Surrogate Endpoints in CV Research: Regulatory implications for the use of surrogate endpoints

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Definitions of endpoints (NIH)

- *Biomarkers*
  - # Indicator of biologic/pathogenic processes
  - # Pharmacologic response to therapeutic intervention
- *Surrogate endpoints*
  - # A biomarker intended to substitute for a clinical endpoint
- *Clinical endpoints (intermediate vs. ultimate outcome)*
  - # A characteristic or variable that reflects how the patient feels, functions or survives

Clin Pharmacol Ther 2001; 69: 89

Accepted vs. future surrogate endpoints/biomarkers in risk prevention

- Accepted endpoints (CHMP guidelines exist)
  - LDL-C
  - SBP & DBP
  - HbA1C
  - Weight
- Future endpoints (no clear guidance presence)
  - HDL-C, Tg (components of pro-inflammatory and -thrombotic state)
  - Measurement of target organ damage:
    - Vascular: imaging (e.g. Doppler, MRI, IVUS)
    - Heart: LVH (e.g. EKG, MRI)
    - Kidney: proteinuria/microalbuminuria
    - Brain: vessels (imaging)

Metabolic syndrome Kind of Endpoints in terms of expected benefit?

Surrogate endpoints

vs.

Clinical outcome

What is the metabolic syndrome?

- Broadly defined cluster of risk factors (HDL, Tg, HBP, IGT, weight) with one purported cause (?)
- Different definitions based on a binary classification (in contrast to continuous variables, which estimate relative risk)
- Increased incidence op type 2 DM and CHD, but heterogeneous, poorly defined and not shown to different than the sum of it parts

Clinical outcome studies in MetS

Example: Statin studied in patients with MetS

endpoints:

- (CV) mortality
- non-fatal MI
- non-fatal stroke
- hospitalisation for unstable angina
- (urgent) revascularisation

May an indication for MetS be granted without beneficial effects being shown for each component?

Surrogate outcome studies in MetS

- Normalisation of Tg, HDL-C and FPG in a pivotal trial for a combination of a lipid lowering and hypoglycaemic agent

- Improvement of bodyweight, Tg and HDL-C for an anorectic agent

Could different endpoints be defined for different subpopulations?

Progression to Diabetes as an endpoint

- Delay of progression to diabetes in a fixed combination of an oral hypoglycaemic agent and a hypertensive agent

Is progression to DM an acceptable endpoint?

- In which population?
- In conjunction with other relevant endpoints
- How do we distinguish between delay of progression and effective treatment for DM?
- What delay would be considered clinically relevant?

Example of metabolic syndrome

- Q. Should an indication in MS be granted on the basis of surrogate endpoints or a clinical outcome study?

  A. Demonstration of a beneficial effect on morbidity/mortality appears crucial

- Q. Should different surrogate endpoints be defined for different subpopulations?

  A. Surrogacy value of biomarkers/surrogate endpoints is debatable

- Q. Is progression to DM an acceptable endpoint, in which population and when is this delay clinically relevant?

  A. Theoretically yes, but needs further validation, a co-primary outcome variable would still be advisable

EMEA/CHMP expert meeting March 2005

Use of surrogate endpoints (or biomarkers) for registration purposes

Should their development be expedited?

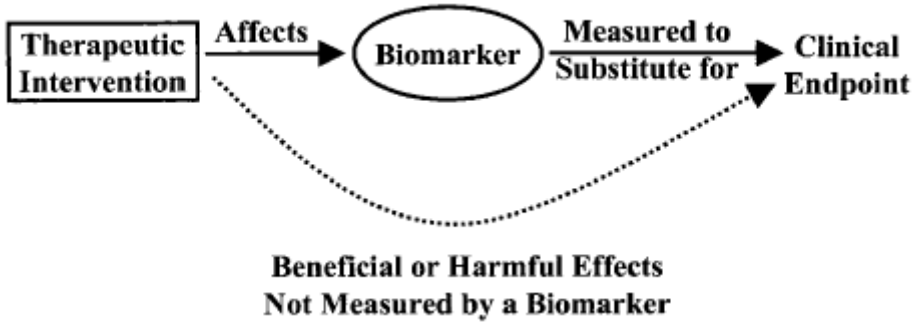
Surrogate endpoints: Advantages

- The ability to bring potentially effective therapies to clinical practice quickly
- Clinical trials evaluating surrogate endpoints require smaller sample sizes, and they can sometimes be completed in weeks or months rather than years

Surrogate endpoints: Disadvantages

- Surrogate endpoint may not be true predictor of clinical outcome
- Proposed surrogate variables may not yield a quantitative measure of clinical benefit that can be weighed directly against adverse effects
- Relationship with clinical oucome may vary between drug classes

Disadvantages of surrogate endpoints/biomarkers



"There is no surrogate for safety"

Temple R. JAMA 2004; 282: 791-5

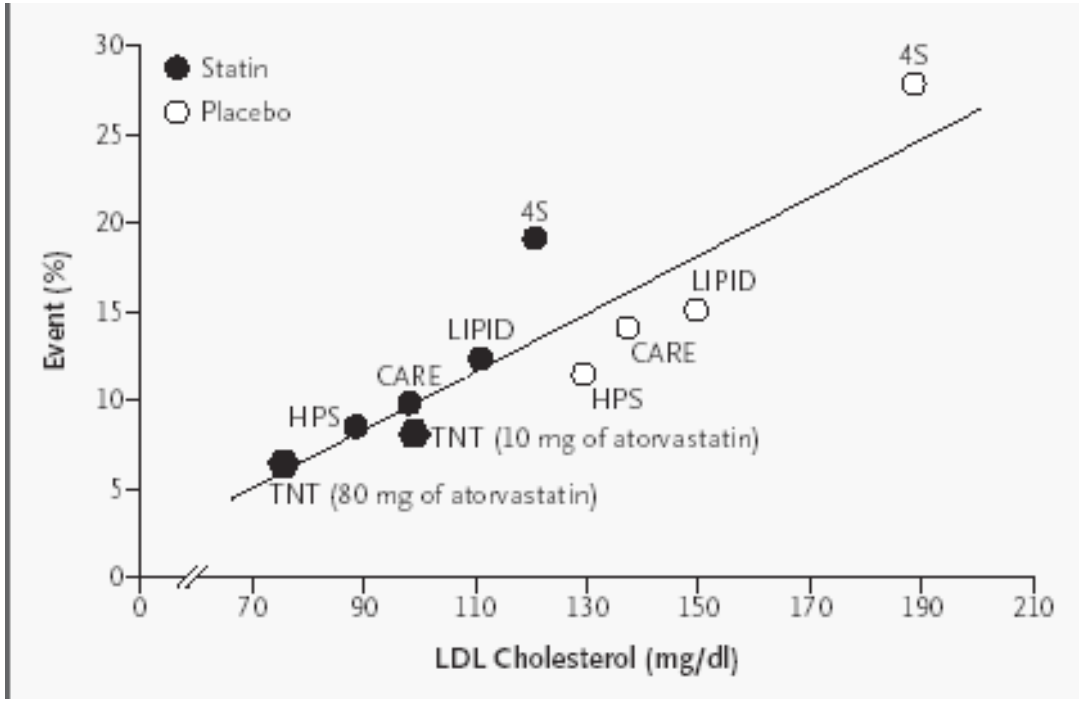
Evidence for surrogacy

- Biological plausibility of the relationship
- Demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome
- Evidence that treatment effects on the surrogate correspond to effects on the clinical outcome

ICH Topic E9: NfG on statistical principles

Example 1

Event Rates Plotted against LDL Cholesterol Levels during Statin therapy in secondary prevention studies



NEJM 2005; 342: 14: 1425

Example 2

systematical review of the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients

Atenolol in hypertension: is it a wise choice?

Lancet. 2005 Feb 19;365(9460):656

Regulatory principles

- A drug must be safe and effective when used according to the label
- The burden is on the sponsor to provide evidence supporting this conclusion
- The regulatory authorities must be able to label the drug with regard to expected benefits and risks

Orloff; Am J cardiol 2001: 87(suppl): 35A-41A

Use of surrogate endpoints (or biomarkers) for registration purposes

- Biomarkers are useful for drug development and risk estimation, but not as endpoint in the pivotal studies
- Surrogate endpoints are primarily important for efficacy reasons
- Distinct criteria for validating new surrogate criteria need to be defined, both in terms of efficacy and safety
- Regulatory implications of new surrogate criteria appear limited, their use should be not expedited