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SUPPLEMENT ABSTRACT

Rare bleeding disorders: Advances in management

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Abstract

Inherited factor coagulation deficiencies and vascular bleeding disorders, associated with bleeding of various severity, are often classified as rare bleeding disorders (RBDs). These include inherited fibrinogen disorders, inherited platelet function disorders (IPFD) and hereditary haemorrhagic telangiectasia (HHT). In the last decades, there have been large increases in knowledge on the epidemiology, genetics, physiopathology, clinical features, and diagnosis of RBDs, but improvements in management have been more limited and remain challenging. The treatment mainstay of RBDs is based only on replacement of a few available coagulation factor concentrates or cryoprecipitates. There is growing interest in therapeutic agents that enhance coagulation or inhibiting anticoagulant pathways in RBDs. In severe IPFD, the optimal platelet transfusion strategy is not yet established. Moreover, data is scarce on the effectiveness and safety of desmopressin and/or antifibrinolytic drugs often used for milder IPFD treatment. The best fibrinogen replacement strategy (prophylaxis vs. on demand) in afibrinogenemia is still debated. Similarly, the optimal trough fibrinogen target level for treatment of acute bleeding, and the role of fibrinogen replacement during pregnancy in mild hypofibrinogenemia and dysfibrinogenemia, have not been properly evaluated. The therapeutic arsenal in HHT includes antifibrinolytics and a series of antiangiogenic agents whose potential efficacy has been tested in small studies or are under investigation for treatment of bleeding. However, there is need to address several issues, including the optimal dosing strategies, the potential emergent toxicity of longer-term use, and the impact of systemic antiangiogenic treatment on visceral arteriovenous malformations.

KEYWORDS
fibrinogen deficiency, hereditary haemorrhagic telangiectasia, inherited platelet dysfunction, rare bleeding disorders

1 | INTRODUCTION

Bleeding disorders are a heterogeneous group of rare inherited defects that manifest with bleeding diathesis, due to a variety of defects in blood components or blood vessels. Haemophilia (H) A and B, together with von Willebrand disease (VWD), are the most frequent coagulation disorders. Other coagulation defects are considered rare bleeding disorders (RBDs).[1,2] According to the 2022 Annual Global Survey of the World Federation of Haemophilia, people affected with RBDs represent 9% of all patients with a bleeding disorder. Though it is often categorized as an RBD, hereditary haemorrhagic telangiectasia (HHT, Osler-Weber-Rendu) is actually the second most common inherited bleeding disorder worldwide, afflicting one in 5000 persons, or 1.4 million people worldwide.[3,4] For every man

with haemophilia, approximately one woman and one man have HHT, and HHT may be the most morbid inherited bleeding disorder of women.[5] The complexity of inherited platelet function disorders (IPFD) has made it difficult to compare their prevalence to these other conditions.

In view of the many causes of abnormal bleeding, an accurate diagnosis strategy is mandatory. As indicated in Figure 1, a step-wise approach to diagnostic investigations is often used, that can be customized based on local test availabilities, practices, and preferences. In the last decades, cohort studies and data from international registries have laid the basis for a better understanding of most of RBDs, but many questions are still open regarding their optimal management. In this review, we summarize the state-of-the art knowledge on available treatments and future possible therapeutics for RBDs and discuss more specifically some of the current challenges with management of IPFD, fibrinogen disorders and HHT.

2 | DISCUSSION

2.1 | Current status of factor concentrates and future possible therapeutics

Clinical symptoms of RBDs are extremely heterogeneous, with spontaneous or post-traumatic bleedings that vary with the type of disorder and the severity of the defect, such as the level of residual coagulation factor in plasma. Bleeding symptoms can be relatively minor, (e.g., mild epistaxis), whereas some are life-threatening, such as intracranial haemorrhage. Central nervous system (CNS), umbilical cord bleeding, hemarthroses and soft tissue hematomas are frequent with severe fibrinogen, FVII, FX and FXIII deficiencies; gastrointestinal tract bleeding occurs mainly in FX deficiency and spontaneous abortion is frequent in women with afibrinogenemia and FXIII deficiency.[6] Back in 2007, the European network of rare bleeding disorders (EN-RBD) explored the association between residual clotting levels and clinical bleeding severity.[7] The results of this study showed that the association between coagulant activity and clinical bleeding severity was strong in fibrinogen, combined FV + VIII, FX, and FXIII deficiencies, whereas it was weak in FV and FVII deficiencies and not evident for FXI deficiency (Table 1). The poor correlation between factor level and bleeding for FXI deficiency could be partially explained by a reduced fibrinolytic resistance in patients whose bleedings usually occur after surgery or trauma, particularly at sites with higher fibrinolytic activity, reflecting perhaps a more permeable and more lysable clot following from reduced thrombin formation under conditions where tissue factor (TF) concentrations are low leading to less TAFI activation.[8]

On the whole, RBDs are a heterogeneous group of disorders and could not be considered as a single entity, and the clotting levels necessary to ensure a complete absence of spontaneous bleeding could differ in each RBD.[7] This clinical heterogeneity, and the much lower number of patients affected by RBDs compared to haemophilia, has led to a lack of knowledge, and delays in the design and production of novel therapeutic approaches to RBDs. Nowadays, the presentation and management of HA and HB are well defined whereas the other, less common RBDs are in need of more attention to improve their diagnosis and management.[9,10]

Different novel therapies, such as extended half-life replacement, and non-replacement therapies (such as bispecific antibody, rebalancing therapies, and gene therapy), have become a reality for the treatment of HA and HB, whereas for some rare deficiencies (e.g., FII and FV), specific factor concentrates are not yet available.[2] Evidence-based guidelines are largely absent for RBDs. Instead, individual experiences, observations on bleeding severity, and limited product availabilities, have guided on-demand and prophylactic therapies for RBDs. The treatment mainstay of RBDs is still grounded in replacement of available coagulation factors and the use of adjunctive haemostatic therapies when bleedings are minor or mucosal. When prescribing a replacement therapy for RBDs, a hierarchy should be followed based on the safety of replacement products with regard to blood-borne pathogens: specific concentrates including recombinant (available for FVII and FXIII deficiencies) or plasma-derived products should be considered the first choice for treatment, when available, followed by prothrombin complex (for FII and FX) and virus-free cryoprecipitate when specific products are not available.

In regard to prophylaxis, routine schemes are applied for managing afibrinogenemia, and severe FVII, FX and FXIII deficiency due to the high risk of life-threatening bleeding.[11] Patients with severe bleeding episodes can benefit regular prophylaxis, and in particular, the ease of replacement therapy for severe FXIII deficiency have simplified the prevention of CNS bleedings, and recurrent abortions in affected women.

The recent development of novel haemostatic drugs for haemophilic patients, that target improved haemostasis by decreasing the effect of the natural anticoagulant rather than replacing the missing factor, could probably have a role in treatment of some RBDs. One approach is based on siRNA, that is, ALN-AT3 (fitusiran).[12] Preliminary studies, testing the in vitro effect of reduced antithrombin activity in different RBDs, showed that antithrombin reduction increases thrombin generation and normalizes coagulation parameters by FV-, FVII- and FXI-deficient plasma samples.[13] However, in FXI deficiency without spontaneous bleeding, such strategies might have unacceptable high risks of thrombosis.

Another approach to rebalancing haemostasis, using a monoclonal antibody (VGA039) directed against human protein S that inhibits its cofactor activity for TFPI (tissue factor pathway inhibitor) alpha and activated protein C (APC), can enhance thrombin generation by increasing both the initiation and propagation phases of coagulation.[14] The antibody treatment is administered parenterally at doses of 1 mg/kg—intravenously or subcutaneously with a relatively long half-life of 21 and 12 days, respectively. In vitro studies indicate that VGA039 increases thrombin generation in a concentration dependent manner in congenital VWD and in FVII-, FVIII-, FIX-, FXI-, and FXIII-deficient plasmas, but not in FX- or FV-deficient plasmas, tested in the presence of APC. Drug repurposing[15] and gene editing strategies, mainly those based on CRISPR/Cas technology, have been also investigated as treatment for RBDs.[16] Some interesting novel therapeutic

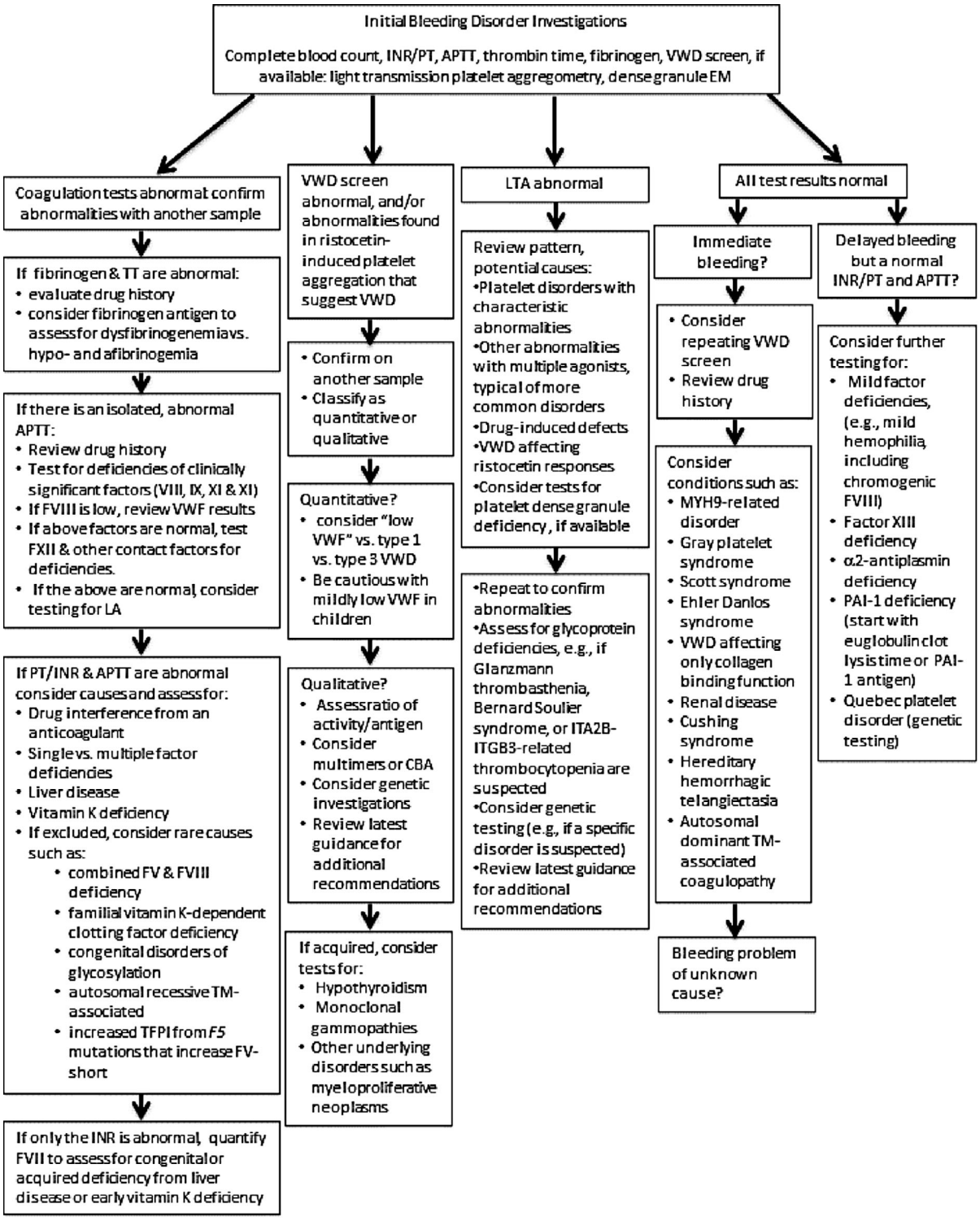

FIGURE 1 Strategic guide to bleeding disorder diagnosis. Bleeding problems have diverse causes that often require step-wise diagnostic investigations, that should be customized based on the suspected conditions, test availability, local practices, and preferences. Follow up investigations are important to confirm or evaluate the cause, based on initial diagnostic test findings.

under exploration include SerpinPC, which was designed to inhibit the anticoagulant function of APC, but it has not been yet investigated in RBDs,[17] and several anti-TFPI agents, Concizumab (currently approved for treating haemophilia B patients with inhibitors in some regions of the world), and Marstacimab that is undergoing testing in clinical trial.[18,19] All these drugs need to be tested in clinical trials involving men and women with bleeding disorders other than haemophilia.

Finally, despite some interesting data from preclinical studies on gene transfer approaches in animal models for FVII deficiency, von Willebrand disease and Glanzmann Thrombasthenia (GT), major steps

TABLE 1 General features of rare bleeding disorders.

Deficiency	Estimated prevalence of severe form[a,b]	Correlation with factor level	Asymptomatic levels[c]	Available products
Fibrinogen	1-50:1′000′000	Strong	>1 g/L	pd concentrate Cryoprecipitate FFP
Prothrombin	1:2′000′000	NA	>10%	PCC, FFP
Factor V	1:1′000′000	Weak	>10%	FFP Platelet concentrates
Combined factor V and VIII	1:1′000′000	Strong	>40%	Desmopressin + FFP Factor VIII concentrate + FFP
Factor VII	1:500′000	Weak	>20%	Recombinant FVIIa pd concentrate PCC FFP
Factor X	1:1′000′000	Strong	>40%	pd concentrate PCC
Factor XI	1:1′000′000	Not evident	>20%	pd concentrate FFP Antifibrinolytics
Factor XIII	1:2′000′000	Strong	>30%	pd concentrate Recombinant FXIII Cryoprecipitate FFP
VKCFD	NA	NA	NA	Vitamine K PCC FFP

Abbreviations: FFP, fresh frozen plasma; NA, not available; PCC, prothrombin complex concentrate; pd, plasma-derived; VKCFD, vtamin-K dependent coagulation factors.
[a]Prevalence is higher in countries with consanguinity.
[b]Mild (heterozygous) forms are more frequents.
[c]Based on EN-RBD.[7]

forward are needed before to be able considering this kind of therapy in patients.[20]

2.2 | Looking to the future for platelet disorders: challenges and opportunities for improved treatment and management

Platelet disorders are important causes of bleeding that include conditions that reduce platelet numbers and/or impair platelet function.[21] IPFD cause more bleeding than inherited thrombocytopenia (IT).[22] IPFD include rare, severe bleeding disorders such as GT and Bernard Soulier syndrome (BSS), and more commonly encountered disorders with milder bleeding risks (e.g., ~17–20-fold greater risks for surgical and childbirth/miscarriage related bleeding, compared to the general population).[22] There are important opportunities to optimize IPFD diagnosis, management, and treatment, particularly for milder IPFD where evidence is more limited and of poor quality.

Like IT, IPFD have quite diverse genetic causes (Figure 2), which suggests that phenotypic characterization (i.e., assessments of: platelet numbers, size, morphology, tests of aggregation function etc., see Figure 1) will remain important for diagnosis.[21,23] Many commonly encountered IPFD are conditions of uncharacterized molecular causes that manifest with non-syndromic dense granule deficiency and/or impaired aggregation responses.[21,24] While genetic testing often yields a diagnosis for suspected IT, the yields for IPFD are lower, particularly for those without a suspected probable cause.[21,24]

Platelet transfusions are generally reserved for treating the more severe IPFD, such as GT and BSS, with increasing emphasis on using platelet-sparing therapies (to limit alloimmunization against HLA and platelet-specific antigens that cause platelet refractoriness) when possible.[22] The optimal platelet transfusion strategy for severe IPFD (i.e., numbers of units and duration of treatment) is uncertain, as dysfunctional autologous platelets may competitively inhibit the localization of transfused platelets to bleeding sites.[25] Considerable data has emerged on the usefulness (and low thrombotic risks) of recombinant activated factor VIIa (rFVIIa) as a platelet-sparing treatment for GT[26] and an ancillary treatment for BSS bleeding[27] and more studies are needed on its role (and cost effectiveness as a treatment) for other IPFD, including storage pool disorders.[28] Thrombopoietin receptor agonist drugs have been used to temporarily increase platelet counts in some IT (e.g., for surgery, during chemotherapy etc.; reviewed in[25]).

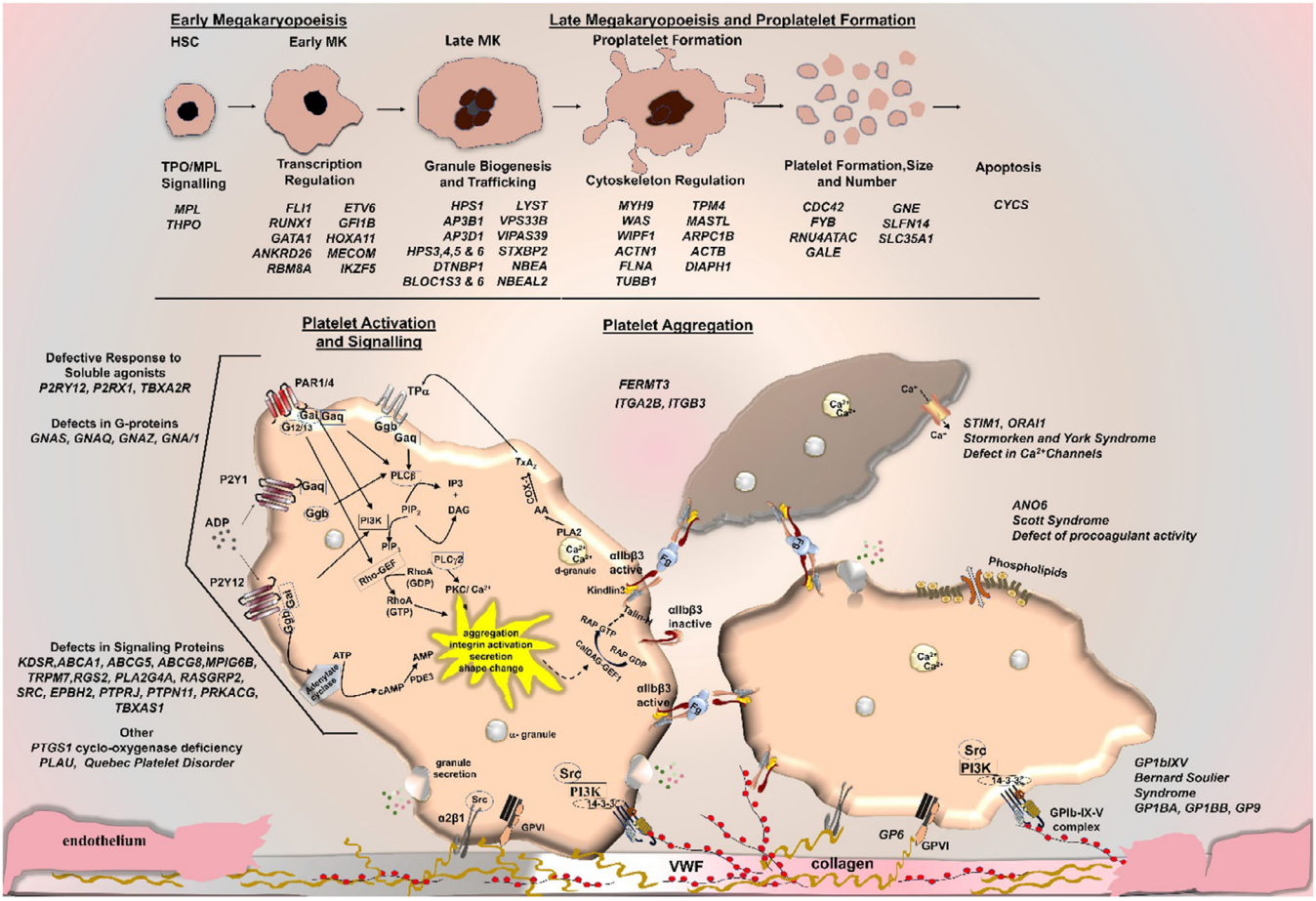

FIGURE 2 Genes and pathways involved in inherited disorders of platelet number and function. The genes involved at different stages of megakaryopoiesis are summarized in the top part of the figure, and those that are involved in platelet disorders that affect activation, signalling, aggregation, adhesion and procoagulant function are shown in the lower part of the figure.

For non-severe IPFD, desmopressin and/or antifibrinolytic drugs (such as tranexamic acid) are the most widely used acute and prophylactic therapies, and challenge-related bleeding is uncommon when these treatments are given (as reported in[22,24]). Unlike VWD, assessment of IPFD 'responsiveness to desmopressin' requires surrogate markers (e.g., assessment of platelet procoagulant function,[29] or shortening of the closure time or the bleeding time—a test that is no longer recommended).[30]

Information on the safety of desmopressin and antifibrinolytic drugs as treatments for bleeding mainly comes from studies of other patient populations (e.g., randomized placebo-controlled trials of these drugs for cardiac surgery, or for limiting bleeding from trauma, major surgery, post-partum haemorrhage, or heavy menstrual bleeding).[31,32] This reflects the current lack of high-quality direct evidence on IPFD treatment safety and benefits, and the much greater use of antifibrinolytic drugs for other populations. It is unclear if the 'usual' tranexamic acid treatment protocols for treating other patient populations (e.g., several doses on day of cardiac or orthopaedic surgery), are optimal for the treatment of persons with IPFD, who typically also receive other therapies (desmopressin; rFVIIa or platelet transfusions if the IPFD is severe). There is also a need for evidence on how often additional desmopressin doses are required postoperatively when desmopressin prophylaxis is given before surgery for IPFD.

Antifibrinolytic drugs remain the treatment of choice (and the only effective treatment) for Quebec platelet disorder, which has a unique, platelet-mediated gain-of-function defect in fibrinolysis due to markedly increased megakaryocyte/platelet urokinase plasminogen activator.[33] Their antifibrinolytic treatment has been given concurrently with anticoagulation for high thrombotic risk situations (e.g., chronic atrial fibrillation, hip surgery, etc.).[34,35]

As desmopressin and/or antifibrinolytic drugs are often used for milder IPFD,[22] prospective studies could help clarify their effectiveness and safety, particularly for surgical and dental prophylaxis. A randomized study is needed to compare treatment of commonly encountered IPFD with either (1) desmopressin, (2) antifibrinolytic drugs or (3) combined desmopressin and antifibrinolytic drugs, with cross-over to combined therapies for single treatment failures. Such studies might lead to improved, cost-effective IPFD treatment and management, and clarify when combined treatments are needed and when desmopressin might be safely omitted given that its use requires careful, temporary fluid restriction. Such studies might also clarify the risks for needing platelets (or other

TABLE 2 Type and sub-types of hereditary fibrinogen disorders.

Fibrinogen levels	Type of fibrinogen disorder	Sub-types
Fibrinogen activity undetectable Fibrinogen antigen undetectable	Afibrinogenemia	1A. Bleeding phenotype 2B. Thrombotic phenotype
Fibrinogen activity decreased Fibrinogen antigen decreased (usually cut-off activity/antigen > .7)	Hypofibrinogenemia	2A. Severe (<.5 g/L) 2B. Moderate (.5 ≤ 1.0 g/L) 2C. Mild (≥1.0 g/L but below RI limit) 2D. Fibrinogen storage disease
Fibrinogen activity[a] decreased Fibrinogen antigen in the normal range	Dysfibrinogenemia	3A. Hotspot and other fibrinogen variants 3B. Thrombotic-related fibrinogen variants (includes Fibrinogens Dusart, Caracas V, Ijmuiden, New York I, Nijmegen, Melun and Naples at homozygous state
Fibrinogen activity decreased Fibrinogen antigen decreased (usually cut-off activity/antigen < .7)	Hypodysfibrinogenemia	4A. Severe (<.5 g/L) 4B. Moderate (.5 ≤ 1.0 g/L) 4C. Mild (≥1.0 g/L but below RI limit)

Abbreviation: RI, reference interval.
[a]Clauss method as in dysfibrinogenemia, the PT-derived fibrinogens overestimate fibrinogen about 5–6-fold.

transfusions) when milder IPFD are managed with platelet-sparing therapies.

There are additional uncertainties about IPFD management that compromise optimal care. For example, the thrombotic risks associated with using combined tranexamic acid and desmopressin for surgical or dental prophylaxis in IPFD have not been estimated, nor have the potential thrombotic risks of prolonged tranexamic acid therapy for postpartum bleeding (which can cause thrombosis).[33] The risks for prolonged or delayed postpartum bleeding, that requires hormonal and/or antifibrinolytic drug therapy, are probably greater for severe IPFD, and optimal management needs clarification.[36] As prophylactic tranexamic acid does not reduce bleeding due to severe thrombocytopenia from haematological malignancy,[37] its role in managing IT bleeding needs evaluation. The thrombotic risk and optimal thromboprophylaxis for persons with milder IPFD has not been established, and there are uncertainties about the safety and benefits of antiplatelet therapy and anticoagulation therapies for persons with IPFD that develop ischemic heart disease, stroke and/or atrial fibrillation.

The future for persons with IPFD and IT will be brighter as more evidence emerges to optimize diagnosis, management, and treatment.

2.3 | Fibrinogen related disorders: current knowledge and future challenges

Hereditary fibrinogen disorders (HFDs) encompass a heterogenous variety of fibrinogen deficiencies, diagnosed and classified according to the fibrinogen activity and antigen levels, the genotype, and clinical phenotype (Table 2).[38] Their specific biological and clinical features are mainly determined by monoallelic or biallelic mutations in *FGA*, *FGB*, and *FGG* genes on chromosome 4. Afibrinogenemia is characterized by the complete absence of fibrinogen into blood, essentially due to homozygous null mutations in *FGA*.[39] The bleeding phenotype is severe and includes frequent muscle hematoma, hemarthrosis and cerebral bleeding.[40,41] Hypofibrinogenemia is generally caused by heterozygosity for a null mutation or a missense mutation especially in the conserved C-terminal domain of the Bβ or γ chains, impairing the assembly or the secretion of the fibrinogen molecule.[42] The bleeding phenotype depends on the fibrinogen level; patients with a fibrinogen level ≥ .7 g/L are mostly protected by spontaneous bleeding.[7,43] Dysfibrinogenemia is defined by normal level of a dysfunctional fibrinogen molecule.[44] Many missense mutations have been reported, up to 85% localized in the exon 2 of *FGA* or exon 8 of *FGG*, including two hotspot mutations (*FGA* p.Arg35His/Cys and *FGG* p.Arg301His/Cys).[45] While most patients with dysfibrinogenemia are asymptomatic, at least at diagnosis, the clinical manifestations can be highly heterogenous over time and can include a tendency to minor or major bleeding and/or recurrent thrombosis.[46] In hypodysfibrinogenemia, both the fibrinogen activity and antigen are decreased, more often due to a combined heterozygosity for mutations causing defect in fibrinogen secretion and modifications in fibrinogen structure. Usually, the clinical symptoms are more severe.[38]

Fibrinogen replacement is highly efficient to treat bleeding in HFDs.[11] Depending on their availability, fresh-frozen plasma, cryoprecipitate, and plasma-derived fibrinogen concentrates can be used as the source of fibrinogen.[2] Plasma-derived fibrinogen concentrates are the first choice as they have a safer profile due to a multistep viral inactivation, supply a precise amount of fibrinogen, and are readily available in some regions of the world. Several fibrinogen concentrates have been licensed in both adults and paediatric populations, with similar pharmacokinetics and pharmacodynamic properties even though head-to-head comparisons have not been performed.[47–53] Presently, evidence is lacking to optimize management of acute bleeding in HFDs. A few national guidelines and experts' consensus have proposed a target fibrinogen level ≥ 1 g/L and ≥ 1.5 g/L in case of minor or major bleeding, respectively.[6,44,54] Similar targets have been proposed to prevent surgical bleeding.[44,48] Tranexamic acid is usually added, even though precaution is needed when planning treatments for patients with thrombotic-related dysfibrinogenemia.

The role of fibrinogen replacement as primary prophylaxis for afibrinogenemia and severe hypofibrinogenemia is still matter of debate.[11] The high prevalence of CNS bleeding in a large series of patients (48/204; 23%)[40] and the high cumulative incidence of intracranial bleeding at 10 years reported in children (35%; 95%CI 23–51)[41] suggest that a primary prophylaxis may be needed early in childhood. However, the limited availability of fibrinogen concentrates or cryoprecipitates in most countries with higher rates of afibrinogenemia is a critical issue. Another concern (and debated point) is the potential thrombotic risk related to the administration of fibrinogen. Why patients with afibrinogenemia have an increased risk of arterial or venous thrombosis and whether this risk is related to the fibrinogen infusion are open questions that deserve further fundamental and clinical investigations. We are eagerly waiting for results from the Prospective Rare Bleeding Disorders Database (proRBDD) which hopefully will help in determine the benefits of primary prophylaxis in afibrinogenemia (http://eu.rbdd.org/, last access 31.01.2024).

Pregnancy is high risk clinical situation in HFDs with an increased risk of miscarriages, haemorrhage, and thrombosis. In a recent international study that evaluated 425 pregnancies, 28 (6.6) were complicated by bleeding, including 16 (3.8%) retroplacental hematoma, and 62/316 (19.6%) live birth by post-partum hemorrhage.[55] While it is well accepted that fibrinogen replacement is mandatory to maintain pregnancy to term in afibrinogenemia or severe hypofibrinogenemia, the optimal trough fibrinogen level to target is not established. Generally, experts suggest keeping a trough fibrinogen level ≥ 1 g/L throughout the pregnancy and ≥1.5 g/L at delivery and in early the post-partum.[6,44,54] The role of fibrinogen infusion in prevent and treat obstetrical complications in mild or moderate hypofibrinogenemia and dysfibrinogenemia has not been specifically investigated. Given the complexity of pregnancy management in HFDs, it is crucial to develop international collaborations and foster prospective studies in order to determine the impact of fibrinogen infusion on obstetrical complications, the minimal fibrinogen threshold to target to decrease the risk of bleeding and to allow a neuraxial anaesthesia, the efficacy and security of oral antifibrinolytics to prevent post-partum haemorrhage.

In dysfibrinogenemia, fibrin clot is formed by abnormal fibrin with defective clot mechanical properties eventually resulting in increased clot permeability or in resistance to fibrinolysis. Infusion of normal fibrinogen could decrease the proportion of abnormal fibrinogen adhering and forming the clot. Polymorphisms in fibrinogen genes, such as *FGB* Bβ Arg478Lys (rs4220) and *FGA* Aα Thr331Ala (rs6050), are associated with structural modifications of the fibrin clot.[56] How these polymorphisms can act as genetic modifiers in response to the fibrinogen replacement is a promising axis of research in dysfibrinogenemia.

2.4 | Hereditary haemorrhagic telangiectasia: promising new therapies but many unanswered questions

Hereditary Haemorrhagic Telangiectasia is autosomal dominant and results from mutations in the transforming growth factor-beta pathway that cause angiogenic dysregulation and the formation of mucocutaneous bleeding telangiectasias and visceral arteriovenous malformations (AVMs). The most common symptom is severe, recurrent epistaxis from nasal telangiectasias, which affects over 95% of persons with HHT.[57] Gastrointestinal telangiectasias occur in approximately 75% of cases, causing chronic gastrointestinal bleeding in approximately one-third of all HHT patients. Visceral AVMs most commonly occur in the liver (~70%), lung (~50%) and brain (~20%) and may result in numerous morbid or fatal complications including embolic or haemorrhagic stroke, haemoptysis or pulmonary haemorrhage, high output heart failure, chronic liver disease and cirrhosis, and others.

Presently, there are no U.S. FDA or EMA-approved therapeutics to treat HHT, and therefore all agents discussed herein are off label. While cyclic, recurrent procedural management, including local ablative procedures in the nose (e.g., laser, electrical, or chemical cautery) and gastrointestinal tract (e.g., argon plasma coagulation) used to be the mainstay of bleeding management over a decade ago, the recognition that tissue injury may stimulate greater telangiectasia formation, and the emergence of effective systemic therapies (Table 3), has resulted in a paradigm shift in therapy for HHT-associated bleeding over the past several years.[58,59] Currently, in addition to a nasal moisturization regimen that is recommended for all patients with HHT, oral antifibrinolytics are recommended for mild-to-moderate epistaxis and gastrointestinal bleeding and systemic antiangiogenic therapies are recommended for moderate-to-severe epistaxis and gastrointestinal bleeding.[59] Generally, patients with mild-to-moderate bleeding are able to maintain a normal haemoglobin with oral iron supplementation or occasional intravenous iron infusions and do not suffer severe social, financial, or psychological repercussions from the frequency and severity of their epistaxis. Patients with moderate-to-severe bleeding, on the other hand, require regular intravenous iron infusions to maintain a normal haemoglobin or regular red cell transfusions to maintain an acceptable haemoglobin, and limit the severe social, financial, or psychological repercussions from their epistaxis.[60–62] At present, local ablative nasal treatments are best reserved for acute situations in which rapid haemostasis is essential ('rescue' circumstances), as these procedures are temporizing.[59] Likewise, argon plasma coagulation should only be employed to treat telangiectasias that are actively bleeding at the time of an endoscopy. Neither is a durable long-term solution.

Oral antifibrinolytics are optimally dosed 2–3 times daily (tranexamic acid) or 3–4 times daily (epsilon-aminocaproic acid) at 1000 to 1500 mg per dose.[60,63] Indefinite therapy is required for ongoing bleeding control. With this approach, patients can enjoy moderate, though often significant, improvement in epistaxis.[3,64] The primary downsides of antifibrinolytic treatment in HHT include gastrointestinal side-effects, high pill burden, and very high frequency of medication administration making compliance difficult. Though antifibrinolytics have a theoretical thrombotic risk, an increased risk of thrombosis with chronic treatment has not been observed in published HHT studies,[64–66] although the body of data is not large. Additional study is needed to uncover potential long-term toxicities of high-dose chronic antifibrinolytic therapy over years to decades.

TABLE 3 Systemic medical therapies for the treatment of bleeding in HHT.

Therapies with efficacy described in large studies	Therapies with potential efficacy described in small studies	Therapies with potential efficacy currently under investigation	Therapies with clear negative studies (should not be used)
• Antifibrinolytic therapies ○ Tranexamic acid ○ ε-Aminocaproic acid[a] • Primary antiangiogenic therapies ○ Bevacizumab ○ Pomalidomide	• Primary antiangiogenic therapies ○ Thalidomide ○ Pazopanib • Somatostatin analogues (octreotide, lanreotide)[b] • Hormonal agents[c] ○ Estrogens and progestins ○ Selective estrogen response modifiers (SERMs)	• Primary antiangiogenic therapies ○ VAD044 ○ Pazopanib ○ Nintedanib • Agents with potential secondary antiangiogenic effects ○ Sirolimus ○ Tacrolimus	• Primary *nonsystemic* antiangiogenic therapies ○ Bevacizumab nasal spray or submucosal nasal injections ○ Oestrogen nasal spray ○ Tranexamic acid nasal spray • Agents with potential secondary antiangiogenic effects ○ Doxycycline

[a]Unlike tranexamic acid, ε-aminocaproic acid has not been evaluated in large prospective trials in HHT but is widely accepted as being generally equivalent in routine clinical use, albeit with a shorter half-life requiring more frequent dosing.
[b]Effective for gastrointestinal bleeding only; no effect on epistaxis.
[c]Not recommended for use in the Second International HHT Guidelines given feminizing effects on men and known, well-defined thromboembolic risk.

For patients in whom antifibrinolytics are inadequate, not tolerated, or contraindicated, systemic antiangiogenic agents may be used. Antiangiogenic agents are believed to have disease-modifying properties in HHT, inducing haemostasis through involution of vascular lesions. These agents can induce profound improvements in bleeding and anaemia in patients with HHT, including significant improvement or cessation of bleeding and normalization of hemoglobin.[67–72] Bevacizumab is an intravenous humanized IgG1 monoclonal antibody directed against vascular endothelial growth factor-A originally developed to treat cancers. Numerous studies have described the effectiveness and safety of bevacizumab use to treat HHT-associated epistaxis and gastrointestinal bleeding.[67,69,71] Intravenous bevacizumab is usually dosed at 5 mg/kg every 2 weeks for 4–6 treatments to induce haemostasis (induction treatment) and then continued at the same dose every 4–8 weeks to maintain haemostasis (maintenance treatment).[60] The most common side-effects associated with bevacizumab are hypertension (~20%) and proteinuria (~10%); thromboembolism rates do not appear to be elevated with this HHT therapy.[67,69,71] Immunomodulatory imide drugs including thalidomide and pomalidomide, which inhibit VEGF-A and basic fibroblast growth factor, among other actions, have also been found to be effective in treating HHT and are an oral antiangiogenic option.[70,73] Thalidomide is used with caution given its known prothrombotic effects and drug-induced neuropathy, which may be permanent. Pomalidomide is a newer thalidomide derivative with much lower thrombotic risk and with minimal neuropathy risk. A large, randomized, controlled, multicentre U.S. clinical trial of pomalidomide in HHT (PATH-HHT) has been completed demonstrating safety and efficacy, and final publication of its results are awaited.[70] But as much as we now understand about the efficacy of these agents, however, much more is still unknown, including optimal dosing strategies, the potential emergent toxicity of longer-term use, and the impact of systemic antiangiogenic treatment on the genesis, progression, and potential involution of visceral AVMs. Other therapeutics, including VAD044, pazopanib, sirolimus, and tacrolimus are currently under investigation for the treatment of bleeding in HHT (Table 3),[58] and if found to be efficacious, the same unanswered questions will apply to them as well.

3 | CONCLUSION

In the last years, there has been fantastic progress in the available products for patients with haemophilia. Unfortunately, in the setting of RBDs, IPFD and HHT, achievements are less remarkable, even yet some molecules developed for haemophilia could be of interest for some RBDs and several promising agents are testing in HHT. Gathering more and more data thank to national and international networks, enhancing the diagnosis, promoting interventional clinical trial with old and new molecules in specific clinical settings are some of the challenges the scientific community involved in bleeding disorders will face in the next future.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

This review is based on previously conducted studies and does not report data from any new studies with human participants or animals by any of the authors.

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