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## ORIGINAL ARTICLE OPEN ACCESS

Rare Bleeding Disorders

## Current Practice Regarding Bleeding Disorders of Unknown Cause in the Netherlands: A National Survey

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## ABSTRACT

**Introduction:** About 40%–70% of persons with a clinically relevant bleeding tendency who are referred to haemostasis experts are classified as having a 'bleeding disorder of unknown cause' (BDUC) as no biological entity can be found after extensive laboratory testing. Currently, guidelines are under development regarding diagnostic assessment and management to minimize variation in clinical practice.

**Aim:** Investigate current practices regarding BDUC in the Netherlands.

**Methods:** An online survey on the best BDUC definition, associated bleeding phenotype, clinical and diagnostic approaches, treatment, registration, and follow-up was distributed amongst healthcare providers working in Dutch haemophilia treatment centres (HTCs).

**Results:** The survey was completed by 39/54 (72%) respondents. Twenty percent did not register BDUC patients in their HTC. Healthcare professionals indicated that follow-up should depend on bleeding phenotype severity and bleeding history, and other potential causes for an increased bleeding tendency should be excluded. Moreover, the use of laboratory tests within the routine diagnostic pathway was demonstrated to be heterogeneous. Regarding treatment, tranexamic acid was most frequently prescribed for minor and major surgical interventions (79% and 86%), dental extractions (93%) and childbirth (93%). Desmopressin was prescribed for major surgical procedures by 79%.

Caroline M. A. Mussert and Amaury L. L. Monard share first authorship.

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**Conclusion:** Our survey shows that Dutch current practice varies but is generally in line with recent ISTH SSC recommendations. Additionally, it describes other clinically relevant topics not included in the international survey, such as follow-up and exclusion of other causes for bleeding. This survey therefore adds to international efforts to unify BDUC definition, diagnostic approach, treatment and follow-up, and to attain broadly supported guidelines.

## 1 | Introduction

In about 40%–70% of persons who are referred to a haemostasis expert with a clinically relevant bleeding tendency, no biological entity can be found after extensive laboratory testing [1, 2]. These persons are classified as having a bleeding disorder of unknown cause (BDUC). The most common bleeding symptoms in persons with BDUC are mucocutaneous bleeding, especially heavy menstrual bleeding and postpartum bleeding, and bleeding after medical and/or dental procedures [3–5]. The bleeding phenotype of persons with BDUC, often quantified using a bleeding assessment tool (BAT) score, is quite comparable to that of individuals with moderate to mild inborn bleeding disorders such as Von Willebrand disease (VWD), mild coagulation factor deficiencies and less severe platelet function disorders [5]. Therefore, the bleeding pattern of persons with BDUC hardly discriminates itself from other established bleeding disorders. Currently, guidelines are under development and urgently needed, as clinical management, including treatment and follow-up and laboratory testing for diagnosis, varies significantly.

In 2024, the BDUC Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Hemostasis (ISTH) published a short list of recommendations to standardize BDUC definition and clinical management of persons with BDUC, including the minimal standards for laboratory testing, treatment strategies and the importance of registration of persons with BDUC based on a worldwide survey [2]. Nevertheless, some clinical aspects of BDUC healthcare were not addressed, and knowledge gaps and challenges remain, especially as underlying pathophysiological mechanisms of bleeding are still unknown. With this study, the Bleeding Disorder of Unknown Cause in the Netherlands (BDUC-iN) working group aims to add to current knowledge of clinical practice by more broadly investigating BDUC approaches in the Netherlands.

## 2 | Materials and Methods

A survey was designed consisting of four open questions and 25 five-point Likert scale questions, ranging from 1 (strongly disagree) to 5 (strongly agree) for statements and from 1 (never) to 5 (always) for frequencies. Questions covered the BDUC definition, associated bleeding phenotype, diagnostic and clinical approaches, applied treatment regimens, and registration and follow-up of persons with BDUC. The questionnaire was designed in concept by C. Mussert and A. Monard and complemented and refined by all members of the BDUC-iN working group. The survey was performed within the online survey and data system SurveyMonkey [6]. On 8, June 2023, this survey was sent to all haematologists (paediatric and adult), internists in vascular medicine, nurse practitioners and clinical chemists working in

one of the six Dutch haemophilia treatment centres (HTCs), which comprised 54 recipients in total. Possible answers included the option ‘not applicable’ that could be filled in by respondents if they considered themselves lacking the required expertise to answer a specific question. A reminder was sent out every 6 weeks until the survey was closed on 6, October 2023. All respondents gave consent to use the collected data for research purposes.

Not all respondents filled in every question, causing missing data. Results were expressed in percentages together with the number of collected responses. Not applicable answers were excluded from the numerator. Answers from laboratory specialists were excluded for clinically orientated questions, which includes the observed bleeding phenotype, other causes for bleeding, registration, follow-up and treatment strategies.

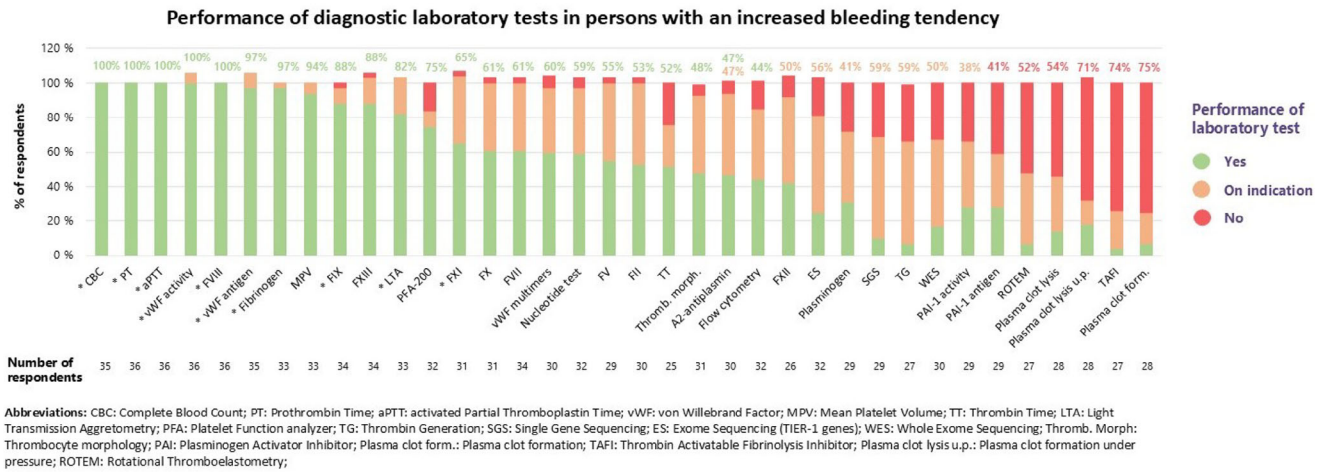
Software IBM SPSS version 28 was used for the descriptive statistics (frequencies in percentages and numbers). Agreement was defined as  $\geq 70\%$  rating a statement as ‘strongly agree/agree’ or ‘strongly disagree/disagree,’ likewise with regard to frequencies. Subgroup analyses were performed comparing physicians with nurse practitioners and comparing respondents working with paediatric patients and adult patients.

## 3 | Results and Discussion

In total, 39/54 (72%) recipients from six HTCs completed the survey, among which were 24 (62%) physicians, 8 (21%) nurse practitioners and 7 (18%) clinical chemists. A total of 13/38 (34%) respondents worked with children, 15/38 (39%) worked with adults and 10/38 (26%) worked with both. The mean years of experience regarding bleeding disorders was 15 years, ranging from 1 to 33 years.

### 3.1 | BDUC Definition

Respondents emphasized the following elements should be included in the BDUC definition: (i) presence of an increased bleeding tendency (100%), (ii) exclusion of other bleeding disorders (95%), (iii) exclusion of acquired causes for an increased bleeding tendency (90%), (iv) absence of abnormal laboratory test results (85%), (v) presence of an elevated BAT score (77%), and (vi) specification of laboratory tests to perform (71%). Only 57% of respondents indicated that bleeding phenotype assessment based on clinical gestalt should be an element in the BDUC definition; however, in a follow-up question on what diagnostic instruments should be used to score bleeding tendency severity, 87% indicated the use of clinical gestalt to assess bleeding phenotype. These elements were in line with the published ISTH SSC BDUC definition, stating that these are patients with a high suspicion



**FIGURE 1** | Use of diagnostic laboratory tests in persons with an increased bleeding tendency. Respondents were asked which laboratory tests they perform and in which order (first round, second round or third round of laboratory tests, on indication or never) for the diagnosis in persons with an increased bleeding tendency. Answers from the different rounds were combined to indicate the overall use of a specific test. Respondents were able to select multiple answers, for example, that a test is performed within a certain round as well as on indication. Therefore, for some tests the sum exceeds 100%. For each test, the percentage of the most common answer, given by respondents, is shown above the bar. \* Laboratory tests in the proposed standard panel in ISTH SSC recommendations.

of a bleeding disorder based on medical history and without abnormal test results in a specified set of laboratory tests [2].

### 3.2 | Bleeding Phenotype

In line with the ISTH SSC communication and previous research [2–5, 7], the types of bleeding reported by our respondents, categorized as ‘often’ or ‘always’ observed in persons with BDUC, were menorrhagia (94%), cutaneous bleeding (90%), and bleeding after surgical (77%) and/or dental procedures (68%). Central nervous system (CNS) bleeding, haematuria, muscle and joint bleeding were reported to be ‘never’ or ‘rarely’ seen by 70%, 71%, 81%, and 84% of respondents, respectively.

Of 31 respondents, 81% ‘often’ or ‘always’ observed a mild bleeding phenotype, according to EHA definitions [8], in persons with BDUC. A moderate bleeding phenotype was ‘often’ or ‘always’ observed by 42% and ‘sometimes’ by 55% of respondents. A severe phenotype was only observed ‘sometimes’ by 48% and ‘never’ or ‘rarely’ by 45%. Ninety percent (27/30) of respondents confirmed the use of a BAT, with the ISTH-BAT being the most frequently used BAT (89%).

### 3.3 | Laboratory Testing

Since BDUC is a diagnosis by exclusion, the use of laboratory tests is essential in the diagnostic pathway. Figure 1 shows which laboratory tests are performed, only performed on specific indication or not performed in the Netherlands. Laboratory tests indicated to be performed by  $\geq 70\%$  of respondents were CBC, PT, aPTT, vWF activity, FVIII, vWF antigen, fibrinogen, MPV, FIX, FXIII, LTA and PFA-200. More than 70% reported not to perform plasma clot formation, TAFI and plasma clot lysis under pressure. No clear consensus was found regarding the use of the remaining laboratory tests.

Overall, tests that were indicated to be performed in our study were comparable to the laboratory tests in the proposed standard panel in ISTH SSC recommendations [2]. A difference was found regarding the measurement of FXI, which is recommended to be in the standard panel of tests by the ISTH, whilst in our survey, consensus on FXI measurement was nearly reached (65%). Another difference was the consensus in our survey to also perform PFA-200. The use of the PFA-200 in BDUC is under debate. It was not recommended by the ISTH SSC, although several studies have shown unexplained PFA-200 prolongations in BDUC patients [9, 10]. Furthermore, within the international ISTH SSC survey, platelet function tests were remarkably much less frequently performed than indicated by our respondents [11]. This was especially the case for nucleotide tests and/or flow cytometry in addition to LTA testing. The ISTH SSC recommends performing these additional platelet function tests if available, but they are not mandatory for a BDUC diagnosis [2]. Although LTA is required for a BDUC diagnosis according to the ISTH SSC, only 82% of our respondents indicated performing this test (some of them only on indication). These results suggest that some HTCs perform extensive platelet function tests, whilst in others there is still room for improvement regarding platelet function diagnostics. A possible explanation for the higher nucleotide test use in the Netherlands could be the higher availability of these specialized tests in Dutch HTCs compared to a more limited availability in other (less developed) countries. Apart from its availability, the high workload and the need of specialized analysts are also important limitations of these tests. Despite this, Dutch healthcare providers seem to agree that it is relevant to perform these tests in patients with a suspicion of a (primary) haemostasis disorder who would otherwise be classified as BDUC.

Tests that were mainly reported to be ‘never performed’ or only ‘on indication’ were more advanced haemostatic laboratory tests such as ROTEM, thrombin generation and fibrinolysis tests, which are often used to investigate underlying pathophysiological mechanisms in research settings and are not broadly available

in all HTC. Moreover, these specialized assays give variable results [4, 12–18]. Therefore, their added value in the diagnosis assessment for BDUC is still unclear.

Subgroup analyses were performed to investigate possible differences in the diagnostic approach between treating physicians working with children and adults. There was a remarkable difference in the use of platelet function tests, showing that LTA and nucleotide tests were more often performed ‘on indication’ in children compared to adults instead of standard measurement. Alternatively, flow cytometry was more often performed in children than adults. This could be explained by the fact that LTA and nucleotide tests require larger blood volumes, which is not always feasible in (small) children, whilst flow cytometry requires little volumes and is therefore easier to perform in children. Another difference was seen in the use of fibrinolytic tests, including plasminogen,  $\alpha$ 2-antiplasmin, PAI-1 antigen, plasma clot lysis and plasma clot formation, showing that these tests were mainly performed ‘on indication’ in children, whilst they were more often performed ‘standard’ in adults.

As BDUC is a diagnosis of exclusion, the question remains, however, what we consider normal investigations, whether a BDUC diagnosis is only based on the reference range of laboratory test results or whether (a combination of) low normal test results could also be an explanation for an increased bleeding tendency.

### 3.4 | Other Causes of Bleeding

Respondents agreed on the importance of the exclusion of the following bleeding disorders: haemophilia A and B, coagulation factor deficiencies, VWD, platelet function disorders (based on LTA, nucleotide test and/or flow cytometry test results), acquired bleeding disorders and fibrin/fibrinogen/fibrinolysis disorders (Figure 2A), which is in concordance with the ISTH SSC recommendations. Furthermore, respondents agreed on the exclusion of other causes of bleeding like ITP/TTP, anaemia, over-the-counter drug use, liver disease, herbal preparations, self-infliction, DIC and renal disease (Figure 2B).

However, respondents highlighted that exclusion of other causes for an increased bleeding tendency is also dependent on information derived by medical history taking, patient interview, and physical examination of the patient. Importantly, ISTH SSC recommendations include a list of laboratory tests that should be performed to exclude known bleeding disorders and also provide some suggestions to exclude acquired medical conditions that can cause bleeding, including hypermobility disorders, use of medication and dietary supplements, liver and kidney disease, thyroid dysfunction, myeloproliferative disease and inflammatory disease [2, 11]. With this survey we have complemented these recommendations to provide a comprehensive overview of other (non-haematological) causes for bleeding.

### 3.5 | Registration and Follow-Up

Within our study we identified follow-up frequency (Figure 3) as well as registration. Forty-seven percent (14/30) indicated

that persons with BDUC are registered as ‘bleeding disorder of unknown cause’ within their diagnosis registration systems. Sometimes (33%) other nomenclature was used, for example, increased bleeding tendency not otherwise indicated (n.o.i.). Twenty percent of respondents indicated no registration of persons with BDUC at all, possibly causing loss to follow-up. Frequency of registration is in line with the international ISTH SSC survey, although we report a higher percentage of registration as BDUC instead of other nomenclature [11].

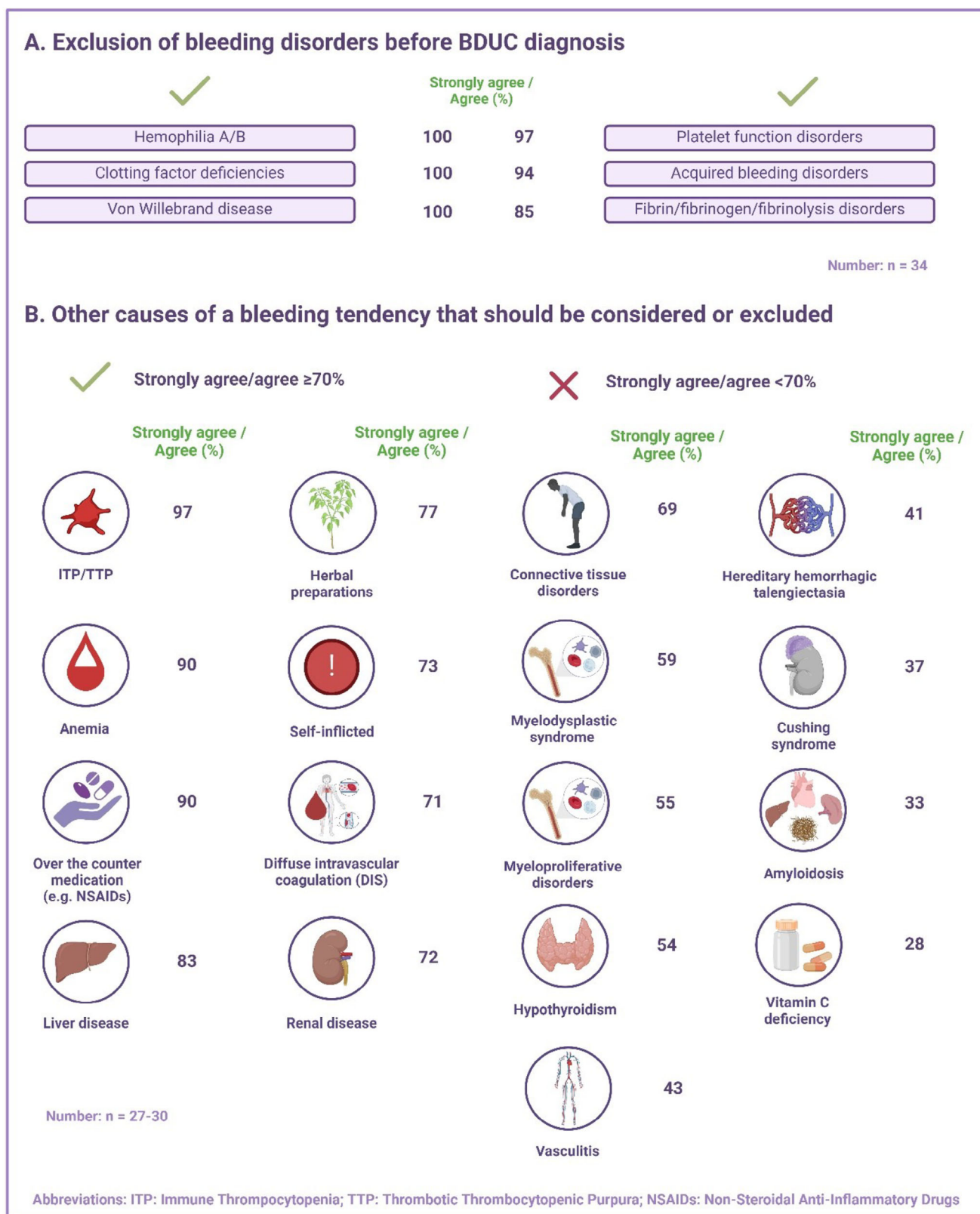
Regarding follow-up, 76% of respondents indicated that follow-up frequency depends on bleeding severity. Definitions published by the EHA for mild, moderate and severe bleeding phenotypes were applied [8]. Patients with moderate and mild bleeding phenotypes should receive follow-up care in case of medical interventions or child delivery (both 73% ‘agree’ or ‘strongly agree’). Moreover, standard follow-up every 2 years was suggested for moderate and mild bleeding phenotypes by 43% and 37% of respondents respectively, with some suggesting follow-up every 2–5 years. For severe bleeding phenotypes a yearly follow-up was recommended by 53% of respondents. Additionally, 67% ‘agreed’ or ‘strongly agreed’ that follow-up should depend on number of experienced serious bleeding events. The ISTH SSC provided advice concerning (prophylactic) treatment in BDUC patients, but did not incorporate recommendations on follow-up [2].

### 3.6 | Treatment Strategies

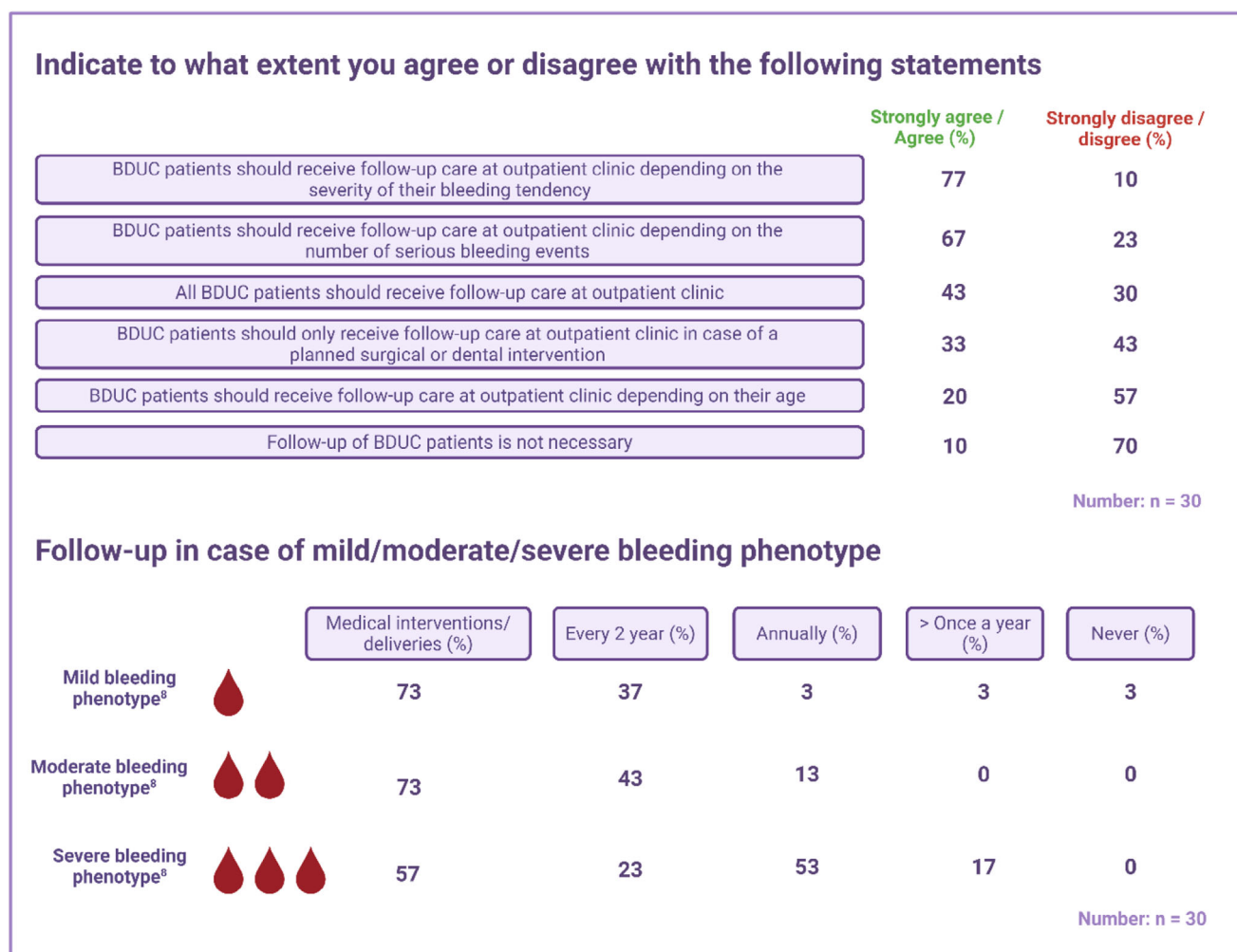
In our study, 97% of respondents ‘often’ or ‘always’ use tranexamic acid as treatment for persons with BDUC, 59% use desmopressin, and 17% use platelet transfusions. Activated recombinant factor VII concentrate was only used ‘sometimes’ by 35% of respondents (Figure 4).

In the Netherlands, persons with BDUC are almost always treated with tranexamic acid when undergoing medical procedures. In case of major surgery, 79% use or add desmopressin to the prescribed medication (Figure 4). This is in alignment with ISTH SSC recommendations, and although studies on treatment in persons with BDUC are scarce, results also show that tranexamic acid and desmopressin are the most used treatment modalities [4, 19].

With this survey we have documented current practice in the Netherlands regarding the BDUC definition, diagnostic process and clinical management. Our results align with an international survey conducted by the ISTH SSC between 2022 and 2023 with a limited number (1–4/216) of Dutch participants [11], although slight differences were found. Moreover, our results showed that not all respondents indicated using all tests recommended by the ISTH. This could be explained by the former lack of consensus and absent guidelines but also by differences in test availability across laboratories. Our survey is an important addition to the ISTH SSC recommendations by documenting clinical practice regarding follow-up and the exclusion of a broad range of (haematological) causes of an increased bleeding tendency, as well as highlighting the heterogeneity in the use of more advanced laboratory tests for diagnostic work-up, such



**FIGURE 2** | Exclusion of bleeding disorders and other causes for an increased bleeding tendency. Fibrin/fibrinogen/fibrinolysis disorders comprise both quantitative and qualitative fibrinogen defects including hyperfibrinogenemia and (hypo)dysfibrinogenemia, as well as fibrinolytic protein deficiencies and/or abnormalities in global fibrinolysis tests (e.g., euglobulin clot lysis time).



**FIGURE 3** | Follow-up prerequisites and frequency in persons with BDUC. Percentages of neutral answers to statements are not shown. Regarding follow-up in case of a mild, moderate or severe bleeding phenotype, the selection of multiple answers was possible.

as advanced platelet tests, anticoagulant and fibrinolytic factors, specific genetic tests and global haemostasis tests [2]. In addition, the inclusion of not only physicians but also specialized nurse practitioners and clinical chemists working with both paediatric and adult populations ensured a multidisciplinary perspective regarding current practice in BDUC. Nevertheless, to safeguard anonymity, respondents were not asked to indicate in which HTC they work, as the number of healthcare providers in Dutch HTC is limited and answers are easily traced back to the respondent. Therefore, comparisons across HTCs were not possible. Based on the survey results, a widely supported concept BDUC definition was formulated, stating that persons with BDUC have an increased bleeding tendency, based on an elevated (ISTH)-BAT score or clinical gestalt, in whom no abnormalities were found in a specific set of laboratory tests and in whom known bleeding disorders are excluded and other causes for bleeding have been considered.

Our survey has only been distributed to specialists working in HTCs, reflecting current practice within highly specialized, mostly academic centres. Thereby it may not reflect daily practice outside HTCs, where laboratory possibilities are more limited.

However, in the Netherlands, persons with BDUC are generally referred to an HTC for extensive diagnostic assessment, so we assume the identified current practice comprises the majority of persons with BDUC.

## 4 | Conclusion

Our survey shows that Dutch current practice is generally in line with ISTH SSC recommendations, although in some cases recommended tests to confirm a BDUC diagnosis are still omitted. Moreover, this survey describes current practice beyond these recommendations. We add that consensus should be established on the exclusion of a broad range of other causes for an increased bleeding tendency, follow-up and the minimal set of laboratory tests that should be conducted. The question remains, however, whether we should expand the diagnostic pathway for BDUC or use a multi-omics approach and deep clinical phenotyping. Together with ISTH SSC recommendations, this survey therefore adds to international efforts to unify BDUC definition, diagnostic approach, treatment and follow-up, and to attain broadly supported guidelines.

## Applied treatment options in persons with BDUC

|                            |                                                                                   | Never/rarely (%) | Sometimes (%) | Always/often (%) |                |
|----------------------------|-----------------------------------------------------------------------------------|------------------|---------------|------------------|----------------|
| Antifibrinolytic agents    |  | 0                | 3             | 97               |                |
| Desmopressin (DDAVP)       |  | 10               | 31            | 59               |                |
| Platelet transfusion       |  | 31               | 52            | 17               |                |
| Recombinant activated FVII |  | 66               | 35            | 0                | Number: n = 29 |

## Applied (prophylactic) treatment options in case of medical interventions

|                            |                                                                                     | Minor surgical intervention (n = 29) |        | Major surgical intervention (n = 29) |        | Dental extraction (n = 29) |        | Delivery (n = 27) |        |
|----------------------------|-------------------------------------------------------------------------------------|--------------------------------------|--------|--------------------------------------|--------|----------------------------|--------|-------------------|--------|
|                            |                                                                                     | Yes (%)                              | No (%) | Yes (%)                              | No (%) | Yes (%)                    | No (%) | Yes (%)           | No (%) |
| Tranexamic Acid tablets    |   | 79                                   | 21     | 86                                   | 14     | 93                         | 7      | 93                | 7      |
| Tranexamic Acid mouthwash  |  | 0                                    | 100    | 0                                    | 100    | 41                         | 59     | 0                 | 100    |
| Desmopressin (DDAVP)       |  | 31                                   | 69     | 79                                   | 21     | 14                         | 86     | 37                | 63     |
| Platelet transfusion       |  | 7                                    | 93     | 14                                   | 86     | 7                          | 93     | 15                | 85     |
| Recombinant activated FVII |  | 0                                    | 100    | 7                                    | 93     | 0                          | 100    | 4                 | 96     |
| No prophylaxis             |  | 3                                    | 97     | 0                                    | 100    | 0                          | 100    | 4                 | 96     |
| Only in case of bleeding   |  | 31                                   | 69     | 7                                    | 93     | 7                          | 93     | 19                | 81     |

**FIGURE 4** | Treatment strategies in persons with BDUC. A selection of multiple answers was possible for (prophylactic) treatment strategies in case of the various medical procedures.

## Author Contributions

**Caroline M. A. Mussert:** study design, data collection, data analysis, data interpretation, original draft, review process, writing. **Amaury L. L. Monard:** study design, data collection, data analysis, data interpretation, original draft, review process, writing. **Tirsa T. van Duijl:** study design, data interpretation, review and editing. **Yvonne M. C. Hensken:** study design, data interpretation, review and editing. **Maartje van den Biggelaar:** study design, data interpretation, review and editing. **Roger E. G. Schutgens:** review and editing. **Saskia E. M. Schols:** review and editing. **Karin J. Fijnvandraat:** review and editing. **Karina Meijer:** review and editing. **Paul L. den Exter:** review and editing. **Laurens Nieuwenhuizen:** review and editing. **Iris van Moort:** review and editing. **Marieke J. H. A. Kruip:** study design, data interpretation, review and editing. **Marjon H. Cnossen:** study design, data interpretation, review and editing, supervision. **Floor C. J. I. Heubel-Moenen:** study design, data interpretation, review and editing, supervision. This manuscript was approved for submission by all authors.

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## Ethics Statement

All participants gave consent to use the collected data for research purposes.

## Conflicts of Interest

Tirsa T. van Duijl has received research funding from the Bertus Kem Stipendium (GNHG). Yvonne M. C. Hensken is professor of clinical chemistry, in particular haemostasis. In this position she collaborates with and tests reagents and equipment from IVD companies in the field of haemostasis (Werfen, Siemens, Roche, Nodia, Stago). She is also an advisor of Promicol. Roger E. G. Schutgens has received research funding from Bayer, CSL Behring, Hemab, NovoNordisk, Novartis, Octapharma, Sanofi and Sobi. All payments go to the institution. Karin J. Fijnvandraat has received unrestricted grants/research funding from CSL Behring, Sobi for research unrelated to the current study, consultancy fees from Sobi, Sanofi, Novo Nordisk and Roche (all fees to the institution). Other boards: ISTH Standardization Subcommittee on Factor VIII, Factor XI, and Rare Coagulation Disorders. Karina Meijer reports speaker fees from Alexion, participation in trial steering committees for Bayer and Astra Zeneca, consulting fees from Therini, participation in data monitoring and endpoint adjudication committee for Octapharma. All payments go to her institution. Marieke J. H. A. Kruip has received an investigator-initiated research grant from Dutch Research Council (NWO), The Netherlands Organisation for Health Research and Development (ZonMw), Netherlands thrombosis foundation and Sobi, and speaker fees from Roche and Sobi. All payments go to the Erasmus MC as an institution.

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## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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