GTH Akademie
Highlights 2019
Aktuelle Entwicklungen in der Hämostaseologie

Hämophilie A und B

Christoph Male
Universitätsklinik für Kinder- und Jugendheilkunde
Medizinische Universität Wien
Österreich

MEDIZINISCHE UNIVERSITÄT WIEN

Urheberrecht, Copyright und Produkthaftung

Veranstalter und Herausgeber:

GTH Gesellschaft für Thrombose-und Hämostaseforschung e.V.
Geschäftsstelle
Hansaring 61
50670 Köln / Germany
Telefon +49 221 1612-516
Telefax +49 221 1612-100
mail@gth-online.org
www.gth-online.org

Wissenschaftliche Leitung / Steering Committee:

Prof. Dr. Andreas Tiede, Hannover
PD Dr. Jan Beyer-Westendorf, Dresden
Prof. Dr. Andreas Greinacher, Greifswald
Prof. Dr. Ingrid Pabinger, Wien
Prof. Dr. Barbara Zieger, Freiburg

Interessenskonflikte

Forschungsunterstützung:
Biotest, CSL Behring

Investigator in Studien:
Bayer, Biotest, CSL Behring, Novo Nordisk,Pfizer, Shire/Takeda

Honorare für Vorträge und Beratung:
Bayer, Biotest, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire/Takeda, SOBI

Unterstützung für Teilnahme an Kongressen und Fortbildungen:
Bayer, Biotest, CSL Behring, Novo Nordisk

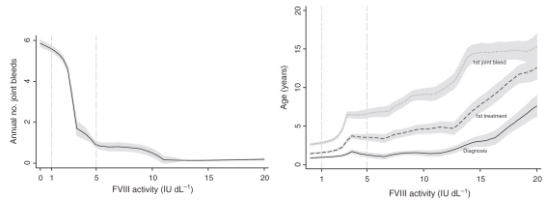
Haemophilie heute

Photo: E. Wissmann

Inhaltsübersicht

1. Hämophilie – die Fakten
2. Herausforderung für das Hämophiliemanagment heute
   a. Optimale Prophylaxe
      - Highlight: *Spinartstudie*
   b. Herausforderung Venenzugang
      - Highlight: *Arterio-venöse Shunts*
   c. Inhibitorentwicklung
      - Highlight: *FranceCoag PUP study*

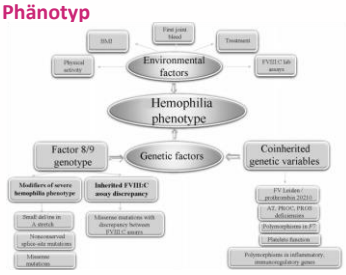
Faktorspiegel und Blutungshäufigkeit



Den Uijl, Clinical severity of haemophilia A: does the classification of the 1950s still stand? *Haemophilia* 2011;17:849-53

Haemophilie – die Fakten

Genotyp – Phänotyp Beziehung



Pavlova & Oldenburg, Defining severity of hemophilia: more than factor levels. Semin Thromb Hemost 2013;39:702–710.

10

Herausforderungen für das Hämophiliemanagment heute

- Optimale Prophylaxe
- Herausforderung Venenzugang
- Inhibitorentwicklung und -managment
- Auswahl des Faktorkonzentrates
- Kosten, globale Versorgung

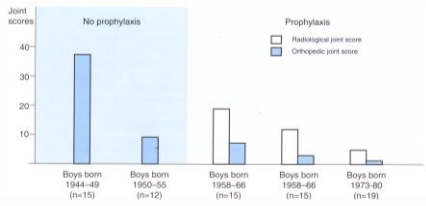
19

Optimale Prophylaxe

20

Haemophilie – Optimale Prophylaxe

Twenty-five years' experience of prophylactic treatment in severe haemophila A and B

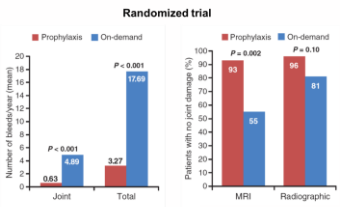


Nilsen IM et al, J Intern Med 1992

21

Haemophilie – Optimale Prophylaxe

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in boys with severe Hemophilia



Manco-Johnson et al, N Engl J Med 2007; 357. Abbildung modifiziert aus: Berntorp, Haemophilia 2009; 15:1219

22

Haemophilie – Optimale Prophylaxe

Prophylaxe

Vorteile

- Vermeidung lebensbedrohlicher Blutungen
- Vermeidung von Gelenksblutungen
- Vorbeugung der Arthropathie
- Verbesserung der Lebensqualität
- Niedrigeres Inhibitorrisiko

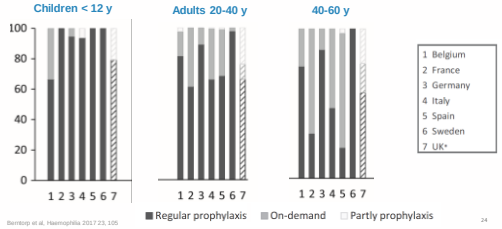
Herausforderungen

- 10% der Patienten bluten auch ohne Prophylaxe wenig
- Venenzugang
- Adhärenz
- Kosten

23

Häufigkeit der Prophylaxe – Europa 2012-2014

Schwere Hämophilie A



Berntorp et al. Haemophilia 2017 23, 105

Häufigkeit der Prophylaxe – USA 1999-2010

Schwere Hämophilie A

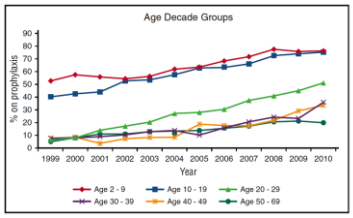


Figure 1. Trends in prophylaxis use for children and adults with severe hemophilia A from 1999 to 2010. The proportion of each participant age cohort (in decades) using continuous prophylaxis is displayed for each year of the study from 1999 to 2010.

Manco-Johnsen, Blood 2017

Prophylaxe - Definitionen

Table 1 Definitions of replacement therapy with clotting factor concentrates

Factor replacement therapy	Definition
Episodic 'on demand' replacement therapy	Replacement therapy given at the time of clinically evident bleeding
Regular replacement therapy	Replacement therapy given to prevent bleeding
Primary prophylaxis	Regular continuous* replacement therapy started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and age 3 years
Secondary prophylaxis	Regular continuous* replacement therapy started after two or more joint bleeds but before the onset of joint disease documented by physical examination and/or imaging studies
Tertiary prophylaxis	Regular continuous* replacement therapy started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent 'periodic' prophylaxis	Replacement therapy given to prevent bleeding for periods not exceeding 45 weeks in a year

*Continuous is defined as the intent to treat for 52 weeks/year and receiving a minimum of an *a priori* defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

Blanchette et al. Definitions in hemophilia: communication from the SSC of the ISTH. Haemophilia 2014; 12: 1935–9.

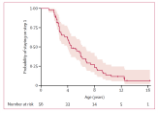
Philosophien für den Prophylaxebeginn

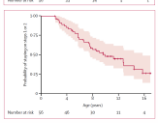
	Regimen	
	Swedish (Malmö model) [7]	Canadian [15]
Initiation criteria	Treatment is initiated early at 1–2 years of age or younger before the onset of joint bleeds	Treatment is initiated between 1 and 2.5 years of age; in the context of normal joints
Study protocol	FVIII (haemophilia A) or FIX (haemophilia B) at 20–40 U kg^{-1} every second/third day or minimum 3 or 2 times/week respectively, following initiation period (initiated at 250 IU/dose) All patients escalated to full-dose prophylaxis by approximately 2 years of age	Step 1* – FVIII administration at 50 U kg^{-1} once per week Step 2* – 30 U kg^{-1} twice weekly Step 3* – 'Full-dose prophylaxis' 25 U kg^{-1} on alternate days (or three times per week)

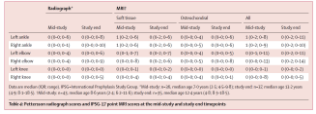
*Escalate if unacceptable bleeding is detected at any stage; unacceptable bleeding defined as 3+ bleeds into any one joint, or 4+ bleeds into any muscle/joint over 3 months, or 5+ bleeds into one joint while on a treatment step.

Aus: Carcao, Haemophilia 2010

Tailored frequency-escalated primary prophylaxis for haemophilia A: Canadian Hemophilia Prophylaxis Study







Konklusionen:

Primary, tailored frequency-escalated Prophylaxe führt zu
- guter Lebensqualität
- wenig Arthropathie
- relativ selten CVAD (38%)
- substantieller Kostenersparnis

im Vergleich mit anderen Prophylaxestudien

Feldman et al, Lancet Haematology 2018; 5: e252-60

Dosisempfehlungen für die Prophylaxe

Prophylactic dosing regimens for hemophilia A and B.

Prophylaxis	Hemophilia A		Hemophilia B	
	Dose (IU kg^{-1})	Frequency dosing (n/week)	Dose (IU kg^{-1})	Frequency dosing (n/week)
Utrecht protocol-Dutch (Low dose prophylactic regimen) [14]	15–30	Three	15–30	Two
Malmö protocol – Nordic (High dose prophylactic regimen) [17]	25–40	Three	25–40	Two
UKHCDO [16]	25–50	Four	Not provided*	
WFH [15]	According to Utrecht or Malmö protocol		According to Utrecht or Malmö protocol	

* Recommendations for patients with hemophilia B are not provided given the paucity of published evidence.

Aus: Hazendonk et al., Blood Reviews 2018.

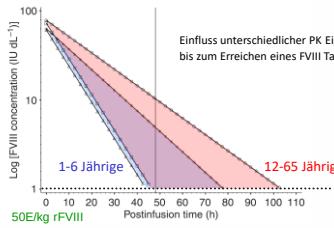
Maßgeschneiderte Prophylaxe

Anpassung von Frequenz und Dosis abhängig von

- Alter
- Gewicht
- Blutungshäufigkeit
- körperlicher Aktivität
- Synovitis bzw. Arthropathie
- individueller Faktor-Pharmakokinetik
- Halbwertszeit des Faktorproduktes

Ljung R et al. Practical considerations in choosing a factor VIII prophylaxis regimen: Role of clinical phenotype and trough levels. Thromb Haemost 2016;115:913-20

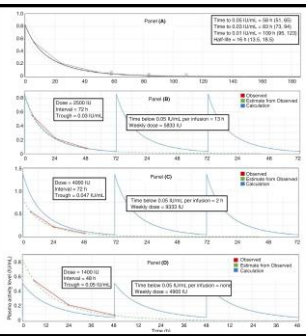
Interindividuelle Pharmakokinetik von FVIII



Collins et al. JTH 2010

PK-guided dosing

WAPPS-Hemo:
PopPK model & Bayesian approach



Iorio et al. Performing and interpreting individual PK Profiles in HA and HB. RPTH 2018; 2: 535-48.

Effect of late prophylaxis in hemophilia on joint status: a randomized trial.

Manco-Johnson MJ, Lundin B, Funk S, Peterfy C, Raunig D, Werk M, Kempton CL, Reding MT, Goranov S, Gercheva L, Rusen L, Uscatescu V, Pierdominici M, Engelen S, Pocoski J, Walker D, Hong W.

J Thromb Haemost 2017; 15: 2115–24.

SPINART study
Fragestellung

- Langzeiteffekte

  einer sekundären oder tertiären Prophylaxe

  im Vergleich mit einer Bedarfsbehandlung

Manco-Johnson et al. JTH 2017; 15: 2115–24.

SPINART study
Methodik

- Randomisiert kontrollierte, offene Studie,
- multiple Zentren USA, Argentinien, Bulgarien, Rumänien
- Studienperiode: 2008 - 2013
- Einschlußkriterien:
  - schwere Hämophilie A (1-2% FVIII, wenn klinisch schwerer Phänotyp)
  - >150 ED
  - kein FVIII Inhibitor
  - keine regelmäßigen Prophylaxe (>12 Monate) letzte 5 Jahre
  - 6-24 behandelten Blutungsereignissen letzte 6 Monate
- 1:1 Randomisierung:
  - Prophylaxe mit 25 E/kg KG 3x pro Woche (P)
  - Bedarfstherapie (OD)

Manco-Johnson et al. JTH 2017; 15: 2115–24.

Haemophilie – Optimale Prophylaxe

SPINART
Patienten-charakteristika

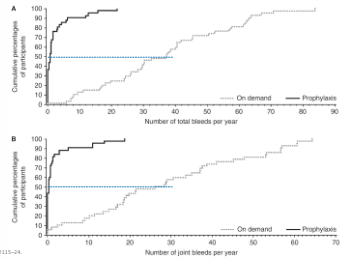
Table 1 Baseline characteristics, bleeding events during the study, and factor VIII exposure during the study

	On demand (n = 42)	Prophylaxis (n = 42)
Age (years)		
Median (range)	29 (17–48)	29 (15–50)
Race, n (%)		
White	38 (90.5)	38 (90.5)
Asian	1 (2.4)	1 (2.4)
Hispanic	3 (7.1)	3 (7.1)
Number of target joints/participant at baseline, n Median (range)	1.5 (0–7)	1.0 (0–5)
Participants with ≥ 1 target joint at baseline (%)	73.8	66.7
Follow-up days during the study		
Median (Q1; Q3)	1097 (1086; 1107)	1104.5 (1092; 1114)
Exposure days during the study		
Median (Q1; Q3)	155 (92; 205)	471 (433; 479)
Total bleeding events during the study (n)	4338	264
FVIII dose/infusion during the study (IU kg^{-1})		
Median (Q1; Q3)	27.8 (25.3; 33.9)	26.6 (26.0; 27.5)
FVIII consumption during the study (IU kg^{-1} per year)		
Median (Q1; Q3)	1700 (1124; 2263)	4102 (3904; 4312)

Manco-Johnson et al. JTH 2017; 15: 2115–24.

Haemophilie – Optimale Prophylaxe

SPINART Studie - Blutungshäufigkeit

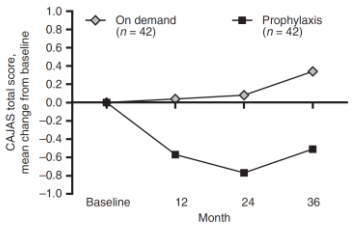


Manco-Johnson et al. JTH 2017; 15: 2115–24.

Haemophilie – Optimale Prophylaxe

SPINART Studie – Gelenksscores im Zeitverlauf

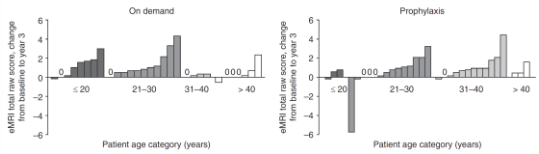
CAJAS: Colorado Adult Joint Assessment Scale



Manco-Johnson et al. JTH 2017; 1

Haemophilie – Optimale Prophylaxe

SPINART Studie – MRI Scores



Manco-Johnson et al. JTH 2017; 15: 2115–24.

Haemophilie – Optimale Prophylaxe

SPINART study
Bedeutung für die klinische Praxis

- Prophylaxe reduziert Blutungsfrequenz anhaltend über 3 Jahre
- gute Adhärenz
- Arthropathie (laut MRI) weiter zunehmend, ohne klare Gruppenunterschiede
  - kann strukturelle Gelenksveränderungen nicht aufhalten/rückgängig machen
- Funktionelle Gelenksscores verbessert
- Lebensqualität, Schmerzen, Aktivität, Teilnahme an Beruf und Freizeitaktivitäten verbessert, weniger Inanspruchnahme medizinischer Leistungen

➢ **Prophylaxe auch beim Erwachsenen als State-of-the-art Behandlung empfohlen**

➢ **Früh beginnen, optimalerweise vor relevanten Gelenksschäden**

Manco-Johnson et al. JTH 2017; 15: 2115–24.

Herausforderung Venenzugang

Haemophilie – Venenzugang

Herausforderung Venenzugang

- **Periphere Venenpunktion erste Wahl**
  - schwierig bei Kleinkindern, Prophylaxe, Immuntoleranztherapie
- **Zentrale Venenkatheter**
  - Risiko von Infektion, Thrombose, mechan. Komplikationen
- **Periphere Arterio-venöse Shunts**

Valentino LA, Ewenstein B, Navickis RJ, Wilkes MM. Central venous access devices in haemophilia. Haemophilia 2004;10:134–46

Haemophilie – Venenzugang

Periphere Arterio-venöse Shunts

GTH Akademie Highlights 2019

Cimino-Brescia Shunt | **Gracz Shunt**

Cimino, NEJM, 1966 | *Gracz, Kidney Int, 1977*

43

Haemophilie – Venenzugang

Periphere Arterio-venöse Shunts bei Hämophilie

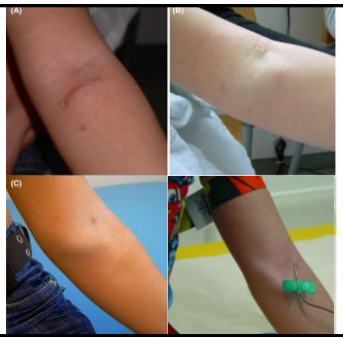
GTH Akademie Highlights 2019

British Journal of Haematology, 2003, **123**, 902–906

Long-term safety and feasibility of arteriovenous fistulae as vascular accesses in children with haemophilia: a prospective study

Elena Santagostino,[1] Alessandro Gringeri,[1] Luisa Berardinelli,[2] Claudio Beretta,[2] Myrvet Muça-Perja[1] and Pier Mannuccio Mannucci[1] [1]*Department of Internal Medicine, A. Bianchi Bonomi Haemophilia and Thrombosis Centre, IRCCS Maggiore Hospital and University of Milan, and* [2]*Division of Vascular Surgery and Kidney Transplantation, IRCCS Maggiore Hospital and University of Milan, Milan, Italy*

44



GTH Akademie Highlights 2019

Thom et al., Haemophilia 2018;24:429-35

45

ORIGINAL ARTICLE

WILEY Haemophilia

Haemophilia. 2018;1–7.

Arteriovenous shunts as venous access in children with haemophilia

K. E. Thom[1] | T. Hölzenbein[2] | N. Jones[3] | K. Zwiauer[4] | W. Streif[5] | S. Gattringer[2] | C. Male[1]

GTH Akademie Highlights 2019

Results	n (%) of patients
	median (minimum (min), quartile 1 (Q1), quartile 3 (Q3), maximum (max)
Cimino shunt (radialis-cephalic)	18 (70)
Gracz shunt (brachialis-cephalic)	8 (30)
Age at shunt creation	1.5 y (min 8 mo; Q1 1.2 y; Q3 3.0 y; max 11.7 y)
Indication for AVS creation and initial treatment	
prophylaxis	20 (74)
ITI	7 (26)
Shunt artery size	1.5 mm (0.5 mm; 2.5 mm)
Shunt vein size	2 mm (1.5 mm; 2.5 mm)
Maturation time (first punctures)	3 wk (min 1.3; max 18)
Punctures per month	12 (min 2; max 30)
Time from AVS surgery to home therapy	5 mo (min 0; max 2.7 y)
Age at start of home therapy	2.1 y (min 9 mo; max 11.7 y)

Complications	
Postoperative haematoma	2 (7)
Surgical revision/new anastomosis	4 (16)[a]
Maturation failure	1 (4)
Infection	0
Thrombosis	0
Follow-up	
Duration of follow-up	4.1 y (min 1.2; Q1 2.8; Q3 7.4; max 9.6 y)
Good long-term AVS function	26 (96)
Surgical shunt ligation	4 (15)
Spontaneous shunt occlusion	2 (7)
Time from AVS insertion to ligation/spontaneous occlusion	4.7 y (min 2.7; max 7.6 y)
AVS currently still functional	19 (70)

46

Haemophilie – Venenzugang

Periphere Arterio-venöse Shunts Bewertung

GTH Akademie Highlights 2019

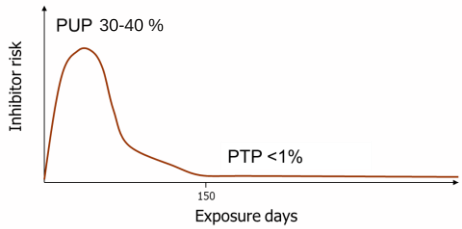
- AV-Shunts gute Alternative zu PACs
- Schlüsselfaktor: erfahrener Gefäßchirurg
- Risiko von Infektionen and Thrombose gering
- Cave: Verletzung, Armwachstum, hämodynamische Belastung
- Ermöglicht frühe Prophylaxe und Heimtherapie

Thom et al. Arteriovenous shunts as venous access in children with haemophilia. Haemophilia 2018;24:429-35

47

Inhibitorentwicklung

FVIII Inhibitorrisiko relativ zur Behandlungsphase



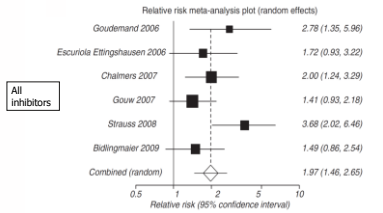
Einflußfaktoren für das Inhibitorrisiko

Endogen	Exogen (→ potentiell beeinflußbar)
Ethnizität	(Alter bei FVIII Erstexposition)
FVIII Genmutation	Intensive Behandlungsepisoden (Operationen; schwere Blutungen)
Familienanamnese für Inhibitor	Prophylaxe
HLA Genotype	Stimuli für das Immunsystem (?)
Polymorphismen in Immunerespons Genen	FVIII Konzentrattyp

Nach: Chambost et al. Haemophilia 2010

Metaanalyse zur Inhibitorentwicklung bei PUPs

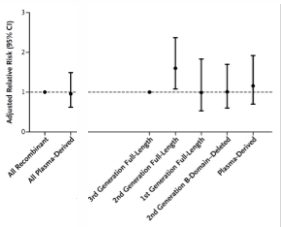
Plasmatische vs rekombinante FVIII Konzentrate



Iorio et al. Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review. J Thromb Haemost 2010; 8: 1256–65

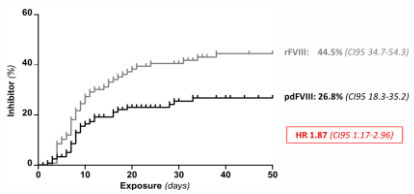
RODIN: FVIII Products and Inhibitor Development in Severe Hemophilia A

Kummulative Inhibitorinzidenz 32.4% (177 von 574)



Gouw et al. N Engl J Med 2013;368:231-9.

SIPPET: A Randomized trial of FVIII and Neutralising Antibodies in Hemophilia A



Peyvandi et al. N Engl J Med 2016

GTH Akademie Highlights 2019

Analyses of the FranceCoag cohort support differences in immunogenicity among one plasma-derived and two recombinant factor VIII brands in boys with severe hemophilia A

Calvez T, Chambost H, d'Oiron R, Dalibard V, Demiguel V, Doncarli A, Gruel Y, Huguenin Y, Lutz P, Rothschild C, Vinciguerra C, Goudemand J, for FranceCoag Collaborators

Haematologica 2018;103:179-89

GTH Akademie Highlights 2019

FranceCoag PUP study
Methodik

- Nationales Pharmakovigilanzsystem für Hämophilie seit 1994
- Subkohorte von PUPs mit schwerer Hämophilie A
- Einschluß vor Erstbehandlung, follow-up bis 75 ED
- Familienanamnese, Ethnik, Genotyp, Behandlungsdetails, schwere Blutungsepisoden, Operationen, etc.
- Studienperiode von 2001-2016
- Erstbehandlung mit
  - pFVIII: Factane
  - rFVIII: Advate, Kogenate FS/Helixate Nex Gen

GTH Akademie Highlights 2019

FranceCoag PUP study
Patienten-charakteristika

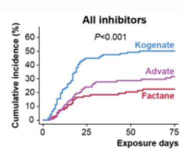
- N=395 PUPs
- 35 Zentren
Beobachtungszeit:
- 18.244 ED bzw.
- 560 Personenjahre

Table 1. Patients' characteristics according to the factor VIII product received.

Fixed risk factors	Factane (N = 131)	Advate (N = 137)	Kogenate (N = 127)	P
F8 gene defect — no. (%)				0.009
Low risk	37 (28.2)	33 (24.1)	27 (21.3)	
High risk*	83 (63.4)	97 (70.8)	100 (78.7)	
Undetermined (e.g., not yet tested, unidentified)	11 (8.4)	7 (5.1)	0 (0.0)	
High risk F8 gene defect known at first FVIII infusion	31 (23.7)	40 (29.2)	35 (27.6)	0.579
Family history — n. (%)				0.128
Hemophilia without inhibitor	47 (35.9)	57 (41.6)	38 (29.9)	
Hemophilia with inhibitor	7 (5.3)	13 (9.5)	15 (11.8)	
No family history of hemophilia	77 (58.8)	67 (48.9)	74 (58.3)	
Family history of hemophilia and inhibitor known at first FVIII infusion	3 (2.3)	9 (6.6)	6 (4.7)	0.243
Ethnic origin — n. (%)				0.372
White only (both parents)	91 (69.5)	100 (73.0)	93 (73.2)	
Other, not African or Afro-American	27 (20.6)	25 (18.2)	29 (22.8)	
African or Afro-American (at least one grandparent)	13 (9.9)	12 (8.8)	5 (3.9)	
Calendar period of first exposure to FVIII — n. (%)				<0.001
2001-2003	21 (16.0)	0 (0.0)	34 (26.8)	
2004-2006	16 (12.2)	35 (25.5)	22 (17.3)	
2007-2009	37 (28.2)	36 (26.3)	35 (27.6)	
2010-2012	18 (13.7)	31 (22.6)	31 (24.4)	
2013-2016	39 (29.8)	35 (25.5)	5 (3.9)	
Age at first exposure to FVIII — n. (%)				0.063
Less than 6 months	44 (33.6)	39 (28.5)	26 (20.5)	
6-11 months	41 (31.3)	54 (39.4)	43 (33.9)	
At least 12 months	46 (35.1)	44 (32.1)	58 (45.7)	
Risk factors at first exposure (fixed risk factors)				
Peak treatment episode at first exposure — n. (%)				
At least 3 consecutive EDs	38 (29.0)	40 (29.2)	37 (29.1)	0.999
At least 5 consecutive EDs	26 (19.8)	20 (14.6)	22 (17.3)	0.523
At least 10 consecutive EDs	14 (10.7)	10 (7.3)	11 (8.7)	0.618
First exposure linked to surgical procedure (with at least 3 EDs) — n. (%)	7 (5.3)	6 (4.4)	2 (1.6)	0.259
First exposure linked to severe bleeding episode — n. (%)	11 (8.4)	14 (10.2)	15 (11.8)	0.661
Risk factors at any time (time-varying risk factors)				
History of peak treatment episodes (≥1 during follow-up) — n. (%)				
≥3 consecutive EDs	86 (65.6)	90 (65.7)	83 (65.4)	0.998
≥5 consecutive EDs	56 (42.7)	50 (36.5)	46 (36.2)	0.470
≥10 consecutive EDs	21 (16.0)	18 (13.1)	18 (14.2)	0.793
History of surgical procedures (with ≥3 EDs) during follow-up — n. (%)	21 (16.0)	19 (13.9)	12 (9.4)	0.282
History of severe bleeding episodes during follow-up — n. (%)	14 (10.7)	17 (12.4)	18 (14.2)	0.687
Initiation of regular prophylaxis				0.1538
N. (% according to Kaplan-Meier estimator) at 25 EDs	51 (65.4)	63 (74.1)	40 (60.6)	
N. (% according to Kaplan-Meier estimator) at 50 EDs	73 (93.6)	80 (94.1)	61 (92.4)	

GTH Akademie Highlights 2019

Kummulative Inhibitorinzidenz
Nach FVIII Produkt



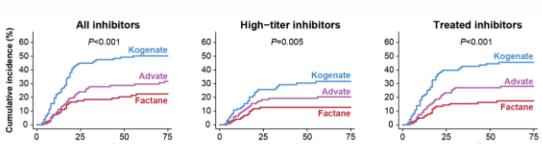
50.1% *(CI95 41.6-59.4)*
31.6% *(CI95 23.9-41.1)*
22.5% *(CI95 15.8-31.5)*

Kogenate vs Factane
Adjusted HR 2.7 (95%CI 1.7-4.5)

Advate vs Factane
Adjusted HR 1.4 (95%CI 0.8-2.4)

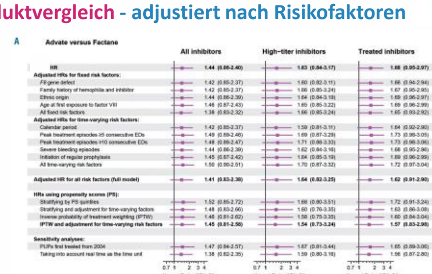
GTH Akademie Highlights 2019

Kummulative Inhibitorinzidenz
Nach FVIII Produkt



GTH Akademie Highlights 2019

Produktvergleich - adjustiert nach Risikofaktoren



Haemophilie – Inhibitoren

FranceCoag PUP study

Bedeutung für die Praxis

- Unterschiede in der Immunogenizität nicht nur zwischen Produktgruppen (pFVIII vs rFVIII), sondern auch zwischen individuellen FVIII Produkten
- pFVIII Produkte sind die erste Wahl für die Erstbehandlung von PUPs
- Systematisches Monitoring der Immunogenizität bei PUPs für alle neuen, vor allem modifizierte Faktorkonzentrate
- Können PUPs, nach Erstbehandlung mit pFVIII, nach darauffolgenden Wechsel auf rFVIII ihre Immuntoleranz aufrecht erhalten?

Calvez et al. Haematologica 2018; 103:179-189.

62

Herausforderungen für das Hämophiliemanagment heute

- Optimale Prophylaxe
- Herausforderung Venenzugang
- Inhibitorentwicklung und -managment
- Auswahl des Faktorkonzentrates (nächste Präsentation)
- Kosten, globale Versorgung

63

Herzlichen Dank für Ihre Aufmerksamkeit.

Fragen?

christoph.male@meduniwien.ac.at

64

GTH Akademie Highlights 2019

Aktuelle Entwicklungen in der Hämostaseologie

GTH Highlights 2020

Save the date: 08. – 09. Mai 2020

Besuchen Sie uns unter **gth-online.org** unter **„Termine"**