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.
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.
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
## PREVALENCE OF FVL & PROTHROMBIN GENE MUTATION

<table>
<thead>
<tr>
<th>Population</th>
<th>FVL%</th>
<th>PG%</th>
</tr>
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<tbody>
<tr>
<td>European</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>5-10</td>
<td>1.7</td>
</tr>
<tr>
<td>Southern</td>
<td>2-3</td>
<td>3</td>
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<tr>
<td>Middle East</td>
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<td></td>
</tr>
<tr>
<td>Israeli</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Arab</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>African/Asian</td>
<td>≤ 1</td>
<td>≤ 1</td>
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</table>
RISK FACTORS FOR VENOUS THROMBOSIS

**ACQUIRED**
- Advancing age
- Prior unprovoked DVT
- Obesity
- Tobacco
- Malignancy

**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- 2\textsuperscript{nd} & 3\textsuperscript{rd} 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.
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
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 ANITICOAGULANT SHOULD I CHOOSE?
COUMADIN

Vitamin K antagonist
Has all indications except pregnancy & malignancy (2\textsuperscript{nd} 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
<table>
<thead>
<tr>
<th>Indication</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
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<tbody>
<tr>
<td>Nonvalvular A. Fib</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DVT/PE</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↓ Recurrent DVT/PE</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Prophylaxis Hip/Knee</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Replacement</td>
<td></td>
<td></td>
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<tr>
<td><strong>T1/2, hr.</strong></td>
<td><strong>12</strong></td>
<td><strong>5-9</strong></td>
<td><strong>12-17</strong></td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>If any 2 characteristics: Age ≥ 80, BW ≤ 60kg, CR ≥ 1.5</td>
<td>DVT/PE/Prophylaxis, CRCL &lt; 30ml/min- Avoid</td>
<td>80% Renal Excreted</td>
</tr>
<tr>
<td></td>
<td>2.5mg BID</td>
<td>A. Fib, CRCL 15-50ml/min- 15mg/day</td>
<td>CRCL &gt; 30, 150 mg. BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not Dialyzable</td>
<td>CRCL 15-30, 75 mg. BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dialyzable</td>
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<tr>
<td><strong>Food</strong></td>
<td>With or Without</td>
<td>With</td>
<td>With or Without</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dyspepsia</td>
</tr>
<tr>
<td><strong>Discontinuation for Surgery</strong></td>
<td>Low Risk- 24 hrs. High Risk ≥ 48 hrs.</td>
<td>≥ 24 hrs.</td>
<td>CRCL ≥ 50 1-2 days pre-op min.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CRCL &lt; 50 3-5 days pre-op min.</td>
</tr>
<tr>
<td><strong>Causes ↑ INR</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
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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.
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 concomitant use of certain drugs.
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
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 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 $\rightarrow$ CYP2C19 $\rightarrow$ active metabolite
Poor metabolizers have worse outcomes
Can check CYP2C19 genotype
Avoid Omeprazole & Esomeprazole (CYP2C19 inhibitors). Can use Dexlansoprazole, Lansoprazole, & Pantoprazole instead $\rightarrow$ have less effect
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
TTP has been reported- can occur with exposure < 2 weeks.
Can give with mild to moderate hepatic impairment.
Can give with H2 blockers & 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.
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.
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.
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.

Hou Y. Abstract # 577
PRIMARY VS SECONDARY POLYCYTHEMIA

Primary:

No obvious etiology $\rightarrow$ EPO level, JAK-2

$\rightarrow$ If EPO low & JAK-2 negative $\rightarrow$ 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
- β 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/ FUNCTIONAL 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.
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.