Identifying the ‘Optimal’ Duration of DAPT

Less is More, More or Less…

David E. Kandzari, MD
Director, Interventional Cardiology Research
Scripps Clinic
La Jolla, California
kandzari.david@scrippshealth.org

Antiplatelet Therapy and DES Revascularization
Timeline Perspective

Stent thrombosis, irrespective of timing or stent type, is associated with considerable morbidity and mortality

- *January 2006, December 2007*
  ACC/AHA/SCAI guidelines consensus-opinion based recommendations of 12 months DAPT following DES for pts without apparent contraindications
- *December 2006*
  FDA Panel concern over annualized ST rates motivate FDA to mandate DES labeling incorporate 12 month DAPT recommendation
- *December 2007*
  Inter-society Scientific Advisory reiterates 12 month guidelines

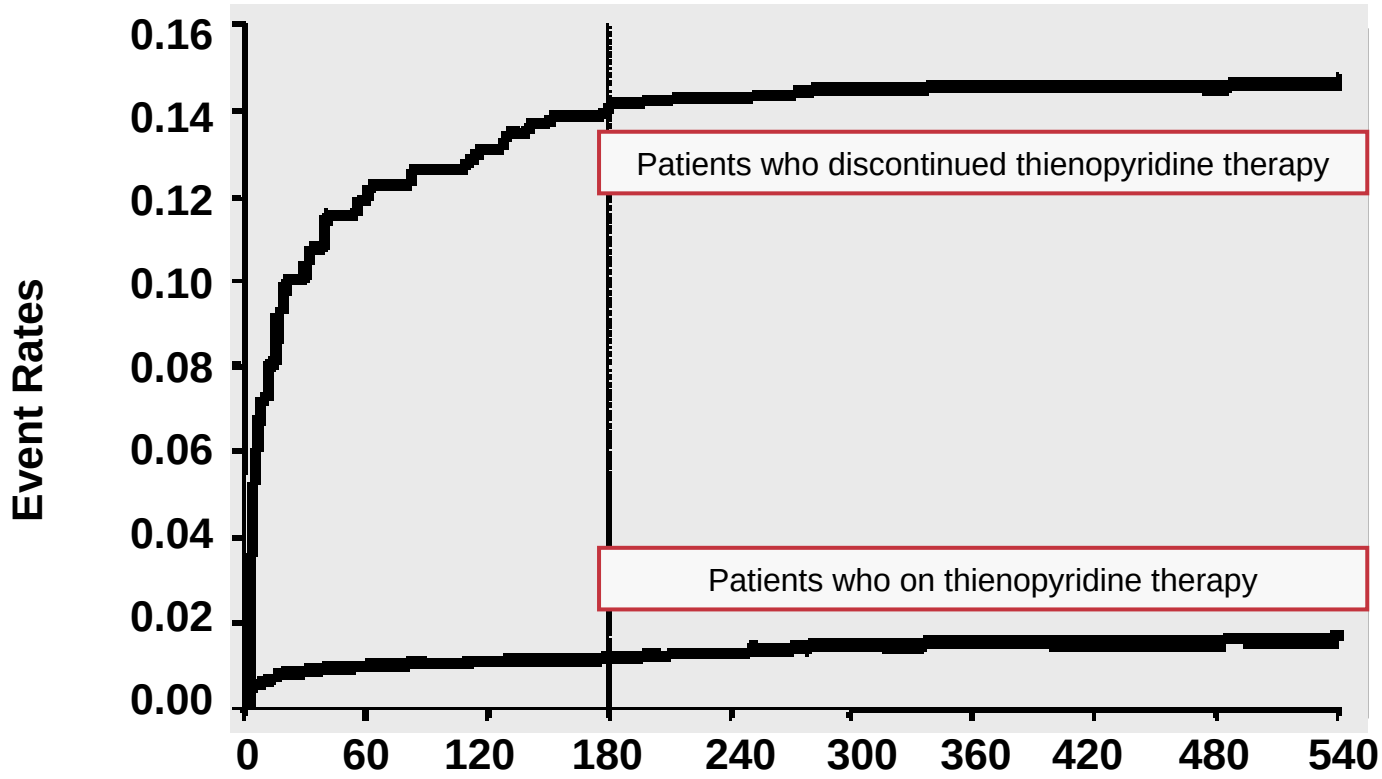
‘Optimal’ DAPT Duration and DES Revascularization
A Less than ‘Optimal’ Evidence Basis

- RCT and RCT substudies (CREDO, PCI-CURE)
  - Pharma trials evaluating pretreatment and dosing strategies
  - Follow-up limited to ≤12 months
  - Majority of treatment effect within initial 30-90 days
- Observational studies consistently demonstrate ‘premature’ thienopyridine discontinuation with increased risk of ST

No prospective, (randomized) data associating long-term DAPT with reductions in ST

  - Duke Cardiovascular Database, Eisenstein et al. JAMA 2007
  - Kaiser Permanente, Brar et al. J Am Coll Cardiol 2008
- No estimate of bleeding risk
  - CHARISMA Severe bleeding: 1.7% over ~2 year follow-up
  - ‘Clopidogrel survivor’ theory reflects selection bias
- Consensus opinion: Emotive, intuitive perception that extended DAPT could reduce ST events

Rate of ST in Patients On Dual-Anti-platelet Therapy and in Patients Who Discontinued Thienopyridine Therapy

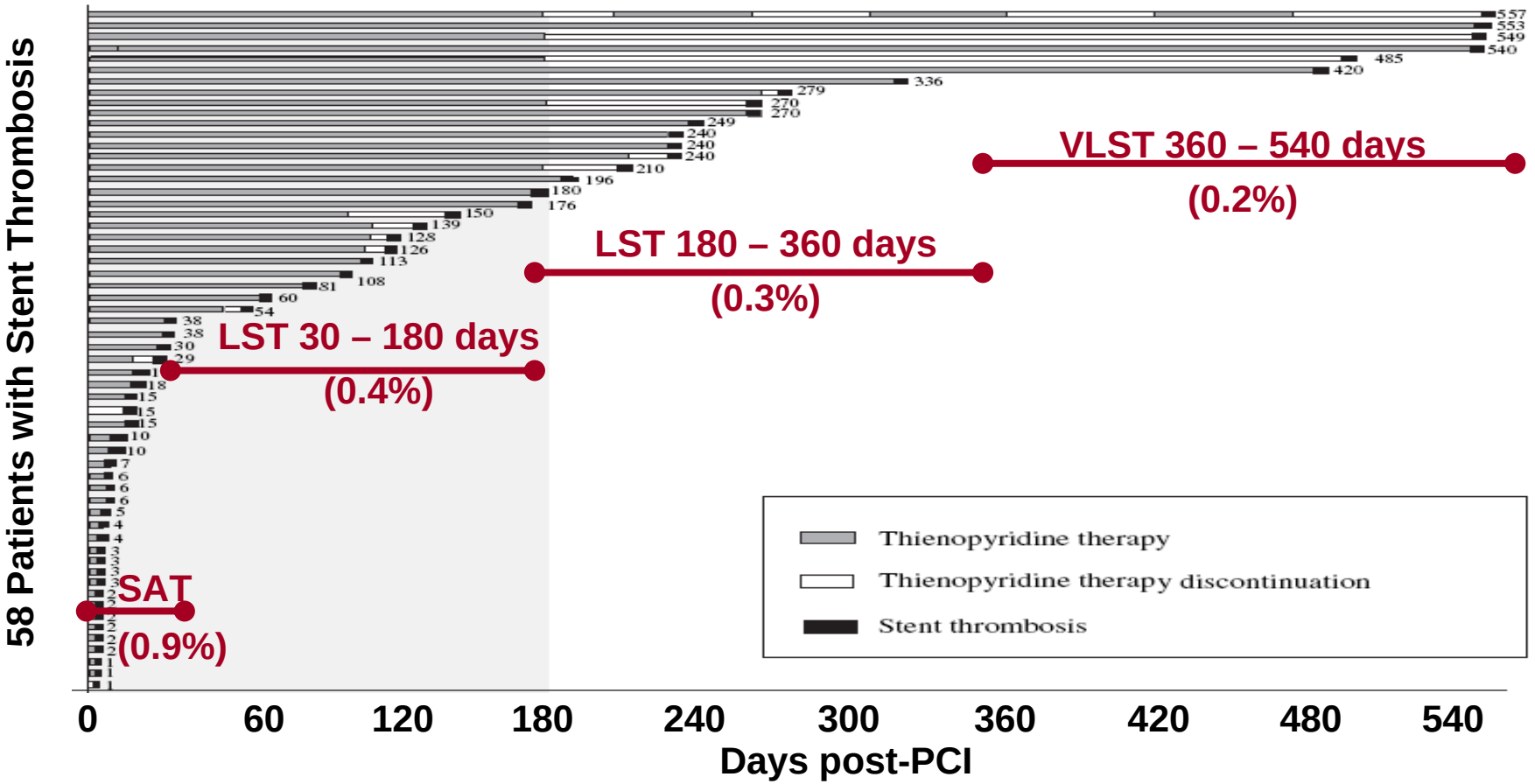


No. of Patients									
Discontinued Thienopyridine	258	422	560	1,128	1,180	1,680	2,044	2,138	2,251
On Thienopyridine	2,750	2,576	2,411	1,829	1,771	1,245	865	756	634

* Aalen-Nelson estimate of cumulative hazard function

Airoldi F, Colombo A, et al., *Circulation* 2007;116:745-54

Relationship Between Thienopyridine Discontinuation and ST

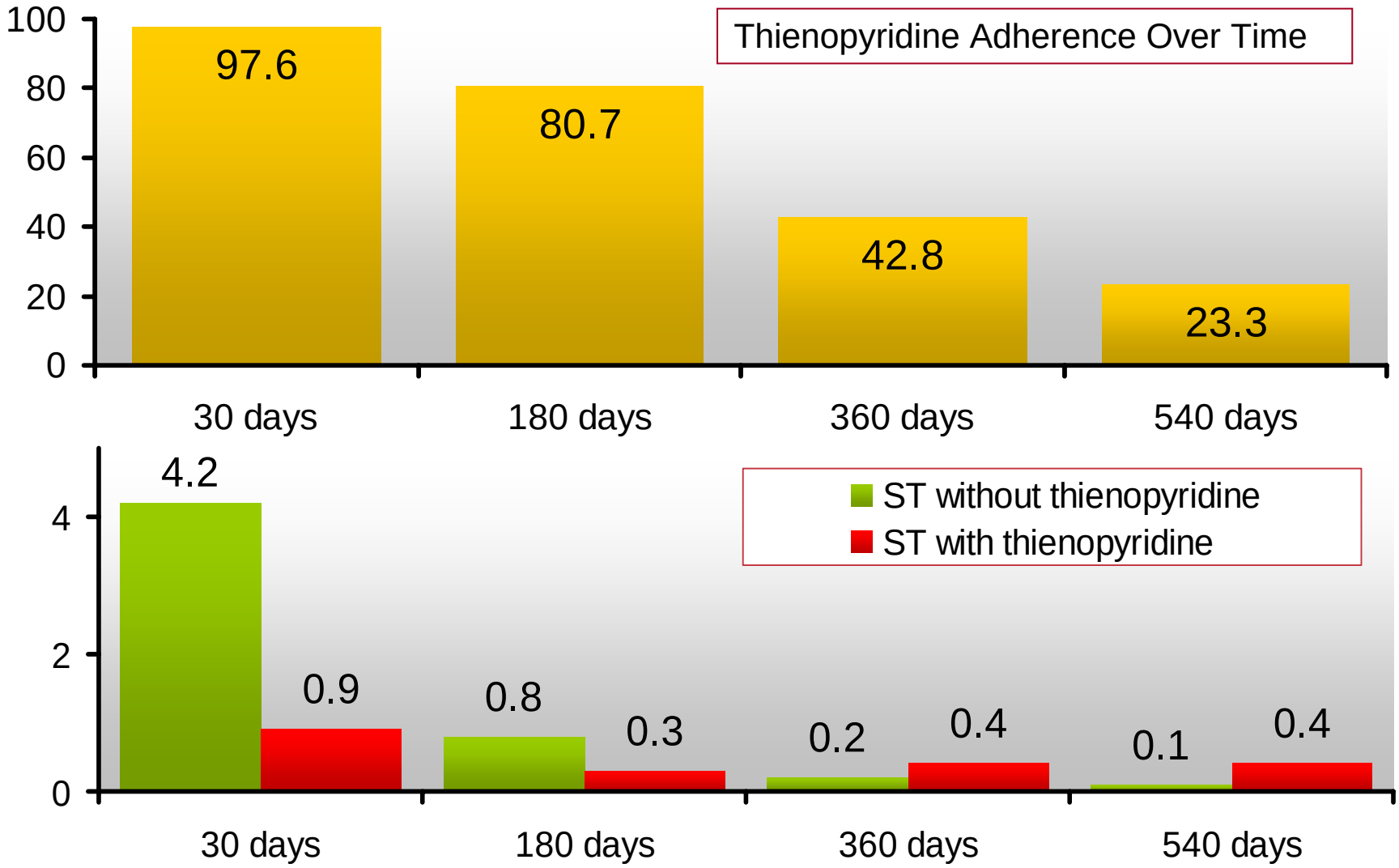


Median time from clopidogrel discontinuation and ST:
- ST within first 6 months: 13.5 days (IQR range, 5.2 to 25.7)
- ST after the first 6 months: 90 days (IQR, 30 to 365 days)

Airoldi F, Colombo A, et al., *Circulation* 2007;116:745-54

Temporal Trends in DAPT Compliance and Incidence of ST while On or Off Thienopyridine Therapy

Is Thienopyridine Discontinuation a Cause or Epiphenomenon?



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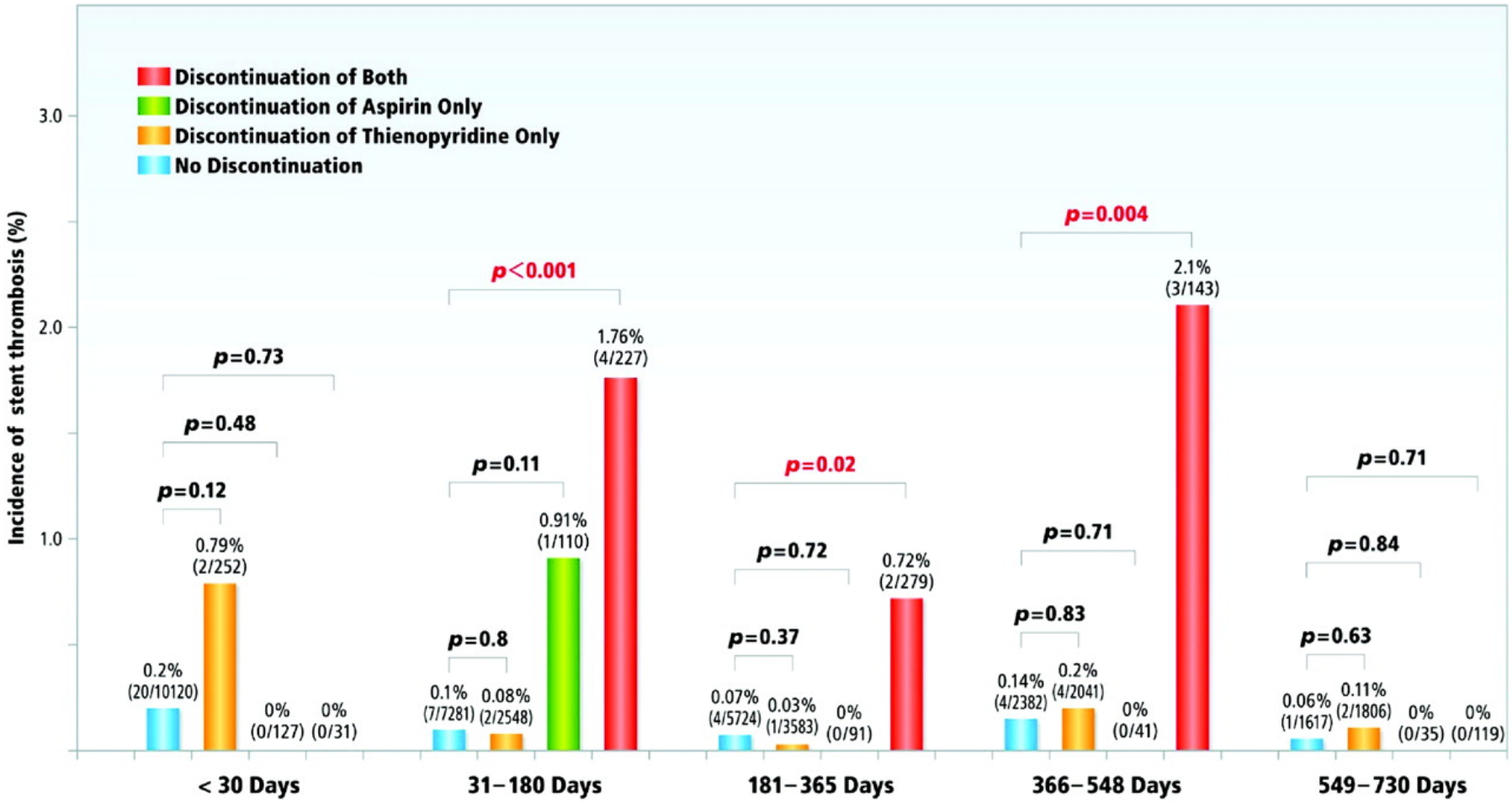
Japan Cypher
2-Year Relationship Between ST Events and APT, N=10,778



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

Japan Cypher

6-Month Landmark Analysis Based on Thienopyridine Use

N=9,875

	ON Thienopyridine N=7,427	OFF Thienopyridine, N=2,628	*P* value
Death	3.4	3.4	0.90
Myocardial Infarction	0.6	0.8	0.42
Death/ Myocardial Infarction	4.1	4.1	0.99
Death, MI or Stroke	4.0	4.1	0.79

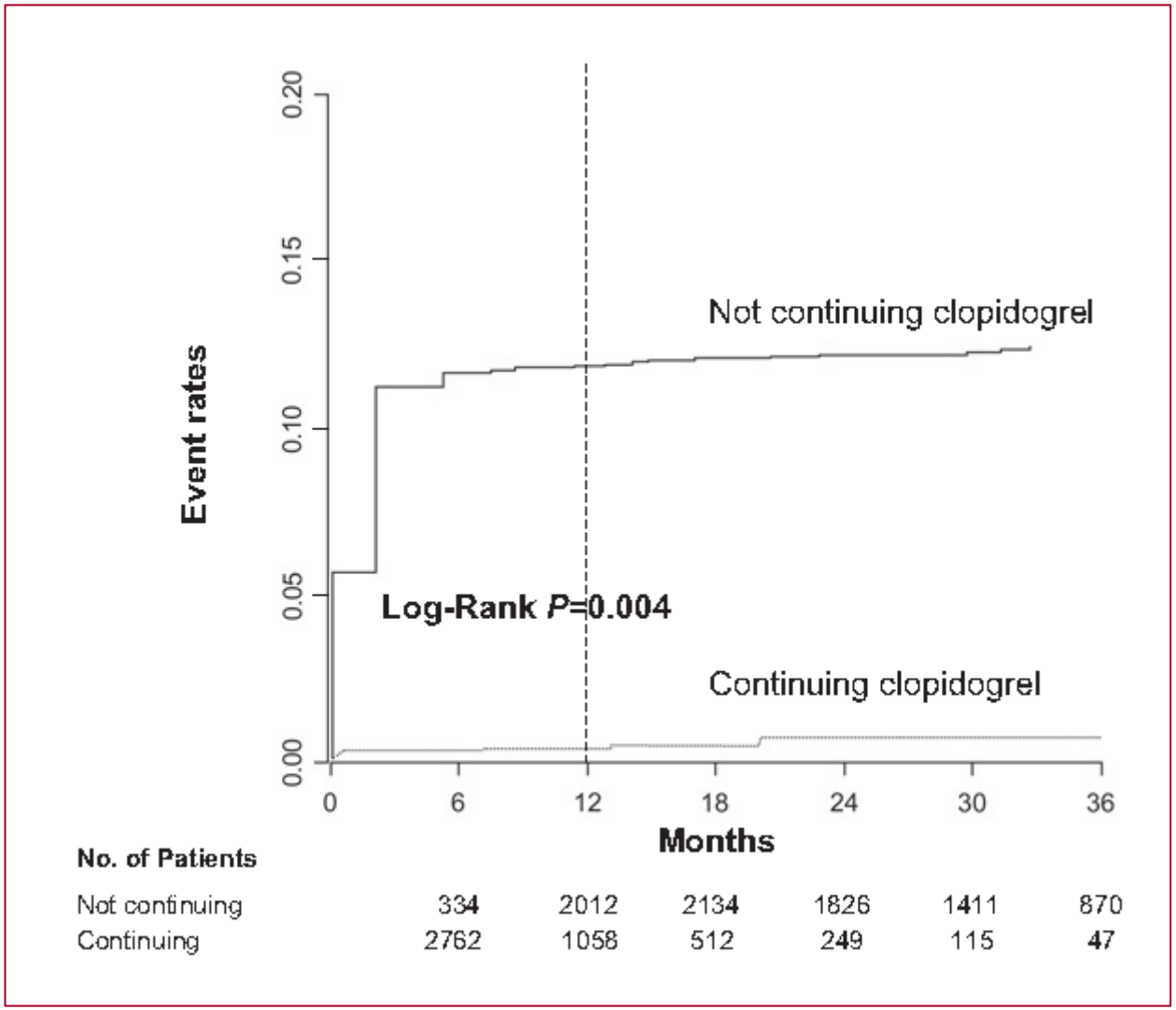
Kimura, T. et al. Circulation 2009;119:987-995

Korean Stent Thrombosis Registry
Multicenter Observational Cohort Study

- 7,221 PCI patients (48.3% DES)
- DES associated with significantly higher risk of ST beyond 1 year
- Adjusted risks of D, D/MI and TLR significantly lower with DES
- Despite increased risk of VLST with DES, thienopyridine continuation beyond 1 year *not* associated with reduced risk of D, D/MI or ST

Park DW, et al. J Am Coll Cardiol Interv 2008

Korean Stent Thrombosis Registry
Multicenter Observational Cohort Study

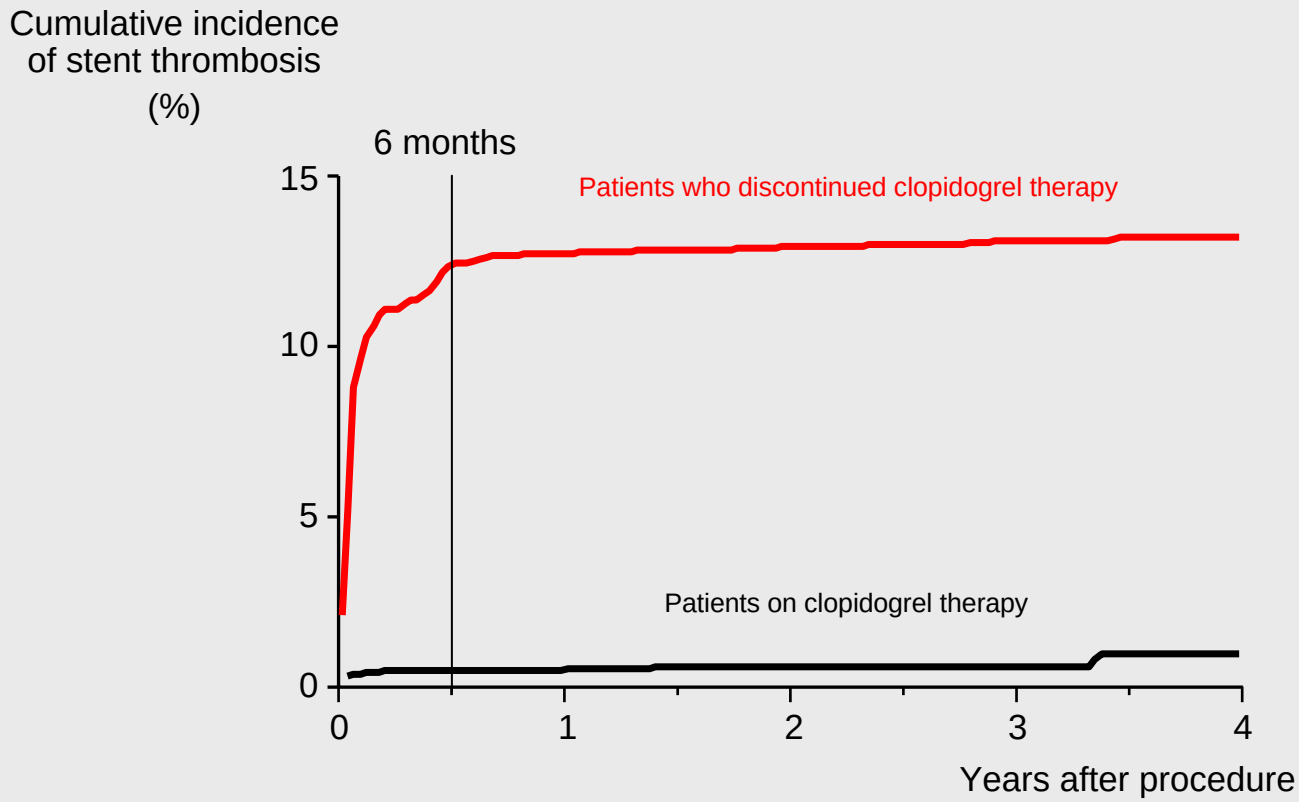


Aalen-Nelson Estimate Curves of Cumulative Hazard Function for Definite ST

Park DW, et al. J Am Coll Cardiol Interv 2008

ISAR

Relationship Between DAPT and ST over 4 year Follow-up, N=6,816

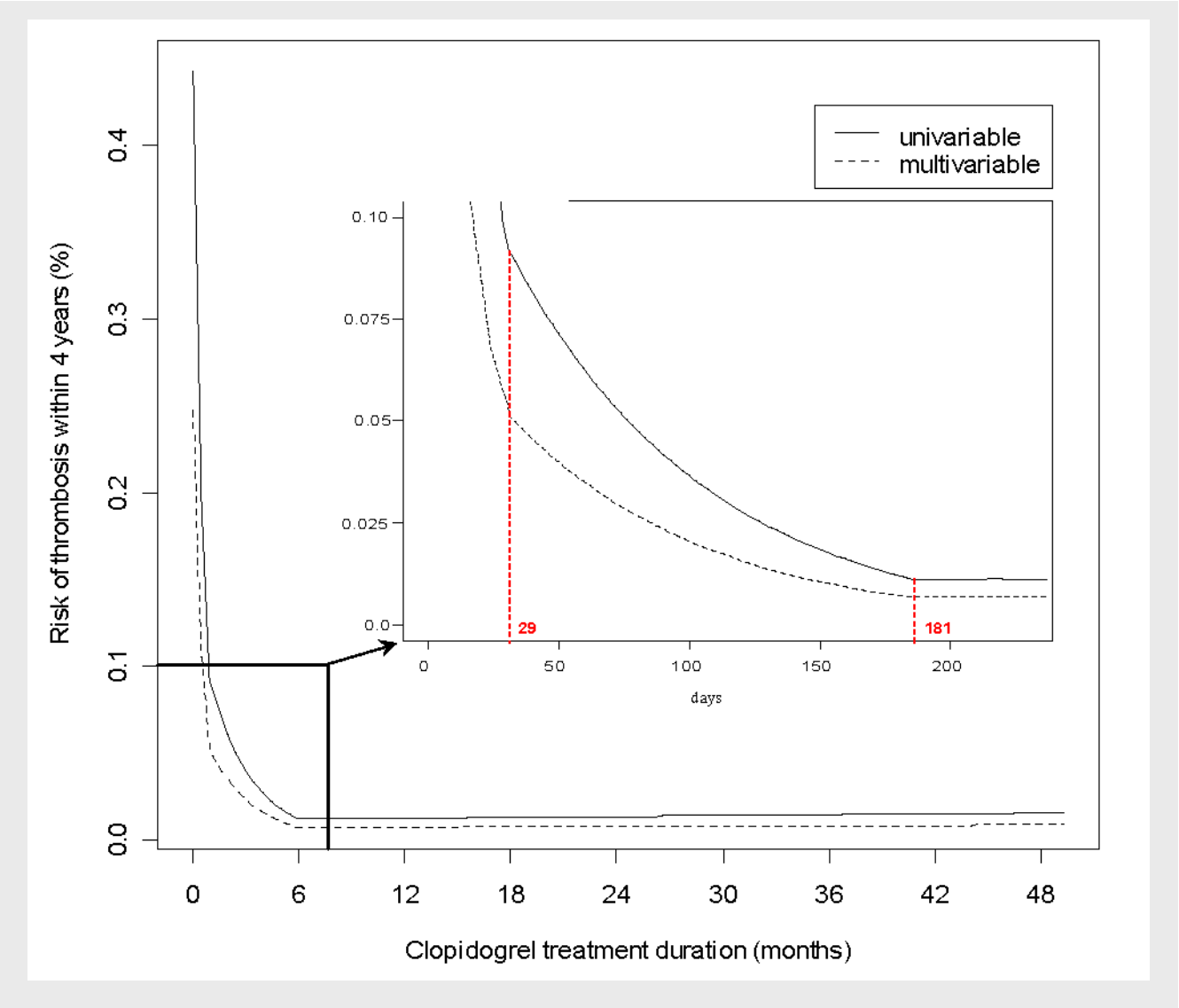


No. of patients					
Discont. clopidogrel	0	1,277	3,934	2,539	1,373
On clopidogrel	6,816	5,181	1,074	398	116

Schulz S, Kastrati A, et al. AHA 2008

ISAR

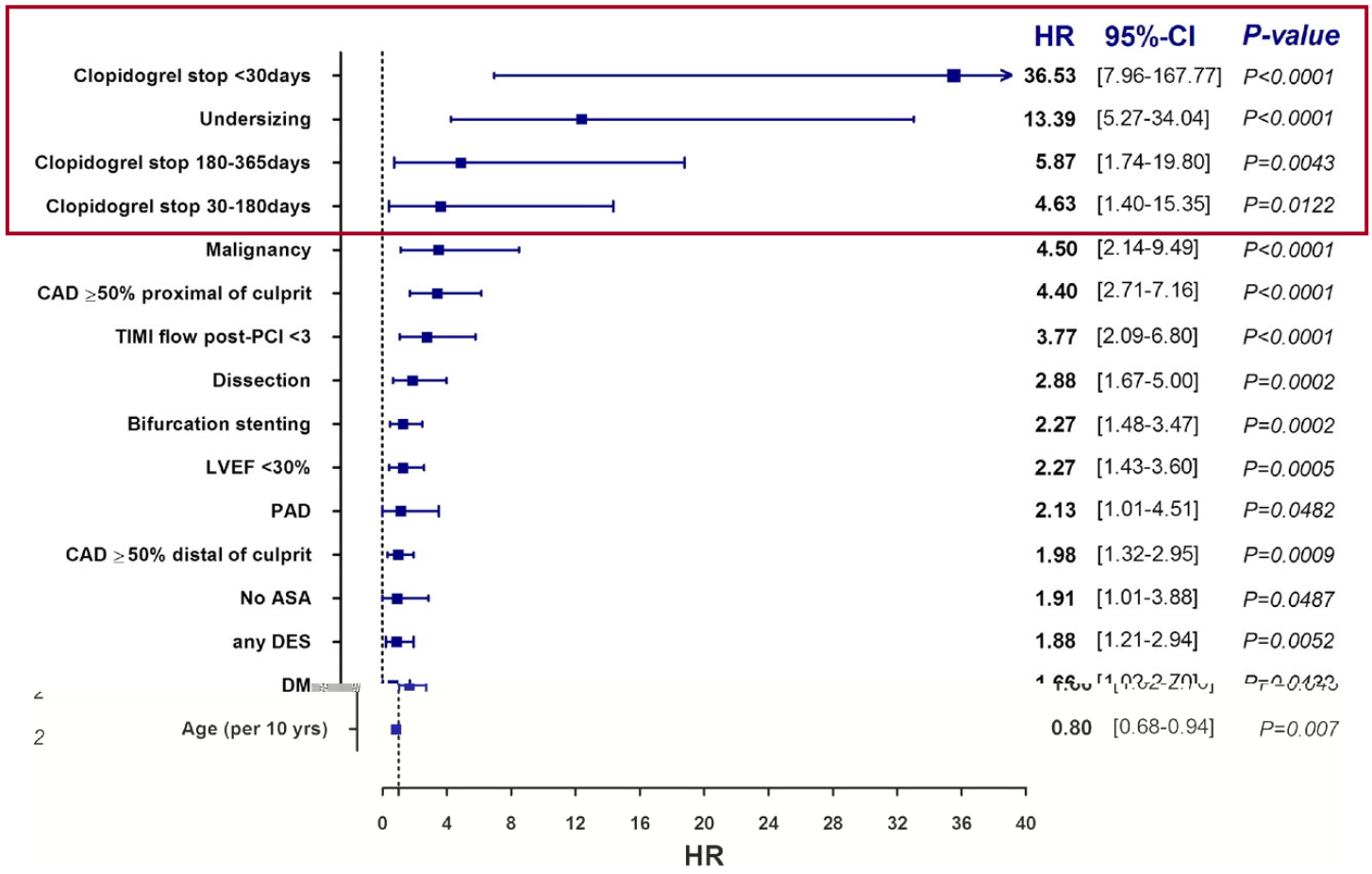
Relationship Between DAPT and ST over 4 year Follow-up, N=6,816



Schulz S, Kastrati A, et al. AHA 2008

Dutch Stent Thrombosis Registry

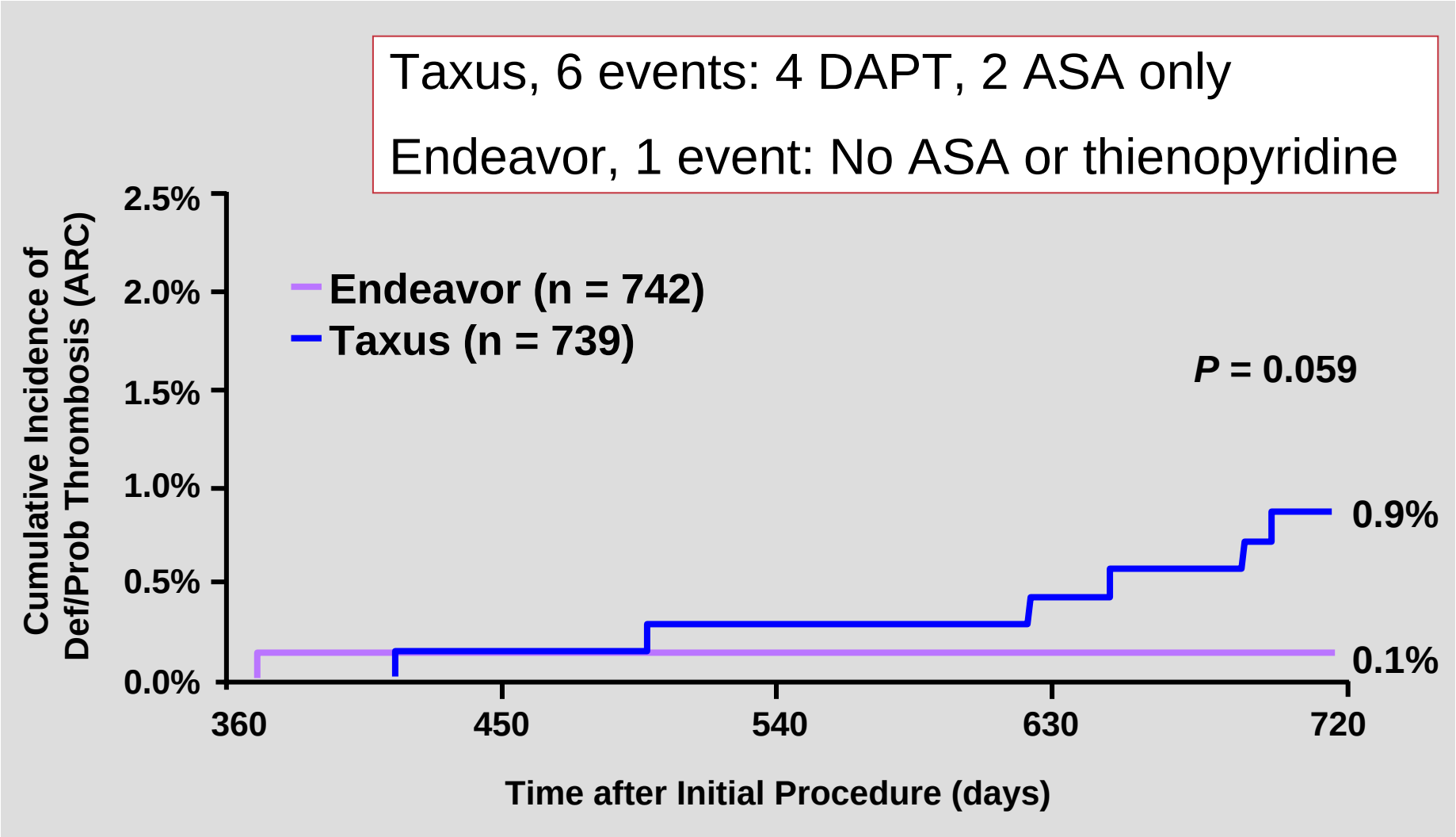
Independent Risk Factors for ST, N=21,009



van Werkum, J. W. et al. J Am Coll Cardiol 2009;53:1399-1409

ENDEAVOR IV

ARC Definite/Probable VLST Δ1-2 years



Leon et al. TCT 2008

Antiplatelet Therapy and DES *2009*

What We Still Don't Know

- What is the 'optimal' duration of DAPT? What is 'premature' discontinuation?
- Is the 'optimal' duration same for all DES?
- What are the consequences of brief DAPT interruption?
- Is there a rebound phenomenon with thienopyridine discontinuation?
- Will there be differences between different APT agents in real world practice?
- Is there a role for platelet and/or genomic testing to individualize therapy?

What is the 'Optimal' Trial for the 'Optimal' DAPT Duration?

DAPT durations, inclusion of BMS, landmarking and 'event-free' patients

	Inclusion Group, N	DAPT Duration	DES Type	1° Endpoint	2° Endpoint(s)
DAPT	20,645 12-month event free	12 vs 30 months	All DES	1. D/MI/Stroke at 33 mos 2. Def/prob ST at 33 mos	GUSTO Bleeding
ISAR-SAFE	6,000 6-month event free	6 vs 12 months	All DES	D/MI/Stroke/TIMI major bleed at 15 mos	Individual component endpoints
REAL-LATE	2,000 12-month event free	12 vs 24 months	All DES	2-yr Cardiac D/MI	ARC ST, Bleeding
ZEST-LATE	2,000 12-month event free	12 vs 24 months	SES, PES, ZES	2-yr D/MI	ARC ST, Bleeding
OPTIMIZE	3,120 non-STEMI	3 vs. 12 months	Endeavor ZES	1-yr D/MI/Stroke/TIMI major bleed	ARC ST
SEASIDE	900 non-ACS	6 months	Endeavor ZES	1-yr D/MI/Stroke	GUSTO Bleeding CYP2C19

Finding the ‘Optimal’ DAPT Duration
Summary

- Given that ST is uniformly associated with MI and ~30% mortality, any measure that may reduce events is clinically meaningful but must be proven and without excessive risk!
  - Role of DAPT in reducing early ST is firmly established
  - Issue is not that thienopyridine should be discontinued for all pts at a predetermined timepoint but whether it is safe to discontinue (ST risk) and if there is acceptable benefit to maintain (D, MI, stroke)
  - While extended DAPT *may* decrease late death or MI proportionate to risk, the benefit is most likely associated with reduction of events independent of stent territory
- Available evidence consistently demonstrates that in all-comer, broad PCI populations, extended DAPT (eg, >6-12 months) does not reduce ST risk

Finding the ‘Optimal’ DAPT Duration
Summary

- Studies are underway to identify the ‘optimal’ DAPT duration, but must consider:
  - Variability in DAPT durations studied
  - Potential differences in DES, thienopyridine therapy, individual patients
  - Bleeding risk
  - Intention to treat vs as treated, “clear” patients vs. those with events