

Venous Thromboembolism

Alvin H. Schmaier, M.D.

Chief, Hematology and Oncology

Robert W. Kellermeyer Professor of Hematology and
Oncology

Case Western Reserve University

University Hospitals Case Medical Center

Cleveland, OH

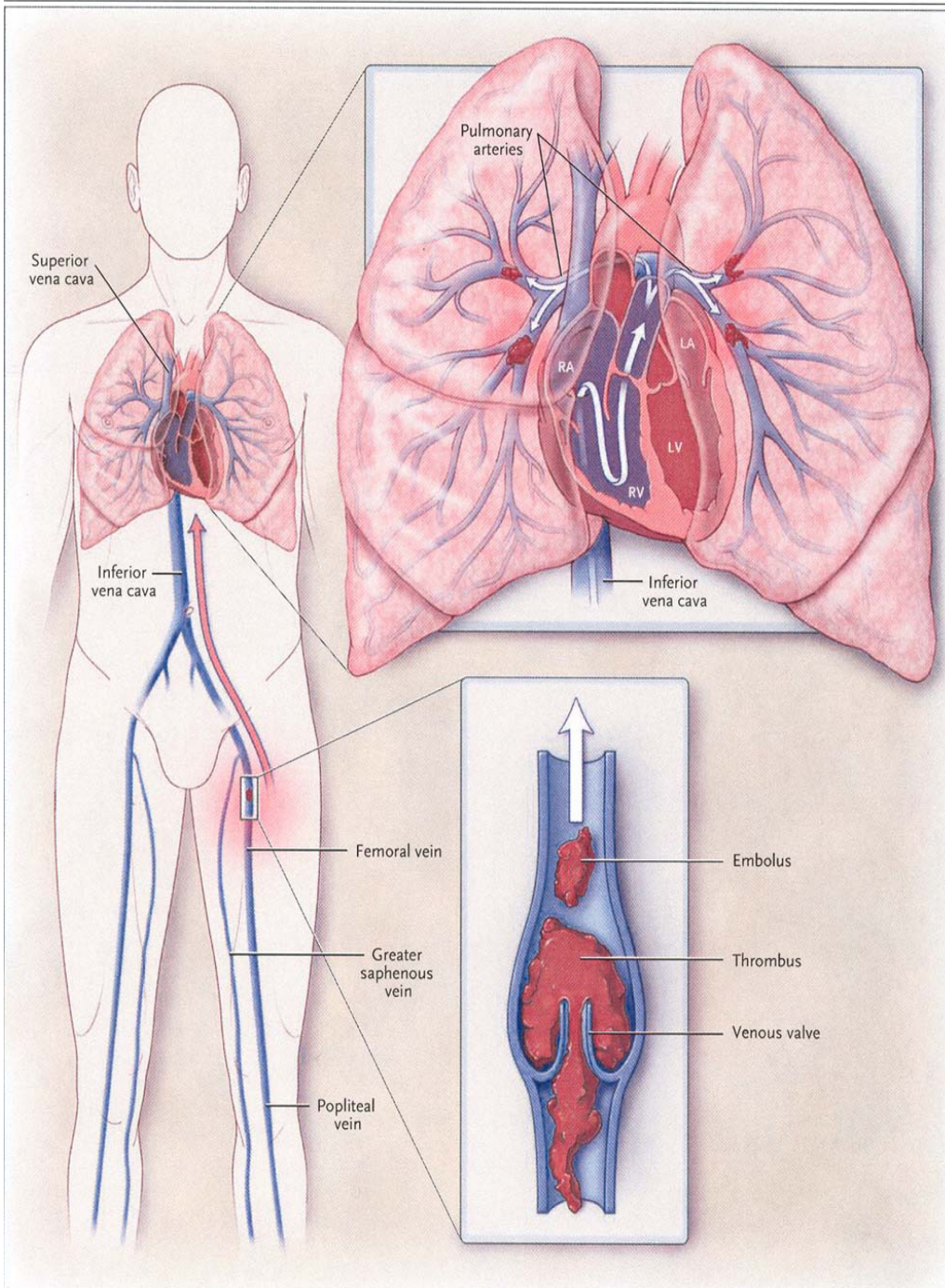
Schmaier@case.edu

Organization of Presentation

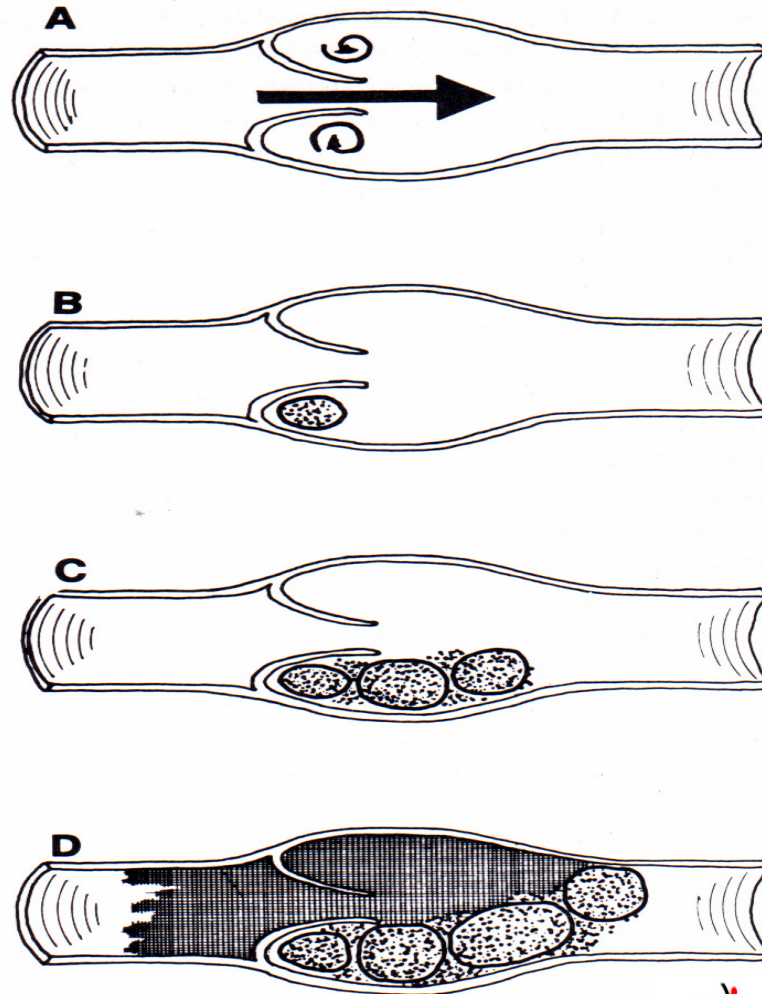
1. Anatomy and pathophysiology of VTE
2. Epidemiology of VTE
3. Clinical manifestations
4. Risk factors: genetic & acquired
5. Laboratory evaluation
6. Treatment
7. Complications & special circumstances

Anatomy and pathophysiology of venous thrombosis.

VTE is a disorder of the veins of the body



VENOUS THROMBOSIS



Epidemiology: VTE: How Bad a Problem it is?

AHA Statistics: 12/17/07

VTE: 0.1% yearly – 33% PE; 67% DVT

- 250,000 patients hospitalized/year
- ~30% die within 30 days; 20% sudden death due to PE;
- 9% DVT; 15% PE; 5% DVT & PE
- 30% develop recurrent DVT with 10 years
- Post-partum VTE 0.2%

VTE Compared to Other Disorders

- 250,000 VTE patients hospitalized/year
- ~30% die within 30 days (~75,000/year)
- 650,000 heart attacks deaths/year
- 325,000 stroke deaths/year
- 652,000 cancer patient deaths/year
 - 32,000 prostate cancer deaths/yr
 - 41,000 breast cancer deaths/yr
 - 42,000 pancreas cancer deaths/yr
 - 40,000 lymphomas/yr

Clinical Manifestations of VTE

Deep venous thrombosis: leg pain, warmth, swelling; 50% of time, clinical symptoms & signs are helpful

Pulmonary embolism: shortness of breath, chest pain, sudden onset, cough, coughing up blood, palpitations, tachycardia, signs of pulmonary hypertension

Objective Diagnosis of VTE

DVT: Doppler study with “no compressibility of vein; venous magnetic resonance; CT venography

Pulmonary embolus: Spiral CT; pulmonary arteriogram, ventilation-perfusion scan

D-Dimer: evidence of big clot!

Risks for Venous Thrombosis

From: John A. Heit, [Hematology 2007](#), Thrombophilia

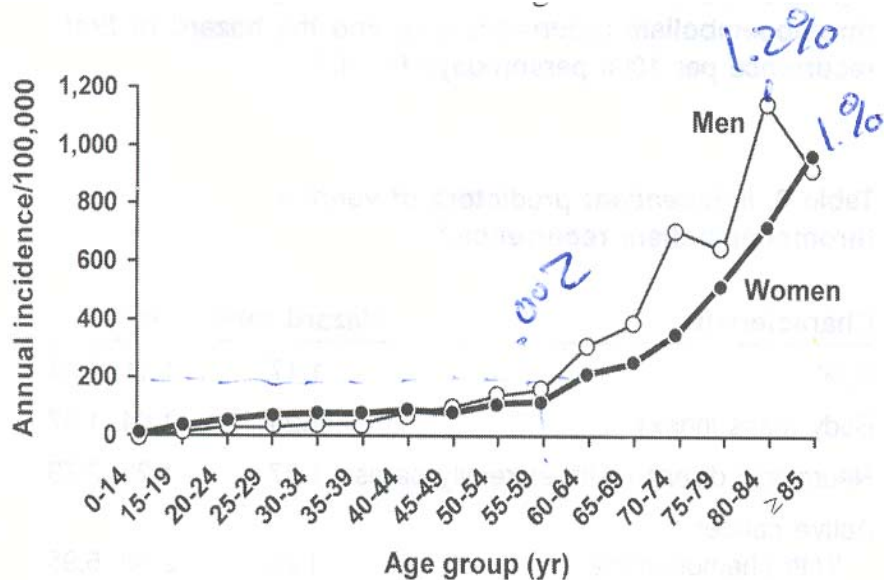


Figure 1. Annual incidence of venous thromboembolism by age and sex.⁴

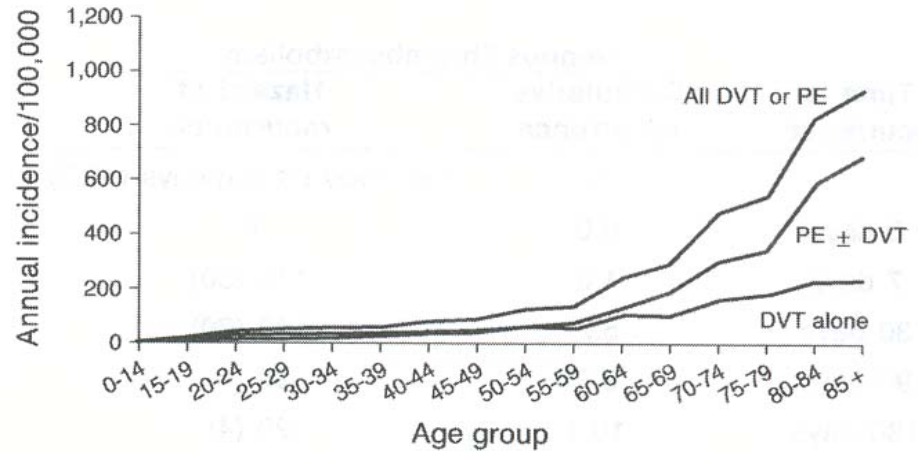


Figure 2. Annual incidence of all venous thromboembolism, deep vein thrombosis (DVT) alone, and pulmonary embolism with or without DVT (PE ± DVT).^{4,22}

Arch Int Med. 158:585, 1998; *Arch Int Med.* 160:761, 2000

Relative/Absolute Risks for Thrombosis

New US Cases/year: 200,000-300,000

Overall Incidence: 0.1%

FVL + oral contraceptive: relative 30-fold
increase, 0.3% absolute risk

Perimenopausal women: 0.123%

Hormonal therapy: relative 7- to 15-fold increase,
1-2% absolute risk

RISK FACTORS FOR VENOUS THROMBOSIS

Age,

Prolonged immobility, reduced mobility

Obesity (>55%)

Neurologic Disease

Cardiac Disease, Trauma & Bed Rest

Pregnancy and postpartum period

Oral Contraceptives, Hormone Replacement

Surgery, Malignancy

THE RISK OF VENOUS THROMBOSIS AFTER SURGICAL PROCEDURES

Orthopedic: Knee (50%), Hip (35-40%)

Thoracoabdominal: 14-35%

Urologic: TUR (7%), Prostatectomy
(35%)

Gynecologic: Vaginal hysterectomy (7%),
Total hysterectomy (27%)

VENOUS THROMBOSIS - MALIGNANCY

Incidence of occult cancer: 0.5-5.8%

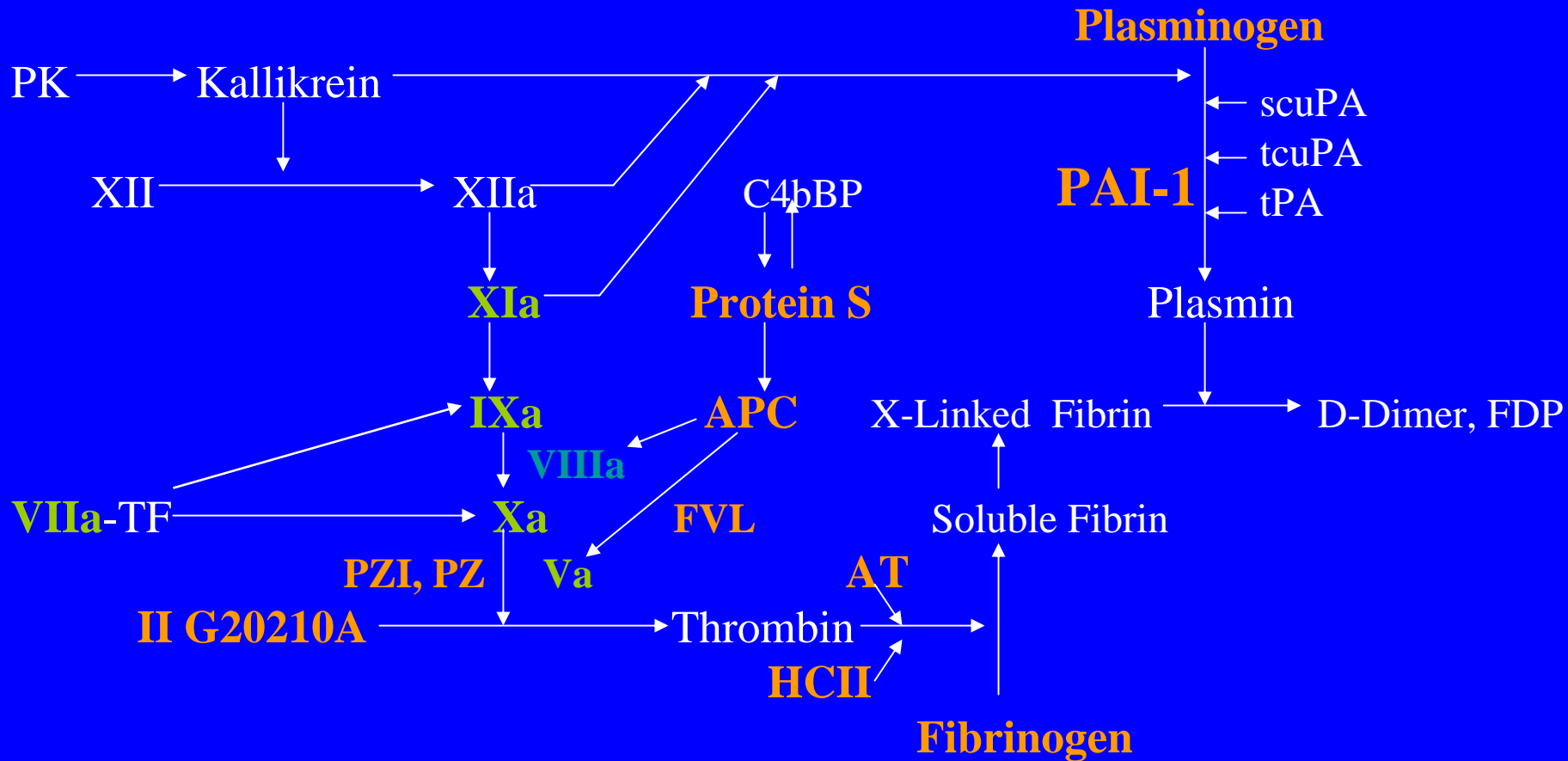
Idiopathic DVT or PE associated with a 3-fold likelihood of presenting with cancer within 3 years

20% of cancer patients have thrombotic events

BIOCHEMISTRY OF VENOUS THROMBOSIS

COAGULATION

FIBRINOLYSIS



ANTICOAGULATION

MOLECULAR CAUSES OF VENOUS THROMBOSIS

Factor V Leiden (20-40%)

Homocysteine (10%)

Prothrombin 20210 (6%)

Protein C (4%)

Protein S (3-4%)

Dysfibrinogenemias (3%)

Antithrombin (1%)

Dysplasminogenemia (<1%)

Elevations of plasminogen activator inhibitor 1, Factors XI
IX, VII, X, and II (Prothrombin)

Heparin Cofactor II

FACTOR V LEIDEN (ACTIVATED PROTEIN C RESISTANCE)

D R R G I

GCA AGG CGA GGA ATA

GAC AGG CAA GGA ATA

D R Q G I

PROTEIN C DEFICIENCY

Protein C: Zymogen of major anticoagulant system; When activated, vitamin K-dependent enzyme that inactivates factors Va & VIIIa & stimulates fibrinolysis

Clinical Syndromes: Venous thrombosis, coumadin skin necrosis, neonatal purpura fulminans, adult purpura fulminans (DIC)

PROTEIN S DEFICIENCY

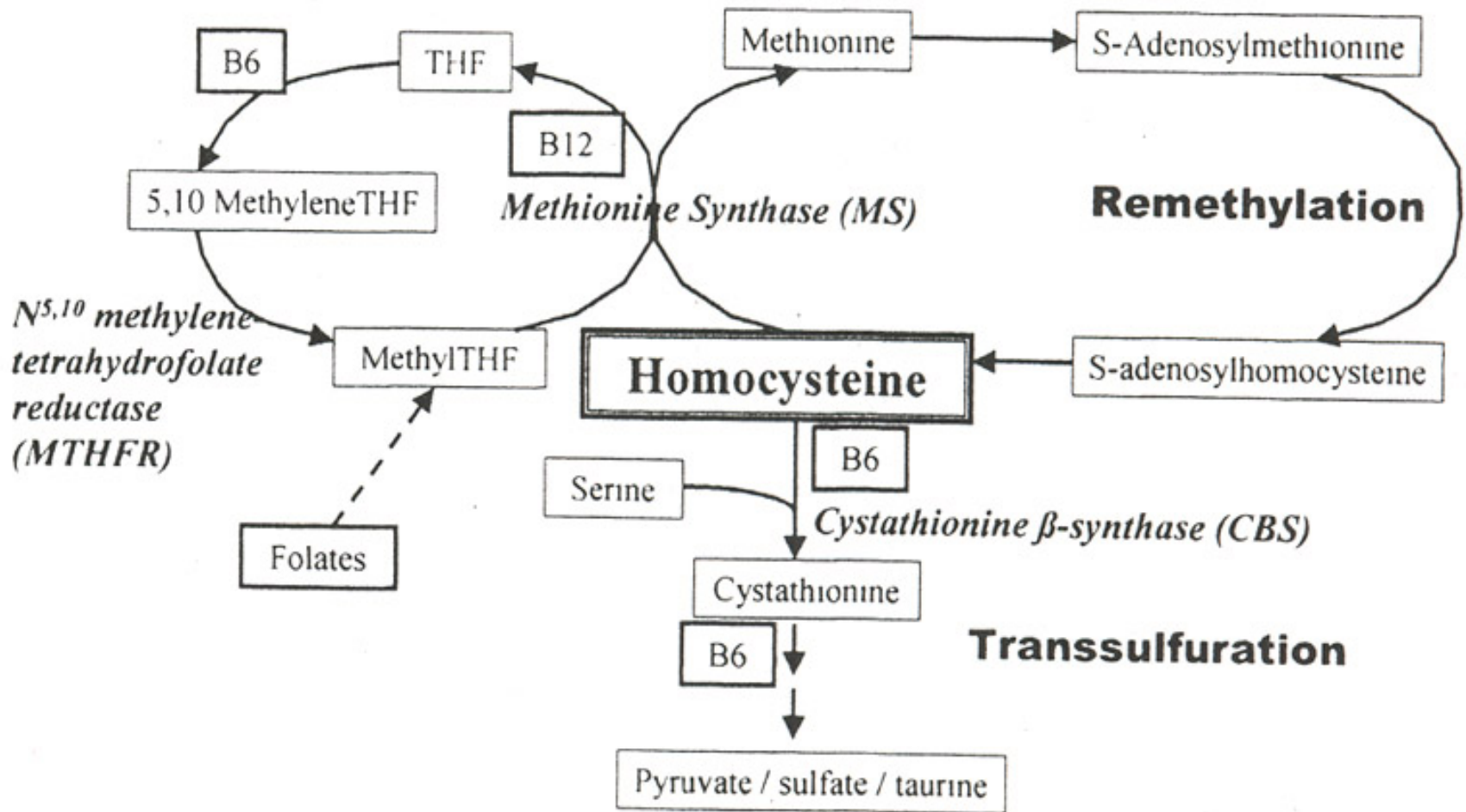
A Vitamin K dependent protein which is not a pro-enzyme

Functions as a cofactor for activated protein C on cell membranes

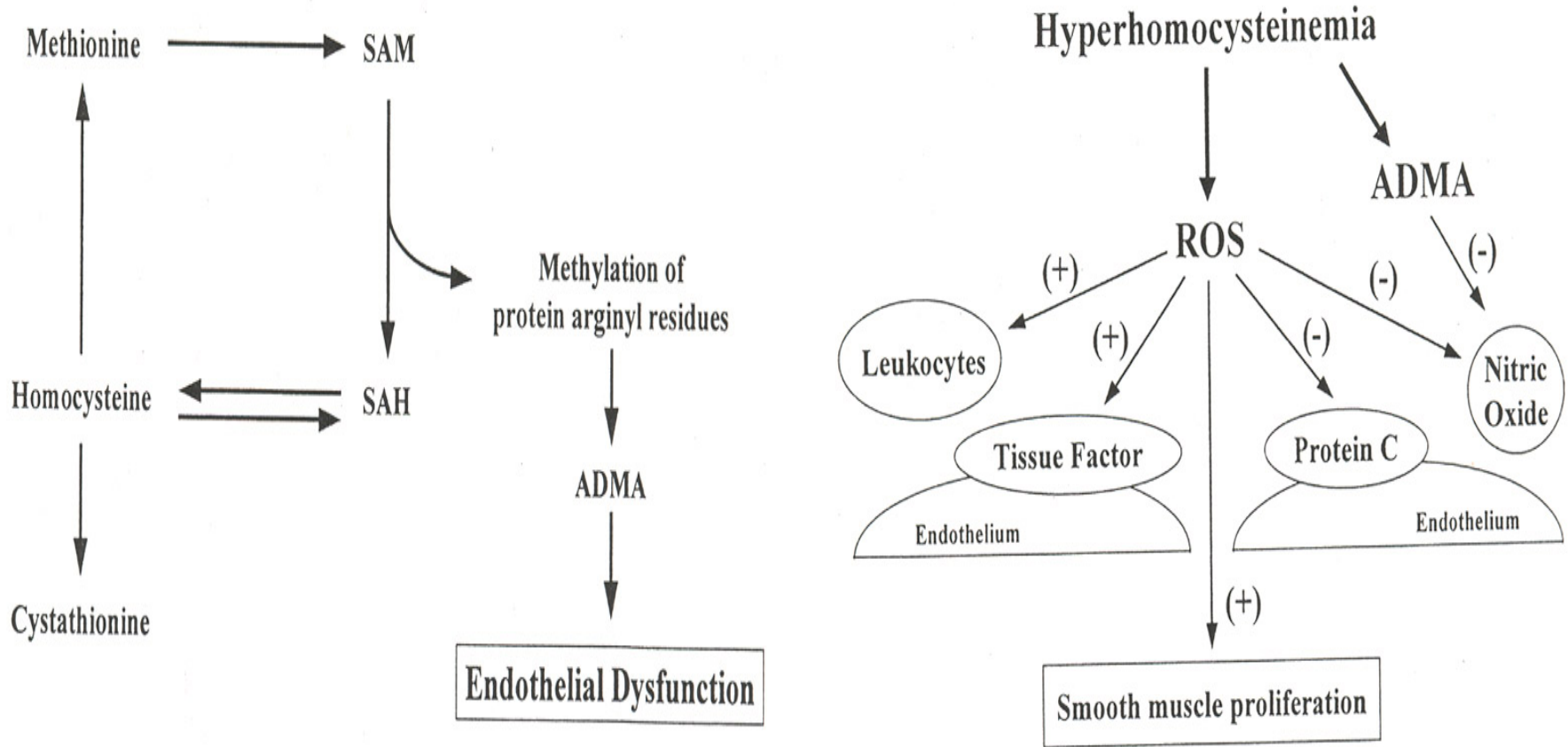
Regulated by C4b binding protein of the complement system

Deficiency associated with a severe prothrombotic state

HOMOCYSTEINE METABOLISM



INFLUENCE OF HOMOCYSTEINE ON VASCULAR BIOLOGY



ADMA = asymmetric dimethylarginine

PROTHROMBIN 20210

Arises from a mutation G to A in the 3' UT of the prothrombin gene

Results in a normal prothrombin molecule at increased levels

Third most common risk factor for thrombosis

Relatively low risk factor for thrombosis

May be associated with Factor V Leiden

ANTITHROMBIN DEFECTS

Antithrombin is a SERPIN that inhibits each of the enzymes of the coagulation system

First protein recognized to be associated with thrombosis

Its presence is the reason heparin functions as an anticoagulant

Venous thrombosis occurs with heterozygotes

Severe prothrombotic defect

Thrombophilia Testing: Hereditary

Strongly Supportive Data:

Antithrombin, Protein C, Protein S deficiencies
Activated Protein C resistance or FVL
Prothrombin G20210A, Homocysteinuria

Supportive Data:

FXIII polymorphisms, Hyperhomocysteinemia,
Dysfibrinogenemias, Reduced TFPI, Increased
Fibrinogen, FII, FVIII, FIX, FXI

Weakly Supportive Data:

tPA deficiency, PAI-1 increase, Dysplasminogenemias,
Reduced PZ & PZI, Hypofibrinolysis

Thrombophilia Testing: Acquired

HITTS: heparin-PF4 Elisa

Antiphospholipid antibody syndrome: anti-cardiolipin and β_2 Glycoprotein I

Myeloproliferative disorders: JAK2 V617F

PNH: uPAR (CD62); DAF

Cancer

Inflammatory bowel disease

Indications for Thrombophilia Testing

Who should be tested?

Does it change management?

No absolute indication for anyone

New DVT/PE

Recurrent DVT/PE

Family history: prior to pregnancy, BCP,
estrogen therapy

High-risk surgery

Chemotherapy with angiogenesis inhibitors

Screening Asymptomatic Family Members

Should be done with caution

? Genetic counseling for genetic tests

Reasons for or not testing:

- + Mental anguish, use of BCPs
- Insurance & employment stigma
- Paternity

Recurrent Thrombosis Risk: Predictors

DVT Recurrence:

30% in 10 years

-For FVL (9%) or G20210 (6.7%)

-Elevated D-Dimer after event

-Warfarin Rx in cancer patients

-Insufficient thromboprophylaxis in In-Patients

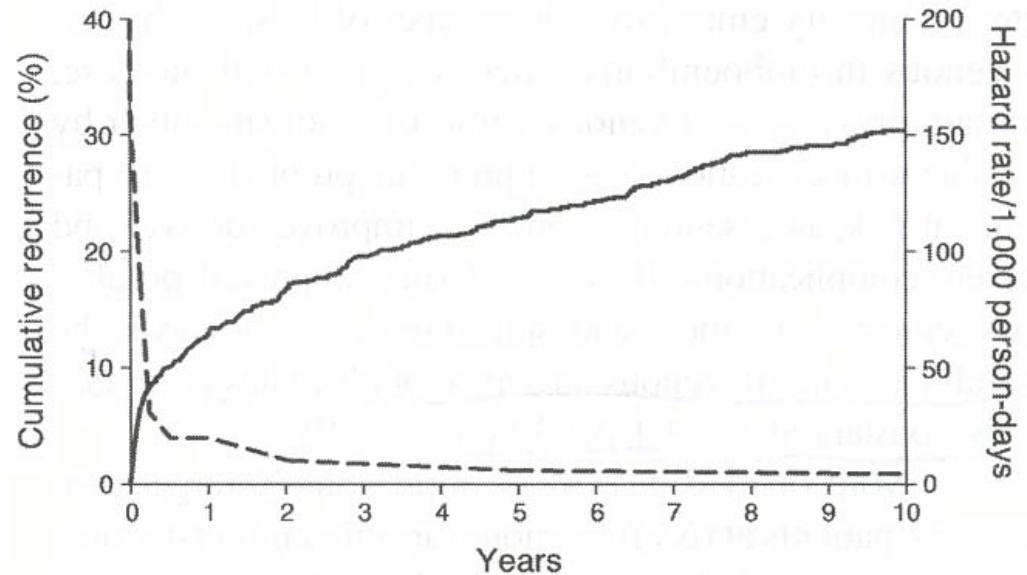
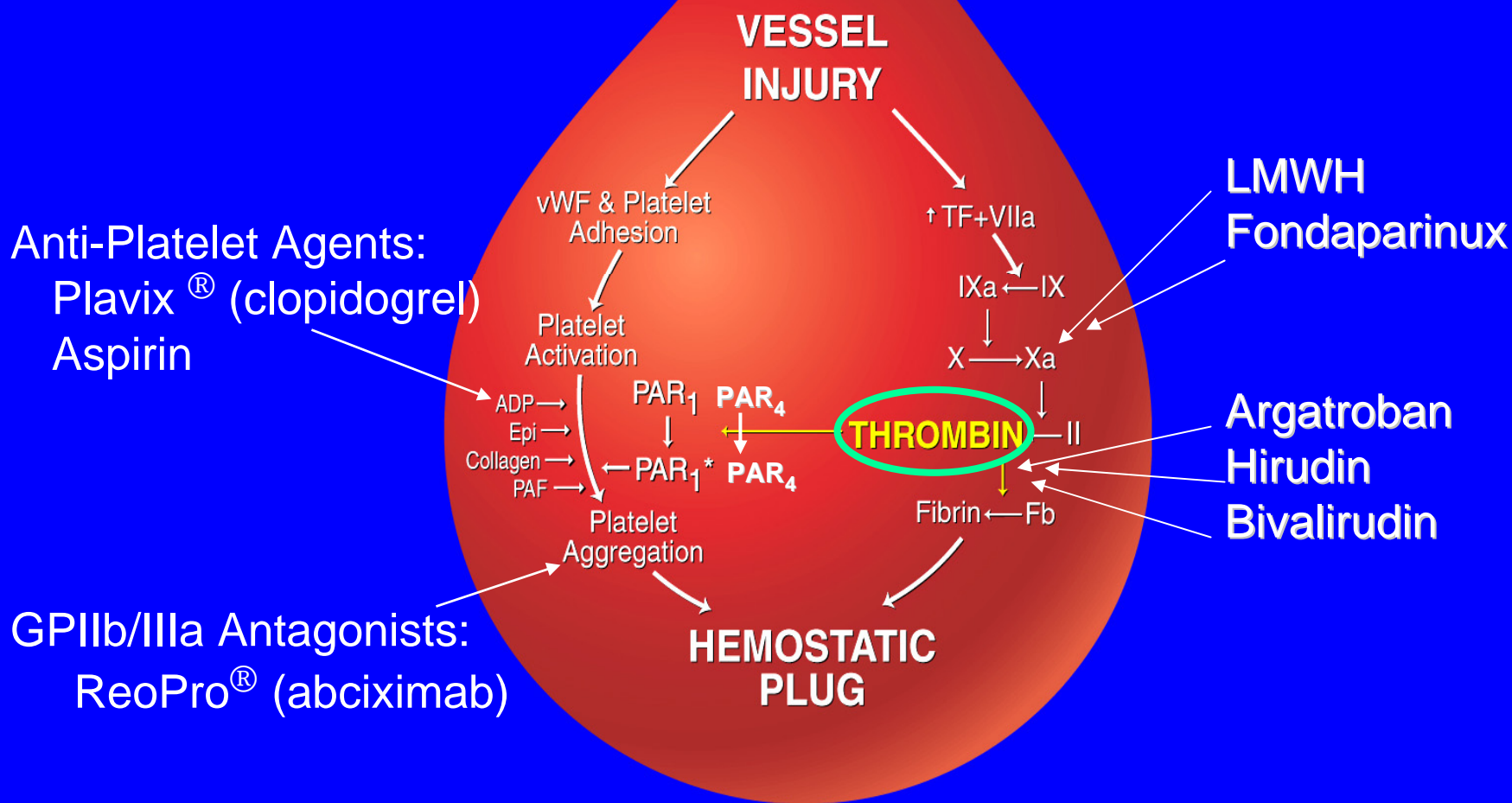


Figure 3. Cumulative incidence of first venous thromboembolism recurrence (—), and the hazard of first recurrence per 1000 person-days (- - -).²²

Arch Int Med 160:761, 2000

Targets of current approved, new Anticoagulants:



THERAPY FOR VENOUS THROMBOSIS

Principles:

Prophylaxis in high risk situation

Prevention of recurrence, propagation,
embolism once thrombus is present

Anti-fibrin agents:

Unfractionated heparin, fondaparinux

Enoxiparin, daltiparin, warfarin

Hirudin, argatroban, bivalirudin

Thrombolytic agents:

Clot lysis of existing thrombosis

Venous Thrombosis: Prophylactic Therapy

Anticoagulation prophylaxis is appropriate in high risk situations:

- 1) Hip, knee surgery
- 2) Major elective surgery
- 3) Trauma
- 4) Medical illness with bed rest
- 5) Previous history of thrombosis
- 6) Pregnancy & thrombosis

Agents:

UFH, LMWH, warfarin

Treatment for VTE

Acute Treatment: DVT, PE

UFH, LMWH, Fondaparinux

(if heparin-induced thrombocytopenia)

Argatroban, Bivalirudin, Lepirudin

Chronic Therapy: Warfarin, LMWH, Fondaparinux

Venous Filters

Employed when anticoagulants cannot be safely used

Permanent or removable filters

Once used, anticoagulants need to be given over long-term

Filter reduce pulmonary emboli, but increase DVT and do not reduce death rate

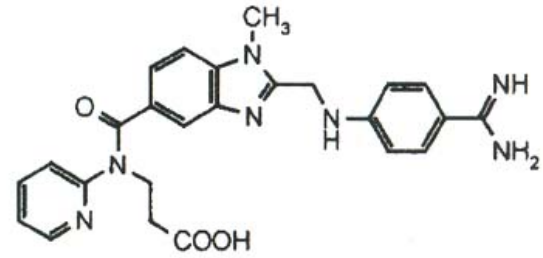
Next Generation of Oral Anticoagulants

Dabigatran - Direct Thrombin Inhibitor

Apixaban - Factor Xa Inhibitor

Rivaroxaban - Factor Xa Inhibitor

Dabigatran



Prodrug of Dabigatran etexilate:

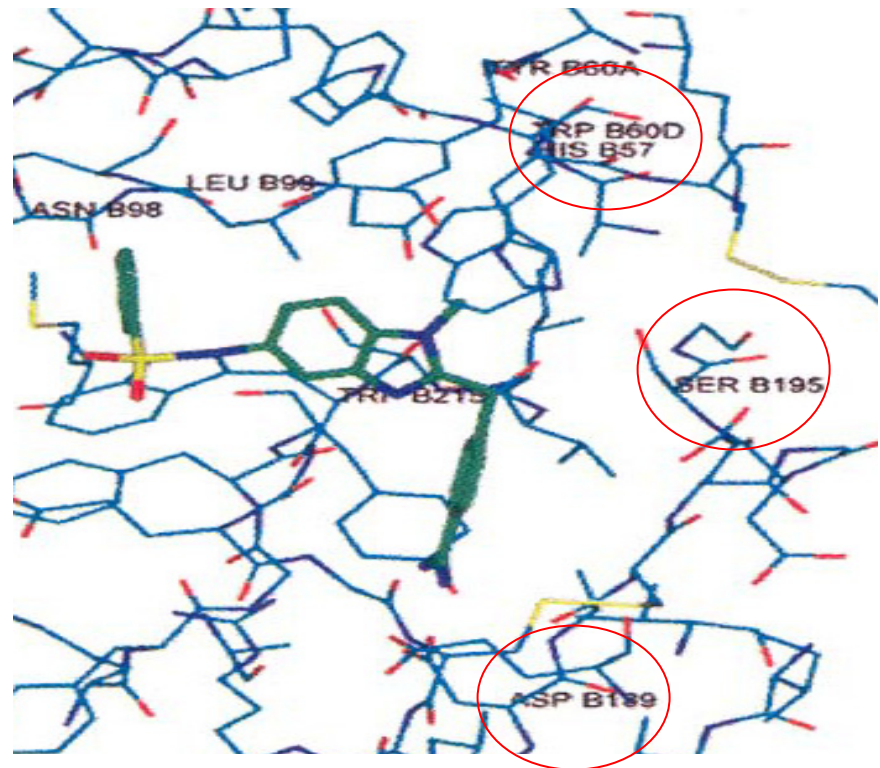
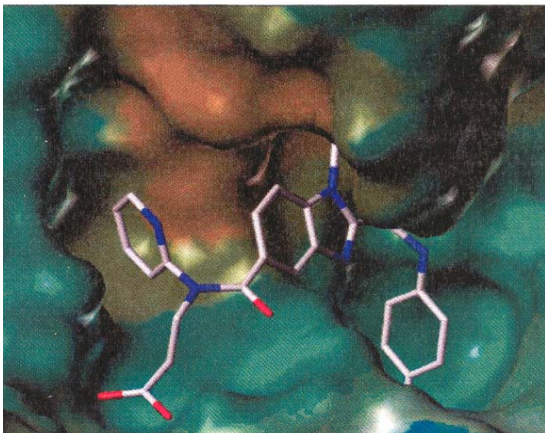
$K_i = 4.5$ nM

$t_{1/2} = 9$ h-14 h, 150 mg po bid

7.2% bioavailability

Mostly excreted in feces

Mostly renal clearance for absorbed
compound

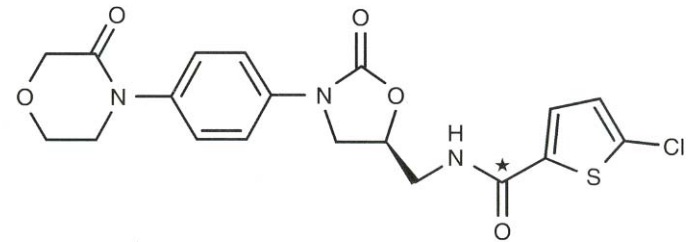


Rivaroxaban

Factor Xa inhibitor, reversible

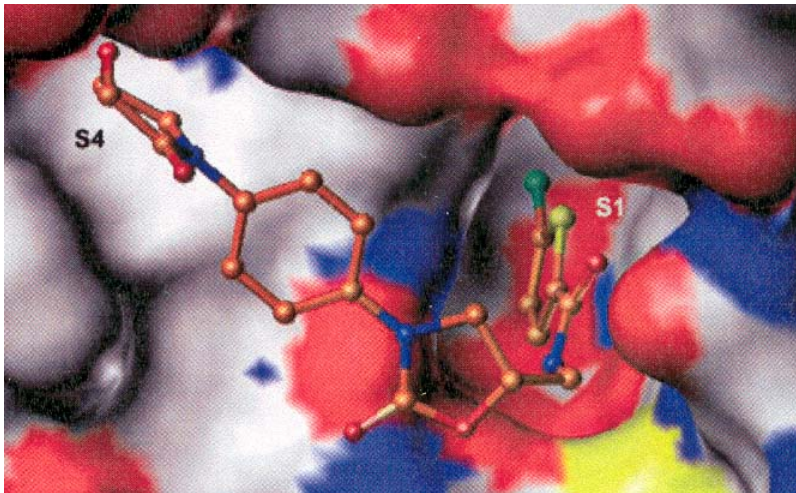
$K_i=0.4$ nM

Renal (66%) and fecal (28%)

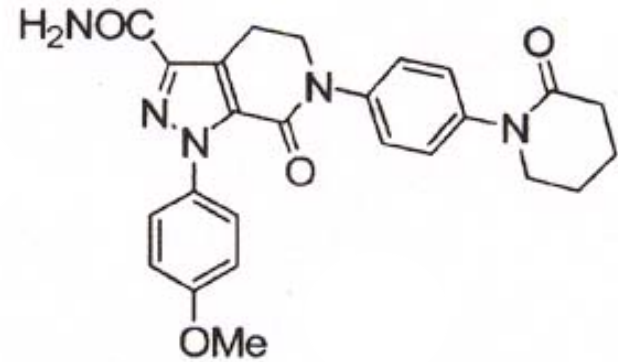


$t_{1/2}=7-9$ h

Gender and body weight
do not appear to effect
pharmacokinetics or
pharmacodynamics



Apixaban



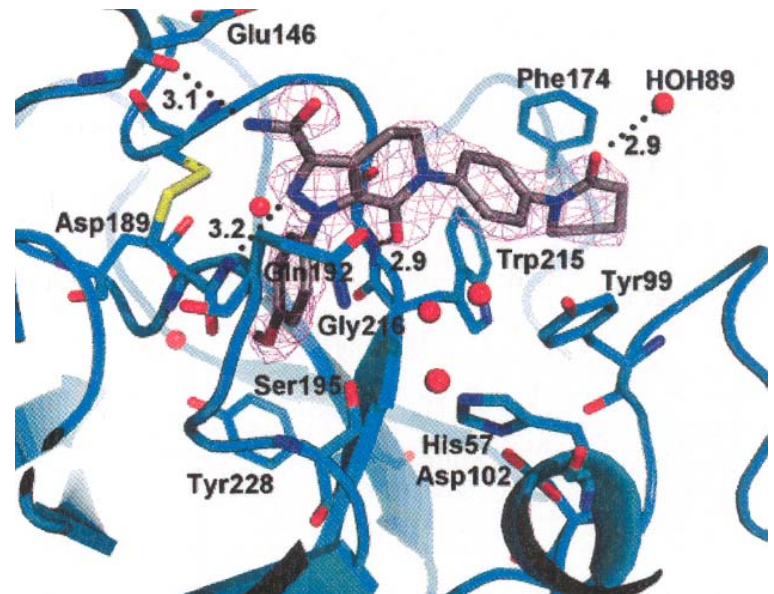
Factor Xa inhibitor

$K_i=0.08$ nM

Peak levels: 3h

$t_{1/2} \sim 12$ h

Elimination: partially
renal (<50%)



Summary of New Oral Anticoagulants

Dabigatran: oral direct thrombin inhibitor with $K_i=4.5$ nM; absorbed agent renal elimination.

Rivaroxaban: oral factor Xa inhibitor with $K_i=0.45$ nM; 67% renal elimination

Apixaban: oral factor Xa inhibitor with $K_i=0.08$ nM; <50% renal elimination