

Old P₂Y₁₂ Inhibitor Still Has The **DOMINANT** Role: Focus on Prasugrel



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Disclosures

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

Dollars, and cents



Plavix is a “Cash Cow”



Net sales 2013

\$2,307

\$508.7

\$283

Q1-Q3 2014

\$1,692

\$384.4

\$343

Markets

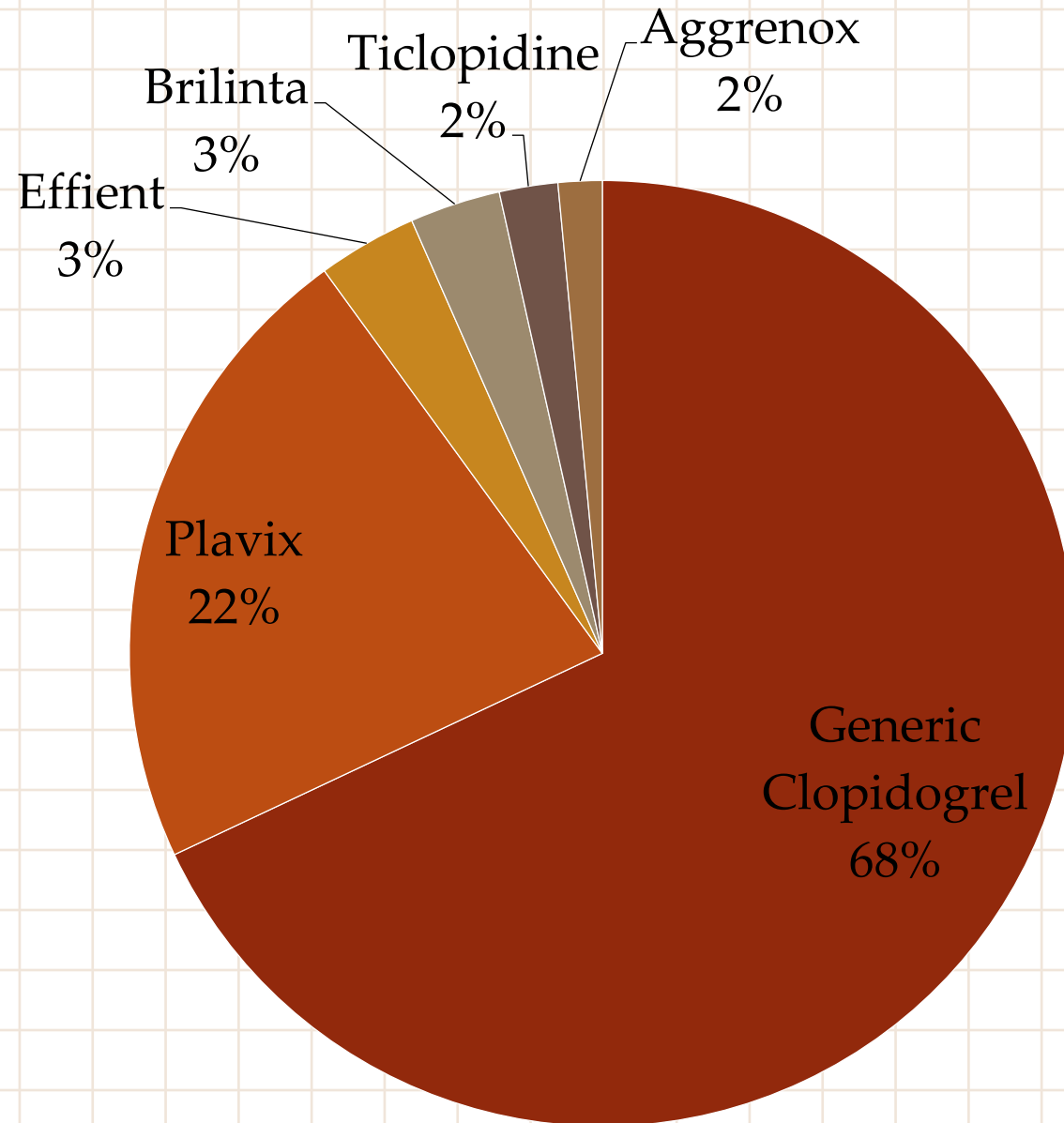
Asia, ME, LA, EU

>75% US

60% Europe

What about pill utilization?



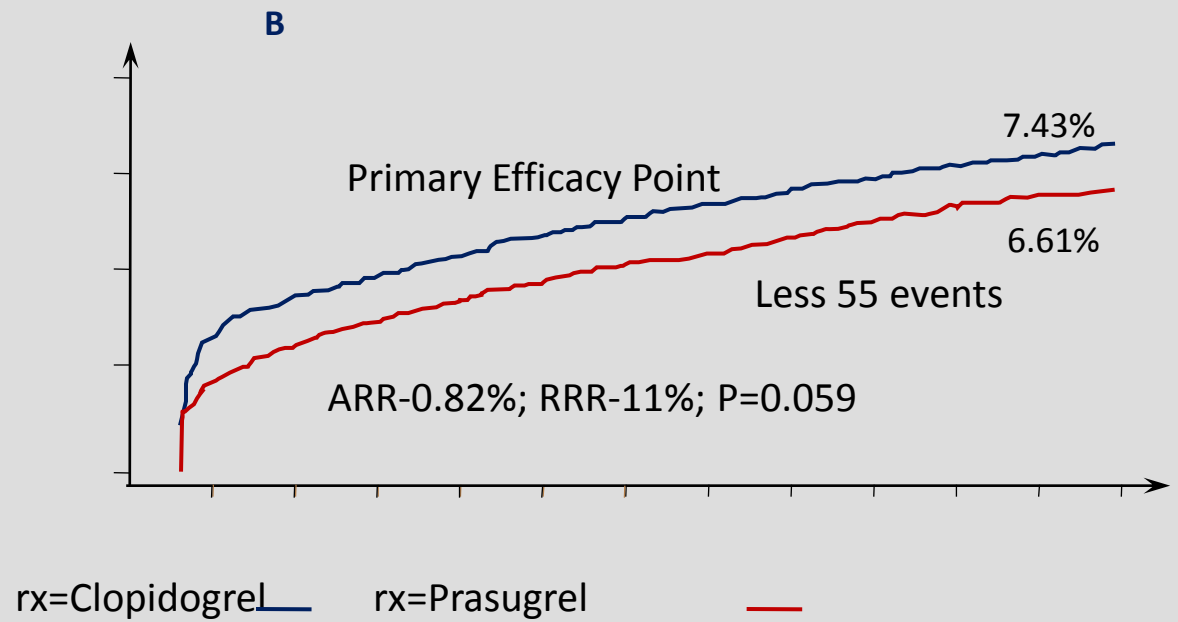
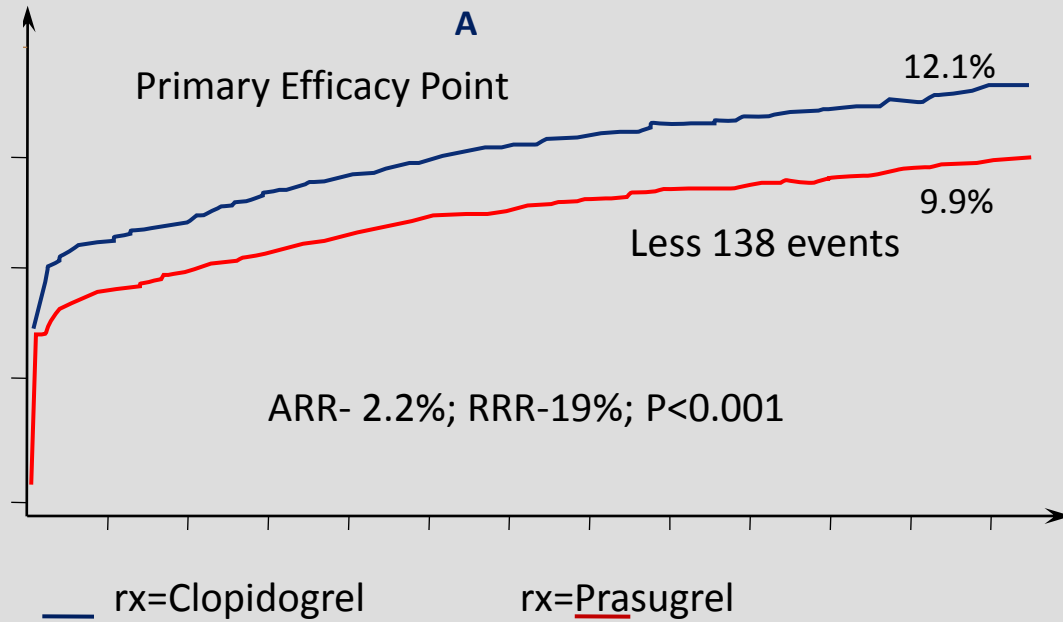


Worldwide Utilization of Oral Antiplatelet Agents

TRITON tricks



The TRITON Efficacy Controversy



A : All Adjudicated Events NEJM; 2007

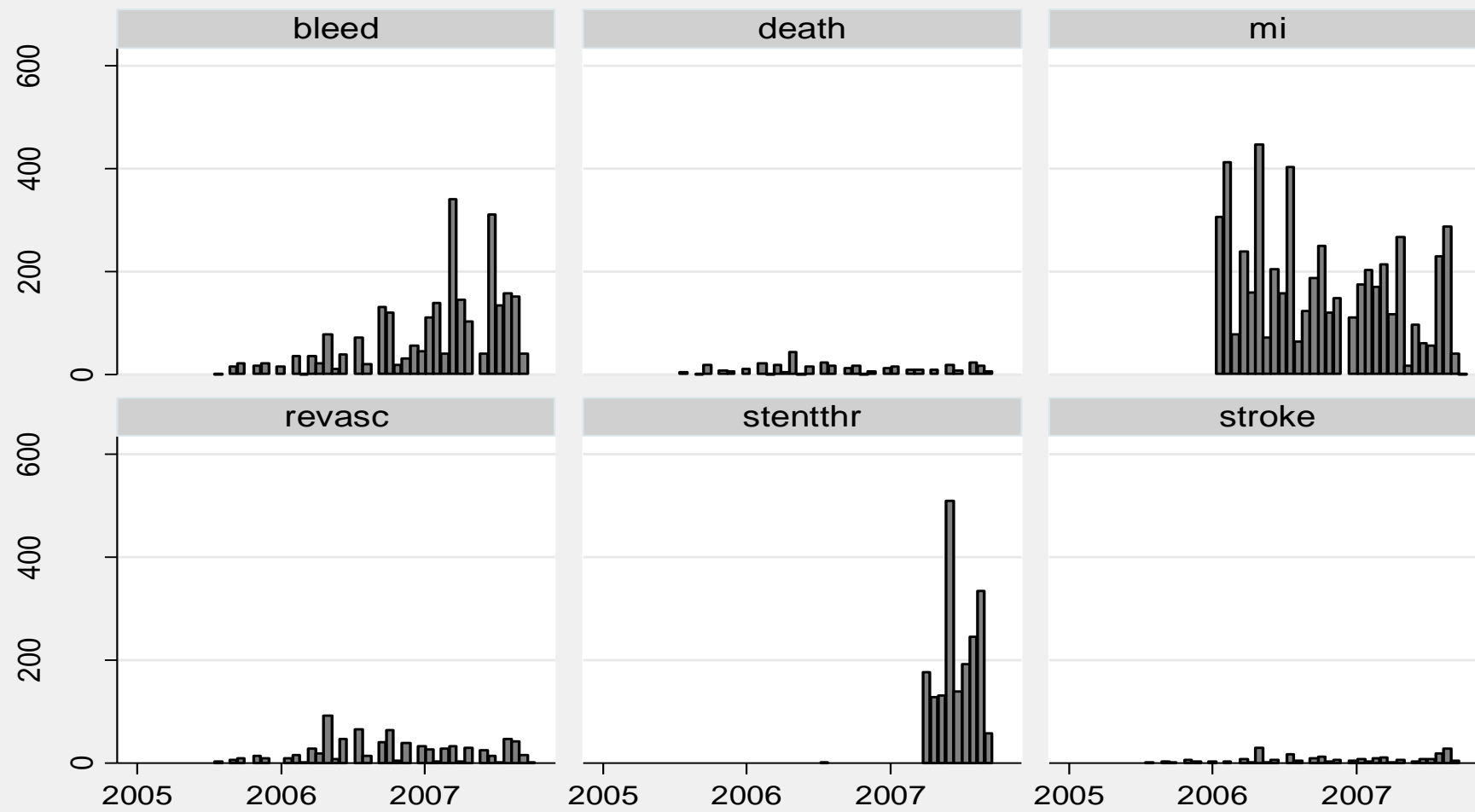
B: Investigator Reported Events FDA; 2009

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>

Timing of Event Adjudications in TRITON



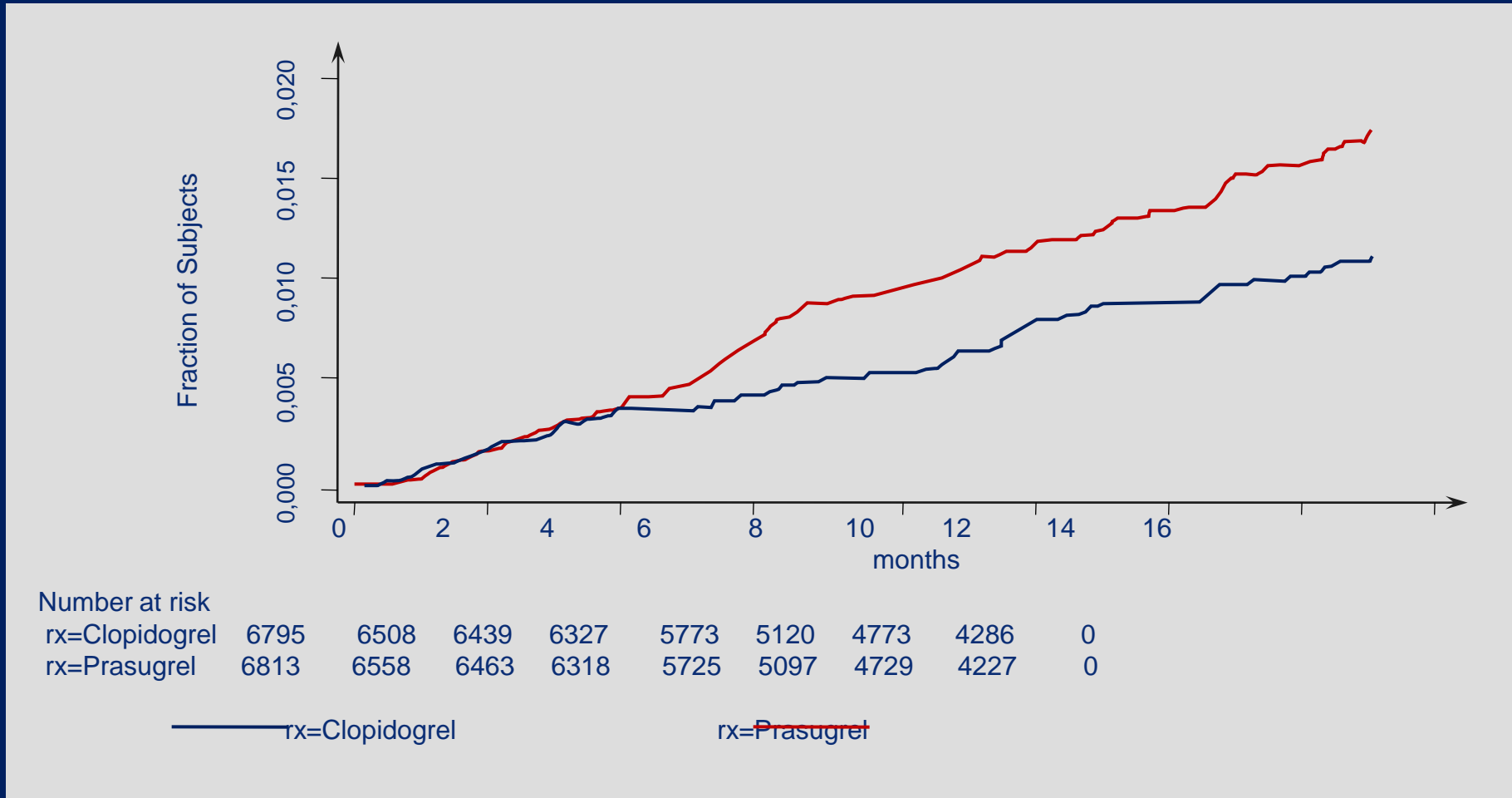
Graphs by evtypes

CEC reviewer signature date

Prasugrel and Cancer

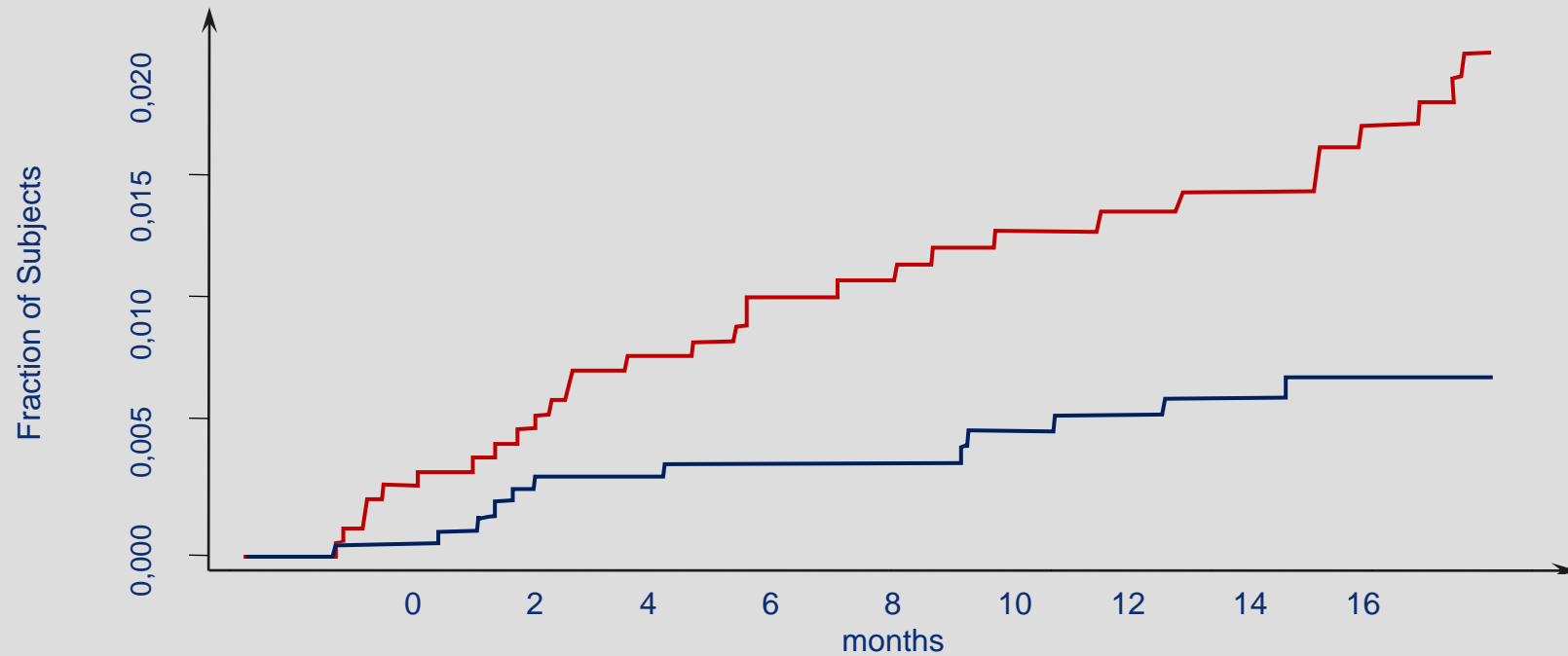


All New Solid Cancers After 7 Days in TRITON



The FDA Secondary Prasugrel Review, 2009

All New Solid Cancers in Women After 7 Days in TRITON



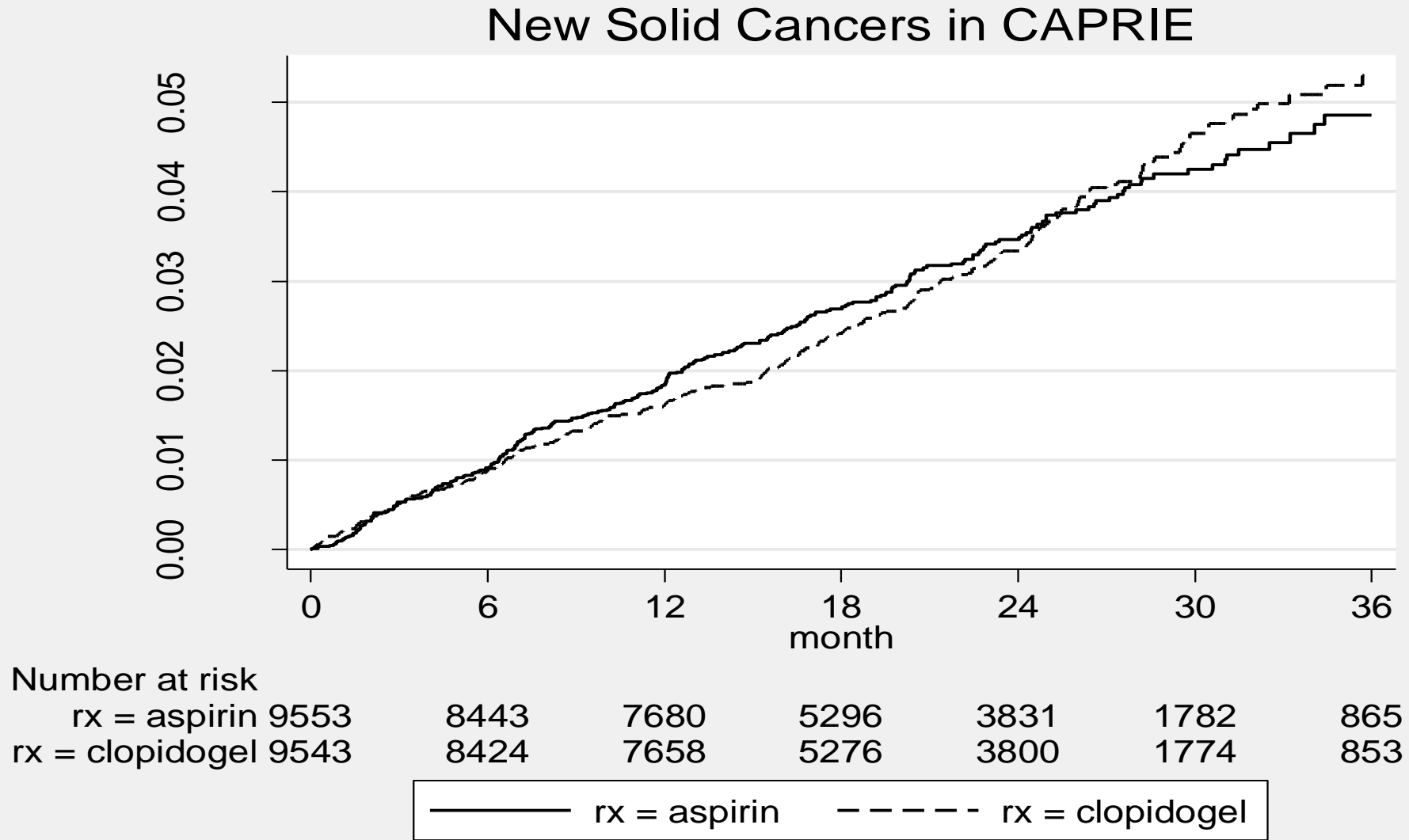
Number at risk

rx=Clopidogrel	1818	1727	1700	1669	1526	1345	1249	1105	0
rx=Prasugrel	1705	1624	1589	1549	1389	1213	1112	991	

— rx=Clopidogrel

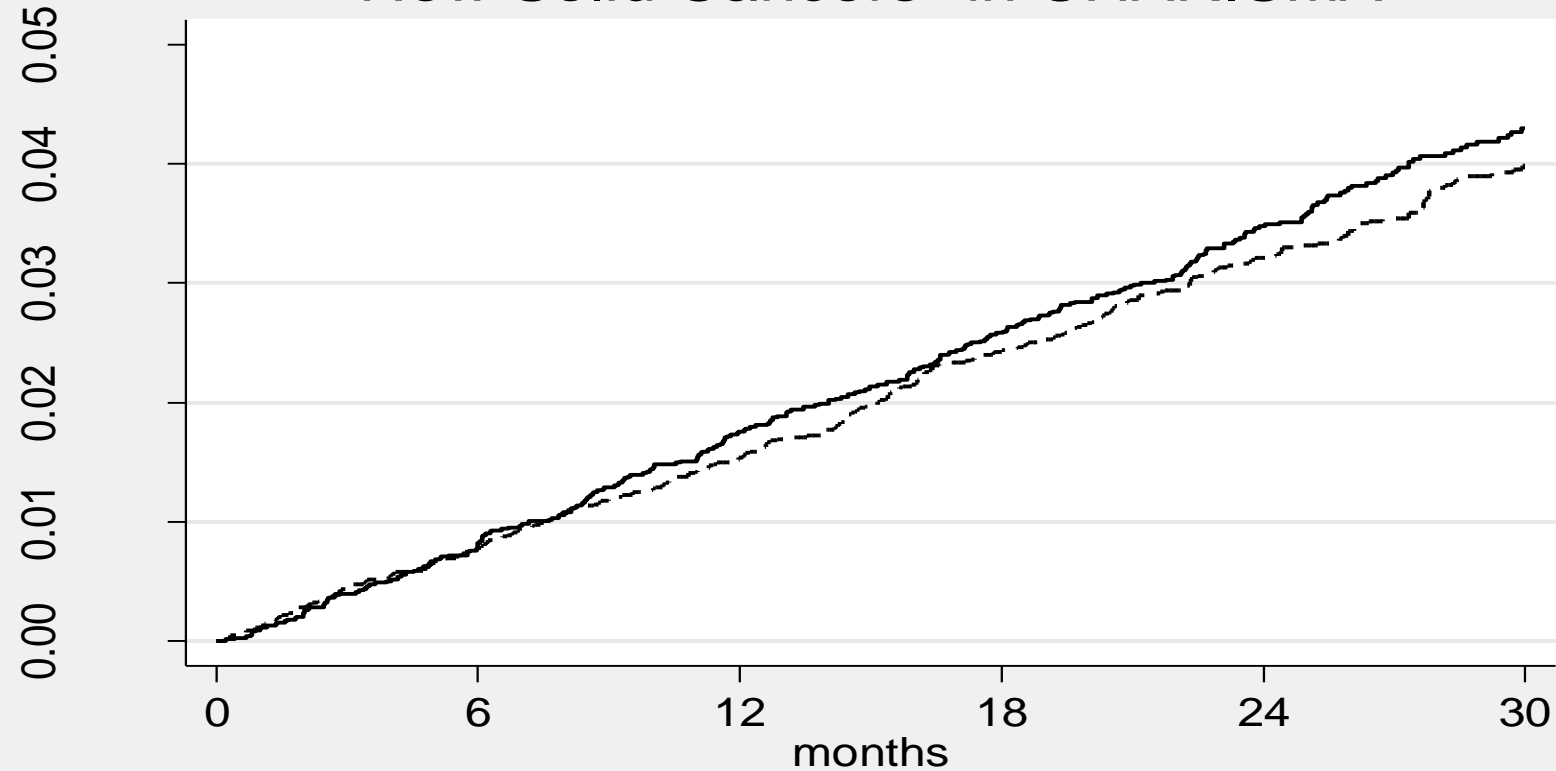
— rx=Prasugrel

New Solid Cancers in CAPRIE



New Solid Cancers in CHARISMA

New Solid Cancers* in CHARISMA



Number at risk	
rx = placebo	7801
rx = clopidogrel	7802

	6	12	18	24	30
rx = placebo	7689	7544	7403	5839	3302
rx = clopidogrel	7686	7562	7424	5885	3307

— rx = placebo - - - - rx = clopidogrel

Malignancies as Adverse Events in TRITON

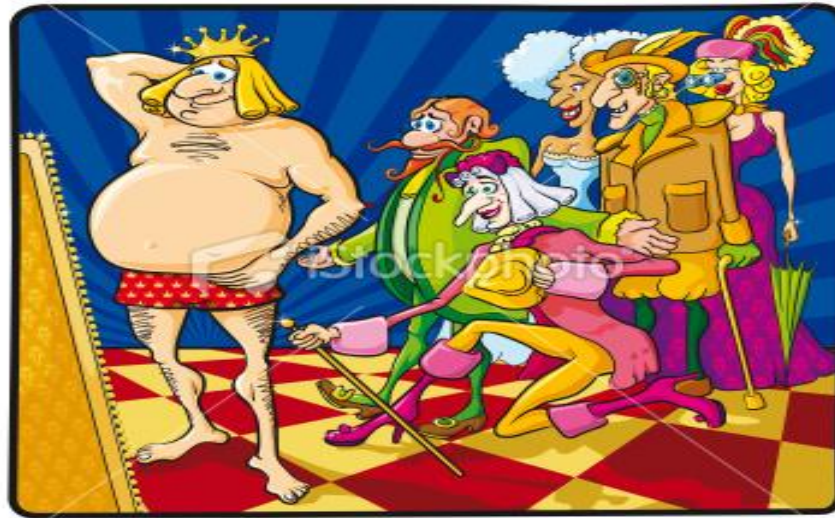
Location	Clopidogrel	Prasugrel
Colorectal	10	22
Breast	1	6
Prostate	11	18
Lung	14	19
All solid cancers	69	112
Relative Risk		1.62
Other malignancies	22	23

The FDA Secondary Prasugrel Review, 2009

Cancer Deaths in TRITON

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

The Good News: Missed Everywhere.... Except Japan and Korea



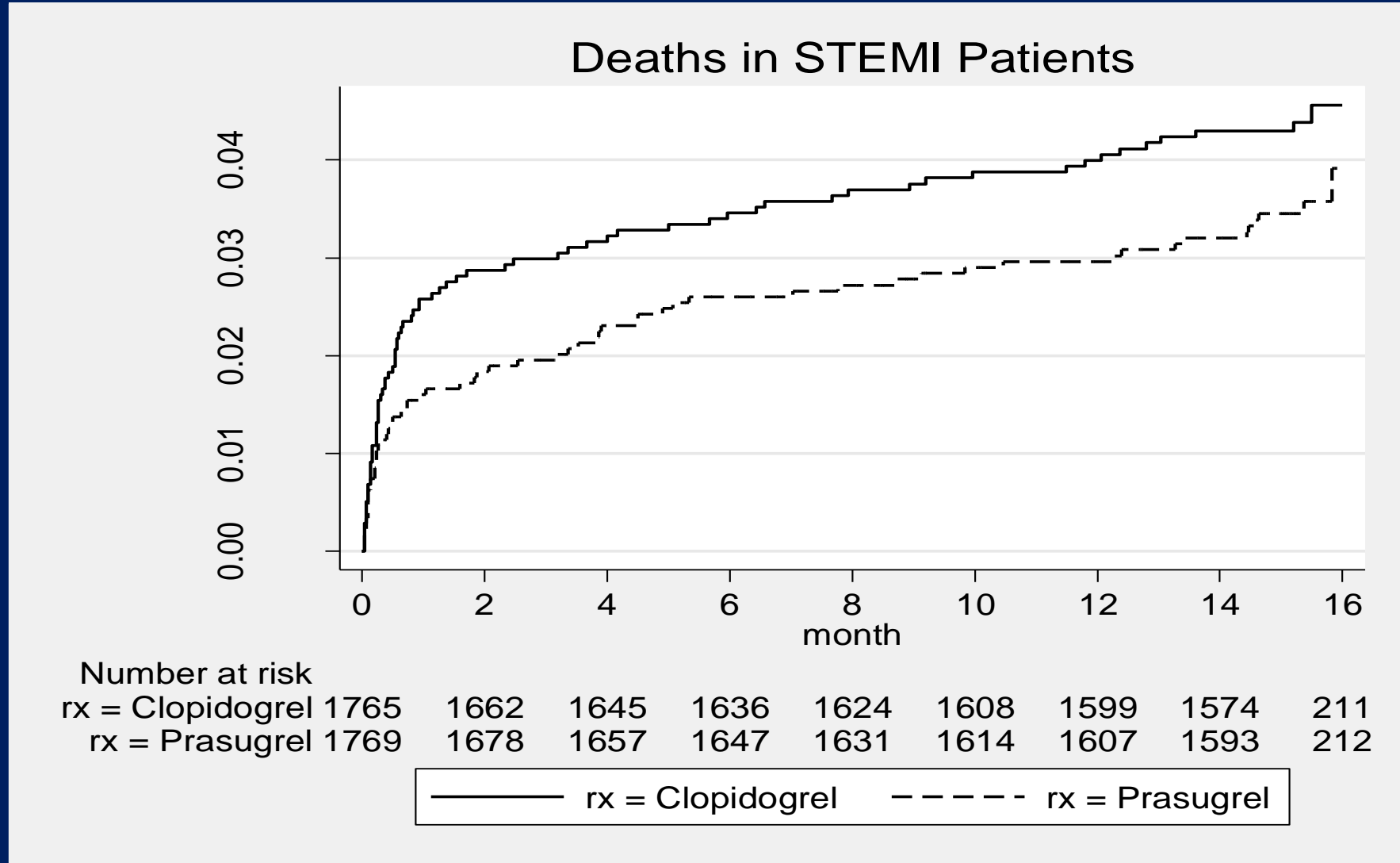
Bone Marrow Toxicity in TRITON: Missed Opportunity

Parameter	Clopidogrel	Prasugrel
Neutropenia (n) *	21	4
Sever Neutropenia (n)	4	2
Leukopenia (n)	236	187
Thrombocytopenia (n)	18	17

* - In PLATO neutropenia was increased 2-fold after ticagrelor versus clopidogrel (0.6% versus 0.3%, RR = 1.99)

The FDA Second Prasugrel Review, 2009

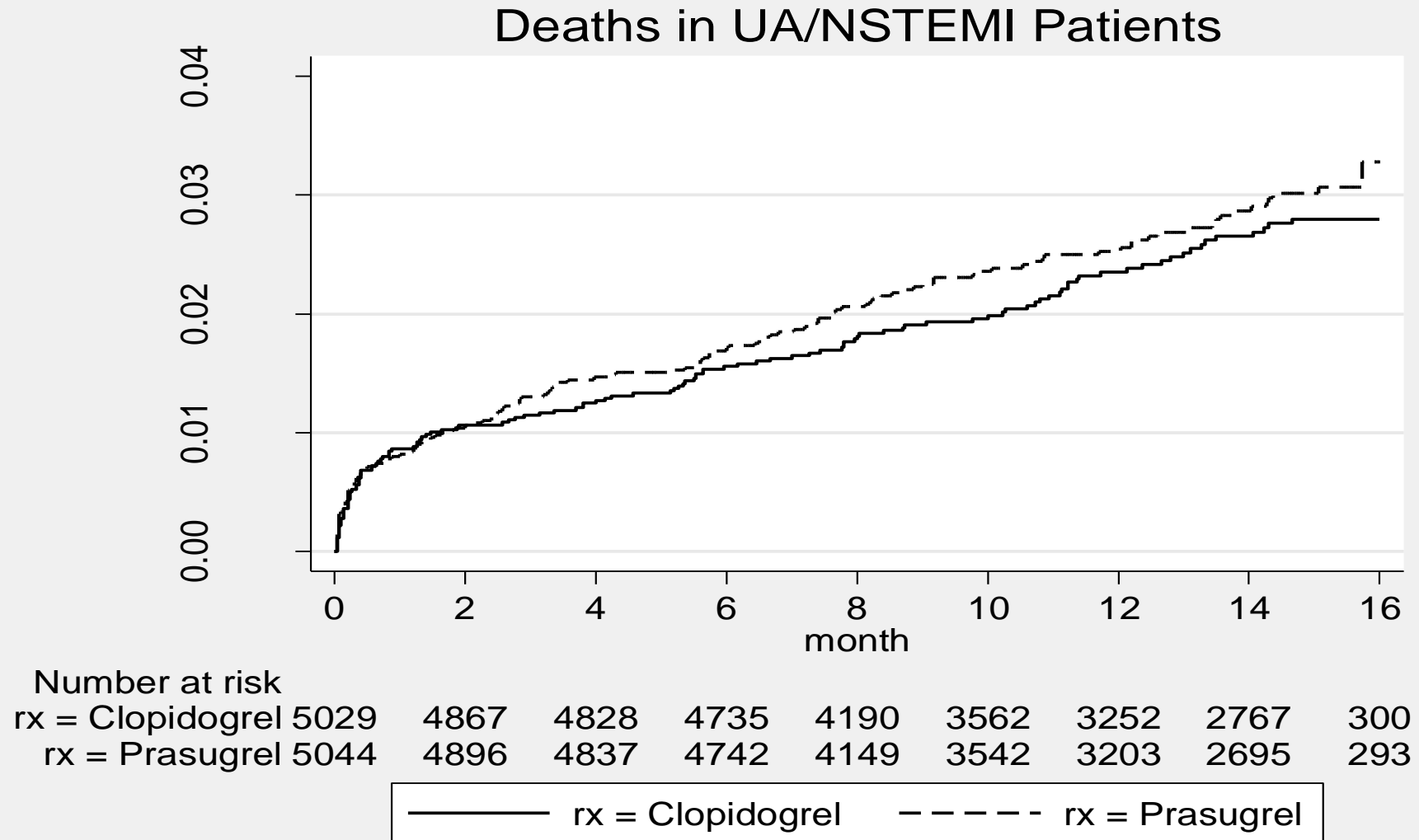
Deaths in STEMI Patients in TRITON



The FDA Secondary Prasugrel Review, 2009

Antithrombotic*	Study: % mortality	Total # of patients	Total # of deaths	Combined % mortality	OR (95% Confidence Interval) [†]	p-value [†]
Clopidogrel	BRAVE4:2.5	275	7	2.6	0.984(0.753 to 1.285)	0.946
	TRITON-TIMI:2.6	1765	45			
	CHAMPION-PCI:3.2	509	16			
	Koshy et al:2.4	866	21			
	Total:3415	Total:89				
Prasugrel	BRAVE4:2.6	269	7	1.75	0.666(0.481 to 0.921)	0.014
	TRITOM-TIMI38:1.6	1769	28			
	Koshy et al:1.8	822	15			
	Total:2860	Total:50				
Heparin	HEAT-PPCI:4.3	907	39	3.0	1.150(0.905 to 1.461)	0.268
	HORIZONS-AMI:3.1	1802	56			
	EUROMAX:2.3	649	15			
	BRIGHT: 1.8	729	13			
	BRAVE4: 2.5	275	7			
	Total:4362	Total:130				
Bivalirudin	BRAVE4: 2.6	269	7	2.8	1.084(0.855 to 1.374)	0.544
	BRIGHT: 1.8	735	13			
	EUROMAX:2.9	1089	32			
	HEAT-PPCI:5.1	905	46			
	HORIZONS-AMI:2.1	1800	37			
	Total:4798	Total:135				
Cangrelor	CHAMPION-PCI:1.7	487	8	1.7	0.625(0.305 to 1.281)	0.229
Tirofiban	BRIGHT:2.1	730	15	2.1	0.815(0.548 to 1.213)	0.341
	ON-TIME2:2.2	677	15			
	Total:1407	Total:30				
Ticagrelor	ATLANTIC (InHospital):2.0	952	19	2.6	-	-
	ATLANTIC(PreHospital):3.3	906	30			
	PLATO-STEMI:2.6 [‡]	3752	97			
	Total:5610	Total:146				

Deaths in UA/NSTEMI Patients



In Search for Grants? Paradigm Shift



MEDICAL
Until 1998



MARKETING
1998-2009



LEGAL
2010-present

Effient: Who Will Pay The Difference?

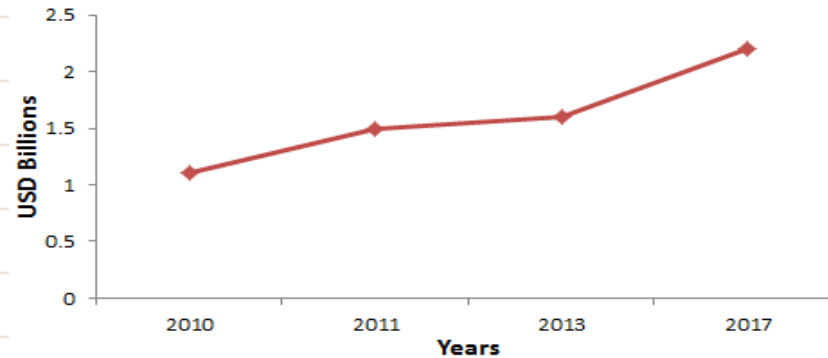
+\$1,600M

-\$3,300M

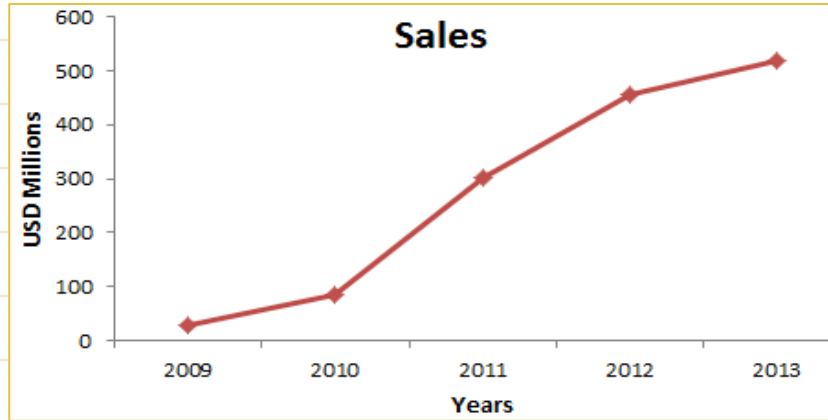


R&D, JUMBO, TRITON = **\$1,200M**
TRILOGY = **\$1,100M**
Operational expenses, split revenue, repeated international launches, IIP, >120 studies, KOL = **\$1,100M**
Legal Costs (cancer, bleeding, sepsis, off-label use) = **???**

Effient Sales Expected by Wall Street



Sales



Impressions:

- Future of prasugrel outside Asian markets depends on cancer analyses in DAPT
- The system does not have enough resources to maintain *status quo*
- Unless we want a complete vacuum (see stroke arena), the radical change of cardiovascular clinical trial philosophy is mandatory
- The guilty party? Name one which is not
- Top priority – restore trust
- Top problem – lack of shareholders control

