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# PROPHYLAXIS IN CHILDREN WITH HAEMOPHILIA IN AN EVOLVING TREATMENT LANDSCAPE

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## SELECTED HIGHLIGHTS

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# SUMMARY

- For children with haemophilia, **early initiation of prophylaxis is crucial** to prevent life-threatening bleeds and maintain joint health

- The authors reviewed **key factors** that determine the **choice of prophylaxis in young children**
  - Based on literature and practical experience, the authors built **consensus** on when to start prophylaxis, the pros and cons of the products available to guide the choice of product, and practical aspects of starting prophylaxis to guide the choice of regimen

- In this era of increasing therapeutic choices, available **information about the range of treatment options** must be considered when initiating prophylaxis in young children
  - Parents or care givers must be sufficiently informed to allow **informed shared decision making**

- Prophylaxis with **clotting factor replacement therapy** in young children brings practical **challenges**

- Brief experience and limited data with **non-replacement therapy** (NRT) in young children imply that starting emicizumab prophylaxis in this patient group requires **careful consideration**, despite the more convenient (subcutaneous) route of administration

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# UNANSWERED QUESTIONS AND UNMET NEEDS IN ESTABLISHING PROPHYLAXIS IN PUPs WITH SEVERE HA

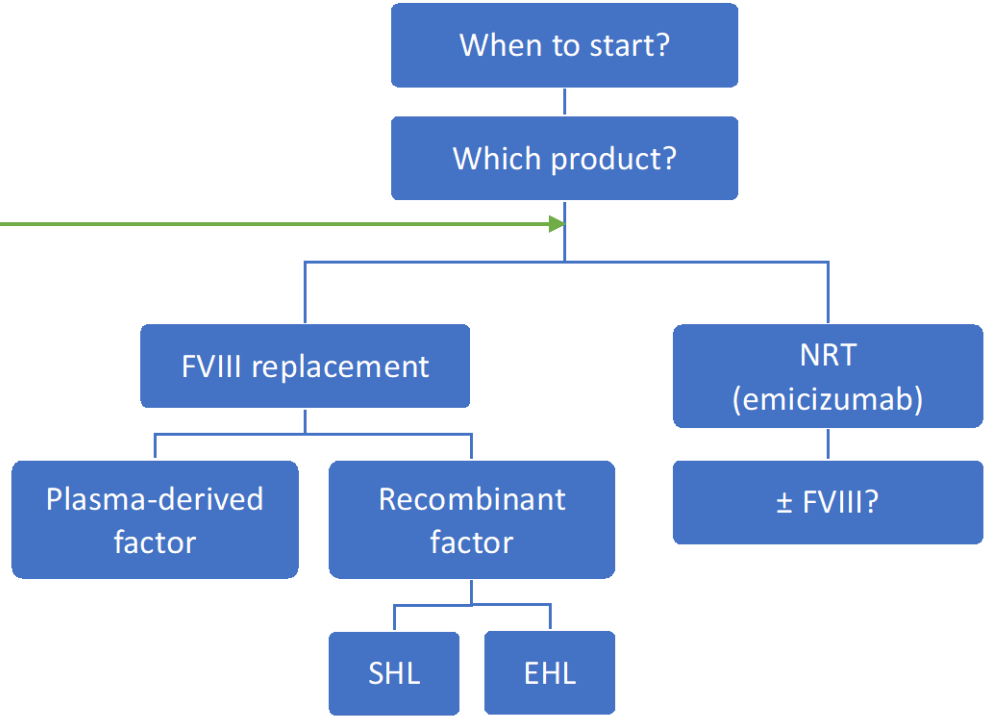
- When initiating prophylaxis, choices should be individually discussed with parents or care givers and decisions should be made in a **shared decision-making process**
  - Based on current and detailed information provided to the parents or care givers

**Shared decision making**

Efficacy considerations
- How best to provide early protection against ICH?
- How best to achieve life-long joint protection?
- Achieving tolerance to FVIII

Safety considerations
- Less experience with NRT than with FVIII products
- Risk of inhibitor development: FVIII product vs NRT
- Lack of a natural antagonist of NRT (FVIII is inhibited by activated protein C)

Practical considerations
- Venous access




EHL, extended half life; HA, haemophilia A; ICH, intra-cranial haemorrhage; NRT, non-replacement therapy; PUP, previously untreated patient; SHL, standard half life

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# WHEN TO START?

**We recommend starting primary prophylaxis as soon as possible, ideally before the occurrence of any joint bleed, and definitely no later than 2 years of age.[1]**

- Regular prophylaxis at least halves the risk of **intracranial haemorrhage** (ICH)[2,3]
  - To protect against ICH, prophylaxis should ideally begin as soon as possible after haemophilia is diagnosed
- **Arthropathy** is better prevented with primary prophylaxis
  - Primary prophylaxis is defined as regular treatment started before any clinical or radiological sign of joint damage and before the second joint bleed, or before the age of 2 years[4]
  - Age at start of prophylaxis is a strong determinant for arthropathy
  - Joint damage is also related to the level of haemostatic coverage and occurrence of non-clinically evident bleeds
- Starting prophylaxis at birth is almost impossible with replacement therapy, whereas use of NRT as primary prophylaxis would allow prophylaxis to be **started very early**[1]

ICH, intracranial haemorrhage

1. Mancuso ME, et al. Haemophilia. 2021 Sep 21. Epub ahead of print. 2. Andersson NG, et al. Br J Haematol. 2017;179:298-307. 3. Witmer C, et al. Br J Haematol. 2011;152:211-16. 4. Blanchette VS, et al. J Thromb Haemost. 2014;12:1935-1939.

# WHICH PRODUCT?

## *FACTOR REPLACEMENT THERAPY*

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**We recommend informing parents or care givers on the potential advantages and drawbacks of plasma-derived and recombinant clotting factor concentrates and assessing the risk-benefit ratio based on individual characteristics.**

| Therapy | Pros | Cons |
|---|---|---|
| **Plasma-derived factor** | • Potentially lower inhibitor incidence observed in PUPs than some recombinant products<br>• Potentially lower cost | • Potential risk of transmission of infectious agents from pooled plasma<br>• Increased risk of thrombosis with products containing a high concentration of VWF (clinically relevant only for children with a central venous catheter)<br>• Larger volume of product<br>• Potentially limited availability |
| **Recombinant factor** | • Low risk of pathogen transmission<br>• Smaller volume can more easily be infused through peripheral veins<br>• Theoretically unlimited production capacity | • Potentially higher inhibitor incidence observed with some rFVIII products<br>• Higher cost |

ICH, intracranial haemorrhage; NRT, non-replacement therapy; PUP, previously untreated patient; rFVII, recombinant factor VIII; VWF, von Willebrand factor

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# WHICH PRODUCT?

## *FACTOR REPLACEMENT THERAPY: SHL VS EHL PRODUCT*

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**For children with severe/moderate HA <12 years, the choice of product type and dosing regimen should be individually tailored according to pharmacokinetic parameters and clinical phenotype or to provide optimal protection against bleeds.**

**For children with severe or moderate HB we recommend starting prophylaxis with an EHL product.**

| Therapy | Pros | Cons |
|---|---|---|
| **SHL** | • Well known safety and efficacy profile | • Frequent dosing carries drawbacks of venous access difficulty, poor adherence to treatment, a higher burden for care givers, and negative impact on family life |
| **EHL** | • Fewer infusions needed to maintain protective trough levels (particularly in HB)<br>• Less disruption of patients' everyday life (fewer bleeds, higher activity levels, and improved well-being and mental health) | • Potentially higher costs (for HA patients switching from SHL to EHL rFVIII) in some countries<br>• Other adverse effects (e.g. anti-PEG antibodies), potential for PEG accumulation<br>• For some concentrates it is not clear which laboratory assay is better to measure these new modified molecules |

EHL, extended half life; HA, haemophilia A; HB, haemophilia B; rFVII, recombinant factor VIII; SHL, standard half life

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# WHICH PRODUCT?

## *NRT*

**We recommend that starting prophylaxis with emicizumab in newborns or very young children should be ideally done in the setting of a clinical trial or a well-managed registry to allow collection of data on safety and efficacy. If this setting is not available, emicizumab prophylaxis should be started in a well-established comprehensive care centre with relevant clinical and laboratory experience.**

| Therapy | Pros | Cons |
|---|---|---|
| **Clotting factor replacement** | • Long-term experience, good safety<br>• Knowledge of AE management<br>• Prophylaxis can be tailored<br>• Possibility to fully normalize coagulation | • I.V. administration (may require CVLs, that may be complicated by infections/ thrombosis)<br>• Inhibitor development<br>• Short half-life<br>• Potentially poor adherence |
| **NRT (emicizumab)** | • Convenience of S.C. administration<br>• Allows for very early start of prophylaxis<br>• Long half-life<br>• Good adherence<br>• Avoidance of CVL-related complications<br>• Stable steady-state levels (may provide better protection against spontaneous bleeding) | • Short-term experience<br>• Lack of experience and data on achieving immune tolerance to FVIII<br>• Potential risk of thrombosis, TMA (mitigated by avoiding FEIBA)<br>• Remains in the body for a long period of time<br>• Need for additional haemostatic agents in case of acute bleeds/ surgery<br>• Parents' and patients' lack of training for venepuncture<br>• Lack of peaks (may be required for haemostatic protection during vigorous sports)<br>• Monitoring may be difficult, esp. when other haemostatic agents are concomitantly used |

AE, adverse event; CVL, central venous line; EHL, extended half life; FEIBA, factor eight inhibitor bypassing activity; HA, haemophilia A; ICH, intra-cranial haemorrhage; NRT, non-replacement therapy; PUP, previously untreated patient; SHL, standard half life; TMA, thrombotic microangiopathy; VWF, von Willebrand factor

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# WHICH PRODUCT?

## *CONSIDERATION OF INHIBITOR DEVELOPMENT*

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**For children whose haemophilia is diagnosed on the occasion of a bleeding episode requiring replacement therapy, we recommend discussing with parents or care givers the risk of inhibitor development in relation to exposure to clotting factor concentrates and unknowns in the use of emicizumab before completion of 50 exposure days.[1]**

- The product should be chosen to **minimise the risk of development of inhibitors**
- Prophylaxis with **emicizumab is expected to delay the patient's exposure to FVIII clotting factor concentrates**, and therefore it may take many years to reach 50 exposure days, currently the main period of risk for inhibitor development[2,3]
- **Regular exposure to FVIII** in a prophylactic regimen appears **protective**, whereas **sporadic and high-dose FVIII exposure** only during on-demand treatment of bleeds is more likely to **induce inhibitors**

1. Mancuso ME, et al. Haemophilia. 2021 Sep 21. Epub ahead of print. 2. Young G. Br J Haematol. 2019;186:400-8. 3. Abdi A, et al. J Thromb Haemost. 2020;18:3203-10

# WHICH REGIMEN?

**If the decision is taken to start prophylaxis with factor concentrate, we recommend starting with once-weekly dosing and gradually escalating to a full regimen in order to let the child and family get used to venepuncture with the aim of maintaining trough levels >3–5 IU/dL and abolishing spontaneous joint bleeds.[1]**

**If the decision is taken to start prophylaxis with NRT, we recommend using it according to the licensed regimens, taking into consideration the limited data available in young children.[1]**

- Prophylaxis should maintain the level of circulating clotting factor above the **WFH recommendation to maintain circulating factor >3–5 IU/dL**[2]
  - A pragmatic approach in young children is to start once-weekly dosing with an SHL or EHL product, let the child and parents or care givers get used to the practice of regular venepuncture, and then gradually escalate to the full regimen according to individual pharmacokinetics and bleeding phenotype[3]
- Several studies have shown that low-dose prophylaxis is less effective than full-dose prophylaxis but offers better bleed protection than can be obtained with on-demand treatment[2,4]
- Once prophylaxis has been initiated, its efficacy and safety should be **regularly monitored**

1. Mancuso ME, et al. Haemophilia. 2021 Sep 21. Epub ahead of print. 2. Srivastava A, et al. Haemophilia. 2020;26 Suppl 6:1-158. 3. Ljung R. Pediatr Blood Cancer. 2013;60 Suppl 1:S23-26. 4. Wu R, et al. Expert Rev Hematol. 2017;10:995-1004

# CONCLUSIONS

- Although standard prophylaxis with clotting factor replacement started before age 3 years has been the cornerstone of joint disease prevention, the advent of non-replacement therapy, of which emicizumab is already available, means there are **now more options for prophylaxis**

- However, the **decision-making process** of when, with what agent, and how to establish prophylaxis is becoming **more complex** and several **questions remain unanswered**
  - When and how should tolerance to FVIII be acquired and maintained in PUPs treated with emicizumab?
  - When and how should children already receiving factor products be switched to emicizumab?
  - How should prophylaxis with emicizumab be monitored?
  - How will the use of NRT prophylaxis affect the incidence and occurrence of FVIII inhibitor?

- **Biomarkers** to detect joint damage must be identified, and guidelines for treatment of breakthrough bleeds during NRT prophylaxis **should be validated**

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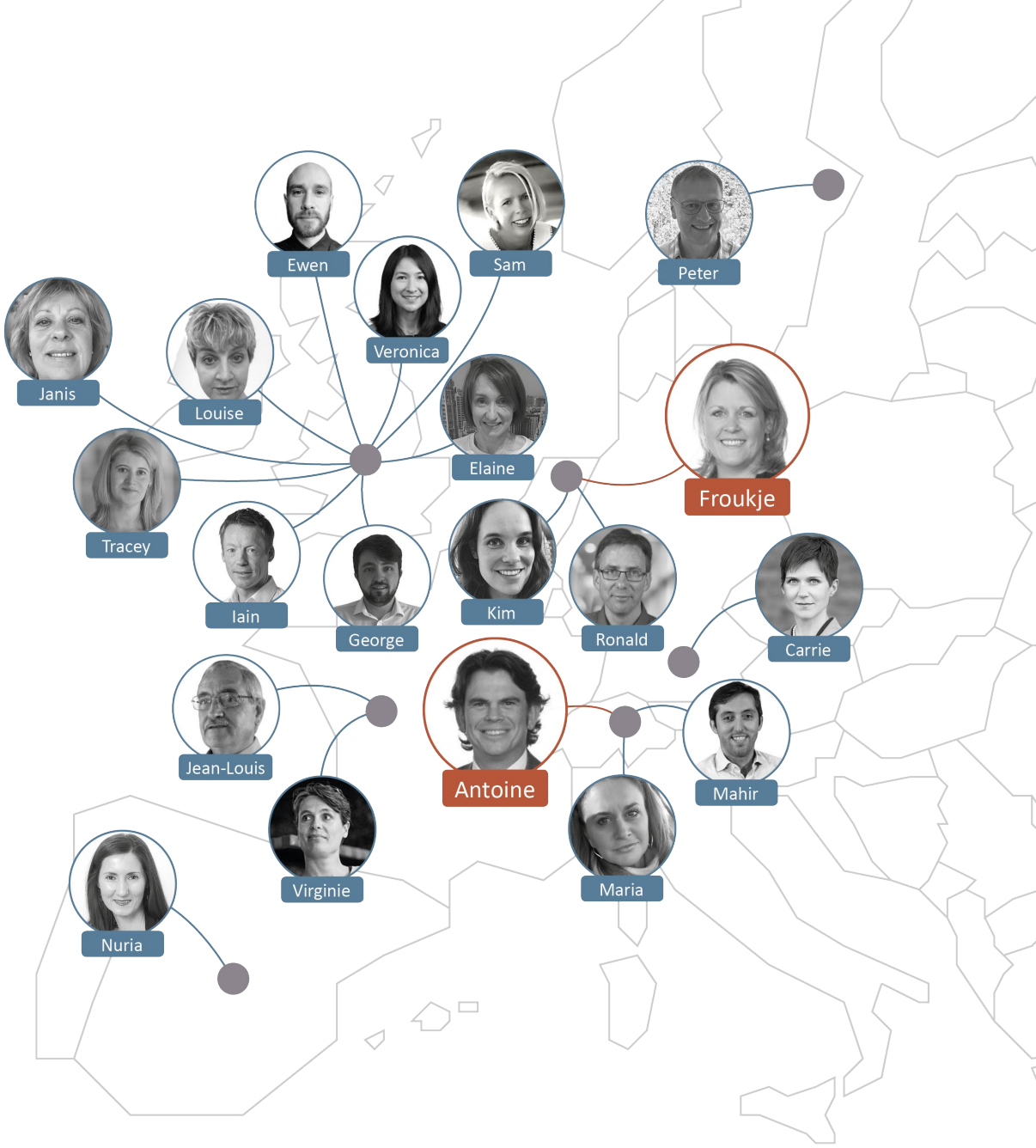


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