Wat maakt een indicatie een indicatie ?

Arno Hoes

Julius Centrum
UMC Utrecht
& College ter Beoordeling van Geneesmiddelen

A plea for *real* indications

Arno W. Hoes, MD, PhD

Julius Center
University Medical Center Utrecht
& Medicines Evaluation Board

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Why?

- ongoing discussions regarding indications in SPC
- *increasing* discussions at MEB and EMEA
- personal (non-pathological) occupation with “indication”

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Example:

SmPC rosuvastatin: indication nr 3

4.1 Therapeutic indications | Go to top of the page

Prevention of Cardiovascular Events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (see Section 5.1), as an adjunct to correction of other risk factors.

10 doctors: none came up with this “indication” when asked

(recent, seriously flawed, study in Berlin, June 1, 2010)

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Definition of “indication”

- In medicine, an indication is a term describing a valid reason to use a certain test, medication, procedure, or surgery. ...

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A *plea* for real indications

- past

- present
- future

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The past

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The first 3 drugs assessed in the Netherlands: 1963

4. Vaststelling van het reglement van orde en van de instructie voor de secretaris.
5. Vaststelling van het ontwerp van het Register van verpakte geneesmiddelen.
6. Vaststelling van het definitieve formulier voor aanvraag tot inschrijving in het Register van verpakte geneesmiddelen.
7. Taakverdeling.
8. Bespreking: I. Dihydrostreptomycine.
   II. Emesafène.
   III. Mauzine.
9. Rondvraag.
10. Sluiting.

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Indicatie emesafène

4.1 Therapeutische indicaties

Misselijkheid en braken van verschillende oorsprong, zoals
- na operaties,
- na röntgenbestraling,
- die gevallen van zwangerschapsbraken, die voor medicamenteuze behandeling door de arts in aanmerking komen.

• clear indication: nausea and vomiting

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SmPC May 1973

N.V. ORGANON
OSS

AZARON
crème

31 jan 1972

OMSCHRIJVING VAN DE AANGEPREZEN WERKING

Azaron bevat tripelennamine-hydrochloride, een stof die - na lokale applicatie - in staat is de werking van histamine op te heffen, waardoor een effectieve symptomatische beschrijding van allergische toestanden mogelijk is.

Indicatiegebied

Aandoeningen die zijn terug te voeren op een in versterkte mate vrijkomen van histamine in het lichaam, zoals urticaria (netelroos) en bij steken en beten van insekten en kwallen.

Contra-indicaties

Toediening

Lokaal

Dosering

Dun laagje crème op het te behandelen gedeelte van de huid aanbrengen. Zo nodig herhale men dit.

Also in 1973: FML ophthalmic suspension

INDICATIONS

FML (fluorometholone) Liquifilm Ophthalmic Suspension is indicated in inflammatory conditions (noninfectious) of the eye such as acute and chronic iritis, iridocyclitis, scleritis, episcleritis, conjunctivitis, keratitis, resistant ocular allergy and inflammation following surgery (where no infectious etiology is suspected). It may be beneficial in the treatment of acute and chronic inflammatory conditions in patients susceptible to pressure elevation with administration of other corticosteroids, such as dexamathasone and betamethasone.

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Present

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SmPC Aclasta

4.1 Therapeutic indications | Go to top of the page

Treatment of osteoporosis

• in post-menopausal women

• in men

at increased risk of fracture, including those with a recent low-trauma hip fracture.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

• in post-menopausal women

• in men

at increased risk of fracture.

- increased risk of fracture?
- example ?
- overlap indications ?

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SmPC Lantus

4. CLINICAL PARTICULARS | Go to top of the page

4.1 Therapeutic indications | Go to top of the page

For the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin is required.

- subgroups of patients?
- when insulin is required?

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Example:

SmPC rosuvastatin: indication nr 3

4.1 Therapeutic indications | Go to top of the page

Prevention of Cardiovascular Events

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Topics / discussions SmPC 4.1

- cause included?
- outcome included ?
- second line treatment ?
- concomitant treatment ?
- overlap incidations ?
- complicated (non-pragmatic) target population ?
- patient subgroups ?

Guidance from EMA

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT 2REVISION 2

PROPOSAL FOR A REVISION OF THE EUROPEAN COMMISSION GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS

TRANSMISSION TO CHMP	December 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	10 December 2007
END OF CONSULTATION ON PROPOSED CHANGES (DEADLINE FOR COMMENTS)	28 March 2008
ADOPTION BY CHMP	20 November 2008

4.1 actually seems very accurate !

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.

No study endpoints in 4.1

"Study endpoints should not normally be included
unless such mention is specified
as being appropriate for the indication
in CHMP Notes for Guidance or Point to Consider documents"

… and referral to 5.1

"Where results from subsequent studies provide further definition or information on a licensed indication,
such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1."

5.1. Also seems quite appropriate

- Clinical efficacy and safety

It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced and summarise evidence from relevant studies supporting the indication.

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Also 5.1. Subgroup and post-hoc analyses ?

"In the exceptional cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations"

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Patient number 1

- 18 months year old girl
- double-sided acute otitis media
- amoxicillin ?

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SPC amoxicillin

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of bacterial infections caused by amoxicillin-susceptible organisms.

It is principally indicated for respiratory, middle ear and urinary tract infections.

Respiratory tract - pneumonia, bronchitis

ENT - otitis media

Urinary tract - cystitis, pyelonephritis

- a *real* indication: otitis media
- cause included? as if one can smell virus or antibiotic resistance

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Patient number 2

- male, 67 years of age
- high cholesterol
- cv risk factors
- rosuvastatin?

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SPC rosuvastatin: first two indications

4.1 Therapeutic indications | Go to top of the page

Treatment of hypercholesterolaemia

Adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

- a *real* indication: defined types of hypercholesterolaemia
- target population: concise
- "second-line" treatment
- concomitant treatment

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SPC rosuvastatin: 3rd indication

4.1 Therapeutic indications | Go to top of the page

Prevention of Cardiovascular Events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (see Section 5.1), as an adjunct to correction of other risk factors.

- indication: is in fact the outcome, not an indication
- target population: not concise, very vague (see section 5.1?)
- concomitant "treatment"
- *high risk?, first?, correction other risk factors?*

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Patient leaflet

1. WAARVOOR WORDT DIT MIDDEL GEBRUIKT?
CRESTOR is een geneesmiddel dat tot de groep van de statines behoort.

Uw arts heeft CRESTOR aan u voorgeschreven omdat:

- U heeft om een andere reden een verhoogde kans op het krijgen van een hartaanval, een beroerte of een soortgelijke aandoening.

Een hartaanval, een beroerte en andere problemen kunnen het gevolg zijn van een ziekte die atherosclerose wordt genoemd. Atherosclerose wordt veroorzaakt door het ophopen van vetachtige stoffen in uw aderen.

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SmPC is not a clinical guideline

Multidisciplinaire richtlijn

Cardiovasculair risicomanagement 2006

Cardiovasculair risicomanagement M84

NHG-Standaard Cardiovasculair risicomanagement

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Back to patient nr 1

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

Summary

Background Individual trials to test effectiveness of antibiotics in children with acute otitis media have been too small for valid subgroup analyses. We aimed to identify subgroups of children who would and would not benefit more than others from treatment with antibiotics.

Methods We did a meta-analysis of data from six randomised trials of the effects of antibiotics in children with acute otitis media. Individual patient data from 1643 children aged from 6 months to 12 years were validated and re-analysed. We defined the primary outcome as an extended course of acute otitis media, consisting of pain, fever, or both at 3–7 days.

Findings Significant effect modifications were noted for otorrhoea, and for age and bilateral acute otitis media. In children younger than 2 years of age with bilateral acute otitis media, 55% of controls and 30% on antibiotics still had pain, fever, or both at 3–7 days, with a rate difference between these groups of –25% (95% CI –36% to –14%), resulting in a number-needed-to-treat (NNT) of four children. We identified no significant differences for age alone. In children with otorrhoea the rate difference and NNT, respectively, were –36% (–53% to –19%) and three, whereas in children without otorrhoea the equivalent values were –14% (–23% to –5%) and eight.

Lancet 2006; 368: 1429–35
See Comment page 1397

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, the Netherlands (M M Rovers PhD, C L Appelman MD, R A Damoiseaux MD, Prof A W Hoes MD); Departments of Paediatrics and Otolaryngology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, the Netherlands (M M Rovers); University of Oxford, Department of Primary Health Care, Institute of Health

Rovers et al. Lancet 2006;368:1429-

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But 5.1 goes on

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Crestor 40mg. The 40mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see Section 4.2).

- reduction in subclinical atherosclerosis (CIMT)
- no direct correlation between CMT reduction and CV events !
- see section 4.2.

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Surrogate endpoints?

- we do accept LDL in statins
- but we do not accept CIMT
- nor do we demand clinical outomces (CV disease)

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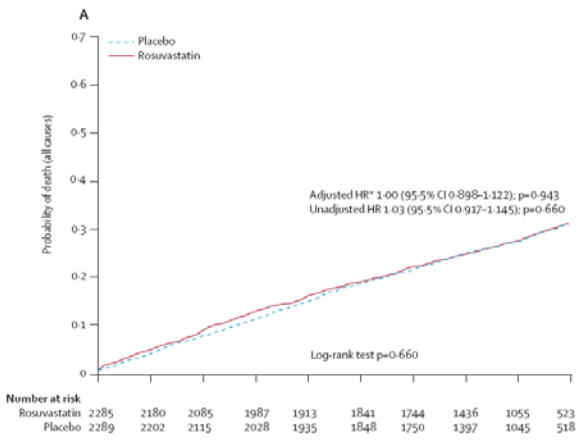
Surrogate endpoint?



Gissi-HF investigators. Lancet 2008;372:1231-9

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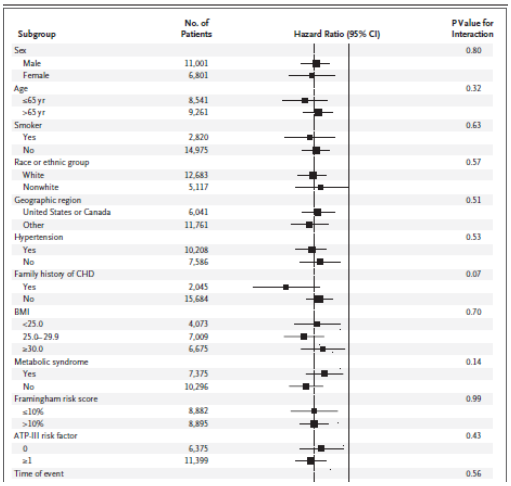
Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*



Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
Sex			0.80
Male	11,001		
Female	6,801		
Age			0.32
≤65 yr	8,541		
>65 yr	9,261		
Smoker			0.63
Yes	2,820		
No	14,975		
Race or ethnic group			0.57
White	12,683		
Nonwhite	5,117		
Geographic region			0.51
United States or Canada	6,041		
Other	11,761		
Hypertension			0.53
Yes	10,208		
No	7,586		
Family history of CHD			0.07
Yes	2,045		
No	15,684		
BMI			0.70
<25.0	4,073		
25.0–29.9	7,009		
≥30.0	6,675		
Metabolic syndrome			0.14
Yes	7,375		
No	10,296		
Framingham risk score			0.99
≤10%	8,882		
>10%	8,895		
ATP-III risk factor			0.43
0	6,375		
≥1	11,399		
Time of event			0.56

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SPC rosuvastatin: 3rd indication

4.1 Therapeutic indications | Go to top of the page

Prevention of Cardiovascular Events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (see Section 5.1), as an adjunct to correction of other risk factors.

- does this comply with JUPITER?
- where is the CRP level?

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First author not amused

"Although we believe this expanded indication for statin therapy to be a move in the right direction, it should be noted that this regulatory recommendation was not made on the basis of the trial's prespecified primary endpoint, did not take into account the enrolment criterion in JUPITER that required all participants to have an hsCRP of 2 mg/L or greater, which augmented absolute risk, and does not address most of the patients actually Studied"

Ridker & Glynn. Lancet 2010; May 21

Reasons for complicated (or non-) indications

- more complicated trial populations
  - eg cardiovascular risk reduction
  - eg second line indication
- a drug needs an indication: subgroup ?
- a new expensive trial: new indication?
- regulators do not pay enough attention to 4.1 (and the SmPC guideline)

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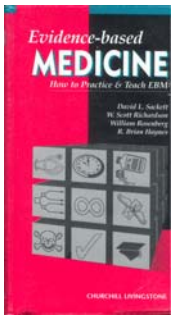
- evidence should be leading in indication
- but clarity for prescribers should be equally leading
- trade-off ???



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Future ?

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Conclusion

- problems with indications in SPC
  - large discrepancies between individual drugs
  - 4.1 (and 5.1) are becoming more and more complicated
- SmPC guidance from EMA is adequate
- trade-off between “evidence” and clarity for prescribers ?
- more focus on simplifying 4.1 (EMA/MEB, ao)
- trial design: clinically relevant target population
  - pre-specified target indication?