Summer Institute in Statistics for Clinical Research

Biomarkers and Replacement Endpoints in Clinical Trials

July 13, 2023

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* Fleming and DeMets, *Annals of Internal Medicine*, 1996
* Fleming, *Health Affairs*, 2005; * IOM (Biomarkers) 2010
* Fleming, Powers. *Statistics in Medicine.* 31: 2973-2984, 2012

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

~ Accelerated and Regular Approval Process

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"

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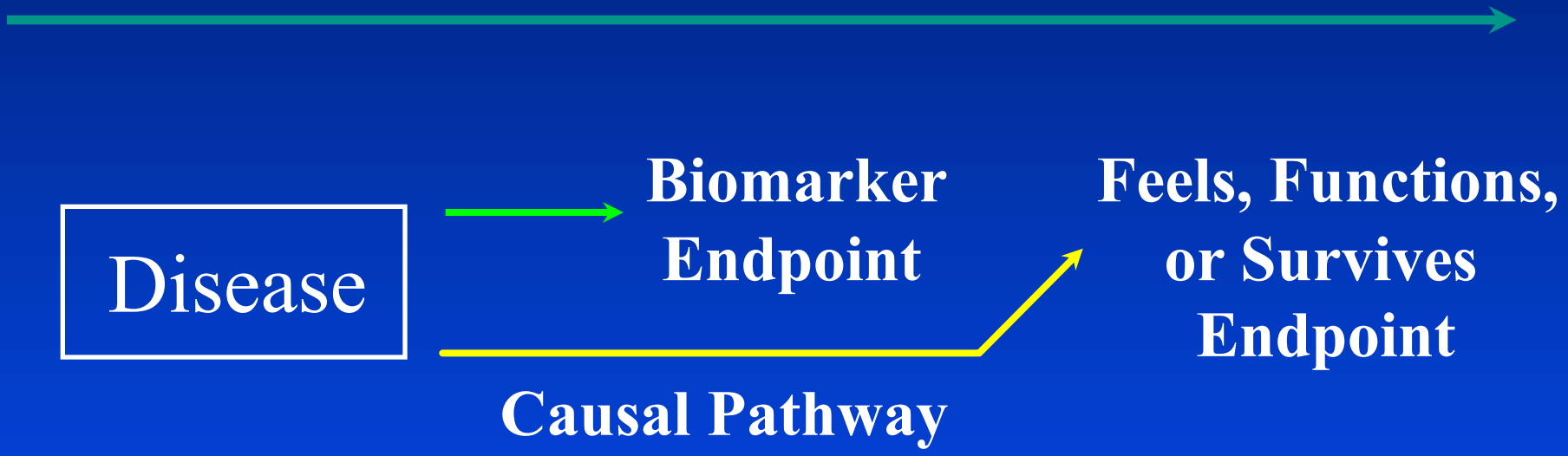
The Biomarker Endpoint is not in the Causal Pathway of Disease Process



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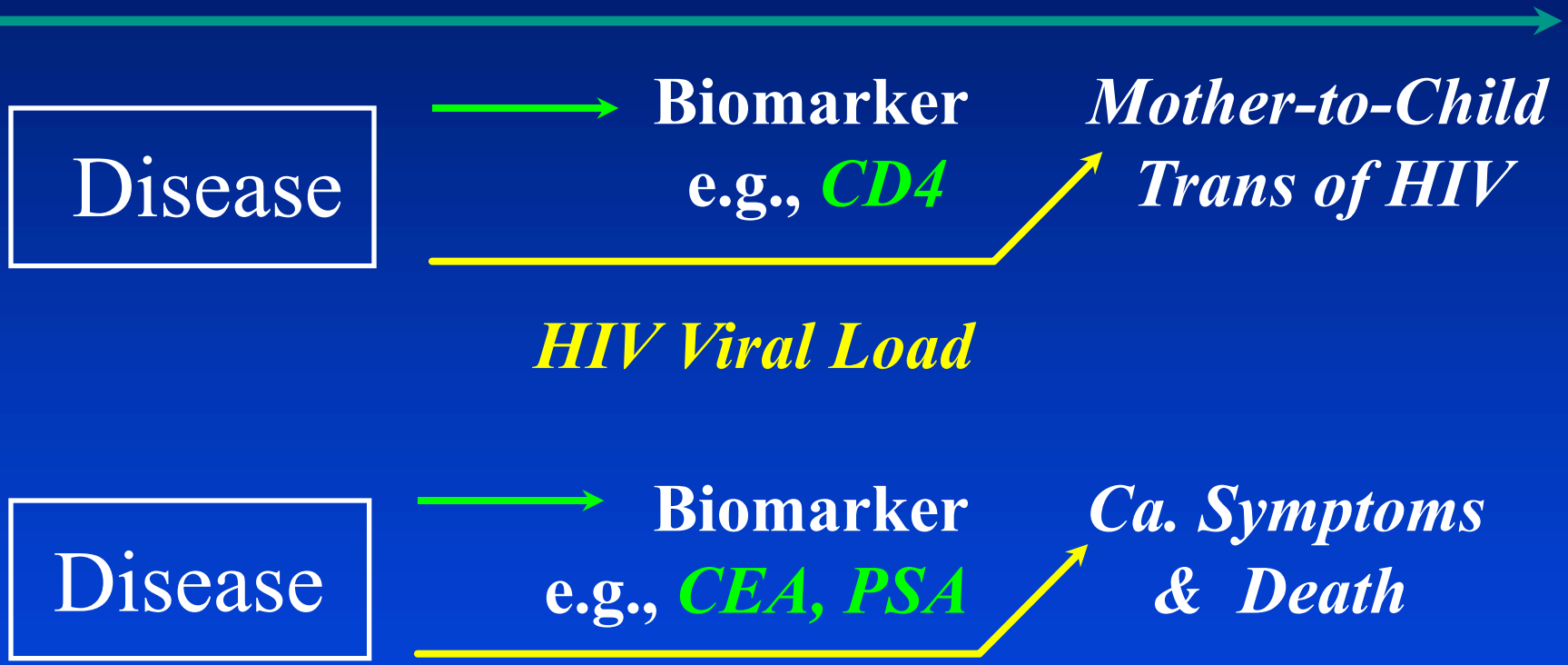
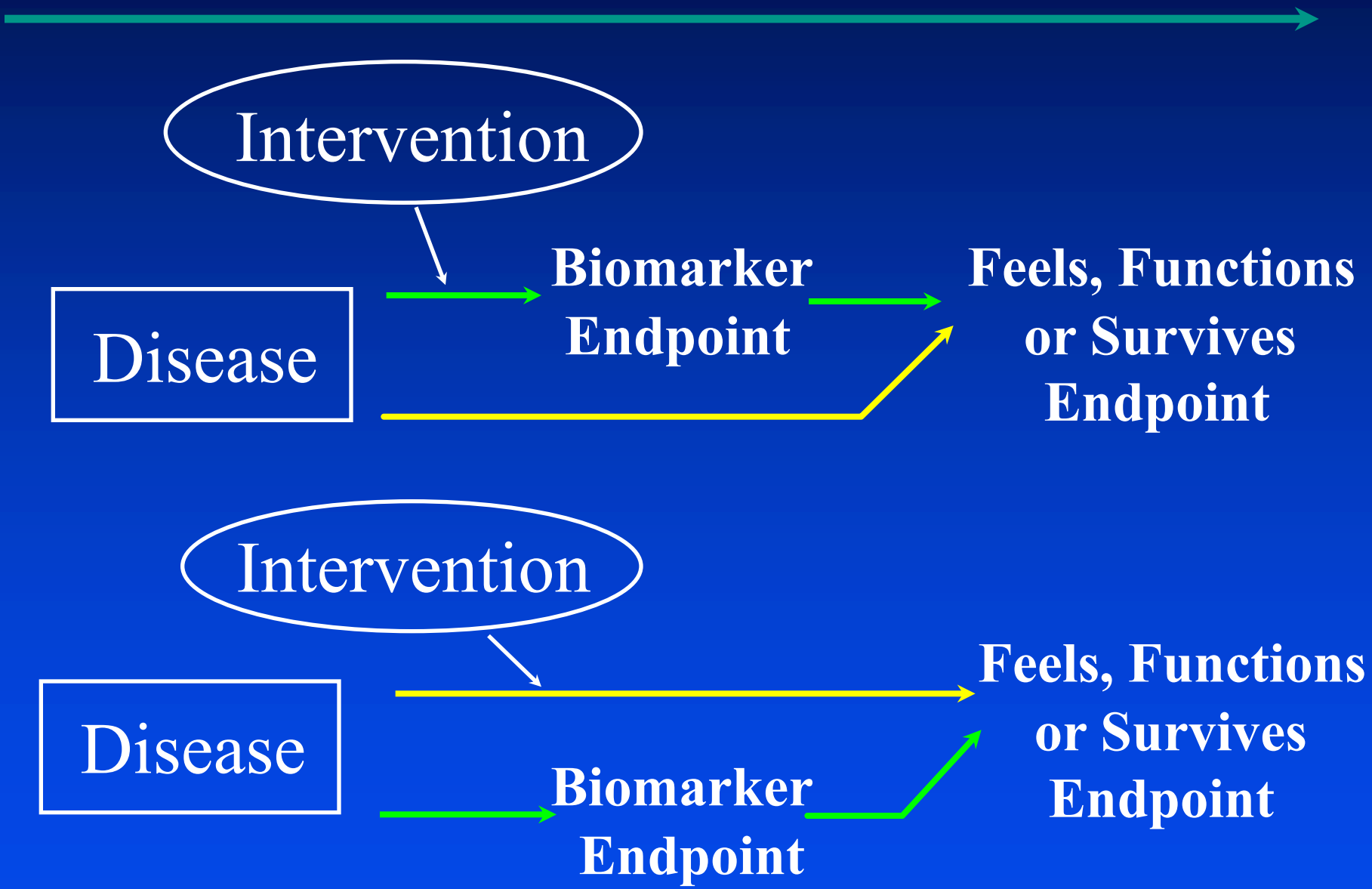
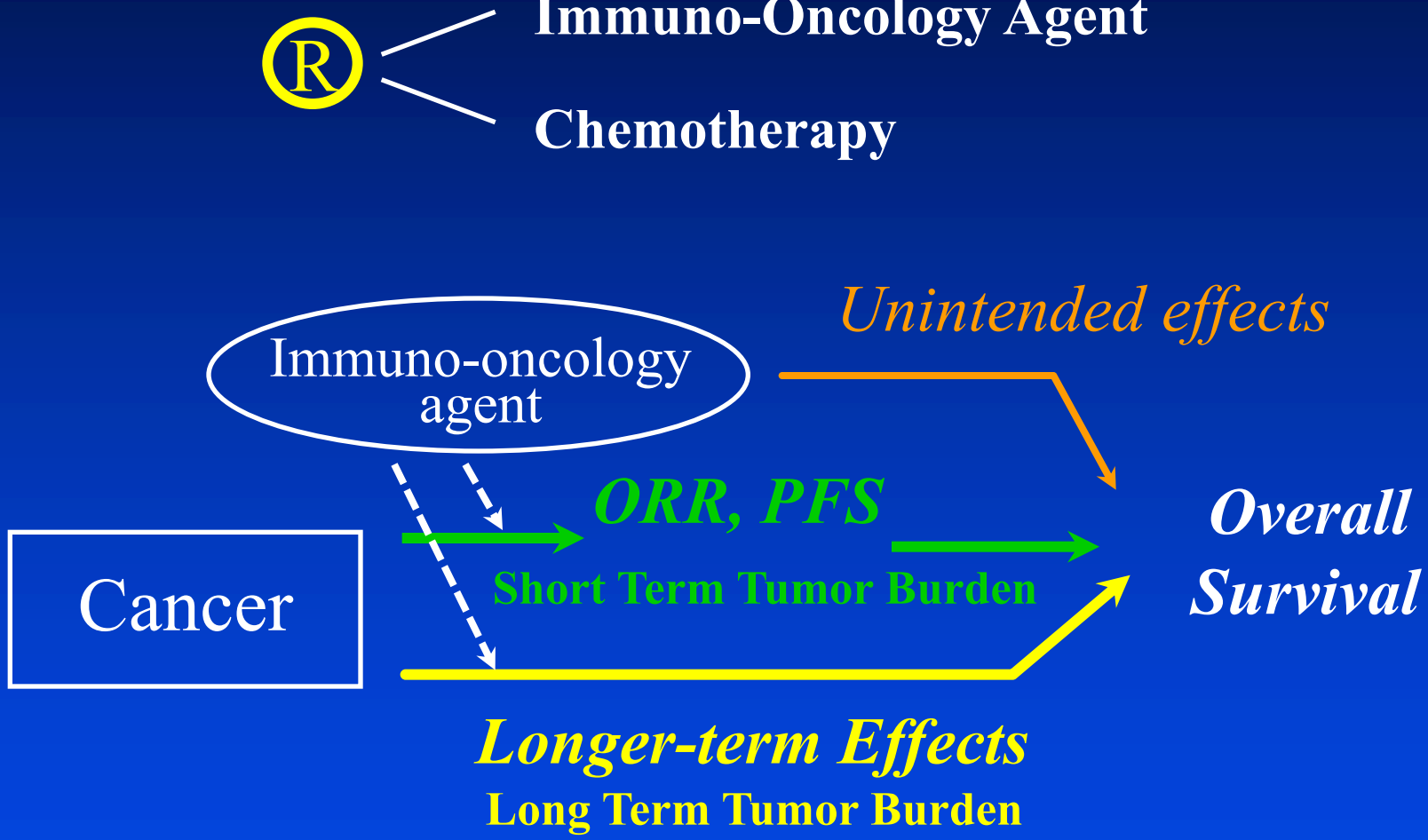


- "Correlates": Useful for Disease Diagnosis, or Assessing Prognosis
- "Valid Surrogates": Replacement Endpoints

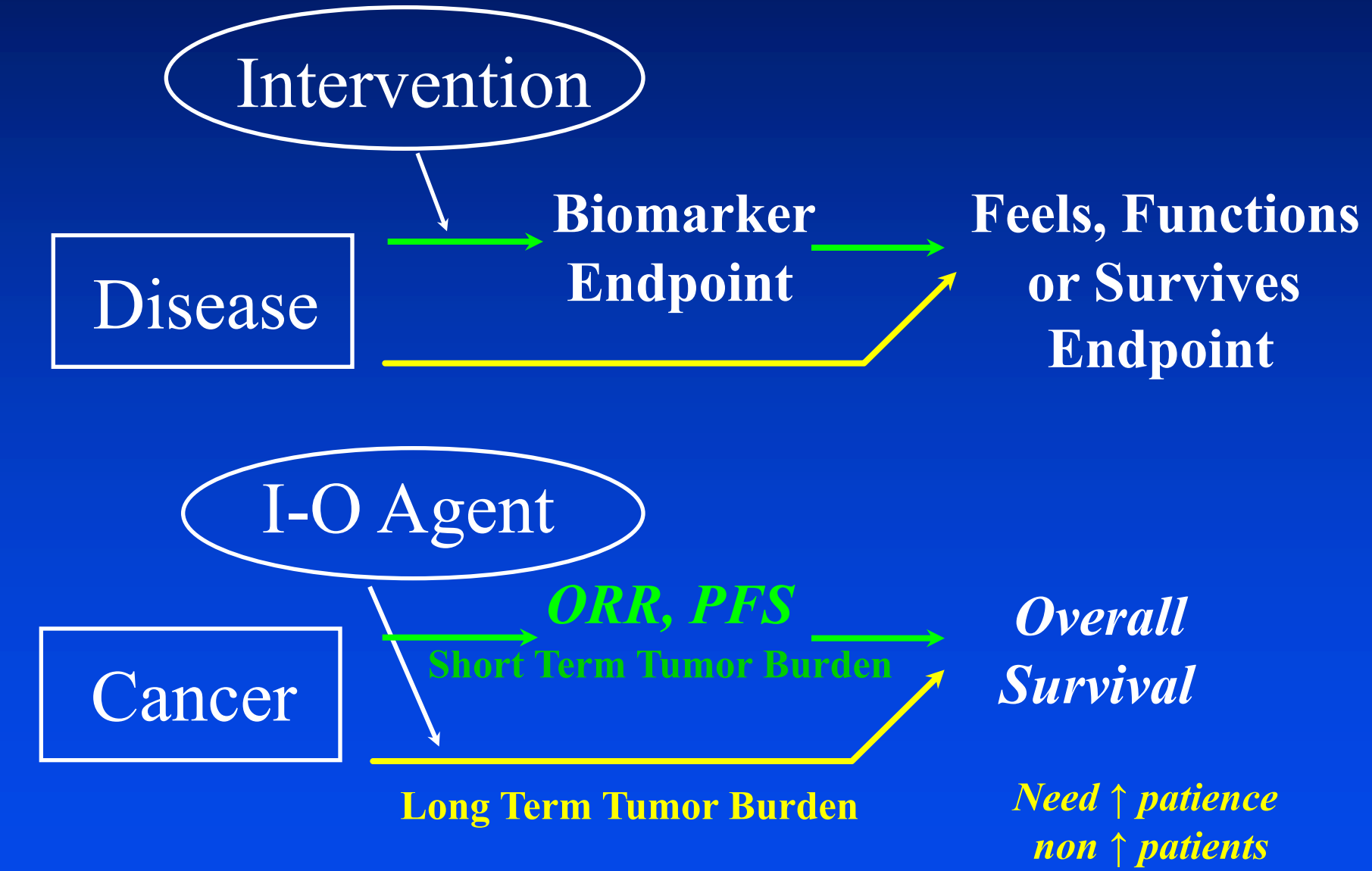
Multiple Pathways of the Disease Process





DeMets DL, Psaty BM, Fleming TR. When can intermediate outcomes be used as surrogate outcomes? *JAMA* February 27, 2020

Multiple Pathways of the Disease Process



Biomarkers in Acellular Pertussis Vaccines

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

- **Vaccine Efficacy**

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

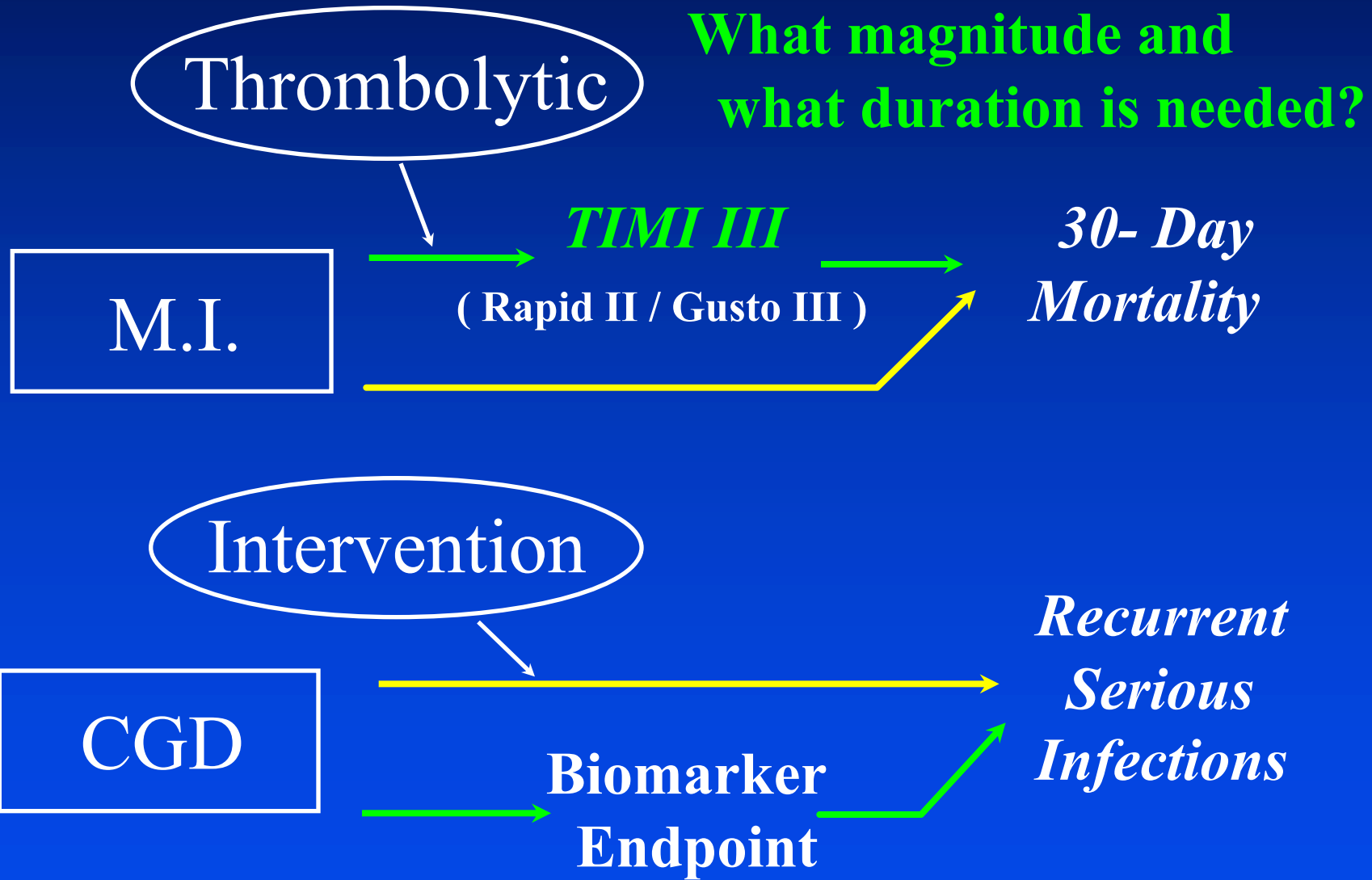
- **Biomarkers**

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

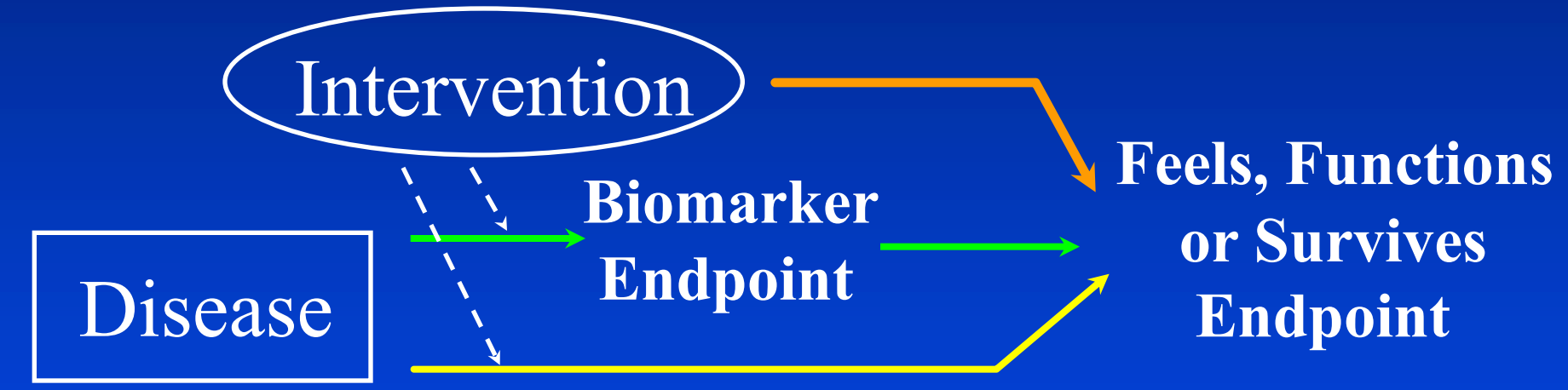


Illustration:
Ventricular Arrhythmia after M.I.

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

Illustration:
Ventricular Arrhythmia after M.I.

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  - Class IC antiarrhythmic agents
    …Strong Sodium-Channel Blockade

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: ↑ **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?

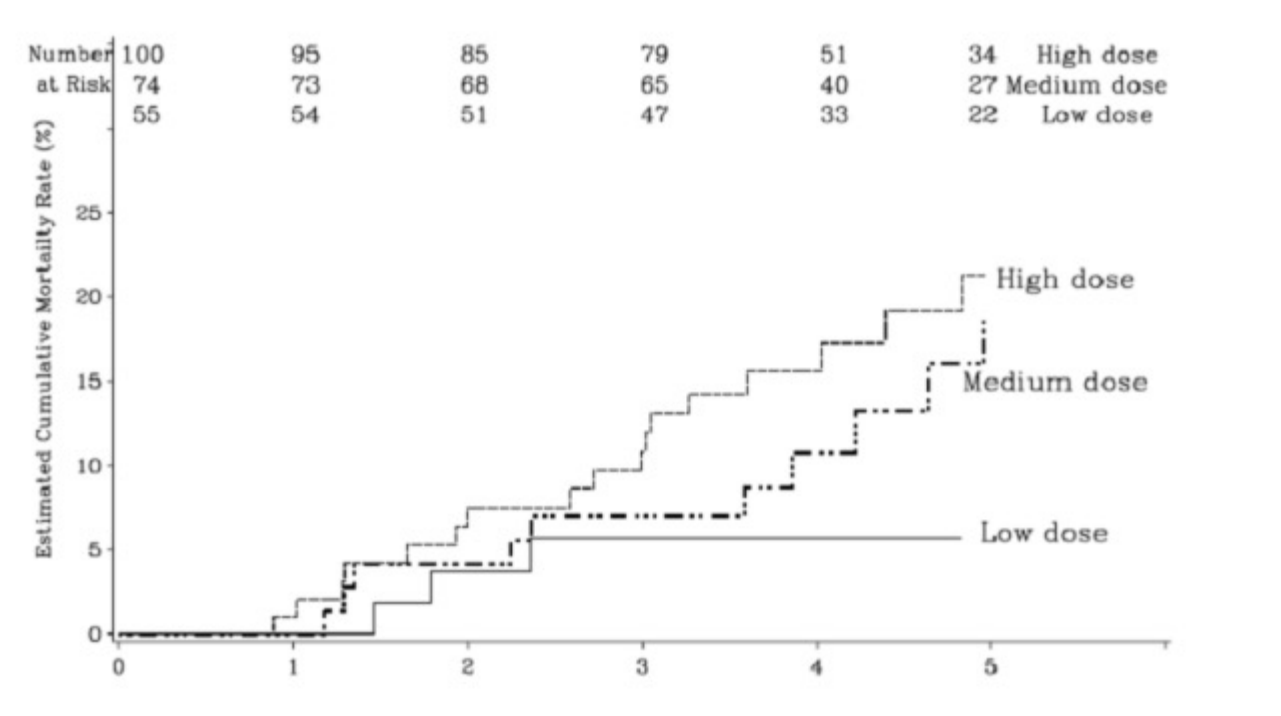
Long Acting β-Agonists: ↑ Asthma-related deaths

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

~ Criteria for Choosing Endpoints

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

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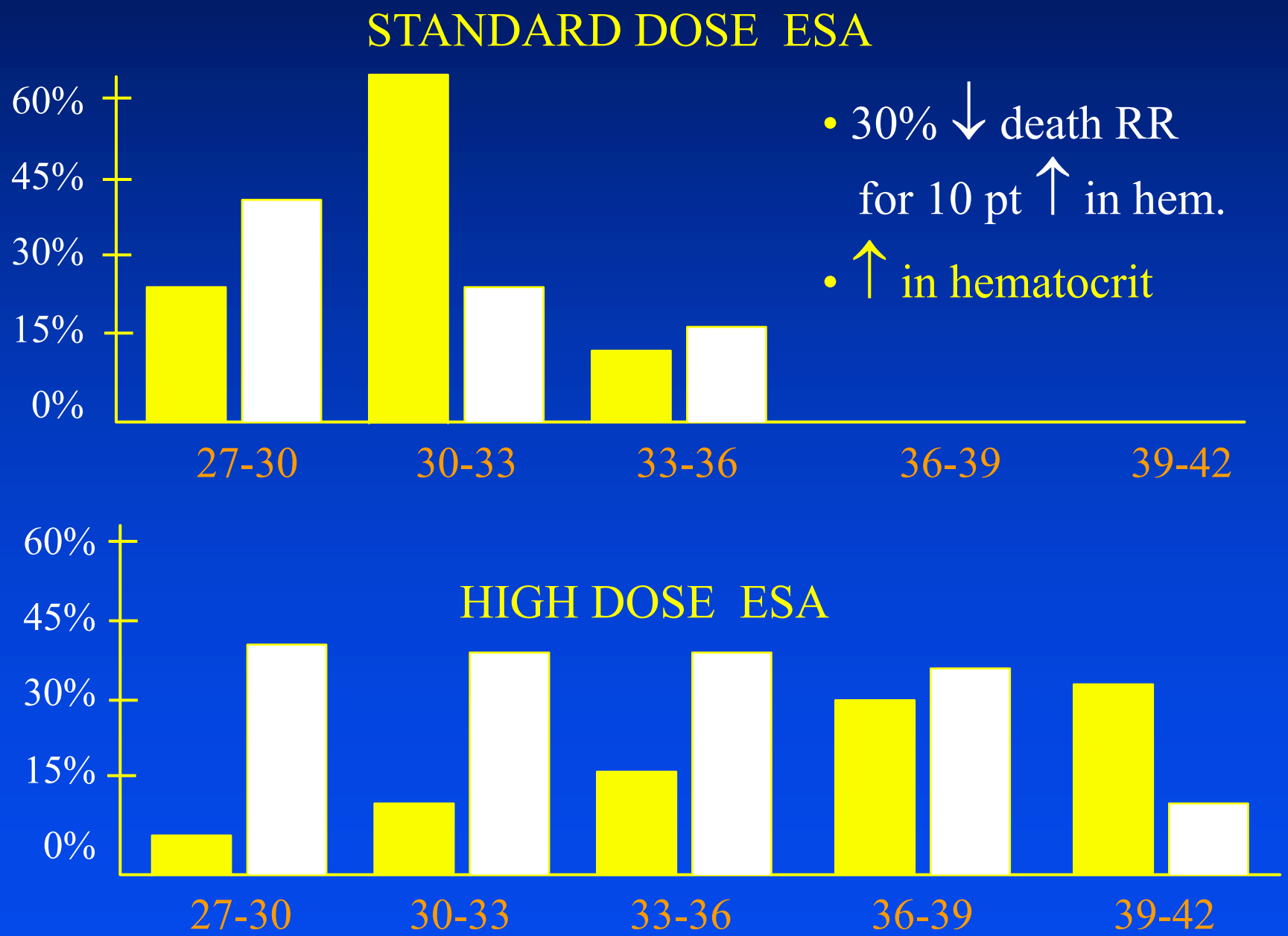
End Stage Renal Disease

Goal: Normalize Hematocrit Values

⇒ reduce Death and MI

* Erythropoietin stimulating agent

Patient Distribution & Percent Deaths by Hematocrit %



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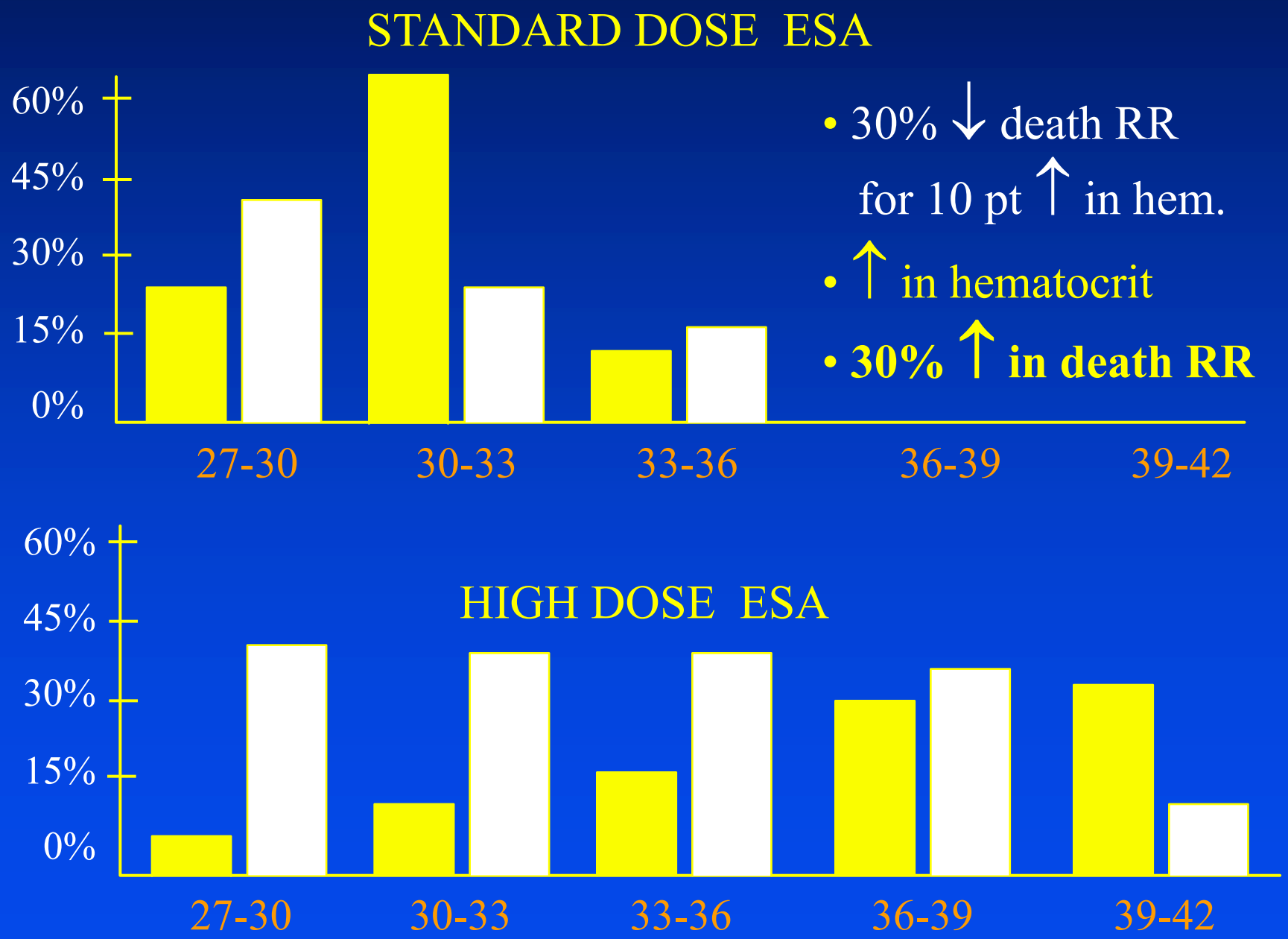


End Stage Renal Disease

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**"

How does one establish
a *biomarker* to be

valid

as a replacement endpoint
for direct measures of
'*feels, functions, survives*' ?

Property of a Valid Replacement Endpoint

Net effect of the Intervention on the '*Replacement*' Endpoint

reliably predicts the

Net effect of the Intervention on the *'Feels, functions, survives'* Endpoint

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

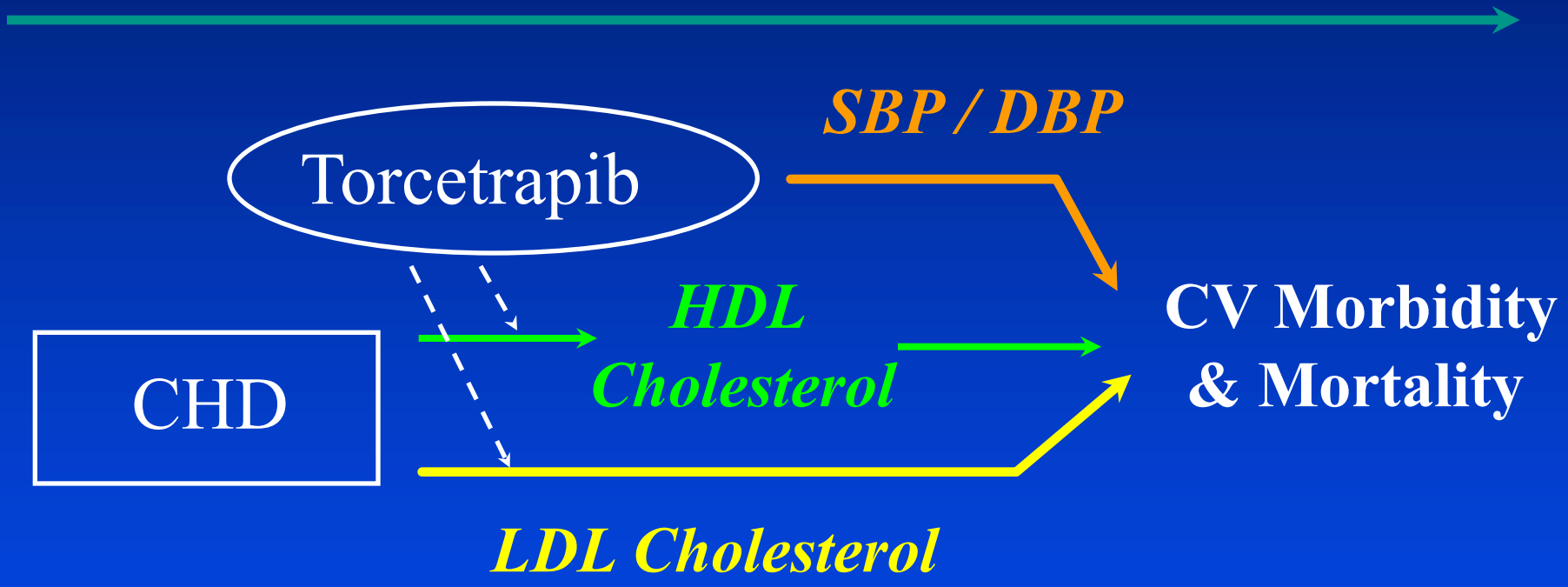
Clinical

- 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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Illustration of Validating a Surrogate

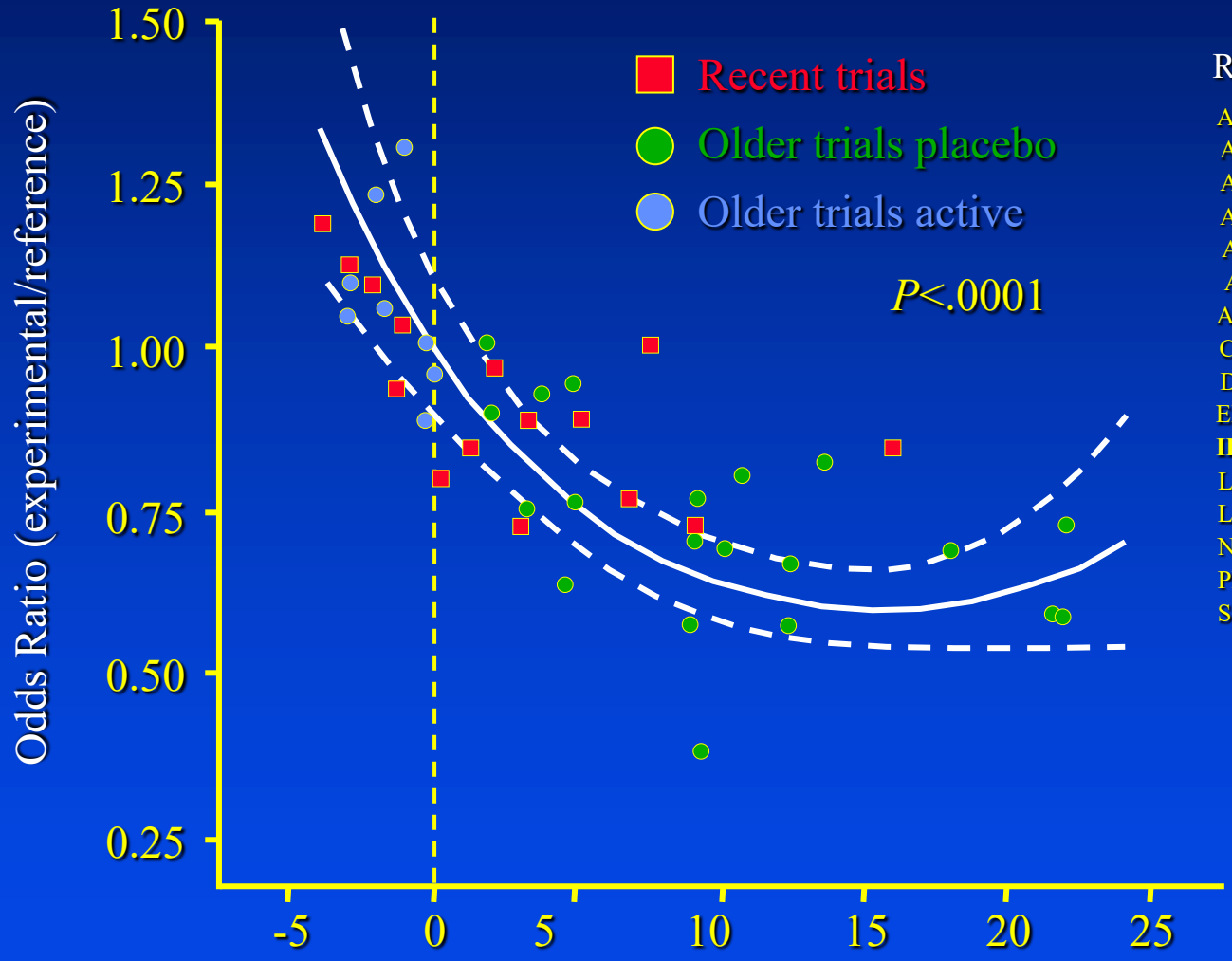
- **Anti-Hypertensives**
  (>500,000 patients from rand trials)

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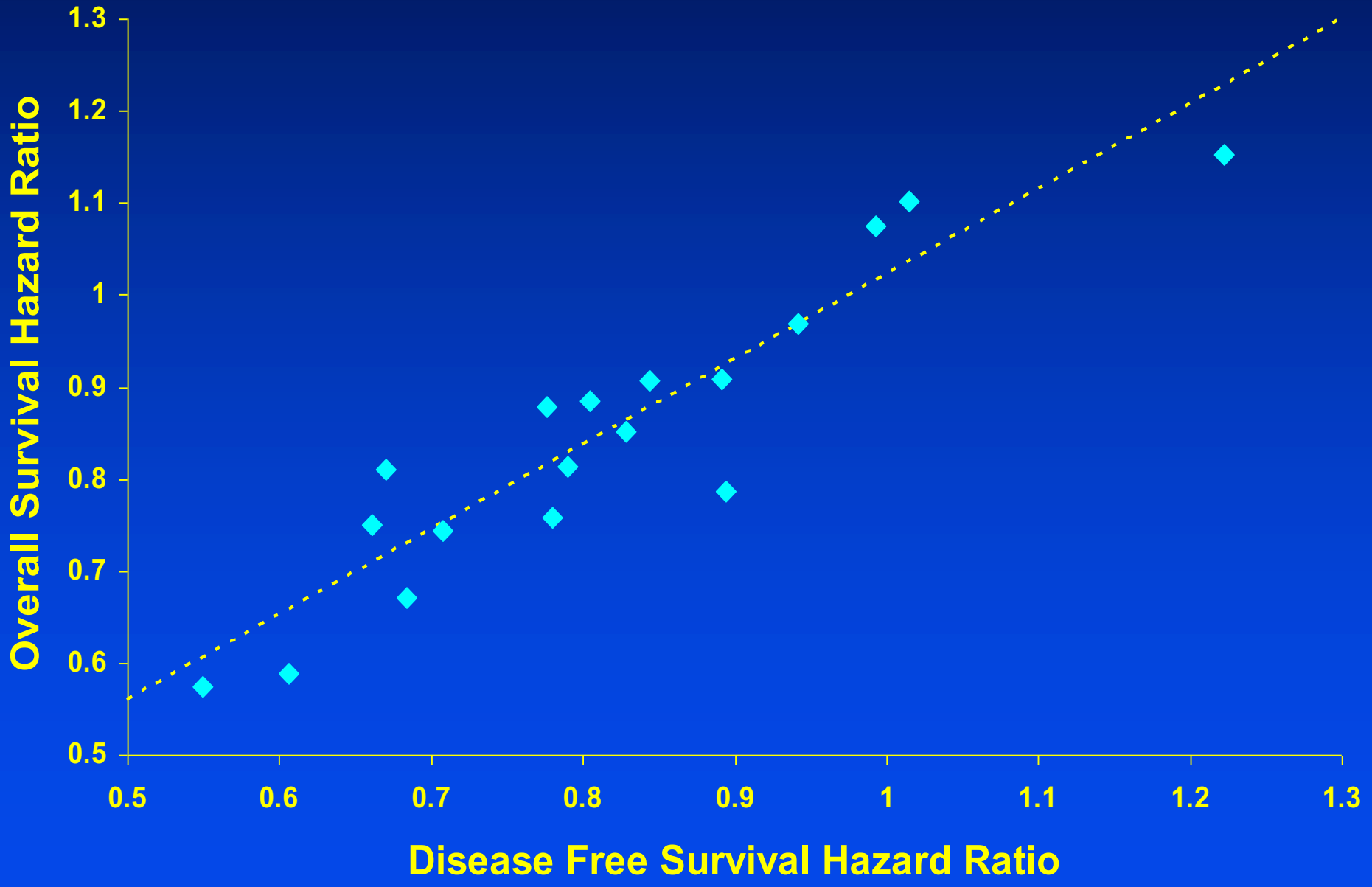
Colon Adjuvant: Hazard Ratios for **DFS** vs. **Overall Survival**



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…

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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  - ~ **Survives**

…Physician or Observer administered & PROs…

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

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Hierarchy for Outcome Measures

- True Clinical Efficacy Measure
- *Validated Surrogate Endpoint (Rare)*
- Non-validated Surrogate Endpoint that is "reasonably likely to predict clinical benefit"
- Correlate that is
  solely a measure of Biological Activity

...Fleming, Health Affairs, 2005

Illustrations of Validated Surrogates

- **Colorectal Adjuvant** (Patients in 18 rand comparisons)

  …5-FU potentiated interventions…

  - Effects on *Dis-Free Survival* predicting effects on:
  - ✓ *Overall Survival* over 5 to 8 years follow-up

- **Anti-Hypertensives** (>500,000 patients from rand trials)

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

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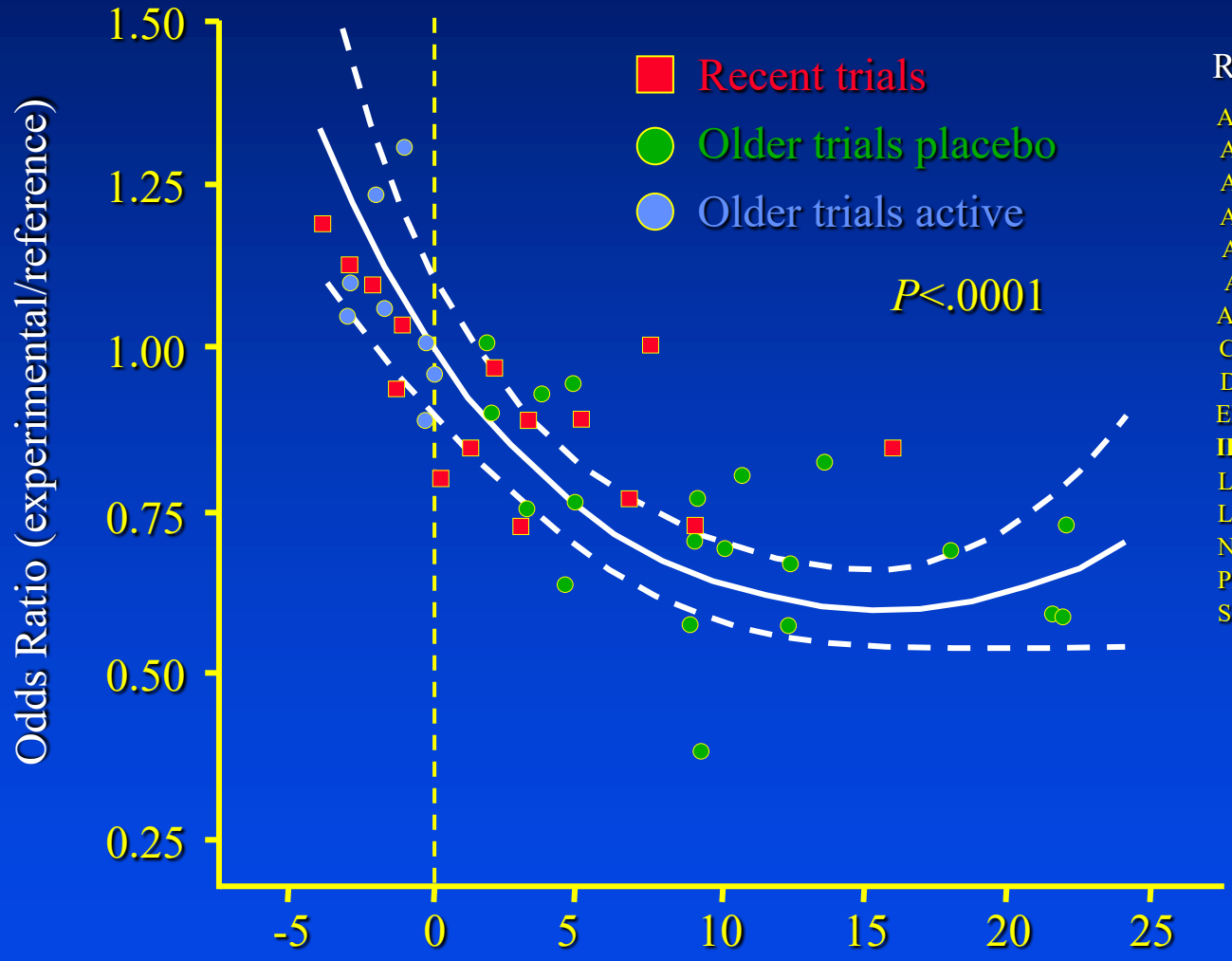

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Establishing a Level #3 Outcome Measure

- Accurately representing the treatment's effect on the predominant mechanism through which the disease process induces clinical risks
- Lack of large adverse effects on clinical endpoint not captured by the outcome measure
- Net effect on the clinical endpoint is consistent with what would be predicted by level of effect on the outcome measure
- Targeted effect on outcome measure sufficiently strong and durable to predict meaningful benefit

* Fleming TR: Surrogate endpoints and FDA's accelerated approval process. *Health Affairs* 24(1): 66-78, 2005

Concerning Issues re Validation Trials:

- *Enrollment difficulties into validation trials*
- *Cross-ins on the control arm*
- *Loss of "sense of urgency" by sponsor*
- *Lack of clear vision for proper process when the validation trial is not conclusively positive*

FDA Oncology Drugs AC: 11/92 - 3/2017

’92-’017: 93 agents received Accelerated Approvals, where a validation trial was required*.

In these validation trials:

- In 19 cases (20%), an effect on OS was established
- In 20 cases (21%), improvement established in another surrogate
- In 19 cases (20%), the validation trial simply confirmed the effect on the original replacement endpoint.

* Gyawali et al. Assessment of the Clinical Benefit of Cancer Drugs receiving Accelerated Approval, JAMA Internal Medicine 179 (7): 906-913, 2019

* DeMets, Psaty, Fleming. When can intermediate outcomes be used as surrogate outcomes? *JAMA* Published online February 27, 2020

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Some Uses of Biological Markers

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

Challenging Uses of Biological Markers

- As "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

Consequences of Reliance on Surrogate Endpoints For Accelerated or Full Regulatory Approval

- Less reliable evidence regarding Efficacy
- Less reliable evidence regarding Safety

…The stronger the efficacy evidence, the greater the resilience regarding uncertainties about safety…

Recent Experiences:

- Tysabri : PML in Crohns Disease & Multiple Sclerosis
- Erythropoiesis Stimulating Agents :
  Chemo-Induced Amemia & Hemodialysis in CHF
- Muraglitazar & Rosiglitazone : Type 2 Diabetes

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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