Emoglobinuria Parossistica Notturna
Focus Clinico e Update Diagnostico

Milano, 12 Dicembre 2018

EPN e Rischio Trombotico. Meccanismi e Approccio Clinico

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Agenda

- PNH: pathogenesis and outcome
- PNH and thrombosis: how they are linked
- Clinical approach to thromboembolic risk and events in PNH

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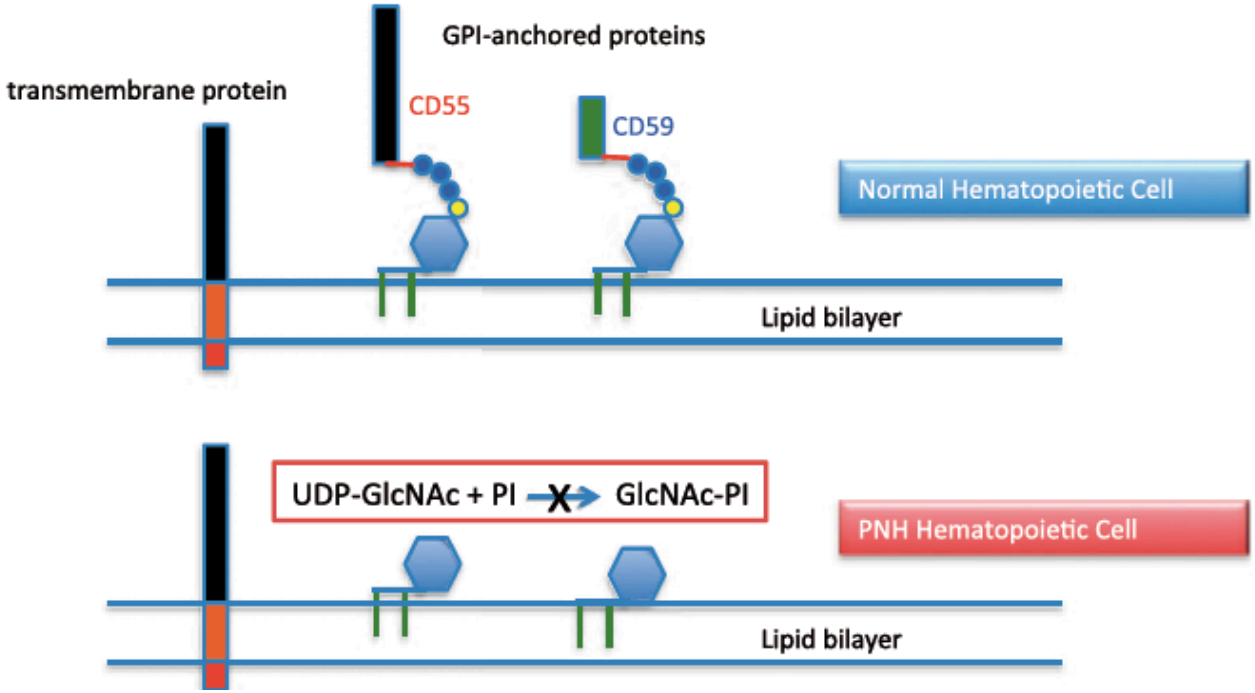
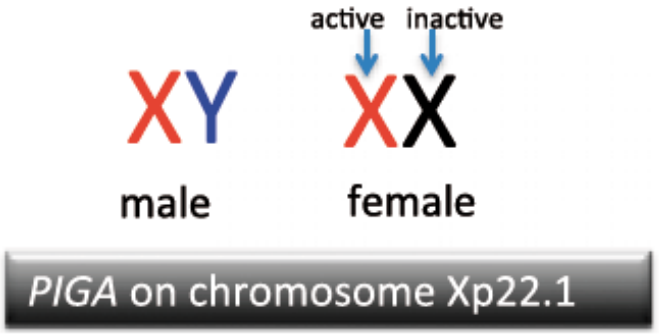
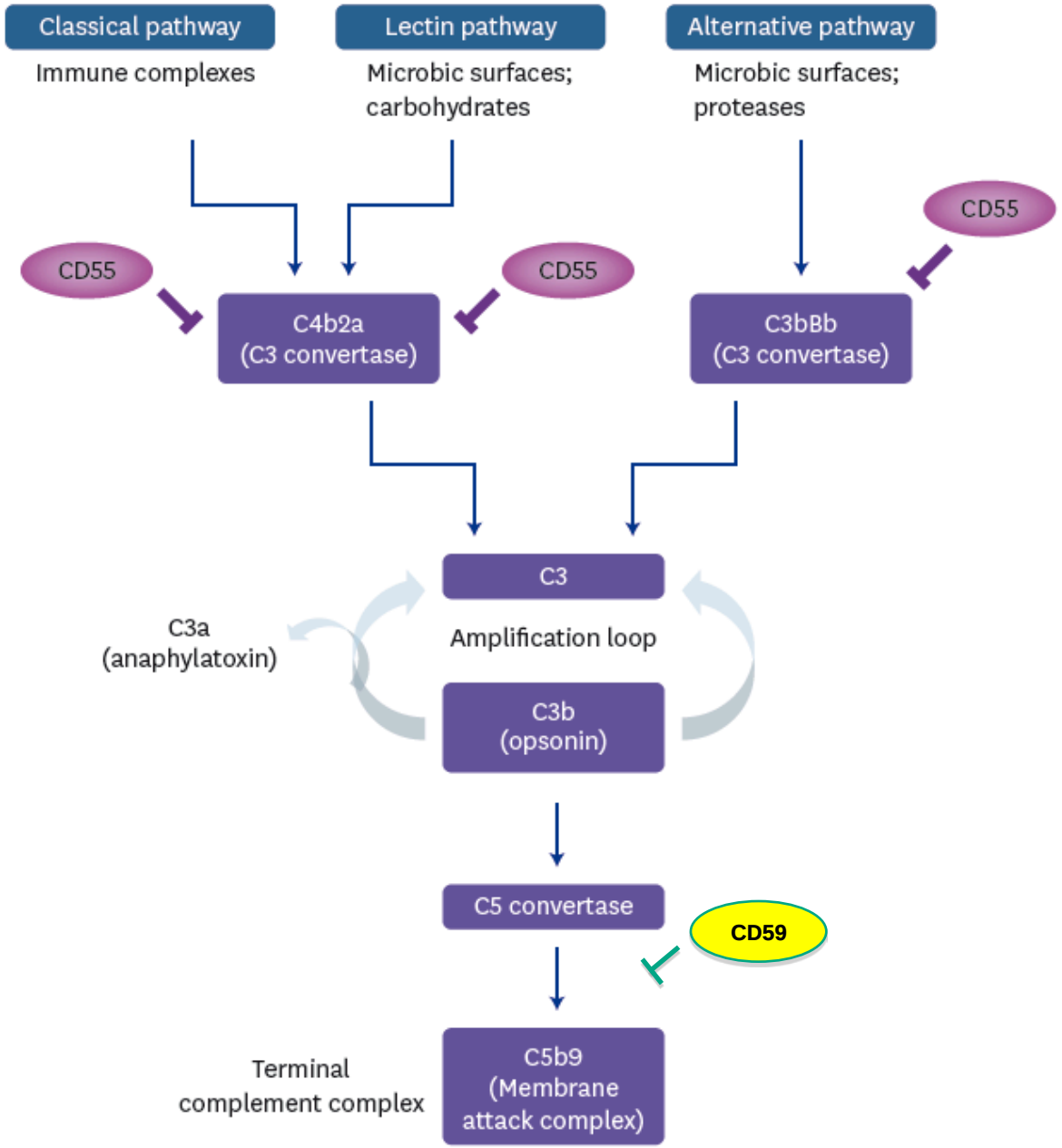
PNH: background

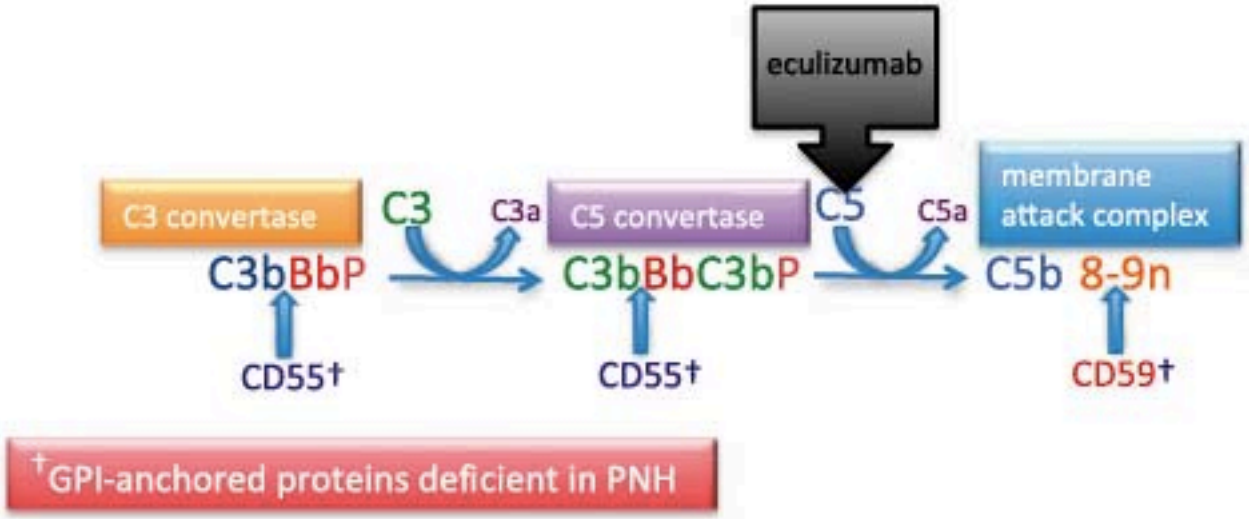


CD55= DAF (Decay accelerating Factor)
CD59= MIRL (membrane inhibitor of reactive lysis)



Parker, Hematology 2016 (ASH educational)

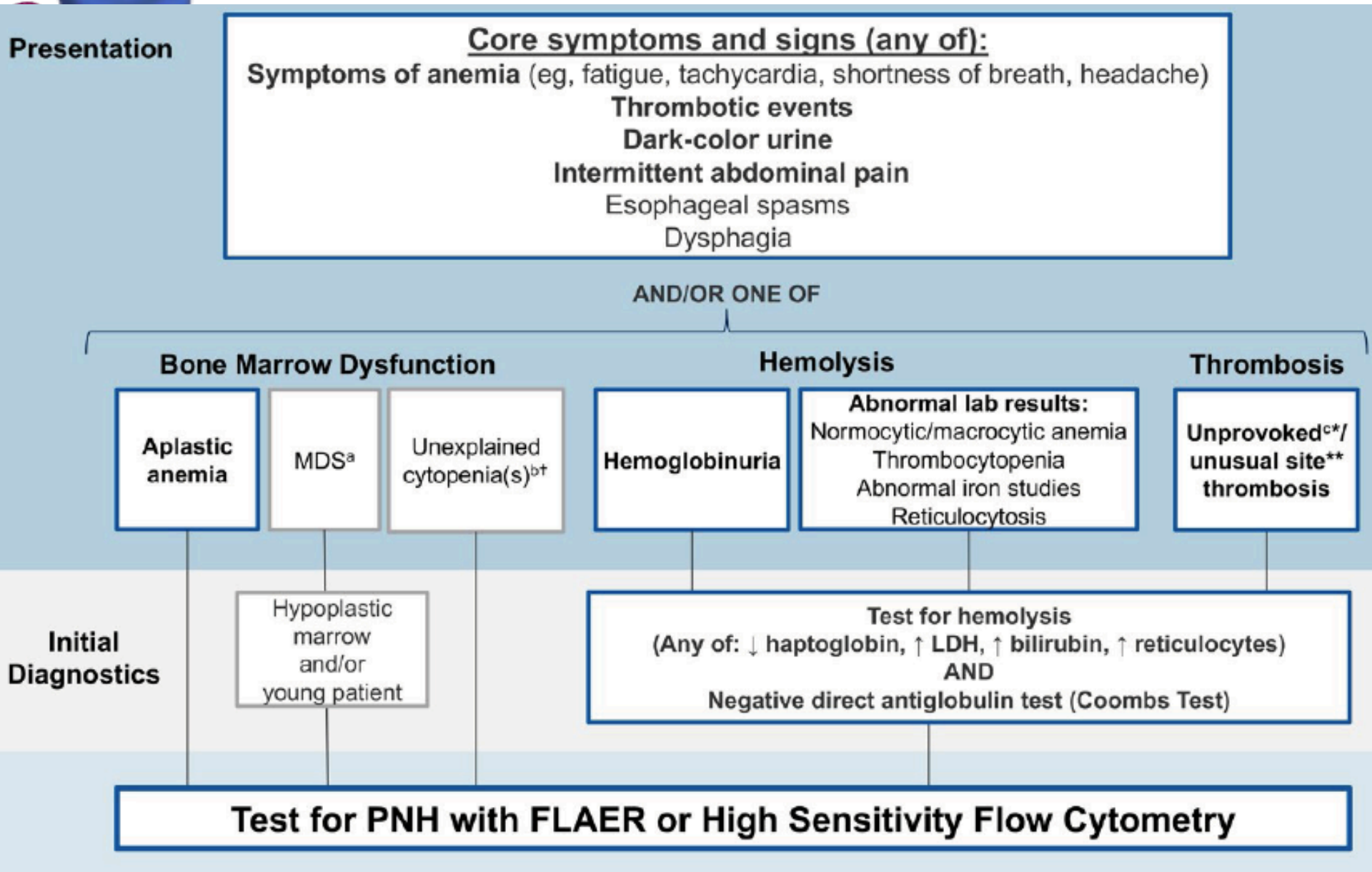

Classical pathway
Immune complexes
Lectin pathway
Microbic surfaces; carbohydrates
Alternative pathway
Microbic surfaces; proteases
CD55
CD55
CD55
C4b2a (C3 convertase)
C3bBb (C3 convertase)
C3
C3a (anaphylatoxin)
Amplification loop
C3b (opsonin)
C5 convertase
CD59
Terminal complement complex
C5b9 (Membrane attack complex)



Complement-Mediated Hemolysis

Normal RBC

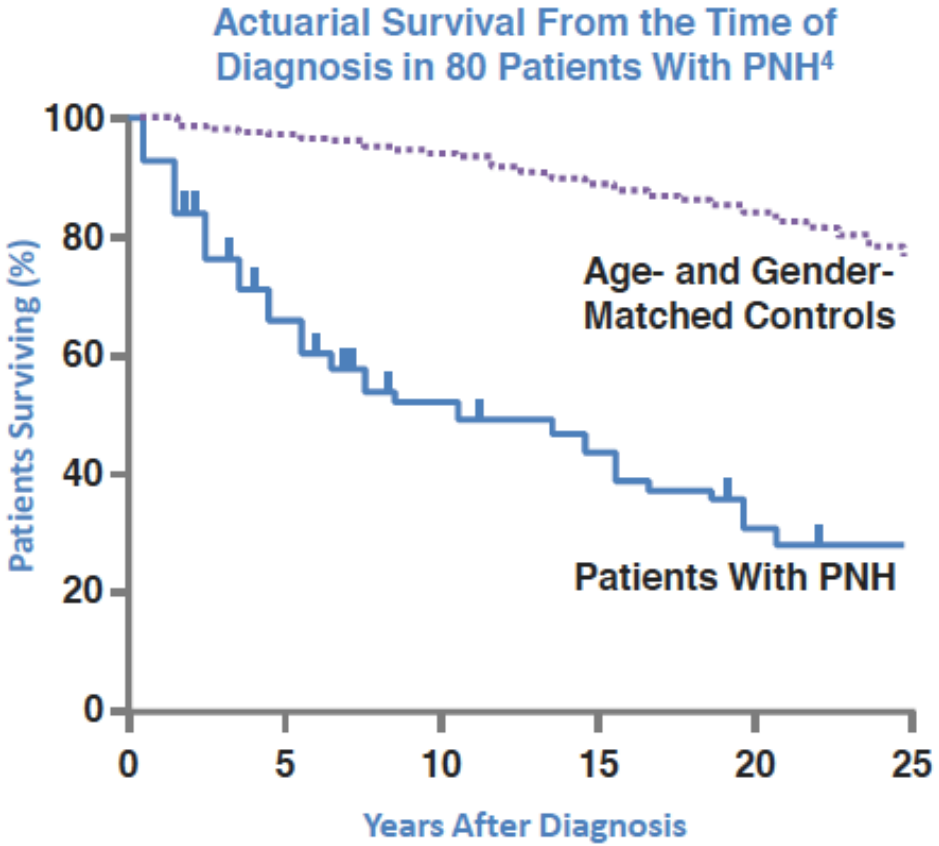
PNH RBC



Roth et al. Eur J Haematol 2018

Once upon a time there was “THIS” PNH

- Prevalence: **15.9/million**[1]
- Median age at diagnosis: **early 30s**[2,3]
- **35% of patients with PNH die within 5 years of diagnosis despite best supportive care**[4]
- **Progressive disease:** characterized by chronic complement-mediated hemolysis

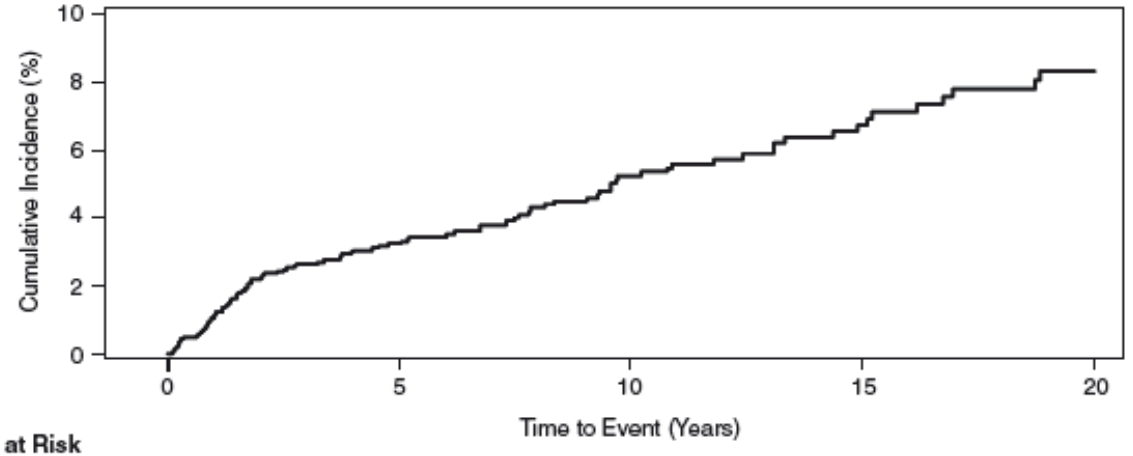


1. Hill A et al. *Blood*. 2006;108:290a. Abstract 985.
2. Nishimura JI et al. *Medicine*. 2004;83:193-207.
3. Socié G et al. *Lancet*. 1996;348:573-577.
4. Hillmen P et al. *N Engl J Med*. 1995;333:1253-1258.

Changing prognosis in paroxysmal nocturnal haemoglobinuria disease subcategories: an analysis of the International PNH Registry

Soci et al. Internal Medical J 2016

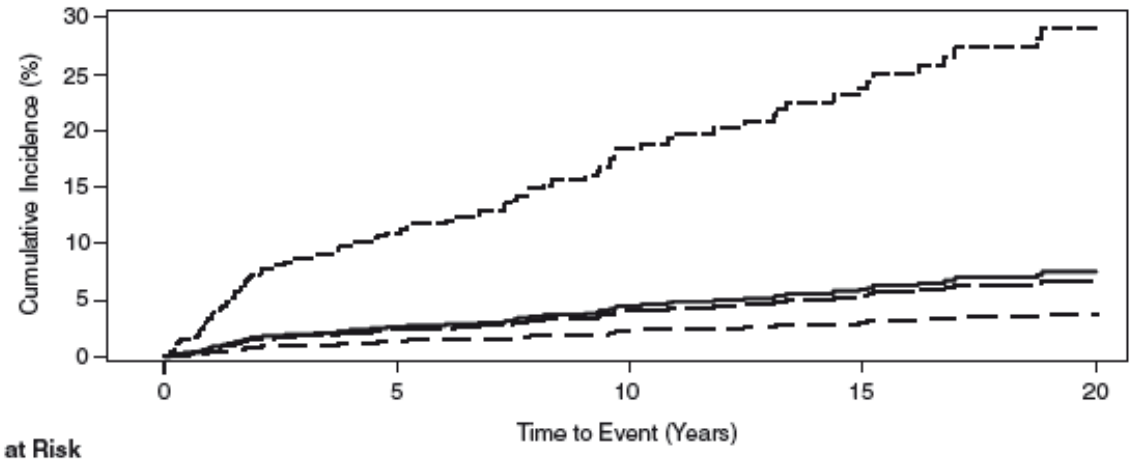
(A)



Number at Risk					
Study Population	2339	1401	799	474	276

(B)

- - AA-PNH Syndrome
___ Hemolytic PNH



Number at Risk					
Hemolytic PNH	698	480	299	181	109
AA-PNH Syndrome	374	85	34	22	8
Intermediate Classification	685	406	192	114	57
Insufficient Data	582	430	274	157	102

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Thrombosis & PNH

- Relationship between "**blood haemolytic system**" and coagulation system described more than 6 decades ago [Crosby WH, Dameshek W, Blood 1950]
- Thromboembolism is ***the most common cause of mortality*** in patients with PNH:

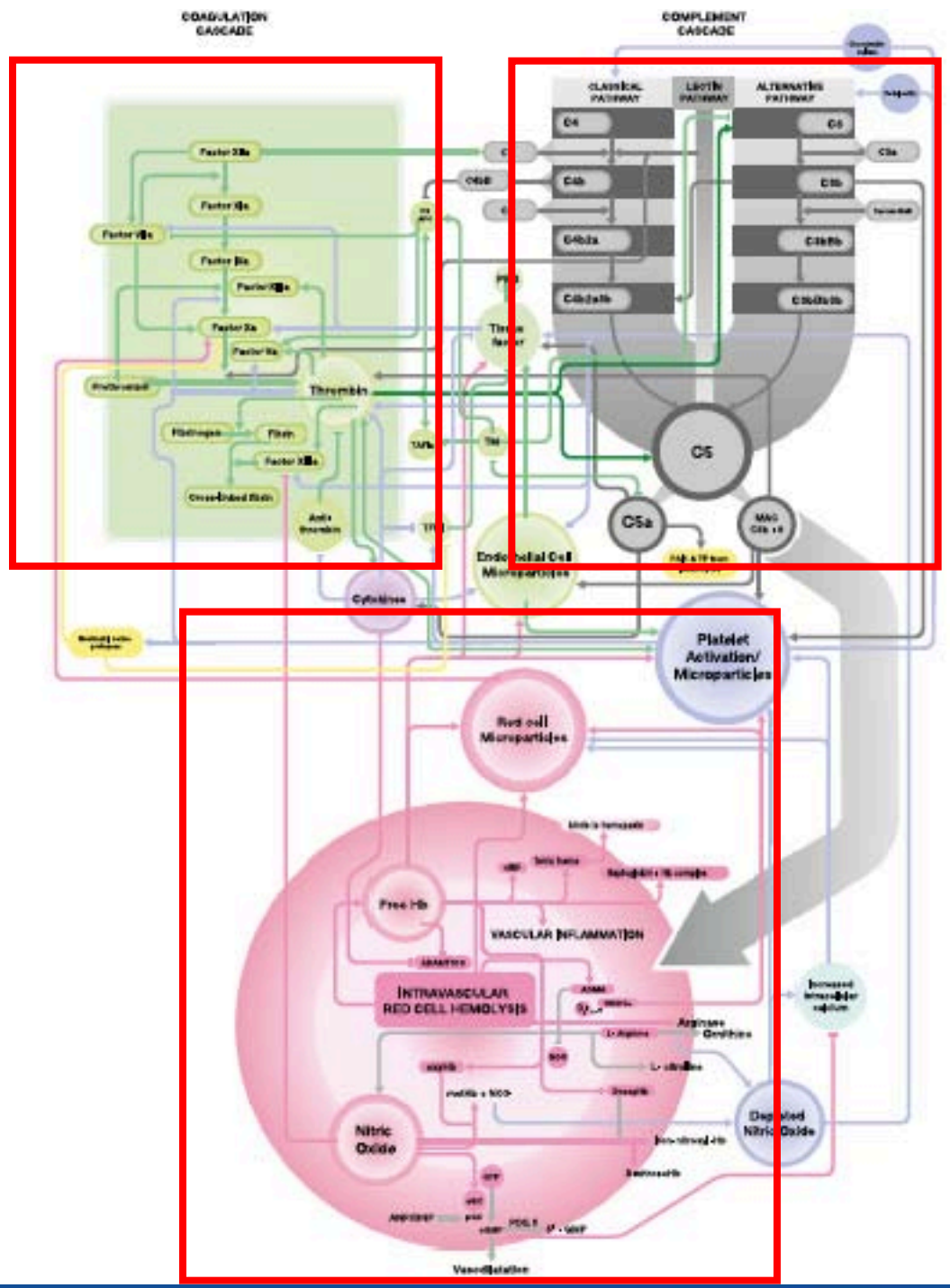
  - ✓Responsible for **40-60%** of deaths in which the cause is known
  - ✓At least one TE event reported in **29-44%** of patients with PNH
  - ✓Visceral thrombosis **preceding diagnosis** of PNH reported in 19% of patients [1]
  - ✓Survival rate only 40% in patients with thrombosis at presentation [2]
  - ✓Relative **risk of death** increased 5 to 15.4 fold [3]

1. Poulou LS et al. Thromb Haemost 2008
2. Sociè G et al. Lancet 1996
3. Nahimura J et al. Medicine 2004

Thrombosis & PNH:
close integration between the complement cascade and the coagulation cascade

Hill A & Hillmen P, Blood. 2013;121: 4985-96

Thrombosis & PNH: close integration between the complement cascade and the coagulation cascade



Hill A & Hillmen P, Blood. 2013;121: 4985-96

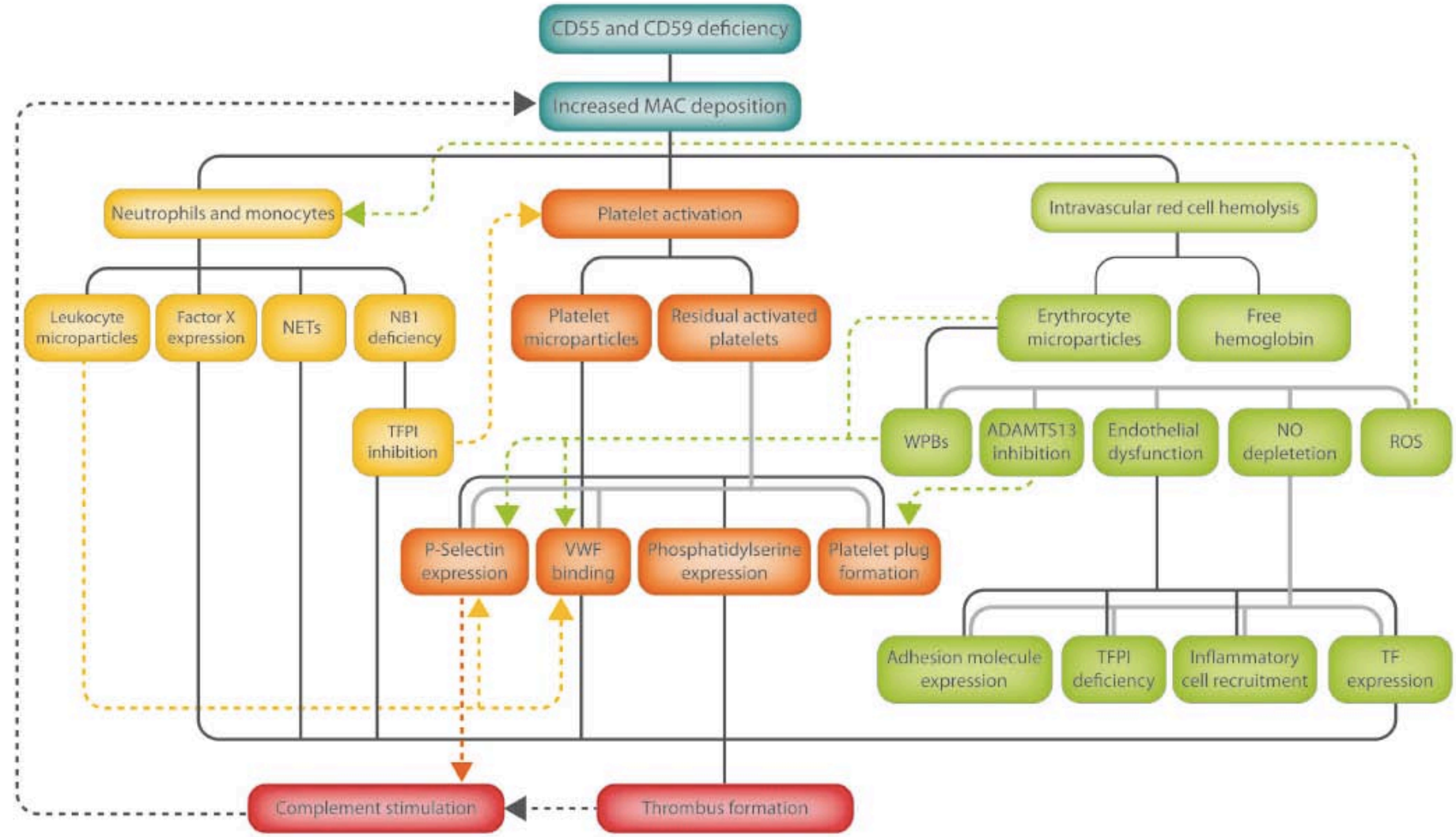


Figure 1. Summary of the multiple factors thought to contribute to the prothrombotic state in paroxymal nocturnal hemoglobinuria (PNH) and interaction. Furthe details are provided in the text. MAC: membrane attack complex; NET: neutrophil extracellular traps; TFPI: tissue factor pathway inhibitor; VWF: von Willebrand factor WPB: Weibel-Palade bodies; NO: nitric oxide; ROS: reactive oxygen species; TF: tissue factor.

Peacock-Young et al. Haematologica 2018

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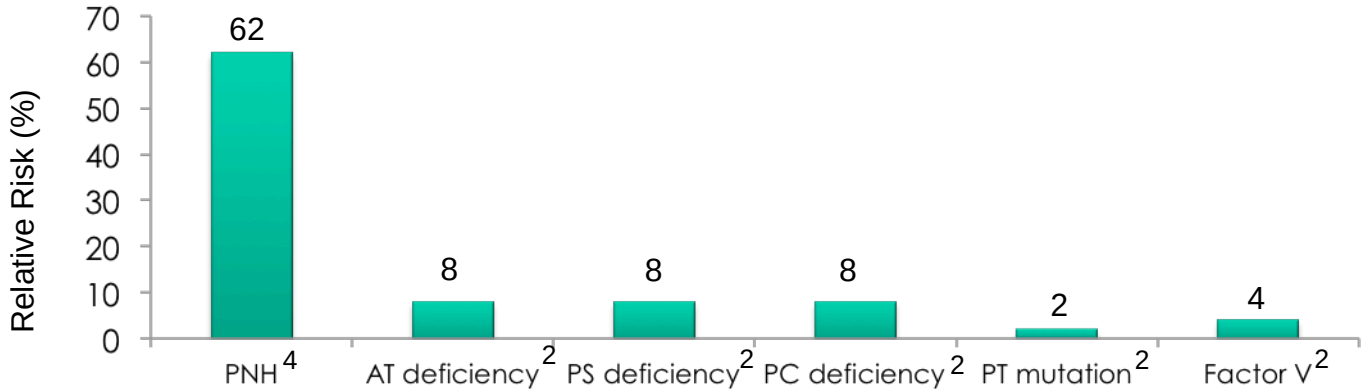
Incidence of VTE and Relative Risk in PNH vs Inherited Hypercoagulable states



% Gen Population	0.0015 [3]	0.02 [1]	0.03 [1]	0.20 [1]	2.0 [1]	4.8 [1]
Expected pts with VTE per yr	280	1020	630	4200	6600	14400

- PNH is a less common disease than inherited hypercoagulable states
- PNH patients have a higher risk for VTE than inherited hypercoalable state patients

1. De Stefano V eta al. Semin Thromb Hemost 2006; 2. De Stefano V et al. Haematologica 2002; 3. Hill A et al. Blood 2006-abstract 985; 4. Relative Risk calculated on 1/1000 in general population as reported in De Stefano V et al Haematologica 2002

Site and Type of Thrombosis in PNH

- Venous thrombosis occours in approx. 40% of patients

Hillmen 1995 (n=80)

Table 2. Sites and Types of Thrombosis.

Site and Type of Thrombosis	No. of Patients
Intraabdominal	
Hepatic vein	8
Inferior vena cava	3
Mesenteric vein	4
Splenic vein	1
Renal vein	1
Unspecified	1
Other venous sites	
Cerebral vein	4
Pulmonary embolism	9
Deep vein	7
Superficial	3
Arterial	
Myocardial infarction	6
Cerebrovascular accident	2

Hillmen 2007 (n=195)

Table 2. Sites of pretreatment thromboembolism events

TE sites	Events, no.	Percentage of total
Venous thrombosis		
Deep vein thrombosis	41	33.1
Lower extremity	23	18.5
Other*	18	14.5
Mesenteric/splenic vein thrombosis	23	18.5
Hepatic/portal vein thrombosis	21	16.9
Pulmonary embolus	8	6.5
Cerebral/internal jugular thrombosis	7	5.6
Superficial vein thrombosis	5	4.0
Arterial thrombosis		
Cerebrovascular accident/transient ischemic attack	17	13.7
Myocardial infarction/unstable angina	2	1.6
Total	124†	100

Under-recognized complications in PNH pts: Raised pulmonary pressure and reduced right ventricular function

Prevalence of PNH in patients with Budd-Chiari syndrome

- Hepatic vein thrombosis (**Budd Chiari syndrome**): 7.5-25% of patients with PNH and may lead to hepatic failure (Hill, 2013)

- Hoekstra et al, 2009
  - Up to 40% of incidence of BCS in pts with EPN

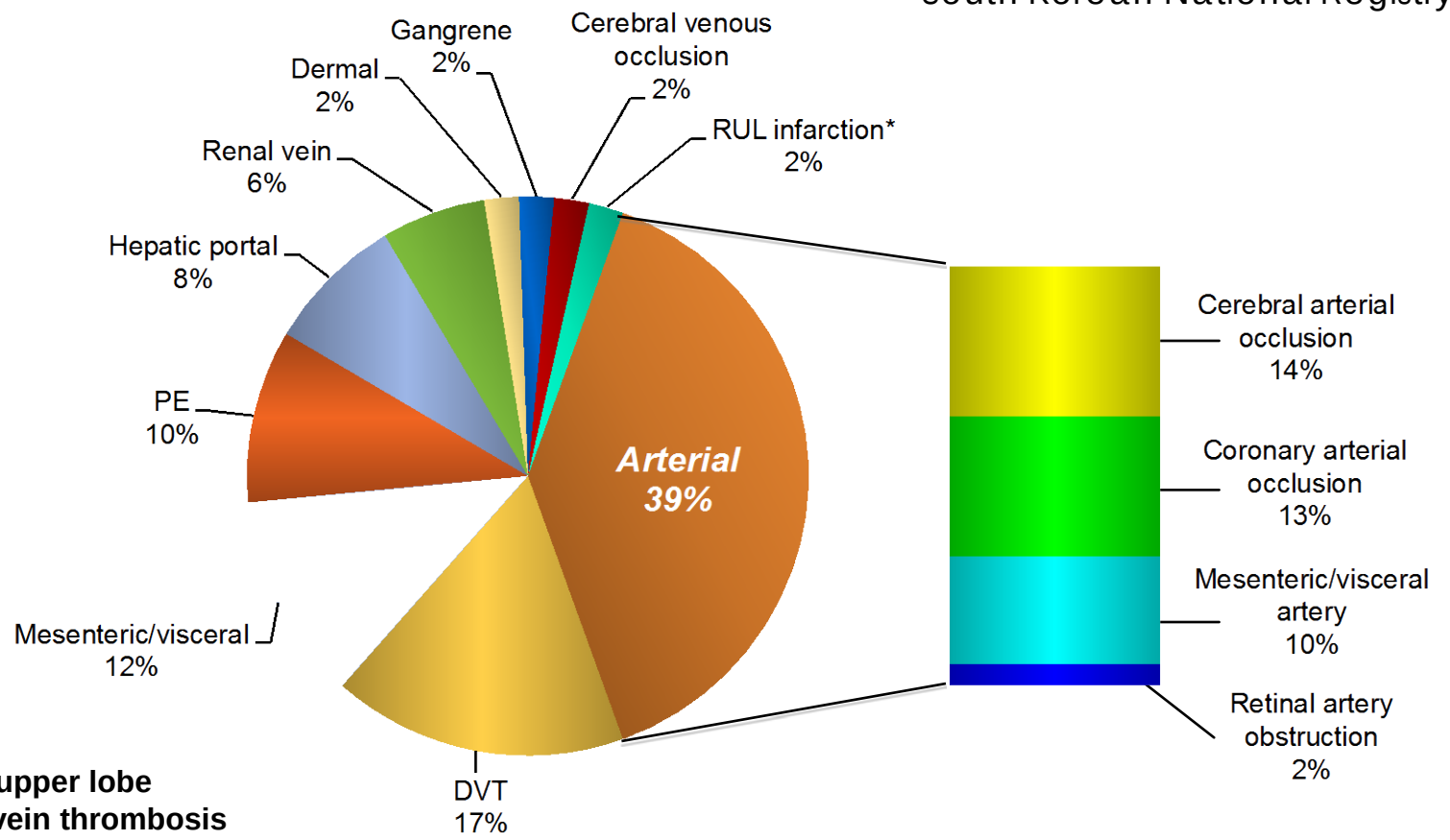
- Garcia Pagan, 2008
  - 128 pts with BCS, 10,5% EPN+

- Darwish et al, 2009
  - 168 pts with BCS, 77 tested for PNH, 15 (19,5%) EPN+

39% of TE Events Occur at Arterial Sites

South Korean National Registry

n = 286



RUL – Right upper lobe
DVT – Deep vein thrombosis

Arterial TE events were common in a large, retrospective analysis

Lee JW *et al*. *Hematologica* 2010;95(s2):abstract 505 and associated poster .

First Ever Ischemic Stroke Incidence in PNH vs General Population

Thrombophilic Condition	First Ever Ischemic Stroke (FEIS) (per 100 patient years)	FEIS Risk Relative to General Population	Median Age at FEIS
PNH	0.42[1,2]	6	46[2]
General Population	0.08[3]		72[3]
PNH <54 year old	0.24[1]	8	
General Population 35-54 year old	0.03[3]		

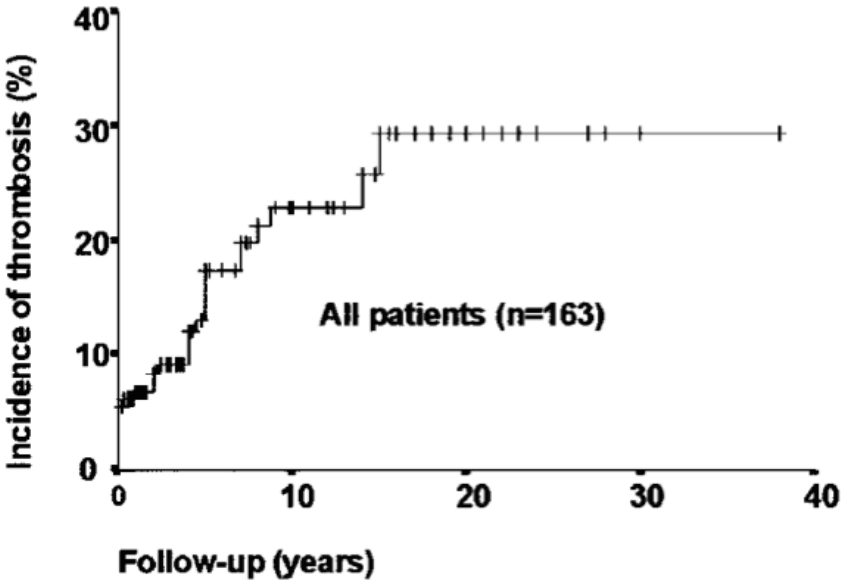
- FEIS risk is elevated in patients with PNH
- Age of FEIS in PNH patients is markedly less than in the general population

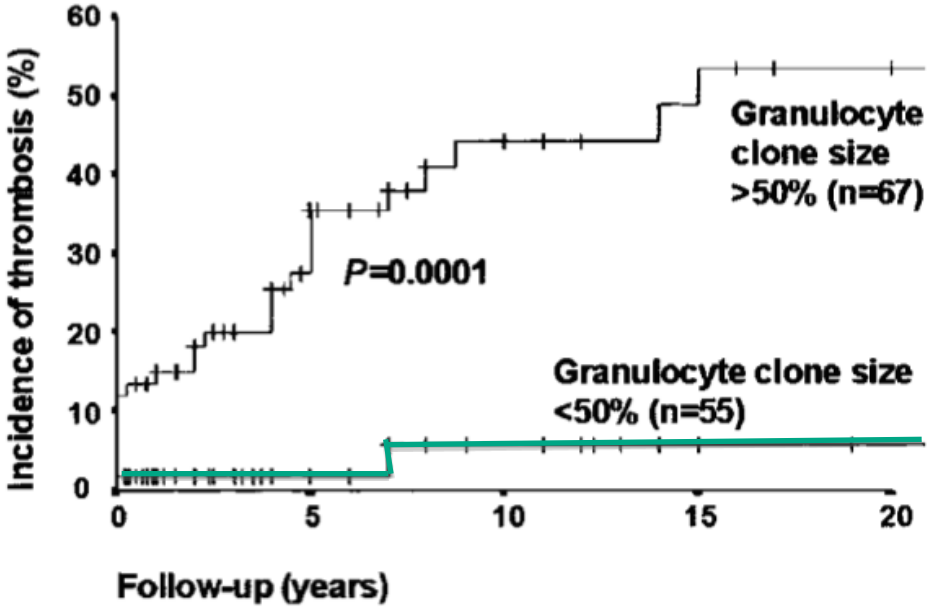
1. Hillmen P et al. *Blood*. 2007;110:4123-81. 2. Data on file. 3. Gostynski M et al. J Neurol.

PNH clone size and thrombosis

Incidence of thrombosis is highest in patients with a large PNH Clone

3.7 thrombosis/100 patient year

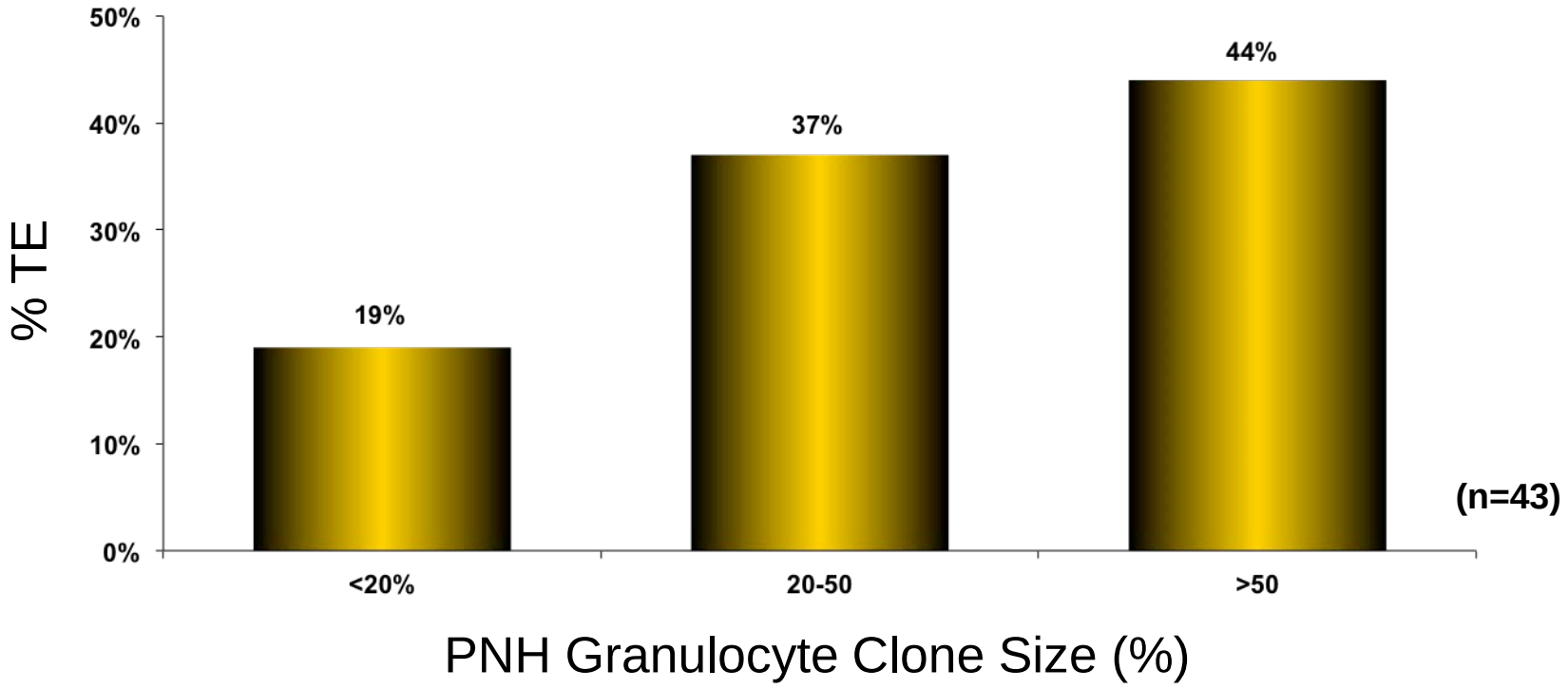




primary prophylaxis patients are excluded

Hall C et al. Blood 2003

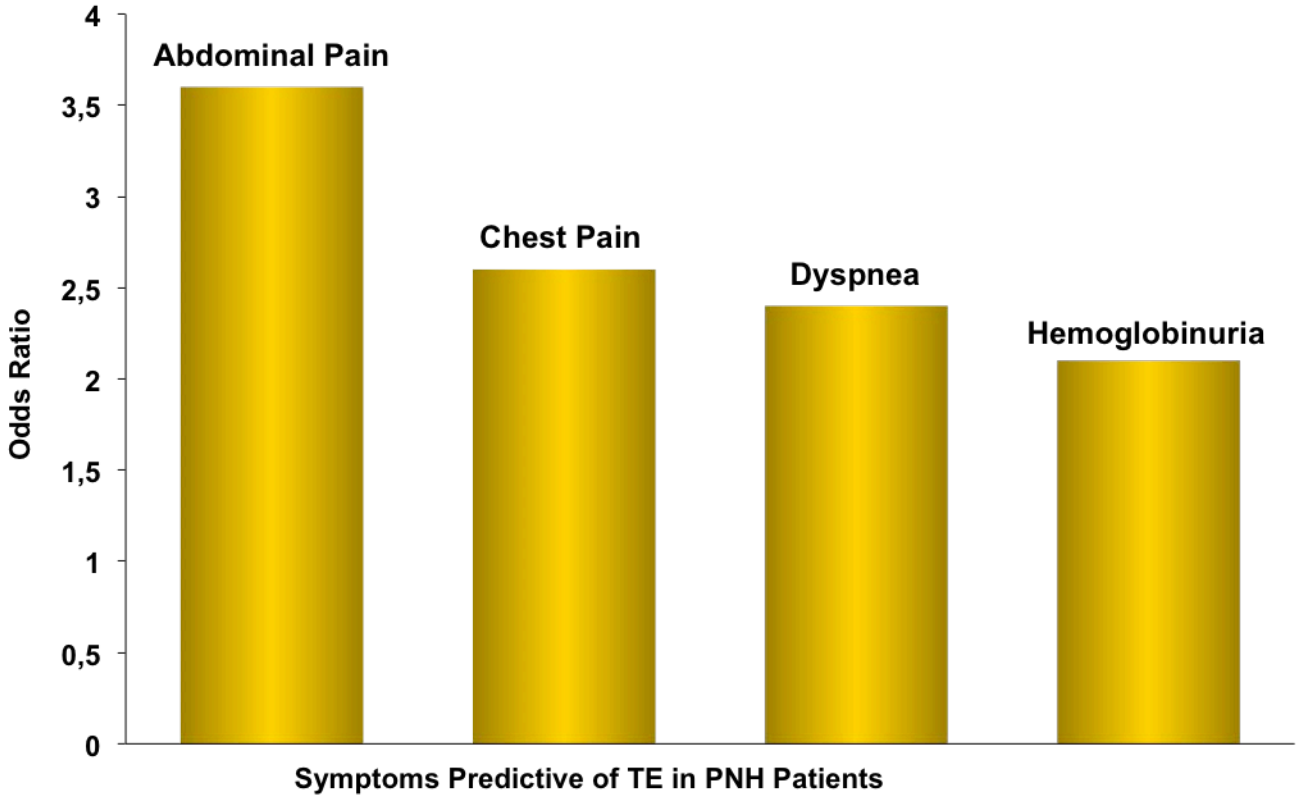
TEs Can Occur Regardless of Clone Size



South Korean National Registry

Lee JW et al. *Hematologica* 2010. 95 (s2): Abstract #505.

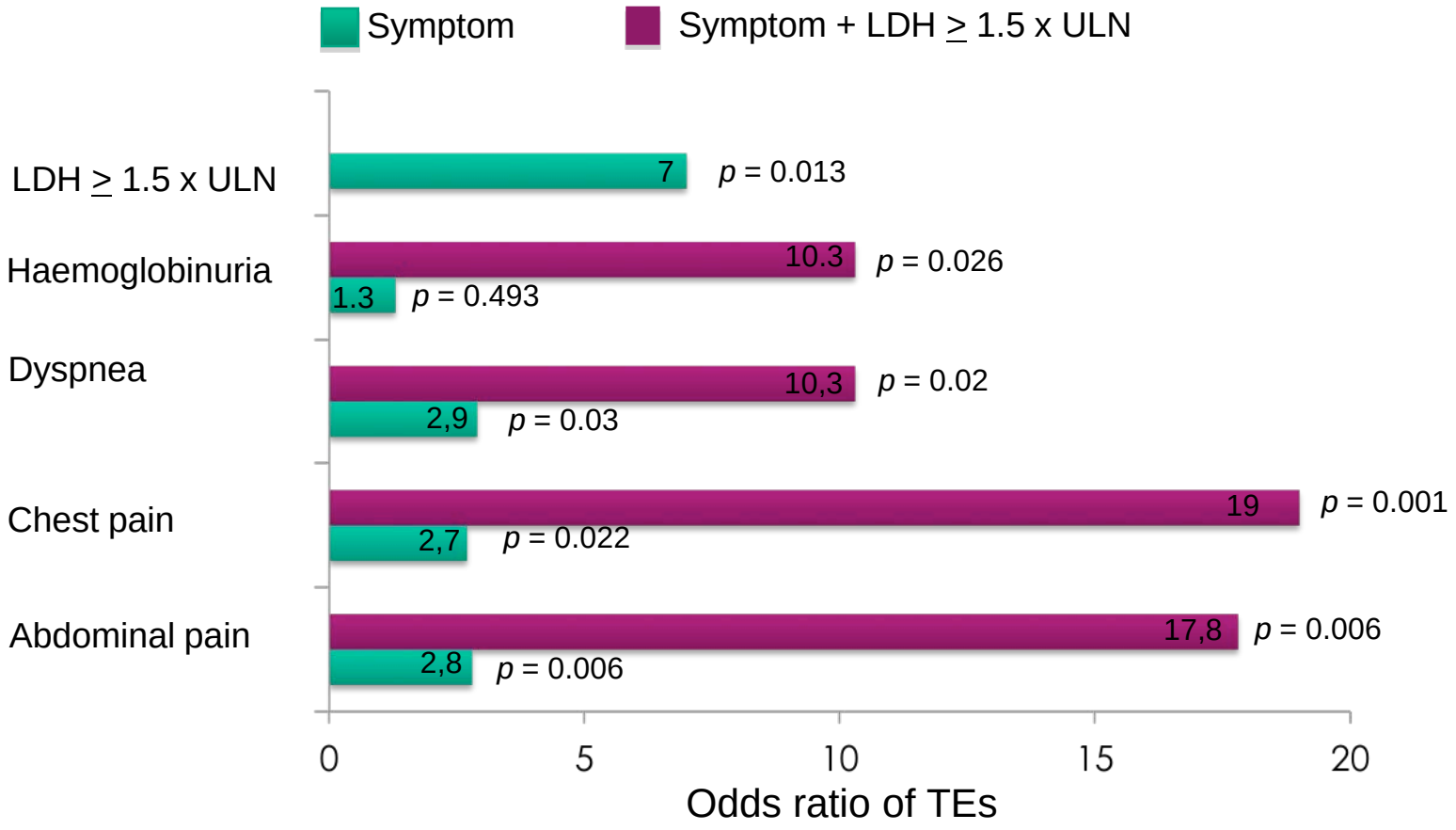
Clinical Symptoms Predictive of TE



South Korean National Registry

Lee JW et al. *Hematologica* 2010. 95 (s2): Abstract #505 and 506.

Elevated Haemolysis and Clinical Symptoms associated with increased risk of TEs



- In addition to LDH >1.5 x ULN, common symptom of PNH are associated risk factors for TEs
- Elevated haemolysis, with any one of these clinical symptom, was associated with a greater risk for Tes than elevated haemolysis or clinical symptoms alone

Lee JW et al. Int J Hematol 2013

EUROPEAN HEMATOLOGY ASSOCIATION
haematologica
Journal of the European Hematology Association

Significant hemolysis is not required for thrombosis in paroxysmal nocturnal hemoglobinuria

by Morag Griffin, Peter Hillmen, Talha Munir, Stephen Richards, Louise Arnold

We report the first case series of patients with PNH who experience thrombosis with low levels of hemolysis. Patients at higher risk of presenting with thrombosis were those with high PNH white cell proportions and low PNH red cells (group I). Patients with a greater proportion of type II

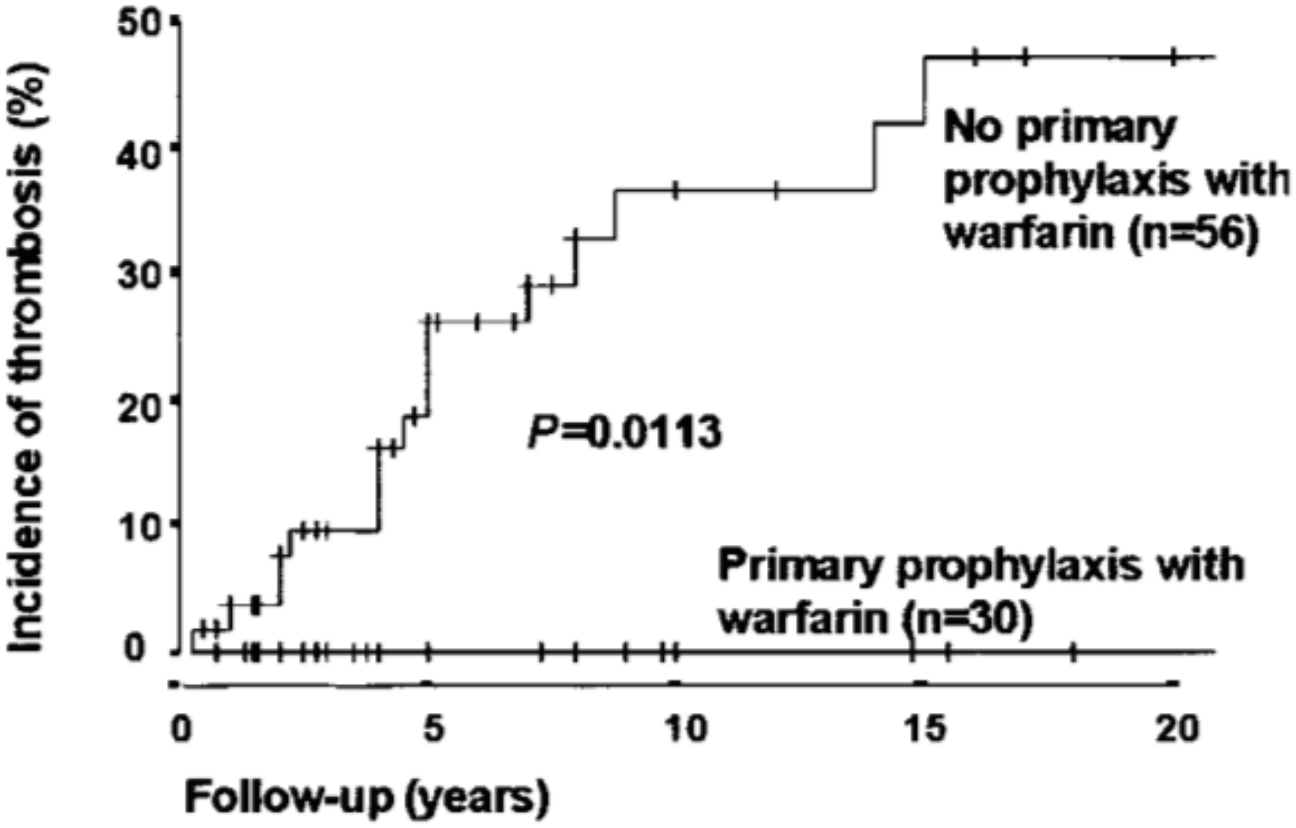
Anonymised clinical data were then analysed to determine risk factors for thrombosis.

Comparisons between those with and without thrombosis were assessed.

Group 1: PNH white cells >30%, PNH red cells <10%, LDH <2xULN

Group 2: PNH white cells >30%, PNH red cells >10%
with higher proportion of type II red cells than type III red cells, LDH <2xULN

Primary prophylaxis with warfarin in PNH (patients with >50% PNH Neutrophils)

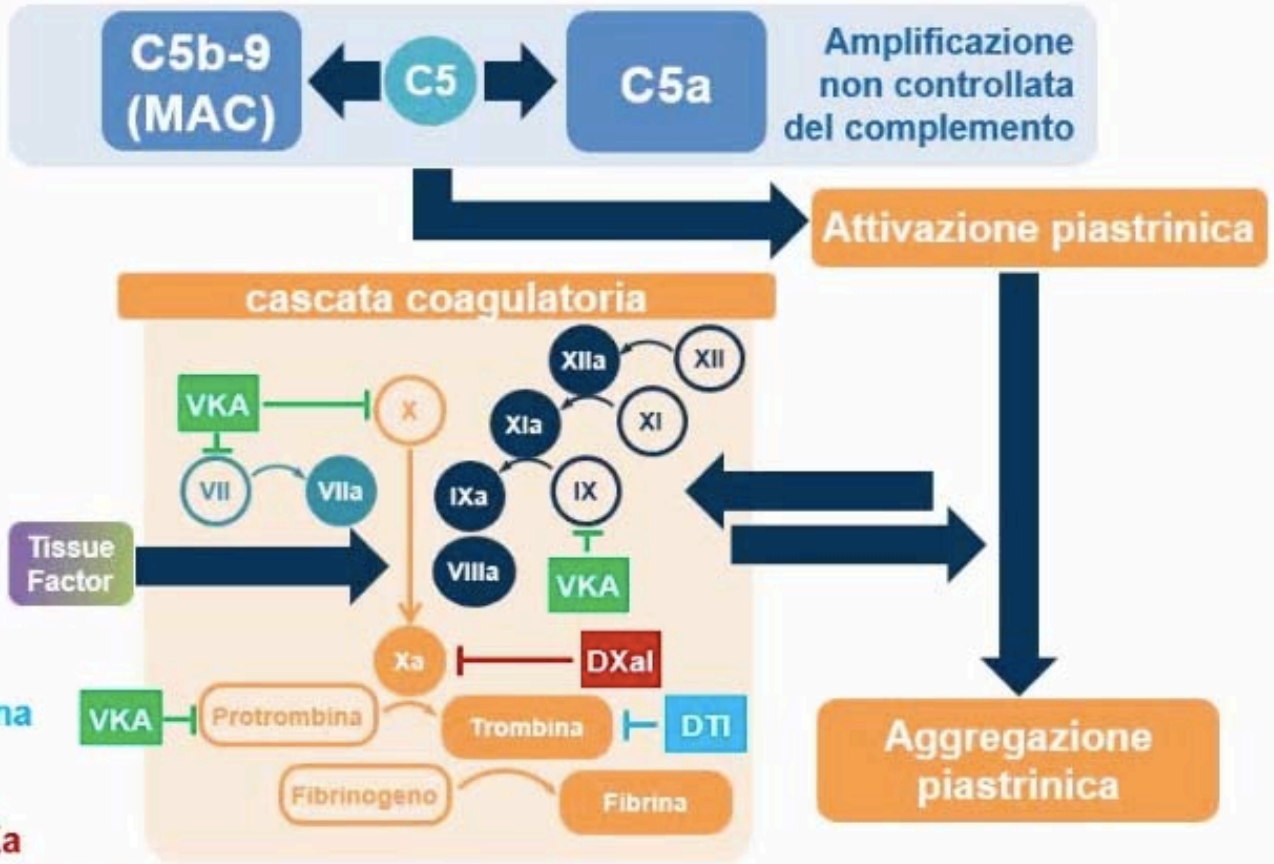


Hall C et al. Blood 2003

To remember

- **Anticoagulation alone is not wholly effective** in reducing the thrombosis risk in patients with PNH compared with the general population.
- Patients are **at risk of thrombosis extension** and recurrence despite prophylactic anticoagulation, in some reports as high as 57%
- **PNH related thrombosis** regardless of LDH level **is an indication to commence treatment**

Gli anticoagulanti orali interferiscono con alcune componenti della cascata coagulatoria, ma non bloccano gli altri meccanismi eziopatogenetici della trombosi secondari all'attivazione del complemento



Anticoagulanti orali di uso comune:

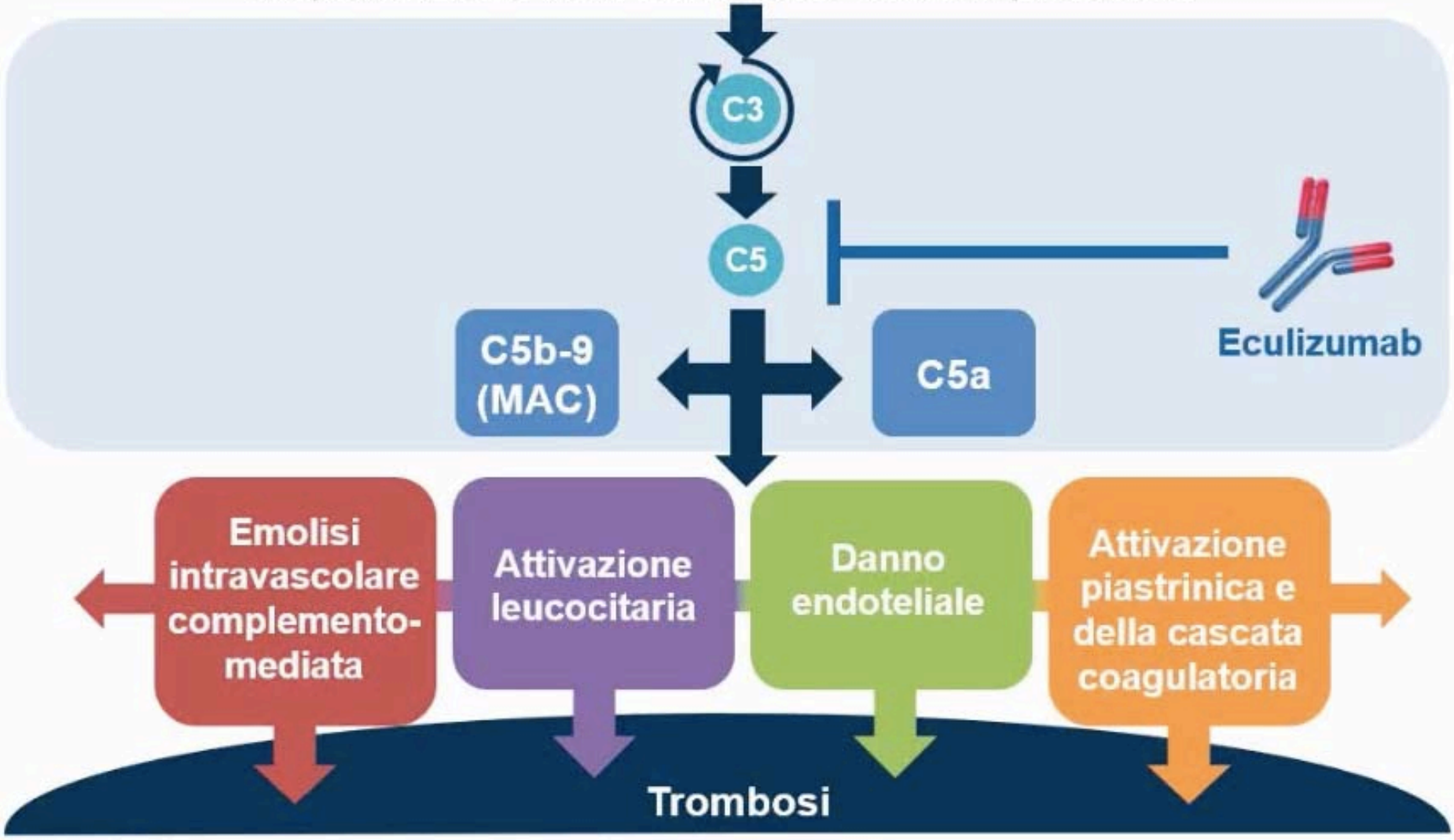
VKA Antagonisti Vitamina K (warfarin, acenocumarolo)

DTI Inibitori diretti della trombina (dabigatran)

DXaI Inibitori diretti del Fattore Xa (rivaroxaban, apixaban, edoxaban)

Trombosi

Amplificazione non controllata del complemento



Thrombosis and Eculizumab: Overall Analysis

	Pilot [1]	TRIUMPH [2]	SHEPERD [3]	Extension (all studies combined)
Patients (n)	11	43	97	195
Pre-Treatment				
TE events (n)	5	16	91	124
Patient years (n)	161,7	309,0	718,3	1683,4
TE Event Rate (n per 100 patent years)	3,09	5,18	12,67	7,37
Eculizumab Treatment				
TE events (n)	0	0	2	3
Patient years (n)	34,19	21,8	96,88	281,03
TE Event Rate	0,00	0,00	2,06	1,07 (p< 0.001)

- 85% reduction in thrombosis with eculizumab
- Reduction with eculizumab observed in each patient cohort

1. Hillmen P, NEJM 2004
2. Hillmen P, NEJM 2006
3. Broadsky, Blood 2008

Acute VTE management in PNH

- Immediate full anticoagulation (in the absence of major contraindications)beginning with **heparin therapy**
- Monoclonal antibody therapy with **eculizumab**
- **Continuing anticoagulation with VKA** (Coumadin) is generally recommended in the long term if there are no contraindications
- There is **no published experience** of the **newer oral anticoagulants** in PNH.

Patriquin et al, Eur J Haematol 2018
Griffin et al , Ther Adv Hematol 2017

VTE “prophylaxis” in PNH

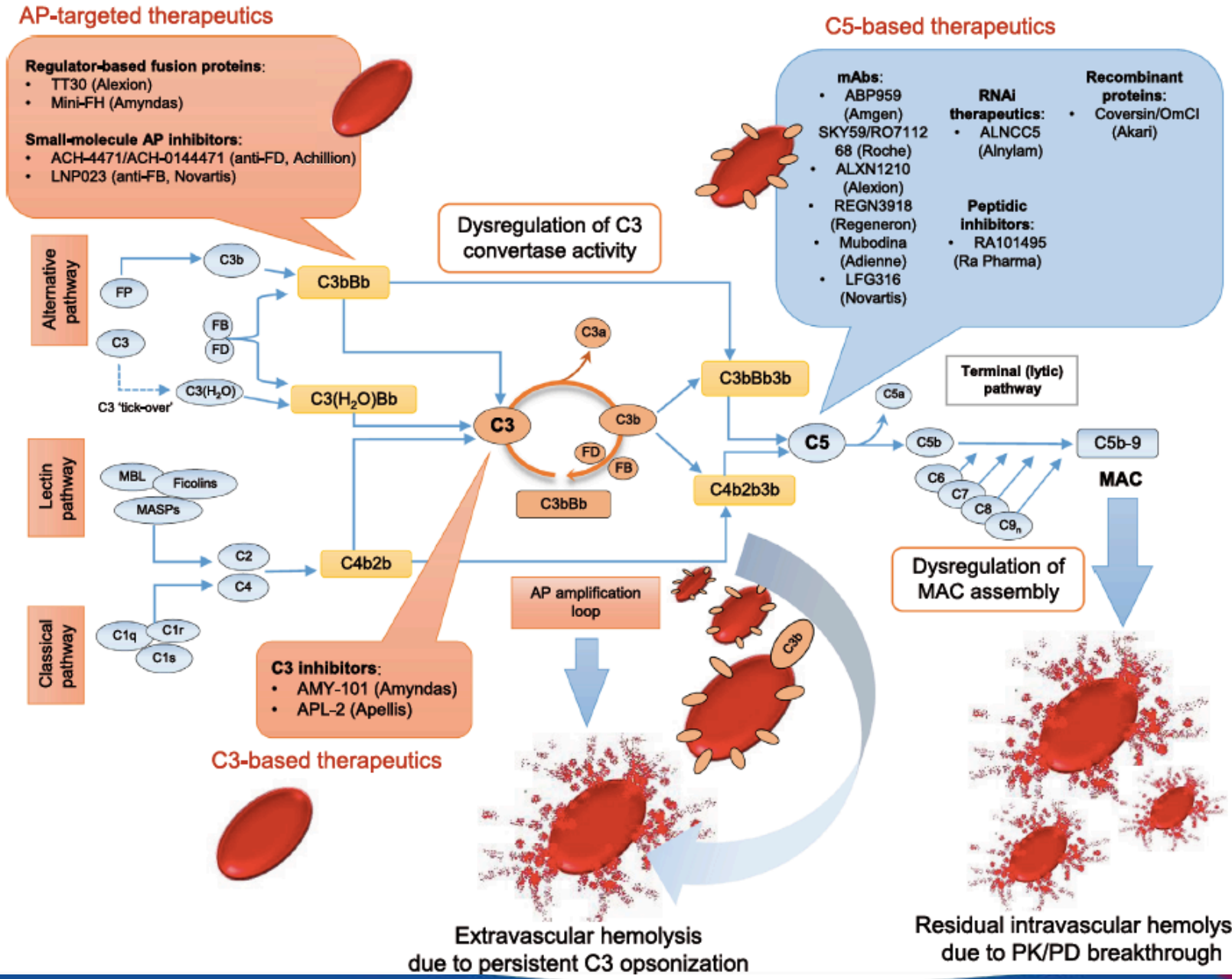
- If PNH neutrophils clone > 50%
- If elevated LDH but do not satisfied eligibility criteria for eculizumab
- If previous history of VTE
- If pregnant (?!)

Pts who start eculizumab without a history of TE do not need anticoagulation and can discontinue primary prophylaxis

Patriquin et al, Eur J Haematol 2018
Griffin et al , Ther Adv Hematol 2017

Novel targets in PNH

Mastellos et al, Sem Hematol 2018



Next Generation Complement Inhibitors

- **Ravulizumab** (Abstracts 625,626,627,2330)
  - **Anti-C5 monoclonal antibody (non-inferior to ecu in randomized phase III trial)**
  - **Intravenous every 8 weeks**
  - **Likely available in 2019**

- **SKY59** (Abstracts 535,3611)
  - **Anti-C5 monoclonal antibody**
  - **Subcutaneous (monthly) terminal ½ life of 25 days**

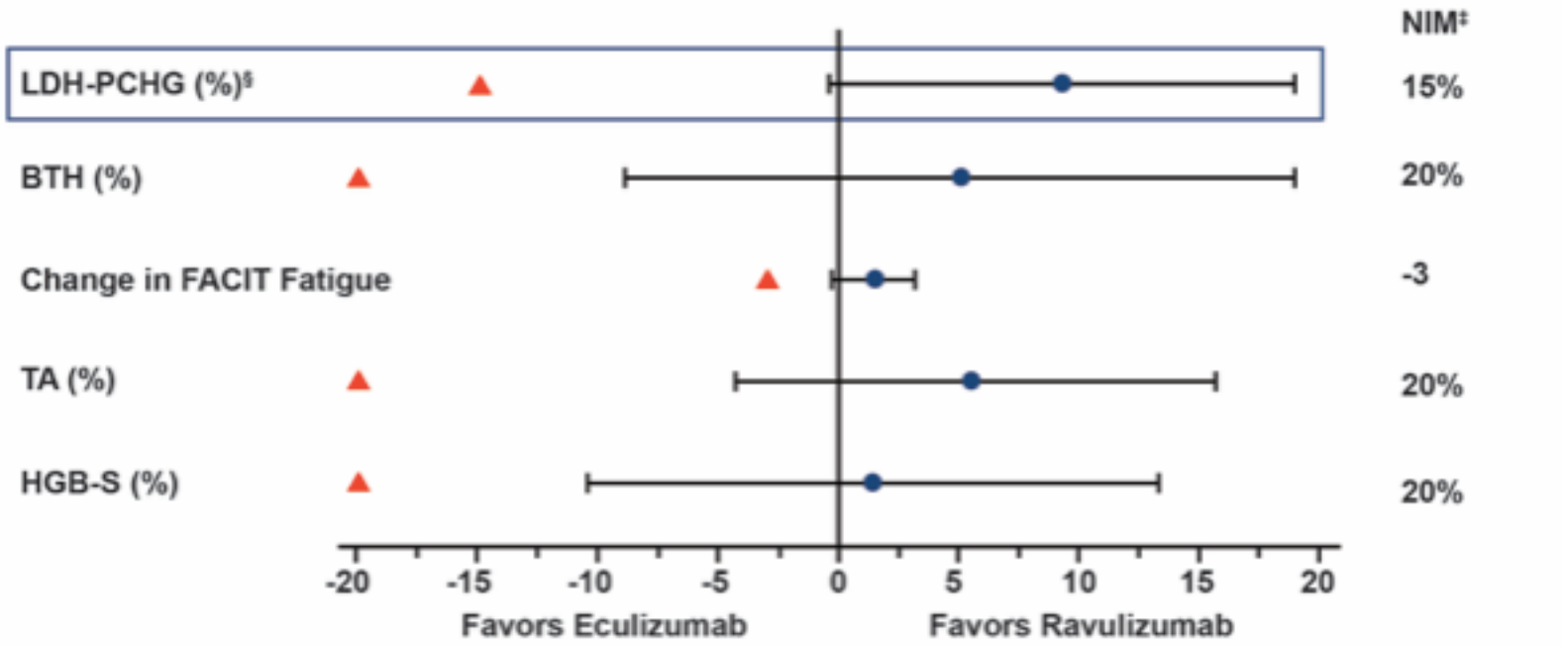
- **APL2** (Abstract 2314)
  - **C3 inhibitor**
  - **Daily subcutaneous**

- **ACH4471**
  - **Factor D inhibitor**
  - **TID oral**

625 Results from a Phase 3, Multicenter, Non-Inferiority Study of Ravulizumab (ALXN1210) Versus Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with Eculizumab

Ravulizumab, is an innovative complement C5 inhibitor given every 8 weeks (q8w)

Adult pts with PNH who were treated with eculizumab for >6 months having LDH levels ≤1.5 times the upper limit of normal at screening were randomly assigned 1:1 to continue eculizumab or switch to ravulizumab



Abbreviations: BL, baseline; BTH, breakthrough hemolysis; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; HGB-S, hemoglobin stabilization; LDH, lactate dehydrogenase; LDH-PCHG, LDH percent change from baseline; TA, transfusion avoidance. LS least squares; NIM, non-inferiority margin; SEM,

Austin G. Kulasekararaj et al, ASH 2018

PNH: it might be