An epidemiologist's view

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EHC Round Table on concentrate-related risk of inhibitor formation in haemophilia A

Brussels, 2 March 2015

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Conflicts of interest

- financial relations with pharmaceutical companies

  none

- royalties from patents

  listed as inventor on patents on prothrombotic genetic variants

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Topics

- side-effects of medicines in general
- the side-effect of inhibitors with certain concentrates
- the future

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Three main aspects

- experimental versus observational studies
  - why and when are randomised studies needed?
  - when is adjustment needed and sufficient?
- Occam's razor
  - William of Ockham (1287–1347)
  - explanation with fewest assumptions is preferred
- in dubio abstine
  - what is best for patients?

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Side-effects in general

- unintended, often unexpected and unpredictable
  - different risk factors than intended effect
- often low incidence
  - high incidence: detected pre-marketing
  - low incidence: detected post-marketing
- often not a class effect
- difficult to detect when rare and quantitative

A few examples

- unintended, often unexpected and unpredictable
  - hormones and venous thrombosis
  - statins and rhabdomyelysis
- often low incidence
  - high incidence: hair loss with chemotherapy
  - low incidence: rofexoxib (Vioxx) and myocardial infarction
- often not a class effect
  - ximegalatran and liver damage
- difficult to detect when rare and quantitative
  - antidepressants and suicide in adolescents
  - 3rd vs 2nd generation oral contraceptives and thrombosis

Experimentation vs observation

- doctors tailor treatment to prognosis
- link between prognosis and treatment
- observational studies confounded (‘by indication’)

examples
- higher cancer death rate with chemotherapy than surgery
- cardioprotective effect of postmenopausal hormones

solution
- randomise
- state-of-the-art in therapeutic studies

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How about side-effects?

- if wholly unpredictable, no link of drug with prognosis
  - prescription is random in respect of side-effect
  - no need to randomise

- if some risk factors known
  - prescription usually still random
  - full adjustment feasible

Bottom line

- randomisation not required for side-effects
- adjustment for confounding or accidental skewness

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How about inhibitors?

- different risk factors than bleeding (in severe haemophilia)
- limited number of known risk factors
- no prior information on immunogenicity of rFVIII types

Therefore
- doctors could not tailor type of rFVIII on risk profile
- no randomisation required

- but if they did: few risk factors that are known
- adjustment feasible and sufficient

Side-effects in general

- often detected post-marketing
- major (financial) stakes
- ‘good doctor bias’
  - prescribed to many patients
  - benefit more common than side effect
- unnecessary complex discussions

Standard discussion process

- flat denial
- authoritative denial
- it is unexpected and unproven
- it might also be ... (something wildly implausible)
- there is no complete understanding of mechanisms
- we need more studies

Counterarguments

- side-effects are by definition unexpected
- apply Occam's razor: simplest solution
  - is it impossible that the drug causes the side-effect?
  - are the alternative explanantions really more likely?
- proof is not necessary
  - for effect we need proof
  - for harm suspicion suffices: in dubio abstine
- knowledge of mechanism is not necessary
  - lots of mechanisms unknown, also for therapies
  - we never found out why FVIII CPS-P caused inhibitors
  - if it works, it works, and if it damages, it damages

It has happened before

A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate.

Peerlinck K[1], Arnout J, Gilles JG, Saint-Remy JM, **Vermylen** J.

Thromb Haemost. 1993 Feb 1;69(2):115-8.

A Sudden Increase in Factor VIII Inhibitor Development in Multitransfused Hemophilia A Patients in The Netherlands

By F.R. Rosendaal, H.K. Nieuwenhuis, H.M. van den Berg, H. Heijboer, E.P. Mauser-Bunschoten, J. van der Meer, C. Smit, P.F.W. Strengers, E. Briët, and the Dutch Hemophilia Study Group

Blood, Vol 81, No 8 (April 15), 1993: pp 2180-2186

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The four studies

The four studies

	design	period	countries	N*
RODIN	cohort	2000-2010	14	574
FCN	cohort	1993-2014	1	353
UKHCDO	cohort	2000-2011	1	407
EUHASS	case-series	2008-2012	26	417

*: number of previously untreated patients (PUPs) reported

(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

The four studies

	N*	inhibitors		adjustments
		all	high	
RODIN	486	145 (30%)	92	race, mutation, age, +
FCN	303	114 (38%)	63	race, mutation, age, +
UKHCDO	319	85 (27%)	43	race, mutation, age, +
EUHASS	259	62 (24%)	n.a.	n.d.

*: number of PUPs using rFVIII, non-overlapping

(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

The four studies

all inhibitors

	RR*	CI95
RODIN	1.60**	(1.08 - 2.37)
FCN	1.55**	(0.97 - 2.49)
UKHCDO	1.64**	(0.94 - 2.87)
EUHASS	0.99	(0.62 - 1.61)

*: 2nd vs 3rd generation

**: adjusted for major confounding variables

(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

The four studies

high-titre inhibitors

	RR*	CI95
RODIN	1.79**	(1.09 - 2.94)
FCN	1.56**	(0.82 - 2.98)
UKHCDO	2.00**	(0.93 – 4.34)
EUHASS	n.d.	

*: 2nd vs 3rd generation

**: adjusted for major confounding variables

(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

Adjustment for confounding

	unadjusted	adjusted
RODIN	1.37	1.60
FCN	1.61	1.55
UKHCDO	1.60	1.64
EUHASS	0.99	n.d.

(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

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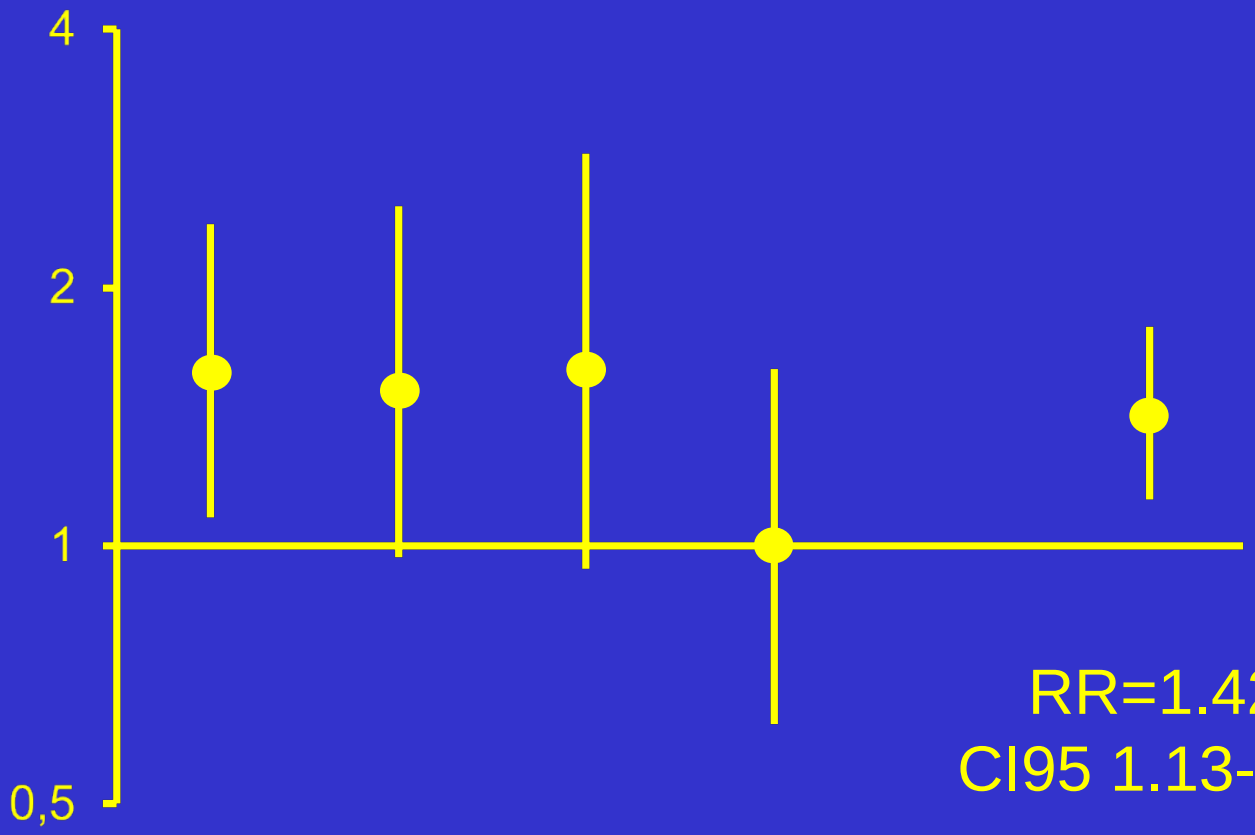
Meta-analysis: all inhibitors



RR=1.42
CI95 1.13-1.80

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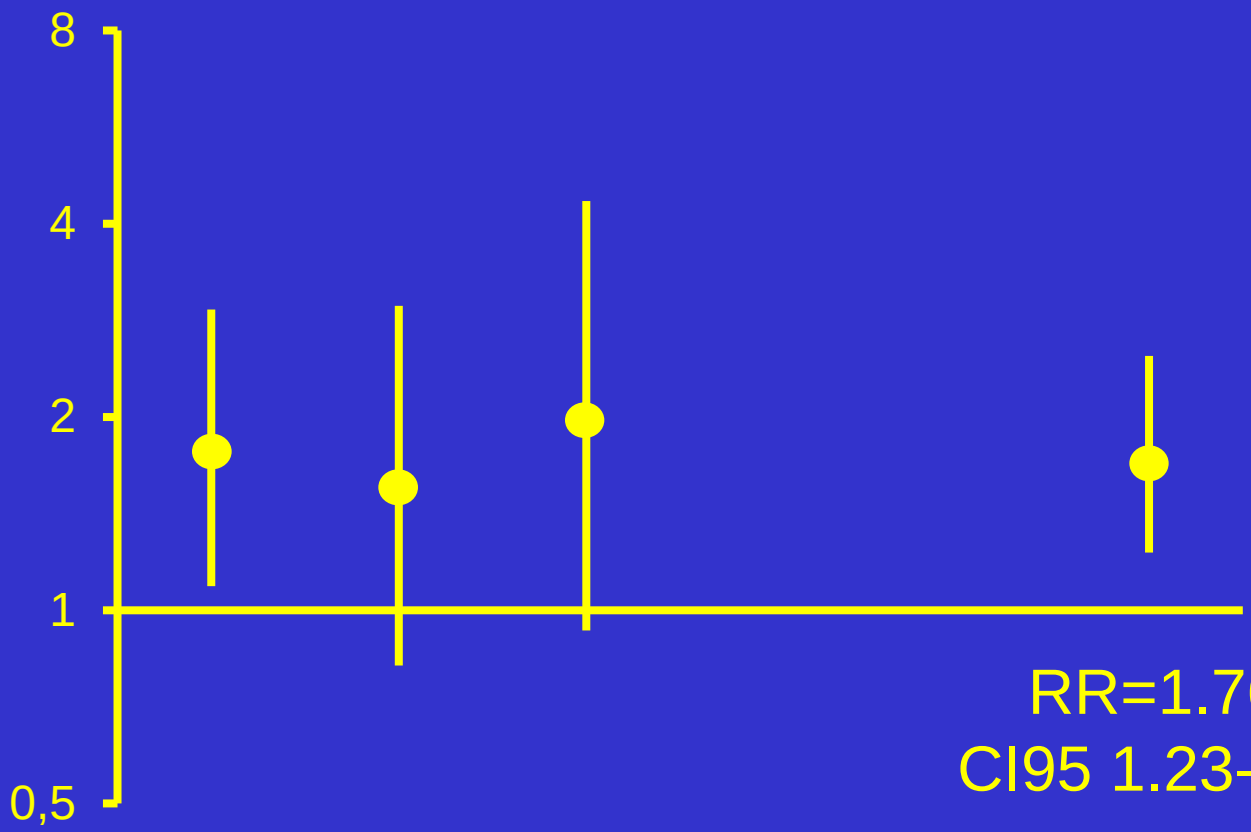
Meta-analysis: high-titre inhibitors



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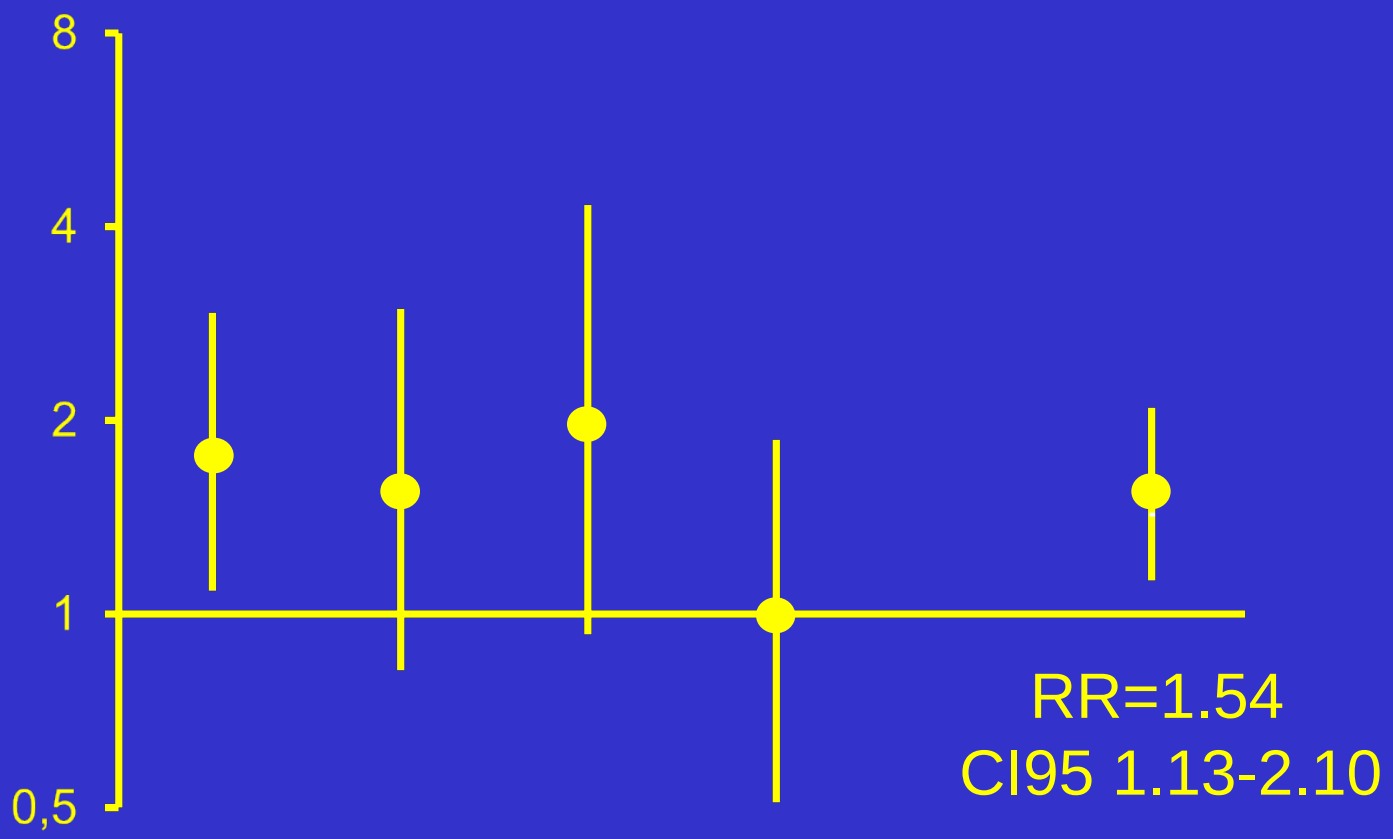
Meta-analysis: high-titre inhibitors



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Conclusion

- is it proven?
  - no
- is it likely?
  - yes
- does this matter?
  - no! In dubio abstine

The future

- positive side: this side-effect was discovered
- question: could it have been seen earlier?
  - will always require some years of use
  - re-analysis by calendar time of the studies
- what is needed
  - properly designed international cohort studies
  - identification and replication cohorts
  - availibility of all information on registration trials
  - open mind: side-effects occur more often then we like
- remaining questions
  - how about peviously treated patients?
  - how many instances of increased risk have we missed?

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