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

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

Background

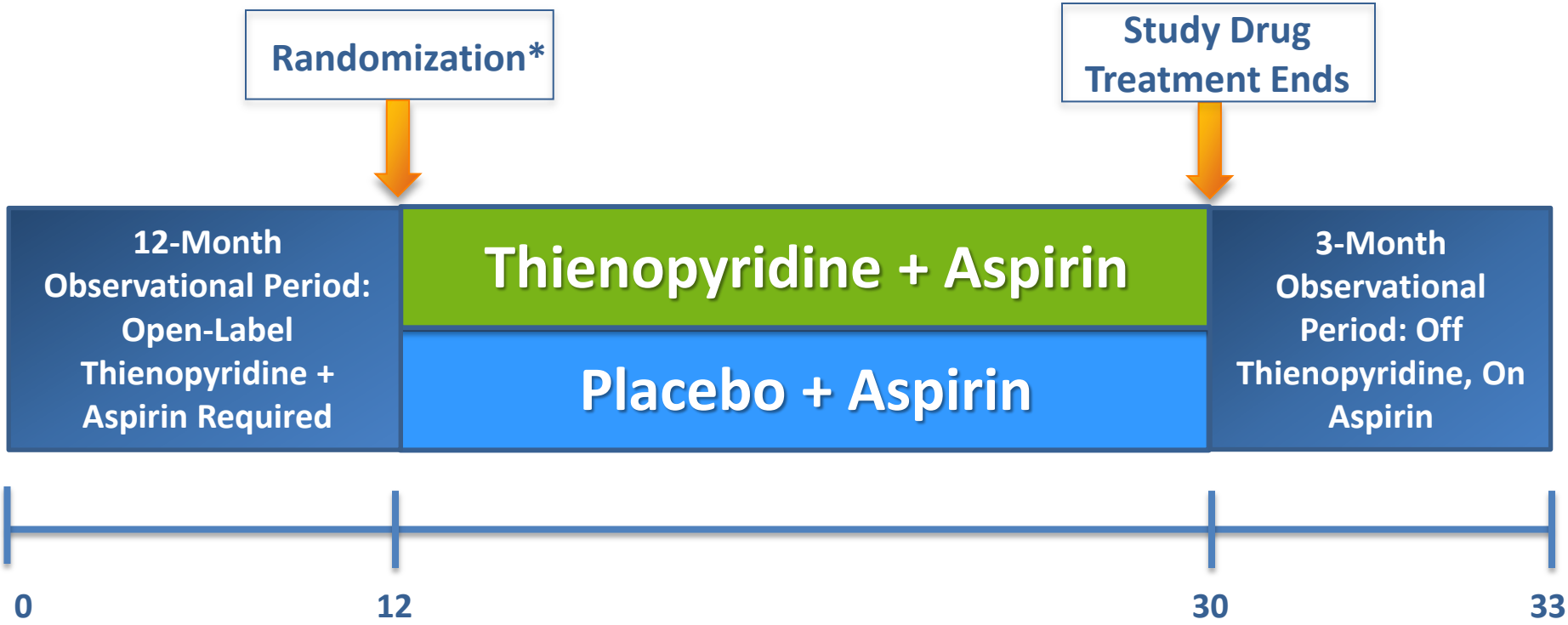
- Coronary stents are placed to relieve angina, or treat myocardial infarction in millions each year
- Drug-eluting stents (DES) reduce restenosis compared with bare metal stents (BMS), but may be associated with stent thrombosis
- Stent thrombosis is rare, but frequently associated with myocardial infarction, and may be fatal
- While risks diminish over time, there is an ongoing risk of stent thrombosis and other ischemic events, beyond one year
- No randomized study of dual antiplatelet therapy duration has been powered to assess stent thrombosis
- The DAPT Study was designed in response to a request from the FDA to evaluate the effect of dual antiplatelet therapy beyond one year in subjects treated with coronary stents

Objectives

- To determine whether dual antiplatelet therapy beyond 12 months is associated with reduction in **stent thrombosis** and/or major adverse cardiovascular and cerebrovascular events (MACCE, **death, myocardial infarction or stroke**)
- To determine the impact of dual antiplatelet therapy beyond 12 months on **moderate or severe bleeding**

In a broadly inclusive population treated with coronary stents

Design



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).

Mauri, Kereiakes et al AHJ 2010; 160(6): 1035-1041

ClinicalTrials.gov number NCT00977938

Design (2)

- Multicenter, international, placebo-controlled
- Operators selected stent and thienopyridine type from those available and approved by FDA
- Single randomized trial incorporating 5 individual component studies for enrollment - each following uniform inclusion criteria and follow-up schedule specified by the DAPT Study protocol
- Randomization and anaylsis stratified by site, DES vs BMS, thienopyridine type, and by presence of risk factors for stent thrombosis
- One overall clinical events committee, blinded to treatment
- One overall data safety monitoring committee

Mauri, Kereiakes et al AHJ 2010; 160(6): 1038-1041

Study Organization

Co-Principal Investigators
Laura Mauri, Dean Kereiakes

Study Statistician
Joseph Massaro

Executive Committee
Laura Mauri, Dean Kereiakes, Donald Cutlip, Sharon-Lise Normand, P. Gabriel Steg, Robert Yeh, Theodora Cohen, Priscilla Driscoll-Shempp

Advisory Committee
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Clinical Events Committee
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National Coordinating Investigators
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Public-Private Partnership

US Food and Drug Administration

(IDE # G080186, 1RO1FD003870-01)

8 Funding Stent and Pharmaceutical Manufacturers: Abbott Vascular, Boston Scientific Corp., Bristol-Myers Squibb Co./Sanofi Pharmaceuticals Partnership, Cordis Corp., Daiichi Sankyo Co. Limited, Eli Lilly & Co., Medtronic Vascular

Harvard Clinical Research Institute (HCRI, Boston, MA) as the study sponsor

Enrolling Countries

11 Countries, 452 Sites

Primary End Points

Two powered co-primary effectiveness end points

- **Definite or probable stent thrombosis** (Academic Research Consortium definition)
- **Major adverse cardiovascular or cerebrovascular events** (MACCE, death, MI or stroke)

Powered primary safety end point

- **Moderate or severe bleeding** (Global Utilization of Streptokinase and TPA for Occluded Arteries classification [GUSTO])

Primary analysis period = drug treatment period of 12-30 m

Primary analysis cohort: randomized DES-treated subjects

Secondary analysis period of 12-33 m

Co-Primary Effectiveness Hypotheses

Continued thienopyridine (vs. placebo)

- Increases survival free from ST over 12-30m period after stenting
- Increases survival free from MACCE over 12-30m period after stenting

Benjamini-Hochberg approach requires either of the following to conclude superiority

1) $p<0.05$ on both end points and both HRs favor continued thienopyridine

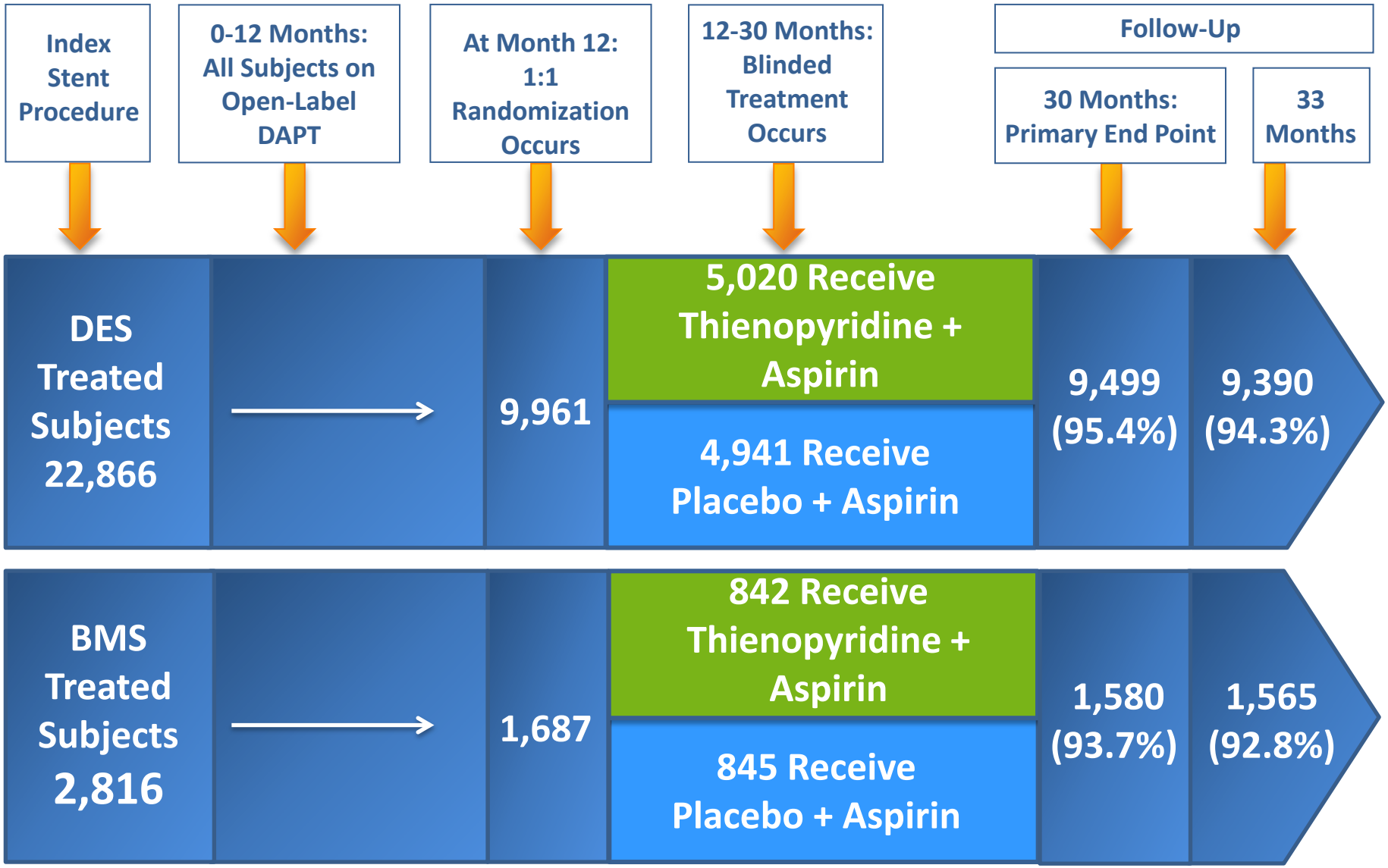
OR

2) $p<0.025$ on one end point with HR favoring continued thienopyridine

Anticipated treatment effect	HR
ST	0.45
MACCE	0.75

A sample size of 9,960 randomized drug-eluting stent subjects had >85% power to detect superiority in terms of ST and/or MACCE from 12-30 m.

Subject Flow



Baseline Demographics

	Thienopyridine N=5020	Placebo N=4941	P-value
Age (years)	61.8	61.6	0.24
Female	24.7%	26.0%	0.15
Race – Non White	8.9%	8.6%	0.67
Ethnicity-Hispanic or Latino	3.2%	3.3%	0.91
Weight – kg	91.5	91.5	0.93
BMI	30.5	30.6	0.92
Diabetes Mellitus	31.1%	30.1%	0.28
Hypertension	75.8%	74.0%	0.03
Cigarette Smoker	24.6%	24.7%	0.91
Prior PCI	30.4%	31.0%	0.50
Prior CABG	11.3%	11.8%	0.49
NSTEMI	15.5%	15.5%	0.93
STEMI	10.6%	10.3%	0.65

Procedure and Lesion Characteristics

DAPT STUDY

	Thienopyridine N=5020 (6594 Lesions)	Placebo N=4941 (6413 Lesions)	P-Value
Number of Treated Vessels	1.11	1.12	0.60
Number of Stents	1.47	1.45	0.23
Total Stent Length (mm)	27.7	27.4	0.43
Stent Diameter <3mm (min per subject	46.6%	46.4%	0.99
Native Coronary	97.1%	96.8%	0.36
Left Main	0.84%	0.86%	0.92
LAD	41.2%	40.4%	0.33
Circumflex	22.4%	23.5%	0.12
RCA	32.7%	32.1%	0.49
Venous Graft	2.3%	2.7%	0.20
Arterial Graft	0.55%	0.47%	0.54
Modified ACC/AHA Lesion Class B2 or C	43.5%	43.1%	0.65

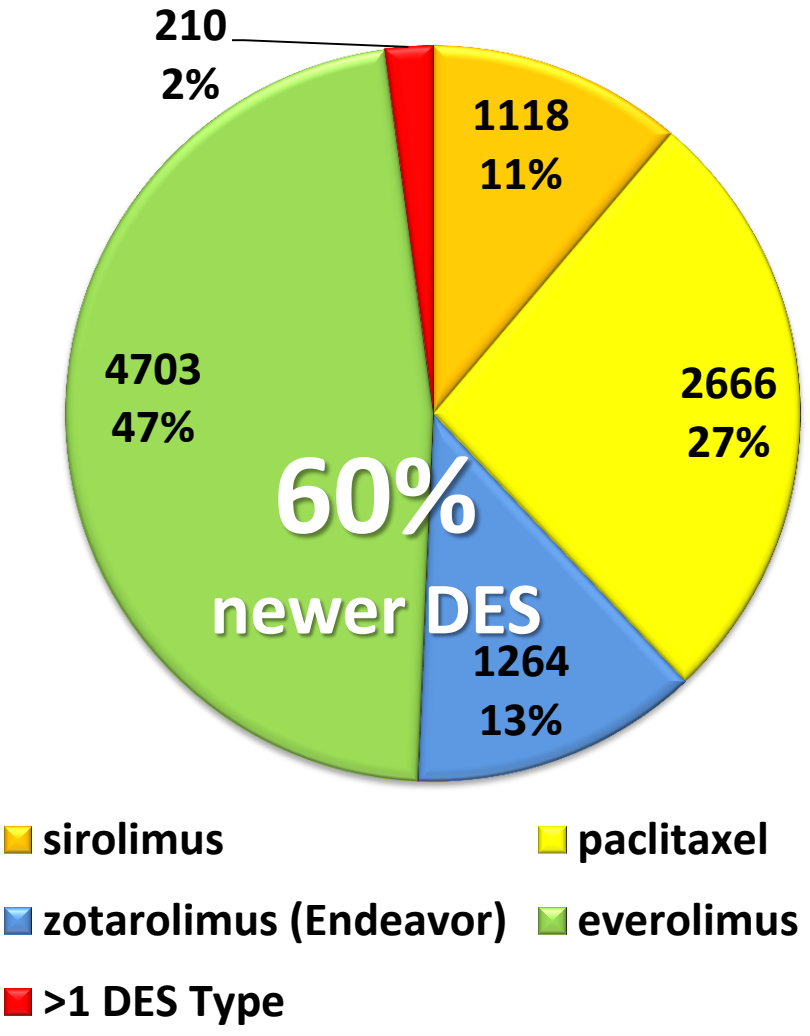
Stent Thrombosis Risk Factors at Index Procedure

DAPT STUDY

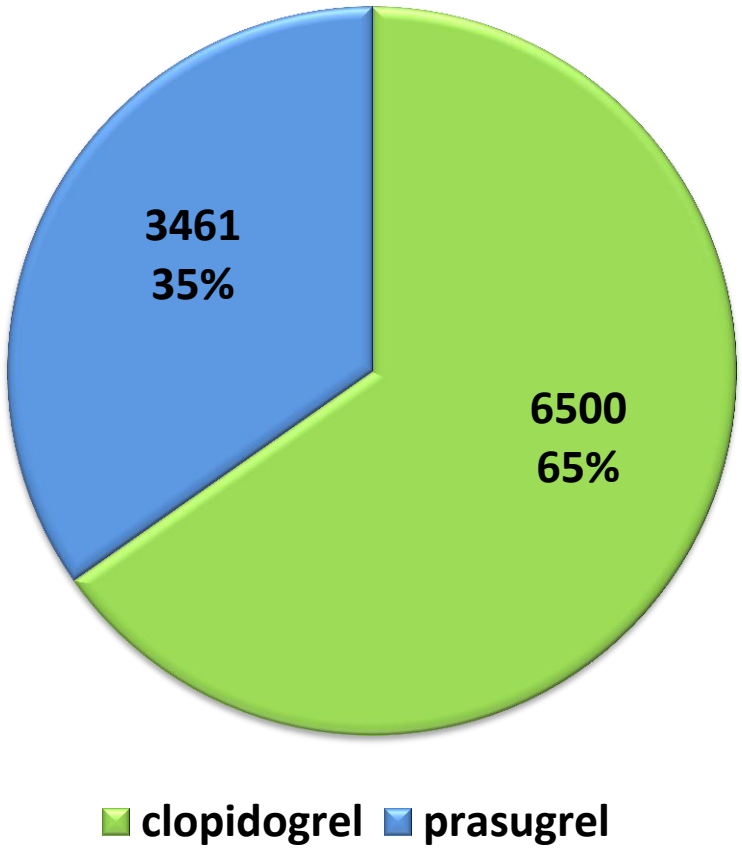
	Thienopyridine N=5020	Placebo N=4941	P-value
STEMI or NSTEMI	26.10%	25.87%	0.80
Renal insufficiency/failure	4.46%	4.00%	0.27
LVEF < 30%	1.72%	1.48%	0.40
> 2 vessels stented	0.38%	0.59%	0.15
> 2 lesions per vessel	1.85%	1.90%	0.88
Lesion length ≥ 30 mm	10.04%	10.15%	0.87
Bifurcation lesion	6.49%	6.52%	0.97
In stent restenosis of DES	3.12%	3.19%	0.86
Vein bypass graft	2.53%	3.10%	0.09
Unprotected left main	0.38%	0.47%	0.54
Thrombus-containing lesion	11.83%	11.71%	0.87
Prior brachytherapy	0.26%	0.26%	1.00
Any Risk Factor	50.73%	50.99%	0.81

Stent & Drug Types

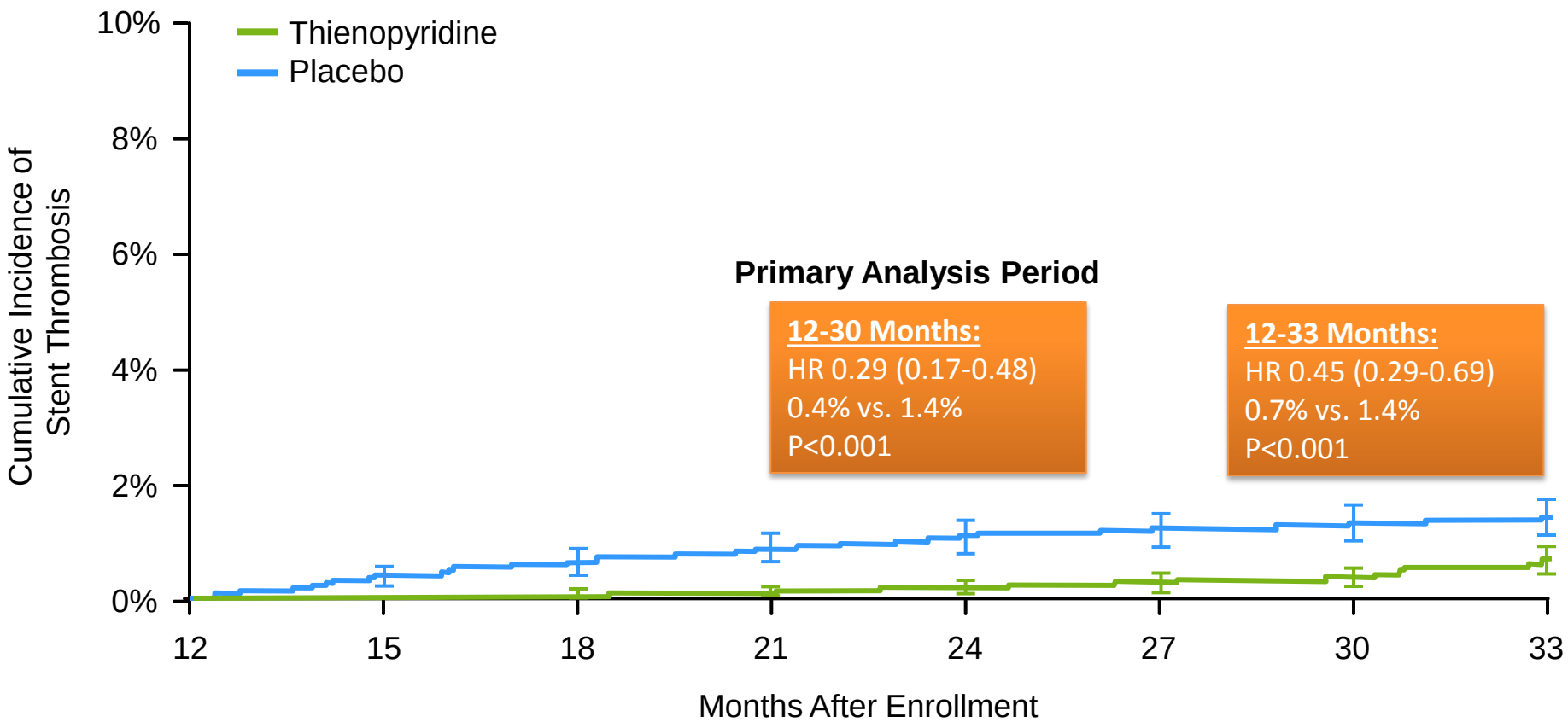
Drug Eluting Stent Type



Thienopyridine Type

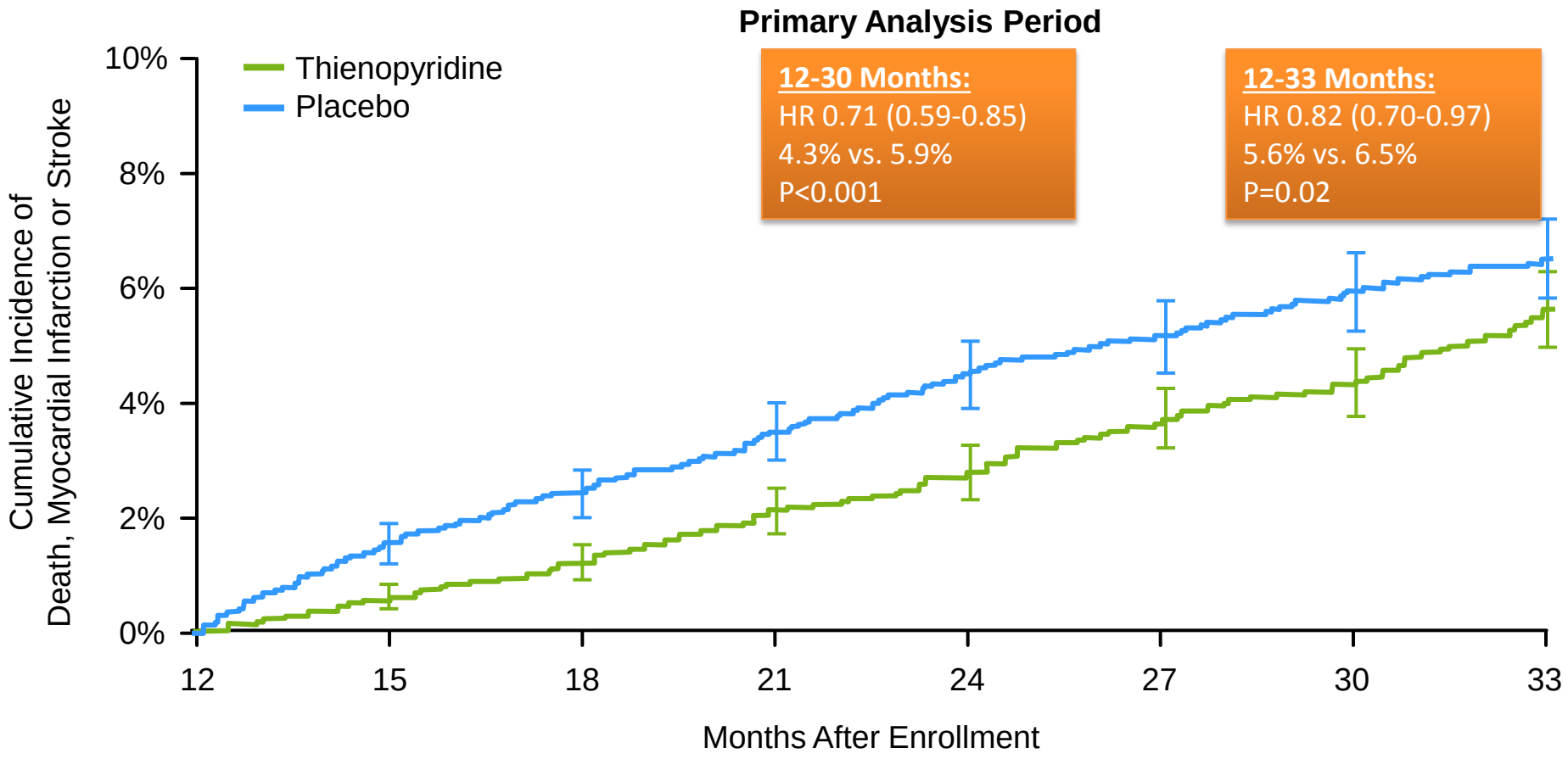


Co-Primary Effectiveness End Point
Stent Thrombosis



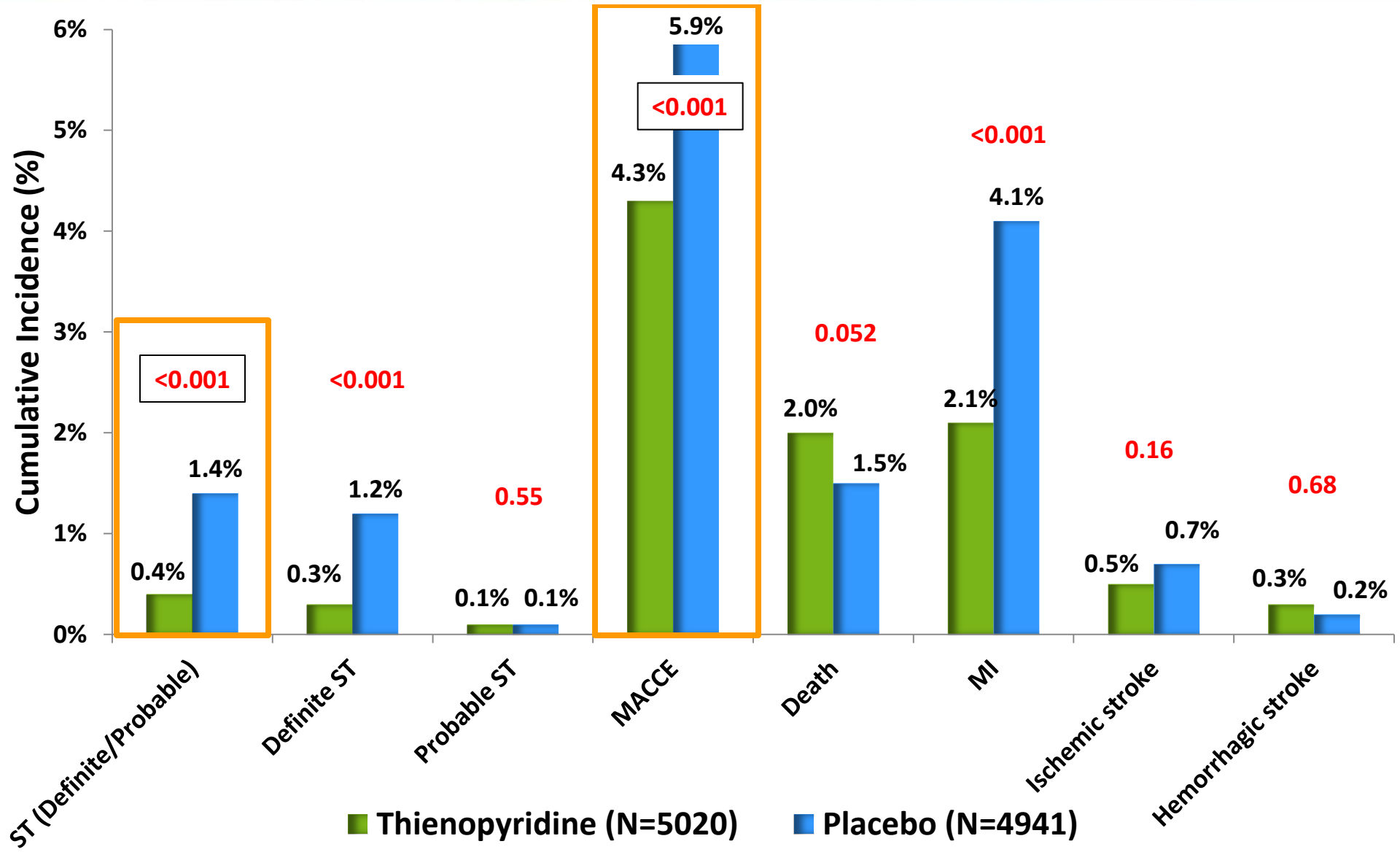
# At Risk								
Thienopyridine	5020	4934	4870	4828	4765	4686	4642	3110
Placebo	4941	4845	4775	4721	4651	4603	4556	3105

Co-Primary Effectiveness End Point MACCE

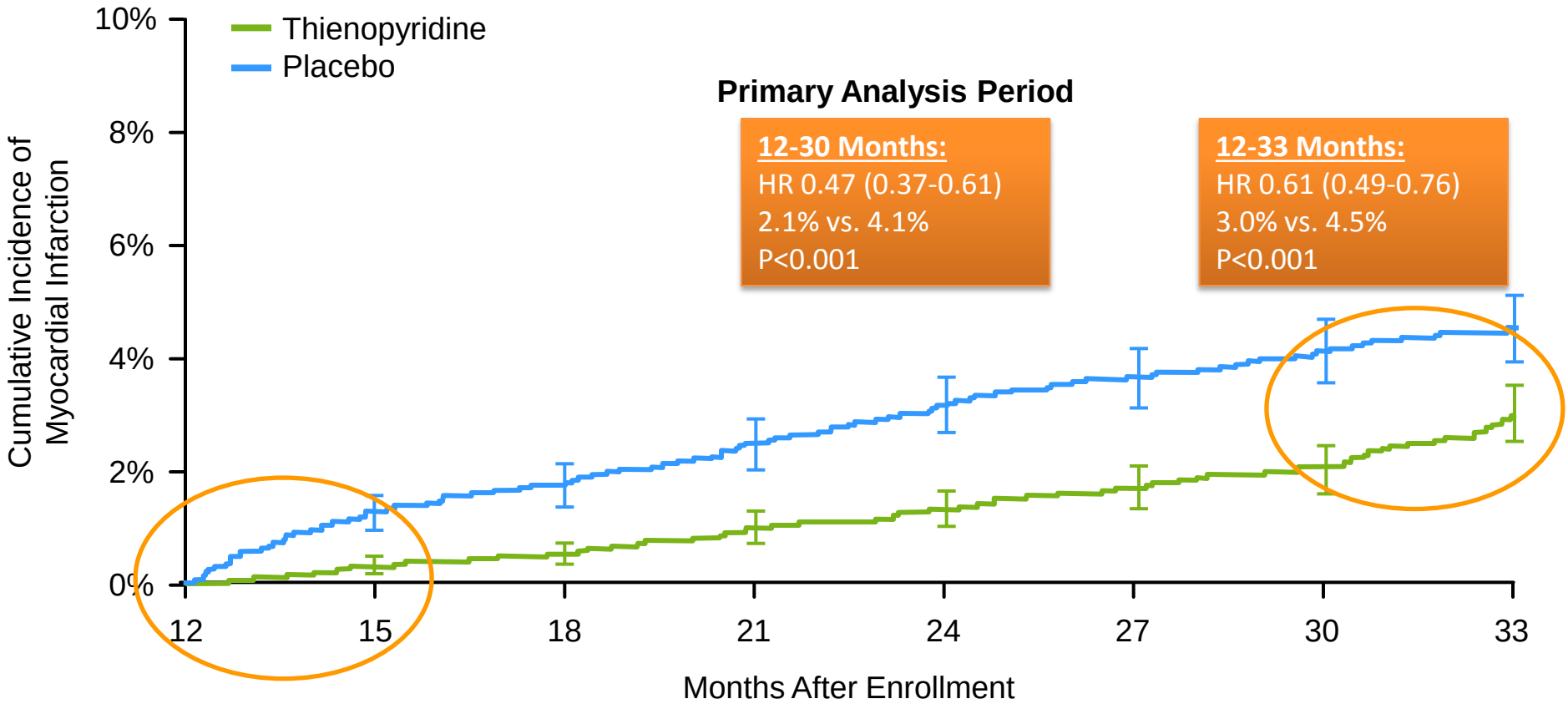


# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

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

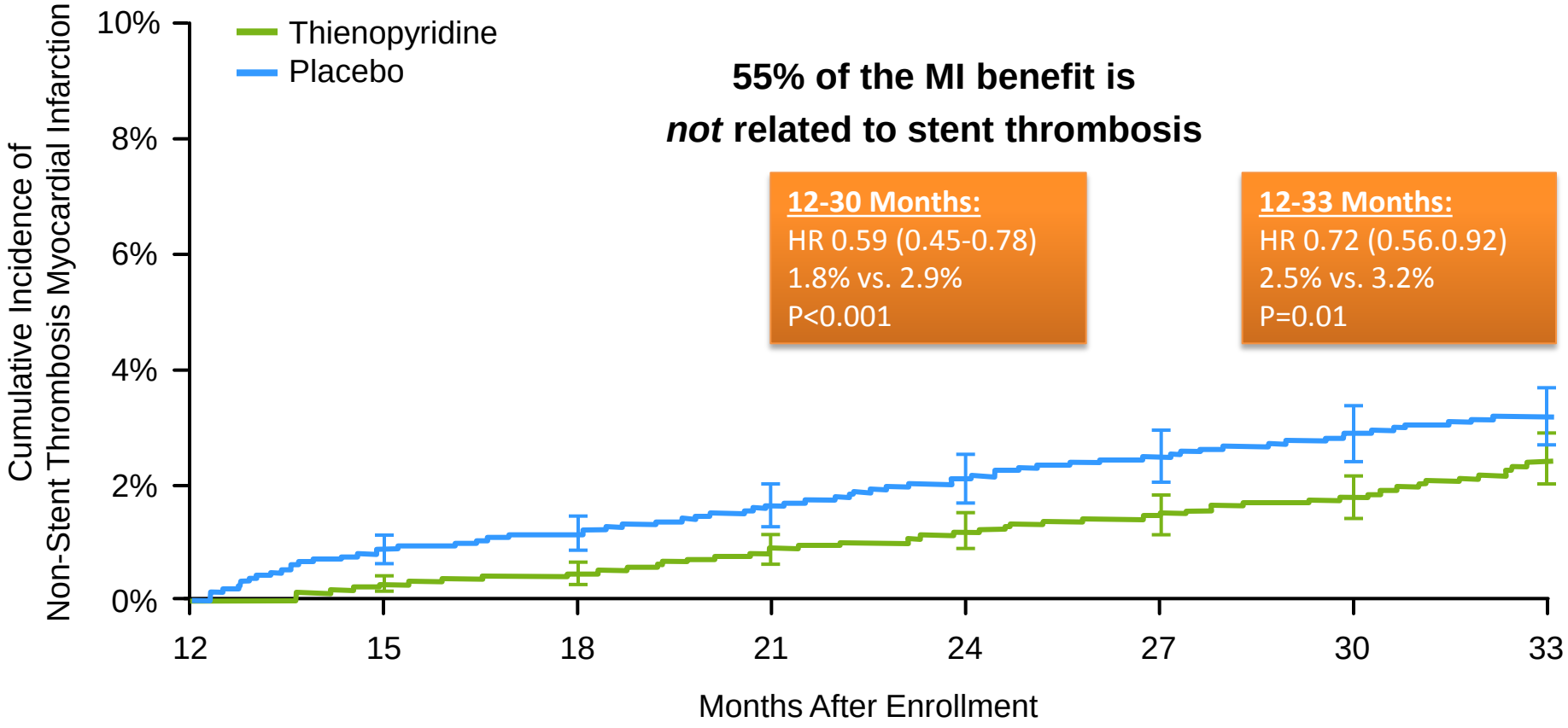


Myocardial Infarction



# At Risk								
Thienopyridine	5020	4920	4849	4789	4717	4634	4580	3051
Placebo	4941	4804	4727	4653	4565	4501	4440	3012

Non-Stent Thrombosis Myocardial Infarction

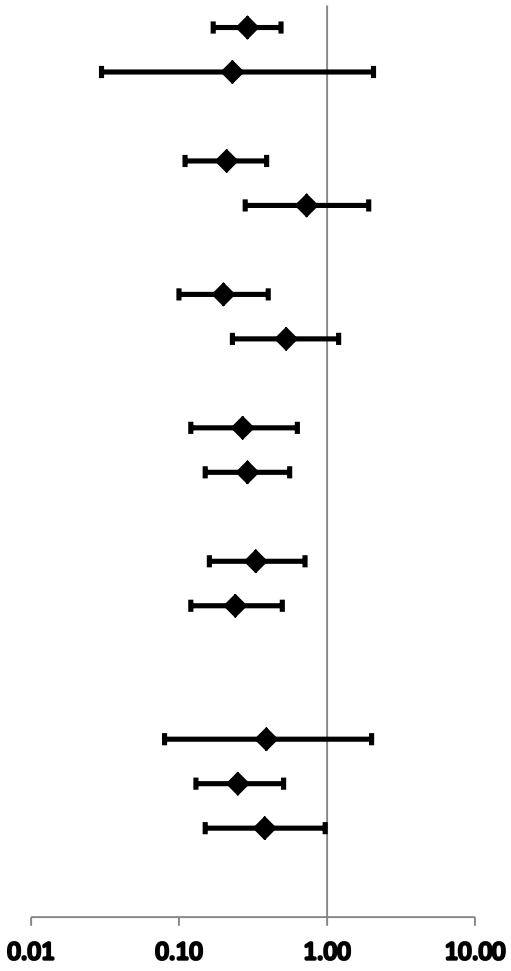


# At Risk								
Thienopyridine	5020	4920	4851	4792	4721	4641	4588	3066
Placebo	4941	4820	4751	4686	4607	4547	4491	3052

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

DAPT STUDY

Factor	N	HR and 95% CI	Interaction P
< 75 Years	N=8929	0.29 (0.17,0.49)	0.84
>= 75 Years	N=1032	0.23 (0.03,2.06)	
Male	N=7435	0.21 (0.11,0.39)	0.04
Female	N=2526	0.73 (0.28,1.91)	
No diabetes	N=6924	0.20 (0.10,0.40)	0.08
Diabetes	N=3037	0.53 (0.23,1.20)	
No Risk Factors for ST	N=5162	0.27 (0.12,0.63)	0.89
Risk Factors for ST	N=4799	0.29 (0.15,0.56)	
Clopiodogrel	N=6500	0.33 (0.16,0.71)	0.54
Prasugrel	N=3461	0.24 (0.12,0.50)	
Sirolimus	N=1118	NA*	
Zotarolimus	N=1264	0.39 (0.08,2.00)	0.76
Paclitaxel	N=2666	0.25 (0.13,0.51)	
Everolimus	N=4703	0.38 (0.15,0.97)	

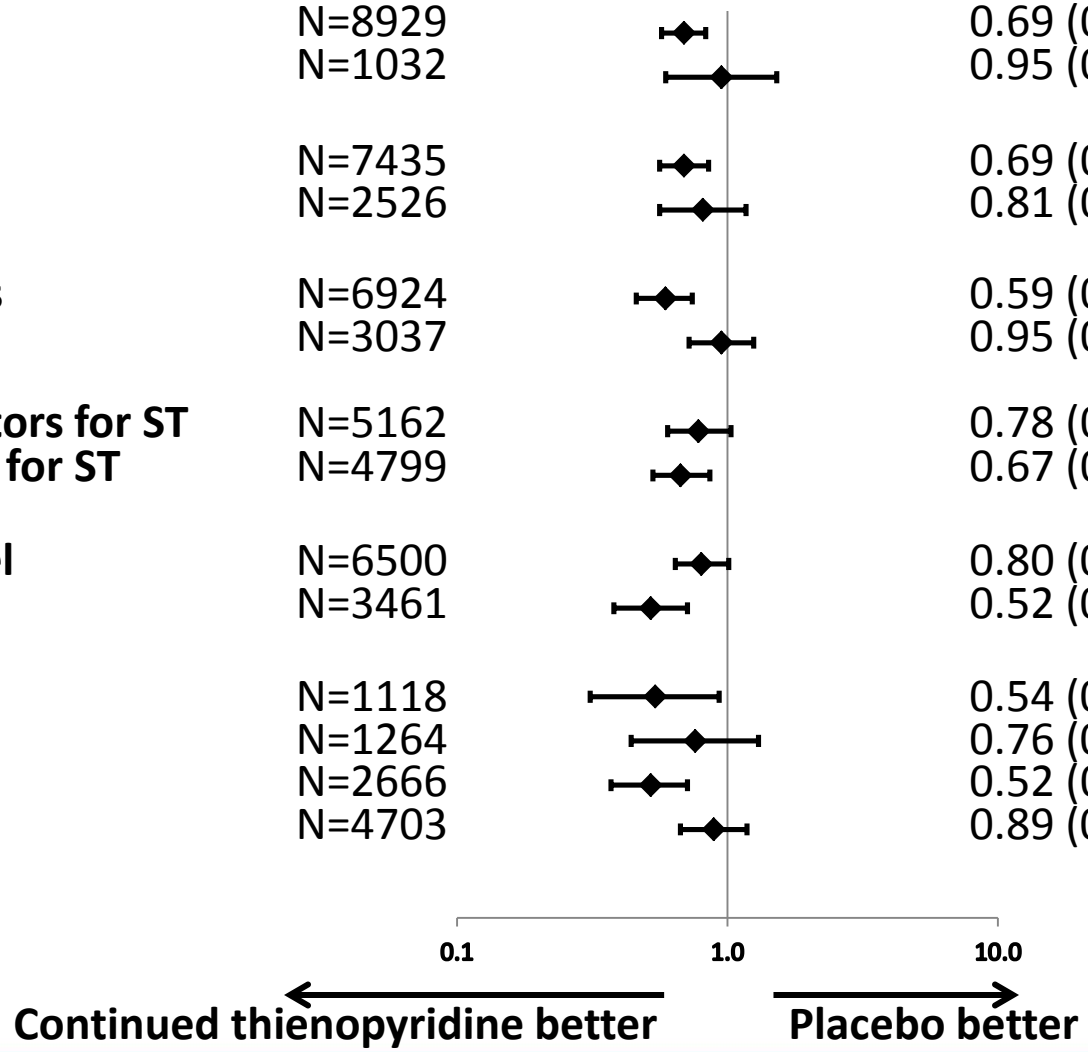


*due to zero events in thienopyridine arm

Consistency of Treatment Effect MACCE (12-30 Months)

DAPT STUDY

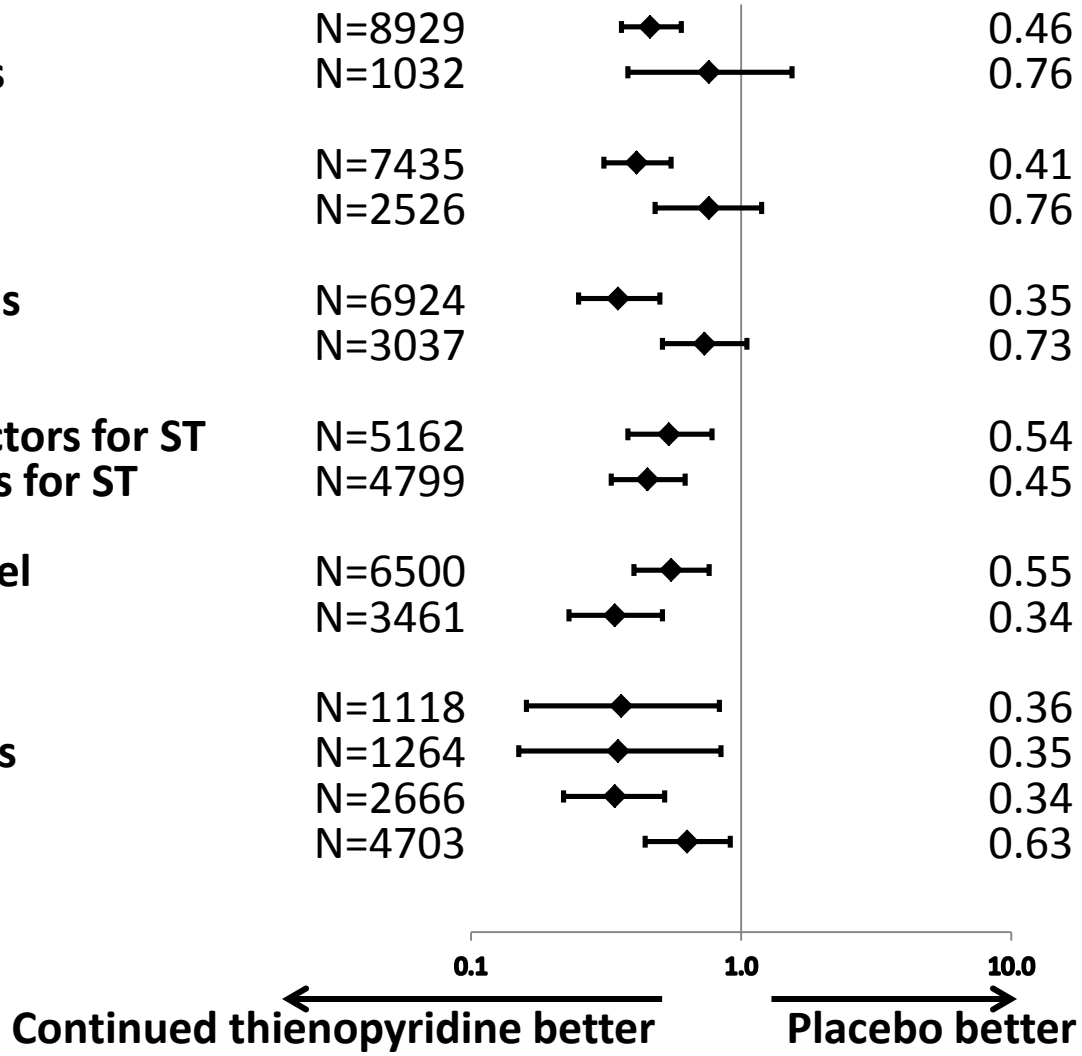
Factor	N	HR and 95% CI	Interaction P
< 75 Years	N=8929	0.69 (0.57,0.83)	0.22
>= 75 Years	N=1032	0.95 (0.59,1.52)	
Male	N=7435	0.69 (0.56,0.85)	0.46
Female	N=2526	0.81 (0.56,1.17)	
No diabetes	N=6924	0.59 (0.46,0.74)	0.01
Diabetes	N=3037	0.95 (0.72,1.25)	
No Risk Factors for ST	N=5162	0.78 (0.60,1.03)	0.41
Risk Factors for ST	N=4799	0.67 (0.53,0.86)	
Clopiodogrel	N=6500	0.80 (0.64,1.01)	0.03
Prasugrel	N=3461	0.52 (0.38,0.71)	
Sirolimus	N=1118	0.54 (0.31,0.93)	
Zotarolimus	N=1264	0.76 (0.44,1.30)	0.048
Paclitaxel	N=2666	0.52 (0.37,0.71)	
Everolimus	N=4703	0.89 (0.67,1.18)	



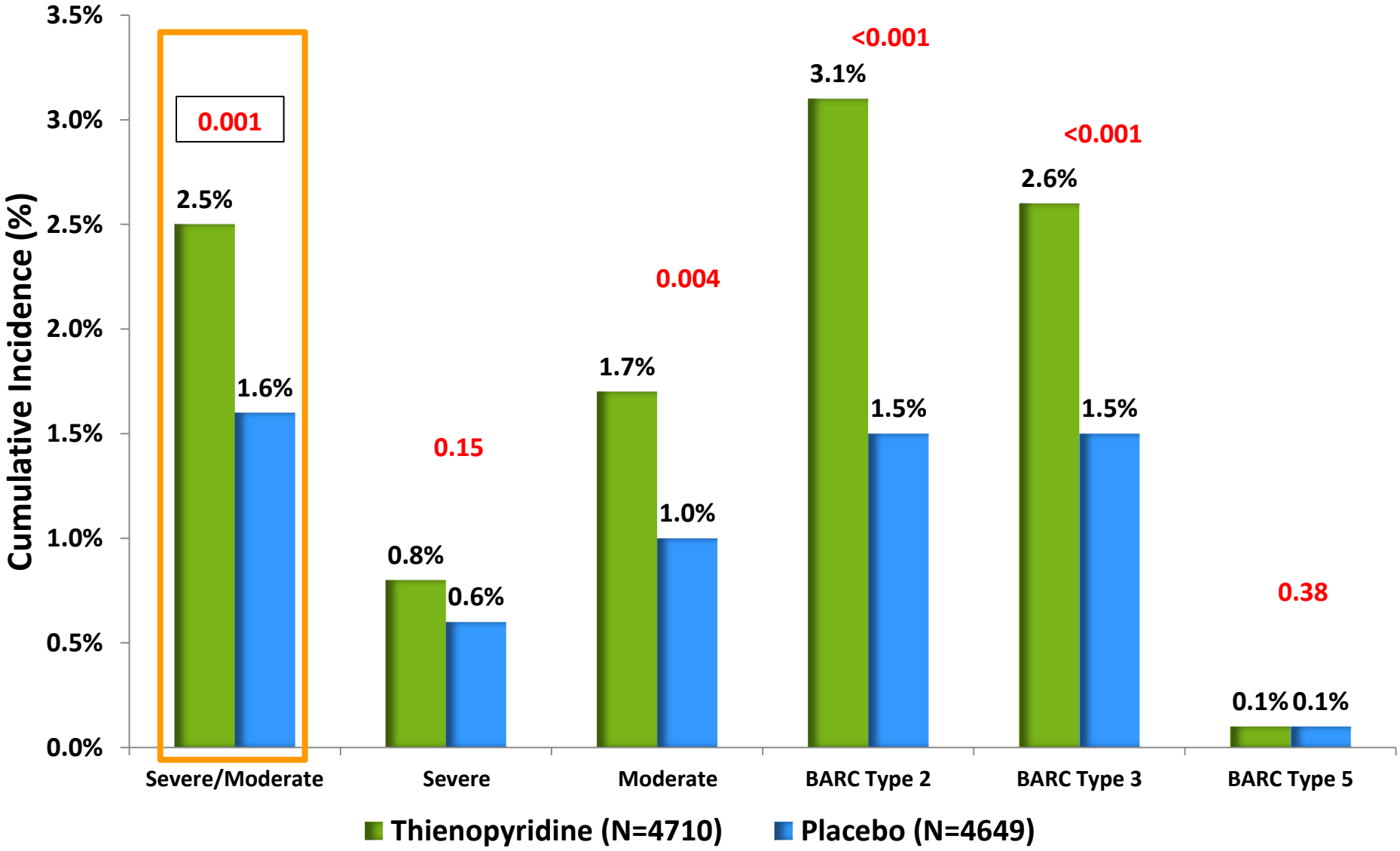
Consistency of Treatment Effect Myocardial Infarction (12-30 Months)

DAPT STUDY

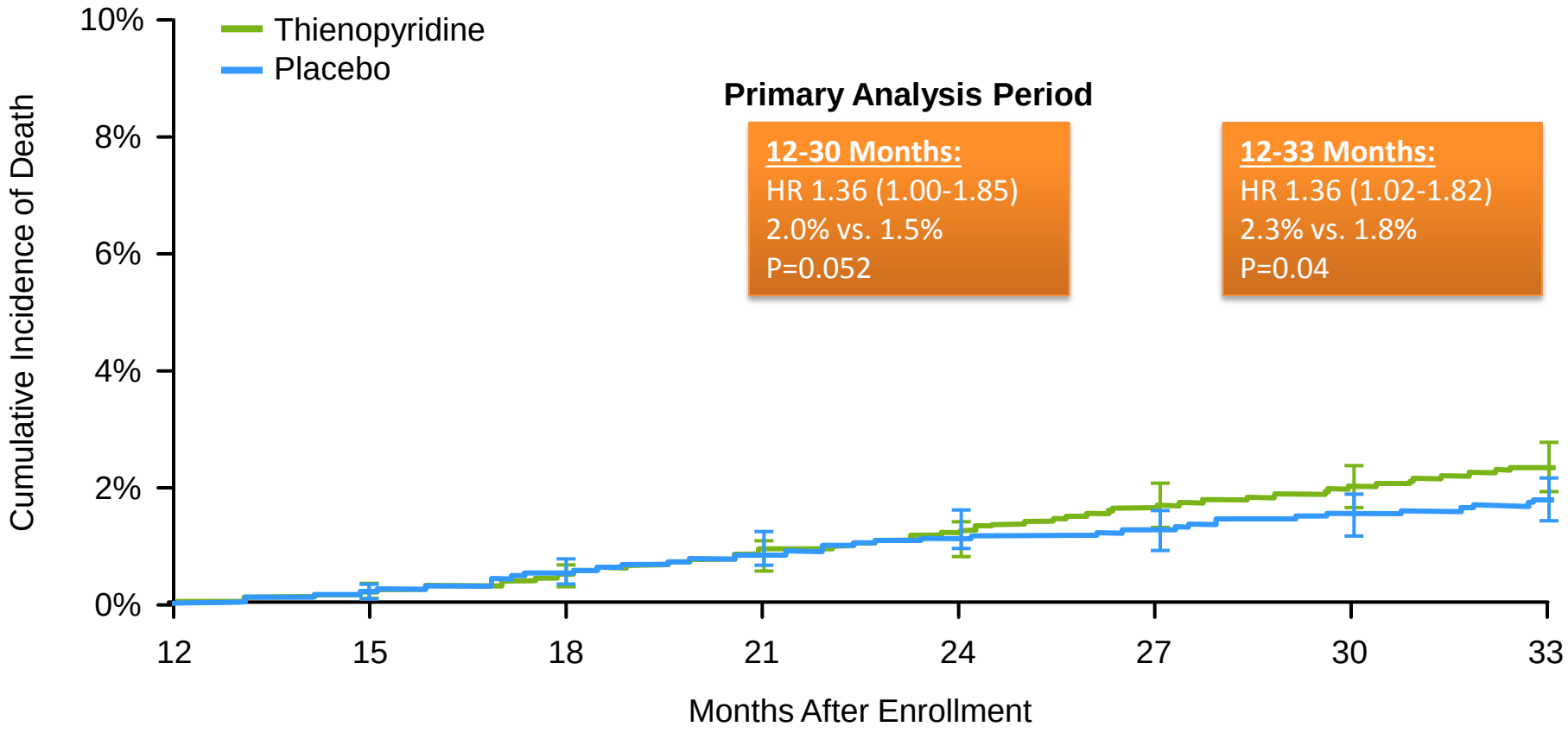
Factor	N	HR and 95% CI	Interaction P
< 75 Years	N=8929	0.46 (0.36,0.60)	0.19
>= 75 Years	N=1032	0.76 (0.38,1.54)	
Male	N=7435	0.41 (0.31,0.55)	0.03
Female	N=2526	0.76 (0.48,1.19)	
No diabetes	N=6924	0.35 (0.25,0.50)	0.004
Diabetes	N=3037	0.73 (0.51,1.05)	
No Risk Factors for ST	N=5162	0.54 (0.38,0.78)	0.46
Risk Factors for ST	N=4799	0.45 (0.33,0.62)	
Clopiodogrel	N=6500	0.55 (0.40,0.76)	0.06
Prasugrel	N=3461	0.34 (0.23,0.51)	
Sirolimus	N=1118	0.36 (0.16,0.83)	
Zotarolimus	N=1264	0.35 (0.15,0.84)	0.11
Paclitaxel	N=2666	0.34 (0.22,0.52)	
Everolimus	N=4703	0.63 (0.44,0.91)	



Primary Safety End Point & Components: 12-30 Months



All-Cause Mortality



# At Risk								
Thienopyridine	5020	4936	4875	4835	4777	4703	4663	3139
Placebo	4941	4866	4805	4761	4700	4659	4618	3159

All-Cause Mortality

12-30 Months				
	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	**98 (2.0%)**	**74 (1.5%)**	**0.052**	**24 (0.5%)**
Cardiac	45 (0.9%)	47 (1.0%)	0.98	-2 (-0.1%)
Vascular	5 (0.1%)	5 (0.1%)	0.98	0 (-)
Non-Cardiovascular	48 (1.0%)	22 (0.5%)	0.002	26 (0.5%)

12-33 Months				
	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	**113 (2.3%)**	**84 (1.8%)**	**0.04**	**29 (0.5%)**
Cardiac	54(1.1%)	49 (1.0%)	0.53	5 (0.1%)
Vascular	7 (0.1%)	6 (0.1%)	0.81	1 (-)
Non-Cardiovascular	52 (1.1%)	29 (0.6%)	0.01	23 (0.5%)

Cumulative incidence is presented according to Kaplan-Meier method

Additional Blinded Adjudication and Meta-Analysis

Additional Adjudication and Analysis

Additional Adjudication Results, Non-Cardiovascular Deaths, 12-33 Months			
Relatedness for Deaths*	**Thienopyridine N=5020**	**Placebo N=4941**	**P-value**
Bleeding-Related Death	11 (0.22%)	3 (0.06%)	0.057
Trauma-Related Death	9 (0.18%)	2 (0.04%)	0.07
Cancer-Related Death	31 (0.62%)	14 (0.28%)	0.02

*not mutually exclusive

Nine (7 vs. 2) of the 11 trauma-related deaths were also bleeding-related.
Three (3 vs. 0) of the 45 cancer-related deaths were also bleeding-related.

Site-Reported Cancer Incidence, 12-33 Months			
	Thienopyridine	**Placebo**	**P-value**
Cancer reported after randomization	102 (2.03%)	80 (1.62%)	0.14

Cancer Prior to Enrollment and Randomization

Site-Reported Cancer			
	Thienopyridine	Placebo	P-value
History of cancer prior to enrollment	488 (9.8%)	466 (9.5%)	0.63

Blinded adjudication results:
Among subjects who died of cancer, 9 were related to cancers known to be present ***prior*** to enrollment and randomization: 8 in the thienopyridine group, and 1 in the placebo group. Sensitivity analysis without these subjects is shown below:

	Thienopyridine N=5012	Placebo N=4940	P-value	All N=9952
Cancer Related Death	25 (0.50%)	14 (0.28%)	0.11	39 (0.39%)
Non-Cardiovascular Death	45 (0.90%)	28 (0.57%)	0.06	73 (0.73%)
All –Cause Mortality	105 (2.09%)	83 (1.68%)	0.14	188 (1.89%)

Limitations

- Net impact of ischemic and bleeding events not quantified, yet decision analysis suggests that small absolute differences in cardiovascular event rates may be sufficient to counterbalance bleeding risks.[1]
- Whether the treatment benefits will be generalizable to other stent types or non-thienopyridine P2Y12 inhibitors is unknown.
- Thienopyridine and stent types not randomized: direct comparisons of different stent or drug types likely confounded. Within-subgroup estimates of treatment effect are underpowered.
- Non-cardiovascular death difference is of uncertain significance, possibly explained by chance imbalance among enrolled subjects, and was not expected based on prior data.

[1]Garg P, Galper BZ, Cohen DJ, Yeh RW, Mauri L. Balancing the Risks of Bleeding and Stent Thrombosis: A Decision Analytic Model to Compare Duration of Dual Antiplatelet Therapy after Drug-Eluting Stents. *Am Heart J* Published online November 10, 2014.

Randomized Trials Thienopyridine+Aspirin vs. Aspirin Alone (N=69644)

Study Name	Clinical Setting	Randomized Treatment Arms	Sample Size			On-Treatment Follow-Up Duration (Months)	Difference in DAPT Duration (Months)
			Total	Study Arm	Control Arm		
CASPAR	Surgical Peripheral Revascularization	DAPT 6-24 mos vs. ASA alone	851	425	426	24	11·6**
SPS3	Lacunar stroke	DAPT vs. ASA alone	3020	1503	1517	40·8*	40·8*
CHARISMA	Documented or high-risk for CVD	DAPT vs. ASA	15603	7802	7801	28**	28**
ACTIVE-A	Atrial fibrillation	DAPT vs. ASA	7554	3772	3782	43·2**	43·2**
OPTIMIZE	CAD - PCI	DAPT 12 mos vs. DAPT 3 mos	3119	1556	1553	12	9
EXCELLENT	CAD - PCI	DAPT 12 mos vs. DAPT 6 mos	1443	721	722	12	6
RESET	CAD - PCI	DAPT 12 mos vs. DAPT 3 mos	2055	1058	997	12	9
CREDO	CAD - PCI	DAPT 12 mos vs. DAPT 1 mos	2116	1053	1063	12	11
PRODIGY	CAD - PCI	DAPT 24 mos vs. DAPT 6 mos	1970	987	983	24	18
CURE	CAD - ACS	DAPT vs. ASA	12562	6259	6303	12	9**
ARCTIC-Interruption	CAD - 1 yr post-PCI	Continued DAPT vs ASA	1259	635	624	17**	17**
DES LATE	CAD - ≥1 yr post-PCI	Continued DAPT vs. ASA	5045	2531	2514	42·0**	42·0**
SECURITY	CAD - PCI	DAPT 12 mos vs. DAPT 6 mos	1399	717	682	12	6
DAPT	CAD - 1 yr post-PCI	Continued DAPT 18 mos vs. ASA	11648	5862	5786	18	18

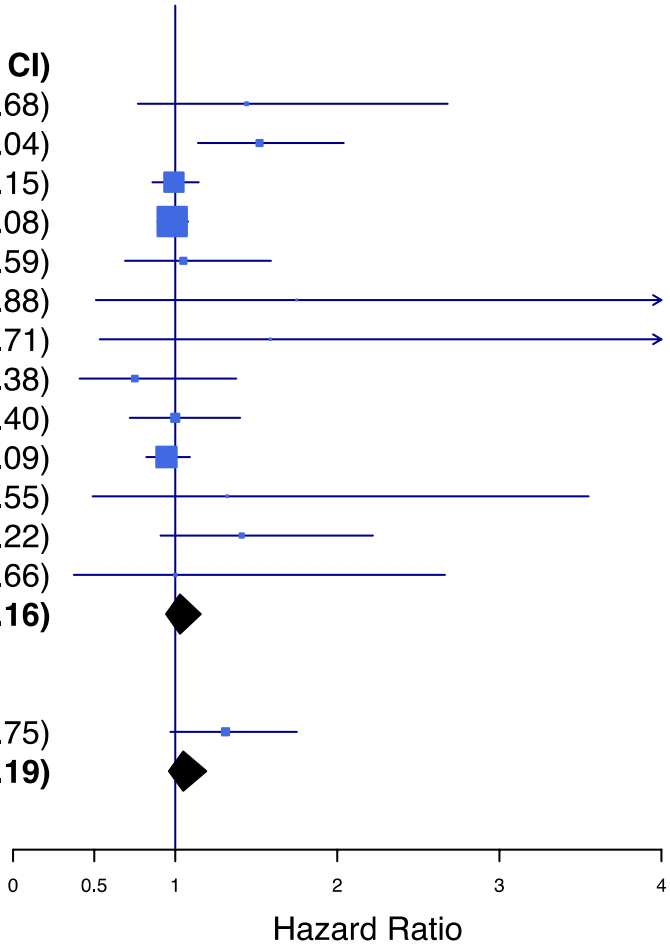
* Mean ** Median

ACS, acute coronary syndrome; ASA, aspirin; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; mos, months; PCI, percutaneous coronary intervention; yr, year

Elmariah S, Mauri L, Doros G, O'Neill KE, Steg PG, Kereiakes DJ, Yeh RW. . Extended Duration Dual Antiplatelet Therapy and Mortality: A Systematic Review and Meta-analysis. *The Lancet*. Online ahead of print November 16, 2014.

Randomized Trials of Thienopyridine+Aspirin vs. Aspirin Alone; All-Cause Mortality

Study	Study Arm N (# Events)	Control Arm N (# Events)	HR (95% CI)
CASPAR	425(24)	426(17)	1.44 (0.77, 2.68)
SPS3	1503(113)	1517(77)	1.52 (1.14, 2.04)
CHARISMA	7802(371)	7801(374)	0.99 (0.86, 1.15)
ACTIVE	3772(825)	3782(841)	0.98 (0.89, 1.08)
OPTIMIZE	1556(45)	1553(43)	1.05 (0.69, 1.59)
EXCELLENT	721(7)	722(4)	1.75 (0.51, 5.88)
RESET	1058(8)	997(5)	1.59 (0.54, 4.71)
CREDO	1053(18)	1063(24)	0.75 (0.41, 1.38)
PRODIGY	987(65)	983(65)	1.00 (0.72, 1.40)
CURE	6259(369)	6303(390)	0.95 (0.82, 1.09)
ARCTIC–Interruption	635(7)	624(9)	1.32 (0.49, 3.55)
DES LATE	2531(46)	2514(32)	1.41 (0.91, 2.22)
SECURITY	717(8)	682(8)	1.00 (0.38, 2.66)
Overall(DAPT NOT Included)	**29019(1906)**	**28967(1889)**	**1.03 (0.94, 1.16)**
Q = 14.87, p = 0.25; I2 = 12.6%			
DAPT	5862(106)	5786(84)	1.31 (0.97, 1.75)
Overall(DAPT Included)	**34881(2012)**	**34753(1973)**	**1.05 (0.96, 1.19)**
Q = 17.68, p = 0.17; I2 = 26.5%			



Elmariah S, Mauri L, Doros G, O'Neill KE, Steg PG, Kereiakes DJ, Yeh RW. . Extended Duration Dual Antiplatelet Therapy and Mortality: A Systematic Review and Meta-analysis. *The Lancet*. Online ahead of print November 16, 2014.

Conclusions

- Following drug-eluting stent treatment, continuation of thienopyridine plus aspirin beyond one year reduces the risk of stent thrombosis and MACCE compared with aspirin alone.
  - This treatment benefit was driven by concurrent reductions in myocardial infarction related to the stent and occurring in other locations.
  - The treatment benefit on ST and MI was consistent across all stent and drug types and across subjects with higher or lower risk of events.
- The benefit of extended thienopyridine treatment was tempered by an increase in bleeding events. Severe and/or fatal bleeding was uncommon.

Conclusions (2)

- An unexpected finding was that all-cause mortality during the treatment period was higher in the continued thienopyridine group, driven by an increase in non-cardiovascular deaths. This finding, not entirely accounted for by bleeding, appeared to reflect a chance imbalance in subjects with known cancer prior to enrollment who were subsequently randomized.

- Meta-analysis of >69,000 subjects in randomized trials does not show a difference in mortality or non-cardiovascular mortality.

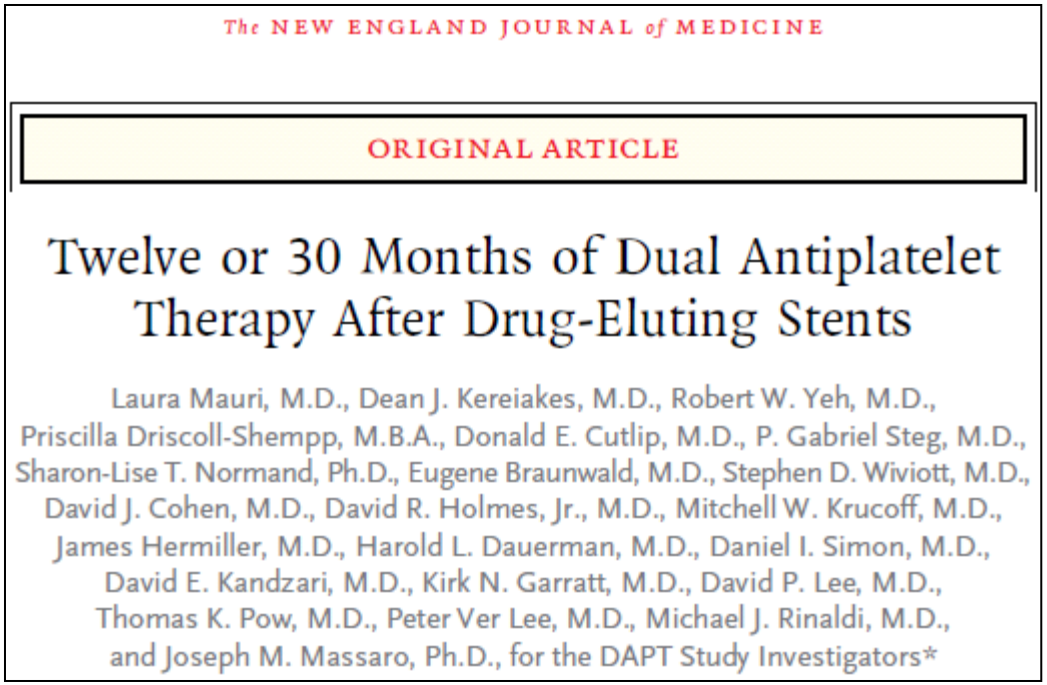
- Continued thienopyridine therapy markedly reduces both stent-related and other ischemic events beyond the stent-treated region in patients who have tolerated one year of DAPT after drug-eluting coronary stent treatment.

Additional results to be presented Tuesday
Dean J. Kereiakes November 18, 2014 4:51 – 5:01 pm, S100ab

“Comparison of Ischemic and Bleeding Events After Drug-Eluting Stents or Bare Metal Stents: Results from the DAPT Study”

- DES non-inferior to BMS on ST and MACCE (over 0-33m follow up) and superior on ST in prospective propensity-matched analysis of 10,026 subjects
- Results in BMS-treated subjects randomized to continued thienopyridine vs placebo (N=1,687) are consistent with DES results on ST (HR 0.49, respectively) and bleeding.
- Randomized BMS-treated cohort did not demonstrate a difference in mortality for continued thienopyridine vs. placebo.

Thank you to the patients and investigators who made this study possible.



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ORIGINAL ARTICLE

Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents

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Mauri L, Kereiakes DJ, Yeh, RW, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-eluting Stents. *New England Journal of Medicine*. Online ahead of print November 16, 2014.

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