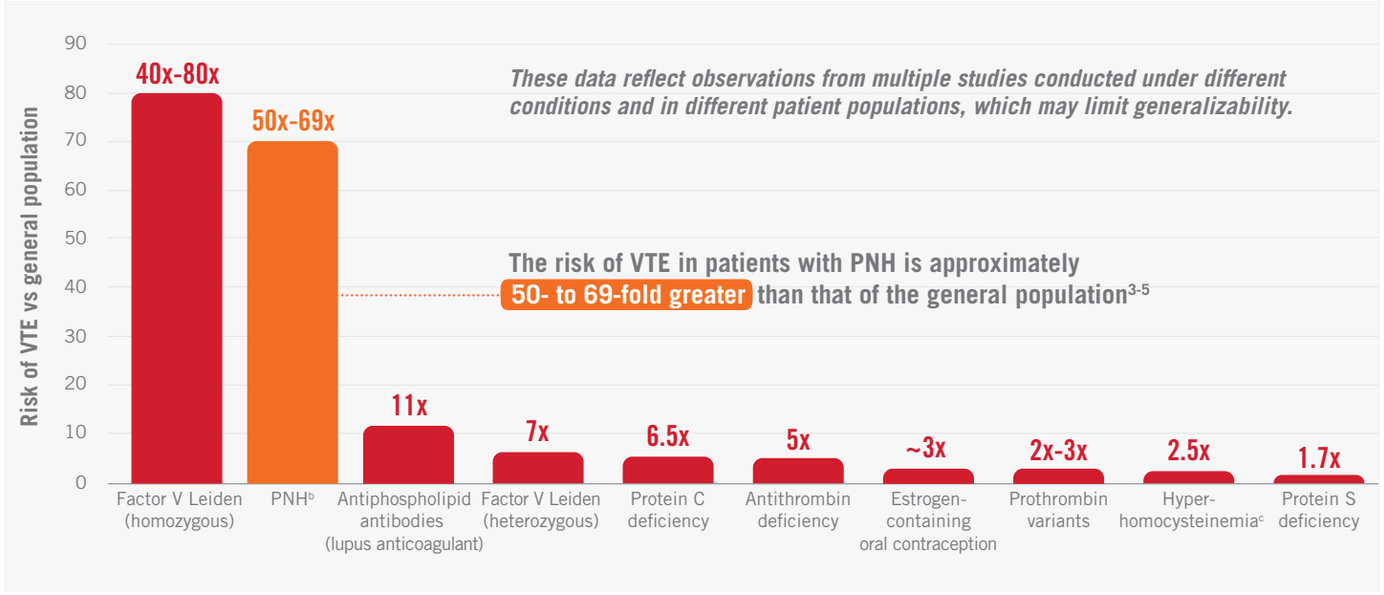
Paroxysmal Nocturnal Hemoglobinuria (PNH):

Risk of Thrombosis

Up to 35% of PNH patients die within 6 years despite historical supportive care.[1,2]

Approximated risk of developing venous thromboembolism in PNH and other inherited hypercoagulable conditions based on data from multiple studies[3-7,a]



Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of PNH-related deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease[8]

Intravascular hemolysis and clinical symptoms are associated with increased risk of thrombosis.[9]

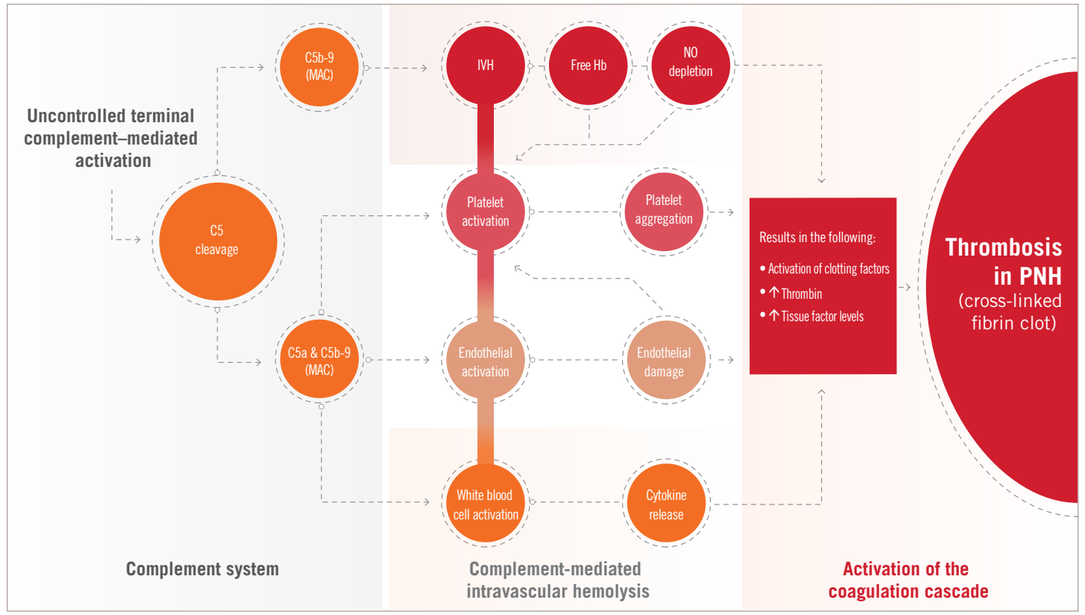
[a]Data for hypercoagulable conditions based on observations from case control studies (with exception of antiphospholipid antibodies [lupus anticoagulant] and estrogen-containing oral contraception).[5] [b]Venous thromboembolism event rate (no. per 1,000 patient-years) is based on 105 events in 1,683.4 patient-years occurring in patients from the pretreatment periods of 3 clinical studies and a phase 3 extension study.[3] Venous thromboembolism rate in the general population based on a retrospective study using linked administrative health care databases to identify a cohort of Québec residents (74,297,764 person-years) with an incident event of venous thromboembolism from January 1, 2000, to December 31, 2009. The incidence rate of definite venous thrombosis (n=67,354) in this study was 0.91 (95% CI, 0.90-0.91) per 1,000 patient-years and the rate of probable venous thrombosis (n=91,761) was 1.24 (95% CI, 1.23-1.24) per 1,000 patient-years.[4] [c]Levels above the 95th percentile of the normal values as an arbitrary cutoff for mild hyperhomocysteinemia.[5]

ALEXION®
AstraZeneca Rare Disease

Multiple terminal complement–mediated actions are implicated in the creation of a prothrombotic state in PNH[8,10,11]

All cell lineages are involved in terminal complement–mediated attack that independently leads to increased risk for thrombosis and combined lead to multifactorial prothrombotic events.[8,10,11]

Multifactorial prothrombotic mechanism in PNH[8]



Anticoagulation therapy does not address the underlying cause of terminal complement–mediated intravascular hemolysis and attack on platelets and white blood cells and the associated morbidities and early mortality in PNH[3,8,12]

- First thrombosis can be fatal.[13,a]
  - A nearly 14-fold higher mortality rate from thrombosis has been observed in patients with PNH compared with the general population.[13,b]
- After the first thrombotic event occurs, patients with PNH have a greater risk of recurrent thrombosis and a 5- to 10-fold increase in risk of mortality.[3,14,15,c,d]

[a]Data from a retrospective chart review of 301 patients with PNH, enrolled into the South Korean PNH registry, to assess the clinical signs and symptoms predictive of mortality using standard mortality ratio compared with an age- and sex-matched general South Korean population.[13] [b](SMR, 13.92 [95% CI, 8.23-19.61]; *P*<0.001).[13] [c]Retrospective data from a French cohort of 454 patients with PNH, diagnosed between 1950 and 1995, to evaluate long-term outcomes of PNH and to search for prognostic factors that affect survival.[15] [d]Retrospective data from 2 large cohorts of patients with PNH from Duke University (N=176) and Japanese institutions (N=209) to determine and directly compare the clinical course of disease in White and Asian populations.[14]

Abbreviations: CI=confidence interval; **FLAER**=fluorescent aerolysin; **Hb**=hemoglobin; **IVH**=intravascular hemolysis; **LDH**=lactate dehydrogenase; **MAC**=membrane attack complex; **NO**=nitric oxide; **OR**=odds ratio; **PNH**=paroxysmal nocturnal hemoglobinuria; **SMR**=standardized mortality ratio; **VTE**=venous thromboembolism.

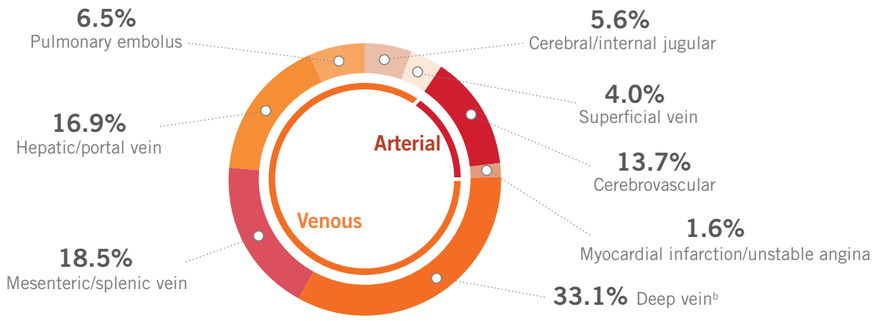
References

1. Kelly RJ, et al. *Blood.* 2011;117(25):6786-6792.
2. Loschi M, et al. *Am J Hematol.* 2016;91(4):366-370.
3. Hillmen P, et al. *Blood.* 2007;110(12):4123-4128.
4. Tagalakis V, et al. *Am J Med.* 2013;126(9):832.e13-832.e21.
5. De Stefano V, et al. *Haematologica.* 2002;87(10):1095-1108.
6. Wahl DG, et al. *Lupus.* 1998;7(1):15-22.
7. Vinogradova Y, et al. *BMJ.* 2015;350:h2135.
8. Hill A, et al. *Blood.* 2013;121(25):4985-4996.
9. Lee JW, et al. *Int J Hematol.* 2013;97(6):749-757.
10. Kelly R, et al. *Ther Clin Risk Manag.* 2009;5:911-921.
11. Rother RP, et al. *JAMA.* 2005;293(13):1653-1662.
12. Sharma VR. *Clin Adv Hematol Oncol.* 2013;11(9)(suppl 13):2-8.
13. Jang JH, et al. *J Korean Med Sci.* 2016;31(2):214-221.
14. Nishimura JI, et al. *Medicine (Baltimore).* 2004;83(3):193-207.
15. Socié G, et al. *Lancet.* 1996;348(9027):573-577.
16. Borowitz MJ, et al. *Cytometry B Clin Cytom.* 2010;78(4):211-230.
17. Richards SJ, Barnett D. *Clin Lab Med.* 2007;27(3):577-590, vii.
18. Sutherland DR, et al. *Cytometry B Clin Cytom.* 2018;94(1):23-48.
19. Parker C, et al. *Blood.* 2005;106(12):3699-3709.
20. Dezern AE, Borowitz MJ. *Cytometry B Clin Cytom.* 2018;94(1):16-22.
21. Brodsky RA. *Hematology: Basic Principles and Practice.* 7th ed. Elsevier; 2018:415-424.
22. Sahin F, et al. *Am J Blood Res.* 2016;6(2):19-27.
23. Hillmen P, et al. *Am J Hematol.* 2010;85(8):553-559.
24. Röth A, et al. *Eur J Haematol.* 2018;101(1):3-11.
25. Canadian PNH Network. Published 2021. Accessed December 6, 2021. https://www.pnhnetwork.ca/patient-screening
26. Schrezenmeier H, et al. *Haematologica.* 2014;99(5):922-929.
27. Morado M, et al. *Cytometry B Clin Cytom.* 2017;92(5):361-370.
28. Seidel MG. *Blood.* 2014;124(15):2337-2344.

Thrombosis in PNH can be life-threatening and can occur at any site[8]

- Multiple sites may be involved in more than one-fifth of cases.[8]

Sites of thrombosis in patients with PNH[3,a]



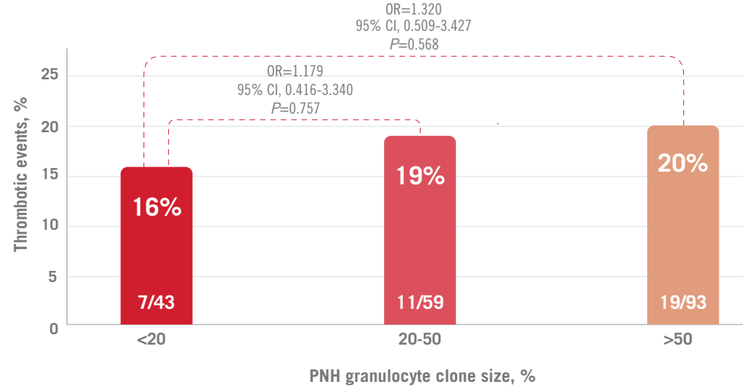
[a]Data pooled from examining the medical histories of patients with PNH (N=195) from 3 independent studies. Thrombotic events occurred in 63 patients: 1 event in 35 patients, 2 events in 15 patients, 3 events in 7 patients, and ≥5 events in 6 patients.[11] [b]Includes events in lower extremity (n=23) and other locations (n=18; including inferior vena cava, bilateral lower extremity, pelvic, ureter, axillary, subclavian, and brachiocephalic veins).[3]

- Venous thromboembolism is approximately 50x to 69x more likely in patients with PNH vs the general population.[3-5]

Patients with PNH are at risk of thrombosis regardless of clone size and bone marrow failure[9]

- Thrombosis leads to severe morbidity and is the most common cause of premature mortality in PNH.[8,9]
- Clone size is the percentage (number) of blood cells that are affected by PNH. The percentage of cells that do not have GPI-anchored complement regulatory proteins is referred to as PNH clone size.[16]
- Even PNH clone sizes <20% are associated with a risk of thrombosis.[9]

Incidence of thrombosis in PNH granulocyte clone size categories[9,a]



- In a retrospective study, the incidence of thromboembolic events in patients with PNH was ~18% (54/301).[9]
  - Thrombotic events reported in 37 patients were stratified by clone size; they occurred in 16% of the patients with a clone size of <20%, in 19% of the patients with a clone size of 20% to 50%, and in 20% of the patients with a clone size >50%.
  - The risk of experiencing thrombosis was not related to clone size (*P*=0.843).

[a]A retrospective analysis of medical charts of 301 patients with PNH in a South Korean registry to describe the burden of disease, the clinical characteristics of thrombosis, and the risk factors associated with thrombosis in PNH; N=number of PNH granulocyte clones.[9]

Rapid recognition of the signs and symptoms of PNH and early diagnosis are important to patient management[16,17]

The International Clinical Cytometry Society and International PNH Interest Group recommend testing high-risk patients.[17-19]

Patients who meet the criteria within any of the high-risk groups for PNH should be tested for PNH with high-sensitivity flow cytometry with FLAER on peripheral blood, the standard diagnostic test for PNH.[16,19-21]

Core signs and symptoms of PNH (any of the following)[16,19-24]

Symptoms of anemia
(eg, fatigue, tachycardia, shortness of breath, headache)

- **Thrombosis**
- **Dark-colored urine**
- **Intermittent abdominal pain**
- **Esophageal spasms**
- **Dysphagia**

in association with 1 of the following or if the patient exhibits 1 of the following (in the absence of an above symptom)

High-risk groups associated with PNH[16,19,22-25]

Bone marrow dysfunction

Unprovoked[a] and unexplained thrombosis

Hemolysis
Any of: ↑ LDH ↓ haptoglobin ↑ reticulocyte count ↑ bilirubin

C A T C H

- **Unexplained cytopenia[b]**
  - With any of the following:
    - Any subtype[c] with evidence of hemolysis
    - Refractory iron deficiency anemia
    - Nonresponsive to therapy
    - Thrombosis
- **Aplastic anemia**
- **Myelodysplastic syndrome**
  - With any of the following:
    - Any subtype with evidence of hemolysis
    - Hypoplastic
    - Refractory cytopenia
- **Thrombosis venous or arterial**
  - With any of the following:
    - Evidence of hemolysis
    - Usual and unusual sites[d]
    - Any cytopenia
    - Nonresponsive to anticoagulant
- **Coombs-negative hemolytic anemia**
- **Hemoglobinuria or hemosiderinuria**

With or without signs of: Renal dysfunction

Test for PNH with high-sensitivity flow cytometry with FLAER on peripheral blood, the gold-standard diagnostic test for PNH[16,20,24,e]

This algorithm is intended as educational information for healthcare providers. It does not replace a healthcare provider's professional judgment or clinical diagnosis.

The risk of thrombosis in PNH is based on terminal complement–mediated attack that leads to the multifactorial prothrombotic risk in PNH[12,19]

Although clone size is not related to thrombosis, LDH is an indicator of disease activity, including thrombosis, organ damage, and early mortality in PNH[9,12,13,26]

International Clinical Cytometry Society Guidelines recommend testing patients with unexplained or unprovoked thrombosis for PNH[16,27]

[a]Deep vein thrombosis and/or pulmonary embolism in a patient with no antecedent major clinical risk factor for venous thromboembolism that is not provoked by surgery, trauma, immobilization, hormonal therapy (oral contraceptive or hormone replacement therapy), or active cancer.[24] [b]Unexplained persistent cytopenia in a patient in whom (minimal) diagnostic criteria for myelodysplastic syndrome are not fulfilled.[24] [c]Anemia, neutropenia, or thrombocytopenia.[28] [d]Unusual sites include hepatic veins (Budd-Chiari syndrome), other intra-abdominal veins (portal, splenic, splanchnic), cerebral sinuses, and dermal veins.[24] [e]Detects PNH cells down to a 0.01% clone size.[16]