Smart Medication™, an Electronic Diary for Surveillance of Haemophilia Home Care and Optimization of Resource Distribution

Wolfgang Mondorf[1] Hermann Eichler[2] Ronald Fischer[3] Katharina Holstein[4] Robert Klamroth[5] Antje Nimtz-Talaska[6] Cornelia Wermes[7] Heinrich Richter[8] Kai Severin[9]

[1] Praxis und Labor Haemostaseologie, Haemostas-Frankfurt, Frankfurt am Main, Germany
[2] Transfusionsmedizin und Hämostaseologie, Universitätsklinikum des Saarlandes, Homburg, Germany
[3] Hämophiliezentrum, Universitätsklinikum Gießen/Marburg, Gießen, Germany
[4] Hämophiliezentrum, Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany
[5] Vivantes Klinikum, Zentrum für Hämophilie und Hämostaseologie, Berlin, Germany
[6] Praxis für Kinder- und Jugendmedizin, Frankfurt (Oder), Germany
[7] Hämophilie-Zentrum Hildesheim und Hannover, Hildesheim, Germany
[8] Hämophilie-Zentrum, Münster Westfahlen, Germany
[9] Praxis für Hämatologie und Onkologie, Köln, Germany

Address for correspondence Dr. Med. Wolfgang Mondorf, MD, Haemostas-Frankfurt, Gartenstraße 134, 60596 Frankfurt am Main, Germany (e-mail: wmondorf@web.de).

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Zusammenfassung

Im Folgenden wird das elektronische Substitutionstagebuch *smart medication*™ vorgestellt, sowie eine Analyse der damit erhobenen Echtzeitdaten. Seit 2012 wurde *smart medication*™ von 663 Patienten in 30 Deutschen Hämophilie Zentren (HZ) genutzt. Daten aus 9 HZ wurden für die nachfolgende Analyse zusammengeführt. Entsprechend der Mittelwerte des jährlichen Faktorenverbrauchs und der Anzahl von Gelenkblutungen wurden vier Gruppen gebildet. Die größte Gruppe (A, 42%) war die mit unterdurchschnittlichem Faktorenverbrauch und weniger als 2,25 Gelenkblutungen pro Jahr. Die zweitgrößte Gruppe (B, 32%) zeigte ähnlich niedrige Blutungsraten bei überdurchschnittlichem Faktorenverbrauch. Eine Reduktion des Faktorenverbrauchs bei einigen dieser Patienten wäre ggf. möglich. Hingegen könnten andere Patienten mit häufigen Gelenkblutungen bei gleichzeitig niedrigem Faktorenverbrauch (D, 13%), von einer Erhöhung der Dosis profitieren. Patienten mit häufigen Gelenkblutungen trotz überdurchschnittlichem Faktorenverbrauch (C, 13%) benötigen eine intensivierte Behandlung jenseits einer Dosisanpassung, wie pharmakokinetisch adaptierte Dosisanpassungen oder orthopädische Maßnahmen. Mit Hilfe von *smart medication*™ können Patienten, die eine Änderung ihrer laufenden Behandlung benötigen, lange vor der nächsten Vorstellung im HZ identifiziert werden. Der ständig wachsende Datenpool erlaubt zudem eine kontinuierliche Analyse von Echtzeitdaten und damit eine Optimierung der zur Verfügung stehenden Ressourcen.

Schlüsselwörter

- Telemedizin
- Hämophilie Hausbehandlung
- Online-Monitoring
- elektronische Dokumentation

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Abstract

This report describes the technical features and potential advantages of the application of electronic haemophilia treatment diary *smart medication*™ and an evaluation of real-life electronic treatment data collected from haemophilia patients. Since 2012, a total of 663 patients from 30 German haemophilia treatment centres (HTCs) have used the device. Data of nine HTCs were merged for real-life data analysis. Patients were divided into four subgroups according to above versus below mean values for annual factor consumption (AFC) and annual joint bleeds (AJB), respectively. The largest subgroup comprised patients with low mean AFC and AJB less than 2.25 (group A: 42%). Second largest was the group with low mean AJB but high AFC (group B: 32%), suggesting that resources could be saved in some patients. The group with low AFC but high AJB may need increased factor dosing (group D: 13%). Patients who showed a high mean AJB despite high AFC (group C: 13%) may require special medical attention, such as pharmacokinetic-adapted treatment modification or orthopaedic measures. *Smart medication*™ enables the HTC to quickly identify patients in need of treatment changes and, thus, to plan individualized therapy modifications prior to patient visits. The growing pool of real-life data facilitates data analysis and may play an important role in the optimization of resource distribution.

Keywords

- telemedicine
- haemophilia home treatment
- online monitoring
- electronic documentation

Introduction

Haemophilia is a hereditary bleeding disorder caused by a deficiency of clotting factor VIII (FVIII) or factor IX (FIX). Patients may repeatedly suffer from joint and muscle bleeding, and, in the long term, progressive joint damage and disability. Factor replacement therapy, administered either prophylactically at regular intervals, or as on-demand therapy in response to bleeding episodes, can minimize the frequency and/or severity of bleeding episodes, reduce complications and improve quality of life. Home-based self-administration of FVIII or FIX concentrates is well established in the care of patients with haemophilia.[1–4] While self-treatment has proved highly effective, it is also costly and requires close surveillance by a medical professional. Furthermore, the concept of home care relies on the willingness of patients and their families to assume responsibility for home infusions, and on their ability to make critical decisions concerning the necessity for, and timing of, infusions, especially in case of sudden onset of bleeding symptoms. In addition, for each application, the patient must carefully document the reason for treatment and quantity of infused factor, as well as the brand name and batch number of the FVIII or FIX concentrate. This documentation is subjected to mandatory medical review by the HTC to promptly identify and correct treatment errors. As, in general, most patients present in an HTC only two to four times per year, the identification of bleeding and treatment problems on the basis of paper diaries alone is difficult at best, and often results in considerable delay. Moreover, the documentation itself is often incomplete, inconclusive or incomprehensible. Thus, vital information regarding target joints, over- or underdosing, may be missed, resulting in suboptimal treatment and/or wasted resources. In addition, copying errors may occur during the time-consuming process of entering handwritten documentation into electronic databases or registries, as required by the German Transfusion Law.[5]

Today, handheld electronic devices and smartphone technology are important tools in many fields of clinical management. Systems for remote disease management, known as telemedicine, are especially useful in the treatment of rare diseases such as haemophilia.[6–13] *Smart medication* is a novel smartphone-based software application for long-term monitoring of patients with haemophilia, which allows real-time management and surveillance of patient self-treatment, bleeding occurrence and factor concentrate usage. The feasibility of handheld electronic devices for haemophilia home care has been reported by several authors. Recently, Hay et al[13] concluded that remote management of haemophilia patients may improve treatment compliance and support physicians in optimizing treatment regimens.

Methods

The Smart Medication™ Platform

The *smart medication*™ platform was developed, classified and registered as a class I medical device according to the Medical Devices Directive of the European Union (Directive 93/42/EEC). This directive certifies conformance to essential requirements for medical products including risk management (ISO 14971), proof of product usability (IEC 62366), software lifecycle management (IEC 62304) and quality management (ISO 13485). To finance further technical development while maintaining commercial independence of the scientific analysis, fundraising was performed by the registered German non-profit organization, VFTH e.V. (Verein zur Förderung der Telemedizin in der Hämostaseologie).

Technical Features of Smart Medication™

The *smart medication*™ software is supported by a wide range of popular smartphone technologies including android- and apple-based systems. It consists of four components: an app used by the patient to enter treatment data on his smartphone,

Fig. 1 Treatment documentation in the patient app. The only mandatory entry is the number of infused units. The pictogram and pain indicator appear only in case of bleeding. A final step screen (not shown) summarizes the current data entry.

tablet or personal computer (►Fig. 1); an app used by the HTC to record the concentrates issued to each individual; an internet-based platform allowing patients to access and visualize their own personal entries; and an internet-based platform giving the HTC an overview of all entries of patients treated in that specific HTC (►Table 1).

To serve as a basis for patient entries, certain data are automatically pre-entered, including date and time of infusion, body weight (first entry), and name and batch number of factor concentrate distributed by the HTC. Thus, repeated entries of brand names and batch numbers by hand or via barcode can be avoided. All data may be manually adapted by the patient if necessary. The patient is required to document only the infusion dose and, if appropriate, the location of bleeding, using a pictogram or a manual text entry, any delay which may have occurred between bleeding and factor transfusion, as well as intensity of pain. Concentrates not distributed by the patient's own HTC can be entered manually by means of a product search or using barcode technology. Before final transfer of data to the HTC database, the patient is able to review all entries and add a personal comment if appropriate. In addition, *smart medication*™ allows easy communication with the HTC by direct telephone contact or text message, and, if required, the app can be used by the patient to send a photograph of the bleeding site. In case of emergency, a single button message, *I was admitted to hospital*, has been implemented, allowing a rapid call-back option for the HTC.

Technical Data Protection Measures

Several technical safety measures have been implemented: The platform is hosted on dedicated server systems located at a German data centre operating according to well-established data protection standards (Information Security Management System based on ISO/IEC 27001). In accordance with the strict German data privacy regulations, no cloud-based services are permitted.

Data protection protocols and proprietary rights concerning software and treatment data were subjected to legal approval according to current German and European law. To prevent commercial interests of foreign network providers, the *smart medication*™ app can be downloaded only from the

Table 1 *Smart Medication*™ overview in haemophilia treatment centre

Search						
Patient ID	Days since last entry	IU in stock	IU infused in 2016 (2015)	Bleeds in 2016 (2015)	Joint bleeds in the last 3 mo	Joint bleeds in the last 7 d
1001	0	12,000	120,000 (175,000)	4 (8)	2	1
1002	3	5,000	85,000 (120,000)	0 (1)	1	0
1003	2	42,000	165,000 (150,000)	6 (1)	0	0
1004	5	2,000	24,000 (36,000)	2 (8)	0	0

Notes: Each column can be sorted according to respective column header. Columns can be hidden, or additional columns, such as distribution factor, can be added. The search field allows entry of words and numbers.

IT provider as an approved source, and is not available in public app stores. All transmitted data are pseudonymized by substituting the patient's name with a unique patient identification number, with the result that it cannot be attributed to a specific individual, except by the treating HTC, which is able to match the identifications of its own patients. Patients using the system can read and change only their own data, and HTCs are able to read and change only the data of patients treated in that specific centre. For scientific data evaluation only, data from different HTCs can be merged.

Patient Characteristics

Data from patients with haemophilia A and B with complete annual datasets were included in the analysis. In addition, one patient consented to the publication of his personal bleeding and treatment history in anonymized form, including both handwritten diaries (2012–2013) and subsequent electronic documentation. Documentation prior to 2012 was not done by the patient and was therefore not available.

Ethical Approval

Prior to data evaluation, written informed consent was obtained from each of the patients, as well as from their respective HTC as owner of the treatment data. Approval was granted by the ethics committee. Pooled data from nine HTCs were blinded for the following analysis.

Data Analysis and Statistics

The electronically documented data were analysed with respect to AJB and AFC. In a subset of data from 2016, age, haemophilia type A or B and reason for each treatment (on-demand vs. prophylaxis) were additionally analysed. As the prescribed treatment regimen was unknown, patients were divided into three treatment groups: the 'prophylactic' group, comprising patients whose treatment was prophylactic in more than 75% of entries; the 'on-demand' group, comprising patients whose treatment was on-demand in more than 75% of entries for bleeding and follow-up treatment and the 'intermediate' group, comprising patients with entries between 25 and 75% of either regimen (►Table 2).

Results

Data Collection via Smartphone Application

Since the introduction of *smart medication*™ on 1 February 2012, and up to 1 February 2017, a total of 663 patients from 30 HTCs in Germany have documented the use of a total of 176 million units of FVIII or FIX (►Fig. 2). A total of 113,530 single entries were made for infusions administered due to bleeding, follow-up or prophylaxis, adding to a constantly growing data pool.

Bleeding history of one patient with severe haemophilia A is shown (►Fig. 3) indicating cumulative number of joint bleeds, all bleeds and infused factor in IU. Paper-based documentation before 2012 is completely missing.

Patient Cohort Outcomes

For the present analysis, nine HTCs merged data entries from 2012, 2013 and 2014, respectively, for the purpose of further evaluation. AFC was found to be similar during each of the three years (►Fig. 4). The mean AFC over a period of 3 years was 2,442 (± 2,038) unit/kg (body weight) BW per year in 2014; 2,701 (± 1,837) unit/kg BW per year in 2015 and 2,575 (± 1,878) unit/kg BW per year in 2016. Respective figures for AJB were 2.04 in 2014, 2.46 in 2015 and 2.27 in 2016. The mean values were used as cut-offs to divide the patients into four groups according to their AFC (below mean vs. above mean) in relation to AJB (below mean vs. above mean), for each of the three years (►Fig. 5). Group A (AJB and

Table 2 Data analysis for groups A–D

	Regimen	*N*	Age	HA/HB (%)	AJB HA (*N*)	AJB HB (*N*)	AFC HA (×1,000 IU)	AFC HB (×1,000 IU)
Group A	P	82	28	87/13	0.33	0.45	104	70
	I	12	30	67/33	0.38	0.50	53	79
	OD	15	41	93/7	0.64	1.00	30	36
Group B	P	79	24	87/13	0.33	0.20	264	353
	I	0						
	OD	0						
Group C	P	31	31	94/6	6.30	5.00	319	324
	I	7	38	71/29	14.20	7.50	288	252
	OD	0						
Group D	P	5	39	100/0	4.60		140	
	I	7	45	57/43	7.50	15.00	54	138
	OD	8	48	100/0	9.70		100	

Abbreviations: AFC, annual factor consumption; AJB, annual joint bleeds; HA, haemophilia A; HB, haemophilia B; I, intermediate; OD, more than 75% of infusions for on-demand treatment; P, more than 75% infusions for prophylaxis.
Note: This table shows treatment regimen, number of patients, mean age, percentage of patients with HA versus HB, mean AJB in HA and HB, and mean AFC in HA and HB in 2016.

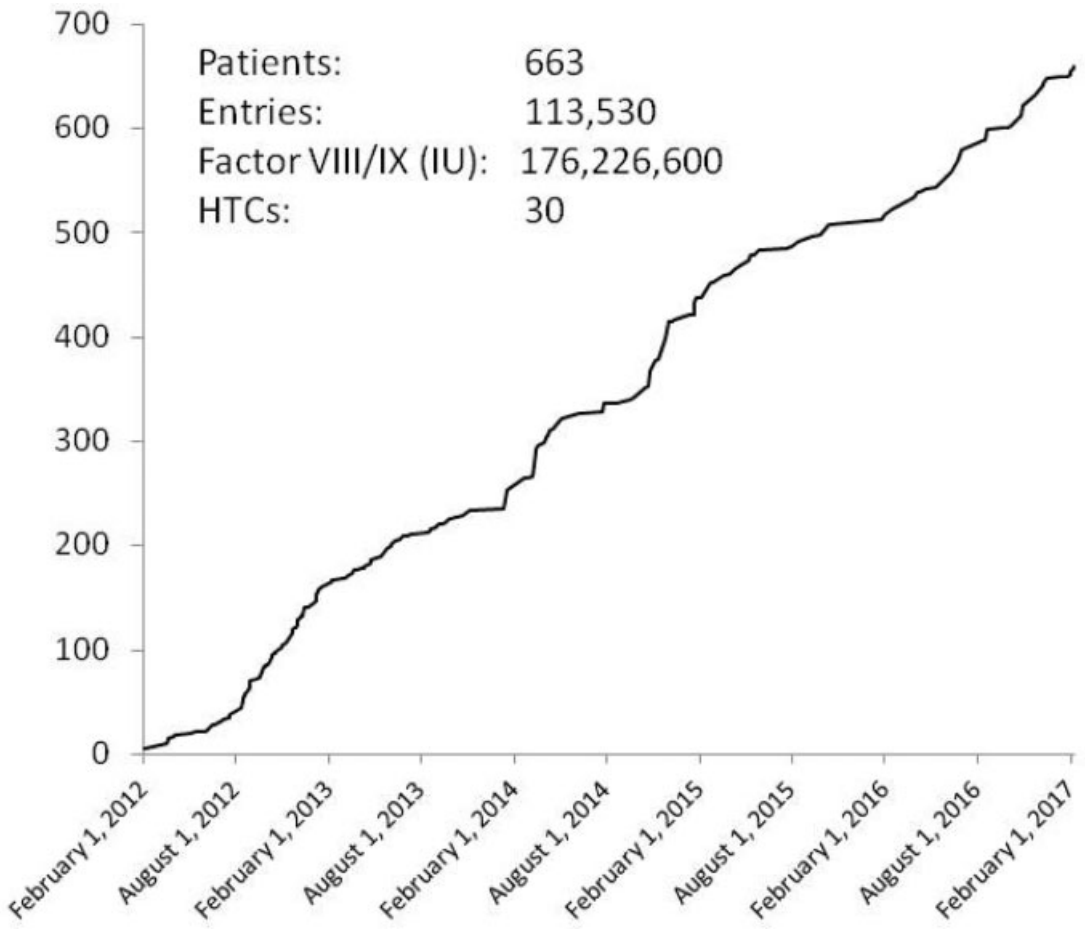

Fig. 2 Number of patients participating in the smart medication™. Cumulative entries, factor consumption and haemophilia treatment centres on 1 February 2017.

AFC both below cut-off) was the largest group (38–45% of the total number of patients) and used 20 to 21% of FVIII/FIX resources. The second largest group (30–35%) was group B (AJB below, AFC above cut-off), using 49 to 50% of distributed concentrates. In mean, patients in groups A and B had less than 2.25 AJB. A high mean AJB was seen in groups C (10–15% of all patients) and D (8–14%), who used 15 to 20% and 5 to 8% of FVIII/FIX resources, respectively. As the data were blinded, it was not possible to analyse whether patients changed from one group to another during the observation period.

In a subset of these patients in 2016, age distribution between haemophilia A and haemophilia B, AJB and AFC was further analysed (►**Table 2**). The mean age of patients on a prophylactic regimen was lower than that of patients treated with intermediate or on-demand regimens. Regarding the four groups separately, AJB increased from prophylactic to on-demand regimens, and vice versa for AFC. No major difference was seen when comparing mean AJB or AFC values between haemophilia A and haemophilia B. Prophylaxis was more common in groups A, B and C when compared with group D.

Discussion

Smartphone technology is widely accepted among the general public, not only as a means of communication but also as an instrument offering a wide variety of private and professional applications. Nevertheless, improved data protection has been a particular focus of further app development. Being unavailable from commercial app stores, the *smart medication*™ app lacks transparency for social networks. In addition, it is entirely independent of commercial interests, its development and realization having been funded by donations via a non-profit organization. *Smart medication*™ was introduced in February 2012, accompanied by individualized training programs for all users. Since then, the number of HTCs and patients using the software in Germany has surged, contributing to an ever increasing data pool. Besides improved data protection, the new *smart medication*™ application offers an enhanced user interface to ease data entry for patients and HTC users. In case of prophylactic treatment, the patient needs only to enter the number of units infused and click on the appropriate concentrate and batch number used, data pre-entered by the HTC. All data pre-entered by the HTC can, however, be changed as required (e.g., if a different concentrate is infused from what was previously distributed by the HCT.

The internet platforms for patients and HTCs are similar. However, while the patient sees only his or her own data entries, the HTC has access to a comprehensive overview of all patients treated in that centre who are participating in the *smart medication*™ program (►**Table 1**). The data are presented in table format, including patient identification, date,

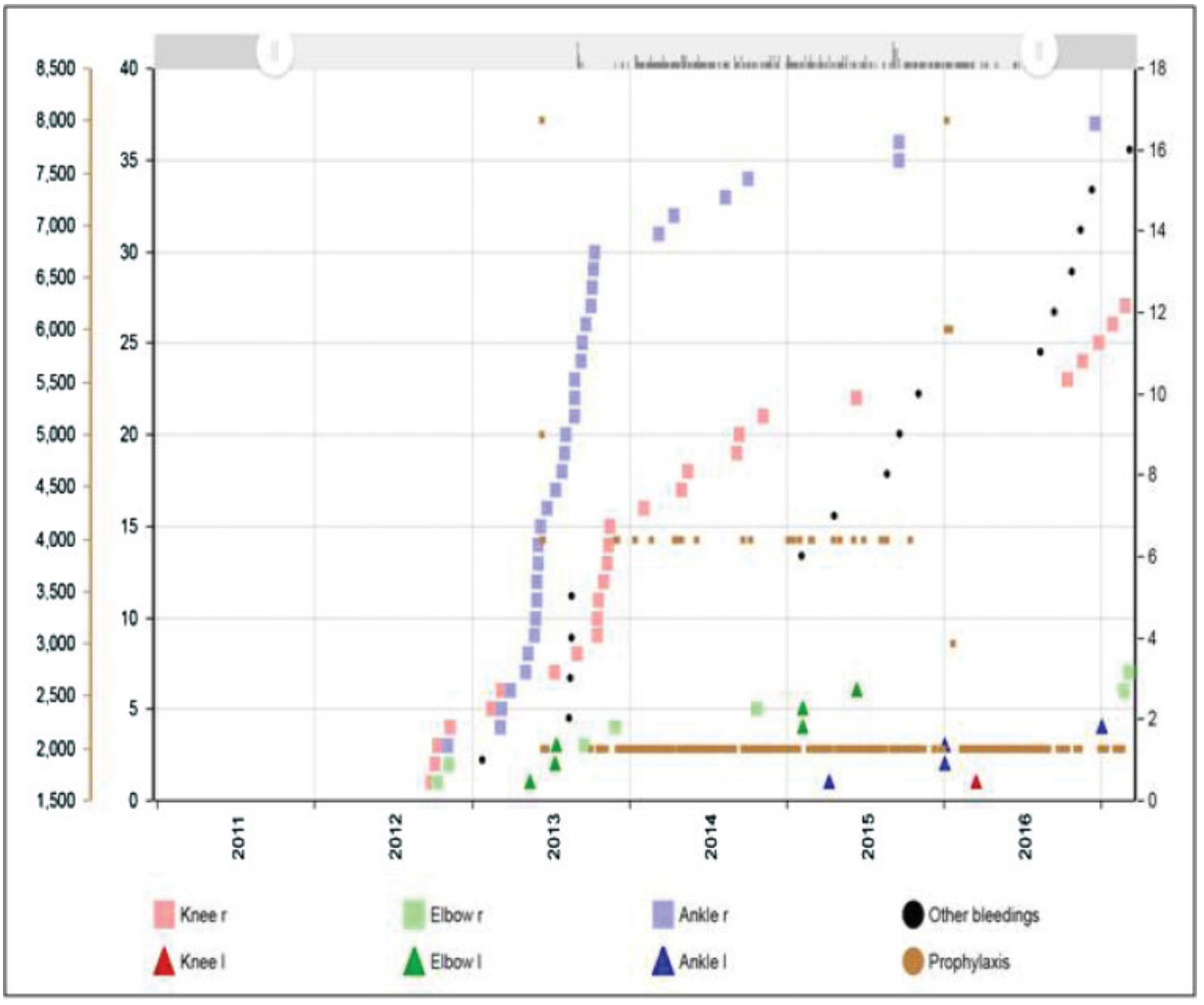

Fig. 3 Documented bleeding history of a patient with severe haemophilia A, indicating the cumulative number of joint bleeds in right axis, all bleeds in left axis and infused factor in IU in far left axis. Electronic documentation started in July 2013, following paper-based documentation since 2012. Data before 2012 are missing completely.

time since last entry, quantity of concentrates distributed, quantity of concentrates still in stock, and number of bleeds during the last 3 months and over the last 7 days. Quantity of infused factor and the number of bleeds are indicated for the current and previous year, to allow comparison. Patients with special problems or requirements can be easily identified by clicking the header box of each column to show particular parameters in ascending or descending order. Further individual information can be accessed in a range of formats such as a graph showing the life-time bleeding history of a particular patient (►**Fig. 3**). Using a zoom function within the graph, it is possible to focus on specific days, months or years. The convenient availability of year-by-year data concerning factor distribution and usage also enables the HCT to follow up on changes of treatment protocol or factor brand and gain an indication of non-adherence if more factors are distributed than used. A search field at the top of the overview table has been implemented for the HTC to find particular information such as batch numbers of concentrates, which may be helpful in case of batch recall.

This comprehensive overview allows rapid analysis of the transmitted data, and the ease of data rearrangement according to specific characteristics can substantially reduce the expenditure of time and effort by HTC personnel. This allows the HTC to focus on patients who may require special attention and/or treatment changes, so that an additional interim appointment at the HTC can be made in the case of high bleeding frequency or unnecessarily high factor consumption. Nevertheless, for data quality, the willingness of patients to consistently complete data entries remains a critical factor. Electronic data capture has greater advantage over paper diaries in that data are generally not lost. The example in ►**Fig. 3** shows that not only have the patient's pre-2012 data remained undocumented, but also that as long as a paper diary was used for treatment documentation (2012–2013), detection of the patient's high bleeding frequency was delayed. Electronic documentation was initiated in early 2013, and proved a helpful aid in convincing the patient to switch from on-demand infusions to a less convenient, but more effective, prophylactic treatment schedule. Following the introduction of the electronic diary and

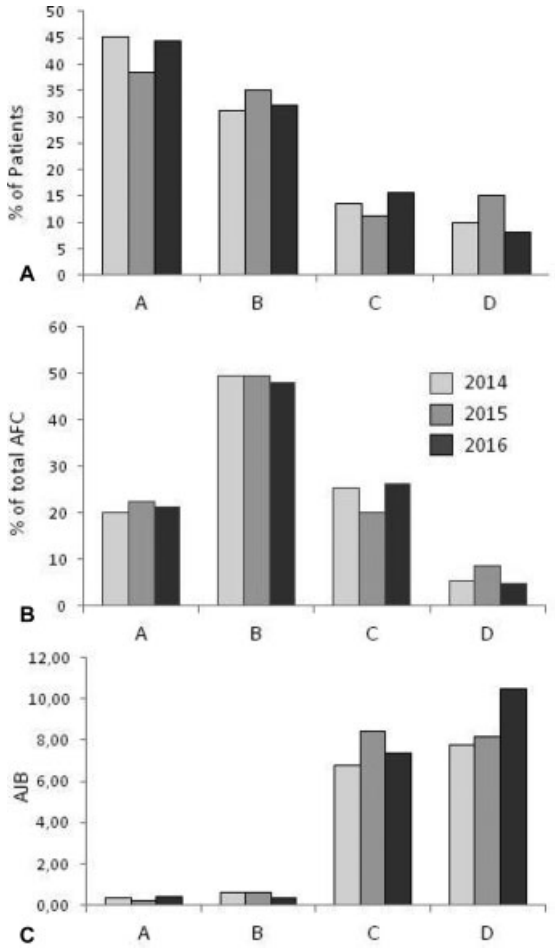

Fig. 4 (**a**) Percentage of patients; (**b**) percentage of total annual factor consumption and (**c**) mean annual joint bleeds (*n*); for groups A to D from 2014 to 2016.

consequent initiation of prophylactic therapy, bleeding frequency was therefore substantially reduced, as shown.

The electronic format allows easy and rapid merging of data from HTCs, thus giving valuable insights into real-life haemophilia home treatment. Results of the present data analysis from nine HTCs are in line with reports suggesting that, while prophylactic treatment reduces annual bleeding rate and AJB, it also necessitates an increased AFC.[14–17] As expected, no major differences were seen between haemophilia A and haemophilia B. The year-to-year comparison was surprisingly constant.

By comparing AJB and AFC, several conclusions may be drawn with regard to future haemophilia treatment options: The majority of patients show low figures for AJB and AFC (group A) and may not need any treatment changes. The second largest group (B) shows a similar low bleeding frequency but considerably higher mean AFC, using approximately half of the total resources. This may not necessarily be a reflection of overdosing, but rather of the necessity to prevent bleeding—and, indeed, of successful bleeding reduction—in these patients. However, a theoretical shift of a small percentage of FVIII/FIX concentrates from group B to patients in group D, who suffer more bleeds but whose dosing is below average, could have a major impact within the latter group. Of special concern are patients in group C who show increased mean AJB in spite of above average dosing. Other strategies for reduction of bleeding tendency besides increase of factor consumption should be considered, such as pharmacokinetic-adapted treatment intervals or orthopaedic measures. Nevertheless, *smart medication*™ supports physicians by allowing them to easily identify patients who may profit from a change in treatment strategy.

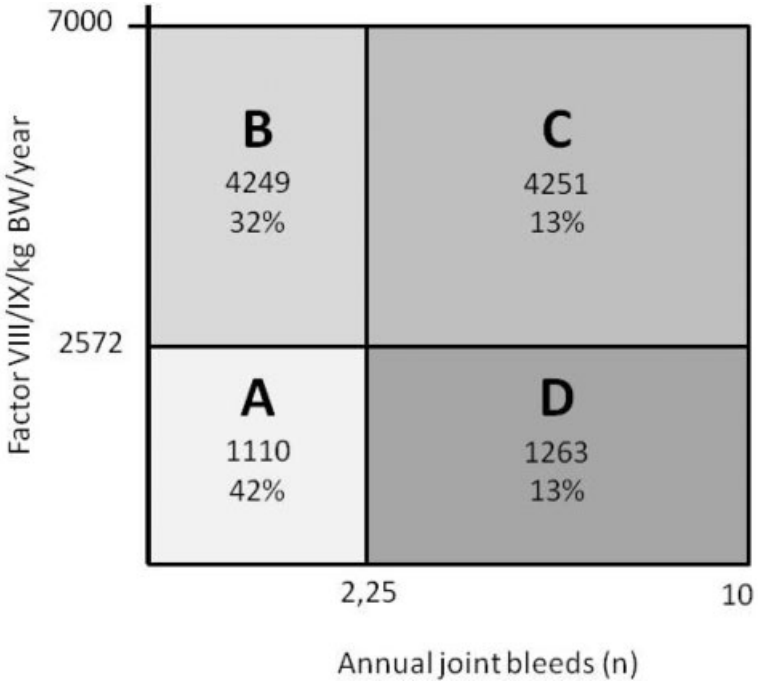

Fig. 5 Mean annual joint bleeds and annual factor consumption among 246 patients (%) with haemophilia A/B in nine haemophilia centres between 2014 and 2016.

In view of the time restraints and budget considerations omnipresent in daily practice, the opportunity to view and compare present and past data, and thus to discuss and prepare therapy changes prior to regular visits, makes *smart medication*™ a valuable tool in everyday clinical practice. However, it has to be kept in mind that several important variables are documented neither by paper diaries nor by electronic devices, such as physical activity, joint status or concurrent clinical and laboratory findings. As these factors have a major influence on the bleeding pattern, the regular personal attention of the treating physician still remains indispensable in the accurate assessment of treatment consequences.

In summary, according to our real-life data analysis and experience in daily clinical practice, the electronic diary *smart medication*™ can play a vital role in the surveillance of haemophilia home treatment. Based on careful observation and evaluation of electronic data, the identification of patients who may benefit from dose modification could facilitate the optimization of concentrate distribution among haemophilia patients and thus improve overall outcome in the haemophilia community. Finally, with the dawn of long-acting concentrates and preparations utilizing alternative pathways, it is necessary to individualize treatment strategies through online monitoring to enhance the cost-effectiveness of available resources.

Disclosure

Wolfgang Mondorf is the head of a non-profit organization for research and development of telemedicine in Haemostaseology (Verein zur Förderung der Telemedizin in der Hämostaseologie, VFTH e.V., Frankfurt/Main, Germany). This organization has received funding from pharmaceutical companies (Baxalta Deutschland GmbH, Bayer Vital GmbH, Biotest AG, CSL Behring GmbH, Novo Nordisk Pharma GmbH, Octapharma GmbH, Pfizer Pharma GmbH) for research performed in this work. Wolfgang Mondorf and Ronald Fischer have received reimbursement for attending and speaking at symposia concerning issues related to the submitted manuscript. Outside of this study and without reimbursement to the VFTH e.V., *smart medication*™ was employed by Baxter/Baxalta and Bayer for post-licensing studies.

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