

Take It Knee-sy & Go With the Flow: Navigating Pharmacologic Choices for VTE Prophylaxis in Major Orthopedic Surgeries

A presentation for HealthTrust Members
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Learning Objectives

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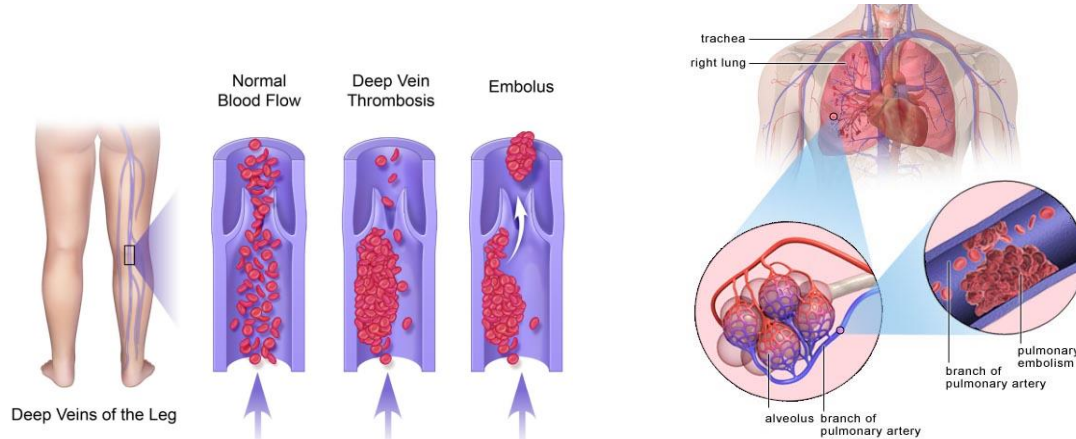
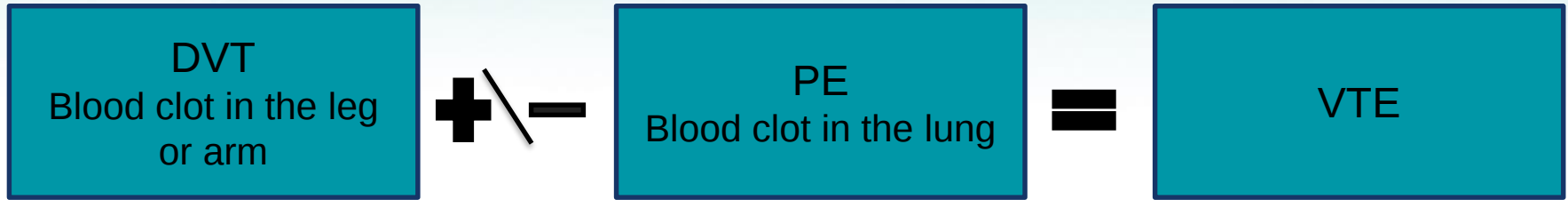
- **Identify** venous thromboembolism (VTE) risk factors for patients undergoing major orthopedic surgical procedures
- **Recall** recommended pharmacological therapies for VTE prophylaxis
- **Recognize** the appropriate duration of VTE prophylaxis and the necessary monitoring for each agent

Definitions

- DVT: deep vein thrombosis
- PE: pulmonary embolism
- VTE: venous thromboembolism
- LMWH: low molecular weight heparin
- DOAC: direct oral anticoagulant
- SQ: subcutaneous
- PO: by mouth
- TKA: total knee arthroplasty
- THA: total hip arthroplasty
- HFS: hip fracture surgery
- BMI: body mass index
- MOA: mechanism of action
- VQ- ventilation perfusion scan
- CTPA- computed tomography pulmonary angiography
- COX: cyclooxygenase
- ASH: American Society of Hematology
- AAOS: American Academy of Orthopaedic Surgeons
- ASA: aspirin
- RCT: randomized controlled trial
- PPX: prophylaxis

Venous Thromboembolism

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Source: About venous thromboembolism (Blood clots). Venous Thromboembolism (Blood Clots). Published May 15, 2024.

Signs and Symptoms of DVT/PE

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DVT

- Pain
- Swelling and/or redness
- Skin warm to the touch

PE

- Sudden onset of chest pain
- Shortness of breath
- Increased heart rate

Signs and Symptoms of DVT/PE

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DVT

- Pain
- Swelling and redness
- Skin warm to the touch

PE

• Sudden onset of chest pain

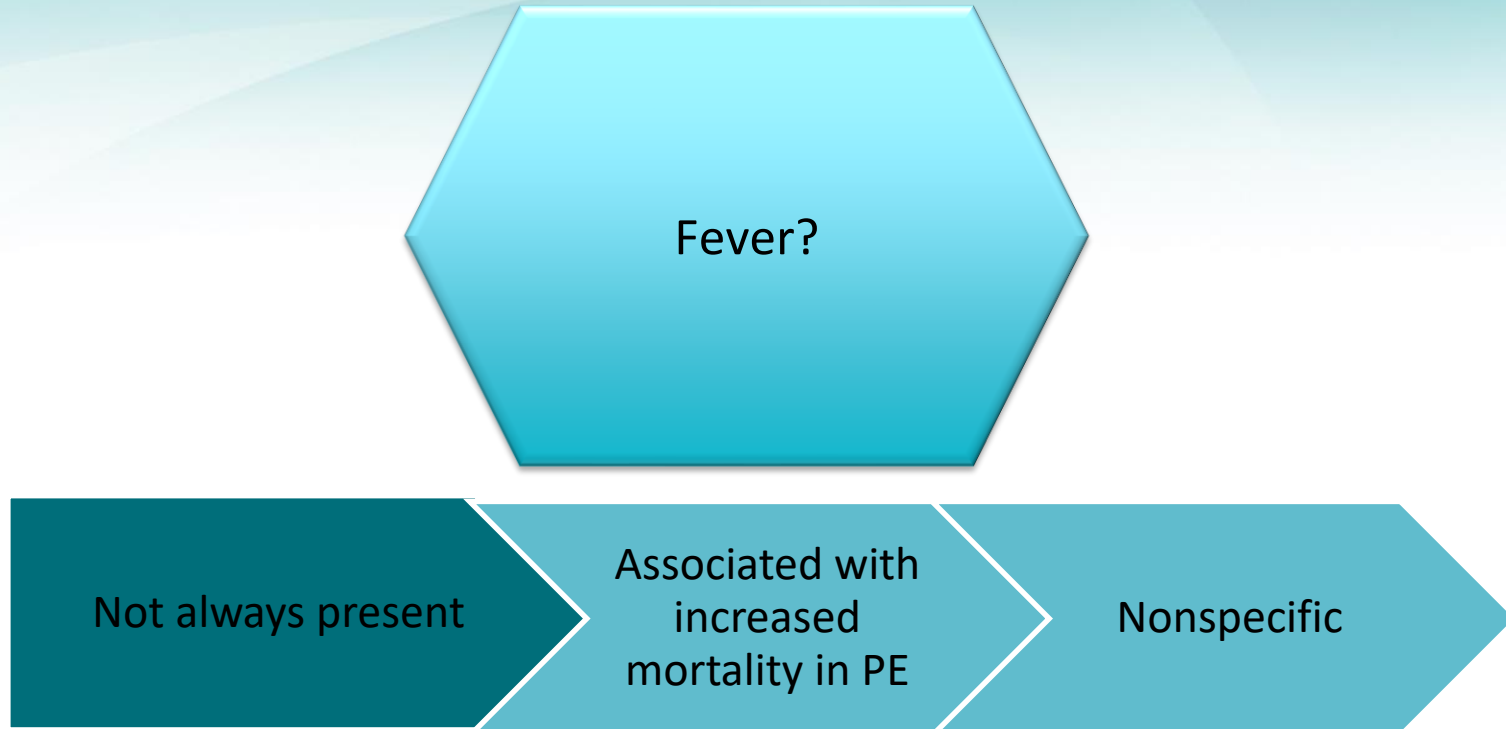
• Shortness of breath

• Increased heart rate

Fever?

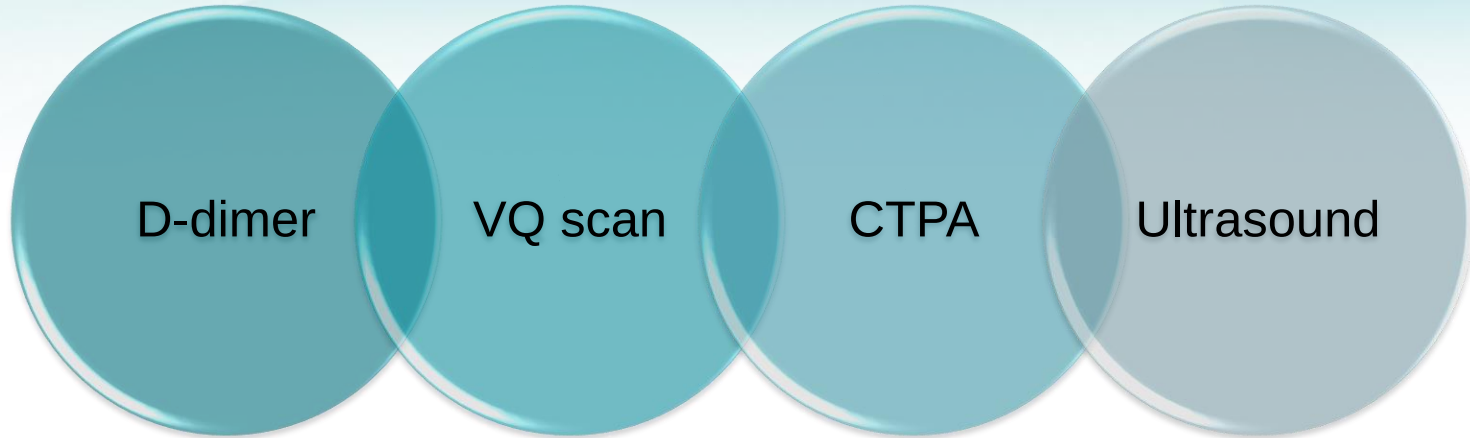
Signs and Symptoms of DVT/PE

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Diagnosis of DVT/PE

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Diagnosis of DVT/PE

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D-dimer

Definition: by-product of the blood clotting and break-down process

Measured by blood sample and helpful to rule out PE/DVT

Sensitive but not specific

- Value <0.5 considered negative result

Should only be used in patients with low suspicion for PE/DVT due to incidence of false negatives

VQ scan

Normal



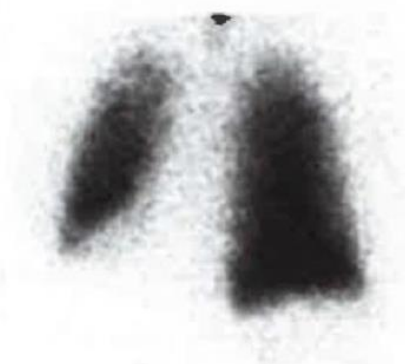
Aerosol, Posterior View

COPD



Aerosol, Posterior View

High Prob. for P.E.



Aerosol, Posterior View



Perfusion, Posterior View



Perfusion, Posterior View

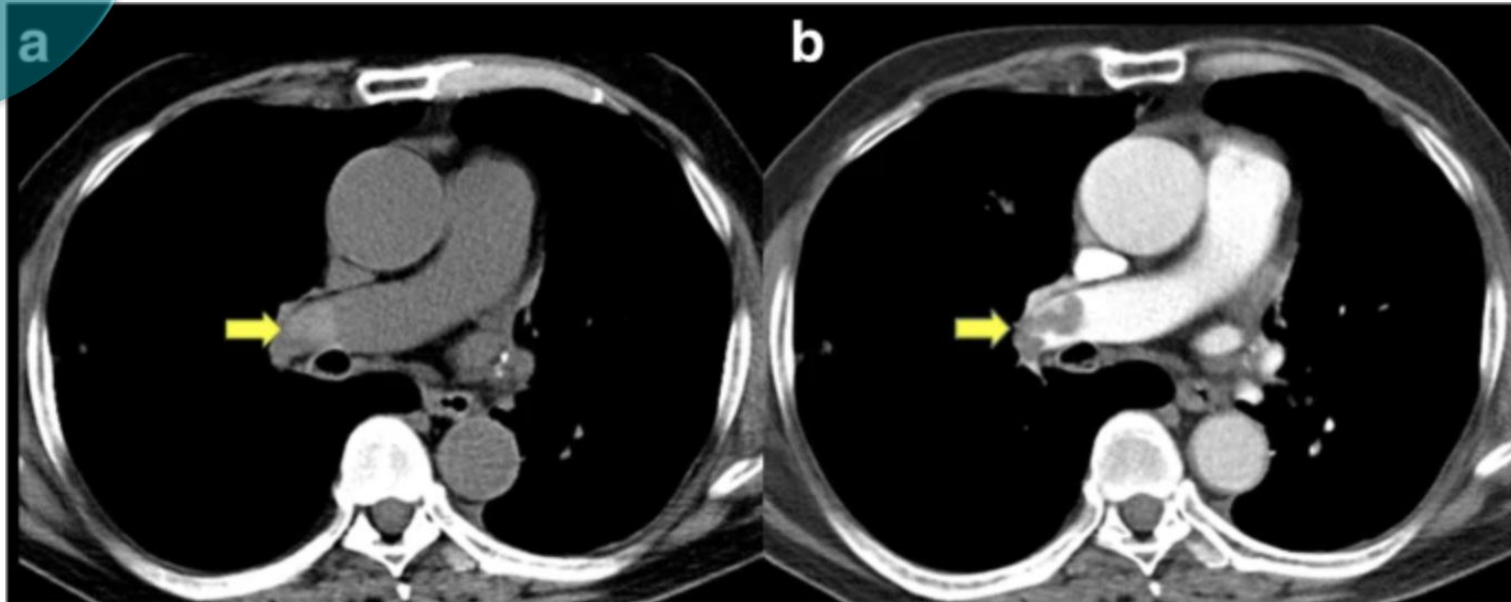


Perfusion, Posterior View

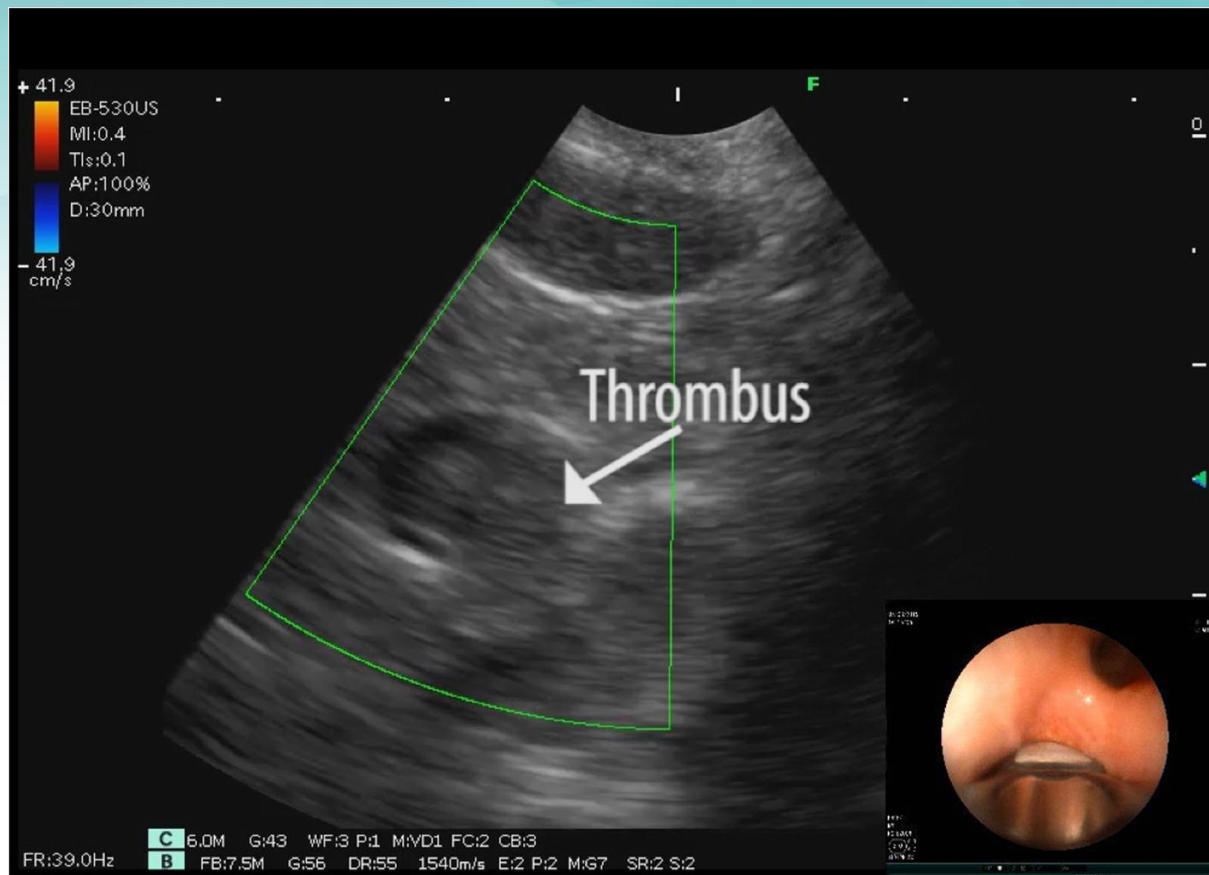
Note the peripheral penetration on all aerosol images, especially COPD.

Images courtesy of Alan Waxman, M.D., Cedars-Sinai Medical Center, Los Angeles

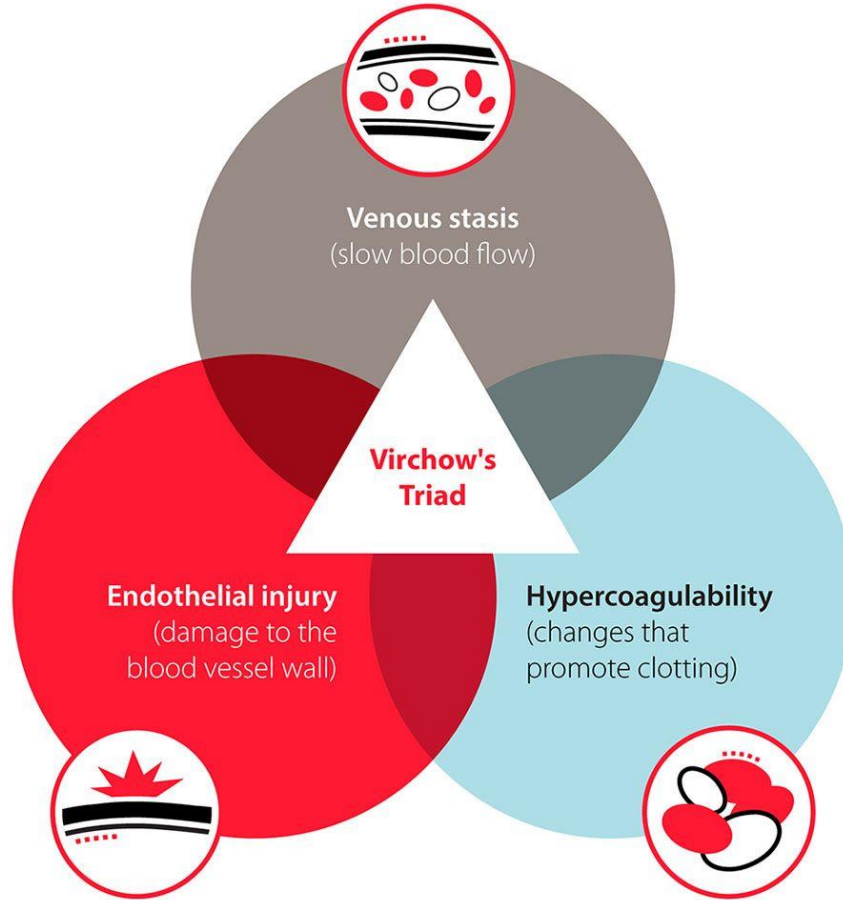
CTPA



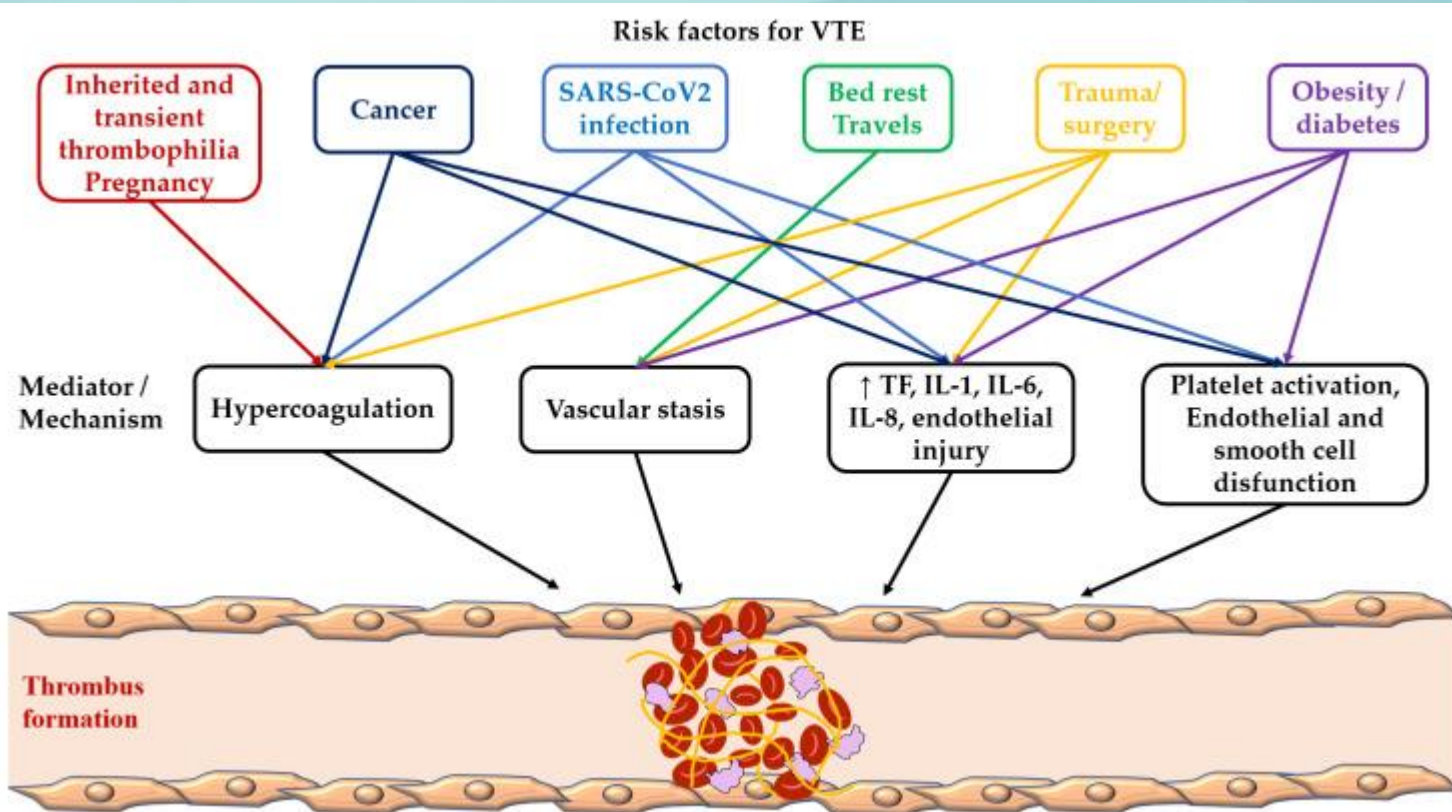
Ultrasound



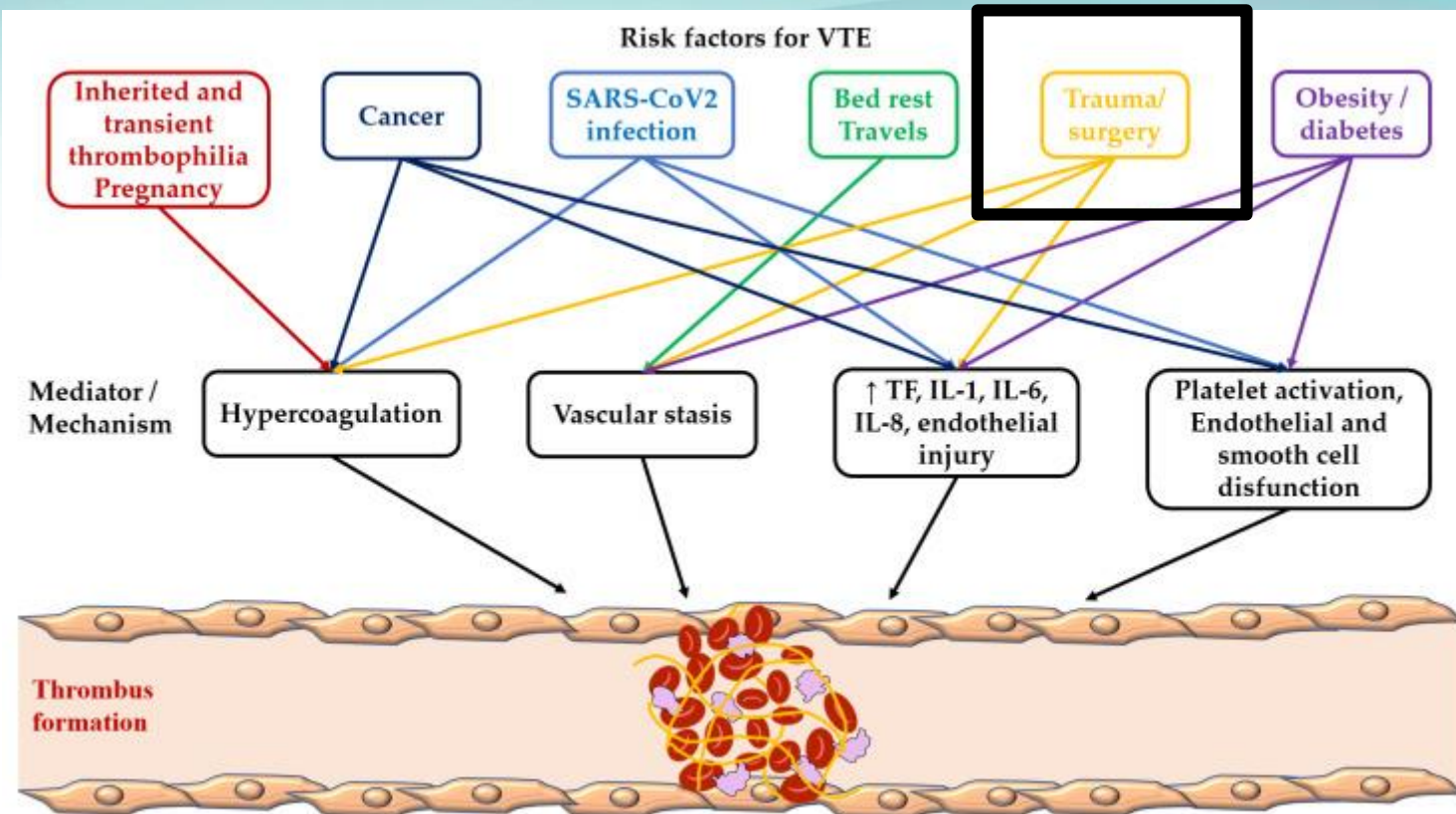
Pathophysiology of VTE



VTE Risk Factors



VTE Risk Factors



Major Orthopedic Surgeries

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Total Hip Arthroplasty

Total Knee Arthroplasty

Hip Fracture Surgery

Incidence of VTE in Major Orthopedic Surgeries

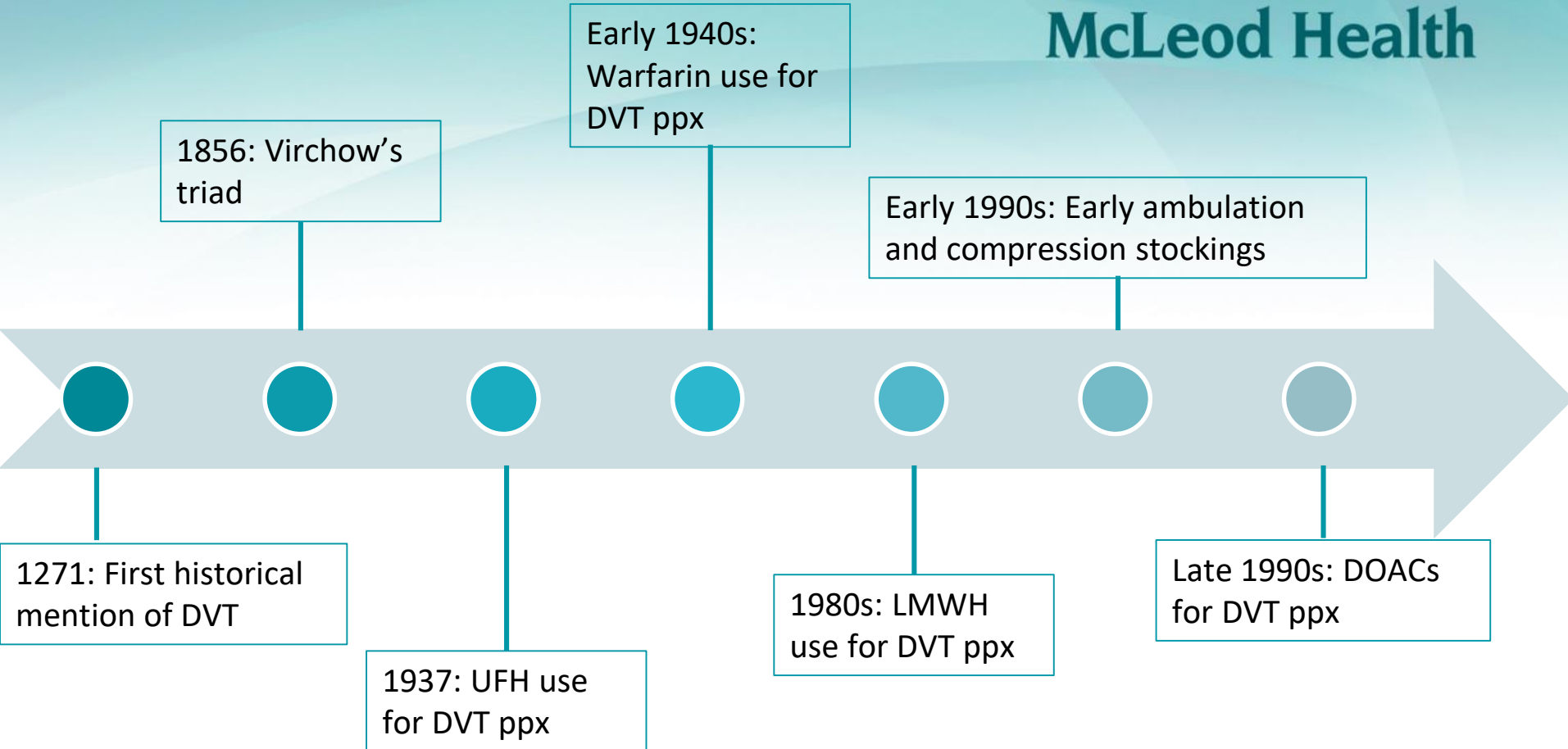
Incidence of DVT

- 10%-40% in hospitalized patients
- 40%-60% in patients undergoing major orthopedic surgery

Occurrence of Fatal PE

- 0.1%-0.8% after elective surgery
- 3.0% after elective hip replacement
- 7.0% after hip fracture surgery

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AAOS Clinical Practice Guideline Summary

Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty

AAOS Guidelines 2011

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Patients undergoing elective hip or knee arthroplasty, and who are not at elevated risk for VTE (besides risk of surgery alone)

- Suggest the use of pharmacological agents and/or mechanical compressive devices

Patients undergoing elective hip or knee arthroplasty and who have had a previous VTE

- Suggest the use of pharmacological prophylaxis and mechanical compressive devices

Unable to recommend specific agents due to evidence at that time being unclear with which prophylactic strategy is/are optimal or suboptimal



CHEST

Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Prevention of VTE in Orthopedic Surgery Patients

**Antithrombotic Therapy and Prevention of Thrombosis,
9th ed: American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines**

*Yngve Falck-Ytter, MD; Charles W. Francis, MD; Norman A. Johanson, MD;
Catherine Curley, MD; Ola E. Dahl, MD; Sam Schulman, MD, PhD;
Thomas L. Ortel, MD, PhD; Stephen G. Pauker, MD; and Clifford W. Colwell Jr, MD*

Patients undergoing THA or TKA

- use of one of the following for minimum 10-14 days rather than no antithrombotic prophylaxis: **LMWH**, fondaparinux, **apixaban**, dabigatran, **rivaroxaban**, LDUH, adjusted-dose VKA, **aspirin** or an IPCD

Patients undergoing HFS

- recommend use of one of the following rather than no antithrombotic prophylaxis for minimum 10-14 days: **LMWH**, fondaparinux, LDUH, adjusted-dose VKA, **aspirin** or an IPCD

Patients undergoing major orthopedic surgery (THA, TKA, HFS) + **receiving LMWH** as thromboprophylaxis

- recommend **starting either 12 h or more preoperatively or 12 h or more postoperatively**

Suggest extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days

Patients **who decline or are uncooperative with injections** or an IPCD

- recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable)

American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients

- Patients undergoing THA or TKA suggest using ASA or anticoagulants
- In patients which anticoagulants are used, recommend using DOACs over LMWH
- In patients that a DOAC is not used, suggest using LMWH over warfarin or UFH
- In patients undergoing hip fracture repair (HFR), suggest using LMWH or UFH

Historical Disagreement: CHEST vs AAOS

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CHEST

- RCTs and meta-analysis of RCTs, ≥ 10 per treatment group
- Randomized data only
- All diagnosed DVTs or PE

AAOS

- RCTs (≥ 10 per group) and prospective studies (≥ 100 per group)
- Observational data only
- Diagnosed symptomatic PE

Non-Pharmacologic Methods of VTE Prophylaxis

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Intermittent
Pneumatic
Compression Device



VTE Prophylaxis Pharmacologic Therapies

ASA

Warfarin

DOACs

Unfractionated heparin

Fondaparinux

LMWH

VTE Prophylaxis Pharmacologic Therapies

ASA

Warfarin

DOACs

Unfractionated heparin

Fondaparinux

LMWH

Mechanism of Action

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Oral Direct Factor Xa Inhibitors

- Apixaban, rivaroxaban

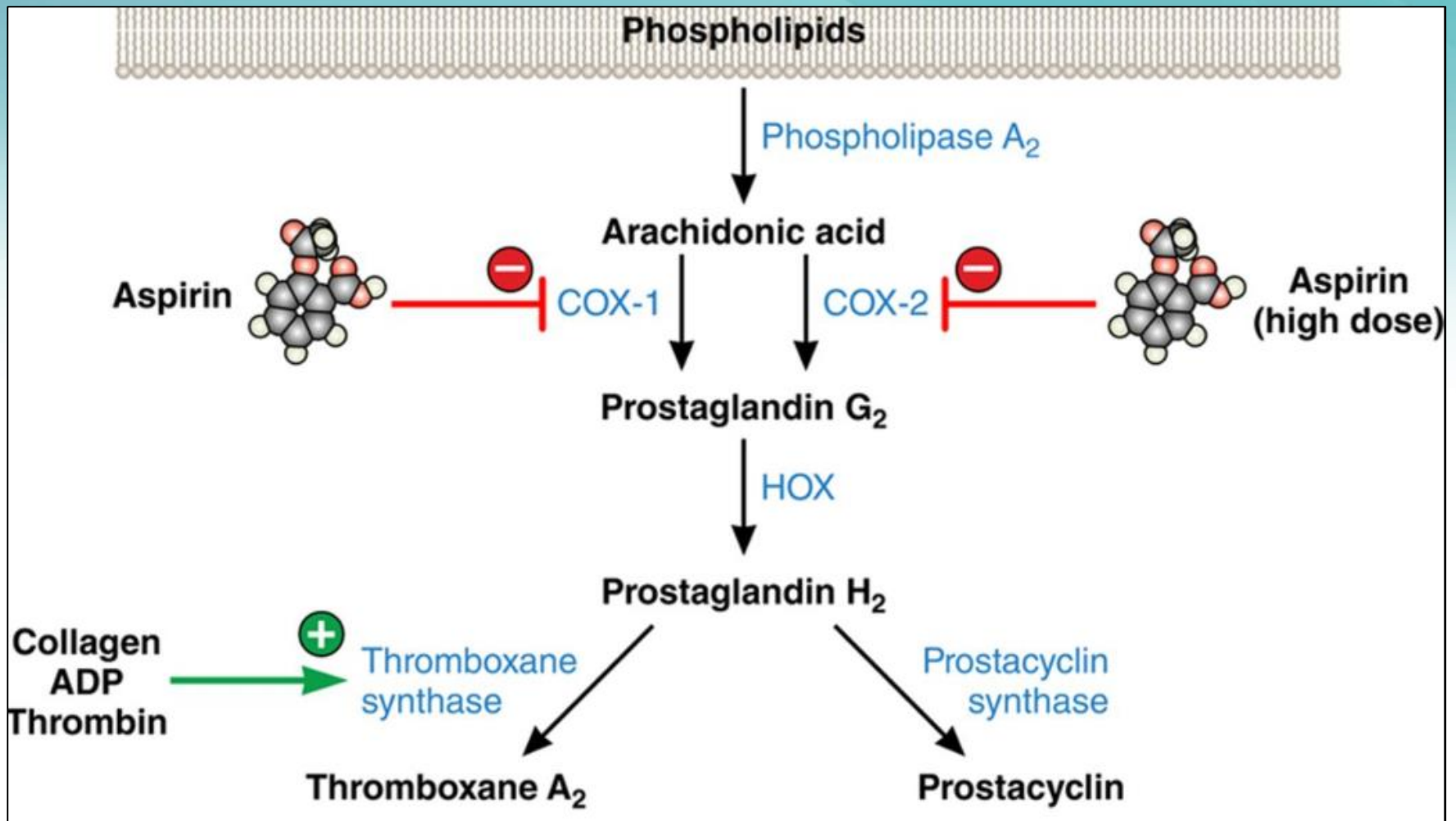
Indirect Thrombin Inhibitors

- LMWH (enoxaparin)

COX Inhibitor

- Aspirin

Aspirin



- **Indication:** VTE prophylaxis for total hip or knee arthroplasty
 - Begin postoperative prophylaxis with rivaroxaban or LMWH, then discontinue therapy after 5 days for TKA or after 5-10 days for THA and initiate aspirin 81 mg once daily
- **Renal dose adjustments:** no dose adjustments when using for antiplatelet effects
- **Duration:** minimum of 10-14 days, but can be extended for up to 35 days
 - Total knee arthroplasty: usually 10-14 days, but 35 days if not fully ambulatory
 - Total hip arthroplasty: continue through postop day 35

Aspirin

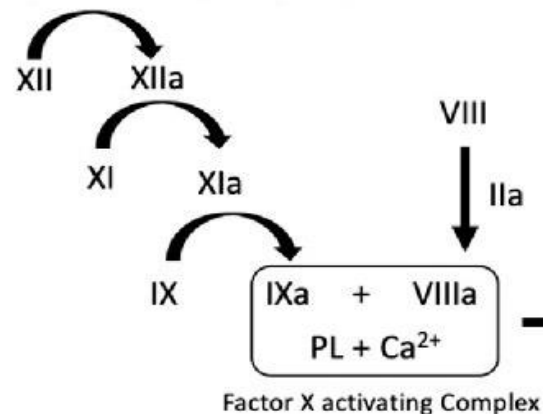
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Study	Methods	N	Treatment	Outcomes
PEP trial (2000)	Randomized, placebo-controlled trial	N=13,356 HFS N=2,648 THA N= 1,440 TKA	ASA 160 mg PO daily or placebo	Low dose ASA reduces the risk of PE and symptomatic DVT for HFS and THA/TKA
ASA vs warfarin for VTE prophylaxis (TKA/THA) (1996)	Prospective, randomized trial	N=388	ASA 325 mg PO BID or warfarin	ASA and warfarin are equivalent in VTE prophylaxis
ASA vs rivaroxaban vs LMWH for DVT prophylaxis after TKA (2014)	Prospective, randomized controlled trial	N= 324	Rivaroxaban 10 mg PO daily Enoxaparin 40 mg SQ daily ASA 100 mg PO daily	No significant difference was found in DVT prophylaxis between enoxaparin & ASA and ASA could be consider as a multimodal therapy

**LMWH
(enoxaparin)**

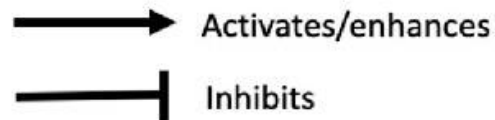
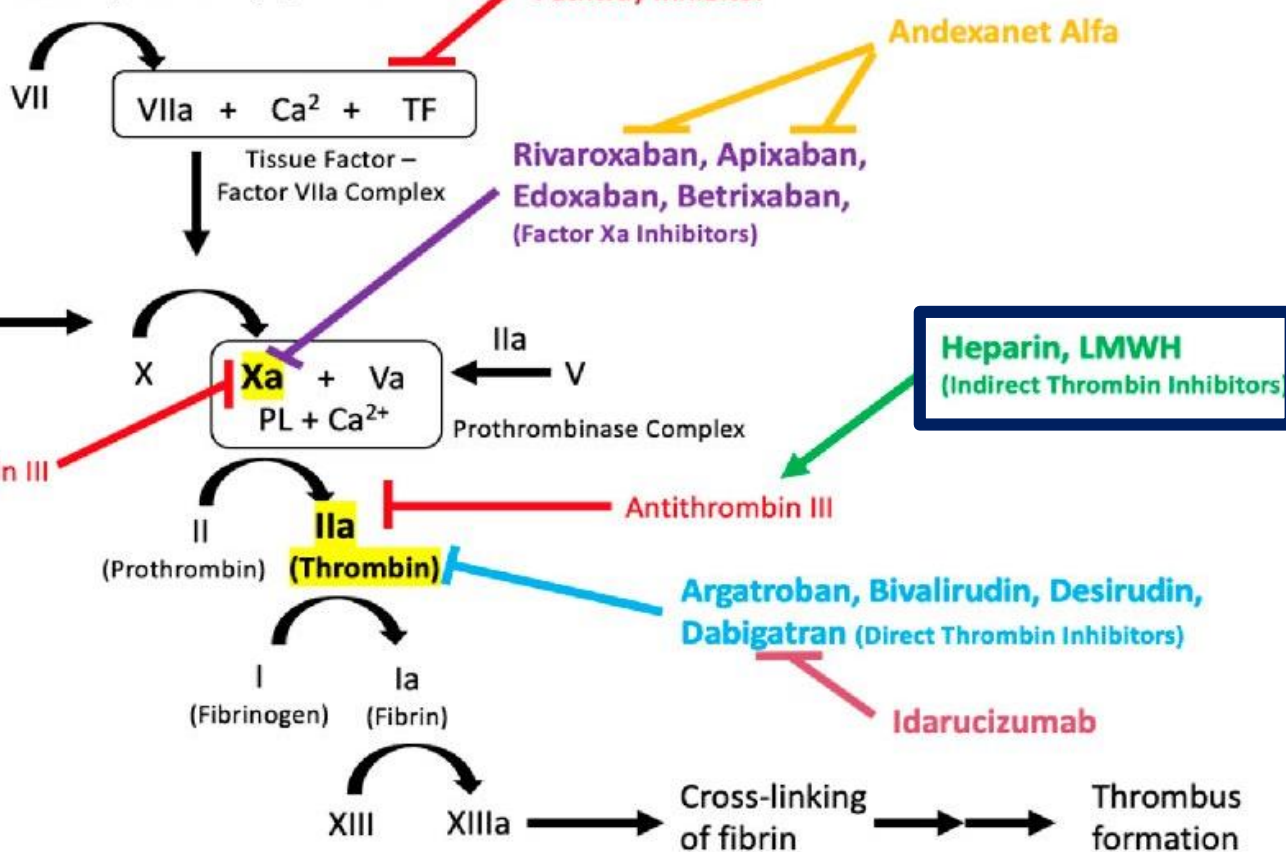
Intrinsic Pathway

Initiated by exposed endothelium → exposure to a negatively charged surface



Extrinsic Pathway

Initiated by tissue factor (factor III) → caused by vascular injury or trauma



LMWH (enoxaparin)

- VTE prophylaxis dose: (SQ) 40 mg once daily **OR** 30 mg every 12 hours
 - Initial dose administered ≥ 12 hours preoperatively or ≥ 12 hours postoperative once hemostasis is achieved
- BMI dose adjustments:
 - ≥ 40 kg/m²: 40 mg every 12 hours OR 0.5 mg/kg every 12 hours (use actual body weight)
 - ≥ 50 kg/m²: consider 60 mg every 12 hours OR 0.5 mg/kg every 12 hours (use actual body weight)
- Renal dose adjustments:
 - CrCl ≤ 30 ml/min: (SQ) 30 mg once daily
- Duration:
 - Total knee arthroplasty: usually 10-14 days, but 35 days if not fully ambulatory
 - Total hip arthroplasty or hip fracture surgery: minimum 10-14 days can be extended up to 35 days

LMWH (enoxaparin)

Study	Methods	N	Treatment	Outcomes
Enoxaparin to prevent DVT in patients undergoing THA (1986)	Randomized, double-blind, controlled trial	N=100	Enoxaparin 30 mg SQ every 12 hours or placebo	Enoxaparin is effective and safe in reducing DVTs in THA
Enoxaparin to prevent DVT after TKA (1992)	Randomized, double-blind trial	N=131	Enoxaparin 30 mg SQ every 12 hours or placebo	Enoxaparin is safe and effective for DVT prophylaxis after TKA
Enoxaparin vs warfarin for VTE prophylaxis in TKA (1996)	Randomized, double-blind controlled trial	N= 670	Enoxaparin 30 mg SQ every 12 hours Warfarin PO titrated to INR 2.0-3.0	Enoxaparin is more effective in VTE prevention following TKA compared to warfarin

Study	Methods	N	Treatment	Outcomes
LMWH (Fragmin) for DVT prophylaxis in hip fracture patients (1992)	Prospective, randomized, double blind trial	N=82	Fragmin 5000 units SQ once daily or placebo	LMWH (Fragmin) offers effective and safe DVT prophylaxis in hip fracture surgery

DOACs

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Apixaban (Eliquis)

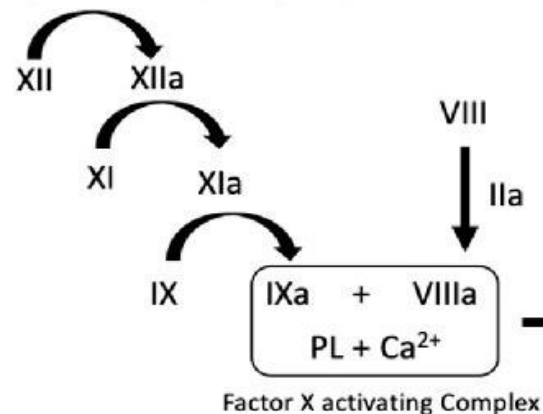
Rivaroxaban (Xarelto)

Dabigatran (Pradaxa)

Edoxaban (Savaysa)

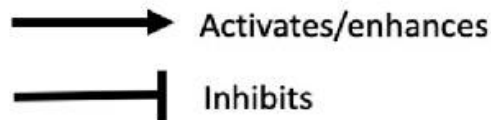
Intrinsic Pathway

Initiated by exposed endothelium → exposure to a negatively charged surface



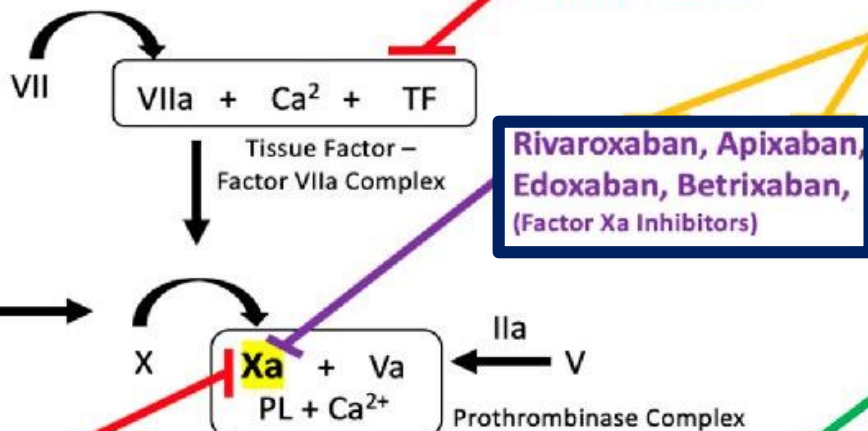
Fondaparinux
(Indirect Factor Xa Inhibitor)

Antithrombin III



Extrinsic Pathway

Initiated by tissue factor (factor III) → caused by vascular injury or trauma



Rivaroxaban, Apixaban, Edoxaban, Betrixaban, (Factor Xa Inhibitors)

Tissue Factor Pathway Inhibitor

Andexanet Alfa

Heparin, LMWH
(Indirect Thrombin Inhibitors)

Antithrombin III

Argatroban, Bivalirudin, Desirudin, Dabigatran (Direct Thrombin Inhibitors)

Idarucizumab

Cross-linking of fibrin → Thrombus formation

Apixaban (Eliquis)

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- VTE prophylaxis dose: (PO) 2.5 mg twice daily
 - Initial dose administered 12-24 hours postoperatively
- BMI dose adjustments: none
- Renal dose adjustments: none
- Duration: minimum of 10-14 days, but can be extended for up to 35 days
 - Total knee arthroplasty: usually 10-14 days
 - Total hip arthroplasty: ~30 days

Apixaban (Eliquis)

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Study	Methods	N	Treatment	Outcomes
ADVANCE-1 (knee) (2009)	Randomized, double-blind trial	N= 3,184	Apixaban 2.5 mg PO BID Enoxaparin 30 mg SQ every 12 hours	Apixaban may have potential to be effective VTE prophylaxis with low risk of bleeding
ADVANCE-2 (knee) (2010)	Randomized double-blind, phase III trial	N= 3,009	Apixaban 2.5 mg PO BID Enoxaparin 40 mg SQ daily	Apixaban is safe and effective for VTE prevention following knee surgery
ADVANCE-3 (hip) (2010)	Randomized double-blind, phase III trial	N= 5,332	Apixaban 2.5 mg PO BID Enoxaparin 40 mg SQ daily *continued 35 days after procedure	Apixaban is safe and effective for VTE prevention following hip surgery
APROPOS (knee) (2007)	Randomized, eight arm, parallel group, multi center, Phase II trial	N=1,217	Enoxaparin 30 mg SQ q12h Warfarin PO titrated to INR 1.8-3.0 Apixaban 5mg, 10mg or 20 mg PO daily or twice daily	Apixaban administered at 2.5 mg PO BID after TKA, exhibits benefit-risk profile comparable to standards of care at that time

Rivaroxaban (Xarelto)

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- VTE prophylaxis dose: (PO) 10 mg once daily
 - Initial dose administered 6-10 hours postoperative or once hemostasis is achieved
 - *low risk of VTE undergoing unilateral THA or TKA: 10 mg once daily for 5 days, then switch to aspirin for an additional 30 days for THA or 9 days for TKA
- BMI dose adjustments: none
- Renal dose adjustments: CrCl <15 mL/min - avoid use
- Duration: minimum of 10-14 days, but can be extended for up to 35 days
 - Total knee arthroplasty: usually 10-14 days
 - Total hip arthroplasty: ~30 days

Rivaroxaban (Xarelto)

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Study	Methods	N	Treatment	Outcomes
RECORD-1 (hip) (2008)	Randomized, double-blind phase III study	N= 4,433	Rivaroxaban 10 mg PO daily Enoxaparin 40 mg SQ daily	Rivaroxaban was significantly more effective than enoxaparin for VTE prophylaxis w/out significant increase of major bleeding events
RECORD-2 (hip) (2008)	Randomized, double-blind study	N=2,457	Rivaroxaban 10 mg PO daily x31-39 days Enoxaparin 40mg SQ daily x10-14 days	Extended VTE prophylaxis with rivaroxaban was more effective than short term prophylaxis with enoxaparin following THA
RECORD-3 (knee)(2008)	Randomized, double-blind study	N= 2,459	Rivaroxaban 10 mg PO daily Enoxaparin 40 mg SQ daily	Rivaroxaban is more effective than enoxaparin for VTE prophylaxis following TKA
RECORD-4 (knee)(2009)	Multicenter, randomized, double-blind, phase III study	N=3,034	Rivaroxaban 10 mg PO daily Enoxaparin 30 mg SQ every 12 hours	Rivaroxaban is safe and effective in preventing major VTE in patients undergoing TKA

Sources: *N Engl J Med.* 2008;358(26):2765-2775, *Lancet.* 2008;372(9632):31-39., *N Engl J Med.* 2008;358(26):2776-2786., *Lancet.* 2009;373(9676):1673-1680.

Signs/Symptoms of Bleeding

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- Gums bleeding (Gingivitis)
- Nose bleeds (Epistaxis)
- Bruising (Ecchymosis)
- Bloody urine
- Bloody/tarry stools (Melena)
- Vomiting blood or coffee ground emesis (Hematemesis)

Bleeding Risk Assessment

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Previous major bleeding (+
bleeding risk similar to
current)

Severe Renal Failure

Concomitant antiplatelet
agent

Surgical factors

- revision surgery, extensive surgical dissection, bleeding complications during procedure

Time to Brace Ourselves for the Most Recent Literature



Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

Anderson DR, *et al.* 2018

Study Design and Methods

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Multicenter, double-blind, randomized controlled trial at 15 university-affiliated health centers in Canada

Included patients undergoing unilateral primary or revision hip or knee arthroplasty

Excluded patients with hip or lower limb fracture during previous 3 months and metastatic cancer

Interventions: rivaroxaban 10 mg PO once daily for 5 days, patients were then randomized to receive either continue rivaroxaban 10 mg daily or ASA 81 mg PO daily

Patients undergoing TKA were continued on the intervention for 9 days, patients undergoing THA were continued for 30 days

Baseline Characteristics

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Total of 3424 patients were included in the primary analysis

Majority of patients were undergoing primary surgery (~90% in both groups)

Risk factors for VTE were balanced between groups

Primary Effectiveness Outcome

- Symptomatic proximal DVT or PE
 - Developed in 0.64% in the ASA group vs 0.70% in the rivaroxaban group
 - ASA was found to be non-inferior ($p < 0.001$) but not superior ($p = 0.84$)

Primary Safety Outcome

- Major bleeding events
 - Occurred in 0.47% in the ASA group and 0.29% in the rivaroxaban group ($p = 0.42$)

Author's Conclusions

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Aspirin was not significantly different from rivaroxaban for the prevention of clinically important, symptomatic events of proximal DVT or PE after THA or TKA with an initial 5-day postoperative course of rivaroxaban

Presenter's Critique

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Strengths

- Large sample size
- Randomized, double blind study

Limitations

- Mean body mass index of patients in both groups was $\sim 30 \text{ kg/m}^2$

Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in
Patients Undergoing Hip or Knee Arthroplasty:
The CRISTAL Randomized Trial.

Sidhu VS, et al. 2022

CRISTAL Trial

McLeod Health

- Aspirin monotherapy vs enoxaparin for prophylaxis of symptomatic VTE after THA or TKA
- Cluster-randomized, crossover, registry-nested trial across 31 hospitals in Australia
 - N= 9,711
 - Aspirin 100 mg PO daily
 - Enoxaparin 40 mg subcutaneously daily
- **Duration:** 35 days after THA or 14 days after TKA
- **Primary outcome:** symptomatic VTE within 90 days of surgery
- **Secondary outcomes:** joint related readmission, joint related reoperation, major bleeding events (resulting in readmission, reoperation or death) and mortality within 90 days, joint-related reoperation within 6 months of surgery, and adherence rates as assessed by audits

CRISTAL Trial

- **Primary outcome:** symptomatic VTE within 90 days of surgery
 - 187 of 5416 patients (3.45%) in the aspirin group
 - 69 of 3787 patients (1.82%) in the enoxaparin group

Secondary Outcome	Aspirin	Enoxaparin	P value
Major bleeding events w/in 90 days	0.31%	0.40%	0.75
Joint related readmission w/in 90 days	2.4%	2.3%	0.13
Joint related reoperation w/in 90 days	2.1%	1.9%	0.10
Joint related reoperation w/in 6 months	3.4%	3.4%	0.75
Death within 90 days	0.07%	0.05%	0.36
Drug adherence	85%	86%	0.85

Authors conclusions

- Among patients undergoing THA or TKA for osteoarthritis, aspirin compared to enoxaparin resulted in a significantly higher rate of symptomatic VTE within 90 days

Personal Conclusions

- Further studies are needed to assess the role of ASA vs enoxaparin in preventing clinically relevant VTE such as above the knee DVT and PE

Aspirin Dose and Venous Thromboembolism Prevention after Total Hip and Knee Arthroplasty

Cleveland Clinic, 2017

Study Methods

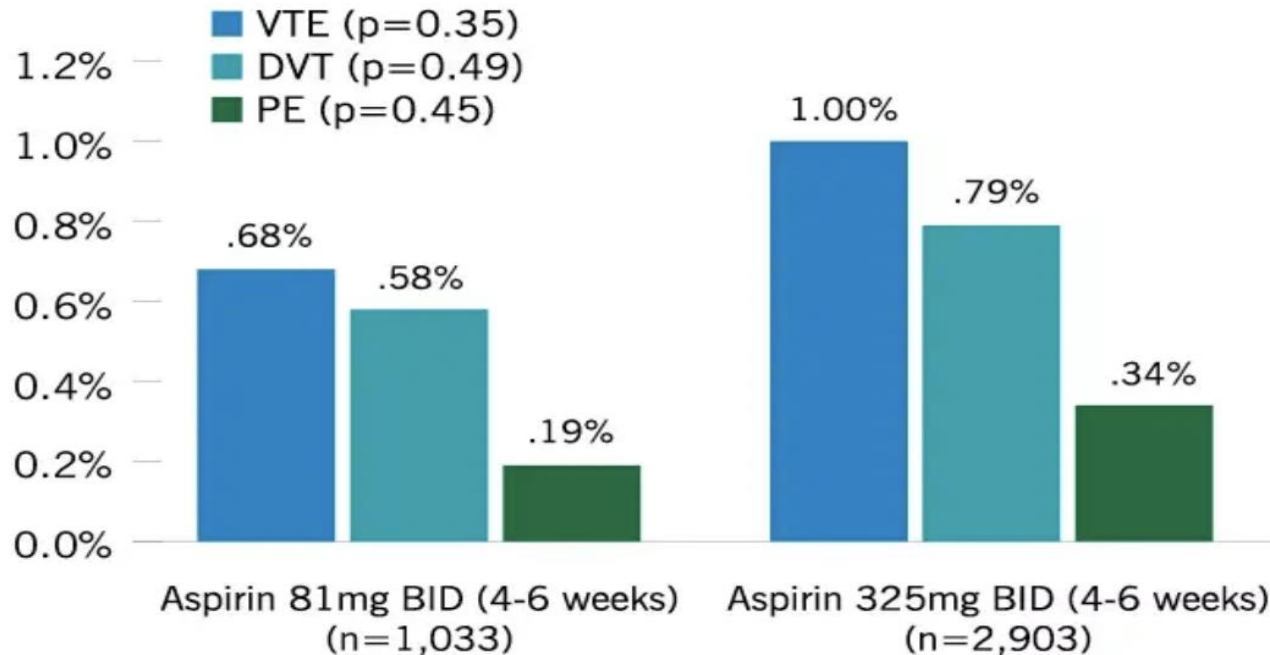
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- Retrospective review of 16,000 medical records for primary total joint arthroplasty patients between 2012 and 2016
- 9,602 patients identified who received enteric-coated aspirin twice daily after surgery for 4-6 weeks
 - N= 2,360 patients received 81 mg (low dose group)
 - N= 7,242 patients received 325 mg (high-dose group)
- **Outcomes:** complications collected within 90 days after surgery were VTEs, bleeding (GI and wound bleeding), and mortality

Results of THA

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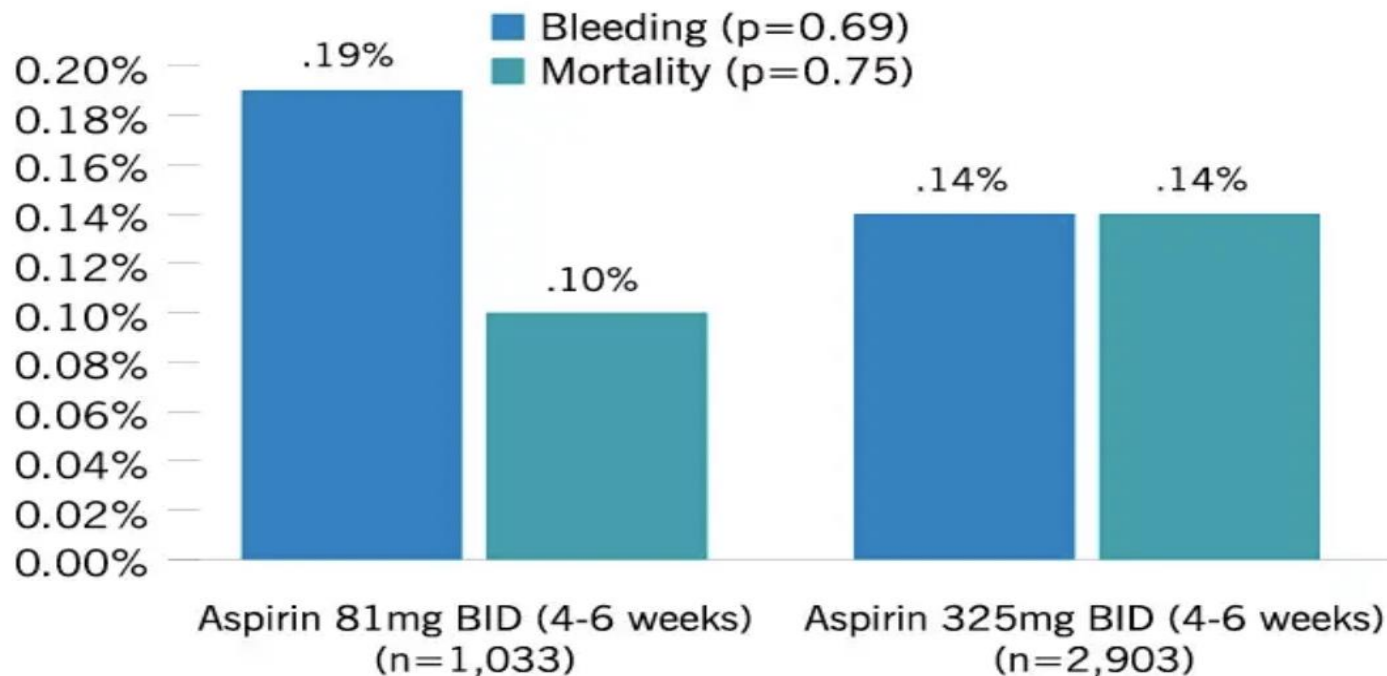
VTE Incidence following THA



Results of THA

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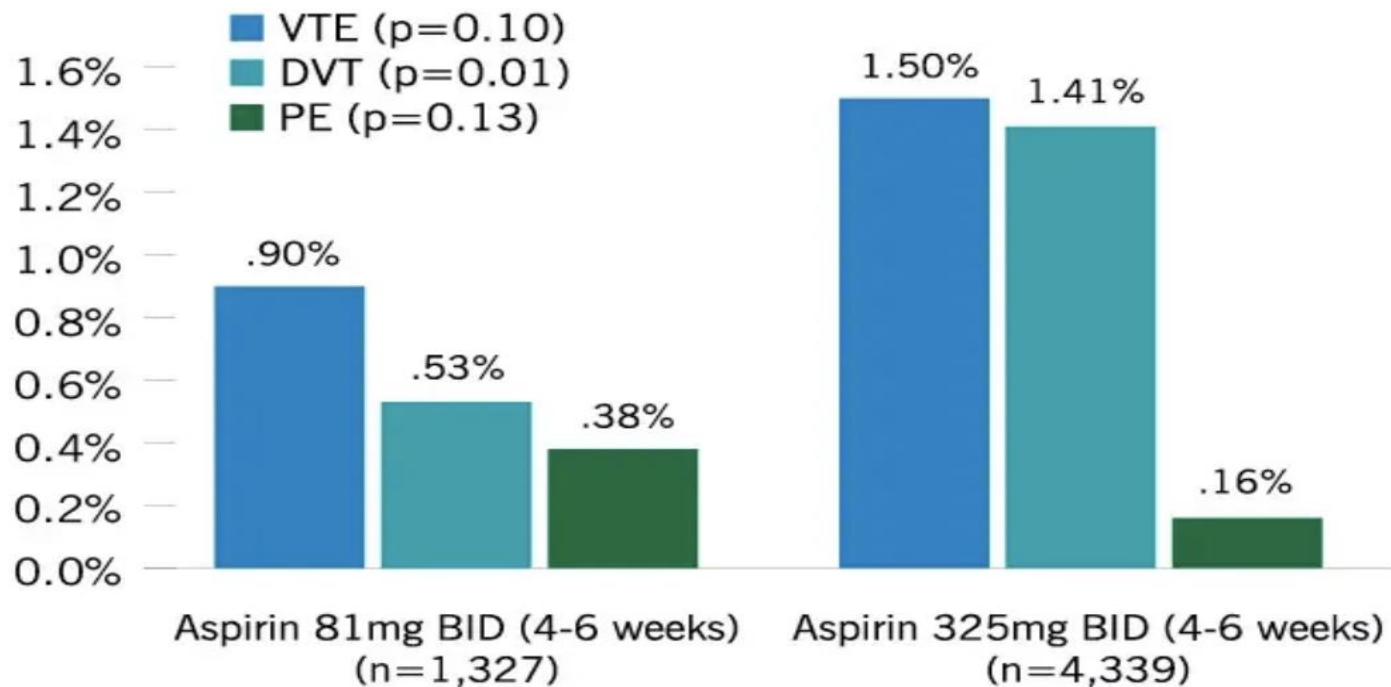
Bleeding and Mortality after THA



Results of TKA

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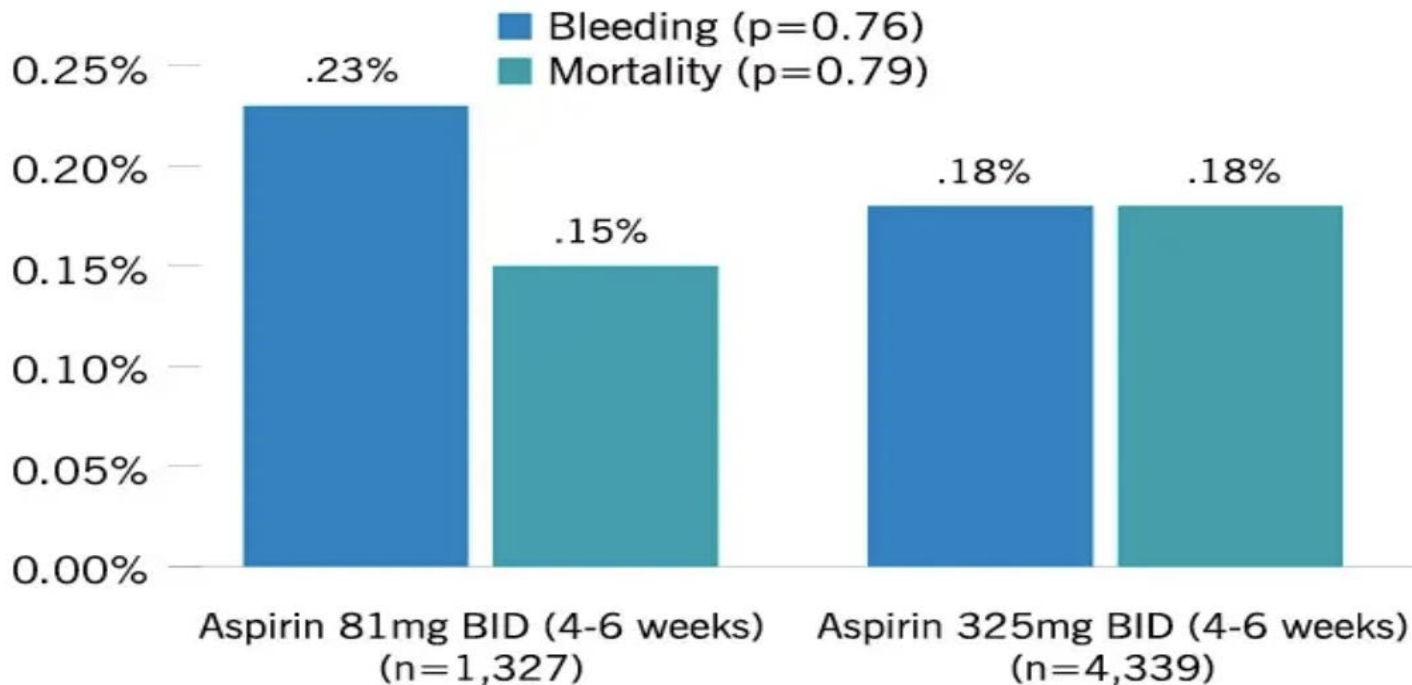
VTE Incidence following TKA



Results of TKA

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Bleeding and Mortality after TKA



Author's Conclusions

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- Overall, no statistical difference in VTE incidence following TKAs/THAs in low-dose versus high-dose aspirin groups.
- Both aspirin regimens showed similar results in terms of risk of bleeding (GI and wound) and mortality after TJA.
- Low dose of aspirin (81 mg twice a day) is not inferior to a higher dose of aspirin (325 mg twice a day) in the prevention of VTE following. We currently use ASA 81 mg PO BID for four weeks in primary arthroplasty procedures in low-risk patients.

Key Take-aways

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- Patients undergoing major orthopedic surgery are at an increased risk of VTE and should be given appropriate prophylaxis
- Overall, no difference in VTE incidence following TKAs/THAs in low-dose versus high-dose aspirin groups.
- Appropriate duration of agents used for VTE prophylaxis is important following major orthopedic surgeries to prevent major complications

In Summary

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Type of Procedure	Low Baseline Risk of VTE	Intermediate Risk of VTE	High Risk of VTE	Duration of VTE Prophylaxis
THA/TKA	Enoxaparin 40 mg SQ daily OR 30 mg SQ q12h ASA 81 mg PO BID	Enoxaparin 40 mg SQ daily OR 30 mg SQ q12h Consider 5 days of rivaroxaban 10 mg PO daily then ASA 81 mg PO daily	Enoxaparin 40 mg SQ daily OR 30 mg SQ q12h Alternative: DOAC (apixaban 2.5 mg PO BID OR rivaroxaban 10 mg PO daily)	THA: 35 days post-op TKA: 10-14 days post-op or up to 35 days if not ambulatory day 14
HFS	Enoxaparin 40 mg SQ daily OR 30 mg SQ q12h	Enoxaparin 40 mg SQ daily OR 30 mg SQ q12h	Enoxaparin 40 mg SQ daily OR 30 mg SQ q12h	Minimum 10-14 days, up to 35 days if not fully ambulatory

Assessment Questions



Assessment Question #1

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How does orthopedic surgery increase the risk for DVT based on Virchow's triad?

- A. Increased blood flow
- B. Hypocoagulability
- C. Endothelial injury

Assessment Question #1

Correct Response

How does orthopedic surgery increase the risk for DVT based on Virchow's triad?

- A. Increased blood flow
- B. Hypocoagulability
- C. **Endothelial injury**

Assessment Question #2

McLeod Health

Which anticoagulation option is not recommended in hip fracture surgery patients due to limited evidence?

- A. Enoxaparin
- B. Aspirin
- C. Graduated compression stockings
- D. Apixaban

Assessment Question #2

Correct Response

Which anticoagulation option is not recommended in hip fracture surgery patients?

- A. Enoxaparin
- B. Aspirin
- C. Graduated compression stockings
- D. **Apixaban**

Assessment Question #3

McLeod Health

What is the recommended duration of antithrombotic prophylaxis in total knee arthroplasty when using low molecular weight heparin?

- A. 3 days
- B. 60 days
- C. 10-14 days
- D. 45 days

Assessment Question #3

Correct Response

What is the recommended duration of antithrombotic prophylaxis in total knee arthroplasty when using low molecular weight heparin?

- A. 3 days
- B. 60 days
- C. 10-14 days**
- D. 45 days

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