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Perspectives on analysing subgroup effects of clinical trials and their meta-analyses

Kit CB Roes

2011, London

Perspective of treating physician

Evidence based decision for the (next) patient to treat, selecting from the available treatment options.

Perspective of market authorisation of a new drug

Evidence based decision of allowing physicians to add a new drug to their treatment options.

Provide information to guide the prescribing physician.

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Subgroups: Perspectives from regulatory*

- To confirm consistency across subgroups (all) of clinical importance.

- To identify safety problems limited to a subgroup.
- To identify subgroups with larger effect, in positive study.
- The check specific subgroups that a priori are suspected to show less or no treatment effect.

- To identify subgroup(s) that demonstrate relevant effect, in case the overall effect is not significant.

*Grouin, Coste, Lewis (2005), J. of Biopharm. Stat.

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Regulatory environment moving towards

- Including relative efficacy and comparative effectiveness into drug development plans.*
- Information from patient and payer perspective available at market authorisation.
- Perspective of stratified prediction of treatment effects increasingly important.

Eichler, Bloechl-Daum, Abadie, Barnett, König and Pearson (2010). Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Disc

Subgroups in trials and meta-analyses

- An example
- Subgroup analyses: same caveats as observational studies
- Guidance at the individual patient level
- Estimate effects at population level

Example

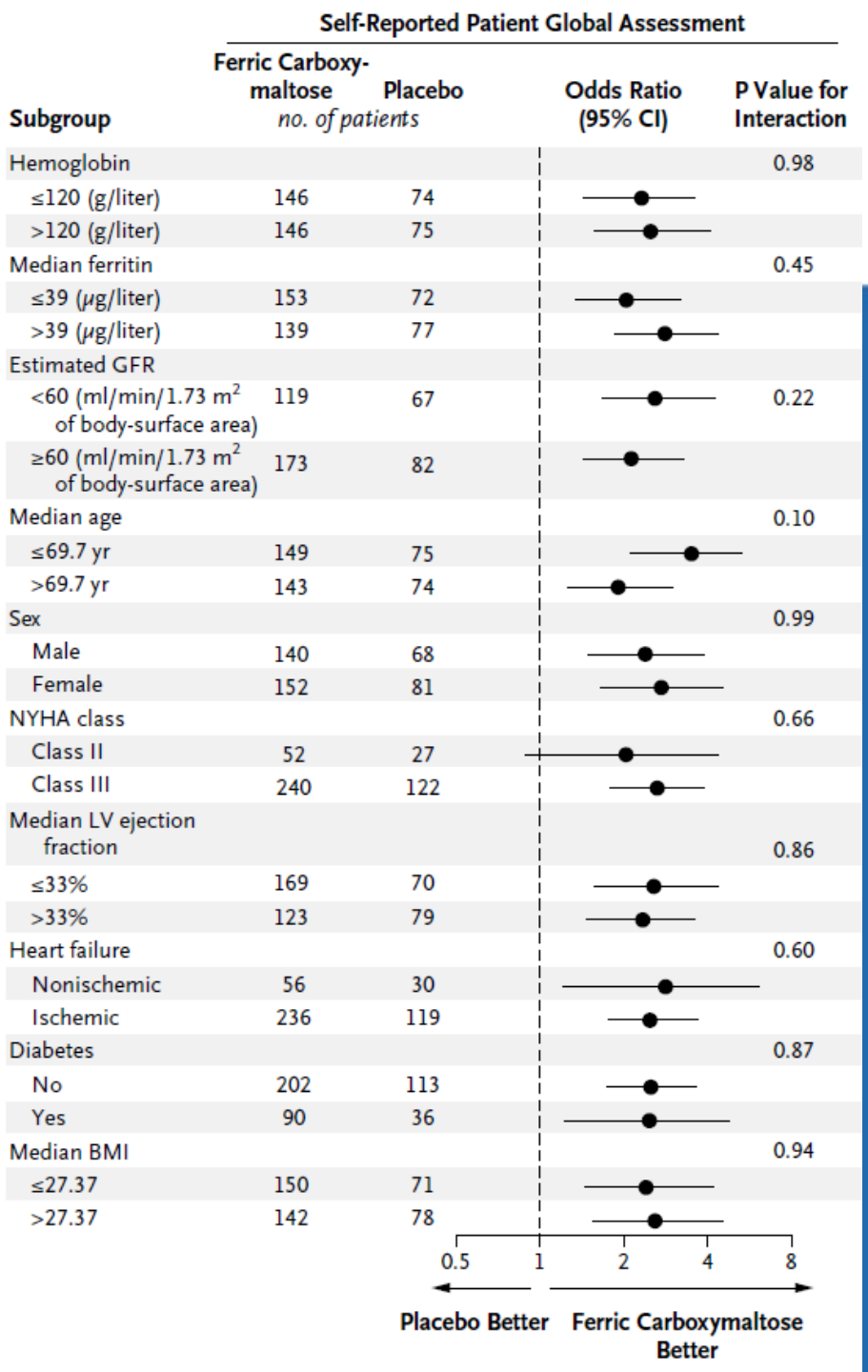
FAIR-HF Trial

459 patients with chronic heart failure of New York Heart Association (NYHA) functional class II or III, and iron-deficiency.

Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of intravenous iron (ferric carboxymaltose) or saline (placebo).

Primary end points

- Self-reported Patient Global Assessment
- NYHA functional class, both at week 24.



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Primary end points

- Self-reported Patient Global Assessment
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Discussion point

Should we split for each subgroup or (also) require joint modeling of subgroups (and covariates)?

Subgroup analyses: same caveats as observational studies.

Lancet 2006

Antibiotics for acute otitis media: a meta-analysis with individual patient data

Maroeska M Rovers, Paul Glasziou, Cees L Appelman, Peter Burke, David P McCormick, Roger A Damoiseaux, Isabelle Gaboury, Paul Little, Arno W Hoes

IPD Meta analysis of 6 trials evaluating antibiotic treatment in acute otitis media.

Primary outcome: extended course of OM (pain and/or fever days 3-7).

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Pain, fever, or both at 3–7 days

	Antibiotics (n=819)	Control (n=824)	RD (95% CI)	p for int*
Age				
<2 years	91 (33%)	137 (48%)	−15% (−23%, −7%)	
≥2 years	107 (20%)	166 (31%)	−11% (−16%, −6%)	0.83
Bilateral				
No	104 (24%)	132 (30%)	−6% (−12%, 0%)	
Yes	64 (27%)	104 (47%)	−20% (−28%, −11%)	0.021

* Fixed effects logistic regression

Confounding in RCTs……

	<2 years	≥2 years	
Unilateral	261	611	872
Bilateral	273	183	456
	534*	794*	1328

*Missing data on uni vs bilateral.

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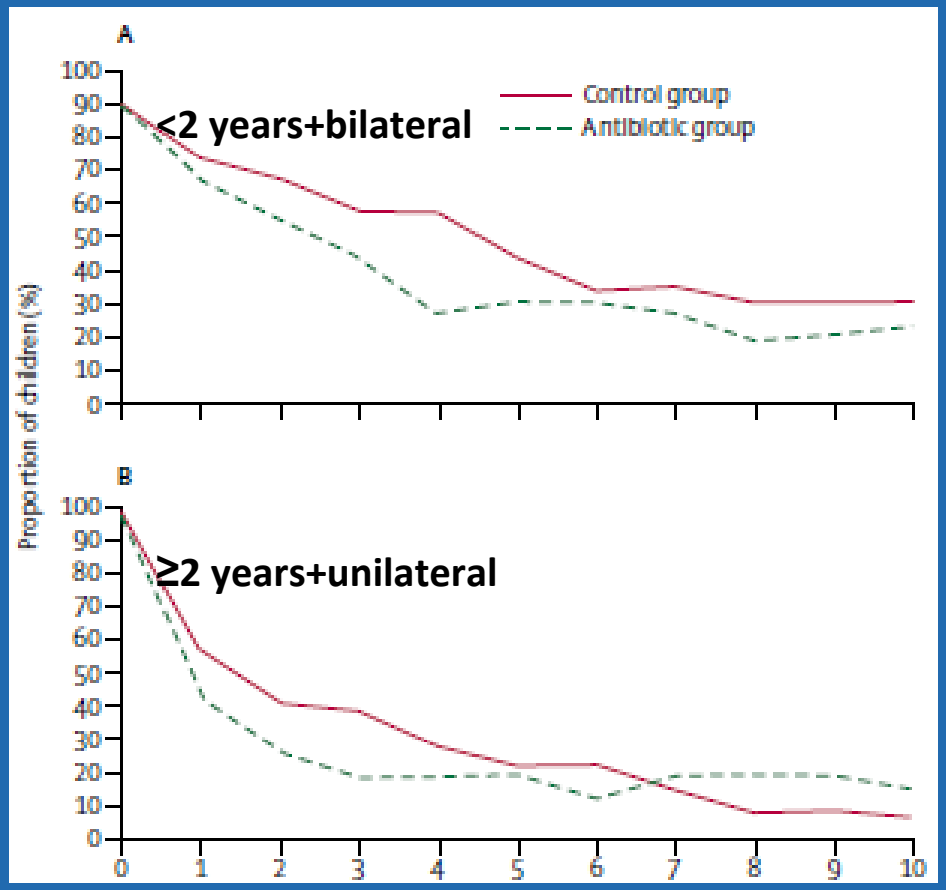
Pain, fever, or both at 3–7 days

	Antibiotics (n=819)	Control (n=824)	RD (95% CI)	p for int*
Age and bilateral				
<2 yrs+bilat	42 (30%)	74 (55%)	−25% (−36,−14)	
<2 yrs+unilat	45 (35%)	53 (40%)	−5% (−17, 7)	
≥2 yrs+bilat	20 (23%)	30 (35%)	−12% (−25, 1)	
≥2 yrs+unilat	59 (19%	79 (26%)	−7% (−14, 0)	0.022

* Fixed effects logistic regression



Results of this meta-analysis

- Included in treatment guideline
- Antibiotics Indicated

  < 2yrs + bilateral

Discussion points

Is there a fundamental difference in level of evidence required to guide treatment of subgroups vs to license vs to include in the label?

(if this analysis was presented at the time of licensing, what would have been the consequences)

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BMJ 2011;343:d5888 doi: 10.1136/bmj.d5888

RESEARCH

Estimating treatment effects for individual patients based on the results of randomised clinical trials

Johannes A N Dorresteijn , Frank L J Visseren,Paul M Ridker, Annemarie M J Wassink, Nina P Paynter, Ewout W Steyerberg, Yolanda van der Graaf, Nancy R Cook

Justification for the Use of Statins in Prevention (JUPITER) trial

Randomised controlled trial evaluating the effect of rosuvastatin 20 mg daily versus placebo on the occurrence of cardiovascular events

- MI, stroke, arterial revascularisation, admission to hospital for UA, or CV death.

17 802 healthy men and women

- low density lipoprotein cholesterol levels of less than 3.4 mmol/L
- high sensitivity C reactive protein levels of 2.0 mg/L or more.

Modeling of individual risk

- Framingham or Reynolds risk score (external)
- Modeling based on trial data (internal)
- Treatment effect estimated based on trial
  - Hazard ratio rosuvastatin versus placebo (0.56)

Modeling choices

External risk score model

Residual 10 year absolute risk (%) with rosuvastatin treatment

- Framingham risk score:
  0.56 × baseline 10 year absolute risk (%) without treatment

- Strong assumption on how treatment effect behaves

Modeling choices (2)

Optimal fit model with rosuvastatin treatment

$(1-0.985433^{(5\times\exp[B])})\times 100\%$, where:

B = 0.09379363 × AGE + 3.34656382 x GENDER − 0.03698750 × AGE*GENDER + 0.81823698 x SMOKER + 0.54045383 x BP DRUGS ***+ 0.00932154 x FAM HISTORY – 7.484613***

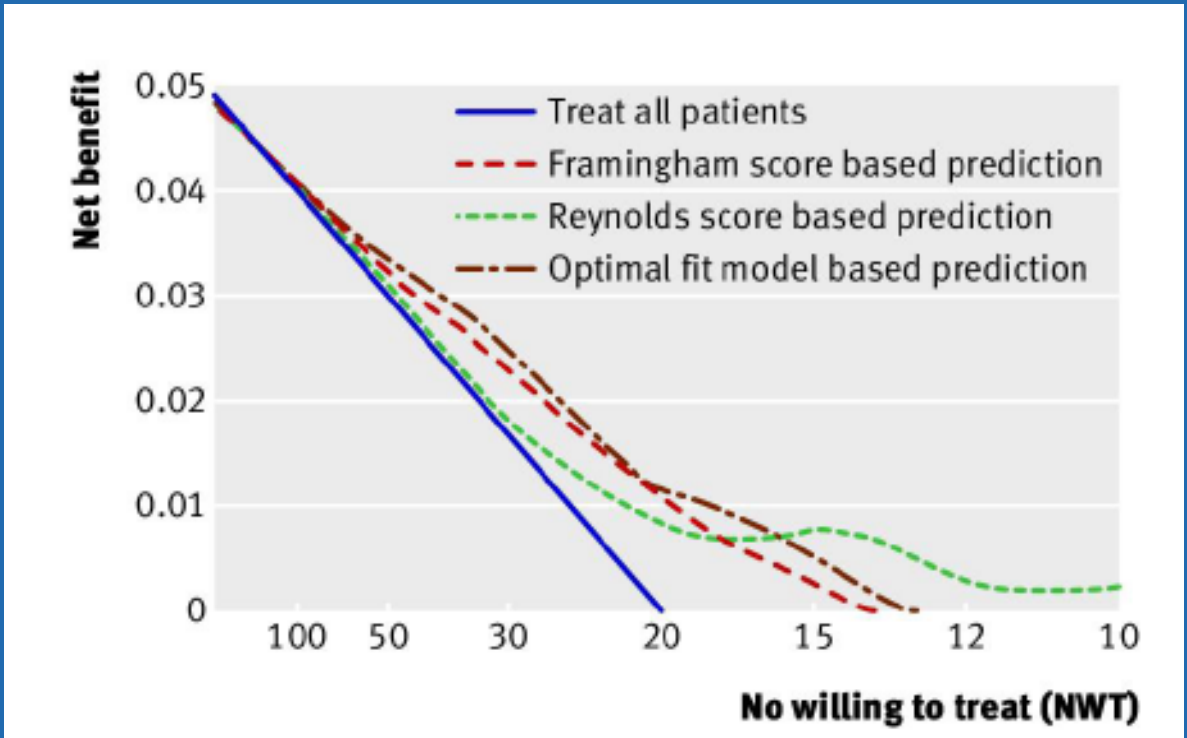
Optimal fit model without rosuvastatin treatment

$(1-0.985433^{(5\times\exp[B])})\times 100\%$, where:

B = 0.09379363 × AGE + 3.34656382 x GENDER − 0.03698750 × AGE*GENDER + 0.81823698 x SMOKER + 0.54045383 x BP DRUGS ***+ 0.60281674 x FAM HISTORY – 6.9932***

(not too different from adjusting for important baseline covariates – as recommended)

Used for treatment scenario patients



Determined by associated harm

Discussion points

This is stratified treatment as well as benefit risk.
Should this enter the process and at what point?

Effect estimates for benefit (risk)

What would the gain in effect be if all patients would be treated with the new treatment versus if all patients would be treated with the control?

- *Within* randomised trials this is estimated (unbiased) by the (regular) estimates of the treatment effect.

- Which holds for the group of patients that actually entered the trial.

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CLINICAL TRIALS EDITORIAL

Clinical Trials 2009; **6**: 136–140

The calibration of treatment effects from clinical trials to target populations

For benefit / risk, cost effectiveness etc.

What would the gain in effect be if (all) patients *in a target population* would be treated with the new treatment, instead of the control?

Calibration of effects to target population

- Needs prediction of outcomes in the target population, and thus modeling.
- Estimation of “causal effects”.
- Models would incorporate subgroup effects, or more general covariates.

Concluding

- Clinical necessity of estimating effects for subgroups.
- Address proper modeling instead of / in addition to “splitting for *all* relevant subgroups”
- Deal with the caveats inherited from observational research
- Make step towards extrapolation at population level