

# Preventing Venous Thromboembolism in the Hospitalized Patient

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# Objectives

- Epidemiology
- Identify risk factors
- Review general treatment principles in the medical and orthopedic patient
- Review of latest CHEST guidelines (ACCP 9th edition- 2012) – leading resource of evidence based guidelines
- Review the data for newer oral anticoagulants for VTE prophylaxis



**Which patient being discharged DOES NOT require VTE prophylaxis?**

- A. Total knee arthroplasty**
- B. Hip fracture**
- C. Elective hip replacement**
- D. Knee arthroscopy**

# Hospitalized patients are at significant risk for venous thromboembolism (VTE)

If thromboprophylaxis was not administered:

- Highest risk are surgical/trauma patients: 40-80% risk for VTE event
- Moderate risk are medical patients: 10-20% medical patient, 40% stroke

Yet...50-75% of cases overall of VTE occur on the medical service

(ACCP 9<sup>th</sup> edition guidelines;133:Suppl:381S-453S)

# #1 cause of **preventable** death in the hospital setting



Autopsy data of 6833 patients:

- VTE contributes to more than 10% deaths among hospitalized medical patients
- 70-80% of **fatal** PE's occur on the medical service

# ENDORSE study

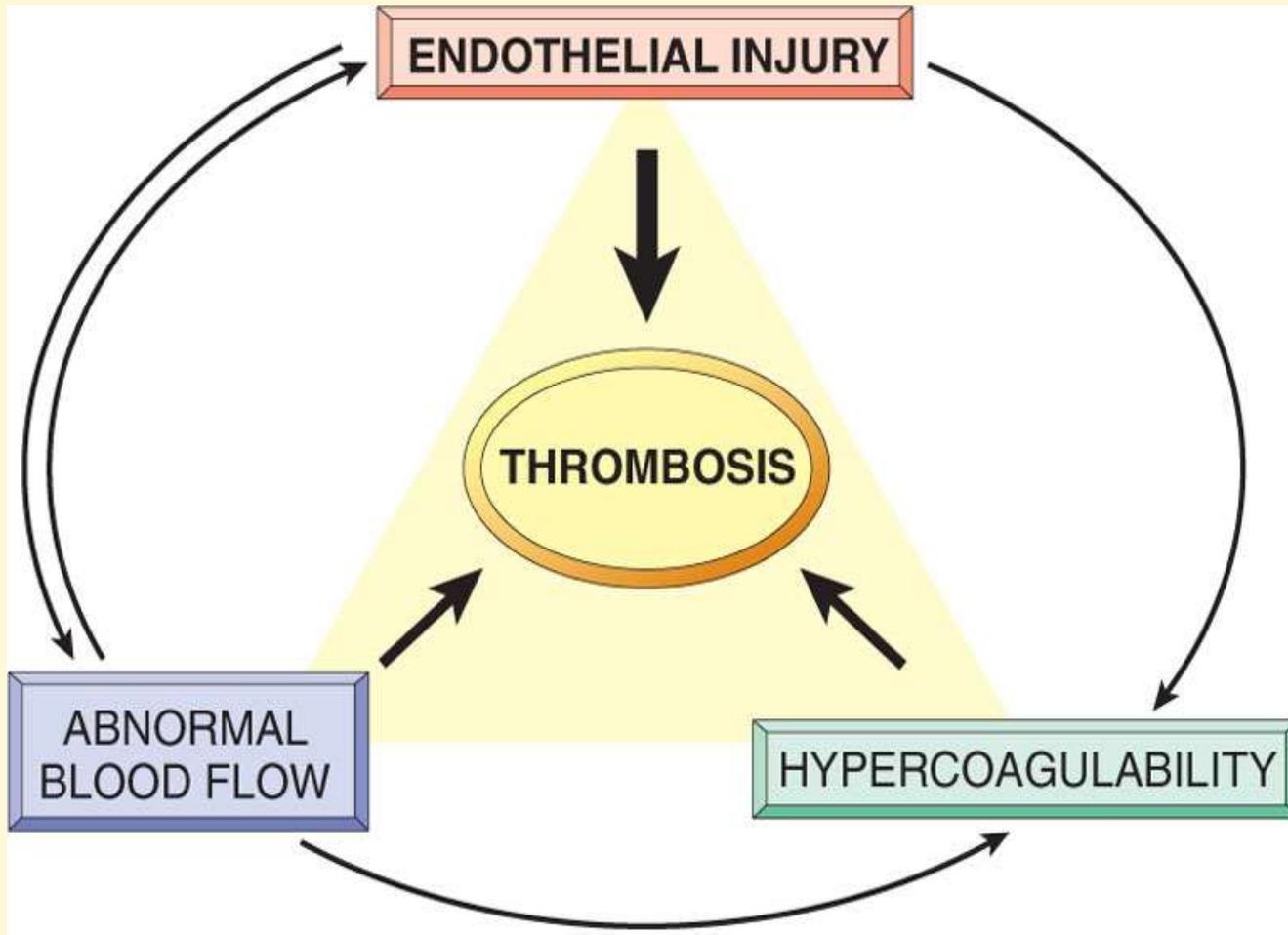
Out of ~70,000 patients in 358 hospitals, appropriate prophylaxis was administered in:

- 58.5% of surgical patients.
- 39.5% of medical patients.

Cohen, Tapson, Bergmann, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008; 371:387-94.

# Why VTE prophylaxis?

- Decreased morbidity
  - Risk of VTE overall reduced by 50%-65%
- Cost
- Length of Stay
- Desirable risk: benefit ratio
- Decreased mortality (surgical patient)



# VTE Risk Factors

## Strong risk factors (odds ratio >10)

Fracture (hip or leg)  
Hip or knee replacement  
Major general surgery  
Major trauma  
Spinal cord injury

## Moderate risk factors (odds ratio 2–9)

Central venous lines  
Chemotherapy  
Congestive heart or respiratory failure  
Hormone replacement therapy  
Malignancy  
Oral contraceptive therapy  
Paralytic stroke  
Pregnancy/, postpartum  
Previous venous thromboembolism  
Thrombophilia

## Weak risk factors (odds ratio <2)

Bed rest >3 days  
Immobility due to sitting (e.g. prolonged car or air travel)  
Increasing age (esp >75yr)  
Laparoscopic surgery (e.g. cholecystectomy)  
Obesity (BMI >30)  
Pregnancy, antepartum  
Varicose veins

# High Risk for VTE in the Medical Inpatient

Who is most at risk?

- Congestive heart failure (NYHA III/IV)
- Acute COPD exacerbation
- Acute infectious disease or sepsis
- Acute myocardial infarction
- Stroke with lower limb paralysis
- Inflammatory bowel disease

# Risk is cumulative

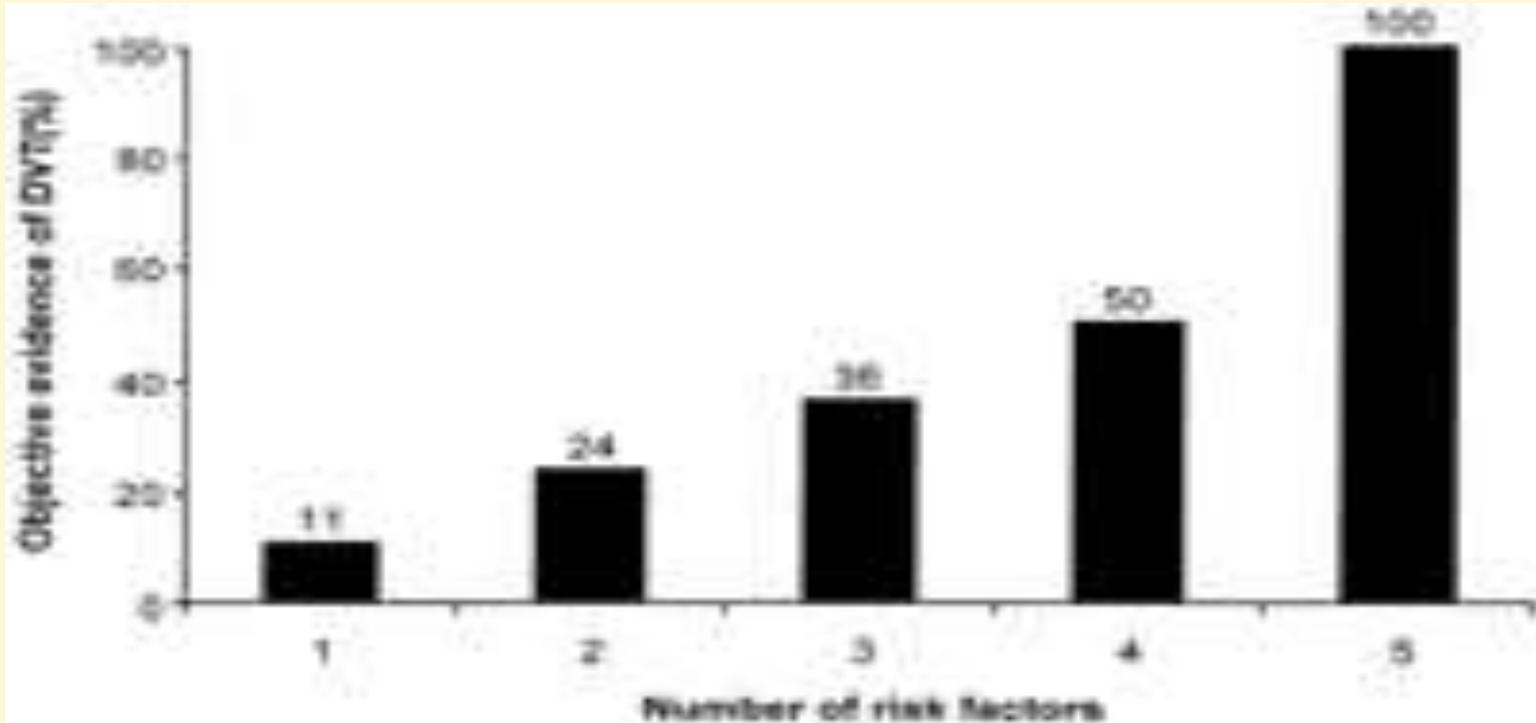


Figure 1. The proportion of patients with clinically suspected deep vein thrombosis in whom the diagnosis was confirmed by objective testing increases with the number of risk factors. (Arch Surg. 1982;117:1206–1209.<sup>3</sup>)

# No validated risk assessment model exists

## Individualized approach

### Bleeding Risk

**High risk:** Any 1 of 3

- Active bleed
- Bleeding within 3 months before admission
- Platelet count of < 50

Age>85, hepatic failure, severe renal failure, ICU admission



### Risk of VTE

**Low risk** if all 3:

- Younger than 40
- Mobile
- No thrombotic risk factors

**Moderate or high risk:**  
All other patients

# ACCP 9<sup>th</sup> edition guidelines

## Medical Inpatient



### Recommended

- Pharmacologic prophylaxis for those that are NOT low risk: age > 40, have limited mobility for > 3 days, and have at least one risk factor
- Mechanical prophylaxis for those that have a contraindication to pharmacologic prophylaxis

### Not Recommended

- The use of prophylaxis beyond the period of immobilization or hospitalization
- The use of prophylaxis in patients that are low risk (age < 40, immobility for < 3 days, no risk factors)

ACCP 9<sup>th</sup> edition :Grade 1B

# Mechanical prophylaxis

## Medical Inpatient

Use of mechanical prophylaxis is poorly studied

- Intermittent pneumatic compression (IPC) or Sequential Compression Device (SCD) use is recommended based on surgical literature data
  - it has not been studied in medical patients
  - should be used if bleeding risk is high
  - use is contraindicated in patients with evidence of leg ischemia due to peripheral vascular disease, leg ulcerations, dermatitis, or severe edema
  - should not be started beyond 72 hours in the immobile patient
- Graduated compression stockings have unproven efficacy
  - they have been studied in stroke patients and are of no benefit
  - risk for LE skin damage
  - ACCP does recommend their use rather than NO prophylaxis



To be effective, they should remain on the patient >18 hours/day

# Pharmacologic Prophylaxis

## Medical Inpatient

**Table 2.** Various Pharmacologic Agents for Medical Prophylaxis

	<b>Unfractionated heparin</b>	<b>Enoxaparin</b>	<b>Dalteparin</b>	<b>Fondaparinux</b>
<b>Class</b>	UFH	LMWH	LMWH	Synthetic pentasaccharide, Factor Xa inhibitor
<b>FDA approved for medical prophylaxis</b>	Yes	Yes	Yes	No
<b>Approved dose</b>	5,000 units SC three times daily	40 mg SC once daily	5,000 units SC once daily	2.5 mg SC once daily*
<b>Dosing in renal insufficiency (creatinine clearance 10 to 30 mL/min)</b>	Consider UFH 5,000 units SC twice daily	Adjust to 30 mg SC once daily	Not indicated	Contraindicated
<b>Reversal agent</b>	Protamine Sulfate (complete reversal)	Protamine sulfate (60-75% reversal)	Protamine sulfate (60-75% reversal)	Recombinant Factor VIIa

\*Fondaparinux is not FDA approved for medical prophylaxis.

# Newer oral anticoagulants

## Medical Inpatient

The ADOPT trial, comparing an extended course of **apixaban** to a standard course of **enoxaparin** in medical patients

- Nonsignificant decrease in VTE events but a significant increase in bleeding risk (RR = 2.6; 95%CI 1.02-7.24)).

The MAGELLAN trial evaluated an extended course of **rivaroxaban** against a standard course of **enoxaparin** among hospitalized medical patients.

- Rivaroxaban was noninferior at day 10 and superior at days 30 to 35 with regards to VTE prevention
- However, clinically relevant bleeding rates were increased in the rivaroxaban arm (RR of 2.3 at day 10 and an RR of 3.0 at days 30 to 35.)

*Further data are required before clinical use of any of these newer agents among medical patients for either short-term or extended prophylaxis*

# Optimal Duration of VTE PPX in the Medical Inpatient

- The 3 large trials of LMWHs (MEDENOX, PREVENT, and ARTEMIS) all involved protocols of between **6 and 14 days of prophylaxis**.
- EXCLAIM trial has shown that a protocol of extending prophylaxis with LMWH by 28 days (beyond an initial 10 days) resulted in a 38% RR reduction in VTE events.
  - However, there was a significant major bleeding rates, with an RR of 2.5.
  - Subgroup analysis women, those age >75yrs, and with reduced mobility did have benefit

Hull RD, Schellong SM, Tapson VF, et al. Extended-duration thromboprophylaxis in acutely ill medical patients with recent reduced mobility: Methodology for the EXCLAIM study. *J Thromb Thrombolysis* 2006; 22:31-38.

*Although there is evidence that the risk of VTE may persist beyond hospitalization, the benefits of extended thromboprophylaxis have not been shown to outweigh the risks of bleeding (Grade 2b)*

# Miscellaneous

## Morbidly obese

- Consider increasing prophylactic dose by 25% when BMI >40 kg/m<sup>2</sup>
  - No evidence based data to support this

## Stroke

- PREVAIL trial demonstrated superiority of LMWH over UFH for DVT prophylaxis
- For acute ischemic stroke, start LMWH (or UFH) within 48 hours (at least 24 hours after tPA)
- For acute intracranial hemorrhage, start LMWH after 2-4 days
- Additive benefit to using SCD's (but no benefit in using alone) but not GCS

## Neuroaxial anesthesia or lumbar puncture

- Hold UFH/LMWH 8-12 hours before procedure
- Restart 4 hours after procedure

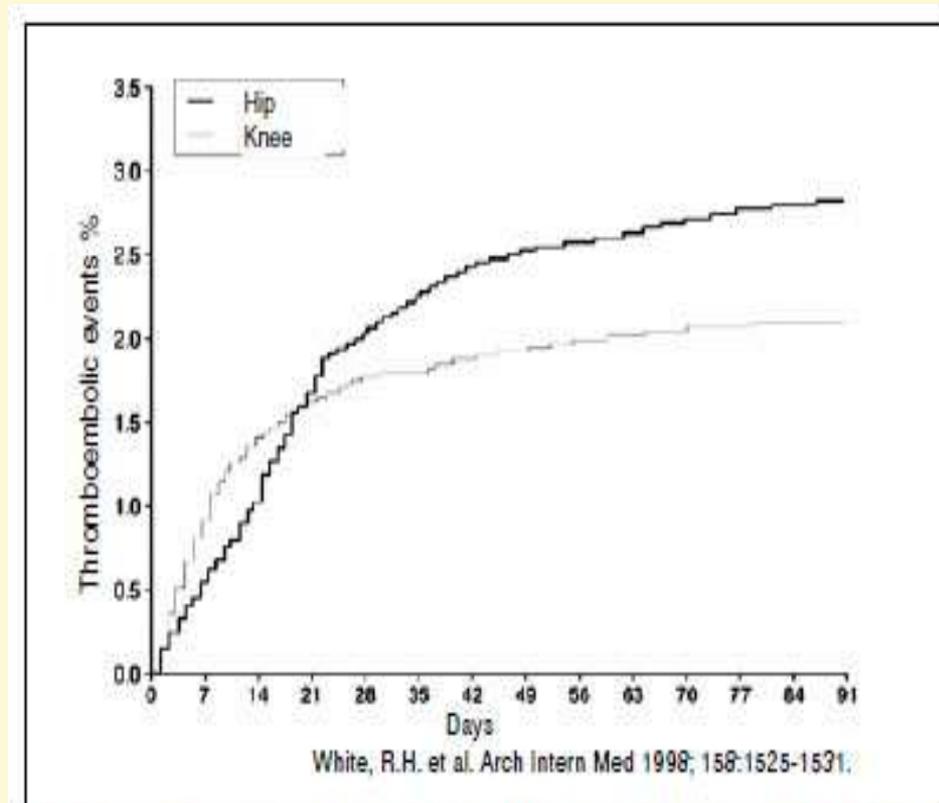
# Prophylaxis in the Surgical patient

## General Recommendations

- Early ambulation
- SCD's in patients at high risk for bleed (1C)
- In patients receiving pharmacologic prophylaxis, the addition of SCD's during hospital stay (2C)
- Patients with orthopedic surgeries, abdominal or gyn surgeries for malignancy, or previous VTE
  - should receive prophylaxis for up to 35 days after surgery (2c)
- IVC filters indicated for those with high risk of VTE (if they've had it within 1-3 months before surgery) and for whom AC is C/I (1C)
  - no evidence to support its use in other populations

# Orthopedic surgeries

## Why 35 days of prophylaxis?



**Figure 2** – Incidence of events/days after primary arthroplasties of the hip or knee (Kaplan-Meier).

Adapted from White RH, et al. Arch Intern Med. 1998;158:1525-31.

**Table 3. American College of Chest Physicians guidelines, 8th edition, for thromboprophylaxis in orthopedic surgery [1].**

	First choice treatment	LMWH initiation	Duration	High risk of bleeding
Hip arthroplasty	LMWH, fondaparinux, or adjusted-dose VKA (INR range 2.0–3.0)	Preoperatively or postoperatively	At least 10 days; recommendation to extend up to 35 days	Optimal use of mechanical thromboprophylaxis
Knee arthroplasty	LMWH, fondaparinux, or adjusted-dose VKA (INR range 2.0–3.0)	Preoperatively or postoperatively	At least 10 days; suggestion to extend up to 35 days	Optimal use of mechanical thromboprophylaxis
Hip fracture surgery	Fondaparinux, LMWH, adjusted-dose VKA (INR range 2.0–3.0), or UFH	Preoperatively or postoperatively	At least 10 days; recommendation to extend up to 35 days	Optimal use of mechanical thromboprophylaxis

Fondaparinux for LMWH initiation should be started either 6–8 h after surgery or the next day. INR: international normalized ratio; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; VKA: vitamin K antagonist.

Image courtesy of Remedica Journals  
<http://www.remedicajournals.com/Advances-in-Venous-Arterial-Thrombosis/BrowseIssues/Volume-1-Issue-2/Article-Venous-Thromboembolic-Risk-and-the-Current-Strategies>

For patients undergoing knee arthroscopy without a history of VTE, no thromboprophylaxis is indicated (Grade 2b)

# The options...

Vitamin K antagonists (VKA) inhibit the synthesis of the coagulation Factors II, VII, IX, X

## Legend:

 = inactive factor

 = active factor

 = transformation

 = catalysis

Direct Factor Xa inhibition:

- Rivaroxaban
- Apixaban
- Edoxaban

Indirect via antithrombin:

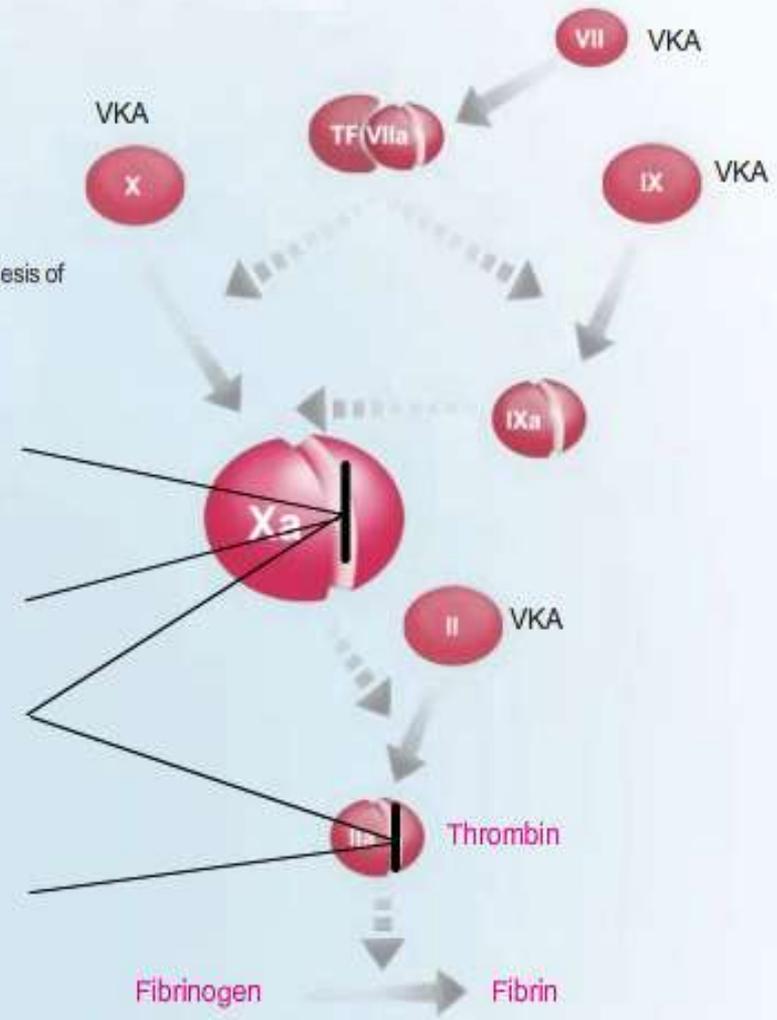
- Fondaparinux

Indirect via antithrombin:

- Low molecular weight heparin
- Unfractionated heparin

Direct thrombin inhibition:

- Hirudin
- Argatroban
- Bivalirudin
- Dabigatran



# Which agent to use?

## **LMWH or Enoxaparin – GOLD STANDARD**

- Subcutaneous injection, no monitoring, best data: compared to LDUFH, fewer clinical VTE events
- 30mg bid dosing is used in North America, in Europe, 40mg qd
- LMWH can begin preoperatively (>12 hours) and resume post-operatively (>12hours) (1B)

## **Low Dose Unfractionated Heparin (LDUFH)**

- Subcutaneous injection, no monitoring
- 5K bid dosing if age >75 or weight < 50kg; otherwise tid dosing
- No valid data to compare bid vs tid dosing

## **Fondaparinux (Arixtra)**

- Dose 2.5mg SC qday
- Data shows superior efficacy to LMWH but with increased risk of bleeding (clinically insignificant)
- Contraindicated if CrCL <30 but can be used at 1.5 mg dose if CrCl 30-50

## **Warfarin**

- Requires frequent monitoring, INR goal 2.5, many drug interactions
- Reversible

All are grade 1B recommendations (ACCP CHEST 9<sup>th</sup> edition)

## **Apixaban (Eliquis)**

- Dose 2.5 mg orally twice daily ; contraindications are based on age, weight, and sCr
- Compared with LMWH, Apixaban has equivalent efficacy in DVT prophylaxis, and is not associated with more bleeding events but did not meet noninferiority criteria (ADVANCE3 trial)

## **Rivaroxaban (Xarelto)**

- Dose: 10 mg orally once daily (no monitoring needed); do not give if CrCL <30
- ORTHO-TEP (retrospective cohort) compared to LMWH
  - Rates of symptomatic VTE were lower (2.1 vs 4.1%)
  - Rates of bleeding were significantly lower and (2.9 vs 7.0%)
- Prospective studies needed to confirm

## **Dabigatran (Pradaxa)**

- Not available in appropriate 220 mg dose for VTE prophylaxis in United States

Head to head comparison's of antiFactorXa inhibitors have not been done

# Aspirin



- 2012 ACCP Guidelines: Aspirin use in hip fracture/THA/TKA patients as an alternative agent (not a first line), as opposed to no VTE ppx (1b recommendation)
  - Taking low-dose ASA for 35 days will result in seven fewer symptomatic VTEs per 1000 patients as compared to nothing.
  - ASA may also result in more major nonfatal bleeding episodes compared to placebo (RR 1.12), but there was no difference in bleeding requiring reoperation or bleeding death.
  - Dosing of Aspirin 325mg po bid has been used in some studies

# Summary

## Medical Patient

- Prophylaxis is not recommended for all hospitalized patients- low risk groups: early ambulation +/- mechanical prophylaxis
- Consider pharmacologic prophylaxis for patients on the medical service who are older than 40 years, have limited mobility for 3 days or more, and have at least one risk factor
- No data to support the use of newer oral anticoagulants
- Careful assessment must be made in regards to bleeding risk, renal function
- No data to support its use in chronically immobile patients, rehab/SNF patients

# Summary

## Surgical Patient

- Extended prophylaxis is only recommended for surgical patients- up to 35 days after hip or knee surgery
- No prophylaxis needed for total knee arthroscopies
- Not known what to do for below the knee surgeries.
- IPC/SCD's should be added to pharmacologic therapy in the surgical patient
- Aspirin can be used if other agents pose to high a bleeding risk – in the surgical patient only

**Which patient being discharged DOES NOT require VTE prophylaxis?**

- A. Total knee arthroplasty**
- B. Hip fracture**
- C. Elective hip replacement**
- D. Knee arthroscopy**

Gracias!



# References

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