Clinical Trials and Clinical Practice: Surrogates at the Clinician/Patient Interface

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Outline

- Definitions & history

- Use in clinical practice

- Advantages & limitations

- Critical appraisal framework

Clinical scenario

- *67 year old, established ASHD*

- *Recent myocardial infarction*

- *LDL-C on target with a statin*

- *HDL-C below target*
  - *Well established as prognostic factor*
  - *Has not tolerated niacin*

- *Novel antilipemic agent recently marketed*
  - *Consistently increases HDL-C by up to 70%*
  - *No data on effect on clinical outcomes*
  - *Hailed as "a major therapeutic breakthrough"*
  - *"One of the most important compounds of our generation"*

- *Would you consider recommending this agent to your patient?*
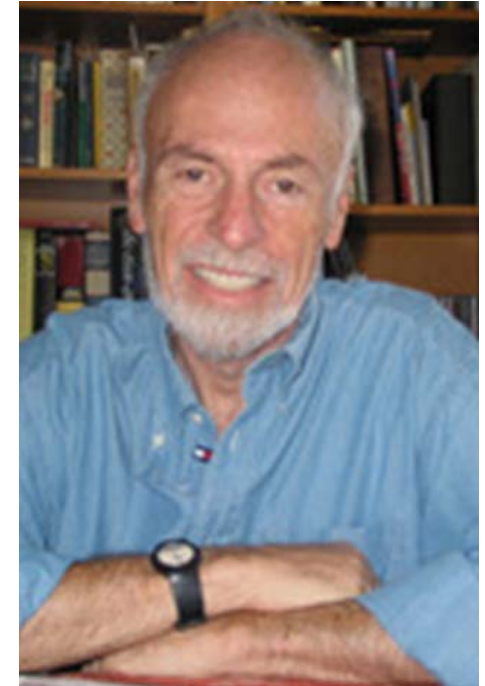
Definitions

- **Surrogate endpoint**
  - From Latin word *"subrogare"*
    - To substitute; to elect or ask in place of
  - "A laboratory or physical measurement that is used as a substitute for a clinically meaningful endpoint that is a *direct* measure of how a person:
    - Feels
    - Functions
    - Survives

Temple 1989

Definitions

- Biomarker
  - 'A characteristic that provides an indication of:
    - Normal biologic processes
    - Pathogenic processes
    - Pharmacological responses
  - Biomarker ≠ surrogate endpoint
  - Surrogate endpoint ≠ biomarker

Examples of surrogate endpoints

Disease	Surrogate endpoint	Clinical endpoint
Multiple sclerosis	MRI imaging of lesions	MS relapses
		Disability progression
Cardiovascular diseases	HDL-C	Acute myocardial infarction
	Carotid intima-media thickness (CIMT)	Ischemic stroke
Diabetes	HgA1c	Acute myocardial infarction
		Ischemic stroke
Prostate cancer	Prostate-specific antigen (PSA) Distant metastasis	Cancer-specific mortality
Cancer	Tumour response	Cancer-specific mortality
	Progression-free survival (PFS)	Overall survival

History

- 1980 – Biomarker

- 1988 – Surrogate marker

- 1989 – Surrogate endpoint

Applications in clinical practice

❑ Can be used for:

- Diagnosis

- Disease staging

- Monitoring disease

- Assessing response to therapy

Advantages

- Increase understanding of pathophysiology

- Identify novel therapeutic targets

- Enable clinical monitoring

- Reduce sample size & duration of trials
  - Reduced cost
  - Expedited access
  - Improved feasibility

Limitations

- ↓ power to detect harms

- Based on incomplete evidence
  - Underlying disease processes
  - Effects of intervention

- Surrogate failures
  - Excess morbidity & mortality
    - Human & economic cost

MORTALITY AND MORBIDITY IN PATIENTS RECEIVING ENCAINIDE, FLECAINIDE, OR PLACEBO

The Cardiac Arrhythmia Suppression Trial

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Dulce Obias-Manno, R.N., Allan H. Barker, M.D., Daniel Arensberg, M.D., Andrea Baker, R.N.,
Lawrence Friedman, M.D., H. Leon Greene, M.D., Melissa L. Huther,
David W. Richardson, M.D., and the CAST Investigators*

Abstract *Background and Methods.* In the Cardiac Arrhythmia Suppression Trial, designed to test the hypothesis that suppression of ventricular ectopy after a myocardial infarction reduces the incidence of sudden death, patients in whom ventricular ectopy could be suppressed with encainide, flecainide, or moricizine were randomly assigned to receive either active drug or placebo. The use of encainide and flecainide was discontinued because of excess mortality. We examined the mortality and morbidity after randomization to encainide or flecainide or their respective placebo.

Results. Of 1498 patients, 857 were assigned to receive encainide or its placebo (432 to active drug and 425 to placebo) and 641 were assigned to receive flecainide or its placebo (323 to active drug and 318 to

ceiving drug vs. 5 receiving placebo). Almost all cardiac deaths not due to arrhythmia were attributed to acute myocardial infarction with shock (11 patients receiving drug and 3 receiving placebo) or to chronic congestive heart failure (4 receiving drug and 2 receiving placebo). There were no differences between the patients receiving active drug and those receiving placebo in the incidence of nonlethal disqualifying ventricular tachycardia, proarrhythmia, syncope, need for a permanent pacemaker, congestive heart failure, recurrent myocardial infarction, angina, or need for coronary-artery bypass grafting or angioplasty.

Conclusions. There was an excess of deaths due to arrhythmia and deaths due to shock after acute recurrent myocardial infarction in patients treated with encainide or

CAST Trial – preliminary results

- **Surrogate endpoint**
  - Arrhythmia suppression:
    - 75% for encainide, flecainide or moricizine

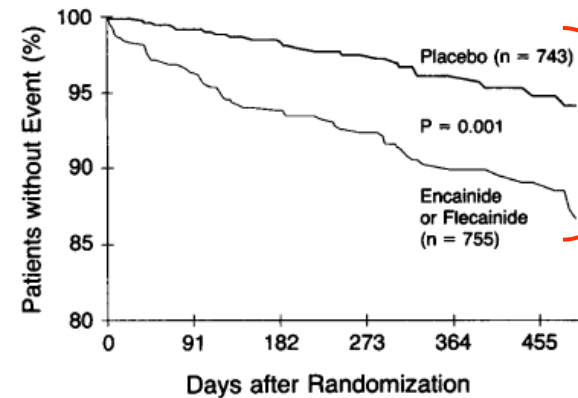**Death from arrhythmia or cardiac arrest**

Death from any cause
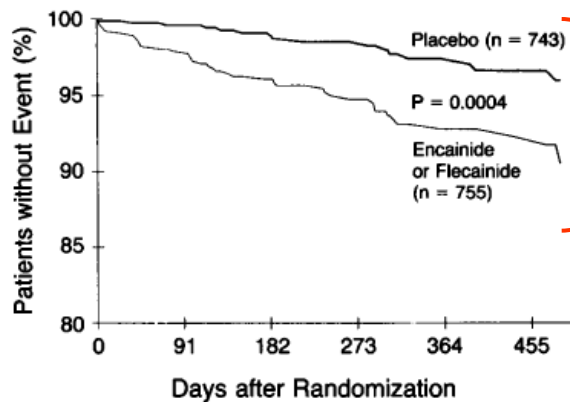
Treated = 4.5%
Placebo = 1.2%
RR = 3.6 (1.7-8.5)

Treated = 7.7%
Placebo = 3.0%
RR = 2.5 (1.6-4.5)

Placebo (n = 743)

P = 0.0004

Encainide or Flecainide (n = 755)

Patients without Event (%)

Days after Randomization

Placebo	743	632	516	412	292	201
Active drug	755	631	507	392	286	198

Figure 1. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Arrhythmia in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.

Placebo (n = 743)

P = 0.001

Encainide or Flecainide (n = 755)

Patients without Event (%)

Days after Randomization

Placebo	743	625	516	412	292	181
Active drug	755	619	507	392	286	186

Figure 2. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Any Cause in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.

Surrogate failures

Year	Intervention	Surrogate	Findings
1991	Milrinone	Exercise capacity Left ventricular function	↑ mortality
1993	Flosequinan	Exercise capacity Left ventricular function	↑ mortality
1993	Enalapril *vs* Hydralazine + ISDN	Exercise capacity Left ventricular function	Enalapril ↓ mortality (contrary to surrogate findings)
1998	Vesnarinone	Exercise capacity Left ventricular function	↑ mortality
2005	Fenofibrate	LDL-C	↔ Overall mortality
2008	Intensive glucose ↓	HgA1c	↑ mortality

Surrogate failures

Year	Intervention	Surrogate	Findings
2007	Torcetrapib [†]	HDL-C	↑ cardiovascular events ↑ mortality
2008	Ezetimibe (add on)	LDL-C Carotid IMT	↔ carotid IMT
2009	Androgen deprivation	Distant metastasis Prostate cancer mortality	↑ CVD mortality
2010	Fenofibrate (add on)	LDL-C	↔ overall mortality
2010	Bevacizumab	Disease-free progression	↔ overall mortality
2011	Niacin ER (add on)	HDL-C	↔ cardiovascular events ↑ ischemic stroke

[†] Findings published before torcetrapib was approved for use by the FDA

Validity assessment

- **Epidemiology**
  - Important but imperfect science
    - Measures 'associations' not 'causation'
    - "*A perfect correlate does not a surrogate make*"

      (Baker & Kramer 2003)

- **Framework needed for determining the validity of the surrogate endpoint**

Critical appraisal framework

- Surrogate-clinical outcome relationship causal?
  - Biological plausibility
  - Strong association
  - Independent association
  - Consistent association
    - Across studies
    - Across drug classes
    - Drugs within same class
 - Evidence of dose-response

Critical appraisal framework

- Effect of intervention on surrogate consistent with its effect on clinical outcome?
  - Study with both endpoints
  - Ideally RCT evidence
- Intervention mediates all of its impact via the surrogate
    - Within a drug class
    - Across drug classes of similar action
  - Unintended adverse effect?

Clinical scenario

- Torcetrapib

- Efficacy tested in two RCT of patients at

- High risk of coronary events

- Endpoints

  - HDL-C

  - Progression of coronary atherosclerosis

  - Carotid IMT

  - Cardiovascular events

  - All-cause mortality

- Results

  - Increased risk of cardiovascular events and all-cause mortality
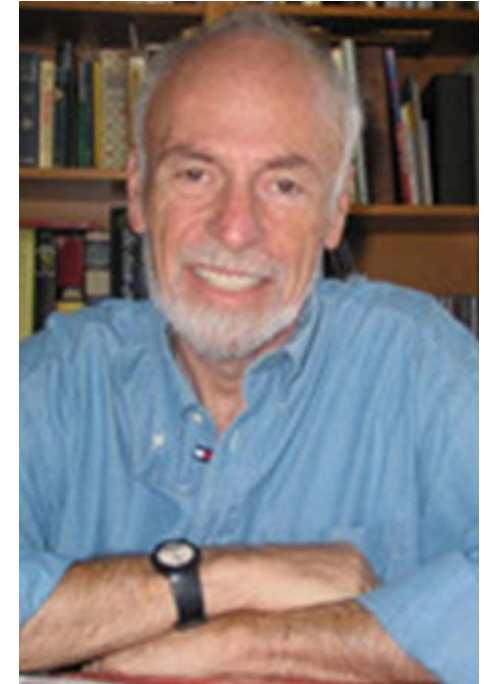
Conclusions

- ## Role of surrogate endpoints
  - Advancing our understanding of disease
  - Identifying novel therapeutic targets
  - Indispensable in early phases of drug development
  - Not for drug approval ... some exceptions

- ## In clinical practice
  - Evaluate using critical appraisal framework

Skating on thin ice