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## Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

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### ABSTRACT

#### BACKGROUND

Effective ways to prevent arthropathy in severe hemophilia are unknown.

#### METHODS

We randomly assigned young boys with severe hemophilia A to regular infusions of recombinant factor VIII (prophylaxis) or to an enhanced episodic infusion schedule of at least three doses totaling a minimum of 80 IU of factor VIII per kilogram of body weight at the time of a joint hemorrhage. The primary outcome was the incidence of bone or cartilage damage as detected in index joints (ankles, knees, and elbows) by radiography or magnetic resonance imaging (MRI).

#### RESULTS

Sixty-five boys younger than 30 months of age were randomly assigned to prophylaxis (32 boys) or enhanced episodic therapy (33 boys). When the boys reached 6 years of age, 93% of those in the prophylaxis group and 55% of those in the episodic-therapy group were considered to have normal index-joint structure on MRI ( $P=0.006$ ). The relative risk of MRI-detected joint damage with episodic therapy as compared with prophylaxis was 6.1 (95% confidence interval, 1.5 to 24.4). The mean annual numbers of joint and total hemorrhages were higher at study exit in the episodic-therapy group than in the prophylaxis group ( $P<0.001$  for both comparisons). High titers of inhibitors of factor VIII developed in two boys who received prophylaxis; three boys in the episodic-therapy group had a life-threatening hemorrhage. Hospitalizations and infections associated with central-catheter placement did not differ significantly between the two groups.

#### CONCLUSIONS

Prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A. (ClinicalTrials.gov number, NCT00207597)

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**B**EFORE THE DEVELOPMENT OF CRYOPRE-  
cipitate, a plasma fraction that contains con-  
centrated factor VIII, boys with severe he-  
mophilia A had a diminished life expectancy.<sup>1-3</sup>  
These children are at risk for many types of hem-  
orrhages, but the predominant source of chronic  
coexisting disease is crippling, painful arthritis  
due to hemarthrosis.<sup>4</sup> Small trials were conducted  
in the 1960s to determine whether routine admin-  
istration of factor VIII concentrate was effective  
as prophylaxis against hemophilic arthropathy.<sup>5-8</sup>  
Clinically effective prophylactic schedules were de-  
veloped empirically, without the benefit of data  
from controlled trials,<sup>9</sup> and many clinicians began  
to recommend prophylaxis with factor VIII.<sup>10</sup>

In the 1980s, when it was discovered that  
plasma-derived factor VIII concentrates were con-  
taminated by human immunodeficiency and hep-  
atitis viruses, the use of prophylaxis was severely  
curtailed.<sup>4</sup> In 1992, approval of the first recombi-  
nant factor VIII molecule for replacement therapy  
in the United States allowed for safe prophylaxis in  
patients with hemophilia.<sup>11</sup> Petrini and colleagues  
reported the prevention of hemophilic arthropathy  
when prophylaxis was initiated before patients  
reached 2 years of age.<sup>12</sup> Aledort and others report-  
ed that prophylaxis slowed the progression of es-  
tablished joint damage.<sup>13</sup> Nevertheless, questions  
remained as to when prophylaxis should begin,  
what dose of recombinant factor VIII should be  
administered, and how long prophylaxis should  
be provided. An important question that could be  
answered by a clinical trial was whether prophyl-  
axis prevents joint hemorrhage and damage.<sup>14</sup>

The aim of our randomized trial was to deter-  
mine whether prophylactic factor VIII infusions,  
given every other day, are more effective in pre-  
venting joint damage than an intensive replace-  
ment regimen given at the time of a hemarthro-  
sis. The study focused on the index joints — ankles,  
knees, and elbows — because these joints are the  
most susceptible to hemophilic arthropathy. This  
trial was conducted in the context of a national  
hemophilia comprehensive care system.<sup>15</sup>

## METHODS

### STUDY DESIGN

We conducted a multicenter, randomized, open-  
label trial, with written informed consent obtained  
from the parents or guardians of all patients. En-  
rollment began in August 1996, and the last sub-

ject to be enrolled completed the study in April  
2005. The power calculation was based on pilot  
data indicating that normal joint structure would  
be maintained in 70% of children receiving prophyl-  
axis and 20% of those receiving enhanced episodic  
therapy. Estimated proportions of loss of partici-  
pants were 10% for the assessment of early joint  
damage, 7% for the development of high-titer fac-  
tor VIII antibodies, 7% for the assessment of life-  
threatening hemorrhage, and 10% for follow-up.  
Thus, 64 participants were needed to detect a sig-  
nificant difference between the two treatments  
with a two-sided test (0.05 alpha level and 95%  
power). Randomization was performed centrally  
and stratified by site in permuted blocks of 2, 4,  
or 6. The radiologists who reviewed joint images,  
the physiotherapists who performed joint exami-  
nations, and the laboratory technologists who  
performed assays were unaware of the patients'  
treatment assignments and status with respect to  
a history of bleeding.

### ELIGIBILITY AND EXCLUSION CRITERIA

Eligibility criteria were an age of less than 30  
months, a factor VIII activity level of 2 U per deci-  
liter or less, a history of two or fewer hemorrhages  
into each index joint, normal baseline joint imag-  
ing, undetectable levels of factor VIII inhibitor,  
a normal platelet count, and normal joint motion.

### TREATMENT

Children in the prophylaxis group received infu-  
sions of 25 IU of factor VIII (Kogenate or Koge-  
nate FS, Bayer HealthCare) per kilogram of body  
weight every other day to prevent bleeding. The  
dose and the frequency of administration were  
based on pharmacokinetic studies and clinical ex-  
perience.<sup>9,16</sup> Hemarthroses were defined as acute  
episodes of joint pain with decreased joint motion.  
When hemarthroses occurred during prophylaxis,  
patients were treated with 40 IU per kilogram, and  
the assigned prophylaxis schedule was resumed  
the next day.

Children assigned to receive enhanced episodic  
therapy were treated only at the time of clinically  
recognized joint hemorrhage. The rationale for  
this treatment was to decrease inflammation  
and prevent joint damage by preventing rebleeding  
after a joint hemorrhage. Children in this group  
received 40 IU of factor VIII per kilogram at the  
time of joint hemorrhage and 20 IU at 24 hours  
and 72 hours after the first dose. Parents were

encouraged to continue infusions of 20 IU of factor VIII per kilogram every other day until joint pain and impairment of mobility had completely resolved, for a maximum of 4 weeks. All other therapies, including surgery, and all bleeding events other than hemarthroses, including nasal, muscle, parenchymal, gastrointestinal, and intracranial hemorrhages, were managed according to local standards of practice. In both groups, the protocol allowed for two dose escalations of 5 IU of factor VIII per kilogram in the case of an inadequate response. The protocol did not require the use of central-venous-access devices, and all decisions regarding placement of the devices were made according to local standards.

#### OUTCOME MEASURES

The primary outcome was preservation of index-joint structure, as determined by means of magnetic resonance imaging (MRI) and plain-film radiography at the completion of the study, when participants were 6 years old. Secondary outcomes were number of joint and other bleeding events, number of infusions, and total units of factor VIII administered. MRI and plain-film radiography were performed as described previously.<sup>17,18</sup> Joint failure was defined as an MRI or radiograph score that indicated a subchondral cyst, surface erosion, or joint-space narrowing. MRIs and radiographs were read independently by two radiologists; discrepant readings were adjudicated by a third radiologist.

Reports of infusions of factor VIII and emergency-room and clinic visits were collected monthly. At quarterly visits, data were collected on hospitalizations, port placements, port removals, and infections. Each child was examined quarterly and weighed for calculation of the dose of factor VIII. Race and ethnic group were reported by the parent or guardian of each child.

Compliance was monitored by a review of infusion logs. However, no child was removed from the study for any level of noncompliance. Death, recurrent life-threatening hemorrhage, an inhibitory titer of 10 or more Bethesda units (BU), and hospitalization were classified as serious adverse events.

#### LABORATORY ASSAYS

Blood was collected quarterly for the detection and measurement of factor VIII inhibitors, measurement of factor VIII trough levels (in the prophylaxis group only), and serologic tests for hepatitis B and C, human immunodeficiency virus, and parvovirus. Titers of factor VIII inhibitors were determined with the use of the Bethesda assay.<sup>19</sup> Factor VIII trough levels were not used to alter dosing.

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#### CLINICAL ASSESSMENT OF JOINTS

Clinical examination of joints, with assessment of swelling, strength, range of motion, pain, and gait, was performed semiannually, as previously described, and videotaped for central review at study entry, midpoint, and completion.<sup>20,21</sup>

#### PROTOCOL FAILURE BEFORE STUDY COMPLETION

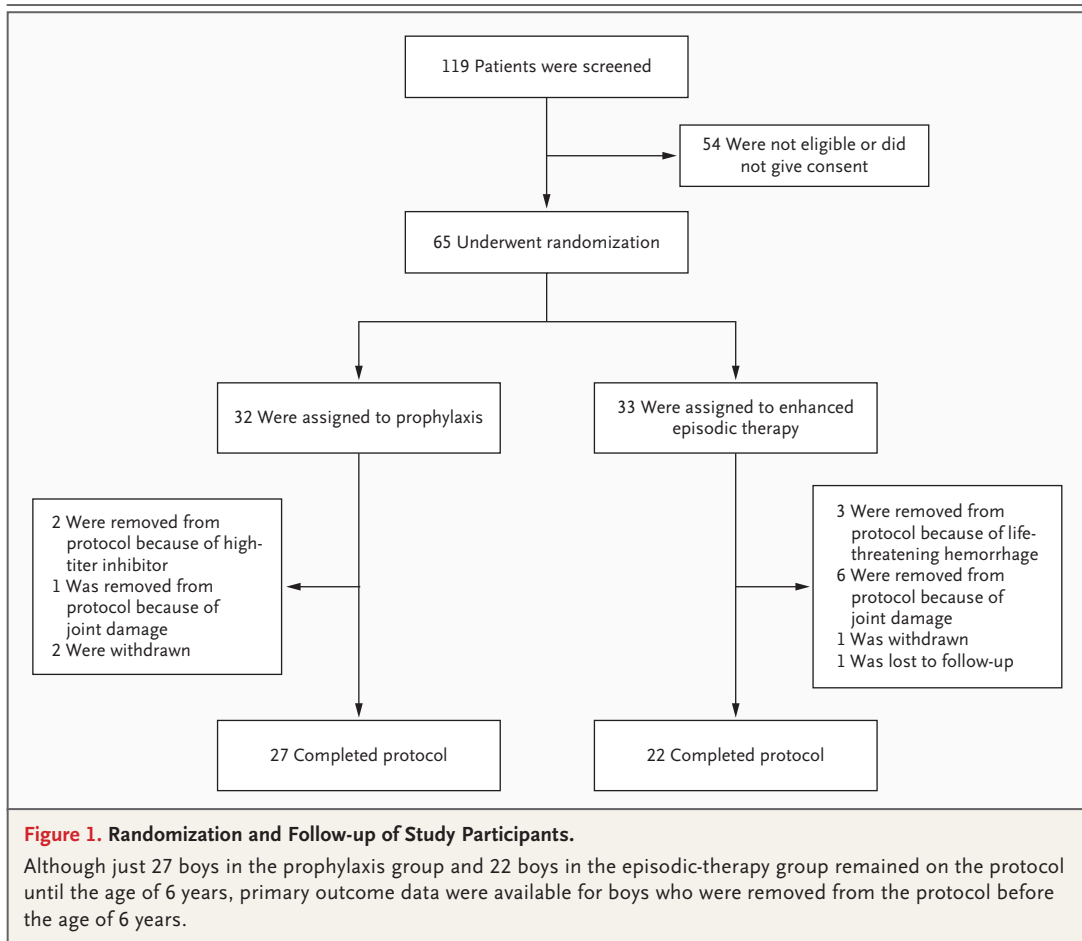
The protocol allowed for early termination of participation if the assigned treatment was deemed inadequate for the child as evidenced by the development of factor VIII inhibitors, life-threatening hemorrhage, or bone or cartilage damage on joint imaging. If an inhibitory titer exceeded 25 BU in duplicate testing of the sample or if it exceeded 10 BU for more than 3 months, the child was withdrawn from the study. These thresholds were chosen to avoid the withdrawal of a child with a transient factor VIII inhibitor (Lusher JM: personal communication).<sup>22</sup>

Life-threatening hemorrhages were treated in accordance with local standards. After the resolution of the first such event, the assigned treatment was resumed. In the event of recurrence, the child was removed from the study, but data were retained for inclusion in intention-to-treat analyses.

Participants with clinically suspected early joint failure were eligible for an early joint evaluation. The joint (or joints) in question were evaluated by means of MRI, radiography, or both if the child had had 8 hemorrhages into an index joint within 12 consecutive months or 20 hemorrhages into an index joint since study enrollment or if the highest score obtainable on any one item of the joint physical examination had been recorded at least 2 weeks after hemarthrosis. If the imaging evaluation showed bone or cartilage damage, the child was removed from the study.

#### STATISTICAL ANALYSIS

We used Fisher's exact test to compare the two groups with respect to the primary outcome — the proportion of children in whom normal joint structure was maintained, as determined by MRI or radiography. The relative risk of joint damage



and 95% confidence intervals were calculated for the episodic-therapy group as compared with the prophylaxis group. Differences in secondary outcomes were evaluated with the t-test or the Mann-Whitney U test, as appropriate. The Spearman correlation coefficient was calculated for data that were not normally distributed. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

Two interim analyses were planned and conducted by an independent data and safety monitoring board after one third and two thirds of participants had undergone evaluation of the outcome measures. Data used for interim analyses included MRI and radiographic findings, the number of joint hemorrhages, the occurrence of life-threatening hemorrhages, and the total number of hemorrhages and hospitalizations. All participants randomly assigned to a treatment group were included in the intention-to-treat analysis of the primary outcome. Data used for this analysis

included interim joint imaging studies in children who were withdrawn from the study because of early joint damage and joint imaging studies performed in the remaining children at the age of 6 years. For the secondary analyses, data were included until withdrawal from the study, loss to follow-up, early protocol failure, or completion of the study at the age of 6 years.

The proportion of data collected was calculated by dividing the number of data forms received by the number of forms expected. Compliance was determined by calculating the proportion of prescribed infusions that were actually administered.

## RESULTS

Sixty-five children were enrolled in the study between August 1996 and March 2000; 32 children were randomly assigned to prophylaxis and 33 to enhanced episodic treatment (Fig 1). The two groups showed no differences in baseline demo-

graphic characteristics (Table 1). The median factor VIII activity level for all the children was 0.6 U per deciliter, with a range of 0.3 to 2.0; 31 of the 65 participants (48%) had one or more hemarthroses into index joints before enrollment.

The mean period of participation in the study was 49 months (interquartile range, 48 to 58). Primary outcome data from both MRI and radiographic studies were obtained for 50 of 65 participants (77%); partial data (with either MRI or radiography) were obtained for 11 participants (17%); and there were no data available for 4 participants (6%). Mean compliance was 96% (interquartile range, 96 to 100) in the prophylaxis group and 98% (interquartile range, 98 to 100) in the episodic therapy group. Among all participants, an average of 94% of data forms were received.

Outcome results are shown in Table 2. According to the findings on MRI, the proportion of participants in whom all six index joints were normal at 6 years of age was 25 of 27 (93%) in the prophylaxis group and 16 of 29 (55%) in the enhanced episodic-therapy group ( $P=0.002$ ). As compared with the prophylaxis group, the episodic-therapy group had a relative risk of damage to one or more joints, as shown by MRI, of 6.1 (95% confidence [CI], 1.5 to 24.4). The corresponding relative risk for the prophylaxis group, as compared with the episodic-therapy group, was 0.17, indicating an 83% reduction in the risk of joint damage as determined by MRI. With the use of radiography to assess joint damage, the relative risk was 5.2 (95% CI, 0.65 to 41.5) with episodic therapy as compared with prophylaxis. Radiographic and MRI readings were concordant in 97% of index joints.

A total of 18 abnormal joints (13 ankles, 3 elbows, and 2 knees) were detected in 15 children — 2 in the prophylaxis group and 13 in the episodic-therapy group. Six of the abnormalities were detected by both MRI and radiography, seven by MRI alone, and one by radiography alone. Only one type of imaging was available for the four remaining abnormal joints.

For each joint, the MRI score was compared with the total number of hemarthroses. As shown in Figure 2, some joints had abnormal MRI scores but no hemarthrosis, and some had normal MRI scores despite many hemarthroses. Bone and cartilage damage detected on MRI was not correlated with hemarthroses ( $P=0.63$ ), and overall the correlation of hemarthroses with MRI scores was

**Table 1. Baseline Demographic and Clinical Characteristics of All Randomized Participants.**

| Characteristic   | Prophylaxis (N=32) | Enhanced Episodic Therapy (N=33) | P Value |
|--|--------------------|----------------------------------|---------|
| Mean age (yr)  | 1.6                | 1.6                              | 0.78    |
| Race or ethnic group — no. (%) <sup>*</sup>              |                    |                                  | 0.33    |
| White  | 24 (75)            | 25 (76)                          |         |
| Black  | 0                  | 3 (9)                            |         |
| Hispanic   | 4 (13)             | 4 (12)                           |         |
| Asian or Pacific Islander                                | 1 (3)              | 1 (3)                            |         |
| American Indian or Alaskan native                        | 1 (3)              | 0                                |         |
| Other  | 2 (6)              | 0                                |         |
| Educational level of parent or guardian — no. (%)        |                    |                                  | 0.06    |
| ≤12 yr   | 20 (63)            | 13 (39)                          |         |
| >12 yr   | 12 (37)            | 20 (61)                          |         |
| First index-joint hemorrhage before enrollment — no. (%) |                    |                                  | 0.17    |
| Yes  | 18 (56)            | 13 (39)                          |         |
| No   | 14 (44)            | 20 (61)                          |         |
| No. of previous index-joint hemorrhages                  |                    |                                  | 0.17    |
| Mean   | 1.0                | 0.6                              |         |
| Range  | 0–5                | 0–3                              |         |
| No. of previous total hemorrhages                        |                    |                                  | 0.74    |
| Mean   | 6.2                | 6.8                              |         |
| Range  | 0–35               | 0–32                             |         |

<sup>\*</sup> Race and ethnic group were reported by the parent or guardian of each child.

weak ( $r=0.14$ ,  $P=0.02$ ). Joint physical-examination scores showed a weak correlation with MRI scores ( $r=0.26$ ,  $P<0.001$ ).

Table 2 shows secondary outcomes. Table 3 shows serious adverse events. Average monthly factor VIII use and hemorrhages, as well as joint physical examination scores, stratified by year of age, are shown in Figure 3. No statistically significant differences between the two treatment groups were found with respect to joint scores on physical examination (Fig. 3A).

A central-venous-access device was placed in 54 children (83%). In 12 of these boys (22%), at least one infection associated with the device developed. The median number of hospitalizations per year was similar for both study groups. Most hemophilia-related hospitalizations were for place-

| Variable                                      | Prophylaxis<br>(N=32) | Enhanced<br>Episodic Therapy<br>(N=33) | P Value |
|---|-----------------------|--|---------|
| MRI findings                                  |                       |  |         |
| No. of participants with primary outcome data | 27                    | 29                                     | 0.73    |
| Joint damage — no. (%)                        | 2 (7)                 | 13 (45)                                | 0.002   |
| No joint damage — no. (%)                     | 25 (93)               | 16 (55)                                |         |
| Radiographic findings                         |                       |  |         |
| No. of participants with primary outcome data | 28                    | 27                                     | 0.73    |
| Joint damage — no. (%)                        | 1 (4)                 | 5 (19)                                 | 0.10    |
| No joint damage — no. (%)                     | 27 (96)               | 22 (81)                                |         |
| No. of days in study                          |                       |  |         |
| Mean  | 1,497                 | 1,490                                  | 0.95    |
| Total   | 47,895                | 49,179                                 |         |
| Reported no. of factor VIII infusions         |                       |  |         |
| Mean  | 653±246               | 187±100                                | <0.001  |
| Total   | 20,896                | 6,176                                  |         |
| Reported no. of factor VIII units infused     |                       |  |         |
| Mean  | 352,793±150,454       | 113,237±65,494                         | <0.001  |
| Total   | 11,289,372            | 3,736,807                              |         |
| Joint hemorrhages (no./participant/yr)        |                       |  |         |
| Mean  | 0.63±1.35             | 4.89±3.57                              | <0.001  |
| Median  | 0.20                  | 4.35                                   |         |
| Total hemorrhages (no./participant/yr)        |                       |  |         |
| Mean  | 3.27±6.24             | 17.69±9.25                             | <0.001  |
| Median  | 1.15                  | 17.13                                  |         |

\* Plus-minus values are means ±SD. The data on MRI and radiographic findings include interim-analysis data for children who were removed from the study because of early joint failure.

ment and removal of central-venous-access devices.

## DISCUSSION

We found that prophylaxis with recombinant factor VIII was effective in preventing hemarthroses and structural joint damage (as detected by MRI) in young boys with hemophilia A.<sup>23</sup> Reported suggestions for the best time to begin prophylaxis range from before the first joint hemorrhage<sup>9</sup> to before 1 to 2 years of age to before the occurrence of five hemarthroses.<sup>24</sup> In our trial, prophylaxis was initiated between the ages of 6 and 30 months

and was based on a history of joint hemorrhage rather than age. In the prophylaxis group, radiologic evidence of preserved joint architecture was found in 93% of participants at 6 years of age. In this group, 18 of 32 (56%) of the children had one or two hemarthroses into one or more index joints before prophylaxis, and 17 (53%) had one to five hemorrhages into one or more index joints during prophylaxis. Prophylaxis was efficacious in decreasing bleeding and joint damage after up to five hemarthroses.

More than half of the joint abnormalities that were detected by MRI were not apparent in radiographic studies, whereas only one joint abnormal-

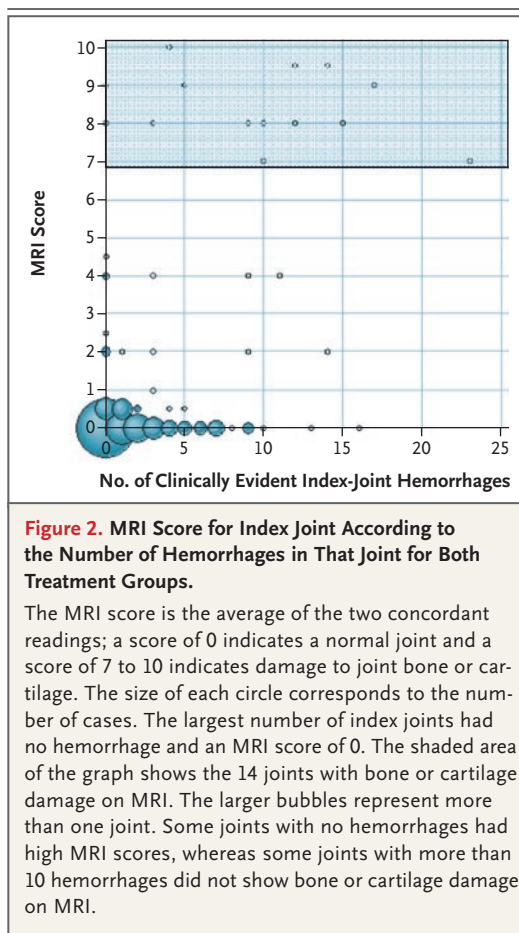
ity that was detected by radiography was not detected by MRI, indicating that MRI is more sensitive than radiography. We believe that MRI is the preferable imaging technique for young boys with hemophilia.

Surprisingly, the number of clinically evident hemarthroses correlated weakly with the outcome as determined by MRI. In addition, joint abnormalities were not apparent on physical examination in the very young children in our study. It is possible that the joint score we used was insufficiently sensitive for the detection of early arthropathy, even though our physical-examination scoring system is more sensitive for the detection of mild abnormalities of gait, joint swelling, muscle strength, and atrophy than is that of the World Federation of Hemophilia.<sup>9,12,13,20</sup> Thus, the absence of overt hemarthroses and abnormalities of joints on physical examination can lead to the erroneous assumption that episodic therapy in young children with hemophilia is effective. We propose that chronic microhemorrhage into the joints or subchondral bone in young boys with hemophilia causes deterioration of joints without clinical evidence of hemarthroses and that prophylaxis prevents this subclinical process.

The enhanced episodic therapy used in this trial was experimental because it involved higher doses and more infusions of factor VIII than are provided in standard care. Enhanced episodic therapy was used because the outcome of standard care is poor.<sup>13</sup> Clearly, however, the results of enhanced episodic therapy were inferior to those of alternate-day prophylaxis.

Children who received enhanced episodic therapy had extra-articular bleeding in addition to hemarthroses; 10% had recurrent, life-threatening hemorrhage, including intracranial and gastrointestinal hemorrhage. Two children in the prophylaxis group were found to have high titers of factor VIII inhibitors. This finding was not unexpected, since inhibitors develop in 30% of children with severe hemophilia, usually within the first 50 exposures to factor VIII, and most of the children in our study had fewer than 50 factor VIII exposures at the time of enrollment.

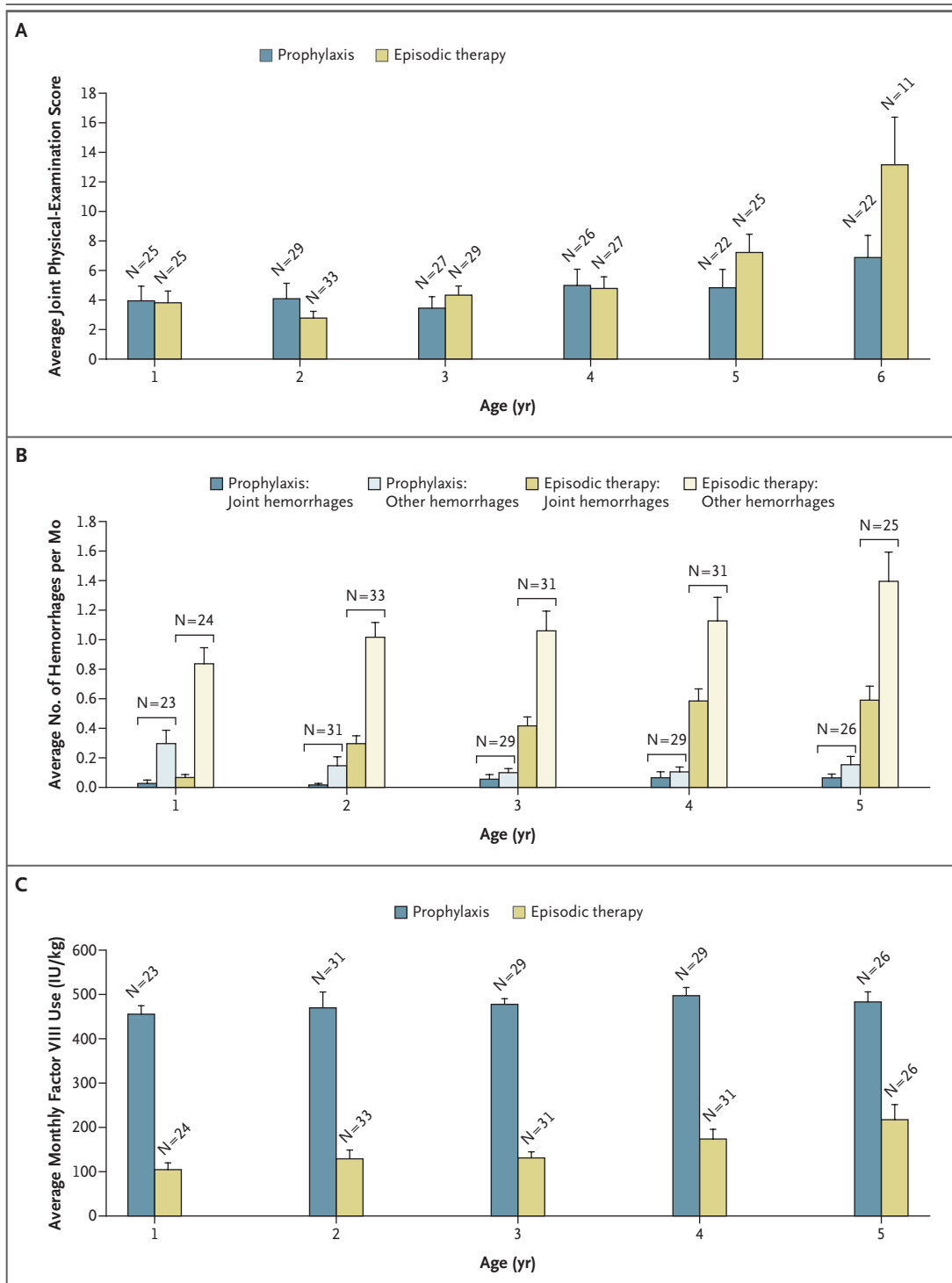
Use of recombinant factor VIII has been estimated to account for more than 90% of the cost of hemophilia care.<sup>25,26</sup> By the age of 6 years, the children in the prophylaxis group in our study



**Table 3. Serious Adverse Events.\***

| Event   | Prophylaxis (N=32) | Enhanced Episodic Therapy (N=33) | P Value |
|---|--------------------|----------------------------------|---------|
| Detection of high-titer inhibitor (no. of participants) | 2                  | 0                                | 0.24    |
| Life-threatening hemorrhage (no. of participants)       | 0                  | 3                                | 0.24    |
| Hemophilia-related hospitalization (no./participant/yr) |                    |                                  |         |
| Mean  | 1.70±8.03          | 0.47±0.85                        | 0.90    |
| Median  | 0.25               | 0.24                             |         |
| CVAD (no. of participants)                              | 29                 | 25                               | 0.19    |
| ≥1 CVAD-related infection (no. of participants)         | 6                  | 6                                | 0.95    |

\* Plus-minus values are means ±SD. CVAD denotes central-venous-access device.



were receiving 6000 IU of factor VIII per kilogram per year, as compared with approximately 2500 IU per kilogram in the enhanced episodic group. At a price of \$1 per unit of recombinant factor VIII, the cost of prophylaxis for a child weighing 50 kg could reach \$300,000 per year.

Prophylaxis has not been widely used in the care of patients with hemophilia. In 1995, when the current study was conceived, only 33% of U.S. children with hemophilia received prophylaxis.<sup>27</sup> The Centers for Disease Control and Prevention reported that 51.5% of children with severe

**Figure 3 (facing page). Joint Scores on Physical Examination, Frequency of Bleeding Events, and Factor VIII Use According to Age and Study Group.**

Panel A shows the mean joint score on physical examination. The scale sums the scores of all six index joints. Mean joint scores for the two study groups were not significantly different at any age. In Panel B, mean joint and other hemorrhages increased progressively throughout the study in children receiving enhanced episodic therapy, whereas the mean numbers of joint and other hemorrhages remained at a low level in children receiving prophylaxis. As shown in Panel C, factor VIII use per kilogram rose progressively throughout the study period in the episode-therapy group; overall, however, there was greater use in the prophylaxis group than in the episodic-therapy group ( $P < 0.001$  for each year of age). T bars indicate standard errors. N denotes the number of participants at risk in each age group.

hemophilia who were younger than 6 years of age received prophylaxis during 2004.<sup>28</sup> We previously reported that the time required for infusions, unwillingness on the part of the child, limitations in venous access, and difficulty in balancing prophylaxis with other family needs were major barriers to the implementation of prophylaxis.<sup>29</sup> Even in the present group of highly motivated, intensively supported families, the infusion schedule was inadequate for 2 of the 32 participants in the prophylaxis group.

This study demonstrates the efficacy of prophylaxis with recombinant factor VIII in reducing the incidence of joint hemorrhages, life-threatening hemorrhages, and other hemorrhages and in lowering the risk of joint damage among young boys with severe factor VIII deficiency. However, the high cost of recombinant factor VIII is a barrier to widespread acceptance of prophylaxis.

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#### APPENDIX

The authors are affiliated with the following institutions: the University of Colorado and Health Sciences Center (M.J.M.-J., B.R., R.K., M.L.M.-J., S.F., L.J.) and Children's Hospital (M.J.M.-J., J.D.I.), Denver; Emory University, Atlanta (T.C.A.); Indiana Hemophilia and Thrombosis Center, Indianapolis (A.D.S.); Beth Israel Deaconess Medical Center, Harvard Medical School, Boston (M.R.H.); Rush Children's Hospital, Chicago (L.A.V.); University of Texas, Houston (W.K.H., D.B.); University of Texas Southwestern Medical Center and Children's Medical Center at Dallas (G.R.B.); Weill Medical College of Cornell University, New York (D.D.); Phoenix Children's Hospital, Phoenix, AZ (M.R.); Tulane University, New Orleans (C.L.); Primary Children's Hospital, Salt Lake City (S.B.); University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia (A.C.); University of New Mexico, Albuquerque (P.M.); Oakland Children's Hospital, Oakland, CA (A.M.); University of Hawaii, Honolulu (D.M.); Children's Hospital of Orange County, CA (A.N.); Oregon Health and Science University, Portland (G.A.T.); Children's Memorial Hospital and Northwestern University, Chicago (A.A.T.); Palmetto Health Richland, Columbia, SC (K.M.); and Centers for Disease Control and Prevention, Atlanta (J.M.S., H.A., B.L.E.).

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