

Real-World Prophylaxis Experience: Perspectives from Clinical Practice

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BeneFix® (nonacog alfa) is not currently approved for once-weekly prophylaxis treatment



Disclosures for: Alfonso Iorio

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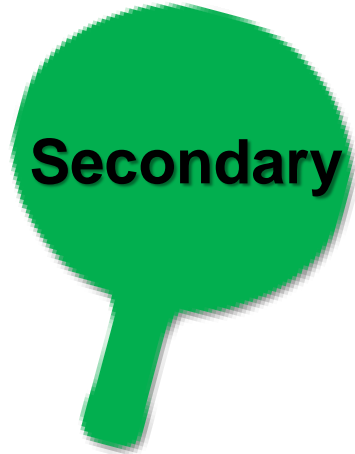
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Goals of the presentation

- Review usage of prophylaxis in adult haemophilia B patients
 - Indications and uptake
 - Frequency of administration
 - Dosing

Question 1

- How do you define prophylaxis started in adulthood?



Prophylaxis in adult patients

- Tertiary prophylaxis
- Definition
 - Regular continuous treatment started after the onset of joint disease
- Source
 - Srivastava A, Brewer AK, Mauser-Bunschoten EP et al. Guidelines for the management of hemophilia. *Haemophilia* 2013;19:e1–47.

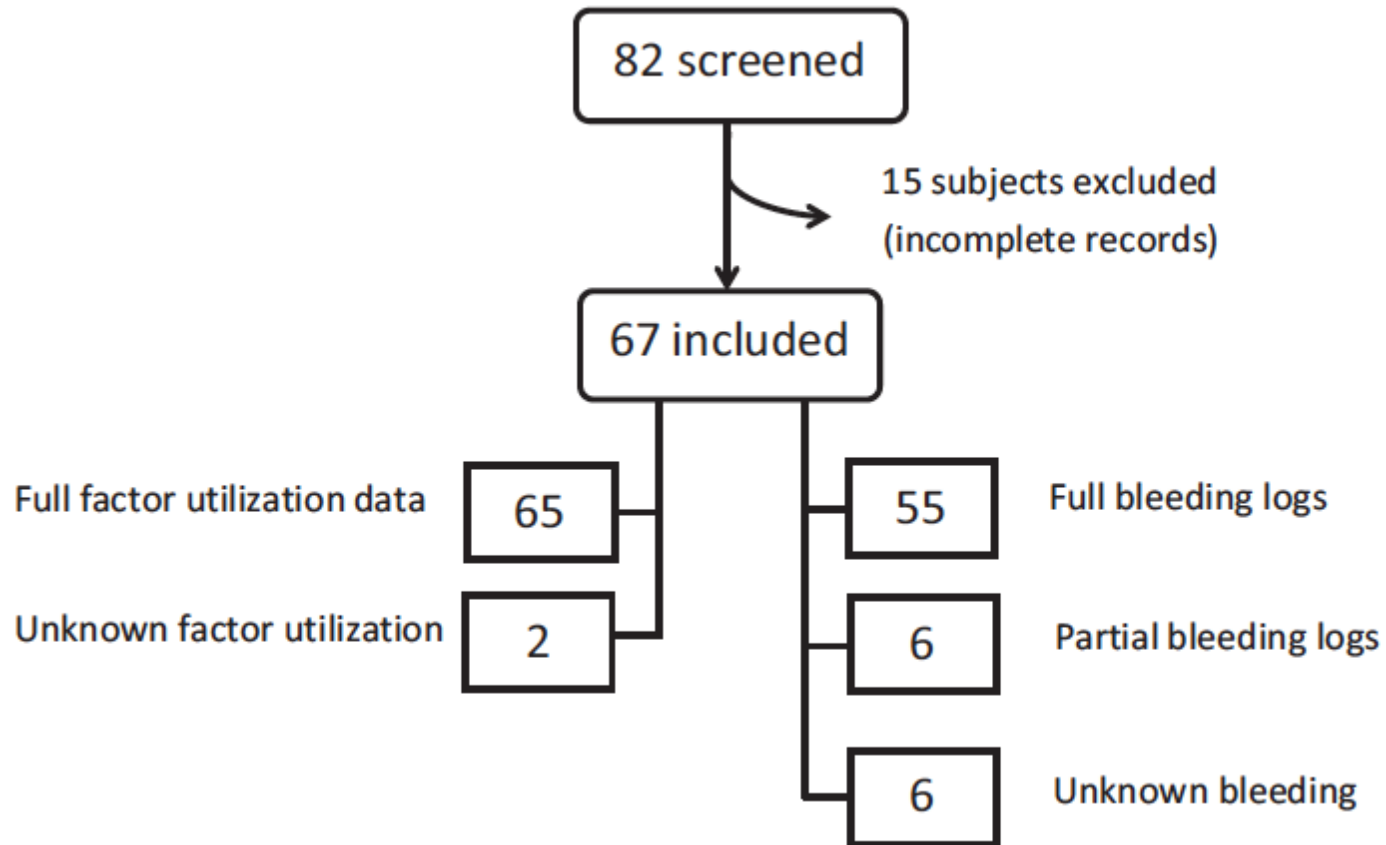


Table 1. Characteristics of study population ($n = 67$).

Median age, years (IQR)	35 (26.9; 45.1)
Age range, years	19–83
Baseline FIX:C	
<1%	33 (49%)
1%	16 (24%)
2%	18 (27%)
Joints affected (n)	
0–1	39 (58%)
2–4	25 (37%)
>4	3 (5%)
HIV positive	7 (11%)
Hepatitis C antibody positive	42 (62%)
Hepatitis B positive (HBsAg)	8 (12%)

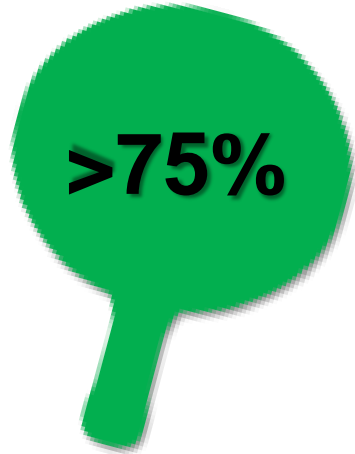
Question 2

- How many adult patients do you expect to be on prophylaxis?



If green wins: Question 3

- How many adult patients do you expect to be on prophylaxis?



If red wins: Question 4

- How many adult patients do you expect to be on prophylaxis?



Table 2. Prophylaxis and on-demand exposure during observation period (2009–2011).

	Prophylaxis	On-Demand
Number of subjects exposed	23 (34%)	44 (66%)
Median age, years	34	37
Annualized bleeding rate (mean)	8	10
Once weekly ($n = 3$)	4	–
Twice weekly ($n = 12$)	7	–
Annualized bleeding rate (median, IQR)	5 (1; 12)	4 (1; 14)
Prophylaxis exposure prestudy*	20 (87%)	5 (11%)
Weight (during study period), kg, median	72	84
No. joints affected, median	2	1
Self-infusion skills	21 (88%)	32 (73%)

*None had exposure to primary prophylaxis.

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 Jackson SC et al. *Haemophilia* 2014; 20(3), e199–204.

Prophylaxis in adult patients in Canada

- Previous large Canadian survey in 2006¹
 - 17/86 (20%) adults ≥ 18 with severe hemophilia B were on prophylaxis (≥ 45 w/year)
- Current 2014 study: 34/67 (34%)
- Factor concentrate utilisation (U/Kg/year):
 - **Pre-2009:** prophylaxis: 2148; on-demand: 812
 - **Observation period:** prophylaxis: 2936; on-demand: 611

1. Biss TT. *Haemophilia* 2008; 14: 923–30.

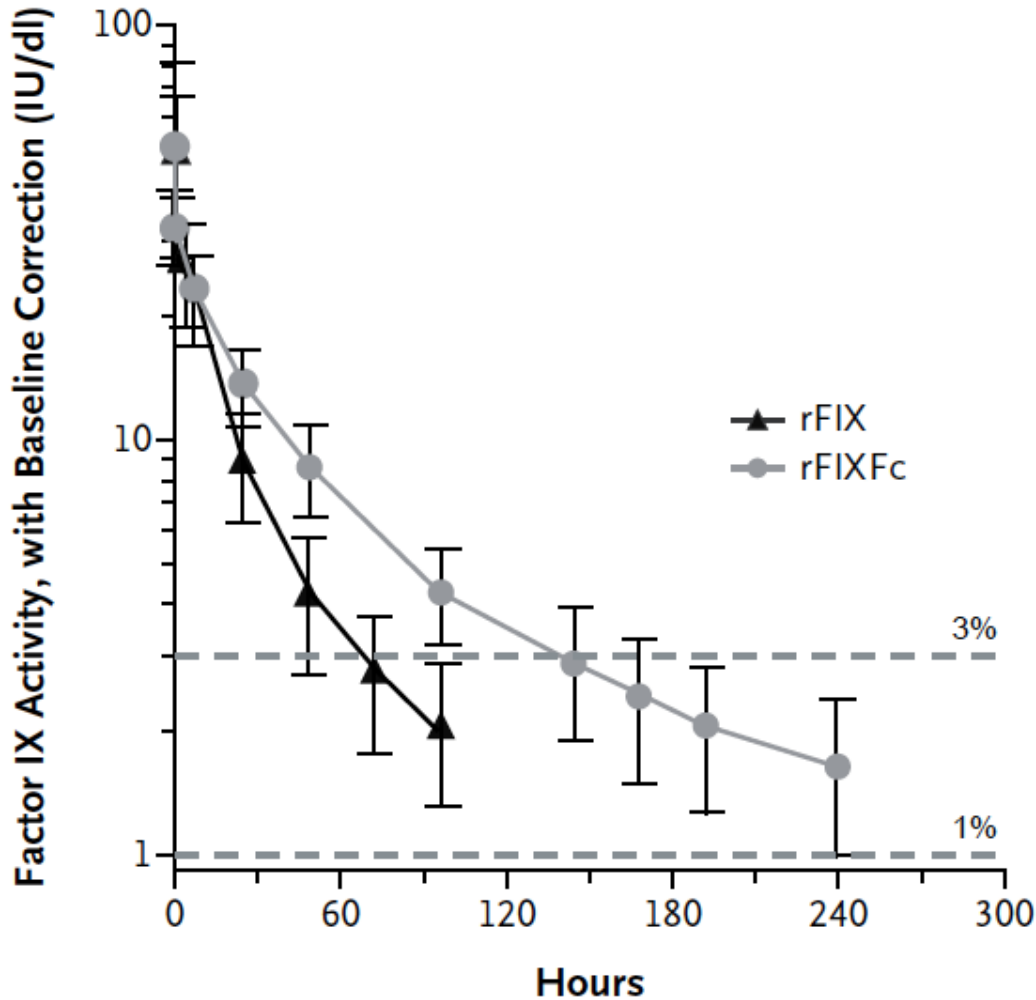
Once-weekly dosing with rFIX

- 2/3 subjects treating weekly with 33–36 U/kg/week
 - ABR = 0
- 1/3 subjects treating weekly with 39 U/kg/week
 - ABR = 12

PK estimation of rFIX half-life

Powell JS et al. *NEJM*
2013; 369(24), 2313–23.

Phase III study of recombinant factor IX Fc fusion protein in hemophilia B



PK estimates 96 vs 48 hrs sampling

	Arithmetic Estimates (hours)		Geometric Estimates (hours)	
	Mean	SD	Mean	95% CI
BeneFIX package insert ²	18.1	5.1	--	--
Study BeneFIX estimate (48 hours) *	17.2	2.7	17.0	(15.9, 18.3)
Study BeneFIX estimate (96 hours) *	35.7	13.6	33.8	(29.1, 39.2)

2-comp model analysis following injection of 50 IU/kg (*) IU/dl per IU/kg using one-stage clotting assay for FIX measurement

Question 5

- Are you surprised to see a longer than expected half-life rFIX?



Recombinant FIX vs pdFIX

Parameter	AlphaNine ^{®†} (n = 25)	BeneFix [®] (n = 22)
Recovery IU/dL per IU/Kg	1.30 +/- 0.4	1.00 +/- 0.3
Half-life (h)	32.7 +/- 7.4	36.0 +/- 12.8
VDss (dl/Kg)	1.34 +/- 0.42	1.75 +/- 0.52

VDss: Volume of distribution

†AlphaNine[®] is not approved in Australia

Lissitchkov T. *Haemophilia* 2013;19(5):674–8,
Berntorp E. *Haemophilia* 2013;19(6), 805–7.

Question 6

- How do you dose rFIX? Do you use a conversion factor (e.g. 1.2 or higher?)



**No / don't
understand**



**Yes,
for sure**

Interpatient variability in dosing HB patients

Study	Pts & Age (years)	Prophylaxis (U/Kg)	On-demand (U/Kg)
	N° mean (range)	Median (range)	Median (range)
Roth ¹ (*)	56 23 (4–56)	35.1 (9.7–170.6)	42.8 (6.5–224.6)
Shapiro ²	56 9 (0–14)	60.6 (8.7–230.4)	62.7 (82–292.0)
Lambert ³	34 28 (12–68)	51.7 (13.9–184.2)	87.4 (30.3 –147.2)
Monahan ⁴	25 2 (0–4)	57.6 (27.9–187.2)	58.2 (27.5–115.2)

(*) 43% of 46 patients did not require dose increase

1. Roth D *Blood* 2001; 98: 3600-6; 2. Shapiro A, et al. *Blood*. 2005;105:518–525; 3. Lambert T, et al. *Haemophilia*. 2007;13:233–243; 4. Monahan PE et al. *Haemophilia* 2010;16:460-468

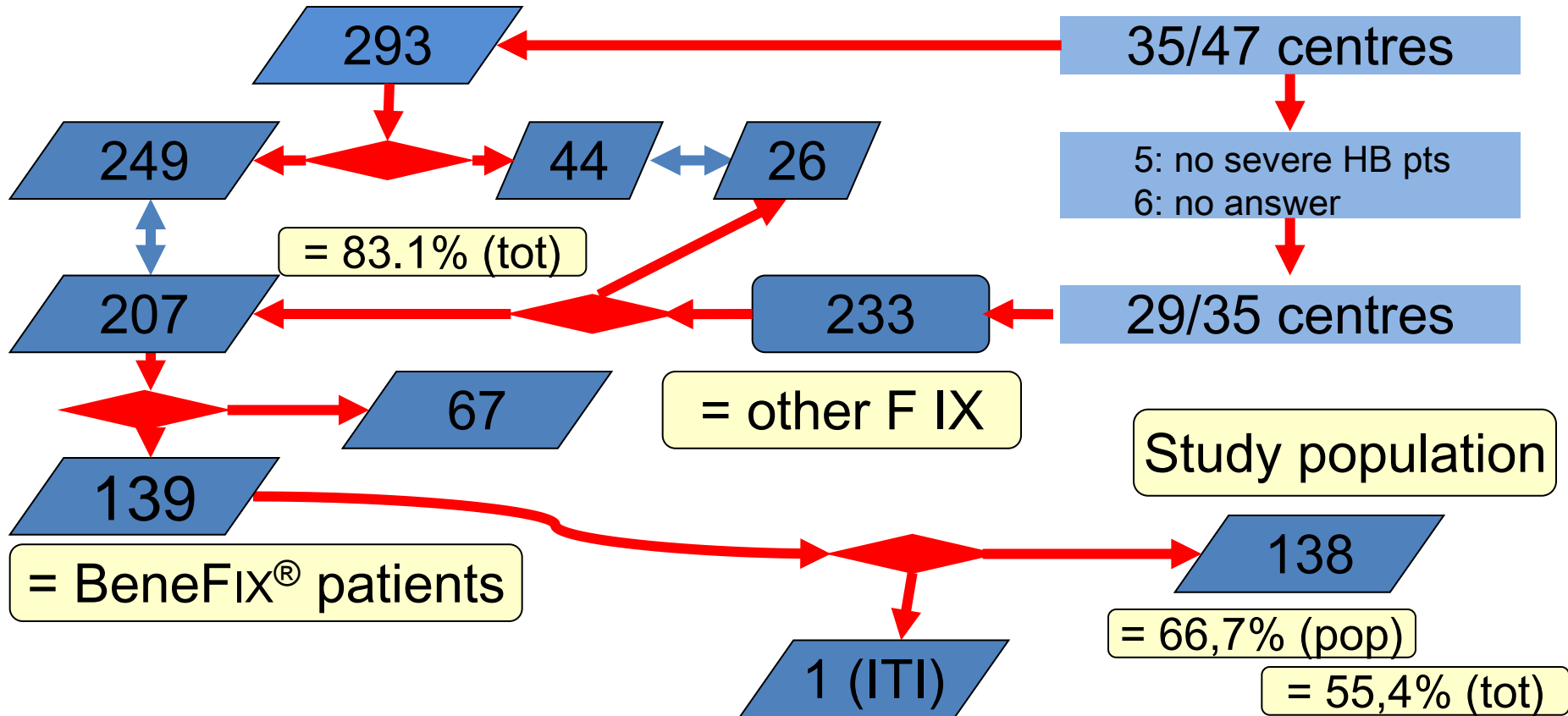
Recovery data from study 400

Table 3. FIX:C and recovery during prophylactic dosing.

	$C_{0\text{ h}}$ (IU dL ⁻¹)	$C_{0.5\text{ h}}$ (IU dL ⁻¹)	Recovery (IU ⁻¹ dL ⁻¹ /IU ⁻¹ kg ⁻¹)
50 IU kg ⁻¹ twice weekly ($n = 41$)			
Mean	3.57	49.9	0.93
SD	3.11	16.1	0.31
Min, max	0, 14	0.6, 83	0.002, 1.51
100 IU kg ⁻¹ once weekly ($n = 43$)			
Mean	3.10	91.5	0.91
SD	2.19	28.9	0.35
Min, max	0, 10	1.12, 146	0.011, 2.32

Max, maximum; min, minimum; SD, standard deviation.

Survey flow chart



Conversion factor estimate

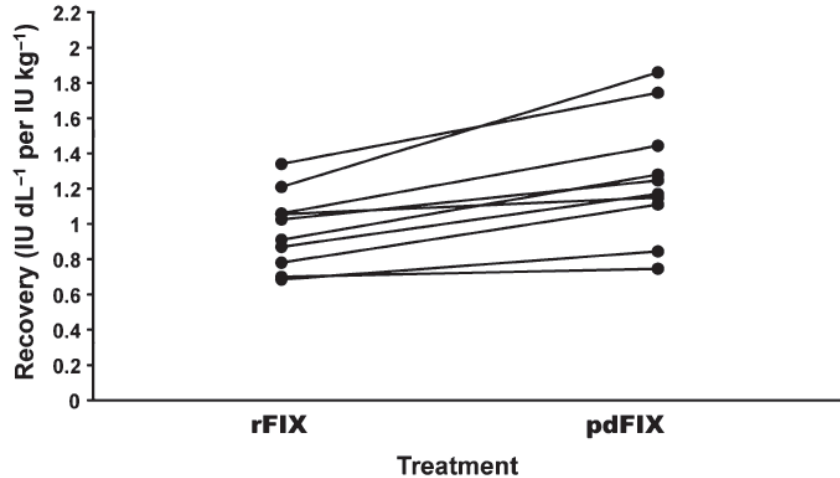
Mean \pm standard deviation	95% Confidence interval
1.10 \pm 0.36	0.39 – 1.83
Median	Range
1	0.51 – 2.08

LETTER TO THE EDITOR

Recovery of recombinant factor IX determined in clinical practice

M. MARTORELL, C. ALTISENT and R. PARRA

Haemophilia Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain



Mean recovery for
rFIX:
 0.98 ± 0.19 IU/dL/IU/kg

*(32 samples
from 23 patients)*

Fig. 1. Recovery rates of rFIX compared with historical rates of pdFIX in 10 haemophilia B patients.

Summary

- Increasing use of prophylaxis in hemophilia B
- Once-weekly treatment with rFIX *might be reasonable* in selected cases and with optimal dosage
- Half-life longer than it was thought
- Recovery does not need correction

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Disclaimer: These conclusions reflect literature evidence as interpreted by the speaker and not necessarily the opinion of the sponsor