Role of Old versus New P_2Y12 Agents In ACS Patients: Focus on Ticagrelor

DR. VICTOR SEREBRUANY
JOHNS HOPKINS UNIVERSITY
HEART*DRUG* RESEARCH LLC
PUSAN, DECEMBER 2014

Disclosures

- ***Ownership:*** Heart*Drug*™ Research, LLC
- ***Grants:*** Pfizer, Sanofi-BMS, Novartis, Lundbeck, Boehringer Ingelheim, Eli Lilly, AtheroGenics, Guilford, J&J, Bayer, Merck, Fibrex, Cardax, Eisai, Abbott, Pronova-GSK
- ***Consulting:*** Sanofi-BMS, McNeil, NPS Pharma, Bayer, Eisai, mutual funds, hedge funds
- ***Speaking:*** Sanofi-BMS, Boehringer Ingelheim
- ***Legal:*** Relator on behalf of US Government against AstraZeneca in sealed case BAH #12-1563 in Washington DC Federal Court
- ***Patents:*** Novartis (valsartan), Boehringer Ingelheim (Aggrenox), Eli Lilly (prasugrel), AtheroGenics (AGI-1067), Eisai (E-5555), Heart*Drug*™ (ticagrelor, statins, PAR-1, sertraline, BleedScore)

PLATO: Publishing the …. truth

PLATO: Background

Variable	NEJM	FDA Reviews
Baseline Age (≥ 75 years)	15% for ticagrelor, 16% for clopidogrel	P=0.06
Past Medical History: Carotid Stenosis (≥ 50%)	Not Reported	1.8% for ticagrelor, 2.3% for clopidogrel; P=0.02

PLATO: Outcomes

Variable	NEJM	FDA Reviews
Stroke	19 more for ticagrelor; P=0.22 for the difference	23 or 27 more for ticagrelor; P=0.09
Myocardial Infarction	89 more for clopidogrel	44 by sites, and 45 by ICAC extra adjudication exclusively to clopidogrel
Primary End Point	9.8% for ticagrelor, 11.7% for clopidogrel	At least 23 end point event for ticagrelor were inactivated, not adjudicated, soft-deleted or downgraded to "softer" endpoints.

PLATO: Adverse Events

Event	NEJM	FDA-Reviews
GI Ulcers/Perforations	Not reported	0.4% (n=38) for ticagrelor; 0.2% (n=18) for clopidogrel (P=0.009)
Cerebrovascular accident	Not reported	0.7% (n=62) for ticagrelor; 0.5% (n=42) for clopidogrel (P=0.05)
Other arterial thrombosis	19 patients (0.2%) after ticagrelor, and 31 patients (0.4%) after clopidogrel (p=0.09)	Peripheral ischemia with the relative risk (RR=1.3); claudication (RR=1.3); amputation (RR=1.4); pulmonary embolism (RR=1.5); and retinal ischemia (RR=1.3) were all more frequent for ticagrelor.
Severe epistaxis	Not reported	0.4% (n=36) for ticagrelor; 0.1% (n=12) for clopidogrel (P=0.005)

PLATO: Conduct

Event	NEJM	FDA-Reviews
Blinding	Double-blind trial	At least 452 patients were unblinded prior to database lock
Premature withdrawal	Not reported	3.3% (n=307) for ticagrelor; 2.7% (n=255) for clopidogrel: (p=0.03)
Premature discontinuation	Slightly more common in the ticagrelor group than in the clopidogrel group (in 23.4% of patients vs. 21.5%); p-value not provided	23.7% (n=2186) for ticagrelor; 21.8% (n=1999) for clopidogrel (p=0.002 for the difference)
Withdrawn Informed Consent	Not reported	3.2% (n=296) for ticagrelor; 2.7% (n=249) for clopidogrel: (p=0.002 for the difference)

PLATO: Conduct - II

Event	NEJM	FDA-Reviews
Lack of vital status	5 patients	At least 106 patients
Missing vital status follow up	Outpatient visits were scheduled at 1, 3, 6, 9, and 12 months	3.1% (n=289) for ticagrelor; 2.6% (n=242) for clopidogrel (p=0.04)
Alive at the end of study but no visit with vital signs on or after the earliest study completion date	Not reported	19.7% for ticagrelor; 18.1% for clopidogrel This difference (n=148) exceeds the difference in primary endpoint (n=147).

PLATO: Integrity Challenge

International Central Adjudication Committee in PLATO: No strangers, please

ICAC Role	DCRI	TIMI	UCRC	Sweden*	Others
Co-Chairmen	1	-	1	-	-
Coordinators	2	-	1	-	-
Adjudicators	14	4	11	10	11**
Study Sponsor	-	-	-	1	4***

DCRI – Duke Clinical Research Institute, Durham, North Carolina, USA;
TIMI – Thrombolysis in Myocardial Infarction, Boston, MA, USA;
UCRC – Uppsala Clinical Research Center, Uppsala, Sweden
* = except UCRC, Uppsala, Sweden
** = including at least 5 former Duke cardiology fellows
*** = from sponsor headquarters, Wilmington, Delaware, USA

PLATO ICAC: At Your Service, Sire!

Who count	Ticagrelor/Clopidogrel	Δ MI	HR	p-value
Sites	504/548	44	0.92	(0.095) NS
ICAC	504/**593**	**89**	0.84	>0.001

Thromb Haemost, 2012

PLATO: Efficacy Challenge

PLATO Efficacy "Magic"

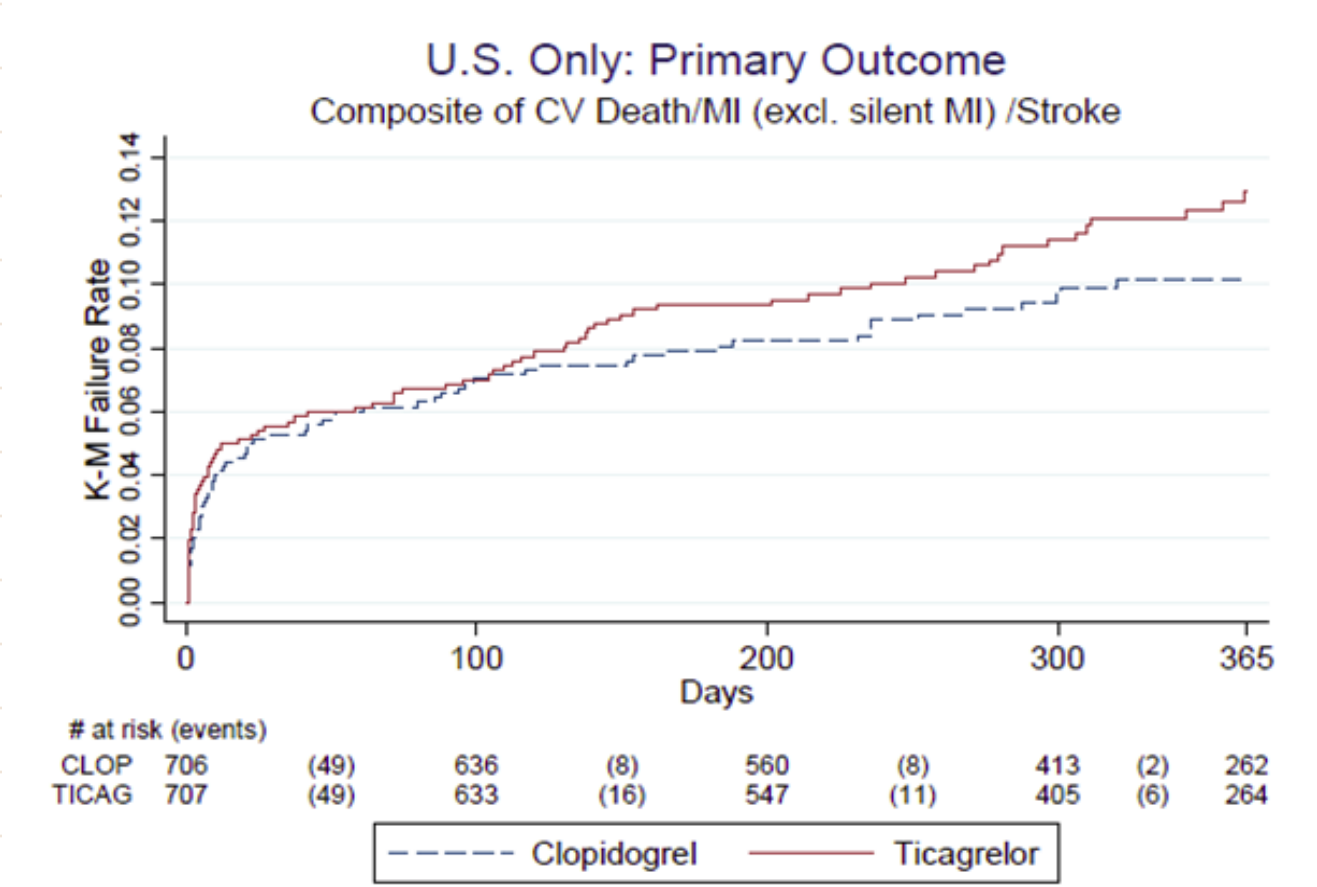
Variable	Sites	Adjudicated	FDA
Non-fatal MI's	-44	-89	-89
Non-fatal Strokes	+19	+19	+23/+27
Vascular Deaths	-89?	-89	-89
Baseline DM	25% e a	25% e a	25% e a
Baseline PAD	6.2% e a	6.2% e a	6.2 % e a

"-" Favors ticagrelor; "+" favors clopidogrel; "e a" – each arm

Controversies in the clopidogrel PLATO arm

Variable	C+A	Paradox
Vascular Death	5.1%	Extreme
All-cause mortality	5.9%	Unseen
MI/Death rate	6.9/5.1	74% - Absurd
Site Reported Events	0.095	Not significant

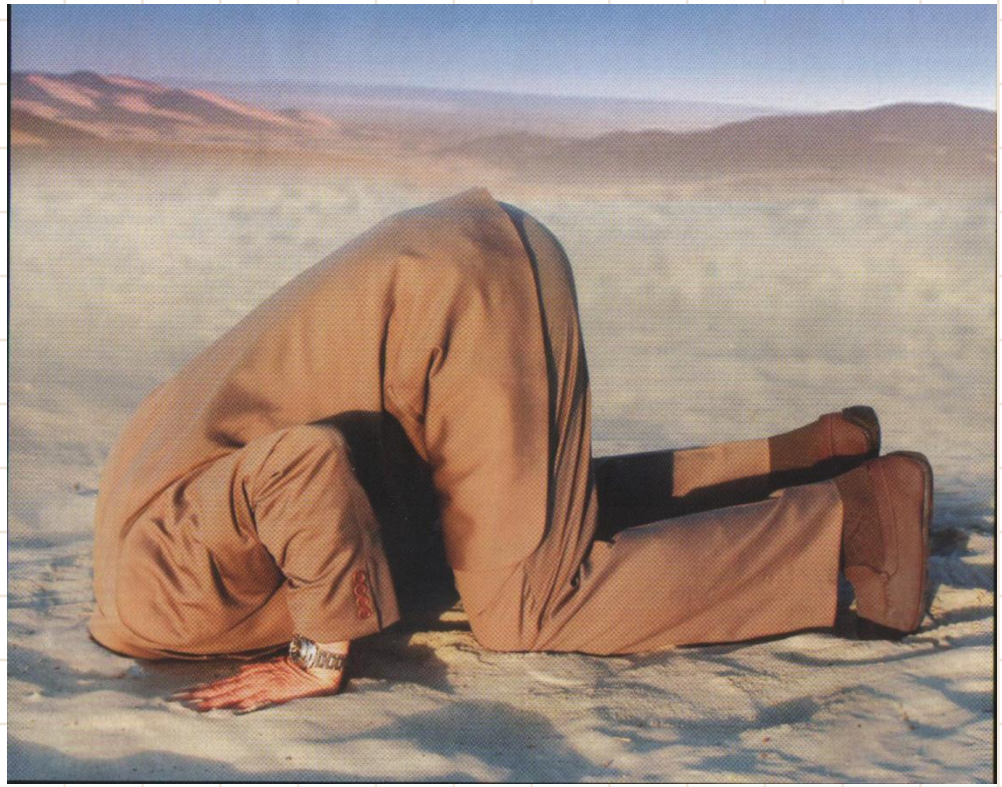
US Outcomes in PLATO: Where are clopidogrel sudden deaths?



Source: R. Fiorentino, Clinical Reviewer

FDA Ticagrelor Review, 2010

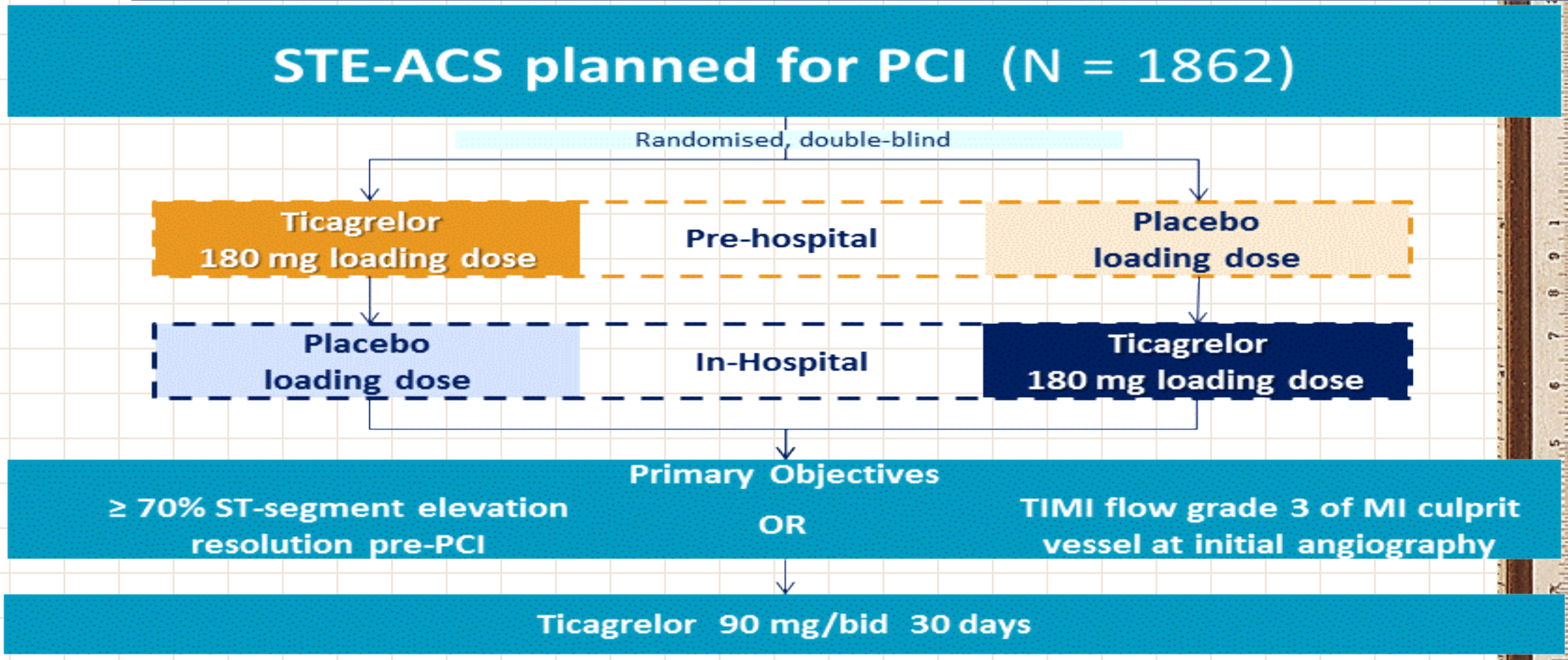
ATLANTIC: Under Scope



Study population and design

Atlantic Population

- Documented evidence of **STEMI**
- Planned for **angioplasty (PCI)**
- **onset of ischaemic symptoms within 6 h**
- **initially managed by ambulance physician/personnel**; also concerning patients not pre-treated for STEMI in **emergency rooms of non-PCI hospitals**



Montalescot G et al. *Am Heart J.* 2013;165:515–522.

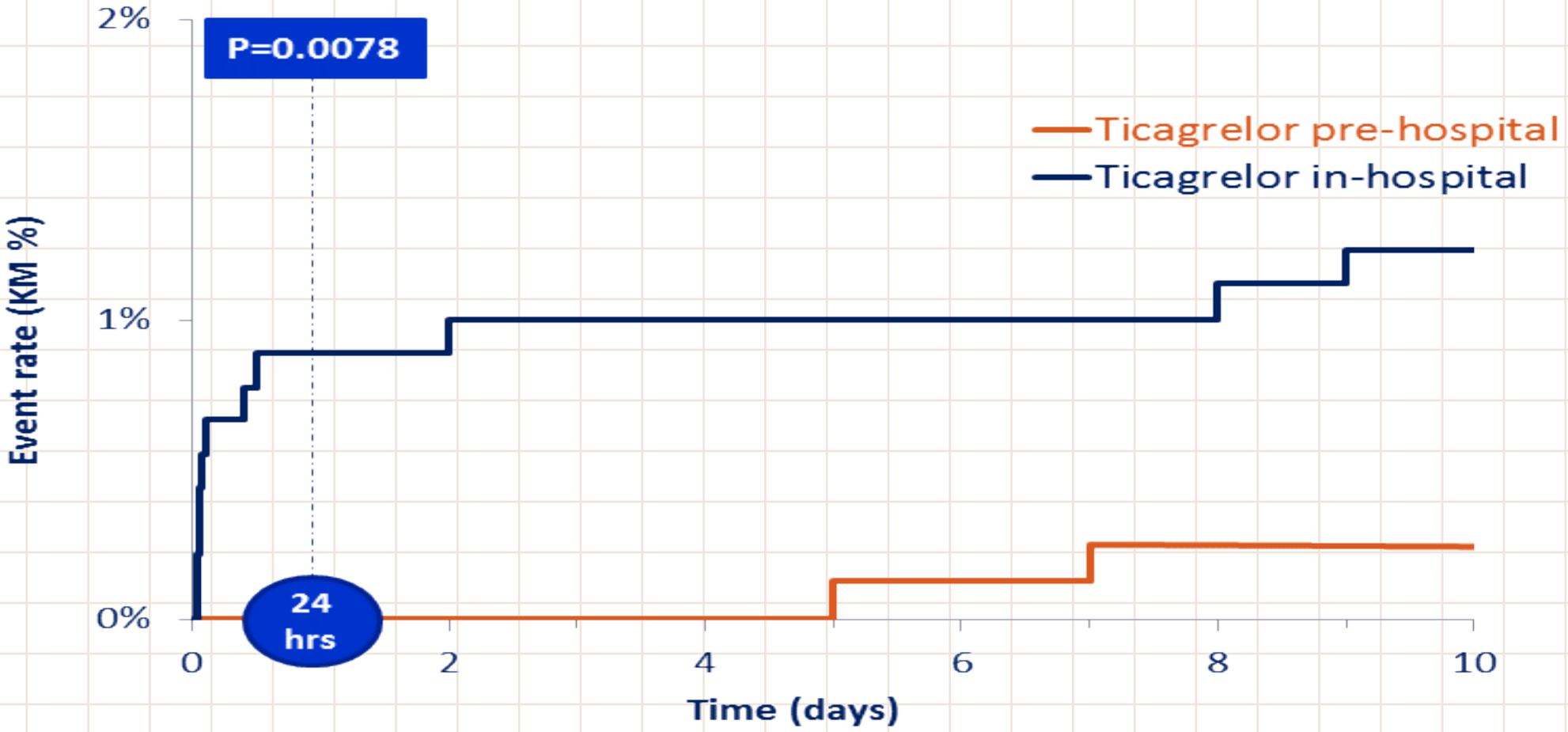
PLATO Angiographic Study Primary Endpoint: Post PCI TIMI Myocardial Perfusion Grade(TMPG)

	Overall n (%)	Ticagrelor n (%)	Clopidogrel n (%)	P value
All Patients				
Normal (TMPG 3)	779/1657 (47.0)	396/841 (47.1)	383/816 (46.9)	0.9608
STEMI				
Normal (TMPG 3)	412/989 (41.7)	213/502 (42.4)	199/487 (40.9)	0.6517
NSTE-ACS				
Normal (TMPG 3)	367/668 (54.9)	183/339 (54.0)	184/329 (55.9)	0.6411

PLATO Angiographic Study: Post PCI TMPG by Aspirin Dose

	Overall n (%) N = 1657	Ticagrelor n (%) N = 841	Clopidogrel n (%) N = 816	p-value
Aspirin Dose on Randomization Day				
Less than 100 mg				
Normal	168 (54.9)	82 (54.3)	86 (55.5)	0.8358
Abnormal	138 (45.1)	69 (45.7)	69 (44.5)	
100 – 299 mg				
Normal	180 (48.8)	93 (48.9)	87 (48.6)	0.9473
Abnormal	189 (51.2)	97 (51.1)	92 (51.4)	
300 mg or more				
Normal	431 (43.9)	221 (44.2)	210 (43.6)	0.8420
Abnormal	551 (56.1)	279 (55.8)	272 (56.4)	
Aspirin Dose on Day 1 After Randomization				
Less than 100 mg				
Normal	364 (46.8)	191 (47.4)	173 (46.3)	0.7508
Abnormal	413 (53.2)	212 (52.6)	201 (53.7)	
100 – 299 mg				
Normal	345 (46.0)	171 (45.7)	174 (46.3)	0.8789
Abnormal	405 (54.0)	203 (54.3)	202 (53.7)	
300 mg or more				
Normal	69 (53.5)	33 (52.4)	36 (54.6)	0.8054
Abnormal	60 (46.5)	30 (47.6)	30 (45.4)	

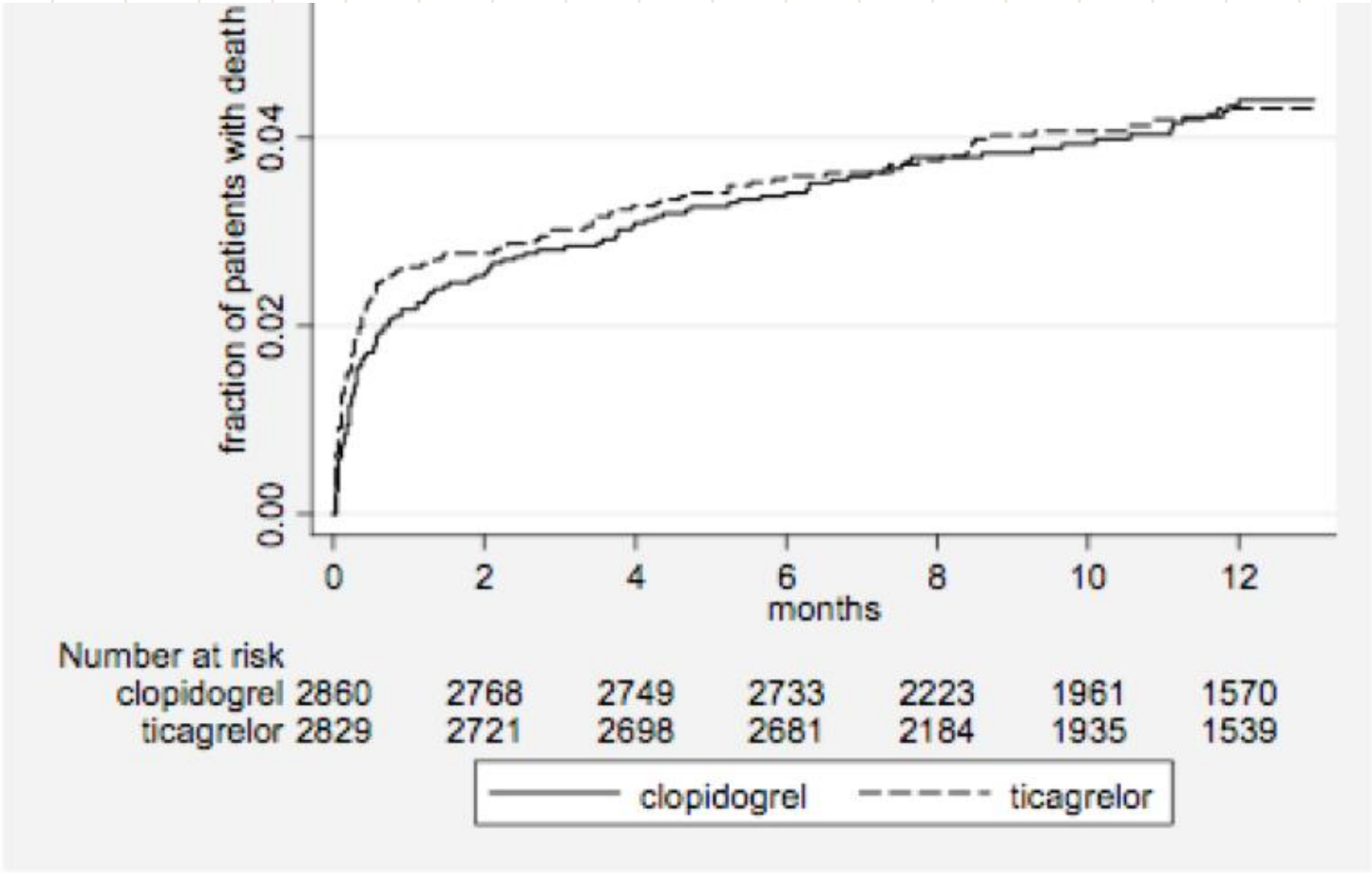
Definite stent thrombosis in ATLANTIC up to 10 days



Clinical endpoints at 30 days in ATLANTIC

Values are %	Ticagrelor pre-hosp (n=906)	Ticagrelor in-hosp (n=952)	Odds ratio (95% CI)	p-value
Death (all-cause)	30 (3.3%)	19 (2.0%)	1.68 (0.94, 3.01)	0.08
Death (all-cause) 24 hours	12 (1.3%)	4 (0.4%)	3.18 (1.02-9.90)	0.043
MI	0.8	1.1	0.73 (0.28, 1.94)	0.53
Stroke	0.4	0.2	2.11 (0.39, 11.53)	0.39
TIA	0	0.1		Not estimable
Urgent coronary revascularization	0.6	0.8	0.66 (0.21, 2.01)	0.46
Bail-out GP IIb/IIIa inhibitors	8.6	10.5	0.80 (0.59, 1.10)	0.17

The Early PCI PLATO Death "Paradox"



The FDA Review of Complete Response; Thomas A. Marciniak, MD – Medical Team Leader, p.18

Impressions:

- Current data with ticagrelor are confusing, and ATLANTIC brings more uncertainty.
- The future of ticagrelor heavily depends on the confirmation of mortality benefit in PEGASIS (TIMI-54) trial
- Full disclosure and publication of the PHILO (NCT01294462) trial is needed to properly assess risks in Asians