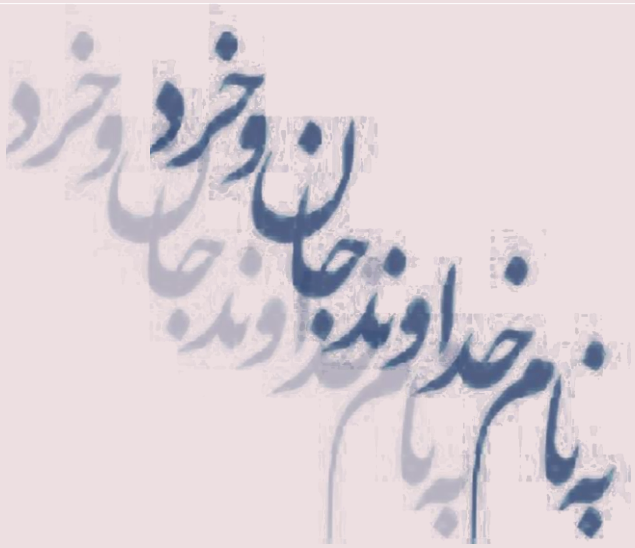

Management of Thrombosis in Elderly Persons with Hemophilia

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Starting in the early 1970s, hemophilia, previously a **life-threatening** condition, became a gratifying example of successful secondary prevention of a chronic disease

Devastating impact of infections with HIV & HCV in the last 2 decades of the 20th century

Safe and effective treatment is available for PWHs, whose life expectancy approaches that of the general population

increasing number of elderly PWH developing comorbidities typical for aging, such as **CAD, AF, IS, VTE**

J Thromb Haemost. 2020 Dec 18;19(3):645–653. doi: 10.1111/jth.15182

Mortality, life expectancy, and causes of death of persons with hemophilia in the Netherlands 2001–2018

Shermarke Hassan [1], Rory C Monahan [1], Evelien P Mauser-Bunschoten [2], Lize F D van Vulpen [2], Jeroen Eikenboom [3], Erik A M Beckers [4], Louise Hooimeijer [5], Paula F Ypma [6], Laurens Nieuwenhuizen [7], Michiel Coppens [8], Saskia E M Schols [9], Frank W G Leebeek [10], Cees Smit [1], Mariëtte H Driessens [11], Saskia le Cessie [1], Erna C van Balen [1], Frits R Rosendaal [1], Johanna G van der Bom [1,12], Samantha C Gouw [1,13]✉

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For decades, hemophilia has been considered a condition protecting against thromboembolism …

Aging PWH are exposed to:
obesity, smoking, hyperlipidemia, metabolic syndrome, and arterial hypertension

PWH are also susceptible to VTE

Hemophilia does **not eliminate** the risk of TE

J Comp Eff Res. 2021 Dec;10(18):1323-1336. doi: 10.2217/cer-2021-0120. Epub 2021 Oct 22.

Estimating the risk of thrombotic events in people with congenital hemophilia A using US claims data

Imi Faghmous [1 2], Francis Nissen [1], Peter Kuebler [3], Carlos Flores [4], Anisha M Patel [5], Steven W Pipe [6]

Affiliations + expand

PMID: 34676773 DOI: 10.2217/cer-2021-0120

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Are people with hemophilia naturally anticoagulated?

TABLE 1 Endogenous thrombin potential in people with hemophilia A, patients on vitamin K antagonists and healthy controls

Population factor levels, IU/dl	Median ETP, nM/min, IQR/% of normal	Percentage of individuals with ETP <400 nM/min
PWHA FVIII <1	185 (116–307/20.6)	93
PWHA FVIII 1–9	278 (210–408/31)	74
PWHA FVIII 10–19	338 (197–541/37.6)	63
PWHA FVIII 20–50	397 (219–632/44.2)	52
Patients on VKA with INR >2	156 (90–225/17)	100
Patients on VKA with INR 1.5–1.9	340 (238–429/37.9)	63
Healthy controls	898 (803–1104/100)	0

Abbreviations: ETP, endogenous thrombin potential; F, factor; INR, international normalized ratio; IQR, interquartile range; PWHA, people with hemophilia A; VKA, vitamin K antagonist

In general, untreated people with severe hemophilia have deep hypocoagulability, and therefore antithrombotic drugs, as well as other drugs compromising hemostasis, should be avoided

What is the impact of antithrombotic agents on the risk of bleeding complications in people with hemophilia?

prospective case-control COCHE study:

several factors that increased the risk of bleeding in PWH

- baseline level of FVIII or FIX below 20 IU/dl
- antihemorrhagic regimen (episodic vs prophylaxis)
- type of antithrombotic therapy
- HAS-BLED score equal to or above 3

An important finding of the COCHE study:
antithrombotic therapy (particularly on antiplatelet agents) had significantly increased risk of GI bleeding

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COCHE study indicate:

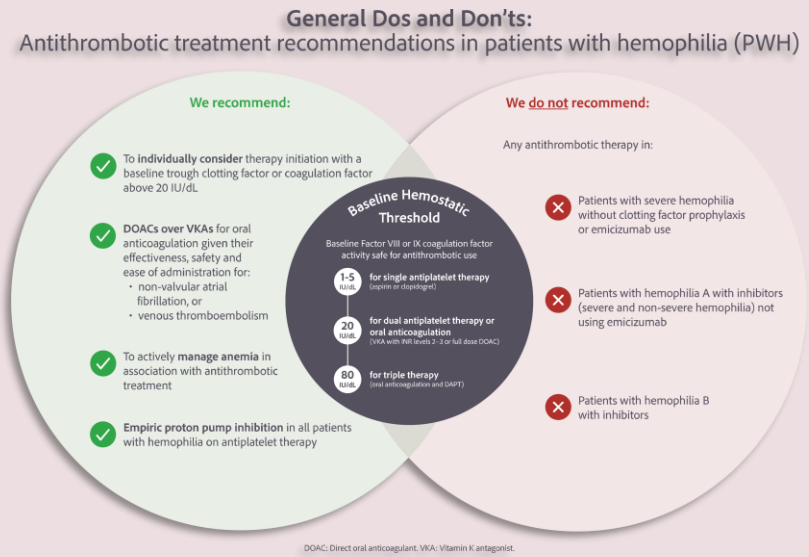
Antithrombotic therapy should be avoided in people with severe or moderate hemophilia, not receiving antihemorrhagic prophylaxis

If indications for antithrombotic therapy are very strong, commencement of antithrombotic treatment should be combined with regular anti - hemorrhagic prophylaxis

In PWH with plasma activity of FVIII or FIX permanently equal to or above 20 IU/dl, the use of antithrombotic therapy is most likely safer

Before starting antithrombotic therapy, contraindications to this treatment should be evaluated

What are the safety concerns of antithrombotic therapy in people with hemophilia on factor replacement or on emicizumab?



- Treatment of COVID-19:
  - Above 30 IU/dl — Prophylactic doses of LMWH
  - 50–100 IU/dl — Therapeutic doses of LMWH

- No sufficient data to draw firm conclusions on the safety of DAPT or OACs in PWHA receiving solely emicizumab for long-term

- Antihemorrhagic prophylaxis coagulation potential of PWHA on emicizumab seems sufficient to safely use SAPT

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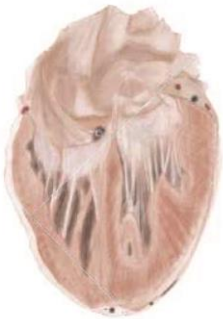
Should one prefer specific antithrombotic drugs and antithrombotic regimens in people with hemophilia?

- **DOACs** are the first choice
- we recommend using UFH or bivalirudin over enoxaparin given their shorter half-lives (PCI).
- SAPT (low-dose aspirin or clopidogrel) is acceptable
- clopidogrel is a preferred P2Y12 inhibitor

How to manage nonvalvular atrial fibrillation?

In PWH undergoing a **cardiac intervention**
FVIII or FIX:

100 IU/dl	usually 48h	UFH + DAPT
20–30 IU/dl	4 weeks	DAPT
1–5 IU/dl	2months	SAPT



Atrial Fibrillation

CHADS2 score: An appropriate framework to evaluate the risk of thrombosis in PWH.

Direct Oral Anticoagulants (DOACs) are to be preferred over VKAs.

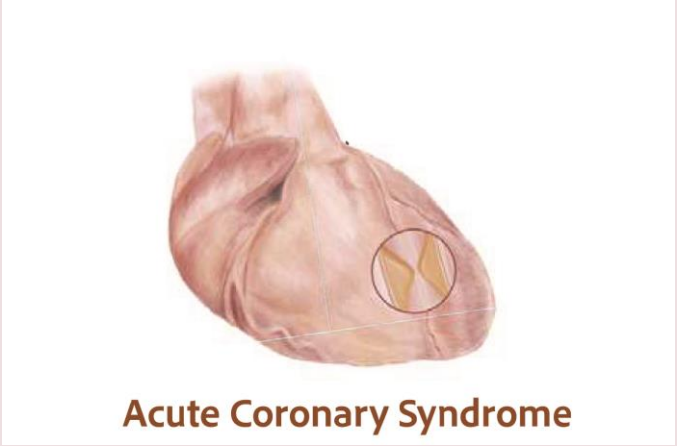
Left atrial appendage occlusion (LAAO): An alternative treatment that may avoid the long-term anticoagulation in PWH.

Heart Valves

We recommend the use of **bioprosthetic over mechanical valves** to evade the need for long-term anticoagulation.

How to manage Coronary syndromes?

As long as therapeutic doses of anticoagulants are used (usually for 24–48 h in patients undergoing PCI), PWH should receive replacement therapy to maintain plasma levels of FVIII/FIX at 50–100 IU/dl



PCI:

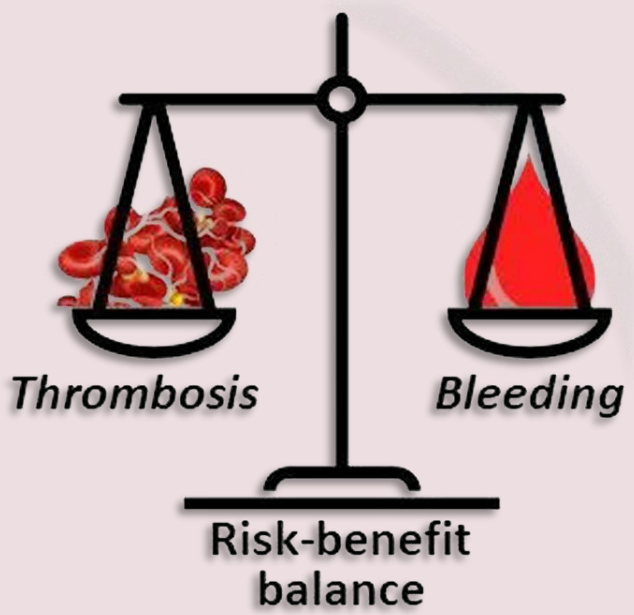
80–100 IU/dL	before PCI
50_100 IU/dL	24–48 h
>20 IU/dL	4wk (during DAPT)
>1–5 IU/dL	SAPT

In case of a **coronary angiography**, where no antithrombotic therapy is given and no intervention is performed, a shorter duration of clotting factor supplementation is feasible (12–24h)

Radial artery access route is recommended for Cardiac interventions in PWH

How should people with hemophilia at a risk of or with atrial or venous thromboembolism be managed to minimize the risk of bleeding?

we believe that antithrombotic agents should be reserved for PWH with strong indications for this type of therapy. By the same token, if **alternative treatment strategies**, carrying a lower risk of bleeding complications are available, one should consider their use in PWH, for example, left atrial appendage occlusion (LAAO) in AF



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ISTH GUIDEANCE AND GUIDELINES

Use of antithrombotic therapy in patients with hemophilia: a selected synopsis of the European Hematology Association - International Society on Thrombosis and Haemostasis - European Association for Hemophilia and Allied Disorders - European Stroke Organization Clinical Practice Guidance document

Miguel Escobar[1] | Riitta Lassila[2] | Carine Bekdache[3] | Tarek Owaidah[4] | Michelle Sholzberg[5]

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Guideline Article - Expert opinion

Open Access

Antithrombotic Treatment in Patients With Hemophilia: an EHA-ISTH-EAHAD-ESO Clinical Practice Guidance

Roger E.G. Schutgens[1], Victor Jimenez-Yuste[2], Miguel Escobar[3], Anna Falanga[4,5], Bruna Gigante[6,7], Robert Klamroth[8,9], Riitta Lassila[10], Frank W.G. Leebeek[11], Michael Makris[12], Tarek Owaidah[13], Michelle Sholzberg[14], Andreas Tiede[15], David J. Werring[16], H. Bart van der Worp[17], Jerzy Windyga[18], Giancarlo Castaman[19]

blood

How I treat age-related morbidities in elderly persons with hemophilia

Pier M. Mannucci, Roger E. G. Schutgens, Elena Santagostino, Evelien P. Mauser-Bunschoten

REVIEW ARTICLES

Antithrombotic therapy in patients with inherited bleeding disorders: practical considerations

Jerzy Windyga[1], Riitta Lassila[2]

DOI: 10.20452/pamw.16993

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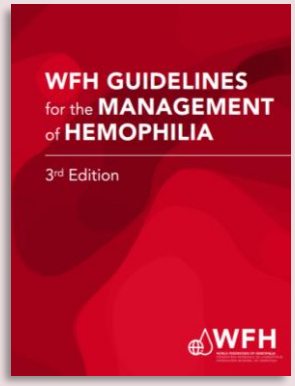

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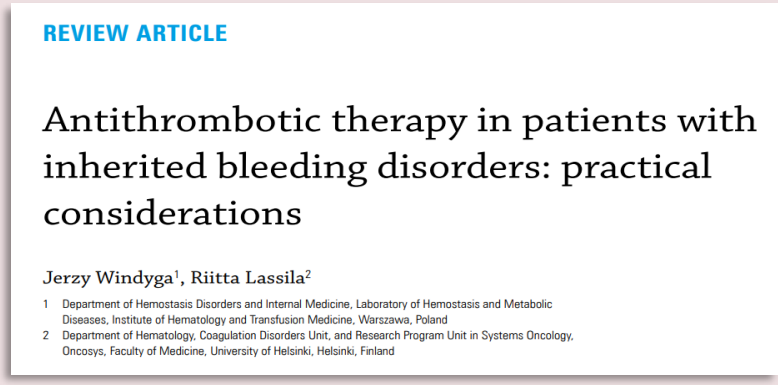

REVIEW ARTICLE

Antithrombotic therapy in patients with inherited bleeding disorders: practical considerations

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