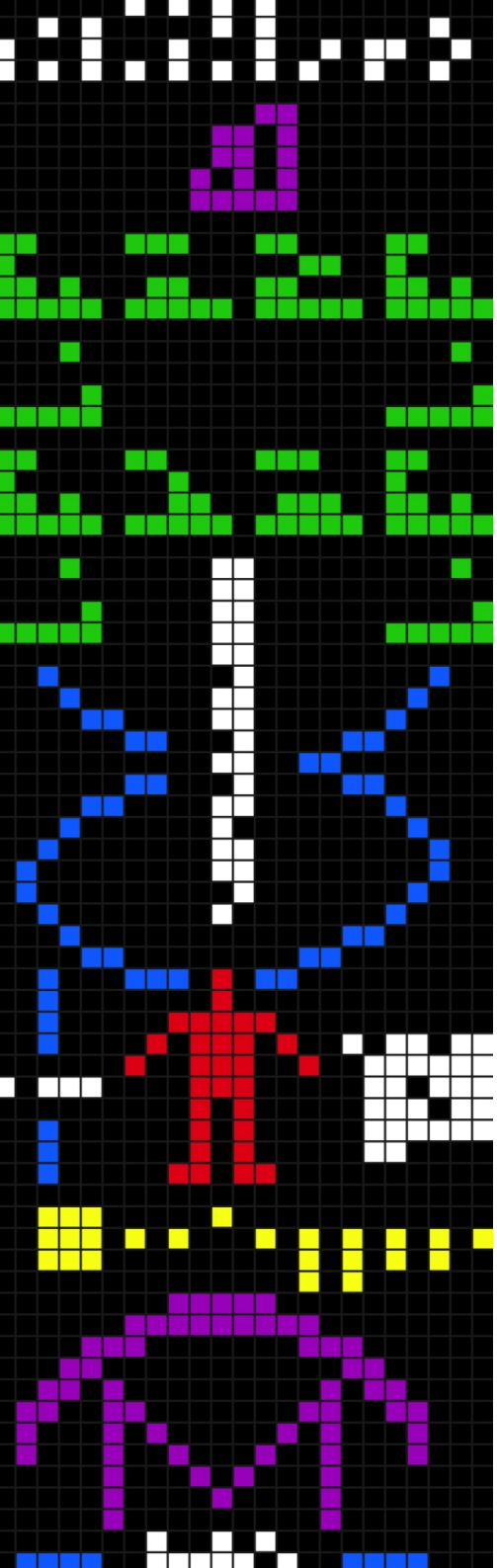


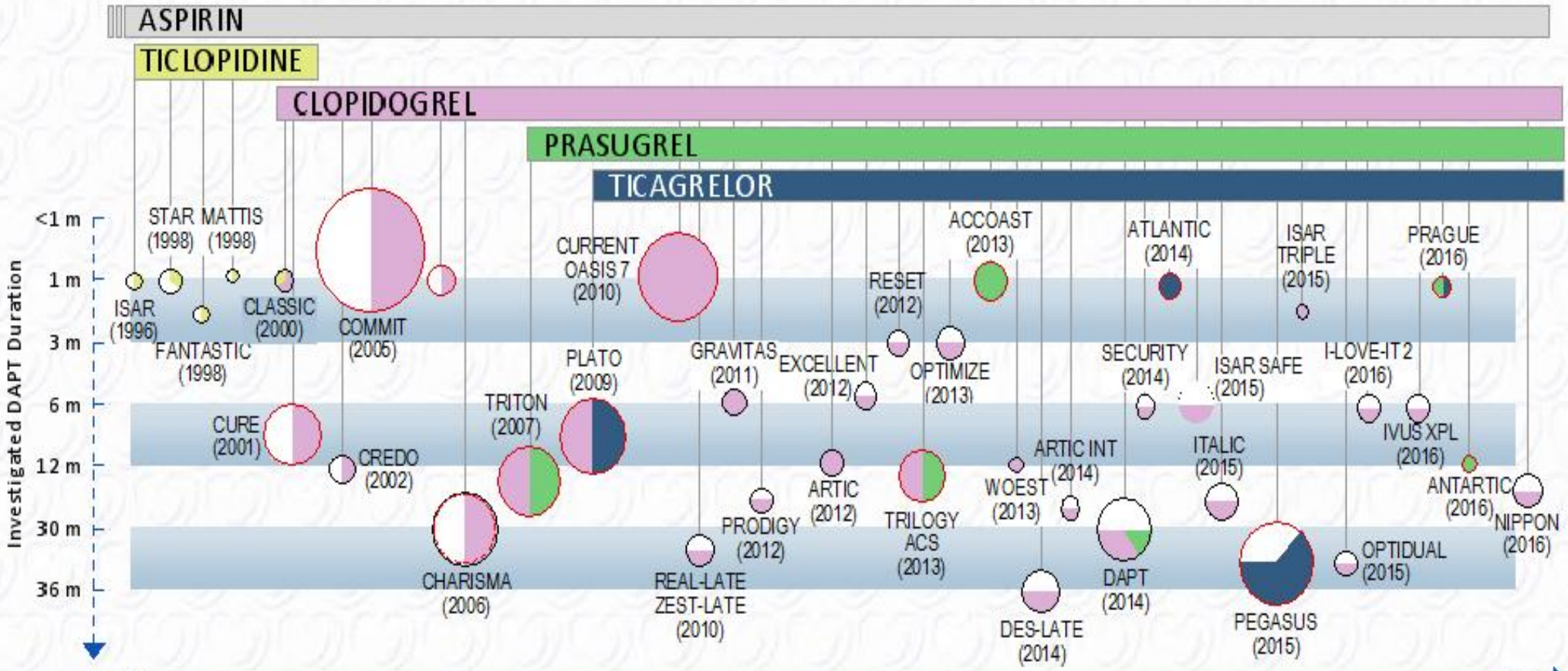
AGGIORNAMENTI IN CARDIOLOGIA
PAOLA 28 Ottobre 2017

DAPT a Lungo Termine nella ACS

Vittorio Emanuele
Cardiologia UMG

History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease

ESC
European Society of Cardiology



Size of the circles denotes sample size

2 5 10 20 K pts

Perimeter of the circles denotes type of investigated population

- Mixed clinical presentation at the time of stent implantation
- Acute coronary syndrome at presentation
- DAPT initiated in patients with prior myocardia infarction
- DAPT for primary prevention

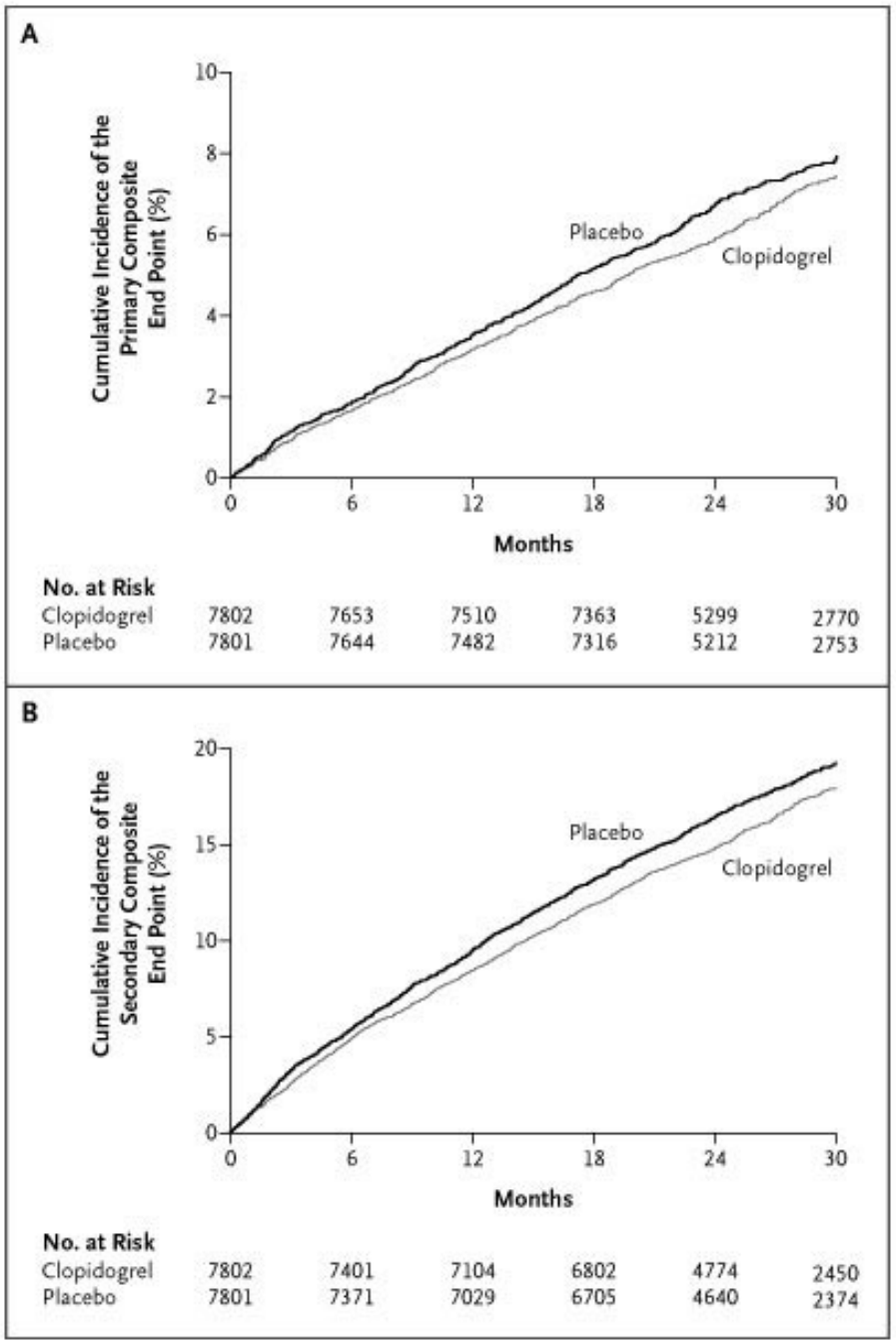
www.escardio.org/guidelines 2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

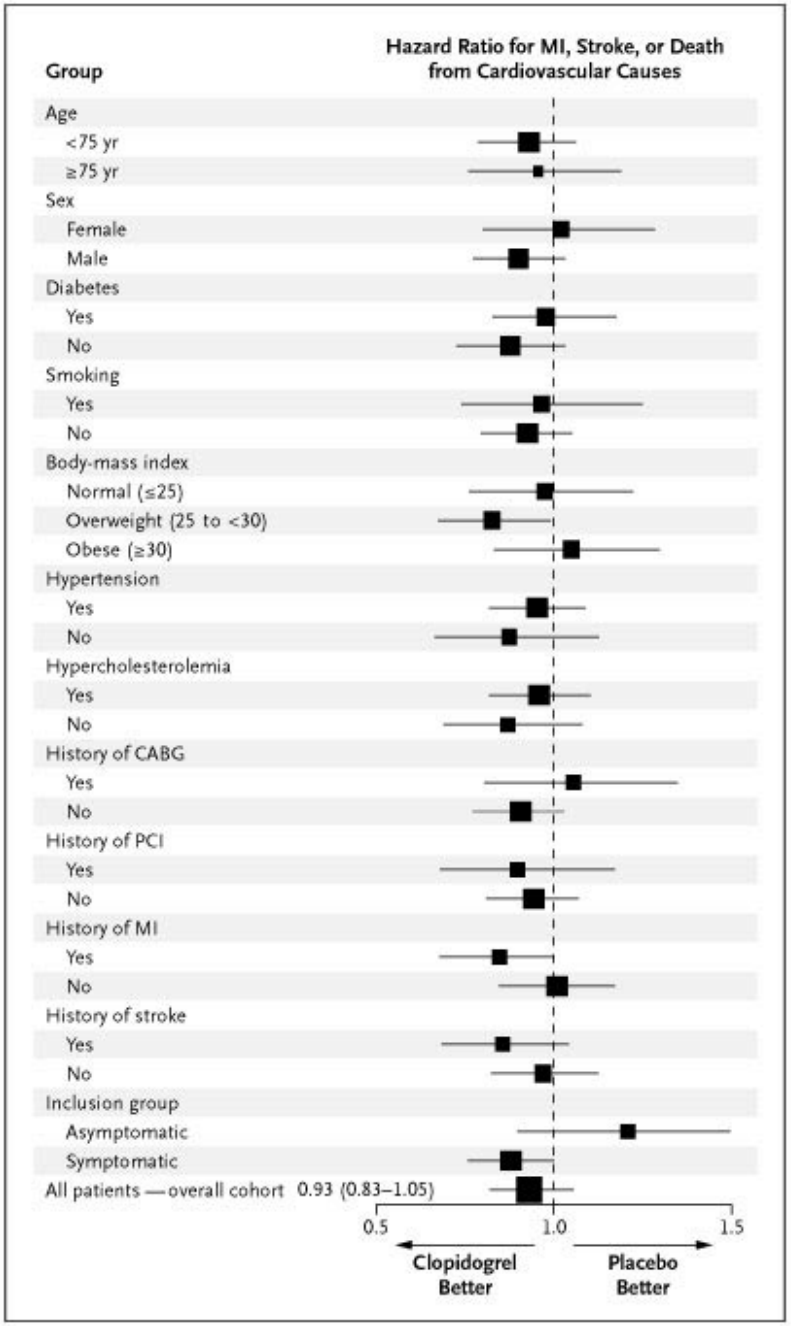
DAPT SETTING

- Prevenzione I o II ?
- Alto o Basso RE ?
- Alto o Basso RT ?

CHARISMA

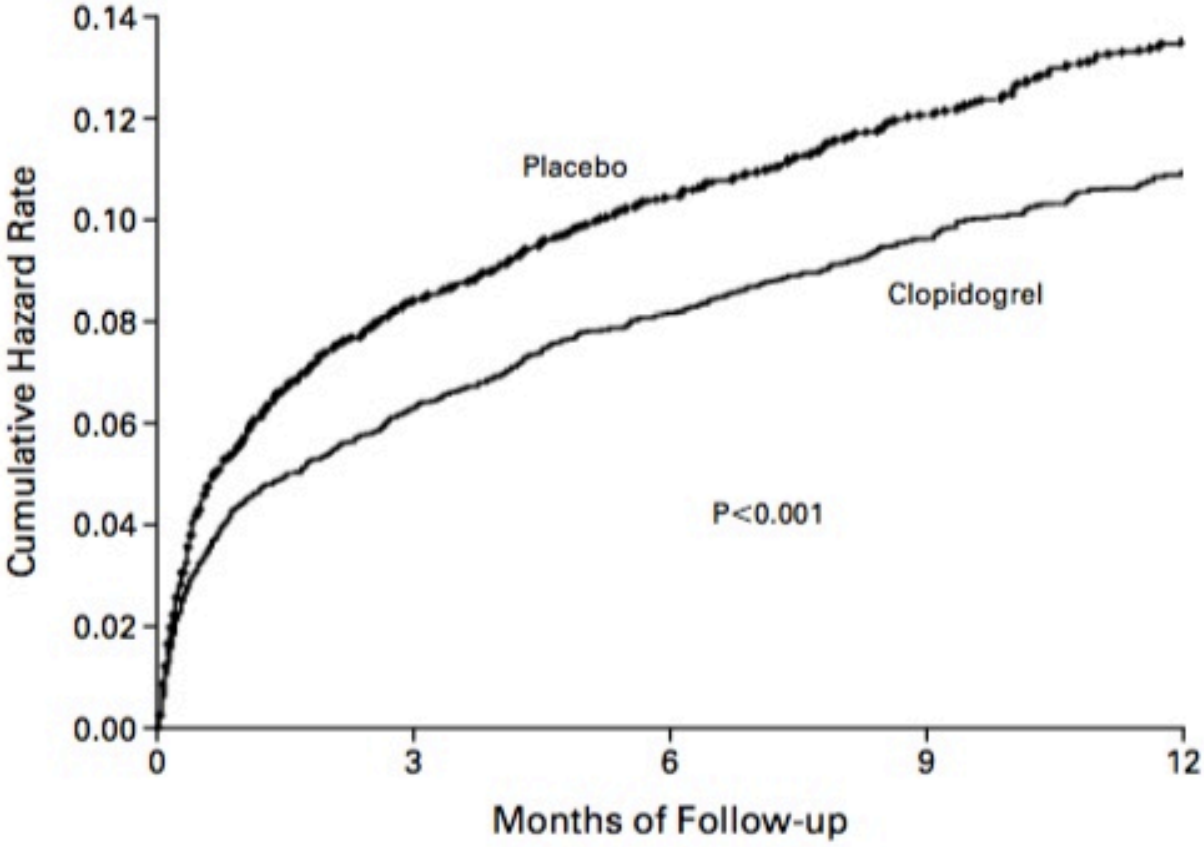
Bhatt, D. et al. N Engl J Med 2006;354:1706-1717





CURE

CLOPIDOGREL IN ADDITION TO ASPIRIN FOR ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

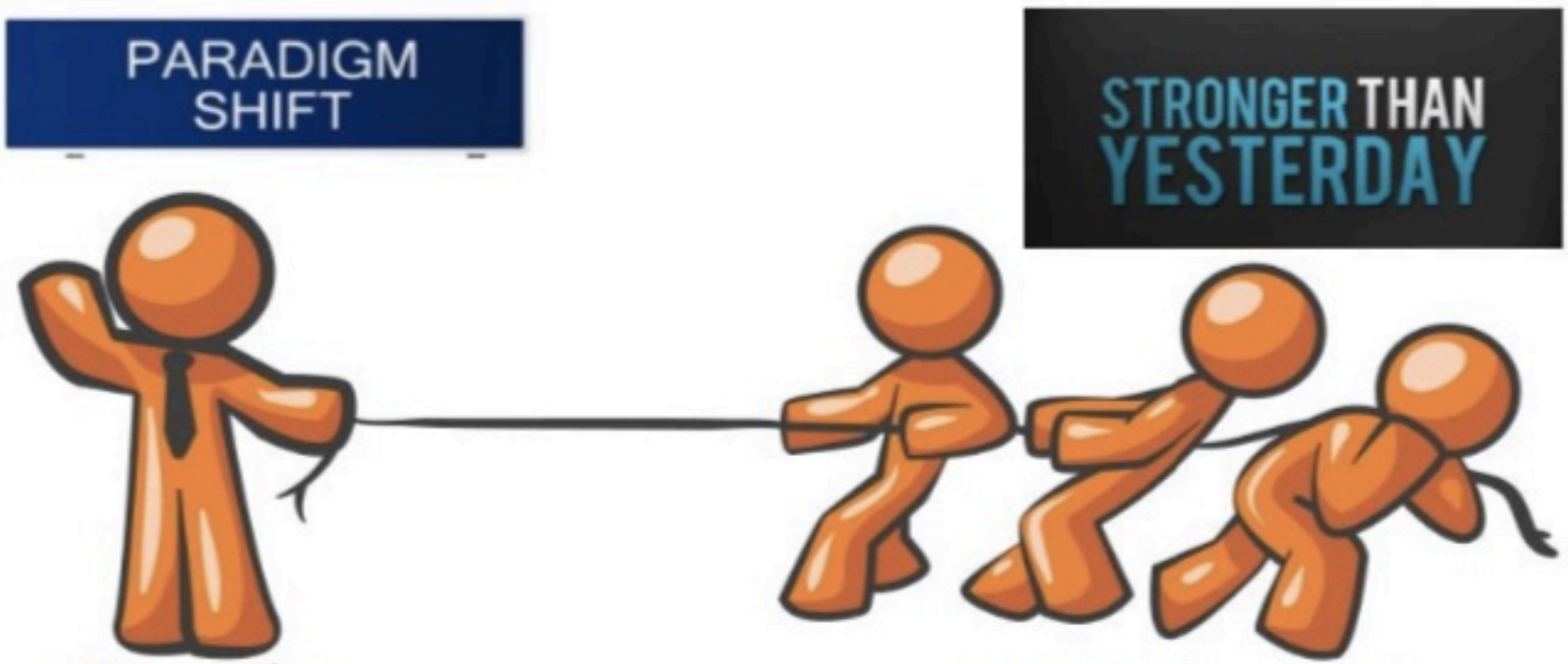


No. at Risk					
Placebo	6303	5780	4664	3600	2388
Clopidogrel	6259	5866	4779	3644	2418

Figure 1. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study.

The results demonstrate the sustained effect of clopidogrel.

(N Engl J Med **2001**;345: 494-502.)



>12 months Better

DAPT-PEGASUS

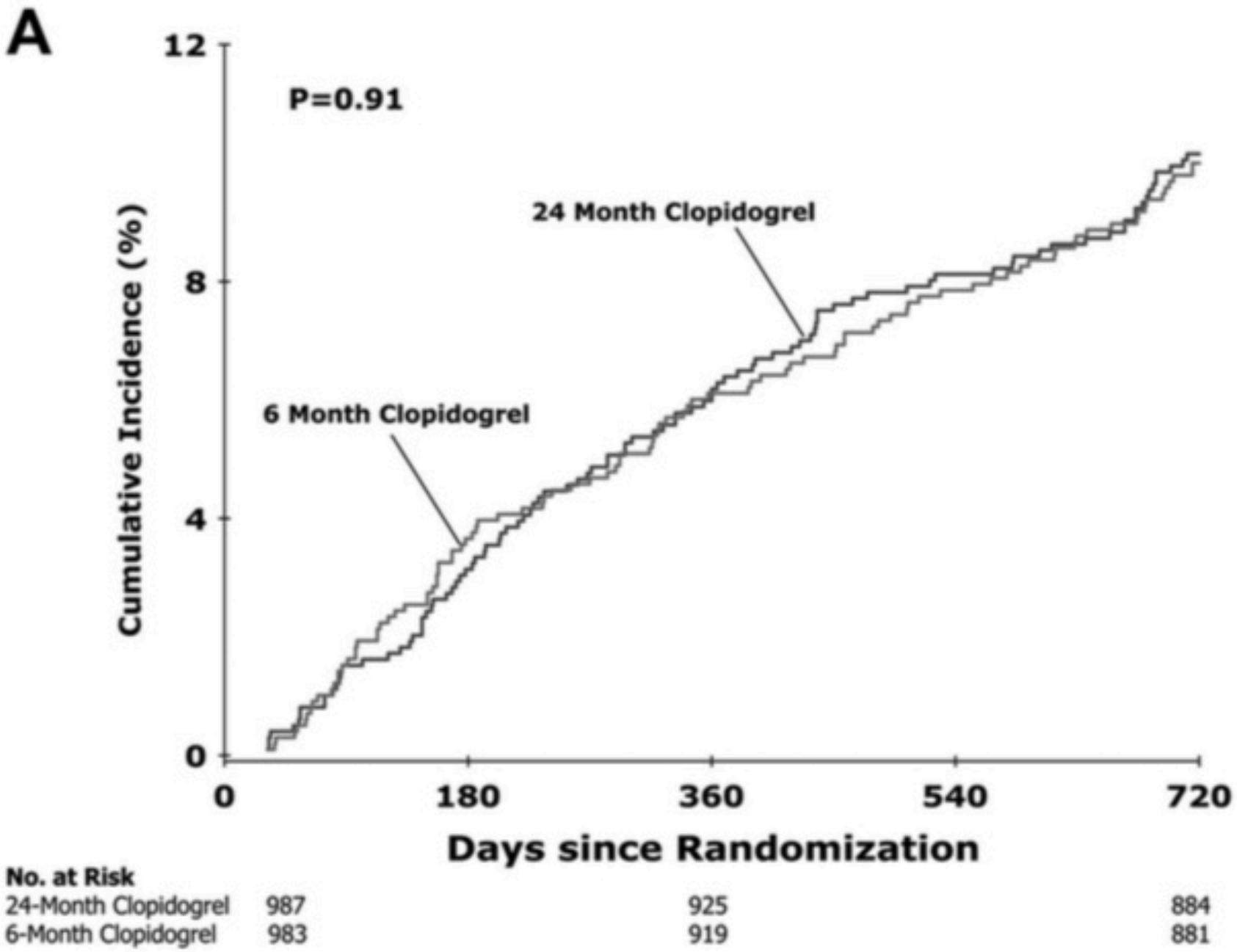
≤12 months Better

DES LATE, EXCELLENT, PRODIGY, RESET, OPTIMAZE, ARTIC, SECURITY, ISAR SAFE, ITALIC*

≤12 months Better

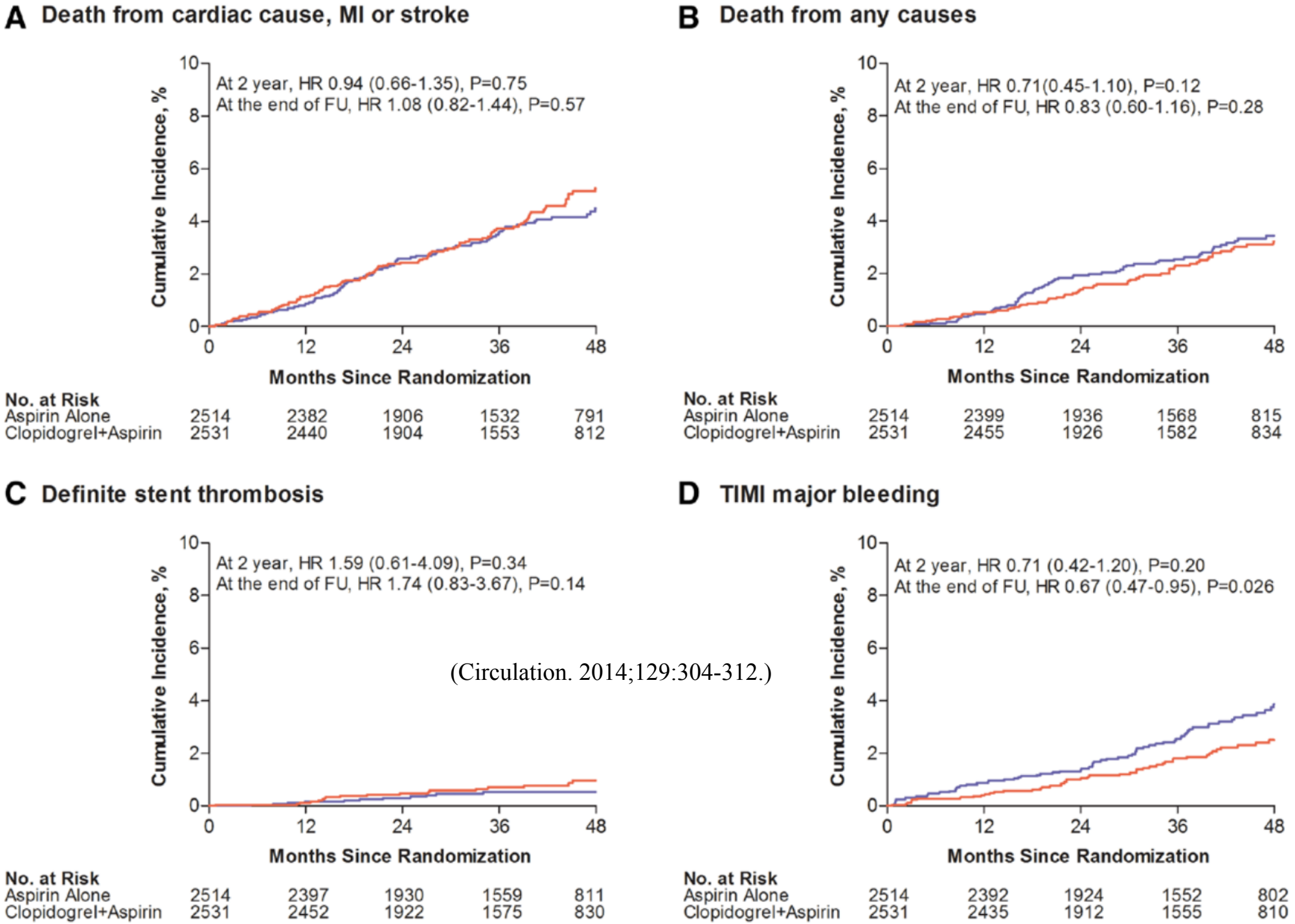
DES LATE, EXCELLENT, PRODIGY, RESET, OPTIMAZE, ARTIC, SECURITY, ISAR SAFE, ITALIC*

PRODIGY

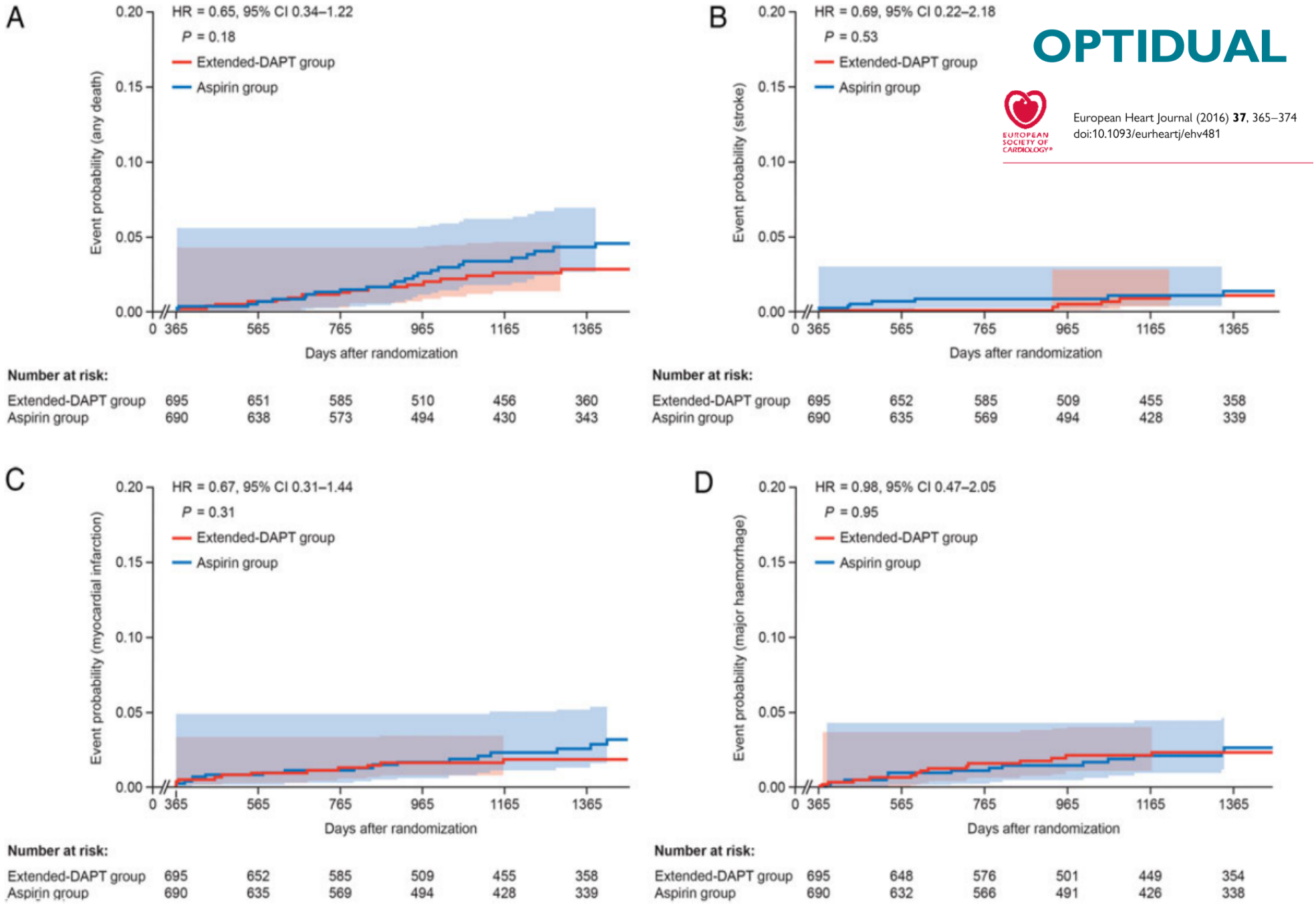


Circulation. **2012;125:2015-2026.**

DES LATE



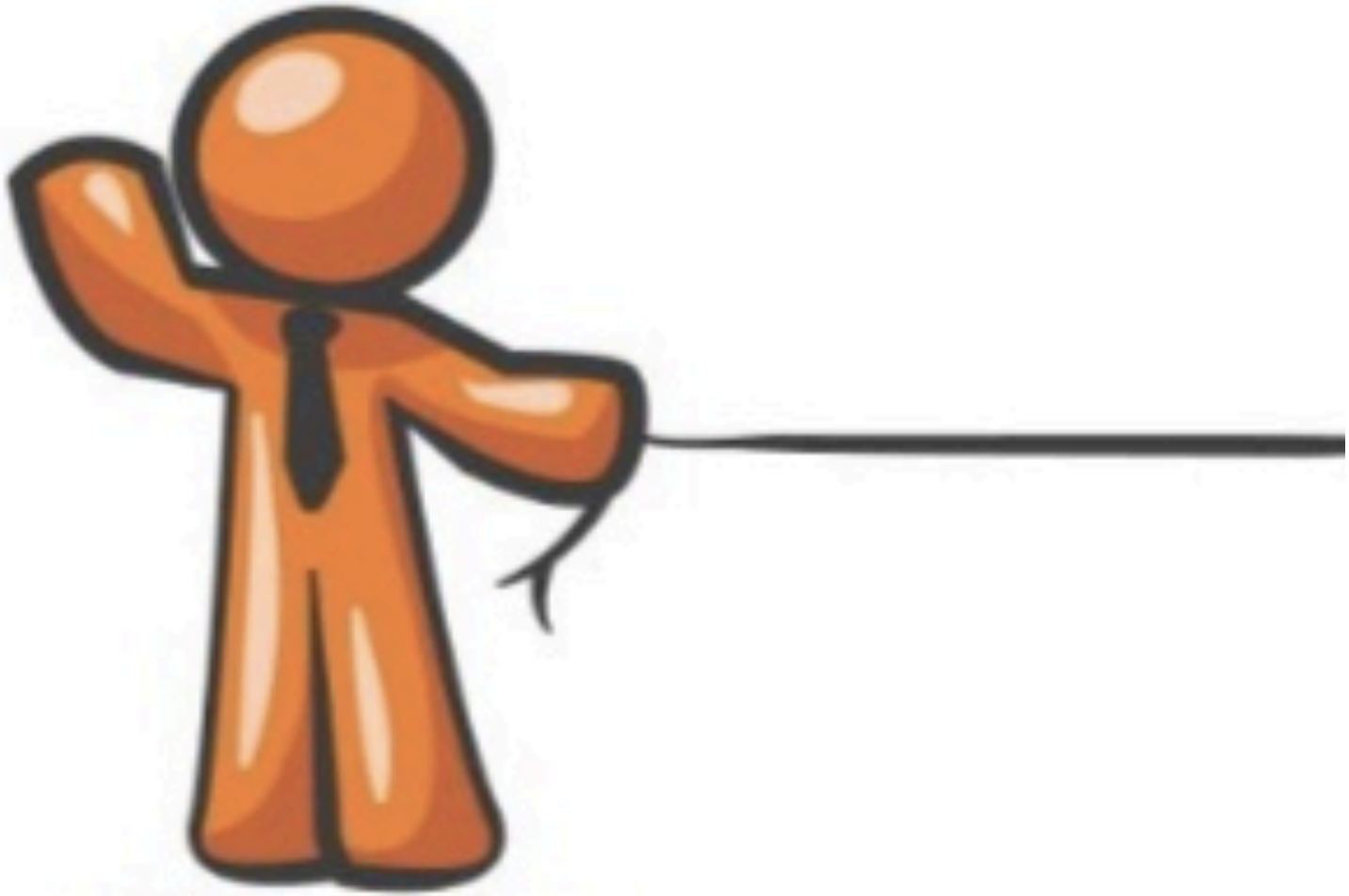
(Circulation. 2014;129:304-312.)



OPTIDUAL

European Heart Journal (2016) **37**, 365–374
doi:10.1093/eurheartj/ehv481

Figure 3 (*A*) All-cause mortality, (*B*) stroke, (*C*) myocardial infarction, and (*D*) major ISTH bleeding. CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.



>12 months
Better

DAPT-PEGASUS

2014

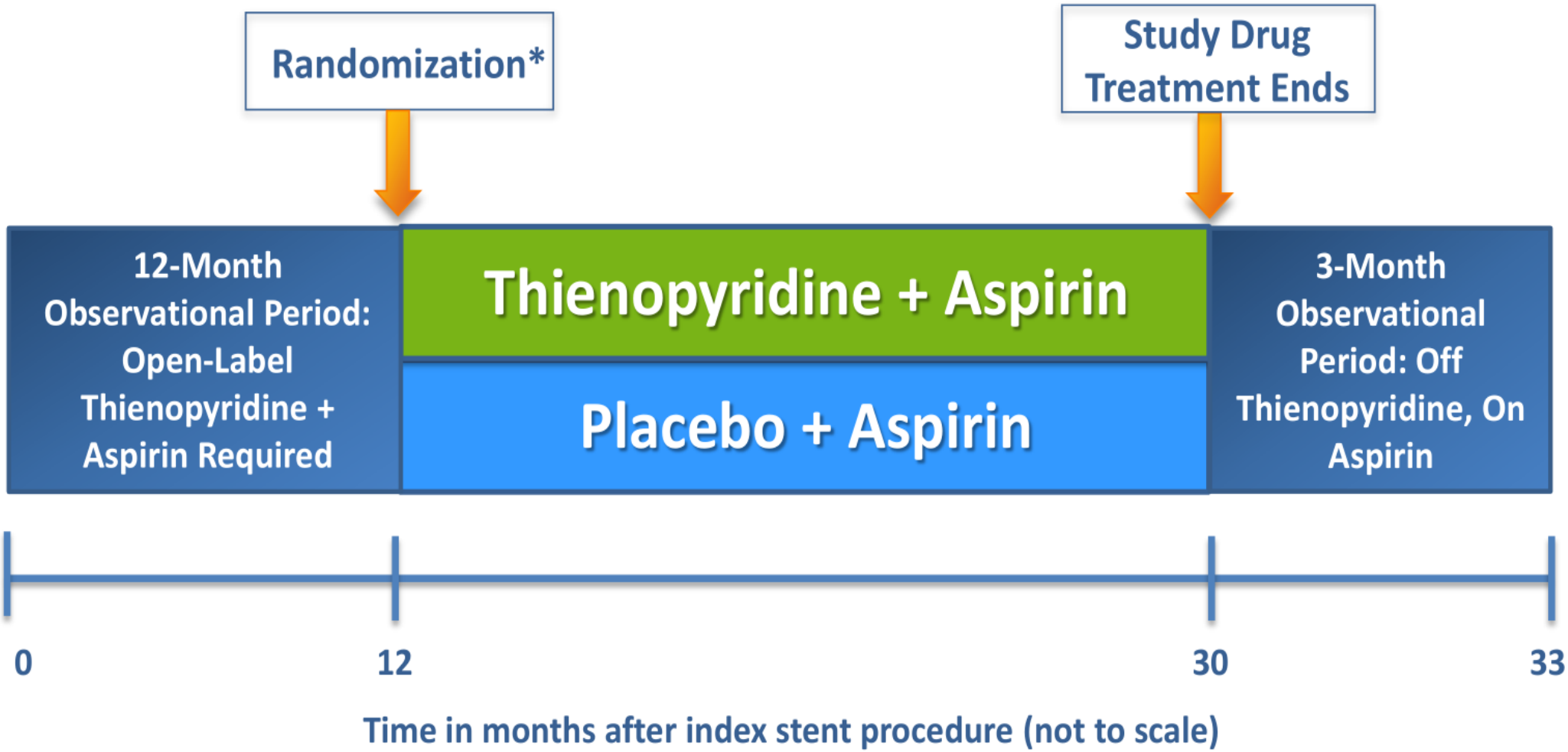
TITLE: Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

GROUP: Dual Anti- platelet Therapy (DAPT) study

CONCLUSIONS: Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding.

Design

DAPT STUDY



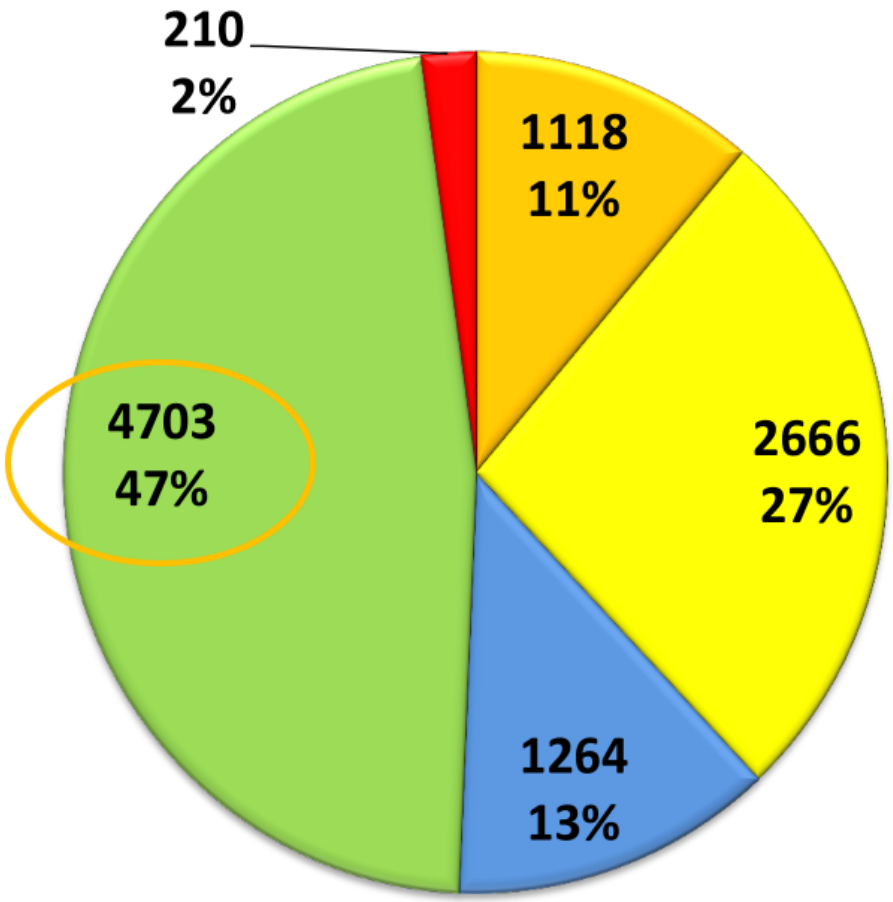
Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

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).

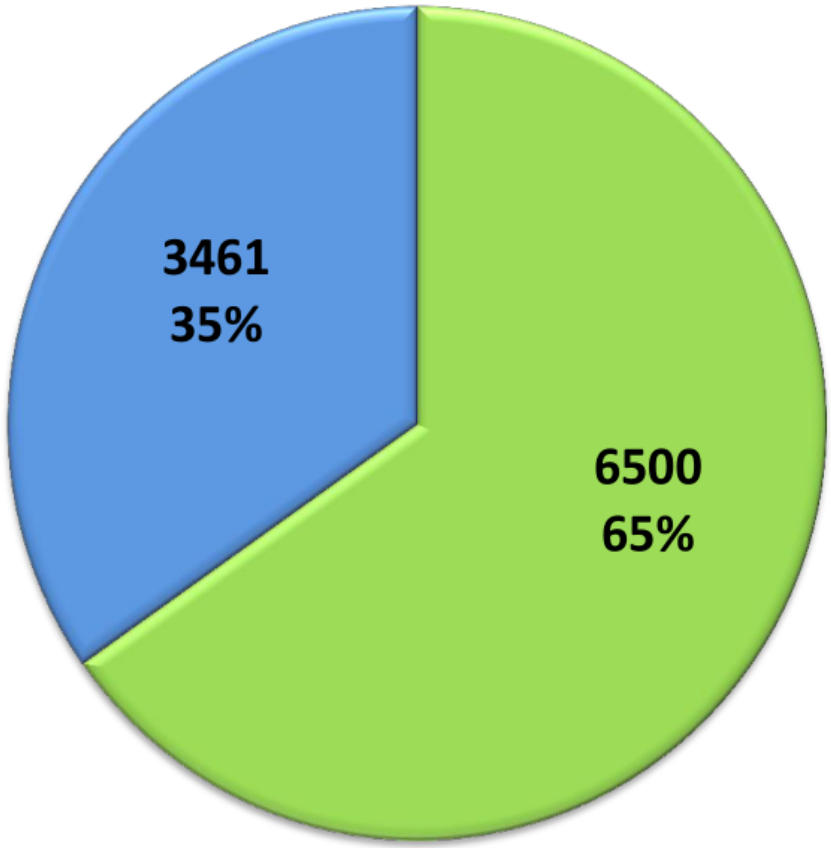
Stent & Drug Types

DAPT STUDY

Drug Eluting Stent Type



Thienopyridine Type

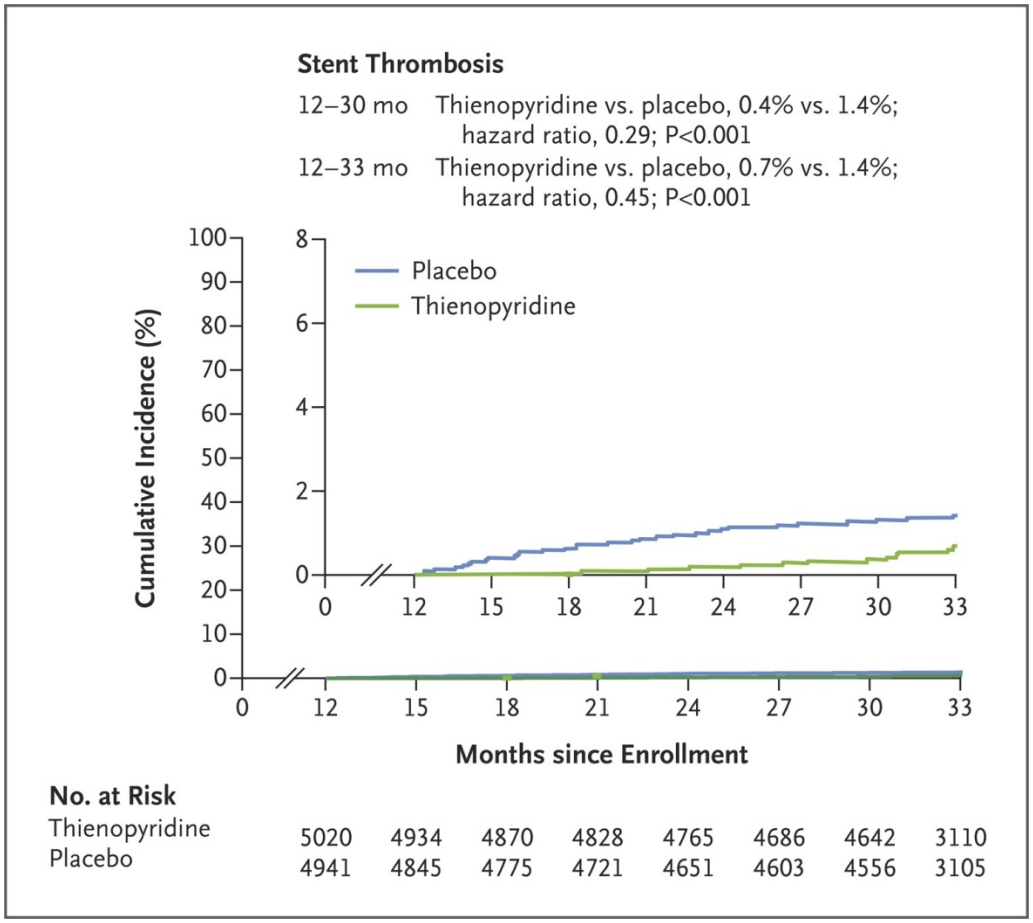


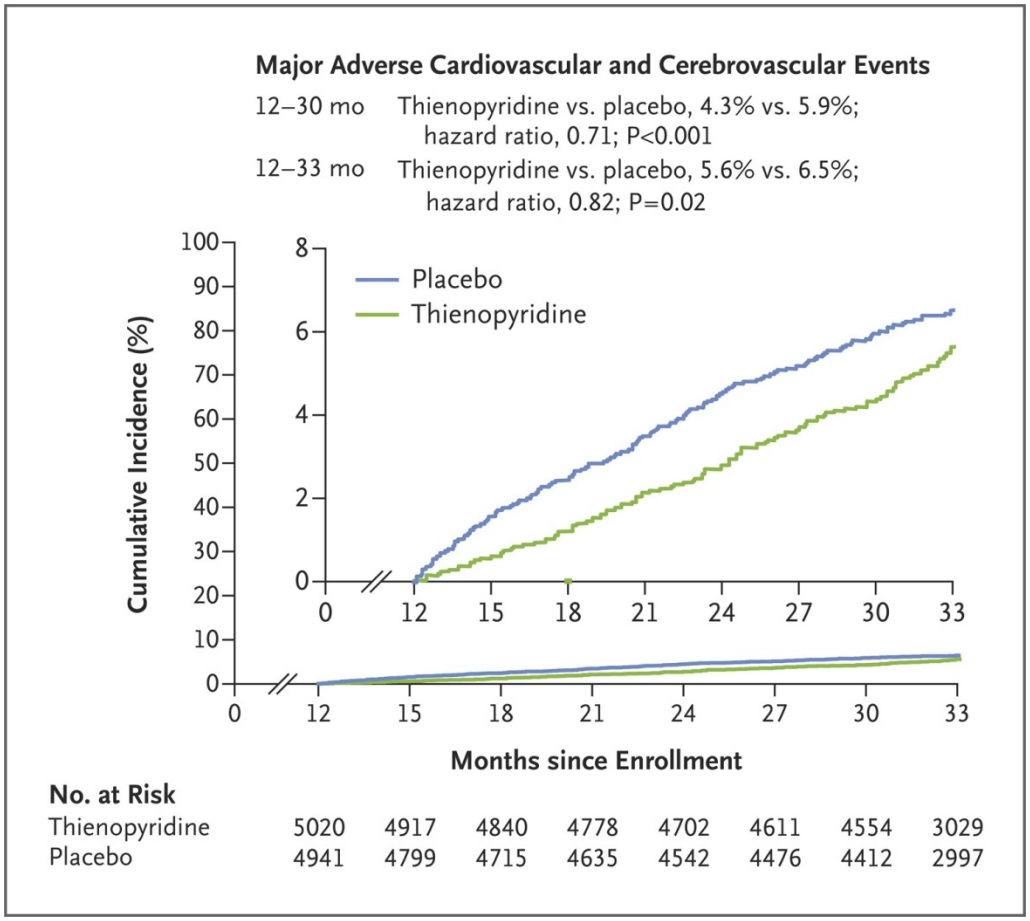
12 or 30 Months of Dual Antiplatelet Therapy after DES

DAPT Study. NEJM V371(23):2155; 2014

Cumulative Incidence of Stent Thrombosis, According to Study Group.

Cumulative Incidence of Major Adverse Cardiovascular and Cerebrovascular Events, According to Study Group.





Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding.

Bleeding End Point during Month 12 to Month 30.

Table 3. Bleeding End Point during Month 12 to Month 30.*

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

* The primary safety end point was moderate or severe bleeding as assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria. The one-sided test of noninferiority (based on a noninferiority margin of 0.8%) was calculated according to the Farrington–Manning approach. Only patients who could be evaluated were included in this analysis (i.e., patients whose last contact date was ≥510 days after randomization or who had any adjudicated bleeding event at or before 540 days). Patients could have had more than one bleeding episode. The secondary analysis of bleeding, as assessed according to the criteria of the Bleeding Academic Research Consortium (BARC), is shown according to subtype in Table S5 in the Supplementary Appendix.

† One-sided P=0.70 for noninferiority.

Mauri L et al. N Engl J Med 2014;371:2155-2166

DAPT STUDY

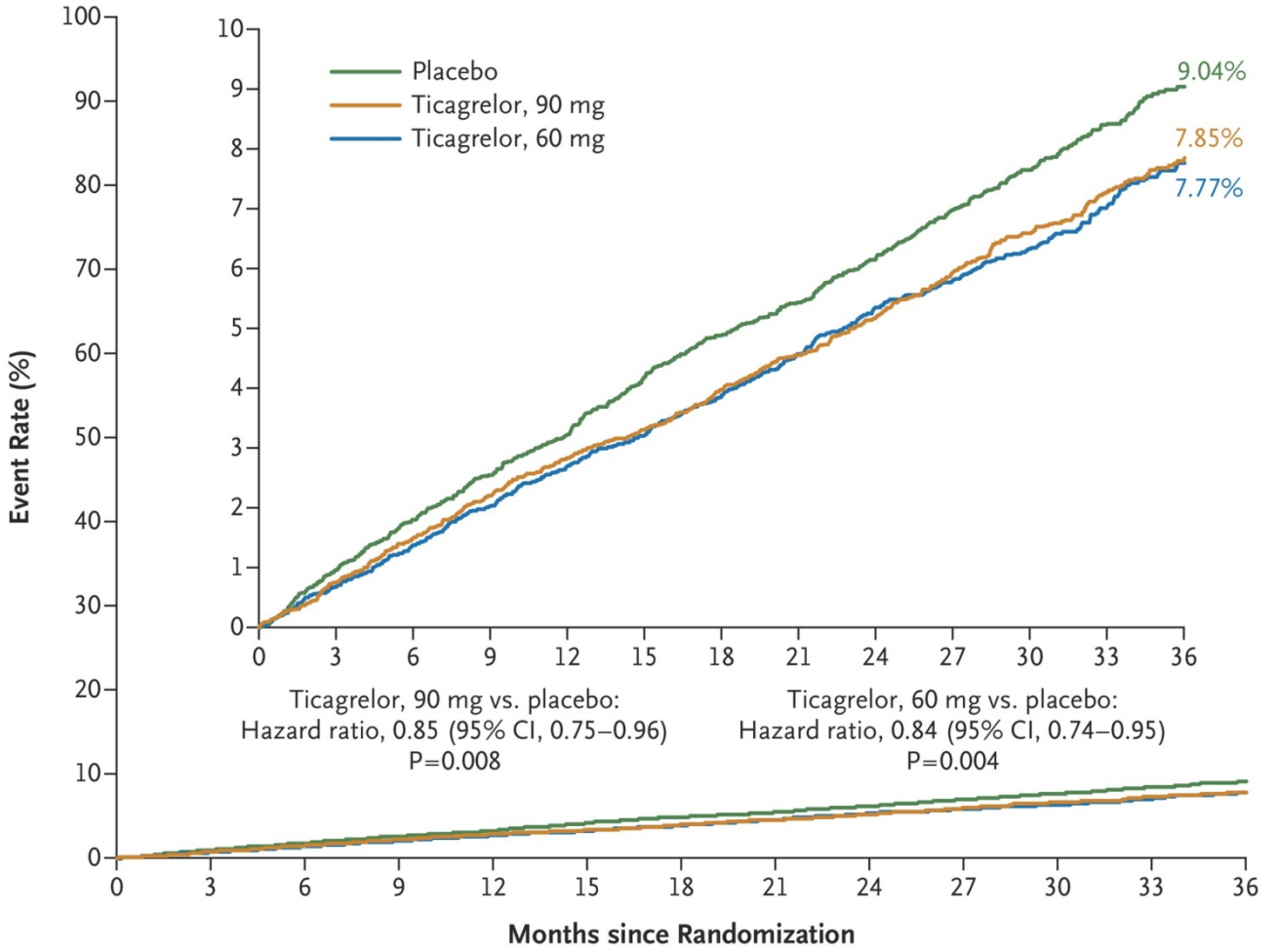
2015

TITLE: Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

GROUP: Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI54)

CONCLUSIONS: In patients with a myocardial infarction more than 1 year previously, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding.

Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. **PEGASUS-TIMI 54**



No. at Risk

Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

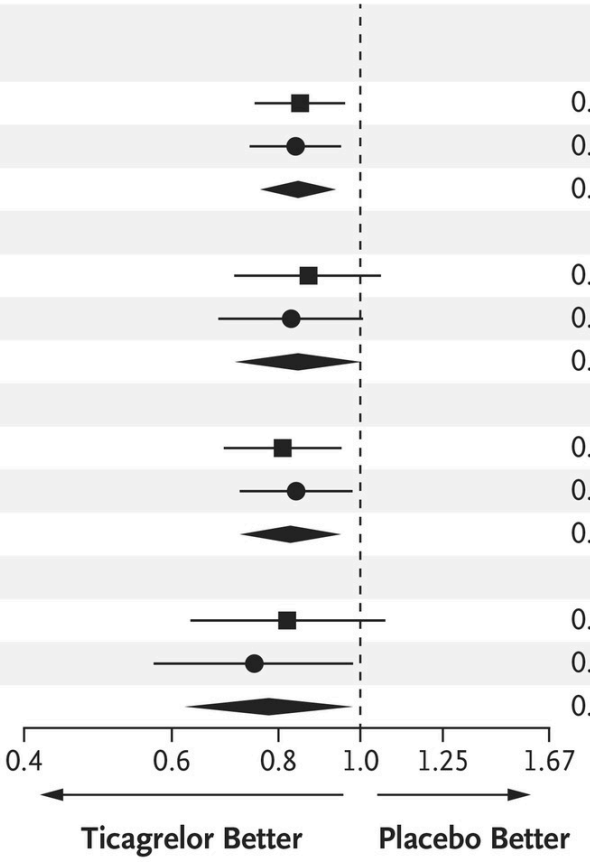
Kaplan–Meier Rates of Cardiovascular Death, Myocardial Infarction, and Stroke through 3 Years, According to Study Group.

NEJM, V372(19):1791; 2015

Hazard Ratios and Rates of the Primary End Point and Individual Components for Each Dose of Ticagrelor and for the Two Doses Pooled.

PEGASUS-TIMI 54

End Point	Ticagrelor	Placebo	Hazard Ratio (95% CI)	P Value
	3-yr Kaplan–Meier event rate (%)			
Cardiovascular death, myocardial infarction, or stroke				
Ticagrelor, 90 mg	7.85	9.04	0.85 (0.75–0.96)	0.008
Ticagrelor, 60 mg	7.77	9.04	0.84 (0.74–0.95)	0.004
Ticagrelor pooled	7.81	9.04	0.84 (0.76–0.94)	0.001
Cardiovascular death				
Ticagrelor, 90 mg	2.94	3.39	0.87 (0.71–1.06)	0.15
Ticagrelor, 60 mg	2.86	3.39	0.83 (0.68–1.01)	0.07
Ticagrelor pooled	2.90	3.39	0.85 (0.71–1.00)	0.06
Myocardial infarction				
Ticagrelor, 90 mg	4.40	5.25	0.81 (0.69–0.95)	0.01
Ticagrelor, 60 mg	4.53	5.25	0.84 (0.72–0.98)	0.03
Ticagrelor pooled	4.47	5.25	0.83 (0.72–0.95)	0.005
Stroke				
Ticagrelor, 90 mg	1.61	1.94	0.82 (0.63–1.07)	0.14
Ticagrelor, 60 mg	1.47	1.94	0.75 (0.57–0.98)	0.03
Ticagrelor pooled	1.54	1.94	0.78 (0.62–0.98)	0.03



NEJM, V372(19):1791; 2015

Safety End Points as 3-Year Kaplan–Meier Estimates. PEGASUS-TIMI 54

Table 3. Safety End Points as 3-Year Kaplan–Meier Estimates.*

End Point	Ticagrelor, 90 mg (N=6988)	Ticagrelor, 60 mg (N=6958)	Placebo (N=6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42)	<0.001	3.08 (2.12–4.48)	<0.001
Bleeding leading to study-drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29)	<0.001	4.40 (3.48–5.57)	<0.001
Fatal bleeding or nonfatal intracranial hemorrhage	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
Intracranial hemorrhage	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
Hemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64)	0.26	0.97 (0.37–2.51)	0.94
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00
Other adverse event							
Dyspnea	1205 (18.93)	987 (15.84)	383 (6.38)	3.55 (3.16–3.98)	<0.001	2.81 (2.50–3.17)	<0.001
Event leading to study-drug discontinuation	430 (6.50)	297 (4.55)	51 (0.79)	8.89 (6.65–11.88)	<0.001	6.06 (4.50–8.15)	<0.001
Serious adverse event	22 (0.41)	23 (0.45)	9 (0.15)	2.68 (1.24–5.83)	0.01	2.70 (1.25–5.84)	0.01
Renal event	166 (3.30)	173 (3.43)	161 (2.89)	1.17 (0.94–1.46)	0.15	1.17 (0.94–1.45)	0.15
Bradyarrhythmia	107 (2.04)	121 (2.32)	106 (1.98)	1.15 (0.88–1.50)	0.31	1.24 (0.96–1.61)	0.10
Gout	115 (2.28)	101 (1.97)	74 (1.51)	1.77 (1.32–2.37)	<0.001	1.48 (1.10–2.00)	0.01

* TIMI denotes Thrombolysis in Myocardial Infarction.

NEJM, V372(19):1791; 2015

2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with EACTS

ESC
European Society of Cardiology

The Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

ESC Chairperson: Marco Valgimigli (Switzerland).

Authors/Task Force Members: Héctor Bueno (Spain), Robert Byrne (Germany), Jean-Philippe Collet (France), Francesco Costa (Italy), Anders Jeppsson (Sweden), Peter Jüni (Canada), Adnan Kastrati (Germany), Philippe Kolh (Belgium), Laura Mauri (USA), Gilles Montalescot (France), Franz-Josef Neumann (Germany), Mate Petricevic (Croatia), Marco Roffi (Switzerland), Philippe Gabriel Steg (France), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain).

Additional Contributor: Glenn Levine (USA).

What is new in the 2017 ESC focussed update on DAPT?

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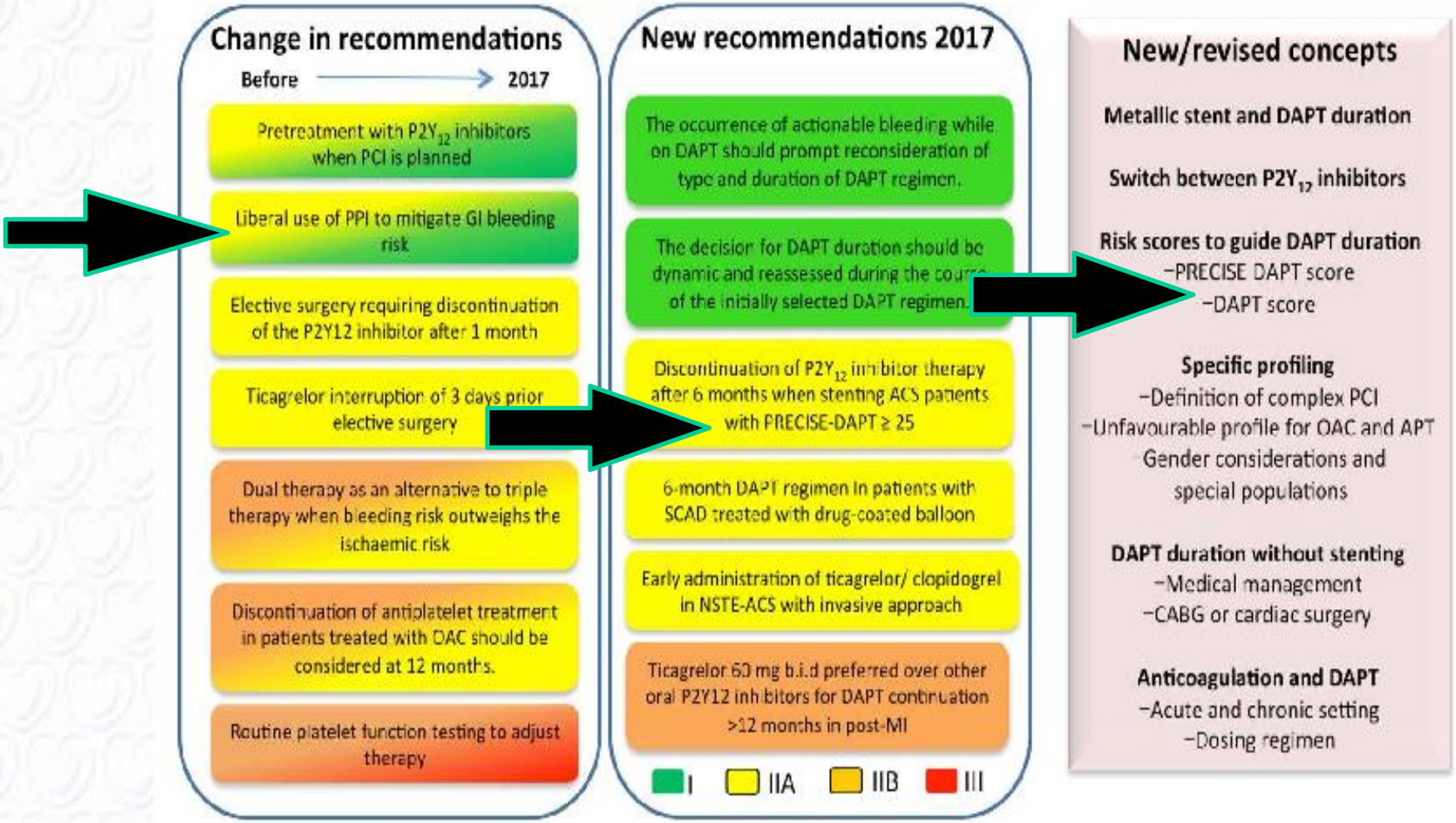
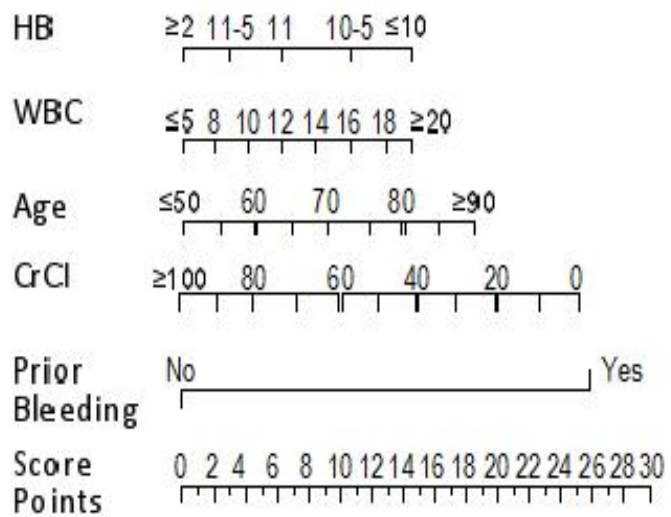


2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Risk scores validated for dual antiplatelet therapy duration decision-making

ESC European Society of Cardiology

	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 −2 pt −1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	−2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Measures to minimize bleeding while on dual antiplatelet therapy

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European Society of Cardiology

Recommendations	Class	Level
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.	I	A
In patients treated with DAPT, a daily aspirin dose of 75–100 mg is recommended.	I	A
A PPI in combination with DAPT is recommended.	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention

ESC
European Society of Cardiology

Recommendations	Class	Level
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contra-indications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).	I	A
In patients with ACS and stent implantation who are at high-risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	B
In patients with ACS treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C

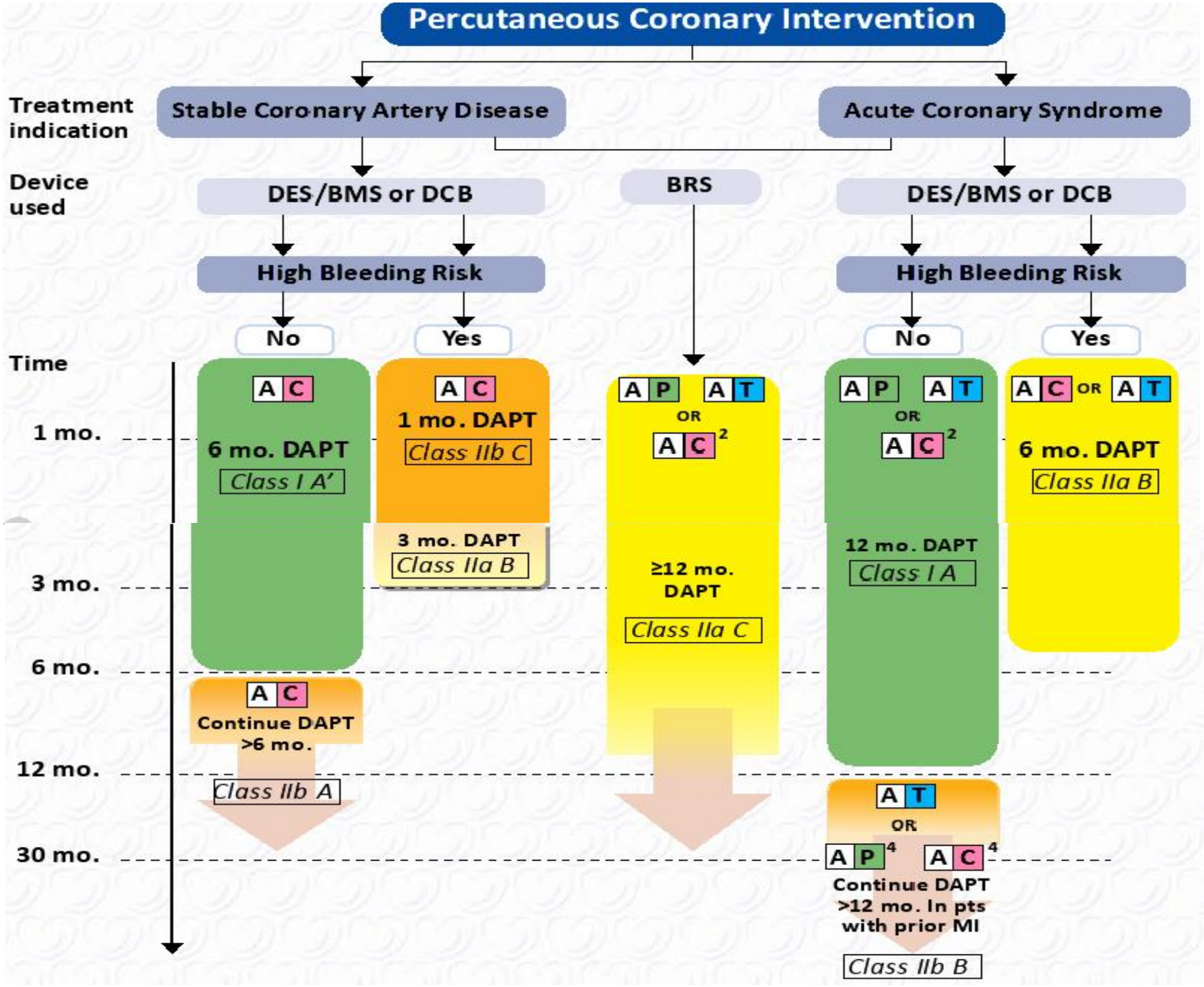
2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

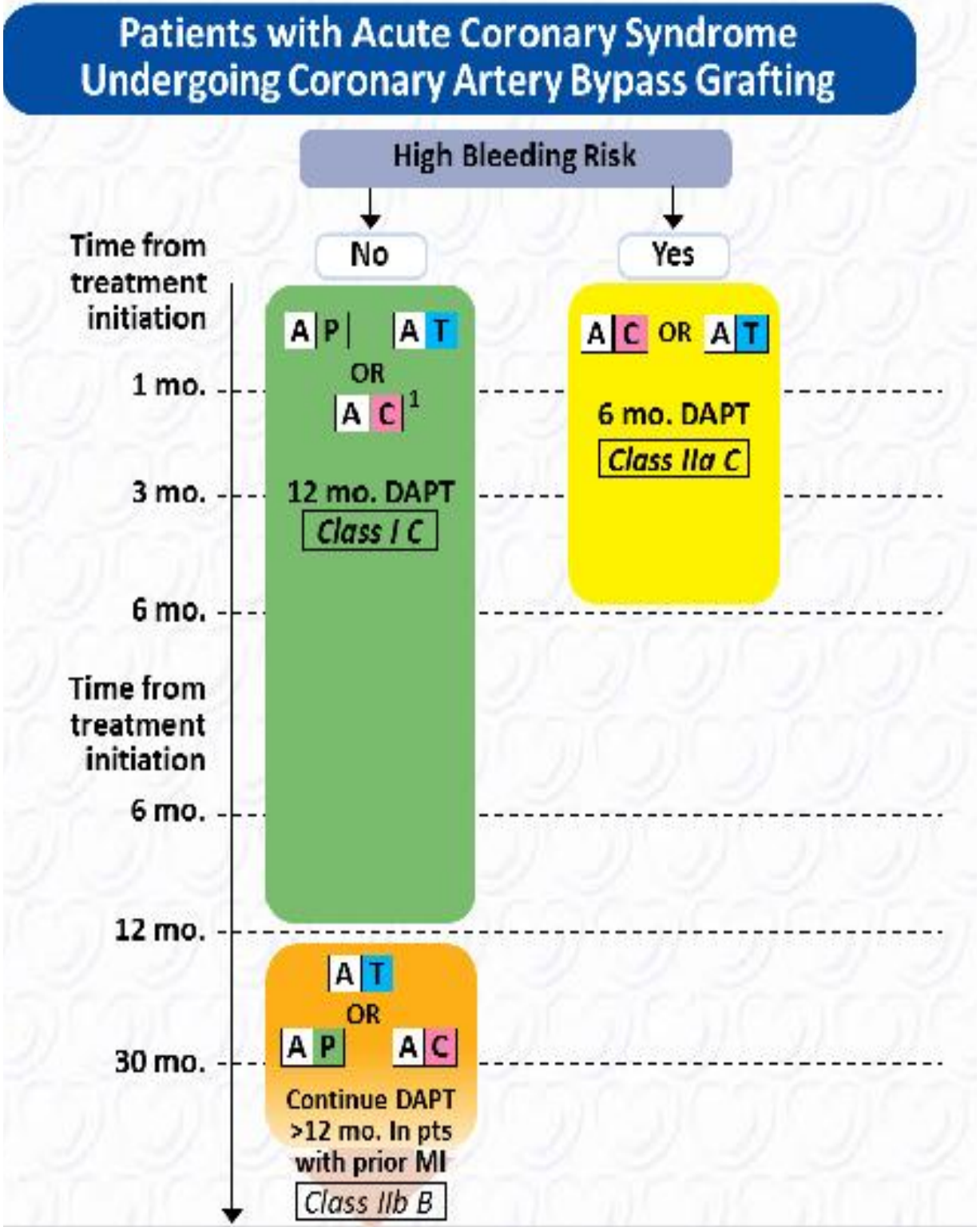
Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention *(continued)*

ESC
European Society of Cardiology

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

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)


Percutaneous Coronary Intervention
Treatment indication
Stable Coronary Artery Disease
Acute Coronary Syndrome
Device used
DES/BMS or DCB
BRS
DES/BMS or DCB
High Bleeding Risk
High Bleeding Risk
No
Yes
No
Yes
Time
1 mo.
3 mo.
6 mo.
12 mo.
30 mo.
A C
6 mo. DAPT
Class I A'
A C
1 mo. DAPT
Class IIb C
3 mo. DAPT
Class IIa B
A P A T
OR
A C 2
≥12 mo. DAPT
Class IIa C
A P A T
OR
A C 2
12 mo. DAPT
Class I A
A C OR A T
6 mo. DAPT
Class IIa B
A C
Continue DAPT >6 mo.
Class IIb A
A T
OR
A P 4 A C 4
Continue DAPT >12 mo. In pts with prior MI
Class IIb B


Patients with Acute Coronary Syndrome Undergoing Coronary Artery Bypass Grafting
High Bleeding Risk
No
Yes
Time from treatment initiation
1 mo.
3 mo.
6 mo.
Time from treatment initiation
6 mo.
12 mo.
30 mo.
A P | A T
OR
A C [1]
12 mo. DAPT
Class I C
A C OR A T
6 mo. DAPT
Class IIa C
A T
OR
A P A C
Continue DAPT >12 mo. In pts with prior MI
Class IIb B

Dual antiplatelet therapy duration in patients with acute coronary syndrome undergoing medical therapy management

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Recommendations	Class	Level
In patients with ACS who are managed with medical therapy alone and treated with DAPT, it is recommended to continue $P2Y_{12}$ inhibitor therapy (either ticagrelor or clopidogrel) for 12 months.	I	A
Ticagrelor is recommended over clopidogrel, unless the bleeding risk outweighs the potential ischaemic benefit.	I	B
In patients with medically managed ACS who are at high-risk of bleeding (e.g. PRECISE-DAPT ≥25), DAPT for at least 1 month should be considered.	IIa	C

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(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Dual antiplatelet therapy duration in patients with acute coronary syndrome undergoing medical therapy management *(continued)*

ESC
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Recommendations	Class	Level
In patients with prior MI at high ischaemic risk who are managed with medical therapy alone and have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg *b.i.d.* on top of aspirin for longer than 12 months and up to 36 months may be considered.	IIb	B
In patients with prior MI not treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not eligible for treatment with ticagrelor, continuation of clopidogrel on top of aspirin for longer than 12 months may be considered.	IIb	C
Prasugrel is not recommended in medically managed ACS patients.	III	B

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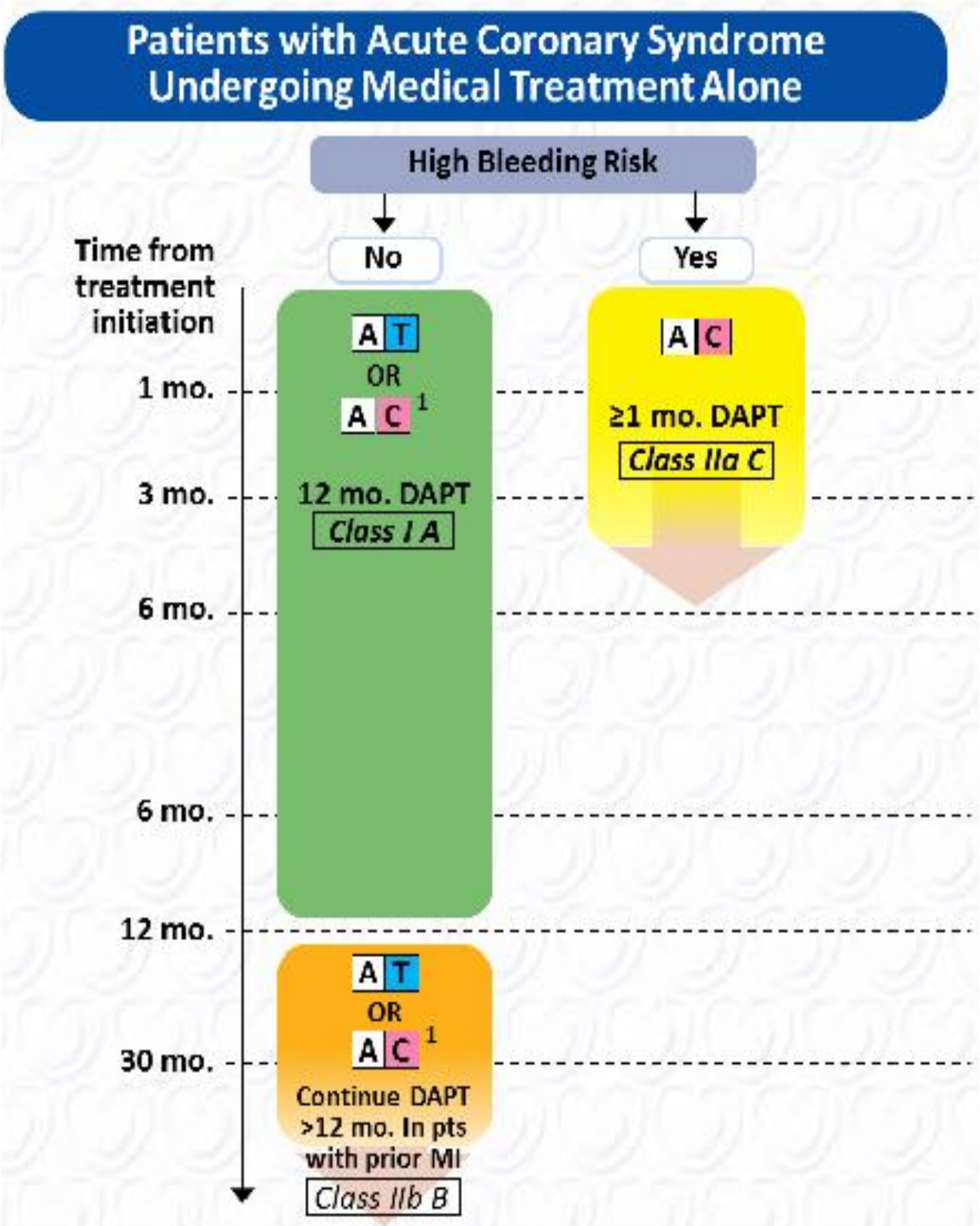
Patients with Acute Coronary Syndrome Undergoing Medical Treatment Alone
High Bleeding Risk
No
Yes
Time from treatment initiation
1 mo.
3 mo.
6 mo.
6 mo.
12 mo.
30 mo.
A T
OR
A C 1
12 mo. DAPT
Class I A
A C
≥1 mo. DAPT
Class IIa C
A T
OR
A C 1
Continue DAPT >12 mo. In pts with prior MI
Class IIb B

Strategies to avoid bleeding complications in patients treated with oral anticoagulant

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• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
• Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.
• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.
• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.
• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
• Use low-dose (≤100 mg daily) aspirin.
• Routine use of PPIs.

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High-risk features of stent-driven recurrent ischaemic events

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• Prior stent thrombosis on adequate antiplatelet therapy.
• Stenting of the last remaining patent coronary artery.
• Diffuse multivessel disease especially in diabetic patients.
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min).
• At least three stents implanted.
• At least three lesions treated.
• Bifurcation with two stents implanted.
• Total stent length >60 mm.
• Treatment of a chronic total occlusion.

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Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

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• Short life expectancy.
• Ongoing malignancy.
• Poor expected adherence.
• Poor mental status.
• End stage renal failure.
• Advanced age.
• Prior major bleeding/prior haemorrhagic stroke.
• Chronic alcohol abuse.
• Anaemia.
• Clinically significant bleeding on dual antithrombotic therapy.

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GRAZIE