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

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ABSTRACT

Cardiovascular disease is an emerging medical issue in patients with hemophilia (PWH) and its prevalence is increasing up to 15% in PWH in the United States. Atrial fibrillation, acute and chronic coronary syndromes, venous thromboembolism, and cerebral thrombosis are frequent thrombotic or prothrombotic situations, which require a careful approach to fine-tune the delicate balance between thrombosis and hemostasis in PWH when using both procoagulant and anticoagulant treatments. Generally, PWH could be considered as being naturally anticoagulated when clotting factors are <20 IU/dL, but specific recommendations in patients with very low levels according to the different clinical situations are lacking and mainly based on the anecdotal series. For PWH with baseline clotting factor levels >20 IU/dL in need for any form of antithrombotic therapy, usually treatment without additional clotting factor prophylaxis could be used, but careful monitoring for bleeding is recommended. For antiplatelet treatment, this threshold could be lower with single-antiplatelet agent, but again factor level should be at least 20 IU/dL for dual antiplatelet treatment. In this complex growing scenario, the European Hematology Association in collaboration with the International Society on Thrombosis and Haemostasis, the European Association for Hemophilia and Allied Disorders, the European Stroke Organization, and a representative of the European Society of Cardiology Working Group on Thrombosis has produced this current guidance document to provide clinical practice recommendations for health care providers who care for PWH.

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Supplemental digital content is available for this article.

HemaSphere (2023) 7:6(e900).
http://dx.doi.org/10.1097/HS9.0000000000000900.
Received: December 21, 2022 / Accepted: April 24, 2023

INTRODUCTION

Antiplatelet and anticoagulant drugs represent a cornerstone in the management and prevention of arterial and venous thromboembolic events.

The beneficial effects of aspirin for secondary prevention in high-risk patients has been unequivocally demonstrated in a series of meta-analyses of randomized controlled trials. In established atherosclerotic disease, aspirin is associated with significant reductions in serious vascular events, including stroke and coronary events, and a 10% reduction in total mortality.[1] Current guidelines suggest life-long aspirin 75–100 mg/day in patients with history of myocardial infarction and/or coronary revascularization and in patients with known coronary artery disease.[1] In addition, after acute coronary syndromes (ACS), there is a need for dual antiplatelet therapy (DAPT) up to 1 year, and in some cases at high risk of recurrences or in cases where the atherosclerotic disease is very severe, there is indication to prolonged treatment with single-antiplatelet therapy (SAPT) or DAPT and low-dose oral anticoagulant.[1]

In patients with atrial fibrillation (AF), anticoagulants are widely used for the prevention of ischemic stroke and systemic embolism. Decisions surrounding anticoagulation in a patient with AF is based on the individual risk assessment, where the risk of ischemic stroke/systemic embolism is balanced by the risk of anticoagulation-associated hemorrhage. When comparing vitamin K antagonists (VKAs) with a direct oral anticoagulant (DOAC), the DOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (relative risk [RR], 0.81; 95% confidence interval [CI], 0.73-0.91; $P < 0.000$), mainly driven by a reduction of hemorrhagic stroke (0.49 [0.38-0.64]; $P < 0.000$).[2,3] Therefore, the majority of patients with AF are preferably treated with a DOAC due to enhanced efficacy and ease of administration.[4]

Major bleeding is the primary safety concern with long-term use of antiplatelet or anticoagulation therapy. In primary prevention, the use of aspirin versus no aspirin use has a relative risk for a major bleed of 1.5, with no effect on mortality.[5] In secondary prevention in the general population, the benefit overweighs the risk of bleeding associated with aspirin treatment.[1] The risks of any bleeding are more pronounced (~3-fold) with the use of DAPT.[6] In a recent meta-analysis of trials in patients with AF, VKAs had 2-fold increased risk of fatal bleeding as compared with DOACs, 2.4-fold of intracerebral hemorrhage, and 1.5-fold of a major hemorrhage, while there was no difference in risk of gastrointestinal bleeding.[7] However, these data should be interpreted with caution, as the definition of bleeding and the risk of ischemic stroke, exclusion criteria, and bleeding tendency were different in the pivotal trials testing DOAC compared with warfarin and these trials included patients at relatively high thromboembolic risk and relatively low bleeding risk.

In the community of patients with hemophilia (PWH), cardiovascular disease represents an emerging medical issue as the lifespan of these individuals continues to approach that of the general population. The prevalence of cardiovascular disease was 15% in a cohort of PWH in the United States.[8] The overall AF prevalence in PWH in Europe was 0.84% and increased to 3.4% in patients >60 years of age.[9] Age is associated with other risk factors such as hypertension and comorbidity including renal disease and polypharmacy. In addition, obesity, diabetes, and hypercholesterolemia are present also in PWH.[10,11] Although the occurrence of atherothrombotic events in PWH might be lower when compared with the general population,[12] it has been shown that PWH are not protected against the development of atherosclerosis.[13,14] The prevalence of cardiovascular disease (CVD) in PWH as compared with the general population was the subject of a scoping review in 2015, which demonstrated considerable conflicting evidence.[15] In a prospective multicenter trial, the exact prevalence of CVD in adult PWH was 1.5% over a 5-year period.[12] All the risk factors mentioned above are also associated with an increased risk of venous thromboembolism (VTE). Specifically, major orthopedic surgery, which is a common surgical procedure in PWH, is a well-known risk factor for VTE. It is obvious that the use of any antithrombotic therapy exposes PWH to an increased bleeding risk. The balance between thrombosis and hemostasis is, therefore, even more delicate in this patient population. From a French registry[16] and the European Hemophilia Safety Surveillance programme, it is evident that PWH do have ischemic events supporting the use of antithrombotic therapy in certain patients.

The purpose of the current guidance document is to provide clinical practice recommendations on antithrombotic therapy for health care providers who care for PWH.

METHODOLOGY

These recommendations were proposed by the Scientific working Group (SWG) on Bleeding and Thrombosis of the European Hematology Association (EHA). The chair of the SWG formulated an initial list of experts as a steering committee and through EHA a working group was proposed to the International Society on Thrombosis and Haemostasis and European Association for Hemophilia and Allied Disorders, which agreed and within April to August 2021 nominated 4 and 3 members, respectively, to take part. Furthermore, a representative of the European Society of Cardiology (ESC) Working Group on Thrombosis and 2 neurologists linked to the European Stroke Organization (ESO) were also included. The recommendations were generated based on a literature review to December 2021 from established databases (Medline and PubMed) using keywords including hemophilia, cardiovascular disease, AF, CHA2DS2-VASc (congestive heart failure, hypertension, age, diabetes, stroke, vascular diseases), HAS-BLED (hypertension, abnormal renal/liver failure, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol, concomitantly), myocardial infarction, heart valve, VTE, anticoagulation, thrombin generation (TG), and emicizumab. The coordinator and the initial steering committee designated the field into 6 sections and used case vignettes to develop clinically relevant questions. As we aimed to develop a practice guidance document, recommendations were based on the clinical questions. The lack of randomized controlled trials in this field was recognized, and thus the development of recommendations was based on the best available evidence from nonrandomized trials, observational studies including case series and reports, literature reviews (including narratives), and expert consensus. An overview of the literature is given in Suppl. Table S1. Discussion and review of these recommendations was carried out by all members of the working group during virtual meetings and through email correspondence. In case of nonunanimous agreement on a recommendation, a consensus was reached during virtual meeting by voting. In the end, unanimous consensus was reached on all recommendations. The draft article was circulated to all members after each new version for approval of changes. The grading of recommendations, assessment, development and evaluation (GRADE) nomenclature was not used because evidence was largely derived from nonrandomized case series and expert-informed standard care. Instead, 3-level grading system (from the strong to weak) was used: recommendation-consideration-suggestion. The grading system was proposed by the Coordinator and the steering Committee to the panelists who agreed on the statements. Recommend means that it should be applied in most cases; consider means that the option proposed is useful, although clear evidence is lacking; and suggest means that evidence is completely lacking but the proposal might be useful in the selected conditions.

SECTION 1: GENERAL CONSIDERATIONS

Clinical question 1: Are PWH naturally anticoagulated?

TG may be a biomarker of coagulation potential beyond coagulation factor levels. The TG curve provides a perspective of global hemostasis, triggered with low concentration of tissue factor, particularly in relation to fibrin-rich clot formation. The area under the curve, that is, the endogenous thrombin potential (ETP), represents the total amount of thrombin formed over time. ETP can be used to measure hypocoagulability or hypercoagulability. It has been used to compare patients on oral anticoagulation with patients with hemophilia A (PWHA) and normal controls as described below.

Two studies have compared ETP in PWHA with patients on oral anticoagulants and healthy controls. In the first, ETP was measured in 15 patients on oral anticoagulants (VKAs), 18 PWHA, and 19 healthy controls.[17] Where healthy controls were set to 100% ETP, patients on VKAs had values of 19% and PWHA of 25% (at low levels of phospholipid in the assay). A significant correlation was seen between ETP% and both international normalized ratio (INR) and FVIII. Patients with an INR of 2 had an ETP between 30% and 50%; patients with an INR of 4 all had ETP <20%. In PWHA with FVIII levels <10 IU/dL, ETP was 5%–65% and showed a log-linear correlation. In PWHA with <1 IU/dL, ETP was <30%, in PWHA with FVIII <10 IU/dL, ETP was <60%. The second study compared 143 PWHA with 97 patients on VKAs and healthy donors[18] (Table 1). ETP of 400 nM/min (44.5% of normal) was considered as the threshold for therapeutic anticoagulation. Almost all PWHA with severe hemophilia had ETP < 400 nM/min, as had all patients with therapeutic INR levels. PWHA with FVIII levels 1–10 IU/dL had considerably lower ETP as compared with controls (31%) and also lower compared with patients who had a subtherapeutic INR. PWHA with FVIII levels 10–19 IU/dL were comparable to patients with subtherapeutic INR, although still far from normal. In mild PWHA with FVIII 20–50 IU/dL, half of them had ETP < 400 nM/min, but the variability was very high. In PWHA with FVIII levels > 20 IU/dL, ETP ranges were wide with half of the patients reaching the ETP threshold associated with a therapeutic INR.

To further characterize the ETP in mild PWHA, several investigators have compared ETP between PWHA and healthy controls (Table 2).[19–23] In 13 mild PWHA, ETP was 72% lower than healthy controls.[19] In mild PWHA with a mean FVIII level of 21 IU/dL (11–31 IU/dL), mean ETP was 758 nM/min as compared with 1301 nM/min in healthy controls (58% of normal).[20] In 31 mild PWHA, mean ETP was 312 nM/min versus 931 nM/min (34% of normal).[21] Despite large interindividual variation in ETP, it correlated significantly with FVIII levels; in PWHA with FVIII levels >25 IU/dL, most patients were above the lower limit of normal. A third article evaluated ETP in 61 mild PWHA.[22] FVIII levels correlated significantly with ETP, especially when FVIII levels were <20 IU/dL. It can be appreciated that the absolute ETP values differ in the various studies, although in all reports we chose to depict the low TF concentration (0.5 or 1 pM) only.

As TG as a surrogate indicator of "natural anticoagulation," several considerations should be made. First, although this provides useful information on the thrombin potential of an individual, it has not been evaluated prospectively as a clinical outcome for association with bleeding or thrombosis. Second, it might be overly simplistic as the TG assay does not evaluate different mechanisms by which normal hemostasis is impaired. VKAs deplete multiple pivotal procoagulant and anticoagulant factors, DOACs lead to stoichiometric inhibition of FIIa, thrombin, or FXa, and hemophilia results in a congenital stable shortage of a single clotting factor VIII or IX. Third, it should be noted that in the general population, patients with AF on VKAs have INR levels <2.0, 31% of the time.[24] Thus, the conceptual threshold for "natural anticoagulation" may not be strict. There are various ranges of the degree of anticoagulation in patients on anticoagulants and in PWH.

We did not find literature that compared ETP in patients on oral anticoagulants and PWHB. ETP between hemophilia A and B was compared previously and did not appear to be significantly different.[25] Therefore, it seems plausible that PWHA and PWHB can be considered somewhat equal in this respect.

Based on the studies mentioned above, it can be concluded that PWHA have lower ETP than healthy controls with expected overlap among those with mild HA. In relation to patients on oral anticoagulation with INR > 2.0, PWHA with FVIII levels <10 IU/dL have comparable ETP and therefore may be considered to have some degree of "natural anticoagulation." As expected, PWHA with FVIII levels 10–20 IU/dL do not appear to be as deeply anticoagulated as patients on therapeutic anticoagulation, but still have significantly impaired ETP, comparable to subtherapeutic INR levels (1.5–1.9).

To conclude:

- PWH and clotting factor levels <10 IU/dL appear "naturally anticoagulated" to a similar extent as patients on VKAs with therapeutic INR levels.
- PWH and clotting factor levels 10–20 IU/dL appear "naturally anticoagulated" to a similar extent as patients on lower level of oral anticoagulation (ie, INR 1.5–1.9 in people on VKAs).
- In patients with FVIII/FIX levels >20 IU/dL, the interindividual variance is wide and there is some overlap with ETP of normal controls.

Table 1

ETP in Patients on VKAs and Patients With Varying Degrees of Severity of Hemophilia A

Patients	Median ETP nM/min (IQR) (% of Normal)	ETP < 400 nM/min
Healthy controls	898 (803–1104) (100%)	0%
INR 1.5–1.9	340 (238–429) (37.9%)	63%
INR > 2.0	156 (90–225) (17.0%)	100%
PWH FVIII <1 IU/dL	185 (116–307) (20.6%)	93%
PWH FVIII 1–9 IU/dL	278 (210–408) (31.0%)	74%
PWH FVIII 10–19 IU/dL	338 (197–541) (37.6%)	63%
PWH FVIII 20–50 IU/dL	397 (219–632) (44.2%)	52%

INR = international normalized ratio; PWH = patients with hemophilia; VKAs = vitamin K antagonists; ETP = endogenous thrombin potential; IQR = interquartile range.
Adapted from de Koning et al.[18]

Table 2

ETP in Patients With Mild Hemophilia A

Author	Patients	Median ETP nM/min ± SD or (95% CI) (% of Normal)
Dargaud[19]	Healthy controls	1495 ± 175 (100%)
	PWH FVIII >5 IU/dL	1083 ± 388 (72%)
Gilmore[20]	Healthy controls	1301 (1196-1407) (100%)
	PWH FVIII 11–31 IU/dL	758 (628-888) (58%)
Veen[21]	Healthy controls	931 (802-1042) (100%)
	PWH FVIII 6–50 IU/dL	312 (264-360) (34%)
Trossaërt[22]	Healthy controls	1579 ± 359 (100%)
	PWH FVIII <10 IU/dL	756 ± 402 (48%)
	PWH FVIII 10–20 IU/dL	1201 ± 326 (76%)
	PWH FVIII 20–30 IU/dL	1413 ± 329 (89%)

PWH = patients with hemophilia; ETP = endogenous thrombin potential; CI = confidence interval.

Clinical question 2: What is the FVIII/FIX threshold to safely start aspirin or oral anticoagulation in PWH?

Most literature on this topic is based on the individual expert opinion or expert panel consensus statements (Table 3).

A guidance document was first drafted in 2009[26] and later evaluated and adapted in 2013.[28,29] In 2013 and 2014, a panel of experts was convened and consensus was achieved using a Delphi methodology to determine clotting factor thresholds for anticoagulation.[30,31] The consensus was that a mean factor VIII/IX level of 1–5 IU/dL should be sufficient to start SAPT and a mean of 24 IU/dL (range 10–50 IU/dL) was considered to be high enough to start oral anticoagulation, although the individual opinions varied widely. A consensus review from Wisconsin was published in 2015.[32] In 2009 and 2016, an article, How I Treat, was published on the topic.[27,33,34] A case series from London provided evidence suggesting that trough levels of around 1% are not sufficient for SAPT.[39] A recent consensus guideline from the World Federation of Hemophilia on the treatment of COVID-19 in PWH suggests trough levels >30 IU/dL to start prophylactic dose with low-molecular-weight-heparin and 50–100 IU/dL for therapeutic dose.[35] A recent British review suggests a trough of 20 IU/dL for oral anticoagulation.[36] In 2023, 2 more expert opinion articles have been published on the topic.[37,38]

There are no data on the safety of triple therapy (oral anticoagulation and DAPT) in PWH. We think it is acceptable only after full correction of the clotting factor deficiency (levels 80–100 IU/dL). In all other cases, we should refrain from triple therapy.

There are no randomized trials on this topic. Data from the COmorbidités Cardiovasculaires chez les patients HEmophiles (COCHE) study reveal that the bleeding risk in PWH with AF taking any form of anticoagulation is higher than in control PWH.[16] Oral anticoagulation was given only to mild hemophilia patients and none of them received FVIII/FIX replacement treatment. Ten patients reached a total follow-up of 102 months and the overall hazard ratio (HR) for bleeding was 9.9. Unfortunately, no information is given on factor levels at the time of bleeding nor on types of bleeding events. The bleeding rate in mild hemophilia patients using oral anticoagulation was slightly higher, although not statistically significantly, than that of PWH with SAPT (OR 8.6 versus 5.5).

In a case series, 8 PWH were on oral anticoagulant therapy around pulmonary vein isolation for AF.[40] Patients used therapeutic doses of VKA or dabigatran 110 mg twice daily for 6 weeks to several months, with trough FVIII/IX levels of >20 IU/dL. There were no spontaneous bleeding episodes. A review of cases in PWH with AF describes 2 patients on VKA during 6 weeks without bleeding.[41] Trough FVIII/IX levels were kept >30 IU/dL.

It is well known that there is discrepancy between clotting factor levels measured with 1-stage or chromogenic assays, especially in mild hemophilia.[42] We propose to use the lowest factor level measured to make clinical decisions.

There might be a preference for a specific antithrombotic drug over others. This is being addressed in specific clinical questions (clinical questions 5 and 18).

To conclude:

- We do not recommend the use of any form of antithrombotic therapy (including SAPT) in patients with severe hemophilia without clotting factor prophylaxis.
- We do not recommend the use of any form of antithrombotic therapy (including SAPT) in PWH with inhibitors (severe and nonsevere hemophilia) not using emicizumab.
- We recommend a minimum trough FVIII/IX level of 1–5 IU/dL for SAPT (aspirin or clopidogrel).
- We recommend a minimum trough FVIII/IX level of 20 IU/dL for DAPT.
- We recommend a minimum trough FVIII/IX level of 20 IU/dL for oral anticoagulation (VKA with INR levels 2–3 or full dose DOAC).
- We recommend a minimum trough FVIII/IX level of 80 IU/dL for triple therapy (oral anticoagulation and DAPT).
- We recommend to adjust the treatment according to the lowest factor level measured in case of discrepancy between 1-stage or chromogenic assays.

Clinical question 3: What is the bleeding risk in PWH using antiplatelet or oral anticoagulant therapy?

Although data are limited, the French COCHE study provides the most information on this topic.[16] The study was a prospective registry from 2011 to 2017 and included PWHA or PWHB who started an antithrombotic treatment for coronary heart disease, valvular disease, or AF. The control group included PWH without anticoagulation and data were retrospectively collected. In total, 18 PWH with AF were included, of whom 1 patient also had coronary artery disease; 16 of 18 patients had mild hemophilia, 1 moderate, and 1 severe. The latter patient stopped anticoagulation within a month after inclusion due to a CHA2DS2-VASc score of 1. In 5 of 18 patients (4 mild and 1 moderate), SAPT was given. DAPT

Table 3

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.

was started in 2 patients, oral anticoagulation in 10 (6 VKA and 4 DOAC). In 2 years of follow-up, anticoagulation therapy was downgraded in most patients: 3 of 5 SAPT stopped, all DAPT went to SAPT and from the 10 on oral anticoagulation, 3 stopped completely and 3 switched to SAPT of whom 1 stopped later. The 1 patient (with mild hemophilia) with AF and coronary disease used triple therapy first and turned to SAPT.

In the oral anticoagulation group, the mean annualized bleeding rate (ABR) of patients taking VKA and DOAC could not be compared, due to their limited number. However, the mean ABR was not significantly higher in patients treated with oral anticoagulation than in those treated with SAPT. In patients with mild hemophilia without prophylaxis (factor levels 6–20 IU/dL), significantly more bleeding episodes were seen in COCHE patients with oral anticoagulation. For basal FVIII/FIX levels >20 IU/dL, no difference was observed between patients receiving oral anticoagulation and controls.

The COCHE study also included 50 PWH and coronary artery disease. A total of 18 PWH received DAPT (of whom 9 switched to SAPT) and 32 SAPT (of whom 4 stopped treatment and 1 switched to DAPT). The complete cohort of 68 PWH (AF and coronary disease) was analyzed for bleeding events. The number of patients who had at least 1 major bleeding event was higher in the COCHE group (29/68; 42.6%) than in the control group (14/68; 20.6%). There were 100 bleeding events in the COCHE group: 52 hemarthrosis, 30 hematoma, 10 gastrointestinal bleeds (GIBs), and 8 others. Especially, GIB episodes were significantly more frequent in the COCHE group than in controls (8/68 patients versus 0/68 patients; odds ratio (OR) = 15.00 [95% CI, 1.84-268]; $P = 0.014$). It should be noted that all GIBs occurred in patients taking antiplatelet therapy, and none of the patients were on proton pump inhibitors. In addition, a total of 13 cardiovascular events occurred in 11 of 68 COCHE patients (16.2%) versus only 1 of 68 controls (1.5%).

In general, the HR for bleeding in PWH taking any form of anticoagulation in the COCHE registry was 2.7 as compared with the control group. In severe/moderate hemophilia, the HR with SAPT was 2.1 and with DAPT 5.6. In mild hemophilia, the HR for SAPT was 3.8, DAPT 5.3, and oral anticoagulation 9.9. These numbers were not adjusted for use of clotting factor prophylaxis, which might explain why the HR for bleeding with SAPT was higher in severe hemophilia than mild hemophilia.

In COCHE patients, severe PWH using any form of anticoagulation without factor prophylaxis had a mean ABR significantly higher than patients on prophylaxis (6.9 [95% CI, 6.9-7.2] versus 1.2 [95% CI, 0.97-1.5]; OR 16.7 [8.2-47.3]; $P < 0.0001$). In COCHE patients on prophylaxis, the mean ABR was 3-fold higher than in control PWH with prophylaxis without anticoagulation (1.2 versus 0.4 [95% CI, 0.03-0.77]; OR 3.7 [1.1-12.6]; $P = 0.037$). The beneficial effect of prophylaxis was also observed in COCHE patients with moderate hemophilia.

Based on the above data, it appears that the bleeding risk in PWH taking antithrombotic treatment is higher than in PWH not on antithrombotic treatment. In PWH with factor levels >20 IU/dL, oral anticoagulation appears not to increase the bleeding risk, but this judgement is based on limited case series. Prophylaxis with clotting factor concentrates (CFCs) decreases the bleeding risk in PWH using any form of antithrombotic therapy.

Finally, in the general population, anemia has shown to be a major risk factor for adverse outcome in patients using antithrombotic therapy in several trials.[43–45]

To conclude:

- The use of antiplatelet therapy increases the risk of gastrointestinal bleeds; thus, we recommend the use of empiric proton pump inhibition in all PWH on antiplatelet therapy.
- We recommend to actively manage anemia in association with antithrombotic treatment.

Clinical question 4: Should clotting factor prophylaxis be adapted in PWH in need for anticoagulation therapy?

As a general remark, the indication for antithrombotic therapy should be considered individually based on the thromboembolic risk. For instance, the indication for anticoagulation in lone AF is not comparable with that in mitral valve replacement. After the need for antithrombotic therapy has been confirmed, a possible adaptation of prophylaxis should be considered. Based on the evidence mentioned above, a trough clotting factor level of 20 IU/dL is suggested as a minimum in start anticoagulation therapy. It is, therefore, the question whether these levels should be raised merely to start anticoagulation therapy in PWH with baseline clotting factors <20 IU/dL.

From the COCHE study, it was clear that for severe hemophilia, patients without clotting factor prophylaxis had a mean ABR significantly higher than patients on prophylaxis (6.9 [95% CI, 6.6-7.2] versus 1.2 [95% CI, 0.97-1.5]; OR 16.7 [8.2-47.3]; $P < 0.0001$).[16] However, in patients using anticoagulation and prophylaxis, the mean ABR remained 3-fold higher than in controls with prophylaxis (1.2 versus 0.4 [95% CI, 0.03-0.8]; OR 3.7 [1.1-12.6]; $P = 0.037$). The beneficial effect of prophylaxis was also observed in patients with moderate hemophilia.

We consider it feasible to maintain factor levels >20 IU/dL with adapted prophylaxis for a limited time period. For instance, after initial periprocedural peak levels of 80–100 IU/dL, this can be achieved with daily infusion of appropriately weight-based FVIII (eg, 2.000 IU) in PWHA through home care delivery or self-infusion. On the contrary, we consider this not feasible or desirable for the long-term in terms of logistics and costs. In patients with AF, anticoagulation therapy is given for long-term prevention of ischemic stroke. Therefore, we do not advocate starting or increasing clotting factor prophylaxis for this purpose. Indeed, we consider PWH with factor levels <20 IU/dL to be naturally anticoagulated to some extent (see above). In the specific case of mitral valve replacement, this general concept could be overruled as discussed in the valve replacement section in this article.

For coverage of anticoagulation therapy for a limited time period, for example, after cardiac intervention, the reason to start or increase clotting factor therapy depends on the type of anticoagulation therapy. If anticoagulation therapy with oral anticoagulants is considered in PWH with clotting factor levels <20 IU/dL, we generally consider not to start anticoagulation therapy nor clotting factor replacement, except in cases with a very high thrombotic risk. In the latter case, anticoagulation therapy might be indicated, while trough clotting factor levels of >20 IU/dL should be aimed for during a limited period. An example of this could be the placement of a left atrial appendix closure device (see later). If DAPT is needed, we recommend to temporarily start or increase clotting factor prophylaxis for the time DAPT is given. Again, there are substantial differences in the indication for antithrombotic therapy thus requiring individual assessment.

Considering a PWH using regular prophylaxis with CFCs, it should be noted that factor FVIII/IX levels vary dynamically. Depending (among others) on dose, frequency, and product type, the time spent above or below 20 IU/dL is not always predictable and treatment should be individually determined. When regular prophylaxis is administered at a dose of 15–25 IU/kg every other day, one might state that PWH will be >20 IU/dL directly after infusion of prophylaxis and <20 IU/dL 12 hours later until the next infusion. Likewise, these patients will have less natural antithrombotic protection the first hours after prophylaxis and more in the last hours before the next infusion. The use of emicizumab will change this perspective and provide patients with a prolonged continuous state of increased thrombin potential. This will be discussed in association with clinical question 7.

To conclude:

- For PWH with baseline clotting factor levels >20 IU/dL in need for any form of antithrombotic therapy, we

recommend to initiate antithrombotic therapy and not to start additional clotting factor prophylaxis. Careful monitoring for bleeding is recommended.

- For PWH with baseline clotting factor levels <20 IU/dL with an indication for long-term prevention of thrombotic complications with oral anticoagulation (VKA or DOAC), we recommend not to start with oral anticoagulation therapy. Instead, PWH should be considered as being naturally anticoagulated when clotting factors are <20 IU/dL.
- For patients with severe hemophilia using clotting factor prophylaxis in whom long-term oral anticoagulation therapy is considered, we recommend adapting clotting factor prophylaxis to maximum peak levels of 25 IU/dL and not to administer additional anticoagulation therapy. This means a more frequent lower dose rather than once weekly higher dose clotting factor prophylaxis.
- For patients with severe hemophilia with an indication for long-term prevention of thrombotic complications with SAPT (aspirin or clopidogrel), we recommend to start SAPT and maintain FVIII/FIX >1 IU/dL using regular clotting factor prophylaxis. In patients with severe hemophilia with on demand clotting factor supplementation, we recommend to switch to regular prophylaxis and SAPT.
- For patients with severe hemophilia in need of short-term DAPT or oral anticoagulation, we recommend adapting clotting factor prophylaxis to maintain a factor trough level of ≥20 IU/dL.
- For patients with nonsevere hemophilia with baseline clotting factor levels <20 IU/dL and a very high thrombotic risk in need of (short-term) DAPT or oral anticoagulation, we recommend adapting clotting factor prophylaxis to maintain a factor trough level of ≥20 IU/dL for as long as DAPT or oral anticoagulation is given.

Clinical question 5: If the decision for oral anticoagulation in PWH has been made, is there a preference for a specific type of drug?

Given their efficacy, safety, and convenience, DOACs are generally the first choice as oral anticoagulation therapy for stroke prevention in AF in the general population.[4,46]

A recent meta-analysis evaluated multiple retrospective cohort studies that were performed for the European Medicines Agency to study the safety profile of DOACs (dabigatran, rivaroxaban, and apixaban).[47] The pooled HR for bleeding for DOACs compared with VKAs was found to be 0.94 (95% CI, 0.87-1.02). Rivaroxaban showed a modest increased risk (HR, 1.11 [95% CI, 1.06-1.16]); apixaban showed a decreased risk (HR, 0.76 [95% CI, 0.69-0.84]) as did dabigatran (HR, 0.85 [95% CI, 0.75-0.96]). The overall risk for GIB for DOACs compared with VKAs was slightly higher (HR, 1.16 [95% CI, 1.05-1.28]). Only apixaban had a lower risk for GIB with a HR of 0.77 (95% CI, 0.67-0.87). The risk for intracranial hemorrhage was significantly lower with all DOACs than with VKA (HR, 0.49 [95% CI, 0.39-0.62]).

Another systematic review determined the safety of DOACs for stroke prevention and treatment in patients with AF, including edoxaban.[7] For fatal bleedings, VKAs had a statistically significant greater risk (OR, 2.02) compared with rivaroxaban, apixaban, and edoxaban. There was no difference in the risk of fatal bleeding between dabigatran and VKAs, edoxaban had the highest level of safety. For major bleedings, VKAs had a greater risk as compared with apixaban (OR, 1.51), but a similar risk as compared with the other DOACs. For GI-bleedings, no differences between VKAs and DOACs were found, nor between the different DOACs. In terms of intracranial hemorrhage, dabigatran has the highest level of safety, followed by edoxaban and apixaban, and rivaroxaban has the lowest level of safety.

In PWH, bleeding is the major concern when using oral anticoagulation therapy. A drug choice should, therefore, primarily be based on the consideration of bleeding risk. There is no reason to assume that the difference in bleeding risk of DOACs versus VKA is substantially different in PWH, but specific data in PWH on this topic are lacking.

A second criterion for drug selection could be the potential to reverse the drug effect by an antidote. As all anticoagulation drugs effects can currently be reversed or diminished, either by prothrombin complex concentrates (PCC), vitamin K or specific antidotes (idarucizumab or andexanet alpha),[48] we suggest that this should not be an important consideration in anticoagulant drug choice.

The interpretation of the INR might be hampered in PWHB by the interference of FIX deficiency. The use of VKAs will lead to very low FIX levels in PWHB and these low levels are not reflected by the INR. This could be a reason to choose a DOAC over VKA in these patients. In PWHA using VKAs, we recommend promoting INR self-monitoring.

As mentioned earlier, PWH on regular prophylaxis will have peaks and troughs throughout the week. During peaks, patients may be at risk for thrombotic events, but during troughs they will likely be naturally protected.

To conclude:

- We recommend using DOACs over VKA in nonvalvular AF or VTE due to their favorable safety profile and the ability to individualize treatment regimens.
- We recommend DOACs over VKAs in PWHB.
- In PWH using VKAs, we recommend promoting INR self-monitoring.
- In the general population, different DOACs have different bleeding profiles; we consider taking these profiles into account in making individualized decisions on drug choice.

Clinical question 6: If the decision for oral anticoagulation in PWH has been made, is there a need for monitoring anticoagulation treatment and dose adjustment?

Since the dose-response relationship of VKAs varies significantly between individuals (due to genetic and environmental factors, including diet and drug–drug interactions), the use of VKAs requires close monitoring to prevent underdosing and overdosing, which may lead to thromboembolic and bleeding complications, respectively.[49] Laboratory monitoring is performed by measuring prothrombin time (PT) and reported as the INR. INR should be determined at least weekly during initiation of VKA therapy and at least monthly afterwards provided INR is stable.[50] The recommended INR range in AF patients without hemophilia and other bleeding disorders is 2.0–3.0.[51] Randomized trials have demonstrated that compared with placebo or untreated control, warfarin adjusted to INR 2.0–3.0 reduces the risk of stroke and systemic embolism by 64%, and despite that warfarin increases the risk of major bleeding, it reduces all-cause mortality by 26% in comparison to no treatment.[51]

However, fluctuations of INR are often observed in patients on VKA. In well-designed clinical trials, the time in therapeutic range (TTR) of INR in those taking warfarin was between 55% and 66%.[52–54] In some community settings, TTR has been even lower (~50%).[55] The patient education about VKA treatment (eg, drug–drug and diet interactions), using point-of-care testing with portable finger-prick monitors, and—in case of PWH—supervision of Hemophilia Treatment Centers may increase the reliability of laboratory monitoring of INR as well as TTR.

Although hemophilia increases the risk of bleeding complications and excessive bleeding is the most common side effect of anticoagulation, there is no evidence that target range of INR in PWH and AF receiving VKA should differ from that of other

patients with AF treated with VKA, provided the trough level of a deficient clotting factor is maintained >20 IU/dL with an adequate replacement therapy (see above). A close clinical monitoring is always needed, and in the case of bleeding or thromboembolic complications, a modification of VKA or replacement therapy dosing should be made.

The most recent guidelines for the management of patients with AF recommends DOACs over VKAs, with exception of some subpopulations, that is, with moderate-to-severe mitral stenosis, with mechanical heart valve, or with end-stage chronic kidney disease or on dialysis.[4,50] It should be noted, however, that apixaban is the only DOAC approved for end-stage renal disease and appears to have a better safety profile as compared with VKAs.[56]

Due to the predictable dose-response relationship, DOACs are usually administered at fixed doses and do not require routine laboratory monitoring for dose adjustments. Nevertheless, it is recognized that the fixed-dose strategy of DOACs may not be optimal for patients at extremes of weight, kidney failure, gastrointestinal absorption impairment, as well as in the case of potential drug–drug interactions, and in patients requiring urgent surgery or experiencing thromboembolic or bleeding complications while on a DOAC.[57–59]

The routine coagulation tests (activated partial thromboplastin time [APTT], PT, or thrombin time [TT]) are inadequate for monitoring anticoagulant/antithrombotic effect of DOAC, yet commercial assays to measure DOAC plasma concentrations have been developed.[59,60] Dilute thrombin time, ecarin clotting time, chromogenic ecarin assay, and chromogenic anti-FIIa assay are recommended to measure plasma concentration of dabigatran.[59] Dedicated anti-Xa chromogenic assays using specific rivaroxaban, apixaban, and edoxaban calibrators are used to assay plasma concentrations of direct FXa inhibitors. The results of recently published observational studies demonstrated association between DOAC plasma levels and thromboembolic and hemorrhagic complications.[61,62] The Measure and See study (NCT03803579) is currently ongoing in Italy, with the aim to define the relationship between DOAC levels at trough at steady state (within the first 2–4 wk) and occurrence of bleeding and thromboembolic episodes during a 1-year follow-up in patients with nonvalvular AF.[59,61]

However, unlike VKA, for which the target INR is defined, the optimal DOAC levels are unknown.[57–59] Therefore, the International Council for Standardization in Hematology recommends a comment with each reported DOAC result to indicate lack of DOAC TTRs, but cite expected levels (correlating with dose and time between the last dose of DOAC and blood sampling) for DOAC-treated patients from published studies.[60] Accordingly, monitoring of DOAC plasma levels is not useful in patients doing well on this therapy (no bleeding or thromboembolic complications), not requiring urgent surgery, not suffering from kidney failure, and not receiving drugs that may interact with DOAC.

To the best of our knowledge, there are no data on DOAC monitoring in PWH. We believe that the aforementioned principles of DOAC use should apply also to AF in PWH. The criteria of DOAC dose reduction in patients with AF in the general population are mainly based on age, creatinine clearance, and interacting comedication.[63] These criteria identify patients who are at increased risk of hemorrhagic complications with standard DOAC dose. Hemophilia also increases the risk of bleeding complications; however, we have not identified any data supporting the use of lower DOAC doses in PWH who do not meet the common criteria.

To conclude:

- We recommend INR ranges in PWH using VKA similar to that of the general population.
- If PWH with AF receive a DOAC, we recommend administering it at fixed standard dose without routine laboratory monitoring for dose adjustments.
- We recommend giving DOACs in reduced dose to those PWH who meet the criteria of anticoagulant dose reduction as in the general population.
- We recommend re-evaluation of the need for and choice of anticoagulant therapy on a regular basis.

Clinical question 7: Does the use of emicizumab suggest a safe threshold for antithrombotic therapy?

Emicizumab is a bispecific monoclonal antibody mimicking the cofactor effect of FVIII in the activation of FX by activated FIX. This agent has proved effective as prophylactic treatment in PWHA with and without FVIII inhibitors. There are very limited data on the use of emicizumab to facilitate anticoagulation in PWHA, whether inherited or acquired.[64,65] It is possible that emicizumab may provide sufficient hemostasis to allow for anticoagulation. It is a particularly attractive prohemostatic agent to allow for anticoagulation as it has a long half-life, on the range of ~30 days, and stably increases TG compared with clotting factor replacement.[66,67] As argued earlier, we recommend FVIII activity levels >20 IU/dL to allow for anticoagulation in PWHA. The main question to answer therefore is how does emicizumab-associated hemostasis compare to FVIII activity levels?

It must be appreciated that emicizumab, while a mimicker of FVIII, is mechanistically different from it and lacks FVIII's regulatory mechanisms.[68] Therefore, it is likely inappropriate to assign a truly bioequivalent factor VIII level to stable emicizumab plasma concentrations.[69] That said, the hemostatic efficacy of emicizumab demonstrated in numerous clinical trials is unquestionable and unparalleled by intermittent clotting factor replacement.[70] Earlier studies hypothesized that ~300 nM (44 µg/mL) of plasma ACE910 (now known as emicizumab) would exert an in vivo hemostatic activity equivalent to 10 IU/dL FVIII, as 300 nM ACE910 showed in vitro cofactor activity similar to that of 10 IU/dL FVIII, in terms of the peak height in the TG assay in human FVIII-deficient plasma.[71] However, these studies were done in a nonhuman primate model of acquired hemophilia A and the FVIII used was recombinant porcine FVIII.

Global hemostasis assays have been performed to evaluate the hemostatic potential of emicizumab. Data from the HAVEN trials have shown that parameters of the rotational thromboelastometry (ROTEM) were related to the concentration of emicizumab (although more pronounced using the NATEM technique than with EXTEM or INTEM).[72] Patients considered to be in the TTR (emicizumab concentrations ~50 µg/mL) showed ROTEM parameters equal to PWHA with FVIII levels 12–60 IU/dL. However, there was a large interindividual variation in emicizumab levels and in ROTEM parameters. A recent study using ROTEM confirmed that emicizumab had similar global hemostatic function as PWHA with FVIII levels of 13 IU/dL.[73] Another study using modified clot waveform analysis (CWA) showed the equivalent FVIII activity of ~15 IU/dL of emicizumab during the maintenance phase of treatment.[74]

Using a TG assay, patients on emicizumab had ETP values that were comparable with mild hemophilia patients with FVIII levels between 10 and 40 IU/dL.[75] Again, there was considerable interindividual variation. As ETP responses were related to body weight, one might argue that it could be related to emicizumab plasma levels. Indeed, using CWA, a strong correlation between emicizumab concentrations and hemostatic potential was found.[76] This dose-dependent relation was confirmed by others and suggested a conversion factor of 0.3 relating emicizumab concentration to comparable FVIII activity.[77]

Therefore, we speculate that the hemostatic potential in PWH on emicizumab appears to be in the range of 10–40 IU/dL equivalent FVIII activity and is likely to be dependent on the emicizumab concentration. For SAPT, we consider this well above our suggested minimum hemostatic level. Due to the large

interindividual variation in TG parameters in patients on emicizumab and the lack of standards for both global hemostatic assays and emicizumab level testing, we cannot make recommendations on the safety of emicizumab in PWHA in need for DAPT or oral anticoagulation therapy. Clinical reports on this topic are emerging and they will provide data on the feasibility of antithrombotic therapy in PWHA using emicizumab. In each patient, an individualized approach should be followed, considering the need for anticoagulation (primary prevention or treatment of an acute thromboembolic event) and the bleeding phenotype. Meanwhile, we advocate cautiousness in prescribing high-dose SAPT, combination therapies, and long-term use of antithrombotics in these patients.

To conclude:

- In PWHA using emicizumab (with or without inhibitors), we consider it acceptable to use SAPT.
- There are currently insufficient data to draw conclusions on the safety of DAPT or oral anticoagulation in PWHA using emicizumab; therefore, we suggest not to switch PWHA from FVIII prophylaxis to emicizumab for this purpose.

SECTION 2: ATRIAL FIBRILLATION

A cross-sectional European evaluation showed that AF is as common in PWH as in the general population.[9] From the total of 3952 adult PWH, 33 had AF with a mean age of 69 years (interquartile range, 62–76). Hemophilia was severe in 7 (21%), moderate in 6 (18%), and mild in 20 (61%) patients. The overall AF prevalence was 0.84% and increased with age; 0.42% in patients 40–60 years and 3.4% in patients >60 years. In a multicenter prospective trial in the Netherlands and United Kingdom, the prevalence of AF in 709 PWH aged ≥30 years was 2.3%.[12] In a 5 years follow-up period, 5 PWH experienced an ischemic cerebral event (1 transient ischemic attack [TIA] and 4 strokes) (0.7%); 3 patients had severe hemophilia, 1 moderate, and 1 mild (FVIII 5%). None of these patients had AF. It was stated that the occurrence of cardiovascular events was significantly lower as compared with the general population.

There are multiple retrospective studies that describe the prevalence of ischemic stroke in PWH, but there are no data on ischemic stroke risk in PWH with AF. The ARCHER study described 294 PWH of whom 7 had AF (2.4%); 4 ischemic cerebral events occurred in 294 PWH (1.4%), but no information was given on the presence of AF in these 4 patients.[78] The Atherosclerosis Risk in Communities (ARIC) study described 201 PWH of whom 15 had AF (7.5%) and 4 had a history of TIA or ischemic stroke (2%).[8] Again, the relation between AF and stroke was not given.

Clinical question 8: What tool can be used for ischemic stroke risk assessment in PWH with AF?

In the general population, stroke risk assessment in patients with AF is typically done using the CHA2DS2-VASc score (Suppl. Table S2).[46] The higher the CHA2DS2-VASc score, the higher the annual ischemic stroke risk (Suppl. Table S3).[79,80]

At present, there is little known about stroke risk assessment in PWH. In the European evaluation mentioned above, the median CHA2DS2-VASc score was 1.0 (range, 0–2), predominantly determined by age and hypertension (48% of patients).[9] In the general population with AF, the median CHA2DS2-VASc score is 3.0 (range, 2–4).[81]

A recent report from a French registry describes 18 PWH with AF.[16] The median CHA2DS2-VASc score was 3 (1–7). A case series of 7 PWH undergoing left atrial appendix occlusion (LAAO) shows a median CHA2DS2-VASc score of 3 in these patients (range, 1–6).[82] Another case series describes 9 patients with LAAO, with a median CHA2DS2-VASc score of 3 (range, 3–7).[41] It should be noted that these patients all had an indication for LAAO thus may not represent the average PWH with AF. A small case series in 3 PWH with AF show a CHA2DS2-VASc score of 2 in all 3 patients.[39]

The CHA2DS2-VASc score has not been prospectively evaluated in PWH; therefore, it is unknown whether the risk assessment in PWH is equally accurate in prediction of arterial thromboembolism to the score in the general population. As the CHA2DS2-VASc score is easy to use, well established, and there are no data on other stroke risk assessments in PWH with AF, we advocate its use for individual risk assessment in PWH. Due to the hypocoagulable state of PWH, the actual ischemic stroke risk could be lower than predicted. It can, therefore, be argued to adapt the threshold for starting anticoagulation to compensate for the assumed overestimation of the CHA2DS2-VASc score. In general, we suggest that the sum of the risk score is subordinate to the individual components. For instance, a CHA2DS2-VASc score of 2 in a patient at high risk of bleeding has a different value in the decision-making process if a previous stroke/TIA has occurred or if the patient is >65 years and has hypertension.

Finally, the CHA2DS2-VASc was originally designed to avoid missing patients at risk for stroke/systemic embolism in the general population and therefore brings down the threshold for oral anticoagulation. In a population at high bleeding risk, it is more relevant to initiate treatment in those at high risk of stroke. One could therefore consider the use of the CHADS2 score instead of CHA2DS2-Vasc in PWH, as it is better in identifying patients at high risk for ischemic stroke.

To conclude:

- We suggest use of the CHADS2 score for individual stroke risk assessment as a general guide in PWH, but we cannot recommend specific predictive thresholds. Thus, expert-provided balance of thrombotic and bleeding risk must be taken into consideration for PWH.

Clinical question 9: What tool can be used as bleeding risk assessment in PWH with AF?

In a systematic review of 5 different risk scores in 38 studies, the HAS-BLED score (Suppl. Table S4) had the best evidence predicting bleeding events.[46,83,84]

Bleeding rates according to the HAS-BLED score is depicted in Suppl. Table S5. A recent meta-analysis shows similar C-statistics of this score in patients using VKAs or DOACs.[85]

Data on HAS-BLED scores in PWH are scarce. The French registry reports a median score of 2 (0–4) in 18 PWH with AF.[16] The number of patients who reported bleeding episodes was significantly higher in patients with HAS-BLED score >3 than in those with HAS-BLED score <3 (5/8 patients versus 0/10), OR 33 ([95% CI, 1.43-761.2]; $P = 0.0065$). The median FVIII levels were similar (16.5% versus 19.5%) as well as the proportion of patients on prophylaxis. It was, however, not stated whether the bleeding episodes were in patients on oral anticoagulation or on antiplatelet therapy. Moreover, the definition of major hemorrhage in the COCHE was somewhat different than that from the HAS-BLED score, as major bleeds were considered bleeding episodes that required prohemostatic substitutive treatment, which are common in PWH.

In the European AF study in 33 PWH with AF, the HAS-BLED could not be calculated as no data on liver and renal function, alcohol, and drugs use were available.[9] However, based on the data they gathered on age and hypertension, already 64% had a HAS-BLED score of at least 2 and 36% a score of at least 3. The HAS-BLED score has not been validated in PWH using oral anticoagulants. Therefore, there is no evidence to use the HAS-BLED as a formal tool to guide clinical decision-making in this patient population. It does provide the clinician with a baseline assessment of bleeding risk based on

the nonhemophilia population that can be adopted for individual therapy and shared-decision making. Finally, other risk factors for bleeding should be considered, such as the risk of falling and anemia.

To conclude:

- We consider PWH as being at high risk for bleeding in any bleeding score, regardless of factor level.

Clinical question 10: Is there a place for aspirin in the treatment of AF in PWH?

In the AVERROES trial in patients who have failed or are unsuitable for VKA treatment, apixaban 5 mg b.i.d. (twice a day) significantly reduced the risk of stroke/systemic embolism with no significant difference in major bleeding or ICH compared with aspirin.[86] There were 44 cases of major bleeding (1.4%/year) in the apixaban group and 39 (1.2%/year) in the aspirin group (HR, 1.13 [95% CI, 0.74-1.75]). There were 11 cases of intracranial hemorrhage with apixaban and 13 with aspirin.

A meta-analysis of bleeding outcomes in randomized controlled trials comparing DOACs versus aspirin was performed in 20,000 patients.[87] The overall rate of major bleeding was 1.8% (189 events) in DOAC-assigned patients and 1.3% (129 events) in aspirin-assigned patients (OR, 1.55 [95% CI, 0.99-2.45]). Compared with aspirin, the ORs were 1.12 (95% CI, 0.73-1.73) for apixaban, 1.21 (95% CI, 0.86-1.69) for dabigatran, and 2.64 (95% CI, 1.68-4.16) for rivaroxaban. The findings from this meta-analysis do not support the use of aspirin over DOACs for antithrombotic treatment of AF in the general population.

In the ESC guideline, it is stated that overall, antiplatelet monotherapy is ineffective for stroke prevention and is potentially harmful (especially among elderly AF patients). Hence, antiplatelet therapy should not be used for stroke prevention in AF patients.[46]

There is no comparison of oral anticoagulation versus aspirin in PWH. As described earlier, GIB were more common in PWH using antiplatelet drugs. The available evidence in patients without hemophilia does not support the common notion that aspirin is more safe than oral anticoagulation in patients with AF; there is no evidence to support or refute this evidence in PWH.

To conclude:

- In PWH with AF, we recommend against the use of aspirin over oral anticoagulation.

Clinical question 11: What is the role for alternative strategies in PWH with AF, such as left atrial appendix closure or pulmonary vein isolation?

The risk of ischemic stroke in the general population is usually estimated by the CHA2DS2-Vasc score, which, however, has been questioned in PWH.[9] Data from the COCHE study reveal that the bleeding risk in PWH with AF taking any form of anticoagulation is higher than in control PWH[16] and this risk could be even increased with long-term anticoagulation. Catheter ablation using a femoral vein approach has been used for symptomatic arrhythmia control and it has proved similarly effective as anticoagulation in preventing long-term thromboembolic events with less risk of major bleeding in patients considered at high risk of bleeding (HAS-BLED ≥ 3).[88] This of course would be an attractive option to manage symptomatic AF in PWH. In a case series, 5 PWH were treated with this approach, with good long-term results and 1 patient only relapsing after 42 months.[40] The incidence of groin bleeds was, however, increased compared with that of general population. Usually, anticoagulation for 4 weeks before the procedure has been advised for those having factor levels >20 IU/dL.

Left atrial appendage occlusion (LAAO) has recently been proposed as an alternative for long-term management of AF. The LAA is the main site of clot formation in patients with AF and a potential source of cardiac arrhythmia; furthermore, it contributes to regulating intravascular volume status and hemodynamic conditions. In randomized trials, this approach had similar efficacy as VKAs in preventing stroke with a trend for lower bleeding rates and AF recurrences on long-term follow-up.[89] The Left Atrial Appendage Ligation and Ablation for Persistent Atrial Fibrillation (LAALA-AF) registry study showed that, at 1-year follow-up after 1 ablation procedure and off antiarrhythmic therapy, 65% (P = 0.002) of patients who had LAAO with a LARIAT device and ablation were free from AF compared with 39% of those undergoing ablation only (P = 0.002).[90] Recently, there have been a series of case reports describing the experience with LAAO in PWH.[41,82,91–94] Overall, there were very few minor periprocedural bleeding events, with excellent clinical results. Some patients, however, had FVIII levels <20 IU/dL. In the largest series,[82] 7 PWHA underwent LAAO after multidisciplinary discussion either with Watchman or Amulated implanted device. Four had basal FVIII levels ≥20 IU/dL, one 14, one 4, and one <1 IU/dL. Various anticoagulation regimes were adopted before the procedure. Periprocedural treatment targeted a FVIII level of 100 IU/dL. Minor bleeding occurred in almost all patients and SAPT with aspirin after the procedure ranged from 5 months to indefinite, in the latter case because of current coronary disease and prior percutaneous cardiac intervention (PCI). In 2 of them, clopidogrel was also added for 1 and 3 months. No stroke or systemic embolism occurred during follow-up. A single patient had GIB while on aspirin. The implantation procedure could be complicated and it is not clear how long these patients should use antiplatelet and/or anticoagulation treatment after the procedure. In another study, 2 additional patients while on clopidogrel after the procedure had bleeding complications.[41] There are no comparative studies addressing the role of LAAO over anticoagulation in PWH and AF. Patients with high risk of bleeding because of more severe bleeding phenotype or presence of comorbidities (eg, treated hypertension, significant cardiovascular or coronary disease) could probably be carefully considered for the procedure. Accurate prophylaxis is anyway needed after the procedure, also to allow antiplatelet treatment.

To conclude:

- We consider LAAO a feasible option in PWH not eligible to long-term anticoagulant treatment for AF. However, accurate selection of eligible patients should consider the risk of bleeding during follow-up and temporary adapted prophylaxis is warranted if the baseline factor level is <20 IU/dL

SECTION 3: ACUTE AND CHRONIC CORONARY SYNDROMES

ACS include unstable angina, ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation myocardial infarction (NSTEMI). STEMI requires acute intervention with a PCI started as soon as possible and preferably <12 hours after symptom onset or systemic thrombolysis to immediately restore flow in the occluded coronary artery.[95] An NSTEMI is usually treated with DAPT and parenteral anticoagulation until PCI is done, usually within 24–72 hours. According to the 2020 ESC guidelines for NSTEMI, PCI is performed through radial arterial access, antiplatelet and/or coagulation therapy is administered, and the culprit lesion is being treated with new-generation drug-eluting stents (DES).[96] Chronic coronary syndromes refer to the presence of known coronary heart disease, its biological and clinical evolution, when symptoms and signs of ACS are not present.[97]

Several case reports and case series have been published on this topic in PWH.[28,39,98,99] A review of published cases was reported

Table 4

Antithrombotic Treatment in PWH With Chronic and Acute Coronary Syndrome With Indication to Conservative or Invasive (PCI) Treatment

Condition	Recommendation	Hemostatic Therapy
Chronic coronary syndrome	Low-dose aspirin (75–100 mg OD) or clopidogrel 75 mg OD if aspirin is not tolerated	CFC to maintain FVIII/FIX trough levels >1–5 IU/dL
UA/NSTEMI/STEMI (>12 h) where a conservative treatment is indicated	- UFH or bivalirudin (dose and duration according to the guidelines) - DAPT: clopidogrel + aspirin for 4 wk (dose according to the guidelines) - SAPT: aspirin 75–100 mg OD long-term	CFC to maintain trough FVIII/FIX levels >20 IU/dL for as long as antithrombotic drug is given[a]; trough levels >20 IU/dL for 4 wk (during DAPT) followed by >1–5 IU/dL long-term (during SAPT)
UA/STEMI or NSTEMI where PCI is indicated as primary management strategy	- UFH or bivalirudin periprocedural (dose according to the guidelines) - DAPT: clopidogrel + aspirin for 4 wk (dose according to the guidelines) - SAPT: aspirin 75–100 mg OD long-term	CFC to reach FVIII/FIX peak level of 80–100 IU/dL before PCI and maintain >50 IU/dL for 24–48 h; trough levels >20 IU/dL for 4 wk (during DAPT) followed by >1–5 IU/dL long-term (during SAPT)

[a]There is no consensus on duration of UFH in this patient category and it ranges from 1 to 5 days (most patients will proceed to PCI).

ACS = acute coronary syndrome; OD = once daily; CFC = clotting factor concentrate; UA = unstable angina; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; h = hours; UFH = unfractionated heparin; DAPT = dual antiplatelet therapy; SAPT = single-antiplatelet therapy; PCI = percutaneous coronary intervention.

in 2018 with publications rates ranging from 1968 to 2013.[100] In total, 54 PWH were described undergoing a coronary angiography, in whom 38 PCI procedures were performed. In 3 patients, a periprocedural bleeding was reported, of whom 2 had a femoral access site hemorrhage. A total of 33 stents were placed (31 bare metal stents [BMS] and 2 DES). In 28 patients, DAPT was used, for whom 21 received additional clotting factor prophylaxis during DAPT. In 11 patients (20%), a bleeding episode occurred during follow-up, most of them were minor bleeds. Two major bleeds were documented, both during monotherapy with aspirin: 1 tongue bleed after a tongue bite and 1 with a GIB. Another 4 cases were reported in PWH (2 moderate and 2 severe) undergoing PCI between 2010 and 2016.[39] All received periprocedural clotting factor supplementation with target levels >80 IU/dL, 1 BMS and 3 DES were placed, and DAPT with aspirin and clopidogrel was given for 1–3 months. All patients received additional CFCs during DAPT. No bleeding complications occurred.

In the following clinical questions, we will specify our recommendations on antithrombotic therapy, stent type, and PCI in PWH (Table 4).

Clinical question 12: Can systemic thrombolysis be given in PWH?

In general, primary PCI has been shown to be superior to thrombolytic therapy in ACS.[95] Fibrinolytic therapy is recommended only in cases in which primary PCI is not immediately available and the delay from hospital presentation to PCI is anticipated to be >120 minutes. In patients taking oral anticoagulation, the use of thrombolysis is, in general, not recommended.[101] Although there are no data to support this, we consider systemic thrombolysis to be relatively contraindicated in all PWH. If primary PCI is not available, we recommend transfer of the patient to a PCI center as soon as possible. If this is not possible and fibrinolysis is considered as the only option, this can only be performed after full correction of FVIII/FIX and careful monitoring of hemostatic parameters and bleeding phenotype. In this, we make no distinction between systemic or local fibrinolysis.

To conclude:

- We consider systemic thrombolysis to be relatively contraindicated in all PWH.

Clinical question 13: Is there an indication for pretreatment with antiplatelet therapy in PWH with ACS before invasive (PCI) treatment?

During an acute myocardial infarction, antiplatelet therapy is the cornerstone of treatment. Pretreatment with an antiplatelet therapy (usually P2Y12 receptor inhibition) before cardiac intervention in NSTEMI seems attractive, but this was not associated with improved ischemic outcomes in nonhemophilia patients and instead, with a significantly increased risk of bleeding. Therefore, the ESC does not recommend to administer routine pretreatment with a P2Y12 receptor inhibitor in NSTEMI patients in whom coronary anatomy is not known and an early invasive management is planned.[96] Likewise, in nonhemophilia patients with STEMI, pretreatment with a P2Y12 inhibitor did not improve clinical outcomes.[102]

To conclude:

- We do not recommend pretreatment with a P2Y12 receptor inhibitor in PWH with an ACS if an early invasive management is planned.

Clinical question 14: Is there an indication for clotting factor replacement in PWH before cardiac intervention?

In an earlier section, we described the rationale behind "natural anticoagulation" of PWH, which could be extended to consideration of the pericardiac intervention period. Indeed, one may consider that PWH with factor levels <20 IU/dL may not need anticoagulation with heparin or bivalirudin. However, arterial punctures can be complicated by pseudo-aneurysm formation in PWH.[103] Therefore, a bolus infusion of CFC is recommended before arterial puncture for cardiac interventional procedures. We suggest to aim for a peak factor activity level of ~80–100 IU/dL and to maintain a trough level >50 IUI/dL for 24–48 hours (Table 4), where peak levels >150 IU/dL should be avoided. As bleeding risk using a femoral approach is larger than the radial approach,[104] we recommend radial access in all PWH undergoing a PCI.

In PWHA using emicizumab, we discussed the patient's hemostatic potential in clinical question 7. In general, we consider the FVIII mimicking activity to be inadequate for PCI and therefore recommend additional FVIII replacement. There is 1 case report on a patient with acquired hemophilia A who underwent successful PCI with bivalirudin, a DES and DAPT (aspirin and clopidogrel) while on emicizumab.[105] However, the arterial access route was not reported. There are no reports of patients with congenital hemophilia on emicizumab treated with PCI. In PWH with inhibitors, additional supplementation with bypassing agents is indicated. In inhibitor patients using emicizumab, we recommend rFVIIa at a dosage of 90 µg/kg every 3–4 hours for 24–48 hours, but do not recommend the use of activated PCC (aPCC). In inhibitor patients not using emicizumab, bolus infusions with aPCC 50–80 IU/kg every 12 hours are an alternative. In all cases, the use of full dose anticoagulation should be limited to the shortest period possible and close monitoring for bleeding complications is in place.

During cardiac interventions, additional antithrombotic medication might be administered as described in the section below. Most commonly, a single infusion of unfractionated heparin (UFH) or a continuous infusion for maximum of 4 hours after

the procedure with bivalirudin is used. This window can be covered by the initial bolus infusion of FVIII/FIX that is given for arterial access. We recommend additional clotting factor infusions depending on the procedure (Table 4).

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 (12–24 h).

To conclude:

- In PWH undergoing a cardiac intervention, we recommend clotting factor supplementation with a target FVIII/FIX peak level of 80–100 IU/dL before the procedure. We recommend additional bolus infusions to maintain trough levels according to the procedure (see Table 4).
- We recommend radial artery access over femoral in cardiac interventions.
- In PWHA on emicizumab without inhibitors undergoing a cardiac intervention, we recommend additional FVIII supplementation as in PWH without emicizumab.
- In PWHA on emicizumab with inhibitors undergoing a cardiac intervention, we recommend supplementation with rFVIIa, but do not recommend the use of aPCC.

Clinical question 15: Which anticoagulant is preferred in PWH before and during PCI?

Currently, there are 3 antithrombotic agents that have been studied in PCI. These are UFH, bivalirudin, and enoxaparin without evidence for superiority of one over the other.[95,96] Fondaparinux is no longer recommended as the sole anticoagulant used in PCI due to a higher associated incidence of guiding-catheter thrombosis.[95] UFH and bivalirudin have shorter half-lives as compared with enoxaparin, which make them a more desirable anticoagulant for PWH undergoing PCI. The 2017 ESC guideline mentions that bivalirudin should be considered in STEMI, especially in patients at high bleeding.[106] However, the 2020 ESC guideline on NSTEMI indicates that a significant association between bivalirudin and decreased risk of bleeding was only found with unbalanced use of GP IIb/IIIa inhibitors in conjunction with UFH.[96]

To conclude:

- In PWH with ACS where PCI is indicated, we recommend using UFH or bivalirudin over enoxaparin given their shorter half-lives.
- We recommend the use of UFH or bivalirudin only after replacement of clotting factor levels.

Clinical question 16: Is there a formal bleeding risk assessment tool for bleeds in PWH with ACS?

In the general population, the CRUSADE and ACUITY bleeding scores have been developed in NSTEMI. Overall, the 2 scores have reasonable predictive value for major bleeding in ACS patients undergoing coronary angiography, with CRUSADE being the most discriminatory.[96] The CRUSADE includes heart rate, systemic blood pressure, gender, hematocrit, creatinine clearance, and history of cardiovascular disease or diabetes.

Presently there is no formal bleeding risk assessment tool for PWH. More recently, the Academic Research Consortium for High Bleeding Risk tool was developed. This scoring system has been used in clinical trials to provide consistency in evaluating safety and effectiveness of drugs and devices in patients undergoing PCI. Patients are considered at high risk for bleeding when at least 1 major criterion has been met; as chronic bleeding diathesis is one of those major criteria, PWH can be considered as having high bleeding risk.

To conclude:

- We consider all PWH at higher risk for bleeding and therefore recommend that they should be treated as such according to the existing guidelines. We recommend that the severity of hemophilia and the individual bleeding risk are guiding the clinician, not a formal score.

Clinical question 17: What type of stent is preferred in PWH with ASC?

Earlier studies comparing outcomes with first-generation DES and BMS reported an increase in late stent thrombosis and increased mortality rate with DES. To prevent late stent thrombosis, the earlier DES needed longer and intensive DAPT to prevent restenosis. That is why in the past, it was suggested to prefer BMS over DES in PWH, to reduce the time for DAPT.[26,27,33]

New generation DES have overcome these problems and have higher efficacy and safety and lower restenosis rates than both first-generation DES and BMS.[95] This also implied that shorter duration (4 weeks) of DAPT could be given in patients at high risk for bleeding.[107]

To conclude:

- We recommend a newer generation DES as these allow the shortest DAPT time without an increase in the risk of stent thrombosis.

Clinical question 18: What DAPT regimen is preferred in PWH?

Clopidogrel is considered a weaker P2Y12 receptor agonist than prasugrel or ticagrelor. It also has the more favorable safety profile in terms of bleeding risk. The ESC guidelines recommend treating patients with a high bleeding risk with clopidogrel over the other P2Y12 receptor agonists.[96] For minimum suggested FVIII/IX levels in this context, please refer to clinical question 2.

Both in the STEMI and NSTEMI guidelines, the duration of DAPT has been highlighted by a summary of clinical trials in ~30,000 patients. Shorter (1–3 mo) duration of DAPT followed by monotherapy with a P2Y12 receptor agonist after DAPT was favored over longer duration, due to lesser bleeding events without increasing thrombotic risk. In patients with high risk of bleeding, the shorter DAPT duration is recommended.[96]

In PWHA with inhibitors using emicizumab in a strong need for DAPT, we consider an individual approach, a short DAPT duration (maximum 4 wk), but only with careful monitoring of the bleeding phenotype. In the rare event of a PWHA with inhibitors not using emicizumab, we do not recommend the use of DAPT.

To conclude:

- We recommend the use of clopidogrel over ticagrelor or prasugrel in PWH in need for DAPT due to its lower bleeding risk.
- We recommend short duration of DAPT (1 mo) after newer generation DES placement followed by long-term monotherapy with clopidogrel or aspirin.
- In inhibitor patients, we consider an individual approach depending on the use of emicizumab and other risk factors for bleeding.

SECTION 4: HEART VALVES

Clinical question 19: How to manage valve replacement in PWH?

It is beyond the scope of this guidance document to describe in detail all treatment modalities for aortic and mitral valve repair. In general, there are 2 types of heart valves: mechanical and biologic. Both have risks and benefits, which may vary with the age of implantation. The choice of prosthesis (mechanical valve versus bioprosthesis) is important in valve disease. The major problems with mechanical valves are the risks of thromboembolism and bleeding from chronic anticoagulation; these are 4.4% per year and 8.5% per year, respectively, in the nonhemophilia population.[108] This bleeding is 3- to 5-fold in patients

with a history of bleeding. The problem with bioprosthesis is its limited durability due to valve degeneration, but it has the major advantage of the lack for long-term anticoagulation.

The few case reports that are available describe the use of prosthetic valves in PWH.[109–113] Tang et al describe 3 PWH undergoing aortic valve replacement (all bioprostheses) and 1 mitral valve reconstruction.[109] Patients received thromboprophylaxis using LMWH 1–2 times 5000 IU/d for 1–3 months, during which clotting factor levels were kept >50 IU/dL. A PWHB (FIX 14 IU/dL) underwent replacement of both the mitral and aortic valve by mechanical valves.[110] His FIX was supplemented until day 11 postoperatively. He was discharged with low-dose acenocoumarol (INR 1.5–2.0) and was followed uneventfully for 9 months. Another PWHA (FVIII 7 IU/dL) underwent successful replacement of his aortic valve by a mechanical valve. He was treated with warfarin (INR 2–2.5) without complications.[111] A patient with mild hemophilia (FVIII 19 IU/dL) underwent a successful mitral valve annuloplasty. He received VKA for 1 month with FVIII supplementation (trough level >70 IU/dL), after which VKA was switched to aspirin without further FVIII prophylaxis.[112]

In patients that are unable to receive a bioprosthetic valve, the use of the mechanical On-X valve might be considered, which requires a less intense anticoagulation after 3 months of insertion.[114]

To conclude:

- We recommend bioprosthetic valves over mechanical valves to avoid life-long anticoagulation in PWH.
- Anticoagulation postoperatively is variable and can be given, observing the suggested minimum trough factor levels as described earlier (in general, we recommend FVIII/IX levels >20 IU/dL).

SECTION 5: VENOUS THROMBOEMBOLISM

Clinical question 20: Is routine thromboprophylaxis needed in PWH undergoing surgery or who are medically ill?

VTE and PE are critical postoperative complications following major orthopedic surgery, particularly total knee replacement (TKR) or total hip replacement (THR). In the general population, the cumulative rate of symptomatic VTE up to 35 days is estimated to be 4.3% without VTE prophylaxis. The subclinical and asymptomatic VTE rate identified by imaging techniques is much higher reaching 40% to 60% when bilateral phlebography is used. The incidence of VTE in THR appears to be slightly higher than TKR. The cumulative risk of VTE lasted for up to 3 months after hip surgery and 1 month after total knee replacement.

The published literature suggests that VTE is an uncommon event in PWH, including those with acquired thrombophilia.[115–117] Most of the events described in this population are related to additional risk factors, such as surgical procedures and substitutive treatment-related complications.[118] Before introducing emicizumab prophylaxis in clinical practice, an expert panel analyzed the rates of venous and arterial thrombotic events associated with CFCs. The VTE rate was low, the adverse event rate per treated patient was 0.05% and 1.5% for hemophilia A and B, respectively, after analysis of 5168 patients from a total of 50 studies. There were no arterial or venous thrombotic events, all of which were thrombophlebitis.[119] The estimated risk of symptomatic VTE in PWH who undergo arthroplasty without pharmacological thromboprophylaxis is 0.5%. The incidence of subclinical deep vein thrombosis (DVT) detected by routine Doppler ultrasound has also been found to be very low, ranging from 0% to 10%.[120] More recently, contrast-enhanced computed tomography (CT) has seen DVT in 18% of hemophilia A patients undergoing TKA surgery, despite not being detected by ultrasound.[121]

There is still controversy whether thromboprophylaxis is indicated in PWH undergoing surgery. As described earlier, PWH have some form of "natural anticoagulation" and the VTE events are extremely low. FVIII levels are normalized during surgery, with the administration of exogenous FVIII being adequate for hemostasis but lower than in nonhemophilic patients. As is known, FVIII is an acute phase reactant in patients without hemophilia; however, in PWH plasma levels are monitored to avoid an excessive increase over prolonged periods.[33,122] This phenomenon does not occur in hemophilia B patients. In fact, unlike factor IX levels, which are monitored and adjusted, postoperative FVIII can reach very high levels in hemophilia B patients. Whether these patients are at increased risk of VTE is unknown and it is more likely that thromboprophylaxis is warranted in PWHB.

The classical complication resulting from surgery in PWH has been hemorrhagic events.[120,123–125] Bleeding in the prosthetic joint, including microbleeds, can be a source of infection, as a significant relationship between bleeding and infection has been observed.[126,127] Essential factors play a role in the complex interplay between coagulopathy, intensive replacement therapy, bleeding, thrombosis, and thromboprophylaxis.[126]

Thus, recently, the WFH guidelines for managing hemophilia recommend against routine pharmacologic thromboprophylaxis in major surgery.[128] These guidelines recommend to assess the individual risk of VTE during surgical procedures that carry a high risk of developing VTE. The WFH guidelines recommend considering the use of mechanical methods for thromboprophylaxis for PWH undergoing surgery associated with a high risk of VTE and bleeding complications. In contrast to pharmacological thromboprophylaxis, mechanical methods of thromboprophylaxis are not associated with the risk of bleeding complications.[128] Nevertheless, for PWH in whom the balance of the risk of bleeding compared with the risk of developing VTE favors pharmacological thromboprophylaxis, the WFH recommends the same practice as that applied in the general population, provided that adequate replacement therapy is administered. We recommend an individual assessment in every PWH having a surgical intervention, recognizing personal and surgery-related VTE risks. We do not make a difference between clotting factor correction with bolus infusions or continuous infusion.

We did not find any evidence in the literature for thromboprophylaxis in the medically ill PWH. In most cases, these patients will not receive intensive clotting factor supplementation and the thrombotic risk is less than in the context of surgery. Therefore, we do not recommend routine pharmacological thromboprophylaxis in these patients. However, there is one guidance document on COVID-19-associated coagulopathy in PWH.[39] There, a trough FVIII/FIX level of 30 IU/dL is recommended to allow for pharmacological thromboprophylaxis. In light of our considerations mentioned in section 1, where we consider a level of 20 IU/dL for full dose anticoagulation and consider PWH with lower levels as being naturally anticoagulated, we do not support this recommendation.

To conclude:

- Considering the low prevalence of postoperative VTE in PWH and the potential chance of bleeding complications, we do not recommend the use of routine pharmacological thromboprophylaxis in the perioperative period.
- We recommend an individual approach in surgery with high VTE risk.
- We recommend against extended duration of pharmacological thromboprophylaxis.
- We do not recommend routine pharmacological thromboprophylaxis in PWH that are medically ill.
- We recommend mechanical over pharmacological thromboprophylaxis, if indicated.

Clinical question 21: Is the recommendation for routine thromboprophylaxis in PWH different according to the hemostatic product that is used (bypassing agents/emicizumab)?

Although emicizumab prophylaxis has demonstrated hemostatic efficacy, patients may require concomitant administration of a bypassing agent or FVIII clotting factor replacement to prevent bleeding in the perioperative period.[129]

The occurrence of thrombotic events and thrombotic microangiopathy (TMA) following aPCC administration in adult PWHA and inhibitors on emicizumab prompted several recommendations for managing patients with inhibitors on emicizumab prophylaxis in favor of rFVIIa.[130,131] In surgical and emergency settings, low doses of aPCC may be considered to manage cases of patients who do not respond to first-line treatment with rFVIIa. However, in PWHA without inhibitors, the rate of thrombotic events (including TMA) in association with emicizumab and FVIII is negligible,[132] because the combination of emicizumab and FVIII does not appear to enhance hemostatic activity.[133]

Recently, an overview of surgical procedures from the HAVEN 1–4 trials has been reported.[134] In this overview, thromboprophylaxis was not mentioned. No thrombotic events occurred, but bleeding was observed in 14% and 20% of minor and major procedures, respectively. Similar results were shown in a smaller single-center overview[135] and there are other reports, mainly on minor surgeries in patients on emicizumab.[136,137] In all these reports, no mention of thromboprophylaxis is available. It appears that the bleeding risk is dominant over the thrombotic risk in PWHA and emicizumab. Recently, 75 surgeries in 28 PWHA using emicizumab were reported from a single center.[138] No thromboprophylaxis was given in the 21 major surgeries in PWHA with inhibitors, without observing VTE.

For the medically ill there is no literature, but in line with our earlier recommendations, we suggest not to use routine pharmacological thromboprophylaxis in PWH using emicizumab. However, the clotting potential in PWH using emicizumab is sufficient to start pharmacological thromboprophylaxis on an individual case-by-case basis.

To conclude:

- We do not consider the routine use of pharmacological thromboprophylaxis as necessary for surgical or medically ill PWH using emicizumab or bypassing agents.

Clinical question 22: What is the management of an acute venous thromboembolic event in PWH?

The occurrence of an acute VTE in PWH is a rare event. Almost all reported events are provoked VTE due to catheter insertion, clotting factor supplementation with or without surgery, or the use of nonfactor replacement therapies.[139] As the occurrence of acute VTE in PWH is very heterogeneous, a simple recommendation is not feasible. In most cases, removal of the catheter or cessation of the procoagulant therapy will be sufficient and no additional antithrombotic therapy is needed in patients with severe hemophilia. When anticoagulation therapy is deemed necessary, we suggest a shorter course (eg, 6 wk), while maintaining trough factor levels of >20 IU/dL. However, this may be different in patients with mild hemophilia with higher basal factor levels and, therefore, care should be individualized.

CHAPTER 6: ACUTE NEUROLOGY

Clinical question 23: What is the optimal antithrombotic management of transient ischemic attack in PWH?

A TIA has traditionally been defined as a sudden, focal, neurological deficit of presumed vascular origin lasting <24 hours. Because many patients with symptoms lasting shorter than 24 hours have an associated ischemic brain lesion on imaging, American guidelines define a TIA as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of infarction by pathology or imaging.[140] Fortunately, the difference in definition has no major impact on the antithrombotic management, although ischemic lesions seen on diffusion-weighted magnetic resonance imaging (MRI) are associated with an increased risk of recurrent TIA and ischemic stroke.

In a recent study of patients with minor ischemic stroke or TIA in the general population, the overall risk of stroke, ACS, or death from cardiovascular causes within the first year who were evaluated and treated by stroke specialists was 6.2% and the risk of stroke alone was 5.1%.[141] Risk prediction can be refined using the ABCD^2 score, composed of demographic and clinical parameters[142] (Suppl. Table S6). In the study mentioned above, patients with an ABCD^2 score of 0–3 had a risk of stroke of 3.2% at 1 year as compared with 7.6% in patients with a score of 6 or 7.[141] However, the recent ESO guideline does not advocate its use for clinical decision-making because of its limited ability to reliably identify patients who are truly at low risk of recurrence.[143]

In patients with TIA or ischemic stroke in the general population, aspirin reduces the risk of (recurrent) stroke by 13%.[144] Meta-analysis of RCTs in patients with noncardioembolic high-risk TIA or minor ischemic stroke showed that as compared with aspirin alone, DAPT with clopidogrel and aspirin reduced the risk of ischemic stroke at 90 days (RR, 0.70) but was associated with a trend toward a greater risk of hemorrhagic stroke.[143] The benefit of DAPT was confined to the first 21 days.[145] As compared with aspirin alone, DAPT with ticagrelor and aspirin reduced the risk of ischemic stroke at 30 days (RR, 0.79) but increased the risk of intracranial hemorrhage (HR, 3.3).

The ESO guidelines recommend 21 days of DAPT (aspirin and clopidogrel) followed by SAPT thereafter in people with noncardioembolic minor ischemic stroke (NIHSS score ≤3) or high-risk TIA (ABCD^2 score ≥4) in the past 24 hours. There is no comparative trial on this topic in PWH. Aligned with previous recommendations, we suggest using SAPT in PWH with noncardioembolic TIA and factor levels <20 IU/dL, regardless of the ABCD^2 risk score (Figure 1). DAPT (aspirin and clopidogrel) for the first 21 days after TIA can be considered for PWH with factor levels >20 IU/dL and a high-risk noncardioembolic TIA. For cardioembolic TIA, oral anticoagulation is indicated as described in earlier sections.

To conclude:

- In PWH with a noncardioembolic TIA and factor levels <20 IU/dL, we recommend starting aspirin.
- In patients with severe hemophilia with a noncardioembolic TIA without clotting factor prophylaxis (FVIII/FIX <1 IU/dL), we do not recommend the use of antithrombotic medication.
- In PWH with a noncardioembolic TIA and factor levels >20 IU/dL, we recommend starting aspirin. In patients with high-risk noncardioembolic TIA, DAPT with aspirin and clopidogrel may be considered for a maximum of 21 days after the TIA, followed by long-term aspirin.
- We do not recommend the use of starting or adapting clotting factor prophylaxis merely to be able to start DAPT in the setting of a TIA.

Clinical question 24: What is the antithrombotic management of acute ischemic stroke in PWH?

Patients in the general population who have acute ischemic stroke and who fulfill specific eligibility criteria should be treated with intravenous thrombolysis with alteplase if this

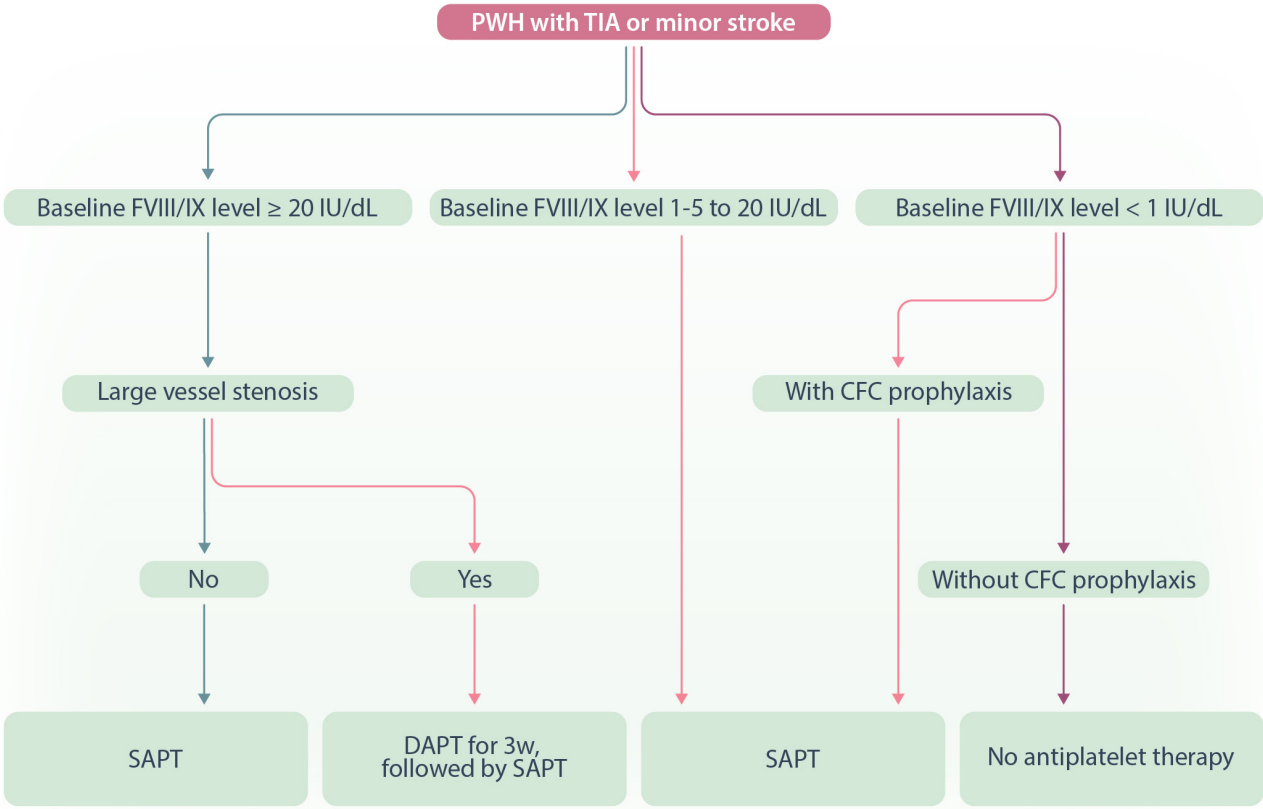

Figure 1. Anticoagulation management of patients with hemophilia having a transient ischemic attack or minor stroke. PWH = patient with hemophilia; CFC = clotting factor concentrate; SAPT = single-antiplatelet therapy; DAPT = dual antiplatelet therapy.

can be started within 4.5 hours of stroke onset. Treatment may be started up to 9 hours of stroke onset in selected patients in whom CT or MRI shows evidence of substantial salvageable tissue (ie, core/perfusion or clinical/perfusion mismatch) and if endovascular thrombectomy is not planned. The use of antiplatelet medication or anticoagulants is contraindicated in the first 24 hours after intravenous thrombolysis.[146,147] In patients with noncardioembolic ischemic stroke, SAPT may be started thereafter. For patients with cardioembolic stroke associated with AF, oral anticoagulation is indicated as described in earlier sections.

Intravenous thrombolysis is contraindicated in patients taking VKAs who have an INR >1.7 or in whom the results of coagulation testing are unknown.[146,147] The safety and efficacy of intravenous alteplase in PWH who have ischemic stroke are unknown. Because of the considerable theoretical risk of intracranial hemorrhage and lack of any safety data, we argue against the use of intravenous thrombolysis in PWH who have acute ischemic stroke. In addition, in many cases of severe ischemic stroke, endovascular thrombectomy appears a safer alternative.

In patients with minor noncardioembolic ischemic stroke who are not treated with intravenous thrombolysis, the antithrombotic management is similar to that in patients with TIA.[143,147,148] "Minor" has been defined as having a score on the NIHSS score ≤3. In patients with more severe noncardioembolic ischemic stroke who are not treated with intravenous thrombolysis, SAPT is recommended unless there is a compelling reason (eg, recently symptomatic extracranial or intracranial stenosis).[147]

Mechanical thrombectomy (MT) is now the established first-line therapy together with thrombolysis, in selected patients with acute ischemic stroke and anterior circulation large vessel occlusion.[149] Although ~25% of all strokes are large vessels occlusions, only a fraction of these patients would likely be eligible for thrombectomy, based on the current guidelines.[150] In practice, ~10% of all stroke admissions are eligible for endovascular thrombectomy.[151] For clotting factor correction, we suggest using the same thresholds as for cardiac intervention, with a target clotting factor level of 80–100 IU/dL and maintaining levels >50 IU/dL for 24–48 hours.

Figure 2 depicts our recommended treatment flowchart for PWH with stroke.

To conclude:

- In PWH with acute ischemic stroke, we do not recommend intravenous thrombolysis.
- In anterior circulation ischemic stroke due to large vessel occlusion, fulfilling established eligibility criteria, we consider mechanical thrombectomy to be appropriate in PWH.
- In PWH with acute minor ischemic stroke (NIHSS score ≤3), we recommend similar treatment to PWH and TIA.
- In PWH with acute, nonminor, ischemic stroke (NIHSS score >3), we recommend starting aspirin.

CLOSING REMARKS

Although cardiovascular disease in PWH has been a subject faced by many clinicians and studied by researchers over the last decade, still there is little scientific evidence on the optimal management approach. In this clinical practice guidance document, we have provided evidence and expert-opinion-based recommendations on how to handle antithrombotic therapy in PWH. The need for antithrombotic therapy in PWH should be individually balanced and holistically approached (ie, taking into account more than just clotting factor activity levels). Furthermore, the clinical indication for antithrombotic therapy will have a major impact on patient management.

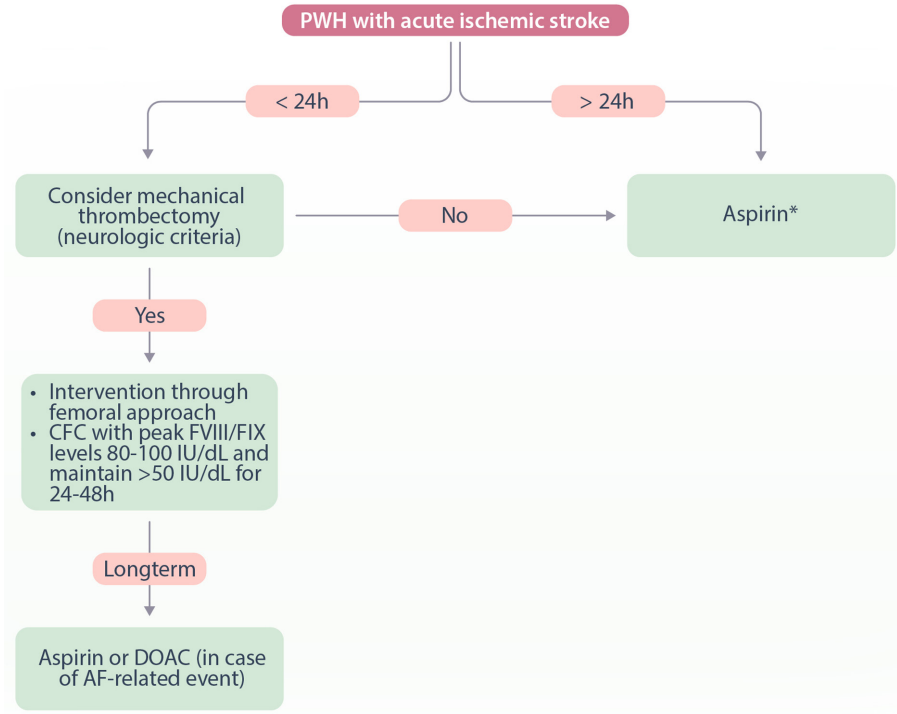

Figure 2. Anticoagulation management of patients with hemophilia having an acute ischemic stroke. *Typically, a loading dose of 300 mg, followed by daily 80–100 mg is used. CFC = clotting factor concentrate; DOAC = direct oral anticoagulant; AF = atrial fibrillation.

Therefore, recommendations should always be adapted according to the individual patient variables and the clinical context.

As the field of hemophilia treatment is changing rapidly with the availability of new generation therapeutic agents, including ultra-long acting FVIII products, nonfactor replacements, and gene therapy, our current recommendations likely will require future adaptation. Furthermore, it is also clear that many data on this topic stems from PWHA and that future research is urgently required for those with hemophilia B.

There remains a large gap in knowledge due to the lack of availability of a large prospective international dataset on the effectiveness and safety of antithrombotic therapies in PWH. Thus, future research is necessary to properly inform future care, and as such we recommend an international multicenter prospective registry in PWH receiving antithrombotic therapy for a wide range of clinical indications. The goal of this guidance document was to provide streamlined recommendations to facilitate a sound approach based on the best available evidence and international expert consensus to these vulnerable patients and highlight the need for international collaboration.

Summary of Recommendations

Section 1: General Considerations

What is the FVIII/FIX threshold to safely start aspirin or oral anticoagulation in patients with hemophilia (PWH)?

- We do not recommend the use of any form of antithrombotic therapy (including single-antiplatelet therapy [SAPT]) in patients with severe hemophilia without clotting factor prophylaxis.
- We do not recommend the use of any form of antithrombotic therapy (including SAPT) in PWH with inhibitors (severe and nonsevere hemophilia) not using emicizumab.
- We recommend a minimum trough FVIII/IX level of 1–5 IU/dL for 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 (vitamin K antagonist [VKA] with international normalized ratio [INR] levels 2–3 or full dose direct oral anticoagulant [DOAC]).
- We recommend a minimum trough FVIII/IX level of 80 IU/dL for triple therapy (oral anticoagulation and DAPT).
- We recommend to apply the lowest factor level measured in case of discrepancy between 1-stage or chromogenic assays.

What is the bleeding risk in PWH using antiplatelet or oral anticoagulant therapy?

- The use of antiplatelet therapy increases the risk of gastrointestinal bleeding complications; thus, we recommend the use of empiric proton pump inhibition in all PWH on antiplatelet therapy.
- We recommend to actively manage anemia in association with antithrombotic treatment.

Should clotting factor prophylaxis be adapted in PWH in need for anticoagulation therapy?

- For PWH with baseline clotting factor levels >20 IU/dL in need for any form of antithrombotic therapy, we recommend to start antithrombotic therapy and not to start additional clotting factor prophylaxis. Careful monitoring for bleeding is recommended.
- For PWH with baseline clotting factor levels <20 IU/dL with an indication for long-term prevention of thrombotic complications with oral anticoagulation (VKA or DOAC), we recommend not to start with oral anticoagulation therapy. Instead, PWH should be considered as being naturally anticoagulated when clotting factors are <20 IU/dL.

- For patients with severe hemophilia using clotting factor prophylaxis in whom long-term oral anticoagulation therapy is considered, we recommend adapting clotting factor prophylaxis to maximum peak levels of 25 IU/dL and not to start additional anticoagulation therapy. This means a more frequent lower dose rather than once weekly higher dose clotting factor prophylaxis.
- For patients with severe hemophilia with an indication for long-term prevention of thrombotic complications with SAPT (aspirin or clopidogrel), we recommend to start SAPT and maintain FVIII/FIX trough levels >1 IU/dL using regular clotting factor prophylaxis. In patients with severe hemophilia with on demand clotting factor supplementation, we recommend to switch to regular prophylaxis and SAPT.
- For patients with severe hemophilia in need of short-term DAPT or oral anticoagulation, we recommend adapting clotting factor prophylaxis to maintain a factor trough level of ≥20 IU/dL.
- For patients with nonsevere hemophilia with baseline clotting factor levels <20 IU/dL with a very high thrombotic risk in need of (short-term) DAPT or oral anticoagulation, we recommend adapting clotting factor prophylaxis to maintain a factor trough level of ≥20 IU/dL for as long as DAPT or oral anticoagulation is given

If the decision for oral anticoagulation in PWH has been made, is there a preference for a specific type of drug?

- We recommend using DOACs over VKA in nonvalvular AF or venous thromboembolism (VTE) due to their favorable safety profile and the ability to individualize treatment regimens.
- We recommend DOACs over VKAs in PWHB.
- In PWH using VKAs, we recommend promoting INR self-monitoring.
- In the general population, different DOACs have different bleeding profiles; we consider taking these profiles into account in making individualized decisions on drug choice

If the decision for oral anticoagulation in PWH has been made, is there a need for monitoring anticoagulation treatment and dose adjustment?

- We recommended similar INR ranges in PWH VKA as that of the general population.
- If PWH with AF receive a DOAC, we recommend administering it at fixed standard dose without routine laboratory monitoring for dose adjustments.
- We recommend giving DOACs in reduced dose to those PWH who meet the criteria of anticoagulant dose reduction as in the general population.
- We recommend re-evaluation of the need for and choice of anticoagulant therapy on a regular basis.

Does the use of emicizumab suggest a safe threshold for antithrombotic therapy?

- In patients with hemophilia A (PWHA) using emicizumab (with or without inhibitors), we consider it acceptable to use SAPT.
- There is currently insufficient data to draw conclusions on the safety of DAPT or oral anticoagulation in PWHA using emicizumab; therefore, we suggest not to switch PWHA from FVIII prophylaxis to emicizumab for this purpose.

Section 2: Atrial fibrillation

What tool can be used for ischemic stroke risk assessment in PWH with AF?

- We suggest use of the CHADS2 score for individual stroke risk assessment as a general guide in PWH, but we cannot recommend specific predictive thresholds. Thus, expert-provided balance of thrombotic and bleeding risk must be taken into consideration for PWH.

What tool can be used as bleeding risk assessment in PWH with AF?

- We consider PWH as being at high risk for bleeding in any bleeding score, regardless of factor level.

Is there a place for aspirin in the treatment of AF in PWH?

- In PWH with AF, we recommend against the use of aspirin over oral anticoagulation.

What is the role for alternative strategies in PWH with AF, such as left atrial appendix closure or pulmonary vein isolation?

- We consider left atrial appendix occlusion (LAAO) a feasible option in PWH not eligible to long-term anticoagulant treatment for AF. However, accurate selection of eligible patients should consider the risk of bleeding during follow-up and temporary adapted prophylaxis is warranted if baseline level is <20 IU/dL.

Section 3: Acute and Chronic Coronary Syndromes

Can systemic thrombolysis be given in PWH?

- We consider systemic thrombolysis to be relatively contraindicated in all PWH.

Is there an indication for pretreatment with antiplatelet therapy in PWH with acute coronary syndromes (ACS) before invasive (percutaneous cardiac intervention [PCI]) treatment?

- We do not recommend pretreatment with a P2Y12 receptor inhibitor in PWH with an ACS if an early invasive management is planned.

Is there an indication for clotting factor replacement in PWH before cardiac intervention?

- In PWH undergoing a cardiac intervention, we recommend clotting factor supplementation with a target FVIII/FIX peak level of 80–100 IU/dL before the procedure. We recommend additional bolus infusions to maintain trough levels according to the procedure (see Table 4).
- We recommend radial artery access over femoral in cardiac interventions.
- In PWHA on emicizumab without inhibitors undergoing a cardiac intervention, we recommend additional FVIII supplementation as in PWH without emicizumab.
- In PWHA on emicizumab with inhibitors undergoing a cardiac intervention, we recommend supplementation with rFVIIa and do not recommend the use of activated prothrombin complex concentrates (aPCC).

Which anticoagulant is preferred in PWH before and during PCI?

- In PWH with ACS where PCI is indicated, we recommend using unfractionated heparin (UFH) or bivalirudin over enoxaparin given their shorter half-lives.
- We recommend the use of UFH or bivalirudin only after replacement of clotting factor levels.

Is there a formal bleeding risk assessment tool for bleeds in PWH with ACS?

- We consider all PWH at higher risk for bleeding and therefore recommend they should be treated as such according to the existing guidelines. We recommend that the severity of hemophilia and the individual bleeding risk should guide the clinician, not a formal score.

What type of stent is preferred in PWH with ASC?

- We recommend a newer generation drug-eluting stent (DES) as these allow the shortest DAPT time without an increase in the risk of stent thrombosis.

What DAPT regimen is preferred in PWH?

- We recommend the use of clopidogrel over ticagrelor or prasugrel in PWH in need for DAPT due to its lower bleeding risk.
- We recommend short duration of DAPT (1 mo) after newer generation DES placement followed by long-term monotherapy with clopidogrel or aspirin.
- In inhibitor patients, we consider an individual approach depending on the use of emicizumab and other risk factors for bleeding.

Section 4: Heart Valves

How to manage valve replacement in PWH?

- We recommend bioprosthetic valves over mechanical valves to avoid life-long anticoagulation in PWH.
- Anticoagulation postoperatively is variable and can be administered, observing the suggested minimum trough factor levels as described earlier (in general, we recommend FVIII/IX levels >20 IU/dL).

Section 5: Venous Thromboembolism

Is routine thromboprophylaxis needed in PWH undergoing orthopedic surgery?

- Considering the low prevalence of postoperative VTE in PWH and the potential chance of bleeding complications, we do not recommend the use of routine pharmacological thromboprophylaxis in the perioperative period.
- We recommend an individual approach in surgery with high VTE risk.
- We recommend mechanical over pharmacological thromboprophylaxis if indicated.
- We recommend against extended duration of pharmacological thromboprophylaxis.

Is the recommendation for routine thromboprophylaxis in PWH different according to the hemostatic product that is used (bypassing agents/emicizumab)?

- We do not consider the routine use of pharmacological thromboprophylaxis for surgery in PWH patients using emicizumab or bypassing agents.

Section 6: Acute Neurology

What is the optimal antithrombotic management of transient ischemic attack in PWH?

- In PWH with a noncardioembolic transient ischemic attack (TIA) and factor levels <20 IU/dL, we recommend starting aspirin.
- In patients with severe hemophilia with a noncardioembolic TIA without clotting factor prophylaxis (FVIII/FIX <1 IU/dL), we do not recommend the use of antithrombotic medication.
- In PWH with a noncardioembolic TIA and factor levels >20 IU/dL, we recommend starting aspirin. In patients with high-risk noncardioembolic TIA, DAPT with aspirin and clopidogrel may be considered for a maximum of 21 days after the TIA, followed by long-term aspirin.
- We do not recommend the use of starting or adapting clotting factor prophylaxis merely to be able to start DAPT in the setting of a TIA.

What is the antithrombotic management of acute ischemic stroke in PWH?

- In PWH with acute ischemic stroke, we do not recommend intravenous thrombolysis.
- In anterior circulation ischemic stroke due to large vessel occlusion, fulfilling established eligibility criteria, we consider mechanical thrombectomy to be appropriate in PWH.
- In PWH with acute minor ischemic stroke (NIHSS score < 5), we recommend similar treatment to PWH and TIA.
- In PWH with acute, nonminor, ischemic stroke (NIHSS score > 3), we recommend starting aspirin.

AUTHOR CONTRIBUTIONS

RS, VJ-Y, ME, and GC wrote the initial draft of the article, all authors contributed to the writing and revision and participated in consensus meetings.

DISCLOSURES

RS: scientific editor of HemaSphere. Unrestricted grants or consultancy fees from Bayer, CSL Behring, Hemab, NovoNordisk, Octapharma, Sanofi, Sobi, Takeda [all fees to the institution]. VJ-Y: Consultancy: Pfizer, Shire, NovoNordisk, Sobi, Grifols, Roche, CSL Behring; Research funding: Pfizer, Shire, NovoNordisk, Sobi, Octapharma, Roche, Grifols, CSL Behring; Membership on an entity's board of directors, speaker's bureau, or its advisory committees: NovoNordisk, Pfizer, Shire, Sobi, Grifols, Roche, CSL Behring. MAE: Consultancy fees from NovoNordisk, BioMarin, CSL Behring, Genentech/Roche, Sanofi, Takeda, Pfizer, Bayer, Hemobiologics/LFB, Kedrion, UniQure. Participated in clinical trials sponsored by: NovoNordisk, UniQure, Takeda, Bayer, Genentech/Roche, OPKO Biologics, CSL Behring. AF: honoraria for lectures from Sanofi, Stago, Bayer, and Pfizer. RK: Research grants: Bayer, CSL Behring, LEO, NovoNordisk. Consultancy and speaker fees from BioMarin, Bayer, Biotest, Chugai, CSL Behring, Daiichi Sankyo, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, SOBI, Takeda. RL: Consultancy fees from Alexion, Astra Zeneca, Bayer, BioMarin, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, SOBI, Takeda. FWGL: Unrestricted grants/research funding from CSL Behring, UniQure, Sobi, Takeda; consultancy fees from BioMarin, CSL Behring, Takeda, and uniQure [all fees to the institution], and served as DSMB member for a study sponsored by Roche. MM: Consultancy fees from NovoNordisk, Grifols, Sanofi, Freeline, Biotest. He is the project lead for the European Hemophilia Safety Surveillance (EUHASS) safety reporting scheme which is funded by Bayer, BioMarin, BPL, CSL Behring, Grifols, Kedrion, NovoNordisk, Octapharma, Roche, Sanofi, Sobi, and Takeda. TO: consulting fees from Bayer, Sobi and Novo Nordisk. MS: Unrestricted research funding from Octapharma, Pfizer and Amgen (to institution); honoraria from advisory boards from Amgen, Novartis, Octapharma, Pfizer, and Amgen. AT: grants and personal fees for lectures and consultancy from Bayer, BioMarin, Biotest, Chugai, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, SOBI, and Takeda. DW: has received: grant funding from the Stroke Association and British Heart Foundation; speaking honoraria from Bayer; speaking and chairing honoraria from Alexion and NovoNordisk; and consultancy fees from Bayer and NovoNordisk. HBvdW: funding for consultancy from Bayer and TargED, all paid to institution. JW: Research support and honoraria for lectures from: Alnylam, Amgen, Bayer, CSL Behring, LFB, Novartis, Novo Nordisk, Octapharma, Roche, Sanofi, Siemens, Sobi, Swixx Biopharma, Takeda. GC: Unrestricted grants/research funding from CSL Behring, Sobi, Pfizer; speaker/consultancy fees from Bayer, BioMarin, CSL Behring, Grifols, Kedrion, LFB, NovoNordisk, Roche, Sanofi, Takeda, uniQure and Werfen. All the other authors have no conflicts of interest to disclose.

SOURCES OF FUNDING

The authors declare no sources of funding for this manuscript.

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