Levels of Evidence in Drug Development:

Paediatric Dose Selection for Fondaparinux

Challenge to the use of M&S in lieu of pharmacokinetic bridging

LEADING STATEMENTS:

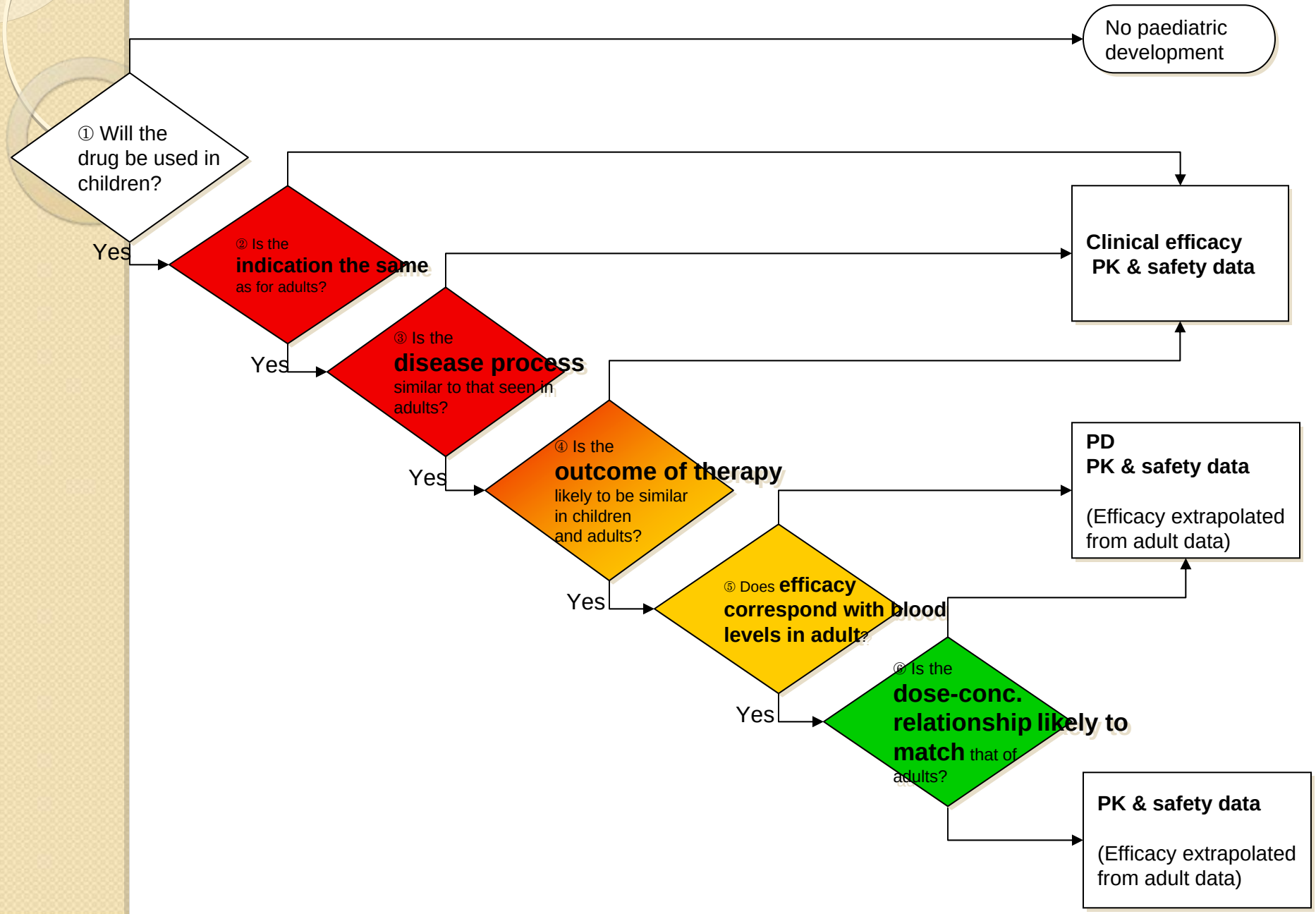
1. Fondaparinux is a Factor Xa inhibitor (anticoagulant) indicated for the prophylaxis of deep vein thrombosis (DVT) in patients undergoing fracture surgery and DVT or acute pulmonary embolism (PE) when administered in conjunction with warfarin.

2. M&S analysis clearly showed that 0.1 mg/kg matched adult exposures and should be the recommended dose in children.

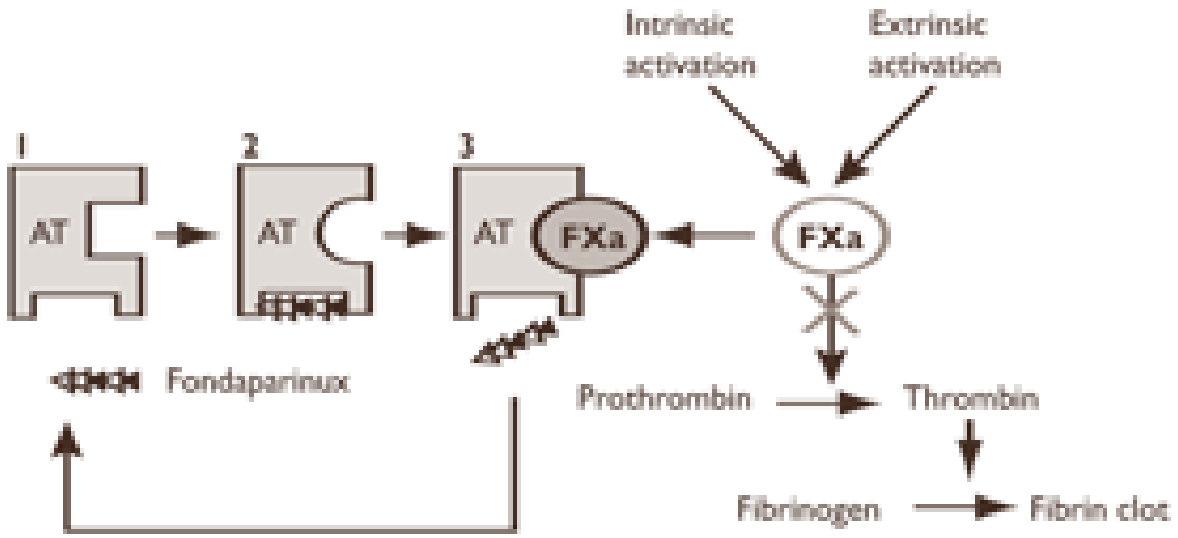
3. The FDA has not accepted the dose rationale based on the **inferences from M&S results** and demanded **prospective trial showing evidence** of safety and efficacy in children taking into account dose titrations.

Argument : the anti-coagulant systems might not be the same in children as compared to adults. One can therefore not assume that similar exposures will yield comparable efficacy.

Paediatric Drug Development



Mechanism of action



Fondaparinux activates antithrombin III (AT) increasing affinity for factor Xa (Fxa) by 340-fold. Activated Fxa inhibits the intrinsic and extrinsic arms of the coagulation cascade, indirectly causing a reduction in thrombin generation

Fondaparinux is devoid of any direct antithrombin activity.

Are there differences in thrombin regulation between children and adults?

Thromb Haemost. 1994 Dec;72(6):836-42.

Thrombin regulation in children differs from adults in the absence and presence of heparin.

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Abstract

The physiologic mechanisms that protect children from thromboembolic complications are not known. We investigated the regulation of thrombin in children because of its central importance to thrombosis. The capacity to generate thrombin in vitro (chromogenic assay) was decreased by 26% in plasmas from children (1-16 yrs; n = 102) compared to adults (20-45 yrs; n = 20; p < 0.001). The addition of purified prothrombin to plasmas from children increased thrombin generation to adult values. The capacity of plasmas to
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PMID: 774045

Thromb Haemost 1998; 80: 570–4

rombin
II

Enhanced Thrombin Regulation during Warfarin Therapy in Children Compared to Adults*

Patricia Massicotte, Michael Leaker, Velma Marzinotto, Margaret Adams, Robert Freedom, William Williams, Patsy Vegh, Leslie Berry, Bianca Shah, Maureen Andrew

Are such differences clinically important?

Therapeutic benefits of factor X inhibitors

- In theory**, inhibition of factor Xa provides a more efficient mechanism for the control of fibrin formation than does inactivation of thrombin**;

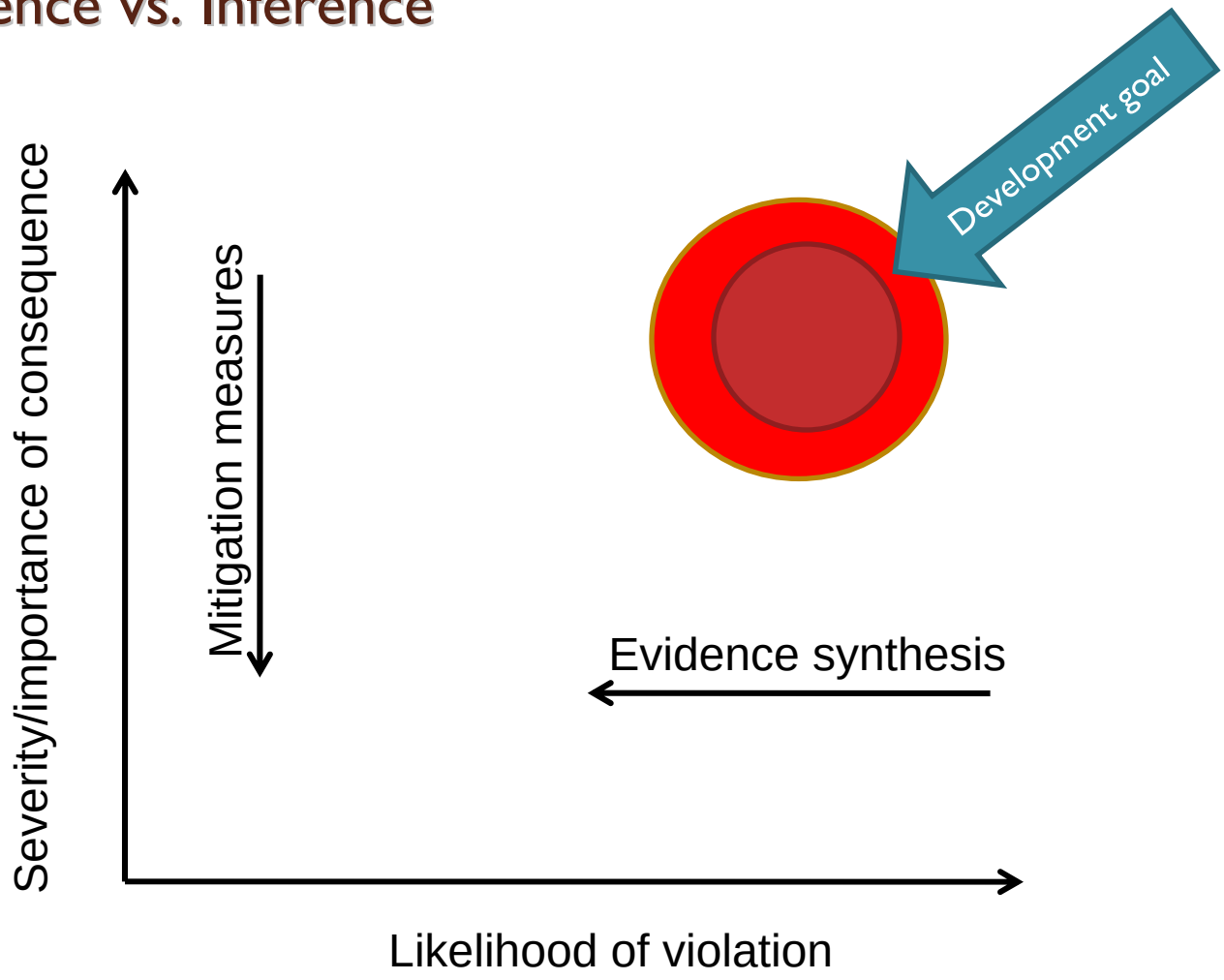
  (*This is suggested by the finding that while inactivation of one molecule of factor Xa by antithrombin III inhibits the generation of 50 thrombin molecules, inactivation of these same 50 thrombin molecules would require 1300 times as much antithrombin III*)

- Since inhibition of factor Xa leads to decreased thrombin generation rather than inactivation of thrombin's catalytic activity**, factor Xa inhibition would not be expected to modulate thrombin's regulatory functions in the control of hemostasis.**

- **These regulatory functions are independent of thrombin's primary role in catalyzing the fibrinogen-fibrin transformation** and include, among others, procoagulant (factors V and VIII activation), anticoagulant (protein C activation), and prothrombotic (platelet and factor XIII activation) activities.

Impact of Assumptions

Evidence vs. Inference



From evidence to inference:

When should model-based approaches be used?

Pediatr Blood Cancer

FondaKIDS: A Prospective Pharmacokinetic and Safety Study of Fondaparinux in Children Between 1 and 18 Years of Age

Guy Young, MD,[1]* Donald L. Yee, MD,[2] Sarah H. O'Brien, MD,[3] Rachna Khanna, MPH,[1] April Barbour, PhD,[4] and Diane J. Nugent, MD[5]

Background. The incidence of thromboembolic disease is increasing in children. New anticoagulants have been licensed in adults and need to be studied in children. This report describes the first prospective study of fondaparinux in children. ***Procedure.*** The purpose of the study was to determine the dosing, pharmacokinetics, and safety of fondaparinux in children with deep vein thrombosis (DVT) or heparin-induced thrombocytopenia (HIT). Hospitalized children between 1 and 18 years of age with DVT or HIT received fondaparinux 0.1 mg/kg once daily. Fondaparinux-based anti-factor Xa levels were assessed at 2, 4, 12, and 24 hr following the first dose, and peak levels were measured twice weekly thereafter. Detailed pharmacokinetic analyses were performed. ***Results.*** Twenty four subjects in 3 age cohorts were enrolled and completed the study. Pharmacokinetic modeling demonstrated that a once-daily dose of fondaparinux at 0.1 mg/kg resulted in similar concentrations known to be efficacious in adults. Safety was demonstrated with only two bleeding events: one which may have pre-dated study drug administration and one which led only to temporary discontinuation of study drug. ***Conclusion.*** Dosing of fondaparinux at 0.1 mg/kg once daily in children resulted in PK profiles comparable to those in adults receiving standard dosing. Fondaparinux can be considered an attractive alternative to LMWH given its once-daily dosing, acceptable safety data, and other favorable properties. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

Key words: anticoagulation; children; fondaparinux; thrombosis

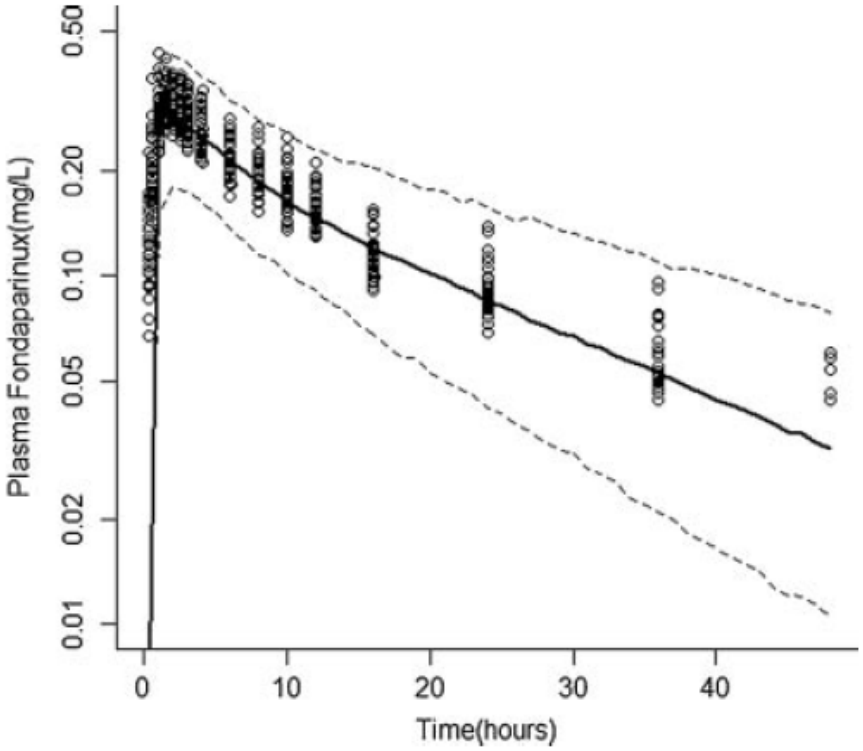
Dose Adjustment of fondaparinux

Dose: 0.1 mg/kg qd.

Level (mg/L)	Dose adjustment
<0.3	Increase dose by 0.03 mg/kg
0.3–0.5	Increase dose by 0.01 mg/kg
0.5–1	No change
1–1.2	Decrease dose by 0.01 mg/kg
>1.2	Decrease dose by 0.03 mg/kg

From evidence to inference:

When should model-based approaches be used?



Model validation using VPC for adult data.
Simulations are represented by lines (median –solid line, 95% prediction intervals - dashed lines) with the observed data overlaid.

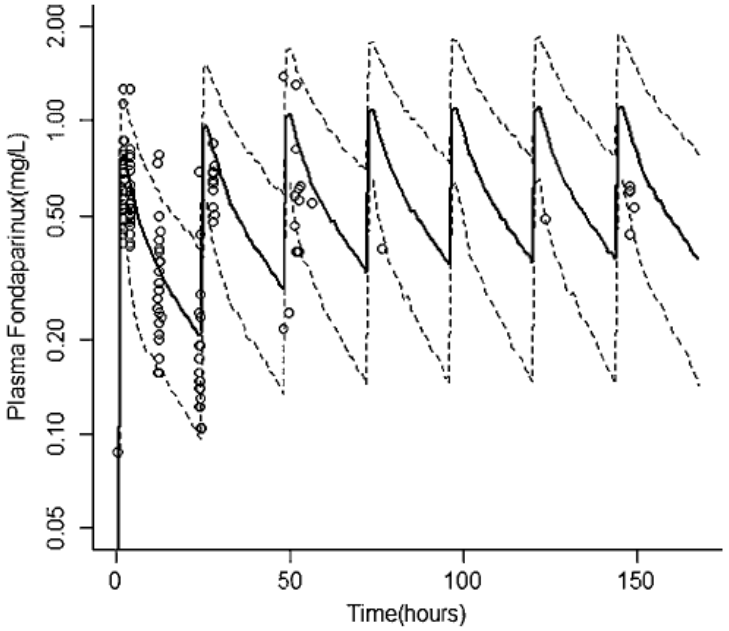
Summary of Parameters in the final population PK model for fondaparinux

PK parameters	Point estimate (% standard error)	Inter-individual variability (% CV)
CL[a]	0.337 (5.52%)	30.1%
V2[b]	5.49 (3.79%)	18.2%
V3	2.21 (5.52%)	NE[c]
Q	0.371 (11.8%)	NE
KA	1.45 (7.93%)	30.1%
$Covariance_{CL,V2}$		21.7%
$Residual\ error_{Adult\ BE}$		8.8%
$Residual\ error_{Pediatric}$		31.3%

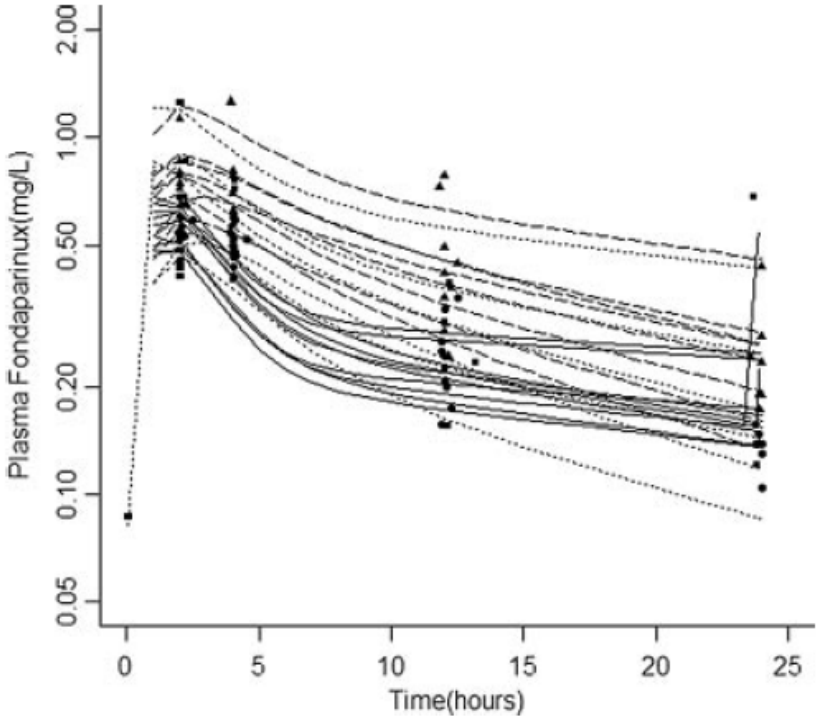
a) $CL = TVCL \times (WT/70)^{0.75}$
b) $V2 = TVV2 \times (WT/70)^{1}$

From evidence to inference:

When should model-based approaches be used?



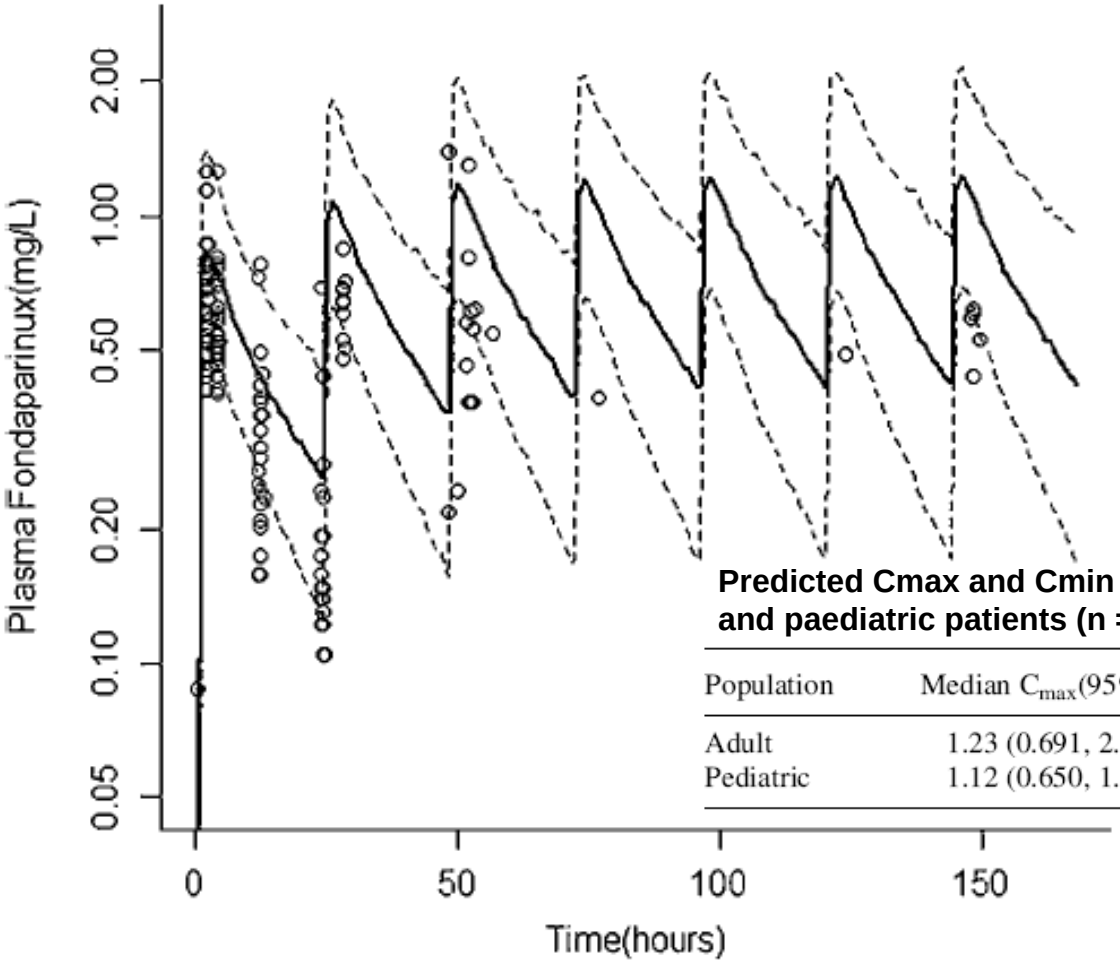
Model validation. VPC for paediatric patients. Simulations are represented by lines (median – solid line, 95% prediction intervals - dashed lines) with the observed data overlaid.



Predicted (lines) and observed (symbols) fondaparinux concentration –time profiles for each subject in the first 24h grouped by body weight. BW $\leq$ 20kg represented by solid lines and close circles, BW 20 -46 kg represented by dotted lines and closed squares. BW >46 kg represented by dashed lines and closed triangles.

From evidence to inference:

When should model-based approaches be used?



Predicted Cmax and Cmin at steady-state in adults and paediatric patients (n = 1000)

Population	Median C_{max}(95% PI)	Median C_{min} (95% PI)
Adult	1.23 (0.691, 2.15)	0.420 (0.170, 0.888)
Pediatric	1.12 (0.650, 1.89)	0.364 (0.144, 0.772)

The observed fondaparinux concentration data from the paediatric study (open circles) were overlaid on a plot of the simulation of 1000 adults receiving the recommended dosing regimen (median – solid line, 95% prediction interval – dashed lines).

Procedural steps taken and scientific information after the authorisation :

Update of sections 4.2, 5.1 and 5.2 of the SmPC with data from a phase II pilot dose-finding and pharmacokinetic study

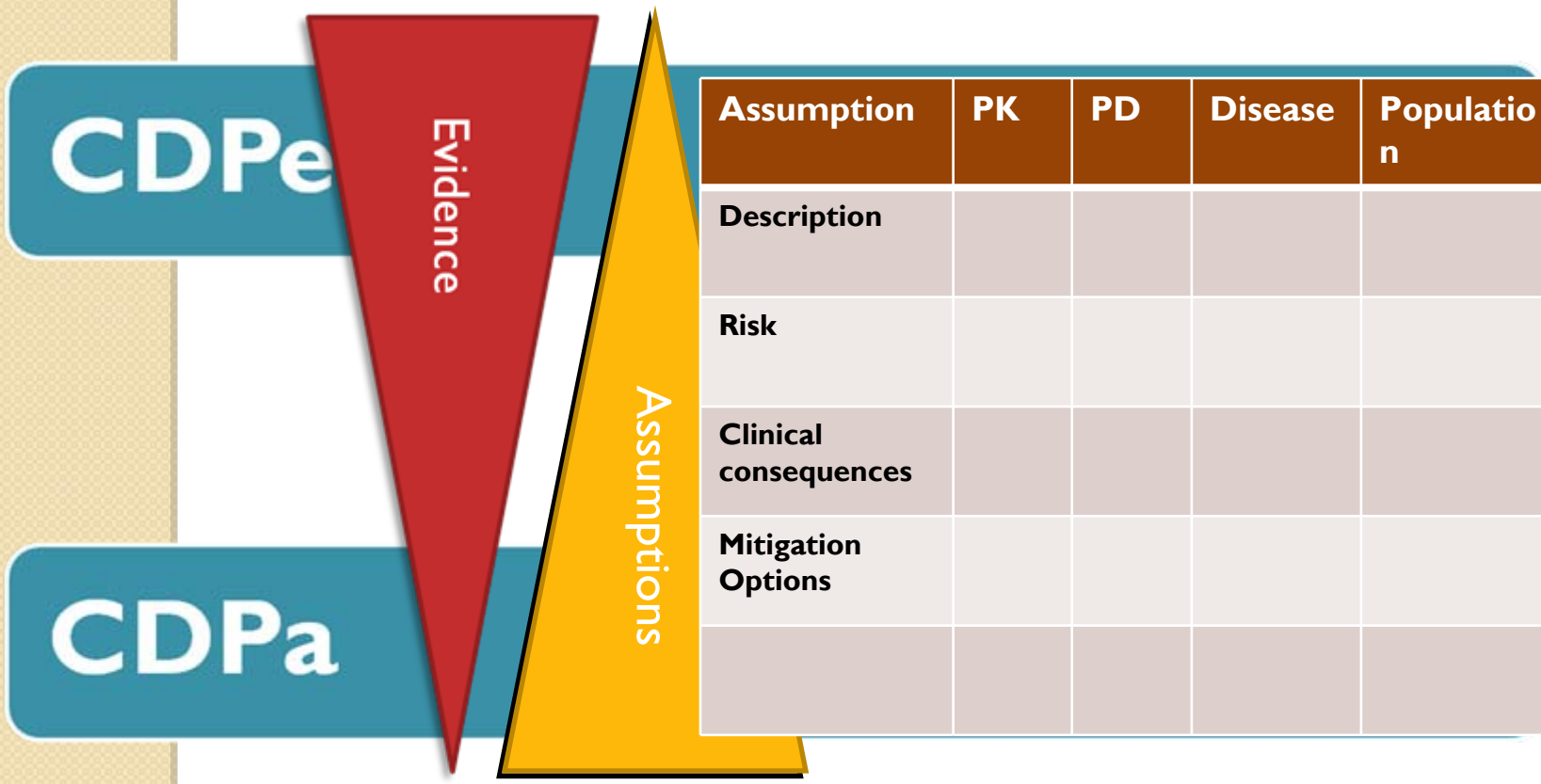
Data from this study were used to create a PK model for the paediatric population to compare concentrations achieved in paediatric patients receiving 0.1mg/kg/day to concentrations known to be efficacious in adults. The PK modelling used data from study ART113100 and study BDR3780, a bioequivalence study in adult healthy subjects. The BDR3780 clinical study report was part of the original Marketing Authorisation Application for Arixtra.

The limited data provided in paediatrics collectively suggest that the exposure in children with dosing 0.1 mg/kg is somewhat lower than that observed in adults and that there is a trend for increased exposure with increased age within the paediatric population.

From the results of this small uncontrolled study no firm conclusions can be drawn on an optimal concentration range to target in children in the treatment of thrombosis in the deep venous system. However, the CHMP was of the opinion that it could be of value for the prescribers to know what concentrations could be expected with a dose that, when adjusted to body-weight, is similar to what is recommended for adults. Therefore the CHMP agreed on the update of the SmPC to include data on this study. As the data concerns children with deep venous thrombosis, this information is only included in the SmPCs relevant for this indication, i.e. the 5, 7.5 and 10 mg strengths.

Communication and level of confidence:

framework to handle M&S assumptions



Assumption	PK	PD	Disease	Population	Statistical aspects
Description					
Risk					
Clinical consequences					
Mitigation Options					

CONCLUSIONS

1. Inferential methods should underpin **evidence synthesis and knowledge integration** in the development of drugs for special populations. Efforts should be made to achieve that objective.

2. M&S Assumptions can be **violated** (this should be addressed accordingly e.g. by additional evidence or by a better model), **mitigated** (e.g., by label restriction, dose titration) or **pertain as risk** to patients and other stakeholders (e.g., regulator/sponsor).

3. The consequences and **clinical implications of M&S assumptions** must be quantified prior to rejection or acceptance of a model

Backup slides

Differences in thrombin regulation in children and its impact on INR

Thromb Haemost 1998; 80: 570–4

Enhanced Thrombin Regulation during Warfarin Therapy in Children Compared to Adults*

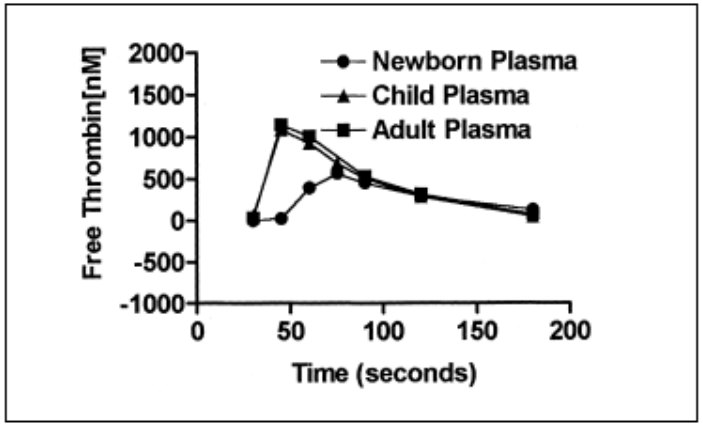
Patricia Massicotte,

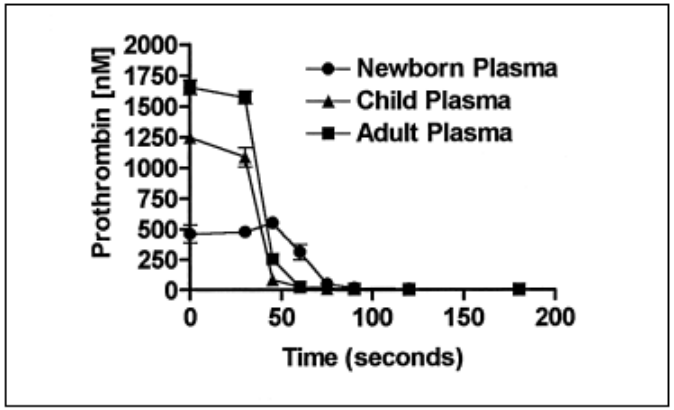
Our study showed that plasmas from children receiving warfarin generated less thrombin compared to plasmas from adults with similar INR values. A similar observation was previously made for plasmas from healthy children compared to adults (14). In healthy children, there are at least two mechanisms contributing to the reduced capacity to generate thrombin; decreased plasma concentrations of prothrombin and increased concentrations of α_2M

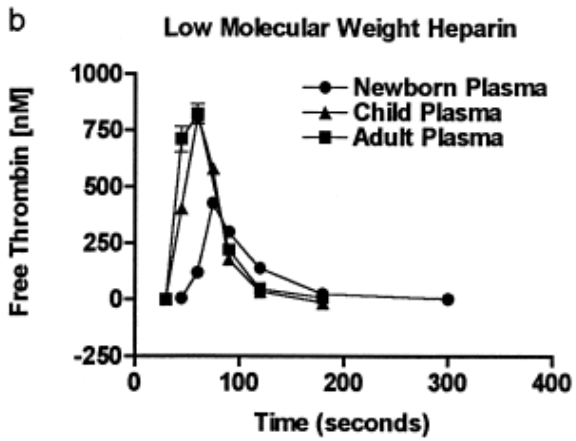
The enhanced regulation of thrombin in paediatric patients with similar INR values compared to adult patients, suggests that lower intensities of oral anticoagulants may be effective in children. This concept is important for several reasons. First, the paediatric population requiring oral anticoagulant therapy is comprised of children with a variety of serious primary disorders including CHD, cancer, trauma/surgery, systemic lupus erythematosis, and others (2). These diseases are frequently associated with a significant risk of bleeding which is increased in the presence of oral anticoagulants. Second, monitoring oral anticoagulant therapy is fraught with difficulties for patients of any age, but even more so in children. These problems include rapidly changing clinical status, need for multiple drugs, variable dietary intake of vitamin K and poor venous access.

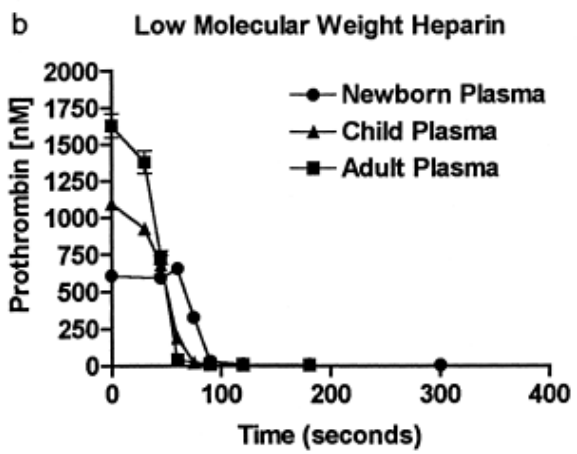
In summary, this study shows that thrombin regulation is increased in children as compared to adults receiving warfarin and with similar INR values. Clinical trials in children evaluating less intense regimens with warfarin therapy may be required to determine optimum treatment.

Are there differences in thrombin regulation between children and adults?





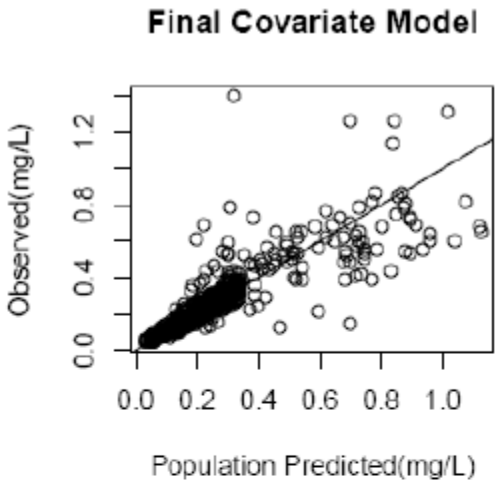


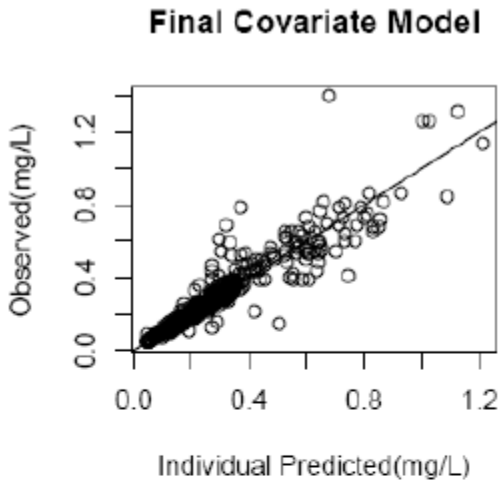


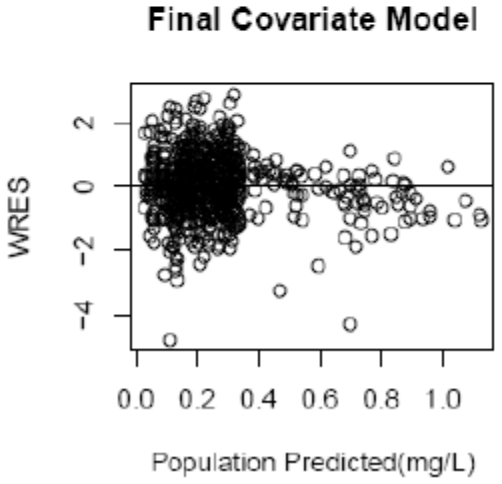
Thromb Haemost 2002; 87: 606–13

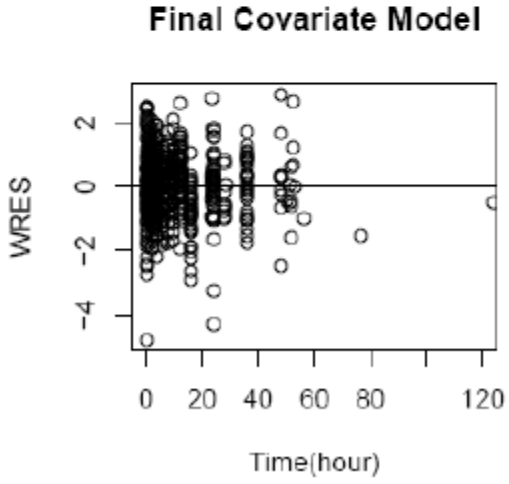
Are such differences clinically important?

Modelling Diagnostics









Acknowledgements

- Michael Fossler
- April Barbour
- Arixtra clinical team members