

# Antithrombotic Therapy in People with Hemophilia—A Narrative Review

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Thromb Haemost 2025;125:1060–1068.

## Abstract

As the life expectancy of individuals with hemophilia continues to increase, the complexity of balancing bleeding risks and thrombotic management has become increasingly critical in people with hemophilia with or at a high risk of thrombosis. Advances in hemophilia therapies such as extended half-life coagulation factors, non-factor therapies, rebalancing agents, and gene therapy have expanded treatment options for a variety of people with hemophilia. The thrombotic risk of people with hemophilia in general are relatively low as compared to those without hemophilia. However, antithrombotic therapy for prevention and treatment for thrombosis should still be considered in some situations, even in hemophilia. This clinical focus highlights the use of antithrombotic therapy in the management of thrombosis in people with hemophilia. A multidisciplinary, personalized approach is essential for optimizing the safety and efficacy of antithrombotic therapy in people with hemophilia with or at a high risk of thrombosis. High performance computer based multidimensional data analysis may help in establishing the personalized antithrombotic therapy in the future.

## Keywords

- ▶ hemophilia
- ▶ antiplatelet therapy
- ▶ anticoagulation
- ▶ thrombosis
- ▶ bleeding management
- ▶ artificial intelligence

## Introduction

Recent advancements in treatments for hemophilia such as extended half-life coagulation factors, non-factor replacement therapies, rebalancing agents, and gene therapies along with widespread access to prophylaxis have collectively extended the life expectancy of individuals with hemophilia.<sup>1–3</sup> In general, the risk of thrombotic cardiovascular (CV) events increases with age,<sup>4</sup> especially when patients are exposed to risk factors such as hypertension, diabetes mellites, smoking, etc.<sup>5</sup> Although this is also true for people with hemophilia, previous reports have suggested that the risks of thrombotic CV events were

lower than those without, even in the presence of CV risk factors of equal or even worse severity.<sup>6,7</sup> However, various antithrombotic therapy may be necessary even in people with hemophilia when they are at a high risk of thrombosis.

In a prospective multicenter hemophilia registry of ADVANCE Japan, Nagao et al showed that 13 out of 600 people with hemophilia age >40 experienced thrombotic CV events requiring antithrombotic therapy at the first year of the 10-year follow-up.<sup>7</sup> These results are reasonable since the important burden of thrombotic disease, such as atherosclerotic plaque formation, is not prevented or delayed in the

received

January 13, 2025

accepted after revision

February 27, 2025

accepted manuscript online

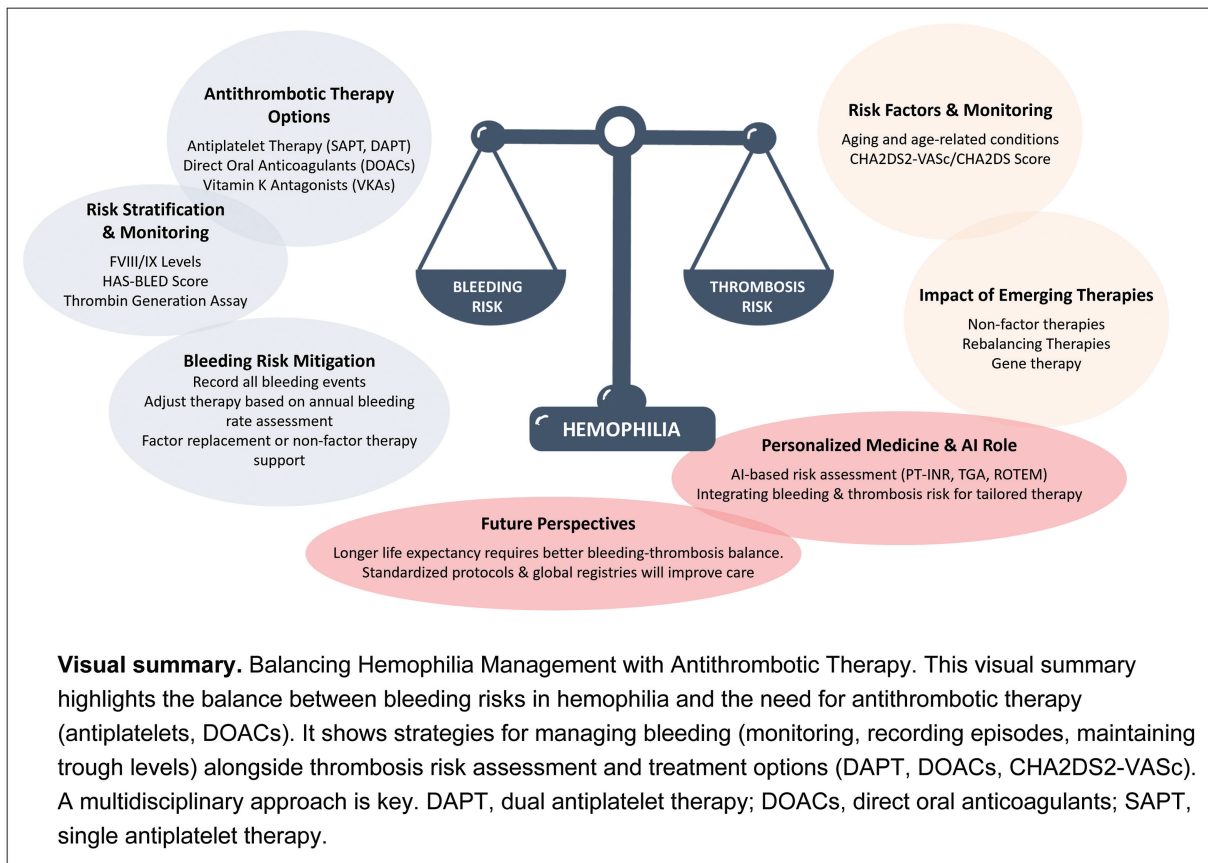
February 28, 2025

article published online

March 28, 2025

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Georg Thieme Verlag KG,  
Oswald-Hesse-Straße 50,  
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-2548-4192>.  
ISSN 0340-6245.



presence of hemophilia.<sup>8</sup> Another report from a European cross-sectional study revealed that the risk of thrombosis in atrial fibrillation, an important factor contributing to the increased risk of thrombotic CV events,<sup>9</sup> was not reduced by the presence of hemophilia.<sup>10</sup> Moreover, venous thrombotic events necessitating anticoagulant therapy have also been documented even in people with hemophilia.<sup>11,12</sup> From these findings, it is logical to assume that the number of people with hemophilia with or at a high risk of thrombosis increases with longer life expectancy through better hemophilia therapy.

The complicated oversight of bleeding and thrombosis is necessary for treating people with hemophilia with or at a high risk of thrombosis. Various consensus documents are published for practice guidance—most notably from EHA (European Hematology Association), ISTH (International Society for Thrombosis and Haemostasis), EAHAD (European Association of Hemophilia and Allied Disorders), and ESO (European Stroke Organization)—and are emerging to address these critical needs.<sup>13–16</sup> Although these guidelines are largely expert consensus, the rarity of hemophilia, particularly in these specific contexts, renders large-scale registry or randomized studies infeasible. Thus, utilizing available guidance as a strategic framework for treatment considerations remains essential.

In this review, we aim to focus on hemophilia care, particularly from the perspective of antiplatelet and anticoagulant therapies, and explore current practices and challenges in this evolving field.

### Evolution of Hemophilia Treatment

The advancements in hemophilia treatment have significantly shifted from mere hemostatic management to comprehensive care as a chronic disease, improving patient survival while introducing new clinical challenges. Understanding the evolution of hemophilia treatment is essential not only for bleeding management but also for developing cardiovascular disease (CVD) treatment strategies that balance the risk of thrombosis.

Traditionally, hemophilia treatment has been centered on coagulation factor replacement therapy. This method involves intravenous administration of factor VIII (FVIII) or factor IX (FIX) to control bleeding, with prophylactic therapy recommended for continuous management. However, this approach had the limitation of a short half-life, necessitating frequent intravenous infusions. To overcome these challenges, extended half-life (EHL) factor products were developed. These formulations utilize technologies such as Fc fusion, PEGylation, and albumin fusion, enabling a more prolonged and stable supply of coagulation factors and reducing the frequency of infusions.<sup>17</sup> However, EHL products still require intravenous administration, and FVIII products are particularly limited in their half-life extension due to interactions with von Willebrand factor (VWF), making FIX products more favorable in this aspect. One breakthrough solution to this limitation is efanesoctocog alfa, a revolutionary FVIII product with a half-life two to three times longer than conventional FVIII formulations. This allows for once-weekly administration while maintaining sufficient coagulation function.<sup>18</sup>

In contrast to traditional factor replacement therapies, non-factor replacement therapies offer a novel approach. Emicizumab, a bispecific antibody that mimics FVIII function, can be administered subcutaneously once a week to once a month, significantly reducing the burden on patients.<sup>19</sup> Other examples include rebalancing therapies, such as fitusiran, an siRNA therapy that suppresses antithrombin to enhance coagulation. This treatment is administered monthly via subcutaneous injection, achieving sufficient hemostatic effects.<sup>20</sup> Additionally, concizumab and marstacimab, both tissue factor pathway inhibitor (TFPI) inhibitors, offer another new approach to bleeding control.<sup>21,22</sup> However, some rebalancing therapies have been associated with an increased risk of thrombosis, raising concerns about their safety. The implications for CVD management remain even more uncertain.

Furthermore, gene therapy has been introduced in Western countries, using adeno-associated virus (AAV) vectors to deliver FVIII or FIX genes into liver cells to promote endogenous factor production.<sup>23–25</sup> This one-time treatment has attracted attention as a new therapeutic option. The major advantage of gene therapy is its potential for long-term factor production, theoretically offering a “functional cure.” However, significant individual variability exists in post-treatment factor levels, and some patients may not achieve sufficient factor production. Additionally, concerns such as a decline in factor production over time and liver toxicity require careful monitoring.

The emergence of these new treatments is altering the coagulation profile of hemophilia patients compared to the past. At the same time, the available therapeutic options for hemophilia have expanded when antiplatelet or anticoagulant therapy is required following the onset of CVD.

## Antiplatelet Therapy in Hemophilia

### Antiplatelet Therapy

Antiplatelet therapy with aspirin and P2Y<sub>12</sub> inhibitors is the standard of care in patients with acute coronary syndrome (ACS) including acute myocardial infarction.<sup>26–28</sup> Even in stable coronary artery disease, antiplatelet therapy is widely used after percutaneous coronary intervention (PCI).<sup>29</sup> Moreover, dual antiplatelet therapy (DAPT) of aspirin and P2Y<sub>12</sub> receptor antagonists showed a reduction of fatal or non-fatal stent thrombosis.<sup>30</sup>

The use of P2Y<sub>12</sub> inhibitors in DAPT for ACS shifted from clopidogrel to a newer generation of agents in patients with ACS.<sup>31,32</sup> Initially, DAPT was considered for at least 12 months after the onset of ACS.<sup>19</sup> Initially, the newer P2Y<sub>12</sub> inhibitors were also tested for 12-month therapy.<sup>33,34</sup> Obviously, strong antiplatelet therapy by DAPT reduced the risk of thrombosis, but increased the risk of serious bleeding complications. To achieve the best balance between thrombosis and bleeding both longer and shorter DAPT strategies were tested as compared to the initially established 12-month DAPT. A longer DAPT strategy achieved a further reduction of thrombotic events but with an increased risk of serious bleeding complications.<sup>35,36</sup> On the other hand, shorter DAPT or de-escalation of DAPT from aspirin plus potent

P2Y<sub>12</sub> inhibitors to aspirin plus a low-dose potent P2Y<sub>12</sub> inhibitor or clopidogrel strategy at 1 month resulted in reduced risk of serious bleeding complication without increasing the risk of thrombotic events.<sup>37</sup> A similar short DAPT strategy for only 1 month also resulted in better clinical outcome as compared to longer DAPT after stenting, even in the absence of ACS.<sup>38</sup> Accordingly, the shorter DAPT strategy also became a standard of care in stable coronary artery disease patients who undergo PCI treatment.<sup>39</sup>

DAPT provides strong antiplatelet therapy to reduce the risk of thrombotic major cardiovascular events (MACE) including myocardial infarction after ACS and endothelial damage by PCI (►Fig. 1). Platelet thrombus formation is induced by endothelial damage. Thus, only 1-month DAPT should be sufficient in theory since the endothelial damage by PCI should be recovered by then. The MACE events become symptomatic when the thrombi become large enough to reduce organ perfusion. The large thrombi are mostly caused by fibrin. The activated platelet provides procoagulant surfaces to initiate fibrin formation, but coagulation factors should play more direct roles than platelets for expanding fibrin thrombi (right part of ►Fig. 1). In other words, antiplatelet therapy may prevent initiation of coagulation cascade by preventing the formation of prothrombinase complex, but its role for fibrin thrombus growth is limited. Indeed, a few case reports suggested that antiplatelet agents could be used even in people with hemophilia in certain conditions of ACS.<sup>40,41</sup> Thus, shorter DAPT in those with ACS and after PCI until endothelial recovery may be possible for the hemophilia population.

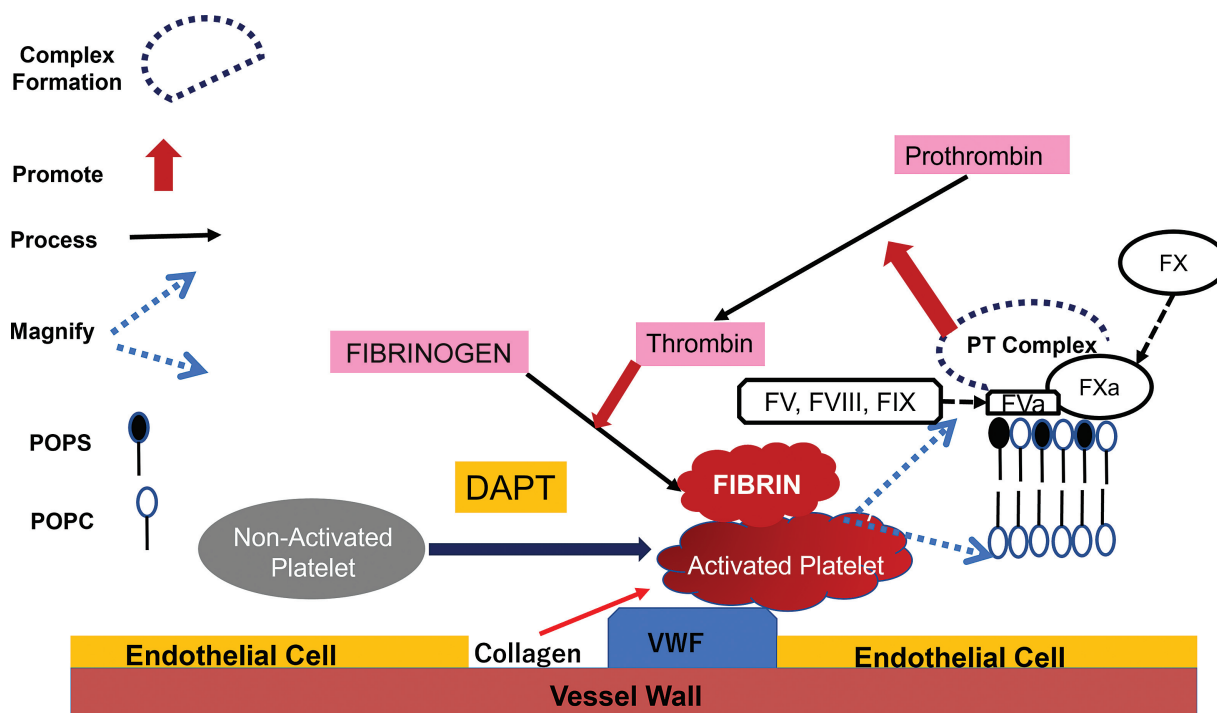
The most frequently used agents in single antiplatelet therapy (SAPT) are aspirin and clopidogrel, with ticagrelor used in some cases. Prasugrel, however, is rarely used as monotherapy due to its high bleeding risk.<sup>42</sup> In patients with high bleeding risk, clopidogrel is often preferred over aspirin due to its lower risk of bleeding.<sup>43</sup>

In contrast, real-world data from France (69,911 patients) suggest that low-dose aspirin carries a lower bleeding risk than clopidogrel and high-dose aspirin, particularly for gastrointestinal and intracranial bleeding.<sup>44</sup> Therefore, the choice of SAPT should be individualized based on patient-specific thrombotic and bleeding risks.

### Maintenance of Coagulation Factor during Antiplatelet Therapy

To prevent serious bleeding complications in hemophilia patient requiring antiplatelet therapy, maintaining a deficient coagulation factor in various levels is recommended by EHA-ISTH-EAHAD-ESO Clinical Practice Guidance.<sup>14</sup> When patients need DAPT with aspirin and P2Y<sub>12</sub> receptor antagonist, the maintenance of FVIII/IX level over 20 IU/dL is recommended while FVIII/IX level of 1 to 5 IU/dL may be fine with an SAPT using either aspirin or clopidogrel.<sup>14</sup> It is likely that relatively small amount of essential coagulation factors is necessary to stop bleeding (►Fig. 1).

It is of note that the practice recommendation by EHA-ISTH-EAHAD-ESO is not based on strong clinical evidence provided by randomized clinical trials. Careful consideration



**Fig. 1** Role of Platelets and Coagulation Factors in Thrombus Formation. Platelets adhere promptly at sites of endothelial damage. Initial adhesion is mediated by platelet glycoprotein Iba binding with von Willebrand factor (VWF) expressed at the damaged endothelium. Then, adhered platelets are activated. Negatively charged phospholipids such as phosphatidyl serine (POPS) are expressed on the activated platelet membrane. Coagulation factors with the gla domain bind with POPS, and those without the gla domain contribute to the formation of prothrombinase complex. Various antiplatelet agents prevent thrombosis by inhibiting platelet activation and procoagulant activity. Symptomatic thrombosis, such as myocardial infarction, occurs when blood perfusion is disturbed by large thrombi mostly caused by fibrin. Essential coagulation factor(s) such as factor VIII or factor IX is lacking in individuals with hemophilia. However, a minimal amount(s) of these essential coagulation factor(s) is necessary for hemostatic thrombus formation. DAPT, dual antiplatelet therapy; POPC, phosphatidyl serine.

of the risk of thrombosis and bleeding in individual patients is necessary to achieve the best personalized outcomes. In practice, maintaining a factor VIII trough level above 20% using currently available FVIII products may need frequent intravenous infusions. More recent anti-hemophilia agents, such as emicizumab, may be a good alternative. The action of emicizumab to stop bleeding is much more complex compared to simple supplemental therapy. However, clinical data on the use of emicizumab remains limited, and existing case reports suggest that severe hemophilia patients were successfully managed during 1 month of DAPT with emicizumab alone without serious bleeding complications.<sup>7,45</sup> Although no bleeding complications were observed in these cases, the small number of patients raises questions about whether this was due to other factors being fortuitously favorable or if emicizumab alone is sufficient for adequate management. Further evidence from larger clinical studies is needed. ► **Table 1** summarizes the necessary maintenance therapy in hemophilia if they need antiplatelet therapy. More clinical evidence with the use of emicizumab alone is expected.

**Oral Anticoagulants in Hemophilia**

**Choice of Oral Anticoagulant**

Vitamin K antagonists (VKAs) were the only available oral anticoagulants for a long period of time. Recently developed

orally available specific inhibitor of coagulation factor Xa, namely, direct oral anticoagulants (DOACs), became a standard of care in various conditions such as stroke prevention in patients with non-valvular cause of atrial fibrillation (AF).<sup>46-48</sup> The global registry of AF at risk of stroke showed the evolving changes in the use of DOAC in stroke prevention in newly diagnosed AF patients at risk of stroke around the globe.<sup>49</sup> Similar rapid transition from VKA to DOACs were observed in various registry mostly due to safe profile of DOACs as compared to VKA with no need for monitoring.<sup>50-52</sup> VKA is still necessary but only in those patients with high thrombotic risk such as AF with mechanical heart valve<sup>53</sup> and hemodynamically overt mitral stenosis.

The risk-benefit balance with the use of DOAC in hemophilia population is more complicated than that with the use of

**Table 1** Maintenance therapy in people with hemophilia requiring antiplatelet therapy

Maintenance therapy in people with hemophilia require antiplatelet therapy	
Single antiplatelet therapy (SAPT)	FVIII/IX level of 1–5 IU/dL for SAPT (aspirin or clopidogrel)
Dual antiplatelet therapy (DAPT)	FVIII/IX level of 20 IU/dL for DAPT
Single and dual antiplatelet therapy	Different parameter may be necessary when using emicizumab

antiplatelet agents because the bleeding risk with the use of oral anticoagulants is much higher than antiplatelets. Indeed, the annual risk of serious bleeding with the use of aspirin of approximately 0.2%/year is substantially lower as compared to that of approximately 2 to 3%/year with the use of DOACs.<sup>46–48</sup> Aspirin could be recommended for almost all secondary prevention cohort patients because the merit of reducing thrombosis in these population is usually much higher than the increased risk of bleeding.<sup>54</sup> For the DOACs, the selection of high-risk patients is necessary. Simple risk calculation based on the CHA2DS2-VASc score is widely accepted. The bleeding risk was previously assessed using the HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly and Drugs or alcohol) score. In the era of DOAC, a few bleeding risk scores have been developed so far.<sup>55</sup> However, the bleeding risk stratification in people with hemophilia requiring oral anticoagulants is still to be elucidated.

A trough FVIII/IX level of 20 IU/dL is recommended when anticoagulants are considered in people with hemophilia by EHA-ISTH-EAHAD-ESO Clinical Practice Guidance.<sup>14</sup> A precise and personalized risk stratification is necessary to avoid bleeding complications in people with hemophilia when using DOACs.

#### Risk Stratification When Using Anticoagulants

Risk stratification using clinical parameters such as CHA2DS2-VASc and HAS-BLED is easy. For further precise risk clarification, biomarker-based risk stratification may be helpful. ABC risk stratification is widely accepted for risk prediction of stroke/systemic embolization<sup>56</sup> and serious bleeding.<sup>57</sup> However, their role in people with hemophilia is unclear. Of the biomarkers, thrombin generation assay (TG) was investigated deeply to select high bleeding risk patients in the VKA era. The quantitative relationship between TG assay and PT-INR was investigated. TG levels below 10% aligned well with the therapeutic INR range for VKAs: 10 to 20% with an INR range of 1.5 to 1.9, and above 20% begin to overlap with normal controls. Maintenance of 20% or higher factor VIII/IX levels recommended by EHA-ISTH-EAHAD-ESO Clinical Practice Guidance for using DOACs is based on TG assay data.<sup>14</sup>

The potential role of TG in understanding the effects of DOACs in people with hemophilia was investigated in a small clinical study.<sup>58</sup> The authors showed that endogenous thrombin potential was higher in anti-Xa treated patients compared to those with mild hemophilia. TG may be useful for assessing hemophilia therapy because people with severe hemophilia

express significantly improved TG parameter if they are treated with emicizumab.<sup>58</sup> If the TG parameters precisely reflect the thrombotic and bleeding risk in hemophilia patients on DOACs treatment, they can be used to make individualized decisions such as no need for DOACs if the TG parameters were low enough in the hemophilia patients even if they have other risk factors that puts them at high risk of thrombosis. Similarly, DOAC may be recommended when TG parameters are higher than the values in patients who are maintain factor level above 20%. **Table 2** summarizes the clinical condition when anticoagulant therapy is necessary, even in hemophilia.

#### Management of Bleeding Complication with the Use of DOACs in Hemophilia

During treatment with antiplatelet drugs or DOACs, it is crucial for patients to keep a detailed record of their bleeding events, which is also necessary for calculating the annual bleeding rate (ABR). In addition to documenting factor replacement therapy for typical bleeding episodes, patients should also be educated to record less severe bleeding events such as subcutaneous hemorrhage, epistaxis, oral cavity bleeding, and mucosal-related bleeding (like changes in menstrual flow), even when factor replacement is not required. If a patient's record suggests frequent bleeding episodes, special caution should be taken for the individual, including adjustment to the antiplatelet/DOAC therapy. Clinical trial suggests that the extremely low dosage of DOAC still bring benefit in elderly patients at high risk of bleeding.<sup>59</sup> A similar dose adjustment might be helpful for hemophilia population.

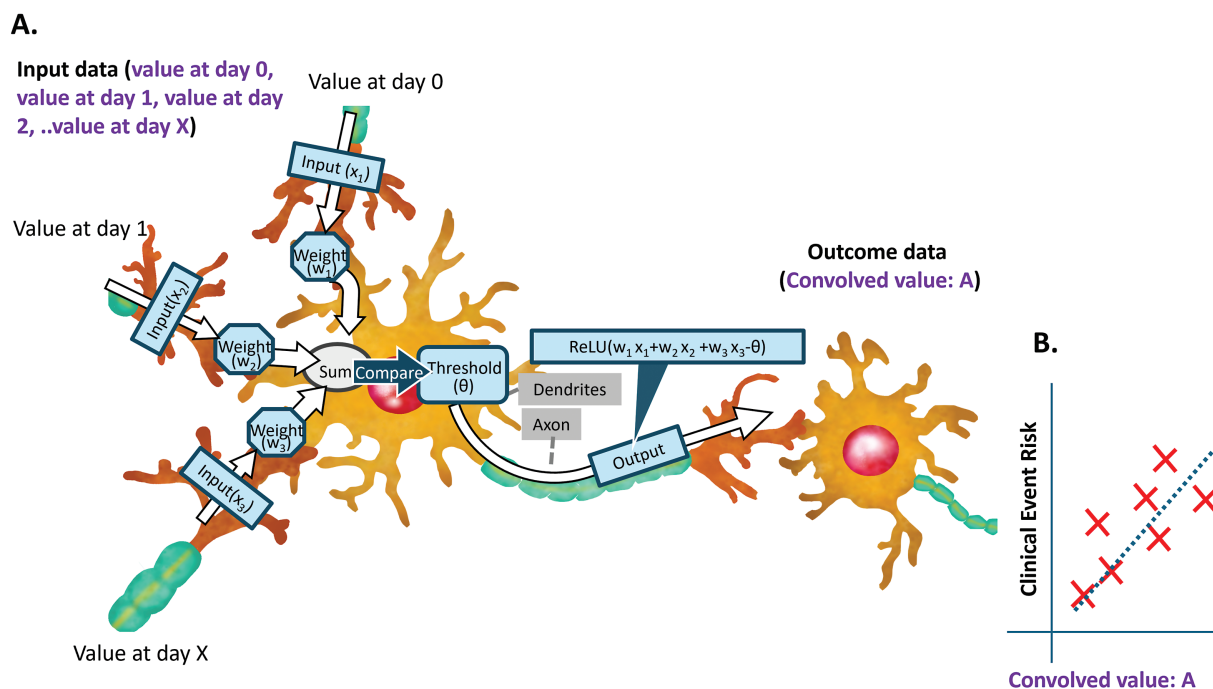
#### Monitoring of Anticoagulant Therapy in People with Hemophilia

PT-INR is an established monitoring marker for patients treated by VKAs. Typically, single-measured PT-INR values are used to adjust the dosage of VKA. Multidimensional data such as serially measured PT-INR should contain more information for predicting future risks of bleeding and thrombotic events. However, the quantitative relationship between multidimensional data and clinical events risks is difficult to calculate. Recently developed neural network on computers enabled reduction of multidimensional data into single dimension (**Fig. 2**). Computer-based artificial intelligence (AI) models using these neural networks successfully predict the future risk of thrombosis/bleeding events in patients starting VKA using serially measured PT-INR dataset obtained from day 1 to 30.<sup>60</sup> These neural network-based AI enables the

**Table 2** Anticoagulation therapy in people with hemophilia with or at a risk of thrombosis

Anticoagulant therapy in people with hemophilia	
DOAC	● Stroke prevention in patients with atrial fibrillation with a trough FVIII/IX level of 20 IU/dL
Risk stratification	● Clinical risk stratification with CHA2DS2-VASc, CHA2DS2, and HAS-BLED should not strong enough ● Thrombin generation (TG) assay may provide necessary level of FVIII/IX
Monitoring	● Serially measured PT-INR may be helpful in patients treated by VKA. ● In patients treated by DOAC, TGA/TEG/ROTEM may provide better monitoring.

Abbreviations: DOAC, direct oral anticoagulant; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly and Drugs or alcohol; TEG, Thromboelastography; TGA, thrombin generation assay; VKA, vitamin K antagonist.



**Fig. 2** Individualized Prediction of Thrombotic and Bleeding Risk in Individuals with Hemophilia and Anticoagulant Therapy Using Multidimensional Data with Artificial Intelligence. Typically, various hemostatic parameters such as PT-INR were used to predict the risk of thrombosis and bleeding by a single-point measurement. Multidimensional data, such as serially measured data sets, should contain more information than single-day measurements. However, it was difficult to quantify the relationship between multidimensional data and the future risk of thrombotic/bleeding events. The neural network enables the reduction of multidimensional data into a single-dimensional space with an established mathematical model. The quantitative relationships between the dimension-reduced data and the risk of thrombosis/bleeding events could be calculated. A multidimensional data-based personalized approach should improve the quality of care in complicated antithrombotic therapy in people with hemophilia.

prediction of various disease risk from multidimensional data.<sup>61–65</sup> Currently, their application to people with hemophilia is still to be elucidated. Precise monitoring of the individual effects of anticoagulants in people with hemophilia should be helpful for monitoring the efficacy and safety of the anticoagulant therapy in individuals with hemophilia.

Unlike PT-INR for VKA, classical screening coagulation assays such as single-time measurements of prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) are not a suitable marker for evaluating the efficacy and safety of DOACs. Liquid chromatography–mass spectrometry measurements of DOAC concentration are considered as the gold standard.<sup>66</sup> So far, the best values for people with hemophilia have not been established. Just like PT-INR in patients on warfarin, the multidimensional data of serially measured monitoring values may include precise information to predict the future risks of thrombotic and bleeding events in individual with hemophilia.

Regarding monitoring during emicizumab treatment, previous reports have shown that global hemostasis assays such as ROTEM or thrombin generation assay (TGA) may provide better predictive accuracy for the risk of thrombosis and bleeding in hemophilia patients.<sup>67</sup> Perhaps, future risk of thrombotic/bleeding events could be more precisely predicted by multidimensional analysis of measured data (► Fig. 2). Again, the use of multidimensional data may further increase the predictive accuracy of future clinical events in individual patients.

## Conclusion

With advancements in hemophilia treatment, individuals with hemophilia are living longer, increasing the need to balance bleeding risks with the management of thrombotic conditions. Our review highlights the evolving role of antithrombotic therapy in this population, emphasizing the necessity of personalized, multidisciplinary approaches that integrate hemophilia-specific considerations into cardiovascular and thrombotic care.

Current evidence suggests that antiplatelet and anticoagulant therapies can be safely administered in hemophilia patients under carefully monitored conditions, with factor replacement or non-factor therapies such as emicizumab playing a crucial role in mitigating bleeding risks. However, given the limited availability of results from large-scale data, treatment decisions should be tailored on an individual basis. Further research should focus on refining risk stratification models specific to hemophilia patients requiring antithrombotic therapy. Prospective studies incorporating thrombin generation assays and AI-based predictive models may enhance clinical decision-making by providing more precise assessments of thrombosis and bleeding risks.

Additionally, although consensus guidelines have begun addressing these challenges, their recommendations are largely based on expert opinion rather than high-level evidence. International registries and collaborative studies are needed

to generate robust data on long-term outcomes, optimal treatment strategies, and the safety of emerging therapies. Establishing standardized protocols for managing antithrombotic therapy in hemophilia patients will be critical to improving clinical outcomes and reducing the risks associated with both thrombosis and bleeding.

#### Conflict of Interest

A.N. has received investigator-initiated research/education grant funding from Bayer Yakuhin Ltd., Pfizer Japan Inc., and Chugai Pharmaceutical Co., Ltd. A.N. is a medical advisor of Chugai Pharmaceutical Co., Ltd. and KM Biologics. A.N. has received honoraria from Sanofi K.K., Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Bayer Yakuhin Ltd., Fujimoto Pharmaceutical Corporation, KM Biologics, Pfizer Japan Inc., Novo Nordisk Pharma Ltd., and CSL Behring. Shinya Goto received modest amount of contracted grant support from Jansen Pharma. Shinya Goto received modest amount of personal fee from Amgen, Merck Sharp and Dohme (MSD), Jansen Pharma, and Anthos Therapeutics. Shinya Goto received quality fee from the American Heart Association as an Associate Editor for *Circulation*, Duke University and Harvard University as a Steering Committee Member for Clinical Trials. Shunichi Goto has nothing to disclose.

#### Acknowledgment

This study was not directly supported by any of the following programs; however, the authors acknowledge the relevance of prior research supported by the Strategic Program for Innovational Research Field 1 for Supercomputational Life Science, MEXT/JSPS KAKENHI Grant-in-Aid (Grant Number 19H03661), AMED (Grant Numbers A368TS and A447TR), the Fukuda Memorial Foundation, a grant from the Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering, Suzuken Memorial Foundation, and the Cross-ministerial Strategic Innovation Promotion Program (SIP) on “Integrated Health Care System” (Grant Number JPJ012425), which were cited in this review.

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