

Biomarkers and Surrogate Endpoints in Clinical Trials

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- * IOM, 2010. *“Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease:.”* Washington DC. National Academies Press
- * Fleming TR, Powers JH: Biomarkers and Surrogate Endpoints in Clinical Trials *Statistics in Medicine* 2012; 31: 2973-2984.

Lecture Objectives

- ~ Recognize strong correlation of a biomarker (replacement) endpoint with a direct measure of how a patient feels, functions or survives doesn't justify a conclusion that treatment effect on biomarker status reliably predicts treatment effect on the direct measure of how a patient feels, functions or survives.
- ~ Explain the integral importance, to the rigorous validation of a biomarker as a replacement (or surrogate) endpoint, of:
 - An in depth clinical understanding of
 - ✓ the causal pathways of the disease process; and
 - ✓ intervention's intended & *unintended* mechanisms of action;
 - Meta-analyses of clinical trials showing the relationship between:
 - ✓ the *net* effect of treatment on the biomarker, and
 - ✓ the *net* effect of treatment on direct measures of how a patient feels, functions and survives

Issues in Replacement (Surrogate) Endpoints

- ~ **Criteria for Choosing Endpoints**
- ~ *“A Correlate does not a Surrogate Make”*
- ~ **Validation of Replacement (Surrogate) Endpoints**

Some Characteristics for Study Endpoints in Phase 3 Clinical Trials

- Consistently & readily measurable
- Sensitive
- Well defined & reliable
- Clinically meaningful

Invasive Procedures:

E.g., Liver Biopsy in PBC
RHC in pediatric PAH

A “*Clinically Meaningful Endpoint*”:

...a direct measure of how a patient

“*feels, functions or survives*” ...

... Robert Temple, FDA

Biomarkers & 'Feels, Functions, Survives' Endpoints

- **Biological Activity:** Hemodynamic Measures in PAH:
PVRI, mPAP, CO
- **Clinical Meaningful Benefit** *SBP, DBP, NT-proBNP*
 - ~ **Functions:** Ability to conduct normal activities
 - *Ability to walk, Ability to engage in recreational activities, Ability for self care, Risk of syncope*
 - *Time in hospital or missing school (overall, or cause specific)*
 - ~ **Feels:**
 - *Chest pain, breathlessness, fatigue, dizziness*
 - ~ **Survives**
 - ...*Physician or Observer administered & PROs...*

Potential ‘*Feels, Functions, Survives*’ Endpoints

Patient Reported Outcomes (PROs):

“Any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else”.

- * FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. (December , 2009)

Patient Reported Outcomes (PROs)

...Direct Measures of 'Feels', but with need to confirm:

Reliability, Sensitivity, Validity (Content, Construct, etc)
Clinical Relevance, Interpretability

Integrity, including need for:

blinded assessment & control of missing data...

...Mobilize disease specific interest groups,
before sponsors plan clinical trials...

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Biomarkers as Replacement Endpoints

“Biomarkers are measurements of biological processes. Biomarkers include physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images.

Cholesterol and blood sugar levels are biomarkers, as are blood pressure, enzyme levels, measurements of tumor size from MRI or CT, and the biochemical and genetic variations observed in age-related macular degeneration...”

IOM, 2010. “Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease”. Washington DC. National Academies Press.

Categorization of Nomenclature Outcome Assessments

Direct Measures of Patient "Functions, Feels, Survives"

Indirect Measures

Biomarkers

Measures depending on patient motivation or clinician judgment to perform the test

e.g. H_bA_{1c} , CD-4, PSA, PVRI, NT-proBNP, CO HR, Blood Pressure Pulm Arterial Pressure TIMI-III flow HDL, LDL, body temperature, urine GAG, urine KS cardiac rhythm, blood cultures, PCR, quantitative measures from radiology imaging.

Patient (symptoms: <i>chest pain, dyspnea, fatigue, dizziness</i>)	Clinician (PANNS for schizophrenia syndrome, Clinician Global Measures)	Observer (<i>seizures, infant behavior, stroke, death</i>)
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Patient (<i>rescue meds for pain, alcohol presentation test</i>)	Clinician (<i>TM bulging, Limb Spasticity, 6MWD, 3MSC PFTs, 9-hole peg test</i>)	Observer (<i>rescue meds for pain</i>)
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John Powers, Dave DeMets, Marc Walton, Laurie Burke, Bob Temple...

Biomarkers (as Replacement Endpoints)

... “*Post hoc, ergo, Propter hoc*” ...

Treatment effects on Biomarkers:

- Establish *Biological Activity*
- But not necessarily the net effects on
 - ~ How a patient feels
 - ~ The ability to conduct normal activities
 - ~ Overall Survival

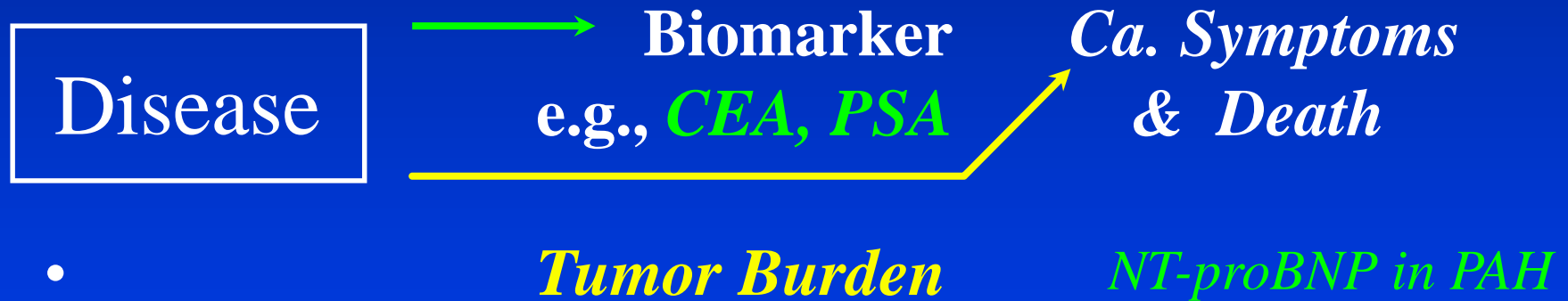
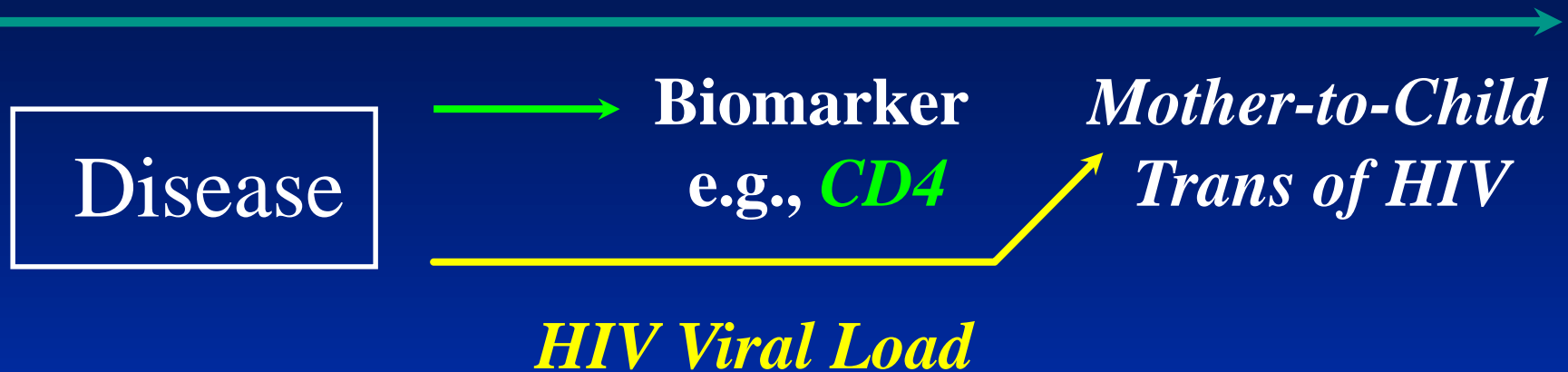
Issues in Replacement (Surrogate) Endpoints

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The Biomarker Endpoint is not in the Causal Pathway of Disease Process

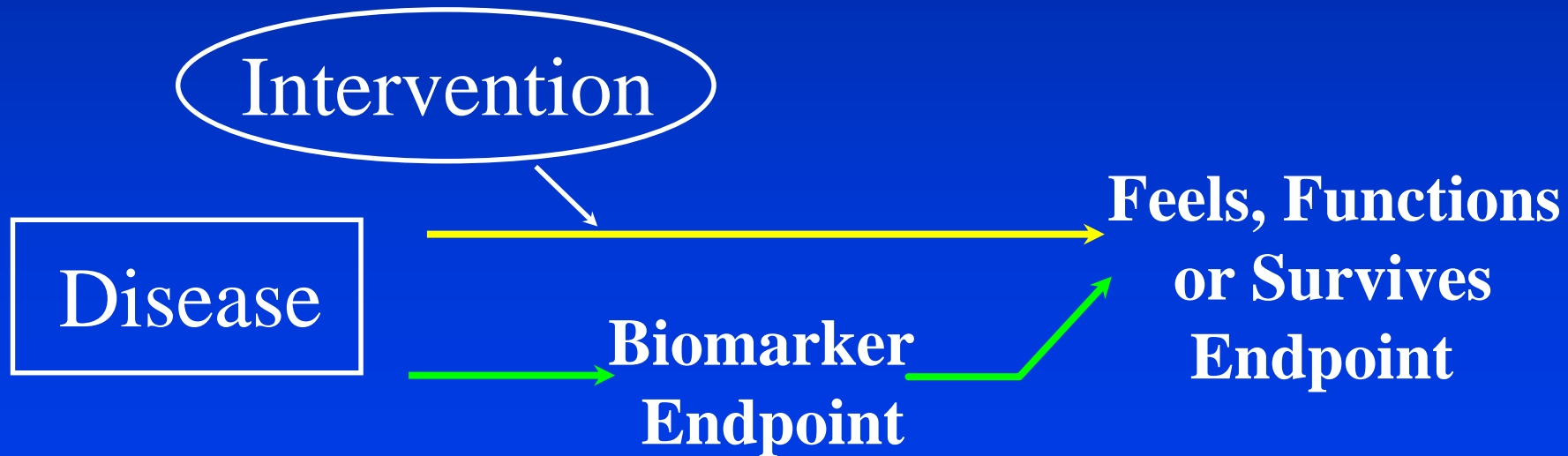
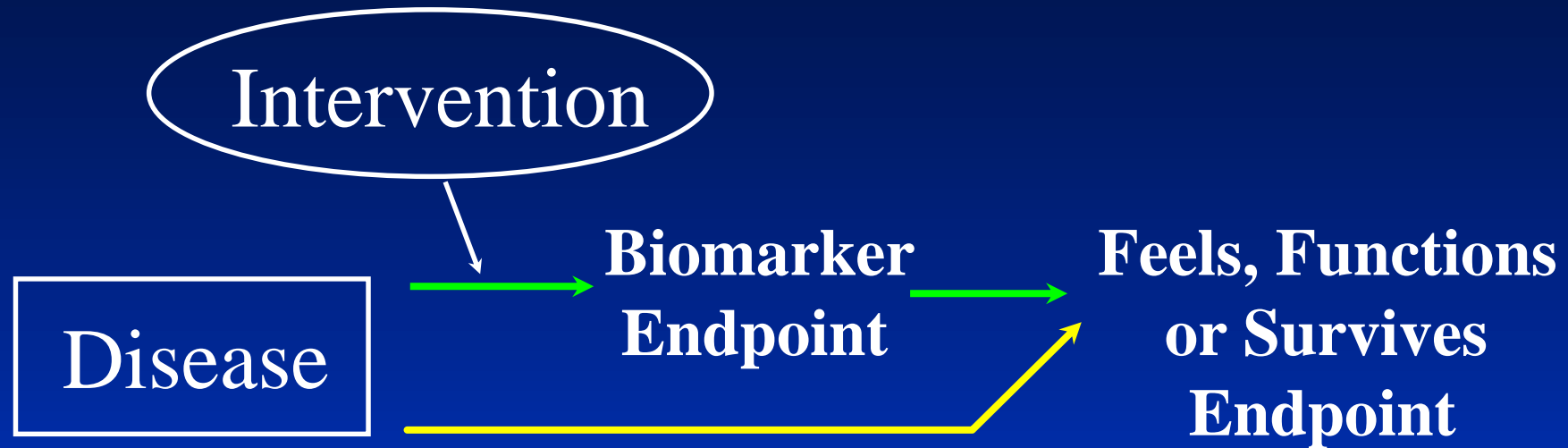


The Biomarker Endpoint is not in the Causal Pathway of the Disease Process.



-
- “Correlates”: Useful for Disease Diagnosis, or Assessing Prognosis
- “Valid Surrogates”: Replacement Endpoints

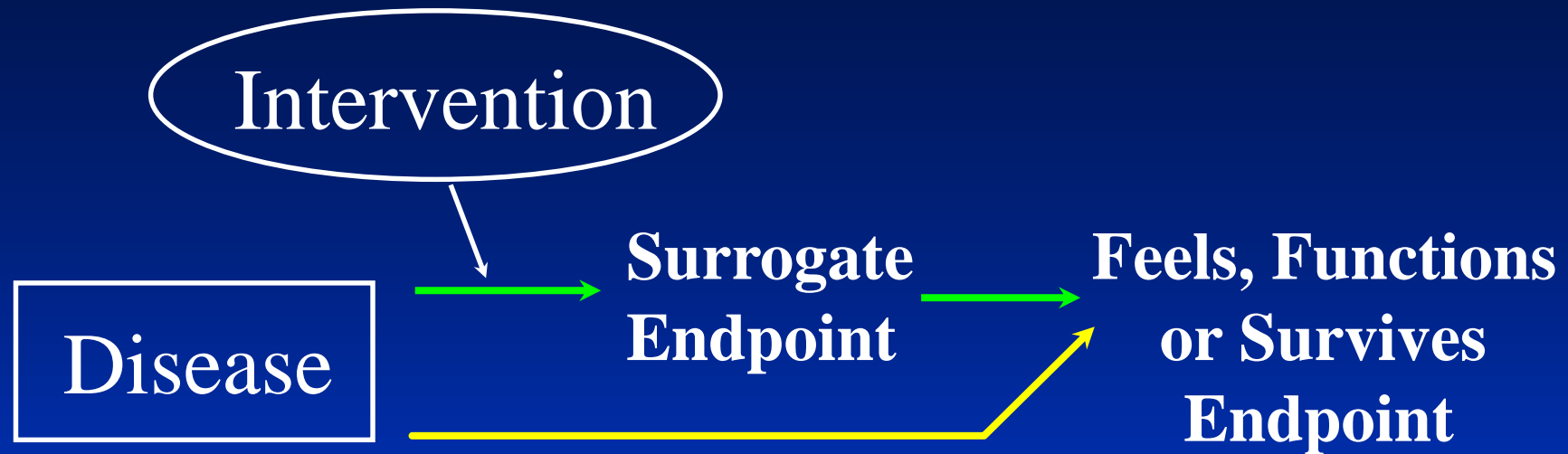
Multiple Pathways of the Disease Process



Biomarker (as a Surrogate) in Chronic Granulomatous Disease

- CGD → Recurrent Serious Infections
- Interferon γ ...Increase Bacterial Killing and Superoxide Production?
- International CGD Study Group Trial
Interferon γ :
 - 70% Reduction in Recurrent Serious Infections
 - Essentially No Effect on Biological Markers

Multiple Pathways of the Disease Process



Biomarkers in Acellular Pertussis Vaccines

(Sweden I Trial with DT control: 10,000 subjects)

- **Vaccine Efficacy**

	<u>VE</u>	<u>95% CI</u>
SKB	58%	(51%, 66%)
Aventis Pasteur	85%	(81%, 89%)

- **Biomarkers**

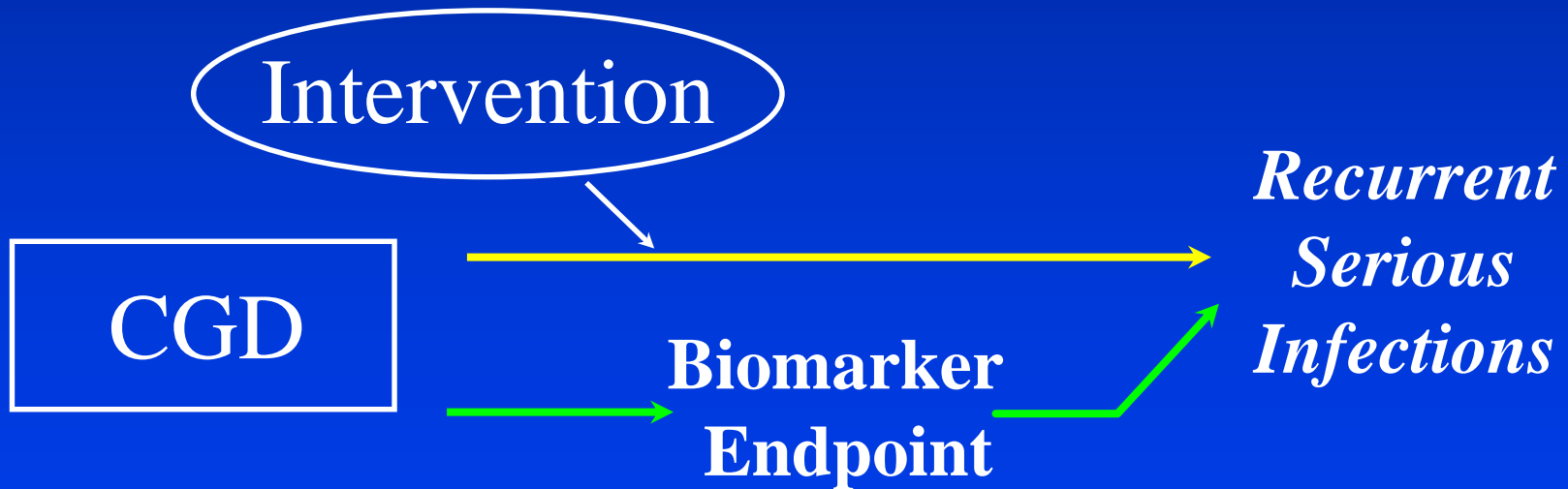
Filamentous Haemagglutinin (FHA)
and Pertussis Toxoid (PT) antibody responses
were superior with the SKB vaccine

Multiple Pathways of the Disease Process



- Other Immune Responses, including those resulting from additional antigens in the vaccines:
 - ~ Pertactin
 - ~ Fimbriae (types 2 and 3)
- **Durability of effect**

Multiple Pathways of the Disease Process



Interventions having Mechanisms of Action Independent of the Disease Process

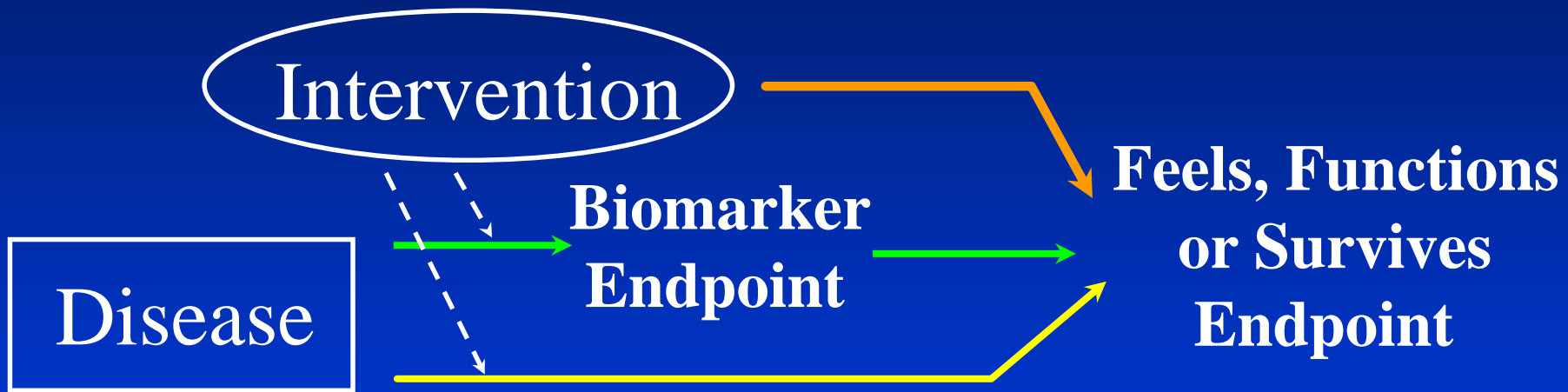


Illustration:

Ventricular Arrhythmia after M.I.

- Arrhythmia:
 - Risk factor for Sudden Death
- Antiarrhythmic Drugs:
 - Class IC antiarrhythmic agents
 - ...Strong Sodium-Channel Blockade

Illustration:

Ventricular Arrhythmia after M.I.

- Arrhythmia:
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Cardiac Arrhythmia Suppression Trial:

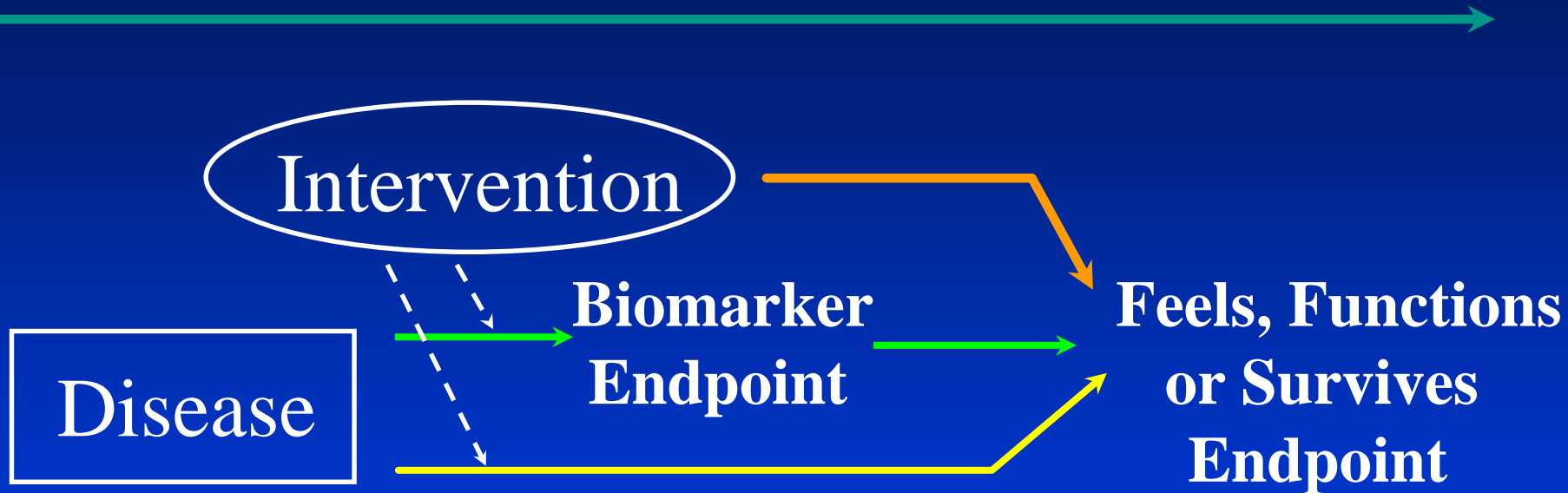
The drugs, relative to placebo,
TRIPLE the death rate.

Interventions having Mechanisms of Action Independent of the Disease Process



"Deadly Medicine" by Thomas Moore

Interventions having Mechanisms of Action Independent of the Disease Process



ESAs: ↑ **Thrombosis** ⇒ ↑ Mortality

Cox-2s, Muraglitazar, Rosiglitazone: ↑ **CV Risk Factors** ⇒ ↑ CV Death/ MI /Stroke

Troglitazone: ↑ **Serious Hepatic Risks** ⇒ ↑ Morbidity

Natalizumab: ↑ **Prog. Multifocal Leukoencephalopathy** ⇒ ↑ Morbidity / Mortality

Ezetimibe/Simvastatin: **Block pathways linked to CA prot.** ⇒ ↑ Cancer Mortality?

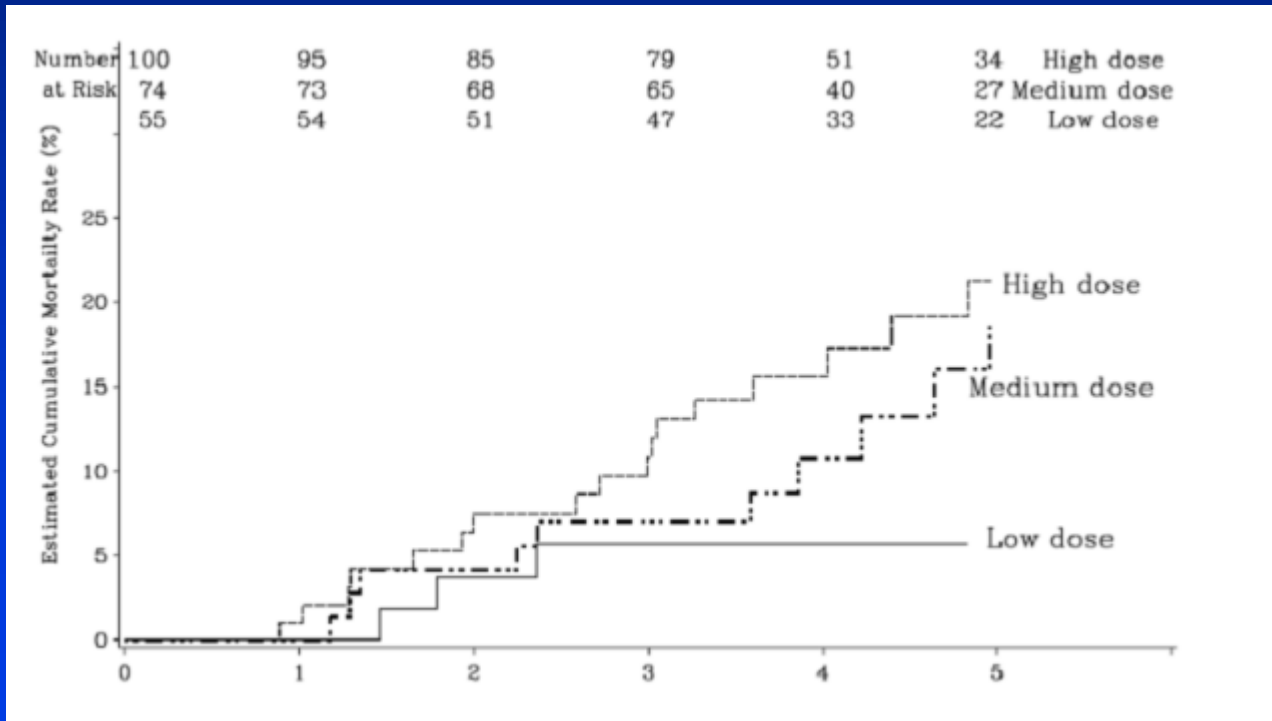
Long Acting β -Agonists: ↑ Asthma-related deaths

Torcetrapib: **Activates renin angiotensin system** ⇒ ↑ **BP** ⇒ ↑ Mortality

Revatio in Pediatric PAH: ↑ doses ⇒ Improved hemodynamics yet ⇒ ↑ Mortality

“FDA Drug Safety Communication: FDA recommends against use of Revatio in children with pulmonary hypertension”

“Plot of mortality in the pediatric clinical trial
as a function of Revatio dose.”



“The hazard ratio for high dose compared to low dose was 3.5 ($p=0.015$)”

Issues in Replacement (Surrogate) Endpoints

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Replacement (Surrogate) Endpoints**

End Stage Renal Disease

R

Standard Dose ESA* \Rightarrow Hematocrit 30%

High Dose ESA* \Rightarrow Hematocrit 42%

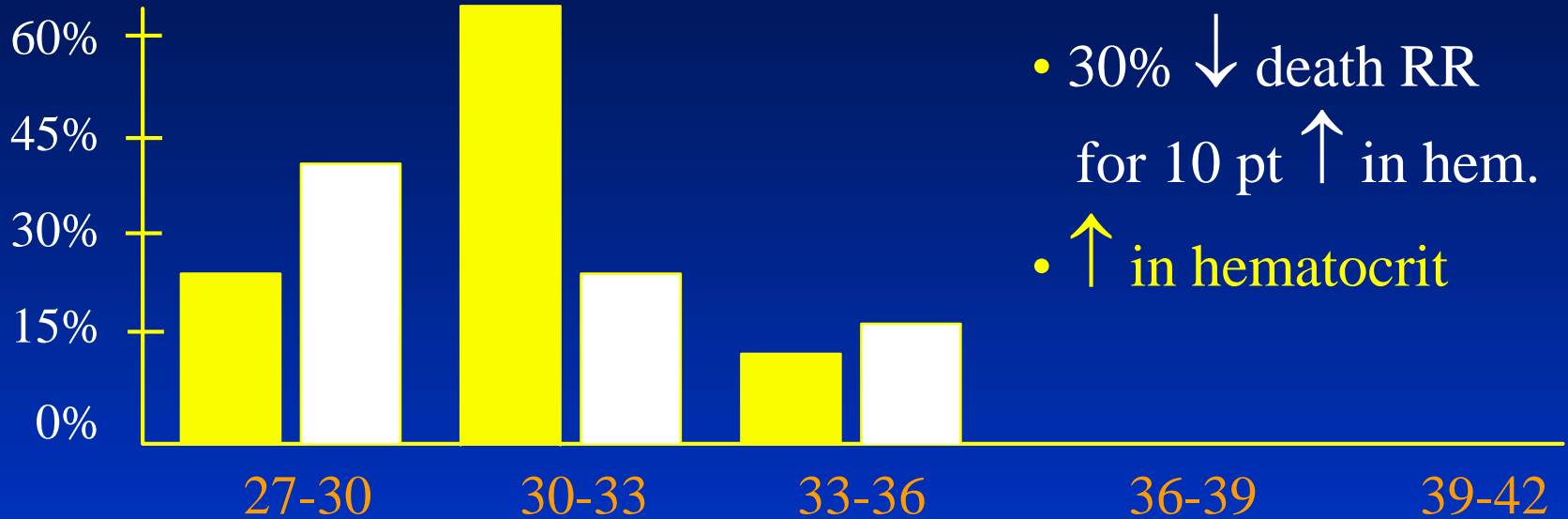
Goal: Normalize Hematocrit Values

\Rightarrow reduce Death and MI

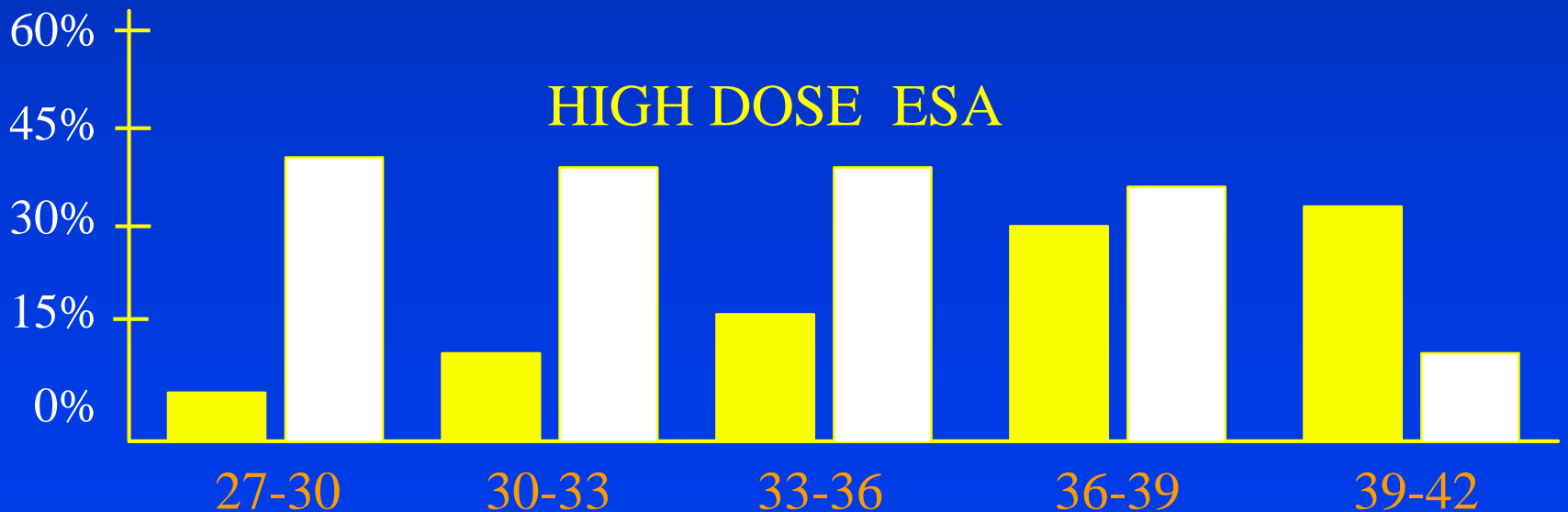
* Erythropoietin stimulating agent

Patient Distribution & Percent Deaths by Hematocrit %

STANDARD DOSE ESA

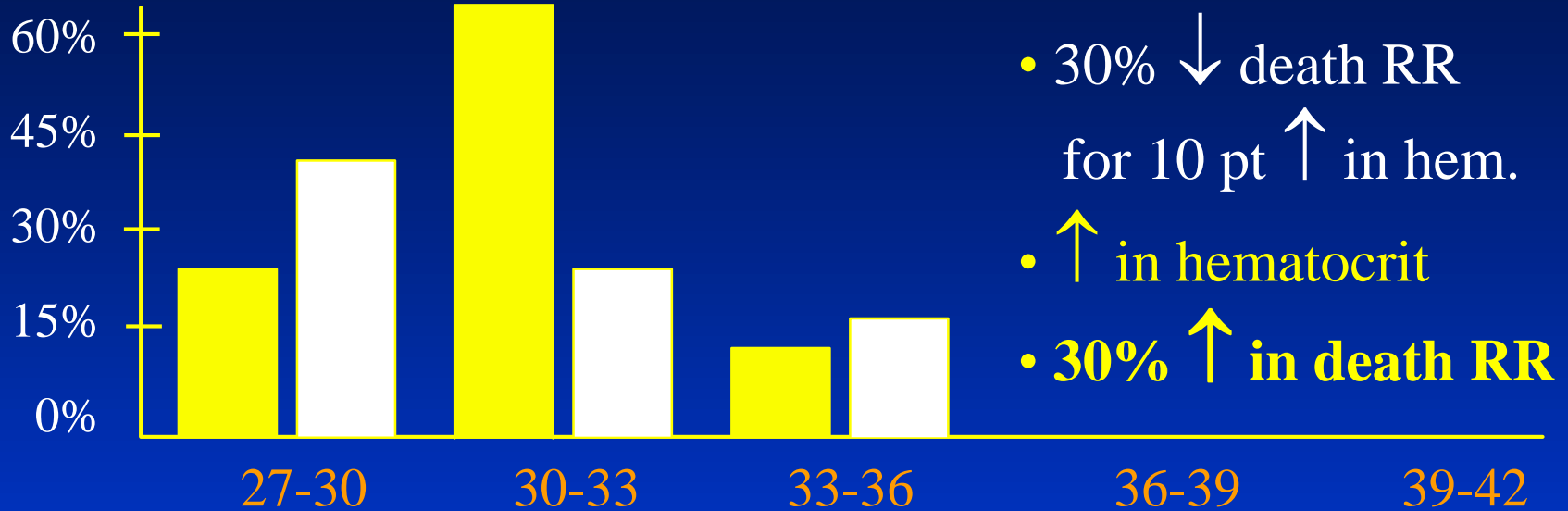


HIGH DOSE ESA

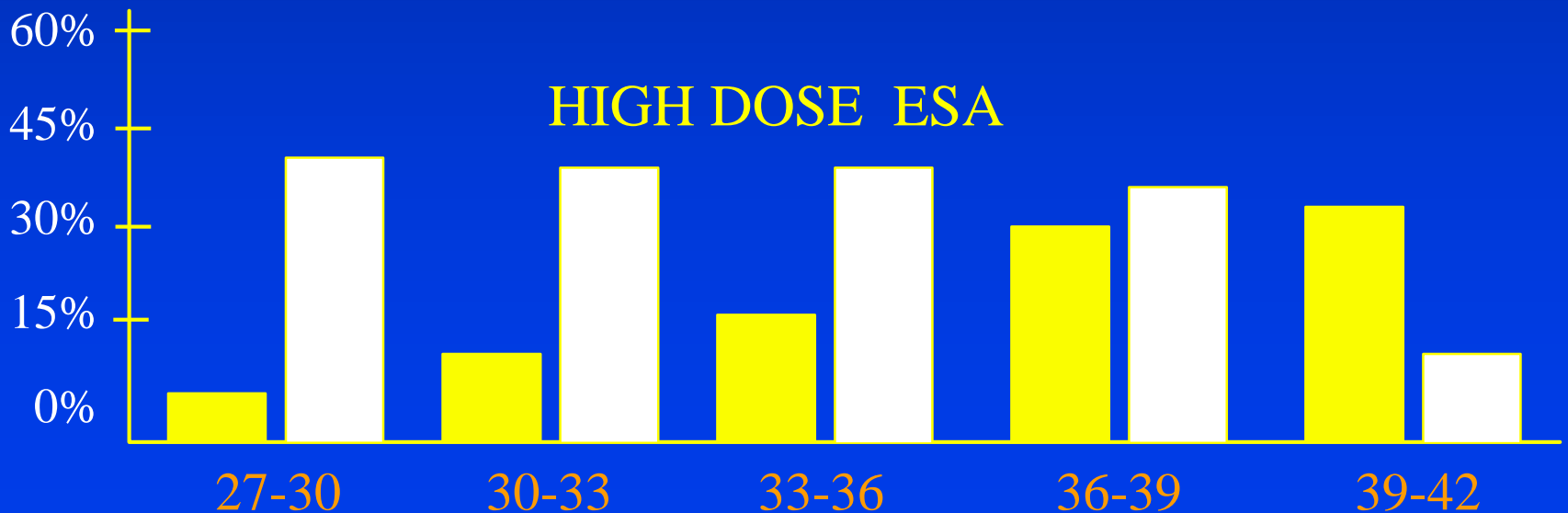


Patient Distribution & Percent Deaths by Hematocrit %

STANDARD DOSE ESA



HIGH DOSE ESA



End Stage Renal Disease



Results (Interim at 1/2 planned endpoints)

	<u>n</u>	<u>Death/MI</u>	<u>Death</u>
Standard Dose	615	164	160
High Dose	618	202	195

Death / MI relative risk: **1.30** (0.94, 1.79)

Besarab et al, NEJM 339:584-590, 1998:

“**↑ in incidence of thrombosis of vascular access sites**”

Validation of Replacement (Surrogate) Endpoints

Property of a Valid

Replacement (Surrogate) Endpoint:

- *Net effect of the Intervention on the Replacement (Surrogate) Endpoint*

reliably predicts the

Net effect of the Intervention on the 'Feels, Functions, or Survives' Endpoint

Using Replacement (Surrogate) Endpoints for Direct Measures of 'Feels, Functions, Survives'

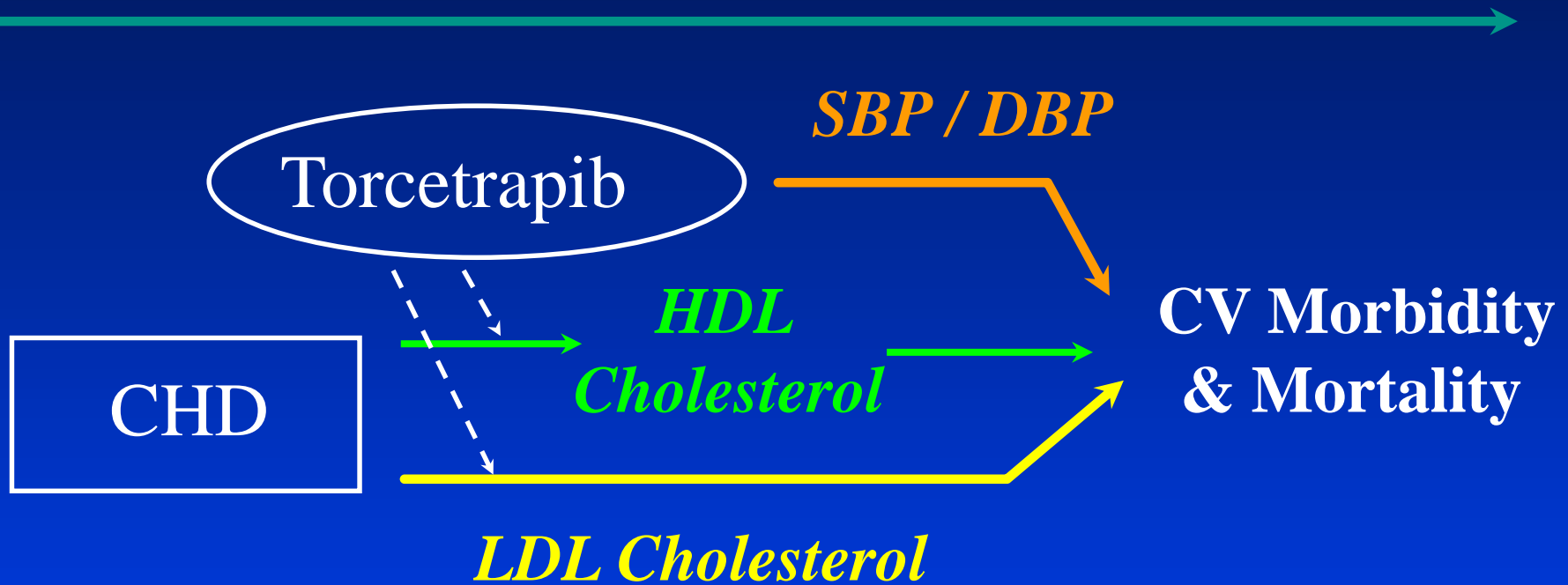
Clinical

- Comprehensive understanding of the
 - ~ Causal pathways of the disease process
 - ~ Intervention's intended and unintended mechanisms of action

Statistical

- Meta-analyses of clinical trials data

Mechanisms of Action of the Intervention & Causal Pathways of the Disease Process



Using Replacement (Surrogate) Endpoints for Direct Measures of 'Feels, Functions, Survives'

Clinical

- Comprehensive understanding of the
 - ~ Causal pathways of the disease process
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Illustration of Validating a Surrogate

➤ Anti-Hypertensives

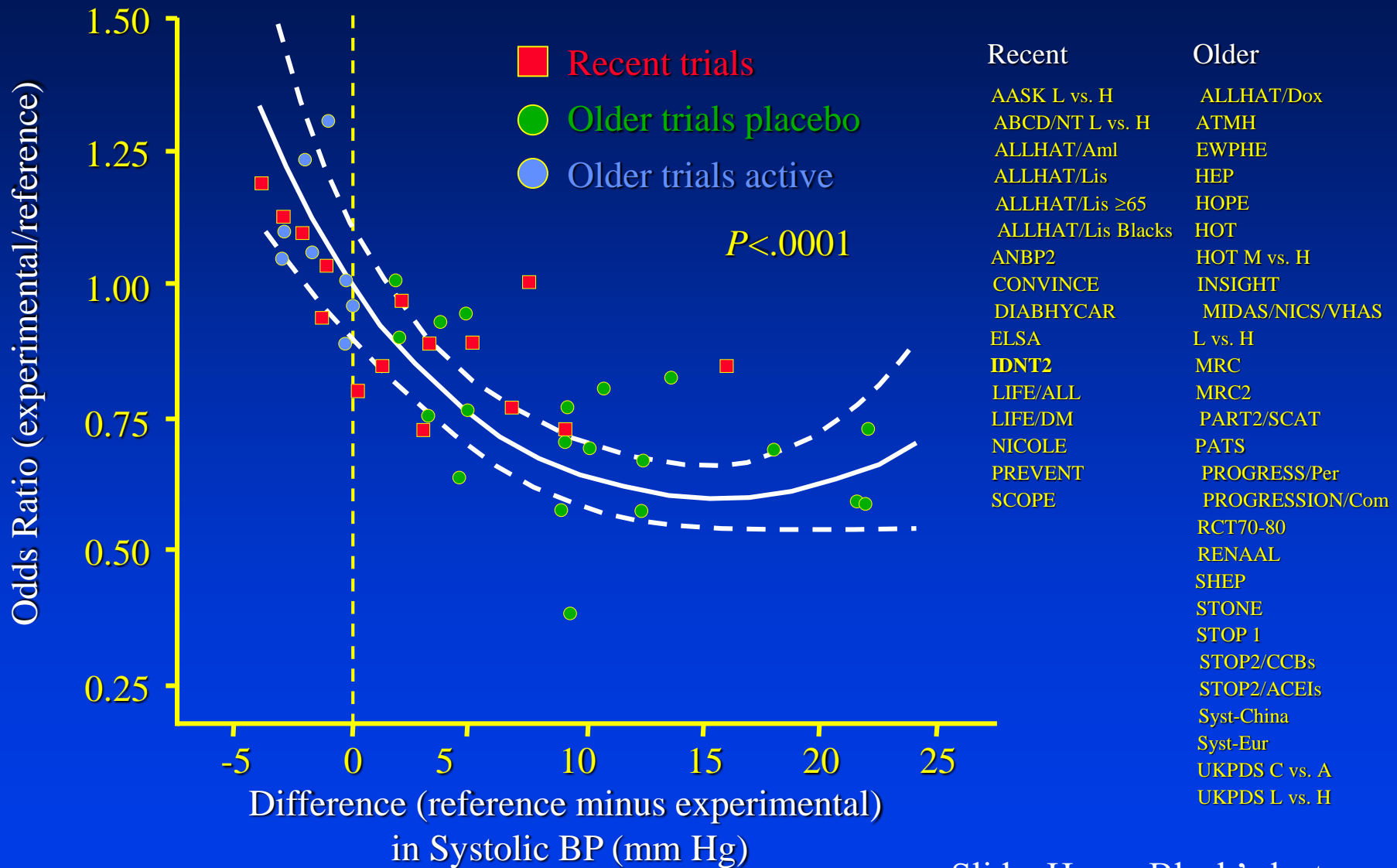
(>500,000 patients from rand trials)

... β -blockers, low dose diuretics, ACE-I, CCBs, ARBs...

FDA Cardio-Renal Advisory Committee: 6/15/2005

- Effects on *Blood Pressure* predicting effects on each of the following, considered individually:
 - ✓ *Stroke, MI, CVD, Mortality, Heart Failure*

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials



Staessen et al. *J Hypertens.* 2003;21:1055-1076.

Slide: Henry Black's lecture

Illustration of Validating a Surrogate

➤ Anti-Hypertensives

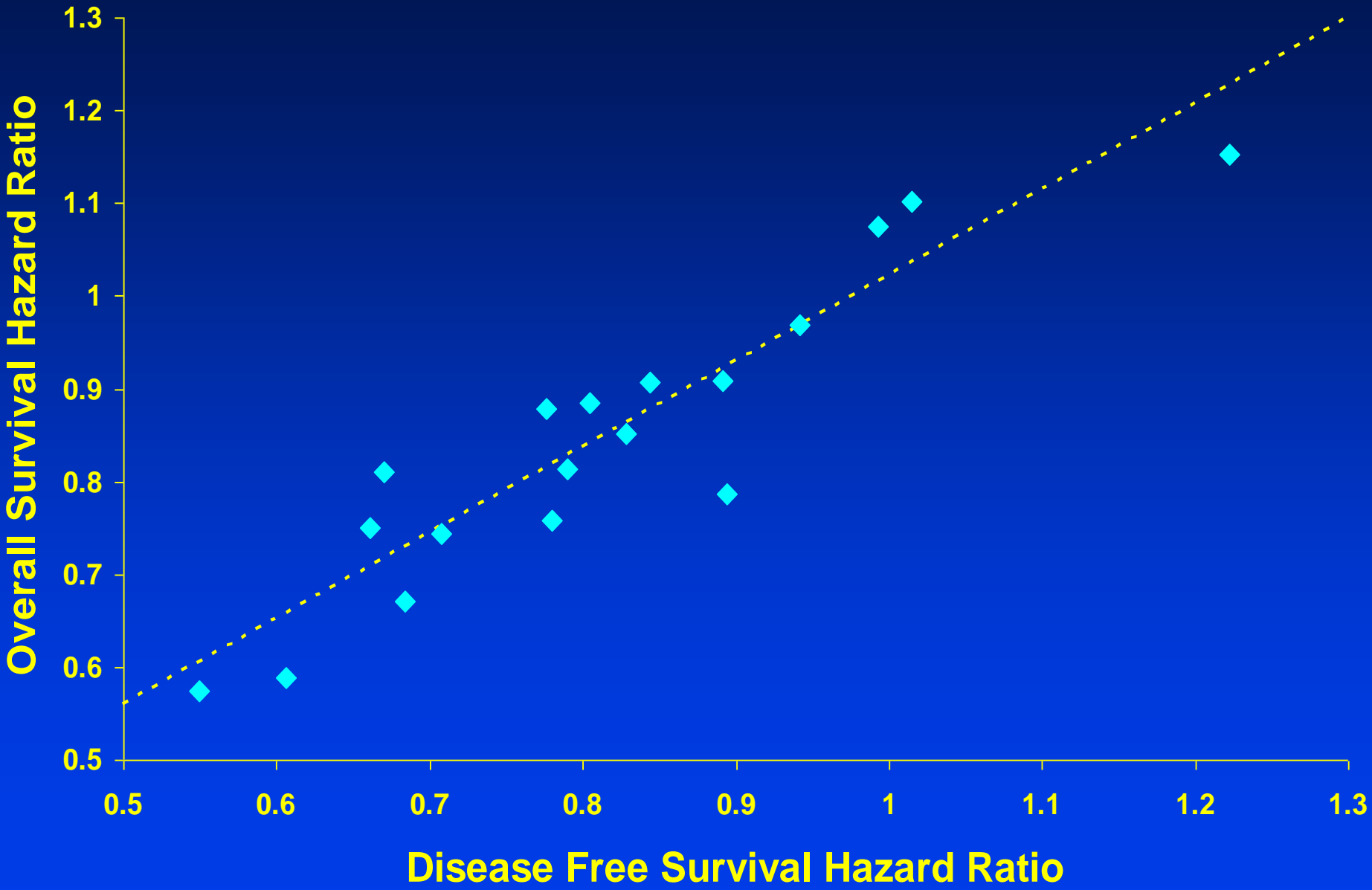
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Colon Adjuvant: Hazard Ratios for **DFS** vs. **Overall Survival**



Validation of Surrogate Endpoints

Illustration:

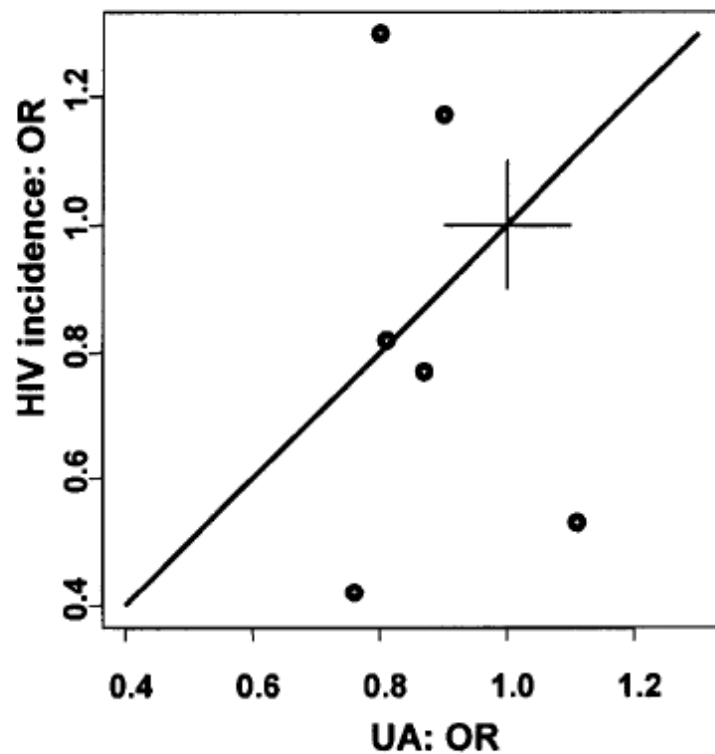
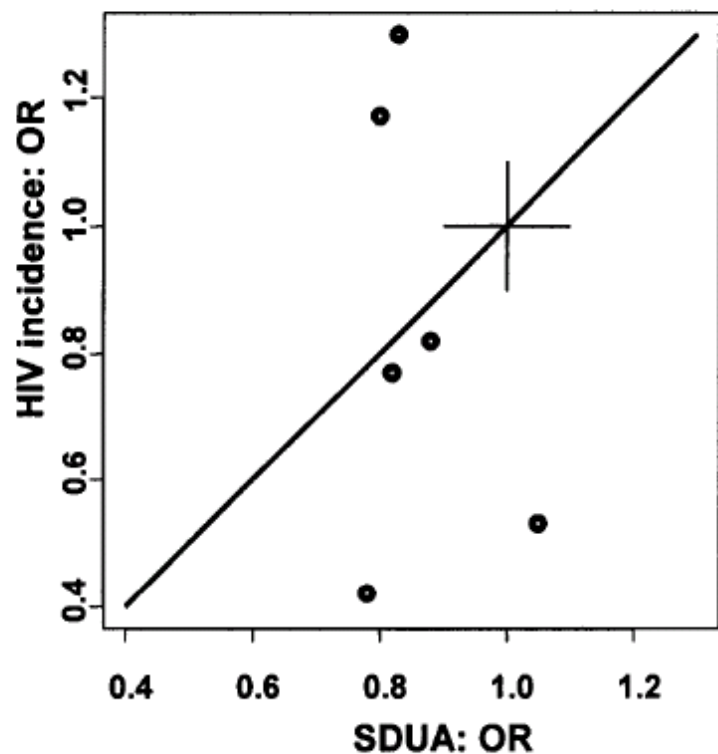
HPTN 015 Trial (EXPLORE)

- Clinical Endpoint
 - ~ HIV Infection
- Behavioral Surrogate Endpoints
 - ~ Serodiscordant Unprotected Anal
 - ~ Unprotected Anal

Enrollment by site

Site	N
Boston	729
Chicago	624
Denver	726
New York	737
San Francisco	736
Seattle	743
TOTAL	4295

Site-specific Intervention Effects: HIV vs. SDUA/UA



IOM, 2010 “Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease”

- *Addressing Assay Performance*
 - ...analysis of analytical performance of an assay...
e.g., limit of quantitation, across lab reproducibility, etc
- *Evidentiary Assessment*
 - ...relationship between biomarker & disease state
 - ...data regarding effects of interventions on both biomarker and clinically meaningful outcomes...
- *Justifying the Proposed Use*
 - ...determining whether available evidence provides sufficient justification for the context of use proposed...

Some Uses of Biomarkers

As “Correlates” ...

- Disease Diagnosis
- Assessing Prognosis
- In Patient-specific Therapeutic Strategies
- Primary Endpoints
in Screening or Proof of Concept Trials
- Measures of Biologic Activity
in Confirmatory (registrational) trials

Uses of Biological Markers: High Clinical Utility

- As Replacement or “Surrogate” Endpoints...
...When one can fully capture effects on the principle causal mechanism of disease process (w treatment lacking key unintended mech)
- In Identifying Enriched Populations...
...When the key mechanism(s) of Rx effect on the causal factor(s) of the disease process are specific to a targeted population (eg, gene) (w treatment possibly having unintended mech)
...EGFR Inhibitors: KRAS Wild Type vs. Mutation

Categorization of Nomenclature Outcome Assessments

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Indirect Measures

Biomarkers

Measures depending on patient motivation or clinician judgment to perform the test

e.g. H_bA_{1c} , CD-4, PSA, PVRI, NT-proBNP, CO HR, Blood Pressure Pulm Arterial Pressure TIMI-III flow HDL, LDL, body temperature, urine GAG, urine KS cardiac rhythm, blood cultures, PCR, quantitative measures from radiology imaging.

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John Powers, Dave DeMets, Marc Walton, Laurie Burke, Bob Temple...

Chest Pain
Dyspnea
Fatigue
Hospitalization
L.T., Death

6-MWD
3-MS
Exercise testing

PVRI
NT-proBNP
HR, BP
m-PAP



**Direct
Measures**



**Indirect Measures
Continuum
in PAH**

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Replacement Endpoints

- A replacement endpoint cannot be deemed to be a generic surrogate endpoint for a particular disease

Reasons why use needs setting-specific justification:

- Multiple causal pathways of the disease process
- *Magnitude* and *duration* of effect matters
- Intended and *unintended* effects of interventions

- How does evaluating replacement endpoints impact the public?

Response: Need “*reliable*” as well as “*timely*” evaluation
...not simply “*a choice*”; rather, “*an informed choice*”

Biomarkers & 'Feels, Functions, Survives' Endpoints

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Direct Measures of 'Feels, Functions, Survives' in PAH

- ~ Overall survival ~ 6MWD @ 48 wks ~ Syncope (freq. & severity)
- ~ NYHA Functional Class (1-2 vs. 3-4) ~ Clinician Global Measures
- ~ Level of successful social interaction with peers (mod. CAMPHOR)
- ~ Days school missed for health-related reasons; Everyday living skills
- ~ Symptoms: SF-36, Borg Dyspnea Score, Pain Measures

Composites of measures of 'Feels, Functions and Survives':

- ~ (E.g. Acute Coronary Syndrome: CV Death, Stroke, MI)
 - ✓ PAH: Death, L.T., PAH Hosp, (NYHA↑ & 6MWT↓)
- ~ (E.g. CABP: Cough, Pleuritic chest pain, Dyspnea, Sputum Prod)
 - ✓ PAH: Chest pain, Dyspnea, Fatigue, Dizziness/Syncope
....scored as Absent, Mild, Moderate, and Severe....

The endpoint: a) one-point improvement in at least two symptoms
& b) no worsening of any other symptoms, at day TBD

Principles & Insights

- * Fleming TR, DeMets DL: Surrogate endpoints in clinical trials: Are we being misled? *Annals of Internal Med* 1996; 125:605-613.
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Principles & Insights

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