GP CME

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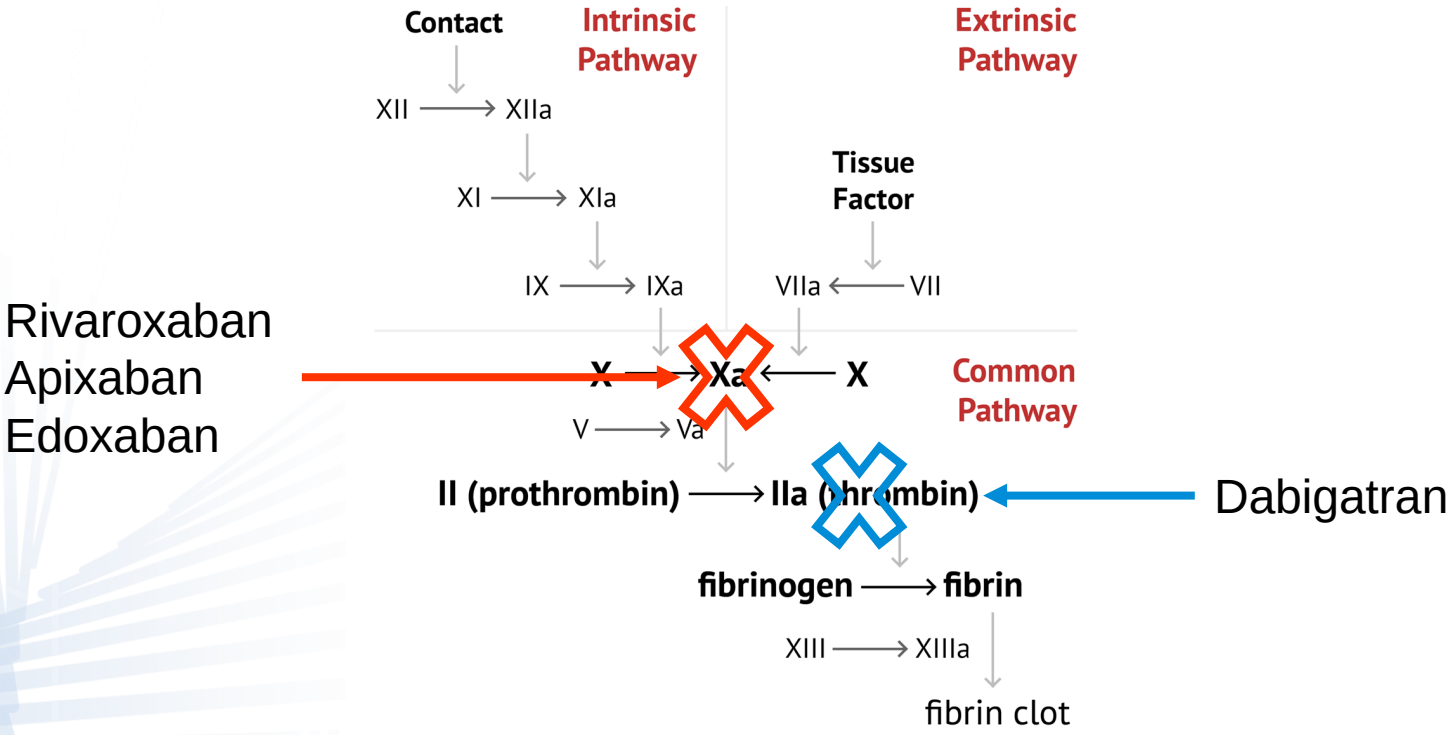
Date:

RIVAROXABAN AND DABIGATRAN

Clotting Cascade



Dosing

Dabigatran

CrCl (mL/min)	Indications		
	Prevention of stroke and systemic embolism in non-valvular AF	Treatment and secondary prevention of DVT and PE	Primary prevention of VTE following joint replacement surgery
>49	150mg BD	Treat with LMWH for minimum of 5 days before starting 150mg BD	Start 110mg 1 to 4hr post-surgery then 220mg OD for: • 10 days following a knee replacement • 4-5 weeks following a hip replacement
30-49	110 mg BD	Treat with LMWH for minimum of 5 days before starting 150mg BD or consider 110mg BD in high risk of bleeding	Start 75mg 1 to 4hr post-surgery then 150mg OD for: • 10 days following a knee replacement 4-5 weeks following a hip replacement
<30	Avoid	Avoid	Avoid
Age 80+	110mg BD	110mg BD	No dose adjustment
Age 75-80	Consider 110mg BD	Consider 110mg BD	

Rivaroxaban

CrCl (mL/min)	Indications		
	Prevention of stroke and systemic embolism in non-valvular AF	Treatment and secondary prevention of DVT and PE	Primary prevention of VTE following joint replacement surgery
>49	20mg OD	15mg BD for 21 days then 20mg OD. Dose reduction may be allowed for secondary prevention	10mg OD starting 6 to 10hr post-surgery for: • 2 weeks following a knee replacement • 5 weeks following a hip replacement
30-49	15mg OD		No change required
15-29	Use with caution	Use with caution	Use with caution
<15	Avoid	Avoid	Avoid

Special Consideration

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Dabigatran

- Metabolism
  - Interaction with P-gp
  - Not affected by cytochrome P450 system

Rivaroxaban

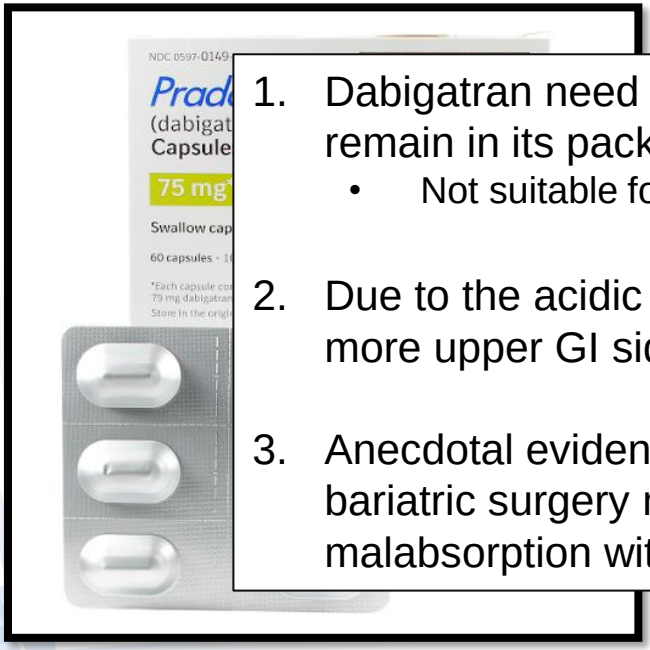
- Metabolism
  - Interaction with P-gp
  - Interaction with CYP3A4

CYP3A4 inhibitors	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
P-gp inhibitors	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil
Combined CYP3A4 and P-gp inhibitors	Itraconazole, lopinavir/ritonavir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan
CYP3A4 inducers	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort
P-gp Inducers	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir
Combined CYP3A4 and P-gp inducers	Avasimibe carbamazepine, phenytoin, rifampin, St John's wort

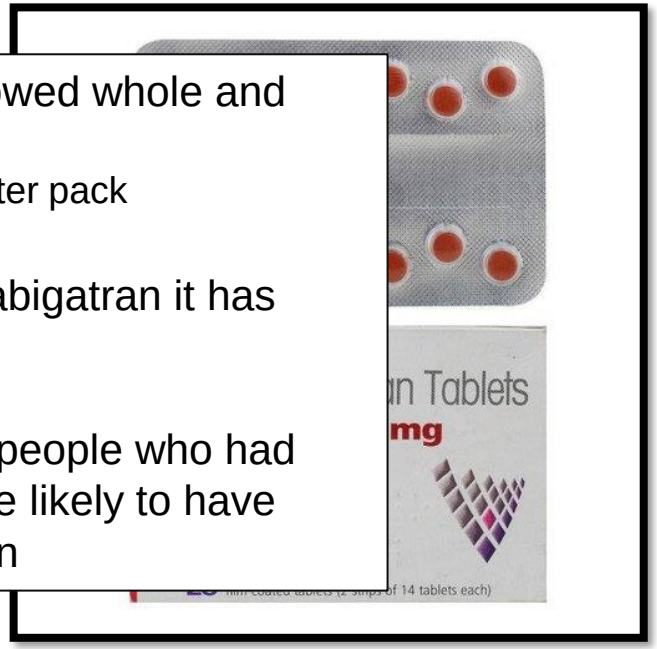
Data from Hellwig et al. [36]

Special Consideration

Dabigatran



Rivaroxaban

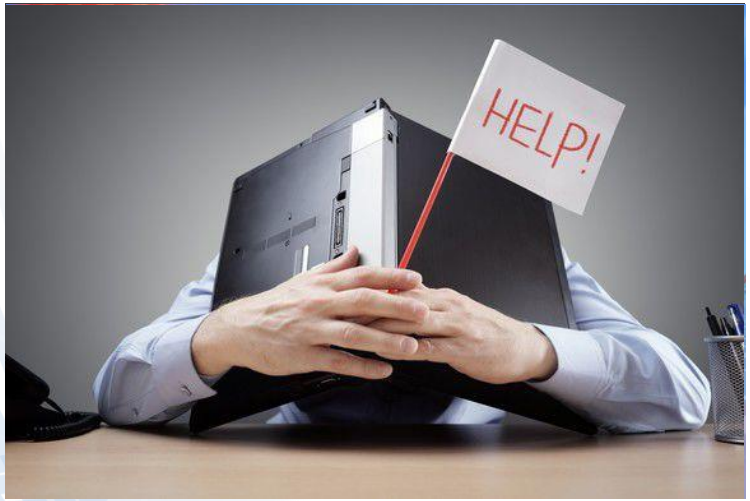


1. Dabigatran need to be swallowed whole and remain in its packaging
   - Not suitable for NGT or blister pack
2. Due to the acidic nature of dabigatran it has more upper GI side effects
3. Anecdotal evidence suggest people who had bariatric surgery may be more likely to have malabsorption with dabigatran

Bleeding

Dabigatran

- Idarucizumab (Praxbind®)



Rivaroxaban

- More GU bleeding
- No effective reversal (in NZ)
  - Not dialysable
  - Variable success with Prothrombinx® or FEIBA
    - Andexanet alfa
  - Need to try and ride it out for 24 - 48hrs
    - Half life ~8 to 12hr

Key Point

- Similar efficacy and bleeding risk between dabigatran and rivaroxaban

- Choice between dabigatran & rivaroxaban depends on
  - Compliance (OD vs BD)
  - Renal function and age
  - LMWH cover required for dabigatran treatment in VTE
  - Special consideration
    - NGT/PEG
    - Blister packing
    - Drug interactions
  - Bleeding risk
  - People requiring long term DOAC for VTE prevention
    - Rivaroxaban 10mg (prophylactic dose) if favoured

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CBC

Interpretation

Case 1

		Ref. Range
Haemoglobin	137	(115 – 155)
RBC	6.14	(3.60 – 5.60)
HCT	0.44	(0.35 – 0.46)
MCV	72	(80 – 99)
MCH	22.3	(27.0 – 33.0)
Platelets	360	(150 – 400)
WBC	15.0	(4.0 – 11.0)
Neutrophils	10.7	(1.90 – 7.50)
Lymphocytes	3.2	(1.00 – 4.00)
Monocytes	0.8	(0.20 – 1.00)
Eosinophils	0.5	(<0.51)
Basophils	0.0	(0.00 – 0.20)

Case 2

		Ref. Range
Haemoglobin	66	(115 – 155)
RBC	3.98	(3.60 – 5.60)
HCT	0.25	(0.35 – 0.46)
MCV	62	(80 – 99)
MCH	16.6	(27.0 – 33.0)
Platelets	523	(150 – 400)
WBC	5.2	(4.0 – 11.0)
Neutrophils	2.74	(1.90 – 7.50)
Lymphocytes	1.66	(1.00 – 4.00)
Monocytes	0.55	(0.20 – 1.00)
Eosinophils	0.17	(<0.51)
Basophils	0.05	(0.00 – 0.20)

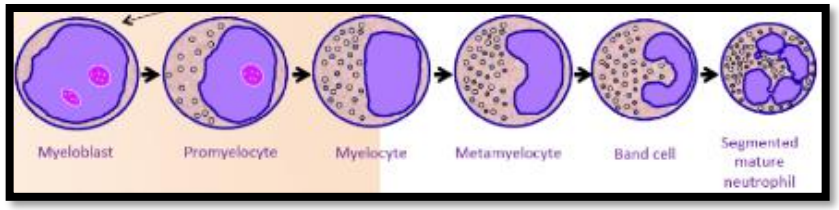
Case 1: WBC Interpretation

- 60yr old Fijian Indian
- Presented with influzena (H1N1) and suffered myocarditis on weekend
  - Treated with abx discharged on Monday
- PMHx
  - HTN
  - Dyslipidaemia
- Social Hx
  - Current smoker (40pk yr)
  - High ETOH

		Ref. Range
Haemoglobin	157	(130 – 175)
RBC	5.25	(4.3 – 6.0)
HCT	0.47	(0.4 – 0.52)
MCV	90	(80 – 99)
MCH	29.9	(27.0 – 33.0)
Platelets	103	(150 – 400)
WBC	36.5	(4.0 – 11.0)
Neutrophils	24.8	(1.90 – 7.50)
Lymphocytes	1.8	(1.00 – 4.00)
Monocytes	2.6	(0.20 – 1.00)
Eosinophils	0.0	(<0.51)
Basophils	0.7	(0.00 – 0.20)
Immature Granulocyte	6.6	(<0.06)

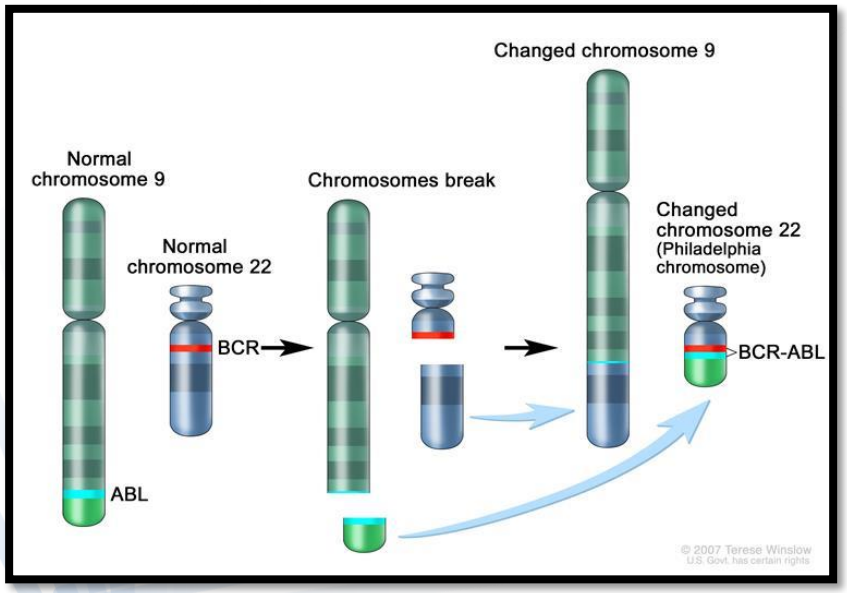
1 Month Later

		Ref. Range
Haemoglobin	151	(130 – 175)
RBC	4.97	(4.3 – 6.0)
HCT	0.46	(0.4 – 0.52)
MCV	93	(80 – 99)
MCH	30.4	(27.0 – 33.0)
Platelets	176	(150 – 400)
WBC	52.0	(4.0 – 11.0)
Myelocytes	7.8	
Metamyelocytes	0.5	
Neutrophils	30.2	(1.90 – 7.50)
Lymphocytes	7.3	(1.00 – 4.00)
Monocytes	3.1	(0.20 – 1.00)
Eosinophils	1.0	(<0.51)
Basophils	2.1	(0.00 – 0.20)



- Blood Film:
  - Leucocytosis with left shift down to promyelocyte stage
  - Twin peak
    - The granulocyte stages are mature neutrophils and myelocytes
  - Basophilia
    - ≥3% of circulating WBC need to exclude CML

Chronic Myeloid Leukaemia



- Readily treatable with tyrosine kinase inhibitor (TKI)
- For minority it could be curable
- Compliance is the most

Take home message

- Concurrent diseases can occur
  - Important to monitor for resolution
    - Recommendation for white cell changes (2 to 6 weeks depend on suspicion)
- Persistent basophilia is almost always sinister

Case 2

- 60 year old woman
- Normally fit and well
- No significant PMHx
- Medication:
  - Nil regular medication
  - NKDA
- Social:
  - Retired widow
  - Non smoker

	18/3/11	Ref. Range
Haemoglobin	134	(115 – 155)
RBC	4.90	(3.60 – 5.60)
HCT	0.43	(0.35 – 0.46)
MCV	87	(80 – 99)
MCH	27.3	(27.0 – 33.0)
Platelets	433	(150 – 400)
WBC	8.0	(4.0 – 11.0)
Neutrophils	5.24	(1.90 – 7.50)
Lymphocytes	1.80	(1.00 – 4.00)
Monocytes	0.78	(0.20 – 1.00)
Eosinophils	0.15	(<0.51)
Basophils	0.02	(0.00 – 0.20)

Causes of Thrombocytosis

- Reactive
  - Increased bone marrow activity
    - Acute bleeding/haemolysis
    - Iron deficiency
  - Infection
  - Splenectomy
    - 30% of platelet is sequestrated in spleen
  - Inflammation
    - Autoimmune
    - Malignancy
    - Trauma/Surgery
    - Smoking
- Primary
  - Myeloproliferative neoplasm

Clinical relevance of thrombocytosis in primary care: a prospective cohort study of cancer incidence using English electronic medical records and cancer registry data

Sarah ER Bailey, Obioha C Ukoumunne, Elizabeth A Shephard and Willie Hamilton
Br J Gen Pract 2017; 67 (659): e405-e413. **DOI:** https://doi.org/10.3399/bjgp17X691109

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- Prospective Registry Data
- Associated
  - Lung
  - Colorectal
  - Urogenital
- Annual Risk of Cancer

	Elevated %/NNT	Persistent (within 6m)	4-12m	13-24m	Baseline
Male	11.6%/(13)	18.1%/(7.1)	3.9%	2.7%	4.1%
Female	6.2%/(25)	10.1%/(12.7)	2.4%	1.8%	2.2%

- Few comment
  - Lack of multivariate analysis is frustrating
  - Clear evidence of chronic inflammation causes cancer
    - Chicken or Egg
- What to do?
  - Debatable but similar to unprovoked VTE
  - Routine CXR
  - Rest symptom guided??

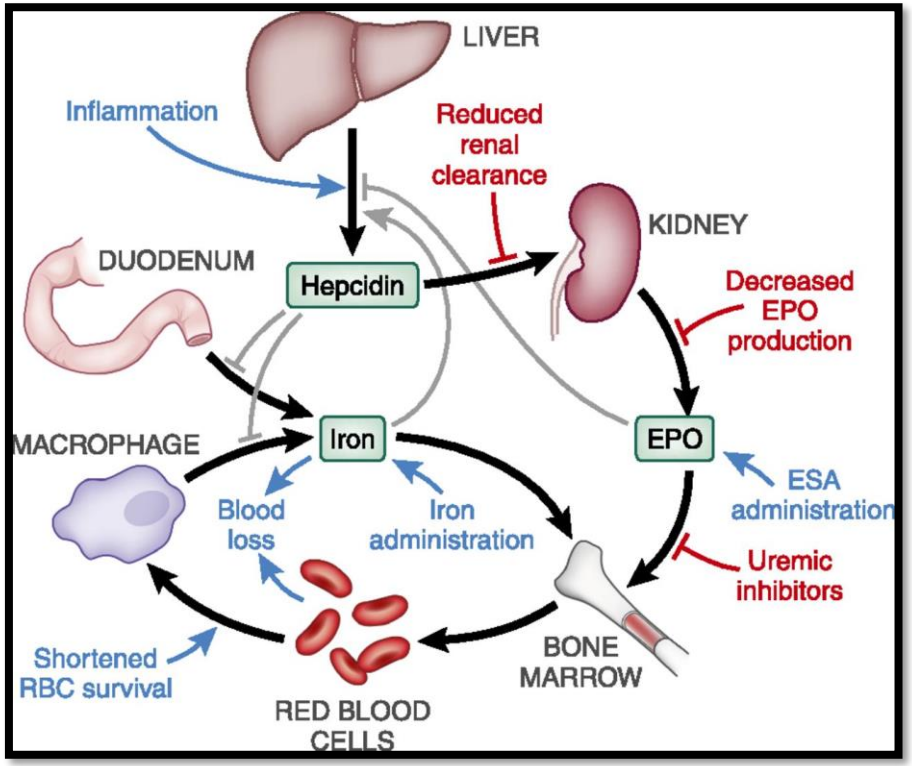
Results

	18/3/11	12/03/13	22/07/16	06/07/17	20/02/19	Ref. Range
Haemoglobin	134	139	136	128	140	(115 – 155)
RBC	4.90	5.11	5.59	5.08	6.26	(3.60 – 5.60)
HCT	0.43	0.43	0.43	0.41	0.46	(0.35 – 0.46)
MCV	87	84	78	80	74	(80 – 99)
MCH	27.3	27.2	24.3	25.2	22.4	(27.0 – 33.0)
Platelets	433	424	424	500	582	(150 – 400)
WBC	8.0	7.2	9.7	10.6	11.6	(4.0 – 11.0)
Neutrophils	5.24	4.63	7.21	8.00	9.9	(1.90 – 7.50)
Lymphocytes	1.80	1.70	1.58	1.35	1.0	(1.00 – 4.00)
Monocytes	0.78	0.7	0.53	0.85	0.2	(0.20 – 1.00)
Eosinophils	0.15	0.14	0.29	0.24	0.2	(<0.51)
Basophils	0.02	0.06	0.1	0.15	0.1	(0.00 – 0.20)

What is happening?
What to do next?
What you should not do?

Polycythaemia

- Diagnosis
  - Driver mutations
    - JAK2 V617F (90-95%)
    - JAK2 exon 12 (1-3%)
  - Serum erythropoietin
    - Should be low
    - Normal or high suggest other cause
- Manage the thrombosis risk factors (PV)
  - Venesection
  - Aspirin
  - Hydroxyurea > 60yr or with CVD RF
- Don't
  - Replace iron



Coagulation Testing

		Ref. Range
Haemoglobin	190	(130 – 175)
RBC	7.9	(4.3 – 6.0)
HCT	0.63	(0.4 – 0.52)
MCV	79	(80 – 99)
MCH	26	(27.0 – 33.0)
Platelets	420	(150 – 400)
WBC	8.9	(4.0 – 11.0)
Neutrophils	6.27	(1.90 – 7.50)
Lymphocytes	1.85	(1.00 – 4.00)
Monocytes	0.26	(0.20 – 1.00)
Eosinophils	0.3	(<0.51)
Basophils	0.22	(0.00 – 0.20)

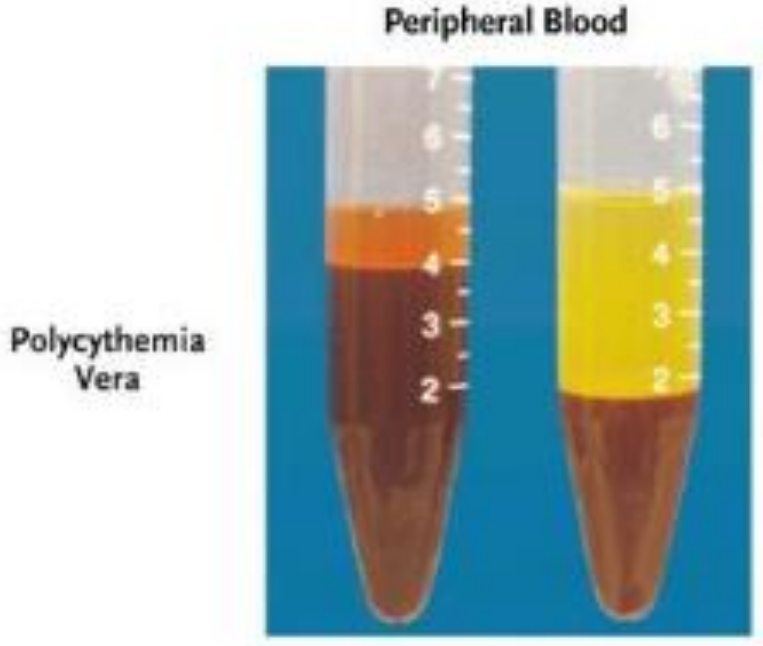
		Ref. Range
APTT	65	(25-40)
PR	1.8	(0.8-1.2)
Fibrinogen	3.6	(1.5-4.0)
Platelet	420	(150 – 400)

Interpretation?

What to do?

		Ref. Range
APTT 1+1	45	(25-40)
PR 1+1	1.3	(0.8-1.2)

- Coagulation Testing
  - Citrate tube
    - Inhibit coagulation process by removing calcium from plasma
  - Re-initiate coagulation process by adding calcium
  - In polycythaemic patient the plasma can be significantly reduced leading to excessive citrate
    - Prolonged coagulation
    - Act as an inhibitor



Take home message

- Access to previous results is extremely useful
  - Disease can evolve over time
- What to do with mild thrombocytosis is controversial
- Polycythaemia can interfere with coagulation