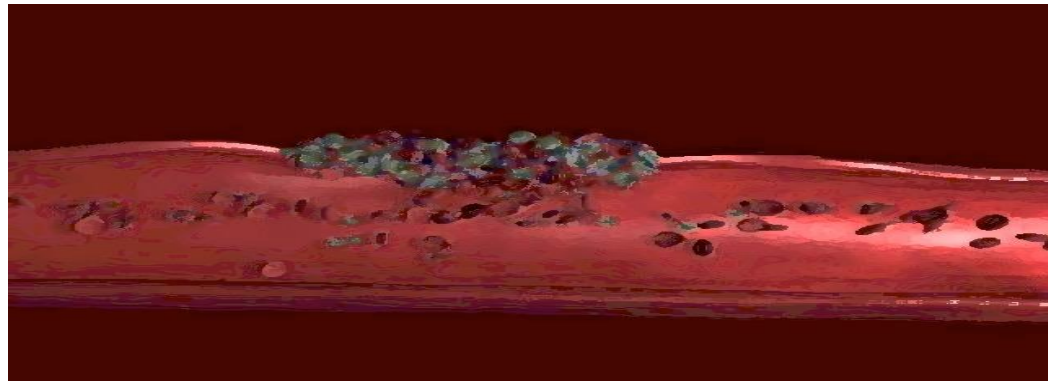


Causes hématologiques et prothrombotiques



Symposium Annuel du Centre Cérébrovasculaire CHUV, 28.09.2017

Alessandro Casini

Service d'angiologie et d'hémostase, HUG

Background



1856

Venous

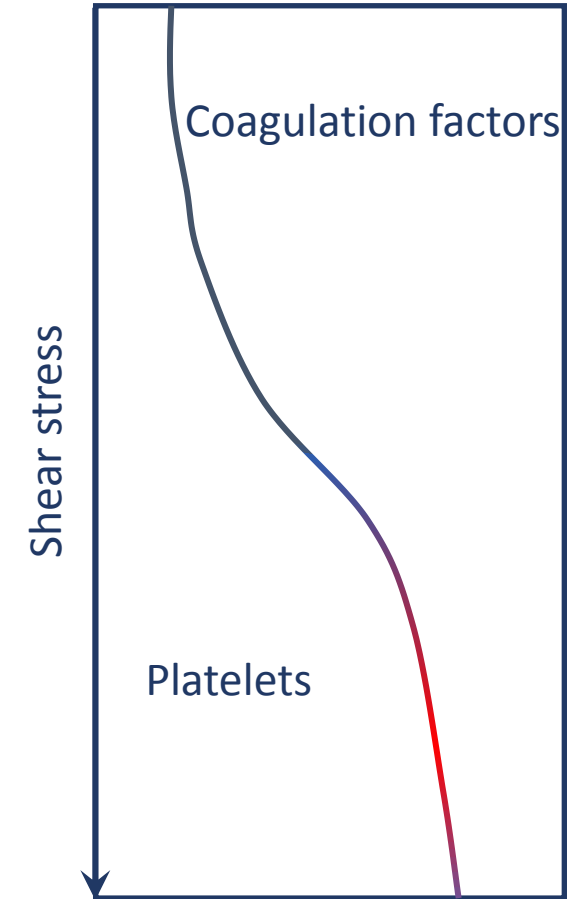
Low shear stress
Role of stasis
Implication of secondary hemostasis

→ ANTICOAGULANT

Arterial

High shear stress
Role of endothelium integrity
Implication of platelet function

→ ANTIPLATELET



Summary

- Hypercoagulable state
- Hematological disease
- Cerebral venous thrombosis
- Conclusions

Hereditary hypercoagulable states

Consolidated evidence	Weak evidence	Lack of evidence
Loss-of-function mechanisms ● Antithrombin deficiency ● Protein S deficiency ● Protein C deficiency Gain-of-function mechanisms ● Factor V Leiden ● Prothrombin G20210A ● Non-O blood group ● High levels of FVIII ● Dysfibrinogenaemia ● Hyperhomocysteinaemia	● High TAFI plasma levels ● High coagulation factor levels (fibrinogen, FIX, FXI) ● EPCR polymorphisms	● Plasminogen deficiency ● High PAI-1 levels ● FXIII leu34val ● Lp(a) ● MTHFR C677T and A1298C polymorphisms ● Low TFPI levels ● High coagulation factor levels (FV, FVII, FX) ● Thrombomodulin polymorphisms ● ACE polymorphisms ● PZ/ZPI polymorphisms ● ADAMTS13 polymorphisms

Thrombophilia testing in ischemic stroke

Table 1. Case-Control Studies of PC, PS, and AT in Patient With Ischemic Stroke

Reference	Age	N Cases and Controls	Thrombophilia Tested	% Identified in Cases	% Identified in Controls	Statistical Significance
Sastry (2006) ⁹	16–39	101	PC, PS, AT	7.9	8.9	NS
		101				
Jerrard-Dunn (2003) ¹⁰	≤65	130	PS, PC, AT	8.5*	6.3*	NS
		130				
Hankey (2001) ¹¹	Mean	219	PC, PS, AT	7.3	6.8	NS
	66	205				
Margaglione (1999) ¹²	3–50	202	PC, PS, AT	0	0	NS
		1036				
De Stefano (1998) ¹³	2–50	72	PC, PS, AT	1.4	0	NS
		198				
Mayer (1993) ¹⁴	>39	94	PS	21	20	NS
		94				

Thrombophilia testing in ischemic stroke

Table 2. Case-Control Studies of FVL and PTM in Young Patients (Younger Than 60 Years) With Ischemic Stroke

Reference	Age	N Cases and Controls	Thrombophilia Tested	% Identified in Cases	% Identified in Controls	Statistical Significance
Sastry (2006) ⁹	16–39	101	FVL	4.0	7.9	NS
		101	PTM	2.0	0.0	NS
Slooter (2005) ¹⁸	20–49 W	193	FVL	7.8	5.5	OR 1.8
		767	PTM	2.7	2.4	OR 1.0
Lalouschek (2005) ¹⁹	<60	468	FVL	6.2	6.4	NS
		468	PTM	5.0	2.0	$P=0.032$
Madonna (2002) ²⁰	0.5–50	132	FVL	5.3	6.5	NS
		262	PTM	7.6	6.1	NS
Austin (2002) ²¹	18–50	67	FVL	7.4	5.1	NS
		79	PTM	4.4	2.5	NS
Lopaciuk (2001) ^{22*}	≤ 45	100	FVL	3.0	4.2	NS
		238	PTM	2.0	2.1	NS
Voetsch (2000) ²³	15–45	153	FVL	3.3	3.6	NS
		225	PTM	4.6	2.2	NS
Margaglione (1999) ¹²	3–50	202	FVL	14.9	4.2	$P<0.0001$
		1036	PTM	5.0	4.2	NS
De Stefano (1998) ¹³	2–50	72	FVL	5.5	2.5	NS
		198	PTM	12.5	2.5	$P=0.0001$

Good evidence of no association with older patients

Ridker PM et al. N Engl J Med. 1995;332:912

Irrespective of pathogenic subtype of the ischemic stroke

Hankey G et al. Stroke 2001;32:1793

Antiphospholipid antibody syndrome

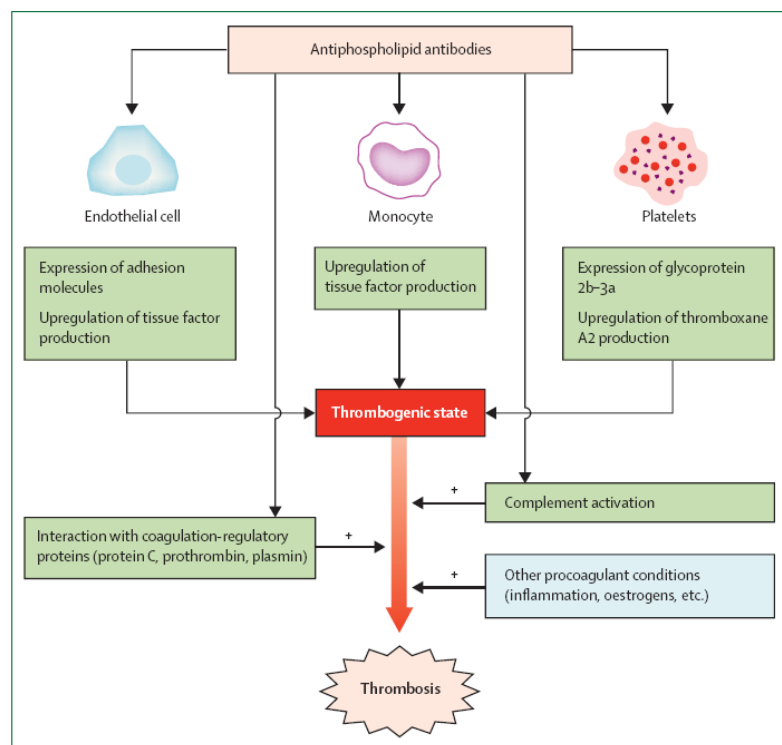
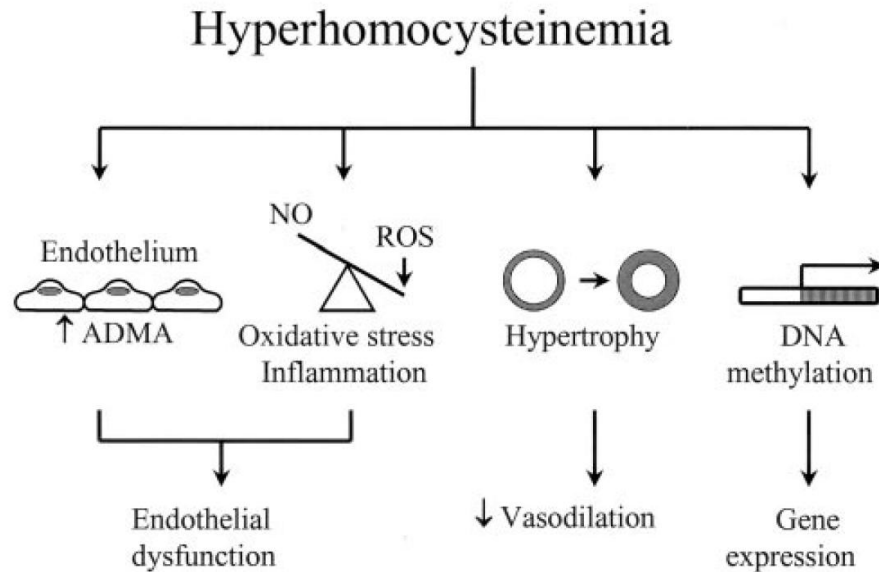


Table 2. Clinical features at disease onset in 1,000 patients with antiphospholipid syndrome*

Manifestation	No. (%) of patients
Deep vein thrombosis	317 (31.7)
Thrombocytopenia (<100,000 platelets/ μ l)	219 (21.9)
Livedo reticularis	204 (20.4)
Stroke	131 (13.1)
Superficial thrombophlebitis	91 (9.1)
Pulmonary embolism	90 (9.0)
Fetal loss	83 (8.3)
Transient ischemic attack	70 (7.0)
Hemolytic anemia	66 (6.6)
Skin ulcers	39 (3.9)
Epilepsy	34 (3.4)
Pseudovasculitic skin lesions	26 (2.6)
Myocardial infarction	28 (2.8)
Amaurosis fugax	28 (2.8)
Digital gangrene	19 (1.9)

>20% in <45 yrs patients

Hyperhomocysteinemia



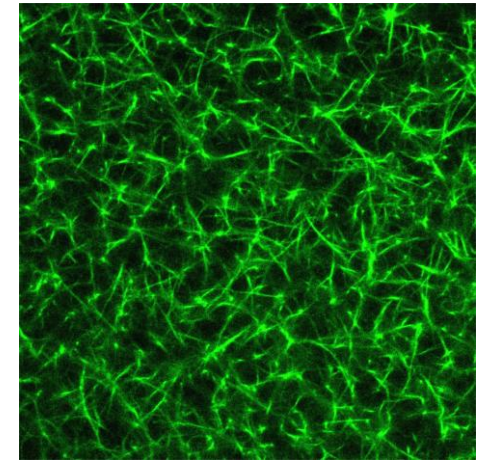
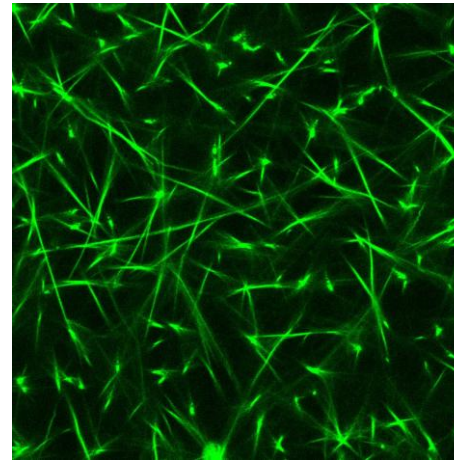
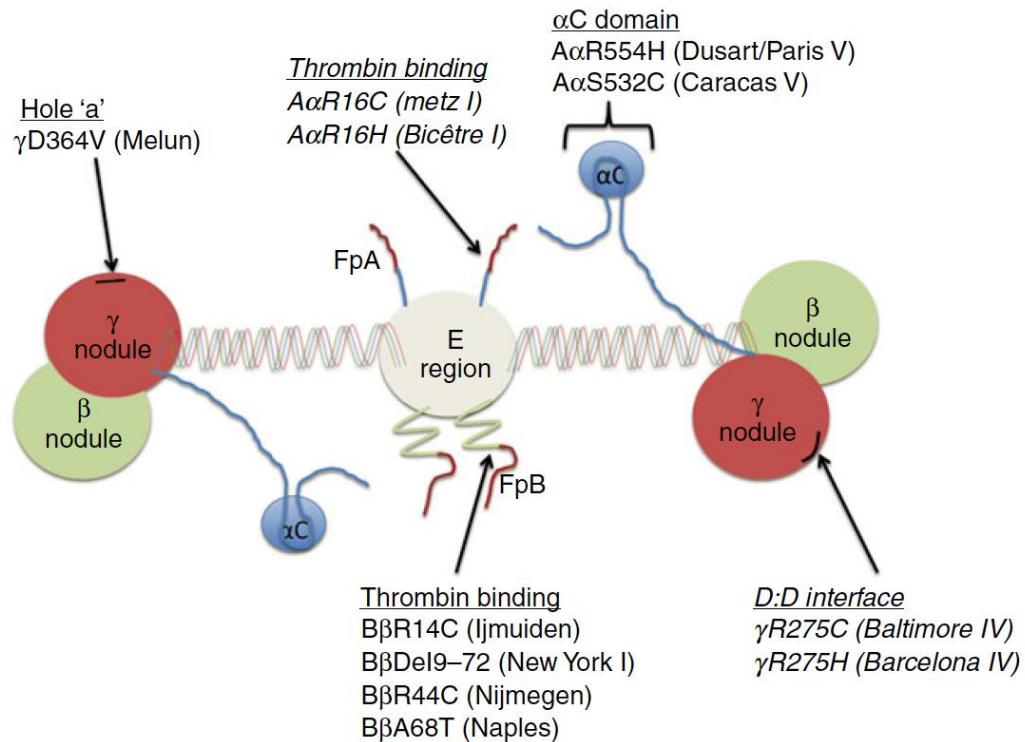
Linear increase of stroke with serum levels

Casas JP et al. Lancet 2005; 365: 224–32.

Treatment does not show clear benefits for stroke prevention

Vitatops Study Lancet Neurol. 2010 Sep;9(9):855-65

Rare causes: dysfibrinogenemia



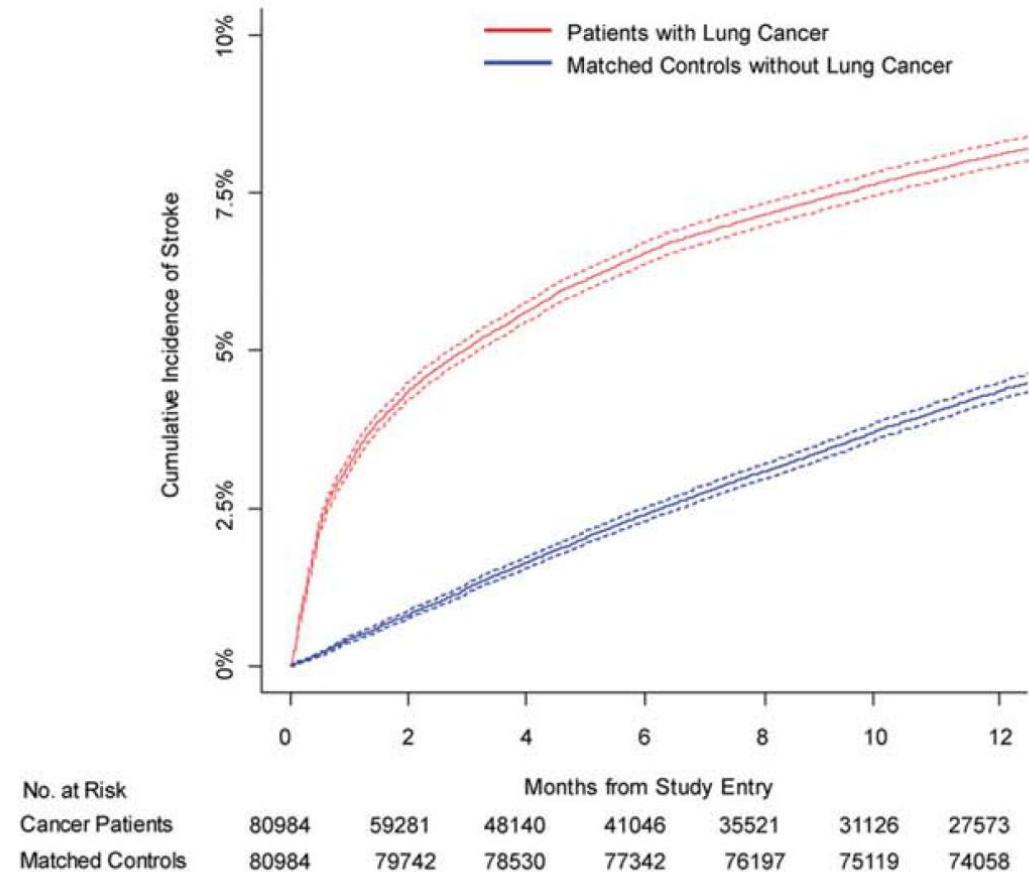
Cancer-related ischemic stroke

Procoagulant substances, endothelial dysfunction, complication of therapy

Prandoni P et al. Lancet Oncol. 2005;6:401

Substantial short-term risk of recurrent ischemic stroke

Navi B et al. Neurology 2014;83:26



Hypercoagulable state screening

Homocysteinemia

Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated (*Class III; Level of Evidence C*).

In adults with a recent ischemic stroke or TIA who are known to have mild to moderate hyperhomocysteinemia, supplementation with folate, vitamin B₆, and vitamin B₁₂ safely reduces levels of homocysteine but has not been shown to prevent stroke (*Class III; Level of Evidence B*).

Hypercoagulation

The usefulness of screening for thrombophilic states in patients with ischemic stroke or TIA is unknown (*Class IIb; Level of Evidence C*).

Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA, depending on the abnormality and the clinical circumstances (*Class IIb; Level of Evidence C*).

Antiplatelet therapy is recommended in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA if anticoagulation therapy is not administered (*Class I; Level of Evidence A*).

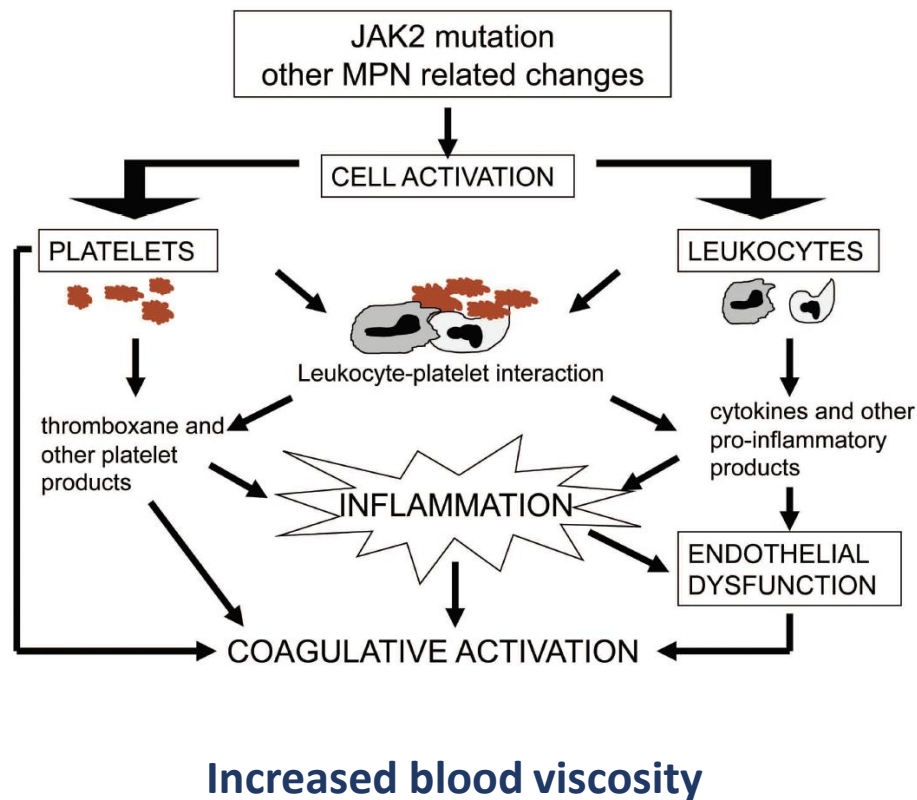
Antiphospholipid antibodies

Routine testing for antiphospholipid antibodies is not recommended for patients with ischemic stroke or TIA who have no other manifestations of the antiphospholipid antibody syndrome and who have an alternative explanation for their ischemic event, such as atherosclerosis, carotid stenosis, or AF (*Class III; Level of Evidence C*).

Summary

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- Hematological disease
- Cerebral venous thrombosis
- Conclusions

Hematological diseases: myeloproliferative neoplasms (MPN)



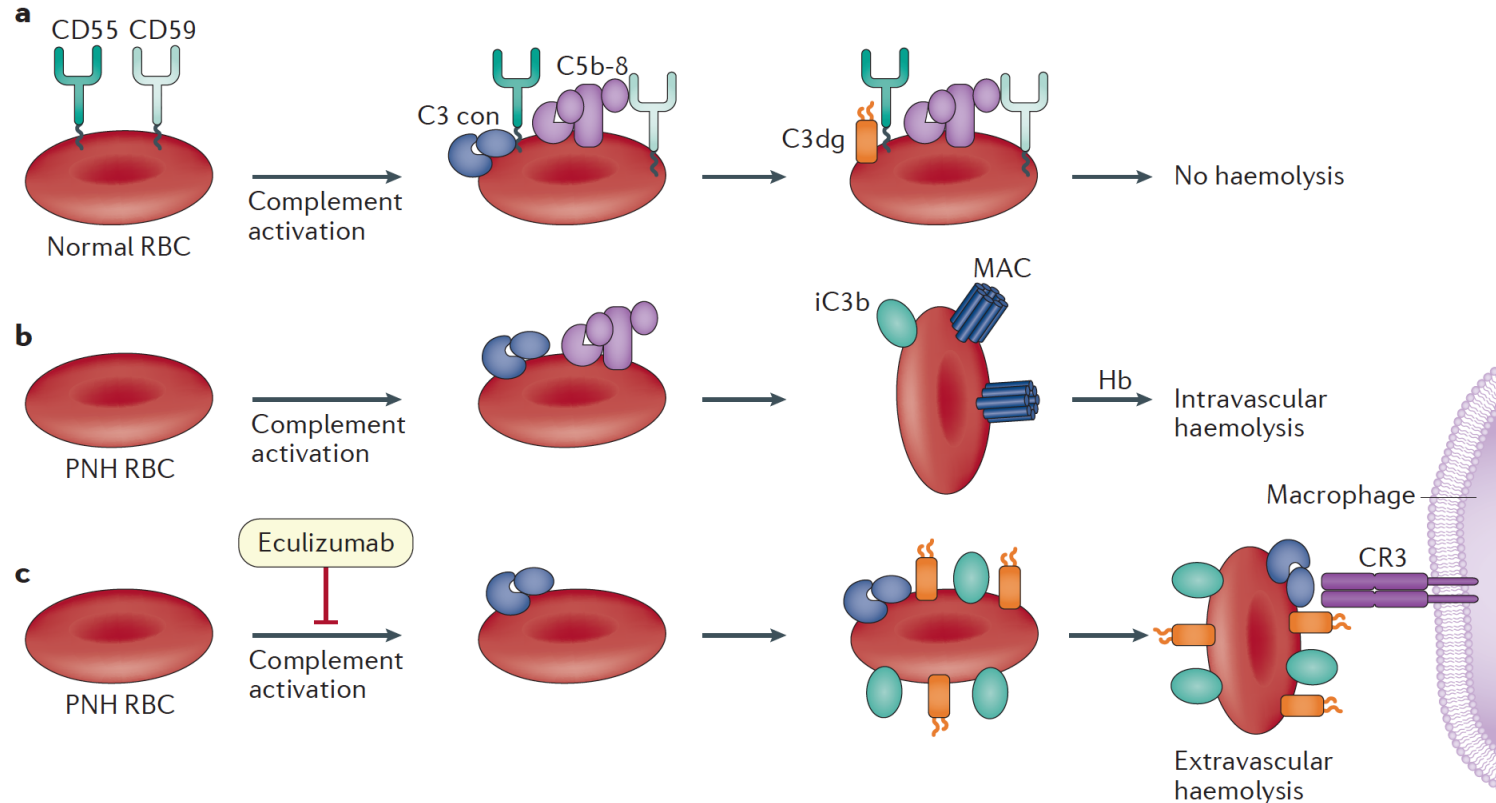
Cerebrovascular accidents are the most prevalent thrombotic events

Landolfi R et al. Blood 2007;109:2446

Incidence rate 16/1000 pt-years in PV and 8.3/1000 in ET

Artori A et al. Curr Neurol Neurosci Rep 2014;14:496

Paroxysmal nocturnal hemoglobinuria (PNH)



Platelet activations
Intravascular hemolysis
Endothelial defects
Complement activation



-30-44% patients
-RR death 15.4
-Stroke as first manifestation

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Cerebral venous thrombosis

Systemic risk factors (%)	
● Inherited	
Antithrombin deficiency	1–7
Protein C deficiency	3–6
Protein S deficiency	3–8
Factor V Leiden	3–12
Prothrombin G20210A	11–21
● Acquired	
Cancer	3–10
Myeloproliferative neoplasms	1–3
Antiphospholipid antibodies	4–17
Behcet disease	1
Autoimmune diseases	8
Paroxysmal nocturnal haemoglobinuria	1
Hyperhomocysteinemia	4–29
Inflammatory bowel diseases	2–3
L-asparaginase and other drugs	1–2
● Circumstantial*	
Oral contraceptives	10–77
Hormone replacement therapy	4–7
Pregnancy or puerperium	2–31

Table 3 Reports on the prevalence of JAK2 V617F in cerebral venous thrombosis

References	No. of patients	Female, n (%)	Age (years), median (range)*	JAK2 V617F, n (%)
De Stefano <i>et al.</i> [33]	45	36 (80)	35 (19–80)†	5 (11)
Xavier <i>et al.</i> [57]	44	30 (68)	28 (15–65)	0 (0)
Bellucci <i>et al.</i> [56]	87	71 (82)	35.3 (16–77)	1 (1.1)
Koopman <i>et al.</i> [54]	59	NA	NA	3 (5)
Shetty <i>et al.</i> [44]	70	NA	NA	2 (3)
Passamonti <i>et al.</i> [55]	152	112 (74)	35 (16–79)	10 (6.6)
De <i>et al.</i> [58]	372	273 (73)	27.15 (SD 7.74)	22 (5.9)

Conclusions

- Low correlation between hypercoagulable state and ischemic stroke
- Hypercoagulable work-up in selected patients, especially younger ones
- Think on haematological causes of strokes (including cerebral venous thrombosis) in case of recurrent events in younger patients