

## Request for further standardization issues for future studies in paediatric haemophilia patients – Rebuttal to “Including the life-time cumulative number of joint bleeds in the definition of primary prophylaxis”

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Dear Sir,

With great interest we read the careful comments of Ingrid den Uijl and Kathelijn Fischer (1) with respect to our article “effects of primary and secondary prophylaxis on the clinical expression of joint damage in children with severe haemophilia A (HA) – Results of a multicenter non-concurrent cohort study” (2). The authors comment on *i)* the classifications used for primary and secondary prophylaxis, *ii)* the inclusion of inhibitor patients in the present database study, and *iii)* the possible calculation of life time cumulative number of joint bleeds.

*Ad i (definition of terms used in the present database study):* In the present non-concurrent cohort study, primary prophylaxis was defined as factor infusions given to prevent bleeding **before the third** but usually starting after the first bleed (3). In addition, patients who did not suffer more than one symptomatic joint bleed into the **same joint within a six-month period** before the start of long-term continuous treatment were classified as primary prophylaxis patients (modification to [4]). Secondary prophylaxis was defined as long-term continuous factor replacement therapy not fulfilling the modified criteria for primary prophylaxis.

As pointed out in the result section in our article (2) none of the patients in the primary prophylaxis group had more than a total of three symptomatic bleeding episodes and no more than one symptomatic joint bleed into the same joint within a six-month period. Vice versa, in patients treated with secondary prophylaxis more than three clinically relevant bleeds including soft-tissue, muscle or joints, or two or more bleeds into the same joint within a six-month period have been recorded before starting long-term continuous therapy. In Table 1 the median annual bleeding frequency was shown on prophylaxis (see comment in

the discussion part), whereas the median frequency of all joint bleeds was shown for the period before initiation of any prophylactic regimen. Thus all HA patients on prophylaxis were correctly classified according to the definitions given with a range of zero to 36 in children *on* secondary prophylaxis, compared with zero to 20 in children treated *on* primary prophylaxis. The range reported for symptomatic joint bleeds occurring *before* prophylaxis included zero in both groups because HA patients receiving secondary prophylaxis not automatically had suffered from joint bleeds prior to treatment start; the upper range of two joint bleeds in the primary prophylaxis group is due to the fact that according to the definitions used a second hemorrhage was diagnosed in a joint different from the first joint affected.

*Ad ii (inclusion of inhibitor patients):* for completeness of the database study inhibitor patients were included. Whereas 31.9% of the boys enrolled developed high-titre inhibitors in the primary prophylaxis group, 12.9% of children with severe HA showed inhibitors when treatment was initiated at a median age of 2.5 years (secondary prophylaxis: Fisher's exact test:  $p = 0.01$ ). In all patients high titre inhibitors were diagnosed within the first 30 exposure days following factor VIII replacement therapy, and children were treated with immune tolerance (IT) protocols using FVIII, vWF/FVIII, or bypassing agents alone or in combination. Since the present non-concurrent cohort study was aimed to evaluate the joint outcome after a median follow-up of 12.5 years, results did not significantly differ from the analysis previously presented when the inhibitor patients were excluded from the analysis: when comparing children on primary prophylaxis with patients on secondary treatment neither the Pettersson score ([5]: median: min-max values) available in a total of 49 children [1(0–11) vs. 2 (0–10); Mann-Whitney U-test:  $p = 0.70$ ] nor the magnet resonance imaging (MRI) joint score according to Nuss ([6]: n=29; 3 (0–9) vs. 8 (0–9);  $p = 0.09$ ) showed a statistically significant difference between the two groups.

*Ad iii) the calculation of cumulative number of bleeds:* According to the definitions given in the German database study, we recalculated the cumulative bleeding-free survival (BFS: cox regression: inhibitor patients not included). When comparing the cumulative BFS, we found a statistically significant difference between the two curves (primary prophylaxis vs. on demand [secondary prophylaxis]: Fig. 1A). However, when additionally comparing joint damage between the two groups (gradual point increase using the radiographic score) we did not find a statistically different hazard ratio (HR)/95% confidence intervals (CI) [HR/CI: 0.98/0.90–1.08;  $p = 0.81$ ].

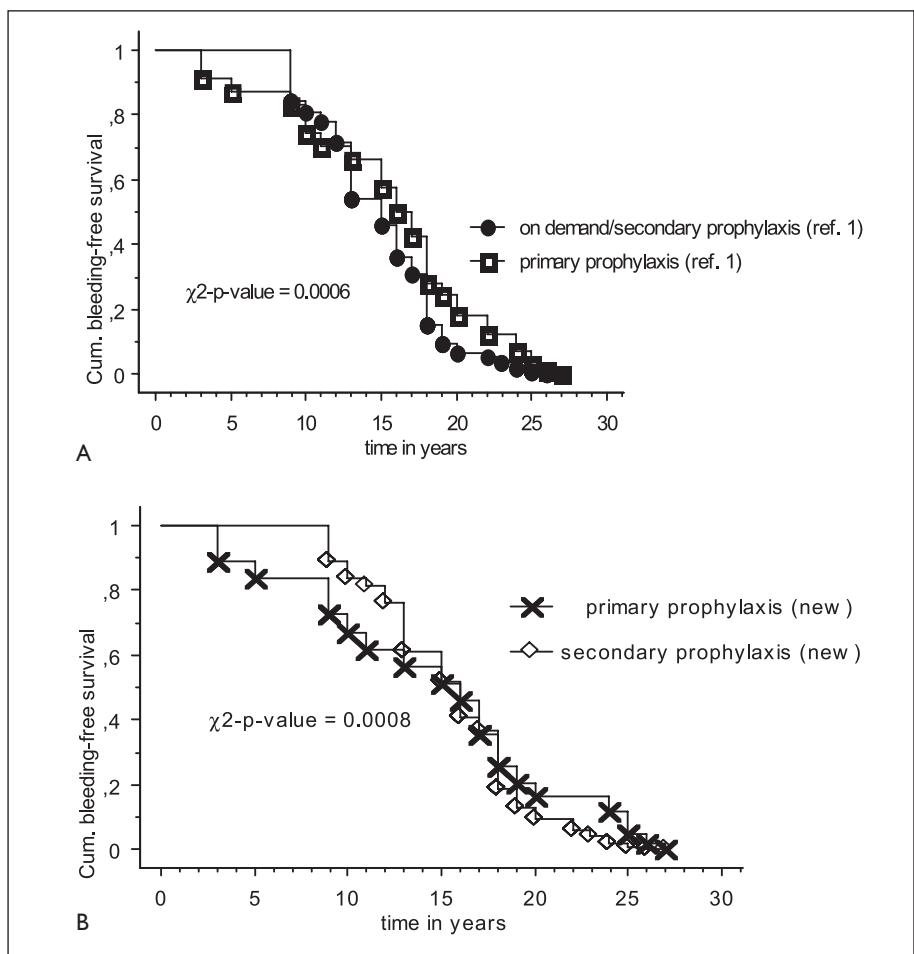
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**Figure 1: Comparison of cumulative bleeding-free survival in HA children.**  
A) Prophylaxis-definition according to ref. 2.  
B) Prophylaxis-definition according to ref. 1.

In addition, as suggested by Uijl and Fischer we have regrouped the patients investigated [ $\leq 2$  joints bleeds (any joint) in the primary prophylaxis group]. When comparing the cumulative BFS, we again found a statistically significant difference between the two curves: the cumulative BFS in patients on secondary prophylaxis was significantly reduced compared with children on primary prophylaxis (Fig. 1B). Again, no statistically significant increased/decreased HR was found when the Pettersson scores were compared between the newly grouped patient cohorts [HR/CI: 0.97/0.88–1.069;  $p = 0.57$ ]. Furthermore, when replacing the radiographic score with the MRI (Nuss) score in the statistical model the HR/CI was 1.0 [0.86–1.14;  $p = 0.91$ ], respectively.

The results presented here along with the previously shown data (2) pointed out that a switch from “on-demand” factor replacement therapy to early secondary prophylaxis can be successfully performed in the majority of young children with severe HA. Here we wish to point out that the different definitions used to define primary and secondary prophylaxis with respect to joint bleeds did not substantially change the results obtained from this non-concurrent cohort study.

With respect to the cohort studies reported by Fischer et al. (7) and Kreuz et al. (8), we clearly have to point out that in both reports the final study endpoint, i.e. joint damage, was scored with a radiographic score (Pettersson) but, unfortunately, did not include a more sensitive MRI score, for example that according to Nuss (6). Taking into account that the radiographic score alone may not be sensitive enough to pick up subtle cartilage or joint changes in future studies sensitive imaging methods such as MRI scores should be implemented, as recently introduced by Manco-Johnson et al. (9).

In summary, we clearly agree with Ingrid den Uijl and Kathelijn Fischer (1) that statistical evaluations such as the calculation of cumulative bleeding events/bleeding-free episodes along with the use of standardized term definitions of primary and secondary prophylaxis will improve future prospective studies in haemophilia. In addition, we wish to thank the authors and the editors of *Thrombosis and Haemostasis* for the possibility to further clarify important issues with respect to our previous database study, thereby underlining the importance of future prospective large-scale and long-term studies in previously untreated haemophilic children.

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