





Management of patients with congenital bleeding disorders and cardiac indications for antithrombotic therapy

A clinical consensus statement of the ESC Working Group on Thrombosis, the Association for Acute Cardiovascular Care (ACVC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA) of the ESC, the ESC Working Group on Cardiovascular Pharmacotherapy and the European Association for Haemophilia and Allied Disorders (EAHAD)

Dan Atar ^{1,2,*}, **Christophe Vandembrielle** ^{3,4}, **Stefan Agewall**⁵,
Bruna Gigante ^{6,7}, **Andreas Goette** ^{8,9,10}, **Diana A. Gorog**^{11,12}, **Pål A. Holme**^{2,13},
Konstantin A. Krychtiuk¹⁴, **Bianca Rocca**¹⁵, **Jolanta M. Siller-Matula**¹⁴,
Marco Valgimigli^{16,17}, **Andrea Rubboli**^{18,†}, and **Robert Klamroth**^{19,20,†}

¹Division of Cardiology, Oslo University Hospital Ulleval, Kirkevn. 166, 0450 Oslo, Norway; ²Institute of Clinical Medicine, University of Oslo, 0316 Oslo, Norway; ³Heart Center, OLV Hospital, 9300 Aalst, Belgium; ⁴Royal Brompton & Harefield Hospitals, Guy's & St. Thomas' NHS Foundation Trust, London SW3 6LR, UK; ⁵Division of Clinical Science, Danderyd Hospital, Karolinska Institute Stockholm, 18257 Danderyd/Stockholm, Sweden; ⁶Unit of Cardiology, Department of Medicine, Karolinska Institutet, 17177 Stockholm, Sweden; ⁷Department of Cardiology, Karolinska University Hospital, 17177 Stockholm, Sweden; ⁸Department of Cardiology and Intensive Care Medicine, St. Vincenz Hospital, 33098 Paderborn, Germany; ⁹Otto-von-Guericke University, Medical Faculty, 39106 Magdeburg, Germany; ¹⁰MAESTRIA Consortium, AFNET, 48149 Münster, Germany; ¹¹Faculty of Medicine, National Heart and Lung Institute, Imperial College, London SW7 5NH, UK; ¹²School of Life and Medical Sciences, Postgraduate Medical School, University of Hertfordshire, Hatfield, Hertfordshire AL10 9AB, UK; ¹³Department of Haematology, Oslo University Hospital, 0372 Oslo, Norway; ¹⁴Department of Internal Medicine II—Division of Cardiology, Medical University of Vienna, 1090 Vienna, Austria; ¹⁵Department of Medicine and Surgery, LUM University, 70010 Casamassima, Bari, Italy; ¹⁶Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, 6900 Lugano, Switzerland; ¹⁷Department of Cardiology, Bern University Hospital, University of Bern, 3010 Bern, Switzerland; ¹⁸Department of Emergency, Internal Medicine and Cardiology, Division of Cardiology, S. Maria delle Croci Hospital, 48121 Ravenna, Italy; ¹⁹Department for Internal Medicine, Haemophilia Treatment Centre, Vivantes Klinikum im Friedrichshain, 10249 Berlin, Germany; and ²⁰Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, 53127 Bonn, Nordrhein-Westfalen, Germany

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* **Corresponding author.** Tel: +47-22119187, Fax: +47-22114250, Email: danat@uio.no

† Shared last-authorship.

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Aims

Cardiologists have only had rare exposure to haemophilia patients and patients with other congenital bleeding disorders during the last decades, as these patients had a reduced life expectancy and were partly protected against thrombosis due to the bleeding disorder. With the availability of effective and safe replacement therapies of clotting factors, the average life expectancy in these populations of patients has significantly increased, and thrombotic complications may occur.

Methods and results

The European Society of Cardiology Working Group on Thrombosis has taken the initiative to broaden the spectrum of these haematological conditions to include patients with a larger variety of *congenital* bleeding disorders with concomitant cardiac conditions as compared to a recent position paper by the European Haematology Association in collaboration with other societies (ISTH, European Association for Haemophilia and Allied Disorders, and ESO). Management of antithrombotic therapy or thromboprophylaxis in these individuals is challenging due to the wide phenotypes encompassed by congenital bleeding disorders. These include abnormalities in both primary haemostasis (involving von Willebrand factor and platelet function) and secondary haemostasis (related to coagulation factors and fibrinogen). Bleeding disorders range from mild to very severe. Based on existing literature, we provide clinical consensus statements on optimizing antithrombotic treatment strategies for patients with congenital bleeding disorders and highlight the current gaps in knowledge in these complex clinical settings.

Conclusion

Of importance, an individualized approach to antithrombotic therapy is warranted to properly balance the two risks of thrombosis and bleeding. Adoption of the safest interventional techniques, reduction of the intensity and/or duration of antithrombotic therapies, and attention to the safe levels of clotting factors is generally advised.

Keywords

Congenital bleeding disorders • Haemophilia • von Willenbrand factor • Congenital platelet disorders • Antithrombotic therapy • Cardiac indications

Introduction

A recent position paper by the European Haematology Association (EHA) in collaboration with allied societies has provided clinical practice recommendations for patients with haemophilia in need of antithrombotic therapies¹ as well as guidelines on acquired thrombocytopenia associated with cancer.² The European Society of Cardiology (ESC) Working Group on Thrombosis has taken the initiative to broaden the spectrum of these haematological conditions to include patients with a larger variety of congenital bleeding disorders and concomitant cardiac conditions. Furthermore, there was a perceived necessity to provide particular direction to the variety of subspecialized cardiologists treating a large spectrum of cardiovascular (CV) conditions in this growing population of congenital bleeding disorder patients.

Indeed, cardiologists have only had rare exposure to haemophilia patients and patients with other severe congenital bleeding disorders during the last decades, due to frequently shortened lifespan in these populations. However, with the advent and the availability of safe replacement therapies of clotting factors, the average life expectancy in these populations of patients has significantly increased, with some even reaching normal life expectancy. This development makes it obvious that more haemophilia patients and patients with congenital bleeding disorders will present with CV disease in the future to a variety of health care providers, not least presenting in cardiology departments. It is only logical that these patients may increasingly encounter conditions that are highly prevalent in higher age groups, such as atrial fibrillation (AF), acute coronary syndromes (ACS), chronic coronary syndromes (CCS), and valvular heart diseases (VHD). In this context, the choice of antithrombotic regimen must be carefully adapted and weighted to their underlying disease. For example, depending on the bleeding disorder, the risk of intracerebral haemorrhage can be higher than in the normal population, thus the indication for anticoagulation must be balanced differently.

The panel of co-authors has been selected based on complementary expertise in clinical cardiology, interventional cardiology, cardiovascular pharmacology, and haematology. In this clinical consen-

sus statement, we summarize the available evidence on antithrombotic treatment of common atherosclerotic cardiovascular diseases (ASCVD), VHD, and AF in patients with haemophilia, and other congenital bleeding disorders affecting platelet function and coagulation. The objectives of this paper are hence, to familiarize clinical cardiologists and other CV physicians with patients with congenital bleeding disorders. The lead was taken by the ESC Working Group on Thrombosis, and the writing group additionally consists both of representatives of the EAHAD (European Association for Haemophilia and Allied Disorders) and experts from the Association for Acute Cardiovascular Care (ACVC), the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Heart Rhythm Association (EHRA), and the Working Group on Cardiovascular Pharmacotherapy. It was thus attempted that all the different CV disorders are authoritatively covered by relevant expertise (Figure 1).

Congenital bleeding disorders covered by this document

Congenital bleeding disorders encompass a wide spectrum of conditions, including abnormalities in both primary haemostasis [involving von Willebrand factor (vWF) and platelet function] and secondary haemostasis [related to coagulation factors and fibrinogen]. These conditions can be either functional (coagulation mechanisms not functioning properly with normal antigen levels) or quantitative (reduced coagulation factors) in nature. Bleeding disorders range from mild to very severe degrees.

Given that primary haemostasis principally involves platelet aggregation in response to endothelial damage, one would naturally expect a reduced incidence of conditions that are attributable to platelet activation, like ACS. Conversely, disorders in secondary haemostasis may protect against conditions where blood coagulation is predominantly involved (such as AF). However, this theoretical protective phenotype is not always clinically evident. In the following sections, we will discuss the available evidence for each bleeding phenotype in the

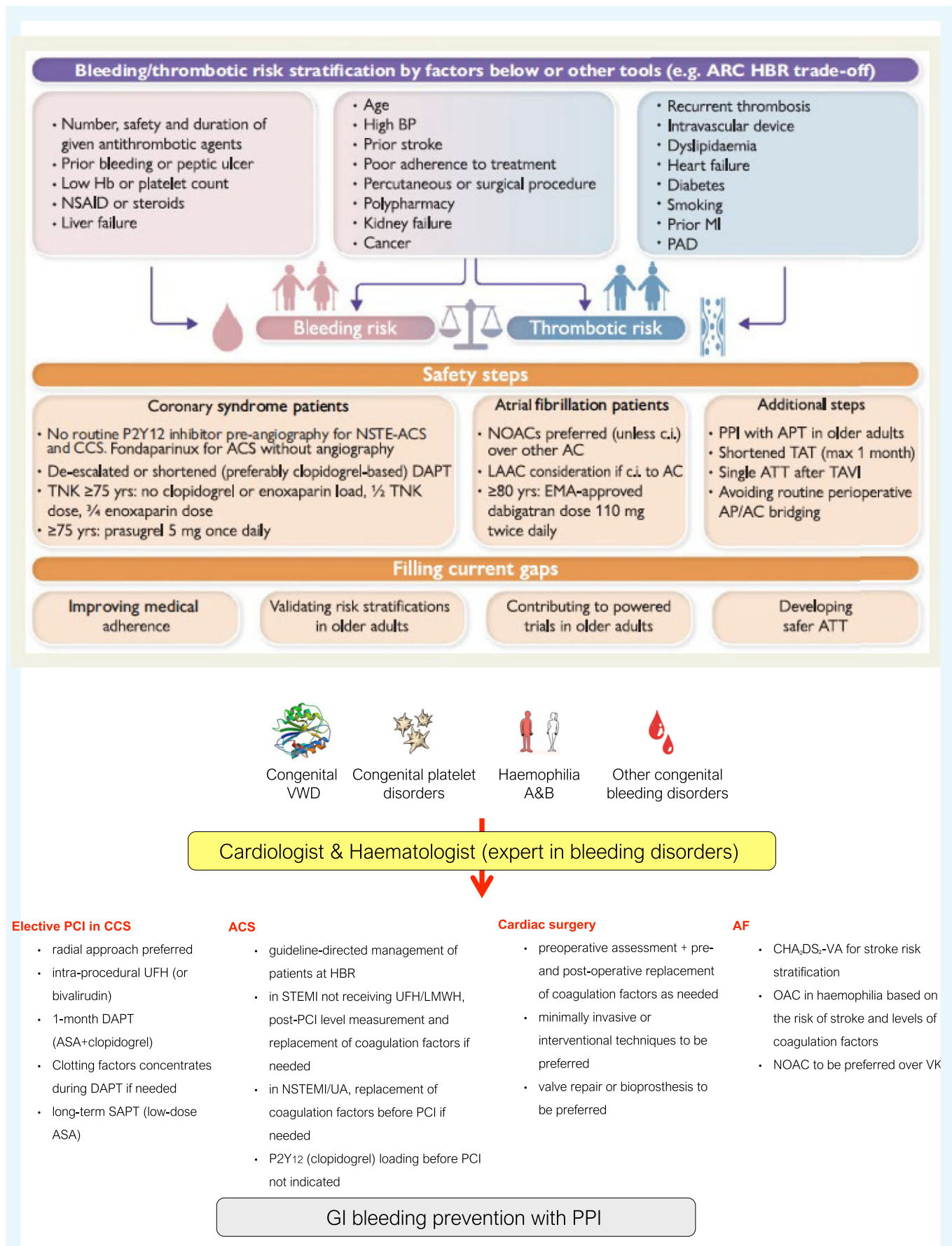


Figure 1 Major pathways and relevant considerations in the cardiovascular management of patients with congenital bleeding disorders.

most common cardiac conditions and provide suggestions regarding antithrombotic therapy.

Change in life expectancy of patients with congenital bleeding disorders and risk of ischaemic events

Until around 1960, severe bleeding disorders like haemophilia were seen almost exclusively in young people. The reason was that few with a severe phenotype survived past adolescence as it was nearly impossible to prevent fatal haemorrhage. In this period when bleeding caused death before ageing, comorbidities were a secondary concern. With the significant advancement in treatment options and strategies available today, life expectancy for people with bleeding disorders is now approaching that of their peers in the general population. The standard of care in patients with severe bleeding disorders is to replace the missing clotting factor to prevent bleeding. In haemophilias, von Willebrand disease (vWD) and several rare bleeding disorders, the regular replacement of the missing clotting factor converts the severe bleeding phenotype to a mild/moderate one. With this approach, life-threatening, and spontaneous bleeds are largely prevented.³

Nowadays, we have an increasing ageing population with bleeding disorders and, in addition to the usual comorbidities associated with advanced age in the general population, several specific additional issues occur in patients with bleeding disorders. In ageing people with congenital bleeding disorders of all severities, an increase in the incidence of cardiovascular disease (CVD), AF, and cancer is to be further expected.

Although past reports have suggested that bleeding disorders like haemophilia may confer some protection against CV events due to the natural hypocoagulant status arising from low levels of coagulation factors (F) VIII/IX, studies of vascular markers of CVD including carotid and coronary artery calcification measures have demonstrated that atherosclerosis develops similarly over time as in the general population.⁴ Ageing itself is a risk factor for ASCVD, and therefore it is reasonable to expect that an increasing number of persons with bleeding disorders may be at risk of acute CV events such as ACS and ischaemic stroke. A recent analysis of the literature showed that while persons with haemophilia are at increased risk of haemorrhagic stroke and intracranial bleeding when compared to a control population (1.4–5.31% vs. 0.2–0.97%; 1.1–10.8% vs. 0.04–0.4% per year, respectively), it remains unclear whether and to what extent persons with haemophilia are protected from arterial, as well as venous thrombosis.⁵ The prevalence of atherothrombosis [myocardial infarction (MI)/stroke] in patients with bleeding disorders compared to the general populations seems conflicting, with some reporting lower, comparable or even higher prevalence in those with haemophilia.¹ Prospective new studies are therefore needed to understand the incidence of bleeding vs. thrombotic events in people with haemophilia. Moreover, as life expectancy increases, the prevalence of AF and secondary thromboembolic stroke is also not well established as compared to a general, age and sex-matched population.⁶

Recent data from a large database showed that vWD is associated with a significantly lower prevalence of ischaemic heart diseases compared to a matched, general population (adjusted odds ratio 0.65, 95% confidence interval 0.63–0.67).⁷

Among other congenital coagulation defects, congenital dysfibrinogenemia (both qualitative and quantitative) has been associated with both spontaneous bleeding and thrombosis complications, depending on the genetics of mutations.^{8,9} Given the rarity of these congenital defects, in a relatively small cohort of subjects with FVII

and FXIII deficiency, a prothrombotic phenotype has also been described.⁹

Congenital platelet disorders (both qualitative and quantitative) are rare and associated with a haemorrhagic phenotype. Exceptional cases of thrombotic complications in these conditions have been reported, usually associated with major CV risk factors.¹⁰

The management of CV comorbidities may therefore be one of the most important challenges in this ageing population at high bleeding risk. Treatment decisions about antithrombotic therapy in persons with bleeding disorders are complex, as they require decisions with respect to the intensity of the anticoagulant and antiplatelet therapy, duration of the therapy and characteristics of the antithrombotic agents, as well as consideration of the individual's bleeding risk and phenotype. It is therefore important to emphasize that these bleeding disorders manifest as a spectrum, ranging from mild (where thrombotic risk may prevail) to severe (where bleeding risk will prevail). This is crucial to consider in decision-making when initiating any therapy for CV prevention or treatment.

The evidence to support treatment strategies in persons with bleeding disorders and CVD or AF is scarce and often based on expert opinion. These are now a primary concern, causing new clinical challenges.

Disease-tailored therapeutic implications

1. VWD

VWF mediates platelet adhesion to damaged endothelium (primary haemostasis), participates in platelet activation, and acts as a protective carrier protein for coagulation FVIII.¹¹ VWD is the most frequent of the inherited rare bleeding disorders (up to 1% of the overall population), caused by defects in the concentration, or function of vWF.^{12,13} It is characterized by mild to severe mucocutaneous bleeding. *Table 1* provides an overview of the different congenital forms of vWD. The acquired vWD^{14,15} (seen in conditions such as aortic stenosis—Heyde's syndrome,^{16,17} mechanical circulatory support,¹⁸ and haematological malignancies¹⁴) is out of the scope of this document. To make the diagnosis and assess the severity of vWD, at a minimum, vWF antigen and activity, and FVIII level should be measured. For the definition of the subtype of vWD, multimers and the testing of the underlying genetic mutation are available.

VWD is treated by antifibrinolytics, desmopressin, and/or intravenous vWF-concentrates with or without FVIII.¹⁹ Due to growing life expectancy in patients with (severe) vWD, common atherosclerotic disorders (e.g. stroke, ACS, CCS), might occur more frequently.²⁰ Most data stem from case reports. Inherent clinical decisions are hence often based on expert opinion and consensus statements. *Table 2* gives a synopsis of some of the suggestions listed below.

ACS

ACS is not typically observed in patients with severe primary haemostasis disorders (35–67% reduction as compared to reference populations; vWD protects against arterial thrombosis).²¹ Therefore, it is not surprising that ACS/ischaemic stroke is primarily observed in patients with milder type 1 vWD,²¹ and less commonly, in patients with dysfunctional vWF (type 2).²² VWD-patients admitted with ACS have a higher 90-day readmission because of bleeding, but not because of thrombotic recurrence²² and have similar rates of in-hospital death (6.4%) and bleeding (3.8%) as non-vWD patients after ACS.²³

Many of the circumstances advised in ACS patients also pertain to CCS patients. For example, the recommendation in the ESC ACS and CCS Guidelines is to prefer radial over femoral access for all patients.

Table 2 In addition to these specific advises for each clinical condition, general measures for each disorder should also be adhered to (e.g. the use of antifibrinolytic therapy, preference for radial access in coronary angiography, dual antiplatelet therapy for as short a duration as possible, adequate control of cardiovascular risk factors, etc.)

Disease	Affected part of haemostasis	ACS	CAD	Treatment ACS	Treatment CAD	Treatment AF	Cardiac valve-surgery
Von Willebrand disease	Primary haemostasis (mild to complete deficiency; dysfunctional vWF); in severe forms combined with FVIII deficiency	Only in mild forms (vWD impairs platelet aggregation)	Probably same incidence as in non-vWD population	- Elective PCI/CABG (\pm vWF concentrates); DES ^a ; radial - Prefer PCI above thrombolysis; - VWF replacement maintaining FVIII:C levels \pm 50% during PCI - Only ASA or shortest duration of DAPT in patients with moderate to severe bleeding - Conventional treatment in patients with very mild disease - Secondary prevention	- Elective PCI/CABG (\pm vWF concentrates); DES; radial - Only ASA or shortest duration of DAPT in patients with moderate to severe bleeding - Conventional treatment in patients with very mild disease - Secondary prevention	- oral anticoagulation should not be withheld in patients with CHA ₂ DS ₂ -VA > 2 and factor VIII levels above 50% but needs to be weighted to the severity of vWD and bleeding history, and monitoring of FVIII:C and VWF:RCo levels.	FVIII:C levels \pm 50% during surgery and combined anticoagulant/antiplatelet treatment and avoiding high FVIII/VWF peak with careful monitoring of FVIII:C and VWF:RCo levels.
Inherited platelet disorders	Primary haemostasis—Platelets; wide spectrum of diseases and disease severity						
Haemophilia A	Secondary haemostasis—FVIII (mild to complete deficiency)						
Haemophilia B	Secondary haemostasis—FIX (mild to complete deficiency)						

Maintaining the spectrum is crucial here: severe platelet dysfunctions do not lead to ACS due to severe primary haemostasis disorders, milder forms of CPDs can often be treated with SAPT. If DAPT is necessary, a combination with clopidogrel should be chosen. During surgery, platelet transfusion may be appropriate before, during, and for a long time after surgery, depending on the severity of the condition. For specific platelet disorders, more targeted therapies may be needed (eg. FVII concentrate for Glanzmann disease, thrombopoietin, ...). A case-by-case approach is the general rule here.

Patients with haemophilia A or B who experience an ACS should receive guideline-directed medical and interventional treatment according to the 2023 ESC guideline for the management of ACS, as indicated for patients at high bleeding risk. However, there are specific considerations that must be taken into account when treating such patients, and involvement of a haematologist with expertise in bleeding disorders at the first opportunity with each patient is essential.

Peak factor activity level of \sim 80–100 IU/dL before PCI if possible, maintain a trough level $>$ 50 IU/dL for 24–48 h after the PCI; Avoid levels $>$ 150 IU/dL; DAPT (ASA plus clopidogrel) for 1 month after ACS or PCI plus achieve trough levels of FVIII/IX \geq 20% during DAPT or use Emicizumab; 1 month of DAPT followed by ASA or clopidogrel SAPT.

CHA₂DS₂-VA score may overestimate stroke risk; clotting factor levels $<$ 10 IU/dL: naturally anticoagulated; clotting factor levels between 10 and 20 IU/dL: subtherapeutic naturally anticoagulated; clotting factor levels above 20 IU/dL: initiate DOAC at the conventional dose.

Achieve a peak factor activity level of $>$ 80–100% and through factor activity level $>$ 20 IU/dL; minimally invasive surgery is preferred; bioprosthetic valves are preferable

CAD, coronary artery disease; ACS, acute coronary syndrome; AF, atrial fibrillation; vWF, von Willebrand factor; vWD, von Willebrand disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ASA, aspirin; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; DES, drug eluting stent; DOAC, direct oral anticoagulants.

^a Most patients with type 1 have a mild bleeding tendency and should be treated with DES.

In addition to platelet count, the diagnosis of platelet disorders requires platelet function testing, e.g. with platelet aggregometry and flow cytometry, to characterize the defect. Platelet disorders are characterized by mild to excessive mucocutaneous bleeding.

The group of CPDs can be divided into:

- Congenital thrombocytopaenias, in which low platelet count and resulting bleeding diathesis are the leading phenotype.
- Congenital thrombocytopathies, which are mainly characterized by functional defects of the platelets (platelet function disorders): defects of receptors, granule content and release, transcription factors, components of signal transduction cascades, the cytoskeleton, various enzymes, or the membrane.³¹
- Platelet defects that combine thrombocytopaenia and impaired platelet function.

Management of CPDs is often limited to strategies to correct low platelet count and manage the risk of bleeding in patients undergoing invasive procedures or surgery, with antifibrinolytics, desmopressin, and platelet transfusion as needed.³² TPO receptor agonists (i.e. eltrombopag and romiplostim) have shown clinical utility in some CPDs to increase platelet count before surgery or intervention.^{33,34}

ACS

In general, ACS is rarely observed in patients with CPDs.³⁵

Coronary angiography and PCI

Coronary angiography should always be performed radially,^{24,25} although no increased incidence of bleeding in (treated) CPD patients was reported via the femoral route compared to a non-CPD population.³⁴ UFH can be administered during the procedure, but in practice, UFH is usually only administered when PCI is indicated (scoop and run diagnostic angiography).

Antiplatelet treatment

Antiplatelet therapy post-ACS and post-PCI depends on the severity of the CPD, the bleeding history of the patient, and the type of PCI (stent type, location, etc.). Low-dose aspirin is generally well tolerated and has the largest evidence in most patients.³⁶ In cases where DAPT is necessary, therapy is best combined with clopidogrel and administered for the shortest duration possible to prevent serious bleeding. If the patient has a known severe bleeding diathesis, SAPT (of short duration) is advised usually with low-dose aspirin, although definite studies and guidelines are lacking. Therefore, antiplatelet therapy in patients with CPDs should be assessed and weighed on a case-by-case basis.

CCS and/or elective PCI

CCS can theoretically occur in all forms of patients with CPDs, as it is primarily a consequence of atherosclerotic disease in older age.³⁷ Therefore, these patients should be treated in the same manner regarding clinic, diagnostics, and treatment as other patients. The same precautions should be taken pre-, peri-, and post-procedurally during (elective) PCI as in ACS (see above). Paramount here is again the adequate control of other CV risk factors.

VHD

There are basically no scientific data on patients with VHD and platelet disorders. Similar to the other disease entities discussed in this work, a close collaboration with a haematologist is advised in order to define the degree of functional platelet abnormality and to decide on adequate oral anticoagulation (OAC).

AF

In patients with AF, withholding therapeutic anticoagulation in high ischaemic risk patients may increase the risk of stroke. On the other hand, even reduced-intensity therapeutic anticoagulation carries a higher risk of bleeding in patients with thrombocytopaenia.^{38,39} Thus, the stroke risks should exceed the bleeding risk in case of CPD in order to justify the continued use of OAC. Due to the rarity of platelet defects no recommendations can be given, but therapeutic decisions should follow the analogy of patients with (acquired) thrombocytopaenia.

OAC has generally been considered safe in patients with platelets $>50 \times 10^9/L$.³⁸ Accordingly, published surveys showed a predominant threshold of $50\,000/\mu L$ for initial management changes.³⁸ At present, there are no specific recommendations for the management of OAC in patients with thrombocytopaenia and AF in current guidelines, apart from a set of recommendations in patients with thrombocytopaenia and cancer.²

An AF-team approach, including a cardiologist and haematologist or internal medicine physician who is familiar with platelet disorders, is of importance when initiating therapeutic anticoagulation.

1. Standard-intensity anticoagulation with platelet count $>50 \times 10^9/L$ appears to be appropriate for patients with AF and a CHA₂DS₂-VA score of ≥ 2 . In some congenital thrombocytopaenias, a lower threshold might be feasible depending on the bleeding phenotype.⁴⁰
2. In patients with AF with a CHA₂DS₂-VA score of ≥ 2 , and platelet count of $25\text{--}49 \times 10^9/L$, a dose-modification strategy may be appropriate, defined as lower approved doses of DOAC.

At present, there are no prospective data to validate the above statements. Studies are urgently warranted to determine the best level of therapeutic anticoagulation in patients with CPDs and AF.

3. Haemophilia A and B

Haemophilia A and B are X-linked congenital bleeding disorders with no or reduced factor VIII (haemophilia A) or factor IX (haemophilia B) and a similar bleeding phenotype closely linked to the residual factor activity. Severe disease is defined as factor levels $<1\%$, moderate disease as $1\text{--}5\%$, and mild disease as $5\text{--}40\%$.³ Standard of care is the intravenous prophylactic replacement of the missing clotting factor in patients with a severe bleeding phenotype. For haemophilia A, plasma derived and recombinant standard half-life (SHL) factor VIII concentrates (half-life around 12 h) and recombinant extended half-life factor VIII concentrates (half-life around 18 h) are available. In addition, for haemophilia A emicizumab, a bispecific antibody mimicking factor VIIIa is available for sc replacement therapy. For the treatment of haemophilia B, plasma derived and recombinant standard half-life (SHL) factor IX concentrates (half-life around 18 h) and recombinant extended half-life factor XI concentrates (half-life around 90 h) are used.

Since there is an absence of large studies, the recommendations for antithrombotic therapy in patients with haemophilia and cardiac disease are based on case reports, expert opinion, and consensus statements. [Table 2](#) summarizes some of the therapeutic considerations.

ACS

Patients with haemophilia A or B who experience ACS should receive guideline-directed medical and interventional treatment according to the 2023 ESC Guidelines for the management of ACS, as indicated for patients at high bleeding risk.⁴¹ However, there are specific considerations that must be taken into account when treating such patients, and involvement of a haematologist with expertise in bleeding disorders is essential.

Replacement of coagulation factors for patients undergoing cardiac catheterization

In patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI without UHF or LMWH (e.g. when factor levels are not known), it is advised to measure factor levels immediately after the PCI, and replacement treatment instituted as soon as possible. In patients with non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina, coagulation factors should be replaced before PCI. The specific doses and levels below are based on international consensus, developed from case series, observational data, and experience, as no randomized controlled trials have been performed in such patients.^{1,42–44}

A bolus infusion of clotting factor concentrate factor VIII or factor IX (CFC) is recommended before arterial puncture for cardiac interventional procedures, aiming for a peak factor activity level of ~80–100 IU/dL before the procedure,⁴⁴ with additional doses as needed to maintain a trough level >50 IU/dL for 24–48 h (usually with bolus infusions of FVIII or FIX every 12–24 h depending on the used concentrate). Compared to those with severe disease, those with mild haemophilia generally require less CFC replacement. Peak factor levels >150 IU/dL impose a thrombotic risk and are not advised, underscoring the importance of individualized and specialist treatment.^{45,46}

Approximately 1 in 4 people with haemophilia A and about 3–10 in 100 people with haemophilia B will develop an antibody—called an inhibitor—to the treatment product (medicine) used to treat or prevent their bleeding episodes.⁴⁷ In patients with inhibitors, additional supplementation with bypassing agents is indicated. In patients with inhibitors who are using emicizumab, recombinant FVIIa replacement can be used at a dosage of 90 μ g/kg every 3–4 h for 24–48 h, but the use of activated PCC (aPCC) is not advisable. In patients with inhibitors not using emicizumab, bolus infusions with aPCC 50–80 IU/kg every 12 h are an alternative.¹

Coronary angiography and PCI

Radial access is preferred over the femoral approach,^{24,25} as it allows easier haemostatic compression and is associated with a much lower rate of bleeding complications,⁴⁸ although case series have reported catheterization via the femoral route in patients with haemophilia with negligible complications.⁴⁹ PCI should be undertaken using the latest generation drug-eluting stents, to allow the minimum duration of DAPT (1 month) without increasing the risk of stent thrombosis.¹

Anticoagulant strategy during PCI

Guidelines recommend anticoagulation during coronary intervention.^{41,50} UFH are advised to be given intravenously after replacement of clotting factor levels reaching levels of 70–100%, and is preferable to LMWH because of its shorter half-life and ease of reversibility with an antidote, in case of bleeding. Bivalirudin, which has a half-life of 1.5 h, is an alternative in patients who cannot receive UFH (for instance, due to congenital AT deficiency) and case reports document that it can be safely used in patients with haemophilia undergoing PCI.^{48,51}

In the 2023 ESC Guidelines for the management of ACS, glycoprotein IIb/IIIa inhibitors, which significantly increase the risk of major bleeding, are not recommended for routine use, only for very high thrombus burden/bailout/no-reflow situations.⁴¹ But even in these difficult therapeutic situations, one must keep in mind that glycoprotein IIb/IIIa inhibitors have not been sufficiently evaluated in patients with haemophilia and so their use should be avoided as much as possible.⁴⁸

Antiplatelet therapy

Patients with ACS with haemophilia are advised to be treated with DAPT after PCI, following usual loading doses. While aspirin administration is advised upon diagnosis, pre-PCI loading with a P2Y₁₂

inhibitor is not advised in patients in whom an early interventional strategy is planned, in order to minimize the risk of bleeding.¹

Clopidogrel is the P2Y₁₂ inhibitor of choice, since it is associated with lower bleeding risk than either ticagrelor or prasugrel, and since the latter has not been evaluated in patients with haemophilia.^{1,42,51} Conventional guideline-directed loading doses of both aspirin and clopidogrel are advised should be given, followed by maintenance therapy.

The duration of DAPT following an ACS with or without PCI should be kept to one month, followed by monotherapy with aspirin or clopidogrel.

The duration of clotting factor replacement is dependent on the duration of DAPT. After the initial clotting factor infusion, clotting factor measurements are required with clotting factor substitution appropriate to achieve trough levels of FVIII/FIX \geq 20% during DAPT,^{36,52–54} although some recommend trough clotting factor \geq 30%^{42,53,55} or as long as DAPT is given. Afterwards, the regular factor replacement schedule of the patient can be continued to keep FVIII/FIX trough levels at least >1–5% long-term SAPT.^{1,53,54,56}

In a consensus document, the majority (70%) of respondents agreed that the use of DAPT in patients with haemophilia A being treated with emicizumab would *not* require additional factor replacement.⁴² In patients with inhibitors, management is advised to be individualized, depending on the use of emicizumab and other risk factors for bleeding.

Persons with haemophilia receiving antiplatelet therapy should be offered gastric protection with a proton pump inhibitor.

CCS and/or elective PCI

In patients with haemophilia and documented, significant CCS, the recommendation for long term SAPT use is less robust than that for patients without haemophilia, although antiplatelet agents in haemophilia tend to be well tolerated.⁵⁷ SAPT comprising of aspirin (75–100 mg daily), or clopidogrel 75 mg daily if aspirin is not tolerated, is advised with CFC to maintain FVIII/FIX trough levels >1–5 IU/dL.^{1,48} Low dose aspirin is generally advised for patients with established ischaemic cardiovascular disease (CVD) who have mild haemophilia or who are receiving routine prophylactic factor for moderate or severe haemophilia.^{48,58} If bleeding complications occur, aspirin should be discontinued. If no clotting factor prophylaxis is given, aspirin for primary prevention may not be needed.⁵¹

Following elective PCI, DAPT duration should be kept to a minimum, ideally no more than 1 month, in line with ESC guidelines for high bleeding risk patients.^{50,59} Whilst patients are on DAPT, clotting factor substitution is advised to achieve FVIII/FIX trough levels \geq 20%,^{36,52–54} although some experts prefer levels \geq 30%.^{44,53,55} Afterward, the regular factor replacement schedule of the patient should be reinstated to maintain FVIII/FIX trough levels \geq 5–10% during SAPT.^{53,55,56}

Persons with haemophilia receiving antiplatelet therapy should be offered gastric protection with a proton pump inhibitor.

VHD

In patients with haemophilia who require valve surgery, careful consideration of options is required, to minimize the risk of bleeding perioperatively and long term, postoperatively.

For patients undergoing cardiac surgery, early involvement of a haematologist is essential, including the assessment of factor levels and inhibitors, with CFC given preoperatively to achieve a peak factor activity level of >80–100%. A literature review of 72 patients with haemophilia A undergoing cardiac surgery⁶⁰ predominantly comprising of coronary artery bypass grafting procedures and/or valve surgeries, showed uneventful clinical outcomes in the majority of cases, but a complication rate of 20%, most commonly bleeding.

Postoperatively, anticoagulation is variable, with consensus papers advising trough FVIII/IX levels to be maintained >20 IU/dL,¹ although higher levels have been advised by others.⁶⁰

When possible, minimally invasive surgery is preferred over open-heart surgery, to reduce the risk of perioperative bleeding.

For mitral regurgitation, valve repair is preferable to replacement especially in patients with haemophilia, as it avoids the need for long-term anticoagulation, with a number of successful cases described in the literature.^{61–64} For valve replacement, although successful outcomes have been reported with mechanical valve replacement in patients with haemophilia,^{1,64–66} the use of bioprosthetic valves is preferable to mechanical valves, if possible, to avoid the long-term risks of OAC.²⁷ For aortic stenosis, case reports detail successful transcatheter aortic valve implantation in patients with haemophilia,^{64,67,68} which is likely to become the treatment of choice, given the relatively low risk of periprocedural bleeding and the lack of requirement for long-term anticoagulation. In patients who require aortic valve replacement who are unsuitable for a bioprosthesis, the mechanical On-X valve may be considered, which allows reduction in the intensity of anticoagulation 3 months after surgery. In patients with On-X valves in the aortic position, a target INR of 1.5–2.0 with warfarin, in combination with low-dose aspirin, resulted in similar rates of valve thrombosis or thromboembolism and lower rates of bleeding, than a target INR of 2.0–3.0.⁶⁹

Following coronary artery bypass surgery, the need for SAPT should follow those for CCS with low dose aspirin, including the need for prophylactic CFC administration to patients with severe haemophilia.⁶⁰

AF

OAC to prevent ischaemic stroke or systemic embolism represents a cornerstone in the management of AF and individual treatment decisions are based on estimated underlying stroke and bleeding risks.^{72,73} The prevalence of AF in patients with haemophilia appears comparable to that in the general population^{74–77} and while the risk of ischaemic stroke was reported to be higher in some analyses,^{75,76,78–80} none of those studies specifically reported stroke rates in patients with AF.

As stated above, current European clinical practice guidelines for the management of AF recommend individual assessment of ischaemic stroke and systemic embolism risk based on the CHA₂DS₂VA score and recommend treatment with OAC in all patients with an estimated annual risk of $\geq 2\%$ (a score of ≥ 2).^{72,73} For patients at intermediate risk (a score of 1), OAC should be considered according to these guidelines. However, in patients with haemophilia, data on risk assessment for ischaemic complications is scarce and the CHA₂DS₂VA score has not been validated.^{1,81} Given the hypo-coagulable state caused by FVIII or FIX deficiency, the presumably lower rates of certain variables of the score such as very advanced age and peripheral artery disease, the CHA₂DS₂VA score may overestimate stroke risk in patients with haemophilia, and observational data suggest that OAC prescription does not follow CHA₂DS₂VA scoring.⁷⁶ A consensus view from 2014 by the ADVANCE working group suggested that a higher CHA₂DS₂VASc score of ≥ 3 might better reflect high stroke risk in this population.⁸² However, as the CHA₂DS₂VA score differs from the CHADS₂-score only by the addition of high age and peripheral artery disease, all factors uncommon in patients with haemophilia, the most recent EHA-ISTH-EAHAD-ESO clinical practice guidance on antithrombotic treatment in patients with haemophilia recommends the use of the CHADS₂-score without recommending specific thresholds to guide initiation of OAC.¹ Furthermore, it discourages the use of bleeding risk scores in patients with haemophilia as suggested by clinical practice guidelines for the general population, as all patients with haemophilia are considered to be at high bleeding risk.¹

A major consideration in the decision-making regarding the initiation of OAC in patients with haemophilia is whether such patients can be considered, at least in part, 'physiologically anticoagulated'. Laboratory studies based on the endogenous thrombin potential (ETP) have been used to compare the coagulation potential of patients with haemophilia A and B with patients on OAC and healthy untreated controls.⁸³ Given that the ETP between patients with haemophilia A and B did not appear to be significantly different,⁸⁴ expert consensus is to consider the following observations applicable to both patients with haemophilia A and B, as outlined in the recent EHA-ISTH-EAHAD-ESO clinical practice guidance.^{83,85}

- Patients with haemophilia and clotting factor levels <10 IU/dL (i.e. patients with levels at diagnosis $<10\%$ and with trough levels below 10% on prophylactic treatment with factor VIII or factor IX) can be considered 'physiologically anticoagulated', comparable to patients on vitamin K antagonists (VKA) with INR levels between 2 and 3.
- Patients with haemophilia and clotting factor levels between 10 and 20 IU/dL can be considered 'subtherapeutically anticoagulated' to a similar extent as patients on VKA with INR levels between 1.5 and 1.9.
- Patients with haemophilia and clotting factor levels above 20 IU/dL are characterized by strong interindividual ETP variance and overlap to some extent with healthy controls.

Several expert consensus documents and practice guidelines have formulated minimal clotting factor thresholds required for the safe initiation of OAC.^{1,43,50,82,86} The above mentioned most recent clinical practice guideline recommends a minimal trough F VIII/IX level of 20 IU/dL for the initiation of OAC.¹ In such patients, OAC can be started without prophylaxis. Patients with factor levels <20 IU/dL should be considered naturally anticoagulated, and if short-term OAC is necessary or the patient is deemed at very high thrombotic risk, the guidelines recommend adapting clotting factor prophylaxis to maintain trough levels of >20 IU/dL. In patients with severe haemophilia on clotting factor prophylaxis, therapy should be adapted to maximum peak levels of 25 IU/dL and no OAC should be administered.^{1,83,85}

If the decision for OAC treatment has been made, we believe that the favourable clinical trial data supporting DOAC treatment over VKA with regard to major bleeding events including ICH^{39,87} may be extrapolated to the haemophilia population, and the availability of effective reversal agents supports such a preference for DOACs. We believe that OAC should be given in the approved dose. Given the clearly superior performance of DOACs compared to antiplatelet agents in reducing ischaemic stroke or systemic embolism at comparable bleeding risk, there is no role for SAPT in patients with haemophilia and AF.^{88,89}

In this specific patient population characterized by high bleeding risk, strategies that may allow avoidance of antithrombotic drugs seem attractive. Transcatheter occlusion of the left atrial appendage (LAA), the main site of thrombus formation in AF, has shown promising results in the general population⁷³ and has successfully been tested in a small case series of patients with haemophilia.⁹⁰ Patients, however, require preprocedural aspirin loading and at least daily low dose aspirin until endothelialization of the device as well as full heparinization periprocedurally. Together with the thrombogenicity of the intervention and the possible need for rescue surgery, factor substitution to achieve 80–100% activity during and shortly after the procedure is standard of care.^{90–92} No data exist on long-term antithrombotic management in patients with haemophilia.

Pulmonary vein isolation (PVI) represents yet another potential approach for rhythm control, which has been successfully tested in patients with haemophilia.³⁰ Procedures are performed under full heparinization, and 80–100% peak coagulation factor levels and patients require OAC for several weeks to months after the procedure. There are no data to support the safety of omitting OAC in patients

Table 3 Rare bleeding disorders and associated factor deficiencies

	Prevalence	Bleeding phenotype	Risk of thrombosis
Fibrinogen—Factor I Fibrinogen deficiency is complex: one distinguishes between afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia. Patients with dysfibrinogenaemia may have an elevated thrombotic risk and no bleeding risk.	1:1000000	Usually mild and heterogenous even in afibrinogenaemia	Severe thromboembolic events might occur: both venous and arterial, independent of age.
Prothrombin—Factor II	1:2000000	Moderate to severe (when factor levels are low)	Non reported
Factor V Factor V Leiden does not lead to factor V deficiency and is different from the bleeding disorder 'Factor V-deficiency'.	1:1000000	Usually mild to moderate depending on factor level	Severe thromboembolic events might occur: both venous and arterial, independent of age.
Combined factor V + VIII	1:1000000	Usually mild to moderate depending on factor levels	Severe thromboembolic events might occur: both venous and arterial, independent of age.
Factor VII	1:500000	Mild to severe (no proportional correlation to factor level)	Severe thromboembolic events might occur: both venous and arterial, independent of age.
Factor X	1:1000000	Moderate to severe depending on factor level	Not reported.
Factor XI	1:1000000	Usually mild and mainly soft tissue bleeding	Severe thromboembolic events might occur: both venous and arterial, independent of age.
Factor XIII	1:2000000	Moderate to severe depending on factor level	Severe thromboembolic events might occur: both venous and arterial, independent of age.

with factor levels of >20 IU/dL following PVI. Patients with AF undergoing cardiac surgery should undergo concomitant AF ablation and/or LAA ligation/exclusion.

4. Rare bleeding disorders

Rare inherited bleeding disorders are a heterogeneous group of coagulation disorders resulting from deficiencies in coagulation factors: I (fibrinogen), II (prothrombin), V, VII, X, XI, XIII, or combined factor V and VIII deficiency.⁹³ The rare congenital bleeding disorders are usually transmitted in an autosomal recessive fashion and account for up to 5% of all the inherited deficiencies of coagulation factors.⁹⁴ Rare bleeding disorders have a low prevalence in the general population (one case in 500 000 for FVII up to one in 2 000 000 for FXIII) and have a highly variable clinical presentation.⁹⁵ In most of these rare bleeding disorders, the degree of factor deficiency correlates with the severity of bleeding, with the exception of factor XI.⁹⁶ In general, major bleeds, such as those occurring in the central nervous system or musculoskeletal systems, appear to be less frequent in rare bleeding disorders than in haemophilia or vWD.⁹⁷ The treatment of these disorders is based on the replacement of the deficient factor, where available. However, e.g. for FII or FV deficiency, there is no single factor concentrate available.⁹⁷ Table 3 provides an overview of these disease entities.

ACS

ACS in patients with rare bleeding disorders has been reported.⁹⁸ Published case series and registry studies indicate that the prevalence of ACS in patients with rare bleeding disorders might be similar to that expected in the general population.⁹⁹ However, ischaemic stroke

or acute peripheral artery occlusion might occur less frequently than MI in patients with rare bleeding disorders.^{99,100}

A systematic review of published case reports until 2015 revealed overall 45 cases of MI/ACS (four with fibrinogen deficiency, two with FV deficiency, two with FVII deficiency, 36 with FXI deficiency and one with FXIII deficiency).¹⁰¹ Another paper including case series and the authors' own cases until 2006 reported on 42 patients with rare bleeding disorders suffering from arterial thromboses (MI in 28 cases; ischaemic stroke in four; arterial occlusion in eight).⁹⁸ Nevertheless, information is lacking in respect to the type of the MI/ischaemia and the occurrence of intracoronary thrombus (complete thrombotic vessel closure by plaque rupture vs. subtotal calcified lesions without a thrombus formation). In the majority of patients with MI and rare bleeding disorders, common atherosclerotic risk factors were present, confirming that in the presence of atherosclerosis, a congenital hypocoagulability does not fully protect from ischaemia.¹⁰¹ Importantly, no patients with FII or X deficiency and arterial or venous thromboses were reported in the literature. However, this does not necessarily indicate that these two severe bleeding conditions protect from thrombosis, but rather reflect the rarity of the disease. Of interest, higher occurrence of MI was reported in patients with FXI deficiency than in the other rare factor defects.¹⁰¹ Additionally, two patients with FXI deficiency also showed acute peripheral arterial occlusions.¹⁰¹ It has been postulated that the severe FXI deficiency might be protective against ischaemic stroke but not against acute MI.⁹⁹ The critical evaluation of the literature also suggests that thrombosis in FVII deficiency may be associated with the common prothrombotic risk factors, confirming the assumption that FVII deficiency also does not protect from thrombosis.⁹³ The most frequent prothrombotic risk factors were surgery, old age, and factor substitution therapy.⁹³

Antiplatelet therapy

The use of antiplatelet and anticoagulant agents for acute and chronic management of ACS patients with rare bleeding disorders has not been established so far. The majority of published cases (most of them occurred between 1990 and 2015) underwent CABG or were treated with first generation drug-eluting stents (DES) for PCI.¹⁰¹ After PCI, aspirin and clopidogrel were the main antiplatelet drugs used (with an unknown duration of treatment and lacking data for safety profile on DAPT or aspirin monotherapy during the long-term treatment).¹⁰¹ Yet, the thrombogenicity of the new generation DES improved and modern PCI, with use of intravascular imaging, allows optimization of the procedure and therefore, the risk of stent thrombosis is decreased substantially. In line with these improvements in device and procedural techniques, the results of multiple trials support the use of very short duration DAPT (1 month) after DES-PCI in the general population and especially for patients at high bleeding risk (HBR) undergoing PCI for ACS or electively.¹⁰² Notably, bleeding diathesis or a previous bleeding are major variables in the ARC-HBR score, which can be used to guide the duration of DAPT after PCI. In this respect, all patients with rare bleeding disorders would undergo HBR-PCI, and therefore very short DAPT duration of no more than 1 month might be justified in such patients.¹⁰³ Interestingly, in addition to the antithrombotic treatment for ACS, factor replacement therapy was reported to be administered simultaneously only in some cases with rare bleeding disorders.¹⁰¹

CCS; VHD

Since these conditions are so rare, all decisions must be done individually with regards to initiation of OAC and antiplatelet treatment, type of OAC as well as alternative procedures. Those should be taken in an interdisciplinary fashion, with close liaison between haematologists and cardiologists.

AF

Data regarding the incidence of AF and the indication for use of OAC in patients with rare bleeding disorders are lacking.

Scientific statements/clinical consensus statements

- For all management decisions, we advise to involve a haematologist with expertise in bleeding disorders (3/4).
- For patients undergoing coronary angiography and PCI is advised to:
 - Prefer radial over femoral approach (3/4).
 - Use UFH (or bivalirudin if patients cannot take UFH) following replacement of clotting factors (3/4).
 - Keep duration of DAPT comprising aspirin and clopidogrel to no more than 1 month (3/4).
 - To administer, while on DAPT, clotting factor concentrate, although may not be needed in patients with haemophilia A treated with emicizumab (2/4).
 - After DAPT, continuing SAPT with low-dose aspirin with continuation of the regular factor replacement schedule of the patient during long-term SAPT (2/4).
- For patients with ACS, it is advised to:
 - Use guideline-directed medical and interventional treatment according to the 2023 ESC Guidelines for the management of ACS, as indicated for patients at high bleeding risk (2/4).
 - In STEMI undergoing primary PCI without UFH or LMWH, to measure factor levels immediately after PCI and use replacement therapy as needed (2/4).

- In NSTEMI or unstable angina, to use replacement of coagulation factors before PCI (clotting factor replacement will depend on the severity of the haemophilia/clotting factor deficiency) (2/4).
 - To use aspirin loading upon diagnosis, followed by maintenance dose, while pre-PCI loading with a P2Y12 inhibitor is generally not advisable (3/4).
 - To avoid thrombolysis, glycoprotein IIb/IIIa inhibitors and ticagrelor or prasugrel as P2Y12 inhibitors (3/4).
- We advise using gastric protection with a proton pump inhibitor in patients on antiplatelet therapy (3/4).
 - Low-dose aspirin is generally advised for patients with established ischaemic CVD who have mild haemophilia or who are receiving routine prophylactic factor for moderate or severe haemophilia (3/4).
 - For patients undergoing cardiac surgery, we advise:
 - To assess preoperative factor levels and inhibitors, with CFC administration preoperatively and postoperatively, as needed (3/4).
 - To use, when possible, minimally invasive cardiac surgery or interventional procedures over open-heart surgery, to reduce the risk of bleeding (2/4).
 - To prefer mitral valve repair and use of aortic bioprosthesis, as needed, over mechanical valve replacement, to reduce the long term bleeding risk with anticoagulation (2/4).
 - For patients with AF, we advise to:
 - To prefer the CHADS₂-score over the CHA₂DS₂-VA score, which may overestimate stroke risk in patients with haemophilia (2/4).
 - To assess the need for OAC based on the risk of stroke and by the severity of haemophilia (clotting factor levels) (3/4).
 - To prefer DOACs over VKA if OAC is deemed necessary (3/4).

Conclusions

Because of better haemostatic management and increased life expectancy of patients with congenital bleeding disorders, CVD requiring antithrombotic therapy can be encountered nowadays in the ageing adult population. While it is controversial whether congenital bleeding disorders may confer protection against thrombosis, both atherothrombosis and cardioembolic complications, an increased risk of bleeding is established in both coagulation and platelet abnormalities. Thus, an individualized approach to antithrombotic therapy is warranted to balance the two opposing risks. Adoption of the safest interventional and surgical techniques, reduction of the intensity and/or duration of single or combined antithrombotic therapies, and attention to the safe levels of clotting factors, with their replacement when indicated, should generally be considered. Larger, high-quality evidence is urgently needed. Each treatment decision must be carefully considered based on both the CV context and the severity of the bleeding disorder, and in consultation with the treating haematologist.

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Data availability

In the present article, there are no data to share, as all resources are published articles or expert opinion expressions.

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