EMA EFPIA workshop, Break-out session no. 3

Case Study:

Sample size estimation for a paediatric clinical trial utilising external information from historical trials in adults and children

Wolfgang Köpcke[1], Joachim Gerß[1], Raphael Koch[1], Christoph Male[2]

1 University Clinic Münster (Germany) Institute of Biometry and Clinical Research

2 Medical University Vienna (Austria), Department of Paediatrics

Objective

- Extrapolation of efficacy from adults to children
- Use of historical data from adults and children
- Modelling of clinical response data
- Age-appropriate dosing established
  - Weight-based; adjusted by TDM to similar PD levels as in adults

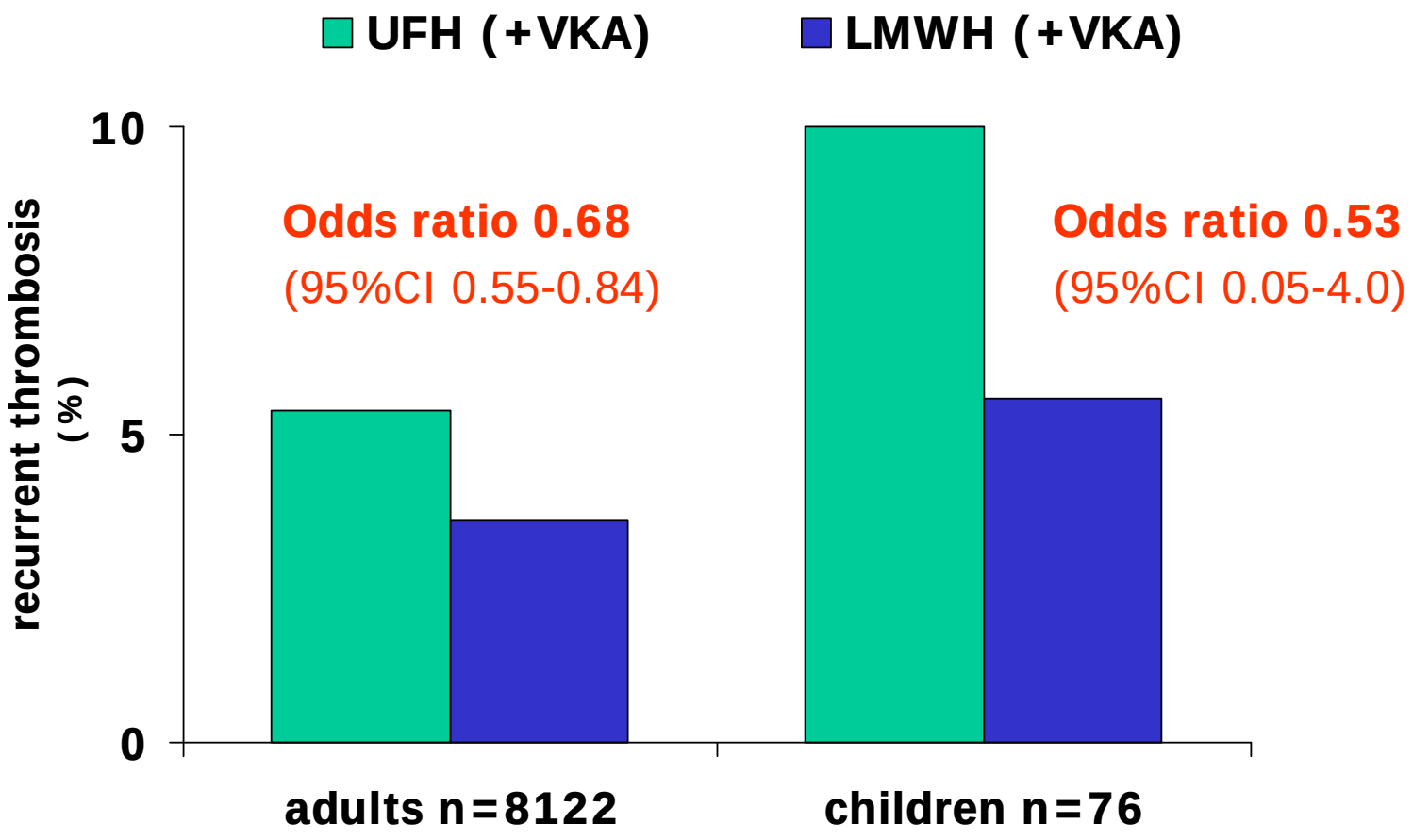
Clinical setting

Treatment of acute venous thromboembolism

- **Venous thromboembolism:**
  - Different triggers in adults vs children
  - Common pathophysiologic pathway: thrombotic vessel occlusion,

    embolism
- **Anticoagulants:**
  - mode of action: inhibition/reduction of clotting factors
  - Unfractionated heparin (UFH) versus low molecular heparin (LMWH)
  - followed by Vitamin K antagonist (VKA)
  - Future development: new oral anticoagulants
- **Endpoints:** (during follow-up of 3-6 months)
  - Efficacy: recurrent thrombosis

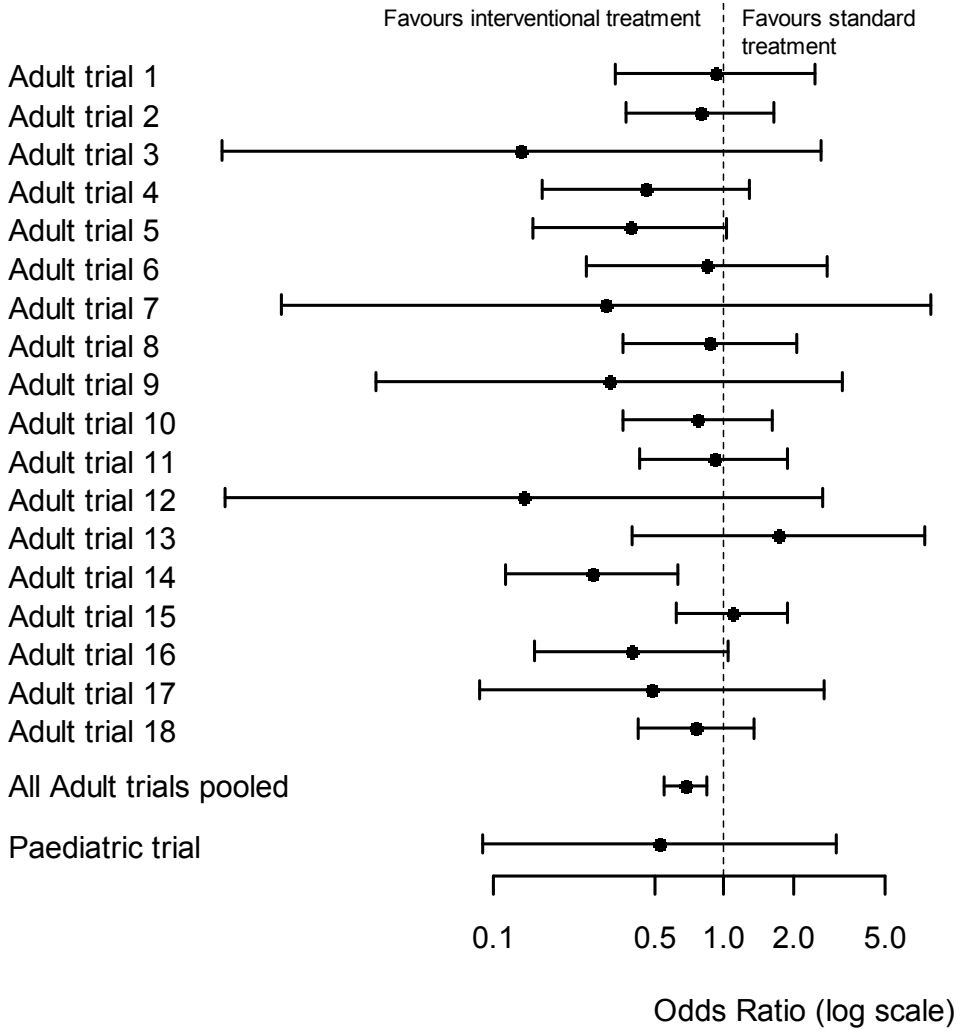
Historical data



Van Dongen, Cochr datab SR 2004

Massicotte, Thromb Res 2003

Background & Rationale



Background & Rationale

The available information of all historical trials shall be extrapolated to a future paediatric trial, that is planned in order to show that the interventional treatment is non-inferior (noninferiority margin $\Delta=1.3$) to the standard treatment in paediatric patients with venous thromboembolism.

Background & Rationale

- **Bayesian** meta-analytic-predictive approach
- **Extension** of the Neuenschwander et al. [3] model
- Data of control **and** interventional treatment
- Extrapolation to a planned paediatric trial with a **potential shift** in mean treatment effects between adults and children

M&S Assumptions

- Two important features of study-specific effects
- Random variation of study-specific effects (between-trial variation)
- Possible difference in mean pooled effects between adults and children
- Determine the amount of evidence that the historical data contributes in a future trial
- The determined evidential weight can be translated to an estimated “prior effective sample size” (virtual subjects)

M&S Assumptions

- Bayesian analysis with posterior distribution [θ|observed data] θ=ln(OR)
- Bayesian analogon of a classically “significant” noninferiority test
- Calculated posterior 95% credible interval of the OR ranges entirely below the noninferiority margin Δ=1.3
- Empirical determination of Bayesian power with simulated data
- Marcov chain Monte Carlo (MCMC) sampling via the WinBUGS software [4]
- Generation of Markov chains with a burn-in=10000 and a

M&S Results

- Existing data of 8122 adult plus 76 paediatric patients (=8198 patients in total) equates to 116 “virtual subjects” (small to moderate variability)

- For new trial with 80% Bayesian power without utilising historical information the sample size is 2*290=580 children

- Utilizing the 116 “virtual subjects the required sample size is reduced by 20% from 580 to 580-116=464

M&S Results

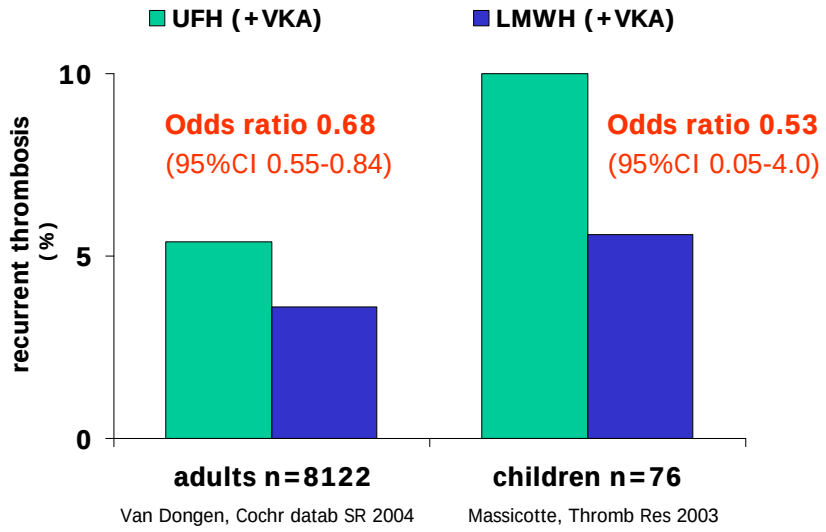
Prior log Odds Ratio	-	-0.6514 ± 0.9373	-0.6514 ± 0.9373
Prior effective sample size	-	116	116
Expected Event Rate (Intervention group)	5.56%	5.56%	5.56%
Expected Event Rate (Control group)	10%	10%	10%
Sample size in new trial (total)	580	468	580
Bayesian Power (simulated)	0.8016	0.8017	0.8757

Conclusions & Lessons learned

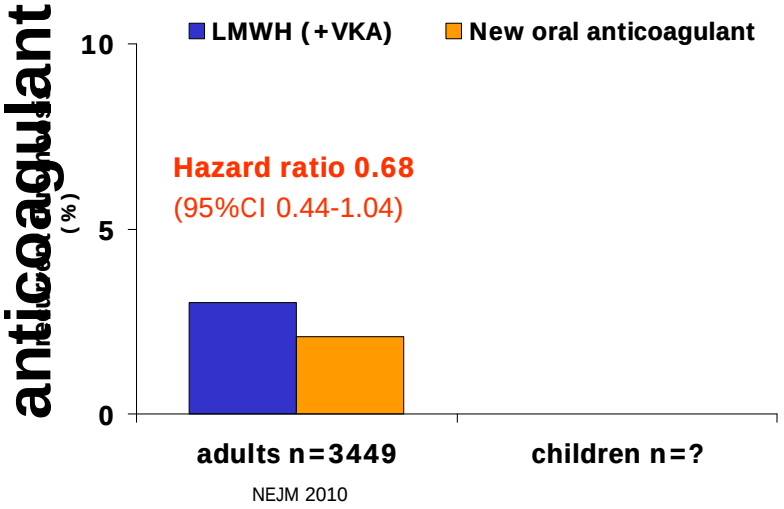
- With Bayesian modelling it is possible to use external historical information for planning a new study
- This could either increase the power or reduce the sample size of the future trial
- If the use of historical data is an option, the suggested Bayesian meta-analytic-predictive approach may be a valuable tool for regulators, stakeholders, and experts

Future perspective
Extrapolation for new oral anticoagulant

Historical data

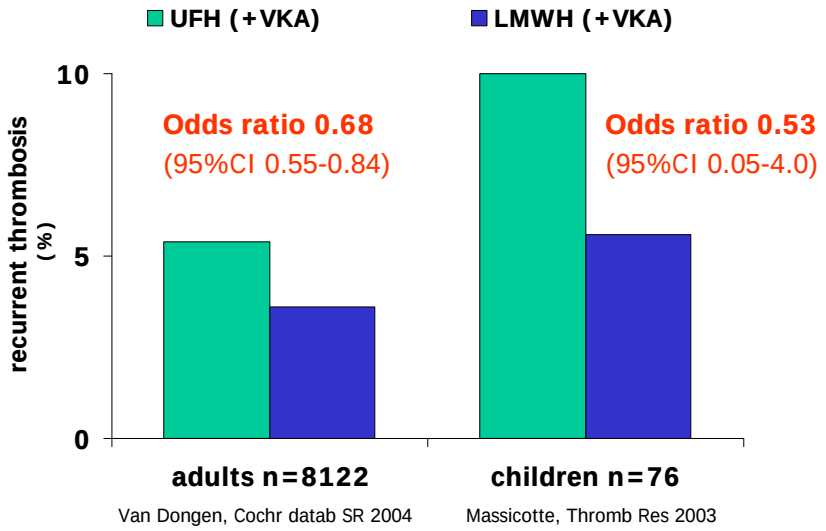


New anticoagulant

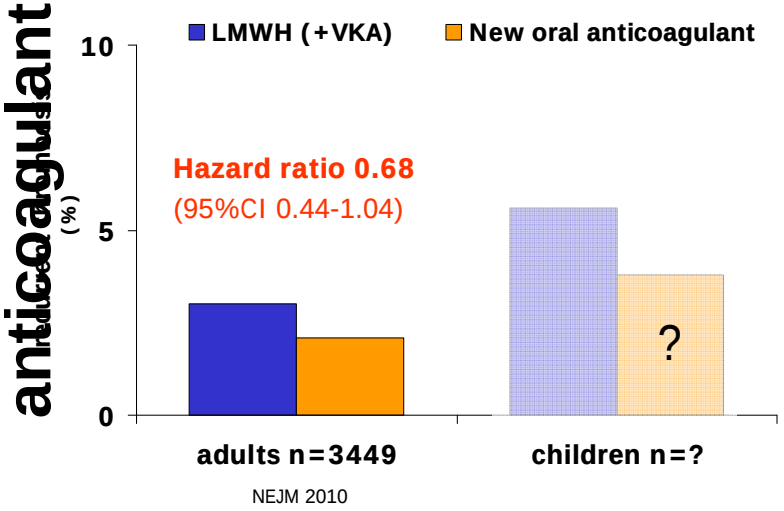


Future perspective
Extrapolation for new oral anticoagulant

Historical data



New anticoagulant



Paediatric Investigation Plan for new oral anticoagulant:

- PBPK-modelling
- In-vitro concentration-response
- PK/PD studies
- Efficacy & safety RCT, 3 mo VTE treatment, sample size ?

Model adaption for the future perspective

- After a small paediatric pilot trial using the same methodology for a bigger trial
- Modelling without a paediatric pilot trial with different scenarios (high degree of uncertainty)

References

[1] van Dongen CJJ, van den Belt AGM, Prins MH, Lensing AWA.
Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism
Cochrane Database of Systematic Reviews 2004, Issue 4.
Art.No.: CD001100. DOI: 10.1002/14651858.CD001100.pub2.

[2] Massicotte P, Julian JA, Gent M, Shields K, Marzinotto V, Szechtm
Andrew M for the REVIVE Study Group.
An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial.
Thromb Res. 2003; 109(2-3): 85-92.

[3] Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter D
Summarizing historical information on controls in clinical trials.
Clinical Trials 2010;7: 5-18.

[4] Lunn DJ, Thomas A, Best N, Spiegelhalter D.
WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing 2000; 10: 325-337.