Composite Outcomes and Net Adverse Events:

Implications for Trial Design and Interpretation

David J. Cohen, M.D., M.Sc.

Director of Clinical and Outcomes Research
Cardiovascular Research Foundation, New York, NY

Director of Academic Affairs
St. Francis Hospital, Roslyn NY

Disclosures

Grant Support/Drugs

- Daiichi-Sankyo - MyoKardia/BMS

Grant Support/Devices

- Edwards Lifesciences - Abbott Vascular
- Medtronic - Boston Scientific
- Corvia - Phillips
- I-Rhythm

Consulting/Advisory Boards

- Medtronic - Edwards Lifesciences
- Boston Scientific - Abbott Vascular
- Corvia - Impulse Dynamics

Composite Endpoints

- Most contemporary CV trials use composite endpoints
  - *Lipid-lowering: CV death, MI, stroke*
  - *HF Trials: Death or HF hospitalization*
  - *DES trials: Target lesion failure (CV death, TV MI, TLR)*
- Rationale for composite endpoints
  - *Improve statistical power and reduce sample size*
  - *Avoid analytic challenges related to competing risks and multiple comparisons*

Composite Endpoints- Drawbacks

- Interpretation can be challenging or even misleading, particularly if endpoint components have differential clinical impact and the endpoint is driven by the “less severe” components
  - *Usual interpretation implies that all endpoint components carry the same “clinical weight”*
  - *Alternative weighting schemes are conceptually attractive but difficult to implement*
- Even greater challenge occurs if different endpoint components move in different directions

Best Case Scenario

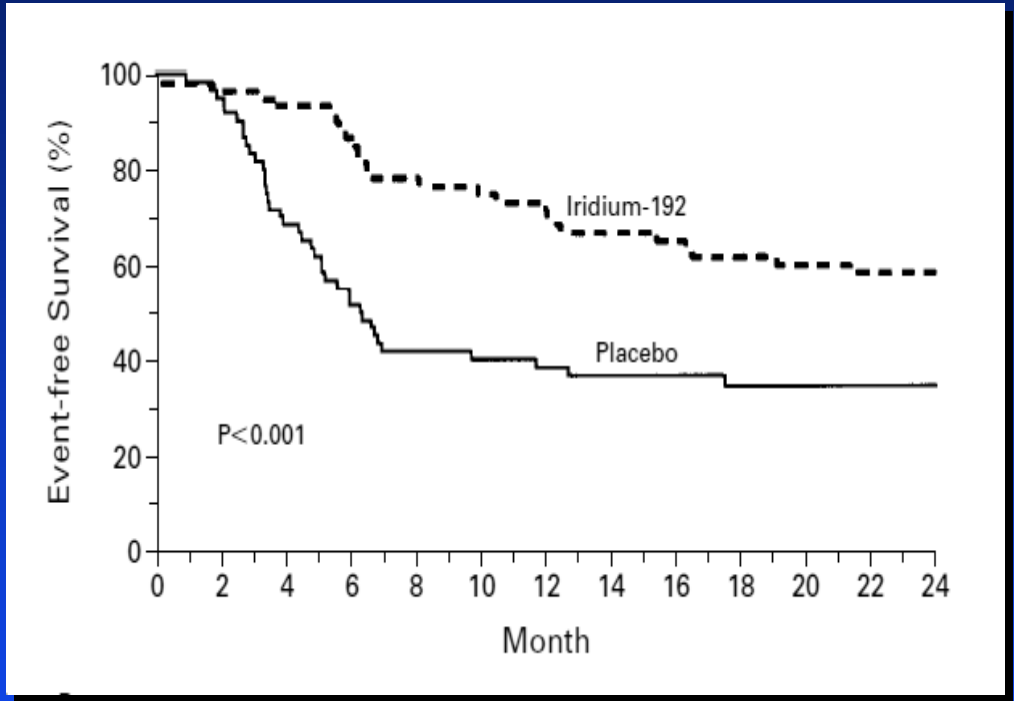
	Stent + Abcix	Stent + Placebo	RR (95% CI)
Primary composite	5.3%	10.8%	0.48
Death	0.3%	0.6%	0.50
MI	4.5%	9.6%	0.47
U-TVR	1.3%	2.1%	0.62

EPISTENT Trial

- 2399 pts undergoing PCI randomized to 1 of 3 arms:
  - *Stent + placebo*
  - *Stent + abciximab*
  - *PTCA + abciximab*
- Primary endpoint = 30-day composite of:
  - *Death*
  - *MI*
  - *Urgent TVR*

Lancet 1998;352:87-92

Usual Scenario: Single Dominant Component



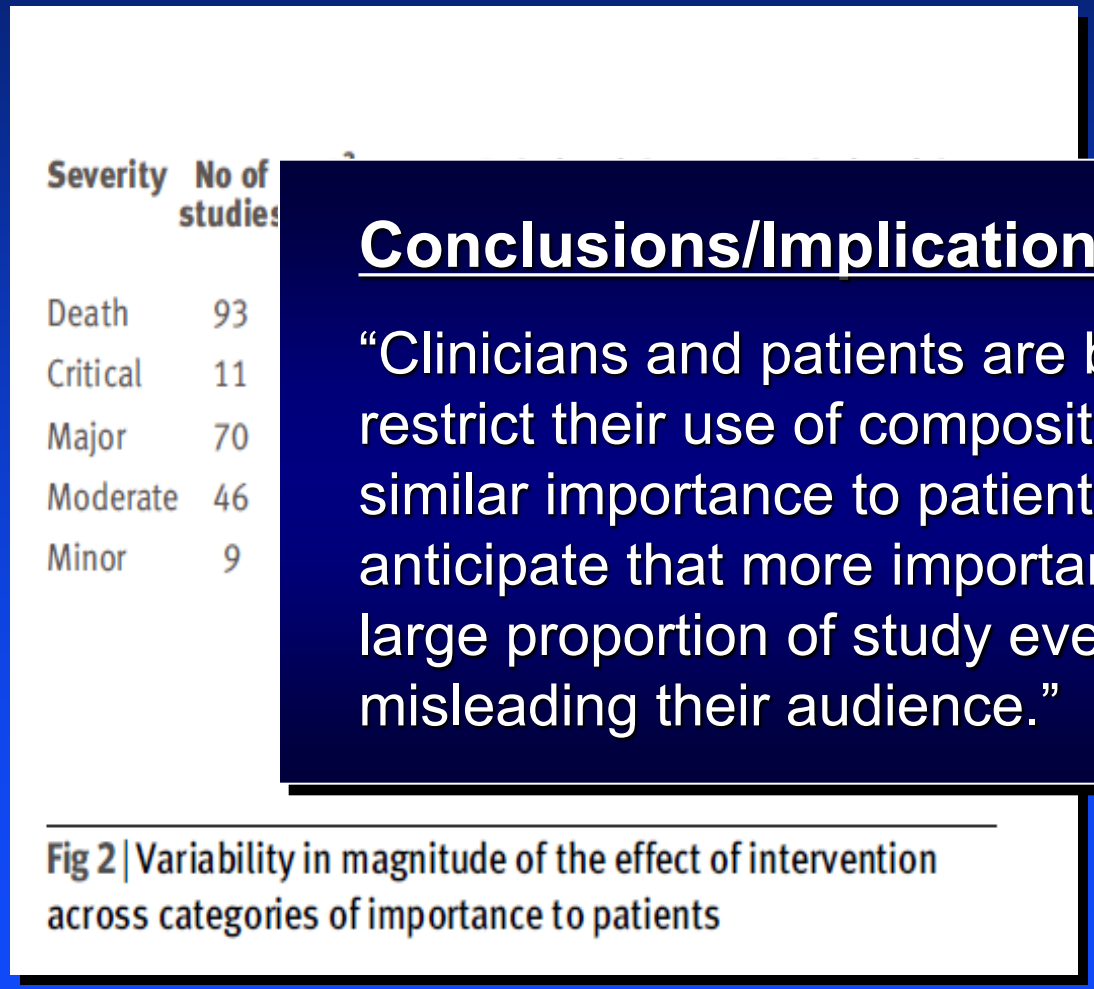
	Brachy	Control	RR (95% CI)
Cardiac death	7%	7%	1.0 (0.24-4.20)
Q-MI	2%	3%	0.49 (0.42-5.57)
TVR	28%	62%	0.25 (0.11-0.53)

Authors' Conclusion

- "In patients with SVG in-stent restenosis, brachytherapy reduced the composite of cardiac death, Q-wave MI, or target vessel revascularization by 73%"

Waksman R et al. N Engl J Med 2002;346:1194-9

Impact of Endpoint Components



Severity	No of studies
Death	93
Critical	11
Major	70
Moderate	46
Minor	9

Fig 2 | Variability in magnitude of the effect of intervention across categories of importance to patients

- Systematic review of 114
- blished in

of clinical

ences in
endpoint

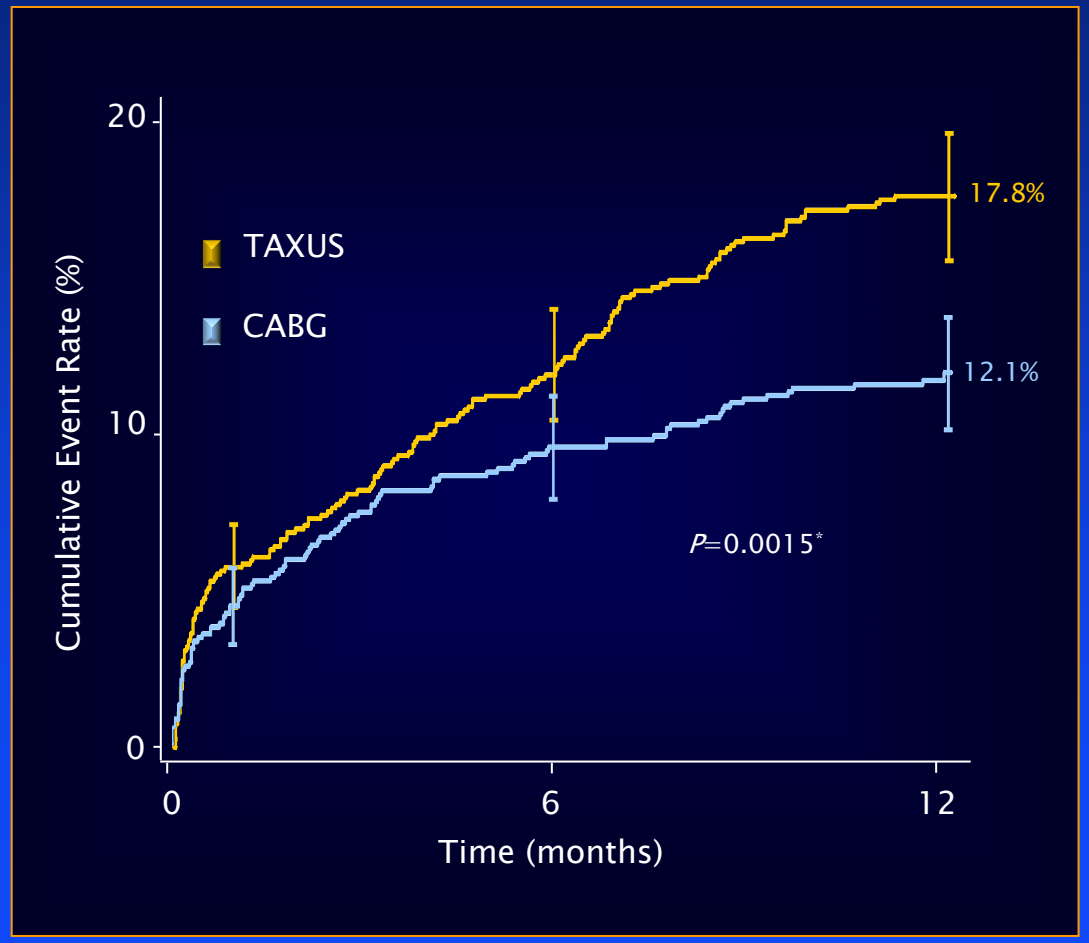
Conclusions/Implications

"Clinicians and patients are best served when trialists restrict their use of composite endpoints to endpoints of similar importance to patients and contexts in which they anticipate that more important endpoints will contribute a large proportion of study events. If they do not, they risk misleading their audience."

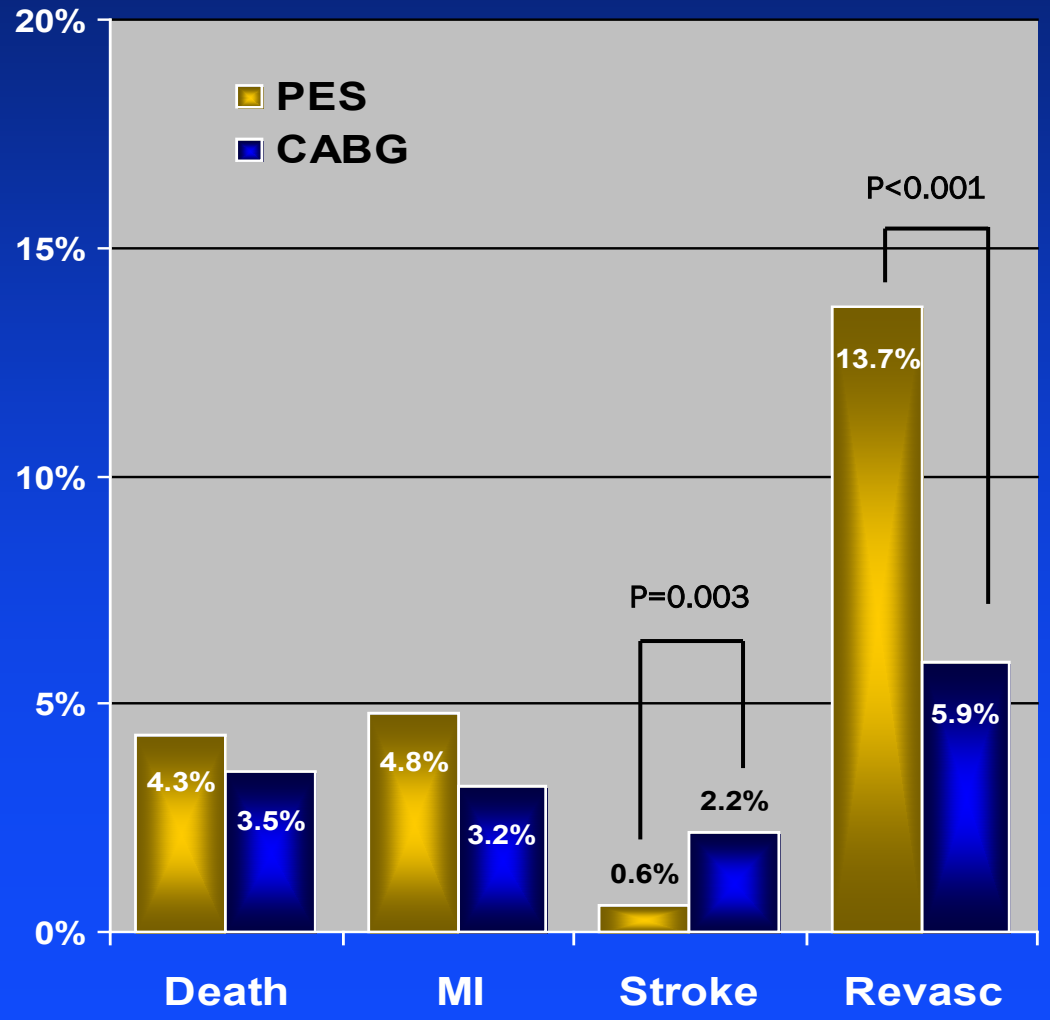
Ferreira-Gonzalez I, et al. BMJ 2007;334:786

Worst Case Scenario: Conflicting Endpoints

Primary Endpoint



Endpoint Components



What does all this have to do with trials of antiplatelet and antithrombotic therapy in PCI/ACS?

Endpoints in Trials of PCI/ACS

Trial	Intervention	Ischemic Events	Bleeding Events
REPLACE-2	Bivalirudin vs. Heparin/GP2b3a	↑	↓
TRITON/TIMI-38	Prasugrel vs. Clopidogrel	↓	↑
DAPT	Long vs. short DAPT	↓	↑
COMPASS	Low dose rivaroxaban	↓	↑

- Key challenge is tradeoff between ischemic/thrombotic and bleeding events
- Are “net adverse events” (NAE) the solution?

Balancing Safety and Efficacy in PCI/ACS Trials

Approach #1

Net Adverse Events

Composite of death, MI, stroke,and bleeding

Strengths

- Incorporates full spectrum of adverse outcomes (patient-centered)

Limitations

- Weights all endpoints the same
- Only helps with sample size if rx has directionally consistent effect on all endpoints
- Challenging to use in a non-inferiority design (why accept possibility of net harm?)

Balancing Safety and Efficacy in PCI/ACS Trials

Approach #2

Ordinal Composite Endpoint

Strengths

- Incorporates full spectrum of adverse outcomes (similar to traditional composite)
- Allows for more impactful endpoints to take precedence (death >> MI)

Limitations

- Interpretation challenging if components move in different directions
- Only informative for the "average patient"→ cannot easily adapt to different risk profiles

Balancing Safety and Efficacy in PCI/ACS Trials

Approach #3

Separate Endpoints for Efficacy and Safety

Strengths

- Incorporates full spectrum of adverse outcomes
- Can combine non-inferiority for one component and superiority for the other (e.g., TWILIGHT)
- Allows for explicit modeling of risk-benefit tradeoffs for specific patient profiles (personalized medicine)

Limitations

- Does not take advantage of improved power if both endpoints move in the same direction

Personalized PCI: Antiplatelet Therapy

Original Article

Selecting Antiplatelet Therapy at the Time of Percutaneous Intervention for an Acute Coronary Syndrome

Weighing the Benefits and Risks of Prasugrel Versus Clopidogrel

Adam C. Salisbury, MD, MSc; Kaijun Wang, PhD; David J. Cohen, MD, MSc; Yan Li, PhD; Philip G. Jones, MS; John A. Spertus, MD, MPH

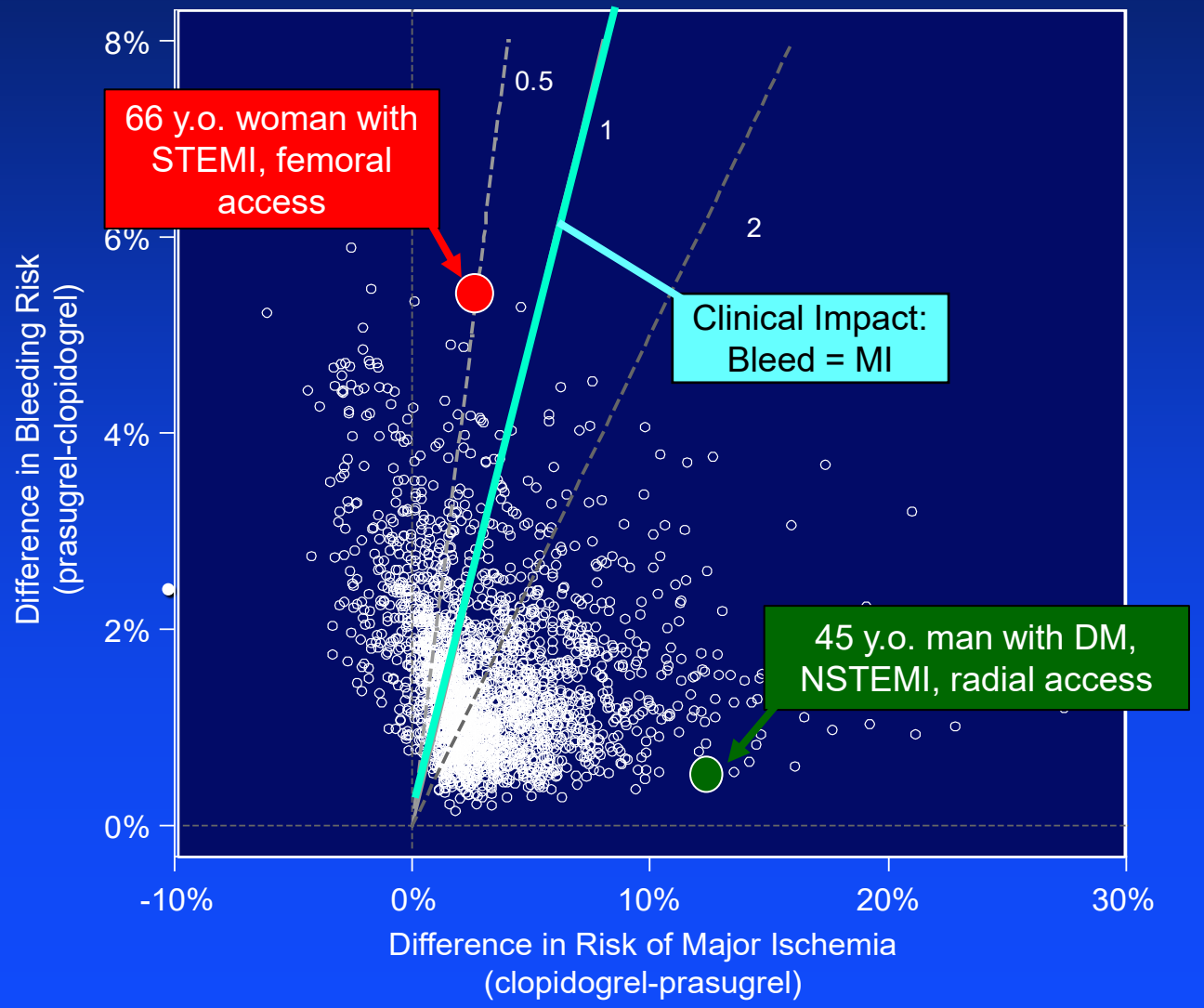
Background—On average, acute coronary syndrome patients treated with prasugrel experience fewer ischemic complications, but more bleeding, than those receiving clopidogrel. However, heterogeneity in treatment effects can alter the likelihood of benefits and risks of an individual patient. We developed predictive models of the benefits (reduced ischemic events) and risks (increased bleeding) to support targeting prasugrel to those who benefit most from treatment.

Methods and Results—Using 12 579 patients from Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), we fit risk models for ischemic events (cardiovascular death, spontaneous myocardial infarction, stroke) and bleeding (TIMI major/minor) over a 14.8-month follow-up and then calculated each patient's predicted risk for major ischemia and bleeding with both prasugrel and clopidogrel. We found substantial heterogeneity of the treatment effect of prasugrel (mean absolute reduction in the ischemia risk with prasugrel=1.5±3.0%, ranging from an 8.4% increased risk to a 31.2% reduction in risk for ischemia compared with clopidogrel). The mean absolute increase in the bleeding risk with prasugrel versus clopidogrel was 1.3±1.4% and ranged from a 7.9% lower risk to an 11.2% higher risk with prasugrel. The ratio of the difference in predicted ischemia risk/difference in predicted bleeding risk between prasugrel and clopidogrel was calculated for each patient to identify the proportion likely to benefit from prasugrel. Considering both ischemia and bleeding risk, a large proportion of TRITON participants (42%) were predicted to experience net benefit with prasugrel, a rate that increased if patients more strongly preferred avoiding ischemic events than bleeding.

Conclusions—The expected benefits and risks of prasugrel versus clopidogrel depend highly on patient characteristics. The use of risk models could support individualized thienopyridine selection to maximize the benefits and safety of these drugs. (***Circ Cardiovasc Qual Outcomes.* 2013;6:00-00.**)

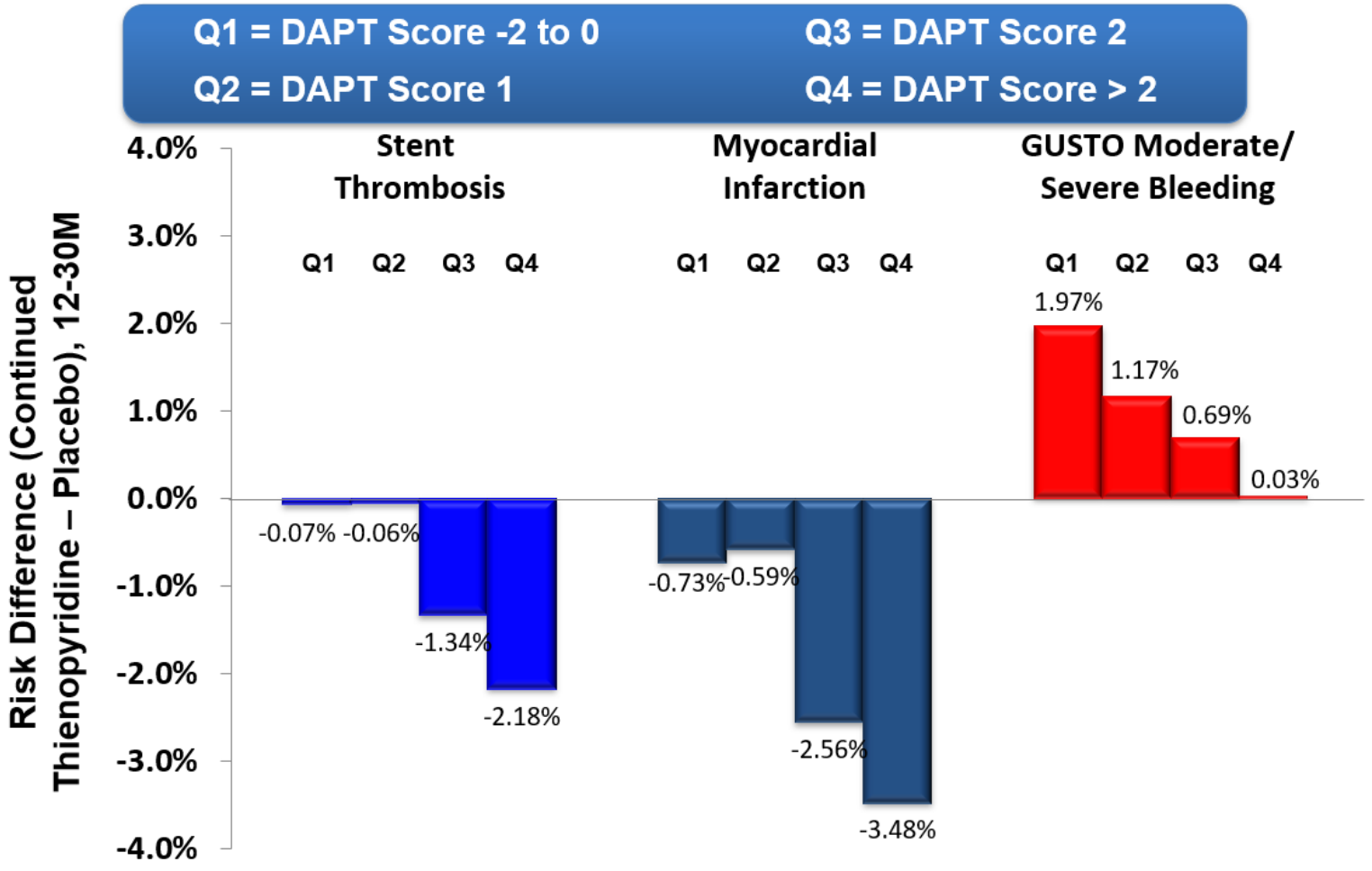
Key Words: acute coronary syndromes ■ antiplatelet therapy ■ individualized medicine ■ percutaneous coronary intervention ■ prediction

Circulation
Cardiovascular Quality and Outcomes
JOURNAL OF THE AMERICAN HEART ASSOCIATION



Salisbury AC, et al. Circ CV Qual Outcomes 2013

Individualizing Antiplatelet Therapy: DAPT Score



Yeh RW, et al. JAMA 2016

Summary

- Despite several important limitations, composite endpoints for clinical trials are likely here to stay
- Use of net adverse events addresses some (but not all) concerns around composite endpoints
  - *Does not address concerns related to equal event rating*
  - *Only helps to improve study power if a treatment has directionally consistent effects on both safety and efficacy*
  - *Main value of NAE is providing a basic framework for balancing benefits and harms*
- Novel approaches including ordinal composite endpoints and modeling heterogeneity of treatment benefit are likely to assume increasing importance for both regulatory and clinical decision-making in the future