Inhibitors in Patients With Hemophilia

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Inhibitors in Hemophilia A

- Alloantibodies neutralizing FVIII coagulant activity
- Inhibitor incidence:
  - All patients with hemophilia A: 10%-15%
  - Patients with severe hemophilia A : 20%-30%
- The vast majority of inhibitors develops within the first 20 exposures to FVIII concentrate
- Detected by routine monitoring (Bethesda assay) or after lack of response to FVIII treatment

Inhibitors in Hemophilia A (cont)[a,b]

- Antibodies (IgG4) which neutralize FVIII
- Inhibitor titer assayed by Bethesda method

LOW TITER
< 5 BU/mL

HIGH TITER
≥ 5 BU/mL

- Inhibitor patients are distinguished on the basis of the anamnestic response to FVIII exposure

LOW RESPONDERS **HIGH RESPONDERS**

- **Transient inhibitors**:
  - Disappear spontaneously
  - No relevant impact on clinical management
  - Low titer inhibitors are often transient

a. Benson G, et al. *Eur J Haematol*. 2012;88:371-379. b. Kempton CL, et al. *Blood*. 2009;113:11-17.

Inhibitor Incidence by Age:
UKHCDO 1990-2009

Age, yr	Incidence, per 1000 pt yr
0-4	**64.3**
5-9	9.4
10-49	5.3
50-59	5.2
>60	**10.5**

Hay CR, et al. Blood. 2011;117:6367-6370.

Risk Factors for Inhibitor Development in PUPs[a-c]

Patient-related factors

Genetic factors

- *F8* gene mutation
- Family history of inhibitor formation
- Ethnicity
- Polymorphisms
  - Immune-regulating genes
  - MHC class II molecules

Non-genetic factors

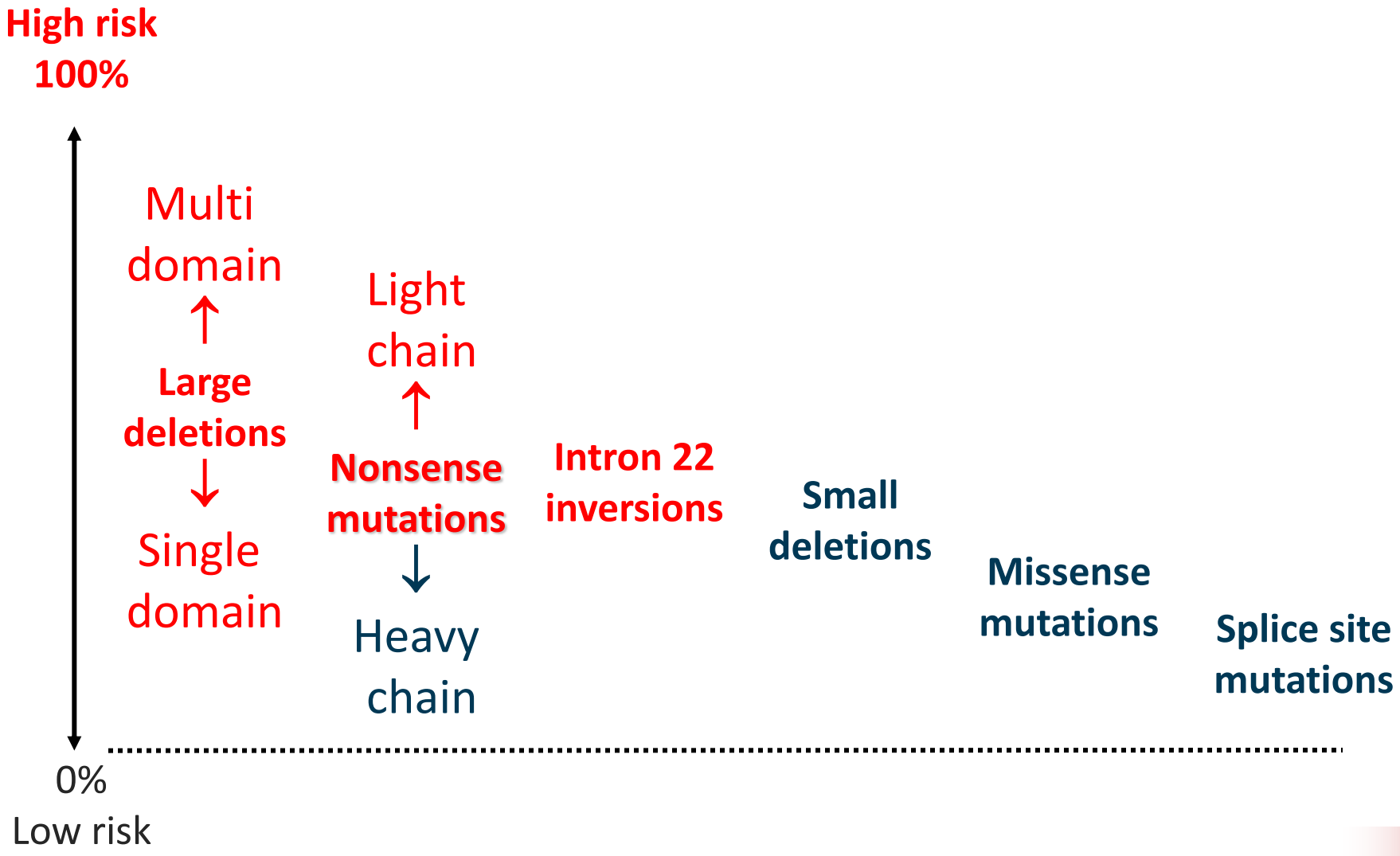
- Age
- Infections
- Vaccinations
- Trauma/surgery

Treatment-related factors

- Intensity and mode of FVIII treatment
- Prophylaxis
- Source of FVIII product (plasma-derived *vs* recombinant)
- Switching between products
- Extravasation of FVIII and continuous infusion

a. Tunstall O, et al. Eur J Haematol. 2015;94(Suppl 77):45-50. b. Álvarez T et al. Eur J Haematol. 2015;94(Suppl 77):2-6. c. Carcao M et al. Haemophilia. 2016;22:22-31.

Inhibitor risk and type of mutation



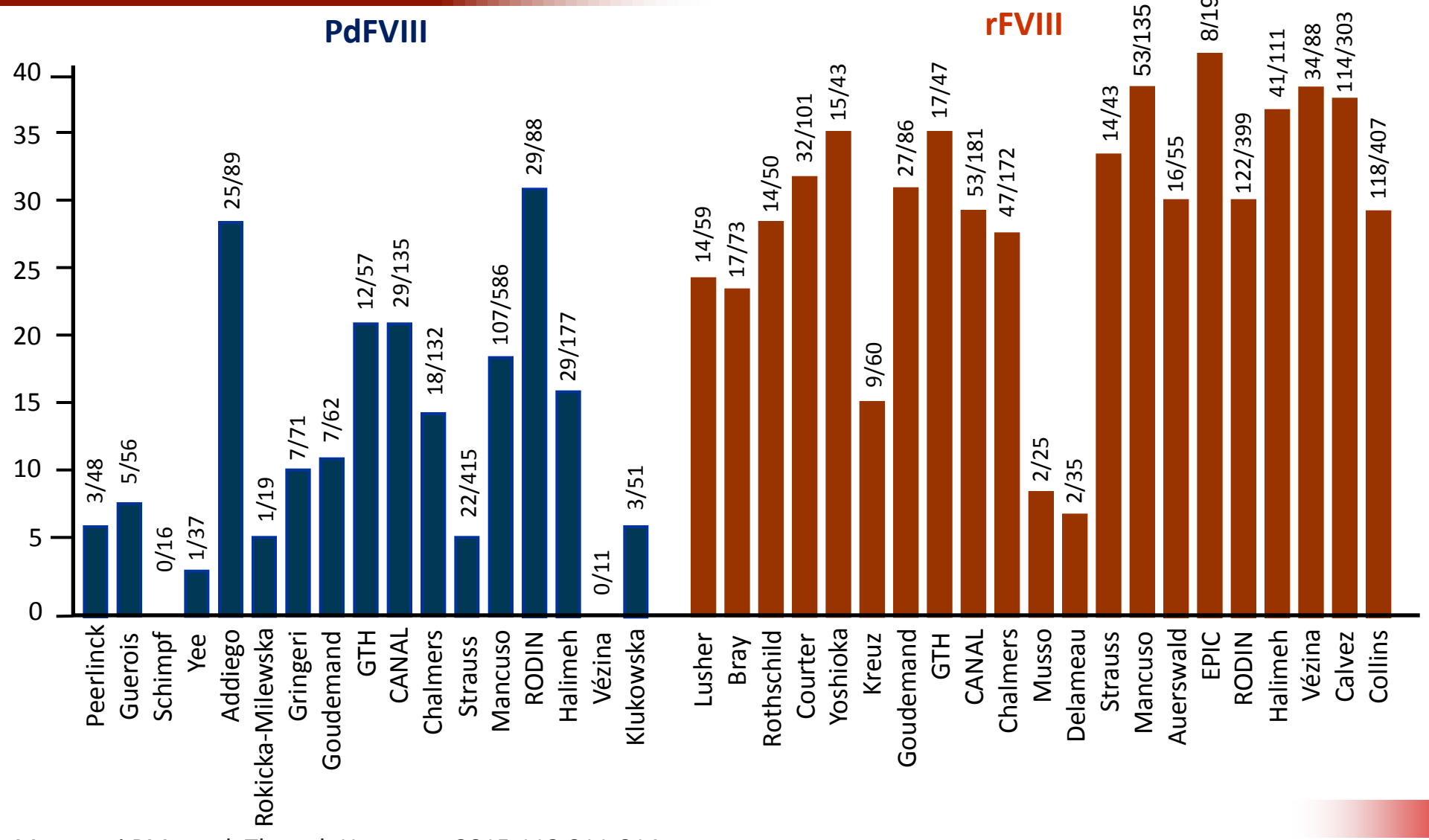
Gouw SC, et al. *Blood*. 2012;119:2922-2934.

Inhibitor Prevention in PUPs

Is It Possible? How?

- Treatment modality
- Intensive treatment
- Invasive procedures
- Inflammation/vaccinations
- Source/type of factor VIII

Crude Incidence of Inhibitors in Observational PUP Studies



Mannucci PM, et al. Thromb Haemost. 2015;113:911-914.

Results From Large Observational Studies

	rFVIII, no of patients (%)	pdFVIII, no of patients (%)
CANAL[a]	181	135
Inhibitor development (%)	53 (29%)	29 (21%)
RODIN[b]	486	88
Inhibitor development (%)	145 (30%)	29 (33%)
EUHASS[c]	366	51
Inhibitor development (%)	97 (26.5%)	11 (21.6%)

No difference in inhibitor rates between plasma-derived and recombinant FVIII product

a. Gouw SC, et al. Blood. 2007;109:4693-4697. b. Gouw SC, et al. Blood. 2013;121:4046-4055. c. Fischer K, et al. Thromb Haemost. 2015;113:968-975

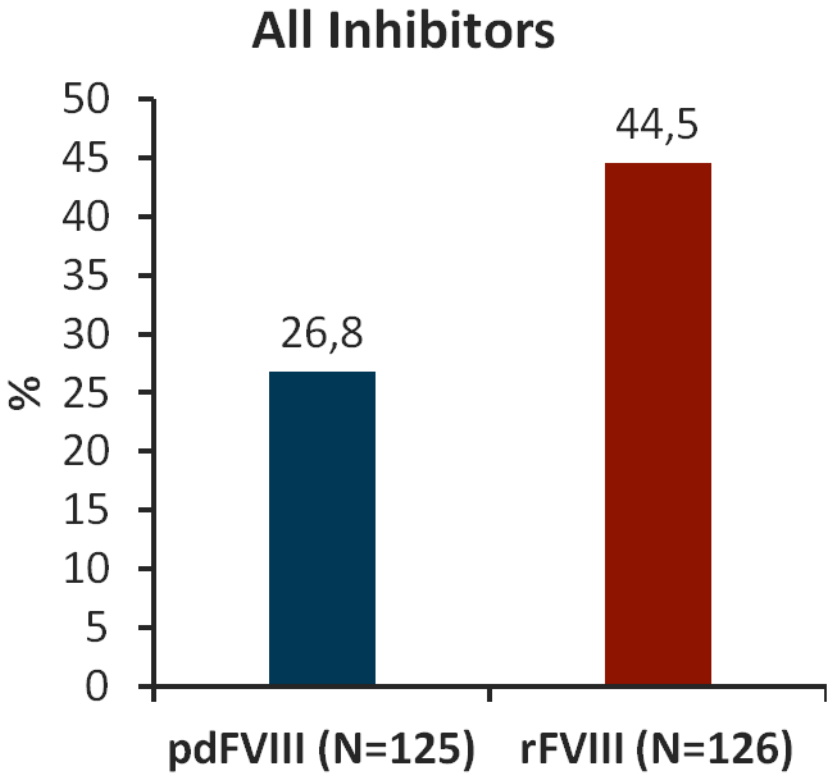
The SIPPET Study

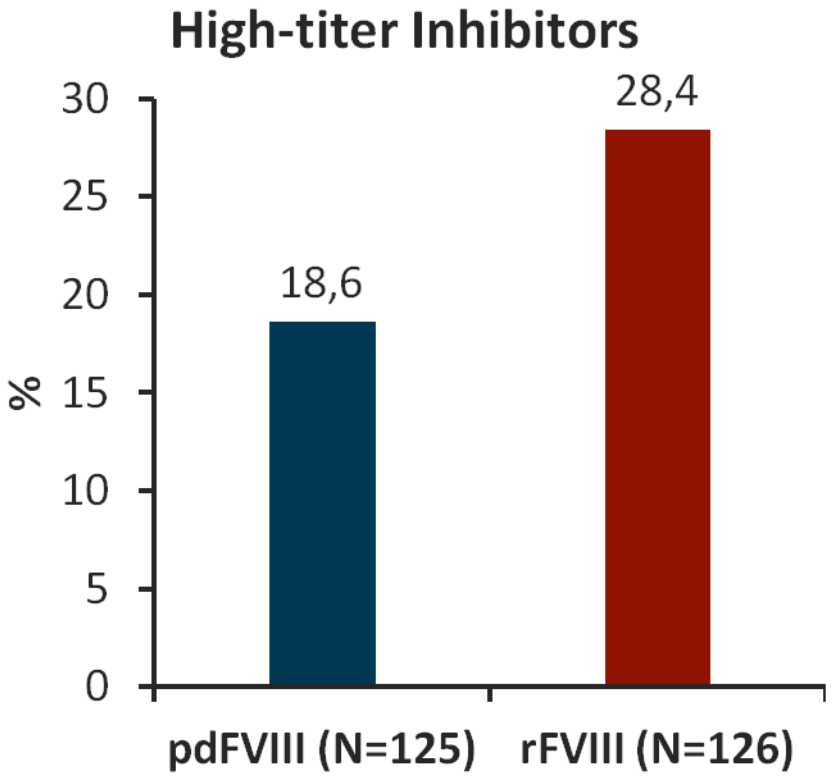
Randomized Trial of FVIII and Neutralizing Antibodies in Hemophilia A

- International, multicenter
- Open label
- Randomization block size 1:1
- Severe hemophilia A
- 0-5 years old
- PUPs or minimally exposed [<5 EDs with blood components, no concentrates]
- Negative for inhibitor at central lab
- Follow-up for 3 yrs, or 50 ED, or inhibitor development
- Primary endpoint: all inhibitors >0.4 BU/mL (Nijmegen Bethesda)
  - Secondary endpoint: high-titer inhibitors >5 BU/mL

Peyvandi F, et al. *N Engl J Med.* 2016;374:2054-2064.

Results: Inhibitor Development:
Cumulative Incidence

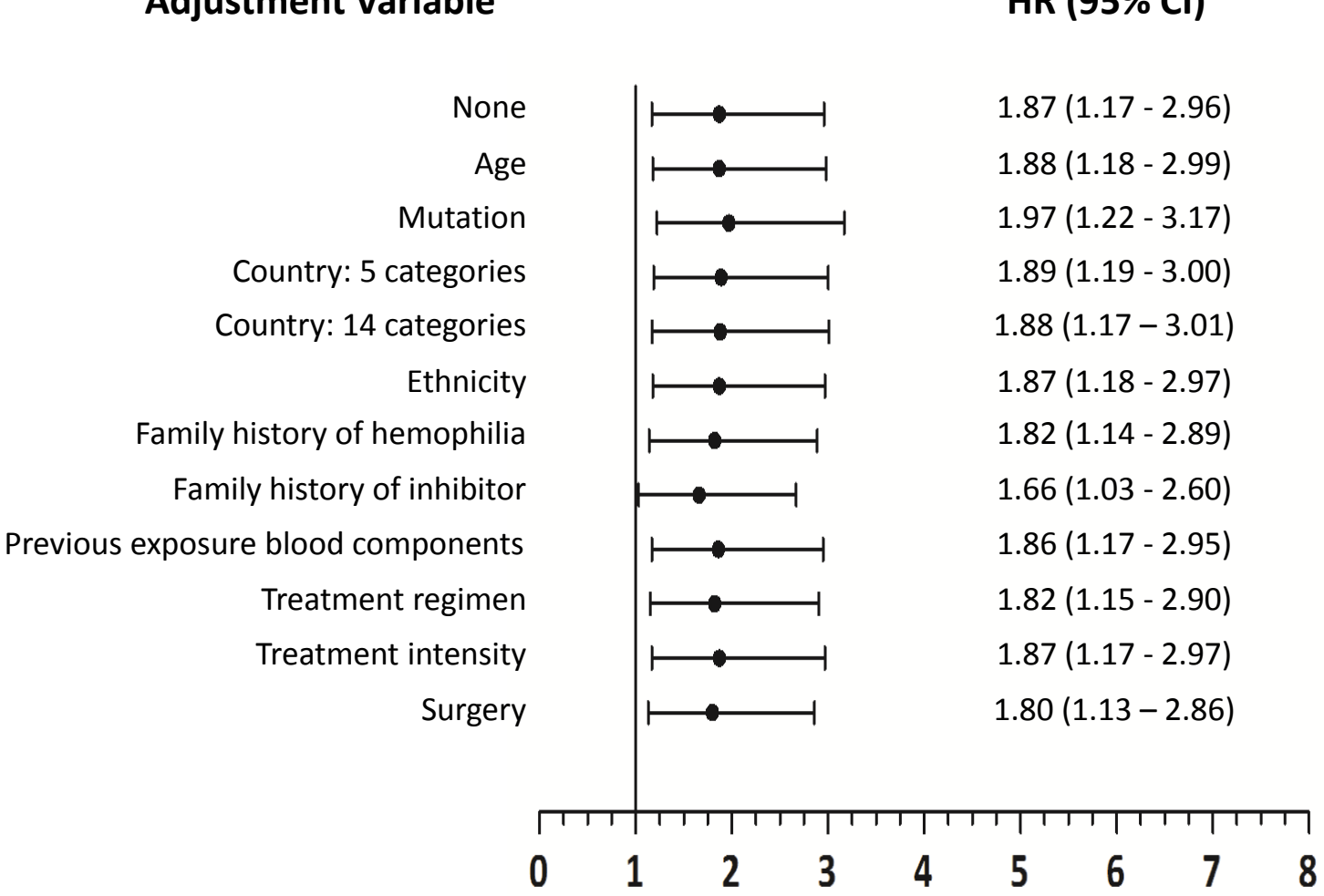




Peyvandi F, et al. *N Engl J Med.* 2016;374:2054-2064.

Results: Adjusted Estimates

Cox Regression Models



Peyvandi F, et al. *N Engl J Med.* 2016;374:2054-2064.

Prevention of FVIII Inhibitor Development in PUPs

- Inhibitors are a multi-factorial event
- A single targeted approach cannot expect to fully abolish their onset

Inhibitor risk (PTPs)

- ✓ Outbreaks of inhibitors occurred in multitransfused hemophiliacs in association with the use of new plasma-derived FVIII concentrates.
- ✓ Surveillance is important when a new product is introduced
- ✓ There is little evidence of inhibitor development in hemophiliacs switched from pdFVIII to rFVIII.

Inhibitor development in mild hemophilia A

International, retrospective data collection of 26 pts with mild hemophilia A and inhibitors:

- **median age at inhibitor onset: 33 years**
- **symptoms at onset: as acquired INHs**
- **response to exogenous FVIII: POOR**
- **response to DDAVP or rFVIIa: SATISFACTORY**
- **family history of inhibitors: 41%**
- **gene mutations: missense in A2 and C2 domains**

Thromb Haemost 79: 762-766, 1998

Inhibitors in hemophilia B (HB)

Much lower prevalence than in HA (3% vs 20-30%)

No apparent race effect

Anaphylactic reactions upon replacement therapy (10x more frequent than in HA with inhibitors)

Anaphylactic reactions

- Anaphylaxis arises more frequently than in HA, after a median of 11 exposure days
- Premedication only partly effective
- Not associated with dosage and inhibitor titer
- Patients with anaphylaxis may develop (sometimes irreversible) nephrotic syndrome
- Low success rate for ITI

Surveillance of anaphylaction reactions

Increased risk with complete gene deletion

Proceed to genotyping as soon as hemophilia B is diagnosed

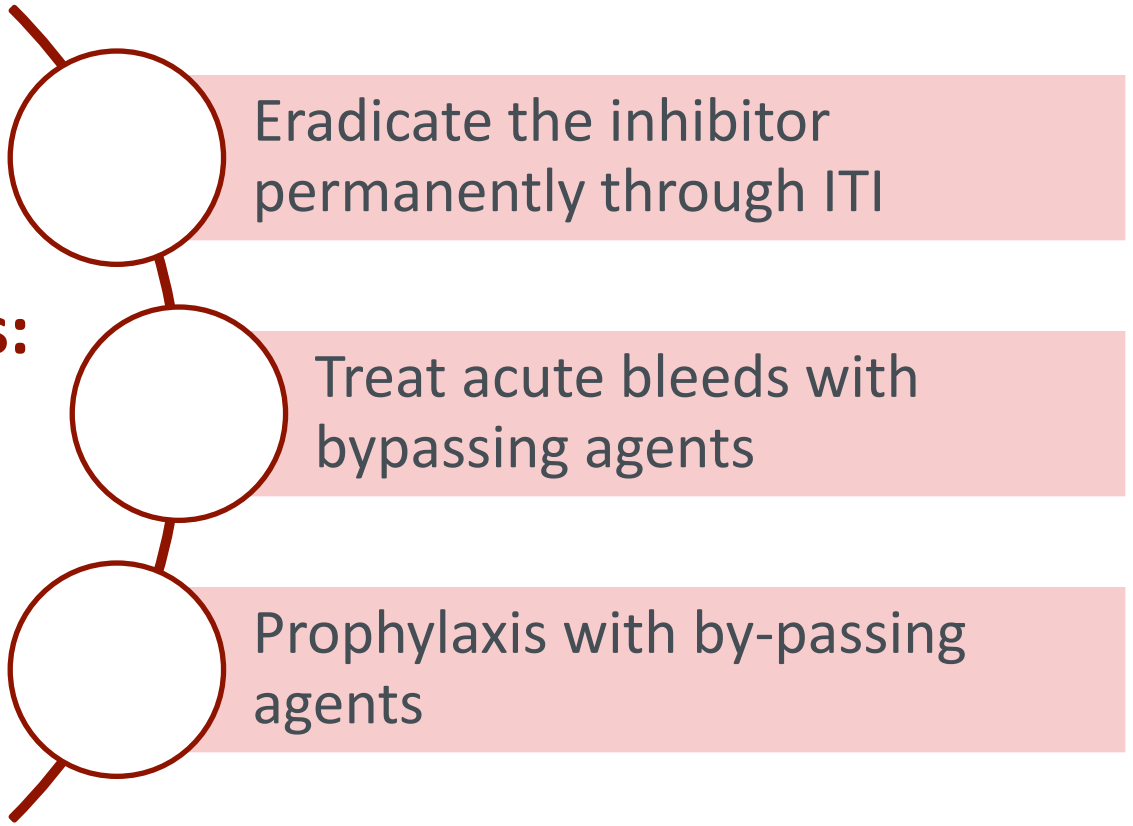
Replacement therapy in hospital for 10-15 exposure days

Management of bleeding (with anaphylaxis):

- **rFVIIa**

Current Treatment Options for Inhibitors[a,b]

Three approaches:



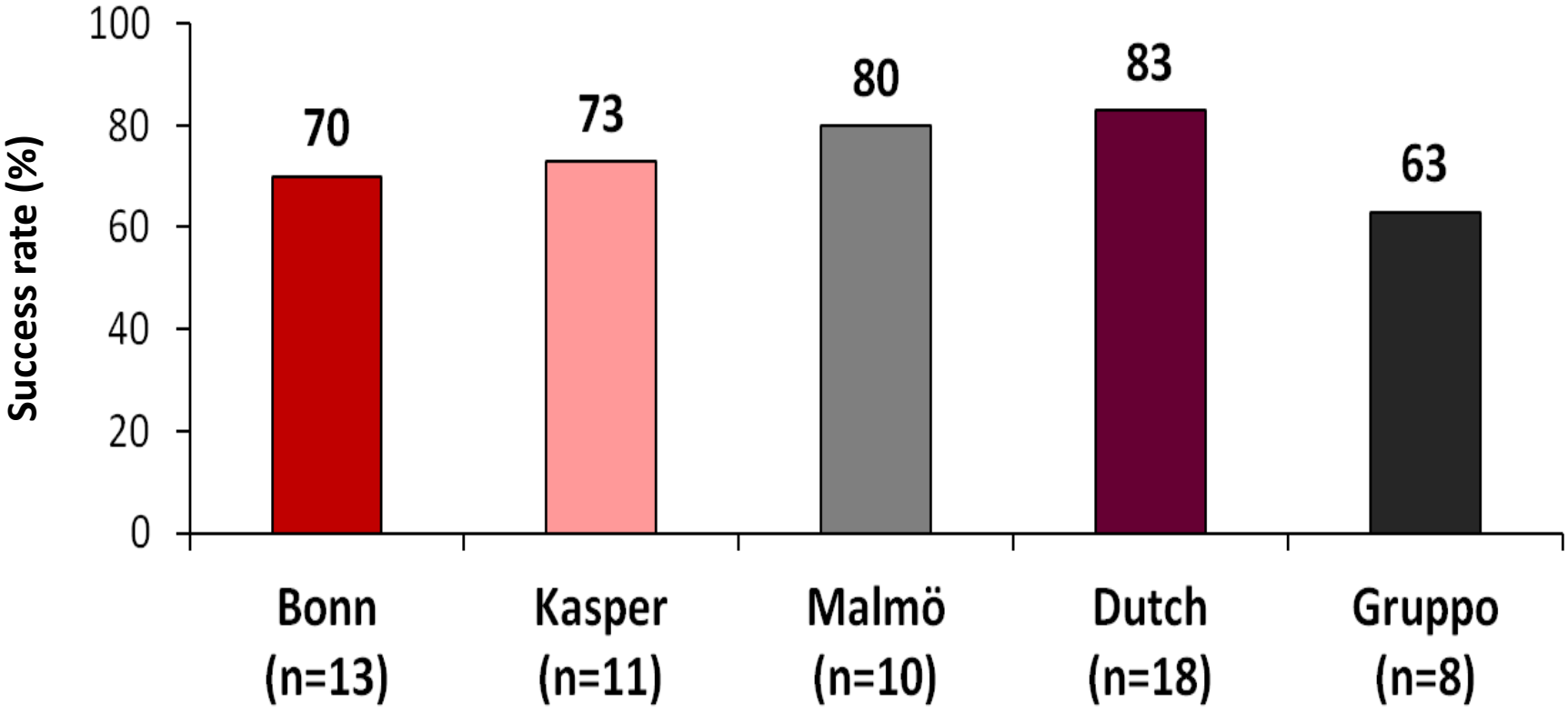
a. Haya S *et al. Haemophilia* 2007;13 (Suppl 5):52-60. b. Carcao M, et al. *Haemophilia* 2010;16(Suppl 2):16-23.

Immune Tolerance Induction Regimens

- Optimal ITI regimens are highly debated[a]
- 3 commonly used regimens:[b]
  - Bonn protocol: Twice-daily high-dose FVIII (100–150 IU/kg) + aPCC bypassing agent (50 IU/kg twice daily)
  - Malmö protocol: High-dose FVIII (100–150 IU/kg) + immunosuppressive therapies
  - Van Creveld protocol: Low-dose FVIII (25–50 IU/kg every second day) in patients with an inhibitor titre <10 BU at start of therapy
- Variations of these protocols are often used in real-life clinical practice

a. Coppola A et al. Blood Transfus 2014; 12 (Suppl 3): s554-62. b. Oldenburg J et al. Haemophilia 2014; 20(Suppl 6): 17-26.

Overall Success Rates Similar for Low vs High Doses of Clotting Factors in Hemophilia A



Median time on ITI regimen (months):	15.0	3.0	1.3	11.5	24.0

Di Michele DM. *Haemophilia.* 1998;4:568-573.

Bypassing Agents for Acute Bleeding Management

- Mainstay of treatment of bleeding episodes for patients with haemophilia with high-titre inhibitors[a]
- Available agents[b]:
  - rFVIIa[c] and activated prothrombin complex concentrates (aPCC)
- Limitations[b,d]:
  - Lack of laboratory assays to determine haemostatic dose, lack of convenience, cost, risk of thrombosis

a. Butros L et al. *Drug Des Devel Ther.* 2011; 5: 275-282. b. Kempton CL, et al. . *Hematology Am Soc Hematol Educ Program.* 2014; 2014: 364-371. c. Mathew P. *Semin Hematol.* 2006;43 (2 Suppl 4):S8-S13. d. Tjønnfjord GE, et al. *Vasc Health Risk Manag.* 2007; 3: 527-531.

Risk/Safety/Efficacy Assessments

	Bypassing Therapy	
	aPCC	**rFVIIa**
Infection risk[a]	Plasma-derived	Recombinant
Thrombotic risk	Low[a-c]	Low[a,b,c]
Anti-FVIII immune response	Yes[e]	No
Duration of influsion	+	+++
Volume	+	+++
Cost	+++	++++
Efficacy	64%-90%[a,b,e]	80%-95%[a,b,f]

a. Tjønnfjord et al. *Vasc Health Risk Manag*. 2007;3:527-531. b. Freydin. *J Young Investig* [serial online]. 2009;19(13). c. Ehrlich et al. *Haemophilia*. 2002;8:83-90. d. O'Connell et al. *JAMA*. 2006;295(3):293-298. e. Negrier et al. Thromb *Haemost*. 1997;77:1113-1119. f. Key et al. *Thromb Haemost*. 1998;80:912-918.

Prophylactic Use of Bypassing Agents

- Prophylaxis with bypassing agents can:[a]
  - Reduce bleeding episodes by ~50–70%
- 3 randomised clinical trials of bypassing agents for secondary prophylaxis showed:[b-d]
  - Significant reduction in bleeding episodes in joints and other tissues
  - Improvement in quality of life
  - Reduced hospitalisations
  - Reduced days missed from work or school

a. Kempton CL, et al. *Hematology Am Soc Hematol Educ Program* 2014; 2014: 364-371. b. Antunes SV, et al. *Haemophilia*. 2014;20: 65-72. c. Leissinger C, et al. *N Engl J Med*. 2011;365:1684-1692. d. Konkle BA, et al. *J Thromb Haemost*. 2007; 5:1904-1913.

Summary and Conclusions

- Inhibitors are far more likely to develop in very young patients
  - In patients with severe hemophilia A, inhibitor incidence is 20-30%
- Risk factors for developing inhibitors are both patient- and treatment-specific
- A number of strategies exist for the treatment of inhibitors, including use of bypassing agents and immune tolerance induction
- Inhibitor formation still represents the major complication of severe hemophilia A
- Current management of inhibitor patients is complex, burdensome, expensive and still associated with a greater risk of sequelae