Inhibitors, EIN and inhibitor treatment guidelines

Cedric HERMANS

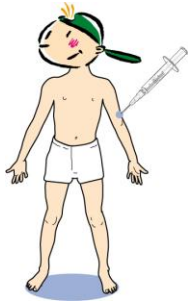
European Haemophilia Consortium / World Haemophilia Day

Wednesday 19 April 2017

EDQM

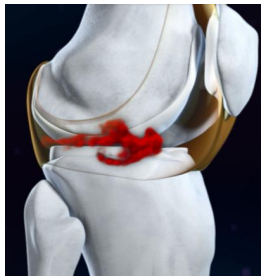
Strasbourg, France

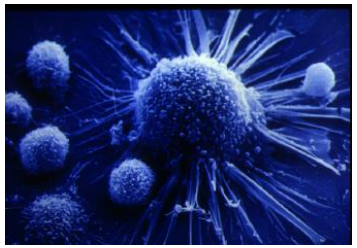
Positive and negative impact of substitution with FVIII in a patient with severe HA

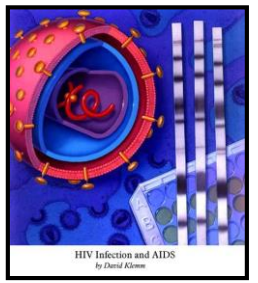


Safety

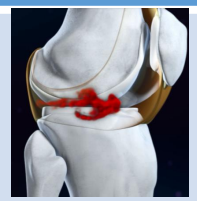
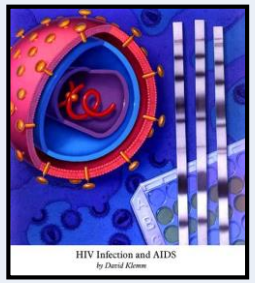
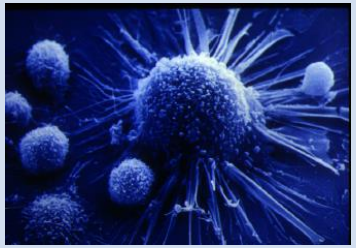
Haemostatic Efficacy	Inhibitor formation	Infectious complications	Adverse Events
Bleeding : control / prevention	**Formation of antibodies to FVIII**	**Pathogen transmission**	**Adverse events (AEs)**







Current ambitions in haemophilia therapy

Goals		In clinical practice
« Zero » bleed		Achievable with personalized primary or secondary prophylaxis
« Zero » infection		Achievable with current plasma-derived or recombinant concentrates Eradication of HCV now possible in most patients
« Zero » Inhibitor		Currently impossible to avoid INH formation in many patients Currently impossible to eradicate INH in many patients

Improvement in infectious safety of replacement therapy has been successful

The current reduction in infective risk of fractionated plasma products has been achieved through a multi-step process.

No transmission of HBV, HCV or HIV attributable to manufactured plasma derivatives licensed for use in the US has been reported since 1985.

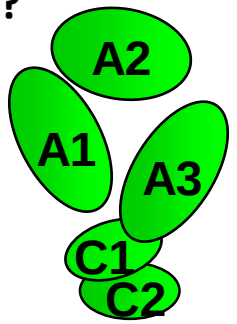
The most modern recombinant products do not contain exogenous animal or human components and therefore do not carry a risk of transmission of known or unknown pathogens.

Not all previously untreated patients (PUPs) with severe HA are tolerant to exogenous FVIII

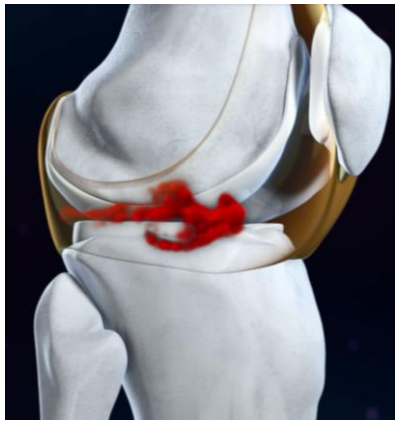
70-95% of the patients do not develop an INH

Ignorance of therapeutic FVIII ?

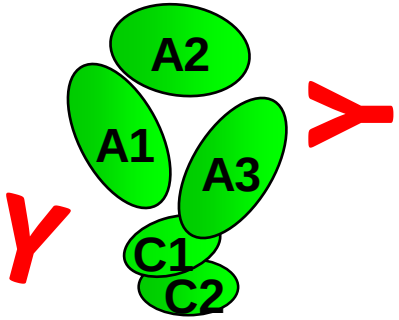
Induction of tolerance ?



FVIII



5-30% of previously untreated patients receiving FVIII develop an INH



FVIII inhibitors

The worst complication that commonly occurs to PUPS with severe hemophilia

(30-40%)

Inhibitor development

Development of an inhibitor is devastating – it results in ...

Need for ports

Need for ITI

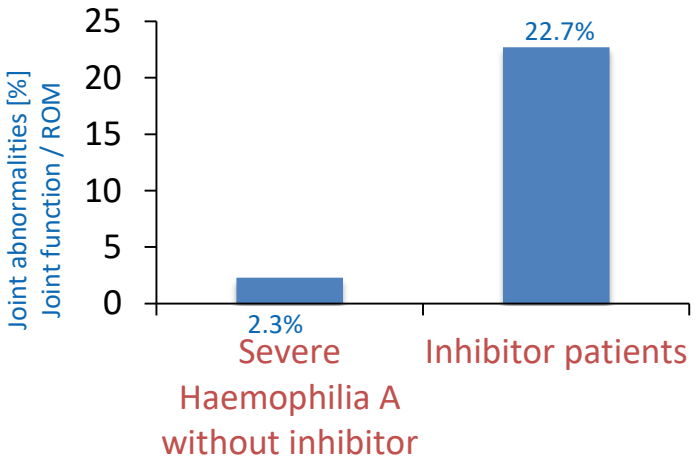
More difficult to treat bleeds

↑ susceptibility to life-threatening bleeds

Worse quality of life

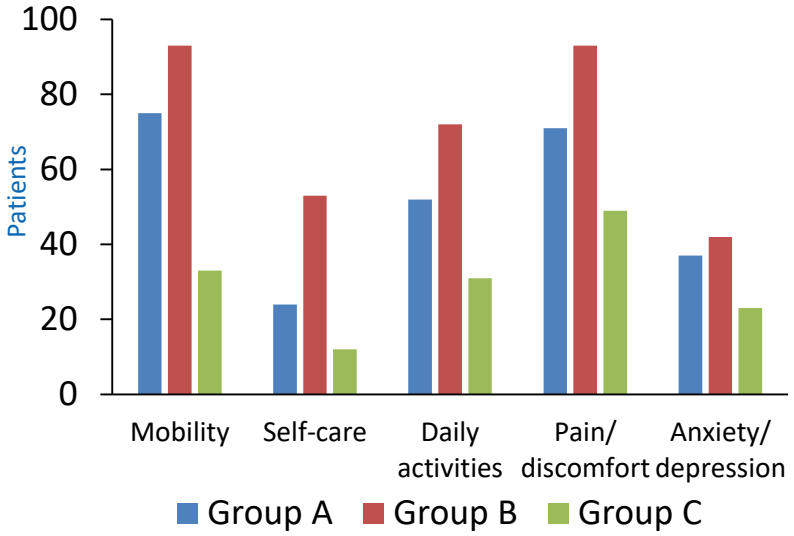
The poor long-term outcome in patients with persistent inhibitor compared with haemophilia without inhibitors ....

Worse Joint Status



Leissinger et al, Blood 2001

Worse Quality of Life



Morfini et al, Haemophilia, 13:606-12 2007

Group A - Severe haemophilia A *with* inhibitors >5 yrs, age 14-35 years

Group B - Severe haemophilia A *with* inhibitors >5 yrs, age 36-65 years

Group C - Severe haemophilia A *without* inhibitors, age 14-35 years

Impact of inhibitors on hemophilia A mortality in the US

- Retrospective analysis (CDC) – 7386 patients with severe HA
- 627 patients with active inhibitors
- Active inhibitor patients more likely among young (<11yrs) and older age group (>45 yrs)
- Intracranial hemorrhage was the major cause of death among inhibitor (70%) and non-inhibitor (67%) patients
- ***Haemophilia related (bleeding events) cause of death was significantly more frequent among patients with active inhibitors (42%) than among those without (12%) (p<0.0001)***

Walsh et al, AJH 2015

Improvement in immunological safety has been less successful than infectious safety

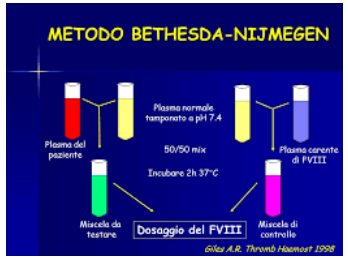
Many risk factors for INH development have been identified and studied

Strategies to bypass FVIII / FIX and eradicate INH have been successfully developed and validated

Strategies have been proposed to estimate, reduce or minimize the risk of INH development

For many PUPS with severe HA, INH development remains a fatality

INHIBITOR in patients with haemophilia : short history of diagnosis, risk factors and treatment strategies



FEIBA

PedNet Haemophilia Registry

Réseau FranceCoag

UKHCDO
UNITED KINGDOM HAEMOPHILIA CENTRES DOCTORS' ORGANISATION

SIPPET PROJECT

1980 1990 2000 2010

Brackmann & Gormsen, Lancet 1977, 2: 933.

Cohort studies

Bonn protocol
Malmö protocol
Dutch protocol
Low/intermediate dose protocols

National and International Registries

IITR
NAITR
GITR

Randomized trials

RESIST
Response
Studies
Immunotolerance

Successful treatment of hemophilia a inhibitor patients with an induced immunotolerance

RISK FACTORS FOR INHIBITOR DEVELOPMENT

Non-modifiable

- Haemophilia severity
- FVIII/IX mutations
- HLA Class II

Genetics

- Polymorphisms in immunoregulatory genes
- Family history
- Ethnicity

Modifiable

Treatment-related

- Intensive FVIII/IX exposure
- Immunological challenge

FVIII/FIX ANTIBODIES

Type of treatment

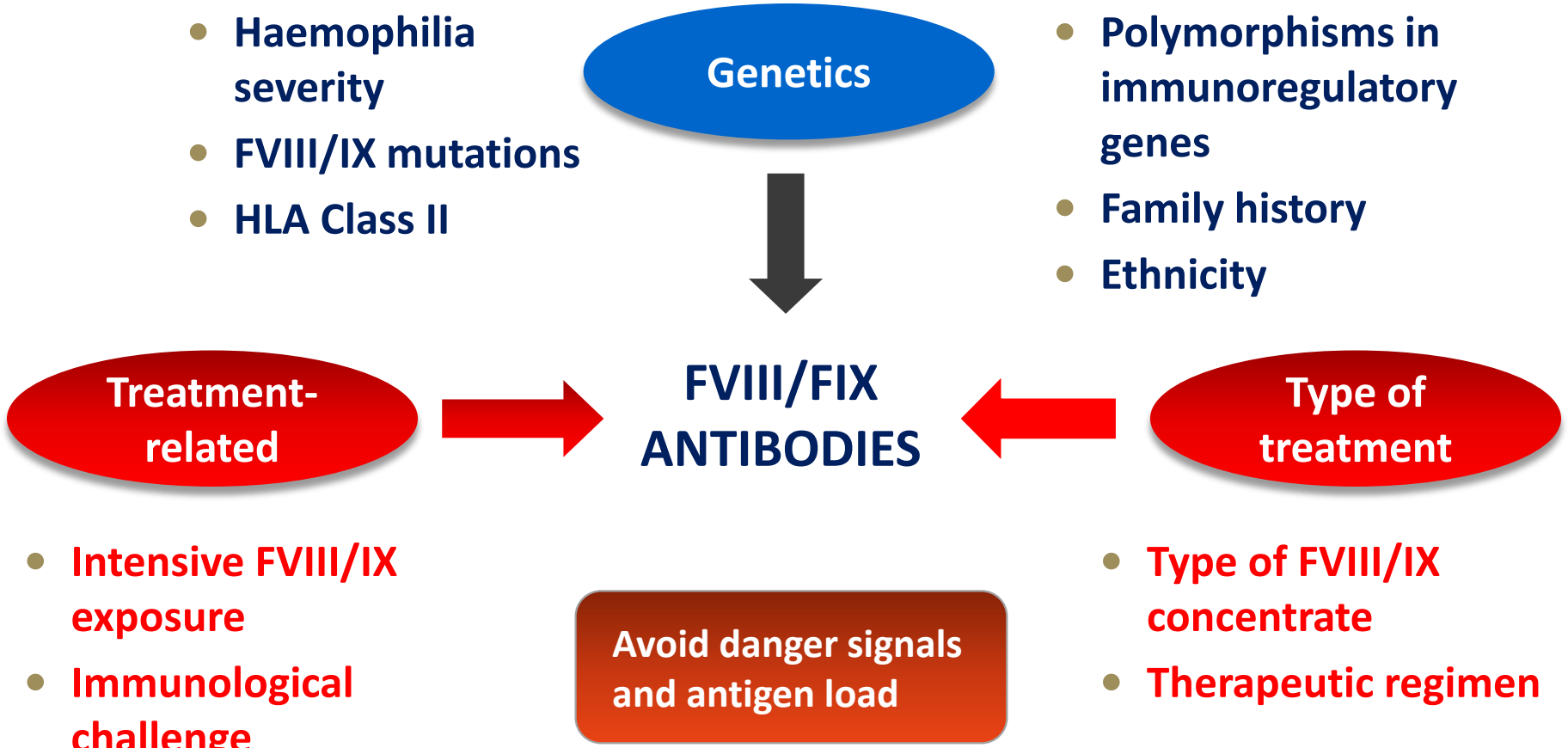
- Type of FVIII/IX concentrate
- Therapeutic regimen

Inhibitor risk factors in previously untreated patients

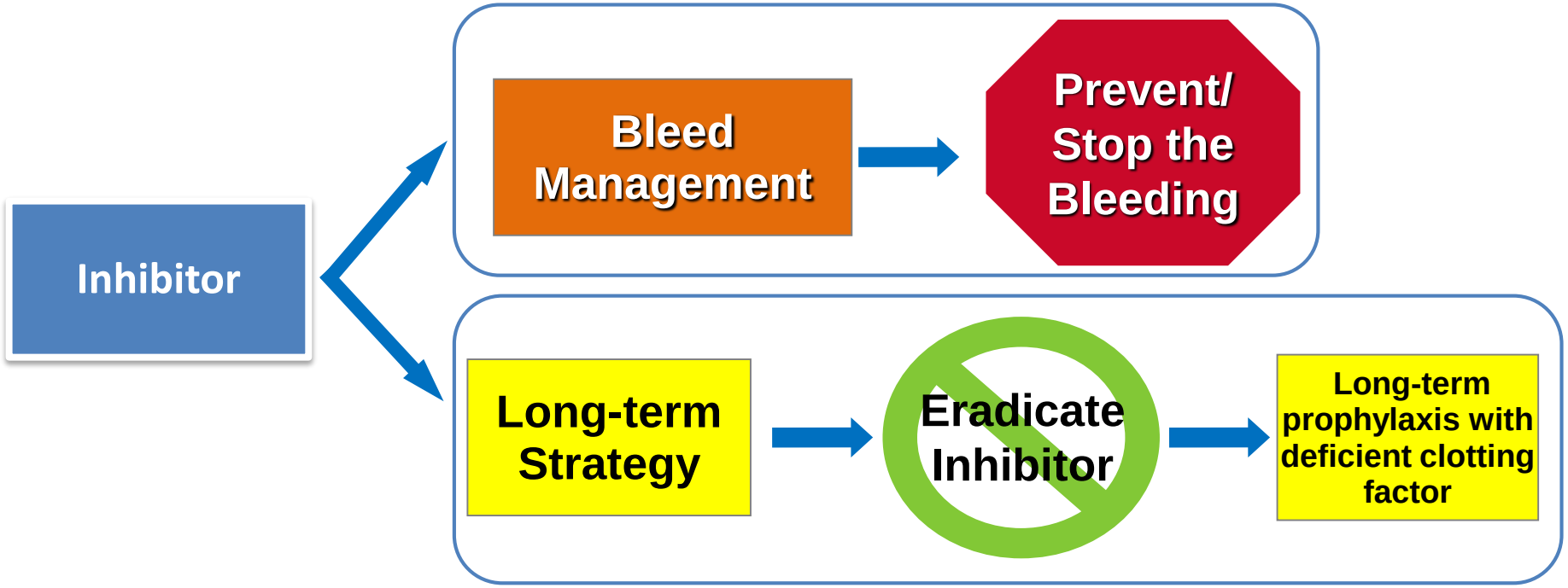
Inhibitor risk factor	Level of evidence
Family history	Well established
Race	Established but not well understood
F8 mutation type	Well established
F8 polymorphisms	Conflicting reports
MHC classes I/II	Conflicting reports
Polymorphisms in cytokines and inflammatory genes	Some evidence but not well understood
Trauma/surgery	Established but not well understood
Inflammation/infection	Established but not well understood
Early intense exposure	Established but not well understood
Age at first exposure	No clear evidence
Early Prophylaxis	Some evidence but not well understood
Vaccinations	No clear evidence

Adapted from Carcao M. and Ewenstein B. Haemophilia, Volume 22, Issue 1 January 2016 Pages 22–31

RISK FACTORS FOR INHIBITOR DEVELOPMENT

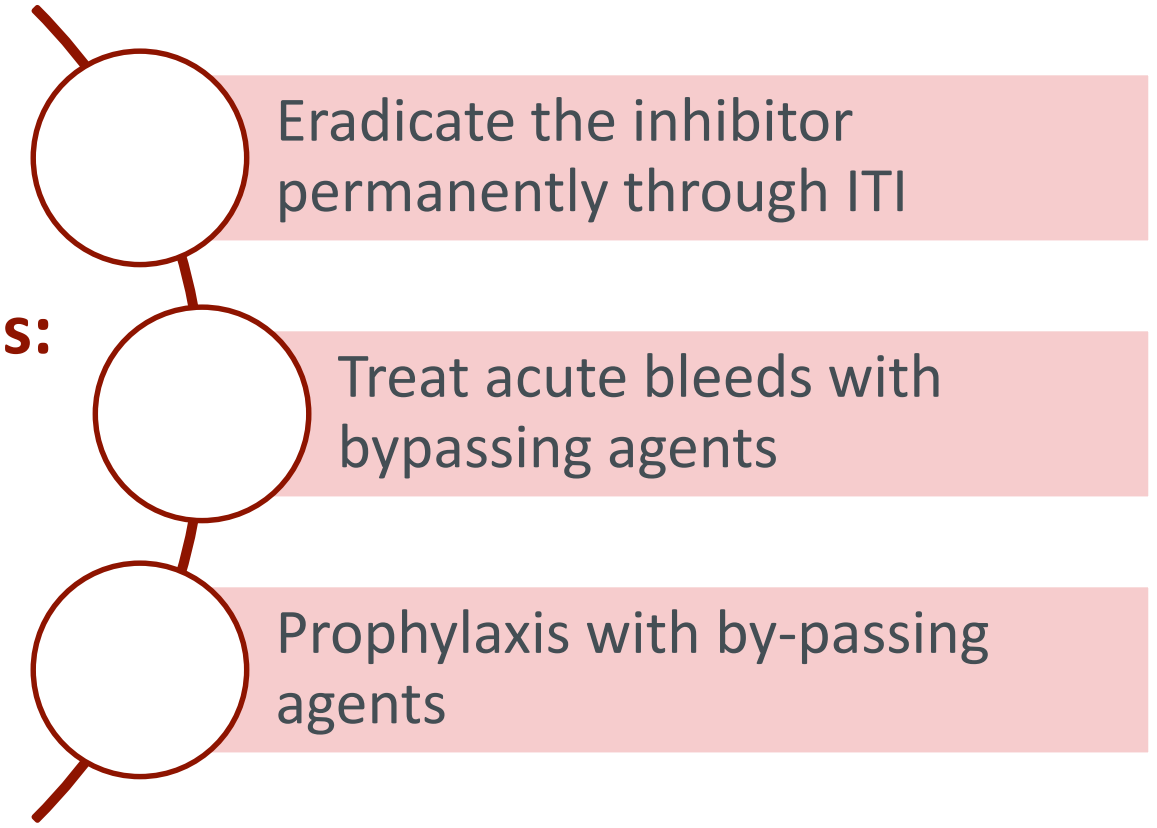


INHIBITOR: TREATMENT STRATEGIES



Current Treatment Options for Inhibitors

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.

Treatment strategies in inhibitor patients

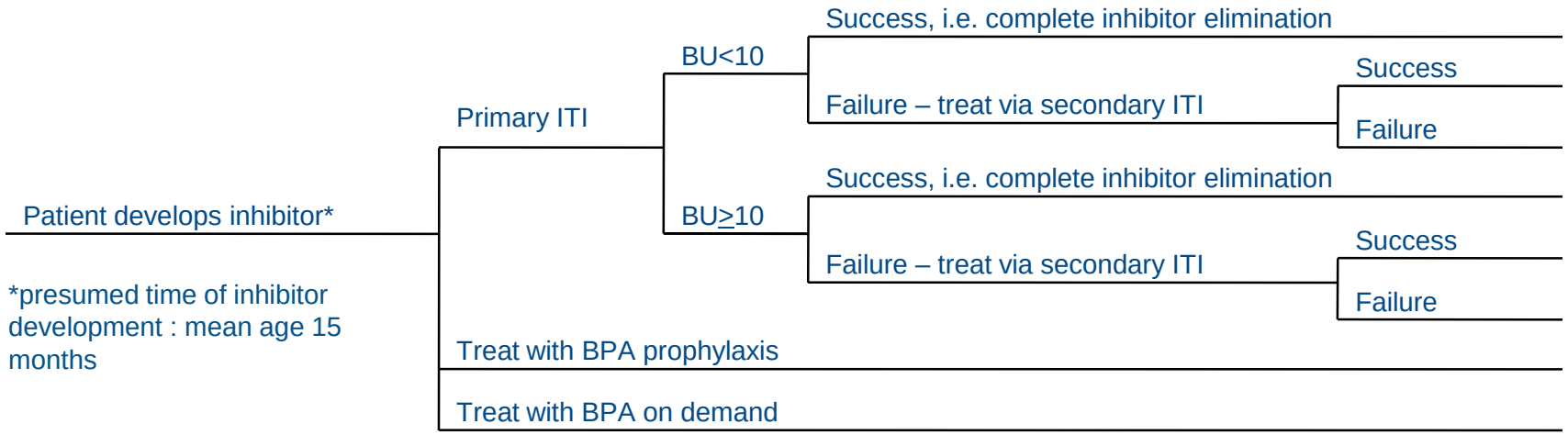


Table 5. Preliminary results from the decision analytic model, estimated over the lifetime of the patient. Costs are in 2013 US dollars; discounting is at 3%.

	ITI	On-demand	Prophylaxis
Drug and hospitalization cost (discounted)	$22,201,832	$38,656,756	$42,104,865
Life years (projected)	74.3	69.6	69.6
QALYs (discounted)	25.1	14.7	20.5
Bleeding events (projected)	801	1819	694

ITI, immune tolerance induction; QALYs, quality-adjusted life years.

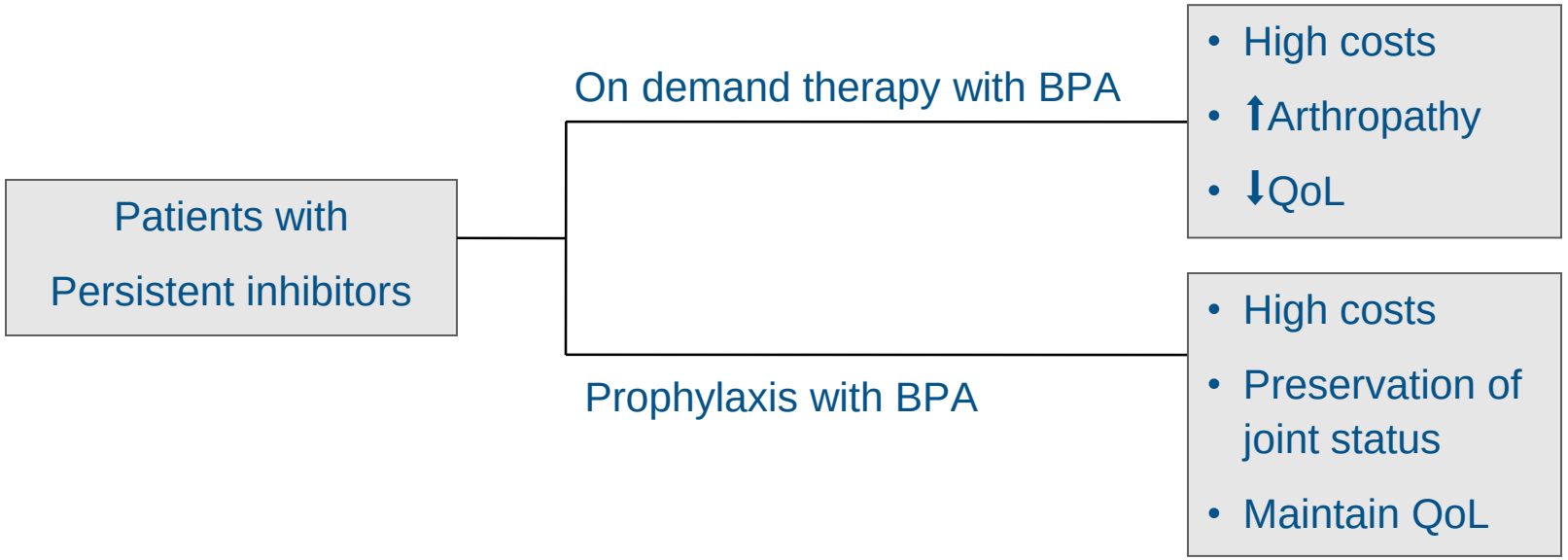
ITI associated with

- *lower drug and hospitalization costs*
- *longer projected life expectancy*
- *Higher QALY´s*
- *Fewer projected bleeding events*

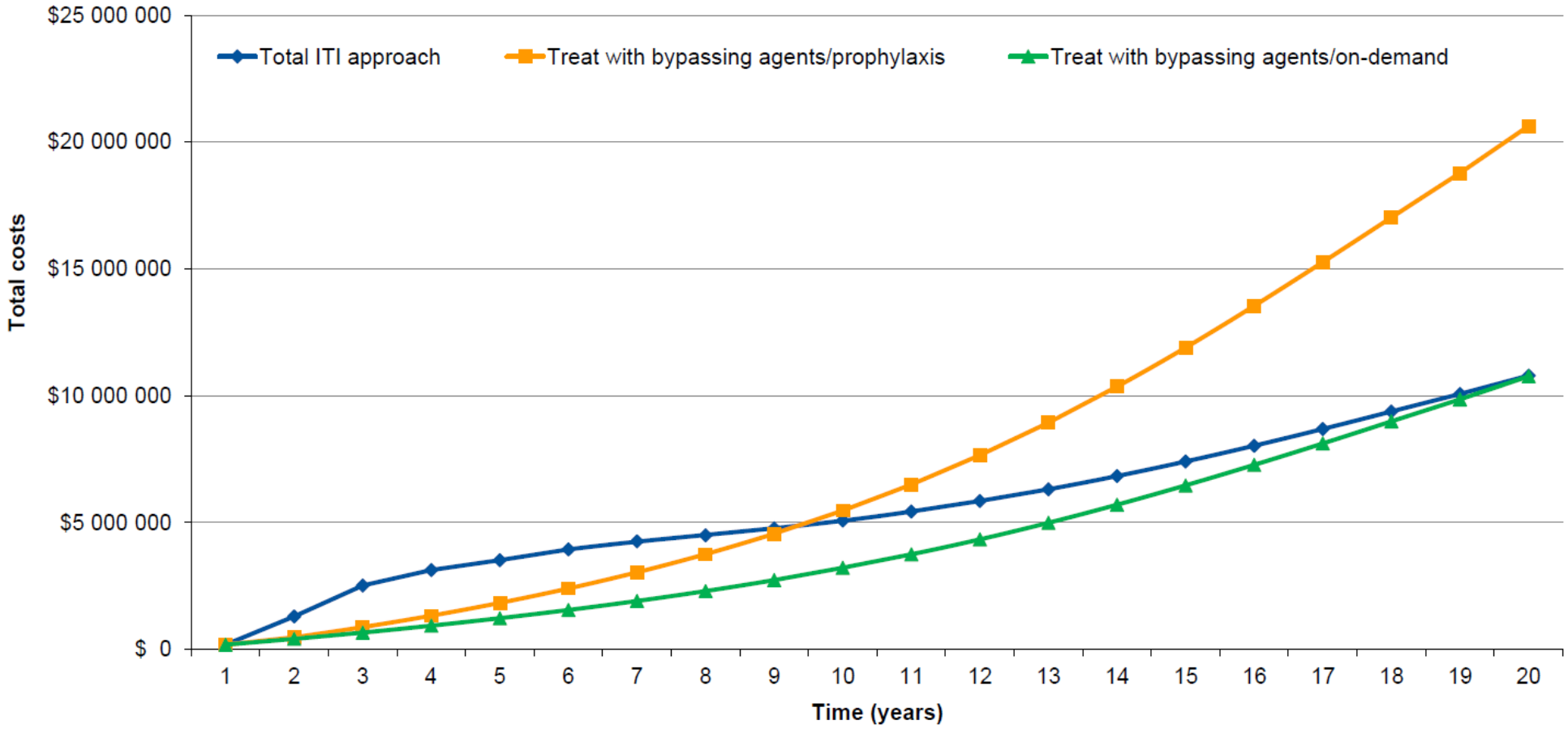
compared to prophylaxis or on demand therapy with BPA

Kessler et al, *Haemophilia*, 2014

Treatment strategies in inhibitor patients who failed ITI / not eligible for ITI



Cumulative Costs Over Time for Patients Treated via ITI, Prophylaxis, and On-demand Treatment with BPA



Patients with INH :
An heterogenous population

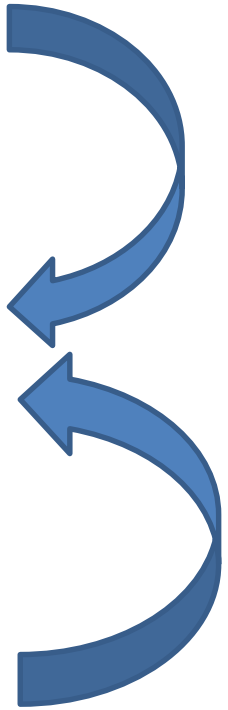
Three groups

Patients with a recently diagnosed INH (Low or High Titre) candidates for ITI

Patients who underwent successful eradication

Patients with long-standing or persistent INH

ITI failure or never treated with ITI How many ?



?

Immune tolerance induction (ITI)

- Immune tolerance induction (ITI) is the only therapeutic approach proven to eradicate persistent inhibitors in haemophilic patients, thus allowing one to restore safe and effective FVIII replacement treatment and, particularly, the feasibility of prophylaxis.

- This objective is crucial in children with inhibitors to preserve their joints from haemophilic arthropathy, to provide a satisfactory quality of life, and to reduce long-term morbidity and mortality and the impact of inhibitor-related complications on healthcare costs.

ITI : A long-term fruitful investment

The huge economic investment of ITI may provide long-term FVIII tolerance and consequent benefits in the large majority of patients

The many current challenges that INH patients and treaters are facing daily :

- Difficult diagnosis
- Complex management (choice of optimal treatment modalities, cost of ITI, venous access, need for highly specific multidisciplinary care…)
- Major need for patients' active involvement / commitment
- Patients' isolation, under-representation
- Limited scientific evidence / lack of valid data
- Lack of ambition / perceived as an unoivadable fatality

Ambitions in haemophilia care

Goals	Clinical practice
« Zero » bleed	YES WE CAN
« Zero » infection	YES WE CAN
« Zero » Inhibitor	WE CANNOT HOWEVER WE CAN DO MUCH BETTER IN TERMS OF MANAGEMENT, AWARENESS, PATIENTS' SUPPORT, PROMOTION OF PATIENTS RIGHTS AND ACCESS TO CARE,…

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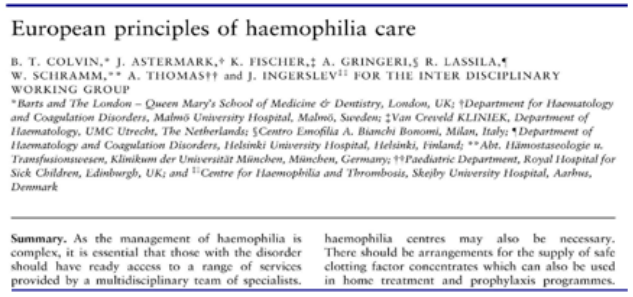
How can we realistically and practically achieve this ?

The 10 European Principles of Hemophilia Care

1. A central hemophilia organisation with supporting local groups
2. National hemophilia patient registries
3. Comprehensive care centres and hemophilia treatment centres
4. Partnership in the delivery of hemophilia care
5. Safe and effective concentrates at optimum treatment levels
6. Home treatment and delivery
7. Prophylaxis treatment
8. Specialist services and emergency care
9. Management of inhibitors
10. Education and research



European principles of haemophilia care

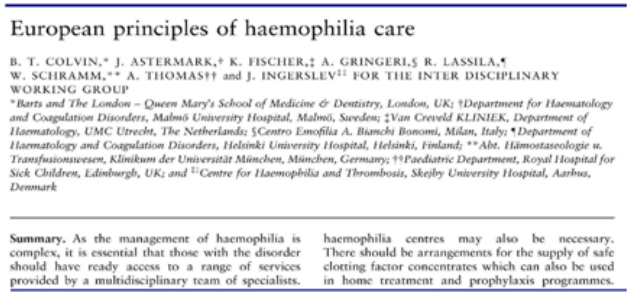
B. T. COLVIN,* J. ASTERMARK,† K. FISCHER,‡ A. GRINGERI,§ R. LASSILA,¶ W. SCHRAMM,** A. THOMAS†† and J. INGERSLEV‡‡ FOR THE INTER DISCIPLINARY WORKING GROUP

*Barts and The London – Queen Mary's School of Medicine & Dentistry, London, UK; †Department for Haematology and Coagulation Disorders, Malmö University Hospital, Malmö, Sweden; ‡Van Creveld KLINIEK, Department of Haematology, UMC Utrecht, The Netherlands; §Centro Emofilia A. Bianchi Bonomi, Milan, Italy; ¶Department of Haematology and Coagulation Disorders, Helsinki University Hospital, Helsinki, Finland; **Abt. Hämostaseologie u. Transfusionswesen, Klinikum der Universität München, München, Germany; ††Paediatric Department, Royal Hospital for Sick Children, Edinburgh, UK; and ‡‡Centre for Haemophilia and Thrombosis, Skejby University Hospital, Aarhus, Denmark*

Summary. As the management of haemophilia is complex, it is essential that those with the disorder should have ready access to a range of services provided by a multidisciplinary team of specialists. haemophilia centres may also be necessary. There should be arrangements for the supply of safe clotting factor concentrates which can also be used in home treatment and prophylaxis programmes.

Colvin BT, Astermark J, Fischer K, et al. *Haemophilia* 2008; 14: 361-374

Principle 9



European principles of haemophilia care

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- **Management of Inhibitors**

  – Some people with haemophilia develop “inhibitors”, when their bodies inactivate the replacement clotting factor treatment. Those affected need to have immediate access to optimum treatments

  – Where appropriate, immune therapy induction therapy (ITT) and the management of bleeding should be administered by clinicians with the necessary expertise, in hospitals with appropriate clinical and laboratory resources

Kreuth IV: European consensus proposals for treatment of haemophilia with coagulation factor concentrates

Recommendation 7: People with inhibitors should have access to immune tolerance.

- With immune tolerance induction, 70% of patients achieve complete tolerance and a further 5% achieve a partial response.
- ITI is cost effective in the long term through the avoidance of repeated treatment of bleeding episodes with much more expensive bypassing agents.
- Immune tolerance induction therapy is still not readily available in several European countries.

Hay CR & DiMichele DM. Blood 2012; 119: 1335-44
Haemophilia. 2017 Apr 12. doi: 10.1111/hae.13211.

Kreuth IV: European consensus proposals for treatment of haemophilia with coagulation factor concentrates

People with inhibitors should have access to elective surgery at a specialist centre with relevant experience

- Surgery in patients with haemophilia and inhibitors can be performed safely using bypassing agents.

- Many patients with inhibitors are denied elective surgery which such as arthroplasty which could improve their quality of life.

- Some treatment centres still have reservations about the potential for bleeding. The initial high cost may be a considerable barrier. A number of economic evaluations indicate that surgery may prove cost effective in the longer term.

- Surgery in patients with inhibitors should only be carried out in centres with previous experience. Where this is not feasible locally, patients should be referred to another centre with the requisite experience (across national borders if necessary).

Santagostino E et al. Blood Reviews 2015; 29 (Suppl 1): S9-18. Négrier C et al. Haemophilia 2013;19: e143-150. Dekoven M, et al. J Med Econ 2012; 15: 305-312. Lyseng-Williamson KA & Plosker GL. Pharmacoeconomics 2007; 25: 1007-1029. Ali JM, Howieson AJ et al. J Arthroplasty 2012; 27; 1413.e11-1413.e14. Haemophilia. 2017 Apr 12. doi: 10.1111/hae.13211.

Establishment of European principles of inhibitor treatment (EHC – EAHAD)

1. Lifelong Awareness of the Incidence of Inhibitors and Risk Factors
2. Early Recognition and accurate diagnosis
3. Organisation of Care and Communication Between All Stakeholders
4. Inhibitor eradication by Immune Tolerance Induction Therapy
5. Hemostatic Treatment with Bypassing Agents
6. Access to and Optimal Preparation for Surgery and Invasive Procedures
7. Delivery of Specialist Nursing Care
8. Provision of Tailored Physiotherapy Care
9. Access to Psychosocial Support
10. Involvement in the Research and Innovation

EHC

EAHAD
European Association for Haemophilia and Allied Disorders

EIN

European Inhibitor Network

WORLD HAEMOPHILIA DAY

Strasbourg, 19 April 2017

THANK YOU FOR YOUR ATTENTION