

European Regulatory View on Cardiovascular Biomarkers and Surrogate Endpoints in Clinical Trials

Dr. med. Clemens Mittmann

**Federal Institute for Drug and Medical Devices
(BfArM)
Bonn Germany**

Bethesda, Maryland, Sept 20 2006

European Regulatory View on Cardiovascular Biomarkers and Surrogate Endpoints in Clinical Trials

**Disclaimer: These are personal views that do
not necessarily reflect a BfArM or an EMEA
opinion**

**(Credits to Pieter de Graeff, ESC Workshop on „Imaging Biomarkers“,
Amsterdam 2006)**

Definitions

- **Biomarker:** A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process, or pharmacologic responses to a therapeutic intervention.¹
- A **surrogate endpoint** is a biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of clinical benefit or harm) ...¹
- „**Intermediate endpoint?**“: Surrogate endpoint directly representing the stage of the key pathophysiological process leading to clinical events but not constituting clinical benefit or harm on its own.

¹ Biomarker Definitions Working Group Clin Pharm and Ther 2001; 69: 89

European Regulatory View on Cardiovascular Biomarkers and Surrogate Endpoints in Clinical Trials

Biomarkers

- important role in the development of new drugs and the approval process for scientists, industry and regulators
- increase the rate of success of new developments and to expedite the development of drugs
- key in the shift to 'the right drug at the right dose in the right patient' approach.

Report on the 16 December 2005 EMEA/CHMP Biomarkers Workshop, 16 February 2006, European Medicines Agency, (www.emea.eu.int)

Clinical development

Possible application of biomarkers

Identification of diseases

enrollment of patients

Stratification

efficacy: identify responders

safety: identify patients at risk

dosage: identify special dosage requirements

Parameter of efficacy

clinical trials

individual patients

ICH Topic E 9

Statistical Principles for Clinical Trials

CPMP/ICH/363/96

Surrogate Variables

- may not be a true predictor of the clinical outcome of interest
- may not yield a quantitative measure of clinical benefit that can be weighed directly against adverse effects

ICH Topic E 9

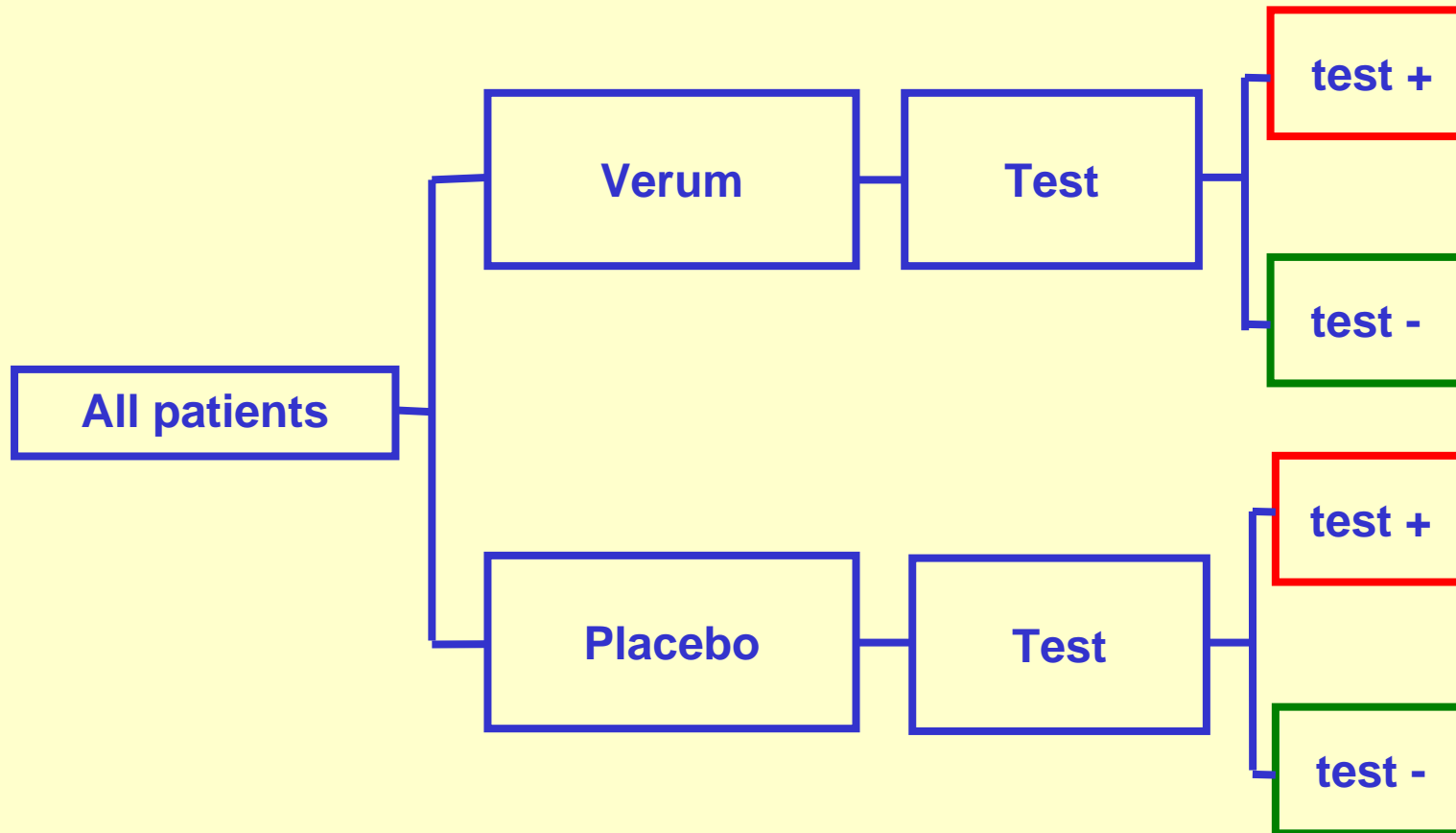
Statistical Principles for Clinical Trials

CPMP/ICH/363/96

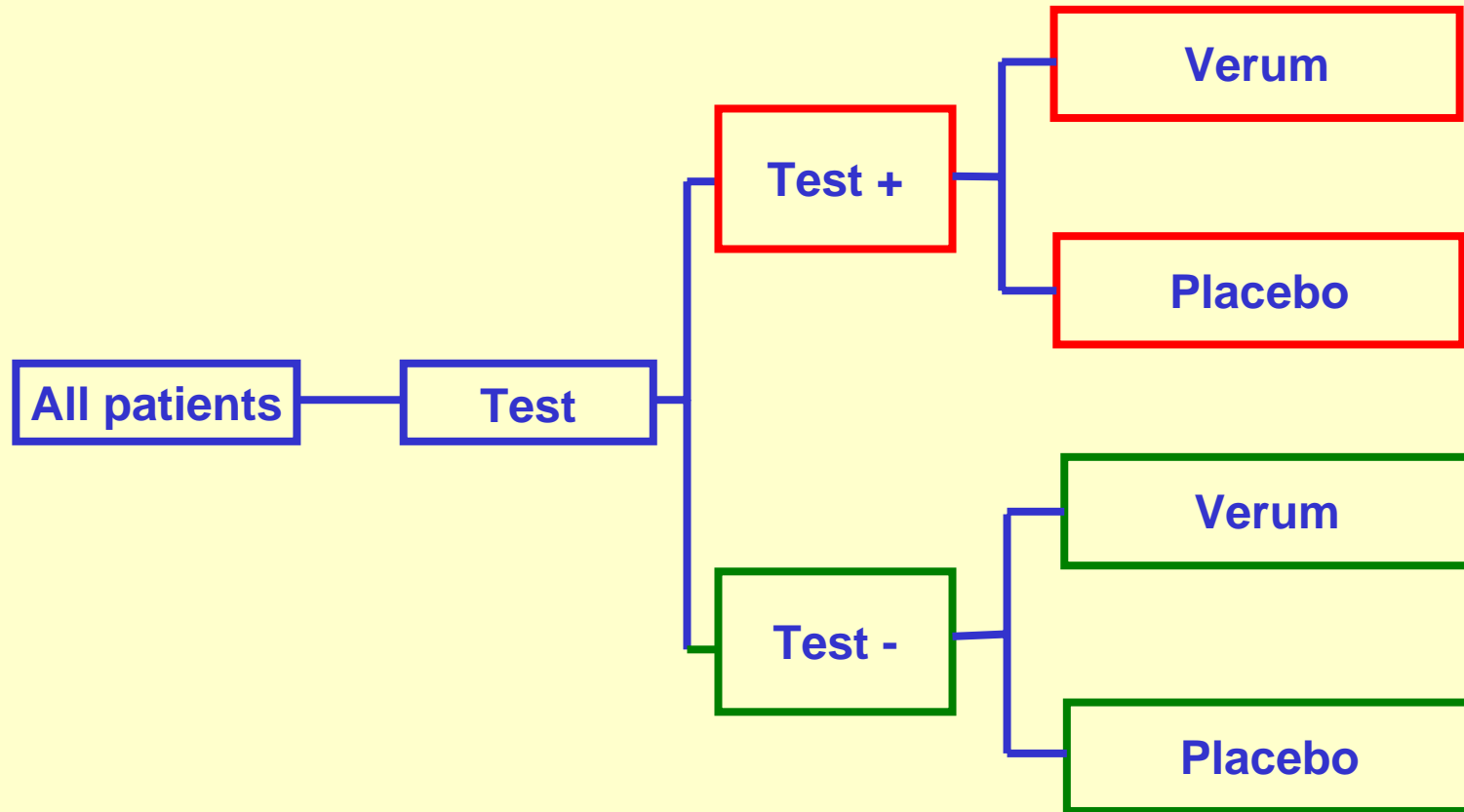
Validity of surrogate endpoints

- biological plausibility
- epidemiological studies: prognostic value for clinical outcome
- clinical trials: corresponding treatment effects on surrogate and on clinical outcome

Validation of a biomarker (Type A)



Validation of a biomarker (Type B)



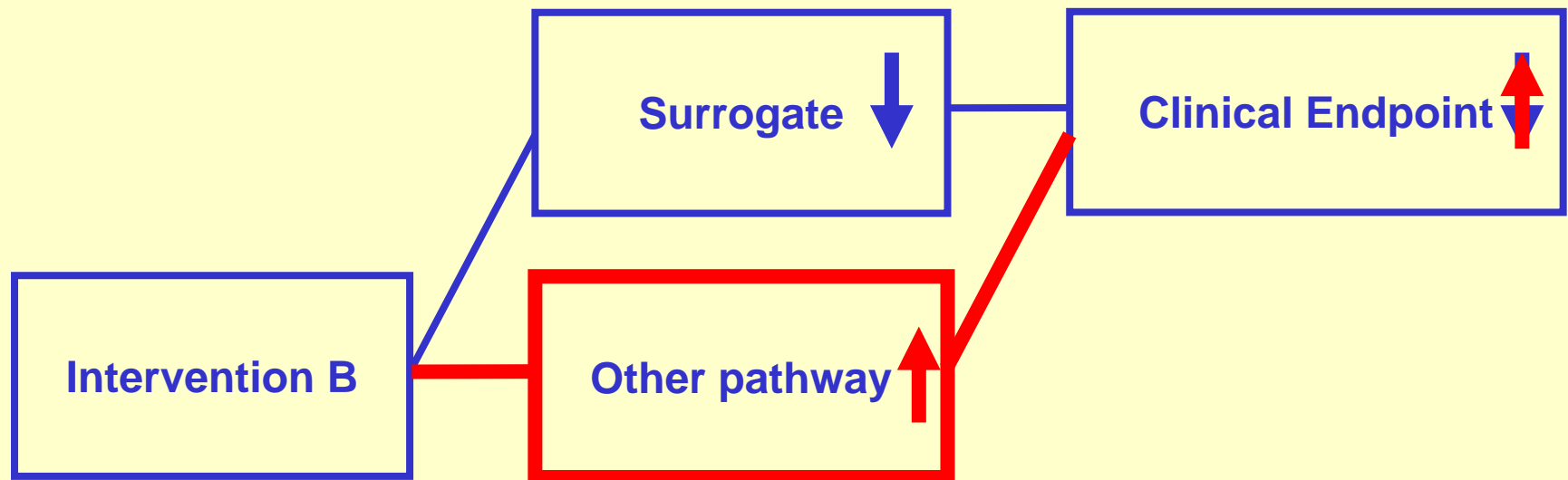
Validation of a biomarker



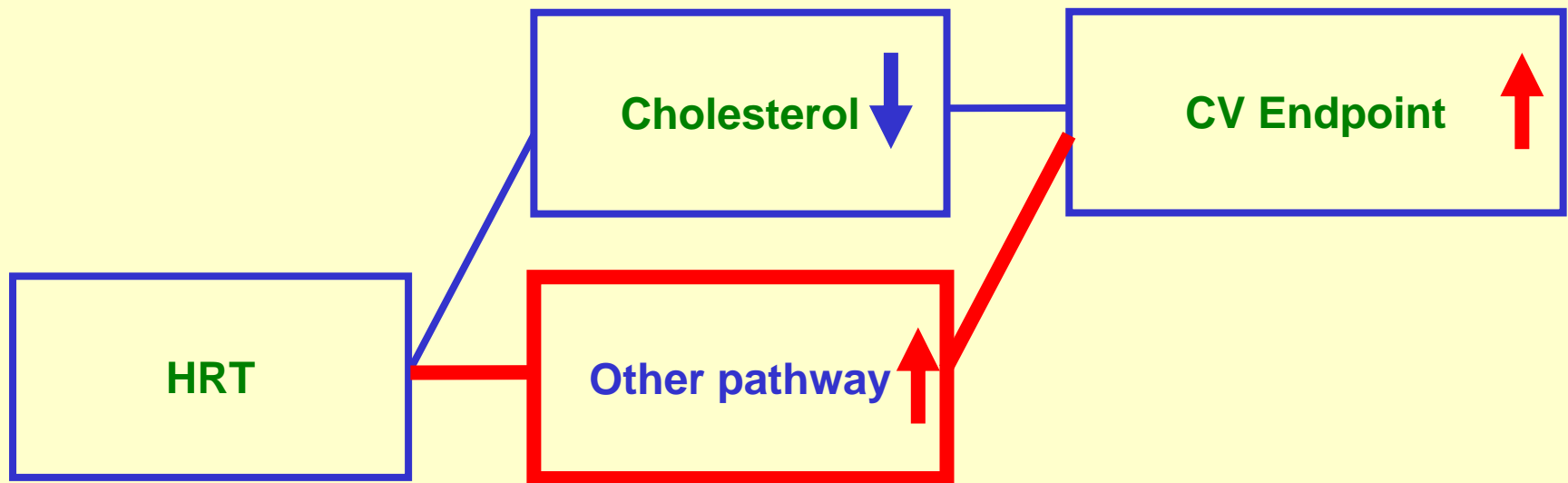
Validation of a biomarker



Validation of a biomarker



Validation of a biomarker



Accepted cardiovascular surrogates

for **phase III** studies

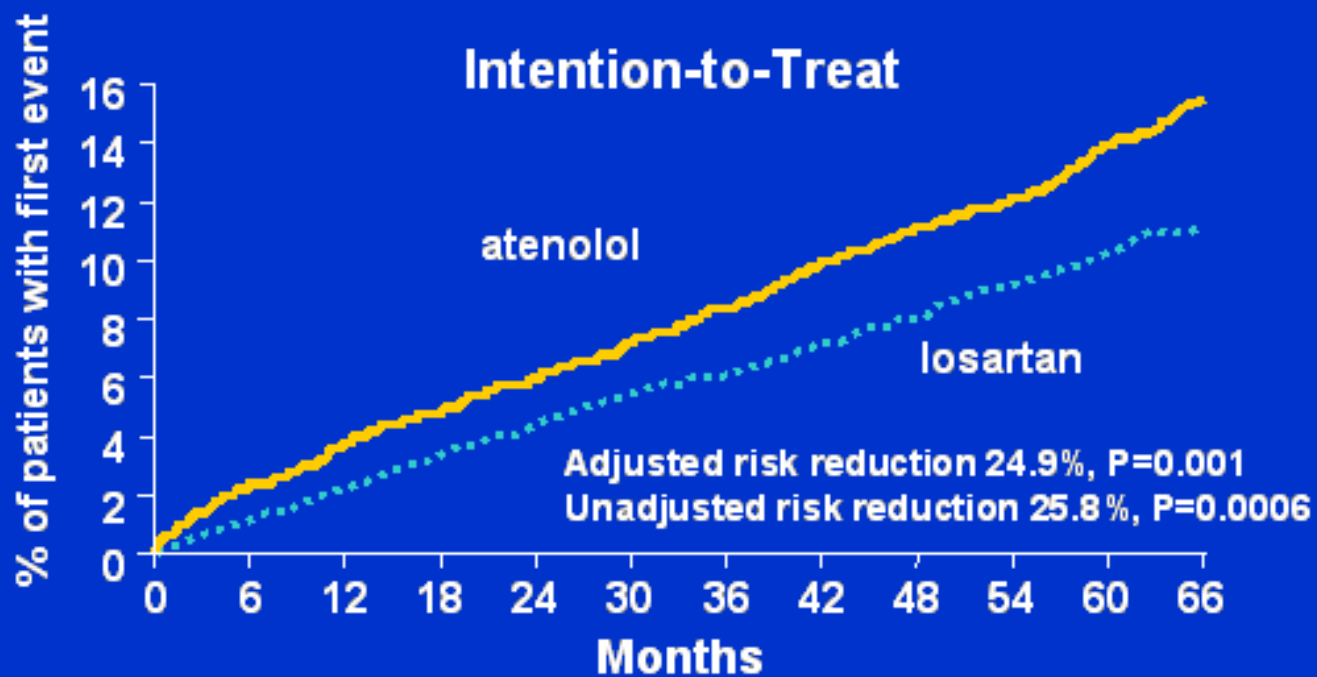
- LDL-C
- sBP and dBP
- HBA1c
- Weight

Surrogates

Do CV surrogate parameter uniformly predict effects in different target organs?

LIFE Study

LIFE: Fatal/Nonfatal Stroke



Dahlöf et al. Lancet. 2002;359:995.

Effect of betablockers on CV endpoints in arterial hypertension

Betablocker vs. others

	RR (95% CI)	p
Stroke	1.16 (1.04 – 1.30)	0.02
MI	1.02 (0.93 – 1.12)	0.04
Death	1.02 (0.99 – 1.08)	0.20

Atenolol vs. others

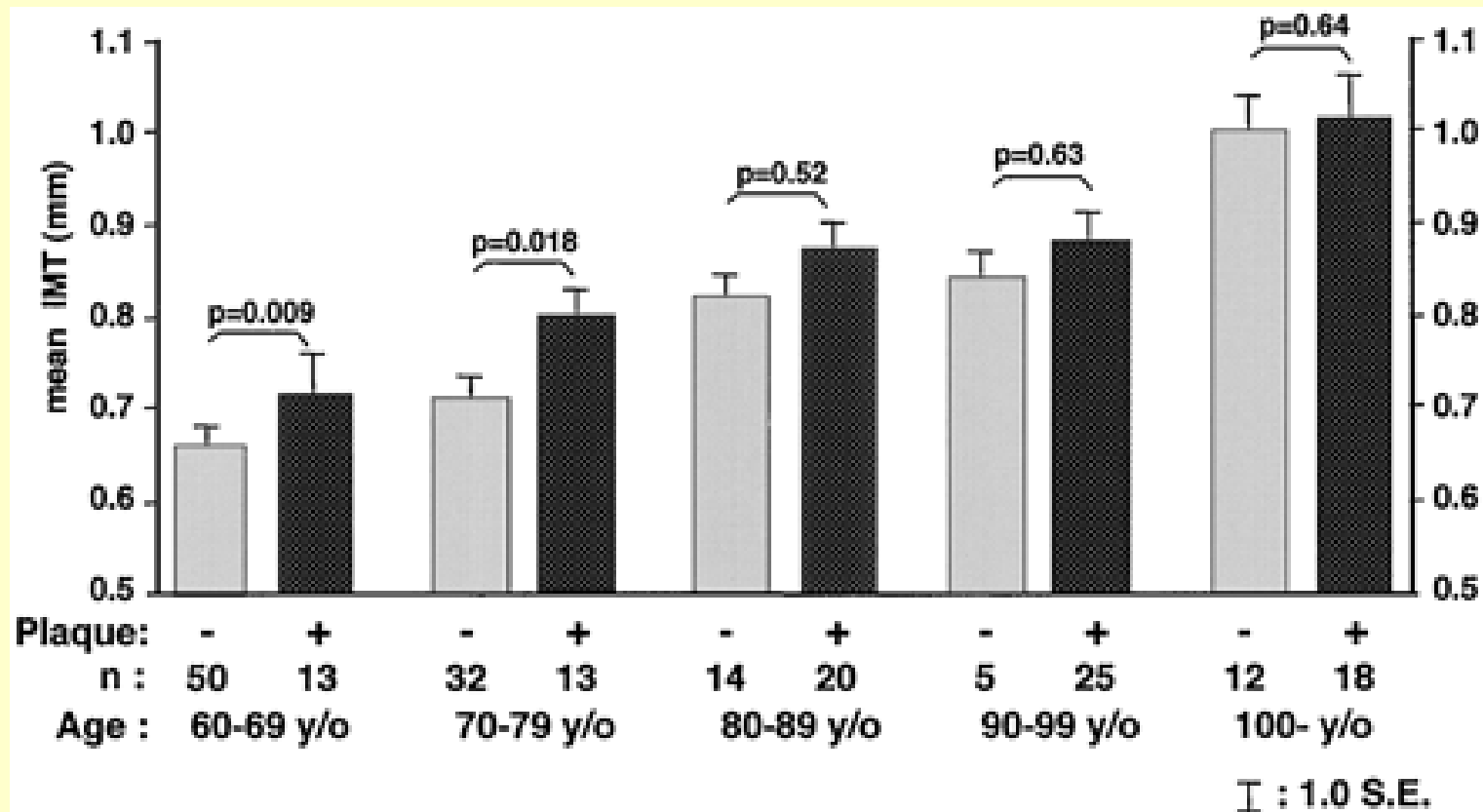
Stroke	1.26 (1.15 – 1.38)	0.70
MI	1.05 (0.91 – 1.21)	0.04
Death	1.08 (1.02 – 1.14)	0.33

Lindholm et al., The Lancet 2005; 366: 1545

Surrogates

Translation into clinical endpoints?

Relation between Plaque and IMT is age dependent



Relationship between IMT and plaque occurrence. Mean common carotid artery IMT in subjects with and without plaque.

Homma et al., *Stroke*. 2001;32:830

Safety

Biomarkers



Safety

Biomarkers

- May raise safety concerns but cannot prove safety
- „there is no surrogate for safety“

(R. Temple, *JAMA* 1999; 282: 790)



CHMP Guidelines

... Trials on outcomes of antihypertensive therapy, monitoring progression and regression of organ damage may provide relevant information on the comparative effectiveness of a new antihypertensive agent, but **the prognostic value of drug effects with regard to morbidity and mortality remains to be established.**

Thus, these endpoints are considered of secondary value and specific studies are only mandatory when specific claims are made or when there are suspicions of a detrimental effect.

CHMP Guidelines

Although target organ damage ... is presumably and plausibly associated with morbidity and mortality the prognostic values of these drug effects with regard to morbidity and mortality remains to be established; this holds particularly true for changes in intima media thickness (IMT) and plaque stability. For the time being, the effect ... on the atherosclerotic burden at a particular site cannot be considered as a valid surrogate for cardiovascular morbidity and mortality.

CPMP/EWP/3020/03 (Lipid disorders)

CHMP Guidelines

Surrogate parameters like carotide IMT ... may be accepted as primary endpoints in studies aiming at therapeutic equivalence between formulations of the same active substance.

Draft NfG on CV prevention

Acceptability of maging related indications

e.g. „slowing/reversal of progression of atherosclerosis“
based on imaging data?

REVERSAL study (published data)

Percent change in atheroma volume

Pravastatin	2.5 %
Atorvastatin	0.5 %

Total atheroma volume

Pravastatin	4.4 %
Atorvastatin	-0.9 %

Obstructive atheroma volume

Pravastatin	1.6 %
Atorvastatin	-0.18 %

How does it
translate into
stroke, MI, CV
death, overall
mortality?

Risk/benefit in
subgroups?

Nissen et al., JAMA 2004; 291: 1071

Acceptability of maging related indications

e.g. „slowing/reversal of progression of atherosclerosis“
based on imaging data?

- does not define a patient population
 - does not describe relevant clinical endpoints
-
- Not accepted as an indication
 - Information may be included in section 5.1
(pharmacodynamic properties)

Regulatory decision making based on biomarkers

At present imaging based biomarkers of efficacy may be acceptable in **phase I/II** and in **bridging studies**

Regulatory decision making based on biomarkers

At present imaging based biomarkers of efficacy may be acceptable in **phase I/II** and in **bridging studies**

- Feasibility in phase I/II
- Dose finding
- Proof of principle
- Therapeutic equivalence for a new formulation

Vascular imaging issues to be adressed

Validation

- ICH prerequisites
- class specific validation?

Clinical relevance

- quantification
- correlation with different clinical endpoints (MI, stroke, CV death, overall mortality)
- subgroups?

Safety

- (long term) mortality and morbidity
- rare AEs

Use biomarkers appropriately

