Surrogate Endpoints in rare cancers

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Surrogate Endpoint - Definition

1. A clinical, instrumental or laboratory variable

2. which can be used in a clinical trial as the primary endpoint (instead of the true endpoint)

3. because it allows to assess/estimate the effect of the test treatment on the ‘true’ (natural) endpoint

Possible uses of a surrogate endpoint

To assess the efficacy of a new treament:

a) In trials

- In less time
- With less patients

b) In the individual patient

Surrogate endpoints in Cancer

- Activity Endpoints
  - % Responders, % pts with “Disease Control”, % pts with ETS, DoR
  - CTC’s, Circulating DNA
  - PET response
- Endpoints “Time to Event”
  - RFS/DFS, PFS
  - Time to “disease control”

Surrogate Endpoints and dilution

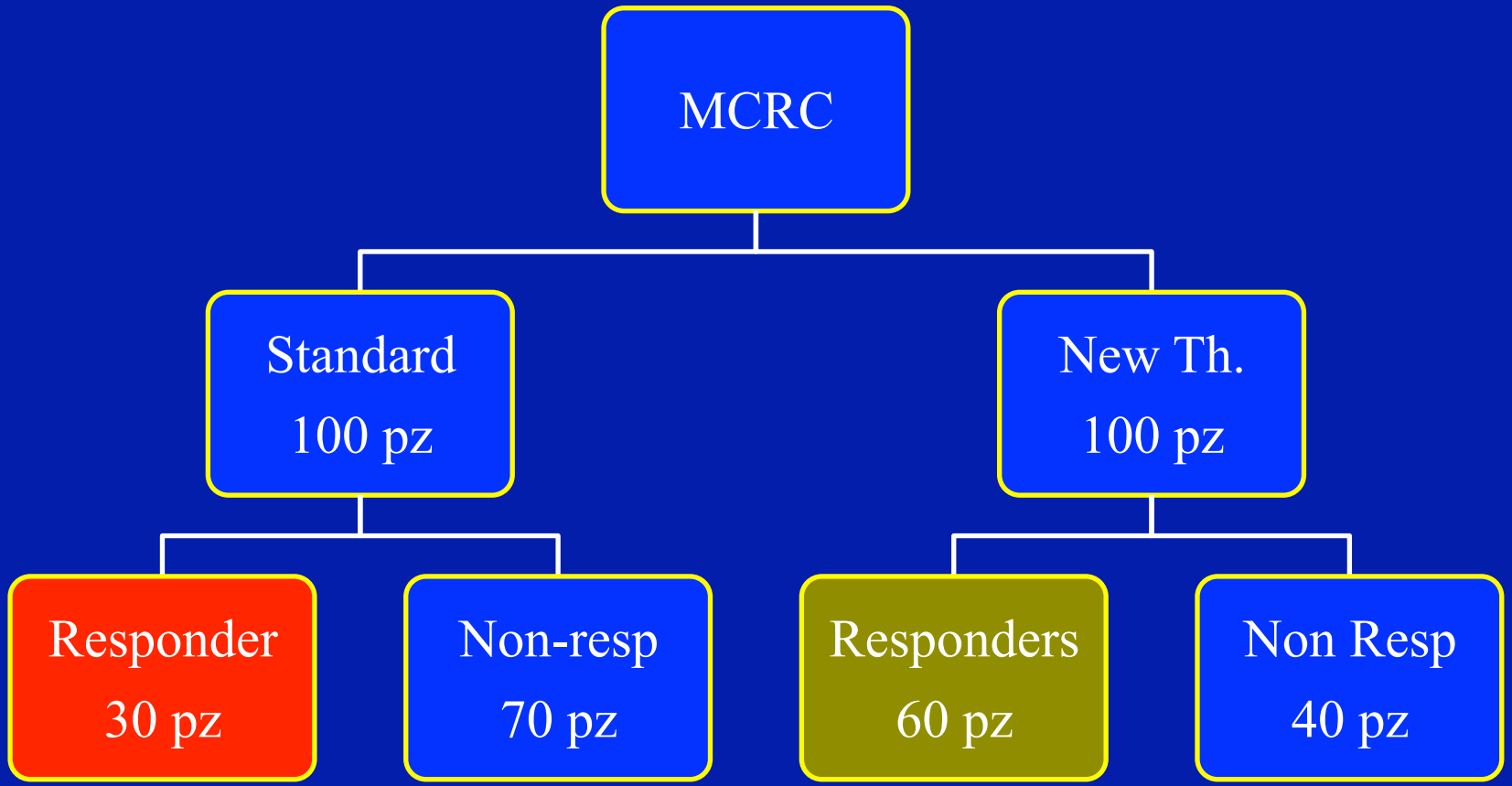
The effects of a treatment on a VALID surrogate endpoint, for mathematical reasons, are always larger than those on the true endpoint

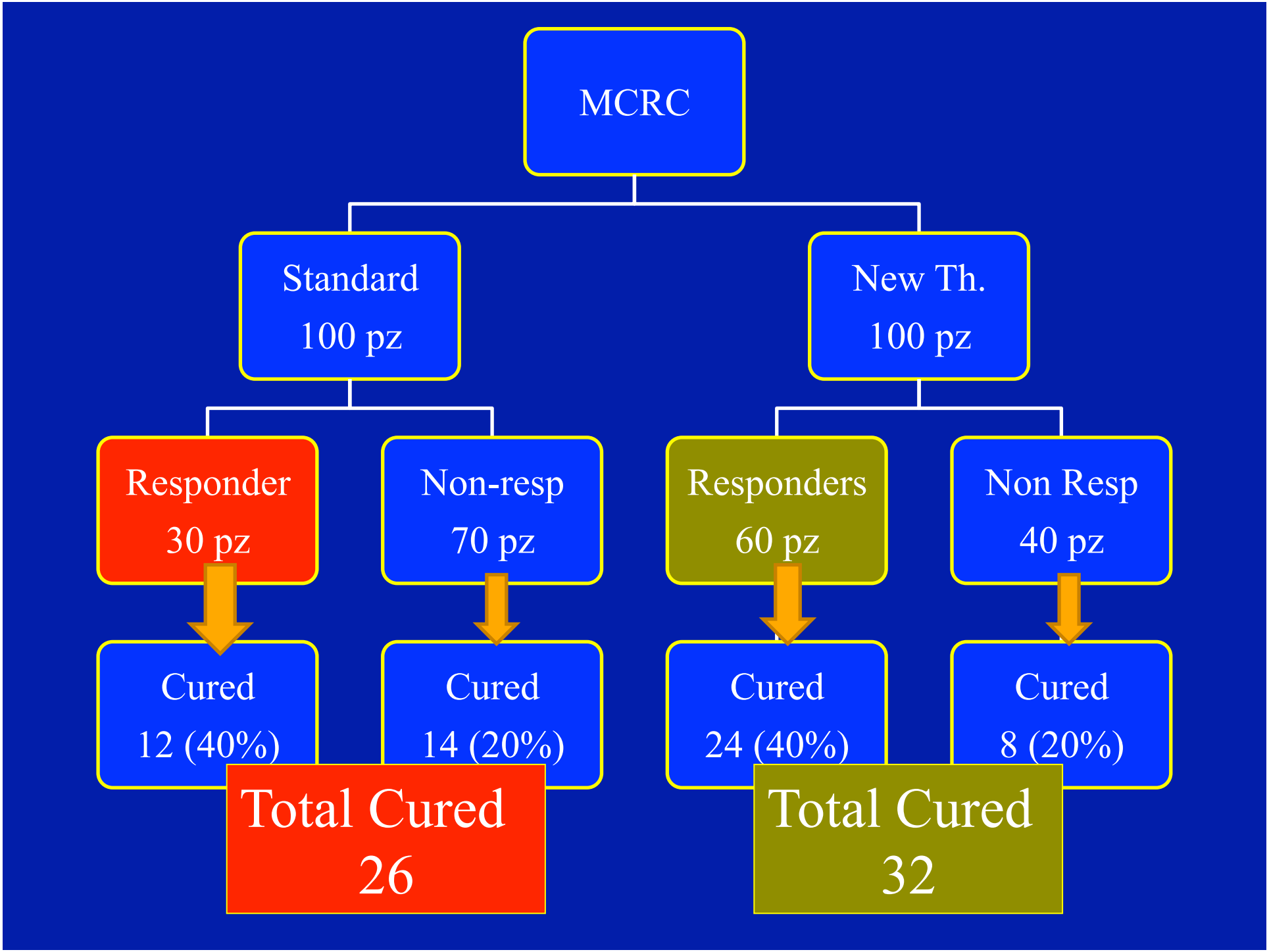
Dilution

Hypothesis:

1. Response doubles the proportion of “cures” (from 20% to 40%)

2. If an experimental treatment doubles the proportion of responses (from 30 to 60%) what is going to be its effect on the proportion of “cures”?


MCRC
Standard
100 pz
New Th.
100 pz
Responder
30 pz
Non-resp
70 pz
Responders
60 pz
Non Resp
40 pz


MCRC
Standard
100 pz
New Th.
100 pz
Responder
30 pz
Non-resp
70 pz
Responders
60 pz
Non Resp
40 pz
Cured
12 (40%)
Cured
14 (20%)
Cured
24 (40%)
Cured
8 (20%)
Total Cured
26
Total Cured
32

Diluition

Response doubles % cures (from 20 to 40%)

Exp doubles % response vs St. (from 30 to 60%)

Standard: **26% CURES**

Experimental: **32% CURES**

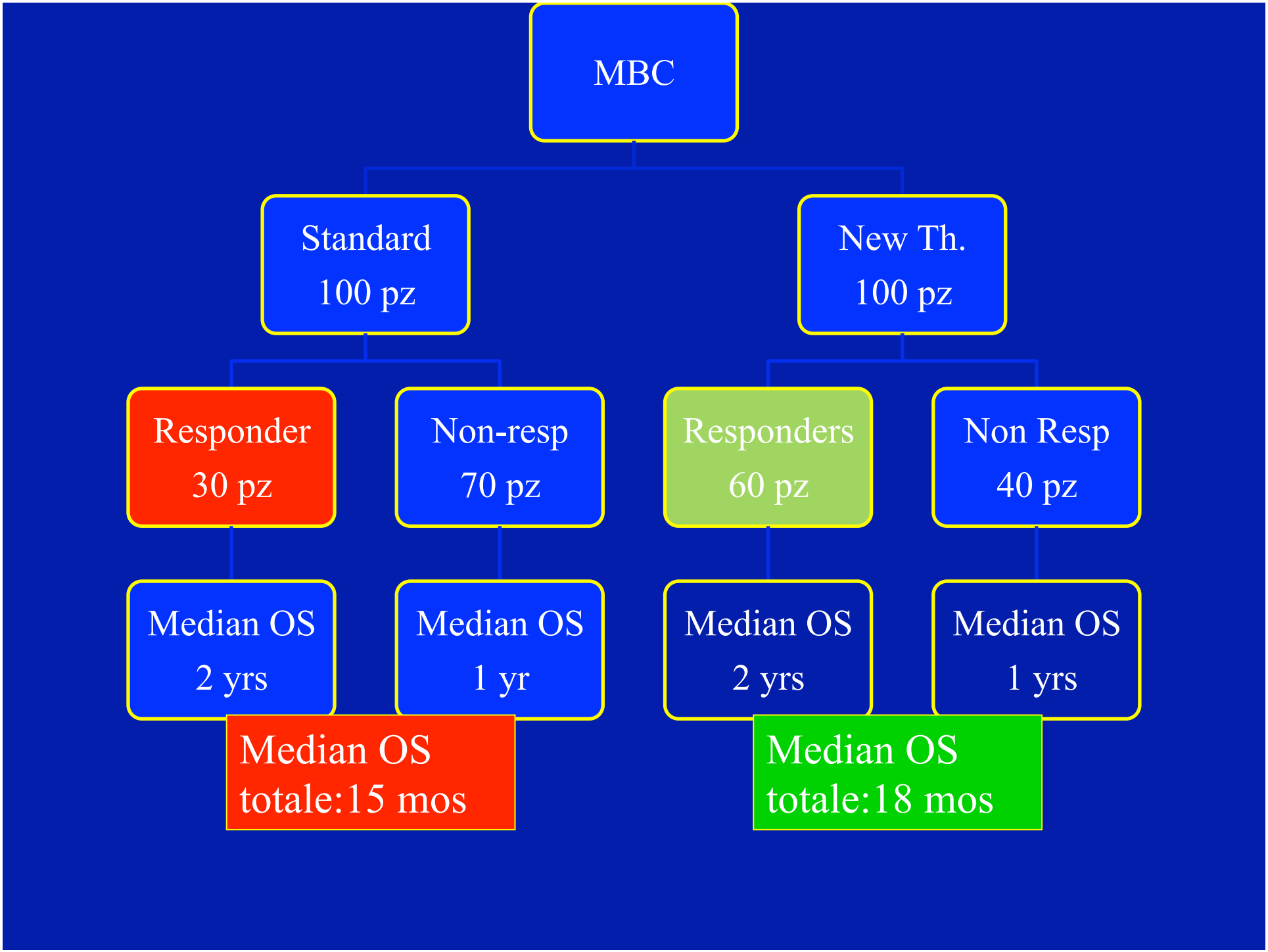
Dilution & Sample Size

Number of patients that are needed in a trial to asssess with power =80% if the effect of the experimental treatment is to raise

- Response Rate from 30% to 60% = **100 pts**

- Cure Rate from 26% to 32%= **1860 pz**

TIME: 3 months vs several years


MBC
Standard
100 pz
New Th.
100 pz
Responder
30 pz
Non-resp
70 pz
Responders
60 pz
Non Resp
40 pz
Median OS
2 yrs
Median OS
1 yr
Median OS
2 yrs
Median OS
1 yrs
Median OS
totale:15 mos
Median OS
totale:18 mos

?

If surrogate endpoints are so effective in reducing required sample size and study duration, why don't we always use them in clinical trials?

Only valid surrogate endpoints can be used!

Validity of a Surrogate Endpoint

‘Surrogacy requires that the effect of the intervention on the ‘candidate’surrogate predicts its effect on true clinical outcome’

Prentice RL

Plausible but Invalid Surrogate Endpoints

Intervention	Surrogate	True endpoint
Screening	Stage/Survival	Mortality
Antiaritmics	Arithmias	Sudden Deaths
Tolbutamide	Glycemia	Mortality CVD
Oral Contr.	BBD	B.C. Risk
Ormonotherapy in Prostate c.	PSA changes	Survival

‘True’ (Natural) Endpoint in efficacy (phase III) trials

- Efficacy = treatment benefit looked for by the patient
- Treatment benefit looked for by cancer patient = To live longer and/or better
  - Longer: True endpoint = Overall Survival
  - Better: True Endpoint = Quality of Life

‘True’ (Natural) Endpoint in efficacy (phase III) trials

- Efficacy = treatment benefit desired by the patient
- Treatment benefit desired by the (cancer) patient = To live longer and/or better
  - Longer: True endpoint = Overall Survival
  - Better: True Endpoint = **Quality of Life**
- **Difficult to study (S.E. major problems)**
- **PB not an expert**

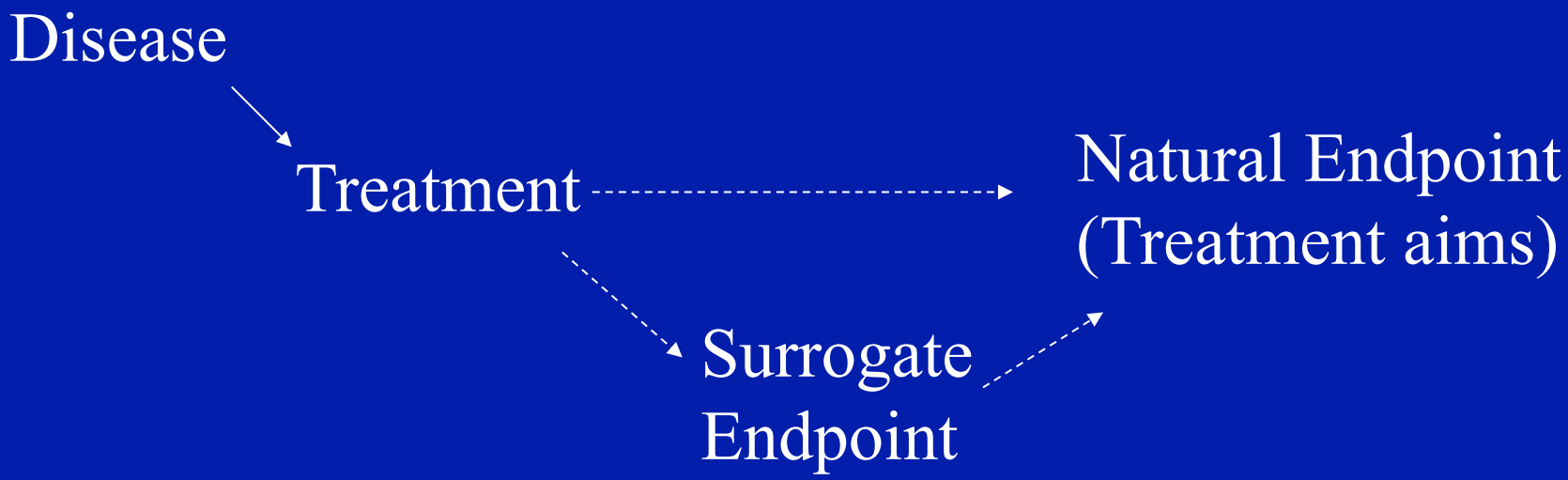
‘True’ (Natural) Endpoint in efficacy (phase III) trials

- Efficacy = treatment benefit desired by the patient
- Treatment benefit desired by the (cancer) patient = To live longer and/or better
- Longer: True endpoint = **Overall Survival**

Surrogate Endpoints of Survival

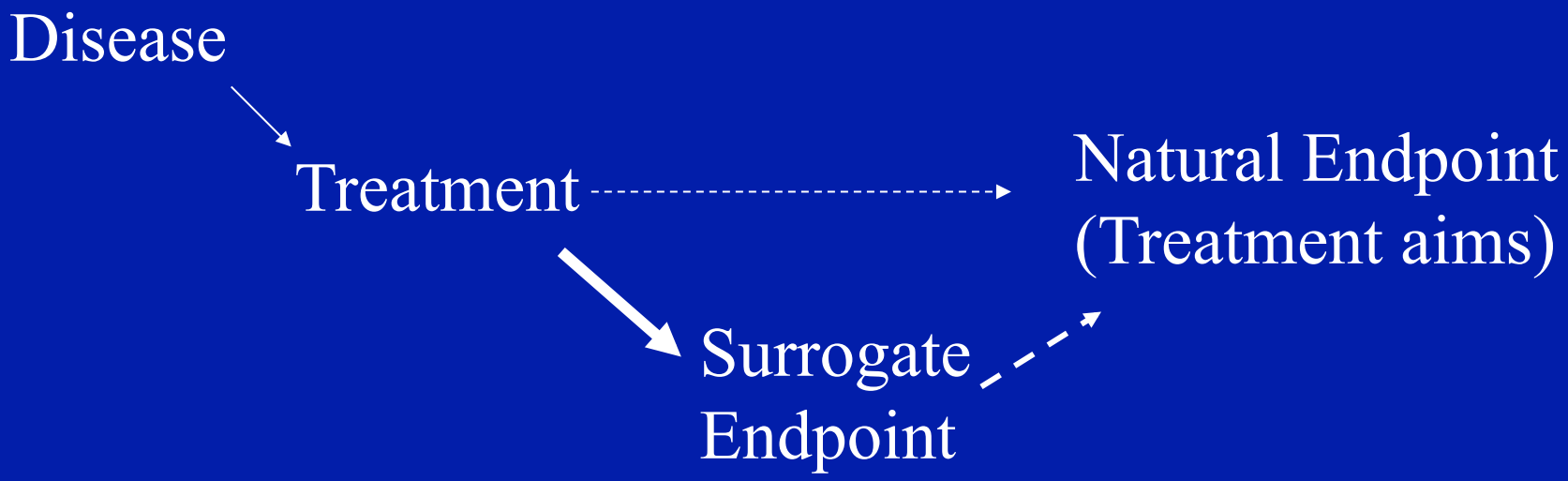
Endpoints that, when measured in a clinical trial, allow to predict the effect of a treatment on Survival

Surrogate Endpoint ≈ Intermediate Marker

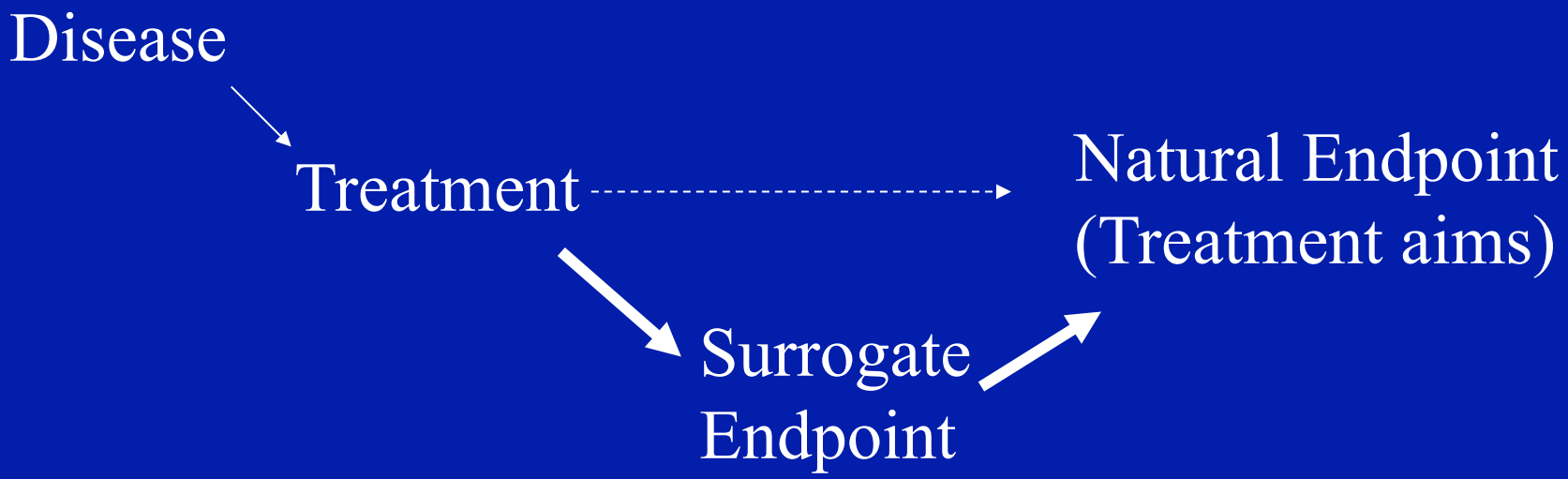


A surrogate endpoint may or may not precede the natural endpoint, and may or may not be involved in the pathway of events leading to treatment effect

Surrogate Endpoint: Sensitive to the effects of treatment



Surrogate Endpoint: Correlated with outcome



Surrogate endpoints vs Prognostic Factors

- **Prognostic Factor:** Predicts the outcome (e.g. Stage): Measured at any time

- **Surrogate Endpoint:** Used to assess the efficacy of the treatment: Assessed AFTER therapy – It is prognostic

Surrogate endpoints vs Predictive Factors

- **Predictive Factor:** Predicts the efficacy of a therapy (e.g. Estrogen Rec. and Tamoxifen): Assessed BEFORE therapy

- **Surrogate Endpoint:** Used to assess the efficacy of the treatment: Assessed AFTER therapy – It is prognostic

Activity Endpoints vs Surrogate endpoints

- Activity Endpoints:

To assess if the treatment is sufficiently active to warrant efficacy trials

  - Tumor shrinkage
  - PET response
  - Markers
  - Molecular changes (Target)

- Surrogate Endpoint

To assess if the treatment is effective

Activity Endpoints vs Surrogate endpoints

- Activity Endpoints:
  - Not always prognostic
  - Sensitive to treatment effects on its target
  - Specific
  - Often not surrogate

- Surrogate Endpoint
  - Prognostic
  - Sensitive to treatment effect
  - Often not activity endp.
  - **Must adsorb the effect of treatment on the true endpoint**

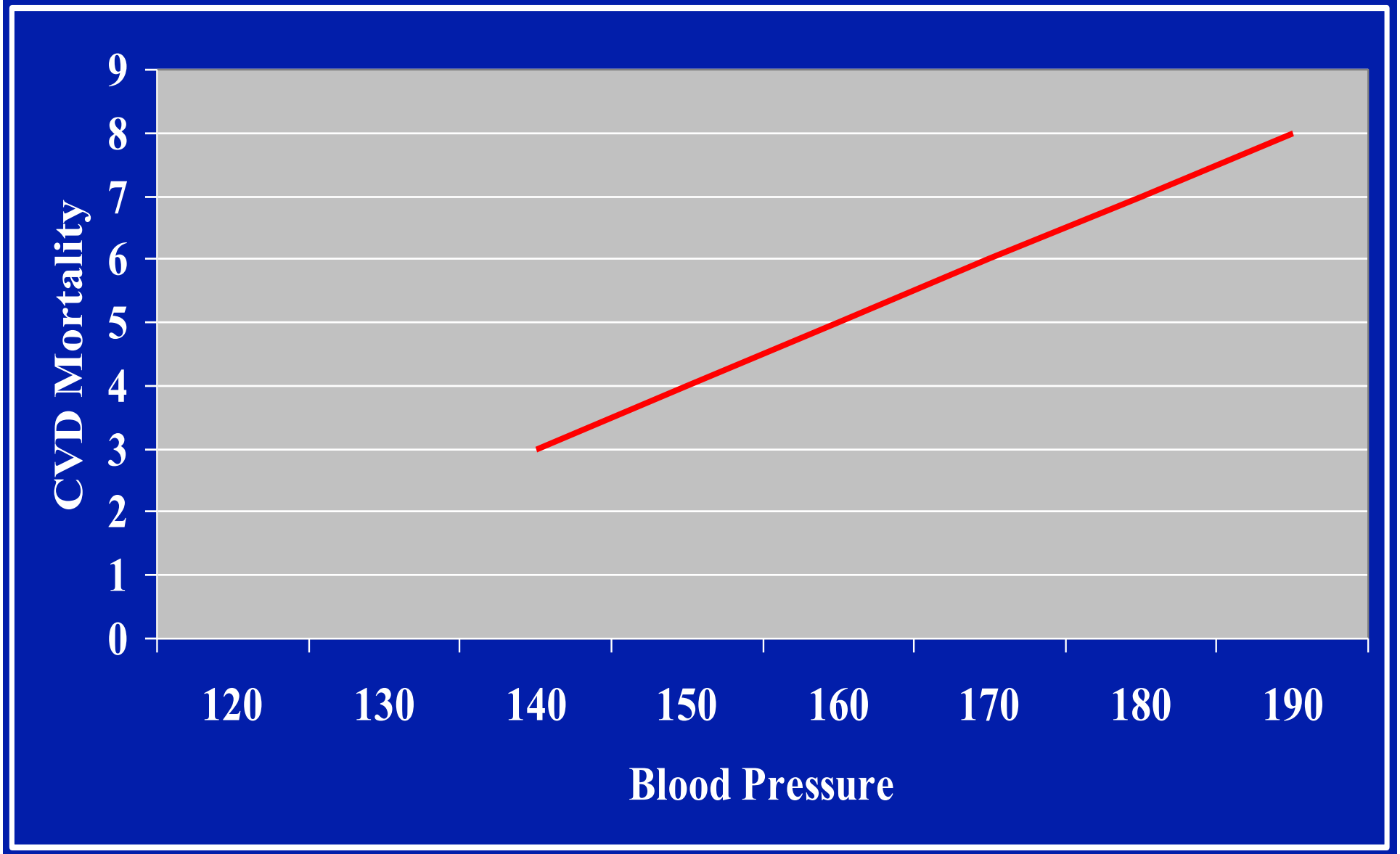
Activity Endpoints vs Valid Surrogate Endpoints

	• Activity Endpoint	• Surrogate Endpoint
SBP, DBP	Yes	(Yes?)
Blood Sugar	Yes	No
Earlier Diagnosis	Yes	NO!
Disease Incidence	yes	?
RFS, PFS	NO	Yes?
Objective response	YES	Yes?

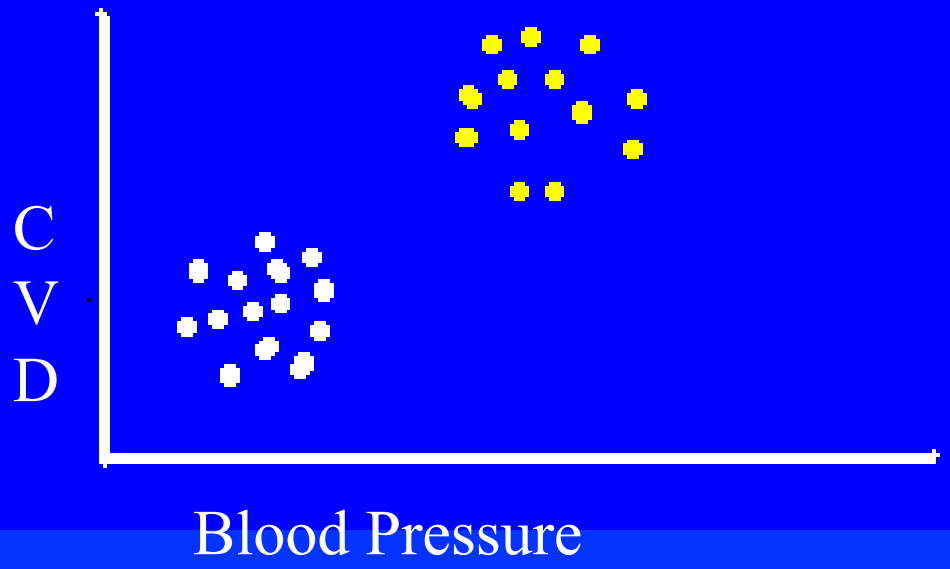
Theory of surrogate endpoints

Blood Pressure and Cardiovascular Mortality

Blood Pressure and CVD Mortality



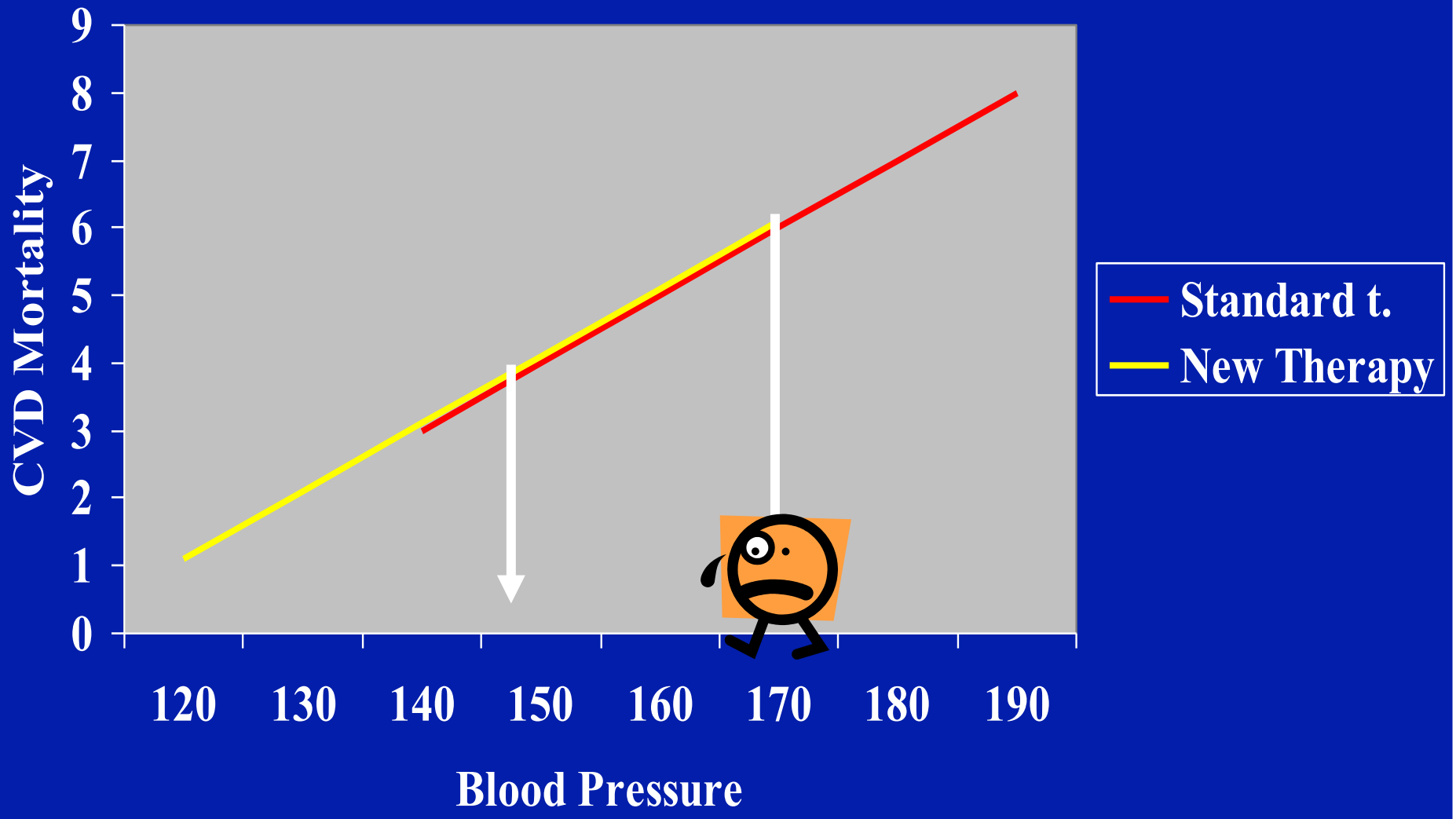
Many trials showed that treatments lowering Blood Pressure reduce CVD mortality



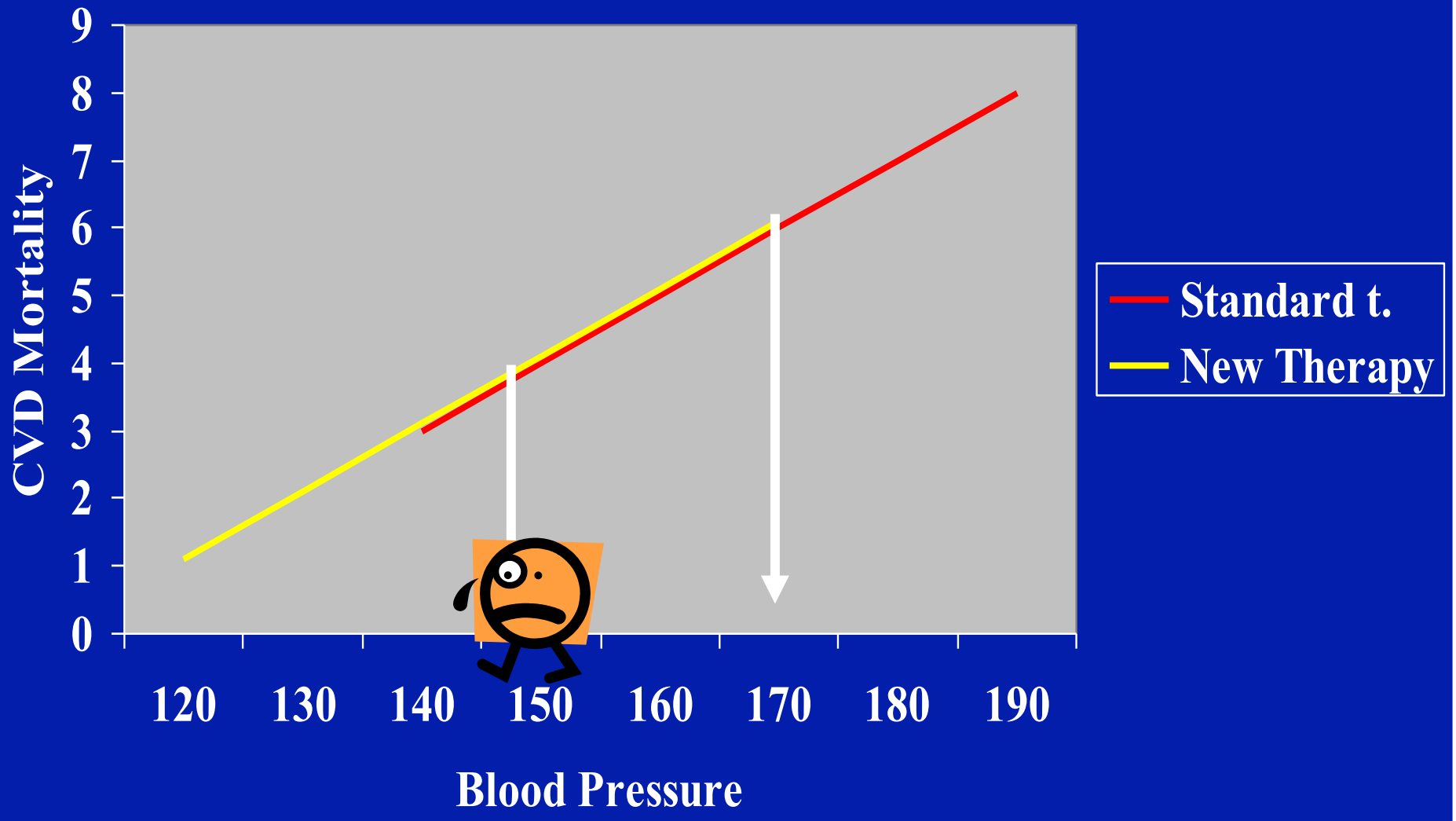
Based on this evidence…

- Can we use a new therapy only because it is effective in lowering blood pressure?
- Can we use Blood Pressure to monitor and modify therapy in a patient?

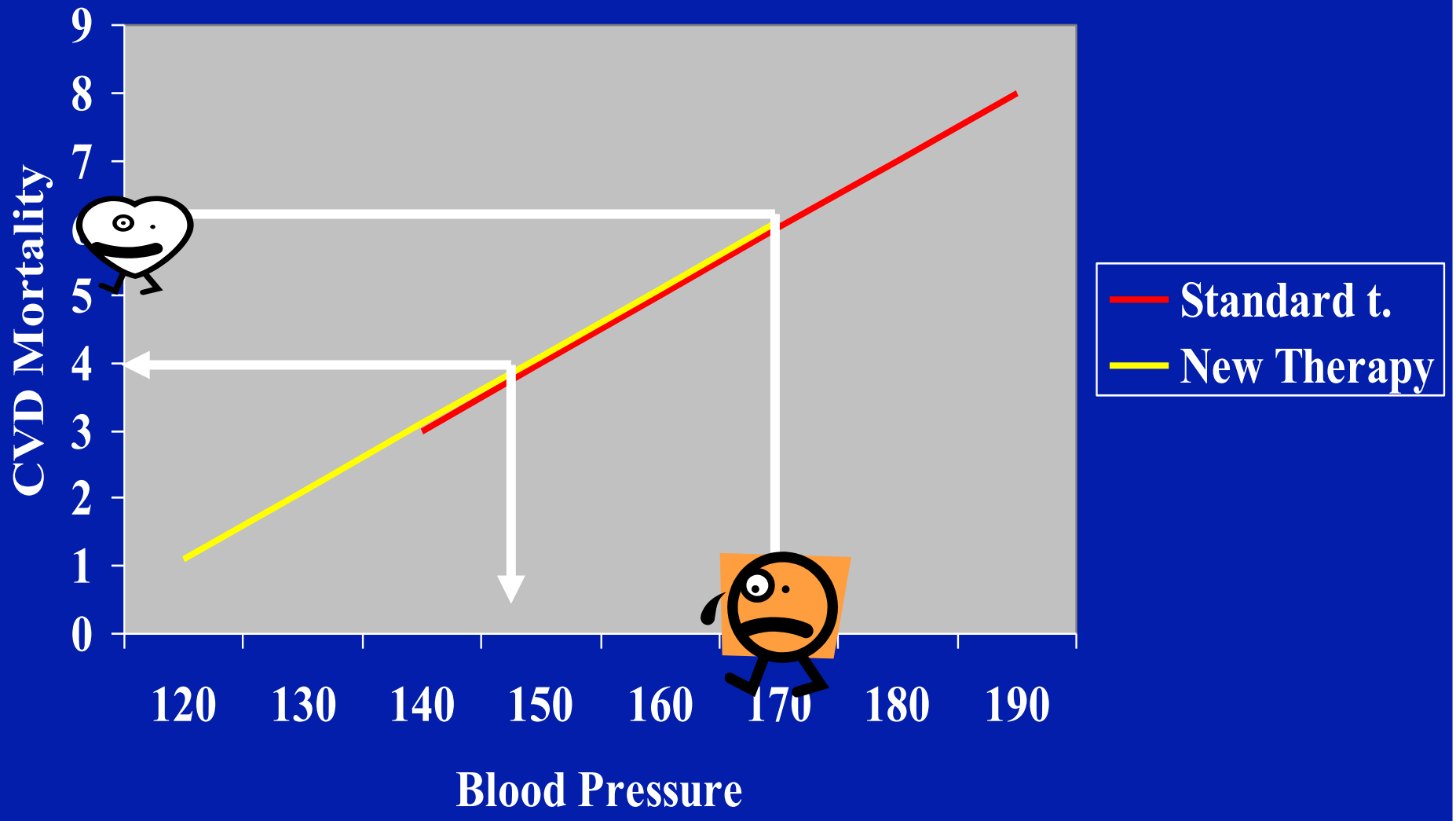
Blood Pressure and CVD Mortality



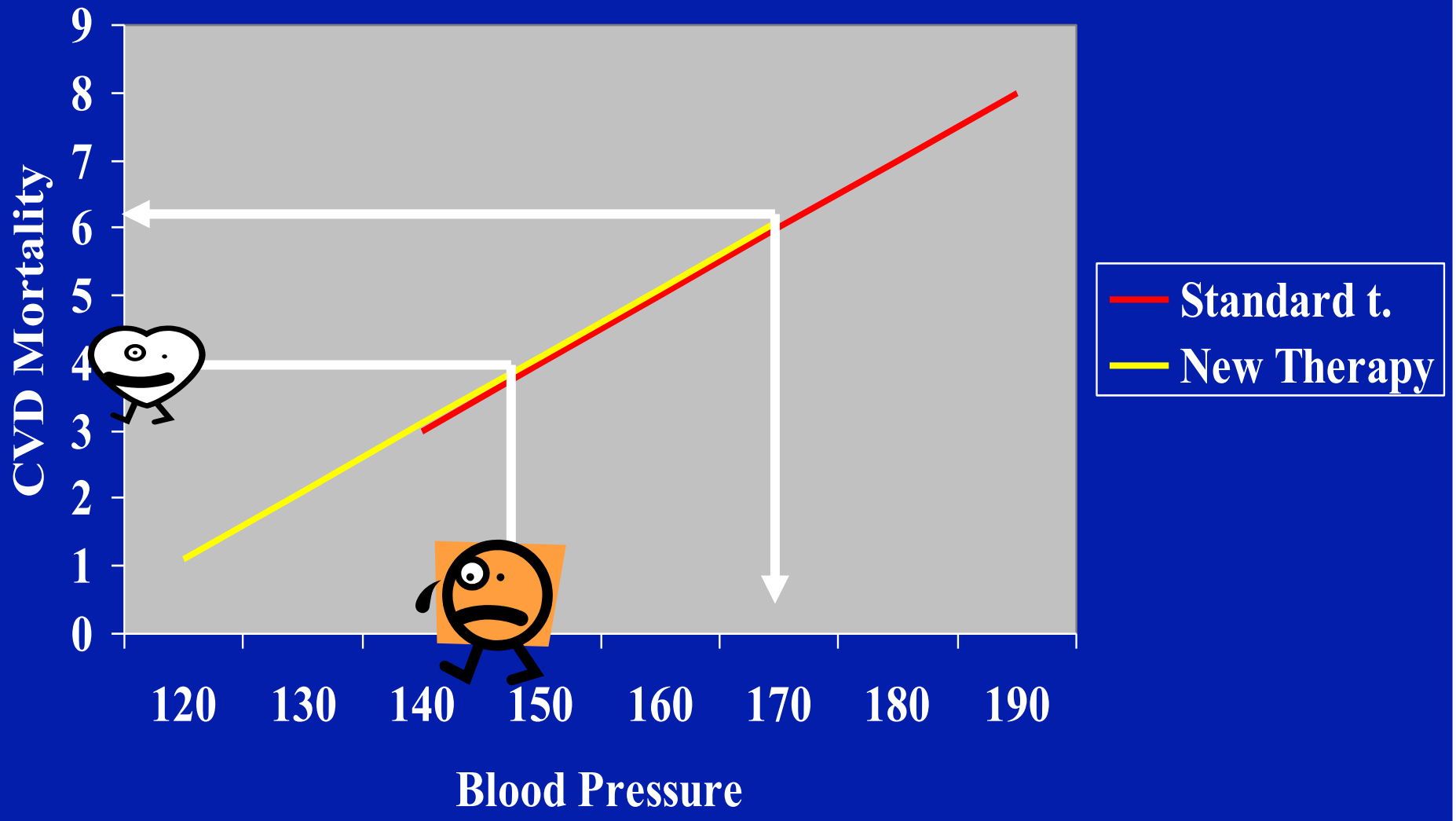
Blood Pressure and CVD Mortality



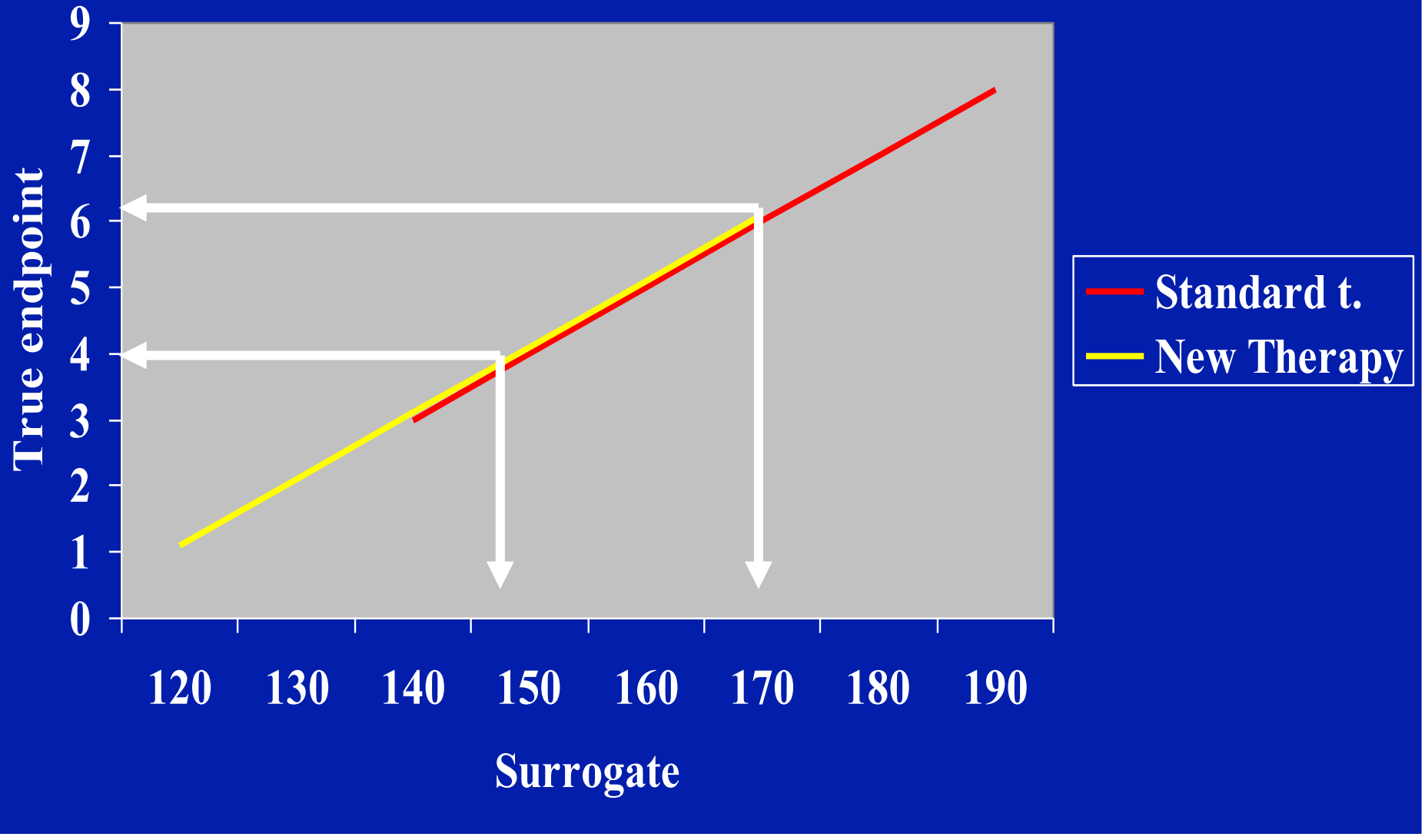
Blood Pressure and CVD Mortality



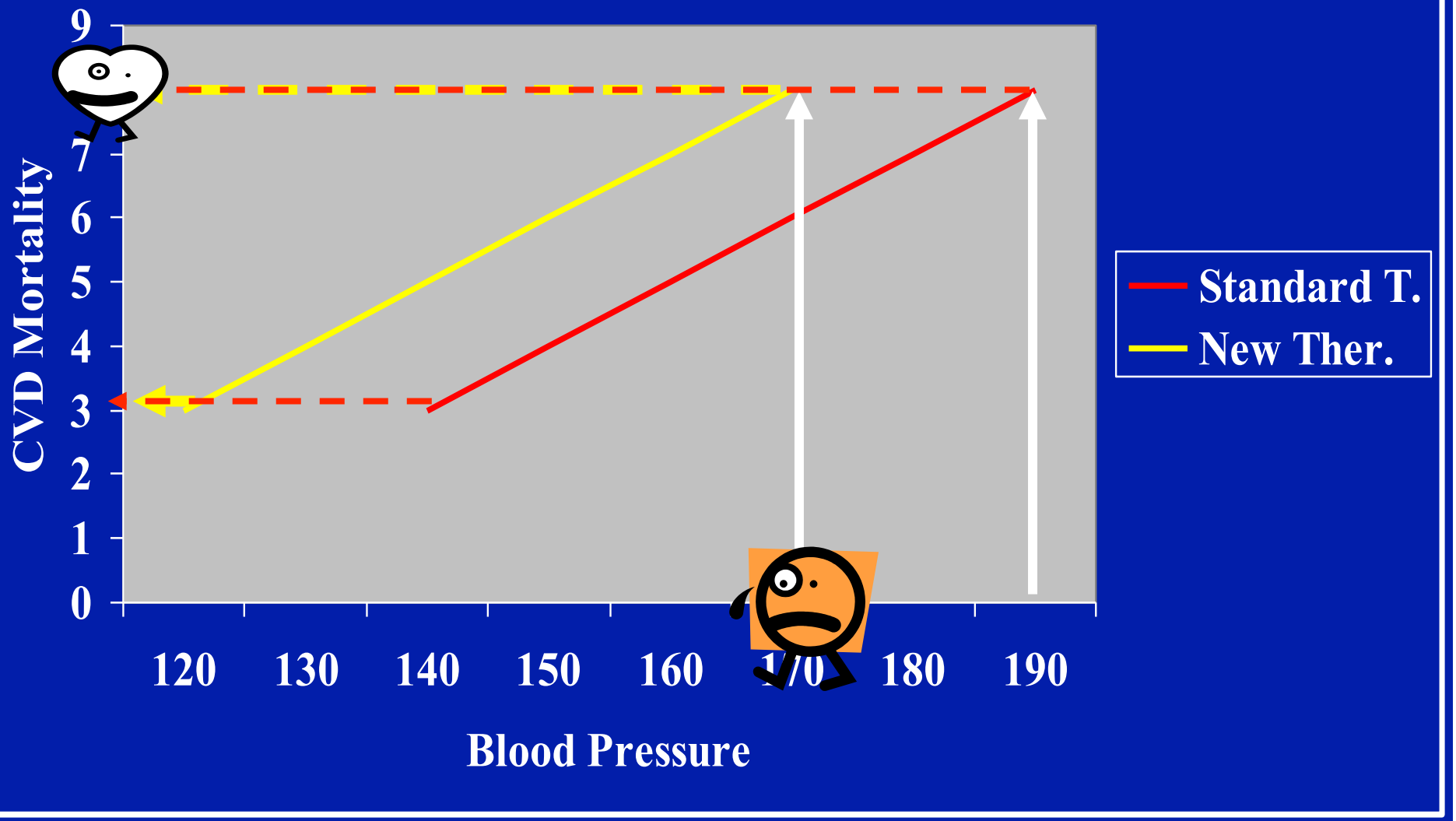
Blood Pressure and CVD Mortality



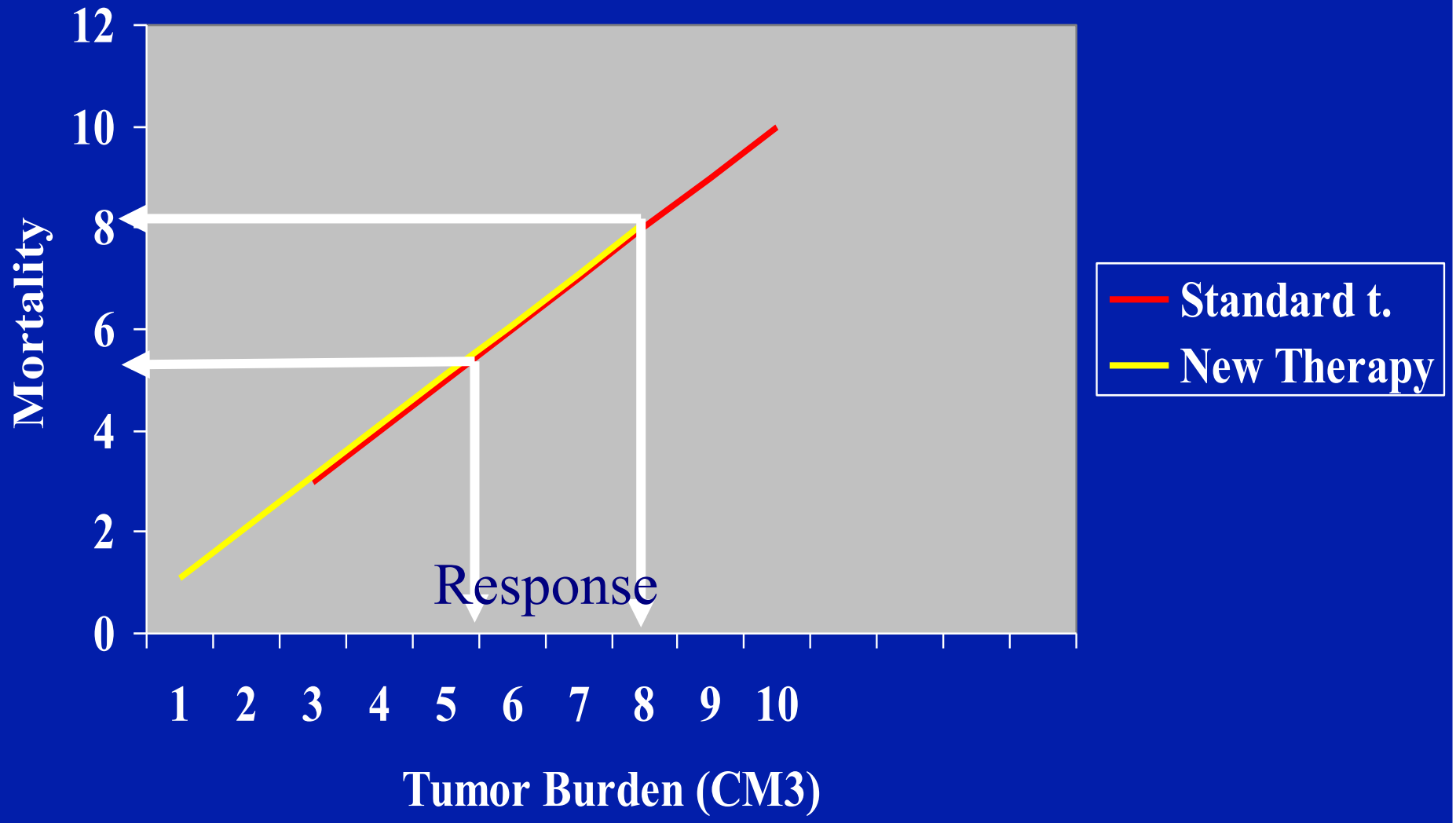
The outcome depends only on the surrogate and not on the treatment



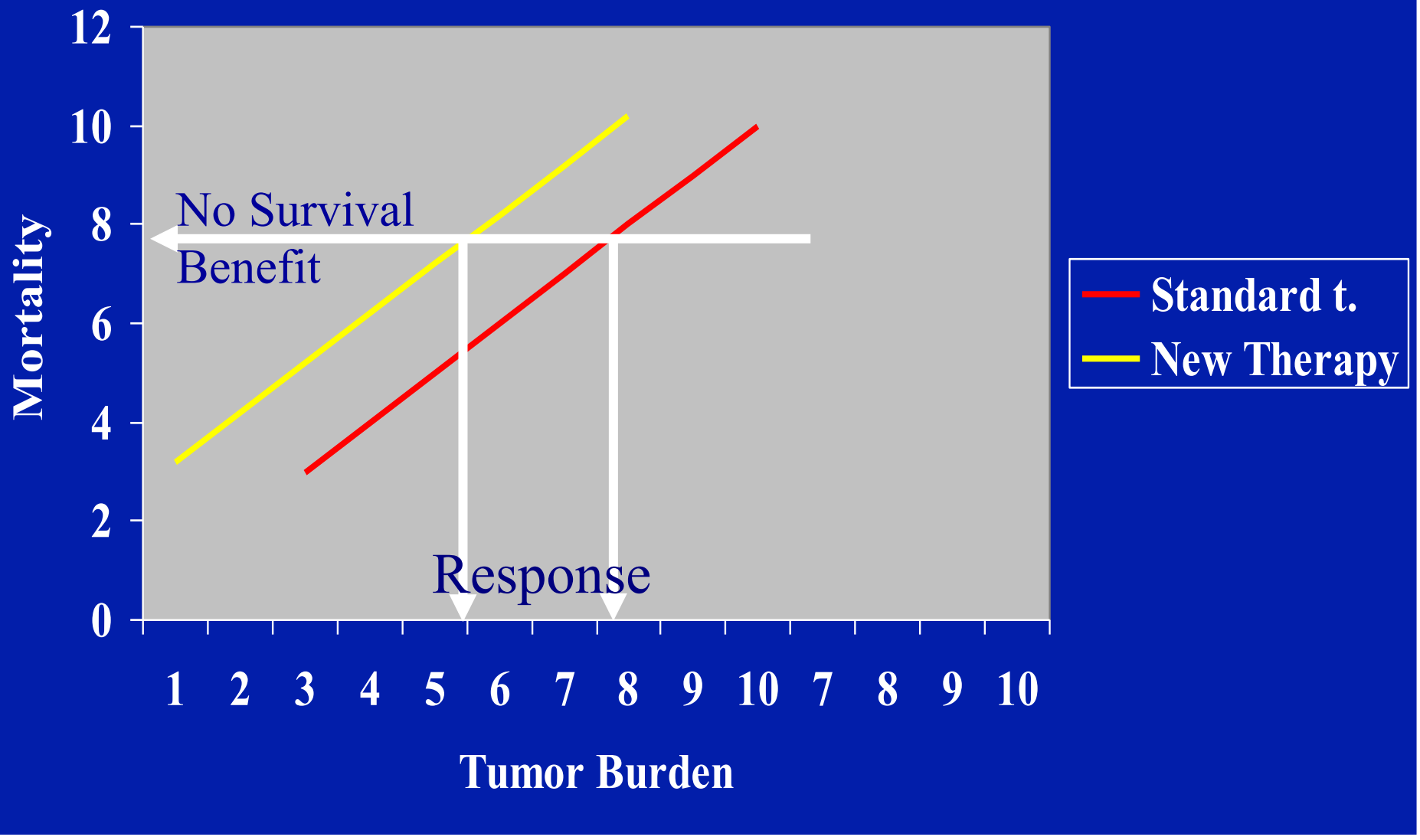
Blood Pressure and CVD Mortality –Alternative possibility



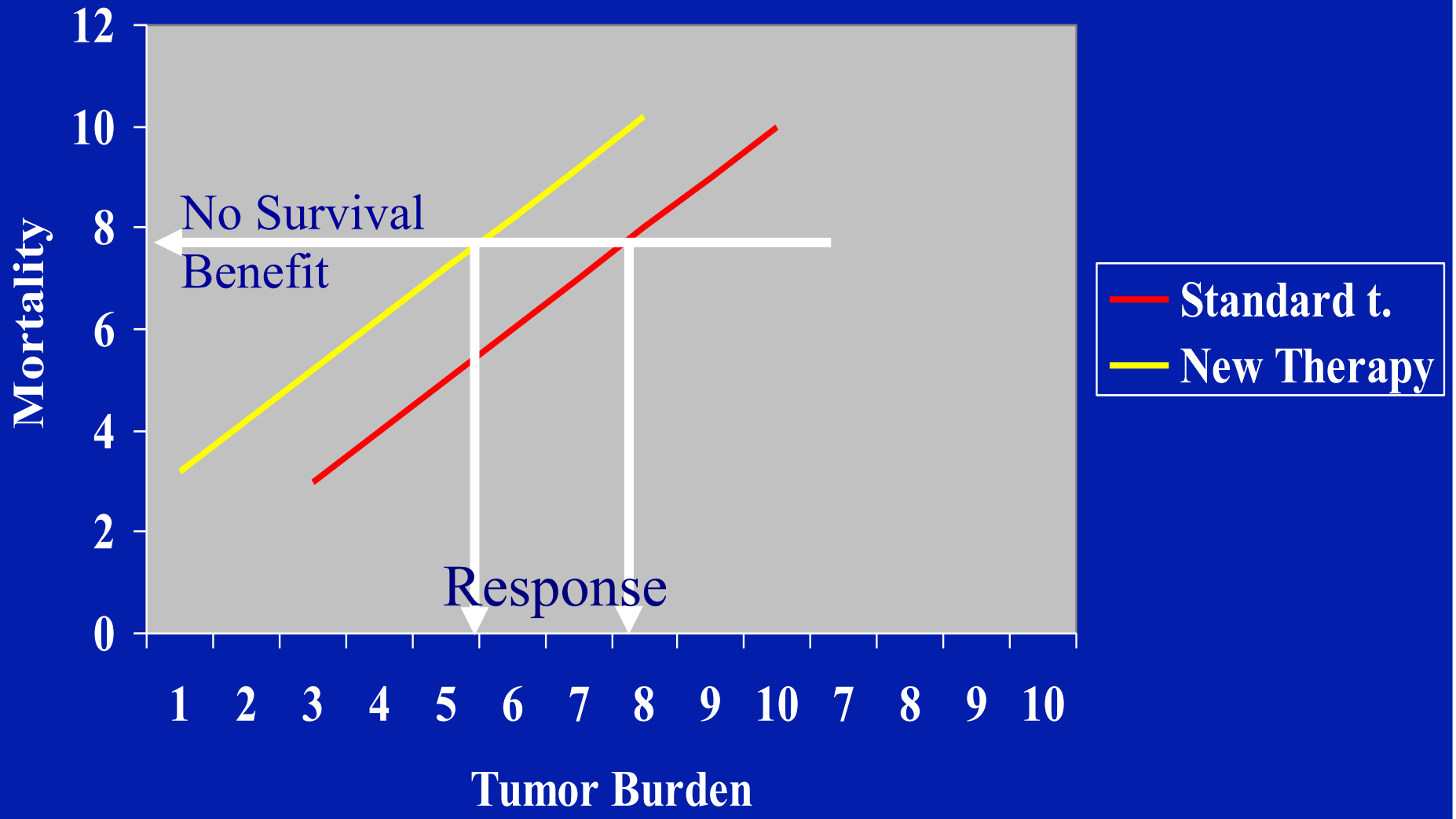
Tumor Burden and Mortality



Tumor Burden and Mortality



Responders to the experimental treatment ≠ Responders to standard therapy



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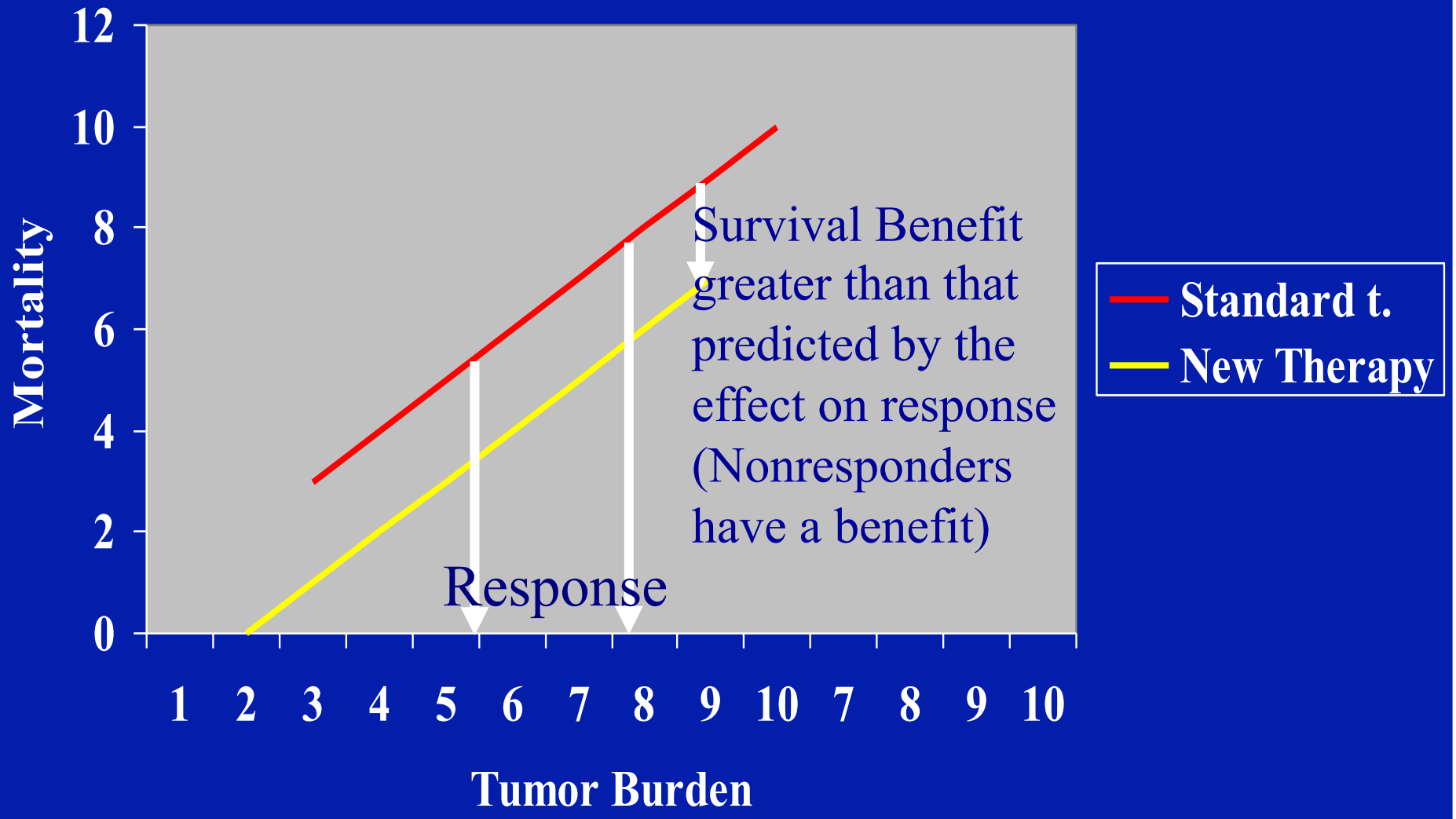

The correlation between an intermediate endpoint and the true endpoint, **is necessary but not sufficient** to justify the use of this intermediate endpoint in the assessment of treatment efficacy

Validation of surrogate enpoints

Validation of surrogate endpoints

- Prentice's Criteria

(Individual level surrogacy)

- Meta-analytic Approach

(Trial level surrogacy)

Validation of a surrogate endpoint

- Correlation with outcome
- Sensitivity to treatment effects
- *Individual level surrogacy*

  Outcome related to surrogate & independent of therapy
- *Trial level surrogacy*

  Correlation across trials between effect on surrogate and effect on true endpoint

Requirements for validation

- **Individual level**
  - **Large database** (usually meta-analysis) from **RCT(s)** where both surrogate and true are recorded
- **Trial level**
  - Meta-Analysis of **RCTs** in which adequate variation in treatment effects on surrogate and true was observed

Validated Surrogate Endpoints in cancer

Intervention	**Surrogate**	**True endpoint**
CTX in metastatic CRC, BC, NSCLC	Objective response	Survival
CTX in metastatic CRC (BC)	PFS	Survival
Adjuvant CTX in Early CRC (BC)	DFS	Survival

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Intervention	Surrogate	True endpoint
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NONE in Rare Cancers (incl. Sarcomas)

Main Limitation of Surrogate Endpoints

1. To validate a Surrogate it takes a large randomised Trial demonstrating the efficacy of the experimental treatment on the true endpoint (or a meta-analysis)

2. Validation is
   - disease-specific
   - treatment-specific
   - natural endpoint-specific

Limitations of Surrogate Endpoints

If there is already a RCT showing efficacy, and it is not possible to extrapolate to other diseases or treatments…..

- Trials of new therapies in the same disease? NO!
- Trials of same therapy on other endpoints? NO!
- Trials of same therapy in other diseases? NO!

what is the use of SURROGATE ENPOINTS?

?

(to keep biostatisticians busy?)

Possible Uses

- Confirmatory Trials
- Trials of analogues with the same mechanism of action
- Quality of care (Districts, Groups of patients, Hospitals)

- **Phase II Trials**

- **Medical decision and Treatment Modulation in the Individual patient**

Phase II trials

Primary Endpoint: A Surrogate Endpoint validated for different therapies/diseases

- When no activity endpoint can be measured (e.g. no biopsies)
- Stronger Plausibility for subsequent phase III trial
- Smaller sample size ?

Surrogate endpoints for the individual patient

Experimental treatment vs Standard treatment

Gain in Median survival: From 6 to 12 months

All patients have the same benefit (4 months)

Only responders (30%) have a benefit

- Partial reponders (25%) 1 year
- Complete resp.s (5%) 5 years

Note

The requirements to use Surrogate Endpoints

- in rare tumors
- in the individual patient

may be much less strict than those for phase III trials

“Bayesian” validation of a S.E.

- A SE already validated in other types of cancer
- Confirmed to be correlated with true endpoint also in the rare cancer X
- Modified by treatment
- Prognosis seems to be similar between “responders” to different treatments

Example

- Response to an immunotherapic agent has been shown to be a VALID surrogate endpoint in lung c. colon c. and kidney c.
- In rare tumor X, the agent doubles the % of responders
- Responders to the agent have the same OS as responders to standard therapy and live longer than non-responders
- Do you need more evidence?

Bayesian validation of surrogate endpoints

Prentice Criteria

1. SE Correlated with outcome
2. SE sensitive to treatment effects
3. Treatment affects outcome
4. Treatment effect disappears when SE is adjusted for

New Criteria

1. SE Correlated with outcome
2. SE sensitive to treatment effects
3. (- shown to be a valid SE in other cancers)
4. Test: Outcome SE-specific independent of treatment

Conclusions

- Surrogate endpoints are a neglected area of methodological research
- They may prove extremely important in rare cancers
- Need to start new studies (prospective data collection)