“Opzioni terapeutiche consolidate in emofilia acquisita"

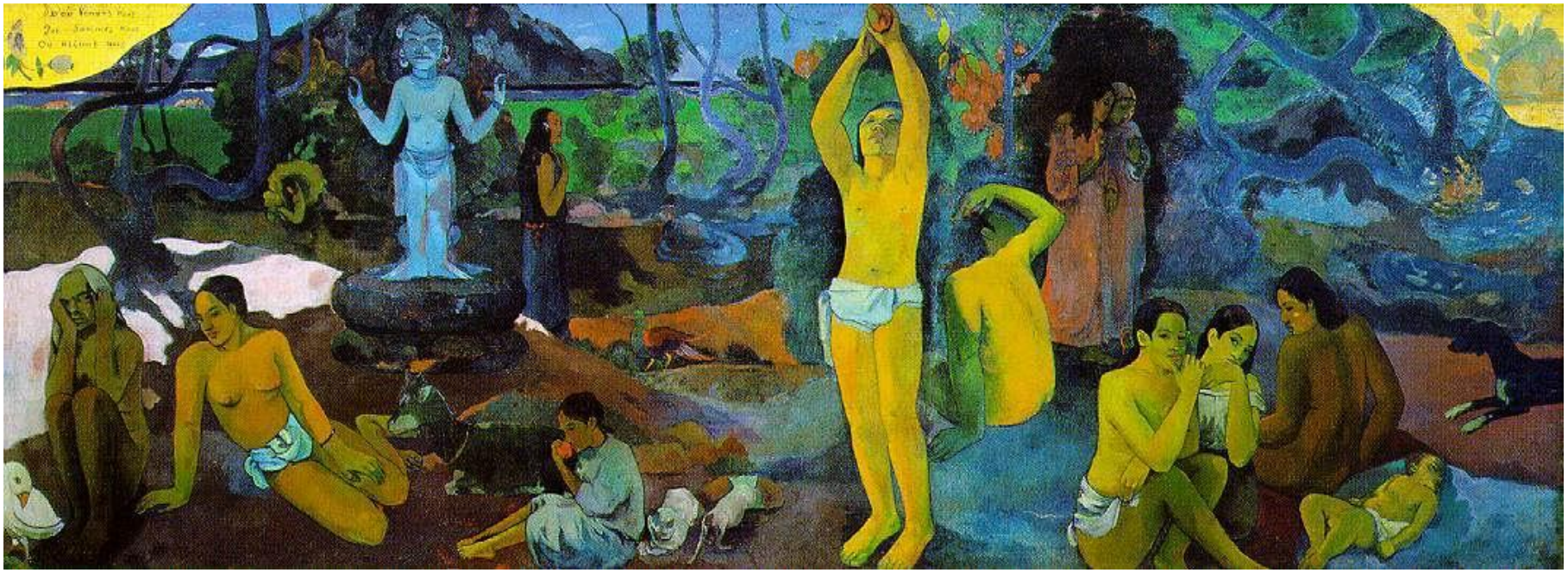
rFVIIa in emofilia acquisita: quando un controllo ottimale e sicuro dell'emostasi diventa fondamentale

Marco Marietta

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

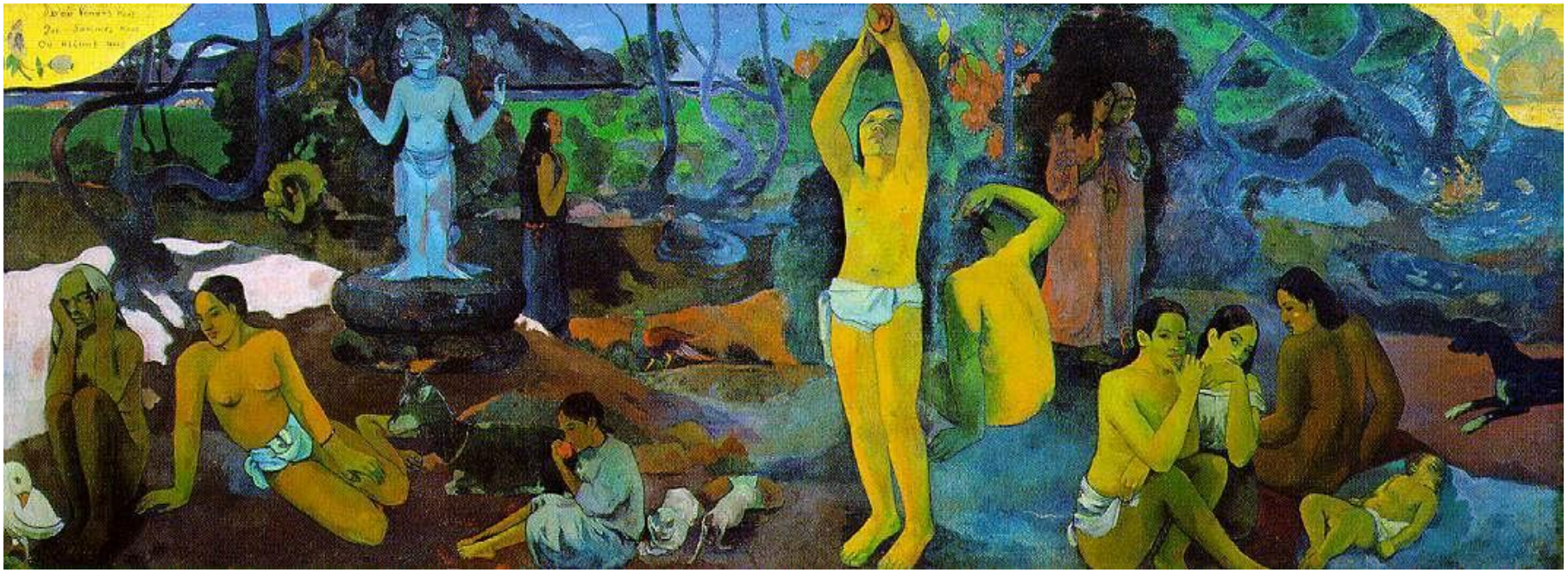
Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Regolamento Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, io sottoscritto **Dott. Marco Marietta** dichiaro che negli ultimi due anni ho avuto i seguenti rapporti ricevendo compens individuali con soggetti portatori di interessi commerciali in campo sanitario:

- **Partecipazione ad Advisory Board per Novo-Nordisk**
- **Consulenze / Relazioni a congressi per Kedrion, Orphan, Novo-Nordisk**



Da dove veniamo? Che siamo? Dove andiamo?

Paul Gauguin, 1897



Da dove veniamo? Che siamo? Dove andiamo?

Paul Gauguin, 1897

EMA/109367/2016
EMEA/H/C/000074

EPAR summary for the public

NovoSeven

eptacog alfa

Other information about NovoSeven

The European Commission granted a marketing authorisation valid throughout the European Union for NovoSeven on 23 February 1996.

EACH registry

- Registro multicentrico, prospettico, osservazionale
- 117 centri in 13 paesi (Austria, Finlandia, Francia, Germania, Grecia, Italia, Olanda, Portogallo, Regno Unito, Spagna, Svezia, Svizzera, Ungheria)
- **Arruolamento: 1/2003 – 12/2008**
- End-point maggiori: controllo delle emorragie e eradicazione dell'inibitore
- Pazienti trattati in accordo alla pratica clinica locale
- Sponsorizzato da Novo Nordisk, Danimarca

ORIGINAL ARTICLE

J Thromb Haemost 2012; **10**: 622–31.

Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

P. KNOEBL,* P. MARCO,† F. BAUDO,‡ P. COLLINS,§ A. HUTH-KÜHNE,¶ L. NEMES,** F. PELLEGRINI,†† L. TENGBORN,‡‡ and H. LÉVESQUE,§§ ON BEHALF OF THE EACH2 REGISTRY CONTRIBUTORS[1]

Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry

BJOG 2012;119:1529–1537.

L Tengborn,[a] F Baudo,[b] A Huth-Kühne,[c] P Knoebl,[d] H Lévesque,[e] P Marco,[f] F Pellegrini,[g] L Nemes,[h,*] P Collins,[i,*] on behalf of the EACH2 registry contributors†

blood

2012 120: 39-46
Prepublished online May 22, 2012;
doi:10.1182/blood-2012-02-408930

Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry

Francesco Baudo, Peter Collins, Angela Huth-Kühne, Hervé Lévesque, Pascual Marco, László Nemes, Fabio Pellegrini, Lilian Tengborn and Paul Knoebl

blood

2012 120: 47-55
Prepublished online April 18, 2012;
doi:10.1182/blood-2012-02-409185

Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

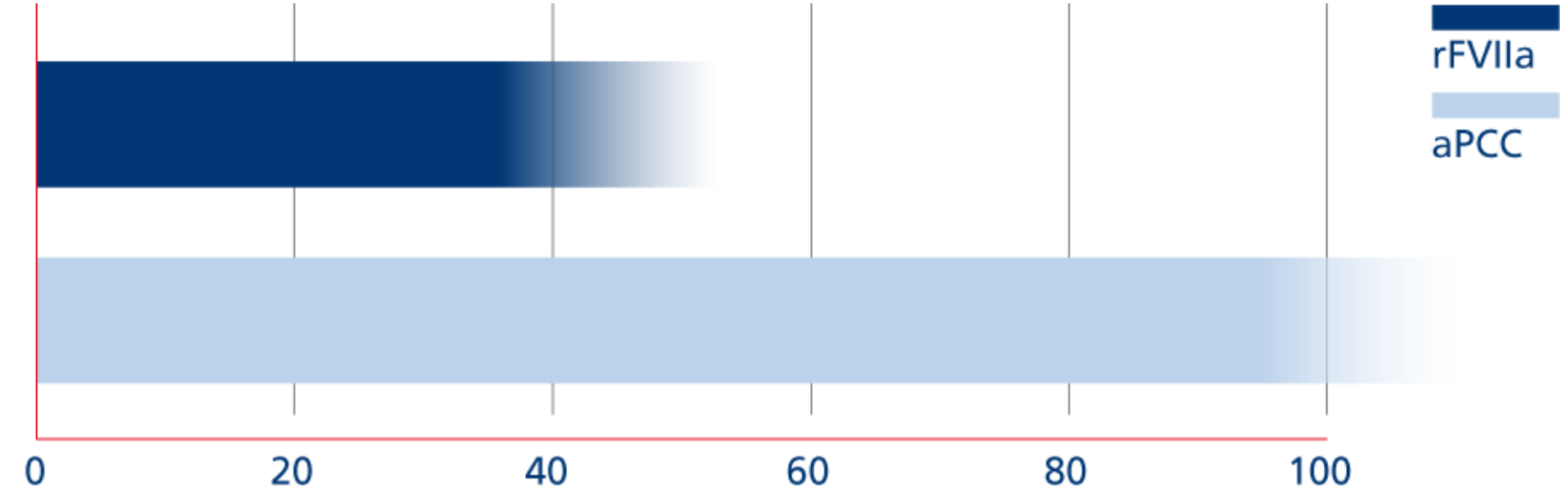
Peter Collins, Francesco Baudo, Paul Knoebl, Hervé Lévesque, László Nemes, Fabio Pellegrini, Pascual Marco, Lilian Tengborn and Angela Huth-Kühne

blood

2012 120: 39-46
Prepublished online May 22, 2012;
doi:10.1182/blood-2012-02-408930

Table 1. Unmatched sample baseline characteristics according to treatment of the first bleeding episode (bypassing agent vs FVIII or DDAVP and rFVIIa vs aPCC)

Variable	Bypassing agent, median (IQR)	FVIII or DDAVP, median (IQR)	P*	rFVIIa, median (IQR)	aPCC, median (IQR)	P†
Patients, n	219	69		159	60	
Age, y	73.0 (15.0-92.0)	73.0 (13.0-104.0)	.94	73.0 (15.0-91.0)	76.5 (24.0-92.0)	.02
Sex, n (%)			.07			.06
Female	109 (49.7)	26 (37.7)		73 (45.9)	36 (60.0)	
Male	110 (50.8)	43 (62.3)		86 (54.1)	24 (40.0)	
Weight, kg	69.0 (40.0-130.0)	69.0 (40.0-113.0)	.92	69.0 (40.0-130.0)	69.2 (44.0-107.0)	.70
FVIII level, IU/dL	1.0 (0.0-40.0)	3.0 (0.0-34.0)	.03	2.0 (0.0-32.0)	1.0 (0.0-40.0)	.13
Hb, g/dL	8.6 (3.0-15.2)	8.8 (3.3-14.4)	.57	8.6 (3.0-15.2)	8.4 (4.6-14.8)	.90
Inhibitor titer, BU/mL	15.4 (0.1-2765.0)	8.0 (0.3-200.0)	.0003	15.0 (1.0-2765.0)	17.0 (0.1-1700.0)	.99
Therapy delay, days	0.01 (0.0-0.5)	0.01 (0.00-0.11)	.34	0.01 (0.00-0.27)	0.01 (0.00-0.54)	.76
Ancillary antifibrinolytic therapy, n (%)	30 (13.7)	20 (29.0)‡	.0035	27 (17.0)	3 (5.0)	.0215
Cause of bleeding, n (%)			.715			.08
Unknown	1	0		1	0	
Traumatic	46 (21.1)	16 (23.2)		38 (24.1)	8 (13.3)	
Spontaneous	172 (78.9)	53 (76.8)		120 (75.9)	52 (86.7)	
Bleeding site, n (%)			.04			.12
CNS	5 (2.3)	0 (0.0)		5 (3.1)	0 (0.0)	
Deep muscle	139 (63.4)	32 (46.4)		94 (59.1)	45 (75.0)	
Hemarthrosis	6 (2.7)	3 (4.3)		5 (3.1)	1 (1.7)	
Mucosa	34 (15.6)	21 (30.5)		30 (18.8)	4 (6.6)	
Skin	34 (15.6)	13 (18.8)		24 (15.2)	10 (16.7)	
Multiple sites	1 (0.4)	0 (0.0)		1 (0.7)	0 (0.0)	
Severity of bleeding, n (%)			.031			.31
Unknown	1	0		1	0	
Severe	193 (88.5)	54 (78.2)		142 (89.8)	51 (85.0)	
Nonsevere	25 (11.5)	15 (21.8)		16 (10.1)	9 (15.0)	



Time to bleeding control (hrs)

blood

2012 120: 39-46
Prepublished online May 22, 2012;
doi:10.1182/blood-2012-02-408930

Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry

Francesco Baudo, Peter Collins, Angela Huth-Kühne, Hervé Lévesque, Pascual Marco, László

Table 2. Matched sample baseline characteristics according to treatment of the first bleeding episode (bypassing agent vs FVIII or DDAVP and rFVIIa vs aPCC)

Variable	Bypassing agent, median (IQR)	FVIII or DDAVP, median (IQR)	*P**	rFVIIa,† median (IQR)	aPCC, median (IQR)	*P**
Patients, n	60	60		57	57	
Age, y	74.0 (24.0-91.0)	72.5 (13.0-104.0)	.95	72.00 (39.00-91.00)	77.00 (24.00-92.00)	.41
Sex, n (%)			.69			.41
Female	25 (41.7)	23 (38.3)		37 (64.91)	33 (57.89)	
Male	35 (58.3)	37 (61.7)		20 (35.09)	24 (42.11)	
Weight, kg	70.0 (40.0-107.0)	68.0 (40.0-113.0)	.49	70.00 (40.00-120.00)	70.00 (44.00-107.00)	.66
FVIII level, IU/dL	2.0 (0.0-40.0)	3.0 (0.0-34.0)	.61	1.25 (0.00-32.00)	1.00 (0.00-40.00)	.41
Hb, g/dL	8.4 (3.0-14.2)	8.8 (3.3-14.4)	.41	8.50 (3.00-14.00)	8.40 (4.60-14.80)	.84
Inhibitor titer, BU/mL	9.3 (1.0-2765.0)	8.0 (0.3-200.0)	.52	16.00 (1.00-2765.00)	17.00 (0.10-1700.00)	.52
Therapy delay, d	0.01 (0.0-0.13)	0.01 (0.0-0.11)	.46	0.01 (0.00-0.09)	0.01 (0.00-0.54)	.64
Cause of bleeding, n (%)			.51			.62
Traumatic	16 (26.7)	13 (21.7)		10 (17.54)	8 (14.04)	
Spontaneous	44 (73.3)	47 (78.3)		47 (82.46)	49 (85.96)	
Bleeding site, n (%)			.99			.55
Deep	30 (50.0)	30 (50.0)		44 (77.19)	44 (77.19)	
Hemarthrosis	3 (5.0)	2 (3.3)		0 (0.00)	1 (1.75)	
Mucosa	15 (25.0)	16 (26.7)		5 (8.77)	4 (7.02)	
Skin	12 (20.0)	12 (20.0)		8 (14.04)	8 (14.04)	
Severity of bleeding, n (%)			.63			.56
Severe	47 (78.3)	49 (81.7)		49 (85.96)	51 (89.47)	
Nonsevere	13 (21.6)	11 (18.3)		8 (14.04)	6 (10.53)	

blood

2012 120: 39-46
Prepublished online May 22, 2012;
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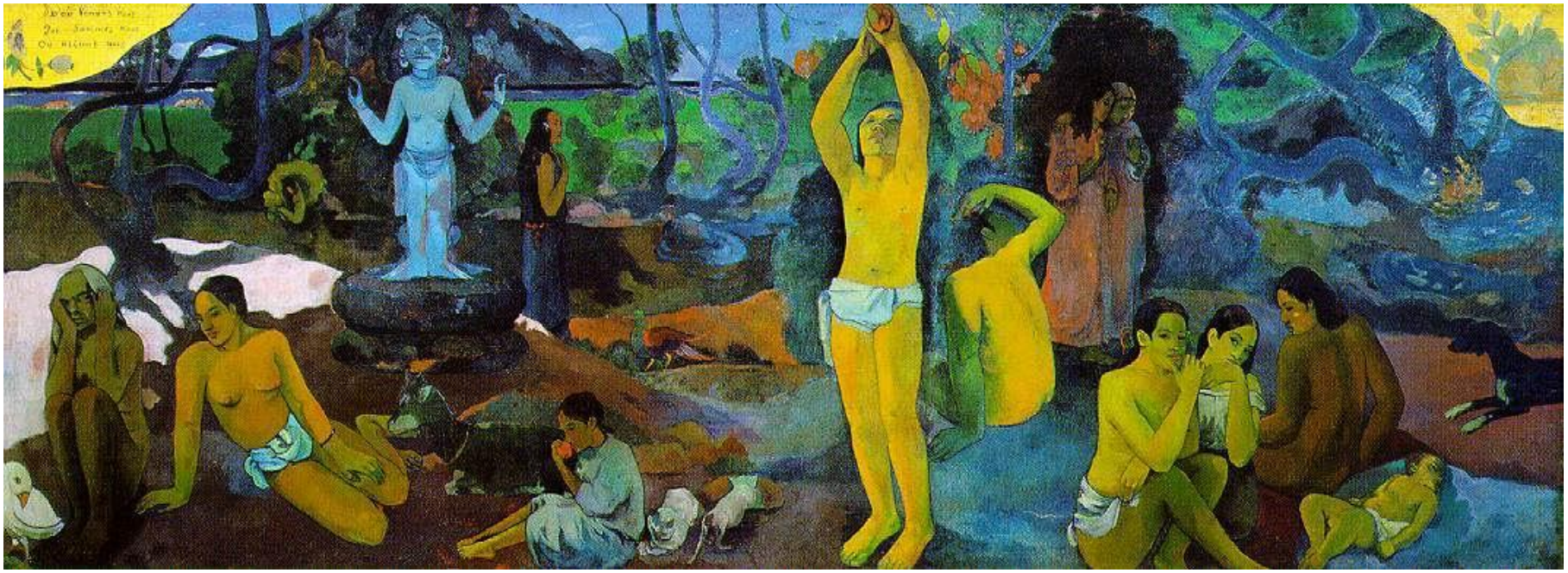
	rFVIIa	aPCC	FVIII/DDAVP
	Pts = 174	Pts = 63	Pts = 70
Thromboembolic events n (%)	5 (2.9)	3 (4.8)	0



Da dove veniamo? Che siamo? Dove andiamo?

Paul Gauguin, 1897

Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management

Massimo Franchini[1], Giancarlo Castaman[2], Antonio Coppola[3], Cristina Santoro[4], Ezio Zanon[5], Giovanni Di Minno[3,6], Massimo Morfini[7], Elena Santagostino[8], Angiola Rocino[9], on behalf of the AICE Working Group*

- Not all patients manifest clinically relevant bleeding when an acquired inhibitor develops/is diagnosed. In such cases treatment with haemostatic agents may not be required and the patients may be managed conservatively adopting a "wait and watch" approach **(Grade 2C recommendation)**.

- In patients with AHA and clinically significant bleeding, bypassing agents (APCC or rFVIIa) are the first-line treatment **(Grade 1B recommendation)**.

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), 1–9 DOI: 10.1111/hae.13033

Site of bleeding	n	Number of doses		Duration of therapy (days)		
		median	IQR	median	mean	IQR
Intramuscolar	110	5	3 - 13	2	3.4	1 – 4
Subcutaneous	33	3	3 - 7	1	2.3	1 – 2
Intra-articular	27	3	2 - 12	1	3.3	1 – 3
Genitourinary	11	8	3 - 24	2	4.2	2 – 6
Gastrointestinal	9	4	3.5 - 15	2	2.7	1 – 3
Intracranial	4	4.5	2 - 34.5	2	4.3	2 - 6.5
Oral	3	4	3.5 – 20.5	2.5	3	1.5 – 4.5
Intraperitoneal	2	19.5	3 - 36	4	4	2 – 6
Total	280	3	2 – 9	2	2.9	1 - 3

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Haemophilia (2016), 1–9 DOI: 10.1111/hae.13033

ORIGINAL ARTICLE

Treatment of acute bleeding in acquired haemophilia A with recombinant activated factor VII: analysis of 10-year

Table 4. Odds ratios (OR) for the response rate (300 bleeding episodes).

		OR	95% CI	*P* value
Initial dose (μg kg^{-1})	≥90	2.3	(1.4–3.9)	0.001
	<90			
Dosing interval (h)	≤3	1.5	(0.9–2.6)	0.136
	>3			

Response rate = (markedly effective + effective)/total. Bleeding episodes with insufficient dosage information are not included in this analysis.
CI, confidence interval.

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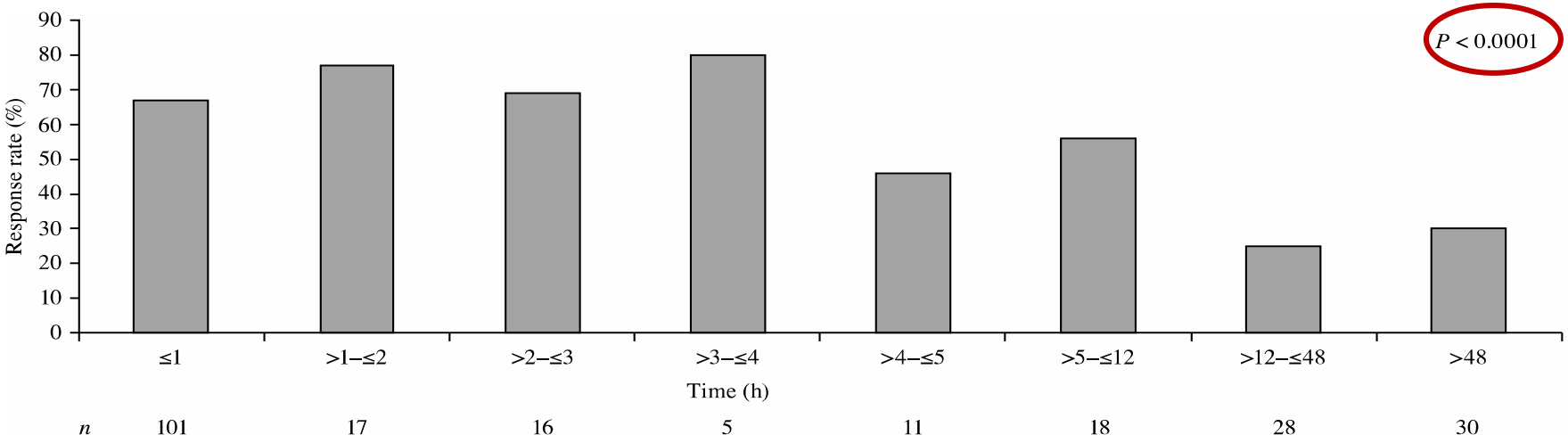
Haemophilia (2016), 1–9 DOI: 10.1111/hae.13033

Response rate according to the time from the onset of bleeding to the first dose of rFVIIa.



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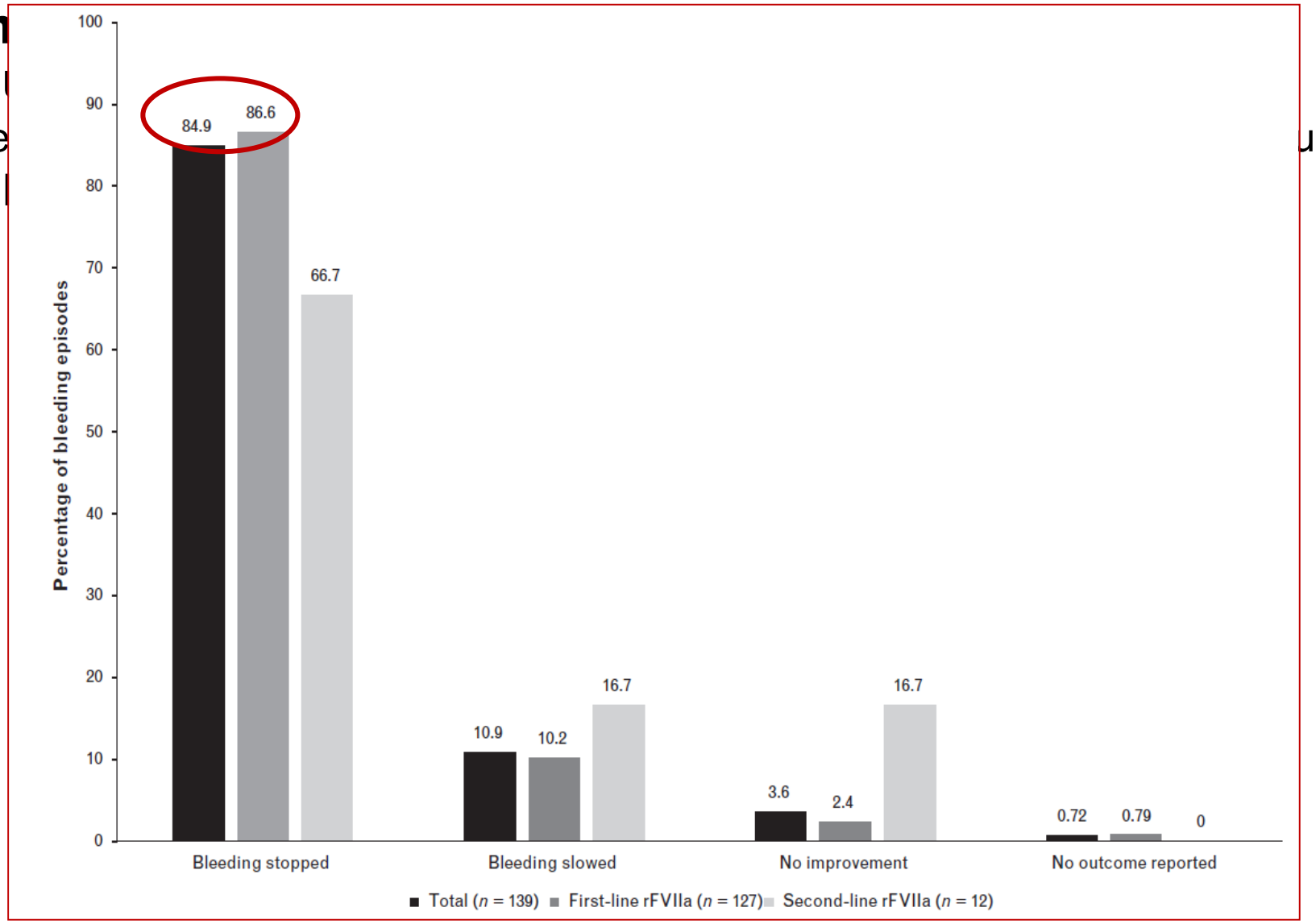
Haemophilia (2016), 1–9 DOI: 10.1111/hae.13033

Serious adverse events (SAE)

Case#	Pt y/sex	Underlying disease	SAE
1	87, F	Cholelithiasis Chronic rheumatoid arthritis	Pre-DIC (plt ↓ to 424 to 331) Acute cholecystitis
2	81,M	Lithotomy for choledocholitiasis Aspiration pneumonia	Sepsis DIC (**16 days after rFVIIa**)
3	70,M	Pontine haemorrhage due to AHA Aspiration pneumonia	Hydrocephalus Intestinal ischemia Intestinal necrosis (**6 days after rFVIIa**)
4	76,M	Prostate cancer	Hypotension (**4 days after rFVIIa**)
5	75,M	Pemphigus Pneumonia	Hepatic dysfunction (**24 days after rFVIIa**) Acute renal failure **(on the day of the 6th dose of rFVIIa)**

Use of recombinant activated factor VII for acute bleeding episodes in acquired hemophilia: final analysis from the Hem acqu

Alice ut[d] and



Blood Coagulation and Fibrinolysis 2016, **27**:753–760

Use of recombinant activated factor VII for acute bleeding episodes in acquired hemophilia: final analysis from the Hemostasis and Thrombosis Research Society Registry acquired hemophilia study

Alice D. Ma[a], Craig M. Kessler[b], Hamid A.B. Al-Mondhiry[c], Robert Z. Gut[d] and David L. Cooper[d]

Blood Coagulation and Fibrinolysis 2016, **27**:753–760

Table 2 Median (interquartile range) values for rFVIIa dosing and exposure in treatment of bleeding episodes

	First-line rFVIIa	Second-line rFVIIa
Number of episodes	127	12
Initial dose (μg/kg)	90 (87.1–100.0)	90 (90.0–97.0)
Dose per infusion (μg/kg)	90 (87.6–98.7)	90 (90.0–97.0)
Total dose per episode (μg/kg)	300 (118.7–1345.3)	576.9 (275.3–3430.0)
Number of injections (doses)	3 (1.0–13.5)	7 (3.5–25.0)
rFVIIa treatment duration (days)	1 (0–2.5)	1.5 (0.8–4.1)
Total treatment duration (days)	1 (0–4.0)	7.5 (0.8–13.5)

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Blood Coagulation and Fibrinolysis 2016, **27**:753–760

Thromboembolic events			
Case#	**Pt y/sex**	**Underlying disease**	**SAE**
1	31, F	*AHA post-partum, initially treated with FFP (3-day period), 24 units of pRBCs (unknown period), and platelets (?) without improvement. Then the patient began treatment with rFVIIa and the bleeding episode was resolved after 72 h. Despite resolution of the bleeding episode, rFVIIa treatment regimen was continued for an additional 7 days.*	The patient developed an acute cerebrovascular accident. NMR revealed multiple small infarcts bilaterally in the frontal lobes. The neurologist reported that it was most likely related to eclampsia and vasculitis given the patient's medical history.

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), 22, e18–e24 DOI: 10.1111/hae.12852

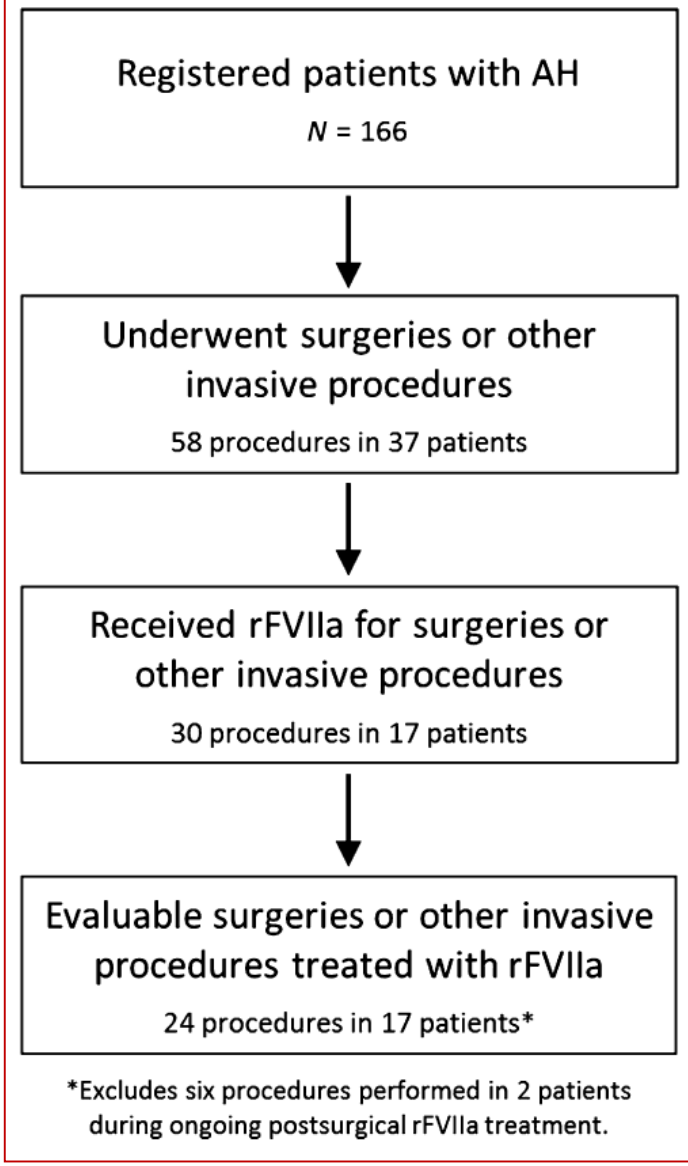

Table 3. rFVIIa treatment.

Dosing parameter (per procedure)	Preoperative median (range), $n = 11$	Postoperative median (range), $n = 13$	Total treatment median (range), $n = 24$
Initial dose (μg per kg)	90.0 (44–187)	106.0 (56–270)	96.1 (44–270)
Average infused dose (μg per kg)	90.0 (44–155)	93.0 (43–200)	91.5 (43–200)
Total dose (μg per kg)	120.0 (44–4802)	1770 (96–6229)	399.0 (44–6229)
Number of injections	1.0 (1–31)	15.0 (1–77)	4.0 (1–77)
rFVIIa treatment duration (days)	0 (0–9)	4.5 (0–19)	0 (0–19)
Total treatment duration (days)	0 (0–9)	5.0 (0–41)	2 (0–41)

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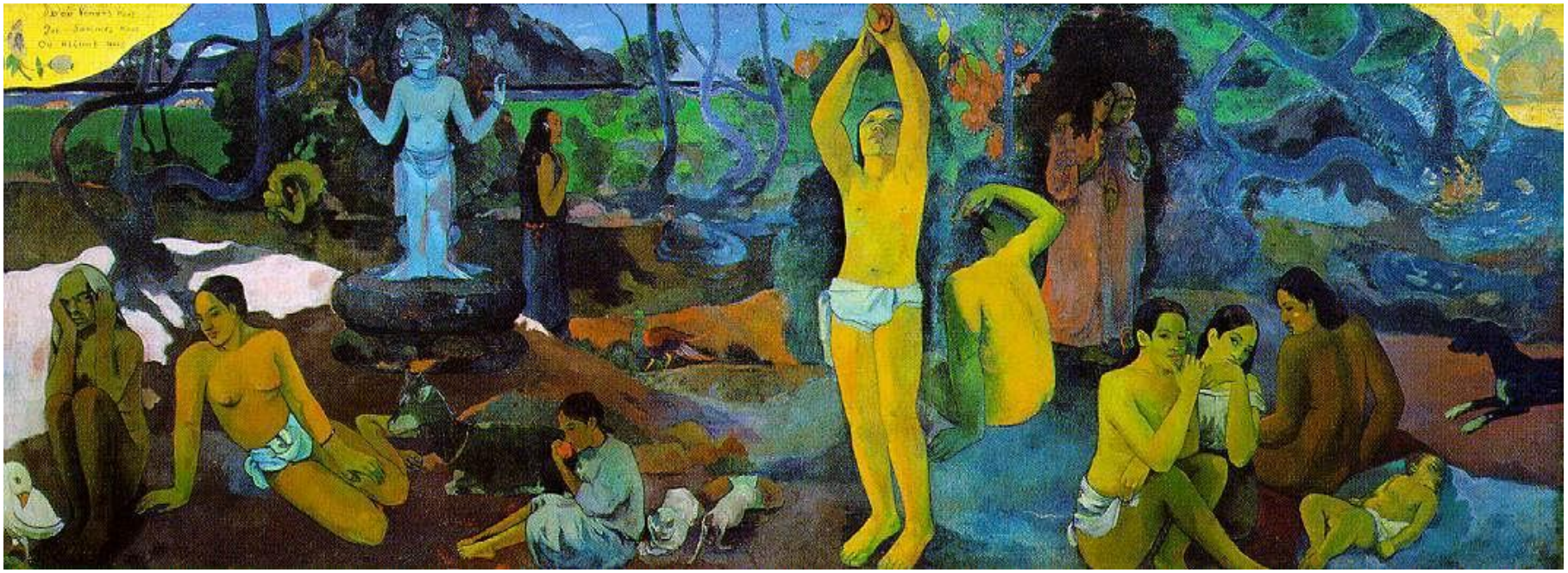
Haemophilia (2016), **22**, e18–e24 DOI: 10.1111/hae.12852

- ✓ *In 20 of 22 (91%) rFVIIa-treated surgical and other invasive procedures with a reported haemostatic outcome, investigator assessments were judged as excellent/good or no other haemostatic agents were administered*
- ✓ *17 rFVIIa-treated procedures were rated excellent/good and three additional procedures were rated fair/partially effective or poor/ineffective, although no other medications were required for haemostasis*
- ✓ *No AEs, including thromboembolic events or CVAD related thromboses, were reported in relation to rFVIIa treatment in surgical or other invasive procedures in patients with AH.*



Da dove veniamo? Che siamo? Dove andiamo?

Paul Gauguin, 1897

Blood Transfus 2015; 13; 498-513

Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management

Massimo Franchini[1], Giancarlo Castaman[2], Antonio Coppola[3], Cristina Santoro[4], Ezio Zanon[5], Giovanni Di Minno[3,6], Massimo Morfini[7], Elena Santagostino[8], Angiola Rocino[9], on behalf of the AICE Working Group*

?

- If the initial bypassing agent is ineffective, the switch to treatment with the alternative agent should be considered at an early stage **(Grade 2C recommendation)**.

Haemophilia
The Official Journal of the World Federation of Hemophilia,
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the Hemostasis & Thrombosis Research Society

Haemophilia (2016), 1–9 DOI: 10.1111/hae.13033

ORIGINAL ARTICLE

Treatment of acute bleeding in acquired haemophilia A with recombinant activated factor VII: analysis of 10-year Japanese postmarketing surveillance data

For each bleeding episode, the investigators rated treatment as:

- ✓ *markedly effective (a haemostatic effect was observed <8 h after administration of the first dose of rFVIIa),*
- ✓ *effective (a haemostatic effect was observed after 8–12 h),*
- ✓ *moderate (a haemostatic effect was observed after >12 h) or*
- ✓ *ineffective (no haemostatic effect was observed or bleeding worsened).*

Haemostatic response was defined as the proportion of patients with either a markedly effective or effective response.

Use of recombinant activated factor VII for acute bleeding episodes in acquired hemophilia: final analysis from the Hemostasis and Thrombosis Research Society Registry acquired hemophilia study

Alice D. Ma[a], Craig M. Kessler[b], Hamid A.B. Al-Mondhiry[c], Robert Z. Gut[d] and David L. Cooper[d]

Blood Coagulation and Fibrinolysis 2016, **27**:753–760

Treatment response was classified by investigators into the following categories:

- ✓ *bleeding stopped,*
- ✓ *bleeding slowed, but not stopped (with additional subclassifications of 'no additional medications given after rFVIIa,' 'additional blood products given after rFVIIa, with bleeding stopped,' and 'additional hemostatic agents given, with bleeding stopped'),*
- ✓ *no improvement (with additional subclassifications)*
- ✓ *inadequate rFVIIa trial*

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), 1–8 DOI: 10.1111/hae.13040

ORIGINAL ARTICLE

Table 1. Patient and disease characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Male	Female	Male	Male	Female	Male	Male
Age, years	90	24	78	83	56	83	64
Initial presentation (location)	ED	Academic hospital	Community hospital	Nursing home	PCP	ED	ED
Time from presentation to haematology consultation	14 days	6 days	10 days*	6 weeks	17 days	15 days	5 days
Conditions potentially associated with AHA	None identified	Abdominal sepsis and ertapenem exposure	Carcinoid tumour	None identified	Osteomyelitis	Prostate cancer	None identified
Major comorbidities	HTN, renal insufficiency	N/A	HTN, prostate cancer	HTN, prostate cancer, CKD stage III	Alcoholism, Charcot feet, morbid obesity, history of DVT	Dementia, prostate cancer	Diabetes, COPD, HTN, renal insufficiency
Time to cessation of bleeding	48 h	24 h	Bleeding did not stop	N/A*	24 h	A few hours	4 days
Other efficacy assessments	pRBC requirements, haematuria	Abdominal pain, transfusion requirements	CT	CT	Pain reduction	Cessation of haematuria	Arterial duplex
Adverse events	None	None	None	None	None	None	None
Outcome	Death not related to AHA after 168 days	Bleeding stopped and inhibitor eradicated	Death related to AHA in hospital from continued bleeding and sepsis with inhibitor present	Death related to AHA in hospital with inhibitor present	Survived with inhibitor eradication	Survived with inhibitor eradication	Bleeding resolved

Haemophilia
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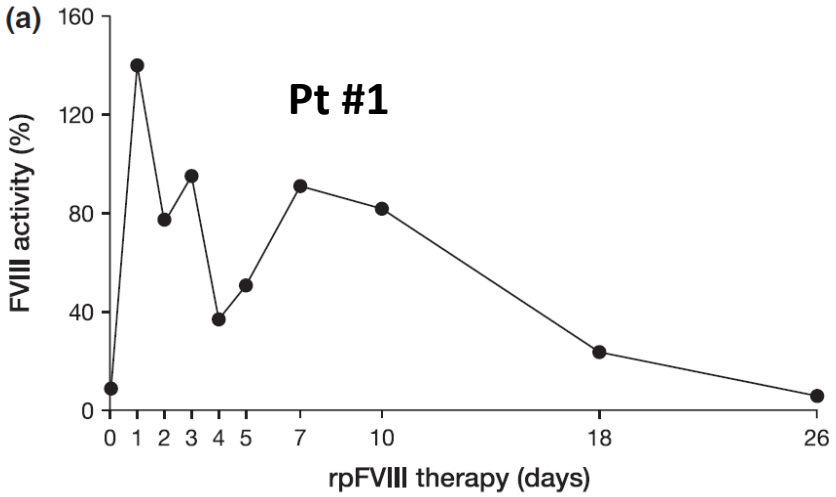
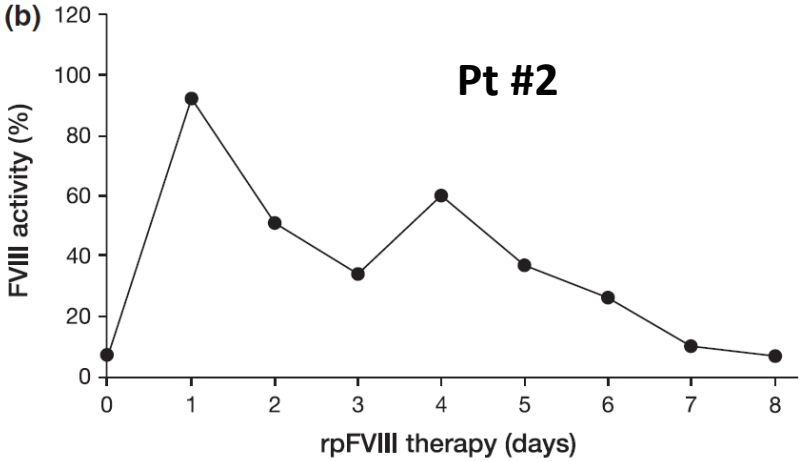
Haemophilia (2016), 1–8 DOI: 10.1111/hae.13040





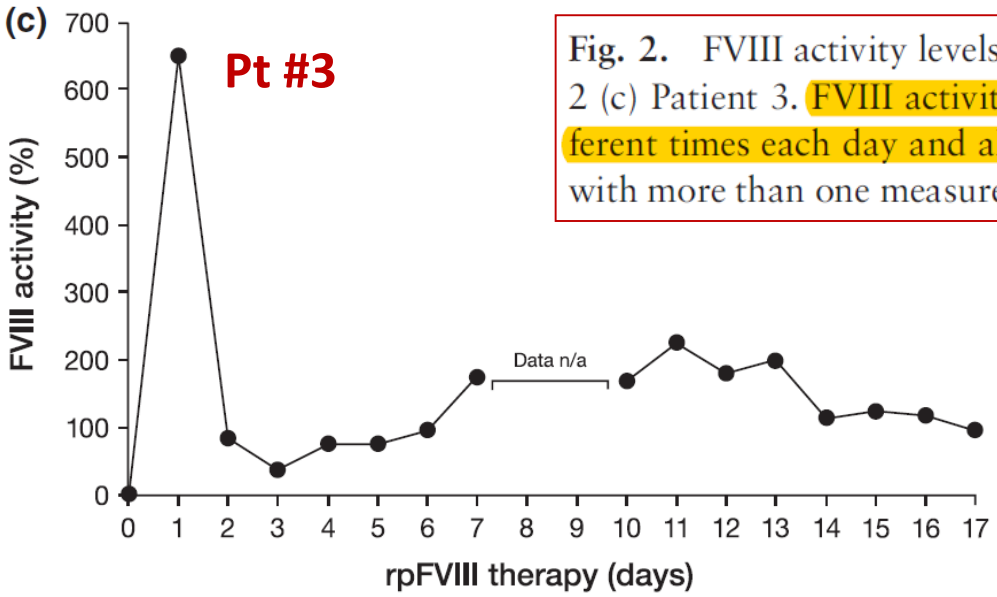


Fig. 2. FVIII activity levels during rpFVIII therapy (a) Patient 1 (b) Patient 2 (c) Patient 3. FVIII activity levels were measured 1–6 times a day, at different times each day and also with respect to rpFVIII dose. For those days with more than one measurement, the lowest was used in the figure.

Haemophilia
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the Hemostasis & Thrombosis Research Society

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ORIGINAL ARTICLE

Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients

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Table 3. Detailed summary of rpFVIII exposure.

Patient	Dose to stop bleeding U kg^{-1} (U)	Dose to prevent re-bleed U kg^{-1} (U)	Total dose U kg^{-1} (U)	Median dose U kg^{-1} (range)	Median infusions/day (range)	Total infusions	Total exposure days
1	290 (20 880)	1790 (128 880)	2080 (149 760)	50 (40–100)	2 (0.5–3)	43	26
2	100 (4500)	2000 (90 000)	2100 (94 500)	100 (100–200)	2 (1–3)	15	8
3*			1500 (162 000)	30 (30–100)	2 (1–4)	42	17
4*			427 (35 526)	71 (47–96)	3 (1–3)	6	3
5	250 (31 500)	1200 (151 200)	1450 (182 700)	50 (50–100)	1 (1–2)	28	24
6	200 (17 628)	200 (17 628)	400 (35 256)	50 (50–200)	1 (1–2)	5	4
7	100 (9702)	550 (53 362)	650 (63 064)	100 (50–100)	1 (1)	7	14
Mean			1230 (103 258)			21	14
Median			1450 (94 500)			15	14

*Bleeding did not completely stop.

(*Blood*. 2015;125(7):1091-1097)

Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study

Andreas Tiede,[1] Robert Klamroth,[2] Rüdiger E. Scharf,[3] Ralf U. Trappe,[4,5] Katharina Holstein,[6] Angela Huth-Kühne,[7]

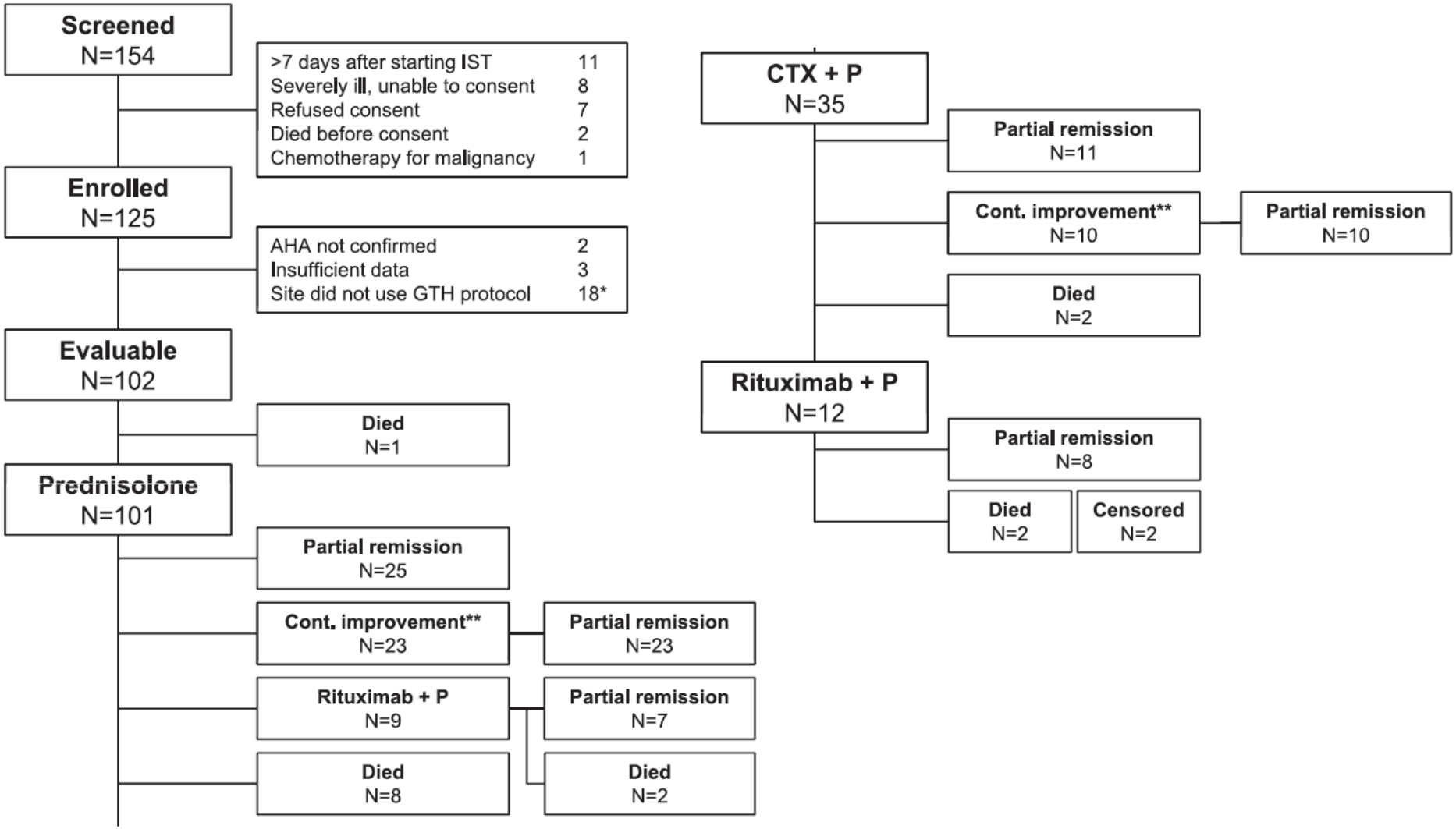

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Table 4. Predictors of remission and survival: multivariate analysis

Baseline variable	PR	CR	OS
FVIII activity <1 IU/dL	0.52 (0.33-0.81)**	0.49 (0.29-0.85)*	2.40 (1.10-5.22)*
Inhibitor concentration >20 BU/mL	0.77 (0.49-1.21)	0.75 (0.43-1.29)	1.20 (0.54-2.67)
Female gender	1.22 (0.77-1.91)	1.30 (0.76-2.24)	0.58 (0.26-1.31)
Age >74 y	0.94 (0.58-1.50)	0.76 (0.43-1.32)	1.76 (0.82-3.78)
Underlying disorder			
Autoimmunity	1.32 (0.77-2.28)	0.88 (0.45-1.72)	1.02 (0.36-2.84)
Malignancy	0.58 (0.28-1.21)	0.62 (0.27-1.44)	2.91 (1.12-7.52)*
Pregnancy	0.61 (0.23-1.65)	0.74 (0.27-2.04)	—
WHO-PS >2	0.76 (0.48-1.21)	0.39 (0.21-0.72)**	3.38 (1.55-7.37)**

Data are presented as adjusted HR (CI).
*$P < .05$.
**$P < .01$.

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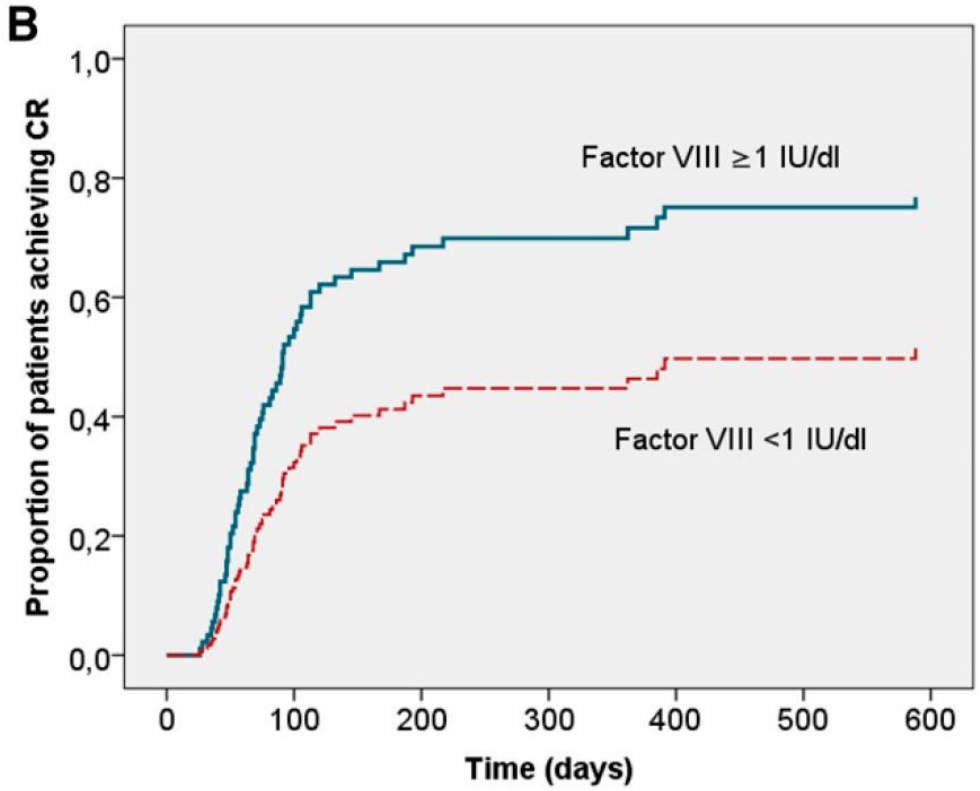

The challenge for future studies will be to develop IST regimens that reduce the burden of side effects, potentially by ***tailoring their intensity*** *to prognostic baseline characteristics established in the current study.*

J Thromb Haemost 2016; 14: 546–50.

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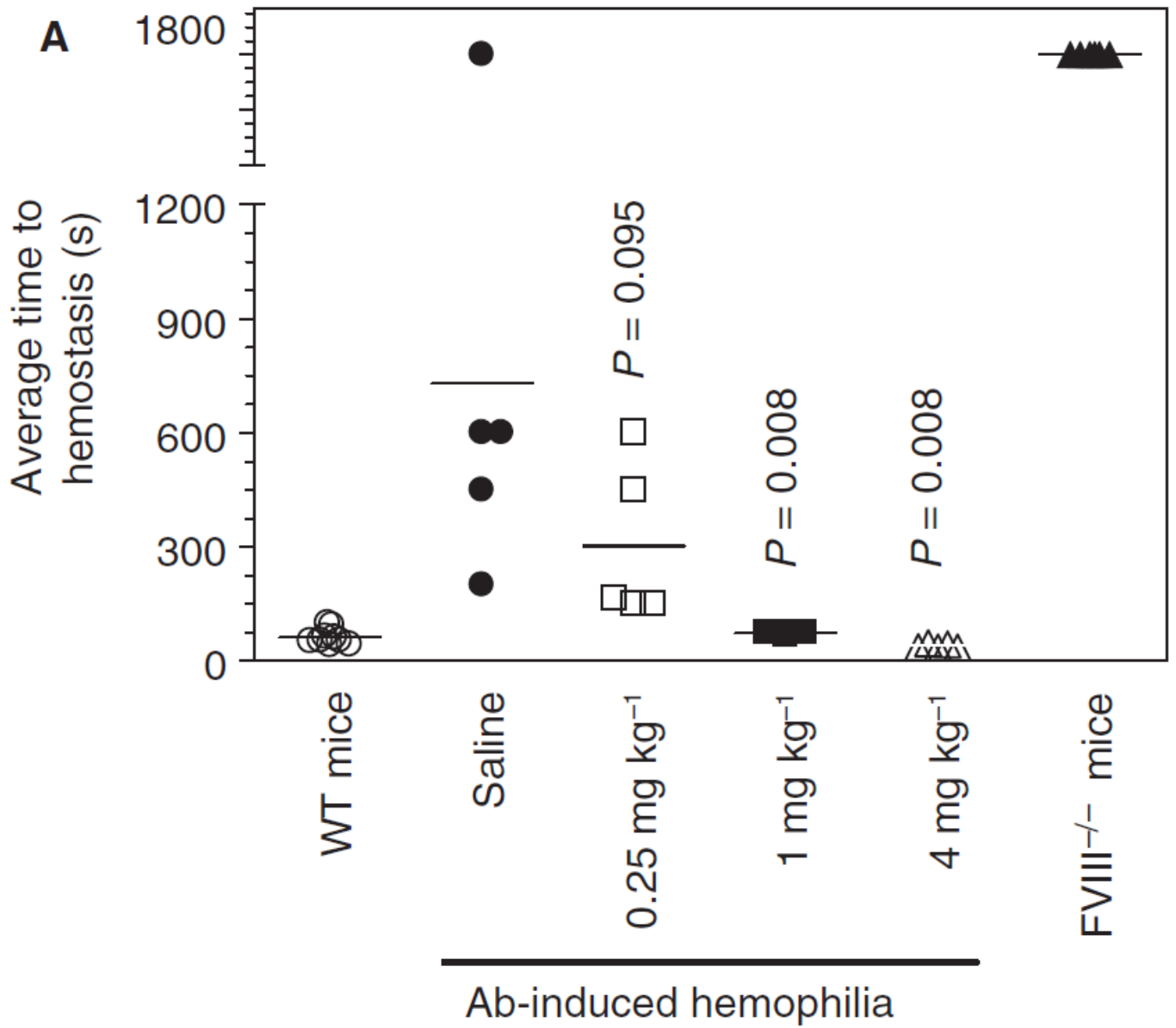
S. KESHA



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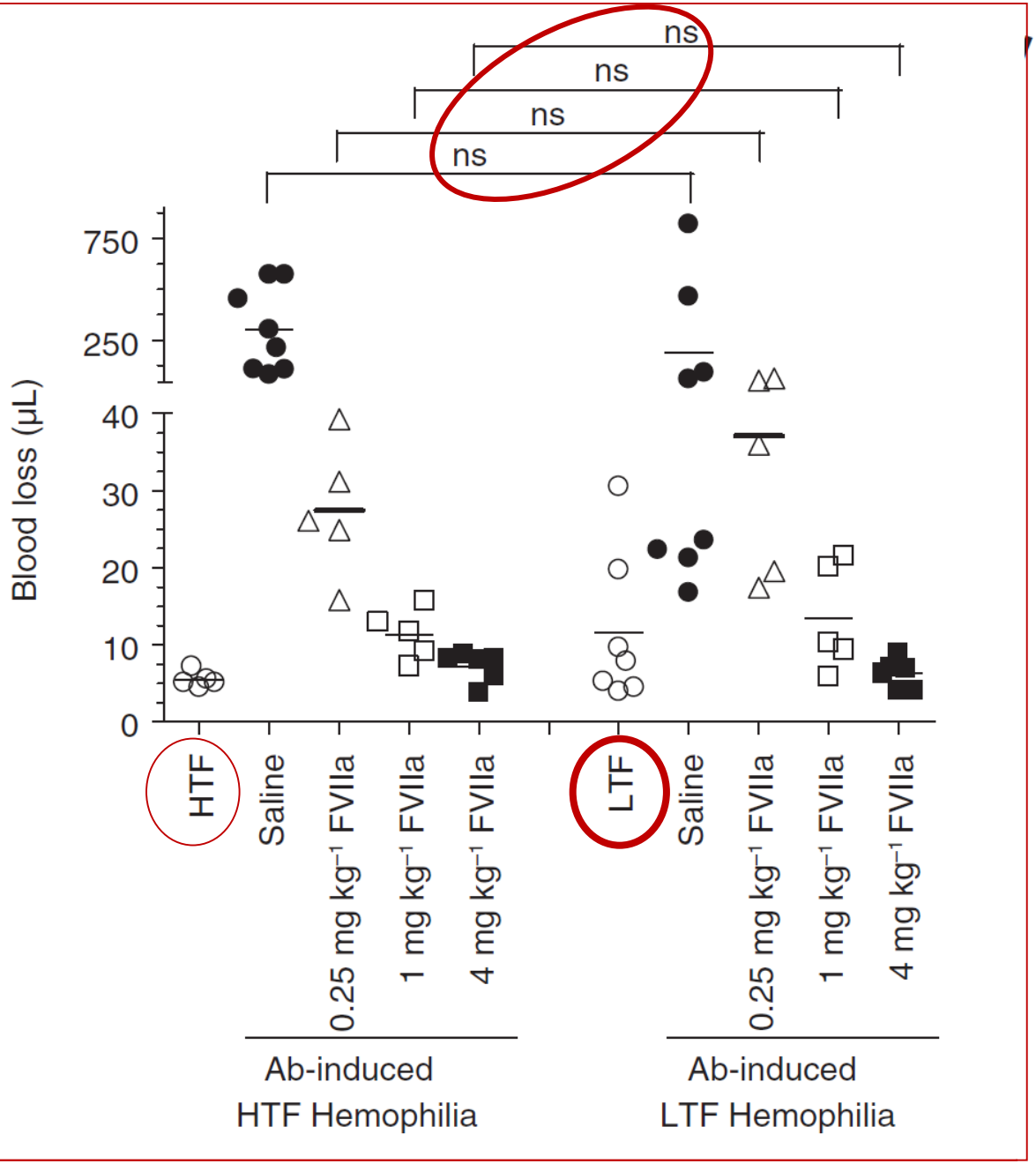
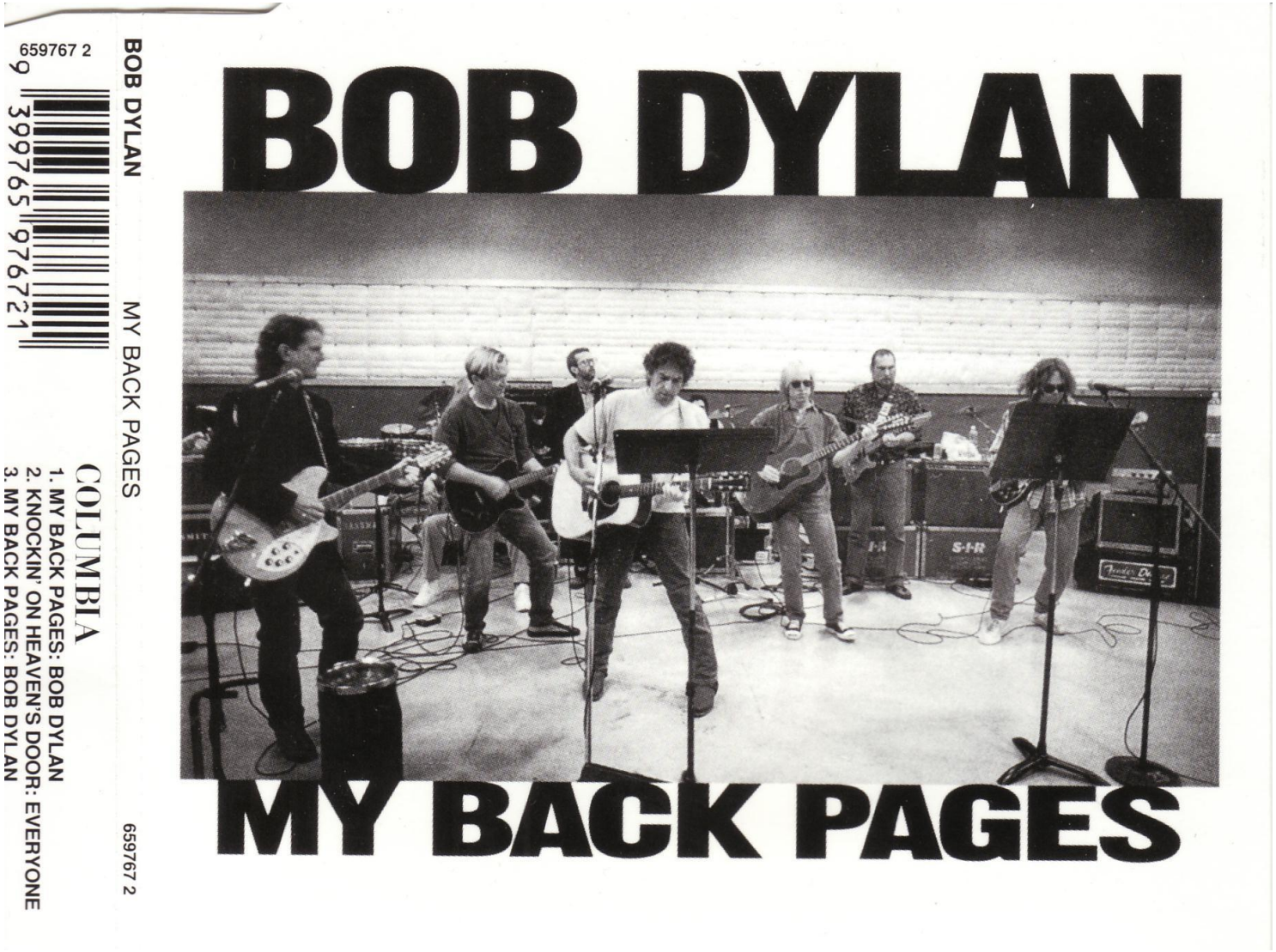


FOREVER YOUNG

BOB DYLAN



Ah, but I was so much older then
I'm younger than that now.