Addendum to British Society for Haematology guideline on the investigation, management and prevention of venous thrombosis in children (*British Journal of Haematology.* 2011;154: 196-207)

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Options for the prevention and treatment of venous thromboembolism (VTE) in childhood have largely been limited to oral vitamin K antagonists (VKA), injectable low molecular weight heparins (LMWH) or unfractionated heparin (UFH). The direct oral anticoagulants (DOACs), which are now extensively used in adult practice, have the advantage of an oral agent that does not require monitoring. This is attractive in children, particularly younger children, in whom daily subcutaneous injections of LMWH or poor stability of anticoagulant control with a VKA can be problematic. The use of DOACs in individuals <18 years of age has previously been limited by a lack of clinical trial data on efficacy and safety in this age group.

Paediatric development programmes have followed the successful DOAC studies in adult populations and include paediatric studies of the direct thrombin inhibitor dabigatran and the factor Xa antagonists rivaroxaban, apixaban and edoxaban.

Studies of single dose or short duration DOAC therapy were initially used to establish pharmacokinetic and pharmacodynamic characteristics in children and adolescents.[1-5] These studies confirmed that administration of a bodyweight-adjusted dose in all age groups resulted in DOAC concentrations that were comparable to those of a therapeutic dose in

adults. In addition, there were no significant safety or tolerability concerns in these early studies.

Rivaroxaban

The EINSTEIN Junior Phase 3 study (EINSTEIN-Jr) randomised 500 children aged <18 years in a 2:1 ratio of rivaroxaban:standard anticoagulant (heparin or VKA) to receive a bodyweight-adjusted dose of oral rivaroxaban, providing equivalent exposure to an adult dose of 20mg daily, for treatment of venous thrombosis.[6] Children received a minimum of 5 days parenteral anticoagulation prior to commencing rivaroxaban. Rivaroxaban, as film-coated tablets or granules for suspension, was administered 1-3 times daily depending on body weight.[6] Duration of therapeutic anticoagulation was a minimum of 3 months, reduced to 1 month for line-associated thrombosis in children <2 years of age. This non-inferiority study showed a low rate of VTE recurrence with rivaroxaban (1%) and standard anticoagulants (3%). Complete thrombus resolution occurred in a greater proportion of children treated with rivaroxaban over standard anticoagulants (38% vs. 26%, respectively, p=0.012) without an increase in major or clinically relevant non-major bleeding (3% vs. 2%).

A subgroup analysis of children with cerebral venous thrombosis (CVT, N=114) who were randomised in EINSTEIN-Jr and evaluated after an initial 3 months of treatment, reported complete recanalisation of the cerebral venous sinuses in a greater proportion of children who received rivaroxaban compared to standard anticoagulants (25% vs. 15%, p=0.012) with no VTE recurrence in the rivaroxaban arm and equivalent safety characteristics to standard anticoagulants.[7] The study included only 9 term neonates and infants, 4 of whom were randomised to receive rivaroxaban.

Children who were anticoagulated for symptomatic or asymptomatic central venous catheter (CVC)-related VTE in EINSTEIN-Jr (N=126) received rivaroxaban or standard anticoagulants for 1 month (<2-year-old children) or 3 months (all other children) and were reported in a further subgroup analysis.[8] There was no recurrent VTE, none had a major bleeding event and complete/partial vein recanalization occurred in 92%. Continuation beyond the initial 1 or 3 months, due to residual thrombosis and/or ongoing CVC requirement, was indicated in 48% including 61% of those <2 years. There was no comparison of outcomes between those treated with rivaroxaban or standard anticoagulants due to low numbers.

Dabigatran

The DIVERSITY Phase 2b/3 study randomised 267 children aged <18 years of age in a 2:1 ratio of dabigatran:standard anticoagulant (heparin, VKA or fondaparinux) to receive age- and bodyweight-adjusted doses of oral dabigatran for treatment of venous thrombosis.[9] Children received a minimum of 5 days parenteral anticoagulation prior to commencing dabigatran. Dabigatran tablets, pellets or oral suspension were administered twice daily to provide exposure similar to adult populations treated therapeutically with dabigatran.[10] Participants received therapeutic anticoagulation for a minimum of 3 months. Dabigatran dose adjustment was permitted once to achieve trough dabigatran level of 50-250 ng/ml, required in 62/117 (35%) patients assigned to dabigatran with 56 requiring an increase in dose. Dabigatran was non-inferior to standard anticoagulants in terms of a composite efficacy endpoint of the proportion of children with complete thrombus resolution (46% of those treated with dabigatran vs. 42% standard of care), freedom from recurrent VTE (96% vs. 92%) and freedom from VTE-related death (100% vs. 99%). Major bleeding occurred at a frequency of 2% in both groups. Adverse events related to the gastrointestinal tract were

reported more often in the group treated with dabigatran but there was no gastrointestinal bleeding. The impact of dose adjustment was minimal and trough dabigatran concentrations were similar to those seen in adults: the authors concluded that dabigatran concentrations did not need to be monitored or doses adjusted in children in routine clinical practice.[9]

In a single arm, open-label trial anticoagulation with dabigatran was continued as secondary prophylaxis in children (N=203) who had been treated with either dabigatran or standard anticoagulants for 3 months and who had a risk of recurrent VTE. Dabigatran was given for up to 12 months, less if the risk factor(s) for VTE resolved. Rates of recurrence (1%), major bleeding events (1.5%) and post-thrombotic syndrome (1.2% in those with extremity or central line thrombosis) were acceptable.[11]

Phase 3 studies of the factor Xa antagonists apixaban and edoxaban for the prevention and treatment of childhood VTE are ongoing [NCT02464969; NCT02369653[12]; NCT02981472[13]; NCT02798471[14]; NCT03395639].

While the results of paediatric DOAC trials provide a valuable evidence base for the management of childhood VTE there are a number of limitations to the currently available data:

- Eligibility for trial inclusion was limited to venous thrombosis, with no data available on thromboprophylaxis in children with cardiac disease or therapeutic anticoagulation in those with arterial thrombosis;
- Some populations of children were excluded from the studies, e.g. premature and low birth weight infants, those having had less than a defined period of oral feeding; [6,9]

- Children who were recruited to phase 3 studies were generally older, with lower numbers in the youngest age groups (37 children <12 months old treated with rivaroxaban in EINSTEIN-Jr, 22 children <2 years old treated with dabigatran in DIVERSITY) which does not reflect the early peak in incidence of childhood VTE that is seen during infancy;[6,9]
- A relatively low proportion of recruits had CVC-related thrombosis in both phase 3 DOAC studies (18-25% of the study population)[6,9] and those with CVT were over-represented in EINSTEIN-Jr (23%).[6] There were few cases of antiphospholipid antibody-associated thrombosis meaning that concerns raised in adults treated with a DOAC cannot necessarily be extrapolated to children;[15]
- There are no data on prophylactic dosing for primary or secondary prevention of VTE;
- There is a lack of data on dosing, efficacy and safety of reversal agents or other means of managing DOAC-related bleeding in children although there is evidence in adults for the use of Idaracizumab for dabigatran-related bleeding[16] and Andexanet or prothrombin complex concentrate for factor Xa antagonist-related bleeding.[17,18]

Paediatric formulations were available during clinical trials of the DOACs, usually in the form of powder or granules for suspension. Commercially available tablets or capsules can be used in larger children in order to deliver a weight-based dose. However, the administration of bodyweight-adjusted doses of a DOAC to smaller children, including those who are unable to swallow tablets, will be reliant on the availability of a suitable liquid oral preparation.

Monitoring of LMWH and VKA therapy in children, in addition to the training of parents/ carers in the administration of subcutaneous injections and point-of-care monitoring of VKAs, provides opportunities to develop the relationship between the parent/carer and the

prescribing team. The introduction of DOACs into paediatric practice is likely to reduce the number of contacts with the prescriber but there will remain a need to provide counselling, education and advice, along with a point of contact. The young person and/or their parent or carer should be counselled about the risk of bleeding during anticoagulation with a DOAC and informed about the lack of data on the dosing, efficacy and safety of reversal agents in the paediatric population.

Post-authorisation studies of DOAC use in children and real-life data will be valuable, particularly for very young children and those with specific indications who were either under-represented or excluded from participation in clinical trials.

Recommendations:

- **Rivaroxaban and dabigatran should be offered for the treatment of venous thrombosis in people <18 years of age (Grade 1B)**

- **At least 5 days of parenteral anticoagulation (with UFH, LMWH, or fondaparinux) should be given prior to starting rivaroxaban or dabigatran for the treatment of venous thrombosis in people <18 years of age (Grade 1B)**

- **Based on adult data, we recommend warfarin for people <18 years of age who have triple-positive antiphospholipid syndrome (Grade 1B). We suggest that an alternative to a DOAC is considered in those with antiphospholipid syndrome who are not triple-positive (Grade 2B)**

References

1. Kubitza D, Willmann S, Becka M, Thelen K, Young G, Brandao LR et al. Exploratory evaluation of pharmacodynamics, pharmacokinetics and safety of rivaroxaban in children and adolescents: an EINSTEIN-Jr phase I study. *Thrombosis Journal*. 2018;16: 31. doi: 10.1186/s12959-018-0186-0.

2. Halton JML, Albisetti M, Biss B, Bomgaars L, Brueckmann M, Gropper S. Phase IIa study of dabigatran etexilate in children with venous thrombosis: pharmacokinetics, safety, and tolerability. *Journal of Thrombosis and Haemostasis*. 2017;15: 2147-2157.

3. Halton JML, Picard A-C, Harper R, Huang F, Brueckmann M, Gropper S et al. Pharmacokinetics, pharmacodynamics, safety and tolerability of dabigatran etexilate oral liquid formulation in infants with venous thromboembolism. *Thrombosis and Haemostasis*. 2017;117(11): 2168-2175.

4. Monagle P, Lensing AWA, Thelen K, Martinelli I, Male C, Santamaria A et al. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies. *Lancet Haematology*. 2019;6(10): e500-e509.

5. Roshammer D, Huang F, Albisetti M, Bomgaars L, Chalmers E, Luciani M et al. Pharmacokinetic modelling and simulation support for age- and weight-adjusted dosing of dabigatran etexilate in children with venous thromboembolism. *Journal of Thrombosis and Haemostasis.* 2021;00: 1-12.

6. Male C, Lensing AWA, Palumbo JS, Kumar R, Nurmeev K, Hege K et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous

thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematology*. 2019;7(1): e18-e27.

7. Connor P, Sanchez van Kammen M, Lensing AWA, Chalmers E, Kallay K, Hege K et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). *Blood Advances*. 2020;4(24): 6250-6258.

8. Thom K, Lensing AWA, Nurmeev I, Bajolle F, Bonnet D, Kenet G et al. Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE). *Blood Advances*. 2020;4(19): 4632-4639.

9. Halton J, Brandao LR, Luciani M, Bomgaars L, Chalmers E, Mitchell LG et al. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial*. Lancet Haematology*. 2020;8(1): e22-e33.

10. Albisetti M, Biss B, Bomgaars L, Brandao LR, Brueckmann M, Chalmers E et al. Design and rationale for the DIVERSITY study: an open-label, randomized study of dabigatran etexilate for pediatric venous thromboembolism. *Research and Practice in Thrombosis and Haemostasis.* 2018;2: 347-356.

11. Brandao LR, Albisetti M, Halton J, Bomgaars L, Chalmers E, Mitchell LG et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. *Blood*. 2020;135(7): 491-504.

12. O'Brien SH, Li D, Mitchell LG, Hess T, Zee P, Yee DL et al. PREVAPIX-ALL: Apixaban compared to standard of care for prevention of venous thrombosis in paediatric acute

lymphoblastic leukaemia (ALL)- Rationale and Design. *Thrombosis and Haemostasis*. 2019;119(5): 844-853.

13. Payne RM, Burns KM, Glatz AC, Li D, Xiaodong L, Monagle P et al. A multi-national trial of a direct oral anticoagulant in children with cardiac disease: Design and rationale of the SAXOPHONE study. *American Heart Journal*. 2019;217: 52-63.

14. Van Ommen CH, Albisetti M, Chan AK, Estepp J, Jaffray J, Kenet G et al. The Edoxaban Hokusai VTE PEDIATRICS Study: An open-label, multicenter, randomized study of edoxaban for pediatric venous thromboembolic disease. *Research and Practice in Thrombosis and Haemostasis.* 2020;4: 886-892.

15. Arachchillage DRJ, Gomez K, Alikhan R, Anderson JAM, Lester W, Laffan M. Addendum to British Society for Haematology guidelines on investigation and management of antiphospholipid syndrome, 2012 (Br. J. Haematol. 2012; 157: 47-58): use of direct acting anticoagulants. *British Journal of Haematology*. 2020;189: 212-215.

16. Pollack CV, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA et al. Idaracizumab for dabigatran reversal- Full cohort analysis. *New England Journal of Medicine*. 2017;377:431-441.

17.

17. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *New England Journal of Medicine*. 2019;380: 1326-1335.

18. Nederpelt CJ, Naar L, Krijnen P, le Cessie S, Kaafarani HMA, Huisman MV et al. Andexanet alfa or prothrombin complex concentrate for factor Xa inhibitor reversal in acute major bleeding: A systematic review and meta-analysis. *Critical Care Medicine*. 2021 May 7. doi: 10.1097/CCM.0000000000005059. Online ahead of print.