

**CV Biomarkers in FDA Regulatory
Science – Metabolism and
Endocrine
What's New in 2007**

Mary H. Parks, M.D.

Director

Center for Drug Evaluation and Research

US Food and Drug Administration

DEFINITION

■ NIH Working Group Definition

- A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Clinical Application of Biomarkers

- Relied upon in clinical practice
 - Screening for preclinical disease (e.g., BP monitoring)
 - Diagnostic tool in detecting disease (e.g., troponin or CK levels)
 - Risk stratification (e.g., tumor grading and staging)
 - Guide selection or titration of therapy (e.g., treatment goals for cholesterol)

Clinical Application of Biomarkers

- Relied upon for drug development
 - Biomarkers for screening, diagnosis, prognostication, and treatment decisions also applicable in drug development
 - In CVD, utility of biomarkers can be considered in 3 categories:
 - Predictor of risk
 - Modifier of treatment or target of intervention
 - Target of pharmacologic intervention

Utility of Biomarkers

- Selecting out target population
 - Risk stratification or selecting out drug responders
- Dose selection
 - Phase 2 dose-finding studies; rely on biomarker to narrow the candidates to a few to take into Phase 3
- Exploring pharmacologic effect of drug
 - Exploratory – correlate change in new biomarker w/ the accepted surrogate
- Comparative efficacy or safety
 - Address the difficulties and expense of head-to-head studies

Biomarker as Target of Pharmacologic Intervention

- Often forms basis for approval of NDA/BLA
- Biomarker = Surrogate endpoint
 - “a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.”

Approvals Based on Biomarkers

- Evidence favoring use of such biomarkers includes
 1. Extensive and consistent epidemiologic support (different cohorts/patient population) demonstrating correlation b/w biomarker and risk of disease
 2. Animal models and/or genetic disorders
 3. RCTs in which targeting the biomarker impacts disease outcome
 4. Effect of biomarker on clinical outcome consistent in drug class or across drug classes
 5. Favorable effect of targeting biomarker on various clinical presentation of disease (CV death, nonfatal MI, stroke)

LDL-C

- Relied upon as predictor of risk, modifier of treatment, and target of pharmacologic intervention (surrogate endpoint)
- Meets all 5 levels of evidence as favorable candidate for drug approval
- Approved LDL-lowering drugs: statins, bile acid sequestrants, intestinal cholesterol inhibitors (niacin, fibrates)
- Candidates in development: MTP-inhibitors, squalene synthase inhibitors, anti-sense therapies to apoB

HbA1c

- Relied upon as predictor of risk?
- Relied upon to modify treatment?
- Target of pharmacologic intervention?

Predictor of risk

- Diabetics have 2-4 fold risk of experiencing a CV event compared to non-diabetics
- Prospective studies support higher risk of CV events in diabetic patients

Increased CV risk in Diabetic Population – Statin trials

| | Non-diabetic | Diabetic |
|------------------------|-----------------|------------------|
| LIPID | 326/4116 (7.9%) | 47/386 (12.2%) |
| Heart Protection Study | 468/7282 (6.4%) | 239/2985 (8.0%) |
| With CHD | 409/5683 (7.2%) | 145/1009 (14.3%) |
| Without CHD | 59/1599 (3.7%) | 94/1976 (4.8%) |

Modifier of treatment

■ Treating to New Targets (TNT)

- ~10,000 5-yr study of Atorva 80 vs Atorva 10 on CVD risk reduction
- 1501 diabetics enrolled
 - Atorva 10 achieved LDL 98 mg/dL; atorva 80 achieved LDL 77 mg/dL
 - Aggressive LDL-lowering resulted in 25% reduction in risk of major CV events ($p=0.026$)

HbA1c – as targeted intervention

- DCCT - type 1 diabetics. F/u cohort demonstrated trend in CV risk reduction for intensive glycemic control
- UKPDS – nonsignificant risk reduction for MI; significant macrovascular risk reduction in subgroup of overweight patients tx'd w/ metformin
- No established CV risk reduction with any one oral anti-diabetic agent
- Reflection of multiple pathologic processes in CVD in diabetics

HbA1c – beyond CV benefits

- Symptomatic improvement from hyperglycemia
- Infections/wound healing
- Microvascular risk reductions

HbA1c as a Surrogate for Drug Approval

- Not labeled for CV risk reduction
- HbA1c is a validated surrogate marker and should remain as an endpoint for approval of diabetes drug
- Requirement for CV outcomes trials
 - Pre-approval
 - Post-approval
 - Every anti-diabetic drug

What next in DMEP?

- Reasonable to expect that the weight of evidence applied to currently accepted biomarkers relied upon for approval will be similarly applied for new biomarkers

When is more evidence required?

- Insufficient evidence to validate biomarker
- Safety concerns which offset biomarker's putative clinical benefit
 - Findings negating CV benefit
 - e.g., higher CV events in P2/3 trials, unfavorable effects on other established biomarkers
 - Findings counterbalancing CV benefit
 - e.g., myotoxicity, hepatotoxicity

What kind of evidence?

- Imaging study
 - Validate a biomarker w/ another biomarker?
- Enough exposure to reassure us nothing real bad will happen
- Directed safety study
- CV outcomes trial