Controversies in Cancer Associated Venous Thrombosis

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Disclosures

- Consulting- Riegel and Alexion Pharmaceuticals

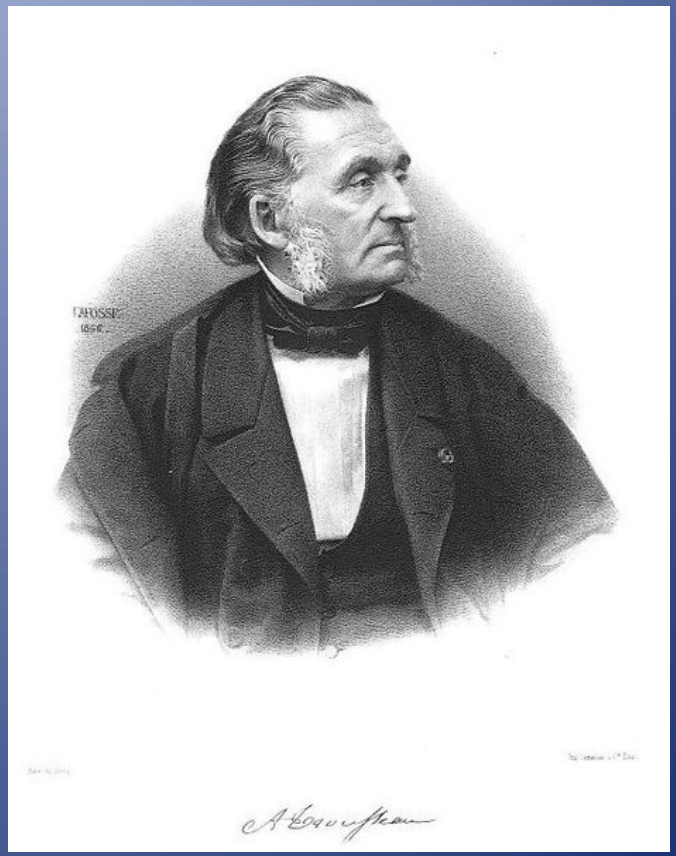
- From the perspective of a clinical hematologist

Overview

- Scope of Venous Thromboembolism (VTE) in Cancer
- Challenge scenarios with anticoagulation
  - -Cancer Associated Thrombosis
  - -Renal dysfunction
  - -Thrombocytopenia
  - -Bleeding and reversal

Incidence of VTE in Malignancy

- Trousseau first associated venous thrombosis and gastric carcinoma in 1865
- Died of gastric cancer 1 year after the development of a DVT in 1867
- In 1871 Bilroth identified increased fibrin deposition around tumors on autopsy series
- In 1938, autopsy studies identified VTE in 30% of patients who died from pancreas cancer



Sproul, EE. Am J Cancer 1938; 34:5666.

Pathophysiology of Thrombosis: Virchow's Triad

Endothelial Injury

Tumor invasion

Chemotherapy

Venous access catheters

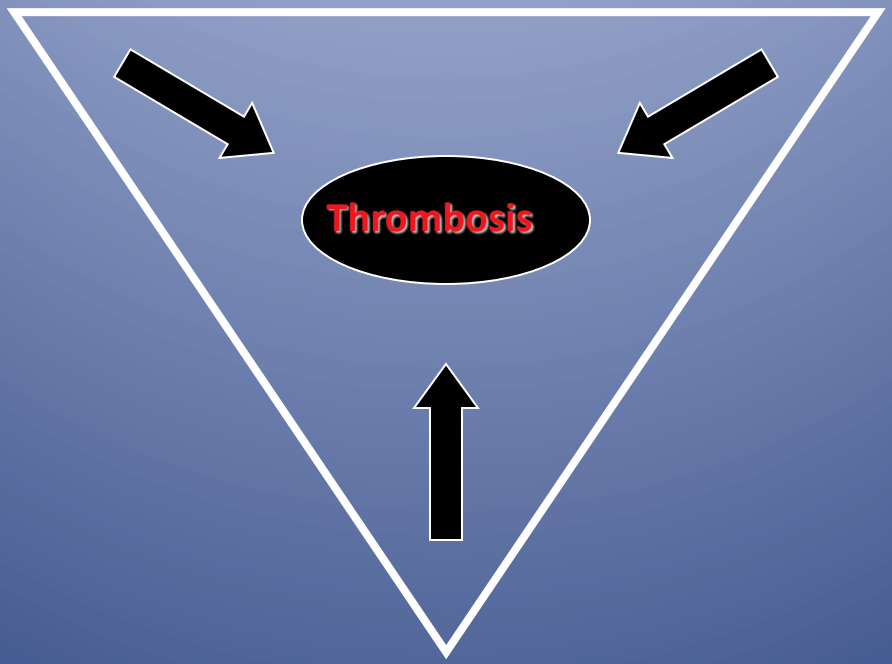
Venous Stasis

Immobilization

Tumor compression

Tumor invasion

Adenopathy



Hypercoagulability

Interaction between tumor cell and host, including genetic predisposition and inflammation

Incidence of VTE in Malignancy

- Annual incidence of first episode DVT or PE in the general population is 117 / 100,000
- Cancer is associated with a 4 fold increased risk
- Patients with cancer represent 15 - 20% of all patients with thrombosis
- 15% of all cancer patient will develop VTE
- Approximately 10% of those presenting with unprovoked or idiopathic thrombosis will be diagnosed with malignancy within 1 - 2 years
- Chemotherapy increases risk to 7 fold
- Cancer patients undergoing surgery have 2x increased risk

Silverstein MD, et al. Arch Intern Med 1998; 158:585-93.
Moore RA, et al. J Clin Oncol 2011;29; 3466-73.
Khorana AA et al, J Thromb Haemost 2011; O-MO-131

Tumors Associated with VTE

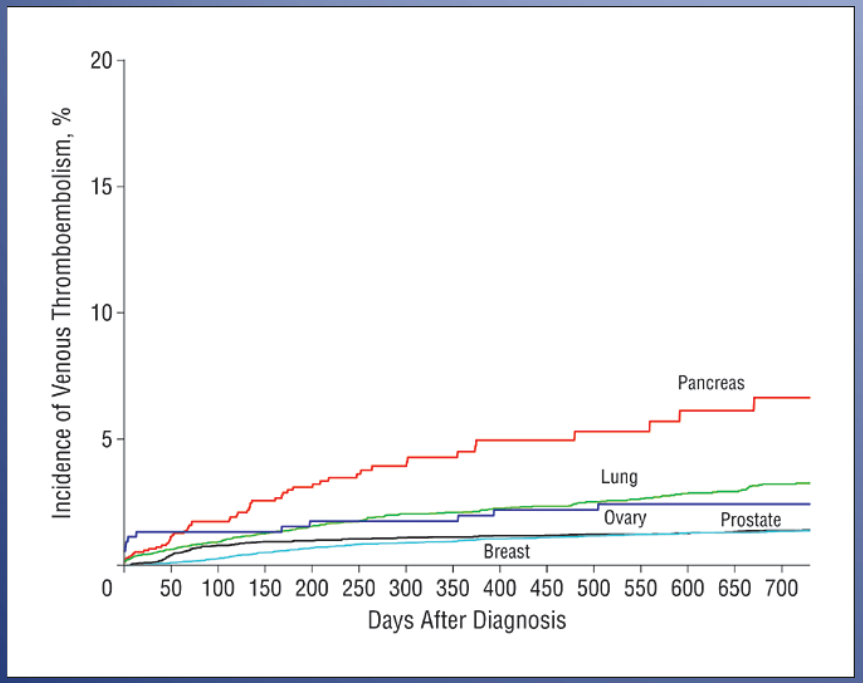
Tumor type	Adjusted OR
Any malignancy	6.7 (5.2-8.6)
Hematologic	28
Lung	22
GI tract (including pancreas)	20
Brain	6.7
Renal	6.2
Breast	4.9

- 3220 patients with cancer and 1st VTE and 2131 controls

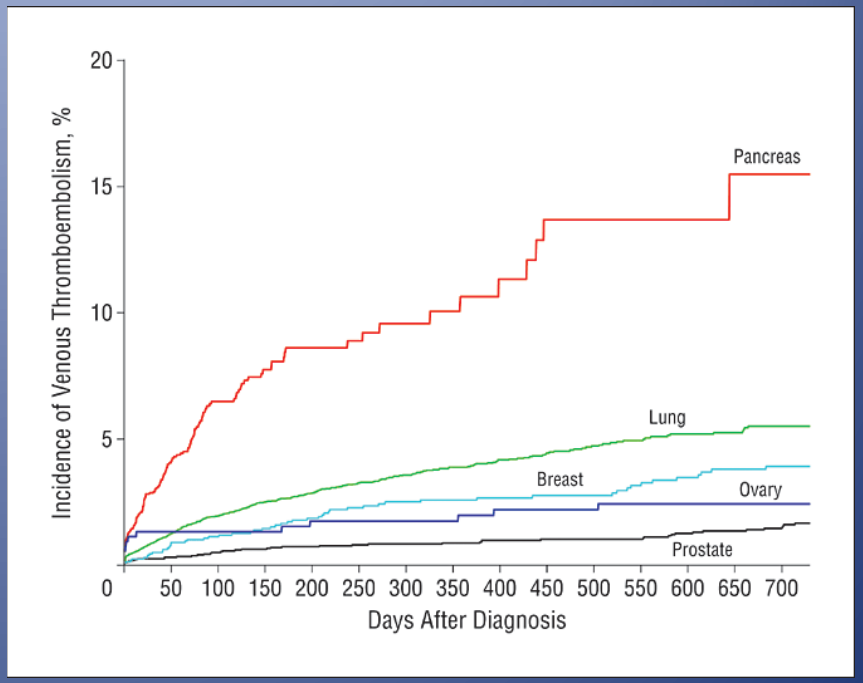
Blom JW et al. JAMA 2005; 293:715

Incidence of VTE in Malignancy

Regional Disease



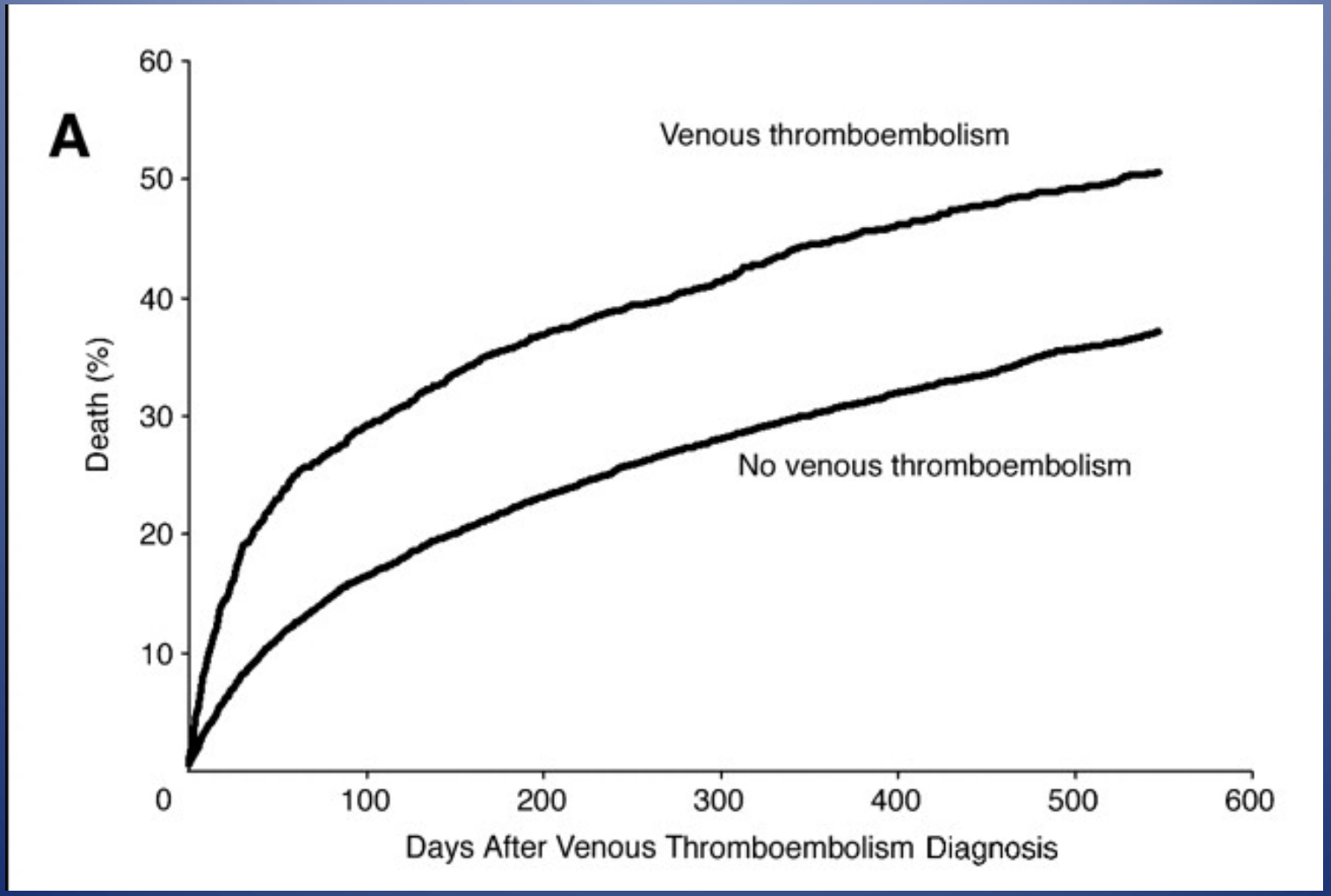
Metastatic Disease



- Review of 235,149 cancer cases in California
- Hazard ratio for metastatic vs regional disease was 3.7 (1.3- 14.4)

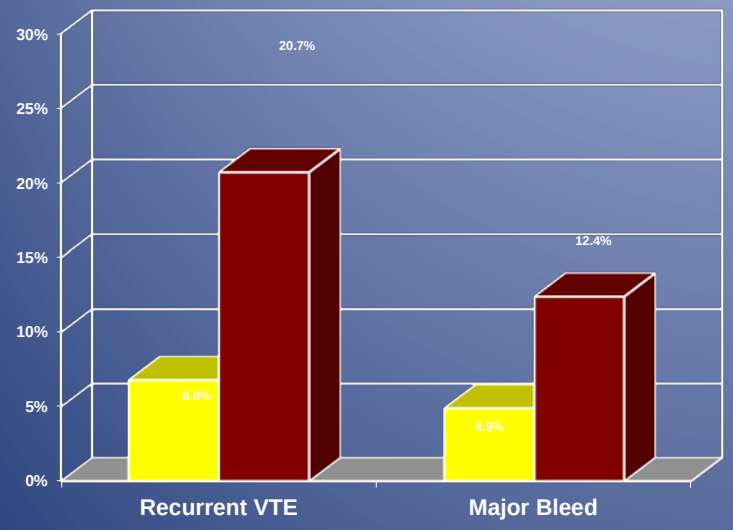
Chew HK et al. Arch Int Med 2006; 166:458

Morbidity and Mortality of Cancer Associated VTE

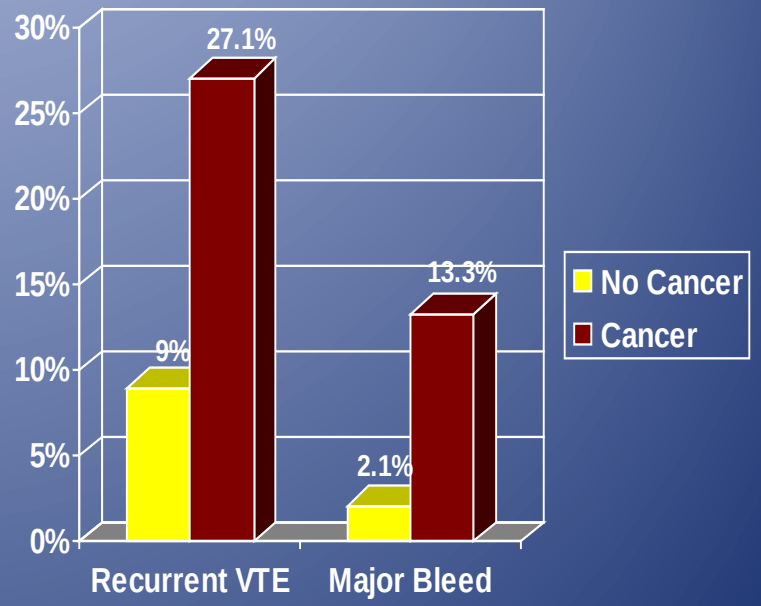


Alcalay A et al, *J Clin Onc* 2006 24;1112-8..

Morbidity and Mortality of Cancer Associated VTE



Prandoni, 2002

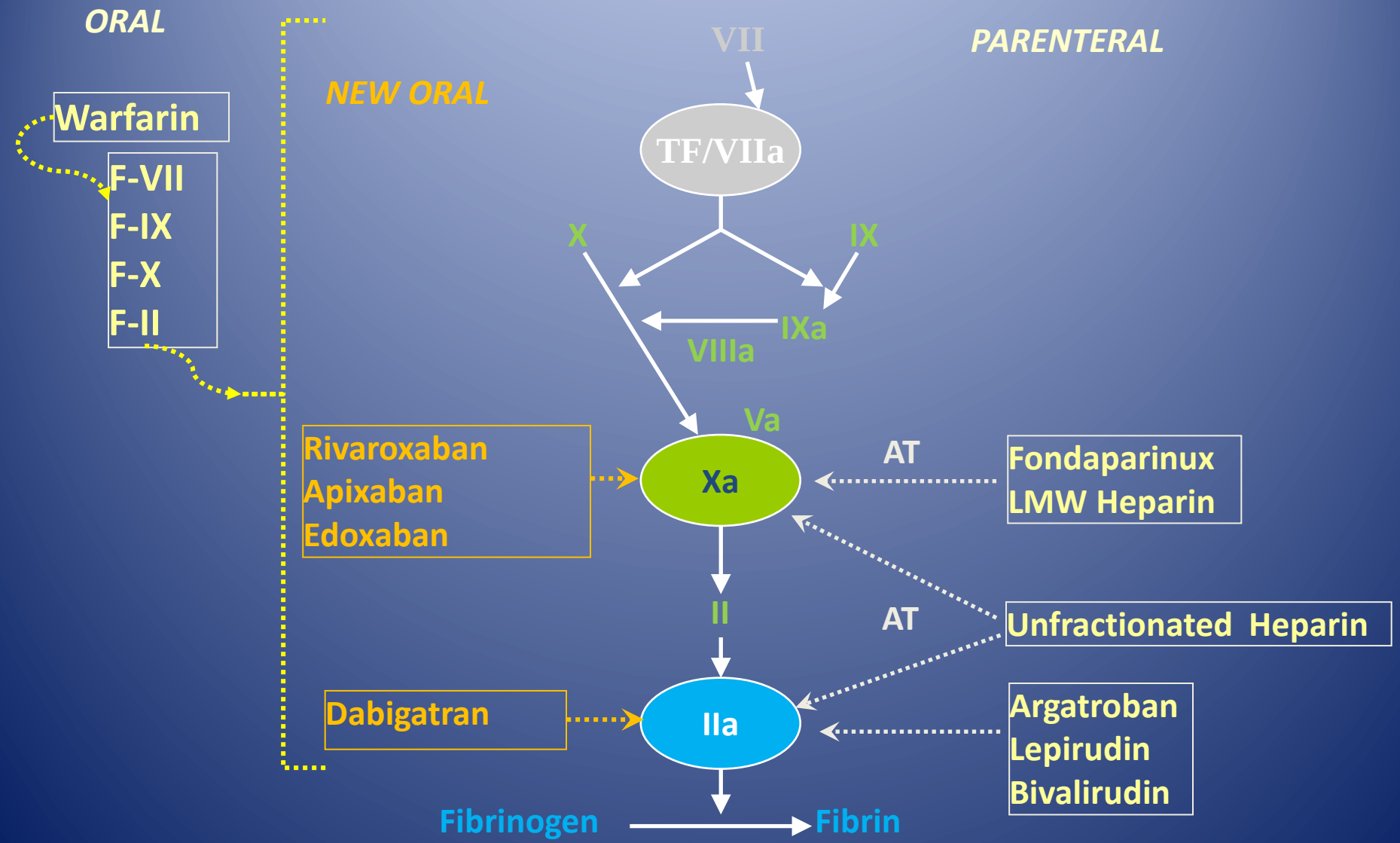


Hutten, 2000

Hutten BA, et al. *J Clin Oncol* 2000; 18:3078-83.

Prandoni P, et al. *Blood* 2002; 100;3484-8.

Anticoagulant Drugs



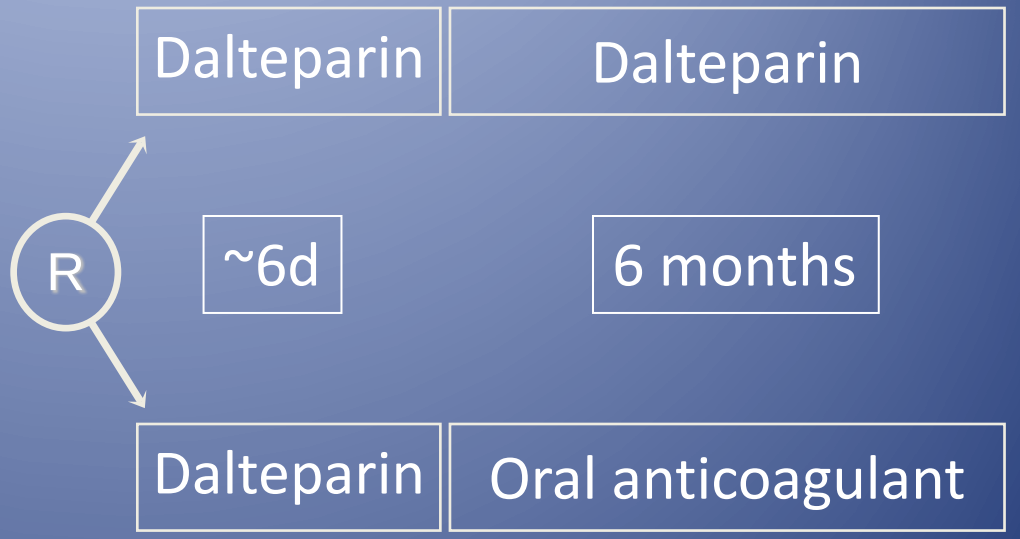
Modified from Eriksson BI, et al. Annu Rev Med 2011; 62: 41-57

Warfarin vs. Direct Oral Anticoagulants

Features	Warfarin	Direct Agents	Clinical Implications
Onset	Slow	Rapid	No need for bridging
Food Interactions	Significant	Minimal	No dietary precautions
Drug interactions	Many	Few	Few drug restrictions
Predictable drug effect	No	Yes	No need for routine monitoring
Antidote	Yes	Yes	

CLOT: LMWH vs. Warfarin for Established VTE & Cancer

Cancer patients with acute DVT and/or PE (n=336 per group)



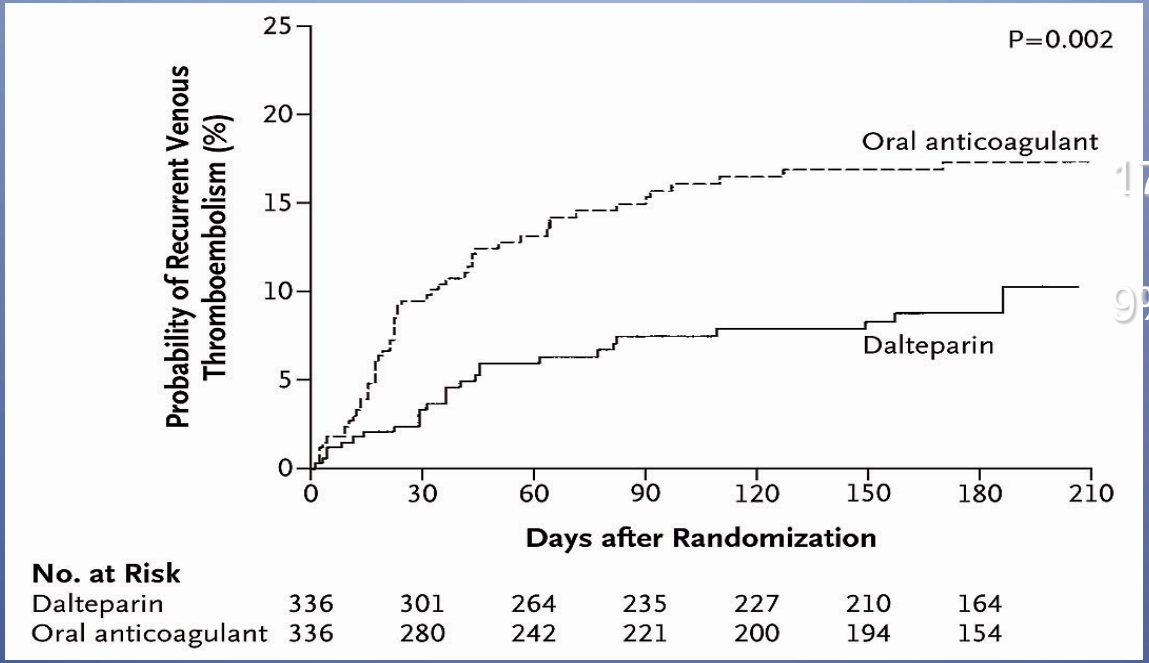
Dalteparin sc q Day: 200 IU/kg for 1 mo, then ~150 IU/kg for 5 mo

Major bleeding (p = NS)
- dalteparin = 6%
- oral anticoagulant = 4%

Any bleeding (p = NS)
- dalteparin = 14%
- oral anticoagulant = 19%

Lee, AYY et al, *NEJM* 2003;349:146-153

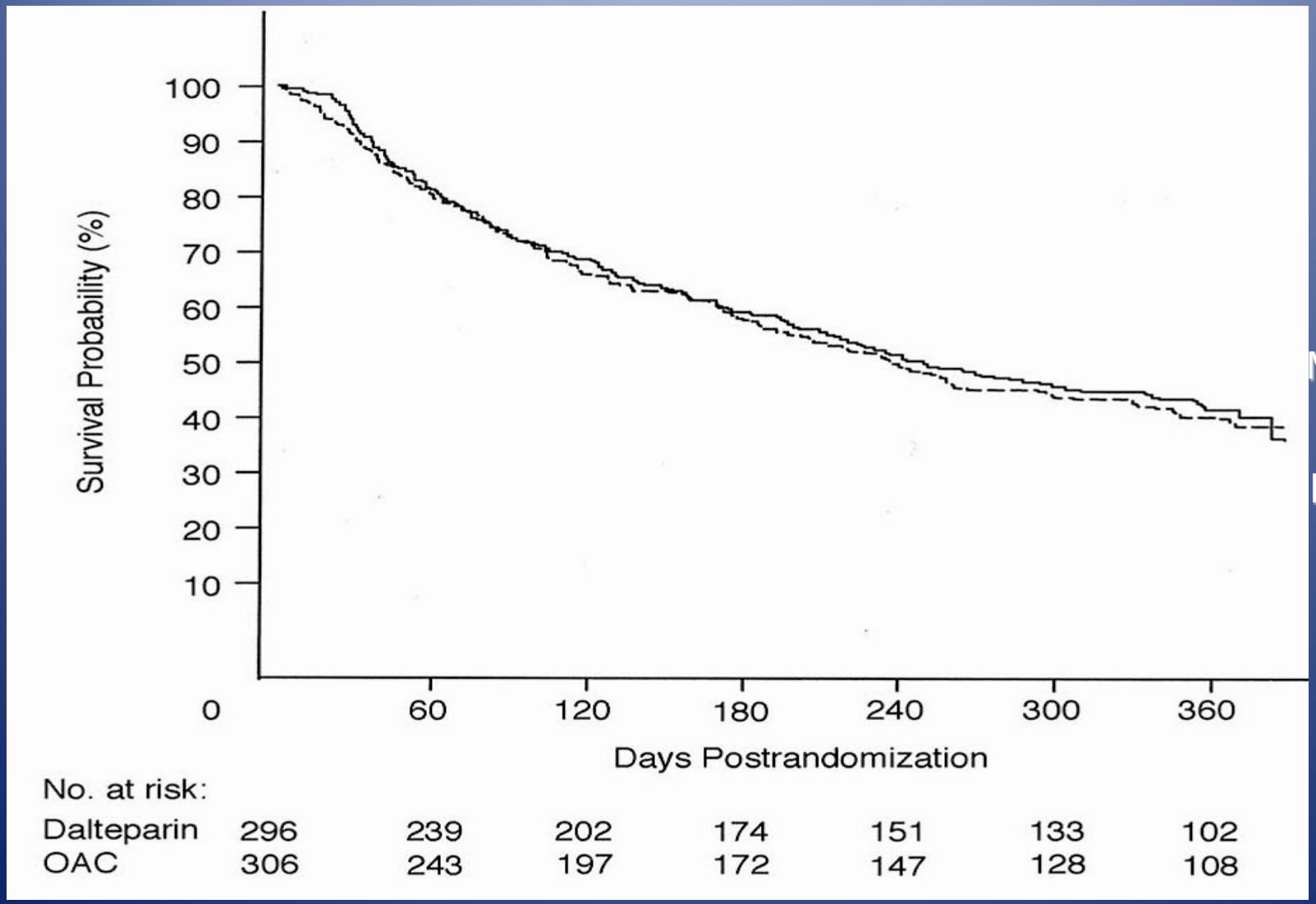
CLOT Study - Recurrent VTE



	Recur	Major Bleed	Minor Bleed
Warfarin	17%	3.6%	18.5
Dalteparin	9%	5.6%	13.6
P	0.002	0.27 (ns)	0.09 (ns)

Lee, AYY et al, *NEJM* 2003;349:146-153

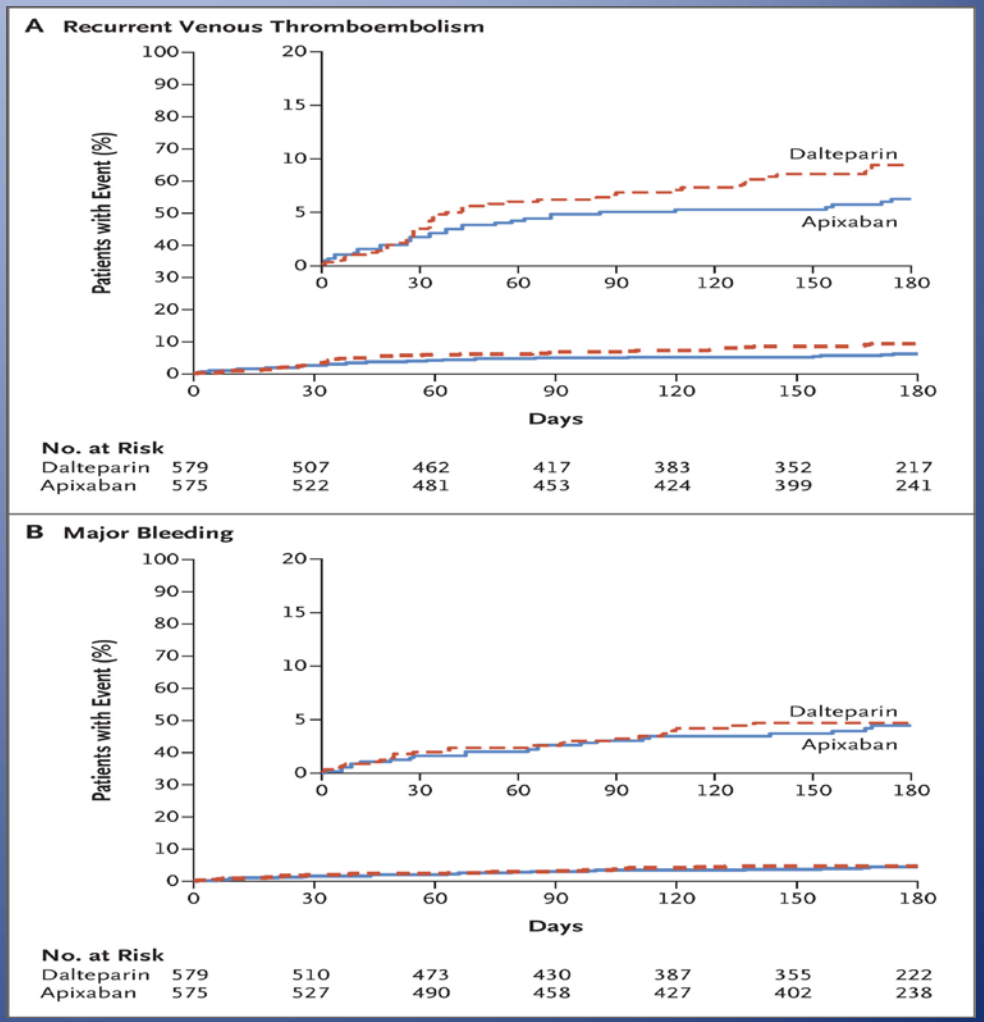
CLOT Study – Overall Survival



Mortality
59%
p=0.62

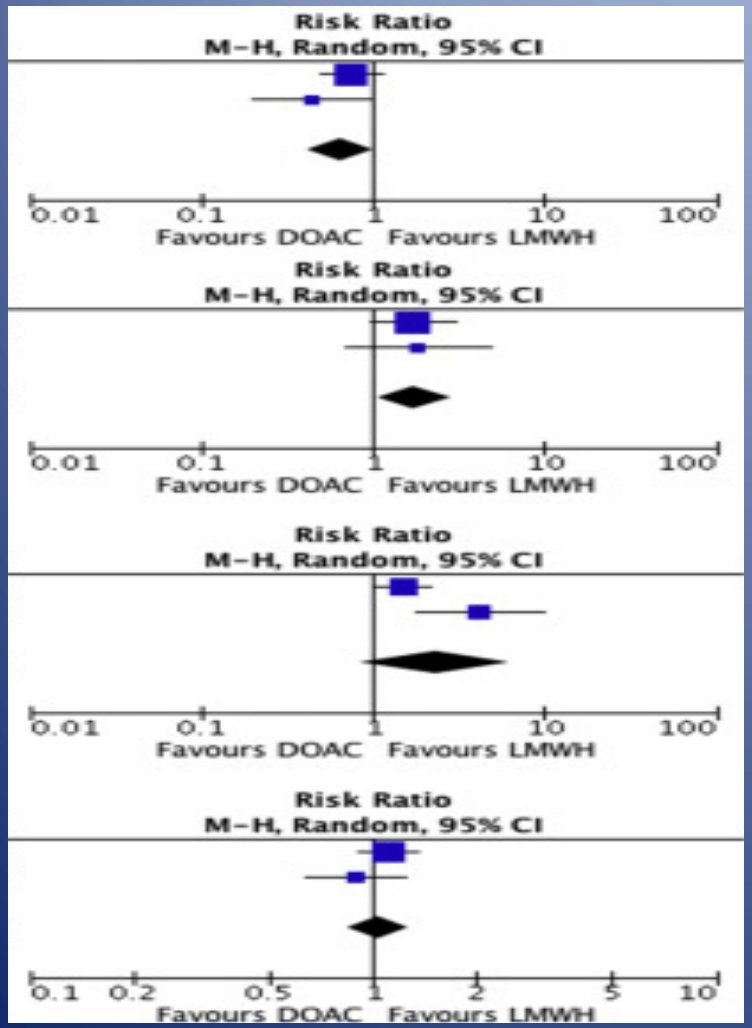
Lee, AYY, et al, *J Clin Oncol* 2005; 23 (10):2123-2129

- Caravaggio Study evaluated apixaban vs dalteparin for cancer associated VTE in 576 patients
- Rates of recurrent VTE and bleeding were non-inferior in the apixaban group compared to dalteparin
- Data to support use of rivaroxaban and edoxaban in cancer associated malignancy with increased risk of GI bleeding
  - Agnelli G et al, *NEJM*, 2020



DOAC in Cancer associated VTE

Meta-analysis of DOAC vs LMWH in Cancer associated VTE



- A- Recurrent VTE
- B- Major Bleeding
- C- Clinically significant non-major bleeding
- D- Overall Mortality

Li A, *et al. Thromb Research,* 219

Patients in whom I have reservations about using DOACs

- Valvular heart disease
- Prosthetic heart valves
- Renal dysfunction (GFR <30)
- GI malabsorption
- GI malignancy (particularly with rivaroxaban)
- Persons at high risk of failure (either bleeding or clotting) whom monitoring may be beneficial
- Non-compliance with anticoagulation therapy
- Cost prohibition
- Extremes of body weight
- High fall risk
- Dementia

Case 1

- 76 year-old female with a history of metastatic ER+ breast cancer on active therapy and stage 4 CKD with GFR of 25 ml/min admitted to the hospital with near-syncope without falls. Found to have a new, single lobe segmental PE She is hemodynamically stable with normal oxygenation. She has no history of bleeding.

.

- What anticoagulant should be selected?
  - No anticoagulant
  - Vitamin K antagonist (warfarin)
  - Apixaban 2.5 mg BID
  - Rivaroxaban 15 mg daily
  - Enoxaparin 1 mg/kg daily

Renal function & DOACs

Dabigatran

- 80% is renally eliminated as active drug
- Average half-life increases with renal insufficiency
  - CrCl 50-80 ml/min: 15.3 hrs
  - CrCl 30-49 ml/min: 18.4 hrs
  - CrCl 15-30 ml/min: 27.2 hrs
- All trials exclude pts with CrCl < 30
- FDA Approved dose
  - CrCl > 30 ml/min: 150 mg bid for Afib patients
  - CrCl 15-30 ml/min: 75 mg bid for Afib patients based on pharmacokinetic data

Renal Function

Rivaroxaban

- FDA approved doses
  - CrCl > 50 ml/min: 20 mg daily dose for afib
  - CrCl 15-50 ml/min: 15 mg daily dose for Afib

Apixaban

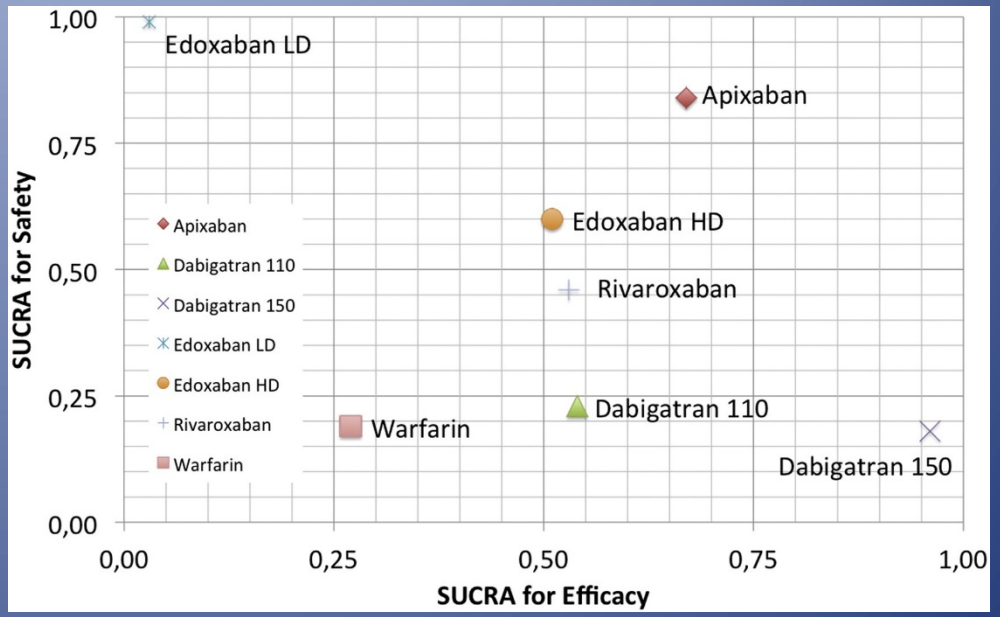
- FDA approved doses
  - CrCl > 25 ml/min: 5 mg bid for afib
  - Cr Cl 15-24 ml/min: 2.5 mg bid for afib

Edoxaban

- FDA approved dose:
  - CrCl >50 ml/min: 60 mg daily
  - CrCl 15-50 ml/min: 30 mg daily

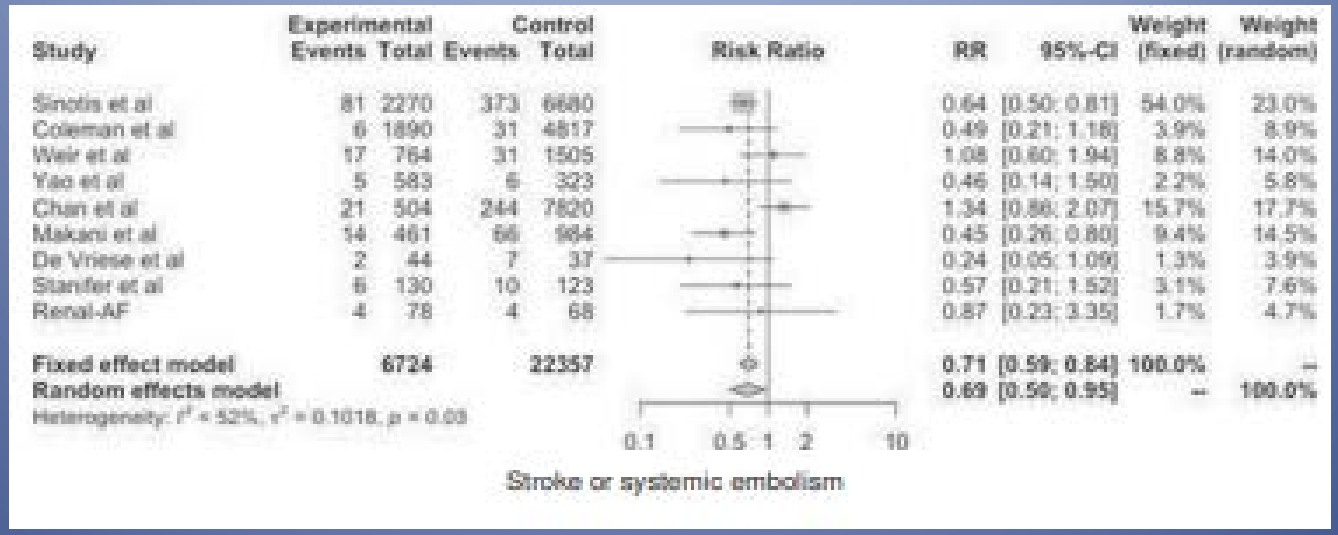
DOACs in Renal Impairment Meta Analyses

- Meta-analyses reviewing 13,000 patient with GFR 30-50 in atrial fib trials.
- Compared different drugs and dosages and then generated models to predict efficacy and safety.



Ando G and Caprazano P. *Int J Cardio*. 2017. 231:162-67.

DOACs in Renal Impairment Meta Analyses



- DOACs vs warfarin in atrial fib and CKD stage IV-V showed decreased risk of embolic stroke with no significant difference in major bleeding or mortality
  - Wartanian A, et al*, Euro Heart J*, 2021

- What anticoagulant should be selected?
  - No anticoagulant
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Case 2:

- 75 year old male with metastatic pancreas cancer with previous PE on apixaban needs additional therapy. Platelet count is 65K and plan is to begin a gemcitabine based regimen. What should be done with anticoagulation?
  - Stop apixaban
  - Reduce dose of apixaban
  - Change to LMW heparin
  - Transfuse platelets to keep platelet count >50k

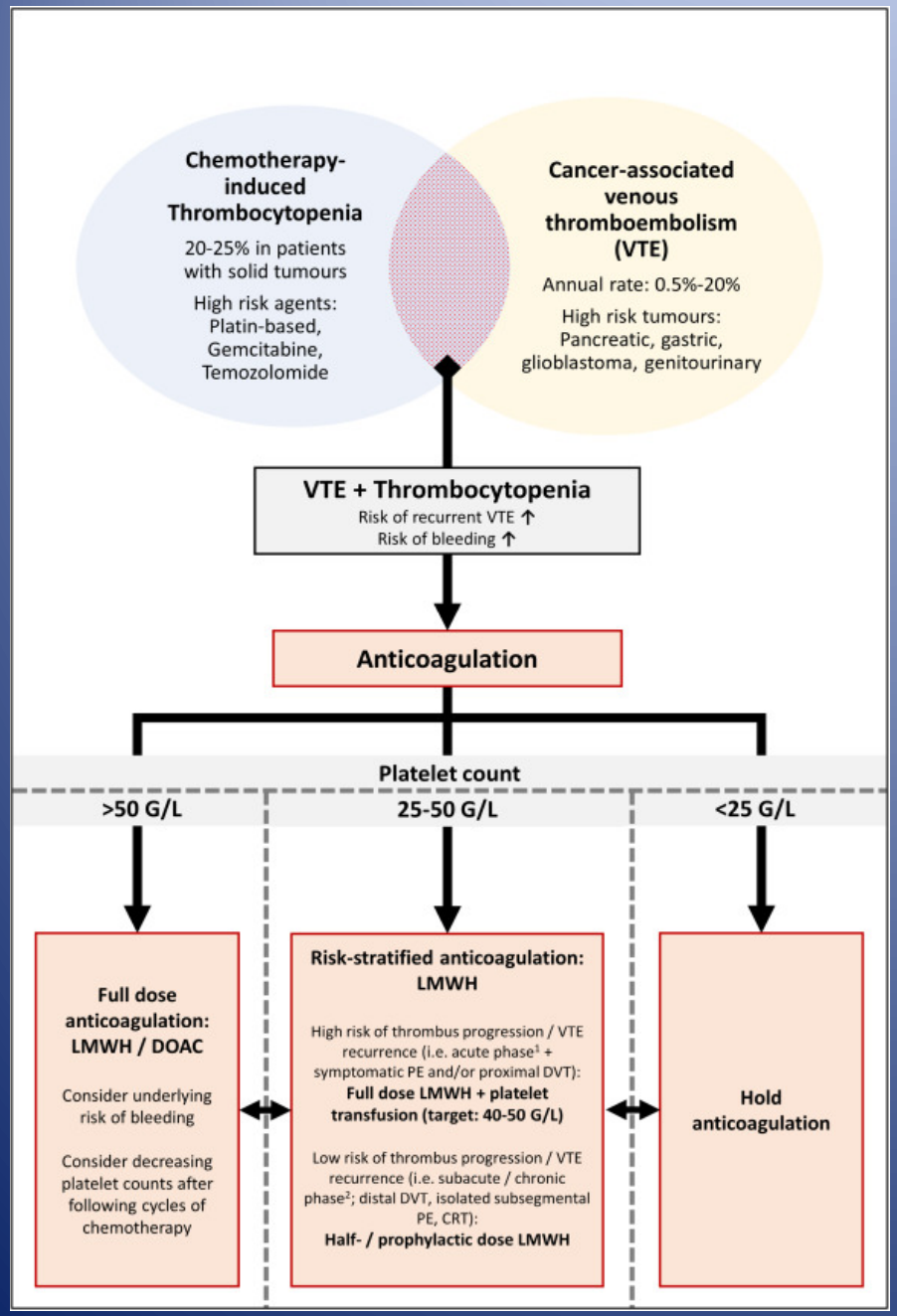
Weighing the risk of bleeding versus thromboembolism

Continuation of anticoagulation

- Increases risk of major bleeding

Discontinuation of anticoagulation

- **Myocardial infarction**
- **Stroke**
- **Venous thromboembolic events**



- ISTH recommendations for cancer associated thrombosis in patients with thrombocytopenia
  - Plt >50: no adjustment
  - Plt 25-50k: ½ dose
  - Plt < 25 stop anticoagulation

Samuelson Bannow BT et al, *J Thromb Haemost* 2018

Cancer Patients with Thrombocytopenia

- Prospective multi-center observational trial
- 121 patients: 62% on full intensity, 40% on modified anticoagulation
- Risk of major bleeding at 60 days
  - Full intensity 12.8%
  - Reduced intensity 6.6% (HR 2.18, CI 1.21-3.93)
- Risk of recurrent thrombosis
  - Full intensity 5.6%
  - Reduced intensity 0%

Carney BJ et al, *Blood Adv*, Oct 2021

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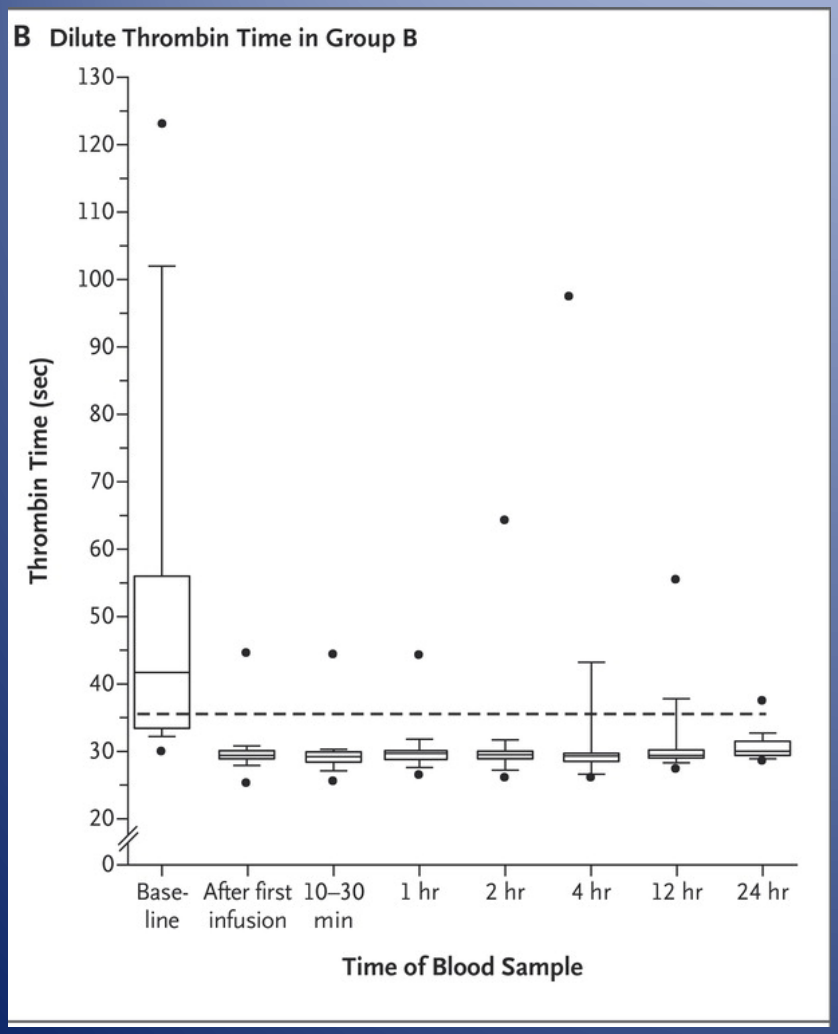
Case 3:

- 79 year-old female on chronic anticoagulation with apixaban for cancer associated PE with right sided hemiparesis after falling at home. CT scan shows large left sided subdural hemorrhage with mass effect. Neurosurgery plans urgent evacuation. Renal function is normal.
- How should anticoagulation be managed?
  - Delay surgery 12 hours
  - Give prothrombin complex concentrate (PCC) and/or recombinant factor VIIa
  - Perform emergent dialysis
  - Give andexanet alfa

Reversal of DOACs for surgery

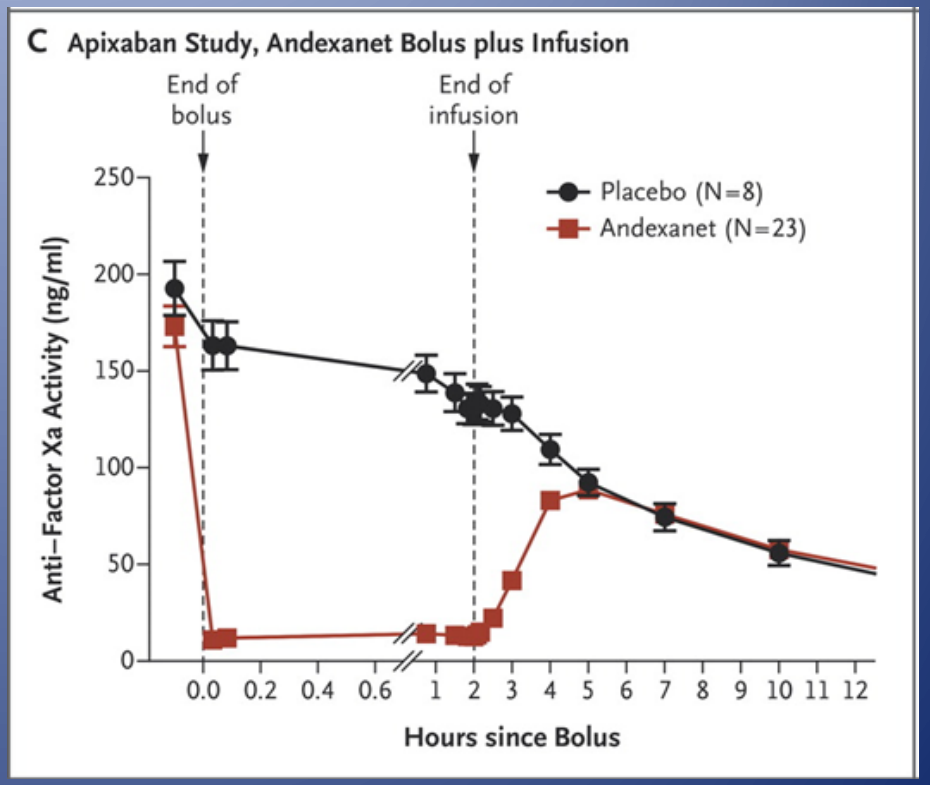


- Idarucizumab is approved for dabigatran reversal
- Monoclonal Ab that binds dabigatran with an affinity 350x > thrombin
- 2.5 gm doses x2 over 15 minutes IV puch
- Decreases both drug levels, ecarin clotting time and thrombin time in patient requiring

Pollack, et al. *NEJM*, 2015

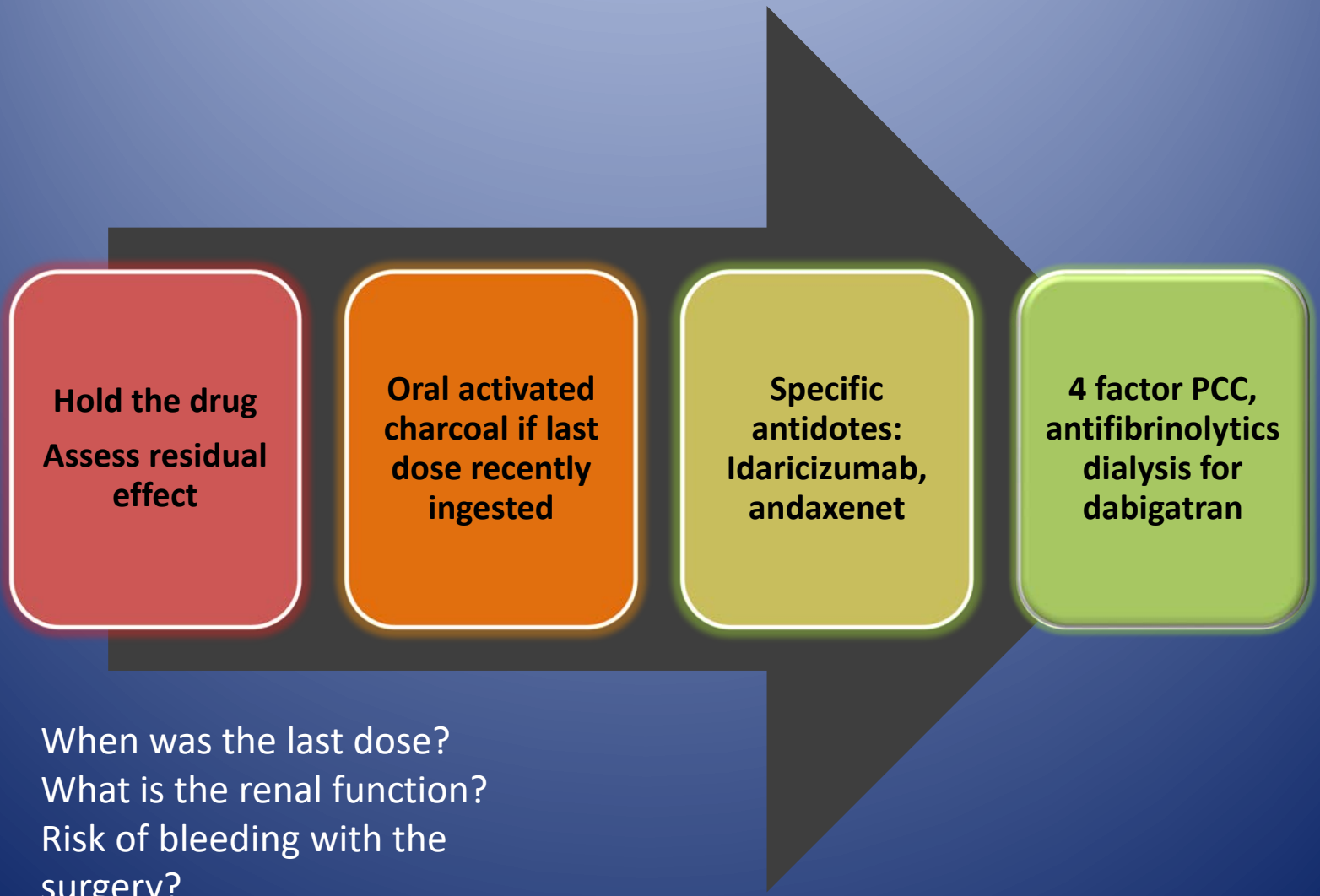
Reversal of DOACs for surgery

- Andexanet alfa is a recombinant human fXa decoy that binds fXa inhibitors (apixaban, rivaroxaban) , but itself is inactive
- Given as an IV bolus followed by infusion
- Tested in healthy volunteers with reversal of clotting times, Xa activity, and thrombin generation; drug levels decreased
- FDA approved in summer of 2018

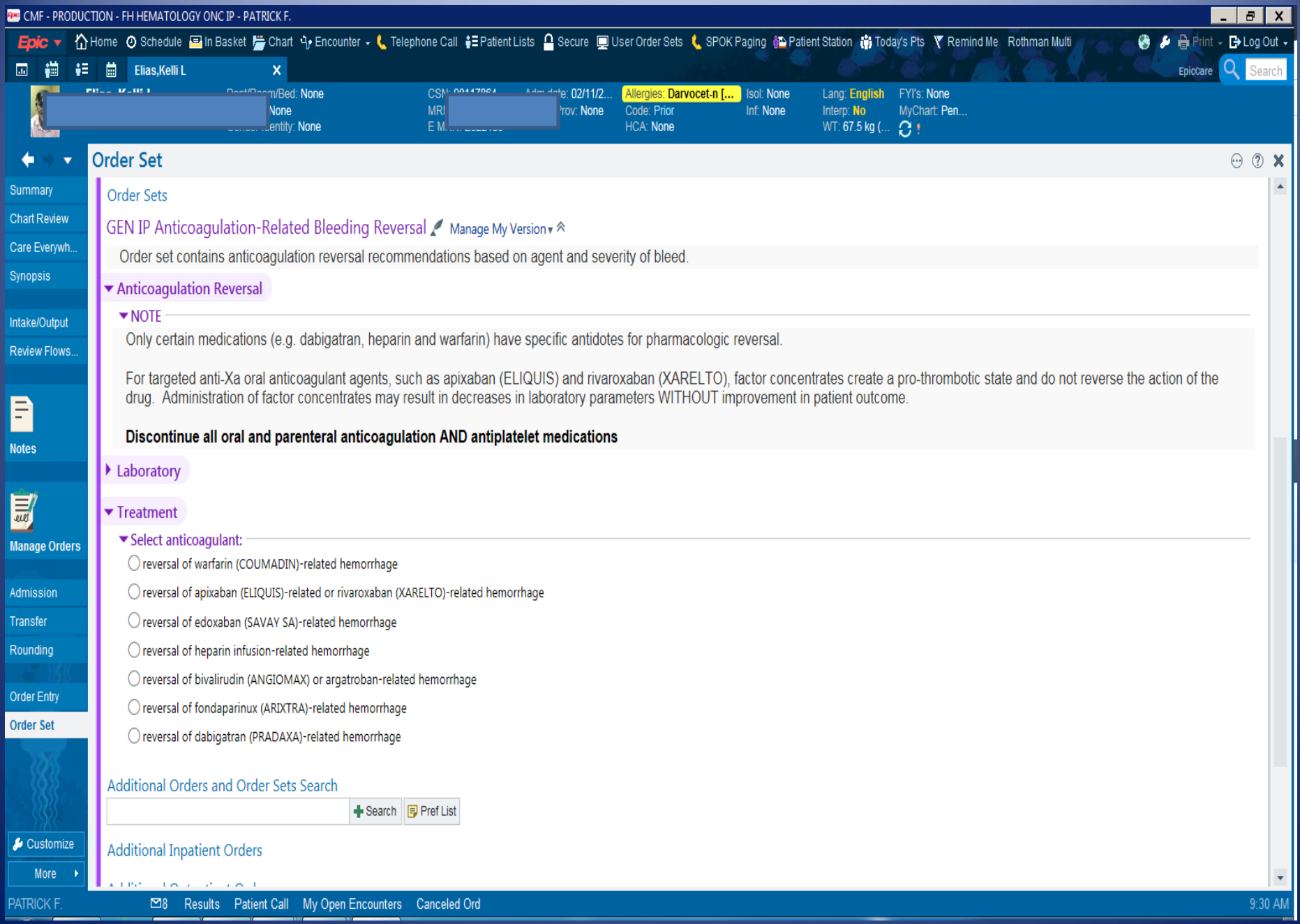


Siegal et al, *NEJM*, 2015

DOAC reversal



When was the last dose?
What is the renal function?
Risk of bleeding with the surgery?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Epic
Home
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In Basket
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Encounter
Telephone Call
Patient Lists
Secure
User Order Sets
SPOK Paging
Patient Station
Today's Pts
Remind Me
Rothman Multi
Print
Log Out
Elias,Kelli L
EpicCare
Search
Allergies: Darvocet-n [...
Isol: None
Inf: None
Lang: English
Interp: No
FYI's: None
MyChart: Pen...
Code: Prior
HCA: None
WT: 67.5 kg (...
Order Set
Summary
Chart Review
Care Everywh...
Synopsis
Intake/Output
Review Flows...
Notes
Manage Orders
Admission
Transfer
Rounding
Order Entry
Order Set
Customize
More
Order Sets
GEN IP Anticoagulation-Related Bleeding Reversal
Manage My Version
Order set contains anticoagulation reversal recommendations based on agent and severity of bleed.
Anticoagulation Reversal
NOTE
Only certain medications (e.g. dabigatran, heparin and warfarin) have specific antidotes for pharmacologic reversal.
For targeted anti-Xa oral anticoagulant agents, such as apixaban (ELIQUIS) and rivaroxaban (XARELTO), factor concentrates create a pro-thrombotic state and do not reverse the action of the drug. Administration of factor concentrates may result in decreases in laboratory parameters WITHOUT improvement in patient outcome.
Discontinue all oral and parenteral anticoagulation AND antiplatelet medications
Laboratory
Treatment
Select anticoagulant:
reversal of warfarin (COUMADIN)-related hemorrhage
reversal of apixaban (ELIQUIS)-related or rivaroxaban (XARELTO)-related hemorrhage
reversal of edoxaban (SAVAY SA)-related hemorrhage
reversal of heparin infusion-related hemorrhage
reversal of bivalirudin (ANGIOMAX) or argatroban-related hemorrhage
reversal of fondaparinux (ARIXTRA)-related hemorrhage
reversal of dabigatran (PRADAXA)-related hemorrhage
Additional Orders and Order Sets Search
Search
Pref List
Additional Inpatient Orders
PATRICK F.
8
Results
Patient Call
My Open Encounters
Canceled Ord
9:30 AM

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MCW

LEARN. LIVE. CARE. CURE.

Special thanks to my colleagues, students, and residents at the Medical College of Wisconsin- Lisa Baumann Kreuziger, Ken Friedman, Josh Field, Juliana Perez Botero, Lynn Malec and Parameswaran Hari.