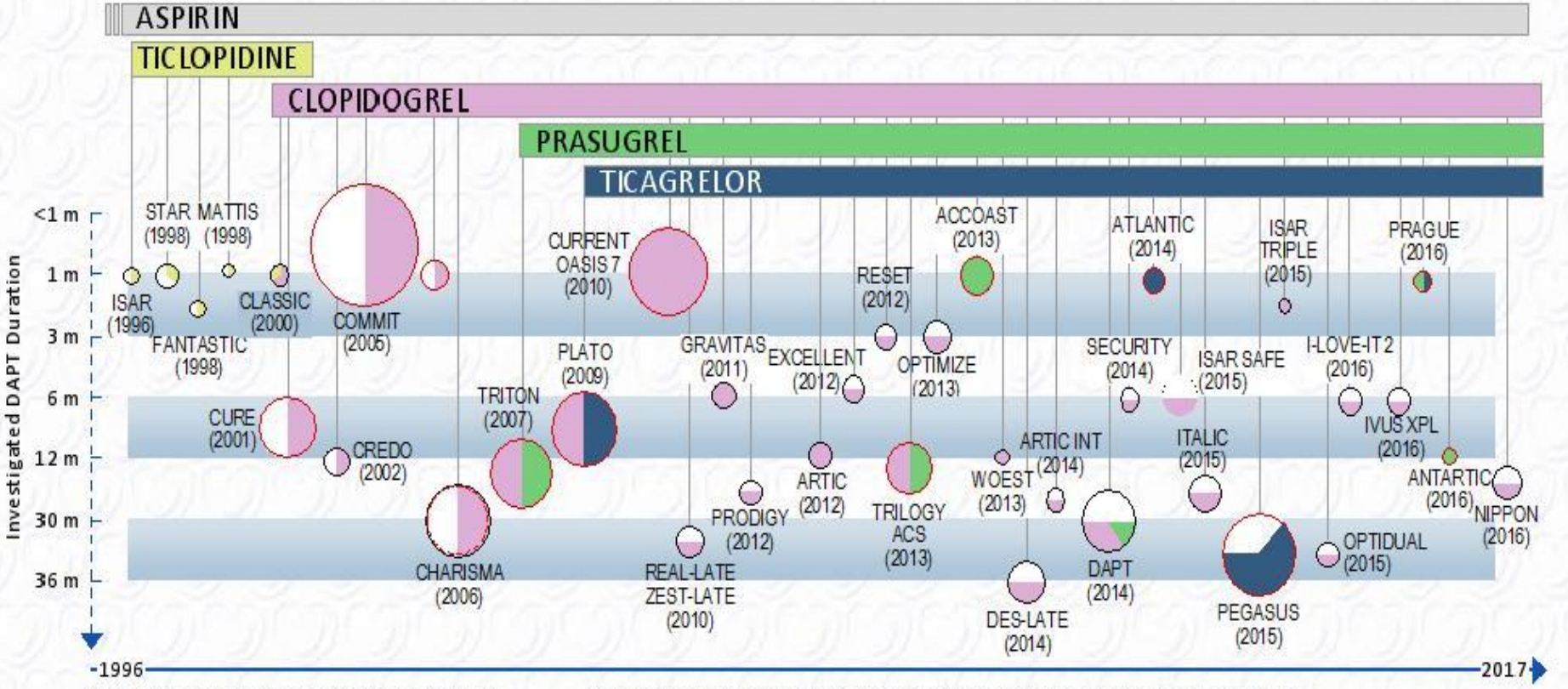
Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

Luigi Oltrona Visconti
Divisione di Cardiologia
IRCCS Fondazione Policlinico S. Matteo
Pavia

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)

Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

Novara 7 Giugno 2018

The question is : how long ?

Reducing or prolonging the recommended period of treatment ?

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VOL. 65, NO. 13, 2015
ISSN 0735-1097/$36.00

Extended duration dual antiplatelet therapy and mortality:

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwi
random

Tullio Palmerini, U
Myeong-Ki Hong,
Stefano De Servi,

Summary
Background D
drug-eluting st
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Methods We
Nov 20, 2014,
implantation.
DAPT duration
longer than 1 y

Findings We ide
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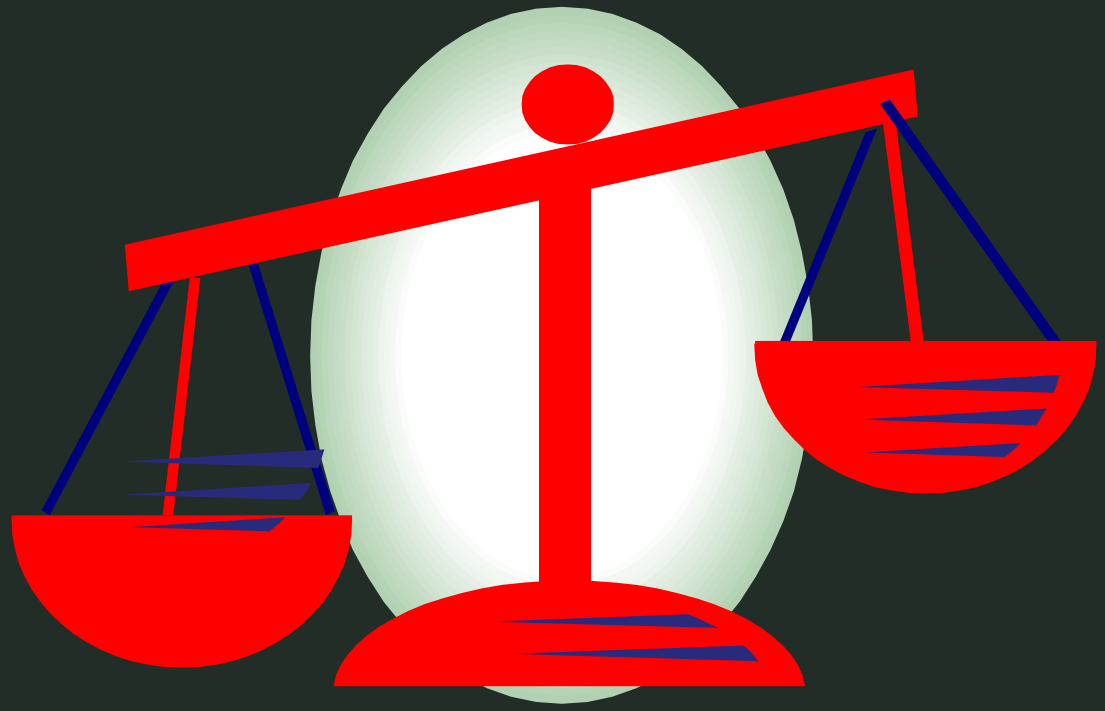
Interpretation
infarction and
cardiovascular

OPEN ACCESS

Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials

Eliano Pio Navarese,[1,2] Felicita Andreotti,[2,3] Volker Schulze,[1,2] Michalina Kołodziejczak,[1,2,4] Antonino Buffon,[3,2] Marc Brouwer,[5,2] Francesco Costa,[6] Mariusz Kowalewski,[2,7] Gianfranco Parati,[8] Gregory Y H Lip,[9,2] Malte Kelm,[1,2] Marco Valgimigli[6]



Haemorragic risk **Thrombotic risk**

Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

Novara 7 Giugno 2018

Definitions

a) stented stable coronary disease

b) acute coronary syndromes

Gestione della DAPT nel primo anno dopo SCA o PCI :
bastano le attuali Linee Guida ?

Novara 7 Giugno 2018

a) stented stable coronary disease

Considerations

- **stent-related strategy (neither disease nor patient)**
- **clopidogrel only available (beyond clopidogrel ?)**
- **duration of treatment**

Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

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The future

Trial	Population	Reference Tx	Experimental Tx	1° E-point
GLOBAL LEADERS 16,000 pts	All-comers PCI (stable pts)	12 M asa+clopidogrel + 24 M asa (stable pts)	1 M asa+ticagrelor + 23 M ticagrelor	2 year death/MI
TWILIGHT 9,000 pts	All-comers PCI (h-risk stable)	15 M asa+ticagrelor	3 M asa+ticagrelor + 12 M ticagrelor	BARC bleeding
ALPHEUS 1,900 pts	Stable pts PCI	30-D asa+clopidogrel	30-D asa+ticagrelor	48h ischemic episodes

Dual antiplatelet therapy duration and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with stable CAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type.	I	A
Irrespective of the intended DAPT duration, DES is the preferred treatment option.	I	A
In patients with stable CAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT for 3 months should be considered*.	IIa	B
In patients with stable CAD treated with drug-coated balloon, DAPT for 6 months should be considered.	IIa	B

*:The evidence supporting this recommendation comes from two studies where zotarolimus-eluting Endeavour sprint stent has been investigated in conjunction with a 3-month DAPT regimen.

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 and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention *(continued)*

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Recommendations	Class	Level
In patients with stable CAD treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C
In patients with stable CAD who have tolerated DAPT without a bleeding complication and who are at low bleeding but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and ≤30 months may be considered.	IIb	A
In patients with stable CAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month may be considered*.	IIb	C

*;1-month DAPT after implantation of zotarolimus-eluting Endeavour sprint stent or drug coated stent reduced risks of reintervention, myocardial infarction and inconsistently of stent thrombosis compared to bare-metal stent under similar DAPT duration. It is unclear if this evidence applies to other contemporary DES.

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Gestione della DAPT nel primo anno dopo SCA o PCI :
bastano le attuali Linee Guida ?

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DAPT administration after stenting

with respect to the recommemded time

Short		Prolonged
?	stent thrombosis	
?	MACCE*	
reduced ?	bleeding	

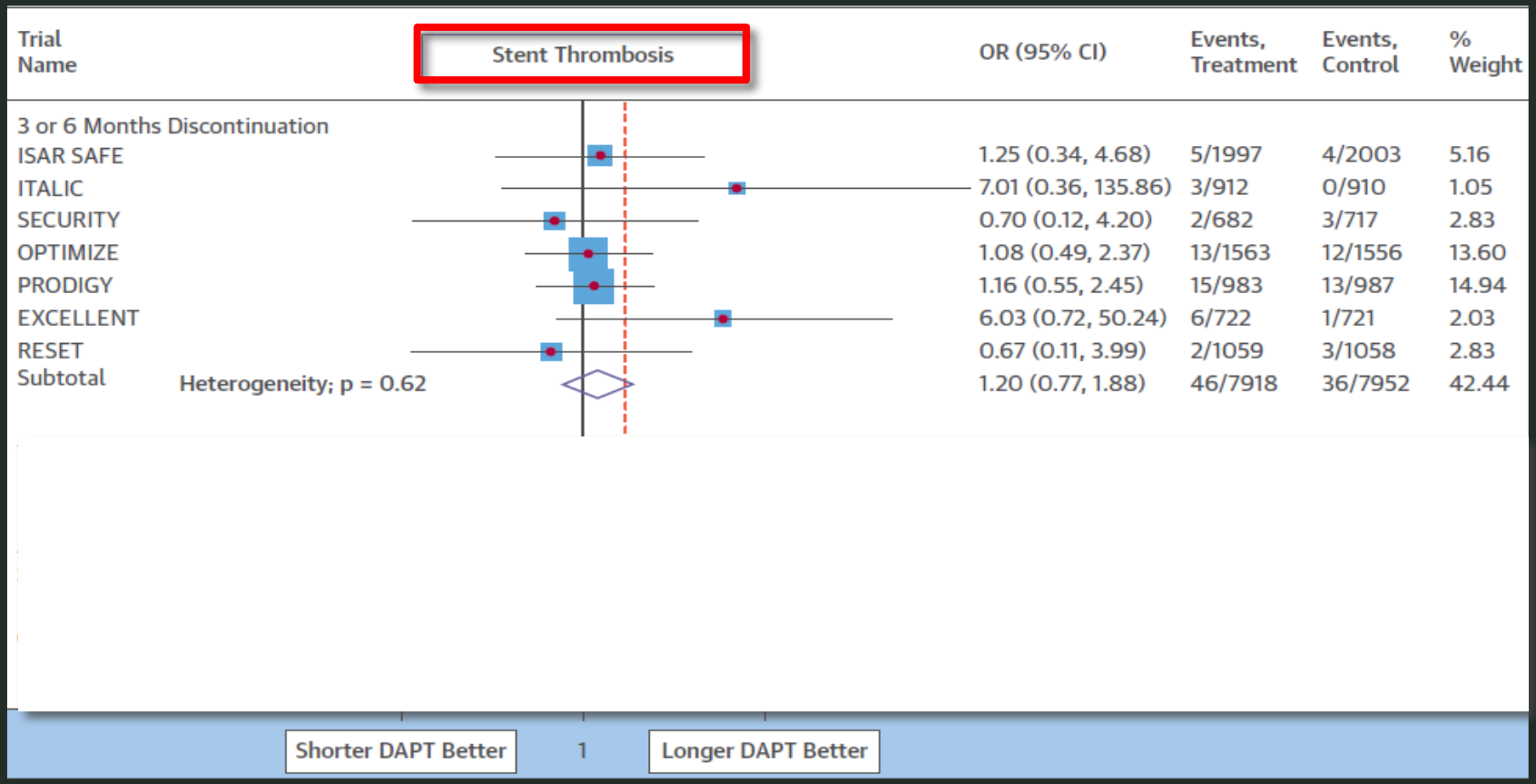
* = mortality (total, CV, non-CV), MI, stroke

Randomized Trials of DAPT Duration (DES stents)

Trial	Pts N°	Months	Randomization	Design	% ACS	1° EP
Abbreviated DAPT		*Plus a 3M washout				
EXCELLENT	1,443	6 vs. 12	asa vs. asa + clop	Noninferiority	52	D/MI/TVR
ISAR-SAFE	4,000	6 vs. 12*	asa vs. asa + clop	Noninferiority	40	D/MI/CVA/ST, Bleed
ITALIC	3,700	6 vs. 12	asa vs. asa + clop	Noninferiority	24	D/MI/CVA/Rev/MB
OPTIMIZE	3,120	3 vs. 12	asa vs. asa + clop	Noninferiority	32	D/MI/CVA/MB
RESET	2,148	3 vs. 12	asa vs. asa + clop	Strategy	54	CVD/MI/ST/TVR, Bleed
SECURITY	1,399	6 vs 12	asa vs. asa + clop	Noninferiority	38	CD/MI/CVA/ST, Bleed

Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

Novara 7 Giugno 2018



Giustino G et al JACC 2015;65:1298-1310

LOV 2015

Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

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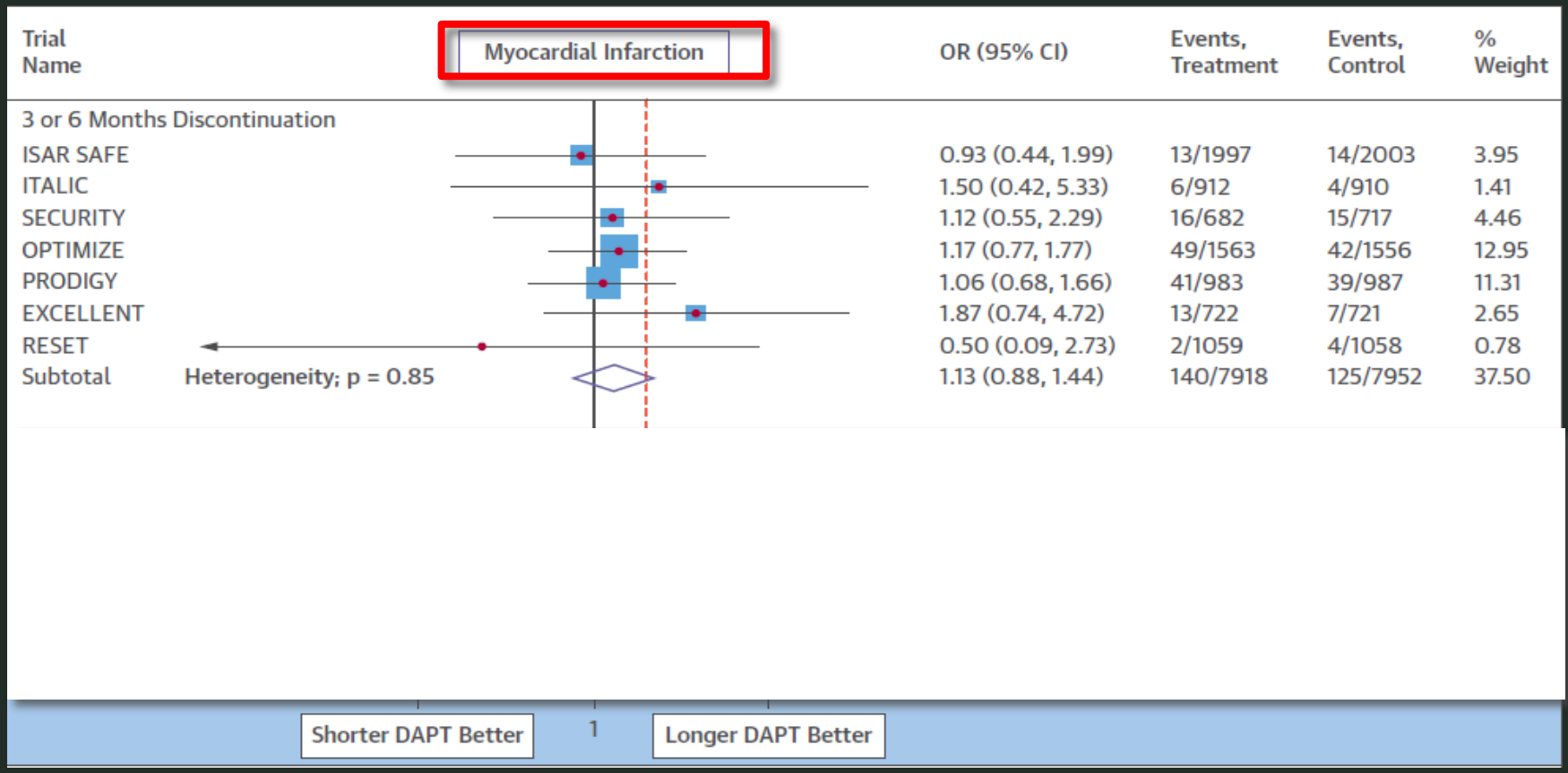

LOV 2015

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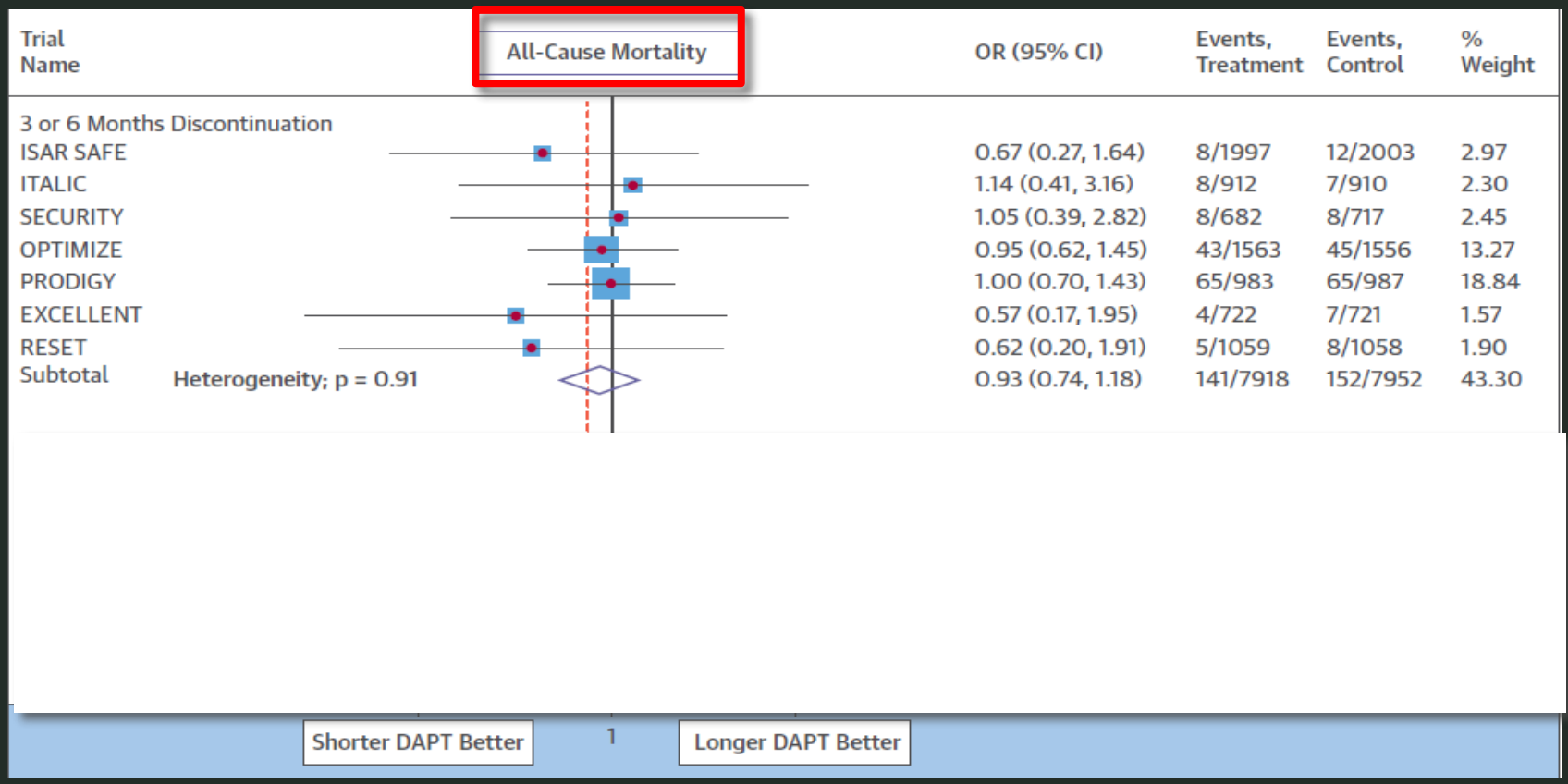
Novara 7 Giugno 2018



LOV 2015

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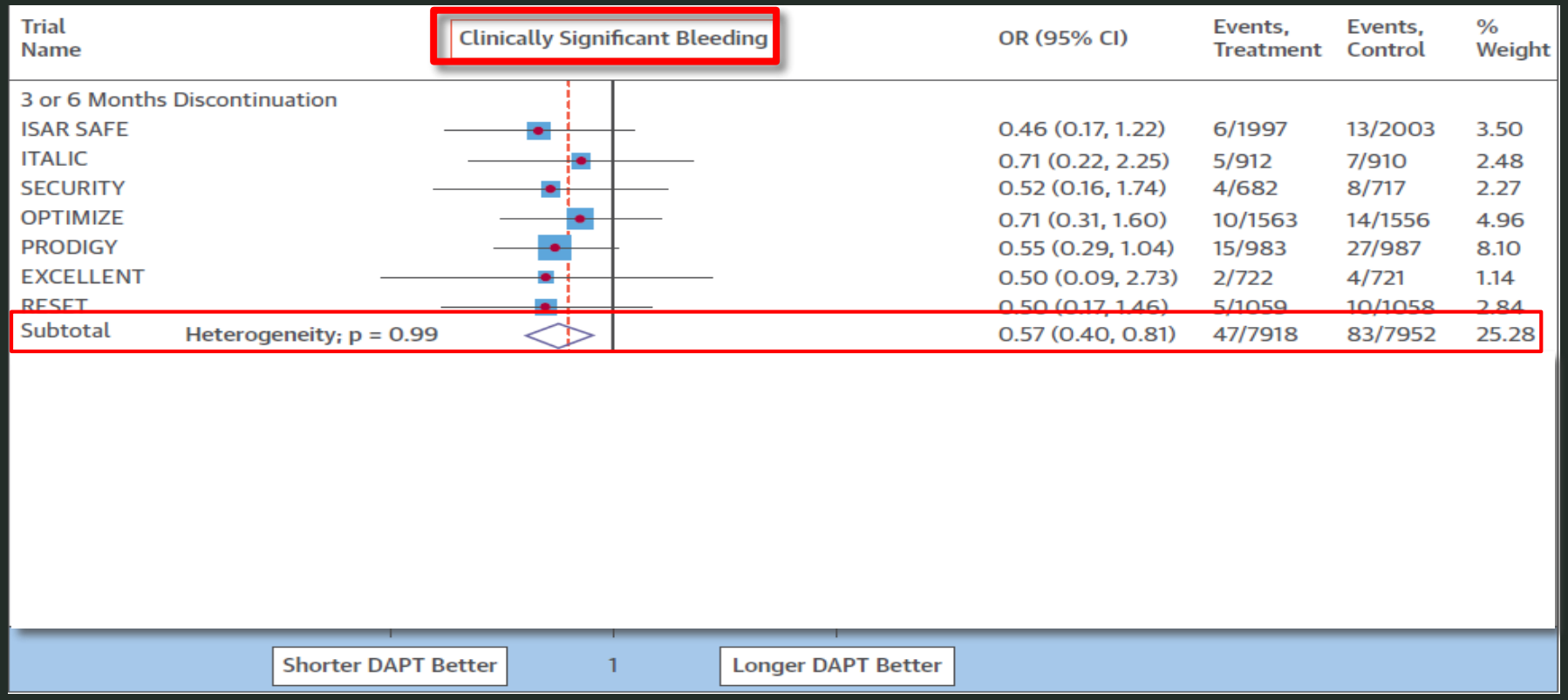
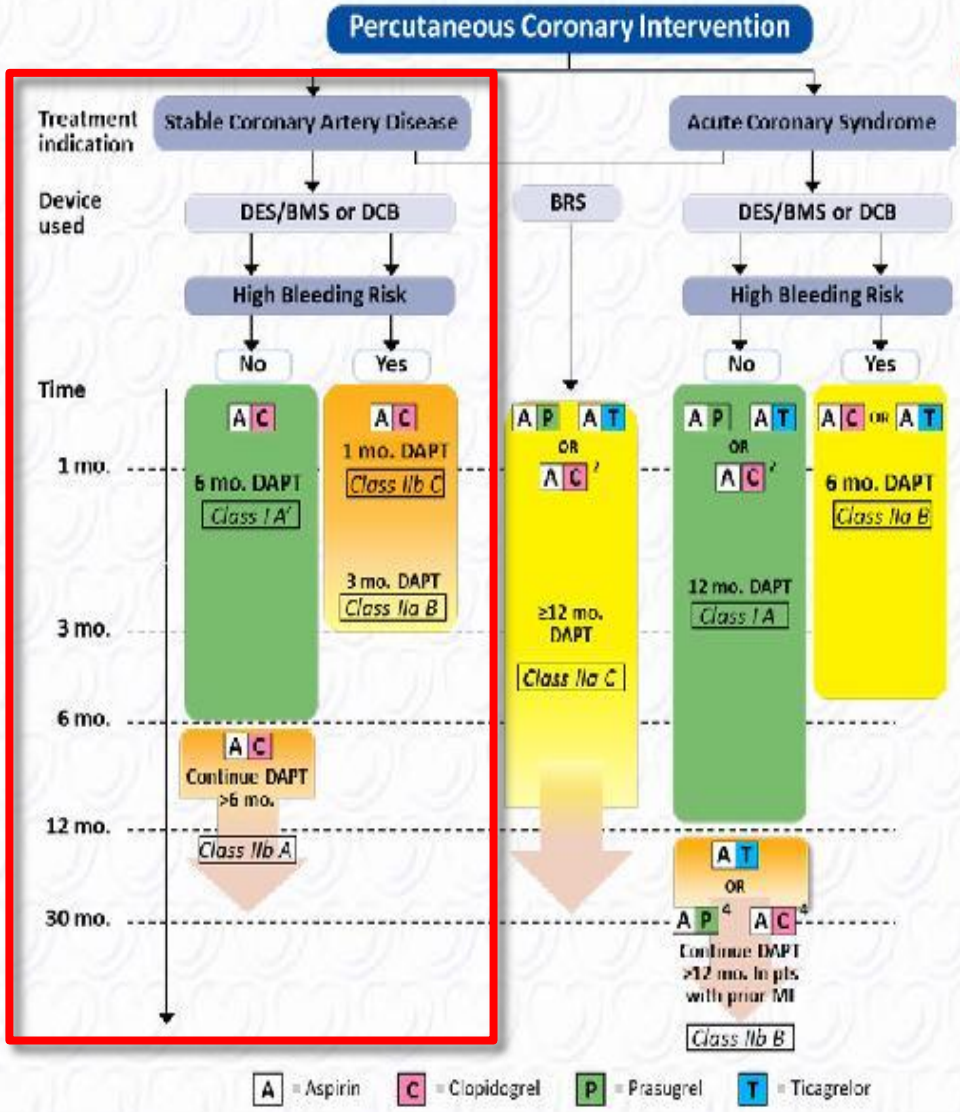
Novara 7 Giugno 2018



LOV 2015

Giustino G et al JACC 2015;65:1298-1310

Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention



ESC European Society of Cardiology

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

Compared to 12 months of DAPT administration

short		prolonged
unchanged	stent thrombosis	
unchanged	MACCE*	
reduced	bleeding	

* = mortality (total, CV, non-CV), MI, stroke

Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

Novara 7 Giugno 2018

Definitions

a) stented stable coronary disease

b) acute coronary syndromes

b) acute coronary syndromes

Considerations

- not stent-related strategy (?)
- not only clopidogrel available
- duration of treatment

Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

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The question is : how long ?

Reducing or prolonging the recommended period of treatment ?

$P2Y_{12}$ inhibitor selection and timing

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Recommendations	Class	Level
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contra-indications.	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high-risk of life-threatening bleeding or other contra-indications.	I	B

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

$P2Y_{12}$ inhibitor selection and timing *(continued)*

ESC European Society of Cardiology

Recommendations	Class	Level
Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC.	I	A
Clopidogrel (300 mg loading dose in patients ≤75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis.	I	A

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(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

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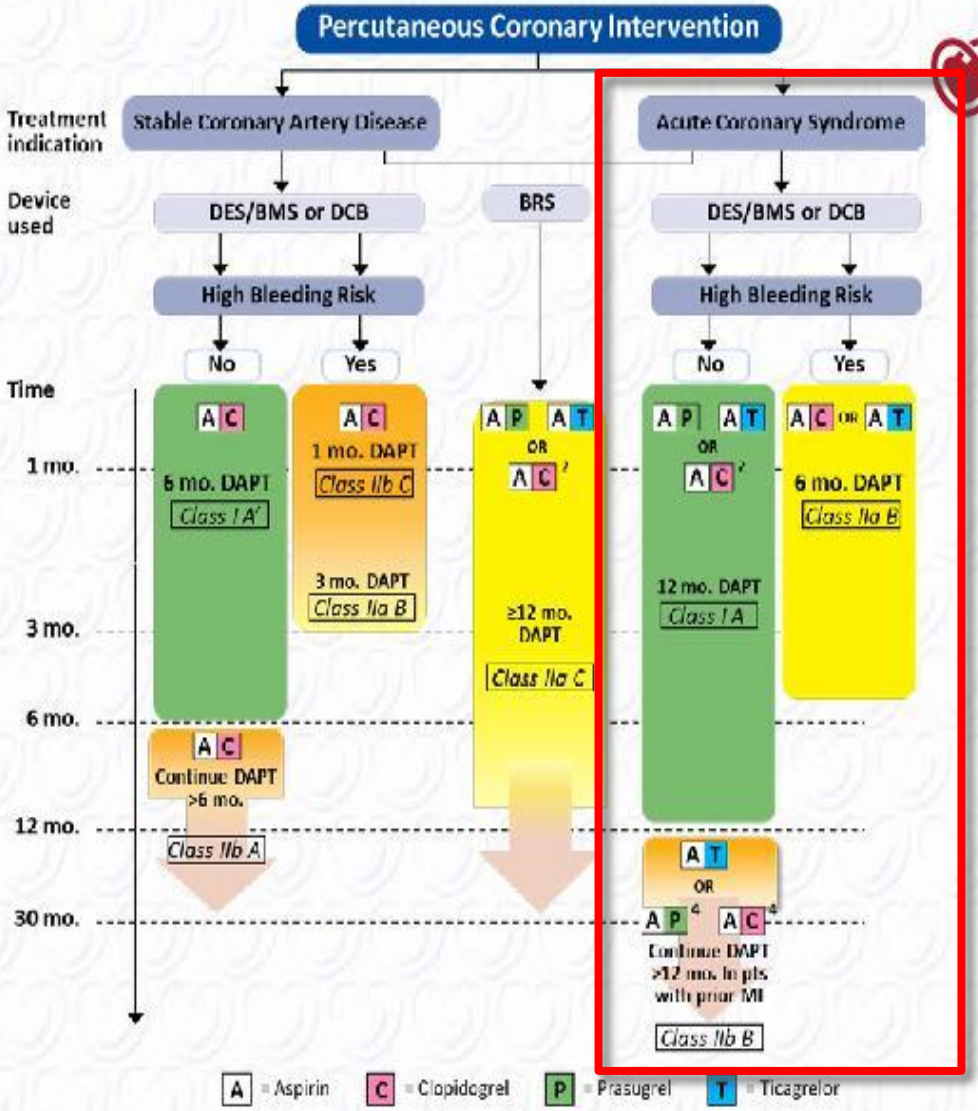
Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention



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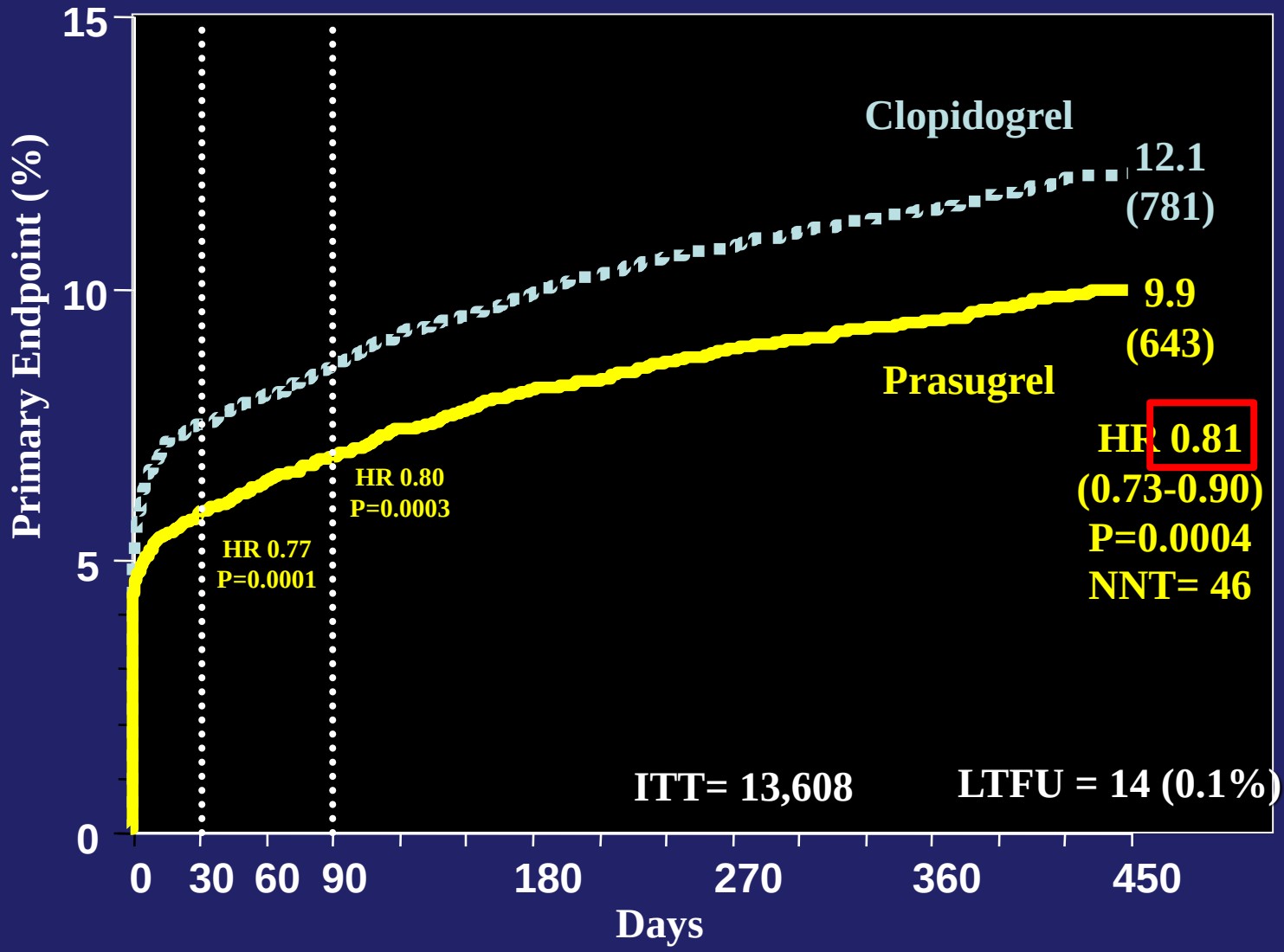
Nuovi antiaggreganti orali : prasugrel – evidenze cliniche di efficacia

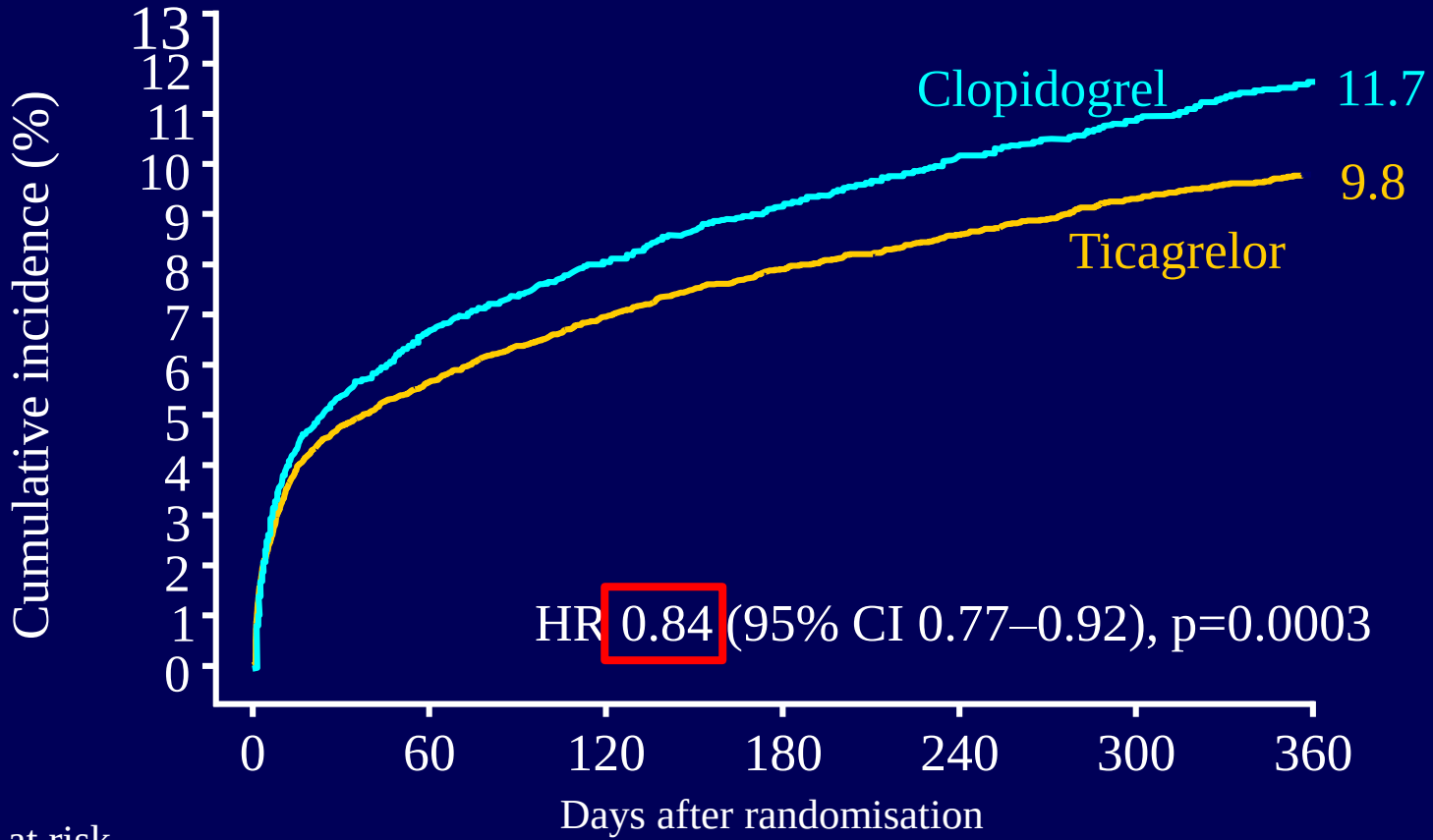
TRITON TIMI-38

Primary Endpoint CV Death,MI,Stroke



K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

PLATO

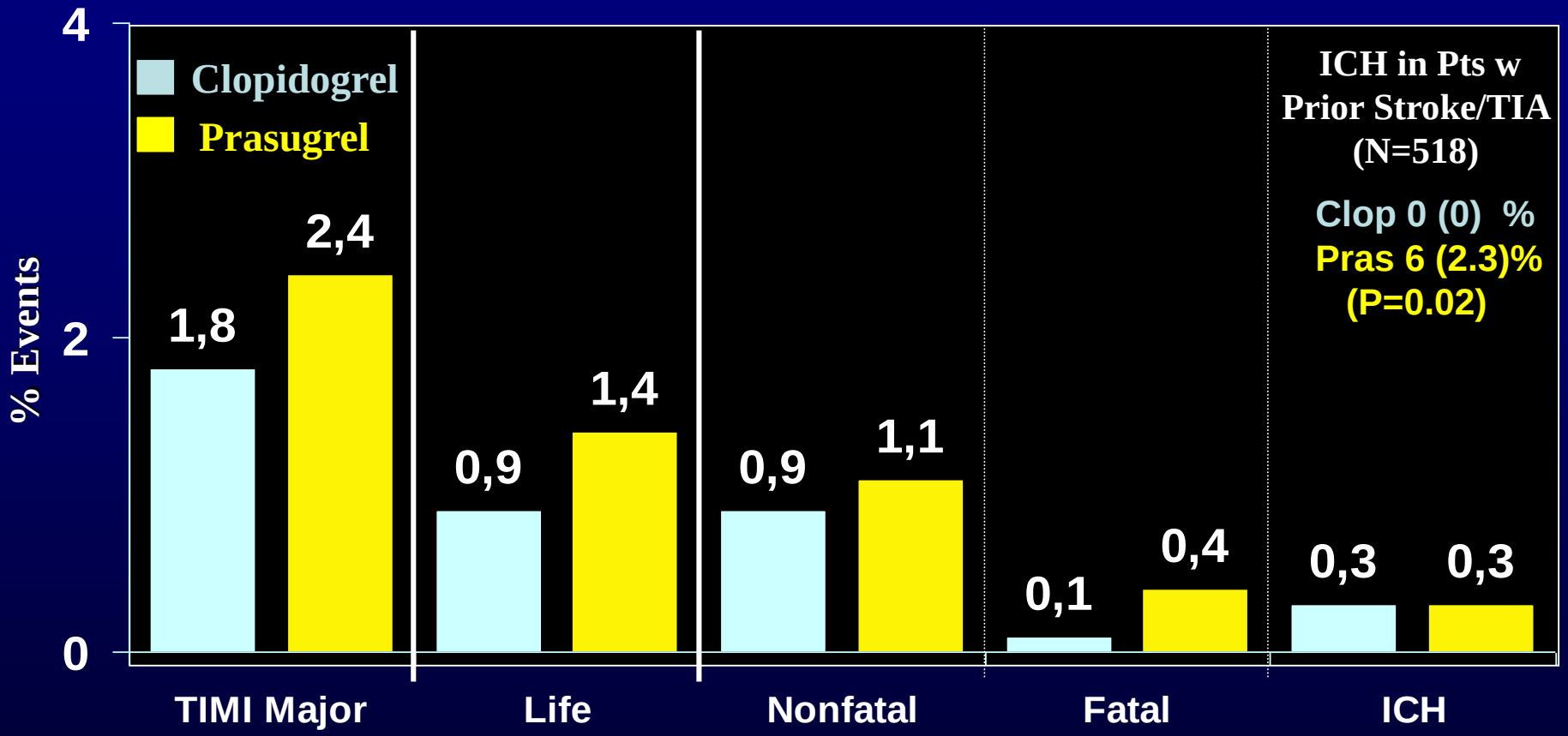


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

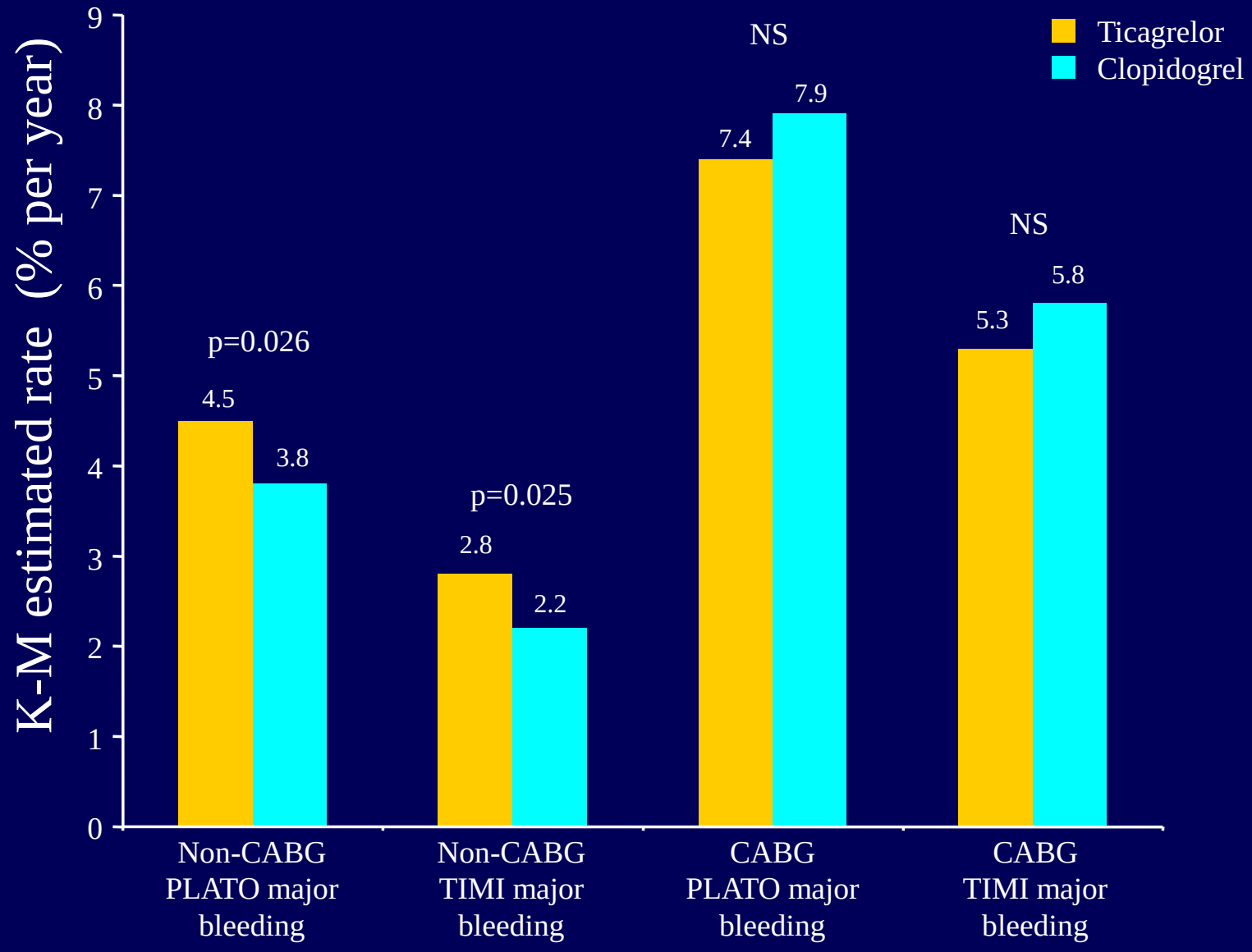
TRITON TIMI·38

Bleeding Events
Safety Cohort
(N=13,457)



Non-CABG and CABG-related major bleeding

PLATO

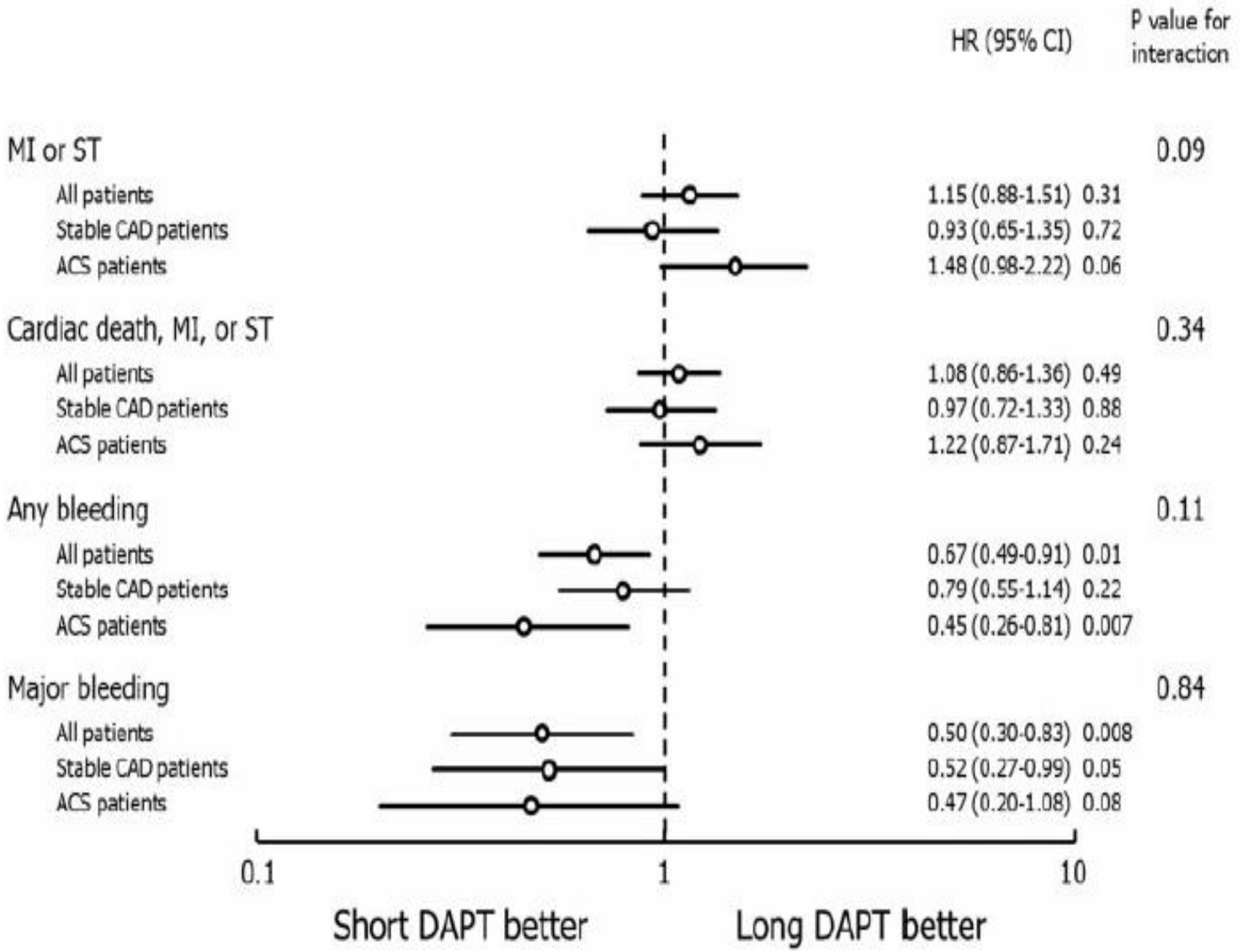


CURE – Safety
Bleeding complications

	Clopidogrel + standard therapy including ASA (%)	Standard therapy alone including ASA (%)
Major	3.7	2.7*
life-threatening	2.2	1.8
non-life-threatening	1.5	0.9**
Transfusion	2.8	2.2***

The CURE Investigators. *N Eng J Med* August 2001
Data on file

*p=0.001; **p=0.002; ***p=0.02



Palmerini T et al EurHJ 2017;38:1034-1043

Randomized Trials of DAPT Duration (DES stents)

Trial	Pts N°	Months	Randomization	Design	% ACS	1° EP
Abbreviated DAPT		*Plus a 3M washout				
EXCELLENT	1,443	6 vs. 12	asa vs. asa + clop	Noninferiority	52	D/MI/TVR
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ITALIC	3,700	6 vs. 12	asa vs. asa + clop	Noninferiority	24	D/MI/CVA/Rev/MB
OPTIMIZE	3,120	3 vs. 12	asa vs. asa + clop	Noninferiority	32	D/MI/CVA/MB
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Gestione della DAPT nel primo anno dopo SCA o PCI : bastano le attuali Linee Guida ?

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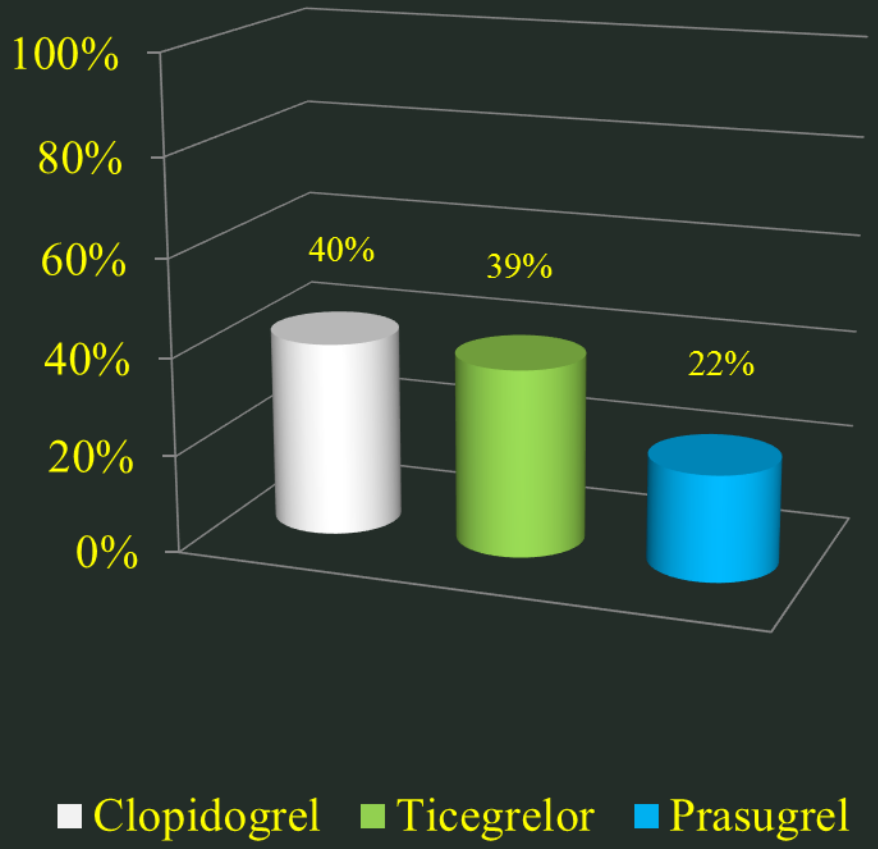
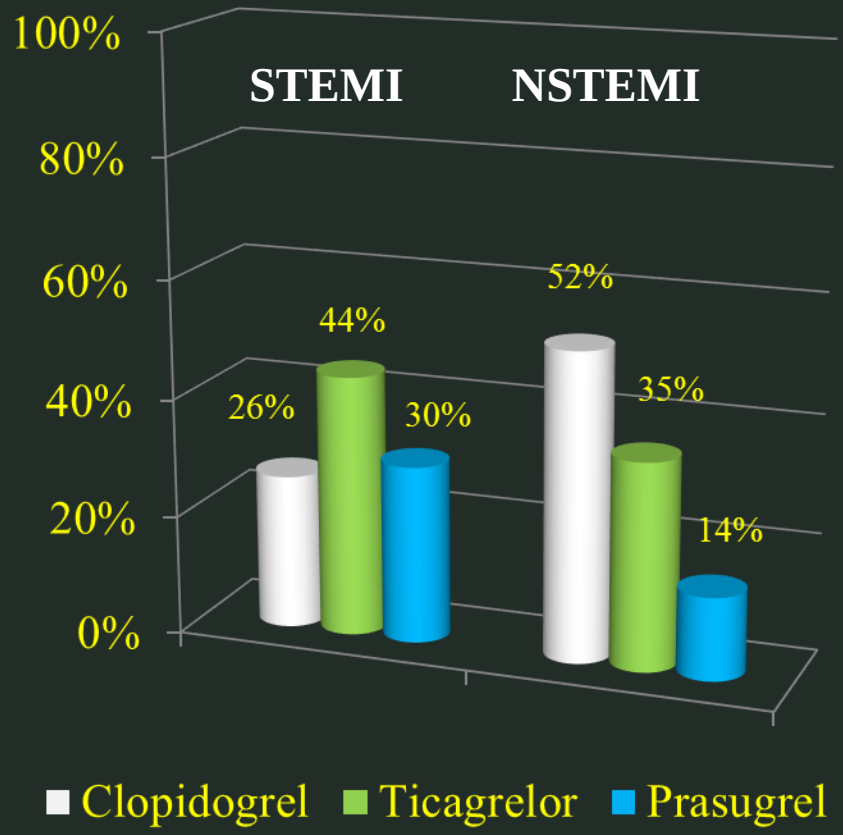
Optimal duration of antiplatelet treatment after DES (or ACS)

What to do ?

Il progetto SCA e Diabete :
dal documento di consenso al Registro GISE

Inibitori P2Y12 alla dimissione
(89% dei pazienti)





Gestione della DAPT nel primo anno dopo SCA o PCI :
bastano le attuali Linee Guida ?

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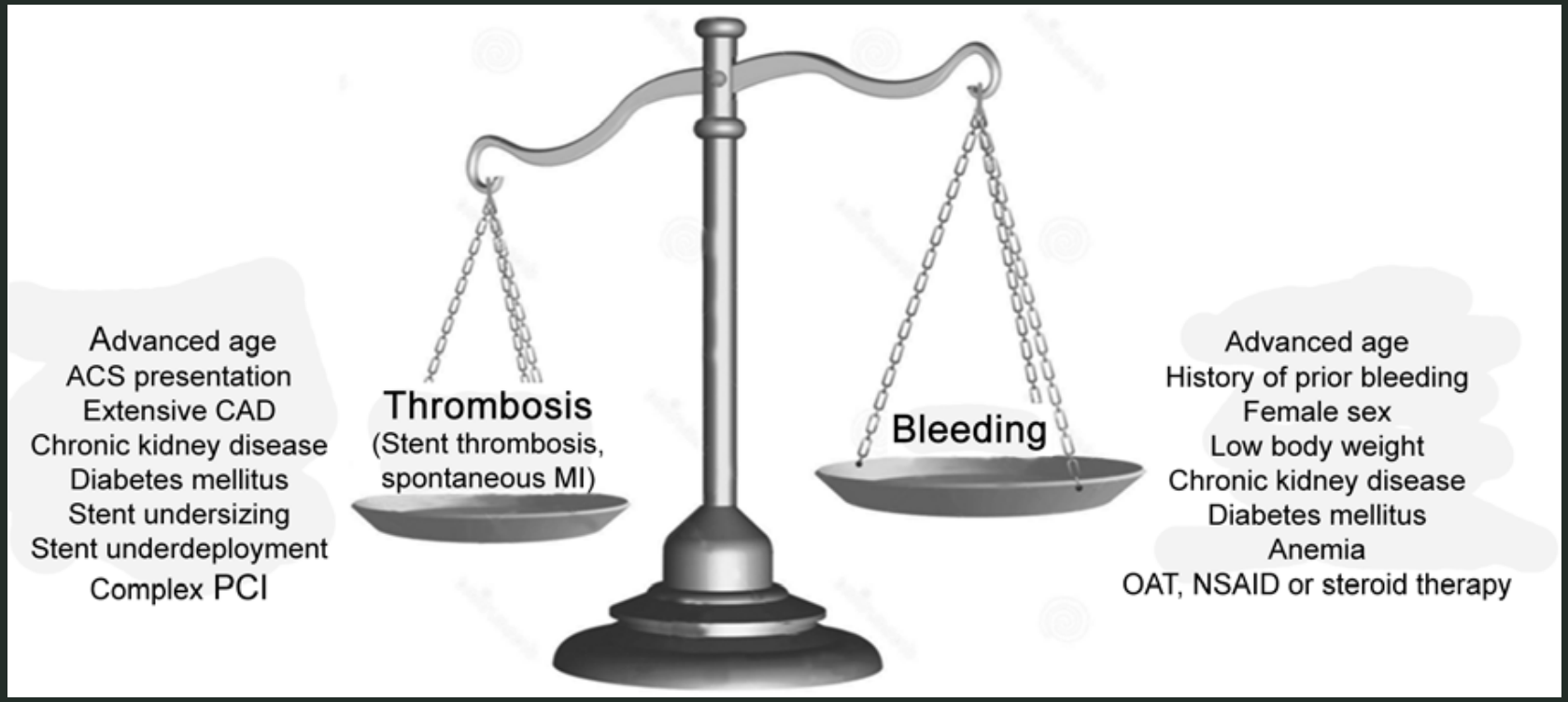
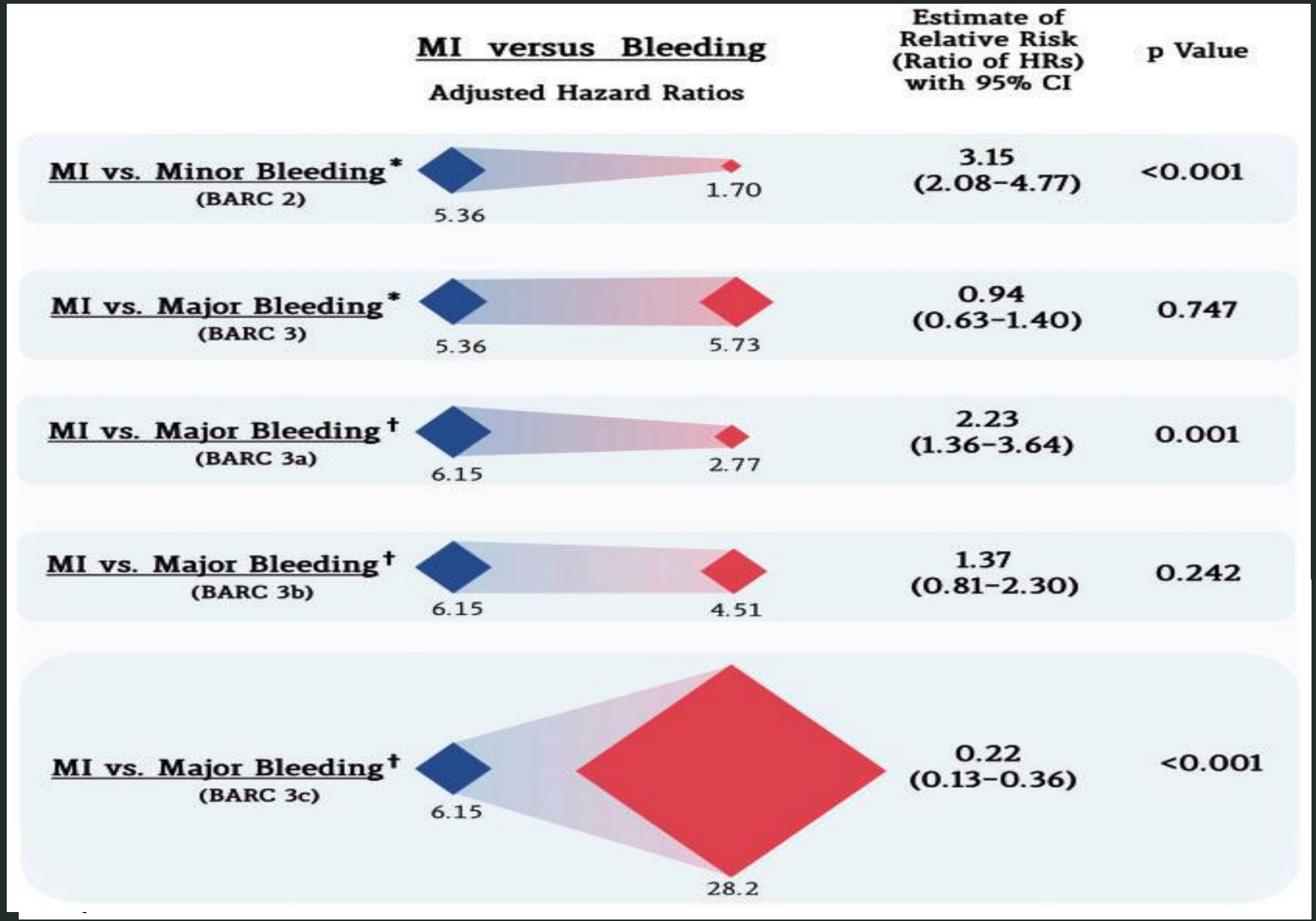
Optimal duration of antiplatelet treatment after DES (or ACS)

Changing the perspective :

“treat the patient not the stent”



Levine GN et al Circulation 2017;135:2451-2453



TRACER NSTEMI 12.944 pts

Valgimigli M et al. EurHJ 2017; 38:804-810

Risk scores validated for dual antiplatelet therapy duration decision-making

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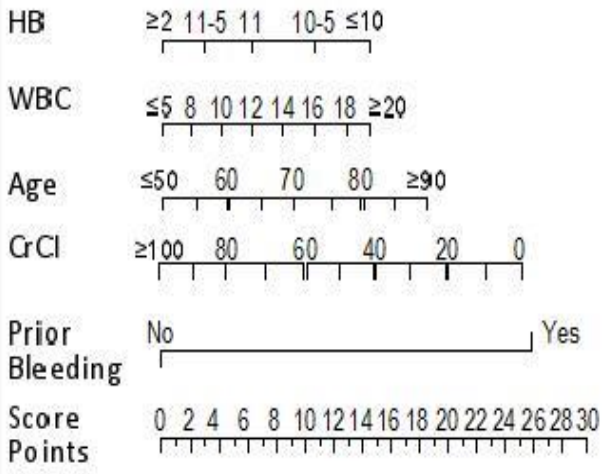
	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 to <75 <65 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	

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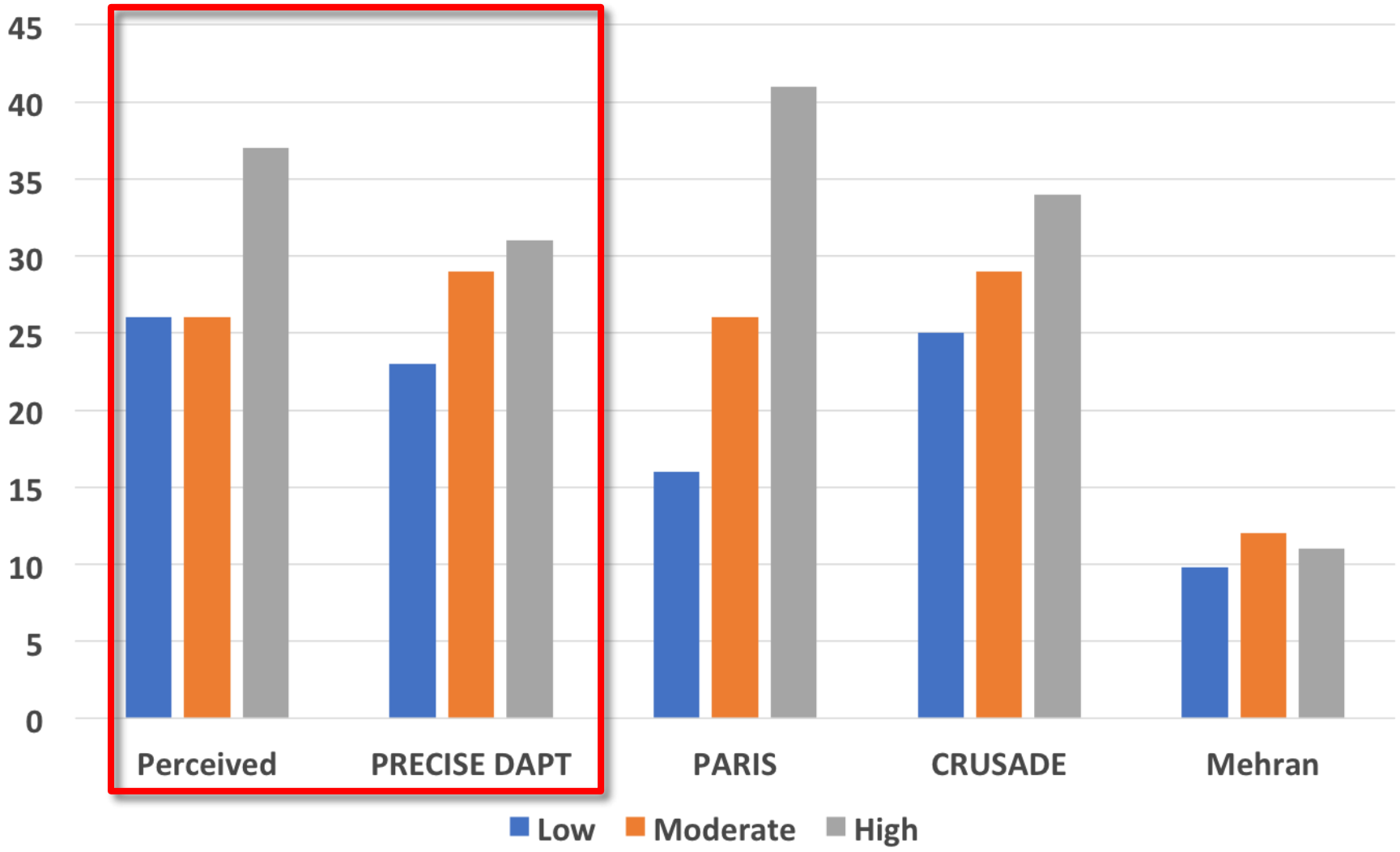
Short DAPT


45
40
35
30
25
20
15
10
5
0
Perceived
PRECISE DAPT
PARIS
CRUSADE
Mehran
Low
Moderate
High

DAPT STUDY

ORIGINAL ARTICLE

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*

Dual Antiplatelet Therapy Beyond One Year After Drug-eluting Coronary Stent Procedures

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

on behalf of the Dual Antiplatelet Therapy (DAPT) Study Investigators

DAPT therapy (ACS patients)

Guidelines	Condition	Recommandation/ Evidence Level	Year	Duration
ESC	NSTEMI STEMI	I A I A	2015 2017	12 months 12 months
AHA/ACC	NSTEMI STEMI	I B I B	2014 2013	12 months 12 months

LOV 2017

Periprocedural and postprocedural antithrombotic therapyc in patients undergoing primary percutaneous coronary intervention

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STEMI ESC 2017

Recommendations	Class	Level
Antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.	IIb	A

www.escardio.org/guidelines 2017 ESC Guidelines for the Management of AMI-STEMI (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx095)

La durata della DAPT dopo SCA :

dallo stent al paziente

The question is : how long ?

Prolonging the recommended period of treatment ?

Randomized Trials of DAPT Duration (DES stents)

Trial	Pts N°	Months	Randomization	Design	1° EP
Abbreviated DAPT		*Plus a 3M washout			
EXCELLENT	1,443	6 vs. 12	asa vs. asa + clop	Noninferiority	D/MI/TVR
ISAR-SAFE	4,000	6 vs. 12*	asa vs. asa + clop	Noninferiority	D/MI/CVA/ST, Bleed
ITALIC	3,700	6 vs. 12	asa vs. asa + clop	Noninferiority	D/MI/CVA/Rev/MB
OPTIMIZE	3,120	3 vs. 12	asa vs. asa + clop	Noninferiority	D/MI/CVA/MB
RESET	2,148	3 vs. 12	asa vs. asa + clop	Strategy	CVD/MI/ST/TVR, Bleed
SECURITY	1,399	6 vs 12	asa vs. asa + clop	Noninferiority	CD/MI/CVA/ST, Bleed
Prolonged DAPT		*Plus a 3M washout			
REAL/ZEST Late	2,701	12 vs. 24	asa vs. asa + clop	Superiority	D/MI
DAPT	20,645	12 vs. 30*	asa vs. asa + clop (pras)	NI and Sup	D/MI/CVA/ST, Bleed
PRODIGY	1,800	6 vs. 24	asa vs. asa + clop	Superiority	D/MI/CVA
ARCTIC Interr	1,260	12 vs 18	asa vs. asa + clop	Superiority	D/MI/CVA/TVR/ST

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ISSN 0735-1097/$36.00

Extended duration dual antiplatelet therapy and mortality:

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwi
random

Tullio Palmerini, U
Myeong-Ki Hong,
Stefano De Servi,

Summary
Background D
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Nov 20, 2014,
implantation.
DAPT duration
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Findings We ide
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Interpretation
infarction and
cardiovascular

OPEN ACCESS

Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials

Eliano Pio Navarese,[1,2] Felicita Andreotti,[2,3] Volker Schulze,[1,2] Michalina Kołodziejczak,[1,2,4] Antonino Buffon,[3,2] Marc Brouwer,[5,2] Francesco Costa,[6] Mariusz Kowalewski,[2,7] Gianfranco Parati,[8] Gregory Y H Lip,[9,2] Malte Kelm,[1,2] Marco Valgimigli[6]

DAPT STUDY

ORIGINAL ARTICLE

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*

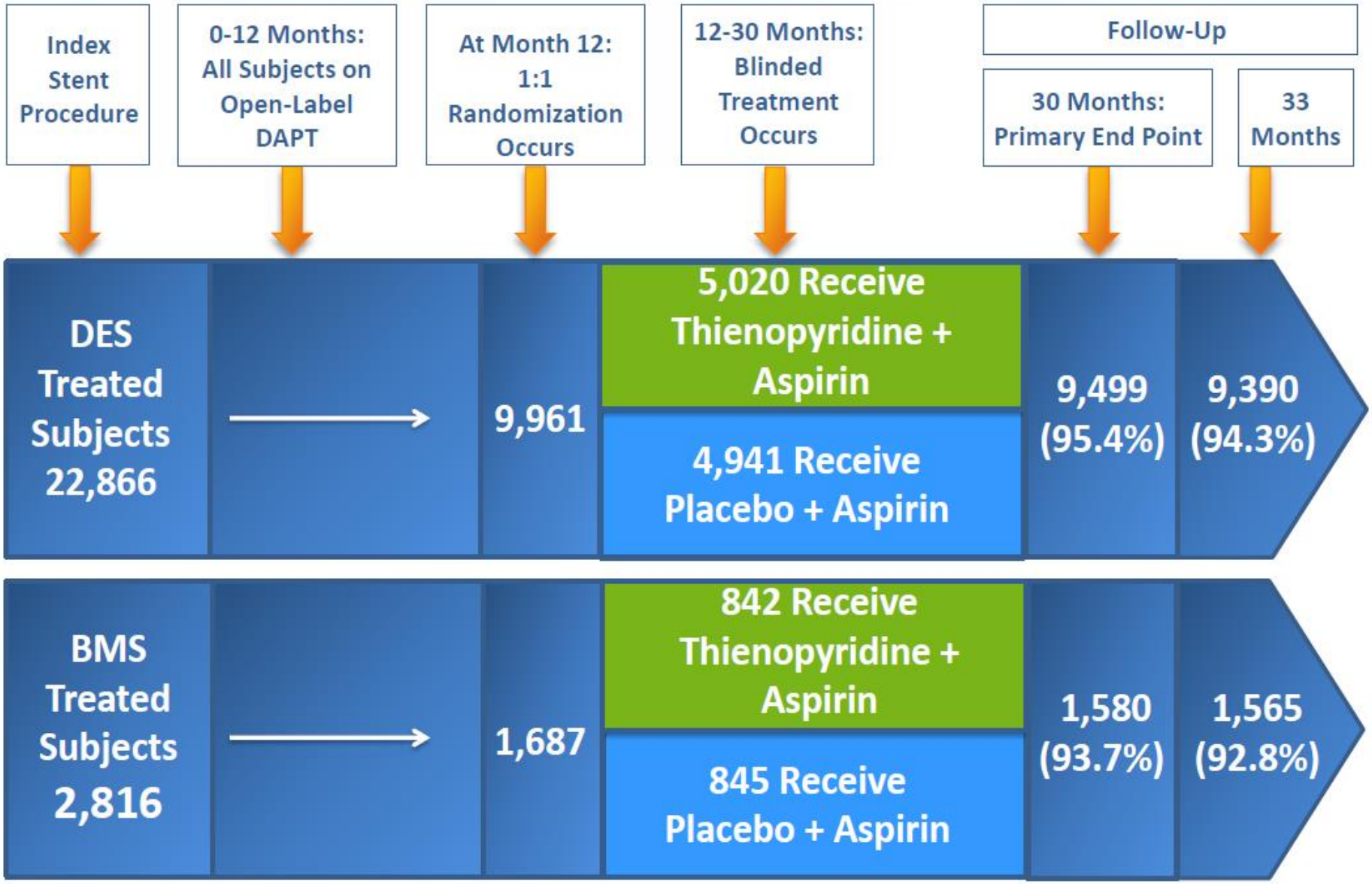
Dual Antiplatelet Therapy Beyond One Year After Drug-eluting Coronary Stent Procedures

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

on behalf of the Dual Antiplatelet Therapy (DAPT) Study Investigators

Subject Flow

DAPT STUDY



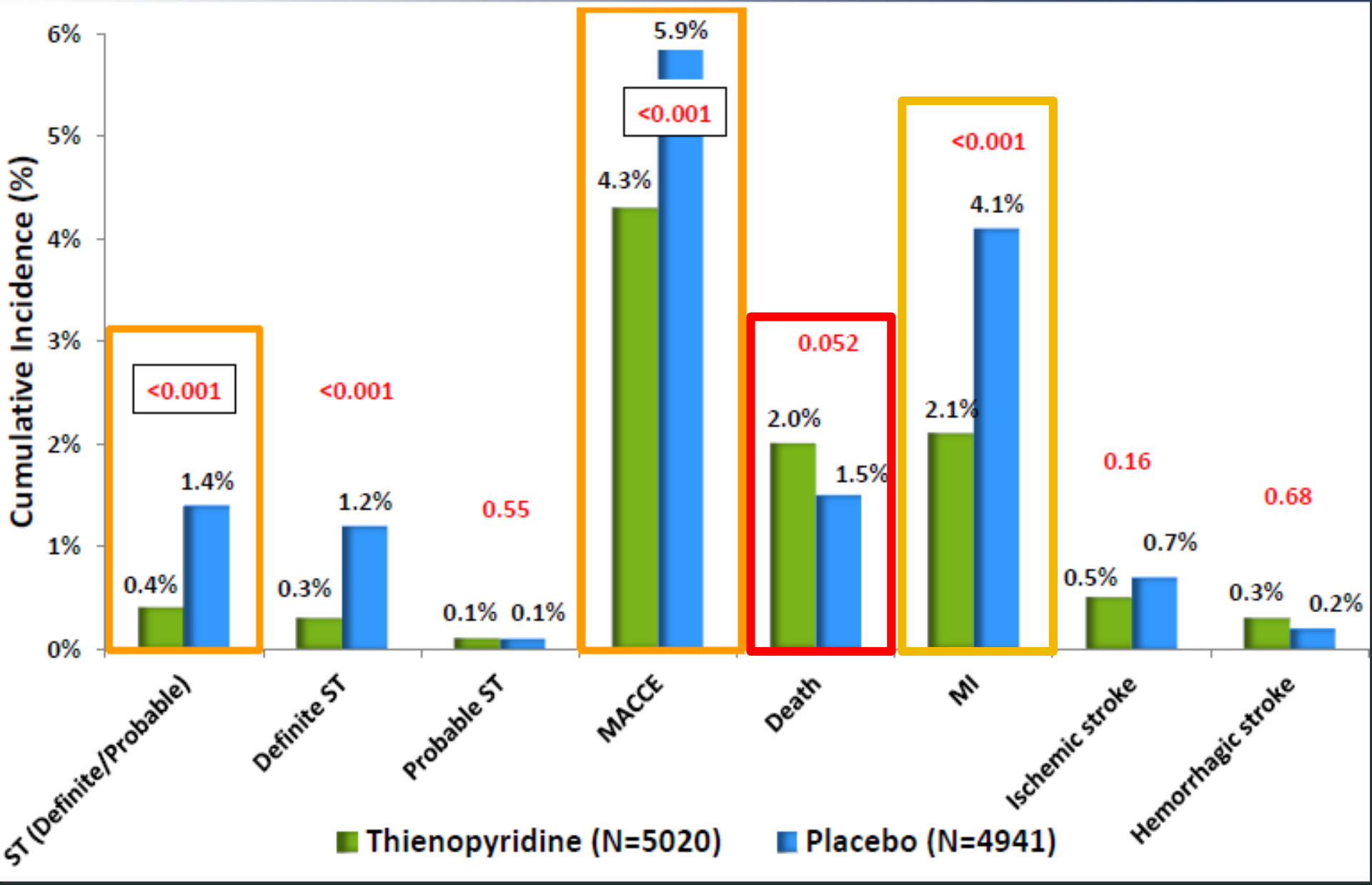
Baseline Demographics

DAPT STUDY

	Thienopyridine N=5020	Placebo N=4941	P-value
Age (years)	61.8	61.6	0.24
Female	24.7%	26.0%	0.15
Race – Non White	8.9%	8.6%	0.67
Ethnicity-Hispanic or Latino	3.2%	3.3%	0.91
Weight – kg	91.5	91.5	0.93
BMI	30.5	30.6	0.92
Diabetes Mellitus	31.1%	30.1%	0.28
Hypertension	75.8%	74.0%	0.03
Cigarette Smoker	24.6%	24.7%	0.91
Prior PCI	30.4%	31.0%	0.50
Prior CABG	11.3%	11.8%	0.49
NSTEMI	15.5%	15.5%	0.93
STEMI	10.6%	10.3%	0.65

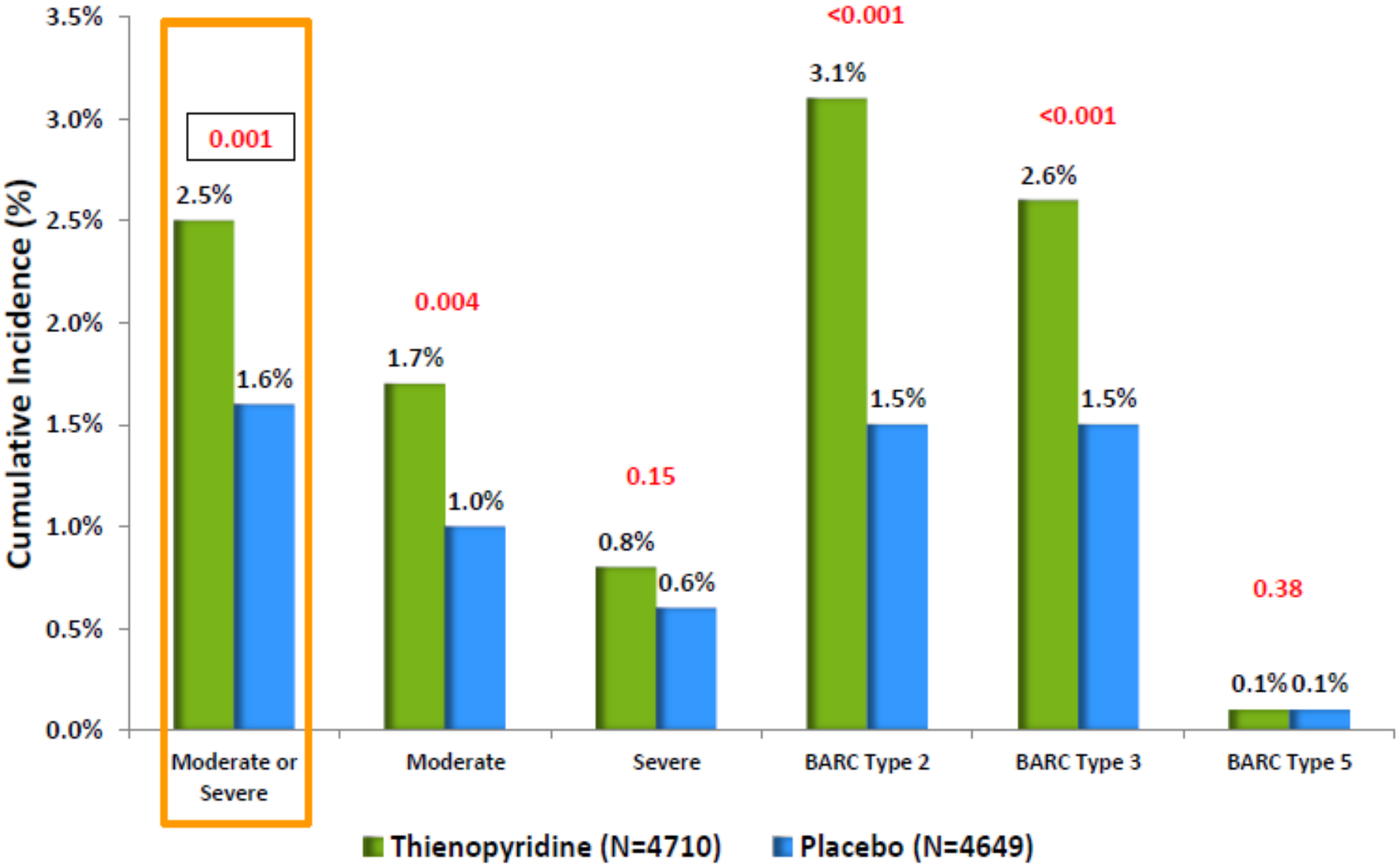
Co-Primary Effectiveness End Points & Components: 12-30 Months

DAPT STUDY



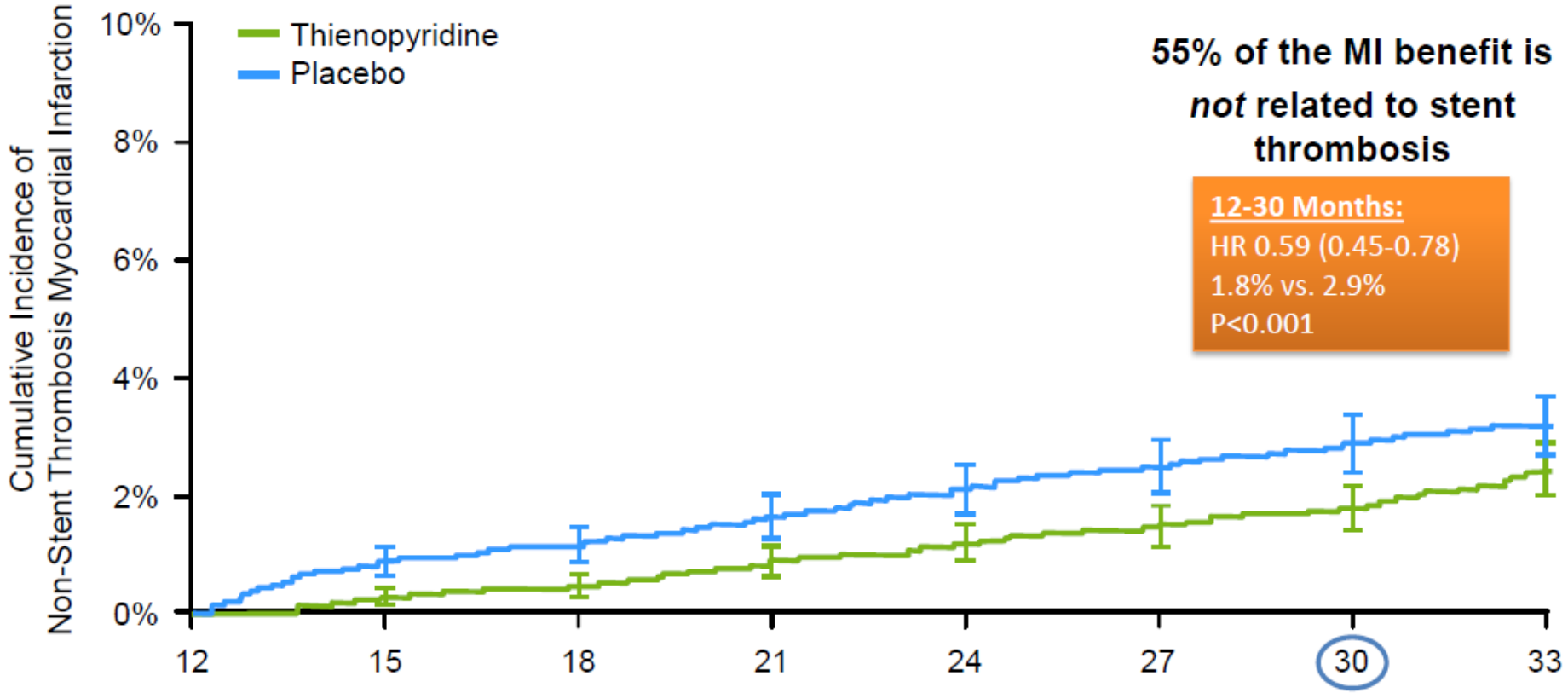
Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

DAPT STUDY



Non-Stent Thrombosis Myocardial Infarction

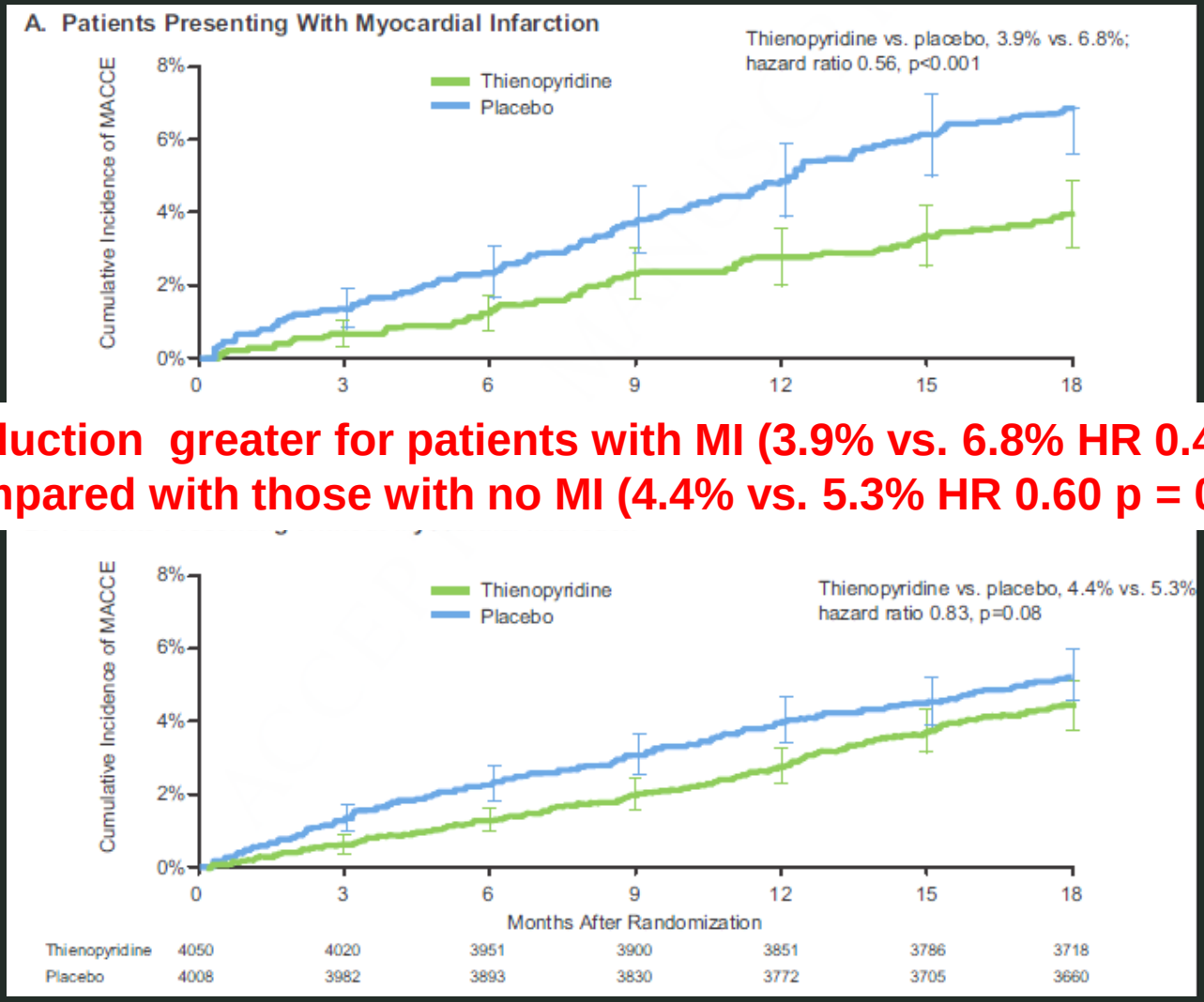
DAPT STUDY



55% of the MI benefit is *not* related to stent thrombosis

12-30 Months:
HR 0.59 (0.45-0.78)
1.8% vs. 2.9%
P<0.001

# At Risk								
Thienopyridine	5020	4920	4851	4792	4721	4641	4588	3066
Placebo	4941	4820	4751	4686	4607	4547	4491	3052



MACE reduction greater for patients with MI (3.9% vs. 6.8% HR 0.42 p < 0.001) compared with those with no MI (4.4% vs. 5.3% HR 0.60 p = 0.08)

Yeh RW, et al. J Am Coll Cardiol 2015;65:2211-2221

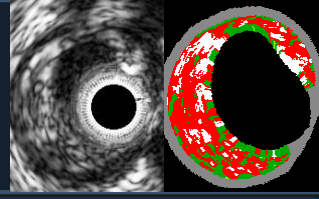
La durata della DAPT dopo SCA :

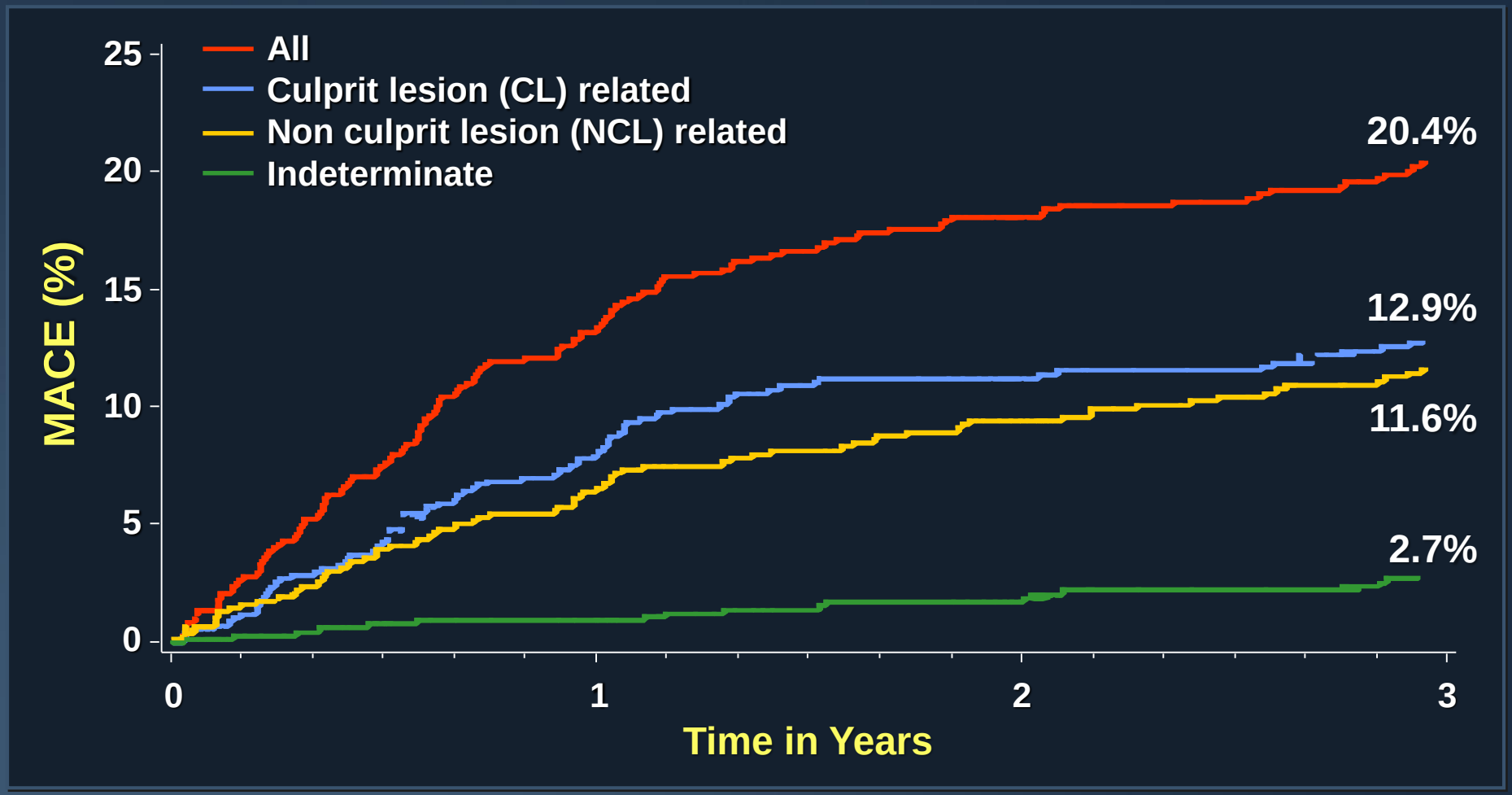
dallo stent al paziente

Changing the perspective :

“treat the patient not the stent”

PROSPECT: MACE (N=697)





Number at risk

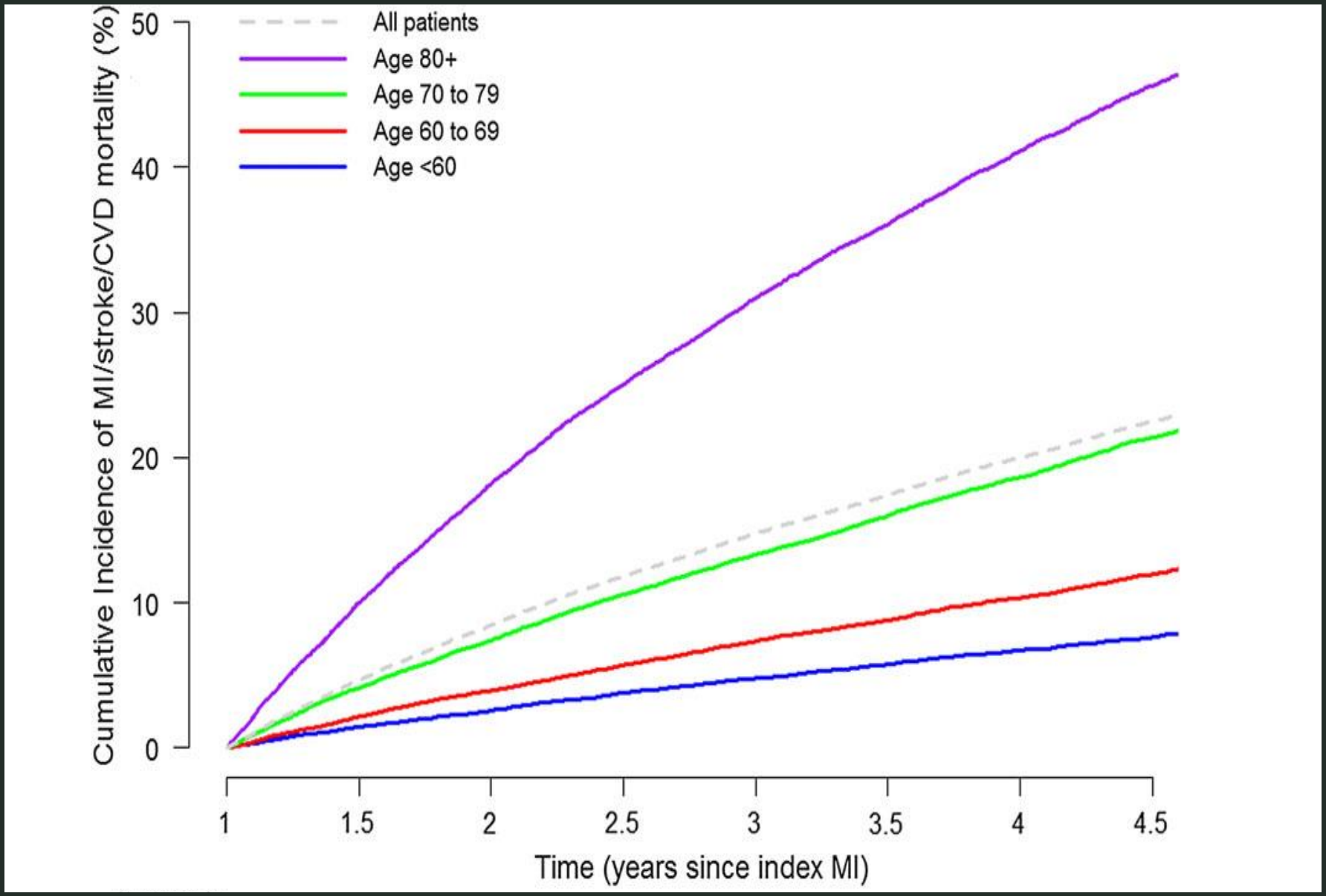
ALL	697	557	506	480
CL related	697	590	543	518
NCL related	697	595	553	521
Indeterminate	697	634	604	583

MACE = cardiac death, cardiac arrest, MI, or rehospitalization for unstable or progressive angina

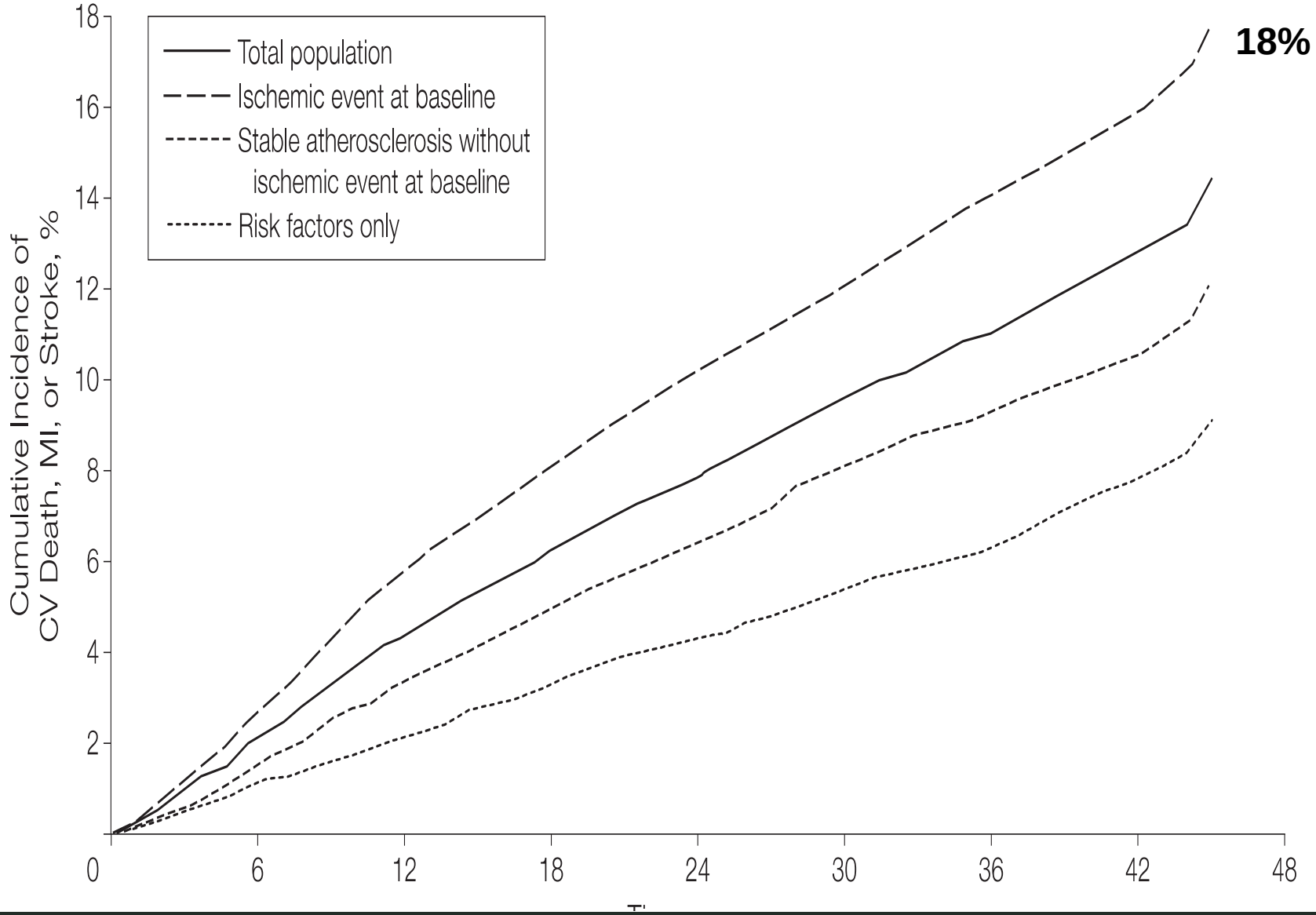
Long-term management post NSTE-ACS (1)

Recommendations	Class	Level
It is recommended to advise all patients on life style changes (including smoking cessation, regular physical activity and a healthy diet).	I	A
It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term.	I	A
An ACE inhibitor is recommended in patients with LVEF ≤40%, or heart failure, hypertension or diabetes, unless contraindicated. An ARB provides an alternative, particularly if ACE inhibitors are not tolerated.	I	A
Beta-blocker therapy is recommended in patients with LVEF ≤40%, unless contraindicated.	I	A

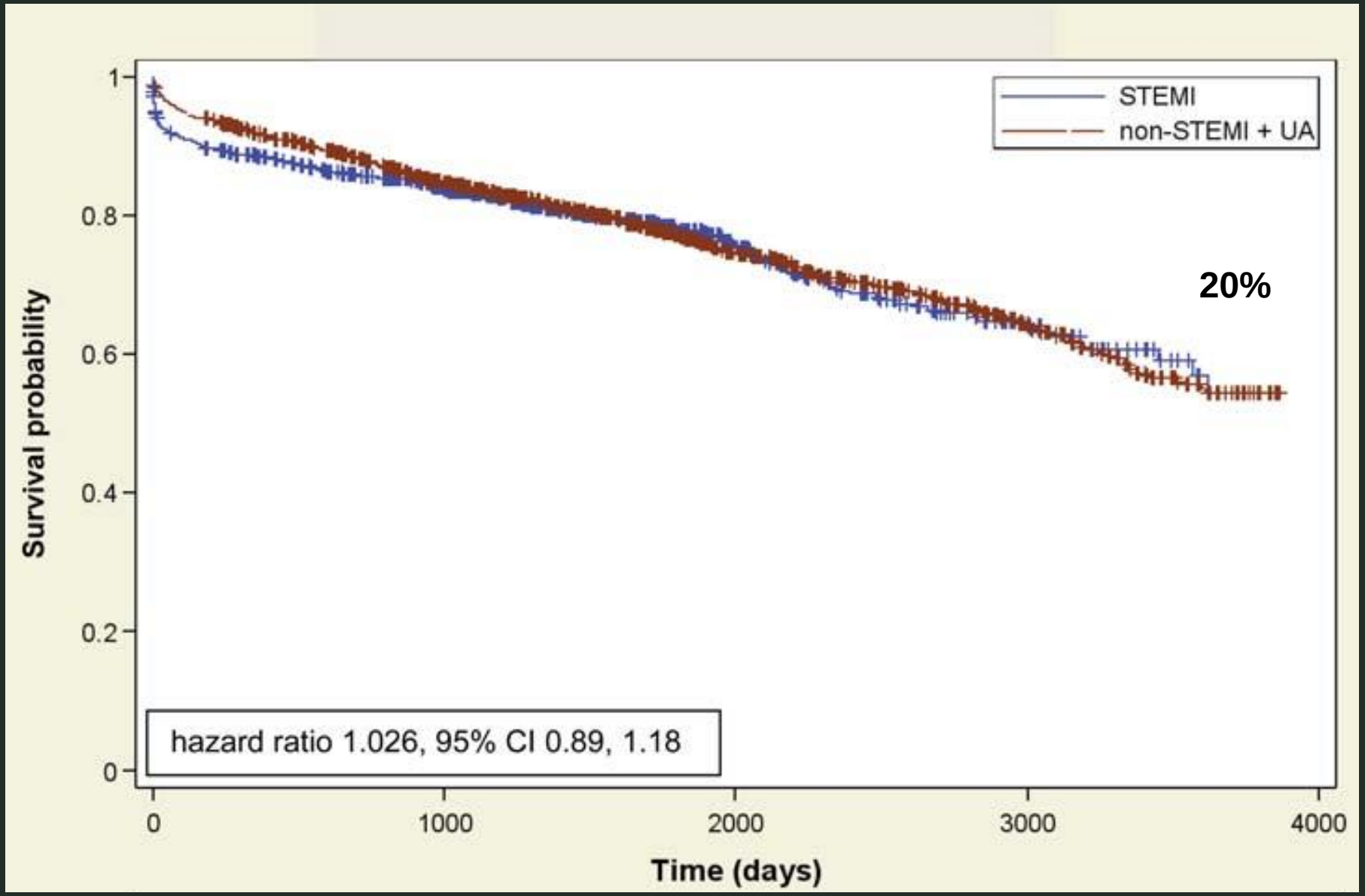
European Heart Journal 2016;37:267-315 - doi: 10.1093/eurheartj/ehv320



Jernberg T et al. EurHJ 2015; 36:1163-1170

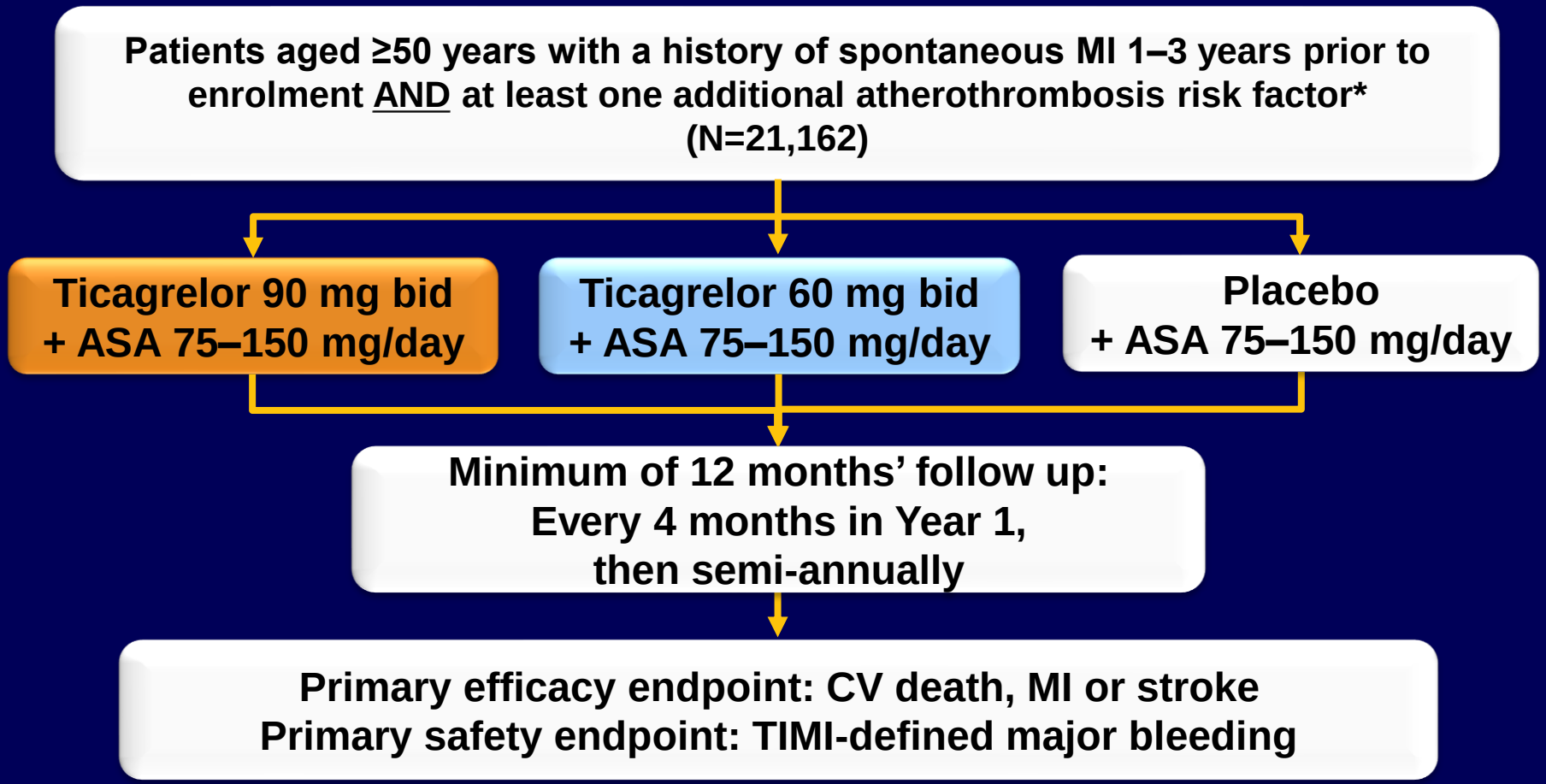


Bhatt DL et al. JAMA 2010;304:1350-1357



Fox KAA et al. EurHJ 2010;31:2755-2764

PEGASUS-TIMI 54: Study Design



*Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-end stage renal disease
bid, twice daily; CAD, coronary artery disease; TIMI, Thrombolysis in Myocardial Infarction

Bonaca MP *et al. Am Heart J* 2014;167:437–444
Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800

Key Inclusion & Exclusion Criteria

PEGASUS TIMI 54

TIMI

KEY INCLUSION

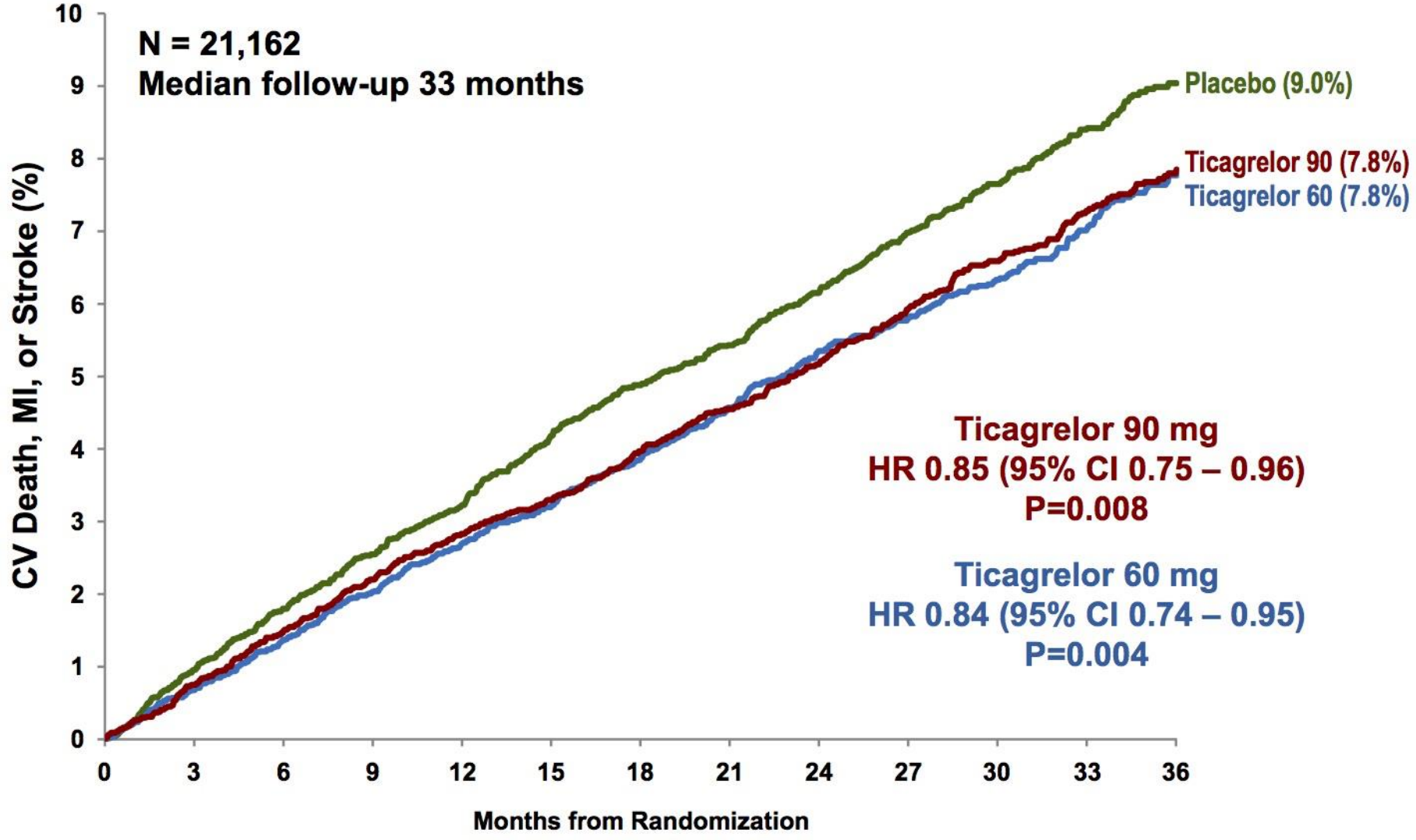
- Age ≥50 years
- At least 1 of the following:
  - Age ≥65 years
  - Diabetes requiring medication
  - 2nd prior MI (>1 year ago)
  - Multivessel CAD
  - CrCl <60 mL/min
- Tolerating ASA and able to be dosed at 75-150 mg/d

KEY EXCLUSION

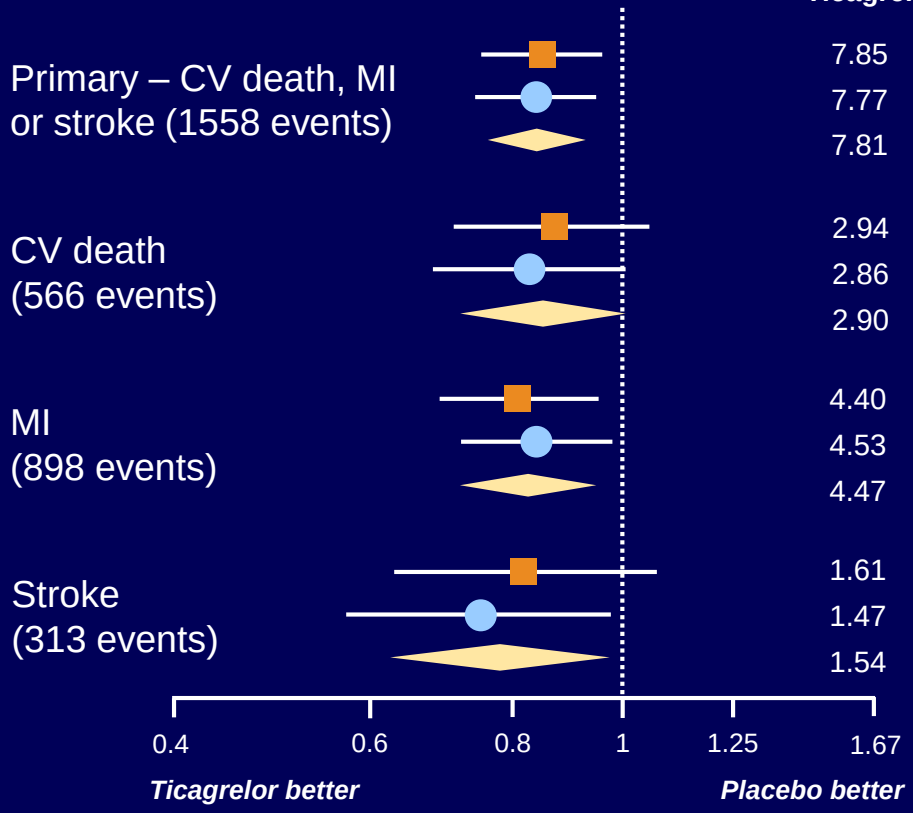
- Planned use of $P2Y_{12}$ antagonist, dipyridamole, cilostazol, or anticoag
- Bleeding disorder
- History of ischemic stroke, ICH, CNS tumor or vascular abnormality
- Recent GI bleed or major surgery
- At risk for bradycardia
- Dialysis or severe liver disease

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

Primary Endpoint



PEGASUS-TIMI 54: Efficacy Endpoints



Endpoint	3-year KM event rates (%) Ticagrelor	Placebo	HR (95% CI)	P value
Primary – CV death, MI or stroke (1558 events)	7.85	9.04	0.85 (0.75–0.96)	0.008
	7.77	9.04	0.84 (0.74–0.95)	0.004
	7.81	9.04	0.84 (0.76–0.94)	0.001
CV death (566 events)	2.94	3.39	0.87 (0.71–1.06)	0.15
	2.86	3.39	0.83 (0.68–1.01)	0.07
	2.90	3.39	0.85 (0.71–1.00)	0.06
MI (898 events)	4.40	5.25	0.81 (0.69–0.95)	0.01*
	4.53	5.25	0.84 (0.72–0.98)	0.03*
	4.47	5.25	0.83 (0.72–0.95)	0.005*
Stroke (313 events)	1.61	1.94	0.82 (0.63–1.07)	0.14*
	1.47	1.94	0.75 (0.57–0.98)	0.03*
	1.54	1.94	0.78 (0.62–0.98)	0.03*

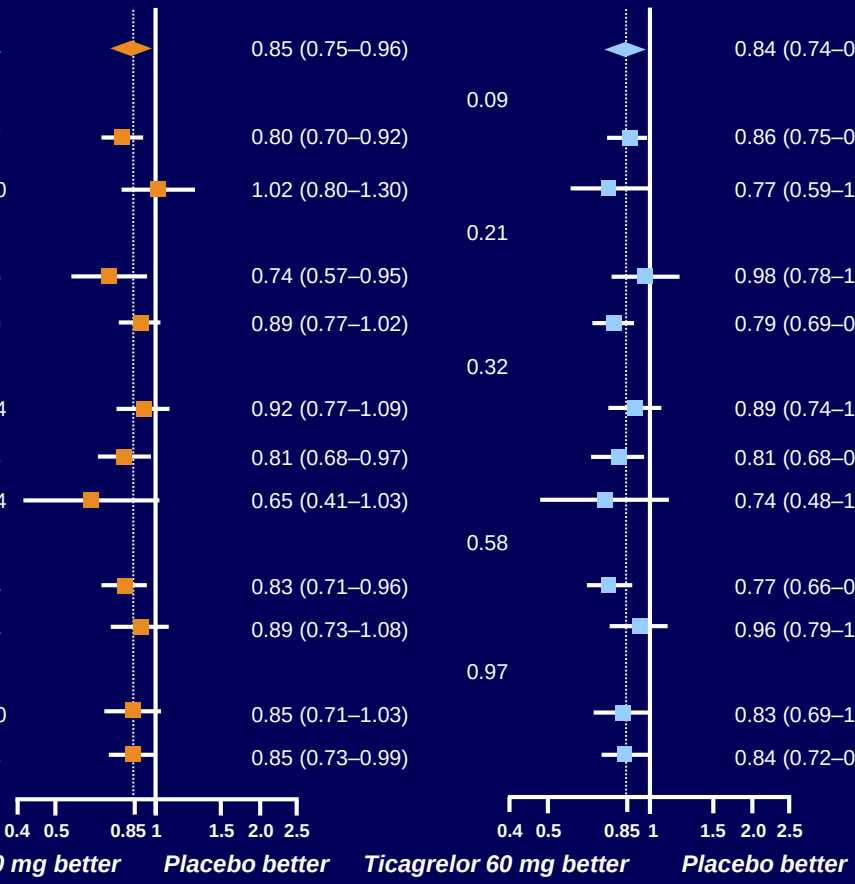
Ticagrelor 90 mg bid
Ticagrelor 60 mg bid
Ticagrelor pooled

*Indicates nominal P value; P<0.026 indicates statistical significance

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

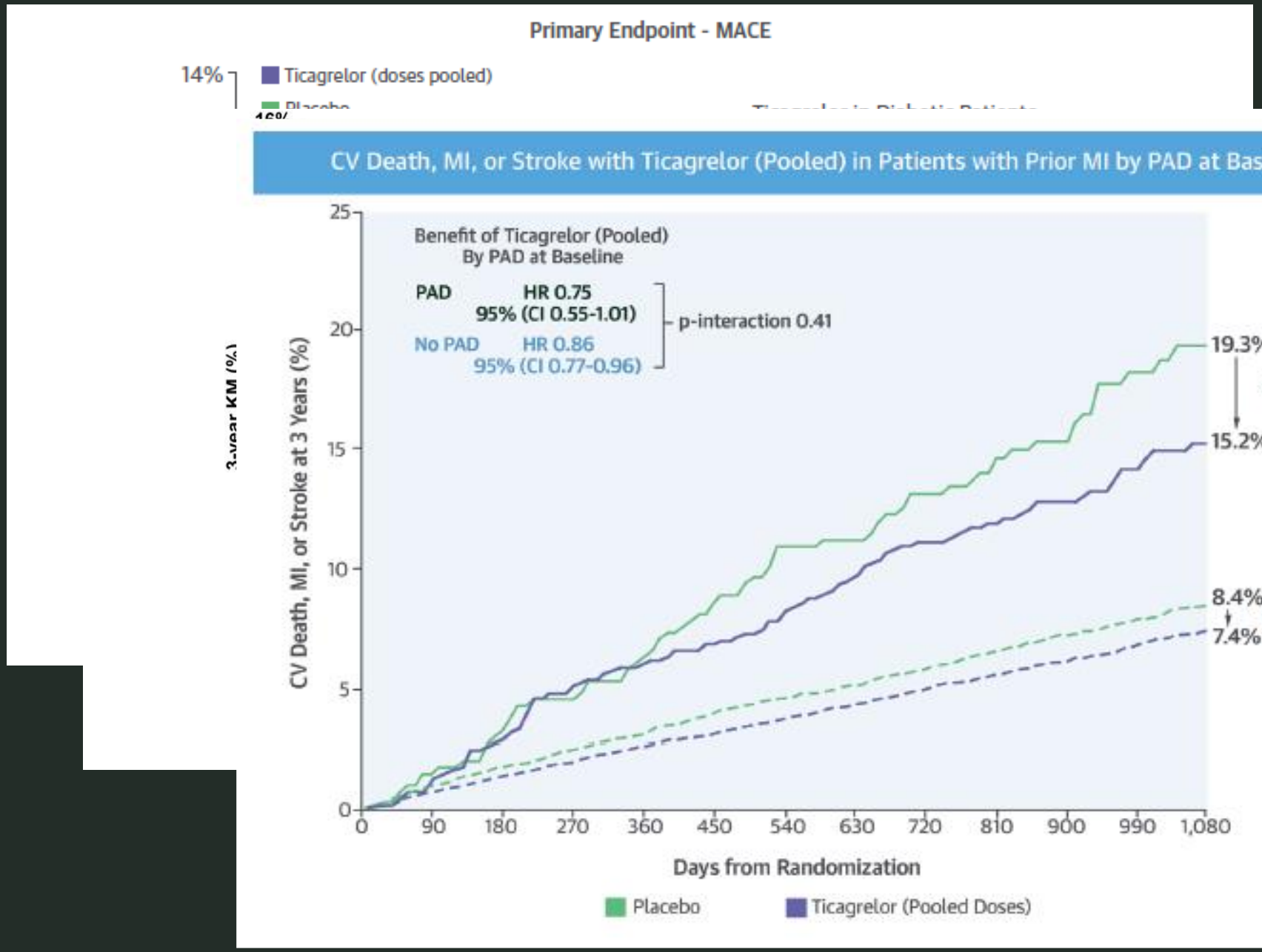
PEGASUS-TIMI 54: Primary Endpoint* by Subgroup (1)

Subgroup	Patients	Ticagrelor 90 mg 3-year KM (%)	Ticagrelor 60 mg 3-year KM (%)	Placebo 3-year KM (%)	HR (95% CI) ticagrelor 90 mg bid vs placebo	Interaction P value	HR (95% CI) ticagrelor 60 mg bid vs placebo	Interaction P value
All patients	21,162	7.85	7.77	9.04	0.85 (0.75–0.96)		0.84 (0.74–0.95)	
Age at randomisation						0.09		0.50
<75 years	18,079	6.77	7.23	8.27	0.80 (0.70–0.92)		0.86 (0.75–0.98)	
≥75 years	3083	13.94	11.02	13.50	1.02 (0.80–1.30)		0.77 (0.59–1.01)	
Sex						0.21		0.12
Female	5060	6.67	9.03	9.15	0.74 (0.57–0.95)		0.98 (0.78–1.24)	
Male	16,102	8.23	7.37	8.99	0.89 (0.77–1.02)		0.79 (0.69–0.91)	
Qualifying MI						0.32		0.67
NSTEMI	8583	9.53	9.32	10.14	0.92 (0.77–1.09)		0.89 (0.74–1.06)	
STEMI	11,329	6.52	6.43	7.83	0.81 (0.68–0.97)		0.81 (0.68–0.97)	
Unknown	1223	7.78	9.46	12.34	0.65 (0.41–1.03)		0.74 (0.48–1.13)	
Time from qualifying MI						0.58		0.09
<2 years	12,980	8.15	7.79	9.74	0.83 (0.71–0.96)		0.77 (0.66–0.90)	
≥2 years	8155	7.33	7.76	7.94	0.89 (0.73–1.08)		0.96 (0.79–1.17)	
History of diabetes						0.97		0.96
Diabetes	6806	10.14	10.00	11.60	0.85 (0.71–1.03)		0.83 (0.69–1.00)	
No diabetes	14,355	6.77	6.68	7.83	0.85 (0.73–0.99)		0.84 (0.72–0.98)	



*Composite of CV death, MI or stroke
KM, Kaplan-Meier

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

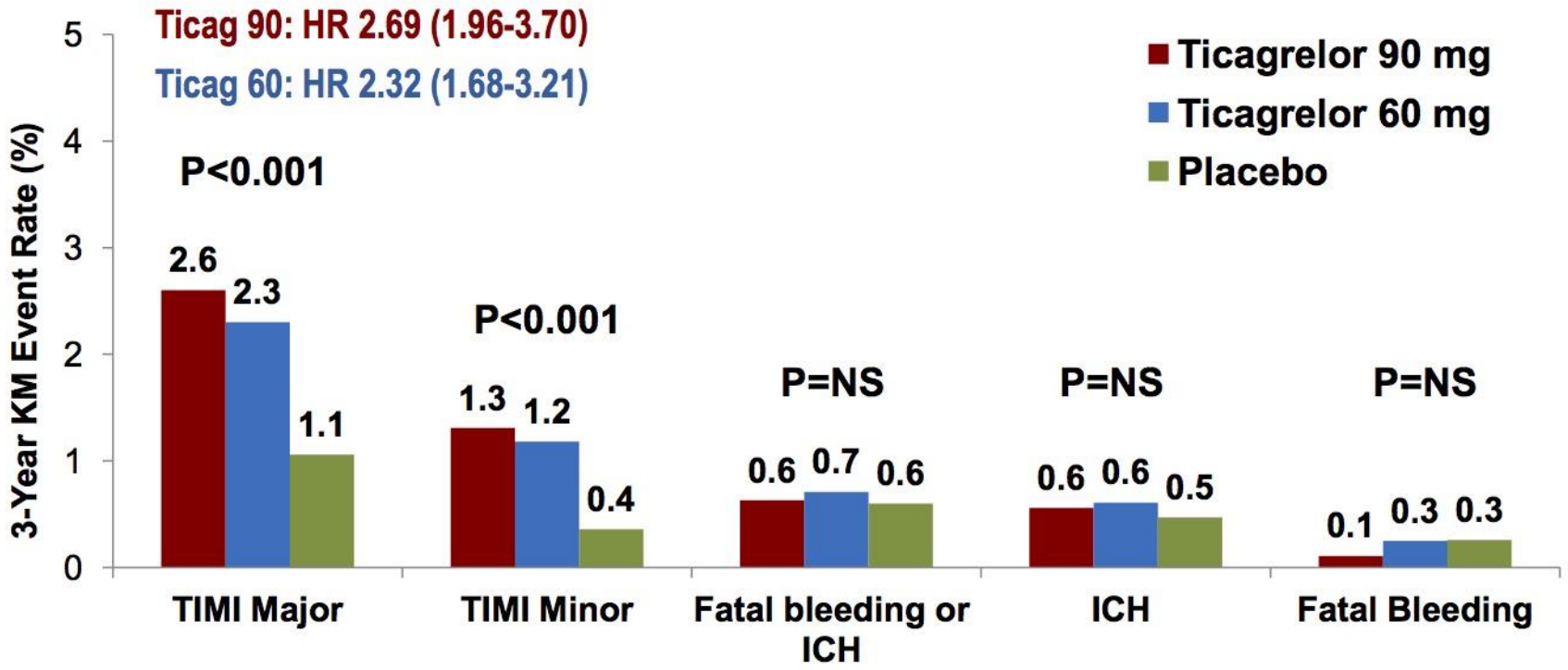


Bhatt DL, et al. *JACC* 2016;67:2732-2740

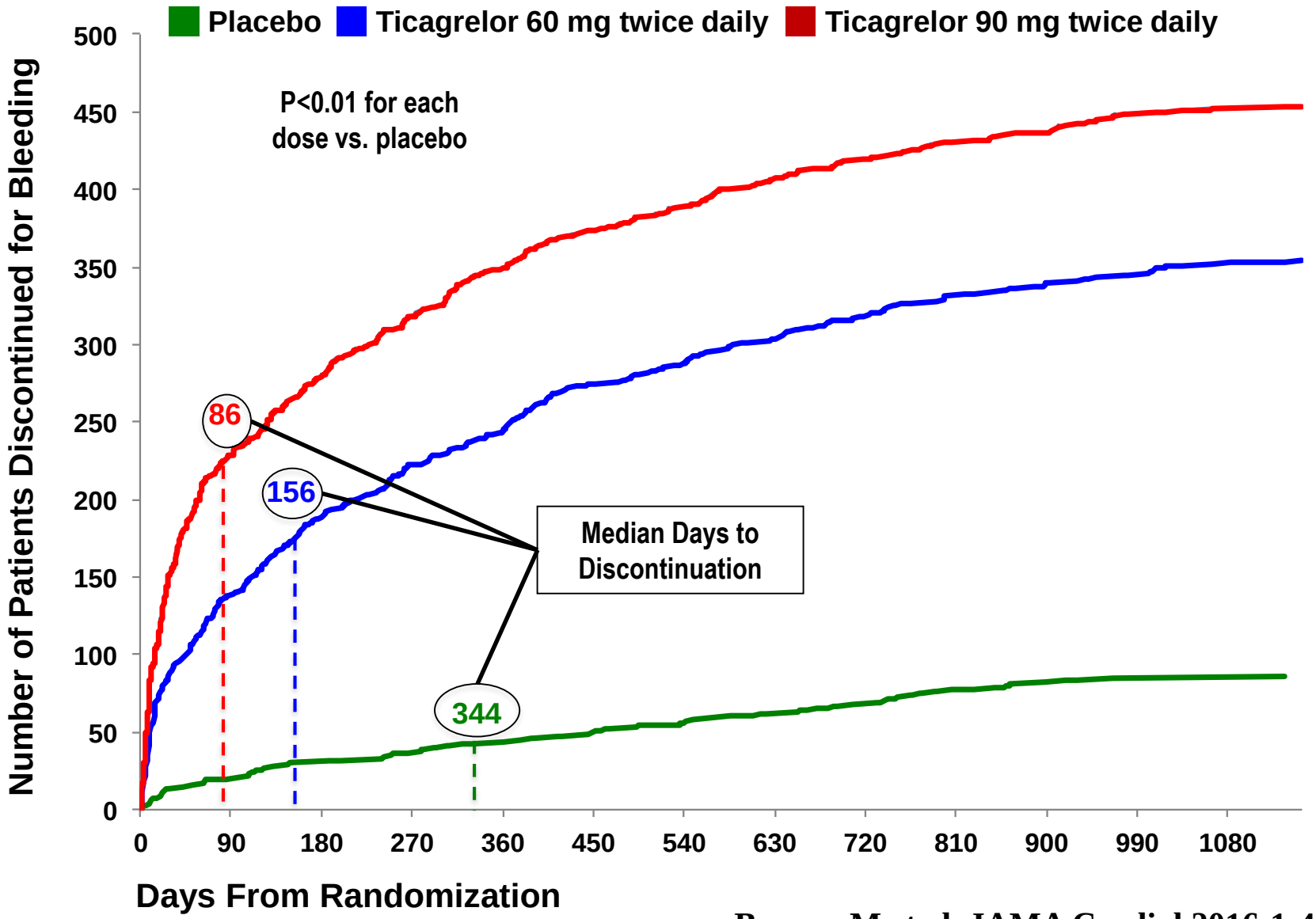
Magnani G, et al. *EurHJ* 2015;doi10.1093/eurheartj/ehv482

Bonaca M et al. JACC 2016;67:2719-2728

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

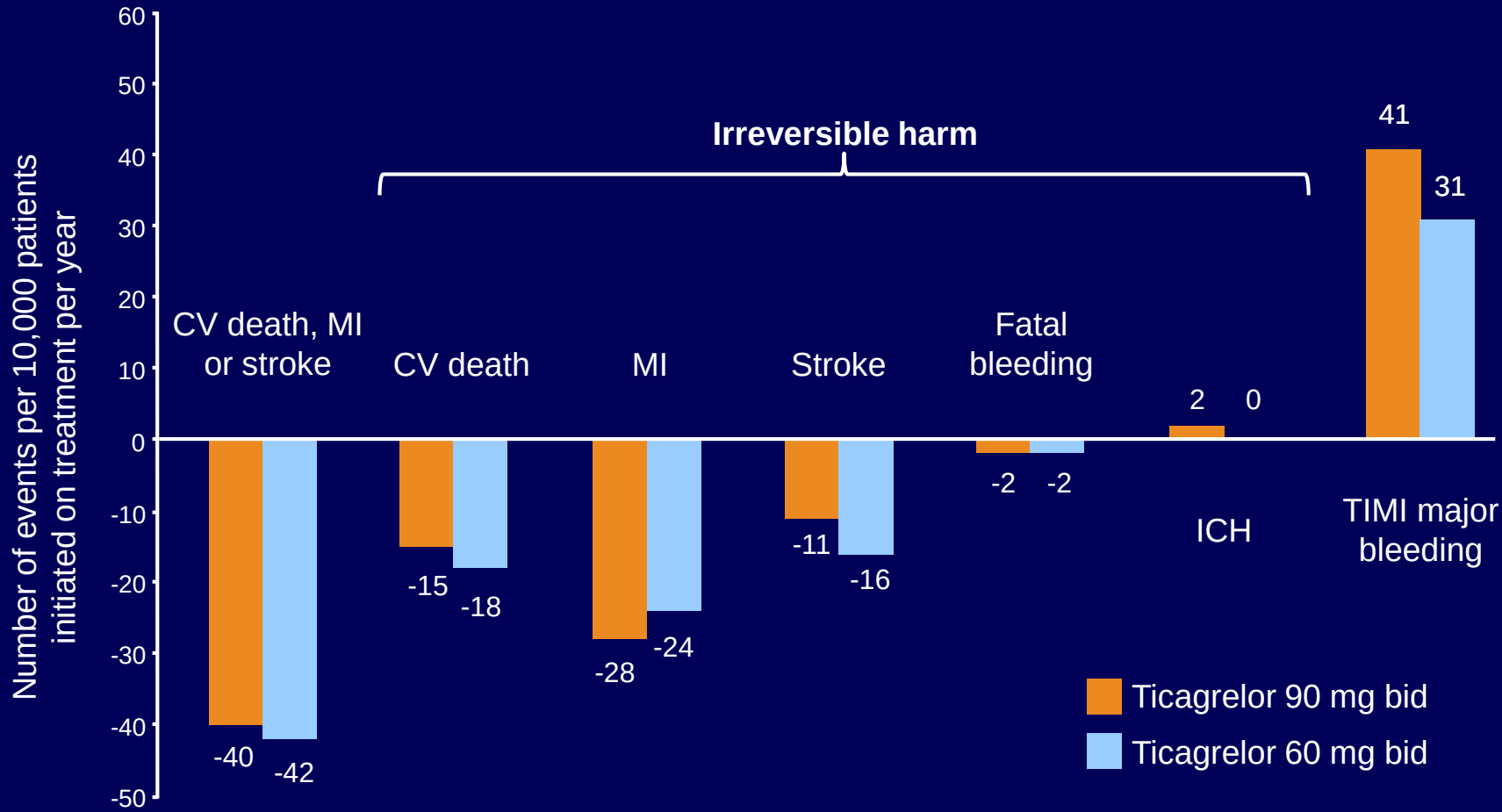
Discontinuation over time for Bleeding by Randomization Group



Bonaca M et al. JAMA Cardiol 2016;1:425-432

PEGASUS-TIMI 54: Estimates of First Efficacy and Bleeding Events 'Prevented' and 'Caused'

Annualized from 3-year Kaplan-Meier event rates in the intention-to-treat population



Net clinical benefit is defined as the comparison of first occurrence of CV death, MI or stroke with first occurrence of TIMI major bleeding; irreversible events are defined as CV death, MI, stroke, fatal bleeding and ICH

Note these are estimated events based on calculations made from the observed ARRs in the PEGASUS-TIMI 54 study and therefore should be viewed as estimates of events 'prevented' and 'caused' rather than specific indicators of efficacy. Also note that these analyses are based on Kaplan-Meier time to first event curves, and therefore the sum of the events for CV death, MI and stroke individually do not equal that for the composite of CV death/MI/stroke

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800, Supplementary Appendix
Data on file: ATLAS approval ID 773,116.011

La durata della DAPT dopo SCA :

dallo stent al paziente

Pegasus

N° events/1000 patients/year

Ticagrelor	90 mg	60 mg
Ischemic ev. prevented	40	42
Bleeding	41	31

European Heart Journal Advance Access published August 31, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv443

FASTTRACK
ESC Clinical Trial Update

Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials

Jacob A. Udell[1,2*], Marc P. Bonaca[3], Jean-Philippe Collet[4], A. Michael Lincoff[5], Dean J. Kereiakes[6], Francesco Costa[7], Cheol Whan Lee[8], Laura Mauri[9], Marco Valgimigli[7,10], Seung-Jung Park[8], Gilles Montalescot[4], Marc S. Sabatine[3], Eugene Braunwald[3], and Deepak L. Bhatt[3*]

33.435 pts

Charisma	3.846
Prodigy	1.465
Arctic-Int	323
DAPT	3.576
DES-Late	3.063
Pegasus	21.162

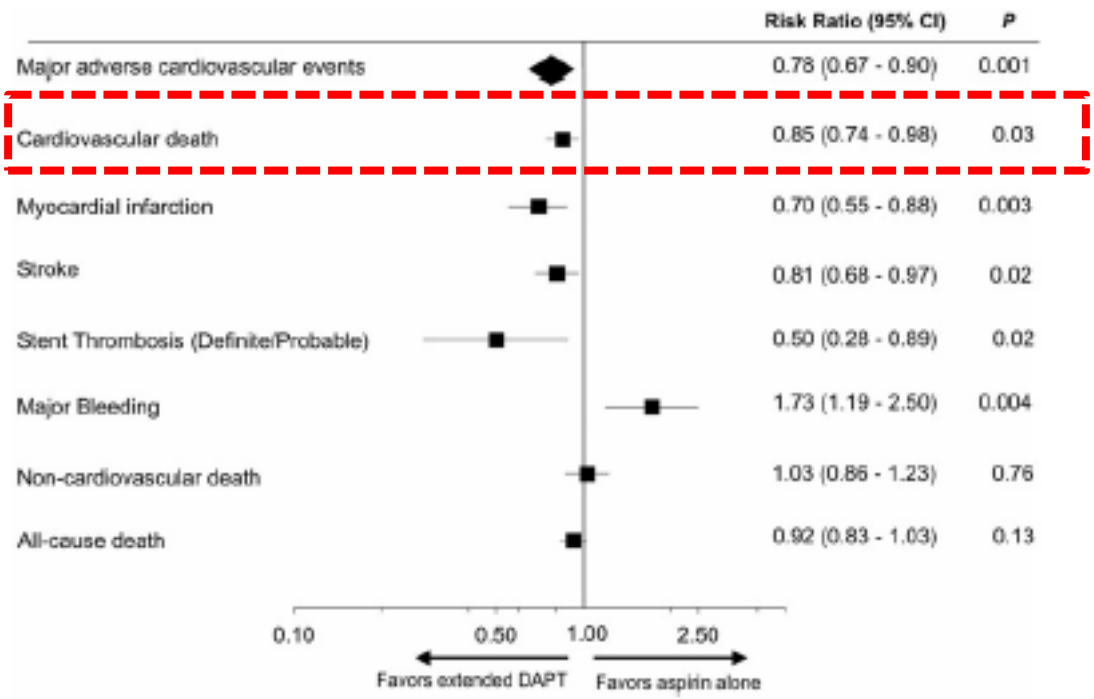


Figure 2 Risk of individual cardiovascular and bleeding endpoints comparing extended dual antiplatelet therapy vs. aspirin alone. Square data markers represent risk ratios and horizontal lines the 95% confidence intervals using inverse variance random effects meta-analysis.

La durata della DAPT dopo SCA :

dallo stent al paziente

Who and when to treat after 12 months

La durata della DAPT dopo SCA :

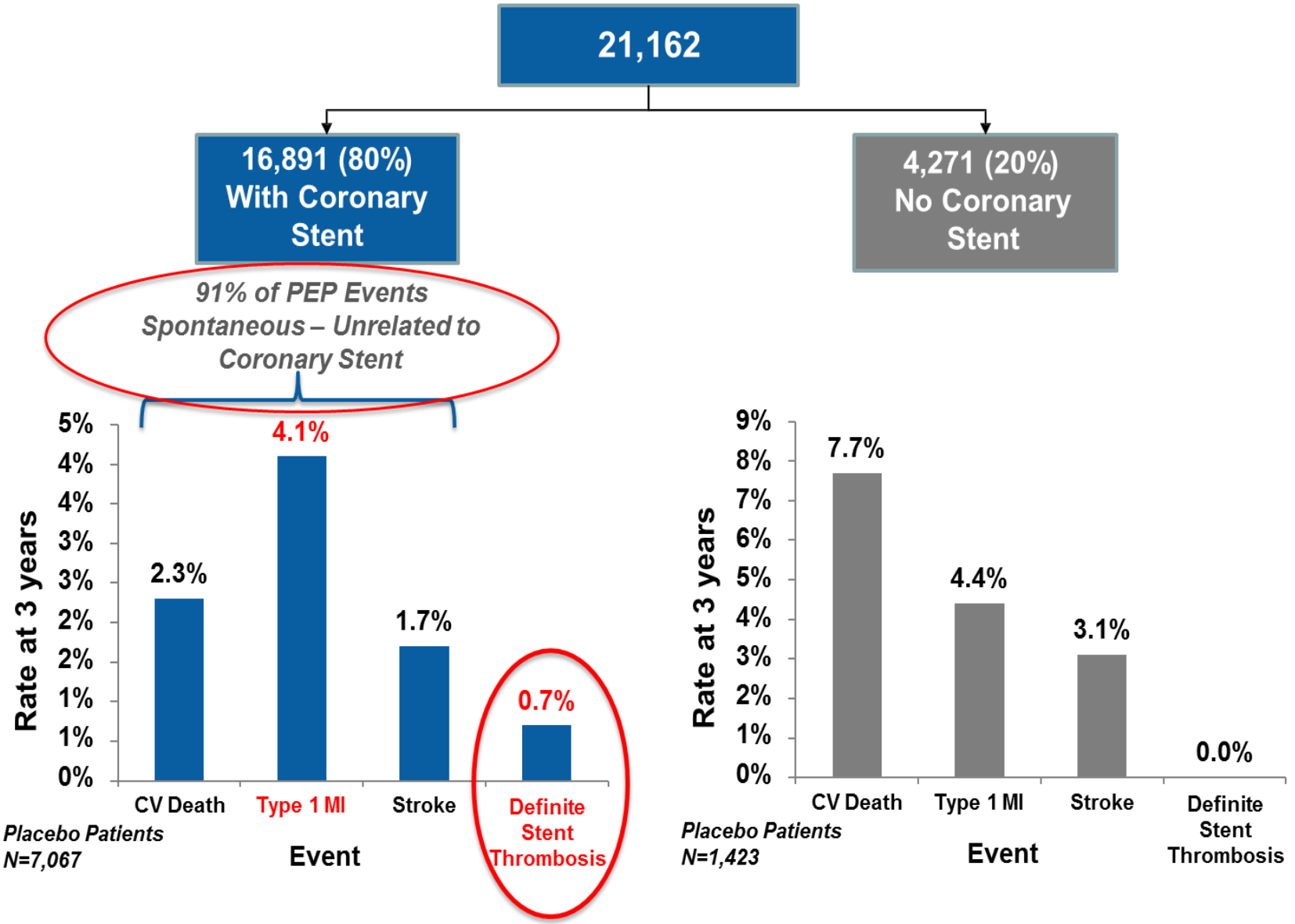
dallo stent al paziente

Who

- **Patients with prior MI at high risk:**
  - **Diabetes mellitus**
  - **Multiple prior MIs**
  - **Renal dysfunction**
  - **Multiple vascular disease**
  - **Prior CABG**
  - **PAD**

- **Not at high risk for bleeding**
  - **Prior/risk of ICH**
  - **Recent major Bleeding**
  - **Bleeding diathesis**
  - **On anticoagulation**
  - **Anemia**

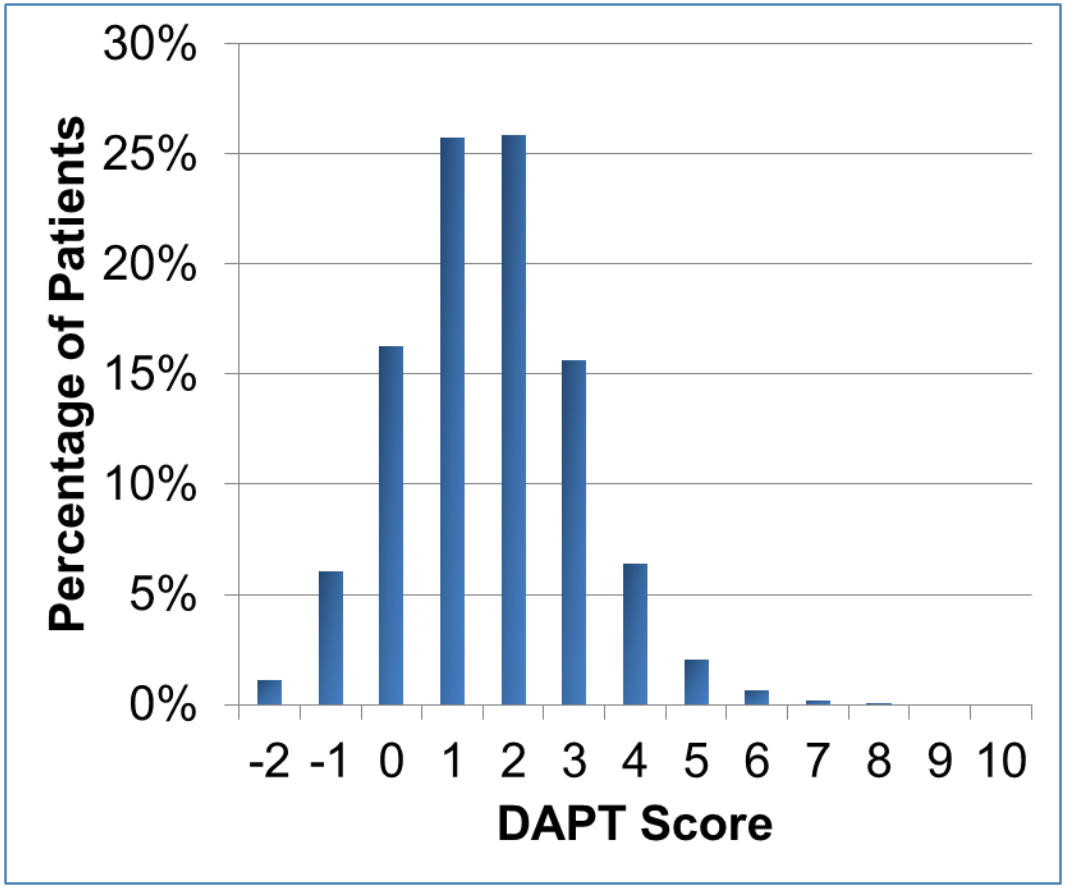
Events at 3 Years by Prior Coronary Stent



The DAPT Score

Variable	Points
Patient Characteristic	
Age	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

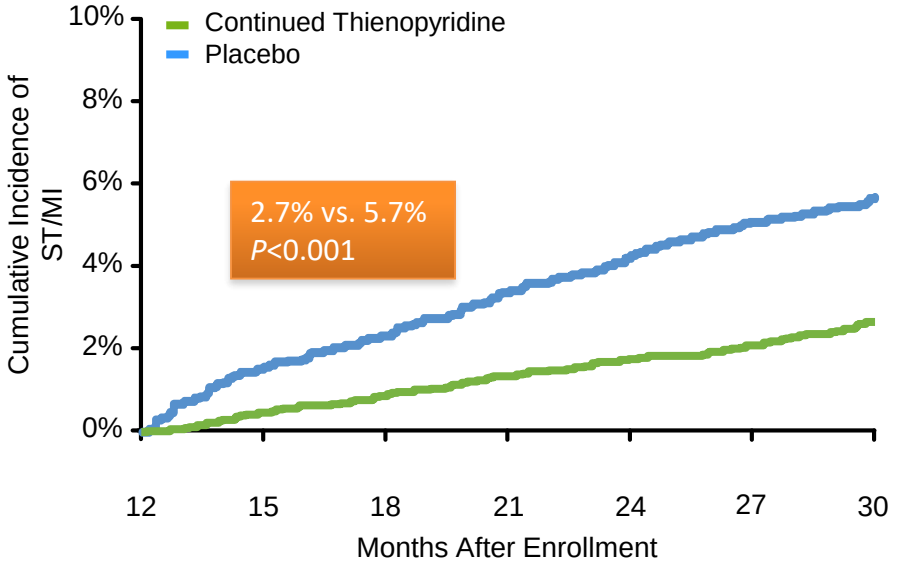
Distribution of DAPT Scores among all randomized subjects in the DAPT Study



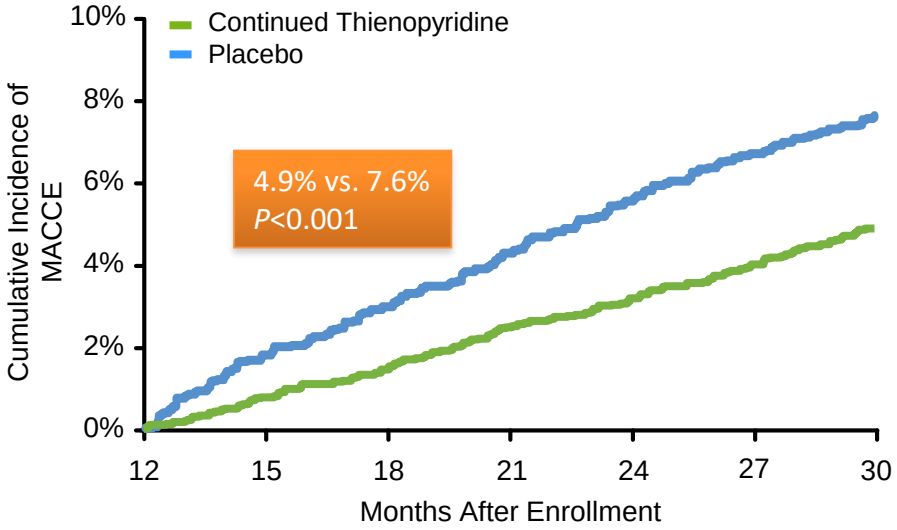
Continued Thienopyridine vs. Placebo
DAPT Score ≥ 2 (High); N=5917

DAPT STUDY

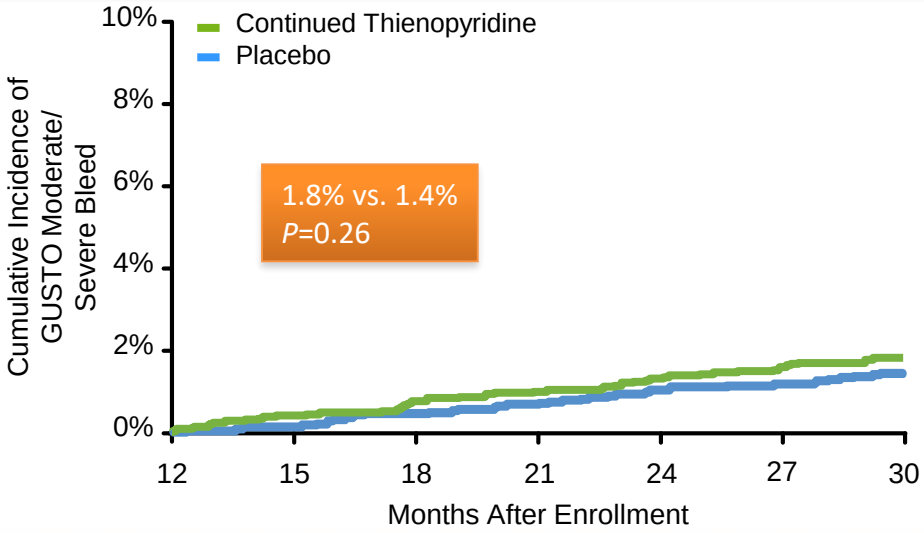
Myocardial Infarction or Stent Thrombosis



Death, MI or Stroke (MACCE)

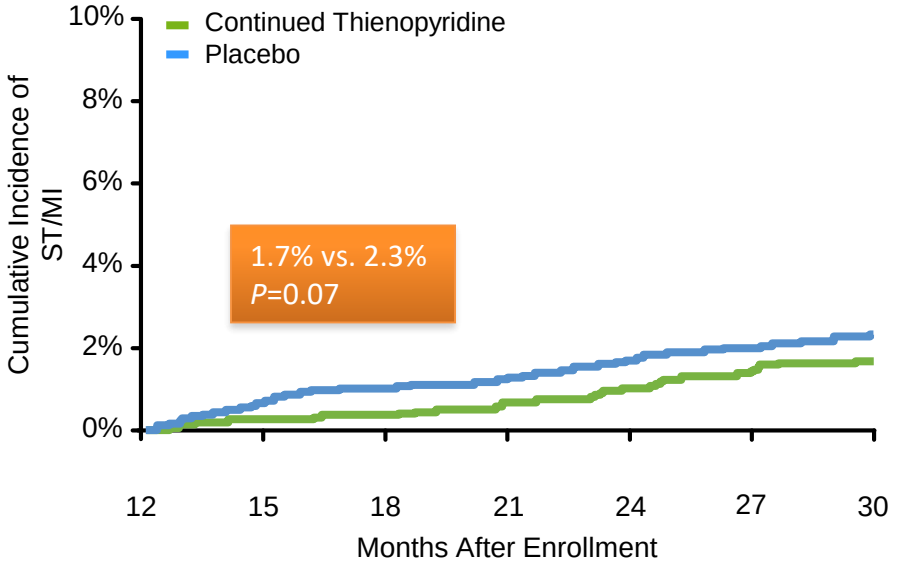


GUSTO Moderate/ Severe Bleeding

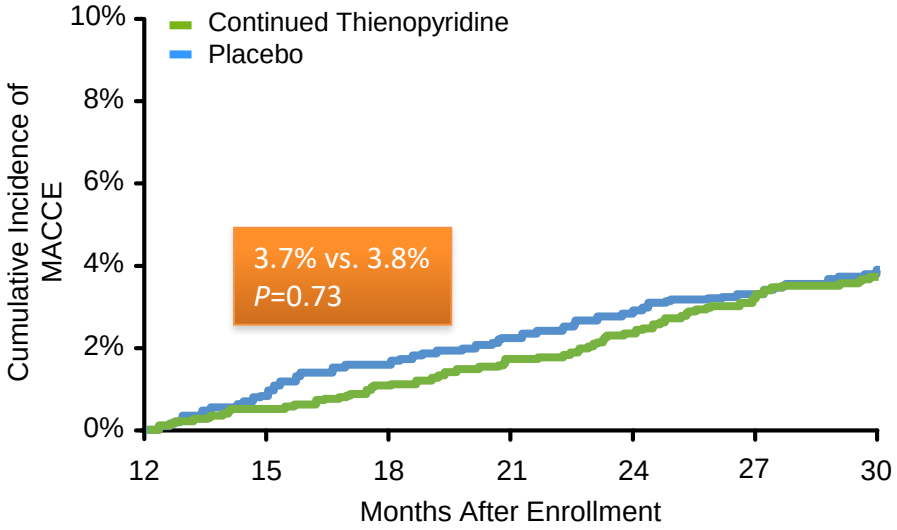


Continued Thienopyridine vs. Placebo
DAPT Score <2 (Low); N=5731

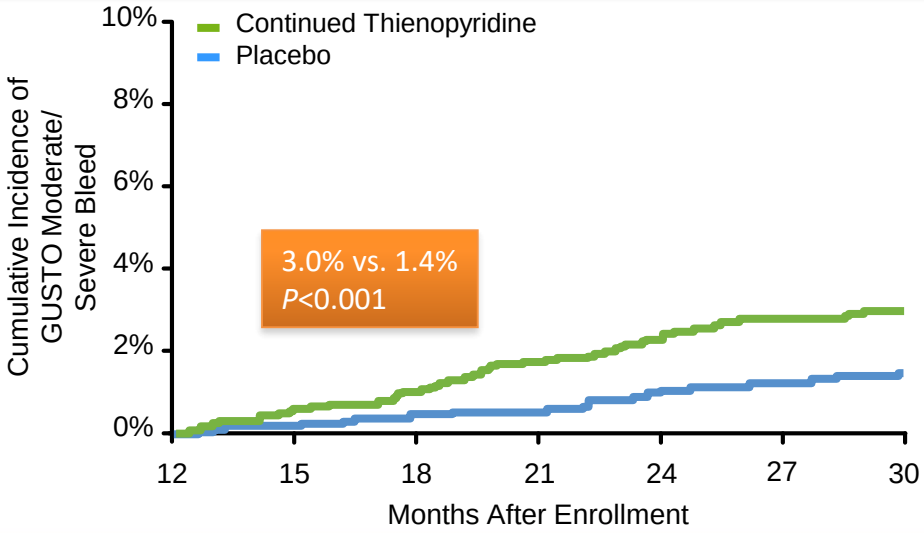
Myocardial Infarction or Stent Thrombosis



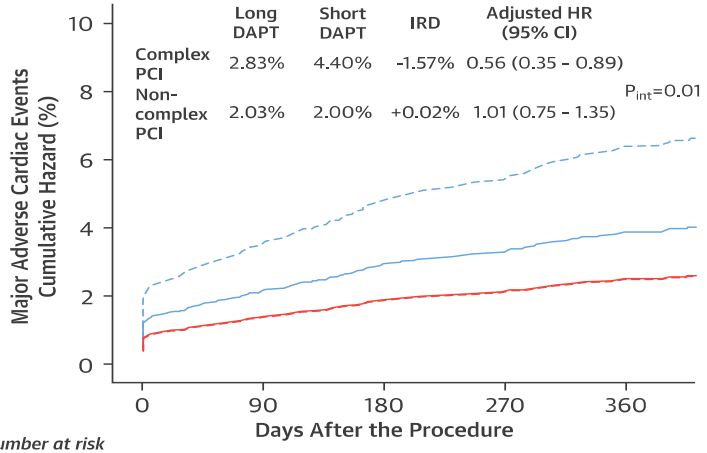
Death, MI, or Stroke (MACCE)



GUSTO Moderate/ Severe Bleeding



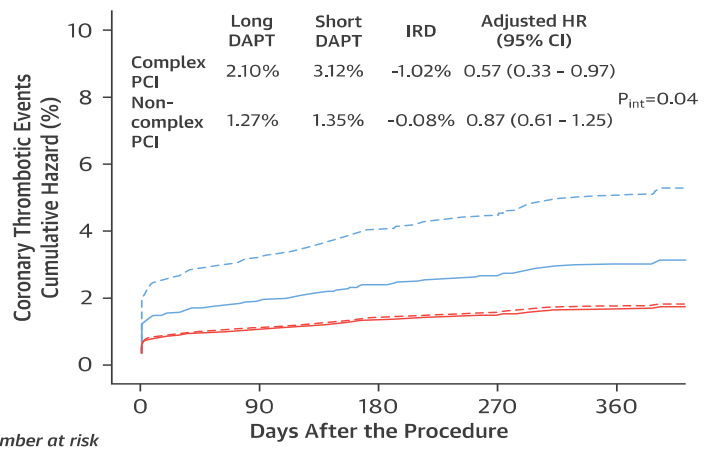
A



Number at risk

Non-complex PCI - Short DAPT	3938	3875	3816	3782	3511
Non-complex PCI - Long DAPT	3932	3874	3824	3794	3520
Complex PCI - Short DAPT	802	777	768	759	668
Complex PCI - Long DAPT	840	816	805	796	693

B



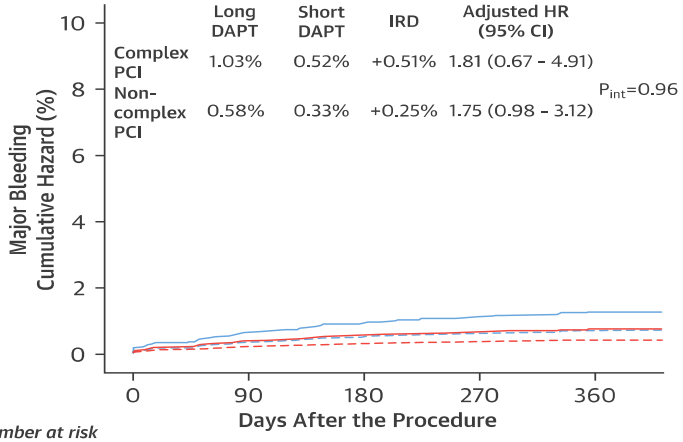
Number at risk

Non-complex PCI - Short DAPT	3938	3873	3817	3784	3515
Non-complex PCI - Long DAPT	3932	3875	3828	3797	3524
Complex PCI - Short DAPT	801	776	767	760	671
Complex PCI - Long DAPT	840	817	806	797	694

C

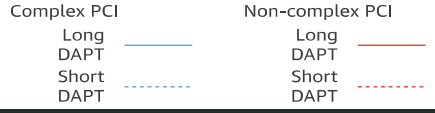
Complex PCI was defined
(<u>at least 1</u> of the following features) :

- **3 vessels treated**
- **≥3 stents implanted**
- **≥3 lesions treated**
- **bifurcation with 2 stents implanted**
- **total stent length >60 mm**
- **or chronic total occlusion**



Number at risk

Non-complex PCI - Short DAPT	3947	3900	3849	3814	3550
Non-complex PCI - Long DAPT	3941	3892	3844	3811	3540
Complex PCI - Short DAPT	816	801	794	787	692
Complex PCI - Long DAPT	846	826	815	808	706



Giustino G et al. JACC 2016;68:1851-1864

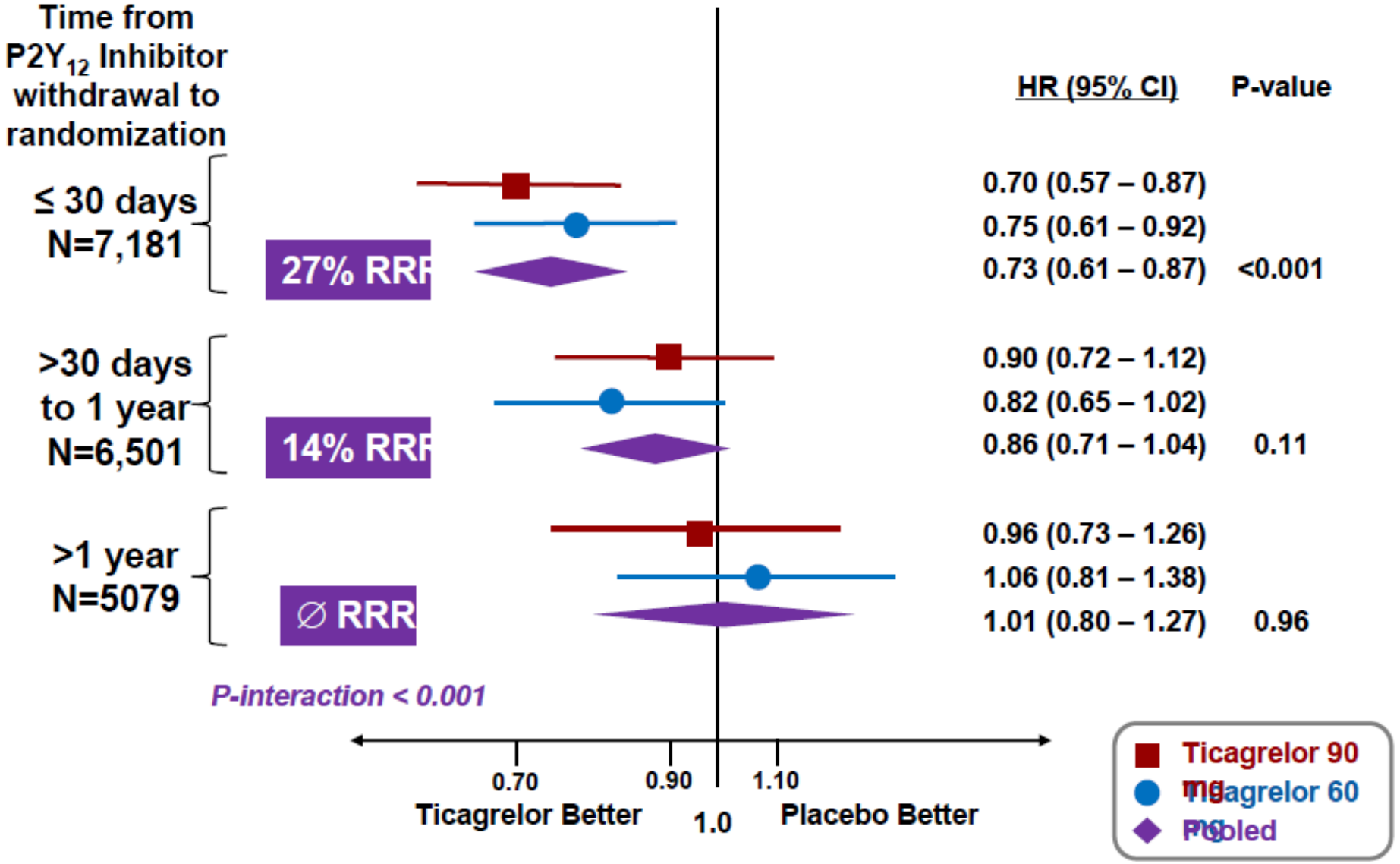
La durata della DAPT dopo SCA :

dallo stent al paziente

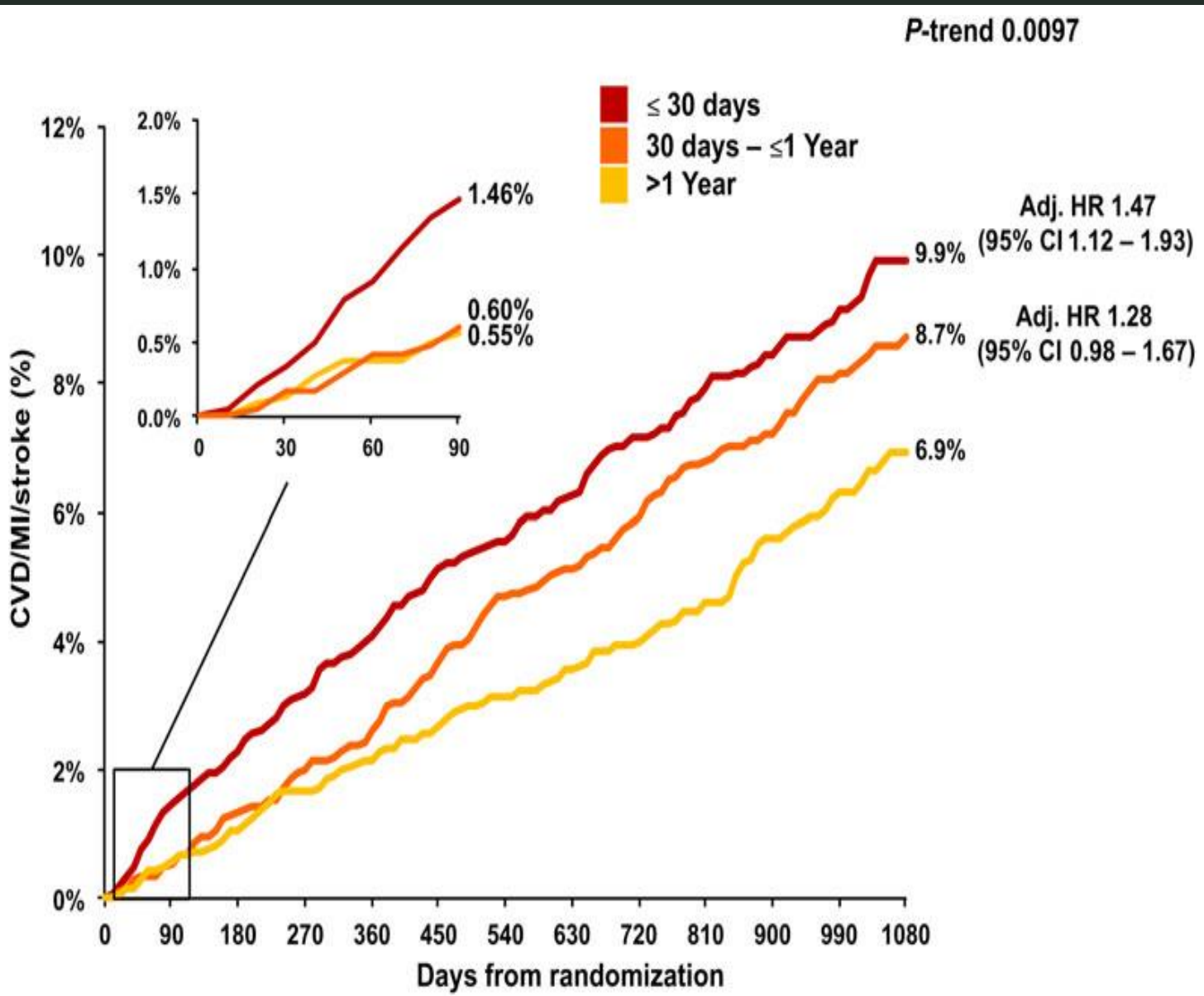
When

- **Continue after started for MI and re-evaluate at each visit:**
  - **Recent bleeding?**
  - **Are they tolerating?**
  - **Are they adherent?**
  - **Contraindications ? (e.g. AF requiring anticoagulation)**

Reduction in MACE with Ticagrelor by Time from $P2Y_{12}$ Inhibitor Withdrawal



Bonaca M et al. EurHJ 2016;37:1133-1142



Bonaca M et al. EurHJ 2016;37:1133-1142

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Long-term $P2Y_{12}$ inhibition

$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	A	184, 186

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

ESC European Society of Cardiology

Recommendations
In patients with ACS who have tolerated D bleeding complication, continuation of DA 12 months may be considered.
In patients with MI and high ischaemic risl tolerated DAPT without a bleeding compli 60 mg *b.i.d.* for longer than 12 months on be preferred over clopidogrel or prasugrel

www.escardio.org/guidelines

2017 ESC Focused Update on DA (European Heart Journal 2017 - d

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

ESC European Society of Cardiology

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

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)

La durata della DAPT dopo SCA :

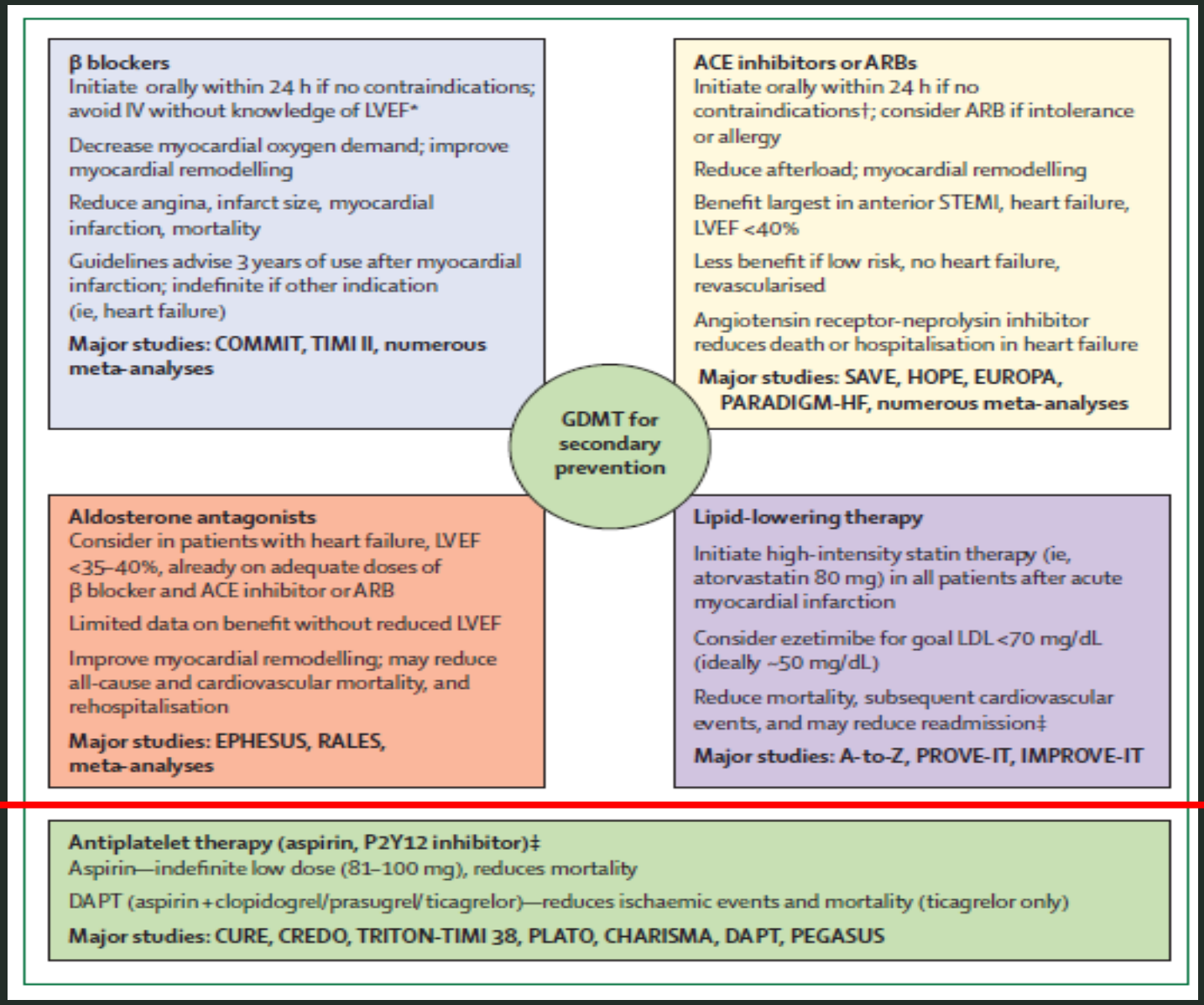
dallo stent al paziente

Prolonging DAPT duration in ACS pts

“treat the patient not the stent”

“one size may not fit all”

(carefully assessing the balance between thrombotic and bleeding risk)



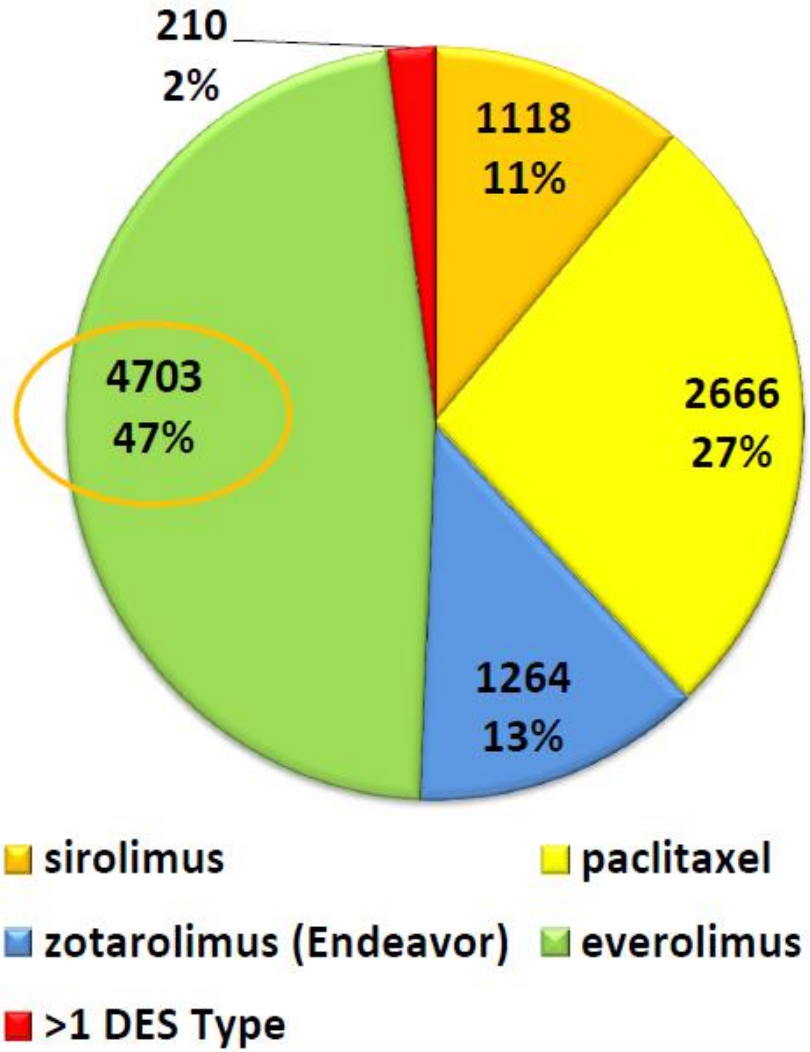
Reed GW et al. Lancet 2017; 389:197-210

Backup

Stent & Drug Types

DAPT STUDY

Drug Eluting Stent Type



Thienopyridine Type

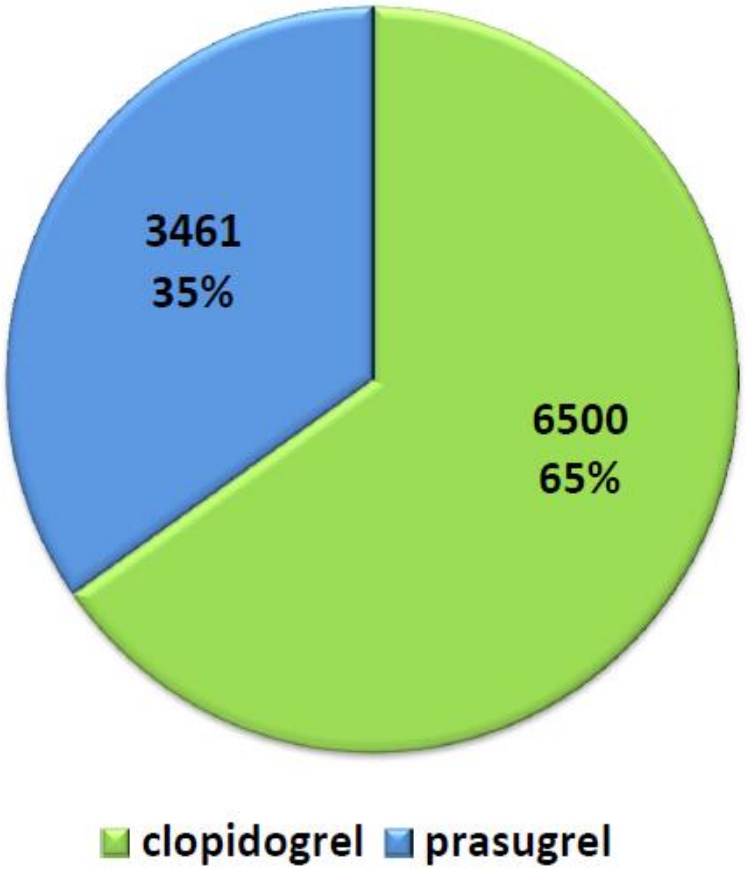
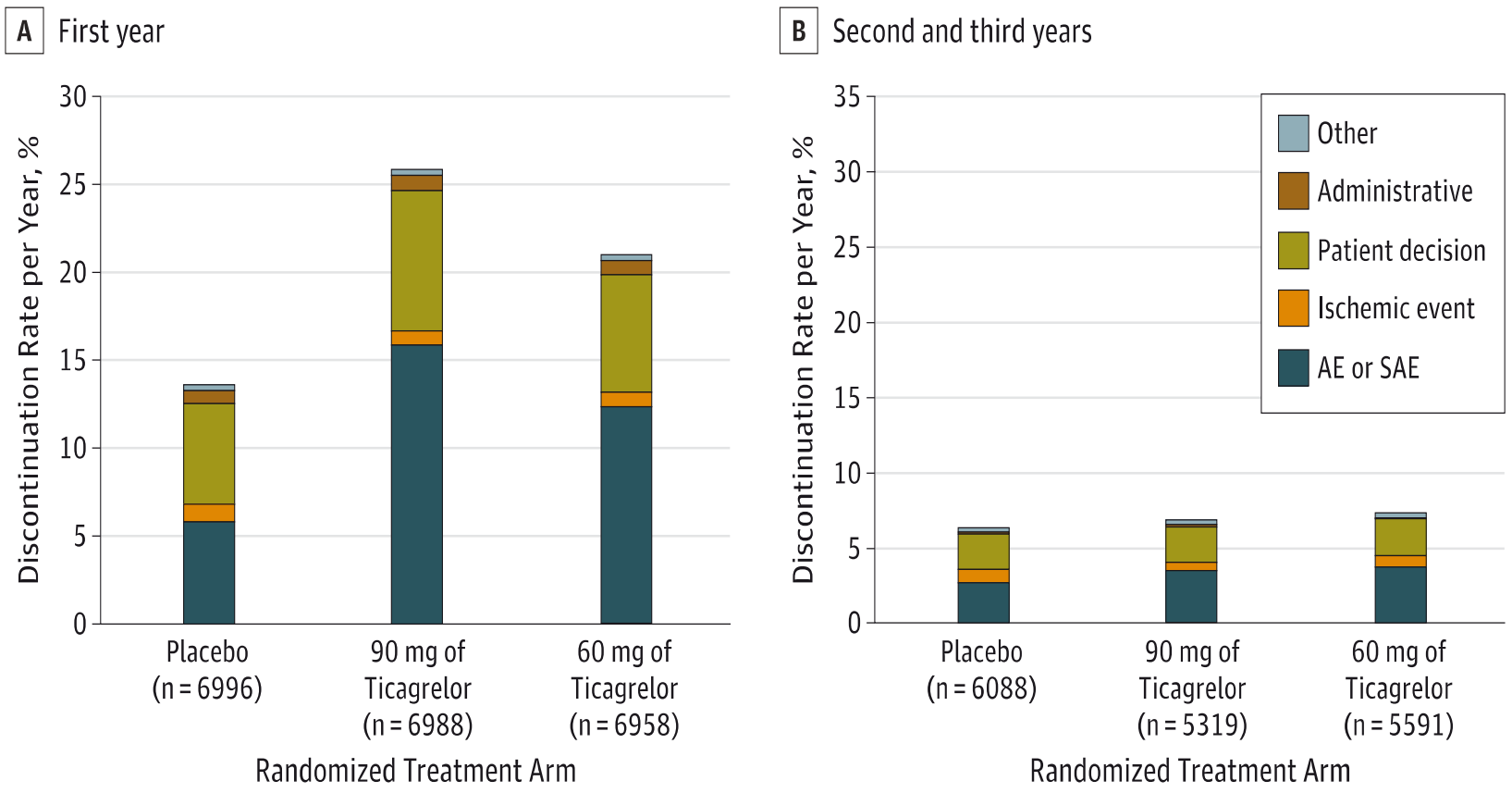
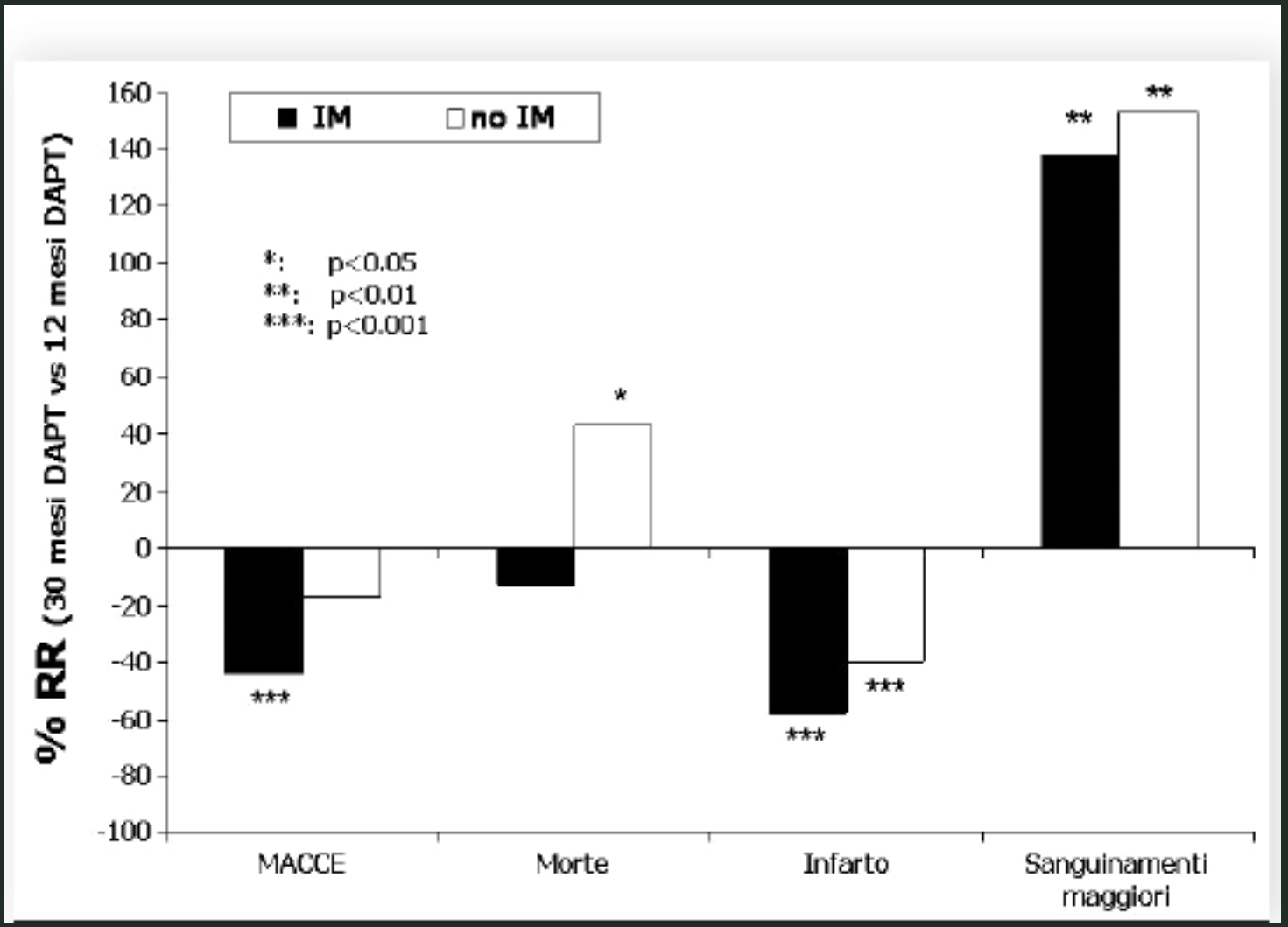


Figure 2. Distribution of Reasons for Drug Discontinuation by Treatment Arm



Bonaca M et al. JAMA Cardiol 2016;1:425-432



G Ital Cardiol 2015;16(7-8):393-398

PEGASUS-TIMI 54: Safety Endpoints

Endpoint	Ticagrelor 90 mg bid N=6988; n (%)	Ticagrelor 60 mg bid N=6958; n (%)	Placebo N=6996; n (%)	Ticagrelor 90 mg bid vs placebo HR (95% CI)	Ticagrelor 60 mg bid vs placebo HR (95% CI)
Primary safety endpoint					
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70) P<0.001	2.32 (1.68–3.21) P<0.001
Secondary safety endpoints					
ICH	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49) P=0.19	1.33 (0.77–2.31) P=0.31
Haemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64) P=0.26	0.97 (0.37–2.51) P=0.94
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54) P=0.27	1.00 (0.44–2.27) P=1.00
Fatal bleeding or non-fatal ICH	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01) P=0.43	1.20 (0.73–1.97) P=0.47

Rates are presented as 3-year Kaplan-Meier estimates
n = number of patients with events, not the number of events

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

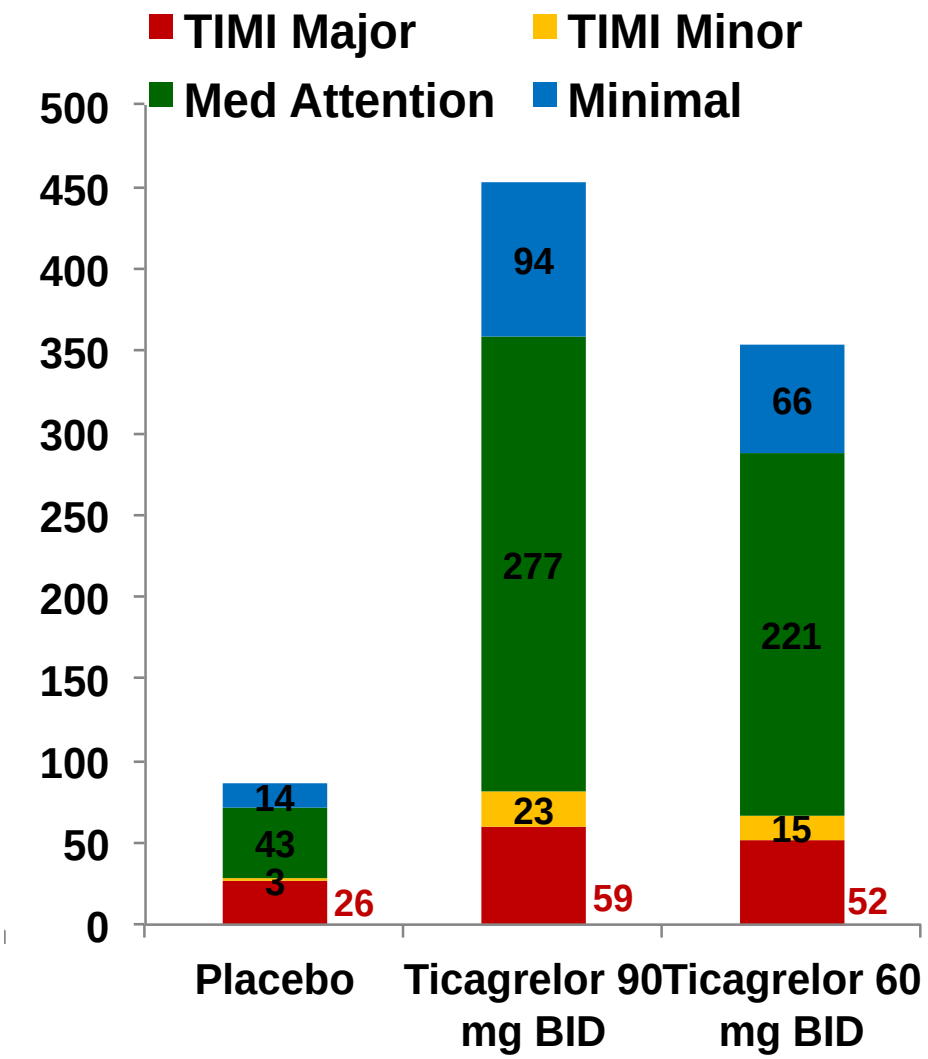
PEGASUS-TIMI 54: Safety Endpoints

Endpoint	Ticagrelor 90 mg bid N=6988; n (%)	Ticagrelor 60 mg bid N=6958; n (%)	Placebo N=6996; n (%)	Ticagrelor 90 mg bid vs placebo HR (95% CI)	Ticagrelor 60 mg bid vs placebo HR (95% CI)
Secondary safety endpoints					
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00) P<0.001	3.31 (1.94–5.63) P<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42) P<0.001	3.08 (2.12–4.48) P<0.001
Bleeding leading to study drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29) P<0.001	4.40 (3.48–5.57) P<0.001

Rates are presented as 3-year Kaplan-Meier estimates
n = number of patients with events, not the number of events

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

Bleeding



Bonaca M et al. JAMA Cardiol 2016;1:425-432

All-Cause Mortality

DAPT STUDY

	12-30 Months			
	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	**98 (2.0%)**	**74 (1.5%)**	**0.052**	**24 (0.5%)**
Cardiac	45 (0.9%)	47 (1.0%)	0.98	-2 (-0.1%)
Vascular	5 (0.1%)	5 (0.1%)	0.98	0 (-)
Non-Cardiovascular	48 (1.0%)	22 (0.5%)	0.002	26 (0.5%)

Cumulative incidence is presented according to Kaplan-Meier method

ATBV
Gruppo di studio Aterosclerosi, Trombosi, Biologia Vascolare

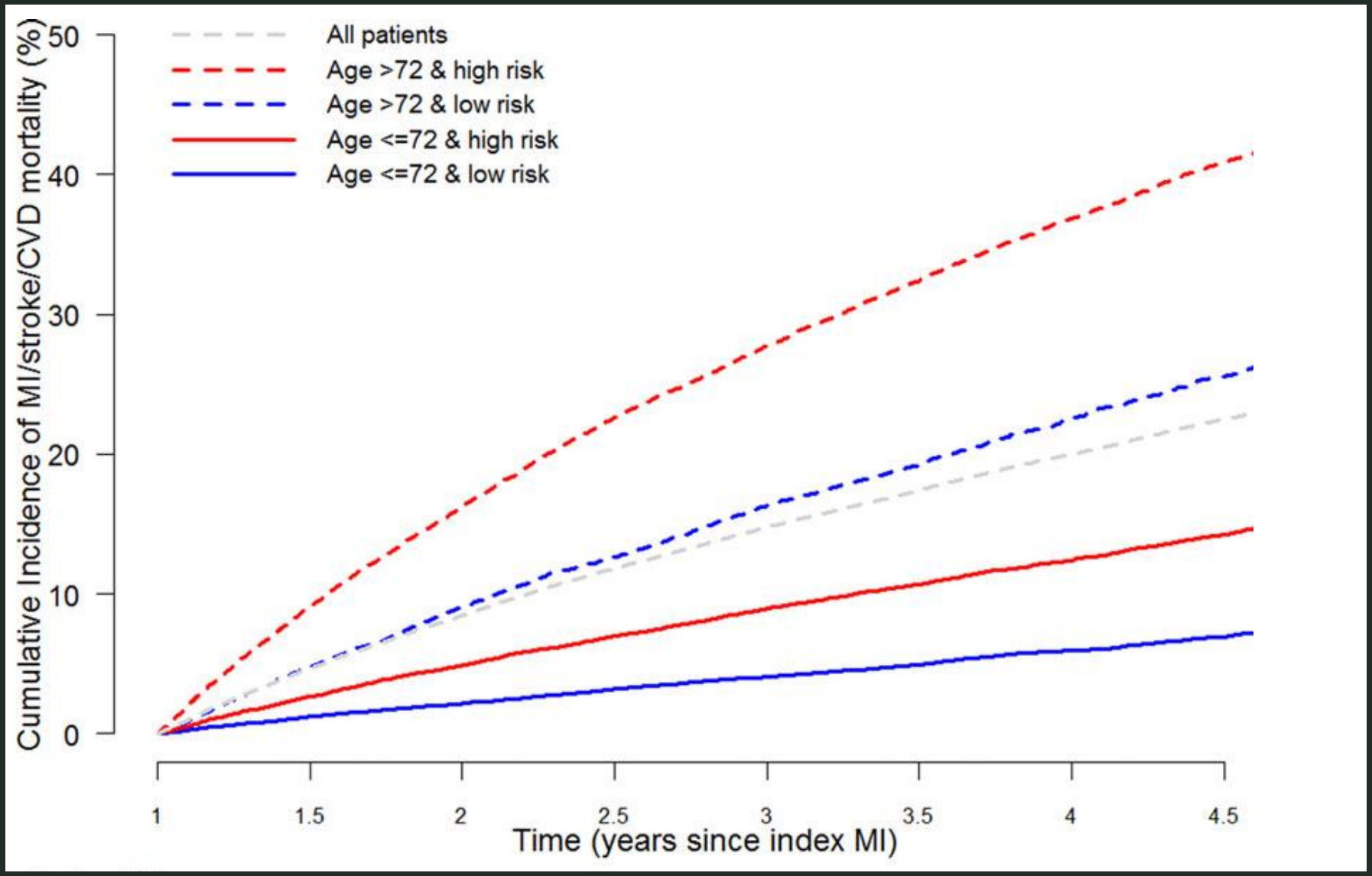
Congresso Nazionale
ATBV 2015
Hot-Topics in tema di terapia antitrombotica

Optimal duration of antiplatelet treatment after ACS

Compared to 12 months of DAPT administration

short (3 or 6 m)		> 12 (30 ?) m
unchanged	stent thrombosis	reduced
unchanged	MACCE*	reduced
reduced	bleeding	increased

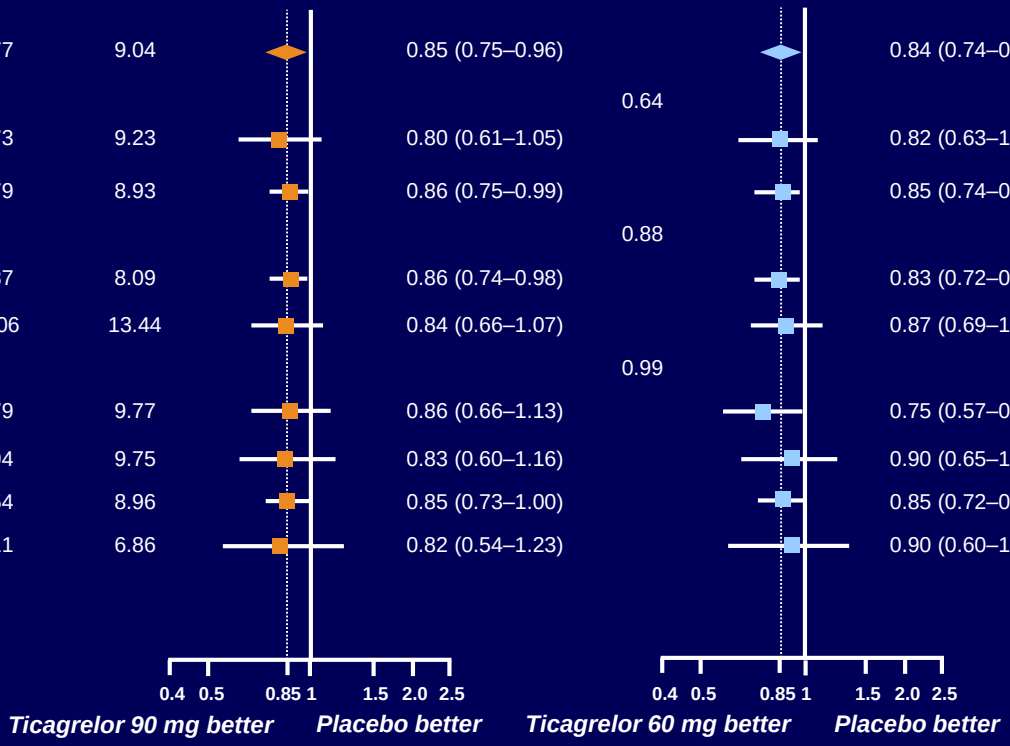
* = mortality (total, CV, non-CV), MI, stroke



Jernberg T et al. EurHJ 2015; 36:1163-1170

PEGASUS-TIMI 54: Primary Endpoint* by Subgroup (2)

Subgroup	Patients	Ticagrelor 90 mg 3-year KM (%)	Ticagrelor 60 mg 3-year KM (%)	Placebo 3-year KM (%)	HR (95% CI) ticagrelor 90 mg bid vs placebo	HR (95% CI)	Interaction P value	HR (95% CI) ticagrelor 60 mg bid vs placebo	HR (95% CI)	Interaction P value
All patients	21,162	7.85	7.77	9.04		0.85 (0.75–0.96)			0.84 (0.74–0.95)	
ASA dose							0.64			0.80
≤75 mg	4182	7.52	7.73	9.23		0.80 (0.61–1.05)			0.82 (0.63–1.07)	
>75 mg	16,950	7.89	7.79	8.93		0.86 (0.75–0.99)			0.85 (0.74–0.97)	
History of PCI							0.88			0.72
Prior PCI	17,568	7.20	6.87	8.09		0.86 (0.74–0.98)			0.83 (0.72–0.96)	
No prior PCI	3591	10.97	12.06	13.44		0.84 (0.66–1.07)			0.87 (0.69–1.11)	
Region							0.99			0.83
North America	3907	9.12	7.79	9.77		0.86 (0.66–1.13)			0.75 (0.57–0.99)	
South America	2458	8.60	9.94	9.75		0.83 (0.60–1.16)			0.90 (0.65–1.24)	
Europe	12,428	7.64	7.54	8.96		0.85 (0.73–1.00)			0.85 (0.72–0.99)	
Asia	2369	6.08	7.11	6.86		0.82 (0.54–1.23)			0.90 (0.60–1.34)	

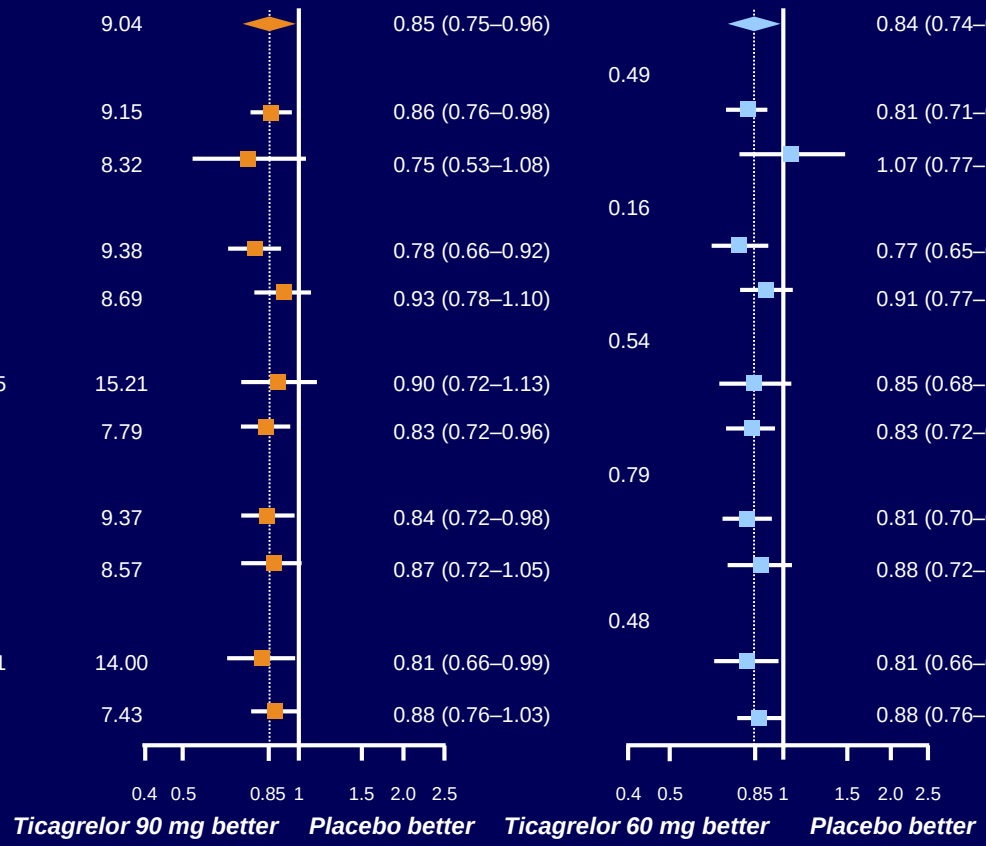


*Composite of CV death, MI or stroke

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

PEGASUS-TIMI 54: Primary Endpoint* by Subgroup (3)

Subgroup	Patients	Ticagrelor 90 mg 3-year KM (%)	Ticagrelor 60 mg 3-year KM (%)	Placebo 3-year KM (%)	HR (95% CI) ticagrelor 90 mg bid vs placebo	HR (95% CI)	Interaction P value	HR (95% CI) ticagrelor 60 mg bid vs placebo	HR (95% CI)	Interaction P value
All patients	21,162	7.85	7.77	9.04		0.85 (0.75–0.96)			0.84 (0.74–0.95)	
Race							0.49			0.12
Caucasian	18,327	8.10	7.61	9.15		0.86 (0.76–0.98)			0.81 (0.71–0.92)	
Non-Caucasian	2835	5.88	8.78	8.32		0.75 (0.53–1.08)			1.07 (0.77–1.48)	
Weight							0.16			0.18
< Median (81 kg)	10,550	7.66	7.62	9.38		0.78 (0.66–0.92)			0.77 (0.65–0.92)	
≥ Median (81 kg)	10,581	7.97	7.89	8.69		0.93 (0.78–1.10)			0.91 (0.77–1.08)	
Second prior MI							0.54			0.88
Second MI	3499	14.68	13.65	15.21		0.90 (0.72–1.13)			0.85 (0.68–1.06)	
No second MI	17,662	6.53	6.59	7.79		0.83 (0.72–0.96)			0.83 (0.72–0.96)	
Multivessel disease							0.79			0.55
Multivessel disease	12,558	8.07	7.80	9.37		0.84 (0.72–0.98)			0.81 (0.70–0.95)	
No multivessel disease	8600	7.51	7.69	8.57		0.87 (0.72–1.05)			0.88 (0.72–1.06)	
Non-endstage renal dysfunction							0.48			0.54
Renal dysfunction	4849	11.26	11.31	14.00		0.81 (0.66–0.99)			0.81 (0.66–0.99)	
No renal dysfunction	16,049	6.81	6.79	7.43		0.88 (0.76–1.03)			0.88 (0.76–1.02)	



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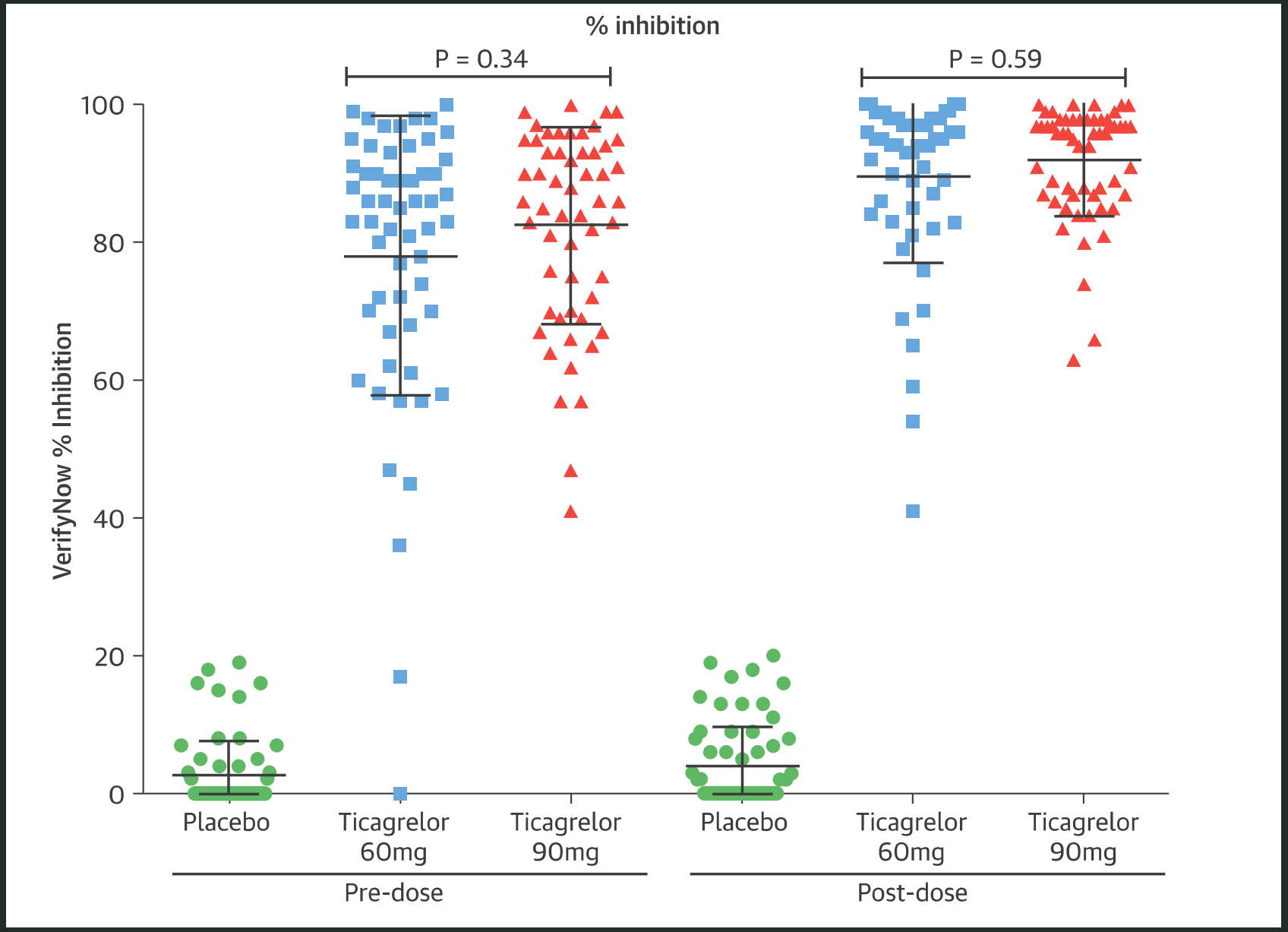
n = number of patients with events, not the number of events

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800



Storey RF, et al. *JACC* 2016;67:1145-1154

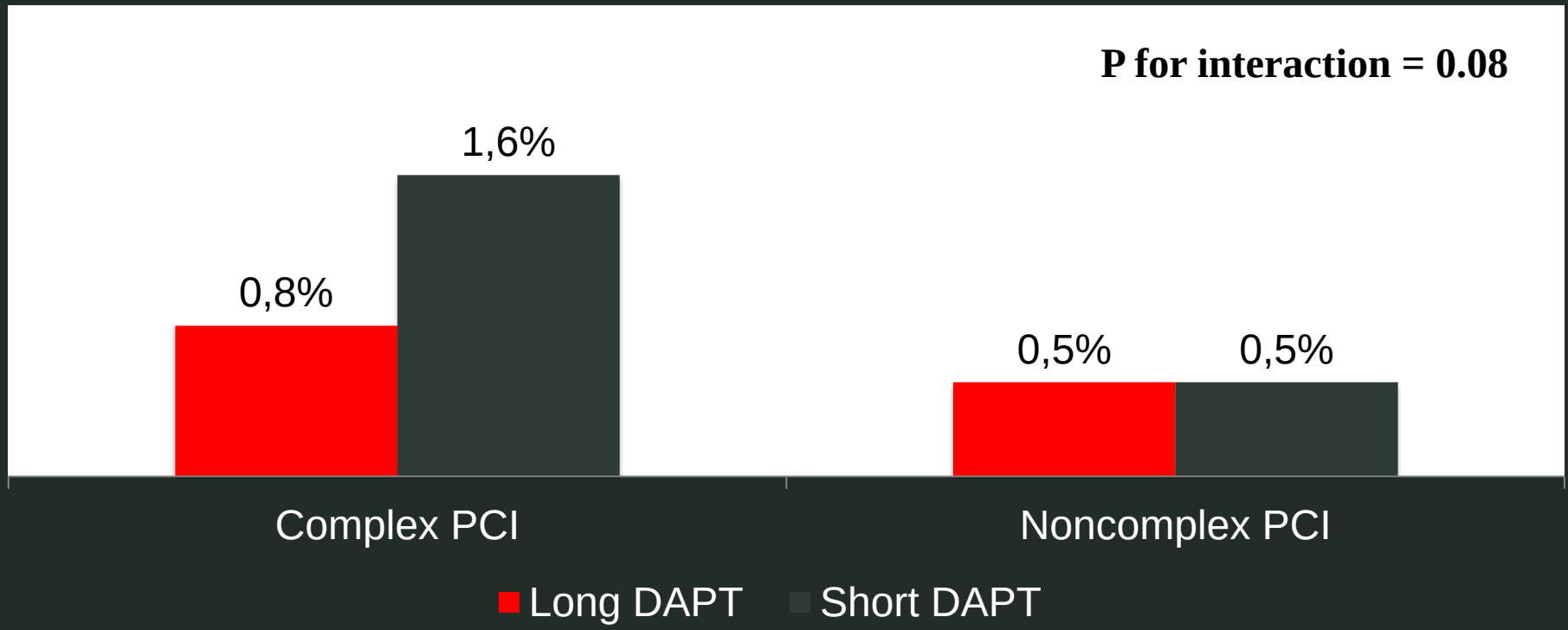
La doppia antiaggregazione prolungata : gli aggiornamenti dal PEGASUS

- robusto disegno e risultati convincenti
- coerenza dei risultati in numerosi sottogruppi prespecificati
- spalanca il focus sul paziente stabile nella fase successiva a una sindrome coronarica acuta

DAPT Duration for Complex PCI

Patient-level meta-analysis of 9,577 pts from 6 PCI trials of DAPT duration

Definite or probable stent thrombosis



Complex PCI was defined as having at least 1 of the following features: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion

Giustino G et al. JACC 2016;68:1851-1864

DAPT a lungo termine : un nuovo paradigma

Il rischio residuo del paziente nella pratica clinica

It’s time to re-focus our attention and resources on the chronic phase after an acute coronary event

LOV 2017

The EYESHOT Post-MI Snapshot

EYESHOT (EmployEd antithrombotic therapies in patients with acute coronary Syndromes HOspitalized in iTaly) Post-MI Registry

230 centers

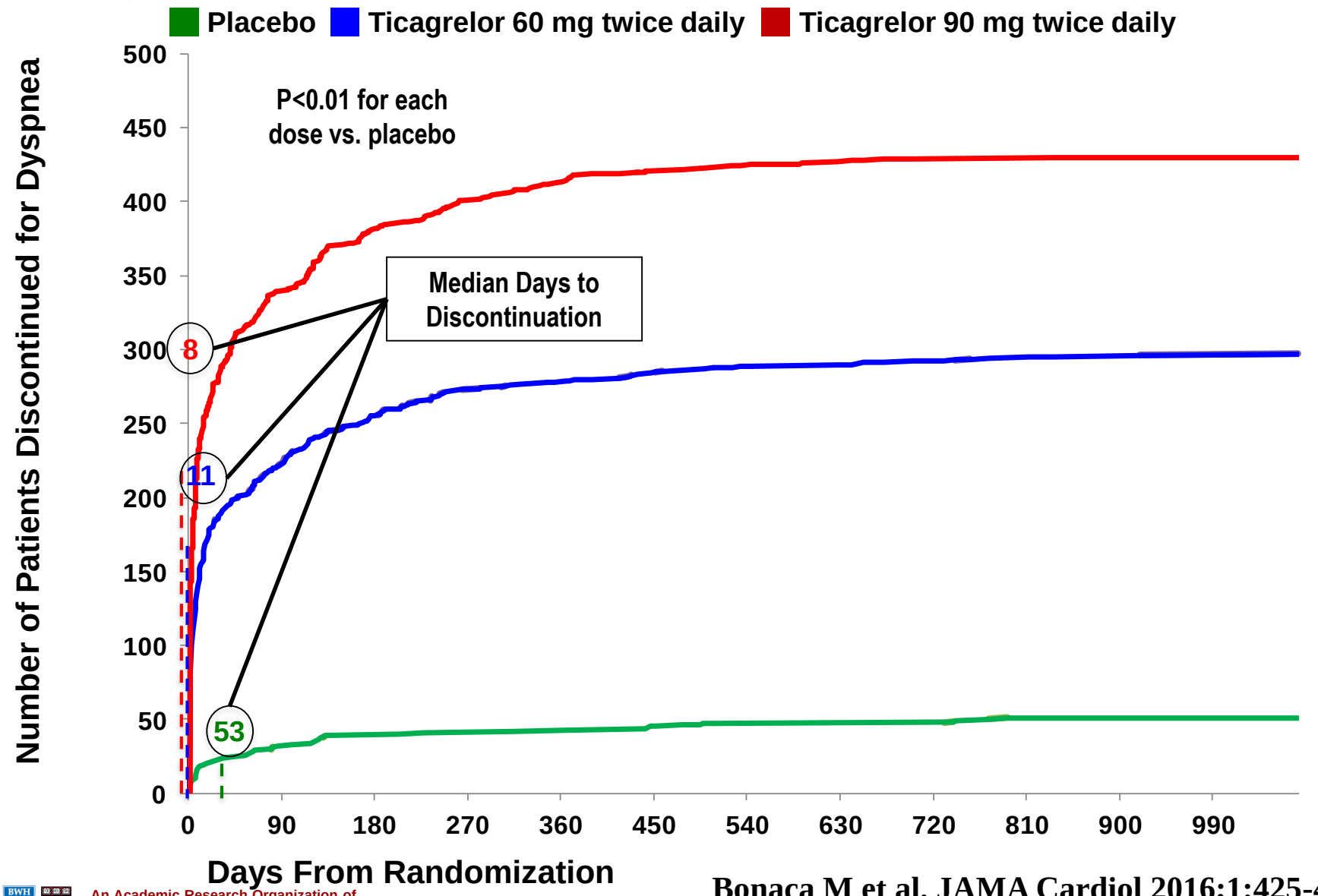
Post-PCI

Registro prospettico multicentrico dei pazienti dimessi dalle Cardiologie della Lombardia rivascolarizzati con angioplastica coronarica

Sponsor - Società Italiana di Cardiologia Interventistica GISE

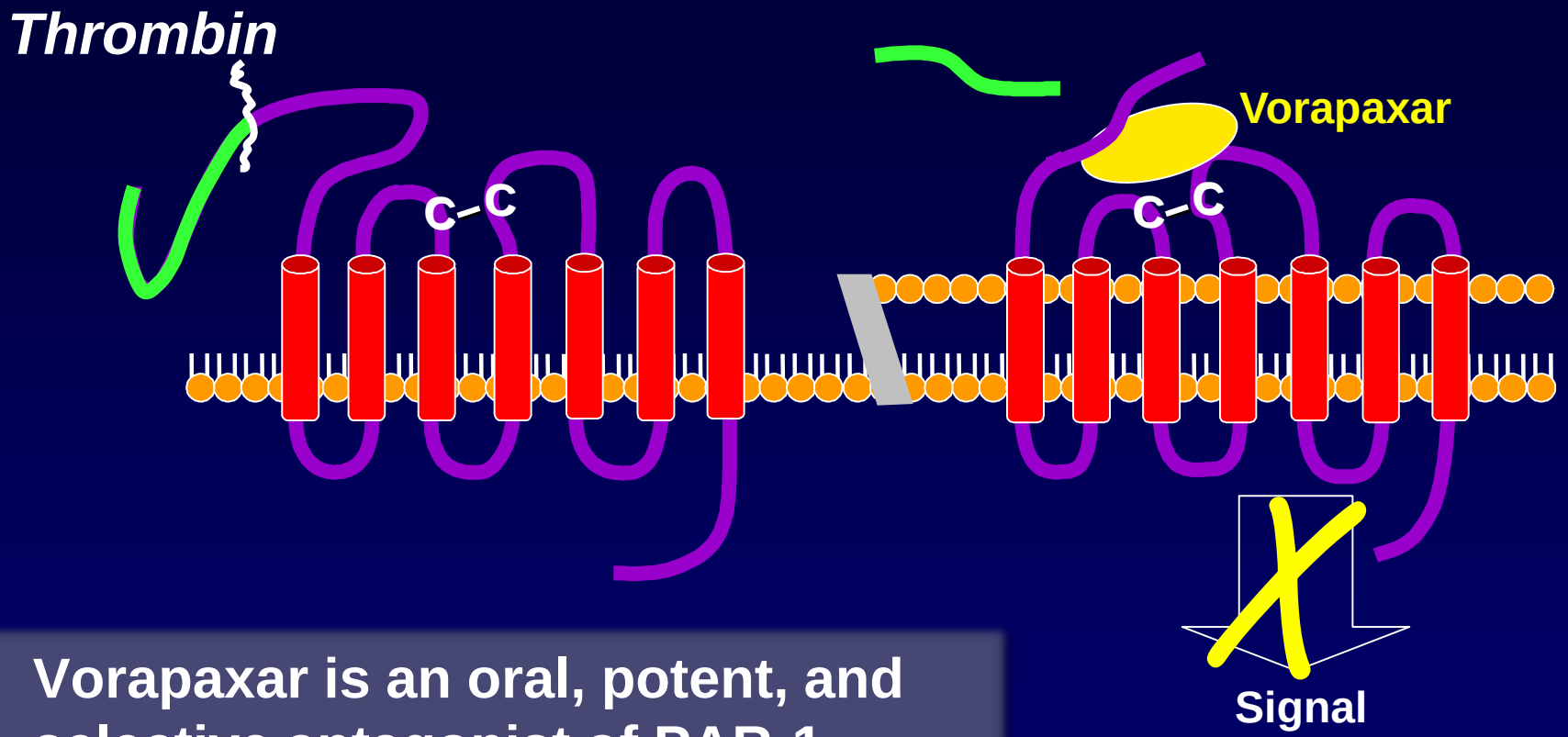
Unrestricted grant : Astra Zeneca

Discontinuation over time for Dyspnea by Randomization Group



Bonaca M et al. JAMA Cardiol 2016;1:425-432

Protease-activated receptor (PAR)-1



- Vorapaxar is an oral, potent, and selective antagonist of PAR-1
- Metabolism by CYP3A4 enzymes
- No meaningful renal clearance
- Long half-life (T1/2 > 100 hrs)

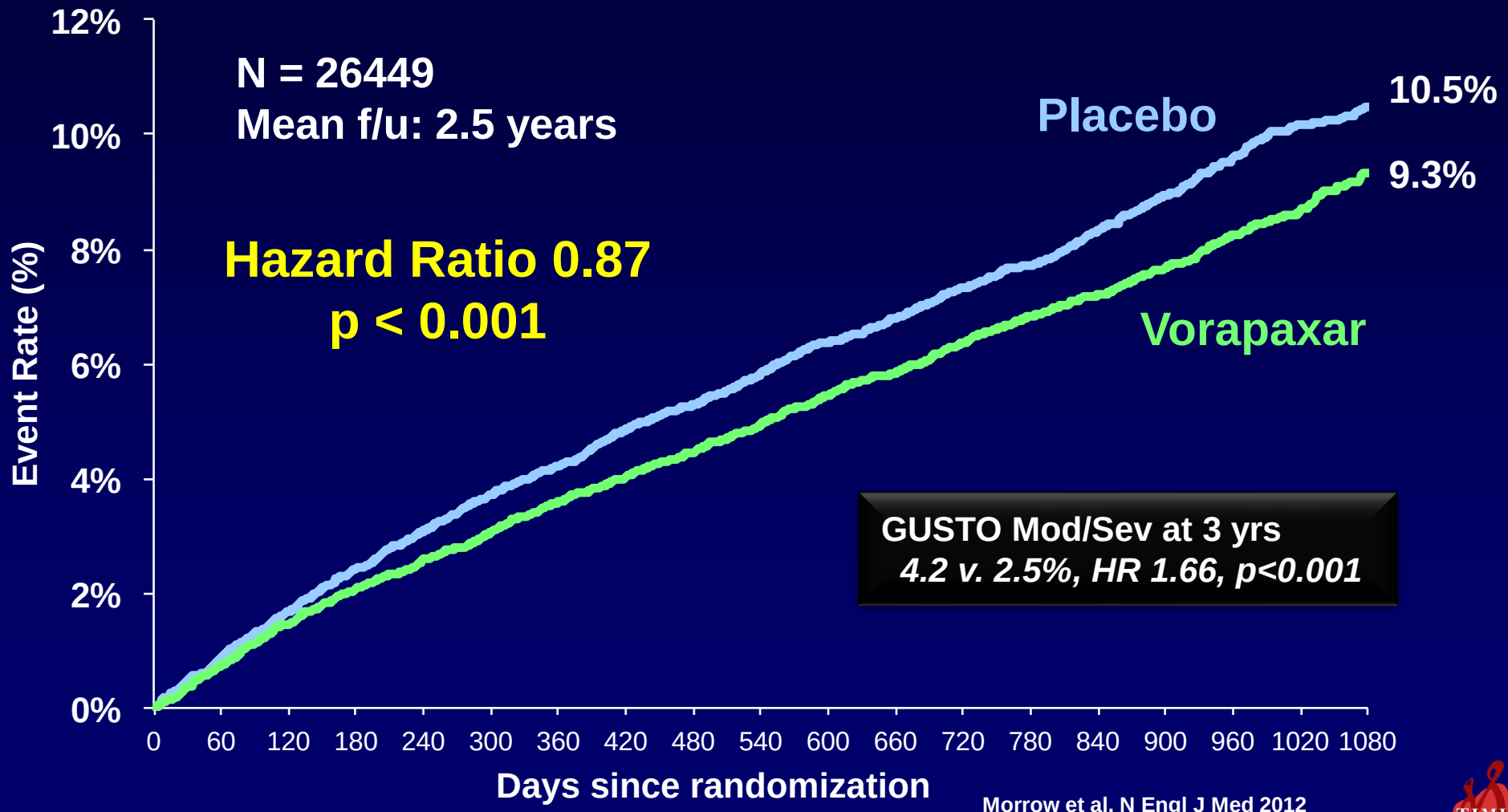
Shape Change
Activation
Aggregation

Adapted from Vu TH et al. *Cell* 1991;64:1057–66.

Background – 1° Efficacy Evaluation

Overall Population

CV Death, MI, or Stroke



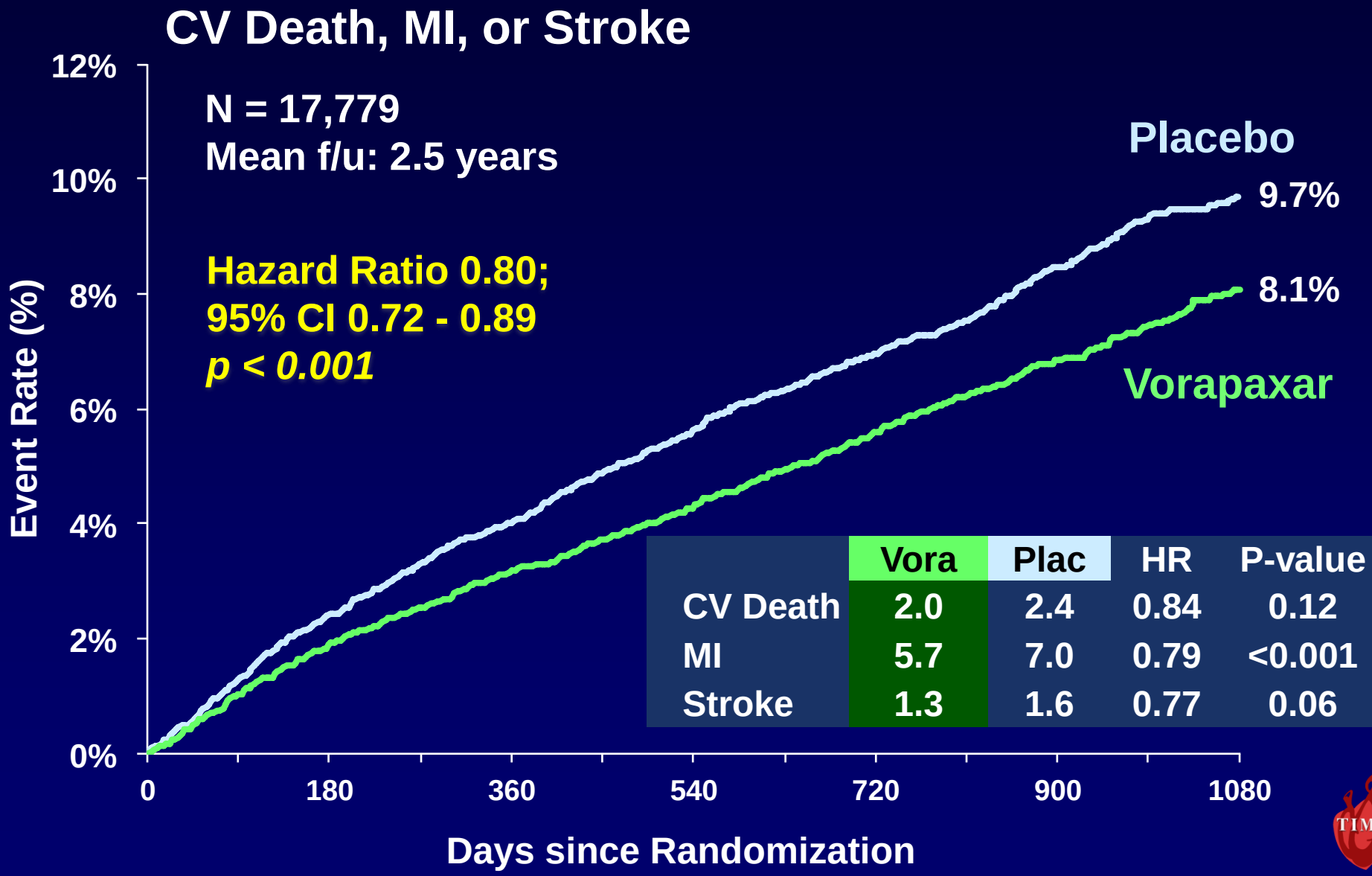
Morrow et al. N Engl J Med 2012
ClinicalTrials.gov NCT00526474c

MI Cohort

TRA 2°P TIMI 50

Primary Efficacy Evaluation

Prior MI Cohort



	Vora	Plac	HR	P-value
CV Death	2.0	2.4	0.84	0.12
MI	5.7	7.0	0.79	<0.001
Stroke	1.3	1.6	0.77	0.06

TIMI