MAZANKOWSKI
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A New Era of Anti-Platelet Therapy to Support PCI in ACS Patients

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Speaker Disclosures

- Endpoint Committees
  - Pfizer
- Speakers Honoraria
  - Eli Lilly
  - Astra Zeneca
  - Boehringer-Ingelheim
- Research Support
  - Pfizer
  - Merck
  - Eli Lily

Learning Objectives

- Review the new anti-platelet agents
- Focus on patient subgroups where they may be particularly advantageous
- Discuss patient characteristics that favour one agent over another
- Review the most recent guidelines for use

Mortality rates in acute coronary syndromes

- Despite improvements in the treatment of ACS, ACS mortality and morbidity rates remain high [Fox 2007:A]
  - In UA, 30% evolve to an MI – 24% to NSTEMI and 6% to STEMI [Fox 2002:A]
  - 5 year risk of re-MI in NSTEMI is 12%-14% and 7% for CV death [Damman 2010:A]
  - In-hospital and 6-month death from STEMI rates are nearly 5% [Fox 2007:A]

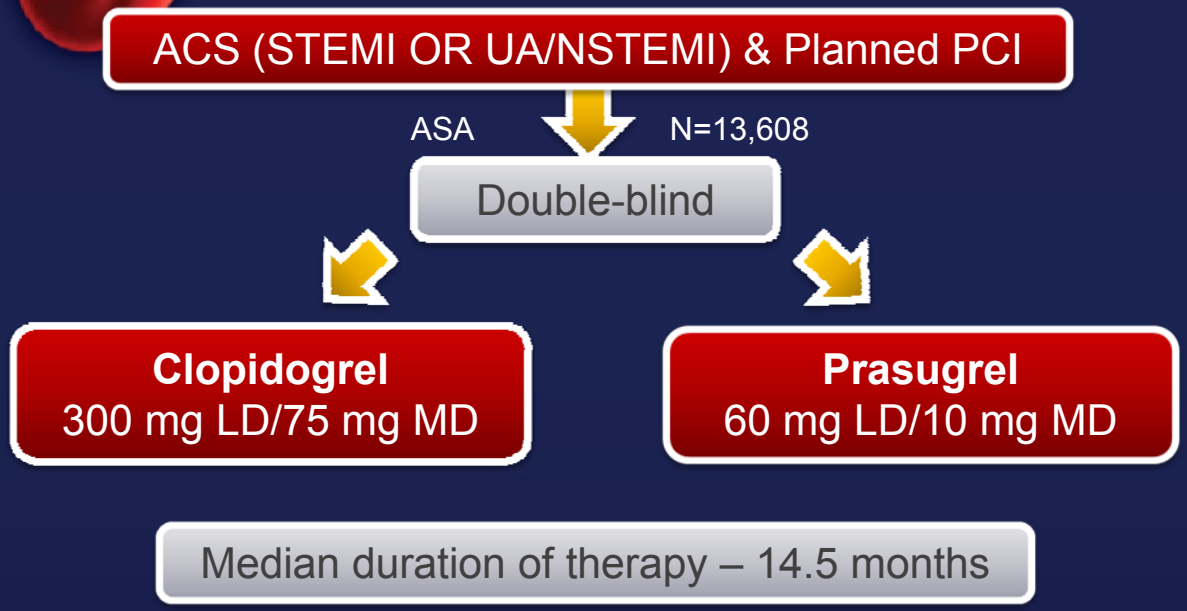
Fox KA, et al. *JAMA.* 2007;297:1892-19002; Fox KA, et al. *Eur Heart J.* 2002; 23:1177-1189; Damman P, et al. *J Am Coll Cardiol*. 2010;55:858-864.

Comparison of currently approved anti-platelet agents

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolism	Prodrug, not limited by metabolism	Active Drug
Onset of Effect*	2-4 h	30 mins	30 mins
Duration of Effect	3-10 days	5-10 days	3-4 days
Withdrawal before major Surgery	5 days	7 days	3-5 days

* 50% inhibition of platelet aggregation

TRITON-TIMI 38 – Trial Design



1º Endpoint: CV death, MI, stroke
2º Endpoint: All cause death, MI, stroke, CV death, rehosp-rec isch., UTVR, stent thrombosis (ARC definite/prob.)
Safety Endpoints: TIMI major bleeds, life-threatening bleeds
Key Substudies: Pharmacokinetic, genomic

ARC, Academic Research Consortium; Rehosp-rec isch, rehospitalization due to recurrent ischemia; TIMI: thrombolysis in myocardial infarction; UTVR, urgent target vessel revascularization.

1. Adapted from Wiviott et al. Am Heart J. 2006;152:627-35.

PLATO – Study Design

NSTEACS (moderate-high risk), STEMI (if primary PCI),
Clopidogrel-treated or -naive;
randomized within 24 h of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional LD;
if naive, standard 300 mg LD;
then 75 mg once daily MD;
(additional 300 mg allowed pre-PCI)

Ticagrelor
180 mg LD, then 90 mg twice daily MD;
(additional 90 mg pre-PCI)

6-12 month exposure

1º Endpoint: CV death, MI, stroke
1º Safety Endpoint: Total major bleeding

NSTEACS, non-ST-elevation acute coronary syndrome.

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

The Two Newest Agents in DAPT
Factors to Consider from Pivotal Trials

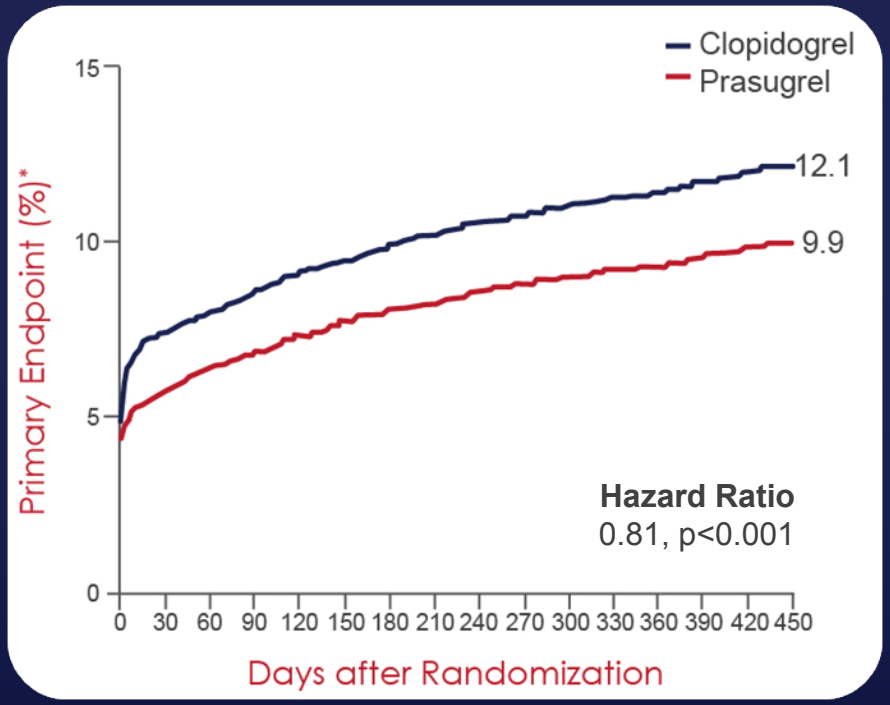
- TRITON-TIMI 38 (Prasugrel) and PLATO (Ticagrelor)

Factor	TRITON-TIMI 38[1]	PLATO[2]
Patient population	ACS undergoing PCI with known coronary anatomy (not required for STEMI pts undergoing 1° PCI)	Full spectrum ACS
Number of patients	13,608	18,624
Pretreatment with clopidogrel	None (except STEMI)	Pretreatment 79.1% → ≥ 300 mg* 19.6% → ≥600 mg*
Clopidogrel loading dose	300 mg	300-600 mg
GPIIb/IIIa use	~55%	~27%
Trial duration (median)	14.5 months	9.1 months

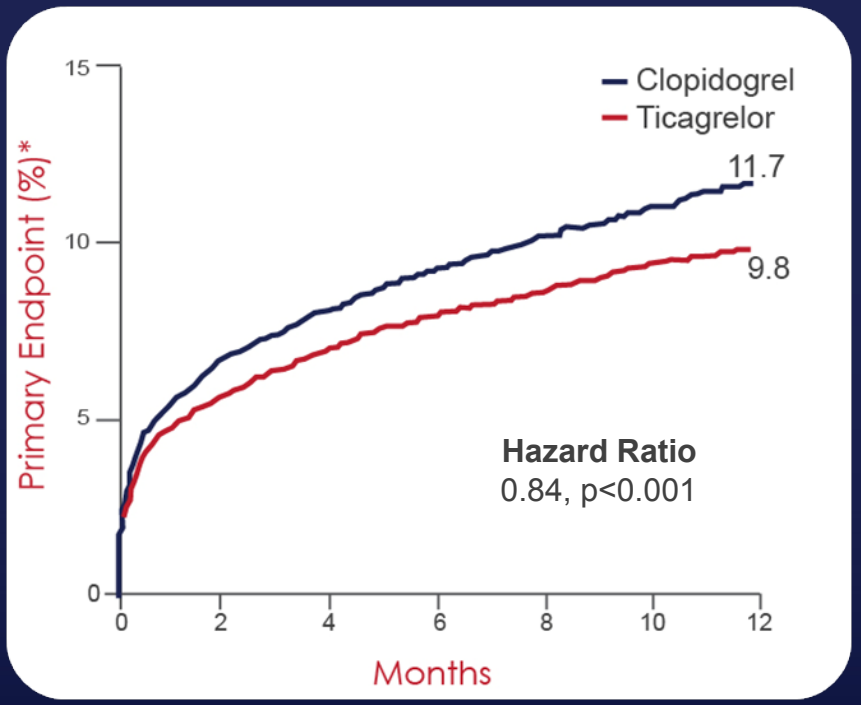
*Clopidogrel group. GP, glycoprotein. 1. Wiviott et al. NEJM. 2007;357:2001-15; 2. Wallentin et al. NEJM. 2009;361:1045-57.

Patients with ACS
Efficacy of Prasugrel and Ticagrelor

TRITON-TIMI 38[1]



PLATO[2]



*Composite endpoint of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke.

Adapted from 1. Wiviott et al. NEJM. 2007;357:2001-15; 2. Wallentin et al. NEJM. 2009;361:1045-57.

TRITON-TIMI 38: primary endpoint components and secondary endpoints

Endpoint[a]	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard ratio (95% CI)	*P* value
	N (%)			
CV death/nonfatal MI/nonfatal stroke	643 (9.9)	781 (12.1)	0.81 (0.73-0.90)	<0.001
CV death	133 (2.1)	150 (2.4)	0.89 (0.70-1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67-0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71-1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78-1.16)	0.64
Death from any cause, NFMI, or nonfatal stroke	797 (12.3)	938 (14.6)	0.84 (0.76-0.92)	<0.001
Stent thrombosis	68 (1.1)	142 (2.4)	0.48 (0.36-0.64)	<0.001

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

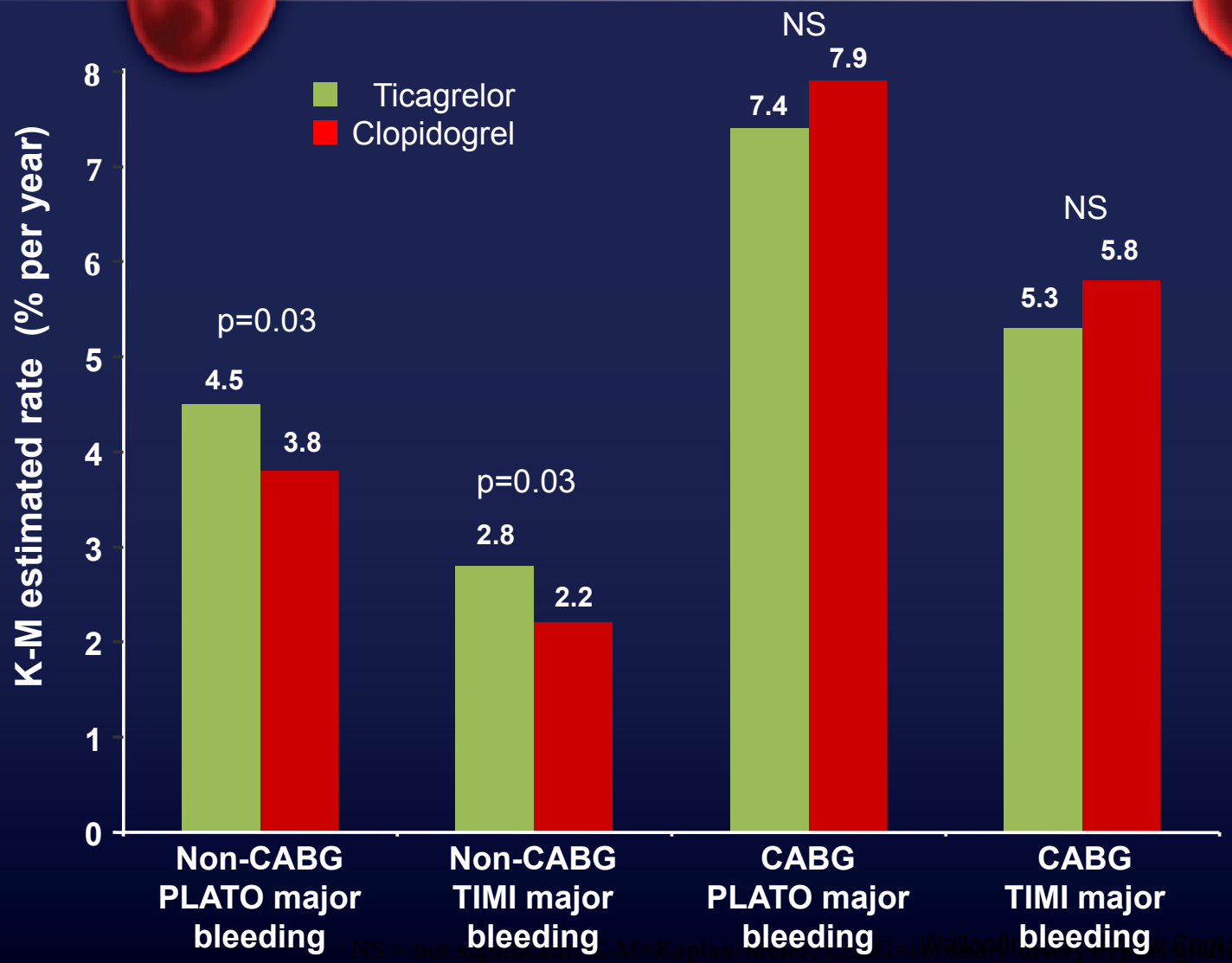
PLATO: secondary endpoints

Endpoint	Ticagrelor (N=9333) n (%)	Clopidogrel (N=9291) n (%)	Hazard ratio (95% CI)	*P* value
Death from vascular causes, MI, or stroke in planned invasive treatment	569 (8.9)	668 (10.6)	0.84 (0.75-0.94)	0.003
Death from any cause, MI, or stroke	901 (10.2)	1065 (12.3)	0.84 (0.77-0.92)	<0.001
CV death, MI, stroke, recurrent ischemia, TIA, or arterial thrombotic events	1290 (14.6)	1456 (16.7)	0.88 (0.81-0.95)	<0.001
MI	504 (5.8)	593 (6.9)	0.84 (0.85-0.95	0.005
Death from vascular causes	353 (4.0)	442 (5.1)	0.79 (0.69-0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91-1.52)	0.22
Death from any cause[a]	399 (4.5)	506 (5.9)	0.78 (0.69-0.89)	<0.001

[a]Death from any cause was tested after stroke, which was nonsignificant, so the results should be considered nominally significant

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

PLATO: Ticagrelor
Non-CABG and CABG-related Major Bleeding



NS = not significant; K-M=Kaplan-Meier; CABG=coronary artery bypass grafting

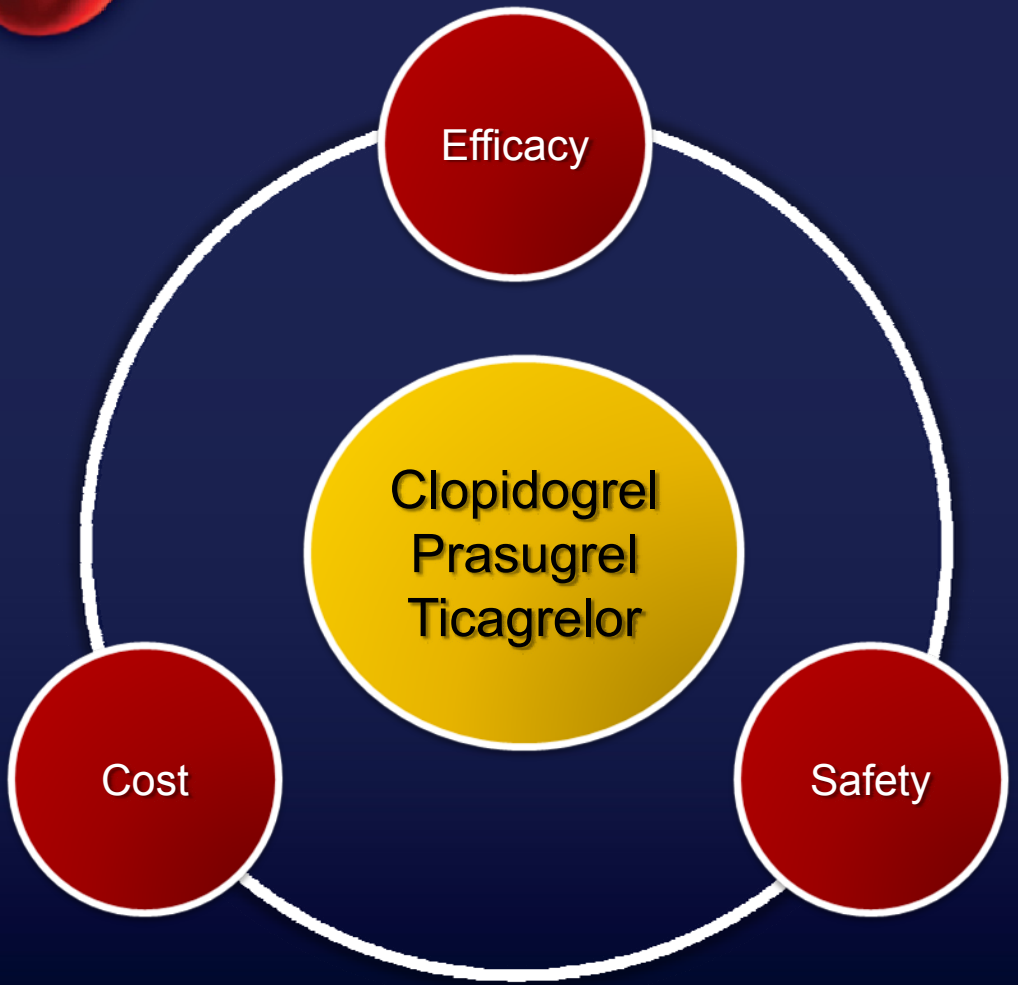
Wallentin L, et al. N Engl J Med. 2009;361.

TRITON TIMI 38: bleeding endpoints

Endpoint	Prasugrel	Clopidogrel	Hazard ratio (95% CI)	*P* value
	N (%)			
Non-CABG-related TIMI Major bleeding	***146 (2.4)***	***111 (1.8)***	***1.32 (1.03-1.68)***	***0.03***
Life-threatening	85 (1.4)	56 (0.9)	1.52 (1.08-2.13)	0.01
Fatal[a]	21 (0.4)	5 (0.1)	4.19 (1.58-11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87-1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58-2.15)	0.74
Major or Minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31. (1.11-1.56)	0.002
Bleeding requiring transfusion	244 (4.0)	182 (3.0)	1.34 (1.11-1.63)	<0.001
CABG-related TIMI Major bleeding	***24 (13.4)***	***6 (3.2)***	***4.73 (1.90-11.82)***	***<0.001***

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

New Agents, New Challenges
Special Populations

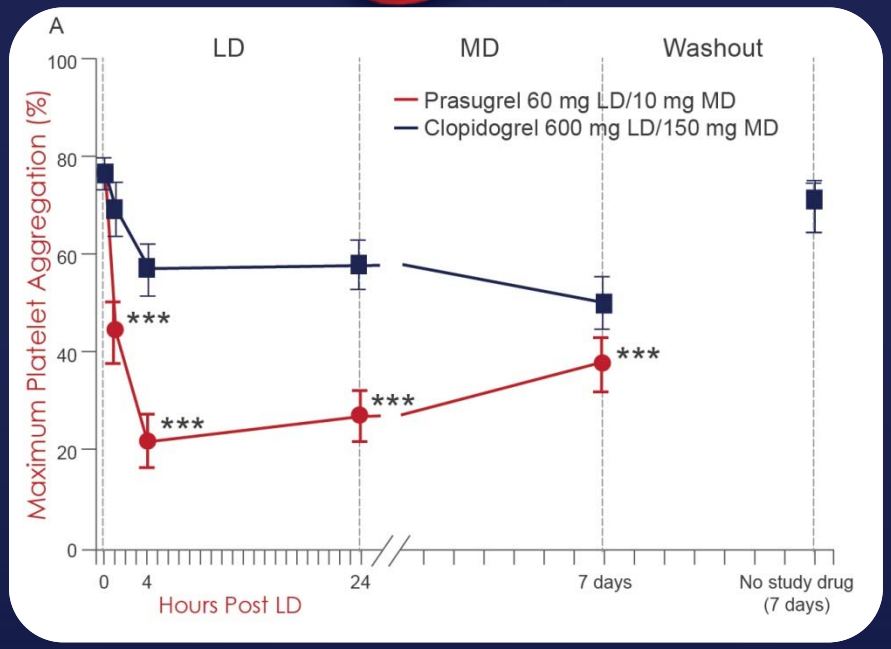


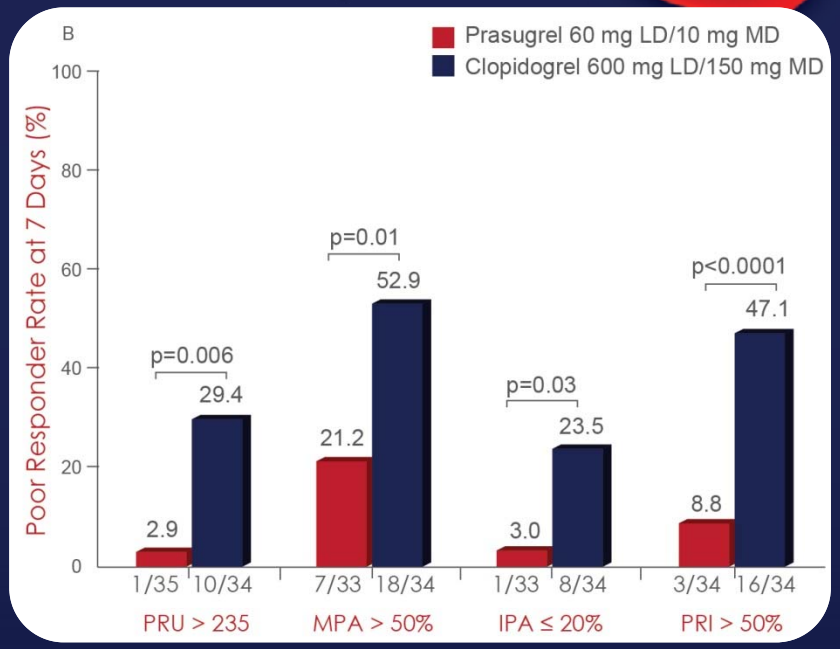
Special Populations

Diabetics

Optimizing Antiplatelet Therapy in Diabetes
OPTIMUS-3 – Cross-over Study

Platelet Aggregation N=35 **Poor Responder Rate – 7 d**





Significantly greater platelet inhibition was observed with prasugrel from Hour 1 to Day 7 (p=0.0001).* Prasugrel resulted in fewer poor responders at all time points irrespective of the definition used.

*Similar results obtained using other platelet function measures. IPA, induced platelet aggregation; LD, loading dose; MD, maintenance dose; MPA, maximum platelet aggregation; PRI, platelet reactivity index; PRU, platelet reaction units.

1. Angiolillo et al. Eur Heart J. 2011;32:838-46.

AntiPlatelet therapy is effective in Patients with Diabetes Mellitus

TRITON-TIMI 38
Prasugrel vs. Clopidogrel:* median 14.5 month follow-up

Endpoint	Cohort	Event Rate (%) Prasugrel vs. Clopidogrel	ARR (%)	RRR (%)	NNT
Primary endpoint[†]	Overall	9.9 vs. 12.1	2.2	18	46
	NSTEMI or UA	9.9 vs. 12.1	2.2	18	46
	Diabetes mellitus	12.2 vs. 17.0	4.8	28	21

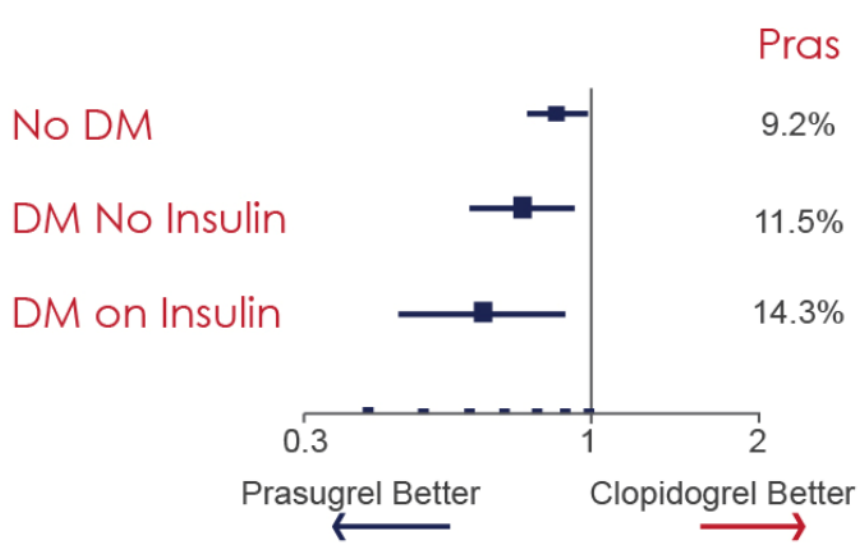
PLATO
Ticagrelor vs. Clopidogrel:* median 9.1 month follow-up

Endpoint	Cohort	Event Rate (%) Ticagrelor vs. Clopidogrel	ARR (%)	RRR (%)	NNT
Primary endpoint[†]	Overall	9.8 vs. 11.7	1.9	16	53
	NSTEMI or UA	10.1 vs. 12.3	2.2	18	46
	Diabetes mellitus	14.1 vs. 16.2	2.1	12	48

Alber et al. Wien Klin Wochenschr. 2011 Aug 3. [Epub ahead of print].

Insulin-treated vs. Non-insulin-treated Patients with Diabetes: TRITON-TIMI 38 Subgroup

Reduction in the Primary Endpoint* by Diabetes Status and Treatment Group



Among insulin-treated and non-insulin-treated patients with diabetes, highly significant relative reductions in the primary endpoint* (37% and 26%, respectively) were observed for prasugrel.

*Cardiovascular death/nonfatal MI, nonfatal stroke. DM, diabetes mellitus.

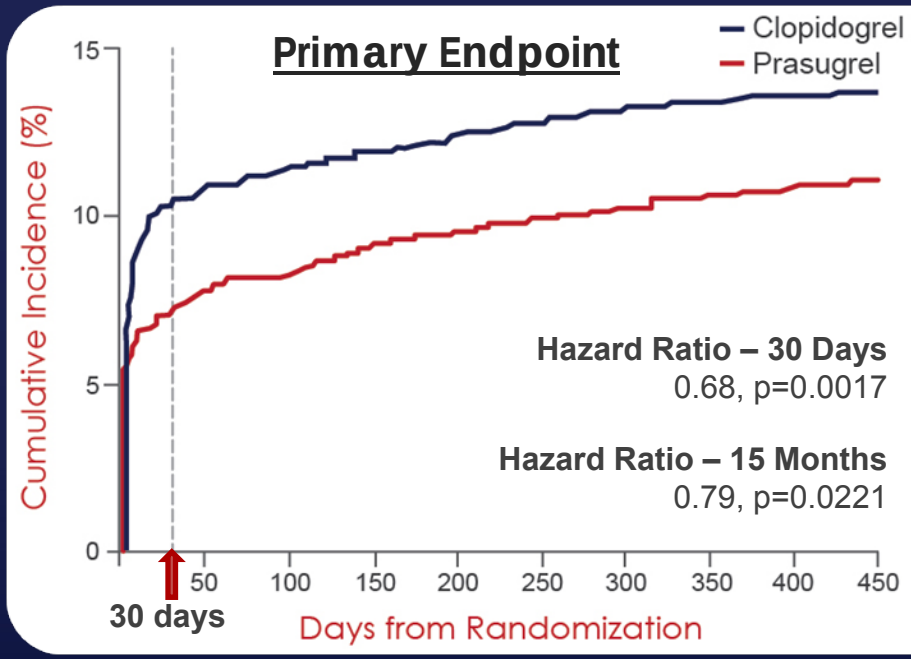
1. Wiviott et al. Circulation. 2008;18:1626-36.

Special Populations

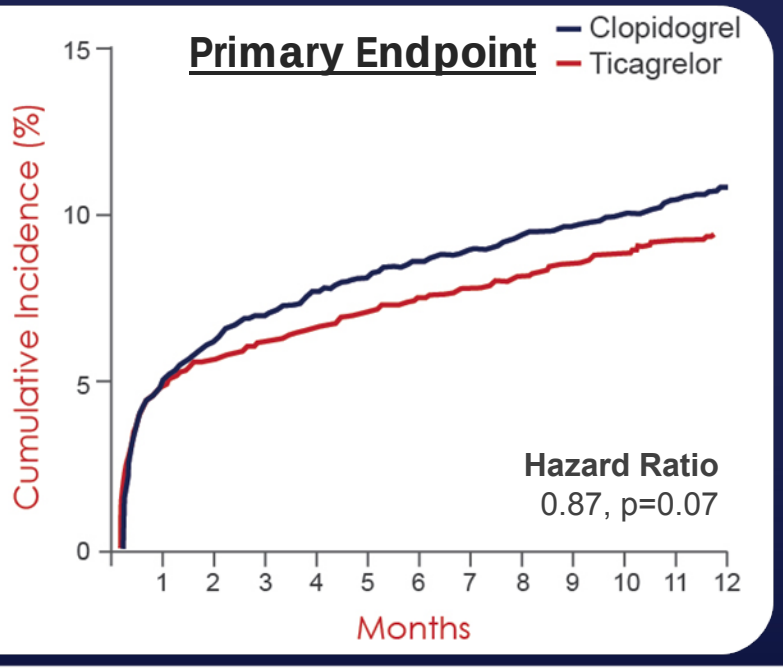
STEMI

Patients with STEMI
Efficacy of Prasugrel and Ticagrelor

TRITON-TIMI 38[1] Prespecified analysis of STEMI patients → prasugrel vs. clopidogrel



PLATO[2] Subgroup analysis of STEMI patients → ticagrelor vs. clopidogrel



Both ticagrelor and prasugrel were superior to clopidogrel in reducing the incidence of CV death, MI or stroke in patients with STEMI. A statistically significant benefit emerged with prasugrel as early as 30 days.

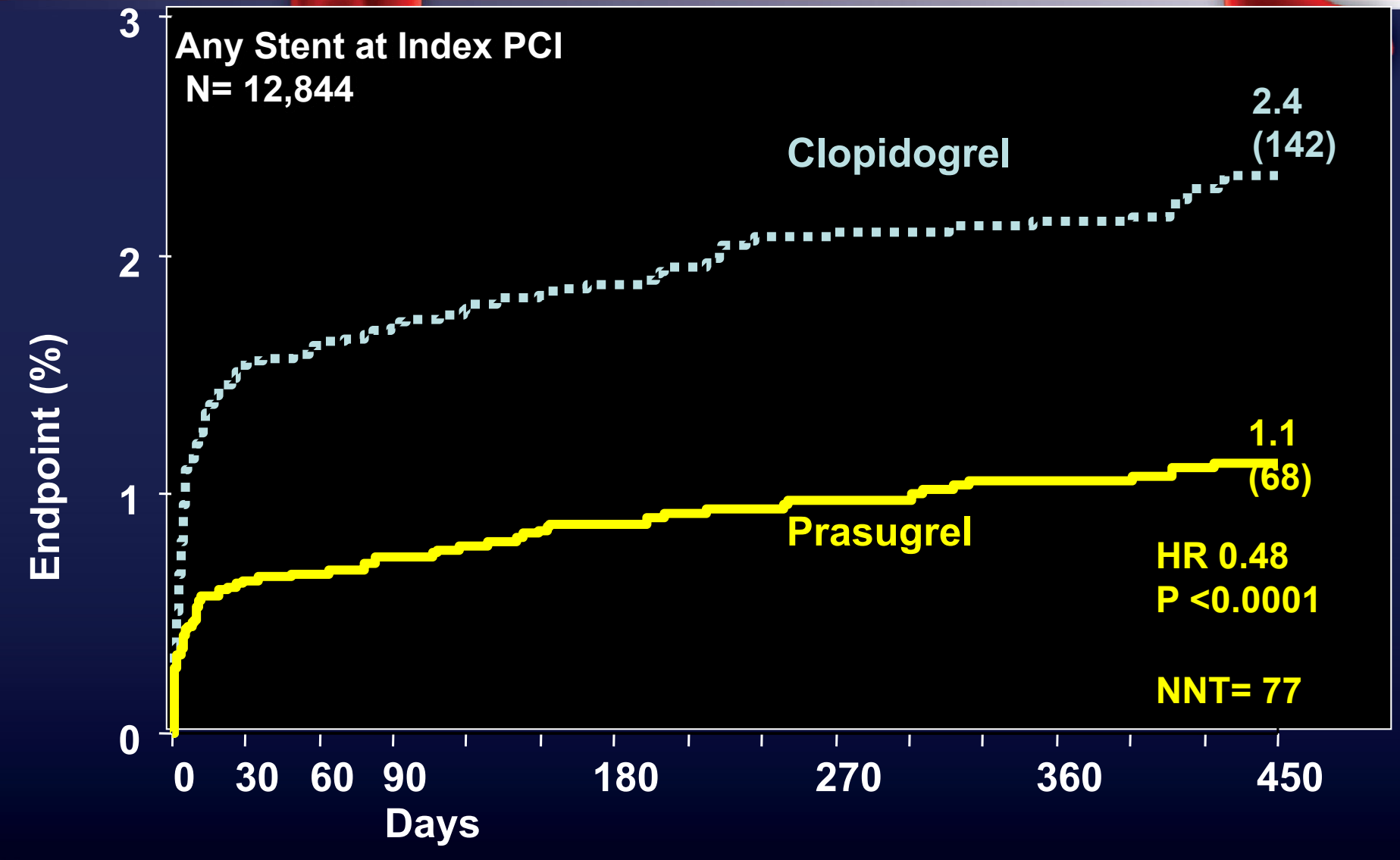
1. Montalescot et al. Lancet. 2009;373:723-31; 2. Steg et al. Circulation. 2010;122:2131-41.

Special Populations

Stent Thrombosis

TRITON TIMI·38

Stent Thrombosis (ARC Definite + Probable)

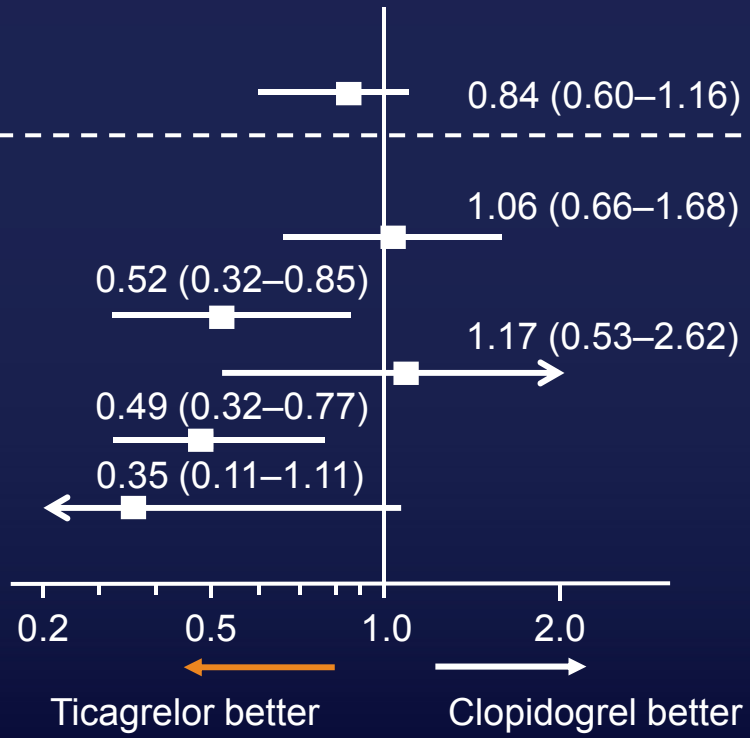


Special Populations

Those requiring CABG

PLATO CABG: Primary and secondary outcomes*

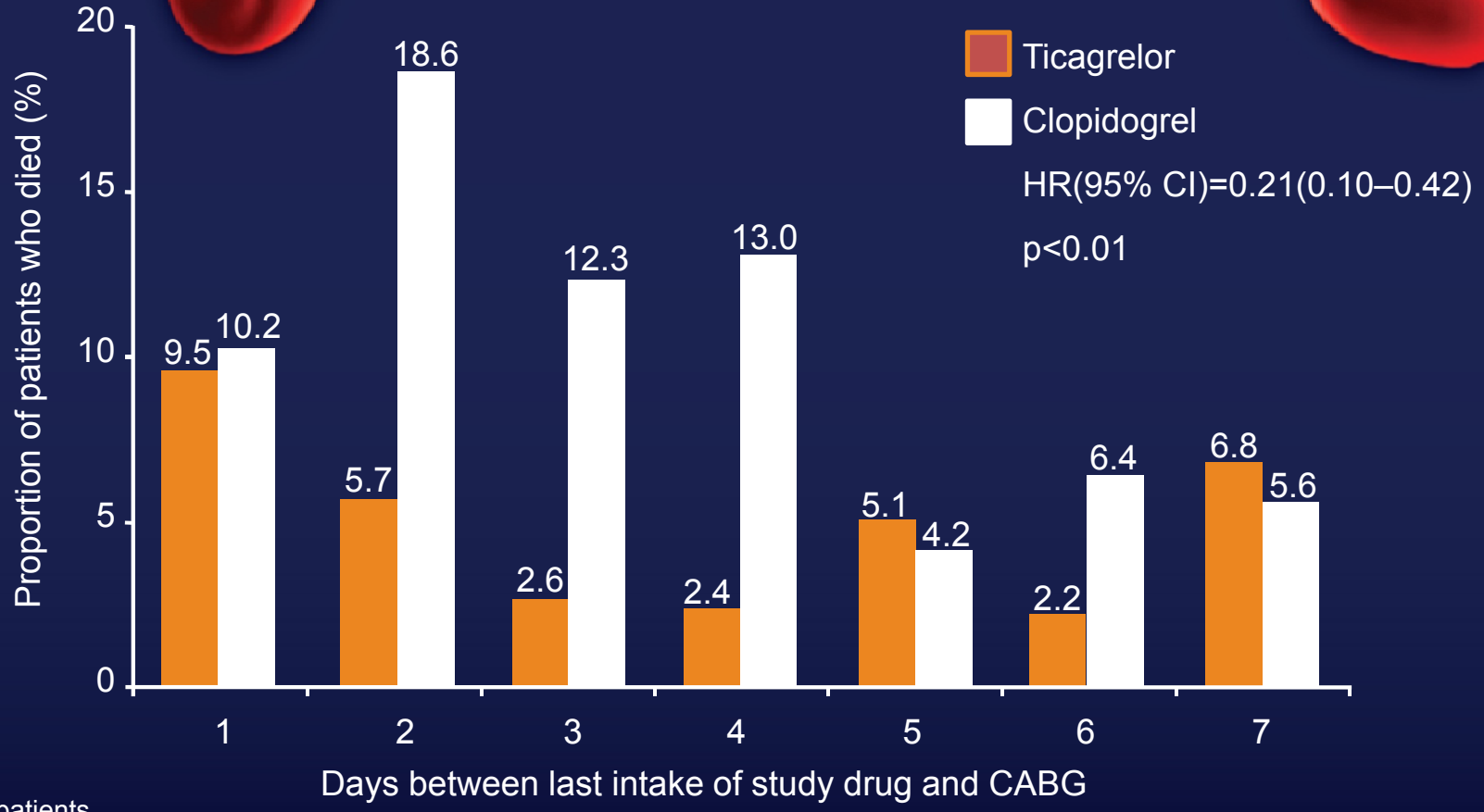
Characteristic	Ticagrelor (n=629)†	Clopidogrel (n=629)	OR (95% CI)	p value
Primary endpoint, %				
CV death/MI/stroke	10.6	13.1	0.84 (0.60–1.16)	0.286
Secondary endpoints, %				
MI, excluding silent	6.0	5.7	1.06 (0.66–1.68)	0.819
CV death	4.1	7.9	0.52 (0.32–0.85)	0.009
Stroke‡	2.1	2.1	1.17 (0.53–2.62)	0.697
All-cause mortality	4.7	9.7	0.49 (0.32–0.77)	0.002
Non-CV death	0.7	2.0	0.35 (0.11–1.11)	0.075



*Over the duration of the study; †Three patients had missing values for the efficacy endpoints due to CABG after the censoring date at 12 months; ‡Results for haemorrhagic stroke: 0.0% (ticagrelor) and 0.2% (clopidogrel); non-haemorrhagic/unknown stroke: 2.1% and 1.9%, respectively (p=0.54).
CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; OR, odds ratio.

Held C, et al. *J Am Coll Cardiol* 2011;57:672–684;
Wallentin L, et al. *N Engl J Med* 2009;361:1045–1057.

PLATO CABG: Mortality and time between last intake of study drug and CABG



Number of patients							
CABG							
Ticagrelor	84	106	114	84	79	91	74
Clopidogrel	88	86	73	69	96	110	107

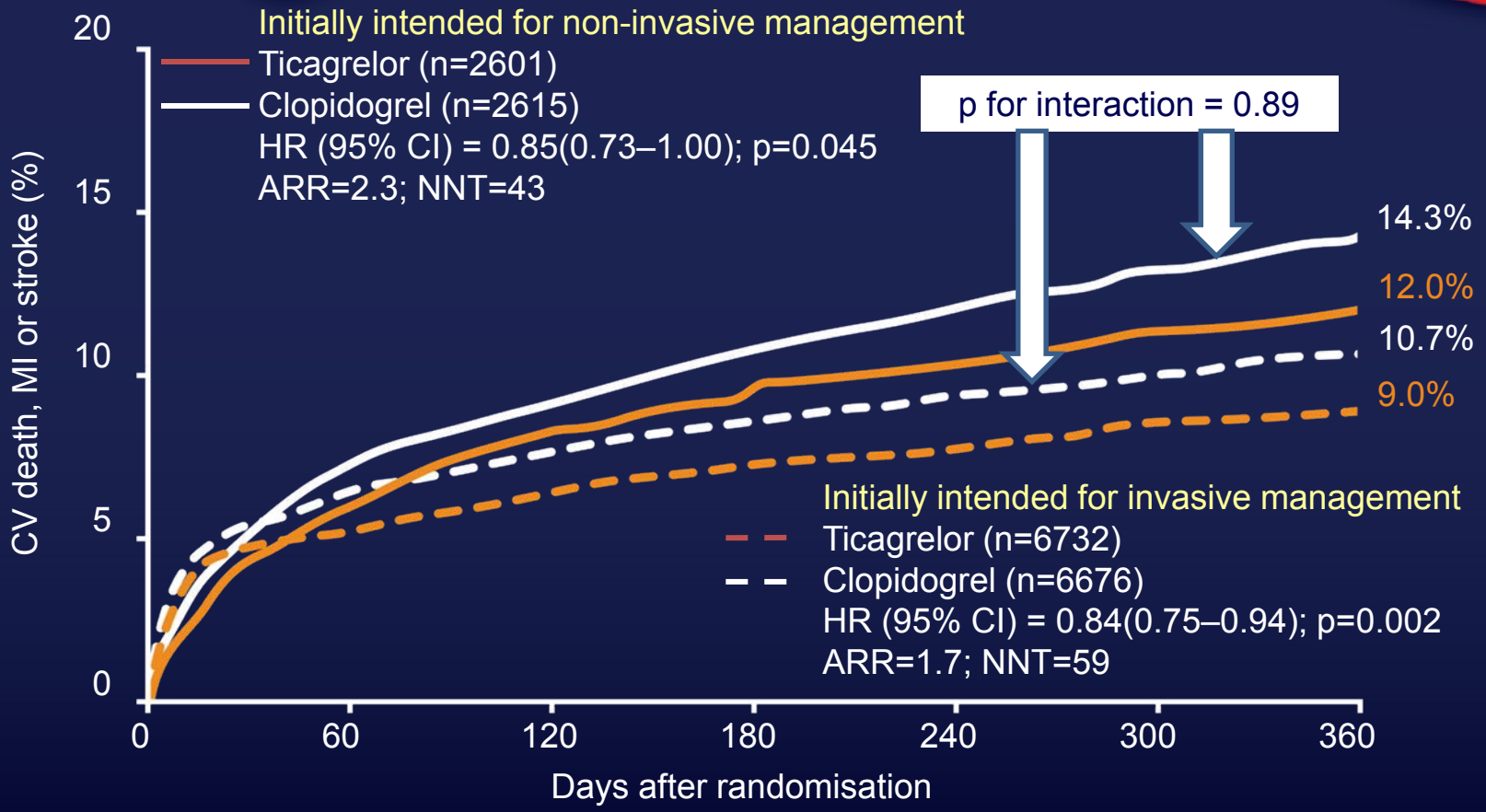
CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio.

Held C, et al. *J Am Coll Cardiol* 2011;57:672–684.

Special Populations

Medical Therapy

Ticagralor maintains superiority when medical management preferred option



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non-ST-segment elevated MI; UA, unstable angina.
James S, et al. *BMJ* 2011;342:d3527.

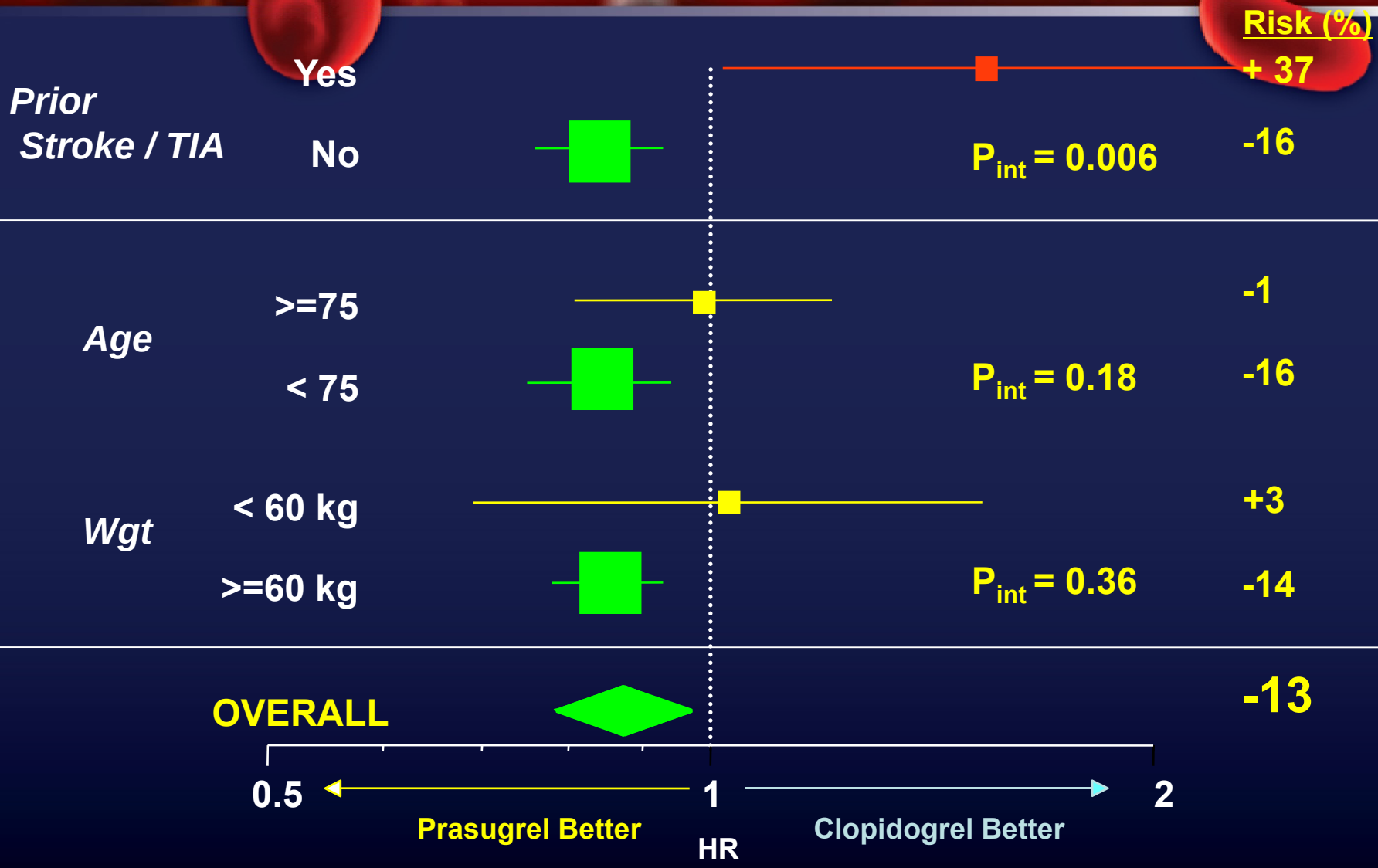
Other Special Populations

Elderly, Stroke/TIA, CKD

TRITON TIMI·38

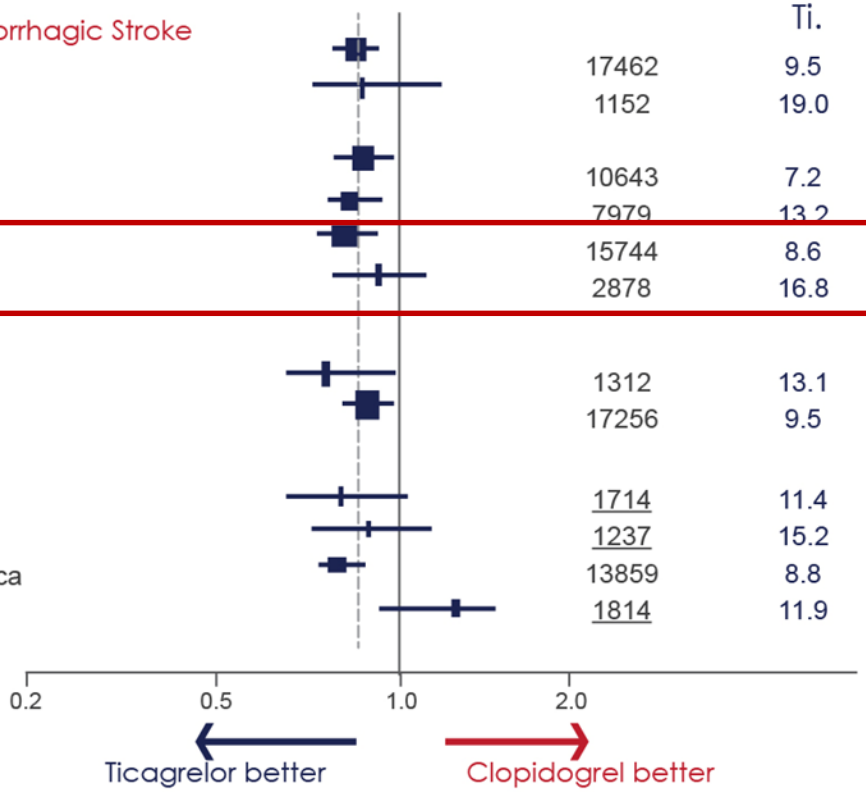
What if Scenarios… Prior Stroke Balance of Efficacy and Safety

Post-hoc analysis



PLATO
Primary Endpoint In Pre-defined Subgroups

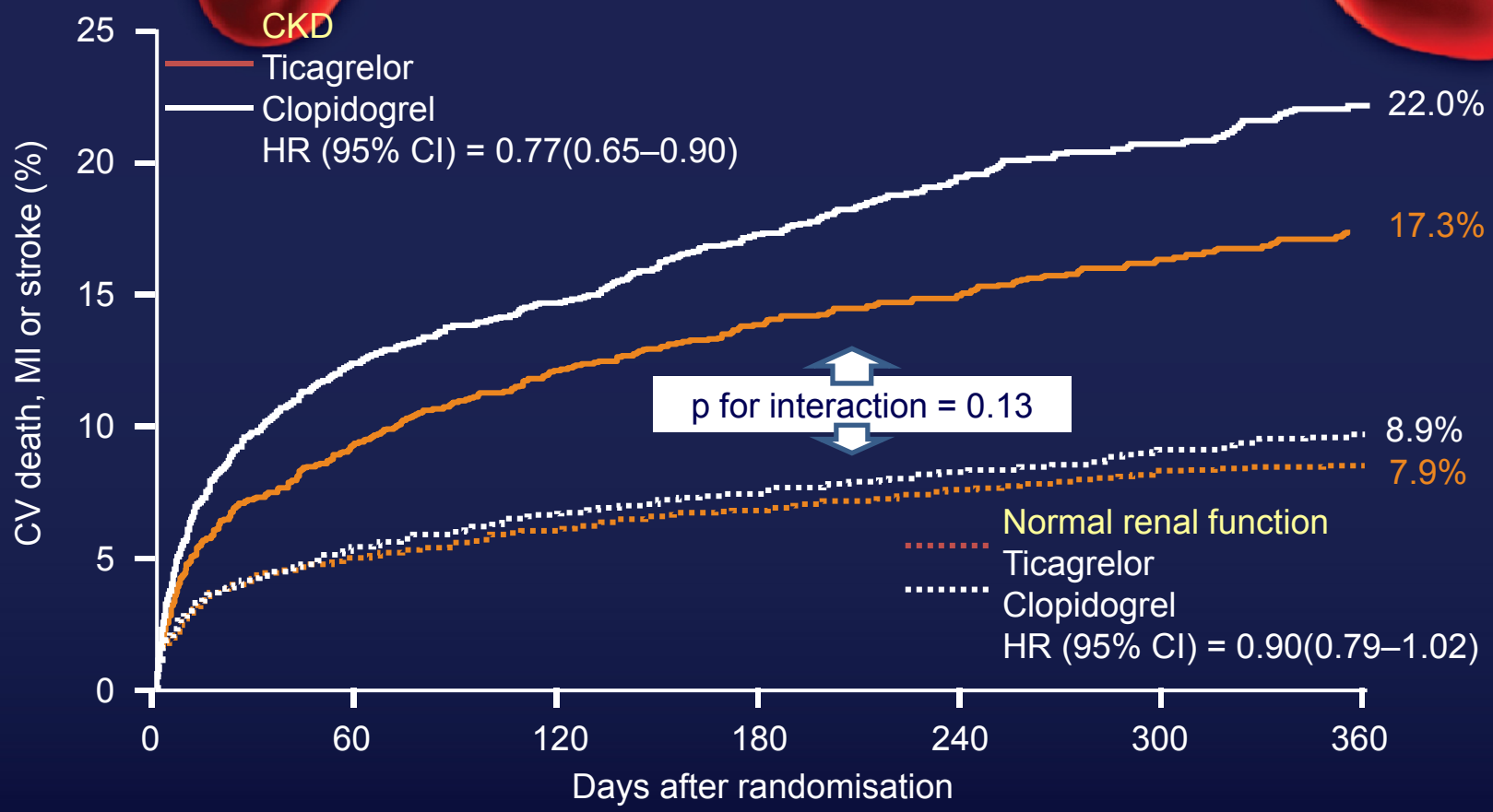
Characteristic	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)	p-Value Interaction
Previous TIA/Non-hemorrhagic Stroke					0.84
No	17462	9.5	11.1	0.84 (0.76, 0.93)	
Yes	1152	19.0	20.8	0.87 (0.66, 1.13)	
Age Group					
<65 Years	10643	7.2	8.5	0.85 (0.74, 0.97)	0.86
≥65 Years	7979	13.2	16.0	0.83 (0.74, 0.94)	
<75 Years	15744	8.6	10.4	0.82 (0.74, 0.91)	0.22
≥75 Years	2878	16.8	18.3	0.94 (0.78, 1.12)	
Weight Group					
<60 kg	1312	13.1	17.3	0.75 (0.60, 0.99)	0.36
≥60 kg	17256	9.5	11.2	0.86 (0.78, 0.94)	
Region					0.05
Asia/Australia	1714	11.4	14.1	0.80 (0.61, 1.04)	
Central/South America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Europe/Middle East/Africa	13859	8.8	11.0	0.80 (0.72, 0.90)	
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



CI, confidence interval; Cl., clopidogrel; KM, Kaplan-Meier; Ti., ticagrelor.

1. Adapted from Wallentin et al. NEJM. 2009;361:1045-57.

Renal function and outcomes in PLATO: Primary composite endpoint

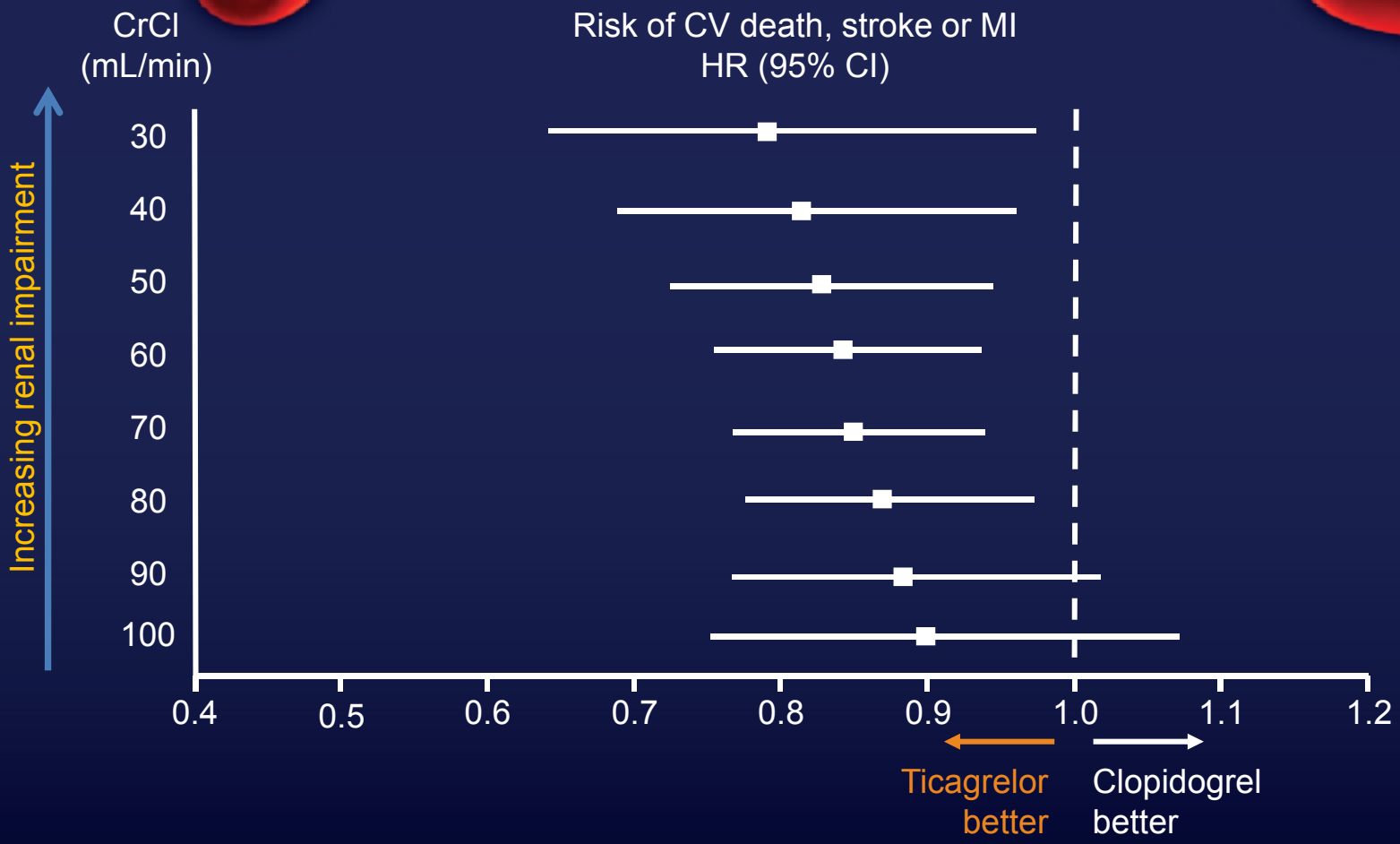


No interaction between treatment and renal function (p=0.13)[James 2010:J,K]

CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

James S, et al. *Circulation* 2010;122:1056–1067;
Wallentin L, et al. *N Engl J Med* 2009;361:1045–1057.

Renal function and outcomes in PLATO: Primary composite endpoint by CrCl



CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

James S, et al. *Circulation* 2010;122:1056–1067.

Approach to Treatment: Considering Patient Factors

Patients with:	Treatment you may wish to consider…		
	Clopidogrel	Prasugrel	Ticagrelor
High bleeding risk (i.e. prior bleed/stroke, ≥75 years of age, severe renal failure, prior ICH*)[1,2,3]	++	-	+
Thrombosis on clopidogrel[1,4]	-	++	+
Risk for bradycardic events†[2]	+	+	-
Dyspnea/COPD[2]	+	+	-
STEMI[1,4]	-	+	+
UA/NSTEMI[1,5,6]	+	+	++
Diabetes mellitus[4]	-	++	+
Body weight <60 kg[3]	+	-	+
Uncertain compliance[1]	+	+	-

*Ticagrelor is contraindicated in patients with a history of ICH; †For example, patients with sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope not protected with a pacemaker. COPD, chronic obstructive pulmonary disorder; ICH, intracranial hemorrhage.

1. Biondi-Zoccai et al. Int J Cardiol. 2011;150:325-31;
4. Alber et al. Wien Klin Wochenschr. 2011 Aug 3. [Epub ahead of print]; 5. CURE Trial Investigators. NEJM. 2001;345:494-502;
6. Mehta et al. Lancet. 2001;358:527-33.

2011 ESC Guidelines for the Management of ACS in patients presenting without persistent ST-segment elevation

Recommendations	Class	Level

European Heart Journal doi:10.1093/eurheartj/ehr236

DAPT in 2013

- Thank You!!!