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Bleeding before prophylaxis in severe hemophilia: paradigm shift over two decades.

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Prophylaxis for hemophilia is the scheduled infusion of the missing clotting factor with pre-specified dose, with the intention of preventing bleeds and subsequent hemophilic arthropathy. It is the treatment of choice for patients with severe hemophilia A in countries with available resources.[1] Around the year 2000 it was published that prophylaxis is most efficient when initiated early: before the age of three years,[2] or directly after the first joint bleed.[3,4] These strategies are reflected in the two most frequently used definitions of primary prophylaxis. The European Pediatric Network for Hemophilia Management (PedNet) first specified primary prophylaxis as starting before two years of age *or* before the second joint bleed,[5] and The World Federation of Hemophilia (WFH) as starting before the age of three years *and* before the second joint bleed, in the documented absence of osteochondral joint disease.[1]

Early prophylaxis may require placing a central venous access device (CVAD) to facilitate frequent venous access, but these devices carry a risk of infections and thrombotic complications.[6] Attempting to reduce the need for CVADs while initiating early prophylaxis, Petrini and colleagues started prophylaxis with once weekly infusions.[2,7] Many have subsequently published or recommended protocols starting with once weekly infusions.[8-10]

The present study assesses how the increasing awareness of the importance of early prophylaxis affected bleeding before prophylaxis, CVAD use, initial prophylactic regimens, and achievement of primary prophylaxis.

Data on 919 patients with severe hemophilia A (FVIII<0.01 IU/mL), born 1990-2010, collected for the CANAL study[11] (n=313) and the PedNet registry[12] (n= 606), were used. From CANAL and PedNet respectively 9 and 16 patients were excluded for not having any treatment data. Case Report Forms and in- and exclusion criteria were the same for both datasets.[11,12]

Anonymized data on patients' demographics, bleeding and details on all factor

administrations were collected by the participating centers until 01-May-2013. For the present analysis patients were followed from birth until the 50th treatment day with FVIII or the development of a clinically relevant inhibitor, defined as at least two positive inhibitor titers, combined with a decreased *in vivo* Factor VIII recovery. Start of prophylaxis was defined as the regular infusion of FVIII, at least once weekly, continued for at least two months. Data were analyzed in 5-year birth cohorts. Most parameters had a skewed distribution and were therefore presented as medians and interquartile range (IQR). Trends over time were analyzed using univariable linear or logistic regression. Kaplan-Meier survival analysis was used to assess the occurrence of the first joint bleed and cumulative incidences of start of prophylaxis and CVAD use, while accounting for differences in follow up due to inhibitor development. Differences in survival curves across birth cohorts were assessed using the log-rank test.

Initiation of treatment and prophylaxis: The median age at initiation of prophylaxis decreased from 1.6 years in the first birth cohort, to 1.3 years in the last birth cohort (P<0.01; Table 1). Concomitantly, the proportion of patients starting prophylaxis before the age of three years increased from 45% to 84% (P<0.01).

Bleeding before prophylaxis: The first joint bleed occurred at a median of 1.7 years (IQR 1.0-2.8). Over time, fewer bleeds were accepted before initiating prophylaxis (Table 1). While the median number of joint bleeds before initiation of prophylaxis decreased, the proportion of patients starting prophylaxis before any joint bleed increased from 29% to 43% (Figure 1; P=0.06). Since 1990, especially the proportion of patients starting prophylaxis before the second joint bleed increased (from 43% to 72%; P<0.01).

The proportion of patients receiving primary prophylaxis according to the first PedNet definition (< 2 years *or* <2nd joint bleed) [5] increased from 65% in the first, to 88% in the last

birth cohort (P<0.01). According to the WFH definition (< 3 years *and* < 2nd joint bleed), fewer patients started primary prophylaxis, yet the proportion still doubled from 35% to 70% (P<0.01). The WFH definition however, excludes the 21% of patients who had their first joint bleed after the age of three years and initiated prophylaxis afterwards.

Initiating prophylaxis, how: CVAD use in patients on prophylaxis was relatively stable over time (P=0.85): by age four years, about 40% of patients who started prophylaxis had used a CVAD. Prophylaxis was increasingly started using once weekly regimens: from only 18% in the early 1990s to 59% in the last birth cohort (P<0.01). The increase was most prominent after the year 2000. Concomitantly, starting prophylaxis ≥3x/week decreased from 41% to 18% (P<0.01).

Study design: As this study focused on prophylaxis initiated within the first 50 treatment days, results should not be extrapolated to starting prophylaxis later in life. Therefore, limiting the window of observation to the first 50 treatment days will have resulted in an underestimation of the overall age at starting prophylaxis and the number of bleeds incurred before prophylaxis, especially in the earlier cohorts. Differences between the first and last two cohorts could therefore be larger than presented in this study.

Comparison with other studies: National guidelines and recommendations issued in several European countries advised starting prophylaxis early,[8,13] often combining criteria of both age and number of bleeds at the initiation of prophylaxis. The results of this study confirm that prophylaxis is not only increasingly started before the age of three years or before the second joint bleed, but also that more patients start on primary prophylaxis. The two circulating definitions of primary prophylaxis have different benefits and drawbacks. The 1999 PedNet definition uses a maximum age of two years *or* a maximum of 1 joint bleed, and therefore potentially includes patients suffering many joint bleeds before the age of two

years. The WFH definition, on the other hand, uses a maximum age of three years *and* a maximum of 1 joint bleed.[1] This makes it impossible to start 'primary prophylaxis' in the 21% of patients with a milder phenotype, characterized by the onset of joint bleeding after the age of three years.

The idea to initiate prophylaxis with once weekly infusions originated in Sweden where it was applied with the aim of reducing the need for CVADs.[2,7] This study shows that once weekly infusions are now used in the majority of patients, even in countries without a formal protocol advising this strategy. CVAD use in this study was stable around 40%. The two trends, starting prophylaxis earlier and starting with once weekly infusions, likely balanced out and caused the stable use of CVADs. In addition, the frequency of venous access may be associated with the occurrence of CVAD complications. This question requires longer follow-up and will be addressed in an ongoing study on CVAD management and complications.

Reports on the effects of early and/or low dose prophylaxis on inhibitor development have been conflicting.[9,14] As the etiology of inhibitor development is multifactorial, any analysis on the effects of timing and/or regimen of prophylaxis on inhibitor development should be adjusted for other risk factors of inhibitor development. The recent multivariable analysis by Gouw et al on the RODIN data showed that early start of prophylaxis was associated with reduced inhibitor development in patients with low risk mutations. However, the infusion frequency at start of prophylaxis was not associated with inhibitor development.[15]

In summary, publications in the late 1990s on the importance of early prophylaxis have led to a paradigm shift in clinical practice. Less bleeding is now accepted before the initiation of prophylaxis and consequently more patients are started before three years of age and before the second joint bleed. In addition, initial prophylactic regimens increasingly use once weekly infusions. To determine the consequences of the different regimens used to start

prophylaxis, subsequent treatment and outcome, especially long-term joint status, need to be documented and analyzed.

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Tables

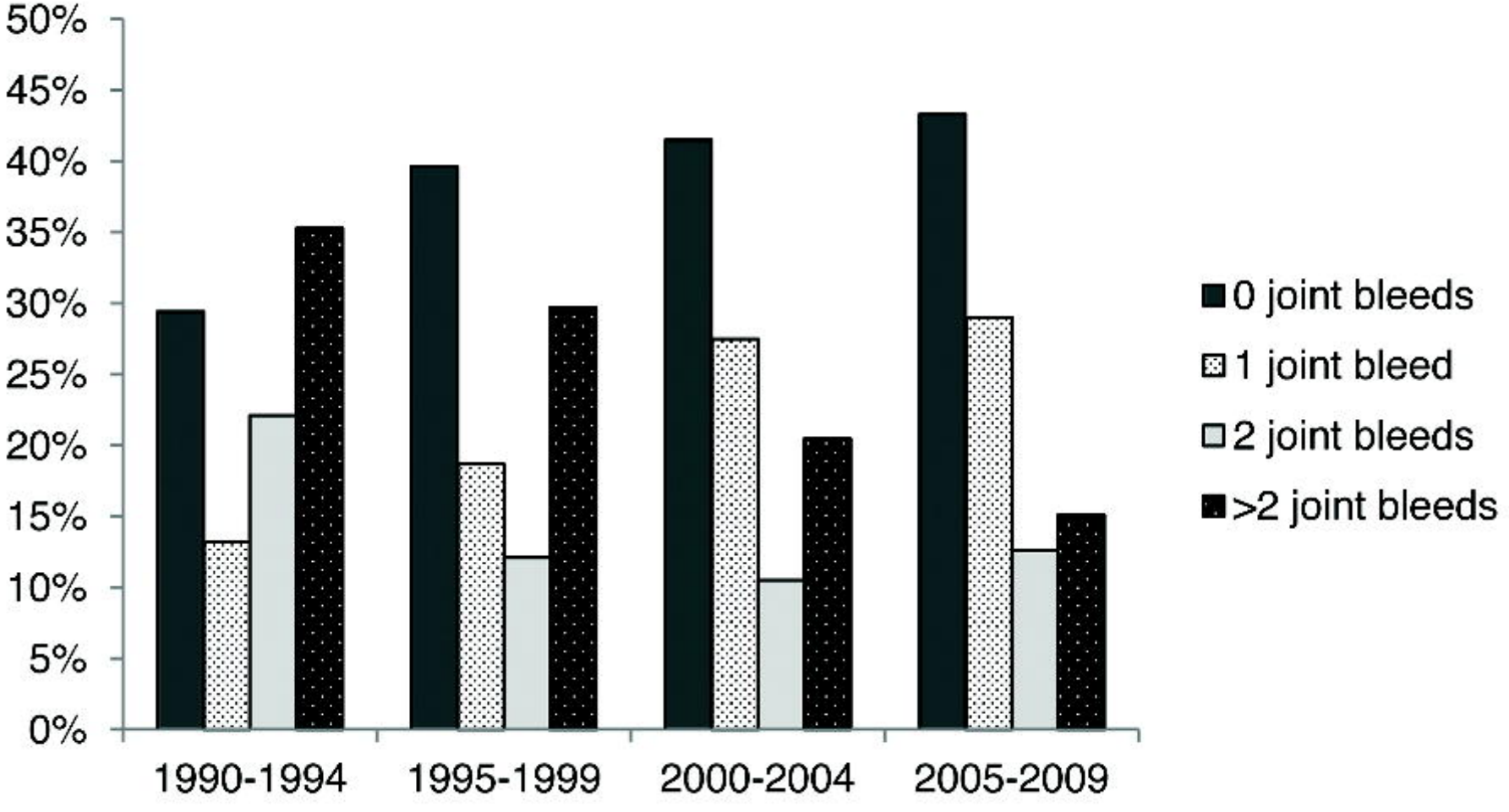
Table 1: Bleeding before prophylaxis and primary prophylaxis according to birth cohort.

Birth cohort	**1990-94**	**1995-99**	**2000-04**	**2005-09**	**P-value**
(*n*)	138	172	302	307	**trend**
On prophylaxis (*n*)	74	101	202	238	
Age at start of prophylaxis (y)	1.6 (1.1-3.1)	2.1 (1.1-2.9)	1.4 (1.1-2.1)	1.3 (0.9-1.9)	<0.01
Bleeding before prophylaxis					
Bleeds (*n*)	6.5 (3.0-12.0)	4.0 (1.0-12.0)	4.0 (1.5-9.0)	3.0 (1.0-7.0)	<0.01
Joint bleeds (*n*)	2.0 (0.0-4.0)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	<0.01
Primary prophylaxis					
PedNet definition (%)	65%	67%	86%	88%	<0.01
WFH definition (%)	35%	49%	67%	70%	<0.01

Values are numbers (*n*), medians (IQR) and percentages (%).

Legends to Figures

Figure 1. Joint bleeding before prophylaxis according to birth cohort.


50%
45%
40%
35%
30%
25%
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1990-1994
1995-1999
2000-2004
2005-2009
0 joint bleeds
1 joint bleed
2 joint bleeds
>2 joint bleeds