Role and Potential of Surrogate Outcomes

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Surrogate Response Variables

- **Laboratory measurement used as alternative or substitute for desired or ideal clinically relevant response (i.e. live longer or feel better)**

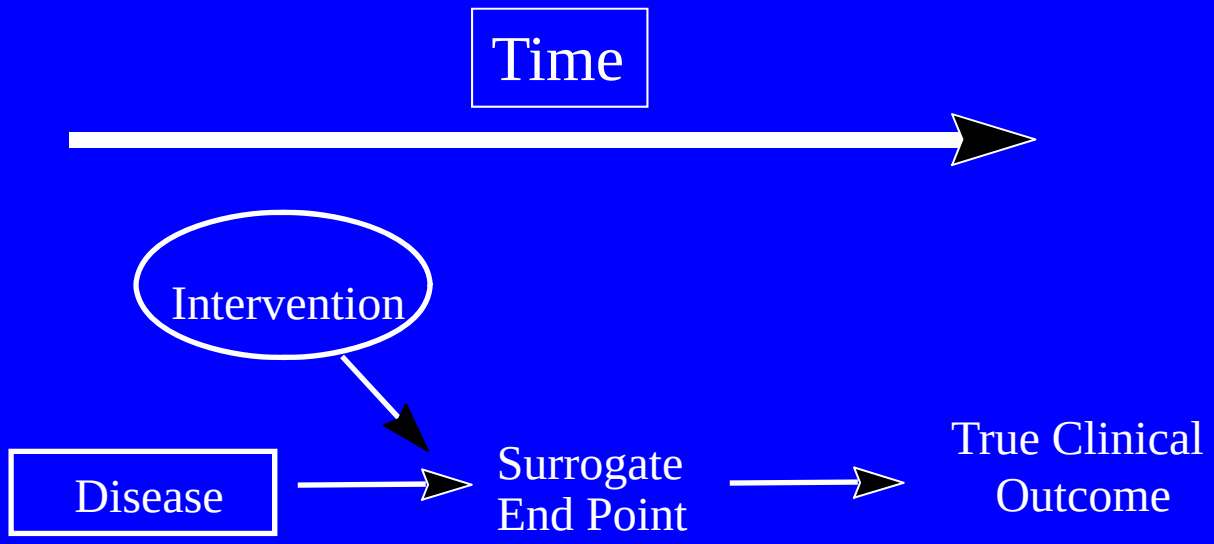
- **Advantages**
  - Smaller sample size
  - Shorter follow-up
  - Easier
  - Cheaper

Validity of Surrogate Outcome Measures

- Surrogate must be predictive of clinical outcome
- All effects of intervention on clinical outcome must be captured by the surrogate
- Implies that biological mechanism and pathway of action is known

Surrogate Response Variables

- **Requirements (Prentice, 1989)**
  T = True clinical endpoint
  S = Surrogate
  Z = Treatment
- **H_0: P(T|Z) = P(T |S,Z) P(S|Z) = P(S)**
- **Sufficient Conditions**
  1. S fully captures effect of Z on T
     P(T|S,Z) = P(T|S)
  2. S is informative about T
     P(T|S) = P(T)



The setting that provides the greatest potential for the surrogate endpoint to be valid. Reprinted from *Ann Intern Med* 1996; 125:605-13.

Reasons for failure of surrogate end points:

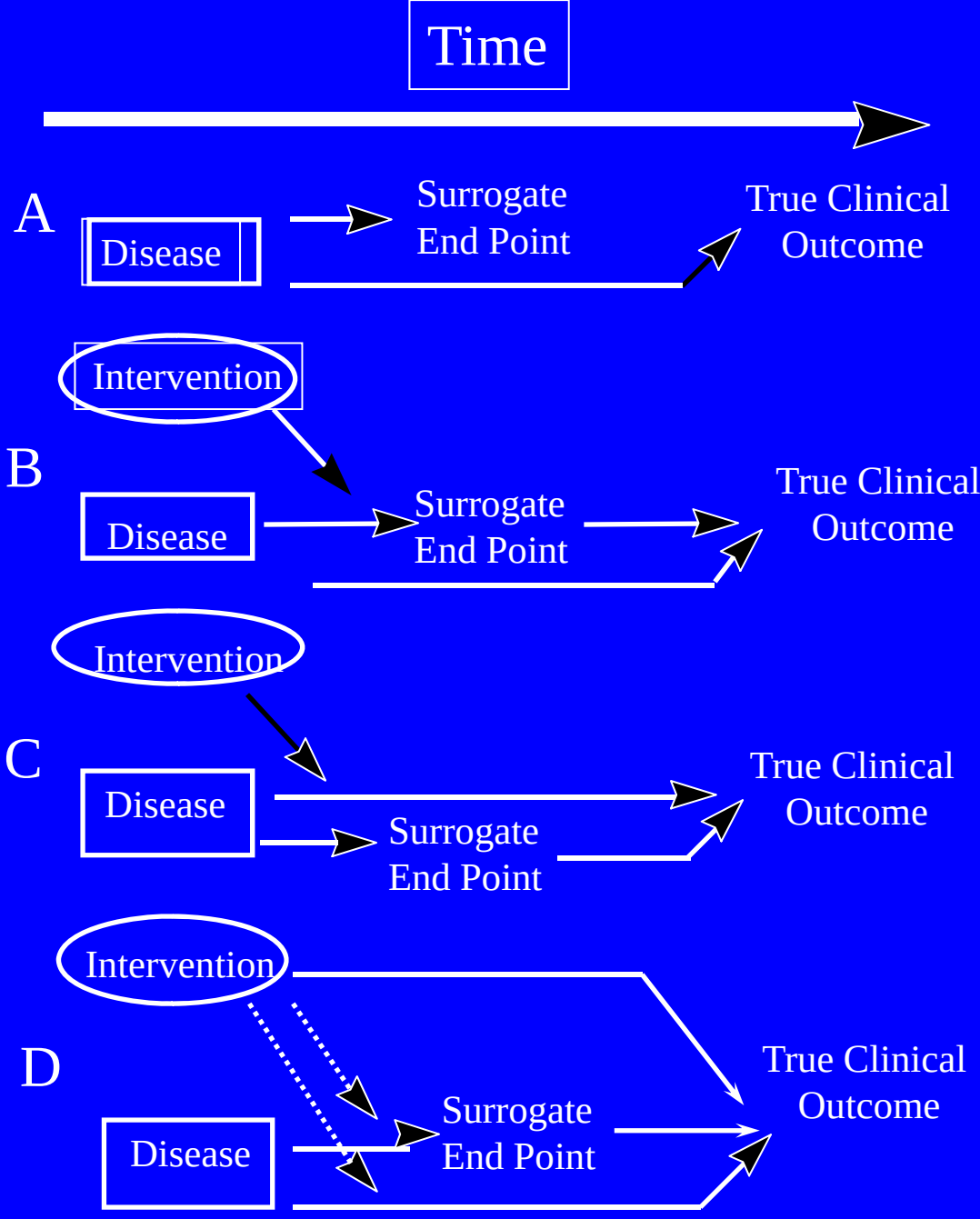
A. The surrogate is not in the causal pathway of the disease process.

B. Of several causal pathways of disease, the intervention affects only the pathway mediated
through the surrogate.

C. The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect.

D. The intervention has mechanisms for action independent of the disease process.

Dotted lines = mechanisms of action that might exist.



Concerns About Surrogates

1. Relationship between surrogate and true endpoint may not be causal, but coincidental to a third factor

2. Other unfavorable effects of the drug, drug, device, procedure or nutritional intervention

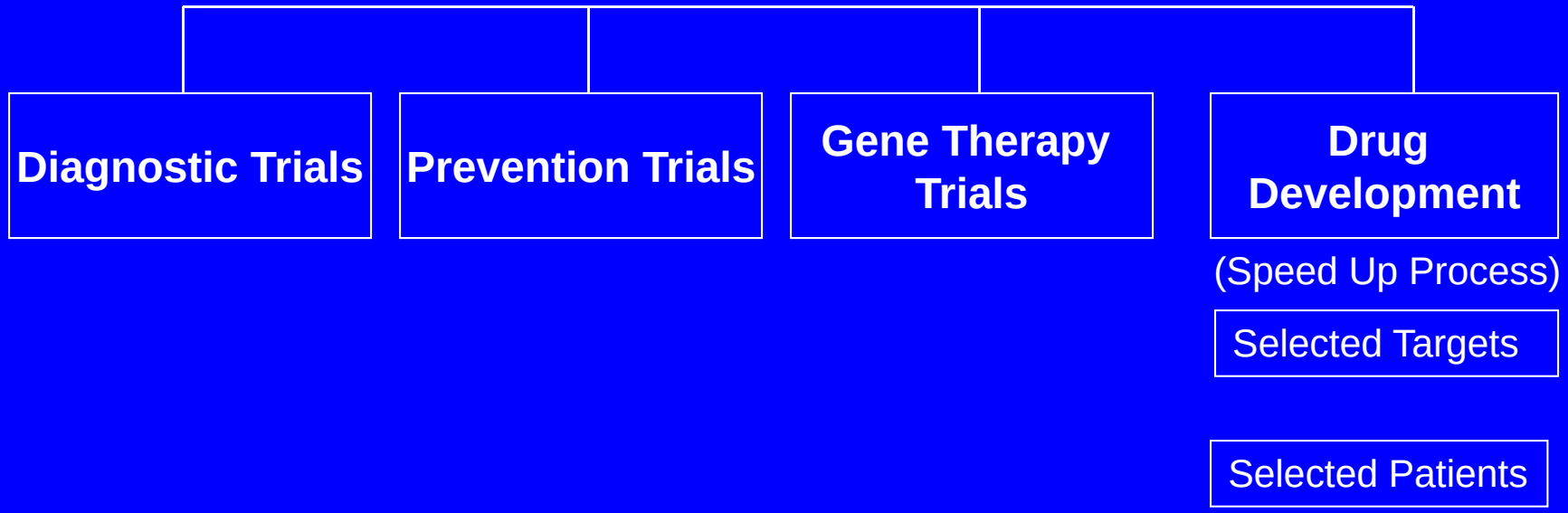
3. Effect on surrogate may correlate with one clinical endpoint, but not others

Surrogates Can Be Useful

- **Phase I Trials**
  - **Maximum Dose**
- **Phase II Trials**
  - **Measures of Activity**
  - **Dose response**
- **Phase III Trials**
  - **Supporting Evidence/Secondary Outcomes**
    e.g., Cholesterol Changes

Surrogates To Evaluate New Frontiers?

Genomics



Francis Collins (3/2001)

Reliance on “surrogates” can be problematic

- Many examples where use of surrogates as a primary outcome has been misleading
- Includes variety of diseases
- If a surrogate is validated for one member of a class, it is valid for
  - Other members of the same class?
  - Another class?

Problematic Surrogate Use

- **Lower cholesterol** without evidence of survival benefit
- **Increase bone density** without evidence of decreased fractures in osteoporosis
- **Increase cardiac function** in CHF without improving survival
- **Decrease rates of arrhythmias** without evidence of improving survival
- **Lower blood sugar** without evidence about diabetic complications or survival

NOTT
(Nocturnal Oxygen Therapy Trial)

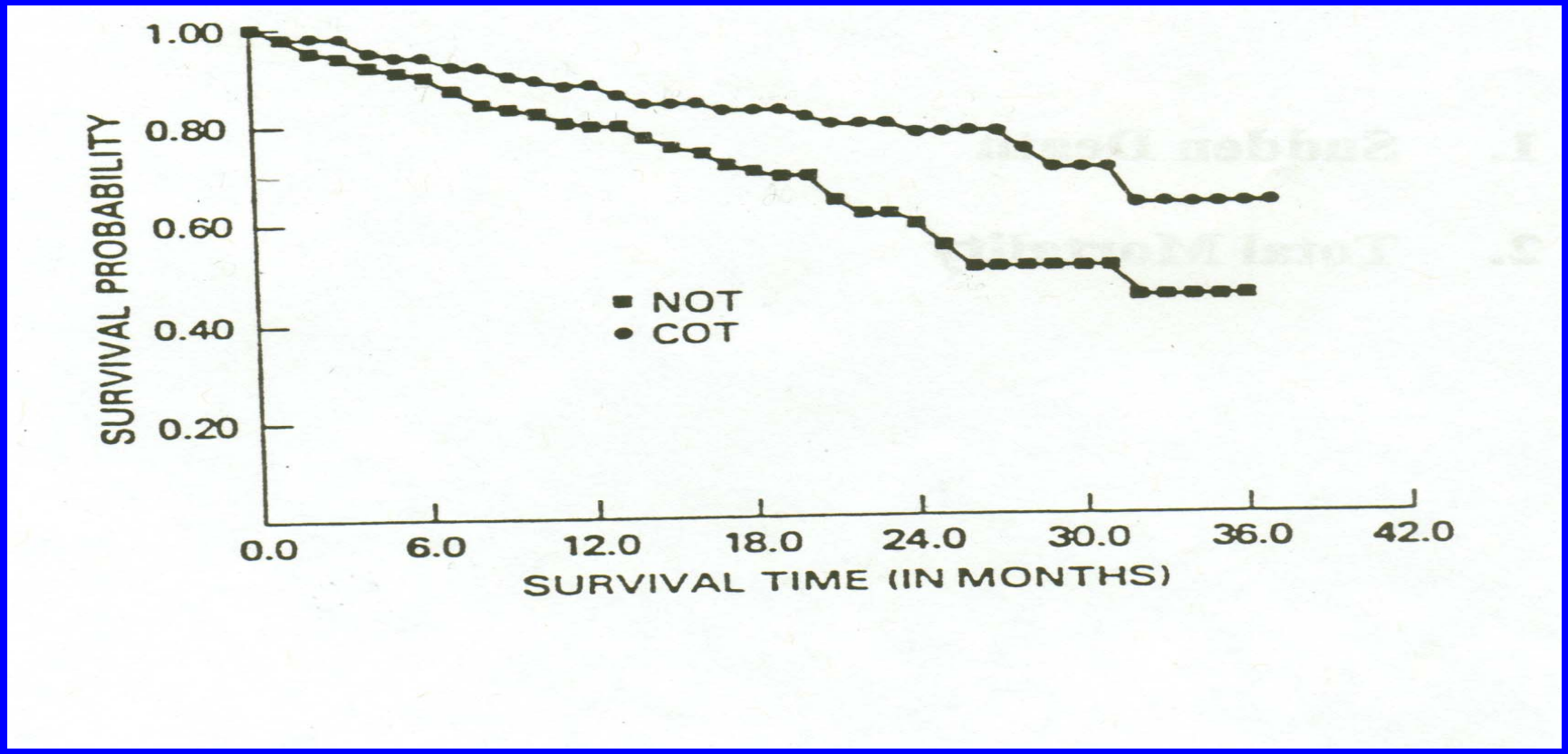
- **Hypothesis**
  Is continuous oxygen therapy better than nocturnal oxygen therapy in chronic obstructive lung disease patients?
  - **Surrogates, Neurological, Quality of Life**
  - **Survival?**
- **Design**
  - **203 Patients**
  - **Two-sided 0.05 Type I error**
  - **Randomized**
  - **Multicenter**
  - **Sequential data monitoring**

Possible NOTT Surrogates

- PaO_2
- Hematocrit
- FEV_1 % Predicted
- FVC % Predicted
- Maximum Workload
- Heart Rate
- Mean Pulmonary Artery Pressure
- Cardiac Index
- Pulmonary Vascular Resistance

The Nocturnal Oxygen Therapy Trial

NOTT Survival Experience for 102 Patients on Nocturnal Oxygen (NOT) and 101 Patients on Continuous Oxygen Therapy (COT)



CAST
(Cardiac Arrhythmia Suppression Trial)

- Arrhythmias are associated with sudden death
- Drugs developed to suppress arrhythmias
- Hypothesis: Does suppression of arrhythmia following an MI reduce incidence of:
    1. Sudden Death
    2. Total Mortality

Cardiac Arrhythmia Suppression Trial (CAST)

- Randomized Double Blind
- Three Drug Arms vs. Placebo
- Multicenter Study
- Group Sequential Data Monitoring
- One Sided boundary (0.025 Type I Error) for Benefit
- Advisory One Sided boundary (0.025) for Harm

CAST
Early Termination in 2 Drug Arms

	Drugs	Placebo
Sudden Death	33	9
Total Mortality	56	22

PROMISE

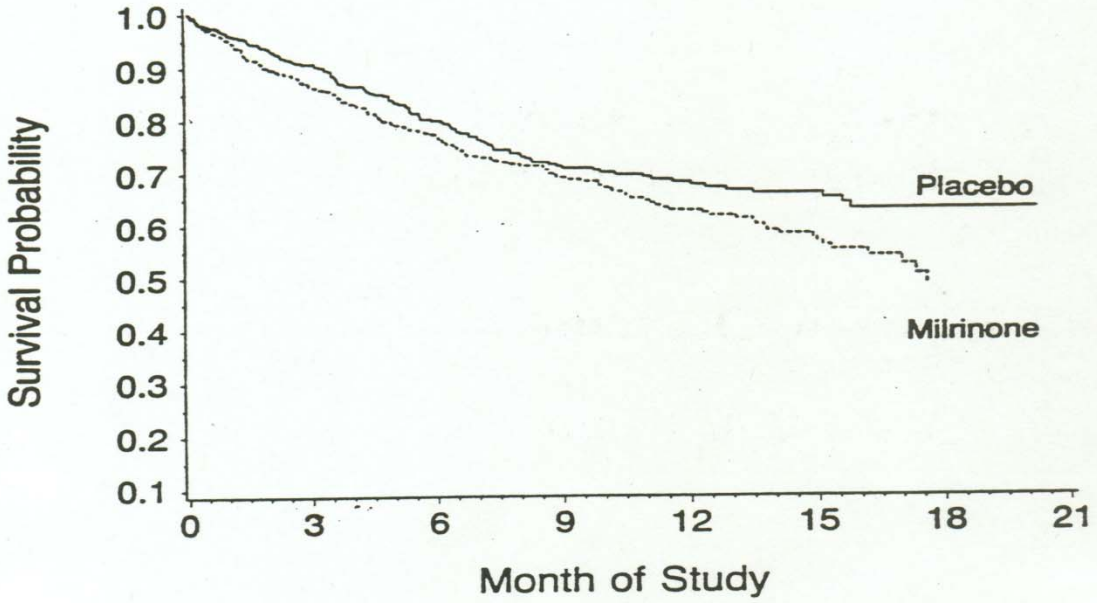
(Packer et al. NEJM, 1991)

- **Rationale**
  - **Patients with advanced (Class IV) congestive heart failure have 40% one year mortality**
  - **Milrinone enhances cardiac contractility**
  - **Milrinone improved cardiac output, exercise tolerance, and symptoms**
- **Hypothesis**
  Does milrinone increase survival in severe (Class III or IV) CHF patients?

PROMISE Design

- Randomized multicenter double-blind, placebo-control trial
- Patients with Class III or IV congestive heart failure for 3 months
- Two-sided 5% significance level, 90% power for 25% reduction in mortality
- 1088 patients entered
- Milrinone (10 mg/4 times per day) vs. matched placebo
- Standard therapy of digoxin, diuretics, and a converting enzyme inhibitor

PROMISE Mortality Results



Placebo	527	375	270	185	137	77	21
Milrinone	561	395	284	184	132	74	14

Figure 1. Kaplan–Meier Analysis Showing Cumulative Rates of Survival in Patients with Chronic Heart Failure Treated with Milrinone or Placebo.

Mortality was 28 percent higher in the milrinone group than in the placebo group ($P = 0.038$). The numbers of patients at risk are shown at the bottom of the figure.

Vesnarinone: Trial I

(Temple, 1995)

- An inotrope and vasodilator
- A 60 mg dose had no effect on exercise tolerance or symptoms
- A 120 mg dose increases exercise tolerance and reduces symptoms
- 120 mg arm stopped early with increased mortality (6 vs. 16, p < .01)
- 60 mg arm continued

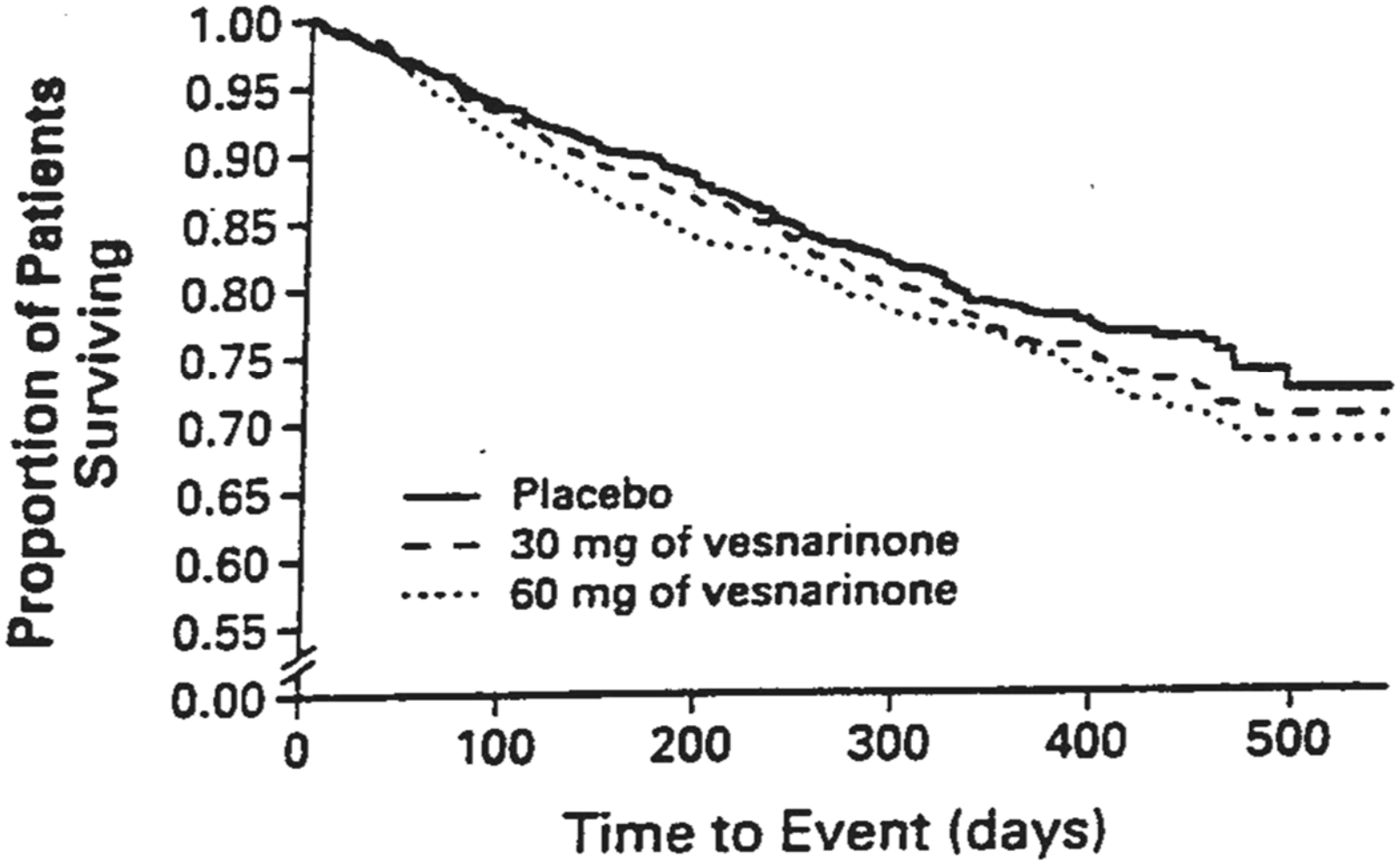
	Plbo	60 mg	P
Mortality	33/238	13/239	.002
Morality & Morbidity	50/238	26/239	.003

Trial II: VEST

(NEJM, 1998)

- Vesnarinone vs. Placebo
- 60mg vs. 30 mg vs. placebo
- NYHA Class III/IV CHF patients
- LVEF less than 30%
- 3833 patients randomized
- Primary Outcome: All cause mortality
- Secondary Outcome
  - Mortality plus CHF hospitalization
  - Quality of Life

VEST



NEJM, 1998

AIDS Clinical Trials

- **Clinical Outcomes**
  - **Death**
  - **Progression to AIDS**
  - **Progression to ARC**
- **Surrogate Outcome**
  - **CD4 Cell Count?**

CPCRA #002

(Community Program for Clinical Research in AIDS)

- **Comparative trial of ddI vs. ddC**
- **HIV infected patients; AZT intolerant**
- **Randomized open label**
- **467 patients**
- **Primary outcome**

  Time to AIDS or death
- **Secondary**

  Changes in CD4 cell count

Results

	ddI vs. ddC		p
Death RR = 0.76	100 (43%)	88 (35%)	0.070
Progression to AIDS or death	157 (93%)	152 (88%)	0.930
Change in CD4 cell count at 2 months	20 cells		0.009

Diabetes

- Diabetes affects several organ systems (heart, kidney, eyes)
- Long duration causes visual impairment (diabetic retinopathy)
- Clinical Outcome
  - Blindness
  - Severe visual loss
- Surrogate
  - Micro-aneurysm (retinal small vessel deformity filled with blood)

DCCT

(Diabetes Complication and Control Trial)

(*NEJM*, 1994)

- **Hypothesis**
  Does tight control of glucose reduce visual impairment compared to normal control?
- **Design**
  - Tight control achieved by intense monitoring of an insulin pump
  - Randomized multicenter trial
  - 1441 diabetic patients
  - Followed for average of 6 years

DCCT
(Diabetes Complication and Control Trial)

- **Results**
  - Early trends for microaneurysm were in negative direction
  - Longer term follow-up showed definite reduction in visual impairment and need for laser surgery

Osteoporosis

(Riggs et al. *NEJM*, 1990)

- **Bone loss in postmenopausal women leads to increase risk of fracture**
- **Sodium Fluoride stimulates bone formation and increases bone mass (double)**
- **Hypothesis: Will fluoride treatment decrease rate of vertebral fractures?**
- **Design**
  - Randomized, double-blind, placebo-controlled
  - 202 post menopausal women randomized
  - All received calcium supplementation

Osteoporosis Fluoride Trial Results

- **Fluoride increased bone density by**
  - 35% (p=0.0002) in spine
  - 12% (p=0.0002) in femoral neck
- **Vertebral fractures higher on Fluoride**

  (F 163, P 136, $p<0.05$)
- **Non-vertebral fractures higher on Fluoride**

  (72 vs 24; $p = 0.01$)
- **Fluoride concluded not effective as a treatment for post-menopausal osteoporosis**

Concluding Remarks on Surrogates

- Surrogates play an important role in Phase I, II, and Pilot Phase III studies.
- Results for Phase III very mixed
- Treatments may affect more than one mechanism.
- "Surrogates" do not reliably predict treatment effect on clinical outcome.
- Success for one drug in a class does not guarantee success for the next drug in same class
- Success in one class does not guarantee the next
- Reliance on "surrogates" should be minimized.