Use of Oral Antiplatelet: Guidelines Implementation in Clinical Practice

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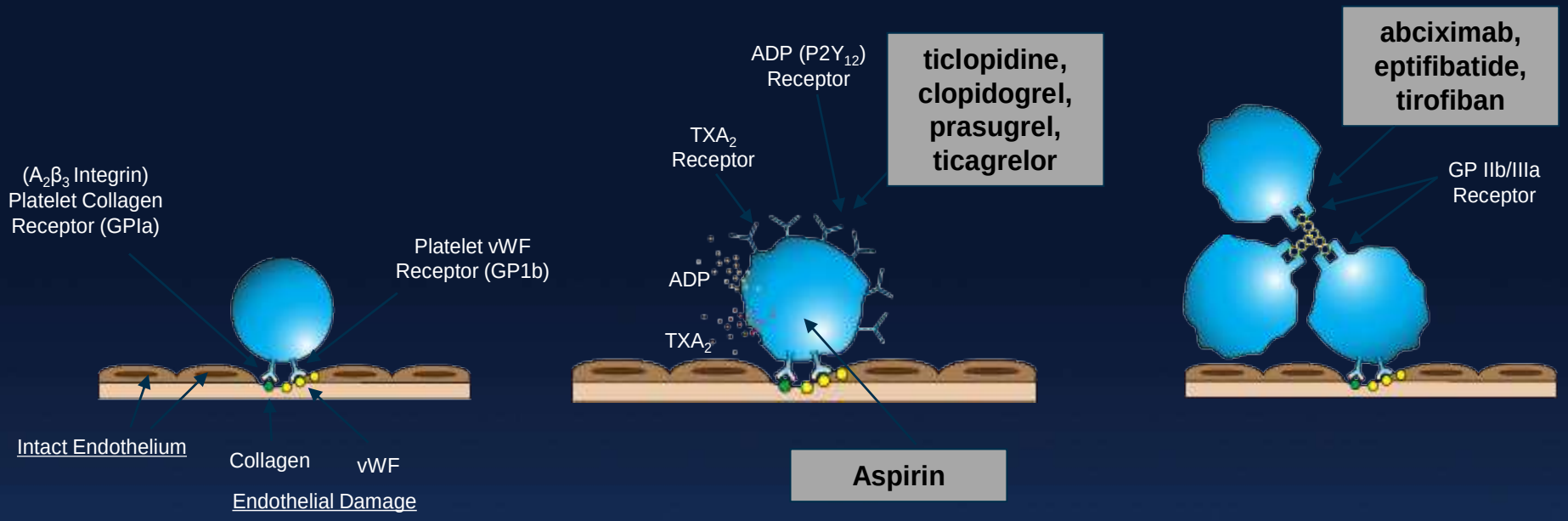
I, Dimitrios Alexopoulos, have received honoraria for lecturing
and research grants from:

Astra Zeneca

Boeringer Ingelheim

Platelet-Mediated Thrombosis Targets



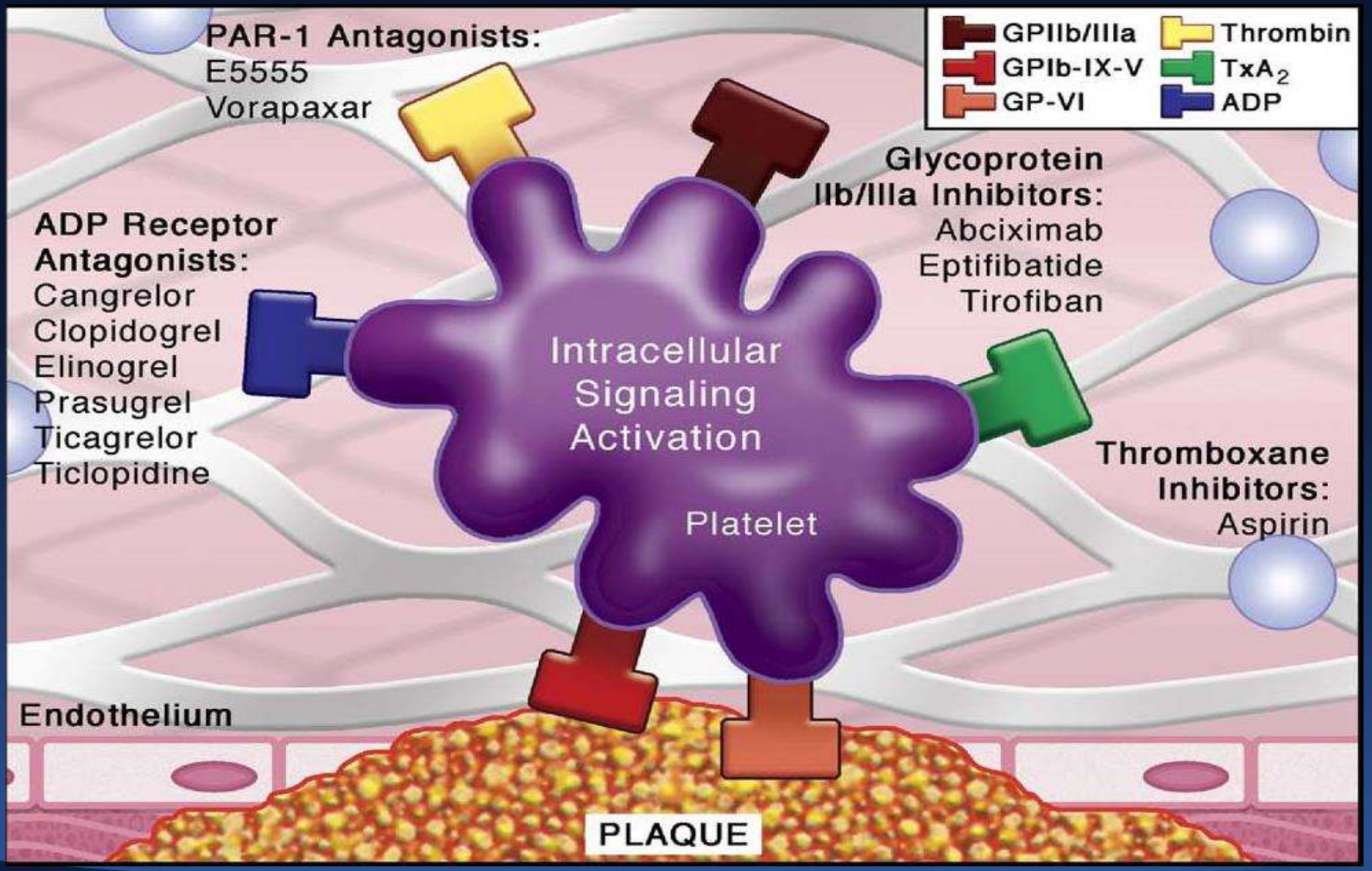
No currently approved antiplatelet agents specifically target **Adhesion**

Most approved antiplatelet agents affect different aspects of platelet **Activation**

GP IIb/IIIa inhibitors inhibit thef“ inal common pathway,” **Aggregation**

GP = glycoprotein; vWF = von Willebrand factor; ADP = adenosine diphosphate; TX = thromboxane.

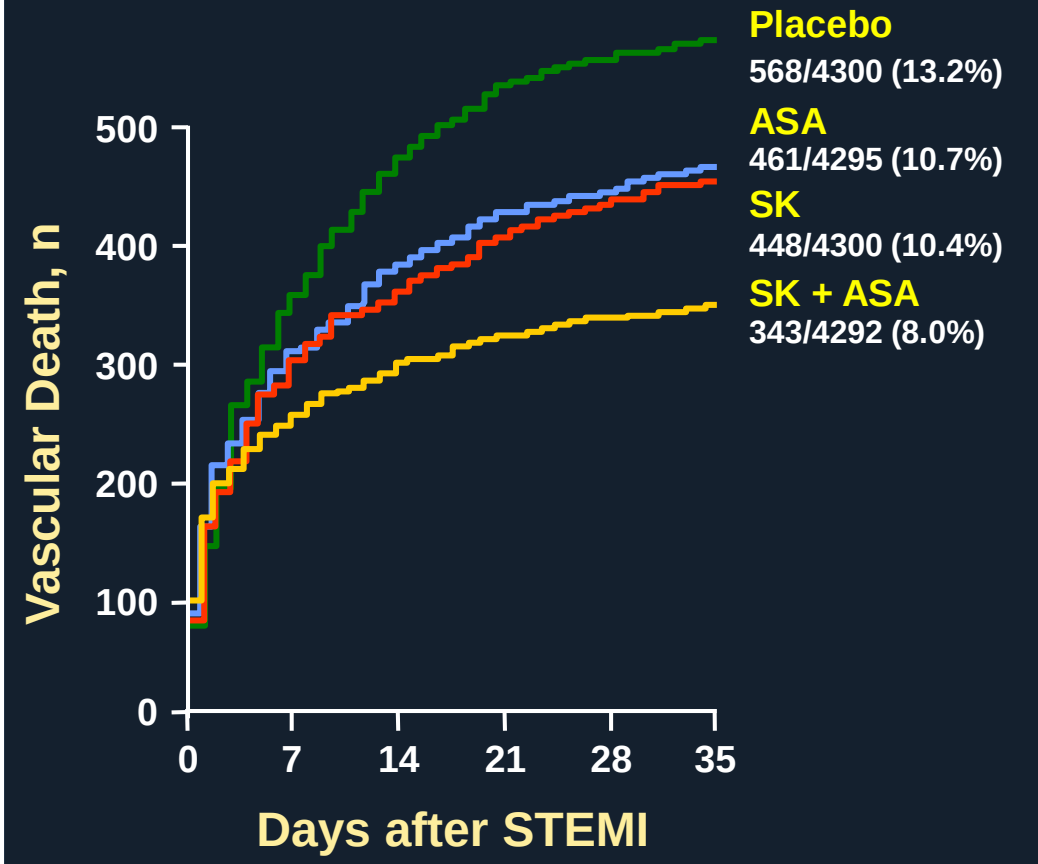
Antiplatelet Agents



Desai NR, Bhatt DL. *JACC CV int.* 2010;3:571-83

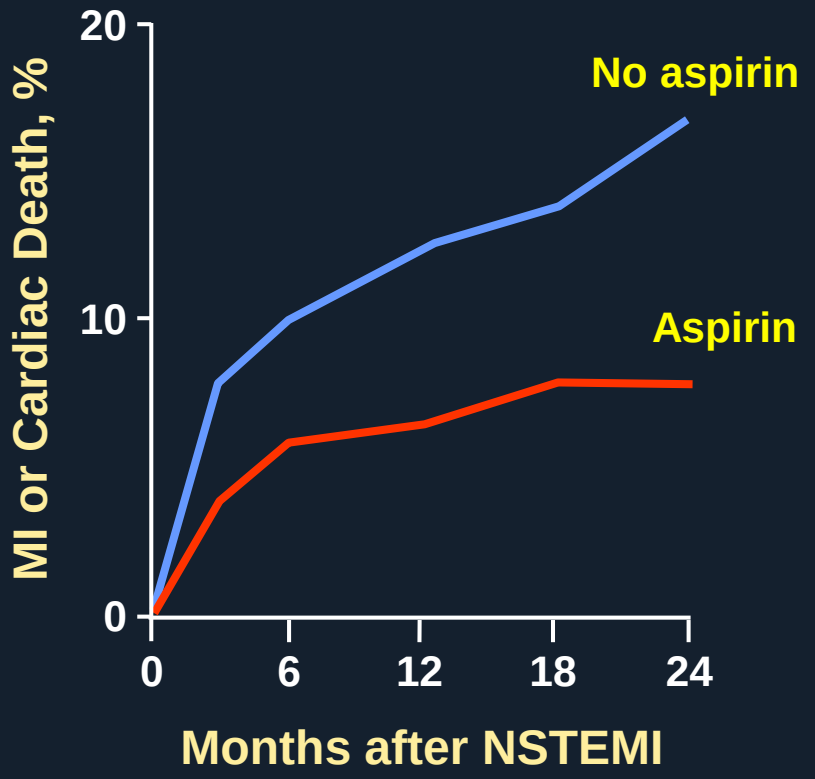
Aspirin is Effective in Acute Coronary Syndromes

STEMI



Lancet 1988;2:349-60

NSTE-ACS

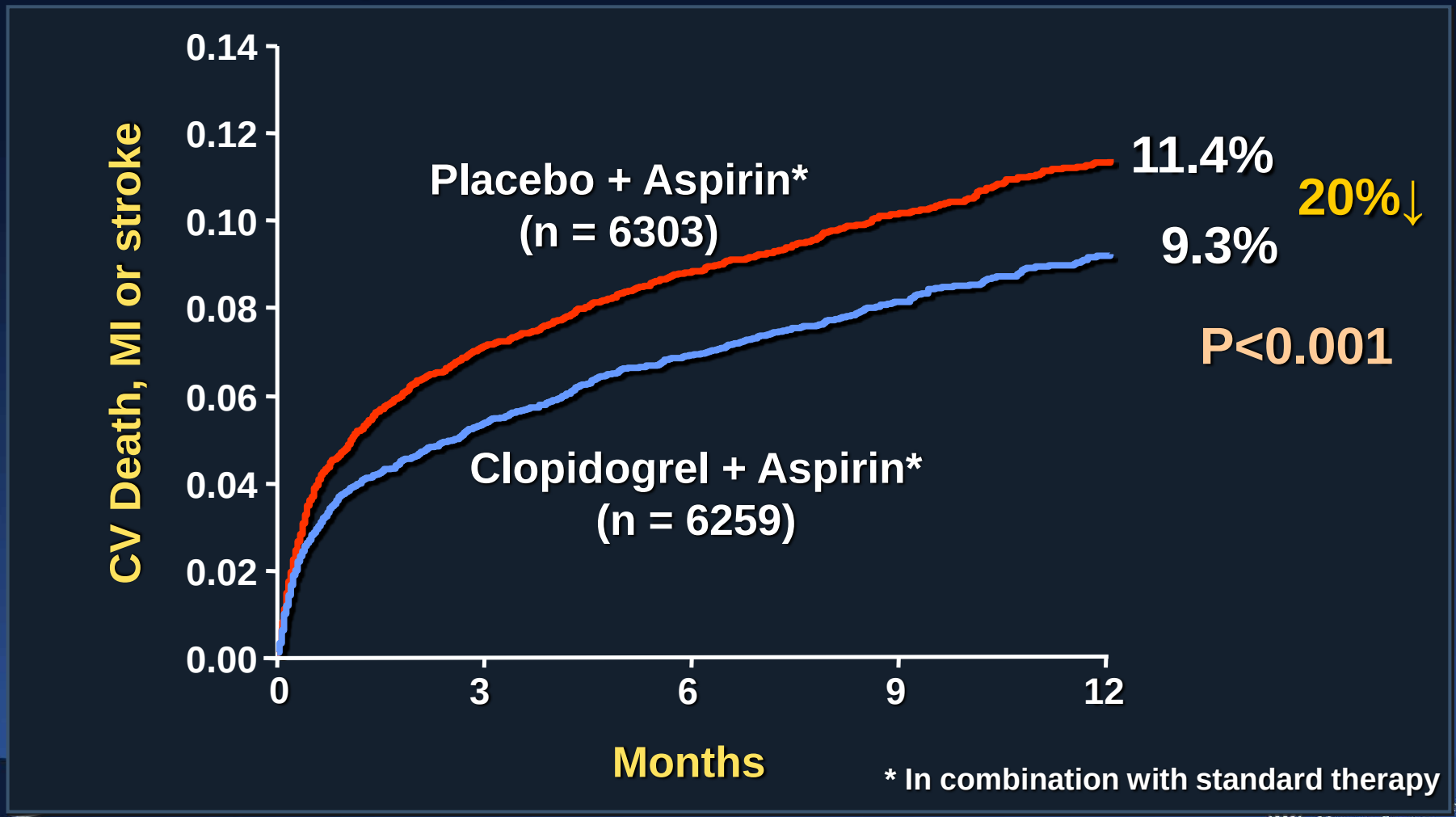


Cairns JA et al. *NEJM* 1985;313:1369-76

CURE

12,562 pts with NSTE-ACS were treated with aspirin and randomized to clopidogrel vs. placebo and followed for up to 12 months

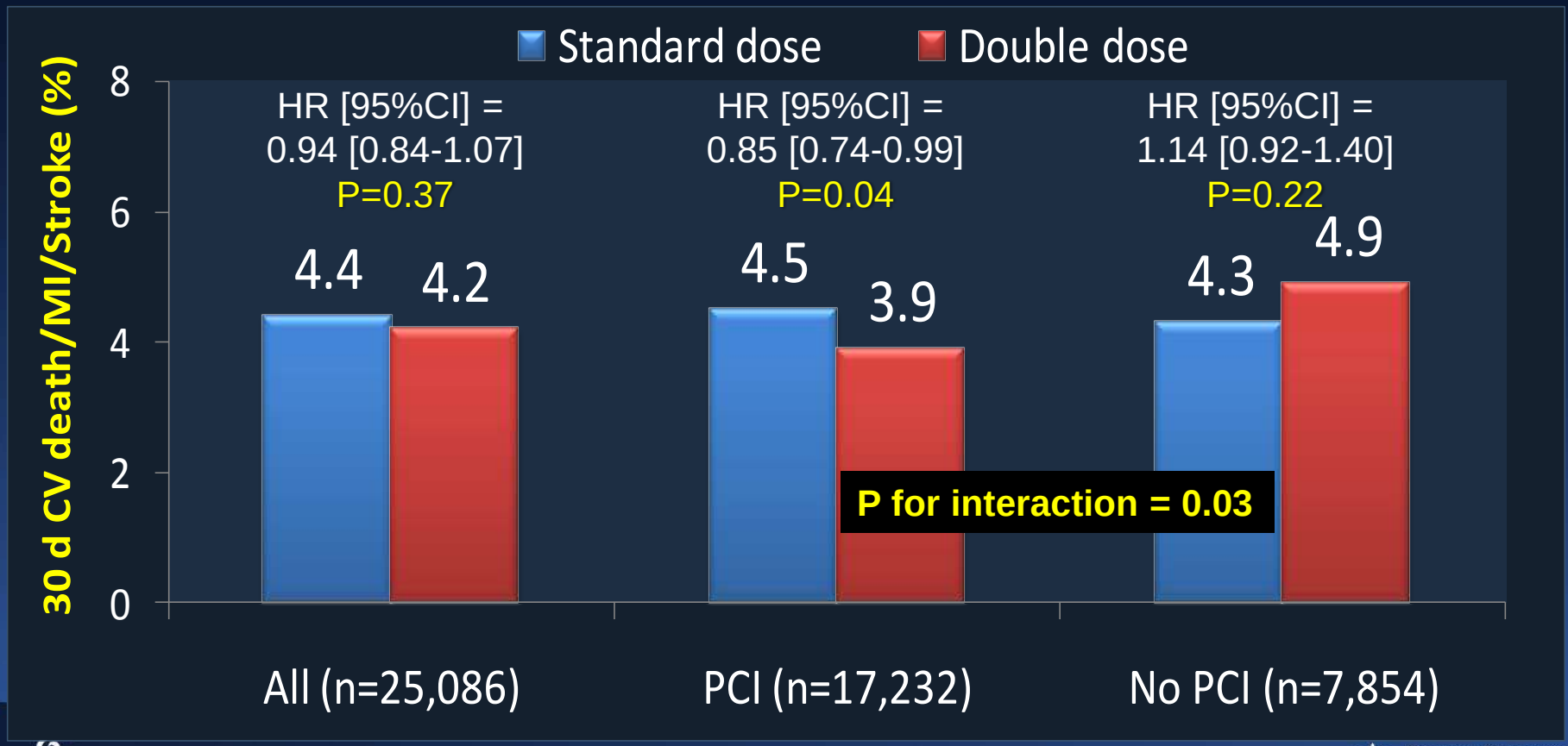
Primary endpoint = CV Death, MI, or Stroke



CURE Trial Investigators. N *Engl J Med* 2001;345:494–502.

CURRENT

25,086 pts with ACS (UA/NSTEMI 70.8%, STEMI 29.2%) undergoing early invasive management randomized to clopidogrel double-dose (600 mg then150 mg/d x 7d then 75 mg/d) vs standard dose (300 mg then 75 mg/d) for 30 days



Mehta S et al. NEJM 2010;363:930-42 and Lancet 2010;on-line

CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

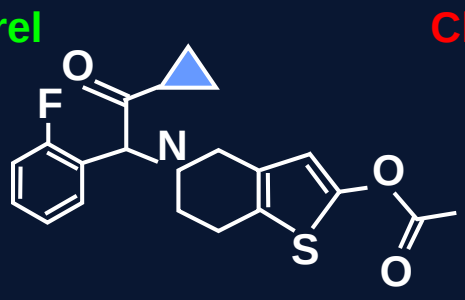
Clopidogrel Double vs Standard Dose: Bleeding Overall Population

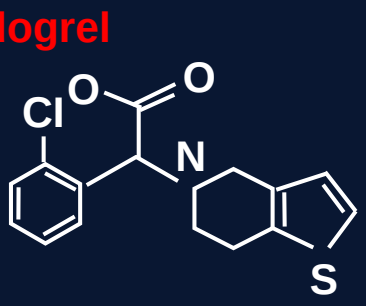
	Clopidogrel				
	Standard N=12,566	Double N=12,520	Hazard Ratio	95% CI	P
TIMI Major[1]	1.3	1.7	1.23	1.06-1.54	0.03
CURRENT Major[2]	2.0	2.5	1.25	1.05-1.46	0.01
CURRENT Severe[3]	1.6	1.9	1.22	1.01-1.47	0.04
CURRENT Minor	4.3	5.1	1.18	1.05-1.33	0.01
Fatal	0.1	0.1	1.07	0.53-2.16	0.85
ICH	0.05	0.03	0.67	0.19-2.37	0.53
RBC transfusion ≥ 2U	1.7	2.2	1.28	1.07-1.54	0.01
CABG-related Major	0.9	1.0	1.09	0.84-1.40	0.53

[1] ICH, Hb drop ≥5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal; [2] Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units; [3] Fatal or ↓Hb ≥5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥4 units

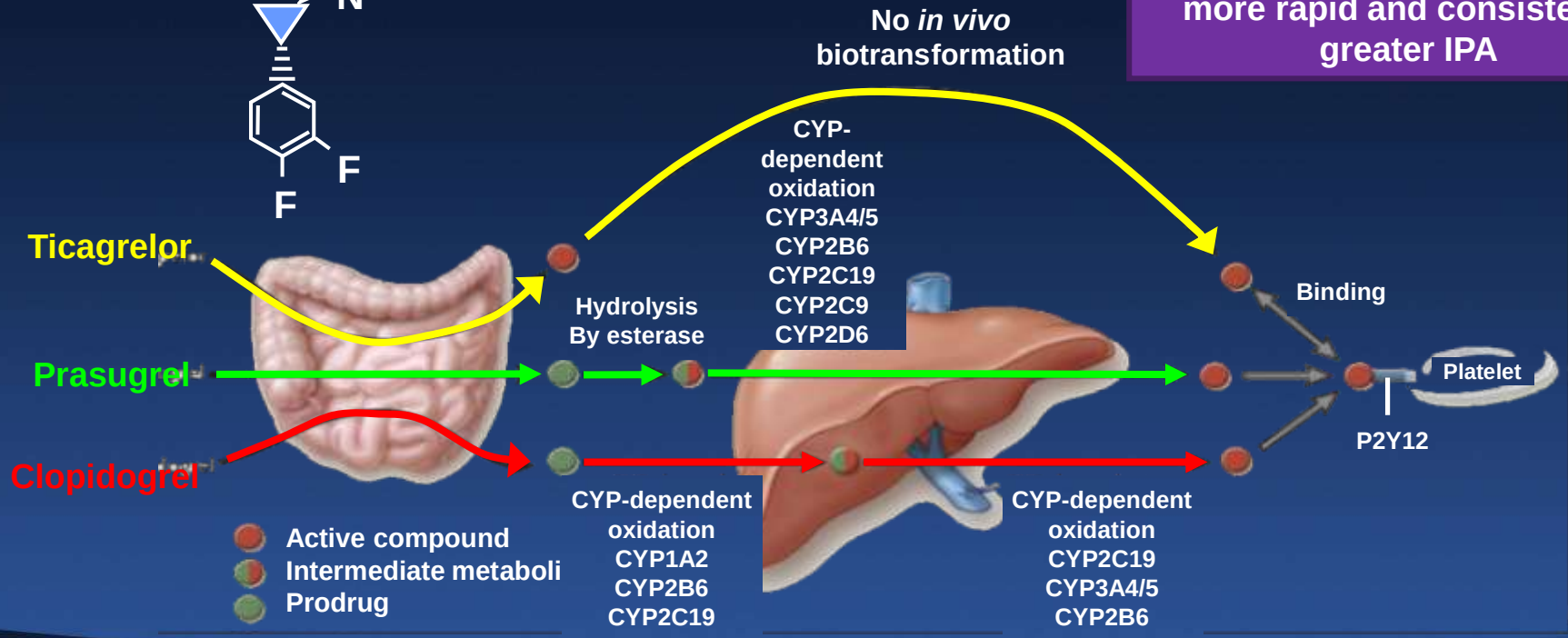
Mehta S et al. NEJM 2010;363:930-42

Metabolism of P2Y12 Receptor Blockers





Ticagrelor and prasugrel have more rapid and consistently greater IPA



Schomig A. *NEJM* 361;11:1108-11

TRITON TIMI-38

Study Design

ACS (UA/NSTEMI or STEMI) **& Planned PCI***

ASA ↓ **N= 13,600**

*Except STEMI

Double-blind

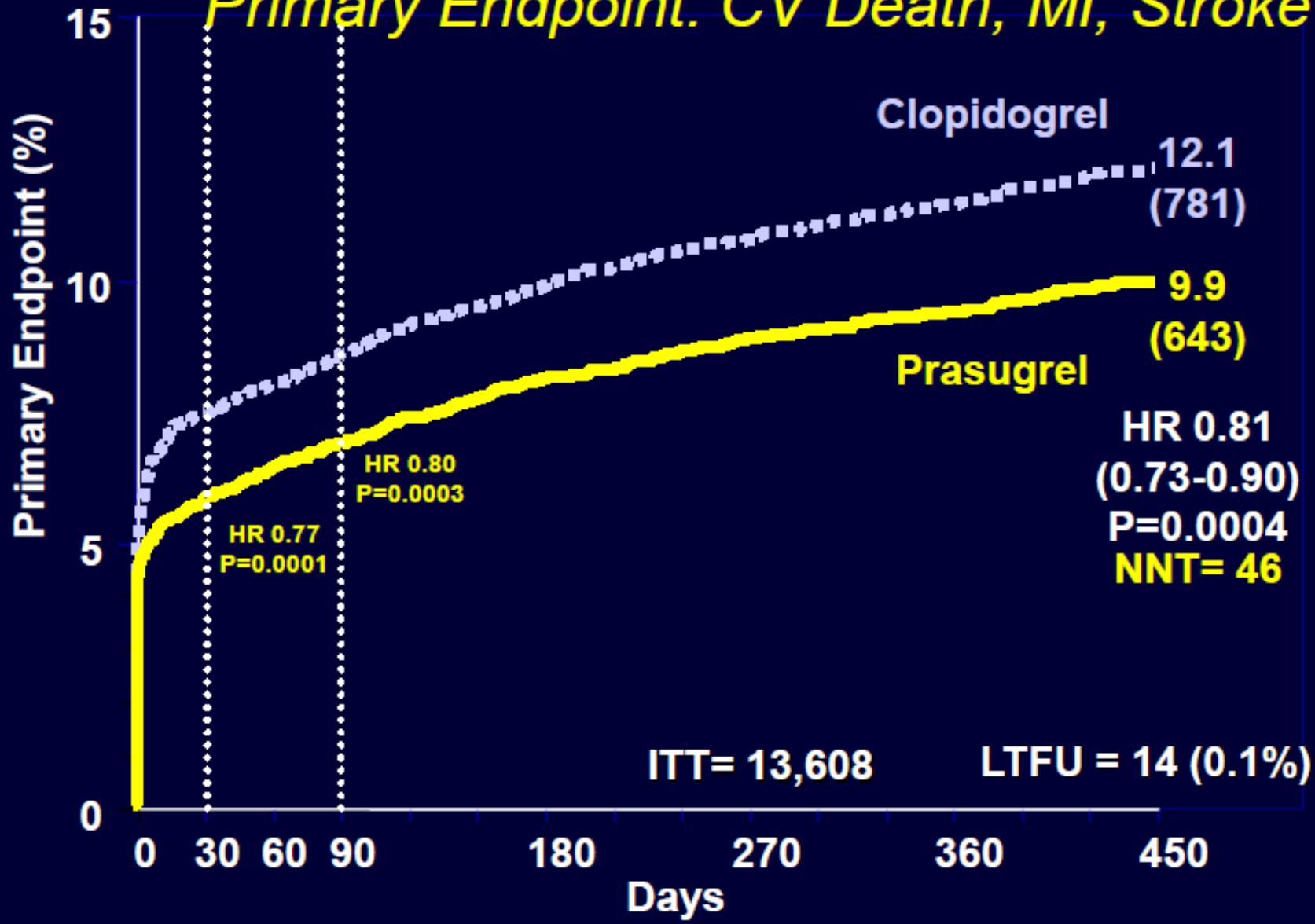
CLOPIDOGREL	**PRASUGREL**
300 mg LD/ 75 mg MD	**60 mg LD/ 10 mg MD**

Median duration of therapy – 12 months

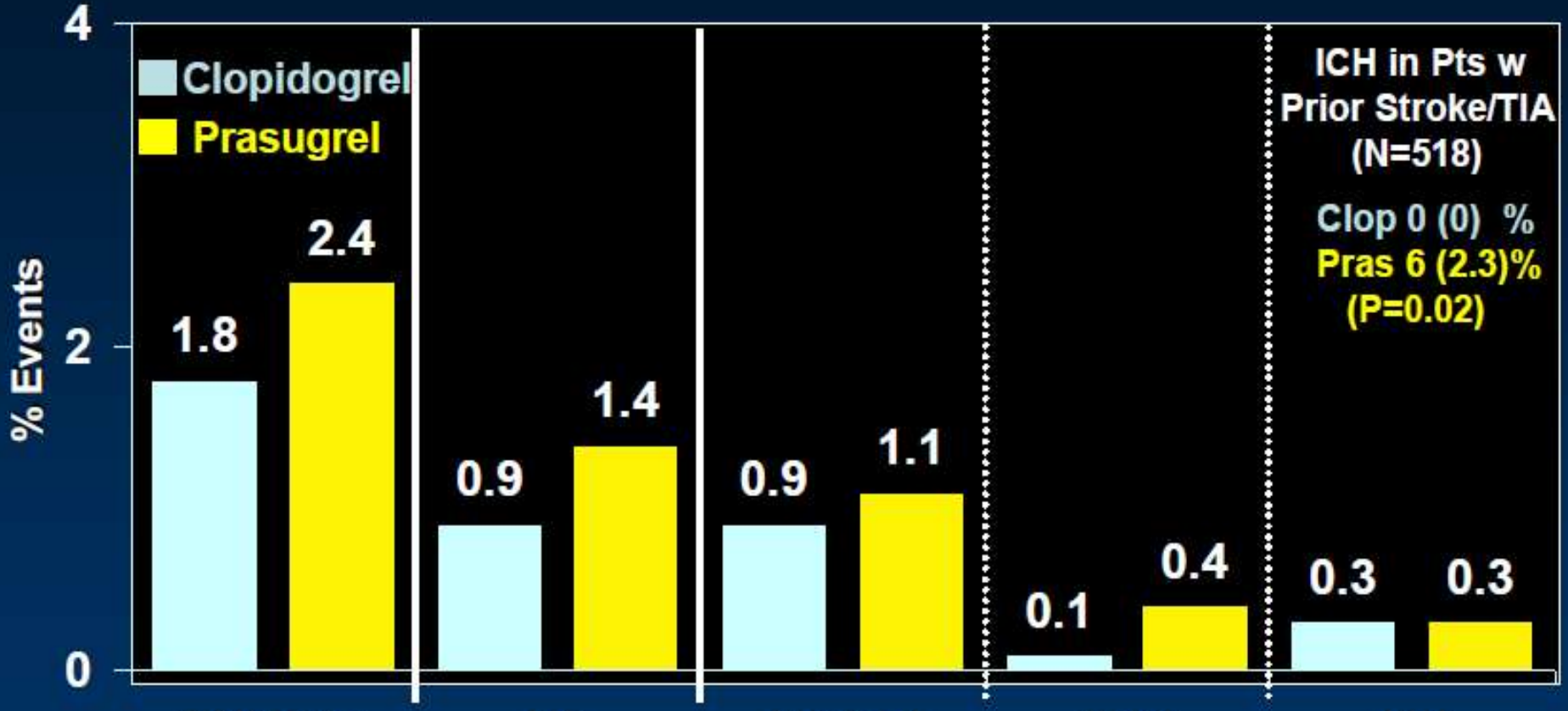
1º endpoint:	CV death, MI, Stroke
2º endpoints:	CV death, MI, Stroke, Rehosp-Rec Isch
	CV death, MI, UTVR
	Stent Thrombosis (ARC definite/prob.)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key Substudies:	Pharmacokinetic, Genomic

Triton TIMI 38 – Prasugrel vs. Clopidogrel

Wiviott SD et al. *N Engl J Med* 2007;357:2001-15



TRITON : bleeding events
Safety Cohort (N=13,457)



PLATO Study Design

NSTE-ACS (moderate-to-high risk) or STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel	Ticagrelor
If pre-treated, no additional loading dose; if naive, standard 300 mg loading dose, then 75 mg qd maintenance; (additional 300 mg allowed pre PCI)	180 mg loading dose, then 90 mg bid maintenance; (additional 90 mg pre-PCI)

6–12-month exposure (median 9 mos)

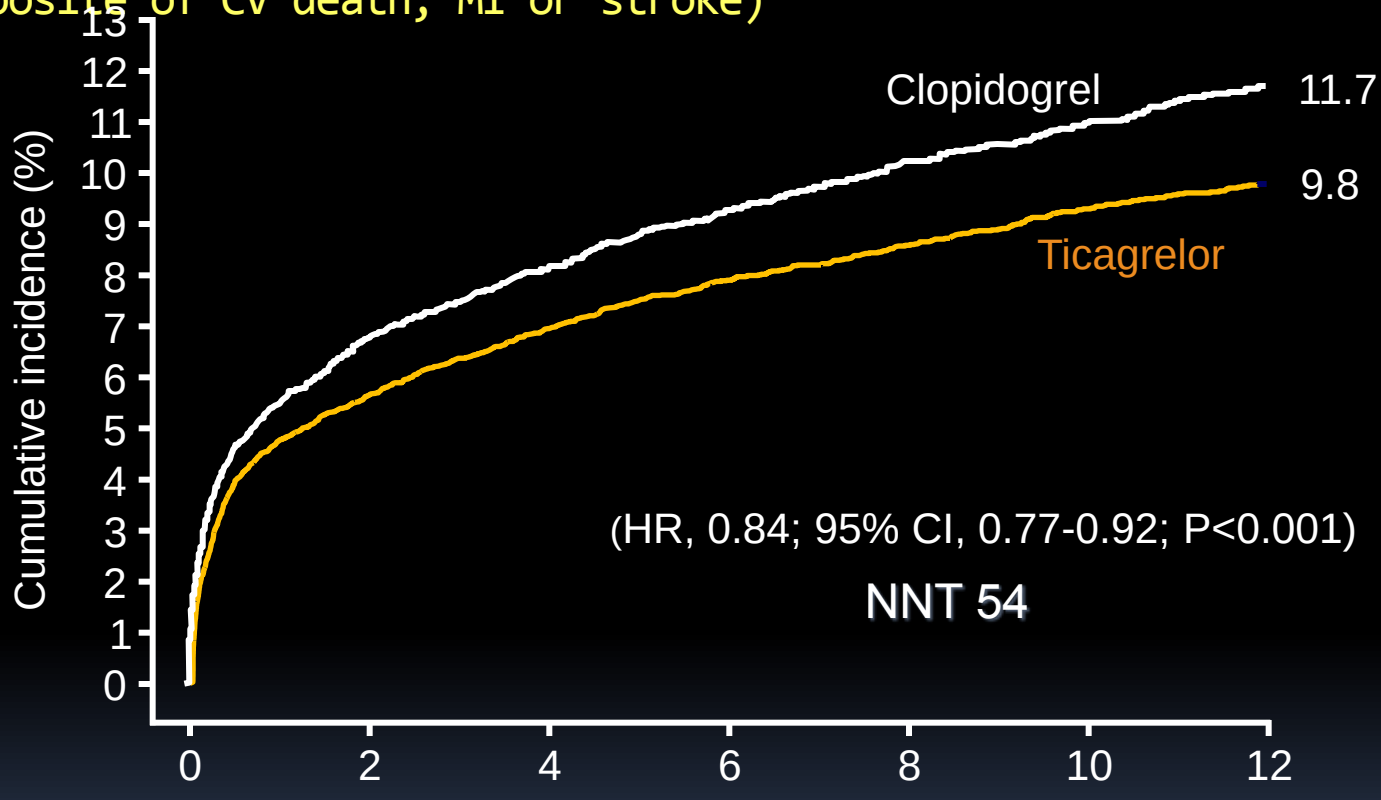
Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

Note: ASA 325 mg load, then 75-100 mg QD (325 mg x6 mo permitted if stented

Wallentin L et al. *NEJM* 2009;361:1045-57

PLATO: primary endpoint:

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



No. at risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

Wallentin L, et al. N Engl J Med. 2009;361:1045.

PLATO : Summary
Consistent Benefit Across Sub-groups

Primary Efficacy Endpoint

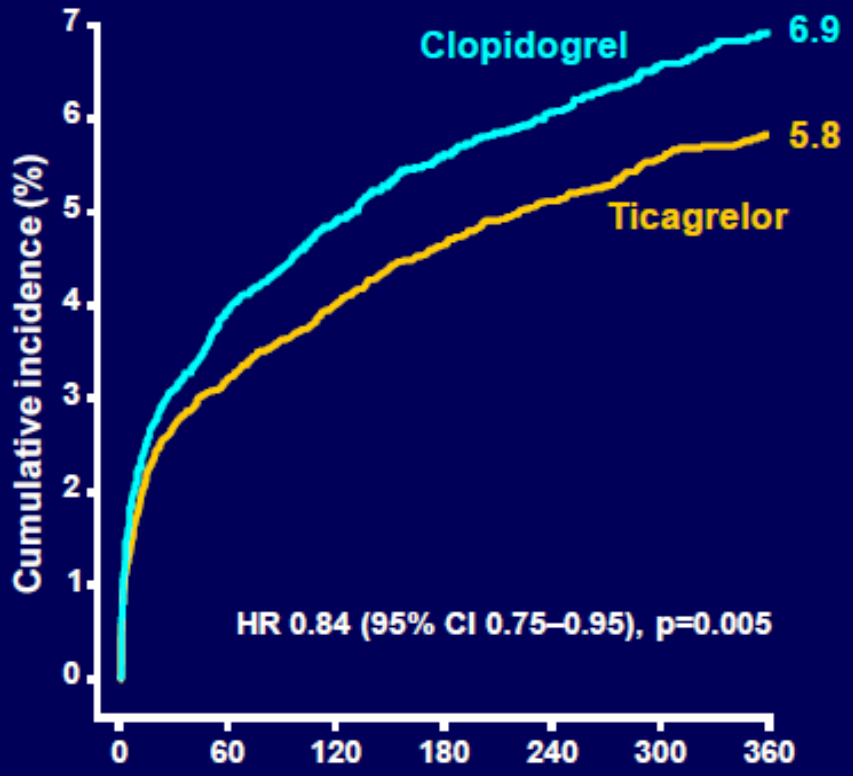
	Ticagrelor Group	Clopidogrel Group	HR for (95% CI)	p	p*
MI / CV Death / Stroke, K-M %					
PLATO (n=18,624)	9.8	11.7	0.84 (0.74-0.92)	<0.001	
PLATO-INVASIVE (n=13,408)	9.0	10.7	0.84 (0.75-0.97)	<0.01	
PLATO-MEDICAL (n=5,216)	12.0	14.5	0.85 (0.73-1.00)	0.04	NS
PLATO-STEMI (n=8,430)	9.3	11.0	0.85 (0.74-0.97)	0.02	NS
PLATO-CABG (n=1,261)	10.5	12.6	0.84 (0.60-1.16)	0.29	NS
PLATO Diabetes (n=2664)	14.1	16.2	0.88(0.76–1.03)		NS
PLATO Renal (n=3237)	17.3	22.0	0.77(0.65–0.90)		NS

* p for interaction

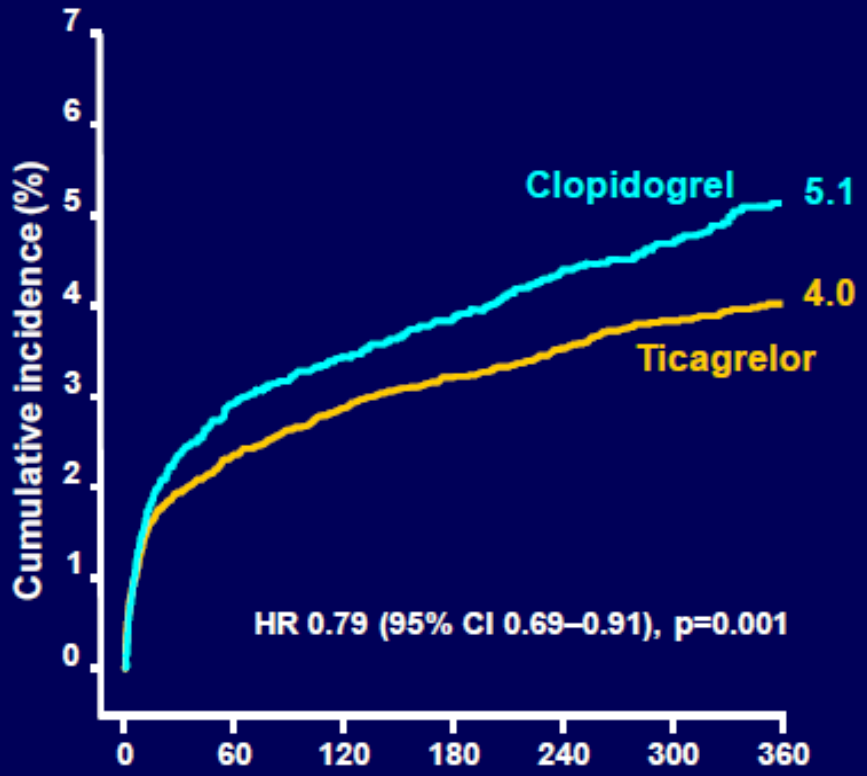
Secondary efficacy endpoints over time

PLATO

Myocardial infarction



Cardiovascular death



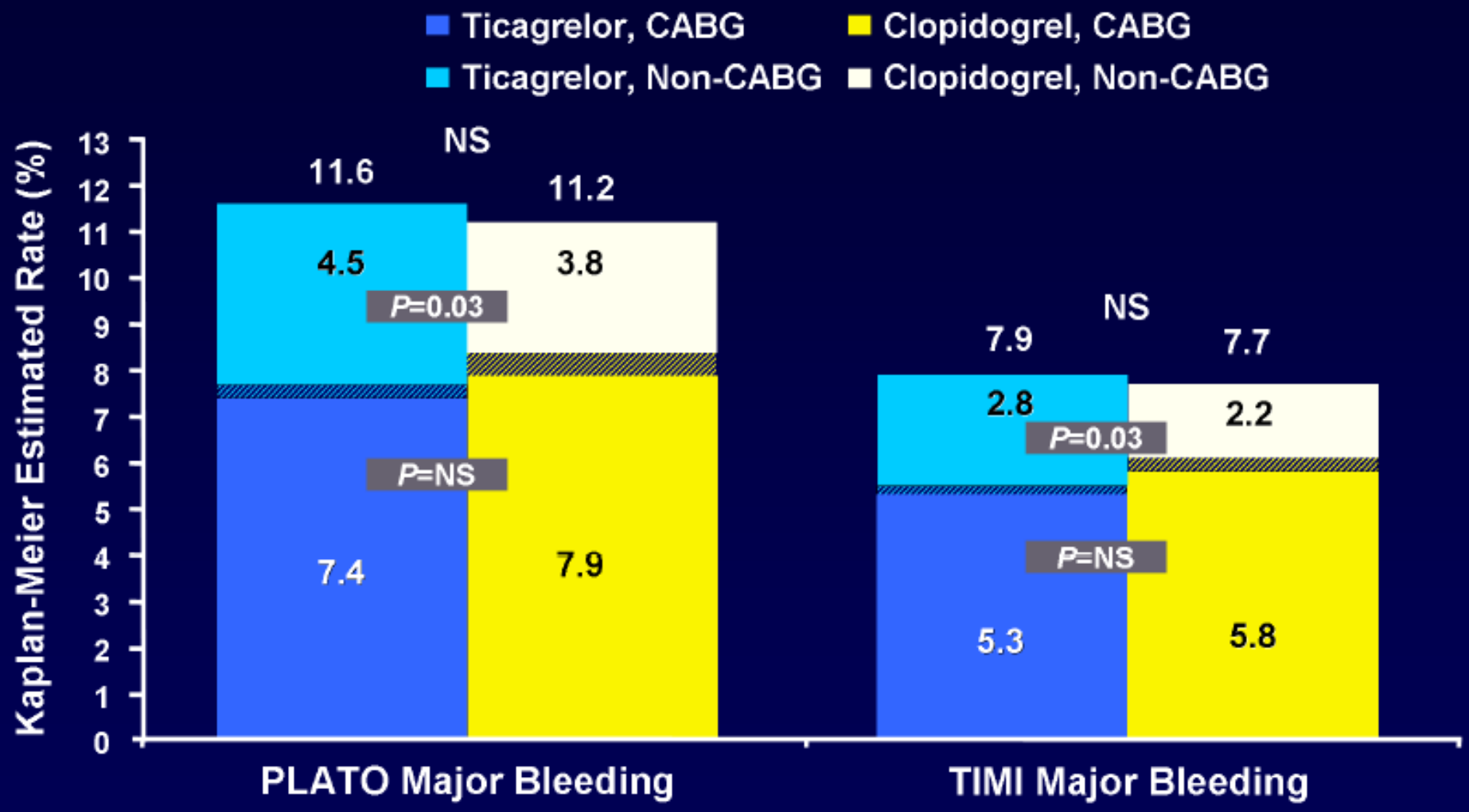
No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

Adapted from Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

PLATO: CABG vs. Non-CABG Major Bleeding



Wallentin L, et al. N Engl J Med. 2009;361:1045.

PLATO Asian substudy

Net clinical benefit of ticagrelor vs clopidogrel in Asian ACS patients

Hyun-Jae Kang,et al
AHA, Dallas, 2013

RESULTS

Table 1. Baseline characteristics

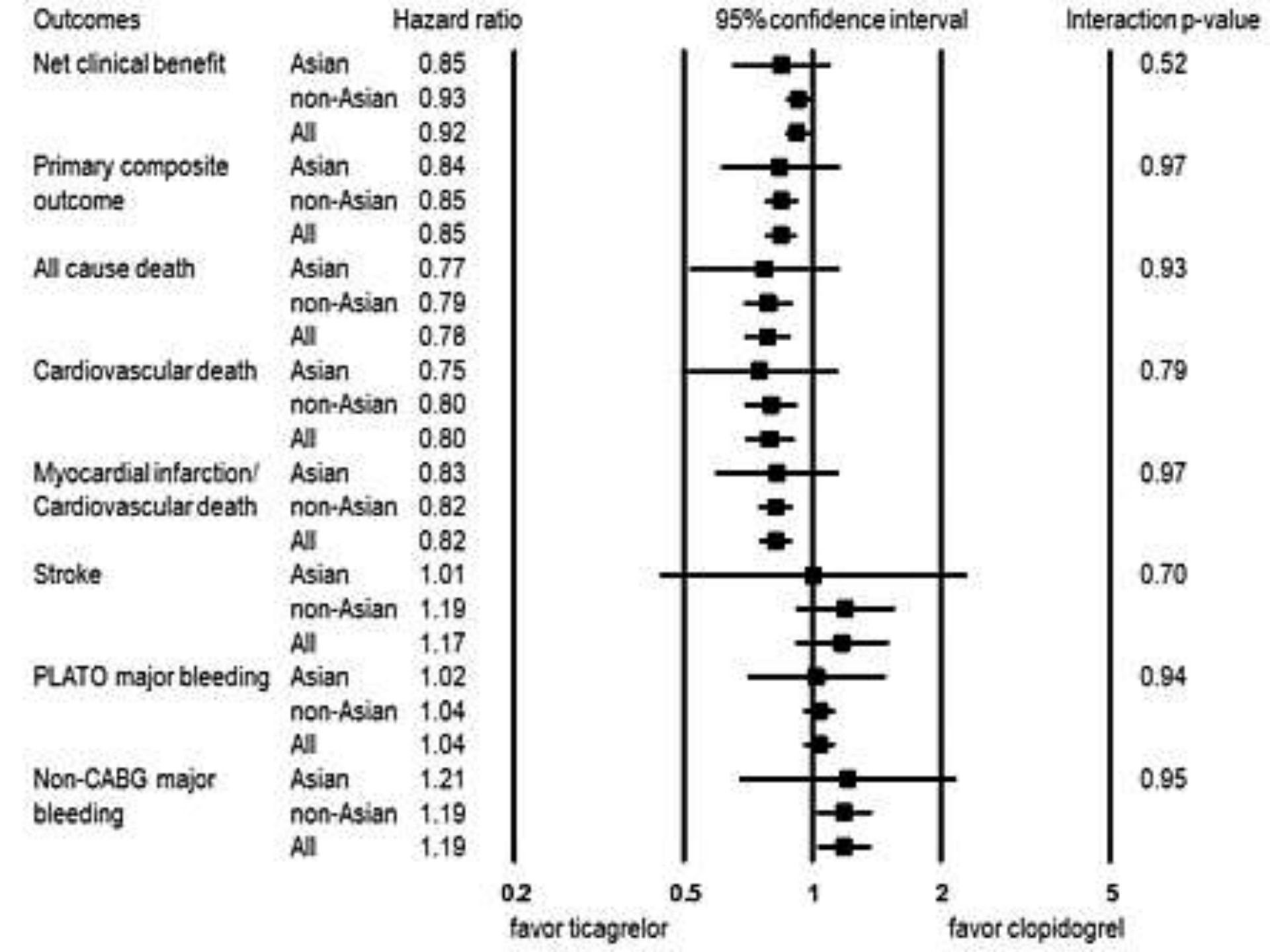
	Non-Asian (n=17515)	Asian (n=1106)	P-value
Demographics			
Age, year (Q1, Q3)	62 (54, 71)	61 (52, 69)	<0.001
Female, n (%)	28.5	26.3	0.113
Weight, kg (Q1, Q3)	80 (70, 90)	65 (58, 75)	<0.001
Body mass index, kg/m^2 (Q1, Q3)	27.6 (24.9, 30.6)	24.2 (22.1, 26.6)	<0.001
Cardiovascular risk factors			
Current smoker, n (%)	35.6	39.8	0.005
Diabetes mellitus, n (%)	24.8	29.4	0.001
Hypertension, n (%)	65.7	61.3	0.003
Dyslipidemia, n (%)	47.5	33.1	<0.001
Prior disease status			
Angina pectoris, n (%)	44.9	44.8	0.919
Myocardial infarction, n (%)	20.9	14.9	<0.001
Congestive heart failure, n (%)	5.6	5.6	0.958
Prior PCI, n (%)	13.7	7.9	<0.001
Prior CABG, n (%)	6.2	1.6	<0.001
Prior TIA, n (%)	2.7	1.7	0.041
Non-hemorrhagic stroke, n (%)	3.7	6.4	<0.001
Peripheral artery disease, n (%)	6.5	1.2	<0.001
Chronic renal disease, n (%)	4.2	4.3	0.834
Baseline Laboratory findings			
Hemoglobin A1C, % (Q1, Q3)	6.0 (5.6, 6.6)	6.1 (5.7, 7.2)	<0.001
Creatinine clearance, ml/minute (Q1, Q3)	80.6 (63.3, 99.2)	75.0 (57.8, 93.6)	<0.001

RESULTS

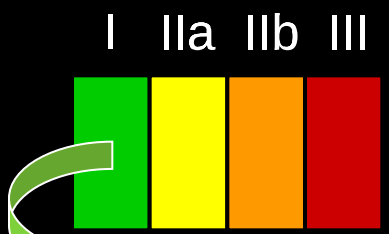
Table 1. Baseline characteristics

	Non-Asian (n=17515)	Asian (n=1106)	P-value
Index event			<0.001
Unstable angina, n (%)	16.9	14.6	
NSTEMI n (%)	43.2	36.7	
STEMI, n (%)	37.3	45.5	
Others, n (%)	2.6	3.3	
Concomitant medications			
Baseline aspirin use, n (%)	93.8	89.8	<0.001
ACEi/ARB, n (%)	65.2	63.2	0.191
Beta blocker, n (%)	72.7	54.2	<0.001
Calcium channel blocker, n (%)	16.7	15.7	0.386
Statin, n (%)	80.0	75.1	<0.001
Proton pump inhibitor, n (%)	35.2	34.1	0.890
GP IIb/IIIa inhibitor, n (%)	25.6	12.5	<0.001
Planned invasive approach, n(%)	71.7	76.2	0.001

Q1: 1st quartile, Q3: 3rd quartile, PCI: percutaneous intervention, CABG: coronary artery bypass grafts urgery, STEMI: ST segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, ACEi/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor blocker, GP: glycoprotein


Outcomes
Hazard ratio
95% confidence interval
Interaction p-value
Net clinical benefit
Asian 0.85
non-Asian 0.93
All 0.92
0.52
Primary composite outcome
Asian 0.84
non-Asian 0.85
All 0.85
0.97
All cause death
Asian 0.77
non-Asian 0.79
All 0.78
0.93
Cardiovascular death
Asian 0.75
non-Asian 0.80
All 0.80
0.79
Myocardial infarction/ Cardiovascular death
Asian 0.83
non-Asian 0.82
All 0.82
0.97
Stroke
Asian 1.01
non-Asian 1.19
All 1.17
0.70
PLATO major bleeding
Asian 1.02
non-Asian 1.04
All 1.04
0.94
Non-CABG major bleeding
Asian 1.21
non-Asian 1.19
All 1.19
0.95
0.2
0.5
1
2
5
favor ticagrelor
favor clopidogrel

Antiplatelet Therapy



Modified 2012

Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected should receive dual antiplatelet therapy on presentation. *(Level of Evidence: A)* Aspirin should be initiated on presentation. *(Level of Evidence: A)* The choice of a second antiplatelet therapy to be added to aspirin on presentation includes 1 of the following (note that there are no data for therapy with 2 concurrent $P2Y_{12}$ receptor inhibitors, and this is not recommended in the case of aspirin allergy):

Before PCI:

- Clopidogrel *(Level of Evidence: B);* or
- Ticagrelor *(Level of Evidence: B);* or
- An IV GP IIb/IIIa inhibitor. *(Level of Evidence: A)* IV eptifibatide and tirofiban are the preferred GP IIb/IIIa inhibitors. *(Level of Evidence: B)*

At the time of PCI:

- Clopidogrel if not started before PCI *(Level of Evidence: A);* or
- Prasugrel *(Level of Evidence: B);* or
- Ticagrelor *(Level of Evidence: B);* or
- An IV GP IIb/IIIa inhibitor. *(Level of Evidence: A)*

Table 3. Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI

	COR	LOE	References
Antiplatelet therapy			
Aspirin			
• 162- to 325-mg load before procedure	I	B	(251–253)
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A	(254,255,257)
• 81 mg daily is the preferred maintenance dose*	IIa	B	(253,254,263,264)
$P2Y_{12}$ inhibitors			
Loading doses			
• Clopidogrel: 600 mg as early as possible or at time of PCI	I	B	(253,258,259)
• Prasugrel: 60 mg as early as possible or at time of PCI	I	B	(260)
• Ticagrelor: 180 mg as early as possible or at time of PCI	I	B	(261)
Maintenance doses and duration of therapy			
DES placed: Continue therapy for 1 y with:			
• Clopidogrel: 75 mg daily	I	B	(260,262)
• Prasugrel: 10 mg daily	I	B	(262)
• Ticagrelor: 90 mg twice a day*	I	B	(261)
BMS† placed: Continue therapy for 1 y with:			
• Clopidogrel: 75 mg daily	I	B	(260,262)
• Prasugrel: 10 mg daily	I	B	(262)
• Ticagrelor: 90 mg twice a day*	I	B	(261)
DES placed:			
• Clopidogrel, prasugrel, or ticagrelor* continued beyond 1 y	IIb	C	N/A
• Patients with STEMI with prior stroke or TIA: prasugrel	III: Harm	B	(260)

Recommendations for oral antiplatelet agents (1)

Recommendations	Class	Level
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
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
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 *(H. elicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
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.	I	B

European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

Recommendations for oral antiplatelet agents (2)

Recommendations	Class	Level
Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600 mg loading dose of clopidogrel (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
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
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B
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
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

Periprocedural anti thrombotic medication in primary PCI

Recommendations	Class	Level
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.

European Heart Journal (2012) 33, 2569–2619
doi:10.1093/eurheartj/ehs215

Recent guidelines published by the ESC and the ACCF/AHA: an evidence-based rationale for antiplatelet treatment

Rapid evolution of treatment options
antiplatelet therapy management quite complex

Successful implementation of practice guidelines incorporating new treatments into practice challenging.

Implementation of new evidence-based and guideline-recommended treatments in real life: possibly result in better survival of ACS patients.

Temporal and geographic variations in guideline therapy adherence is well appreciated.

Although early use of clopidogrel therapy has increased over time, a significant proportion of eligible patients still does not receive the evidence-based therapy.

More pronounced for the novel antiplatelet agents-prasugrel and ticagrelor??

GReek AntiPlatelet rEgistry (GRAPE),

Initiated on January 2012, Patras University Hospital/8 PCI centers/supported by HCS

represents the ‘real life’ experience incorporating –for the first time-the contemporary use of all the 3 oral P2Y12 inhibitors (clopidogrel, prasugrel and ticagrelor).

Recruitment completed (7/2013) n=2047

International Journal of Cardiology 168 (2013) 5329–5335

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journal homepage: www.elsevier.com/locate/ijcard

Implementation of contemporary oral antiplatelet treatment guidelines in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A report from the GReek AntiPlatelet rEgistry (GRAPE)☆

Dimitrios Alexopoulos [a,*], John A. Goudevenos [b], Ioanna Xanthopoulou [a], Spyridon Deftereos [c], George Sitafidis [d], Ioannis Kanakakis [e], Michalis Hamilos [f], Haralambos Parissis [d], Ioannis V. Ntalas [b], Christos Angelidis [c], Stylianos Petousis [f], Manolis Vavuranakis [g], George Hahalis [a], Christodoulos Stefanadis [g]on behalf of the GRAPE Investigators

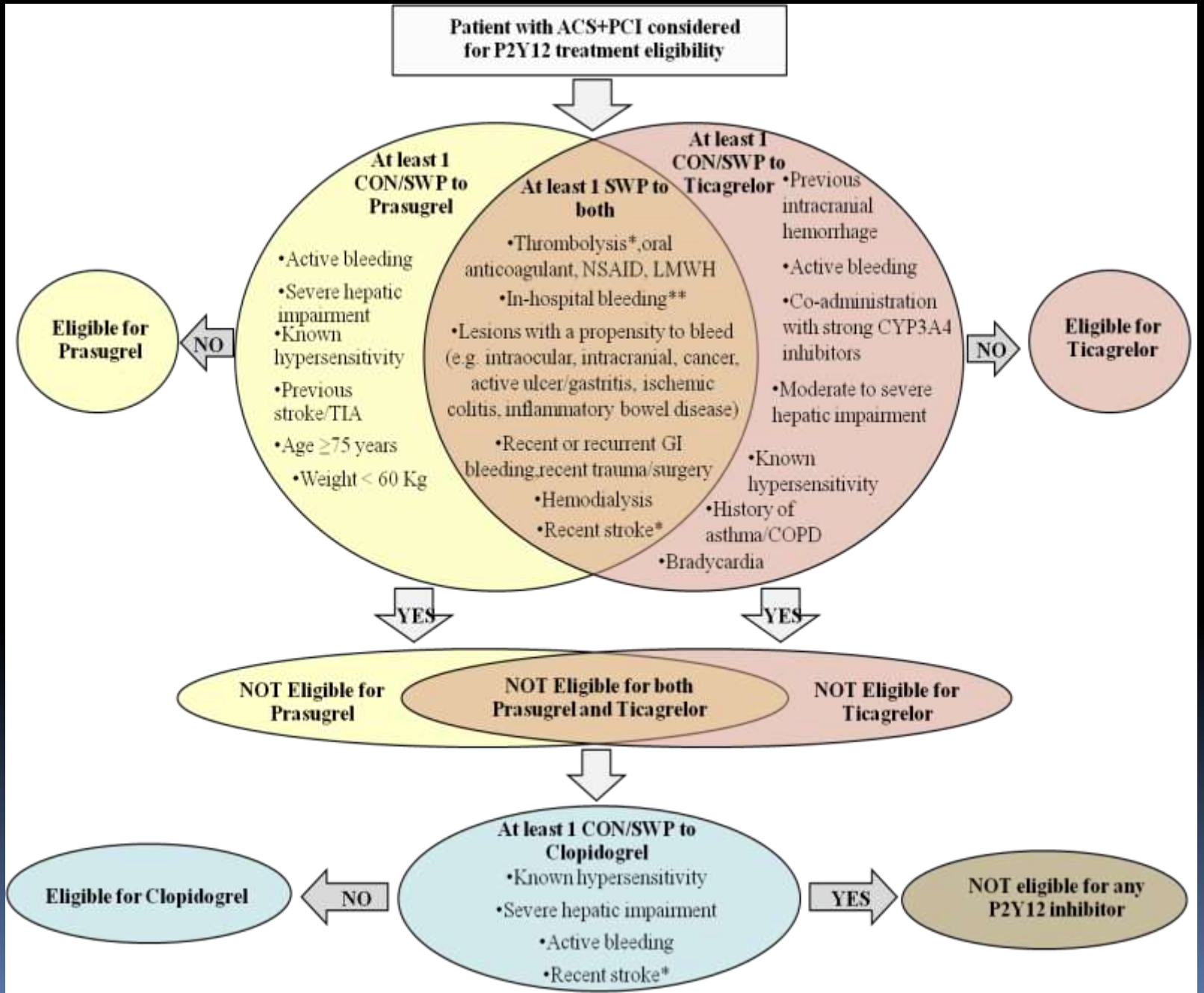
Decision-making algorithm

To determine eligibility to clopidogrel, prasugrel and ticagrelor,

initially,

according to the presence of contraindications (CON) and certain special warnings and precautions (SWP) -considered as the most important clinically- for each agent as reported by European Medicines Agency.

Eligibility criteria for P2Y12 inhibitor selection



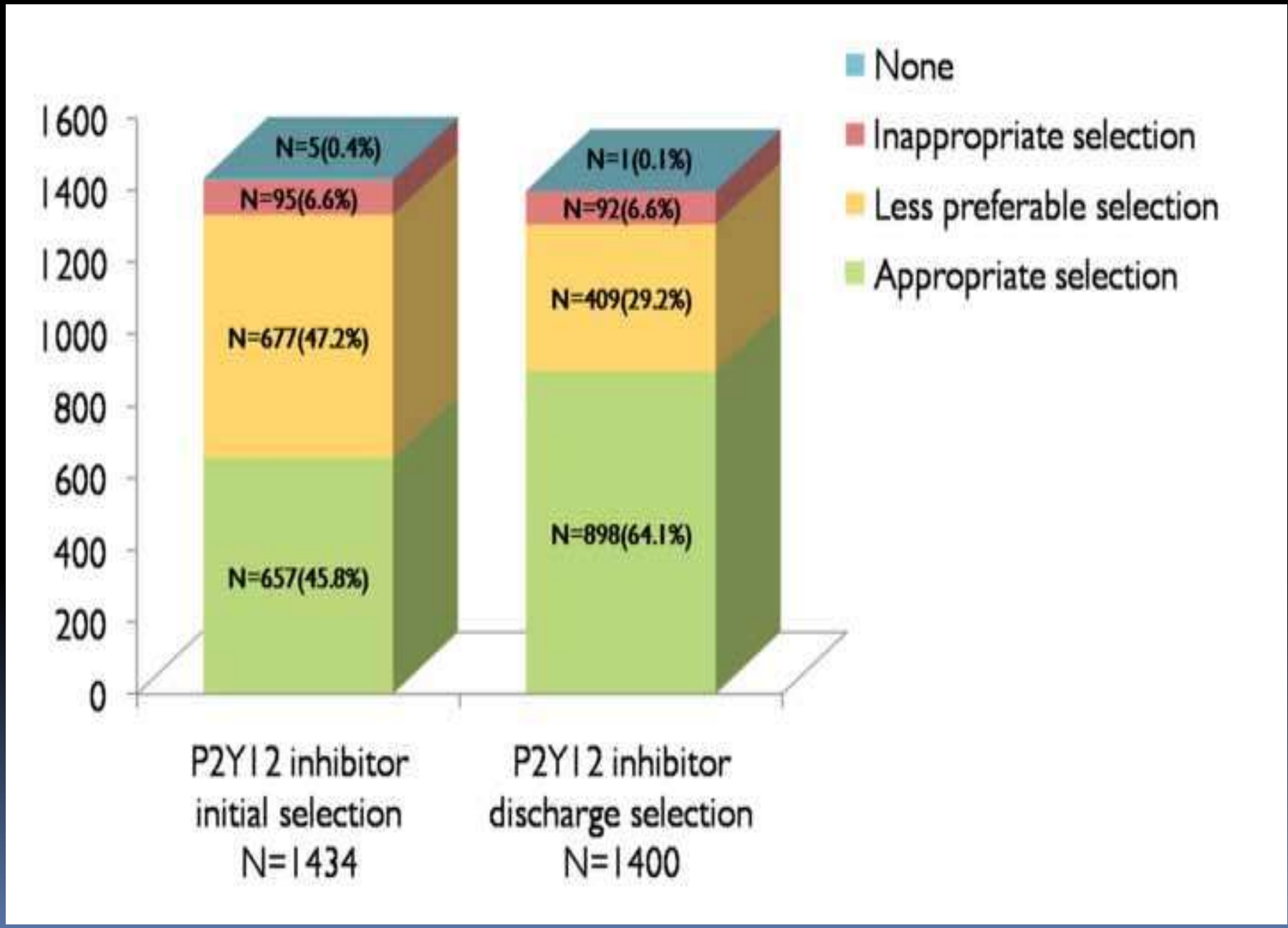
P2Y12 inhibitor selection was considered as

appropriate if patients were eligible to the actual P2Y12 inhibitor used,

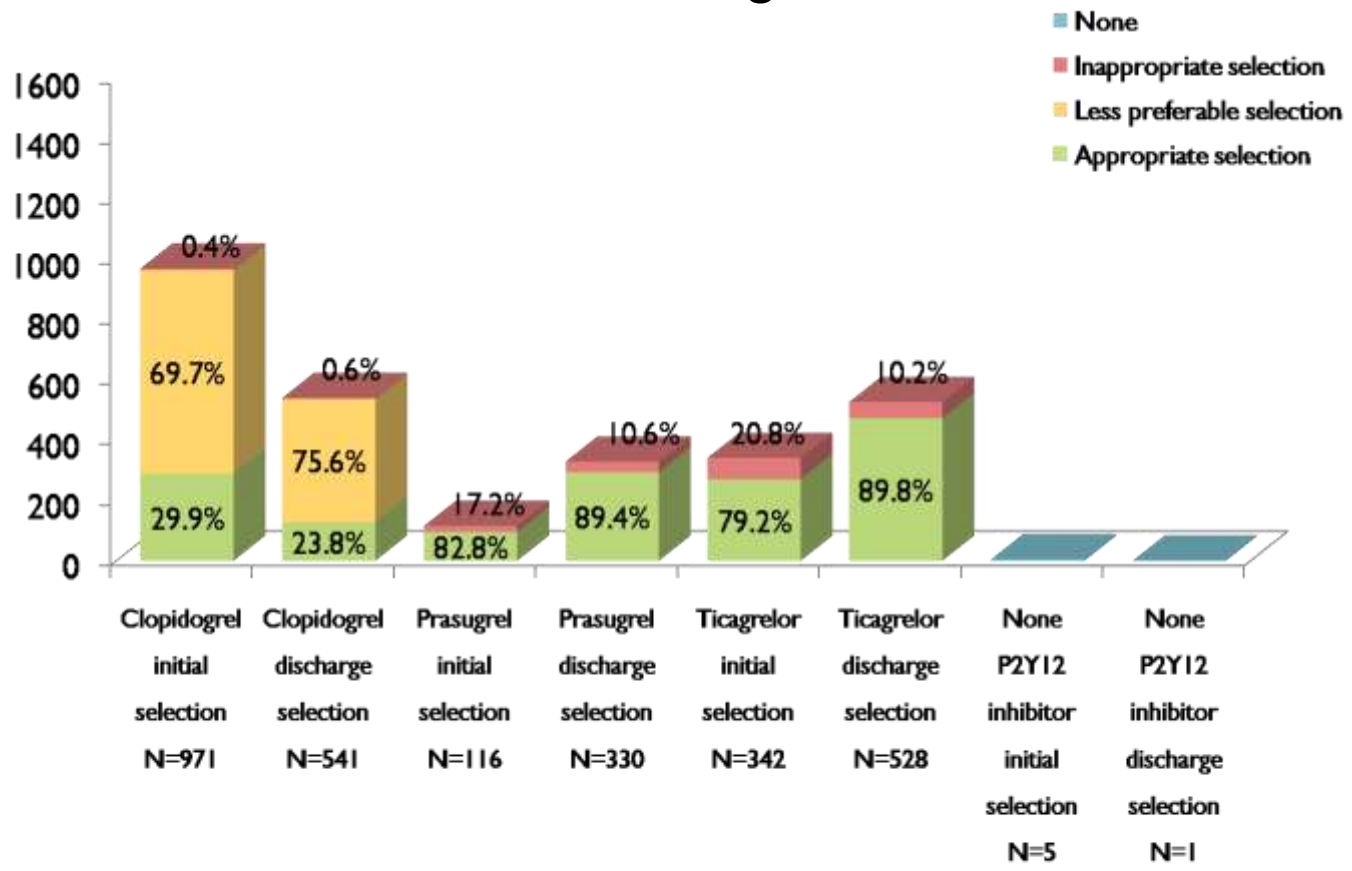
less preferable if patients eligible to ticagrelor and/or prasugrel received clopidogrel and

inappropriate for all the other cases.

Appropriateness of overall P2Y12 inhibitor selection initially and at discharge.



Appropriateness of each P2Y12 inhibitor selection initially and at discharge.



Alexopoulos D, et al. Intern J Cardiol 2013;168:5329

Overall use of P2Y12 inhibitors was almost universal (99.7-99.9%) both initially and at discharge.

Clopidogrel was the most frequently selected agent initially while at discharge, the majority of patients received a novel agent.

Prevalence of contraindications/ special warnings and precautions (CON/SWP) for clopidogrel, prasugrel and ticagrelor use:

not adequately studied

might affect P2Y12 inhibitor choice

Randomized studies (CURE, TRITON TIMI38, PLATO):

excluded patients with many of the CON/SWP for these agents mainly because of the accompanying increased risk of bleeding

no report on the prevalence of these characteristics on populations screened

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Contraindications/Special Warnings and Precautions for Use of Contemporary Oral Antiplatelet Treatment in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

– Insights From the GReek AntiPlatelet rEgistry (GRAPE) –

Dimitrios Alexopoulos, MD; Ioanna Xanthopoulou, MD; Spyridon Deftereos, MD; George Sitafidis, MD; Ioannis Kanakakis, MD; Michalis Hamilos, MD; Manolis Vavuranakis, MD; Periklis Davlouros, MD; Ioannis Ntalas, MD; Christos Angelidis, MD; George Hahalis, MD; Filippos Triposkiadis, MD; Panos Vardas, MD; Christodoulos Stefanadis, MD; John A. Goudevenos, MD on behalf of the GRAPE Investigators

2013;78:180

Prevalence of CON/SWP for use of P2Y12 inhibitors

	N=1280		
	Clopidogrel	Prasugrel	Ticagrelor
CON			
-Hypersensitivity	1(0.1)	0(0)	1(0.1)
-Active pathological bleeding	4(0.3)	4(0.3)	4(0.3)
-Previous stroke/TIA	NA	45(3.5)	NA
-History of intracranial hemorrhage	NA	NA	6(0.5)
-Severe hepatic impairment (Child Pugh class C)	0(0)	0(0)	NA
-Moderate or severe hepatic impairment (Child Pugh class B or C)	NA	NA	1(0.1)

Prevalence of CON/SWP for use of P2Y12 inhibitors (continued)

	N=1280		
	Clopidogrel	Prasugrel	Ticagrelor
SWP			
-Age ≥75 years	NA	229 (17.9)	NA
-Weight< 60Kg	NA	45 (3.5)	NA
-Moderate hepatic impairement (Child Pugh class B)	1(0.1)	1(0.1)	NA
-Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption	2(0.2)	2(0.2)	NA
-Renal impairment (CrCl<60ml including hemodialysis)	211(16.5)	211(16.5)	211(16.5)
-Recent stroke (<7 days)	4(0.3)	NA	4(0.3)

Prevalence of CON/SWP for use of P2Y12 inhibitors (continued)

	N=1280		
	Clopidogrel	Prasugrel	Ticagrelor
SWP			
-History of asthma/COPD	NA	NA	65(5.1)
-Increased risk of bradycardiac events	NA	NA	10(0.8)
-History of hyperuricaemia, gouty arthritis, uric acid nephropathy	NA	NA	81(6.3)
-Coadministration with strong CYP3A4 inducers	NA	NA	6(0.5)
-Coadministration with moderate/strong CYP2C19 inhibitors	242(18.9)	NA	NA
Conditions related to increased bleeding risk			
-Recent trauma/surgery	4(0.3)	4(0.3)	4(0.3)
-Recent/recurrent GI bleeding	13(1.0)	13(1.0)	13(1.0)
-Lesions with a propensity to bleed (e.g. intraocular, intracranial, cancer, active ulcer/gastritis, ischemic colitis, inflammatory bowel disease)	74(5.8)	74(5.8)	74(5.8)

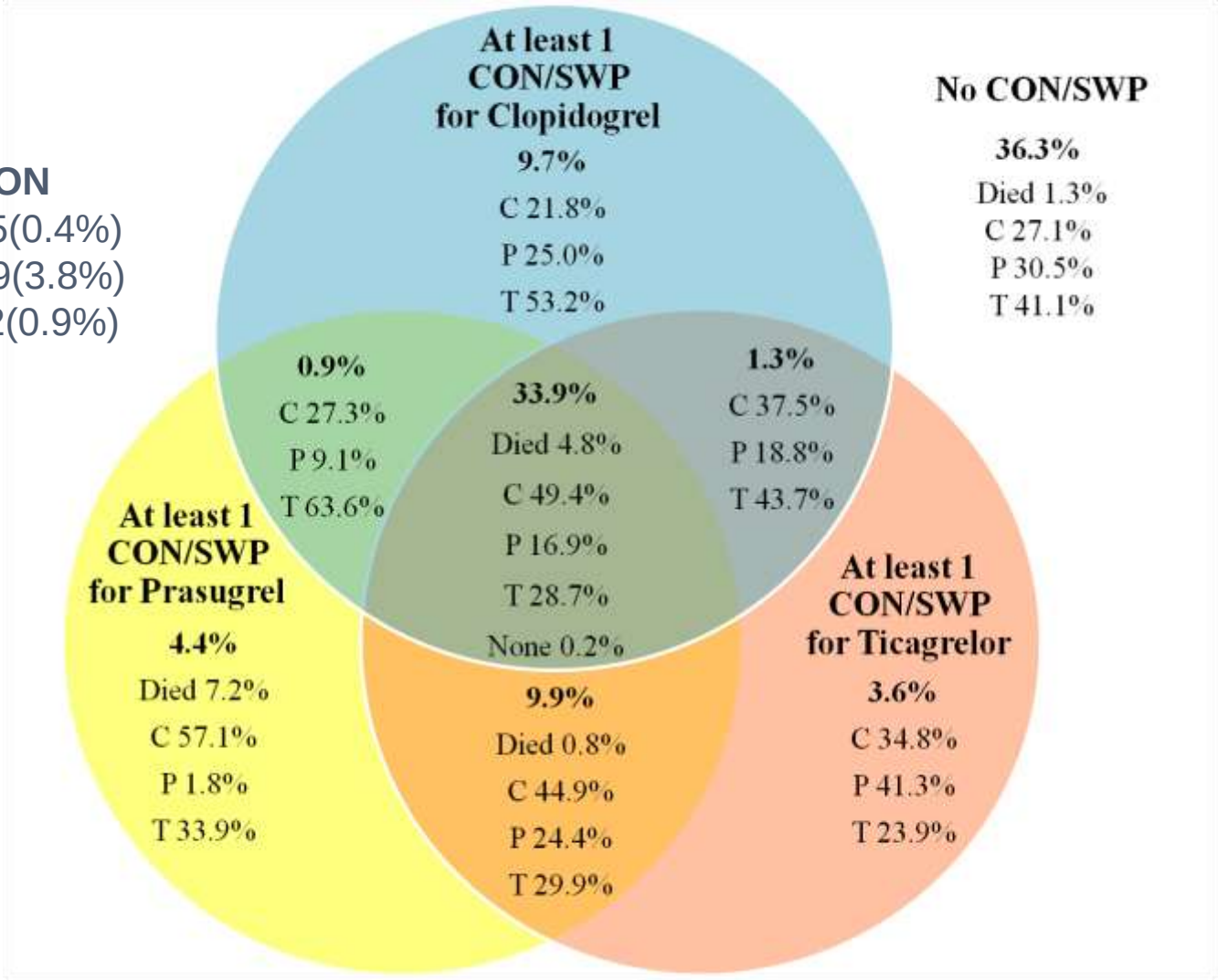
Prevalence of CON/SWP for use of P2Y12 inhibitors (continued)

N=1280

	Clopidogrel	Prasugrel	Ticagrelor
SWP			
Co-medication related to increased bleeding risk			
In hospital e.g. IIb/IIIa inhibitor, thrombolytic agent, oral anticoagulant	160(12.5)	306(23.9)	306(23.9)
-in hospital oral anticoagulant	7(0.5)	7(0.5)	7(0.5)
At discharge e.g. NSAIDs, oral anticoagulant, LMWH	51(4.0)	51(4.0)	51(4.0)
-at discharge oral anticoagulant	49(3.8)	49(3.8)	49(3.8)

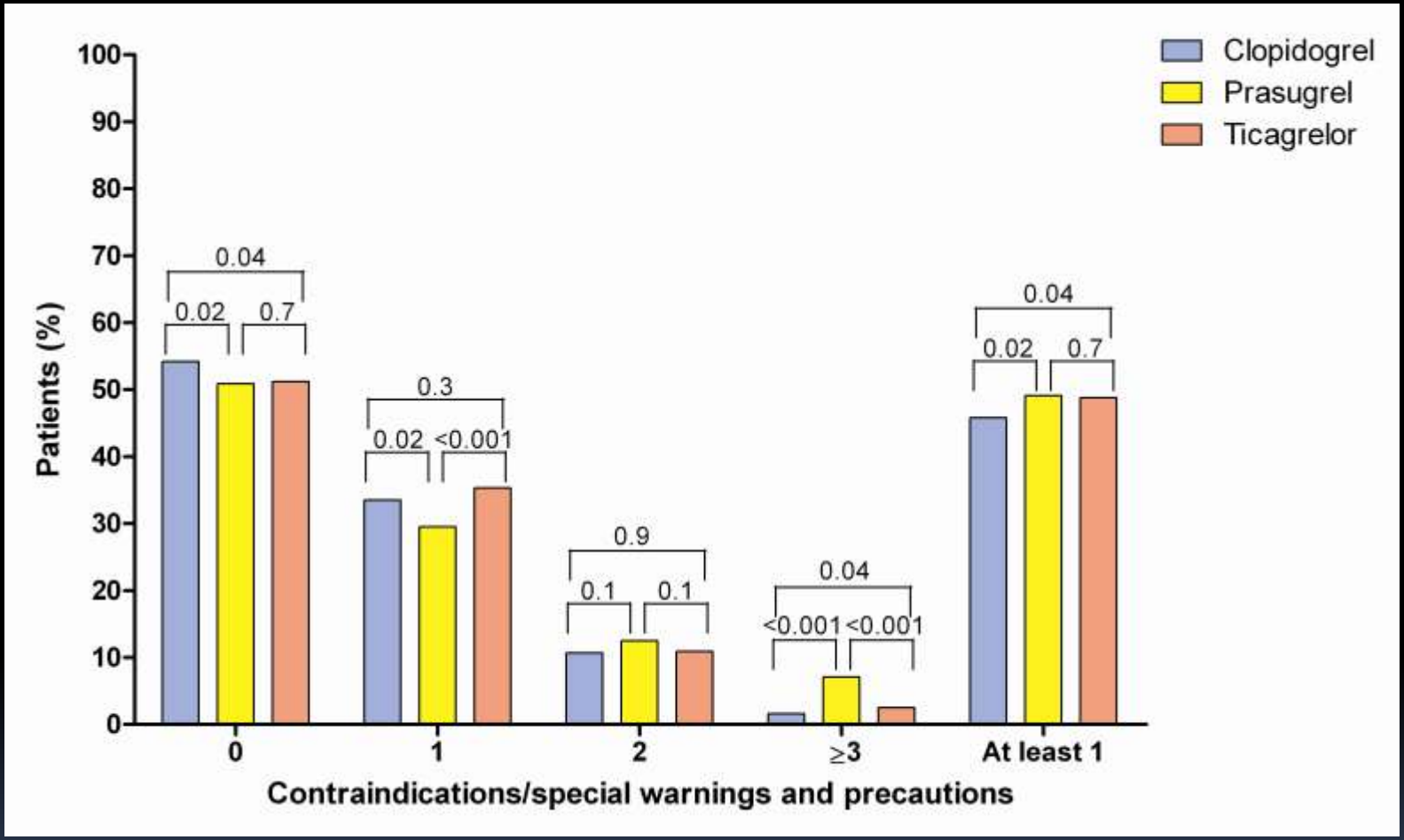
Prevalence of at least 1 CON/SWP and the prescription rates at discharge for each P2Y12 inhibitor.

At least 1 CON
Clopidogrel 5(0.4%)
Prasugrel 49(3.8%)
Ticagrelor 12(0.9%)



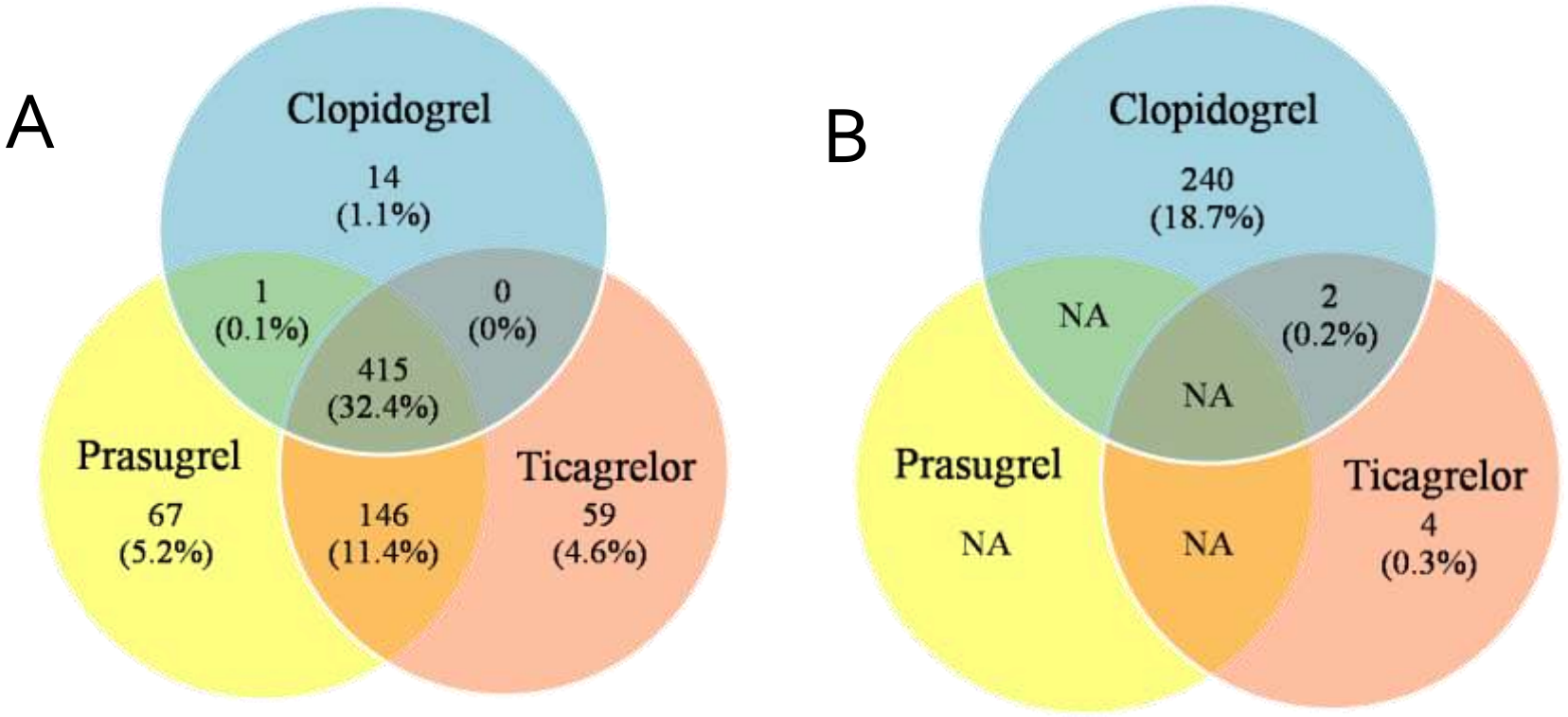
Patients with CON/SWP to all the 3 P2Y12 inhibitors were prescribed with descending frequency clopidogrel, ticagrelor and prasugrel

Distribution of patients according to the number of C/SWP for each P2Y12 inhibitor



At least 1 CON/SWP for use was less prevalent for clopidogrel (45.8%) than prasugrel (49.1%) or ticagrelor (48.8%). Significantly more patients had a high number (≥3) CON/SWP for use of prasugrel than clopidogrel or ticagrelor.

Prevalence of at least 1 C/SWP concerning safety or efficacy



Venn diagram showing the prevalence of at least 1 C/SWP for each P2Y12 inhibitor concerning safety (A) and efficacy (B) separately

Ticagrelor or prasugrel for pre-hospital protocols in STEMI? ☆

Nathalie Fournier [a], Richard Toesca [a], Jacques Bessereau [a], Anne Champenois [a], André Mazille [b], Stéphane Luigi [b], Serge Yvorra [c], Franck Paganelli [d], Pierre-Marie Brun [e], Pierre Michelet [a], Daniel Meyran [e], Jean-Pierre Auffray [a], Laurent Bonello [e,*]

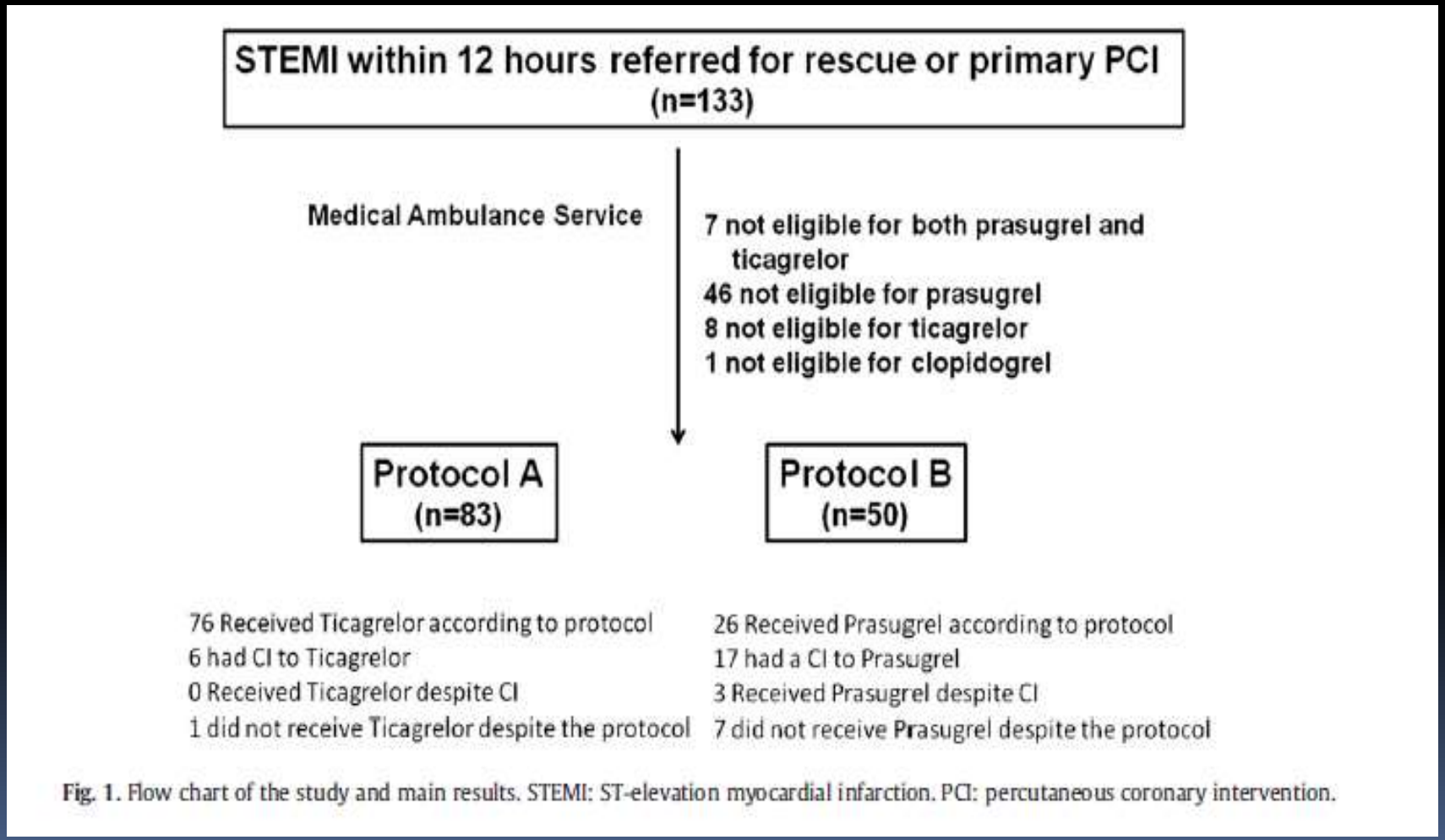


Fig. 1. Flow chart of the study and main results. STEMI: ST-elevation myocardial infarction. PCI: percutaneous coronary intervention.

Intern J Cardiol 2013;168:4566

Availability of 3 oral P2Y12 inhibitors

Different efficacy and safety profile along with contraindications and special warnings and precautions for use

in-hospital switching

Lack of a PCI indication at the early phase of hospitalization may also lead to selection of clopidogrel initially, with a novel P2Y12 inhibitor indication appearing at a later stage.

Switching from clop to pras or tic:
an alternative for clinical settings in which the novel agents have shown to be more beneficial compared with clop.

Switching from the novel P2Y12 inhibitors to clop:
for patients in whom the former are either contraindicated or special warnings and precautions for their use exist.

In-hospital switching of oral P2Y12 inhibitor treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention: Prevalence, predictors and short-term outcome

Dimitrios Alexopoulos, MD, [a,i] **Ioanna Xanthopoulou, MD,** [a,i] **Spyridon Deftereos, MD,** [b,i] **George Sitafidis, MD,** [c,i] **Ioannis Kanakakis, MD,** [d,i] **Michalis Hamilos, MD,** [e,i] **Christos Angelidis, MD,** [b,i] **Stylianos Petousis, MD,** [e,i] **Dimitrios Stakos, MD,** [f,i] **Haralambos Parissis, MD,** [c,i] **Manolis Vavouranakis, MD,** [g,i] **Periklis Davlouros, MD,** [a,i] **John Goudevenos, MD,** [h,i] **and Christodoulos Stefanadis, MD** [g,i] ***Patras, Athens, Larissa, Iraklion, Alexandroupolis, and Ioannina, Greece***

Background P2Y12 inhibitor switching has appeared in clinical practice as a consequence of prasugrel and ticagrelor availability, apart from clopidogrel, for use in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

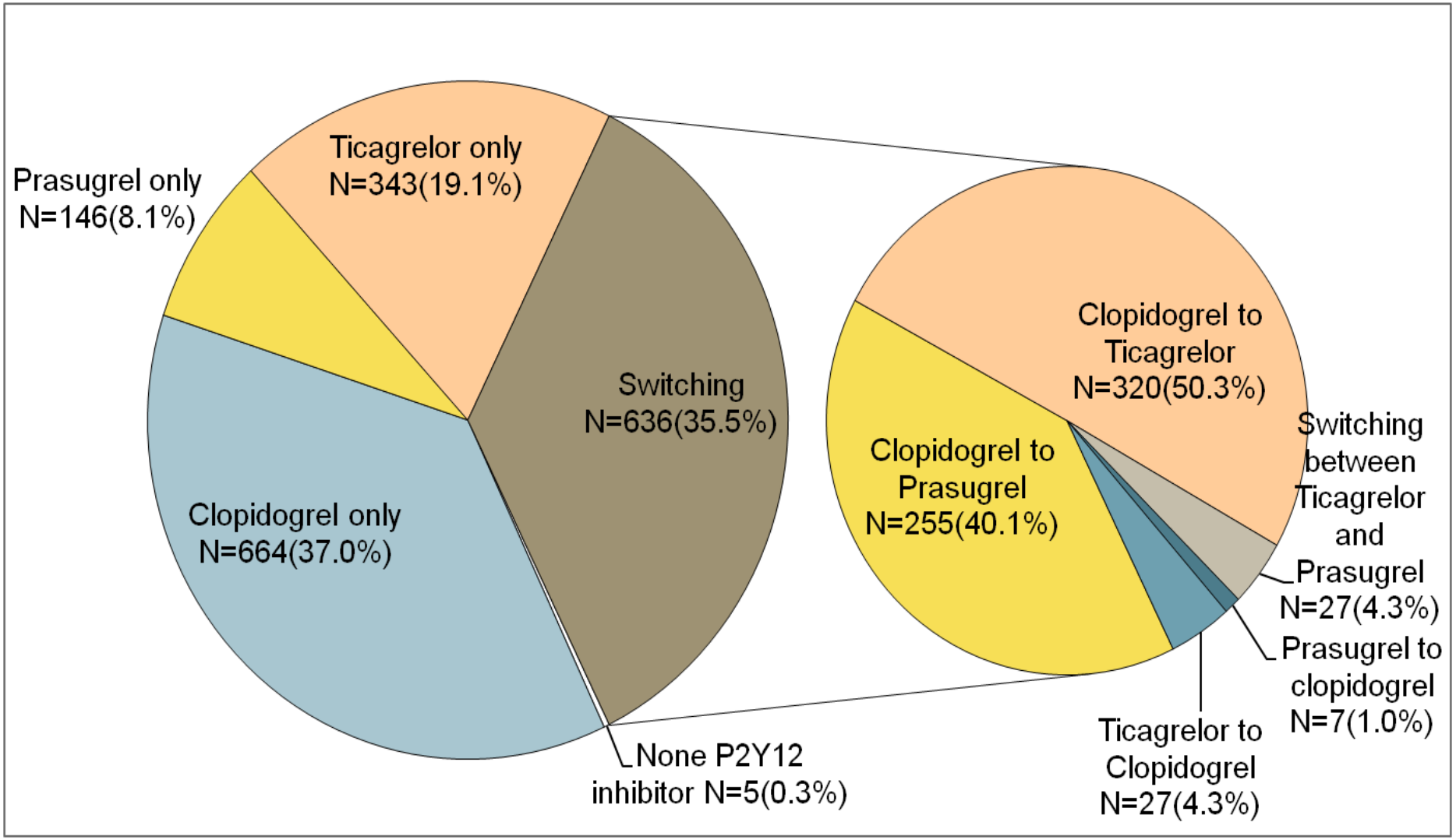
Methods In the context of the GReek AntiPlatelet REgistry (GRAPE) we assessed the prevalence, predictive factors and short-term outcome of in-hospital P2Y12 inhibitor switching in 1794 ACS patients undergoing PCI.

Results Switching occurred in 636 (35.5%) patients of which in the form of clopidogrel to a novel agent, novel agent to clopidogrel and between prasugrel and ticagrelor in 574 (90.4%), 34 (5.3%) and 27 (4.3%) patients, respectively.

Presentation to non PCI-capable hospital, bivalirudin use, age ≥75 years (inverse predictor), and regional trends emerged as predictive factors of switching to a novel agent. At combined in-hospital and one-month follow-up, propensity matched pairs analysis showed no differences in major adverse cardiovascular (MACE) or bleeding events between switching from clopidogrel to a novel agent vs novel agent constant administration. More Bleeding Academic Research Consortium type 1, type 2 and any type events and fewer MACE were seen when switching from clopidogrel to a novel agent vs only clopidogrel administration (23.7%, 3.8%, 30.6%, 1.2% vs 8.9%, 1.2%, 12.0%, 3.8% with $P < .001$, $P = .03$, $P < .001$ and $P = .03$ respectively).

Conclusions In a real-life experience with contemporary antiplatelet treatment in ACS patients undergoing PCI, in-hospital switching represents common clinical practice. Clinical factors and regional practice differences seem to affect this strategy's choice, while switching to a novel agent may be associated with higher risk of bleeding. (Am Heart J 2014;167:68-76.e2.)

Prevalence of in-hospital P2Y12 inhibitors use and switching.



Switching occurred mostly in the form of changing from clopidogrel to ticagrelor (50.3%) or prasugrel (40.1%).

Table III. One-month outcome in propensity matched pairs of patients who were only ticagrelor/prasugrel treated or switched from clopidogrel to ticagrelor/prasugrel

	Prasugrel/ticagrelor treated N = 269	Switched from clopidogrel to ticagrelor/prasugrel N = 269	*P*
Bleeding BARC type 1	66 (24.5)	62 (23.0)	0.8
Bleeding BARC type 2	7 (2.6)	9 (3.3)	0.8
Bleeding BARC type 3	4 (1.5)	9 (3.3)	0.3
Bleeding BARC any type	77 (28.6)	80 (29.7)	0.9
MACE	6 (2.2)	4 (1.5)	0.8

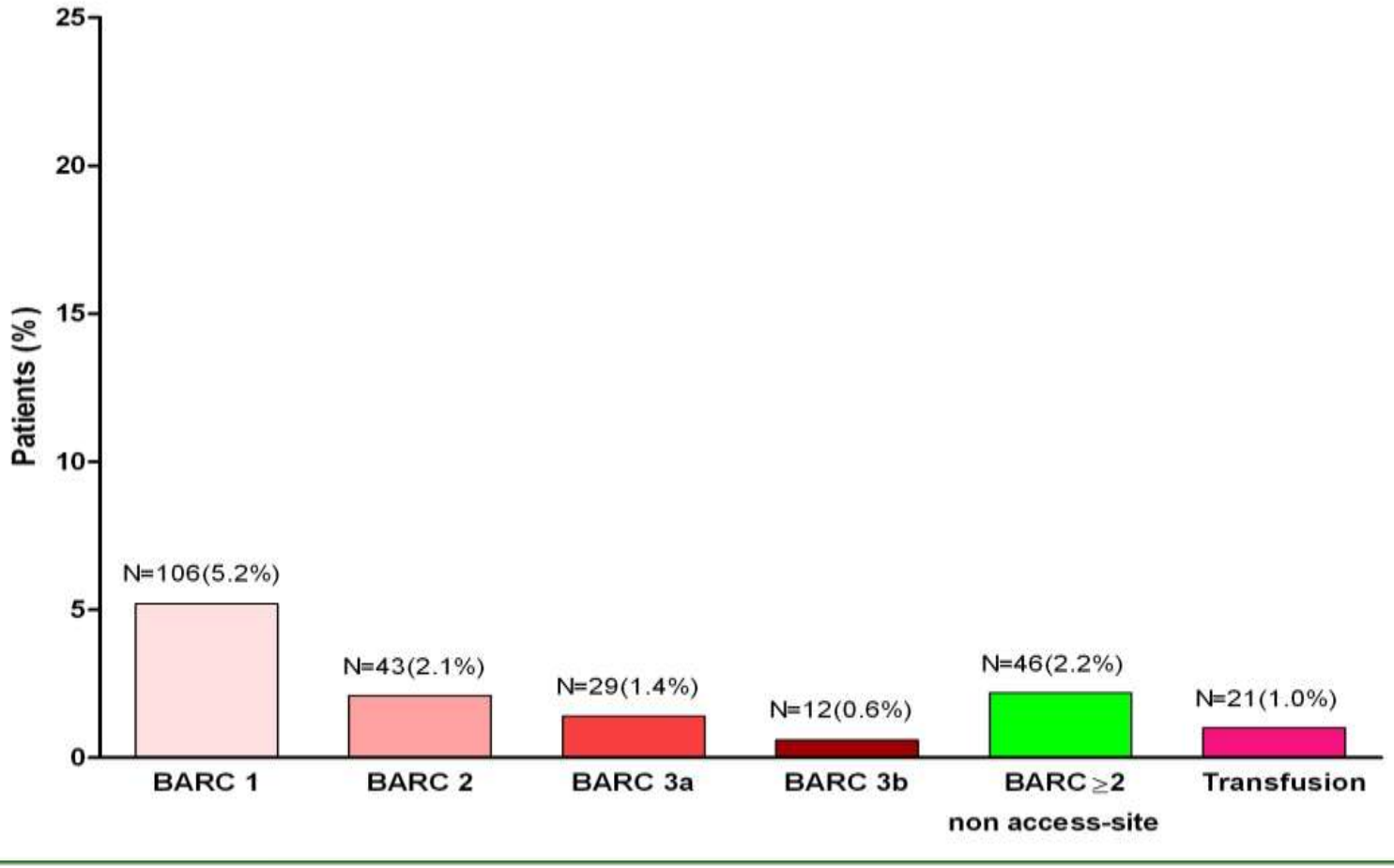
MACE, Major adverse cardiovascular events.

Table IV. One-month outcome in propensity matched pairs of patients who were only clopidogrel treated or switched from clopidogrel to ticagrelor/prasugrel

	Clopidogrel treated N = 418	Switched from clopidogrel to ticagrelor/prasugrel N = 418	*P*
Bleeding BARC type 1	37 (8.9)	99 (23.7)	<.001
Bleeding BARC type 2	5 (1.2)	16 (3.8)	.03
Bleeding BARC type 3	8 (1.9)	13 (3.1)	.4
Bleeding BARC any type	50 (12.0)	128 (30.6)	<.001
MACE	16 (3.8)	5 (1.2)	.03

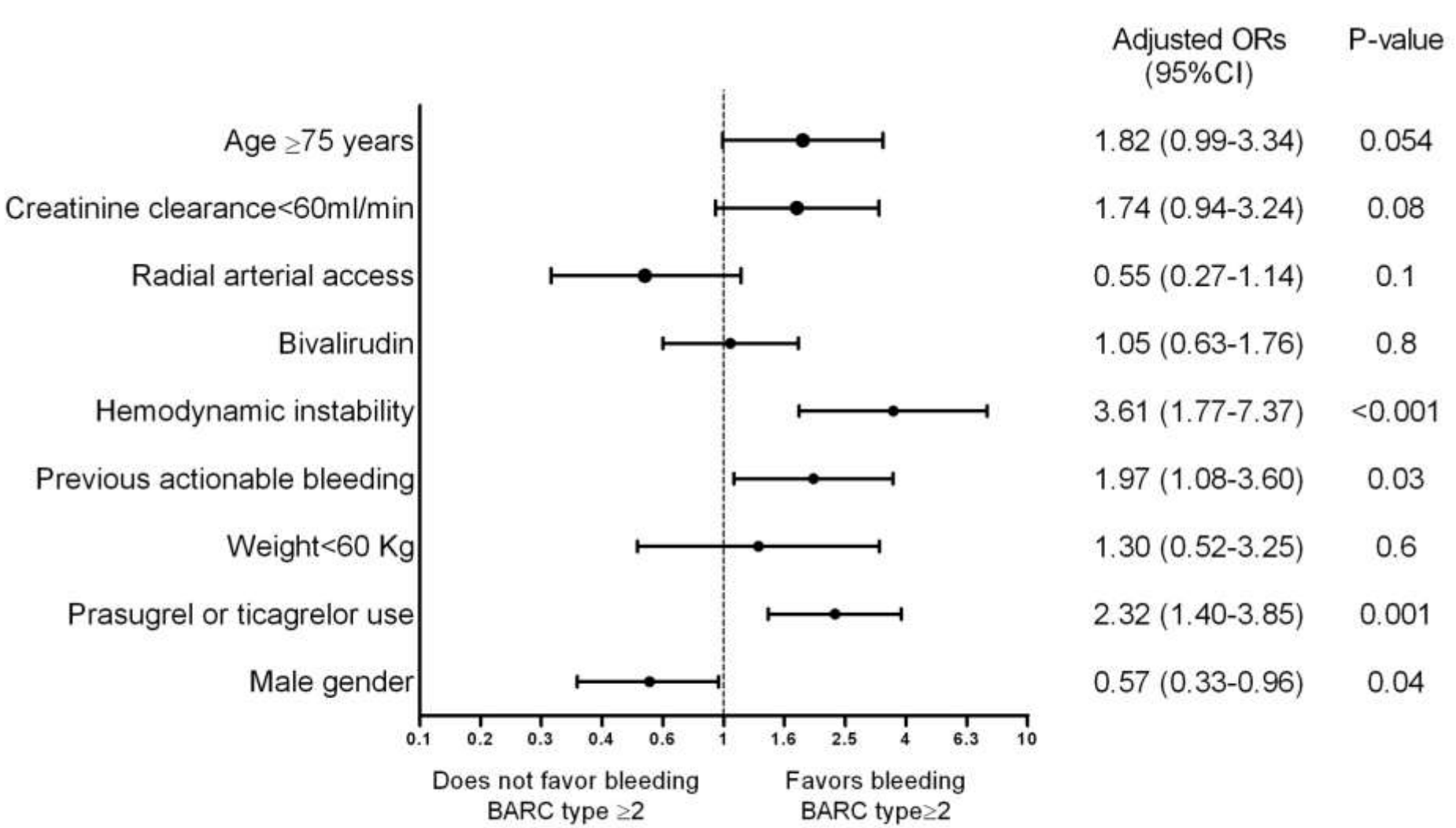
MACE, Major adverse cardiovascular events.

In-hospital bleeding events in acute coronary syndrome patients undergoing percutaneous coronary intervention in the era of novel P2Y12 inhibitors: Insights from the GReek AntiPlatelet rEgistry–GRAPE☆,☆☆



Incidence of in-hospital bleeding by BARC type and transfusions.

Xanthopoulou et al. *Intern J Cardiol* 2014



Multivariate predictors of in-hospital BARC type≥2 bleeding events.

Xanthopoulou et al. *Intern J Cardiol* 2014

In-hospital bleeding rates in propensity matched pairs of patients who were clopidogrel-treated or novel P2Y12 inhibitor-treated (n=552)

	Clopidogrel	**Novel P2Y12 inhibitor**	P value
Bleeding BARC type 1	16(2.9)	29(5.3)	0.07
Bleeding BARC type ≥2	15(2.7)	33(6.0)	0.01
Bleeding BARC type ≥2 access site related	4(0.7)	15(2.7)	0.02
Bleeding BARC type ≥2 non access site related	11(2.0)	18(3.3)	0.2
Transfusion	5(0.9)	9(1.6)	0.2

In-hospital bleeding rates in propensity matched pairs of patients who were ticagrelor or prasugrel-treated (n=329)

	Ticagrelor	**Prasugrel**	P value
Bleeding BARC type 1	25(7.6)	19(5.8)	0.4
Bleeding BARC type ≥2	21(6.4)	12(3.6)	0.2
Bleeding BARC type ≥2 access site related	10(3.0)	7(2.1)	0.5
Bleeding BARC type ≥2 non access site related	11(3.3)	5(1.5)	0.2
Transfusion	4(1.2)	3(0.9)	0.7

ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

Bivalirudin Use and One-Month Outcome in the Context of Contemporary Antiplatelet Treatment: Insights from the Greek Antiplatelet Registry

Dimitrios Alexopoulos,[1] Ioanna Xanthopoulou,[1] Spyridon Deftereos,[2] George Sitafidis,[3] Ioannis Kanakakis,[4] Michalis Hamilos,[5] George Karayannis,[3] Christos Angelidis,[2] Katerina Stavrou,[1] Manolis Vavuranakis,[6] John A. Goudevenos,[7] Christodoulos Stefanadis[6] & on behalf of the GRAPE Investigators

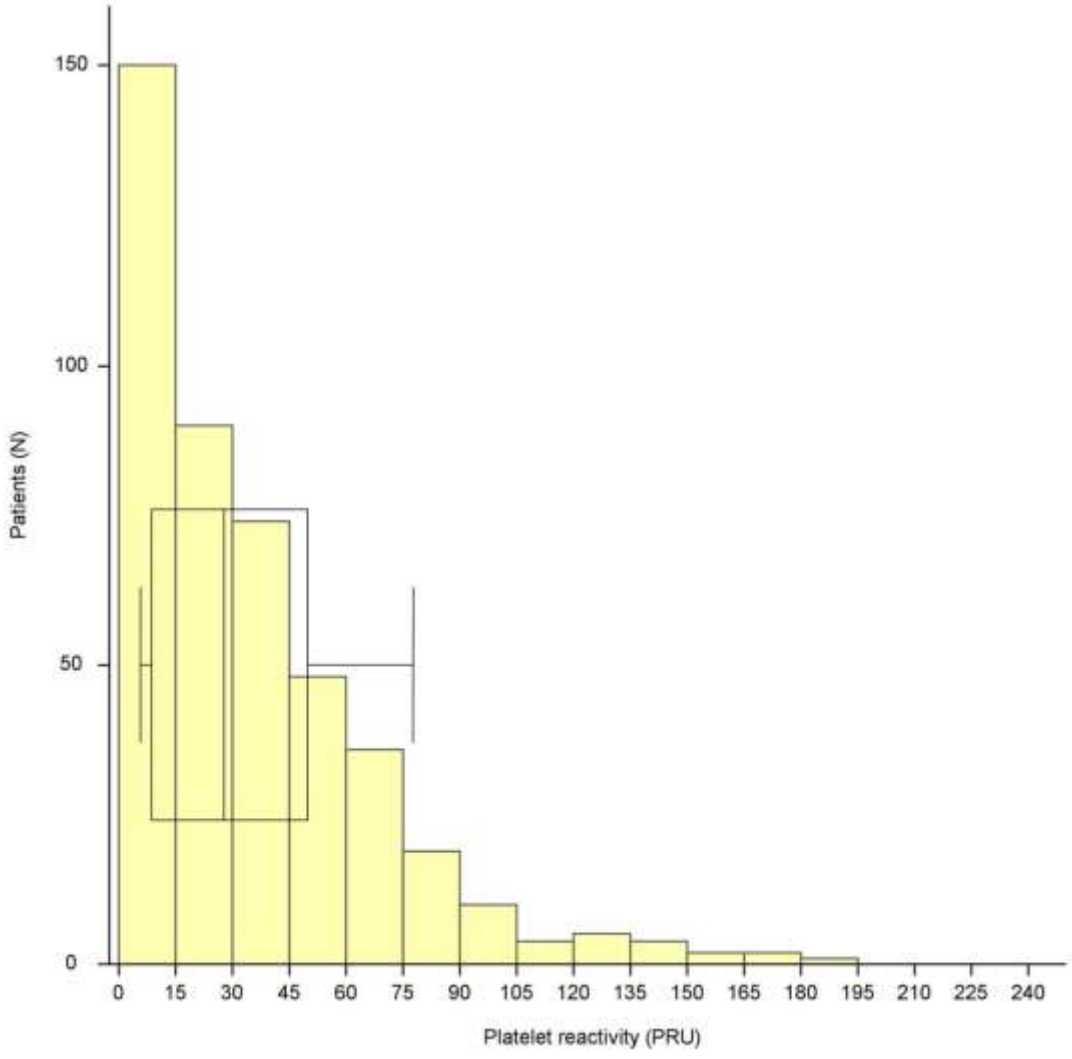
Table 3 Outcomes in propensity-matched pairs of patients who were or were not bivalirudin treated

	No bivalirudin treated N = 370	Bivalirudin treated N = 370	*P* value
Bleeding BARC type 1	70 (18.9)	81 (21.9)	0.3
Bleeding BARC type 2	10 (2.7)	12 (3.2)	0.8
Bleeding BARC type 3	16 (4.3)	13 (3.5)	0.7
Bleeding BARC type 3a	11 (3.0)	12 (3.2)	1.0
Bleeding BARC type 3b	5 (1.4)	1 (0.3)	0.2
Any transfusion	6 (1.6)	8 (2.2)	0.8
MACE	19 (5.1)	15 (4.1)	0.6
Definite stent thrombosis	3 (0.8)	1 (0.3)	0.6
NACE	24 (6.5)	16 (4.3)	0.3

BARC, bleeding academic research consortium; MACE, major adverse cardiovascular events; and NACE, net adverse cardiovascular events.

Platelet reactivity during ticagrelor maintenance therapy: a patient-level data meta-analysis

Dimitrios Alexopoulos, MD,* Ioanna Xanthopoulou, MD,* Robert F. Storey, MD,† Kevin P. Bliden, BS, ‡ Udaya S. Tantry, PhD, ‡ Dominick J. Angiolillo, MD, PhD, § Paul A. Gurbel, MD‡



N=445

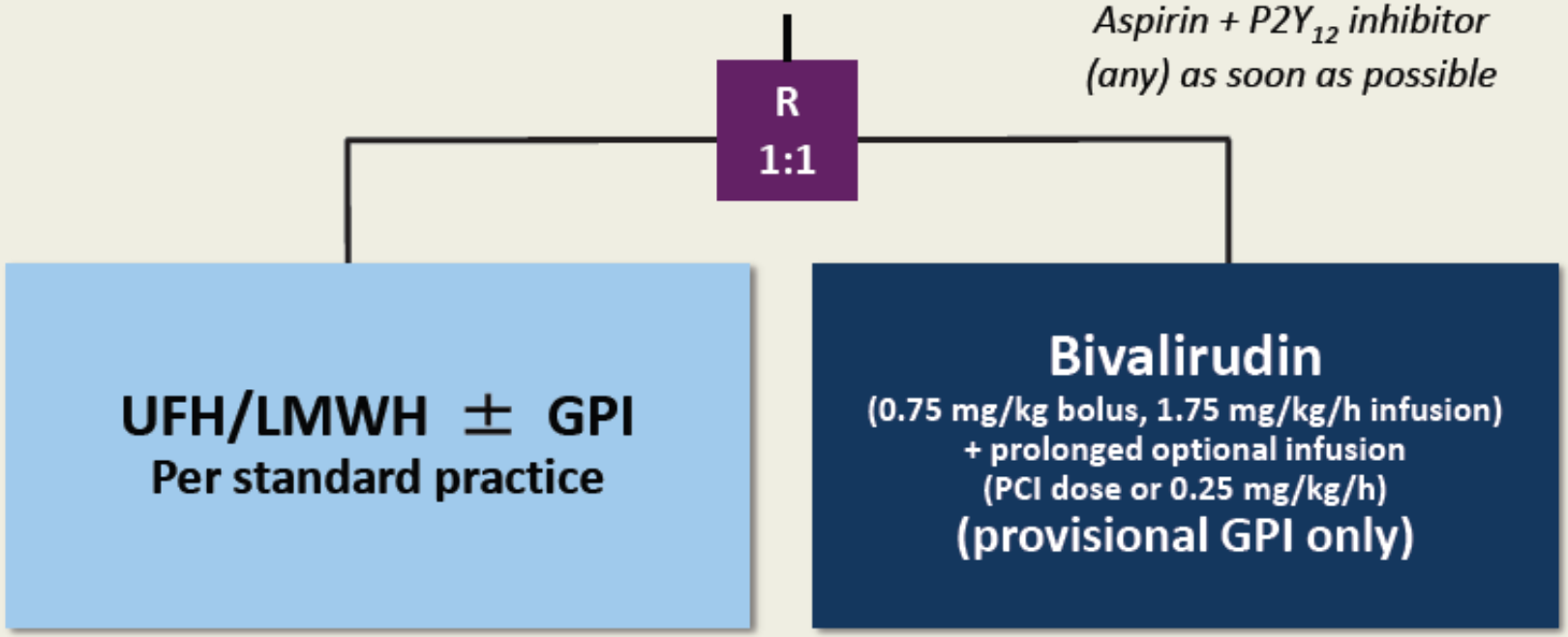
Age and BMI positively affected PR, with every increase in decade and 5 units of BMI resulting in 7.9% and 4.1% increase in PR, respectively.

Current smoking status negatively affected PR with 13.7% decrease in PR in current smokers, compared to non-smokers.

EUROMAX Trial Design

2218 patients with STEMI with symptom onset >20 min and ≤12h
Randomized in ambulance or non-PCI hospital
Intent for primary PCI

Aspirin + $P2Y_{12}$ inhibitor (any) as soon as possible



Primary endpoint: 30-day death or non-CABG related major bleeding

Key Secondary endpoint: Death, Re-infarction or non-CABG major bleeding at 30 days

Clinical FU at 30 days and 1 year

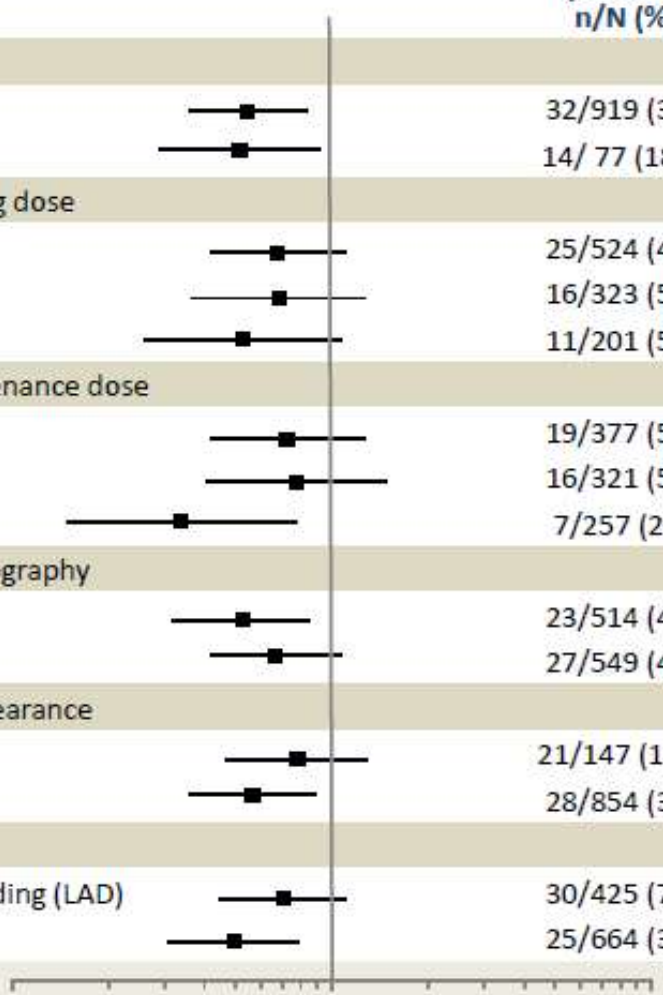
clinicaltrials.gov NCT01087723

Procedures, Medications

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)
Randomized in ambulance no. (%)	1030 (94.6)	1045 (94.2)
Randomized in non–PCI-capable hospital— no. (%)	59 (5.4)	64 (5.8)
Aspirin use — no. (%)	1088 (100)	1107 (99.8)
$P2Y_{12}$ inhibitor loading dose — no. (%)		
Yes	1048/1066 (98.3)	1058/1083 (97.7)
Clopidogrel	524/1048 (50.0)	545/1058 (51.5)
Ticlopidine	0 (0.0)	2 (0.2)
Prasugrel	323/1048 (30.8)	306/1058 (28.9)
Ticagrelor	201/1048 (19.2)	205/1058 (19.4)
$P2Y_{12}$ loading before angiography — no. (%)	913/1011 (90.3)	923/1010 (91.4)
Maintenance dose - yes	957/1065 (89.9)	969/1082 (89.6)
Clopidogrel	377/957 (39.4)	407/969 (42.0)
Ticlopidine	2/957 (0.2)	5/969 (0.5)
Prasugrel	321/957 (33.5)	298/969 (30.8)
Ticagrelor	257/957 (26.9)	259/969 (26.7)

Subgroup Analysis:
Death/Major Bleed at 30 Days (ITT)

	Bivalirudin (N=1089) n/N (%)	Heparins with optional GPI (N=1109) n/N (%)	Relative Risk (95% CI)	Interaction P-value
Killip class				
1	32/919 (3.5)	59/931 (6.3)	0.55 [0.36, 0.84]	0.58
2-4	14/ 77 (18.2)	24/ 69 (34.8)	0.52 [0.29, 0.93]	
$P2Y_{12}$ inhibitor loading dose				
Clopidogrel	25/524 (4.8)	38/545 (7.0)	0.68 [0.42, 1.12]	0.82
Prasugrel	16/323 (5.0)	22/306 (7.2)	0.69 [0.37, 1.29]	
Ticagrelor	11/201 (5.5)	21/205 (10.2)	0.53 [0.26, 1.08]	
$P2Y_{12}$ inhibitor maintenance dose				
Clopidogrel	19/377 (5.0)	28/407 (6.9)	0.73 [0.42, 1.29]	0.24
Prasugrel	16/321 (5.0)	19/298 (6.4)	0.78 [0.41, 1.49]	
Ticagrelor	7/257 (2.7)	21/259 (8.1)	0.34 [0.15, 0.78]	
Time on drug to angiography				
<50 min	23/514 (4.5)	42/495 (8.5)	0.53 [0.32, 0.86]	0.48
≥50 min	27/549 (4.9)	42/576 (7.3)	0.67 [0.42, 1.08]	
Baseline creatinine clearance				
≤60	21/147 (14.3)	30/165 (18.2)	0.79 [0.47, 1.31]	0.44
>60	28/854 (3.3)	48/833 (5.8)	0.57 [0.36, 0.90]	
Target Vessel				
Left anterior descending (LAD)	30/425 (7.1)	42/423 (9.9)	0.71 [0.45, 1.11]	0.30
No LAD	25/664 (3.8)	52/686 (7.6)	0.50 [0.31, 0.79]	



HEAT PPCI

***H**ow **E**ffective are*
A**ntithrombotic **T**herapies in **PPCI

Heparin versus Bivalirudin in PPCI

Dr Adeel Shahzad
Dr Rod Stables (PI)
Liverpool Heart and Chest Hospital
Liverpool, UK

Procedural Information

Characteristic	Bivalirudin (%)	Heparin (%)
P2Y12 use - Any	99.6	99.5
- Clopidogrel	11.8	10.0
- Prasugrel	27.3	27.6
- Ticagrelor	61.2	62.7
GPI use	13.5	15.5
Radial arterial access	80.3	82.0
PCI performed	83.0	81.6

ESC Guidelines on myocardial revascularization 2010

(b) Recommended duration of dual antiplatelet therapy

After percutaneous coronary intervention

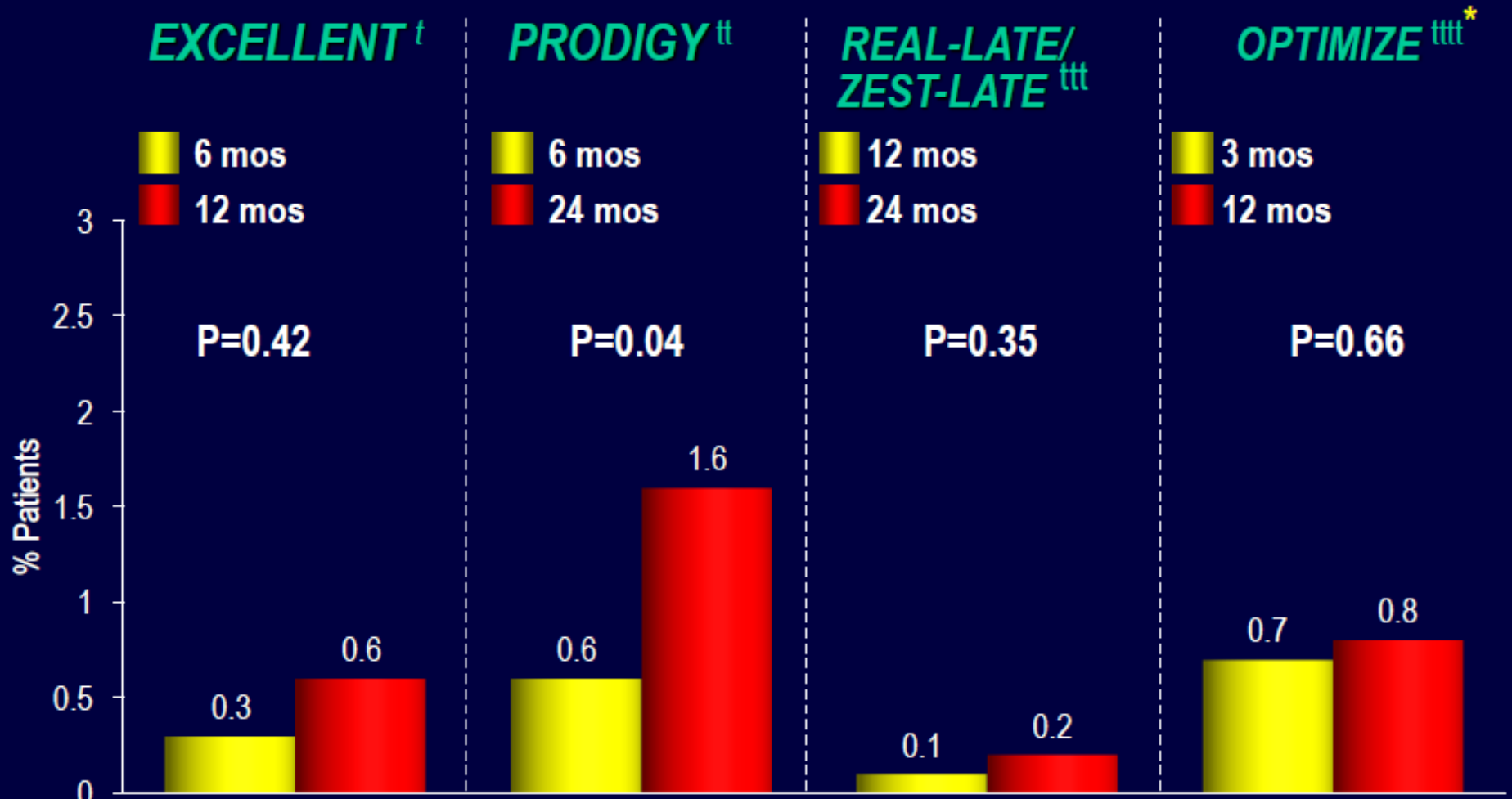
- 1 month after BMS implantation in stable angina;[55,60,94]
- 6–12 months after DES implantation in all patients;[60,94]
- 1 year in all patients after ACS, irrespective of revascularization strategy.

Randomized Trials of DES DAPT Duration

Trial	Pts	Duration test	Randomization	1° EP
Prolonged DAPT studies				
DES Late	5,405 DES	1 vs. 4.5 yrs	A vs. A+C Superiority	CD/MI/CVA BARC 2,3,5 bleed
PRODIGY	N=1,800 DES, BMS	6 mos vs. 2 yrs	A vs. A+C Superiority	D/MI/CVA
ARCTIC-Interruption	N=2,126 DES	1 vs. 1.5-2.5 yrs	A vs. A+C>>P Superiority	D/MI/ST/Urev/CVA
DAPT	N=20,645 (15,245 DES) (5,400 BMS)	1 vs. 2.5 yrs*	A+P vs DAPT (clop or pras) NI and Sup	D/MI/CVA ST, Bleeding
Abbreviated DAPT studies				
EXCELLENT	N=1443 SES and EES	6 vs. 12 mos	A vs. A+C Noninferiority	D/MI/TVR
ISAR-SAFE	N=6,000 DES	6 vs. 12 mos*	A+P vs. A+C Noninferiority	D/MI/CVA/ ST/TIMI MB
ITALIC	N=3,700 EES	6 vs. 12 mos	A vs. A+C Noninferiority	D/MI/CVA/ Urg Revasc/MB
OPTIMIZE	N=3,120 ZES	3 vs. 12 mos	A vs. A+C Noninferiority	D/MI/CVA/MB

*Plus a 3 month washout period

Major Bleeding (TIMI or GUSTO/REPLACE 2*) By DAPT Duration In Randomized Trials



Adapted from

t Gwon et al. ACC 2011
tt Valgimigli et al. ESC 2011
ttt Park et al. NEJM 2010;362:1374
tttt Feres et al. TCT 2013 LBCT

PLATO: landmark analyses indicate persistent benefit of ticagrelor over 1 year

Death from vascular causes, MI, stroke

Time Interval	Ticagrelor n/N (KM%)	Clopidogrel n/N (KM%)	Hazard Ratio (95% CI)	P-value
1-30 days	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77-1.00)	0.045
1-90 days	590/9333 (6.4)	683/9291(7.4)	0.86 (0.77,0.94)	0.0063
91-360 days	266/8543 (3.7)	329/8437 (4.6)	0.80 (0.68,0.94)	0.0063
1-180 days	729/9333 (7.9)	848/9291 (9.2)	0.85 (0.77,0.94)	0.0016
181-360 days	127/8219 (2.1)	164/8124 (2.7)	0.76 (0.61,0.96)	0.0232

Source: EMEA submission: Section 2.7.3 Summary of Clinical Efficacy

CONCLUSIONS

- Novel antiplatelet agents are increasingly used in ‘real world’
- Contra’s are rare, though SWP are common- for clop too
- Switching occurs frequently

CONCLUSIONS

- Overall actionable bleeding (BARC≥2) is low
- No difference in in-hospital bleeding between ticagrelor and prasugrel
- Persistent benefit of ticagrelor over 1 year treatment