Folding to function

Rising insights in nonsevere hemophilia A and DDAVP treatment

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CHAPTER 11
Summary and Discussion
SUMMARY & GENERAL DISCUSSION

Hemophilia A is a bleeding disorder caused by a defect in the \textit{F8} gene, leading to decreased clotting factor VIII (FVIII) levels. Patients are classified based on residual FVIII concentration (FVIII:C) in the plasma. Severely affected patients have no detectable FVIII:C levels, whereas nonsevere patients have some activity (FVIII:C moderate patients 1-5, mild patients 6-40 IU/dL).\textsuperscript{1}

The focus of this thesis is nonsevere hemophilia A. The mainstay of nonsevere hemophilia A treatment is the replacement of defective FVIII. Replacement therapy by using FVIII concentrates has three downsides. Unfortunately, there is a lifelong risk of the development of inhibiting antibodies against FVIII (inhibitors). When this occurs, the treatment of future bleeding episodes is jeopardized. Furthermore, the frequent intravenous administration of FVIII concentrate due to its short half-life is inconvenient for patients. Lastly, the costs of treatment are a major burden on national healthcare budgets. Resources are limited to treat patients in developing countries. For these reasons, the avoidance of FVIII concentrates by using safer, convenient and cheaper treatment options is preferable.

A safer and relatively cheaper treatment option is desmopressin (DDAVP). DDAVP is a synthetic hormone that increases endogenous FVIII in most, but not all nonsevere hemophilia A patients. Deciphering the biomolecular processes underlying the therapeutic effect of DDAVP may help to optimize treatment strategies.

Despite rapid developments in the treatment or possible future cure of nonsevere hemophilia A, a permanent solution to restore hemostasis in these patients is not yet available.\textsuperscript{2} With this thesis I aimed to gain rising insights into nonsevere hemophilia A and DDAVP treatment. In the next section I will summarize and discuss the evidence that has been obtained in the studies presented in this thesis that consists of three parts that provide:

I. Insight into morbidity and mechanistic aspects of nonsevere hemophilia A
II. Rise in knowledge on determinants of DDAVP response in nonsevere hemophilia A
III. Rising insights in the mechanisms of action of DDAVP treatment
Part I INSIGHT

In the first part of this thesis, we show that nonsevere hemophilia A is not a mild disease at all. The life expectancy of nonsevere hemophilia A patients has been approaching that of the normal male population since the introduction of FVIII replacement therapy in high income countries.\(^3\)\(^-\)\(^5\) Despite this important development, several studies have indicated that inhibitor development upon replacement therapy jeopardizes the clinical outcome and may increase the risk of mortality.\(^6\)\(^-\)\(^9\) Moreover, the life expectancy of nonsevere hemophilia A patients in developing countries is believed to be much lower.\(^10\)

In chapter 2 we assess the association between inhibitor development and mortality. In order to address this association, we analyzed clinical data and the vital status of 2709 patients from the INSIGHT study over 30 years. During the follow-up period, 107 patients developed an inhibitor. At the end of follow-up, a total of 148 patients had died at a median age of 64 years, 16 of them were inhibitor patients. The cause of death was hemophilia-related in 62 deceased patients (42%). Fatal bleeding complications were a major cause of death, especially in patients with an inhibitor at time of death (in 7/16, 44%). We compared the all-cause mortality rate in inhibitor-patients with non-inhibitor patients. The mortality rate was more than five times higher in inhibitor-patients. These findings stress the importance of close monitoring and safer treatment alternatives in nonsevere hemophilia A patients.

Our findings are in line with previously reported results of Darby et al., who also demonstrated an association between inhibitor development and mortality in nonsevere hemophilia A patients in the UK.\(^8\) However, we report on a more recent and unique international cohort of nonsevere hemophilia A patients, and observe a higher mortality rate ratio (MRR, >2-fold versus >5-fold). This may be due to older nonsevere hemophilia A patients in our cohort, who may be affected by age-induced co-morbidities. Adequate multidisciplinary management and care for the nonsevere hemophilia patients with comorbidities in specialized hemophilia treatment centers will be a clinical challenge.

Treatment with FVIII replacement therapy necessitates close follow-up and monitoring, as these patients are at lifelong risk for inhibitor development.\(^11\) This will become increasingly important as life expectancy rises in nonsevere hemophilia A patients due to the continuing developments in hemophilia A care, and medical care in general.\(^12\) A new generation of older nonsevere hemophilia A patients will require
specialized care as they develop age-induced co-morbidities, such as cardiovascular disorders or malignant disease, which may need surgical intervention and therefore exposure to FVIII replacement therapy, while these patients remain at risk for inhibitors.\textsuperscript{13} In order to avoid this risk, treatment regimens that are less immunogenic may help these patients. We lack evidence for treatment regimens that are less immunogenic. The development of such regimens may be an implication for future research. In the absence of proven strategies to prevent inhibitors, we should be careful with the use of concentrates and consider DDAVP in adequate-responders.\textsuperscript{14} Data on bleeding-related causes of death in nonsevere hemophilia A patients are scarce. Chapter 3 explores the bleeding-related causes of death in the INSIGHT cohort. Seventeen of the 148 deceased patients in the INSIGHT cohort died from intracranial bleeding (12\%). An inhibitor was present in one of these 17 patients. Fatal intracranial bleeding occurred spontaneously in 13 patients and was traumatic in four. Patients with fatal intracranial bleeding were relatively young, most of them had mild severity of disease = and no clear comorbidities. We calculated the standardized mortality rate to compare death following intracranial bleeding in our study population with the general population. The risk of fatal ICH was 3.5 fold higher than in the general population.

These results further underline the need for specialized care and optimized diagnostic and treatment strategies for these patients, and show that not only inhibitor-patients are at increased risk for bleeding complications. All nonsevere patients carry a considerable risk for (fatal) bleeding complications, including fatal intracranial bleeding, compared to the general population.\textsuperscript{4} This is the first international cohort study to report specific mortality rates for fatal intracranial bleeding in nonsevere hemophilia A patients. As the clinical profile and comorbidities of the patients dying from intracranial bleeding show no clear pattern identifying high-risk patients, adequate follow-up and instruction of all nonsevere hemophilia A patients is essential. Recent studies of genetic risk factors for intracranial bleeding in the general population have identified several genetic variants and risk alleles.\textsuperscript{15} In association with hemophilia A, these variants may increase the risk of fatal intracranial bleeding. This information might help to identify patients at risk for intracranial bleeding in the future.

Furthermore, as eminently rightly stated by Patil et al., patients in developing countries, such as India, do not have access to the treatment modalities that are available in the developed countries.\textsuperscript{16} As a result, hemophilia-related mortality rates, also for fatal
intracranial bleeding, are higher in these countries. The focus in hemophilia research is mostly on care and treatment possibilities available in developed countries. However, developing countries harbor the majority of the hemophilia population, where care and treatment options are restricted and there is an urgent demand for knowledge to improve care. Collaboration is therefore essential. Only with combined forces can we try to close the remaining gaps of knowledge in translational and clinical research to improve hemophilia care.

In addition to provide insight into morbidity and mortality of patients with nonsevere HA, the first part of the thesis is also meant to gain insight into biomolecular aspects of the disease. Our understanding of the biomolecular process by which the causative genetic event leads to reduced baseline FVIII concentration (FVIII:C) in nonsevere patients is still limited. Besides the F8 genotype, several other determinants are known to influence the endogenous FVIII:C. Environmental factors, such as assay variation, but also individual determinants such as age, blood group and von Willebrand Factor (VWF) level are described to play a role. Our limited knowledge on the origin of variation in baseline FVIII:C contributes to ongoing diagnostic uncertainties, as patients with the same mutation might have a different baseline FVIII:C. Estimation of the variability of FVIII:C in patients with the same F8 genotype and identification of the determinants that influence FVIII:C in nonsevere hemophilia A patients are essential for optimizing both diagnostic and individual treatment strategies, and to understand the molecular basis of the development of hemophilia A.

In chapter 4 we estimate the variation in baseline FVIII:C in patients with the same mutation. We selected 346 patients from both the INSIGHT and the RISE study aged ≥ 10 years who carried missense mutations that were present in at least 10 patients. We found large inter- and intra-individual variation in baseline FVIII:C. Age and genotype explained 59% of the observed inter-individual variation in factor VIII:C. Intra-individual variation accounted for 45% of the variation in the three mutations that were most prevalent. The increase in baseline FVIII:C with age varies between different mutations.

Our results demonstrate that baseline FVIII:C is multifactorial in origin, and not only determined by the F8 mutation. This awareness is essential in diagnostic patient management, as the diagnosis of the severity of disease is based on residual FVIII, which may vary in patients with the same mutation.

Our study is unique in its large size. Owing to the broad spectrum of missense mutations in nonsevere hemophilia A patients, knowledge of the association
between \textit{F8} mutation and baseline FVIII:C is difficult to obtain, as smaller studies lack the statistical power to analyze the association. Our results show that different patients with the same mutation have a variation in FVIII levels and may therefore differ in disease severity. Although baseline FVIII:C increases with age, it is questionable whether the phenotype becomes milder with advanced age. Baseline FVIII:C also increases in healthy individuals. This age-induced rise may be required to maintain hemostasis in the more fragile circumstances of elderly individuals. Thus, the increasing clotting factor levels may reflect a physiologic response to the increased hemostatic requirement of old age, in analogy to higher physiologic FVIII levels at the end of pregnancy. To investigate whether the age-induced rise in baseline FVIII:C is needed to maintain hemostasis, baseline FVIII:C should be coupled to bleeding phenotype data in the future. The precise relation between FVIII levels and bleeding phenotype remains to be elucidated. This is the aim of the recently started DYNAMO project. Furthermore, attention should be paid to the type of assays used to diagnose patients, as discrepancies between FVIII assays have been described. Studies have shown that there can be a large inter- and intra-individual variation in measured FVIII:C, depending on the type of assay used (chromogenic versus one-stage). In 40% of the patients, the level determined with the one-stage clotting assay has been found to be up to twice as high as that determined with the two-stage clotting or chromogenic clotting assays. It has been proposed that chromogenic assays may better predict bleeding phenotype. If only a one-stage assay is performed in the diagnostic work-up, then the plasma level of FVIII may be overestimated and consequently the bleeding risk may be underestimated in these patients. Moreover, alterations of genes other than \textit{F8}, e.g. those involved in the fibrinolytic pathway, may also influence the bleeding phenotype, and should be further investigated as potential indicators of bleeding risk.
Part II RISE

The second part of this thesis focuses on DDAVP treatment: a safer and cheaper alternative compared to FVIII concentrates, and therefore also suitable to use in developing countries. Since its discovery 40 years ago, DDAVP has proven to be a pivotal treatment alternative in nonsevere hemophilia A. DDAVP acts via stimulation of the vasopressin-2 receptors in endothelial cells. This causes a transient change in blood pressure and an antidiuretic effect. Cardiovascular disease is a contra-indication for its use because it may elicit acute thrombosis due to the rise in FVIII and VWF. Reported side effects of DDAVP include headache, flushing, and nausea, but these are described to be temporary and that are generally not clinically relevant.

Besides its anti-diuretic effects, DDAVP induces the release of a person’s own (endogenous) FVIII and VWF. FVIII rises on average three- to fivefold and the response lasts for about 12-24 hours. We need more insight into the origins of the large inter-individual variation in DDAVP response to optimize its use. For this reason, the chapters of part II aim to unravel knowledge on the determinants of DDAVP response in moderately affected hemophilia A patients, and on the effect of age and genotype on DDAVP response. For this purpose, we set up the RISE study including of 1474 nonsevere hemophilia A patients from 24 hemophilia treatment centers in Europe, Australia and Canada.

Patients with a lower baseline FVIII:C tend to show a reduced DDAVP response, therefore DDAVP is less frequently used in moderate hemophilia A patients (baseline FVIII:C 1-5 international units/deciliter (IU/dL)), even though FVIII levels may rise substantially in 20% of them. Moderate hemophilia A patients generally have a more severe bleeding phenotype compared to mild patients and are therefore more frequently exposed to FVIII concentrates. We analyzed the response to DDAVP in the 169 moderate patients in our cohort in chapter 5. Adequate response to DDAVP was defined as a peak FVIII level ≥ 30, and excellent response as ≥ 50 IU/dL after DDAVP administration. The response was adequate in 68 patients (40%), of whom 25 (15%) showed excellent response. Moreover, half of the patients with high inhibitor risk mutations respond to DDAVP. Finally, we addressed the predictors of the response in moderate patients. Among the six predictors explaining 65% of DDAVP-induced FVIII rise, FVIII baseline activity and DDAVP-induced rise in VWF had the strongest effect. The use of DDAVP in moderate hemophilia A patients in clinical practice has been
limited over the last 40 years. However, the drug is effective in almost half of them. Our study is unique in its size. Other studies have also described the DDAVP response, but were limited to small patient groups (one to 17 patients). The DDAVP response rates in our study among moderately affected patients were higher (40 versus 21%). Varying response rates might be due to differences in population characteristics, such as age, genetic background, and different routes of administration.

In light of the potential risks, complications and costs of treatment with FVIII replacement therapy, DDAVP should not be withheld as a treatment option from moderate hemophilia A patients. Importantly, half of the moderate hemophilia A patients carrying mutations associated with a high inhibitor risk respond to DDAVP, and all moderate patients should therefore be tested for DDAVP responsiveness. This will reduce exposure to FVIII concentrates, limiting the risk for inhibitor development, and concomitantly reducing costs of treatment. Furthermore, because of its safety, relatively low costs, and the multiple administration possibilities, DDAVP may be a suitable drug for moderately affected hemophilia A patients in developing countries as well. The potential value of DDAVP is also reflected by its place on the World Health Organization’s Model Lists of Essential Medicines, which is a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions.

All moderately affected patients should be tested for their response to DDAVP. Future studies should be performed prospectively to confirm ours. This could be done by the standardized and controlled administration of DDAVP to all moderately affected hemophilia A patients in multiple centers. Furthermore, as stated in an editorial in Haematologica, written by Prof. Mannucci in response to our article, it is important to study the efficacy of DDAVP in preventing or treating bleeding episodes as outcome of DDAVP response in a future prospective study.

An important predictor of DDAVP response is genotype. However, analysis of this predictor is hampered by the heterogeneity of the missense mutations causing nonsevere hemophilia A. In chapter 6, we explore the association between genotype and DDAVP response. Our study is the first to use a functional classification of F8 missense mutations according to the Sengupta score in addressing this association. This enabled us to analyze 587 of the 1474 patients from the RISE study (40%). The selection was based on patients with mutations that could be classified according to the Sengupta score. We demonstrate that F8 mutations producing multiple functional FVIII defects are associated with a lower absolute response to DDAVP than...
mutations associated with single functional defects, explaining 12% of the variation in absolute DDAVP response. In a subanalysis we demonstrate that mutations located in conserved regions of the \textit{F8} gene are associated with a lower DDAVP response compared to other single functional defects (mean absolute FVIII increase was 26 IU/dL lower).

Thus, genotype partially explains DDAVP response. Mutations in highly conserved regions of the \textit{F8} gene have a profound effect on the DDAVP response. Sites with highly conserved regions are required for important basic functions. In the evolution of the blood coagulation system, highly conserved sites of the \textit{F8} gene that evolved under negative selection pressure are more likely to be associated with disease-causing mutations.\(^{45}\) As important basic cell functions may be impaired in patients with these mutations, this may affect the release of FVIII upon DDAVP stimulation or the function of FVIII after its release. The Sengupta grading system needs further refinement for precise prediction, but can be used in further analyses addressing the effect of mutation on DDAVP response. Furthermore, it would be useful to include measurements of FVIII antigen as well. This information could help to analyze discrepancies between FVIII activity and antigen to further explain the functional effects of mutations.

Another important predictor of DDAVP response is age, which is evaluated in chapter 7. Age partially explains the observed variation in response, hence, older patients may show a slightly better response compared to younger patients. However, limited data was available in the published literature on the magnitude of the intra-individual effect of advancing age among re-exposed patients. We first evaluated the effect of age on DDAVP response cross-sectionally in the total cohort of 1474 patients, next we addressed the intra-individual variation of DDAVP response among a subgroup of 100 re-exposed patients. In the total study population, older patients showed a better absolute response compared to younger patients (Spearman’s correlation coefficient \(P<0.001, R^2=0.005\)). Aging of a patient was also significantly associated with a better response among the re-exposed patients. For every year increase in age, the absolute response increased by 0.5 IU/dL. Patients who were \(\leq 10\) years at their first DDAVP administration seem to be more likely to show an improved absolute response over time compared to patients who were 20 years or older at first administration.

This information may help the optimization of DDAVP use, as nonsevere patients who fail to respond early in life, especially when tested before they are 10 years of age, may respond better at a later age. This is the first study that analyzes the magnitude of
the intra-individual effect of advancing age among such a large group of re-exposed patients. The precise mechanism underlying the increase of DDAVP response with age remains to be unraveled. Multiple factors may play a role. The observed effect may be partially explained by differences in drug clearance in older patients compared to younger patients, whereby children show higher clearance rates compared to adults.\textsuperscript{46} Clearance is associated with body surface area. Children have a larger body surface area in relation to their weight compared to adults. As DDAVP dosing is generally based on body weight instead of body surface area, young children need a relatively higher weight-based dose. In addition, children have a higher blood volume per kg body weight compared to adults. Therefore, the relative lower doses that are administered to younger patients further result in a lower absolute response to DDAVP in younger patients. Another reason for the improved DDAVP response with advancing age may be the natural increase in baseline FVIII levels with age, that is also present in healthy individuals.\textsuperscript{47} Baseline FVIII levels predict DDAVP response in nonsevere hemophilia A patients. As discussed in chapter 4, the increase in baseline FVIII levels in older individuals might be required to maintain hemostasis in the more fragile circumstances of old age.\textsuperscript{23} However, even when adjusted for baseline FVIII levels at time of DDAVP administration, the response to DDAVP still increases with age. Therefore the effect of aging is supplementary to the natural aging effect on FVIII baseline levels. Future studies may address the effect of dosage on the response to DDAVP. Plasma levels of DDAVP should be measured to further elucidate potential differences. Lastly, we should recheck DDAVP response in all patients, to ensure the inclusion of patients who seemed to lack a good response to DDAVP early in life.

We incorporate the identified predictors of DDAVP response in a covariate analysis, based on an integrated population pharmacokinetic (PK) model in chapter 8. Currently identified predictors of DDAVP response do not completely explain the observed inter-patient variability. Conventional statistical methods that have been employed in previous studies did not take the individual pharmacokinetics (PK) of FVIII for individual patients into account. A PK model dynamically predicts the course of PK parameters over time for a DDAVP induced rise in FVIII, such as bioavailability, volume of distribution and clearance of FVIII. We aimed to identify and explain inter-patient variability in FVIII PK by using PK modeling.

When taking the predictors weight, genotype, and administration route, into account we can explain 30% of the total inter-patient variation in DDAVP response. Heavier patients showed a better response. Mutations in highly conserved regions
of the \textit{F8} gene were negatively associated with the response (36% lower than patient without this mutation type). Intranasal and subcutaneous administration of DDAVP demonstrate a 27% respectively 28% lower response relative to intravenous administration. As these factors only account for 30% of the inter-patient variation, this implies that there are other factors affecting DDAVP response which are currently unknown.

One recent study used PK modeling to describe the response to DDAVP.\textsuperscript{48} They found similar inter-patient variability in response, but a different covariate was identified that explained variation: recent FVIII. The explained inter-patient variability may vary due to population differences, different approaches in structural model construction and outcomes, or differences in the inclusion of covariates in the covariate analyses. Furthermore, our study had more power (1455 versus 128 patients). Another difference is that we constructed a model taking physiological concepts such as allometric scaling into account. The clearance and volume of distribution of a drug generally rise with increasing bodyweight. However, this association is nonlinear. This effect can be accounted for by allometric scaling, implying that PK parameters are related to bodyweight via a power function, which results in a more accurate model.

In the future, we aim to construct an integrated pharmacokinetic-pharmacodynamic (PK-PD) model characterizing the relationship between DDAVP levels and FVIII response, as the variability in FVIII response may be explained by variability in the PK or PD of DDAVP. Hopefully, this will help to better understand the exact working mechanism of VWF and FVIII release upon DDAVP administration.

Our results show that, after allometric scaling, heavier patients have a better DDAVP response. This may be due to the fact that the clearance of DDAVP is inversely proportional with weight. Patients with higher weights may have a relatively lower clearance of DDAVP. The economic advantage of DDAVP use in patients with a higher body weight is therefore more pronounced. This insight is important as dosing of FVIII concentrates is based on body weight and therefore heavier patients consume more FVIII concentrates.

\textbf{Part III RISING INSIGHTS}

The third part of this thesis integrates the rising insights in DDAVP treatment. With the chapters in this part of the thesis we address the working mechanism of DDAVP. In chapter 9 we study the combined effect of DDAVP and FVIII replacement therapy.
A major downside of FVIII replacement therapy is the frequent administration that is needed due to a short half-life of FVIII. VWF plasma concentration is positively associated with FVIII half-life. In this chapter we evaluate the effect of a DDAVP-induced rise in VWF concentration on the half-life of FVIII. The results show that doubling pre-infusion VWF concentration by DDAVP did not improve the pharmacokinetics of FVIII concentrate in a clinically significant manner. The lack of effect may be due to the relative short half-life of the VWF released upon DDAVP. Another possible explanation is the shielding of residual VWF in the FVIII concentrates used for the study. Furthermore, patients with lower baseline VWF levels may have an increased clearance of VWF. Although there are several possible explanations for the lack of an effect, we do not completely understand the underlying mechanisms of actions, especially because knowledge is scant on the interaction between VWF and FVIII.

One other study, conducted by Deitcher et al., tested a similar hypothesis. However, they used intranasal DDAVP administration, compared to intravenous administration in our study. They observed a modest increase in VWF Ag levels upon DDAVP stimulation without a significant effect on FVIII concentrate half-life or clearance. These results indicate that no clinical benefit is to be expected from the modification in FVIII pharmacokinetics resulting from DDAVP-administration prior to infusion of FVIII concentrate in hemophilia A patients.

Chapter 10 is a study protocol of the PCURVE project; a prospective explorative study with the aim to further unravel the biological mechanisms causing VWF/FVIII to rise following DDAVP administration. As follows from chapter 8, 70% of the variation in DDAVP can still not be explained by the predictors we could assess in the largest cohort of nonsevere hemophilia A patients with DDAVP administrations studied worldwide up to now. Thus, there have to be other factors that explain the observed heterogeneity in DDAVP response. We will analyze the sequential response of different endothelial markers to DDAVP in a longitudinal observational study design. The response to DDAVP may be unfolded on different levels. We will address the inter-individual variation in DDAVP plasma concentrations, analyze the number and binding characteristics of DDAVP receptors, the efficiency of VWF exocytosis, the multimeric structure of released VWF, the binding capacity of VWF for FVIII and vice versa, and finally assay variation. This may enhance our insight in the mechanisms underlying the DDAVP response and its inter-patient variability. Furthermore, these insights may reveal potential novel therapeutic targets to ameliorate the DDAVP
response. The information following from this study will be used to optimize the population PK model as described in chapter 8 in the future.

I expect that especially the inter-patient variation in the availability of DDAVP (DDAVP plasma concentrations) and the inter- and intra-individual variation in VWF levels will play a pivotal role in explaining the heterogeneity in DDAVP response. Up to now, we could not measure the specific quantity of DDAVP present in each individual, that induce the release of FVIII and VWF from their storage sites. We were unable to address the effect of inter- and intra-individual variation in both VWF activity and antigen levels on DDAVP response because data on these parameters was often missing. As VWF is the carrier molecule of FVIII, I expect that VWF levels will explain a large part of the variation in DDAVP response. Furthermore, the exact origin of FVIII, released upon DDAVP administration, is still unidentified. Future studies on organoid models of the sites at which FVIII is believed to be primarily synthesized, the liver sinusoidal cells and endothelial cells, may help to locate FVIII storage sites. Advanced techniques such as mass spectrometry and stimulated emission depletion microscopy may help to visualize and quantify storages and trafficking of both FVIII and VWF. Maybe we can identify the exact storage sites in the future and find ways to trigger the release from these sites with DDAVP or with other treatment modalities.

CONCLUSION

The studies described in this thesis provide rising insights in nonsevere hemophilia A and DDAVP treatment. Our findings emphasize that the pathophysiological process from mutation to protein formation may be more complex than we think. Patients with the same F8 missense mutation may have variable residual FVIII levels. Nonsevere hemophilia A is not a mild disease at all, as is demonstrated by the inhibitor-related and fatal intracranial bleeding mortality rates. There is an urgent need for optimal treatment modalities in developing as well as in developed countries. In the absence of proven strategies to permanently restore FVIII levels in a safe and affordable manner, DDAVP treatment should be further optimized and individualized, and future studies should focus on elucidating the exact working mechanism of this miraculous blood saving agent. These insights may eventually provide targets for the development of novel therapeutic options for the treatment of hemophilia.
REFERENCES


