Dual Anti-Platelet Therapy Dilemmas- Drug dosing, duration, rebound, and platelet monitoring

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Presenter Disclosure Information

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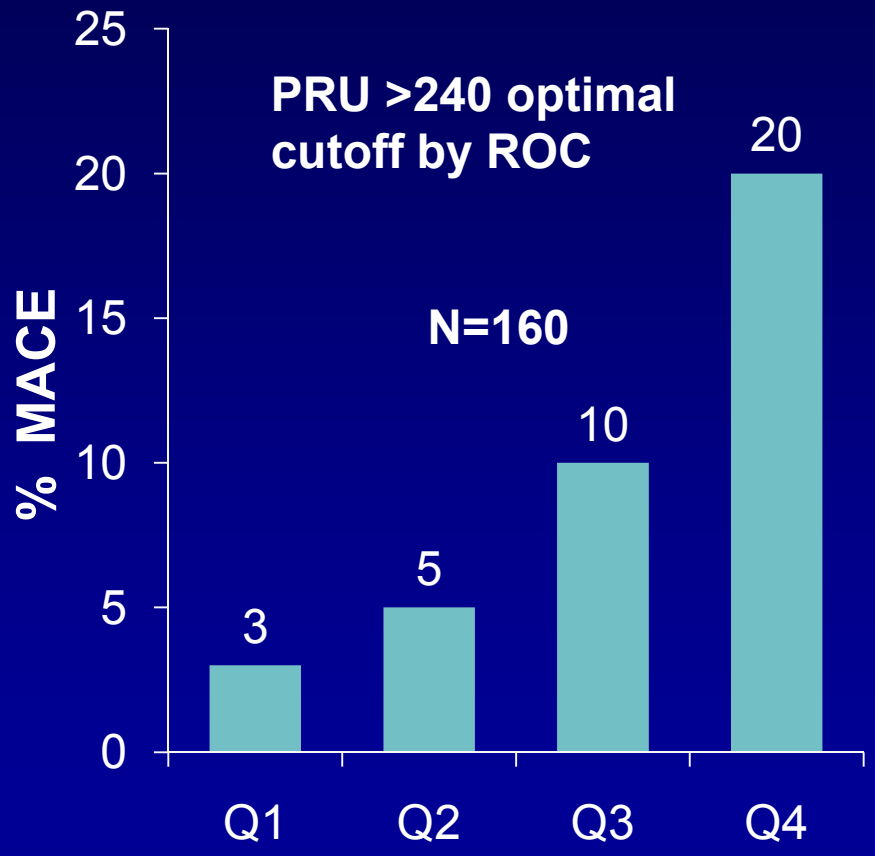
PI Medtronic DAPT (fees paid to Beth Israel Deaconess Medical Center)

Outline

- Platelet responsiveness and clinical outcomes
- Role of platelet function testing
- Agents other than clopidogrel
- DAPT - duration, interruptions, and rebound

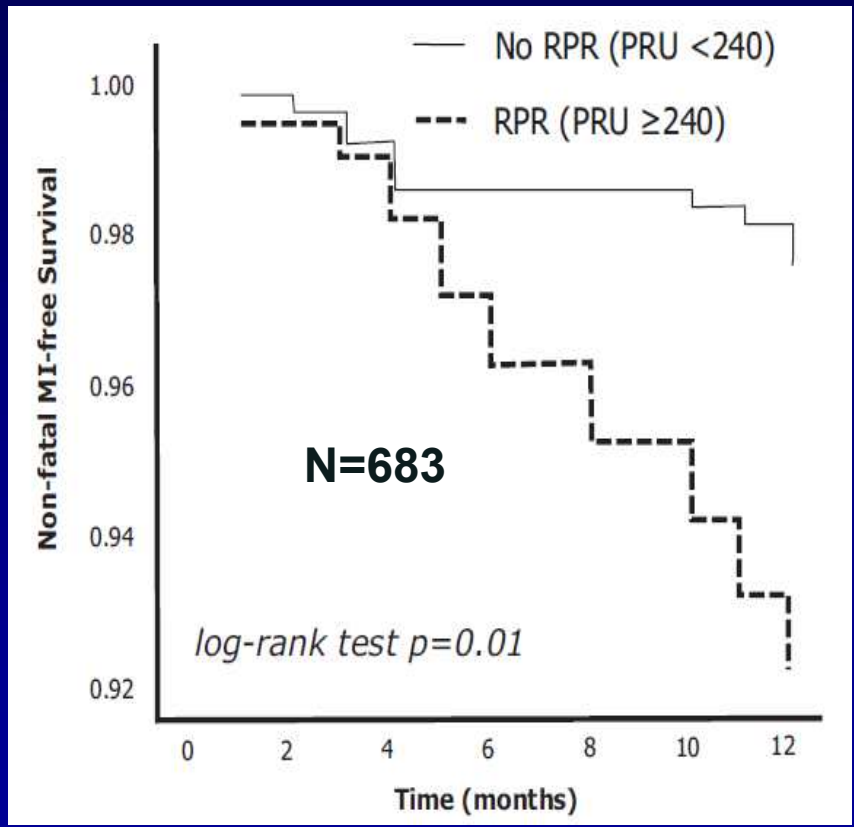
Platelet Response and MACE

30-day MACE by PRU Quartile



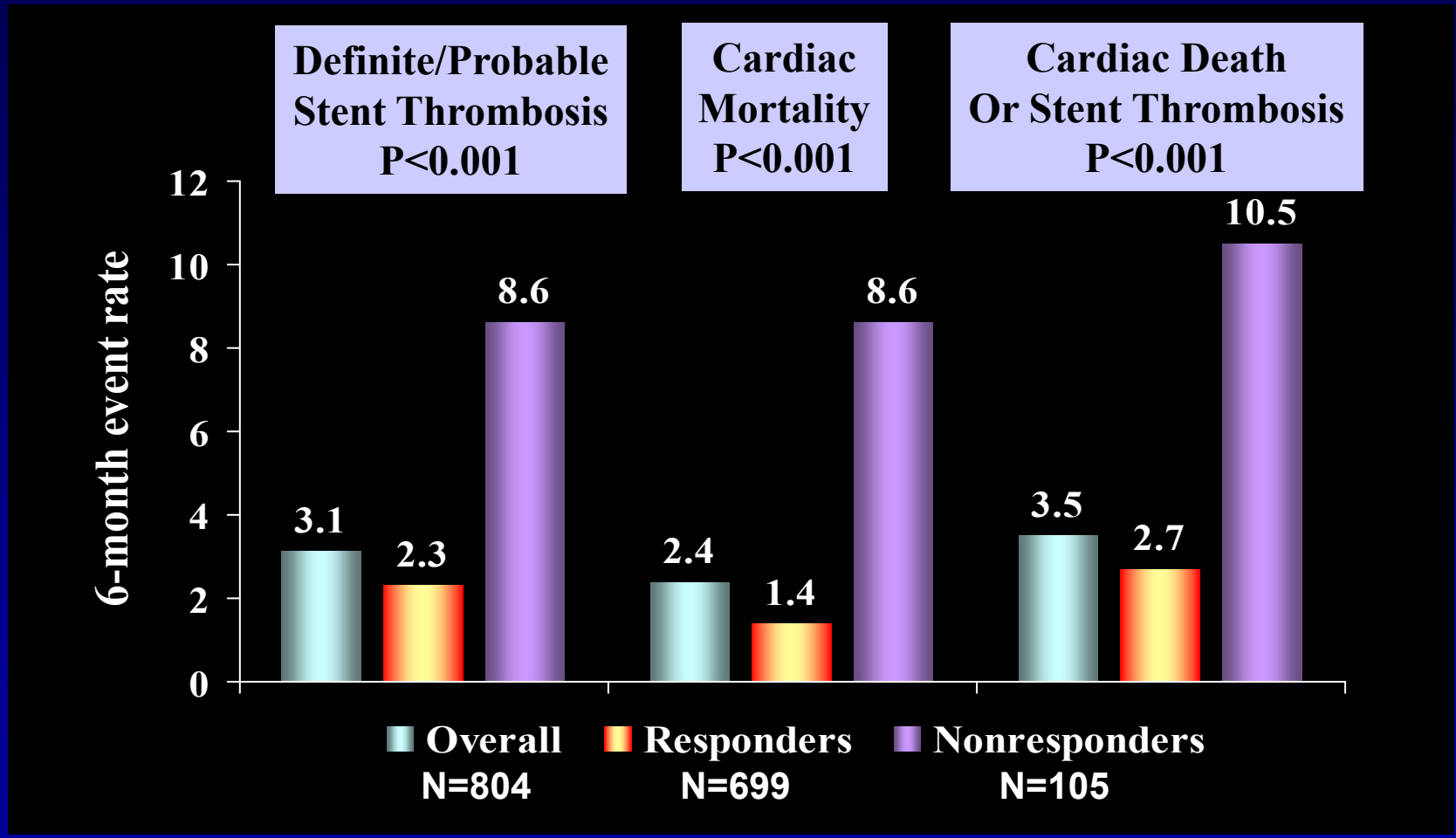
Patti et al. JACC 2008;52:1128-33

1 Year MACE ACS Stent Patients



Marcucci et al. Circulation 2009;119:237-42

Impact of Response or Nonresponse to Clopidogrel on DES Thrombosis



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Buonamici et al. JACC 2007;49:2312-7

Platelet Function Tests

- Light transmission aggregometry (LTA)
  - Requires substantial sample prep
  - Requires trained lab personnel
  - Not practical for real-time clinical decisions
- Bedside assays
  - Most experience with VerifyNow P2Y12 assay
  - Cutoffs of 235 and 240 PRU associated with increased risk for procedural and later events
  - Routine clinical use awaits clinical trials

GRAVITAS

DES for stable angina or non ST elevation ACS
N~2800

VerifyNow assay
12-24 hours

Non-responders

Clopidogrel
Extra load 450 mg
150 mg /d x 6M

Clopidogrel
75 mg/d x 6M

Responders

Clopidogrel
75 mg/d x 6M
Random sample followed

1 EP: Time to CV death, MI, def/prob ST

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FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

Safety Announcement

[03-12-2010] The U.S. Food and Drug Administration (FDA) has added a *Boxed Warning* to the label for Plavix, the anti-blood clotting medication. The *Boxed Warning* is about patients who do not effectively metabolize the drug (i.e. "poor metabolizers") and therefore may not receive the full benefits of the drug.

The *Boxed Warning* in the drug label will include information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

CYP2C19 Polymorphisms

Allele	Prevalence	Effect
CYP2C19*2	9%-45%*	↓ metabolism to active form; ↓ anti-platelet effect; ↑ ST and MACE.
CYP2C19*3	0-16%†	↓ metabolism to active form; ↓ anti-platelet effect;
CYP2C19*17	41% [1] (5% homozygous)	↑ metabolism to active form; ↑ bleeding

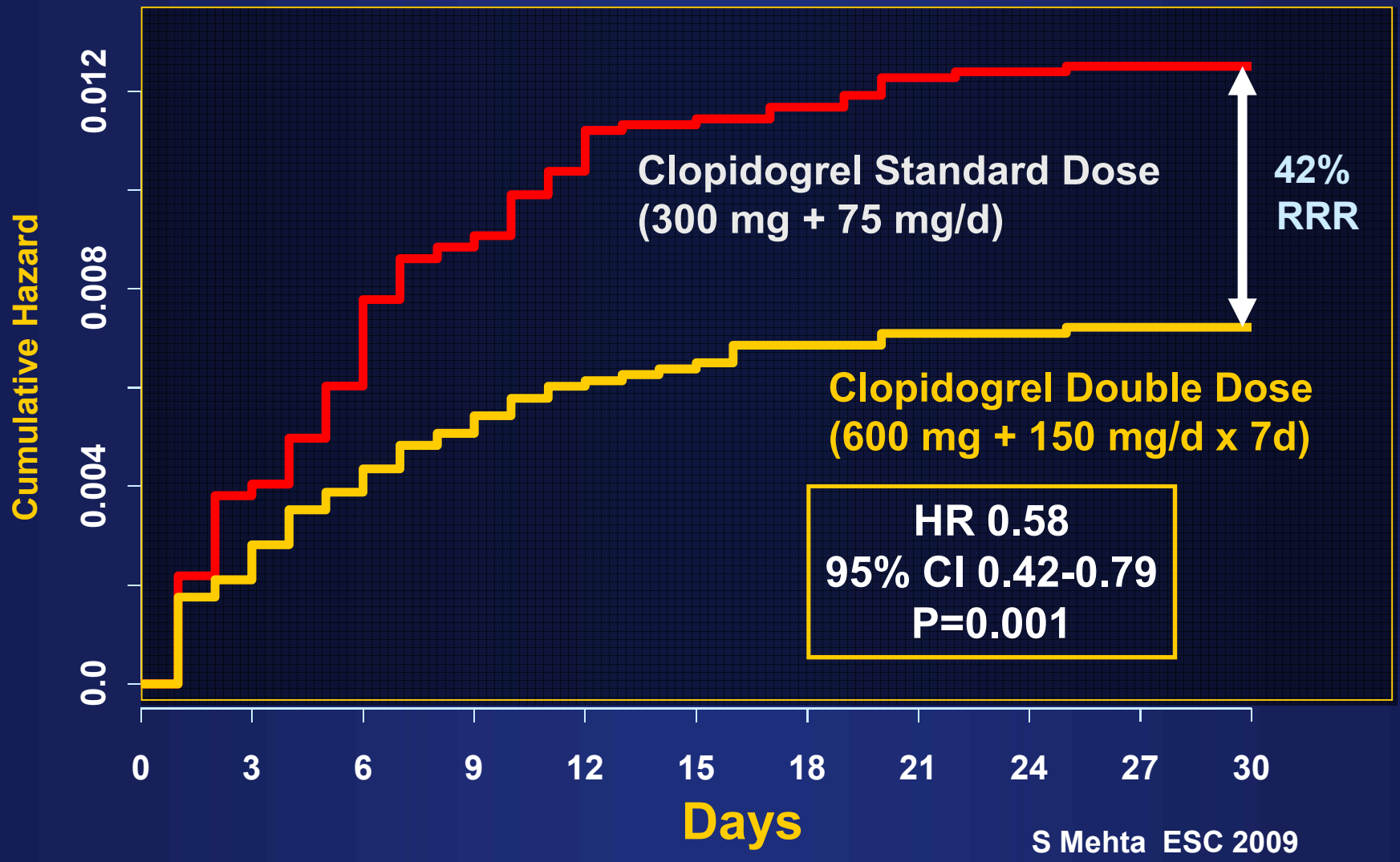
*** Higher prevalence in Asian (29% East Asian) and Pacific Islander (45% Papua New Guinea)**

† Higher prevalence in Asian (9% East Asian) and Pacific Islander (16%)

1. Sibbing et al. Circulation 2010;121:512-18

Options in Non-Responders

CURRENT - OASIS 7

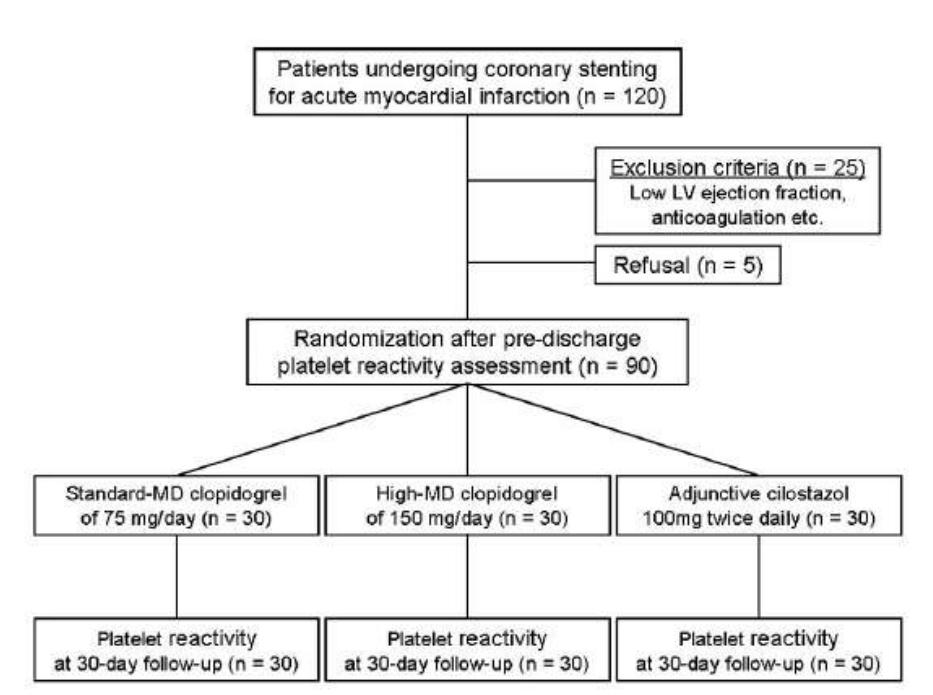


S Mehta ESC 2009

Adding Cilostazol to Dual Antiplatelet Therapy Achieves Greater Platelet Inhibition than High Maintenance Dose Clopidogrel in Patients With Acute Myocardial Infarction

Results of the Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With AMI (ACCEL-AMI) Study

Young-Hoon Jeong, MD, PhD; Jin-Yong Hwang, MD, PhD; In-Suk Kim, MD, PhD; Yongwhi Park, MD, PhD; Seok-Jae Hwang, MD, PhD; Seung-Whan Lee, MD, PhD; Choong Hwan Kwak, MD, PhD; Seong-Wook Park, MD, PhD, FACC



Results

SD vs High MD vs TAPT

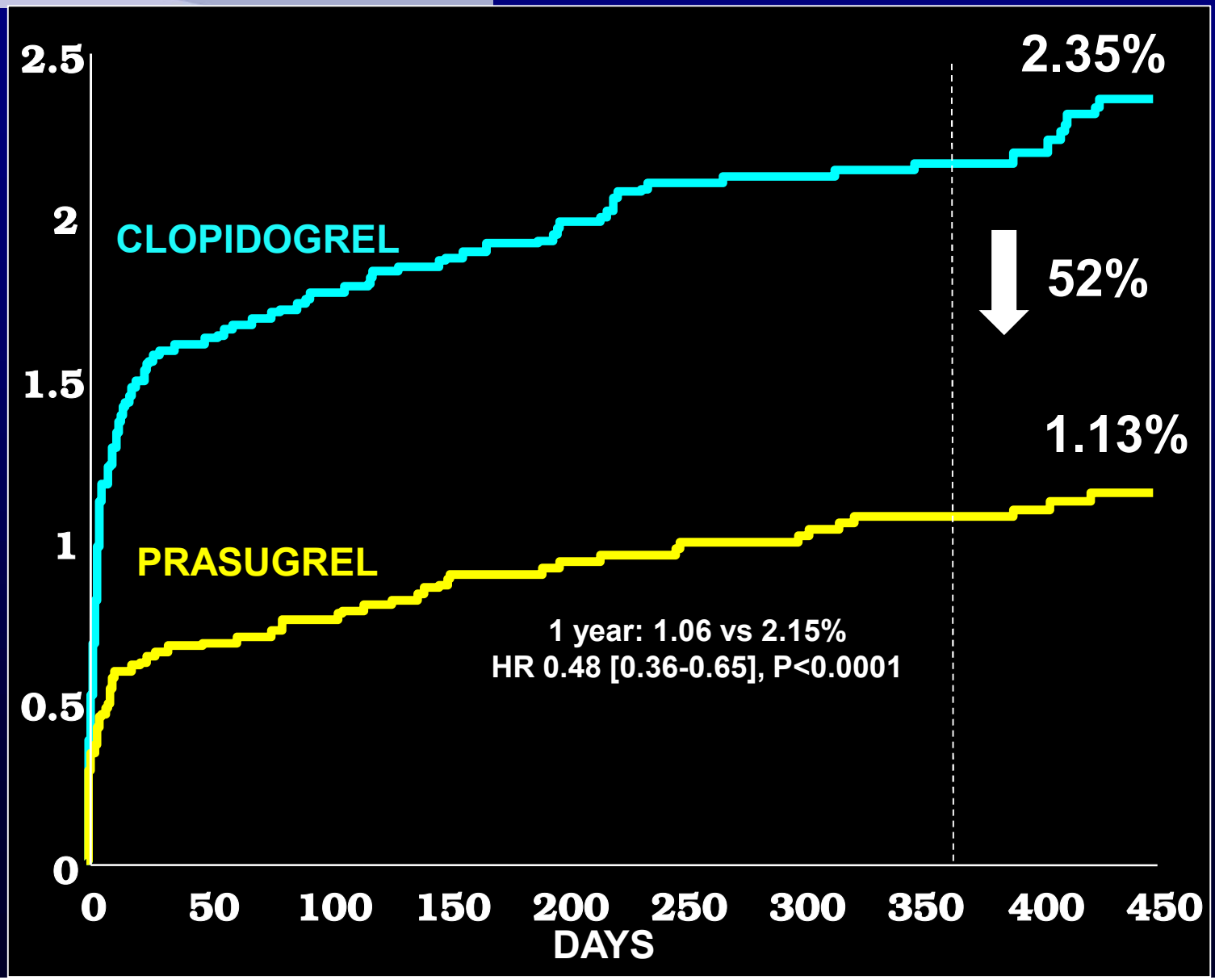
Medians

- **Maximal platelet aggregation (60.2 vs. 54.8 vs. 33.1, p<0.001)**
- **P2Y12 Reaction Units (PRU) (228 vs 185 vs 132, p<0.001)**
- **% Inhibition (27 vs 43 vs 55, p<0.001)**

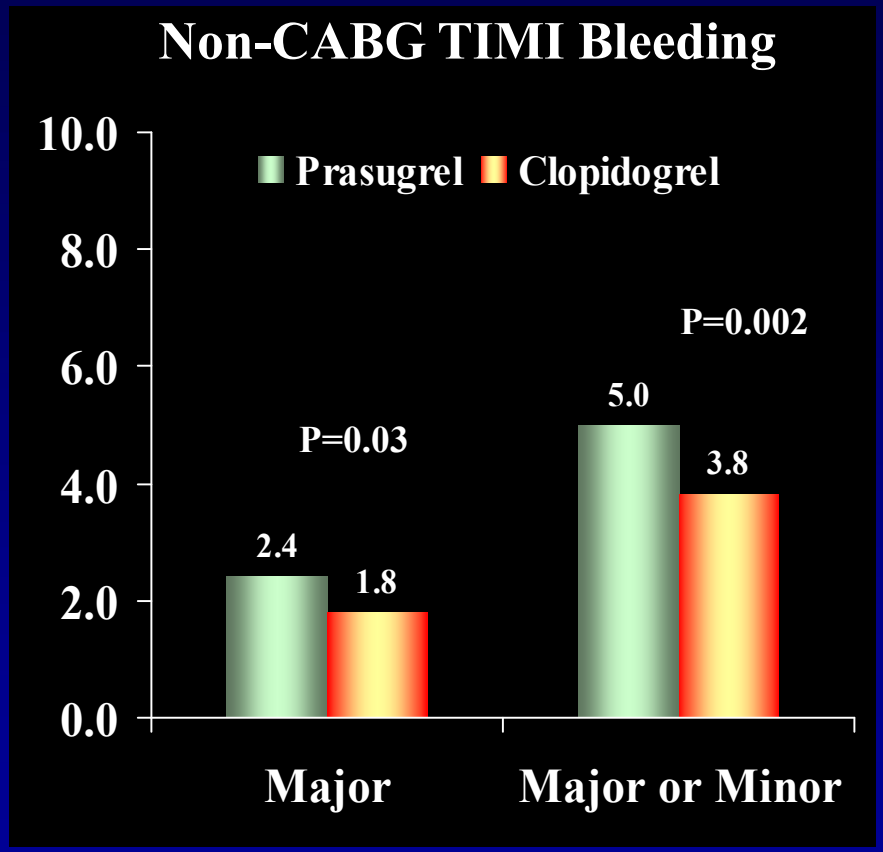
Conclusions—Among patients with AMI undergoing coronary stenting, triple antiplatelet therapy results in a greater antiplatelet effect at 30 days as compared with a high-MD clopidogrel or standard dual antiplatelet therapy. (***Circ Cardiovasc Interv*. 2010;3:17-26.**)

TRITON TIMI-38
STENT ANALYSIS

Definite/Probable ST: Any Stent (N=12844)



Prasugrel and Bleeding Risk



Prasugrel Bleeding Risk

- Higher for age >75, low body weight, and if prior stroke/TIA

Wiviott SD et al. NEJM 2007;357:2001

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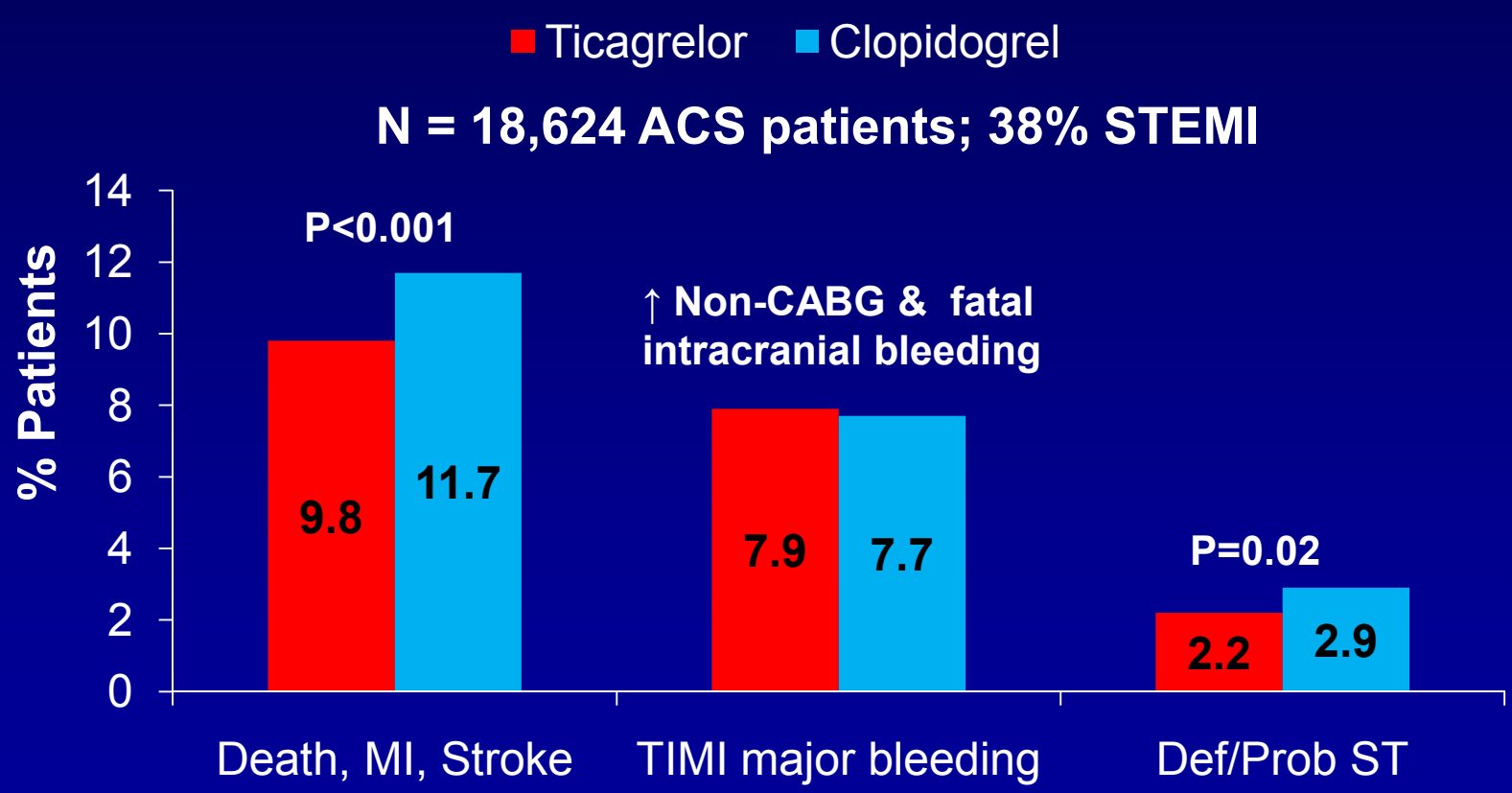
Future Options – Ticagrelor
PLATO Study

One Year Outcomes



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L Wallentin et al. NEJM 2009;361:1045-57

DAPT

Duration, Interruptions, and Rebound

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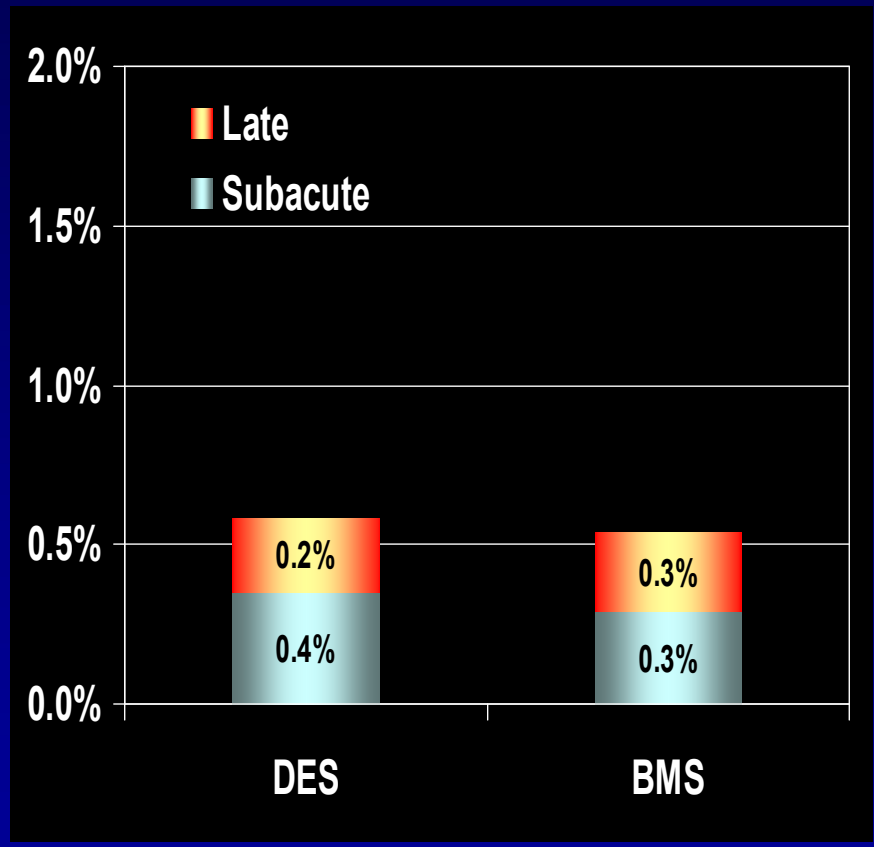
Background

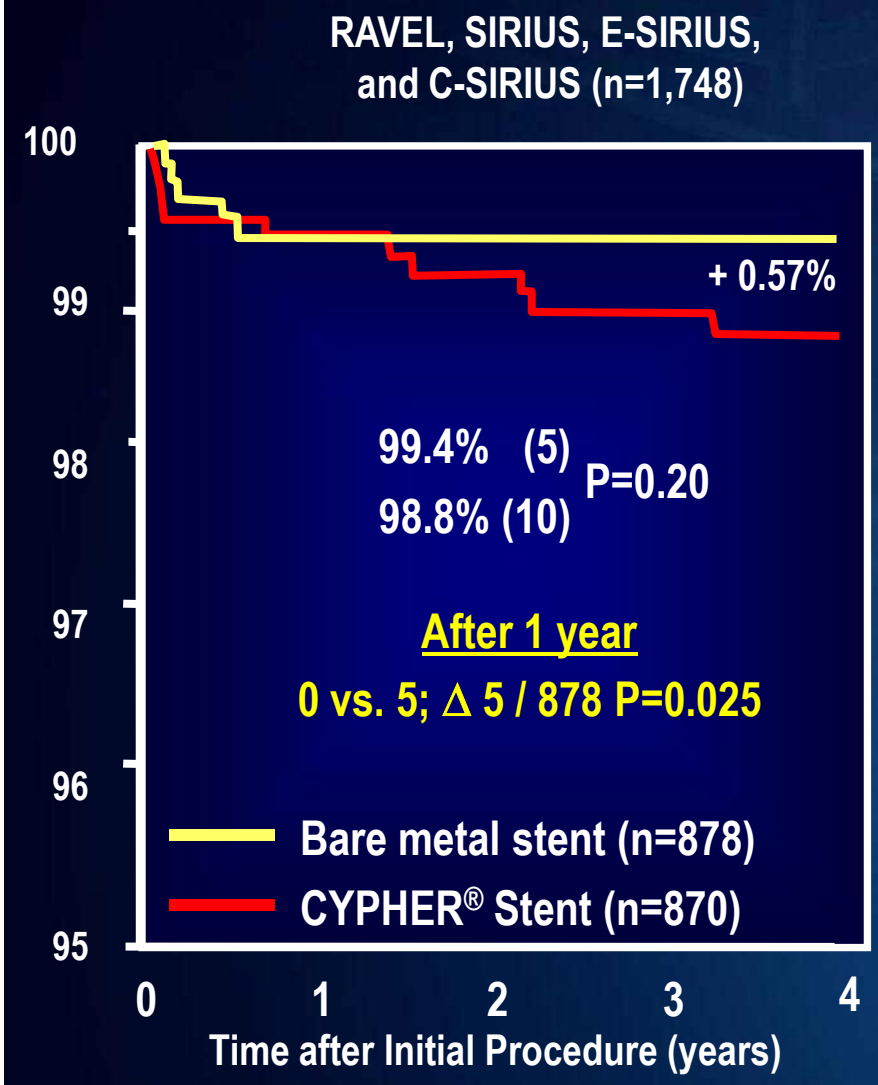
- Early studies of sirolimus- and paclitaxel-eluting stents mandated 3 or 6 months of DAPT, respectively.
- Continuation beyond protocol period infrequent

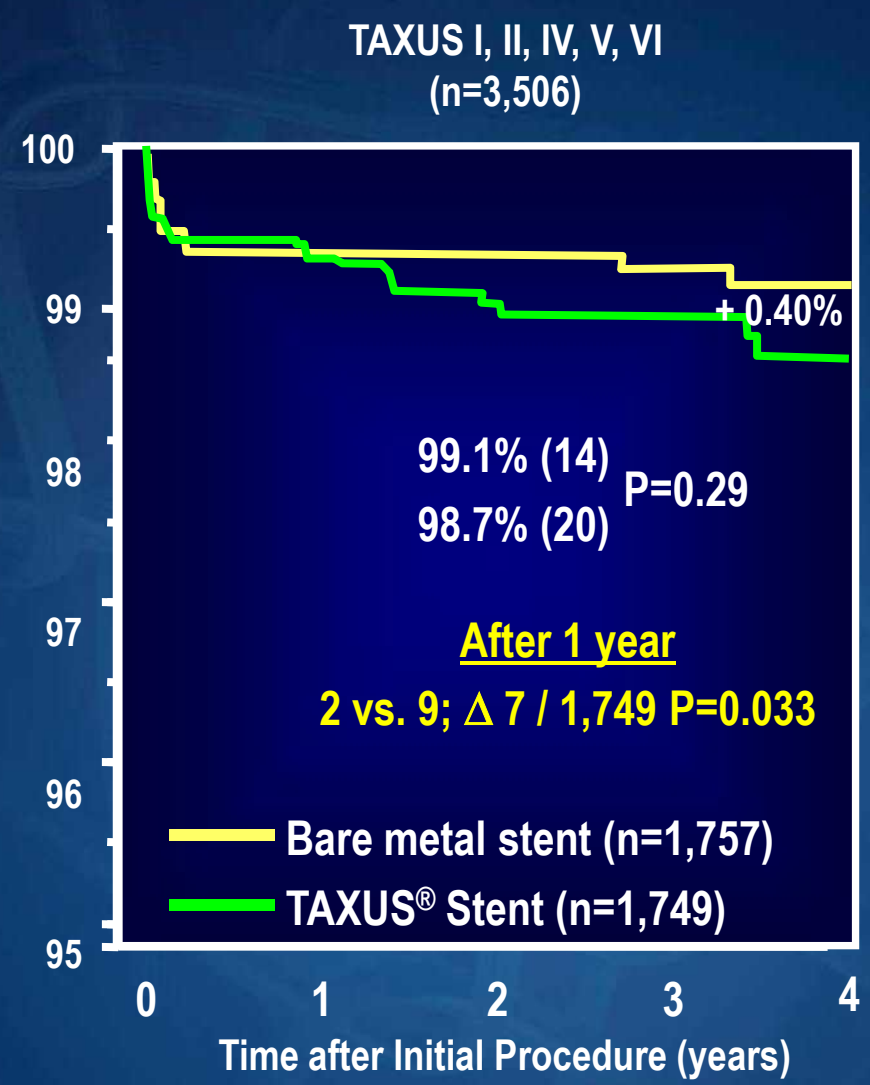


Moreno R, et al. JACC 2005;45:954-9

Pooled Clinical Trials Data

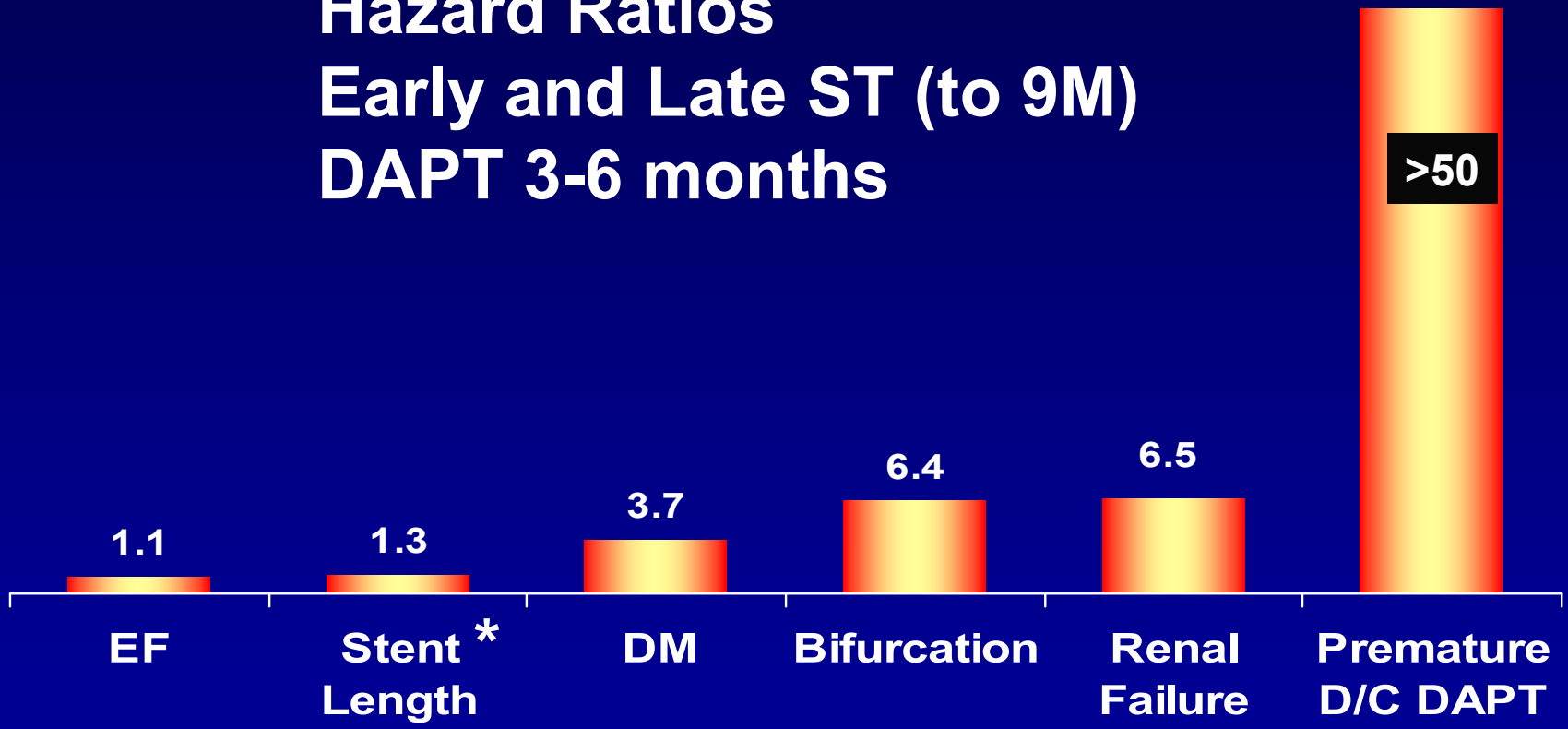
Freedom From Stent Thrombosis (Protocol Defined)





Correlates of Early and Late ST

Hazard Ratios
Early and Late ST (to 9M)
DAPT 3-6 months



* Early ST only

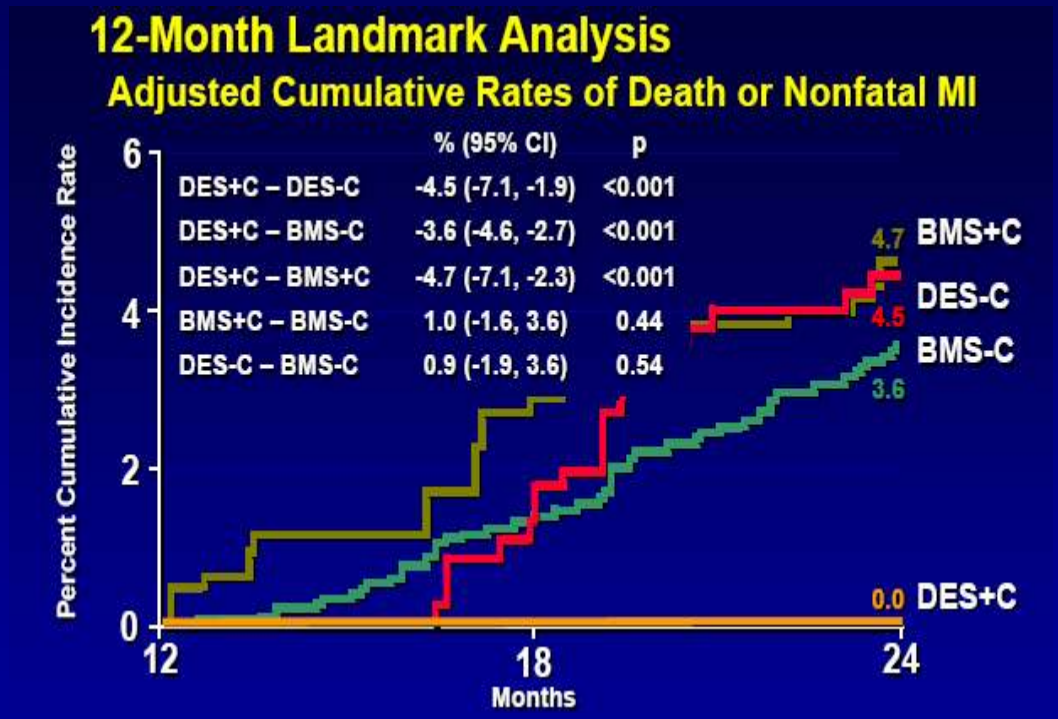
Iakovou et al. JAMA 2005;293:2126-30

FDA Advisory Panel December 2006….

Recognizing that the optimal duration of such therapy remains unknown, the panel requested that the instructions for use of both stents include a reference to the current guidelines for percutaneous coronary interventions, which state that dual antiplatelet therapy should be continued for 12 months in patients who are not at high risk for bleeding.

A Farb and A Boam. NEJM 2007;356:984-987

Duke Registry – "Landmark" Analysis



Limitations

- Non-concurrent enrollment
- Excludes patients with death, MI, repeat revascularization before "landmark" time
- Missing clopidogrel data:
  - 475/3165 (15%) BMS Pts
  - 418/1501(28%) DES Pts
- Confounding by indication and survivor bias

E. Eisenstein et al. JAMA 2007;online Dec 5, 2006

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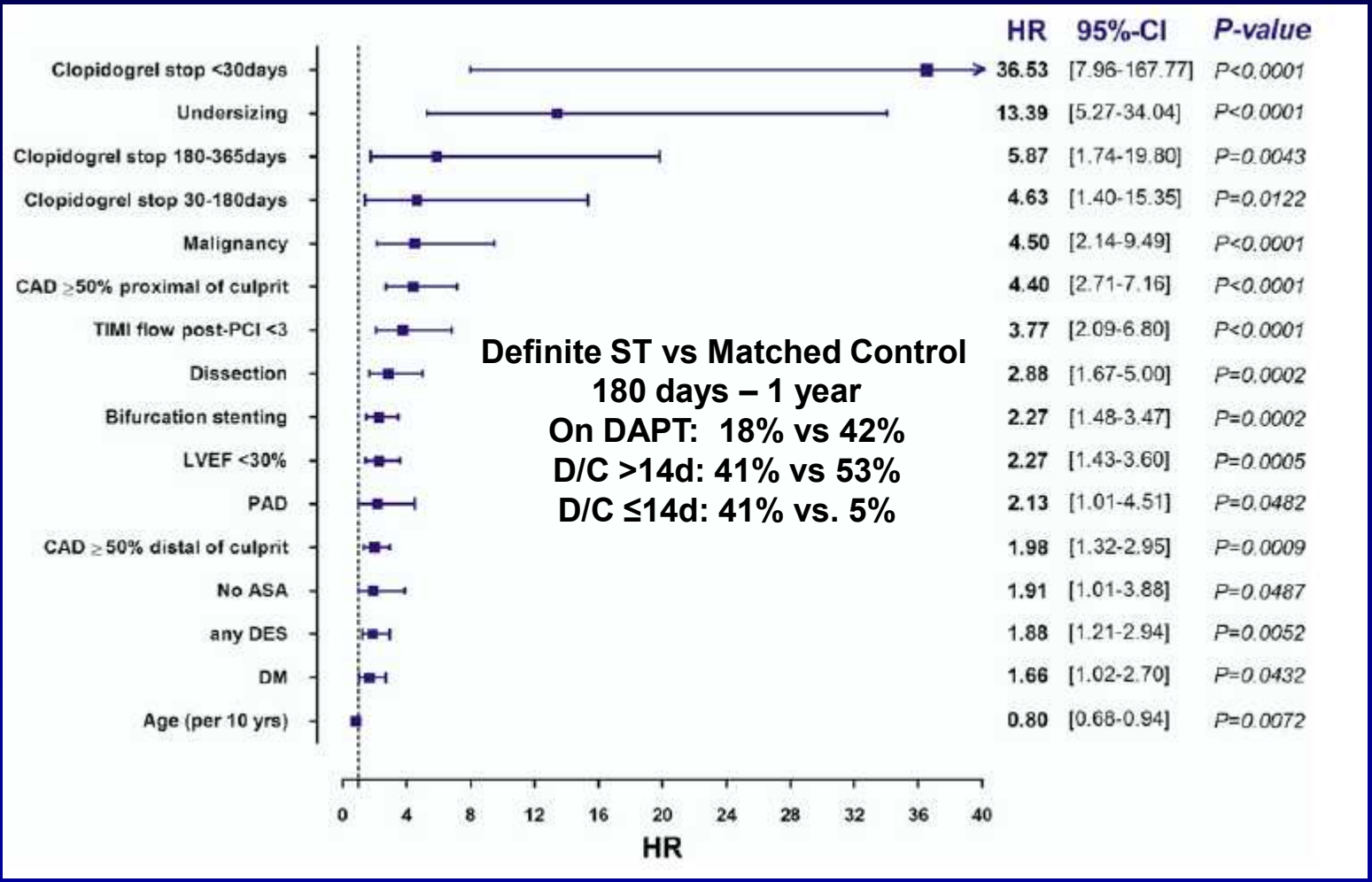
Clopidogrel Duration and ST Risk

Dutch ST Registry



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JW van Werkum et al. JACC 2009;53:1399-1409

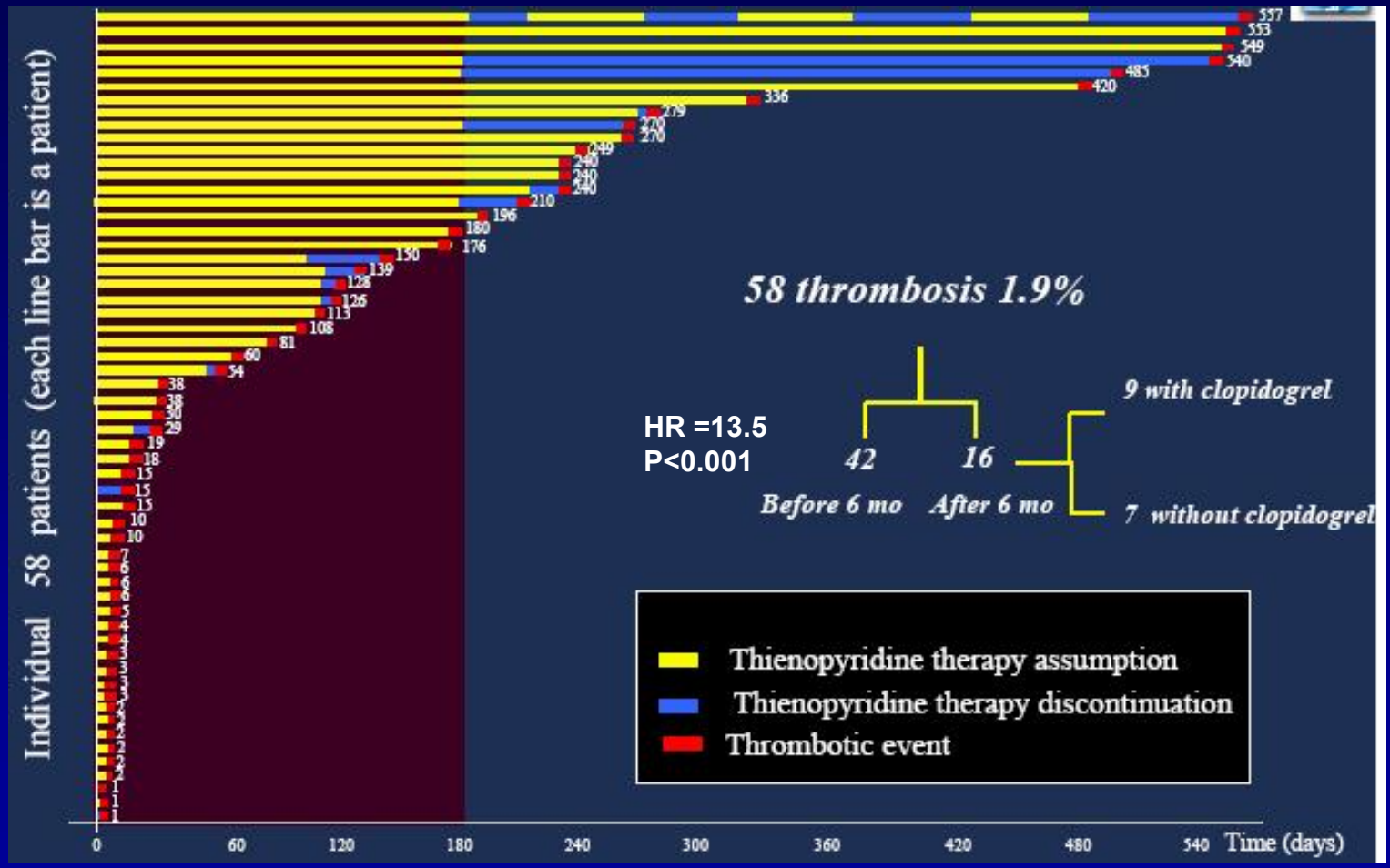
Correlates of Very Late ST

Dual Anti-Platelet Therapy Duration

Study	% LST on DAP	Comments
Pooled SES	25% (2/8)	Protocol D/C after 3 months
Bern-Rotterdam	23% (14/61)	SES 3-6 M; PES 6 M
Airoldi et al	56% (9/16)	D/C clopidogrel not a predictor of ST after 6 M;
Mishkel et al.	54% (21/39)	LST and VLST
Kimura et al	57% LST; 36% VLST	6M landmark analysis negative.
Park et al	HR 0.54 VLST	Not significant beyond 12 months
Schulz et al		Significant <6M ; not >6 months

Time to Stent Thrombosis

Impact of Clopidogrel Discontinuation after 6 Months



A. Colombo et al. presented at FDA panel meeting, December 8, 2006
Airoldi F et al. Circulation 2007;116:745-54

Discontinuation of DAPT and ST Risk

Time to ST after stopping clopidogrel

	Early/Late ST Days	Late/Very Late ST Days (Range)
Kuchulakanti*	6.2 ± 4.9	55.5 ± 34.5 (21-90)
Airoldi**	14	90
Schulz**	9	104

* Early = 30 days and Late 31 days-6 months (mean, range)

** Early = 6 months and Late > 6 months

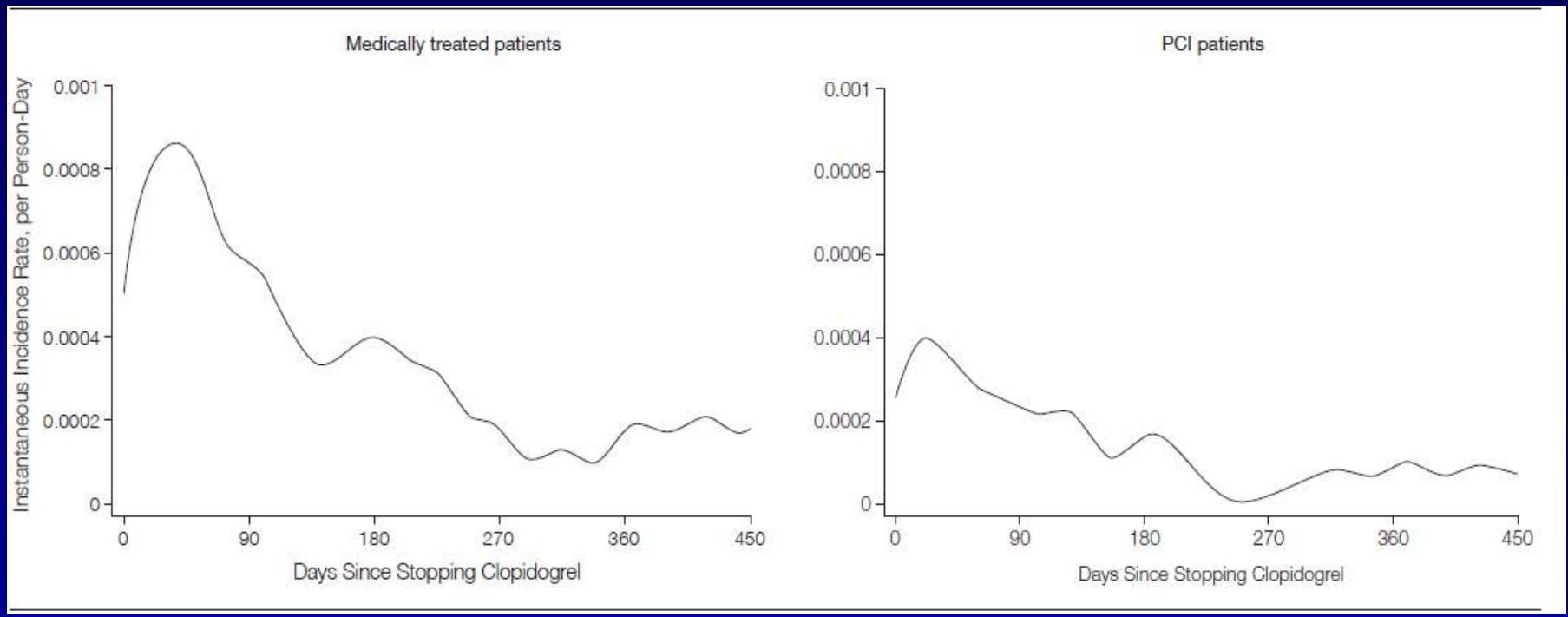
Kuchulakanti P, et al. Circulation 2006;113:1108

Airoldi F, et al. Circulation 2007:116:745

Schulz S et al Eur Heart J 2009;22:2685

Is There Clopidogrel Rebound Effect?

US VA Hospitals – N =3137 ACS Patients



Ho et al. JAMA 2008;299:532-39

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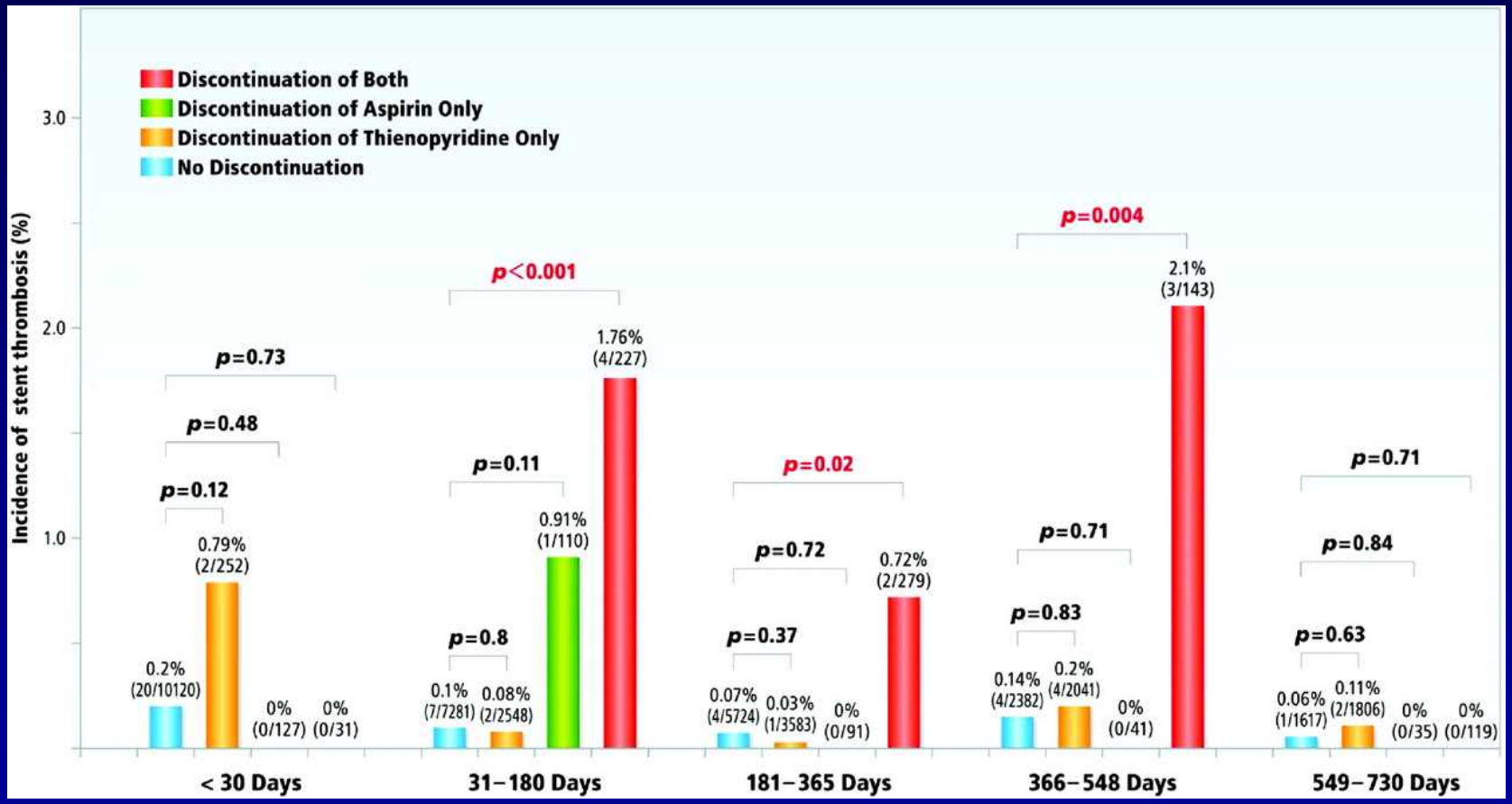
Non-Cardiac Surgery
Short-term Interruption of DAPT

Study	N	DAPT Interruption	Results
SENS[1]	194	w/in 1 year after ZES	2.1% (2 deaths, 2 MI; 3 in 1st 3 months)
Cleveland Clinic[2]	481	Variable – 79% off 1 agent and 63% off both	ST risk declined between 1-6 M but persisted beyond 12M; 4/7 LST off aspirin
Israel[3]	78	Variable; Surgery >6 M post DES	6(7.7%) death, MI, ST; 2 on DAPT; 2 off both;

1. Kim JW et al. JACC 2009;53;suppl A16
2. Anwaruddin S et al. JACC Int 2009;2;542
3. Assali A et al CCI 2009;74:837

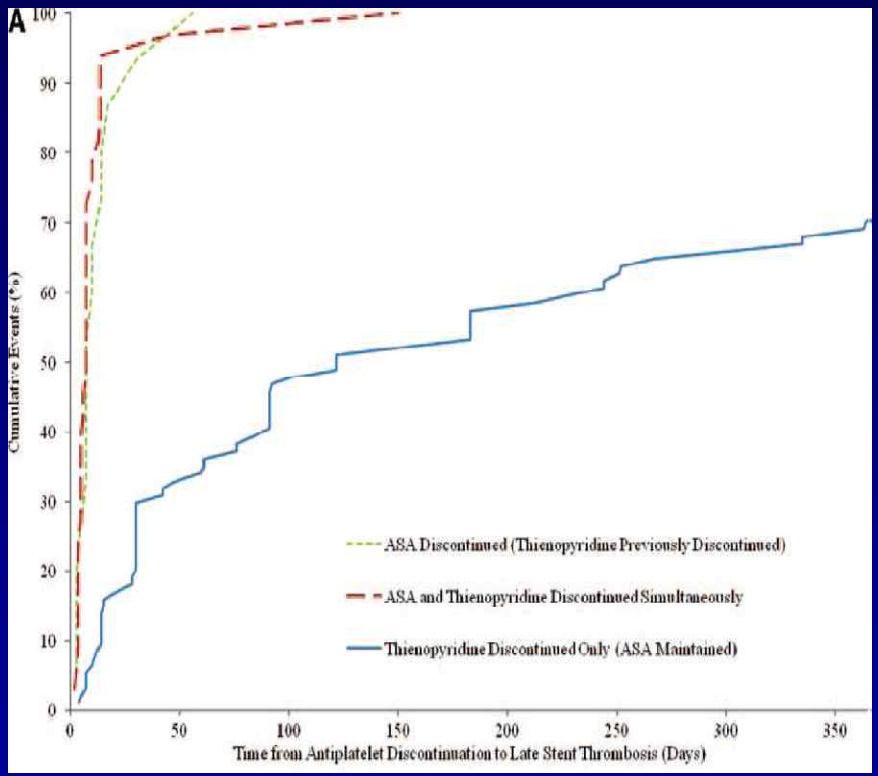
Impact of ASA Discontinuation

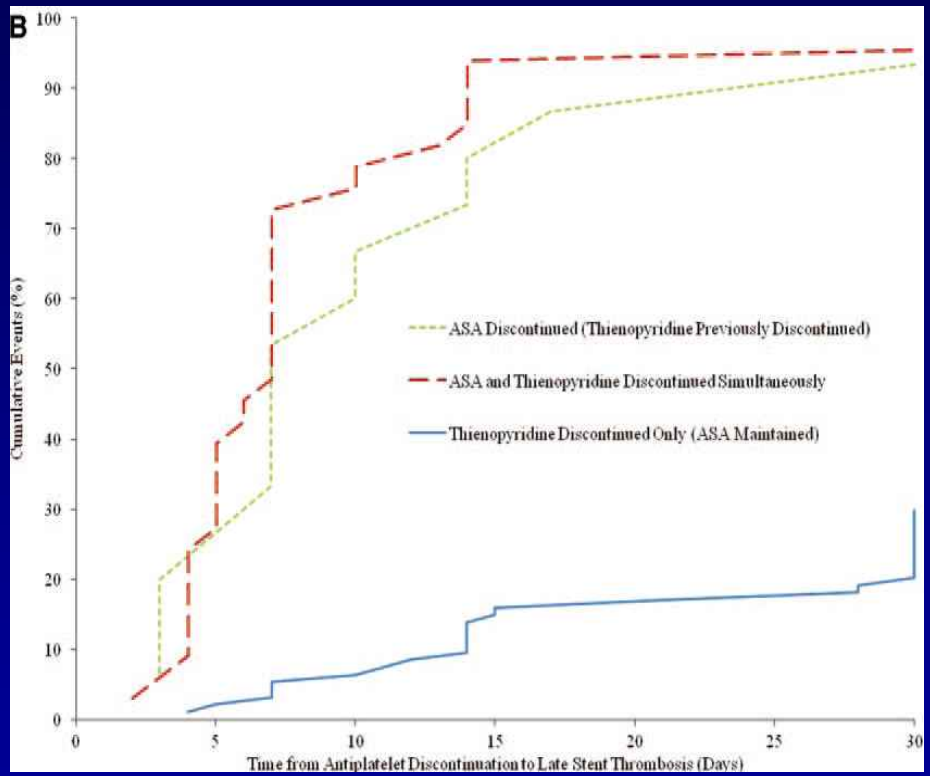


Kimura, T. et al. Circulation 2009;119:987-995

Short-Term Discontinuation of DAPT

Impact on Risk and Timing of ST

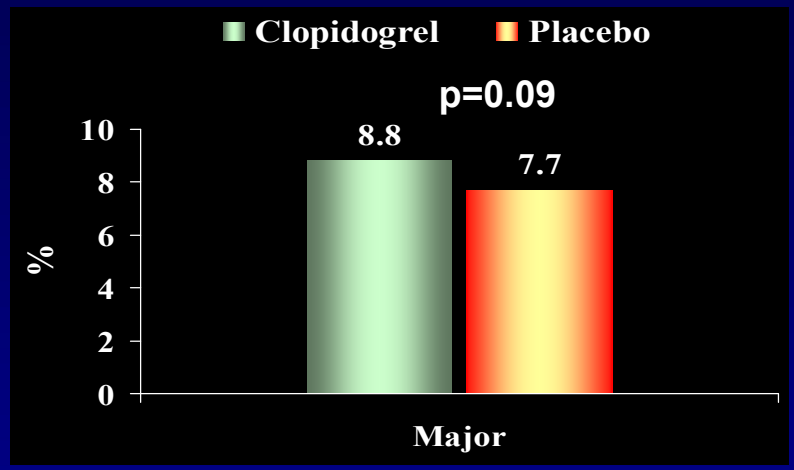




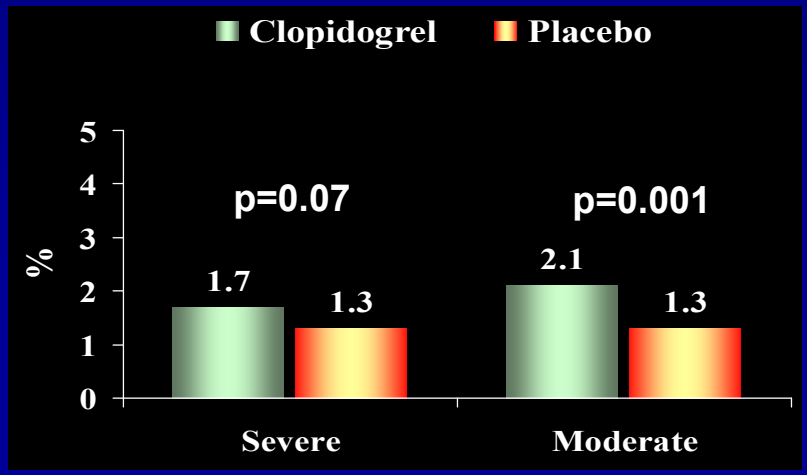
M. Eisenberg et al. Circulation 2009;119:634

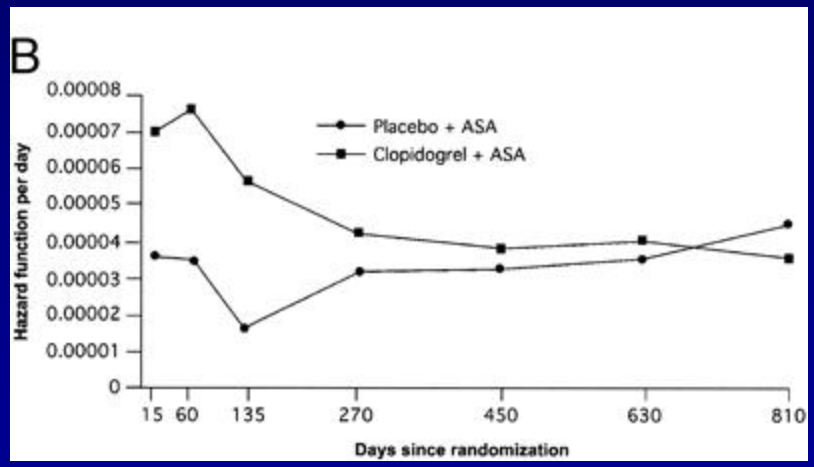
DAPT and Bleeding Risks

CREDO



CHARISMA



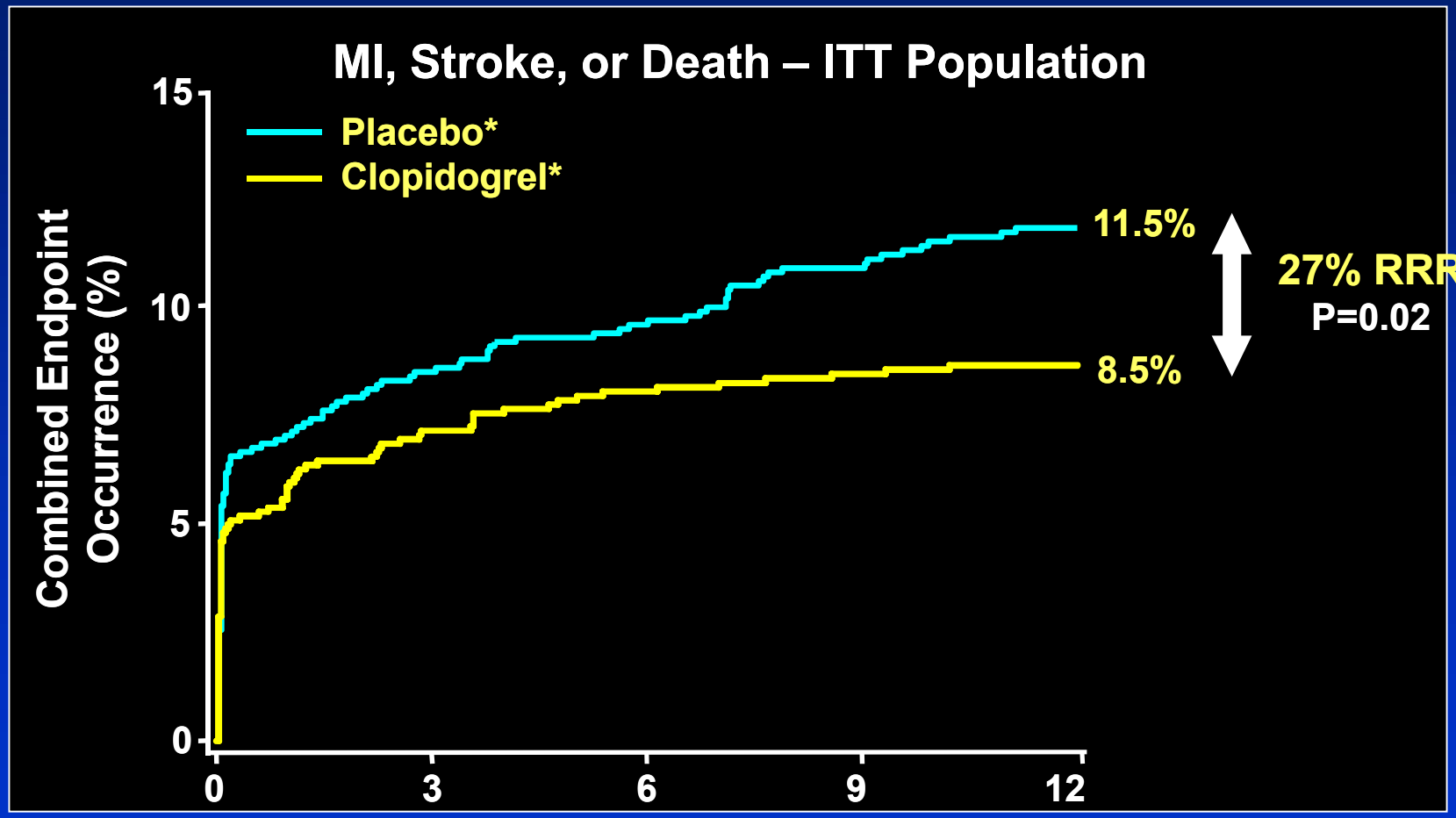


D. Bhatt et al. JACC 2007;49:1982

Clinical Trials

Study	Population	DAPT	1° Endpoint	2° Endpoint
DAPT	20,645	12M vs 30 M	1. Death, MI, stroke 2. ARC def/prob ST	Gusto bleeding
ISAR-SAFE	6,000	6M vs 12 M	Death, MI, stroke, TIMI major bleed	ARC ST
REAL-LATE	2,000	12M vs 24M	Cardiac death or MI	ARC ST Bleeding
OPTIMIZE	3,120	3M vs 12 M	Death, MI, stroke, TIMI major bleed	ARC ST
ZEST-LATE	2,000	12M vs 24M	Death or MI	ARC ST Bleeding
SEASIDE	900	6M	Death, MI, stroke	Gusto bleeding

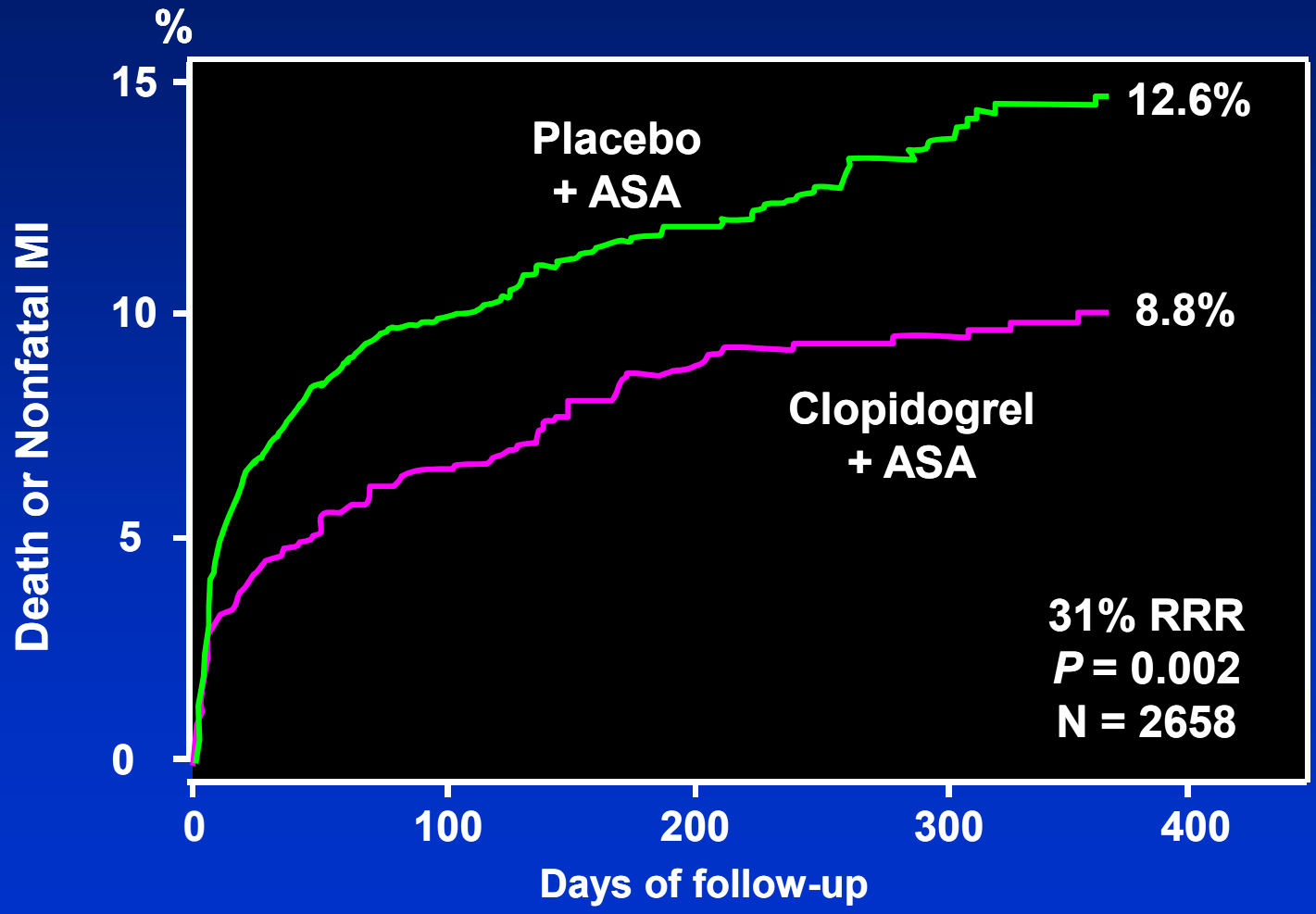
Long-Term (1 Year) Benefits of Clopidogrel in PCI Patients - CREDO



Steinhubl SR et al. JAMA 2002;288:2411-20

CURE PCI Sub-Study

Upstream Clopidogrel Before PCI *



Mehta S, Lancet 2001

* Median Time to PCI = 6 Days

Is longer (>6 or 12M) duration better?

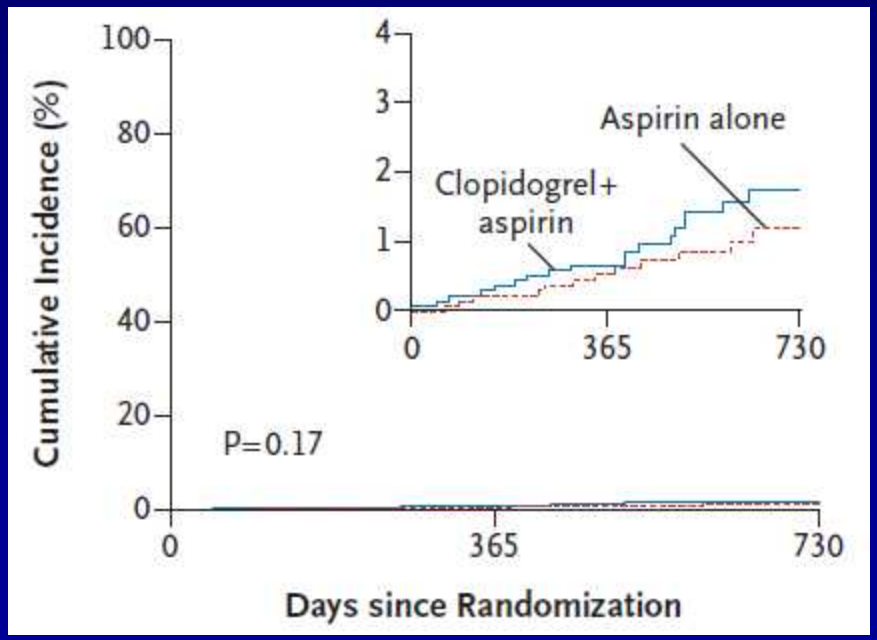
What is the appropriate endpoint?

- Does prolonged dual anti-platelet therapy reduce the risk for **cardiac death or MI** after coronary stenting?
- Is prolonged, **uninterrupted** dual anti-platelet therapy required to reduce the risk for late or very late stent thrombosis?

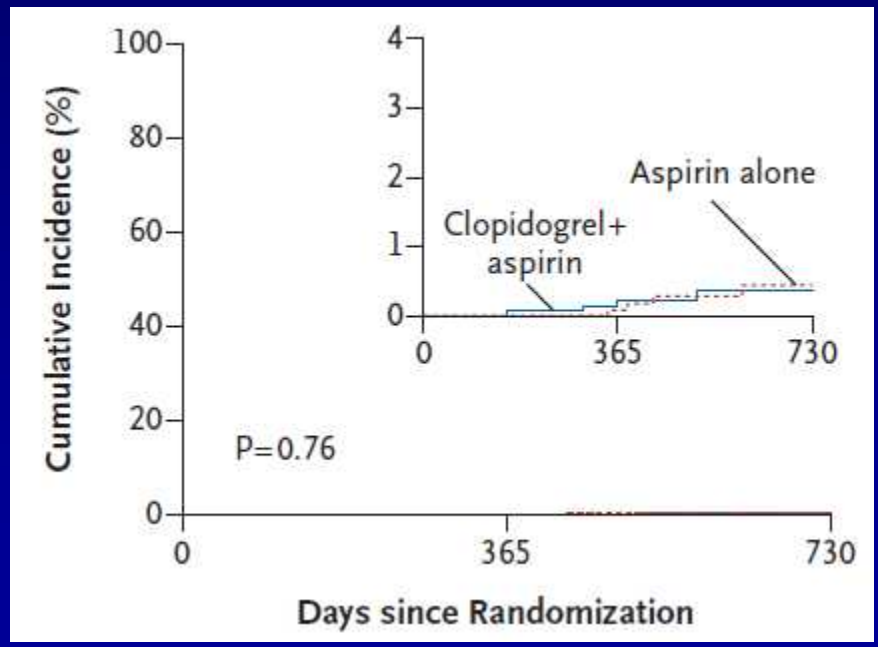
REAL-LATE and ZEST-LATE

- Trials merged due to slow enrollment
- N = 2701 pts free of MACE or major bleed at least 12 months median = 12.8 month
- Randomized to clopidogrel + ASA vs. ASA alone

Cardiac death or MI



Definite ST



SJ Park et al. NEJM 2010;362:1374-82

Conclusions

- Decreased anti-platelet response after clopidogrel therapy associated with increased risk for MACE, including stent thrombosis.
- Decreased anti-platelet response is partly due to genetic polymorphisms of CYP2C19.
- Alternative agents such as prasugrel correct for most causes of clopidogrel poor response, but may be associated with increased bleeding risk
- Early (<6 months) discontinuation of DAPT associated with marked increased risk in ST; Beyond 6 (?12) months, the impact of interrupting or stopping thienopyridine if ASA continued is uncertain