

DMEDP view of surrogates

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History: Weight of evidence in support of use of “metabolic” antiatherosclerosis drugs

- Initial approval: statins, fibrates, niacin, resins, eze
 - LDL-C/non-HDL-C/atherogenic TG lowering
- Corroborative evidence
 - regression or slowing of progression
 - contrast angiography (QCA)
 - carotid ultrasound
- Confirmatory
 - “outcome” studies with statins, fibrates, niacin, BAS
 - testing in subgroups defined by risk
 - testing the total mortality hypothesis

A new era: beyond LDL-C lowering

- Proposed: antiathero drug development (and approval) will proceed more efficiently with use of soluble biomarkers and vascular imaging as opposed to long-term morbidity and mortality trials
- Question: will drug development along these lines be successful in correctly identifying drugs that are safe and effective for use in reducing CV risk?

The landscape

- Increasingly detailed understanding of the pathophysiology/molecular “natural history” of athero
- Rich in potential targets for intervention
- Drugs designed to target specific etiologic mechanisms/pathologic steps

Heinonen's rule

- Measures of effect (like study populations) should be chosen/tailored based on consideration of drug's target within the multistep pathologic process and the expected perturbation(s) of disease natural history

Orloff's corollary

- Given the complexity of athero-pathogenesis, hard to imagine that any biomarker will ultimately prove to be a universal surrogate whereby change observed is independently predictive of benefit, increased risk, or no effect across all drugs and mechanistic targets

Admonition/plea

- Failure of community of investigators to reach consensus on the best methods for clinical assessment of changes in vascular disease risk
- Competition evident; collaboration needed
- Parade of advocates for the merits of a method practiced by each
- No consistent directing of method/technology to aspect of the pathologic process that is the known or hypothesized pharmacologic target
- No comparisons of sensitivity and specificity of different measures as indicators of clinical risk

In the end, how much do we know...

- Weight of evidence always the ultimate way to construct the proof of drug efficacy and safety (we do it all the time)
- The answer does not always lie in a total mortality study (e.g., Baycol)
- Always a leap of faith: We accept some arbitrary level of understanding and assurance of the efficacy and safety of the new drug, given 1) the risks of the target disease (thus risk vs. risk) and 2) the demonstrated benefits of the intervention (thus risk vs. benefit)

And we always rely on
biomarkers and
intermediate endpoints to
varying degrees

Plausibility of a proposed surrogate (gen'l)

- Population studies/epidemiology/experiments of nature support biomarker as predictive of risk
- Epi, animal models, experiments of nature, existing pharmacology, etc. support change in marker as predictive of clinical benefit
- Human physiology, biochemistry, pathophysiology supports marker as clinically meaningful intermediate

Biomarker to surrogate: validation (gen'l)

- Preliminary, by inference
 - follows “validated” surrogates and is reproducible, sensitive, specific
 - multiple mechanistic approaches of known clinical benefit impact the putative surrogate similarly
- Definitive, in trials to disease endpoints
 - change due to intervention independently predictive of benefit
 - clear “correlation” between change in surrogate and change in risk

Validation of imaging methods

- By necessity, multiple stages
- Beware of mismatch between drug target/pathophysiology mechanism and marker

Imaging validation-initial/prelim

- Design: Control/background therapy with known, clinically effective drug with documented or plausible effect on biomarker (e.g. statin)
- Outcome: Effect on biomarker greater than that occurring with tried and true agent(s) is potentially indicative of a salutary health effect
- Inference: Clinically meaningful effect size should (ideally) be defined a priori (historical reference, epi, clinical trial data) and included in statistical plan

Imaging: “clinically significant changes in the vasculature”

- the minimum magnitude change associated with a clinically meaningful alteration in LDL-C or other validated biomarker
- the minimum magnitude change, attributable to a proven clinically effective dose of statin or other anti-atherosclerosis agent (regardless of the effects on the soluble markers)

Inference of efficacy: new drug

- Change in anatomy (quantity and quality), by multiple methods, attributed to new drug must be similar to (or “better” than) that observed in association with clinically meaningful alteration in valid biomarker and/or with proven effective drug
- Expected (other) biomarker effects observed, also similar to those observed with proven effective therapies

Imaging validation: from marker to true “surrogate”

- Biomarker changes correlated with events in context of hard endpoint study
- Huge leap
- Caveat: May still be limited to drug, drug mechanism, disease stage, subpopulation

Examples in DMEDP

- Three instances where CV imaging/biomarkers are proposed
 - 1. Initial approval of NME or first approval for population at risk for CVD
 - 2. Broadening claim for approved CVD-risk-modifying agent (e.g., lipid altering)
 - 3. New claim for approval drug (e.g., diabetes drug as anti-athero)

1. Initial approval (not yet accomplished)

- Two modalities
- Two vascular beds
- Two studies
- Plausible or formally valid soluble biomarker effects
- Large safety experience, no unresolved concerns from animals, drug metabolism, clinical AEs
- Phase 4 hard endpoints

Example: HDL-raising drug

- Studied in combination with statin vs. statin alone
- IVUS (coronaries)
- B-mode (carotids)
- Change from baseline to endpoint
- “Statistical difference” between mono and combo therapy
- Biomarker effects
- HDL functionality in RCT assays

2. Broadening claim for CVD-risk-modifying agent

- (e.g., statin angio/IMT studies)
- Single modality, “plausible”, (clinical benefits already demonstrated)
- Biomarker effects consistent

3. New claim for drug approved based on another expected benefit

- One or two modalities*
- Studies*
- Biomarker effects (plausible)
- Address unique safety issues in new target population
- Address potential countervailing CV effects that might invalidate reliance on biomarker
- Phase 4 endpoints

Conclusions

- Biomarkers must be considered in order to expedite development (they form the rationale for the program in the first place)
- Consensus on utility/applicability, validity, limitations of imaging methods and soluble biomarkers must occur
- Imaging modality/biomarkers must be appropriate to drug mechanism and pathophysiologic target
- Unlikely to be a single, universally “valid” surrogate for clinical outcomes
- Multiple modalities, multiple vascular beds, multiple studies are required for initial approvals of anti-athero drugs
- Endpoint studies are, in the end, the only confirmation of clinical benefit