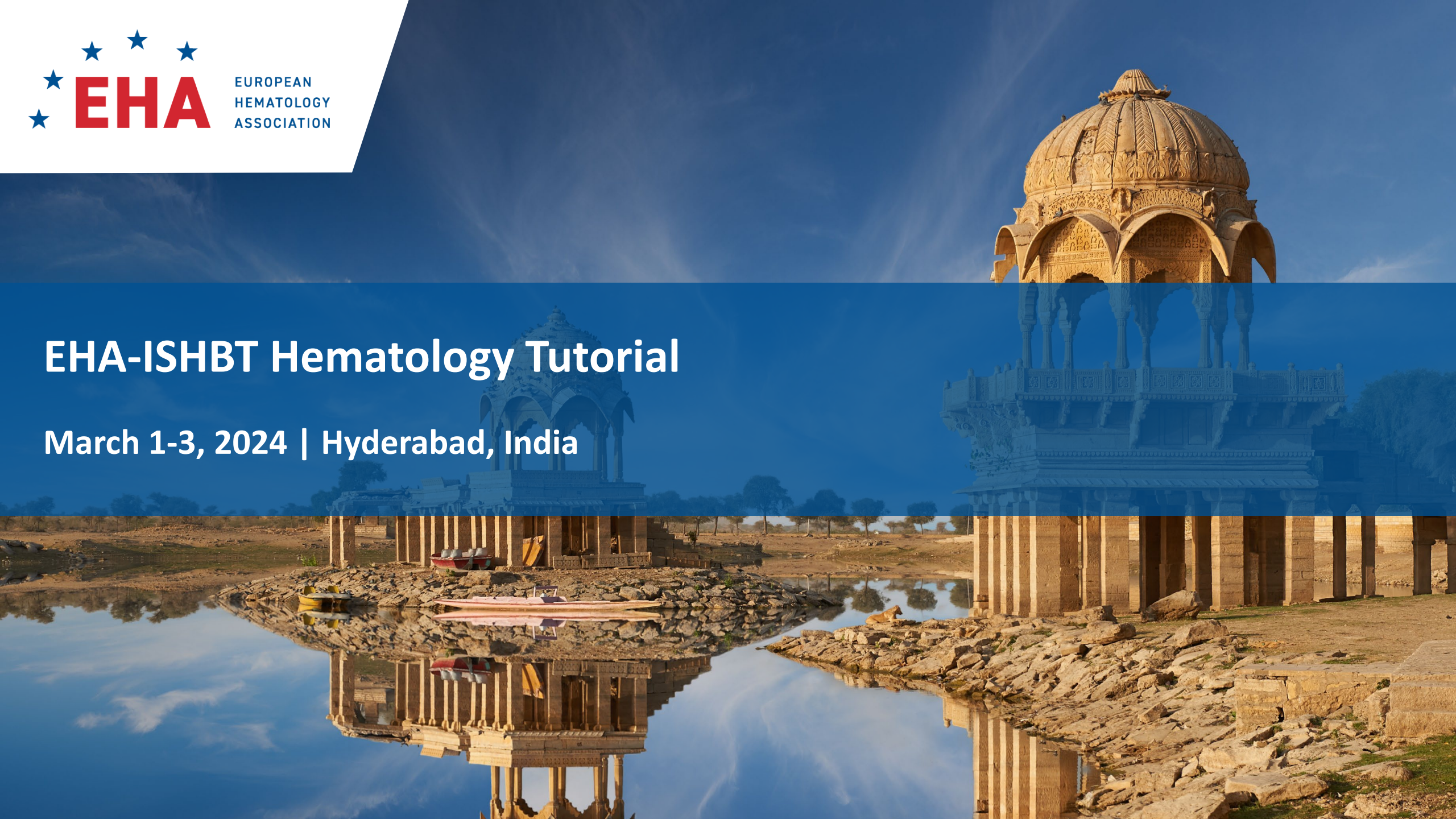
EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

March 1-3, 2024 | Hyderabad, India



EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

Clinical Case – Session Hemophilia

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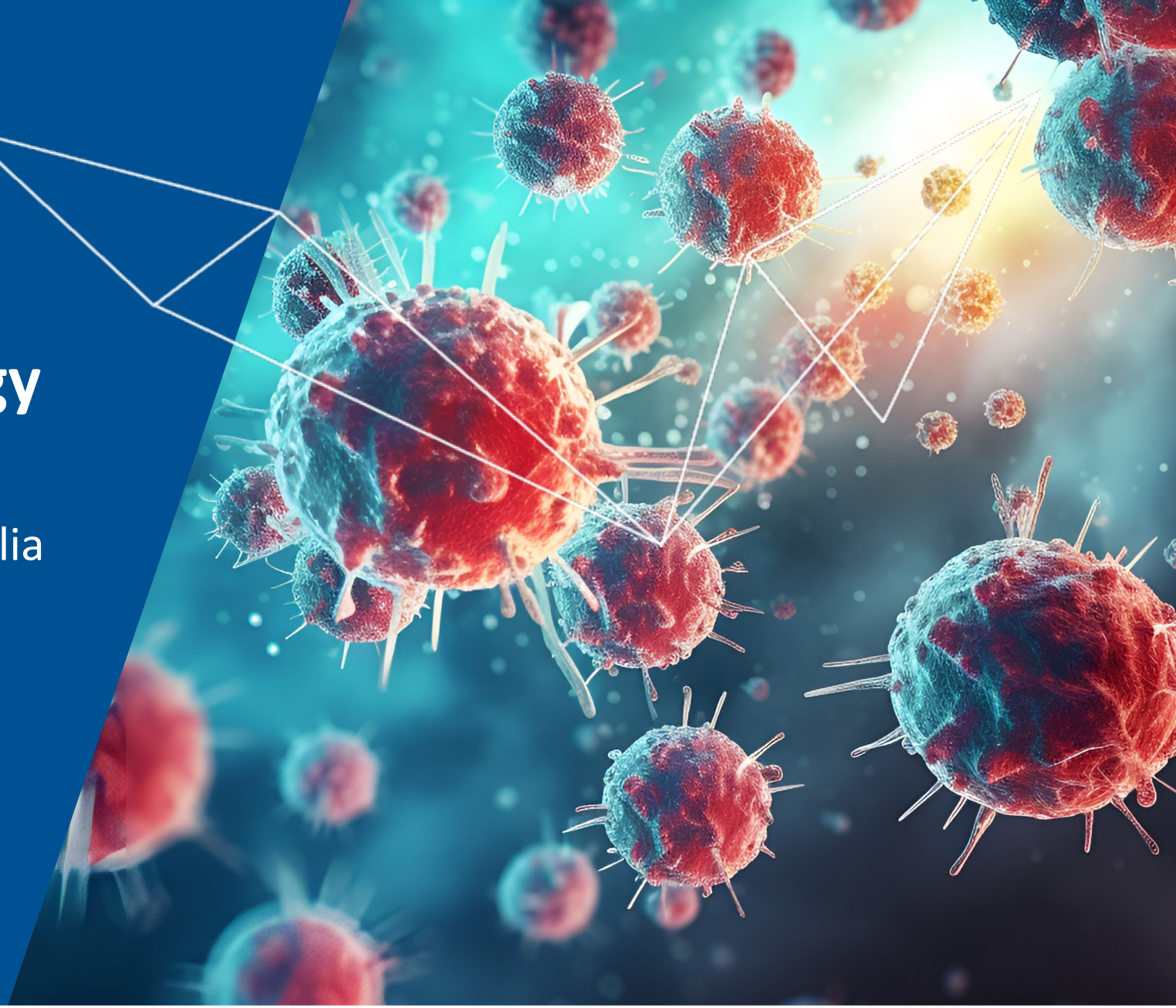
March 1-3, 2024



Clinical case

- 79-year-old man with mild hemophilia A (FVIII 5 IU/dl), who uses on-demand FVIII concentrate, suffers from chest pain and shortness of breath after exercise (stable angina)
- Risk factors for cardiovascular disease (CVD): age, obesity (106 kg, BMI 36 kg/m2), hypertension, smoking

- His general physician considers cardiovascular disease unlikely due to the patient's hemophilia

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Questions can be answered by scanning the QR on your phone to access Slido.

For each question you have 15 seconds.

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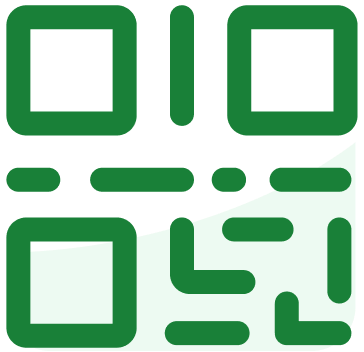

Join at slido.com
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ⓘ Start presenting to display the joining instructions on this slide.

Q1: Which of the following statements is true?

A. Patients with hemophilia are protected against atherosclerosis and cardiovascular disease

B. Patients with hemophilia are **NOT** protected against atherosclerosis and cardiovascular disease

C. Patients with hemophilia should be treated similarly for cardiovascular disease as patients without hemophilia

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4.21 Which of the following statements is true?

ⓘ Start presenting to display the poll results on this slide.

Q1 discussion: Rate of CVD in hemophilia patients

Table 1. Cardiovascular risk factors for calculating QRISK2-2011

Age
Sex
Smoking status
Ethnicity
Systolic blood pressure
Ratio of total serum cholesterol to high-density lipoprotein
Body mass index
Family history of coronary heart disease in a first-degree relative <60 y of age
Townsend deprivation score (optional)
Treated hypertension
Diagnosis of
Rheumatoid arthritis
Atrial fibrillation
Type 2 diabetes
Chronic renal disease

Table 3. Predicted vs observed CVD events

Variable	N	CVD events expected	CVD events observed	RR (95% CI)	Fischer exact test, *P*	Absolute risk reduction
Total	579	4.1% (24)	1.7% (9)	0.38 (0.18-0.80)	.01	2.4%
CVD risk group						
Low	401	1.5% (6)	0.2% (1)	0.17 (0.02-1.38)	.12	1.3%
Intermediate	100	7.0% (7)	3.0% (3)	0.43 (0.11-1.61)	.17	4.0%
High	78	15.3% (12)	6.4% (5)	0.42 (0.15-1.13)	.06	8.9%
Severity						
Mild	201	5.0% (10)	1.0% (2)	0.20 (0.04-0.90)	.02	4.0%
Nonsevere*	275	4.7% (13)	1.8% (5)	0.38 (0.14-1.06)	.045	2.9%
Severe	304	3.9% (12)	1.3% (4)	0.33 (0.11-1.02)	.04	2.6%
On-prophylaxis therapy	182	3.8% (7)	2.2% (4)	0.57 (0.17-1.92)	.27	1.7%
On-demand therapy	122	4.1% (5)	0% (0)	0.00	.03	4.1%

Van der Valk et al, Blood Adv 2022

Clinical case

- 3 months later, his symptoms worsen with progressive chest pain
- Patient was sent to emergency room and seen by cardiologist
- Diagnosis: unstable angina

- Plan: treat him according to acute coronary syndrome (ACS) protocol with triple antithrombotic therapy (aspirin, clopidogrel, low-molecular-weight heparin)

- Cardiologist calls you as attending hematologist / hemophilia specialist to ask if they can start these medications?

Q2: What is your recommendation?

A. Agree to start triple antithrombotic treatment in this patient, seeing the clinical indication

B. Agree to start triple antithrombotic treatment in this patient, but only with FVIII concentrate supplementation

C. Recommend to start aspirin monotherapy only, without FVIII concentrate supplementation

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4.22 What is your recommendation?

ⓘ Start presenting to display the poll results on this slide.

Q3: What (trough) FVIII level do you consider safe to start aspirin monotherapy?

A. FVIII ≥ 1-5 IU/dL

B. FVIII ≥ 10 IU/dL

C. FVIII ≥ 20 IU/dL

D. FVIII ≥ 30 IU/dL

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4.23 What (trough) FVIII level do you consider safe to start aspirin monotherapy?

ⓘ Start presenting to display the poll results on this slide.

Relevant questions when treating hemophilia patients with acute and chronic coronary syndromes

- What FVIII levels are needed to safely allow aspirin monotherapy?
- What FVIII levels should be reached to safely start ACS protocol / double antiplatelet therapy (DAPT)?
- What FVIII levels should be reached before cardiac intervention?
- Should FVIII concentrate / prophylaxis be given during this period?
- Which anticoagulant is preferred before and during percutaneous coronary intervention (PCI)?
- Can the period of DAPT be limited to a minimum duration after cardiac intervention?
- Is there a preference for a specific type of drug in case of DAPT or single antiplatelet therapy (SAPT)?

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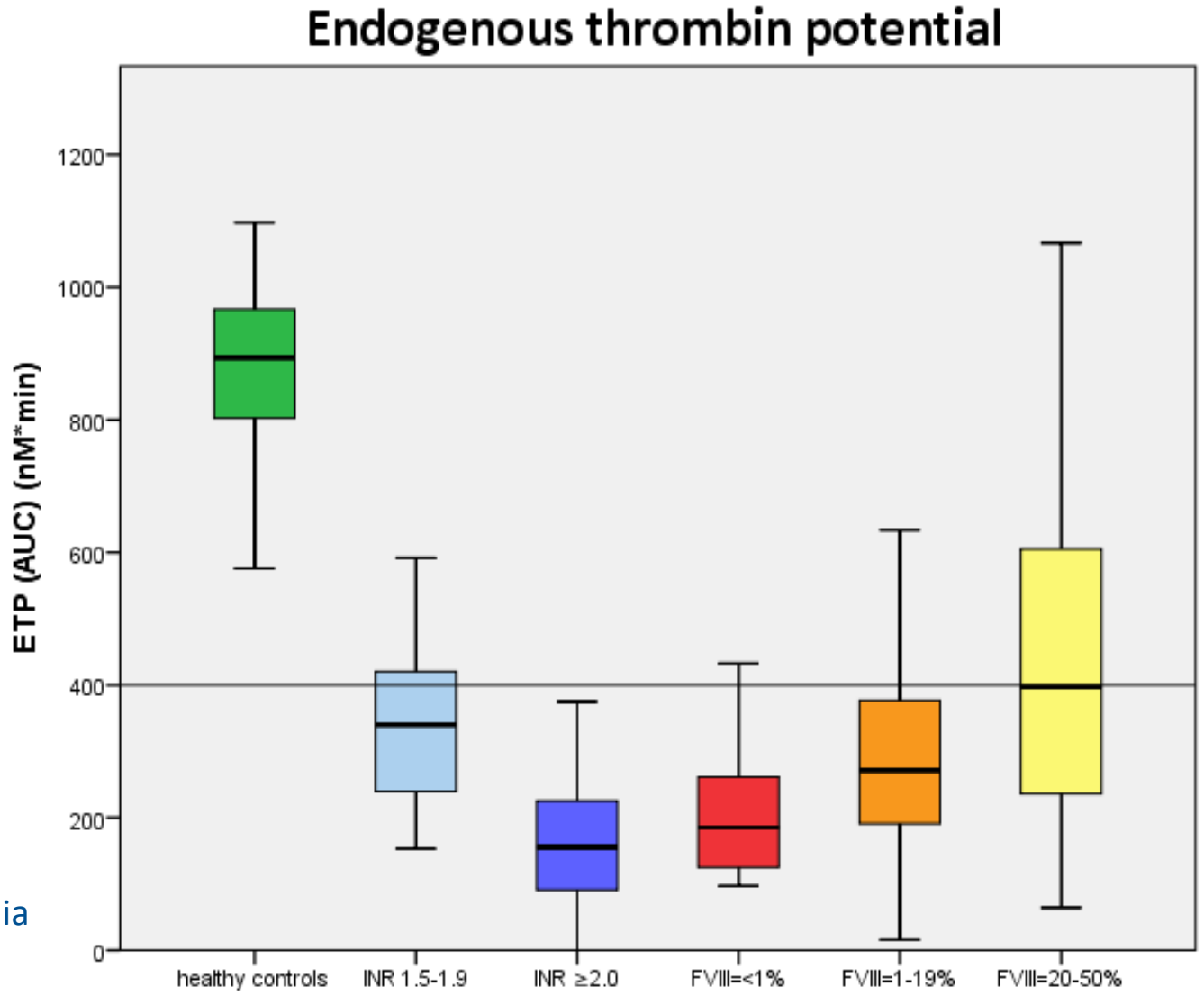
Are patients with hemophilia naturally anticoagulated?

Patients with hemophilia
and **FVIII levels <10 IU/dL**
appear “naturally anticoagulated”
to a similar extent as patients on
vitamin K antagonists (VKA) with
therapeutic INR levels



De Koning et al, JTH 2017; Dargaud et al, Haemophilia 2005; Gilmore et al, Haemophilia 2010; Veen et al, Thromb Res 2009; Trossaërt et al, JTH 2008

Bleeding risk in hemophilia patients on anticoagulation

	Mean ABR (95% CI)	HR for bleeding (95% CI)	*p*
In all patients, whatever the hemophilia severity			
Control group	0.317 (0.226–0.408)	1	
COCHE total	0.961 (0.924–0.999)	2.64 (1.78–3.92)	<0.0001
With AT	1.033 (0.996–1.07)	2.73 (1.82–4.11)	<0.0001
Without AT[a]	0.417 (0.089–0.744)	1.78 (0.40–7.87)	0.448
In patients with moderate/severe hemophilia			
Control group	0.86 (0.77–0.94)	1	
COCHE total	2.22 (2.10–2.31)	1.96 (1.21–3.18)	0.0061
With AT	2.36 (2.17–2.53)	2.04 (1.23–3.39)	0.0058
-SAPT	2.76 (2.64–2.88)	2.05 (1.16–3.62)	0.0132
-DAPT	4.81 (2.42–13.63)	5.58 (1.49–20.96)	0.0109
Without AT	0.889 (0.63–1.15)	1.52 (0.25–9.12)	0.6475
In patients with mild hemophilia			
Control group	0.044 (0–0.09)	1	
COCHE total	0.336 (0.273–0.432)	4.93 (2.21–11)	<0.0001
With AT[b]	0.361 (0.293–0.463)	4.97 (2.16–11.43)	0.0002
-SAPT	0.232 (0.177–0.286)	3.76 (1.13–12.55)	0.0313
-DAPT[c]	0.517 (0.324–0.711)	5.31 (1.23–22.92)	0.0252
-AC	0.353 (0.01–0.606)	9.91 (1.34–73.47)	0.0248
-DPT[d]	1.143 (0.793–1.492)	15.64 (1.57–115.80)	0.019
Without AT	0.133 (0–0.328)	2.39 (0.15–37.24)	0.3173

SAPT = single antiplatelet therapy
DAPT = double antiplatelet therapy
AC = anticoagulation
AT = antithrombotic therapy

Guillet et al, Thromb Haemost 2021 (COCHE study)

FVIII/FIX levels to start aspirin or oral anticoagulation in patients with hemophilia

Suggested Minimum Trough Levels (IU/dL) of FVIII/FIX Considered to Start Antithrombotic Treatment[a]

Author	Setting	SAPT	DAPT	VKA	DOAC
Schutgens 2009[26]	Single center	1	30	-	-
Mannucci 2009[27]	Expert opinion	5	30	30	-
Tuinenburg 2013[28]	Single center	1	25	-	-
Schutgens 2013[29]	Single center	1–5	20-30	20-30	-
Staritz 2013[30]	Delphi consensus	1–5	5-15	-	-
Schutgens 2014[31]	Delphi consensus	3.5 (1–10)	14 (4–30)	24 (10–50)	23 (10–50)
Ferraris 2015[32]	Consensus	5–10	25	30	30
Martin 2016[33]	Expert opinion	1–5	15–30	30	30
Schutgens 2016[34]	Expert opinion	1	-	20	20
Guillet 2021[16]	Registry	-	-	20	20
Pipe 2021[35]	Consensus			50	
Shapiro 2022[36]	Expert opinion	5	20	20	20
Klamroth 2023[37]	Delphi consensus	3	10	20	20
Franchini 2023[38]	Expert opinion	5	30	30	30

[a]No data are available for combination therapy of low-dose DOAC and low-dose aspirin.

SAPT = single-antiplatelet therapy; DAPT = dual antiplatelet therapy; VKA = vitamin K antagonist; DOAC = direct oral anticoagulant.

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Schutgens et al, Hemasphere 2023

Antithrombotic treatment in hemophilia patients

Guidance document with clinical practice recommendations for patients with hemophilia

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]

Schutgens et al, Hemasphere 2023

Recommendations guidance document

- We **do not recommend** the use of any form of antithrombotic therapy in patients with **severe hemophilia without clotting factor prophylaxis**
- We recommend a minimum **trough FVIII/IX level of 1-5 IU/dL** for single antiplatelet therapy (SAPT; aspirin or clopidogrel)
- We recommend a minimum **trough FVIII/IX level of 20 IU/dL** for dual antiplatelet therapy (DAPT)
- We recommend a minimum **trough FVIII/IX level of 20 IU/dL** for oral anticoagulation (VKA with INR level 2-3 or full dose DOAC)
- In patients with hemophilia A using **emicizumab** (with or without inhibitors), we consider it acceptable to use SAPT, but there is insufficient data on the safety of DAPT or oral anticoagulation

Back to the clinical case…

Clinical case

- Hematologist: no triple therapy, aspirin monotherapy OK (FVIII level trough 5 IU/dl)
  - *if need for triple therapy, only with FVIII concentrate supplementation*
- Need for cardiac intervention (PCI)

Peri-operative plan formulated in multidisciplinary team:

- Before PCI: FVIII concentrate supplementation aimed at FVIII peak ≥ 100 IU/dL
- Radial approach
- First 24-48 hours: FVIII concentrate supplementation aimed at FVIII trough ≥ 50 IU/dL
- DAPT for a short period (maximum of **1 week-1 month**), followed by SAPT
- FVIII concentrate daily during DAPT + 5 extra days aimed at FVIII trough ≥ 30 IU/dL

Clinical case

FVIII levels before and after PCI

Test	Ref. waarde	Materiaal	30-09-2022 19:31 KCL	30-09-2022 20:07 KCL	01-10-2022 09:46 KCL	01-10-2022 10:31 KCL	02-10-2022 10:23 KCL	02-10-2022 10:26 KCL	03-10-2022 12:31 KCL	03-10-2022 12:49 KCL	06-10-2022 10:19 KCL	06-10-2022 10:35 KCL	Eenheid
Bloed													
Factor VIII	0.60-1.40	Bloed	0.10	0.84	0.59	1.17	0.59	4.12	0.41	1.36	0.29	1.17	U/mL

- In agreement with cardiologist: **1 week of DAPT** (clopidogrel 75 mg + aspirin 80 mg) followed by clopidogrel monotherapy 75 mg
- CYP2C19 metabolism determination (by initiative of cardiologist): ***intermediate***
  - dose increase of clopidogrel to 150 mg or switch to aspirin
  - in agreement with cardiologist: **aspirin monotherapy after 1 week**

- Good cardiac rehabilitation, non-significant bleeding complications with aspirin

Conclusions: CVD in patients with hemophilia

- Cardiovascular disease (CVD) emerging medical issue with extended lifespan
- Coronary artery disease, atrial fibrillation, venous thrombosis
- Prevalence lower than general population, but hemophilia patients **NOT** protected against atherosclerosis
- No RCTs available, small studies

Bleeding risk inherently increased, delicate balance

- Antithrombotic therapy in patients with hemophilia is feasible
- Limited data, especially for patients with hemophilia B
- Carefully balancing individual risks is mandatory
- **Primary prevention programs** for patients with hemophilia are key

Individual approach for each hemophilia patient

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