Summer Institute in Statistics for Clinical Research

Biomarkers and Surrogate Endpoints in Clinical Trials

July 28, 2016

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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.

Challenge Questions

~ If an outcome measure, such as a biomarker, is expected to be
sensitive to differences between
the effects of the control regimen and the experimental regimen,
is this condition sufficient to justify its use
as the primary endpoint in a registration trial?
…Hemodynamics, 6MWD in Pediatric PAH…

~ If responders live longer than non-responders,
does this justify the conclusion that treatment effect on response rate
reliably predicts treatment effect on patient survival?

~ Similarly, if biomarker status is strongly correlated
with a direct measure of how a patient feels, functions or survives,
does this 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?

Challenge Questions

- For proper rigorous validation of a biomarker as a replacement (or surrogate) endpoint, are the following of integral importance?
  - 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?

- Is it feasible that a biomarker could be validated in the early phases of a clinical development plan, and then be used as a replacement (or surrogate) endpoint in the phase 3 trial that is designed to provide a reliable and interpretable assessment of efficacy?

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., Biopsy, RHC

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"

- Patient (symptoms: ***chest pain, dyspnea, fatigue, dizziness***)
- Clinician (*PANNS for* schizophrenia *syndrome,* ***Clinician Global Measures***)
- Observer (***seizures, infant behavior, stroke, death***)

Indirect Measures

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

- Patient (*rescue meds for pain, alcohol presentation test*)
- Clinician (*TM bulging, Limb Spasticity,* ***6MWD, 3MSC*** *PFTs, 9-hole peg test*)
- Observer (***rescue meds for pain)***

Biomarkers

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.*

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

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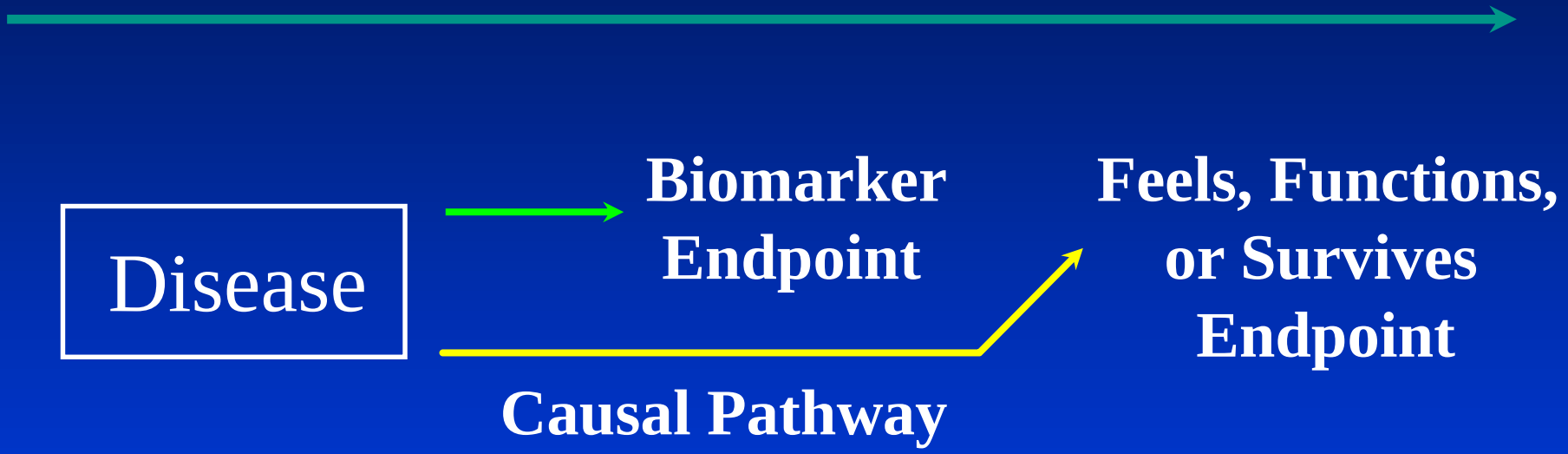
The Biomarker Endpoint is not in the Causal Pathway of Disease Process



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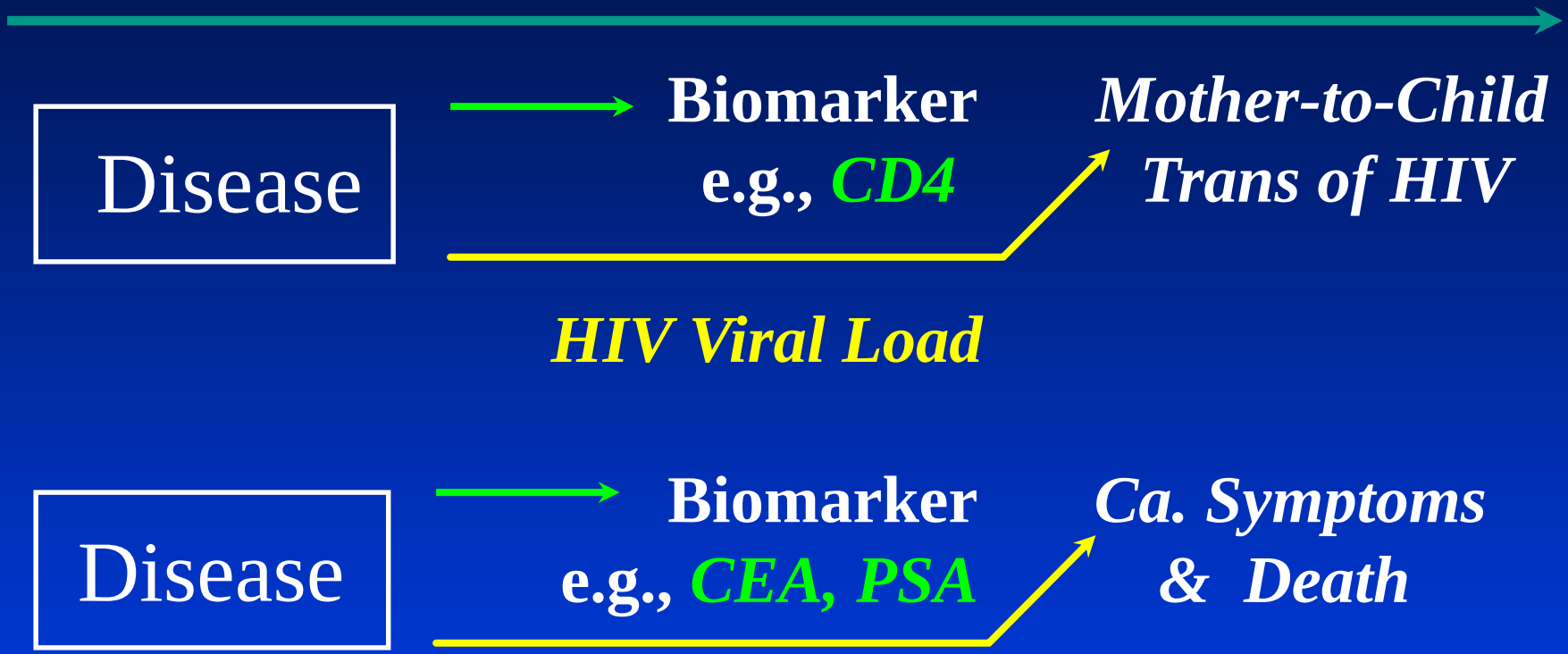
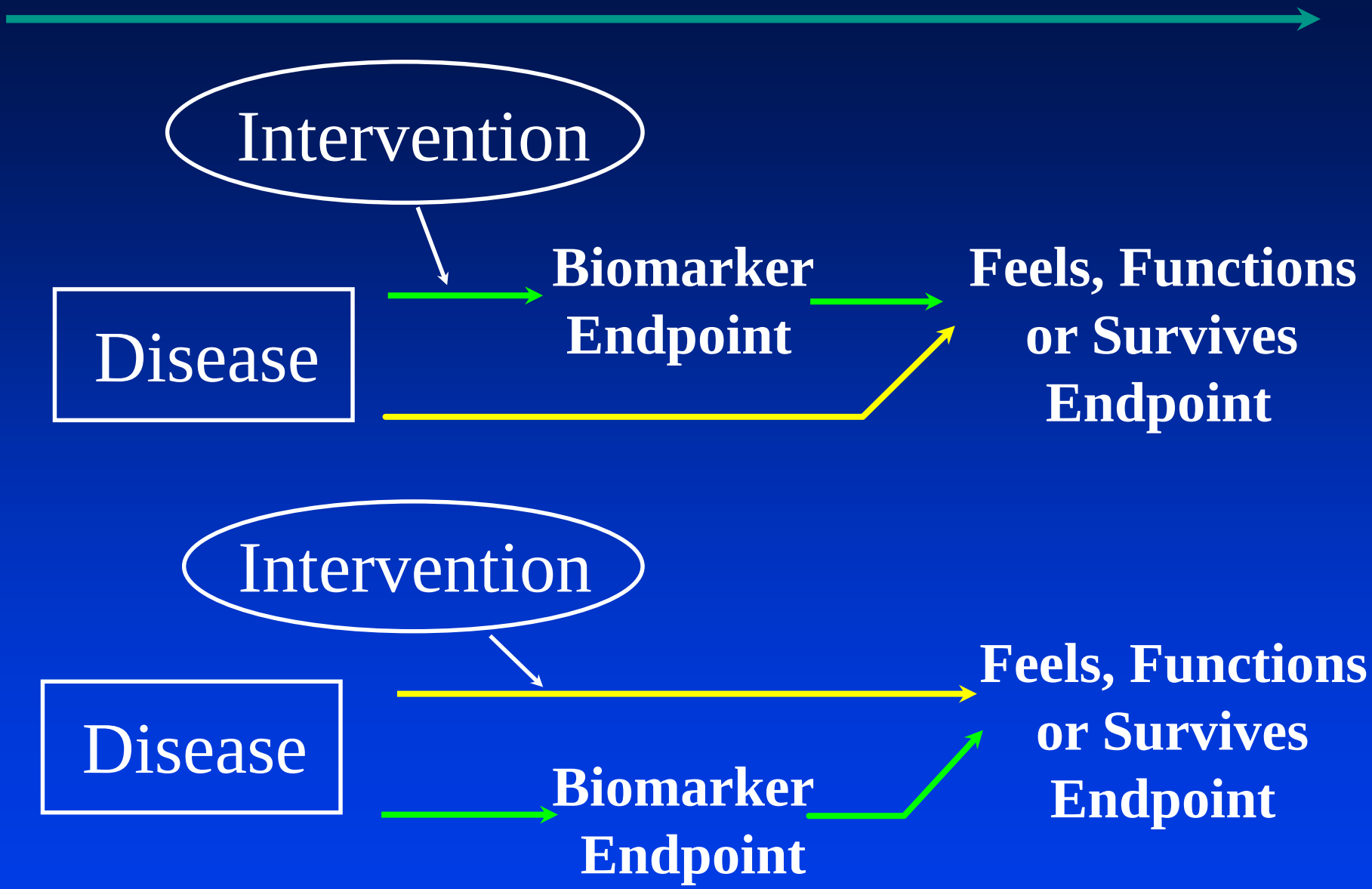


- *NT-proBNP in PAH*
- "Correlates": Useful for Disease Diagnosis, or Assessing Prognosis
- "Valid Surrogates": Replacement Endpoints

Multiple Pathways of the Disease Process

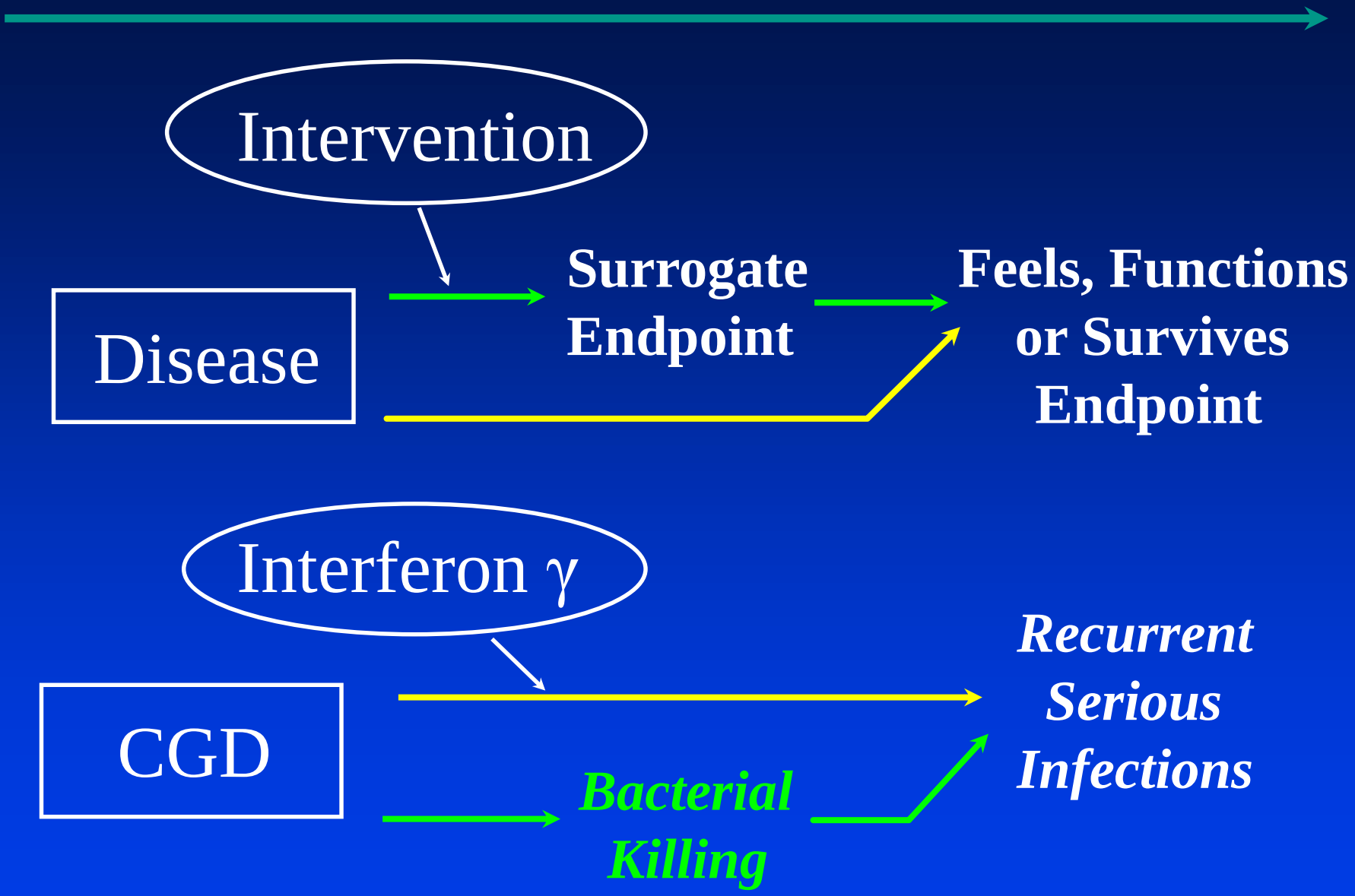


Biomarker (as a Surrogate) in Chronic Granulomatous Disease

- 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)

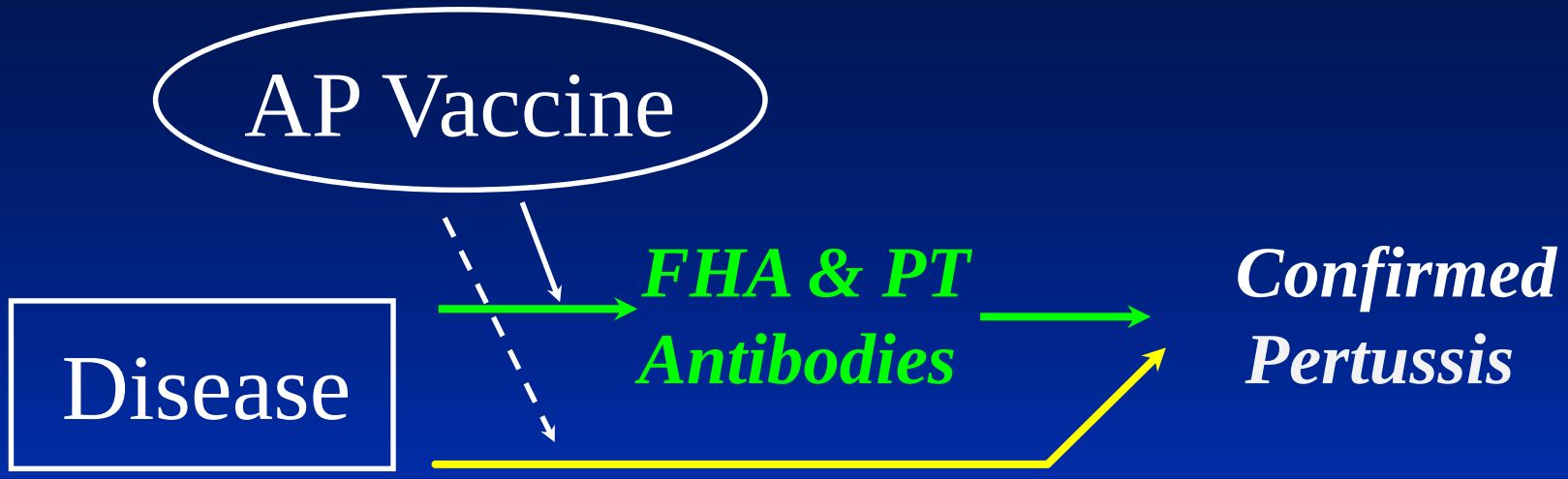
- **VE**

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

- **Biomarkers**

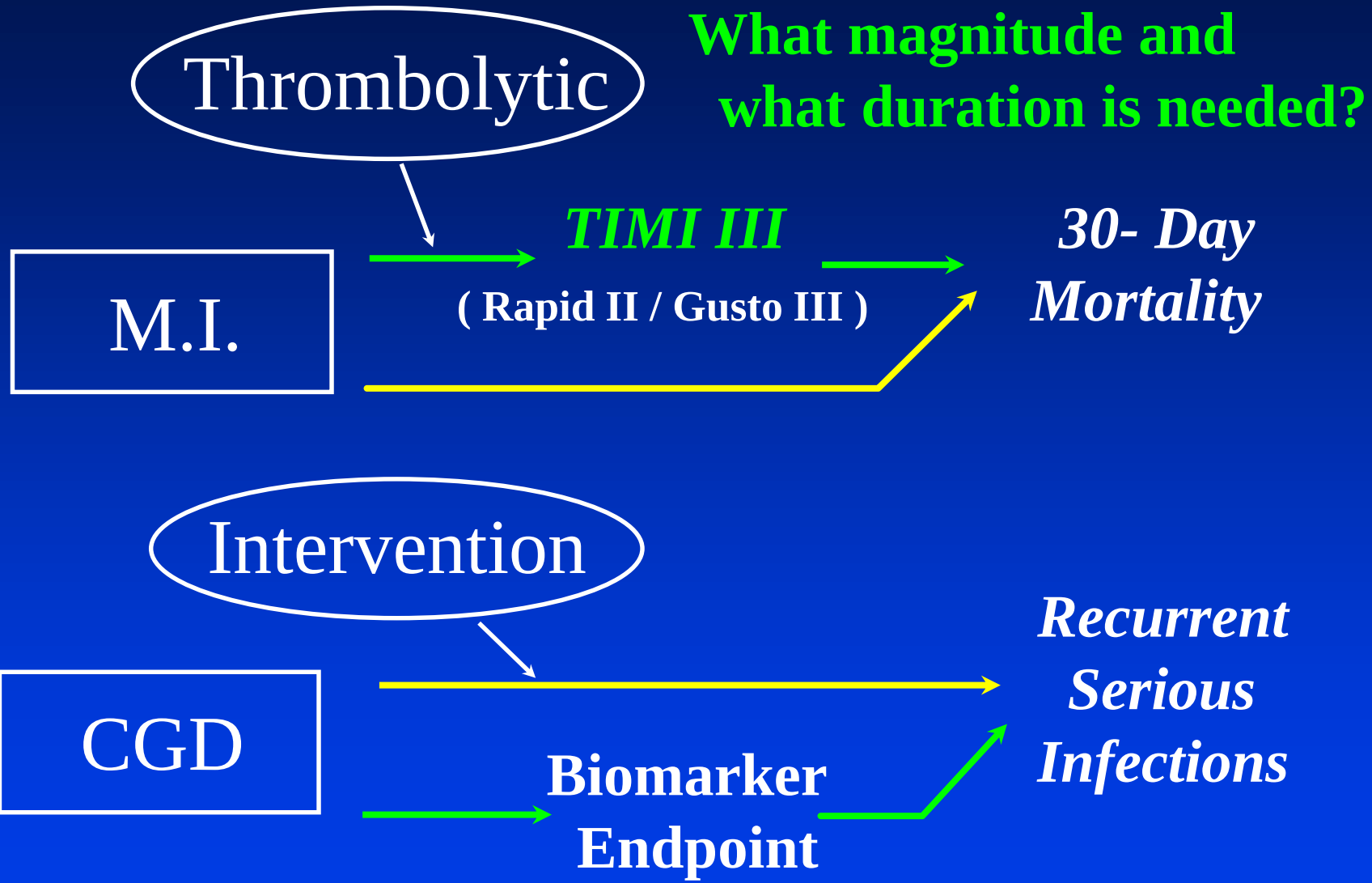
Filamentous Haemagglutinin (FHA) and Pertussis Toxoid (PT) antibody responses were superior with the SKB vaccine

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

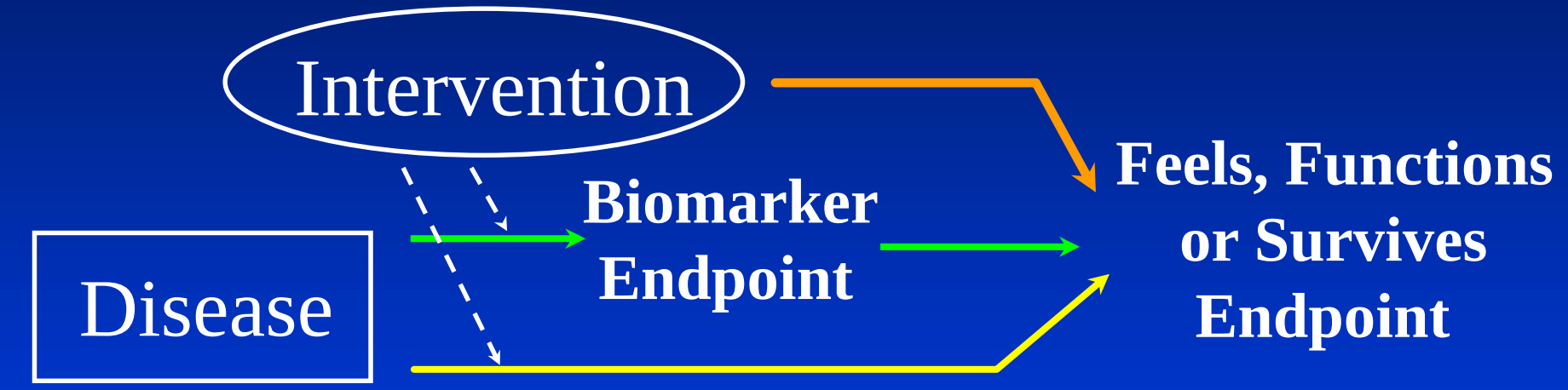


Illustration:
Ventricular Arrhythmia after M.I.

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

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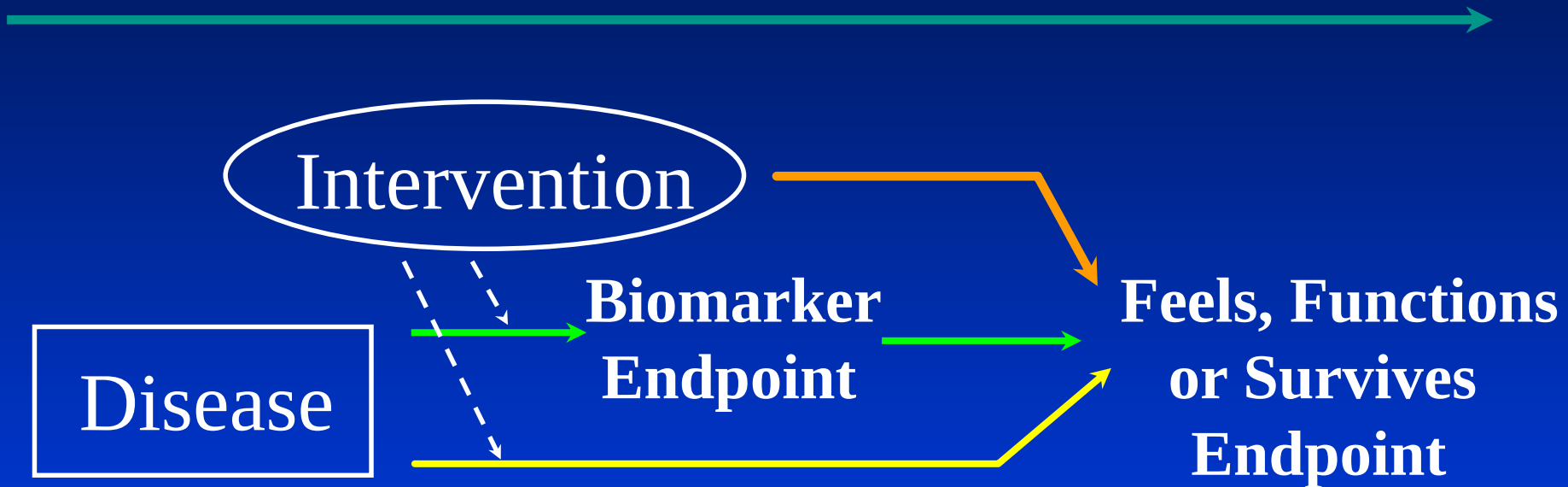
Cardiac Arrhythmia Suppression Trial:
The drugs, relative to placebo,
TRIPLE the death rate.

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?

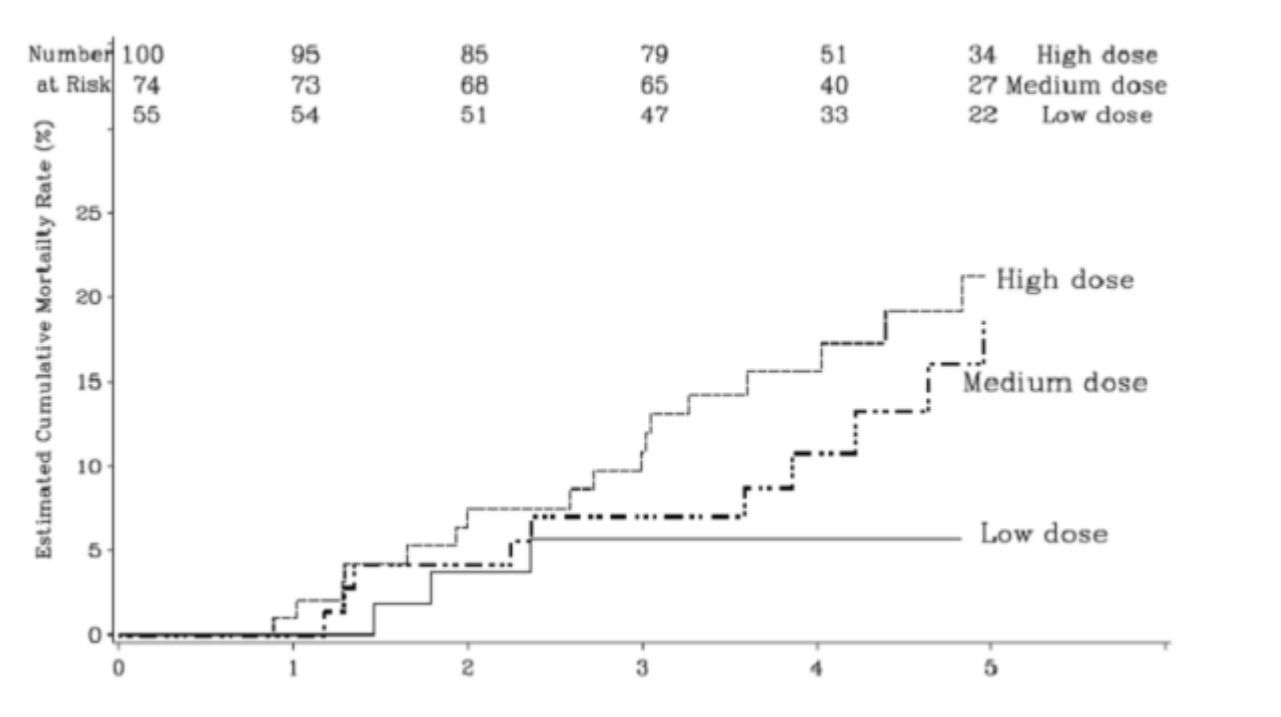
Long Acting β-Agonists: ↑ Asthma-related deaths

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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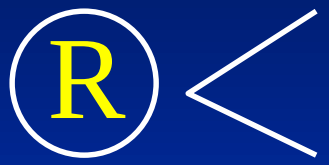
~ **Validation of Replacement (Surrogate) Endpoints**

End Stage Renal Disease



Standard Dose ESA* ⇒ Hematocrit 30%

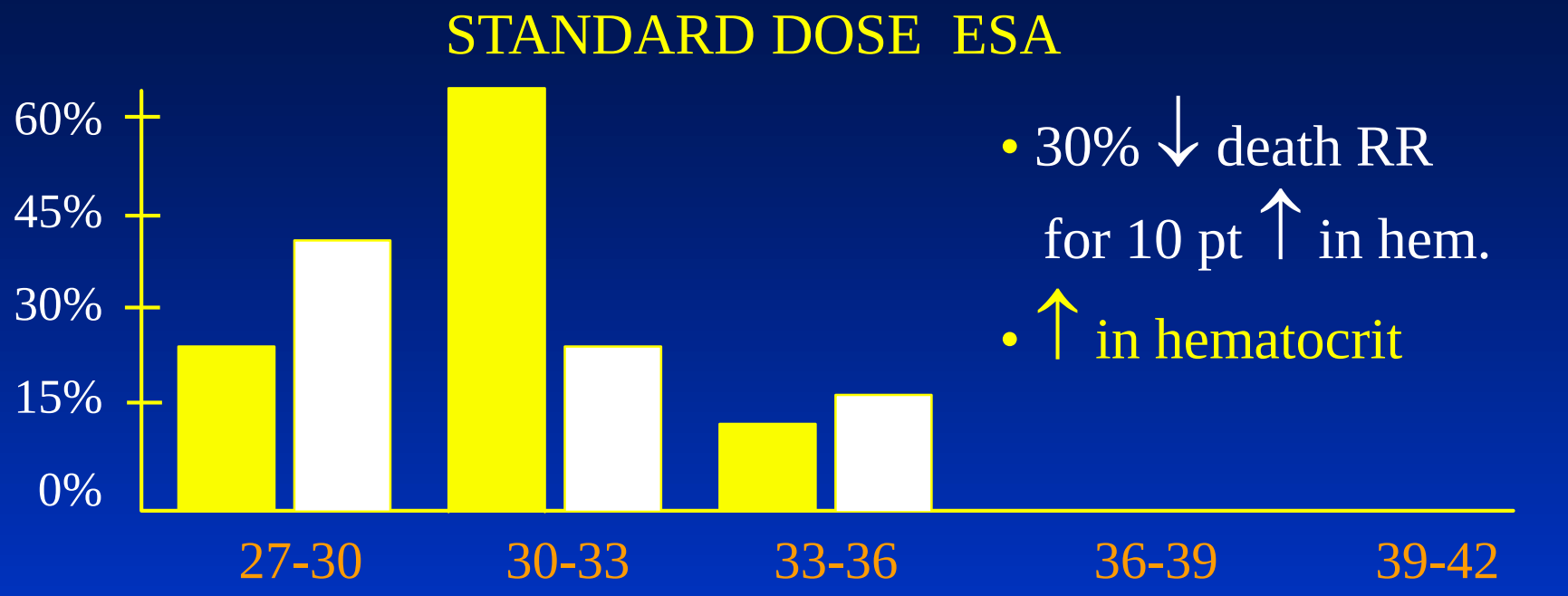
High Dose ESA* ⇒ Hematocrit 42%

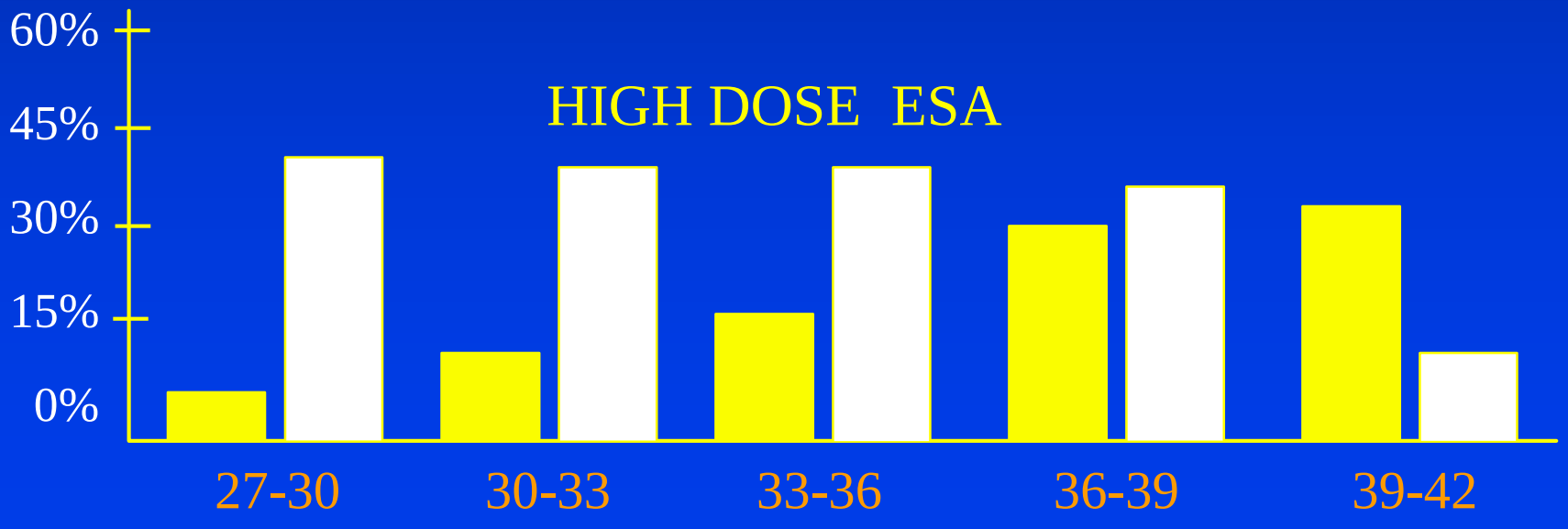
Goal: Normalize Hematocrit Values

⇒ reduce Death and MI

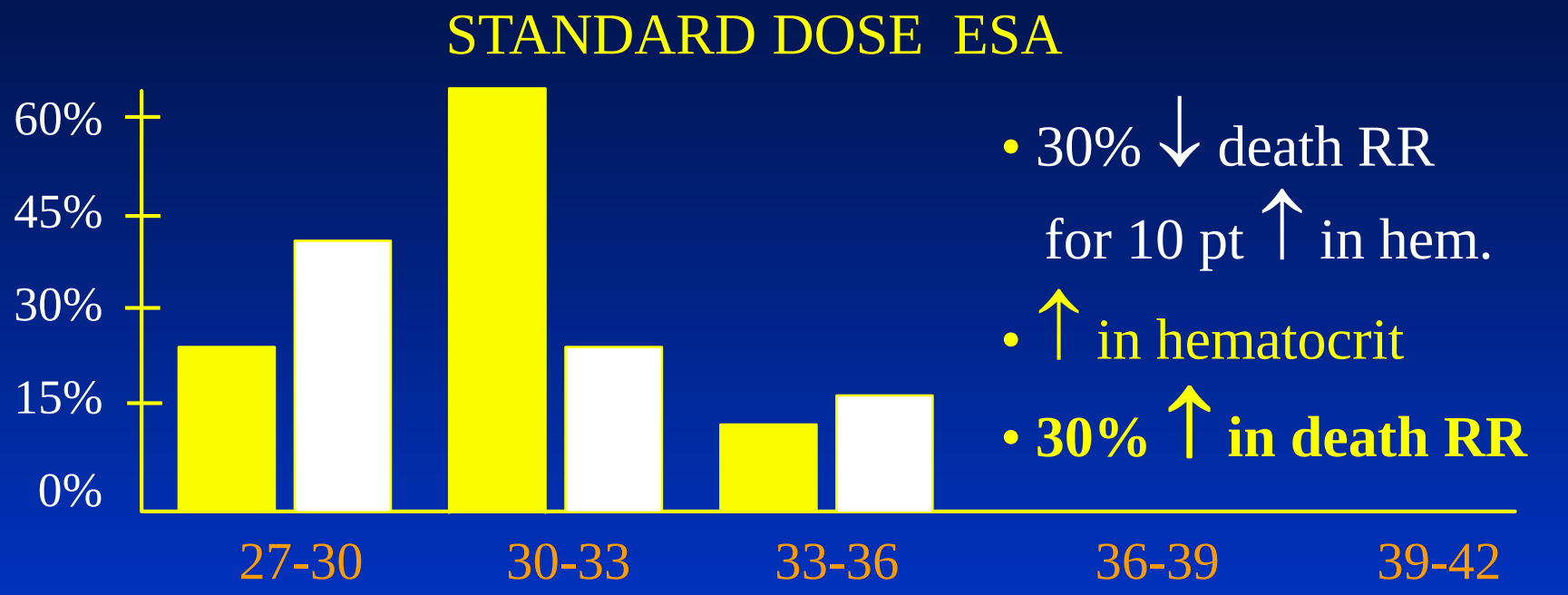
* Erythropoietin stimulating agent

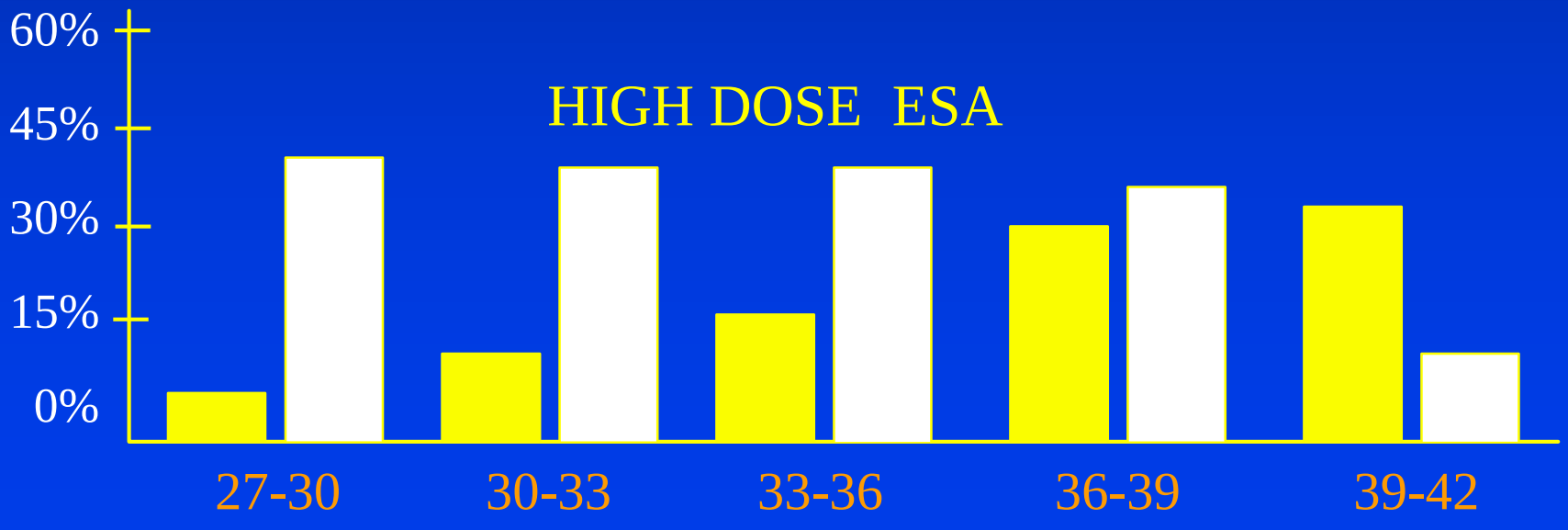
Patient Distribution & Percent Deaths by Hematocrit %





Patient Distribution & Percent Deaths by Hematocrit %





End Stage Renal Disease

Results (Interim at 1/2 planned endpoints)

	n	Death/MI	Death
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'

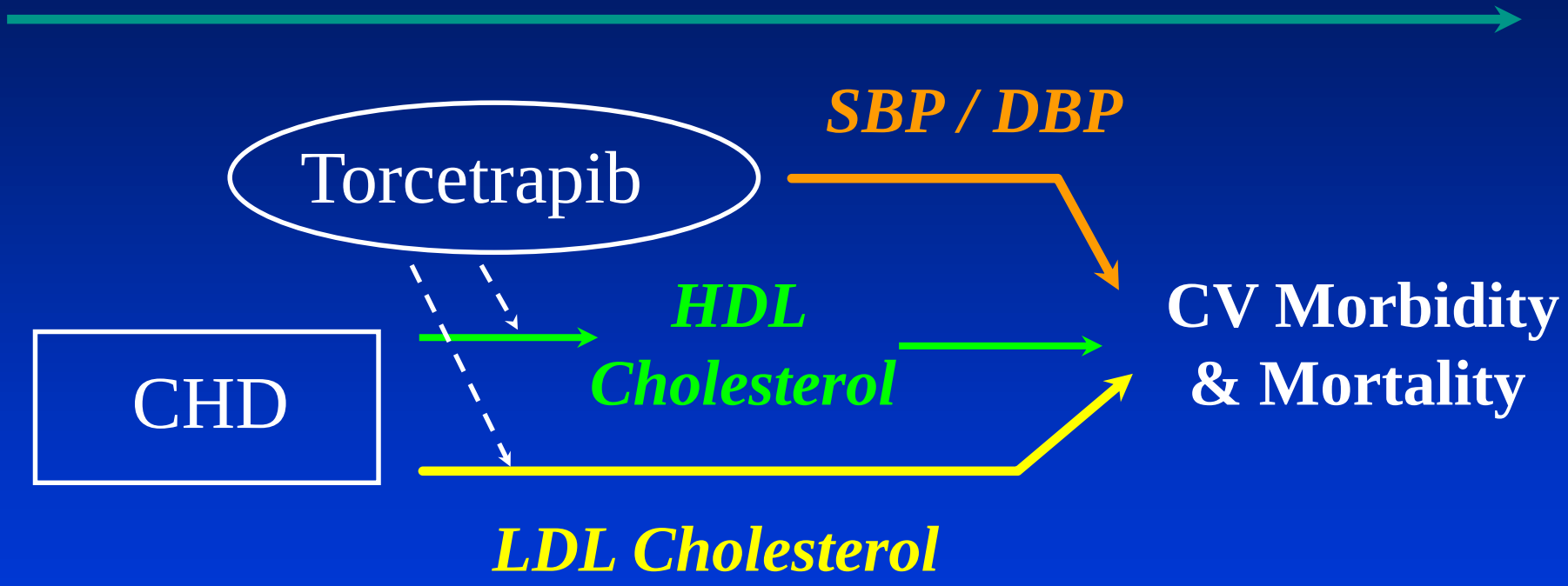
Clinical

- 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'

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- Meta-analyses of clinical trials data

Illustration of Validating a Surrogate

- **Anti-Hypertensives**

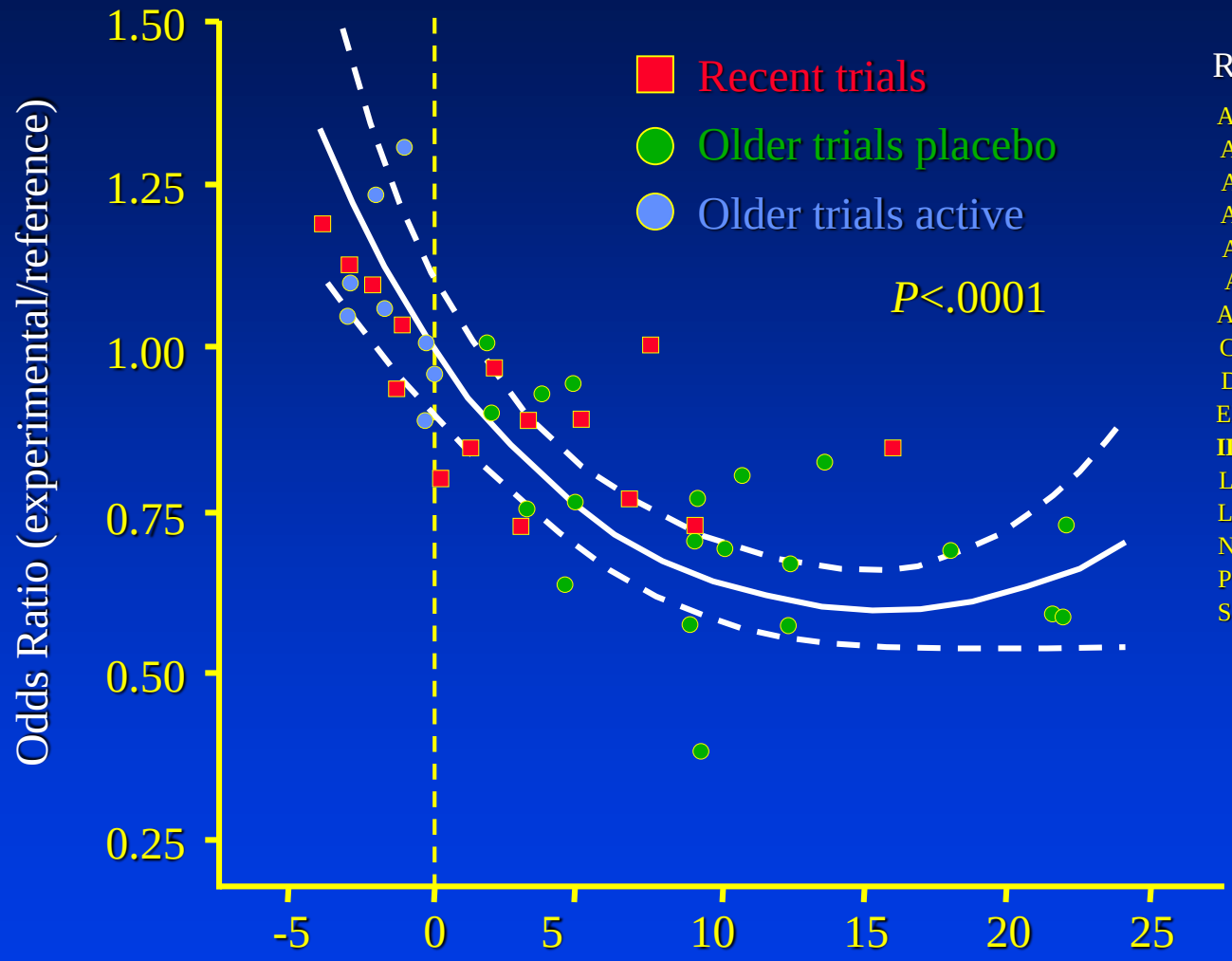
  (>500,000 patients from rand trials)

…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



Recent	Older
AASK L vs. H	ALLHAT/Dox
ABCD/NT L vs. H	ATMH
ALLHAT/Aml	EWPHE
ALLHAT/Lis	HEP
ALLHAT/Lis ≥65	HOPE
ALLHAT/Lis Blacks	HOT
ANBP2	HOT M vs. H
CONVINCE	INSIGHT
DIABHYCAR	MIDAS/NICS/VHAS
ELSA	L vs. H
IDNT2	MRC
LIFE/ALL	MRC2
LIFE/DM	PART2/SCAT
NICOLE	PATS
PREVENT	PROGRESS/Per
SCOPE	PROGRESSION/Com
	RCT70-80
	RENAAL
	SHEP
	STONE
	STOP 1
	STOP2/CCBs
	STOP2/ACEIs
	Syst-China
	Syst-Eur
	UKPDS C vs. A
	UKPDS L vs. H

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

Slide: Henry Black's lecture

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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

Direct Measures of Patient "Functions, Feels, Survives"

- Patient (symptoms: ***chest pain, dyspnea, fatigue, dizziness***)
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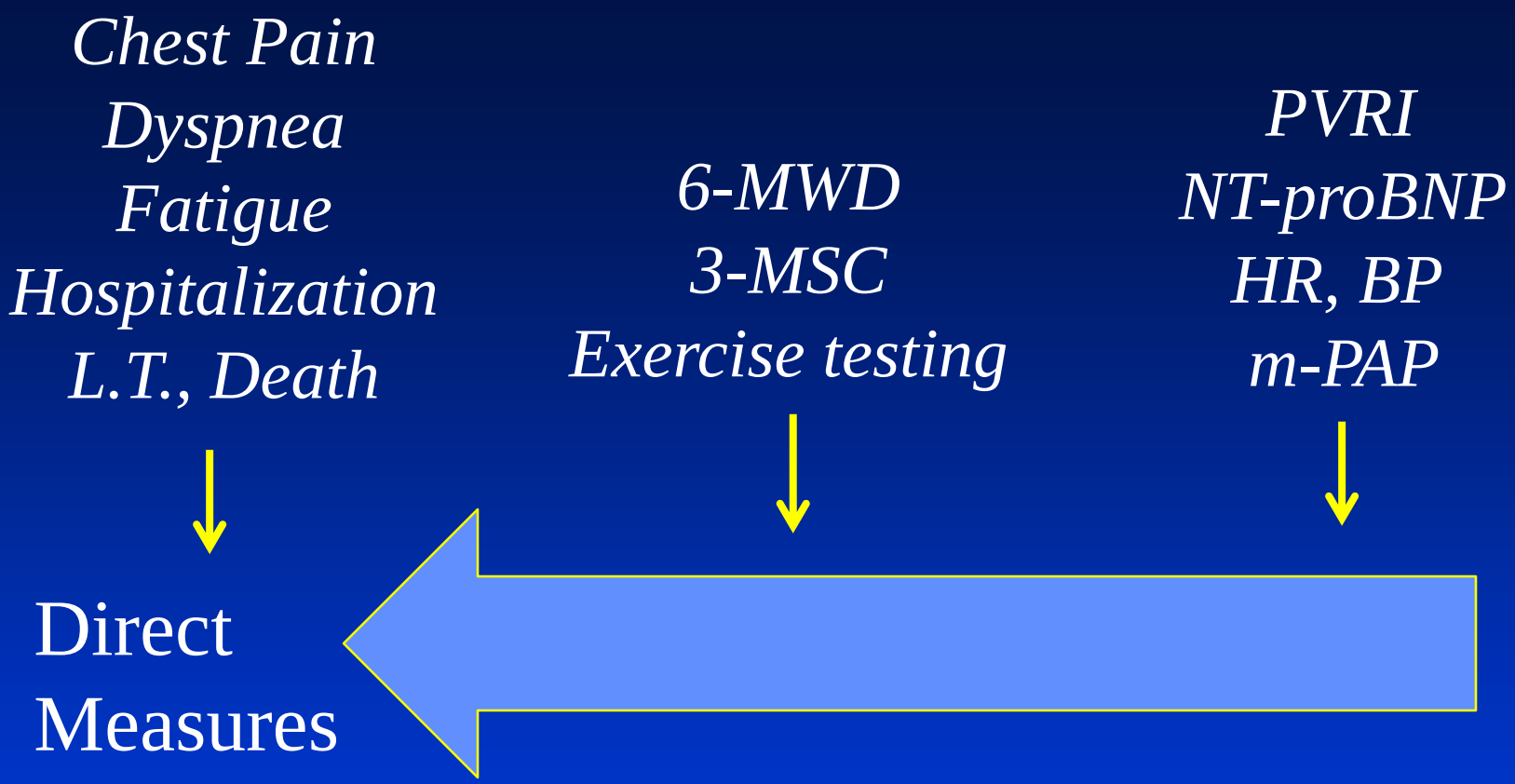
Chest Pain
Dyspnea
Fatigue
Hospitalization
L.T., Death
6-MWD
3-MSC
Exercise testing
PVRI
NT-proBNP
HR, BP
m-PAP
Direct Measures
Indirect Measures Continuum in PAH

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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*"

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  - ~ **Survives**

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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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