

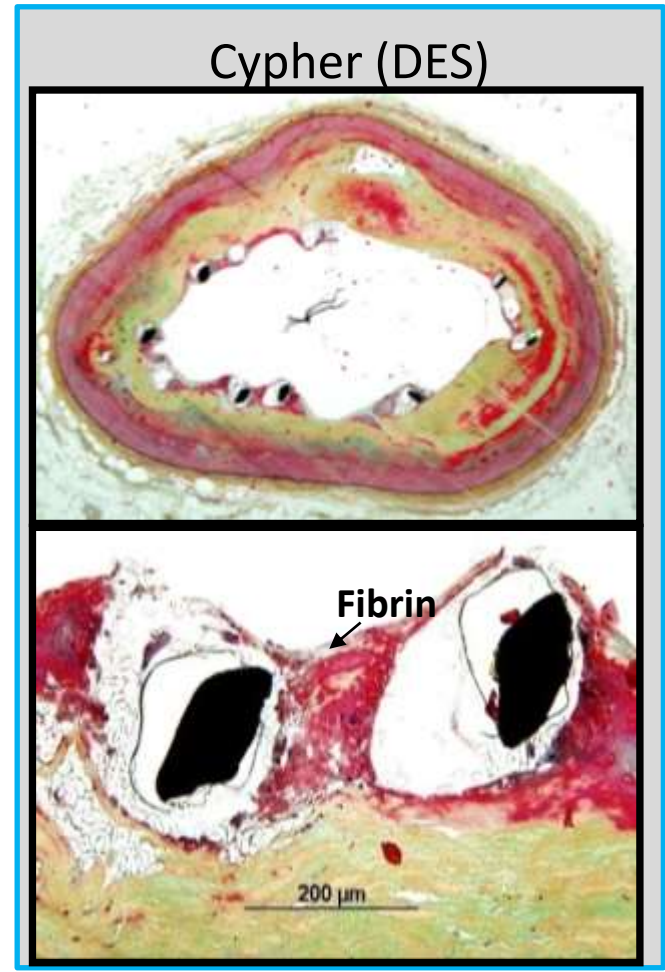
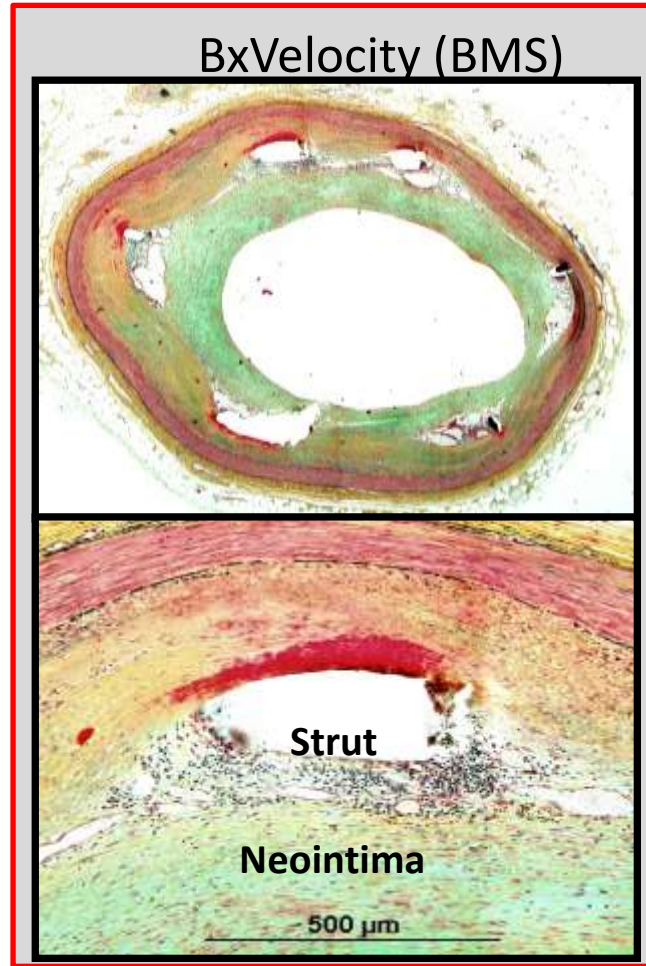
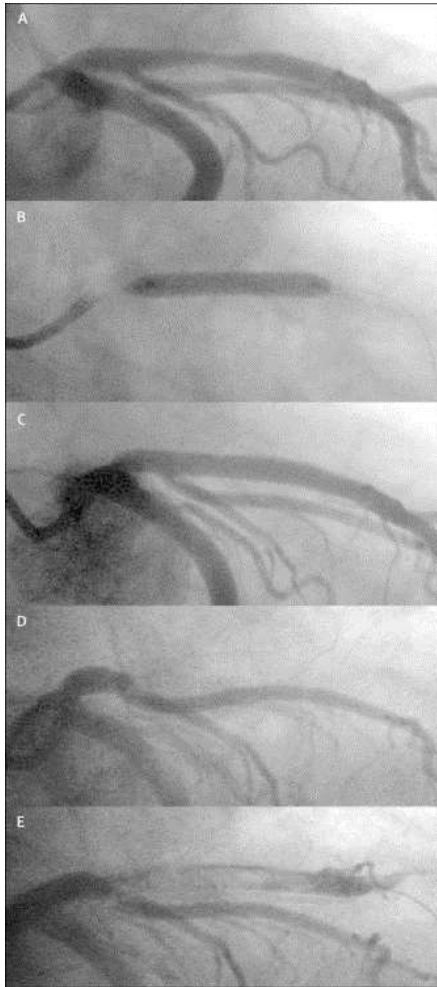
Who is going to bleed ?

NAKAZAWA, G
TOKAI Univ.



Delayed Arterial Healing as a cause of LST

McFadden E et al. Lancet 2004



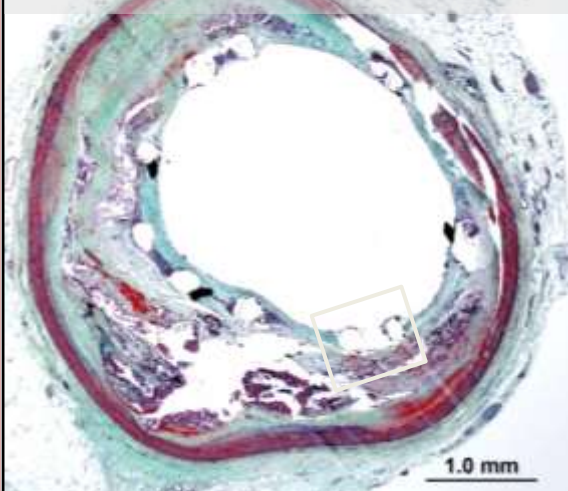
Joner M & Finn AV. J Am Coll Cardiol. 2006;48(1):193-202.



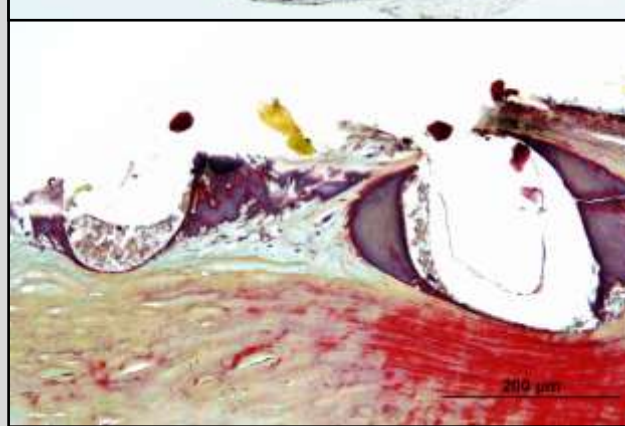
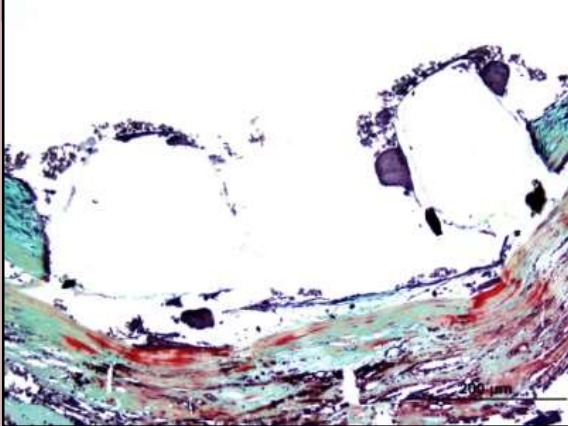
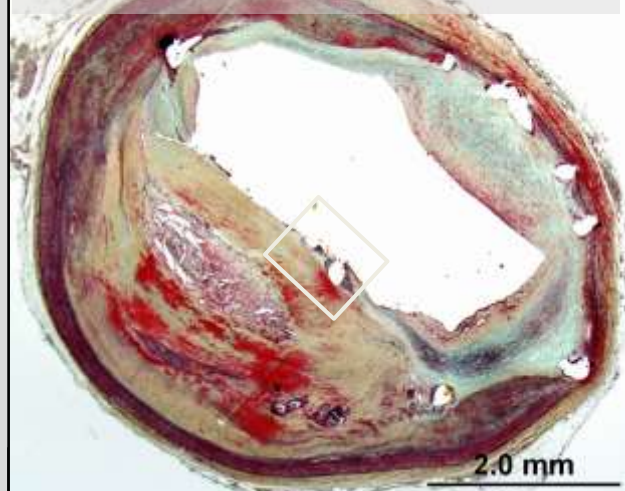
Histologic findings in 2nd Gen DES at autopsy

1st-generation DES

SES 13 months

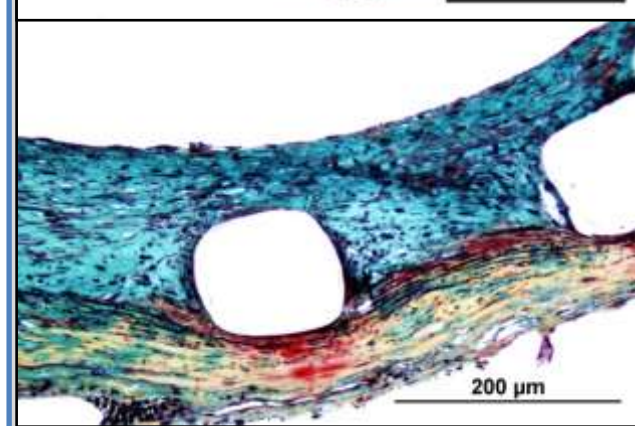
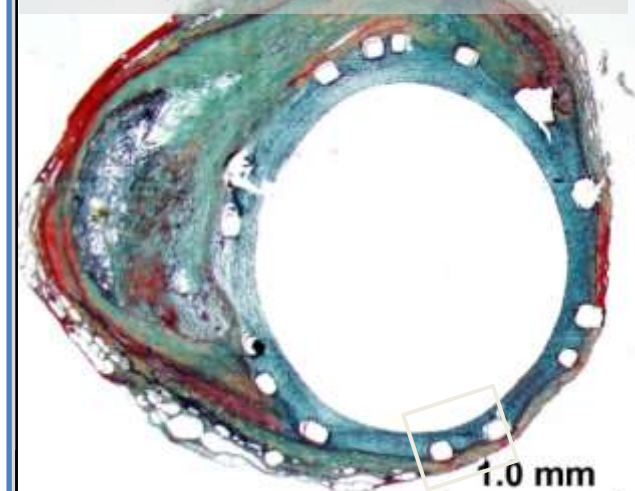


PES 11 months



2nd-generation DES (EES)

EES 6 months



Otsuka F et al. Circulation. 2014;129:211-223



One-Year Outcome of a Prospective Trial Stopping Dual Antiplatelet Therapy at 3-Month after Everolimus-eluting Cobalt-chromium Stent Implantation

**ShorT and OPTimal duration of Dual AntiPlatelet Therapy after
everolimus-eluting cobalt-chromium stent (STOPDAPT) trial**

Masahiro Natsuaki, MD

Kyoto University Graduate School of Medicine, Saiseikai Fukuoka General Hospital

Takeshi Morimoto, MD, MPH; Erika Yamamoto, MD; Hiroki Shiomi, MD

Yutaka Furukawa, MD, Mitsuru Abe, MD, Koichi Nakao, MD; Tetsuya Ishikawa, MD

Kazuya Kawai, MD; Kei Yunoki, MD; Shogo Shimizu, MD; Masaharu Akao, MD; Shinji Miki, MD

Masashi Yamamoto, MD; Hisayuki Okada, MD; Kozo Hoshino, MD; Kazushige Kadota, MD

Yoshihiro Morino, MD; Keichi Igarashi, MD; Kengo Tanabe, MD

Ken Kozuma, MD and Takeshi Kimura, MD

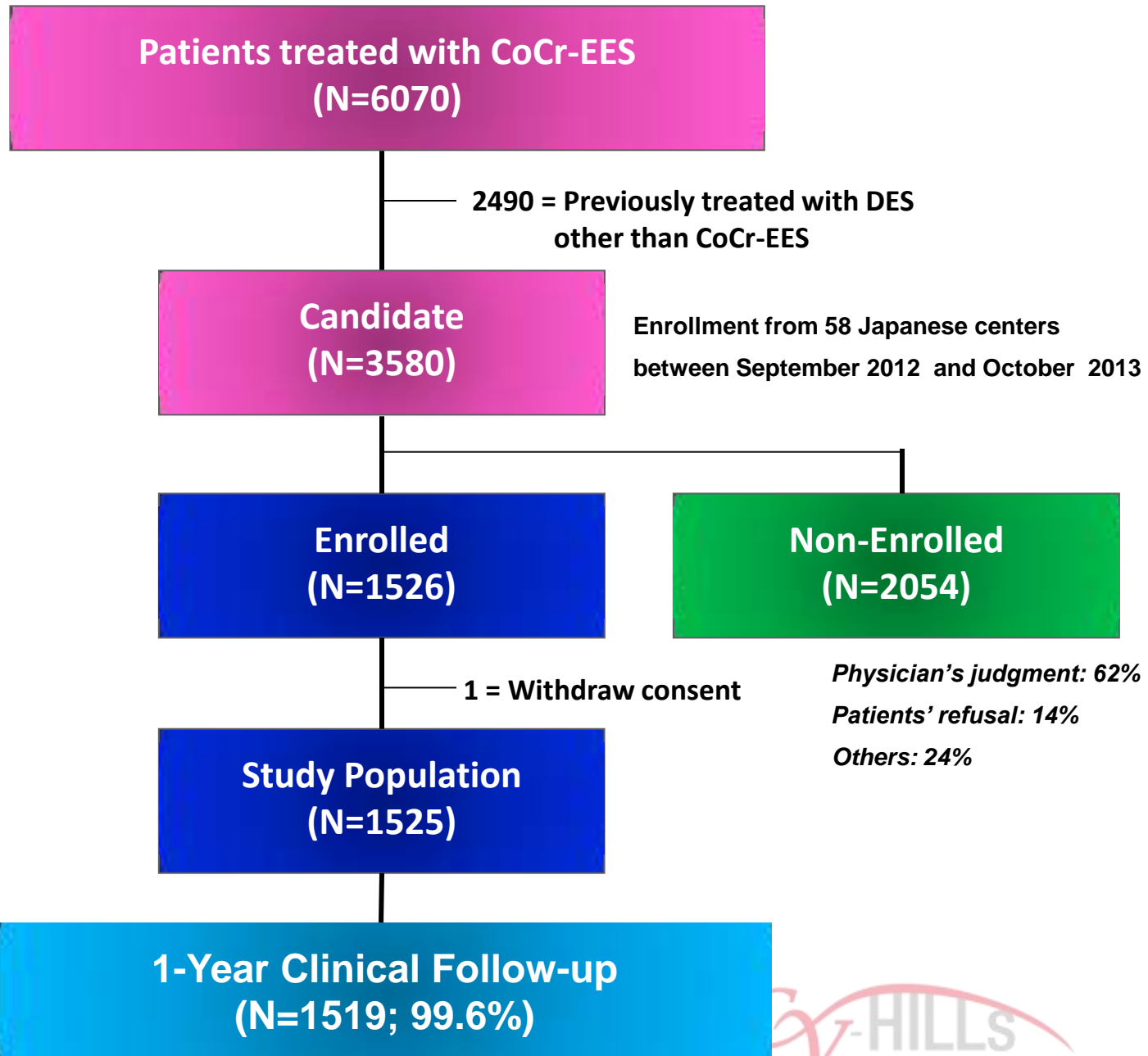
On behalf of the STOPDAPT Investigators



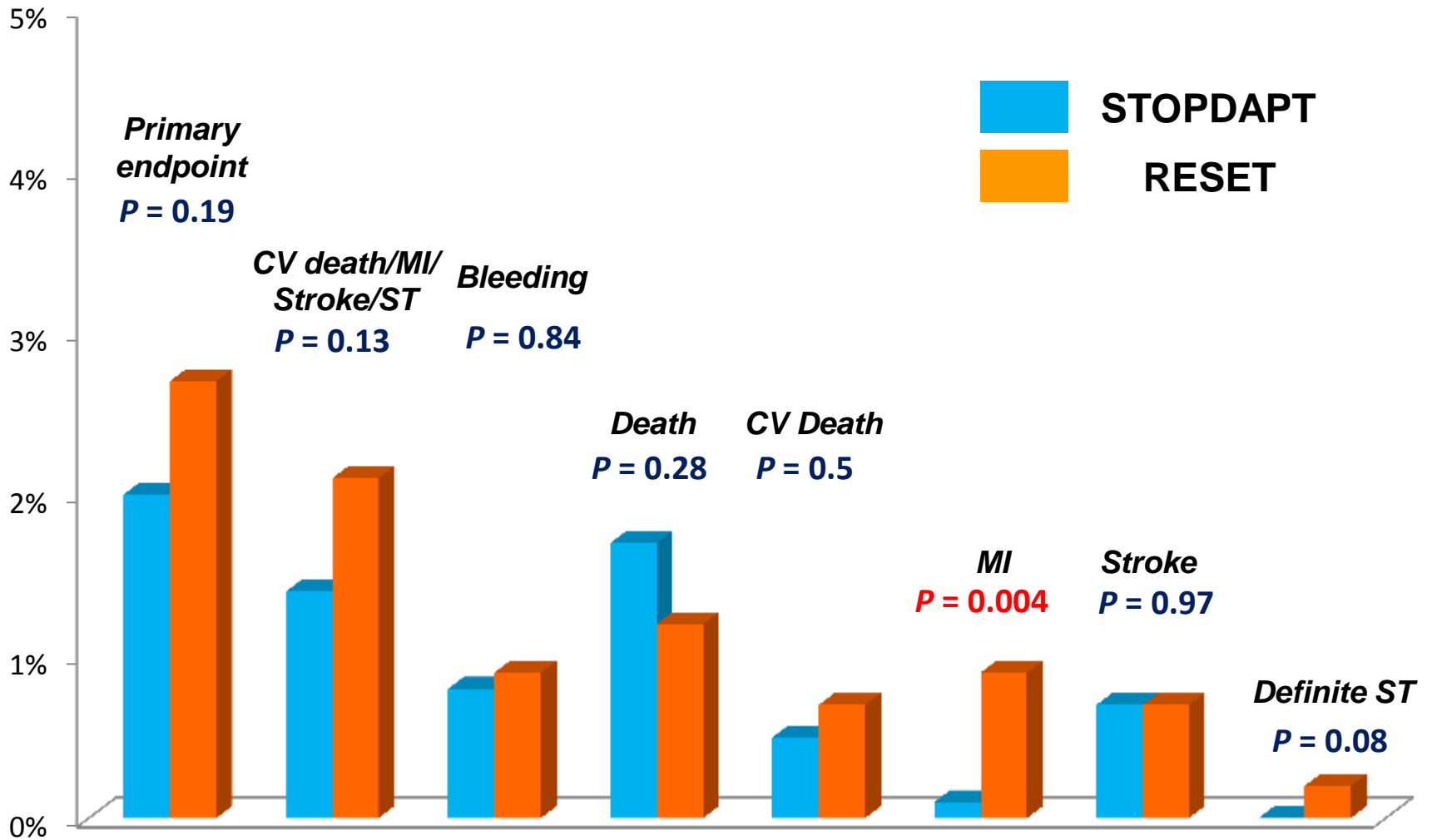
Interventional Cardiology
Int...



STOPDAPT Patient Flow



Landmark Analysis at 3-month



Natsuaki M et al. Cardiovasc Interv Ther. 2016 Jul;31(3):196-209.



Duration of DAPT

Disease / Conf			DES	Recommendation	LOE	
ACS	ESC	2014	12mo	Class I	A	
Stable AP			6mo			
ACS	ACC/AHA	2016	12mo		Class I	B
Stable AP			6mo			B
Stable AP	JCS	2008	12mo			B
STEMI		2011	12mo			A





Dual Antiplatelet Therapy Beyond One Year After Drug-eluting Coronary Stent Procedures

Laura Mauri, Dean J. Kereiakes, Robert W. Yeh, Priscilla Driscoll-Shempp,
Donald E. Cutlip, P. Gabriel Steg, Sharon-Lise T. Normand, Eugene Braunwald,
Stephen D. Wiviott, David J. Cohen, David R. Holmes, Mitchell W. Krucoff,
James Hermiller, Harold L. Dauerman, Daniel I. Simon, David E. Kandzari,
Kirk N. Garratt, David P. Lee, Thomas K. Pow, Peter Ver Lee,
Michael J. Rinaldi, and Joseph M. Massaro

on behalf of the Dual Antiplatelet Therapy (DAPT) Study Investigators₈

Design

Randomization*

Study Drug
Treatment Ends

12-Month
Observational Period:
Open-Label
Thienopyridine +
Aspirin Required

Thienopyridine + Aspirin

Placebo + Aspirin

3-Month
Observational
Period: Off
Thienopyridine, On
Aspirin

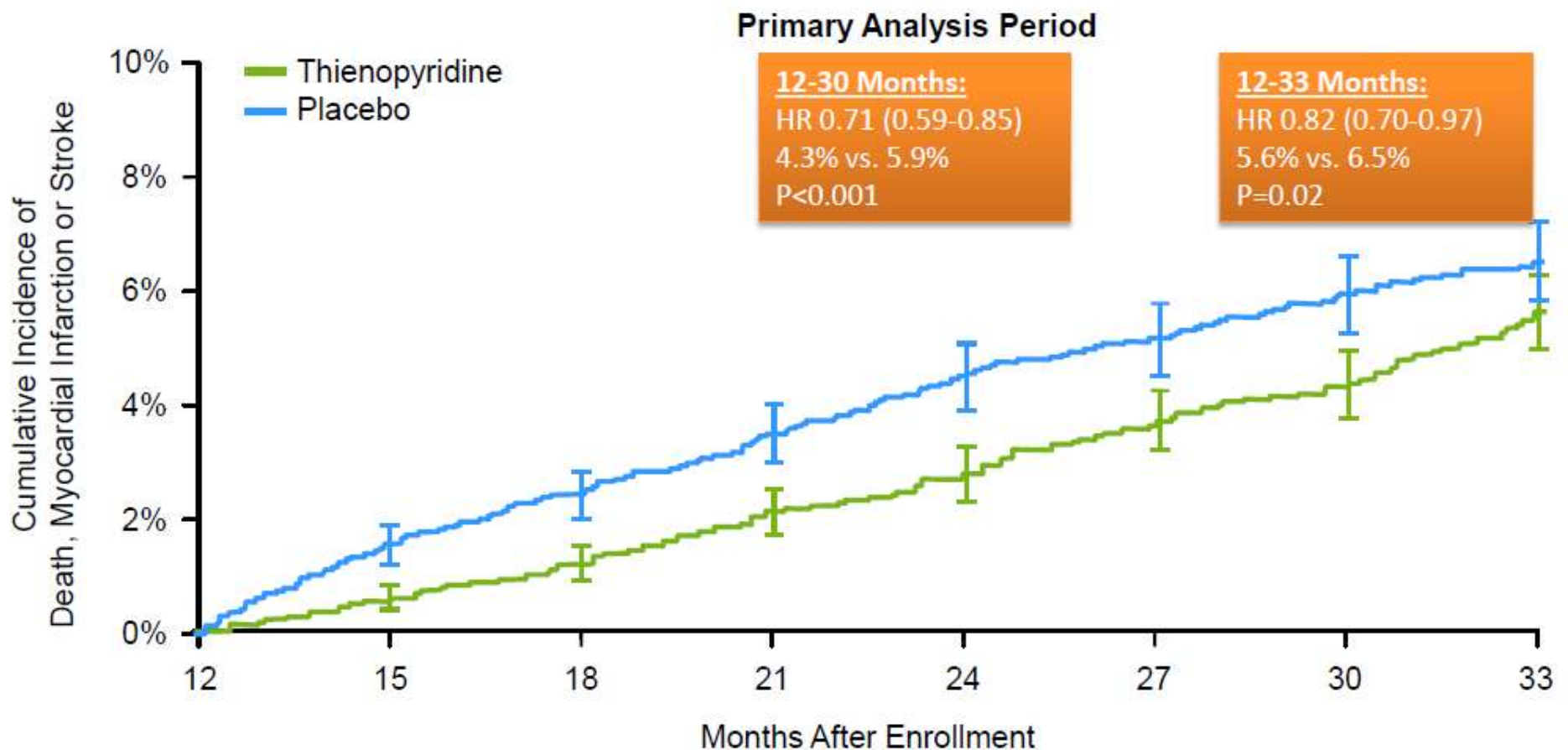


Time in months after index stent procedure (not to scale)

Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

Randomized: Alive and free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).

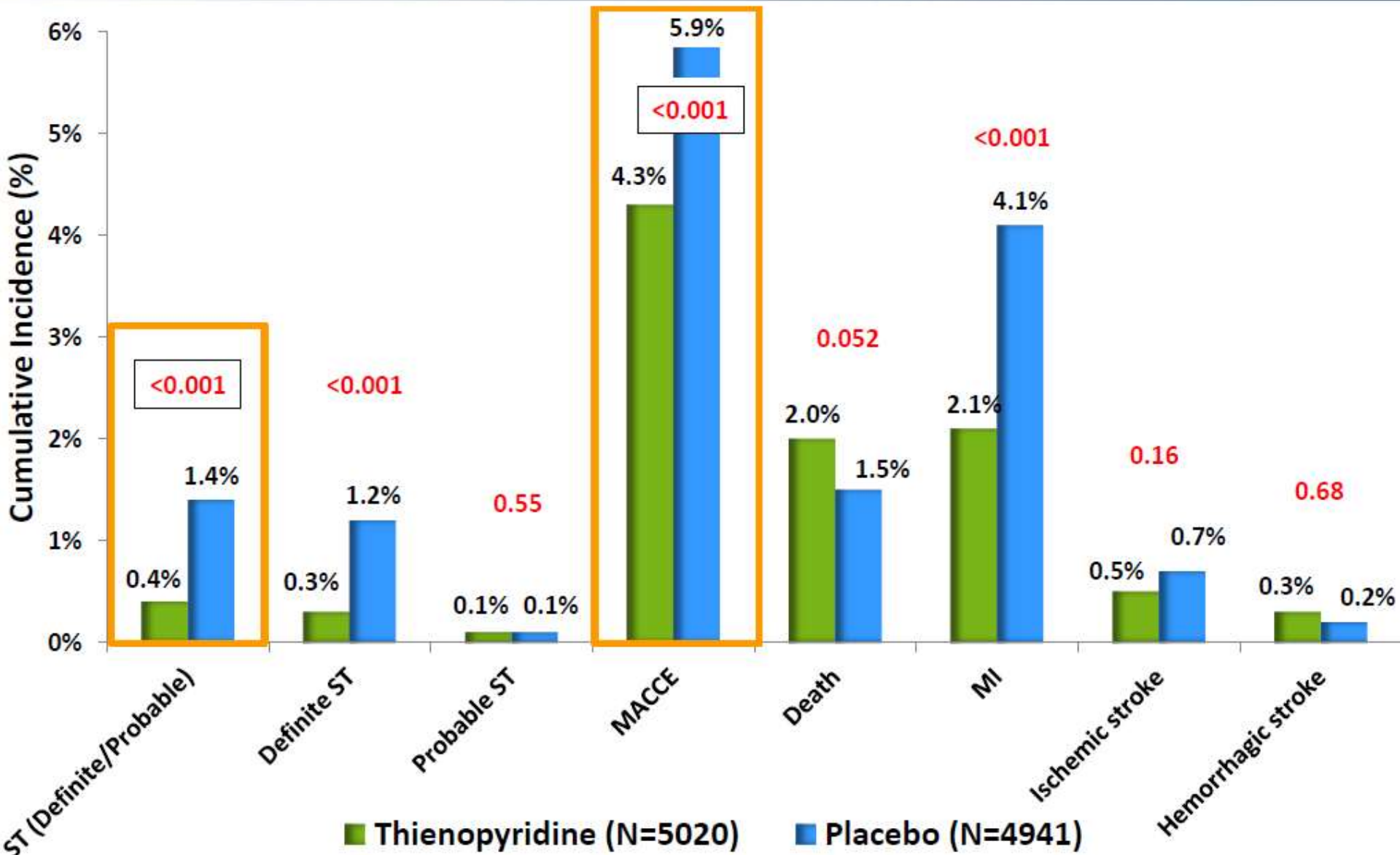
Co-Primary Effectiveness End Point MACCE



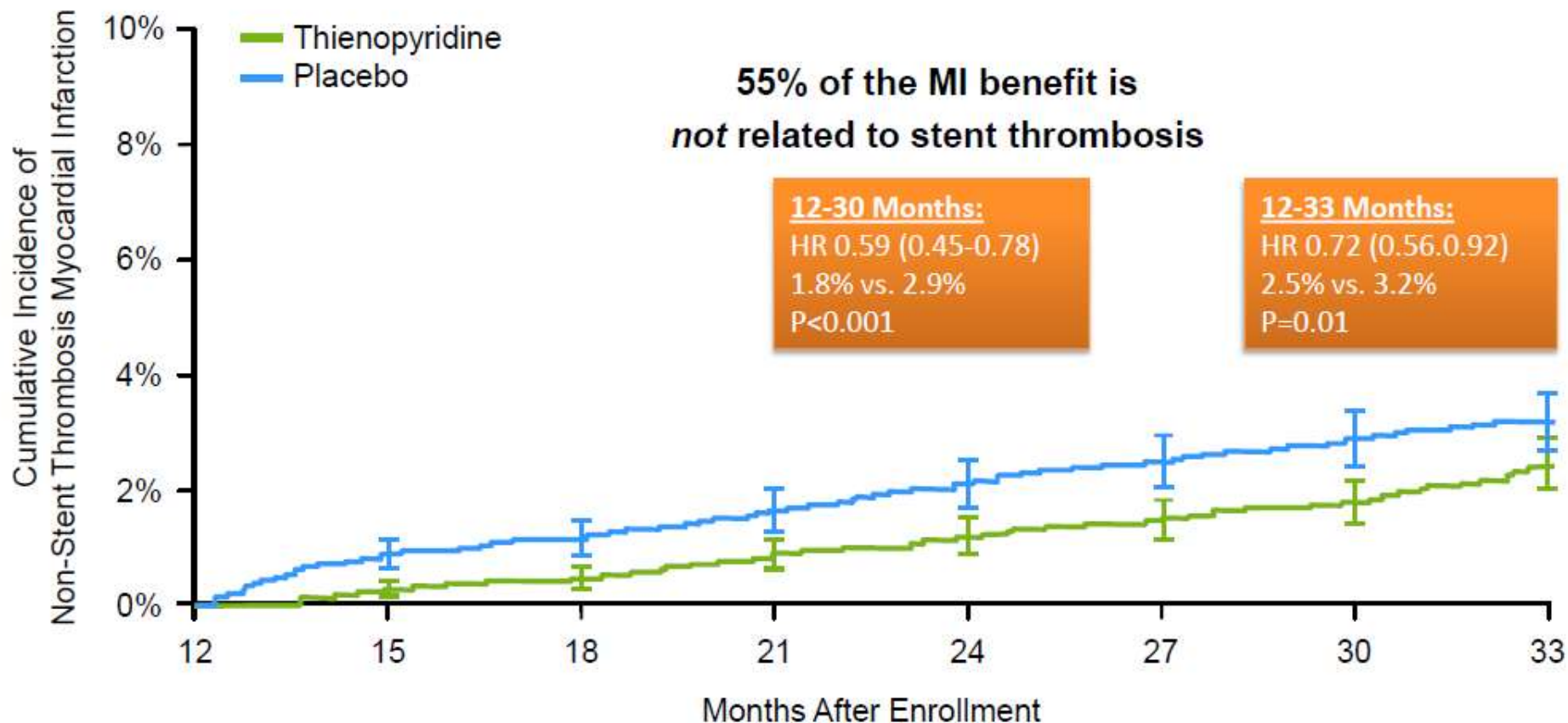
At Risk

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

Co-Primary Effectiveness End Points & Components: 12-30 Months



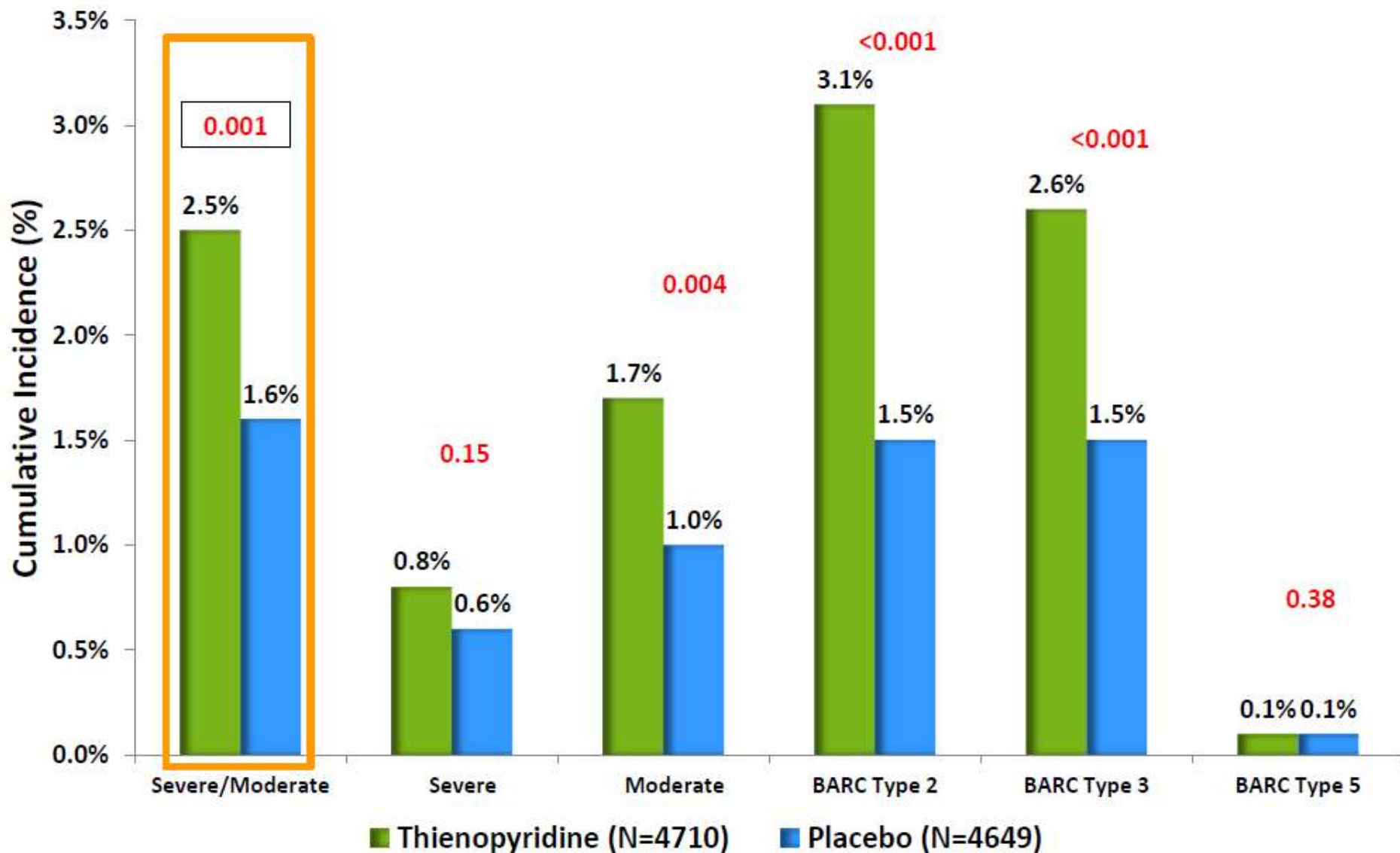
Non-Stent Thrombosis Myocardial Infarction



At Risk

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

Primary Safety End Point & Components: 12-30 Months



Prolonged DAPT and Clinical Event

- Benefit of Prolonged DAPT

- Stent thrombosis → 1% Reduction Neoathero/ Hypersensitivity

- Non-ST MI → 1% Reduction Secondary prevention effect
Of Theinopyridine

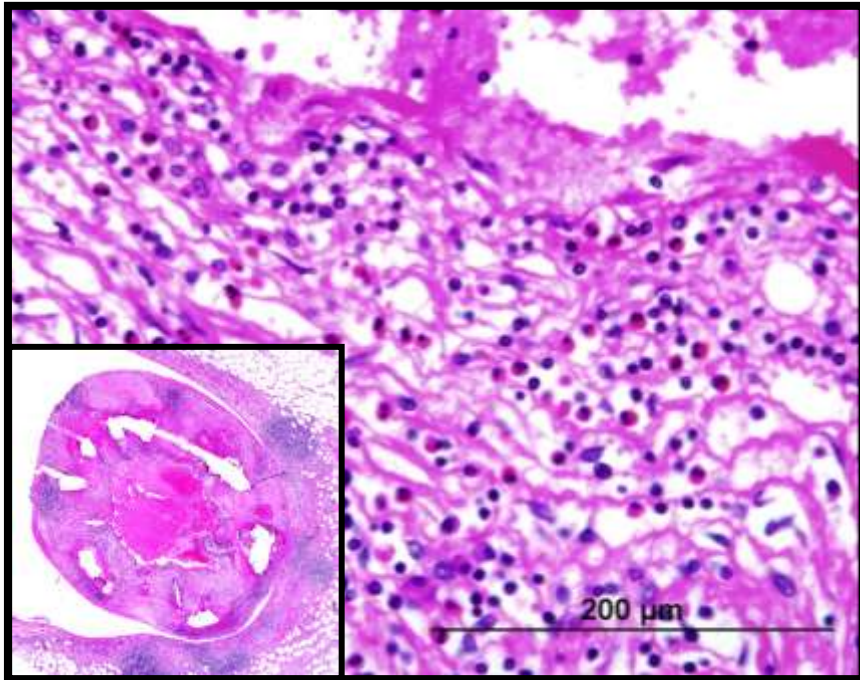
- Drawback of Prolonged DAPT

- Major bleeding → 1% Increase



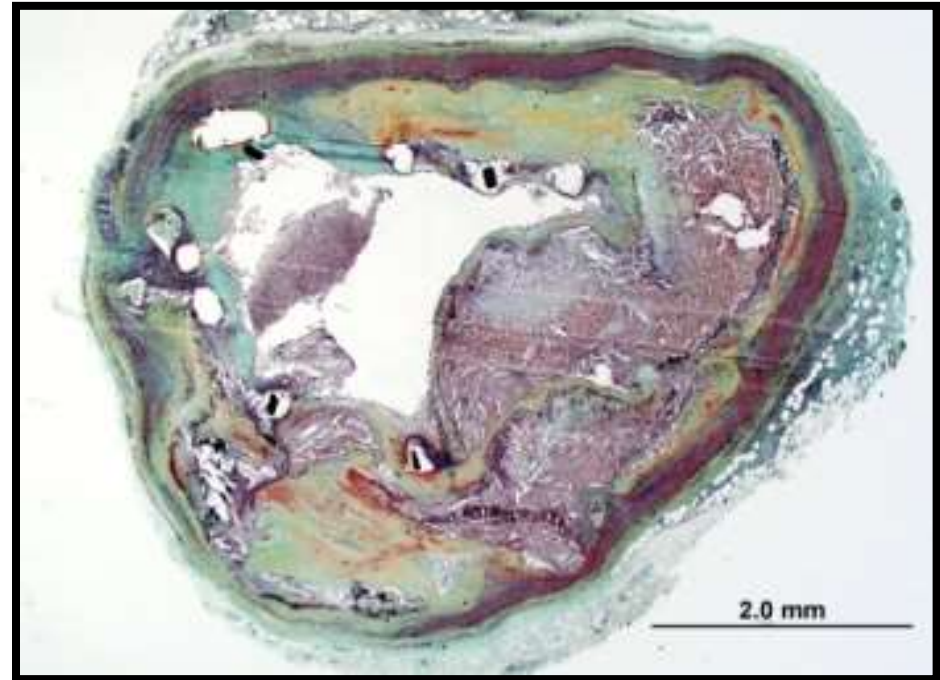
Abnormal Vascular Responses following DES Implantation

Hypersensitivity



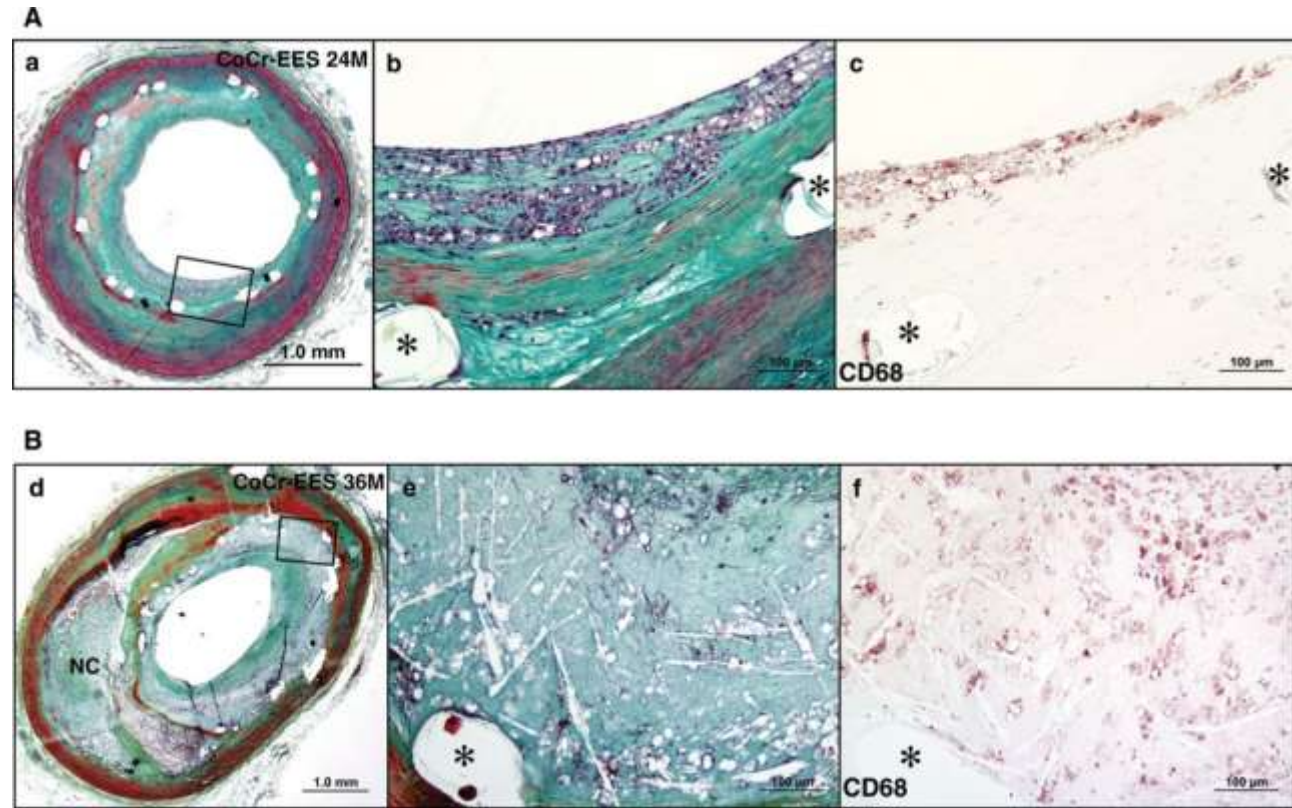
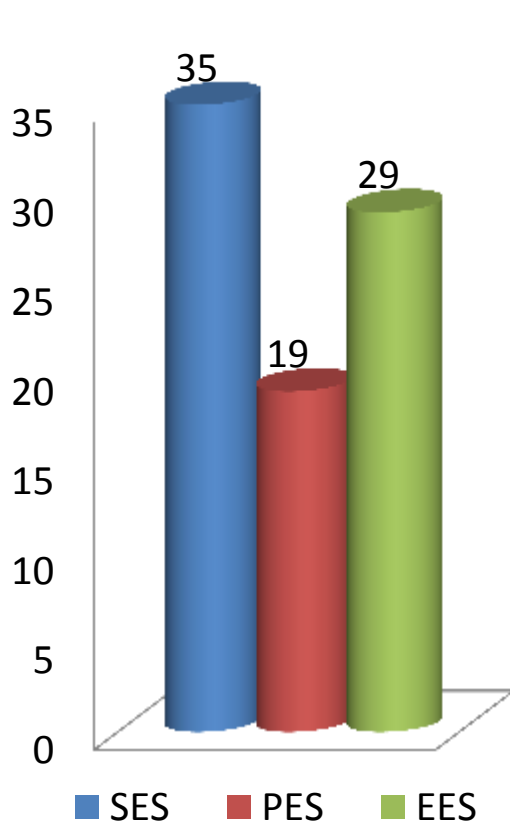
Nakazawa, G et al. J Am Coll Cardiol 2011;57(4):390-8

Neoatherosclerosis



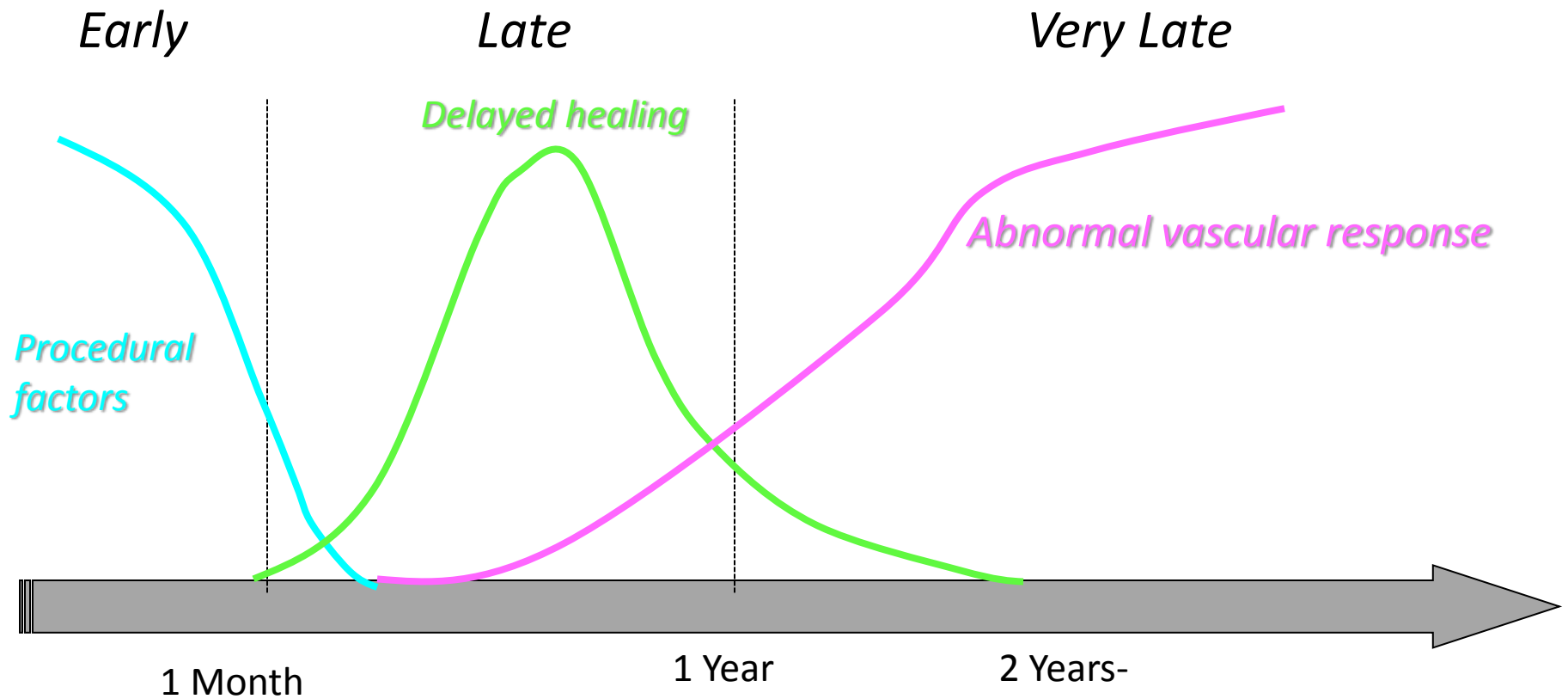
Nakazawa, G & Otsuka, F et al. J Am Coll Cardiol. 2011;57(11):1314-22.

Incidence of Neoatherosclerosis in EES



Otsuka F, et al. Circulation. 2014 Jan 14;129(2):211-23

Different Mechanisms of DES failure with time



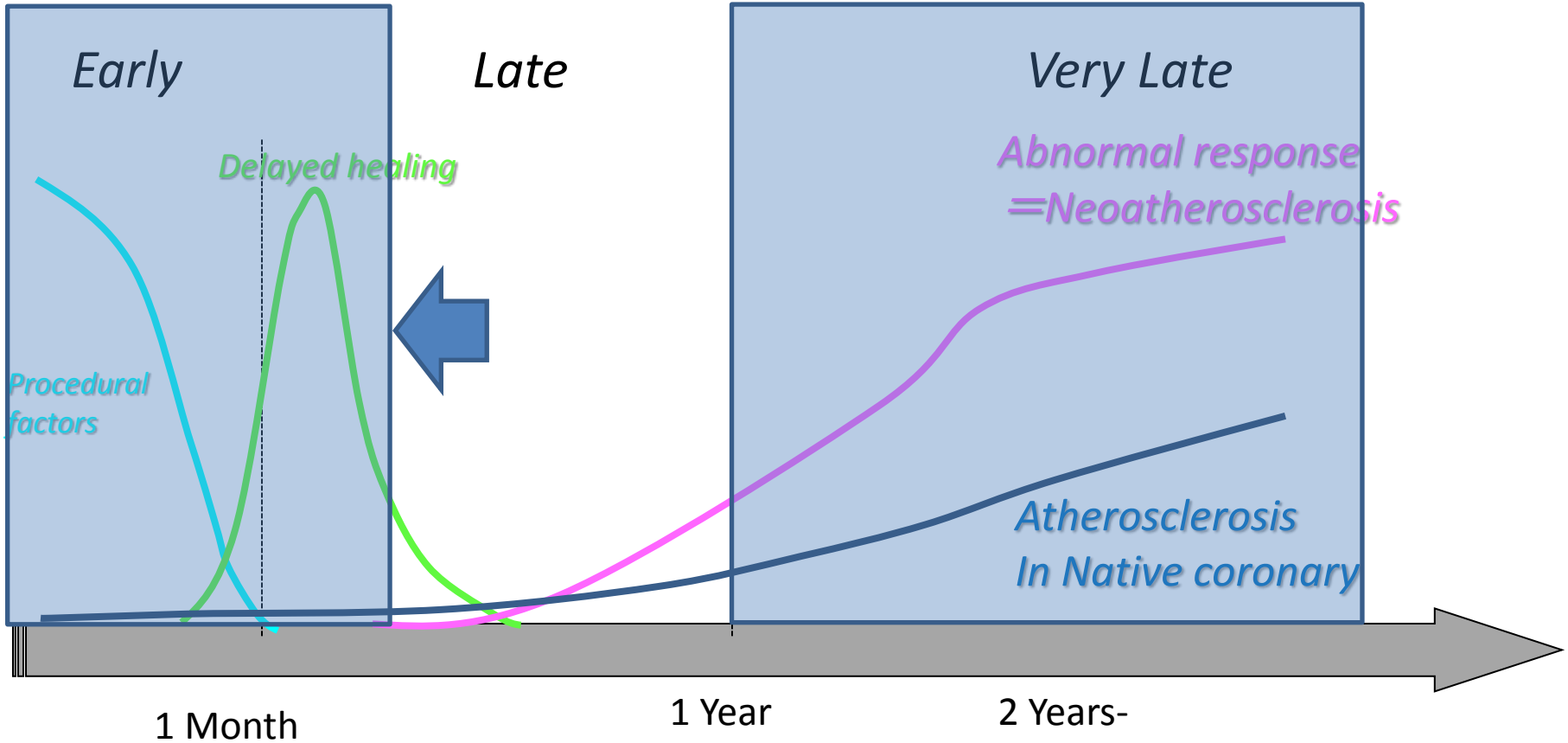
Nakazawa G, J Cardiol. 2011 Sep;58(2):84-91.



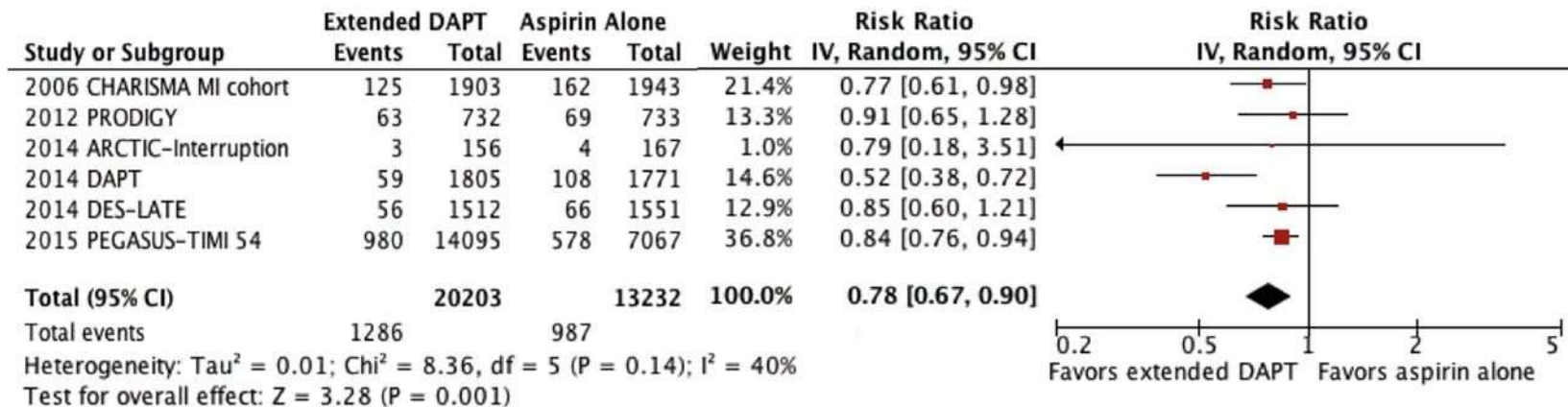
DAPT in 2nd (3rd) Gen DES era

DAPT for prevention of ST

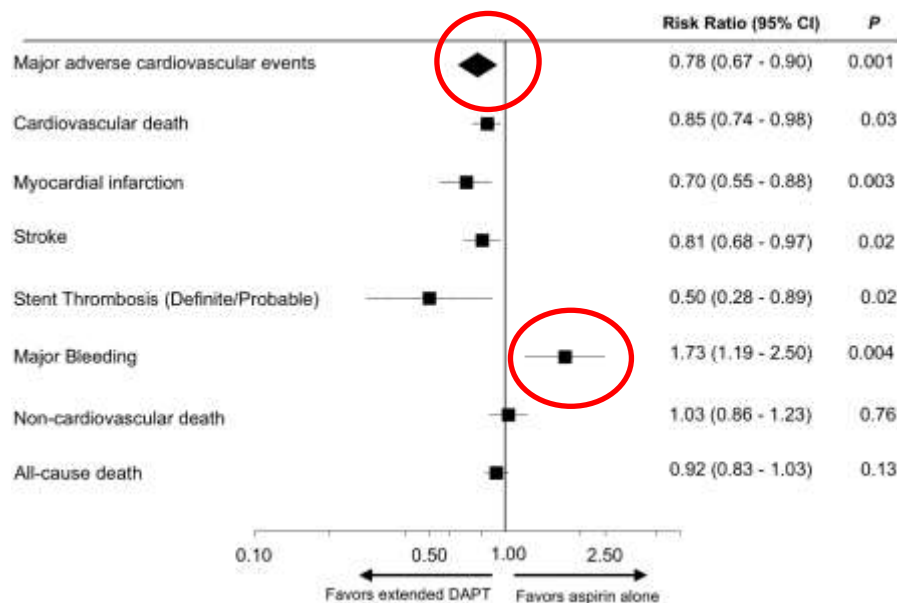
DAPT for secondary prevention for atherosclerosis



Risk of major adverse cardiovascular events comparing extended dual antiplatelet therapy vs. aspirin alone.



Risk of individual cardiovascular and bleeding endpoints comparing extended dual antiplatelet therapy vs. aspirin alone.



Jacob A. Udell et al. Eur Heart J 2015



Association of Spontaneous Bleeding and Myocardial Infarction With Long-Term Mortality After Percutaneous Coronary Intervention



Dhruv S. Kazi, MD, MSc,*†‡ Thomas K. Leong, MPH,§ Tara I. Chang, MD, MS,|| Matthew D. Solomon, MD, PhD,§|| Mark A. Hlatky, MD,||¶ Alan S. Go, MD†§¶

- Retrospective cohort study of patients **who underwent a PCI between 1996 and 2008** in an integrated healthcare delivery system
- **Associations of spontaneous bleeding and MI with all-cause mortality**

Dhruv SK et al; JACC. 2015; 65: 1411-20



The crude annual death rate among patients who had a **spontaneous bleed** and patients who had a **spontaneous MI** was higher than among patients with **neither event**.

Mortality rate of patients with Bleeding was even higher than those who had MI.

TABLE 3 Spontaneous Events and Unadjusted Long-Term Mortality

	Number of Patients	Number of Deaths	Crude Annual Mortality Rate (per 100 Person-Years)	95% Confidence Interval
Spontaneous bleed during follow-up	530	164	9.4	8.1-10.9
Spontaneous MI during follow-up	991	315	7.6	6.8-8.5
Neither event during follow-up	31,424	3,590	2.6	2.5-2.7

MI = myocardial infarction.

Dhruv SK et al; JACC. 2015; 65: 1411-20



Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention



Philippe Généreux, MD,^{*†‡} Gennaro Giustino, MD,[§] Bernhard Witzenbichler, MD,^{||} Giora Weisz, MD,^{*†¶}
Thomas D. Stuckey, MD,[#] Michael J. Rinaldi, MD,^{**} Franz-Josef Neumann, MD,^{††} D. Christopher Metzger, MD,^{‡‡}
Timothy D. Henry, MD,^{§§|||} David A. Cox, MD,^{¶¶} Peter L. Duffy, MD, MMM,^{##} Ernest Mazzaferri, MD,^{***}
Mayank Yadav, MD,^{*} Dominic P. Francese, MPH,^{*} Tullio Palmerini, MD,^{†††} Ajay J. Kirtane, MD, SM,^{*†}
Claire Litherland, MS,^{*} Roxana Mehran, MD,^{*§} Gregg W. Stone, MD^{*†}

ADAPT-DES study;

To determine the incidence and predictors of clinically relevant bleeding events occurring within 2 years after hospital discharge

The effect of Post Discharge Bleeding on subsequent 2-year all-cause mortality was estimated by time-adjusted Cox proportional hazards regression.

Généreux P et al; JACC. 2015; 66: 1036-45



Post Discharge Bleeding was the strongest predictor of 2-year mortality

Variable*	Adjusted HR (95% CI)	p Value
PDB†	5.03 (3.29-7.66)	<0.0001
With transfusion	4.71 (2.76-8.03)	<0.0001
Without transfusion	5.27 (3.32-8.35)	<0.0001
Post-discharge MI‡	1.92 (1.18-3.12)	0.009
Current smoker	1.69 (1.25-2.29)	0.001
Age (per yr increase)	1.04 (1.02-1.05)	<0.0001
Male	1.45 (1.11-1.90)	0.007
Diabetes mellitus	1.48 (1.17-1.88)	0.001
Previous MI	1.42 (1.12-1.81)	0.004
STEMI or non-STEMI presentation	1.41 (1.10-1.83)	0.008
VerifyNow P2Y ₁₂ reactivity units >208	1.22 (0.96-1.54)	0.10
IVUS use	0.83 (0.65-1.06)	0.13
Creatinine clearance (per ml/min increase)‡	0.99 (0.99-1.00)	0.0007
Baseline white blood cells (per 10 ³ /ml increase)	1.03 (1.01-1.04)	<0.0001
Baseline hemoglobin (per g/dl increase)	1.18 (1.09-1.28)	<0.0001

*The magnitude of the effect of post discharge Bleeding on subsequent mortality was roughly **2.6-fold greater** than the effect of post discharge MI.*

Généreux P et al; JACC. 2015; 66: 1036-45



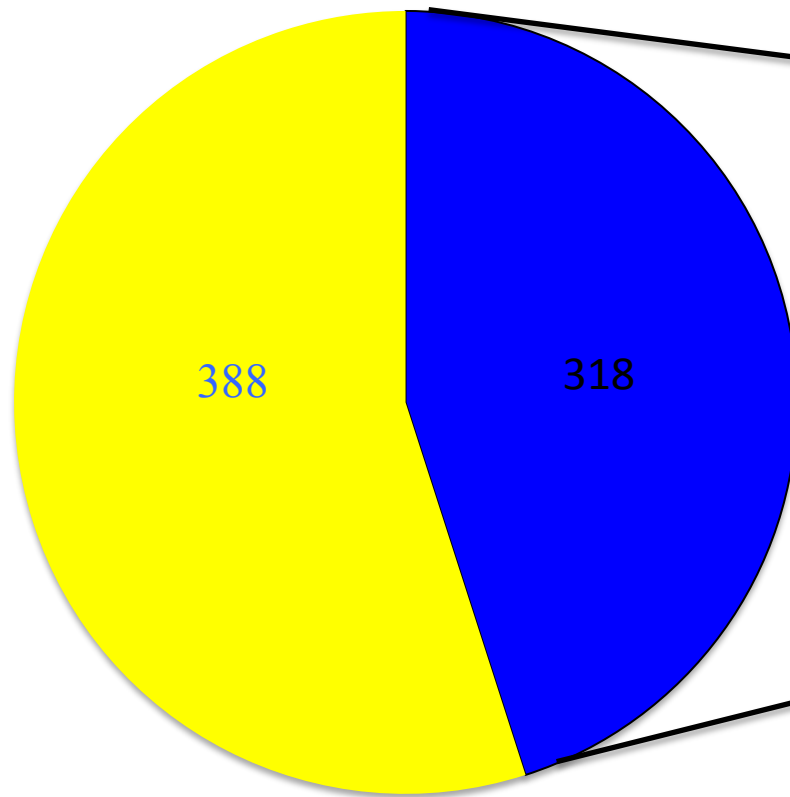
Dual antiplatelet therapy Cessation due to Bleeding Complication is Related to Long-Term Clinical Outcome Following Percutaneous Coronary Intervention

- **S.Tanaka, Y.Ikari, M.Nakamura, T.Ijichi, T.Komai, K.Yanagisawa, Y.Kamiyama, T.Iida, S.Tamiya, E.Toda, M.Shima, T.Fujii, D.Ito, G.Nakazawa, N.Masuda, T.Matsukage, N.Ogata, Y.Morino**
- **Tokai University Hospital, Isehara, Kanagawa, Japan**

Presented@JCS2012

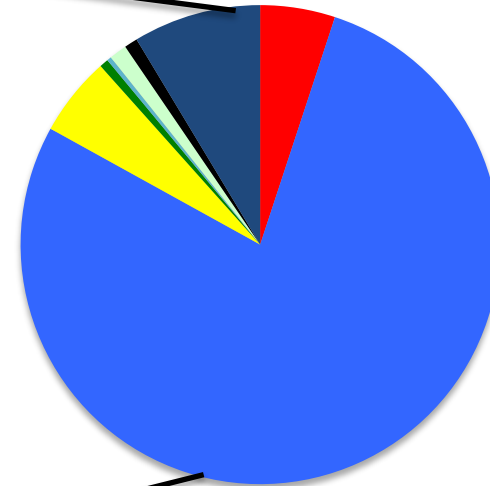


Reasons of P2Y12 inhibitor cessation



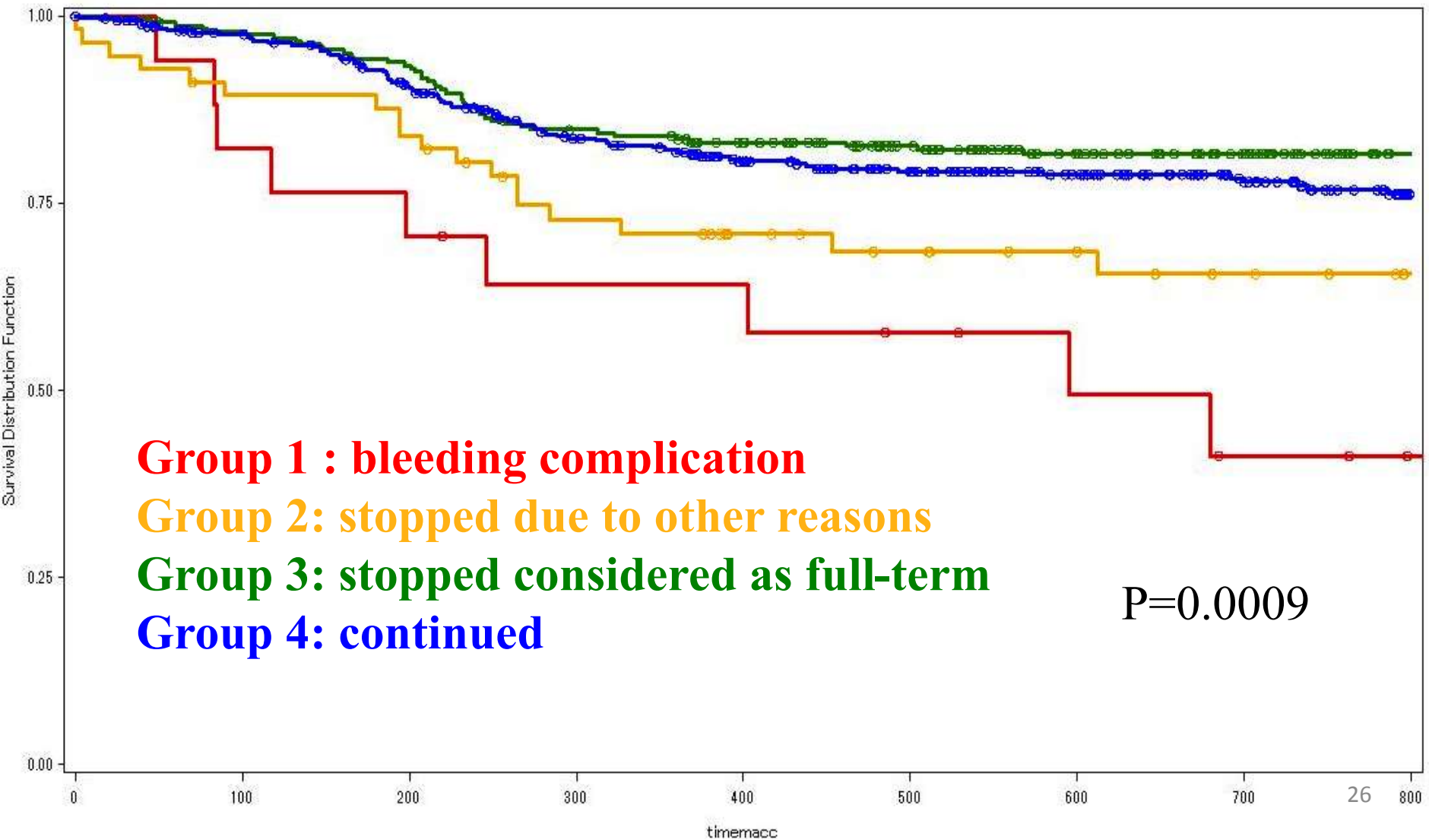
- cessation
- continuing

Reasons of cessation



- bleeding complication(17)
- considered as full-term (262)
- hepatic disorder (18)
- agranulocytosis (2)
- pancytopenia (1)
- skin eruption (4)
- bypass surgery (3)
- others (29)

Kaplan-Meyer Event Free Survival Curve of MACCE



Bleeding and Thrombotic Event

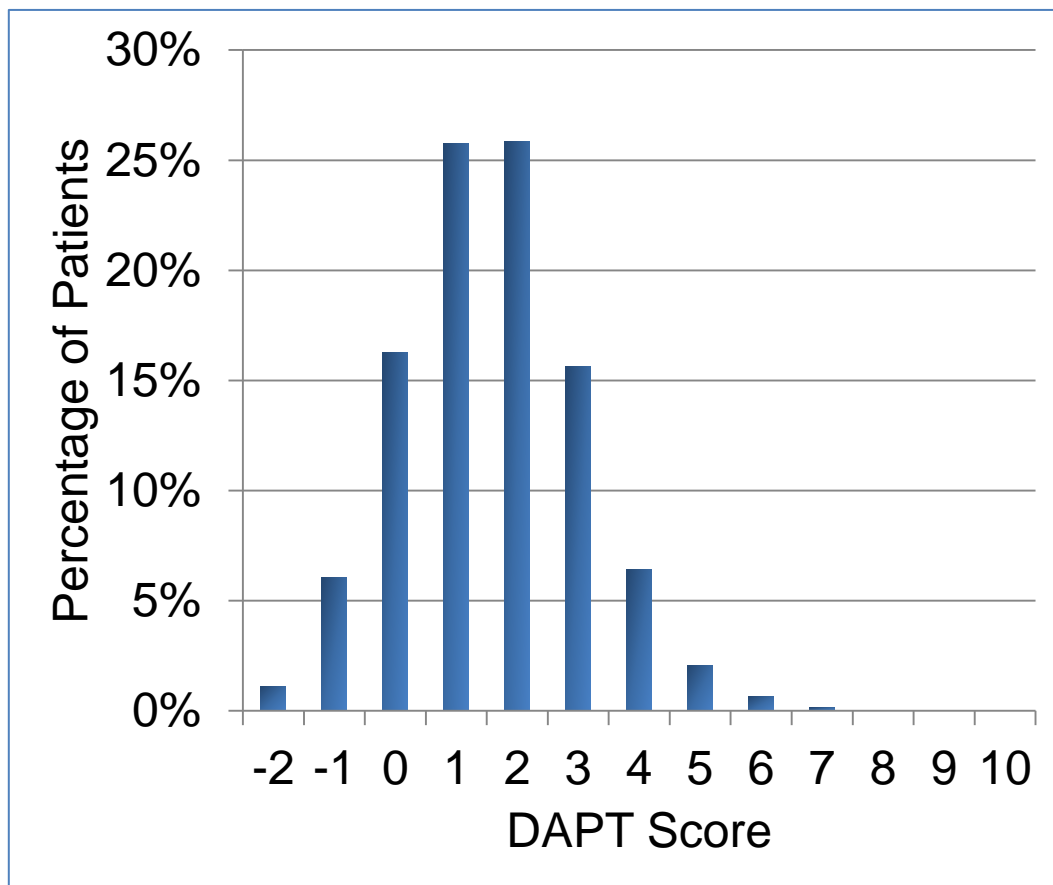
- While thrombotic event is catastrophic, post discharge “bleeding” is also critical (or even worse)
- We need to accurately discriminate the patients who are at risk for thrombotic event or bleeding risk



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



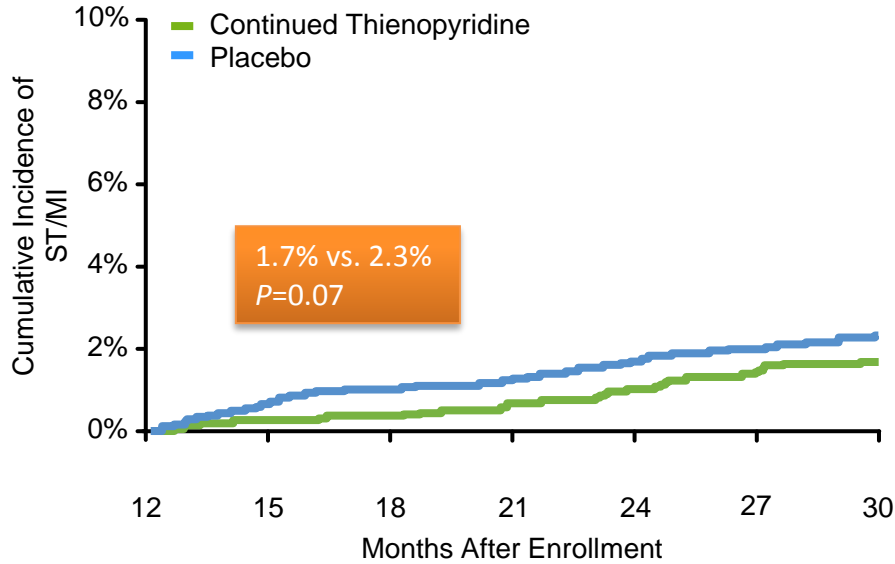
RW et al. Yeh RW et al. JAMA. 2016 Apr 26;315(16):1735-49.



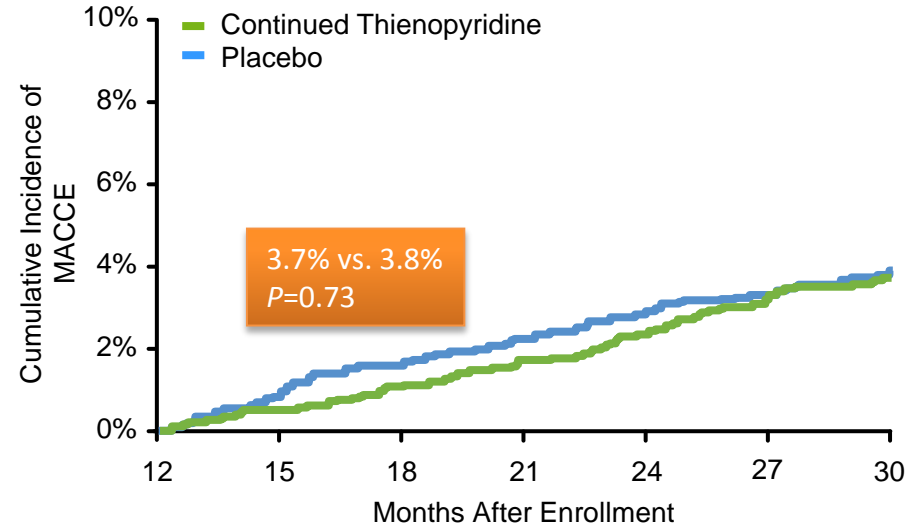
Continued Thienopyridine vs. Placebo

DAPT Score <2 (Low); N=5731

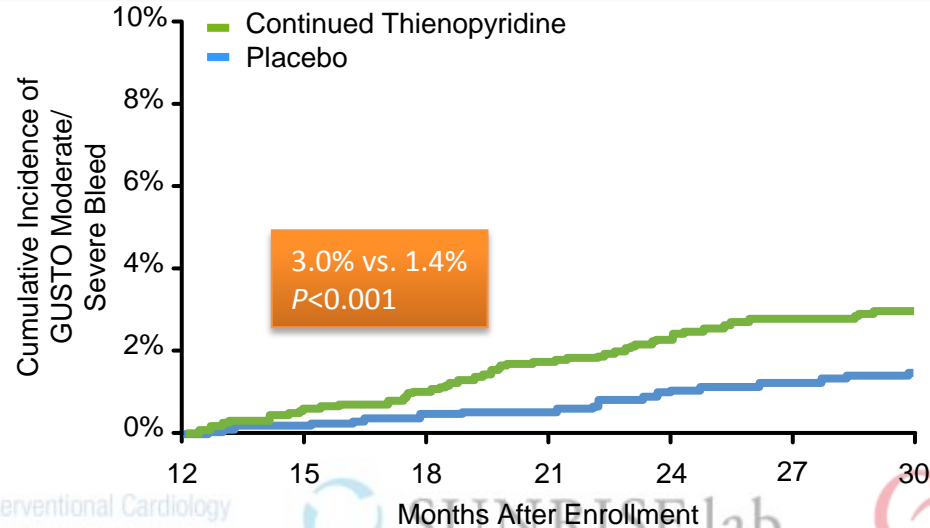
Myocardial Infarction or Stent Thrombosis



Death, MI, or Stroke (MACCE)



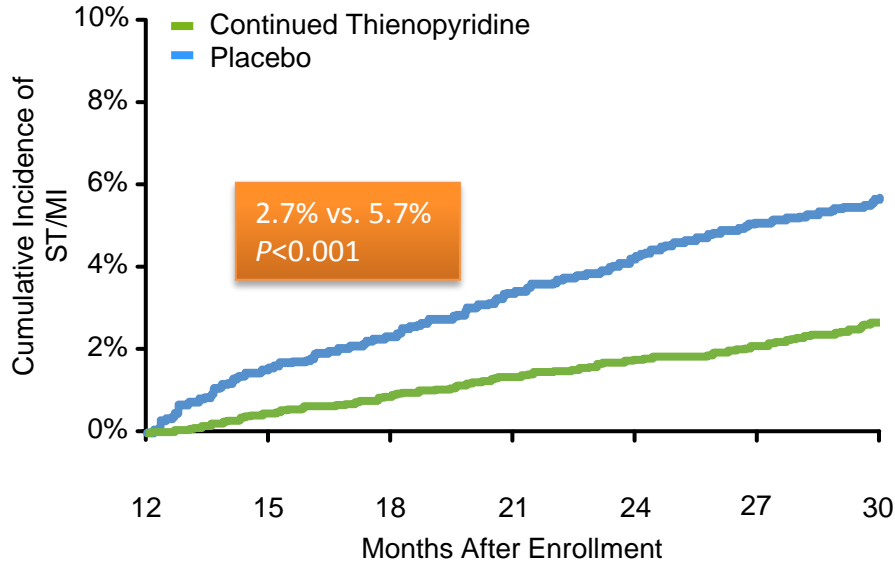
GUSTO Moderate/Severe Bleeding



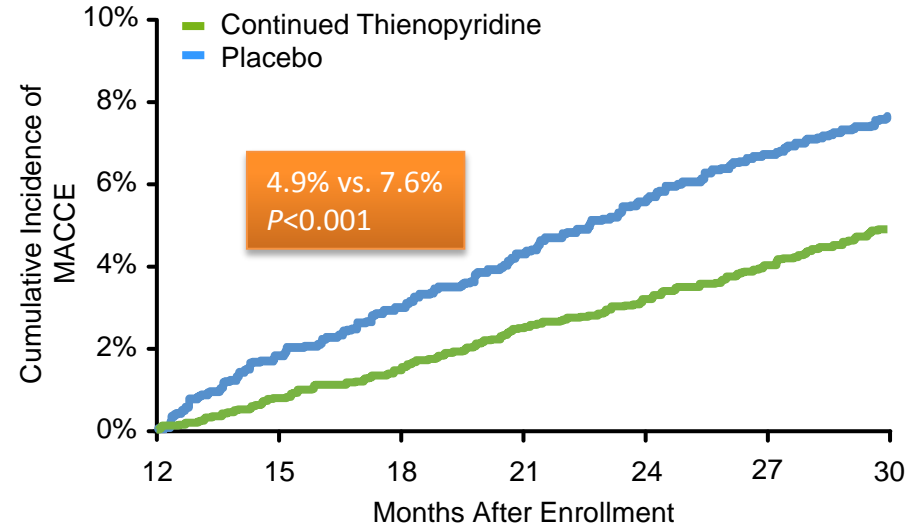
Continued Thienopyridine vs. Placebo

DAPT Score ≥ 2 (High); N=5917

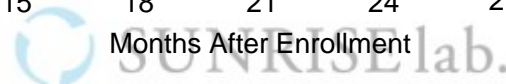
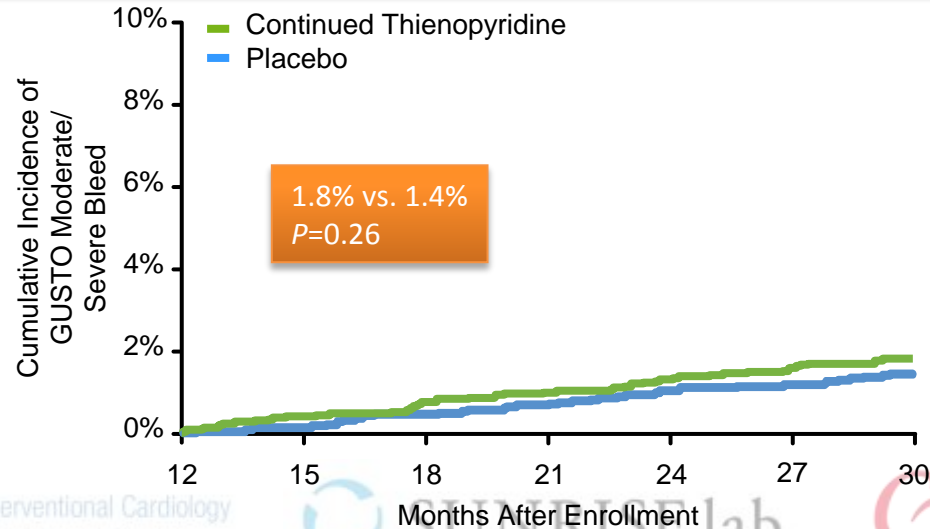
Myocardial Infarction or Stent Thrombosis



Death, MI or Stroke (MACCE)

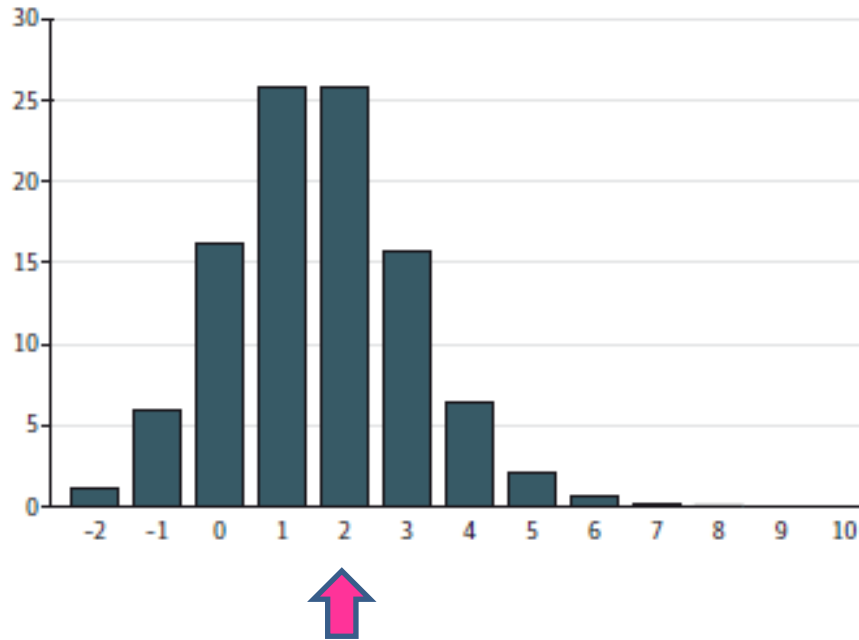


GUSTO Moderate/Severe Bleeding

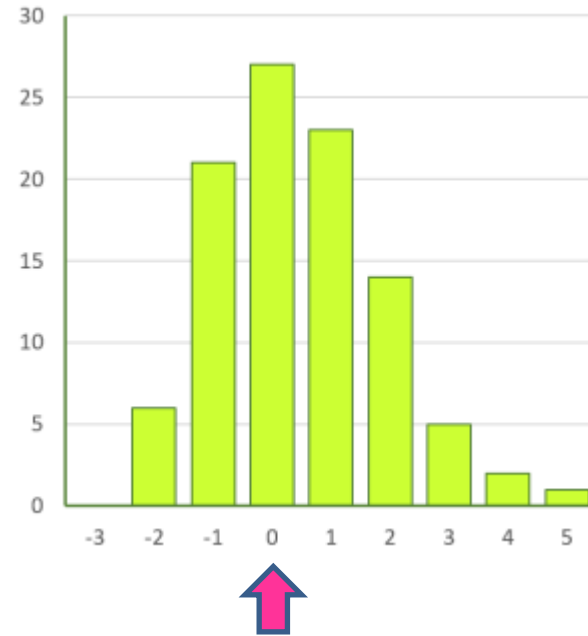


Distribution of DAPT score

DAPT study



Japanese population
Toho University



Courtesy of Dr. Raisuke Iijima @ Toho Ohashi Hosp



Limitation of DAPT study

- Consists of patients who had no thrombotic and bleeding event in the first year
- Patients with anti-coagulant Tx were excluded
- Different population?
 - body size, age, and race



Risk Score from PARIS Study

TABLE 5 Integer Risk Score for Coronary Thrombotic Events

Parameter	Score
Diabetes mellitus	
None	0
Non-insulin-dependent	+1
Insulin-dependent	+3
Acute coronary syndrome	
No	0
Yes, Tn-negative	+1
Yes, Tn-positive	+2
Current smoking	
Yes	+1
No	0
CrCl <60 ml/min	
Present	+2
Absent	0
Prior PCI	
Yes	+2
No	0
Prior CABG	
Yes	+2
No	0

TABLE 4 Integer Risk Score for Major Bleeding

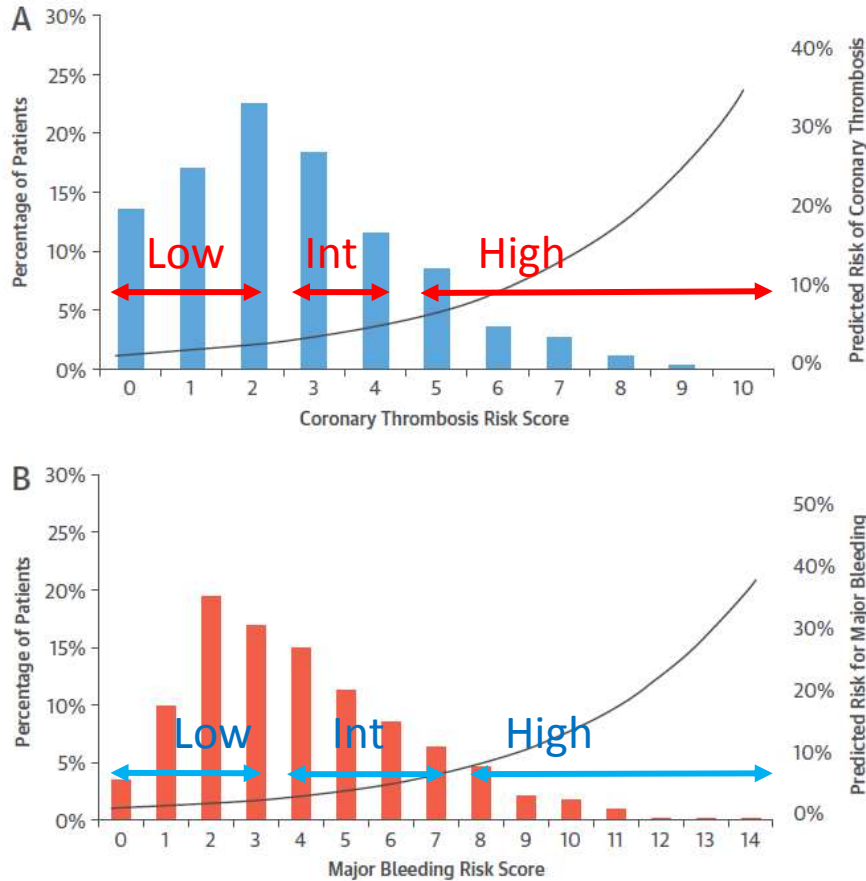
Parameter	Score
Age, yrs	
<50	0
50-59	+1
60-69	+2
70-79	+3
≥80	+4
BMI, kg/m ²	
<25	+2
25-34.9	0
≥35	+2
Current smoking	
Yes	+2
No	0
Anemia	
Present	+3
Absent	0
CrCl <60 ml/min	
Present	+2
Absent	0
Triple therapy on discharge	
Yes	+2
No	0

Usman Baber, MD, J Am Coll Cardiol 2016;67:2224–34)



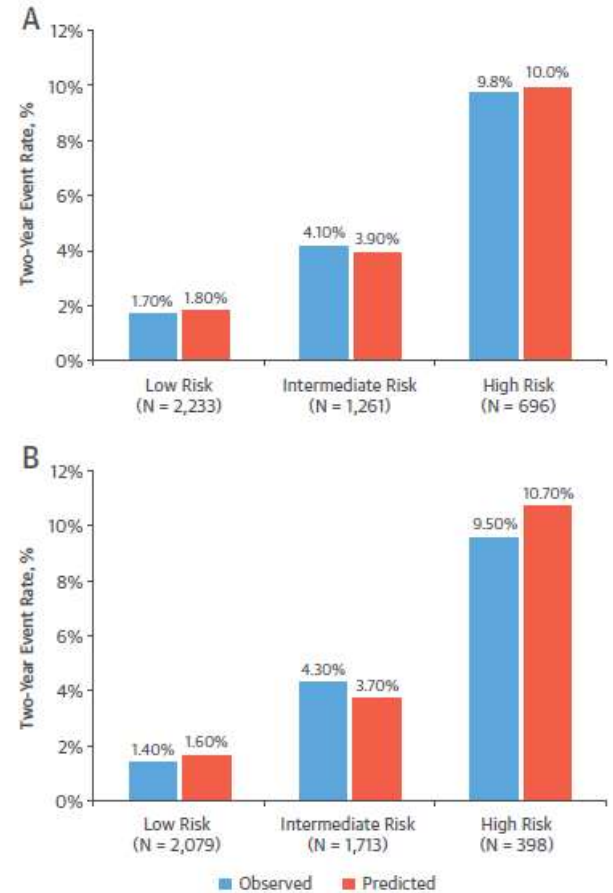
Risk Score from PARIS Study

FIGURE 2 Histograms Displaying the Frequency of Thrombotic and Bleeding Risk Scores



Solid line shows the mean predicted probability of coronary thrombotic and major bleeding events by thrombotic (A) and bleeding (B) integer scores.

FIGURE 4 Observed and Predicted Rates of Events



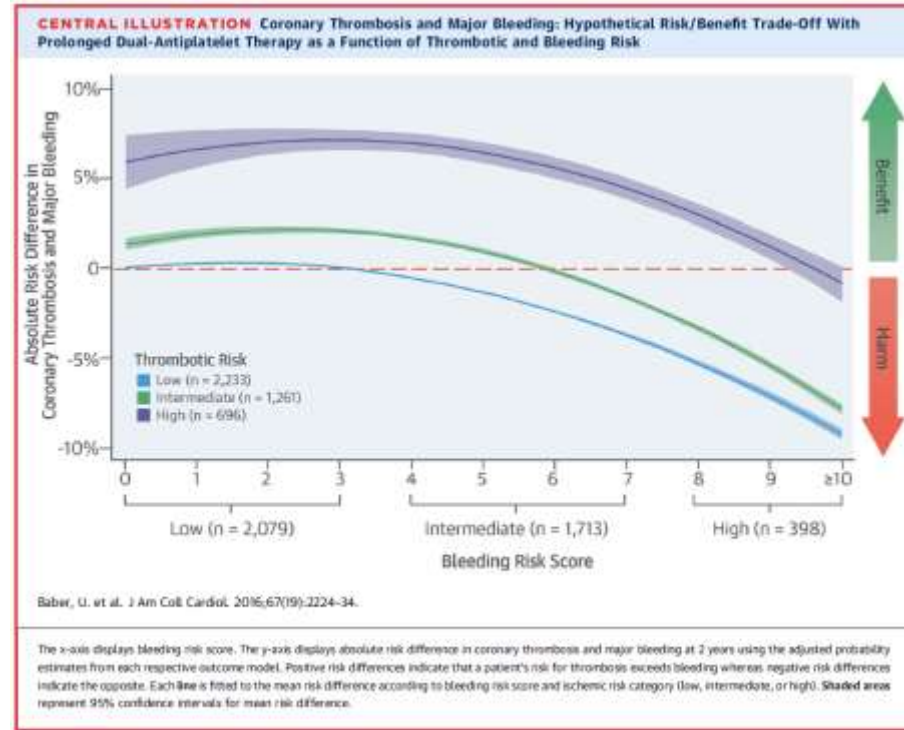
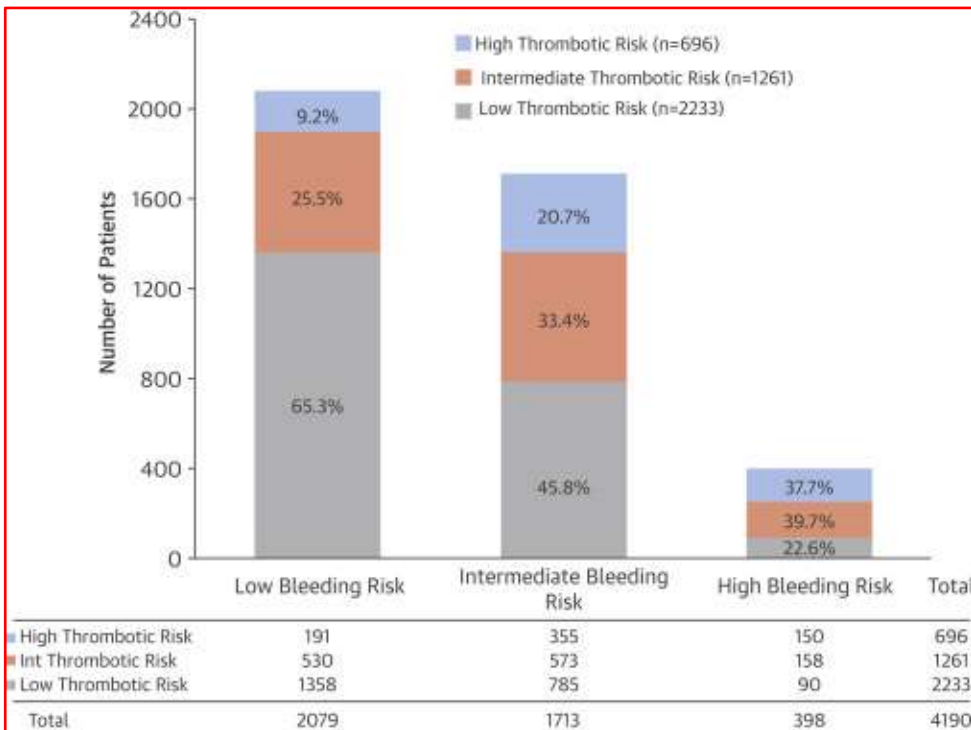
Bar graphs display the observed and predicted rates of coronary thrombotic (A) and major bleeding (B) events over 2 years across the respective risk score categories.

Usman Baber, MD, J Am Coll Cardiol 2016;67:2224–34)



Thrombotic and Bleeding Risk

Many patients are high risk for thrombotic AND bleeding event

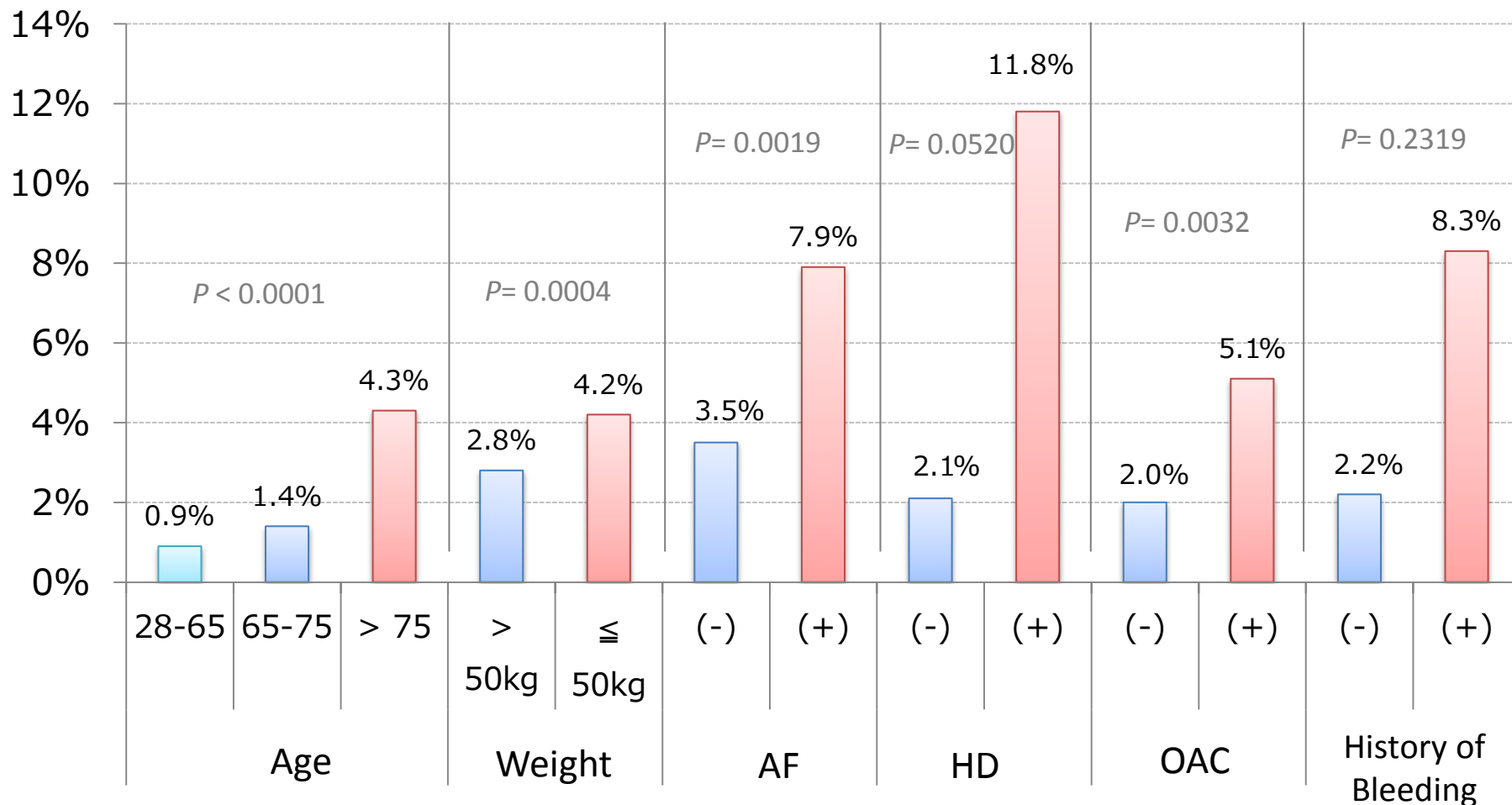


Usman Baber, MD, J Am Coll Cardiol 2016;67:2224-34)



Japanese postmarketing surveillance of clopidogrel for patients with non-ST-segment-elevation acute coronary syndrome indicated for percutaneous coronary intervention (J-PLACE NSTE-ACS)

Cardiovasc Interv Ther. 2013 29: 123-33



Impact of transradial coronary intervention on bleeding complications in OCTOGENARIANS (TOKAI Univ.)

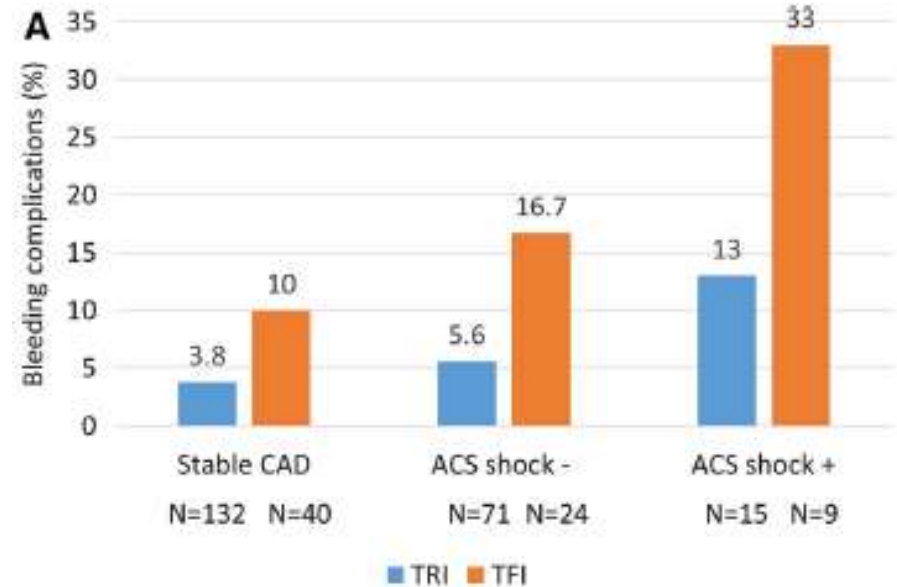
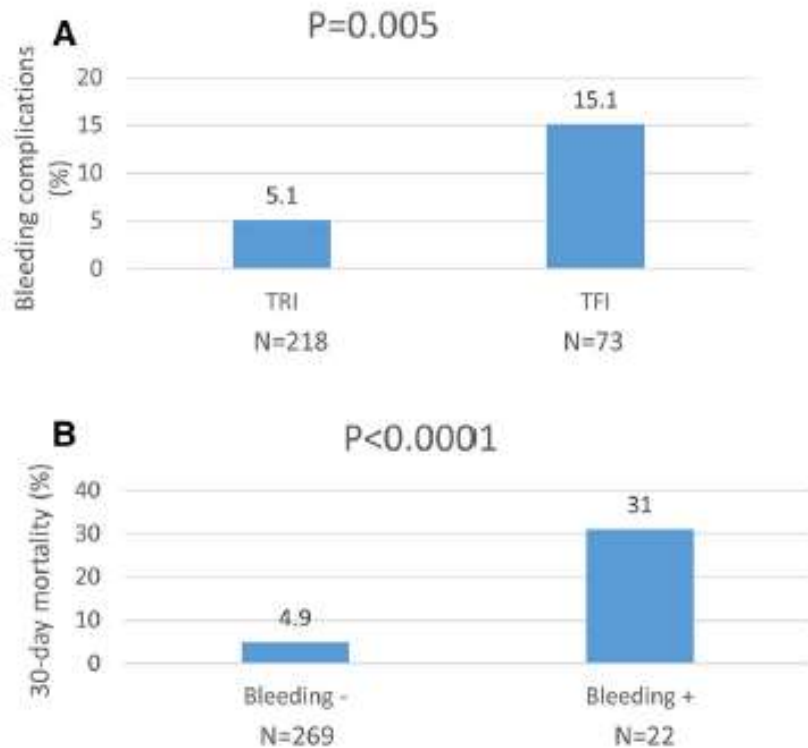
- Among 2530pts receiving PCI, 291 pts (12%) were octogenarian
- Mean Bw : 56kg
- DM 40%
- History of CVD 11%
- Mean Ccr 41
- ACS 40%
- AF 11% (OAC 8%)
- TRI 75% TFI 25%

- BARC Major 7.6%
- TIMI Major bleeding 4.5%, Minor 3.1%

Tammam K, Ikari Y, et al. Cardiovasc Interv and Ther. In Press



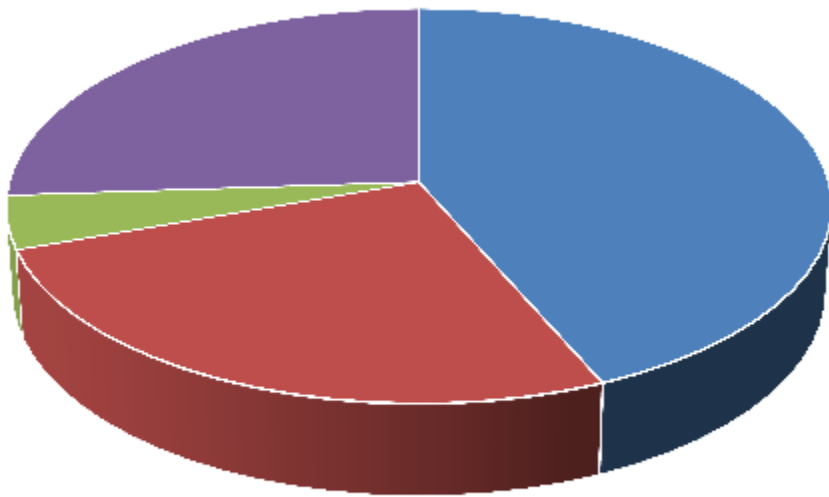
Impact of transradial coronary intervention on bleeding complications in OCTOGENARIANS (>80ys) (TOKAI Univ.)



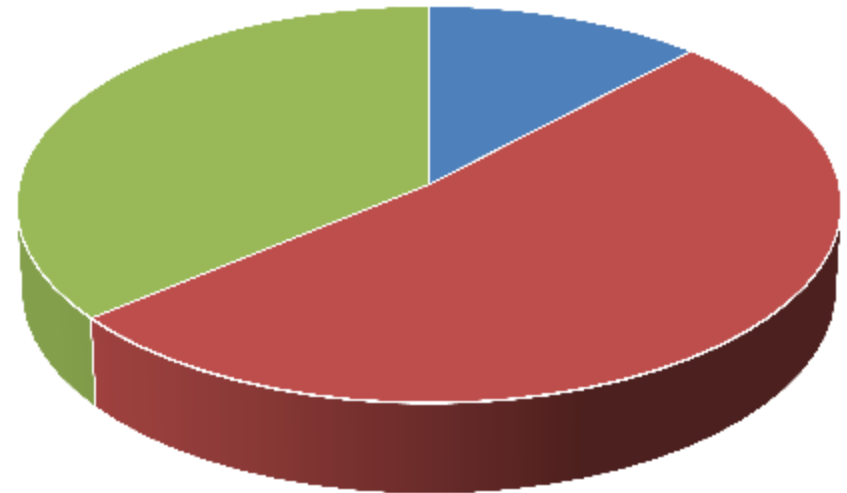
Tammam K, Ikari Y, et al. Cardiovasc Interv and Ther. In Press



Bleeding in Octogenarians



■ Procedure ■ GI
■ Urinary ■ Unknown



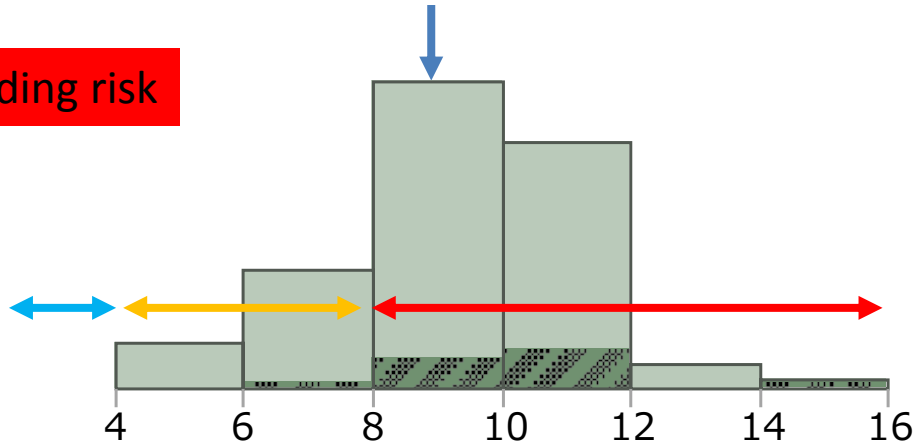
■ BARC2 ■ BARC3ab ■ BARC5

Tammam K, Ikari Y, et al. Cardiovasc Interv and Ther. In Press

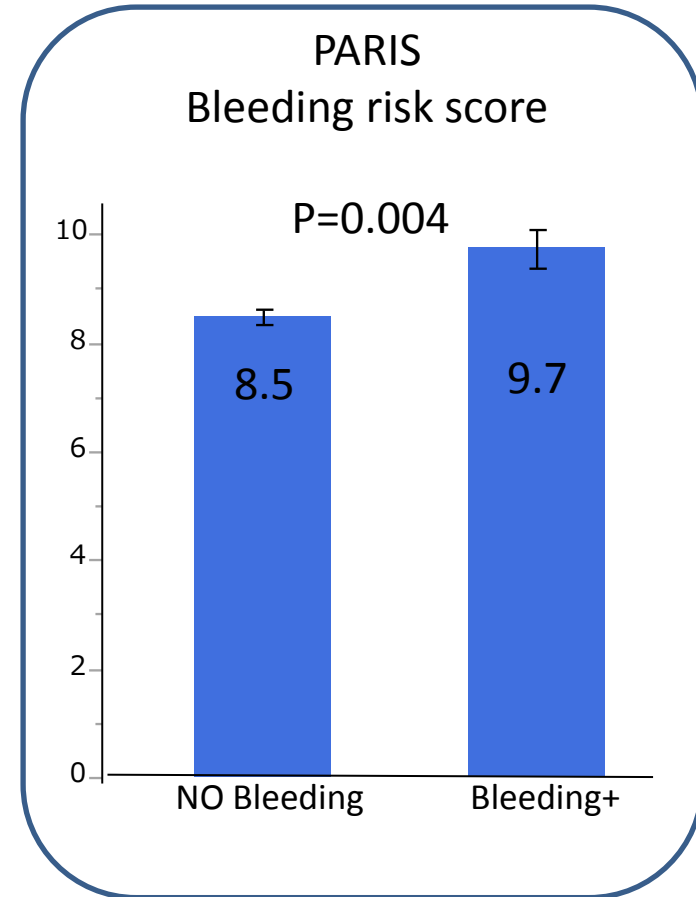
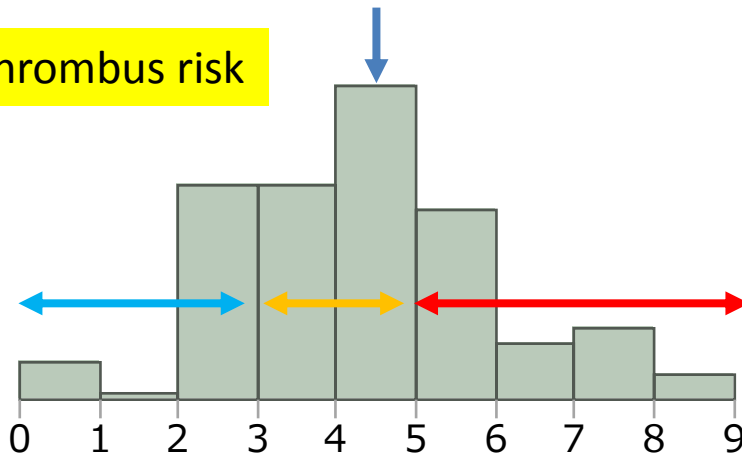


Impact of transradial coronary intervention on bleeding complications in OCTOGENARIANS

Bleeding risk



Coronary Thrombus risk



Re-visit Bleeding risk

- Once patients suffer from bleeding, they have high mortality risk (even higher than MI)
- Bleeding risk is high in old patients
 - Co-morbidity of AF (Taking OAC)
 - Small body size
 - Low renal function
 - History of bleeding and CVA
- ➔ They have not well studied in the previous clinical trials

