Many questions, few answers…

Thrombosis and Bleeding

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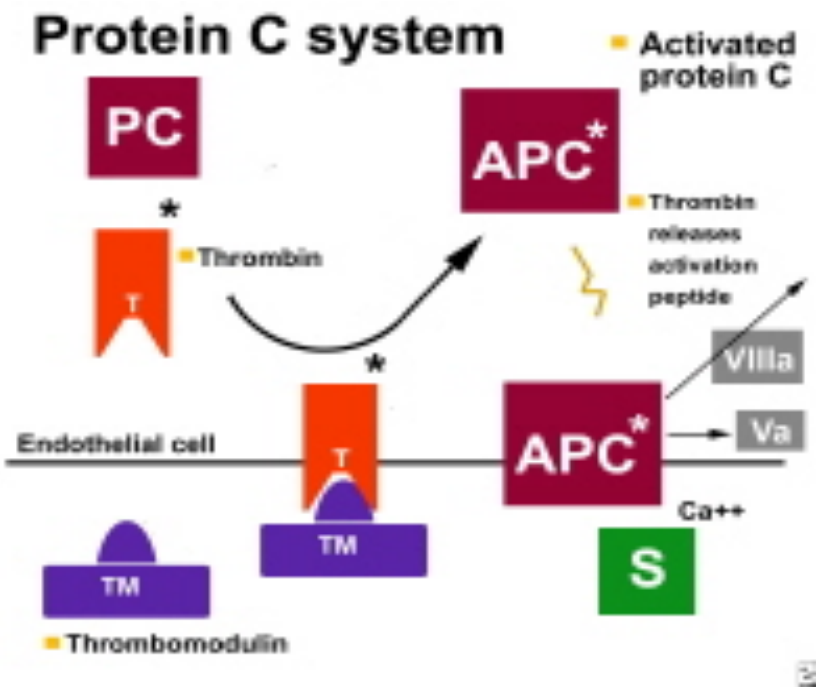
Scope of the Problem

- Thrombosis
  - PV 12-39%
  - ET 11-25%
  - MF 10%
  - 60-70% of thrombosis are arterial
  - Splanchnic and cerebral thrombosis are more common
- Bleeding
  - PV <10%
  - ET 10-15%
  - MF 15-20%

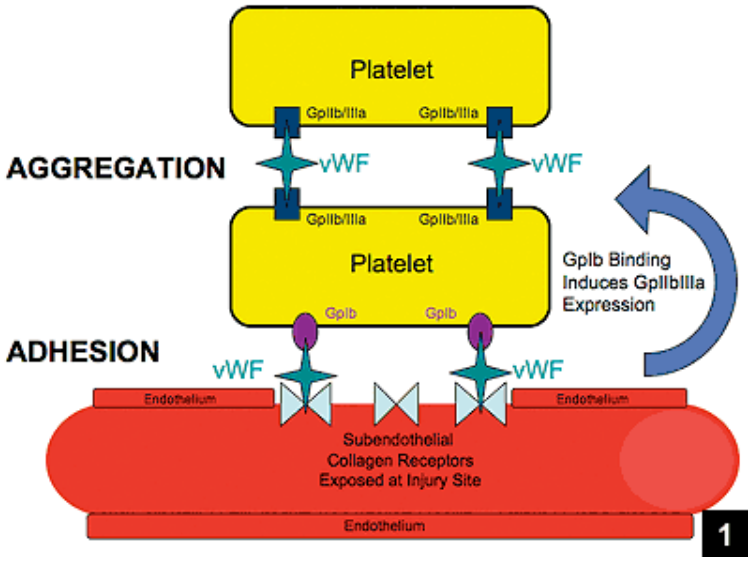
Why do we clot excessively?

- Platelet number ?
- Activated platelets
- Increased hemoglobin
- Increased leukocytes
- JAK2V617F allele burden
- Inflammation
  - CRP, Pentraxin 3
- Decreased protein S (platelet proteases)
- Abnormal lining of blood vessels (Endothelium)
  - Decreased NO in ET



Why do we bleed excessively?

- Decreased platelet granules
- Abnormal aggregation of platelets
- Increased breakdown of Von Willebrand molecule by ADAMTS13
  - Related to platelet count



Tefferi. Hemostasis and Thrombosis.LWW. 2013

Treatment Algorithm

Risk Category	ET	PV	Management Pregnancy
Low-risk Platelets < 1 M <60 No thrombosis hist.	Low-dose ASA	Low-dose ASA Phlebotomy Ht<45	Low-dose ASA + Phlebotomy if PV
Low risk Platelets> 1 M	Low-dose ASA if risto cofactor activity >30%	Low-dose ASA if risto cofactor activity >30% + phelbotomy	Low-dose ASA if risto cofactor activity >30% + phlebotomy if PV
High-risk Age>60 History Thrombosis	Low-dose ASA + HU	Low-dose ASA + phlebotomy +HU	Low-dose ASA + phlebotomy if PV + IFN-alpha
High-risk refractory or intolerant to HU	Low-dose ASA + IFN α (<65) or busulfan (>65)	Low-dose ASA + phlebotomy + IFN-α (<65) or busulfan (>65)	Low-dose ASA + phlebotomy if PV+ IFN-α

Aspirin

THROMBOSIS BLEEDING

From: The Role of Aspirin in Cardiovascular Prevention: Title and subTitle BreakImplications of Aspirin Resistance

J Am Coll Cardiol. 2008;51(19):1829-1843. doi:10.1016/j.jacc.2007.11.080

Aspirin works by irreversibly inhibiting cyclooxygenase-1 (COX-1) on platelets, thereby reducing the production of thromboxane A2.

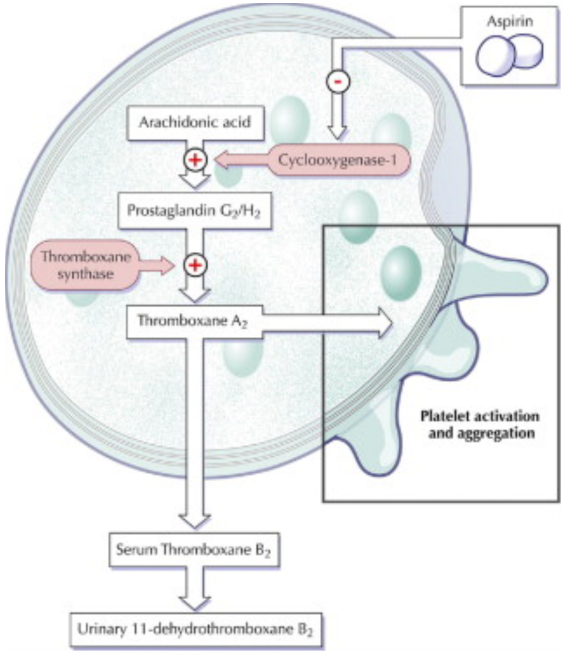


Figure Legend:

Inhibition of Platelet Thromboxane A2 Pathways by Low-Dose Aspirin
Figure illustration by Rob Flewell.

Date of download: 2/6/2013

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Primary prevention

- Antithrombotic Trialists Collaboration
  - Aspirin for primary prevention
  - Metaanalysis
  - Healthy volunteers
  - Rates of thrombosis= 5.4/1000 person-years
  - Reduction in thrombotic events
    - 0.51%/y aspirin vs 0.57%/y controls (p=0.0001)
  - Increase in GI and extracranial bleeds
    - 0.1%/y aspirin vs 0.07%/y controls (p=0.0001)

Baigent et al. Lancet, 2009.

Primary prevention

- I don't tolerate ASA 81 mg very well, it gives me heartburn, can I take Plavix™ instead?
  - MPNs are associated with excessive thromboxane production. ASA impacts thromboxane production.
  - No published data comparing ASA and Plavix™ in primary prevention
  - Take ASA with food, consider proton pump inhibitor.
  - Cumulative incidence of recurrent GI ulcer bleeding at 1 year is 8.6% with Plavix™ and 7.9% with aspirin and omeprazole (Chan FK et al, NEJM, 2005)

Primary Prevention

- Can I take ASA 325 mg instead of a baby aspirin (81 mg)?
  - Majority of MPN studies were performed at doses <100 mg
  - Risk of bleeding is 3X increased >200 mg/day

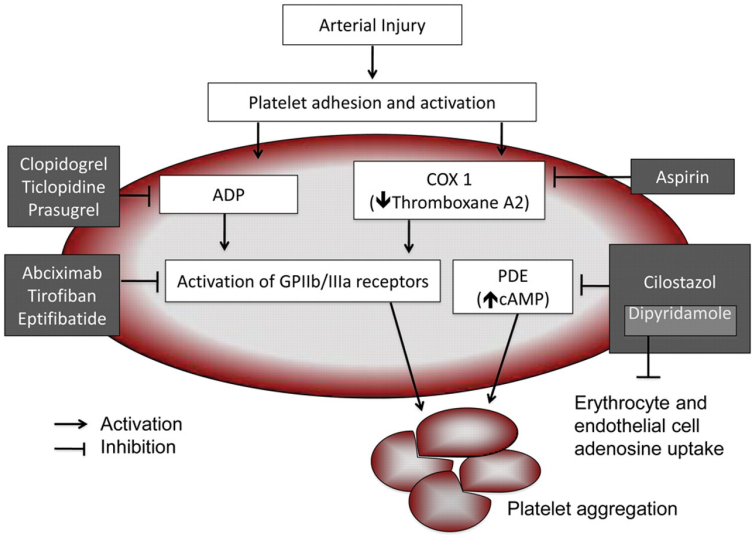
Primary Prevention

- I have an aspirin allergy, should I take Plavix™?
  - Role of Plavix™ in MPN primary prevention has not been studied. Not unreasonable.
- I have ET and am quite concerned about my risk of getting a stroke, can I use ASA 81 mg/day + Plavix™ 75 mg/day?
  - No data for primary prevention
  - Data from ISCALP study is not out (study closed)
  - Risk of bleeding is at least 2X increased

Secondary prevention

- I had a recent TIA which lead to my diagnosis of ET. Should I receive ASA + Plavix™?
- No specific data for MPN patients
- In non MPN patients the combination of ASA 81mg/ day + extended release dipyridamole 200 mg twice appears to be superior to ASA 81 mg alone.
- Indications of combined ASA + Plavix™
  - Acute coronary syndrome
  - Drug eluting stent
  - Bare metal stent

Aspirin resistance



www.neurology.org

- **True resistance is rare!**
- **Compliance** (50%)
- Competition for COX-1 binding site from ibuprofen and naproxen
- Increased platelet turnover (diabetes, cardiac surgery)
- Obesity (leptins increase platelet reactivity)
- Aspirin enteric coating
- Impaired sensitivity to COX-1
- COX-1 polymorphisms
- Stimulation of platelets by ASA insensitive mechanisms

Secondary Prevention

- I had a TIA while taking ASA and Hydroxyurea, should I add Plavix™?
  - Commonly done (viewed by many as standard of care)
  - Evidence of benefit in PV and ET is not proven
  - Increases risk of bleeding (specially in patients >70 y)
  - Role of ASA 325 mg once a day or 81 mg twice a day is unclear.
- I am a 47 yo male with ET, taking ASA 81 mg/d, I had a TIA last week, what should I do?
  - Consider initiating cytoreductive therapy
  - Consider adding Plavix™

Secondary Prevention

- Seventy year old patient with PV, treated with phlebotomies + ASA + hydroxyurea develops a deep venous thrombosis or atrial fibrillation (AF). What is the best treatment?
  - Best treatment for AF is anticoagulation with warfarin or dabigatran (Pradaxa™) or rivaroxaban (Xarelto™)
  - Best treatment for DVT is anticoagulation with either warfarin or rivaroxaban (Xarelto™).
  - Warfarin, rivaroxaban, dabigatran may not provide optimal prophylaxis for arterial thrombotic events (?), ASA may need to be added

Combination Therapy

- United Kingdom General practice Research database- 70,760 patients with Atrial Fibrillation.
- Risk of bleeding
  - Warfarin RR 2.08
  - Clopidrogrel RR 1.57
  - Aspirin RR 1.25
  - Warfarin +ASA RR 2.87
  - Warfarin + clopidogrel RR 2.74
  - ASA + Clopidogrel RR 1.68
  - Triple Therapy RR 3.75

Azoulay et al. Thromb Haemost, 2013.

Hormone replacement and oral contraceptives

- I am a 34 yo woman with ET. I am on ASA 81 mg/ day. Can I take an oral contraceptive?
  - Retrospective study demonstrated an increased risk of venous thrombosis (Gangat et a. Cancer, 2006)
- I am a 52 yo woman with ET. I would like to be on hormone replacement therapy. Is there any data?
  - Retrospective data did not demonstrate increased risk of thrombosis (Gangat et a. Cancer, 2006)

Hormone replacement and oral contraceptives

- I am a 32 yo woman with PV, would like to be on an oral contraceptive.

- Advice
  - PV is a risk factor for thrombosis
  - Oral contraceptives : risk factor for thrombosis
  - Level of protection provided by ASA?
  - Prior history of thrombosis?
  - Family history of thrombosis?
  - Thrombophilia?

Bleeding

- 43 year old man with ET. No history of prior thrombosis. Platelet count of 1.35 million. Treated with ASA 81 mg/day. Presents with recurrent nosebleeds.
  - Platelet aggregation study is abnormal
    - ASA + ET
  - Von Willebrand activity is decreased to 25%
  - Recommend:
    - D/C aspirin
    - Arbitrary threshold to start HU is 1.5 M

Bleeding

- 43 year old man with ET. No history of prior thrombosis. Platelet count of 1.35 million. Treated with ASA 81 mg/day. Presents with recurrent nosebleeds. Patient develops left quadrant pain and requires surgery for diverticulitis.
  - Options:
    - 1- Pheresis < 800,000
    - 2- Desmopressin 0.3 mcg/kg IV(**VW short ½ life**)
    - 3- Cryoprecipitate or antihemophilic factor/Von Willebrand complex (Alphanate™, Humate-P™)

Bleeding

- 78 yo man with history of coronary artery disease and PV, requires a total hip arthroplasty. His hematocrit is 51, his WBC is 12,000 and his platelet count is 1.1 million. He is on ASA 81 mg/day and takes HU intermittently.
  - Pre-op recommendations:
    - Hematocrit <45
    - Platelet count < 400,000
  - Post-op recommendations:
    - Low-molecular heparin for 35 days
    - Hold aspirin
    - Hydroxyurea +/- phlebotomies (Ht <45)

Bleeding

- 67 year old woman with history of coronary heart disease and myelofibrosis, develops painful splenomegaly following portal vein thrombosis. Following splenectomy her platelet count rises > 1.4 M she develops a severe gastrointestinal bleed.
  - 20% develop thrombocytosis post-splenectomy
    - Mortality 20% (2/3 thrombosis, 1/3 GI bleeding)
  - Options:
    - Red cell transfusions
    - Platelet pheresis
    - Desmopressin (increased thrombotic risk)
    - VW complex or cryoprecipitate

Thank you!

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