Dual Antiplatelet duration in ACS: too long or too short?

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Paradigm Shift

the ideal duration of DAPT: a moving target

Early (stent-related) thrombotic events prevention

(Treating the stent)

Seconday CV Prevention

(Treating the patient)

Which way? Drug therapy for Shorter or Longer Time?

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The need for dual antiplatelet therapy

"mandatory"*

"possibly beneficial*"

< 12 months

> 12 months

***** ***Premature discontinuation of DAPT would lead to an unacceptably high rate of ST***

***** ***Mitigating the risk of recurrent ischemic events unrelated to previous PCI***

EXCELLENT
RESET
SECURITY
ISAR SAFE
OPTIMIZE

PRODIGY
ITALIC
NIPPON

ARCTIC INTERRUPTION
DES-LATE
REAL/ZEST
DAPT
PEGASUS
TRA 2° P-TIMI 50

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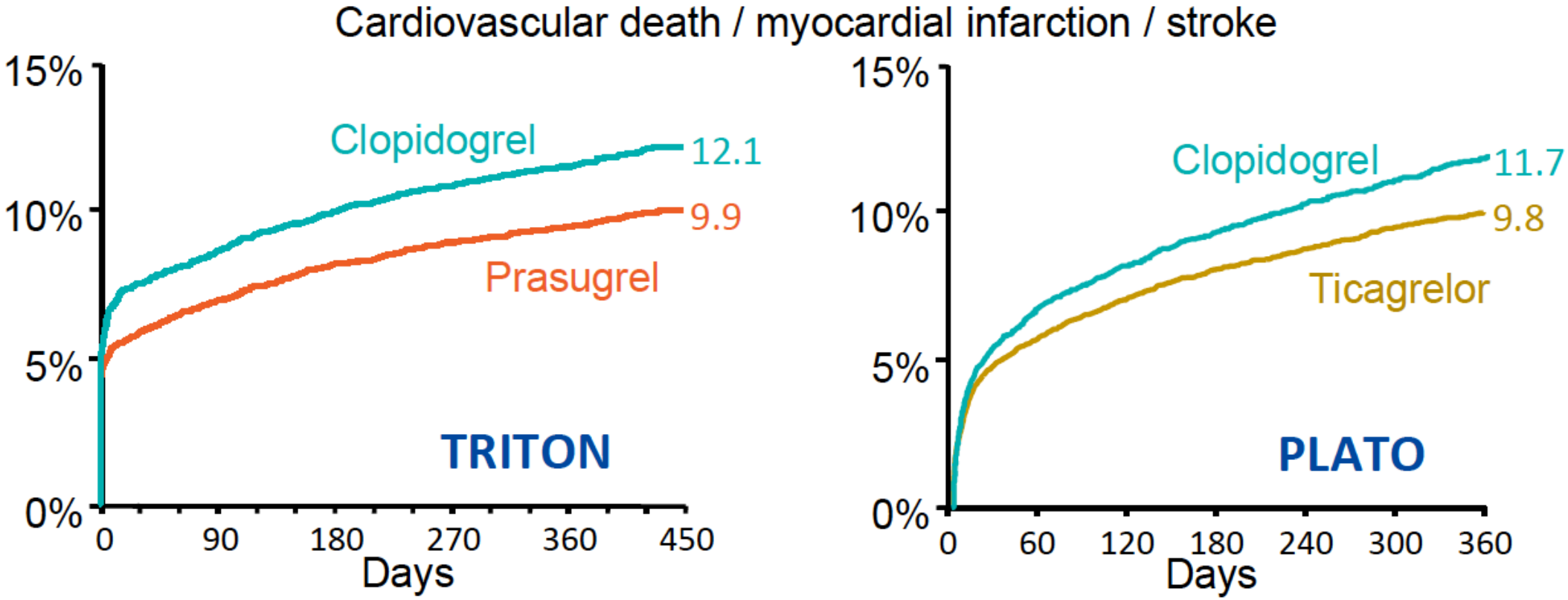
Prasugrel and ticagrelor
Increasing benefit during the first year



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Wiviott SD et al., N Engl J Med 2007; Wallentin L et al., N Engl J Med 2009

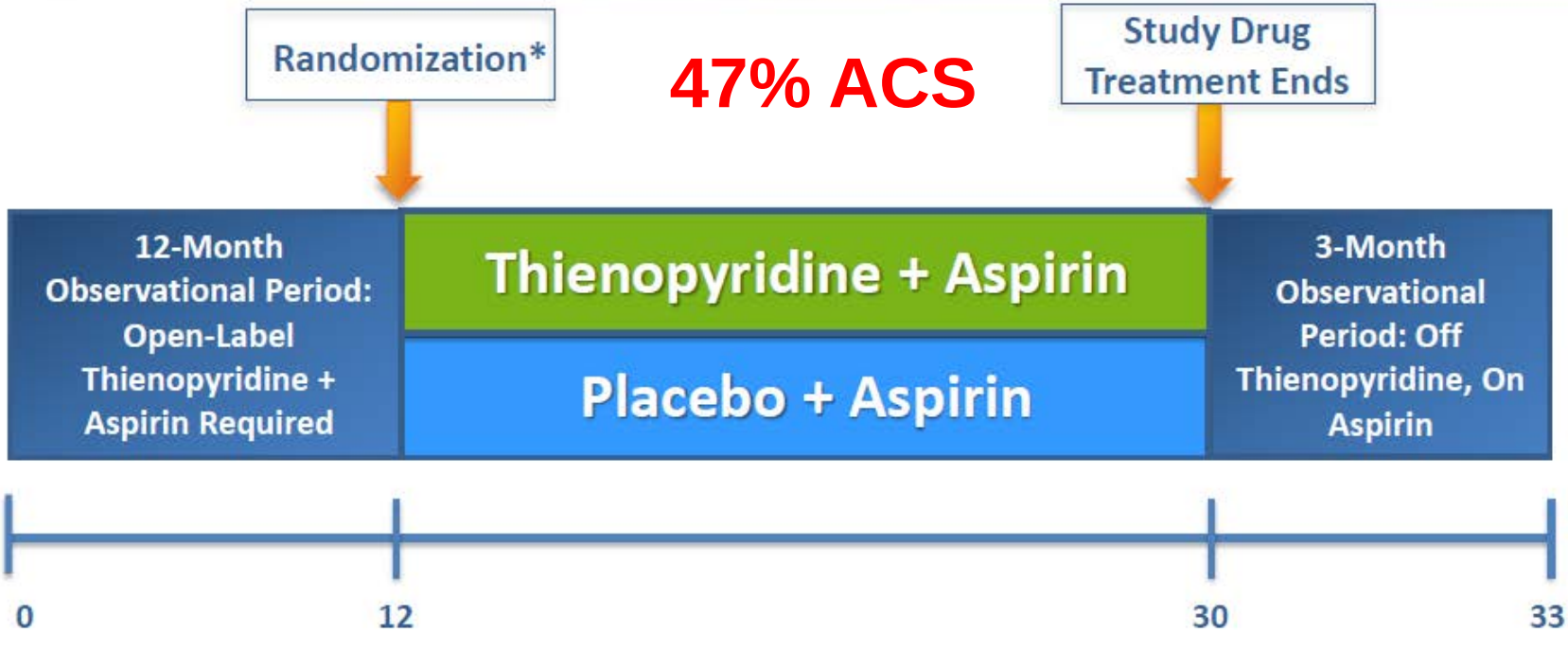
Endpoints in studies evaluating abbreviated duration of DAPT (6 months or less) after stenting in populations having a majority of ACS patients

	Stent thrombosis		MACE		Major bleeding	
	S-DAPT	L-DAPT	S-DAPT	L-DAPT	S-DAPT	L-DAPT
PRODIGY	15 (1.5)	13 (1.3)	98 (10.0)	100 (10.1)	6 (0.6)	16 (1.6)
RESET	2 (0.2)	3 (0.3)	8 (0.8)	11 (1.3)	5 (0.5)	10 (1)
EXCELLENT	6 (0.9)	1 (0.1)	56 (8.0)	60 (8.5)	4 (0.6)	10 (1.4)
Total *n*/*N* (%)	23/2532 (0.9)	17/2529 (0.7)	162/2532 (6.4)	171/2529 (6.8)	15/2532 (0.6)	36/2529 (1.4)

Montalescot G and Sabatine MS Eur Heart J 2016; 37: 344–352

Design

DAPT STUDY



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

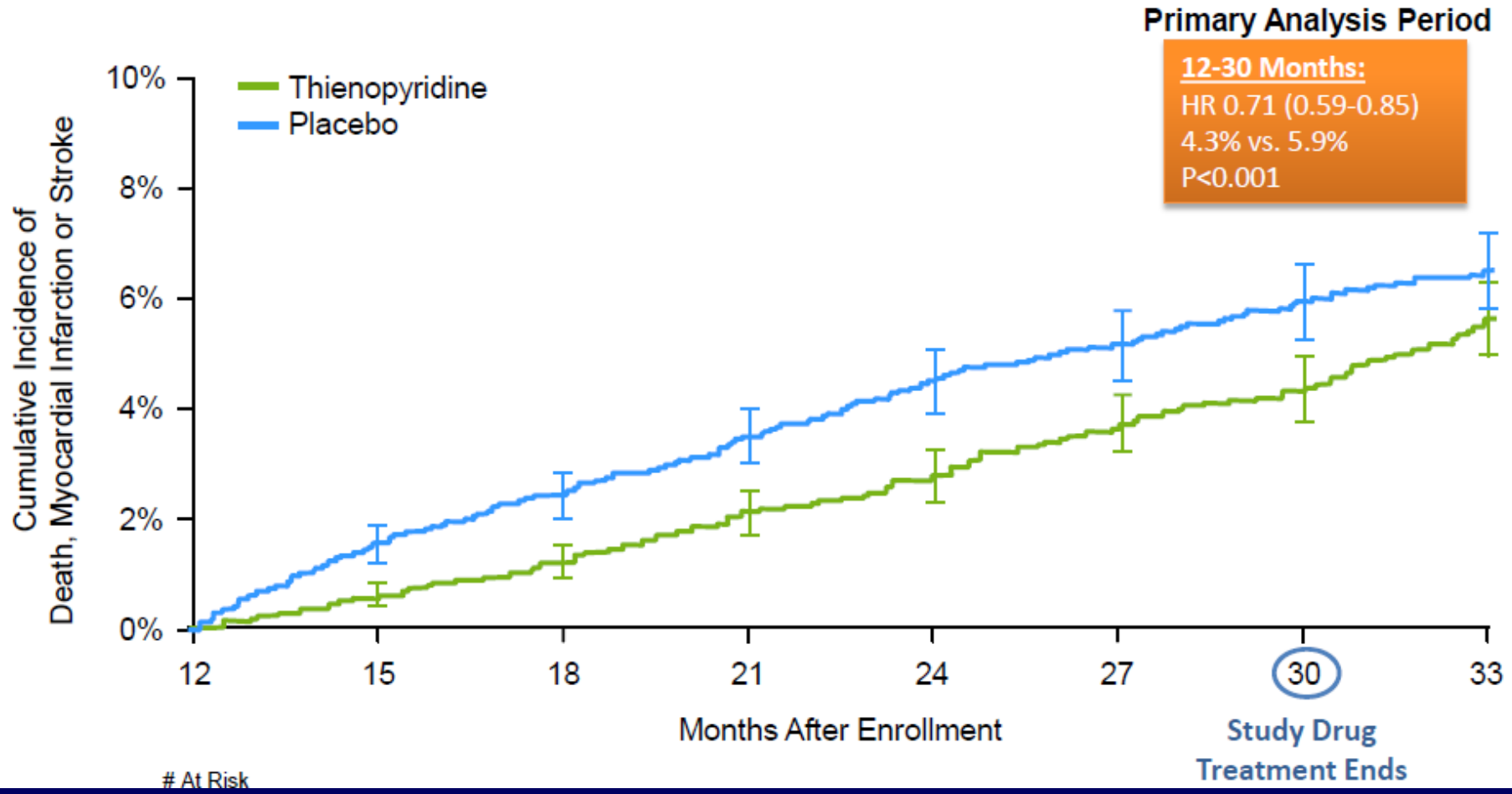
Randomized: Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).

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

ClinicalTrials.gov number NCT00977938

Co-Primary Effectiveness End Point MACCE

DAPT STUDY



Mauri L et al. N Engl J Med 2014;371:2155-66

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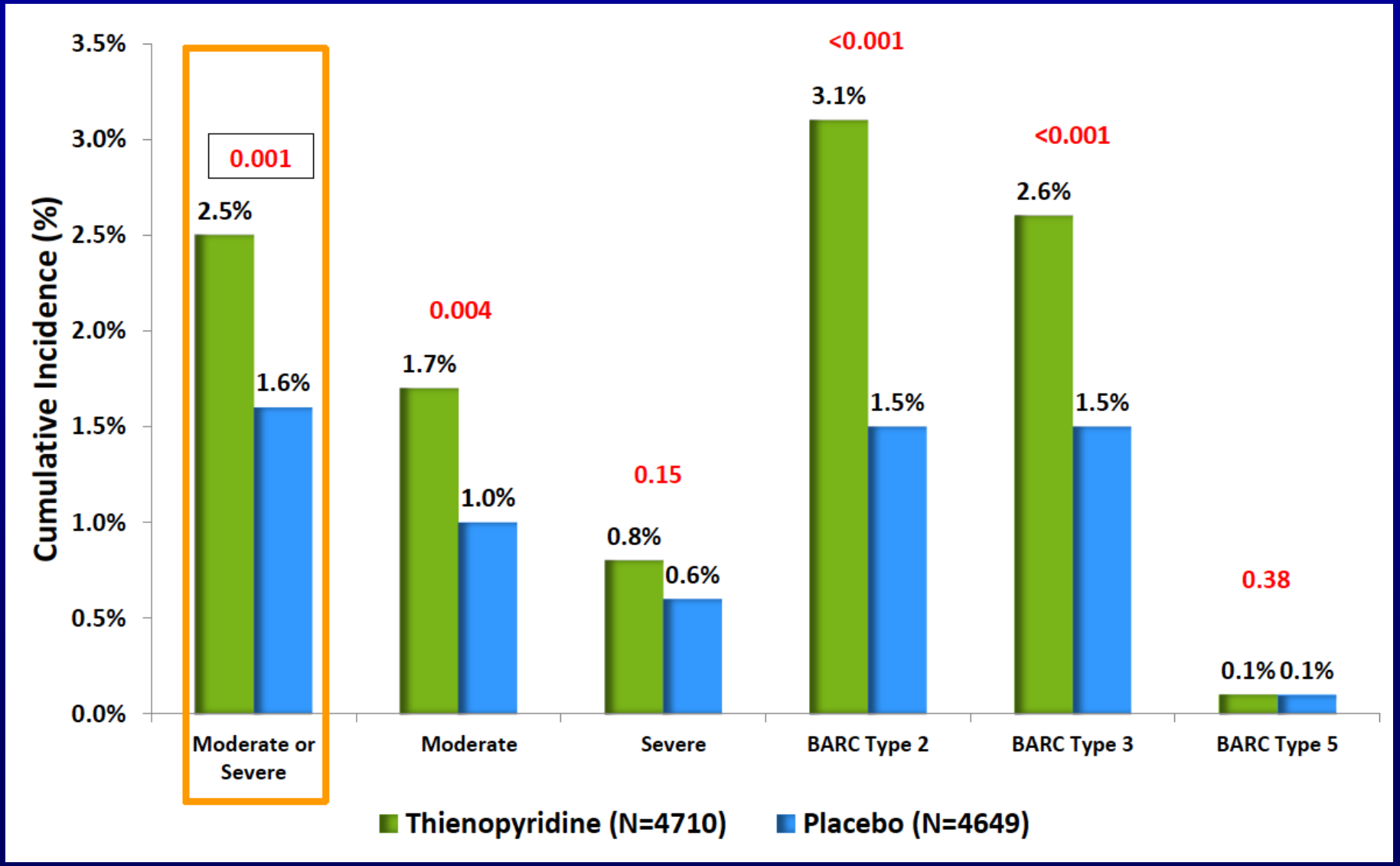
Bleeding End Point during Month 12 to Month 30



Mauri L et al. N Engl J Med 2014;371:2155-66

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Trial Design

-Age ≥65 years
-Diabetes
-2nd prior MI (>1 yr)
-Multivessel CAD
-CrCl <60 mL/min

Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor

RANDOMIZED
DOUBLE BLIND

Planned treatment with ASA 75 – 150 mg/d & Standard background care

- **Ticagrelor 90 mg bid**
- **Ticagrelor 60 mg bid**
- **Placebo**

Follow-up Visits
Q4 mos for 1st yr, then Q6 mos

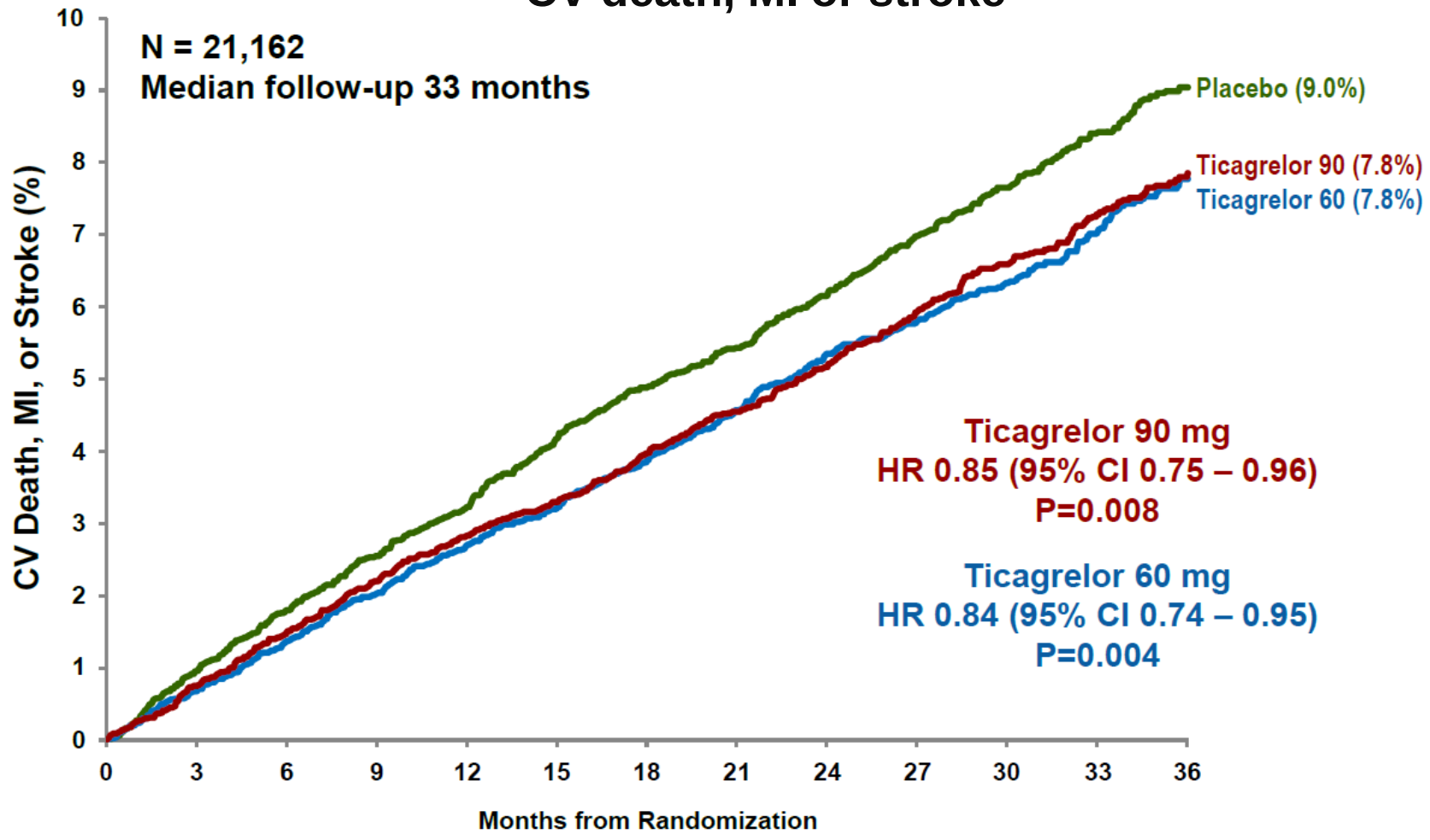
Minimum 1 year follow-up
Event-driven trial

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Bonaca MP et al. *Am Heart J* 2014;167:437-44

Bonaca MP et al. N Engl J Med 2015 March 14

Primary Endpoint



An Academic Research Organization of
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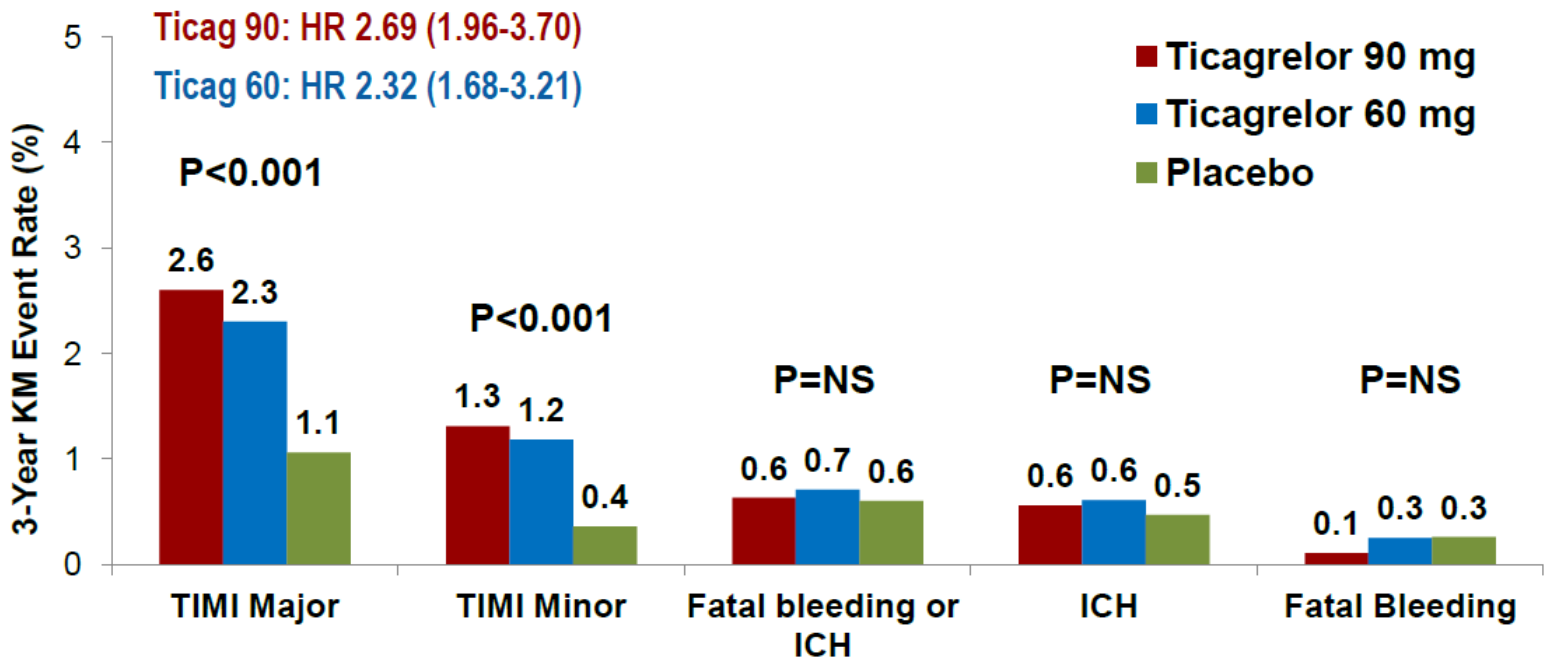
Bonaca MP et al. N Engl J Med 2015 March 14

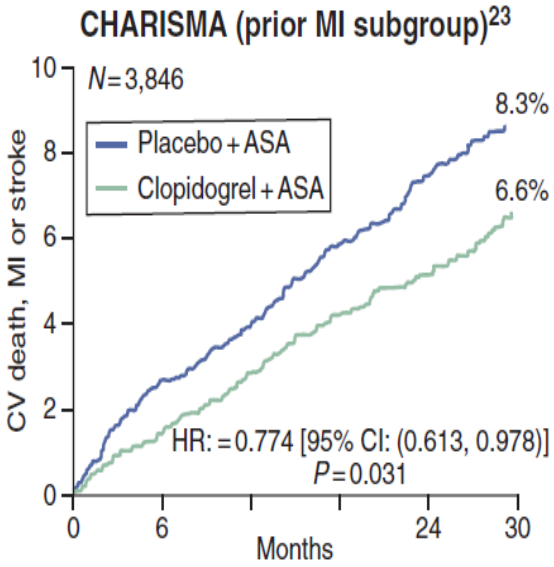
Bleeding

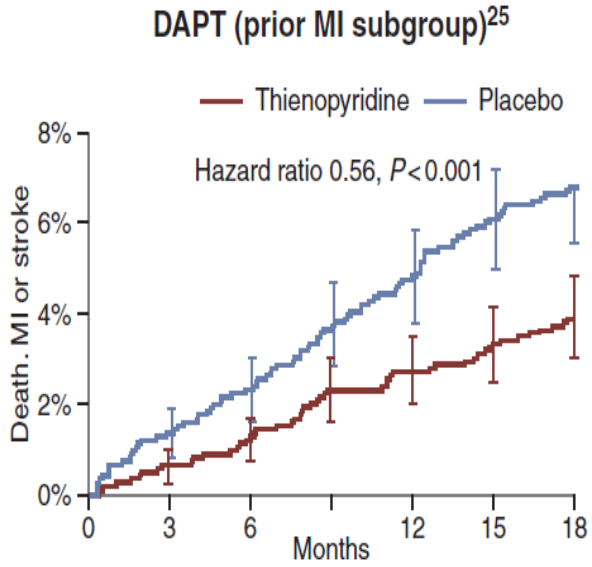


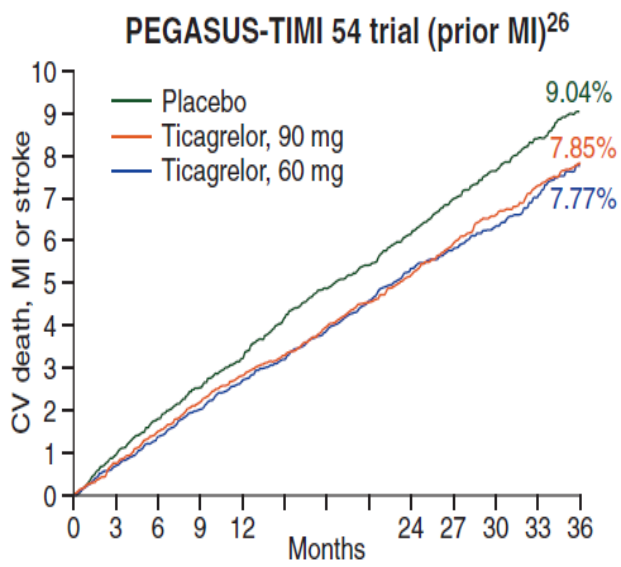
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

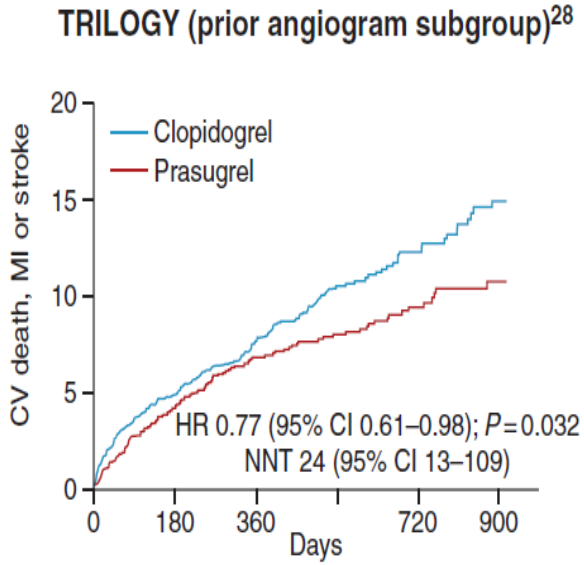
Bonaca MP et al. N Engl J Med 2015 March 14

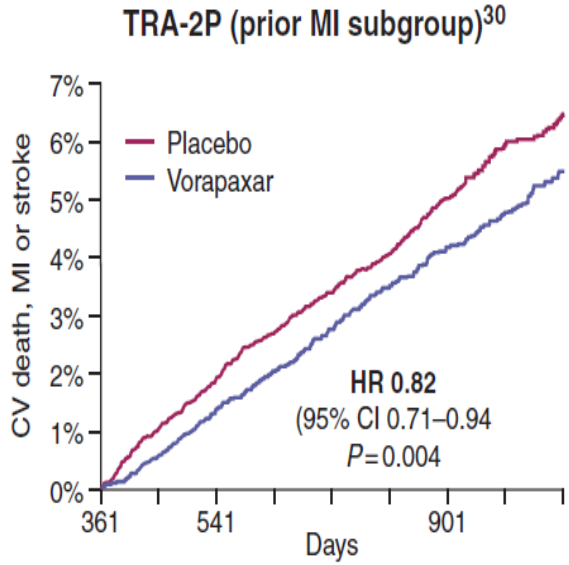
Results of the 5 studies which tested stronger antiplatelet Rx beyond 1 year vs. standard of care, in pts with proven CAD











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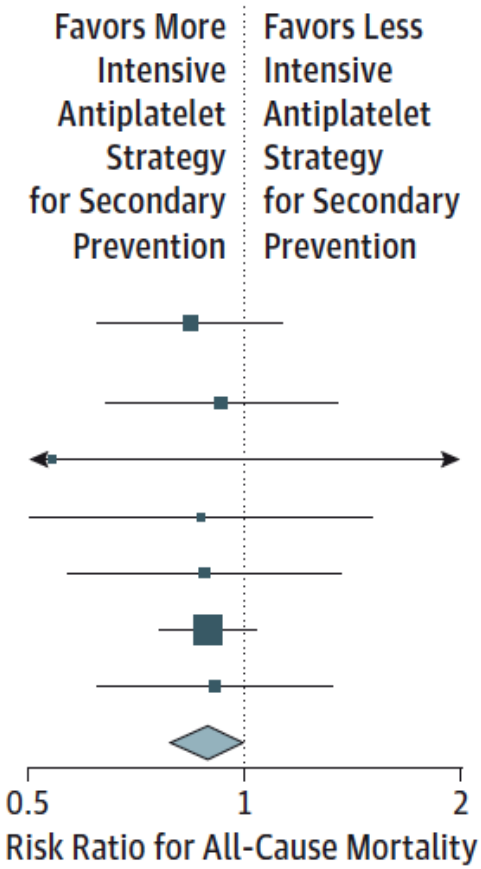
Risk of All-Cause Mortality With More Intensive Antiplatelet Therapy for Long-term Secondary Prevention in Patients With Prior Myocardial Infarction

~11% rededication in all cause mortality

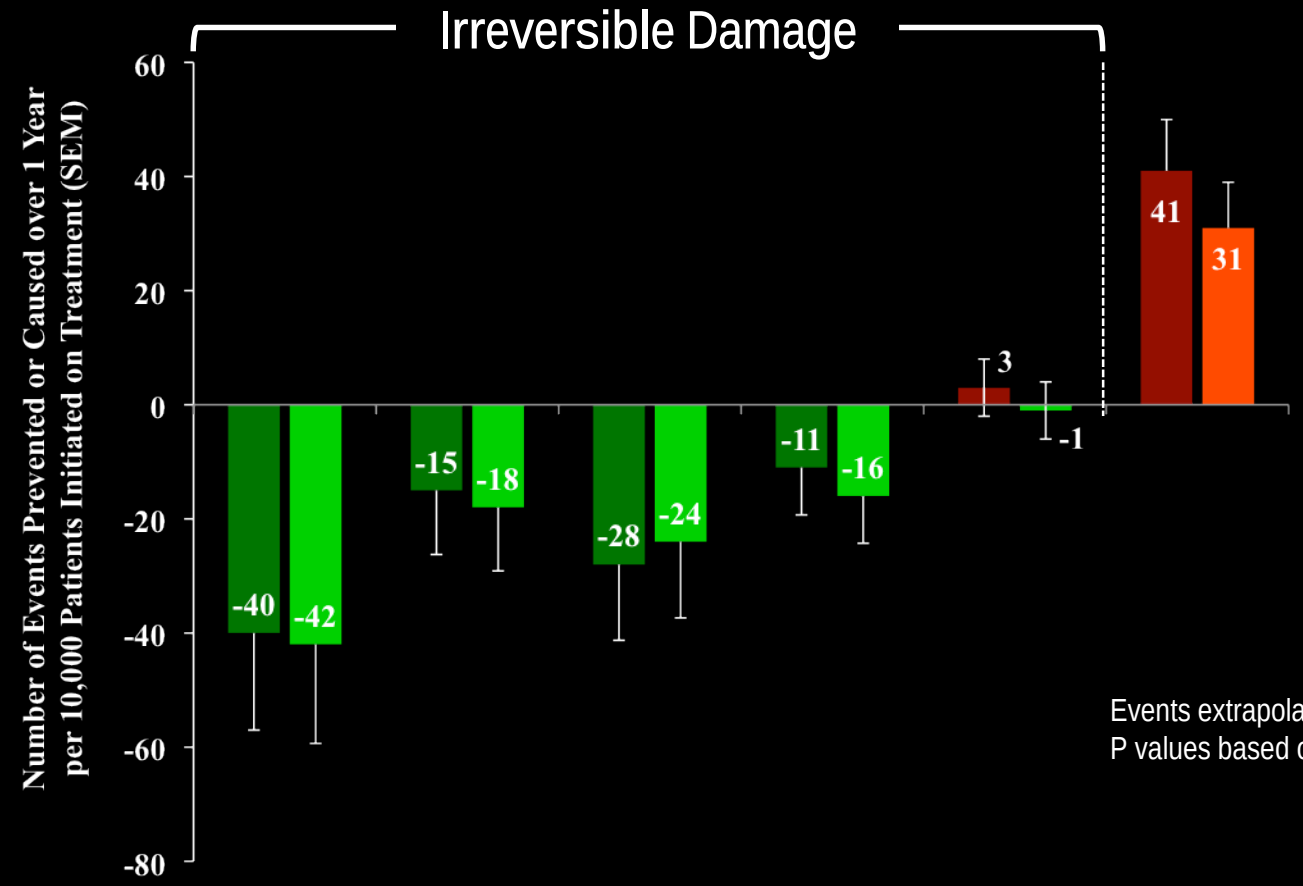
- **~17% reduction in CV Mortality (about 60% of deaths)**
- **No excess in non-CV Mortality (about 40% of deaths)**

Trial	More Intensive No./Total No.	Less Intensive No./Total No.	Hazard Ratio (95% CI)
CHARISMA (prior myocardial infarction cohort)	82/1903	99/1943	0.84 (0.63-1.13)
PRODIGY	52/732	56/733	0.93 (0.64-1.35)
ARCTIC	1/156	2/167	0.54 (0.05-5.87)
DAPT MI	24/1805	27/1771	0.87 (0.50-1.50)
DES-LATE	37/1512	43/1551	0.88 (0.57-1.37)
PEGASUS-TIMI 54 (60 mg twice daily)	289/7045	326/7067	0.89 (0.76-1.04)
TRA2P-TIMI 50 MI (no stroke/TIA)	238/8458	259/8439	0.91 (0.62-1.33)
Total	723/21611	812/21671	0.89 (0.79-0.99)
			P=.04



Bonaca MP, Sabatine MS JAMA Cardiology 2016

Outcomes over 1 Year for 10,000 Patients with Prior MI Initiated on Ticagrelor



Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

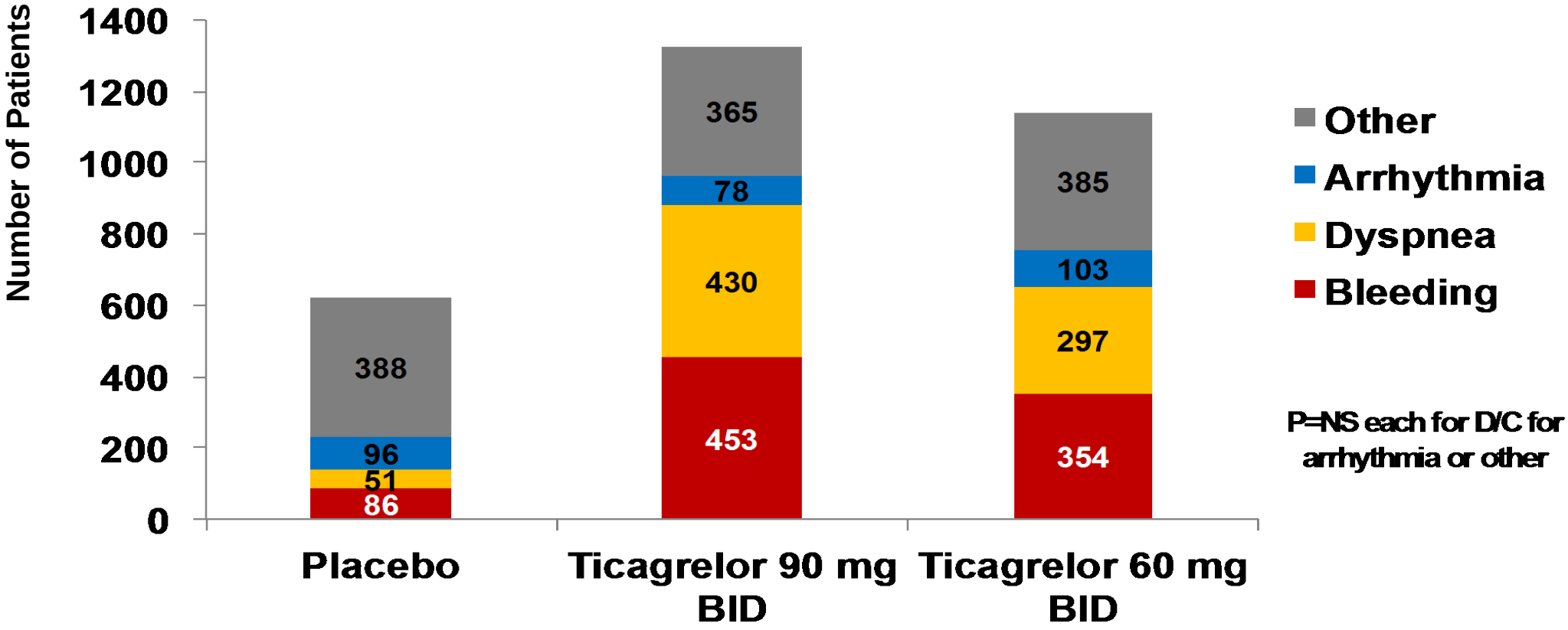
Events extrapolated from 3-yr KM rates from ITT population
P values based on Cox regression

P value		CV Death, MI, or Stroke	CV Death	MI	Stroke	Fatal bleed or ICH	TIMI major bleed
	Ticagrelor 90 mg	0.008	0.15	0.01	0.14	0.43	<0.001
	Ticagrelor 60 mg	0.004	0.07	0.03	0.03	0.47	<0.001

Adverse Events Leading to Discontinuation

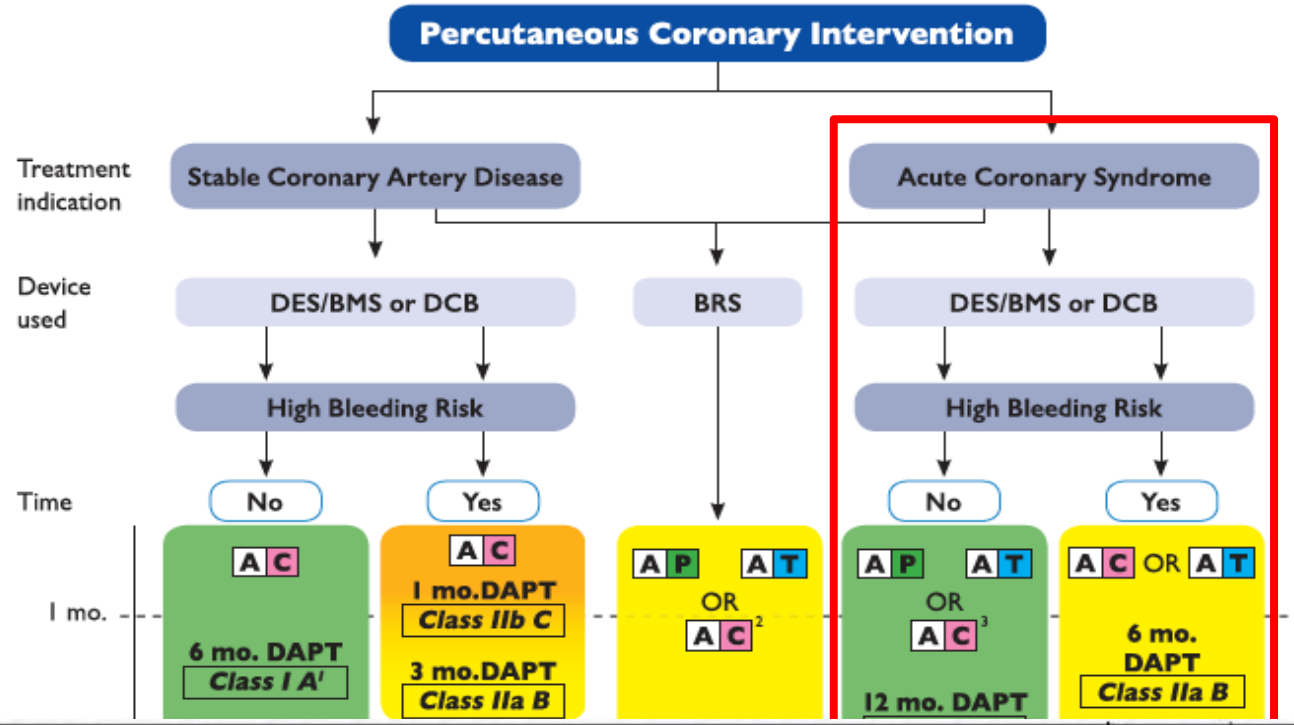
3 Year KM Rate (%) – p-value for each dose vs. placebo <0.001

Treatment Arm	Any AE	Bleeding	Dyspnea
Ticagrelor 90	19.0%	7.8%	6.5%
Ticagrelor 60	16.4%	6.2%	4.6%
Placebo	8.9%	1.5%	0.8%



2017 ESC Focused Update on DAPT

Algorithm for DAPT in pts treated with PCI



Recommendations	Class	Level
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.	IIb	A
In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg *b.i.d.* for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.	IIb	B

Which patients with ACS will likely derive the greatest benefit-risk profile from long-term intensive antiplatelet therapy?

Much of the literature that currently shapes cardiovascular practice fails to offer meaningful information to help clinicians identify or act on heterogeneity

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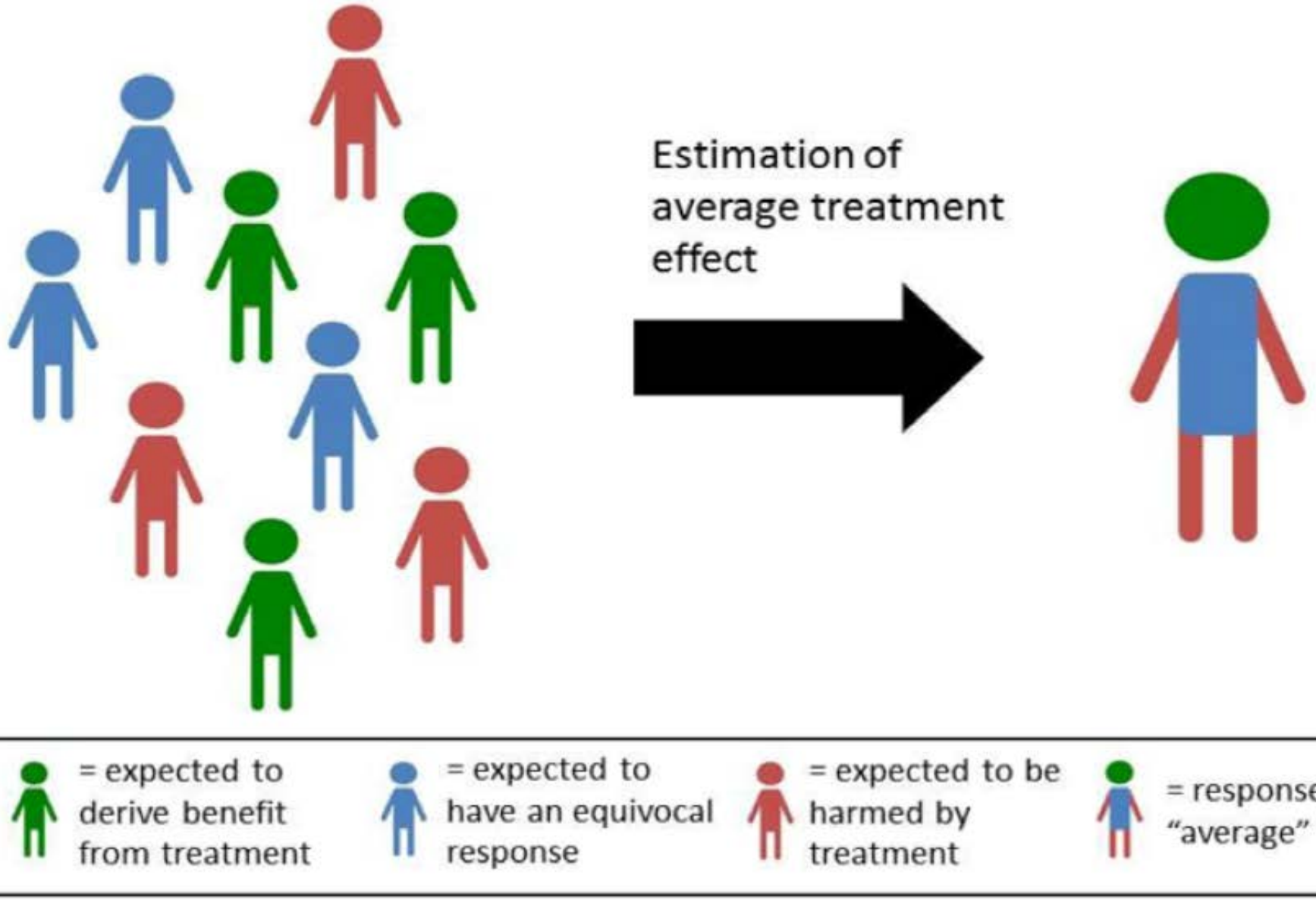
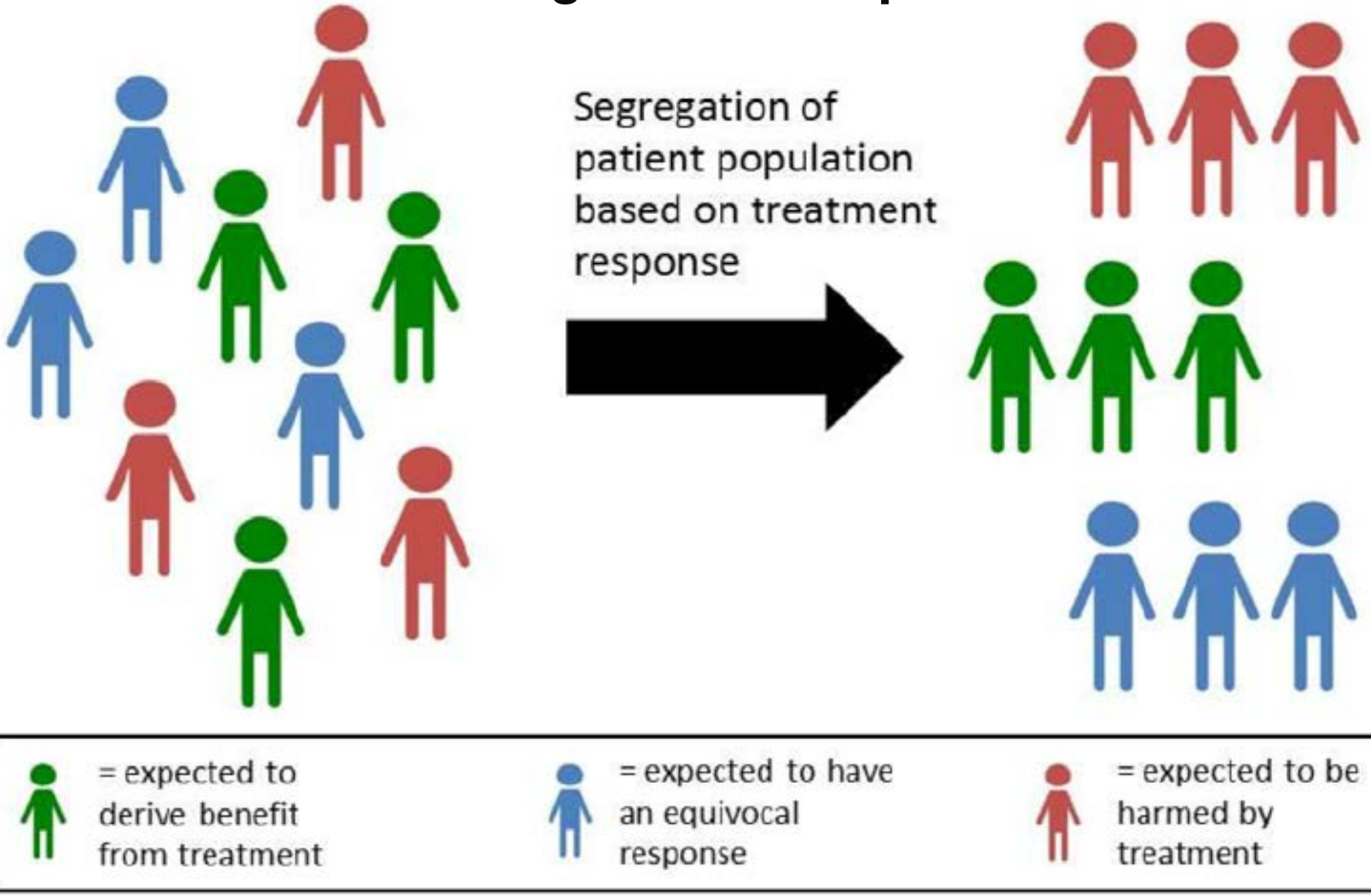
Average treatment effect assessed in a heterogeneous population



Yeh RW Circulation. 2017;135:1097–1100

Identification of heterogeneous responses to treatment



Yeh RW Circulation. 2017;135:1097–1100

Means to Improve Personalized Care in Cardiovascular Disease

- Subgroup Analyses of RCTs
- Risk Models (Scores)
- Decision Tools

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Important Shortcomings in Subgroup Analyses of RCTs

- Heterogeneity in treatment response may be best identified by stratification based on multiple factors rather than single variables.
- RCTs are rarely powered to detect statistical interactions between subgroups.
- The identification of treatment effect heterogeneity has generally examined interactions on the relative rather than absolute scale.

Important Shortcomings in Risk Models

- The events studied are frequently a mix of entities without a common causal pathway
- There may be no evidence that any intervention exists to mitigate the risk being predicted.
- Risk scores to often use predicted risk as a surrogate for the expected treatment effect

Identifing Heterogeneous Treatment Responses

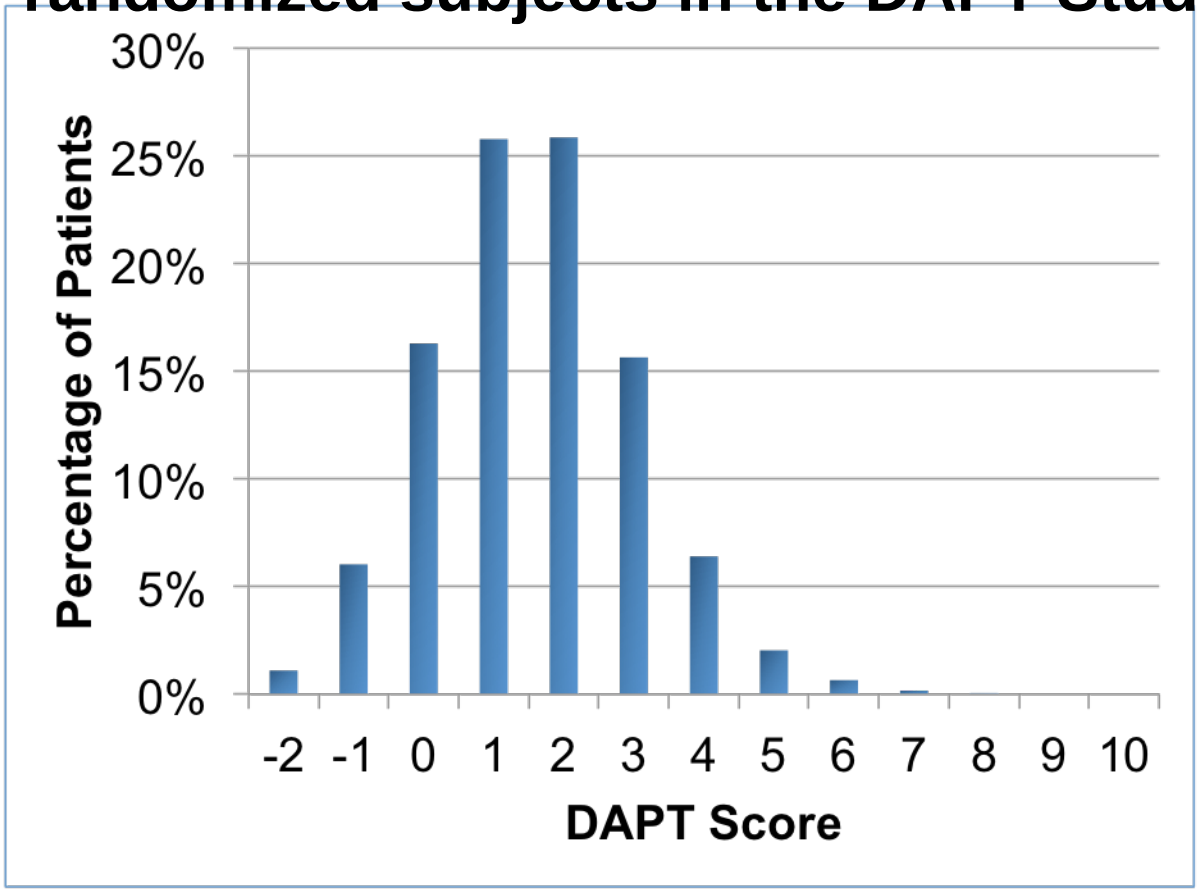
Rationale of Decision Tools

1. **Differences in risk between pts must be identifiable by the tool more reliably than by clinical judgment alone (*identifiable heterogeneity*)**
2. **The identified risks should be modifiable by clinical decisions (*actionability*).**
3. **The tool should be able to be adopted into practice (*implementability*).**

The 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



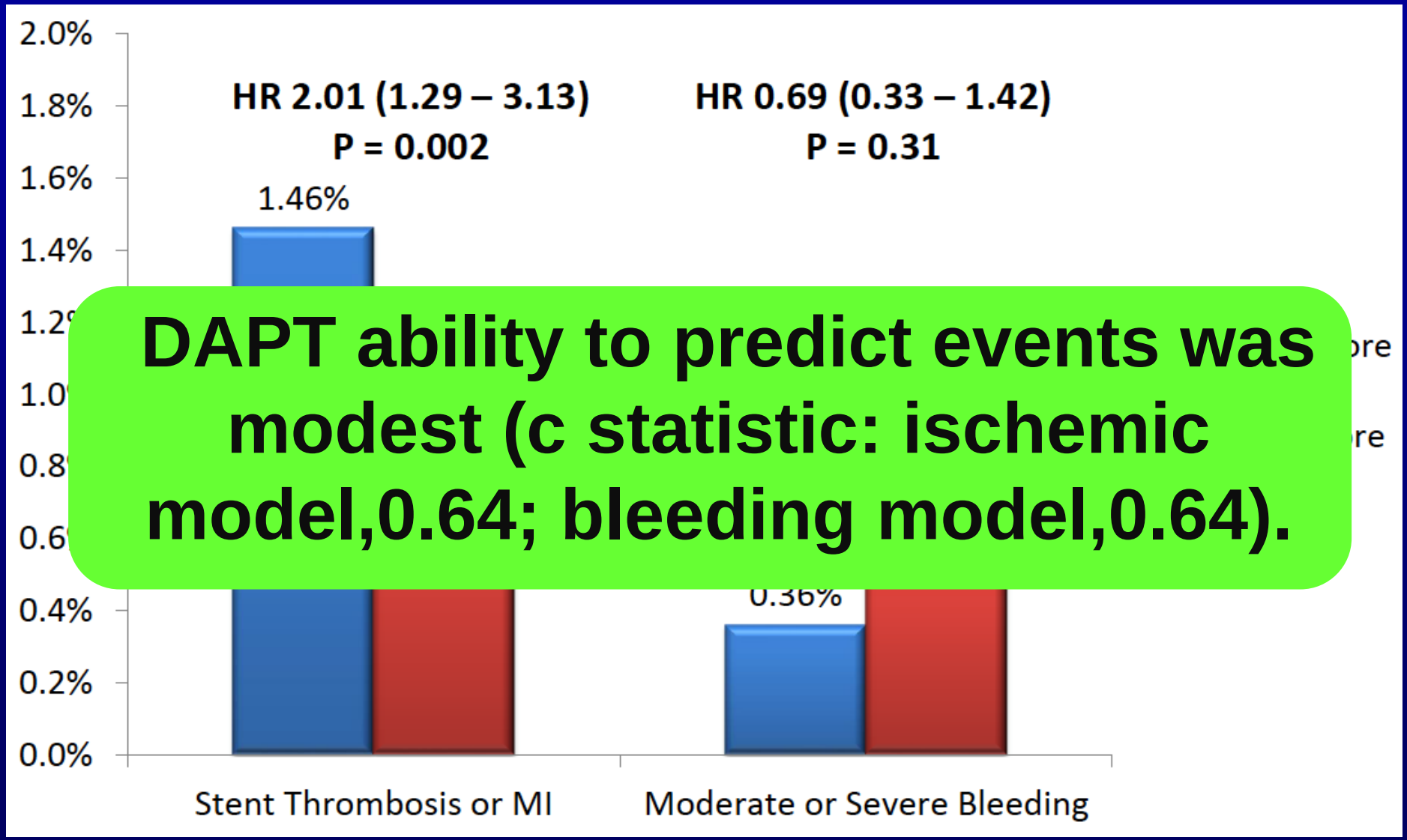
Among patients who have not had a major ischemic or bleeding event within the first year after PCI:

The DAPT Score identified patients for whom ischemic benefits outweighed bleeding risks, and patients for whom bleeding risks outweighed ischemic benefits.

Low DAPT Score (< 2)	High DAPT Score ≥ 2
NNT to prevent ischemia = 153	NNT to prevent ischemia = 34
NNH to cause bleeding = 64	NNH to cause bleeding = 272

DAPT Score may help clinicians decide *who should, and who should not* be treated with extended DAPT

DAPT Score External Validation (PROTECT)



DAPT ability to predict events was modest (c statistic: ischemic model,0.64; bleeding model,0.64).

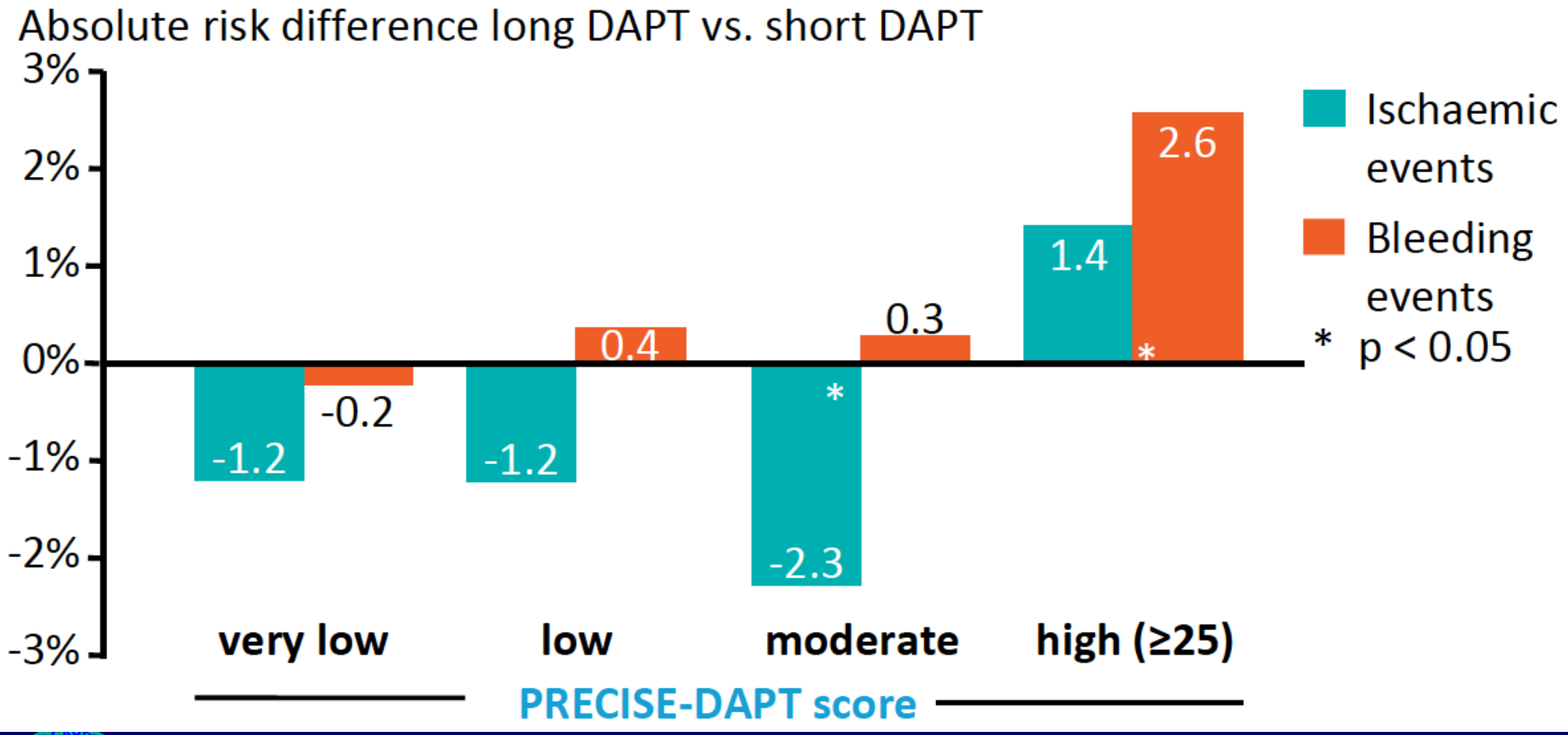
Yeh RW et al JAMA 2016; 315:1735-1749

The PRECISE-DAPT Score

	Hazard ratio (95% CI)	p value
Age (for each increase of 10 years)	1·34 (1·11–1·48)	0·005
Previous bleeding	4·14 (1·22–14·02)	0·023
White-blood-cell count (for each increase of 10^3 cells per µL)	1·06 (0·99–1·13)	0·078
Haemoglobin at baseline (for each increase of 1 g/dL)	0·67 (0·53–0·84)	0·001
Creatinine clearance (for each increase of 10 mL/min)	0·90 (0·82–0·99)	0·004

Costa F et al. Lancet 2017; 389: 1025–34

Personalized stratification of DAPT duration
- PRECISE-DAPT -



Costa F et al. Lancet 2017; 389: 1025–34

ACS Secondary Prevention: Unmet Needs

Tailoring therapy to risk

The challenge:
Develop a model that will account for variation of risk over time in a specific patient

Clinicians must remain aware and vigilant that current risk scores, although useful to improve the accuracy of the prognostic assumptions affecting clinical decisions, *cannot be considered a clear-cut decision rule or a substitute for case-by-case critical judgment*.

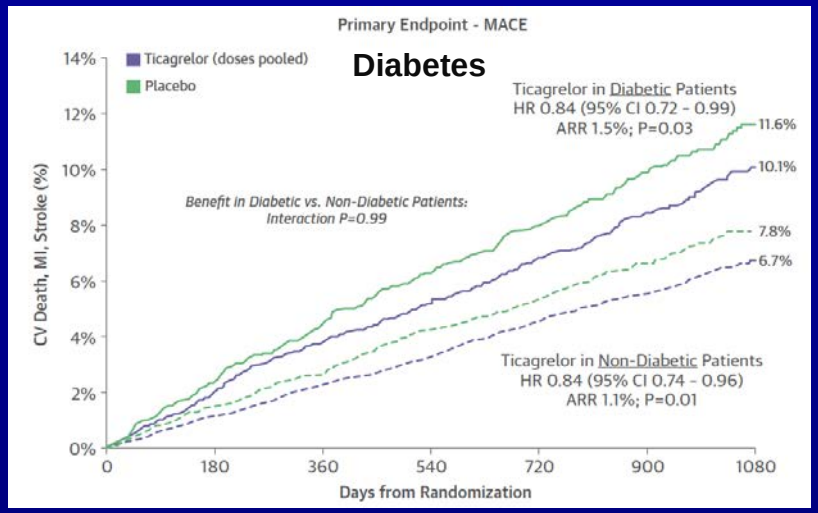
2017 ESC Focused Update on Dual Antiplatelet Therapy

Use of risk scores as guidance for the duration of DAPT therapy

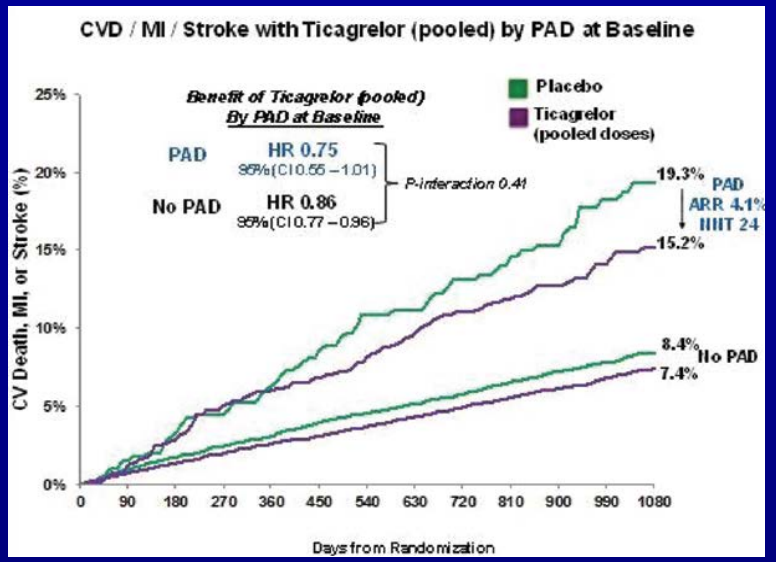
Recommendations	Class[a]	Level[b]
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations[c] may be considered.[15,18]	IIb	A

None of these risk prediction models has been prospectively tested in the setting of prospective randomized controlled studies. Therefore, their value in improving patient outcomes remains unclear.

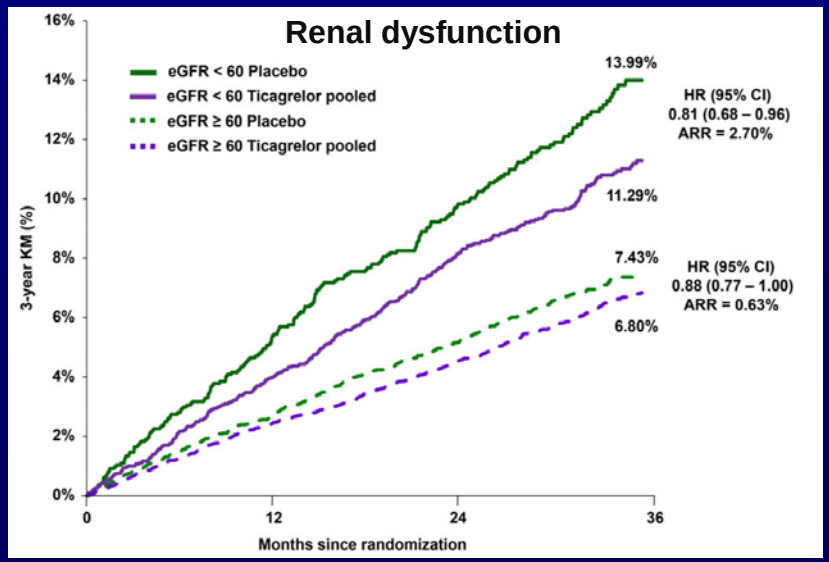
Which patients with an MI will likely derive the greatest benefit-risk profile from long-term intensive antiplatelet therapy?



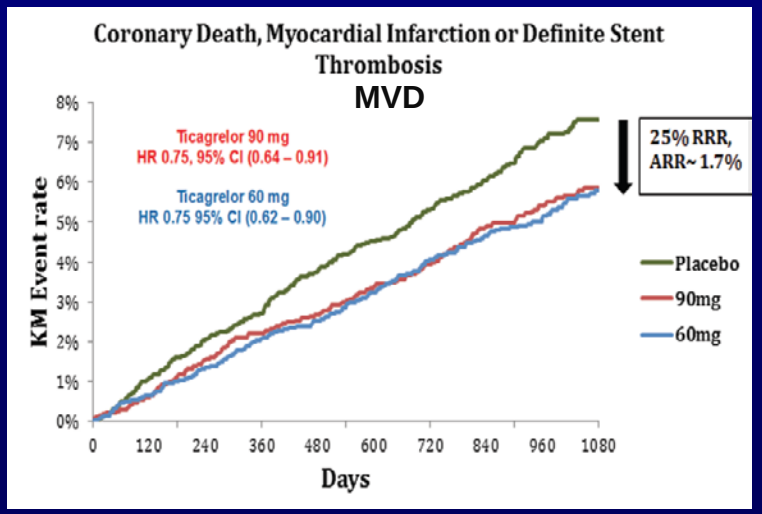
Bhatt DL et al. J Am Coll Cardiol. 2016



Bonaca MP. et al. J Am Coll Cardiol. 2016



Magnani G,et al. Eur Heart J. 2016;37(4):400-408.



Bansilal S. et al. J Am Coll Cardiol. 2016

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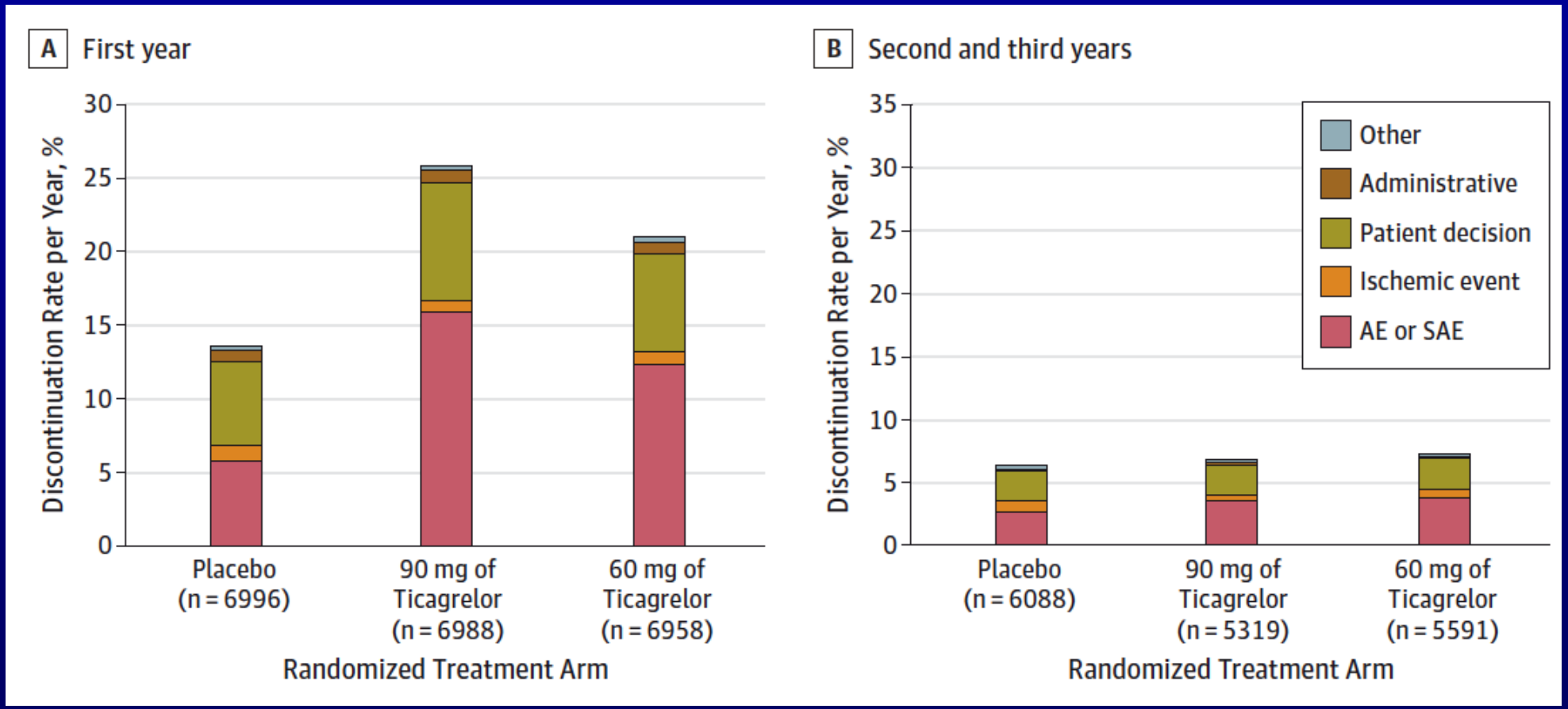
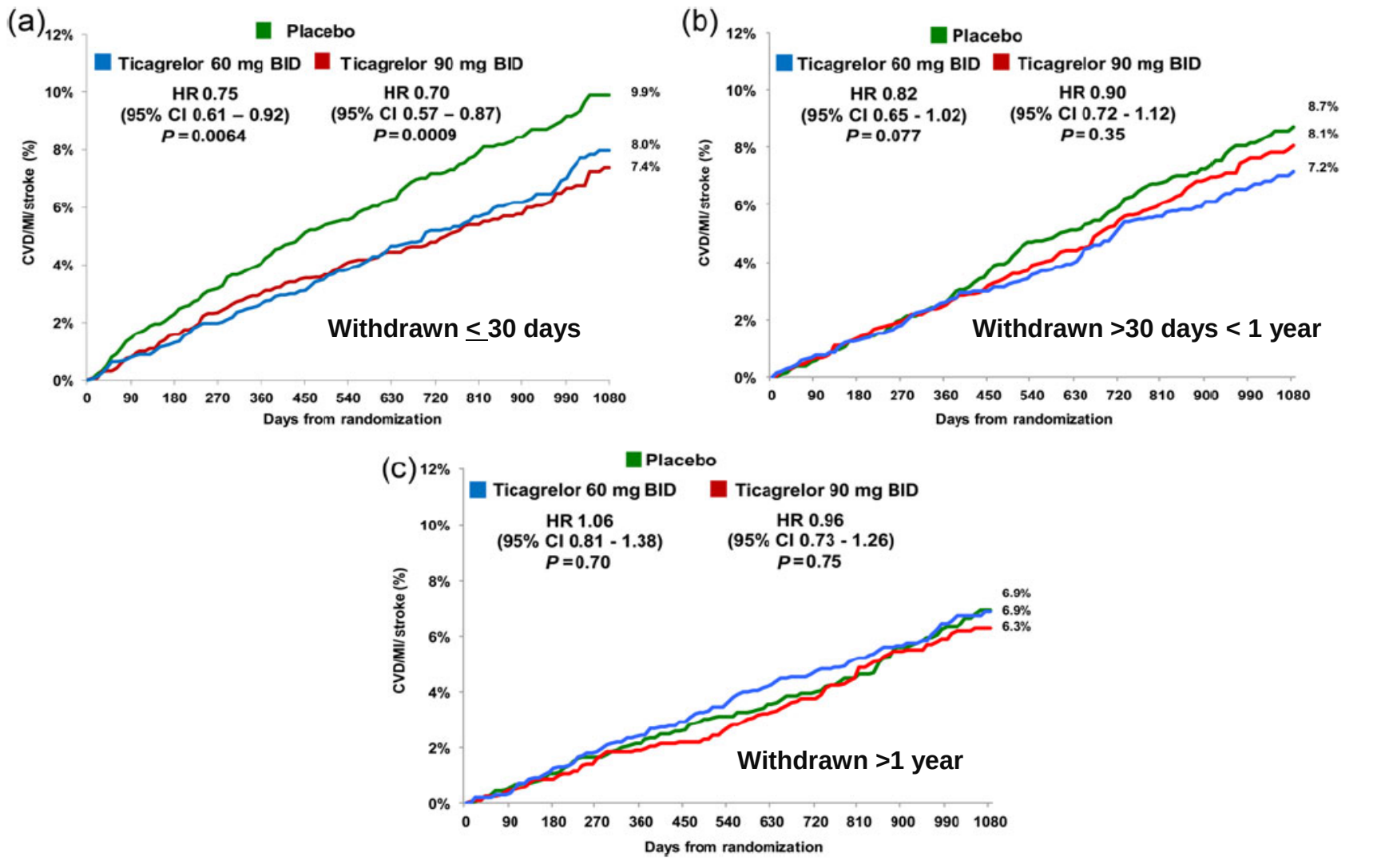
Annualized discontinuation rates in PEGASUS-TIMI 54 Trial



Bonaca MP et al. JAMA Cardiology 2016 doi:10.1001/jamacardio.2016.1017

Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in pts with prior MI



Bonaca MP et al. Eur Heart J. 2016; 37:1133-1142

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Is prolonged intensive antiplatelet therapy the new gold standard after ACS?

"Not for all patients."

- Only patients who have tolerated and adhered to therapy during the previous 12 months should be considered for long-term intensive antiplatelet therapy.
- Prolonged therapy should be avoided in high risk patients for bleeding.
- Although prolonged intensive antiplatelet Rx is effective at reducing MACE across the MI population, such therapy may be particularly attractive in pts with characteristics associated with heightened ischemic risk (diabetes, MVD, renal dysfunction, or PAD) in whom there are greater absolute risk reductions in MACE and/or notable reductions in CV mortality.