Time, Dose, and Duration of Antiplatelet Therapy in ACS Management

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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, Pronova**
- **Consulting: Pfizer, Sanofi-BMS, McNeil, NPS Pharma, Bayer, Eisai, mutual funds, hedge funds**
- **Speaking Bureau: Pfizer, Sanofi-BMS**
- **Patents: British Technology Group, Novartis, Boehringer Ingelheim, Eli Lilly, Pfizer, AtheroGenics, Eisai**
- **Unlabeled/Unapproved use: none**

Topics:

- Compliance
- Resistance and pseudoresistance
- Response and outcomes
- Prasugrel
- Ticagrelor

Non-compliance rates for major CV drug classes

Class	Patients (n)	NC(%)	Reference
Beta-blockers	17,035	55	Kramer J, et al.,*Am Heart J; 2006*
SSRIs	22,947	57	Cantrell C, et al., *Med Care; 2006*
Statins	11,532	21.3	Ho, P, et al., *Arch Intern Med 2006*
ARBs	34,107	29.4	Burke T, et al., *J Hypeptens; 2006*
ACE-Inhibitors	13,830	20	Eagle K, et al., *Am J Med; 2004*
Diuretics	2325	31	Van Wijk B, et al., *J Hypertens; 2005*
Calcium Channel Blockers	73,148	47	Wogen J, et al.,J Man Care Pharm; 2003

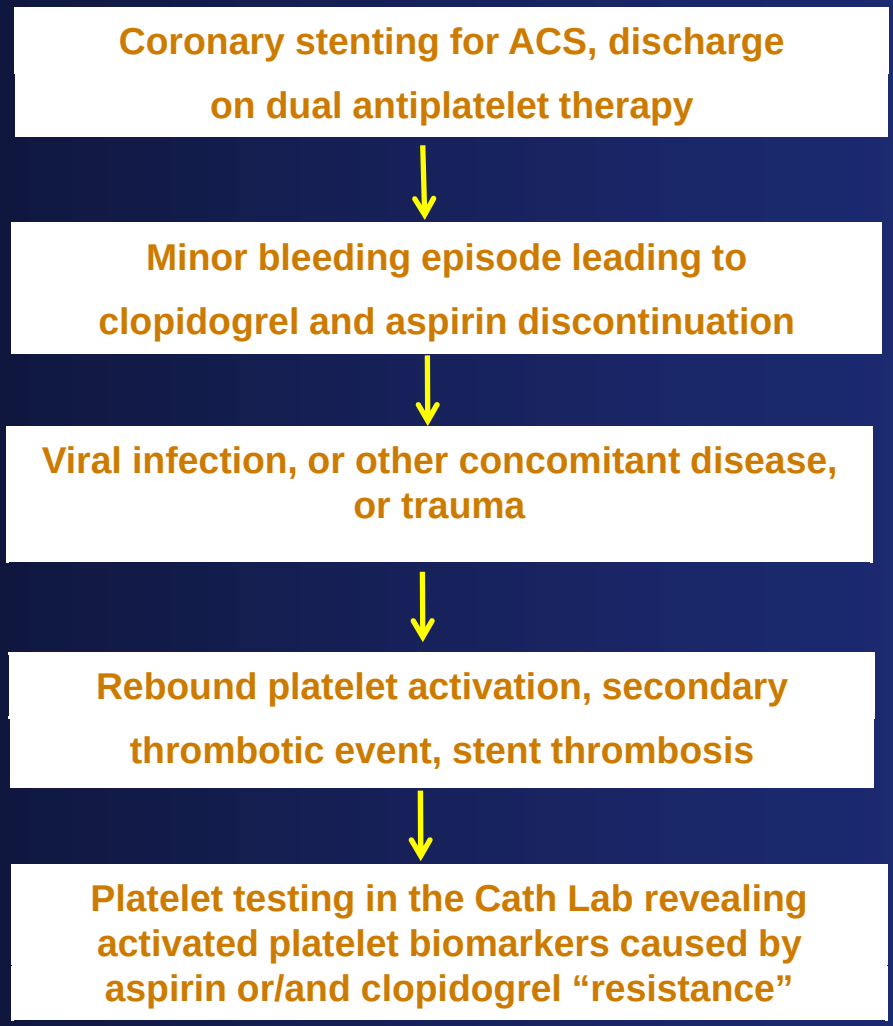
Non-compliance rates with antiplatelet agents

Agent	Patients (n)	Non-Compliance (%)	Reference
Aspirin	**5,337**	**17**	**Newby, et al.,*J Thromb Thrombolys 2003***
Ticlopidine	**159**	**11**	**Komiya, et al., *Stroke 1994***
Dipyridamole	**1,363**	**34**	**ESPRIT Study Group, *Lancet 2006***

Non-compliance rates with clopidogrel

Disease	Patients (n)	Non-Compliance (%)	Reference
CAD	**2,769**	**15.2**	**Kuchulakanti, et al., *Circulation, 2006***
Stroke **(3 months)** **(1 year)**	 **3420** **2640**	 **18.4** **38.4**	**Hamman GF, et al; *Cerebrovasc Dis 2003***
PAD	**67**	**10**	**Cassak K, et al., *Eur J Vasc Endovasc Surg 2006***

How the Patient Becomes “Resistant”?



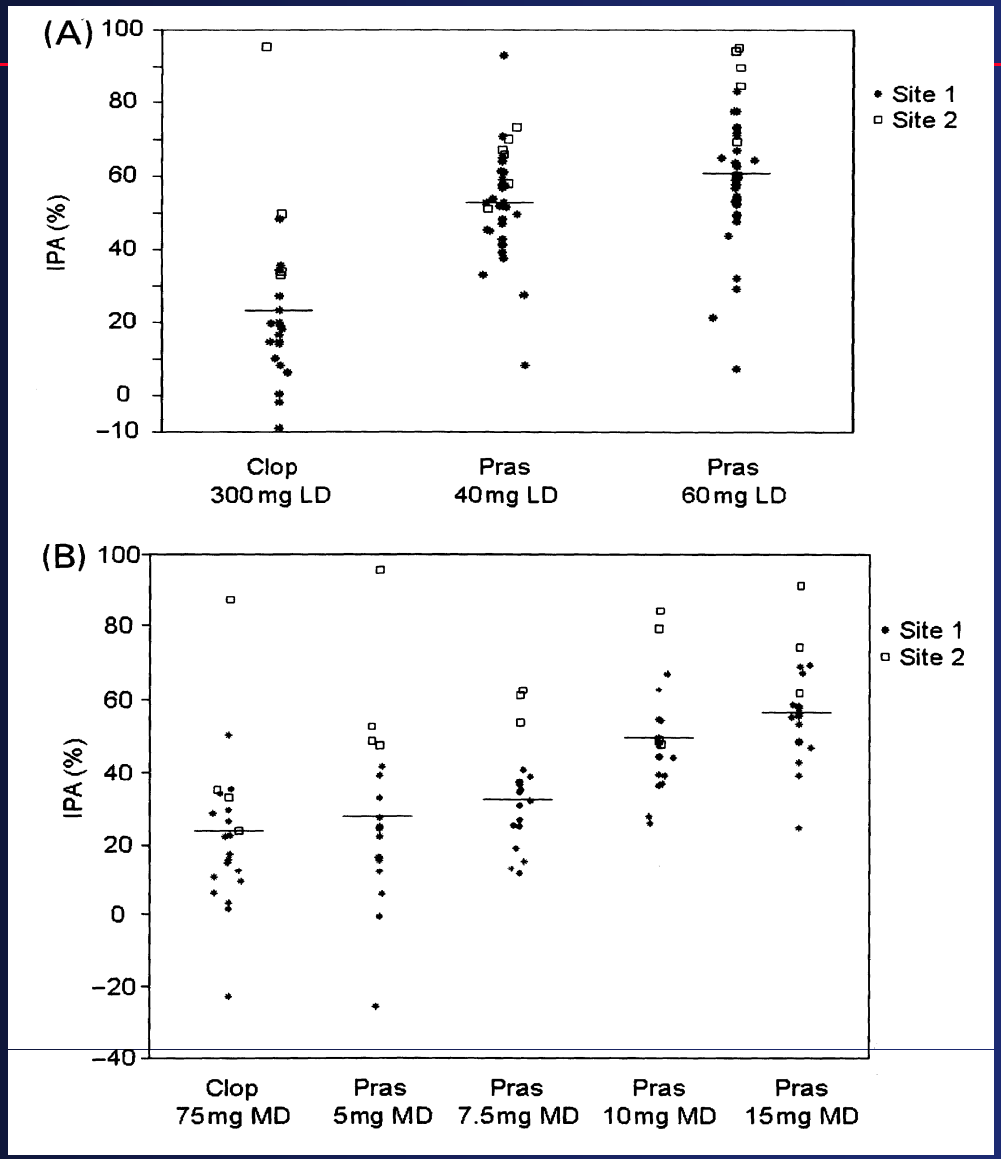
Impression:

- Non-compliance is probably the major practical cause of “resistance”, especially dominant in the outpatient chronic setting
- Claiming “resistance”, or low response requires proof that the antiplatelet agent is on board
- Defining “resistance” based solely on inadequate inhibition of platelet biomarkers is premature.

Controversy:

- “Resistance” is exclusively attributed to aspirin or clopidogrel, and is not associated with more potent antiplatelet agents/regimens

Response variability with prasugrel



Eur Heart J. 2006;

Impression

Variability of response is a common phenomena observed with any agent in general, and with aspirin or clopidogrel in particular

Before claiming “resistance”, we need to have proof that the patient is adherent to antiplatelet medications

Controversy:

- Clopidogrel “resistance” is associated with worsened vascular outcomes

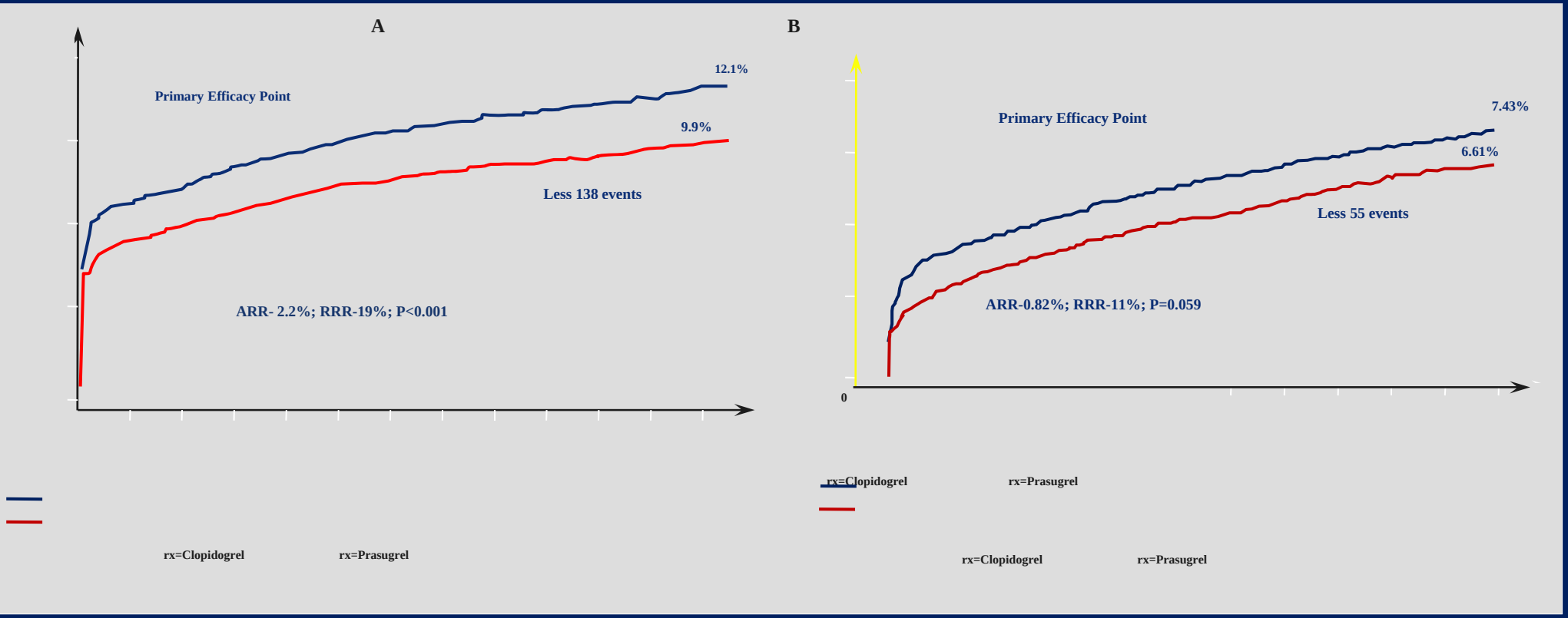
Clinical and epidemiological evidence challenging “clopidogrel resistance”

Finding	Source
A. Randomized evidence	
Absolute mortality benefit with no-load regimen	COMMIT
Excess bleeding + lack of efficacy post-stroke	MATCH
Excess bleeding + lack of efficacy in primary prevention	CHARISMA
B. Epidemiological evidence	
Higher patient non-compliance than “resistance” rates	15-38.4% versus 4.2-15%*
Lower stent thrombosis than “resistance” rates	0.5-3.4% versus 4.2-15%*

*** - multiple publications**

AJC, 2007

The TRITON Efficacy Controversy



A : All Adjudicated Events NEJM; 2007

B: Investigator Reported Events FDA; 2009

Impression:

- Randomized and epidemiological data do not support the concept that clopidogrel “resistance” is clinically relevant

- Unless further evidence became available, clopidogrel “resistance” represents a laboratory finding

Conroversy:

- Higher degree of platelet inhibition is associated with better clinical outcomes

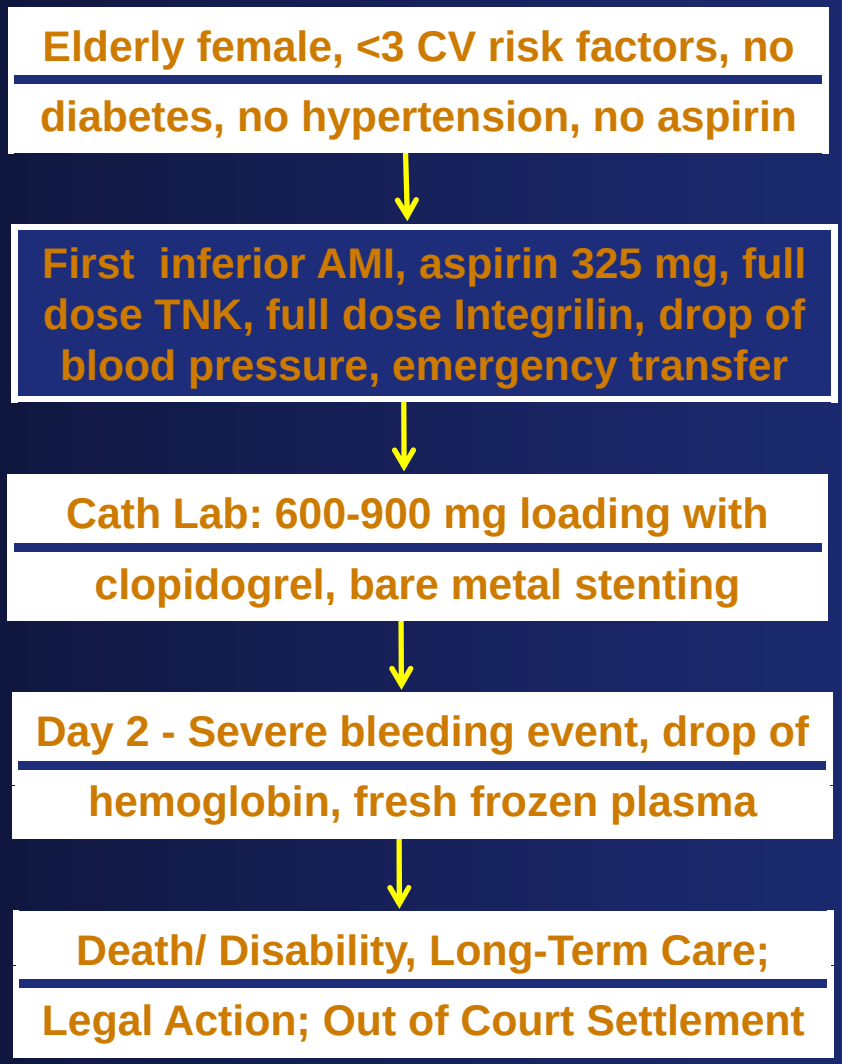
Degree of Platelet Inhibition and Clinical Outcomes (Randomized Evidence)

Trial(s)	Agent/Dose	IPA (%)	Outcome
ESPS-2, ESPRIT	50mg ASA + 400mg Dipyridamole	15-20	ARR - second stroke
ISIS-2	ASA 160 mg	25-35	AMR - AMI
COMMIT	Clopidogrel 75 mg (no load)	40-45	AMR -AMI
CURE, CREDO	Clopidogrel 300/75 mg	45-55	RRR -CV
TRITON	Prasugrel 60/10mg;	60-70	Front loading benefit only, no mortality reduction
PURSUIT, EPIC	GPIIb/IIIa Inhibitors (I/V)	80-85	Periprocedural, combined endpoint benefit
OPUS, BRAVO	GPIIb/IIIa Inhibitors (oral)	80-90	Excess CV deaths

ARR=absolute risk reduction; AMR=absolute mortality reduction; RRR= relative risk reduction; CV = cardiovascular

EHJ, 2007

Pathway to Trouble

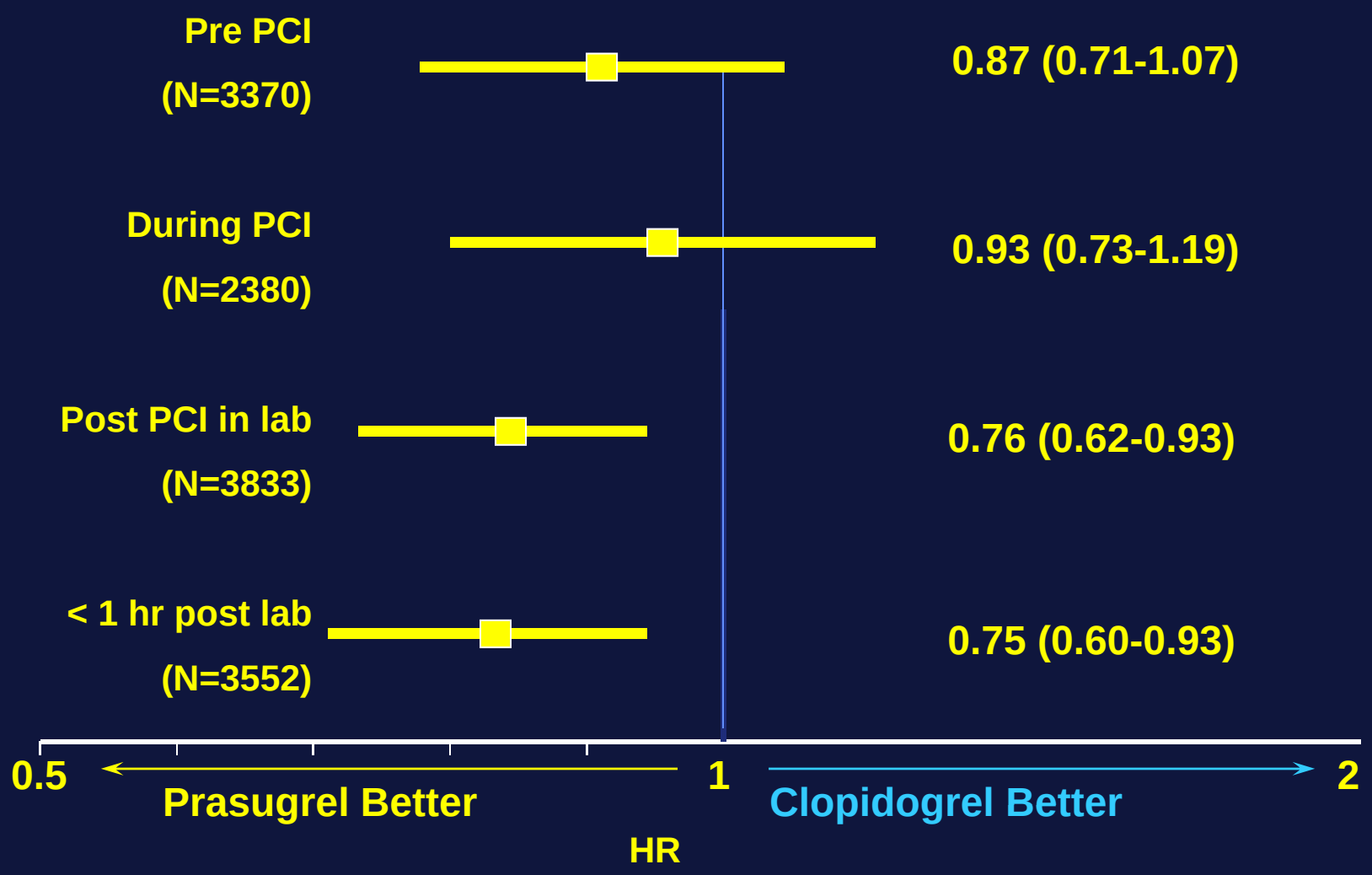


Impression:

- Based on the randomized evidence, higher degree of platelet inhibition is not associated with better vascular outcomes

TRITON TIMI-38

CV Death, MI, Stroke Timing of LD



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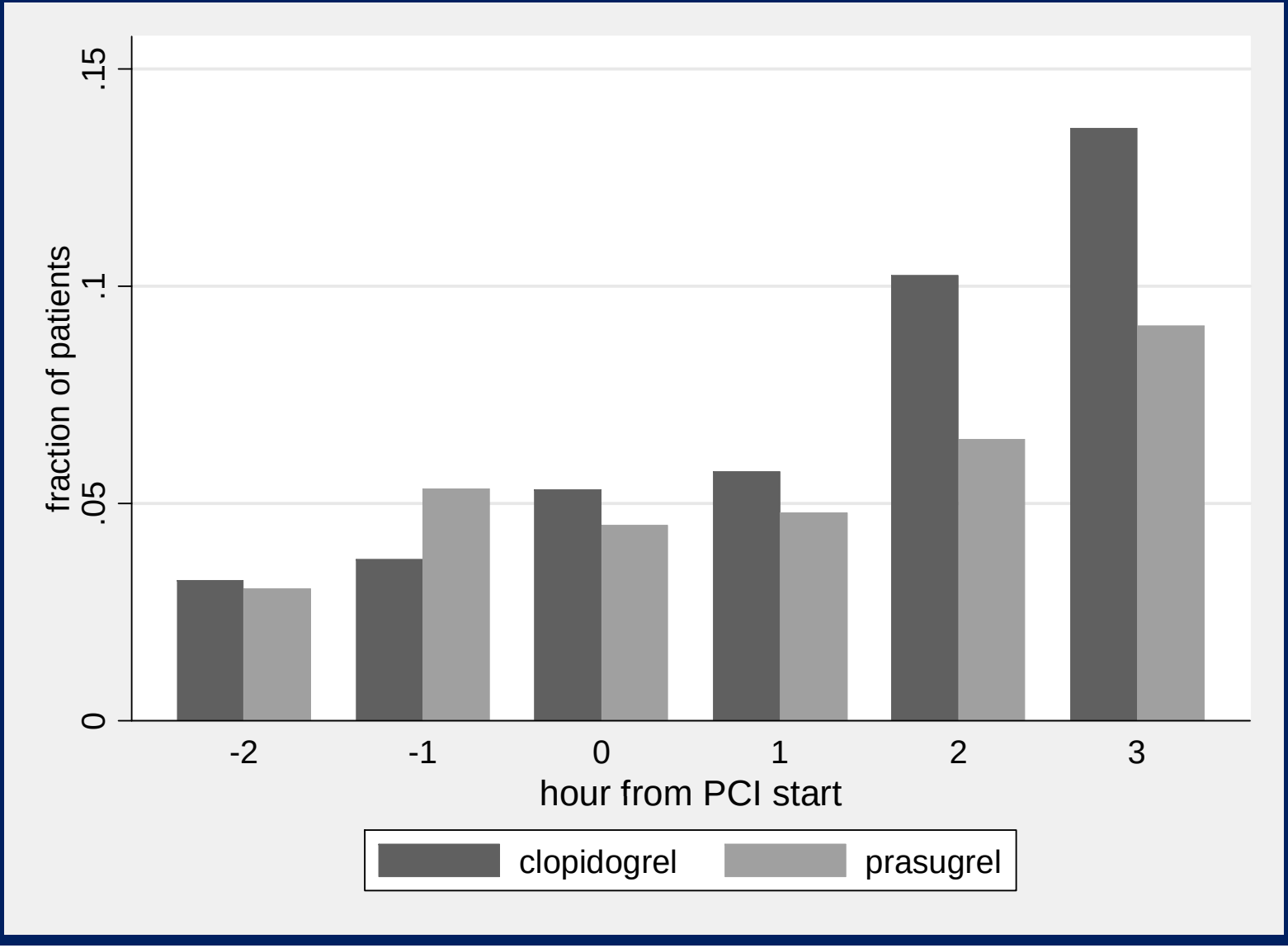
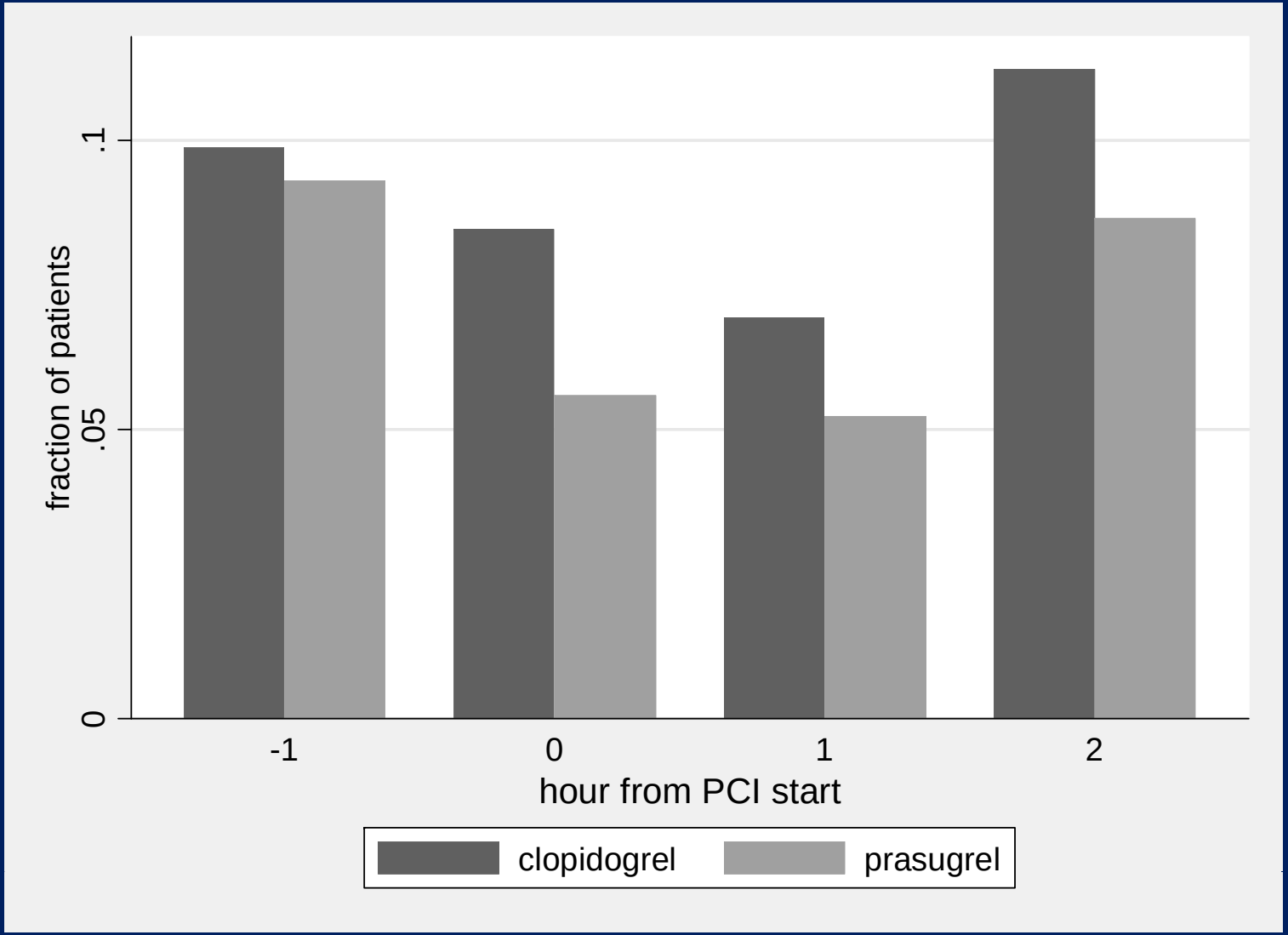
TIMI Study Group. Data on file

Events in UA/NSTEMI and loading time



Endpoint Events in STEMI

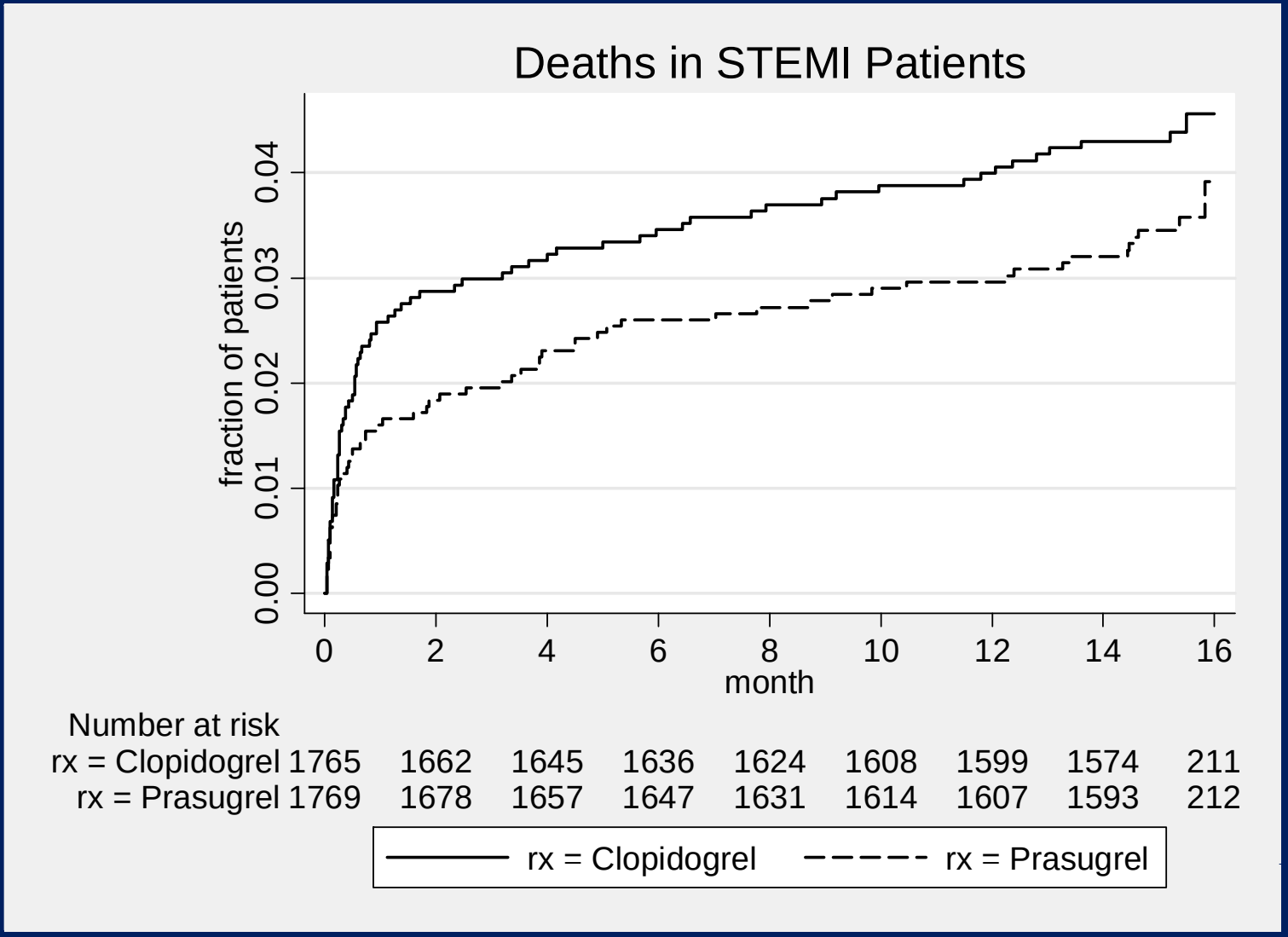


Site-Reported First Event Types in TRITON

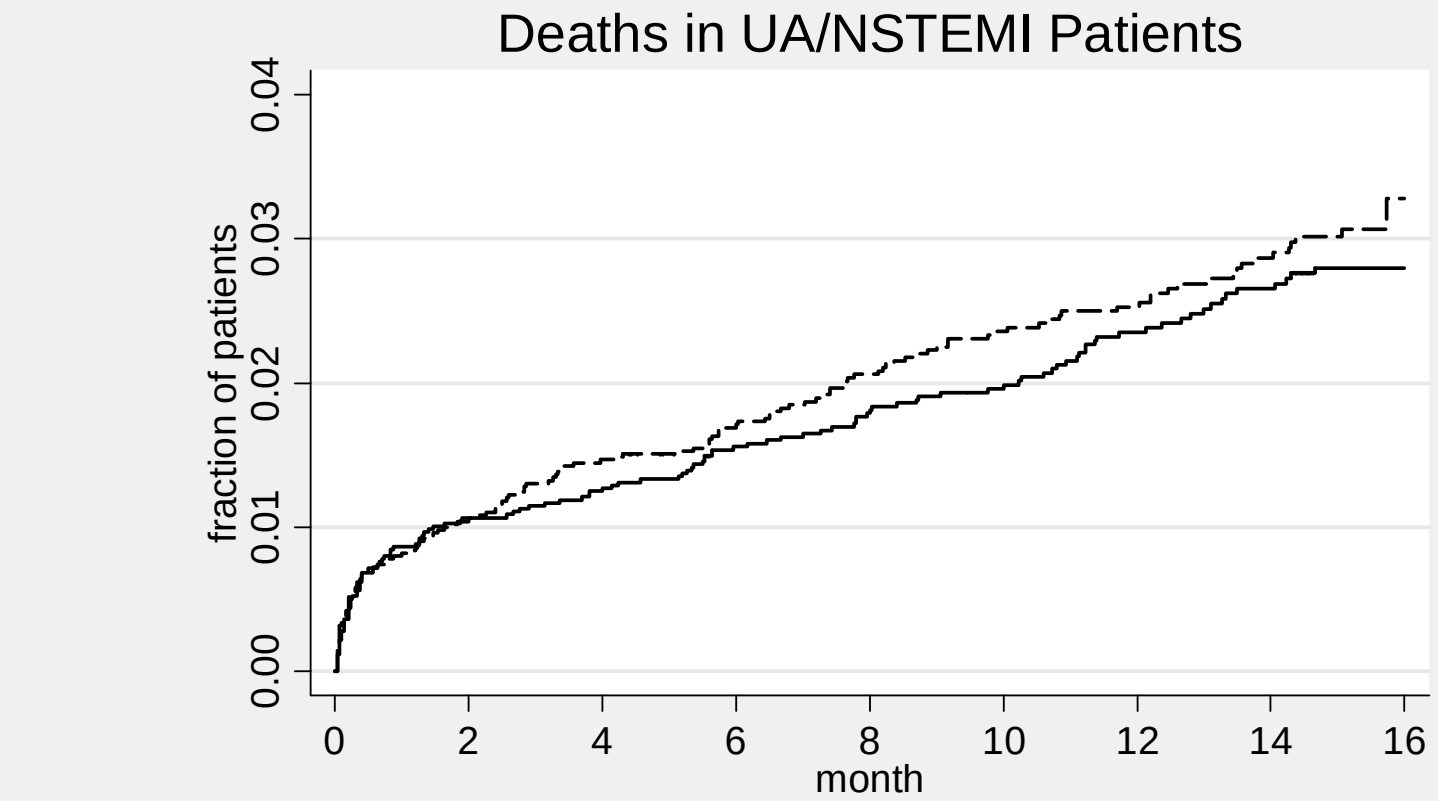
	UA/NSTEMI			STEMI			all		
	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ
MI	235	175	60	62	48	14	297	223	74
stroke	43	43	0	24	22	2	67	65	2
death	83	113	**-30**	58	49	9	141	162	**-21**

The FDA Secondary Prasugrel Review

Deaths in STEMI Patients in TRITON



Deaths in UA/NSTEMI Patients in TAAL



Number at risk									
rx = Clopidogrel	5029	4867	4828	4735	4190	3562	3252	2767	300
rx = Prasugrel	5044	4896	4837	4742	4149	3542	3203	2695	293

rx = Clopidogrel rx = Prasugrel

Adjudication Controversy
Not all MI's are "born equal"

"Ordinarily, the investigator reported events and the adjudicated events differed little, but, in TRITON, only about half of the events were identified by investigators"

The FDA Pasugrel Secondary Report, page 1; Available for download @ http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-00-FDA.htm

PROVE-IT MI Definition

END POINTS

The primary efficacy outcome measure was the time from randomization until the first occurrence of a component of the primary end point: death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting (if these procedures were performed at least 30 days after randomization), and stroke. Myocardial infarction was defined by the presence of symptoms suggestive of ischemia or infarction, with either electrocardiographic evidence (new Q waves in two or more leads) or cardiac-marker evidence of infarction, according to the standard TIMI and American College of Cardiology definition.[12,13] Unstable angina was defined as ischemic discomfort at rest for at least 10 minutes prompting rehospitalization, combined with one of the following: ST-segment or T-wave changes, cardiac-marker elevations that were above the upper limit of normal but did not meet the criteria for myocardial infarction, or a second episode of ischemic chest discomfort lasting more than 10 minutes and that was distinct from the episode that had prompted hospitalization. Secondary end points were the risk of death from coronary heart

board. Rules for stopping the study early in the event that the superiority of either treatment was established were not prespecified.

All efficacy analyses are based on the intention-to-treat principle. Estimates of the hazard ratios and associated 95 percent confidence intervals comparing pravastatin with atorvastatin were obtained with the use of the Cox proportional-hazards model, with randomized treatment as the covariate and stratification according to the receipt of gatifloxacin or placebo. (Using the two-by-two factorial design, we conducted a preliminary test for interaction and found none. For the primary end point, the interaction P value was 0.90 and the hazard ratios comparing pravastatin with atorvastatin were almost identical for the gatifloxacin and placebo groups.) When it was determined that noninferiority was not demonstrated, the subsequent assessment of superiority was carried out with the use of two-sided confidence intervals. The investigators designed the trial and had free and complete access to the data. Data coordination was performed by the Nottingham Clinical Research Group (see the Appendix). Investigators at TIMI, the sponsor, and members of the Nottingham Clinical Research Group performed data analysis jointly.

C.Cannon,et al, NEJM; 2004

JUMBO MI Definition

Trial End Points

The primary end point of the trial was non–CABG-related "significant hemorrhage" at 30 days, defined as the composite of TIMI major and minor hemorrhage. Hemorrhagic events were classified as major or minor by use of standard TIMI definitions[27]: a clinically overt (including imaging) hemorrhage with a hemoglobin drop >5 g/dL was considered major, and a clinically overt hemorrhage with a hemoglobin drop of 3 to ≤5 g/dL was considered minor. A clinically overt bleeding episode with <3 g/dL drop in hemoglobin was considered minimal.[28] Additional safety and efficacy end points included major adverse cardiac event (MACE) components individually and in combination. MACE were defined as any one of the following, occurring through the 30-day visit after PCI: (1) death (all-cause mortality), (2) myocardial infarction (MI), (3) stroke, (4) recurrent myocardial ischemia requiring hospitalization, and (5) clinical target vessel thrombosis (CTVT) defined either as total or subtotal occlusion of the target vessel documented angiographically and occurring ≥2 hours after the loading dose of study drug or as urgent target vessel revascularization (any PCI or CABG) performed in response to ischemic symptoms involving the epicardial coronary artery that was the target vessel for the index procedure. Patients who did not undergo repeated coronary angiography after the initial procedure could not be determined to have CTVT. Major safety and efficacy end points were adjudicated by an independent clinical events committee that was blinded to treatment assignment.

The definition of MI, adapted from the standard American College of Cardiology/American Heart Association (ACC/AHA) definitions,[29,30] was dependent on pre-event biomarkers and the timing of the event. In all cases, if CK-MB was greater than the upper limit of normal (ULN) at the time of the suspected event, both an increase by ≥50% over the previous value and documentation that CK-MB was decreasing before the suspected recurrent MI were required. Within 24 hours after PCI, a subject would be considered to have had an MI with the ensuing CK-MB >3 times the ULN; within 24 hours of CABG, the threshold was CK-MB >10 times the ULN. Periprocedural MI could also be determined by either development of new, abnormal Q waves considered to be distinct from the evolution of an index MI or pathological findings of a new MI thought to be distinct from an MI in evolution before randomization. If the suspected MI was not associated with a procedure, the definition required CK-MB or cardiac troponin greater than ULN and either chest pain or ischemic discomfort lasting >20 minutes at rest or hemodynamic decompensation.

prasugrel, 199; intermediate-dose prasugrel, 200; high-dose prasugrel, 251; and clopidogrel, 254. A total of 848 patients (93.7%) completed the protocol; 53 (6%) discontinued for adverse events, personal decision, protocol violations, or physician decision; and 3 (0.3%) were lost to follow-up. There were no statistically significant differences in reasons for discontinuation from the trial among treatment groups.

Baseline and Procedural Characteristics

The baseline characteristics (Table 1) were balanced, with no significant differences between prasugrel- and clopidogrel-treated patients. Most patients (77%) were men; the median age was 60 years; and diabetes was frequent (27%). Unstable angina or NSTEMI was present in 40% of patients before PCI. Physician investigators elected to use GP IIb/IIIa inhibitors in 71% of patients.

As would be expected from the study design, nearly all patients underwent a PCI (99%), with 99% of patients who had PCI receiving at least 1 intracoronary stent. Multiple (≥2) stents were used in 35%. At least 1 drug-eluting stent was used in 54% of subjects. These procedural characteristics were well balanced among treatment groups.

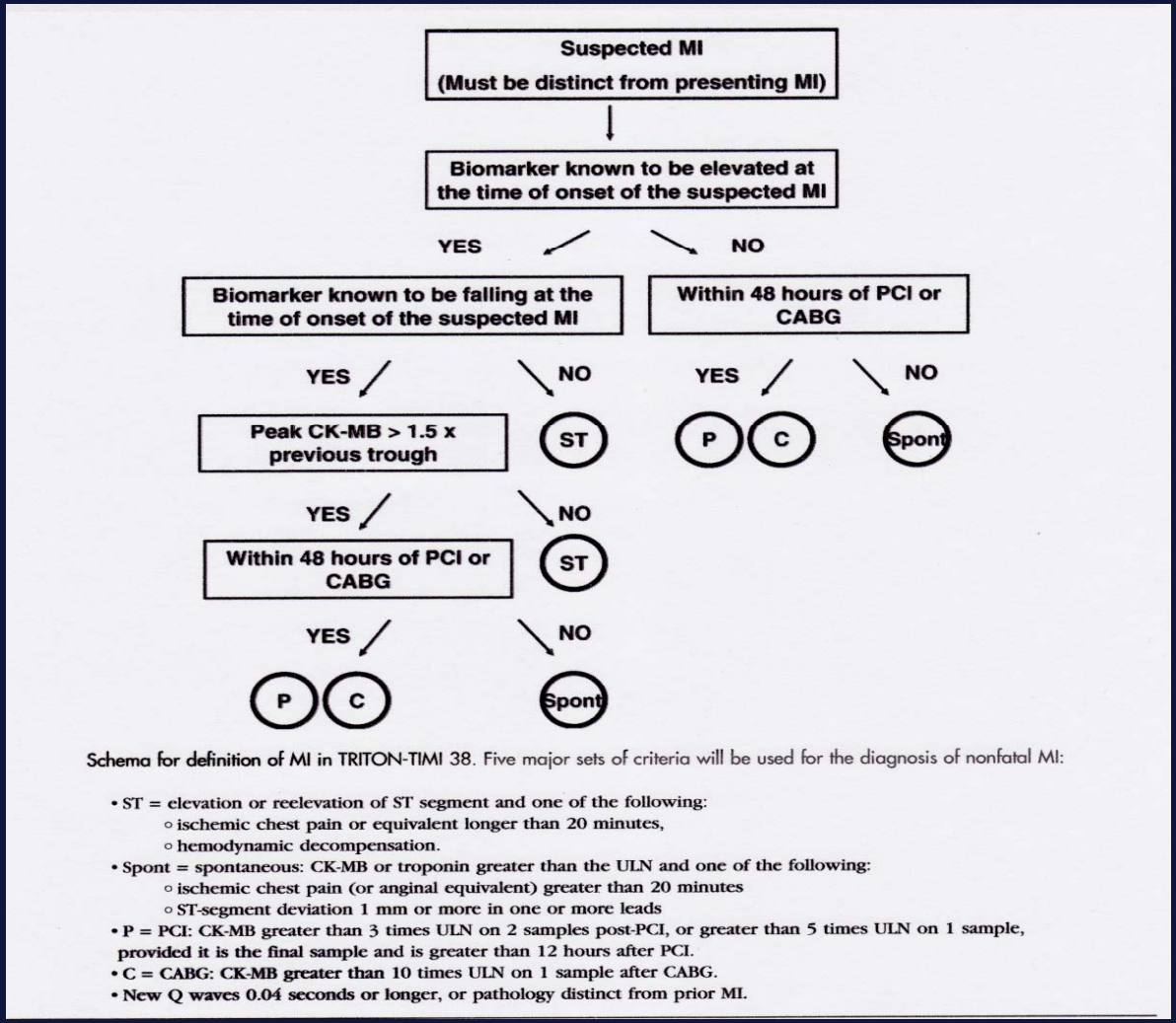
Safety

In all groups combined, bleeding rates were low; 0.7% of patients experienced major bleeding, 1.1% experienced minor bleeding, and 2.4% experienced minimal bleeding. As would be expected in a trial of PCI, most of the bleeding episodes were related to instrumentation (68%), and the most frequent site of bleeding was the vascular access site. Most overall bleeding events (76%), including 4 of the 6 major hemorrhages, occurred during the index hospitalization. An intracranial hemorrhage (subdural hematoma) occurred in 1 patient (0.1%).

Major safety end points are summarized in Table 2. When examined by treatment group, there were low rates of major bleeding for all treatment groups (0.5% for prasugrel com-

S. Wiviott, et al. Circulation 2005

TRITON MI Definition



Schema for definition of MI in TRITON-TIMI 38. Five major sets of criteria will be used for the diagnosis of nonfatal MI:

- ST = elevation or reelevation of ST segment and one of the following:
  - ischemic chest pain or equivalent longer than 20 minutes,
  - hemodynamic decompensation.
- Spont = spontaneous: CK-MB or troponin greater than the ULN and one of the following:
  - ischemic chest pain (or anginal equivalent) greater than 20 minutes
  - ST-segment deviation 1 mm or more in one or more leads
- P = PCI: CK-MB greater than 3 times ULN on 2 samples post-PCI, or greater than 5 times ULN on 1 sample, provided it is the final sample and is greater than 12 hours after PCI.
- C = CABG: CK-MB greater than 10 times ULN on 1 sample after CABG.
- New Q waves 0.04 seconds or longer, or pathology distinct from prior MI.

S. Wiviott, et al. Am Heart J; 2006

End Points in Recent ACS Trials

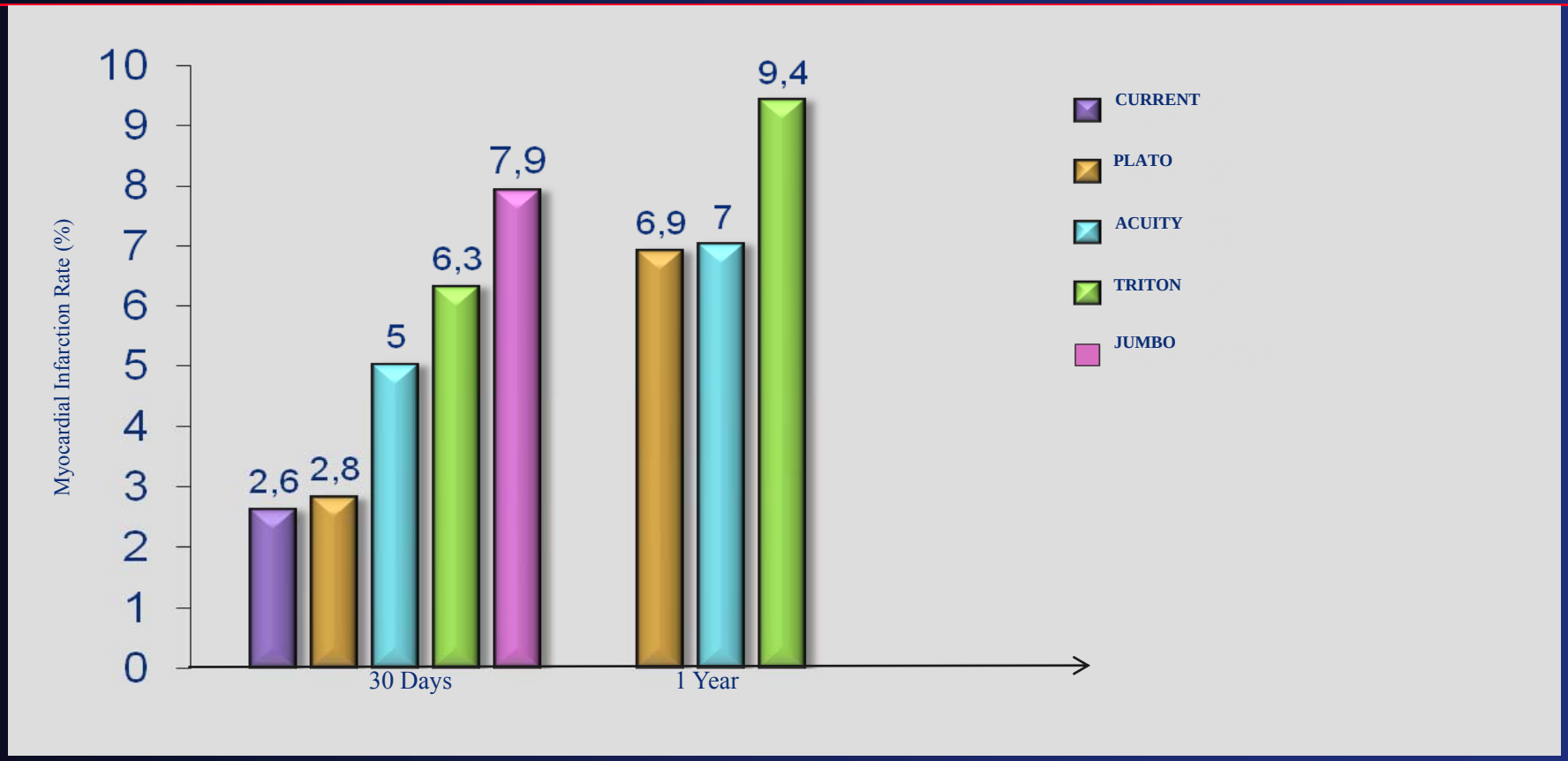
Trial	N	Indication	CABG	STE-MI (%)	Follow-up (months)	Death (%)	Stroke (%)	MI (%)
PROVE-IT	4,162	ACS	No	34	18-36	2.2-3.2	1.0	6.6 - 7.4
ACUITY	13,819	ACS	Yes	35	12	3.9	NR	6.9 -7.1*
TRITON**	6,795	ACS	No	26	6-15	3.2	1.0	9.7*

N - number of patients treated with clopidogrel; ; NR – not reported; * - fatal and non fatal MI's;

**- clopidogrel arm

V. Serebruany, Am J Cardiol; 2008

MI Rates in Recent ACS Trials



Serebruany VL, et al Thromb Haemost 2009; 101:14-22 (updated)

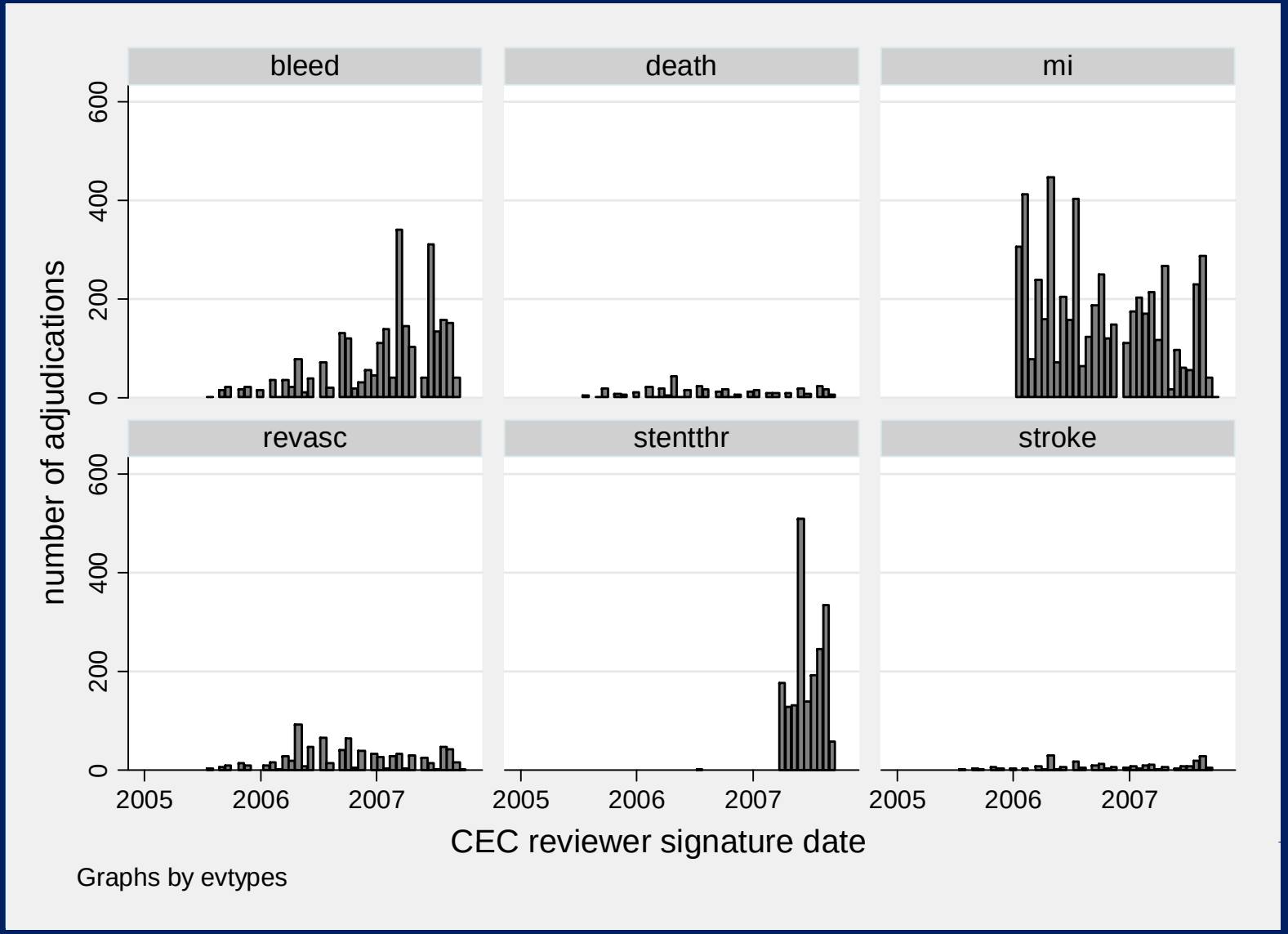
Comparative characteristics of MI's in TRITON trial

Type of MI (n)	Difference between arms (n)	Adjudicated	Associated Mortality (%)	Associated Heart Failure	Timing of MI	Excessive MI rate for ACS trials
SRE* (298/226)	72	Yes	14.2 - 18.8	115-Clopidogrel 114-Prasugrel	Mostly periprocedural	No
AAE** (620/475)	145	Yes	2.8 – 5.3	No	Across the entire follow-up	Yes

* SRE – site reported events; **- AAE - all adjudicated events; *** - to be reported in the FDAA Action Package

Serebruany VL; Cardiology, 2009; 114: 126-9.

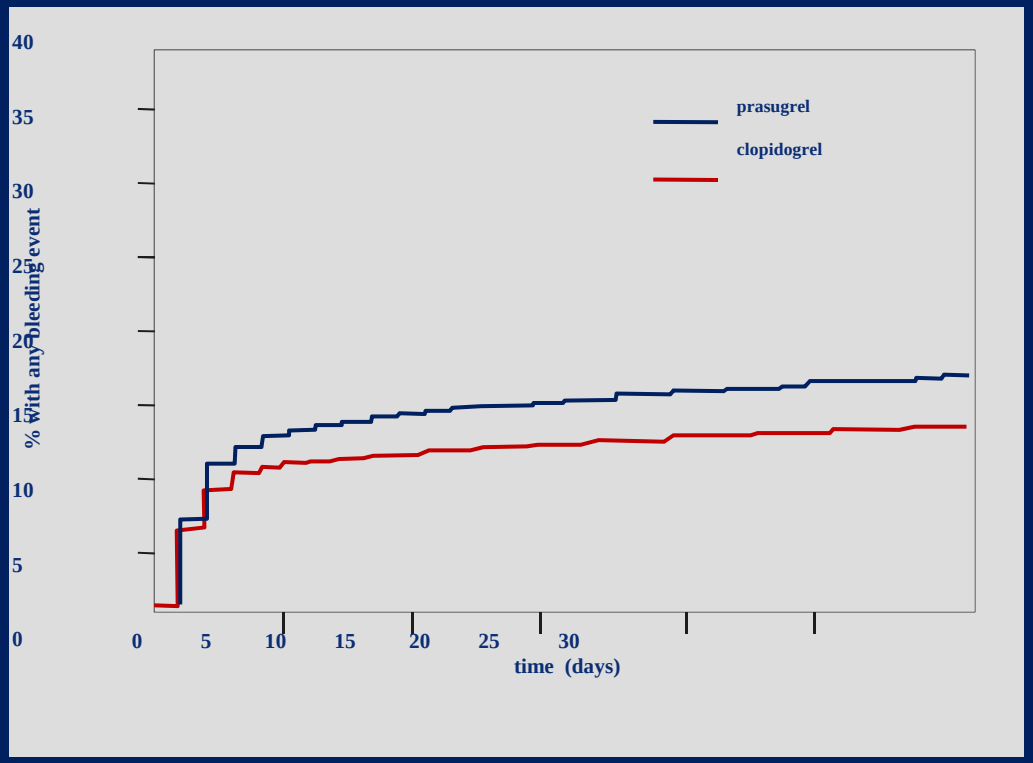
Timing of Event Adjudications in TRITON

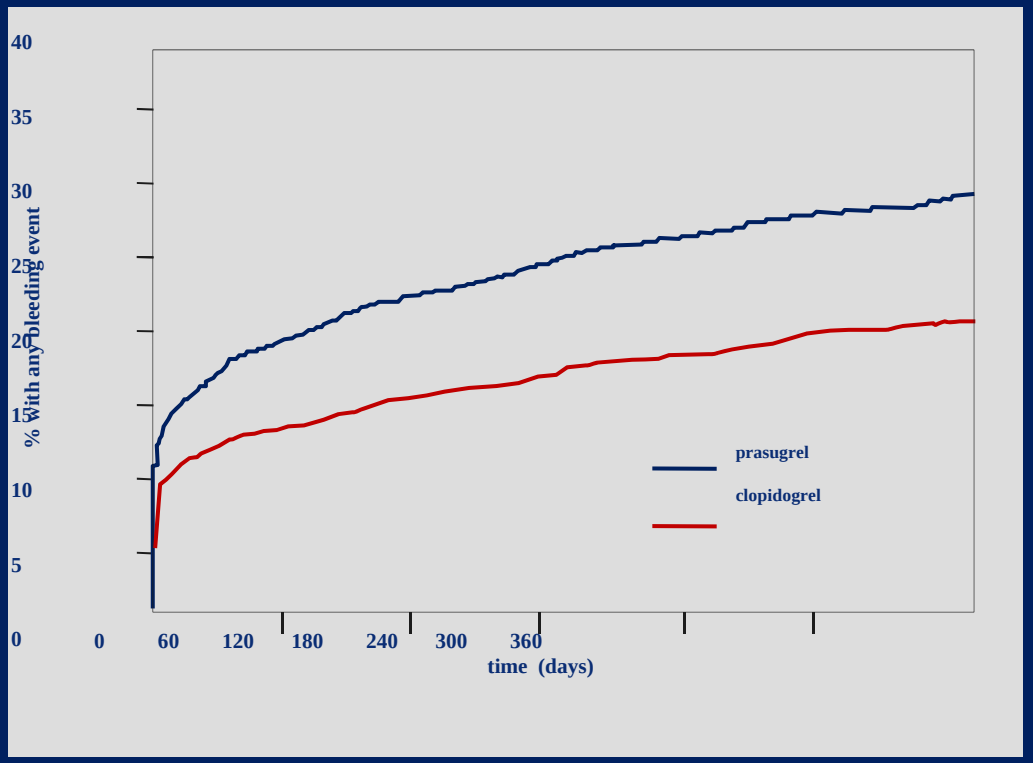


Balanced Primary Endpoint in TRITON

Event	Prasugrel	Clopidogrel	Benefit
CV Death	133	150	
Fatal Bleeding	21	5	
Nonfatal MI	475	620	
Nonfatal Stroke	61	60	
Life-threatening bleeds	85	56	
TOTAL	775	891	13%

Distribution of Any Bleeding Event in TRITON





Day 0 -30

Day 0 - 360

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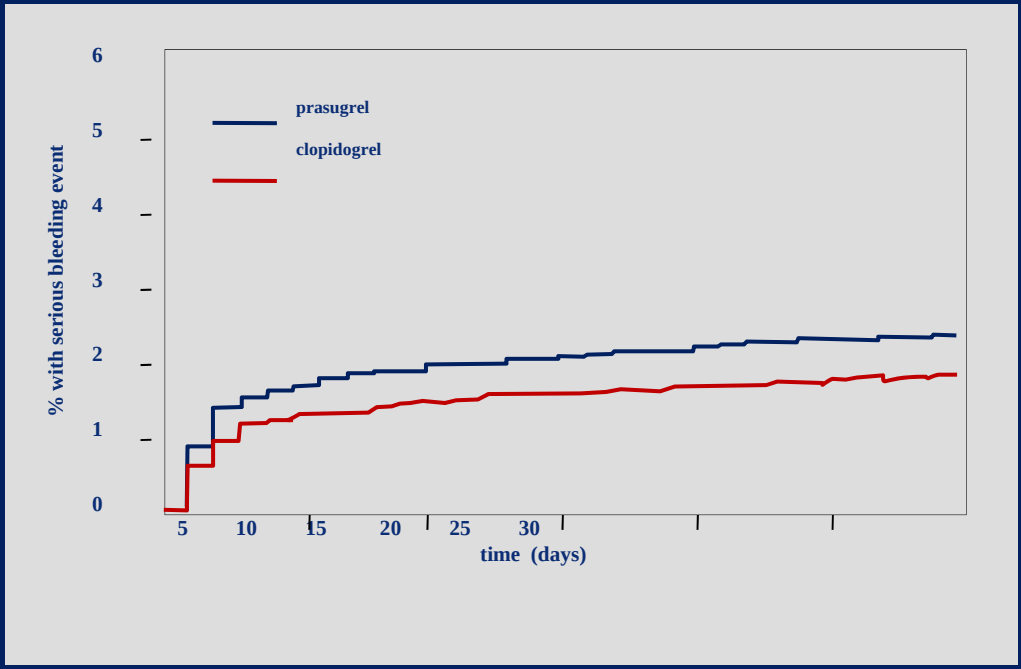
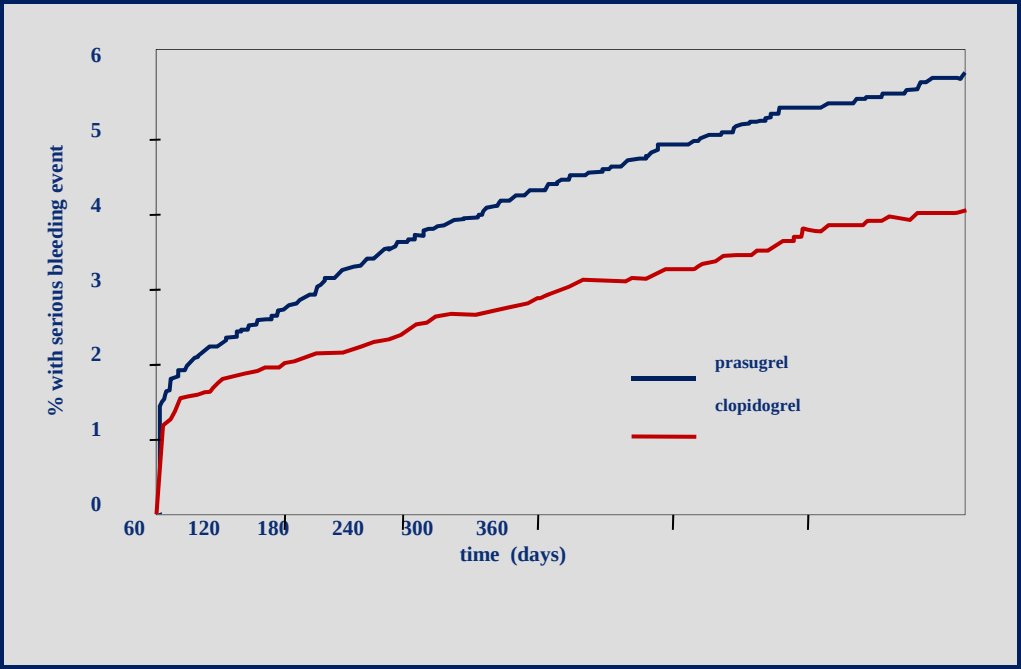
Distribution of Serious Bleeding Events in TRITON



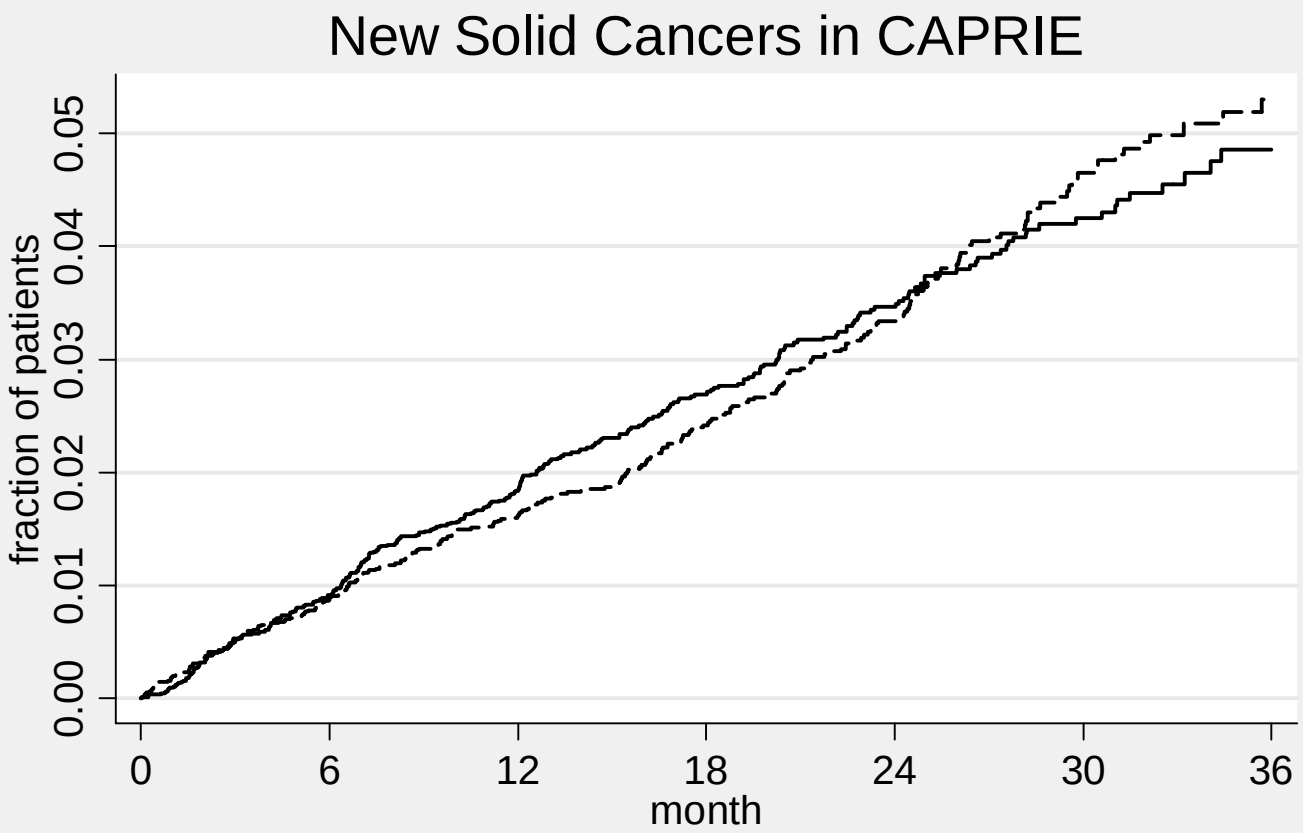


Day 0 -30

Day 0 - 360

The FDA Secondary Prasugrel Review

K-M Incidence Plot of New Solid Cancers in CAPRIE

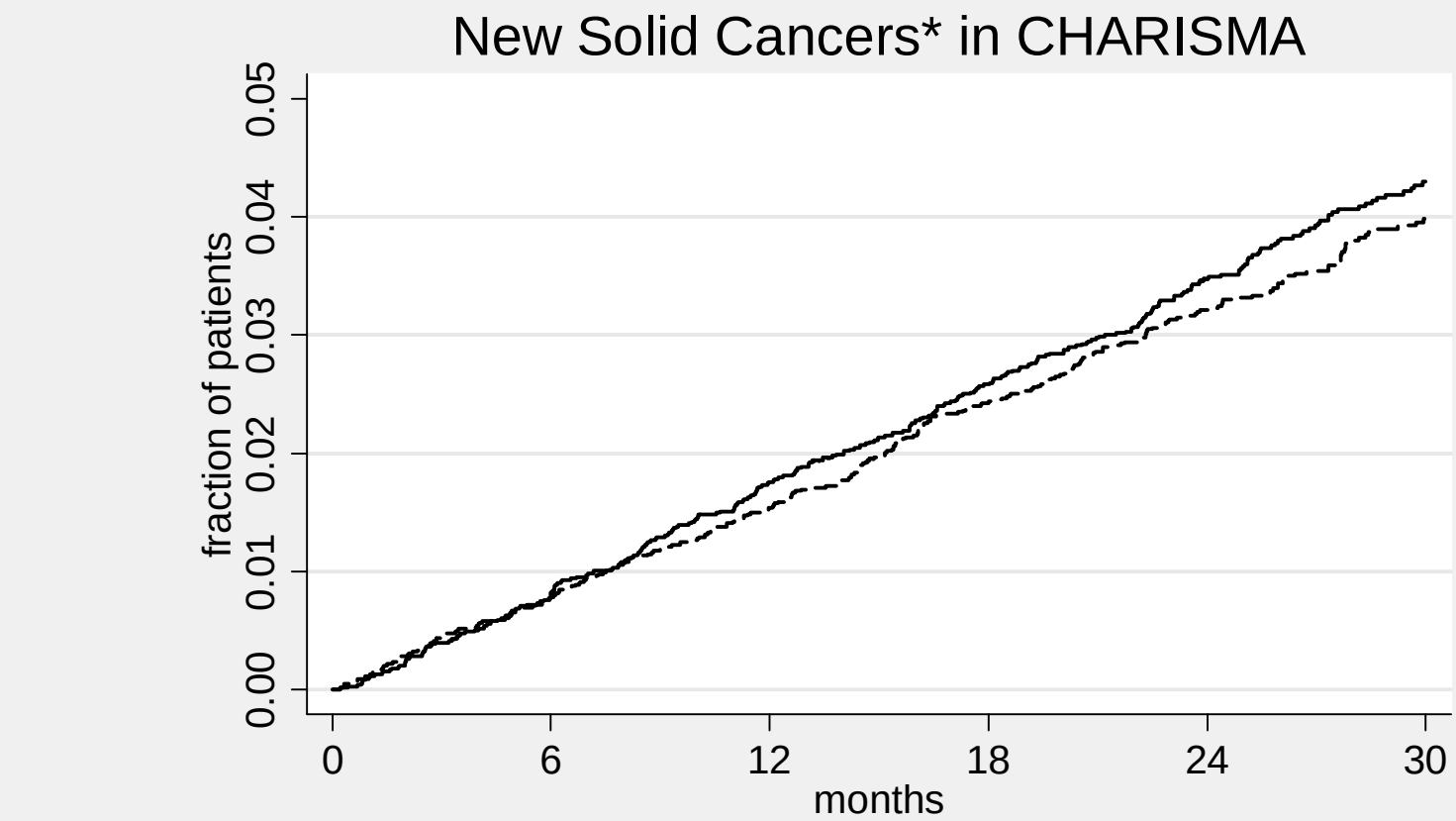


Number at risk

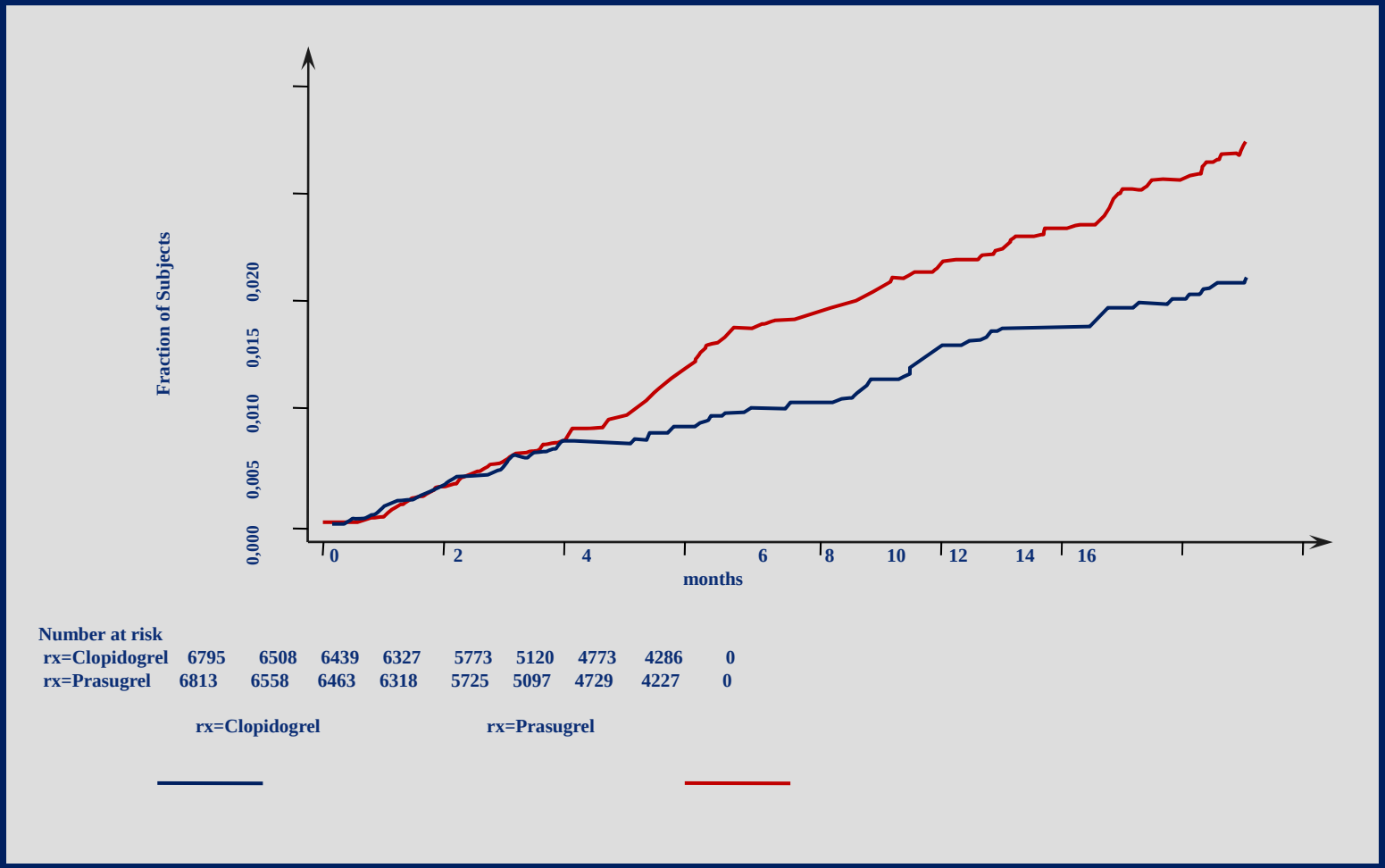
rx = aspirin	9553	8443	7680	5296	3831	1782	865
rx = clopidogel	9543	8424	7658	5276	3800	1774	853

rx = aspirin rx = clopidogel

K-M Incidence Plot for New Solid Cancers in CHARISMA

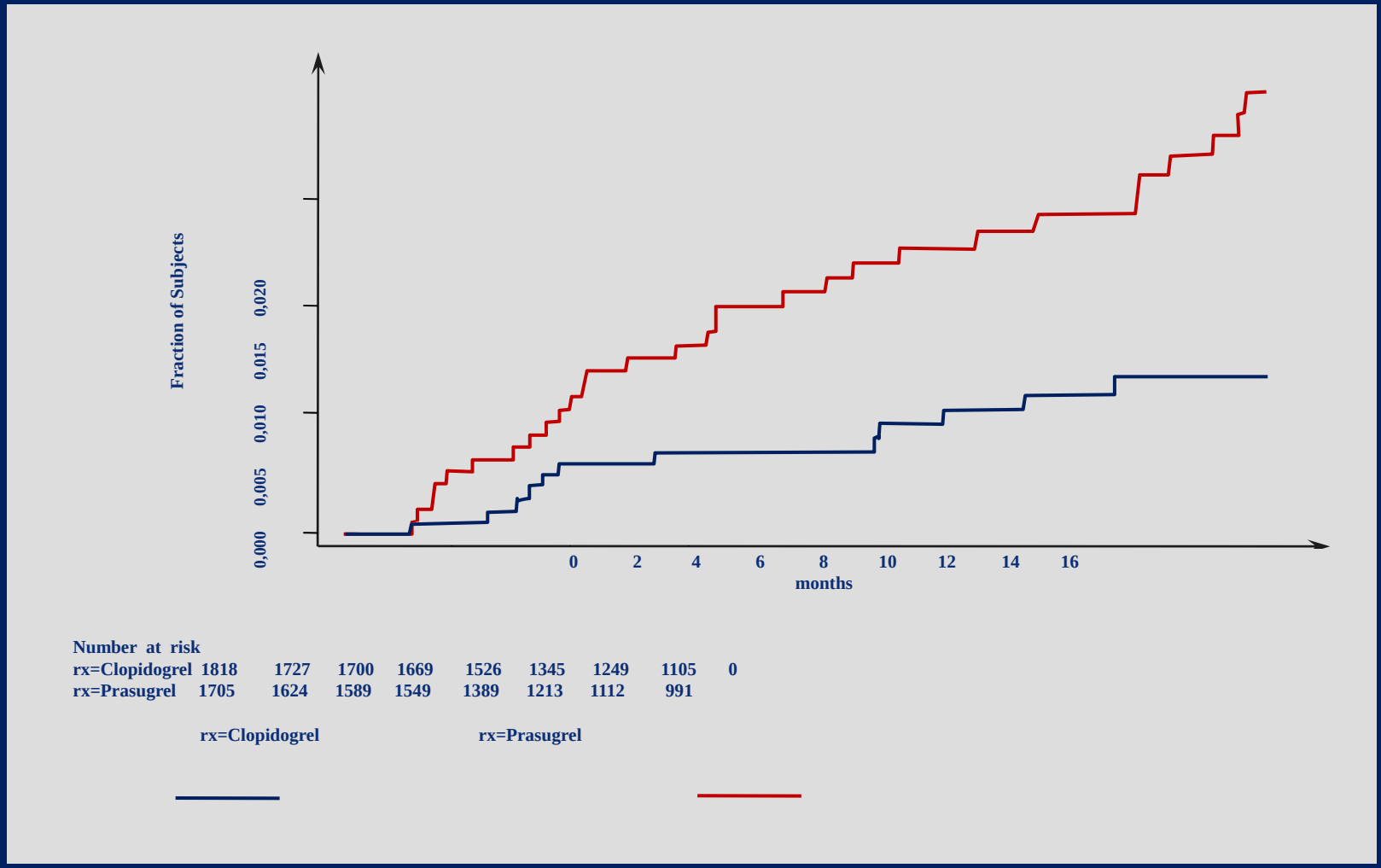


All New Solid Cancers Diagnosed After 7 Days in TRITON



The FDA Secondary Prasugrel Review

All New Solid Cancers in Women After 7 Days in TRITON



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Malignancies as Adverse Events in TRITON

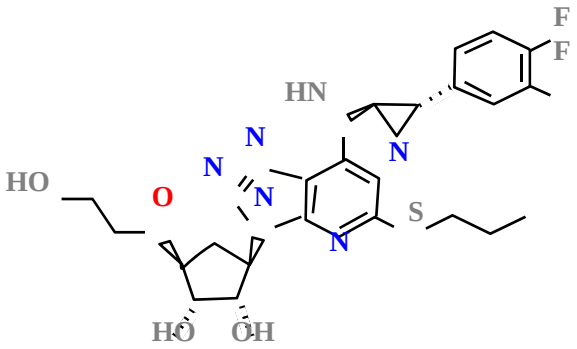
Location	Clopidogrel	Prasugrel
Colorectal	10	22
Breast	1	6
Prostate	11	18
Lung	14	19
All solid cancers	**69**	**112**
Relative Risk		**1.62**
Other malignancies	22	23

Cancer Deaths in TRITON

Assessed by:	Clopidogrel	Prasugrel
Investigators	11	19
Central Adjudication	17	23
FDA Reviewer	15	24

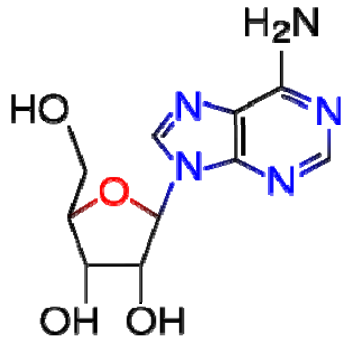
PLATO paradox

A



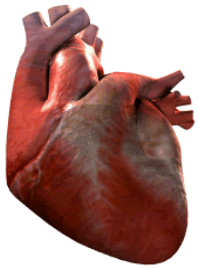
Ticagrelor

B

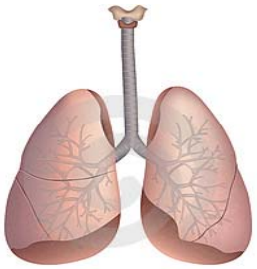


Adenosine

Ticagrelor: Potential Mechanism of Action



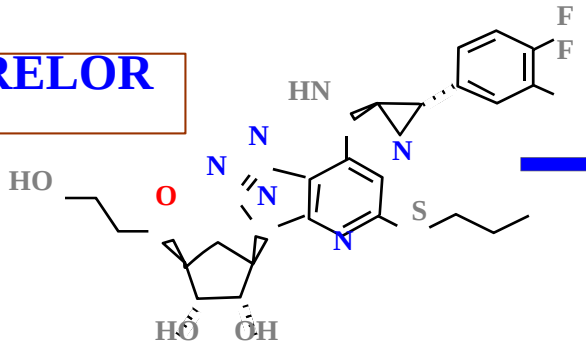
Asystole
Cytoprotection
Apoptosis
Vasodilatation

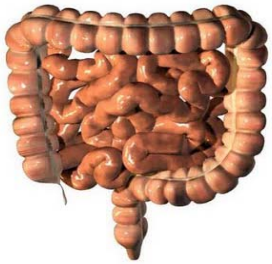


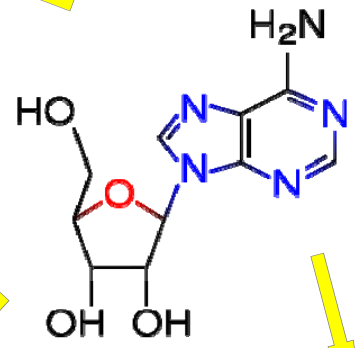
Dyspnea
Bronchospasm

Agitation
Anxiety

TICAGRELOR

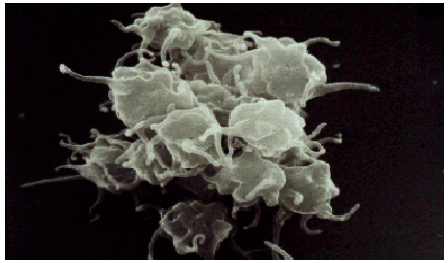




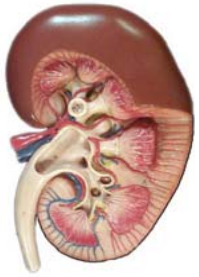


A1
A2
A
A2B
A3

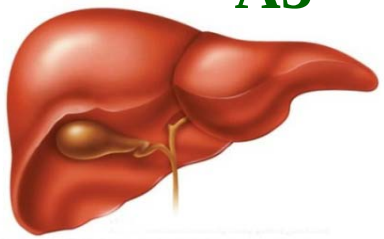
ADENOSINE



P2Y12 inhibition
Aggregation
Secretion



Uric acid
Creatinine



Conclusion:

- There is an alarming disagreement between the potency of antiplatelet therapy and vascular outcomes
- The postulates “the more - the better” may be invalid for future antiplatelet strategies
- Development of novel chronic antiplatelet agents should be more focused on compliance, the safety profile, long-term tolerability, and delicate mild platelet inhibition