Treatment of patients with rare bleeding disorders in the Netherlands

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ORIGINAL ARTICLE

Treatment of patients with rare bleeding disorders in the Netherlands: Real-life data from the RBiN study

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Abstract

Background: Patients with rare inherited bleeding disorders (RBDs) exhibit hemorrhagic symptoms, varying in type and severity, often requiring only on-demand treatment. Prolonged bleeding after invasive procedures is common. Adequate peri-procedural therapy may reduce this bleeding risk.

Objective: To describe general treatment plans of RBD patients and evaluate the use of peri-procedural hemostatic therapy.

Methods: In the Rare Bleeding Disorders in the Netherlands (RBiN) study, RBD patients from all six Dutch Hemophilia Treatment Centers were included. General treatment plans were extracted from patient files. Patients with a dental or surgical procedure in their history were interviewed about use of peri-procedural treatment and bleeding complications.

Results: Two-hundred sixty-three patients with a rare coagulation factor deficiency or fibrinolytic disorder were included. Eighty-four percent had a documented general treatment plan. General treatment plans of patients with the same RBD were heterogeneous, particularly in factor XI deficiency.

Overall, 308 dental and 408 surgical procedures were reported. Bleeding occurred in 50% of dental and 53% of surgical procedures performed without hemostatic treatment and in 28% of dental and 19% of surgical procedures performed with hemostatic treatment. Not only patients with severe RBDs, but also patients with mild deficiencies, experienced increased bleeding without proper hemostatic treatment.

Conclusion: Large heterogeneity in general treatment plans of RBD patients was found. Bleeding after invasive procedures was reported frequently, both before and after RBD diagnosis, irrespective of factor activity levels and particularly when

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A complete list of the members of the RBiN Study Group appears in the Appendix.

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peri-procedural treatment was omitted. Improved guidelines should include uniform recommendations for most appropriate hemostatic products per RBD and emphasize the relevance of individual bleeding history.

KEYWORDS
blood coagulation disorders, fibrinolysis, hemorrhage, hemostasis, surgical procedures

1 | INTRODUCTION

Rare bleeding disorders (RBDs) refer to congenital deficiencies in secondary hemostasis (i.e., fibrinogen, factor [F] II, FV, FVII, FX, FXI, FXIII, and combined FV and FVIII deficiencies) or the fibrinolytic pathway (alpha2-antiplasmin [α2-AP] deficiency, plasminogen activator inhibitor 1 [PAI-1] deficiency, and hyperfibrinolysis).[1] In general, RBDs have an autosomal recessive inheritance pattern with the exception of dysfibrinogenemia and some cases of FXI deficiency.[1–3] The prevalence for homozygous or compound heterozygous deficiencies ranges from approximately 1:500,000 for FVII deficiency to 1:2,000,000 for FII and FXIII deficiencies.[4,5] A significantly higher prevalence is seen in populations with a high rate of consanguinity.[1,3,4]

Patients with RBDs exhibit a wide variety of symptoms, ranging from asymptomatic or only minor bleeding to severe and life-threatening bleeding.[6] In general, characteristic bleeding symptoms for all RBDs are mucosal tract bleeding episodes, such as epistaxis and menorrhagia, and excessive bleeding during and after invasive procedures and delivery.[4,7–11] For a significant number of patients with a (mild) RBD, bleeding complications during invasive procedures are the first presentation after which hemostatic analysis often follows with assessment of the specific RBD.

The hemostatic management of patients with RBDs during invasive procedures or child delivery can be challenging due to the heterogeneous clinical phenotype and the lack of a strong association between residual coagulation factor activity level and bleeding severity in most RBDs. The management of these patients is further complicated by the limited availability of evidence-based guidelines.[3,7,8] In the last few years, a number of national and international registries have emerged for patients with RBDs.[1,12–15]

In a recently performed Dutch nationwide cross-sectional study for patients with an inherited RBD (Rare Bleeding Disorders in the Netherlands, RBiN, study), large heterogeneity in bleeding phenotype was observed among different RBDs, but also between patients suffering from the same type of RBD and identical residual factor activity levels.[1] A potential explanation is the well-known variability in correlation between coagulation factor activity level and clinical bleeding severity in RBDs. This correlation ranged from strong for FII and FX deficiencies to only moderate for deficiencies of fibrinogen, FV, FVII, FXIII, and α2-AP. There was no correlation for FXI-deficient patients between their baseline FXI activity level and their bleeding phenotype.[1] Comparable results were found in a cohort study among 489 RBD patients performed by the European Network of Rare Bleeding Disorders (EN-RBD). This study reported a strong correlation with bleeding phenotype for deficiencies of fibrinogen, FV+FVIII, FX and FXIII, a poor association for FV and FVII deficiency, and no association for FXI deficiency.[5]

Essentials

- General treatment plans of patients with the same rare bleeding disorder (RBD) are heterogeneous.
- Patients with RBDs frequently have bleeding complications after invasive procedures performed without peri-procedural hemostatic treatment, both before and after RBD diagnosis.
- Every patient with a fibrinolytic disorder needs peri-procedural therapy with hemostatic agents to prevent bleeding complications.
- Treatment decisions in coagulation factor deficiencies should be based on both the individual bleeding phenotype as well as individual coagulation factor activity level.

The aim of this RBiN substudy is to describe the general treatment plans of the Dutch RBD population and to evaluate the use of historical peri-procedural hemostatic therapy in relation to the incidence of associated bleeding complications.

2 | PATIENTS AND METHODS

The RBiN study is a nationwide cross-sectional study of patients from all six Dutch Hemophilia Treatment Centers (HTC) who were diagnosed with a congenital RBD, including coagulation factor deficiencies and fibrinolytic disorders, and aged 1 year or older. Patients were included from October 2017 to November 2019. All included patients were diagnosed with an RBD after referral to an HTC for a bleeding diathesis, family history of RBD, or prior abnormal values of screening laboratory tests.[1] The specific patient inclusion criteria and design of the RBiN study have been published previously.[1] Hyperfibrinolysis was defined as an euglobulin clot lysis time (ECLT) ratio before and after application of a tourniquet ≥5.8 (reference range 1.2–5.7, locally validated assay). Patients with an ECLT ratio ≥5.8 were only classified as having hyperfibrinolysis when PAI-1 deficiency and α2-AP deficiency were excluded. The study was approved by the Medical Ethical Committee of Arnhem-Nijmegen.

Written informed consent was obtained from all patients and/or parents in case of minors.

2.1 | General treatment plans

Commonly, general treatment plans describe the advised hemostatic therapy according to the severity and grading of bleeding, classified as mild, moderate—severe, and life-threatening bleeding. When a patient presents with a bleeding, the exact categorization as mild, moderate—severe, or life-threatening depends on the interpretation of the treating physician. In general, mild bleeding refers to minor bleeding symptoms that are easy to control with local support (like epistaxis or cutaneous bleeding). Moderate—severe bleeding refers to major bleeding manifestations like muscle hematoma, joint bleeding, or gastrointestinal bleeding, and life-threatening bleeding to, for instance, intracranial bleeding or bleedings resulting in abnormal vital signs or even hemorrhagic shock.

For each study participant, the most recently documented general treatment plan was extracted from electronic patient files, and therefore treatment plans of all patients were valid at time of inclusion in the RBiN study. General treatment plans of children and adults were analyzed separately.

2.2 | Invasive procedures

In all study patients with a history of tooth extraction or surgical intervention, a structured interview about the type of procedure, use and type of peri-procedural hemostatic treatment, and bleeding complications was conducted by the same investigator during the study visit. Bleeding complications were defined as all patient-reported bleeding events during or after a specific dental or surgical procedure. The patients with a surgical procedure in their medical history were also interviewed about the age at the performance of the intervention. Age at RBD diagnosis was extracted from electronic patient files.

Procedures before RBD diagnosis were almost always performed without hemostatic treatment and were therefore often the patient's first bleeding manifestation. Therefore, surgical procedures performed before RBD diagnosis (age at surgical intervention <age at RBD diagnosis) and after RBD diagnosis (age at surgical intervention >age at RBD diagnosis) were analyzed separately. Procedures were excluded from this subanalysis when age at RBD diagnosis was equal to the age at surgical intervention or in case of missing data about age at diagnosis and/or surgical intervention, due to uncertainty whether the RBD was already known at the time of intervention.

2.3 | Clinical and laboratory phenotype

In all patients, the bleeding assessment tool of the International Society on Thrombosis and Haemostasis (ISTH BAT) was used to determine clinical bleeding phenotype. The ISTH BAT was conducted during the study visit by the same investigator in all included patients. Furthermore, blood was drawn during the study visit for laboratory testing. All coagulation factor activity levels were therefore measured centrally in the same laboratory.

2.4 | Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics, version 25. Continuous variables were presented as medians with interquartile range (IQR). Categorical variables were reported as counts and percentages. Proportions were compared using Fisher's exact tests. All *P*-values are two-sided. *P*-values lower than 0.05 were considered statistically significant.

3 | RESULTS

In total, 263 patients were included in the RBiN study. Baseline patient characteristics are presented in Table 1. The RBiN cohort consisted of 205 adults (78%) and 58 children (22%). Median age at time of inclusion was 38.5 years (range 1–87 years). Fifteen patients had an additional co-existing abnormality of hemostasis besides their specific RBD including hemophilia carriership, (mild) von Willebrand disease, a platelet function defect, and (mild) FVII deficiency. More detailed information is provided in Table 2.

3.1 | General treatment plans

A large variability in type of products registered in general treatment plans was found in all RBDs in both children and adults (Figure 1A,B respectively). Overall, treatment plans were less heterogeneous in children compared to adults, although the absolute number of children included was lower. Heterogeneity was most pronounced in patients with FXI deficiency in both age categories. In adults, least heterogeneity was observed in patients with a fibrinolytic disorder, in whom tranexamic acid is the most frequently used product.

An overview of the exact types of hemostatic products registered in the general treatment plans for mild, moderate—severe, and life-threatening bleeding is provided in Figure S1A–C (in supporting information) for children and in Figure S2A–C (in supporting information) for adults.

In general, the percentage of patients without a general treatment plan decreased with increasing bleeding severity. Sixteen percent of all patients did not have a general treatment plan. These were all patients with mild factor deficiencies, diagnosed after family investigation, and who were not followed actively in the HTC. Their median ISTH BAT score was 5 (IQR 1–7, data available in 28 patients), while the median ISTH BAT score for the entire RBiN cohort was 9 (IQR 5–15).

Overall, tranexamic acid as monotherapy is often used for mild bleeding. For moderate—severe and life-threatening bleeding, treatment shifts toward targeted replacement therapy with factor

TABLE 1 Baseline characteristics of the RBiN study population

Total number of patients, *n*	263
Adults, *n* (%)	205 (78)
Women, *n* (%)	131 (64)
Men, *n* (%)	74 (36)
Children, *n* (%)	58 (22)
Girls, *n* (%)	34 (59)
Boys, *n* (%)	24 (41)
Median age (range), yrs	38.5 (1–87)
Documented treatment plans, *n* (%)	219 (84)
Number of reported tooth extractions, *n*	308
Number of reported surgical procedures, *n*	408
Rare bleeding disorder, *n* (%)	
Fibrinogen[a]	41 (16)
FII	16 (6)
FV	25 (10)
FV Amsterdam	2 (1)
FV + FVIII	6 (2)
FVII	57 (22)
FX	8 (3)
FXI	43 (16)
FXIII	14 (5)
α2-AP	23 (9)
PAI-1	14 (5)
Hyperfibrinolysis	14 (5)

Abbreviations: α2-AP, alpha2-antiplasmin; F, factor; ISTH BAT, bleeding assessment tool of the International Society on Thrombosis and Haemostasis; *n*, number; PAI-1, plasminogen activator inhibitor 1; RBiN, Rare Bleeding Disorders in the Netherlands; yrs, years.

[a]Fibrinogen disorders comprised afibrinogenemia/hypofibrinogenemia and dysfibrinogenemia. Of the 41 patients, 32 patients had afibrinogenemia/hypofibrinogenemia or were heterozygous family members carrying a known pathogenic genetic variant causing a- or hypofibrinogenemia. The remaining nine patients (six adults and three children) had a dysfibrinogenemia. ISTH BAT score was known in five adults (5 – 6 – 8 – 13 – 14). In two adults (ISTH BAT 5 and 14), thrombotic events were also reported. None of the three children with dysfibrinogenemia had a history of thrombosis.

concentrates, plasma, and prothrombin complex concentrate, except in patients with fibrinolytic disorders.

For all three types of bleeding, adult patients without a general treatment plan tend to have lower ISTH BAT scores, although the range is wide and some of these patients do have an ISTH BAT score >10 (Figure S2).

3.2 | Tooth extractions

3.2.1 | General characteristics

A total of 308 tooth extractions were reported in 156 patients. Characteristics are provided in Table 3. Bleeding occurred in 105 tooth extractions (50%) performed without peri-procedural hemostatic treatment, in 11 tooth extractions (36%) performed with anti-fibrinolytics, and in 15 tooth extractions (24%) performed with replacement therapy. The majority of reported bleedings had to be controlled with local measures and/or hemostatic agents (61%; Table S1 in supporting information).

Only 7 out of 308 tooth extractions were reported by children. The only tooth extraction that was performed without peri-procedural hemostatic treatment was complicated by bleeding. Three of six tooth extractions carried out with hemostatic treatment were also associated with bleeding. These three bleeding events were all reported by the same patient with a severe FII deficiency who received a different type of peri-procedural hemostatic prophylaxis in each tooth extraction (anti-fibrinolytic agents, replacement therapy, and platelet transfusion).

3.2.2 | Bleeding rate per RBD

An overview of the bleeding rate after tooth extractions in patients with a fibrinogen, FV, FVII, and FXI deficiency is shown in Figure 2A-D.

Overall, omission of peri-procedural hemostatic treatment was often associated with bleeding in patients with severe coagulation factor deficiencies. Bleeding also occurred frequently in tooth extractions performed without hemostatic treatment in patients with relatively high levels of the specific deficient factor in all coagulation factor deficiencies. In general, use of peri-procedural hemostatic treatment was associated with a lower bleeding rate in patients with a FVII deficiency or a more severe fibrinogen and FV deficiency. In FXI deficiency, more than half of tooth extractions were complicated by bleeding, irrespective of the use of peri-procedural treatment.

In all fibrinolytic disorders, the majority of tooth extractions performed without treatment were complicated by bleeding, and use of peri-procedural hemostatic treatment was associated with a decrease in bleeding events (Figure 2E).

3.3 | Surgical procedures

3.3.1 | General characteristics

A total of 408 surgical procedures were reported in 158 patients. In Figure 3, these procedures were all categorized according to timing of RBD diagnosis, use of peri-operative hemostatic treatment, and occurrence of bleeding complications. Bleeding occurred in 54% of procedures performed without treatment before RBD diagnosis, and in 17% of procedures performed with treatment after RBD diagnosis. Regardless of treatment, the incidence of bleeding complications around procedures performed before RBD diagnosis was significantly higher compared to procedures performed after RBD diagnosis (56% versus 25%, $P < .001$).

Only 17 out of 408 surgical procedures were reported by children. Bleeding occurred in three of ten procedures (30%) carried out

TABLE 2 Overview of co-existing abnormalities of hemostasis per type of rare bleeding disorder

Rare bleeding disorder	Number of patients with a co-existing abnormality of hemostasis	Type of co-existing abnormality of hemostasis
FII deficiency	1	Carrier of hemophilia A (FVIII activity level 143%) and von Willebrand disease type 2N (VWF level 129 IU dL^{-1})
FV+FVIII deficiency	4	Mild von Willebrand disease (VWF level 39–47 IU dL^{-1})
FVII deficiency	1	Platelet function defect
	3	Mild von Willebrand disease
FXIII deficiency	2	Mild FVII deficiency (FVII activity level 51%–52%)
α2-AP deficiency	1	Platelet function defect
PAI-1 deficiency	1	Mild von Willebrand disease (VWF level 41 IU dL^{-1})
	1	Platelet function defect
Hyperfibrinolysis	1	Platelet function defect

Abbreviations: α2-AP, alpha2-antiplasmin; F, factor; PAI-1, plasminogen activator inhibitor 1; VWF, von Willebrand factor.

without peri-operative hemostatic treatment, while none of seven procedures with hemostatic treatment were complicated by bleeding.

Characteristics of the total group of 408 procedures are summarized in Table 4. The different types of included surgical interventions are listed in Table S2 in supporting information.

Overall, measures to control bleeding, including local therapy and/or hemostatic agents, were necessary in 56% of bleedings (Table S1).

3.3.2 | Bleeding rate per RBD including all surgical procedures

Figure 4A–D provide an overview of the bleeding rate after surgical procedures in patients with a fibrinogen, FV, FVII, and FXI deficiency. Overall, omission of peri-operative hemostatic treatment was associated with bleeding in a considerable proportion of surgical procedures in all coagulation factor deficiencies, ranging from 29% in FV deficiency to 59% in FXI deficiency. Bleeding occurred also in patients with relatively high levels of the specific deficient factor. A lower bleeding rate was observed when peri-operative hemostatic treatment was used in patients with fibrinogen, FVII, and FXI deficiency.

Figure 4E shows the bleeding rate after surgical procedures in patients with a fibrinolytic disorder. Most procedures performed without treatment in PAI-1 deficiency and hyperfibrinolysis were accompanied by bleeding (76% and 85%, respectively). Use of peri-operative hemostatic therapy was associated with a significant decrease in bleeding events.

3.3.3 | Bleeding rate during procedures before RBD diagnosis

Bleeding occurred in a substantial proportion of surgical procedures performed without hemostatic treatment before RBD diagnosis, ranging from 31% in patients with a fibrinogen or FV deficiency to 57% in patients with FXI deficiency (Figure S3A in supporting information). The bleeding rate was also quite high in patients with a relatively high activity level of the specific deficient factor. Even more bleeding complications were reported in the procedures performed before diagnosis of a fibrinolytic disorder, especially in PAI-1 deficiency (76%) and hyperfibrinolysis (85%; Figure S3B).

3.3.4 | Bleeding rate during procedures after RBD diagnosis

The subanalysis of surgical procedures after RBD diagnosis showed similar observations as those seen in the main analysis including all surgical procedures for coagulation factor deficiencies (Figure S4A–D in supporting information). In α2-AP deficiency, bleeding occurred in only one procedure (20%) performed without hemostatic treatment, while four procedures (27%) performed with peri-operative hemostatic therapy were associated with bleeding (Figure S4E). Anti-fibrinolytics as monotherapy and a combination of anti-fibrinolytics and plasma were each used in two of these procedures.

4 | DISCUSSION

This substudy of the Dutch RBiN study is the first to explore the occurrence of bleeding in relation to peri-procedural hemostatic therapy in invasive procedures per RBD, including coagulation factor deficiencies and fibrinolytic disorders. General treatment plans of patients with the same type of RBD were heterogeneous. Bleeding occurred frequently after invasive surgical interventions performed without hemostatic treatment, both before and after RBD diagnosis, especially in fibrinolytic disorders, and use of peri-procedural hemostatic agents was mostly associated with a reduced bleeding rate.

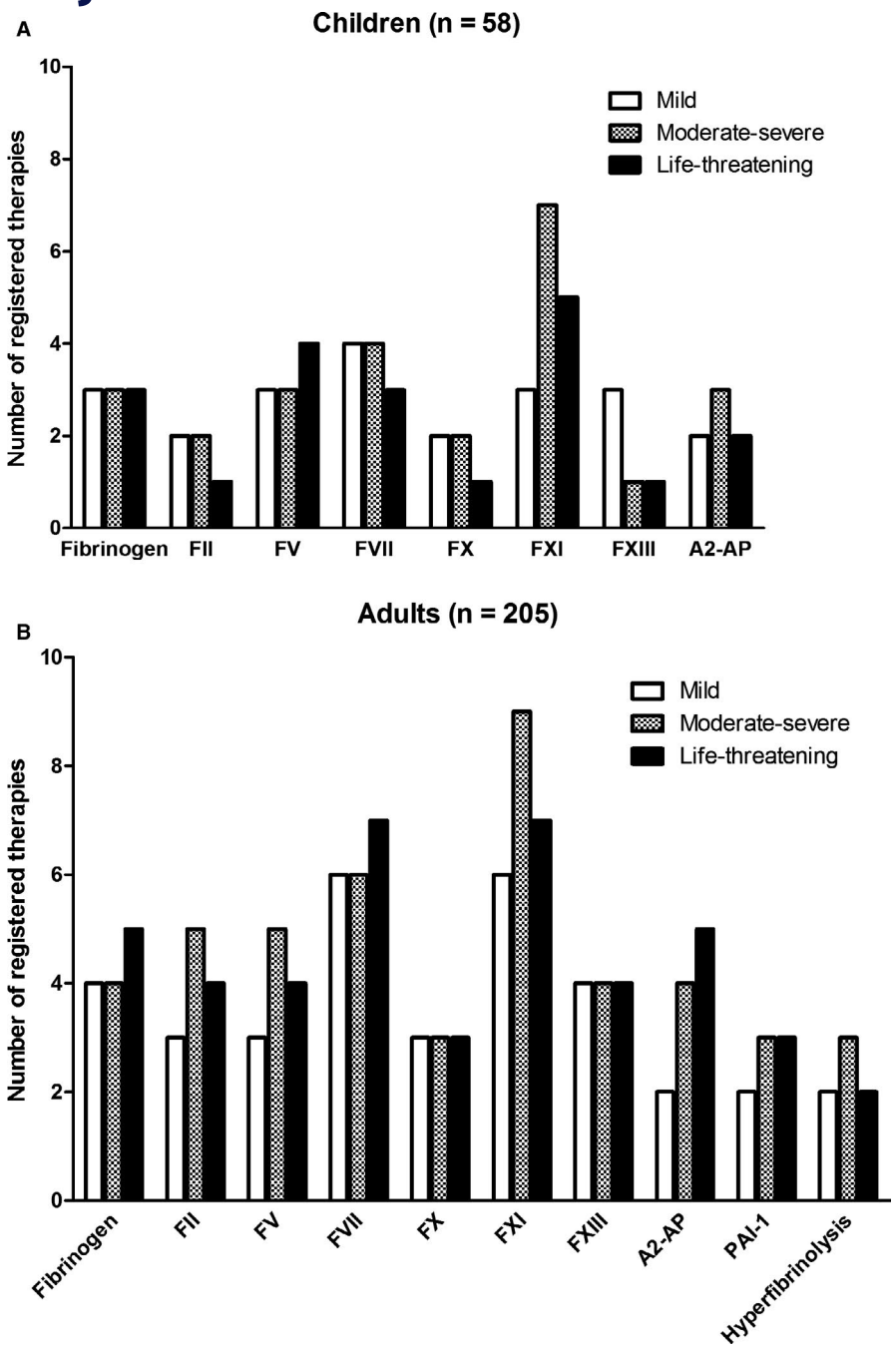

FIGURE 1 Number of registered therapies in general treatment plans for mild, moderate—severe, and life-threatening bleeding in children (A) and adults (B). A2-AP, alpha2-antiplasmin; F, factor; PAI-1, plasminogen activator inhibitor 1

4.1 | General treatment plans

Despite the presence of both national and international guidelines for the diagnosis and treatment of RBDs,[16,17] the general treatment plans of patients with the same type of RBD were heterogeneous for all degrees of bleeding. Heterogeneity is especially seen for the use of tranexamic acid as monotherapy or in combination with factor concentrates and for the use of plasma. The current Dutch guideline (published in 2009) describes several treatment options per RBD, including monotherapy tranexamic acid, plasma or factor concentrates, but does not comprise a stepwise approach to therapy according to the severity of bleeding. Moreover, in some RBDs, plasma is still advised instead of treatment with (currently) available specific factor concentrates, even in the case of severe bleeding. This illustrates the fact that treatment choices change over time, depending on new research evidence and logistic factors such as national availability of and access to new hemostatic agents. Updated and stricter guidelines including advice on the use of combination therapy and a preference for factor concentrates in moderate and severe bleeding are needed and will overcome unnecessary heterogeneity in hemostatic products.

In addition, a minor part of the variability can be explained by additional co-existing abnormalities of hemostasis. In our cohort, 15 patients had such a co-existing disorder of hemostasis (Table 2); 13 of them had a different treatment plan including for instance desmopressin, factor VIII/von Willebrand factor concentrate or platelet transfusion.

TABLE 3 Characteristics of tooth extractions performed in the RBiN study population

Total number of tooth extractions, *n*	308	
Total number of patients with ≥1 tooth extraction, *n*	156	
Tooth extractions complicated by bleeding, *n* (%)[a]	132 (42.9)	
Type of extraction, *n* (%)		
Deciduous	25 (8.1)	
Permanent	35 (11.4)	
Molar	239 (77.6)	
Permanent and molar (simultaneous)	9 (2.9)	
Peri-procedural treatment, *n* (%)[b]		Bleeding, *n* (%)
None	210 (68.6)	105 (50.0)
Anti-fibrinolytics	31 (10.1)	11 (35.5)
Replacement therapy (plasma or clotting factor concentrates)	63 (20.6)	15 (23.8)
Desmopressin	1 (0.3)	0 (0.0)
Platelet transfusion	1 (0.3)	1 (100)
Tooth extractions per rare bleeding disorder, *n* (%)		Bleeding, *n* (%)
Coagulation factor deficiencies	221 (71.8)	84 (38.0)
Fibrinogen	48 (15.6)	17 (35.4)
FII	21 (6.8)	7 (33.3)
FV	32 (10.4)	13 (40.6)
FV Amsterdam	3 (1.0)	3 (100)
FV+FVIII	1 (0.3)	0 (0.0)
FVII	45 (14.6)	10 (22.2)
FX	5 (1.6)	1 (25.0)
FXI	49 (15.9)	27 (55.1)
FXIII	17 (5.5)	6 (35.3)
Fibrinolytic disorders	87 (28.2)	48 (55.2)
α2-AP	31 (10.1)	16 (51.6)
PAI-1	29 (9.4)	14 (48.3)
Hyperfibrinolysis	27 (8.8)	18 (66.7)

Abbreviations: α2-AP, alpha2-antiplasmin; *n*, number; PAI-1, plasminogen activator inhibitor 1; RBiN, Rare Bleeding Disorders in the Netherlands.

[a]Data about bleeding complications were missing for one tooth extraction.

[b]Data about peri-procedural treatment were missing for two tooth extractions.

In general, anti-fibrinolytic agents are commonly recommended for mild or mucosal bleeding in patients with rare coagulation factor deficiencies.[17] However, in our cohort only 51% of these patients had a treatment plan with tranexamic acid for mild bleeding. Instead, many patients had a treatment plan with replacement therapy for mild bleeding. Moreover, tranexamic acid can be used as adjunctive therapy to reduce the need for factor replacement therapy around invasive procedures[8] and in case of moderate–severe or life-threatening bleeding. In the current Dutch guideline, tranexamic acid is not mentioned for these types of bleeding. In our cohort, a combination of tranexamic acid and other therapies was only described in the treatment plans of 25% of patients with a rare coagulation factor deficiency. However, in clinical practice, more patients could have been treated with a combination therapy including tranexamic acid because tranexamic acid is not consequently mentioned in patients' general treatment plans as a separate supportive therapy.

The heterogeneity in treatment plans was especially very large for FXI-deficient patients in whom factor concentrate, plasma, tranexamic acid, and any combination of these three options were used for moderate–severe or life-threatening bleeding. A treatment plan including a combination of factor concentrate (if available) and plasma (in the absence of factor concentrate) can be well explained as FXI concentrate is not always available. Furthermore, plasma is often administered in case of emergency because the maximal efficacy of treatment with FXI concentrate is reached at 12 h after administration. FXI concentrate is a convenient treatment option for elective surgery. However, many FXI-deficient patients had a treatment plan with either factor concentrate or plasma.

Some patients had a treatment plan with both tranexamic acid and FXI concentrate, although this combination should be used with caution due to the enhanced thrombotic risk.[8,17] This also applies for the combined use of tranexamic acid and prothrombin complex concentrate in some patients with FII and FVII deficiency.[8,17]

Patients with α2-AP deficiency were frequently treated with plasma for moderate–severe or life-threatening bleeding, although Omniplasma (a form of solvent-detergent-treated plasma) and fresh frozen plasma (FFP) are not recommended to use in these patients. FFP contains variable levels of α2-AP and its use increases the risk of dilutional coagulopathy as a result of volume overload when infused in high volumes.[18] Compared to FFP, lower levels of α2-AP and shorter rotational thromboelastometry lysis times with a reduction of more than 50% were found in Omniplasma.[18] Therefore, patients with α2-AP deficiency should be treated with tranexamic acid only.

4.2 | Invasive procedures

As expected in the total cohort, bleeding complications around tooth extractions and surgical procedures were frequently reported (43% and 39%, respectively). The majority of these procedures were performed without any hemostatic treatment. Bleeding complications were, however, still described in a relatively large proportion of both tooth extractions and surgical procedures performed with hemostatic treatment (28% and 19%, respectively). Strikingly, these bleedings also occurred after RBD diagnosis, in both treated and non-treated patients.

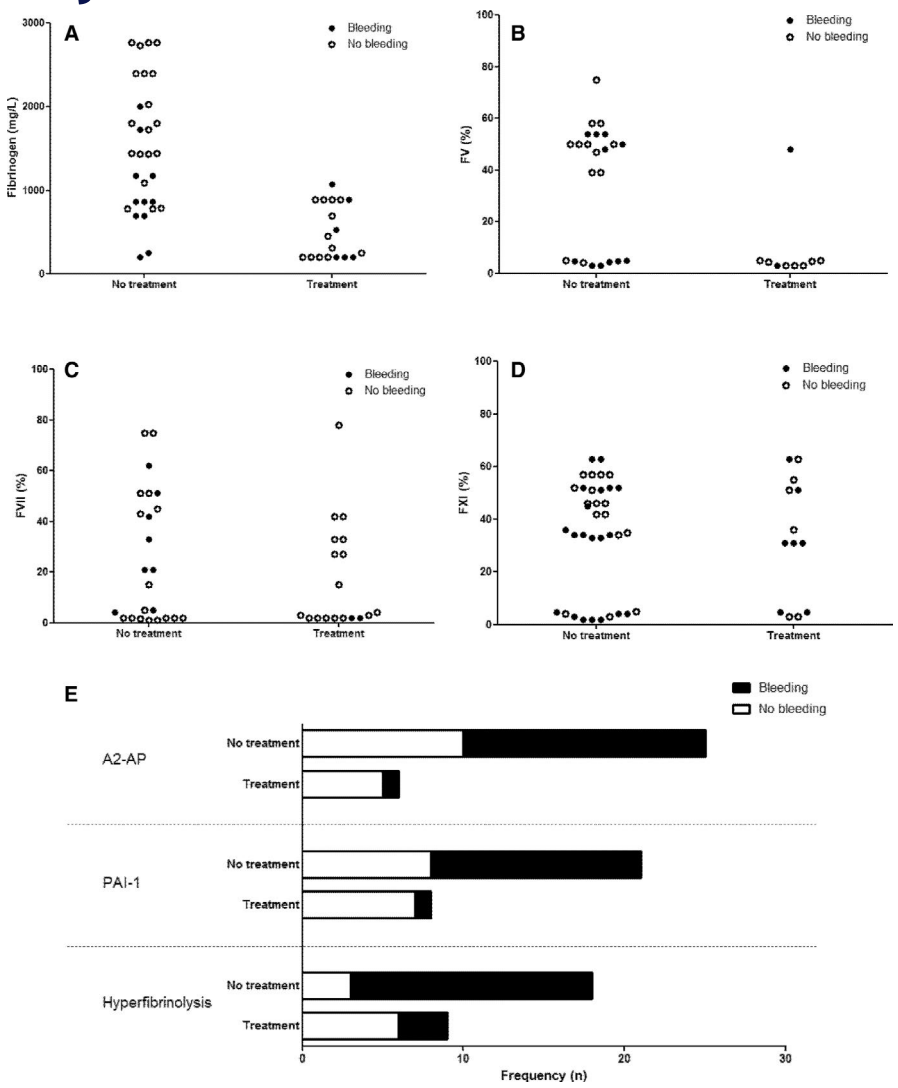

FIGURE 2 Frequency of bleeding complications after tooth extractions in fibrinogen deficiency (A), FV deficiency (B), FVII deficiency (C), FXI deficiency (D), and fibrinolytic disorders (E). In (A–D), each dot represents a single procedure. No treatment: no peri-procedural prophylactic hemostatic treatment was used. Treatment: peri-procedural prophylactic hemostatic treatment was used. A2-AP, alpha2-antiplasmin; F, factor; PAI-1, plasminogen activator inhibitor 1

Bleedings after tooth extractions and surgical procedures were not only frequently reported in patients with severe coagulation factor deficiencies but also in patients with relatively high activity levels of the specific deficient factor. These observations support previous results from the RBiN study and the EN-RBD, in which the variability in correlation between coagulation factor activity level and clinical bleeding severity in RBDs was described.[1,5] In both studies, no correlation was found for FXI deficiency and correlations for FV and FVII deficiency were only moderate or poor. Moreover, 48% of the RBiN patients had a more severe bleeding phenotype than predicted based on proposed threshold levels to remain asymptomatic or free from grade I, II, or III bleeding in the EN-RBD study.[1,5] Unfortunately, we were not able to set novel threshold levels that reliably predict clinical bleeding severity. Median coagulation factor activity levels of patients with and without bleeding after surgical procedures without hemostatic treatment did not differ significantly in deficiency of fibrinogen, FV, FVII, and FXI. Moreover, there was a large variety in factor levels, ranging from severe to mild deficiencies, in both bleeding and non-bleeding patients.

In contrast to many coagulation factor deficiencies, no specific factor concentrate is currently available for the treatment of FV-deficient patients. Replacement therapy is therefore merely accomplished through FFP or Omniplasma. All three surgical procedures performed with hemostatic treatment in patients with a relatively high FV activity level were accompanied by bleeding. These patients were, however, all treated with tranexamic acid only. Furthermore, the clinical phenotype of FV-deficient patients might be influenced by plasma levels of tissue factor pathway inhibitor, which will be further analyzed in another part of the RBiN study, and platelet FV.[19]

In patients with fibrinolytic disorders, the majority of medical interventions performed without hemostatic treatment were accompanied by bleeding and peri-procedural use of hemostatic agents was associated with a significant decrease in bleeding rate in PAI-1 deficiency and hyperfibrinolysis. Only for surgical procedures performed after diagnosis in α2-AP deficiency, bleeding complications occurred more frequently in procedures carried out with hemostatic treatment. Half of these bleeding patients were treated with a combination of tranexamic acid and plasma, which is currently not recommended as standard therapy in α2-AP deficiency.[18]

These results of the RBiN study emphasize that individual bleeding phenotype upon invasive procedures not only depends on the activity level of the deficient factor but probably also on other

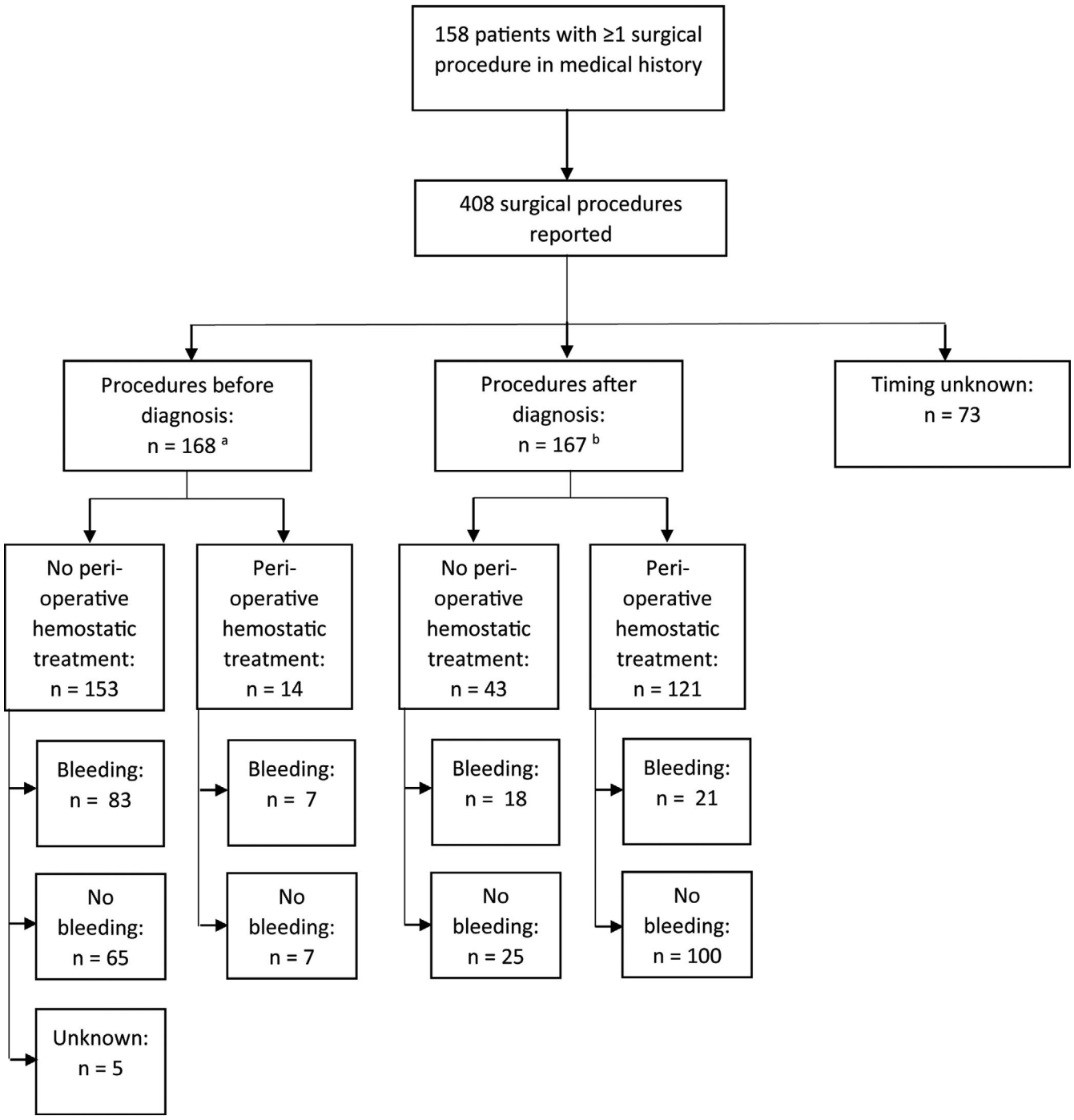

FIGURE 3 Peri-operative hemostatic treatment and bleeding in surgical procedures performed before and after diagnosis of the rare bleeding disorder. n: number. [a]Data missing for one procedure. [b]Data missing for three procedures

pro- and anti-coagulant factors and variability in individual patient characteristics contributing to the total hemostatic balance. Further research, including genetic analysis, is required to gain more insight into these relevant variables. In the future, global assays of coagulation and fibrinolysis may be used for a better characterization of the overall hemostatic potential and may be helpful to guide the peri-procedural treatment of patients with RBDs.[20]

Besides the individual coagulation factor activity level, the decision to administer peri-procedural hemostatic therapy should therefore be dependent on the personal bleeding history of the patient, in which the choice of an adequate hemostatic product is essential.

However, prediction of the bleeding risk in pediatric patients is often difficult due to a lack of prior hemostatic challenges.

TABLE 4 Characteristics of surgical procedures performed in the RBiN study population

Total number of surgical procedures, *n*	408	
Total number of patients with ≥1 surgical procedure, *n*	158	
Surgical procedures complicated by bleeding, *n* (%)[a]	157 (39.1)	
Peri-operative treatment, *n* (%)[b]		Bleeding, *n* (%)
None[c]	240 (59.7)	124 (52.8)
Anti-fibrinolytics	46 (11.4)	8 (17.4)
Replacement therapy (plasma or clotting factor concentrates)	96 (23.9)	13 (13.5)
Desmopressin	3 (0.7)	2 (66.7)
Platelet transfusion	2 (0.5)	0 (0.0)
Anti-fibrinolytics + replacement therapy	8 (2.0)	4 (50.0)
Anti-fibrinolytics + desmopressin	3 (0.7)	2 (66.7)
Anti-fibrinolytics + platelet transfusion	2 (0.5)	0 (0.0)
Anti-fibrinolytics + replacement therapy + desmopressin	1 (0.2)	0 (0.0)
Anti-fibrinolytics + desmopressin + platelet transfusion	1 (0.2)	1 (100)
Surgical procedures per rare bleeding disorder, *n* (%)		Bleeding, *n* (%)
Coagulation factor deficiencies	281 (68.9)	93 (33.1)
Fibrinogen	48 (11.7)	16 (33.3)
FII	16 (3.9)	5 (31.3)
FV	44 (10.8)	14 (32.6)
FV Amsterdam	3 (0.7)	3 (100)
FV + FVIII	3 (0.7)	0 (0.0)
FVII	70 (17.2)	16 (23.2)
FX	7 (1.7)	0 (0.0)
FXI	76 (18.6)	34 (45.3)
FXIII	14 (3.4)	5 (35.7)
Fibrinolytic disorders	127 (31.1)	64 (50.4)
α2-AP	34 (8.3)	11 (33.3)
PAI-1	45 (11.0)	24 (54.5)
Hyperfibrinolysis	48 (11.8)	29 (61.7)

Abbreviations: α2-AP, alpha2-antiplasmin; *N*, number; PAI-1, plasminogen activator inhibitor 1; RBiN, Rare Bleeding Disorders in the Netherlands.

[a]Data about bleeding complications were missing for six procedures.

[b]Data about peri-operative hemostatic treatment were missing for six procedures.

[c]Data about bleeding complications were missing for five procedures.

As RBD patients can experience bleeding complications around invasive procedures after their RBD diagnosis, adequate care and follow-up at HTCs also remain recommended post-diagnosis.

4.3 | Limitations

Our study has some limitations. First, this was a retrospective study and only a small number of patients was included per bleeding disorder due to the rarity of RBDs. A wide variety of surgical procedures was included, ranging from less invasive skin surgery to major abdominal surgery. Subgroup analysis was not possible due to the limited number of patients per RBD and surgical procedure. However, the results of a subanalysis of the surgical procedures categorized as major abdominal, major gynecology, and major thoracic (Table S2) were similar to the results found in the overall analysis.

Moreover, we were not able to perform subanalyses according to the clinical reason for hemostatic analysis after which the RBD was established (i.e., hemorrhagic diathesis, family investigation, or abnormal screening tests) or according to the specific hemostatic therapeutic agent that was used.

Second, the general treatment plans were extracted from electronic patient files for each participant, but data about tooth extractions, surgical procedures, and bleeding complications were patient-reported. An important concern in the interpretation of these self-reported data is the potential for recall bias. Patients may be more likely to remember the procedures that were complicated by bleeding, which may lead to an overestimation of the bleeding rate, or the procedures that were performed after RBD diagnosis. Another difficulty in the interpretation of self-reported bleeding events is the lack of prespecified objective criteria. The significance and severity of all bleeding complications therefore remain unknown. However, treatment to control bleeding was necessary in the majority of bleedings after both tooth extractions and surgical procedures. Because all patients in our cohort were interviewed by the same investigator, bias due to inter-individual differences in interviewing techniques or interpretation of patients' answers is excluded.

Third, there is a potential selection bias as bleeding complications during invasive procedures may be patients' first presenting bleeding episodes, triggering hemostatic analysis resulting in an RBD diagnosis. However, because the aim of this study was to evaluate the occurrence of bleeding complications around invasive procedures in the Dutch RBiN population, we included all reported procedures. To evaluate the association with periprocedural hemostatic therapy, we performed a subanalysis of surgical procedures performed after RBD diagnosis, in which omission of treatment was accompanied with a high bleeding rate, while use of hemostatic agents was associated with a decrease in bleeding complications.

Unfortunately, we were not able to perform the same analysis for tooth extractions as the exact amount of tooth extractions performed before and after RBD diagnosis could not be retrieved. To further minimize the risk of selection bias, we included not only RBD patients actively controlled in an HTC but also heterozygous family members and patients diagnosed after abnormal coagulation screening before invasive procedures.

In the future, international prospective studies are needed to collect data about invasive medical interventions in a larger cohort

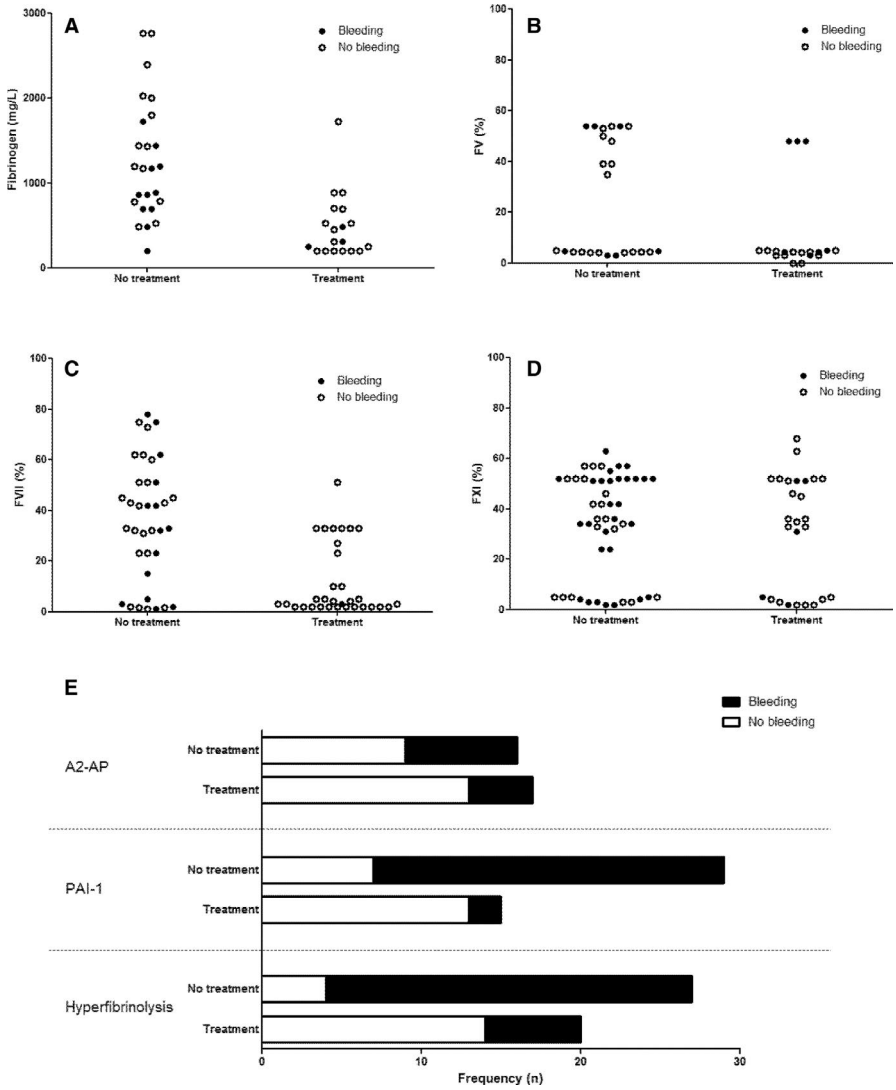

FIGURE 4 Frequency of bleeding complications after surgical procedures in fibrinogen deficiency (A), FV deficiency (B), FVII deficiency (C), FXI deficiency (D), and fibrinolytic disorders (E). In (A – D), each dot represents a single surgical procedure. No treatment: no peri-operative prophylactic hemostatic treatment was used. Treatment: peri-operative prophylactic hemostatic treatment was used. A2-AP, alpha2-antiplasmin; F, factor; PAI-1, plasminogen activator inhibitor 1

of RBD patients. The resulting prospectively collected data will be a source for the development of more evidence-based guidelines for different invasive procedures in RBD patients. Clinical outcome parameters, like bleeding complications and use of hemostatic agents, can be used to define RBD care pathways to eventually unify and enhance quality of care.

5 | CONCLUSION

In the RBiN study, considerable heterogeneity in general treatment plans of patients with RBDs exists, even for life-threatening bleeding episodes. Bleeding complications after dental and surgical procedures were frequently reported in case of omission of peri-procedural treatment in all RBDs, but especially in fibrinolytic disorders. The use of adequate peri-procedural hemostatic therapy was mostly associated with a reduced bleeding rate. Future guidelines should comprise not only uniform treatment recommendations per RBD to ensure all patients receive the most appropriate hemostatic therapy, but should also permit personalized treatment by taking into account both the coagulation factor activity level and individual bleeding history.

CONFLICTS OF INTEREST

K. Meijer reports speaker fees from Bayer and Alexion, participation in trial steering committee for Bayer, consulting fees from Uniqure, and participation in data monitoring and endpoint adjudication committee for Octapharma. M.H. Cnossen has received investigator-initiated research and travel grants as well as speaker fees over the years from the Netherlands Organisation for Scientific Research (NWO), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch "Innovatiefonds Zorgverzekeraars," Baxter, Baxalta, Shire, Takeda, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, and Nordic Pharma, and has served as a steering board member for Roche, Bayer, and Novartis. All grants, awards, and fees go to the Erasmus MC as institution. R.E.G. Schutgens reports grants from Bayer, Baxalta, Pfizer, and Novo Nordisk outside the submitted work. M. Peters reports a grant from Pfizer outside the submitted work. W.L. van Heerde reports personal fees from Takeda, Bayer,

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AUTHOR CONTRIBUTIONS

K. Meijer, M.H. Cnossen, R.E.G. Schutgens, M. Peters, L. Nieuwenhuizen, P.L. den Exter, I.C. Kruis, W.L. van Heerde, and S.E.M. Schols are members of the steering committee that designed the study and are delegates of all Dutch Hemophilia Treatment Centers; N.M.A. Blijlevens is head of the department of Hematology in the Radboud University Medical Center and head of the RBiN project management team. J.L. Saes interviewed the patients; D.P.M.S.M. Maas analyzed the data; D.P.M.S.M. Maas, W.L. van Heerde, and S.E.M. Schols wrote the manuscript; and all authors revised the manuscript and gave final approval.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX

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