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Acquired Haemophilia

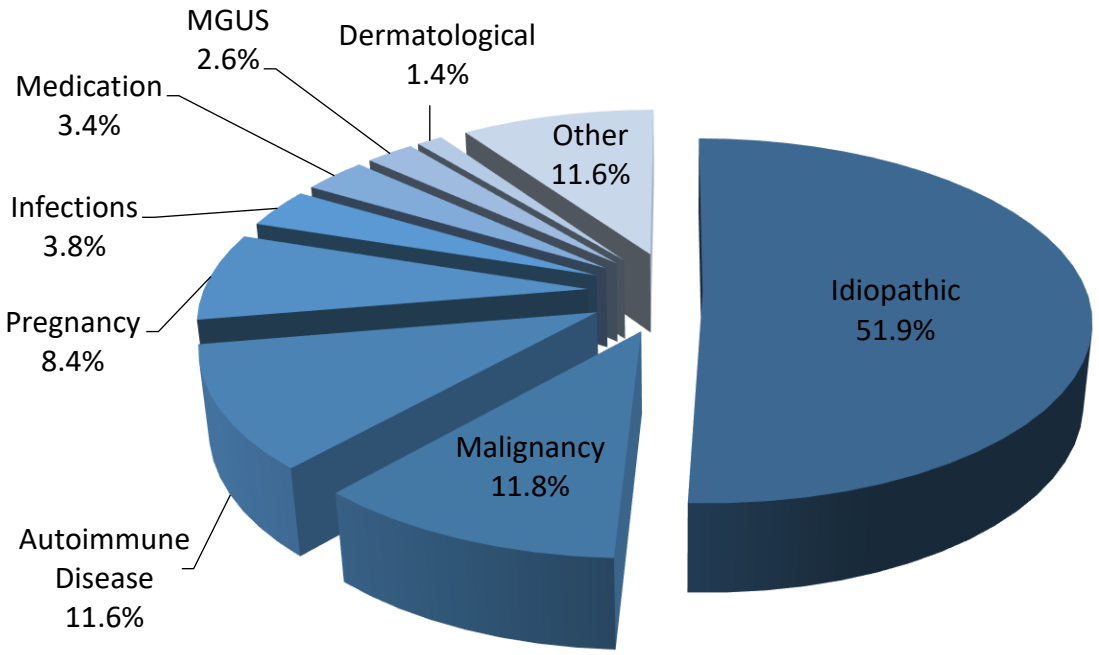
Can we do better with Emicizumab?

HFA conference 2023

Translating our experiencing from inherited haemophilia A to a rare disorder

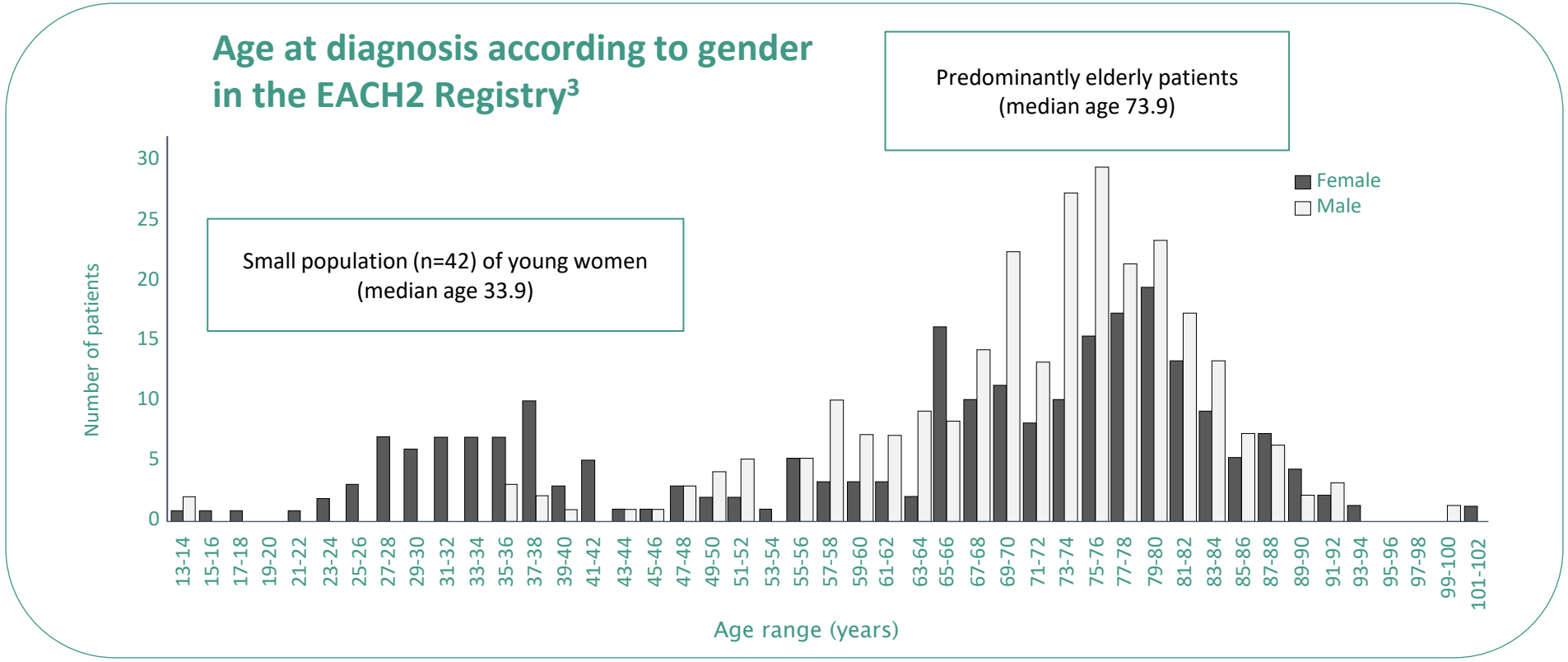
AHA – what is it?

- AHA is a rare, life-threatening, and often fatal bleeding disorder
- Caused by the development of antibodies to the patient's own coagulation factor FVIII
- Approximately 50% of AHA cases are idiopathic in origin (no cause found)



Incidence of AHA: Age and gender distribution

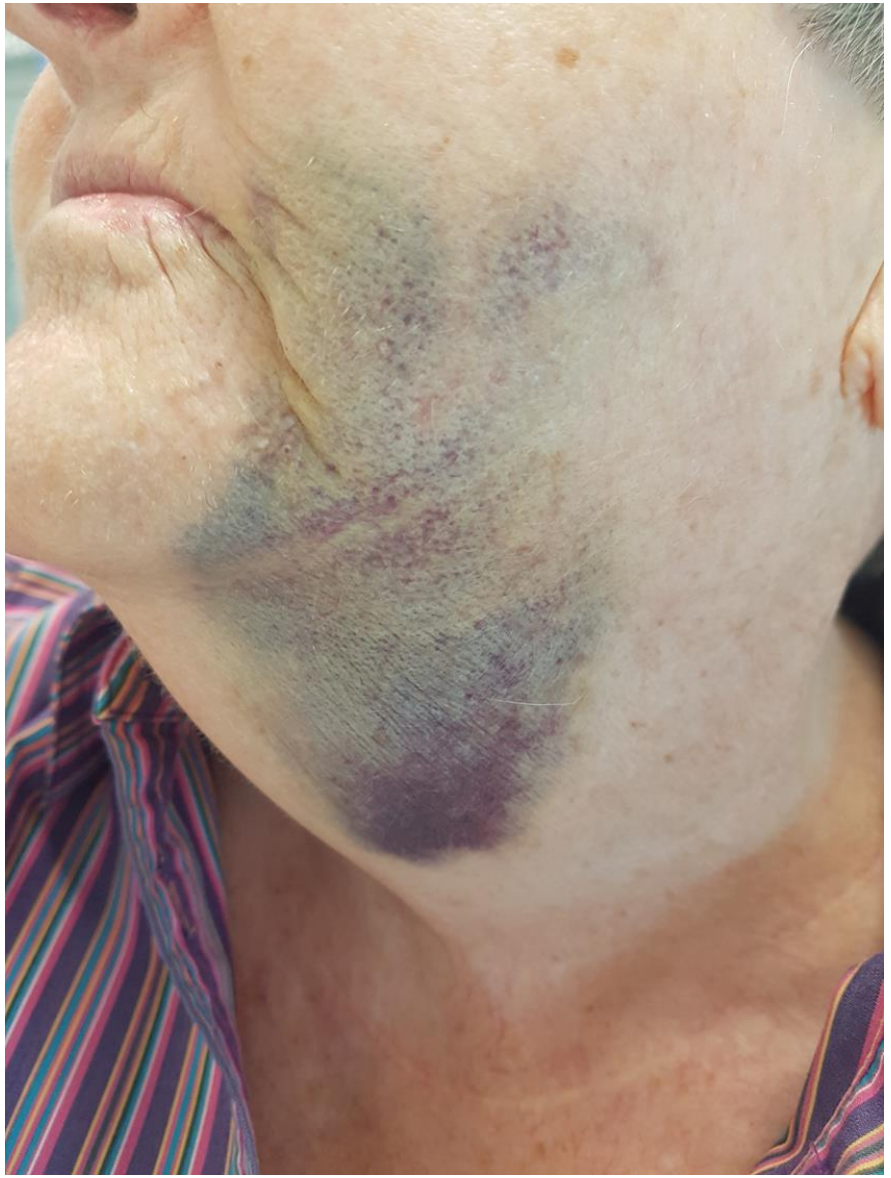
- Estimated incidence of 1.5-2.0 cases per million per year
  - Presents most commonly in the elderly, with a median age at diagnosis of about 74 years
  - Small peak in peripartum women 20-40 years old



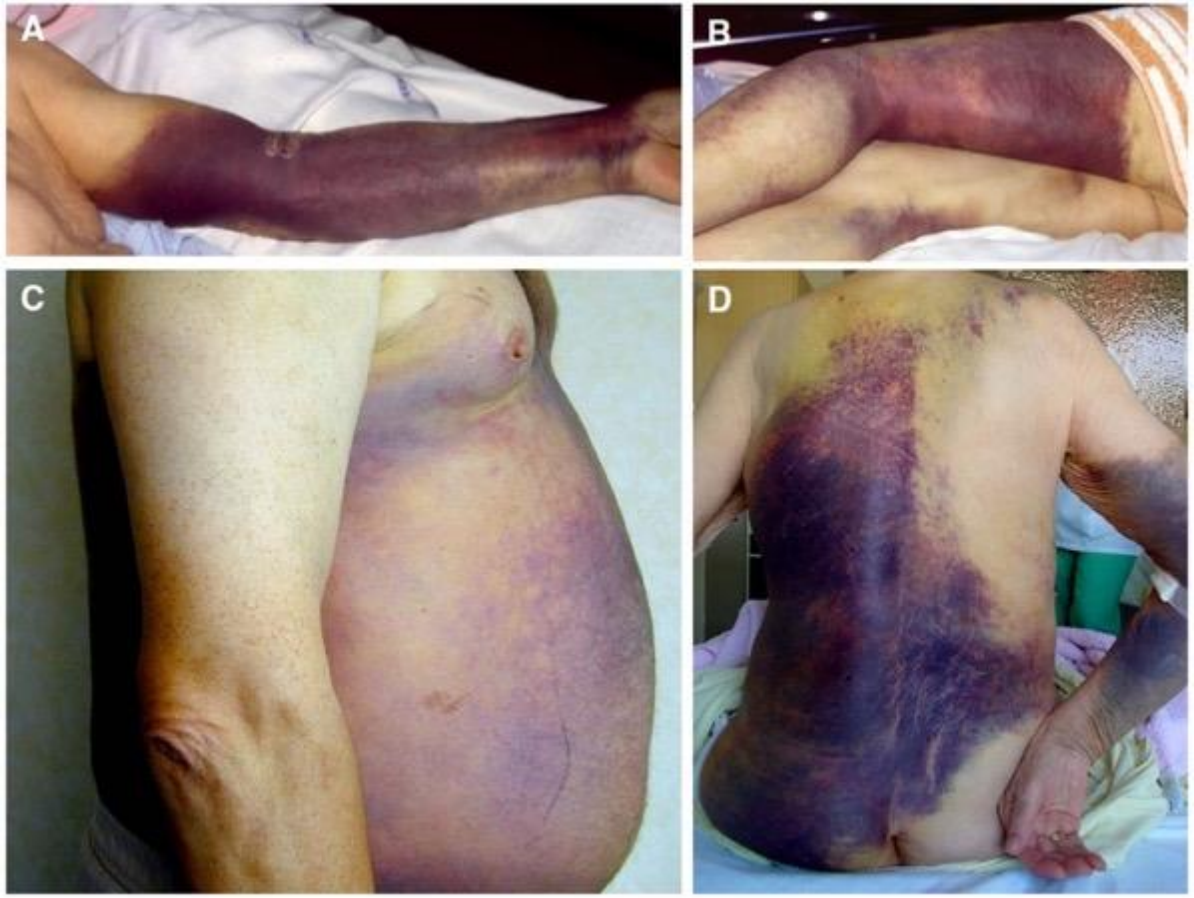
Comparison of acquired and congenital haemophilia

Acquired Haemophilia	Congenital Haemophilia
Diagnosed in older individuals	Diagnosed in young children
No known genetic pattern; males and females equally affected	Sex-linked inheritance pattern; males predominately affected
Haemarthroses rare	Haemarthroses common
Autoantibodies usually exhibit type II kinetics: no correlation between inhibitor titre and residual FVIII inactivation	Alloantibodies usually exhibit type 1 kinetics: direct correlation between inhibitor titre and FVIII inactivation
No correlation between FVIII level and bleeding severity (spontaneous bleeding may occur with FVIII >5%)	Correlation between FVIII level and bleeding severity (spontaneous bleeding may occur with FVIII <1%)
Mortality increased	No immediate impact on mortality

- Spontaneous bruising
- FVIII level 12%
- Inhibitor 50 BU
- Definitions of mild/ moderate/ severe based on FVIII level DO NOT apply to AHA



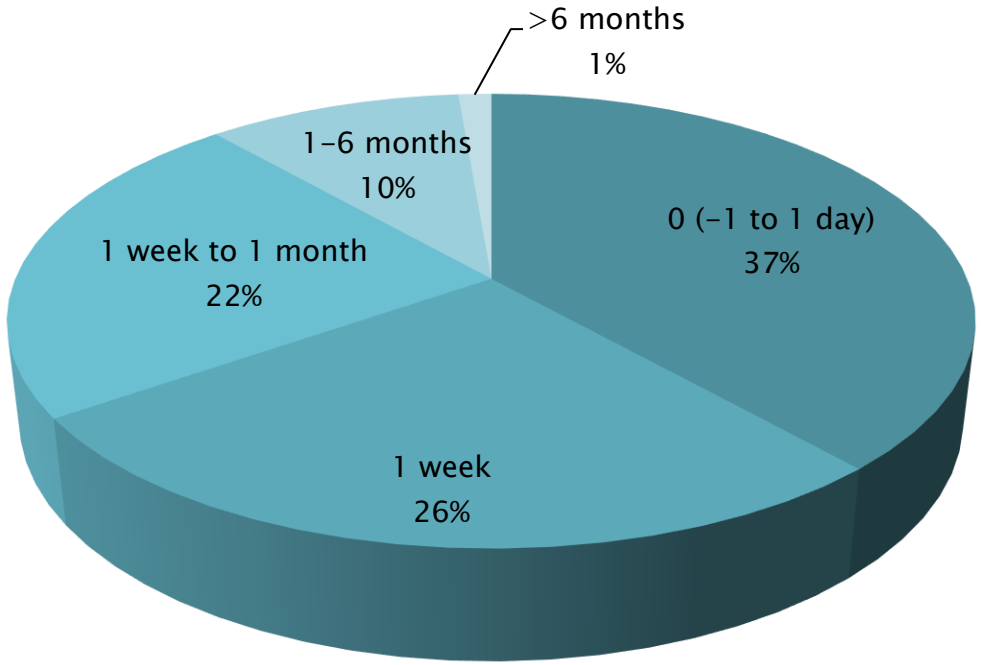
Typical bleeding pattern in AHA



1. Collins P et al. *BMC Res Notes*. 2010;3:161.

Diagnostic and treatment delays in AHA:

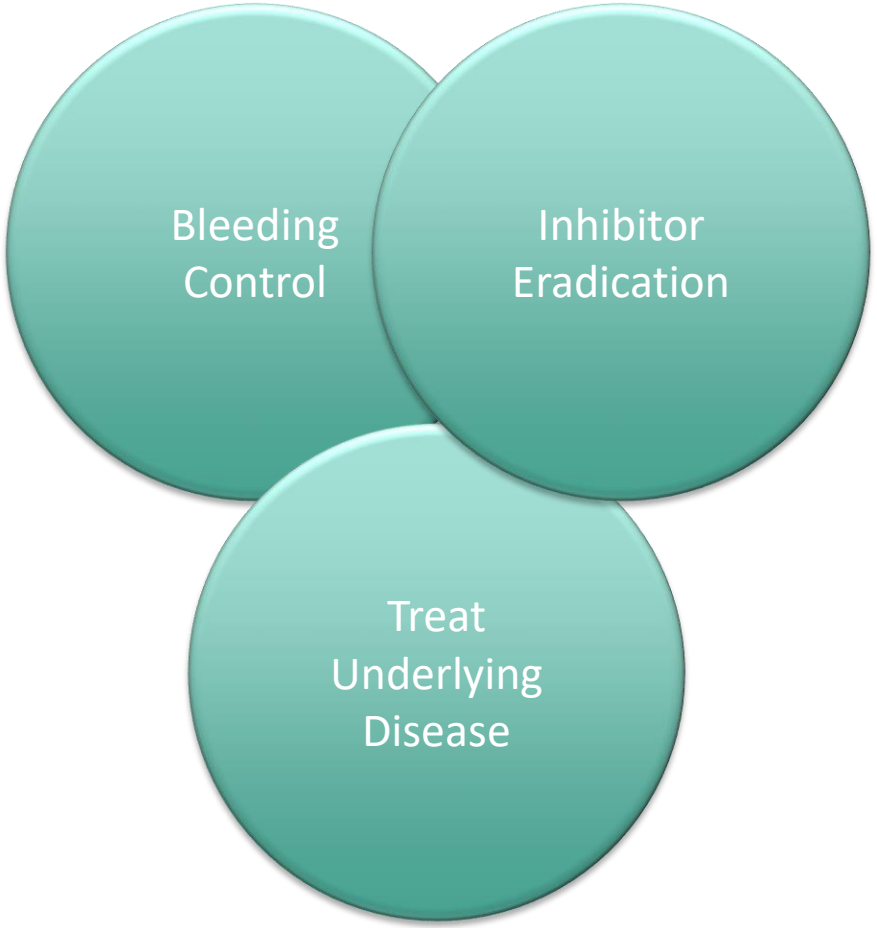
Time from bleeding event to definitive diagnosis in EACH2 registry, n=467*



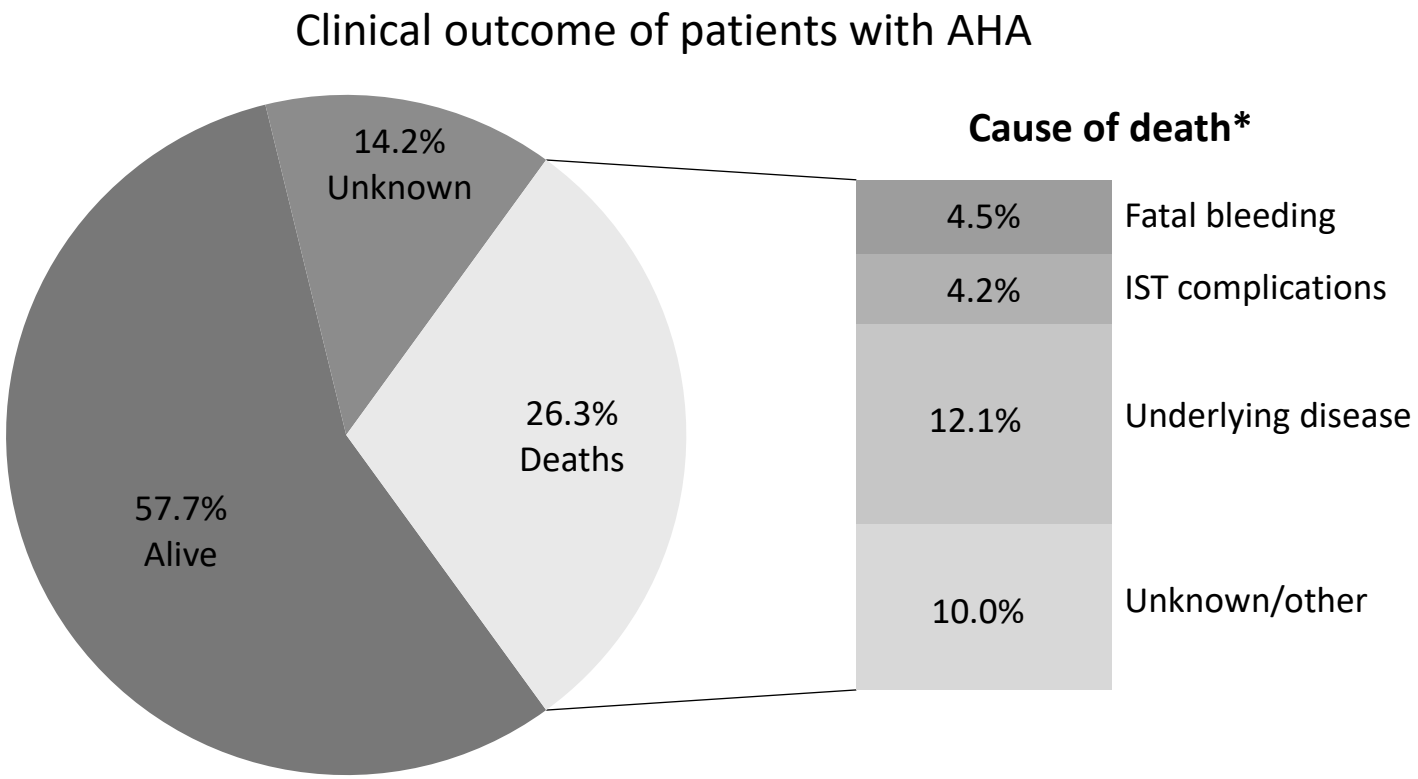
- Median (IQR) time to diagnosis, 3 (0–12) days

1. Knoebl P et al. *J Thromb Haemost*. 2012;10:622-631.

Principles of AHA management



Patient outcomes in AHA (EACH2 registry)



- n=331
- Observation time [median, IQR] 258 (74-685) days

1. Knoebl P et al. *J Thromb Haemost*. 2012;10:622-631.

Which patients with AHA should be treated with haemostatic agents?

- Potentially life-threatening bleeding
  - Intracranial
  - Potentially airway threatening
  - Retroperitoneal/ intra-abdominal
  - Compartment risk
  - Severe GI

- Potentially limb threatening bleeding (compartment risk)

- Invasive procedures (avoid if possible – consider whether really indicated, particularly seemingly innocuous procedures like PICC insertion)

Management of bleeding

- Simple measures are critical:
  - Rest
  - Ice
  - Compression
  - Elevation

- Avoid further tissue trauma
- Patient education on concerning bleeds – early presentation
- Consider adjunctive measures – tranexamic acid (1g TDS) and occasionally DDAVP (look at baseline FVIII level and age – often not appropriate)
- Frequent review of minor bleeding sites – escalate haemostatic therapy if progressive/ compartment risk

Haemostatic agents in AHA

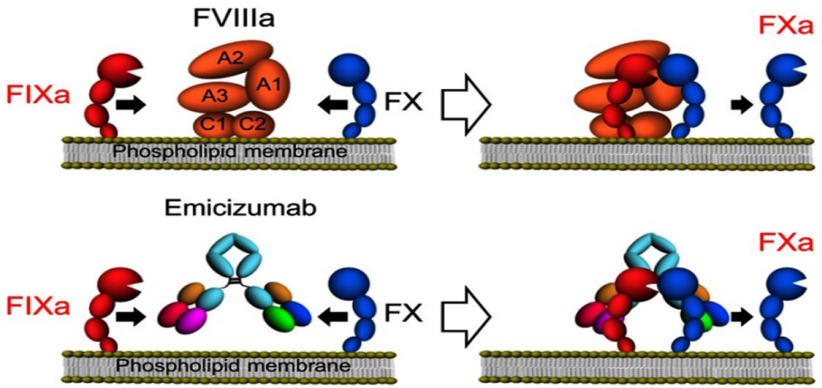
- Bypassing agents
  - Recombinant FVII (rFVIIa)
  - FEIBA
- Replacement therapy
  - Human rFVIII?
    - Rarely may be effective at low BU
  - Recombinant porcine FVIII
    - Effective, not currently NBA funded

Emicizumab

Appears effective, not licensed or NBA funded for AHA

Emicizumab in AHA?

- Well established efficacy and safety in congenital haemophilia A with inhibitors
- Pharmacologic properties (Emi displaced from binding sites when FVIII recovers) attractive for AHA
- Possibilities in AHA: prevention of spontaneous bleeding, subcutaneous application in long intervals, outpatient management, and reducing the need for intensive immunosuppression to achieve rapid inhibitor eradication



blood
Regular Article

THROMBOSIS AND HEMOSTASIS

Emicizumab for the treatment of acquired hemophilia A

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KEY POINTS

- **Emicizumab has good hemostatic efficacy in AHA: within a few days after the first injection, less bypassing therapy is needed.**
- **Low emicizumab concentrations can prevent breakthrough bleeding: outpatient patient management with visits every 1 to 3 weeks is feasible.**

**Acquired hemophilia A (AH
tibodies to coagulation fact
human or porcine FVIII are
mimetic therapeutic antibo
hemophiliacs. Here, we rep
emicizumab (all data media
<1%; inhibitor titer 22.3 Bet
bleeding. Emicizumab was
followed by 1.5 mg/kg eve
monitoring, chromogenic as
received immunosuppressi
emicizumab, activated parti
reagents) exceeded 10% a
bypassing therapy stopped
indicating complete remissi
31 (15-79) days. A median of 5 injections (range, 3-9) wer
no breakthrough bleeding was observed after the first
effective hemostatic therapy for AHA, with the advanta
discharge, and reduction of immunosuppression and a**

♂ 6
♀ 6

Age 74 (51-87) yrs

Acquired hemophilia A

IX, VIII, X

Factor VIII blocked by autoantibodies
Insufficient clot formation
Severe bleeding

Hemostatic treatment:

APCC or rhFVIIa
Multiple daily iv. injections

3 (7) 3 (7) 1.5 (21) 1.5 (21) 1.5 (21) 1.5 (days)

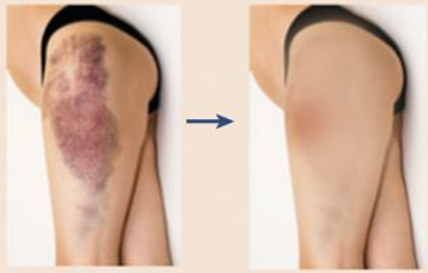
Emicizumab (mg/kg)
sc. every 1-4 weeks

IX, emicizumab, X

Mimics factor VIII
Restored coagulation

Immunosuppression with rituximab +/- corticosteroids

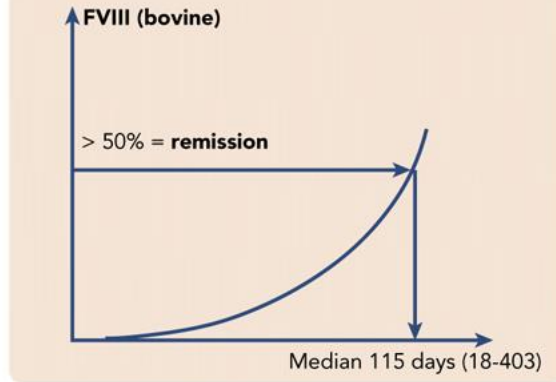
Bleeding stopped
Median 3 days (2-15)



Emicizumab treatment

Median 5 injections (3-9)
Median 31 days (12-175)

Reduction in
Bypassing therapy
Transfusions



AGEHA study – modified loading regimen

ORIGINAL A

A prospe
emicizun

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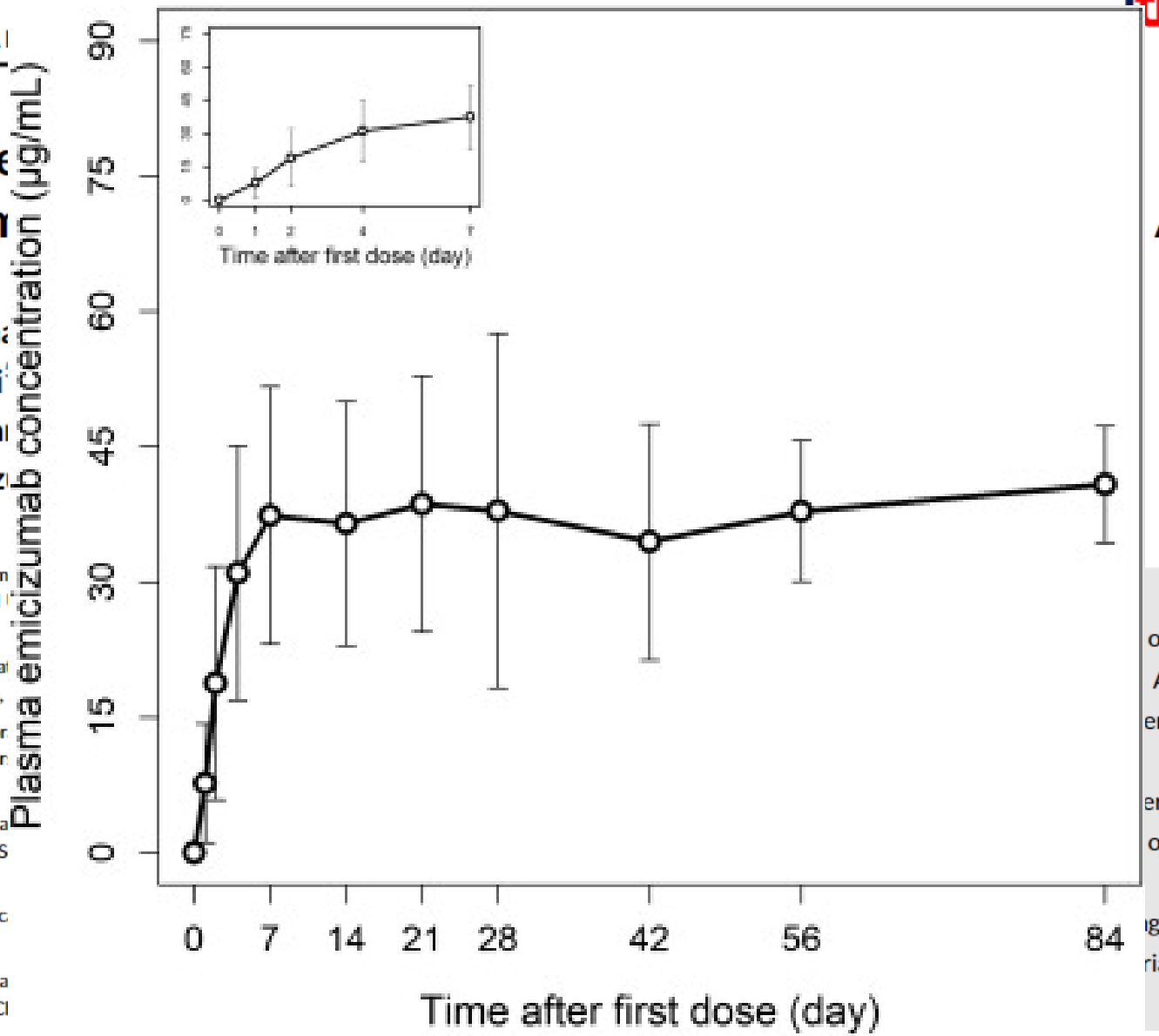

Our experience

- 7 patients (19-67 years)
- Baseline FVIII (median <1%, range <1% to 3%), Inhibitor 234.9 BU (11.9 BU to 870 BU)
- Bleeding – severe in 6/7, non-severe in 1/7
- Emicizumab dosing not uniform (all got initial 3mg/kg dose)
- All patients received immune suppression with prednisone and 6/7 also had addition of low dose Rituximab
- 6 patients had no new bleeding after Emicizumab initiation, one had a new minor non-progressive bleed
- 3 patients required no rFVIIa after the first dose of Emicizumab
- No patients required further bypassing agents after the second dose
- No safety concerns

The patient experience

- Difficult to capture in a treatment naïve group (unlike inherited haemophilia A they have no lived experience of the alternative)
- Shorter length of stay
- Less morbidity from bleeding
- Reduced fear of new bleeding
- (Potentially) less morbidity from immune suppression

Long-term follow-up in AHA

- Relapse occurs in up to 20% of patients[1,2]
  - Median time to relapse:
    - 7.5 months in UKHCDO study[2]
    - 4 months in EACH2[2]
- Patients should be educated about signs/symptoms of recurrence and should promptly report any bleeding or bruising
- Open line of communication with HTC important
- We have diagnosed late relapse following phone call from the patient on several occasions

Our approach to follow up once remission obtained

Testing	Duration
Monthly	First 6 months
Every 2-3 months	Up to 12 months
Every 6 months	Up to 3 years