The DAPT Debate: 2016

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ACC session @ TCTAP 2016

Seoul, Korea

Mount Sinai Heart

21st CardioVascular Summit TCTAP 2016

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
• Grant/Research Support (Institutional)	• The Medicines Co., AZ, BMS, Lilly/Daiichi Sankyo
• Advisory Board	• Janssen (J+J),
• Consulting Fees/Honoraria	• Janssen (J+J), Maya Medical,

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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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Critical (PICOTS-Formatted) Questions on Duration of DAPT Addressed in a Systematic Review Conducted by the Evidence Review Committee (ERC)

- **Q1: In patients treated with newer (non-first) generation DES for (1) SIHD or (2) ACS, compared with 12 months of DAPT, is 3–6 months of DAPT as effective in preventing stent thrombosis, preventing MACE and/or reducing bleeding complications?**
- **Q2: In patients treated with newer (non-first) generation DES, compared with 12 months of DAPT, does >12 (18–48) months of DAPT result in differences in mortality, decreased MACE, decreased stent thrombosis and/or increased bleeding?**
- **Q3: In post-MI (NSTEMI or STEMI) patients who are clinically stable and >12 months past their event, does continued DAPT, compared with aspirin monotherapy, result in differences in mortality, decreased nonfatal MI, decreased MACE and/or increased bleeding?**

Recommendations that are based on a body of evidence that includes a systematic review conducted by the ERC are denoted by the superscript SR (e.g., LOE B-R^{SR})

Bittl VS, et al. Duration of DAPT: A Systematic Review for the 2016 Guideline Update. JACC 2016 & Circulation 2016
Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of DAPT in Patients with CAD. JACC 2016 &

Duration of Dual Antiplatelet Therapy: A Systematic Review for the 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

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Bittl JA, et al. Duration of DAPT: A Systematic Review for the 2016 Guideline Update. JACC 2016 & Circulation 2016

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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 &

Prolonged/Extended DAPT and Mortality:

Analyses of mortality with DAPT Rx performed subsequent to the Dual Antiplatelet Trial (DAPT) finding of borderline significant increase in mortality

Study	Population	Findings
5 Meta-analyses (published prior to OPTIDUAL)	Predominantly newer generation DES-treated patients	Numerically or statistically significant increased risk of all-cause (though not cardiovascular) death
ERC Primary Analysis (including OPTIDUAL)	Predominantly newer generation DES-treated patients	No statistically significant difference in all-cause mortality
1 Meta-analysis (Elmariah S et al)	Post-stent and other indications for DAPT	No increase in CV or non-CV mortality
Analysis of 6 trials (Udell JA et al)	Patients post-MI treated with DAPT	No increase in CV or non-CV mortality
FDA Drug Safety Communication	Long-term trials of patients with CV disease or stroke Rx with clopidogrel	No increase (or decrease) in the risk of all-cause mortality or cancer-related death

Based on all available data, a majority of the 2016 ACC/AHA DAPT Focused Update writing group members believed the data as a whole did not seem to suggest prolonged DAPT resulted in increased mortality

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Overriding Concepts and Recommendations

- Intensification of antiplatelet Rx, with the addition of a $P2Y_{12}$ inhibitor to ASA monotherapy, and prolongation of DAPT, necessitate a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk.
- In general, shorter duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk, whereas longer duration DAPT may be reasonable for patients at higher ischemic risk with lower bleeding risk.
- A Class I recommendation ("should be given") in most clinical settings is made for at least 6-12 months of DAPT (depending on the setting) and a Class IIb recommendation ("may be reasonable") is made for prolonged DAPT beyond this initial 6-12 month period.
- In studies of "prolonged DAPT" after DES or post-MI, duration of therapy was limited to several years. Thus, in patients for whom the benefit/risk ratio seemingly favors prolonged therapy, the true "optimal duration" of therapy is unknown.

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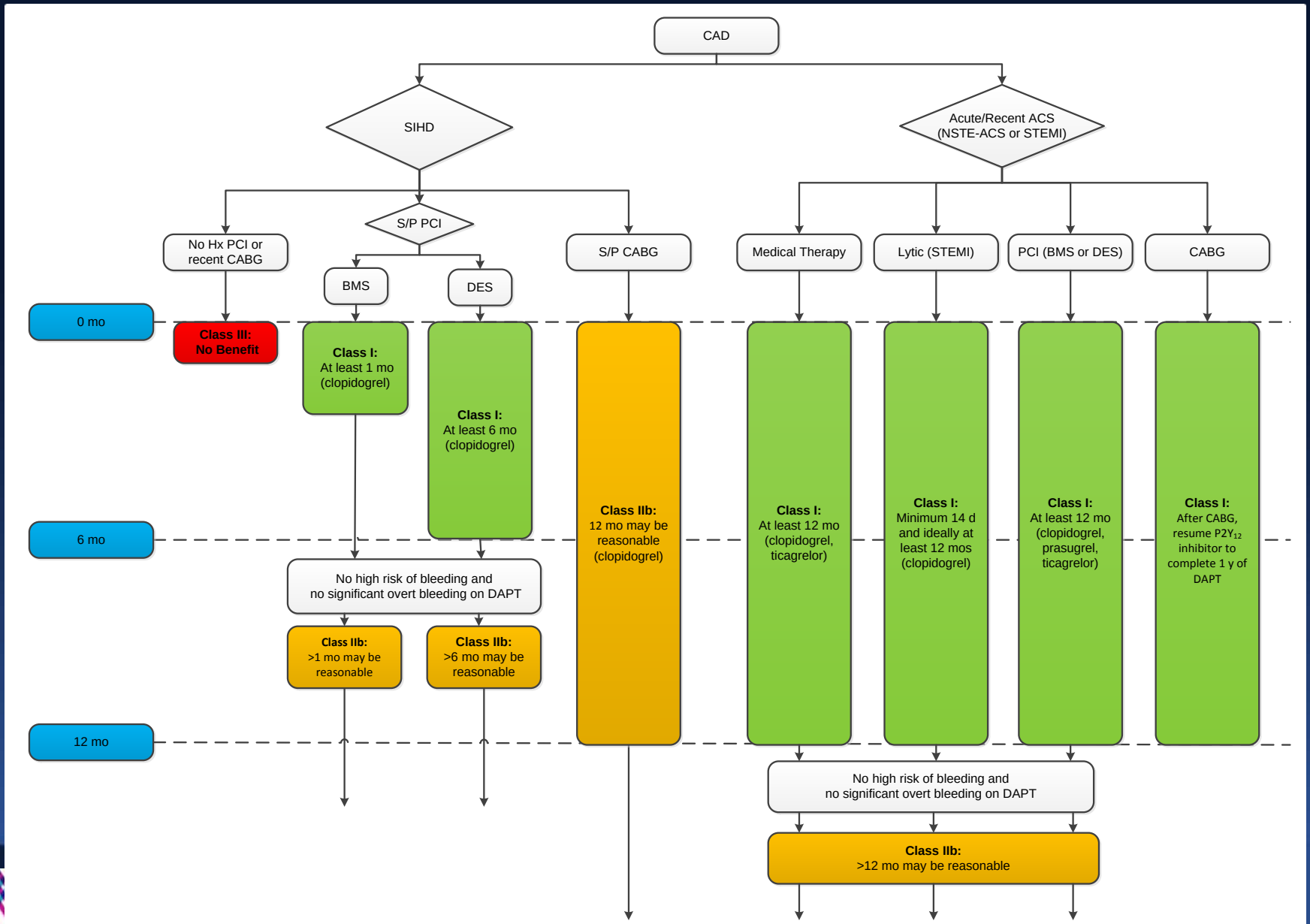
Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of DAPT in Patients with CAD. JACC 2016 &

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



Duration of DAPT in Patients With SIHD

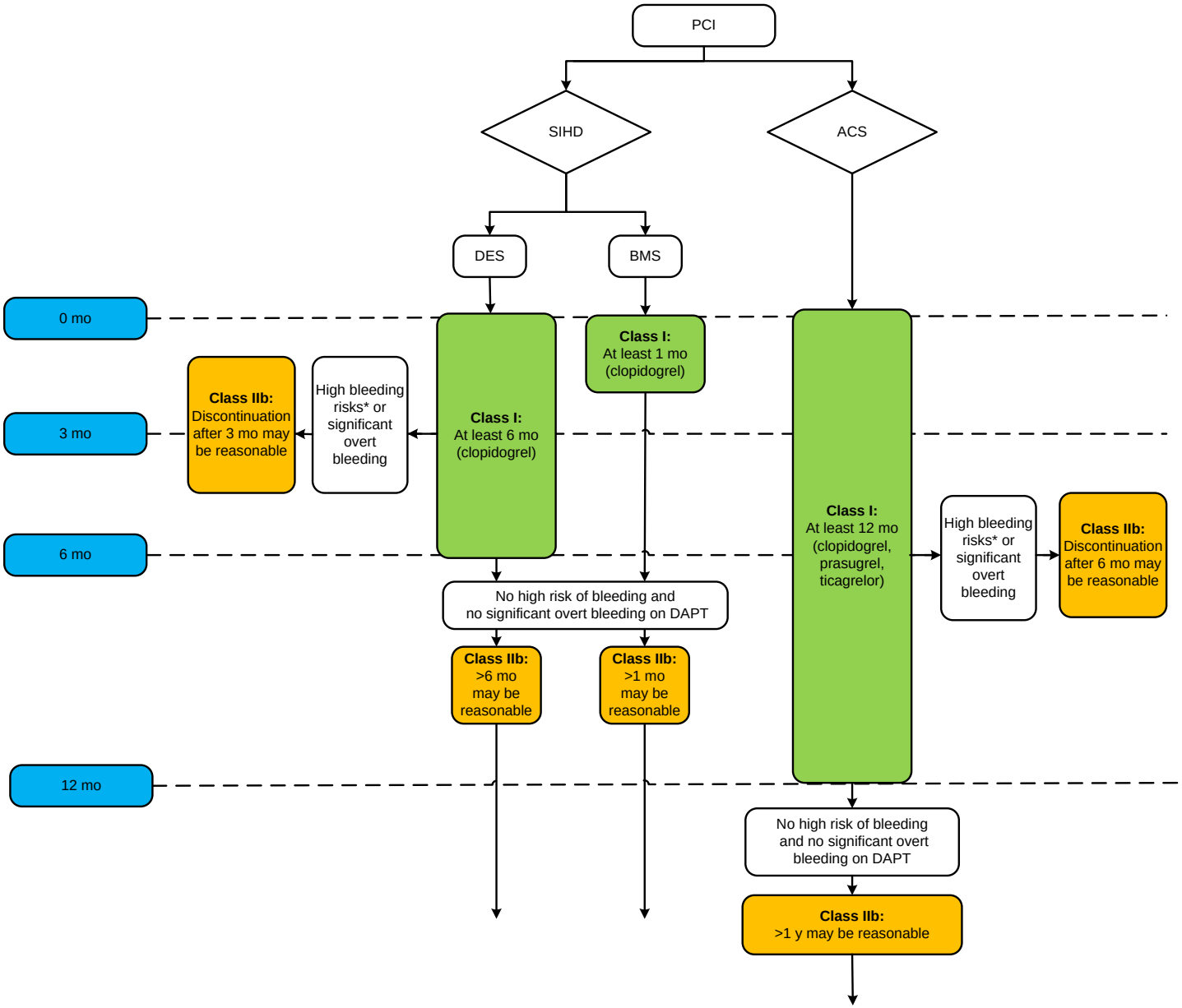
COR	LOE	Recommendations
I	A	In patients with SIHD treated with DAPT after BMS implantation, $P2Y_{12}$ inhibitor therapy with clopidogrel should be given for a minimum of 1 month
I	B-R SR	In patients with SIHD treated with DAPT after DES implantation, $P2Y_{12}$ inhibitor therapy with clopidogrel should 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

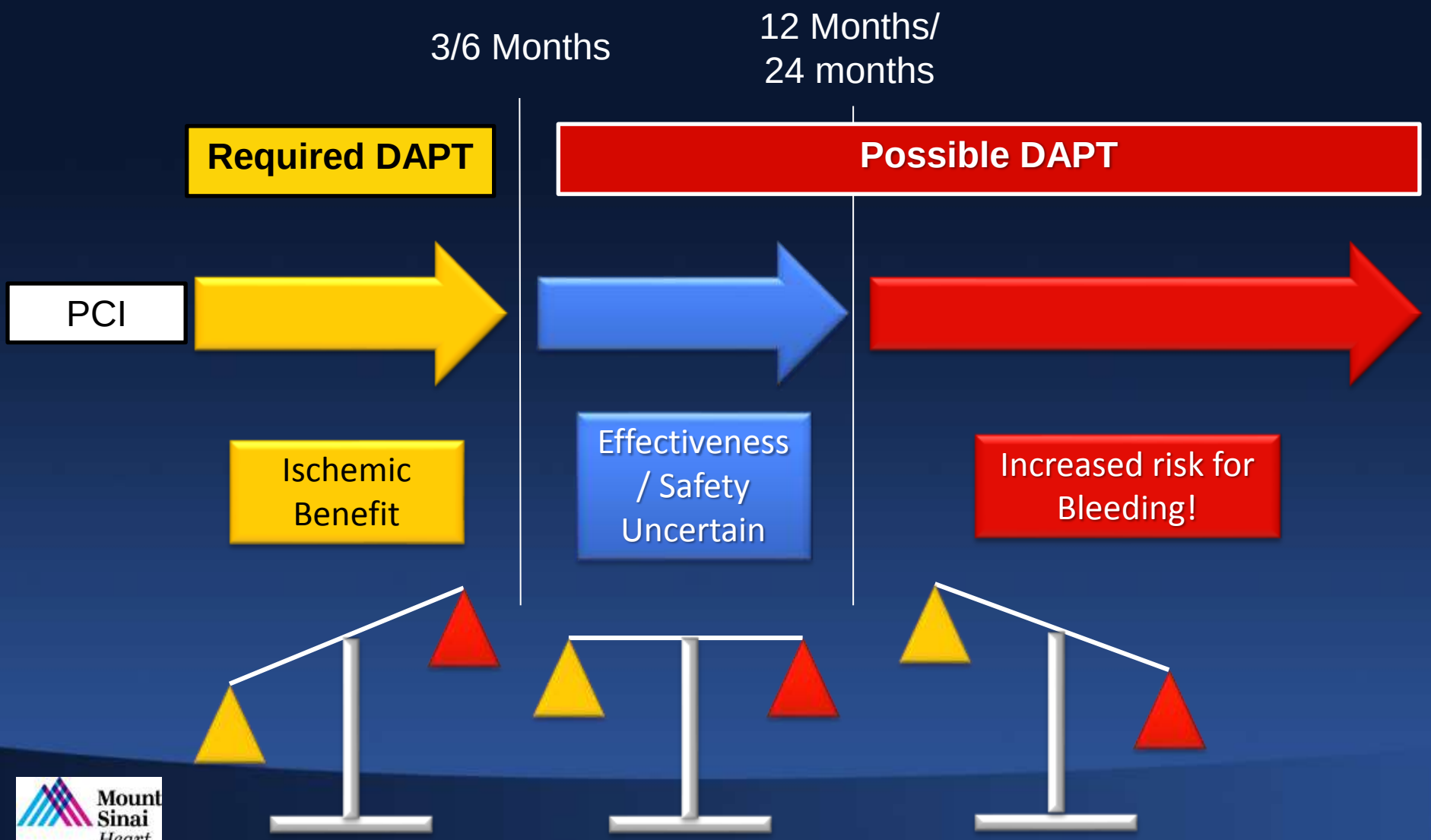
Duration of DAPT in Patients With ACS

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



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



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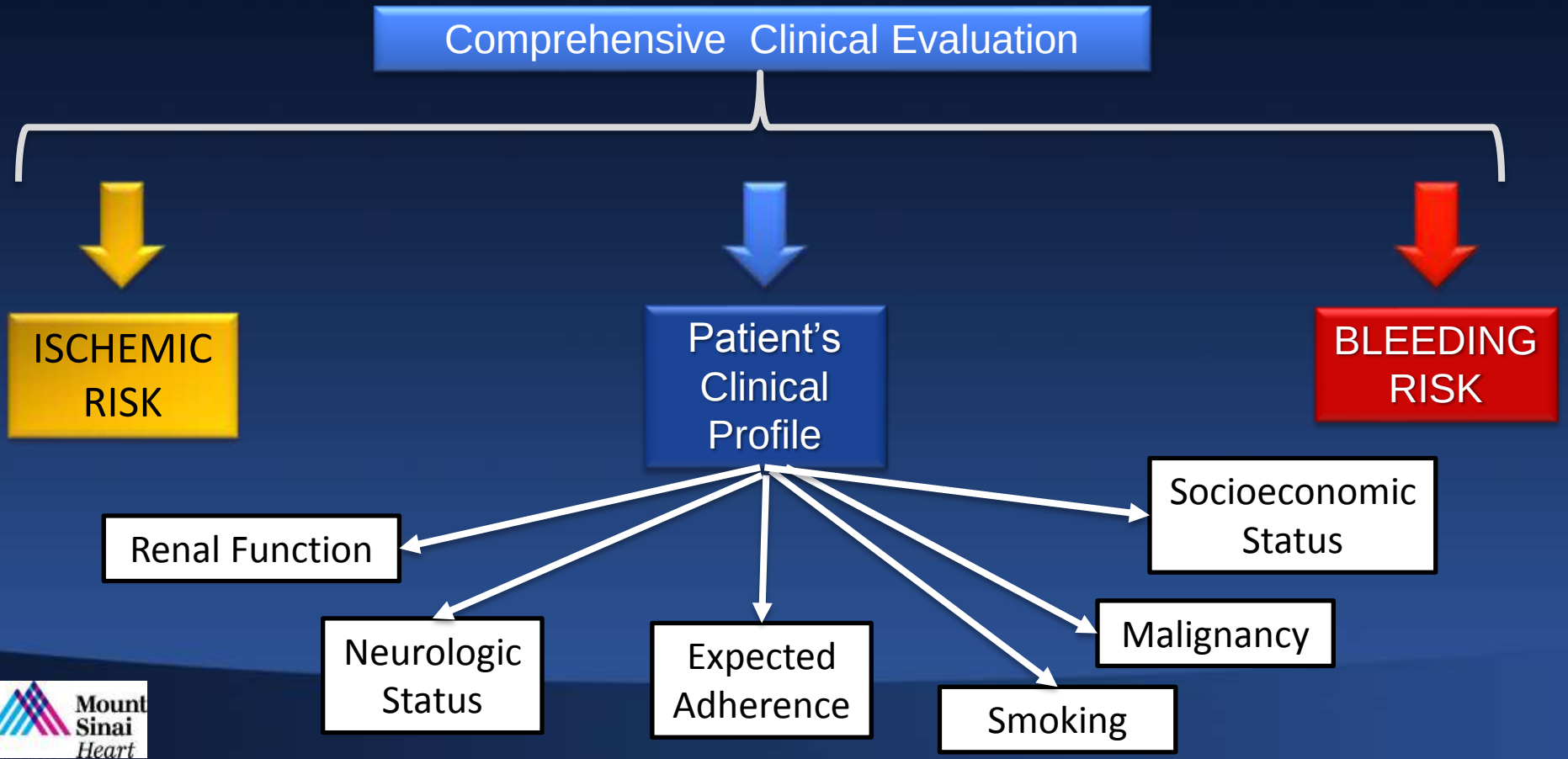
Does one size fit all?

… the answer is NO!



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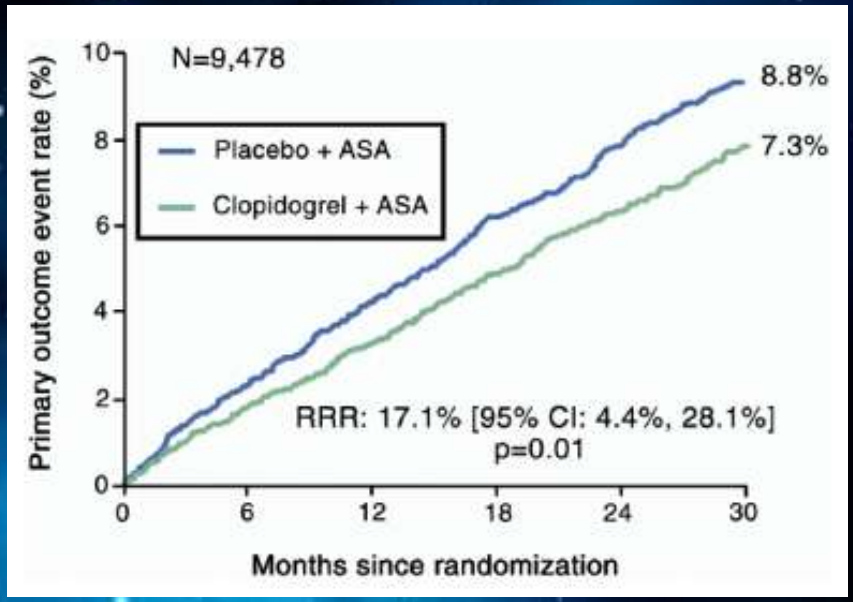
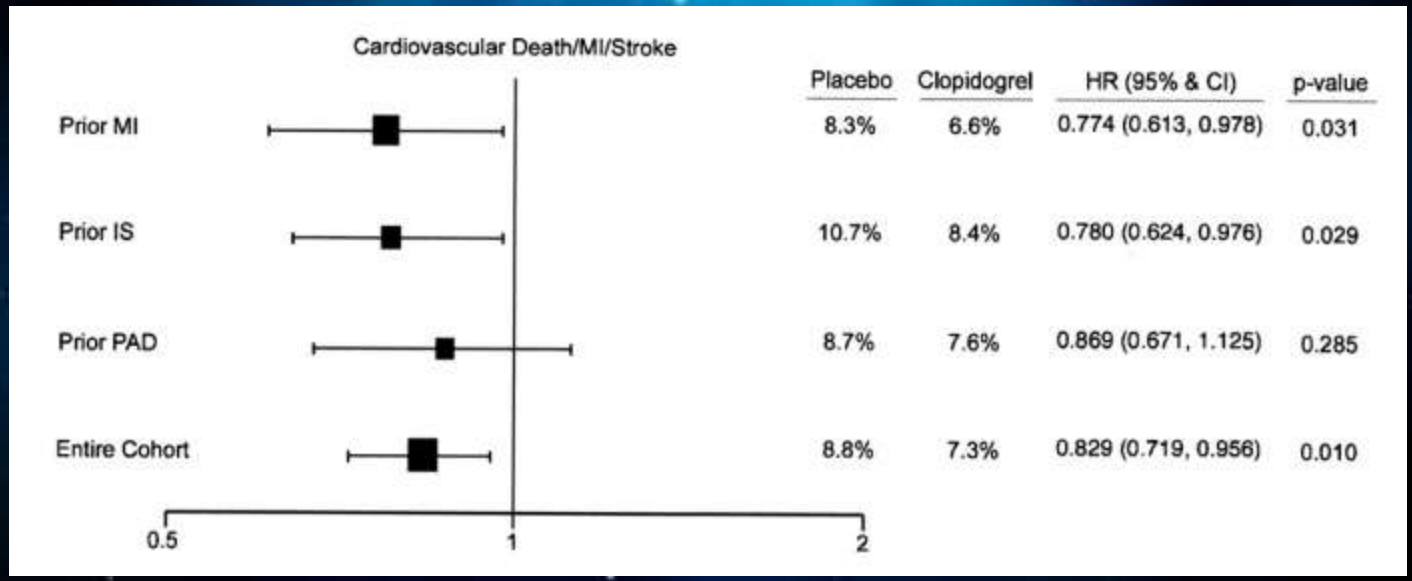
Who may benefit of prolonged DAPT?

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!





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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

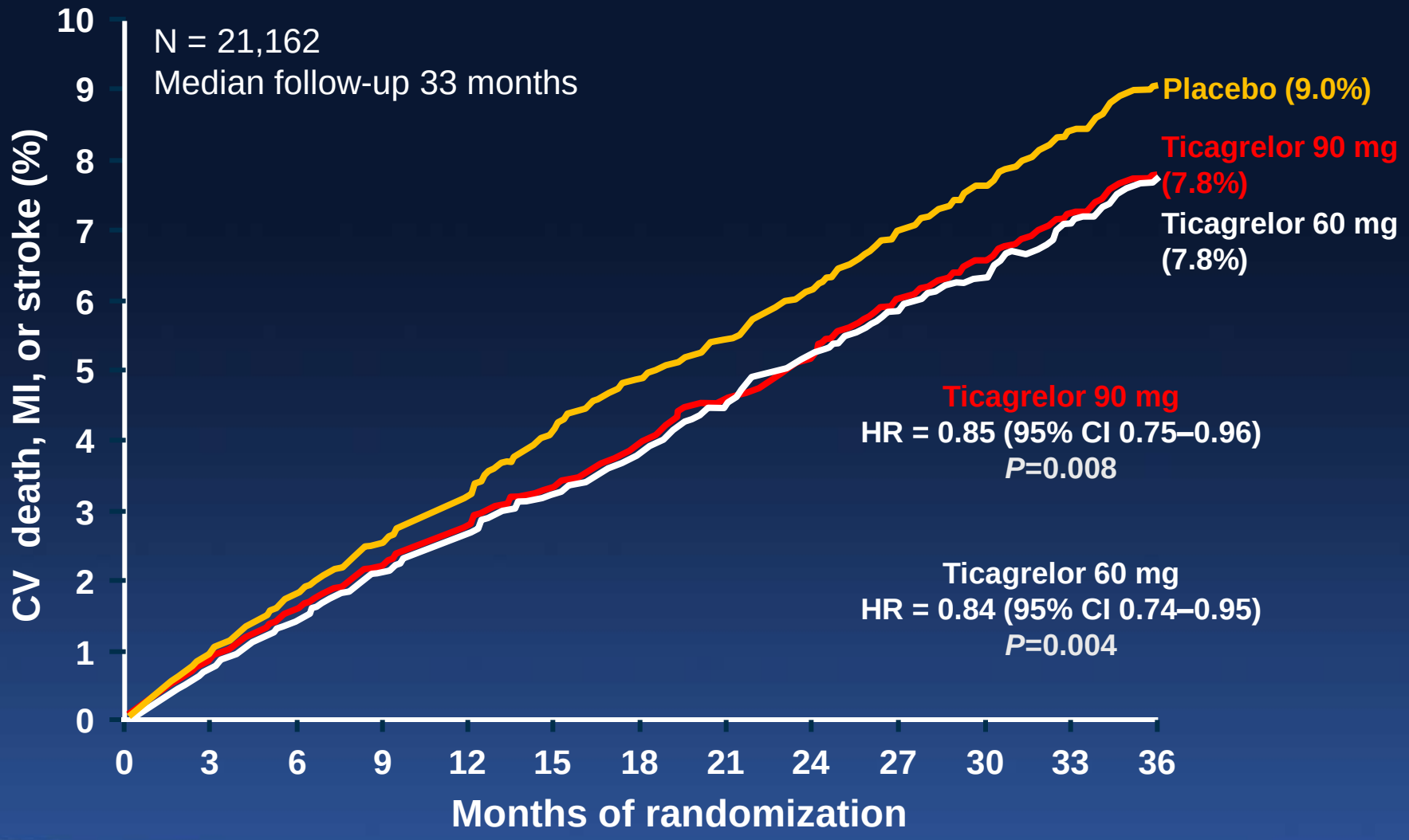
Ticagrelor 90 mg bid (N = 7050)	**Ticagrelor 60 mg bid (N = 7045)**	**Placebo 60 mg bid (N = 7067)**

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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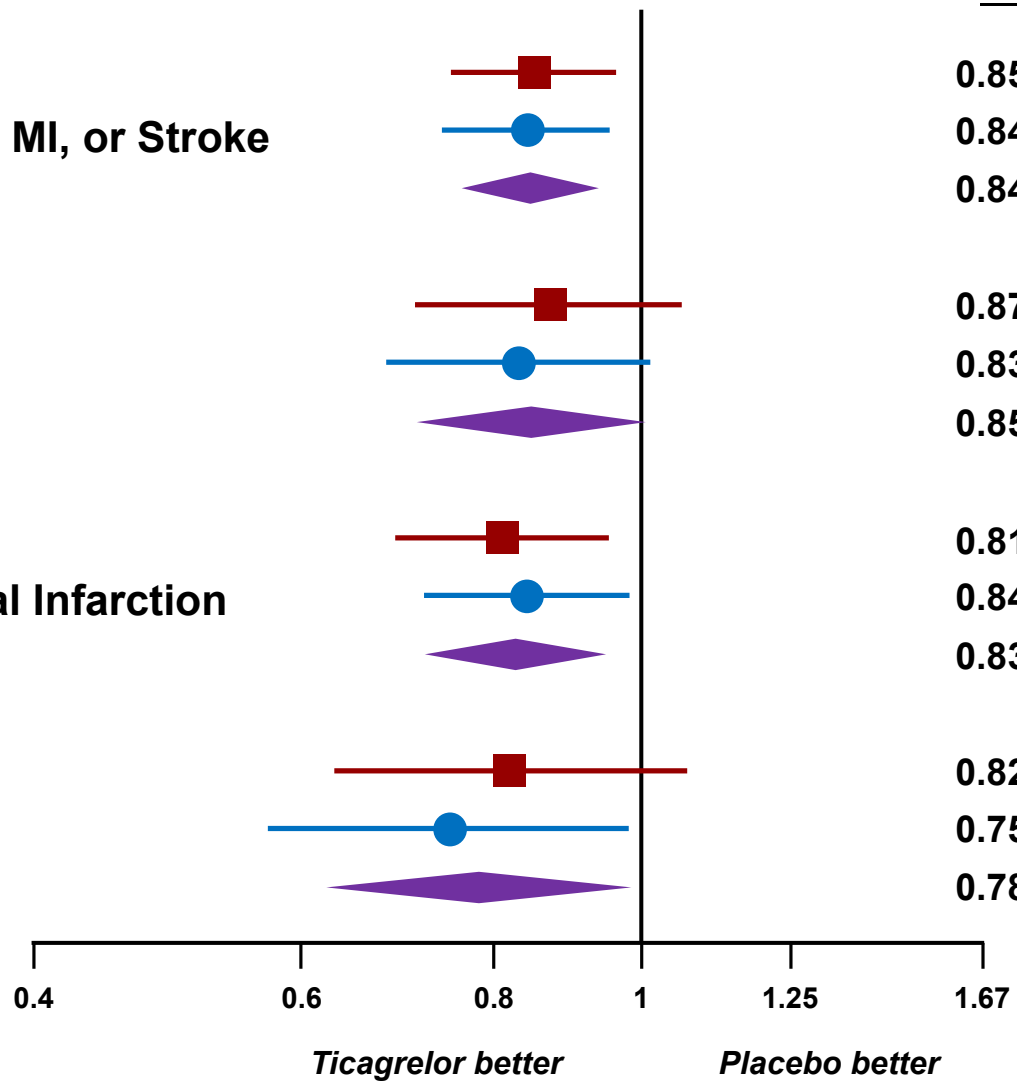
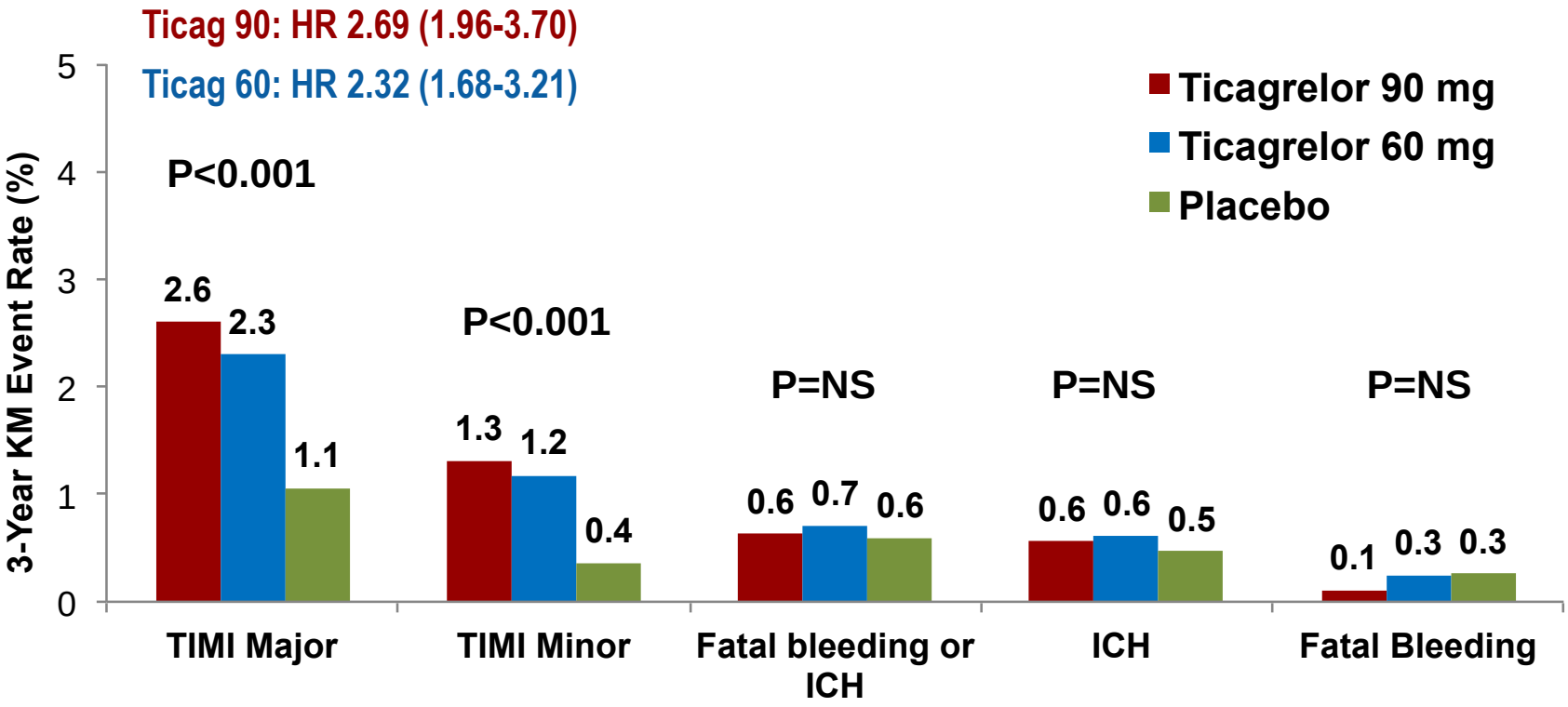
Components of Primary Endpoint



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

DAPT Score: How to individualize therapy?

Characteristics	Impact on Combined Treatment Effect	% of Variation Explained	DAPT Score
Age ≥ 75	-1.2%	6.0%	**-2**
Age 65 - < 75	-0.5%	2.2%	**-1**
Age < 65 (reference)	-	-	**0**
Prior PCI or MI	1.1%	14.6%	**1**
Stent Diameter < 3 mm	0.9%	10.1%	**1**
CHF or LVEF < 30%	1.9%	9.9%	**2**
MI at Presentation	1.0%	9.6%	**1**
Paclitaxel-Eluting Stent	1.0%	8.8%	**1**
Cigarette Smoker	0.7%	4.3%	**1**
Diabetes	0.6%	4.3%	**1**

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

High DAPT Score ≥ 2
NNT to prevent ischemia = 34
NNH to cause bleeding = 272

Yeh, R et al. JAMA 2016

Predicting Risks for Coronary Thrombosis and Major Bleeding After PCI with DES: Risk Scores from PARIS Registry

Integer Risk Score for Major Bleeding

Parameter	Score				
Age, years	< 50	50-59	60-69	70-79	>80
	0	+1	+2	+3	+4
BMI, kg/m^2	<25		25-34.9	> 35	
	+2		0	+2	
Current Smoking	Yes		No		
	+2		0		
Anemia	Present		Absent		
	+3		0		
CKD*	Present		Absent		
	+2		0		
Triple Therapy on discharge	Yes		No		
	+2		0		

*Defined as CrCl < 60 mL/min/1.73 m2

Integer Risk Score for Coronary Thrombosis

Parameter	Score		
Diabetes Mellitus	None	Non-Insulin	Insulin
	0	+1	+3
Acute Coronary Syndrome	No	Yes, Tn (-)	Yes, Tn (+)
	0	+1	+2
Current Smoking	Yes		No
	+1		0
CKD*	Present		Absent
	+2		0
Prior PCI	Yes		No
	+2		0
Prior CABG	Yes		No
	+2		0

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Baber, Mehran, Giustino et al – JACC 2016 in press

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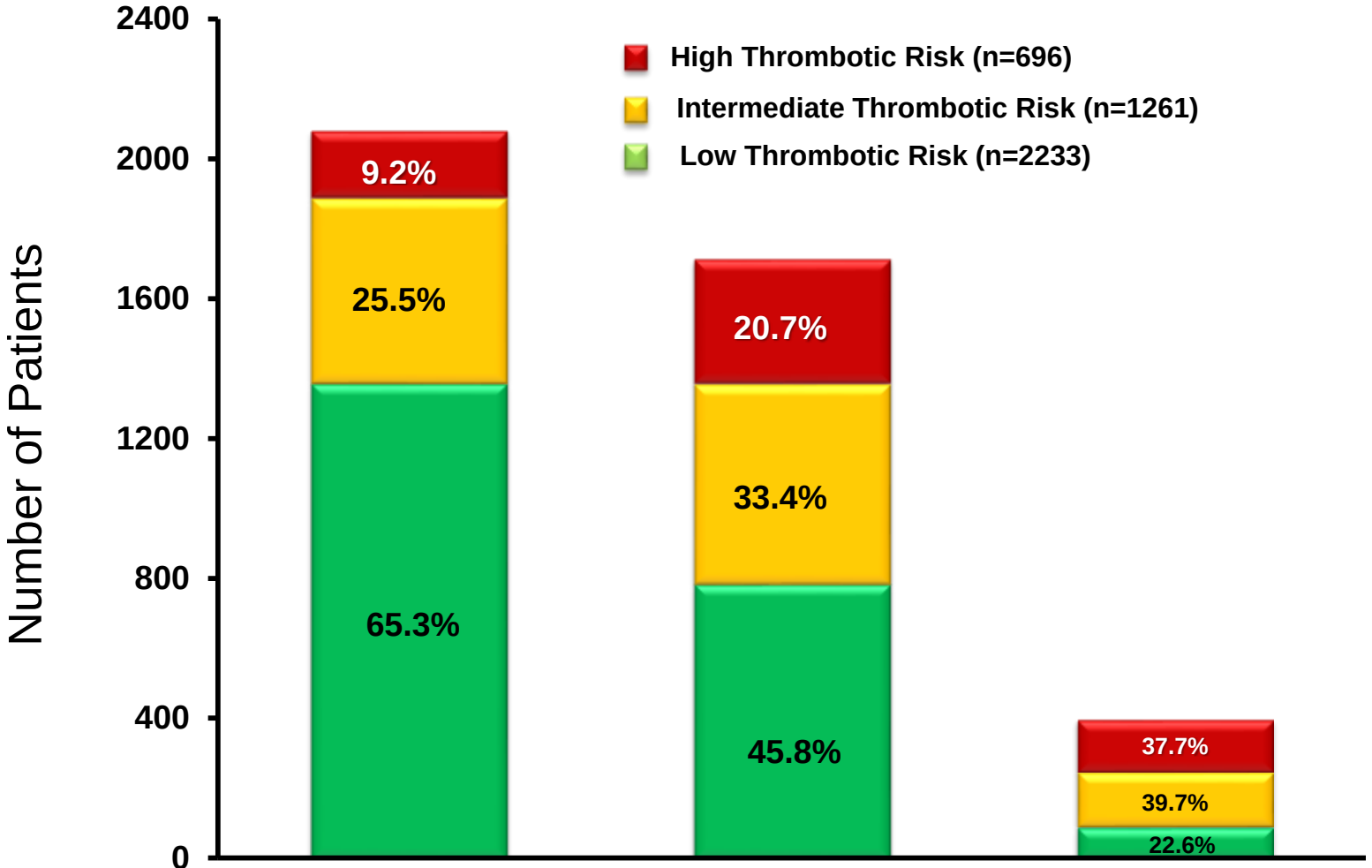
Cross-Classification by Thrombotic and Bleeding PARIS Risk Score Categories



	Low Bleeding Risk	Intermediate Bleeding Risk	High Bleeding Risk	Total
High Thrombotic Risk	191	355	150	696
Int Thrombotic Risk	530	573	158	1261
Low Thrombotic Risk	1358	785	90	2233
Total	2079	1713	398	4190

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Baber, Mehran et al – JACC 2016 in press

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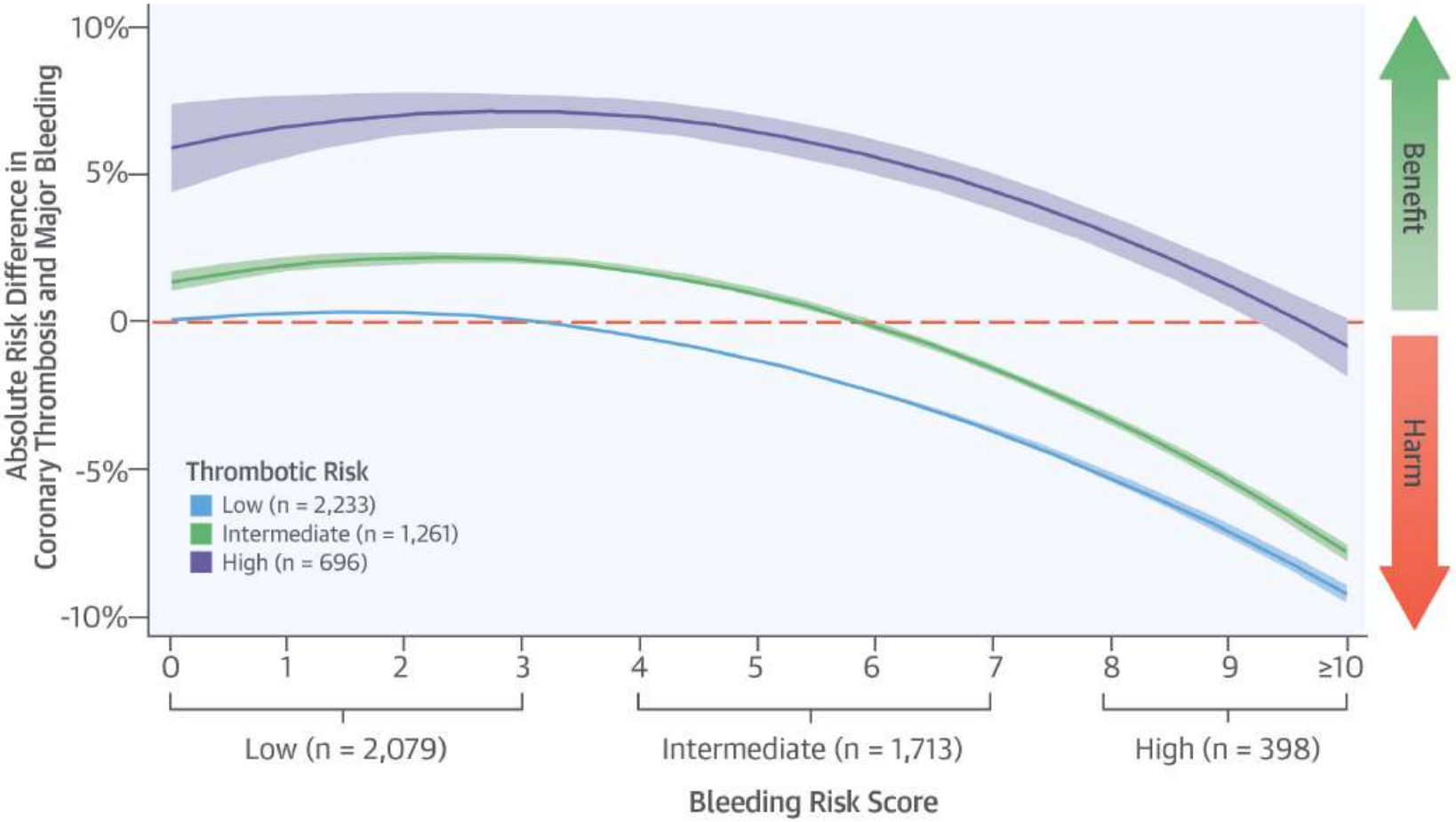
Risk/Benefit Trade-off with Prolonged DAPT as a Function of Thrombotic and Bleeding Risk



Baber, Mehran et al – JACC 2016 in press

Conclusions

1. After DES, longer DAPT is associated with protection against ischemic events but increases the risk of bleeding significantly as well as possibly all-cause mortality!

2. Spontaneous bleeding events are strongly and consistently associated with increased risk of mortality. These parameters are difficult to capture in clinical trials, but extremely important to the patient.

3. New-generation DES have significantly improved the stent-related thrombotic events thus attenuating the benefit of prolonged DAPT in this population- the math just doesn't work for most patients!

4. Prolongation of DAPT **after the mandatory DAPT period** for protection against **non-stent related thrombotic events** might be applied judiciously after careful evaluation of the individual atherothrombotic (stent-related and non-stent-related) and hemorrhagic risk.

The Optimal duration of DAPT in most DES patients should be shorter rather than longer, but should be customized based on the ischemic benefit and bleeding risk for each patient