

Prasugrel for ACS

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Disclosures:

- **US Patent Application: "Method for treating vascular diseases with prasugrel (P-17232)" assigned to Eli Lilly**
- **Grants: Sanofi-BMS, Eli Lilly**
- **Consulting: Sanofi-BMS, McNeil, Bayer, mutual funds, hedge funds**

FDA Question p1-2; Benefit

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

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.

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 definitions²⁷: 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 $\geq 50\%$ 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-

Was TRITON Justified by JUMBO?

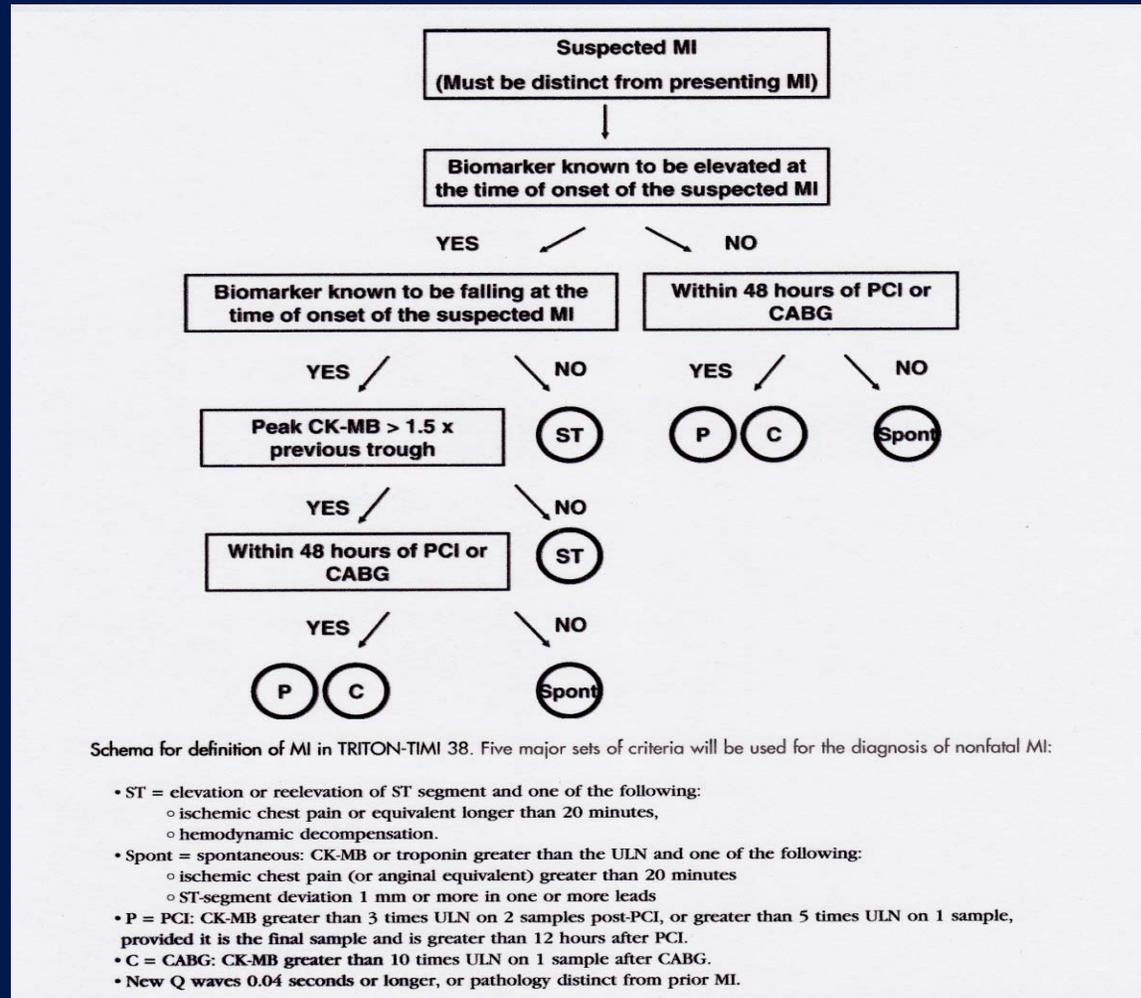
TABLE 2. Major Safety (Bleeding) and Efficacy End Points

Event	Prasugrel, n (%) (n=650)	Clopidogrel, n (%) (n=254)	P*	HR (95% CI)
Bleeding				
Non-CABG TIMI major+minor	11 (1.7)	3 (1.2)	0.590	1.42 (0.40–5.08)
Non-CABG TIMI major	3 (0.5)	2 (0.8)	0.544	0.58 (0.10–3.46)
Non-CABG TIMI major+minor+minimal	27 (4.2)	9 (3.5)	0.685	1.17 (0.55–2.48)
Efficacy events				
MACE	47 (7.2)	24 (9.4)	0.260	0.76 (0.46–1.24)
Death	3 (0.5)	0	0.278	...
Stroke	3 (0.5)	0	0.278	...
MI	37 (5.7)	20 (7.9)	0.226	0.72 (0.42–1.24)
Recurrent ischemia	6 (0.9)	4 (1.6)	0.391	0.58 (0.16–2.05)
Severe ischemia	9 (1.7)	11 (3.5)	0.086	0.47 (0.2–1.14)
CTVT	4 (0.6)	6 (2.4)	0.024	0.26 (0.07–0.92)
Death/MI	40 (6.2)	20 (7.9)	0.349	0.78 (0.46–1.33)
Death/MI/CTVT	41 (6.3)	24 (9.4)	0.101	0.66 (0.40–1.10)

The trial primary end point was non-CABG-related TIMI major plus minor bleeding. Primary safety and efficacy end points are in bold. Recurrent ischemia required rehospitalization. Severe ischemia included patients for whom hospitalization was prolonged as a result of an ischemic episode. HR was not calculable for death and stroke because of zero cell in the clopidogrel group.

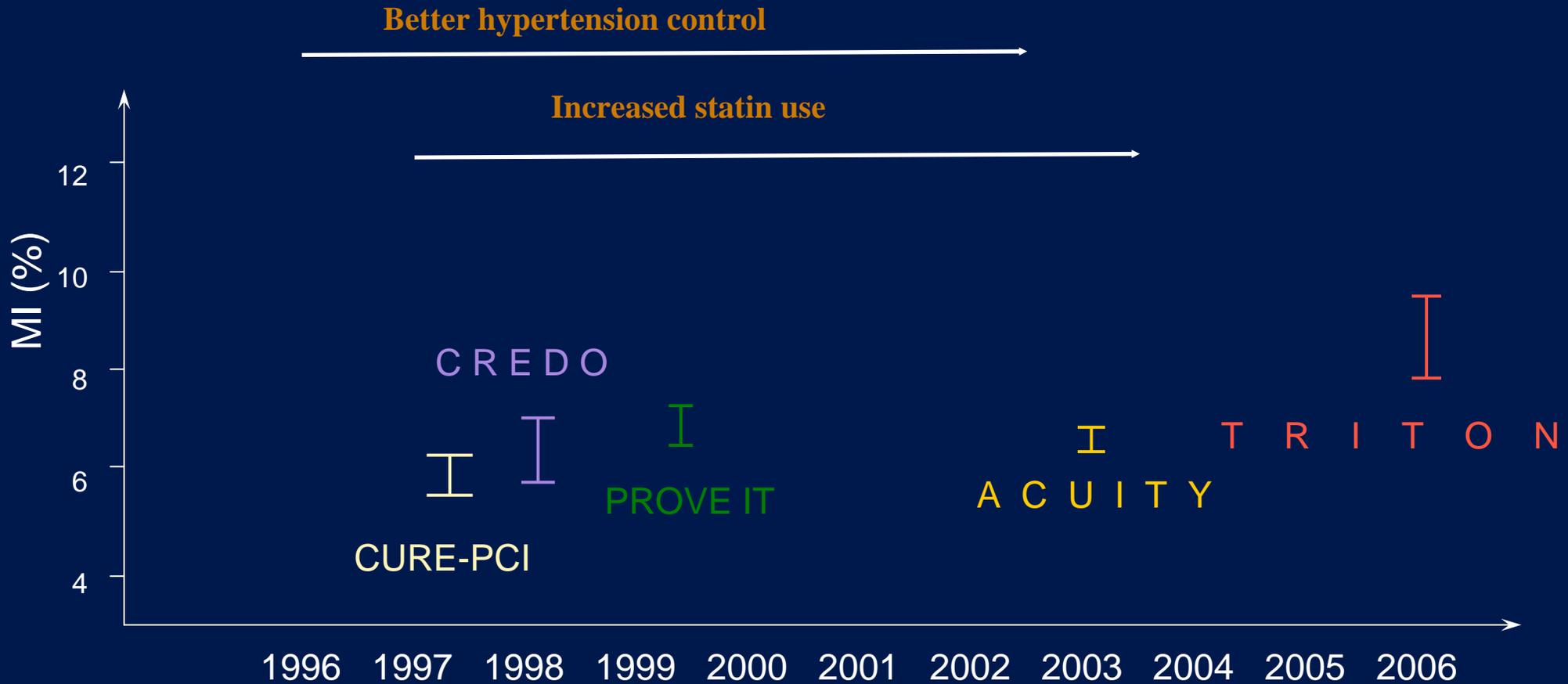
*Log-rank probability value.

TRITON MI Definition

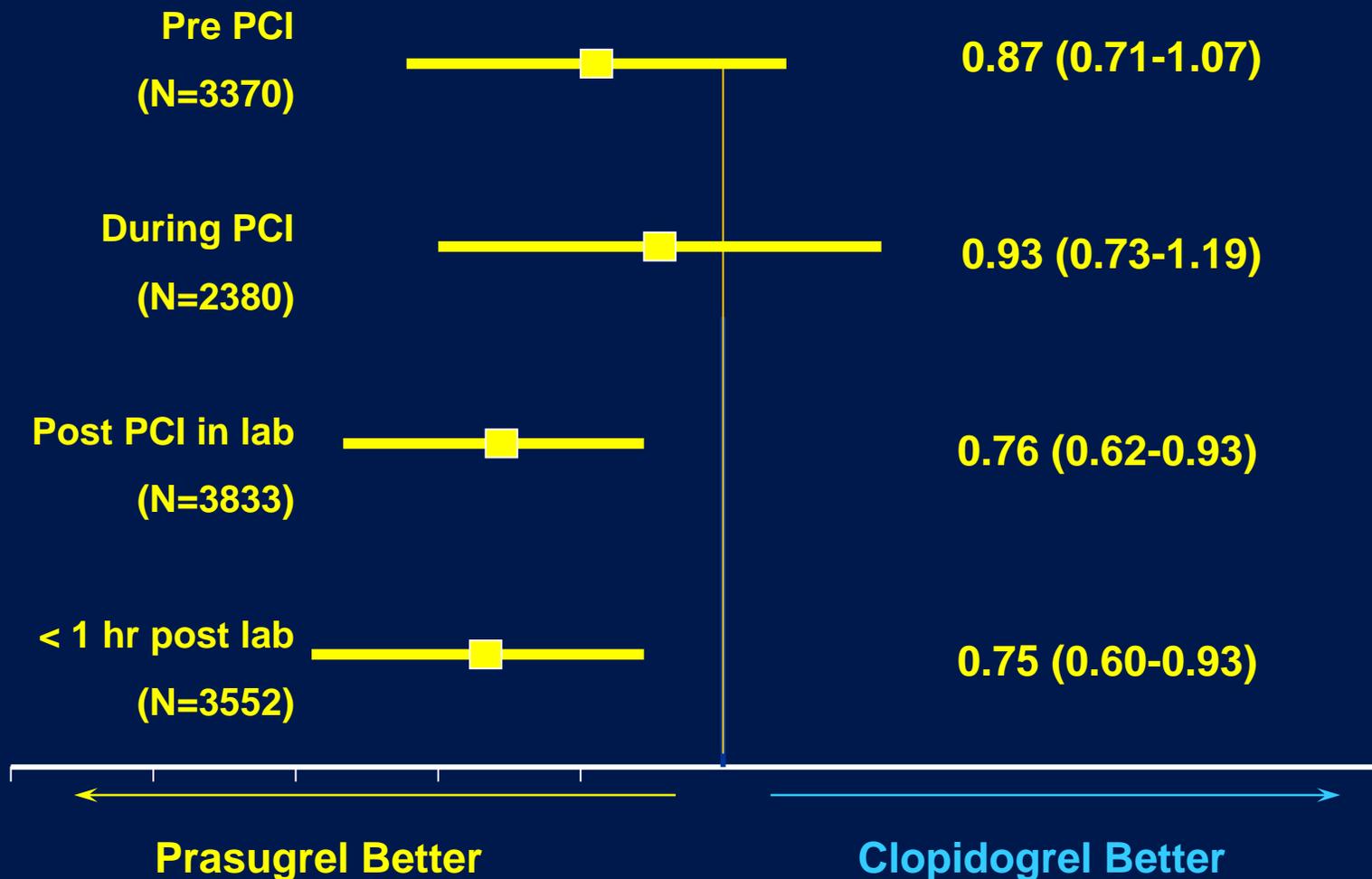


MI rate 9.7% @ 6-15 months

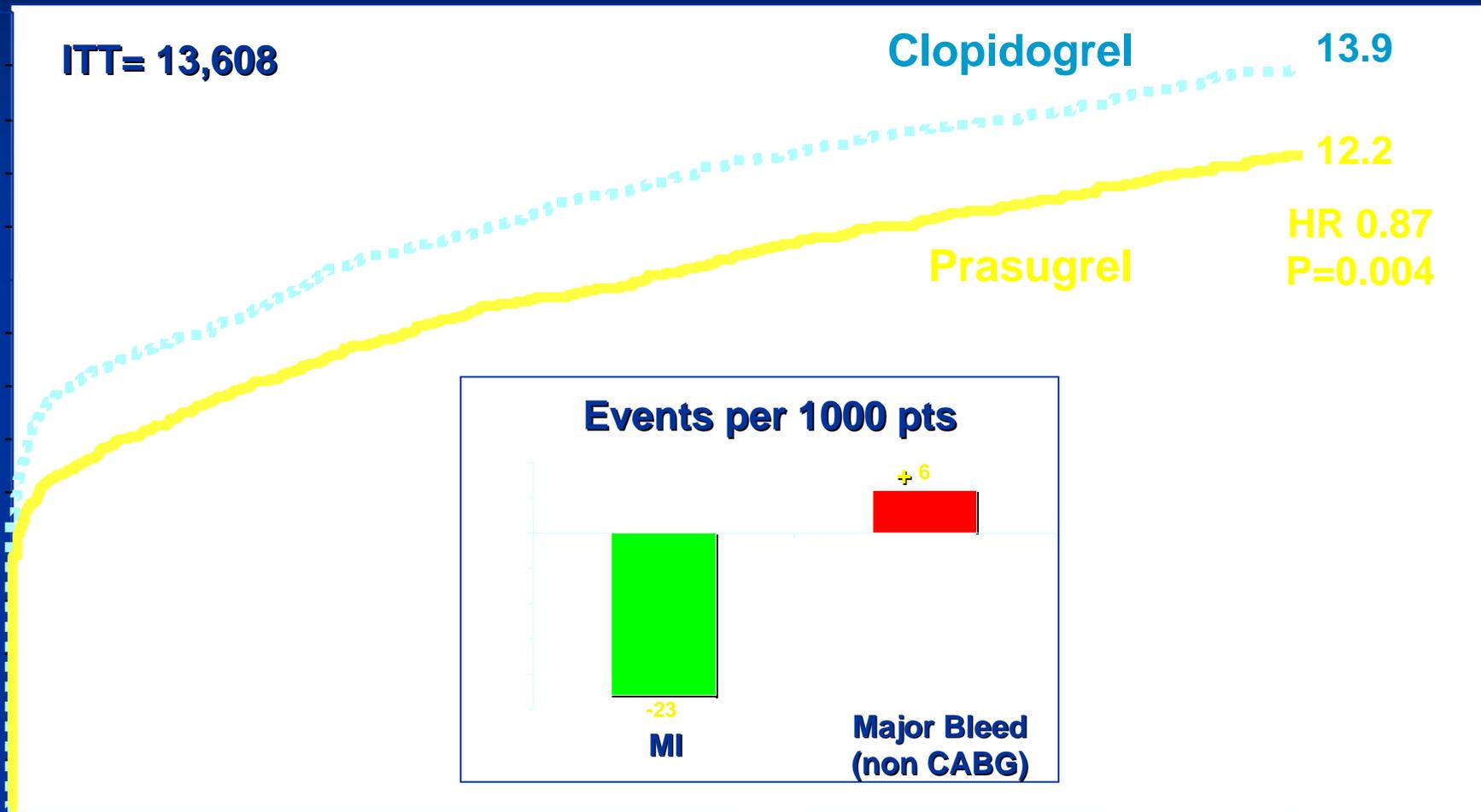
MI Rates and the Timing of the Trial



CV Death, MI, Stroke Timing of LD



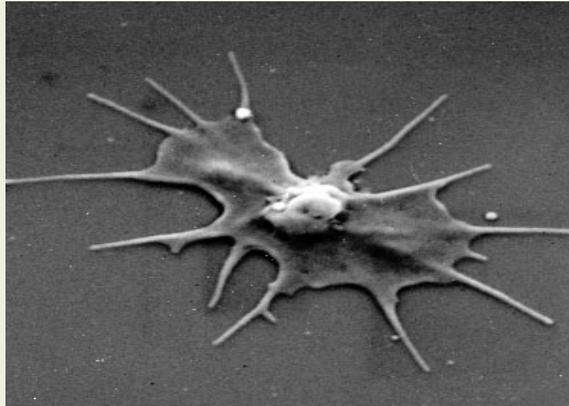
3.1p.4 Net Clinical Benefit ?



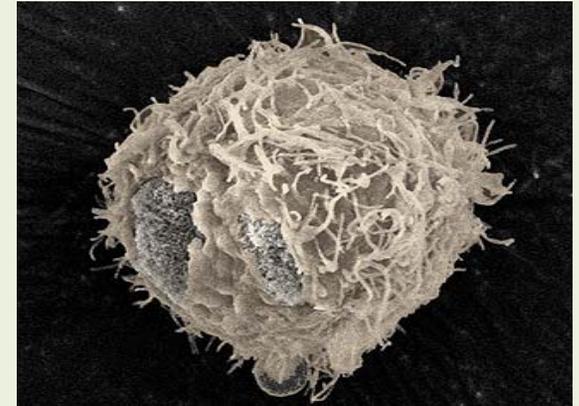
FDA Question p.4; Risk

2.2. Cancer was somewhat more commonly reported in the prasugrel group than in the clopidogrel group.

Prasugrel and increased cancer risks?



Formation of platelet – tumor cells aggregates
Stimulation of neoplasm angiogenesis
Modulation of cancer expansion
Prevention of metastasis



PF-4 release, NOS blockade
P-selectin, GP I,
GP IIb/IIIa activation
VEGF stimulation
PAF modulation

INCREASED CANCER RISKS
AFTER PRASUGREL



CD 44/CD47 expression
Leukocyte attraction
MMP-1 release,
PAR-1 stabilization

Chemical carcinogenicity (highly unlikely)
Stimulation of existing tumor growth (unlikely)
Promoting metastasis (most likely)



Number of New First Cancers in TRITON

CANCER	Prasugrel	Clopidogrel
Breast	5	1
Colorectal	19	8
Esophagus	5	2
Gall Bladder	2	0
Lung	21	13
Prostate	10	8
Sarcoma	2	0
Skin	10	14
Brain	2	0
Unknown/Other	7	2
<u>TOTAL</u>	<u>119</u>	<u>87</u>