Guidelines and Priorities for safe Switching between plasma derived and recombinant Factor VIII

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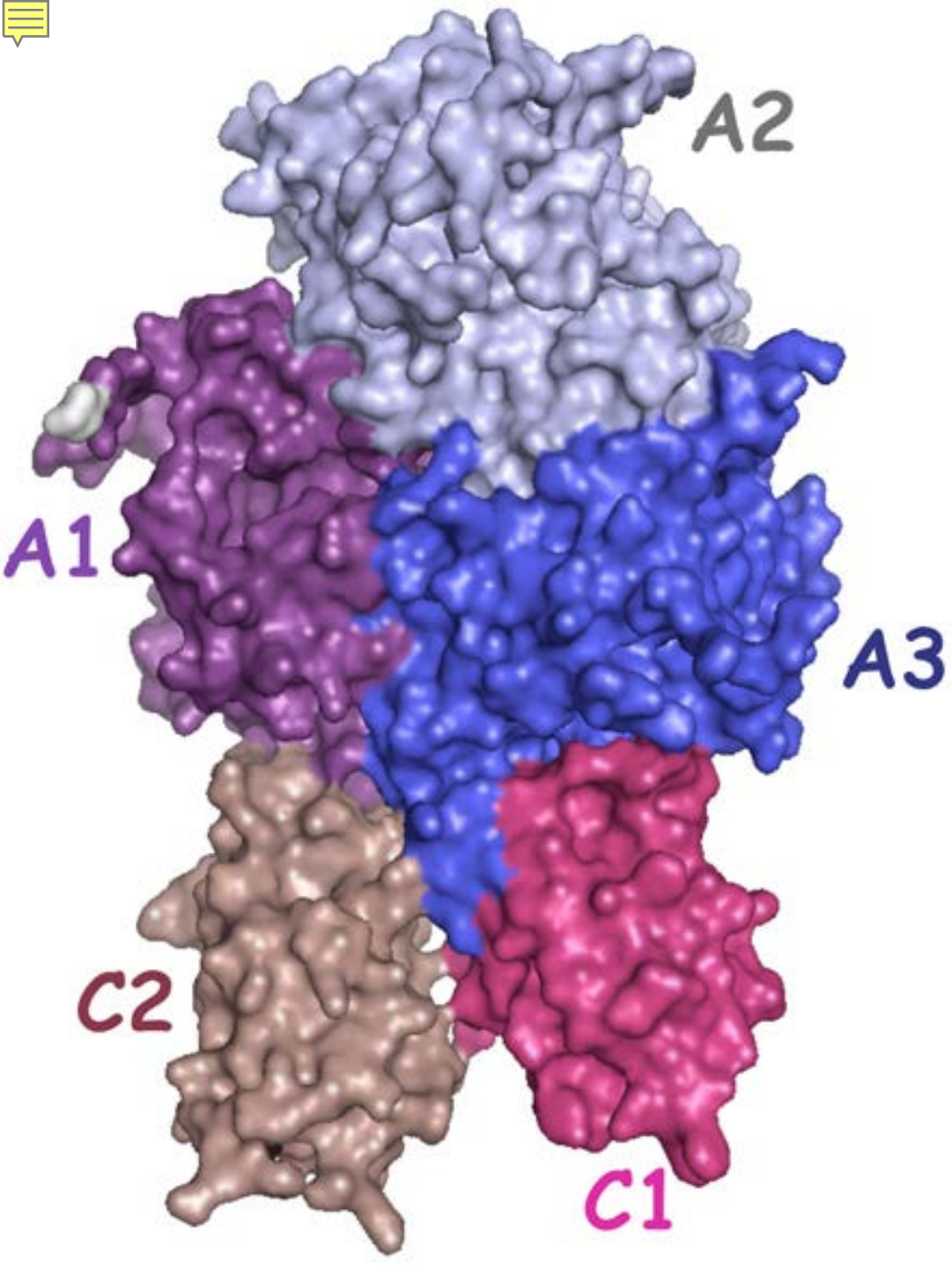
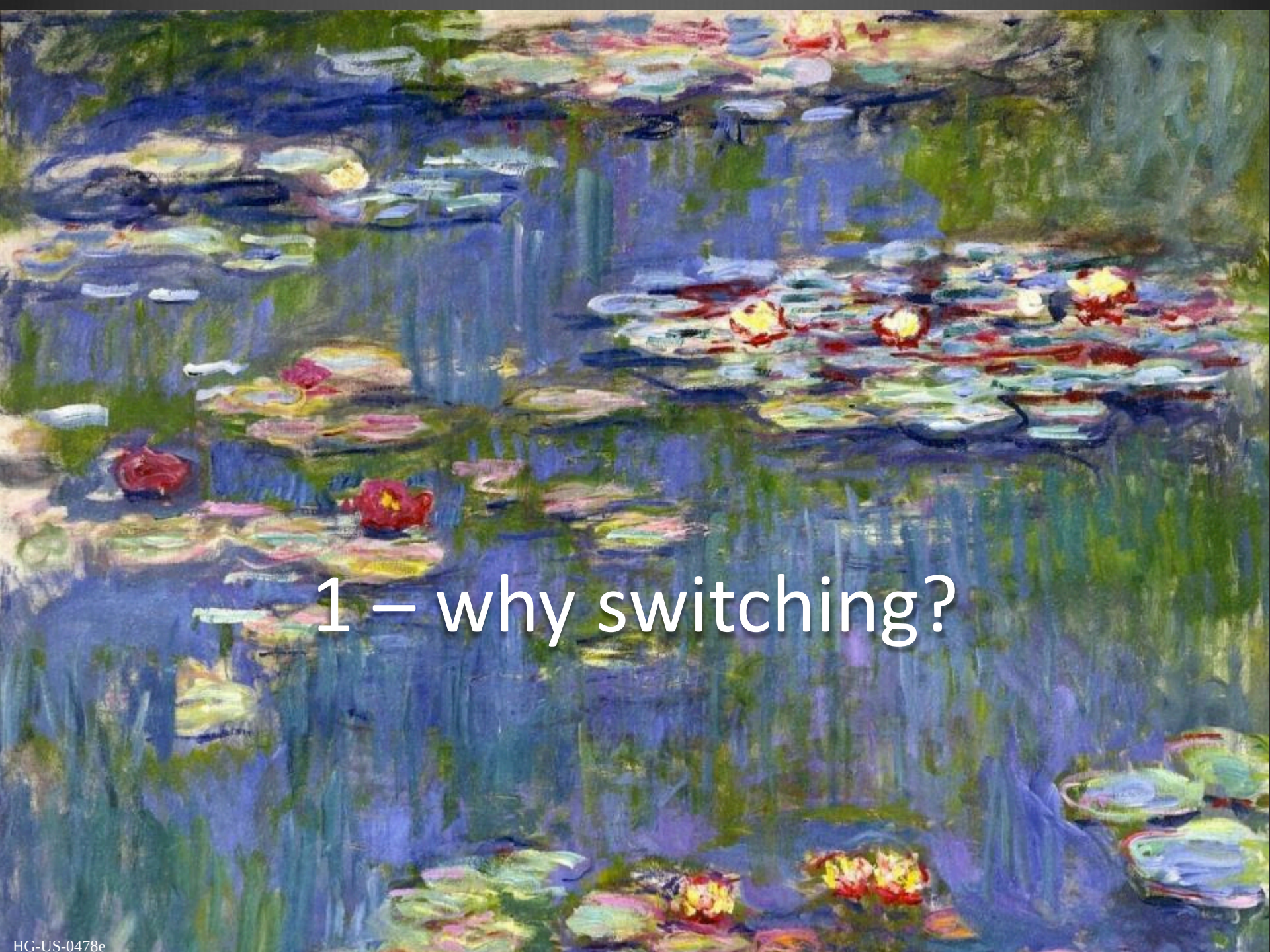
- Chair, Data and Demographics Committee, WFH
- Chair Canadian Hemophilia Registry Program
- Associate Editor: Blood Coagulation Disorders of the Cystic Fibrosis and Genetic Disorders Review Group of the Cochrane Collaboration

References

- Iorio, A. Blood, 2012: 120(4), 720–7.
- Aznar, J. Haemophilia, 2014: 20(5), 624–9.
- Matino D. Haemophilia, 2014: 20(5), 604–6.
- Matino, D. Haemophilia, 2014: 20(2), 200-6.

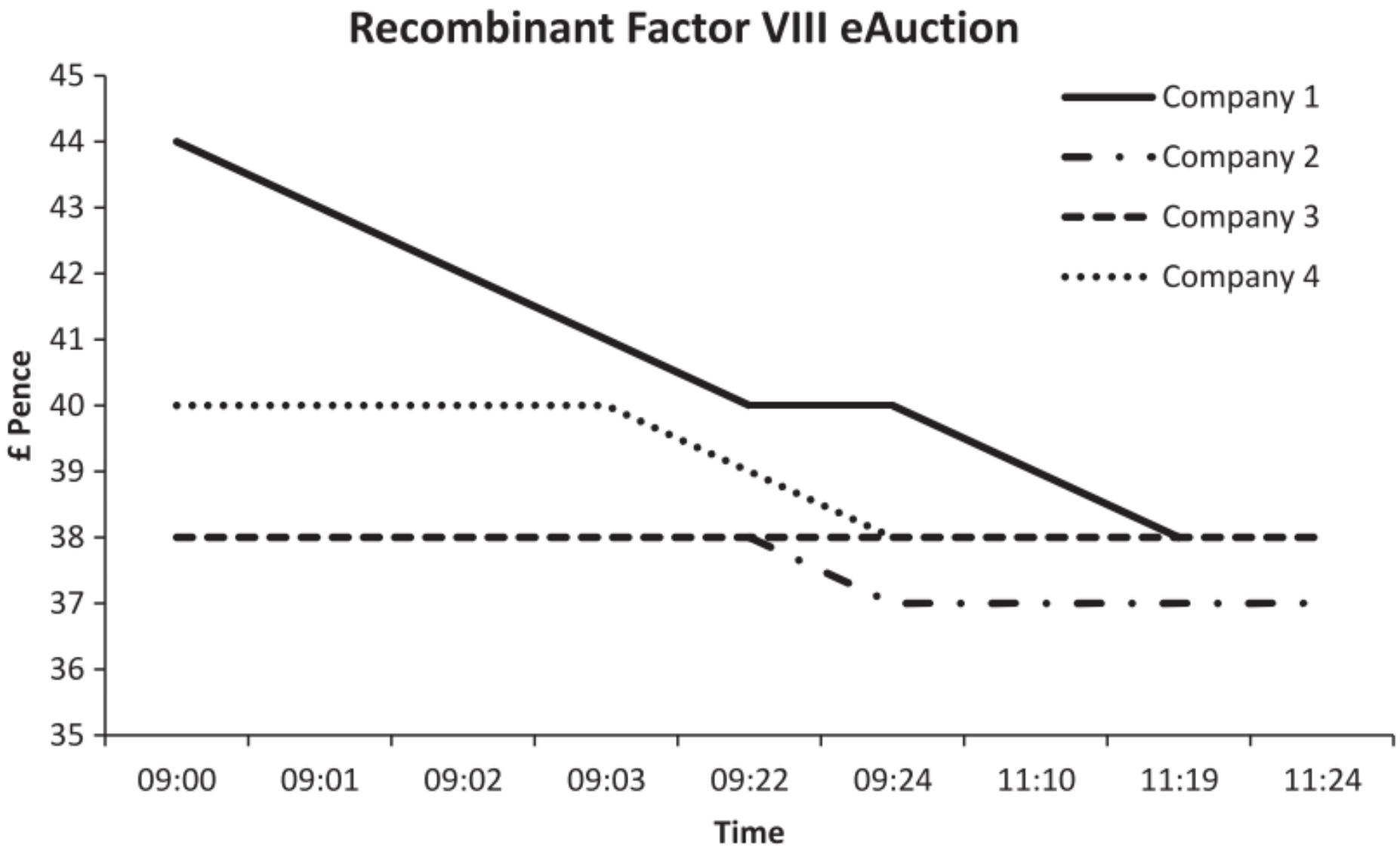


- Why switching?
- Evidence on switching
- Recommendations
- Priorities


1 – why switching?

Reasons for Switching factor concentrate
Improved Safety (real or perceived)
Less risk of infection
Less inhibitor risk
Fewer side-effects (e.g. allergic reactions)
Newer generation product
Price
National contracting
Volume of final product
Mixing and administration device
Storage advantage
Patient/family preference
Participation in clinical trial of new product/formulation
Research study participation that specifies product to be used

Iorio A et al. Blood 2012;120(4):720-727.



Hay, C. R. M. Hemophilia, 2013, 19(5), 660–7.

Barriers

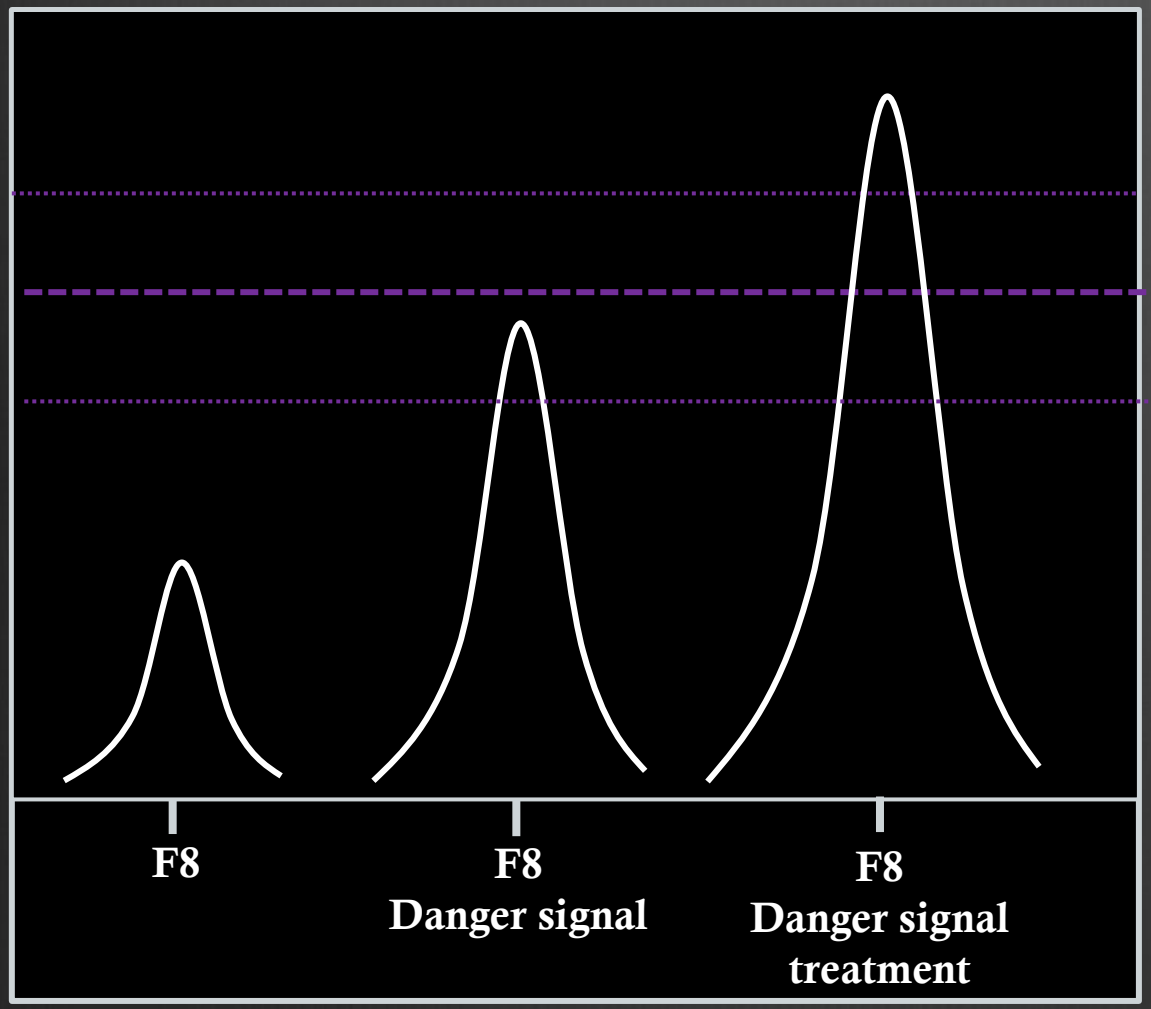
- Safety
  - Viral
  - Immunological
- Efficacy
  - ????

Guides for Assessing Causation

Plausibility	Is there a credible biological or physical mechanism that can explain the association?
Biological gradient	Are increasing exposures (ie dose duration) associated with increasing risks of the disease?
Experimental evidence	Is there any evidence from true experiments in humans?
Strength of association	How strongly associated is the putative risk with the outcome of interest?
Analogy	Is there a known relation between a similar putative cause and effect?
Consistency	Have the results been replicated by different studies, in different settings, by different investigators, and under different conditions?
Temporality	Did the exposure precede the disease?
Coherence	Is the association consistent with the natural history and epidemiology of the disease?
Specificity	Is the exposure associated with a very specific disease rather than a wide range of diseases?

Hill AB. Principles of Medical Statistics. New York: Oxford University Press, 1971.

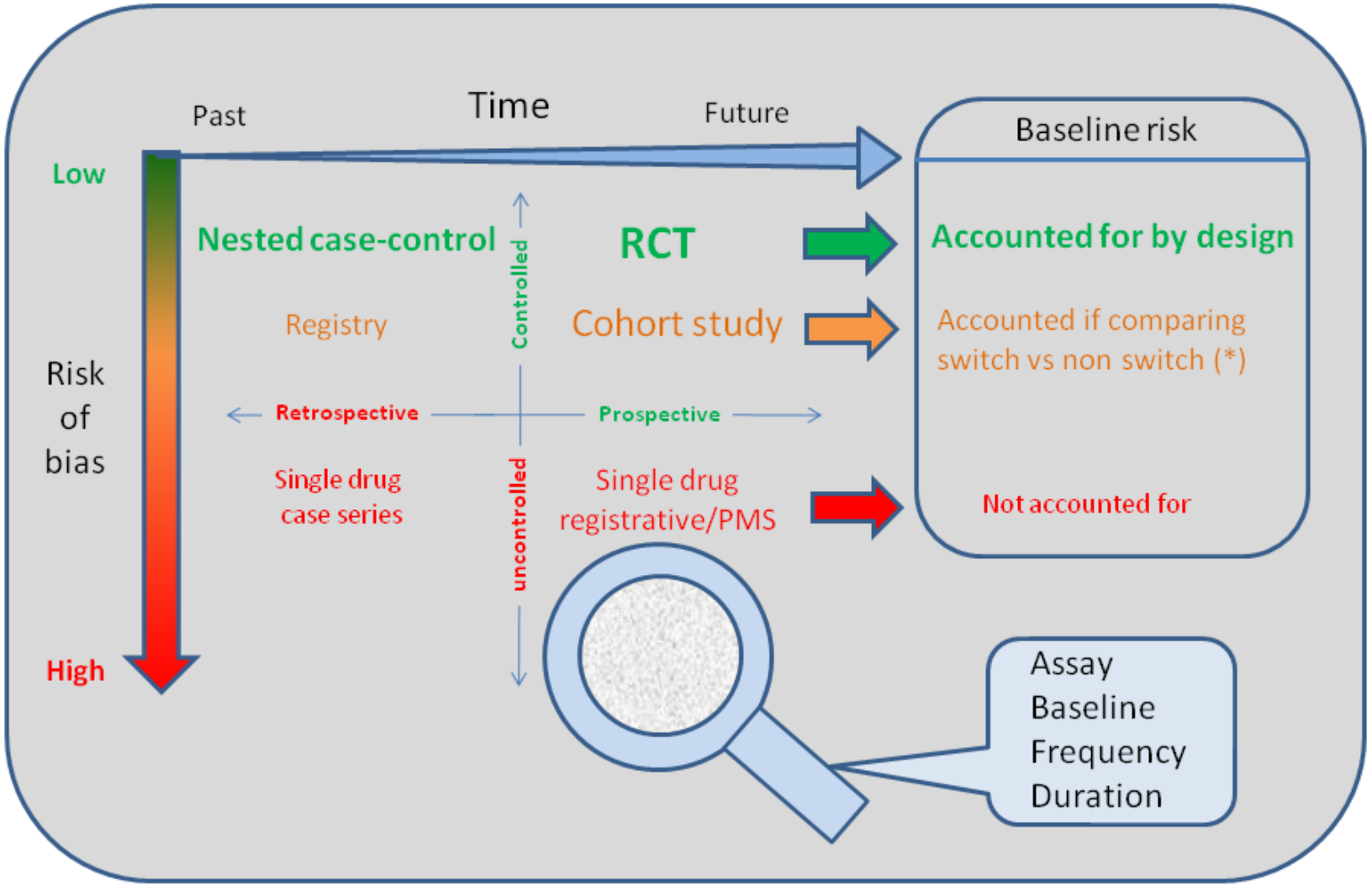
Multicausality principle[1]



Previous F8 exposure
CTL-4 polymorphism
FVIII genotype
(missense / point)

IL10, TNF-a
polymorphism
FVIII genotype
(deletions / inversions)

1. Rothman KJ, Greenland S. *Am J Public Health.* 2005;95:S144–50.
Modified from Gouw S. *Semin Thromb Hemost* 2007;35:723–34.



Iorio A et al. Blood 2012;120(4):720-727.

The baseline risk


2 – the evidence
© Soulia

Published Risk of inhibitor development related to switching

Year	Lead Author	Design	Sample	Follow up months	Inhibitor	Rate X 1000 pts/yr	Notes
1988	Giles et al.	Prospective	478	12	18	0.019	
			339	24	17	0.030	
2007	Singleton et al.	Retrospective	94	≤20	4	0.042	All patients
			77	≤20	1	0.013	(-) history
2007	Gouw et al.	Retrospective	316	(>50 ED)	NR		
2008	Rubinger	Prospective	225	12	0	0	
			189	24	0	0	
2009	Rea et al.	Retrospective	33	>3	1	0.033	
2011	Siegmund et al.	Retrospective #	118	N/A	0		
2011	Bacon et al.	Retrospective	113	Up to > 100 ED	1	0.009	

N/A, not available; NR, not reported; ED, exposure day

Iorio A et al. Blood 2012;120(4):720-727.

Secular trend in the estimated risk of inhibitor development in PTPs

- Cumulative rates observed progressively increased over time from 0.0015 to 0.0053
- What might the effects be due to?:
  - Increased awareness
  - More accurate and frequent inhibitor testing;
  - May reflect more the widespread use of:
    - Prophylaxis
    - Greater factor consumption
    - **More frequent switching**
  - May parallel temporal trends toward more frequent allergic and autoimmune disorders

Pergamon

PII: S0955-3886(98)00024-1

Transfus. Sci. Vol. 19, No. 2, pp. 139–148, 1998

Printed in Great Britain
0955-3886/98 $19.00 + 0.00

Surveillance for Factor VIII Inhibitor Development in the Canadian Hemophilia A Population Following the Widespread Introduction of Recombinant Factor VIII Replacement Therapy

A. R. Giles, MD*†
G. E. Rivard, MD*
J. Teitel, MD*
I. Walker, MD*

Giles, et al. Tranfus. Sci. 1998;19(2): 9-48. .
HG-US-0478e

■ In the Fall of 1994 the majority of Canadian Hemophilia A (Factor VIII (F.VII) deficiency) patients who were referred for evaluation for inhibitor development by the classical Bethesda Assay. By concensus of the referring

Conversion of Canada Hemophilia A Population to High-Purity Products

	Inhibitors/at risk (%)			
	Recombinant FVIII		Affinity purified pdFVIII	
Post	18/478	3.8%	4/57	7%
Missing at baseline	0/55		0/4	
Positive at Baseline	9/423	1.9%	4/53	7.5%
Negative at baseline	9/423	1.9%	0/53	0%

Giles, et al. Tranfus. Sci. 1998;19(2): 9-48

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

Haemophilia (2014), 20, 624–629 DOI: 10.1111/hae.12439

ORIGINAL ARTICLE *Clinical haemophilia*

Inhibitor development after switching of FVIII concentrate in multitransfused patients with severe haemophilia A

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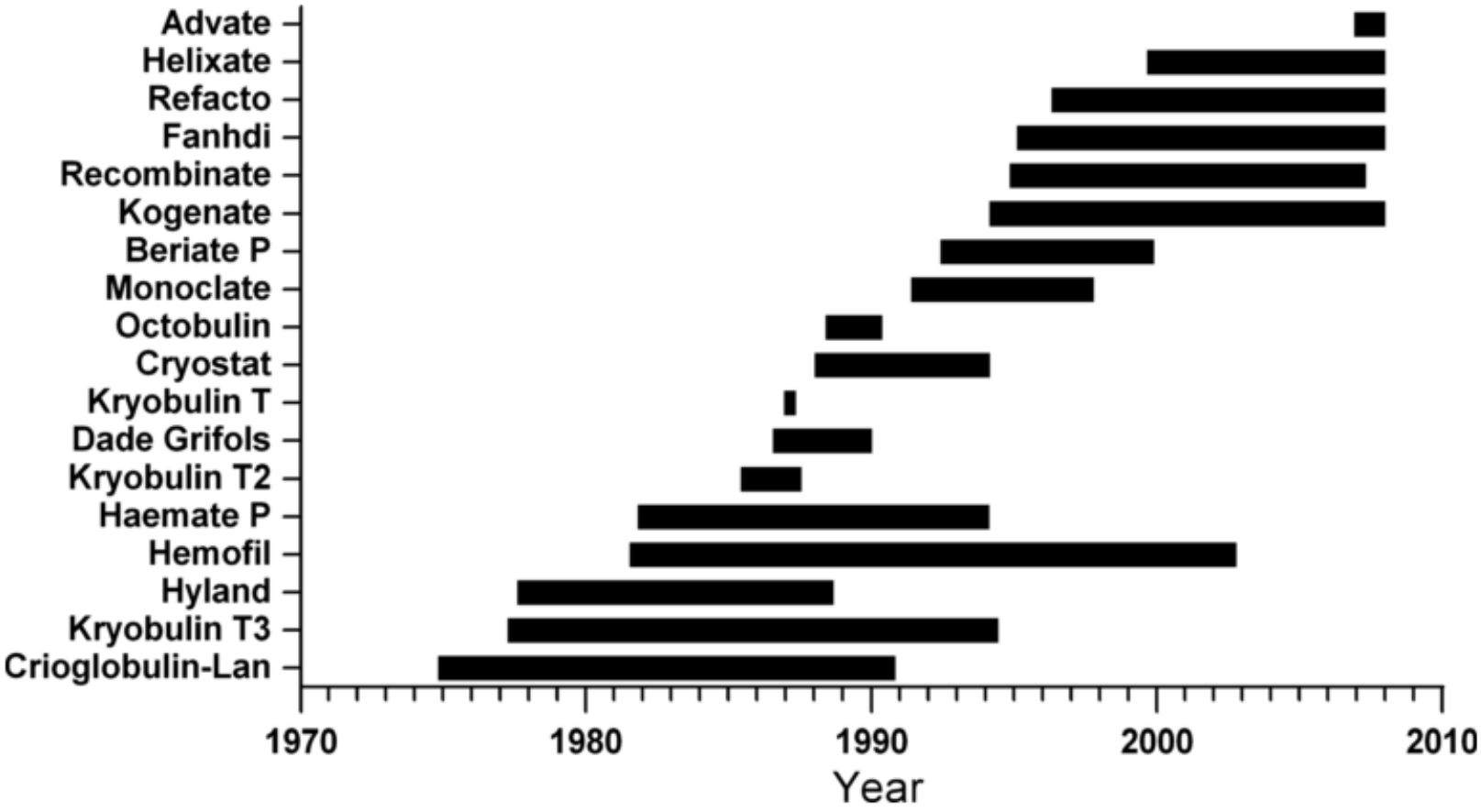
97/167 with > 150 ED

9 inhibitors, all transient

INHIBITORS IN MULTITRANSFUSED SEVERE HAEMOPHILIA A



Aznar, J. Haemophilia, 2014: 20(5), 624–9.

Table 2. Product switch and incidence of inhibitors.

	Patients, *n* (%)	Exposure days, mean ± SD	Exposure days, median (IQR)	Switches, median
All patients				
All	97	958 ± 867	716 (290–1332)	9
No inhibitor	88 (90.7)	1023 ± 881	761 (313–1411)	9
Inhibitor	9 (9.3)	323 ± 287	263 (151–422)	2
Switches between plasmatic products only				
All	50	889 ± 766	694 (316–1139)	9
No inhibitor	45 (90.0)	932 ± 795	718 (317–1241)	10
Inhibitor	5 (10)	503 ± 257	422 (294–678)	4
Switches between recombinant products only				
All	5	748 ± 412	896 (329–1062)	7
No inhibitor	5 (100.0)	748 ± 412	896 (329–1062)	7
Inhibitor	0 (0.0)	–	–	–
Switches between plasmatic and recombinant products				
All	25	1654 ± 871	1332 (755–2424)	13
No inhibitor	25 (100.0)	1654 ± 871	1332 (755–2424)	13
Inhibitor	0 (0.0)	–	–	–
No switches				
All	17	202 ± 363	85 (21–157)	0
No inhibitor	13 (76.5)	230 ± 412	85 (26–157)	0
Inhibitor	4 (23.5)	97 ± 97	86 (18–165)	0

IQR, interquartile range; SD, standard deviation.

Product switch and incidence of inhibitors

Patients	All	PD-only	Rec-only	PD-Rec	No switch
All	97	50	5	25	17
Inhib (-)	88 (91)	45 (90)	5	25	13 (76)
Inhib (+)	9 (9)	5 (10)	0	0	4 (23)

Aznar, J. Haemophilia, 2014: 20(5), 624–9.


3 - Recommendations

Haemophilia
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the Hemostasis & Thrombosis Research Society

Haemophilia (2013), 1–7

DOI: 10.1111/hae.12283

ORIGINAL ARTICLE

Switching clotting factor concentrates: considerations in estimating the risk of immunogenicity

D. MATINO,* D. LILLICRAP,† J. ASTERMARK,‡ G. DOLAN,§ C. KESSLER,¶ T. LAMBERT,** M. MAKRIS,†† J. O'DONNELL,‡‡ S. PIPE,§§ E. SANTAGOSTINO,¶¶ J.-M. SAINT-REMY,*** W. SCHRAMM††† and A. IORIO‡‡‡

- A Modified Delphi Technique was used to add to the considerations of the risk of FVIII immunogenicity associated with product switching
- Structured group communication involving 12 expert panelists
- 14 items were identified and ranked, followed by preparation of statements

Matino D, et al. Haemophilia 2013; 1-7. DOI:10.1111/hae.12283.

Outcome of Delphi Consensus Process: Items and Statements

Item 1. Evidence documenting an increased risk of FVIII inhibitor development with product switching is weak

Item 2. The risk of inhibitor development is likely to be less with FIX product switches compared to FVIII switches

Item 3. FVIII inhibitor development is more likely when product switches occur during the first 50 exposure days

Item 4. The risk of FVIII inhibitor development may be increased with the new FVIII conjugates and fusion proteins

Item 5. The risk of an inhibitor after switching may be different for severe vs. moderate or mild haemophilia

Matino D, et al. Haemophilia 2013; 1-7. DOI:10.1111/hae.12283.

Outcome of Delphi Consensus Process: Items and Statements (cont'd)

Item 6. The risk of FVIII inhibitor development with product switching is increased in patients with a past history of an inhibitor

Item 7. There may be an increased risk of inhibitor development when switching product just prior to surgery or intensive treatment

Item 8. The risk of a FVIII inhibitor development increases with the frequency of product switching

Item 9. There is an increased risk of FVIII inhibitor development when switching concentrates in patients being treated on demand as opposed to prophylactically

Matino D, et al. Haemophilia 2013; 1-7. DOI:10.1111/hae.12283.

Outcome of Delphi Consensus Process: Items and Statements (cont'd)

Item 10. There is an increased risk of FVIII inhibitor development when switching between plasma-derived and recombinant FVIII concentrates

Item 11. There is an increased risk of FVIII inhibitor development when switching between B-domain deleted and full-length FVIII concentrate

Item 12. FVIII inhibitor risk associated with recombinant FVIII use could be influenced by the type of cell employed for FVIII production

Item 13. All recombinant FVIII products have the same risk of inhibitor development

Item 14. The risk of FVIII inhibitor development with product switches can be predicted by genetic analysis

Matino D, et al. Haemophilia 2013; 1-7. DOI:10.1111/hae.12283.

Item 10. There is an increased risk of FVIII inhibitor development when switching between PD and rec FVIII concentrates

A. There is no evidence to support this statement. The Canadian sur- veillance of product switching for the entire population to recombinant FVIII in 1988 did not show any increase in the baseline risk for inhibitor development (92%).

B. There is no evidence that the risk of inhibitor development associated with switching from any plasma-derived concentrate to any recombinant prod- uct is different from that associated with switching between two different plasma-derived or two recombi- nant factor concentrates (77%).

Matino D, et al. Haemophilia 2013; 1-7. DOI:10.1111/hae.12283.

4 – Priorities and directions

Key messages

- No signal of increased immunogenecity for recombinants
- No signal of risk around switching
- “Natural experiments” of switching should be optimized to gain further knowledge

Key Messages

The process	The evidence	The future
Studies around switching are complex	Imperfect but overall reassuring	“Natural experiments” should be optimized

No signal of increased immunogenicity when switching from PD to recombinant FVIII

McMaster University

Inspiring Innovation and Discovery

Hamilton Health Sciences

Thank You

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