A modeling approach to evaluate long-term outcome of prophylactic and on demand treatment strategies for severe hemophilia A

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Online Supplementary Appendix

Distributions of the patients' characteristics

The three characteristics: (i) average number of annual joint bleeds, (ii) age at first bleed, and (iii) expected lifetime of a simulated patient were drawn from their corresponding probability distributions. The first two distributions were derived from the Dutch patient dataset and were estimated using the distribution-fitting tool in Matlab™. The life expectancy was assumed to follow the normal Dutch life expectancy distribution, i.e. a Weibull($\alpha = 8$; $\beta = 80$) distribution.

Average number of annual joint bleeds

The data showed that young children had a lower average number of annual joint bleeds than older children and adults. Therefore, a distinction was made at the age of 7 years. The distribution of the average number of joint bleeds for children younger than 7 years was assumed to follow an Exponential($\lambda = 3.75$) distribution. An Exponential($\lambda = 5$) distribution was chosen to fit the average number of joint bleeds for patients older than 7 years.

Age at first joint bleed

The best fitting distribution of the age at first joint bleed was assumed to be a Weibull($\alpha = 1.71$; $\beta = 2.45$) distribution.

Annual number of joint bleeds

The model allows the annual number of joint bleeds to vary per year. Again, the distributions were based on the Dutch dataset. We observed a positive correlation between the number of bleeds per year and the average number of joint bleeds of a patient. The higher the average number of joint bleeds of a patient, the higher the variance. This is illustrated by *Online Supplementary Figure S1*, where the maximum and minimum annual numbers of joint bleeds of a patient are illustrated. Both relationships were assumed to be linear and were represented by TOBIT models with the restriction of non-negative prediction. The resulting fits were respectively:

MinimumNumJointBleeds =
max(0, −4.7 + 0.91 ∗ AverageNumJointBleeds),
MaximumNumJointBleeds =
2.524 + 1.4 ∗ AverageNumJointBleeds.

Taking into account the drawn average annual number of joint bleeds and the associated minimum and maximum number of annual joint bleeds, the distribution of the annual number of joint bleeds of a patient was estimated to follow a truncated Beta distribution.

Relationship between joint bleeds and Pettersson score

The relationship between joint bleeds and the Pettersson score has been reported previously.[1] The result was a TOBIT model, assuming no increase in Pettersson score until 48.5 bleeds (95% C.I.: 34 – 63) and an increase in Pettersson score with one point per 12.6 bleeds (95% C.I.: 11.1 – 14.7) thereafter.

Relationship between joint bleeds and clotting factor use

The clotting factor VIII consumption in case of prophylaxis was expressed as a log-linear model depending on age

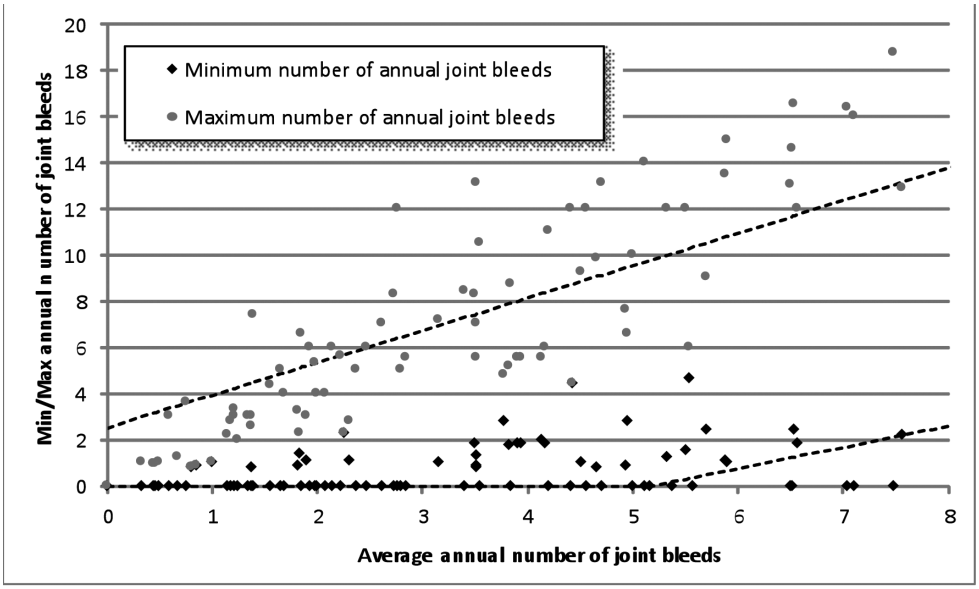
ClottFactConsProphy (IU/kg/yr) = exp($\alpha + \beta$ ∗ log(Age)),
where (95% C.I.):
$\alpha = 7.87$ (7.67 – 8.06),
$\beta = -0.11$ (-0.18 – -0.04).

For on-demand treatment a linear model was assumed depending on the annual number of joint bleeds

ClottFactConsDemand (IU/kg/yr) = α ∗ AnnualNumJointBleeds,
where (95% C.I.):
$\alpha = 50.5$ (42 – 58.9).

References

1. Fischer K, Van Hout BA, Van der Bom JG, Grobbee DE, Van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. Acta Radiol. 2002;43(5):528-32.



Online Supplementary Figure S1. Minimum and maximum number of annual joint bleeds. For each patient the average annual number of joint bleeds and the associated minimum and maximum number of annual joint bleeds are illustrated. Linear trend lines are added for the minimum numbers and for the maximum numbers.