Surrogate Endpoints

C. Michael Gibson, M.S., M.D.

Harvard Medical School

Chairman, PERFUSE Study Group

Founder and Chairman, WikiDoc & WikiPatient, The World's Open Source Textbook of Medicine Viewed 896 Million Times A Year

Surrogate Endpoint

- A laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy
- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clincially meaningful endpoint.

Motivation

- Replace a late endpoint with an earlier
- Can be measured more easily or frequently
- Can be measured with higher precision, or less subject to competing risks
- Less affected by other treatment modalities or patient level variables
- Reduced sample size requirements
- Faster decision making

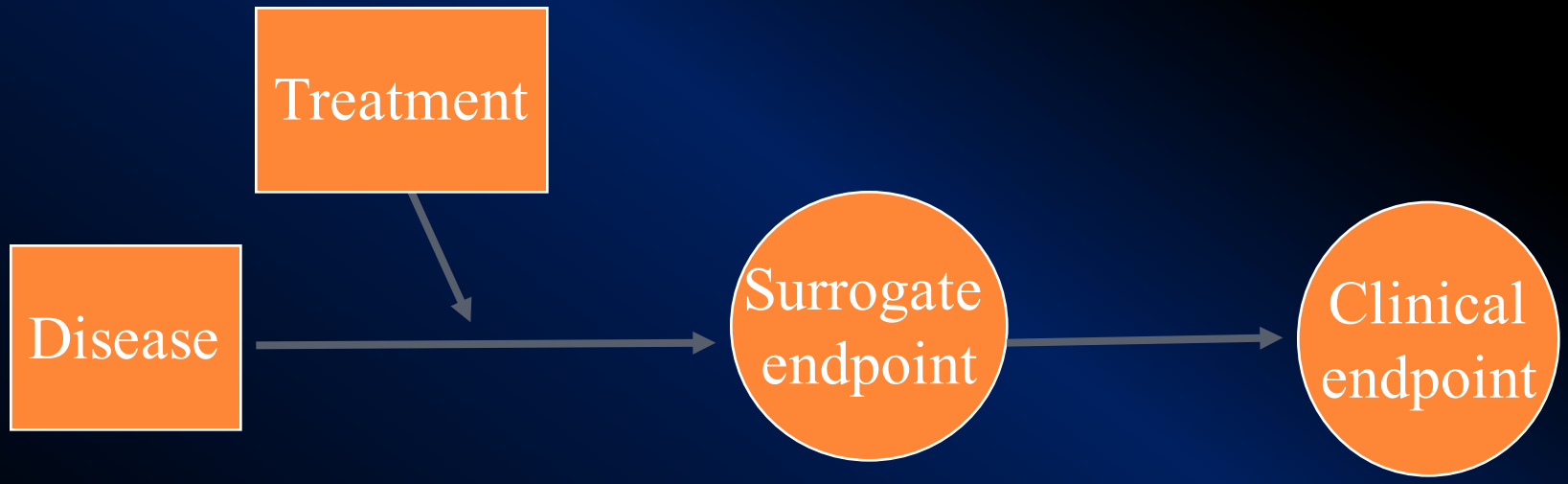
Surrogate Endpoints: Examples

Possible Surrogate	Clinical Endpoint
Blood Pressure	Stroke
LDL cholesterol	Myocardial infarction
Viral load, CD4 count	AIDS/Death

Surrogate Endpoints: The good and the bad

- “Good” surrogate endpoints can reduce exposure of patients to ineffective or toxic treatments (patient-time)
- “Bad” surrogates can give false promise to treatments that do not have real clinical benefit
- How do we tell the difference?

Ideal Surrogate Endpoint

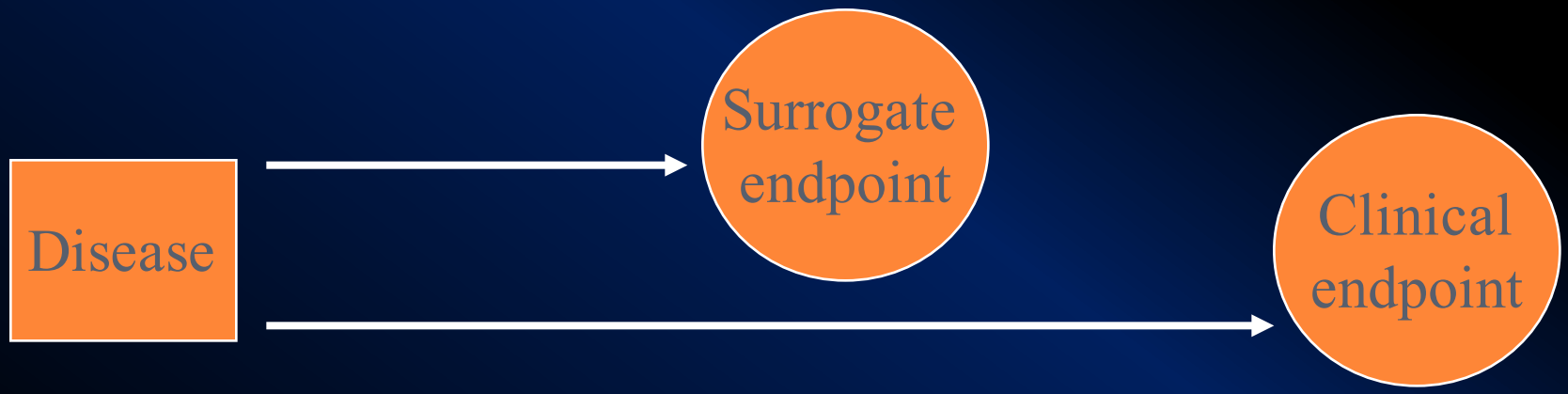


All mechanisms of action of the intervention on the true endpoint are mediated through the surrogate

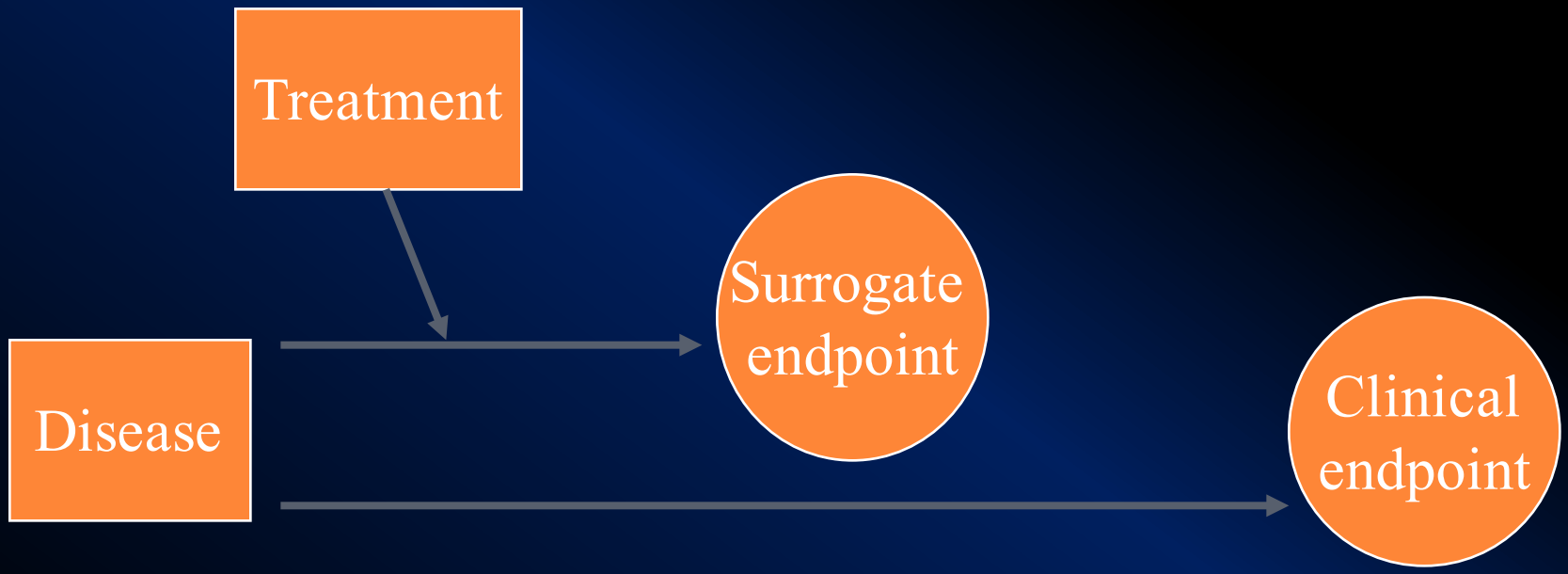
Surrogate Endpoints: vs. Prognostic Marker

- Prognostic marker – predicts the clinical outcome for an individual
- Surrogate endpoint – effect of an intervention on a surrogate endpoint reliably predicts the effect of the intervention on clinical outcome
- “A correlate does not a surrogate make”

Poor Surrogate Endpoint not on the causal pathway

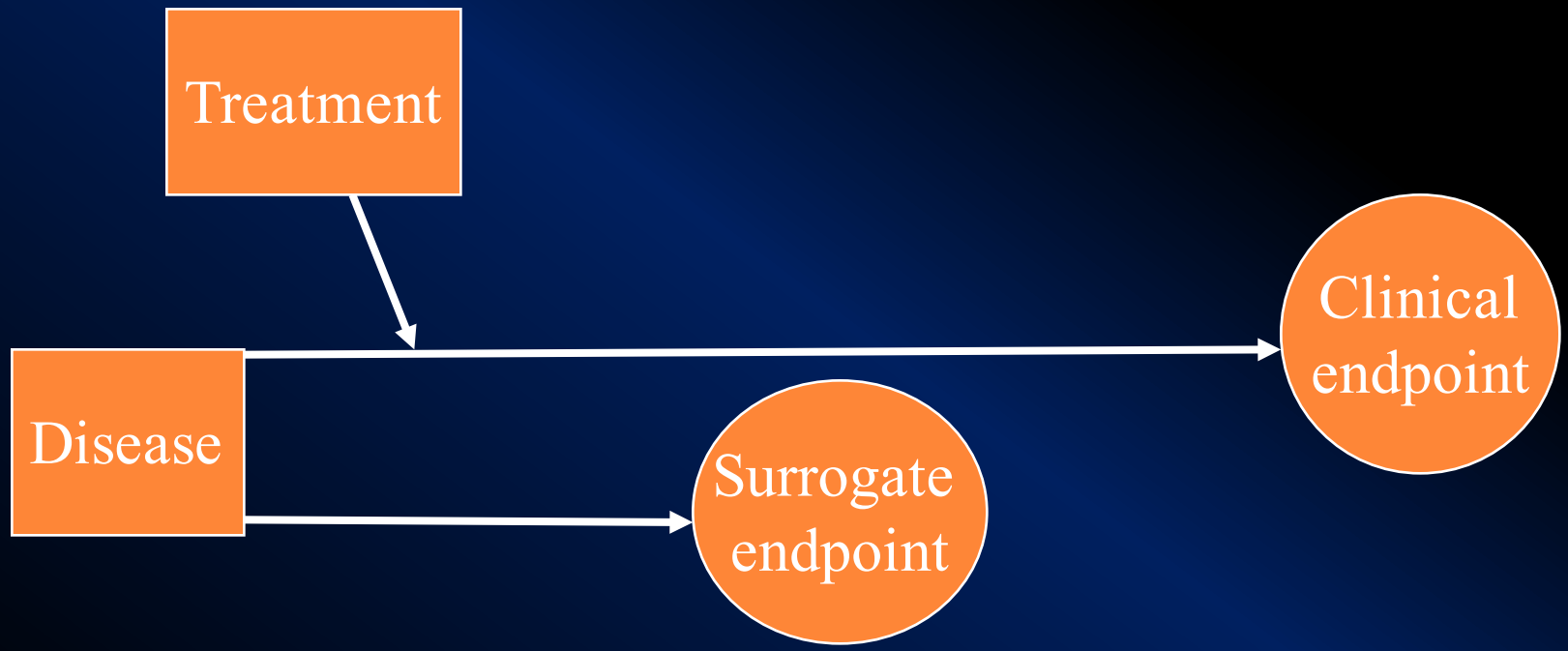


Poor Surrogate Endpoint 1



An intervention could affect the surrogate endpoint but not the clinical outcome (false positive)

Poor Surrogate Endpoint 2



Surrogate is not in the pathway of the interventions effect
(false negative)

Failed Surrogate Endpoints

Cardiac Arrythmia Suppression Trials

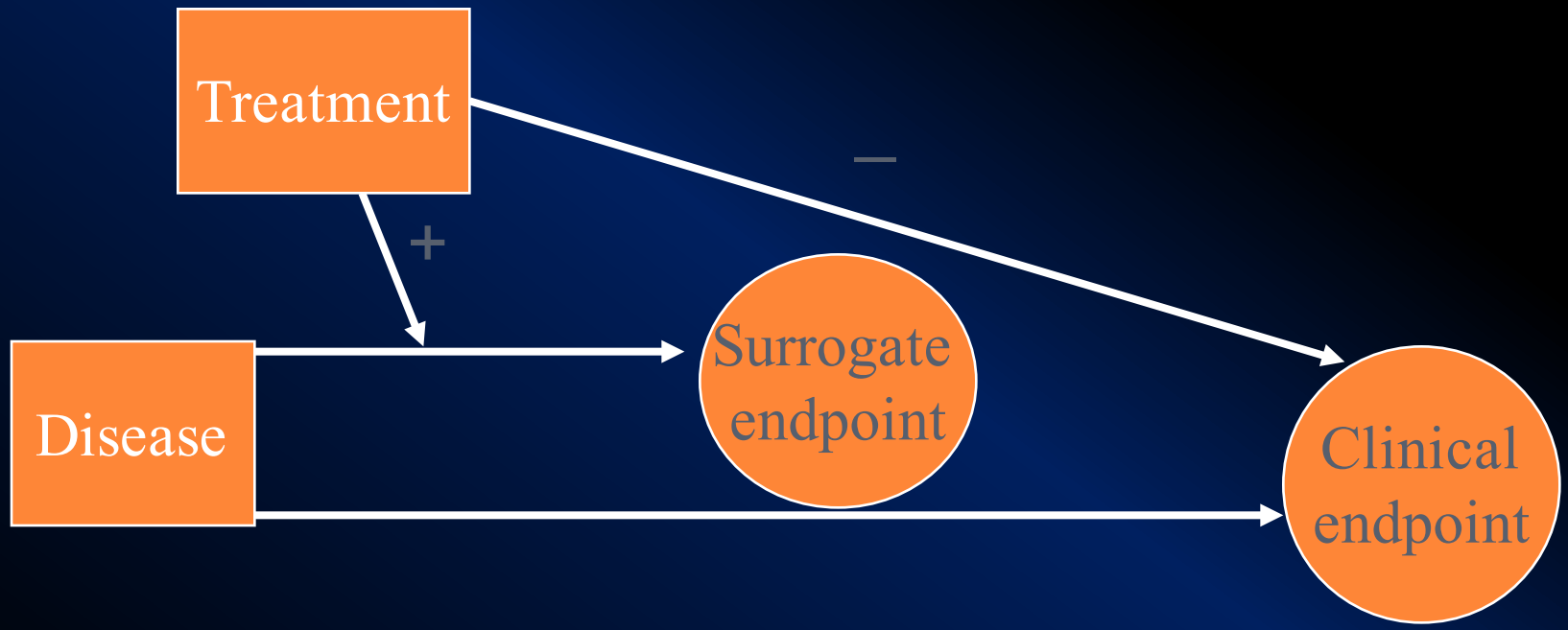
- Ventricular arrhythmias predict mortality after myocardial infarction
  - Patients with >10 VPB/h have 4X risk of death
- Antiarrythmic agents suppress VPBs
- It is logicial that suppression of VPBs might be associated with prevention of arrhythmic deaths

Failed Surrogate Endpoints

Cardiac Arrythmia Suppression Trials

- CAPS: encainide, flecainide and moricizine suppress VPBs c/w placebo control (n=502)
- CAST 1 (n=1498) excess deaths due arrhythmia in encainide and flecainide arms vs placebo
- CAST II (n=1325) stopped early by DSMB for excess deaths in moricizine vs placebo

CAST



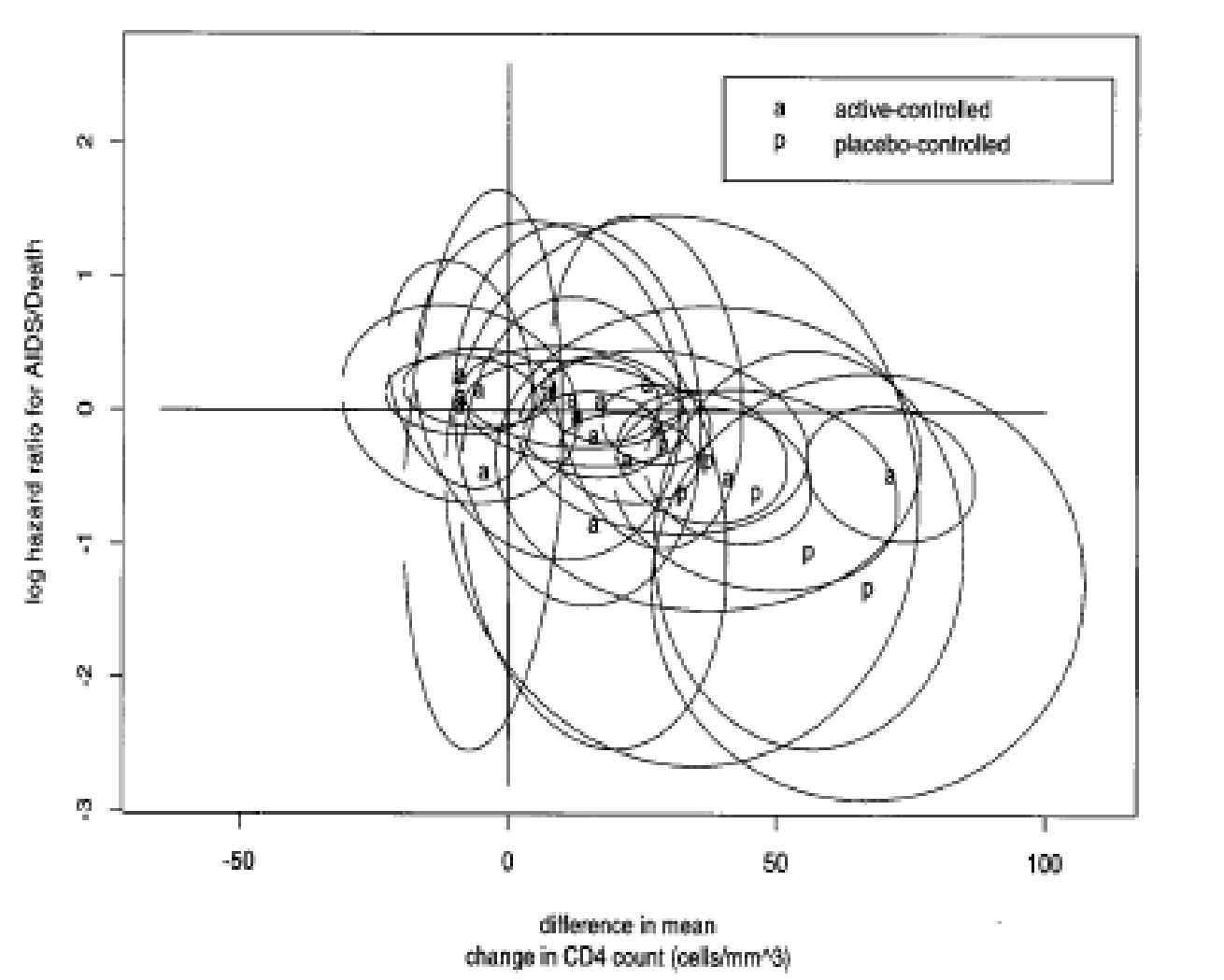
Intervention had a “positive” effect on surrogate but a direct negative effect on the clinical endpoint, not mediated by the surrogate endpoint.

Validating a surrogate endpoint

Need to build up a hierarchy of information

- Should be prognostic
- Changes in the potential surrogate after starting treatment should be prognostic
- Effects of treatments on the surrogate should be associated with effects of treatments on the clinical endpoint
  - –most difficult criterion

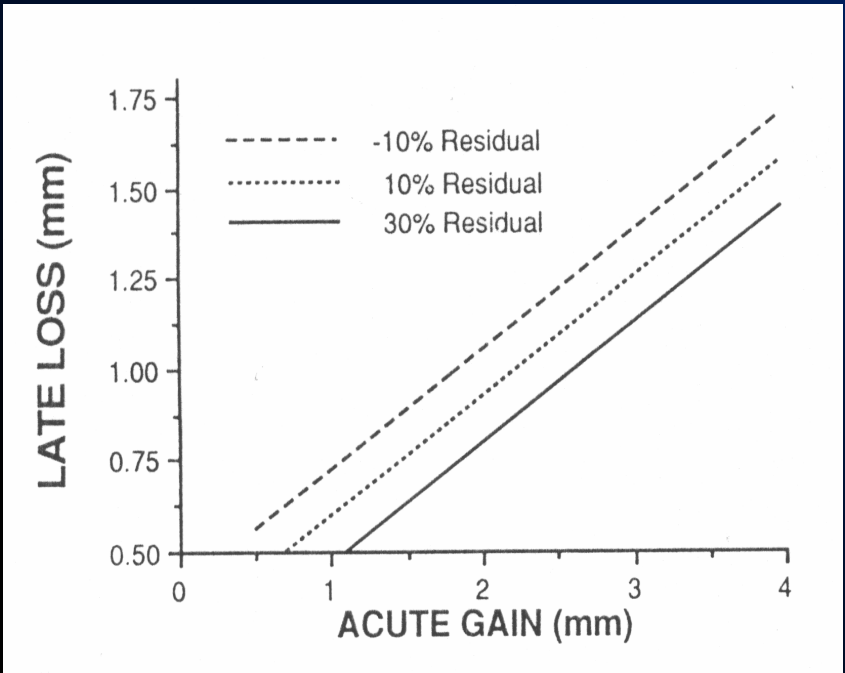
Metaanalysis for HIV surrogates



PERFUSE

Daniels and Hughes Stat Med 1997

Late Lumen Loss



Quantitative measure of coronary restenosis

- Late Loss = Follow-up MLD – Post procedure MLD

It is the target of DES therapy

- *Angiographic measure of neointimal hyperplasia*

In stent late loss predicts clinical restenosis:

c statistic = 0.915, SIRIUS[1]

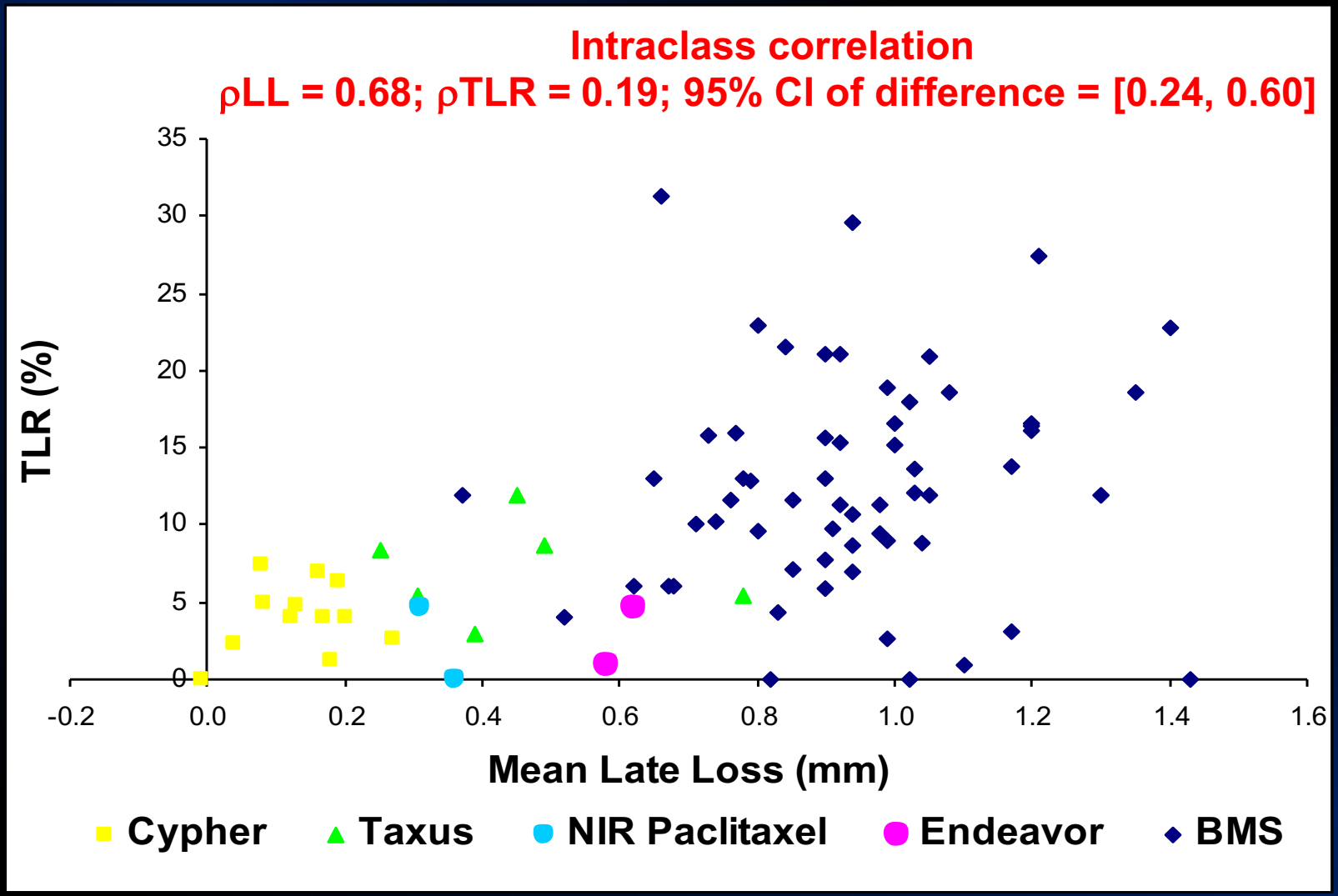
c statistic = 0.918, TAXUS 4[2]

PERFUSE

Kuntz *J Am Coll Cardiol* 1993. [1] Mauri Circ 2005. [2] Ellis et al. JACC 2005.

TLR is variable across trials

DES and BMS Results

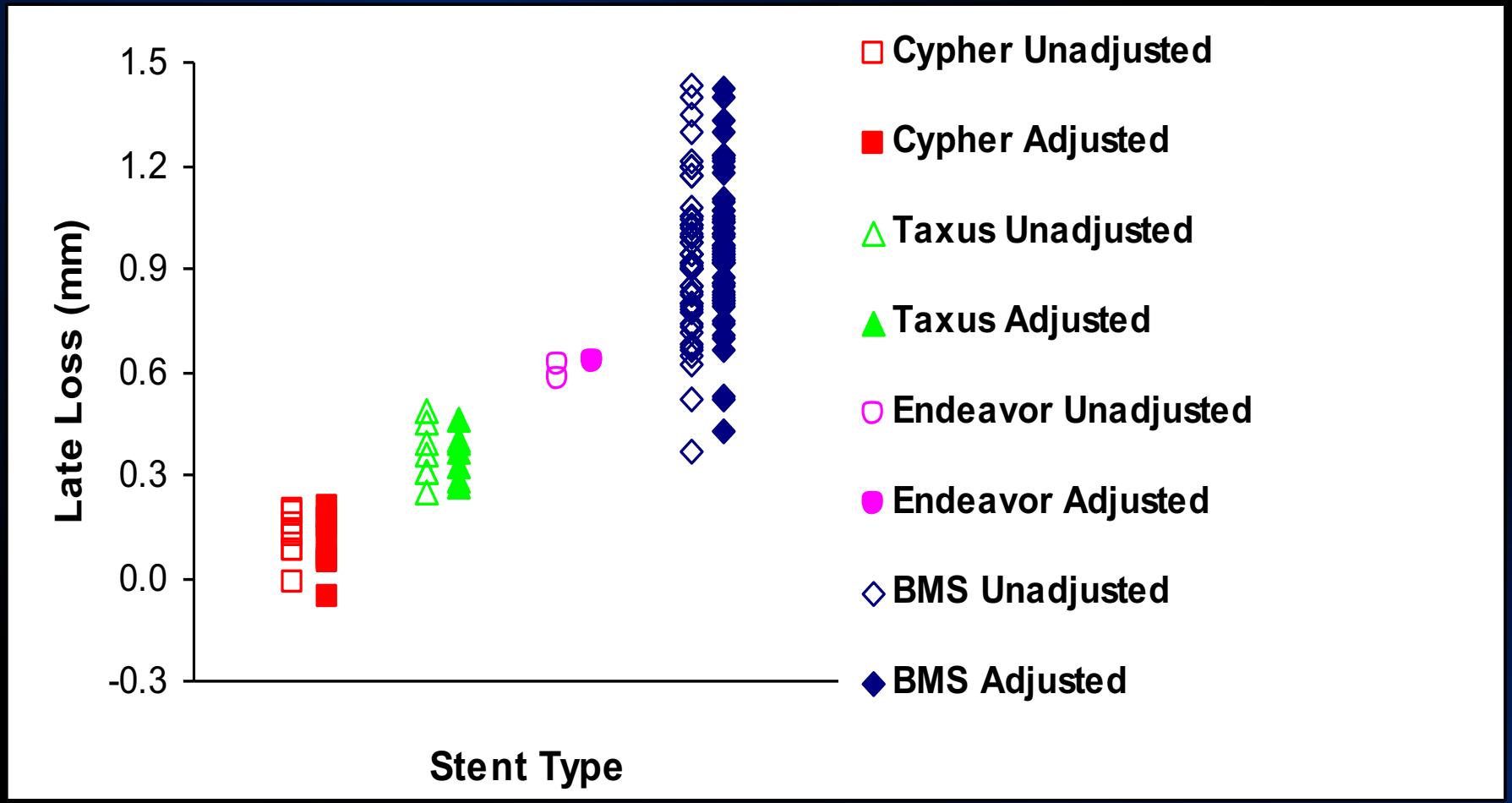


PERFUSE

Mauri et al. Circulation. 2005;112(18):2833-2839

Late Loss is consistent across trials

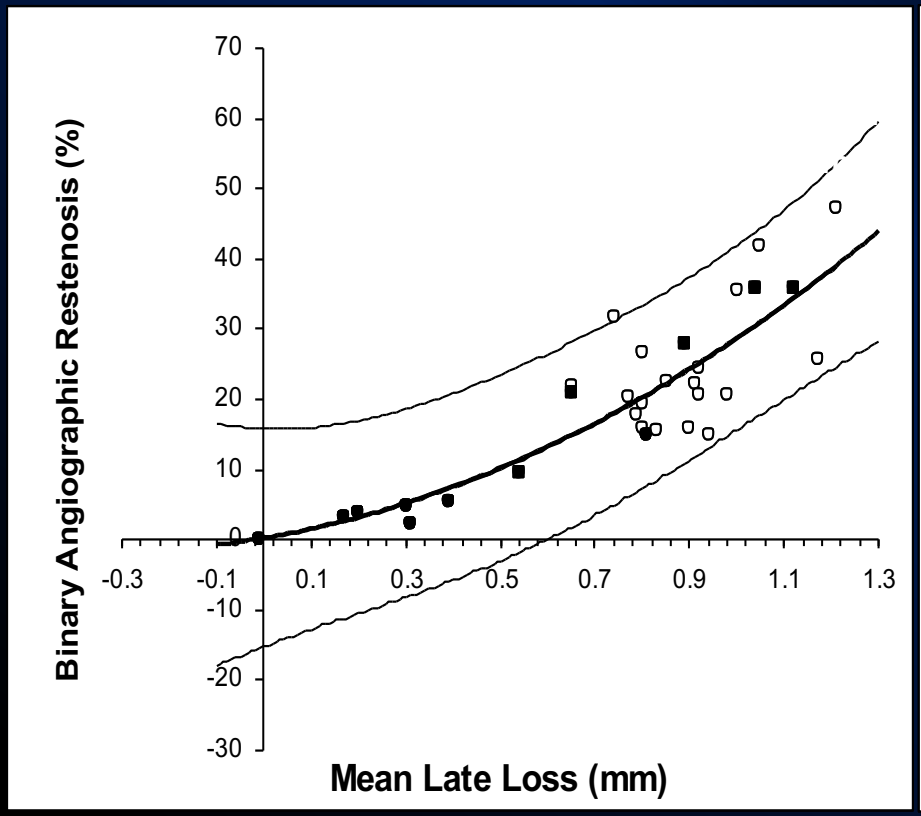
DES and BMS Results

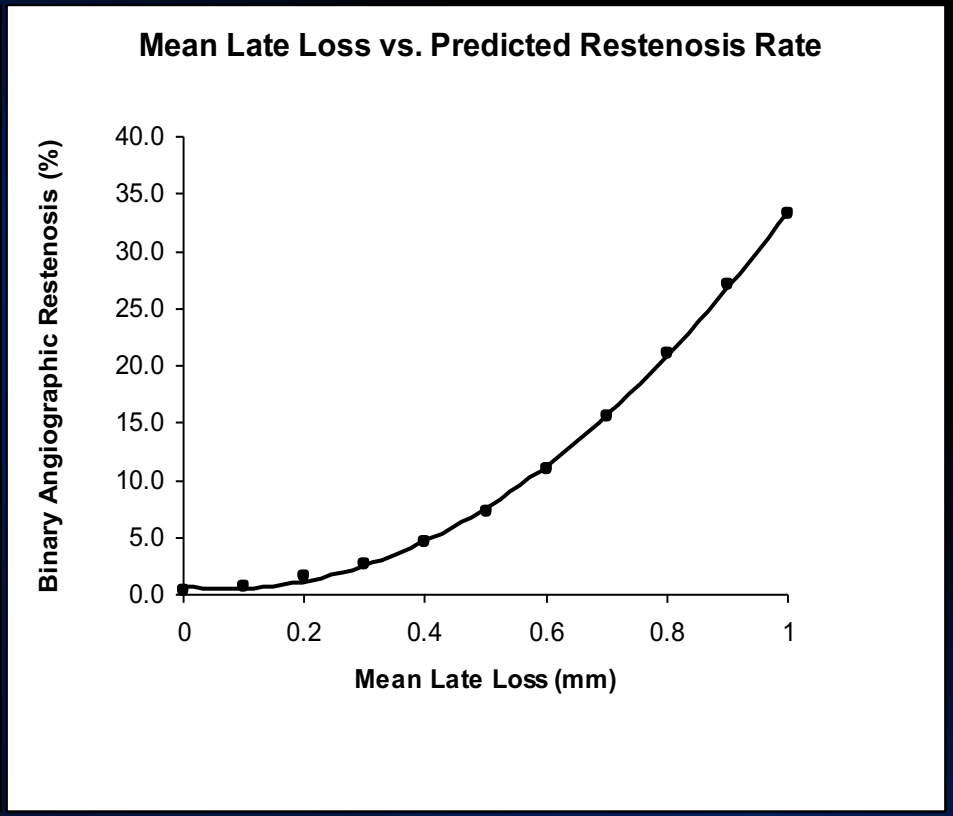


PERFUSE

Mauri et al. Circulation. 2005;112(18):2833-2839.

Late Loss Predicts Restenosis Rate



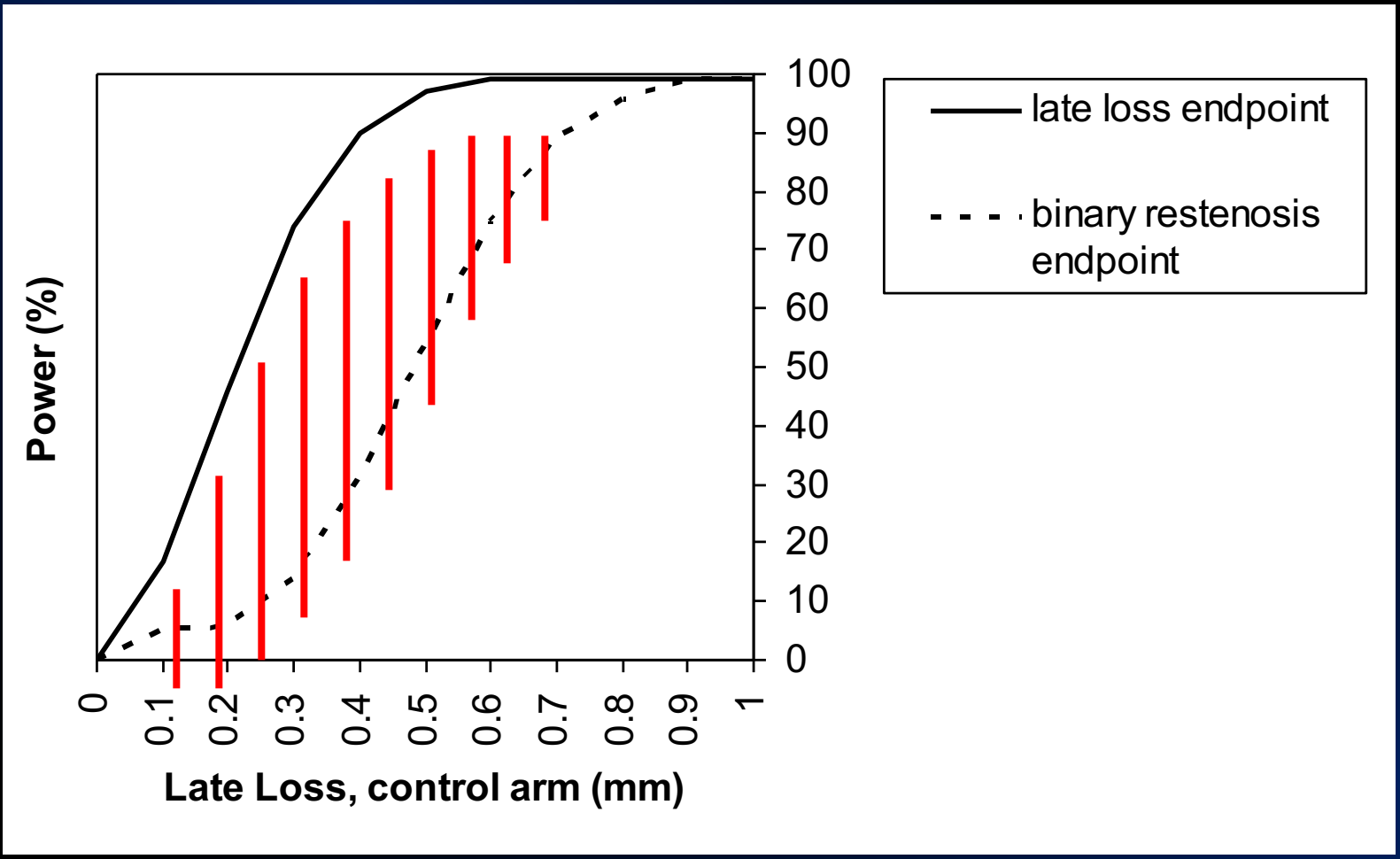


Monotonic relationship means that higher late loss translates to more restenosis

PERFUSE

Mauri et al. Circulation. 2005:111:3435-3442.

Late Loss is more powerful than restenosis rate



PERFUSE

Mauri et al. Circulation. 2005:111:3435-3442.

Late Loss as a Surrogate Endpoint

Across individual patients in-stent late loss correlates with clinical restenosis:

c statistic = 0.915, SIRIUS
c statistic = 0.918, TAXUS 4

Across individual trials in-stent late loss explains the treatment effect of DES fully
(Prentice, Freedman method)
PTE (proportion of treatment effect) = 1.3, SIRIUS
PTE = 0.9, TAXUS 4

PERFUSE

Late Loss as a Surrogate Endpoint

For true surrogacy, treatment-induced changes in the surrogate should reflect treatment-induced changes in the standard clinical endpoint.

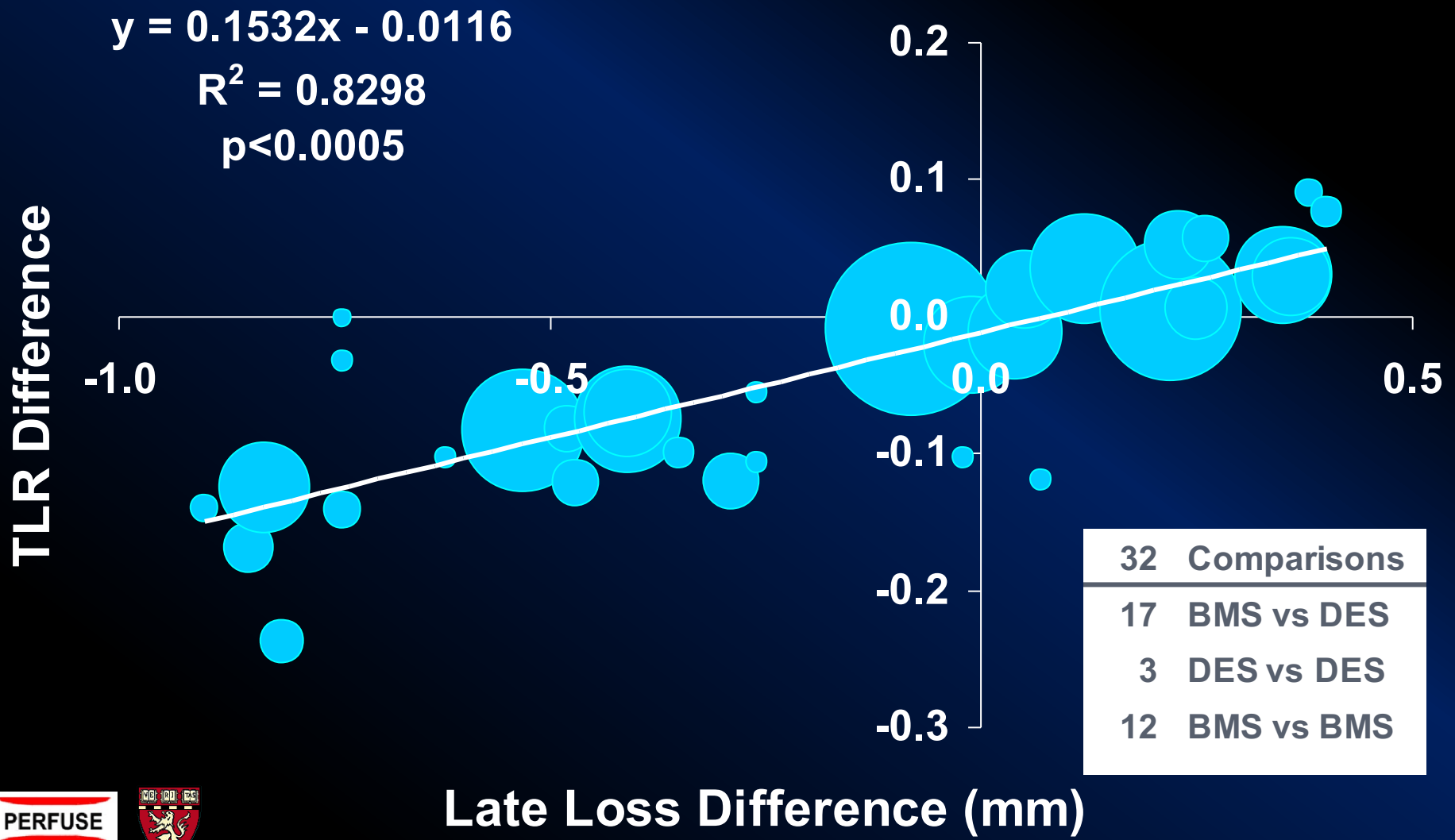
(Hughes-Daniels method)

Requires analysis across randomized trials of different treatments

PERFUSE

Clinical Treatment Efficacy

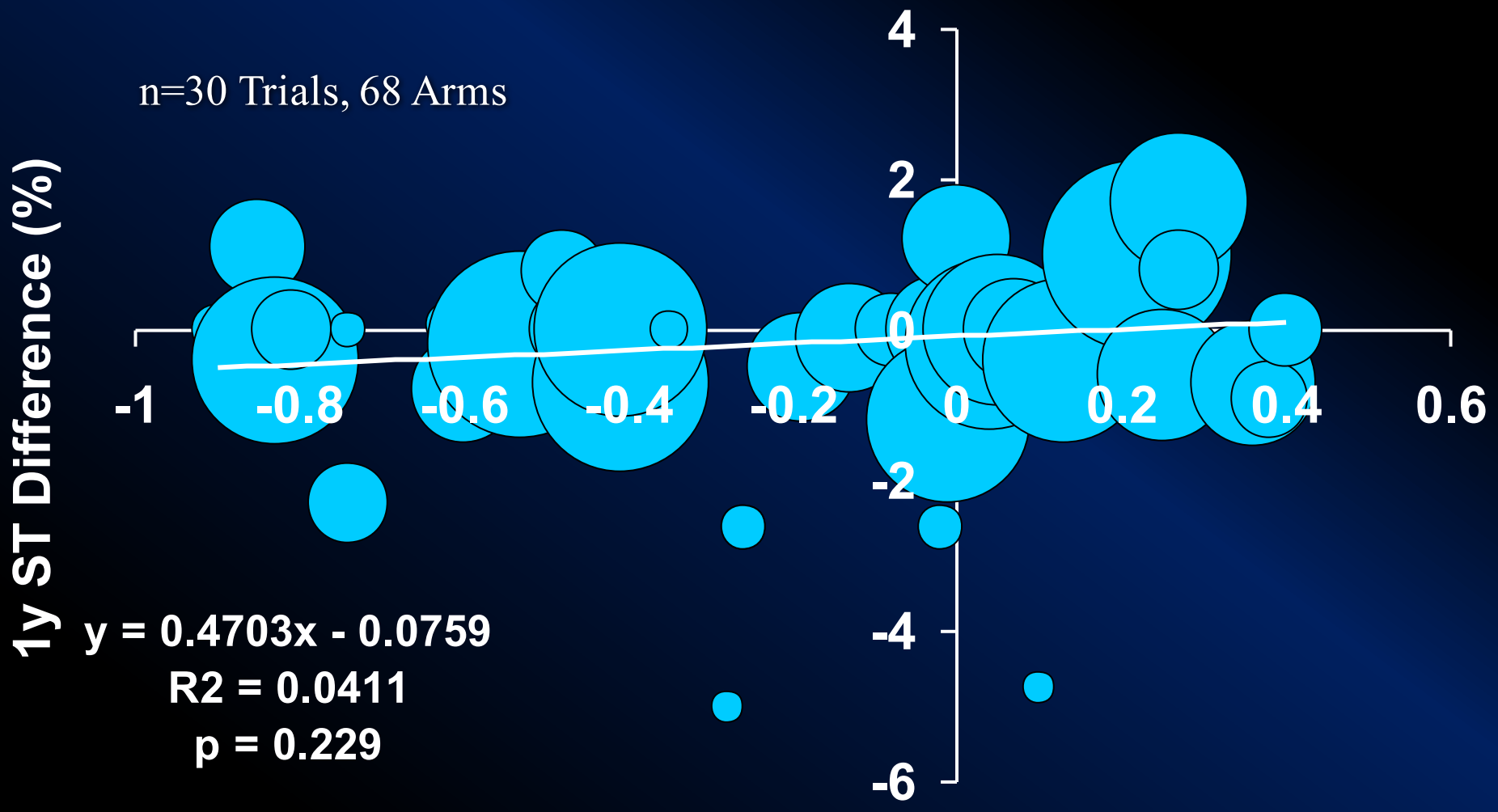
Late Loss Differences vs TLR Differences



PERFUSE

Mauri, Hughes, Kuntz. AHA 2005.

Can Late Loss predict Stent Thrombosis?



PERFUSE

Mauri et al. AHA 2005.

The Value of Surrogate Endpoints

Support Innovation and Rapidly Identify the Best Technologies[1]

- Decrease sample size
- Decrease study duration
- Allow more rapid iterations to allow innovation
- Avoid exposing patients to ineffective therapies

[1]Gould JAMA 2005