Optimal Initiation and Duration of DAPT in ACS Patient: Reviewing the Evidence of Ticagrelor

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Mount Sinai Heart

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below. These relationships may lead to bias in my presentation.

Affiliation/Financial Relationship	Company
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• Advisory Board	• Janssen (J+J),
• Consulting Fees/Honoraria	• Janssen (J+J), Maya Medical,

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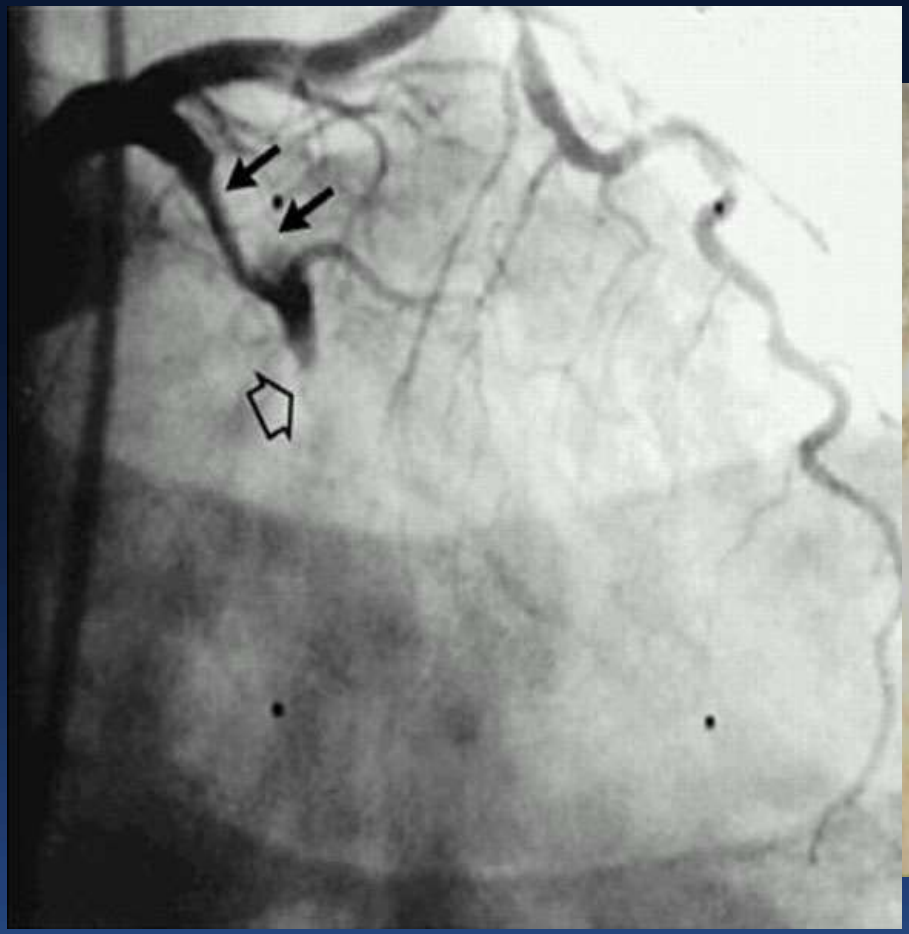
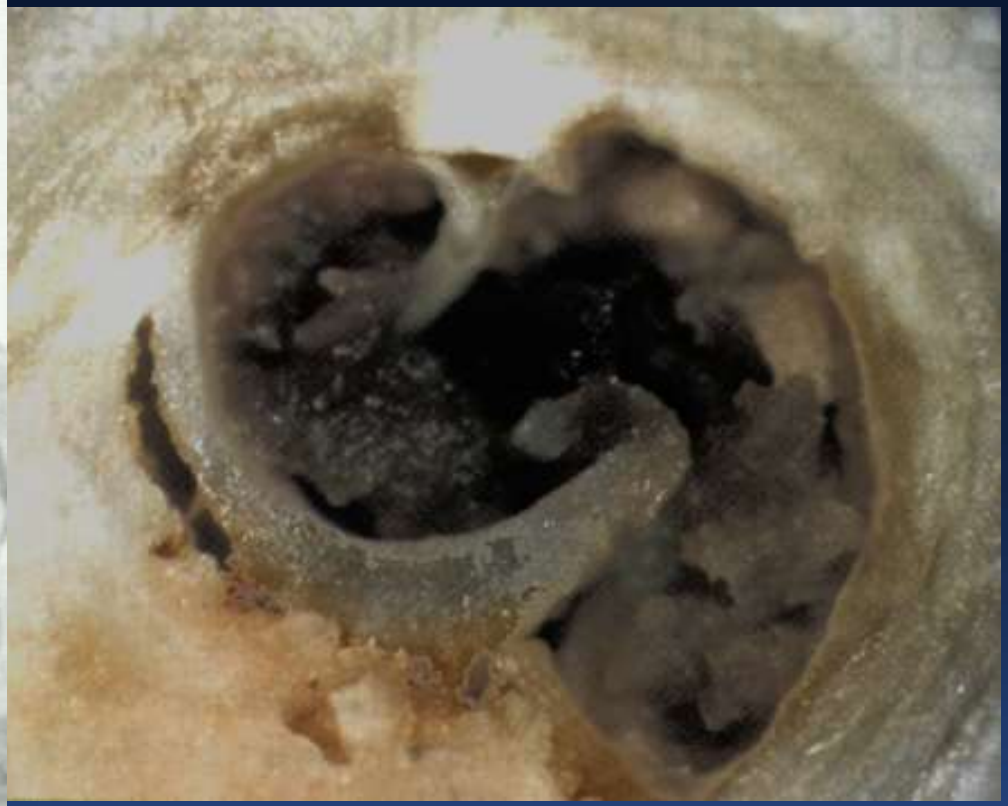
ACS: Pathophysiology





Ruptured plaque with thrombus; systemic inflammation with heightened platelet reactivity

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2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

Endorsed by Preventive Cardiovascular Nurses Association and Society for Vascular Surgery

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Studies of Shorter Duration DAPT After Stent Implantation

- Five RCTs of patients treated with elective DES implantation compared shorter duration (3 to 6 month) DAPT with 12 months of DAPT
- Trials primarily enrolled low-risk (non-ACS) patients
- These studies, several meta-analyses and ERC analysis did not find any increased risk of stent thrombosis
- Shorter duration DAPT resulted in lower bleeding complications

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et al. 2016 ACC/AHA Guideline Focused Update on Duration of DAPT in Patients with CAD. JACC 2016 & Circulation 2016

Studies of Longer Duration DAPT After Stent Implantation

- Six RCTs consisting predominantly of patients treated with elective DES compared prolonged (total therapy duration 18-48 months) DAPT with 6-12 months of DAPT
- Taken as a whole, studies of longer duration ("prolonged" or "extended") DAPT for an *additional* 18-36 months after DES found:
  - ≈1% to 2% absolute decrease in late stent thrombosis and ischemic complications
  - ≈1% absolute increase in bleeding complications
- Weighted risk-benefit analysis by ERC found treatment with prolonged DAPT resulted in:
  - 6 fewer MIs per 1,000 patients per year
  - 3 fewer stent thromboses per 1,000 patients per year
  - 5 additional major bleedings per 1,000 patients per year

Levine, GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of DAPT in Patients with CAD. JACC 2016 &

Prolonged or Extended DAPT >1 Year Post-MI

- **Studies Considered: CHARISMA, Dual Antiplatelet Trial (DAPT) Post-MI Subgroup, PEGASUS-TIMI 54**
- **Taken as a whole, trials of prolonged or extended DAPT suggest:**
  - **Benefit/risk ratio more favorable in those with prior MI (compared to stable ischemic heart disease [SIHD])**
  - **≈1% to 3% absolute decrease in ischemic events over the course of several years of Rx**
  - **≈1% absolute increase in bleeding events over the course of several years of Rx**

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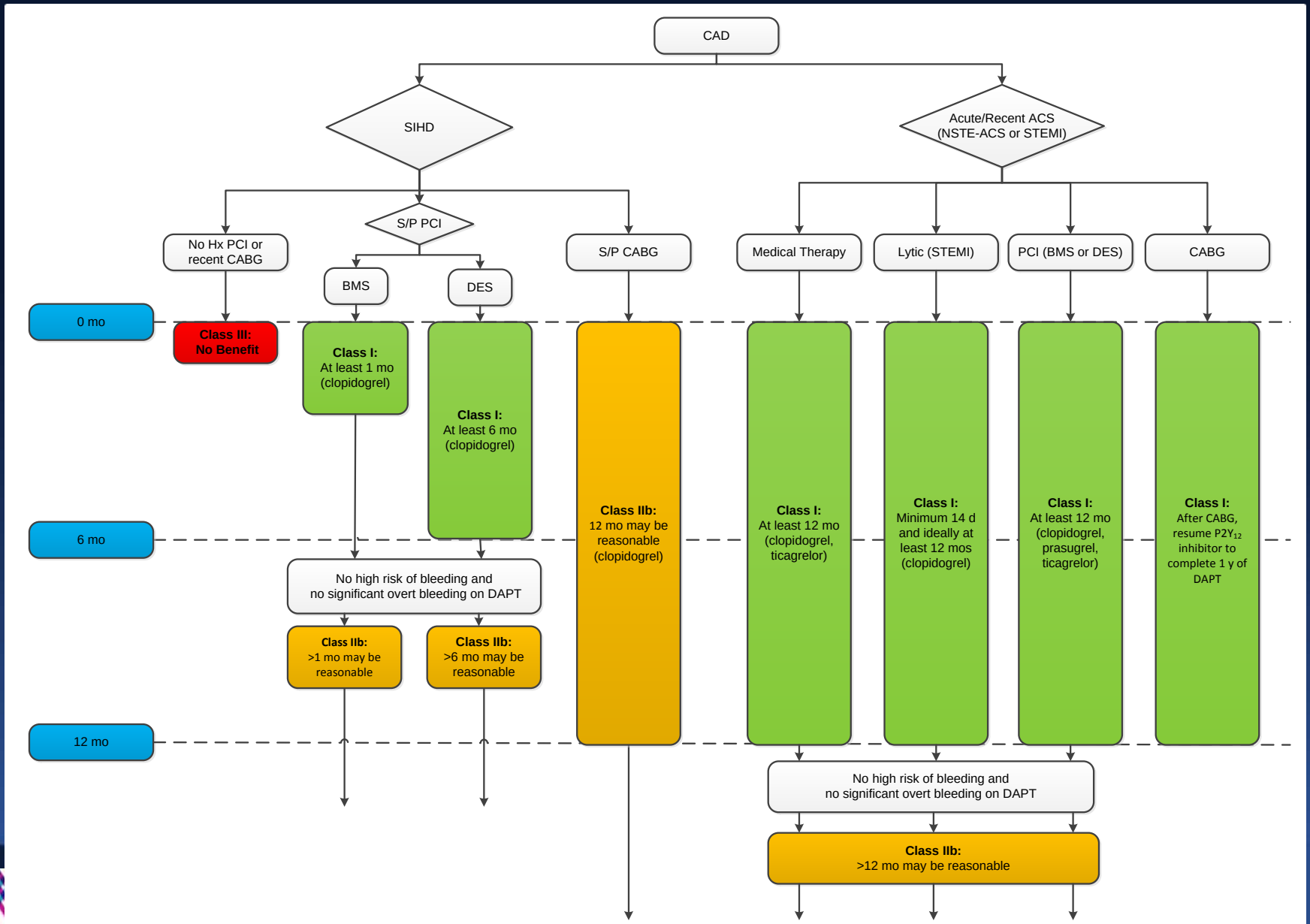
Levine, GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of DAPT in Patients with CAD. JACC 2016 &

Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT



Duration of DAPT in Patients With SIHD

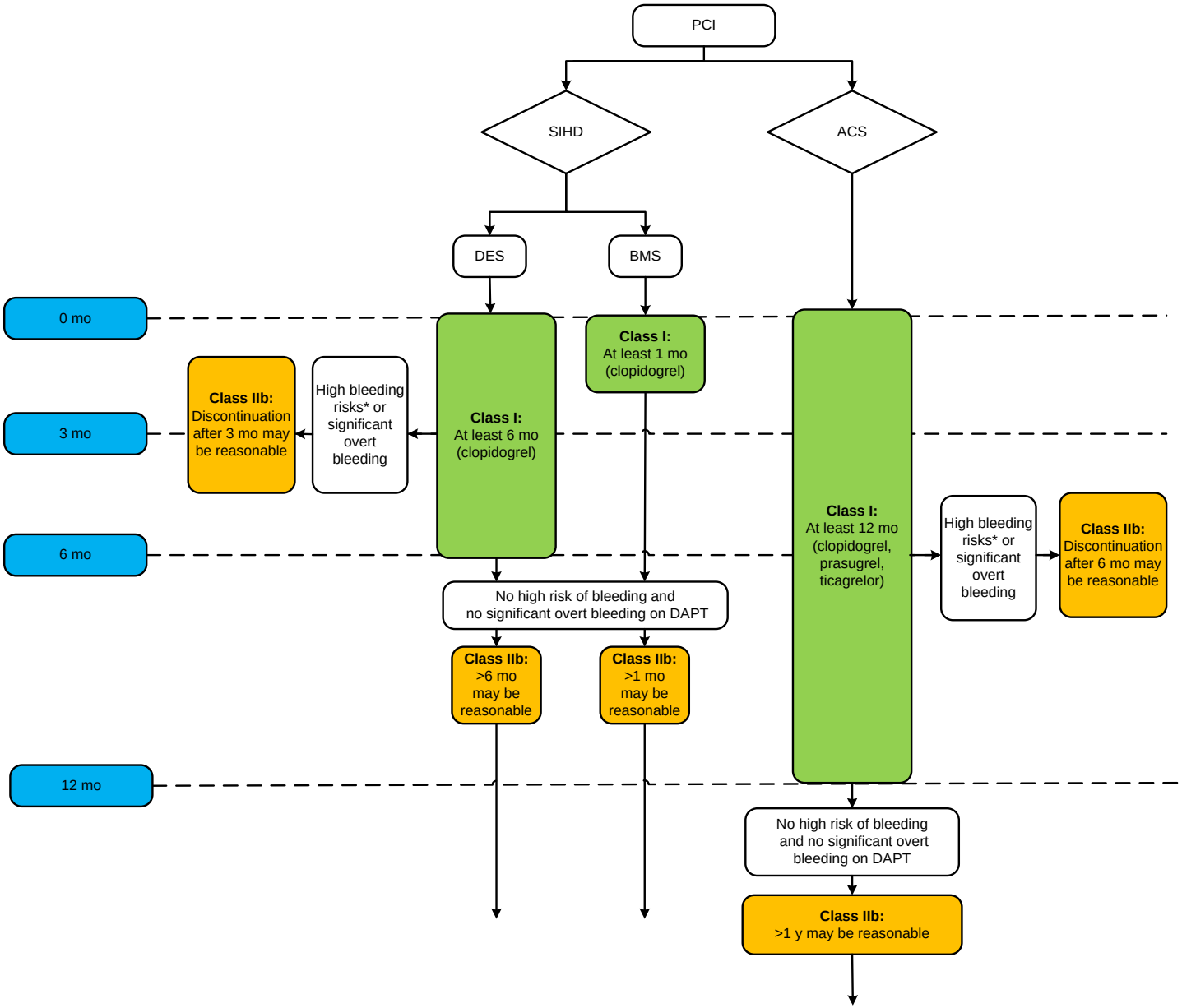
COR	LOE	Recommendations
I	A	In patients with SIHD treated with DAPT after BMS implantation, $P2Y_{12}$ inhibitor therapy with clopidogrel should be given for a minimum of 1 month
I	B-R SR	In patients with SIHD treated with DAPT after DES implantation, $P2Y_{12}$ inhibitor therapy with clopidogrel should be given for at least 6 months
IIb	A SR	In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES months may be reasonable
IIb	C-LD SR	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 3

Levine GN, et al. 2016 AC… …& Circulation 2016

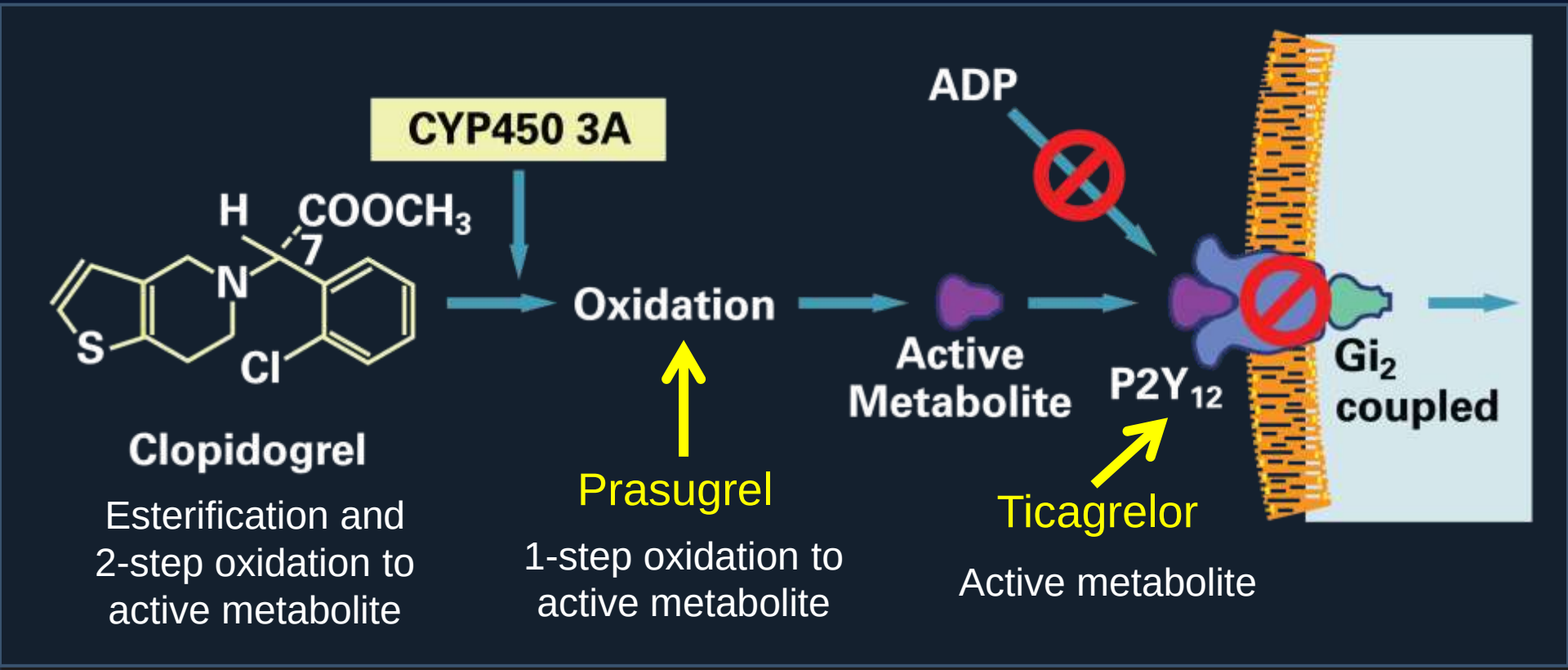
Duration of DAPT in Patients With ACS

COR	LOE	Recommendations
I	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel or ticagrelor) should be given for at least 12 months
I	B-NR	In patients treated with DAPT, the recommended daily dose of aspirin is 81 mg (range 75 to 100 mg)
IIb	A SR	In patients with ACS (NSTE-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable
IIb	C-LD SR	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable

Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Treated With PCI



The therapeutic target for thienopyridines and CPTPs is the platelet $P2Y_{12}$ receptor



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$P2Y_{12}$ Receptor Antagonists

Agent	Class	IPA (20 *uM* ADP) mean	Time to peak onset	Reversibility (d/c before CABG)
Ticlopidine 250 mg bid	thienopyridine (pro-drug)	25%	48 hrs	non reversible 5 days
Clopidogrel 300 mg LD Clopidogrel 600 mg LD Clopidogrel 75 mg qd Clopidogrel 150 mg qd	thienopyridine (pro-drug)	30% - 40% 35% - 50% 30% - 35% 45% - 50%	12 hrs 6 hrs - -	non reversible 5 days
Prasugrel 60 mg LD* Prasugrel 10 mg qd* Prasugrel 5 mg qd*	thienopyridine (pro-drug)	80% 60% 40%	1-2 hrs - -	non reversible 7 days
Ticagrelor 180 mg LD* Ticagrelor 90 mg bid*	cyclo-pentyl-triazolo-pyrimidine*	80% 70%	1-2 hrs -	reversible 2-5 days

*Less affected by genetic polymorphisms and drug interactions (e.g. PPIs)

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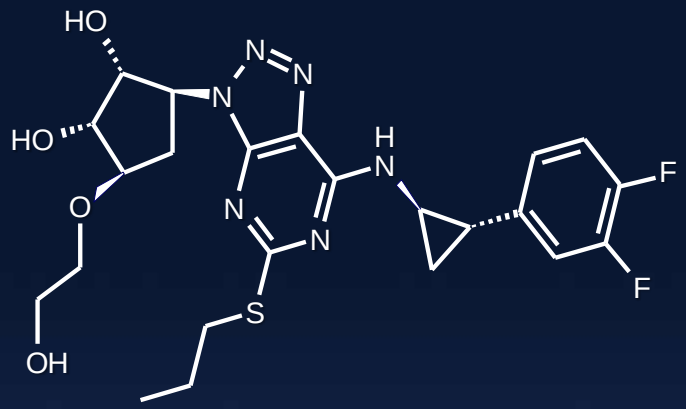
**not a pro-drug

Ticagrelor

Ticagrelor (AZD 6140):
an Oral Reversible $P2Y_{12}$ Antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- Direct acting
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- Reversibly bound
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets
- Off-target effects
  - Blocks red blood cell adenosine re-uptake

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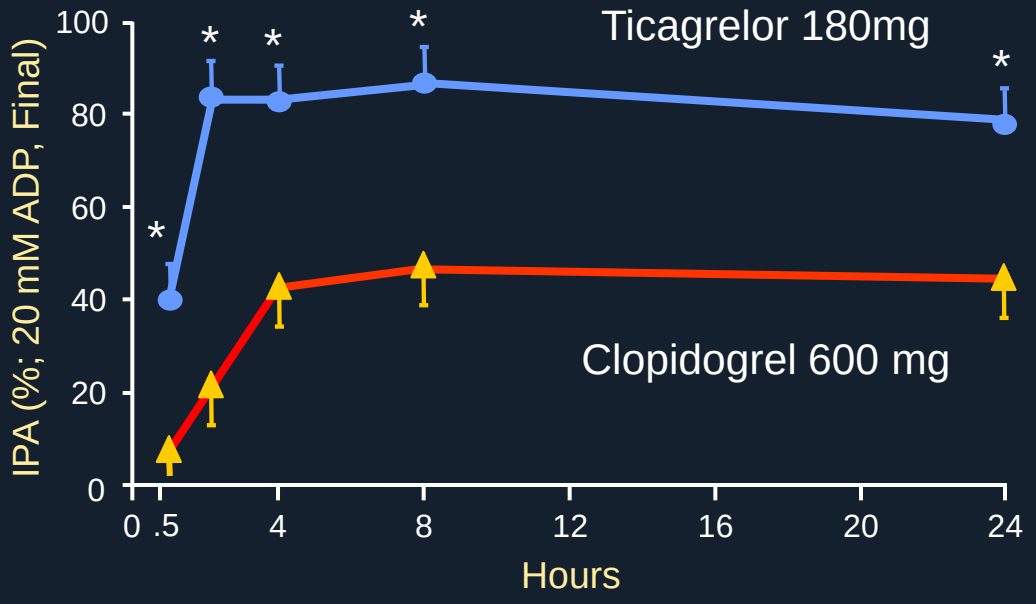
Clopidogrel vs. Ticagrelor

ONSET/OFFSET Study

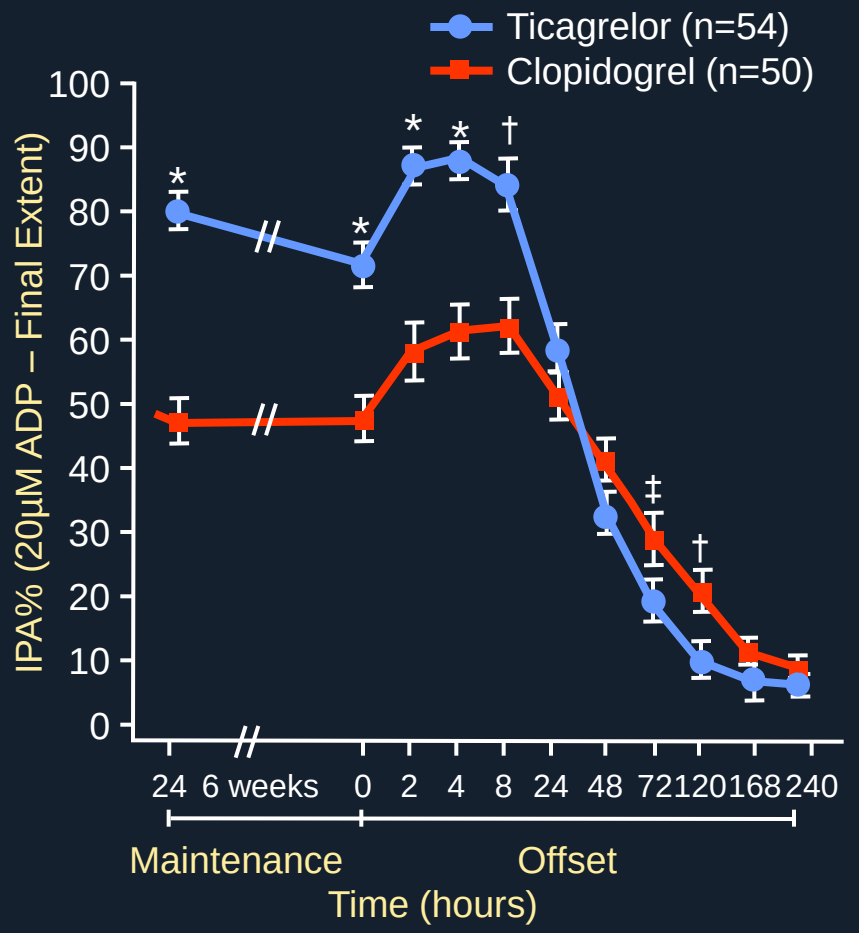
Loading



Ticagrelor vs clopidogrel.

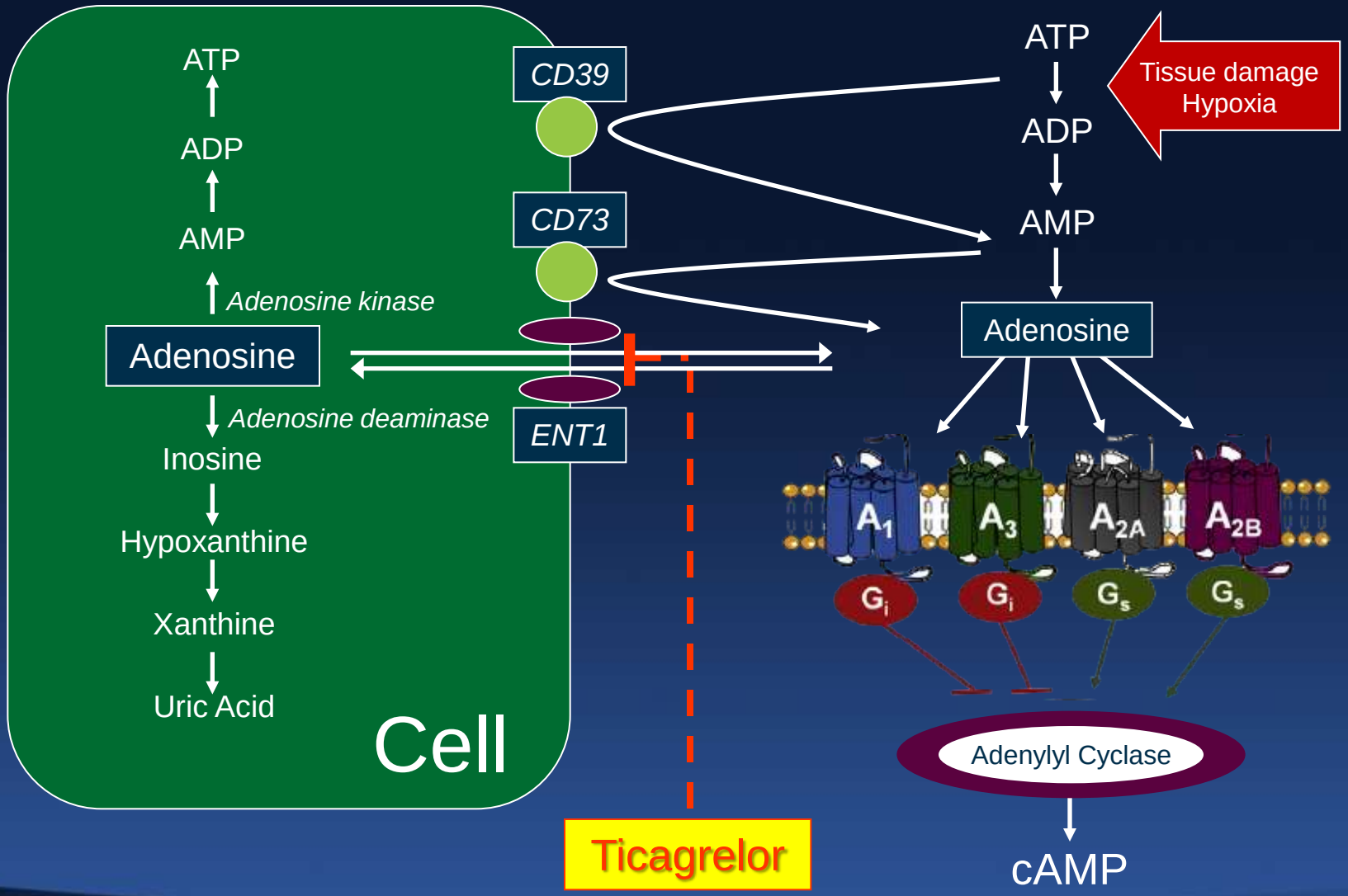
* *P*<0.0001; † *P*<0.005; ‡, *P*<0.05

Maintenance and Offset



Gurbel PA et al. *Circulation*. 2009;120:2577-85.

Ticagrelor Increases Extracellular Adenosine Concentrations by Blocking the Cellular ENT1 Receptor



Cattaneo M et al. *JACC* 2014;63:2503–9

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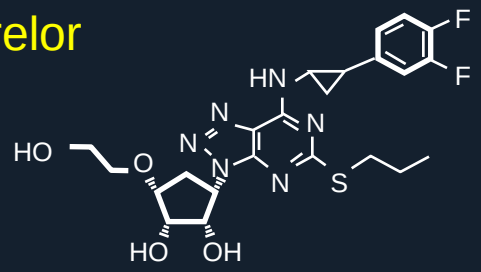
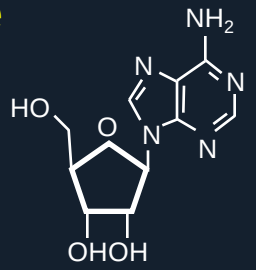
Effects Mediated by Ticagrelor and Adenosine

Ticagrelor

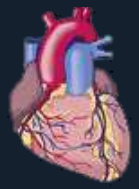


Adenosine



↑ Adenosine-induced increases in coronary blood flow (dogs and humans)
↑ Endothelial function (ACS patients)

↑ Vasodilation
↑ Endothelial progenitor cell migration

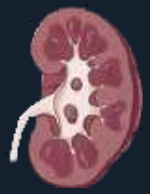


↓ Incidence of MACE (ACS patients)
↓ CV and all cause mortality (ACS patients)
↓ Incidence of ventricular pauses (ACS patients)
↓ Infarct size (animals models)

↓ Ischemia/reperfusion injury
Induces pharmacological reconditioning
↓ Electrical conduction

↓ Adenosine-induced platelet inhibition (in vitro)
↓ Mortality (ACS patient with pulmonary infection)

↑ Platelet inhibition
Modulates inflammation



↑ Creatinine levels (ACS patients)

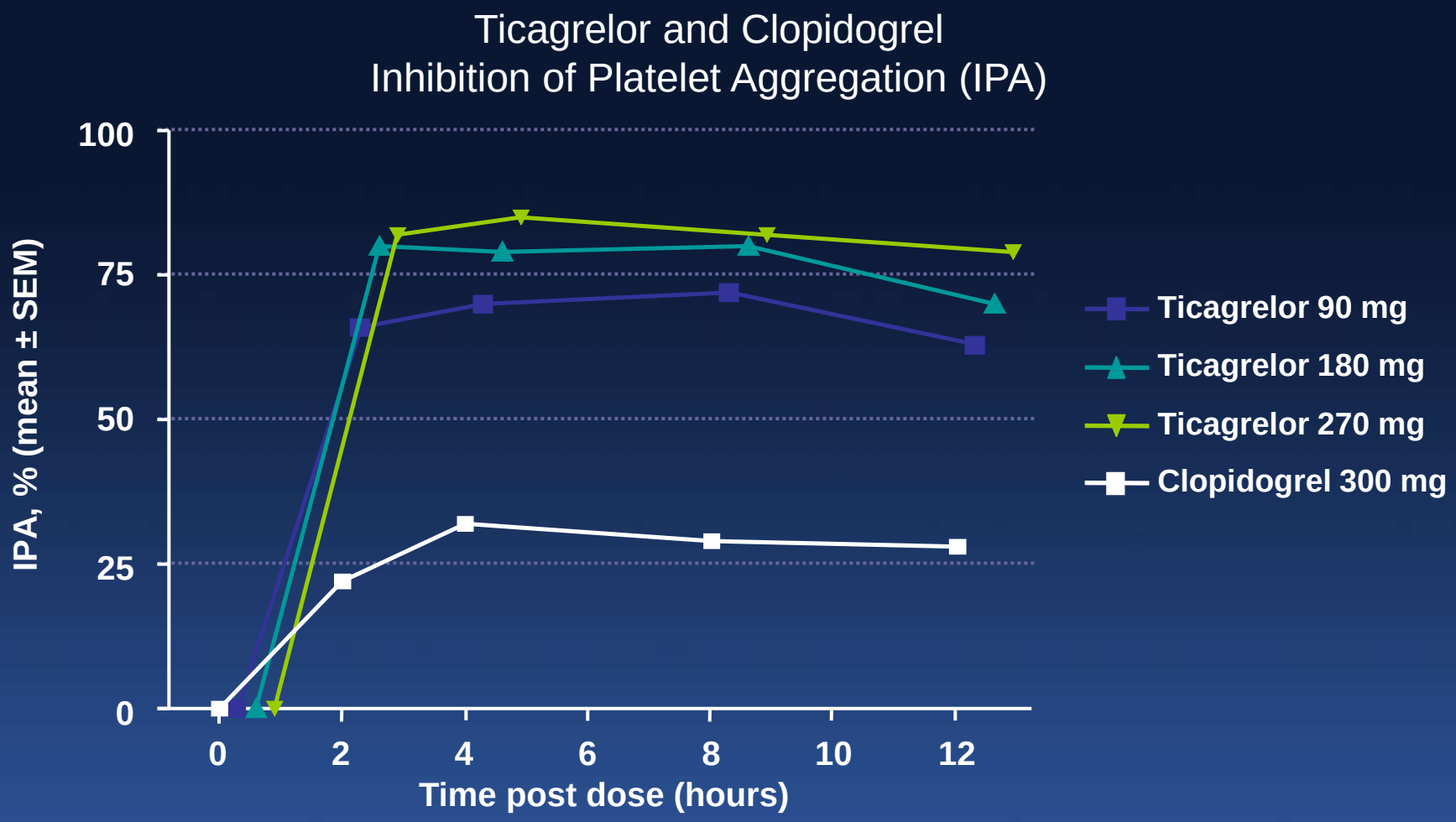
↓ Glomerular filtration

↑ Incidence of dyspnea (ACS patients)
↑ Adenosine-induced dyspnea (healthy subjects)

↑ Incidence of dyspnea

Cattaneo M et al. *JACC* 2014;63:2503–9

DISPERSE 2: Comparative Effects on Platelet Aggregation



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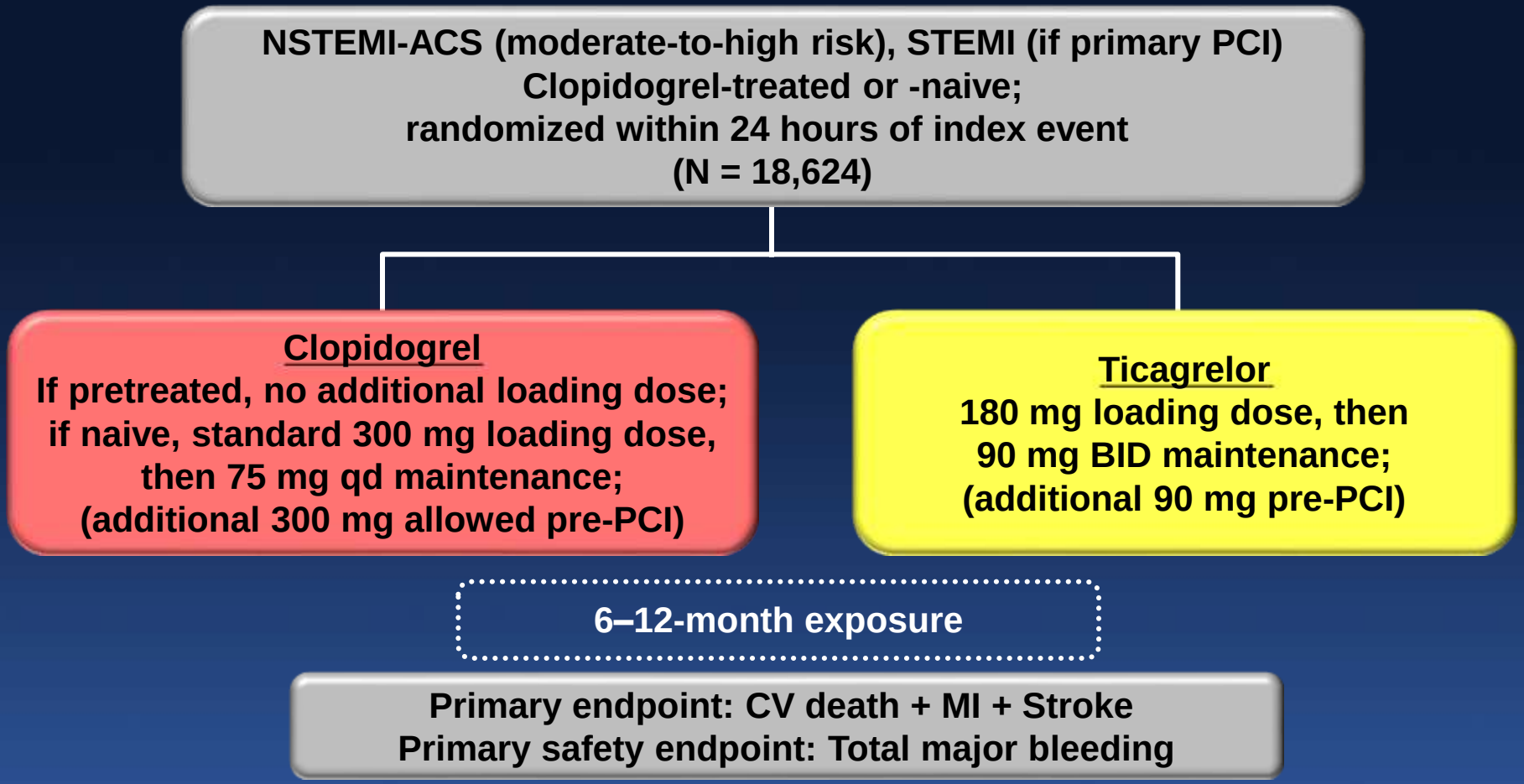
Keeley EC, et al. *Lancet.* 2006.

PLATO Study Design



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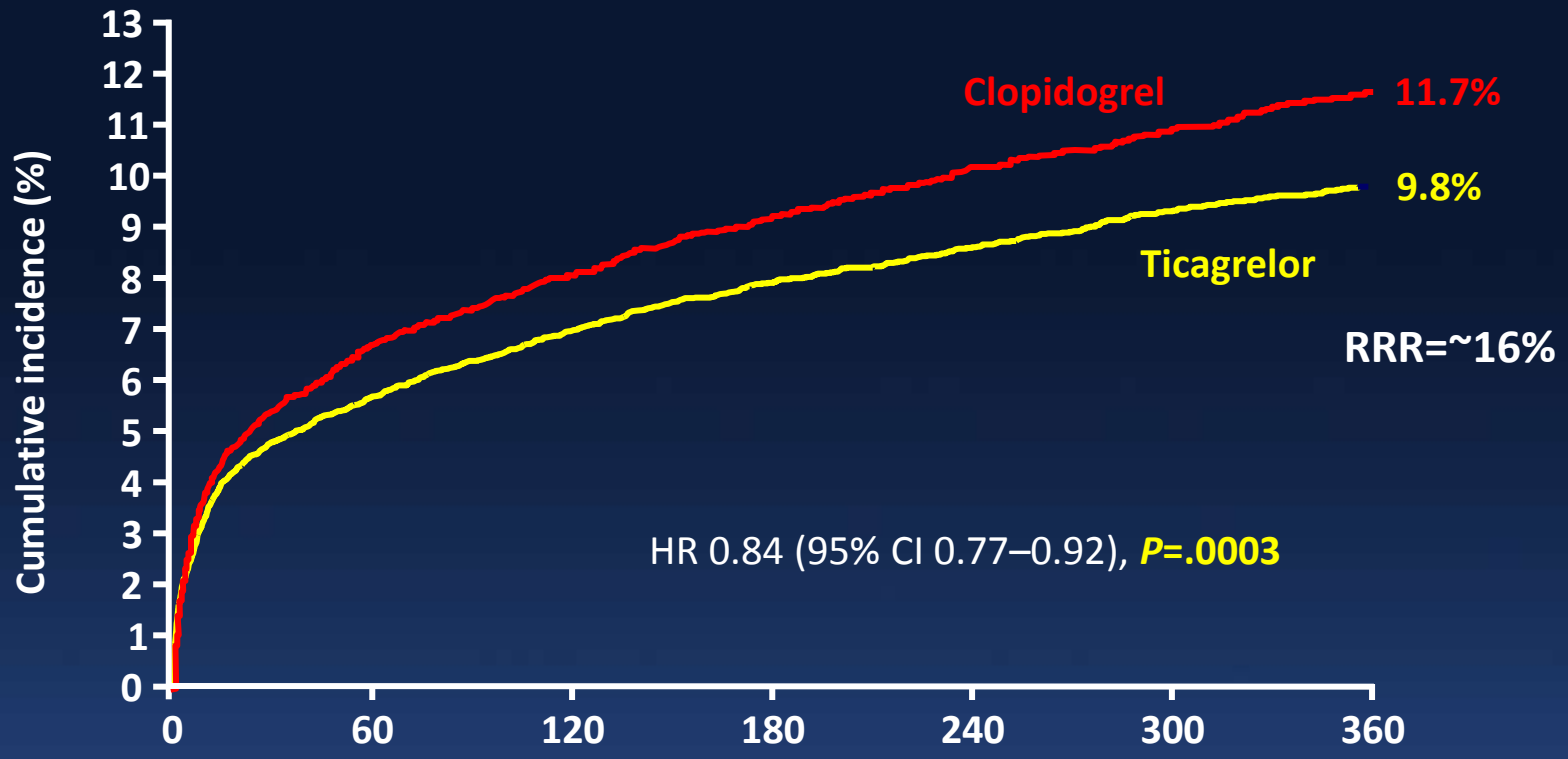
Wallentin L, et al. *N Engl J Med*. 2009.

PLATO:
Time to Primary Efficacy Endpoint*



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,650	5,096	4,047

*Composite of CV death, MI, or stroke

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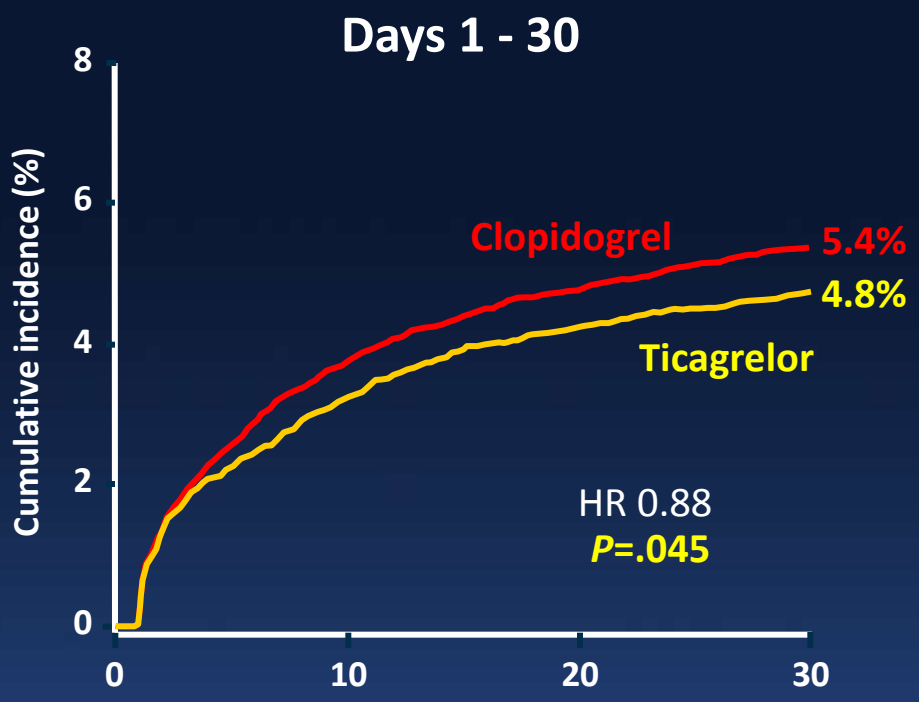
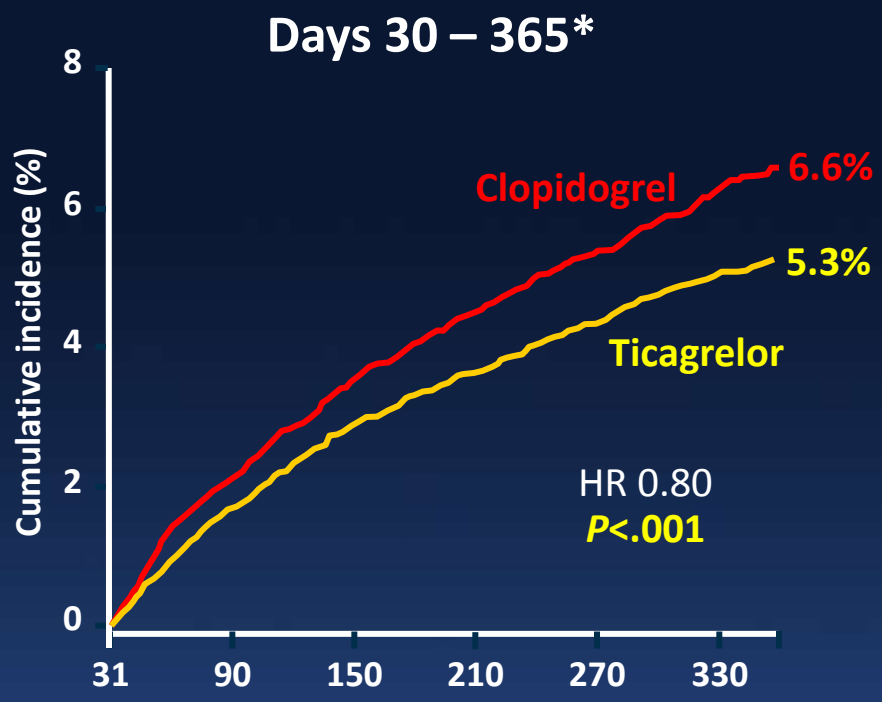
Wallentin L, et al. *N Engl J Med*. 2009.

PLATO: Time to Primary Efficacy Endpoint*





No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

**Excludes patients with any primary event during the first 30 days

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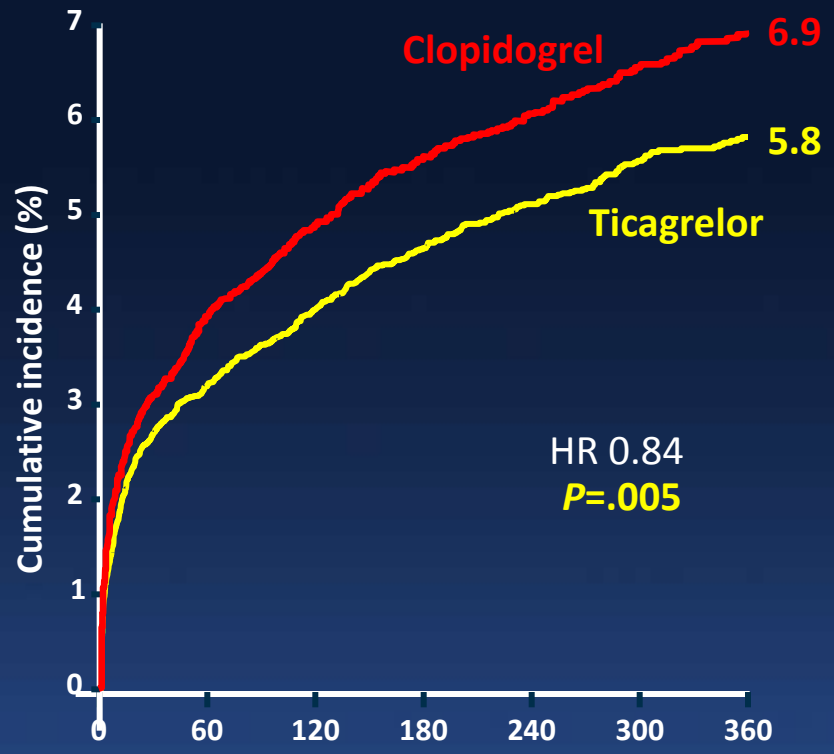
*Composite of CV death, MI, or stroke

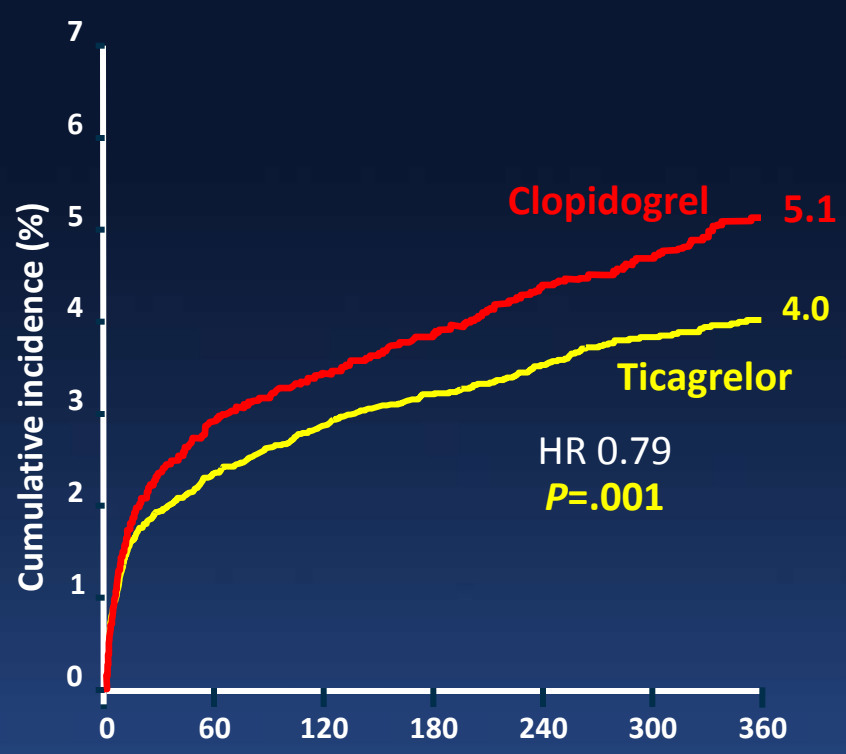
Wallentin L, et al. *N Engl J Med*. 2009.

PLATO:
Time to Secondary Efficacy Endpoints

Myocardial infarction



Cardiovascular death



No. at risk							
Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

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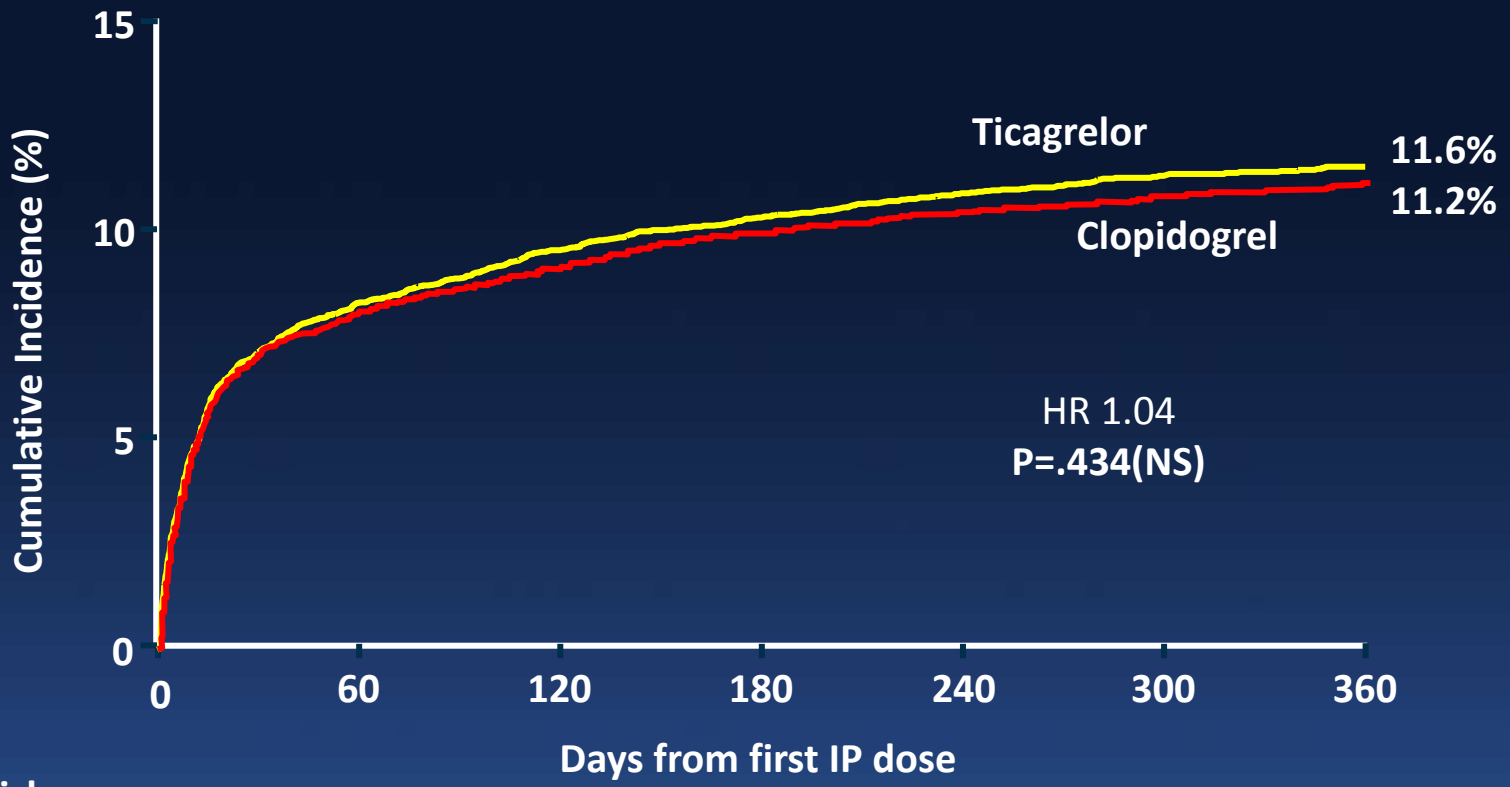
Wallentin L, et al. *N Engl J Med*. 2009.

PLATO:
Time to Primary Safety Endpoint*



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

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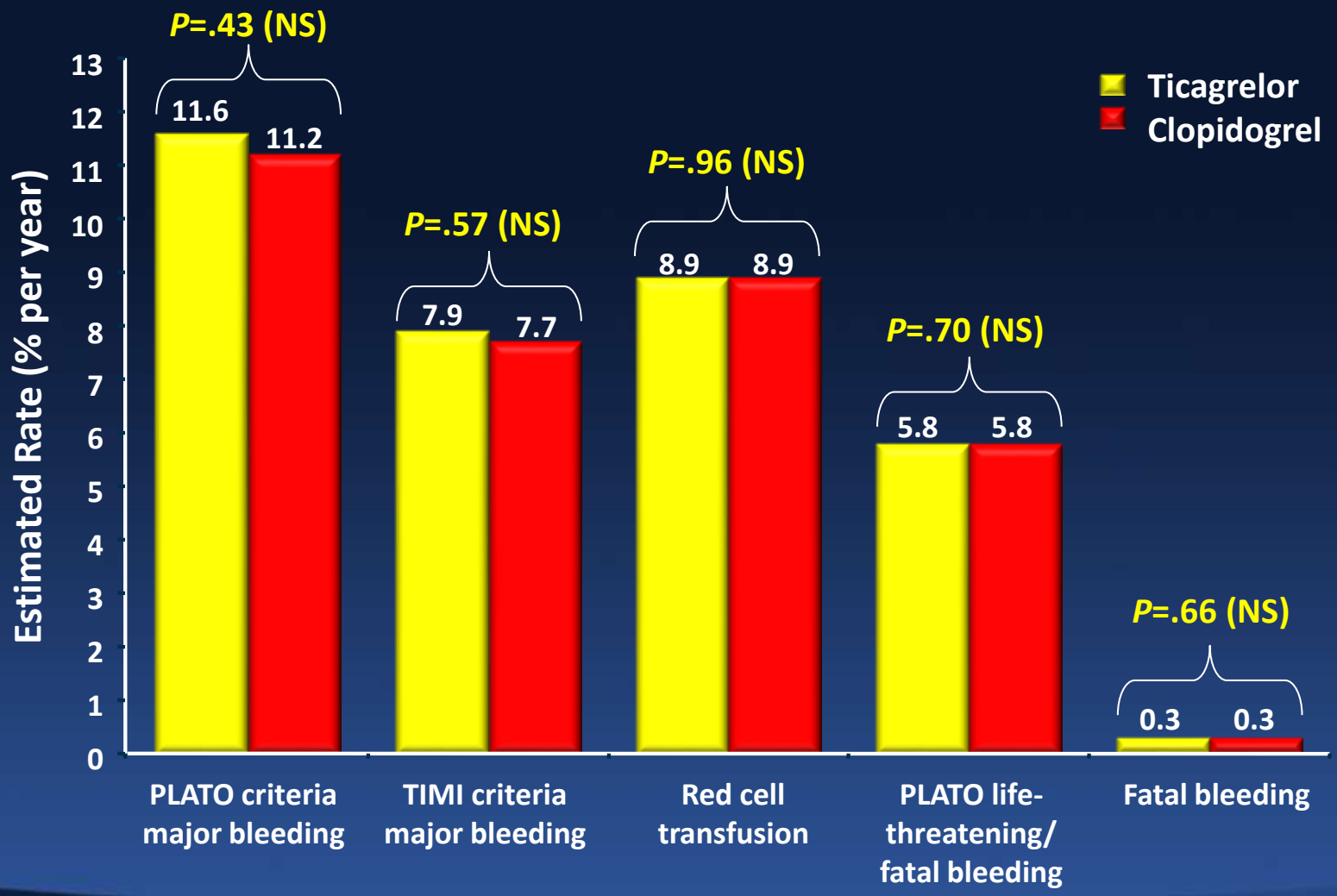
*Major bleed as defined by PLATO criteria

Wallentin L, et al. *N Engl J Med*. 2009.

PLATO: Total Major Bleeding



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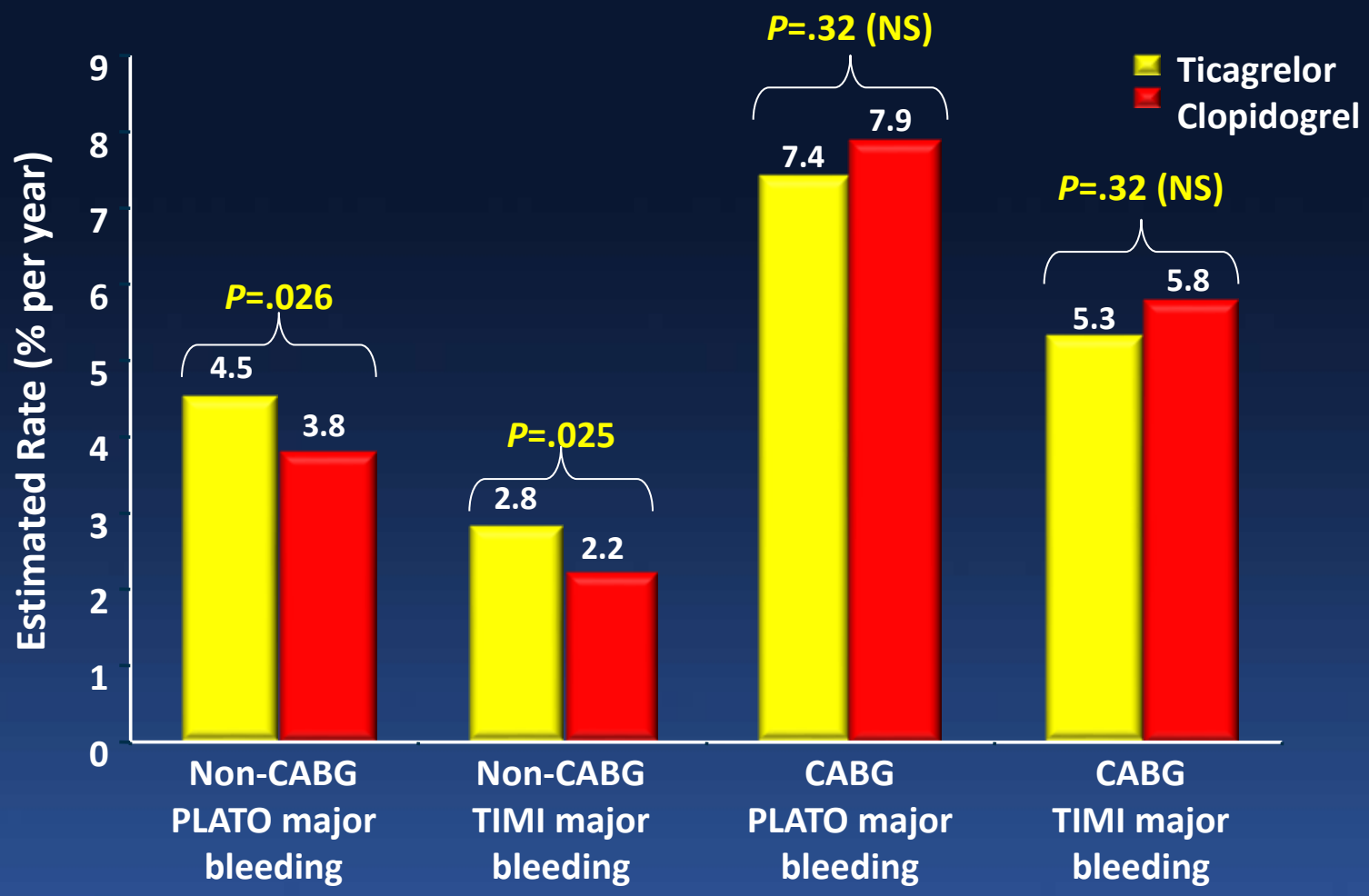
Wallentin L, et al. *N Engl J Med*. 2009.

PLATO: Non-CABG and CABG-related Major Bleeding



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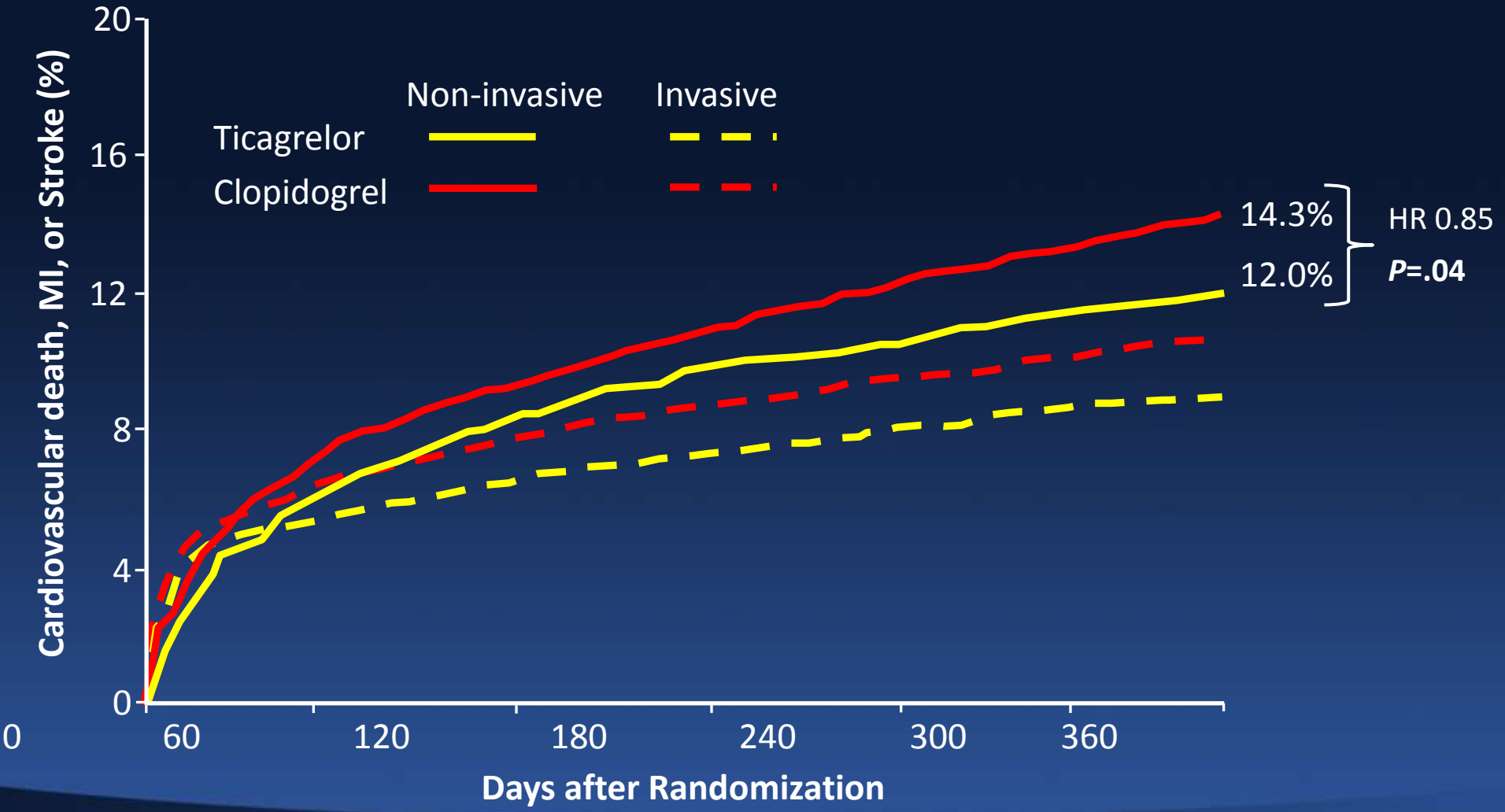
Wallentin L, et al. *N Engl J Med*. 2009.

PLATO: Medical Therapy Subgroup



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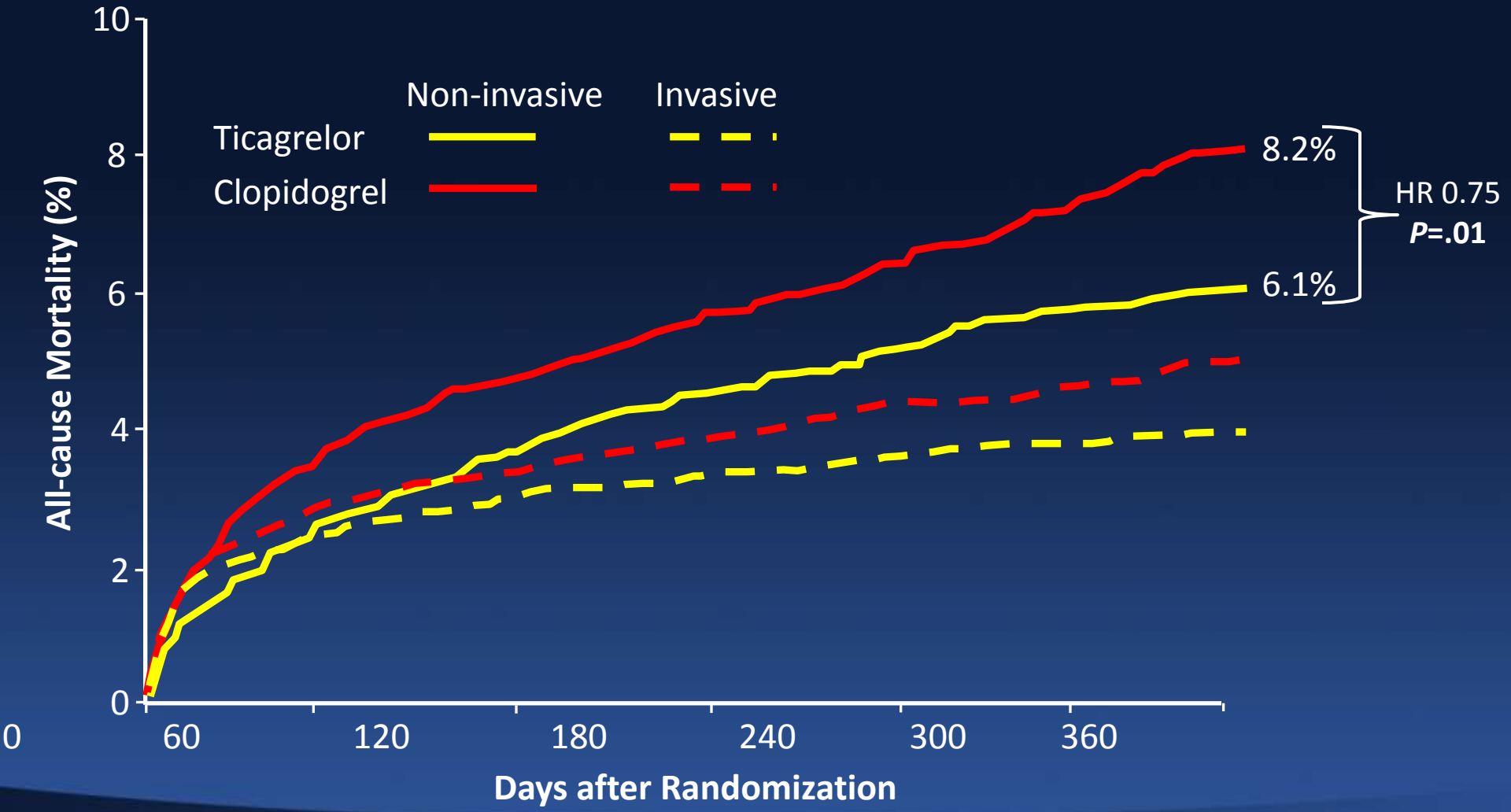
James SK, et al. *BMJ*. 2011.

PLATO:
Medical Therapy Subgroup



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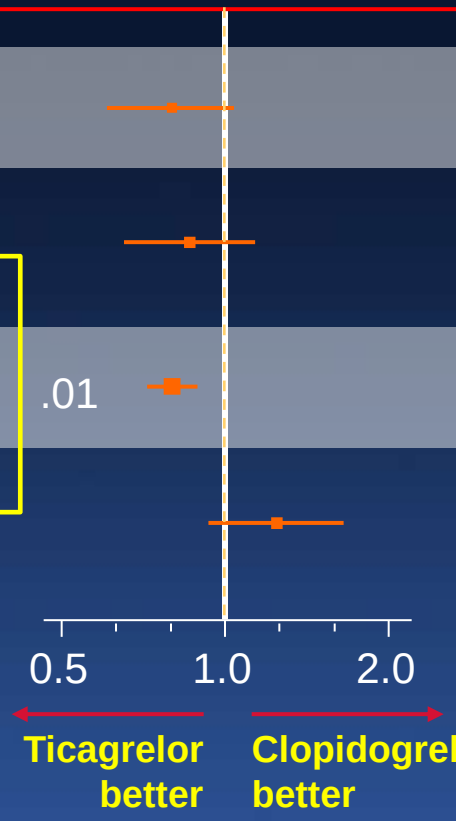
James SK, et al. *BMJ*. 2011.

PLATO: Primary Efficacy Endpoint by Region

Geographic region	Total patients	KM at month 12 Tic	KM at month 12 Clop	HR (95% CI)	Interaction *P*-values
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	
Central America / South America	1237	15.2	17.9	0.86 (0.65, 1.13)	.045
Europe / Middle East / Africa	13859	8.8	11.0	0.80 (0.72, 0.90)	.01
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



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Wallentin L, et al. *N Engl J Med*. 2009.

PLATO: Stent Thrombosis*

Stent Thrombosis, %	Ticagrelor (N=5,640)	Clopidogrel (N=5,649)	HR (95% CI)	P Value
Definite	71 (1.3%)	106 (1.9%)	0.67 (0.52-0.91)	.009
Probable of definite	118 (2.1%)	158 (2.8%)	0.75 (0.59-0.95)	.02
Possible, probable, or definite	155 (2.8%)	202 (3.6%)	0.77 (0.62-0.95)	.01

*Evaluated in patients with any stent during the study

**Time-at-risk is calculated from first stent insertion in the study or date of randomisation

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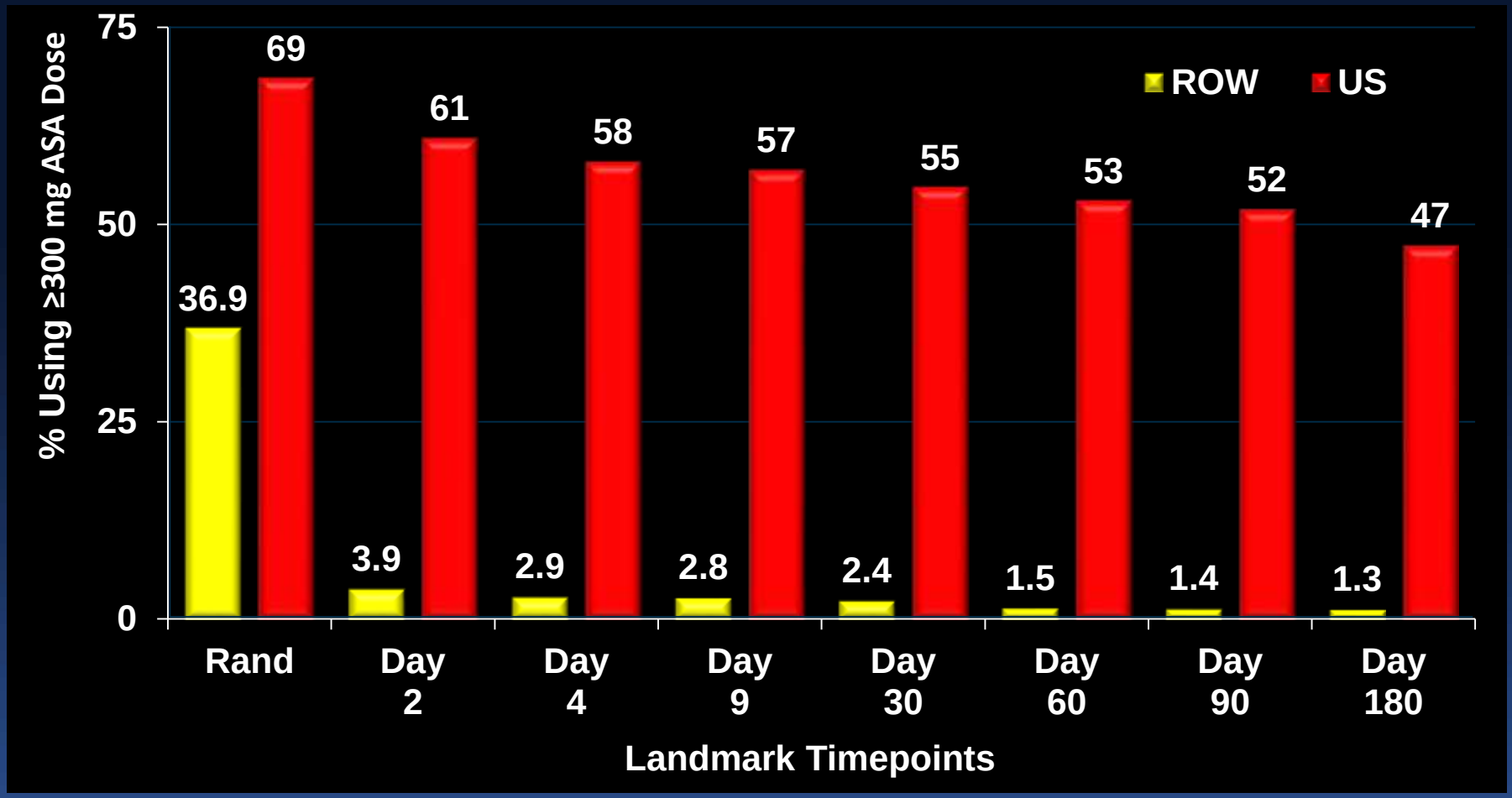
Wallentin L, et al. *N Engl J Med*. 2009.

Ticagrelor – Aspirin Dosing

PLATO: High-Dose Aspirin Use Landmark Time Points



ASA: <300 mg is low-dose; ≥300 mg is high-dose;
ROW = rest of world

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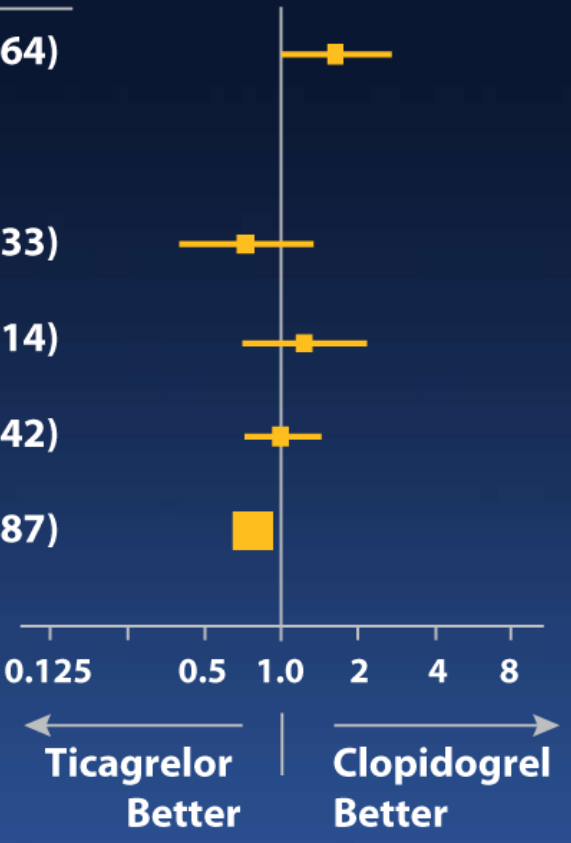
Wallentin L, et al. *N Engl J Med*. 2009.

PLATO: Primary Efficacy Outcome by Region and ASA Dose

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)

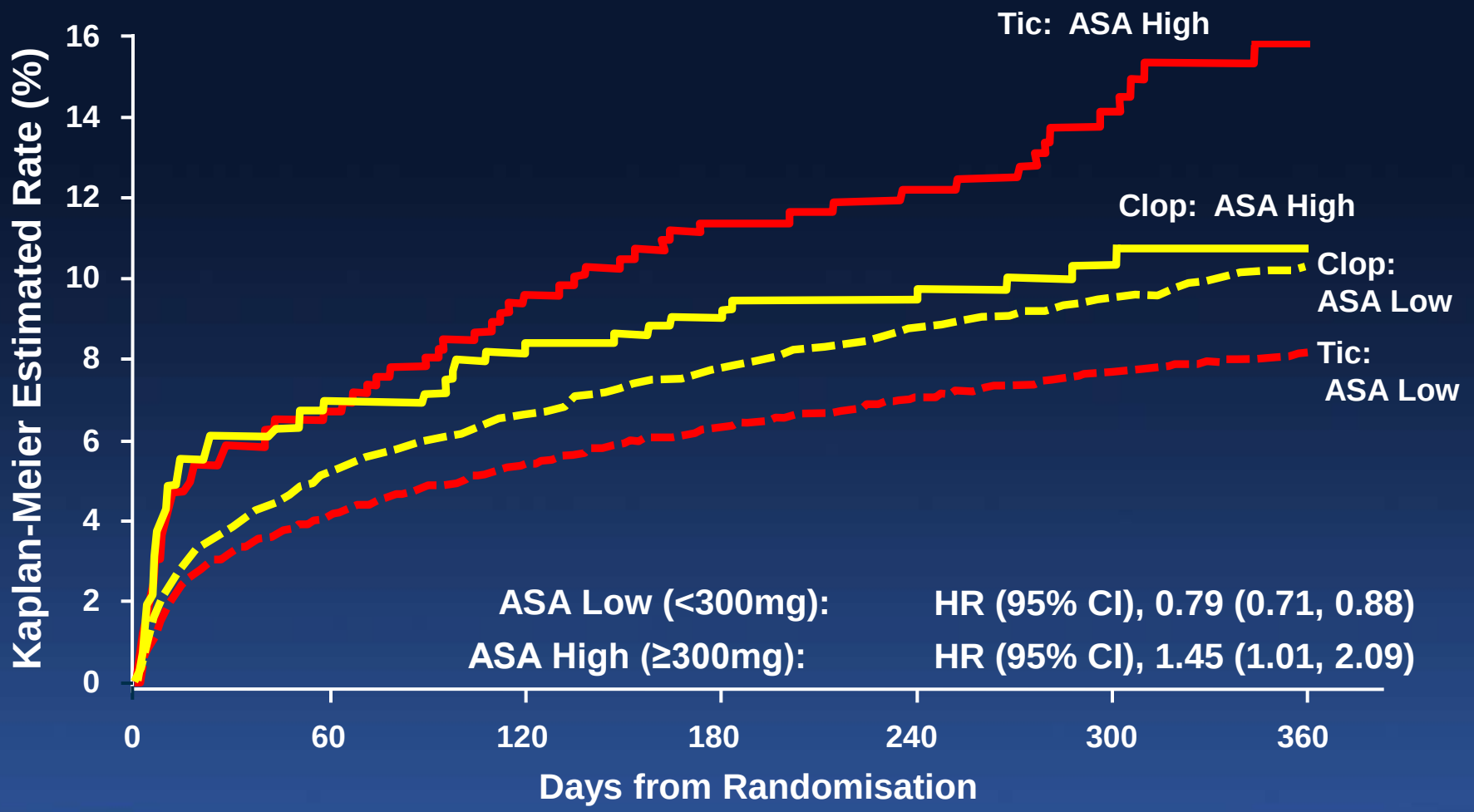


Hazard ratio not calculated due to small number of events.

Mount Sinai Heart

Wallentin L, et al. *N Engl J Med*. 2009.

PLATO: Primary Efficacy Outcome by ASA Maintenance Dose



Mount Sinai Heart

Mahaffey KW, et al. *Circulation*. 2011.

Ticagrelor: FDA Prescribing Information

Warning: Aspirin dose and ticagrelor effectiveness

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided.**
- **After any initial dose, use with aspirin 75-100 mg per day.**

Summary: $P2Y_{12}$ Inhibitor Properties

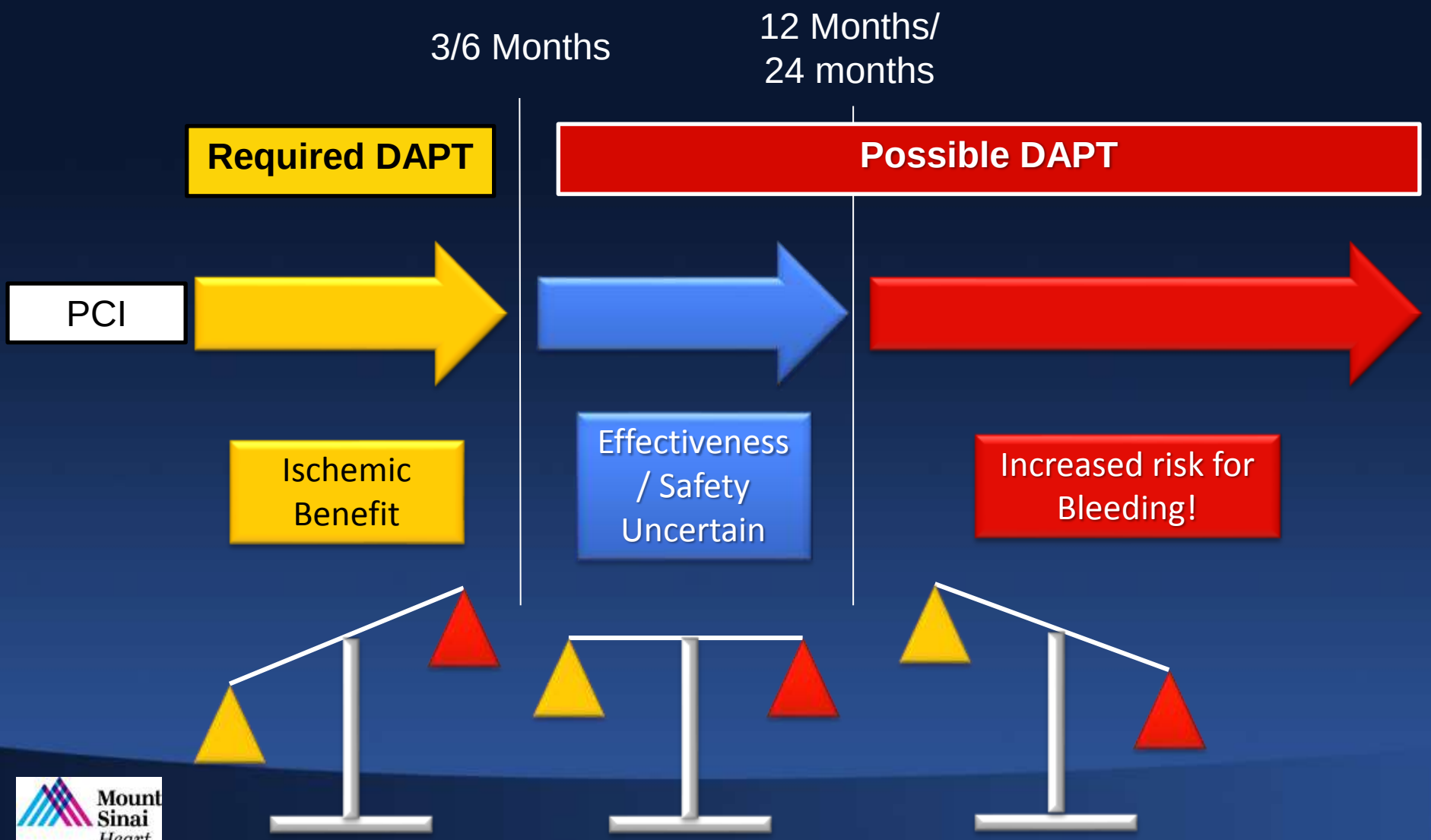
	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolism	Prodrug, not limited by metabolism	Active drug
Onset of effect	2-4 hr	30 min	30 min
Duration of effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days*

*FDA Package recommendation; in the PLATO trial, ticagrelor treatment was recommended to be withheld for 1-3 days

Mount Sinai Heart

Hamm CW, et al. *Eur Heart J*. 2011.

Optimal DAPT duration after DES Implantation: What does it really mean?



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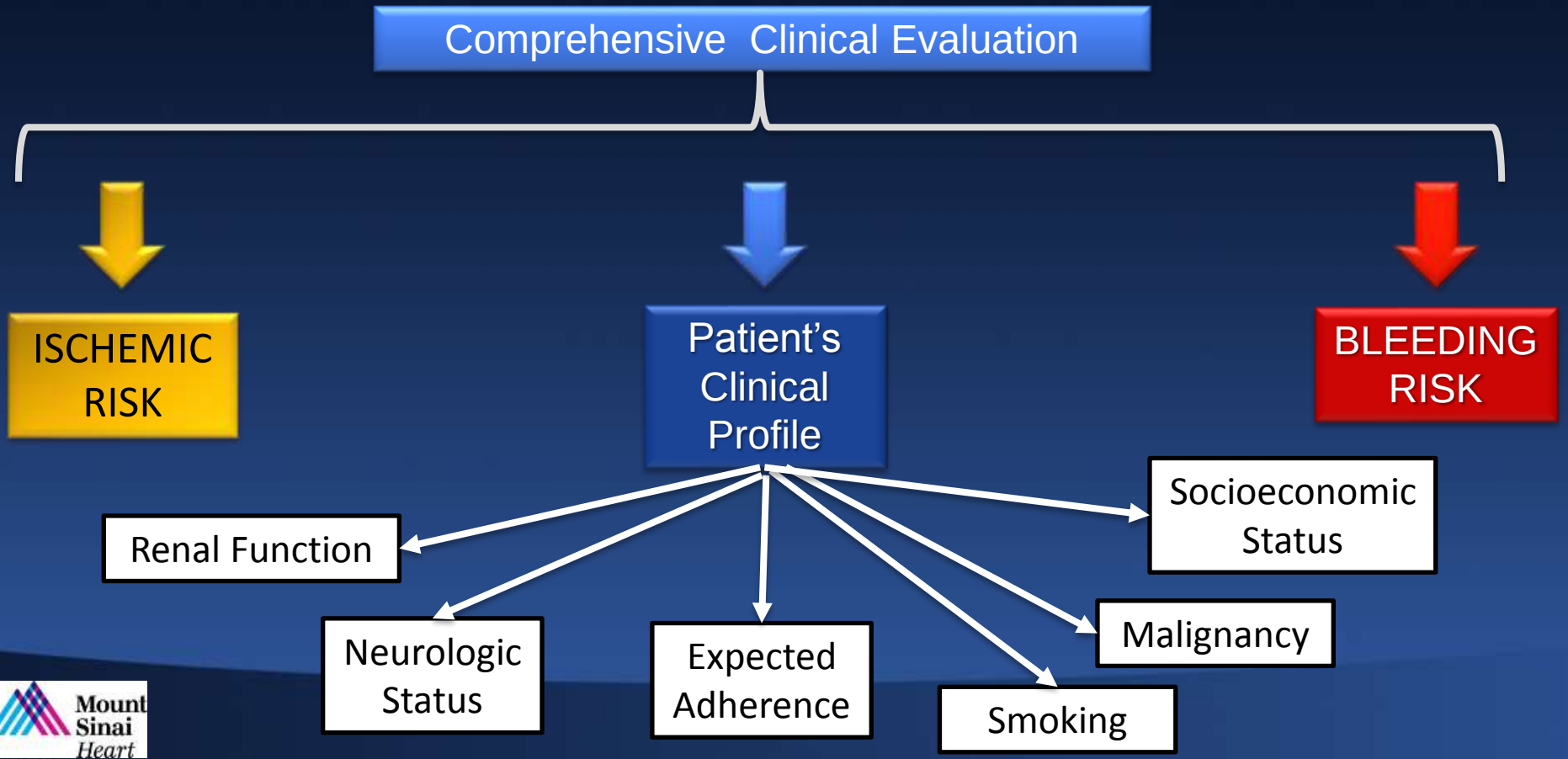
Does one size fit all?

… the answer is NO!



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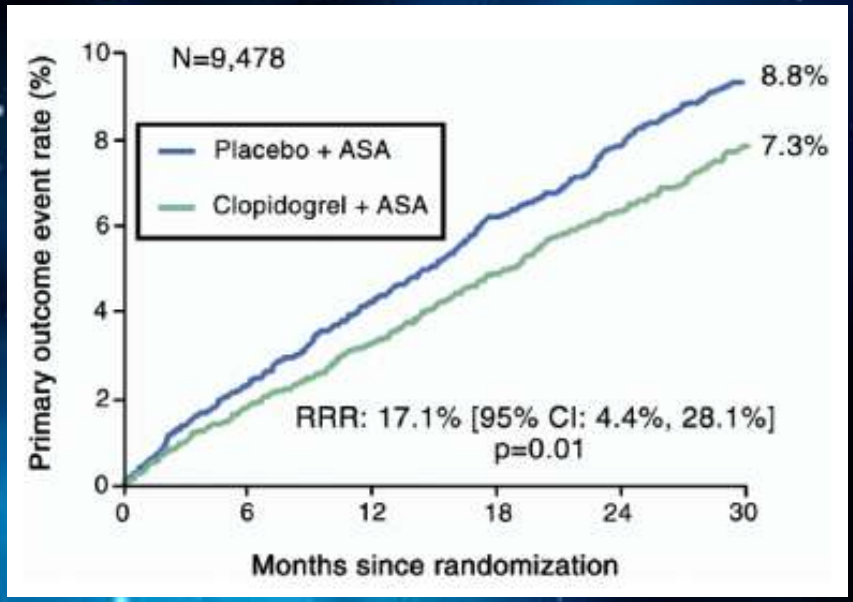
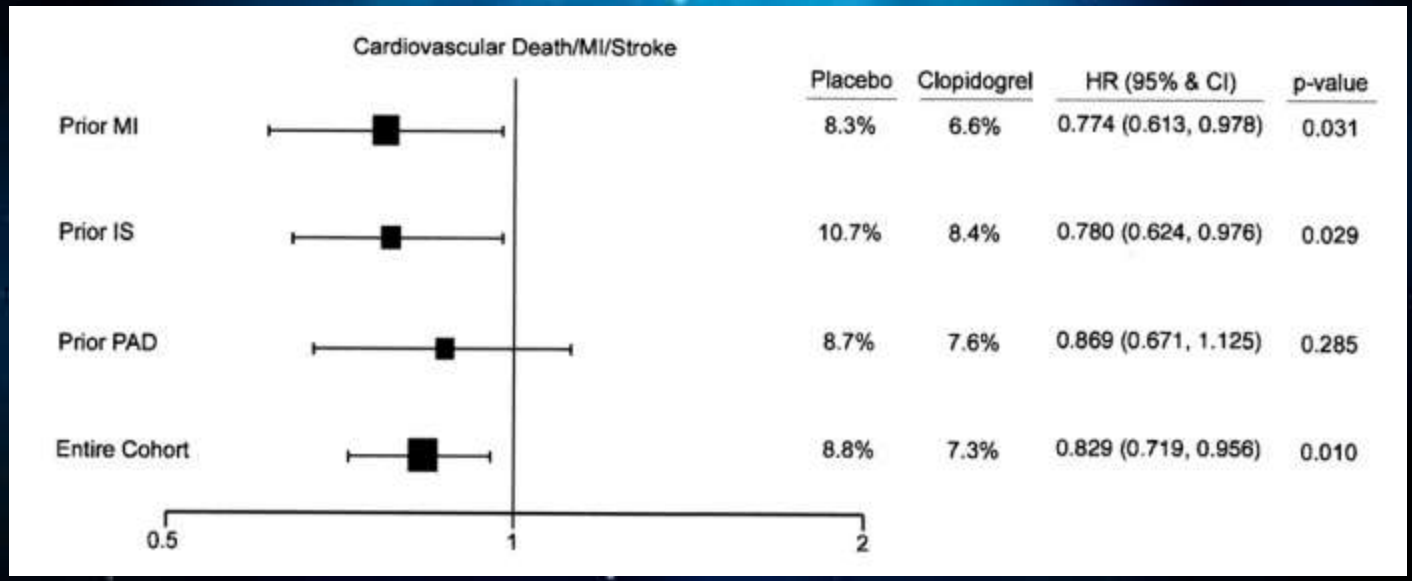
Who may benefit of prolonged DAPT?

Subgroup analysis in patients at high atherothrombotic risk (prior MI, stroke or peripheral arterial disease) from the CHARISMA trial (DAPT versus aspirin for 28 months in 15,603 patients with CAD or multiple risk factors)

Lower risk of cardiac death / MI / stroke in patients on DAPT!





Mount Sinai Heart

Bhatt et al - JACC Vol. 49, No. 19, 2007

PEGASUS: Study Design

Stable pts with MI 1–3 years prior + ≥1 high-risk factor

Randomized 21,162 patients

at 1161 sites in 31 countries between 10/2010–5/2013

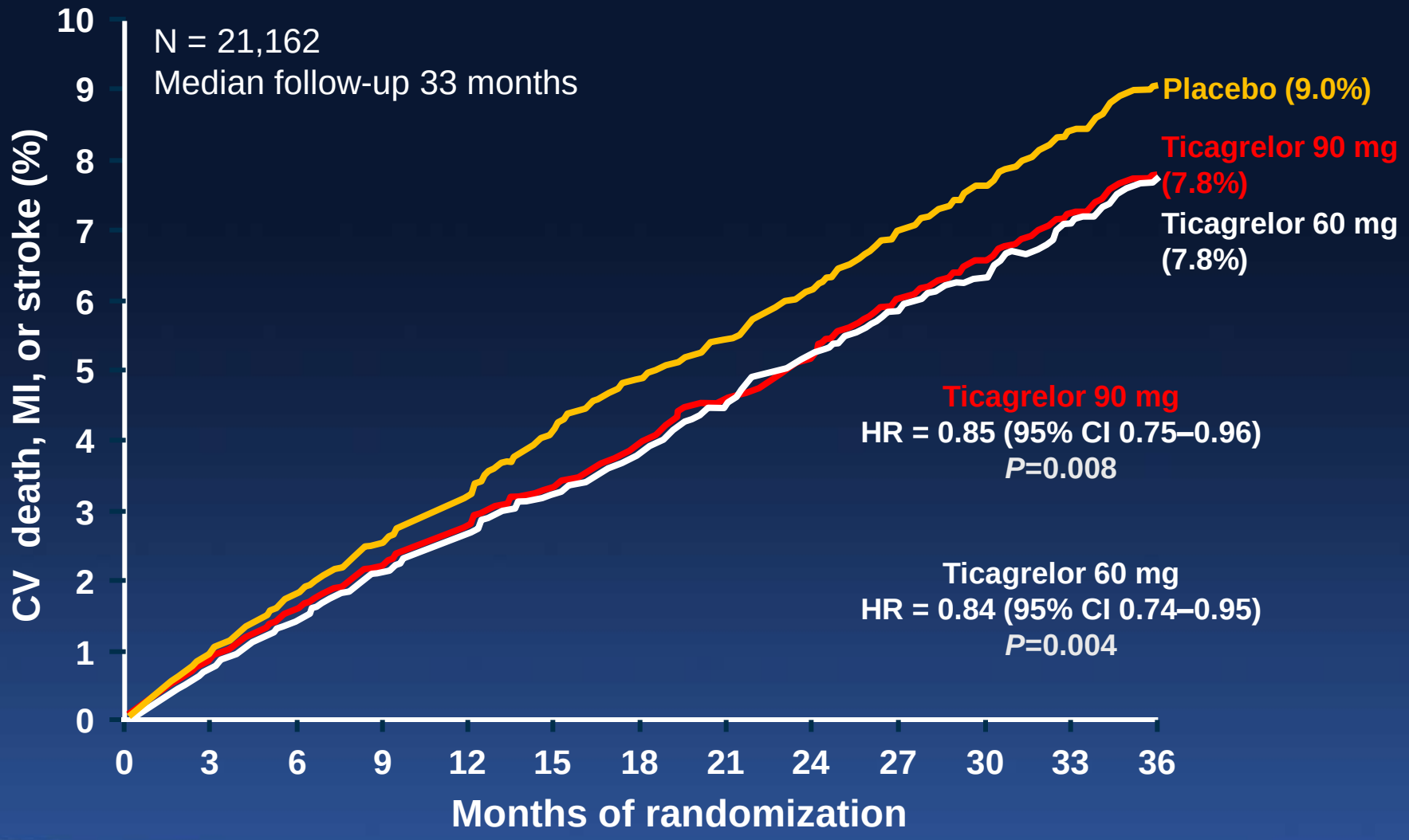
Ticagrelor 90 mg bid (N = 7050)	**Ticagrelor 60 mg bid (N = 7045)**	**Placebo 60 mg bid (N = 7067)**

Follow-up = median 33 months (IQR 28-37)
Minimum 16 months, maximum 47 months

Premature perm. drug discontinuation	12%/year	11%/year	8%/year
Withdrew consent	0.7% total	0.7% total	0.7% total
Lost to follow-up	3 patients	6 patients	1 patient

Bonaca MP et al. *N Engl J Med.* 2015:Epub ahead of print.

PEGASUS: Primary Endpoint



Bonaca MP et al. *N Engl J Med.* 2015:Epub ahead of print.

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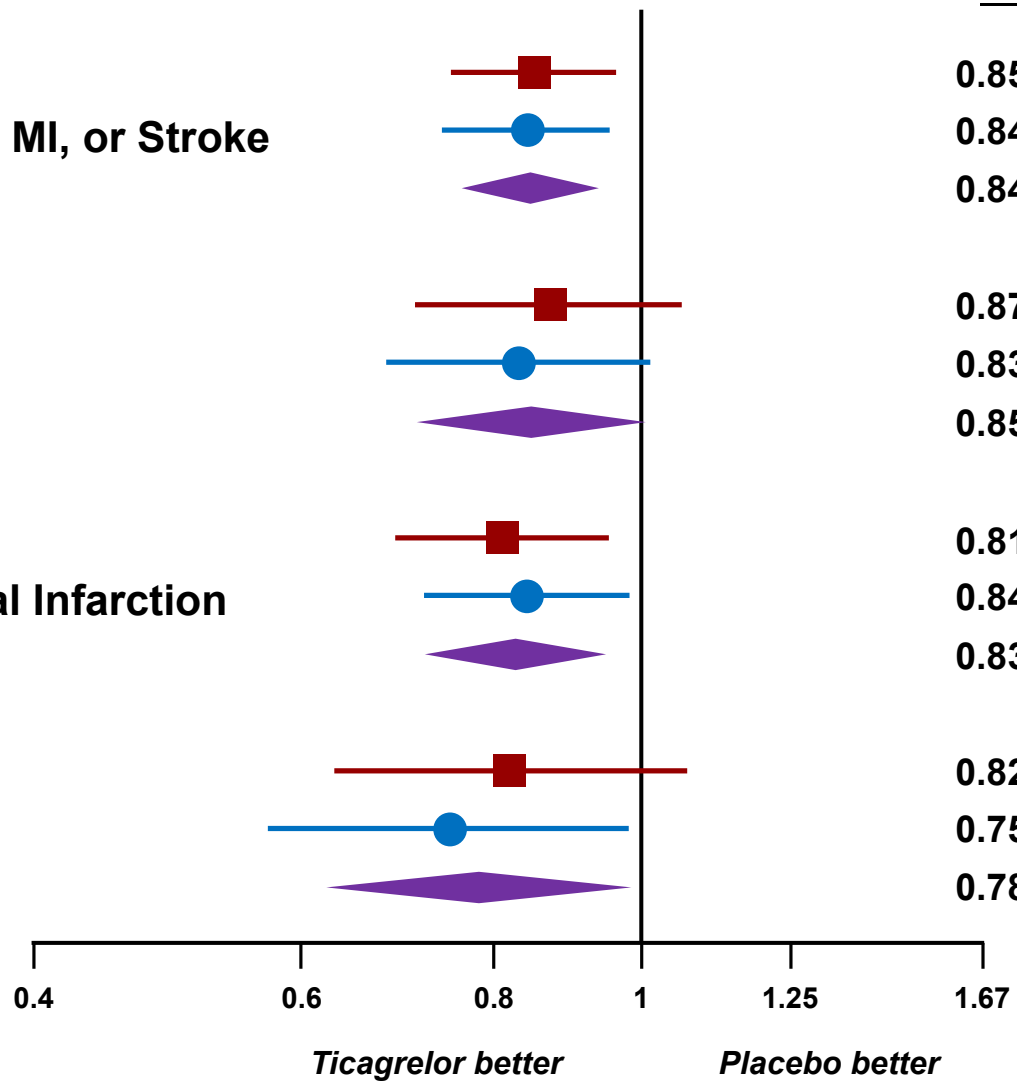
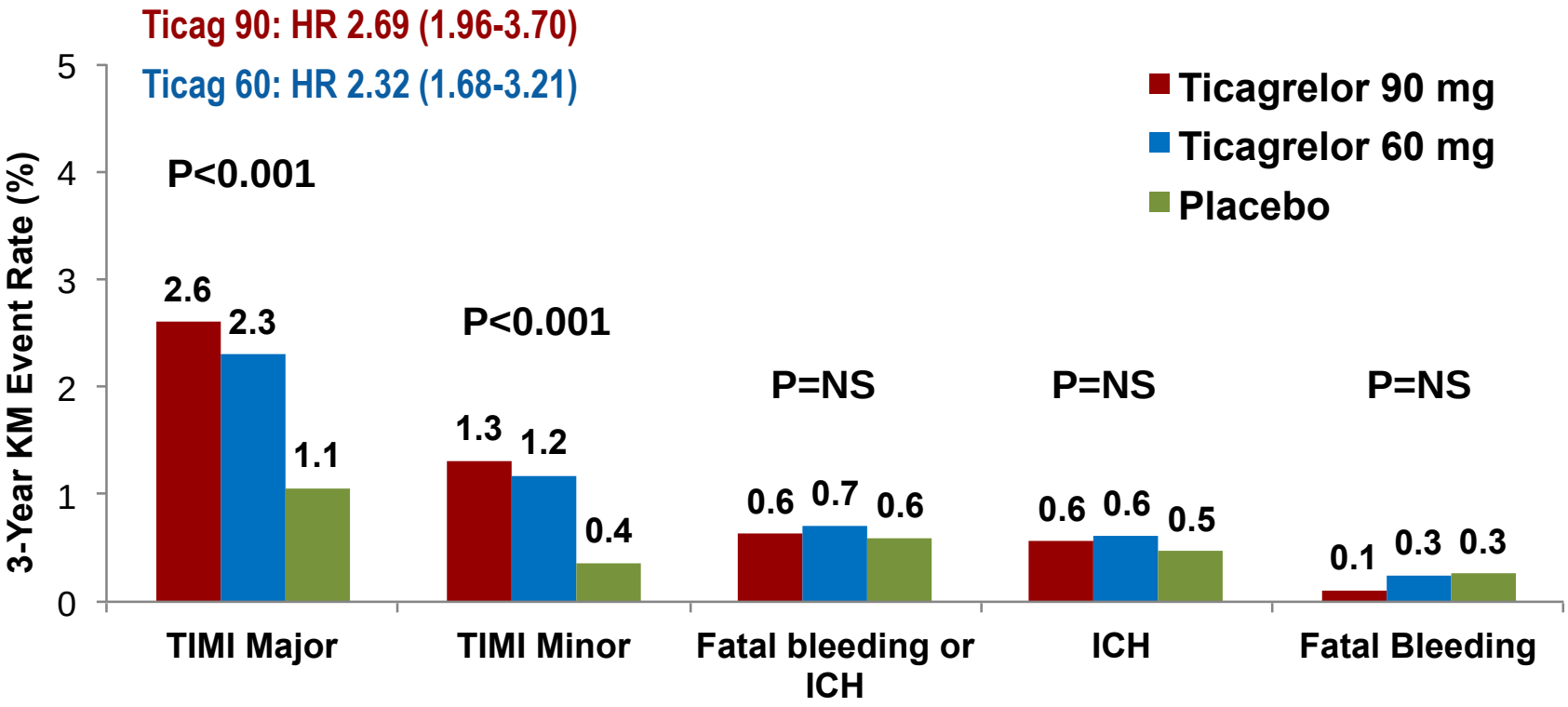
Components of Primary Endpoint



Endpoint	HR (95% CI)	P value
CV Death, MI, or Stroke (1558 events)	0.85 (0.75-0.96)	0.008
	0.84 (0.74-0.95)	0.004
	0.84 (0.76-0.94)	0.001
CV Death (566 events)	0.87 (0.71-1.06)	0.15
	0.83 (0.68-1.01)	0.07
	0.85 (0.71-1.00)	0.06
Myocardial Infarction (898 events)	0.81 (0.69-0.95)	0.01
	0.84 (0.72-0.98)	0.03
	0.83 (0.72-0.95)	0.005
Stroke (313 events)	0.82 (0.63-1.07)	0.14
	0.75 (0.57-0.98)	0.03
	0.78 (0.62-0.98)	0.03

Ticagrelor 90 mg
Ticagrelor 60 mg
Pooled

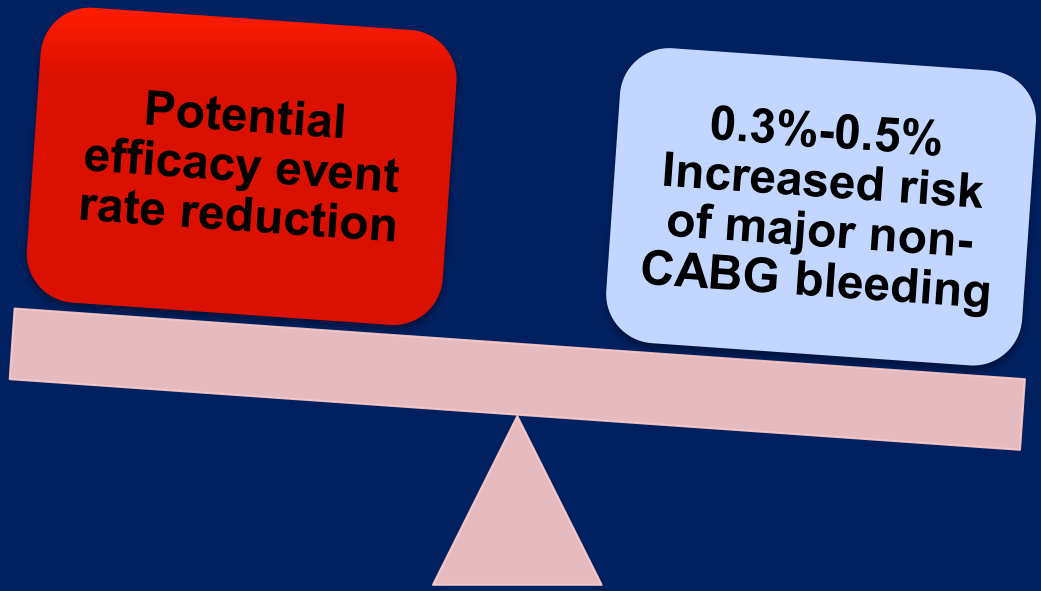
Bleeding


Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)
Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo
3-Year KM Event Rate (%)
0
1
2
3
4
5
P<0.001
2.6
2.3
1.1
P<0.001
1.3
1.2
0.4
P=NS
0.6
0.7
0.6
P=NS
0.6
0.6
0.5
P=NS
0.1
0.3
0.3
TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding

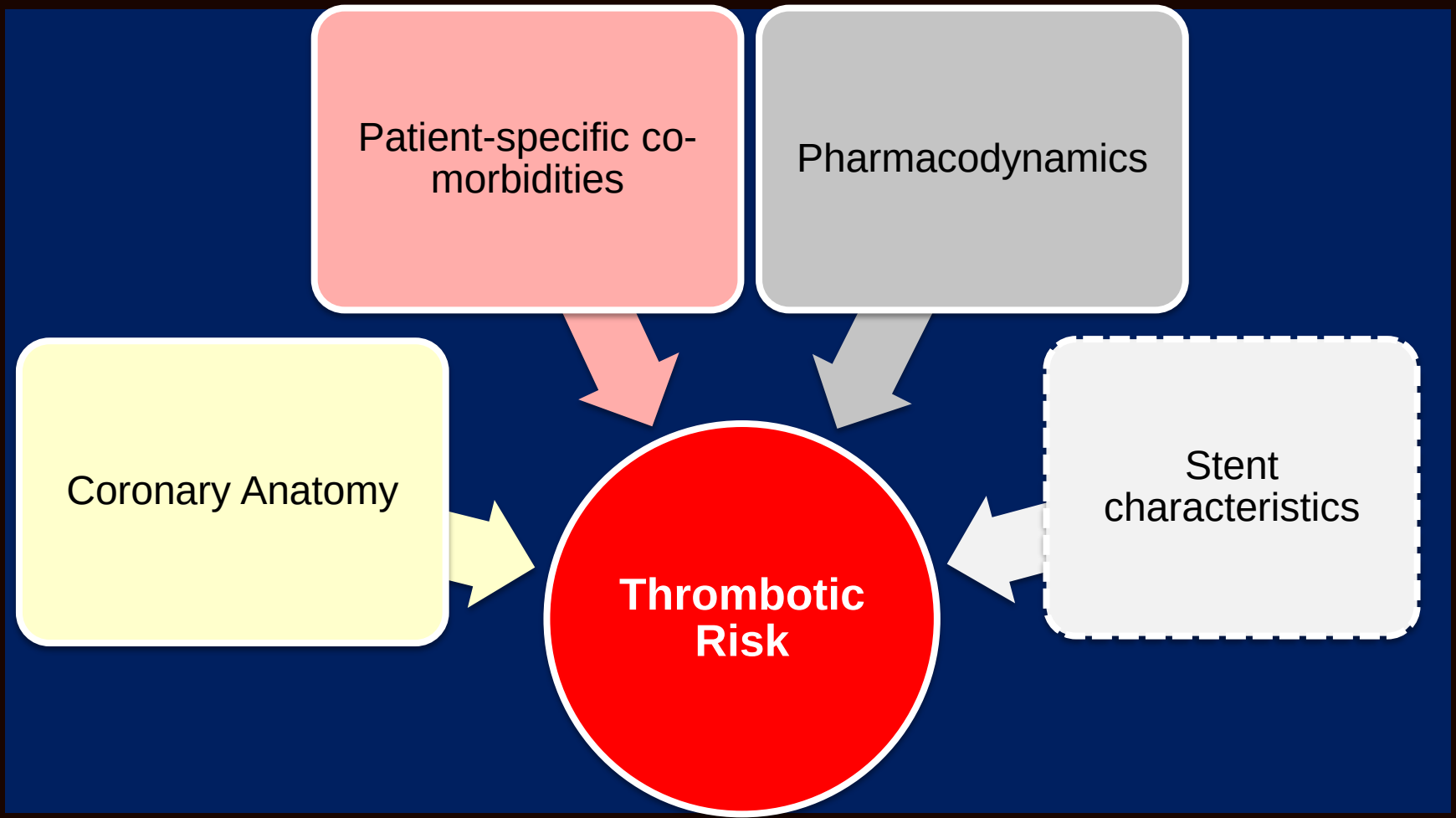
The Challenge of Potent Oral Antiplatelet Therapy in the Setting of Non-Urgent PCI

- Low rate of stent thrombosis
- Low rate of non-culprit lesion thrombotic events

Can we identify the non-urgent PCI patient who would benefit from long-term, potent oral antiplatelet therapy?

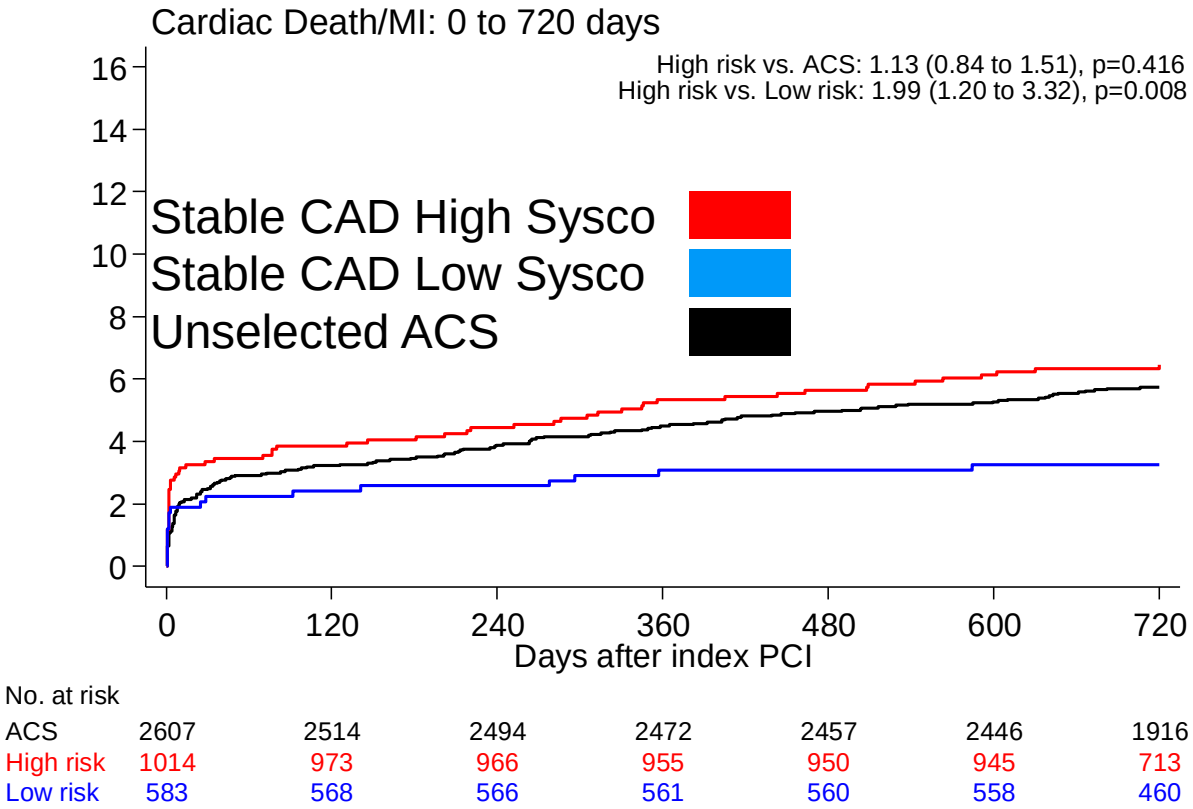


Assessing Thrombotic Risk in the Elective PCI Patient



Can the Syntax score identify a Stable CAD population at risk of events at least as high as compared to ACS ?

Periprocedural MI excluded

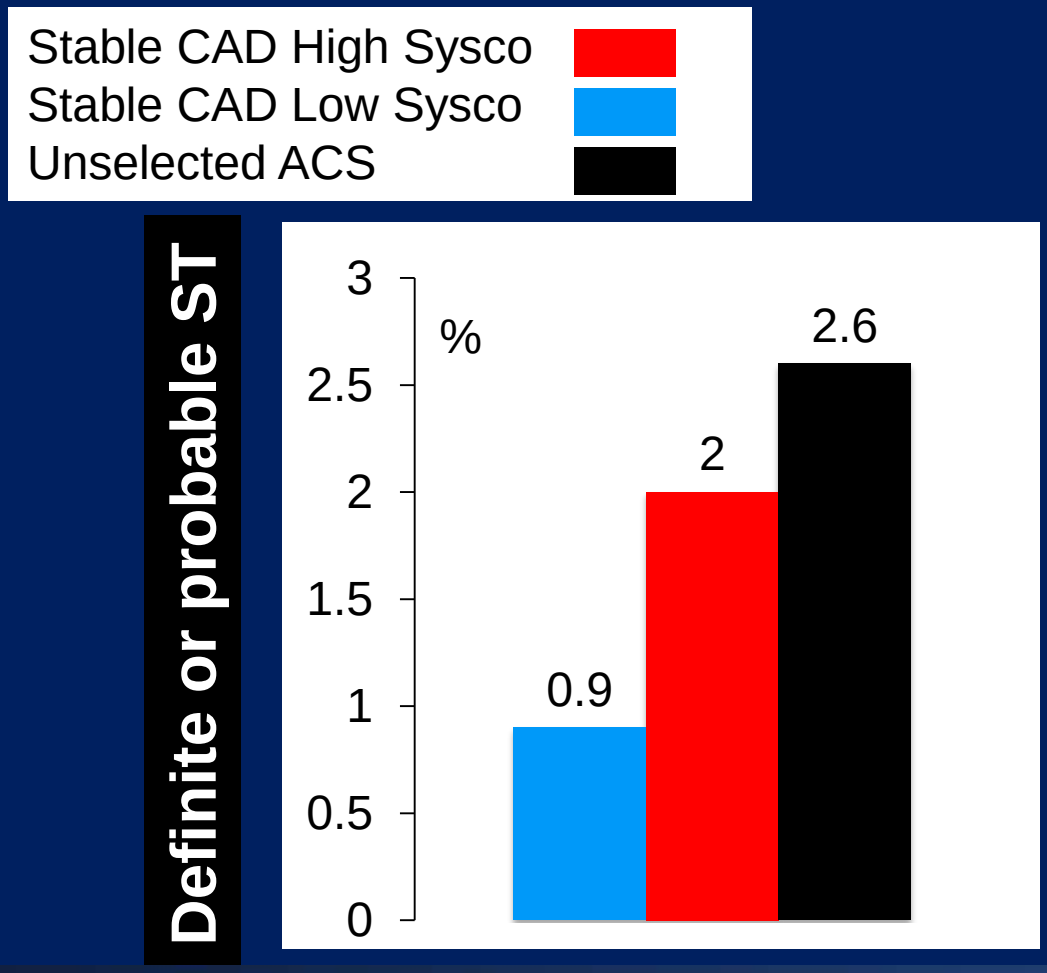


Patient level pooled analysis of RESOLUTE-AC, SIRTAX, LEADERS

Mount Sinai Heart

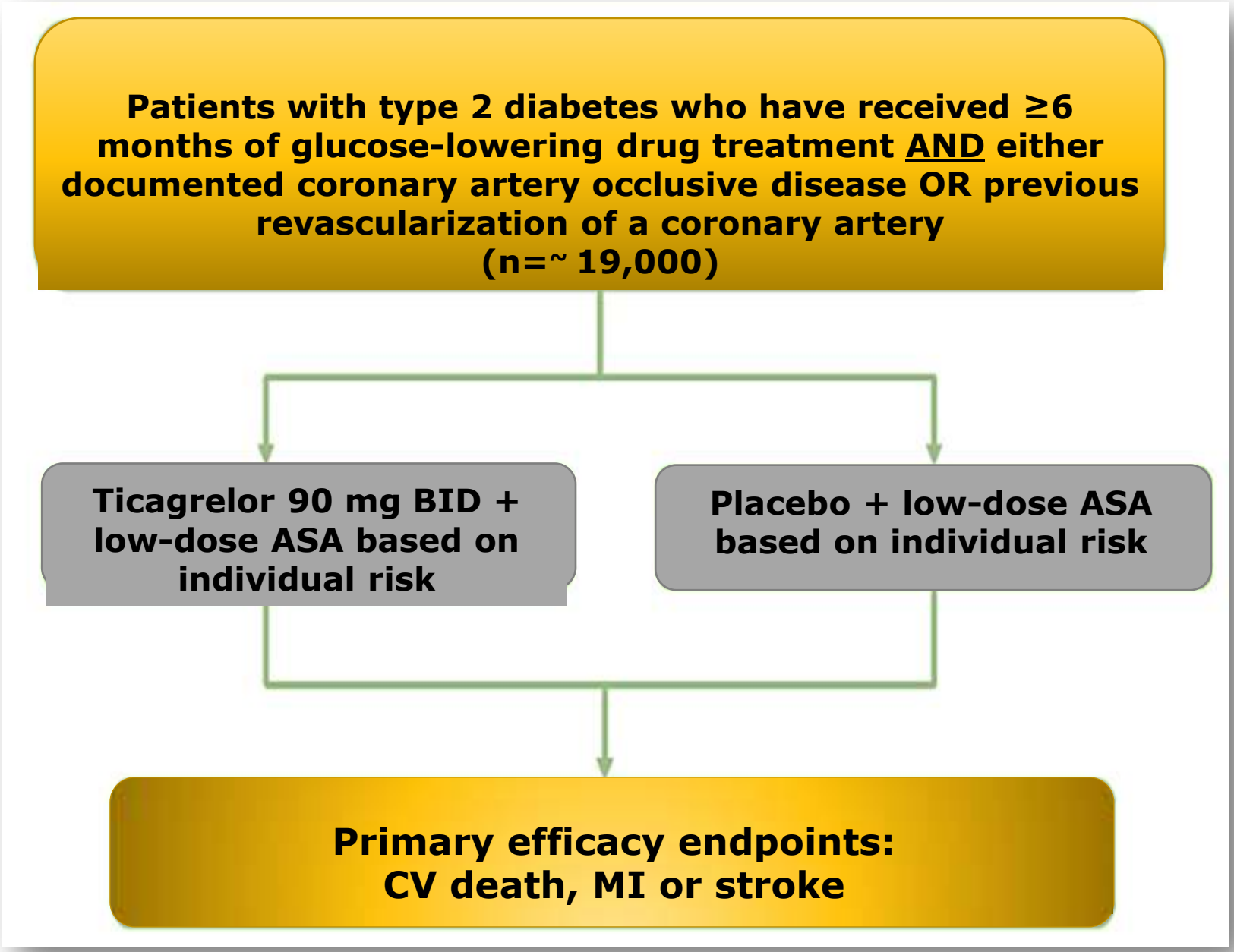
Vranckx P et al, Eurointervention 2014

Can the Syntax score identify a Stable CAD population at risk of events at least as high as compared to ACS ?



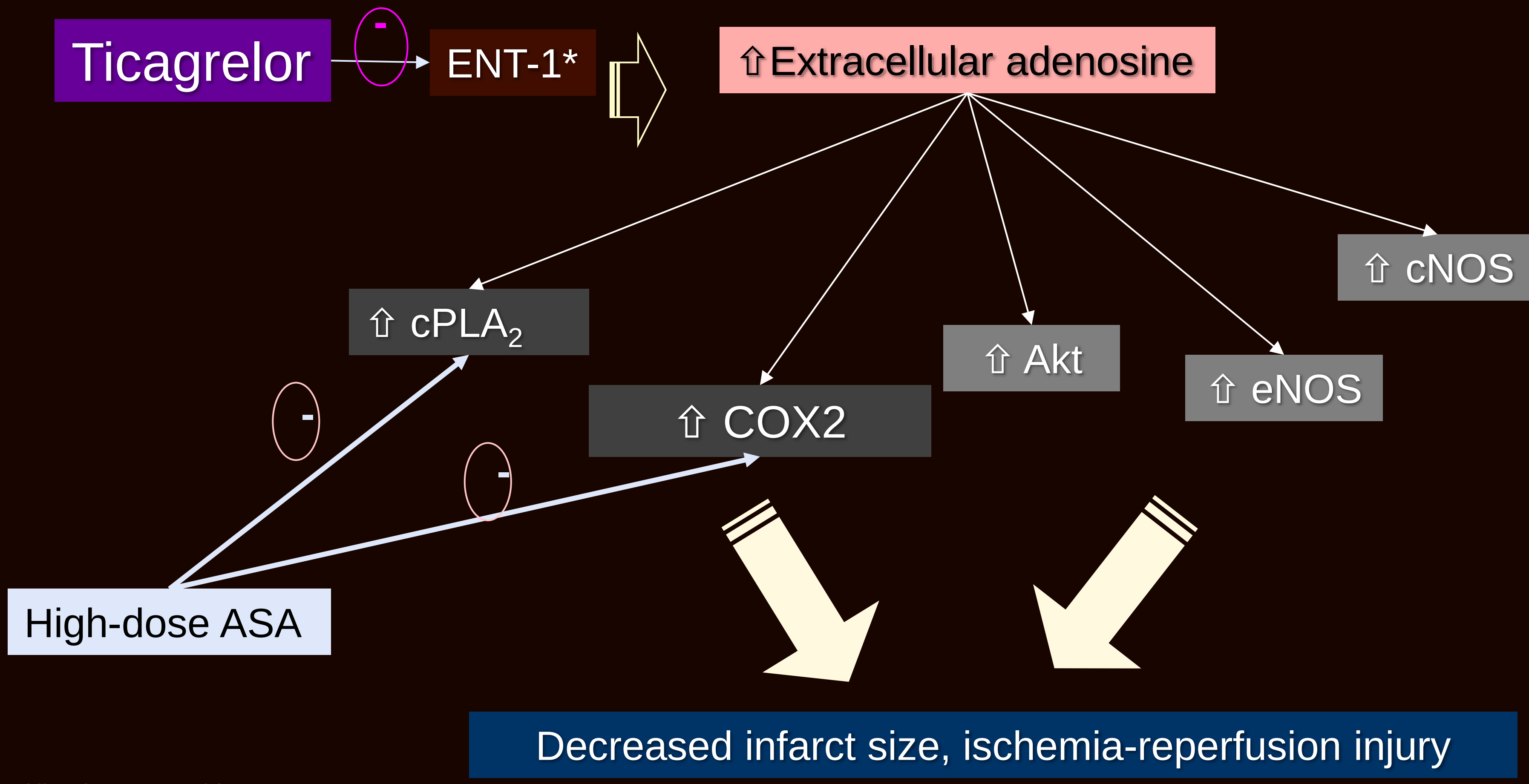
Vranckx P et al, Eurointervention 2014

THEMIS Trial design



NCT01991795

More Than Just Platelet P2Y12 Inhibition?
Off-Target Effects of Ticagrelor

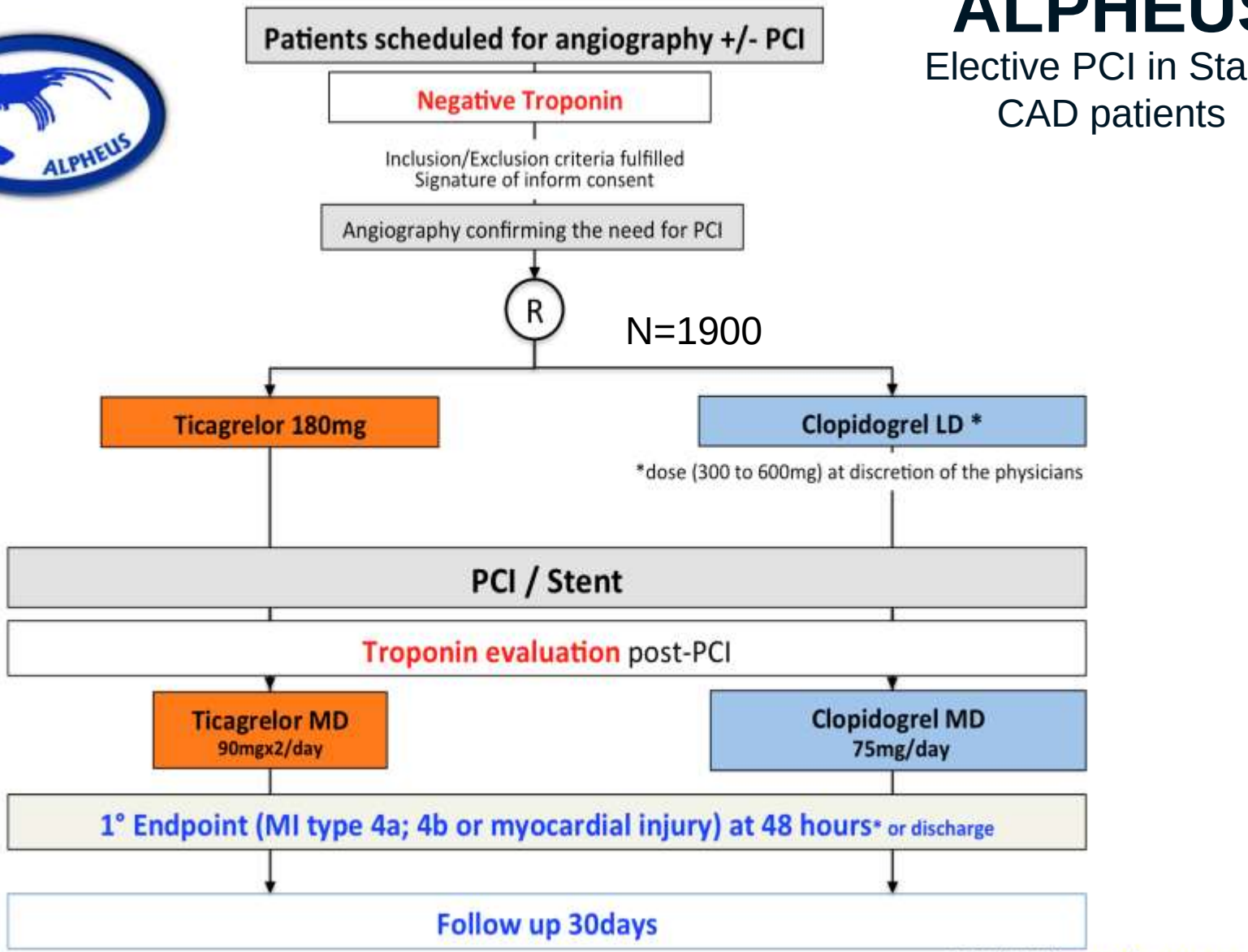


*Equilibrative nucleoside transporter-1

Nanhwal MK et al, Arterioscler Thromb Vasc Biol. 2014

ALPHEUS

Elective PCI in Stable CAD patients



A.C.T.I.O.N.* www.action-cœur.org

Comparative Effectiveness of 2 Pharmaco-Intervention Strategies

GLOBAL LEADERS

All-Comers PCI population
ACS and Elective/Stable patients
80 centres, 10+ countries, (n=16,000)

Biolimus-eluting stent (BES)
BioMatrix Flex ™

1:1 randomization

Study Treatment Strategy

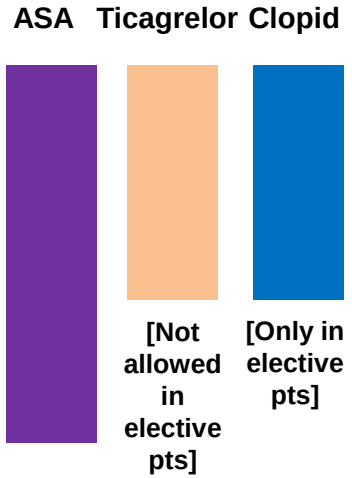
1-month
ASA + Ticagrelor

23-months
monotherapy Ticagrelor

Reference Treatment Strategy

12-months DAPT
ACS pts (ASA + Ticagrelor)
Elective pts (ASA + Clopidogrel)

12-months
monotherapy ASA



Primary Endpoint
Study treatment strategy superior to reference treatment strategy on cumulative **2 years composite of all-cause mortality and new Q-wave MI**

Dual Antiplatelet Therapy After PCI: Paradigm to be tested in TWILIGHT

PCI in high-risk patients

Short course of DAPT to minimize stent-related thrombotic events

Monotherapy with a potent platelet inhibitor protects against systemic thrombosis while reducing ASA-related bleeding

Mount Sinai Heart

21st CardioVascular Summit TCTAP 2016

TWILIGHT: Study Design

- **Multinational, randomized trial among high-risk patients undergoing elective PCI**
  - High-risk based on clinical (renal impairment, recent ACS, diabetes mellitus) or anatomic (complex bifurcation; stent length > 30 mm) criteria
  - Enrollment at time of PCI with randomization 3 months after PCI
- **Primary endpoint**: Clinically relevant (BARC ≥ 2) bleeding
- **Secondary endpoints:** Composite occurrence of death (all-cause, stroke, myocardial infarction, ischemia-driven revascularization, def/prob stent thrombosis)

Conclusions

- ACS is a common diagnosis with high morbidity and mortality
- Early risk stratification informs early treatment stratification
  - Always focus on benefit/risk of ischemic management versus bleeding risk
- Antiplatelet therapy is central to ACS treatment
- Choices among agents and timing of antiplatelet therapy are critical to good outcomes
- The Data supporting use of Ticagrelor in ACS is strong with reduction of mortality in ACS, and redcution of MACE in post MI patients.
- However, bleeding risk should be evaluated and taken into consideration.

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