Intermediaire eindpunten in de geneeskunde: de binnenweg naar de waarheid?

Diederick E. Grobbee, MD, PhD, Professor of Clinical Epidemiology, University Medical Center Utrecht
Endpoint: measures the effects or risks of medical intervention
Measurement of treatment effect: Randomized Controlled Trial

- **Patients**
- **Random assignment**
- **Treatment Group**
- **Control Group**
- **Follow-up**
- **Compare results**
Endpoints of all sorts

primary, secondary, tertiary, multiple, combined, clinically relevant, statistically significant, patient-oriented, hard & soft, surrogate, intermediate........
ICH Tripartite Guideline on endpoints in randomized clinical trials

“ The primary outcome should be the variable capable of providing the most clinically relevant and convincing evidence…”

“There should generally be only one primary variable”

Intermediate endpoint ("proxy", "surrogate", "biomarker")

- Something that reflects the most relevant outcome, but is something else
- Often patho-physiological parameter
- Often either biochemical test presumed to reflect common effect pathway (e.g., BP, cholesterol) or demonstrating end-organ damage as measured by imaging (e.g., angiography, ventricular function)
Surrogate Endpoints

- Changes in the surrogate must be predictive of the relevant clinical outcome
- Surrogate must fully (or nearly so) capture the effect of the intervention on the clinical outcome

DeMets and Califf. Circulation 2002;106:746
The official FDA definition of a surrogate endpoint

“A surrogate endpoint, or ‘marker,’ is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.”
The official NIH definition of a biomarker

"a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."
Why use a surrogate endpoint ...

- Clinical trials are expensive and of long duration
- Particularly true for trials using occurrence of a clinical event as the primary outcome
- Substitute a response variable intermediate or continuous in nature for the clinical outcome
Why use a surrogate endpoint ... 

- Sample size smaller so study less expensive
- Sample size smaller so study feasible (drug risks)
- Changes in surrogate response variable likely to occur before clinical event so less time needed for trial
- For life-threatening diseases ‘speed’ in determining benefit is crucial
Examples of surrogate endpoints

• Atherosclerosis: Cardiovascular mortality or MI
  – Angiography, ultrasound imaging (CIMT), change in cardiac arrhythmia by electrocardiograms
  – Cholesterol level, blood pressure, HbA1c

• HIV infection: AIDS, mortality
  – Change in CD-4 lymphocyte level

• Osteoporosis: Fracture
  – Bone mineral density
## Typical cardiovascular trials with surrogate and true endpoints: comparison of sample sizes and follow-up periods

<table>
<thead>
<tr>
<th>Event</th>
<th>True endpoint</th>
<th>Surrogate endpoint</th>
<th>Size</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>Death</td>
<td>Coronary artery patency</td>
<td>4000</td>
<td>5 yrs</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>Diastolic blood pressure</td>
<td>25000</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Death</td>
<td>Ejection fraction</td>
<td>2500</td>
<td>5 yrs</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td></td>
<td>25000</td>
<td>5 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200</td>
<td>1-2 yrs</td>
</tr>
</tbody>
</table>
“......and is expected to predict the effect of the therapy.”
Regulatory Status of Endpoints

• The law and regulations give no direct guidance on what endpoints can provide evidence of effectiveness.
• A surrogate endpoint can be a legal basis for drug approval in many countries.
Reasons for Failure of Surrogate Endpoints

- Disease → Surrogate Endpoint → True Clinical Outcome
- Intervention → Surrogate Endpoint → True Clinical Outcome
- Disease → Surrogate Endpoint → True Clinical Outcome
- Intervention → Surrogate Endpoint → True Clinical Outcome

A classical example (CAST)

- Patients with myocardial infarction
  - Ventricular arrhythmia risk factor for sudden death
  - Arrhythmia considered a surrogate endpoint

- Encainide and Flecainide known anti-arrhythmic drugs
  - Approved by FDA
  - Marketed for post-mi
  - Effect on *survival* was not established

- CAST randomized more than 2000 myocardial infarction patients to receive either anti-arrhythmic drug or placebo
Actuarial probabilities of freedom from death or cardiac arrest due to arrhythmia

A recent example: Rosiglitazone to prevent diabetes complications

Balfour et al. Drugs 1999;57:921-
Rosiglitazone: Safe and effective?

EMEA / The Netherlands: Registered in 2000

Now you can prescribe AVANDIA on its own.
Rosiglitazone and risk of MI: meta analyses 2007

- GSK ZM2005/00181/01 2005?
  RR 1.31 (1.01-1.70)

- Nissen et al. June 2007
  RR 1.43 (1.03-1.98)

- Home et al. July 2007
  RR 1.11 (0.89-1.31)*

- FDA all July 2007
  RR 1.40 (1.10-1.80)

- FDA placebo controlled July 2007
  RR 1.68 (1.03-2.07)

- Sing et al. September 2007
  RR 1.42 (1.06-1.91)

- Lago et al. October 2007
  RR 0.93 (0.67-1.29)**

- Hospitalization or death from cardiovascular causes

  **Cardiovascular death
Rosiglitazone: aanbeveling van EMA tot schorsing van de vergunning voor het in de handel brengen (VHB) van Avandia en Avandamet en Avaglim

Datum: 23 september 2010
Zoals vermeld in ons bericht van 22/07/2010, zijn de conclusies van de beoordeling van alle gegevens over de risico/baten-verhouding voor de rosiglitazone bevattende geneesmiddelen nu beschikbaar. Gegevens uit recente studies bevestigen de verhoging van het cardiovasculair risico geassocieerd met de toediening van deze geneesmiddelen waarvoor reeds voorzorgsmaatregelen en beperkende maatregelen genomen werden. Het Comité voor geneesmiddelen voor menselijk gebruik (CHMP) van het Europees geneesmiddelenbureau (EMA) is van mening dat de voordelen van rosiglitazone niet meer opwegen tegen de risico’s en adviseert de schorsing van de VHB van rosiglitazone bevattende geneesmiddelen.
Under what conditions can we use surrogate endpoints

Biological plausibility

• Observational evidence extensive and consistent
• Quantitative observational relationship
• Credible animal model shows drug response
• Well-understand disease pathogenesis
• Drug mechanism of action well understood
Under what conditions can we use surrogate endpoints

Statistical considerations:

- Intervention should affect distribution endpoint $T$
- Intervention should affect distribution surrogate $S$
- Distribution of $T$ should be dependent on $S$
- $T$ should conditionally depend on intervention, i.e. $S$ should fully account for impact on $T$

Atherosclerotic vascular disease
Endothelial Dysfunction
Carotid IMT
Plaque
Stenosis
Calcification
Composition
Carotid ultrasound imaging: a window on the disease
Carotid ultrasound imaging
Carotid scan: anatomy and images
Opening research center Rotterdam Study: explanation to Queen-Mother Juliana, 1990
Measurement of intima+media: C(arotid) IMT
CIMT, age and sex

CIMT: smoking

CIMT: Risk of future myocardial infarction

Carotid Intima-Media Thickness Measurements in Intervention Studies
Design Options, Progression Rates, and Sample Size Considerations:
A Point of View

Michiel L. Bots, MD, PhD; Gregory W. Evans, MA; Ward A. Riley, PhD; Diederick E. Grobbee, MD, PhD

Background—Carotid intima-media thickness (CIMT) measurements are currently widely used in randomized controlled trials (RCTs) to study the efficacy of interventions. In designing a RCT with CIMT as a primary outcome, several
CIMT: highly reproducible

![Graph showing reproducibility over time](image)

- Intraclass Correlation: 0.91
- Mean Absolute Difference: 0.04 mm
- N = 361

<table>
<thead>
<tr>
<th>Year</th>
<th>Method</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Rotterdam</td>
<td>0.74</td>
</tr>
<tr>
<td>1994</td>
<td>ACAPS</td>
<td>0.76</td>
</tr>
<tr>
<td>1999</td>
<td>PREVENT</td>
<td>0.80</td>
</tr>
<tr>
<td>2001</td>
<td>OPAL meanmax</td>
<td>0.85</td>
</tr>
<tr>
<td>2001</td>
<td>OPAL meanCCA</td>
<td>0.87</td>
</tr>
<tr>
<td>2002</td>
<td>FACIT meanCCA</td>
<td>0.92</td>
</tr>
<tr>
<td>2002</td>
<td>METEOR</td>
<td>0.90</td>
</tr>
<tr>
<td>2003</td>
<td>Radiance</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Juliuscenter.nl
CIMT

- Graded, quantitative marker of burden of atherosclerosis
- Thickness of IMT gives a summary of the effect of known and unknown risk factors
- Predicts future events
- Dose response with risk factors, e.g., LDL & HDL levels
- Candidate surrogate marker for research on effects of anti-atherosclerotic treatment.
CIMT candidate surrogate marker: statistical consideration

The surrogate (CIMT) should fully account for the impact of the intervention (e.g., statin) on the endpoint (CV events).

Treatment assignment → CIMT reduction → Risk events

i.e. the relation of treatment assignment with risk of events is completely attenuated when CIMT change is adjusted for?

CIMT candidate surrogate marker: statistical consideration

CLAS trial: effect of treatment on clinical endpoint

- Unadjusted for Δ CIMT: OR 0.41
- Adjusted for baseline CIMT: OR 0.45
- Adjusted for Δ CIMT: OR 1.1

CIMT in trials on effects of lipid lowering: fewer patients and shorter duration

Table 1: Clinical trials involving HMG-CoA reductase inhibitors and reporting both carotid IMT and cardiovascular event outcomes.

<table>
<thead>
<tr>
<th>Clinical Trial (N*)</th>
<th>Statin</th>
<th>Relative Impact on IMT Progression of Primary Outcome (mm/yr): Mean [95% CI] (reported p-value)</th>
<th>Relative Impact on Reported Cardiovascular Endpoints: Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS(25) (N = 919)</td>
<td>Lovastatin</td>
<td>-0.015 [-0.023, -0.007] (p = 0.001)</td>
<td>CVD Death, MI, Stroke</td>
</tr>
<tr>
<td>KAPS(26) (N = 447)</td>
<td>Pravastatin</td>
<td>-0.014 [-0.022, -0.006] (p = 0.005)</td>
<td>CVD Death, MI, Stroke</td>
</tr>
<tr>
<td>PLAC-II(47) (N = 151)</td>
<td>Pravastatin</td>
<td>-0.009 [-0.031, 0.013] (p = 0.44)</td>
<td>Clinical Coronary Events</td>
</tr>
<tr>
<td>CAIUS(48) (N = 305)</td>
<td>Pravastatin</td>
<td>-0.014 [-0.021, -0.005] (p = 0.0007)</td>
<td>CVD Death, MI</td>
</tr>
<tr>
<td>REGRESS(28) (N = 255)</td>
<td>Pravastatin</td>
<td>-0.030 [-0.056, -0.004] (p = 0.002)</td>
<td>Clinical Events</td>
</tr>
<tr>
<td>BCAPS(49) (N = 793)</td>
<td>Fluvastatin</td>
<td>-0.008 [-0.013, -0.003] (p = 0.002)</td>
<td>CVD Death, MI, Stroke</td>
</tr>
<tr>
<td>FAST(50) (N = 164)</td>
<td>Pravastatin</td>
<td>Significant Benefit (p &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Pooled Estimate</td>
<td></td>
<td>-0.012 [-0.016, -0.007]**</td>
<td>CVD Death, MI</td>
</tr>
</tbody>
</table>

*Arms used in meta-analysis; **Excludes FAST

**Patients**
Asymptomatic for CHD
Maximum IMT $\geq 1.2-<3.5$ mm
Modest hypercholesterolaemia
Men (aged 45-70)
Women (aged 55-70)

**METEOR - Study design**

- **Rosuvastatin 40 mg**
- **Placebo**

Visit:
- Week: -6 -4 -2 0 6 13 26 39 52 65 78 91 104

- Run in / eligibility
- Lipids
- Safety
- Lipids
- CIMT
- Safety
- CIMT
- Lipids
- Safety
- CIMT
- Safety
- CIMT
- Lipids
- Safety

CIMT = carotid intima media thickness

*Adapted from Crouse JR et al. Cardiovasc Drugs Ther 2004; 18: 231–238*
Effect of Rosuvastatin on Progression of Carotid Intima-Media Thickness in Low-Risk Individuals With Subclinical Atherosclerosis

The METEOR Trial

John R. Crouse III, MD
Joel S. Reichlen, MD
Ward A. Riley, PhD
Gregory W. Evans, MA
Mike K. Palmer, PhD
Daniel H. O'Leary, MD
Diederick E. Grobbbee, MD, PhD
Michiel L. Bois, MD, PhD

for the METEOR Study Group

Lipid-lowering therapy has been shown to reduce cardiovascular events in a large number of studies. A 19% reduction in coronary mortality has been recorded per 1.0-mmol/L (38.7 mg/dL) decrease in low-density lipoprotein cholesterol (LDL-C). Statins are the first-line therapy of choice.

Context  Atherosclerosis is often advanced before symptoms appear and it is not clear whether treatment is beneficial in middle-aged individuals with a low Framingham risk score (FRS) and mild to moderate subclinical atherosclerosis.

Objective  To assess whether statin therapy could slow progression and/or cause regression of carotid intima-media thickness (CIMT) over 2 years.

Design, Setting, and Participants  Randomized, double-blind, placebo-controlled study (Measuring Effects on Intima-Media Thickness; an Evaluation of Rosuvastatin [METEOR]) of 984 individuals, with either age <57 years or the only coronary heart disease risk factor or a 10-year FRS of less than 10%, modest CIMT thickening (>1.2–<3.5 mm), and elevated LDL cholesterol (mean, 154 mg/dL); conducted at 61 primary care centers in the United States and Europe between August 2002 and May 2006.

Intervention  Participants received either a 40-mg dose of rosuvastatin or placebo.

Main Outcome Measures  Rate of change in maximum CIMT (assessed with B-mode ultrasound) for 12 carotid sites; changes in maximum CIMT of the common carotid artery, carotid bulb, and internal carotid artery sites and in mean CIMT of the common carotid artery sites. CIMT regression was assessed in the rosuvastatin group only.

Results  Among participants in the rosuvastatin group, the mean (SD) baseline LDL cholesterol level of 155 (41) mg/dL declined to 78 (27.5) mg/dL, a mean reduction of 49% (p < .001 vs placebo group). The change in maximum CIMT for the 12 carotid sites was a mean decrease of 0.01 mm (95% CI, 0.00 to 0.02 mm; p = .002) for the rosuvastatin group, compared with a mean increase of 0.01 mm (95% CI, 0.00 to 0.02 mm; p = .006) for the placebo group.

JAMA 2007;297:1344-1353
**METEOR primary endpoint:**

Rate of change of maximum IMT  
Rosuvastatin vs placebo

<table>
<thead>
<tr>
<th>Change in IMT of 12 carotid sites (mm)</th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo +0.0131 mm/yr (n=252)</td>
<td>1</td>
</tr>
<tr>
<td>Rosuvastatin 40 mg -0.0014 mm/yr (n=624)</td>
<td>2</td>
</tr>
</tbody>
</table>

P<0.0001  
(Rosuvastatin vs. placebo)  
P=NS  
(Rosuvastatin vs. zero slope)
Radiance: the end of a bright future for Torcetrapib

HDL (mg/dL)

Month 24

Means +/- SD

Treatment Period

Lancet 2007
CIMT in trials on effects of lipid lowering: fewer patients and shorter duration

<table>
<thead>
<tr>
<th>study</th>
<th>patients</th>
<th>years</th>
<th>study</th>
<th>patients</th>
<th>years</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLAC II</td>
<td>151</td>
<td>3</td>
<td>ARBITER 1</td>
<td>200</td>
<td>1</td>
</tr>
<tr>
<td>FAST</td>
<td>164</td>
<td>2</td>
<td>ARBITER 2</td>
<td>167</td>
<td>1</td>
</tr>
<tr>
<td>REGRESS</td>
<td>255</td>
<td>2</td>
<td>ASAP</td>
<td>325</td>
<td>2</td>
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<tr>
<td>CAIUS</td>
<td>305</td>
<td>3</td>
<td>RADIANCE 1</td>
<td>793</td>
<td>2</td>
</tr>
<tr>
<td>KAPS</td>
<td>447</td>
<td>3</td>
<td>RADIANCE 2</td>
<td>752</td>
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<tr>
<td>BCAPS</td>
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<td>ENHANCE</td>
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<td>SANDS</td>
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<tr>
<td>METEOR</td>
<td>984</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surrogate endpoint in side effects: Even more difficult........

- Clinically relevant endpoint too rare for phase 3 trials
- Surrogate endpoints *only* alternative before registration
- Many examples:
  - CK instead of rhabdomyolysis in statin use?
  - QTc interval instead of sudden death in many drugs?
  - Effect on hemostasis instead of thrombosis in OAC?
Surrogate endpoints: strength of the evidence varies

- Arrhythmia, sudden death
- CD4 count, AIDS
- HbA1C, cardiovascular disease
- HDL cholesterol, myocardial infarction
- Bone density, fractures
- CIMT, atherosclerosis
- LDL cholesterol, myocardial infarction
- Blood pressure, stroke
- Intra-ocular pressure, glaucoma
Conclusions

• Surrogate (intermediate) endpoints are highly relevant in medical research
• Criteria for validity of surrogate markers have been well defined, but are often not adhered to
• So far, many have been insufficiently validated to trust with confidence
• While surrogate markers may capture main effects, evidence on safety may be reduced