Management of bleeding in acquired hemophilia A (AHA): results from the European Acquired Haemophilia (EACH2) Registry

Running head: Hemostatic therapy in acquired hemophilia A

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ABSTRACT

Acquired hemophilia A is a rare bleeding disorder caused by autoantibodies to coagulation FVIII. Bleeding episodes at presentation are spontaneous and severe in most cases. Optimal hemostatic therapy is controversial and available data are from observational and retrospective studies only. The EACH2 registry, a multi-center, pan-European, web-based database, reports current patient management. The aim was to assess the control of first bleeding episodes treated with a bypassing agent (rFVIIa or aPCC), FVIII or DDAVP among 501 registered patients. Of 482 patients with one or more bleeding episodes, 144 (30%) received no treatment for bleeding; 31 were treated with symptomatic therapy only. Among 307 patients treated with a first-line haemostatic agent, 174 (56.7%) received rFVIIa, 63 (20.5%) aPCC, 56 (18.2%) FVIII and 14 (4.6%) DDAVP. Bleeding was controlled in 269/338 (79.6%) patients treated with a first-line hemostatic agent or ancillary therapy alone. Propensity score matching was applied to allow unbiased comparison between treatment groups. Bleeding control was significantly higher in patients treated with bypassing agents vs. FVIII/DDAVP (93.3% vs. 68.3%; P=0.003). Bleeding control was similar between rFVIIa and aPCC (93.0%; P=1). Thrombotic events were reported in 3.6% of treated patients with a similar incidence between rFVIIa (2.9%) and aPCC (4.8%).
INTRODUCTION

Acquired hemophilia A (AHA) is a hemorrhagic syndrome characterized by a deficiency of coagulation factor VIII (FVIII) secondary to autoantibodies targeting specific epitopes that cause neutralization and/or accelerated clearance of FVIII from the plasma. The reported incidence of AHA varies between 0.1 and 1.5 cases per million population, although a study in a defined population suggests an incidence of 1.5 per million. AHA is commonly associated with a variety of clinical conditions, including autoimmune disorders, solid tumors, lymphoproliferative diseases and pregnancy; however no underlying condition is identified in about 50% of the cases.

Hemorrhages occur in AHA patients without a family or personal history of bleeding and usually exhibit a sudden onset. Bleeding episodes are spontaneous in the majority of cases, although about 25% of cases occur following trauma or invasive procedures. Retroperitoneal and large intramuscular hematomas may compress nervous and vascular structures, leading to compartmental syndromes. Bleeding at presentation is usually severe (over 67% of the cases) but may be mild, and about 25% of patients do not require hemostatic treatment.

Observed clinical bleeding does not correlate with FVIII level or inhibitor titer and differs from hereditary hemophilia: skin, mucous membranes, muscles and soft tissue bleeds are more common whereas hemarthroses are unusual. The mortality rate due to bleeding or otherwise related to AHA is high and reported to be between 7.9% and 22%.

The hemostatic agents most frequently used to control bleeding in AHA are bypassing agents, recombinant activated FVII (rFVIIa) or activated prothrombin complex concentrate (aPCC), or FVIII replacement therapy with concentrates or induction of FVIII release using 1-desamino-8-D-arginine-vasopressin (DDAVP). The optimal therapy is controversial, and available data are
derived from observational and retrospective studies, including a limited number of patients with
different primary clinical conditions.\textsuperscript{7-12}

To address this problem, the European Acquired Hemophilia (EACH2) registry was established in
2003 to collect information on the current management of patients with AHA. No treatment protocol
was provided, and patients were managed according to local clinical practice. This primary
analysis focuses on the hemostatic treatment of bleeding episodes with rFVIIa, aPCC, FVIII or
DDAVP.
METHODS

117 centers in 13 European countries participated in the web-based registry. The contributing centers are listed in the online supplementary material. The registry was hosted by Parexel International GmbH (Berlin, Germany), supported by an unrestricted grant from Novo Nordisk Region Europe A/S (Zurich, Switzerland), and reviewed by institutional review boards at each center. Informed consent was obtained from all patients or their next of kin in accordance with the Declaration of Helsinki. The study was longitudinal, prospective, observational and registered consecutive patients. Patient characteristics at diagnosis were recorded and have been previously detailed. The characteristics and outcome of patients who received immunosuppressive treatment have also been reported. Data for each bleeding episode were entered separately. The following characteristics of each new bleed were reported: site (CNS, musculoskeletal, retroperitoneal, gastrointestinal, urogenital, skin, none), cause (spontaneous, traumatic, surgical, peri or post-partum), severity [severe defined as life, limb or organ-threatening, central nervous system, hemoglobin (Hb) <8 g/dL or a drop of >2 g/dL; red blood cell (RBC) transfusion requirement of >2 units in 24 h]. All other bleeding episodes were defined as non-severe. The hemoglobin, activated partial thromboplastin time (aPTT), FVIII level and inhibitor titer were recorded at presentation and/or at the time of the bleed.

The hemostatic therapy used was described by agent and dosage regimen (initial dose per bolus, initial interval of successive doses, number of doses and total dose, total days of treatment). For patients treated with aPCC, FVIII or DDAVP anamnestic response was reported as yes or no. The following ancillary therapies were recorded: antifibrinolytic agents, RBC transfusion, topical therapy, immunoadsorption, plasmapheresis, high dose immunoglobulins. The response to therapy was judged clinically by the local investigator and was recorded as bleeding resolved with date or bleeding not resolved. Secondary treatment was initiated due to lack of efficacy or other reasons and was reported using the same data points. Adverse events, including thrombosis, that in the
opinion of the investigator were related to hemostatic therapy, were reported. All bleeding episodes were recorded in the registry, but only first bleeding episodes are analyzed here.

Baseline patient characteristics are reported as frequency (percentage) or median and interquartile range (IQR) for categorical and continuous variables, respectively. The primary endpoint was control of the first bleeding episode treated with first-line hemostatic therapy. Only first bleeds and first-line treatment are reported to avoid any potential indication bias. Reporting of all episodes experienced and therapy lines administered could impair treatment comparison because treatment assignment is highly conditional on previous treatment and non-responsiveness (i.e. correlated endpoints and time-dependent confounding). The first-line hemostatic therapy options analyzed were rFVIIa, aPCC, FVIII and DDAVP. Initial treatment regimens and response are reported descriptively, however because the baseline characteristics of patients and bleeding episodes vary widely, the results cannot be directly compared. In order to make comparisons between treatment strategies, baseline characteristics needed to be matched.

Two separate treatment comparisons were assessed. First, bypassing agents (rFVIIa or aPCC) vs. FVIII or DDAVP were compared, then a specific comparison between rFVIIa and aPCC was performed. Pre-matching comparisons between groups were performed using a Pearson’s $\chi^2$ test or Mann-Whitney U-test. To allow an unbiased comparison between the treatment groups, propensity score (PS) methodology\textsuperscript{15,16} was used.

For each analysis a separate logistic regression model was first applied to predict the probability (propensity score) of receiving either treatment (bypassing agents vs. FVIII replacement or release in the first analysis; rFVIIa vs. aPCC in the second). Both models included the same set of variables: age at diagnosis, gender, factor VIII level and inhibitor titer at time of the bleeding episode, Hb value at diagnosis, bleeding site (CNS, deep, hemarthroses, mucosa, skin, multiple
sites), bleeding severity (severe vs. non-severe), delay of therapy, cause of bleeding (spontaneous vs. traumatic).

Consequently, propensity scores derived from the logistic models were used within a 5→1 greedy 1:1 matching algorithm\textsuperscript{15} to obtain the matched samples. The greedy matching algorithm generated matched pairs of patients identical in their PS value, decreasing from five decimal places to one. Adequacy of covariate balance in the matched samples was eventually assessed with McNemar chi-square or a Wilcoxon signed rank test. Rates of bleeding episodes not resolved with first-line therapy were reported for unmatched and matched samples. PS-matched logistic models were expressed as odds ratios (OR) along with 95% confidence intervals (CI) and were derived from a generalized estimating equations logistic regression to account for the matched design. Where appropriate, to assess robustness of findings a PS quintiles-adjusted model was also used.\textsuperscript{16}

Last, since PS methodology only addresses imbalances due to measured covariates, we also performed a sensitivity analysis\textsuperscript{17} on significant findings to account for potential residual confounding due to an unknown, unmeasured baseline covariate. P-values <0.05 were considered significant. All the analyses were performed using SAS Statistical Package release 9.1 (SAS Institute, Cary, NC).
RESULTS

Between January 2003 and December 2008, 501 patients from 117 centers in 13 European countries (Austria, Finland, France, Germany, Greece, Hungary, Italy, The Netherlands, Portugal, Spain, Sweden, Switzerland, UK) were entered into the database. The demographics and characteristics at presentation of the entire cohort have been reported previously. 13 482 patients experienced at least one bleeding episode and 19 (3.8%) reported no bleeding. The baseline characteristics of the patients who bled and those who did not bleed were similar with respect to age, gender, weight, Hb, FVIII level, inhibitor titer and associated underlying conditions. Among the 482 patients who bled 230 (47.7%) were female and 252 (52.3%) were male. The median (IQR) values for patients who bled were as follows: age 74.0 (61.0-80.0) years; weight 69.4 (60.0-78.0) kg; FVIII activity 2.0 (1.0-6.0) IU/dL; Hb 9.0 (7.5-11.3) g/dL; FVIII inhibitor titer 14.0 (5.0-42.0) Bethesda Units (BU)/mL. The underlying medical condition was reported as an autoimmune disorder in 65 (14.1%), malignancy in 53 (11.5%), pregnancy in 41 (8.9%), drug-induced in 15 (3.3%) and transfusion, dermatological, infection, monoclonal gammopathy of undetermined significance (MGUS) or other in 36 (7.8%). No associated medical condition was identified (idiopathic) in 250 (54.4%), and no information was reported for 22 patients (4.6%). The disposition of patients in the cohort with respect to bleeding and hemostatic treatment is shown in Figure 1.

Of the 482 patients with at least one bleeding episode, 144 (30%) received no hemostatic treatment. Treated and untreated patients differed only in Hb level (8.6 vs 10.9 g/dL), site and severity of bleeding (all P<0.0001). Age, gender, FVIII level, inhibitor titer, cause of bleeding and underlying conditions were similar. The non-treated group included 94 non-severe bleeding episodes and 47 severe bleeds. The reason for not treating patients was not recorded in the registry. Among the patients who experienced a bleeding episode but were not treated, the hemoglobin level (11.0 vs. 9.4 g/dL; P=0.0004), cause (spontaneous vs. non-spontaneous; 86.2% vs. 72.3%; P=0.0459) and site of bleeding (deep 14.9% vs. 46.8%; skin 62.7% vs. 17.0%; mucosal
21.3% vs. 34.0%; P<0.0001) differed between non-severe and severe bleeding episodes. 338 patients received treatment for a first bleed, but 31 (9.2%) were treated with ancillary therapy only (1 immunoadsorption, 13 antifibrinolytic, 17 RBC, 3 topical therapy, 4 high-dose IVIg, 12 other). 307 patients received a first-line hemostatic agent, 174/307 were treated with rFVIIa (56.7%), 63 with aPCC (20.5%), 56 with FVIII (18.2%) and 14 with DDAVP (4.6%). Among patients treated with ancillary therapy only compared to those who received a hemostatic agent, a lower FVIII level at the time of the bleed was noted for the latter (5.9 vs. 4.1 IU/dL; P=0.0334). Fewer non-spontaneous bleeds (45.2% vs. 20.9%; P=0.0023) were reported among those receiving ancillary therapy only. The site of bleeding (deep 48.4% vs. 60.9%; mucosal 41.9% vs. 18.6%; P=0.0661), and severity of bleeding (25.9% vs. 13.4%; P=0.0618) showed a trend toward significance.

Bleeding resolved in 22/31 patients treated with ancillary therapy only; 6/9 patients who did not respond were switched to a bypassing agent and 3 of these episodes resolved. Among the 22 patients with resolved bleeding episodes following ancillary therapy alone, 10 patients received antifibrinolytic therapy, 9 RBC, 3 high-dose IVIg, 1 immunoadsorption and 2 topical therapy.

Overall, ancillary therapy, including that administered to the 307 patients also receiving hemostatic therapy, comprised 20 (5.9%) patients receiving immunoadsorption, 2 (0.6%) plasmapheresis, 64 (18.9%) antifibrinolytic agents, 184 (54.4%) RBC, 10 (3.0%) topical therapy, 38 (11.2%) high-dose IVIg and 53 (15.7%) other therapies. The overall median number of RBC units transfused was 4 (IQR 2-8), with no differences observed between site, severity, cause and bleed resolution.

Bleeding was controlled in 269 patients (79.6%), including those treated with ancillary therapy only. The only parameter that significantly differed between patients who responded to treatment and those who did not was a delay in time to treatment (median 1.00 vs. 4.00 days; P=0.0155). The FVIII level in responders and non-responders at the time of the first bleeding episode did not differ, nor did inhibitor titer (10.0 vs. 13.0; P=0.9294), bleeding cause (traumatic 13.2% vs. spontaneous 15.7%; P=0.5888), bleeding site (P=0.2939) or severity (15.9% vs. 10.4%; P=0.3259).
Among the 69 patients who received second-line therapy, 50 (14.8%) were treated due to lack of efficacy of first-line treatment and 19 (5.6%) for unspecified reasons, 24 (36.9%) were treated with rFVIIa, 15 (23.1%) with aPCC, 23 (35.4%) with FVIII, 1 (1.5%) with DDAVP, 2 (3.1%) received ancillary therapy only, and the type of agent was not reported for 4 patients. Information on the response to second-line treatment was available for 68 patients. Bleeding resolved in 54 patients (79.4%). 11 (16.2%) did not resolve and initiated third-line therapy for lack of efficacy; 3 patients (4.4%) initiated third-line therapy for unspecified reasons other than lack of efficacy. Information on bleeding recurrence was available for 65/69 second-line therapy patients: 18 patients (27.7%) had a recurrence. Of the 269 patients in whom bleeding resolved with first-line therapy, 68 patients had a recurrence (99 episodes) with an overall recurrence rate of 25.3% [median inhibitor titer 8.6 (2.0-37.0) BU/mL]. The median time to recurrence was 14 days (IQR 3-45).

The unmatched and matched baseline covariates comparing bypassing agents (n=219) and FVIII replacement and DDAVP (n=69) according to treatment of the 288 patients for whom the primary outcome data were available, are reported in Table 1 and Table 2. FVIII level, inhibitor titer, bleeding sites and severity of bleeding were significantly different in the two unmatched groups; gender showed a trend toward significance. 219 patients were treated with bypassing agents (159 with rFVIIa, 60 with aPCC) and 69 with FVIII (n=55) or DDAVP (n=14). Bleeding was controlled in 201 patients treated with bypassing agents (91.8%) and 48 patients (69.6%) treated with replacement therapy (P<0.003). Among the patients treated with replacement therapy, bleeding was resolved in 39 (70.1%) of patients treated with FVIII and 9 (64.3%) of those treated with DDAVP. PS 1:1 matching allowed an unbiased comparison between the two groups by matching 60 of 69 available pairs. The baseline covariates after PS matching were balanced. In the matched samples 56/60 patients (93.3%) in the group treated with bypassing agents and 41/60 (68.3%) in the group treated with FVIII or DDAVP, respectively, experienced bleeding episodes that were controlled by first-line therapy (OR=0.15, 95% CI 0.04-0.53; P=0.003). The haemostatic effect of each of the agents is shown in Table 3.
Since the PS matching algorithm selected 41 and 19 patients treated with rFVIIa and aPCC, respectively, to confirm the robustness of the above result, a PS quintiles-adjusted model for treatment comparison was also assessed. The results overlapped completely (OR=0.20, 95% CI 0.10-0.46; P<0.0001). A sensitivity analysis was also performed to disprove that this positive finding may be attributable to an imbalanced unknown, unmeasured baseline covariate. With respect to the results for the risk of unresolved bleeding episodes, the significant effect of bypassing agents (i.e. OR=0.15, 95% CI 0.04-0.53) might be altered by an unmeasured baseline covariate with an OR=2.5 and a prevalence imbalance between the two treatment groups of at least 60%. The risks might be also altered with a prevalence imbalance of 50%, but an OR=3.0, or with a prevalence imbalance of at least 40% but an OR=3.5.

Baseline characteristics of the 159 patients receiving rFVIIa and the 60 receiving aPCC are reported in Table 1. The baseline covariate significantly different in the two unmatched groups was age (P=0.02); gender (P=0.06) and cause of bleeding (P=0.08) were non-significant. The rate of bleeding control was similar for rFVIIa treatment [145/159 (91.2%) and aPCC 56/60 (93.3%)] (P=0.60). The baseline covariates after PS matching overlapped (Table 2). An equal rate of bleeding control was reported for 53/57 patients (93.0%) using both aPCC and rFVIIa, with OR=1 (95% CI 0.23-4.44; P=1) (Table 3).

As a further overall sensitivity analysis, a different approach for treatment comparison was also pursued. The impact of first-line hemostatic therapy for patients who were not treated for their very first bleeding episode but were treated for a subsequent episode was recorded in the registry. The findings obtained via PS matching (data not shown) were completely overlapping with the results reported above. To this end, PS models were further matched for cases for which the first bleeding episode was recorded in the registry vs. for those for which it was not recorded.
Details of first-line hemostatic therapy (initial dose, initial frequency, number of doses given, total dose) are provided in Table 4. In general, lower FVIII levels and higher inhibitor titers were observed in patients treated with bypassing agents, however FVIII levels for all treatment modalities overlapped, suggesting that FVIII level had little influence on treatment decisions.

Thrombotic events in relation to haemostatic therapy were reported in 13 of the 482 patients who experienced a bleeding episode (2.7%), including 2/144 patients who were not treated with a haemostatic agent and 11 of the 307 patients treated with a haemostatic agent (3.6%): 7 myocardial infarctions, 1 stroke, 5 venous thromboembolisms overall, and 6 myocardial infarctions, 1 stroke and 4 venous thromboembolisms in association with haemostatic treatment. The thrombotic events were reported in patients treated with rFVIIa 5/174 (2.9%), aPCC 3/63 (4.8%), FVIII/DDAVP 0/70 (0%) and in 3 cases treatment was not indicated. It is not possible to draw any definite conclusions about the causal relationship between the haemostatic treatment and the thrombotic event from the data available in the registry, except in one case where the local investigator reported that the thrombotic event was suspected to be related to treatment with a haemostatic agent (a myocardial infarction in a patient treated with rFVIIa). Furthermore, thrombotic events were significantly associated with mean age (79.4 vs. 68.3, P=0.0341), but not with underlying clinical conditions (P=0.6302).

Overall mortality among patients in whom treatment was initiated was 66/338 (19.5%). Among patients who received ancillary therapy alone, 6/31 (19.4%) died and survival at years 1-4 remained steady at 83%. Overall, 29/174 (16.7%) who were treated for a first bleeding episode with rFVIIa died, with a survival of 84%, 82%, 79% and 72% at years 1-4, respectively. Similarly, 12/63 (19.0%) patients treated with aPCC died, with 81% surviving at 1 year and 76% surviving at each of years 2-4. 19/56 (33.9%) of patients treated for a first bleeding episode with FVIII died, with survival at years 1-4 of 74%, 70%, 57% and 44%. No deaths were reported among the 14 patients treated with DDAVP. 16/482 patients who experienced at least one bleeding episode and 10/307
patients treated with hemostatic therapy died as a result of bleeding (mortality 3.3%). 4/16 deaths occurred on the first day of therapy. The median time from therapy to death was 23 days. Among the patients who died following hemostatic treatment for the first bleeding episode, 4 received rFVIIa, with a median of 19 (1, 15, 23, 27) days between treatment and death, 3 received aPCC a median of 16 (1, 16, 163) days previously and 3 were treated with FVIII a median of 25 (23, 25, 184) days before death. An anamnestic response to treatment of the first bleeding episode was reported in 6/63 patients (9.5%) treated with aPCC, 15/55 (27.2%) treated with FVIII and 3/14 (21.4%) treated with DDAVP. No information on the kinetics of the inhibitor in these cases was recorded. There were no anaphylactic or allergic reactions reported.
DISCUSSION

The EACH2 registry provides information on routine clinical practice in Europe in the management of this rare but serious hemorrhagic condition. The study is the largest observational dataset reported to date and more than doubles the number of patients in a single cohort previously reported in the literature. The primary aim of this study was to report how the first bleeding episode was managed; the treatment of subsequent bleeds are not discussed in terms of comparison because the outcome may have been influenced by the treatment of and response to first bleeds. 307 patients were included in this analysis, and 288 patients had information on the main outcome (bleeding controlled or not controlled) recorded.

Two therapeutic interventions to control bleeding in patients with AHA are available: bypassing agents (rFVIIa and aPCC) and strategies to increase FVIII levels (FVIII concentrate and DDAVP). Although not administered by any of the participating centers, in the past prothrombin complex concentrates were also used to treat patients with classical hemophilia and FVIII inhibitors and sporadically in AHA, with a similar efficacy and safety profile in both conditions, however, their efficacy appears to be lower than either rFVIIa or aPCC, and their use is not recommended in current guidelines for the treatment of AHA. Bypassing agents are recommended as first-line therapy due to their rapid action and high level of effectiveness. Prospective randomized trials comparing the efficacy of these agents have not been carried out to date, and it is very unlikely that an adequately powered study would be feasible. No high-level evidence is therefore available for the use of either product. The dosage is largely based on experience with the management of patients with FVIII alloantibody inhibitors in congenital hemophilia and is generally based on the clinical assessment.

The EACH2 registry is a representative cohort of patients that largely confirms existing baseline data. Clinical bleeding at presentation was observed in 96.2% of patients and was severe
in 69.5%. Severity of bleeding is widely variable, and it is recognized that many patients do not require hemostatic treatment. The finding that 30% of patients with bleeding in EACH2 did not receive hemostatic therapy is in agreement with previous reports.\(^3\) FVIII level and inhibitor titer were not related to the presence of bleeding, a requirement for hemostatic therapy or severity of bleeding as previously reported.\(^{13}\) Although some patients do not require hemostatic treatment, in many cases bleeding in AHA is an emergency.\(^3,19\) In our cohort 194 patients (38.7%) either did not exhibit any bleeding or did not require hemostatic therapy at presentation. In those that did require hemostatic therapy, bleeding was controlled in 86.7% (269/307) by the initial therapy. rFVIIa was the most commonly used hemostatic treatment, administered in 174/307 patients (56.6%).

The effectiveness of bypassing agents compared to strategies to raise FVIII levels on bleeding resolution was assessed. In the unmatched population the bleeding control with the first-line therapy (primary endpoint) was obtained in 201 patients (91.8%) treated with bypassing agents compared to 48 (69.6%) treated with replacement therapy (P<0.003). This substantial difference was confirmed after PS-matching in 60 pairs and strongly supports the recommended use of bypassing agents.\(^{10-12}\) The control rate of bleeding episodes with bypassing agents as first-line therapy in our registry is similar to that reported by Sumner et al. with rFVIIa (91.8 vs. 95% respectively).\(^9\) The experience with aPCC in AHA derives from single-center cohort studies comprising relatively few patients. The control of bleeding episodes varied between 76 and 100% depending on the severity of hemorrhage.\(^{20,25-27}\) These data are not comparable to the data relating to rFVIIa due to differences in patient characteristics and the type and severity of bleeding episodes.

No studies have compared rFVIIa and aPCC in AHA, although studies in congenital hemophilia with inhibitors suggest similar efficacy.\(^{28,29}\) This PS-matched analysis was carried out in 57 matched pairs and provides the only currently available comparison of rFVIIa and aPCC in AHA. Bleeding control was the same in the PS-matched cohorts, supporting the view that these agents
have a very similar hemostatic efficacy in AHA. The results of the registry, therefore, confirm that bypassing agents are more efficacious than FVIII or DDAVP and should be the agents of choice for the first-line therapy. rFVIIa vs. aPCC have similar efficacy.

The EACH2 database provides important information about thrombotic adverse events associated with hemostatic agents used to treat bleeding episodes in AHA. Adverse events were seen at similar rates with both rFVIIa (2.9%) and aPCC (4.8%) but not with FVIII or DDAVP. Two patients experienced thrombotic events in the absence of hemostatic therapy. Sumner et al. have reported an incidence of thrombosis of 6.5% associated with rFVIIa use in AHA. It is possible that the safety information may be underestimated, as adverse events are infrequently published as part of case reports. On the other hand, a thrombotic event must take into consideration many other factors related to thrombotic risk, possibly independent of hemostatic agents administered. Previous data on thrombotic events in patients with AHA treated with aPCC are lacking, and the agent is reported to be well tolerated. In the papers evaluating the safety of aPCC and rFVIIa in patients with labeled indications (the majority are patients with hemophilia A and inhibitors), the incidence of thrombotic events was similar, at 4/100,000 infusions.

The higher rate of arterial and venous thrombosis in AHA compared to congenital hemophilia with inhibitors may be attributable to the age of the patients studied (median age 74 years here), the likelihood of co-morbidities and the presence of acquired thrombotic risk factors. The finding of a significant number of thrombotic events highlights the importance of avoiding unnecessary treatment of patients with mild or superficial bleeding and supports the view of consensus guidelines that rFVIIa at a dose of 270 µg/kg, commonly used in congenital hemophilia with inhibitors, may not be appropriate in AHA. The registry reports a bleeding mortality rate of 3.3%, much lower than that reported for the UK registry (8%). This difference may reflect improved awareness of the clinical condition and the availability of effective hemostatic agents. It is also possible that the difference may be due to the way in which the cohorts were collected.
Some limitations to the EACH2 registry dataset exist. Considering the total population of the participating countries (374 million) and the estimated incidence of AHA (~1.5/10^6 population/year), as reported in the UK registry,^3^ the estimated number of cases among this population that might have been expected during the 6 years of data collection was approximately 3360. This means that only 14.9% of the potentially eligible patients (501/3360) were enrolled, however this rate of success for a registry is a significant achievement. The low enrollment may be explained by the low number of participating centers within the recruitment area or may reflect the true incidence of critical cases that may differ in different geographical or ethnic backgrounds. The low enrollment and unrestricted patient management are important limits to the dataset. Participating centers entered consecutive patients, therefore some forms of reporting bias were reduced, however, most participating centers were specialist referral centers, therefore some level of referral bias is likely, and the population may reflect a more severely affected cohort than that reported in the UK.^3^ The registry did not try to influence treatment directly, although links to national treatment guidelines were provided. This means that clinicians managed patients according to their routine protocols and hence management was highly variable.

As for all observational sources of data, one major issue is always the lack of randomization and therefore potential selection bias when addressing any treatment comparison. PS methodology is a useful tool to reduce selection bias in observational studies,^15,16^ and has already been used in many therapeutic fields.^^33–36^ Treatment comparisons in such contexts are still prone to residual bias which PS methods cannot take into account, however, and although sensitivity analysis can overcome residual bias by addressing its extent, these attempts to assess treatment effectiveness should be considered exploratory in nature.

In conclusion, this study reports both the largest collection of bleeding episodes recorded in AHA and the most rigorous analysis of treatment outcome. The data show that the optimal treatment of
bleeding in AHA comprises bypassing agents which can be expected to resolve bleeding in more than 90% of cases. The data support caution in the use of bypassing agents in the typical AHA population due to an association with both arterial and venous thrombotic events.
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AUTHORSHIP CONTRIBUTIONS

All of the authors participated in definition of data fields to be collected in the registry and the development of the electronic case report form. FP was primarily responsible for the statistical analyses. The manuscript was drafted by FB and FP. All of the authors participated in the review, revision and approval of the manuscript.
DISCLOSURE OF CONFLICTS OF INTEREST

Within the past two years,

- **FB** has received honoraria directly from Bayer, Baxter, Grifols, Novo Nordisk,
- **PC** has served as a consultant for Novo Nordisk, Baxter Healthcare, CSL Behring and Inspiration Pharmaceuticals. He has received honoraria directly from Novo Nordisk, Baxter Healthcare, Bayer, CSL Behring and Inspiration pharmaceuticals,
- **AH-K** has served as a consultant for Novo Nordisk, Bayer and Pfizer,
- **PK** has served as a consultant, received research and travel funding and has been a member of advisory committees for Novo Nordisk, Baxter, Archemix and Ablynx,
- **HL** has served as consultant for Novo Nordisk and Baxter Healthcare and has received honoraria for lecturing from Novo-Nordisk,
- **PM** has served as consultant and has been member of advisory committees for Novo Nordisk,
- **LN** has received honoraria for lecturing and participation in advisory boards for Baxter, Novo Nordisk and Pfizer,
- **FP** has served as a consultant for Novo Nordisk, and
- **LT** has served as a consultant for Ferring and Novo Nordisk and has received honoraria directly from them.
REFERENCES


### Table 1. Unmatched sample baseline characteristics according to treatment of the first bleeding episode (bypassing agent vs. FVIII or DDAVP and rFVIIa vs. aPCC).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bypassing agent</th>
<th>FVIII or DDAVP</th>
<th>P-value*</th>
<th>rFVIIa</th>
<th>aPCC</th>
<th>P-value**</th>
</tr>
</thead>
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<tr>
<td></td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td></td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td></td>
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<tr>
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<td></td>
<td>159</td>
<td>60</td>
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<tr>
<td>Age, years</td>
<td>73.0 (15.0-92.0)</td>
<td>73.0 (13.0-104.0)</td>
<td>0.94</td>
<td>73.0 (15.0-91.0)</td>
<td>76.5 (24.0-92.0)</td>
<td>0.02</td>
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<td>Gender, n (%)</td>
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<tr>
<td>Female</td>
<td>109 (49.7)</td>
<td>26 (37.7)</td>
<td>0.07</td>
<td>73 (45.9)</td>
<td>36 (60.0)</td>
<td>0.06</td>
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<tr>
<td>Male</td>
<td>110 (50.8)</td>
<td>43 (62.3)</td>
<td></td>
<td>86 (54.1)</td>
<td>24 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.0 (40.0-130.0)</td>
<td>69.0 (40.0-113.0)</td>
<td>0.92</td>
<td>69.0 (40.0-130.0)</td>
<td>69.2 (44.0-107.0)</td>
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<td>FVIII level, IU/dL</td>
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<td>2.0 (0.0-32.0)</td>
<td>1.0 (0.0-40.0)</td>
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<tr>
<td>Hb, g/dL</td>
<td>8.6 (3.0-15.2)</td>
<td>8.8 (3.3-14.4)</td>
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<td>8.6 (3.0-15.2)</td>
<td>8.4 (4.6-14.8)</td>
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<tr>
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<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
<td>Group 3</td>
<td>Group 4</td>
<td>p-value</td>
</tr>
<tr>
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<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Inhibitor titer, BU/mL</strong></td>
<td>15.4 (0.1-2765.0)</td>
<td>8.0 (0.3-200.0)</td>
<td>0.0003</td>
<td>15.0 (1.0-2765.0)</td>
<td>17.0 (0.1-1700.0)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Therapy delay, days</strong></td>
<td>0.01 (0.0-0.5)</td>
<td>0.01 (0.00-0.11)</td>
<td>0.34</td>
<td>0.01 (0.00-0.27)</td>
<td>0.01 (0.00-0.54)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Ancillary antifibrinolytic therapy, n (%)</strong></td>
<td>30 (13.7)</td>
<td>20 (29.0)</td>
<td>0.0035</td>
<td>27 (17.0)</td>
<td>3 (5.0)</td>
<td>0.0215</td>
</tr>
<tr>
<td><strong>Cause of bleeding, n (%)</strong></td>
<td>Unknown</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.715</td>
</tr>
<tr>
<td></td>
<td>Traumatic</td>
<td>46 (21.1)</td>
<td>16 (23.2)</td>
<td>0.715</td>
<td>38 (24.1)</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td></td>
<td>Spontaneous</td>
<td>172 (78.9)</td>
<td>53 (76.8)</td>
<td>120 (75.9)</td>
<td>52 (86.7)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Bleeding site, n (%)</strong></td>
<td>CNS</td>
<td>5 (2.3)</td>
<td>0 (0.0)</td>
<td>5 (3.1)</td>
<td>0 (0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Deep muscle</td>
<td>139 (63.4)</td>
<td>32 (46.4)</td>
<td>94 (59.1)</td>
<td>45 (75.0)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Hemarthrosis</td>
<td>6 (2.7)</td>
<td>3 (4.3)</td>
<td>5 (3.1)</td>
<td>1 (1.7)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Mucosa</td>
<td>34 (15.6)</td>
<td>21 (30.5)</td>
<td>30 (18.8)</td>
<td>4 (6.6)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>34 (15.6)</td>
<td>13 (18.8)</td>
<td>24 (15.2)</td>
<td>10 (16.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Multiple sites</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of bleeding, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>193 (88.5)</td>
<td>54 (78.2)</td>
<td>0.031</td>
<td>142 (89.8)</td>
<td>51 (85.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Non-severe</td>
<td>25 (11.5)</td>
<td>15 (21.8)</td>
<td></td>
<td>16 (10.1)</td>
<td>9 (15.0)</td>
<td></td>
</tr>
</tbody>
</table>

* P-values refer to Pearson chi-square or Mann-Whitney U-test for the comparison between bypassing agent and FVIII or DDAVP.

** P-values refer to Pearson chi-square or Mann-Whitney U-test for the comparison between rFVIIa and aPCC.

‡ 13/55 patients (23.6%) treated with FVIII received ancillary antifibrinolytic treatment; 7/14 (50%) of patients treated with DDAVP also received antifibrinolytics.

Hb, hemoglobin

BU/mL, Bethesda Units per mL

CNS, central nervous system

DDAVP, 1-desamino-8-D-arginine-vasopressin

rFVIIa, recombinant activated factor VII

aPCC, activated prothrombin complex concentrate
Table 2. Matched sample baseline characteristics according to treatment of the first bleeding episode (bypassing agent vs. FVIII or DDAVP and rFVIIa vs. aPCC).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bypassing agent</th>
<th>FVIII or DDAVP</th>
<th>P-value*</th>
<th>rFVIIa§</th>
<th>aPCC</th>
<th>P-value*</th>
</tr>
</thead>
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<tr>
<td></td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td></td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>60</td>
<td>60</td>
<td></td>
<td>57</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>74.0 (24.0-91.0)</td>
<td>72.5 (13.0-104.0)</td>
<td>0.95</td>
<td>72.00 (39.00-91.00)</td>
<td>77.00 (24.00-92.00)</td>
<td>0.41</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25 (41.7)</td>
<td>23 (38.3)</td>
<td>0.69</td>
<td>37 (64.91)</td>
<td>33 (57.89)</td>
<td>0.41</td>
</tr>
<tr>
<td>Male</td>
<td>35 (58.3)</td>
<td>37 (61.7)</td>
<td>0.69</td>
<td>20 (35.09)</td>
<td>24 (42.11)</td>
<td>0.41</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.0 (40.0-107.0)</td>
<td>68.0 (40.0-113.0)</td>
<td>0.49</td>
<td>70.00 (40.00-120.00)</td>
<td>70.00 (44.00-107.00)</td>
<td>0.66</td>
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<tr>
<td>FVIII level, IU/dL</td>
<td>2.0 (0.0-40.0)</td>
<td>3.0 (0.0-34.0)</td>
<td>0.61</td>
<td>1.25 (0.00-32.00)</td>
<td>1.00 (0.00-40.00)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>8.4 (3.0-14.2)</td>
<td>8.8 (3.3-14.4)</td>
<td>0.41</td>
<td>8.50 (3.00-14.00)</td>
<td>8.40 (4.60-14.80)</td>
<td>0.84</td>
</tr>
<tr>
<td>Inhibitor titer, BU/mL</td>
<td>9.3 (1.0-2765.0)</td>
<td>8.0 (0.3-200.0)</td>
<td>0.52</td>
<td>16.00 (1.00-2765.00)</td>
<td>17.00 (0.10-1700.00)</td>
<td>0.52</td>
</tr>
<tr>
<td>Therapy delay, days</td>
<td>0.01 (0.0-0.13)</td>
<td>0.01 (0.0-0.11)</td>
<td>0.46</td>
<td>0.01 (0.00-0.09)</td>
<td>0.01 (0.00-0.54)</td>
<td>0.64</td>
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<tr>
<td>Cause of bleeding, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bleeding site, n (%)</td>
<td>Deep</td>
<td>Hemarthrosis</td>
<td>Mucosa</td>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>------------</td>
<td>--------------</td>
<td>-----------</td>
<td>----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>16 (26.7)</td>
<td>30 (50.0)</td>
<td>15 (25.0)</td>
<td>12 (20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>44 (73.3)</td>
<td>2 (3.3)</td>
<td>16 (26.7)</td>
<td>12 (20.0)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0.51</td>
<td>0.99</td>
<td>0.62</td>
<td></td>
<td></td>
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<tr>
<td>Bleeding site, n (%)</td>
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</tr>
<tr>
<td>Deep</td>
<td>30 (50.0)</td>
<td>44 (77.19)</td>
<td>44 (77.19)</td>
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<td></td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>2 (3.3)</td>
<td>0 (0.00)</td>
<td>1 (1.75)</td>
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<td></td>
</tr>
<tr>
<td>Mucosa</td>
<td>16 (26.7)</td>
<td>5 (8.77)</td>
<td>4 (7.02)</td>
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<tr>
<td>Skin</td>
<td>12 (20.0)</td>
<td>8 (14.04)</td>
<td>8 (14.04)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Severity of bleeding, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Severe</td>
<td>47 (78.3)</td>
<td>49 (81.7)</td>
<td>49 (85.96)</td>
<td>51 (89.47)</td>
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<tr>
<td>Non-severe</td>
<td>13 (21.6)</td>
<td>11 (18.3)</td>
<td>8 (14.04)</td>
<td>6 (10.53)</td>
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<tr>
<td></td>
<td>0.63</td>
<td>0.56</td>
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</tbody>
</table>

* P-values refer to McNemar chi-square or Wilcoxon signed-rank test.

‡ 2 patients (3.5%) among the matched samples treated with rFVIIa also received ancillary immunoabsorption.

IQR, interquartile range

Hb, hemoglobin

BU/mL, Bethesda Units per mL

33
DDAVP, 1-desamino-8-D-arginine-vasopressin

rFVIIa, recombinant activated factor VII

aPCC, activated prothrombin complex concentrate
**Table 3.** Rates of control for first bleeding episodes by first-line therapy.

<table>
<thead>
<tr>
<th>Hemostatic agent</th>
<th>First-line bleeding control</th>
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<tr>
<td></td>
<td>n</td>
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<tr>
<td><strong>Unmatched samples</strong></td>
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<tr>
<td>Bypassing agent</td>
<td>219</td>
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<tr>
<td>aPCC</td>
<td>159</td>
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<tr>
<td>rFVIIa</td>
<td>60</td>
</tr>
<tr>
<td>Replacement therapy</td>
<td>69</td>
</tr>
<tr>
<td>DDAVP</td>
<td>55</td>
</tr>
<tr>
<td>FVIII</td>
<td>14</td>
</tr>
<tr>
<td><strong>PS-matched samples</strong></td>
<td></td>
</tr>
<tr>
<td>Bypassing agent</td>
<td>60</td>
</tr>
<tr>
<td>Replacement therapy</td>
<td>60</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>57</td>
</tr>
<tr>
<td>aPCC</td>
<td>57</td>
</tr>
</tbody>
</table>

PS, propensity score

rFVIIa, recombinant activated factor VII

aPCC, activated prothrombin complex concentrate

FVIII, coagulation factor VIII

DDAVP, 1-desamino-8-D-arginine-vasopressin
Table 4. Types of first-line haemostatic therapy for all first bleeding episodes [median (IQR)].

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n</th>
<th>Baseline FVIII level IU/dL</th>
<th>Baseline inhibitor titer BU/mL</th>
<th>Initial dose Initial dosing interval h</th>
<th>Total doses per patient n</th>
<th>Total dose per patient µg/kg or U/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIIa</td>
<td>174</td>
<td>2.0 (0.0-32.0)</td>
<td>15.5 (1.0-2765)</td>
<td>90 (84.71-102.86)</td>
<td>3 (2-6)</td>
<td>12 (3-35)</td>
</tr>
<tr>
<td>aPCC</td>
<td>63</td>
<td>1.0 (0.0-40.0)</td>
<td>18.0 (0.1-1700)</td>
<td>66.67 (52.63-82.19)</td>
<td>12 (12-12)</td>
<td>8 (3-15)</td>
</tr>
<tr>
<td>FVIII</td>
<td>56</td>
<td>3.0 (0.0-34.0)</td>
<td>7.5 (0.8-180)</td>
<td>52.91 (40.00-81.97)</td>
<td>12 (8-12)</td>
<td>5 (2-10)</td>
</tr>
<tr>
<td>DDAVP</td>
<td>14</td>
<td>3.5 (0.0-17.0)</td>
<td>8.0 (0.3-200)</td>
<td>0.3 (0.3-0.3)</td>
<td>12 (8-24)</td>
<td>2.5 (1-3)</td>
</tr>
</tbody>
</table>

IQR, interquartile range
rFVIIa, recombinant activated factor VII
aPCC, activated prothrombin complex concentrate
DDAVP, 1-desamino-8-D-arginine-vasopressin
FIGURES

Figure 1. EACH2 Registry hemostatic therapy data flow-chart.

EACH2 cohort
n=501

At least one bleeding episode
n=482

Initiated hemostatic/ancillary treatment
n=338

Treated with rFVIIa, aPCC, FVIII or DDAVP
n=307

Main outcome available
(bleeding resolved vs. not resolved)
n=288

No bleeding episodes
n=19

Not treated
n=144

Ancillary therapy only
n=31

Main outcome not available
n=19
Management of bleeding in acquired hemophilia A (AHA): results from the European Acquired Hemophilia (EACH2) Registry

Francesco Baudo, Peter Collins, Angela Huth-Kuehne, Hervé Lévesque, Pascual Marco, László Nemes, Fabio Pellegrini, Lilian Tengborn and Paul Knoebl