Optimal Balancing Ischemic and Bleeding Risks in Contemporary PCI Practice:

TWILIGHT, GLOBAL-LEADER and more...

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Interventional Cardiovascular Research and clinical trials
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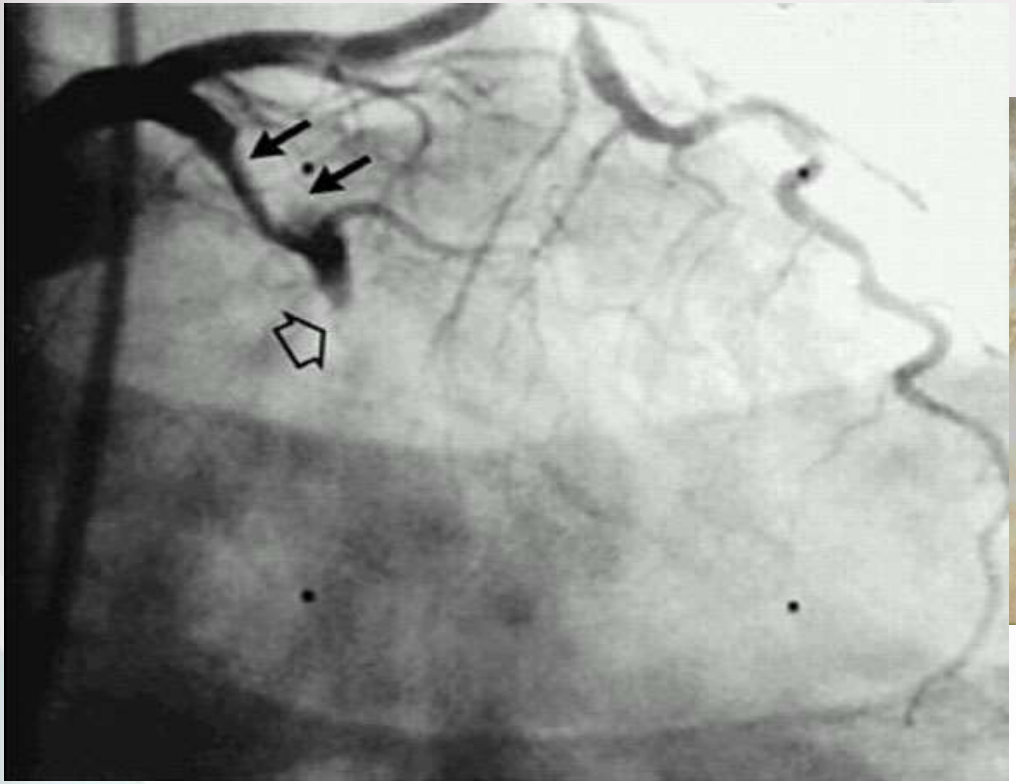
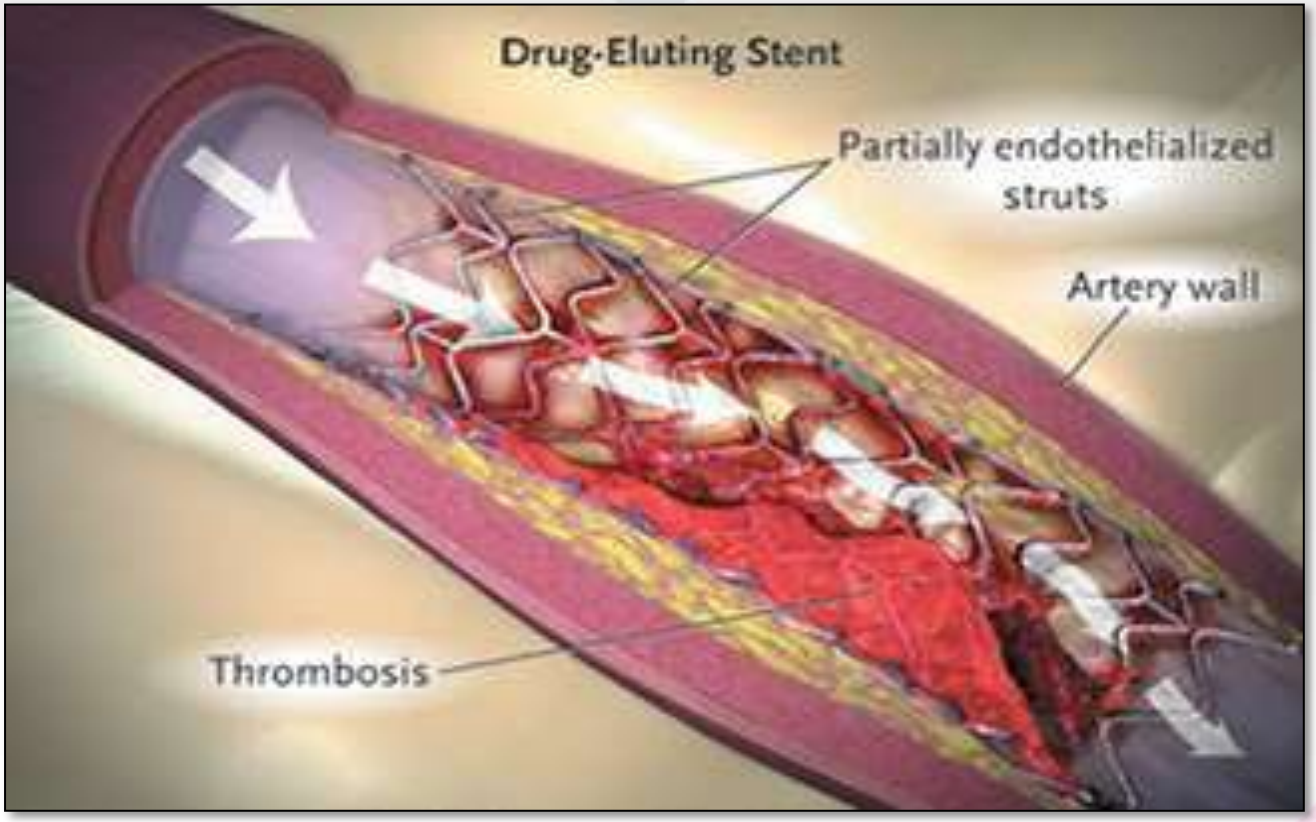
Conflict of interest

- **Consulting Fees/Honoraria**: Abbot Vascular, American College of Cardiology, AstraZeneca, Medscape, Shanghai BraccoSine, Spectranetics, Abiomed, The Medicines Company (spouse)
- **DSMB membership** paid to the institution: Watermark Research Partners
- **Executive Committee**: Janssen Pharmaceuticals
- **Grant/Reseach Support (Institutional):** AstraZeneca, Bayer, Beth Israel Deaconess, Bristol Myers-Squibb, CSL, Behring, Diachi Sankyo, Medtronick, Novartis Pharmaceuticals, OrbusNeich
- **Speaker fees:** Lifescience Conference

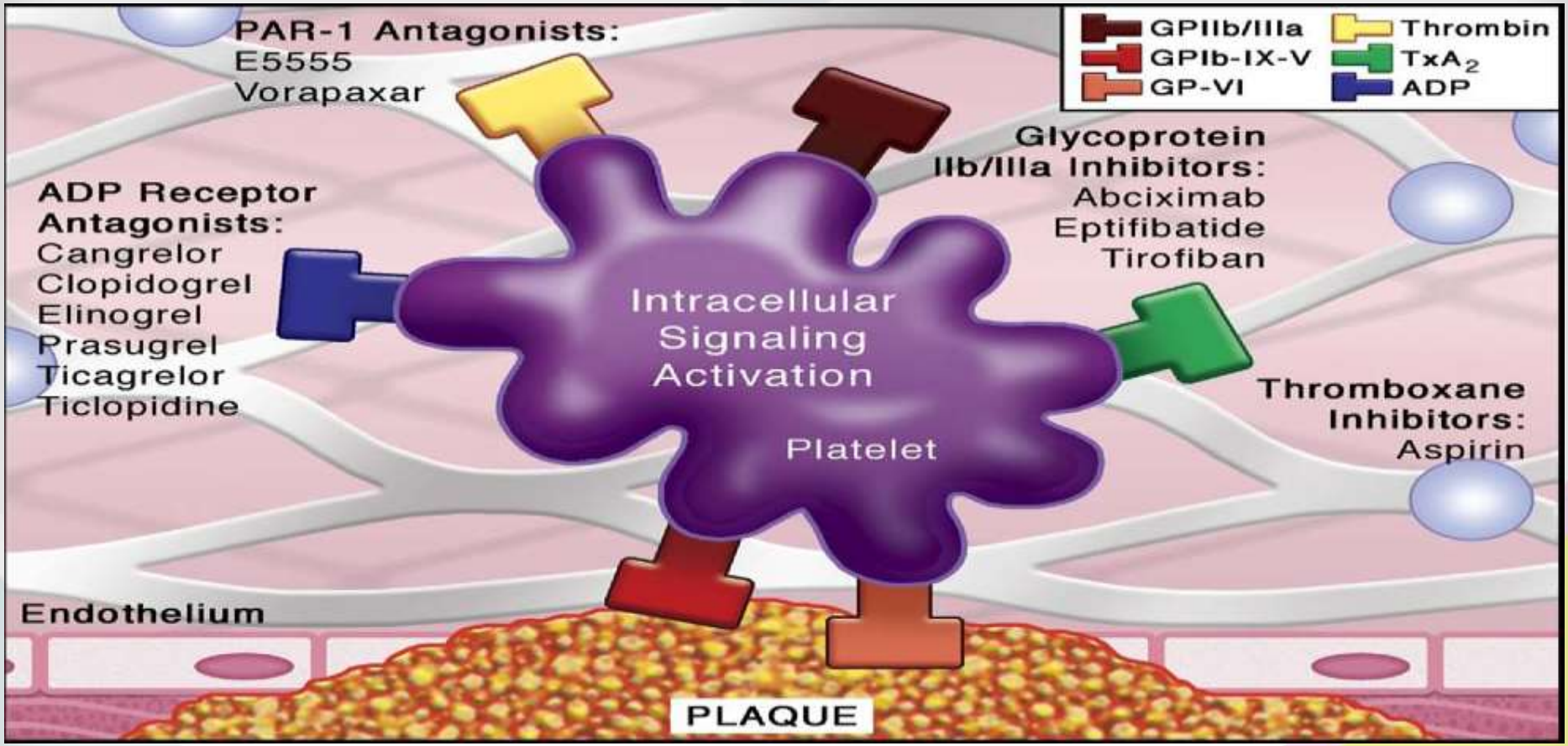
Rupture of atherosclerotic plaque is at the core of acute coronary syndrome



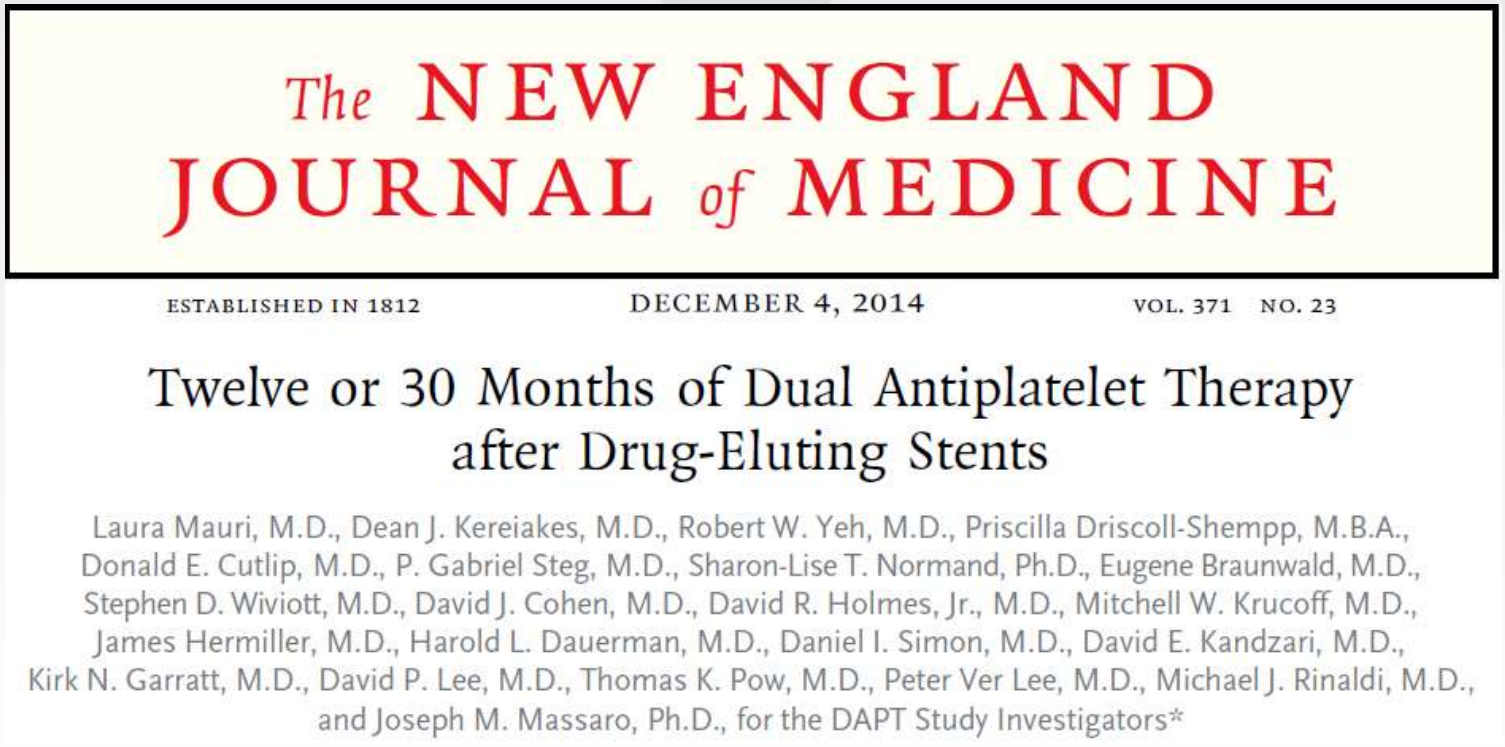
After PCI patient, patients remained exposed to ischemic events



Dual antiplatelet therapy reduced the risk of ischemic event



Longer DAPT reduced the risk of ischemic event



The NEW ENGLAND JOURNAL of MEDICINE

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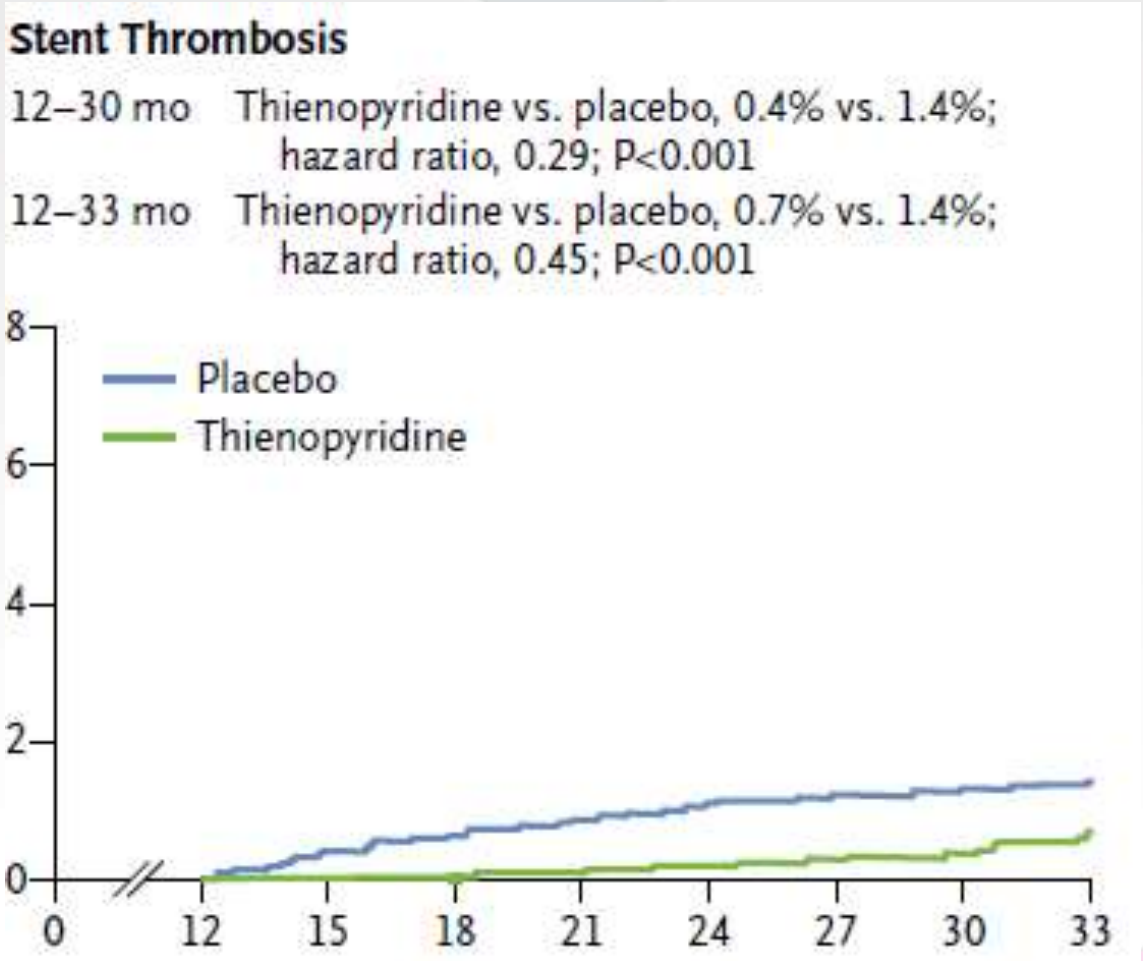
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

Mauri et al, N Engl J Med. 2014 Dec 4;371(23):2155-66.

Longer DAPT reduced the risk of ischemic event



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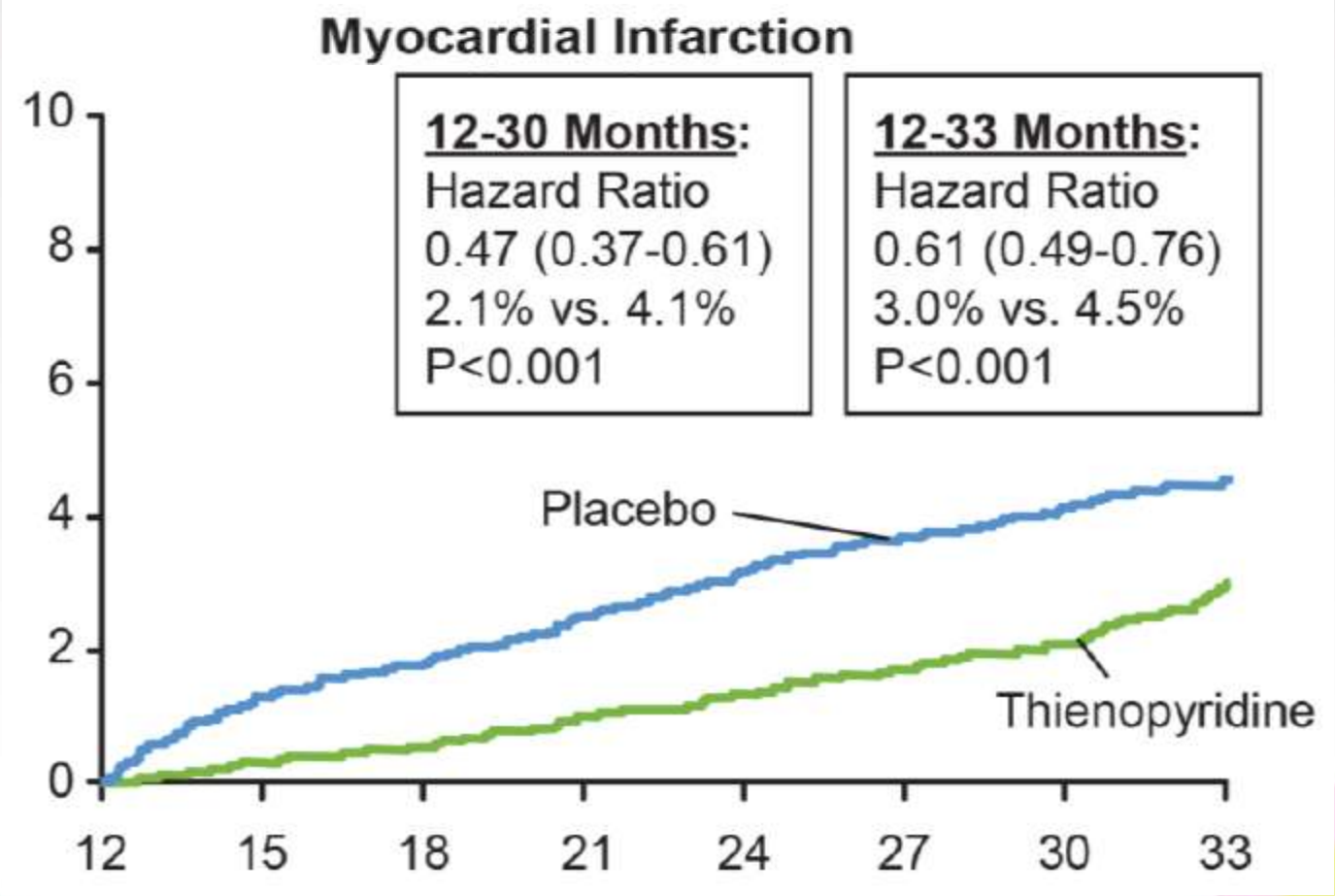

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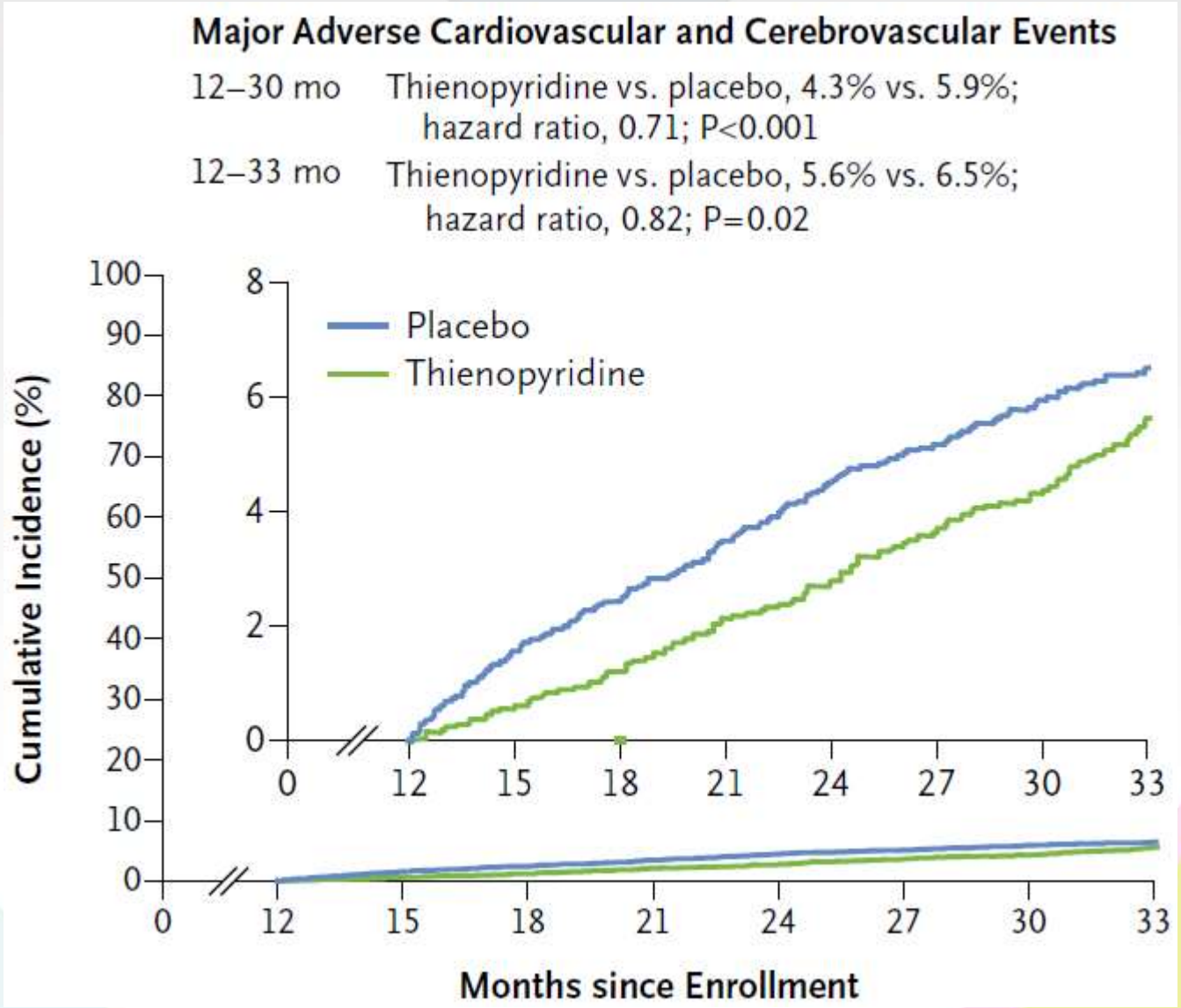
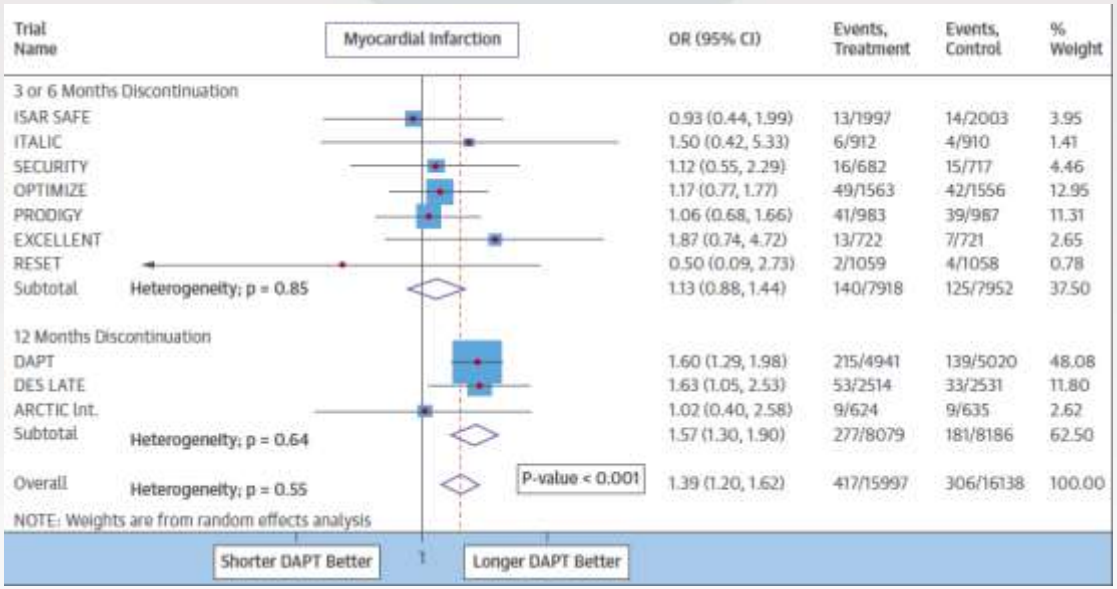
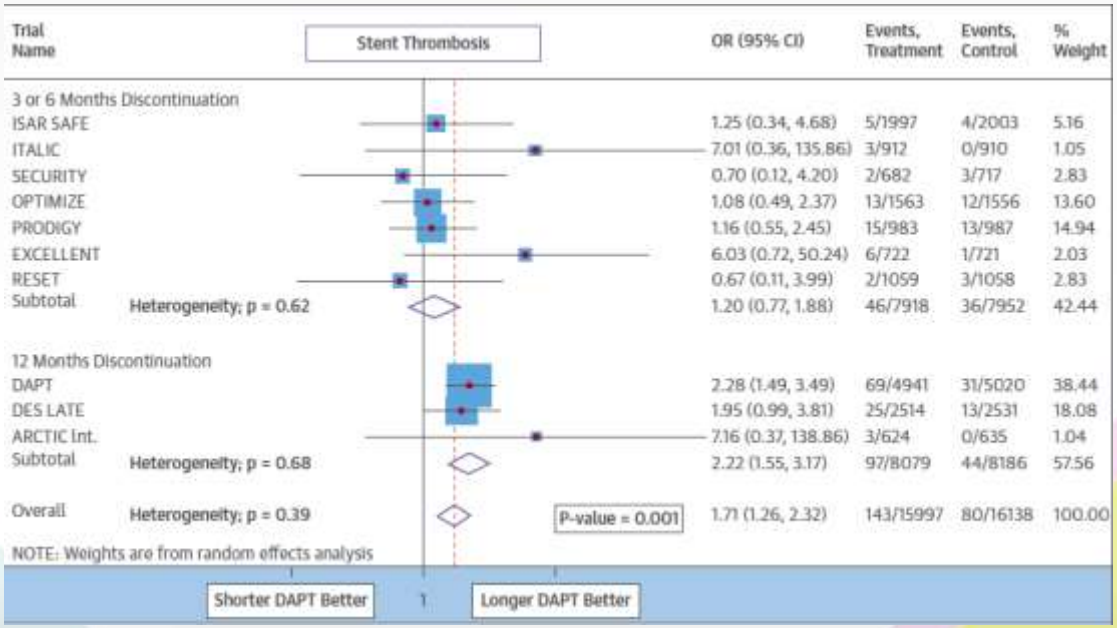


Mauri et al, N Engl J Med. 2014 Dec 4;371(23):2155-66.

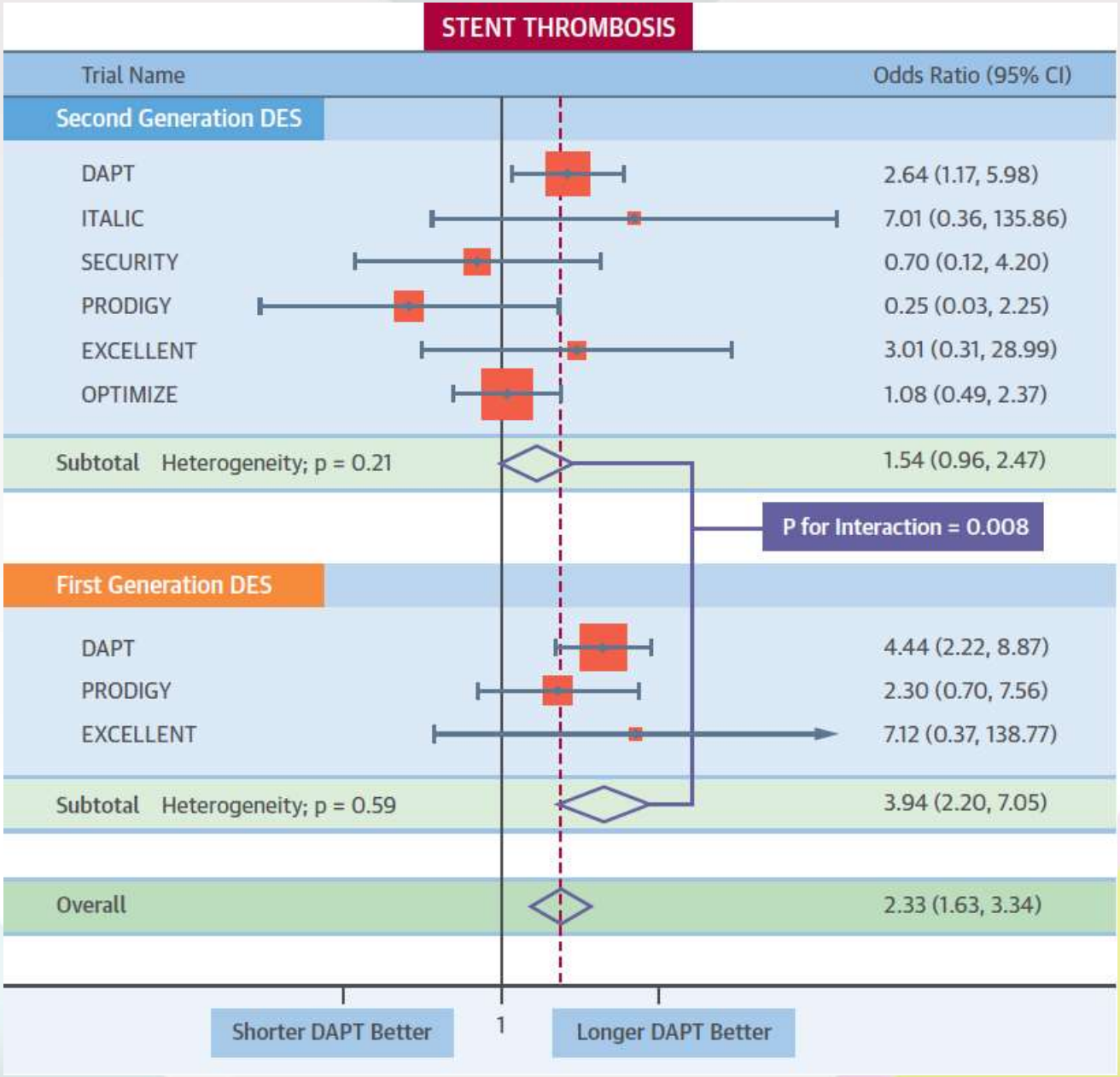
Longer DAPT is associated with reduced risk of ischemic event





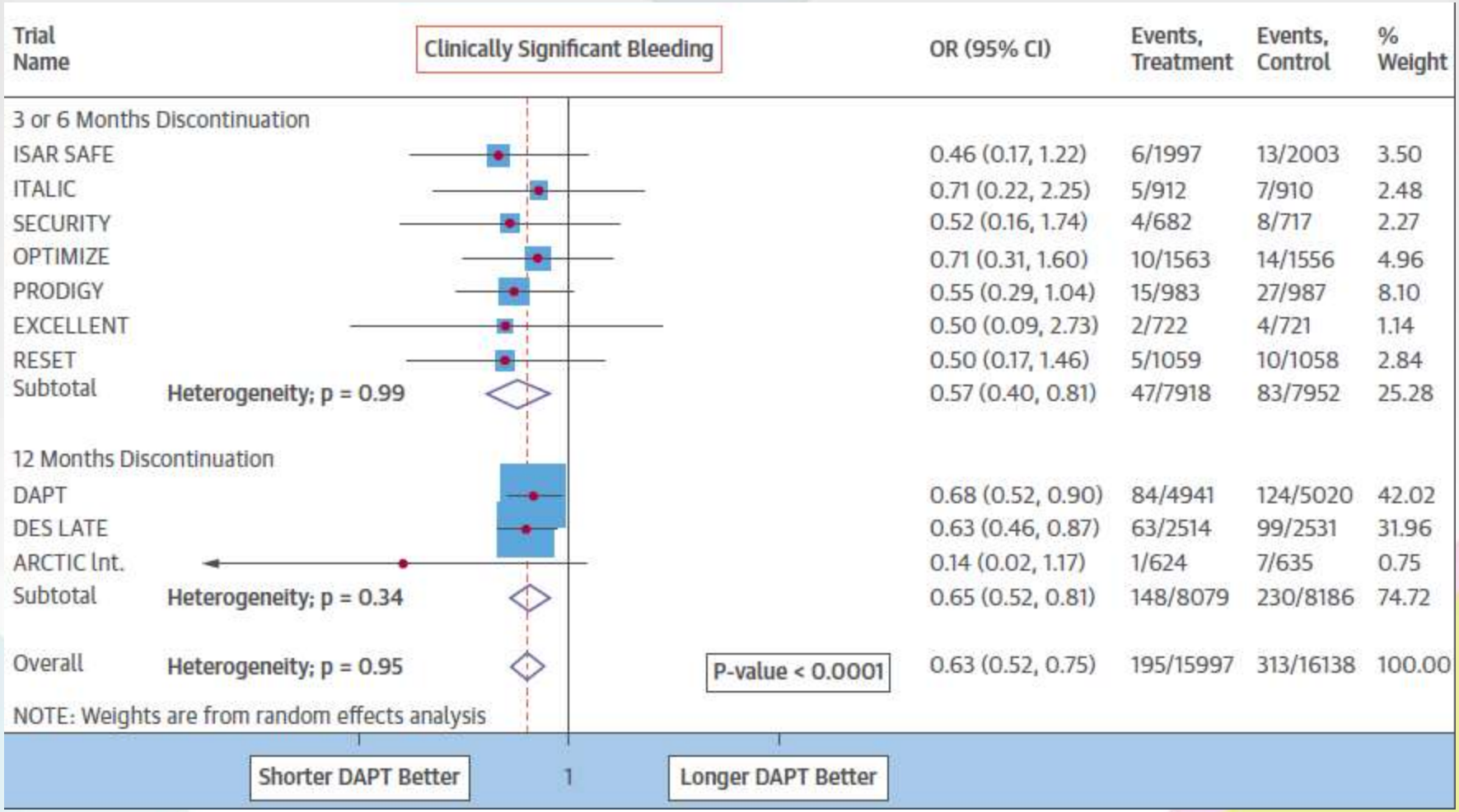
Giustino et al,J Am Coll Cardiol. 2015 Apr 7;65(13):1298-1310

Does new-generation DES still required longer DAPT?



Giustino et al,J Am Coll Cardiol. 2015 Apr 7;65(13):1298-1310

Longer DAPT is associated with increased bleeding

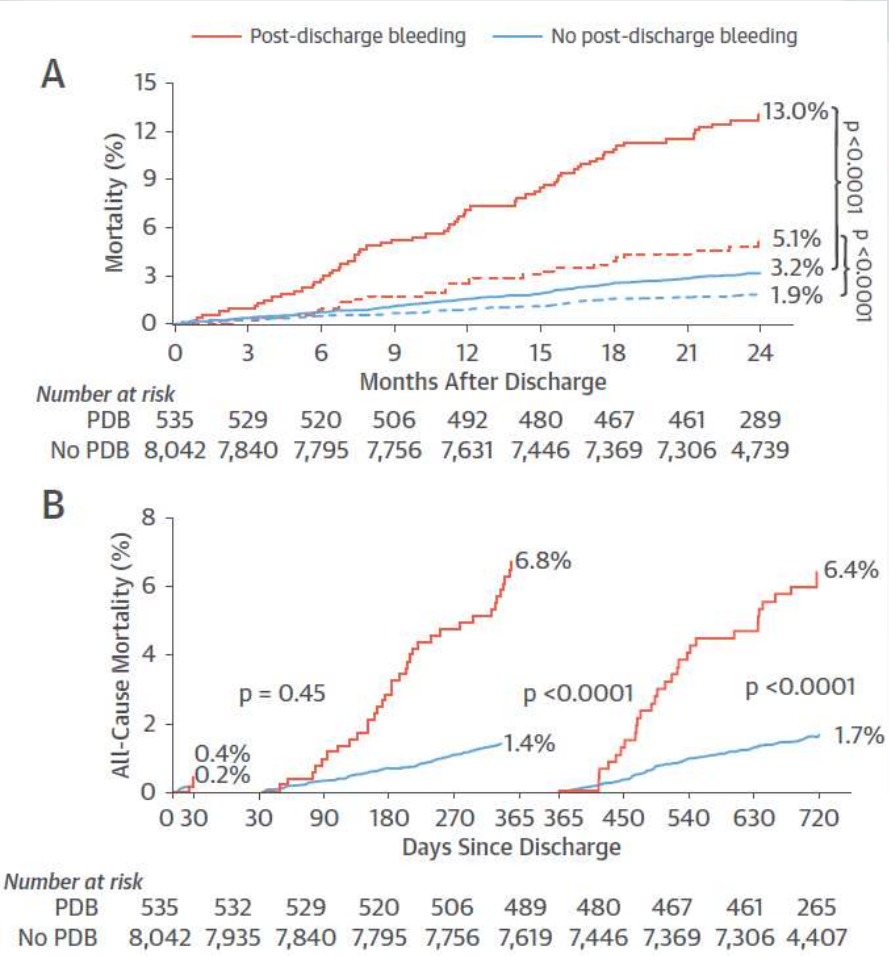


CARDIOVASCULAR SUMMIT TCTAP 2018

CVRF

Giustino et al,J Am Coll Cardiol. 2015 Apr 7;65(13):1298-1310

Bleeding events after PCI leads to ischemic recurrence and overall mortality

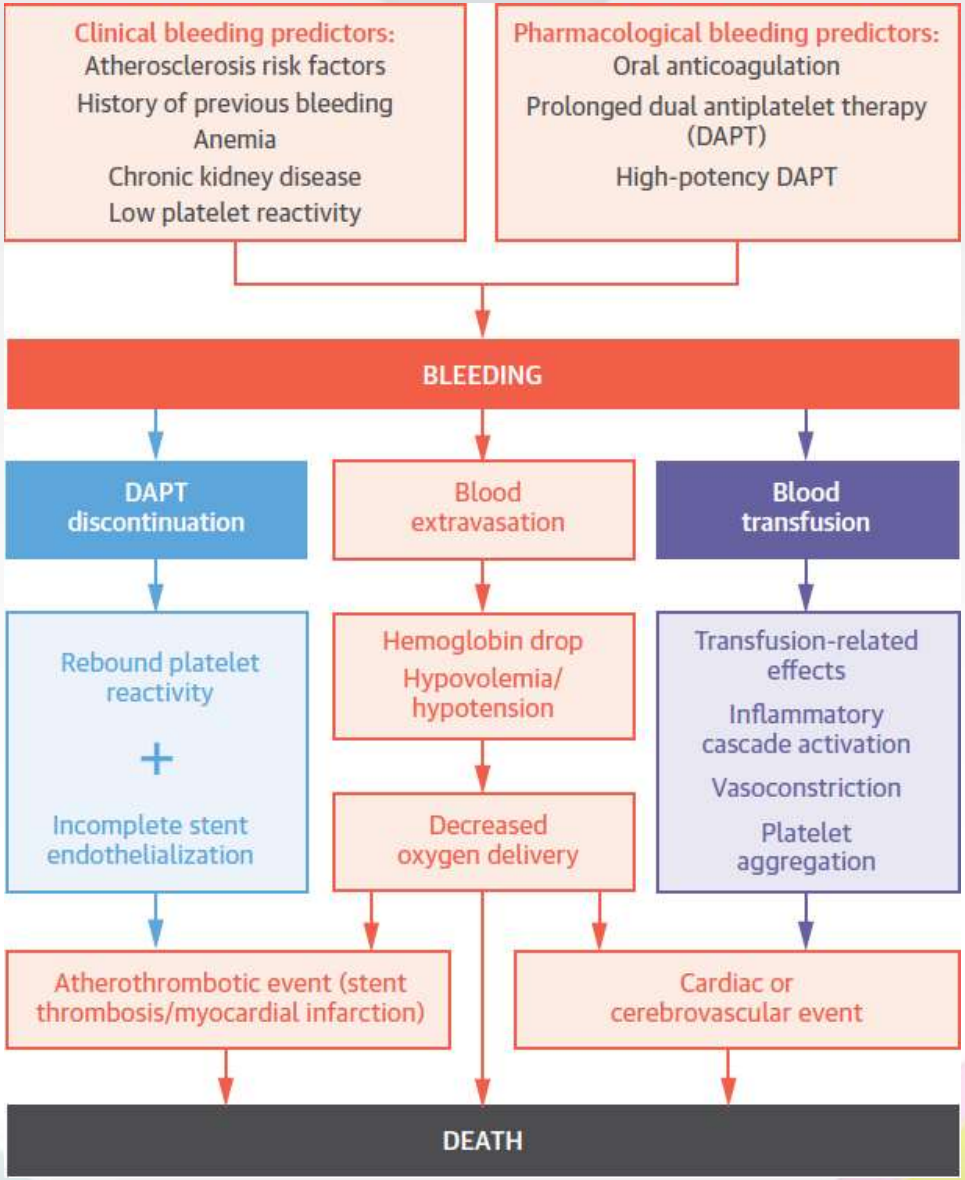


	PDB (n = 535)	No PDB (n = 8,042)	Unadjusted HR (95% CI)	p Value*
All-cause mortality	13.0 (68)	3.2 (243)	8.14 (5.53-12.00)	<0.0001
Cardiac	5.1 (25)	1.9 (144)	4.95 (2.64-9.28)	<0.0001
Noncardiac	6.1 (31)	1.2 (87)	10.52 (5.89-18.81)	<0.0001
MI	13.5 (68)	4.1 (319)	3.14 (2.02-4.90)	<0.0001
Target vessel failure	20.6 (103)	9.0 (685)	2.59 (1.83-3.68)	<0.0001
Definite/probable Stent thrombosis	1.5 (8)	1.0 (81)	3.63 (1.29-10.24)	0.02
MACE†	24.1 (123)	9.9 (758)	2.89 (2.10-3.97)	<0.0001

PDB: post-discharge bleeding

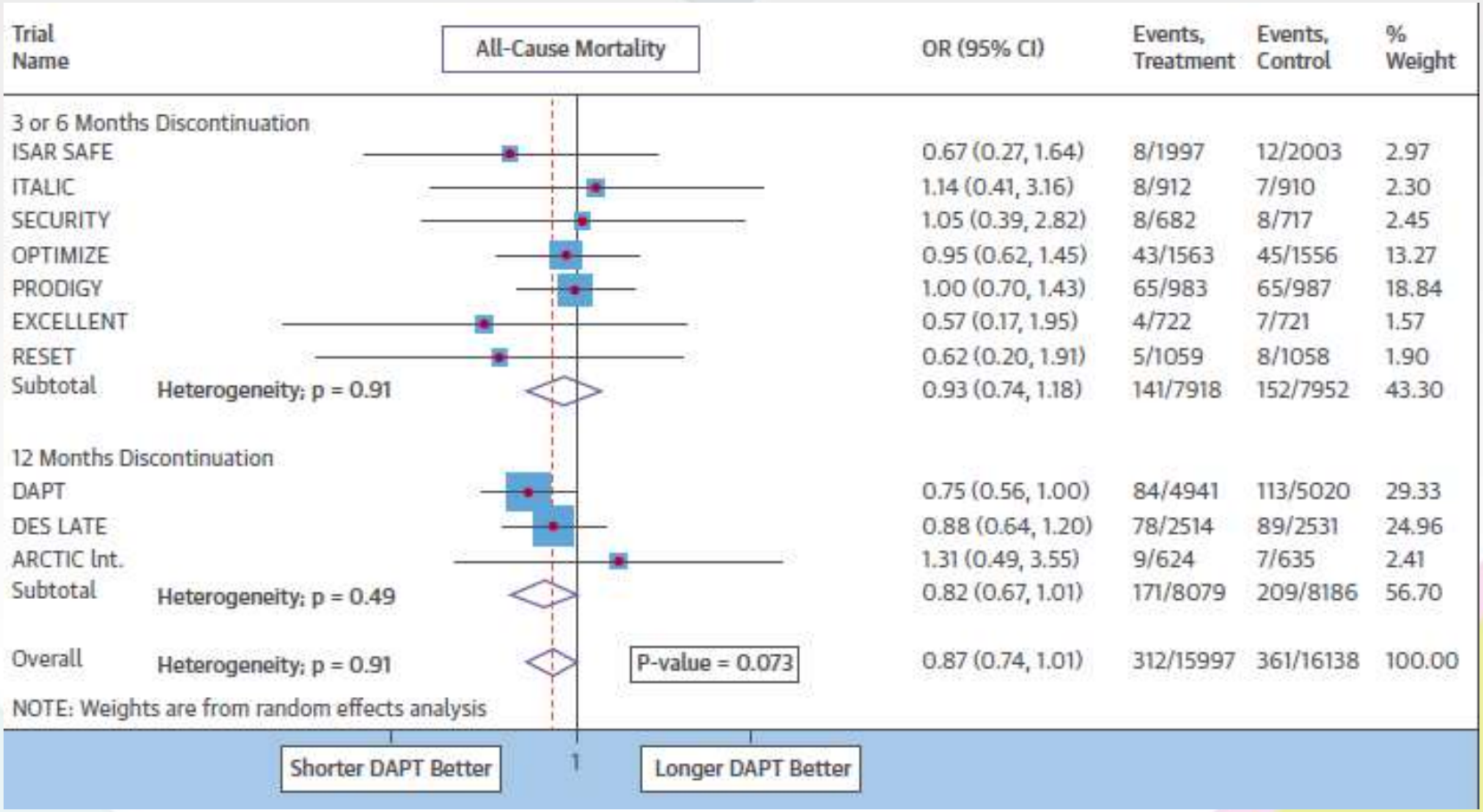
Genereux et al,J Am Coll Cardiol. 2015 Sep 1;66(9):1036-45

Bleeding events after PCI leads to ischemic recurrence and overall mortality



Genereux et al,J Am Coll Cardiol. 2015 Sep 1;66(9):1036-45

Longer DAPT duration associated with increased risk of death?



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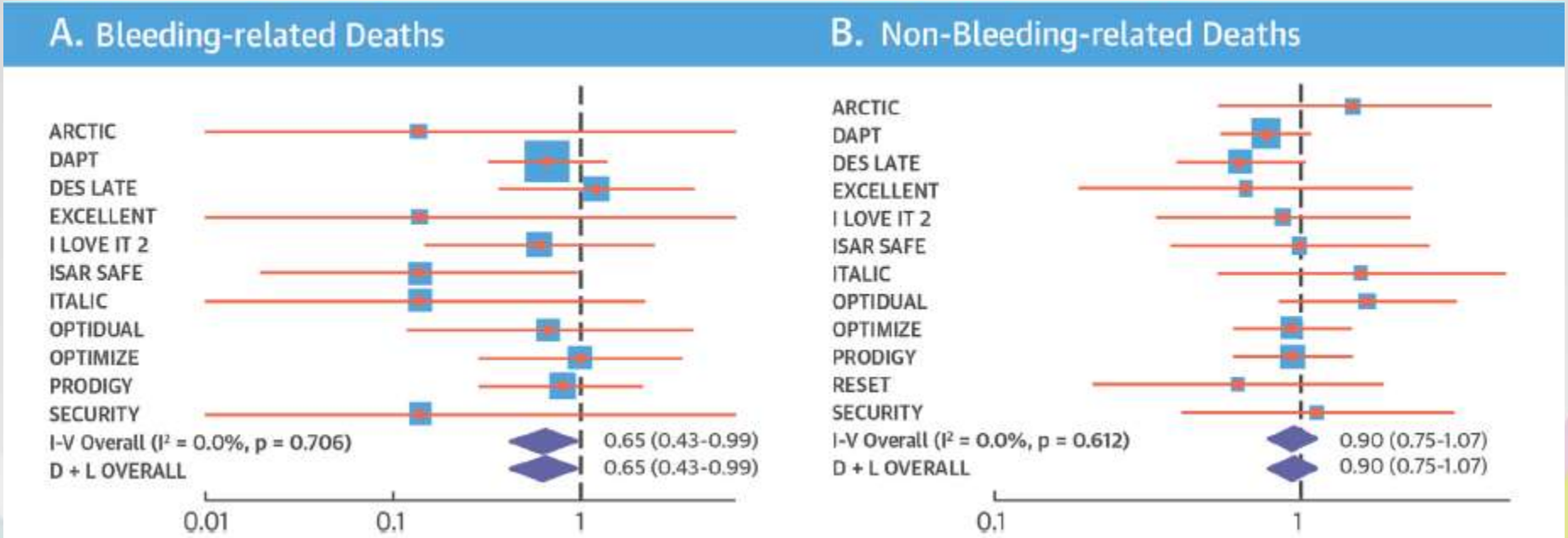
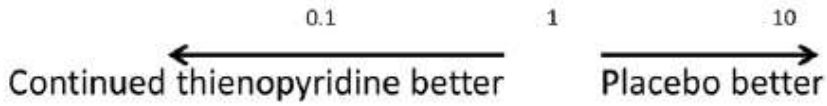


Palmerini et al,J Am Coll Cardiol. 2017;69(16):2011-22

With new-generation DES
Complications of prolonged DAPT may outweigh Ischemic risk reduction

All randomized EES-treated patients

Outcome	Thienopyridine N=2345	Placebo N=2358	HR (95% CI)	P Value
Stent Thrombosis	0.3%	0.7%	0.38 (0.15, 0.97)	0.04
MACCE	4.3%	4.5%	0.89 (0.67, 1.18)	0.42
Death	2.2%	1.1%	1.80 (1.11, 2.92)	0.02
Myocardial Infarction	2.1%	3.2%	0.63 (0.44, 0.91)	0.01
Stroke	0.6%	0.7%	0.79 (0.36, 1.75)	0.56
Bleeding	2.5%	1.3%	1.79 (1.15, 2.80)	0.01



From the DAPT study

Hermiller et al, JACC Cardiovasc Interv. 2016 Jan 25;9(2):138-47

Balancing between ischemic and bleeding risk
Individualized duration of DAPT

> "...a personalized approach should be used, rather than one in which one size fits all"

	≤12 months DAPT	≥12 months DAPT
Patient-related factors 	Patients with stable CAD Patients with a history of bleeding Patients with high risk of bleeding	Patients with ACS Patients with diabetes mellitus Patients with renal dysfunction Patients with CHF Patients with previous ST Patients with PAD
Anatomy-related factors 	Short lesion Single-vessel disease	Long lesion Small vessel Bifurcation lesion Complex anatomy Left-main coronary artery
Stent-related factors 	Second-generation DES	First-generation DES Long stent Multiple stents

Eisen et Bhatt, Nature Review Cardiology. 2015

Tailored DAPT duration: interest of risk scores

PARIS risk score

TABLE 4 Integer Risk Score for Major Bleeding

Parameter	Score
Age, yrs	
<50	0
50-59	+1
60-69	+2
70-79	+3
≥80	+4
BMI, kg/m^2	
<25	+2
25-34.9	0
≥35	+2
Current smoking	
Yes	+2
No	0
Anemia	
Present	+3
Absent	0
CrCl <60 ml/min	
Present	+2
Absent	0
Triple therapy on discharge	
Yes	+2
No	0

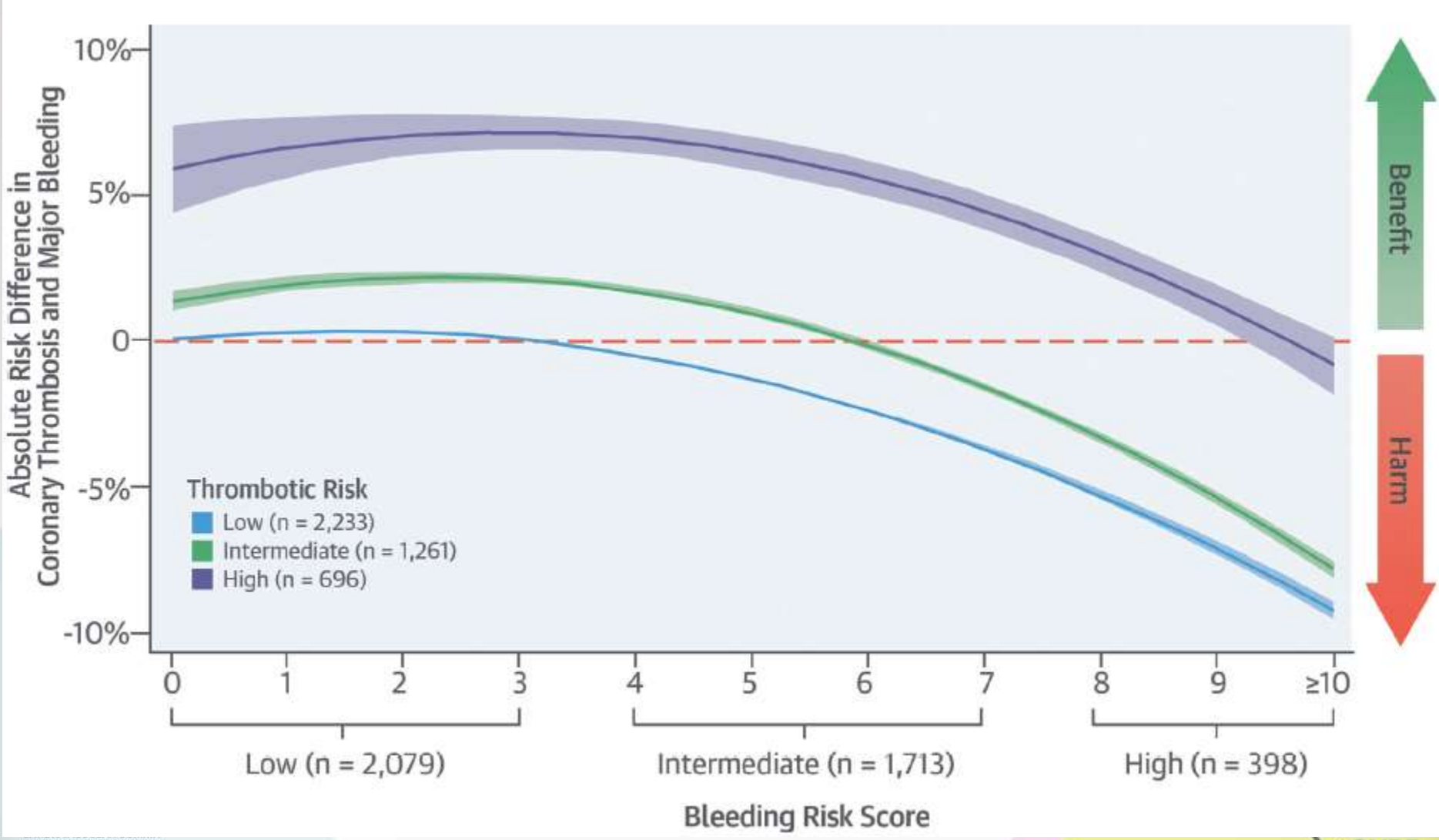
TABLE 5 Integer Risk Score for Coronary Thrombotic Events

Parameter	Score
Diabetes mellitus	
None	0
Non-insulin-dependent	+1
Insulin-dependent	+3
Acute coronary syndrome	
No	0
Yes, Tn-negative	+1
Yes, Tn-positive	+2
Current smoking	
Yes	+1
No	0
CrCl <60 ml/min	
Present	+2
Absent	0
Prior PCI	
Yes	+2
No	0
Prior CABG	
Yes	+2
No	0

Baber, Mehran et al, J AM Coll Cardiol. 2016 17;67(19):2224-34

Tailored DAPT duration: interest of risk scores

PARIS risk score



Baber, Mehran et al, J AM Coll Cardiol. 2016 17;67(19):2224-34

Tailored DAPT duration: interest of risk scores

DAPT score

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

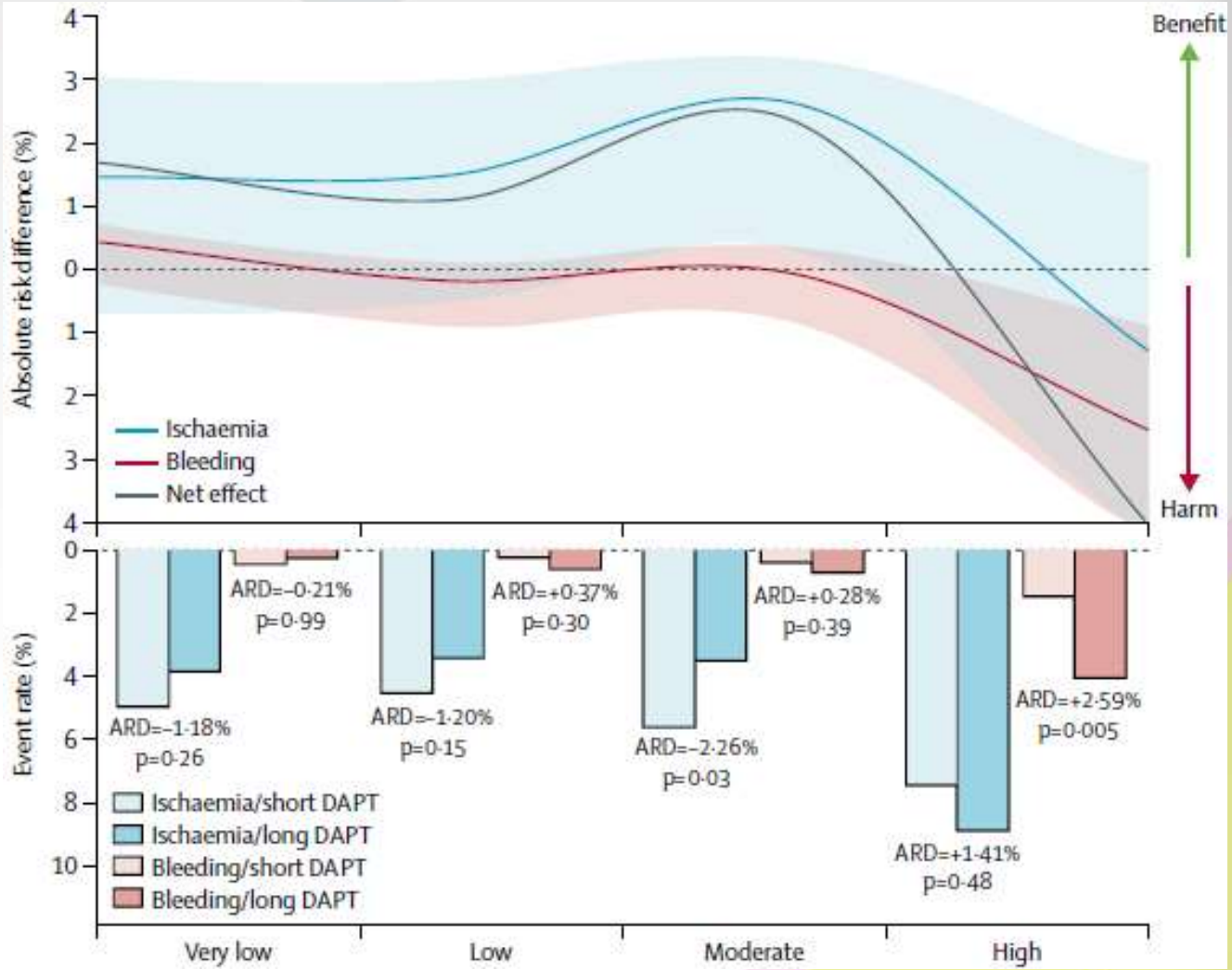
Yeh, R et al. JAMA. 2016 Apr 26;315(16):1735-49

Tailored DAPT duration: interest of risk scores

PRECISE-DAPT score

Variables included

- Age
- White blood cell count
- Hemoglobin at baseline
- Creatinine clearance



Costa, R et al. Lancet. 2017 Mar 11;389(10073):1025-1034

Balancing ischemic and bleeding risk after PCI
ACC/AHA and ESC/EACTS Guidelines

	ACC/AHA	ESC/EACTS
Stable Ischemic heart disease with PCI		
Minimum duration: 6 months	**Class I**	**Class I**
High bleeding risk: 3 months	**Class IIb**	
Very high bleeding risk: 1 month		**Class IIb**
High ischemic risk: > 6 months	**Class IIb**	**Class IIb**
Acute coronary syndrome with PCI		
Minimum duration: 12 months	**Class I**	**Class I**
High bleeding risk: 6 months	**Class IIb**	**Class IIa**
Very high bleeding risk: >12 months	**Class IIb**	**Class IIb**

Levine, R et al. J AM Coll Cardiol. 2016 Sep 6;68(10):1082-115
Valgimigli Eur Heart J.14;39(3):213-260

Balancing ischemic and bleeding risk after PCI

Changing the paradigm with antiplatelet monotherapy

Do Current Clinical Trials Meet Society's Needs?

A Critical Review of Recent Evidence

Stuart J. Pocock, PhD,* Bernard J. Gersh, MB, ChB, DPhil†

THE NEED FOR TRIALS OF TREATMENT WITHDRAWAL

As part of this broader topic of long-term polypharmacy, we need clinical trials that can investigate the withdrawal of certain established medications to see whether such withdrawal induces patient benefit, harm, or no difference compared with continued medication.

Pocock et Gersh J AM Coll Cardiol. 2014 Oct 14;64(15):1615-28

Changing the paradigm with antiplatelet monotherapy

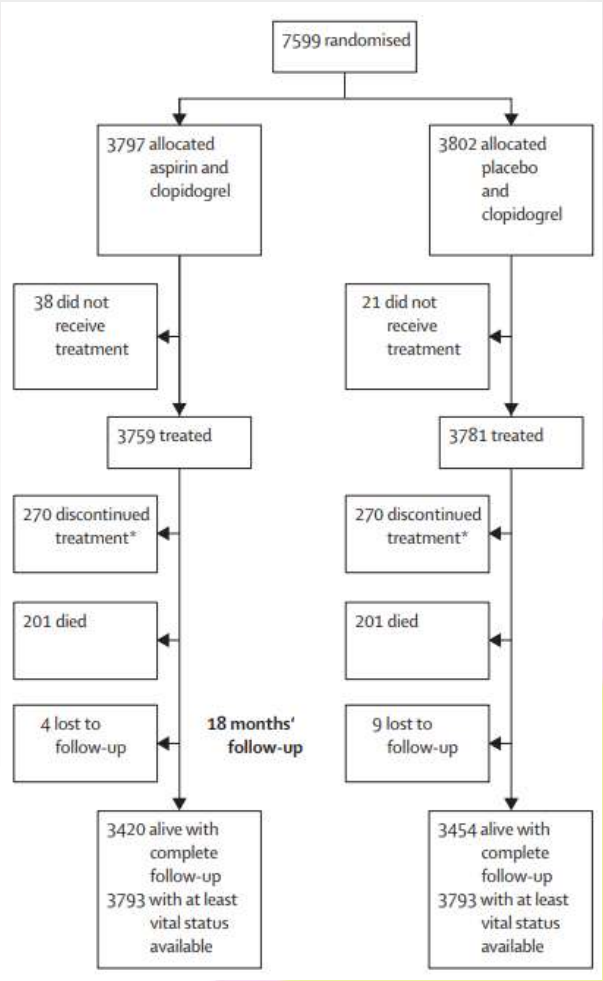
The example of MATCH trial

Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

*Hans-Christoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu, Hans-Jürgen Rupprecht, on behalf of the MATCH investigators**

Aim: whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in prevention of v ascular events with potentially higher bleeding risk

Population: 7599 high-risk patients with recent ischemic s troke or transient ischemic attack and at least one additio nal vascular risk factor who were already receiving clopido grel 75 mg/day



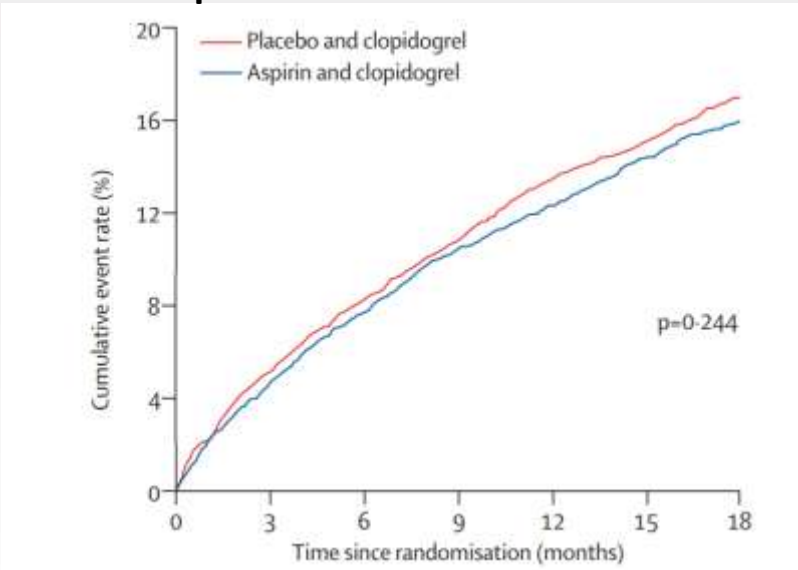
CVRF

Diener Lancet 2004 Jul 24-30;364(9431):331-7

Changing the paradigm with antiplatelet monotherapy

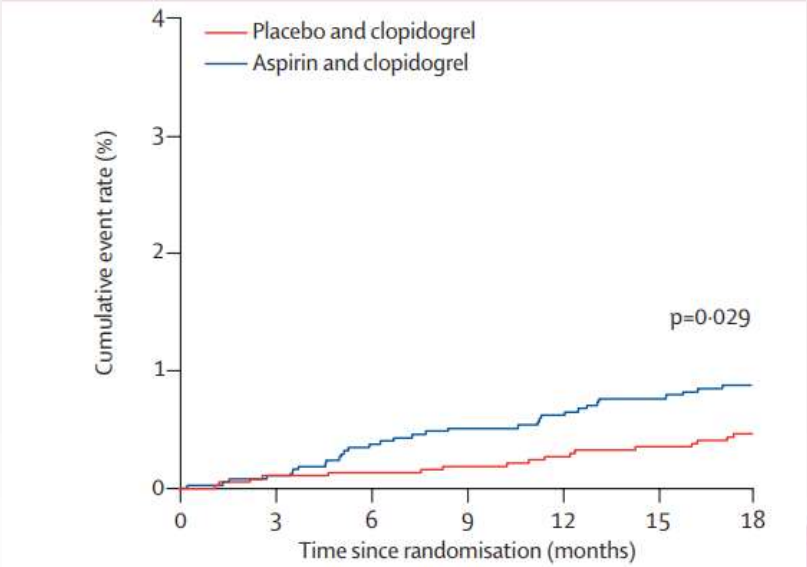
The example of MATCH trial

Ischemic stroke, MI, vascular death or hospitalization for acute ischemia



	Number (%) with event		Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)	p*
	Aspirin and clopidogrel (n=3797)	Placebo and clopidogrel (n=3802)			
Primary outcome†	596 (16%)	636 (17%)	1·0% (−0·6 to 2·7)	6·4% (−4·6 to 16·3)	0·244
Myocardial infarction (fatal or not)	59 (2%)	62 (2%)	..	..	..
Ischaemic stroke (fatal or not)	299 (8%)	319 (8%)	..	..	..
Other vascular death	69 (2%)	74 (2%)	..	..	..
Rehospitalisation for acute ischaemic event	169 (4%)	181 (5%)	..	..	..

Intracranial hemorrhage



	Number (%) with event		Difference (%) between aspirin and placebo (95% CI)	p*
	Aspirin and clopidogrel (n=3759)	Placebo and clopidogrel (n=3781)		
Life-threatening bleeding	96 (3%)	49 (1%)	1·26 (0·64 to 1·88)	<0·0001
Fatal bleeding	16 (<1%)	11 (<1%)	0·13 (−0·14 to 0·40)	
Non-fatal bleeding	81 (2%)	38 (1%)	1·15 (0·59 to 1·71)	
Symptomatic intracranial haemorrhage†	40 (1%)	25 (1%)	0·40 (−0·01 to 0·82)	
Primary intracranial haemorrhage	32 (1%)	17 (<1%)	0·40 (0·04 to 0·76)	
Major bleeding	73 (2%)	22 (1%)	1·36 (0·86 to 1·86)	<0·0001
Minor bleeding	120 (3%)	39 (1%)	2·16 (1·51 to 2·81)	<0·0001

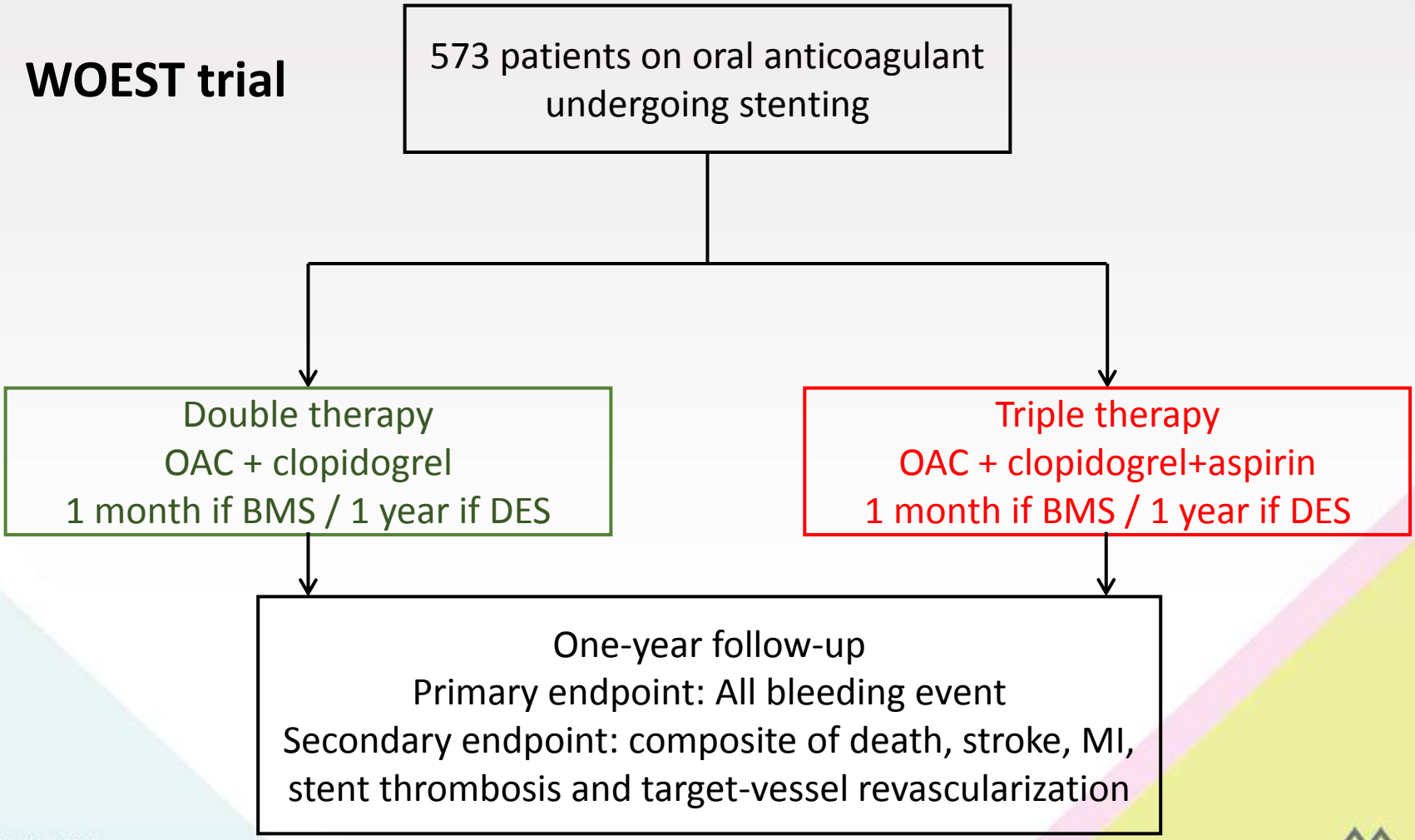
*Pearson's χ^2 test. †All symptomatic (and thus primary) intracranial haemorrhages were life-threatening bleeds.

Diener Lancet 2004 Jul 24-30;364(9431):331-7

Changing the paradigm with antiplatelet monotherapy

The example of PCI in patients on oral anticoagulant

WOEST trial



Dewilde Lancet. 201314;381:1107

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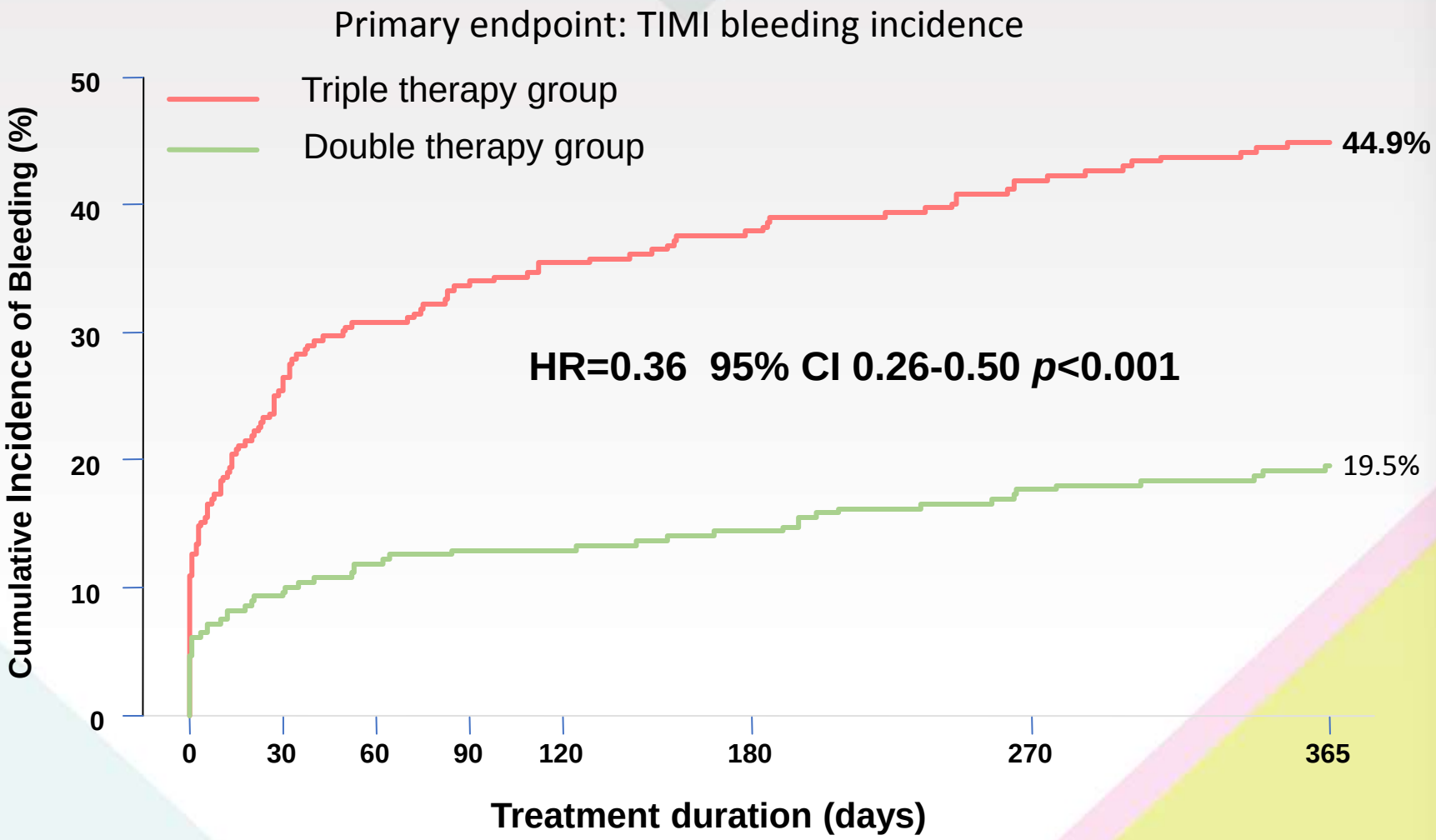
The example of PCI in patients on oral anticoagulant



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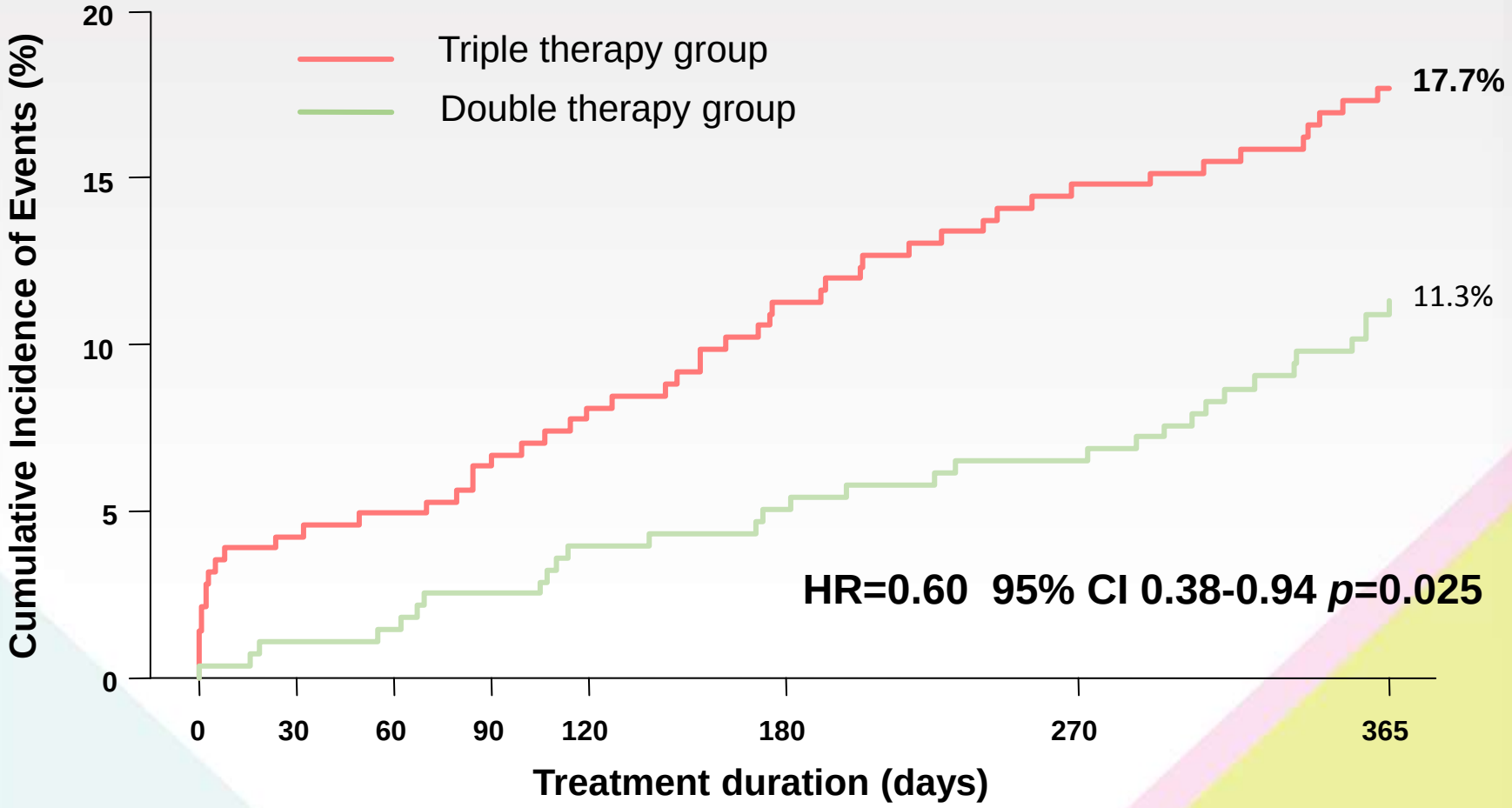
Dewilde Lancet. 201314;381:1107

Changing the paradigm with antiplatelet monotherapy

The example of PCI in patients on oral anticoagulant

Secondary endpoint: Death, MI, stroke, stent thrombosis and target-vessel revascularization



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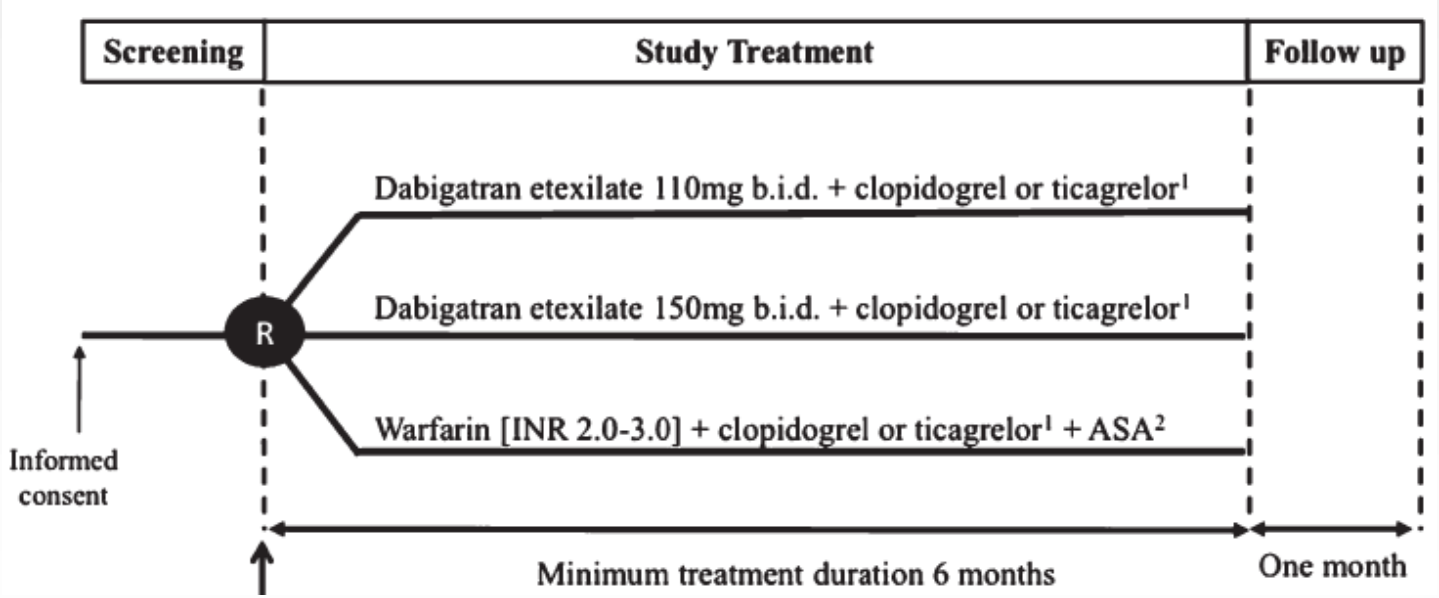
Dewilde Lancet. 201314;381:1107

Changing the paradigm with antiplatelet monotherapy

The example of PCI in patients on oral anticoagulant

RE-DUAL PCI™

Study in NVAF patients undergoing PCI



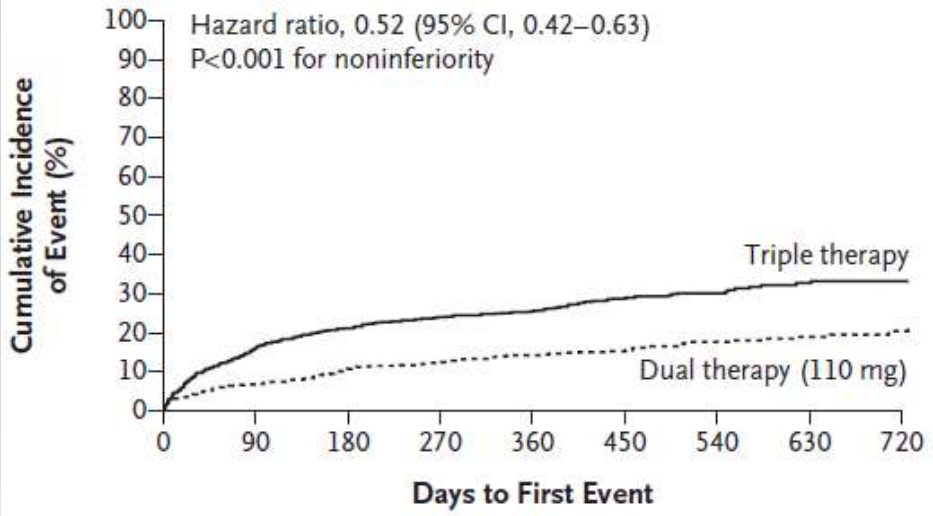
- Primary composite endpoint
  - major bleeding (ISTH)
  - clinically relevant non-major bleeding
- Secondary composite endpoint
  - Thromboembolic events
  - Death

Cannon et al, N Engl J Med. 2017 19;377(16):1513-1524

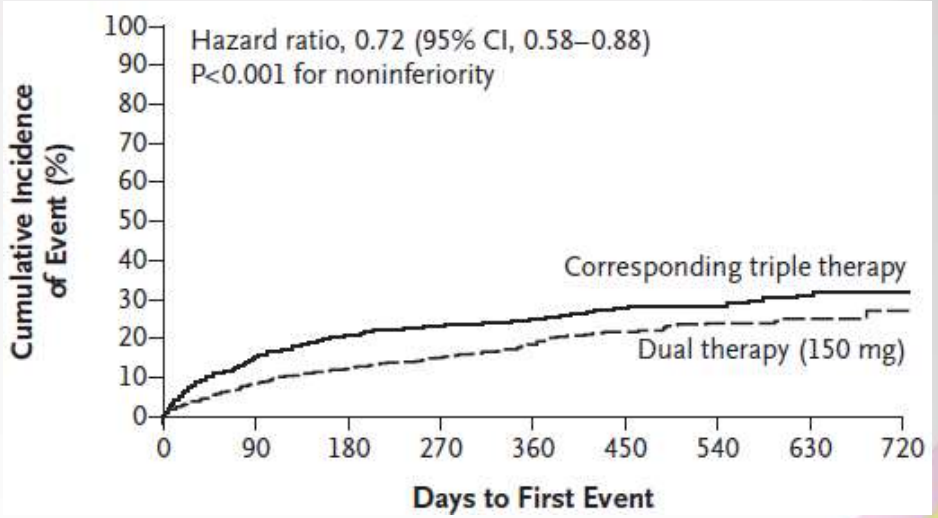
Changing the paradigm with antiplatelet monotherapy

The example of PCI in patients on oral anticoagulant

Primary endpoint: Major or clinically relevant non major bleeding



Dabigatran 110mg BID + P2Y12 inhibitors vs. triple therapy



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Cannon et al, N Engl J Med. 2017 19;377(16):1513-1524

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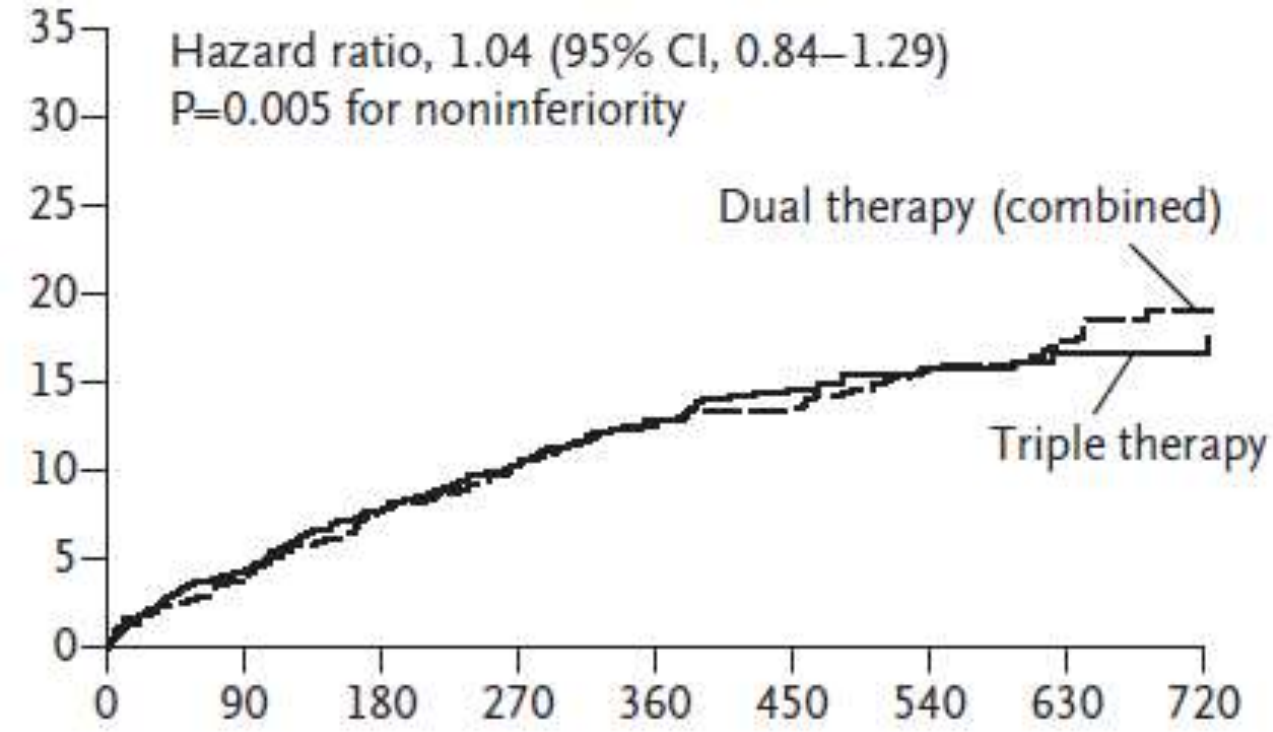
The example of PCI in patients on oral anticoagulant

Secondary endpoint: Death, MI, stroke or systemic embolism or unplanned revascularization



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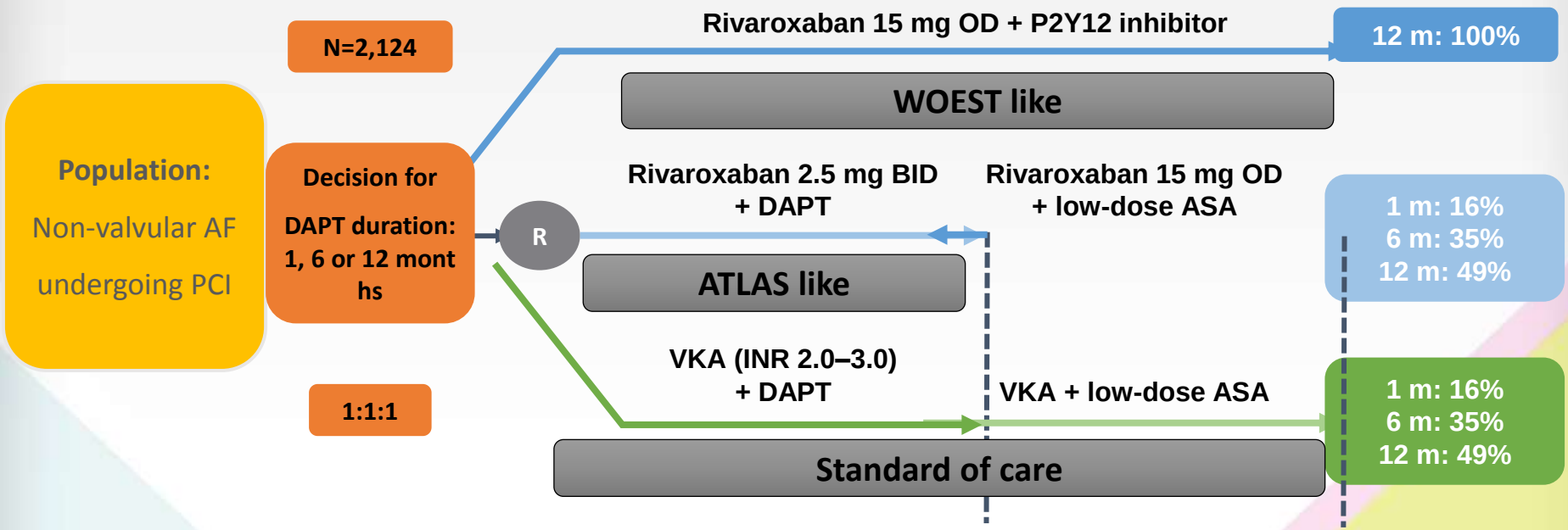
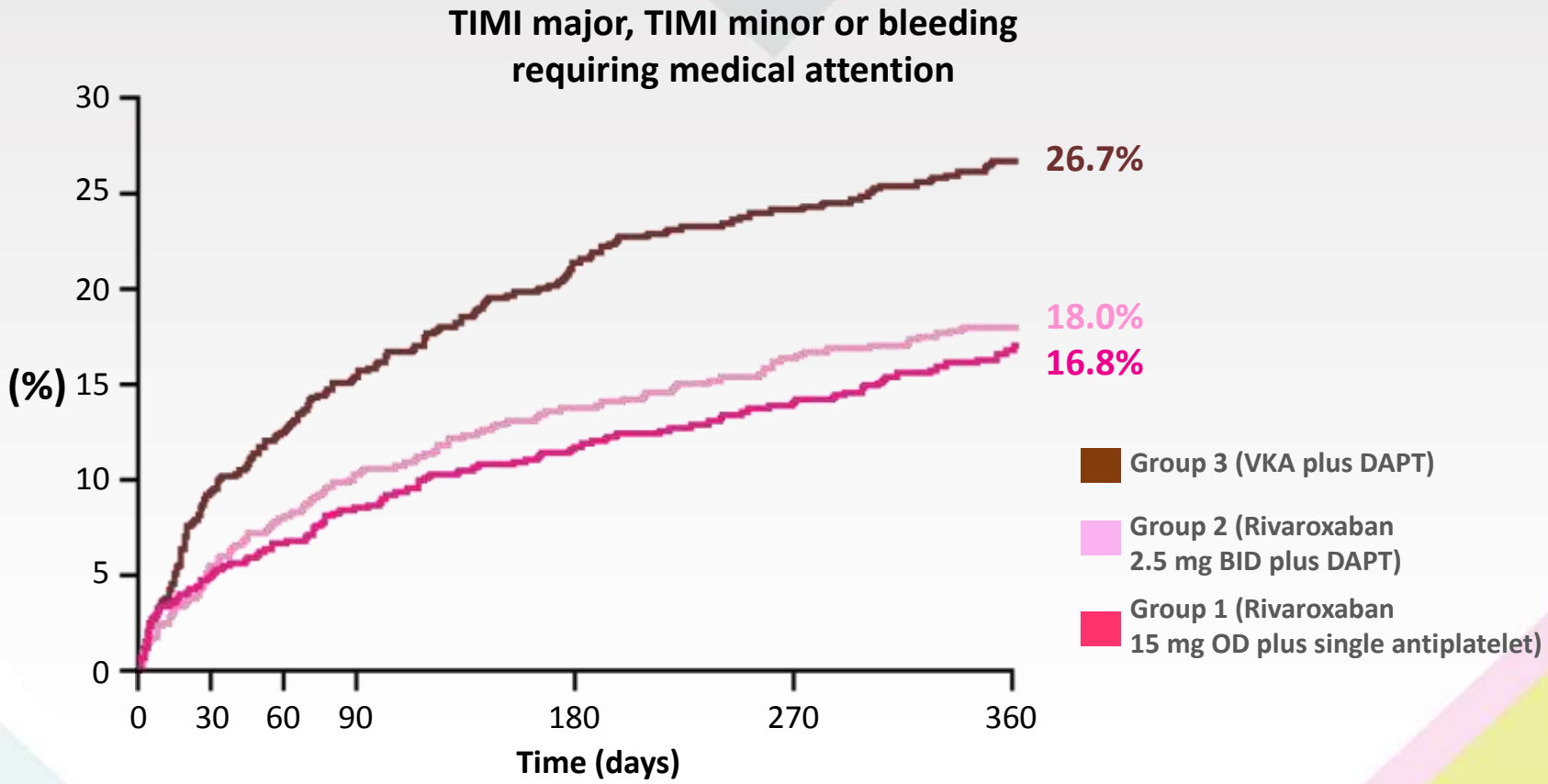


Gibson CM, Mehran et al, N Engl J Med. 2016 22;375(25):2423-2434

Changing the paradigm with antiplatelet monotherapy

The example of PCI in patients on oral anticoagulant

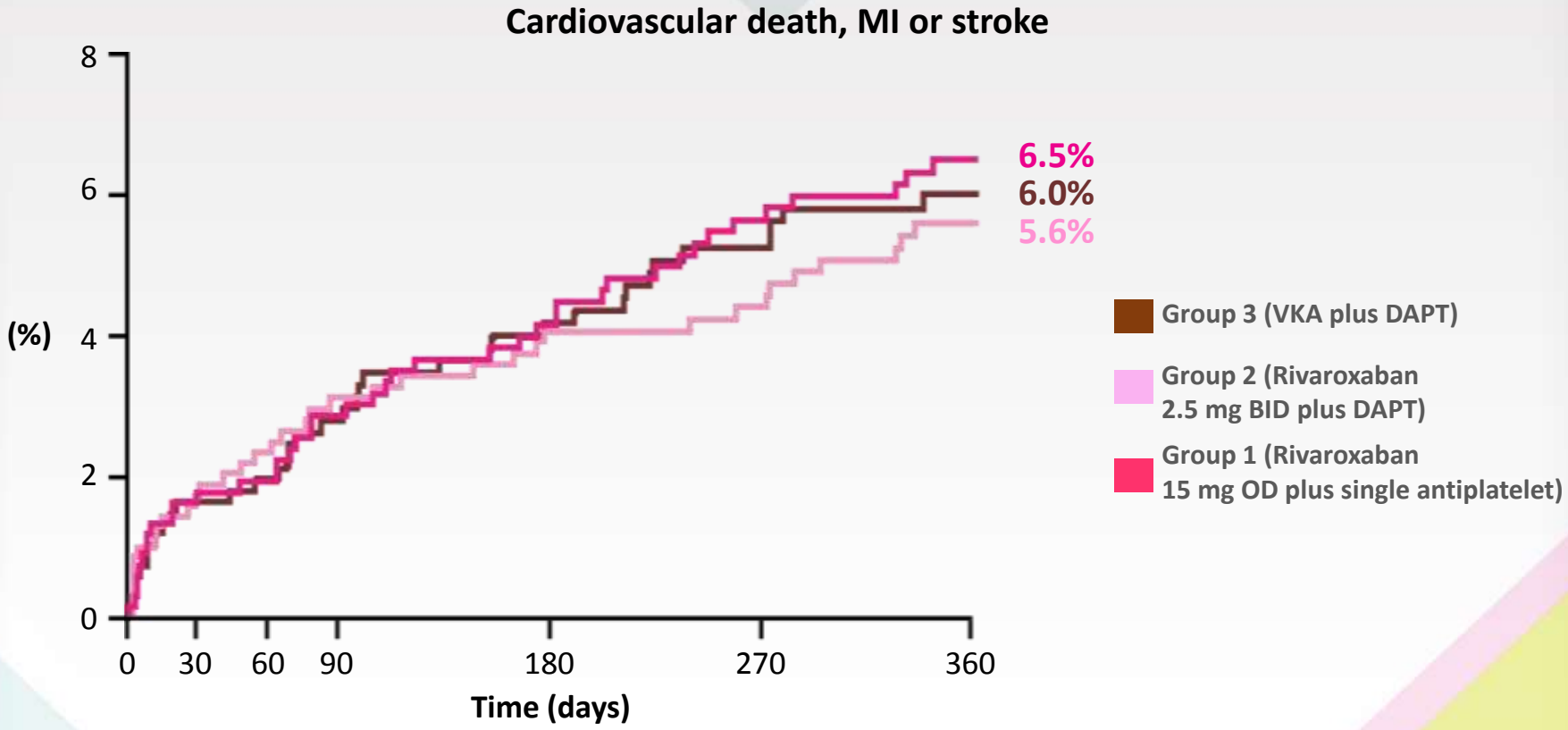


- **Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); *p*<0.001**
- **Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); *p*<0.001**

Gibson CM, Mehran et al, N Engl J Med. 2016 22;375(25):2423-2434

Changing the paradigm with antiplatelet monotherapy

The example of PCI in patients on oral anticoagulant

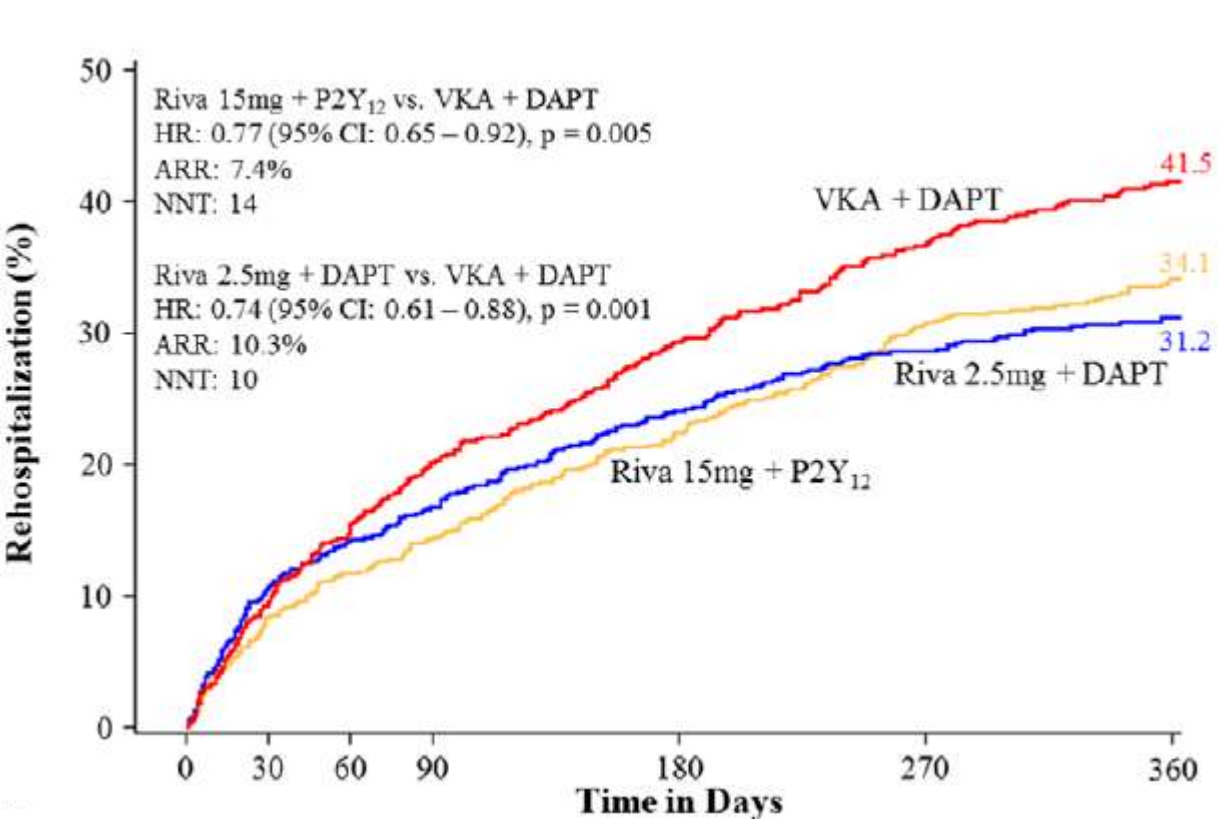


- **Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); p=0.75**
- **Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); p=0.77**

Gibson CM, Mehran et al, N Engl J Med. 2016 22;375(25):2423-2434

Changing the paradigm with antiplatelet monotherapy

The example of PCI in patients on oral anticoagulant

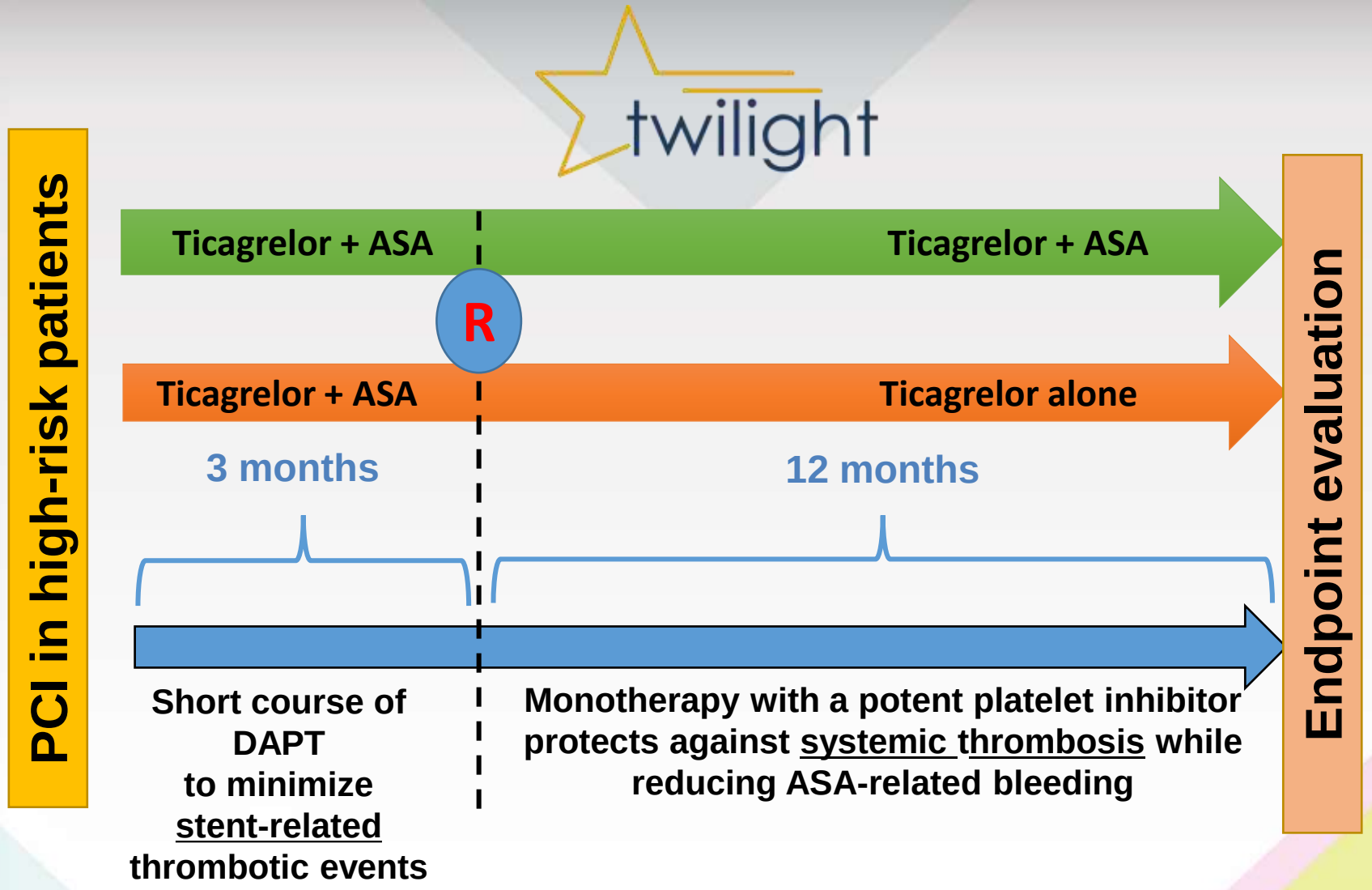


Reduced rates of CV hospitalization with Rivaroxaban+P2Y12inhibitor vs. triple therapy

HR: 0.68 (95%CI 0.54-0.85) p<0.001

Gibson, Circulation. 2017 24;135(4):323-333

Ongoing trials evaluating antiplatelet monotherapy After PCI



Primary endpoint

Time to first clinically relevant bleeding (BARC 2 or more) between 3 and 15 months

Key secondary endpoint

Composite of all-cause death, MI or stroke

Baber et al, Am Heart J. 2016 Dec; 182:125-134

Inclusion criteria: High-risk PCI

At least on of the following clinical criteria:

- Age ≥ 65 years of age
- Female gender
- Troponin positive acute coronary syndrome
- Established vascular disease defined as previous MI, documented PAD or CAP/PAD Revascularization
- Diabetes mellitus treated with medications
- Chronic kidney disease defined as creatinine clearance<60mL/min

At least on of the following clinical criteria:

- Multivessel coronary artery disease
- Target lesion requiring stent length > 30mm
- Thrombotic target lesion
- Bifurcation lesion with Medina X,1,1 classification requiring at least 2 stents
- Left main or proximal LAD lesion
- Calcified target lesion requiring atherectomy

Baber et al, Am Heart J. 2016 Dec; 182:125-134

All-comers PCI population
(ACS and Stable CAD patients)
(N = 16,000)

GLOBAL-LEADERS trial

Bivalirudin-supported BioMatrix family stent implantation

1:1 Randomization, Open-Label Design

Experimental Treatment Strategy

- **ASA** 1 month
- **Ticagrelor** 24 months

Reference Treatment Strategy

- **ASA** 24 months
- **Ticagrelor** 12 months — NOT ALLOWED IN STABLE PTS
- **OR**
- **Clopidogrel** — ONLY ALLOWED IN STABLE PTS

Primary Endpoint (Effectiveness)

Experimental treatment strategy superior to reference treatment strategy on cumulative 2 year composite of all cause mortality and new Q-wave MI

IMPORTANT: In the Reference Treatment Strategy arm, ticagrelor is not allowed in stable patients, and clopidogrel must be given in combination with ASA. However, patients already on stable maintenance treatment with ticagrelor (or prasugrel) can continue with ticagrelor treatment (for 12 months post index-PCI).

* In countries where available.

Vranckx, Eurointervention. 2016 Nov 20;12(10):1239-1245

Primary endpoint

- All-cause death or non-fatal, new Q-wave myocardial infarction

Key secondary endpoint

- Investigator –reported BARC 4 or 5 bleeding events

Other endpoints

- Composite of death, investigator-reported stroke, MI or coronary revascularization
- Investigator-reported stroke
- Investigator-reported myocardial infarction
- Investigator-reported coronary revascularization
- Investigator-reported definite stent thrombosis

Vranck, Eurointervention. 2016 Nov 20;12(10):1239-1245