

Ageing and Haemophilia

Impact of new treatments



IHS Ageing Conference

23rd June 2018

Dr Niamh O'Connell

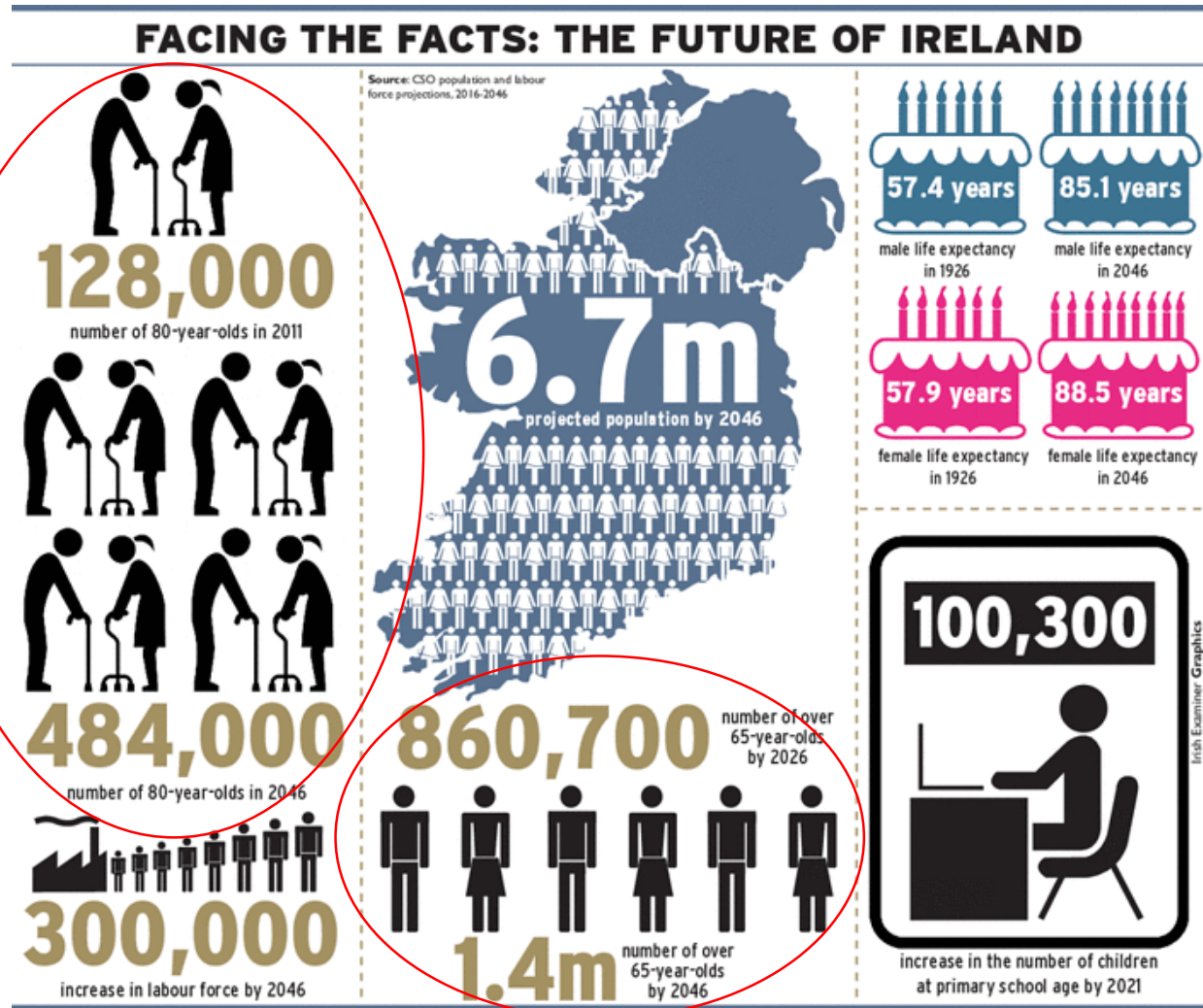
NCC

National Coagulation Centre

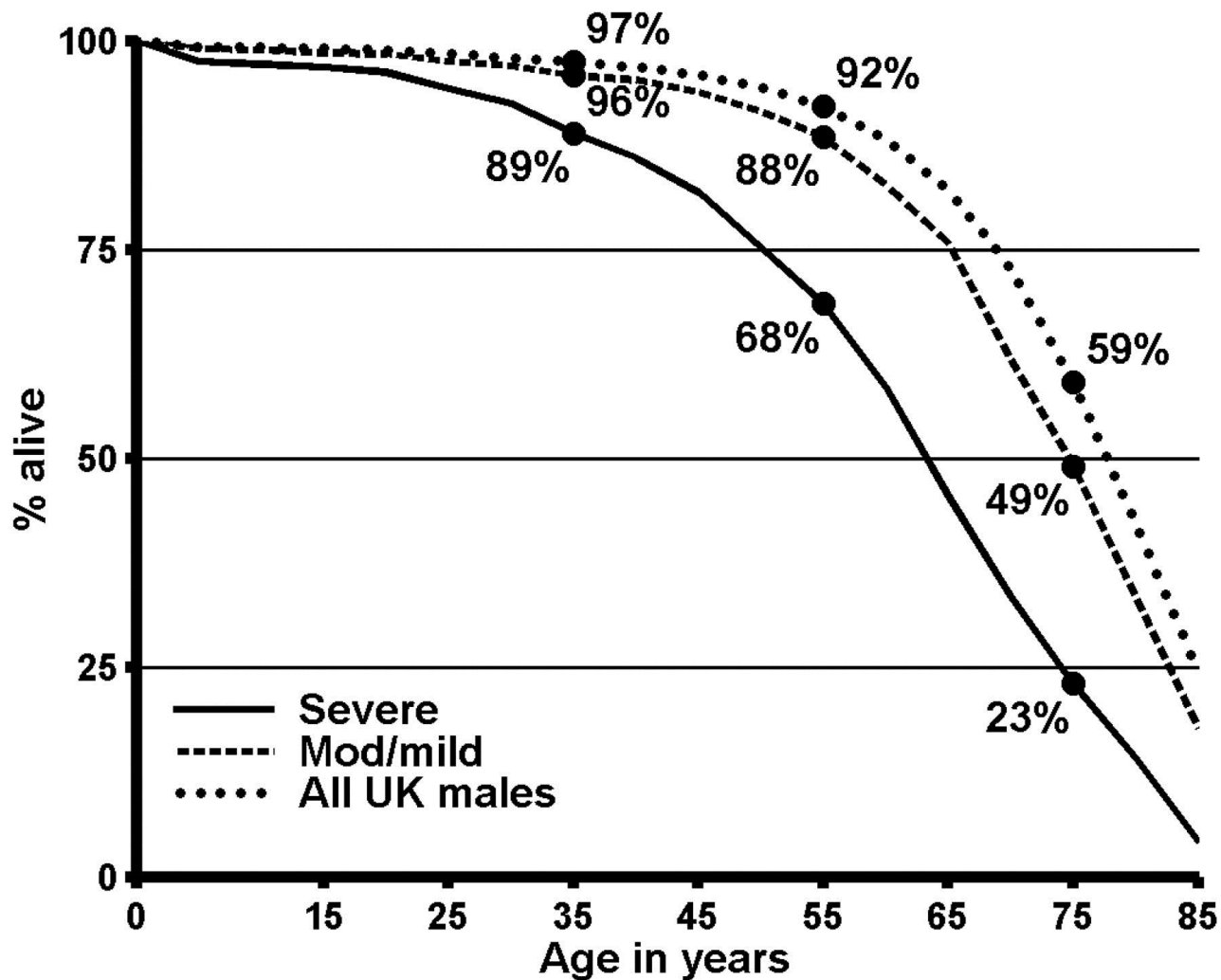


ST. JAMES'S
HOSPITAL

Ireland in 2046 – 60% increase in +65s and 2.8 times increase in +80s

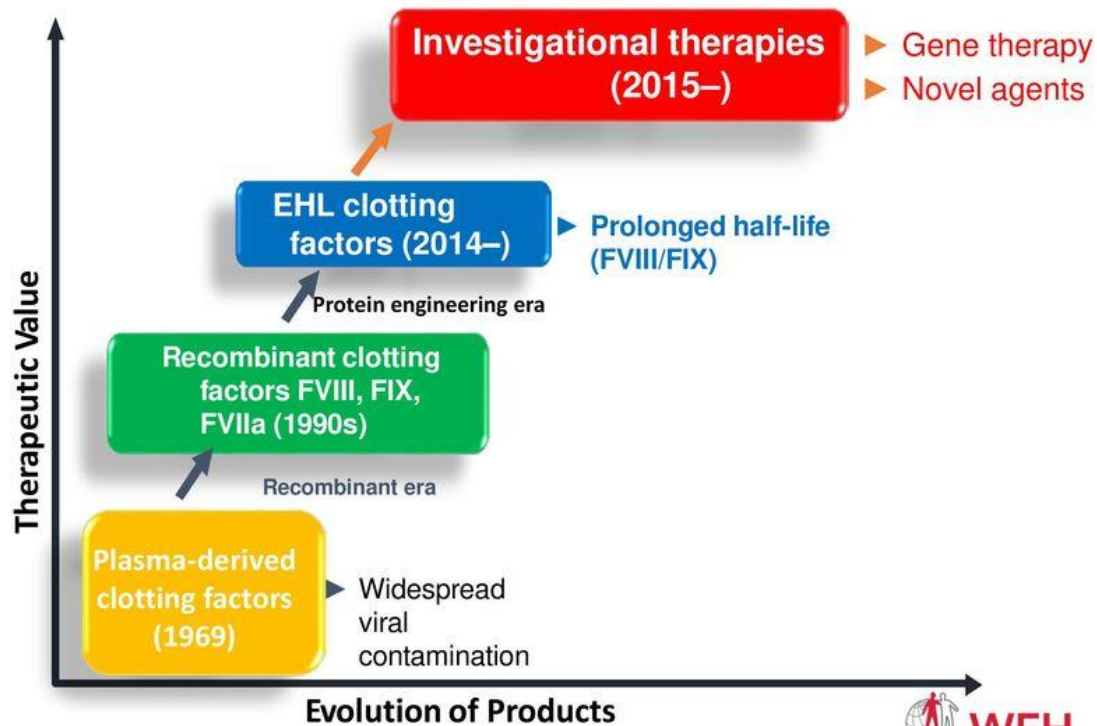


Survival in men in the United Kingdom with hemophilia who were not infected with HIV and in the general male population of the United Kingdom in 1999.



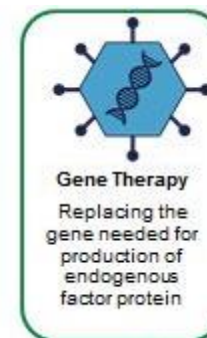
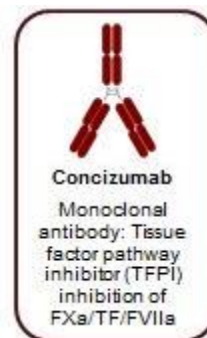
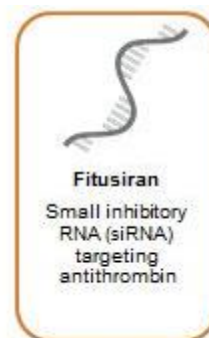
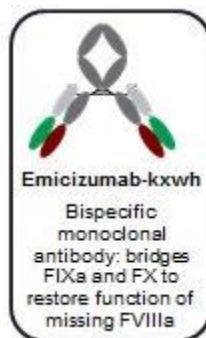
Sarah C. Darby et al. Blood 2007;110:815-825

EVOLUTION OF MODERN HEMOPHILIA TREATMENT



Pierce/WFH

Therapeutic advances in Haemophilia



CFC modifications

- Fusion proteins - Fc, Albumin and PEG
- Xtenylation/VWF fragment
- Gain of function mutations

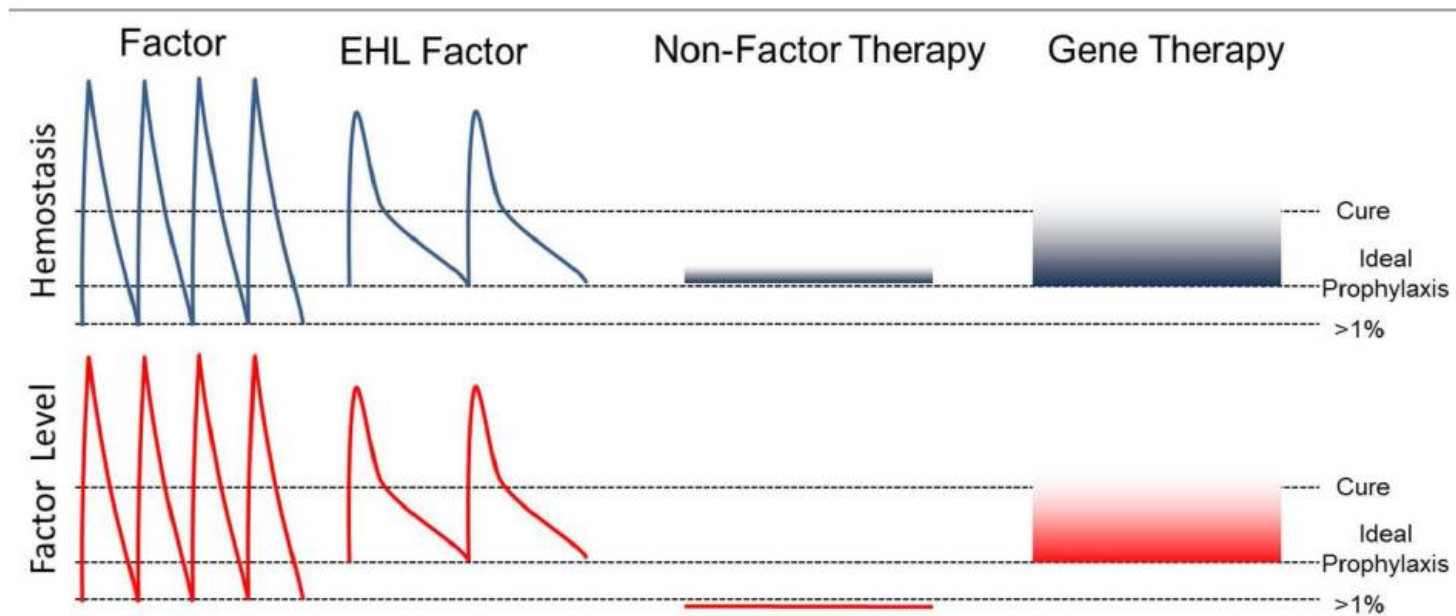
Mimicking and rebalancing

- Emicizumab (hemlibra)
- Fitusiran
- Anti TFPI Ab

Gene therapy

- AAV
- Lentivirus
- Gain of function mutations
- Gene editing

Impact of novel therapies on Haemostasis and Factor levels



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 31, 2017

VOL. 377 NO. 9

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

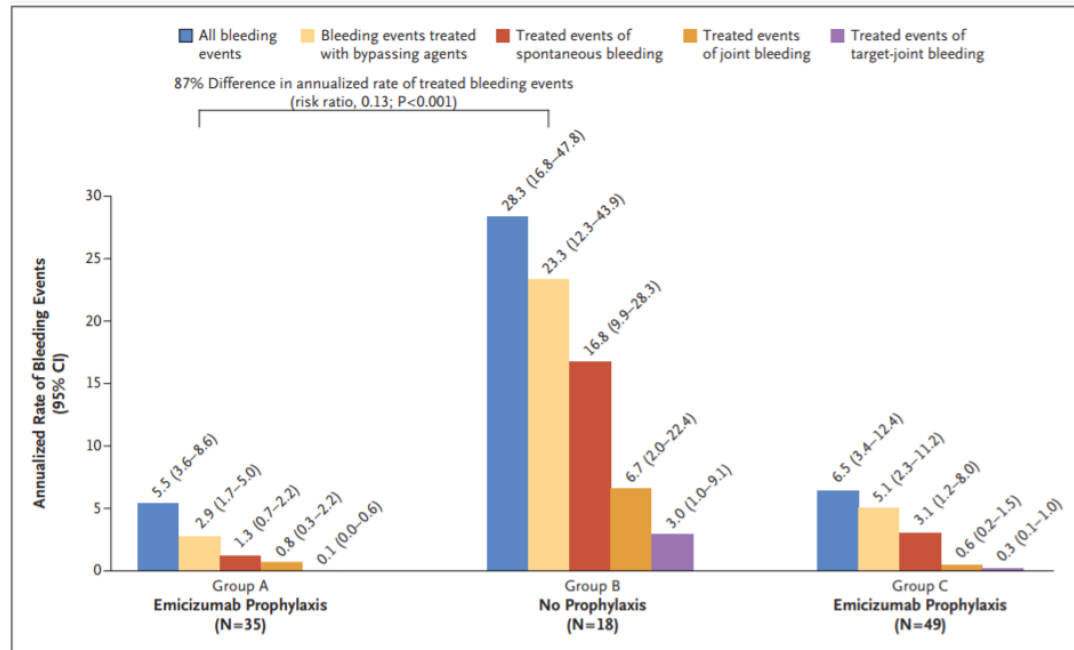
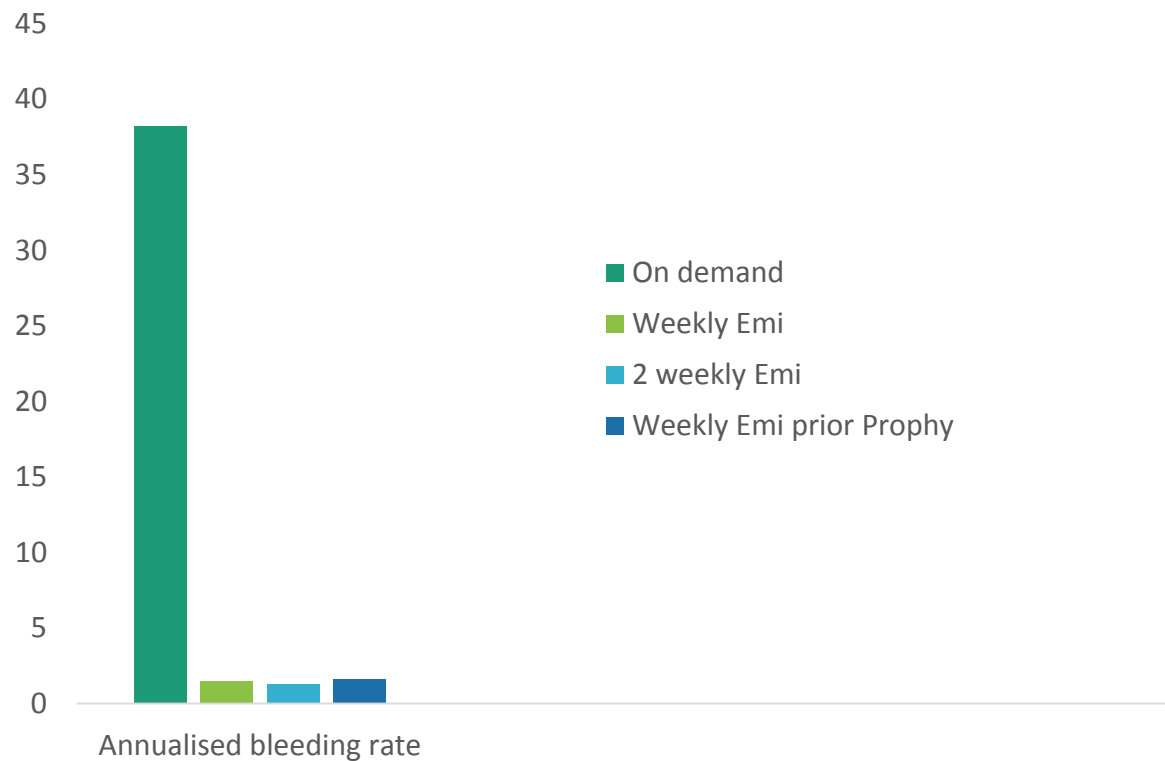


Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C.

The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.

Haven 3 study – Emicizumab in non-inhibitor patients (WFH 2018)

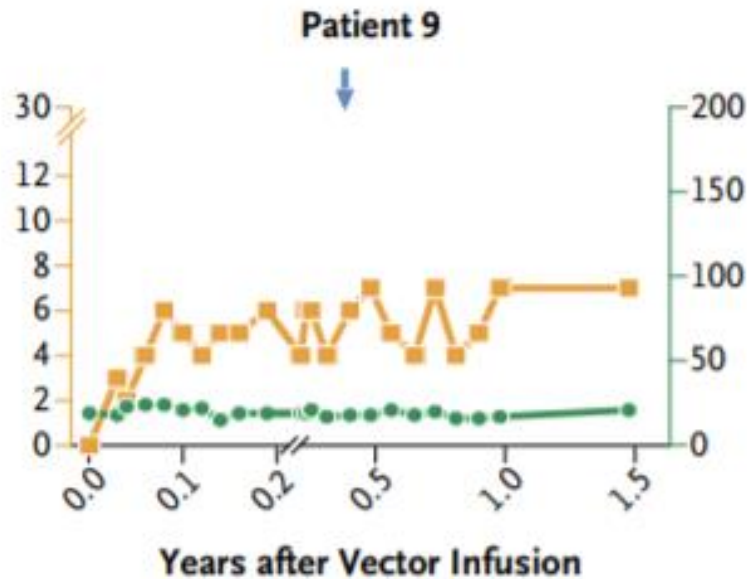


ca. 50% patients on Emi had zero bleeds

ORIGINAL ARTICLE

Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B

A.C. Nathwani, U.M. Reiss, E.G.D. Tuddenham, C. Rosales, P. Chowdary, J. McIntosh, M. Della Peruta, E. Lheriteau, N. Patel, D. Raj, A. Riddell, J. Pie, S. Rangarajan, D. Bevan, M. Recht, Y.-M. Shen, K.G. Halka, E. Basner-Tschakarjan, F. Mingozzi, K.A. High, J. Allay, M.A. Kay, C.Y.C. Ng, J. Zhou, M. Cancio, C.L. Morton, J.T. Gray, D. Srivastava, A.W. Nienhuis, and A.M. Davidoff



Sustained expression for over 7 years

The NEW ENGLAND JOURNAL of MEDICINE

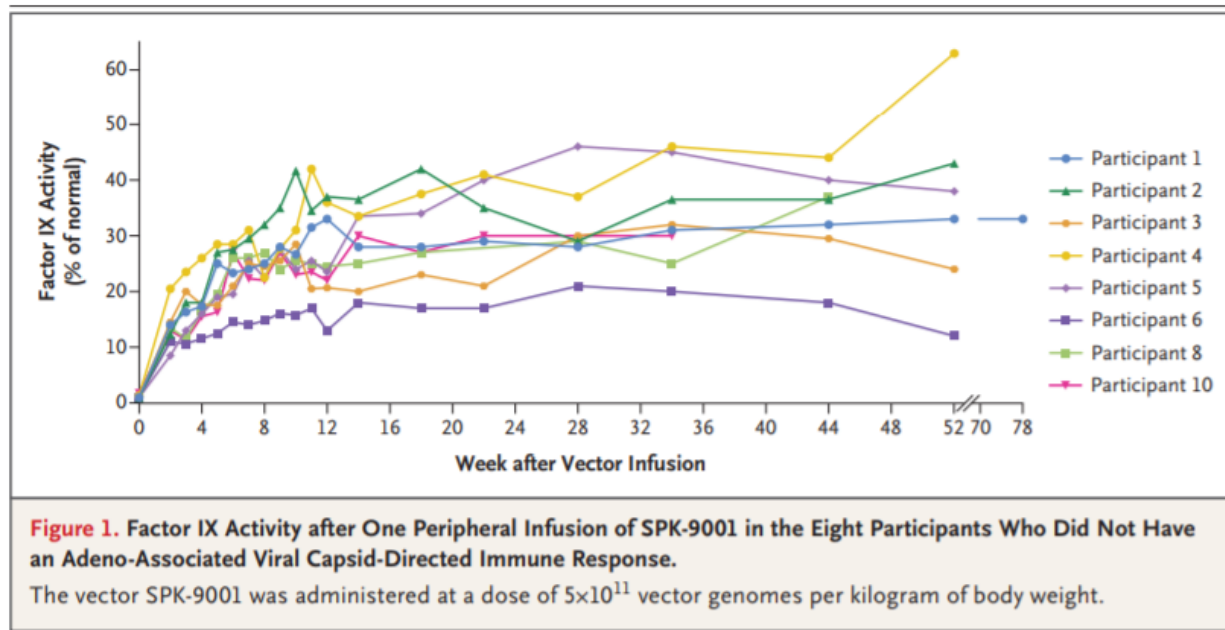
ESTABLISHED IN 1812

DECEMBER 7, 2017

VOL. 377 NO. 23

Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant

L.A. George, S.K. Sullivan, A. Giermasz, J.E.J. Rasko, B.J. Samelson-Jones, J. Ducore, A. Cuker, L.M. Sullivan, S. Majumdar, J. Teitel, C.E. McGuinn, M.V. Ragni, A.Y. Luk, D. Hui, J.F. Wright, Y. Chen, Y. Liu, K. Wachtel, A. Winters, S. Tiefenbacher, V.R. Arruda, J.C.M. van der Loo, O. Zeleniaia, D. Takefman, M.E. Carr, L.B. Couto, X.M. Anguela, and K.A. High



WFH 2018: 27 mths Fup, 98% decrease in bleeding and CFC usage after 4 weeks

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

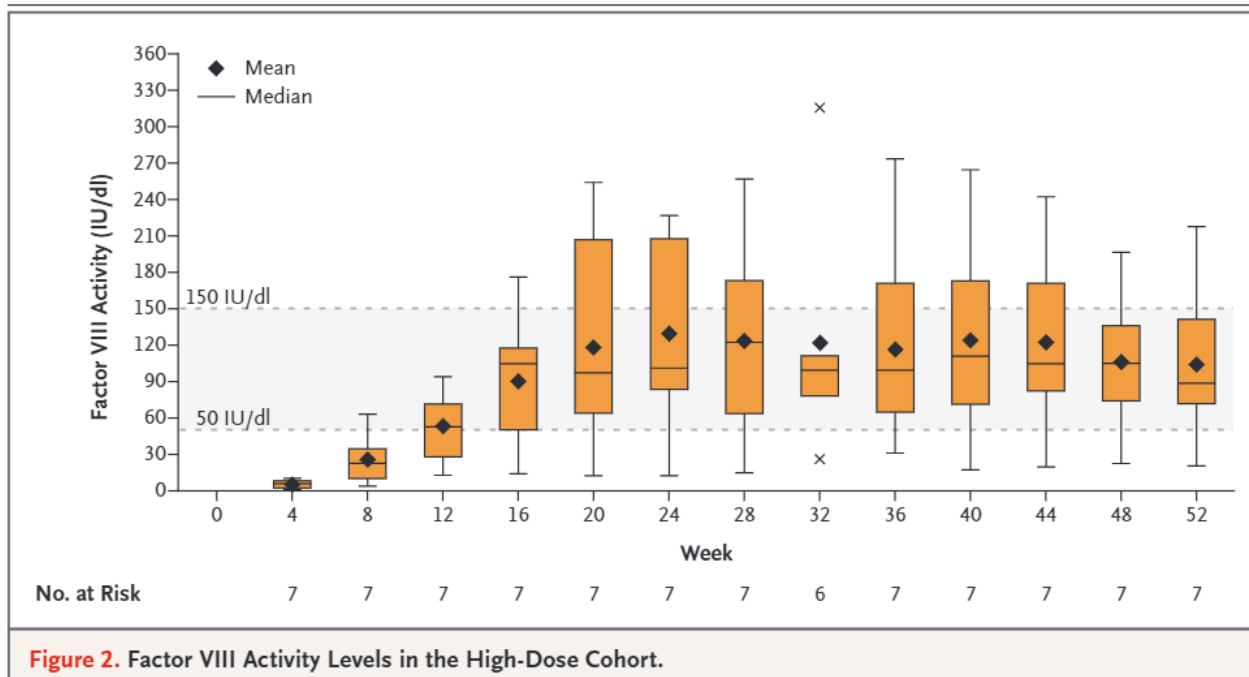
DECEMBER 28, 2017

VOL. 377 NO. 26

AAV5–Factor VIII Gene Transfer in Severe Hemophilia A

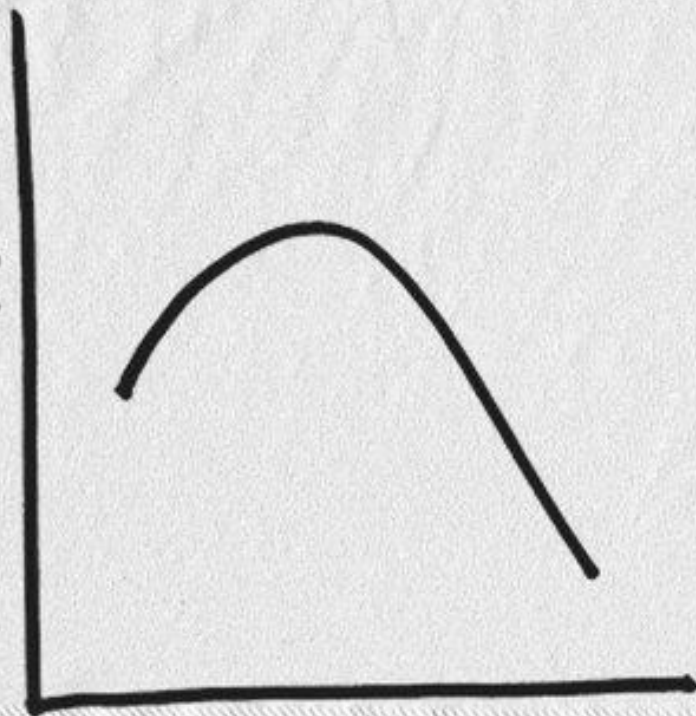
Savita Rangarajan, M.B., B.S., Liron Walsh, M.D., Will Lester, M.B., Ch.B., Ph.D., David Perry, M.D., Ph.D., Bella Madan, M.D., Michael Laffan, D.M., Hua Yu, Ph.D., Christian Vettermann, Ph.D., Glenn F. Pierce, M.D., Ph.D., Wing Y. Wong, M.D., and K. John Pasi, M.B., Ch.B., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE



WFH 2018: 2 years Fup – 83% bleed free, 96-98% reduction in CFC usage, no FVIII >ULN

CHANCE
OF GETTING
ANYTHING
DONE



OF CHOICES

New therapies and Ageing EHL CFC

Pros

Cons

Better bleed protection

Less infusions

Sawtooth factor levels - risk
of acute bleeds

Inability to self infuse e.g
decreased dexterity, poor
veins, cognitive impairment

Inhibitor risk



New therapies and Ageing

FVIII mimetics/Rebalancing molecules



Pros

Consistent bleed protection
Subcutaneous delivery – care givers can administer with minimal training
Long half lives – missed or delayed doses not an issue

Cons

Not well studied in older adults
Thrombotic side effects reported – background risks for thrombosis increase with age
Longterm follow up not available yet

New therapies and Ageing Gene therapy



Pros

Highly protective baseline factor levels

One infusion only

No need for patients/carers to administer regular treatment



Cons

Limited long term follow up, all side effects may not be known

No upper age limits in trials but likely to have few very old participants

Variable levels seen in studies ?thrombosis risk with very high levels

May need factor for trauma/surgery

May need repeat treatment later in life?



Themes and concerns on Ageing for people with Haemophilia

A qualitative exploration of the unique challenges facing older men with haemophilia and the implications for social work practice

Sarah E. Elliott¹, Kelsey L. Deane² and Barbara Staniforth²

VOLUME 29 • NUMBER 2 • 2017
AOTEAROA NEW ZEALAND SOCIAL
WORK

Physical Health

- Decreased mobility and decreased physical activity as the most prominent issue
- Concerns about loss of independence

New Medical Conditions

- “it’s all the other things that now come on top of the challenges that we have already had to face in life”
- “it’s those complexities around all the other things; gall stones, heart problems, liver problems ... where they are required to go inside you [operate] to fix it, that’s where it gets complicated”
- Co-morbidities present challenges which are emotional, physical, logistical and financial

New medical treatments and teams

- “for everything we used to go and see the Haematology Department and get a shot of factor, and that was the answer to every problem we ever had”
- “you can’t give yourself another shot of factor and fix the heart problem”
- Having to educate new medical specialists, no longer a “one-stop shop”

Social connections, education

- The importance of “bonding and friendship” and maintain social connections
- The need to get information on the impacts of ageing and the role of the patient organisation

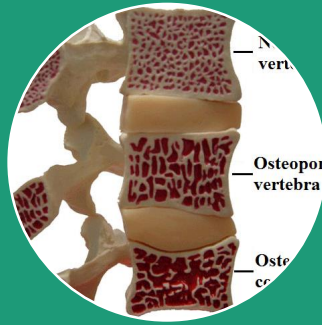
Can novel treatments address some of the treatment concerns?



Preventative health programmes at the NCC



Specialist
Clinics



Bone
Health



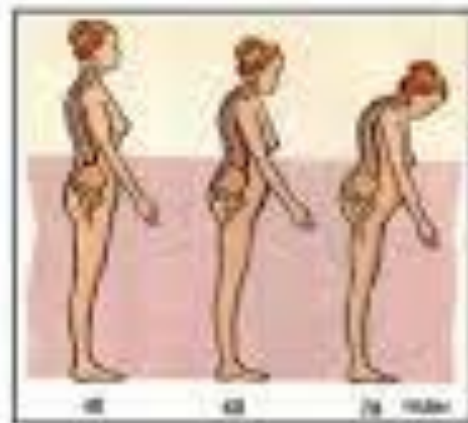
Oral
Health



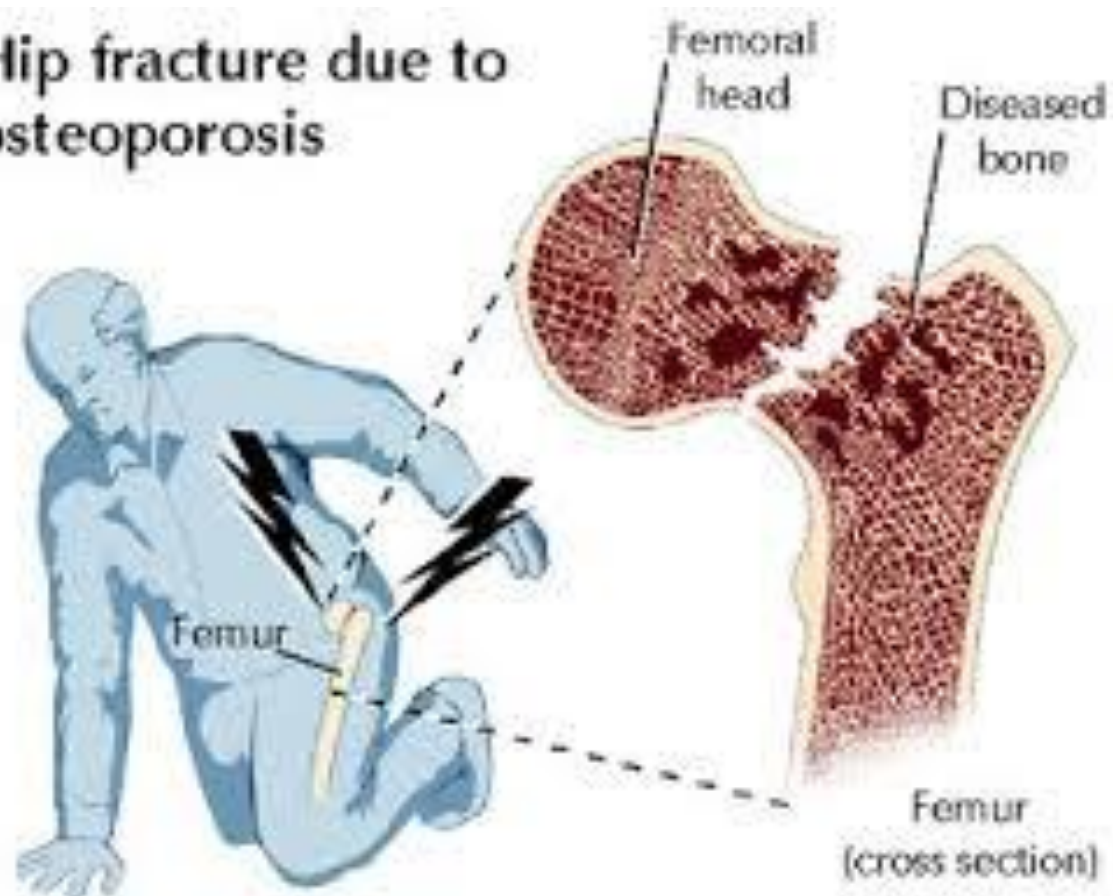
Specialist clinics

- Combined clinics
 - Orthopaedic/Physio
 - Hepatology
 - ID
- Referral as needed
 - Cardiology
 - Urology
 - Renal medicine
 - Dermatology
 - General Surgery

Osteoporosis



Hip fracture due to osteoporosis



Osteoporosis

- Association with Haemophilia
- Risk factors;
 - Reduced peak bone mass in late teens (no prophylaxis, more bleeds, less exercise)
 - Viral infections
 - Vit D deficiency and/or low calcium intake
 - Medications like steroids
 - Alcohol
 - Smoking

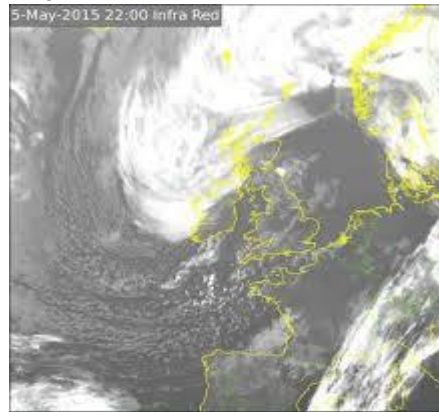
Osteoporosis Prevention

Maximise and maintain bone mass – weight bearing or resistance exercise (adjust the factor treatment if needed)



Osteoporosis – More Prevention!

Vit D – Get out in the Sun (but not too much!)



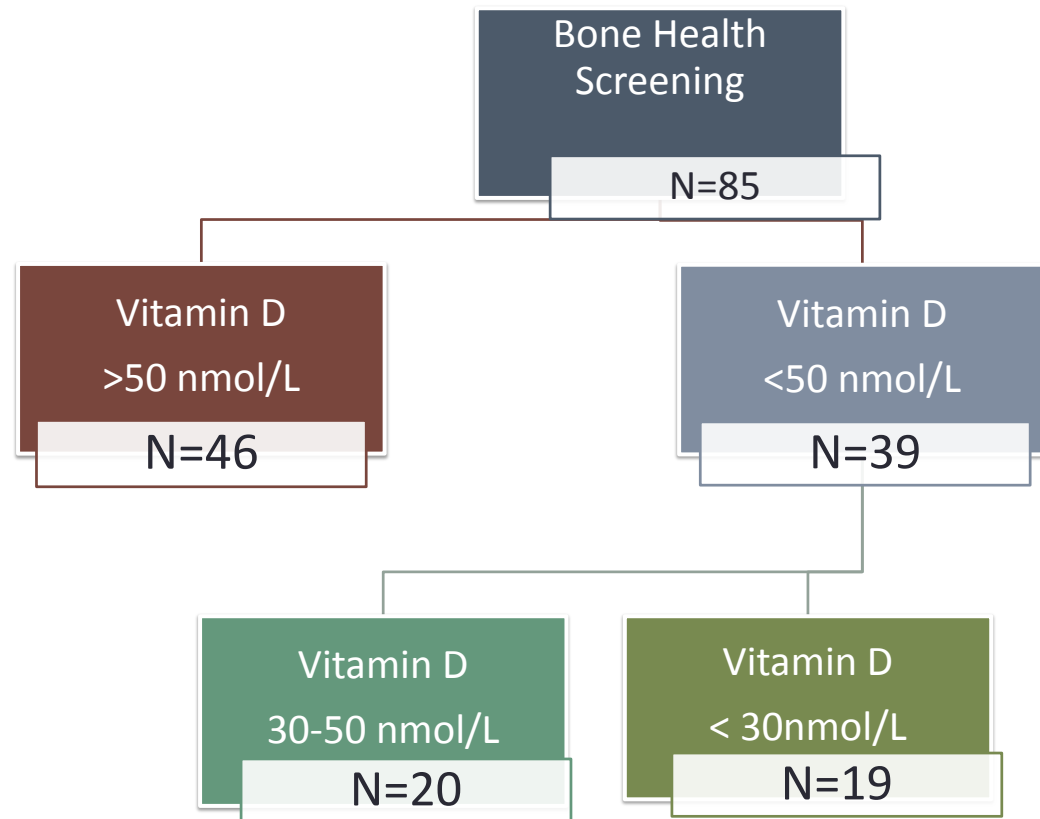
No excess alcohol, No Smoking

Calcium in your diet

Clinic – measure Vit D and Bone Mineral Density

Bone health screening to date NCC

- 78% patients have had bloods for bone health screening
- DEXA scans in progress
- Osteoporosis treated in 7 patients to date



Oral health and Haemophilia



- Oral Health is a significant quality of life determinant in older age
- Periodontal disease has significant impact on general health
- Risks of oral disease increase considerably with age
 - high sugar diet
 - polypharmacy and reduced saliva
 - smoking
 - poor oral hygiene and poor access to care
 - dental fear/phobia
 - reduced dexterity for brushing/flossing



"I'm ninety-seven years old and I still have all my own teeth."

How can we avoid keeping our teeth in a glass?



Oral health aims for the first generation of dentate older people

- Maintain lifelong good oral health
- Reduce invasive procedures with minimal intervention dentistry and preventive biological approaches
- Plan for access to dental care to maintain often complex dentitions

Oral Cancer

- Risk of mouth cancer increases with age and immune status and all adults should have a mouth cancer check at least once a year
- Early detection of mouth cancers improves survival rates and are easier to manage than late presenting cancers



NCC Oral health needs assessment (OHNA)

- Profile the Oral Health Needs of Older People (>60yrs) with Congenital Bleeding Disorders in Ireland - via a oral health risk assessment appointment
- Produce a template OHNA to identify those older people who are most at risk.
- Design nudges within the comprehensive care pathway to safeguard oral health and signpost people towards appropriate dental home using appropriate materials and resources.

The GP

- A Specialist in common health conditions!
- Comprehensive care
- Community care **Access**
- Shared care

HUMORESQUE

by Loren Fishman



An extremely general practitioner

Interlocking services!



What can you do?

- Self-management – partner with your healthcare team

- Make your wishes known



- Changing approach to health and wellbeing



"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"



Thanks!

