

Surrogates and Biomarkers in ASCVD Drug Development

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Basic principles

- FDA's basic standard:
 - "...results of clinical investigations that include adequate tests by all methods reasonably applicable..." must permit the reasonable conclusion that the drug is safe and effective "...under the conditions of use prescribed, recommended, or suggested in the labeling.."
- Labeling must convey expected risks and benefits in the named target population
 - "Indication" is based on expected salutary effects in the named target population

What do we know when a drug goes to market?

- “Proof” of drug efficacy and safety is always based on a weight of evidence
- There is no definition of “enough”: Even the total mortality study may mislead by not revealing risks of serious adverse drug effects
- We never know all
 - Balance of efficacy and safety of the new drug are considered in light of: 1) the risks of the target disease, 2) the demonstrated benefits of the intervention and 3) the known risks of the drug
- We are far from infallible in our predictions of efficacy and safety in open use

LDL-C lowering as a surrogate for reduced CVD risk

- Epidemiology/pathology/clinical observation
- Experiment of nature
- Priors with other means of lowering (drugs, surgery)
- Magic bullet class of drugs
 - Lower LDL-C
 - Alters athero by imaging
 - Reduces angina, MI, stroke, CHD death
 - “safe”

Anti-atherosclerosis therapy: beyond LDL-C lowering

- Proposed: drug development (and approval) will continue to proceed ***more quickly/efficiently*** by at least initial reliance for conclusions regarding efficacy on soluble biomarkers and vascular imaging, reserving long-term morbidity and mortality trials for phase 4

Questions

- Can development along these lines again be *successful* in correctly identifying drugs that are effective for use in reducing CV risk?
- Are the novel pharmacologic approaches so “plausible” as routes to cardioprevention and protection to merit the gamble, as was the case for LDL-C
 - Biochemistry, pathophysiology?
 - Experiments of nature?
 - Priors?
- Have we got the biomarkers to go to work with?

Surrogate endpoint: a biomarker with special status

- A surrogate endpoint is a laboratory measurement or a physical sign (or a pathological finding or diagnostic image) used as a substitute for a clinically meaningful endpoint that measures how a patient feels, functions, or survives.
- Changes induced by therapy on the surrogate are therefore expected to reflect changes in a clinically meaningful endpoint

The Ideal

- A universally accurate marker of clinical risk:
 - 100% sensitive: When clinical risk changes, marker will always change in parallel
 - 100% specific: When the marker changes, it is always because clinical risk has changed in parallel

The Real vs. the Ideal

- ASCVD (like most diseases) is highly complex
 - Multiple factors contribute to pathogenesis such that addressing one (and its marker) may not impact natural history if other factors supervene (e.g., unprevented events after LDL-C lowering)
- Risk may be reduced without a change in the marker (early effects of statins in advance of anatomic changes)
- Not to mention the specificity problem: other processes may impact the marker (CRP as an acute phase reactant)

Biomarkers as Evidence

- Actual mediators of disease
 - LDL-C/apo B
 - BP/PRA?
 - CRP?, others?
- Parallel markers of disease process/severity
 - HbA1c
 - CRP?, others?
- Imaging

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Sensitivity

Specificity

What about safety?

- In the absence of clinically evident safety “signals”, we always rely on markers to support conclusions of acceptably low risk, e.g.:
 - Transaminases, bilirubin
 - Hematology
 - Renal functional studies
 - Pulmonary function studies
 - EKG (QT interval)

Pulling together the evidence

- First rule: assess what you expect to affect
 - Measures of effect (like study populations) should be chosen/tailored based on consideration of drug's target within the multistep pathologic process and its expected effect(s) on disease biochemistry (and in the end, natural history)

But temper your expectations...

- Given the complexity of athero-pathogenesis, no biomarker will ultimately prove to be a universal surrogate whereby the change observed (or lack thereof) on the marker of a potential new therapeutic is independently predictive of benefit, increased risk, or no effect across all mechanistic approaches to disease prevention, treatment, or mitigation

Pieces of the evidentiary puzzle

- Pharmacology: designed to address key points in the disease process (e.g., in vitro)
- Pharmacodynamics: short-term markers of activity as designed (animals, man)
- Effects on clinically monitorable biochemical, physiological, imaging endpoint(s) (patients)
- Effects on disease outcomes/natural history (patients)

Potential limitations

- Effects on biomarkers provide only preliminary proof of benefit (a picture is, in the end, only a picture)
- May not hold up to definitive testing
 - “plausibility” can mislead (e.g., VPB suppression)
 - utility as predictor of benefit may be drug- or mechanism-specific
- Never tells the entire story of drug effect
 - short or long-term unexpected adverse effects may surface (toxicities, drug interactions)
- Consideration must be given to the challenges of conducting definitive trials in the context of the prior(s) of “successful” trial(s) utilizing surrogate endpoints

Conclusions

- Biomarkers of safety and efficacy are central to drug development from initial rationale to proof of concept to late phase clinical trials.
- Most drugs for CVD prevention and treatment affect biomarkers that presumably reflect disease activity/clinical risk.
 - It is how we titrate them to effect and against adverse side effects (ASA is a notable exception).
- But just because they have monitorable effects doesn't automatically mean they confer clinical benefits
 - The “weight of evidence” requirement is often less one of whether a marker is a useful indicator of risk or disease activity in the context of “natural history”, but whether by perturbing it with a new drug, we have done good, bad, or indifferent

Conclusions-2

- For new drugs, we must choose biomarkers for use in assessing efficacy (and safety) according to the mechanism(s) of action of the drugs and the pathophysiology of the target disease.
- It is extremely unlikely that a single, universally “valid” surrogate for clinical outcomes in CVD will be established (or indeed exists)
- Endpoint studies are, in the end, the only confirmation of clinical benefit