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# **DAPT as Part of Long Term Secondary Prevention after ACS**

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***WCN Congress  
November 19, 2015***

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**TIMI Study Group**



**BRIGHAM AND  
WOMEN'S HOSPITAL**



**HARVARD  
MEDICAL SCHOOL**



# Disclosures

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## **Research Grant Support through BWH:**

**Abbott Laboratories; Amgen; AstraZeneca; Critical Diagnostics; Daiichi-Sankyo; Eisai; Gilead; GlaxoSmithKline; Intarcia; Merck; Roche Diagnostics; Sanofi-aventis; Takeda**

## **Scientific Advisory Boards & Consulting:**

**Alnylam; Amgen; AstraZeneca; Cubist; CVS Caremark; Duke (for DMC for trial sponsored by the Medicines Co.); Intarcia; Merck; MyoKardia**

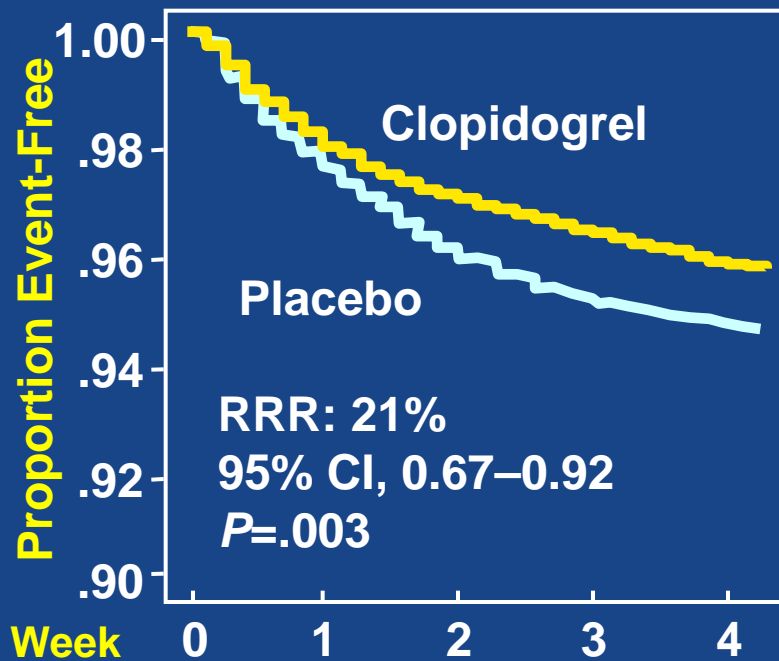
***Investigational, unlabeled and/or unapproved uses of drugs  
or devices will be discussed in this presentation.***



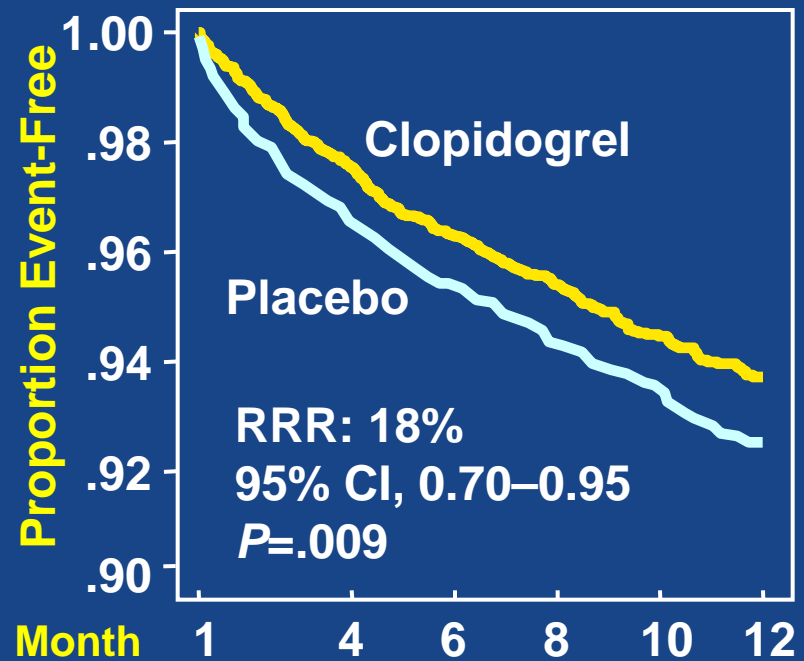
# CURE: Long-term benefit of clopidogrel

12,562 Patients with NSTEMACS (mostly conservatively managed)

CV Death, MI, or Stroke  
First 30 Days



CV Death, MI, or Stroke  
>30 Days–1 Year

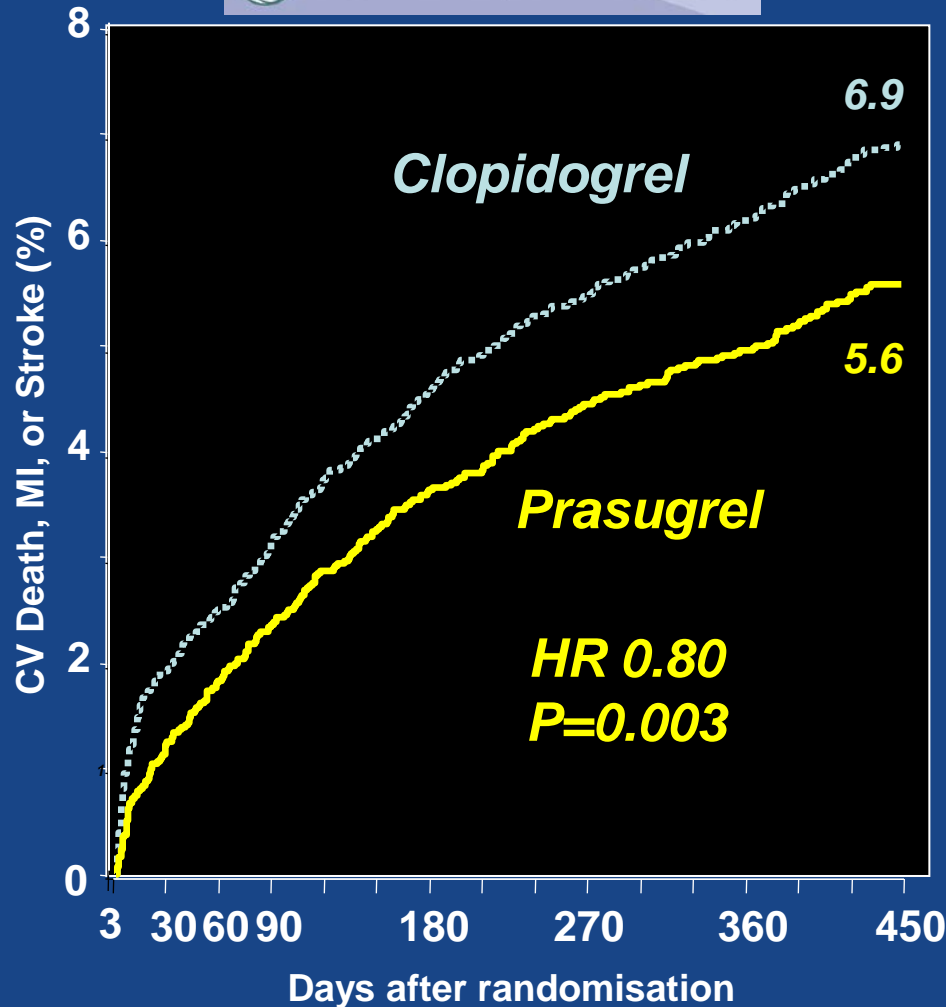


	<u>No. at Risk</u>					<u>No. at Risk</u>					
Clopidogrel	6259	6145	6070	6026	5990	5981	5481	4742	4004	3180	2418
Placebo	6303	6159	6048	5993	5965	5954	5390	4639	3929	3159	2388

Yusuf S, et al. *Circulation*. 2003;107:966-972.

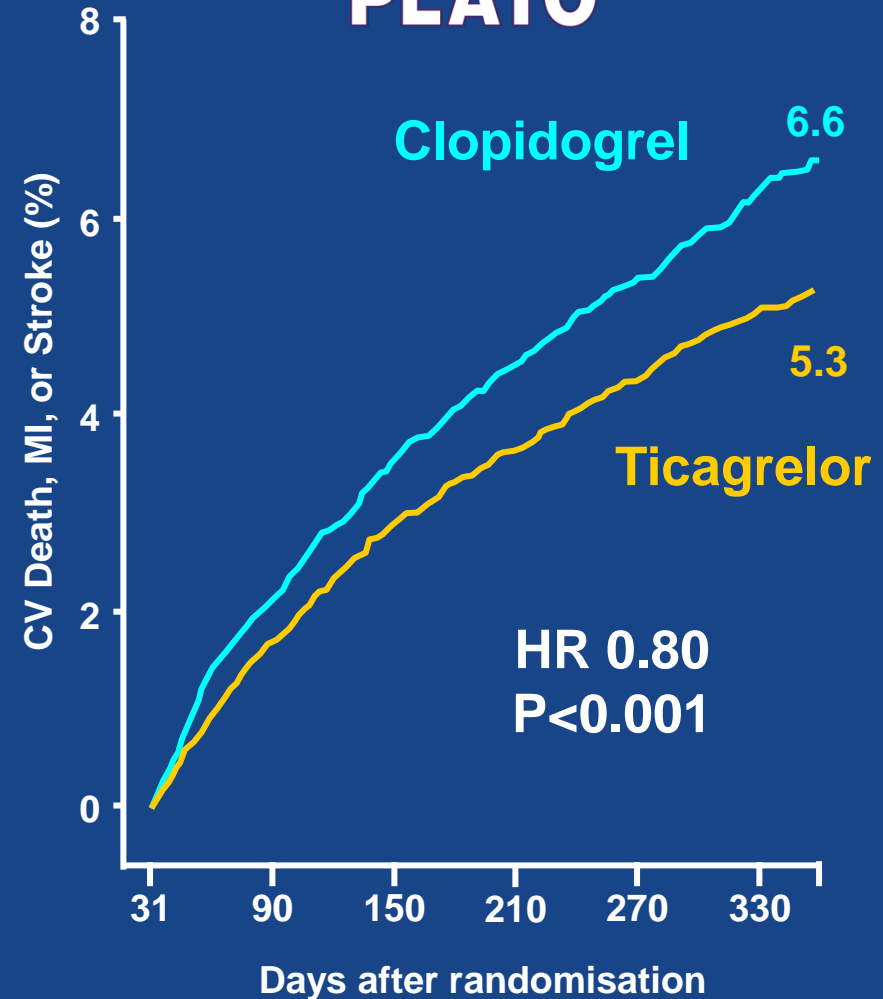
# Continued Divergence of Event Curves With More Potent Long-Term P2Y<sub>12</sub> Inhibition

 **TRITON TIMI-38**



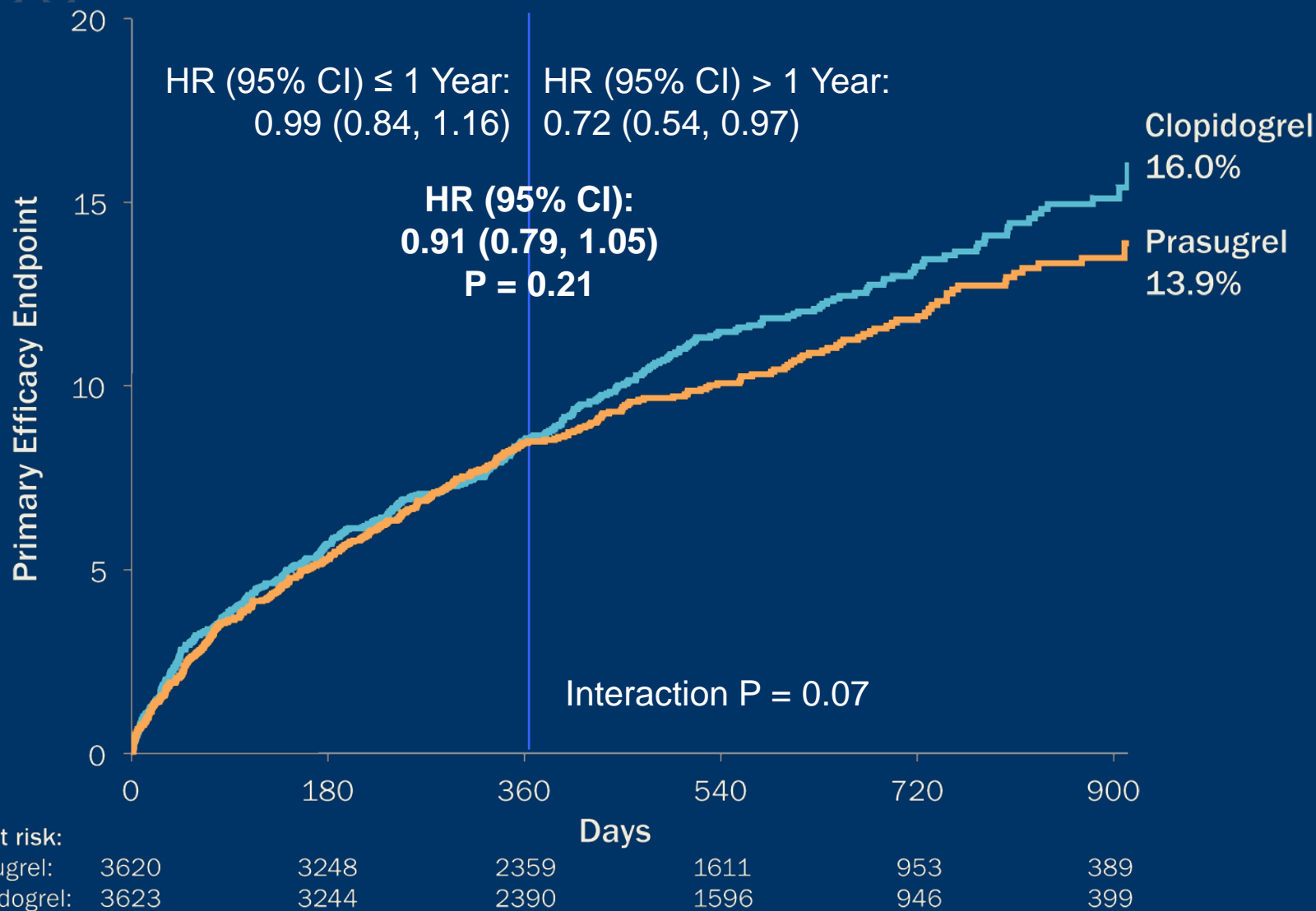
Wiviott SD et al. *NEJM* 2007;357:2001-15

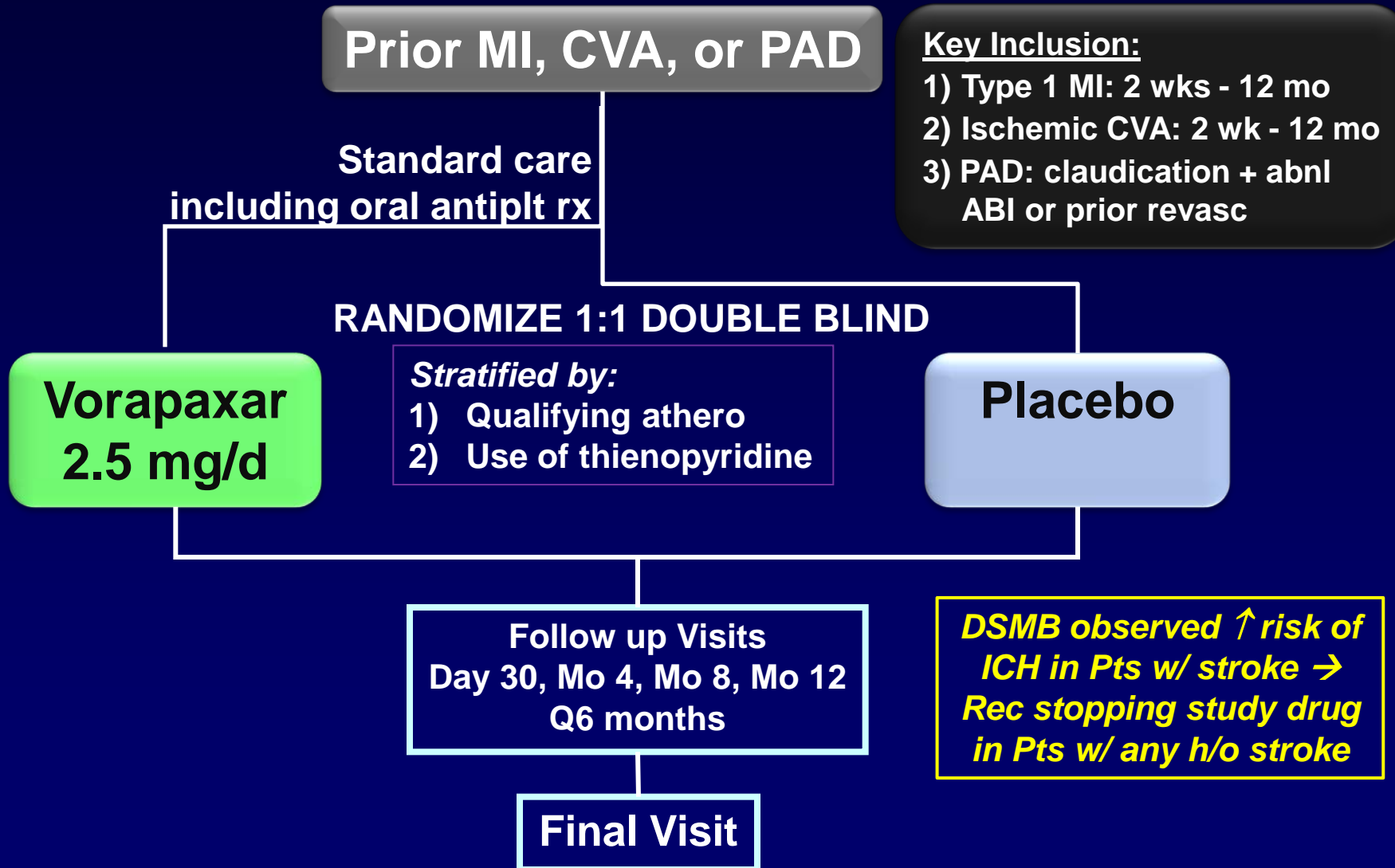
  
**PLATO**



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

# Primary Efficacy Endpoint to 30 Months (Age < 75 years)

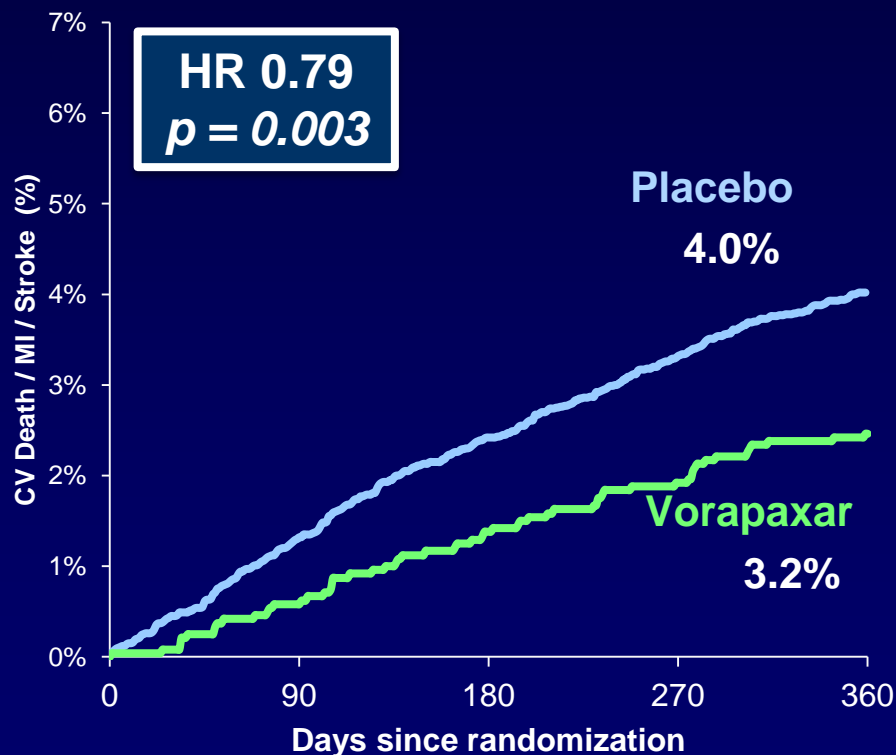




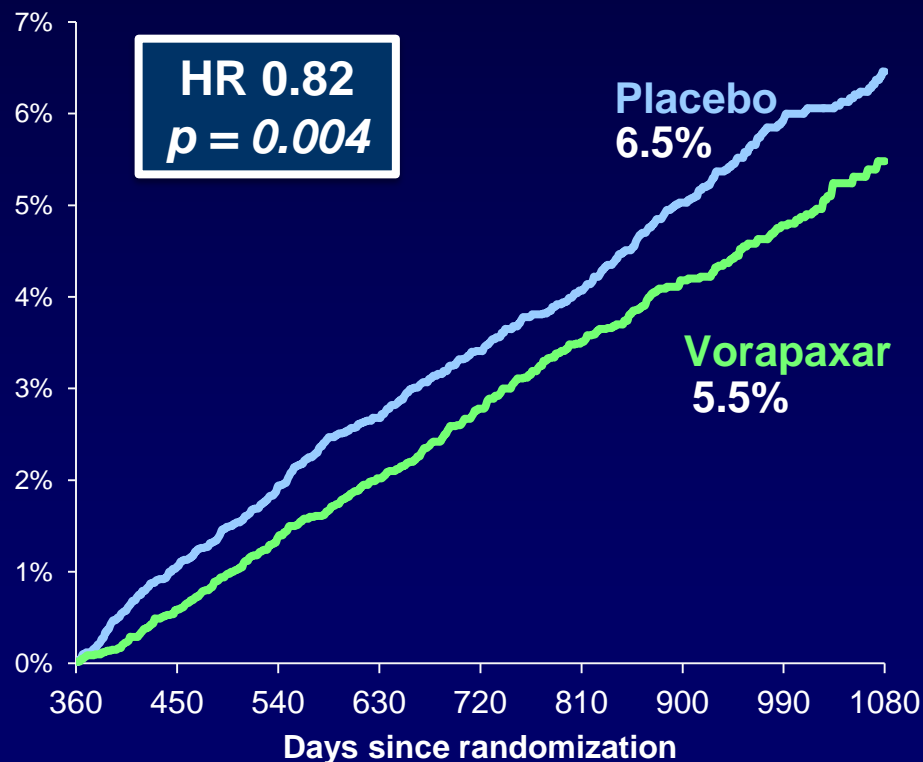
# Efficacy Early and Late

Prior MI Cohort

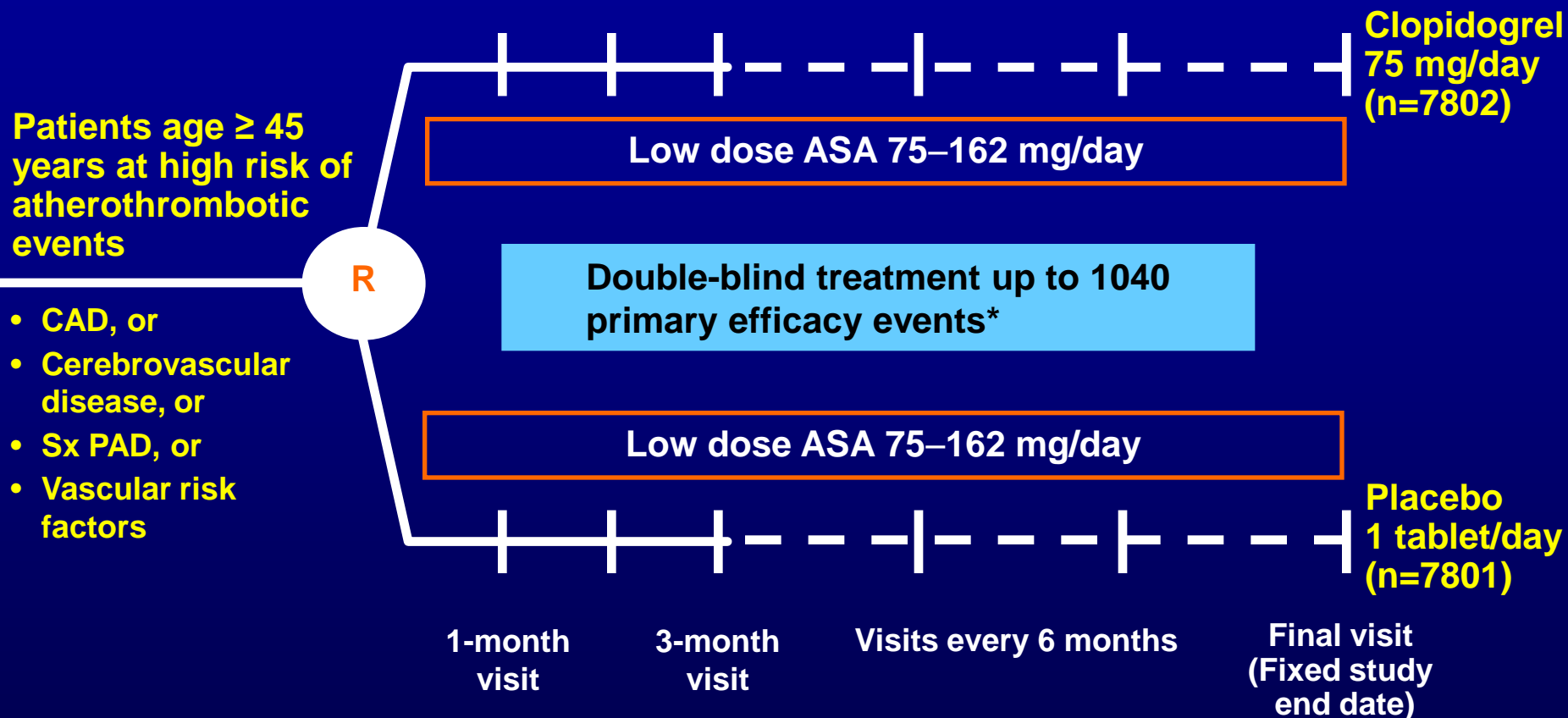
## Days 0 to 360



## Day 360 to 1080



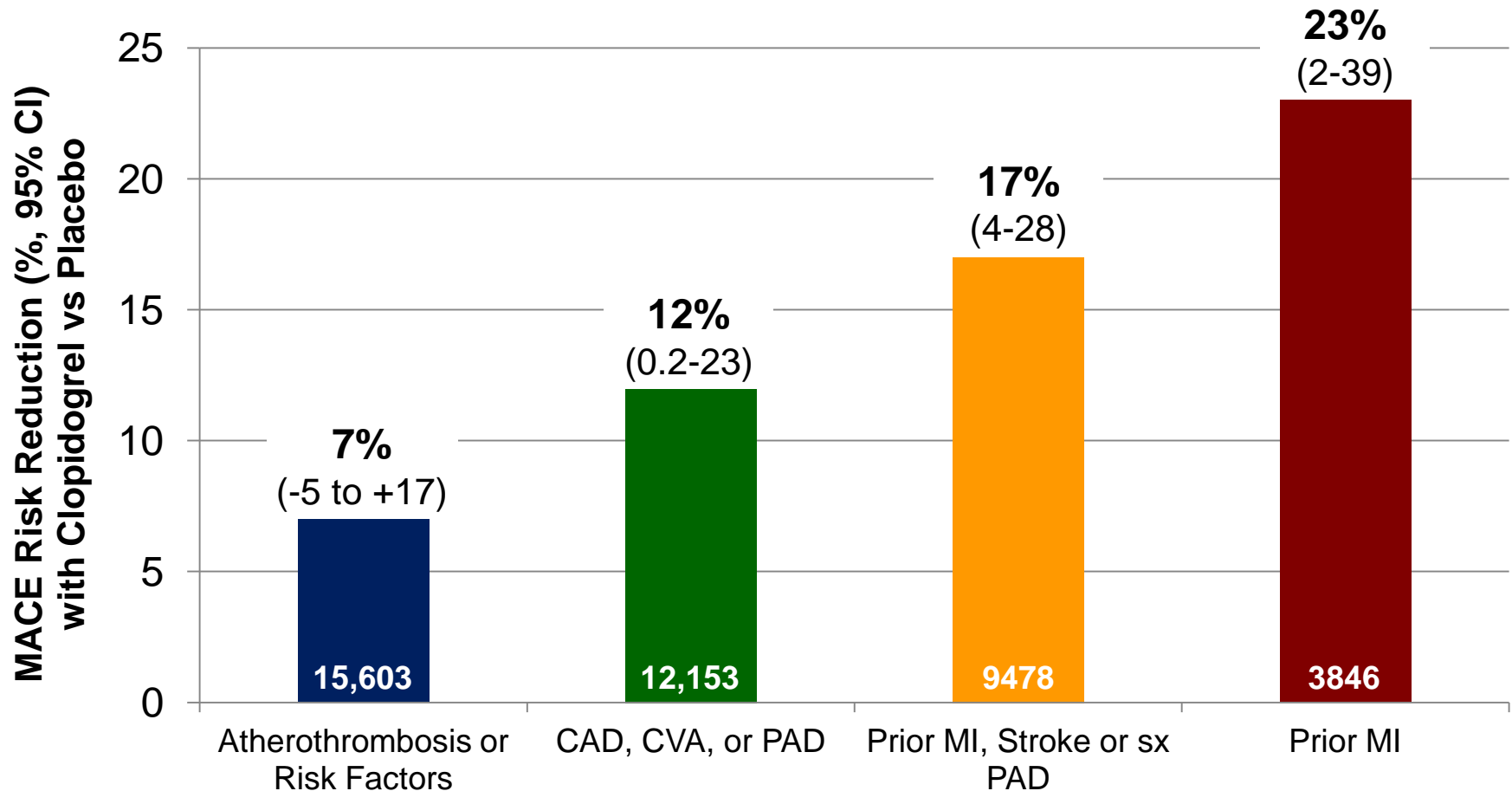
# CHARISMA Trial Design



\* MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death; event-driven trial



# Benefit of Chronic Clopidogrel by Patient Type in CHARISMA



# Dual Antiplatelet Therapy (DAPT) Study: 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

0

12

30

33

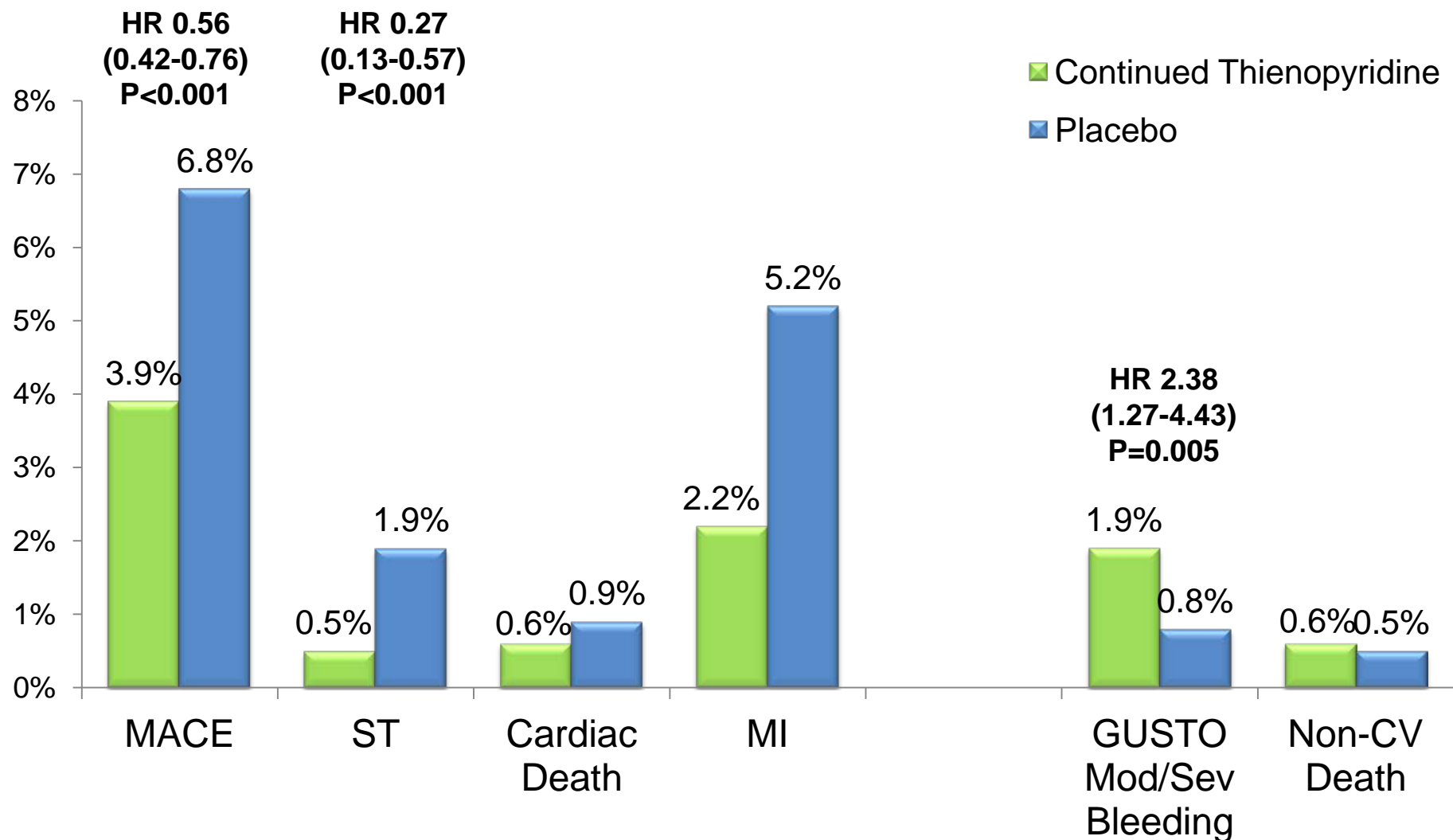
Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

Randomized: 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).

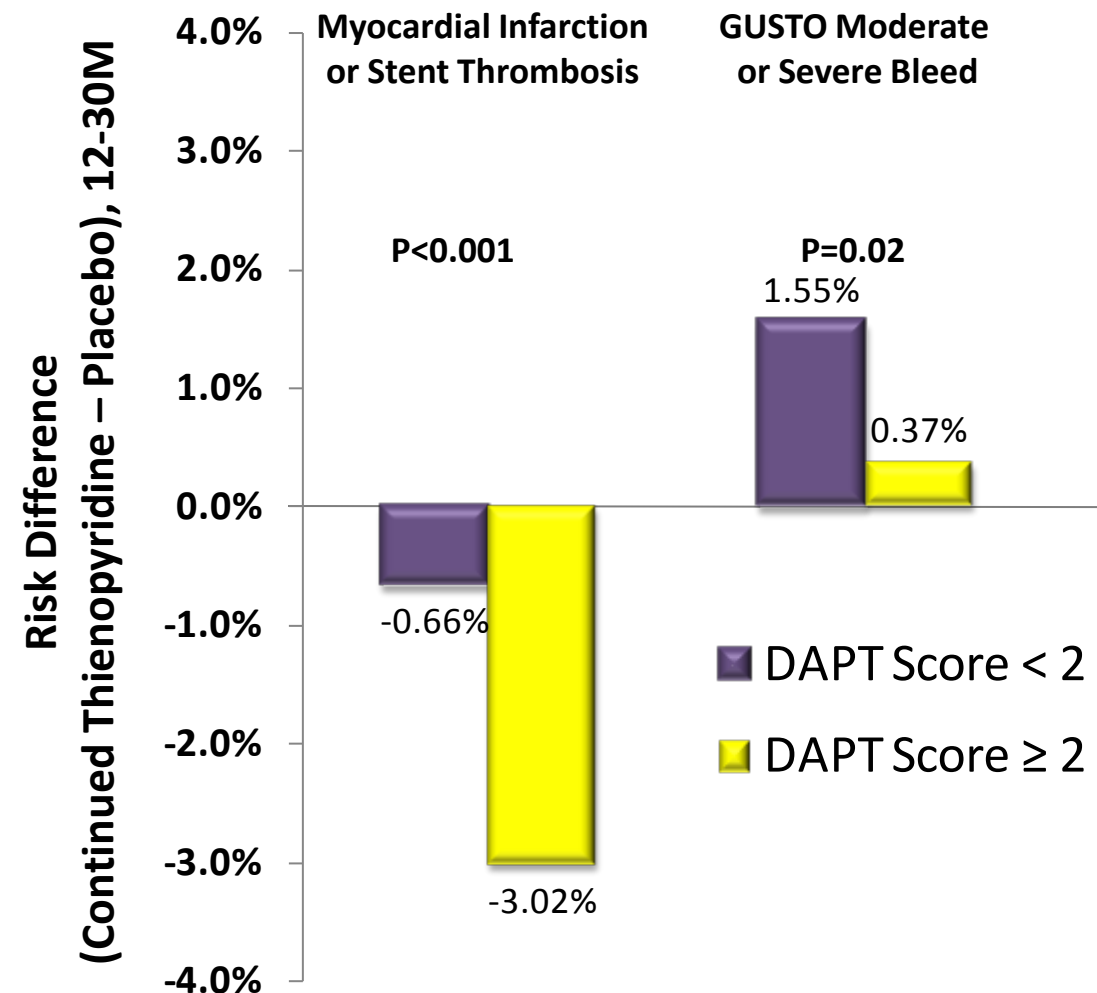
\*Clopidogrel or prasugrel

# MI Subgroup

## *Excellent Benefit-Risk Profile in Patients with MI*

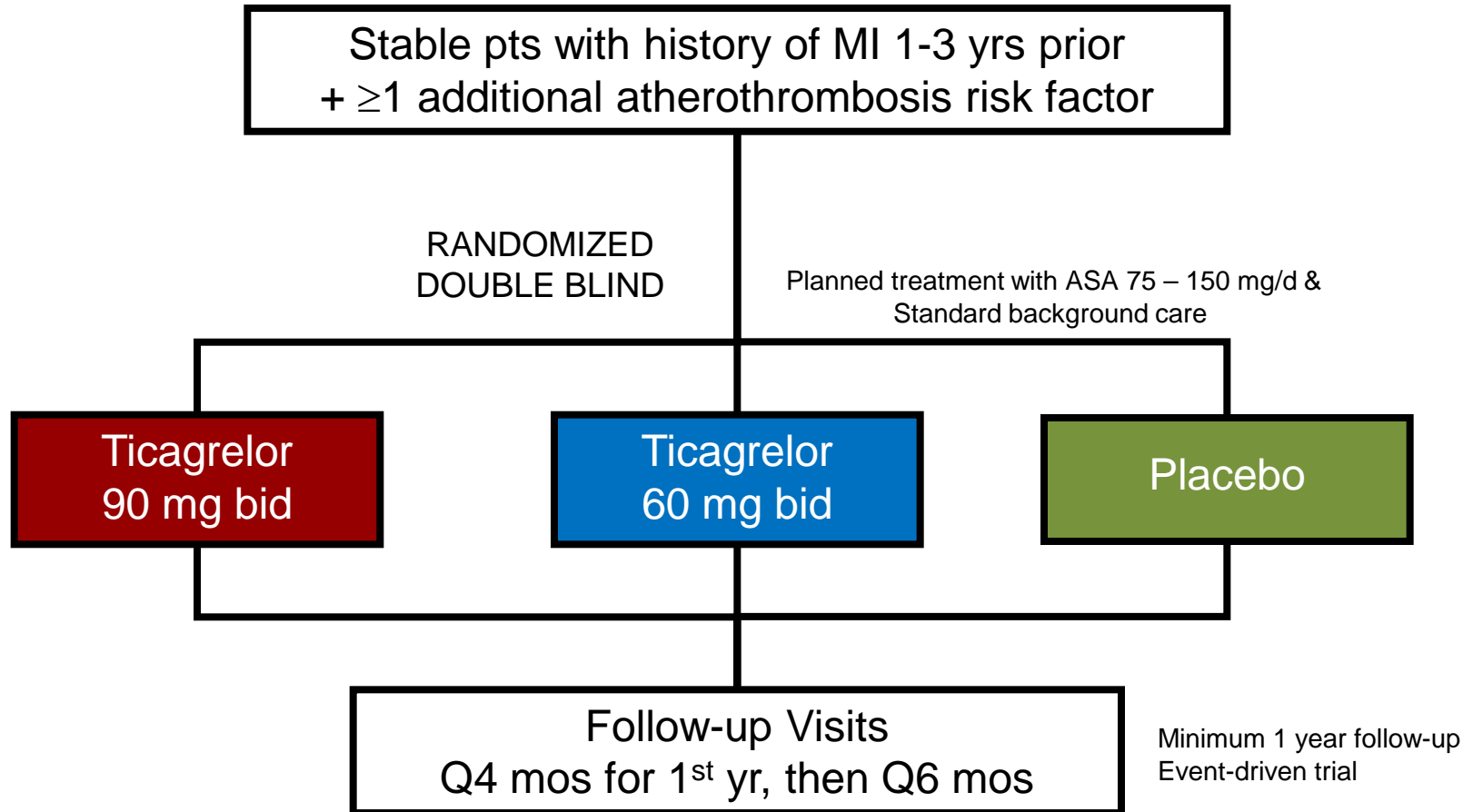


# Continued Thienopyridine vs. Placebo High vs. Low DAPT Score

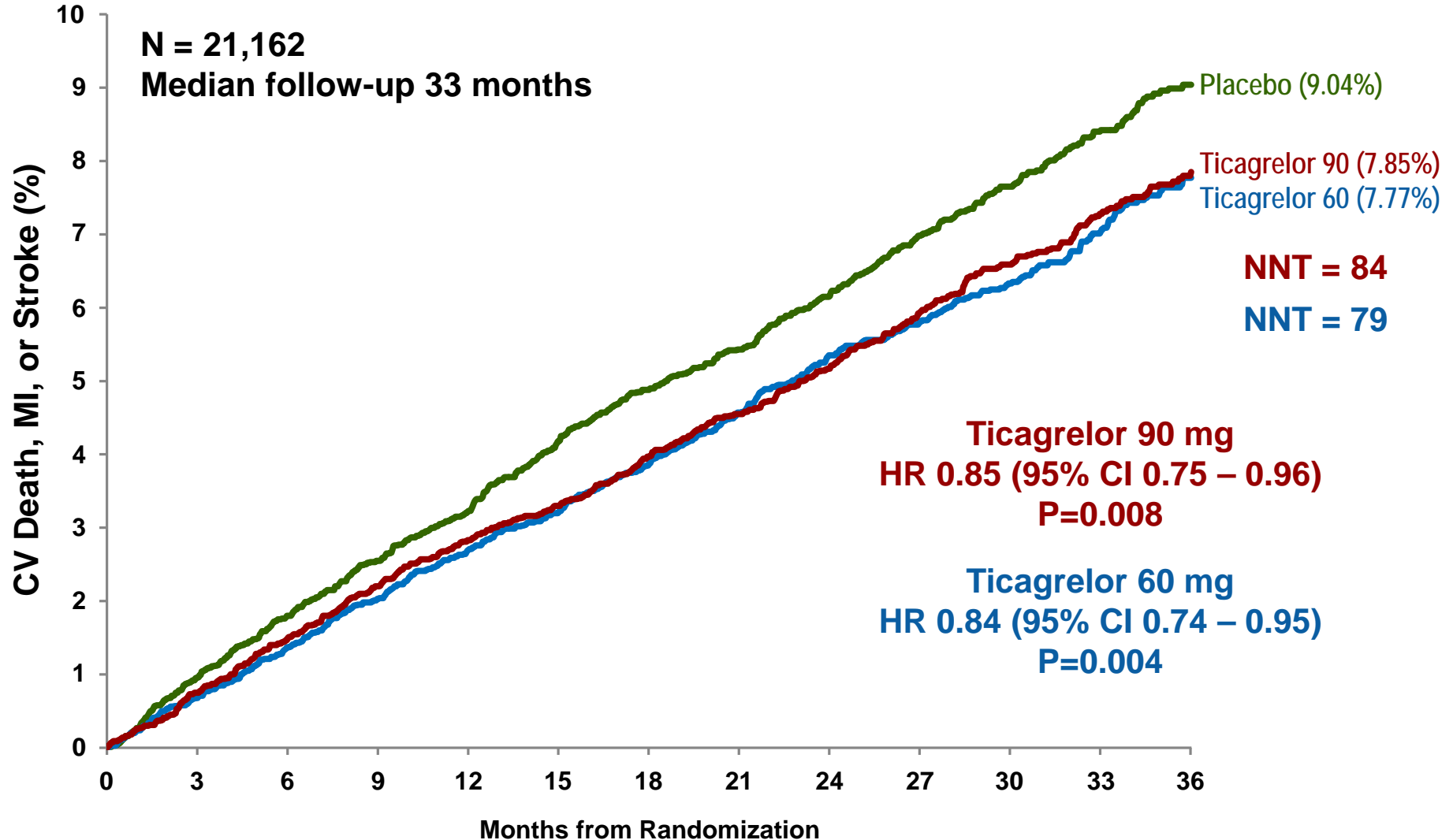


Variable	Points
<b>Patient Characteristic</b>	
<b>Age</b>	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
<b>Index Procedure Characteristic</b>	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

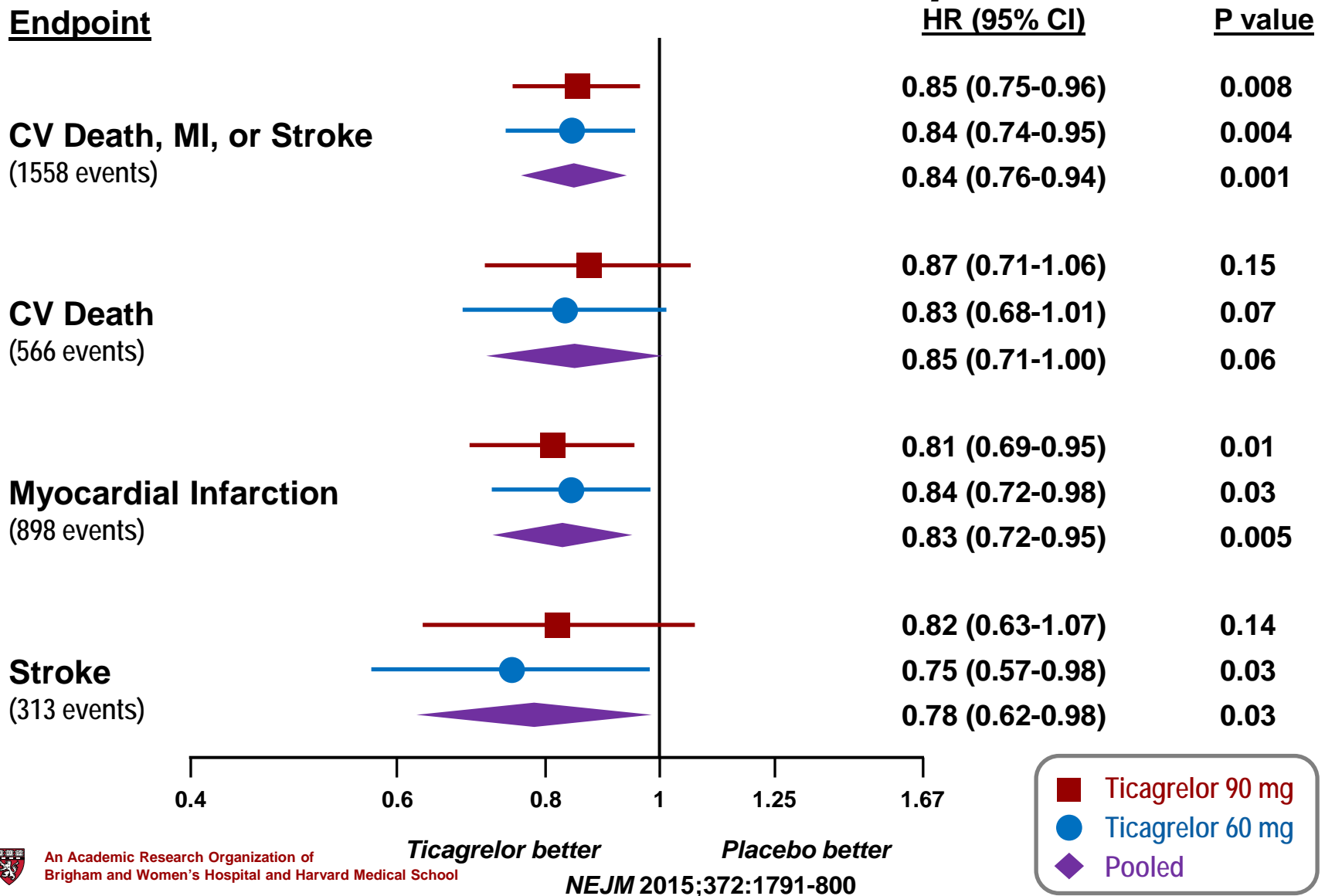
P values are for comparison of risk differences across DAPT Score category (interaction). Yeh et al. *AHA* 2015



# Primary Endpoint

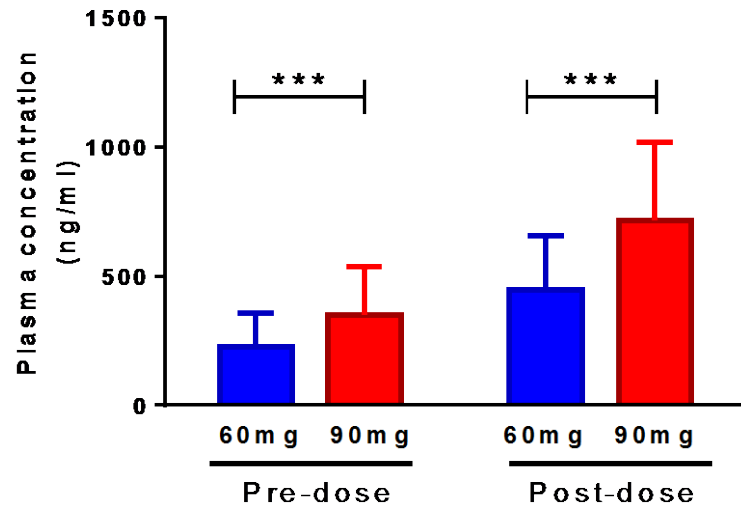


## Consistent Benefit Across Components

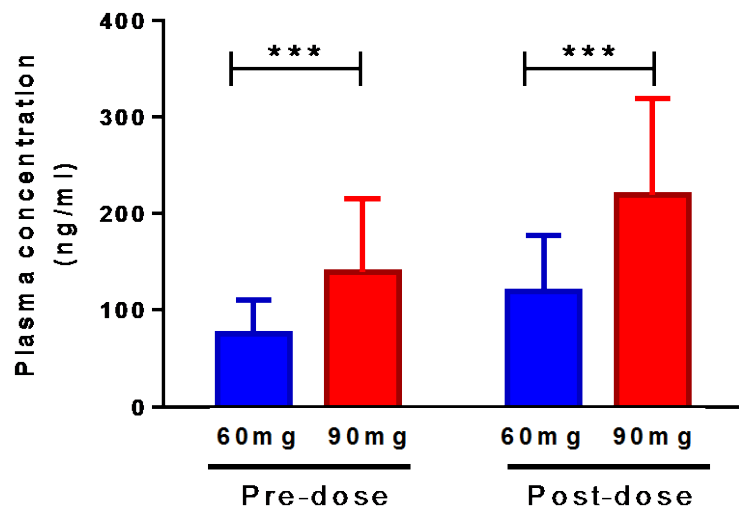


# Doses – PK and PD

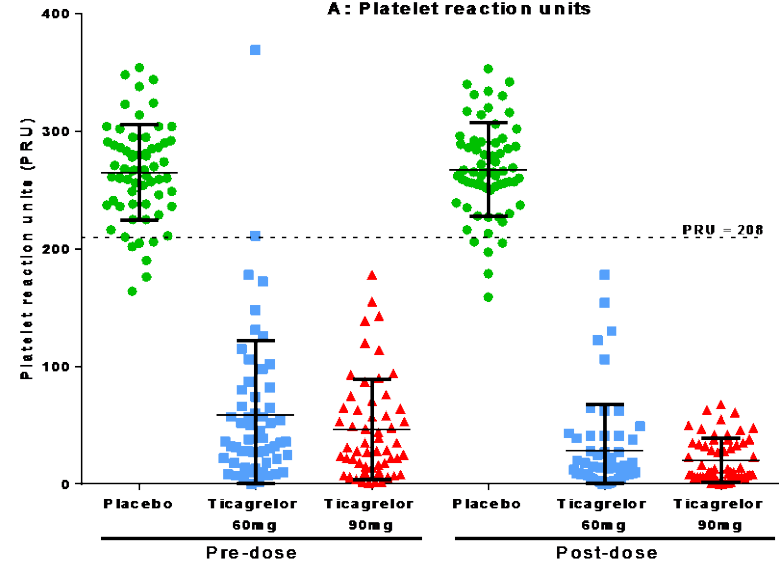
**A: Plasma ticagrelor**



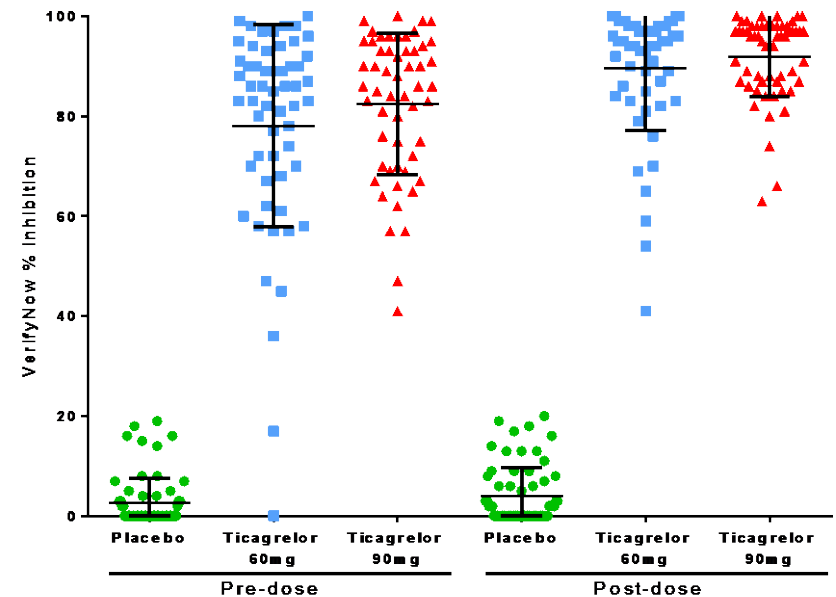
**B: Plasma AR-C124910XX**



**A: Platelet reaction units**

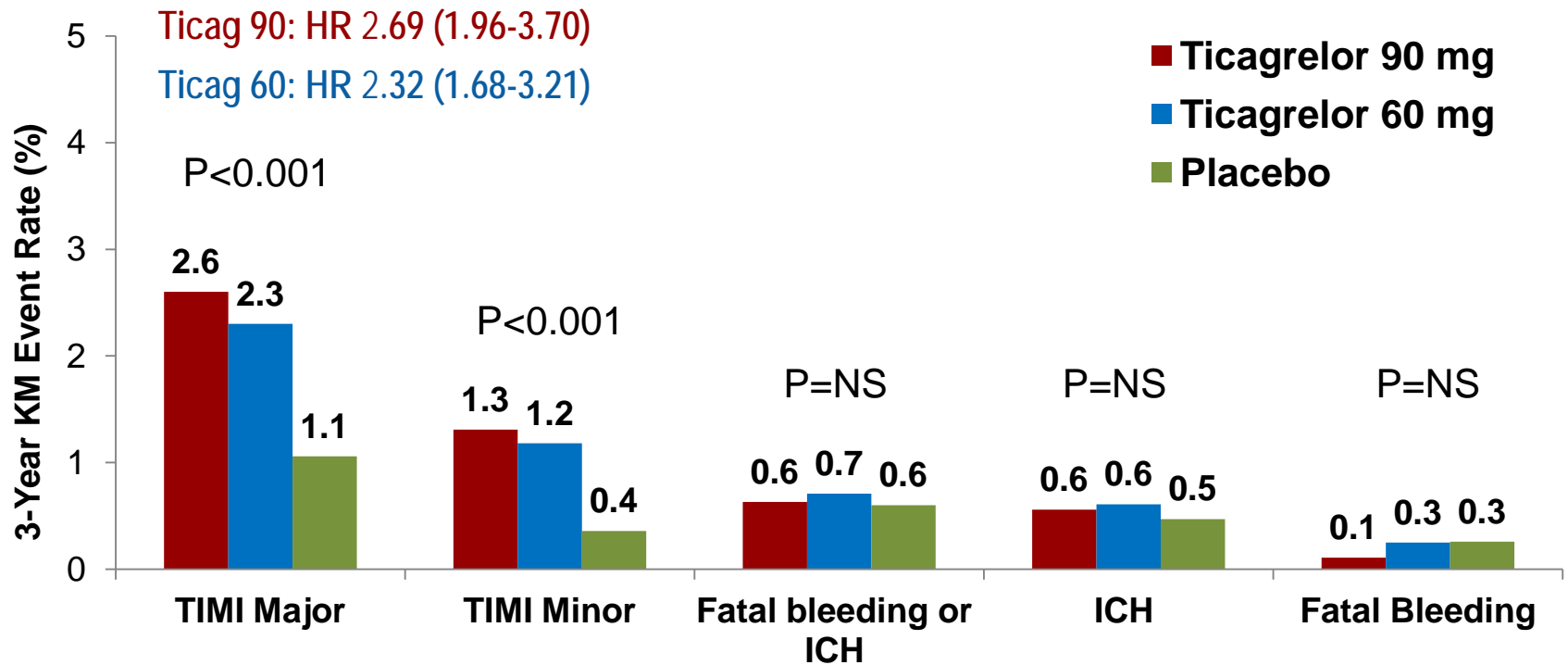


**B: % inhibition**



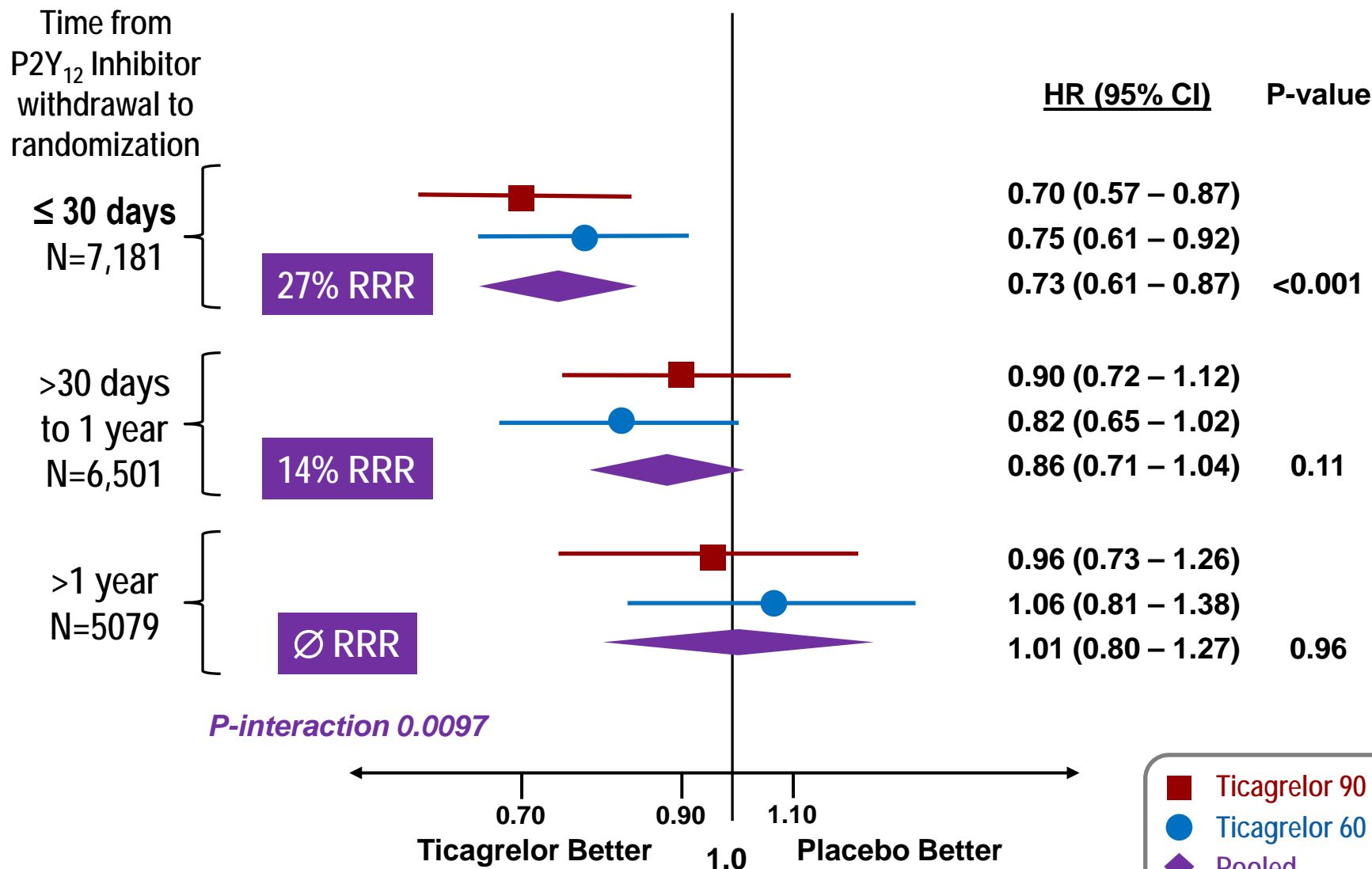


## *Increased Bleeding, But No Increase in Irreversible Bleeding Harm*



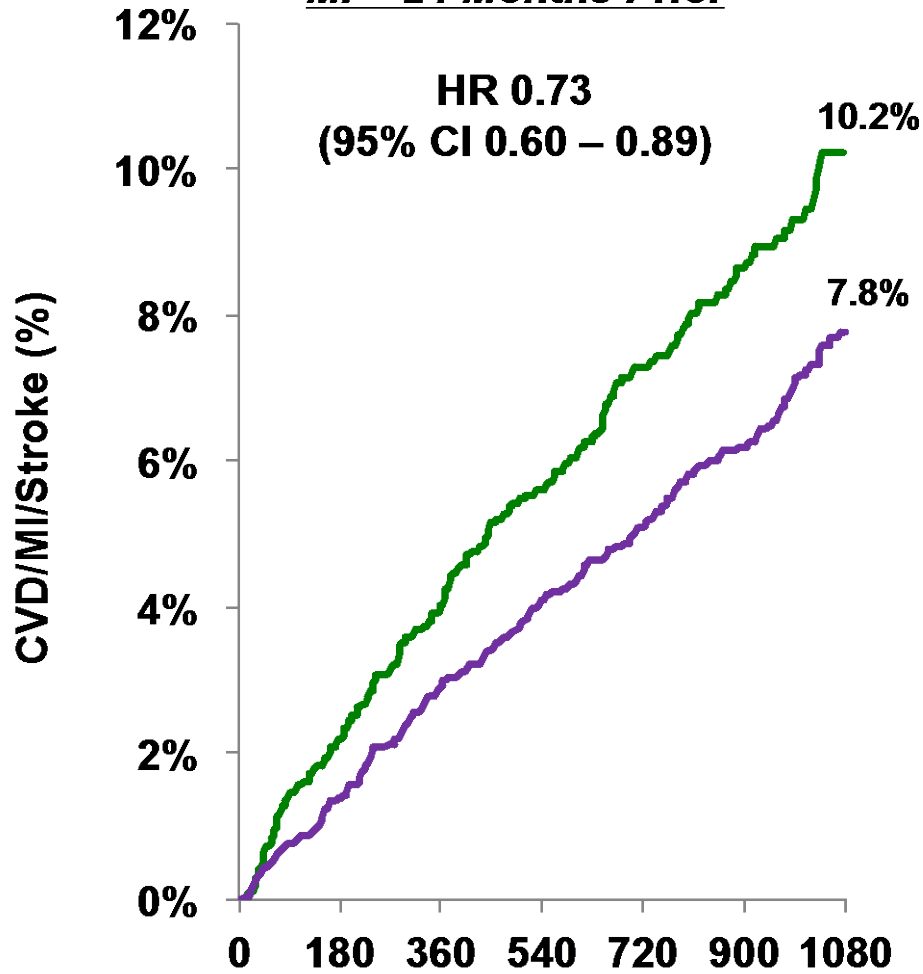
- PEGASUS-TIMI 54 enrolled stable patients 1-3 yrs after MI (median 1.7, IQR 1.2 -2.3) therefore patients ranged from just stopping P2Y<sub>12</sub> inhibition to having been off for several years
- Thus PEGASUS-TIMI 54 functionally studied a continuum from ongoing P2Y<sub>12</sub> inhibition to re-initiating after being off for several years
- Data from other studies suggest that there may be an early risk of ischemic events after P2Y<sub>12</sub> discontinuation
- Conversely, patients who have been event-free on ASA monotherapy for >1 year may, *de facto*, be at low-risk for future ischemic events

# Reduction in MACE with Ticagrelor by Time from P2Y<sub>12</sub> Inhibitor Withdrawal

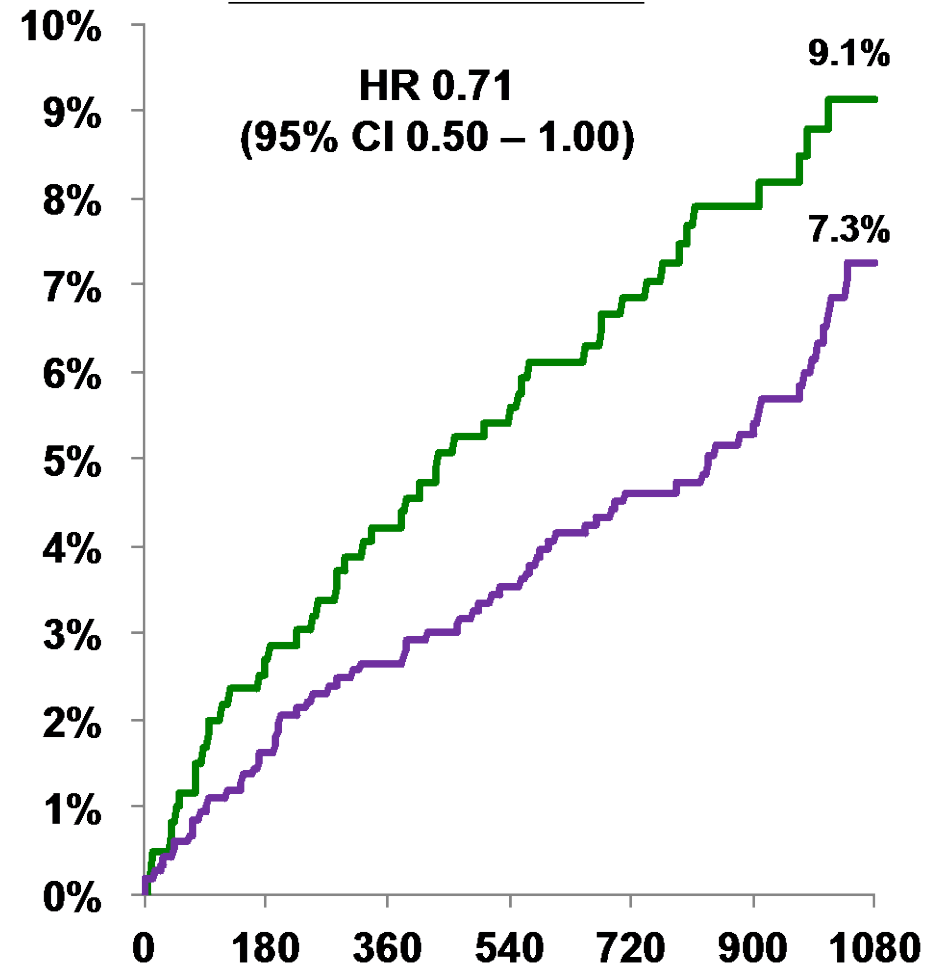


# MACE at 3 Years with Ticagrelor by Time from MI in Patients with P2Y<sub>12</sub> Inhibitor Withdrawal ≤ 30 Days

***MI < 24 Months Prior***



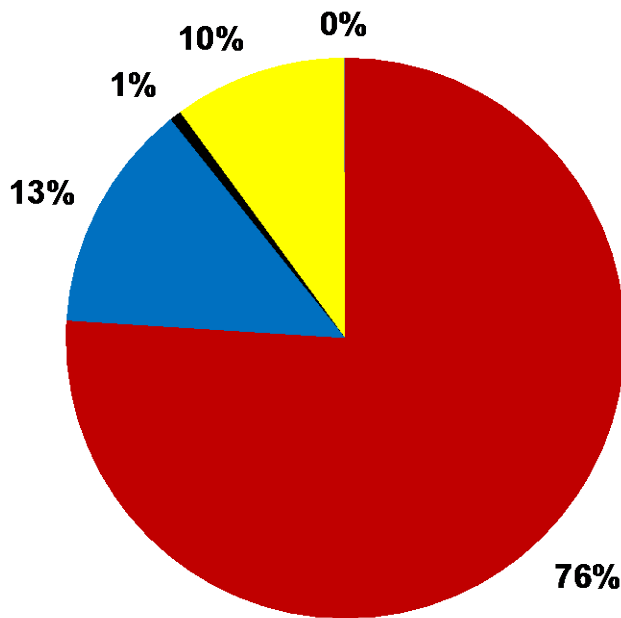
***MI ≥ 24 Months Prior***



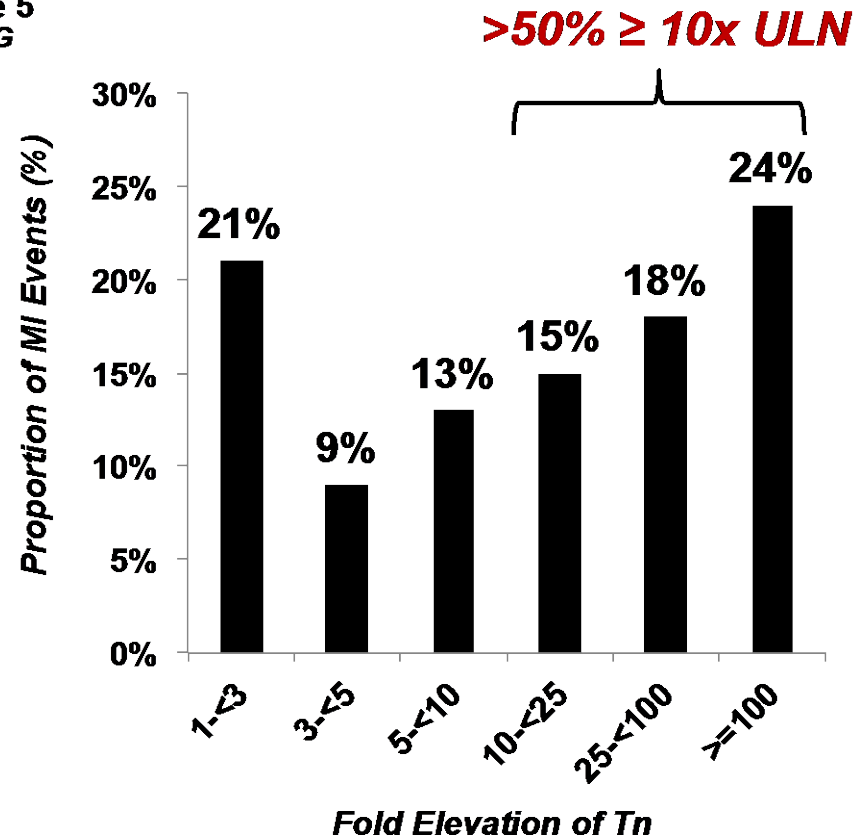
■ Placebo  
■ Ticagrelor Doses Pooled

**1042 total myocardial infarctions occurred in 898 patients at a median of 440 days after randomization (IQR 198 to 705)**

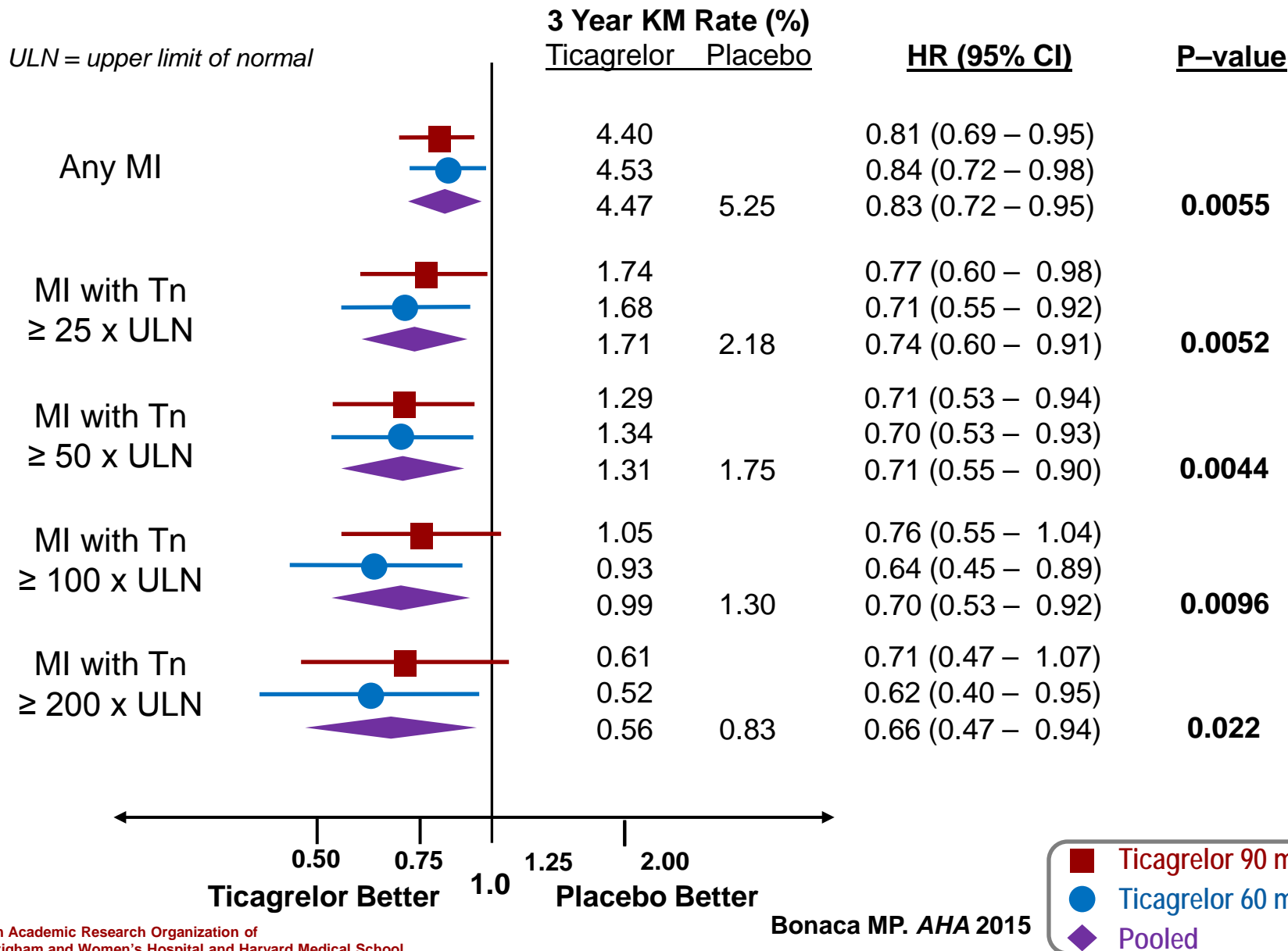
■ Type 1 ■ Type 2 ■ Type 3 ■ Type 4\* ■ Type 5  
*Spontaneous Demand Fatal prior to Tn Testing PCI CABG*



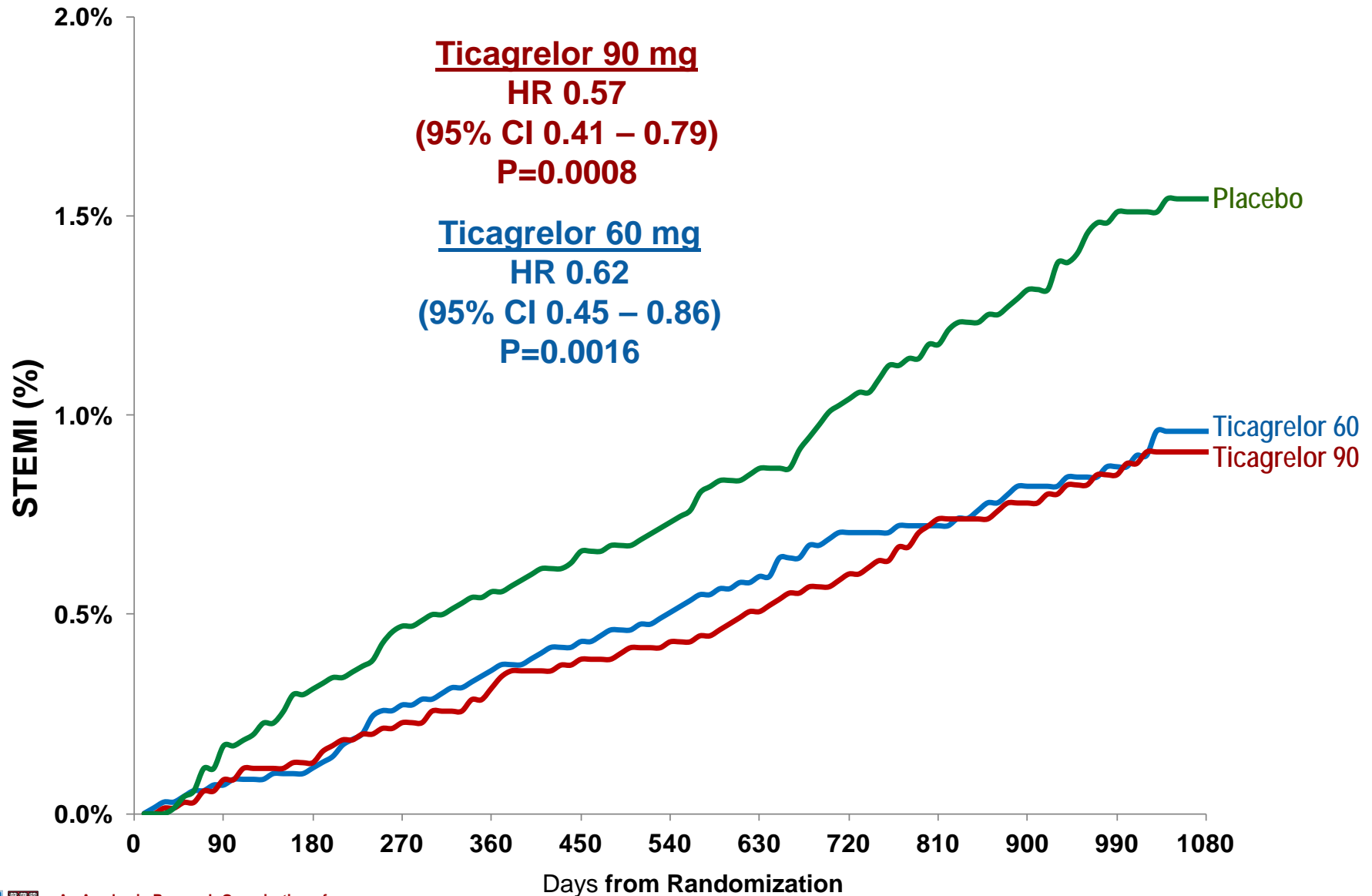
**\*6 Type 4a, 95 Type 4b**



# Benefit of Ticagrelor By Size of MI



# Effect of Ticagrelor on STEMI

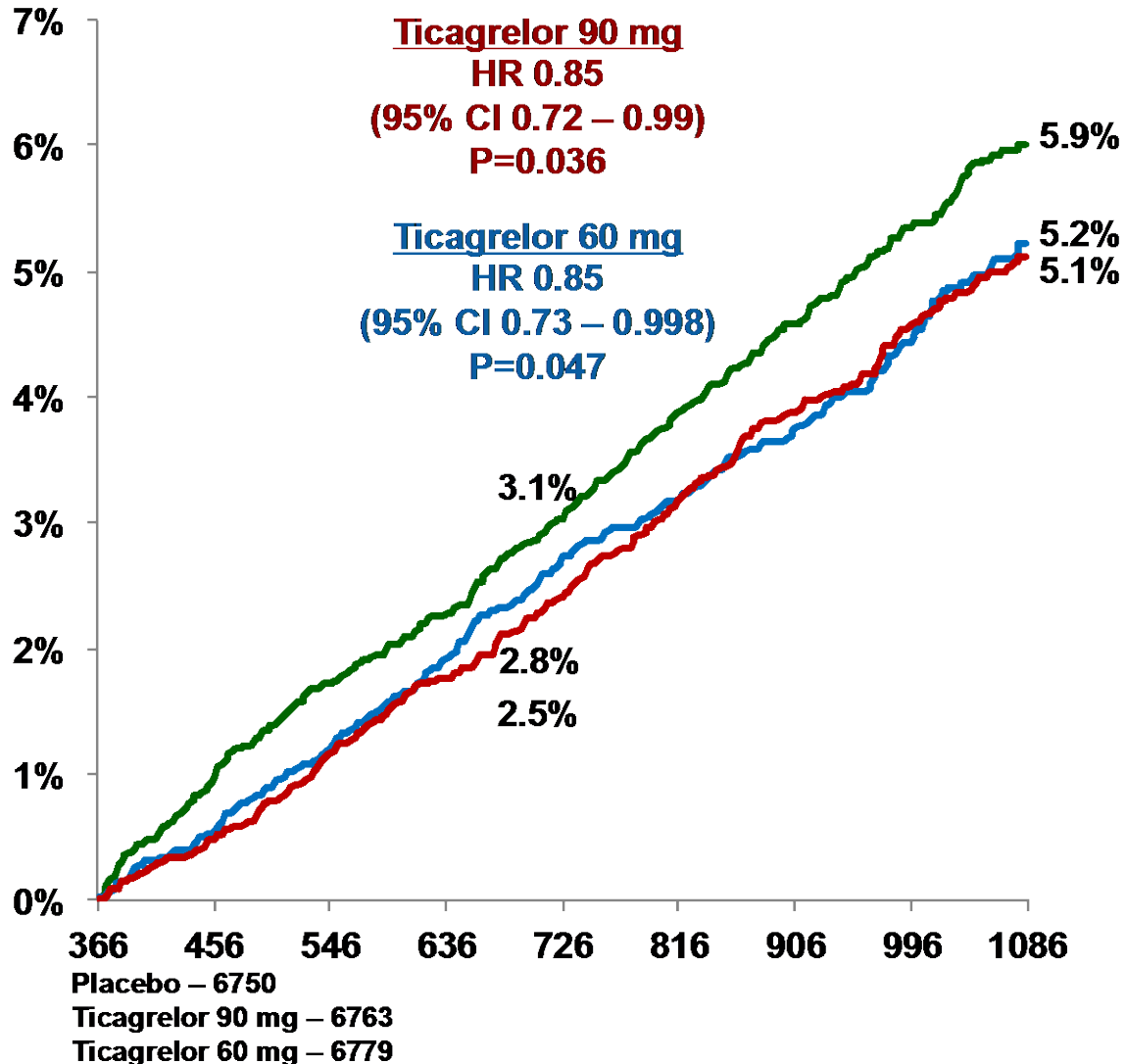
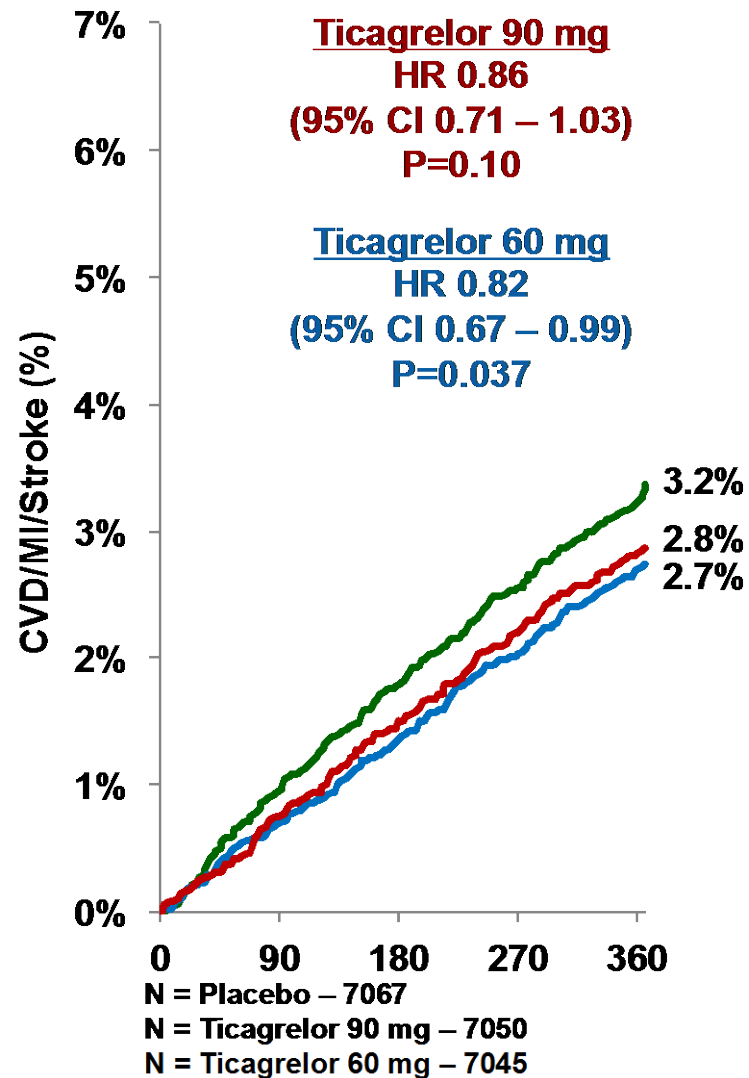


# Primary Endpoint – Landmark (ITT)

First Year of Treatment



Subsequent Two Years of Treatment



Time (Days) from Randomization

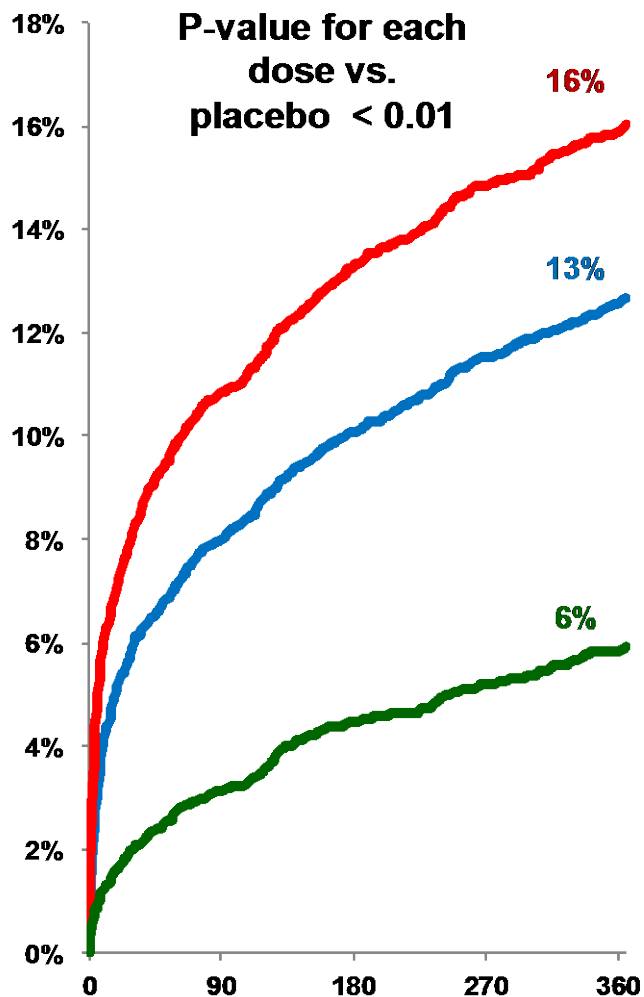


# Drug discontinuation for AE by Treatment

■ Ticagarelor 90 mg twice daily ■ Ticagrelor 60 mg twice daily ■ Placebo

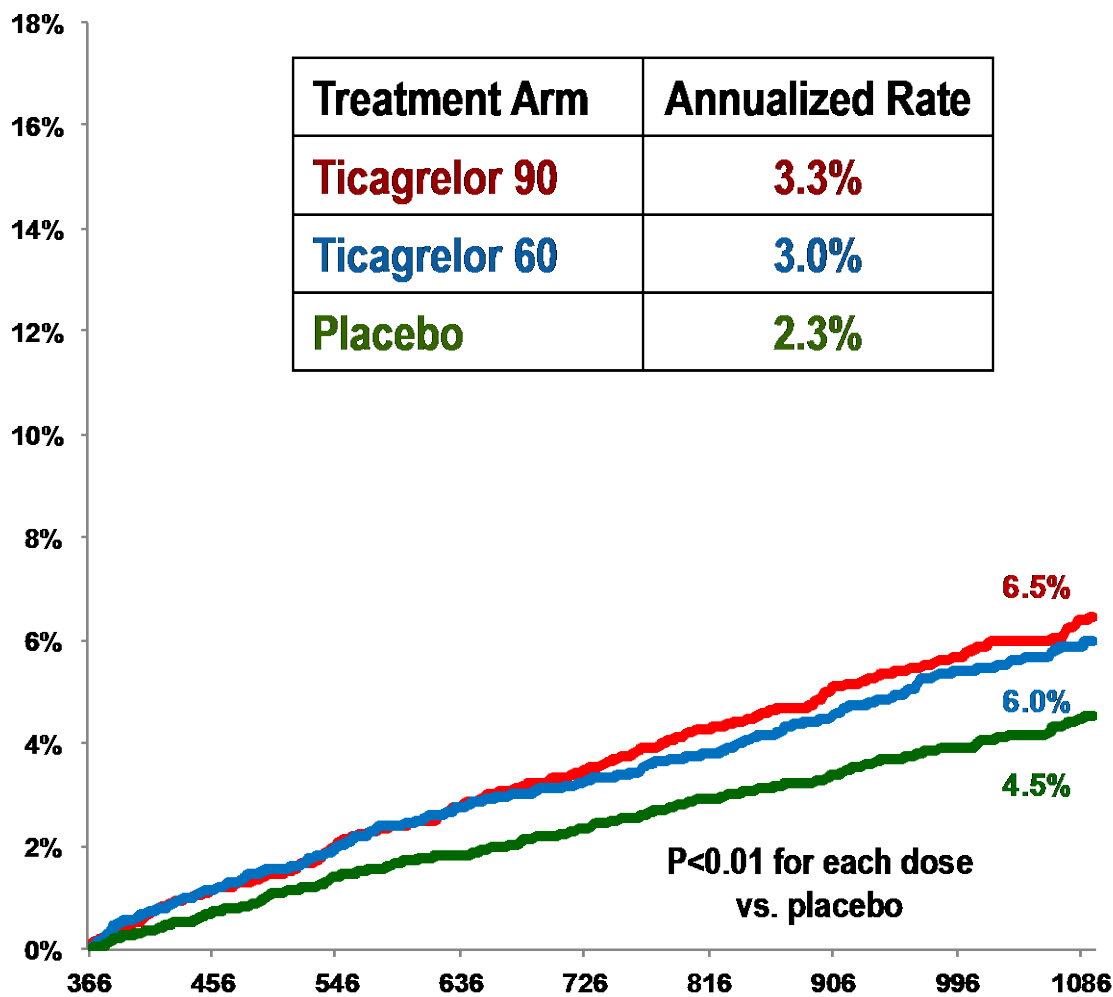
**First Year**

P-value for each  
dose vs.  
placebo < 0.01



**Years 2 + 3**

Treatment Arm	Annualized Rate
Ticagrelor 90	3.3%
Ticagrelor 60	3.0%
Placebo	2.3%

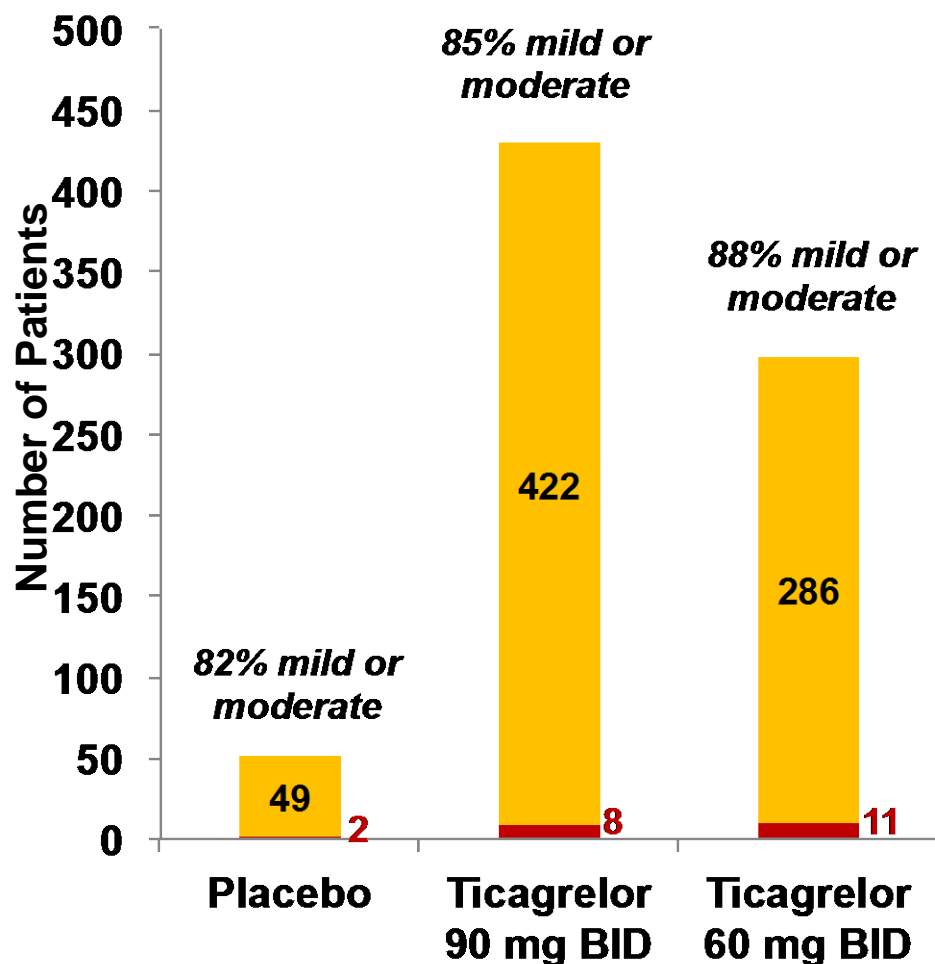


Days from Randomization

# Dyspnea and Bleeding

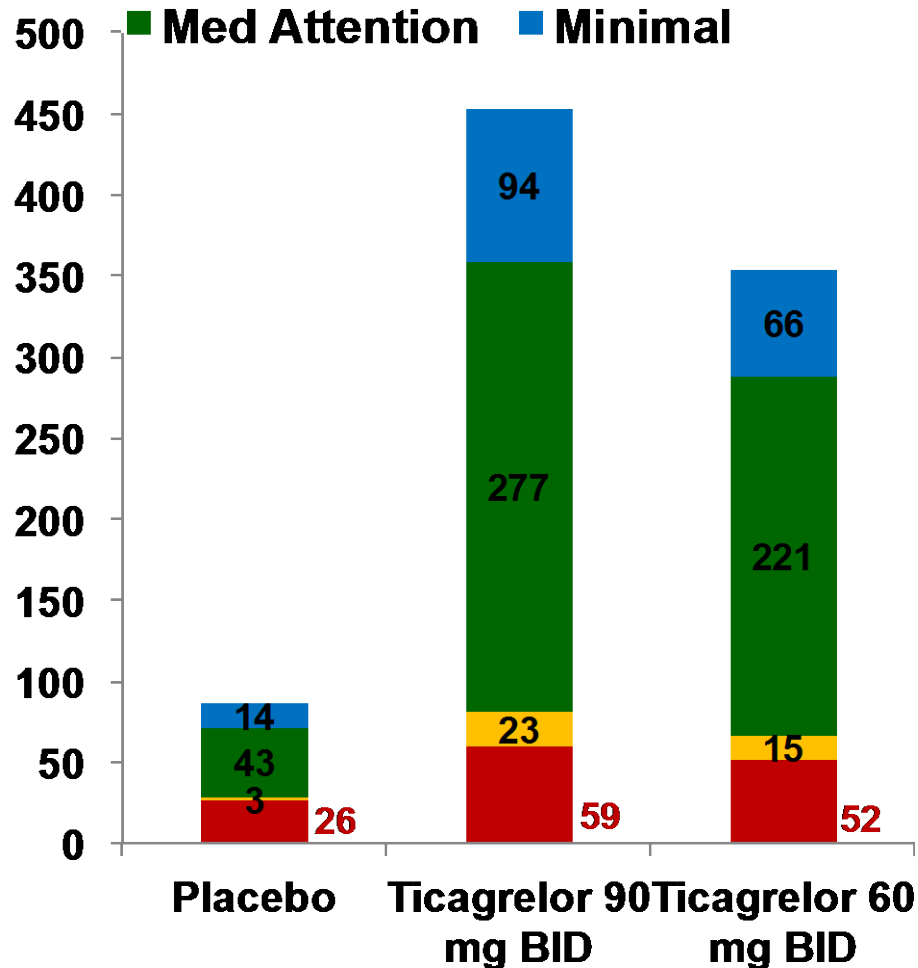
## Dyspnea

■ Non-serious (AE) ■ Serious (SAE)

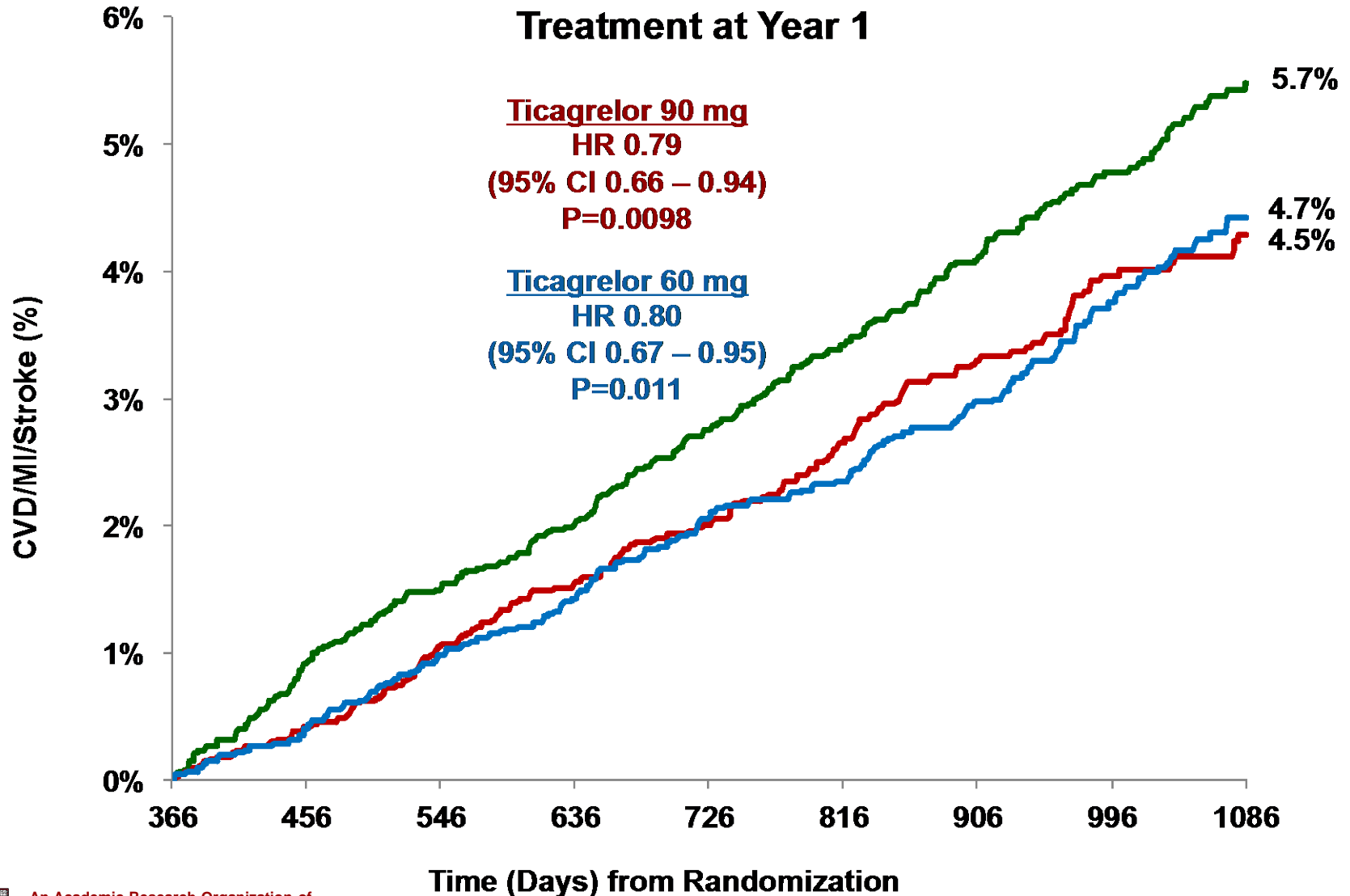


## Bleeding

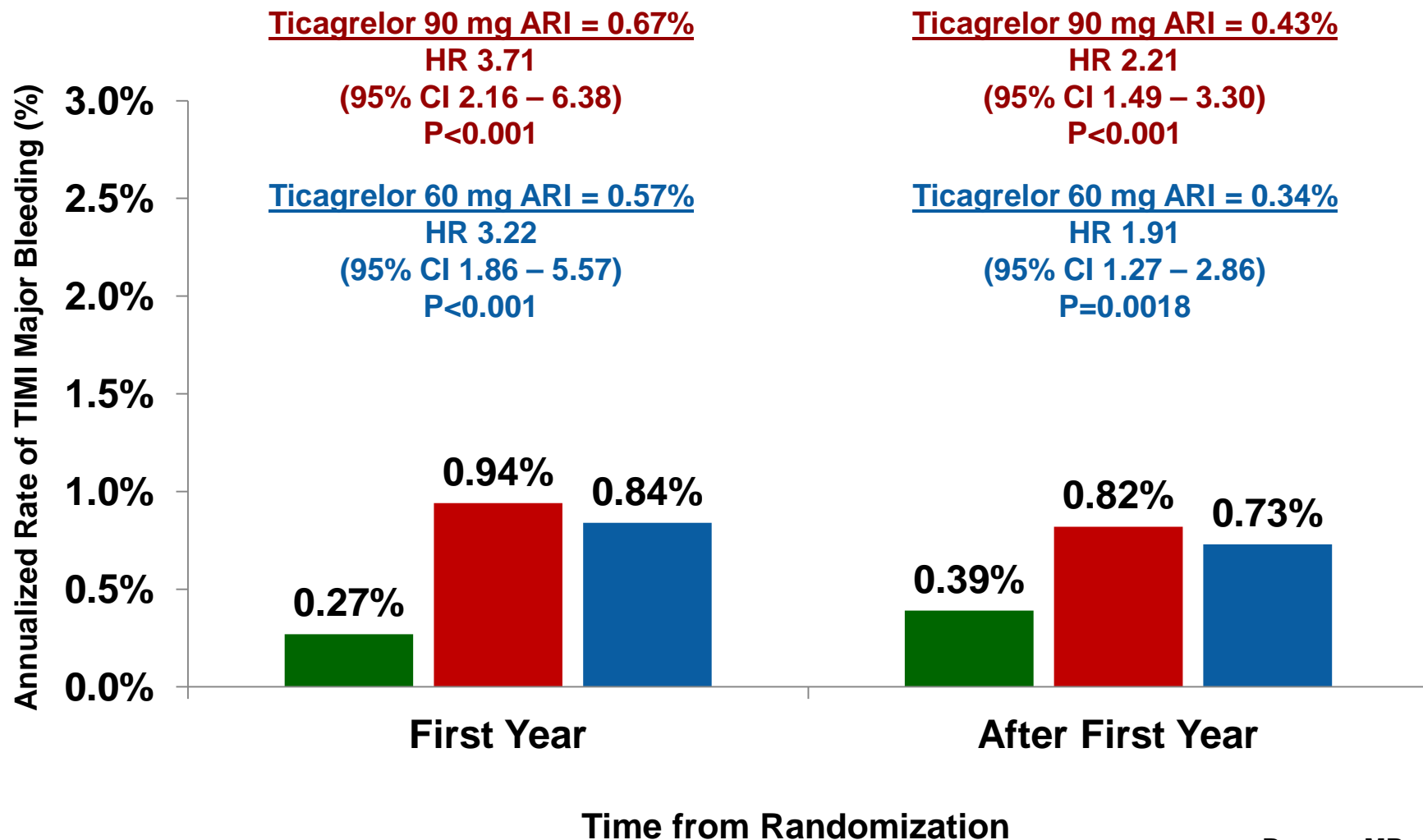
■ TIMI Major ■ TIMI Minor  
■ Med Attention ■ Minimal



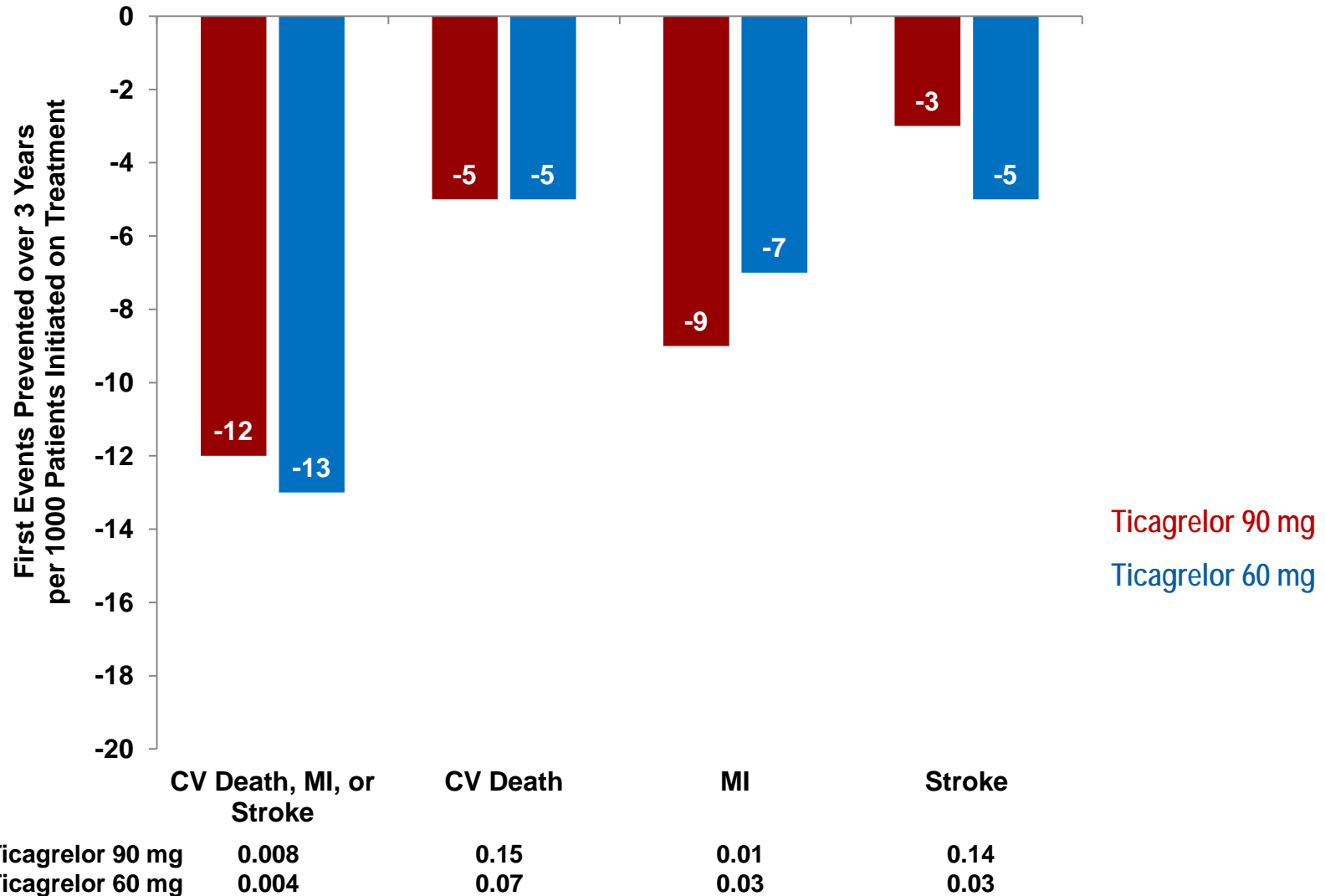
**N=16,480 Patients On  
Treatment at Year 1**



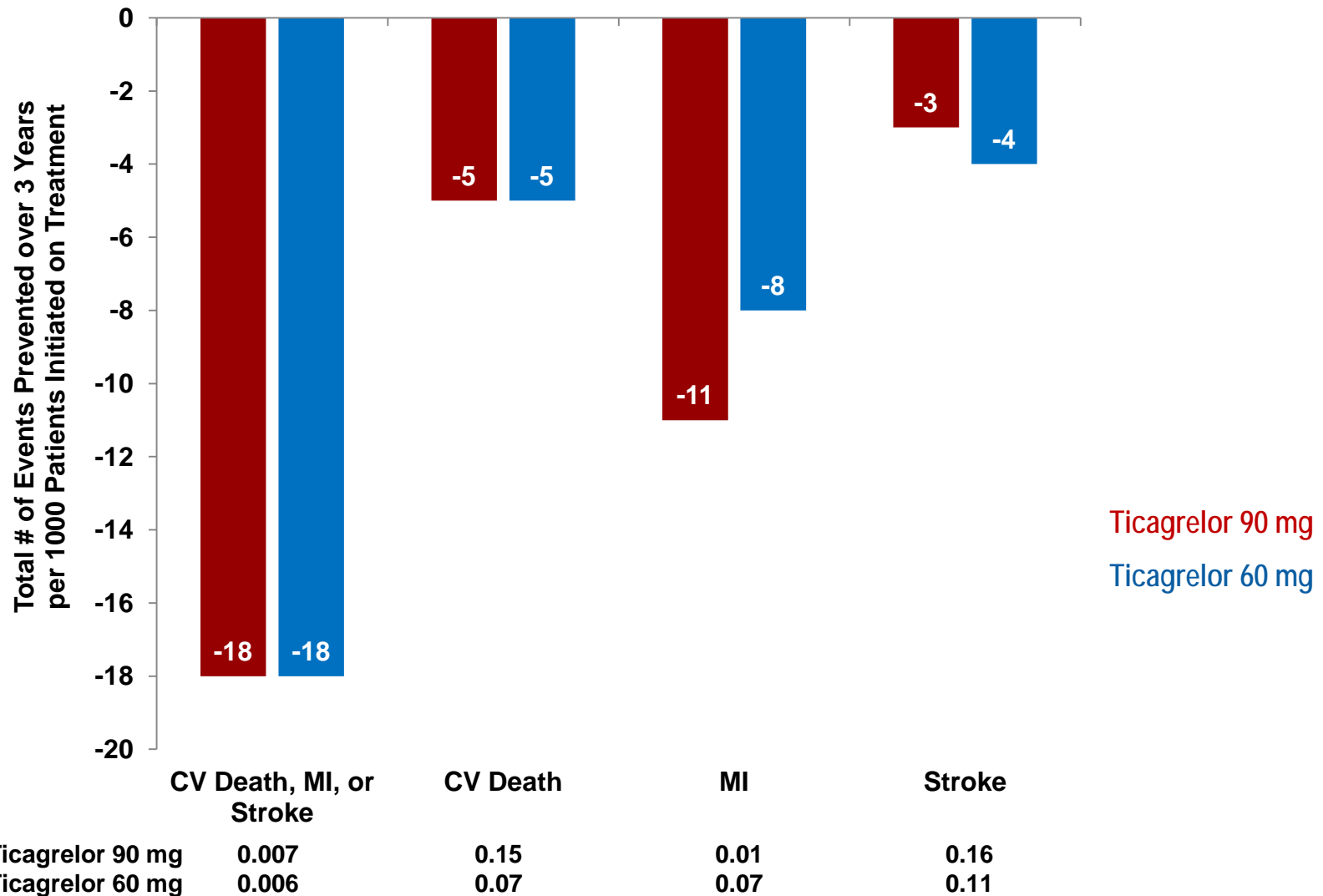
■ Placebo ■ Ticagrelor 90 mg BID ■ Ticagrelor 60 mg BID



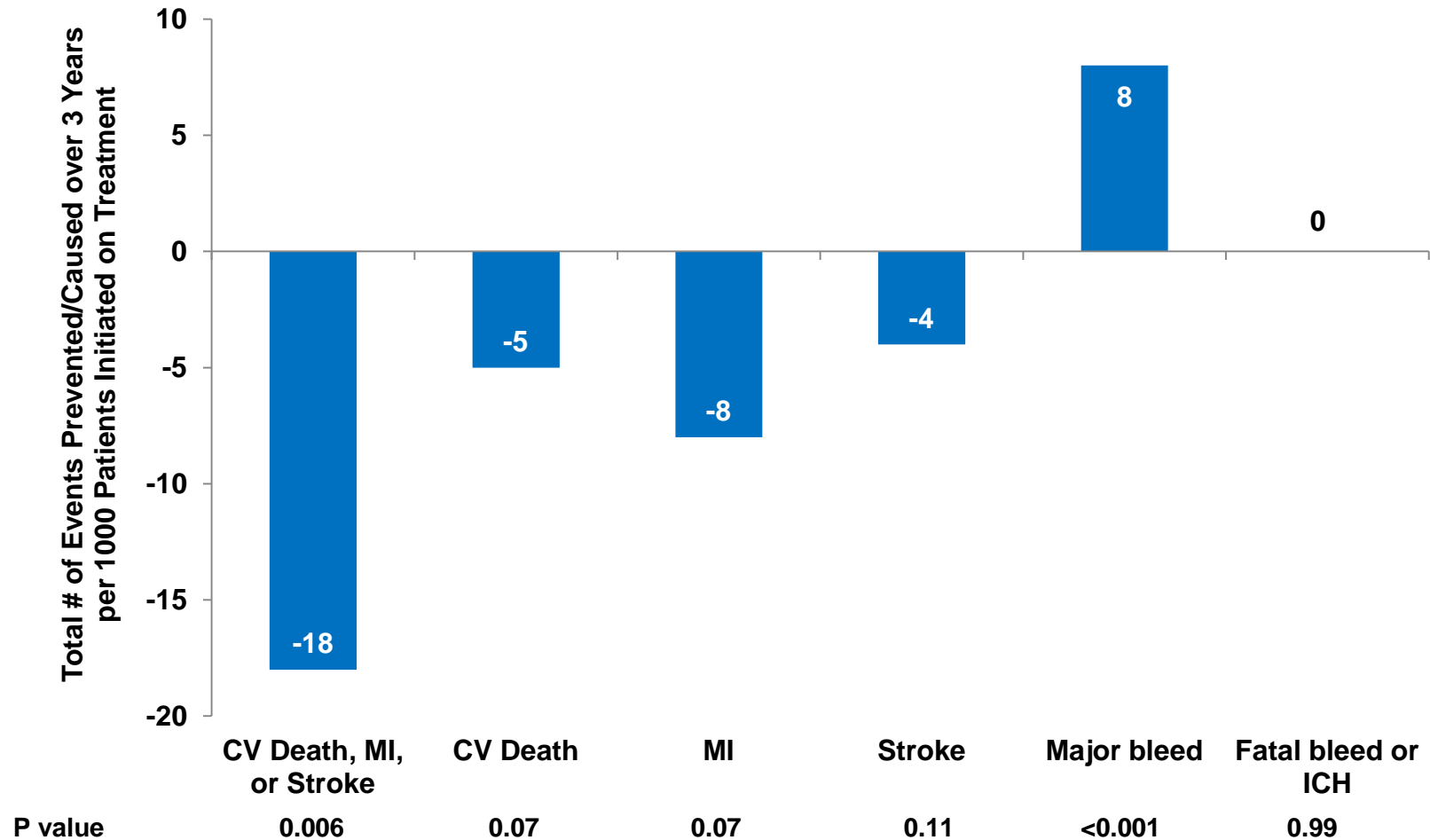
# First MACE Events Prevented



# Total MACE Events Prevented



## Ticagrelor 60 mg bid





# ESC 2015 NSTE-ACS Guideline

## Long-term P2Y<sub>12</sub> inhibition

P2Y<sub>12</sub> inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.

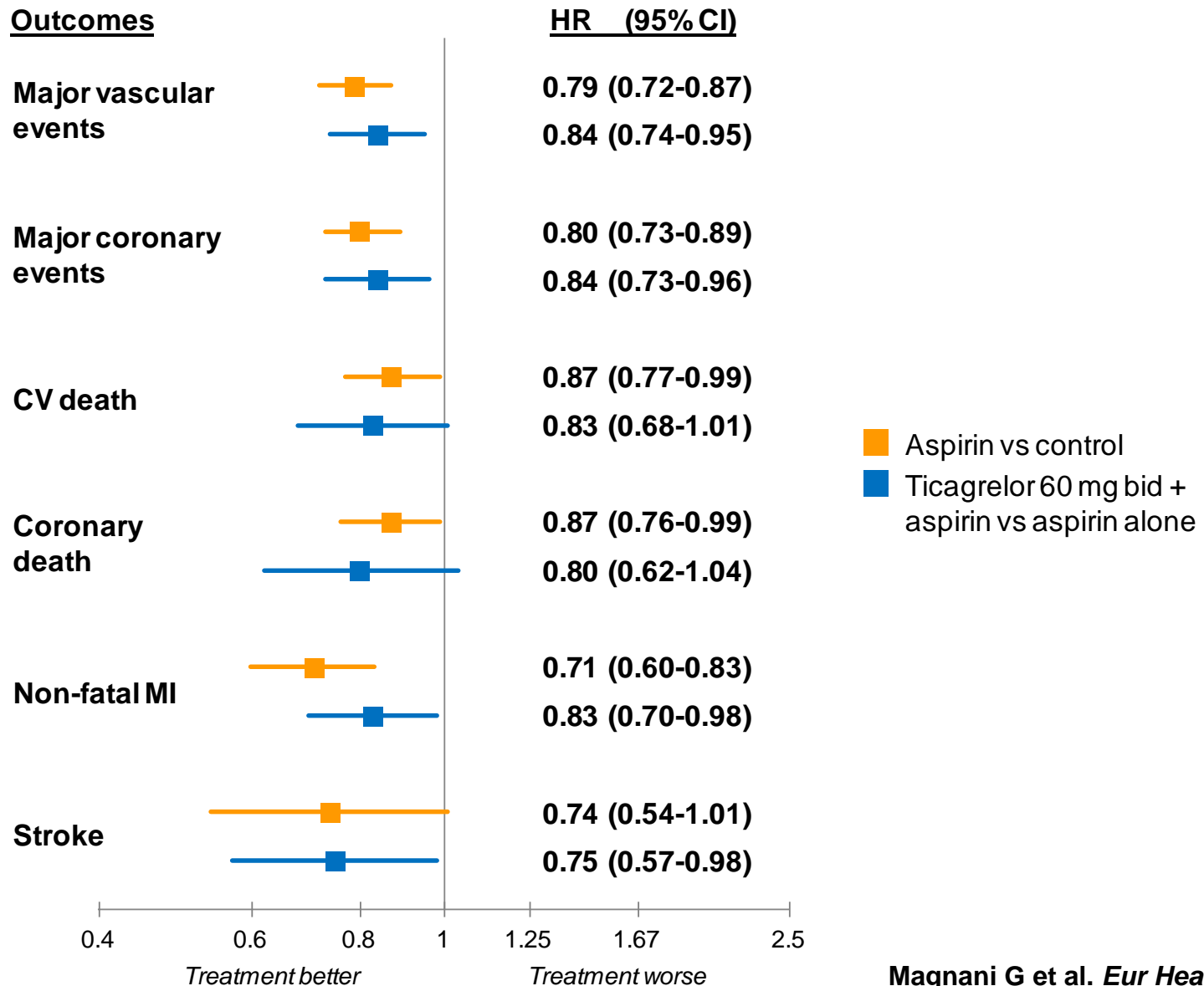
**IIb**

**A**

184,  
186



# Benefit for aspirin vs. ticagrelor 60 mg bid for secondary prevention



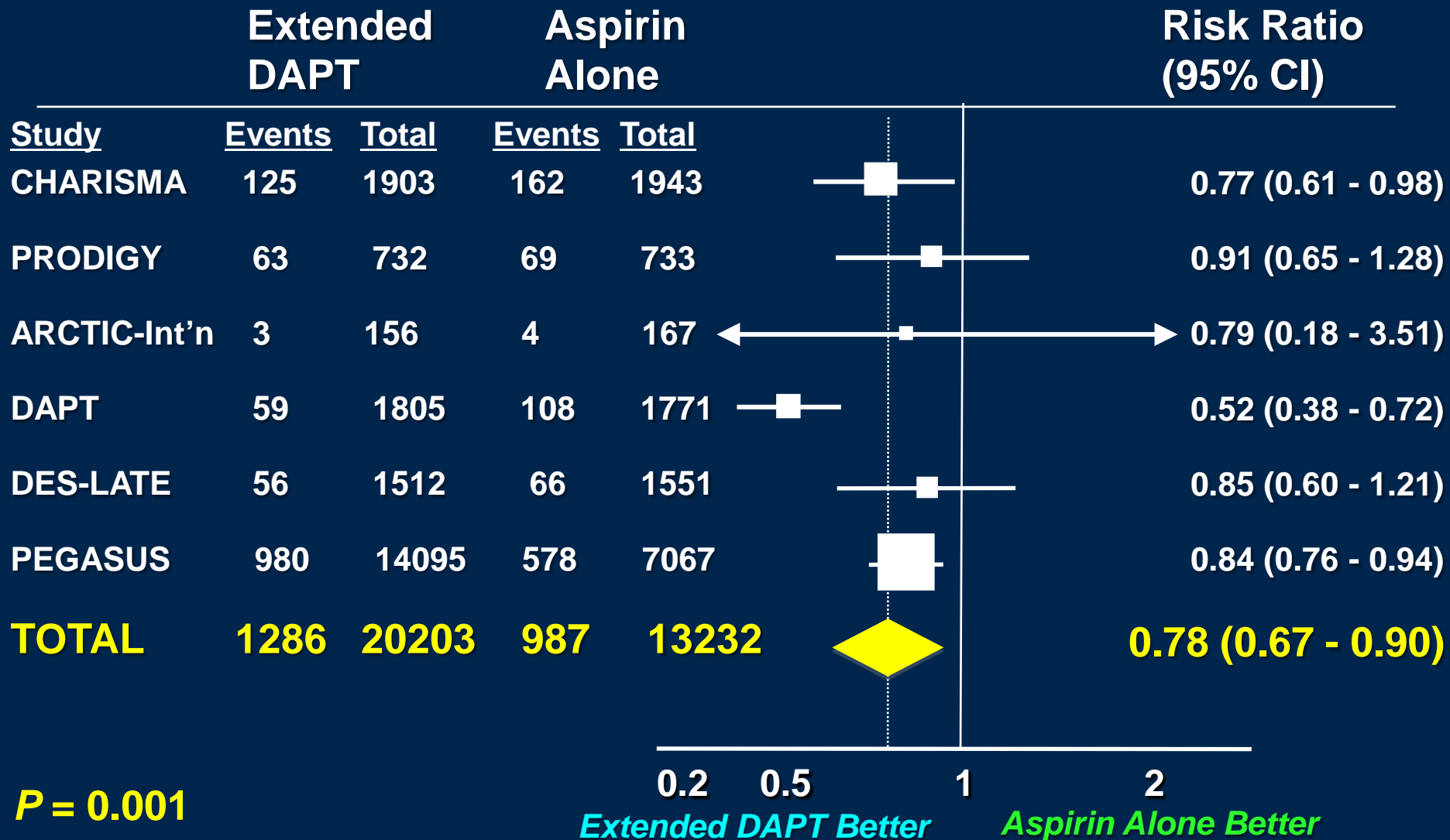


# Bleeding

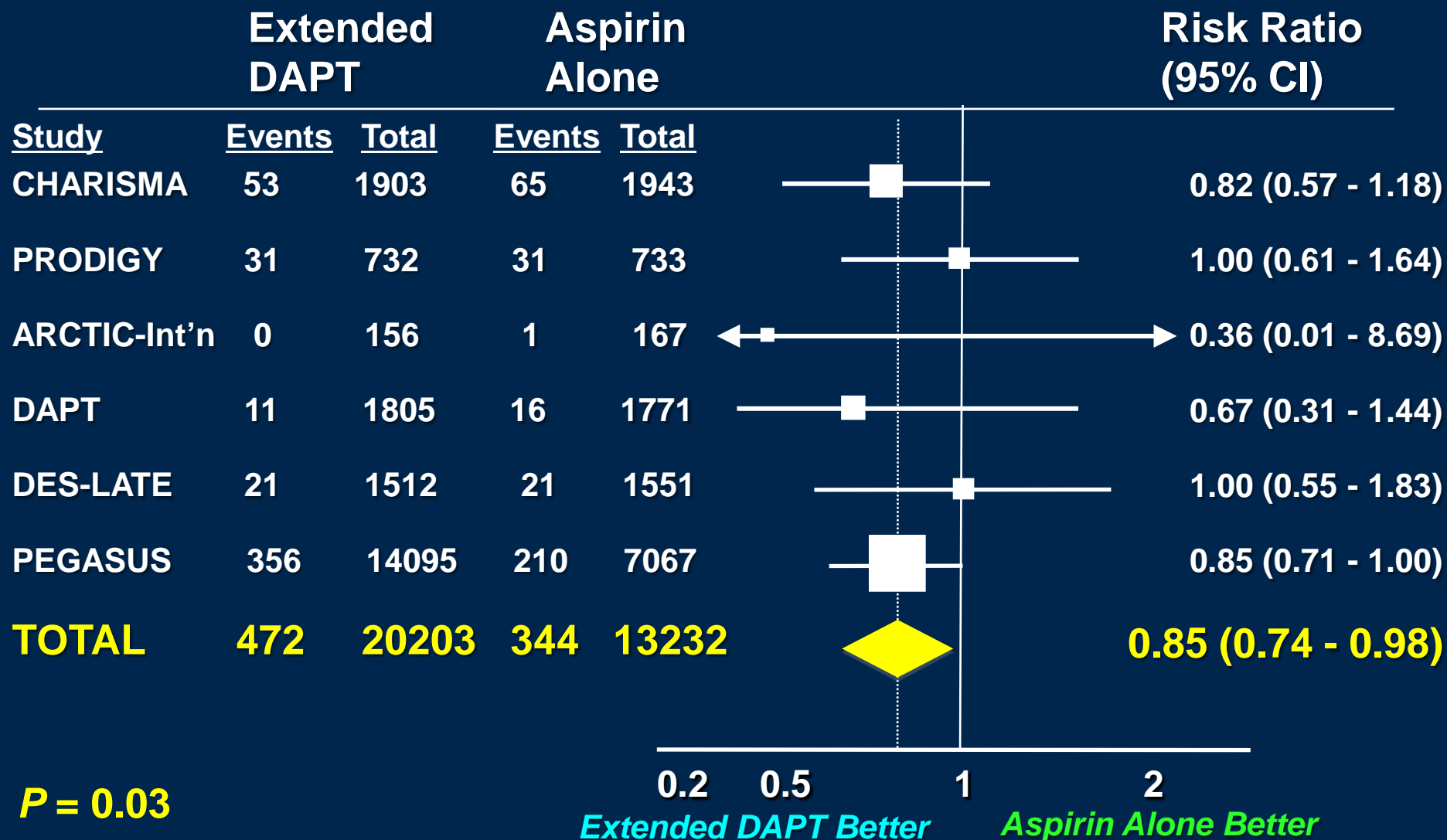
Agent	Relative Risk of Major Bleeding	Absolute Excess per Year
Aspirin	1.5-2.5	~0.5%
Clopidogrel	1.5	0.5%
Ticagrelor 60 mg	2.4	0.5%

*Br J Pharmac* 1993;35:219-26 ; *BMJ* 2002;324:71-86; *Lancet* 2009;373:1849

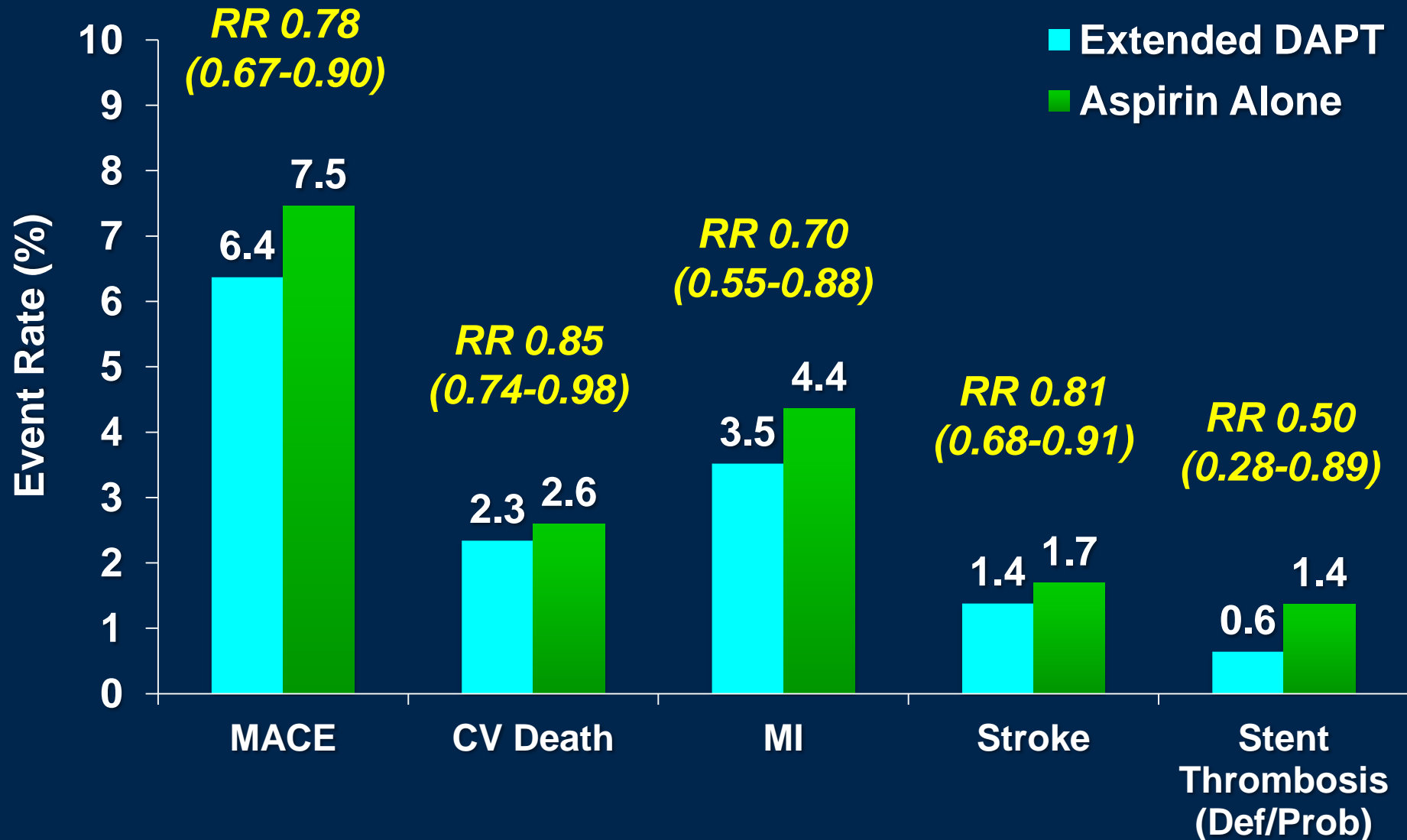
# CV Death, MI, or Stroke in ACS



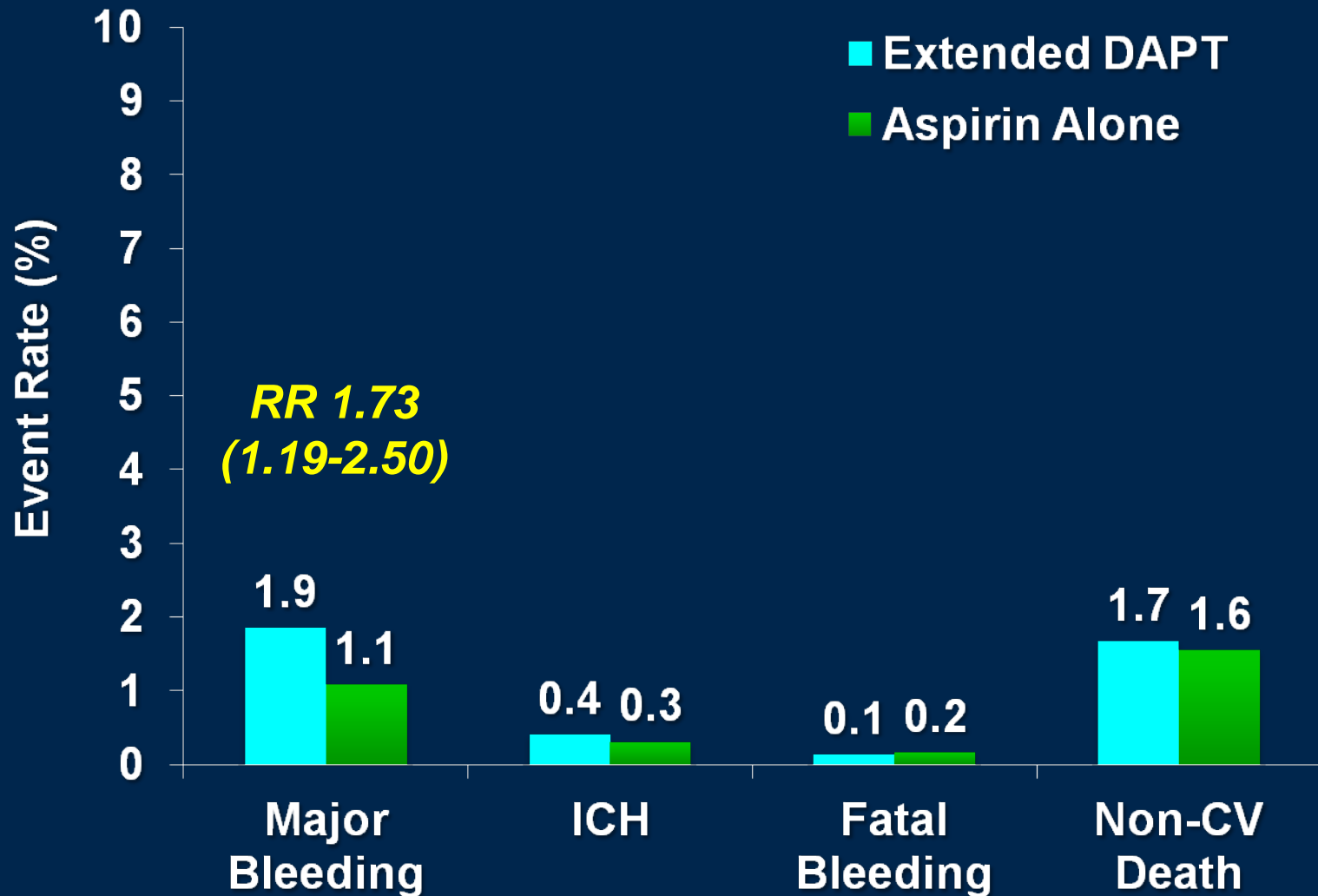
# Cardiovascular Death in ACS



# Individual CV Endpoints in ACS



# Major Bleeding & Safety in ACS





# FDA Approval

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## 1 INDICATIONS AND USAGE

BRILINTA is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel.

BRILINTA also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS [*see Clinical Studies (14.1)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing

In the management of ACS, initiate BRILINTA treatment with a 180 mg loading dose. Administer 90 mg twice daily during the first year after an ACS event. After one year administer 60 mg twice daily.



# Conclusions

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- In patients with MI, continuing P2Y<sub>12</sub> inhibition significantly reduces the composite of CV death, MI or stroke, with consistent and significant effects on all 3 components
- Continuing P2Y<sub>12</sub> inhibition increases the risk of bleeding, but not of fatal bleeding or ICH
- The benefit-risk profile of continuing P2Y<sub>12</sub> inhibition is similar to long-term ASA monoRx
- Future research should investigate criteria that can be used to optimize balance between antithrombotic benefit vs. risk of bleeding