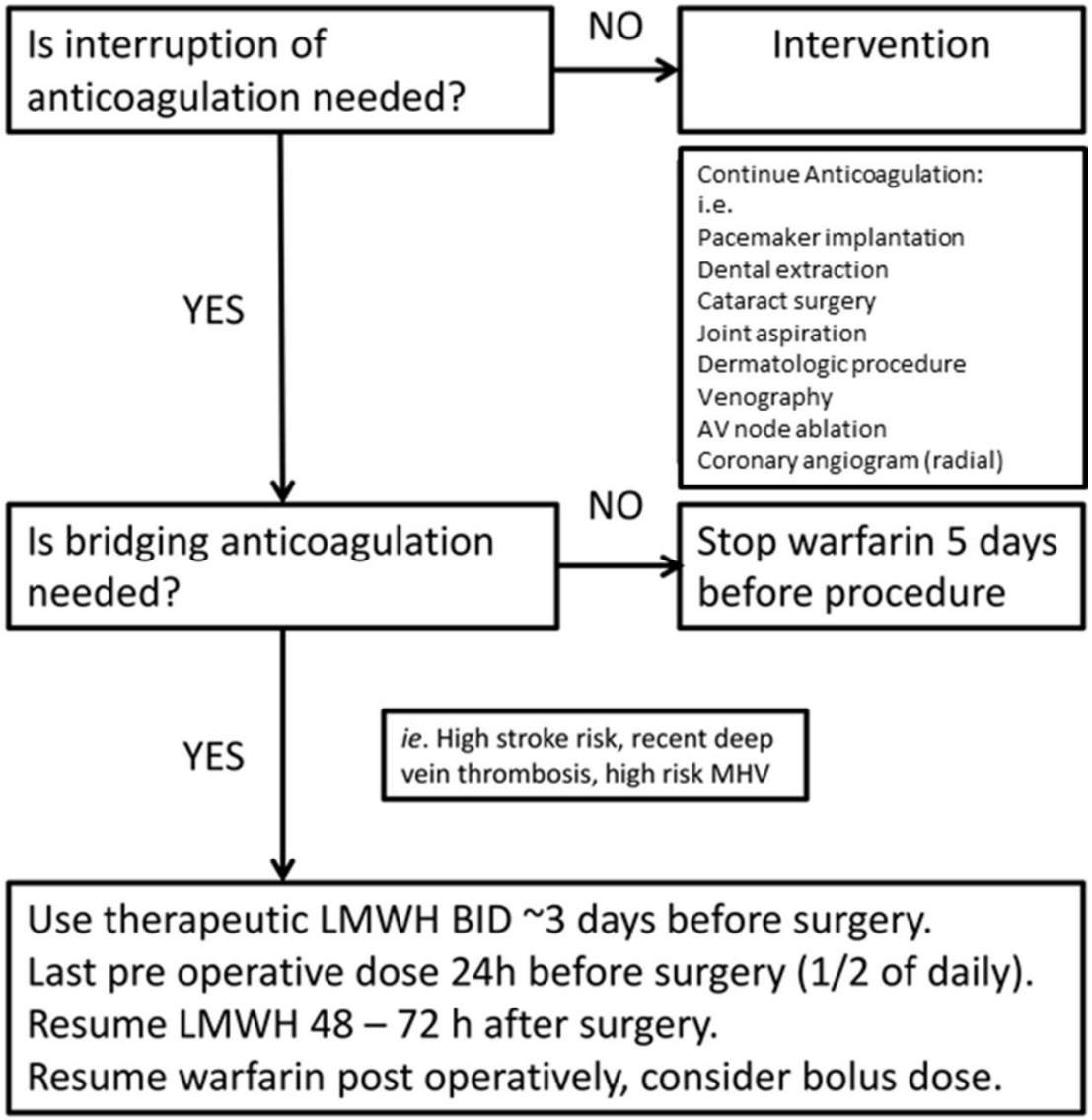
Prostate or bladder biopsy

Shoulder/foot/hand surgery and arthroscopy

# High bleeding risk procedures- REQUIRE interruption of AC

- Any major surgery (procedure duration >45 min)
- Abdominal and gastrointestinal surgeries
  - Bowel resection
- Abdominal aortic aneurysm repair
- Breast cancer surgery
- Cardiac surgeries
  - Coronary artery bypass
  - Heart valve replacement
- Cardiac procedures
  - Complex left-sided ablation (pulmonary vein isolation; VT ablation)
  - Implantation of a pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy defibrillator
- Endoscopically guided fine-needle aspiration
- Head or neck surgery
- Hepatic surgeries and procedures including liver biopsy
- Major orthopedic surgery
  - Joint replacement/arthoplasty
  - Prosthetic revision
- Miscellaneous surgeries and procedures
  - Biliary sphincterectomy
  - PEG placement
  - Pneumatic dilatation
  - Polypectomy
  - Variceal treatment
- Neurosurgeries
- Plastic surgery
  - Major reconstructive surgery
- Spinal surgeries or procedures
  - Spinal or epidural anaesthesia
  - Laminectomy
  - Lumbar diagnostic puncture
- Splenic surgeries or procedures
- Thoracic surgery
- Urologic surgeries or procedures
  - Kidney biopsy
  - Bladder resection
  - Nephrectomy
  - Transurethral prostate resection
  - Urologic cancer surgery or tumor ablation
- Vascular and general surgeries

# Suggested perioperative bridging for patients on warfarin

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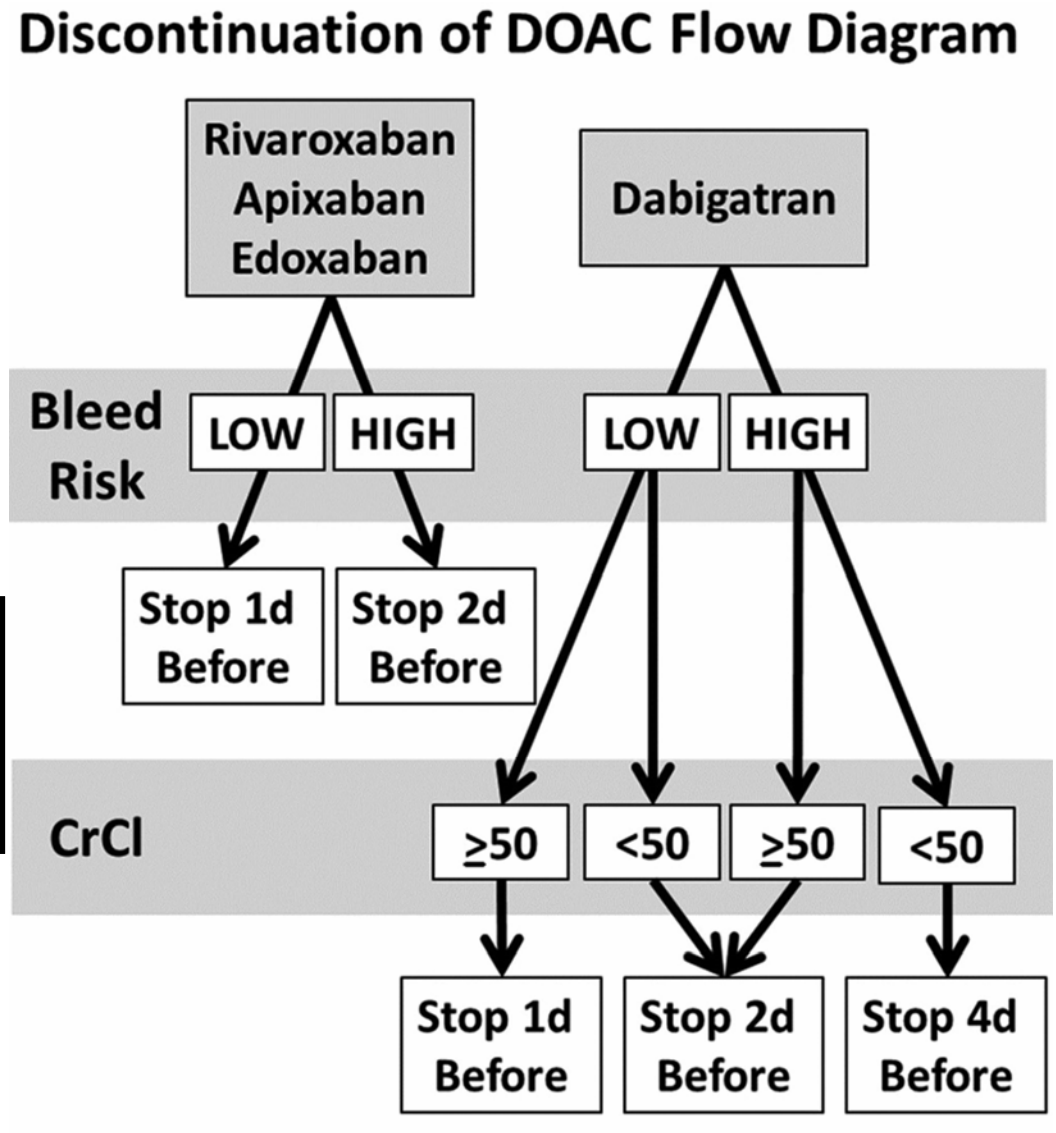
# Suggested DOAC interruption perioperatively

**Postop resumption**
Low risk- 1 day
High risk- 2-3 days

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# THANK YOU!

*Those clamorous harbingers of blood and death.*

-Wm. Shakespeare, Macbeth , Act V, Sc. VI