Selecting Patients for Long-Term DAPT: Insights from the DAPT Trial

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20 minutes
28 slides

Disclosures

Grant Support/Drugs

- Daiichi-Sankyo - Eli Lilly
- Astra-Zeneca - Merck

Grant Support/Devices

- Edwards Lifesciences - Abbott Vascular
- Medtronic - Boston Scientific
- Biomet

Consulting/Advisory Boards

- Medtronic - Astra-Zeneca
- Edwards Lifesciences

Background

- DAPT is currently recommended for 6 months to 1 year (US) after DES implantation
- Some observational studies have suggested that extending DAPT beyond 1 year is associated with a lower risk of MI, but at the price of increased risk of bleeding
- Several modest sized RCTs (ZEST, PRODIGY) have failed to demonstrate a benefit of prolonged DAPT, however

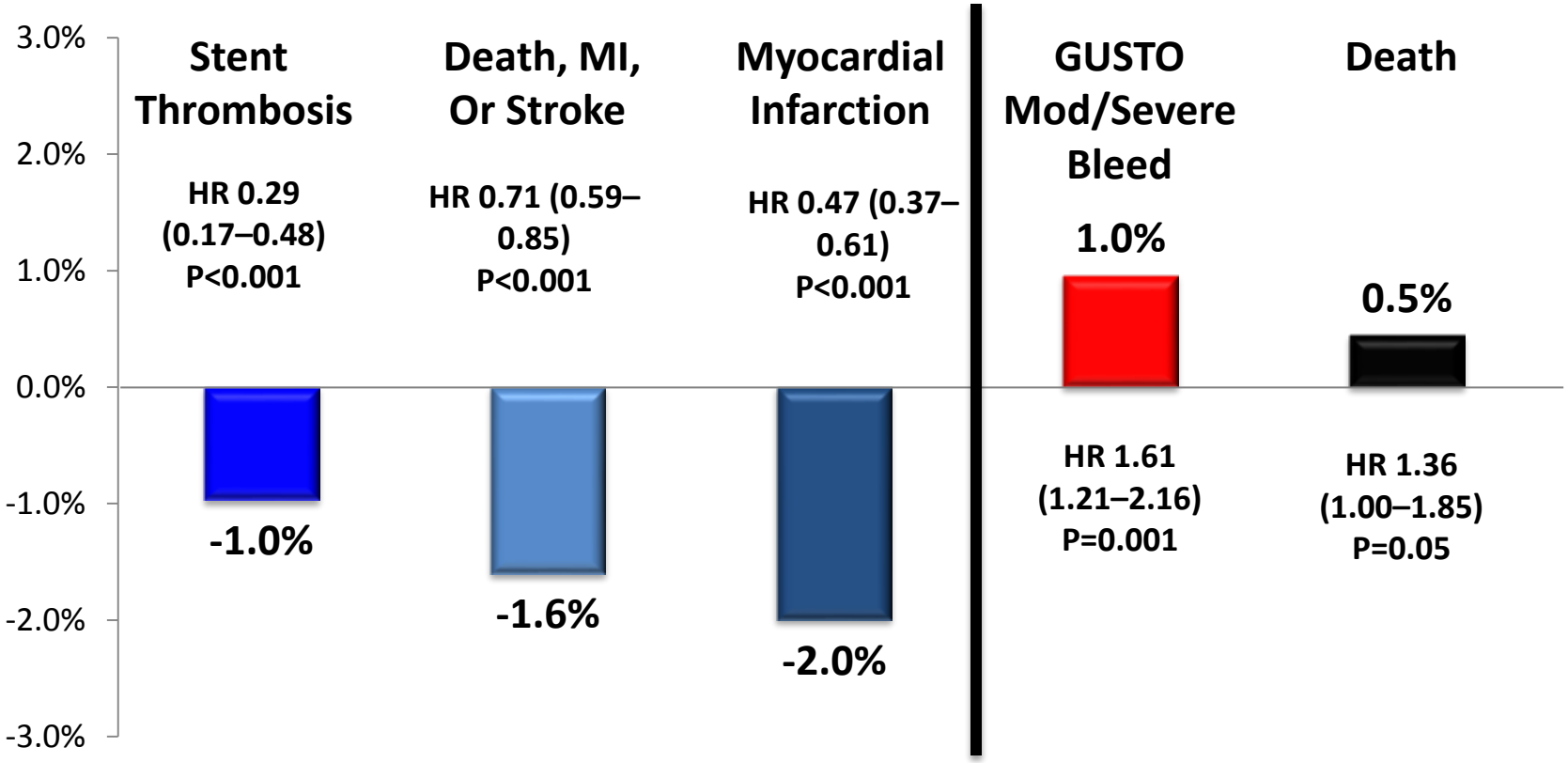
The DAPT trial was designed (in late 2006, at the height of the “DES firestorm”) to determine the benefits and risks of continuing DAPT beyond 1 year after DES implantation

DAPT: Methods

- 9,961 pts who remained event-free 12 months after DES randomized to receive ASA + thienopyridine (clopidogrel or prasugrel) vs. ASA + placebo for an additional 18 months (12 vs. 30 month DAPT)
- Co-Primary Efficacy Endpoints
  - *Stent Thrombosis*
  - *MACCE (composite of death, MI, or stroke)*
- First, second, and third generation DES used in trial (sirolimus, paclitaxel, zotarolimus, and everolimus)

Summary of Results

Absolute Risk Difference: 30 vs. 12 month DAPT



Mauri LM, et al. NEJM 2014;371:2155-66.

DAPT Trial Issues

- Does type of stent matter?
- Is 30 months “enough”?
- Based on the DAPT results, how should we individualize care?

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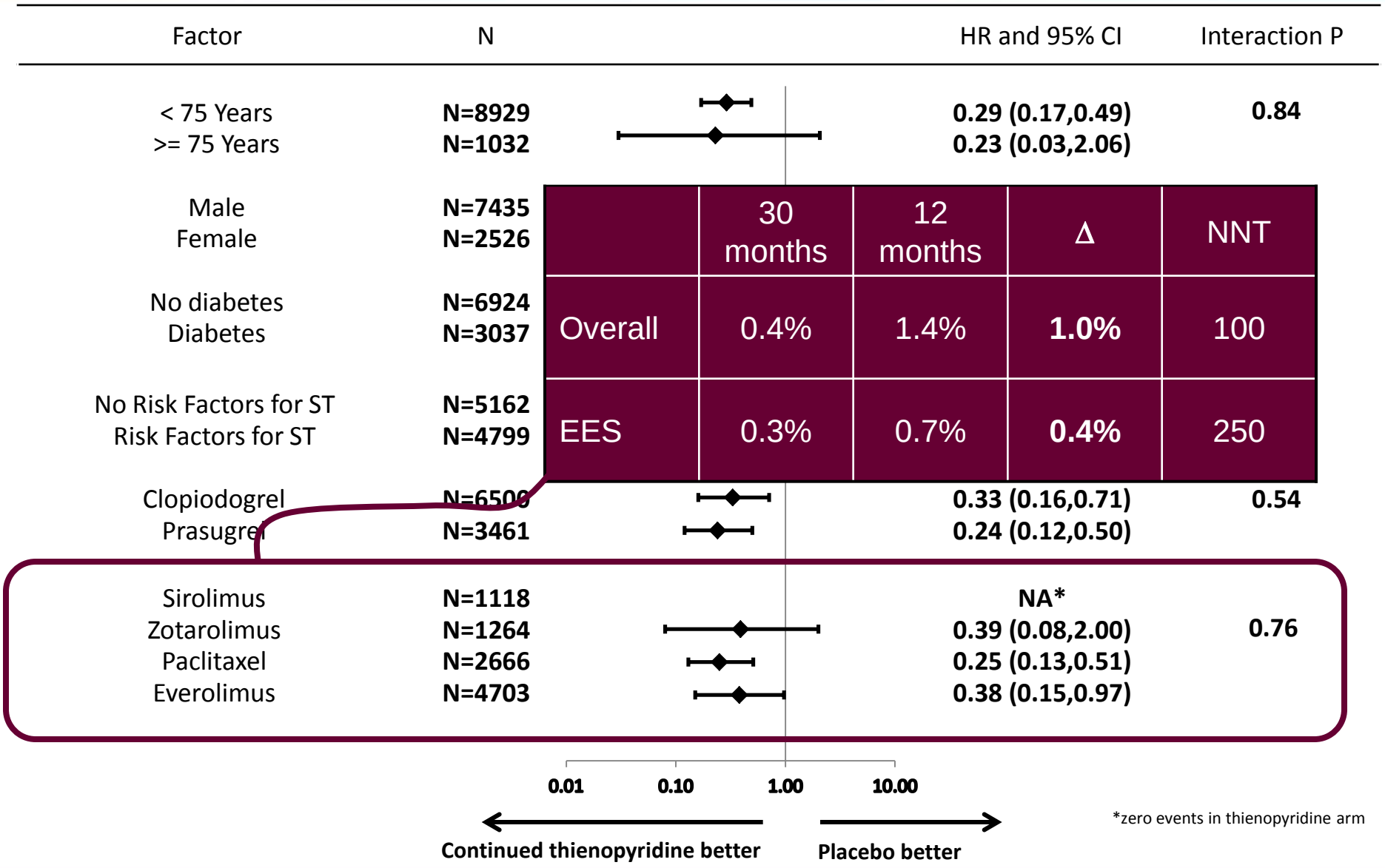
Consistency of Treatment Effect Stent Thrombosis (12-30 Months)



	30 months	12 months	Δ	NNT
Overall	0.4%	1.4%	**1.0%**	100
EES	0.3%	0.7%	**0.4%**	250

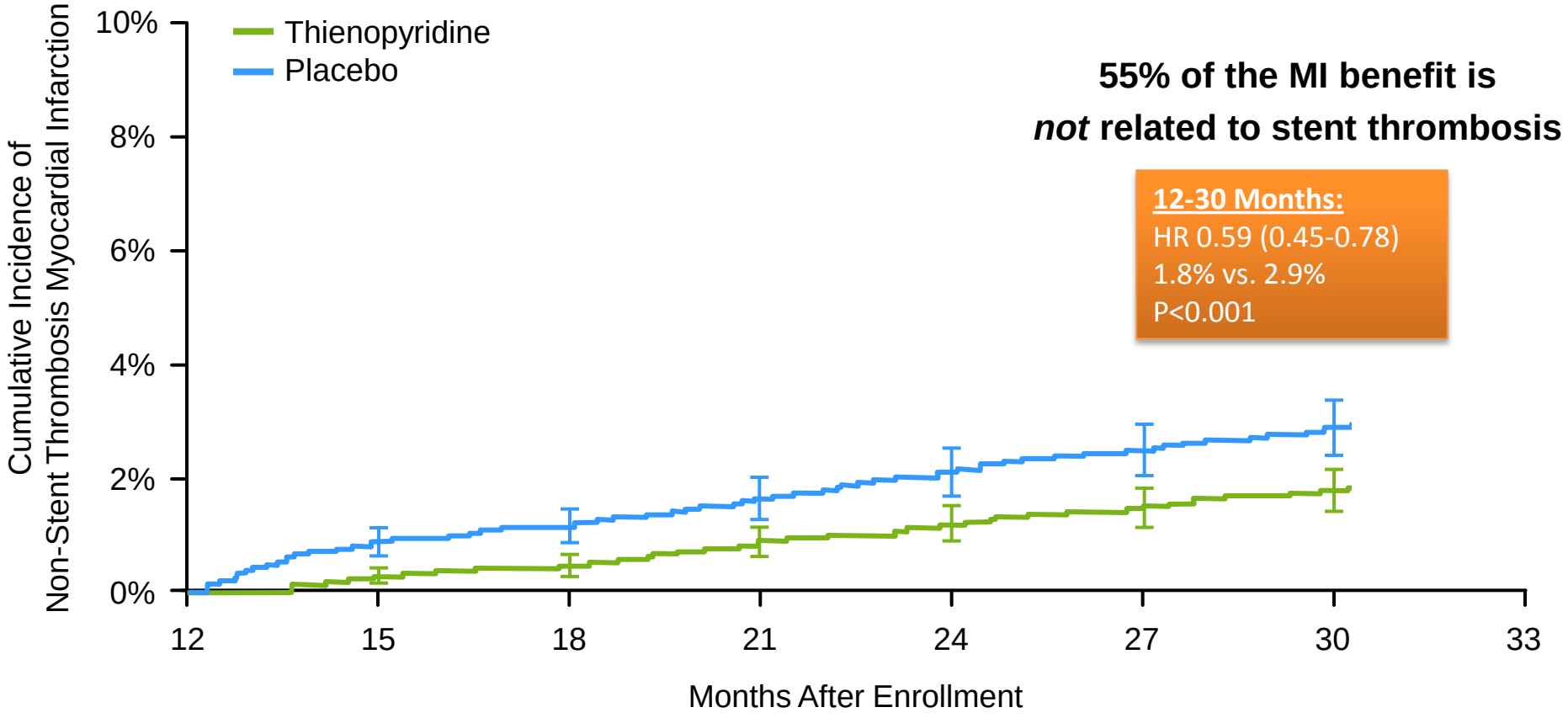
Impact of DES vs. BMS on Treatment Benefit

DAPT STUDY

ARC Definite/Probable ST				
Stent Type	30 Month DAPT N (%)	12 Month DAPT N (%)	HR (95% CI)	P Value Interaction
DES (N=9961)	19 (0.4%)	65 (1.4%)	0.29 (0.17-0.48)	0.42
BMS (N=1687)	4 (0.5%)	9 (1.1%)	0.49 (0.15-1.65)	

MACCE				
Stent Type	30 Month DAPT N (%)	12 Month DAPT N (%)	HR (95% CI)	P Value Interaction
DES (N=9961)	211 (4.3%)	285 (5.9%)	0.71 (0.59-0.85)	0.32
BMS (N=1687)	33 (4.0%)	38 (4.7%)	0.92 (0.57-1.47)	

Non-Stent Thrombosis Myocardial Infarction



55% of the MI benefit is *not* related to stent thrombosis

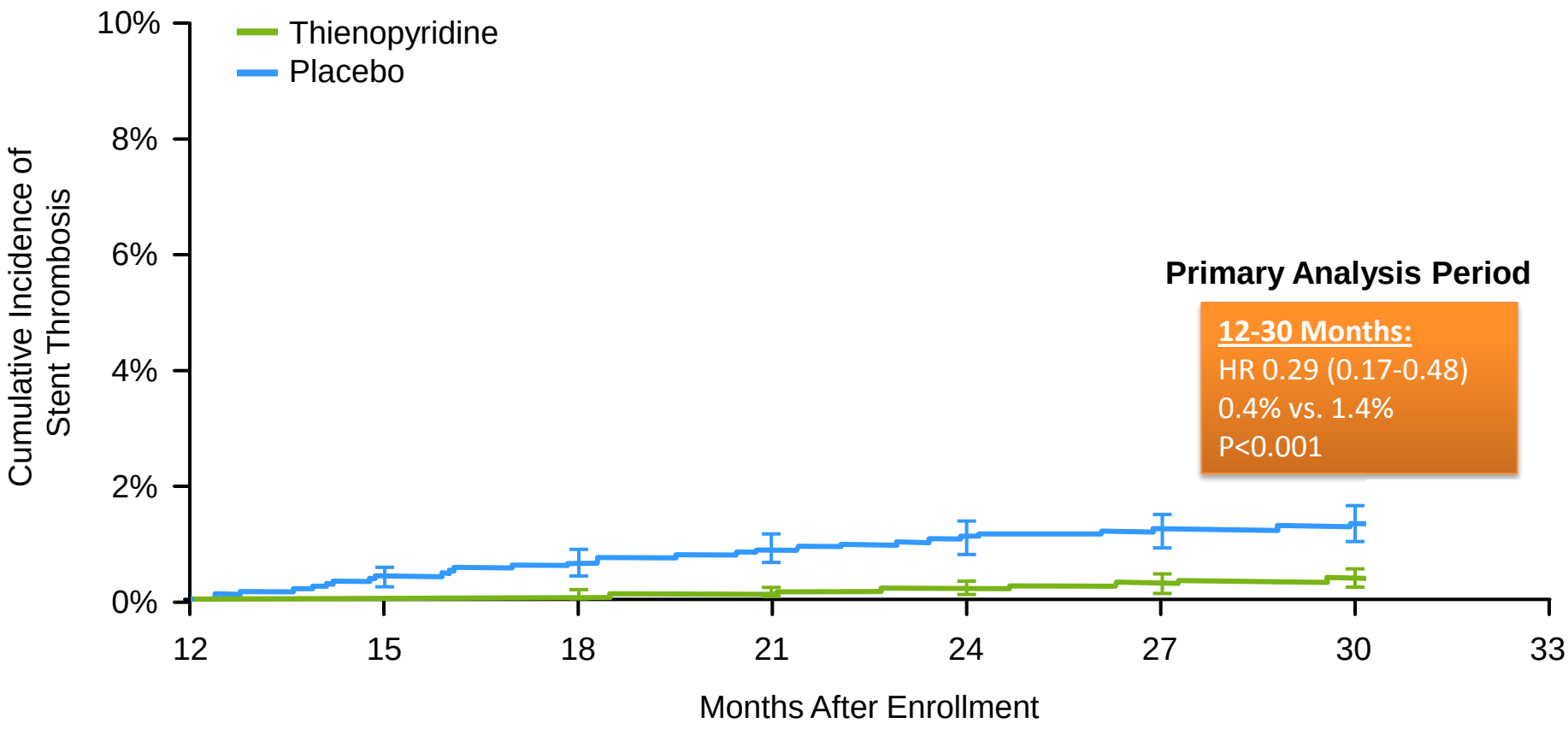
12-30 Months:
HR 0.59 (0.45-0.78)
1.8% vs. 2.9%
P<0.001

# At Risk								
Thienopyridine	5020	4920	4851	4792	4721	4641	4588	3066
Placebo	4941	4820	4751	4686	4607	4547	4491	3052

DAPT Trial Issues

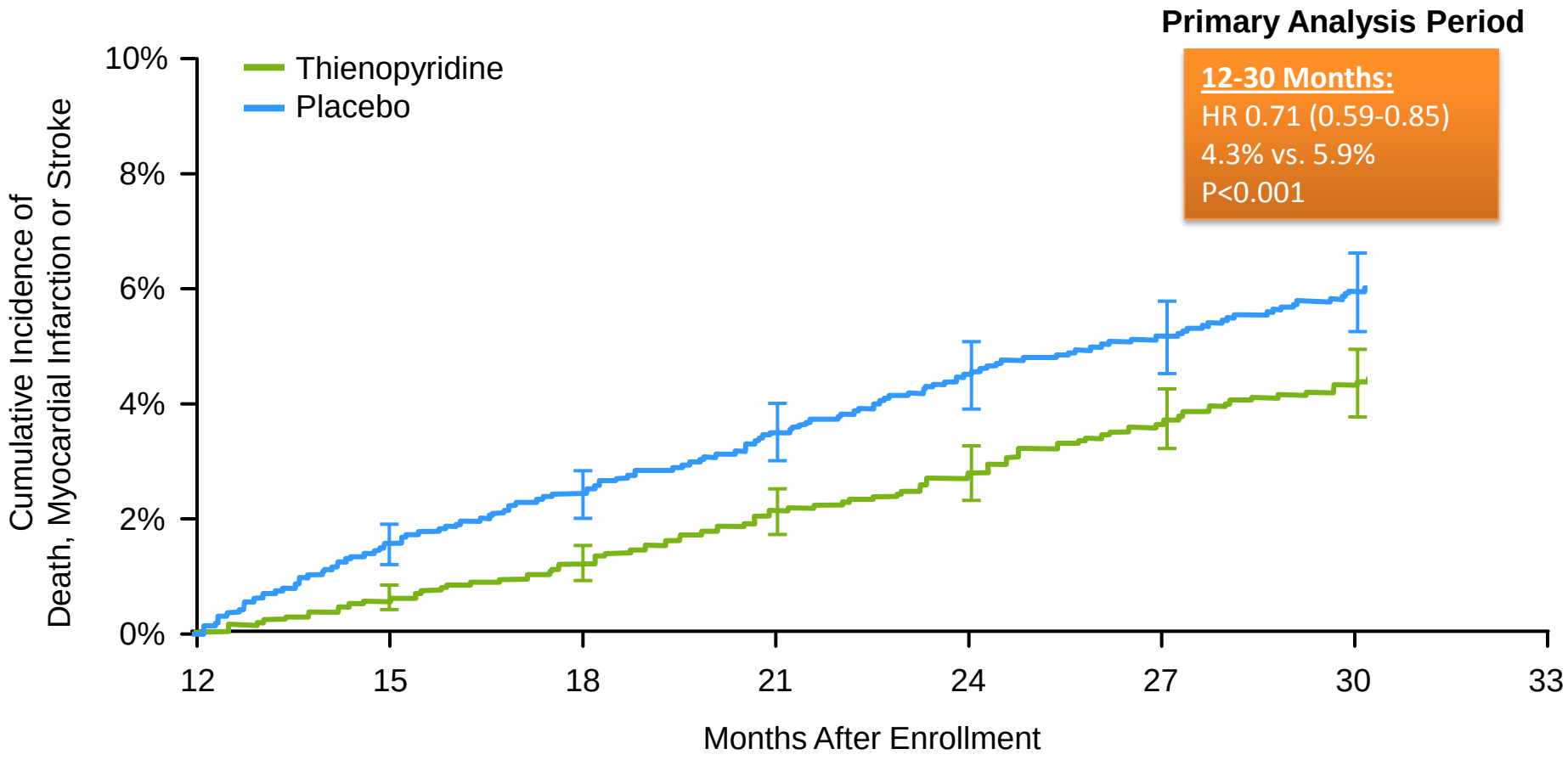
- Does type of stent matter?
- Is 30 months “enough”?
- Based on the DAPT results, how should we individualize care?

Co-Primary Effectiveness End Point
Stent Thrombosis



# At Risk								
Thienopyridine	5020	4934	4870	4828	4765	4686	4642	3110
Placebo	4941	4845	4775	4721	4651	4603	4556	3105

Co-Primary Effectiveness End Point MACCE

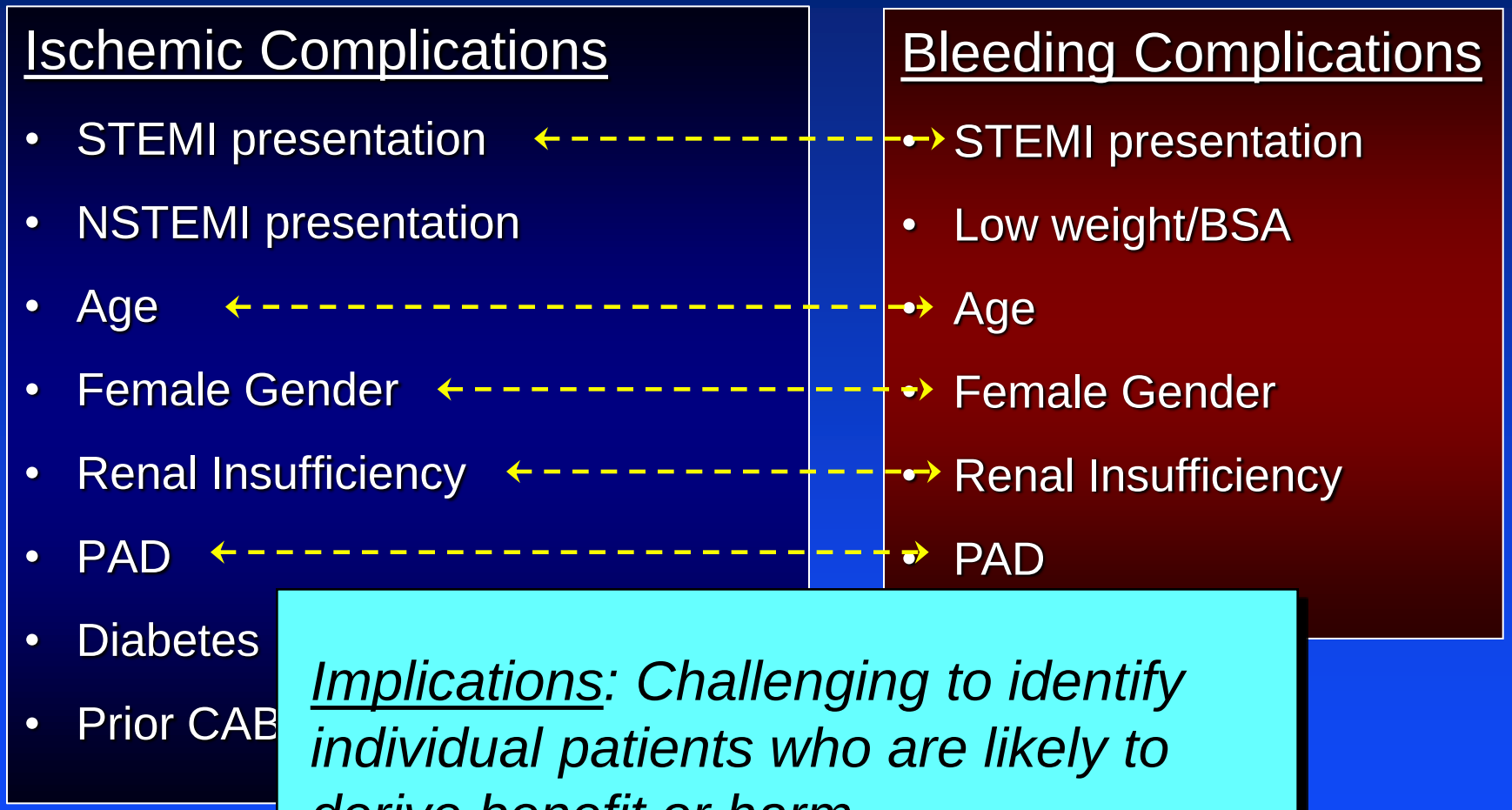


# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

DAPT Trial Issues

- Does type of stent matter?
- Is 30 months “enough”?
- Is the excess mortality real?
- Based on the DAPT results, how should we individualize care?

Predictors of Ischemic vs. Bleeding Events



Salisbury A, et al. ACC 2010

Identifying Patients for Long-Term DAPT after PCI:

The DAPT Score

Research

Original Investigation

Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention

Robert W. Yeh, MD, MSc; Eric A. Secemsky, MD, MSc; Dean J. Kereiakes, MD; Sharon-Lise T. Normand, PhD; Anthony H. Gershlick, MBBS; David J. Cohen, MD, MSc; John A. Spertus, MD, MPH; Philippe Gabriel Steg, MD; Donald E. Cutlip, MD; Michael J. Rinaldi, MD; Edoardo Camenzind, MD; William Wijns, MD, PhD; Patricia K. Apruzzese, MA; Yang Song, MS; Joseph M. Massaro, PhD; Laura Mauri, MD, MSc; for the DAPT Study Investigators

IMPORTANCE Dual antiplatelet therapy after percutaneous coronary intervention (PCI) reduces ischemia but increases bleeding.

OBJECTIVE To develop a clinical decision tool to identify patients expected to derive benefit vs harm from continuing thienopyridine beyond 1 year after PCI.

DESIGN, SETTING, AND PARTICIPANTS Among 11 648 randomized DAPT Study patients from 11 countries (August 2009-May 2014), a prediction rule was derived stratifying patients into groups to distinguish ischemic and bleeding risk 12 to 30 months after PCI. Validation was internal via bootstrap resampling and external among 8136 patients from 36 countries randomized in the PROTECT trial (June 2007-July 2014).

EXPOSURES Twelve months of open-label thienopyridine plus aspirin, then randomized to 18 months of continued thienopyridine plus aspirin vs placebo plus aspirin.

MAIN OUTCOMES AND MEASURES Ischemia (myocardial infarction or stent thrombosis) and bleeding (moderate or severe) 12 to 30 months after PCI.

RESULTS Among DAPT Study patients (derivation cohort; mean age, 61.3 years; women, 25.1%), ischemia occurred in 348 patients (3.0%) and bleeding in 215 (1.8%). Derivation cohort models predicting ischemia and bleeding had *c* statistics of 0.70 and 0.68, respectively. The prediction rule assigned 1 point each for myocardial infarction at presentation, prior myocardial infarction or PCI, diabetes, stent diameter less than 3 mm, smoking, and paclitaxel-eluting stent; 2 points each for history of congestive heart failure/low ejection fraction and vein graft intervention; −1 point for age 65 to younger than 75 years; and −2 points for age 75 years or older. Among the high score group (score ≥2, n = 5917), continued thienopyridine vs placebo was associated with reduced ischemic events (2.7% vs 5.7%; risk difference [RD], −3.0% [95% CI, −4.1% to −2.0%], $P < .001$) compared with the low score group (score <2, n = 5731; 1.7% vs 2.3%; RD, −0.7% [95% CI, −1.4% to 0.09%], $P = .07$; interaction $P < .001$). Conversely, continued thienopyridine was associated with smaller increases in bleeding among the high score group (1.8% vs 1.4%; RD, 0.4% [95% CI, −0.3% to 1.0%], $P = .26$) compared with the low score group (3.0% vs 1.4%; RD, 1.5% [95% CI, 0.8% to 2.3%], $P < .001$; interaction $P = .02$). Among PROTECT patients (validation cohort; mean age, 62 years; women, 23.7%), ischemia occurred in 79 patients (1.0%) and bleeding in 37 (0.5%), with a *c* statistic of 0.64 for ischemia and 0.64 for bleeding. In this cohort, the high-score patients (n = 2848) had increased ischemic events compared with the low-score patients and no significant difference in bleeding.

CONCLUSION AND RELEVANCE Among patients not sustaining major bleeding or ischemic events 1 year after PCI, a prediction rule assessing late ischemic and bleeding risks to inform dual antiplatelet therapy duration showed modest accuracy in derivation and validation cohorts. This rule requires further prospective evaluation to assess potential effects on patient care, as well as validation in other cohorts.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00977938.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: DAPT Study Investigators are listed at the end of this article.

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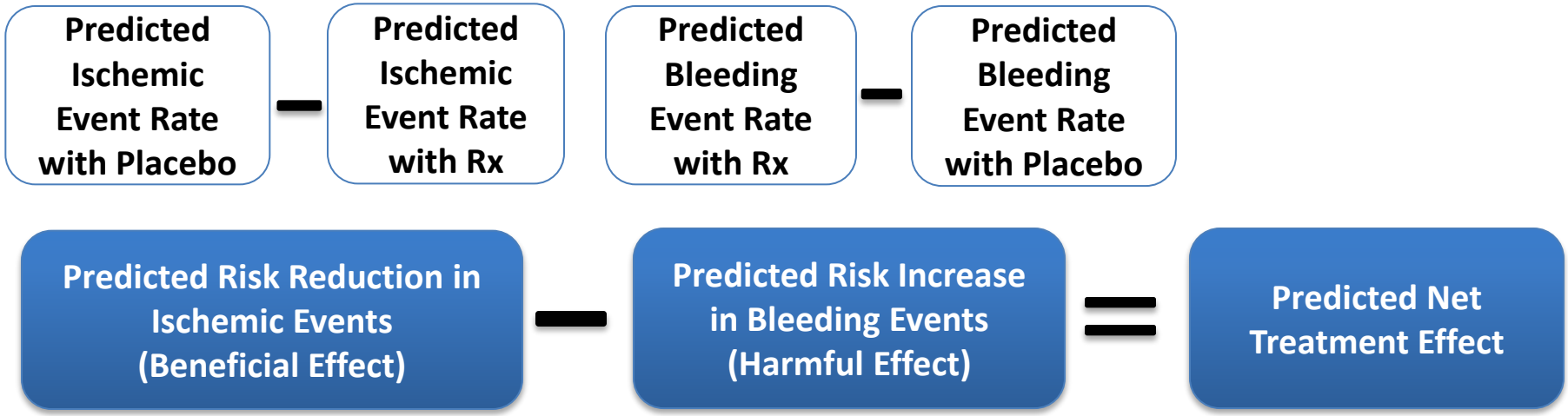
Methods – Predicting Net Treatment Effect

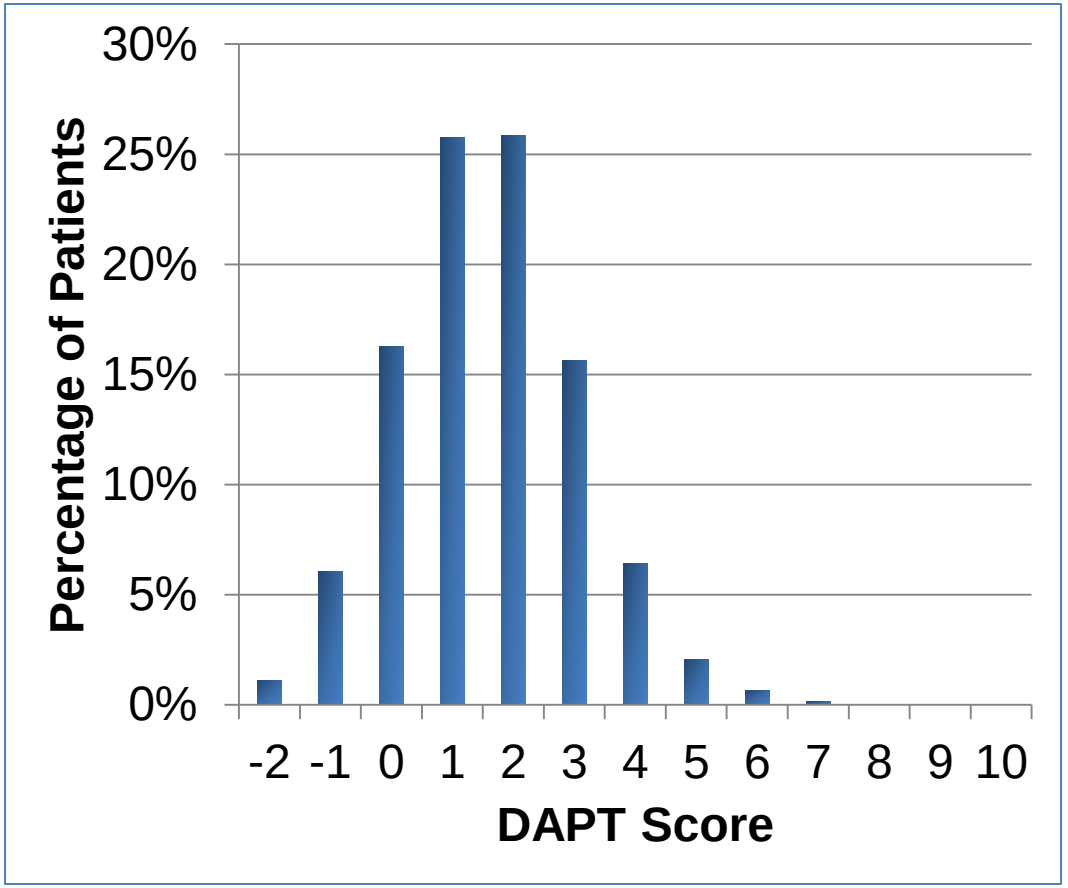


- Predictors of net treatment effect with continued thienopyridine determined from linear regression and simplified to an integer point score ***(DAPT Score***)

The DAPT Score

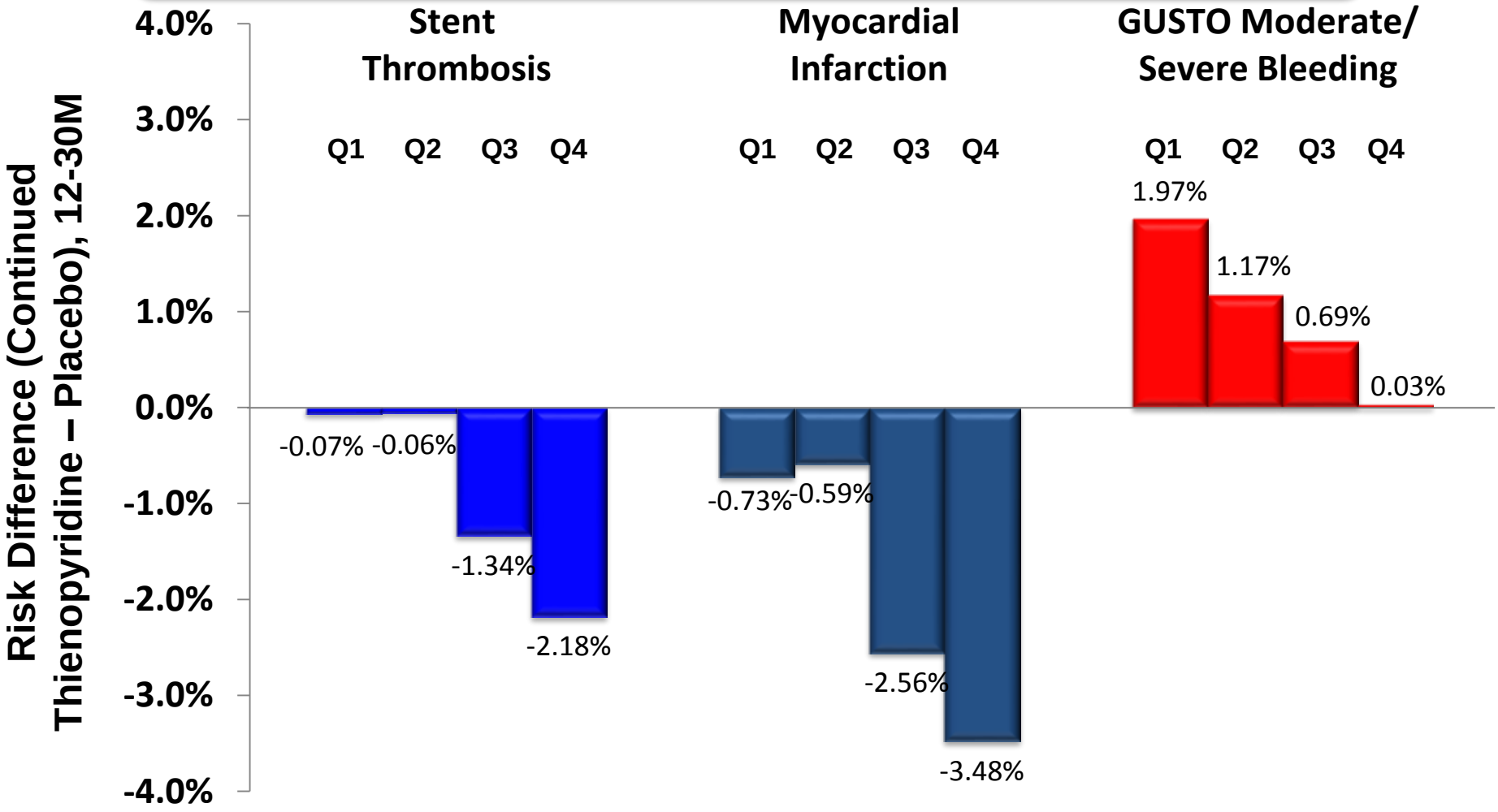
Variable	Points
Patient Characteristic	
Age	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

Distribution of DAPT Scores among all randomized subjects in the DAPT Study



Continued Thienopyridine vs. PlaceboTreatment Effect by DAPT Score Quartile (N = 11,648)

Q1 = DAPT Score -2 to 0
Q2 = DAPT Score 1
Q3 = DAPT Score 2
Q4 = DAPT Score > 2



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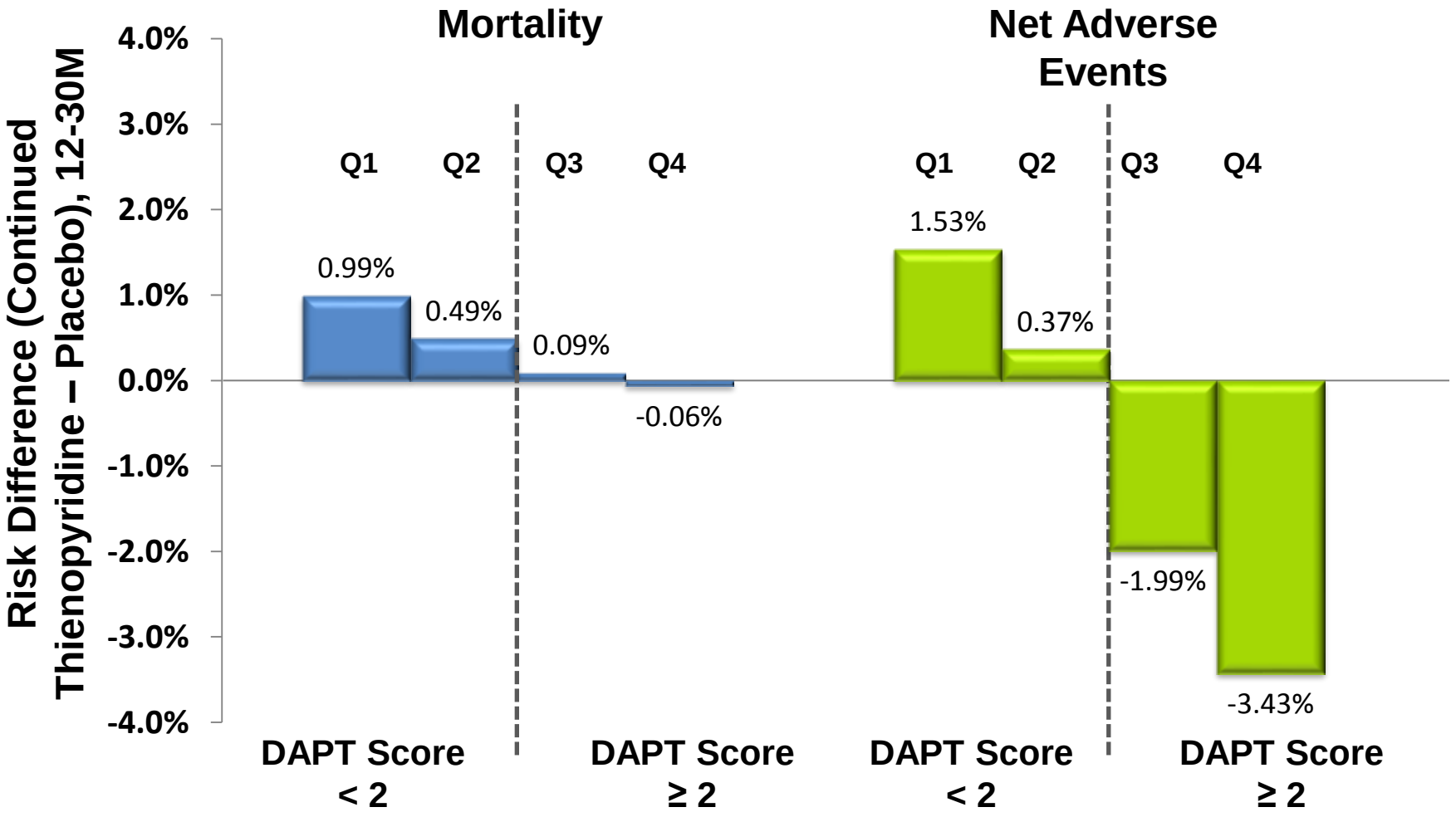
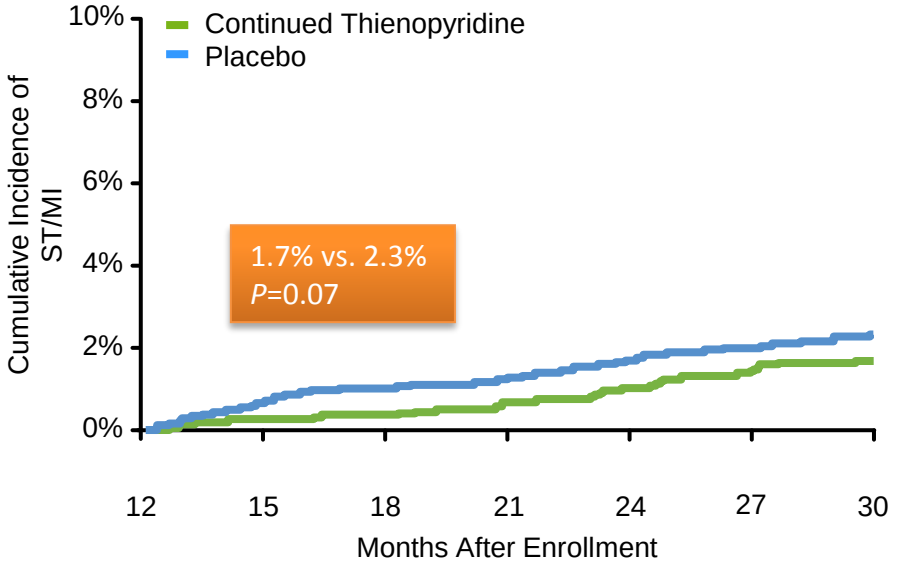


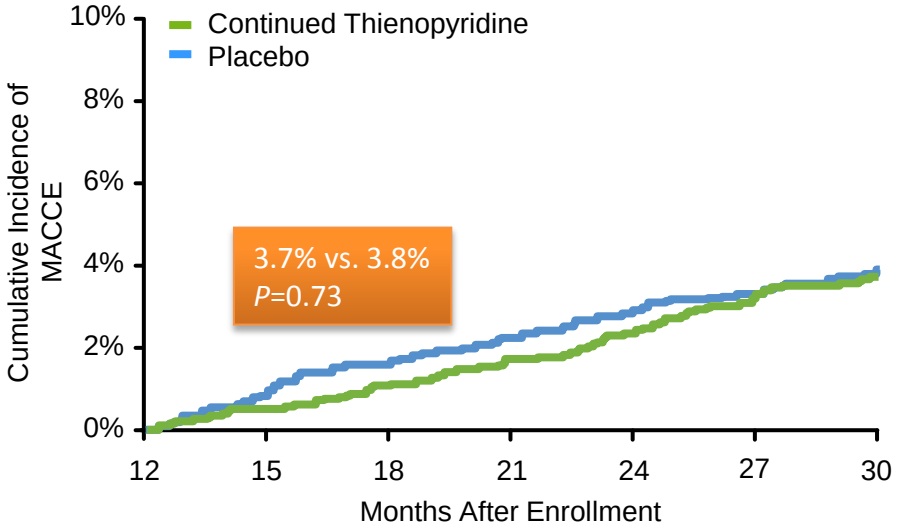
Continued Thienopyridine vs. Placebo
DAPT Score <2 (Low); N=5731

DAPT STUDY

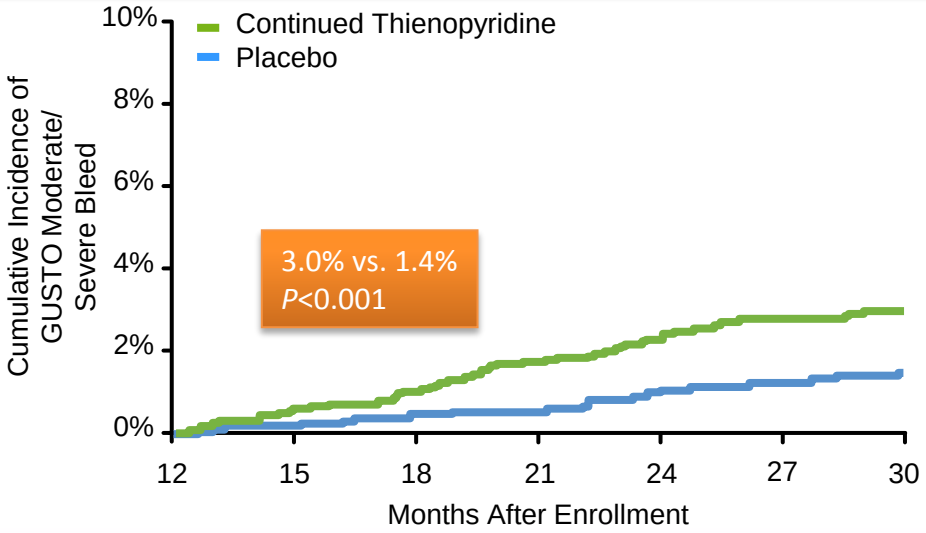
Myocardial Infarction or Stent Thrombosis



Death, MI, or Stroke (MACCE)



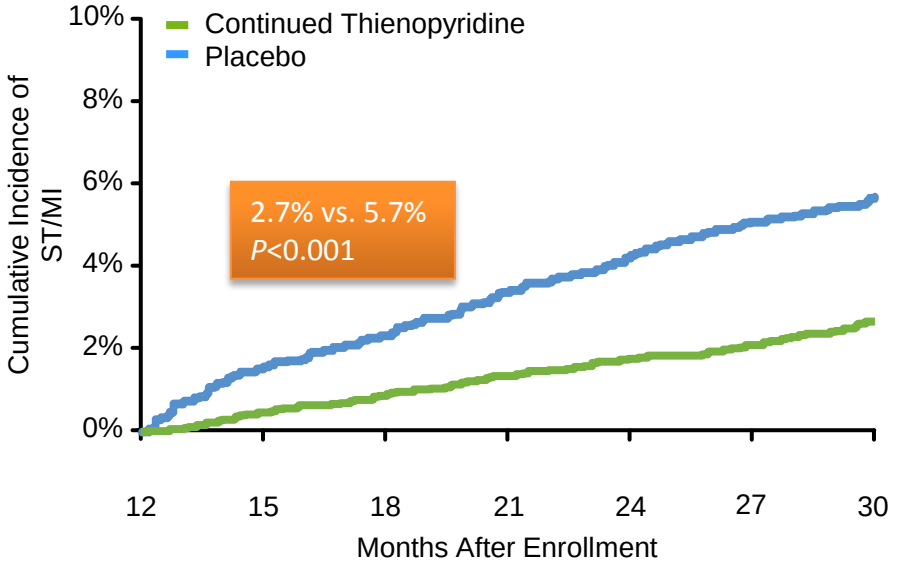
GUSTO Moderate/ Severe Bleeding



Continued Thienopyridine vs. Placebo
DAPT Score ≥ 2 (High); N=5917

DAPT STUDY

Myocardial Infarction or Stent Thrombosis



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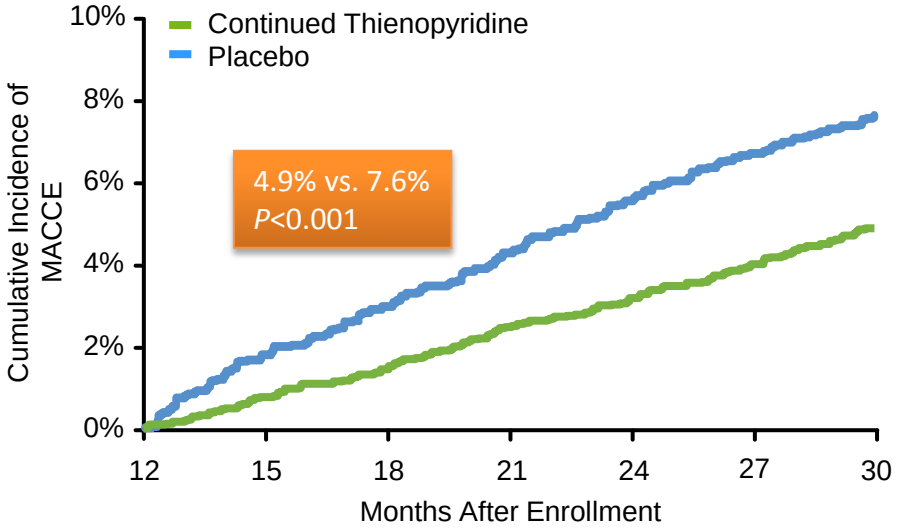

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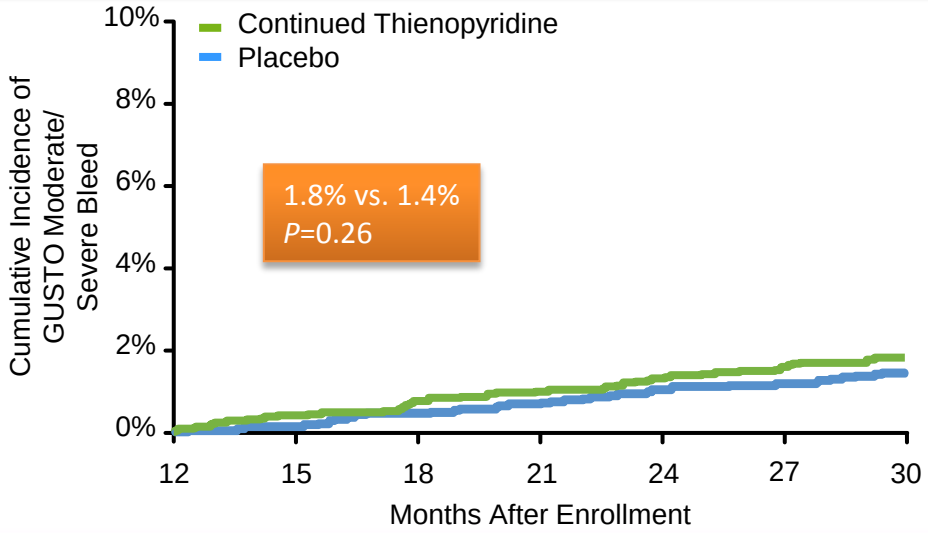
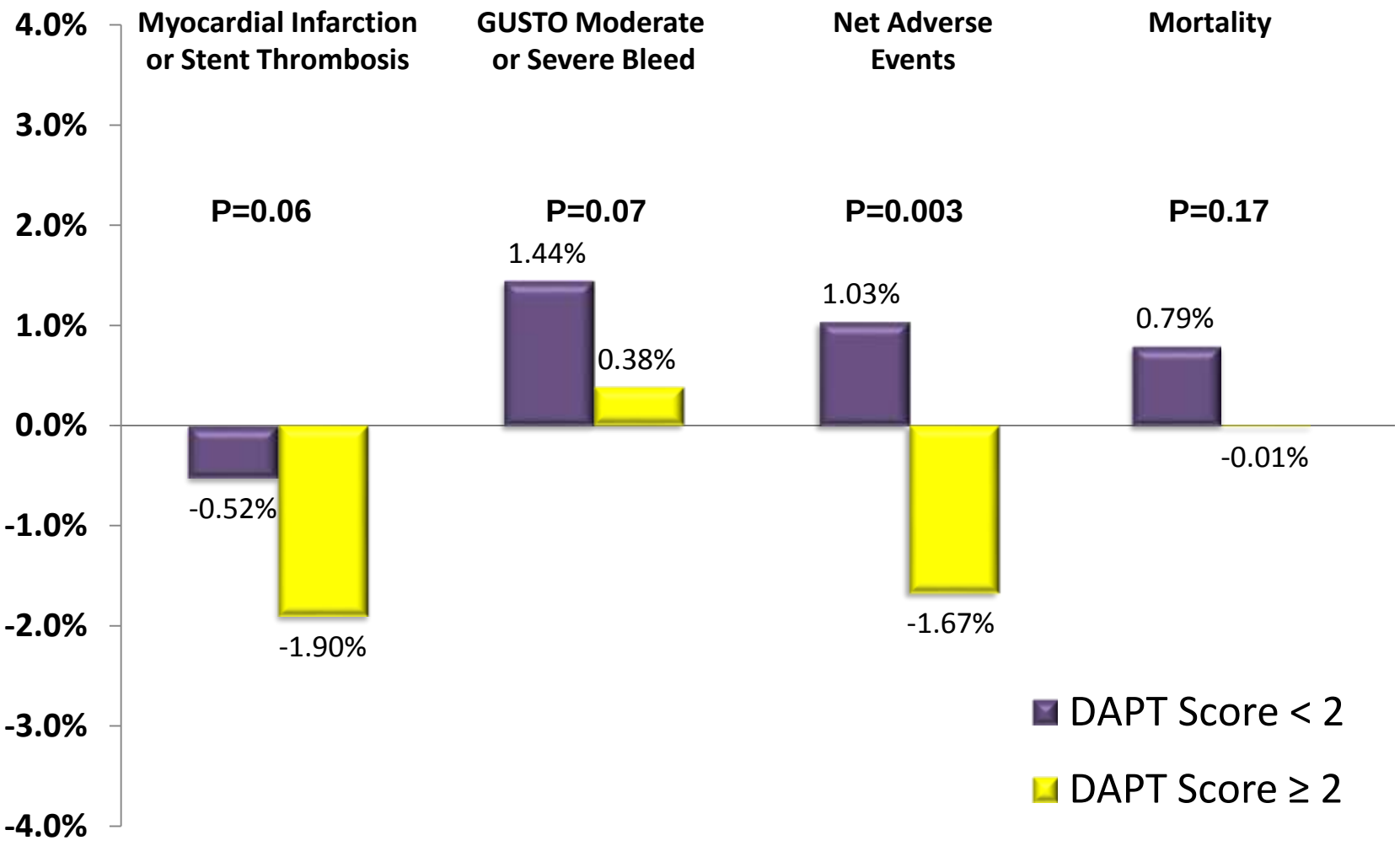


FAQs re: the DAPT Score

Question: Paclitaxel-eluting stents perform poorly, is the DAPT score relevant to today's stents.

Answer: Yes.

Continued Thienopyridine vs. Placebo, by DAPT Score, Excluding PES



P values are for comparison of risk differences across DAPT Score category (interaction).

FAQs re: the DAPT Score

Question: Does use of the DAPT Score assume that bleeding and ischemia are weighted the same?

Answer: No.

Continued Thienopyridine vs. Placebo Treatment Effect by DAPT Score Quartile

DAPT STUDY

Q1 = DAPT Score -2 to 0
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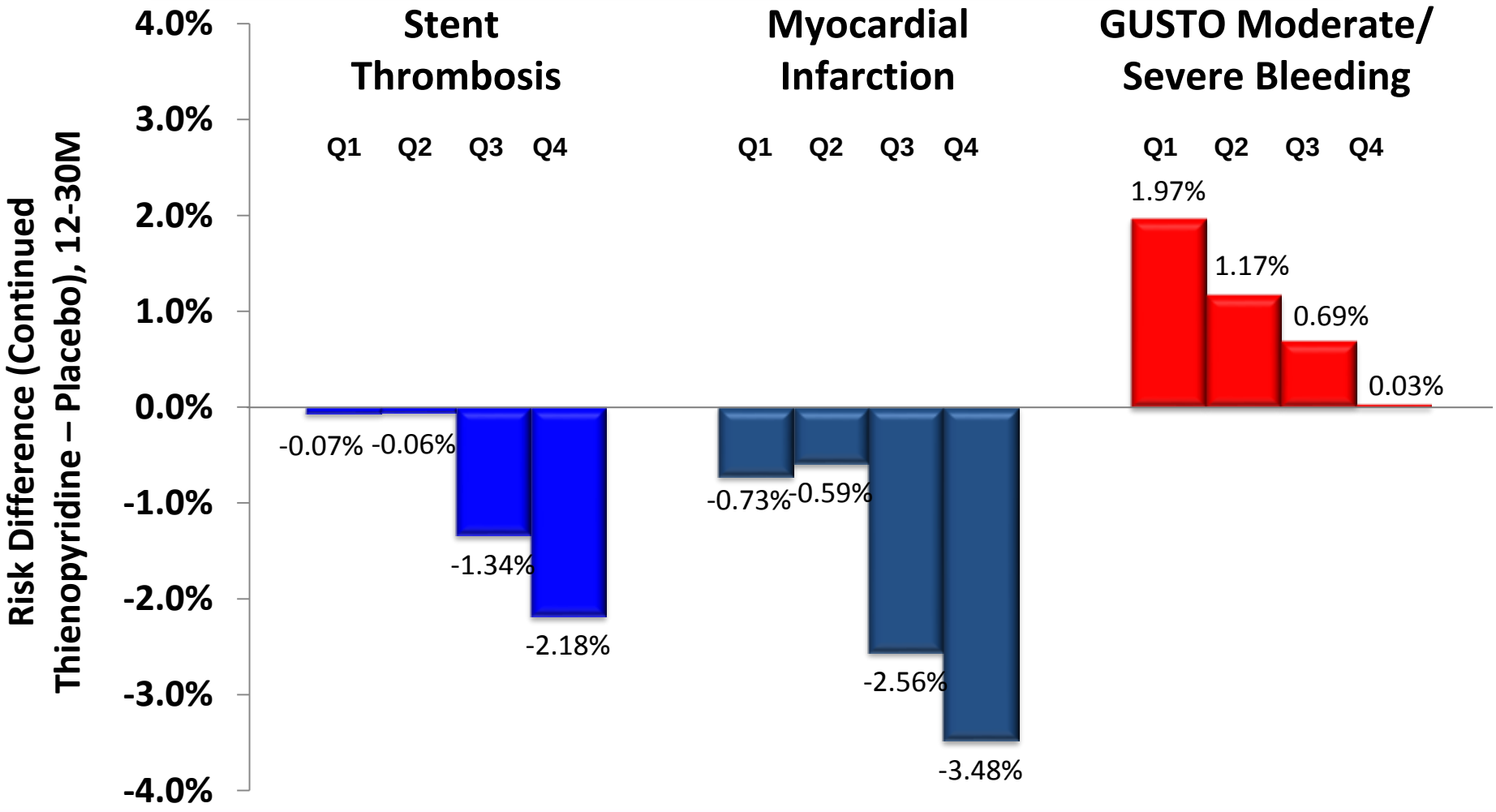

Prolonged DAPT: Who really benefits?

Variable	Points
Patient Characteristic	
Age	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

<u>Age < 65</u>

- MI + one additional factor (e.g., DM, smoker, prior PCI, small stent)

<u>Age >75</u>

- Need 3-4 risk factors for ischemic events

Conclusions

Among patients who have not had a major ischemic or bleeding event within the first year after PCI, the DAPT Score identifies patients for whom ischemic benefits outweigh bleeding risks (and vice versa)

Low DAPT Score (< 2)
NNT to prevent ischemia = 153
NNH to cause bleeding = 64

High DAPT Score ≥ 2
NNT to prevent ischemia = 34
NNH to cause bleeding = 272

DAPT Score may help clinicians decide *who should, and who should not* be treated with extended DAPT