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## “Hemophilia Clinical Consults: Inhibitor Formation, Management, and Therapeutic Options”

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### Introduction

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As a result of advances in hemophilia care over the past 50 years, patients with the disorder are able to lead normal or near normal lives.<sup>1,2</sup> According to World Federation of Hemophilia (WFH) estimates, children with hemophilia who receive adequate treatment can have a life expectancy similar to that of unaffected individuals.<sup>3</sup> Indeed, the life expectancy has increased dramatically, from 7.8 years in the 1930s to 74 years between 1990 and 2001.<sup>4</sup>

A wealth of clinical experience has led to improvements in the management of hemophilia overall, including prophylaxis and use of the bypassing agents. Nevertheless, inhibitors remain the most serious complication,<sup>5</sup> impacting treatment and ultimately quality of life, as inhibitor patients carry a higher burden of physical disability compared to non-inhibitor patients<sup>6,7</sup> and an economic burden that is the highest reported for a chronic disease.<sup>8,9</sup>

No one therapeutic modality exists for managing the various challenges posed by inhibitor patients; however, the following 3 cases depict how several of those challenges have been met in clinical practice.

How many patients with inhibitors do you have in your practice?

- 0
- ≤5
- 6 - 10
- 11 - 15
- ≥16

VOTE

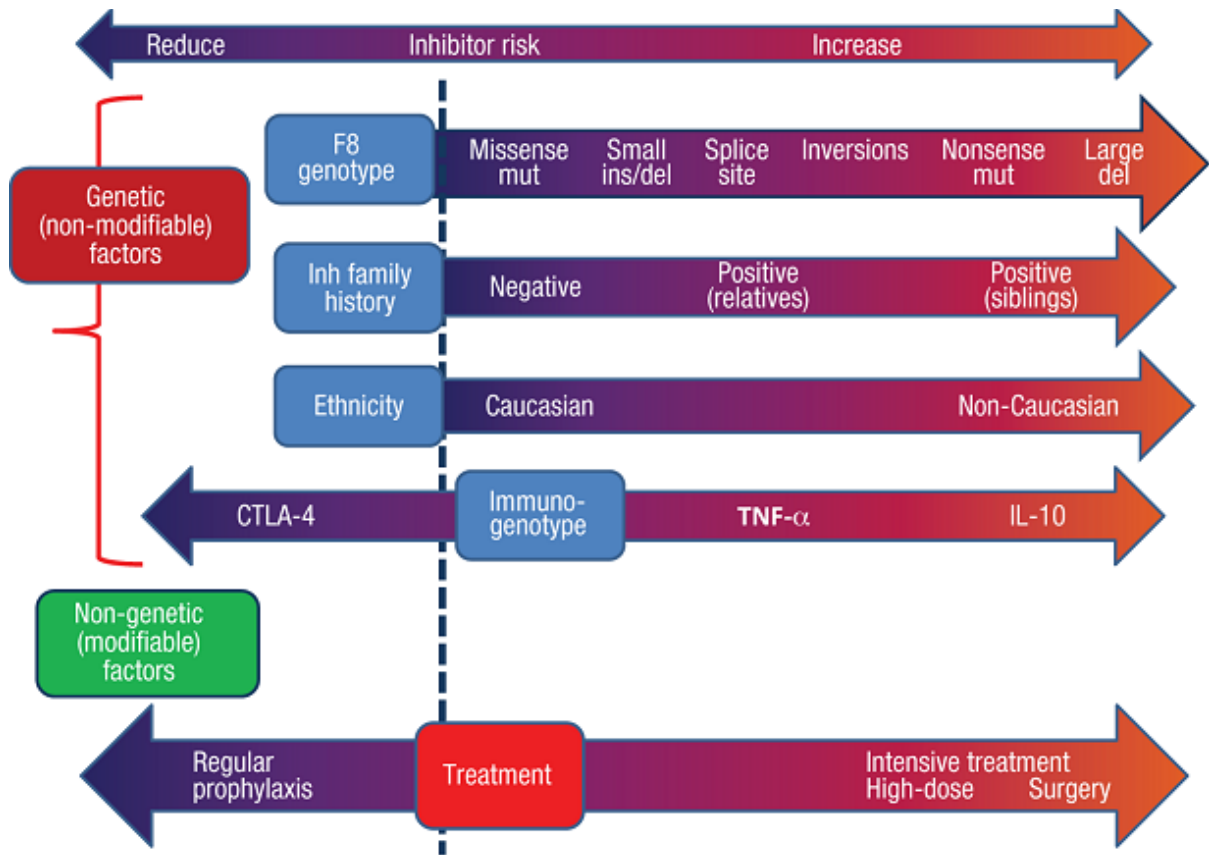
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#### *Inhibitors: Natural History and Risk Factors*

Research has established that inhibitors develop primarily during early childhood, at the average age of 12 years<sup>10</sup>; however, a recent analysis reveals that development may occur as early as 1 to 2 years,<sup>10,11</sup> typically during the first 20 exposure days (EDs),<sup>8,12</sup> when inhibitor risk is greatest.<sup>7,10</sup>

Studies in genetics and molecular immunology have provided a greater understanding of the multifactorial causes of inhibitor development,<sup>8</sup> and recent studies on immunogenetics have focused specifically on the *F8* mutation and haplotype, and their association with race and ethnicity.<sup>13-15</sup> Other studies have recently examined the relevance of immunologic danger signals—alarm signals arising from injured tissues that activate the immune system—and their significance to the timing and intensity of factor VIII (FVIII) exposure (Figure 1).<sup>5,8,11,12,16</sup>

Other factors considered to place hemophilia patients at risk for inhibitor development include disease severity and genotype,<sup>10,11</sup> family history of inhibitors,<sup>5</sup> method of factor administration,<sup>5</sup> and type of concentrate administered (Figure 1).<sup>8</sup>



**Figure 1**

Protective or predisposing effects of genetic and non-genetic factors that may potentially influence the risk of inhibitor development.

Posted with permission from Coppola A, et al. *Haemophilia*. 2010;16 (suppl 1):13-19.

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**Case 1: Jose C.**

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Jose C. is a 2-year-old Hispanic male with severe FVIII deficiency. His mother is a known carrier who has 3 brothers with hemophilia. One of her brothers died at the age of 12 due to bleeding and another brother bleeds frequently and doesn't respond to the treatment he gets in Mexico, although she is not sure what treatments he has received. Jose had his first joint bleed in his right knee at the age of 16 months and received 2 doses of recombinant FVIII, which resolved the bleed.



Image courtesy of Guy Young, MD.

At the age of 22 months, he developed his second joint bleed, this time in the left ankle, and required 3 doses of recombinant FVIII to resolve the bleed. Due to the development of his second joint bleed, the HTC team recommended that Jose be started on prophylaxis. Due to difficult venous access, it was elected to place a port-a-cath. He was admitted to the hospital and underwent surgery to place the port-a-cath. He received a dose of factor prior to the surgery, a second dose 8 hours after the surgery, and a third dose 12 hours later. He remained in the hospital overnight, and the following day (postoperative day 1), the gauze overlying the two incision sites (neck and chest) was noted to be full of fresh blood. This was approximately 6 hours after his last dose of factor. An additional dose of factor was ordered and the dressing was changed. An hour after the dressing was changed and the dose of factor administered, the gauze was again noted to be soaked with blood. The hematologist was called to see the patient, and upon removing the dressings, blood was seen to be oozing from both wounds. An inhibitor was suspected and a dose of rFVIIa was given, which slowed down the bleeding. Two additional doses of rFVIIa were administered and the bleeding stopped. An inhibitor titer was sent and the result was 30 BU.

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## Clinical Discussion

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### *Treatment of Bleeding Episodes in Inhibitor Patients*

Although available treatments and treatment strategies for inhibitor patients may differ, the goals are the same: to control bleeding episodes and improve patient quality of life. Strategies for control of bleeding episodes are based on inhibitor titer and patient response to therapy.<sup>17</sup> Recombinant or plasma-derived FVIII or FIX replacement products are indicated for low-responding inhibitors and low titers as they allow for good monitoring and measuring of plasma levels with standard coagulation assays.<sup>5,10,18</sup> Correspondingly, the most useful therapies

currently available for the treatment of patients with high-responding, high-titer inhibitors are the bypassing agents, recombinant factor VIIa (rFVIIa) and the activated prothrombin complex concentrate (aPCC) FEIBA.<sup>5,6,18,19</sup>

The bypassing agents have been life-changing for inhibitor patients in permitting surgery such as arthroplasty and radiosynovectomy to become routine.<sup>6</sup> However, neither agent is able to achieve hemostasis in all patients or bleeds. Inpatient and outpatient responses have been reported; although both products involve induction and facilitation of thrombin generation (TG), neither agent completely normalizes TG—unlike factor concentrates in non-inhibitor patients. Moreover, the agents have different half-lives (rFVIIa 2.7h/adults, 1.5h children; FEIBA 4-7h).<sup>19</sup> Clinicians should therefore avoid a “one-size-fits-all” approach to managing patients with the bypassing agents, as every bleed may hold a different patient response to treatment.<sup>17</sup>

While an unsatisfactory hemostatic evaluation should result in a change in treatment or treatment strategy, adding to the difficulty of determining patient hemostatic response to a particular bypassing agent is the fact that no reliable laboratory monitoring is available for predicting therapeutic response.<sup>17,19,20</sup> Potentially useful monitoring tools include thromboelastography, closure time assay, and waveform analysis, but these tools have yet to be validated for standardized use.<sup>19,21</sup>

### Emerging Treatment Strategies

Recent trials have evaluated the safety and efficacy of two treatment strategies for inhibitor patients: combination bypassing therapy and comparative bypassing therapy.<sup>22,23</sup> Klintman and colleagues examined how use of saturating levels of FVIII in combination with either aPCC or rFVIIa affected TG in vitro among hemophilia A patients with inhibitors.<sup>22</sup> As part of the study, several treatment strategies were simulated: aPCC with FVIII, rFVIIa with FVIII, and combination aPCC and rFVIIa with no FVIII. Investigators observed a potentiating effect when aPCC was combined with one of the FVIII products, resulting in larger than expected TG; however, when rFVIIa was combined with FVIII, the effect was additive. When aPCC and rFVIIa were combined without FVIII, an additive but not synergistic effect on TG was observed.

In their study of comparative bypassing therapy, Gringeri and colleagues analyzed the efficacy and safety of sequential combined bypassing therapy (SCBT), defined by the study team as administration of rFVIIa and aPCC within 12 hours of each other.<sup>23</sup> Subjects included 2 children and 4 adults with hemophilia A and 1 patient with hemophilia B. All subjects had high-responding inhibitors and were unresponsive to aPCC and rFVIIa. Sequential treatment was administered alternating one aPCC dose (range 50-80 U/kg) with one or two rFVIIa doses (range 90-270 µg/kg) every 4 to 12 hours. Complete bleeding control was achieved in 12 to 24 hours in all patients. SCBT was discontinued after 2 to 15 days, and prophylaxis with aPCC or rFVIIa initiated thereafter

in all patients. No adverse effects were noted, except for a rise in D-dimer levels in 3 of 6 patients.

Larger clinical trials are warranted to confirm the findings of both study teams.

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## Case 2: Andrew P.

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Andrew P. is a 9-year-old with severe FVIII deficiency with inhibitors. He has had two attempts at immune tolerance therapy, neither of which was successful. Currently, he treats bleeds on demand, primarily with rFVIIa, and he usually requires 6 to 8 doses given every 3 to 6 hours to resolve joint bleeds. He recently had a rather severe right knee bleed that required non-weight bearing for several days. After he began to weight bear, he still favored his right leg, and after stepping off a curb on one occasion, he lost his balance and nearly fell. The next day he felt pain in his left hip area, and after consulting with his HTC, began rFVIIa for a possible hip bleed. He received 6 doses of rFVIIa over the next 24 hours, but the next day the pain was worse and he could not walk. He was brought to the HTC, and upon examination was felt to have an iliopsoas bleed. A CT scan was performed to evaluate the hip area as a result of the history of trauma, and the scan confirmed an iliopsoas bleed.



Image courtesy of Guy Young, MD.

The patient was admitted to the hospital and placed on rFVIIa 90 mcg/kg every 2 hours. After 6 doses, he did not feel his bleed was controlled, and the dose was increased to 270 mcg/kg given every 3 hours for 4 doses. The next day, a repeat CT scan showed the bleed to be larger. The rFVIIa was discontinued and he was started on FEIBA 70 units/kg every 8 hours. After one dose, he stated that he felt better, and after 3 doses, his pain was much improved as was his range of

motion. He continued on FEIBA at 75 units/kg every 12 hours, and a repeat CT scan after 2 days of FEIBA showed a slight reduction in the bleed size. He was discharged home in a wheelchair, with strict instructions not to bear weight and to continue FEIBA at the present dose. Five days later, he returned to the HTC and his range of motion was much improved, with only slight pain upon hip extension. He began physical therapy and continued on FEIBA. Three weeks later, he had regained full motion and was back to baseline. FEIBA therapy was continued for one more week and following that, the bleed was felt to be resolved and he went back to his on-demand regimen.

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## Clinical Discussion

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### *Dosing of the Bypassing Agents*

Although numerous studies have examined the safety and efficacy of bypassing agents, their dosing and efficacy have not been fully established. In an important review out of Norway, Tjønnfjord and colleagues provide their early experiences with the use of FEIBA during surgery and invasive diagnostic and therapeutic procedures in adult patients with high-titer FVIII and FIX inhibitors.<sup>24</sup> Between 1996 and 2004, 21 diagnostic or therapeutic procedures, 15 minor procedures, and 6 major procedures were performed in 8 patients with severe hemophilia and 2 with acquired hemophilia. A preoperative loading dose of 100 U/kg was administered. The following doses were adjusted so the total daily dose approximated 200 U/kg. Following the third postoperative day, the dose was gradually tapered to a daily dose of 150-100 U/kg.

Hemostatic efficacy was excellent, with no blood loss following all minor procedures and for 3 of the major procedures (Table 1).<sup>24</sup> One adverse event was observed. A 69-year-old patient experienced an MI on postoperative day 3 following sigmoidectomy; however, he was stabilized, with no discontinuation of FEIBA therapy. This report suggests that minor and major surgical procedures may be performed with use of an aPCC (FEIBA), with a low risk of bleeding complications.

Table 1. Main Characteristics of Surgical Procedures							
Patient No.	Procedure	No. infusions	Duration (days)	Total dose (U)	Dose (U kg <sup>-1</sup> day <sup>-1</sup> )	Complications	Hemostatic outcome
<b>Major procedures</b>							
5	Arthroplasty (knee)	20	9	127	167	Drainage 750 mL Hgb ↓ 45 gL <sup>-1</sup>	Good
6	Nephrectomy/splenectomy	53	17	227	127	Yes, splenic hemorrhage	Good
6	Wound rupture revision	17	5*	82	156	No	Excellent
7	Sigmoidectomy	23	13	118	104	Yes; MI	Excellent
8	Arthroplasty (knee)	32	14	98	127	Hgb ↓ 62 gL <sup>-1</sup> 2 PRC	Good
10	Arthroplasty (knee)	55	23	163	139	No	Excellent
<b>Minor procedures<sup>†</sup></b>							
1	Trephine biopsy	1	1	4000	55		
2	Insertion of Hickman line	3	1	33,000	253		
2	Tooth extraction	3	1	15,000	115		
3	Cataract and intraocular lens implantation	3	1	20,000	267		
3	Cataract and intraocular lens implantation	3	1	14,000	186		
3	Circumcision (phimosis)	3	1	14,000	186		
3	Telangiectasia (tongue)/laser coagulation	1	1	4000	50		
4	Cataract and intraocular lens implantation	3	1	14,000	162		
4	Tooth extraction	10	3	28,000	112		
5	Cystoscopy/pyelography	1	1	4000	47		
5	Endoscopic treatment of eroded vessel in esophageal ulcer	3	1	14,000	165		
8	Excision of prepatellar bursa	10	5	39,000	132		
9	Tooth extraction	12	3	48,000	212		
9	Tooth extraction	3	1	11,000	146		
10	Paronychia/toenail excision	14	5	39,000	156		

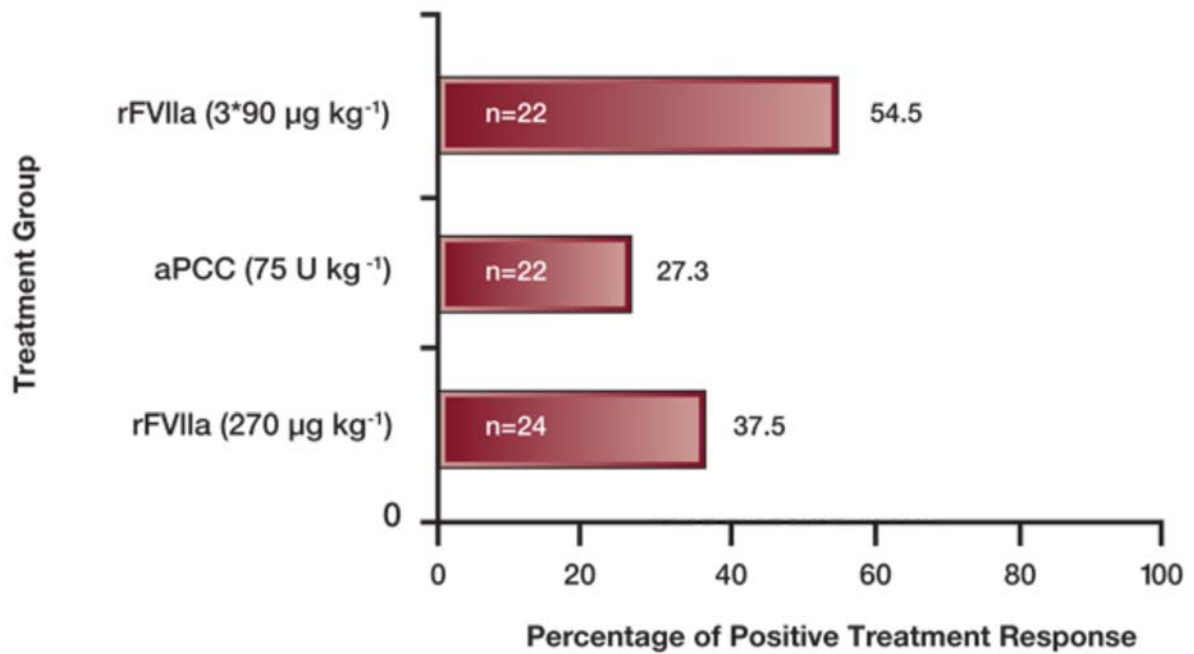
\*Owing to supply shortage, FEIBA was followed by rFVIIa for an additional 3 days; a total dose of 57.6 mg rFVIIa was administered. PRC, packed red cells.

<sup>†</sup>No complications and excellent hemostatic outcome for all minor procedures.

Adapted from Tjønnfjord GE. *Haemophilia*. 2004;10(suppl 2):41-45.

In a major dosing study of rFVIIa, Young and colleagues compared a single 270 µg/kg-dose of rFVIIa with three 90 µg/kg-doses for the management of joint bleeding in inhibitor patients to determine whether there was a difference between doses in safety and efficacy and whether the larger single dose was more effective than aPCC.<sup>25</sup> More than one-third of patients receiving the single 270 µg/kg-dose of rFVIIa had a successful response to treatment, compared to more than half the patients receiving three consecutive doses of 90 µg/kg and more than one-quarter of patients receiving aPCC (Figure 2).<sup>25</sup> Investigators concluded that the single, large dose of rFVIIa was as safe and effective as rFVIIa 90 x 3 µg/kg dosing and could be considered a potentially more effective alternative to aPCCs.

### Global Assessment: Successful Response in ITT Population



**Figure 2**

Global assessment: successful response—intent-to-treat population.  
Adapted from Young G, et al. *Haemophilia*. 2008;14:287-294.

What treatment strategy do you most frequently employ for your patients with hemophilia A and inhibitors?

- On-demand therapy with factor replacement
- On-demand therapy with bypassing agents
- Sequential use of bypassing agents
- Prophylaxis with bypassing agents

VOTE

[View Results](#)

### Case 3: Chris W.

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Chris W. is a 22-year-old African American with severe FVIII deficiency with inhibitors who had failed multiple attempts of immune tolerance therapy. He currently treats bleeds on demand with rFVIIa, generally with an excellent response. He recently began working as an information technologist in a hospital. He has a history of multiple bleeding episodes in both elbows and has somewhat restricted range of motion. He has not had as many elbow bleeds since graduating from high school; however, with the recent start of his new job, he has noted an increase in the number of elbow bleeds. The bleeds occur in both elbows, although about 2 of 3 are in his left elbow.



Image courtesy of Guy Young, MD.

In discussing his new job, the patient states that he has been helping to install computers and printers in offices and has had to do more carrying of heavy objects. When it was suggested that he try to minimize this, he responded by saying he felt it was important to partake in all aspects of his job. While he does minimize carrying heavy objects, the job entails lifting computers and printers from boxes on to desks. His bleeds all respond well to rFVIIa; however, following discontinuation of treatment after a few days, he gets another bleed within a week. In the past 6 months, he has had 5 left elbow bleeds and 3 right elbow bleeds. After discussion with his HTC, he is started on rFVIIa prophylaxis at a dose of 100 mcg/kg per day. He is instructed to use additional doses if a bleed occurs. In the first month of prophylaxis, he experienced 2 left elbow bleeds and 1 right elbow bleed; however, in the next month, he only had 1 left elbow bleed, and in the subsequent 4 months, he only had one left elbow bleed. His daily rFVIIa therapy is continued, and it is decided to continue this therapy indefinitely.

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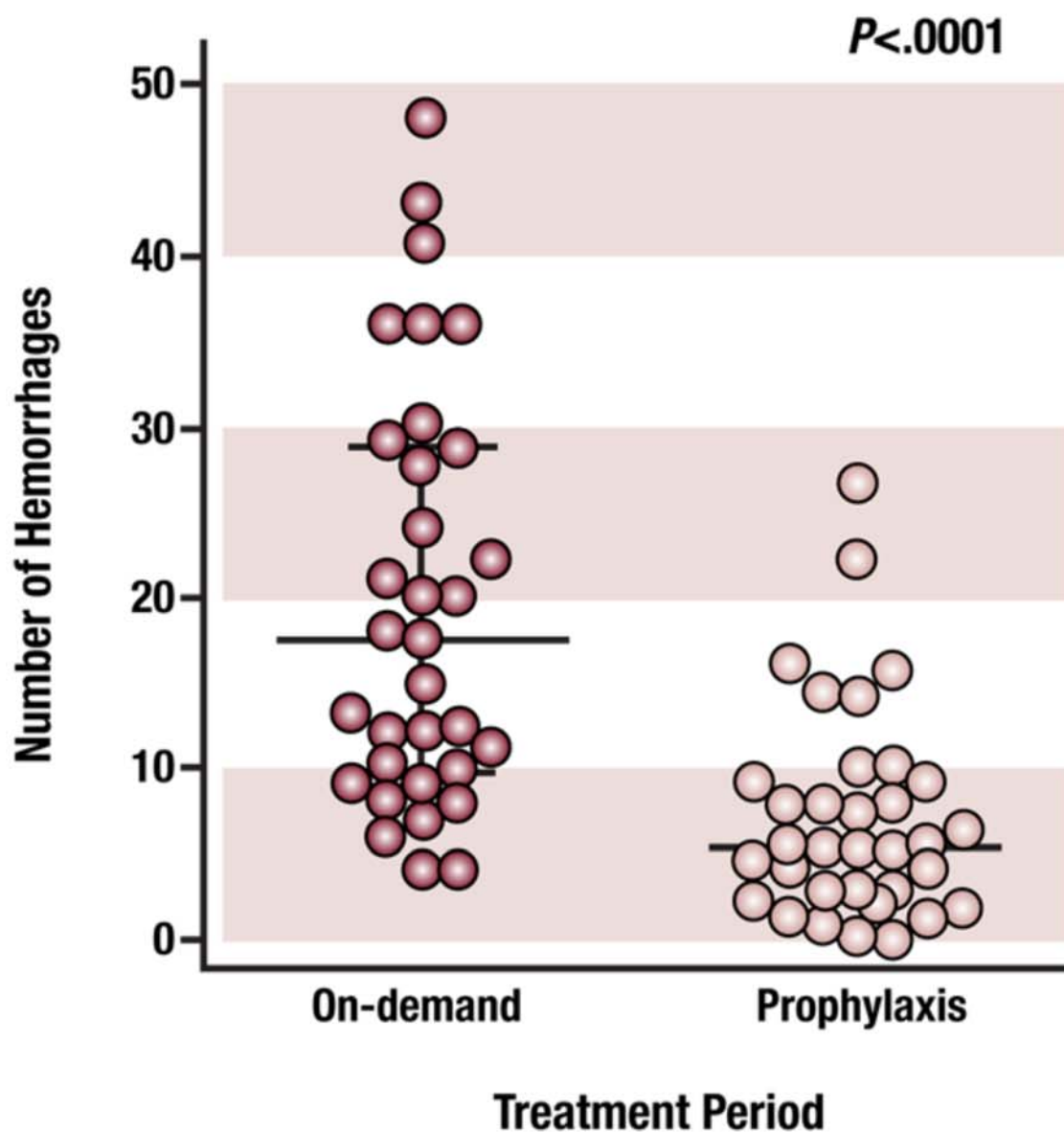
### Clinical Discussion

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### *Prophylactic Bypassing Therapy*

Prophylaxis with factor VIII or factor IX concentrates is considered the standard of care for hemophilia patients without inhibitors.<sup>26</sup> Since the 1990s, it has been supported by WHO, NHF, and WFH as first-line treatment for children with severe hemophilia because of its ability to prevent joint and other bleeding events.<sup>26-29</sup> However, a growing body of evidence suggests that prophylaxis with the bypassing agents provides similar benefits to hemophilia patients with inhibitors.<sup>26,30,31</sup>

Recently, Valentino conducted a meta-analysis of 6 studies and 34 inhibitor patients to assess the efficacy and safety of FEIBA used prophylactically.<sup>26</sup> Patients received a mean prophylactic dose of 78.5 U/kg 3 to 4 times weekly. Prophylaxis resulted in a decrease in hemorrhage rate for 31 of 33 patients for whom bleeding data were available prior to prophylaxis, and among this cohort, on average 63.9% of patients experienced a reduction in bleeding episodes while receiving FEIBA prophylaxis (**Figure 3**).<sup>26</sup> No thrombotic or other adverse effects were reported. Study results suggest that prophylactic FEIBA can be safe and effective for reducing bleeding events in inhibitor patients.



**Figure 3**

Annual frequency of bleeding\* prior to prophylaxis (n=33) and during prophylaxis (n=34). Asterisk indicates that the type of hemorrhage measured differed among the studies. Each point represents the average annual bleeding frequency during the treatment period. The median and interquartile ranges are shown by the horizontal bars. From Valentino LA. Poster presented at: 22nd Congress of the International Society on Thrombosis and Haemostasis; July 11-16, 2009; Boston, MA.

Several years prior to the Valentino meta-analysis, Konkle and investigators conducted a prospective clinical trial of rFVIIa as secondary prophylaxis in hemophilia patients with inhibitors

to determine if this bypassing agent could safely and effectively reduce bleeding frequency compared with on-demand therapy.<sup>30</sup> Twenty-two patients predetermined to have a high bleeding frequency were randomized 1:1 to receive daily rFVIIa prophylaxis with either 90 or 270 µg/kg for 3 months, followed by a 3-month postprophylaxis period.

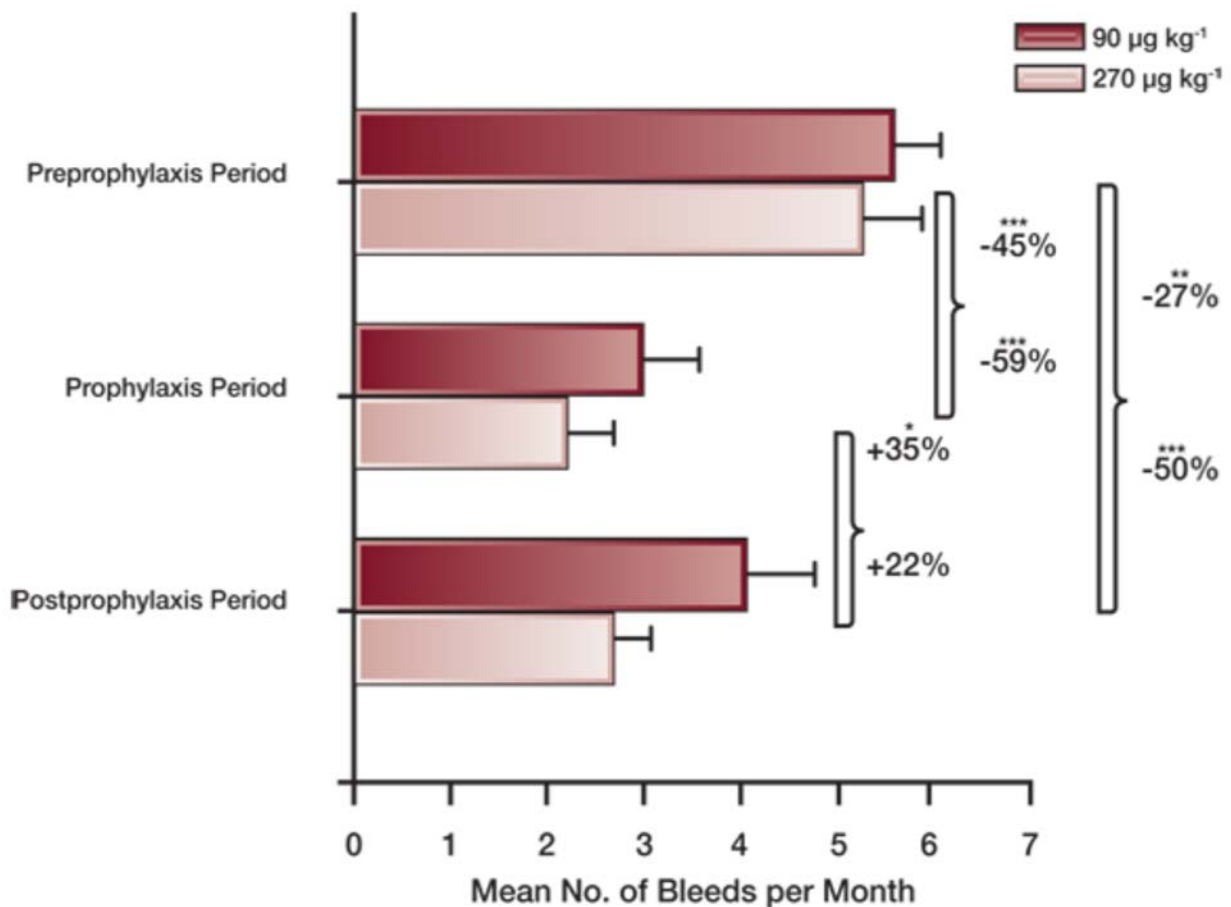
What percentage of your patients with inhibitors receive prophylactic bypassing therapy?

- 0%
- ≤25%
- 26% - 50%
- 51% - 75%
- ≥76%

VOTE

[View Results](#)

Results of the study conducted by Konkle et al indicated clinically relevant reductions in bleeding frequency during prophylaxis compared to on-demand therapy. The number of bleeds per month during the prophylaxis period decreased from 5.6 to 3.0 and from 5.3 to 2.2 with rFVIIa 90 µg/kg and 270 µg/kg, respectively (**Figure 4**).<sup>30</sup> This reduction was maintained postprophylactically with both dosing regimens. No thrombotic events were reported.



**Figure 4**

Number of bleeds per month. The bracketed data are the estimated changes (percentage) in number of bleeds per month (defined as 28 days) for the 90 and 270 µg kg<sup>-1</sup> recombinant factor VIIa treatment groups during the prophylaxis or postprophylaxis period as compared to the preprophylaxis period, and during the prophylaxis period as compared to the postprophylaxis period. Triple asterisks indicate  $P \leq .001$ ; double asterisks,  $P \leq .01$ ; single asterisk,  $P \leq .05$ . Adapted from Konkle BA, et al. *J Thromb Haemost.* 2007;5:1904-1913.

## Summary

Advances within the past 50 years have fundamentally improved the lives of hemophilia patients, enabling them to live out a normal lifespan. Although it remains to be seen what the new millennium holds in terms of hemophilia management, emerging research in such areas as immunogenetics and gene transfer therapy targets inhibitor prevention and, in so doing, brings clinicians closer to resolving this last remaining complication of the disorder.

Additional information about the use of prophylactic bypassing therapy for inhibitor patients can be found by participating in the following Blood CME Center programs:

*“Prophylaxis in Hemophilia: Do Immunologic Danger Signals or Pharmacokinetics Hold Relevance?”* a presentation featuring immunologic danger signals and inhibitor development by Donald L. Yee, MD

[Enter Program](#)

*“Management of High-Titer FVIII Inhibitors,”* a presentation featuring key issues by Michael Recht, MD, PhD

[Enter Program](#)

*“Hemophilia Consults: Should Patients With Inhibitors Receive Prophylaxis With Bypassing Agents?”* a CEnow™ activity and podcast with Michael Recht, MD, PhD, and Guy Young, MD

[Enter the CEnow™ Activity](#)

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