Ticagrelor: From PLATO to PEGASUS
Focus on Facts, not Interpretations!

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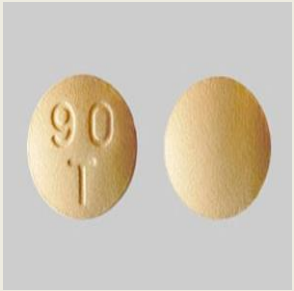
Disclosures

- ***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, KMST**
- ***Consulting:*** **FDA, Pfizer, Sanofi-BMS, McNeil, NPS Pharma, Bayer, Eisai, Daiichi-Sankyo, mutual funds, hedge funds**
- ***Speaking Bureau:*** **Pfizer, Sanofi-BMS, Boehringer-Ingelheim; Daiichi-Sankyo**
- ***Patents:*** **Novartis (valsartan), Boehringer Ingelheim (Aggrenox), Eli Lilly (prasugrel), AtheroGenics (AGI-1067), Eisai (E-5555), Heart*Drug™* (ticagrelor, statins, PAR-1, sertraline, BleedScore)**

Money Talk 2015



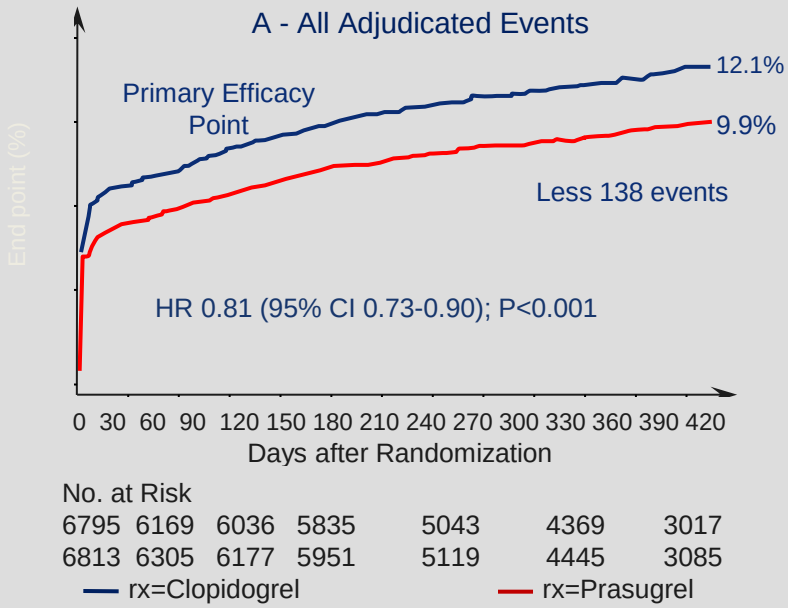
FDA Approval	**October, 1998**	**July, 2009**	**July, 2011**
Total Sales (billion USD)	**≈64.27**	**≈ 2.17**	**≈ 1.14**
WW Sales (Q1-Q2 2015)	**1.19**	**0.26**	**0.275**
Patent Expiration	**2012**	**April, 2017**	**July, 2018**
Sponsor Major Trials	**5**	**2**	**2+3**

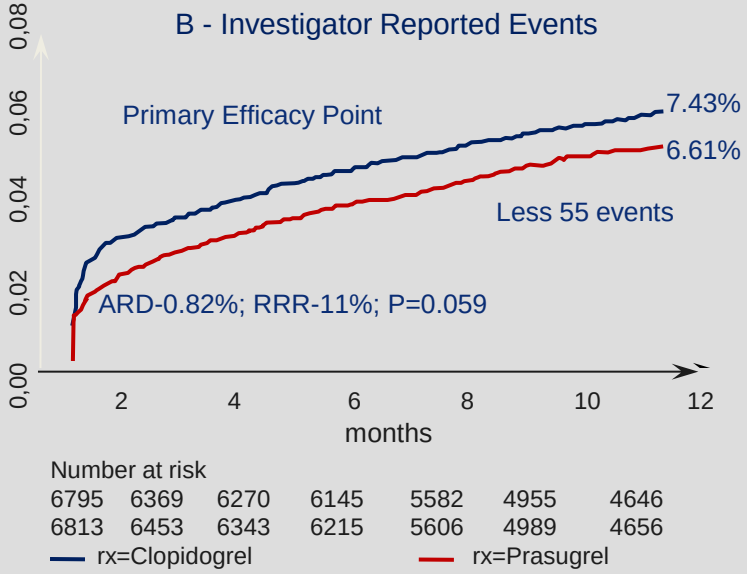
Annual Financial Reports, Sanofi (1999-2015); Lilly (2009-2015), Astra Zeneca (2011-2015); Serebruany, Fortmann. Thromb Faemost, 2014

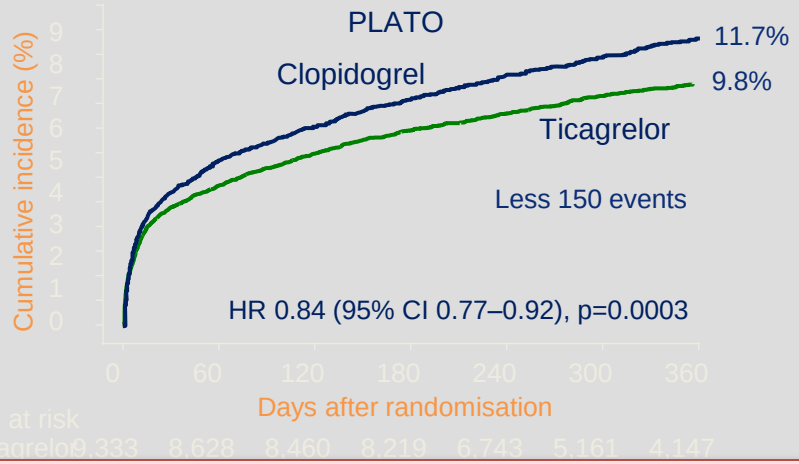
Strategic failures cannot be fixed by tactical victories

"On War" [Vom Kreig];1834

Main Outcomes: TRITON versus PLATO







Wiviott, et al, NEJM 2007; Walentin,et al, NEJM 2009; FDA Prasugrel review, 2008

Was PLATO justified after Phase II DISPERSE и DISPERSE-2?

Outcome (%)	Ticagrelor (n=663)	Clopidogrel (n=327)
CV Death/MI/Stroke	3.9	4.9
CV Death	1.8	1.2
MI	2.4	4.3
Stroke	0.3	0.3
SRI	2.1	0.9
RI	3.3	2.8
Death (13 vs. 4)	**1.96**	**1.2**

DISPERSE + DISPERSE -2, FDA Ticagrelor Review

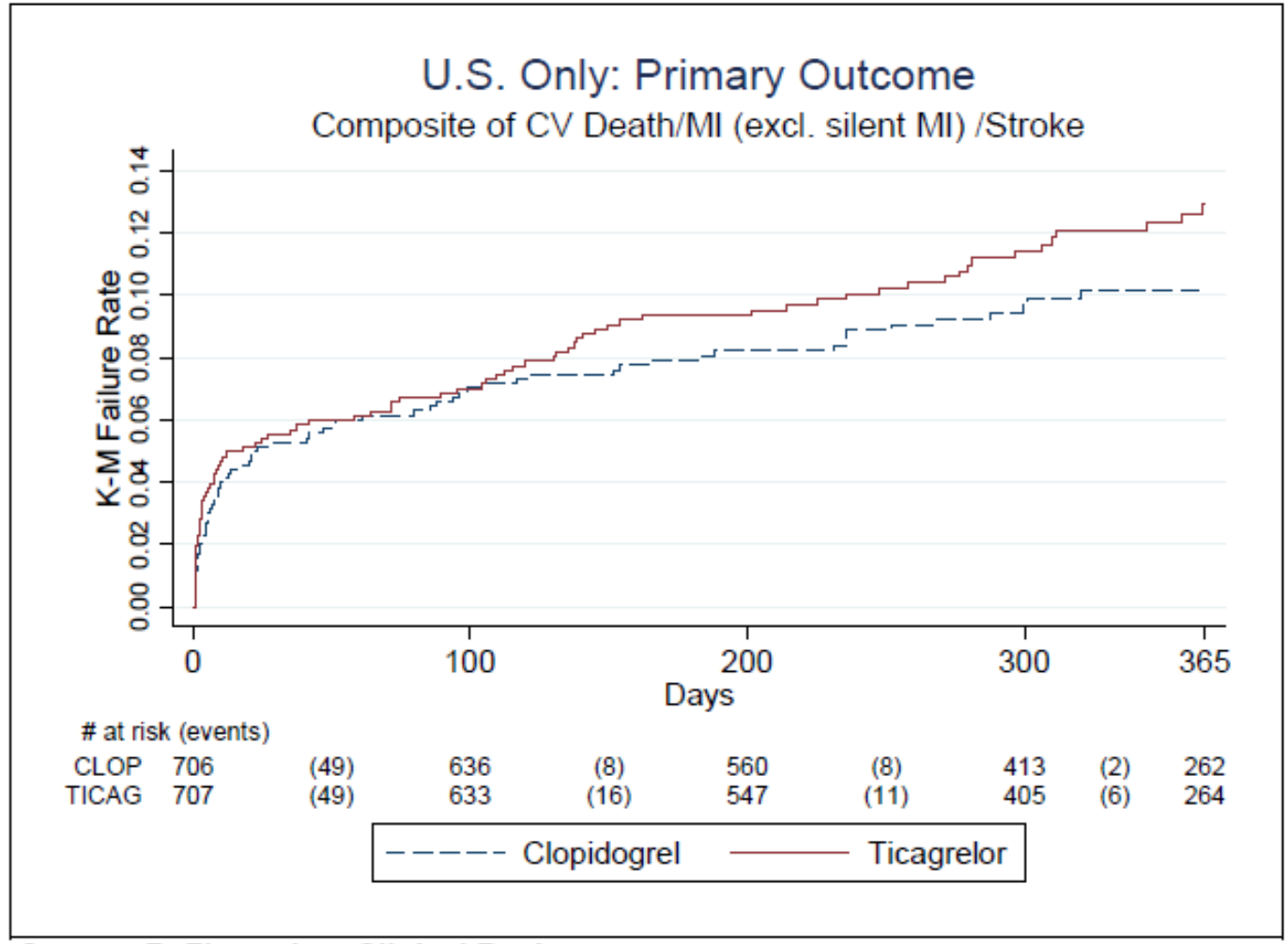
All-cause mortality and length of follow up in latest trials

TRIAL	Follow-up	Overall **ACM**	**ACM Prorated over Follow-up Duration**
CAPRIE	23 months	5.8%	**0.252%/month**
CURE	9 months	5.7%	**0.633%/month**
CREDO	12 months	1.7%	**0.141%/month**
PROVE-IT	24 months	2.7%	**0.113%/month**
CHARISMA	28 months	4.8%	**0.171%/month**
ACUITY	12 months	3.75%	**0.313%/month**
TRITON	14.5 months	3.2%	**0.221%/month**
PLATO	**9 months**	**5.9%**	**0.655%/month**
TRACER	16.7 months	4.9%	**0.293%/month**
ATLAS	13 months	4.5%	**0.346%/month**

*** - data from control arm**

Serebruany, Thromb Haemost 2011

PLATO: Outcomes in the USA



Source: R. Fiorentino, Clinical Reviewer

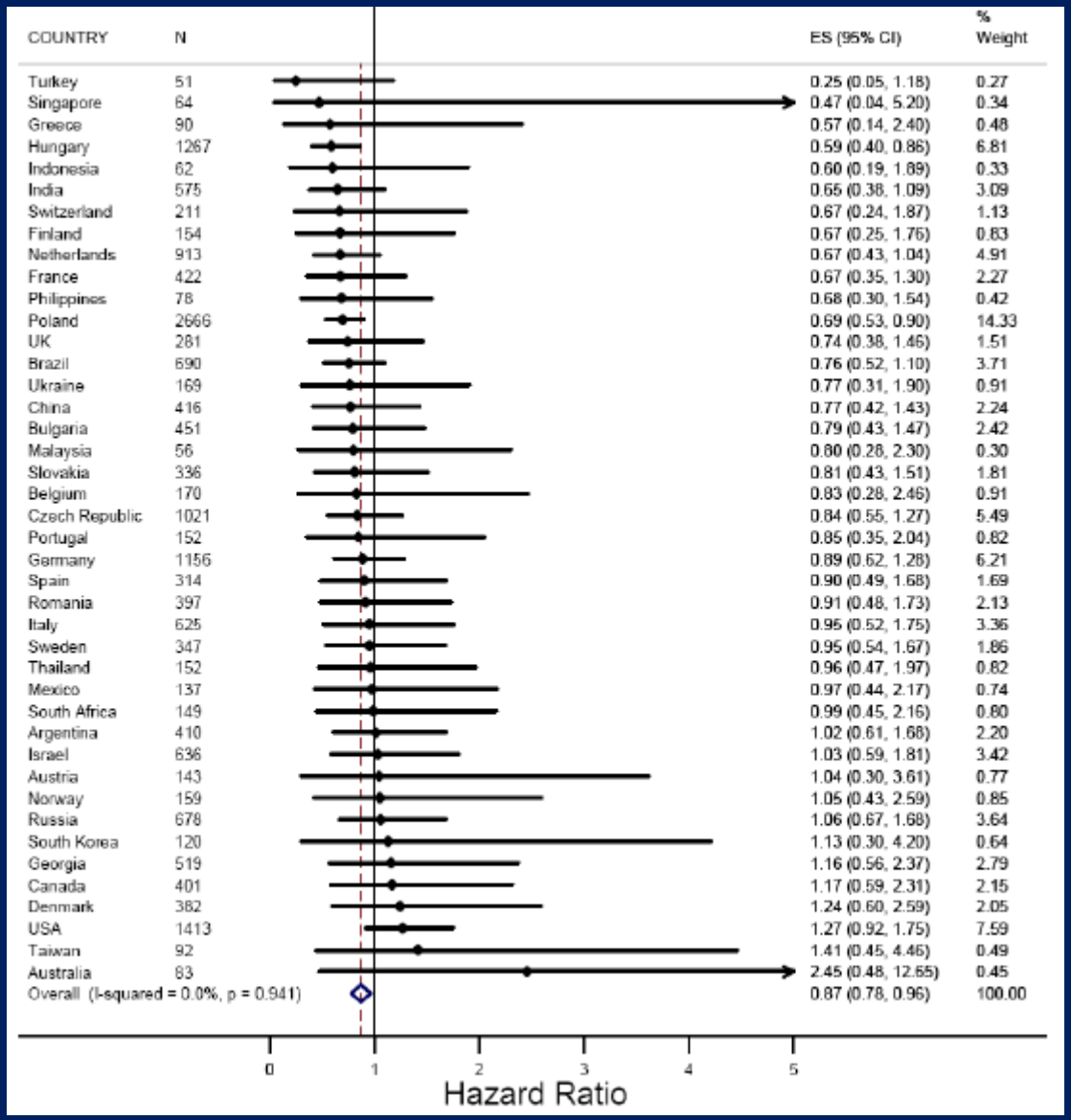
FDA Ticagrelor Review, 2010

Deaths and PCI in PLATO

	All PLATO		US only	
	no early PCI	early PCI	no early PCI	early PCI
ALL CAUSE MORTALITY				
Clopidogrel	7.8%	3.7%	6.1%	**2.3%**
Ticagrelor	5.7%	3.6%	5.2%	**4.1%**
CARDIOVASCULAR MORTALITY				
Clopidogrel	5.8%	2.8%	3.1%	**1.4%**
Ticagrelor	4.6%	2.9%	4.1%	**3.2%**

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

PLATO Outcomes by Country



FDA Review on Ticagrelor; 2010

Magic of Poland and Hungary in PLATO

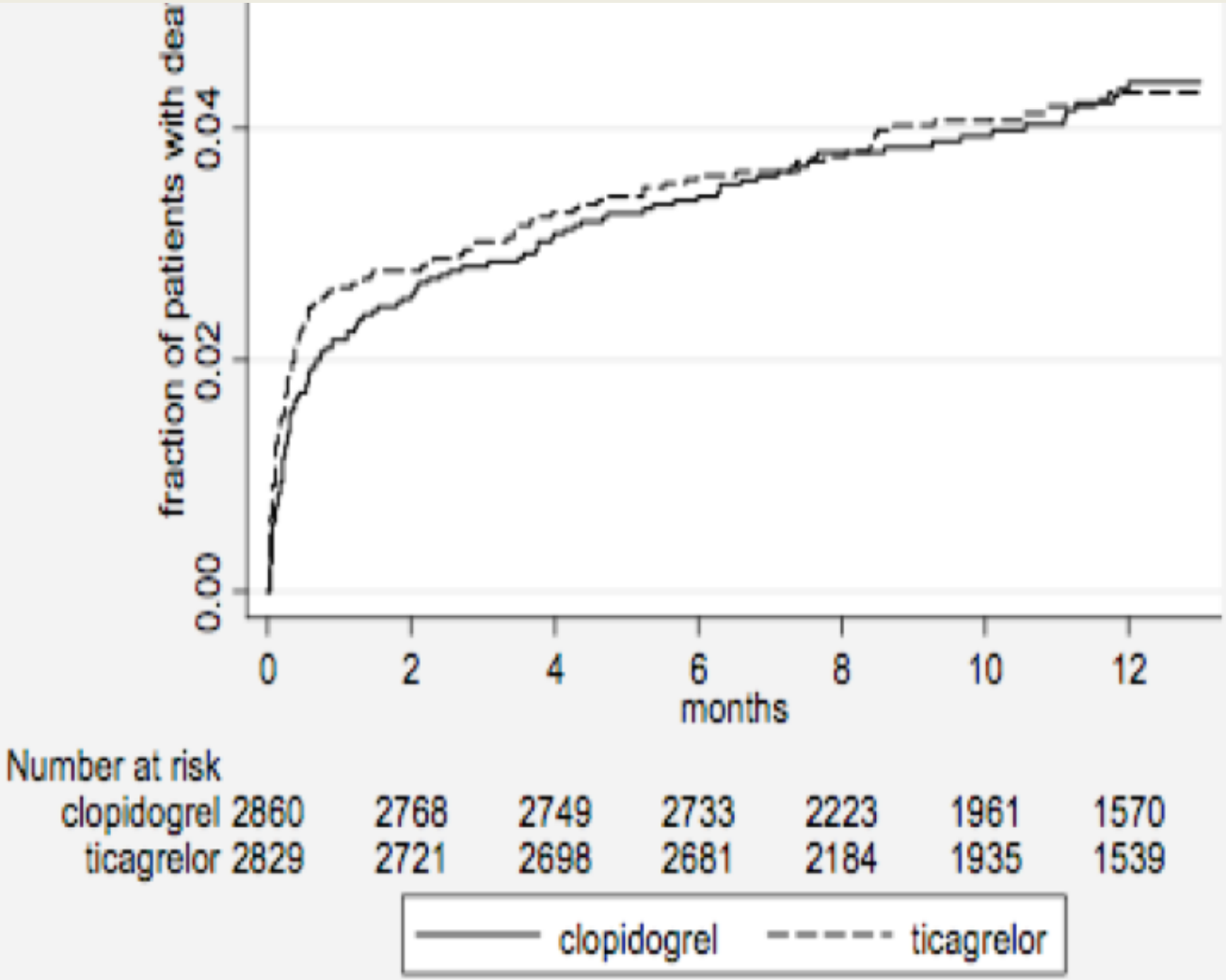
Country/Parameter	Poland	Hungary
Patients enrolled (n)	2,666	1,267
Reported events (n)	96/137	42/70
Events favoring ticagrelor (n)	41	28
Weight in PLATO (%)	14.33	6.81

Combined Enrollment in PLATO - 3,933 patients (21.14%)

Combined Benefit in PLATO - 69/150 events (46%)

FDA Ticagrelor Review, 2010; Serebruany Thromb Haemost, 2011

Early “deaths paradox” for PLATO PCI cohort



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

Major Outcomes in PLATO clopidogrel arm: Something is VERY wrong

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

NEJM, 2007; 2009

Efficacy “Magic” in PLATO

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

Serebruany, Atar. European Heart Journal, 2012

Who was counting events in PLATO?

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

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FDA Secondary Ticahrelor Review, 2010; Serebruany, Atar. EHJ, 2012

FDA recommendations on ticagrelor

Date(s)	FDA Officer(s)	Title	Review	Recommendation
August 12, 2010	Dr. T.Wong	Chemist	Drug/Product	Approval
	Dr. C.Tele	Chemist	Drug/Substance	Approval
August 10, 2010	Dr. E.Hausner	Pharmacologist	Toxicology	Approval
August 29, 2010	Dr. I. Younis	Pharmacologist	Clinical Pharm	Approval
August 31, 2010	Dr. J. Zhang	Statistician	Statistical	No Approval
August 25, 2010	Dr. R.Fiorentino	Medical Officer	Clinical Efficacy	No Approval
August 25, 2010	Dr. M. Blank	Medical Officer	Clinical Safety	No Approval
September 17, 2010	Dr. T. Marciniak	Team Leader	Overall Reviews	Approval*
May 14, 2011	Dr. T. Marciniak	Team Leader	Overall Reviews	No Approval
July 8, 2011	Dr.N.Stockbridge	CRD Director	Submission	Approval
July 20, 2011	Dr. R. Temple	Office Director	Final Decision	Approval

*** - excluding STEMI patients undergoing early PCI;**

FDA Secondary Ticagrelor Review, 2010,2011

ATLANTIC

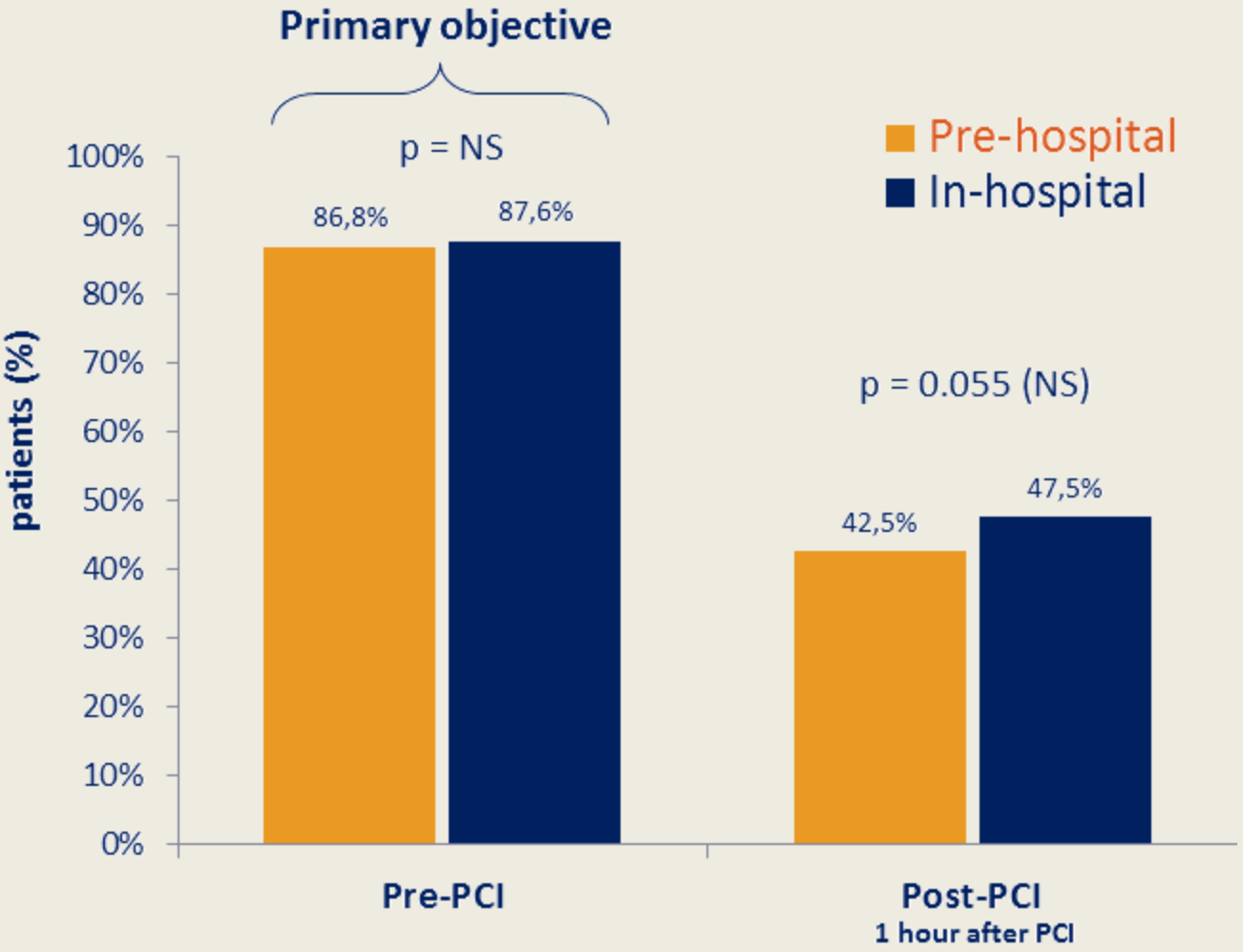
Administration of **T**icagrelor in the cath **L**ab or in the **A**mbulance for **N**ew S**T** elevation myocardial **I**nfarction to open the **C**oronary artery

G. Montalescot, A.W. van't Hof, F. Lapostolle, J Silvain, J.F. Lassen, L. Bolognese, W.J. Cantor, A. Cequier, M. Chettibi, S.G. Goodman, C.J. Hammett, K. Huber, M. Janzon, B. Merkely, R.F. Storey, U. Zeymer, O. Stibbe, P. Ecollan, W.M.J.M. Heutz, E. Swahn, J.P. Collet, F.F. Willems, C. Baradat, M. Licour, A. Tsatsaris, E. Vicaut, C.W. Hamm, for the ATLANTIC investigators

G. Montalescot, COI are available at www.action-coeur.org

1st Co-primary endpoint

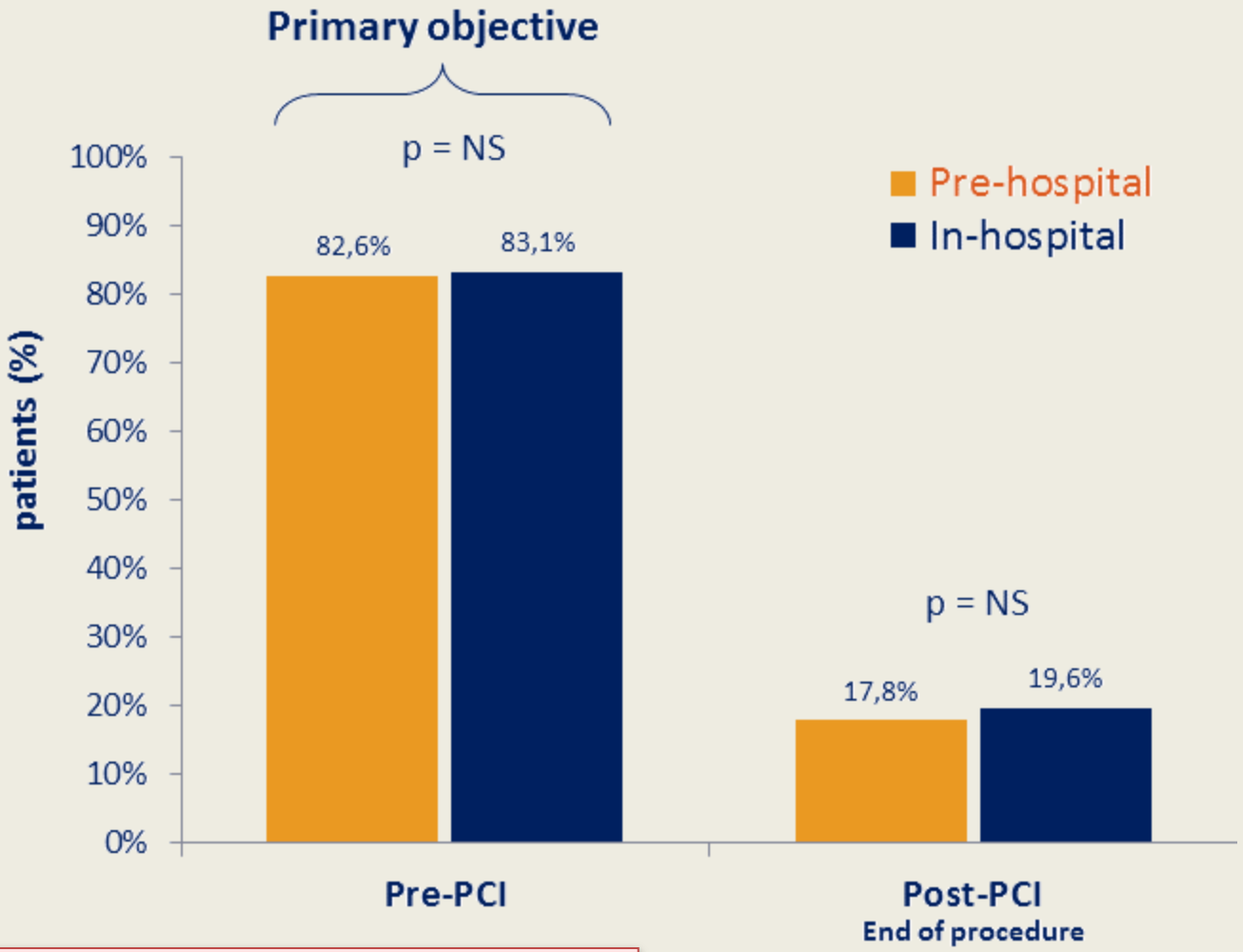
No ST-segment resolution (≥70%)



Montalescot, et al NEJM, 2014

2nd Co-primary endpoint

No TIMI 3 flow in infarct-related artery



Montalescot, et al NEJM, 2014

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)	

ATLANTIC

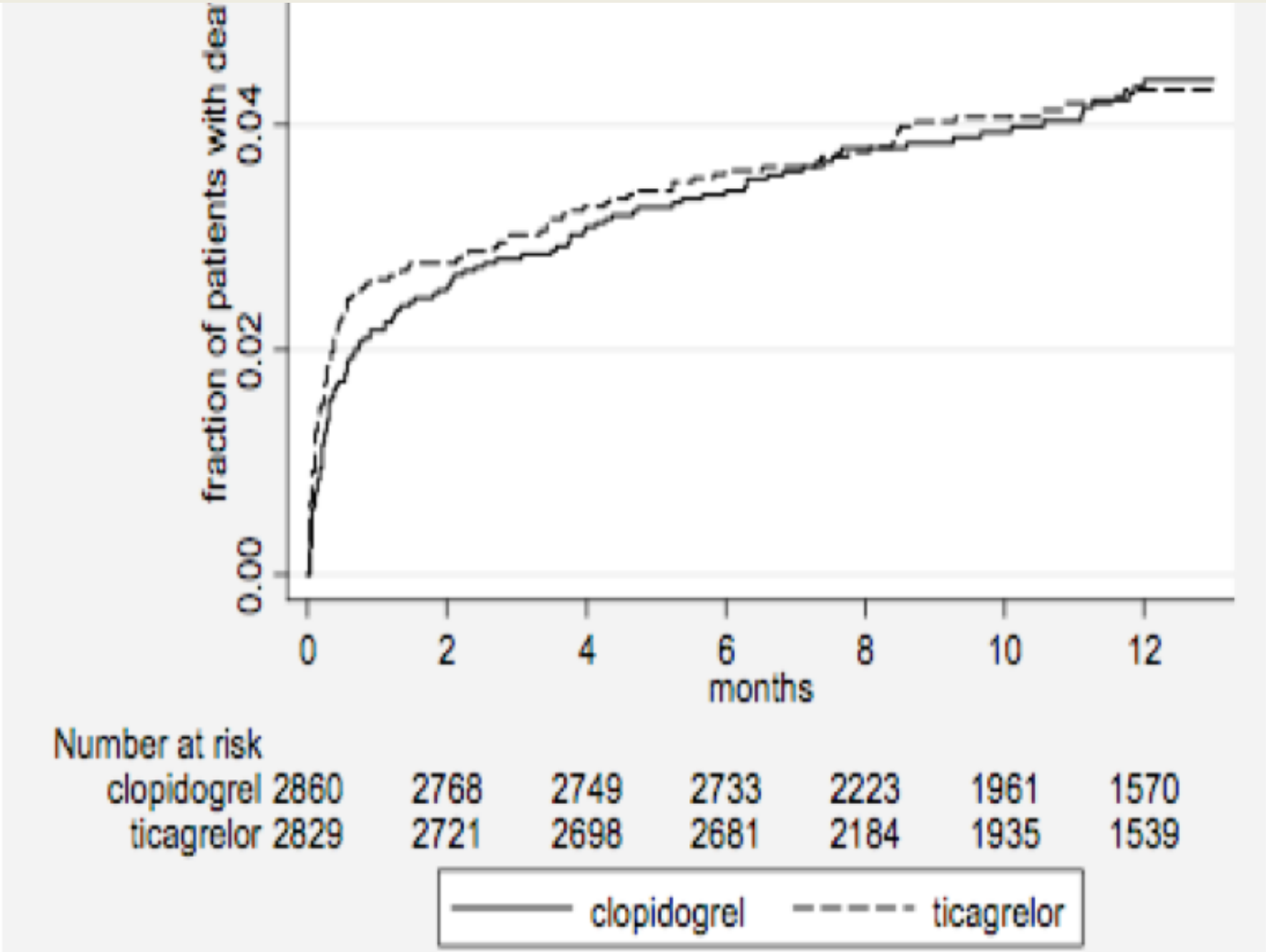
Deaths in ATLANTIC trial dependent on timing of ticagrelor administration

Mortality	Early/Late	HR (95% CI)	p-value*
Overall(30 days)	30/19	1.68 (0.94-3.01	0.08
First 24 hours	12/4	3.18 (1.02-9.90)	0.043

* - by Fisher's exact test

Serebruany, et al. Thromb Haemost, 2015

PLATO: Early “death paradox”?



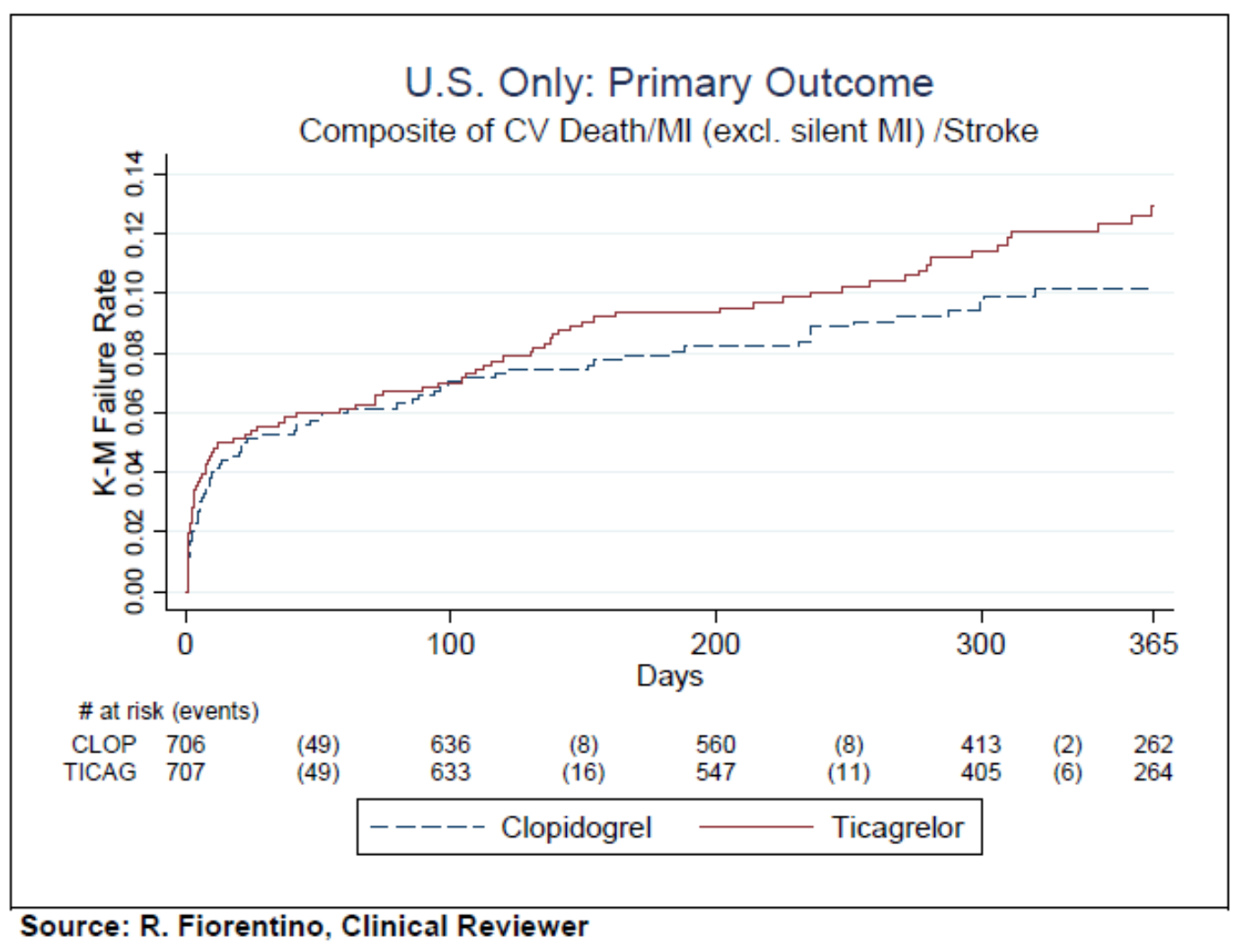
The FDA Review of Complete Response; Thomas A. Marciniak, MD – Medical Team Leader, p.18

Magic Numbers in PHILO

Clinical Outcome	Ticagrelor (n=401)	Clopidogrel (n=400)
Deaths (n)	10	7
Stroke (n)	9	6
Myocardial Infarction (n)	24	15
Major + Minor Bleeding (n)	92	56

Goto S, et al. Circulation J, 2015

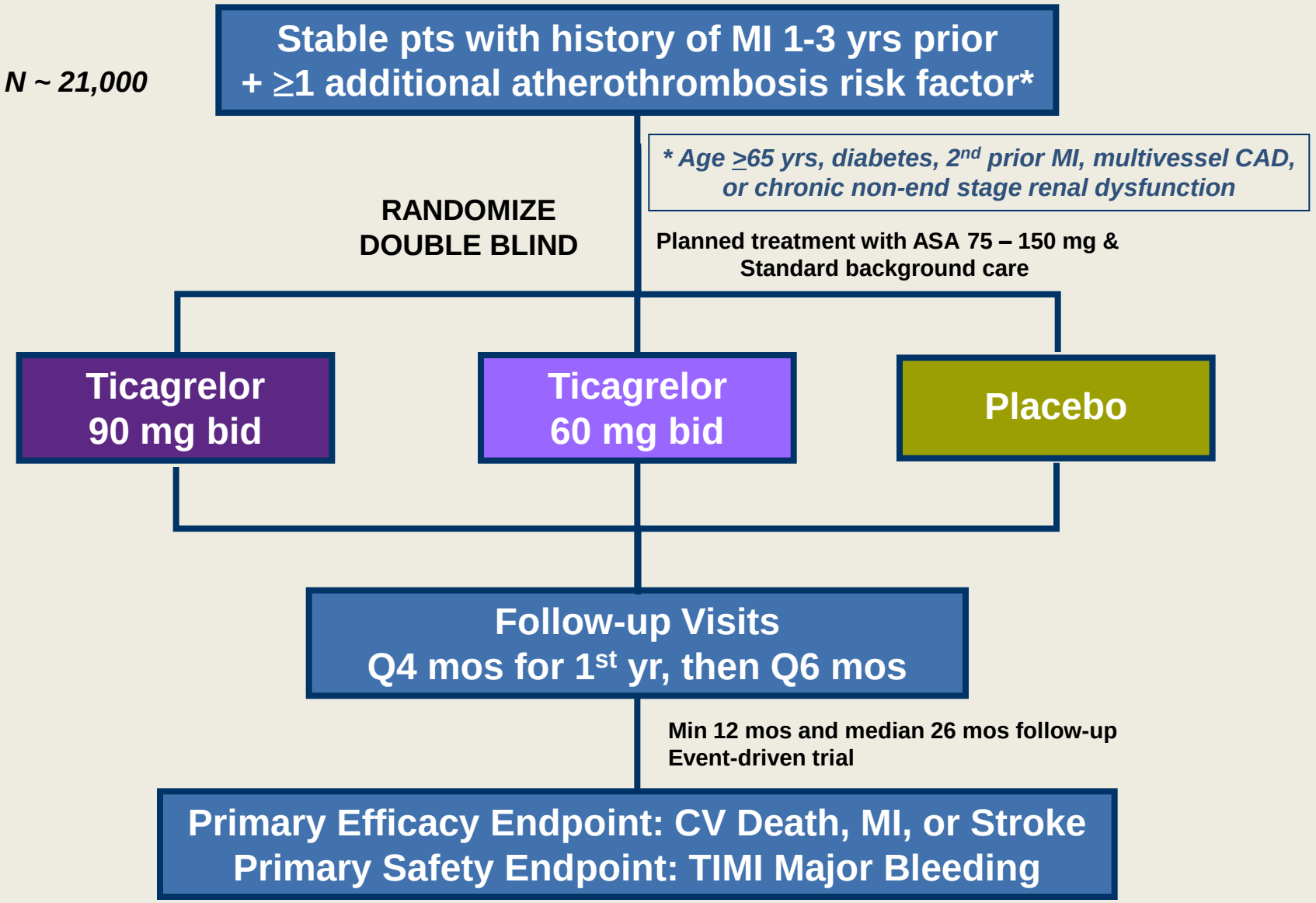
PLATO Outcomes in the USA



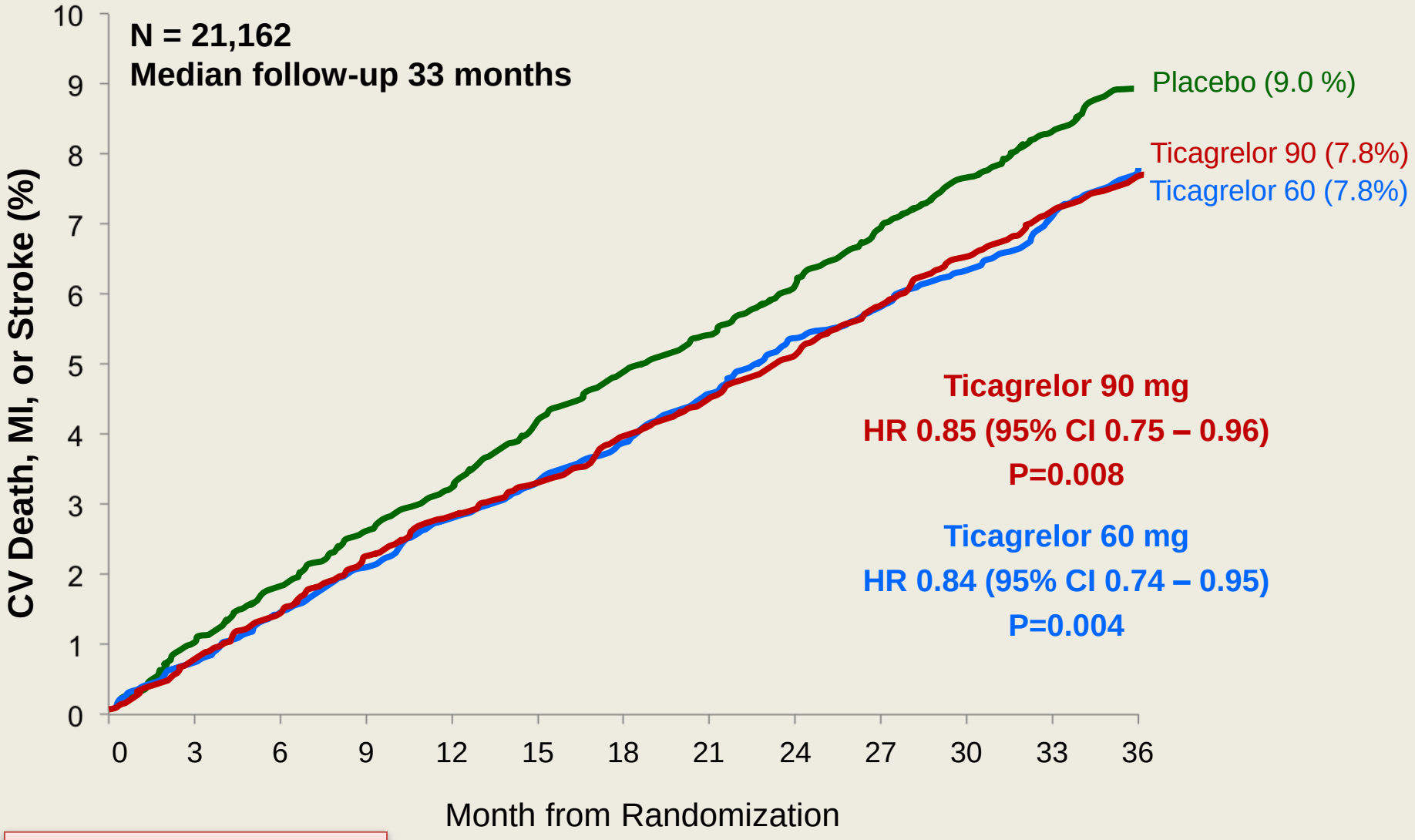
Source: R. Fiorentino, Clinical Reviewer

FDA Ticagrelor Review, 2010

PEGASUS Trial Schema



REGASUS: Primary Endpoint



Bonaca, et al., NEJM, 2015

Primary efficacy measures and discontinuations in PEGASUS

PEGASUS Arm	Efficacy Events		Benefit	Discontinuations	ΔD
	Planned*	Reported**			
Ticagrelor 90 (N=7,050)	417	493	85	1,326	705
Ticagrelor 60 (N=7,045)	425	487	91	1,139	518
Placebo (N=7,067)	518	578	R	621	R

- All data – patient numbers, * - from Statistical Analyses Plan;
- ** - PEGASUS-NEJM publication; R-reference; ΔD – differences in discontinuations compared to placebo

Bonaca et al, NEJM, 2015; Serebruany, Int J Cardiol, 2015

Vanished death benefit in PEGASUS

Trial/ Study/Arm	N	Clopidogrel	Mean follow-up	ACM	Δ-ACM
PLATO					
Ticagrelor 180mg	9,333	46%	9.2 months	399	107
Clopidogrel 75 mg	9,291	100%		506	
(HR-0.78; 95%CI 0.69-0.79, p<0.001)					
PEGASUS					
Ticagrelor 180mg	7,050	None	33 months	326	Zero
Placebo	7,067	None		326	
(HR-1.00; 95%CI 0.86-1.16, p=0.99)					

ACM – all-cause mortality

Walentin, et al NEJM, 2009, Bonaca, et al. NEJM, 2015

Oncology in PLATO vs. PEGASUS

Trial/Arm	Outcomes (n,%)	RR	95% CI	p-value
PLATO	New Onset	0.95	0.73 – 1.22	0.69
Ticagrelor	115 (1.2%)			
Clopidogrel	121 (1.3%)			
PEGASUS	Death	1.46	1.02 – 2.06	0.034
Ticagrelor	77 (1.1%)			
Placebo	53 (0.76%)			

Walentin, et al NEJM, 2009, Bonaca, et al. NEJM, 2015

Impressions:

- Despite some tactical achievements, there are no strategic wins for novel antiplatelet agents beyond clopidogrel glory
- Broad FDA approvals even with the best possible broad indications are still not sufficient for success
- Beyond controlled PLATO mortality evidence, all other studies suggest inferiority of Ticagrelor over Clopidogrel with regard to death benefit.

  Unless we want a complete vacuum (see stroke arena), the radical change of how we do cardiovascular clinical trials is mandatory needed
- The guilty party? Name one which is not
- Top priority – restore trust
- Top problem – lack of shareholders control