



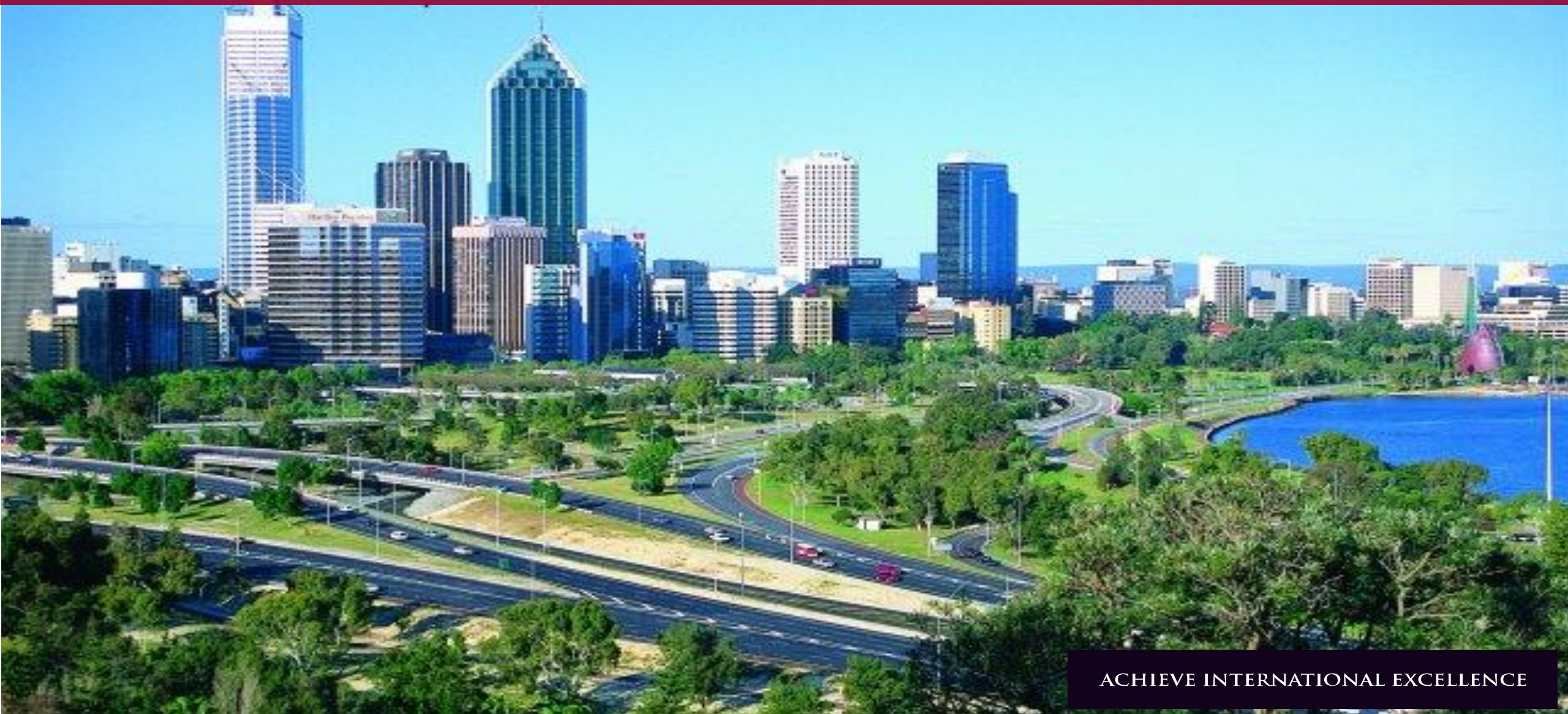
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WESTERN AUSTRALIA



Plasma derived medicines - the evidence for their necessity

FACULTY OF MEDICINE, DENTISTRY AND HEALTH SCIENCES

ALBERT FARRUGIA PHD



ACHIEVE INTERNATIONAL EXCELLENCE

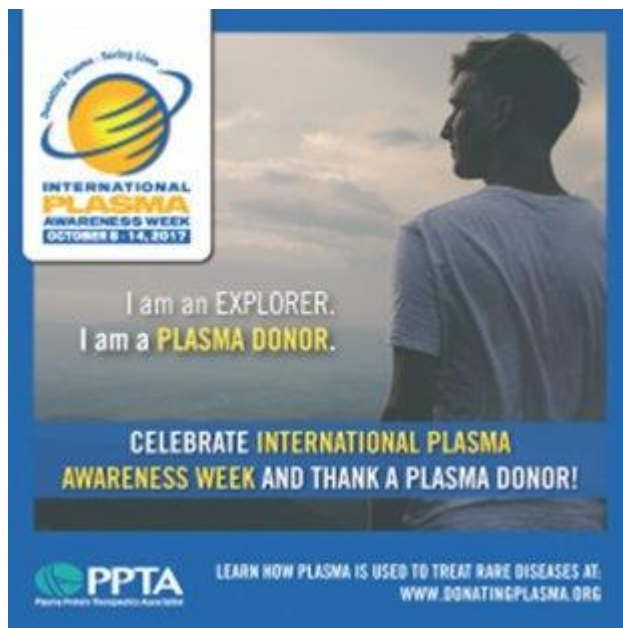
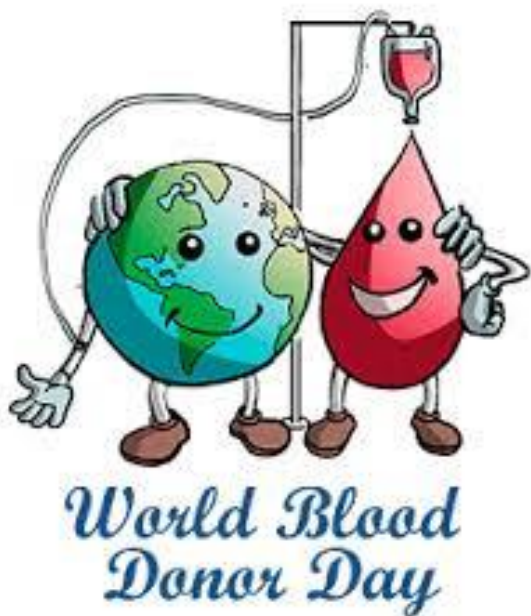


Disclosures

I provide compensated services for the manufacturers of therapies described in this presentation



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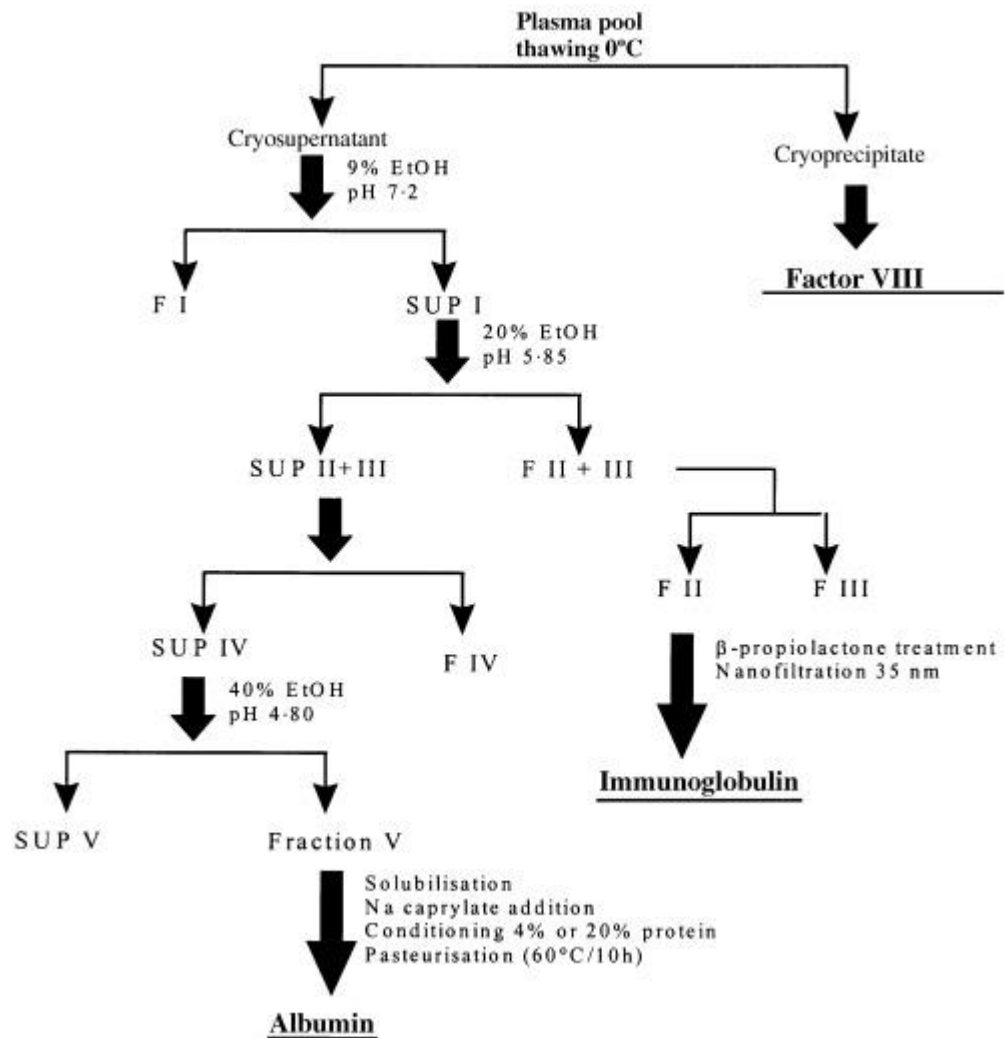


.....the donors of haemotherapies have two things in common – they all save lives, and they all deserve recognition and protection.....

Indian J Med Res 133, June 2011, pp 573-576

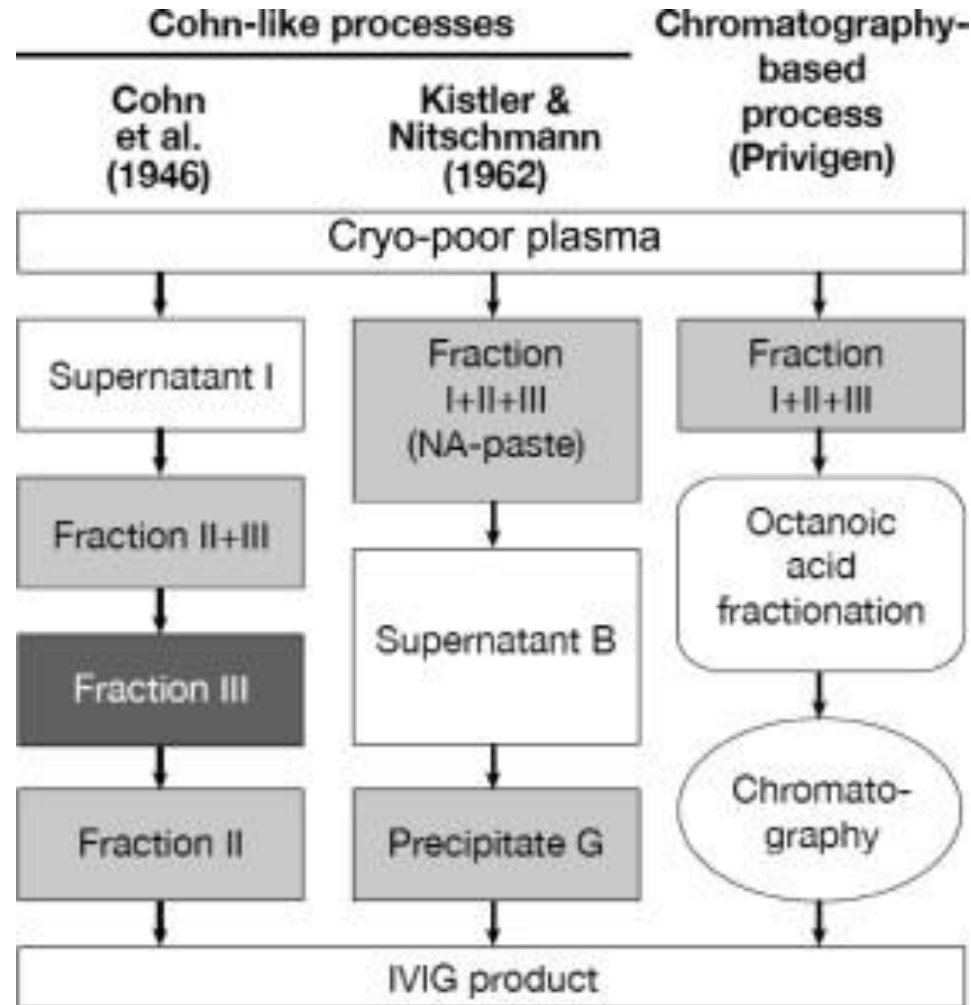


How it all began.....

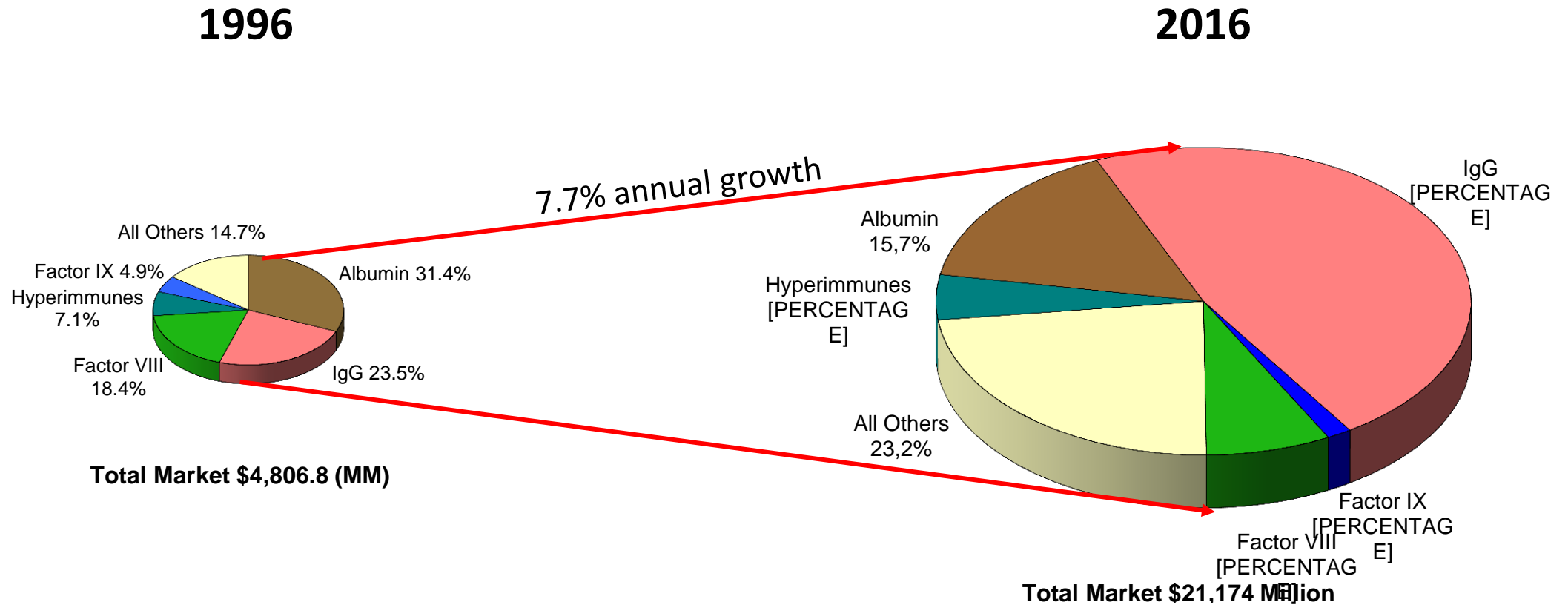




Evolution of the process



20 Years of Worldwide Plasma Proteins Market Growth (Without Recombinants)



Note: Pie charts are drawn to scale



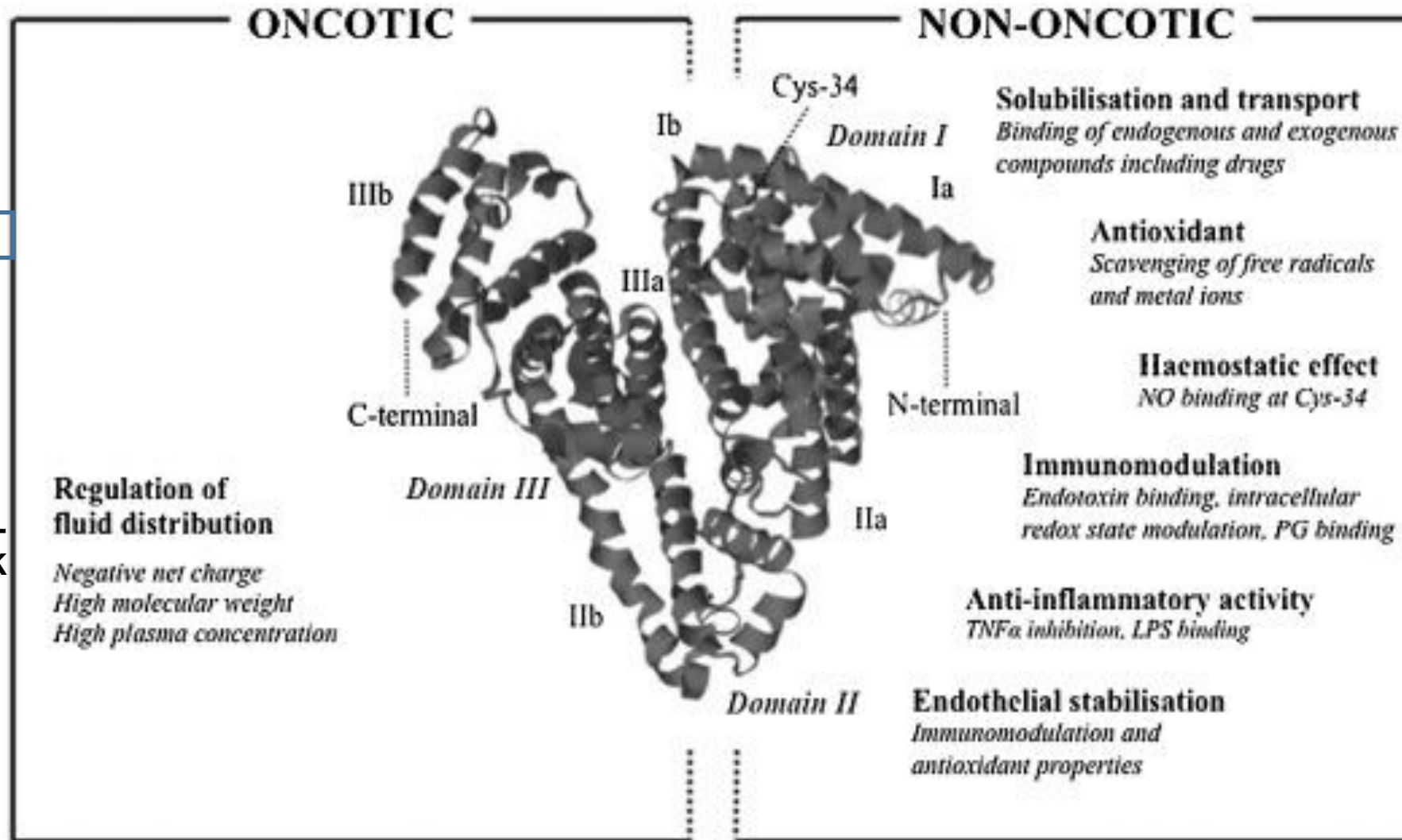
THE FIRST DRIVER



ALBUMIN



Structure and function of human albumin



SEPSIS
LIVER DISEASE

.....

VOLUME
REPLACEMENT –
TRAUMA, SHOCK



Crystalloid vs. colloid

Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review)

Perel P, Roberts I, Ker K

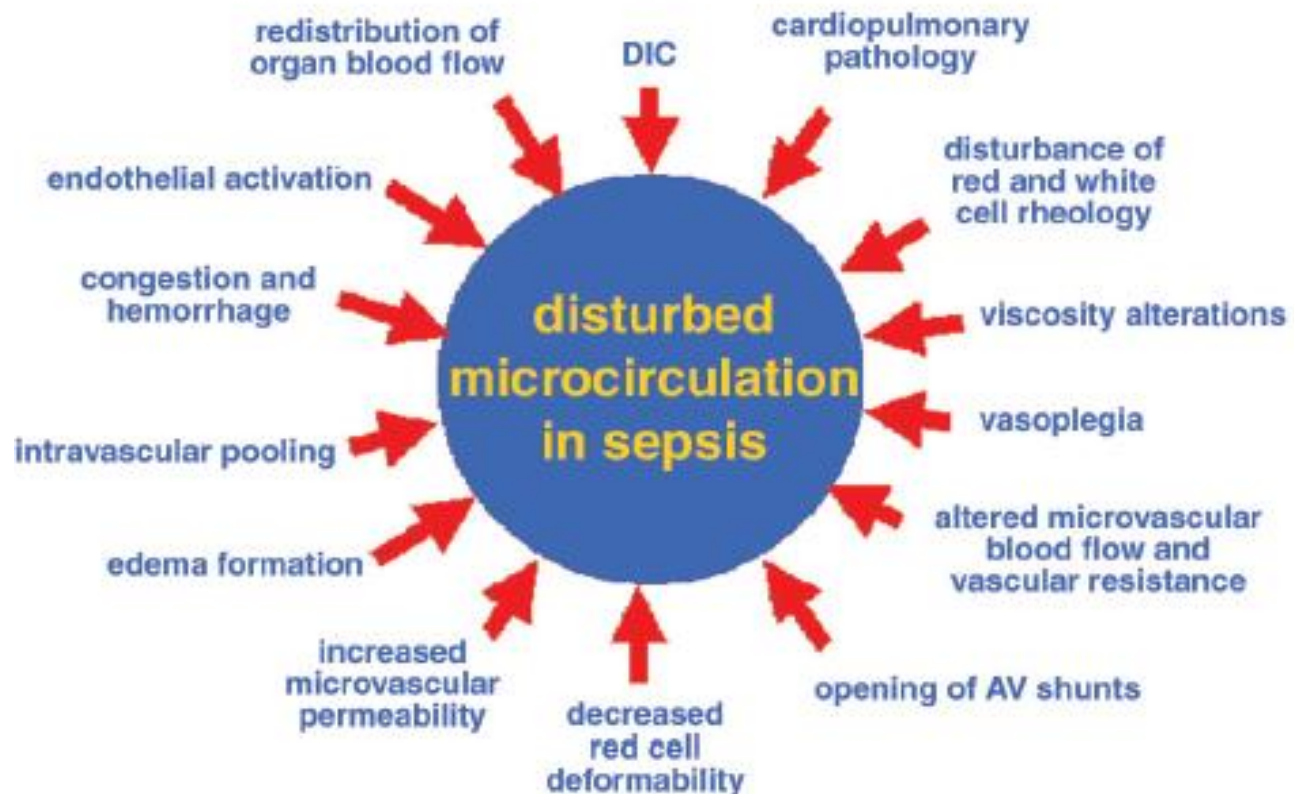


- Randomised controlled trials (RCTs) of colloids compared to crystalloids, in patients requiring volume replacement.
- **COLLOIDS COMPARED TO CRYSTALLOIDS:** Albumin or plasma protein fraction . The pooled risk ratio (RR) from these trials was 1.01 (95% confidence interval (CI) 0.93 to 1.10).
- **NO** evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids.
- Furthermore, the use of hydroxyethyl starch might increase mortality.
- As colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.

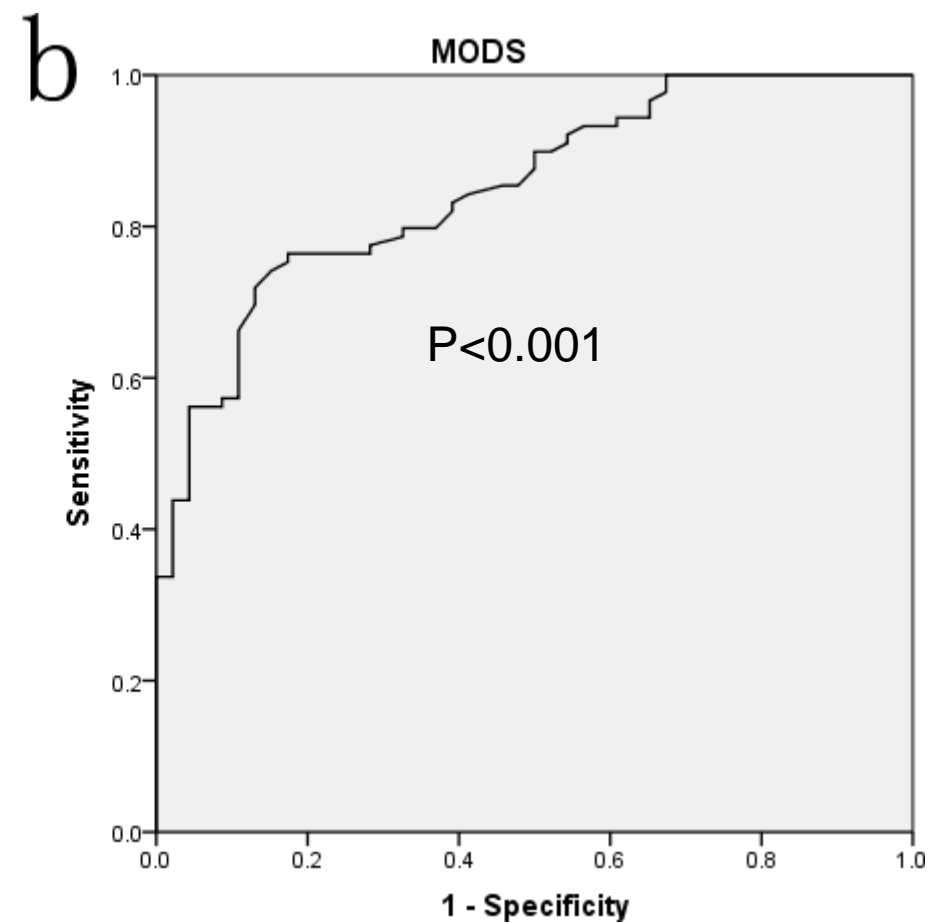
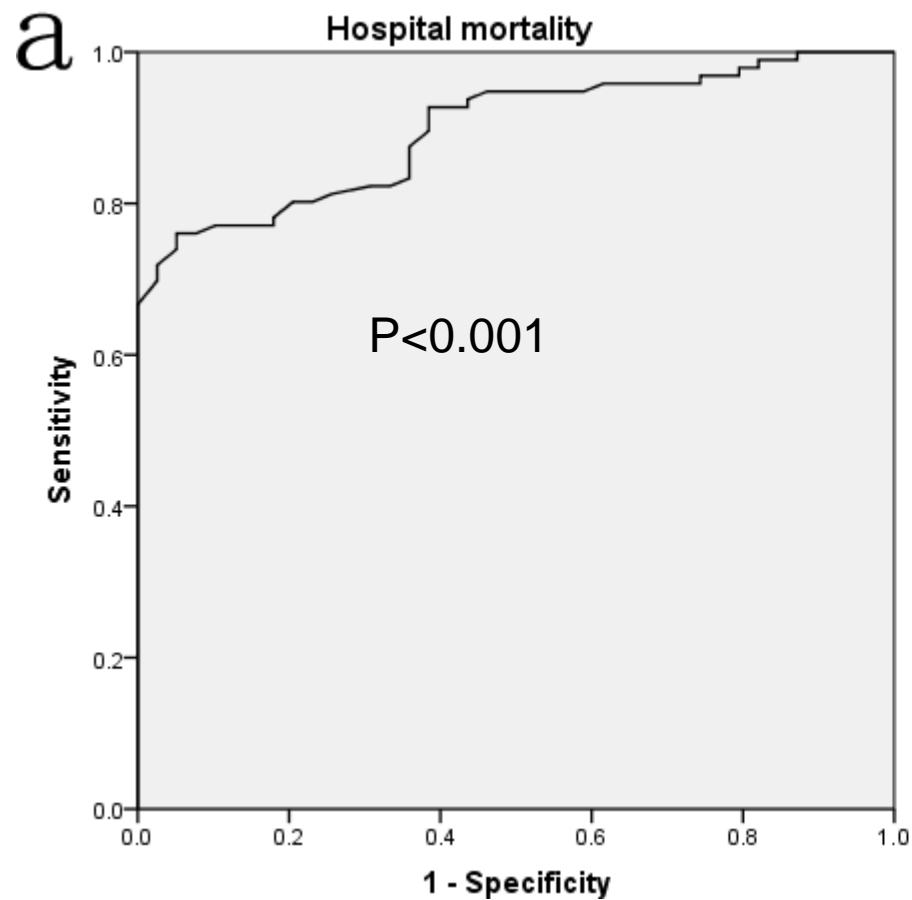
28.2.2013 wiley online library



Why colloids in sepsis? Possible effects of albumin on the disturbed microcirculatory effects of sepsis



- Albumin decreases neutrophil activation induced by fluid infusion, crystalloids and synthetic colloids increase it. Rhee P, et al. *Crit Care Med* 2000; 28(1): 74-78.
- Albumin reduces TNF induced endothelial activation. Nohe et al *Intensive Care Med* 1999; 25: 1381-1385; Zhang et al *Cardiovasc Res.* 2002 Sep;55(4):820-9
- Albumin solution reverses the LPS induced albumin leakage across vessel walls. Powers KA, et al. *Crit Care Med* 2003; 31: 2355-63 ;Anning PB et *Intensive Care Med.* 2004 Oct;30(10):1944-9
- Albumin infusion results in sustained thiol levels in septic patients. Quinlan G, et al. *Clin Sci* 1998; 95: 459-65.

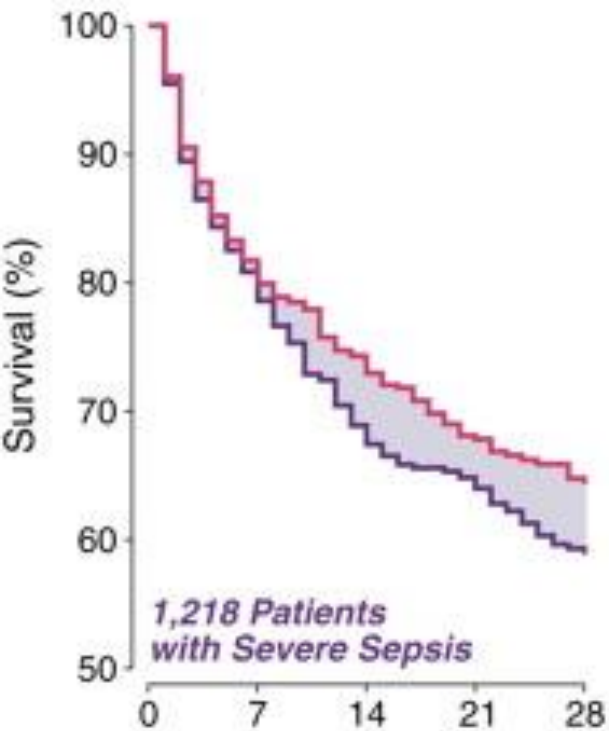




Survival curves of 3 large studies of volume resuscitation with human albumin solutions in severe sepsis

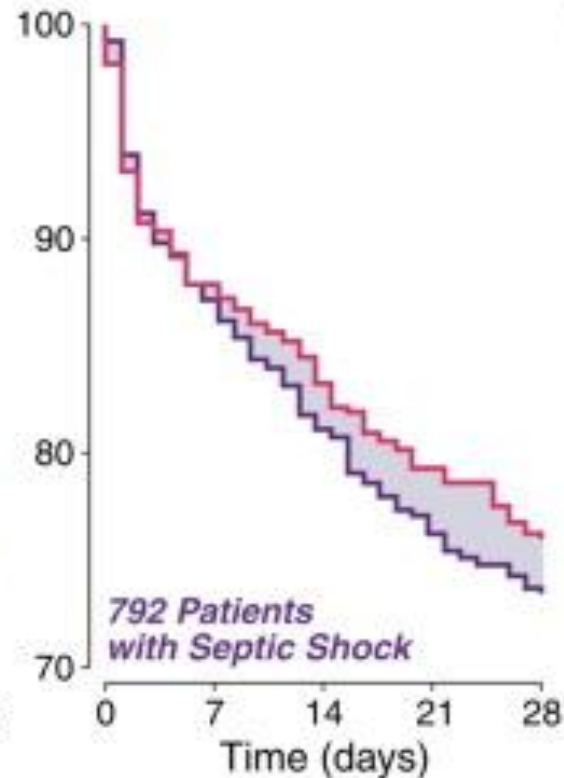
SAFE

A



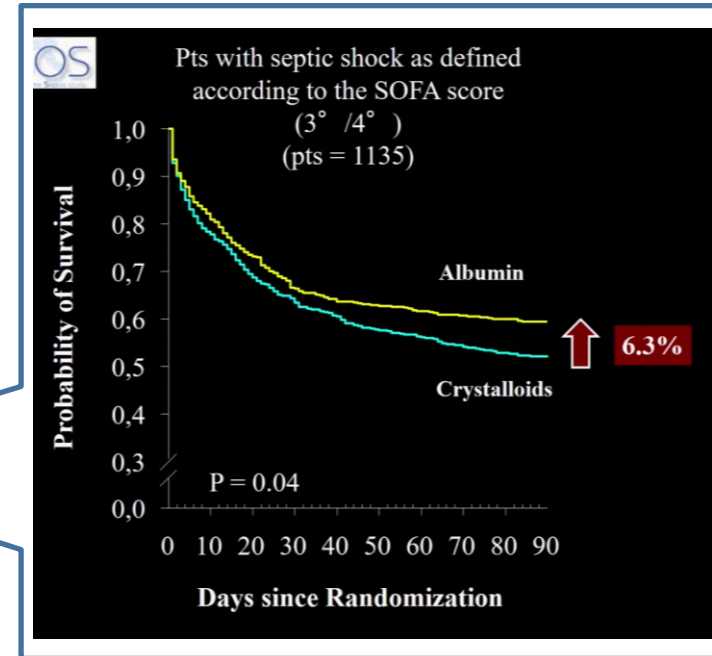
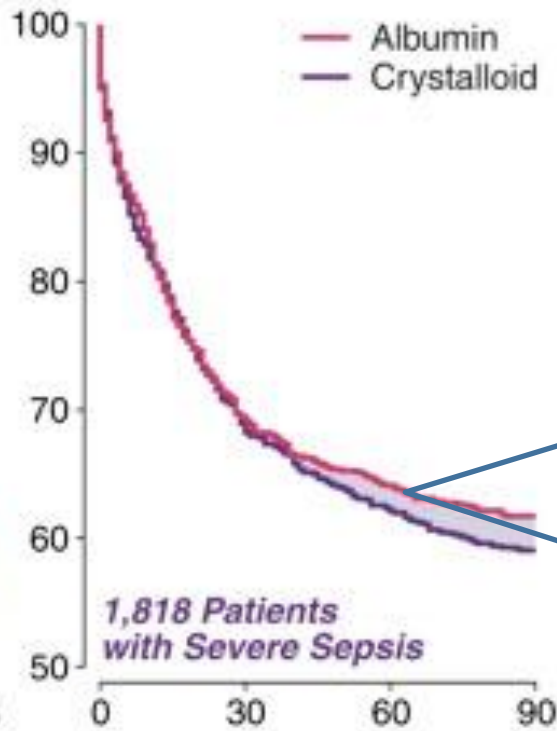
EARSS

B



ALBIOS

C



Fluid Therapy

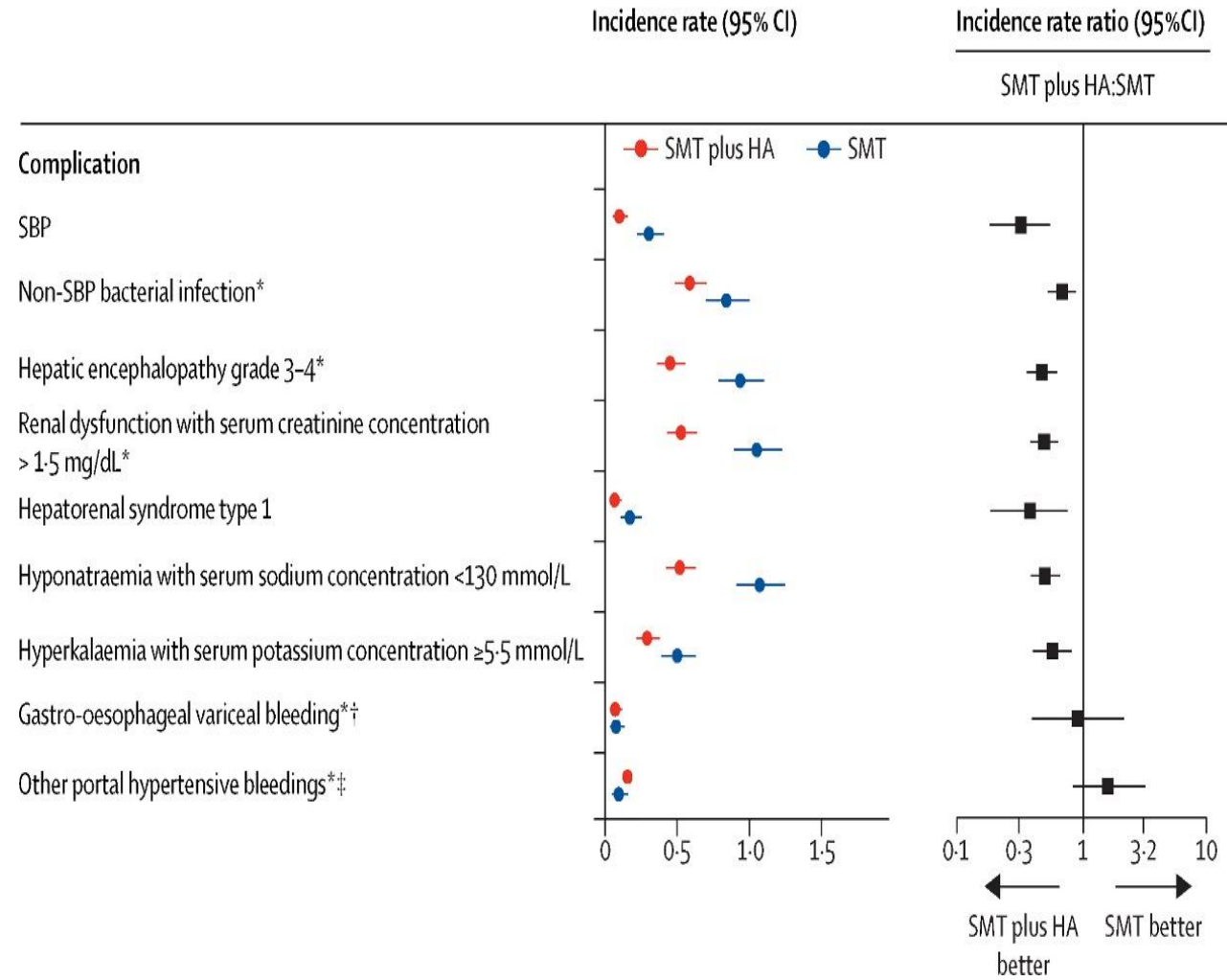
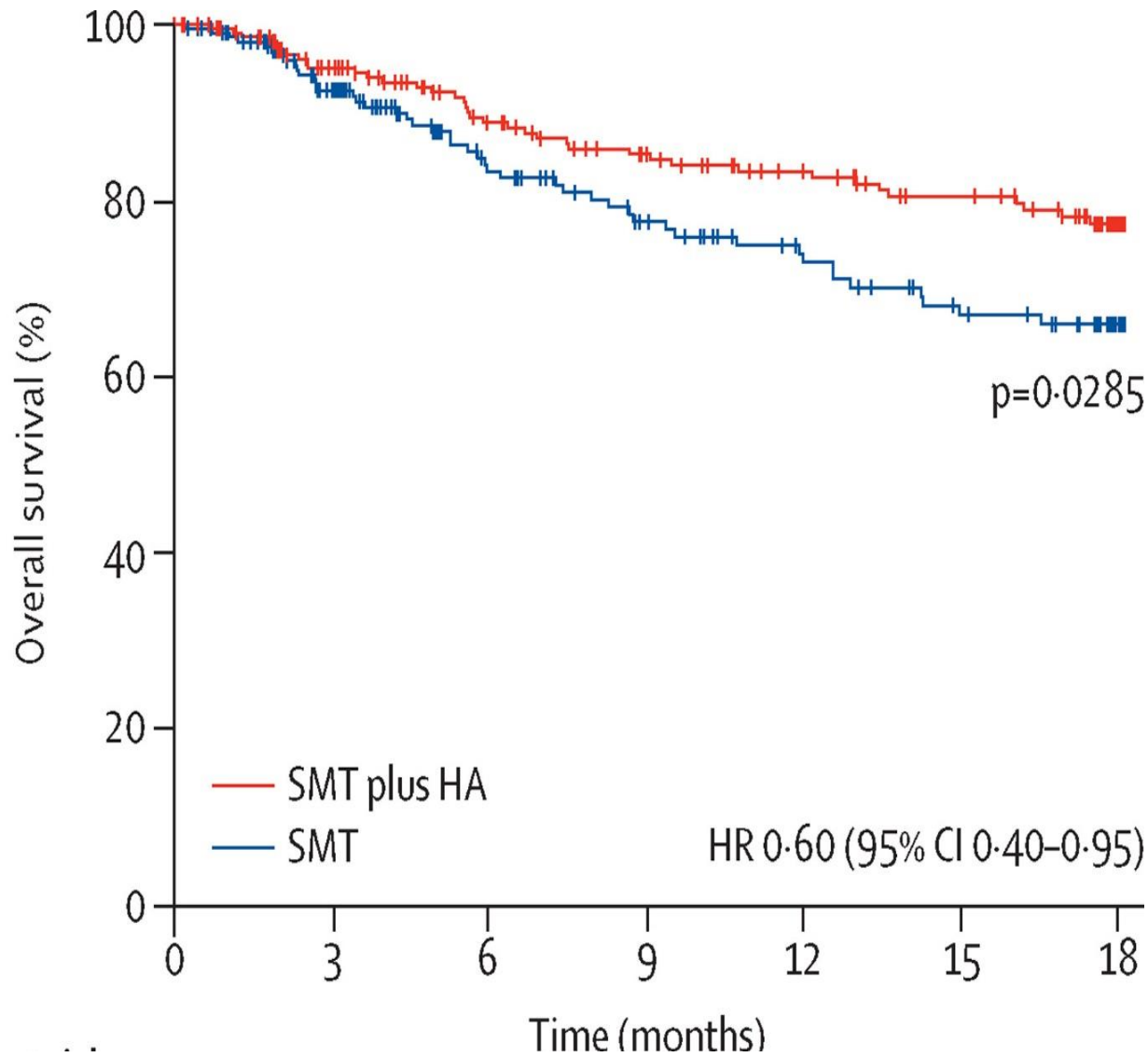
- **We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock**

(Strong recommendation, moderate quality of evidence).

- **We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids**

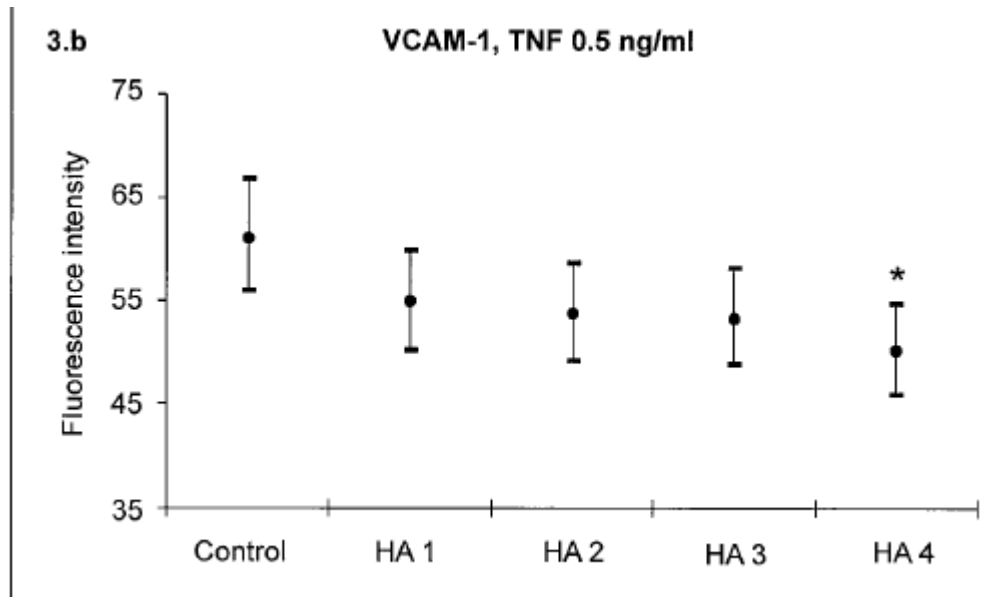
(weak recommendation, low quality of evidence).

Long-term albumin administration in patients with decompensated cirrhosis – The “ANSWER” study



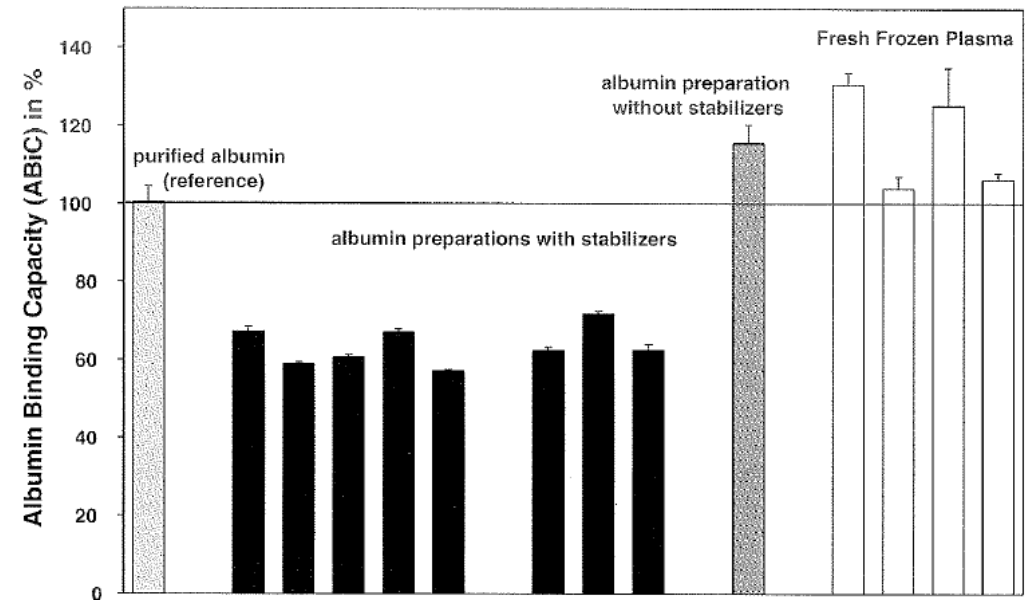
Heterogeneity between albumin products

Expression of endothelial cell adhesion molecules



Intensive Care Med (1999) 25: 1381±1385

Binding site II for diazepam

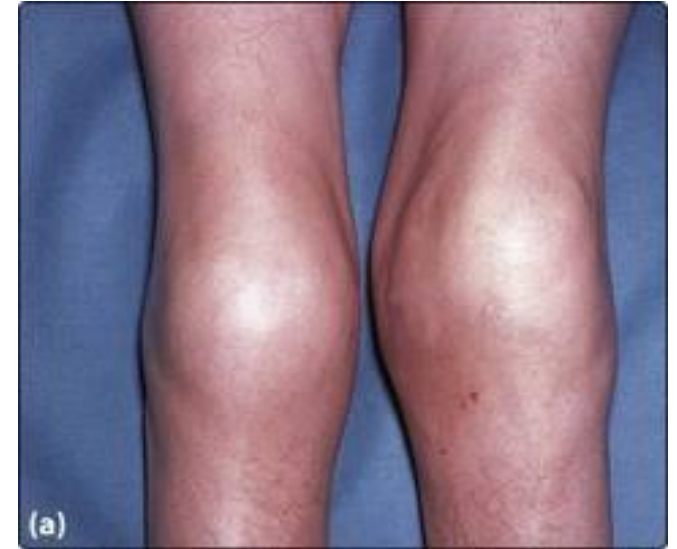


Klammt et al Zeitschrift für
Gastroenterologie 2001;39 Suppl 2():24-7

THE NEXT DRIVER

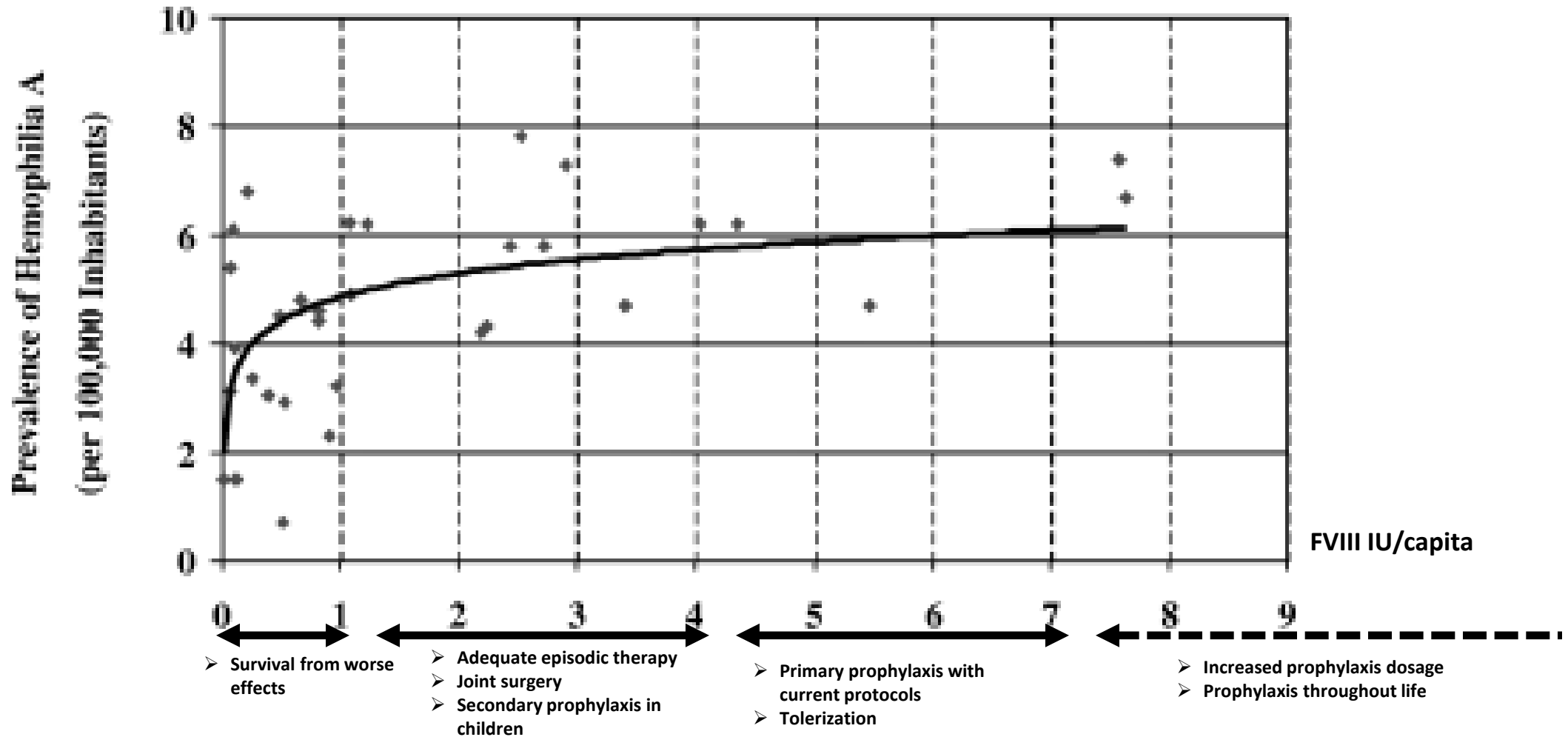


FACTOR VIII



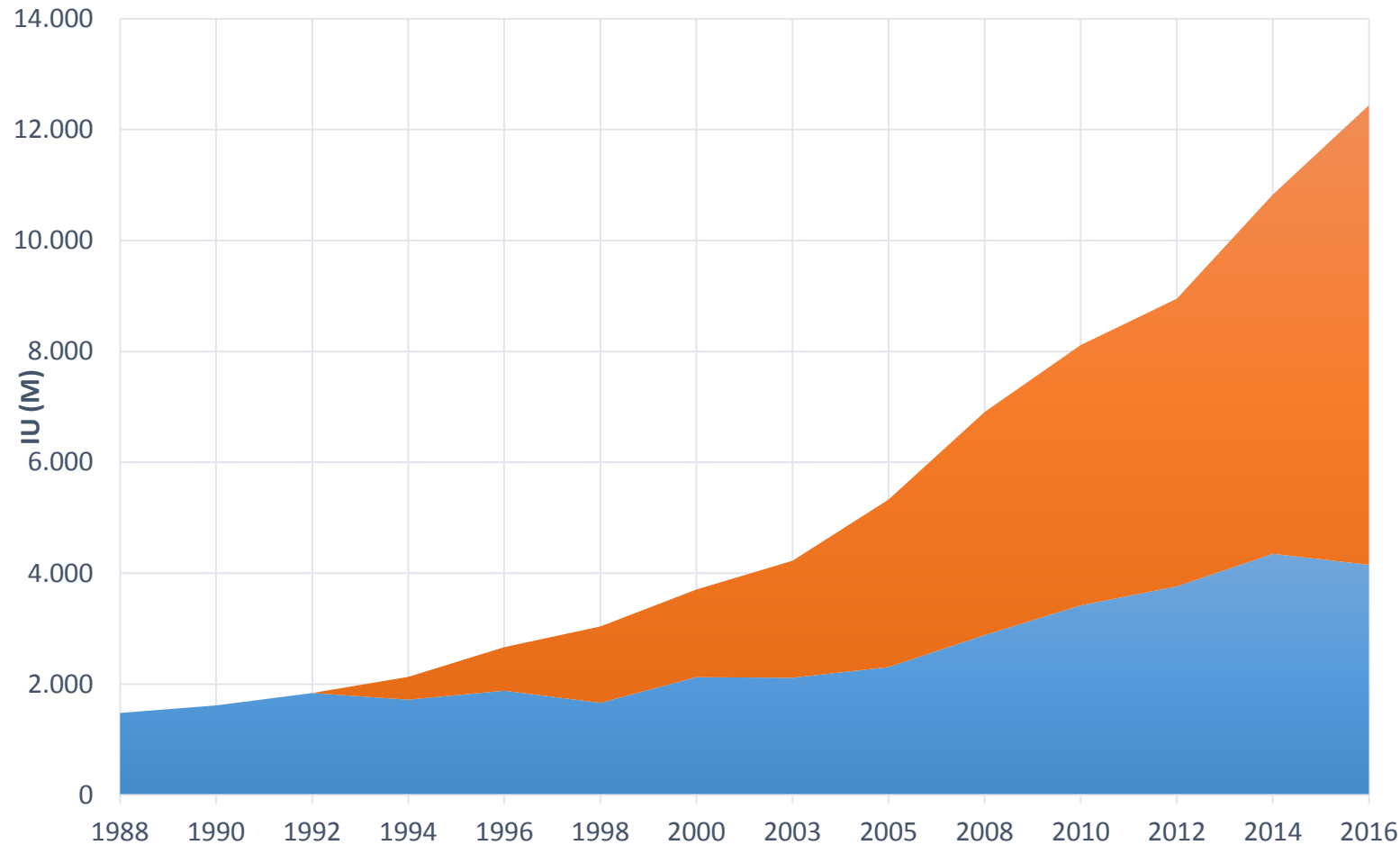
Prevalence of Haemophilia A

Effect of FVIII usage



Growth of Factor VIII in Units over the past 30 years

Worldwide FVIII units sold



2000-2016 CAGR

rFVIII: 10.9%

pdFVIII: 4.3%

Total FVIII: 7.9%

Recombinant Factor VIII

Plasma-derived Factor VIII

Impact of inhibitors on hemophilia A mortality in the United States

Cause of death category	With inhibitors	Without inhibitors	<i>P</i> -value ^ε
	<i>N</i> (%)	<i>N</i> (%)	
Hemophilia related	20 (41.7)	46 (12.0)	<0.001
HIV related	5 (10.4)	71 (18.5)	
Liver disease related	8 (16.7)	123 (32.0)	
Suicide	0	5 (1.3)	
Other	10 (20.8)	104 (27.1)	
Unknown	5 (10.4)	35 (9.1)	

Type of FVIII concentrates

The most controversial risk factor for the development of inhibitors in hemophilia patients depends on the type of the therapeutic molecule used, plasma-derived concentrates or recombinant rFVIII

- **Plasma-derived** products may vary in purity and VWF content
- **Recombinant** products produced in mammalian tissue culture are of high purity and do not contain VWF

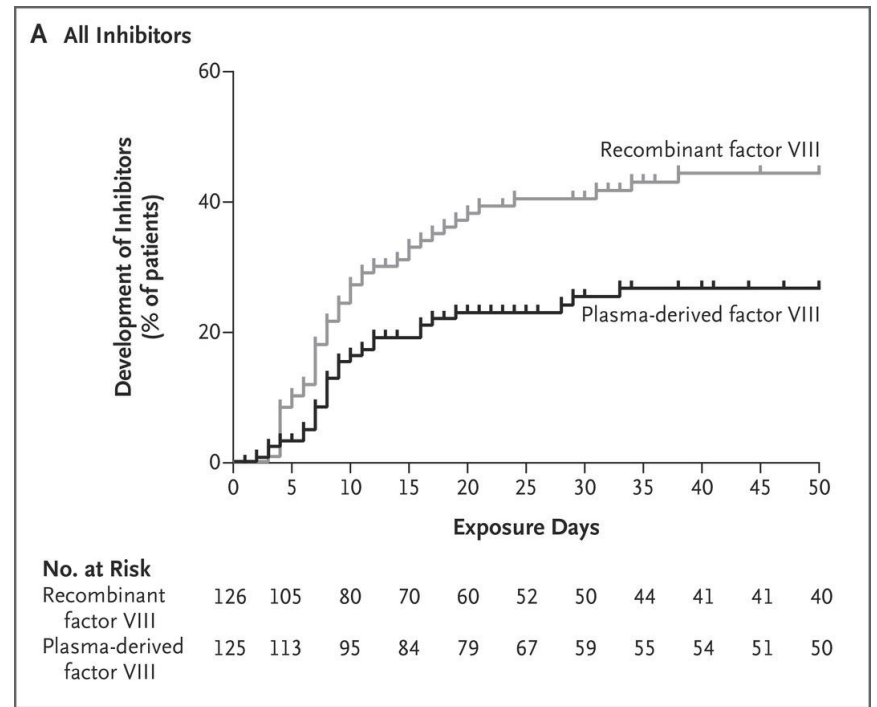
	Components in cell culture medium	Primary stabilizer in formulation
First generation <i>Recombinate</i> ^o	Bovine serum proteins	Human serum albumin
Second generation <i>ReFacto</i> [^] <i>Kogenate FS</i> ^o / <i>Helixate FS</i> ^o	Human serum albumin Human plasma protein solution	Sucrose Sucrose
Third generation <i>Advate</i> ^o <i>Xyntha</i> [^]	<i>Non-human or animal-derived</i> <i>Non-human or animal-derived</i>	Trehalose Sucrose

ORIGINAL ARTICLE

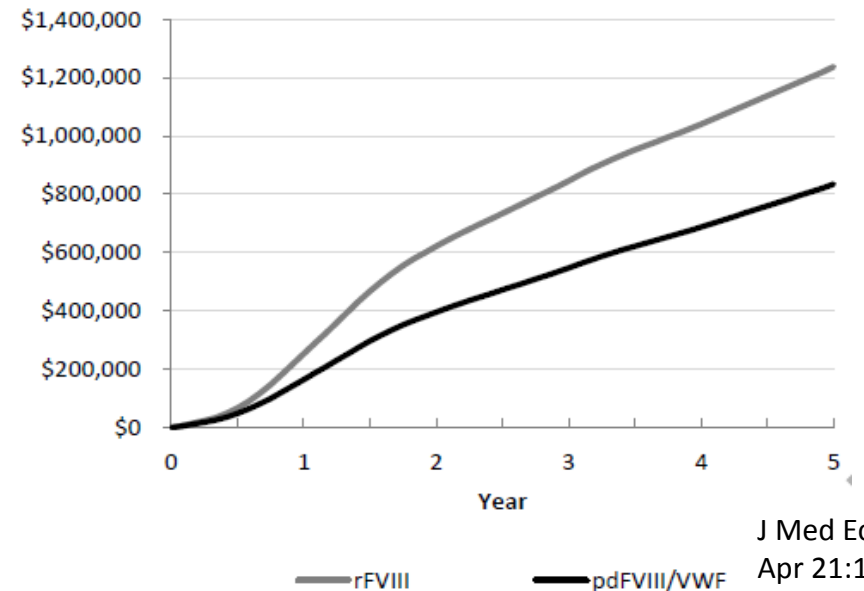
A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

F. Peyvandi, P.M. Mannucci, I. Garagiola, A. El-Beshlawy, M. Elalfy, V. Ramanan, P. Eshghi, S. Hanagavadi, R. Varadarajan, M. Karimi, M.V. Manglani, C. Ross, G. Young, T. Seth, S. Apte, D.M. Nayak, E. Santagostino, M.E. Mancuso, A.C. Sandoval Gonzalez, J.N. Mahlangu, S. Bonanad Boix, M. Cerqueira, N.P. Ewing, C. Male, T. Owaidah, V. Soto Arellano, N.L. Koblinsky, S. Majumdar, R. Perez Garrido, A. Sachdeva, M. Simpson, M. Thomas, E. Zanon, B. Antmen, K. Kavakli, M.J. Manco-Johnson, M. Martinez, E. Marzouka, M.G. Mazzucconi, D. Neme, A. Palomo Bravo, R. Paredes Aguilera, A. Prezotti, K. Schmitt, B.M. Wicklund, B. Zulfikar, and F.R. Rosendaal *N Engl J Med* 2016;

Patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant factor VIII.



. *N Engl J Med* 2016;374:2054-2064



SIPPET – Therapeutic Progression

- The SIPPET study is the first RCT to demonstrate that the risk of inhibitor development in PUPs is nearly doubled when using rVIII vs pdVIII/VWF.
- Inhibitor development in patients has a catastrophic effect on patient well-being and on health care budgets.
- Minimising the risk of inhibitor through the use of pdVIII/VWF for the first 50 ED of treatment is an evidence-based measure, reflecting the therapeutic principle of «Primum Non Nocere».

Hemophilia A Product Choice in the US since 2000

Jan 2000

Alphanate
Koate DVI
Hemofil M
Monoclate
Recombinate
Kogenate
Helixate

Jan 2010

Alphanate
Koate DVI
Hemofil M
Monoclate
Recombinate
Kogenate FS
Helixate FS
Advate
Xyntha

Jan 2018

Alphanate
Koate DVI
Hemofil M
Monoclate
Recombinate
Kogenate FS
Helixate FS*
Advate
Xyntha
Novoeight
Eloctate
Nuwiq
Adynovate
Kovaltry
Afstyla
Hemlibra

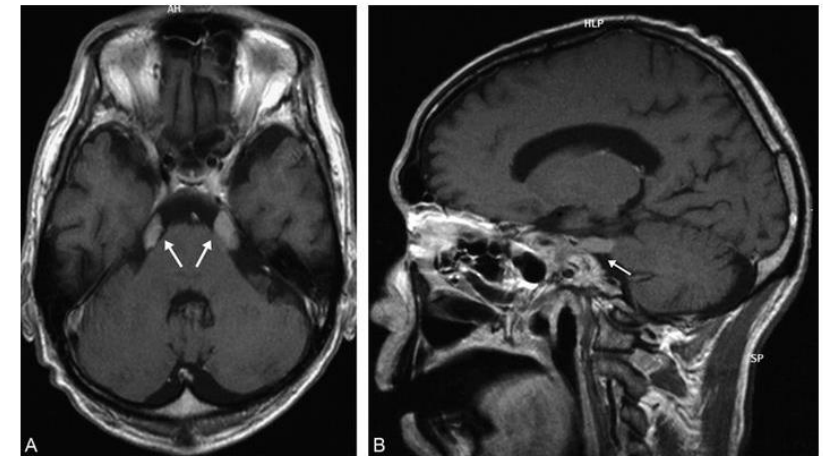
*Helixate FS is no longer produced in 2018, but supplies still exist



THE CURRENT DRIVER



CIDP- MRI



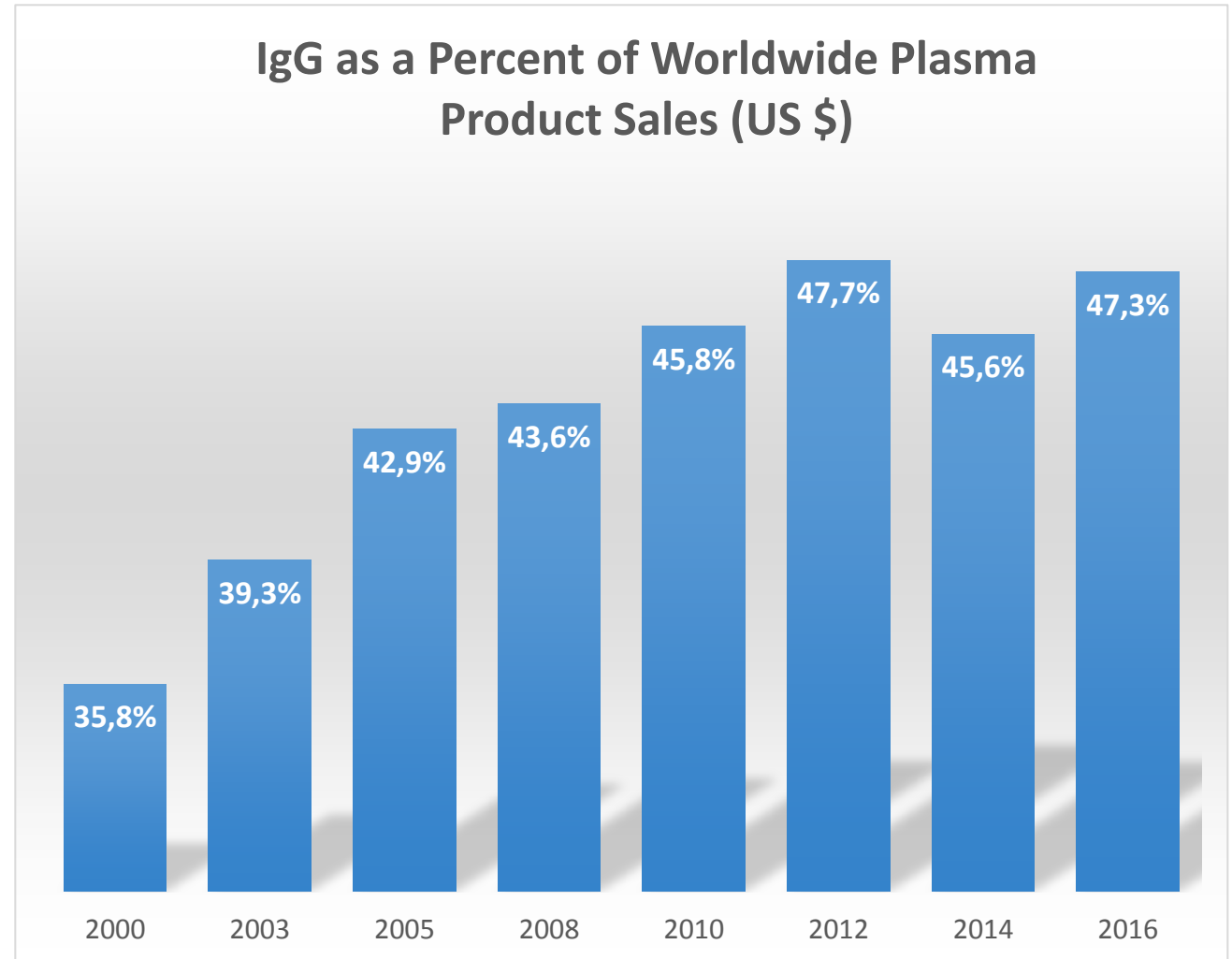
Hypertrophied trigeminal nerves

IMMUNOGLOBULIN

IgG Increasingly Dominates Plasma Protein Sales

Share of IgG went from under 36% in 2000 to almost 48% in 2016 in US dollars

Average annual growth from 2000 to 2016 for IgG was 11.0%, compared to 7.7% for all other proteins

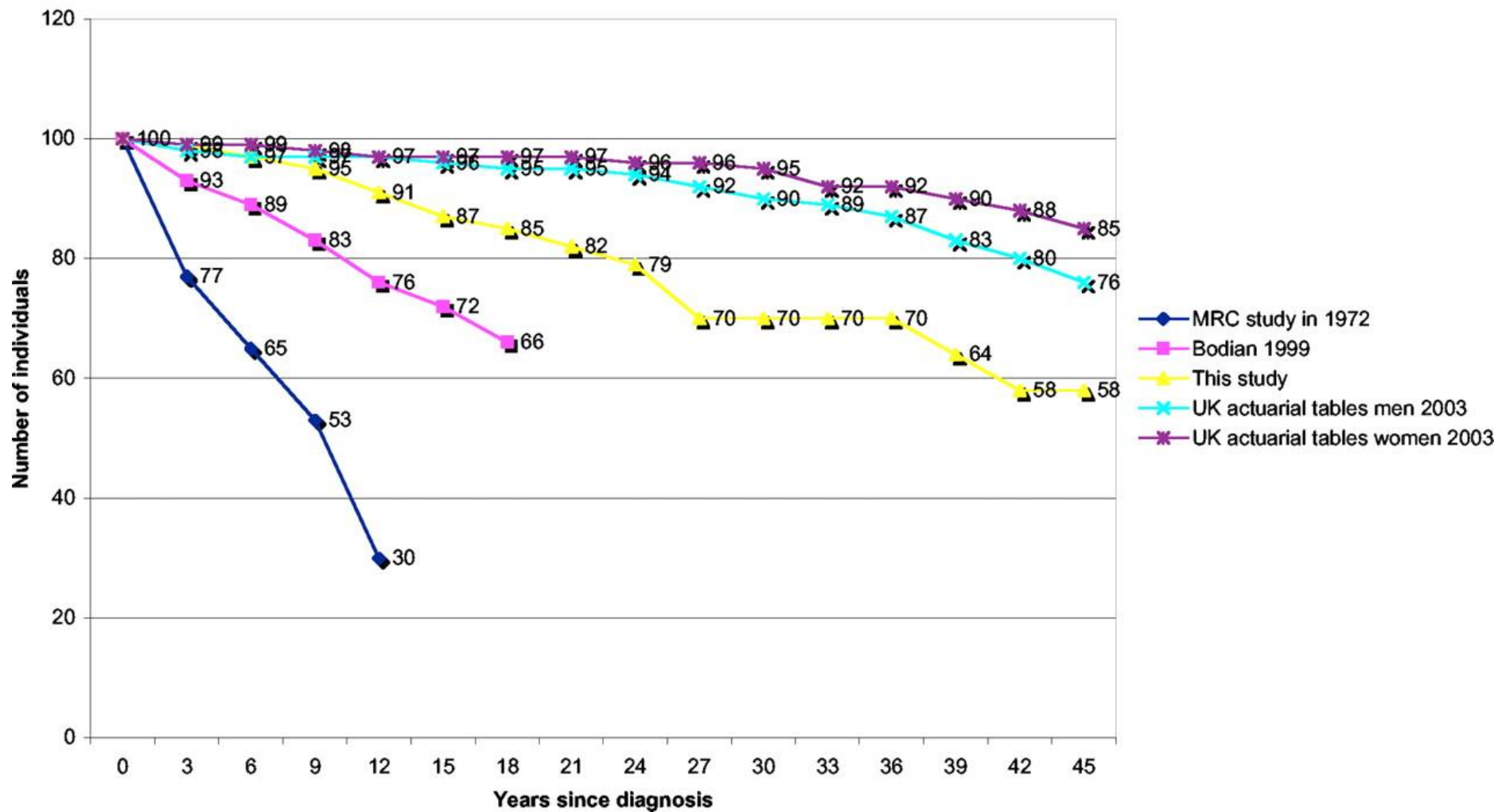




Mortality in Common Variable Immune deficiency

Mortality by year since diagnosis

Survival





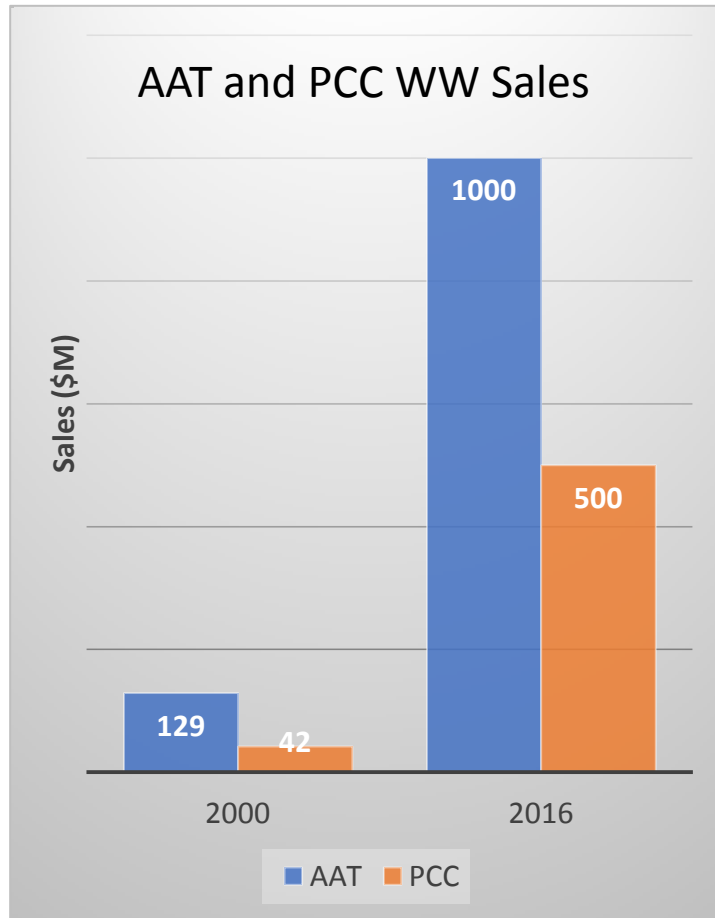
Cochrane Database of Systematic Reviews

Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Review)

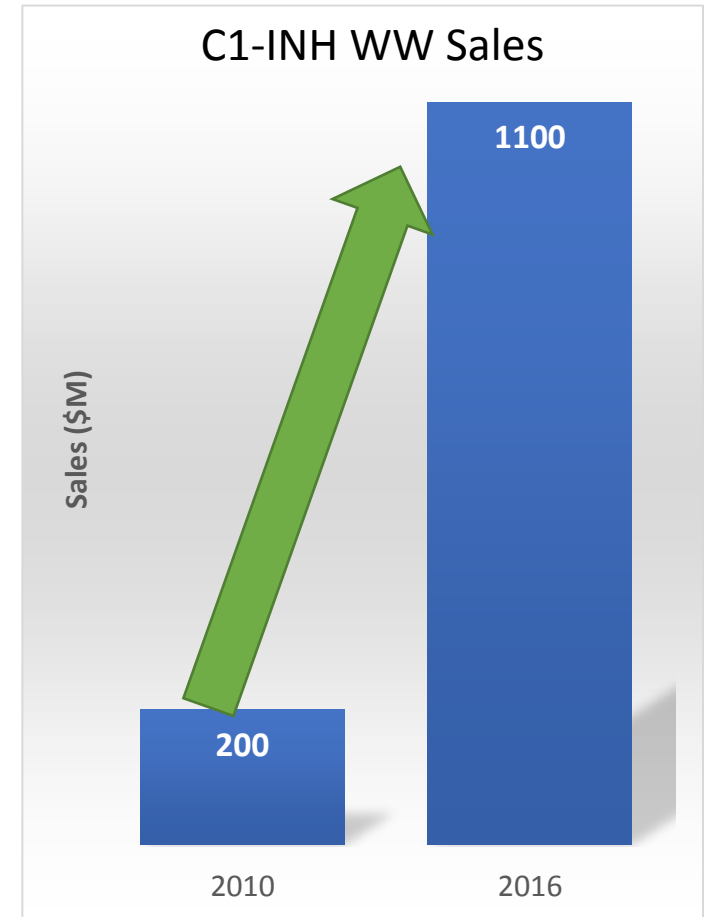
Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN

«The evidence from RCTs shows that IVIg improves disability for at least two to six weeks compared with placebo, with an NNTB of three. During this period it has similar efficacy to plasma exchange, oral prednisolone and intravenous methylprednisolone. In one large trial, the benefit of IVIg persisted for 24 and possibly 48 weeks. Further research is needed to compare the long-term benefits as well as side effects of IVIg with other treatments.»

Other Plasma Proteins with High Growth



- AAT (Alpha-1 Antitrypsin)
 - 2000-2016 annual growth rate of 13.7%
- PCC (Prothrombin Complex Concentrate)
 - 2000-2016 annual growth rate of 16.7%



- C1-INH (C1- Esterase Inhibitor)
 - 4th most valuable plasma protein in 2016





- The plasma therapeutics industry continues to grow and provide a number of important medicines.
- The evidence base for the use of plasma therapies ranges from the robust to the debatable , with chronic, congenital deficiencies having the highest level of evidence.
- The industry's current driver is immunoglobulin, the consumption of which continues to grow, particularly as a therapy for a number of automimmune disorders.
- While alternative treatments to many plasma therapies have been developed, the financial sector appears to be confident in the industry's medium term future.



Acknowledgements

Thanks to Dr Matthew Hotchko and the Market Research Bureau for data and analysis