

Expert Debates in Antithrombotic Therapy

Moderator

Deepak L. Bhatt, MD, MPH

Presenters & Discussants

Robert A. Harrington, MD

P. Gabriel Steg, MD

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Expert Debates in Antithrombotic Therapy

Do Diabetic Patients with CAD Need More Than Just ASA?

Moderator

Deepak L. Bhatt, MD, MPH

Expert Debates in Antithrombotic Therapy

Diabetic Patients with Coronary Artery Disease (CAD) Need More Than Just Aspirin!

Ph. Gabriel Steg

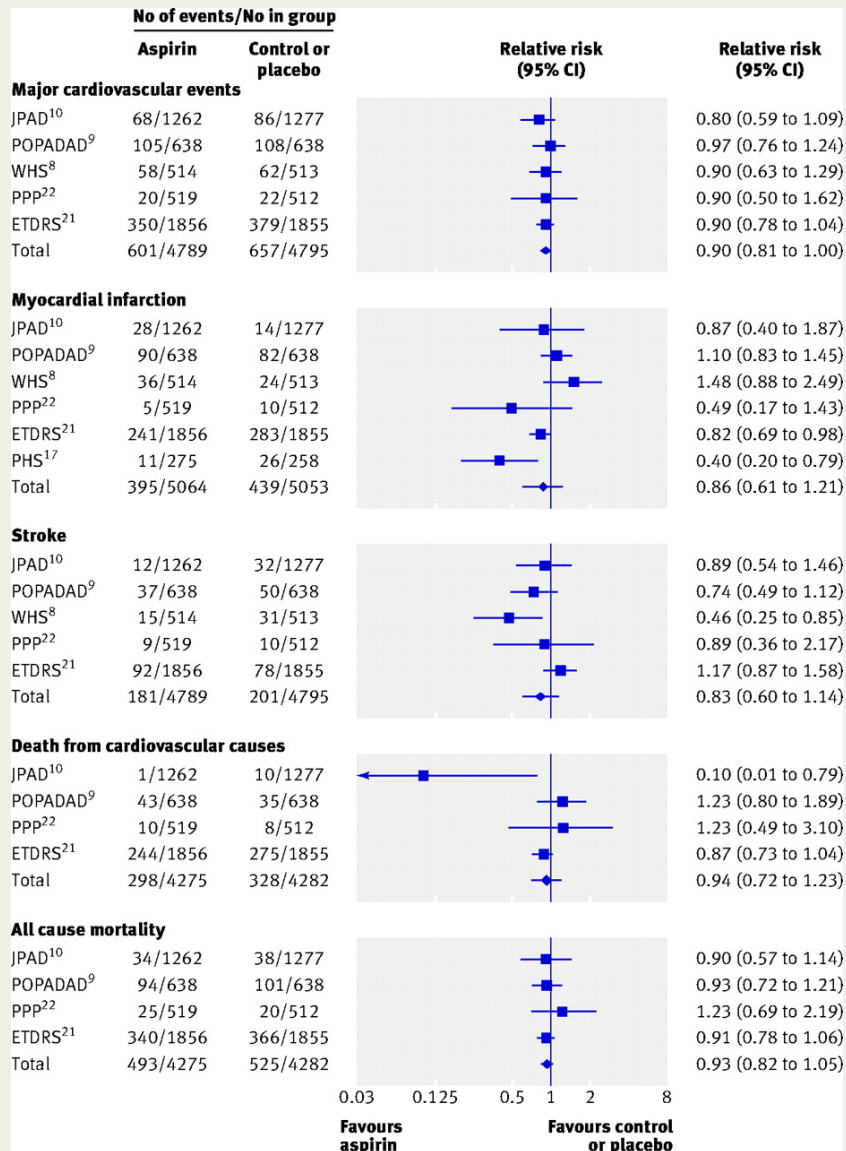
**DHU-FIRE, Hôpital Bichat, Assistance Publique—Hôpitaux de Paris, Université Paris – Diderot, INSERM U-698, Paris, France
French Alliance for Cardiovascular Clinical Trials and Imperial College, Royal Brompton Hospital
London, UK**



« However appealing a strategy is, you should occasionally look at the results »

Sir Winston Churchill

Aspirin for Primary Prevention of Cardiovascular Events in People with Diabetes: Meta-analysis of Randomised Controlled Trials



Aspirin significantly reduced the risk of myocardial infarction in men (0.57, 0.34 to 0.94) but not in women (1.08, 0.71 to 1.65; P for interaction=0.056)

Side effect	No of trials reporting outcome	No of patients	Relative risk (95% CI)
Any bleeding	3	7281	2.50 (0.76 to 8.21)
Gastrointestinal bleeding	3	4846	2.11 (0.64 to 6.95)
Gastrointestinal symptoms*	2	3815	5.09 (0.08 to 314.39)
Cancer	2	2307	0.84 (0.62 to 1.14)

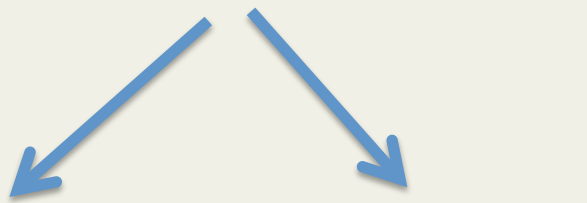
*As generically reported by authors.

Conclusions A clear benefit of aspirin in the primary prevention of major cardiovascular events in people with diabetes remains unproved. Sex may be an important effect modifier. Toxicity is to be explored further.

Primary Prevention Trials with ASA in Diabetes

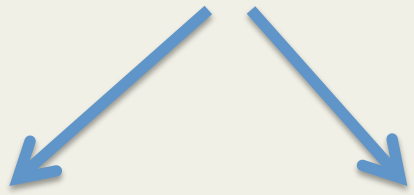
ASCEND

15,000 pts with Type I or II diabetes
No evidence of atherothrombosis



100 mg ASA

Placebo



1g Omega 3 FA

Placebo

Primary endpoint: serious vascular events
Nonfatal MI, nonfatal stroke, CV death,
excluding ICH

NCT00135226

ACCEPT-D

5170 pts with Type I or II diabetes
No evidence of atherothrombosis



100 mg ASA
Simva 20 mg

Placebo
Simva 20 mg

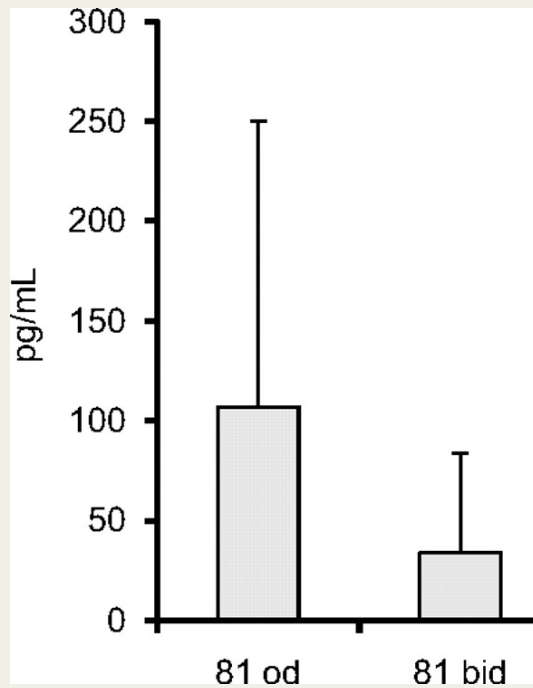
Open Label

Primary endpoint: CV death,
non-fatal MI, nonfatal stroke,
and CV admissions

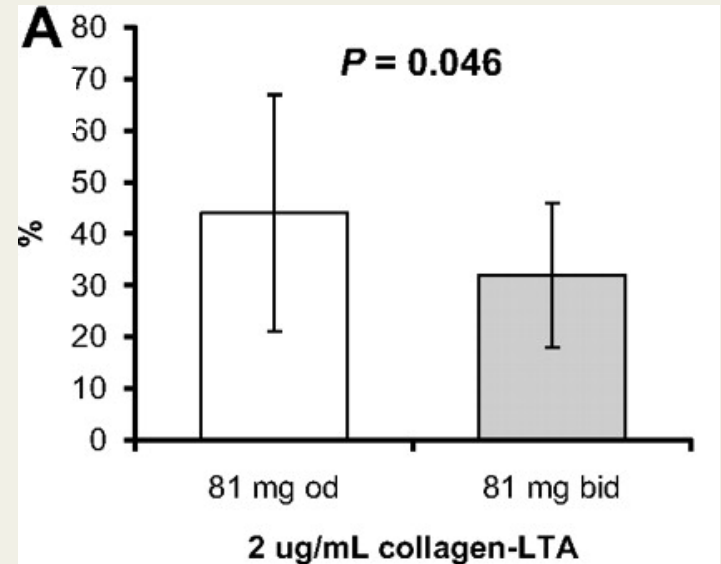
ISRCTN48110081

Value of BID Dosing of Aspirin in Diabetics

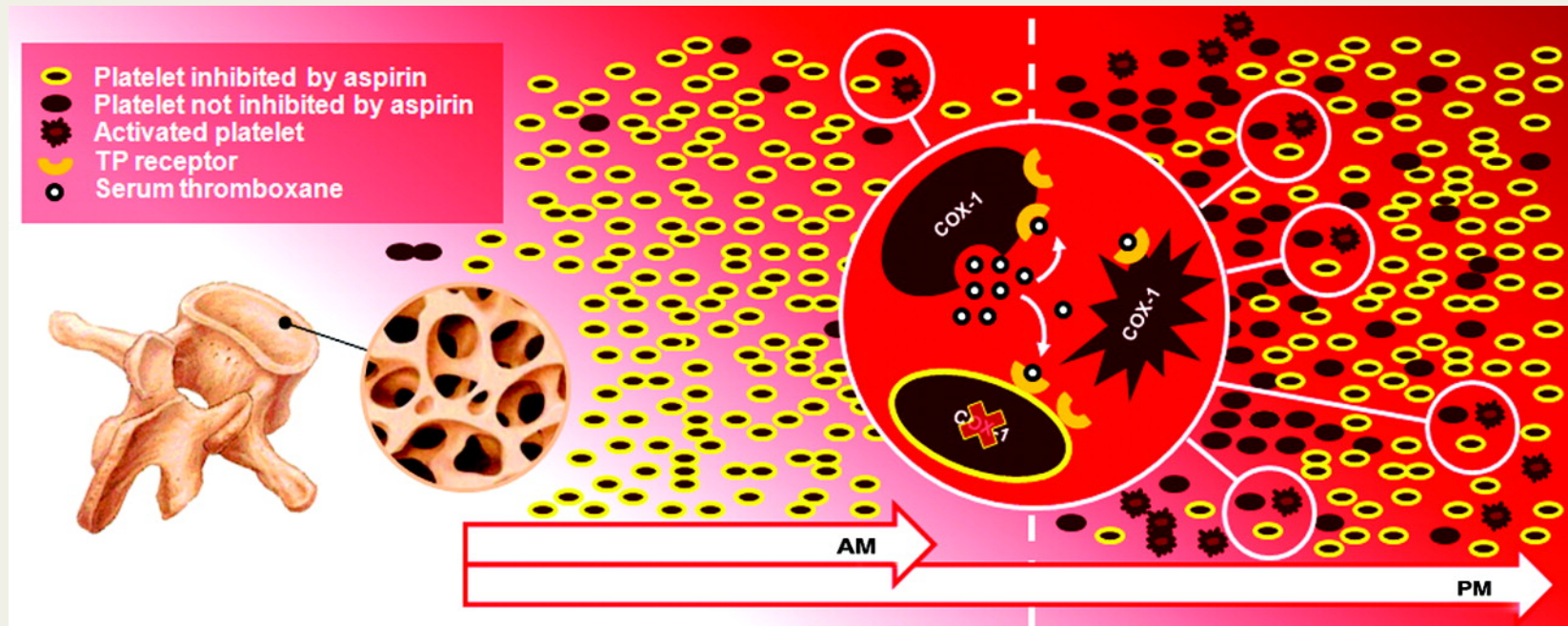
Residual thromboxane B2 level



Residual collagen-induced aggregation - Luminometry

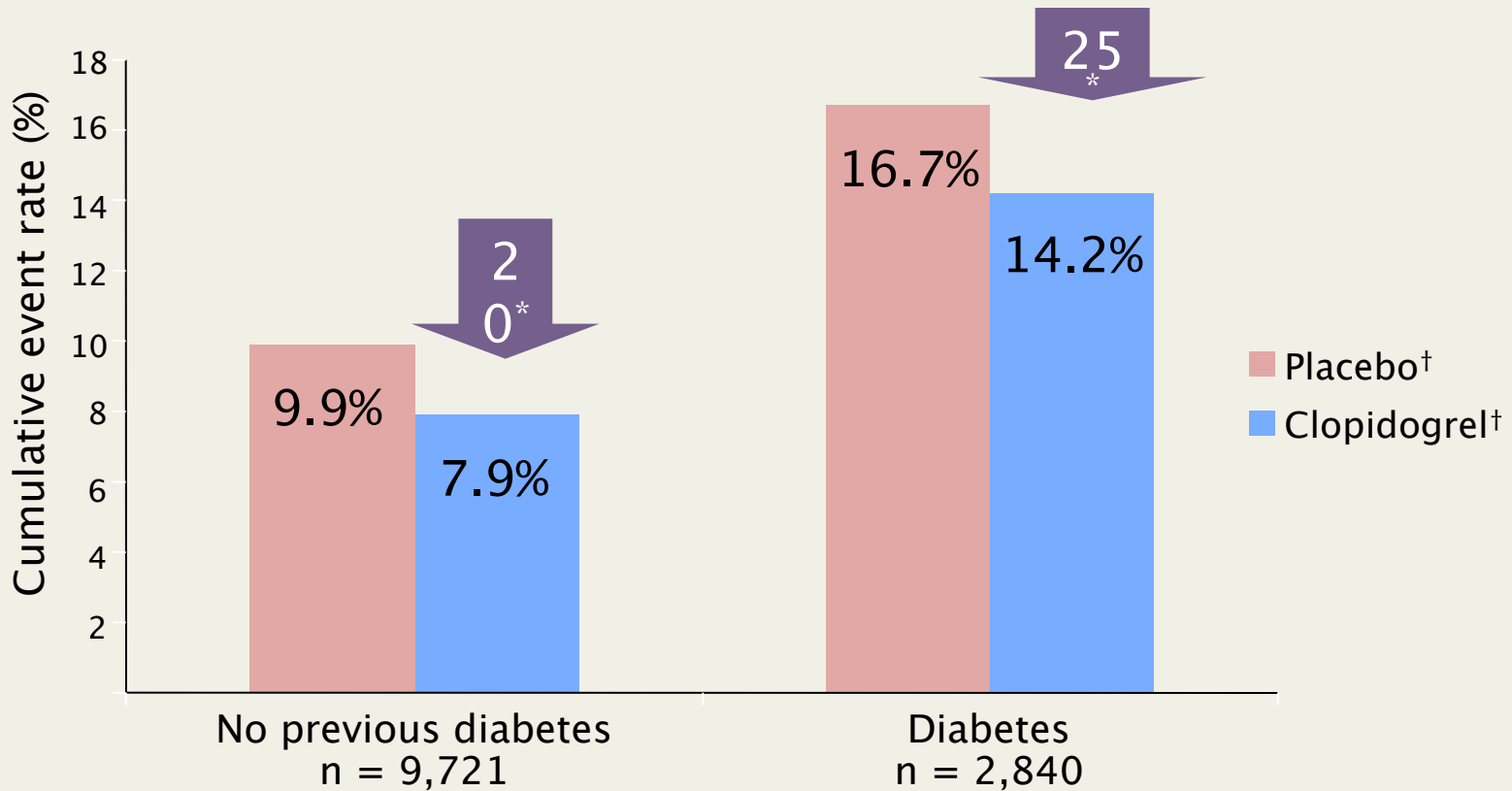


Schematic of Circadian Release of Platelets into Bloodstream from Bone Marrow and Impact of a Single Daily Dose of Aspirin on Newly Generated Platelets in Type 2 Diabetes Mellitus



CURE: Clopidogrel on Top of Aspirin in Patients with ACS and Diabetes

(Myocardial Infarction, Stroke, or Vascular Death)



*Number of events prevented/1,000 patients treated/9 months

†On top of standard therapy (including ASA)

Primary Efficacy – Diabetics vs Non Diabetics

Overall population

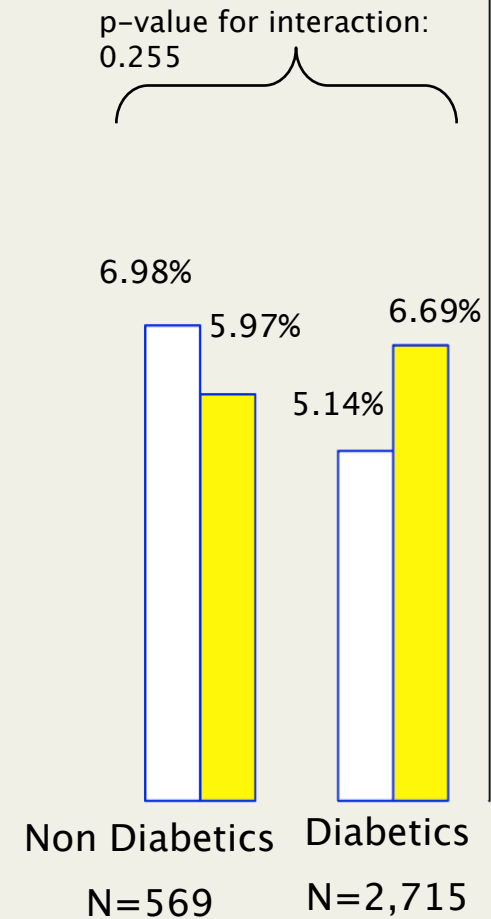
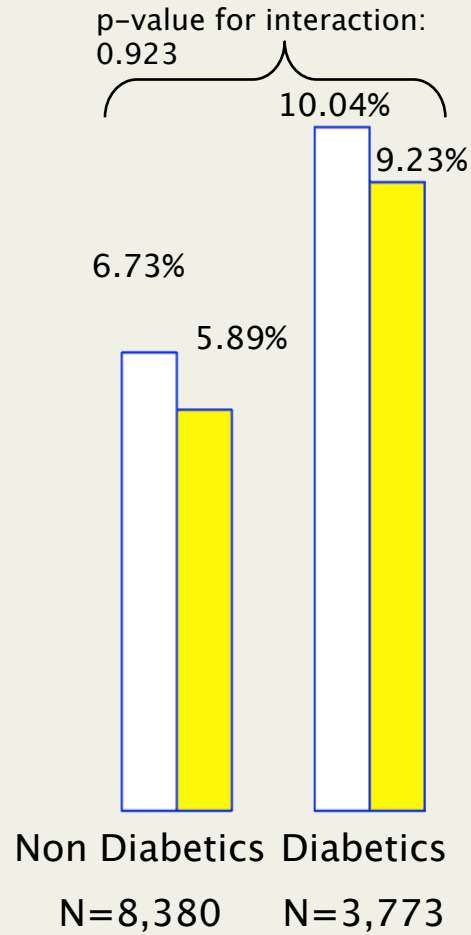
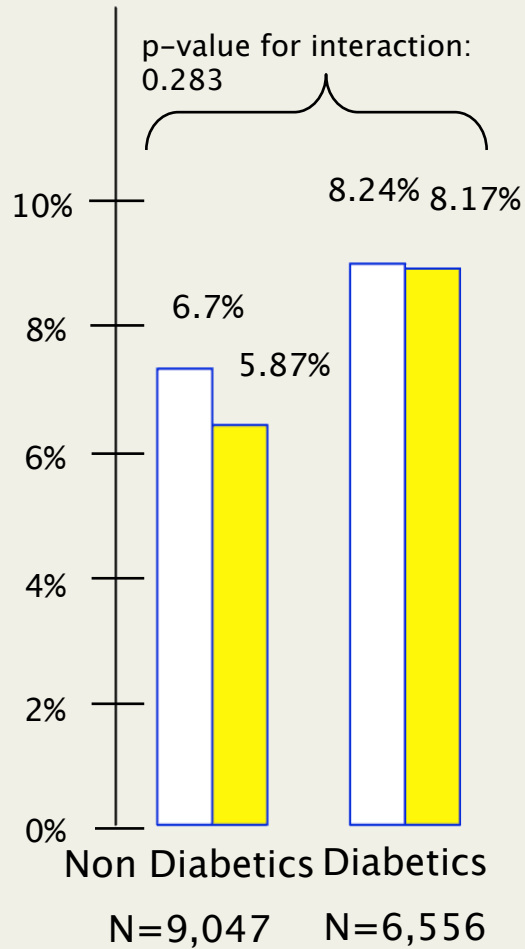
N=15,603

Secondary prevention

N=12,152

Primary prevention

N=3,284

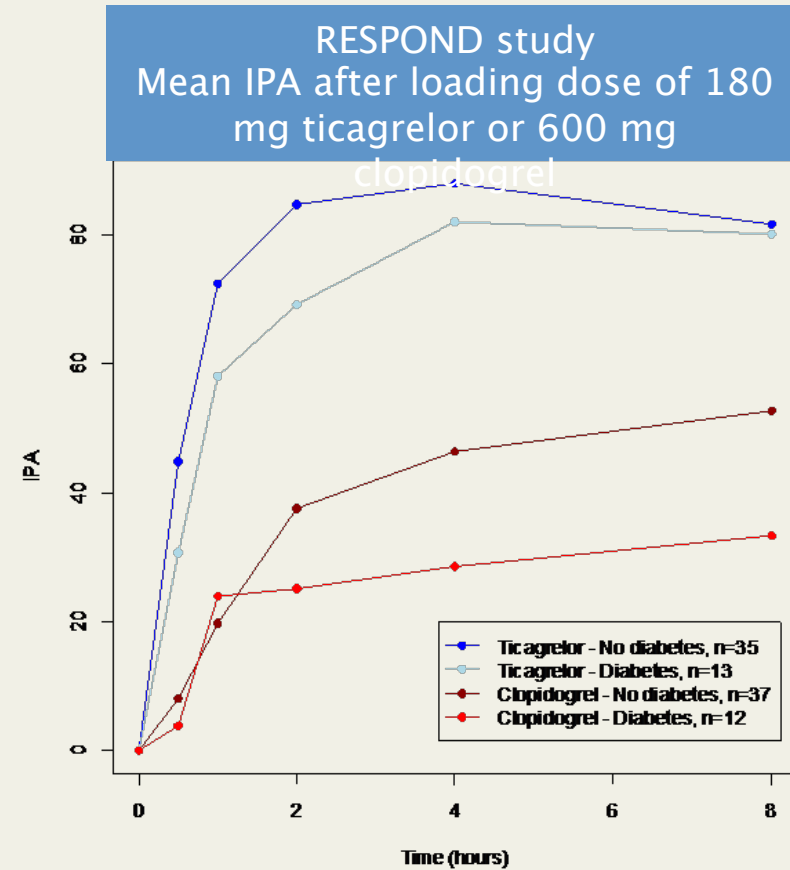
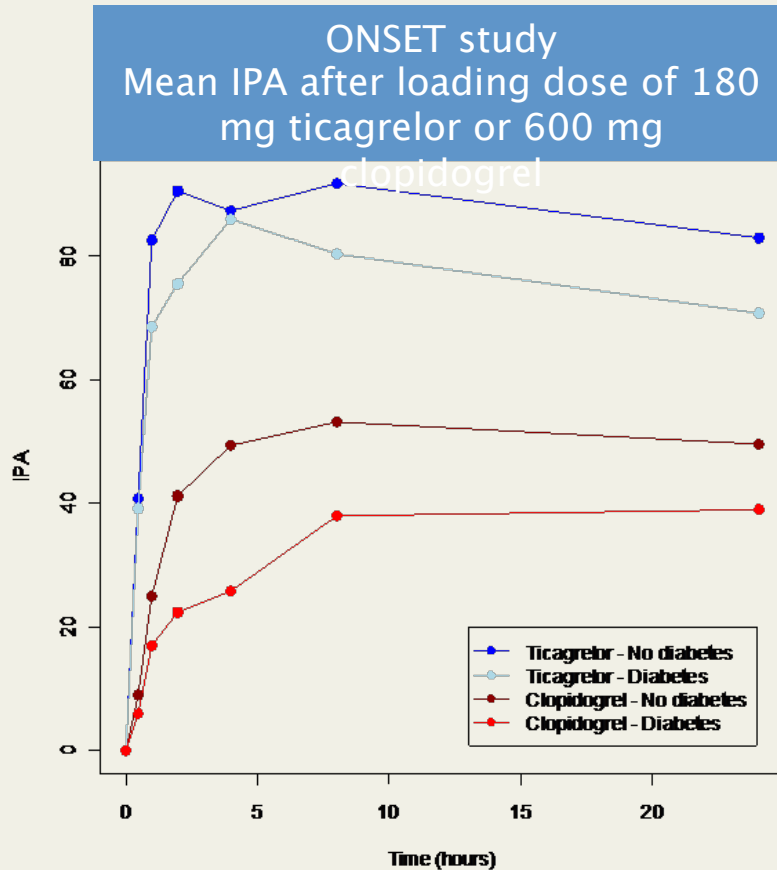


Placebo + ASA

Clopidogrel + ASA

Ticagrelor in Diabetes

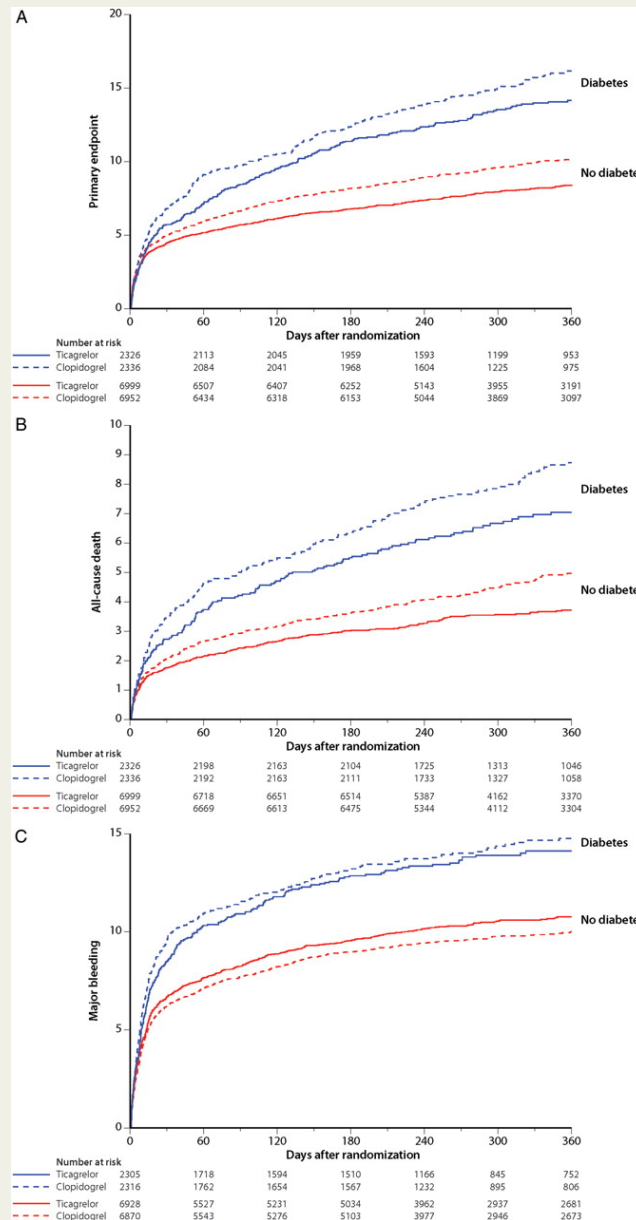
IPA



CV death, MI, and stroke

Total mortality

Major bleeding



PLATO

Diabetes vs No Diabetes

Ticagrelor (solid lines)
Clopidogrel (dotted lines)

Diabetes (blue lines)
No diabetes (red lines)

Prévention CV chez des patients avec diabète de type 2, coronariens, sans antécédents d'IDM ou AVC

Diabète Type 2 à Haut Risque CV*
Traité depuis ≥ 6 mois
Maladie coronaire avérée°
Sans ATCD d'IDM ou AVC

maladie coronaire avérée définie par:

- ATCD d'angioplastie coronaire
- ATCD de pontage aorto coronaire
- sténose $\geq 50\%$ à la coronarographie sur ≥ 1 vaisseau

Ticagrelor*

Placebo*

* En plus du traitement de prévention CV incluant l'aspirine à faible dose

Event-driven study (750), Suivi moyen ~ 3 ans (n = 17 000)

Critère 1aire : Mortalité CV, IDM, AVC

Critères 2aires : Composantes du critère 1aire, mortalité totale, autres

Critère 1aire tolérance : Hémorragies majeures (TIMI - PLATO - BARC)



Thank you!

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Do Diabetic Patients with CAD Need More Than Just ASA? (CON)

Robert A. Harrington, MD

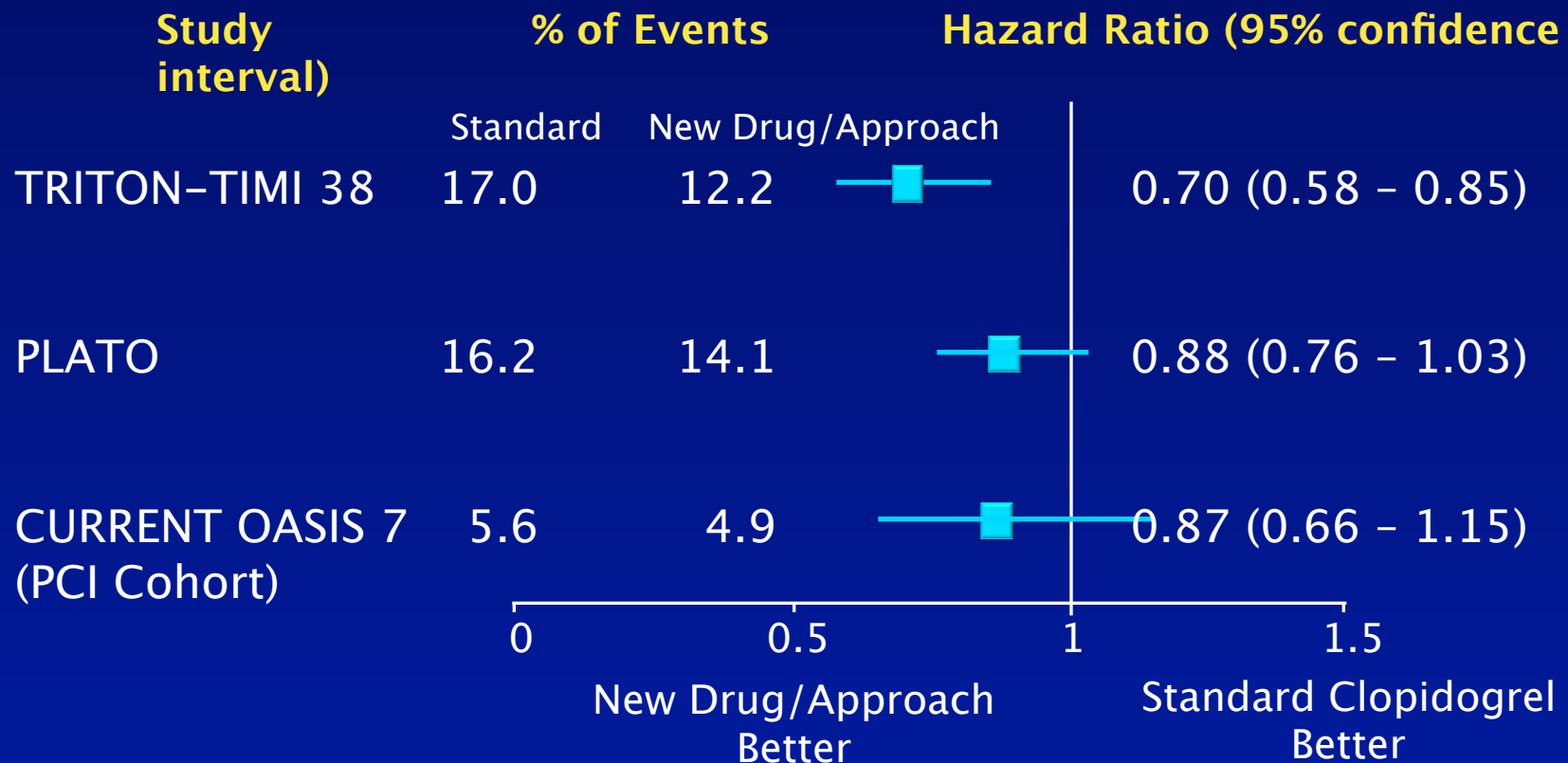
Arthur L. Bloomfield Professor of Medicine

Chair, Department of Medicine

Stanford University

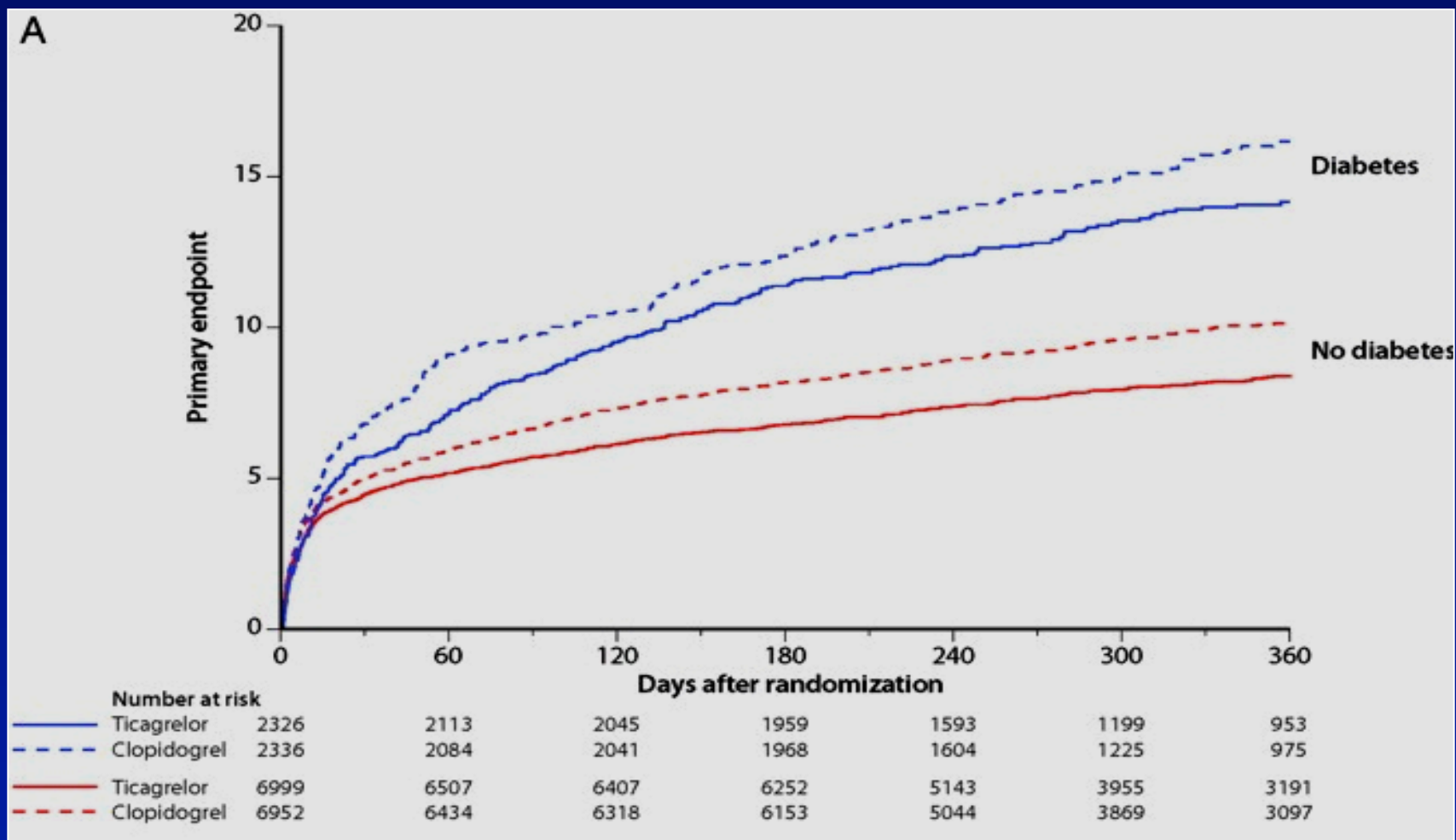
Stanford, California

Efficacy of New Drugs/Approaches in Reducing Adverse Outcomes in Diabetes Mellitus From Large-Scale Clinical Trials



CURRENT-OASIS= Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events Optimal Antiplatelet Strategy for Interventions; PCI=percutaneous intervention; PLATO= A Study of Platelet Inhibition and Patient Outcomes; TRITON-TIMI= Trial To Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction. Ferreiro, Angiolillo. Circulation 2011. 123:798-813.

Ticagrelor in Patients with Diabetes Mellitus PLATO Study



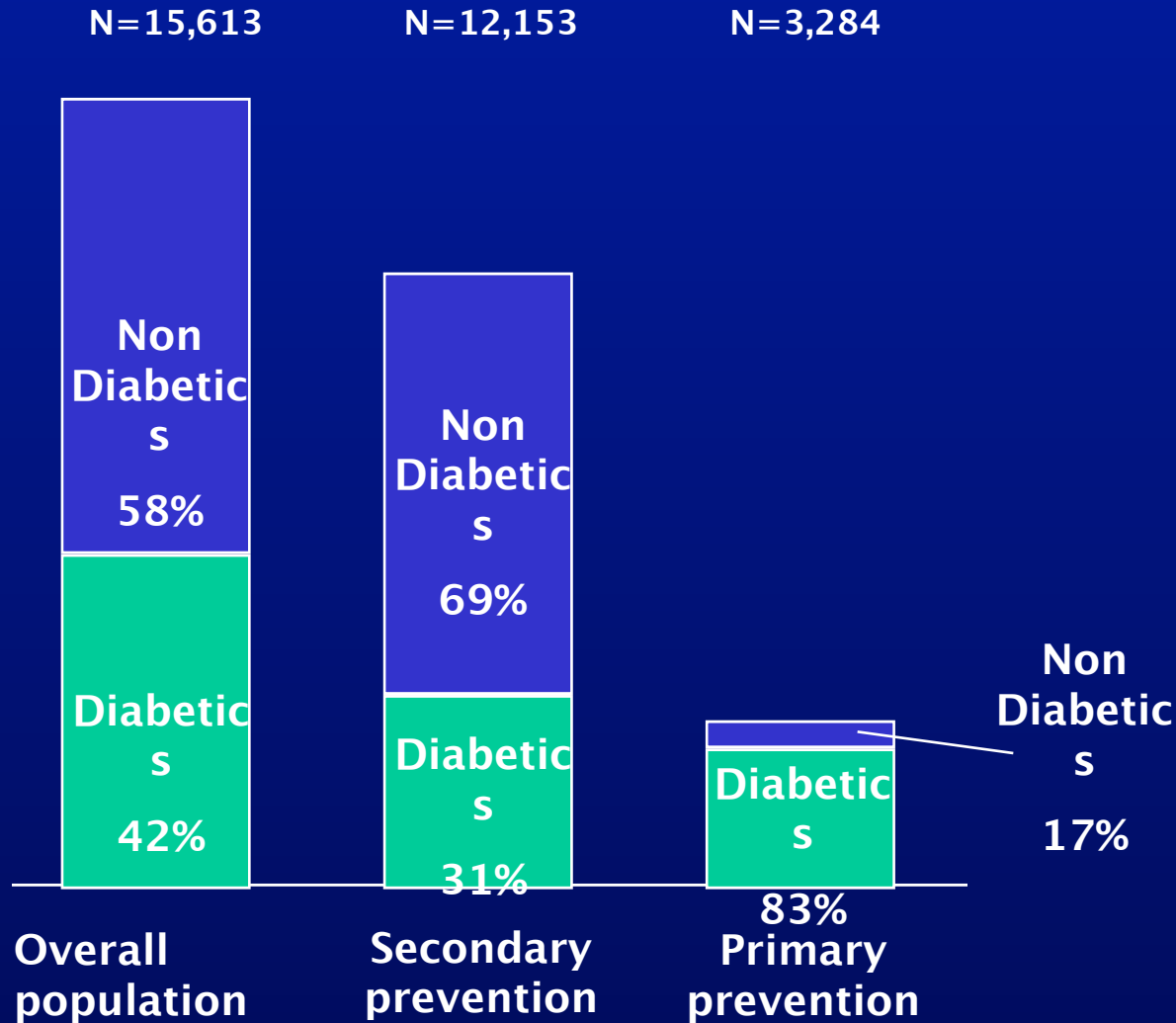
Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials

Giorgia De Berardis, research officer,¹ Michele Sacco, research officer,¹ Giovanni F M Strippoli, editor and regional coordinator of the Cochrane Renal Group,^{1,2} Fabio Pellegrini, senior biostatistician,¹ Giusi Graziano, biostatistician,¹ Gianni Tognoni, institute director,³ Antonio Nicolucci, department head¹

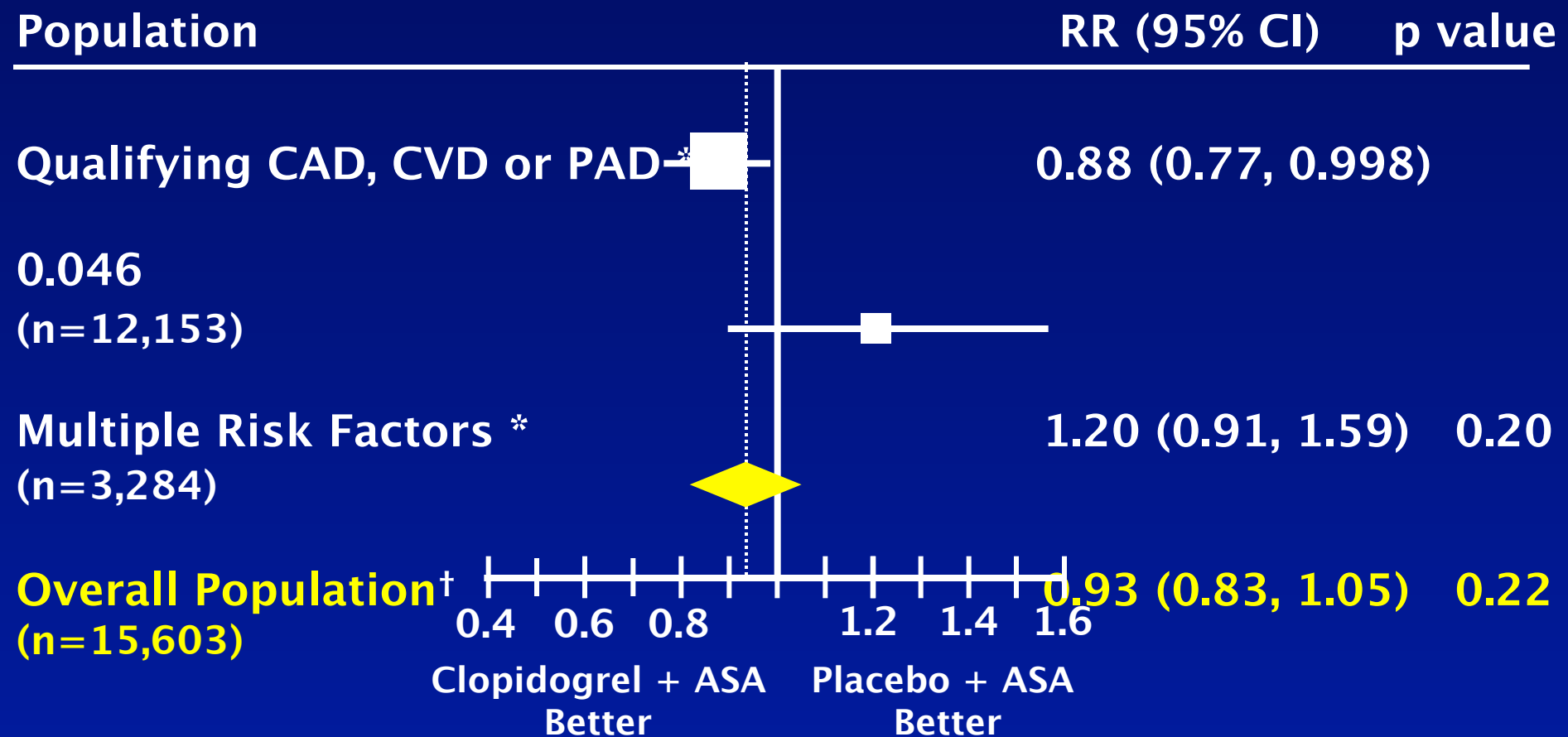
DISCUSSION

A clear benefit of aspirin in the primary prevention of major cardiovascular events or mortality in people with diabetes could not be identified in our meta-analysis. We found no significant reduction in the risk of major cardiac events with aspirin compared with placebo or no treatment. Confidence intervals in this analysis argue for a potential benefit of aspirin, compatible with that observed in other high risk populations, but the benefit was small at best or trials were underpowered to detect it with sufficient precision.

CHARISMA: Proportion of Diabetic Patients in Subgroups



Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category



* A statistical test for interaction showed marginally significant heterogeneity ($p=0.045$) in treatment response for these pre-specified subgroups of patients

† 166 patients did not meet any of the main inclusion criteria

Primary Efficacy - Diabetics vs Non Diabetics

Overall population

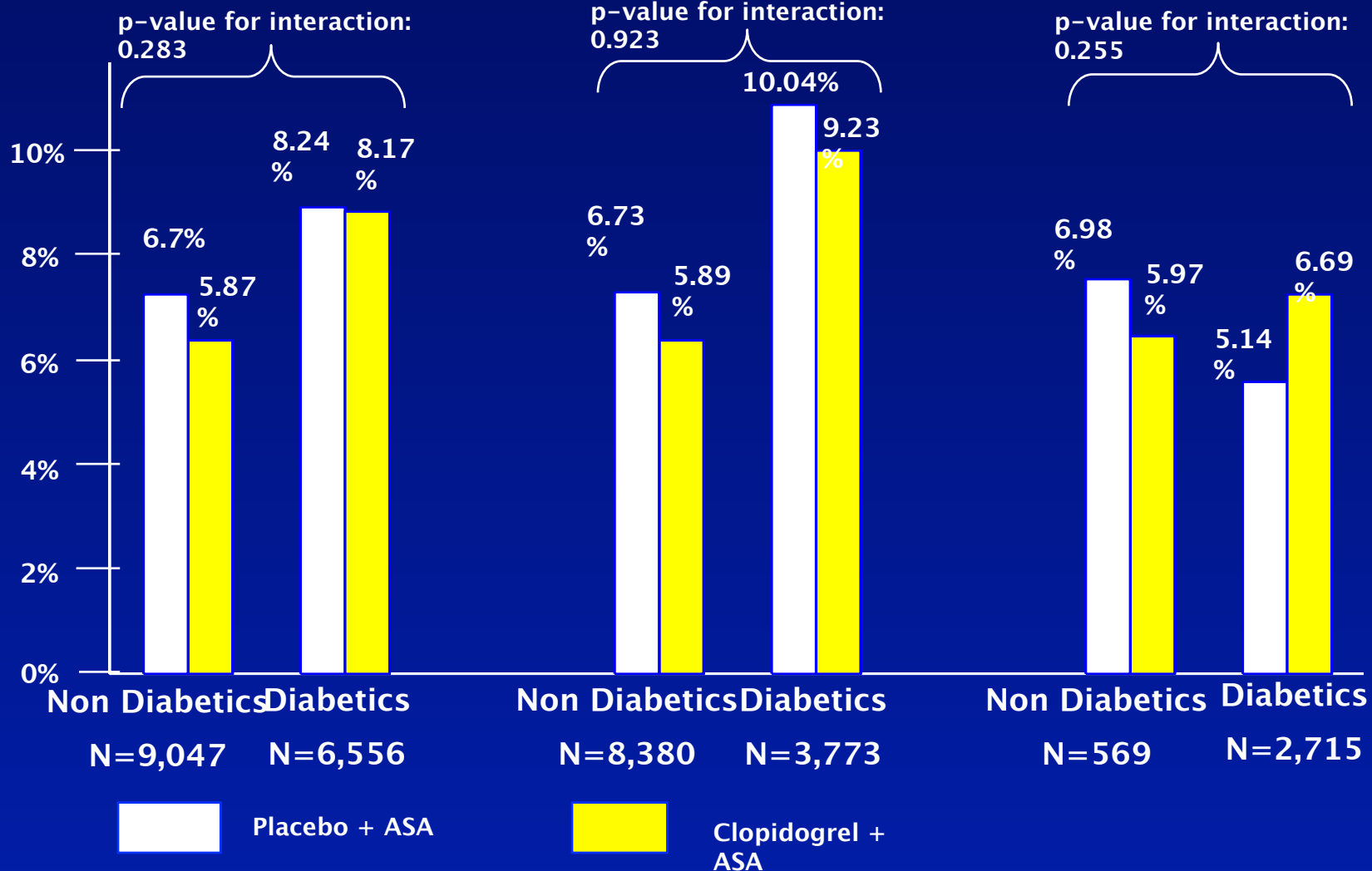
N=15,603

Secondary prevention

N=12,152

Primary prevention

N=3,284



THEMIS

Design and main eligibility criteria

*Type 2 diabetes; men and women ≥ 50 years
 ≥ 6 months glucose lowering drug treatment
At high risk for CV events*
No previous MI or stroke
No planned use of ADP receptor antagonist
or planned revascularisation*

*Low-dose ASA background
therapy based on individual risk*

** At high risk of CV events
defined as history of PCI
or CABG or angiographic
evidence of $\geq 50\%$ lumen
stenosis of at least 1
coronary artery*

Ticagrelor

Placebo

Event driven study; 750 CV events required. 2 years mean follow-up. (n=17 000)

Primary endpoint : Composite of CV death, MI, or stroke

Secondary endpoint: Composite of all-cause death, MI or stroke; CV death; All-cause death

Primary safety: TIMI Major bleeding

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Expert Debates in Antithrombotic Therapy

Should Patients with Stents Receive DAPT for More Than One Year?

Moderator

Deepak L. Bhatt, MD, MPH

Expert Debates in Antithrombotic Therapy

Patients with Stents Should Receive Dual Antiplatelet Therapy (DAPT) for More Than a Year!

Ph. Gabriel Steg

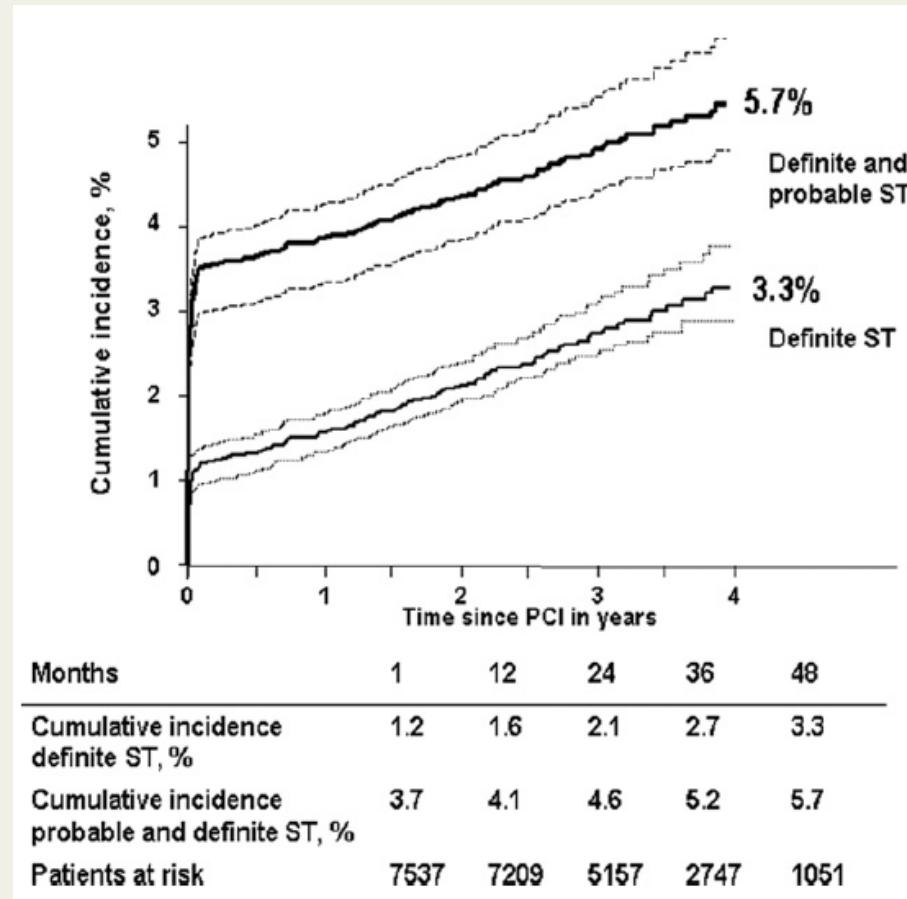
**DHU-FIRE, Hôpital Bichat, Assistance Publique—Hôpitaux de
Paris, Université Paris – Diderot, INSERM U-698, Paris, France
French Alliance for Cardiovascular Clinical Trials and Imperial
College, Royal Brompton Hospital
London, UK**

Incidence of DES Stent Thrombosis: The Bern and Rotterdam Experience

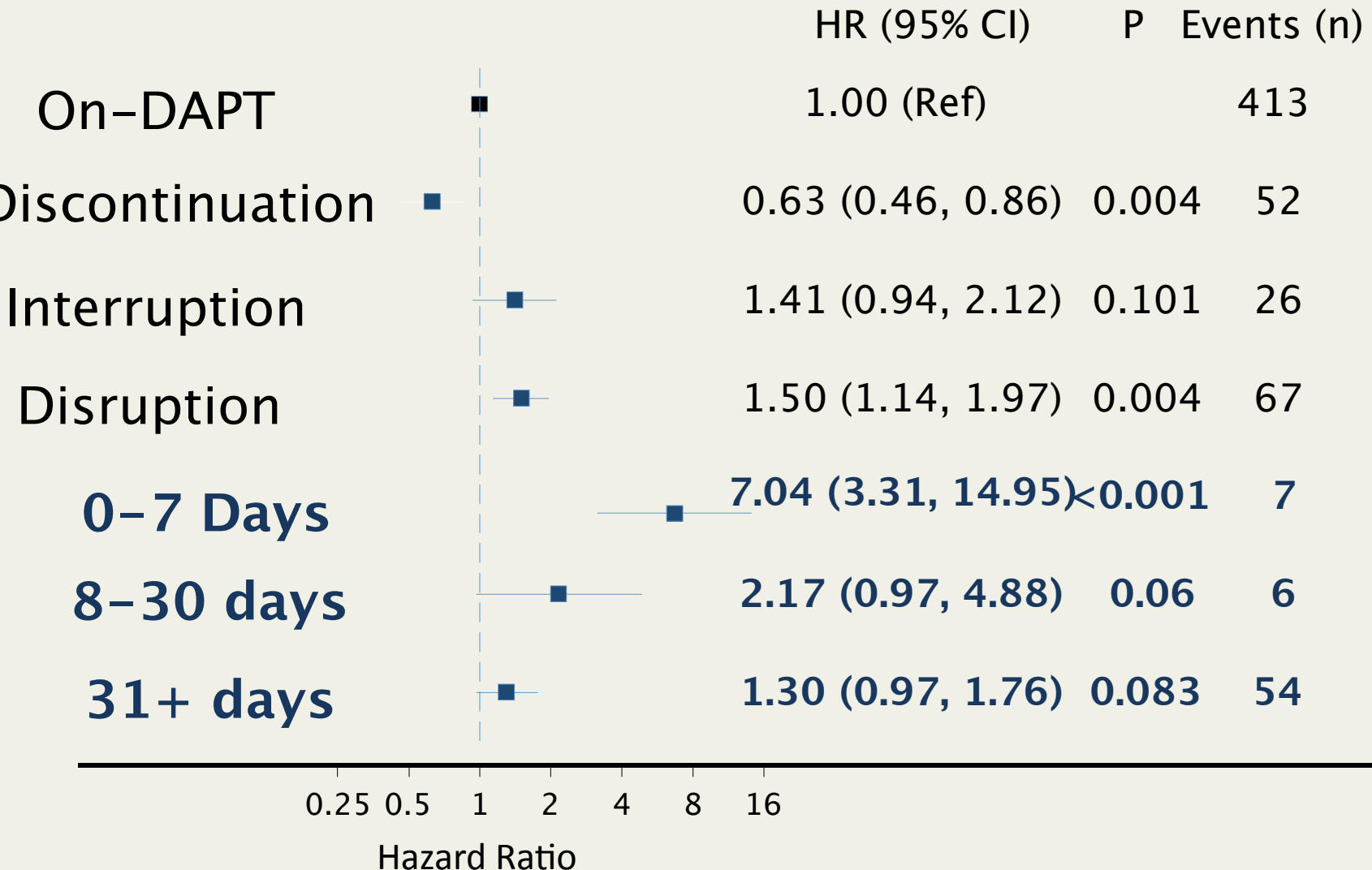
146 patients with dual anti-platelet therapy for 6–12 months

Annual rate of
ST: 0.4% to
0.6%/year

Incidence rate:
1.0/100
patient-years



DAPT Cessation and MACE*

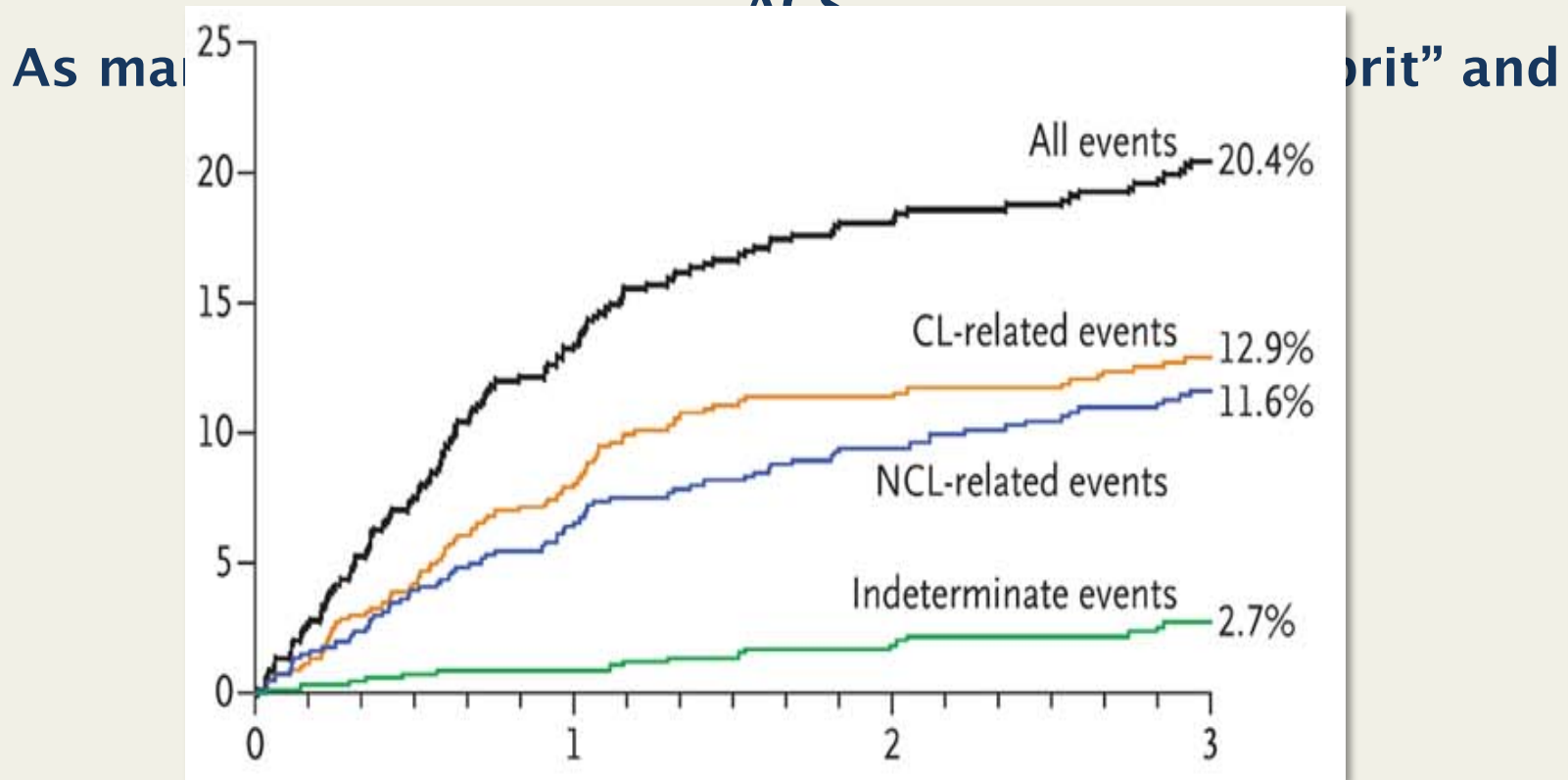


*Cardiac Death, Def/Prob ST, Spontaneous MI, Clinically Driven TLR.

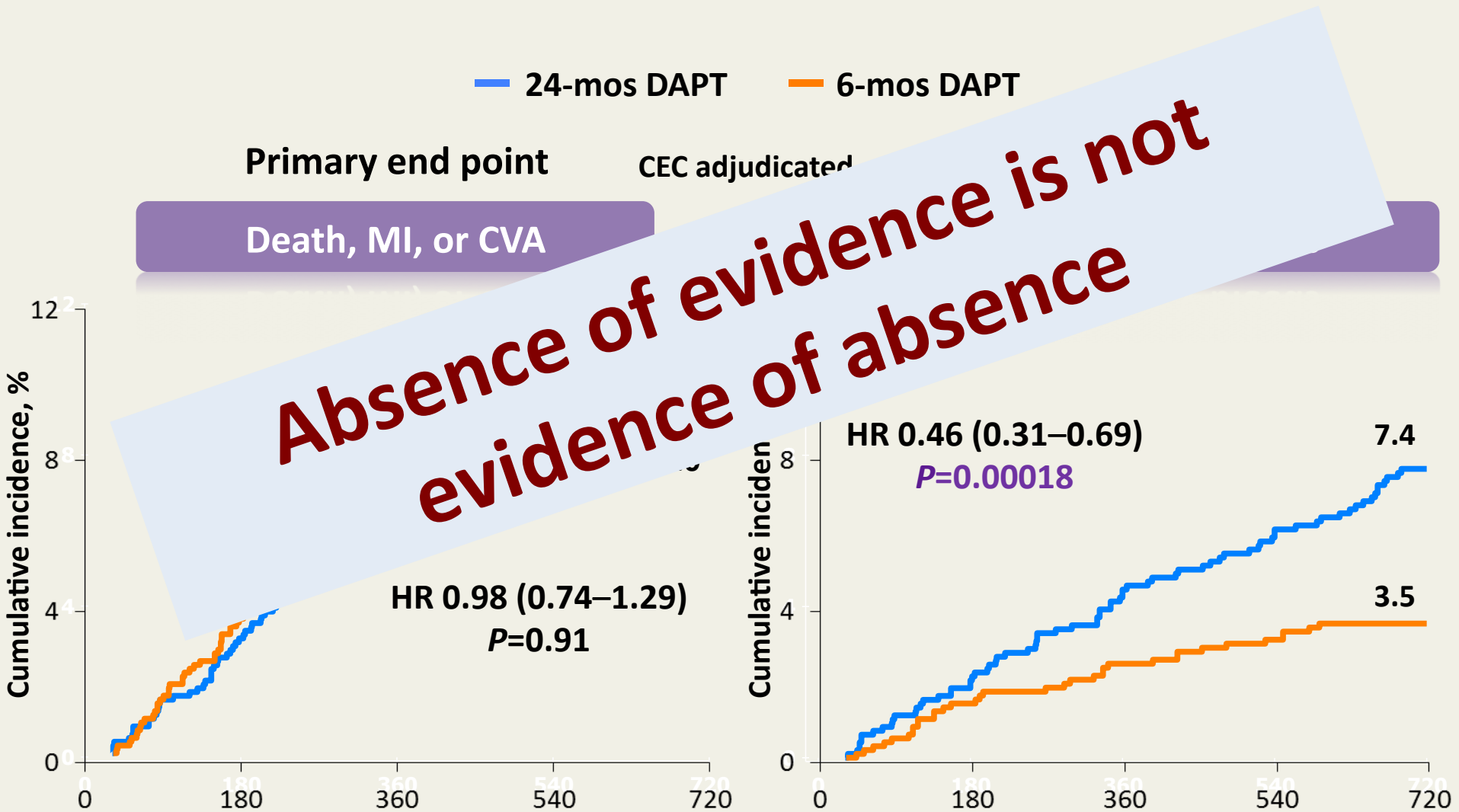
All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, number of stents implanted.

We Should Treat Patients, Not Stents

Findings from the PROSPECT study:
MACE after successful, uncomplicated PCI in 697 patients with ACS

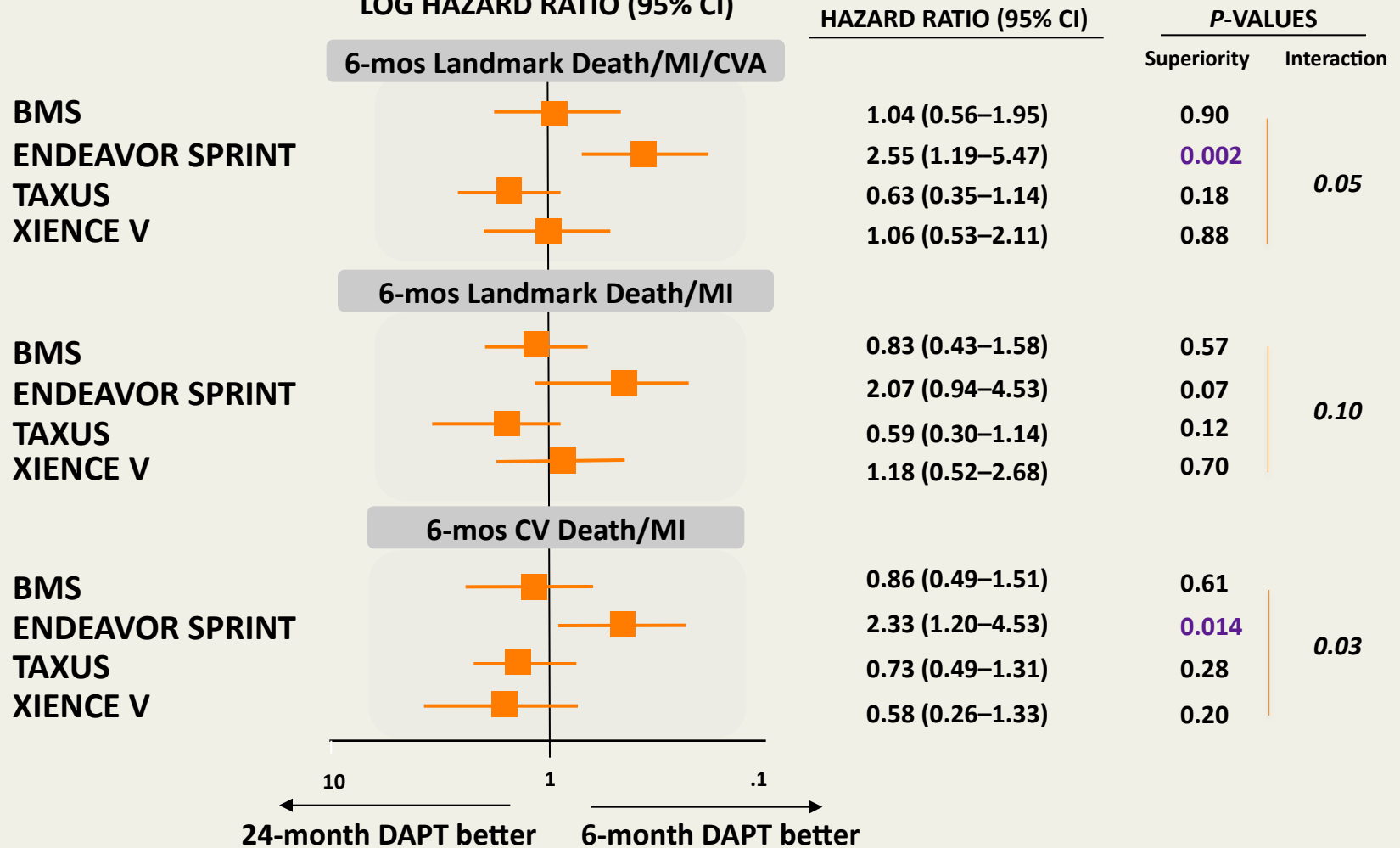


The PRODIGY Trial



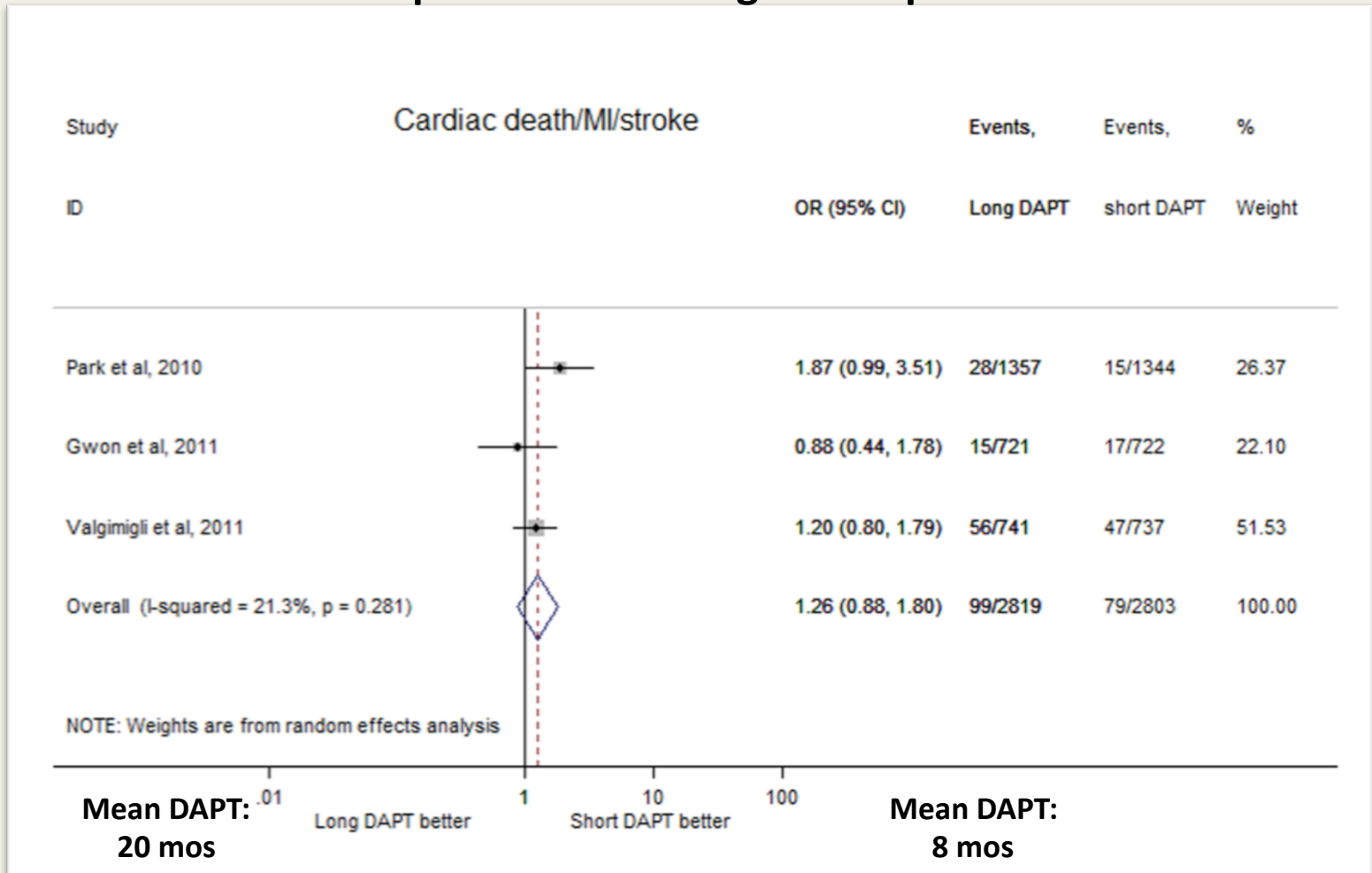
Patient-Oriented Outcome Stratified by Stent

From 6 up to 24 months
LOG HAZARD RATIO (95% CI)



Benefits and Risks of Long-Term Duration of DAPT After Drug-Eluting Stenting: a Meta-Analysis

5622 patients receiving DES implantation



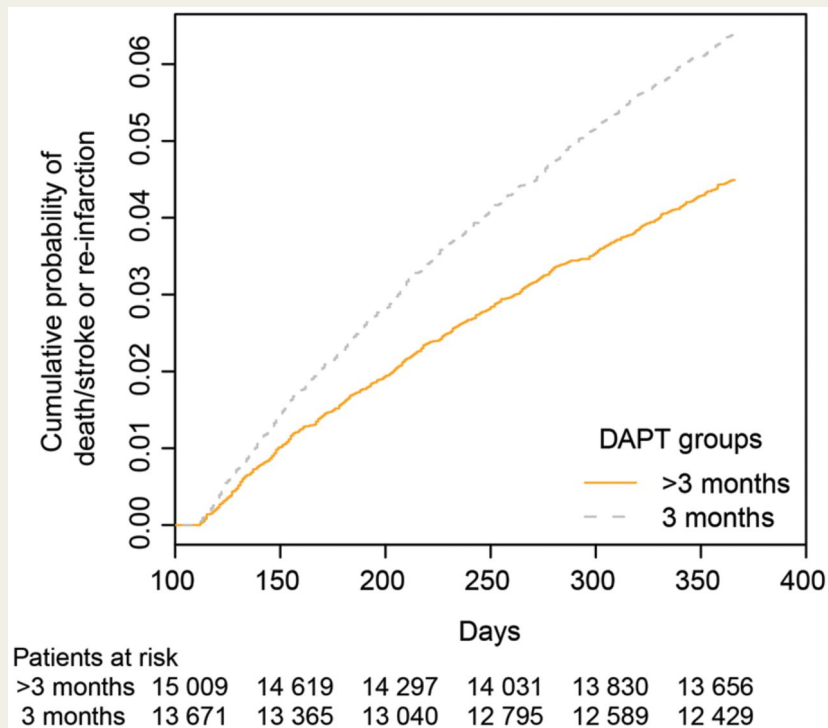
OR, odds ratio.

Valgimigli et al. Int J Cardiol. 2013;168:2579-87.

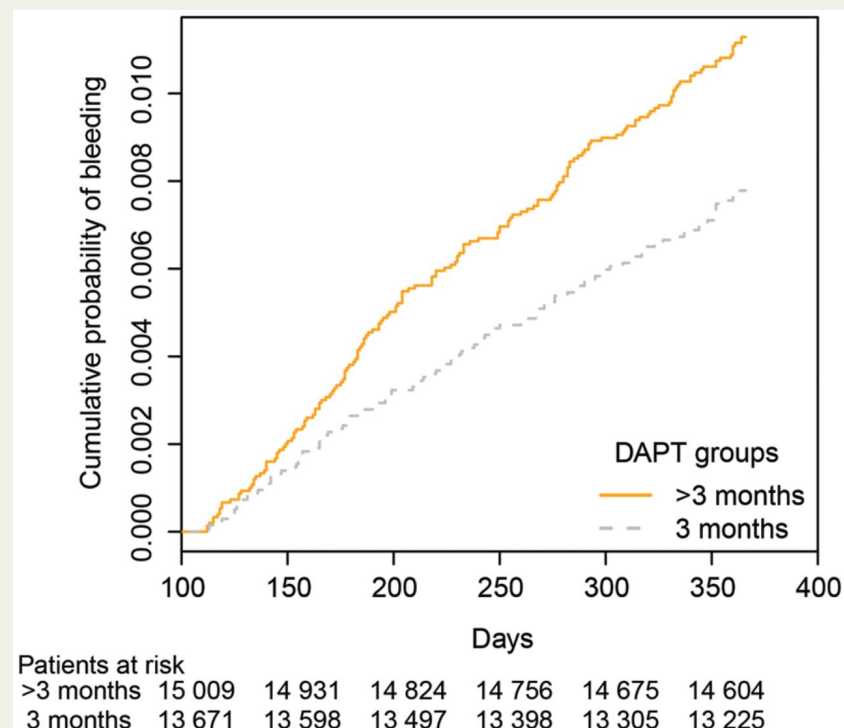
Longer Term Dual Antiplatelet Therapy After ACS Is Associated with Clinical Benefits but More Bleeding

Kaplan-Meier estimate for patients with 3 months' and >3 months' dual antiplatelet treatment duration
 The Swedenheart Registry (n = 56,440)

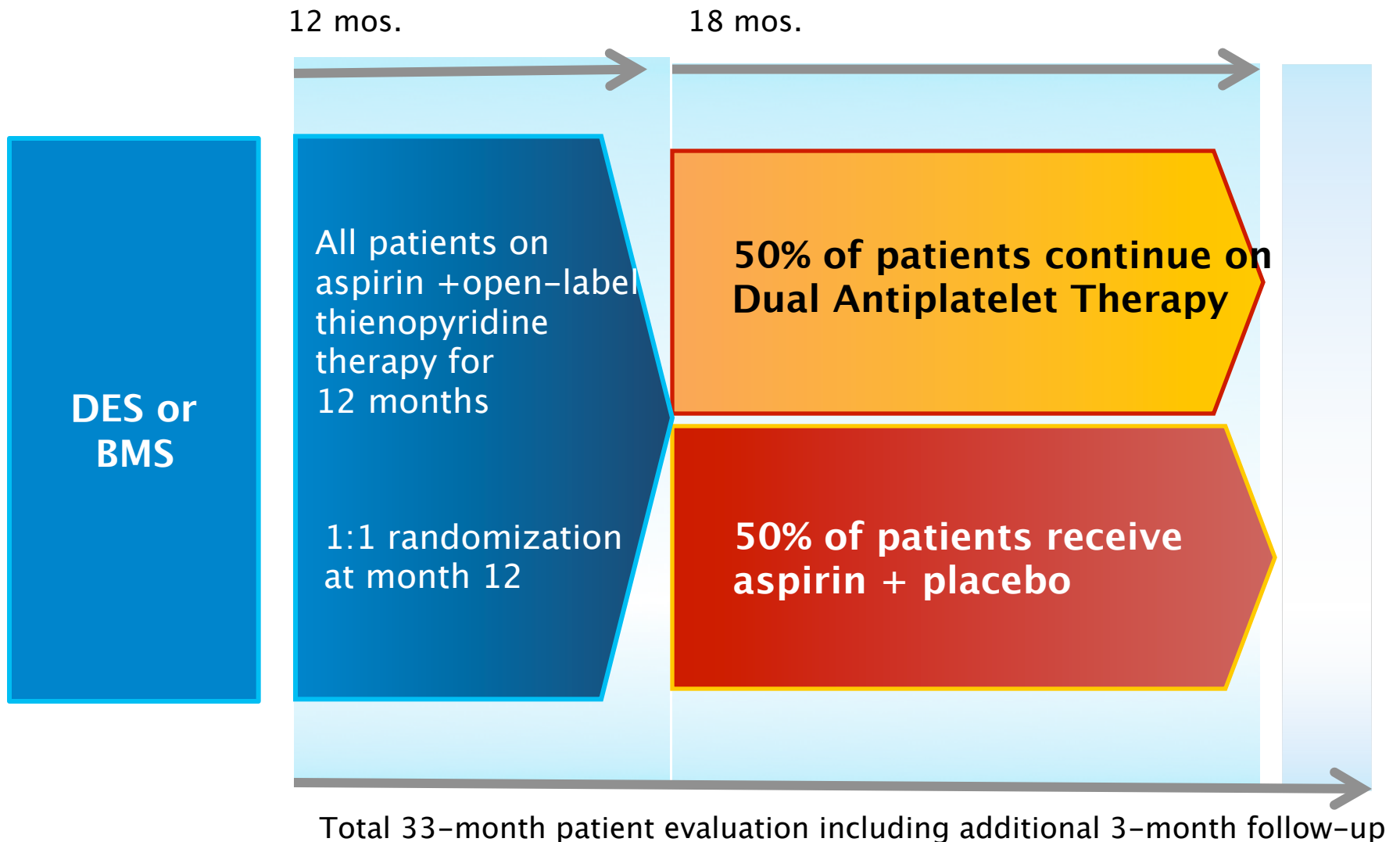
Death/MI/Stroke



Major Bleeding



DAPT Study Design



Patients with Stents Should Receive DAPT for More Than 1 Year !

- **The risk of ST does not stop at 1 year**
- **There is good evidence that stopping DAPT is associated with increased risk**
- **The benefits of DAPT may extend beyond ST to the prevention of MACE**
- **RCTs available so far are dramatically underpowered**
- **Observational studies suggest continued benefit**
- **The DAPT trial should provide a definitive answer**

Expert Debates in Antithrombotic Therapy

Should Patients with Stents Receive DAPT for More Than One Year? (CON)

Robert A. Harrington, MD

Arthur L. Bloomfield Professor of Medicine

Chair, Department of Medicine

Stanford University

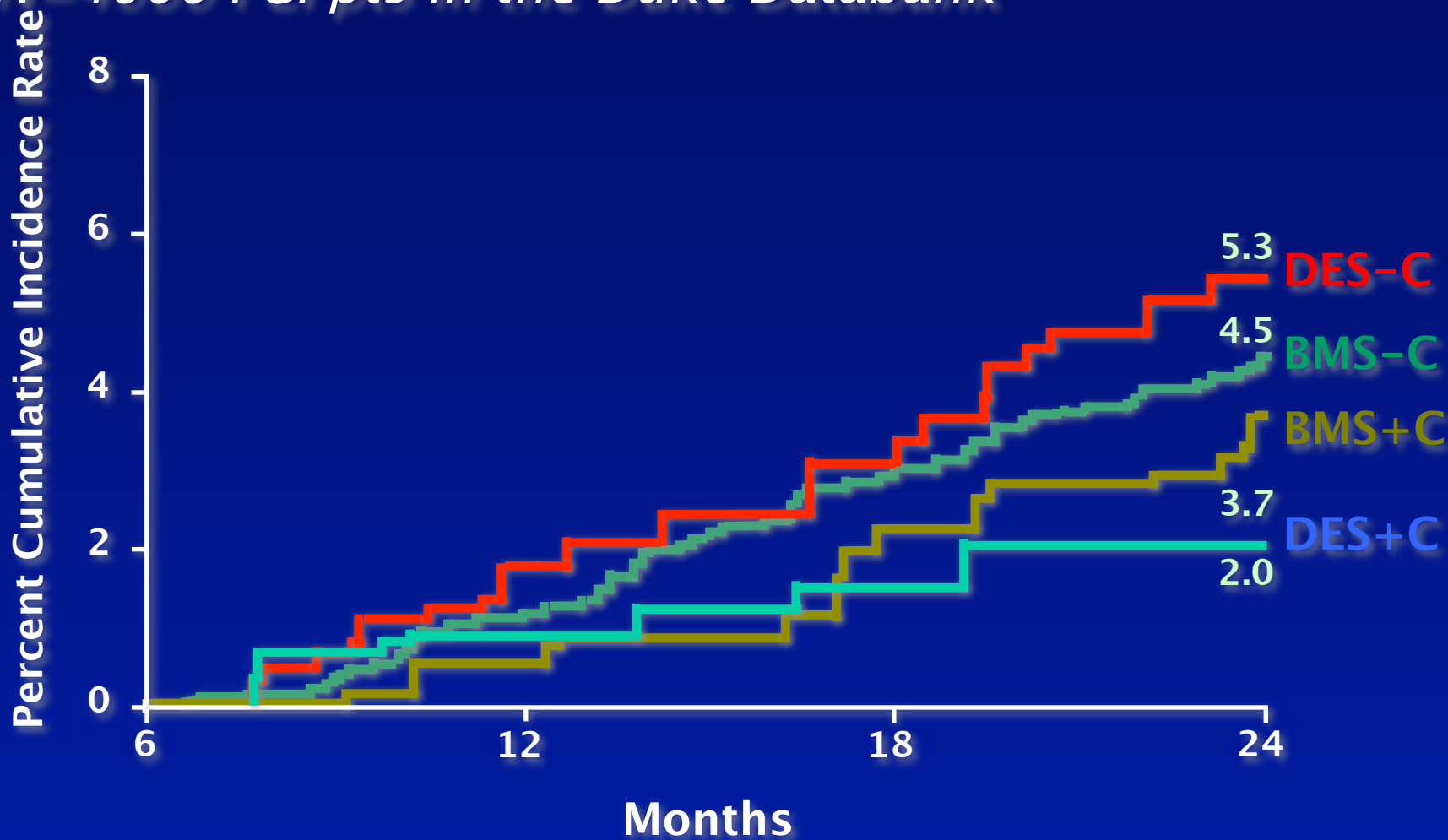
Stanford, California

DAPT Duration of Therapy

- In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y12 inhibitor therapy should be given for ≥ 12 months (*Class IB*)
- In patients receiving DES for a non-ACS indication, clopidogrel 75 mg daily should be given for ≥ 12 months if not at a high risk of bleeding (*Class IB*)
- In patients receiving BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless at an increased risk of bleeding; then it should be given for a minimum of 2 weeks) (*Class*

Adjusted Cumulative Outcomes by Stent Type and Clopidogrel Use

N=4666 PCI pts in the Duke Databank



Study Design

Broad patient population
undergoing PCI with Endeavor ZES
RVD 2.5 mm - 4.0 mm

3 Months DAPT
N = 1560

N = 3120 patients
1:1 Randomization
33 Sites in Brazil

12 Months DAPT
N = 1560

Clinical endpoints

30-d. 3-mo. 6-mo. 12-mo. 18-mo. 24-mo. 36-mo.

Primary Endpoint: NACCE (Death / MI / Stroke / Major Bleeding) at 12 months

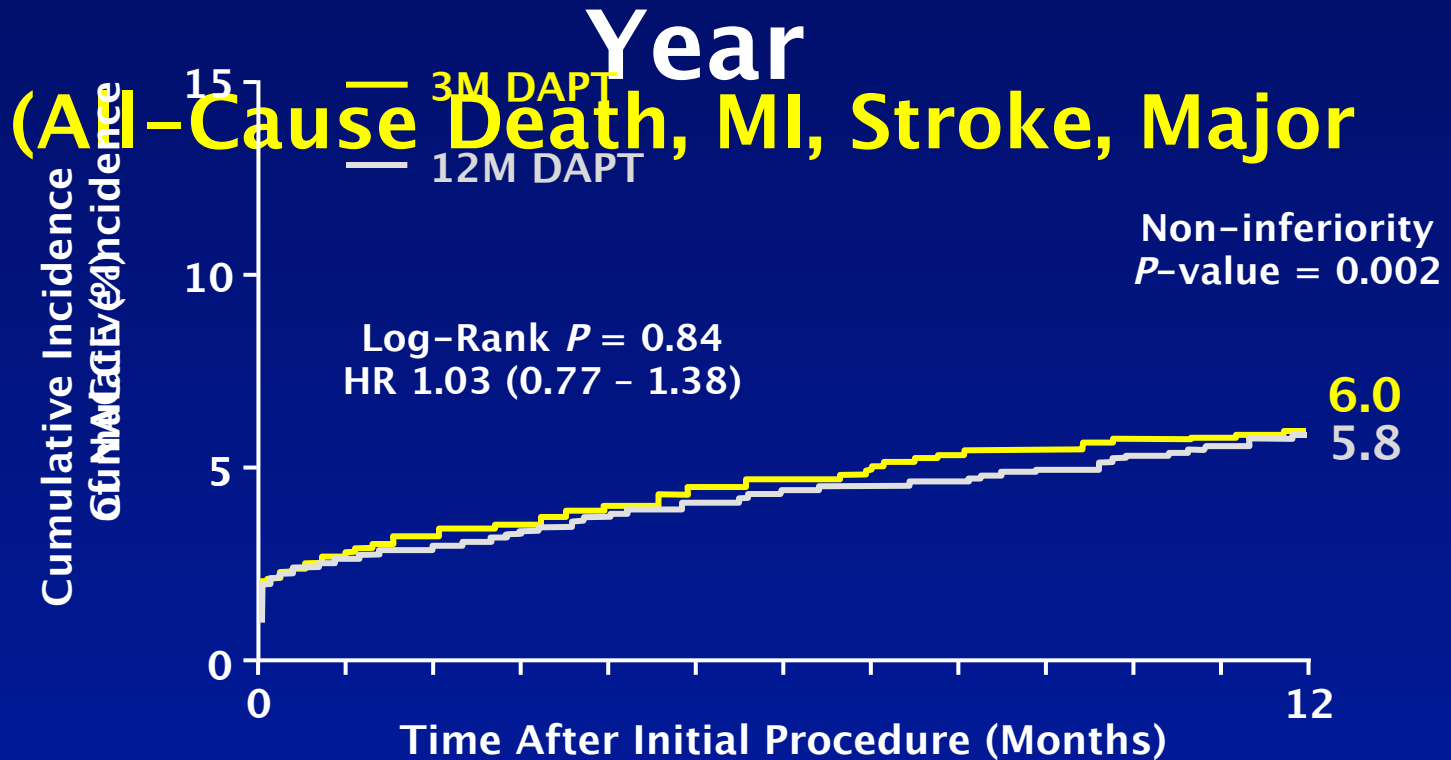
Secondary Endpoints: ARC defined ST, TVR, TLR, MACE, DAPT compliance, and major bleeding (REPLACE-2 & GUSTO definitions)

NACCE = Net Adverse Clinical and Cerebral Events

MACE is composed of Death, MI, Emergent CABG, TLR

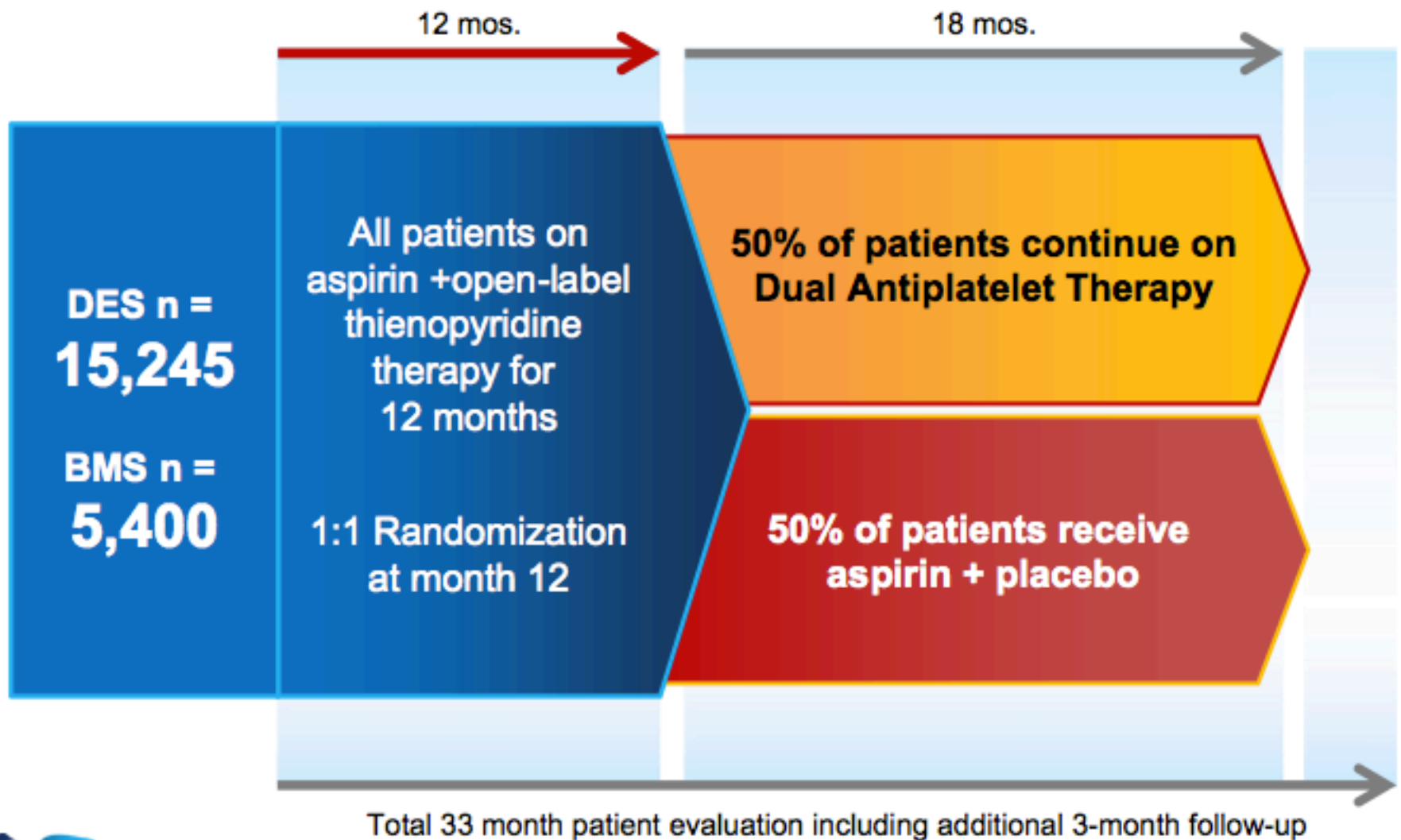
Primary Endpoint: NACCE at 1 Year

Primary Endpoint: NACCE at 1 Year



Month	0	1	3	6	12
No. at risk	156	1520	150	146	138
No. events	3	25	4	8	4
No. at risk	155	1514	149	146	138
No. events	6	25	7	6	1
No. at risk	156	1520	150	146	138
No. events	18	25	11	18	21
No. at risk	155	1514	149	146	138
No. events	16	25	11	16	22

Dual Antiplatelet Therapy (DAPT) Study



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Expert Debates in Antithrombotic Therapy

Should Patients with AF Receive Novel Oral Anticoagulants?

Moderator

Deepak L. Bhatt, MD, MPH

Expert Debates in Antithrombotic Therapy

**Should Patients with AF Receive Novel
Oral Anticoagulants? (PRO)**

Robert A. Harrington, MD

Arthur L. Bloomfield Professor of Medicine

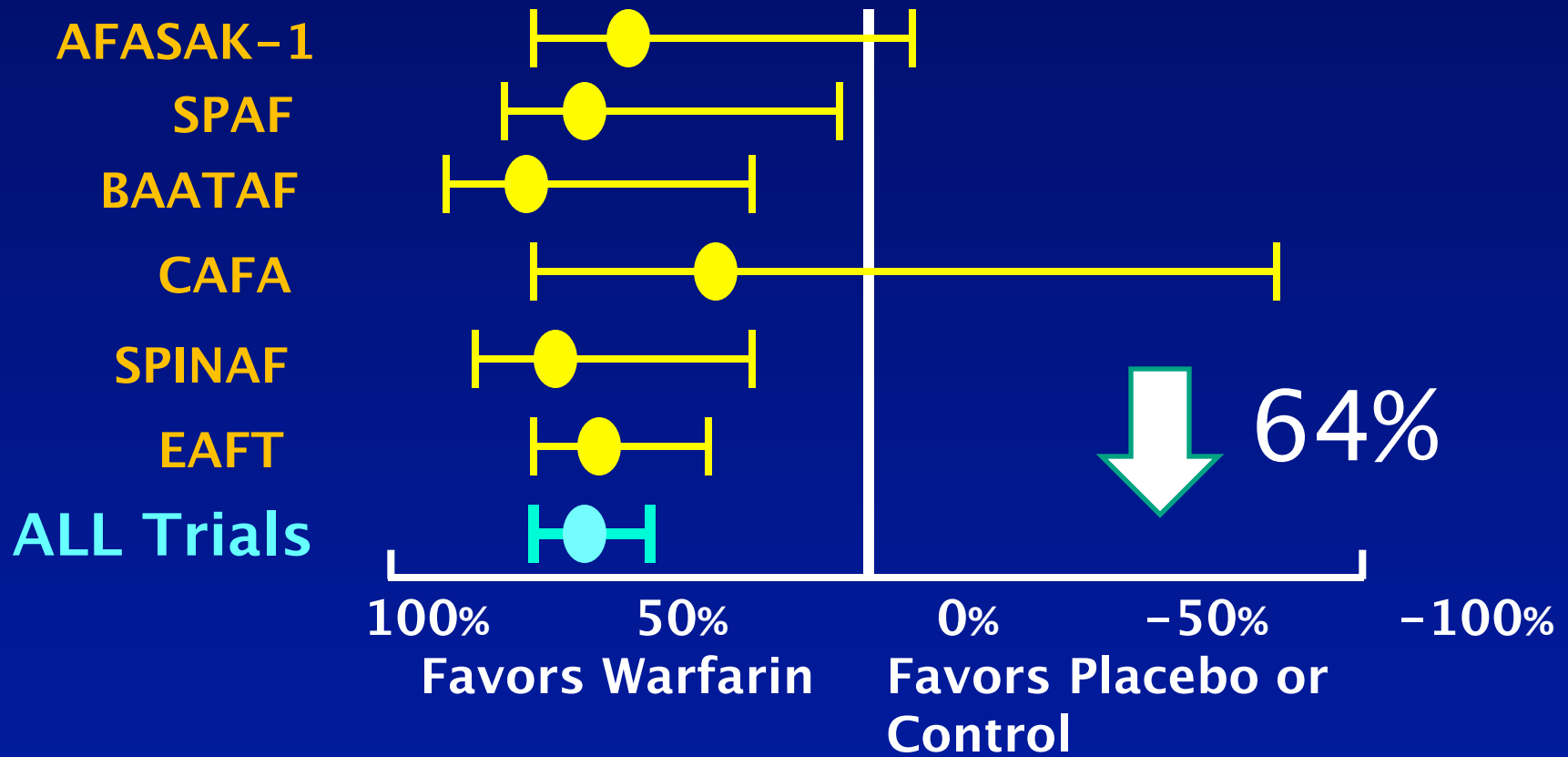
Chair, Department of Medicine

Stanford University

Stanford, California

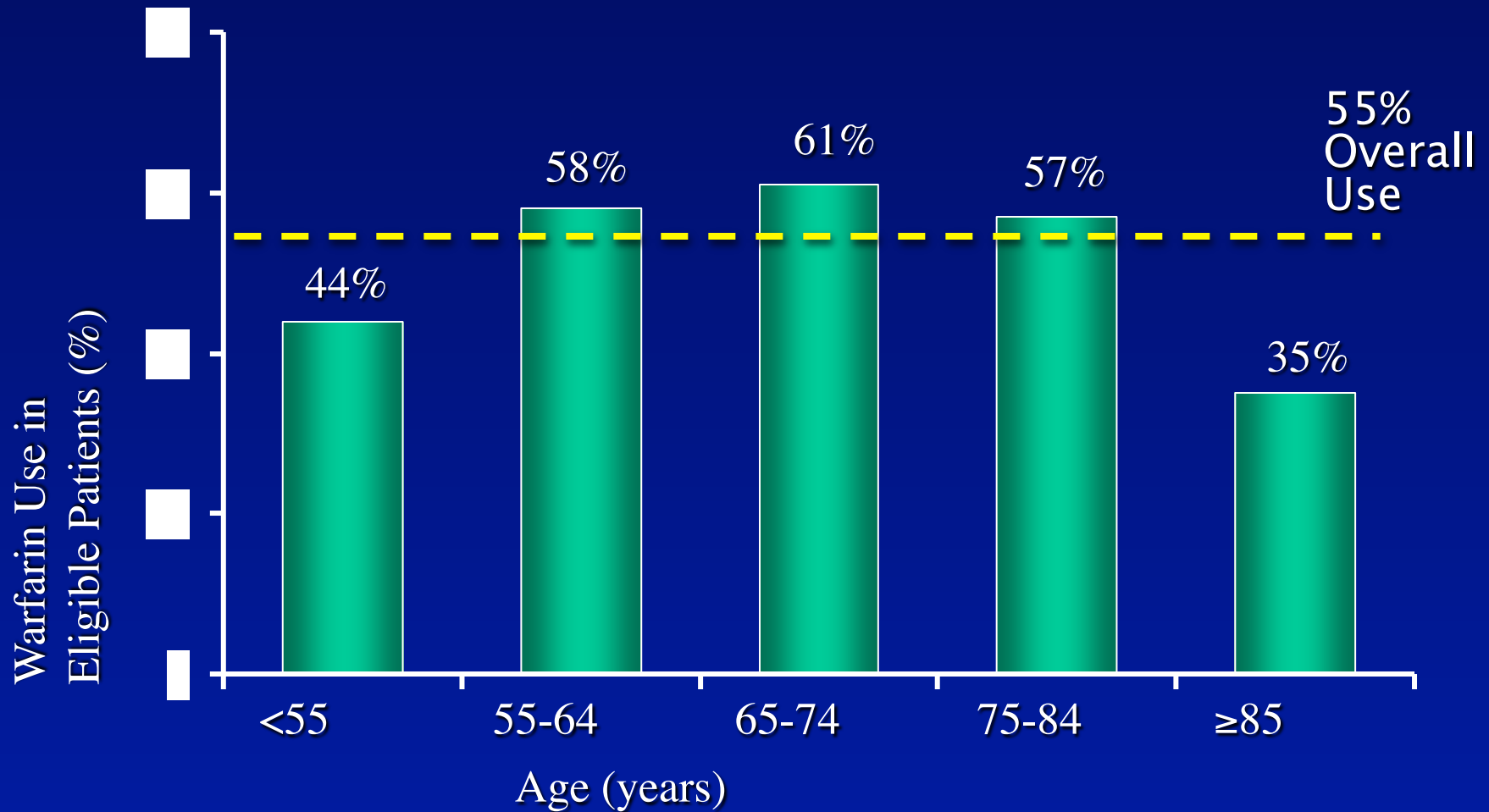
Stroke Prevention in AF

Warfarin vs Placebo



Warfarin for Atrial Fibrillation

Limitations Lead to Undertreatment



Novel Oral Anticoagulants ("NOACs")

Dabigatran

Rivaroxaban

Apixaban

Edoxaban

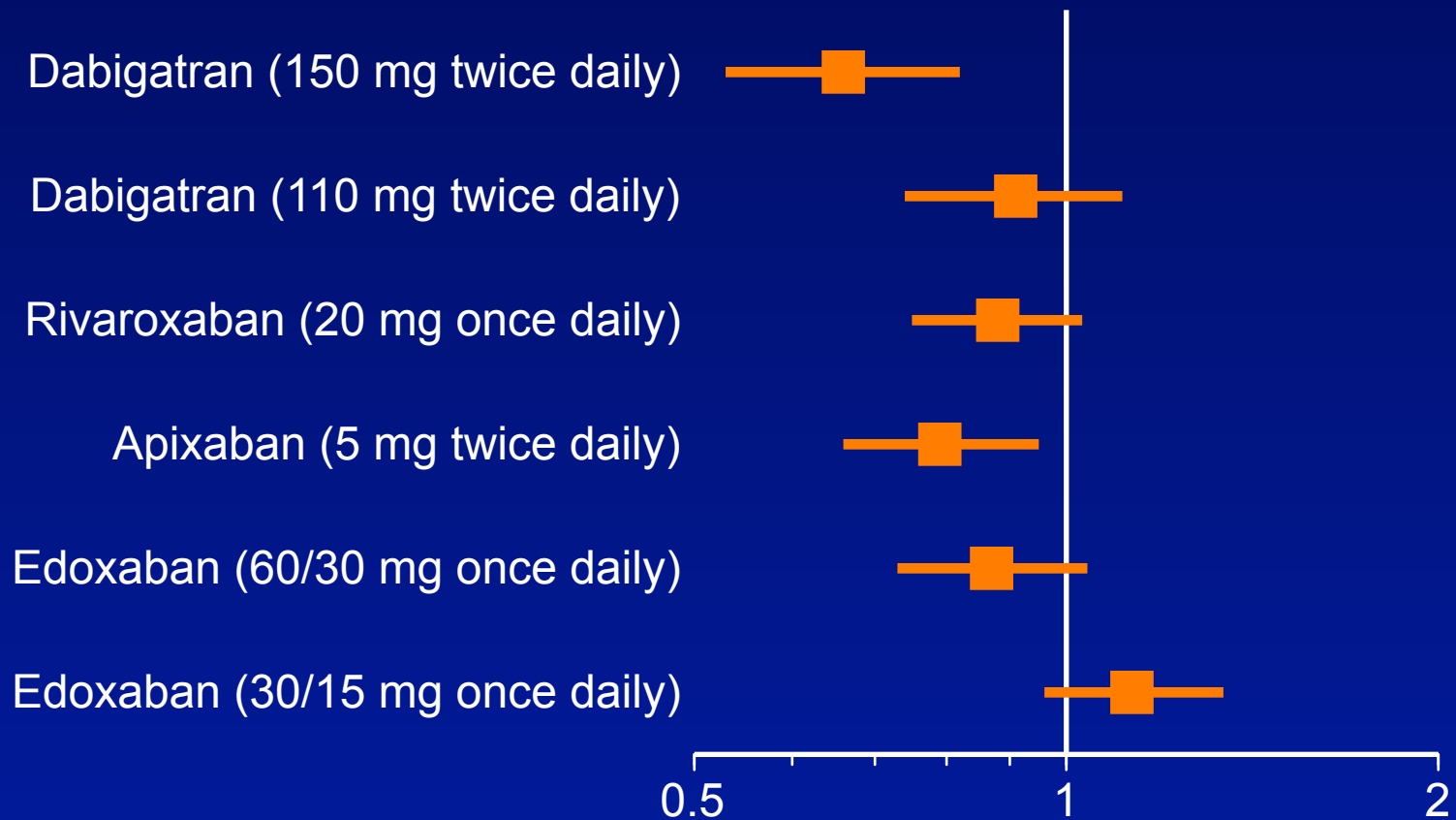
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Bioavailability	Oral prodrug with poor oral bioavailability (6.5%)	Good oral bioavailability	Good oral bioavailability	Good oral bioavailability
T_{1/2}	12 – 17 hours	6 – 9 hours	12 hours	9 – 11 hours
Dosing	Twice daily	Once or twice daily	Twice daily	Once or twice daily
Time action	1 – 4 hrs post-dose for max. inhibition	1 – 4 hrs post-dose for max. inhibition	1 – 4 hrs post-dose for max. inhibition	1 – 4 hrs post-dose for max. inhibition
Platelet aggregation	No direct effect	No direct effect	No direct effect	No direct effect
Elimination	80% renal	35% renal	25% renal	35% renal

Phase 3 Trials of “NOAC” vs Warfarin

	RELY	ROCKET	ARISTOTLE	ENGAGE-AF
Sample size	18,113	14,266	18,201	21,150
New treatment	Dabigatran 110 mg BID Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID	Edoxaban 30/15 mg QD Edoxaban 60/30 mg QD
Design	Non-inferiority PROBE	Non-inferiority Double-blind	Non-inferiority Double-blind	Non-inferiority Double-blind
Patients	AF + CHADS2 \geq 1	AF + CHADS2 \geq 2	AF + CHADS2 \geq 1	AF + CHADS2 \geq 2
Renal Exclusion	CrCl < 30 ml/min	CrCl < 30 ml/min	CrCl < 25 ml/min	CrCl < 30 ml/min
Primary outcome	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism
Safety outcome	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM

New Anticoagulants vs. Warfarin

Stroke (ischemic or hemorrhagic) or Systemic Embolism



Connolly et al. N Engl J Med 2009;361:1139-51.

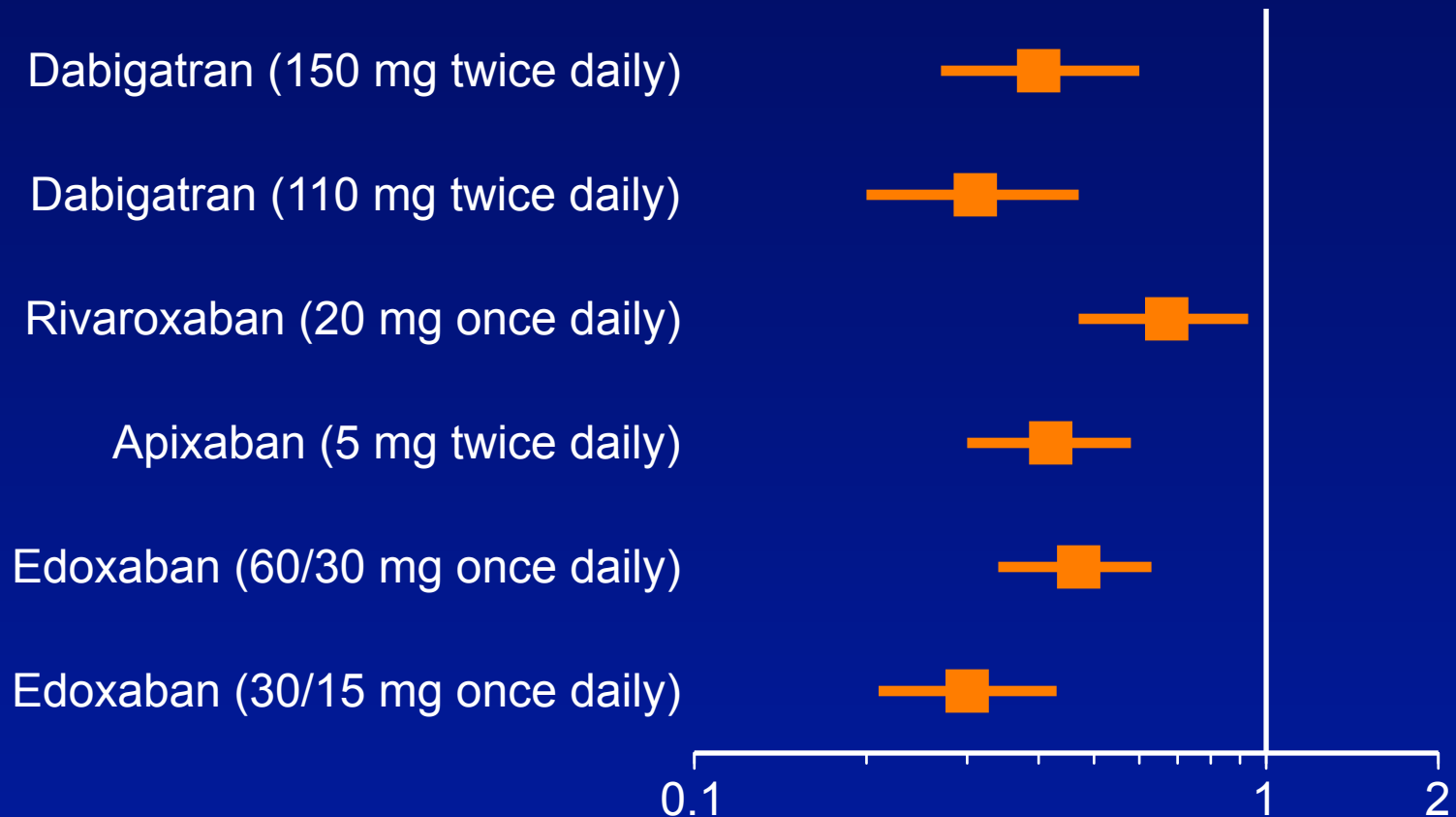
Patel et al. N Engl J Med 2011;365:883-91.

Granger et al. N Engl J Med 2011;365:981-92.

Giugliano et al. N Engl J Med 2013;369:2093-104.

New Anticoagulants vs. Warfarin

Intracranial Hemorrhage



Connolly et al. N Engl J Med 2009;361:1139-51.

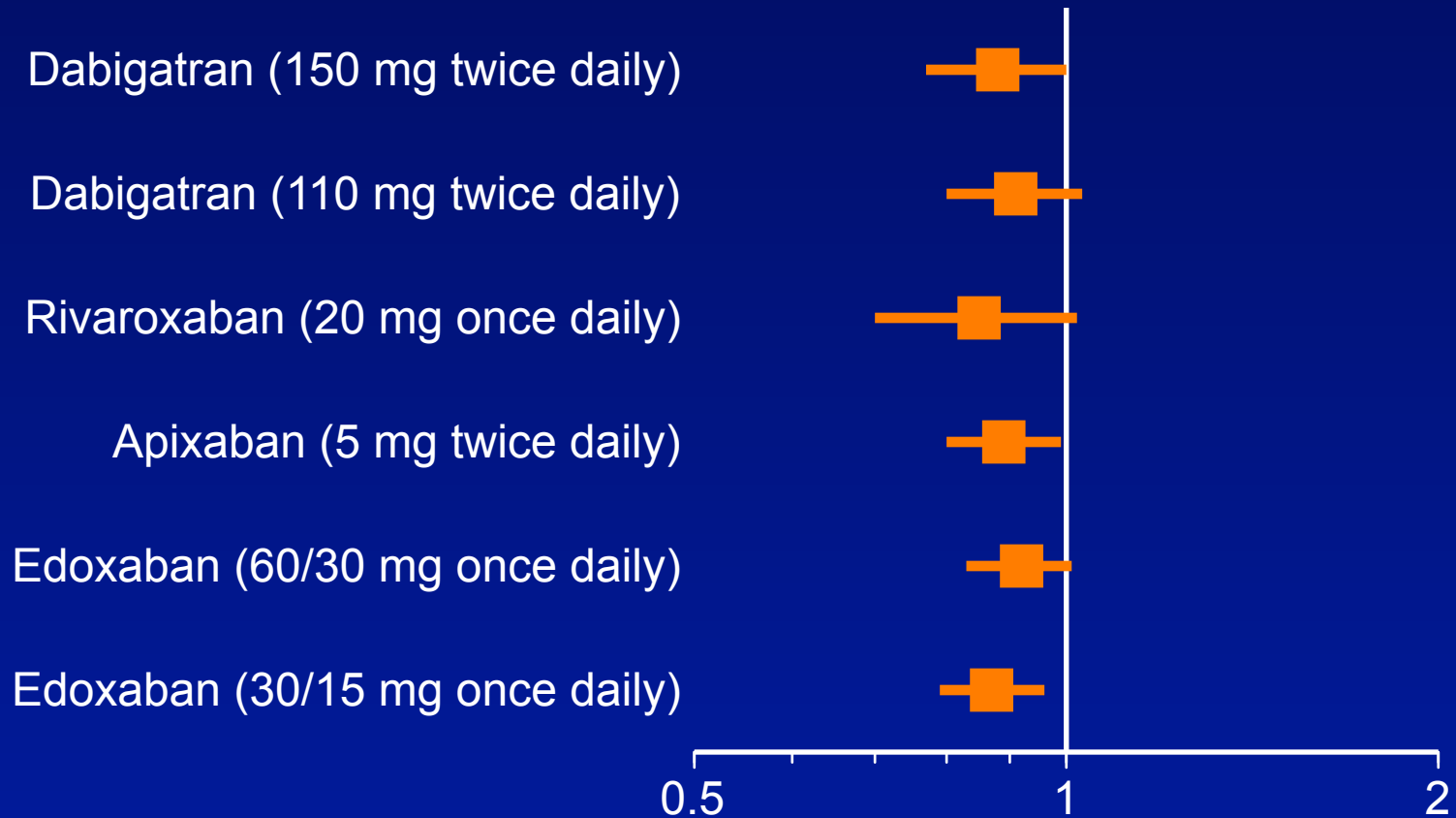
Patel et al. N Engl J Med 2011;365:883-91.

Granger et al. N Engl J Med 2011;365:981-92.

Giugliano et al. N Engl J Med 2013;369:2093-104.

New Anticoagulants vs. Warfarin

Mortality



Connolly et al. N Engl J Med 2009;361:1139-51.

Patel et al. N Engl J Med 2011;365:883-91.

Granger et al. N Engl J Med 2011;365:981-92.

Giugliano et al. N Engl J Med 2013;369:2093-104.

Expert Debates in Antithrombotic Therapy

Patients with Afib Should NOT Receive Novel Anticoagulants!

Ph. Gabriel Steg

**DHU-FIRE, Hôpital Bichat, Assistance Publique—Hôpitaux de
Paris, Université Paris – Diderot, INSERM U-698, Paris, France
French Alliance for Cardiovascular Clinical Trials and Imperial
College, Royal Brompton Hospital
London, UK**

Patients with Afib Should NOT Receive NOACs

1. Marginal superiority over VKA

Patients with Afib Should NOT Receive NOACs

1. Marginal superiority over VKA

2. Considerable clinical experience with VKA

Patients with Afib Should NOT Receive NOACs

1. Marginal superiority over VKA

2. Considerable clinical experience with VKA

3. Impossibility to monitor therapeutic levels or compliance

Patients with Afib Should NOT Receive NOACs

1. Marginal superiority over VKA

2. Considerable clinical experience with VKA

3. Impossibility to monitor therapeutic levels or compliance

4. Lack of antidote in case of life-threatening bleed

Patients with Afib Should NOT Receive NOACs

1. Marginal superiority over VKA

2. Considerable clinical experience with VKA

3. Impossibility to monitor therapeutic levels or compliance

4. Lack of antidote in case of life-threatening bleed

5. No INR monitoring but need to monitor renal function

Patients with Afib Should NOT Receive NOACs

1. Marginal superiority over VKA

2. Considerable clinical experience with VKA

3. Impossibility to monitor therapeutic levels or compliance

4. Lack of antidote in case of life-threatening bleed

5. No INR monitoring but need to monitor renal function

6. Huge cost implications for health systems



Thank you!

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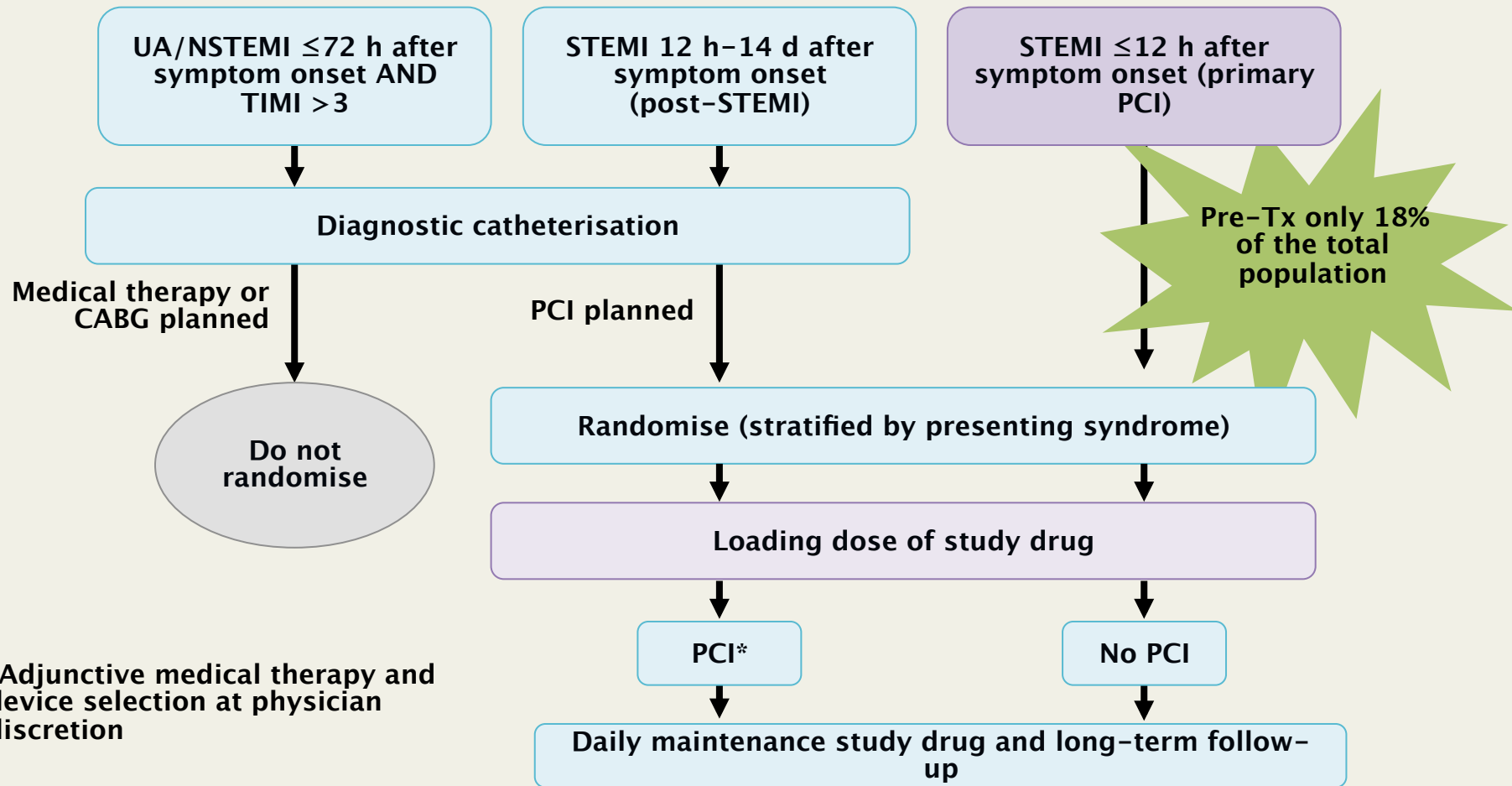
Backup slides

Questions After ACCOAST

- Do the results of ACCOAST apply to settings where intervention is delayed by (often) much more than 4 hours?
- Do the results of ACCOAST apply to clopidogrel, for which efficacy is more delayed than prasugrel?
- Ticagrelor « pre-loading » was effective in PLATO

TRITON-TIMI 38 Enrollment Schema

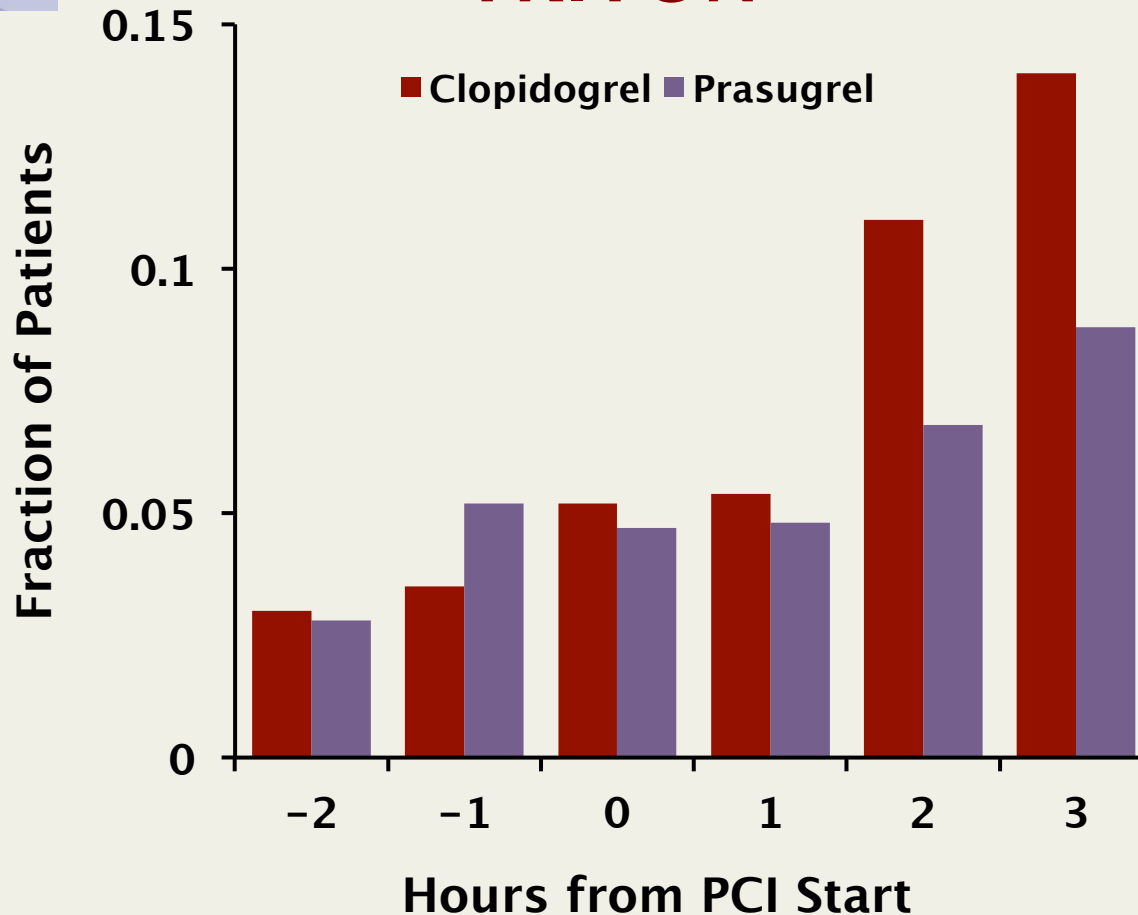
Only P2Y₁₂ inhibitor-naïve patients were allowed



*Adjunctive medical therapy and device selection at physician discretion

CABG, coronary artery bypass grafting; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38; UA, unstable angina.

Primary End-point Events Over the First 10 Days by Timing of Thienopyridine Loading in TRITON





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

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Christian W. Hamm (Chairperson) (Germany)*, Jean-Pierre Bassand (Co-Chairperson)*, (France), Stefan Agewall (Norway), Jeroen Bax (The Netherlands), Eric Boersma (The Netherlands), Hector Bueno (Spain), Pio Caso (Italy), Dariusz Dudek (Poland), Stephan Gielen (Germany), Kurt Huber (Austria), Magnus Ohman (USA), Mark C. Petrie (UK), Frank Sonntag (Germany), Miguel Sousa Uva (Portugal), Robert F. Storey (UK), William Wijns (Belgium), Doron Zahger (Israel).



ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)

Authors/Task Force Members: Ph. Gabriel Steg (Chairperson) (France)*, Stefan K. James (Chairperson) (Sweden)*, Dan Atar (Norway), Luigi P. Badano (Italy), Carina Blomstrom Lundqvist (Sweden), Michael A. Borger (Germany), Carlo Di Mario (United Kingdom), Kenneth Dickstein (Norway), Gregory Ducrocq (France), Francisco Fernandez-Aviles (Spain), Anthony H. Gershlick (United Kingdom), Pantaleo Giannuzzi (Italy), Sigrun Halvorsen (Norway), Kurt Huber (Austria), Peter Juni (Switzerland), Adnan Kastrati (Germany), Juhani Knuuti (Finland), Mattie J. Lenzen (Netherlands), Kenneth W. Mahaffey (USA), Marco Valgimigli (Italy), Arnoud van't Hof (Netherlands), Petr Widimsky (Czech Republic), Doron Zahger (Israel)

ESC 2012 STEMI Guidelines

Periprocedural Antiplatelet Therapy in Primary PCI

Recommendations	Class ^a	Level ^b
Antiplatelet therapy		
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B
• Ticagrelor.	I	B
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C

ADP = adenosine diphosphate

ESC 2011 Guidelines for Non ST-ACS

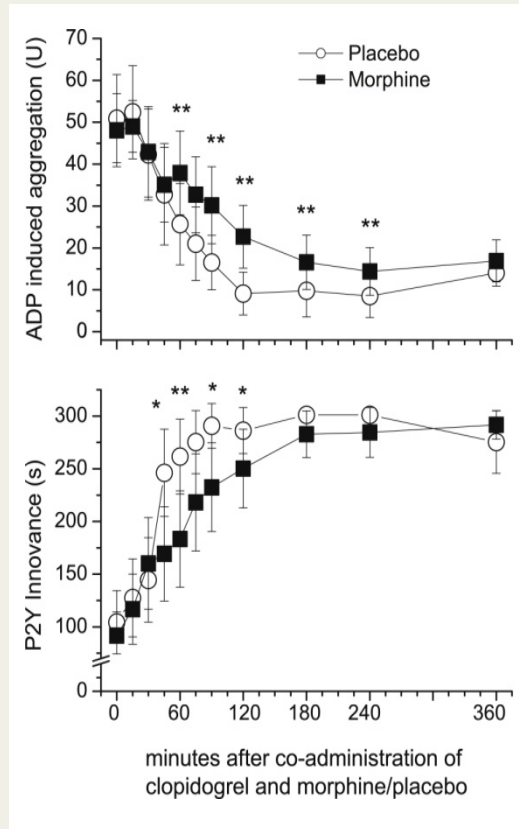
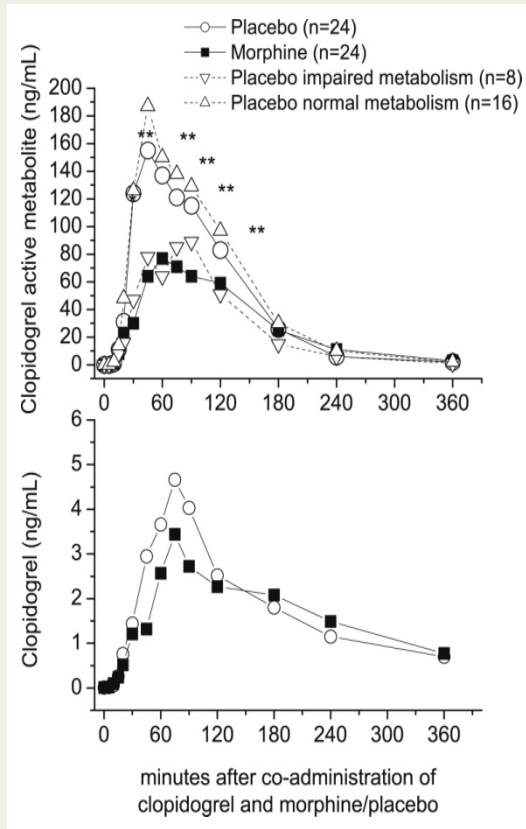
Recommendations for oral antiplatelet agents

Recommendations	Class ^a	Level ^b	Ref ^c
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	107, 108
A P2Y ₁₂ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A	110, 130, 132
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (<i>H. elicobacter pylori</i> infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A	125–127

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y ₁₂ -inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications. ^d	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A

with PCI and without increased risk of bleeding.	IIa	B	108
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B	124
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B	119, 121
In patients pre-treated with P2Y ₁₂ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C	-
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B	134
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C	-

Morphine and Clopidogrel Interaction



Morphine Lowers Plasma Concentrations of Clopidogrel Active Metabolite

Healthy volunteers (n = 24) received a 600-mg loading dose concomitantly with a placebo or 5 mg morphine. P<0.001 repeated measures analysis of variance;

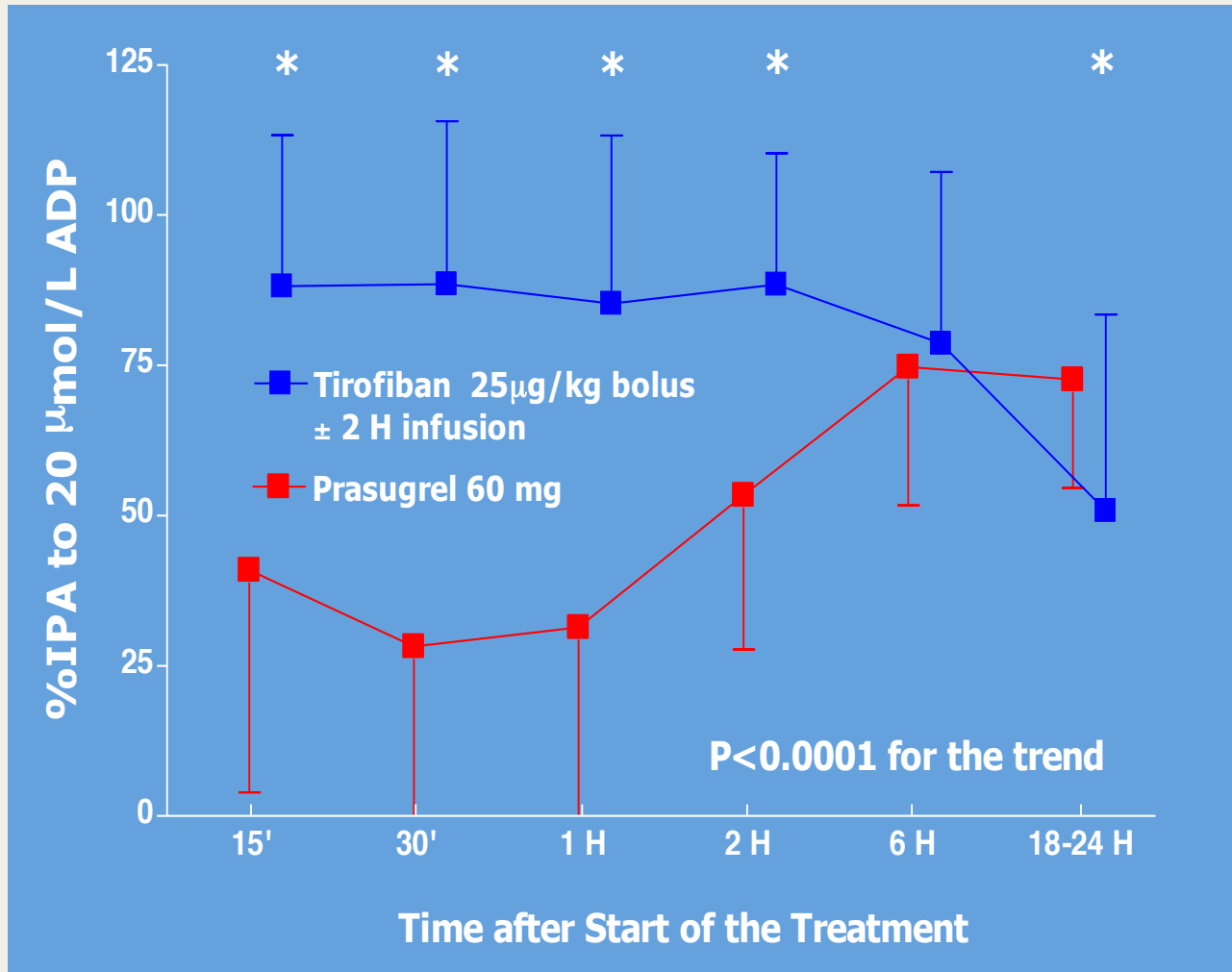
*P<0.05; **P≤0.01 designate differences between treatments (Wilcoxon test). Data present medians without error bars for reasons of clarity

Morphine Retards and Decreases Clopidogrel Effects

Adenosine-diphosphate (ADP)-induced aggregation was measured by whole-blood aggregometry (n = 24) and with the P2Y- cartridge of the platelet function analyzer (n = 21).

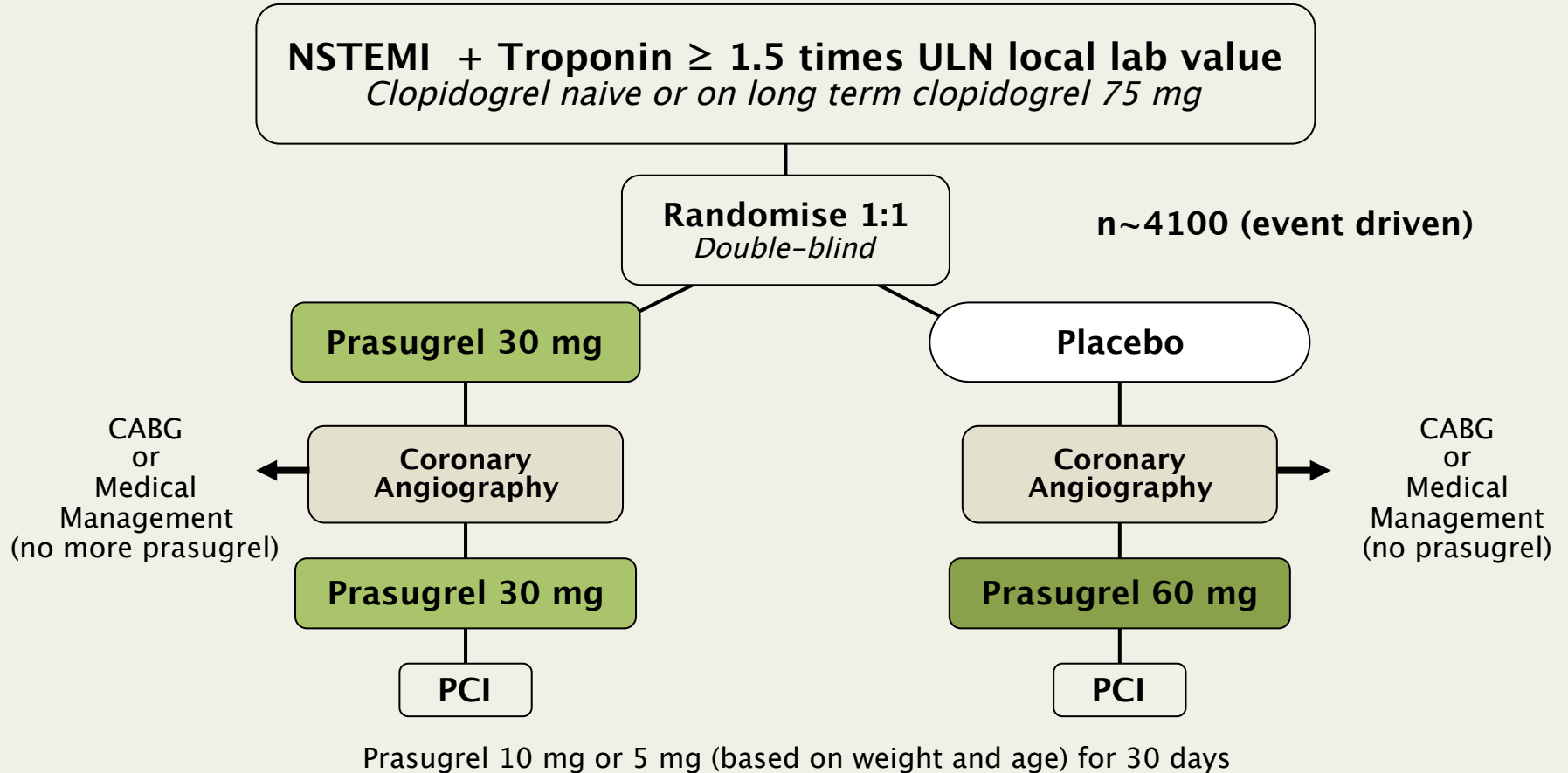
P<0.001 repeated measures analysis of variance; *P<0.05; **P≤0.01 designate differences between treatments (Wilcoxon test). Data present mean ± 95% confidence interval.

Delayed Efficacy of Novel P2Y12 Antagonists in ACS Data from the FABOLUS PRO Study





ACCOAST Design



1°Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

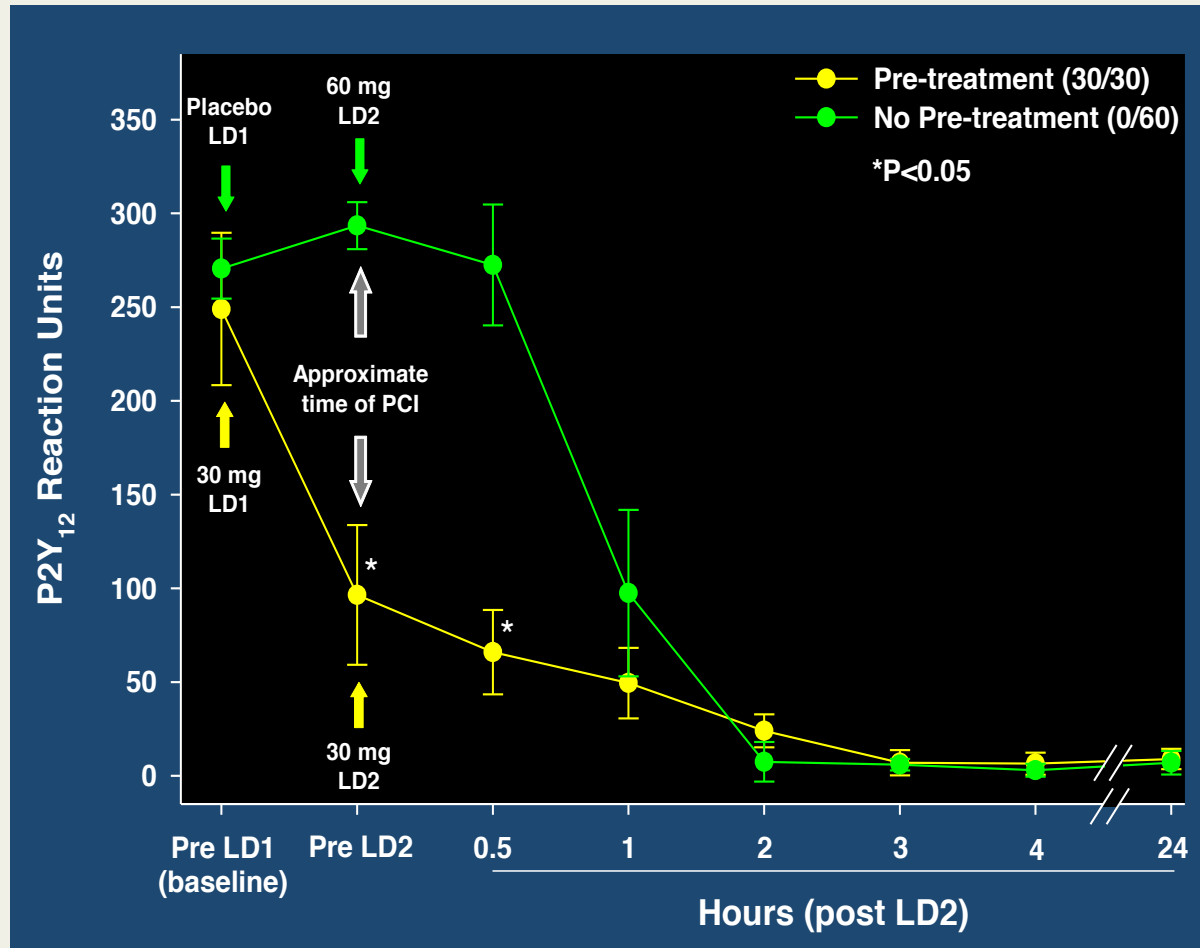


Baseline Characteristics

Characteristics	Pre-treatment (N = 2037)	No Pre-treatment (N = 1996)
GRACE score (%)		
<140	76	78
≥140	24	22
CRUSADE score (median)	34	34
Timing (hr)		
Ⓜ Symptom onset to 1st LD, median	14.6	15.2
Ⓜ 1 st LD to coronary angiogram, median	4.4	4.2
Access (%)		
Femoral	57	57
Radial	43	43



Pharmacodynamic Sub-Study



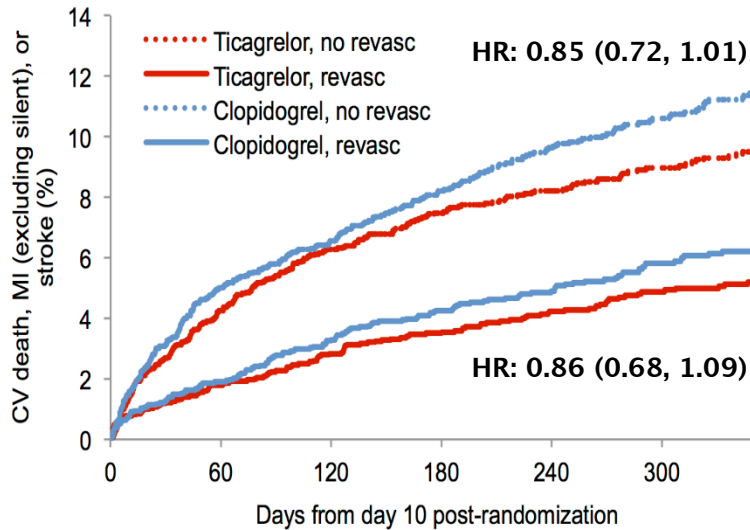
Data presented as median \pm SEM. *P<0.05 relative to the No pre-treatment group. LD = loading dose.

Pretreatment=Prasugrel 30 mg / Prasugrel 30 mg; No Pre-treatment=Placebo / Prasugrel 60 mg



Outcomes in NST-ACS Patients in PLATO as a Function of Actual Revascularisation

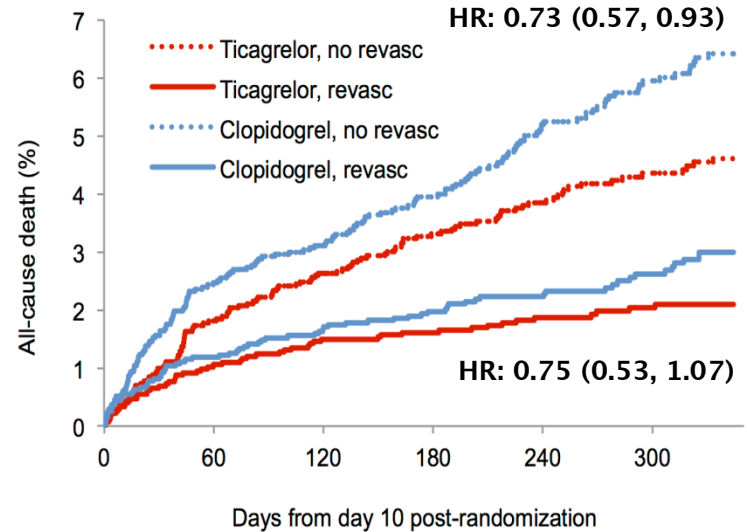
Primary Outcome



C, no rv	2571	2413	2362	2084	1829	1326	1104
C, revasc	2676	2590	2547	2299	2075	1528	1291
T, no rv	2618	2461	2394	2142	1911	1398	1160
T, revasc	2738	2665	2626	2340	2116	1553	1312

Interaction $p=0.93$

All-cause Mortality



C, no rv	2590	2501	2472	2207	1948	1426	1194
C, revasc	2804	2740	2718	2467	2239	1649	1397
T, no rv	2627	2541	2505	2265	2028	1493	1239
T, revasc	2842	2789	2767	2478	2251	1663	1412

Interaction $p=0.89$