PAROXYSMAL NOCTURNAL HEMOGLOBINURIA:
AT THE CROSSROADS OF SOMATIC MUTATIONS, CLONAL EXPANSION AND IMMUNITY
Firenze, Grand Hotel Baglioni, 3-4 ottobre 2024

# Thrombosis: prevention and therapy in anticomplement era

*Anna Paola Iori*

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERO-UNIVERSITARIA
POLICLINICO UMBERTO I

SAPIENZA
UNIVERSITÀ DI ROMA

SESSION V: CONTROVERSIES IN PNH

# Disclosures: Anna Paola Iori

| Company | Speaker,s bureau | Advisory board |
|---|---|---|
| Alexion | ✓ | ✓ |
| Novartis | ✓ | ✓ |
| JAZZ | ✓ | ✗ |
| Roche | ✓ | ✓ |
| Sobi | ✓ | ✓ |

# PNH and Thrombosis

**Luzzato statement** *2011 BJH*

*"We can safely say that PNH is the most vicious acquired thrombophilic state known in medicine"*

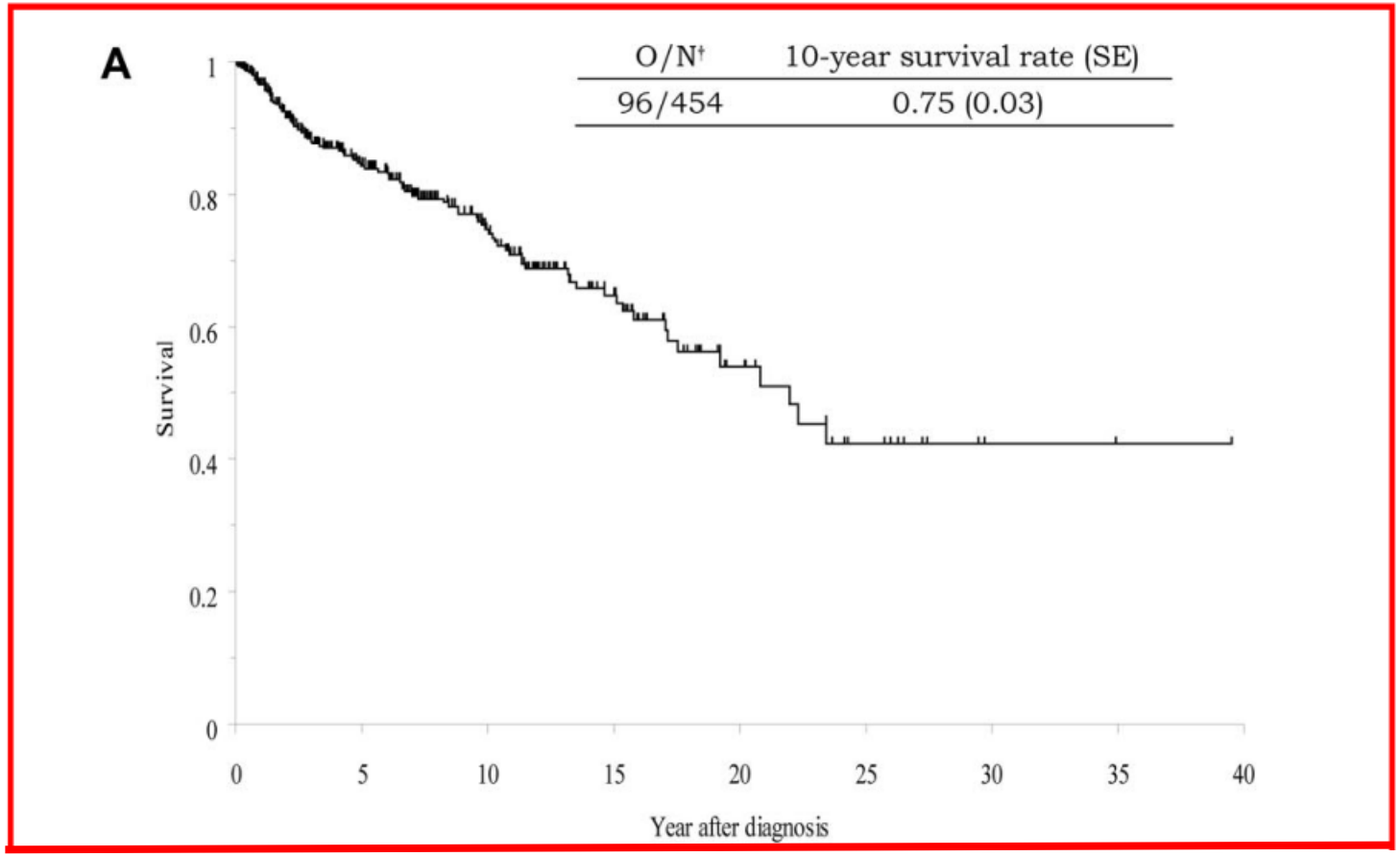
- The life-time **risk** of thrombosis in patients with PNH is of the **order of 50%**
- Thrombosis can be **life-threatening** causing mortality up to 67%
  *(with patients presenting such complication at disease onset having 4-yrs OS of only 40%. It tends to target abdominal veins or/and intracranial veins)*
- Thrombosis is highly **unpredictable**
  *(massive Budd-Chiari as the first episode unexpectedly developing in pts with transfusion-dependent PNH for 10 years)*
- Venous thrombosis can develop **even** in patients **properly anticoagulated.**

Hall et al, 2003; Araten et al, 2005; Peffault De Latour R, Blood 2008; Luzzatto L, BJH 201; Waheed A et al Blood Rev. 2024; Weitz IC, Semin Thromb Hemost. 2011; Weitz IC. Thromb Res. 2010; Griffin M et al. Ther Adv Hematol. 2017; Hill A et al. Blood 2013; Socié G et al. Lancet. 1996;

# Natural history of the disease

blood

*Peffault De Latour R, 2008*



# Issues about the anticoagulant therapy to PNH patients in pre complement inhibitors real life era

- Use primary prophylaxis for all PNH patients at the time of diagnosis without thrombosis?
- What AC molecules?
- How to manage pregnancies?

# Thromboprophylaxis strategies in pre- anticomplement era (A)

*Hall et al, 2003*
*recommendation: to start prophylactic anticoagulants automatically at the time PNH is diagnosed*

**Characteristics of PNH pts considered for primary warfarin phrophylaxis**

| **Granulocytes clone size larger than 50%** |
|---|
| Platelets count stable higher than 100 x $10^9$/L |
| No known controindication to anticoagulant |
| The possibility that thrombotic risk may change with time should be taken into consideration |

**Concerns:**

- INR monitoring is a considerable burden for pts
- the regimen entails the risk of haemorrhage

  *(2 episodes in the 39 pts in primary thromboprophylaxis)*
- an unwarranted risk for that one-half of pts who will never develop thrombosis

# Thromboprophylaxis strategies in pre- anticomplement era (B)

*Luzzatto et al. 2011: «Compromise policy»*

- ≥ 1 episode of thrombosis
- Thrombophilia

*(positive screening: F2 G20210A, ATIII, F5 R506Q, PS, PC, homocysteine level, antiphospholipid antibodies)*

## Drugs

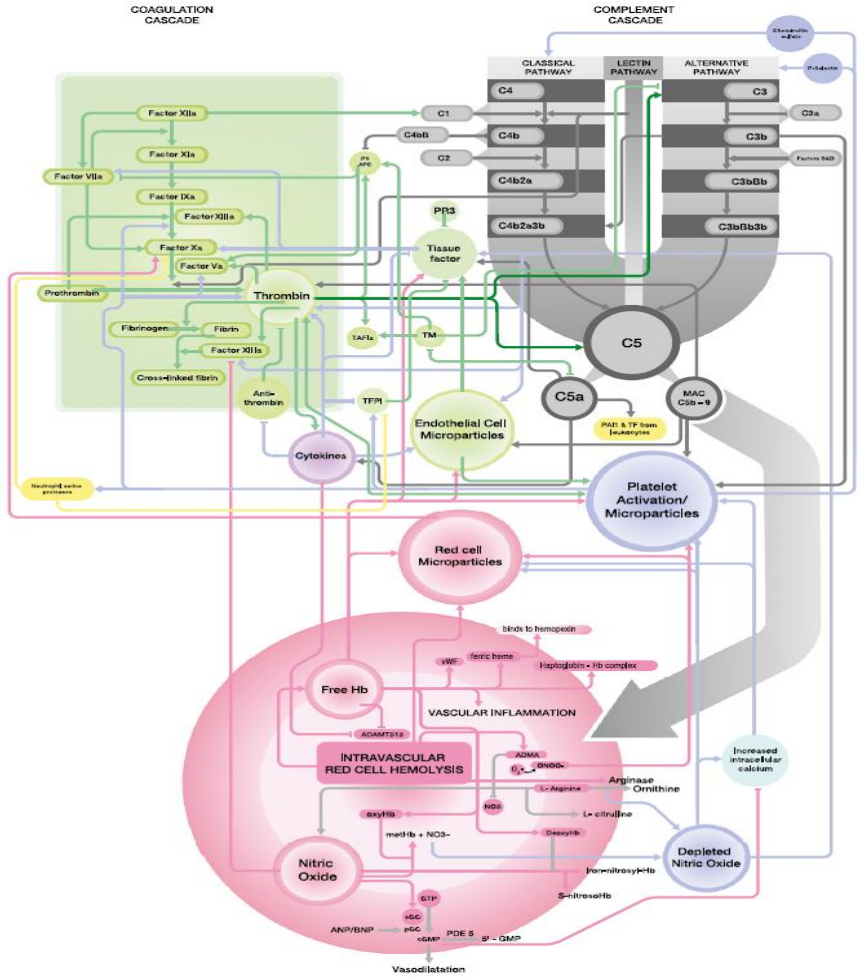
- Warfarin (INR 2.5-3)
- Avoid heparin due to increased incidence of HIT
- Fondaparinux has been successfully used
- There is no priori reason not to use NAO but no relevant experience
- Low molecular weight heparin throughout pregnancy and puerperium

# Relationships between RBC hemolysis, PLTS activation, EC, WBC and complement / coagulation cascades

**Multiple factors are likely to contribute to any one thrombotic event**

*"Complement mediated hemolysis is the major driver of thrombosis in PNH"*

*Anita Hill, Richard J. Kelly, and Peter Hillmen Blood 2013*



# Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria

blood

December 2007

Peter Hillmen,[1] Petra Muus,[2] Ulrich Dührsen,[3] Antonio M. Risitano,[4] Jörg Schubert,[5] Lucio Luzzatto,[6] Hubert Schrezenmeier,[7] Jeffrey Szer,[8] Robert A. Brodsky,[9] Anita Hill,[1] Gerard Socié,[10] Monica Bessler,[11] Scott A. Rollins,[12] Leonard Bell,[12] Russell P. Rother,[12] and Neal S. Young[13]

TE events during ECU treatment period compared with TE events during the same period of time before ECU treatment

| TE events | Pilot* | TRIUMPH | SHEPHERD | Extension† (all studies) |
|---|---|---|---|---|
| **Before treatment** | | | | |
| Patients, no. | 11 | 43 | 97 | 195 |
| Patient-years, no. | 33.0 | 21.8 | 93.6 | 272.1 |
| TE events | 5 | 0 | 21 | 39 |
| **Eculizumab treatment** | | | | |
| Patients, no. | 11 | 43 | 97 | 195 |
| Patient-years, no. | 34.2 | 21.8 | 96.9 | 281.0 |
| TE events | 0.00 | 0.00 | 2 | 3‡ |

*Includes a 1-year and a 2-year extension study.

†Includes TRIUMPH placebo-treated patients who transitioned to eculizumab treatment in the phase 3 extension study.

‡$P < .001$ for comparisons of eculizumab treatment versus before treatment,

TE events in pts receiving previous antithrombotics

| TE events | Pilot* | TRIUMPH | SHEPHERD | Extension† (all studies) |
|---|---|---|---|---|
| **Before treatment** | | | | |
| Patients, no. | 9 | 23 | 51 | 103 |
| TE events, no.‡ | 4 | 9 | 26 | 40 |
| Patient-years, no. | 45.3 | 70.6 | 168.2 | 377.1 |
| TE event rate, no. per 100 patient-years | 8.83 | 12.74 | 15.46 | 10.61 |
| **Eculizumab treatment** | | | | |
| Patients, no. | 9 | 23 | 51 | 103 |
| TE events, no. | 0 | 0 | 0 | 1 |
| Patient-years, no. | 28.8 | 11.9 | 51.0 | 161.9 |
| TE event rate, no. per 100 patient-years | 0.00 | 0.00 | 0.00 | 0.62§ |

*Includes a 1-year and a 2-year extension study.

†Includes TRIUMPH placebo-treated patients who transitioned to eculizumab

# Role of Complement Inhibitors on coagulation activity

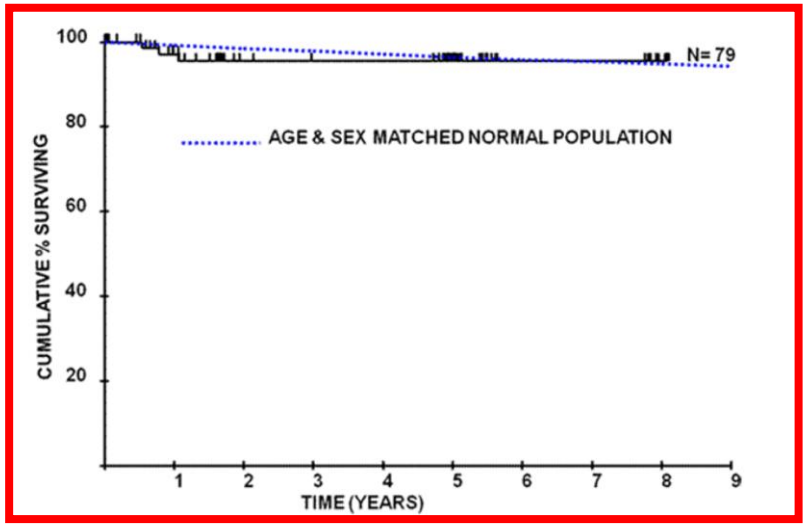
## Eculizumab treatment resulted in decrease of:

- Plasma tissue factor microparticles
- Thrombin generation
- Clote density
- Fibrinogen
- Inflammation
- Thrombin-antithrombin complexes *°as measured by D-dimers*
- Plasmin-antiplasmin complexes
- IL-6, and markers of endothelial cell activation (tissue-plasminogen activator, soluble VCAM, VWF, and TFPI)

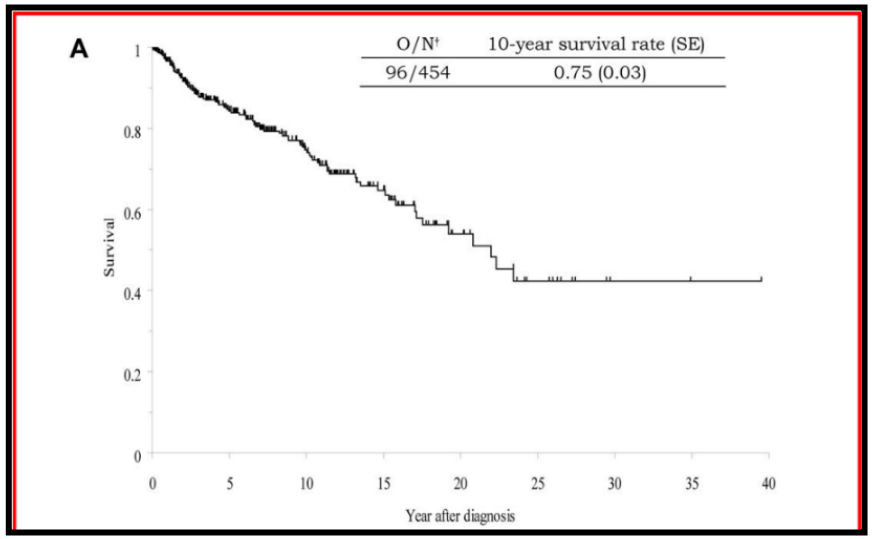
*Helley D, de Latour RP, Porcher R, et al. Haematologica. 2010;*
*Weitz IC, Razavi P, Rochanda L, et al. Thromb Res. 2012;*
*Macrae FL, Peacock-Young B, Bowman P et al. AM J Hematol 2020*

# Survival

The dramatic and lifesaving consequence of the introduction of effective therapy for PNH was a marked reduction in thrombosis risk




*American Journal of Hematology, Vol. 91, No. 4, April 2016*

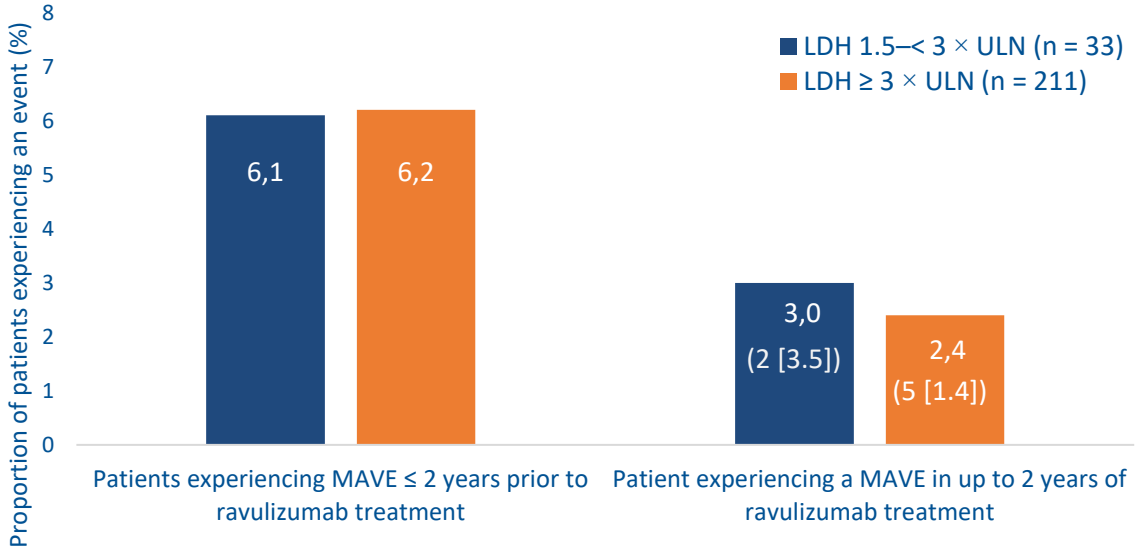



*Peffault De Latour R, Blood 2008*

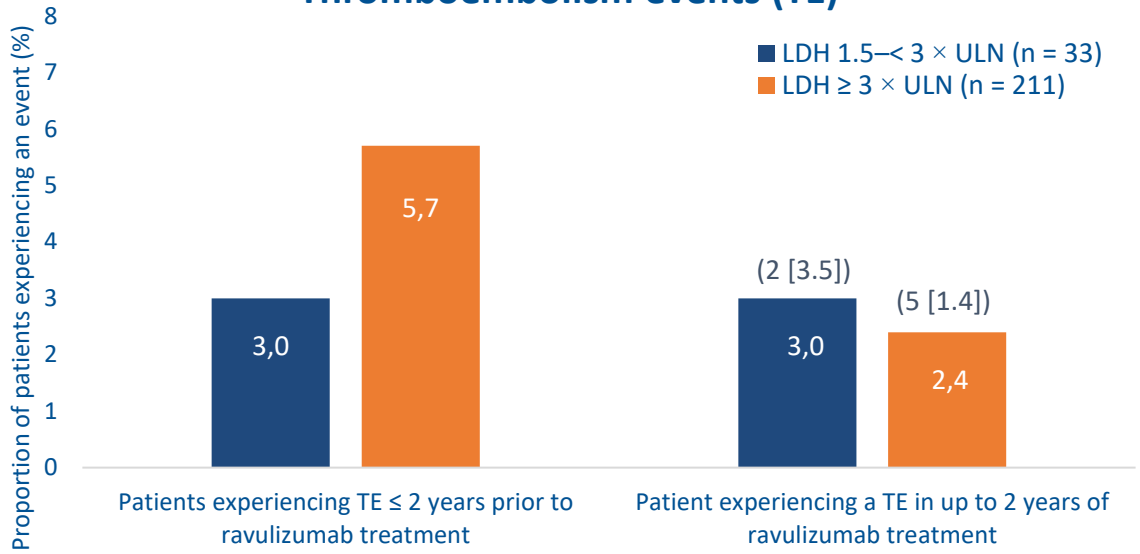
- 96% (76/79) OS
- No difference compared to health population (*P*=0.46)

# Treatment with ravulizumab resulted in fewer reported MAVEs and TEs compared with the 2 years prior to enrollment

## Major adverse vascular events (MAVE)




## Thromboembolism events (TE)




Data in parentheses: (E [rate])*

*E, events; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; TE, thromboembolism; ULN, upper limit of normal.*
**E = number of adverse events (event count) and rate is the event rate per 100 patient-years of exposure, defined as "number of events/100 patient-years"*

# Thrombosis rates in PNH patients treated with Novel Complement Inhibitors

## Pegetacopan

| Exposure and events of interest | PHAROAH[b] | PALOMINO[b] | PADDOCK[b] | PIONEER | PEGASUS[b] | PRINCE[b] | All clinical trials | Postmarketing setting[c] | Total |
|---|---|---|---|---|---|---|---|---|---|
| Cumulative exposure, patient-years | 20.3 | 15.8 | 65.0 | 3.5 | 188.3 | 116.4 | 409.4[d] | 210.0 | 619.4 |
| Thrombotic events, *n* | 1 | 0 | 0 | 0 | 4[e] | 0 | 5 | 2 | 7 |

307 Open-Label Extension Study: no TEs reported

**Thrombosis rates:**

**1.1** /100 patient-years in trials and real world

**1.2** /100 patient-years in trials;

**0.9** /100 patient-years in real world

## Iptacopan

| Endpoint | Adjusted annual rate, % (95% CI) |
|---|---|
| Rate of MAVEs* | 0 (0.00, 0.17) |

Phase III APPOINT-PNH trial

## Crovalimab

Phase I/II Composer trial: 44 pts 1 MAVE

Phase 3 randomized COMMODORE 2 trial: 135 pts crovalimab arm: 1 MAVE

## Danicopan

| | Danicopan plus ravulizumab or eculizumab (n=49) | | |
|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4–5 |
| Anaemia | 0 | 0 | 0 |
| Asthenia | 0 | 0 | 0 |
| Cholecystitis | 0 | 1 (2%) | 0 |
| Contusion | 1 (2%) | 0 | 0 |
| COVID-19 | 1 (2%) | 1 (2%) | 0 |
| Diarrhoea | 4 (8%) | 0 | 0 |
| Headache | 5 (10%) | 0 | 0 |
| Increased ALT concentrations | 0 | 2 (4%) | 0 |
| Increased AST concentrations | 1 (2%) | 1 (2%) | 0 |
| Increased blood pressure | 0 | 1 (2%) | 0 |
| Insomnia | 0 | 0 | 0 |
| Leukopenia* | 0 | 1 (2%) | 0 |
| Neutropenia* | 0 | 2 (4%) | 0 |
| Thrombocytopenia | 0 | 0 | 0 |

ALPHA study

*Novel drugs seem to be at least as protective as ECU… maybe even better*

*Kelly R. et al. Pract Thromb Haemost. 2024; Lee J The Lancet 2023; Risitano A ASH 2023 OP; Szer J Blood 2024; Patriquin GJ et al. Adv Ther (2024); Roth A. et al. Am J Hematol. 2024*

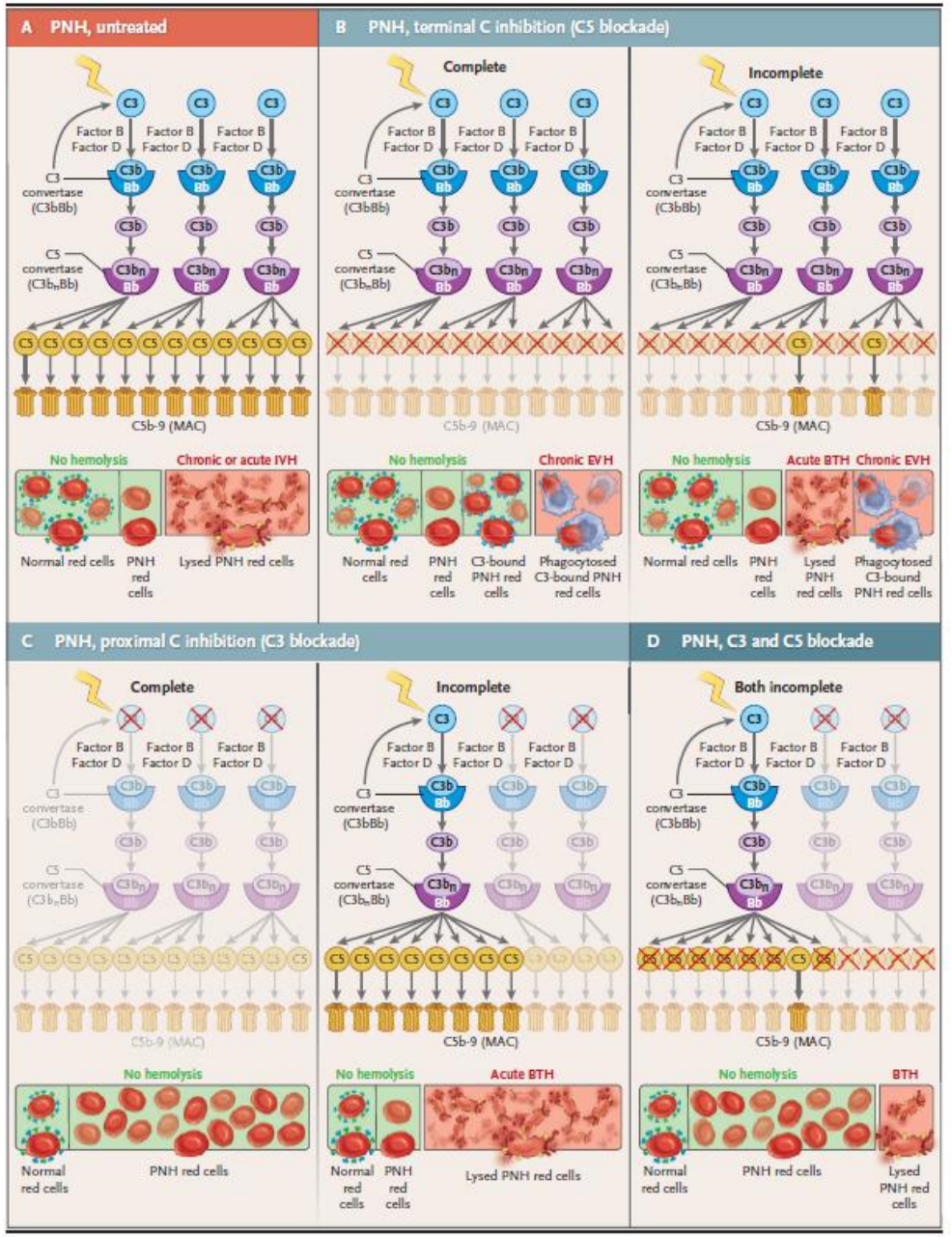
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Breakthrough Hemolysis in PNH with Proximal or Terminal Complement Inhibition

Rosario Notaro, M.D., and Lucio Luzzatto, M.D.



# Prevention and therapy of thrombosis in anticomplement era
# Open issues

- What is the role of primary and secondary prophylaxis of thrombosis with complement inhibitors?
- Does the "ideal" anticoagulant treatment exist?
- Is it possible to discontinue anticoagulation therapy in PNH-patients?
- What is the role of Direct Oral Anticoagulants (DOAC) in PNH-patients?
- What about BTH ?

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REVIEW

ISLH International Journal of Laboratory Hematology WILEY

# Complement inhibition in paroxysmal nocturnal hemoglobinuria: From biology to therapy

Francesco Versino[1,2] | Bruno Fattizzo[1,2] *Int J Lab Hematol. 2024*

## Primary antithrombotic prophylaxis advised:

- in untreated PNH patients with additional risk factors for thrombosis
- in pts  with an indication for anti-complement therapy who do not have access to the drugs
- while waiting to initiate therapy with complement inhibitors
- primary prophylaxis may be stopped once complement inhibitors have been initiated

## Secondary antithombotic prophylaxis :

- Full dose anticoagulants (LMWH and vitamin K antagonists) are to be used in patients presenting with thrombosis
- **Still  debated whether to withhold** them once complement inhibitor has been started or to continue them long term.
- **Debated the role of DOACs** in PNH since thrombosis under DOACs have been reported in this setting

(Brodsky RA 2021).

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- Does it exsist  the "ideal" anticoagulant treatment?
- Is it possible to discontinue anticoagulation therapy in PNH-patients?
- What  is the role of Direct Oral Anticoagulants (DOAC) in PNH-patients?
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# Successful discontinuation of anticoagulation following eculizumab administration in paroxysmal nocturnal hemoglobinuria

**American Journal of Hematology 2009**
*Emadi A, Brodsky RA.*

**TABLE I. Patients Characteristics**

| Patient | Age (years)/Gender | Duration of PNH (years) | PNH granulocyte (FLAER) | WBC × $10^6$ per liter | Hgb (g/dL) (most recent) | Platelets counts × $10^6$ per liter (most recent) | LDH (U/L) before eculizumab/ most recent | *d*-Dimer (mg/dL) before eculizumab/most recent | ECOG-PS (current) | Site of thrombosis | Duration on eculizumab (months) | Duration off anticoagulations (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 34/Male | 17 | 100% | 3790 | 10.4 | 154,000 | 430–2300/161 | 29/1.4 | Zero | Pulmonary emboli, portal vein, splenic vein (status postsplenic embolization), sagital vein, renal and hepatic failure status postliver transplant | 32 | 20 |
| 2 | 22/Female | 7 | 97% | 3420 | 10.7 | 159,000 | 3230/227 | Not available | Zero | CVA (right corona radiata punctate infarct) | 47 | 42 |
| 3 | 31/Male | 9 | 99% | 4120 | 14.9 | 107,000 | 1248/326 | 12.16/2.36 | Zero | Severe extensive dermal thromboses, subacute left cerebellum ischemia | 12 | 10 |

LDH, lactate dehydrogenase; ECOG-PS, Eastern Cooperative Group performance status.

All three patients are transfusion independent on ECU and have remained free of thrombosis from 10 to 42 months after stopping anticoagulation with Warfarin.

*Careful discussion with the patient concerning the potential risks and benefits of lifelong AC should occur*

blood How I Treat Series

2021

ACQUIRED HEMOLYTIC ANEMIA

# How I treat paroxysmal nocturnal hemoglobinuria

Robert A. Brodsky

Division of Hematology, Johns Hopkins Medicine, Baltimore, MD

Patient 1: 45-year-old woman with 3 weeks of intermittent, crampy, right upper quadrant abdominal pain.
Abdomen CT scan positive for hepatic and splenic vein thrombosis with extensive collaterals.
Following the standard ECU dyspnea and abdominal pain resolved
Warfarin was discontinued after 3 months of CI.

I usually overlap anticoagulation and CI for 3 to 6 months as long as there are no other provoking factors. I discontinue AC if thrombotic symptoms are resolved and the patient is well controlled (LDH ,1.53 the upper limit of normal) on a CI

*However, discussion with the patient is advised given the paucity of data concerning the risks vs benefit of this recommendation*

Published in final edited form as:
*Am J Hematol*. 2022 February 01; 97(2): E59–E62. doi:10.1002/ajh.26414.

# A 15-year, single institution experience of anticoagulation management in paroxysmal nocturnal hemoglobinuria patients on terminal complement inhibition with history of thromboembolism

**Gloria F. Gerber**[1], **Amy E. DeZern**[2], **Shruti Chaturvedi**[1], **Robert A. Brodsky**[1,2]

[1]Division of Hematology, Department of Medicine, Johns Hopkins University, Baltimore, MD

[2]Department of Oncology, Sidney Kimmel Cancer Center, Baltimore, MD

- *22 PNH patients evaluated at Johns Hopkins Hospital over a 15-year period from 2005–2020 with a history of TE, treated with C5 inhibition*
- *Anticoagulation included warfarin, DOACs and LWMH at the discretion of the treating physician*
- *The incidence of TE was calculated as TE events per patient-years*

| Group | C5 inhibitor monotherapy | | C5 inhibitor and indefinite anticoagulation (n=4) |
|---|---|---|---|
| | Anticoagulation discontinued after C5 inhibition† (n=12) | C5 inhibitor alone, intolerance to anticoagulation (n=6) | |
| **Before C5 Inhibitor** | | | |
| TE events, no. | 19 | 6 | 6 |
| Patient-years, no. | 69 | 27.5 | 15.5 |
| TE event rate, no. per 100 patient-years | 27.53 | 21.81 | 38.71 |
| **C5 Inhibitor Treatment** | | | |
| TE events, no. | 2‡ | 0 | 2§ |
| Patient-years, no. | 84.5 | 53.5 | 37 |
| TE event rate, no. per 100 patient-years | 2.36 | 0 | 5.41 |

Patients on C5 inhibitor monotherapy had 25.91 events/100 patient-years prior to C5 inhibition (25 events) versus 1.45 events/100 patient-years post-C5 inhibition and off anticoagulation (two events) (P <0.001)

In the four patients who were treated with a C5 inhibitor and indefinite anticoagulation, there were 38.71 events/100 patient-years prior to the C5 inhibitor (six events) and 5.41 events/100 patient-years after (two events) (P =0.01)

This study supports the idea that untreated PNH is a provoking factor for TE

Select patients may not require indefinite anticoagulation if well controlled on CI and there are no other persistent provoking risk factors for TE.

We recommend overlapping AC and CI for 3 to 6 months following the acute TE unless contraindicated due to bleeding risk and/or thrombocytopenia.

The potential additional benefit of continued anticoagulation in reducing thrombosis must be weighed against the risk of bleeding on an individual basis after an informed discussion with patients

# Paroxysmal nocturnal hemoglobinuria–related thrombosis in the era of novel therapies: a 2043-patient-year analysis

blood® 11 JULY 2024

Carmelo Gurnari,[1,2,*] Hussein Awada,[1,*] Simona Pagliuca,[1,3] Danai Dima,[1] Fauzia Ullah,[1] Naomi Kawashima,[1] Yasuo Kubota,[1] Ceylan Colak,[4] Valeria Visconte,[1] Bhumika J. Patel,[1] Vikram Dhillon,[5] Naimisha Marneni,[6] Suresh Kumar Balasubramanian,[5] Ashwin Kishtagari,[6] Taha Bat,[7] and Jaroslaw P. Maciejewski[1]

Accrual of patients with PNH from 4 US centers .
267 patients followed up for a total of 2043 patient years

- CI, either anti-C5 or the anti-C3, pegcetacoplan, according to on label indications
- TEs were managed according to the nature of the TE (arterial/venous) and anticoagulation included either warfarin, DOACs, or LMWH, as per physician's choice and institutional practices
- LMWH was preferred if platelet counts were consistently <100 × 109/L in cases with concomitant AA

| Variable | All PNH cases (N = 267) |
|---|---|
| Follow-up, median (IQR), y | 5.9 (2.1-11.7) |
| Age at diagnosis, median (IQR), y | 46 (27-61) |
| **Sex, n (%)** | |
| Male | 116 (43.4) |
| Female | 151 (56.6) |
| **Total PNH RBC clone, median (IQR)** | 5 (0.6-25.1) |
| Type II–dominant RBC clone, n (%) | 26 (22)* |
| Type III–dominant RBC clone, n (%) | 92 (78)* |
| Total PNH WBC clone, median (IQR) | 43.9 (1.3-81.9) |
| ***PIGA*, n (%)** | |
| Wild-type | 89 (33.6) |
| Mutated | 86 (32.2) |
| Unavailable | 92 (34.2) |
| Post-AA PNH, n (%) | 85 (45.2) |
| Spontaneous remission, n (%) | 4 (1.5) |
| Thrombosis, n (%) | 56 (21) |
| Time to thrombosis, median (IQR), mo | 8 (0-58) |

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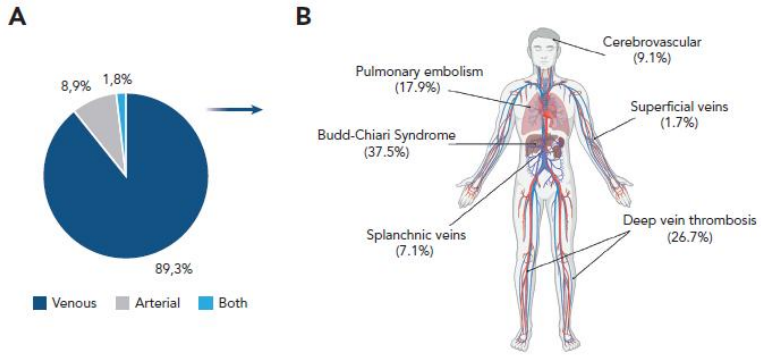
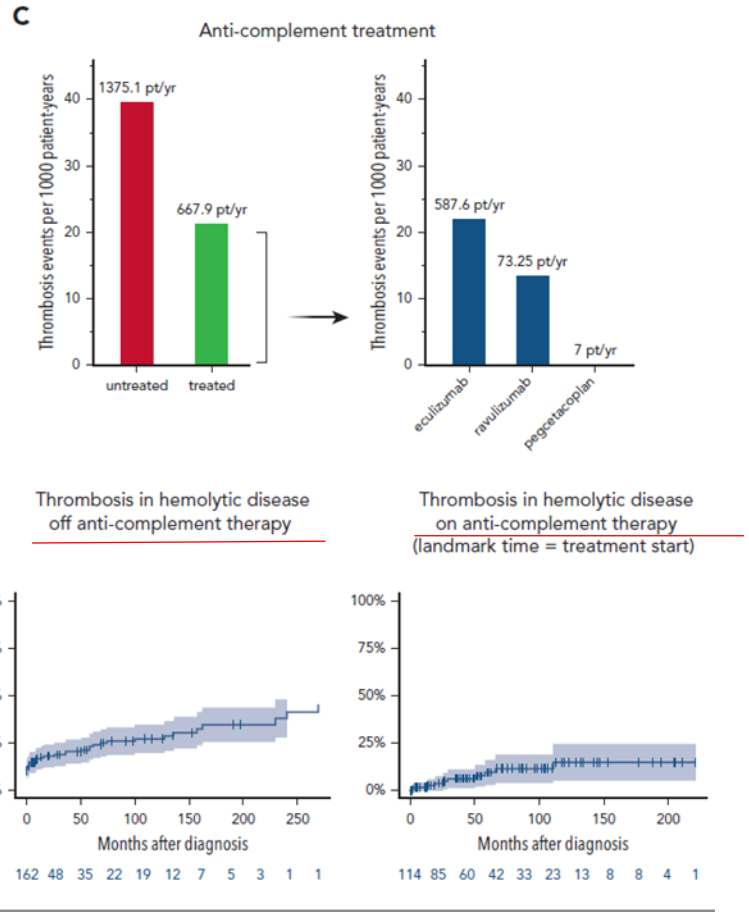



- 56 patients (21%) experienced TEs at a median of 8 months from diagnosis (0-56)
- At disease onset in 43% of cases, involving more frequently the venous system, typically as Budd-Chiari syndrome




- Patients experiencing TEs under CI were more likely poor responders (20% vs 8%).

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Pts with TEs of superficial veins (1.7%) started CI treatment

All other cases added anticoagulation:

Low-dose aspirin in all cases with arterial cerebrovascular events;
In the remaining cases, anticoagulation strategy with warfarin (21;45%), DOACs (19;41%), and LMWH (7; 14%)

## Results

Recurrence of TEs under AC:

- 1 case receiving enoxaparin (14%)
- 3 cases receiving warfarin (14%); 1with sub-therapeutic INR)
- **0 in all 19 patients treated with DOACs**

Bleedings on AC

- 5 pts on warfarin
- **2 pts on DOACs (acute rectal hemorrhage)**

- **14 Pts discontinuation of anticoagulation**
- No TE recurrence at a median time of 51.4 months (29.9-86.8)

*Conclusion:*
*discontinuation of AC therapy is possible and safe without TE recurrence if appropriate CI is prescribed.*
***Selective application of DOACs in the early phase of acute** TEs may not only lead to better TE control but also mitigate risks of prolonged anticoagulation.*

- Primary phrophylaxis if additional risks for thrombosis in meanwhile IC therapy

*Dragoni F, Iori AP, Pignoloni P et al. Br J Haematol 2010*

- Anticoagulant therapy in pts presenting with thrombosis according to Thrombosis Center (TAO Center)
  *Dragoni F, Chiarotti F, Iori AP et al al. Thrombosis Journal 2018*
- Low Molecular Weight Heparin in BTH with HDA

| **CI treatment on label** | **22** |
|---|---|
| CI treatment in clinical trials | 6 |
| **Total CI treatment** | **28** |
| AC treatment: | 8 |
| LMWH | On demand |
| Rivaroxaban (10 mg/die) | 6 |
| Apixaban (2,5 mg x 2/die) | 2 |

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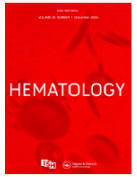


Hematology

HEMATOLOGY 2024

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/yhem20

A 13-member expert panel used a RAND/ UCLA modified Delphi panel to develop consensus on how to classify PD -BTH in CI treated PNH.

## Expert consensus on the management of pharmacodynamic breakthrough-hemolysis in treated paroxysmal nocturnal hemoglobinuria

David Dingli, Carlos De Castro III, Jamie Koprivnikar, Austin Kulasekararaj, Jaroslaw Maciejewski, Brian Mulherin, Jens Panse, Vinod Pullarkat, Alexander Röth, Jamile Shammo, Louis Terriou, Ilene Weitz, Irina Yermilov, Sarah Gibbs, Michael Broder, David Beenhouwer & David Kuter

*Hemolysis is a provoking factor for TE*

Definitions of characteristics included in rating forms
Expert consensus on severity classification of BTH events.
Expert consensus on complement inhibitor dosing.
Expert consensus on strategies to mitigate risk of BTH in special circumstances.

**Table 1.** Potential interventions to manage BTH included in rating forms.

| |
|---|
| Order laboratory tests* every 2–3 days |
| Order laboratory tests daily |
| Transfuse† |
| Treat with corticosteroids |
| Begin prophylactic anticoagulation until hemolysis resolves‡ (if the patient is not currently anticoagulated)° |
| Maintain current complement inhibitor dosing schedule and give no additional complement inhibitor |
| Shorten the dosing interval§ (i.e. give the same dose earlier or add additional dose) of the current complement inhibitor |
| Treat with a complement inhibitor with a different mechanism of action (add proximal inhibitor if on terminal inhibitor; add terminal inhibitor if on proximal inhibitor) |

°We assumed no thrombosis, a low D-dimer (e.g. < 0.50 mg/L), and no ongoing anticoagulation because the patient's PNH is well-controlled on a complement inhibitor.

Unfortunately, we did not reach consensus on whether to treat with corticosteroids or begin prophylactic anticoagulation. For patients already receiving anticoagulation, continue as clinically indicated. Additional data are needed to make a recommendation.

# Survey

Hospital ..... N° Pts .....

- Is primary AC prophylaxis performed in patients with PNH who are not receiving complement inhibitors or while waiting to start treatment, in the absence of a positive history for thrombosis? No/Yes
  If yes:
  In which patients?
  a) If thrombophilia
  b) In all patients before starting therapy with inhibitors
  c) Other
  If yes, which AC drugs are used?
  Do you discontinue primary prophylaxis after CI initiation?

- In your center, which AC drugs are used in secondary prophylaxis?
  Do you discontinue secondary AC prophylaxis in patients with PNH undergoing treatment with complement inhibitors? No/Yes

If yes, in which cases?
Which AC drugs are used?

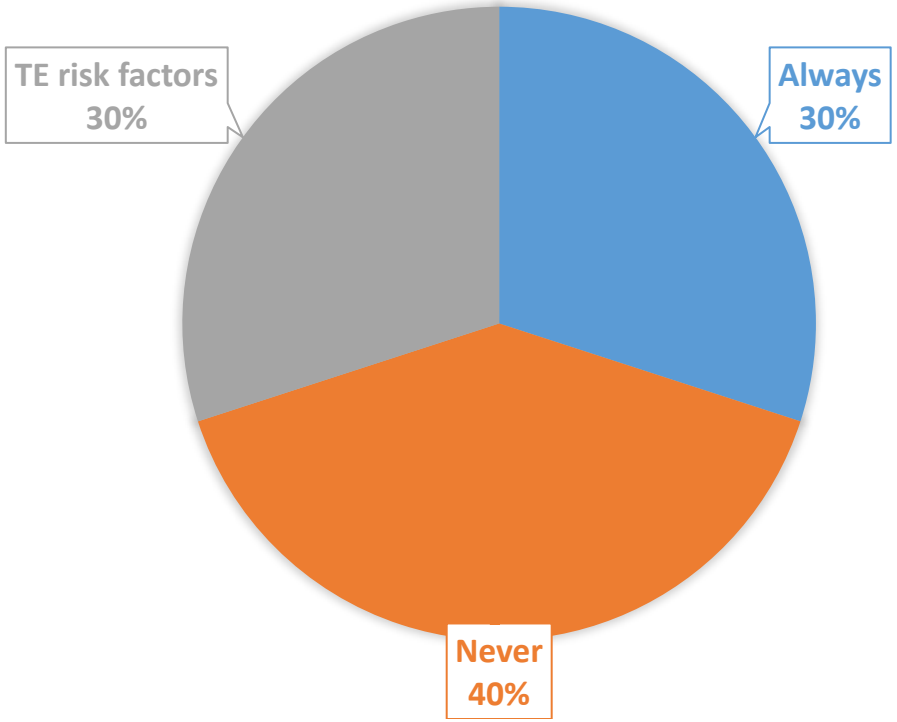
- In patients with BTH, do you administer AC as prophylaxis? No/Yes
  If yes, in which cases?
  If yes, which AC drugs are used?
  If yes, for how long?


# Survey

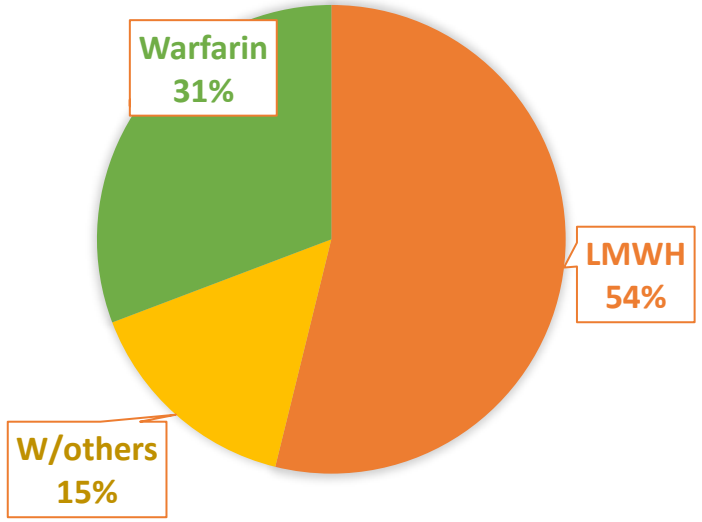
*20 PNH Centers*
*270 Patients*

# Primary Prophylaxis in PNH Pts Out off Complement inhibitors

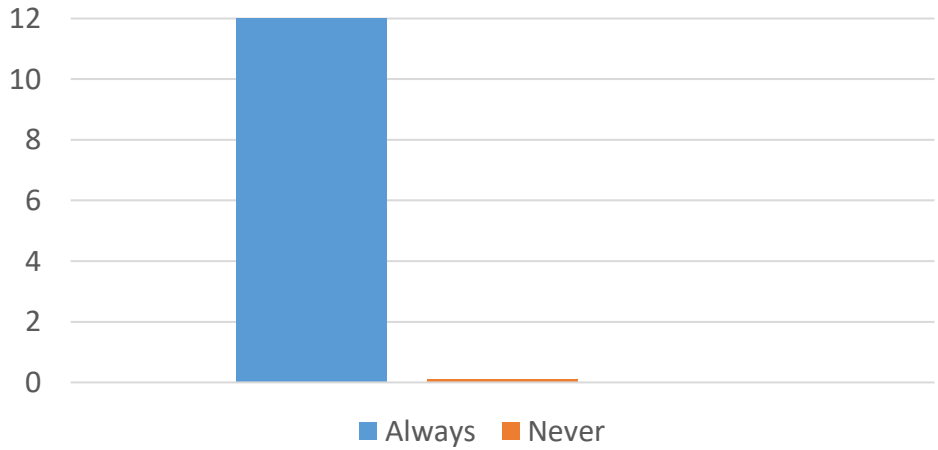
## CENTER POLICY




## AC DRUGS

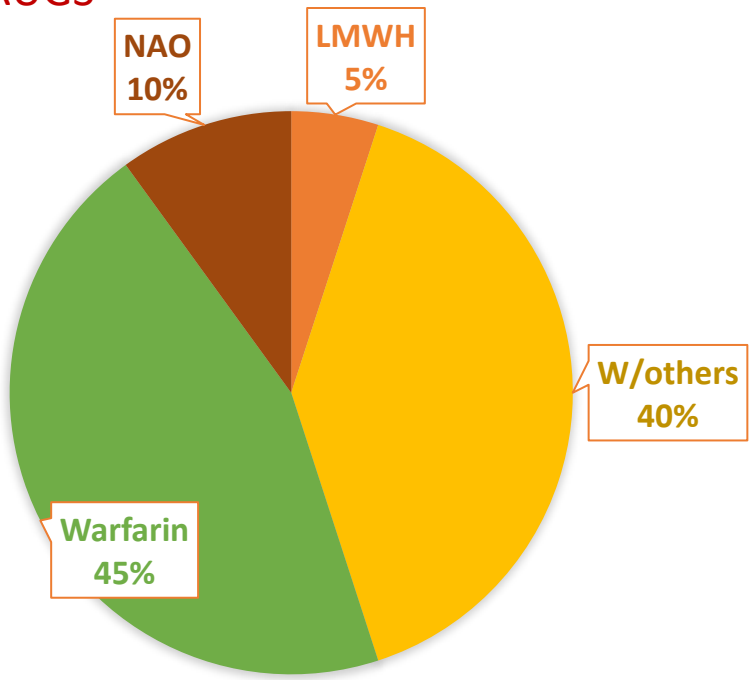



## DISCONTINUATION AFTER CI THERAPY

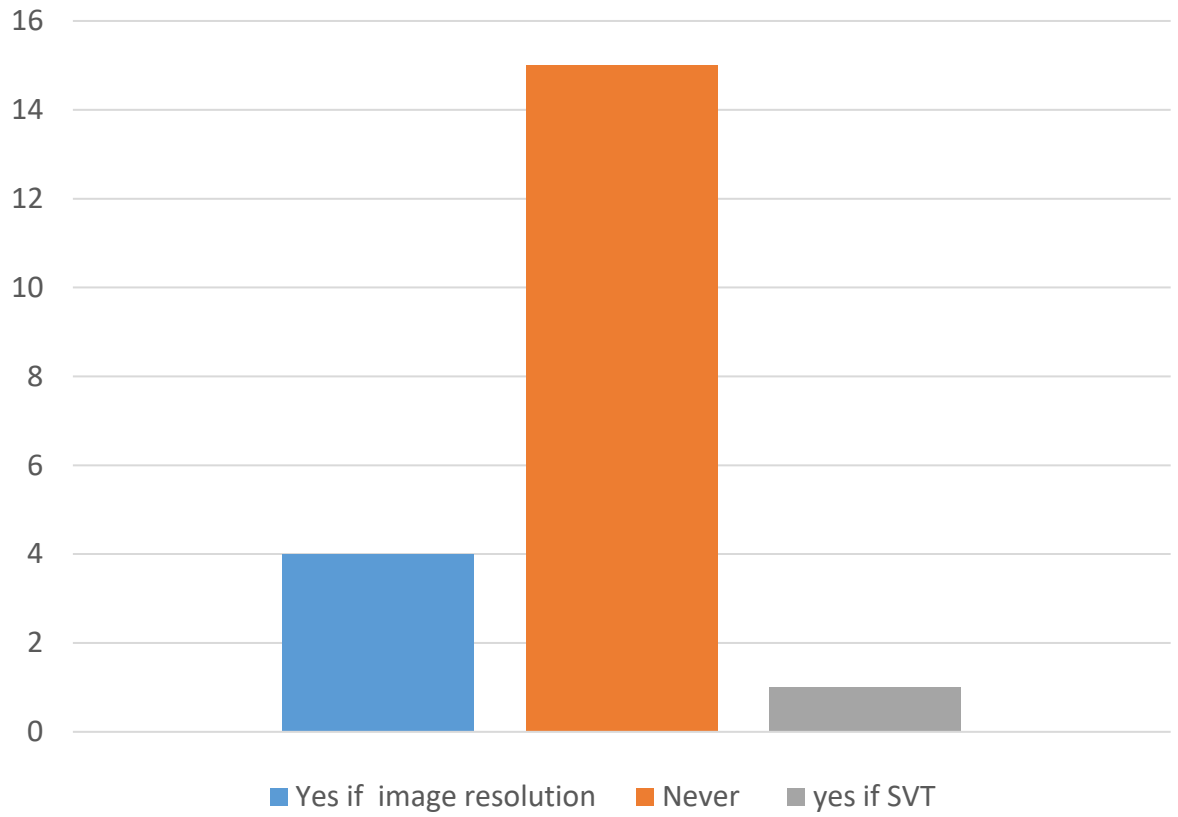


# Secondary Prophylaxis during CI therapy

DRUGS

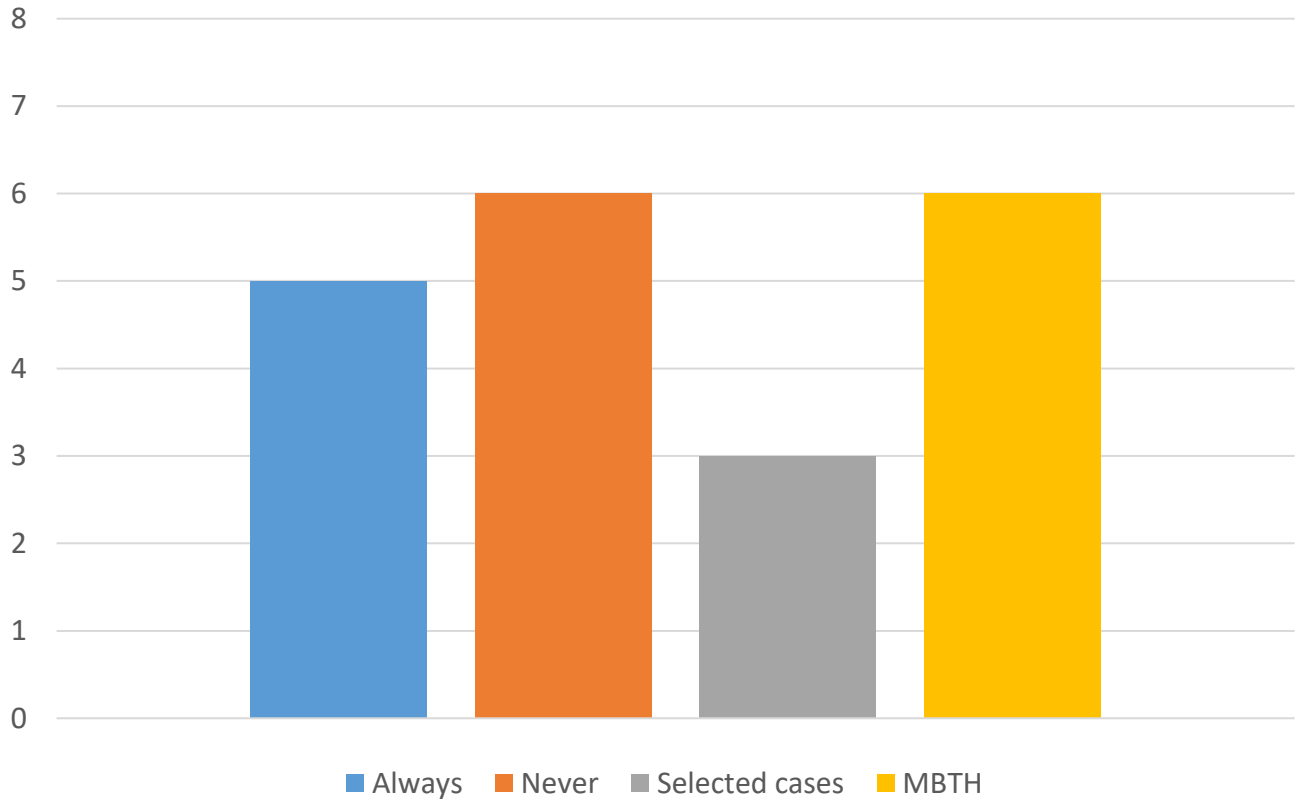



DISCONTINUATION

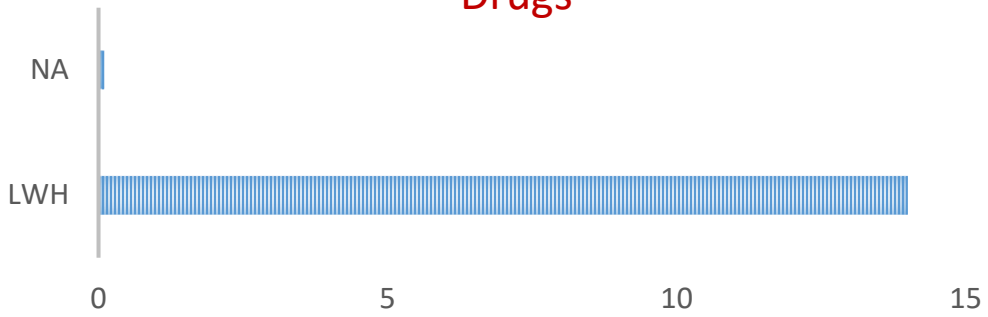


# BTH

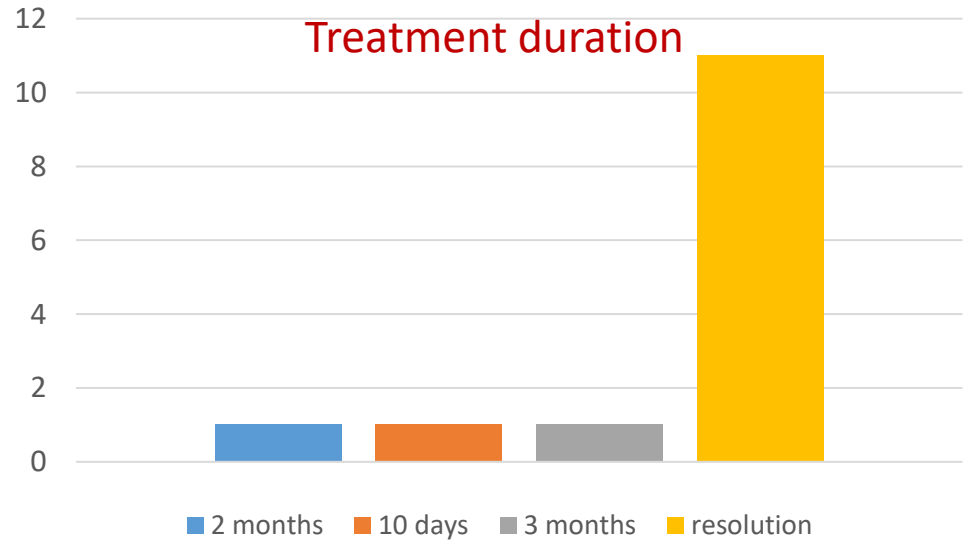
## Anticoagulants in BTH




## Drugs




## Treatment duration



# Considerations II

- A sort of consensus for primary prophylaxis: start and discontinuation
- No consensus for secondary prophylaxis discontinuation
- No consensus for DOACs
- A sort of consensus in BTH

# Considerations I

- What is the role of primary prophylaxis?
  - Primary prophylaxis while waiting to initiate therapy with complement inhibitors
  - in untreated PNH patients with additional risk factors for thrombosis/in pts with indication for CI who do not have access to the drugs
- Does the "ideal" anticoagulant treatment exist?
  - More used: LMWH/ Warfarin
- Is it possible to discontinue secondary prophylaxis of thrombosis in PNH-patients?
  - Initial evidences that discontinuation of AC therapy is possible and safe without TE recurrence if appropriate CI is prescribed.
- What is the role of Direct Oral Anticoagulants (DOAC) in PNH-patients?
  - Recent experiences (even if limited) reported
- BTH? Common use of LMWH during active hemolysis

# Paroxysmal nocturnal hemoglobinuria–related thrombosis in the era of novel therapies: a 2043-patient-year analysis

blood® 11 JULY 2024

Carmelo Gurnari,[1,2,*] Hussein Awada,[1,*] Simona Pagliuca,[1,3] Danai Dima,[1] Fauzia Ullah,[1] Naomi Kawashima,[1] Yasuo Kubota,[1] Ceylan Colak,[4] Valeria Visconte,[1] Bhumika J. Patel,[1] Vikram Dhillon,[5] Naimisha Marneni,[6] Suresh Kumar Balasubramanian,[5] Ashwin Kishtagari,[6] Taha Bat,[7] and Jaroslaw P. Maciejewski[1]

**Table 3. Univariate logistic regression analysis of predictors of thromboembolism in patients with PNH**

| Variable | OR | Low 95% CI | High 95% CI | *P* value |
|---|---|---|---|---|
| AST >40 U/L | 2.28 | 1.14 | 4.55 | **.0203** |
| ALT >40 U/L | 2.15 | 0.99 | 4.59 | .0543 |
| Age >40 y | 0.81 | 0.45 | 1.47 | .4853 |
| Albumin <4.2 g/dL | 3.14 | 1.58 | 6.33 | **.0011** |
| Creatinine >1 mg/dL | 1.2 | 0.54 | 2.53 | .6457 |
| D-dimers >1000 mg/L | 3.92 | 1.47 | 10.71 | **.0064** |
| Hb <10 g/dL | 0.83 | 0.44 | 1.59 | .5726 |
| Reticulocytes >80 × $10^3$/μL | 2.19 | 1.07 | 4.48 | **.0320** |
| ANC <1.5 × $10^9$/L | 0.42 | 0.21 | 0.82 | **.0110** |
| Platelets <100 × $10^9$/L | 0.43 | 0.22 | 0.85 | **.0152** |
| LDH >400 U/L | 3.49 | 1.73 | 7.40 | **.0004** |
| Type II–dominant RBC PNH | 3.65 | 1.46 | 9.23 | **.0057** |
| RBC clonal size >20% | 2.54 | 1.31 | 4.86 | **.0053** |
| Granulocytic clonal size >70% | 3.28 | 1.76 | 6.16 | **.0002** |
| *PIGA* VAF >15% | 3.36 | 1.16 | 9.72 | **.0254** |

**Table 4. Multivariate analysis of predictors of thromboembolism in patients with PNH**

| Variable | OR | Low 95% CI | High 95% CI | *P* value |
|---|---|---|---|---|
| AST >40 U/L | 0.73 | 0.25 | 2.02 | .5434 |
| ALT >40 U/L | 1.79 | 0.66 | 4.81 | .2472 |
| Albumin <4.2 g/dL | 0.49 | 0.21 | 1.11 | .0911 |
| D-dimers >1000 mg/L | 1.96 | 0.54 | 7.19 | .3026 |
| Reticulocytes >80 × $10^3$/μL | 1.05 | 0.39 | 2.76 | .9271 |
| ANC <1.5 × $10^9$/L | 0.82 | 0.32 | 2.13 | .6881 |
| Platelets <100 × $10^9$/L | 0.69 | 0.25 | 1.93 | .4859 |
| LDH >400 U/L | 2.84 | 1.01 | 8.30 | .0514 |
| Type II–dominant RBC PNH | 4.09 | 1.32 | 13.19 | **.0160** |
| RBC clonal size >20% | 0.70 | 0.22 | 2.16 | .5438 |
| Granulocyte clonal size >70% | 2.05 | 0.77 | 5.56 | .1536 |
| *PIGA* VAF >15% | 2.59 | 0.72 | 10.44 | .1600 |

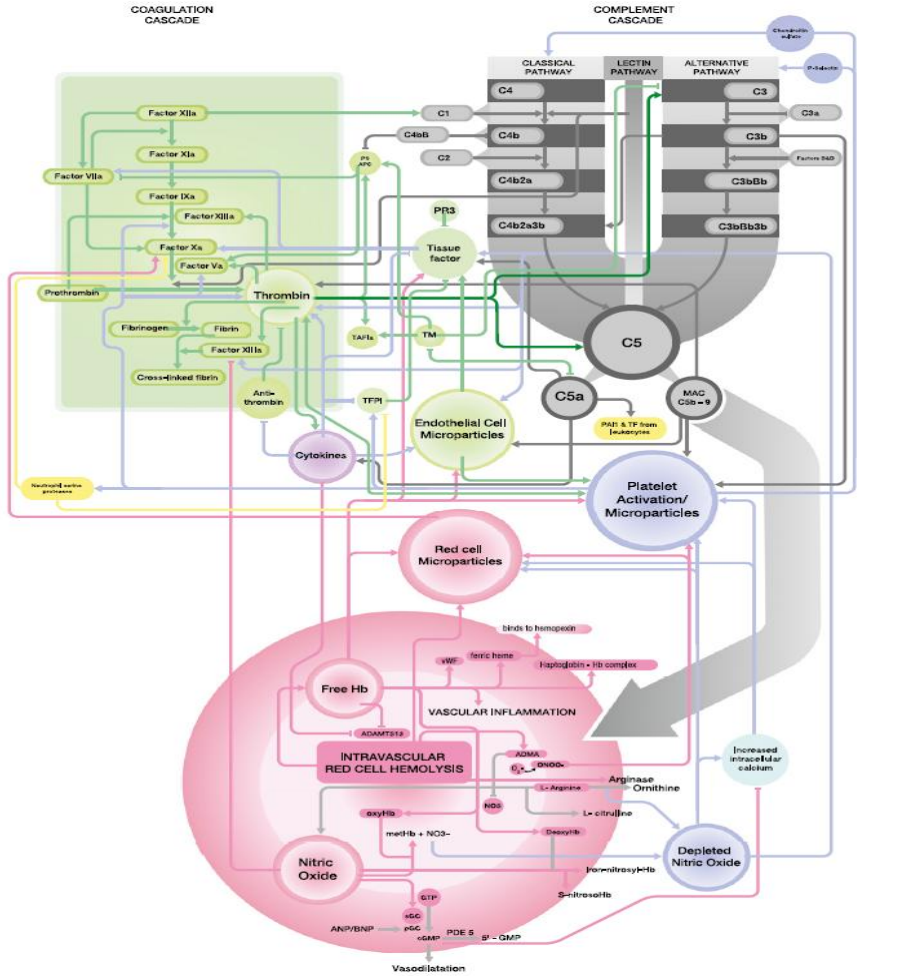
Perhaps, thanks to the recent expansion of the PNH therapeutic arsenal and the increased knowledge of DOACs use in a variety of clinical settings, we are getting close to taming this instance of “the most vicious acquired thrombophilic state known in medicine.”

# Relationships between RBC hemolysis, PLTS activation, EC, WBC and complement / coagulation cascades

Proposed mechanisms:

- Platelet activation
- Complement-mediated hemolysis *"complement is the major driver of thrombosis in PNH"*
- Impaired NO bioavailability
- Impairment of the fibrinolytic system
- Inflammatory mediators

**Multiple factors are likely to contribute to any one thrombotic event**




*Anita Hill, Richard J. Kelly, and Peter Hillmen Blood 2013*