HEMATOLOGY 101- PRACTICAL SOLUTIONS

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FINANCIAL DISCLOSURES

- I WISH…

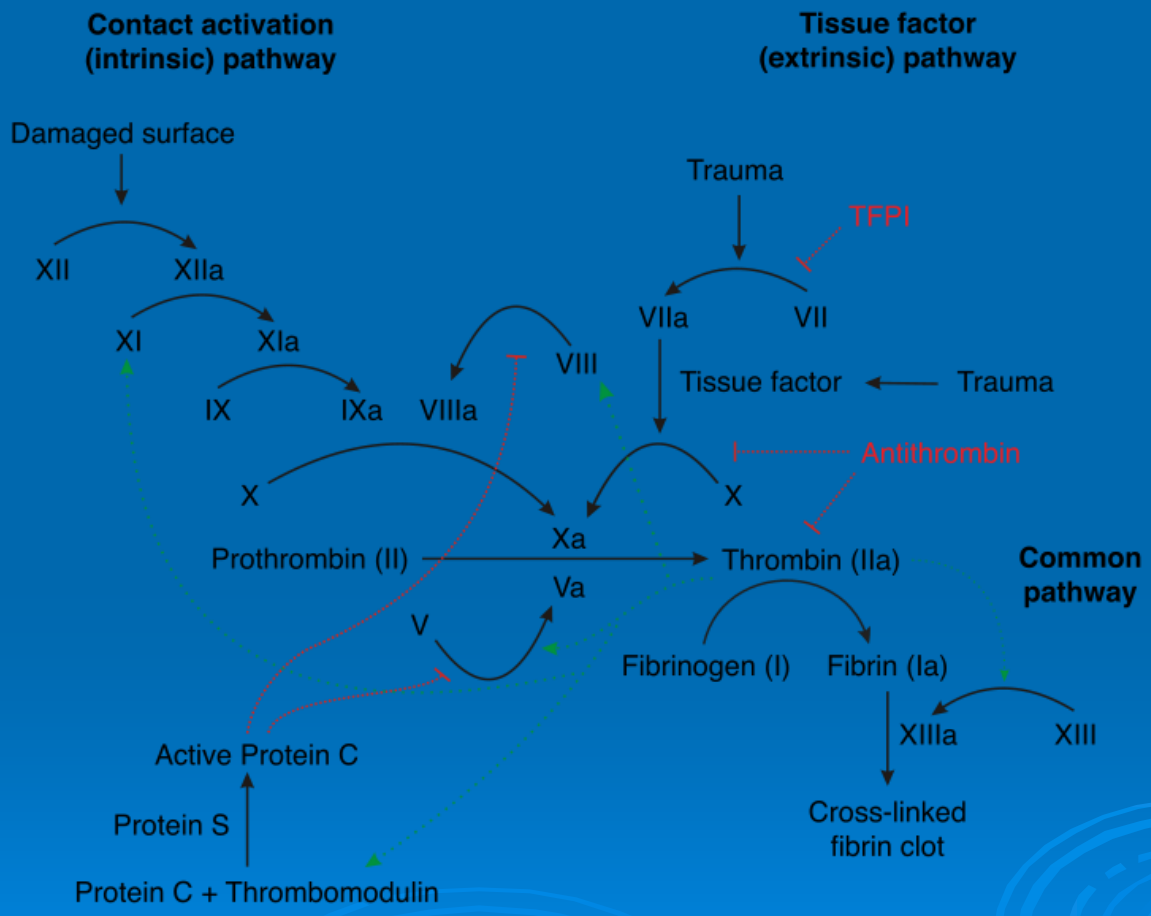
OBJECTIVES

Review hemostasis and the hypercoaguable state.

Review pharmacologic interventions and some reversal agents.

Survey selected common hematologic disorders and discuss their differential diagnosis and their management.

COAGULATION CASCADE



COAGULATION CASCADE

It's all about Thrombin

Under normal circumstances, Antithrombin, Activated Protein C & Tissue Factor Pathway Inhibitor (TFPI) keep the endothelial cells an anticoagulant surface.

Antithrombin inhibits thrombin & FX.

Activated Protein C inhibits Factors V & VIII.

TFPI inhibits FVII.

COAGULATION CASCADE

Thrombin

FVIII amplifies FIXa production, & FV amplifies FXa production.

Thrombin activation accelerates the production of Factors V, VIII, XI, & XIII and promotes platelet aggregation. Thrombin splits fibrinogen to fibrin.

COAGULATION CASCADE

Severe deficiencies of Factors X, V, II, & VII are incompatible with life.

Deficiencies of high molecular weight kininogen, prekallkrein, & FXII increase PTT but are not associated with hemorrhage.

Severe FXIII deficiency does not increase PTT or INR but can be associated with spontaneous intracebral hemorrhage & hemorrhage secondary to trauma/surgery.

RISK FACTORS FOR VENOUS THROMBOSIS

INHERITED

Antithrombin deficiency

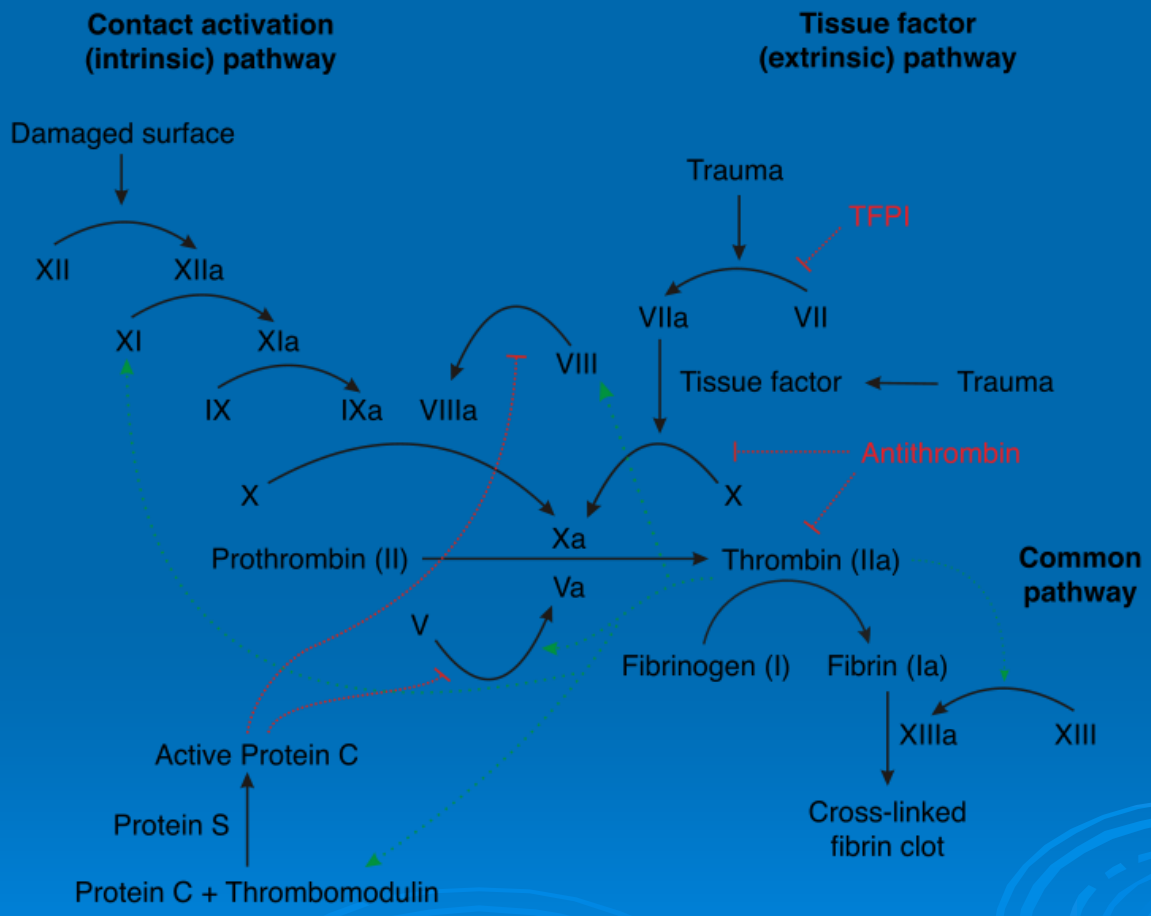
Protein C deficiency

Protein S deficiency

Factor V Leiden (FVL)----A.P.C. resistance

Prothrombin Gene Mutation---Increased prothrombin biosynthesis

COAGULATION CASCADE



PREVALENCE OF FVL & PROTHROMBIN GENE MUTATION

Population	FVL%	PG%
European		
Northern	5-10	1.7
Southern	2-3	3
Middle East		
Israeli	5	5
Arab	15	5
African/Asian	≤ 1	≤ 1

RISK FACTORS FOR VENOUS THROMBOSIS

ACQUIRED

Advancing age
Prior unprovoked DVT
Obesity
Tobacco
Malignancy

APAS
MGUS
MPD
HIT

NS
IBD

TRIGGERS

Pregnancy
Oral contraceptives
H.R.T.
Tamoxifen, Raloxifene
Trauma, immobility, travel
Major surgery

RISK FACTORS FOR VENOUS THROMBOSIS

Obesity→ Single most common risk factor for venous thrombosis. > 50% of patients with thrombosis are obese.

Malignancy→ Patients with unprovoked DVT/PE will have a 3-fold increased risk for presenting with an occult malignancy within 3 years of presentation.

D.V.T. MODEL

Genetics Acquired Risk Factors

\ /

Intrinsic Thrombosis Risk

Prophylaxis | Triggering Factors

|

Thrombosis Threshold

↓

D.V.T.

WHO NEEDS TESTING FOR HEREDITARY THROMBOPHILIA?

- DVT/PE age < 50 with positive family history first degree relatives
- Pregnancy loss- 2nd & 3rd trimester
- DVT/PE in association with OCP/HRT, or pregnancy
- Cerebral venous thrombosis
- Hepatic/Portal/Mesenteric vein thrombosis

"HYPERCOAGULABLE WORKUP"

- Always pursue symptoms or signs which suggest an underlying malignancy and perform age-appropriate cancer screening tests. ~20% of all patients will have a malignancy.
- Antithrombin, Protein C, Protein S functional assays—Omit in patients with 1st thrombus, age >50, & negative family history.

“HYPERCOAGULABLE WORKUP” CONTINUED

- Activated Protein C resistance off Coumadin or order FVL
- Prothrombin Gene Mutation (PGM)
- DRVVT, ACA, Beta 2 Glycoprotein—Tests for Antiphospholipid Antibodies
- Add PNH Panel and MPD workup for hepatic/portal/mesenteric vein thromboses.

CAVEATS

- Acute thrombosis will falsely lower Antithrombin, Protein C, & Protein S levels.
- Antithrombin and Lupus anticoagulant testing affected by Heparin/LMWH.
- Protein C & Protein S levels decreased by Coumadin. Pregnancy & estrogen ↓ Protein S level.
- APA—secondary etiologies: SLE, cancer, infections, & phenothiazines. Must confirm positive results 3 months later.

DURATION OF ANTICOAGULANT THERAPY

- 1ST event with reversible or time limited risk factor-3 to 6 months.
- Unprovoked DVT/PE 1st event. Risk of recurrence with a negative work up ~ 30%. 6 months & then consider long-term anticoagulation VS Aspirin 81mg/day. ASA reduced long-term risk of recurrence by 40% in WARFASA study.

SPECIAL SITUATIONS-INDEFINITE ANTICOAGULATION

- Antiphospholipid antibodies confirmed
- Antithrombin deficiency → 50% lifetime risk for thrombosis
- Protein C & S Deficiency → 75% lifetime risk for thrombosis
- FVL-Homozygous
- Multiple genetic defects-Risk increases multiplicative
- Metastatic cancer
- Site & severity of thrombosis may modify duration

COUNSELING ASYMPTOMATIC HETEROZYGOUS PATIENTS FOR FVL AND/OR PGM

- Avoid estrogen-containing oral contraceptives and HRT.
- Tobacco cessation/ weight loss.
- Anticoagulation prophylaxis for immobility.
- Extended prophylaxis post-op for major surgery.
- Review signs & symptoms of DVT/PE.

PHARMACEUTICAL CONTRACEPTION

- OCP containing estrogens & progestins– increase risk 2-4 times
- Injectable progestins - increase risk 2-4 times
- Progestin only oral formulations- no risk increase

WHICH ANITCOAGULANT SHOULD I CHOOSE?

COUMADIN

Vitamin K antagonist

Has all indications except pregnancy & malignancy (2nd choice)

Least expensive

Has reversal agents

May use with chronic kidney disease

LMWH

Potentiates Antithrombin's inhibition of FXa

1st choice for malignancy

Can use with pregnancy- Enoxaparin

Can use with GI impairment

Fondaparinux used with HIT

Need CRCL of > 30 mls/min.

FXa level may be helpful for patients with CKD, pregnancy, & obesity.

DIRECT THROMBIN INHIBITORS-IV

- Directly binds to thrombin
- Argatroban
- Treatment of Heparin induced thrombocytopenia
- Dose reduce for liver dysfunction

NEWER ORAL ANTICOAGULANTS

Patients having difficulty with consistent INR's

No monitoring desirable

Rivaroxaban has most indications

	Rivaroxaban	Apixaban	Dabigatran
Indication:			
Nonvalvular A. Fib	X	X	X
DVT/PE	X		
↓ Recurrent DVT/PE	X		
Prophylaxis Hip/Knee Replacement	X		

			Inhibitor
T1/2, hr.	12	5-9	12-17
Dosing	If any 2 characteristics: Age ≥ 80 BW ≤ 60kg. CR ≥ 1.5 2.5mg BID	DVT/PE/ Prophylaxis, CRCL < 30ml/min- Avoid A. Fib, CRCL 15-50ml/min- 15mg/day Not Dialyzable	80% Renal Excreted CRCL > 30, 150 mg. BID CRCL 15-30, 75 mg. BID Dialyzable
Food	With or Without	With	With or Without Dyspepsia
Discontinuation for Surgery	Low Risk- 24 hrs. High Risk ≥ 48 hrs.	≥ 24 hrs.	CRCL ≥ 50 1-2 days pre-op min. CRCL < 50 3-5 days pre-op min.
Causes ↑ INR	X	X	X

CONVERSIONS

Parenteral Anticoagulant→ Dabigatran→

Start when Heparin drip is discontinued.

Start 0-2 hours before the next dose LMWH is due.

Dabigatran→ Parenteral Anticoagulant→

Start parenteral anticoagulant 12 hrs. (CRCL≥ mls/min) or 24 hrs. (CRCL <30 mls/min) after last dose of Dabigatran.

CONVERSIONS CONTINUED

Warfarin→ Dabigatran→ Start Dabigatran when INR <2.0

Dabigatran→ Warfarin →

CRCL≥ 50mls/min Start Warfarin 3 days before stopping Dabigatran

CRCL 30-50mls/min Start Warfarin 2 days before stopping Dabigatran

CRCL 15-30mls/min Start Warfarin 1 day before stopping Dabigatran

DABIGATRAN

Drug-Drug Interactions

Avoid Rifampin

With CRCL 30-50mls/min & Dronedarone or Ketoconazole are co-administered, ↓ Dabigatran to 75mg. BID. Avoid with CRCL <30mls/min

RIVAROXABAN & APIXABAN

Drug-Drug Interactions

Itraconazole, Ketoconazole, Ritonavir, & Indiravir coadministration should be avoided- Increased risk for hemorrhage.

With Apixaban, can give at dose 2.5mg BID, if not already at that dose. Carbamazepine, Phenytoin, & Rifampin coadministration should be avoided- decreased efficacy.

RIVAROXABAN & APIXABAN CONTINUED

- Pregnancy category C- Rivaroxaban→ no breastfeeding data & B- Apixaban
- Avoid in patients with moderate/severe hepatic impairment
- No known reversal agent
- With Apixaban, dose ↓ 2.5mg BID if ≥ 2 characteristics present; age ≥ 80, weight ≤ 60 Kg or Creatinine ≥ 1.5. No data for CRCL < 15 mls/ min

SWITCHING TO & FROM RIVAROXABAN OR APIXABAN AND OTHER ANTICOAGULANTS

Warfarin→ start when INR < 3.0 (Rivaroxaban), < 2.0 (Apixaban)

Other anticoagulants→ stop Heparin drip & start at same time

Rivaroxaban→ substitute new drug at time of next scheduled dose. If Warfarin, start parenteral anticoagulant & Warfarin at time of next scheduled dose.

Apixaban→ Same as Rivaroxaban

RIVAROXABAN USE FOR INITIAL DVT/PE TREATMENT:

Who should NOT get it?

- Active Malignancy
- Pregnancy/Breastfeeding
- Massive PE or DVT if thrombolysis is planned
- Weight > 250lbs. Or < 110lbs.
- Severe renal or hepatic dysfunction
- Contraindicated or caution advised with

DVT/PE IN CANCER PATIENTS

RISK FACTORS:

Advanced stage

Major surgical resection

Central venous access devices

Chemotherapy

Antiangiogenic agents

Hormones

ESA

MOST COMMON PRIMARY SITES

Pancreatic

Lung

Brain

Gynecologic

Stomach

DVT/PE TREATMENT GUIDELINES FOR CANCER PATIENTS

- LMWH-1st choice
- Coumadin-2nd choice
- Oral Factor Xa Inhibitors-Limited data cancer patients
- Can stop treatment after 6 months if patient in remission and off treatment.
- With metastatic disease, continue anticoagulation indefinitely.
- Incidental DVT/PE noted on staging/restaging scans should be treated aggressively.

MANAGEMENT OF RECURRENT DVT/PE IN CANCER PATIENTS

9% of patients treated with LMWH & ~ 20% treated with therapeutic Warfarin develop recurrent DVT/PE.

Treatment- Switch Warfarin to full dose LMWH.

-Already on LMWH, increase dose by 20-25%. Check Anti-Xa level 4 hours post injection.

INDICATIONS FOR DVT/PE PROPHYLAXIS IN CANCER PATIENTS

Hospitalized with immobility/ acute illness

-Heparin SQ/ LMWH.

Major surgery-abdominal or pelvic

-Ideally, pre-op Enoxaparin and sequential TEDs. Continue pharmacologic treatment 7-10 days minimum. Up to 4 weeks in high risk patients.

INDICATIONS FOR IVC FILTER

Contraindication to anticoagulation.

Recurrent DVT/PE or extension of existing thrombus despite optimal treatment.

Patient non-compliance.

REVERSAL OF ANTITHROMBOTICS

Heparin: Protamine 1mg/ 100 units Heparin- Max dose 50mg/ 10 minutes.

Enoxaparin: Protamine will partially reverse

Fondaparinux: ? Factor VIIa- 90mcg/kg, prothrombin concentrate 50 units/kg.

Dabigatran: Hemodialysis

Rivaroxaban & Apixaban ?

VITAMIN K PROTEIN CONCENTRATE

Dosing: IU requested=

weight (Kg) x target factor level (~70%) – current level

INR 2-3: 20% factor level

INR 3-4: 10% factor level

Boulis et al. Neurosurgery 45: 1113, 1999

PERIOPERATIVE MANAGEMENT ON CHRONIC WARFARIN

Indication for Warfarin and the procedure will dictate plan.

Low risk procedures:

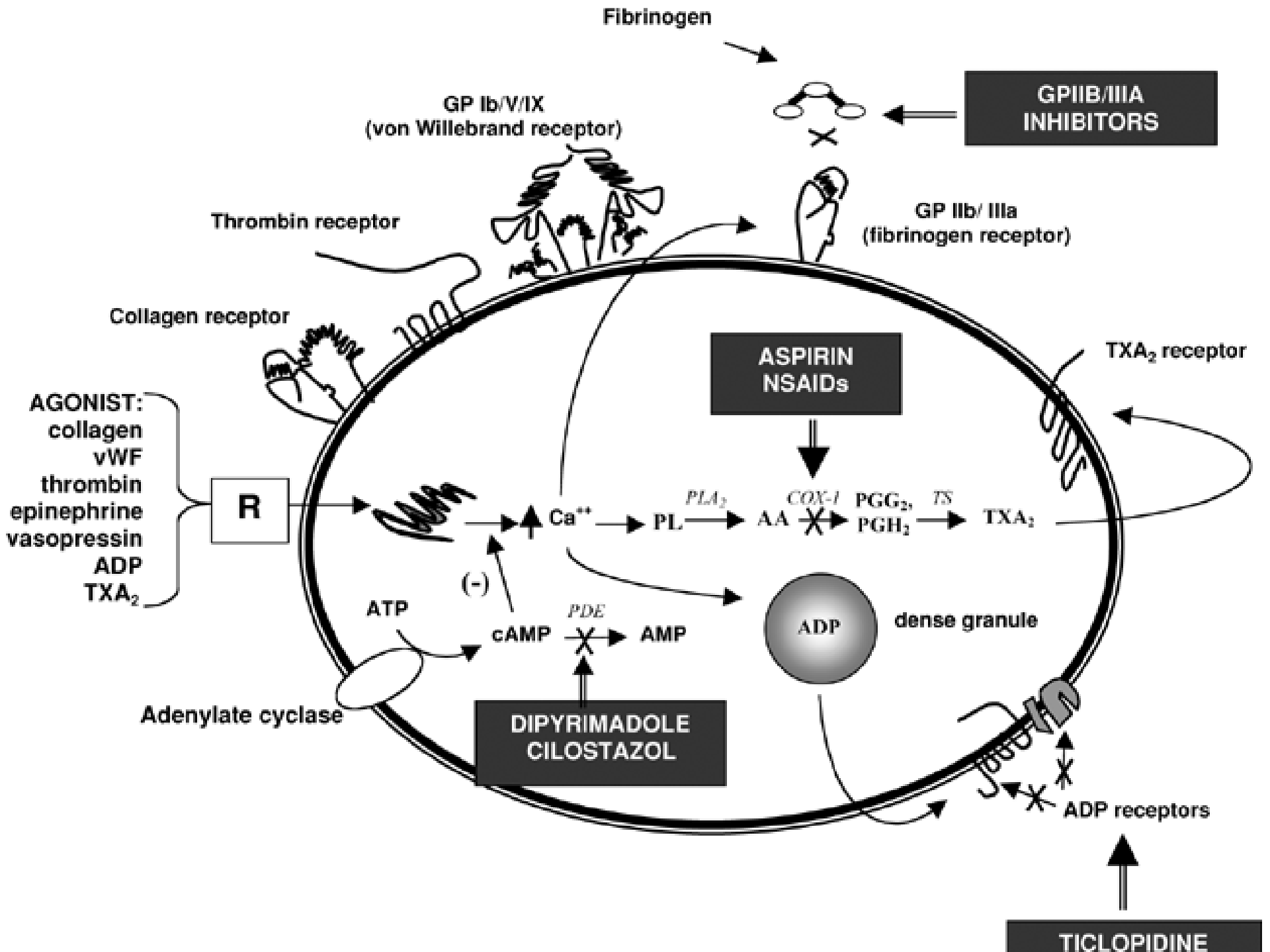
cataract, minor dental, & minor skin

continue Warfarin or stop 2-3 days. Can add Epsilon aminocaproic Acid

Moderate to high risk procedures:

Low risk for thromboembolism: Stop Coumadin for 5 days.

Moderate to high risk: Heparin or LMWH bridge


Fibrinogen
GPIIB/IIIA INHIBITORS
GP Ib/V/IX (von Willebrand receptor)
Thrombin receptor
GP IIb/ IIIa (fibrinogen receptor)
Collagen receptor
ASPIRIN NSAIDs
TXA2 receptor
AGONIST: collagen vWF thrombin epinephrine vasopressin ADP TXA2
R
Ca++
PL
PLA2
AA
COX-1
PGG2, PGH2
TS
TXA2
(-)
ATP
cAMP
PDE
AMP
ADP
dense granule
Adenylate cyclase
DIPYRIMADOLE CILOSTAZOL
ADP receptors
TICLOPIDINE

PLATELET FUNCTION

Adhesion- Platelet glycoprotein (GPIb) receptor interaction with vWf--platelet-vessel wall interaction

Aggregation- Platelet GPIIb-IIIa receptor interaction with Fibrinogen--platelet-platelet interaction

Secretion- Platelets release granule contents

PLATELET FUNCTION CONTINUED

Platelet receptor activation by ADP, thrombin, & collagen mediate aggregation and secretion

Provides membrane surface for activation of thrombin.

ECCHYMOSIS Ddx

Thrombocytopenia: ITP, bone marrow disorders, drugs, CTD

Platelet dysfunction: NSAIDS, alcohol, P2Y12 inhibitors, OTC's, & Herbals

SSRI anti-depressants particularly when combined with other anti-platelet agents

DTI, Factor Xa inhibitors, Warfarin

Vitamin K Deficiency (no Coumadin): Poor diet +/- antibiotics

ECCHYMOSIS Ddx CONTINUED

Steroids

Senile Purpura

CKD, liver disease, paraproteinemia

Congenital: von Willebrand disease (vWd), Hemophilia, Rare platelet function disorders

WARNING SIGNS

Positive family history, prior hemorrhage with trauma, surgery, or procedures.

Multiple sites of hemorrhage- hematomas, menses, epistaxis

WORK UP

If minor hemorrhage, stop offending medications for 10 days and reassess.

Persistent hemorrhage +/- positive family history- check CBC, INR, PTT, & Platelet closure time.

PRE-OPERATIVE CLEARANCE

Isolated elevated PTT: Check F8, 9, 11, & DRVVT

Isolated elevated PT/INR: Check F7, fibrinogen, & HFP. In the correct setting, can give Vitamin K trial first.

Isolated thrombocytopenia: Stop offending agents, Check B12, folate, ANA.

Abnormal platelet closure time: If on offending agents, stop 10 days & repeat. No meds &/or positive family history- check vWd panel.

CLOPIDOGREL (FDA 1997)

- P2Y12 Platelet inhibitor (Thienopyridines)
- Irreversible binding
- Prodrug→CYP2C19→active metabolite
- Poor metabolizers have worse outcomes
- Can check CYP2C19 genotype
- Avoid Omeprazole & Esomeprazole (CYP2C19 inhibitors). Can use Dexlansoprazole, Lansoprazole, & Pantoprazole instead→ have less effect

CLOPIDOGREL (FDA 1997) CONTINUED

TTP after < 2 weeks exposure.
Agranulocytosis/Pancytopenia

Pregnancy B, No breastfeeding

No dose adjustment for elderly or hepatically impaired.

Reverse with platelets.

PRASUGREL (FDA 2009)

P2Y12 ADP receptor irreversible inhibitor of platelet activation & aggregation

ASA dose 81-325mg./ Day

Contraindications→ weight < 60, Prior TIA or stroke- ↑ rate of stroke on Prasugrel unless patients ≥ 75 with history of diabetes or prior MI

PRASUGREL (FDA 2009) CONTINUED

TTP has been reported- can occur with exposure < 2 weeks.

Can give with mild to moderate hepatic impairment.

Can give with H2blockers & proton pump inhibitors.

No drug-drug interactions.

TICAGRELOR (FDA 2011)

P2Y12 reversible platelet inhibitor

ASA dose 81 mg./ Day

Dyspnea

No contraindication based on age

Contraindicated→ History intracranial hemorrhage, & severe hepatic impairment.

Renal impairment→ No dose adjustment

Discontinue 5 days pre-op.

TICAGRELOR (FDA 2011) CONTINUED

Drug-Drug Interaction

Avoid use with strong CYP3A inhibitors- Azole Antifungals, clarithromycin, & Anti-Retrovirals.

Avoid use with Potent CYP3A Inducers- Rifampin, Dexamethasone, Phenytoin, Carbamazepine, & Phenobarbital.

REVERSAL OF ANTIPLATELET AGENTS

Aspirin & Clopidogrel: CAD patients- transfuse platelets. Can try DDAVP for other patients.

Prasugrel: Transfuse platelets

Ticagrelor: T1/2= 8hrs., supportive care, no data for platelet transfusions

PERIOPERATIVE MANAGEMENT OF ANTIPLATELET AGENTS

Low Risk Procedure: Continue medications

Moderate to High Risk:

History of CABG-

continue ASA, stop Clopidogrel

Drug eluting stent-

need ASA & Clopidogrel 12 months

If withholding agents, need at least 7-10 days to clear.

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Anfibatide

- Purified protein from snake venom.
- Intravenous glycoprotein Ib antagonist.
- Phase I dose-finding study- 94 participants.
- The inhibitory effect was undetectable 4 hours post treatment.

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Anfibatide

No significant change in bleeding time, PTT, INR, or platelet count noted.

No serious adverse events or deaths noted.

Phase II trial planned in NSTEMI patients receiving angioplasty.

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PRIMARY VS SECONDARY POLYCYTHEMIA

Primary:

No obvious etiology→ EPO level, JAK-2

→ If EPO low & JAK-2 negative→ EXON-12 deletion

PRIMARY VS SECONDARY POLYCYTHEMIA

Secondary Etiologies:

Tobacco
OSA
Cardiopulmonary disorders
Volume depletion
Renal/liver malignancy
Cerebellar Hemangioblastoma
Polycystic Kidney Disease
Familial

MICROCYTIC ANEMIA

Iron deficiency

Congenital Sideroblastic Anemia-B6

Acquired Sideroblastic Anemia→ lead poisoning, Isoniazid, copper deficiency- bariatric surgery patients

Hemoglobinopathies

-Alpha Thal Minor-Normal Hemoglobin Electrophoresis

-ß Thal Minor-Increase hemoglobin A2 & F

-Hemoglobin C-Trait, Hemoglobin E

Anemia of Chronic disease

RA often MCV-78 if not on Methotrexate and/or Imuran

POST SPLENECTOMY/ FUNTIONAL ASPLENIA SEPSIS PREVENTION

Early antibiotics to cover encapsulated organisms- Streptococcus pneumoniae, & Haemophilus Influenzae (H. flu)

Vaccination

-Pneumovax every 6 years

-H. flu times one

-Meningococcal ? Every 5 years

-Influenza yearly

Tobacco Cessation

POLYCLONAL VS MONOCLONAL GAMMOPATHY

Polyclonal-Ddx.

Infection

HIV

Connective Tissue Disease

Liver Disease

Sarcoidosis

POLYCLONAL VS MONOCLONAL GAMMOPATHY

Monoclonal Gammopathy-Ddx.

MGUS
Plasmacytoma
Smoldering Multiple Myeloma
Multiple Myeloma
Amyloidosis
Non-Hodgkin's Lymphoma

MGUS

3% of general population >50

Associations-osteoporosis, peripheral neuropathy, & venous thrombosis

High risk for MGUS-African Americans 2-3x compared to whites, males, positive family history, & immunosuppression

High risk for MGUS progression-positive serum free light chain, IgA or IgM, & monoclonal protein ≥

1.5g/dl

CONCLUSIONS

- Weight loss, tobacco cessation, exercise, appropriate DVT/PE prophylaxis, & age-appropriate cancer screening will prevent DVT/PE in most patients.
- Proper management of prescription & OTC medications along with patient counseling can significantly reduce life-threatening hemorrhage.

CONCLUSIONS CONTINUED

The history & physical exam along with application of the coagulation cascade and normal platelet function will focus your differential diagnosis & work up of lab abnormalities & their treatments.