

# Identifying the 'Optimal' Duration of DAPT

## Less is More, More or Less...

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# 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

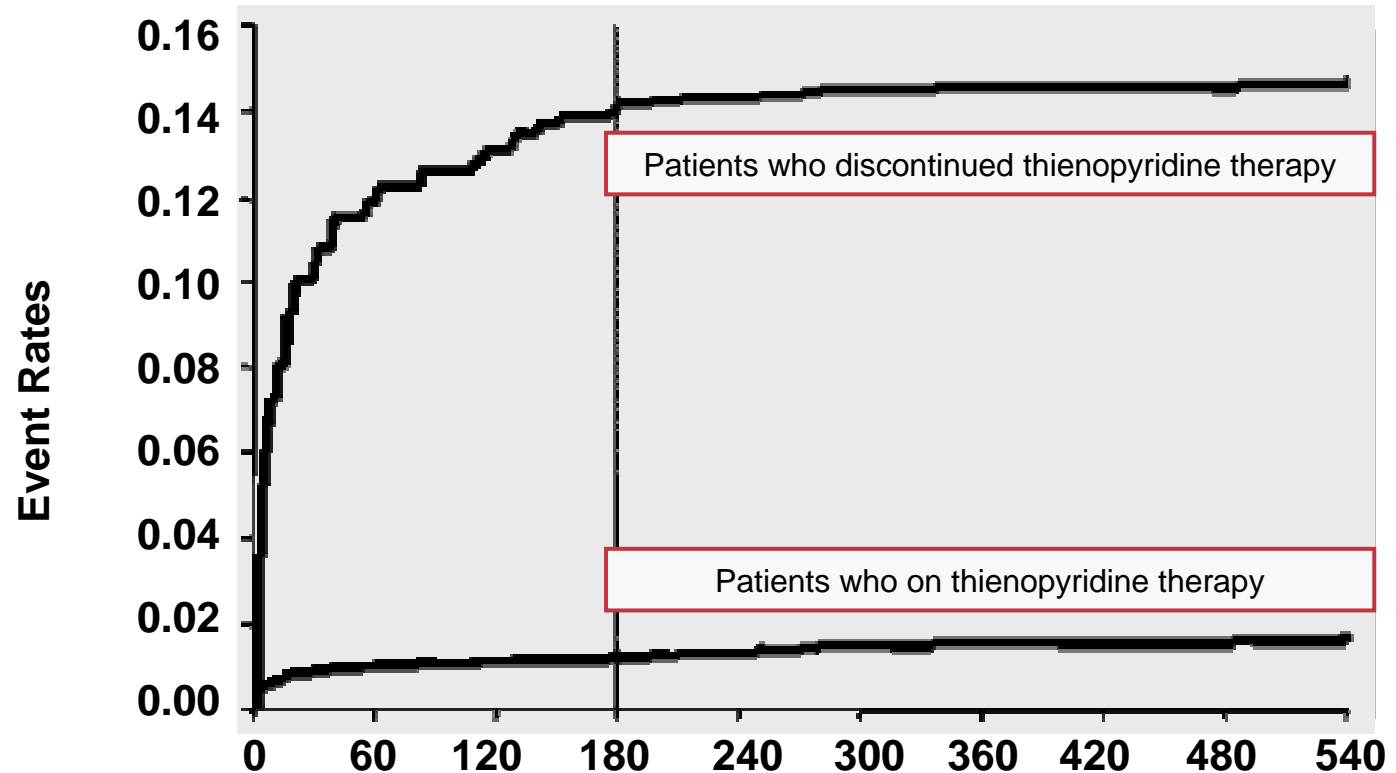
## *A Less than 'Optimal' Evidence Basis*

- › RCT and RCT substudies (CREDO, PCI-CURE)
  - Pharma trials evaluating pretreatment and dosing strategies
  - Follow-up limited to  $\leq 12$  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

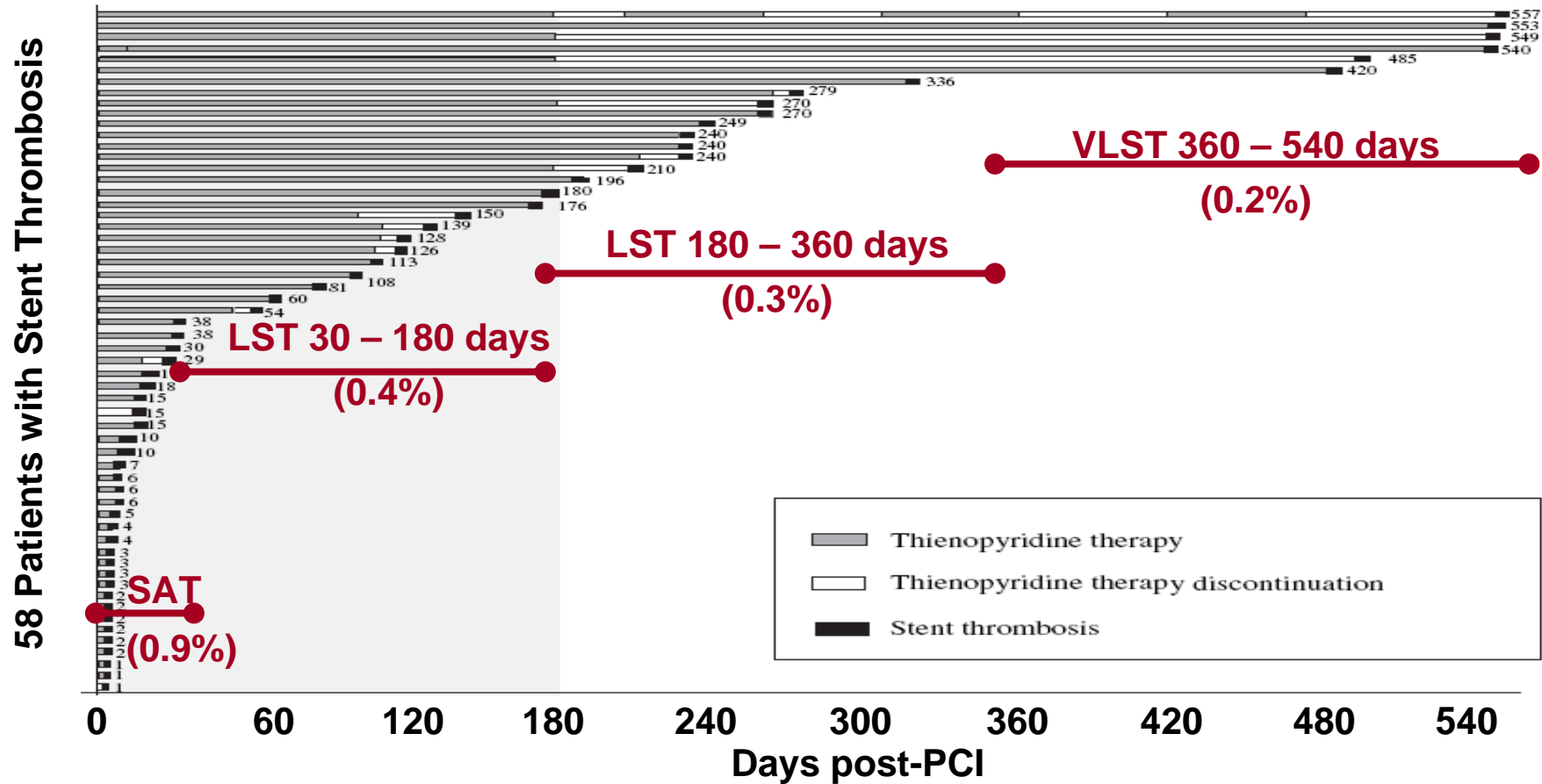


**No. of Patients**

<b>Discontinued Thienopyridine</b>	258	422	560	1,128	1,180	1,680	2,044	2,138	2,251
<b>On Thienopyridine</b>	2,750	2,576	2,411	1,829	1,771	1,245	865	756	634

\* Aalen-Nelson estimate of cumulative hazard function

# Relationship Between Thienopyridine Discontinuation and ST

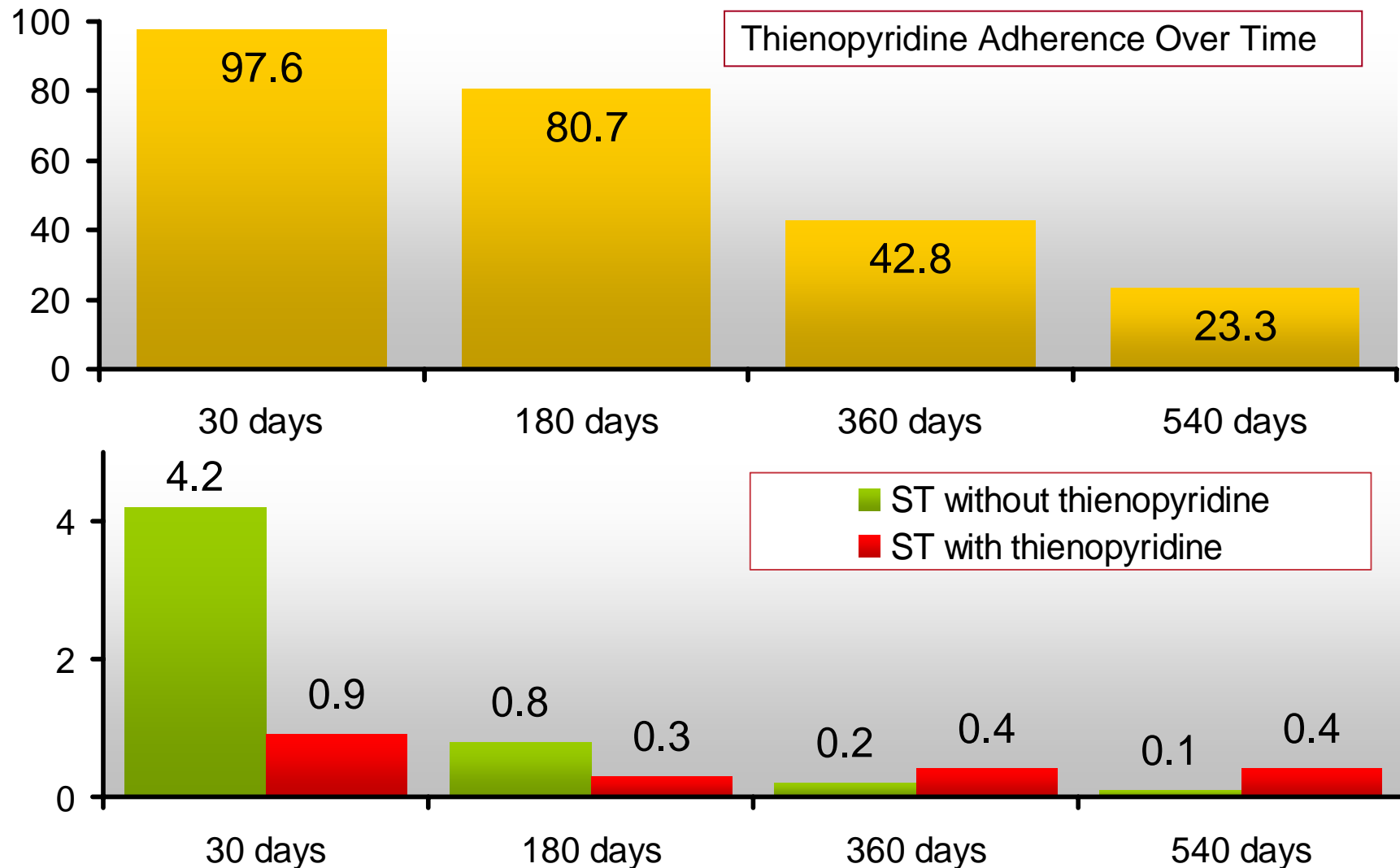


Median time from clopidogrel discontinuation and ST:

- 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)

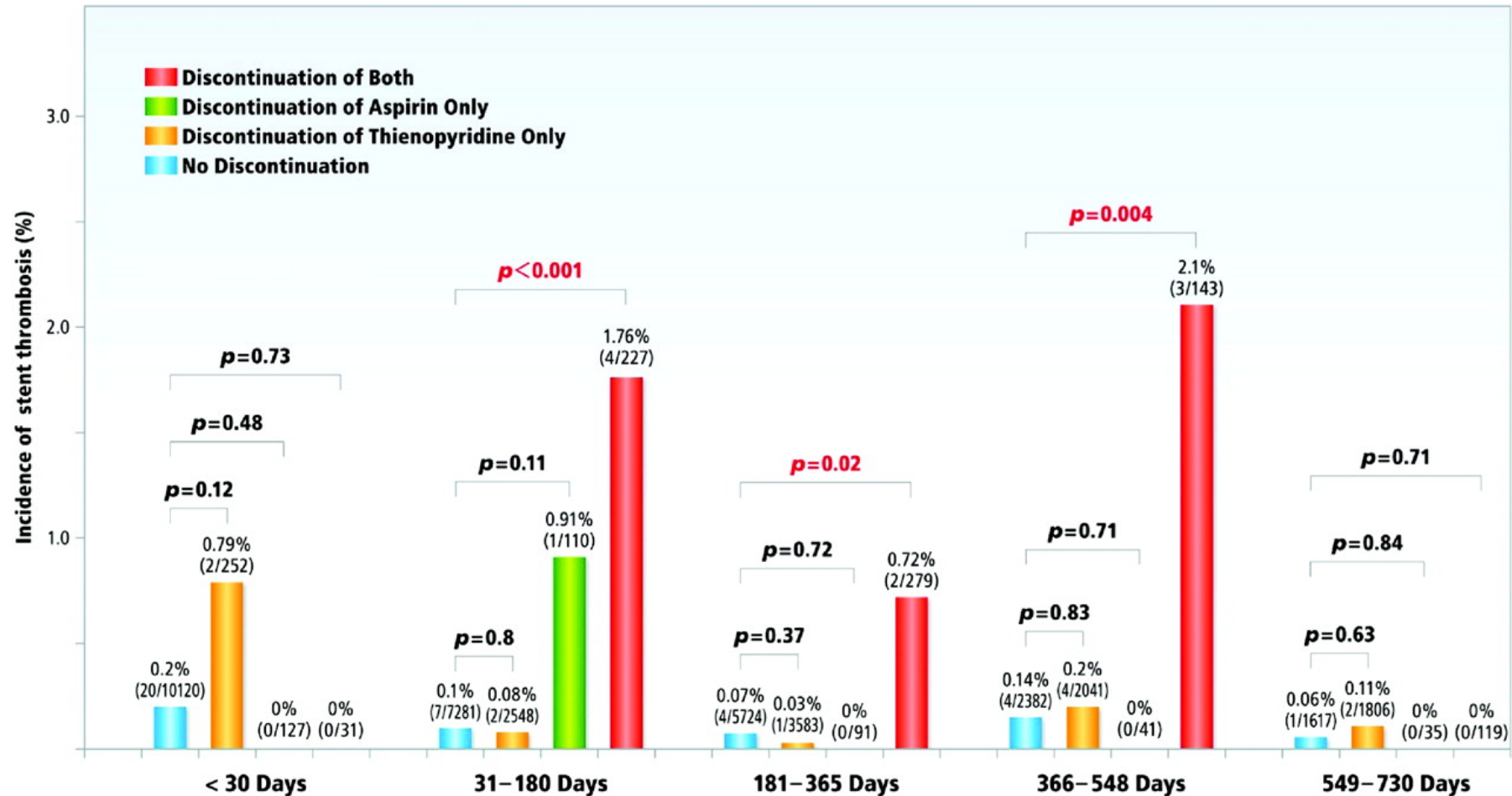
# Temporal Trends in DAPT Compliance and Incidence of ST while On or Off Thienopyridine Therapy

*Is Thienopyridine Discontinuation a Cause or Epiphenomenon?*



# Japan Cypher

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



# Japan Cypher

## 6-Month Landmark Analysis Based on Thienopyridine Use

*N*=9,875

	ON Thienopyridine N=7,427	OFF Thienopyridine, N=2,628	<i>P</i> 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

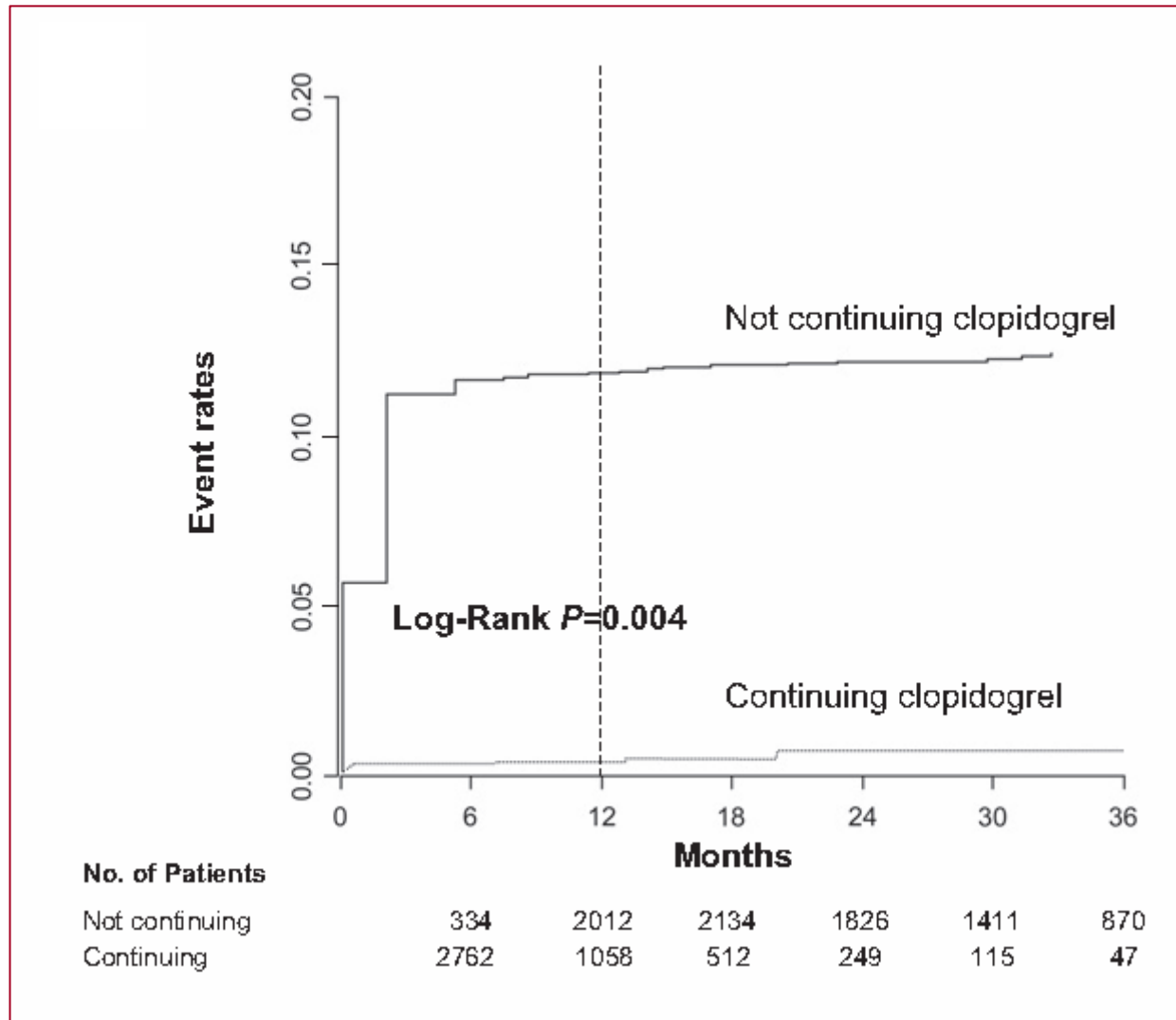


# Korean Stent Thrombosis Registry

## 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

# Korean Stent Thrombosis Registry Multicenter Observational Cohort Study

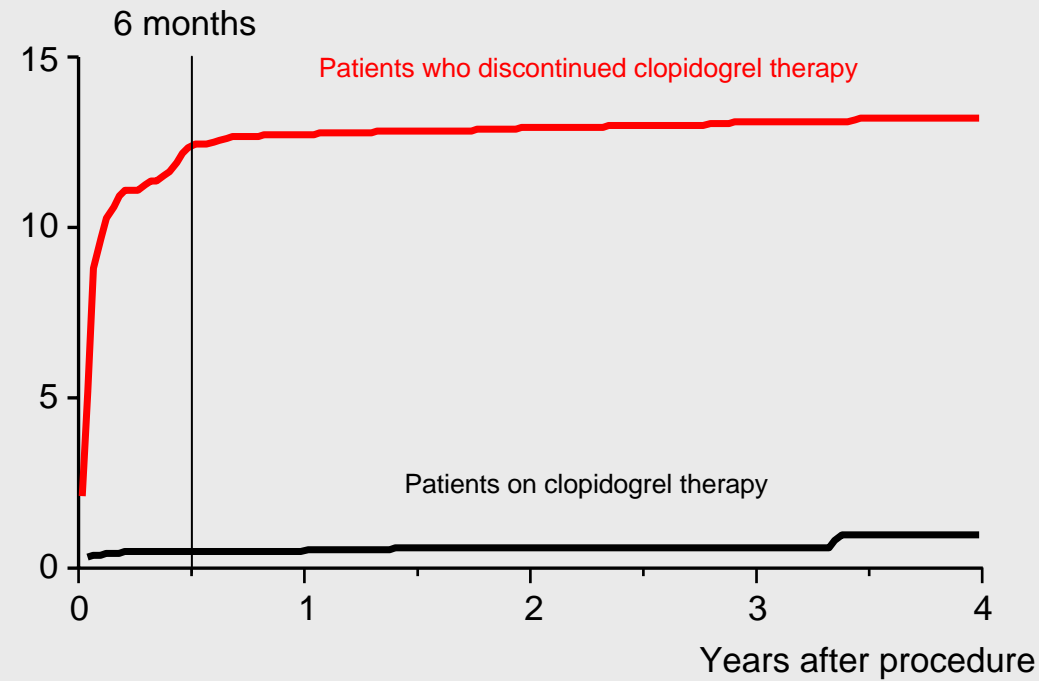


Aalen-Nelson Estimate Curves of Cumulative Hazard Function for Definite ST  
Park DW, et al. J Am Coll Cardiol Interv 2008

# ISAR

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

Cumulative incidence  
of stent thrombosis  
(%)

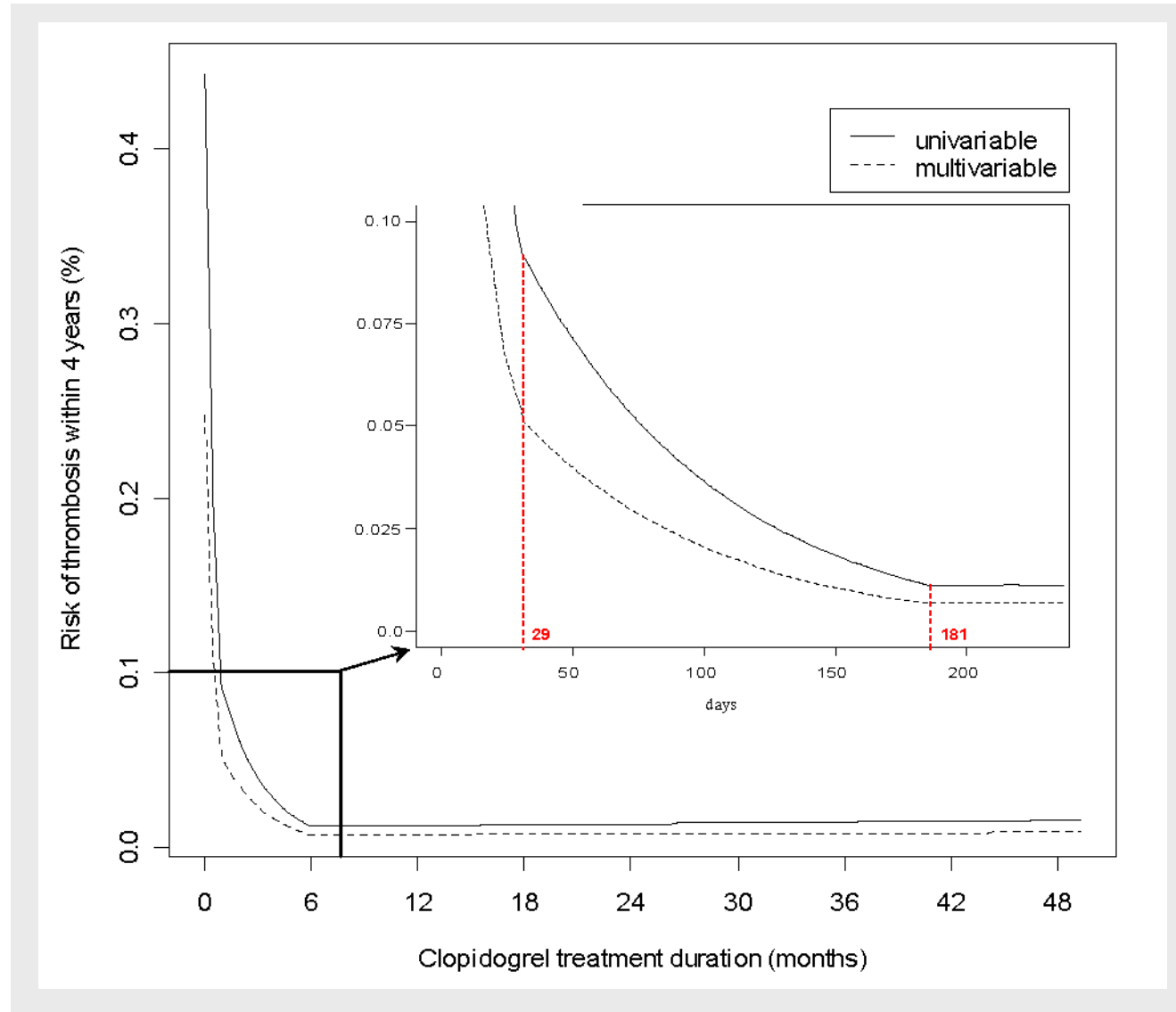


No. of patients

Discont. clopidogrel	0	1,277	3,934	2,539	1,373
On clopidogrel	6,816	5,181	1,074	398	116

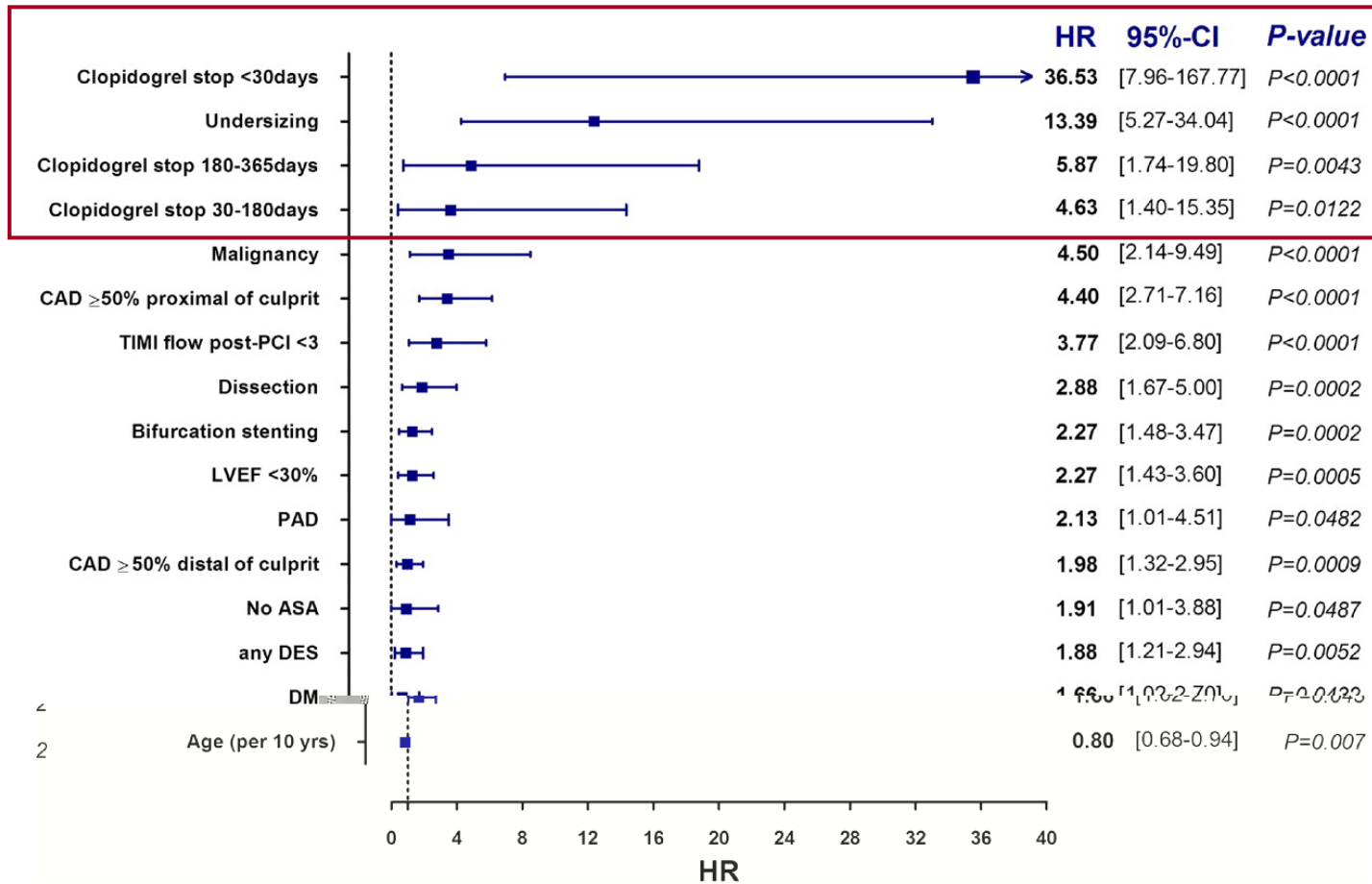
# ISAR

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



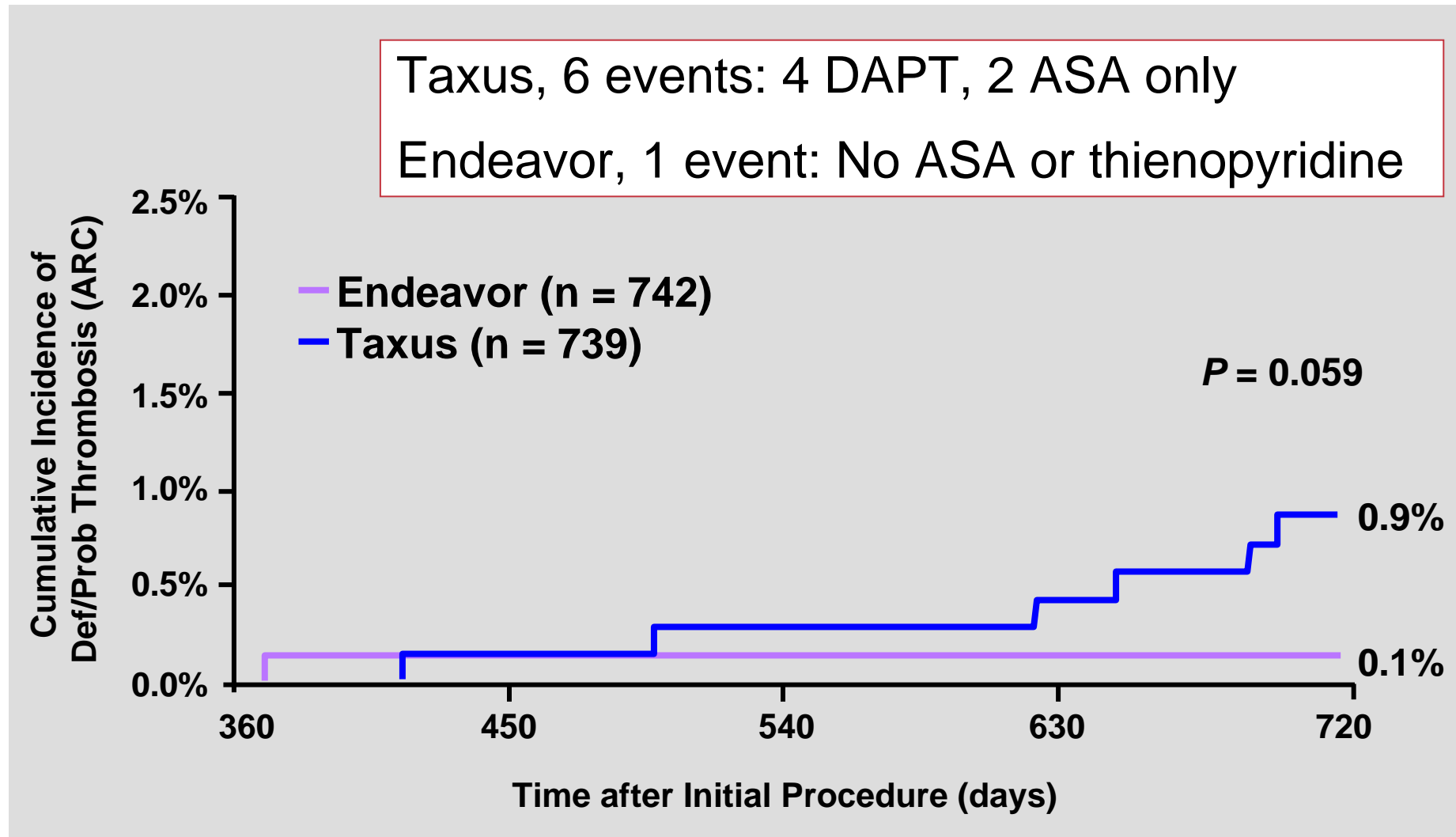
# Dutch Stent Thrombosis Registry

## Independent Risk Factors for ST, N=21,009



# ENDEAVOR IV

ARC Definite/Probable VLST  $\Delta$  1-2 years



# 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)
<b>DAPT</b>	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
<b>ISAR-SAFE</b>	6,000 6-month event free	6 vs 12 months	All DES	D/MI/Stroke/TIMI major bleed at 15 mos	Individual component endpoints
<b>REAL-LATE</b>	2,000 12-month event free	12 vs 24 months	All DES	2-yr Cardiac D/MI	ARC ST, Bleeding
<b>ZEST-LATE</b>	2,000 12-month event free	12 vs 24 months	SES, PES, ZES	2-yr D/MI	ARC ST, Bleeding
<b>OPTIMIZE</b>	3,120 non-STEMI	3 vs. 12 months	Endeavor ZES	1-yr D/MI/Stroke/TIMI major bleed	ARC ST
<b>SEASIDE</b>	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