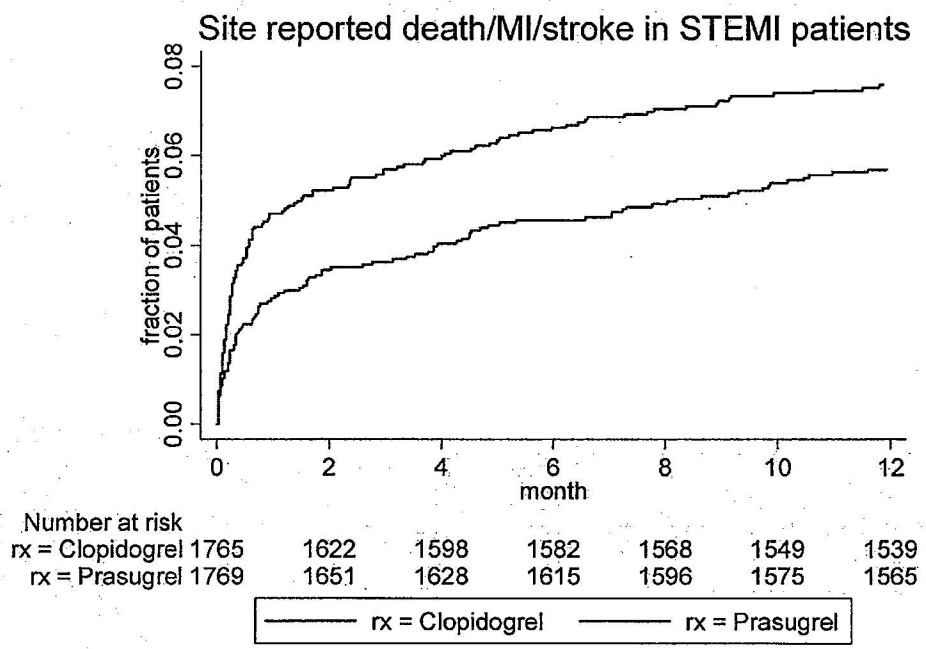
Figure 18: Site-Reported Death/MI/Stroke in TAAL STEMI Patients



p = 0.07 by Gehan test, 0.06 by log rank test

Note the much wider separation of the curves, still mainly early, in the STEMI subgroup. While the sponsor likely picked the UA/NSTEMI group as the group more likely to benefit based on the clopidogrel studies, prasugrel appears to show more benefit in the STEMI population.

The distribution of first site-reported event types is different from that for the CEC-adjudicated events. I show the site-reported first event types in Table 24.

Table 24: Site-Reported First Event Types

	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

While prasugrel's benefit in all patients is due to a reduction in MIs, first events of all-cause deaths go in opposite directions in the two subgroups. That mortality is trending in the wrong direction for prasugrel UA/NSTEMI patients as shown by the Kaplan-Meier death plot in Figure 19, while there is an early mortality benefit in STEMI patients but late detriment as shown in Figure 20.

Figure 19: Deaths in UA/NSTEMI Patients in TAAL

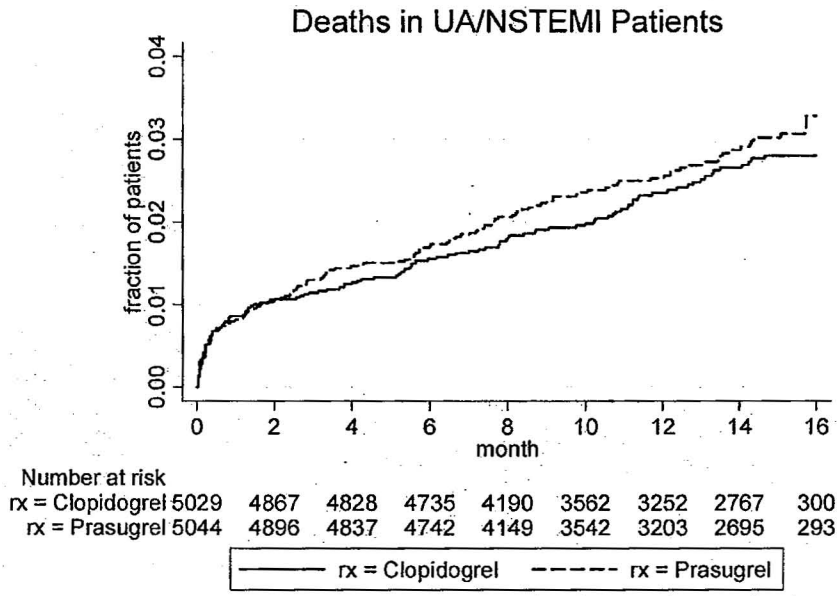
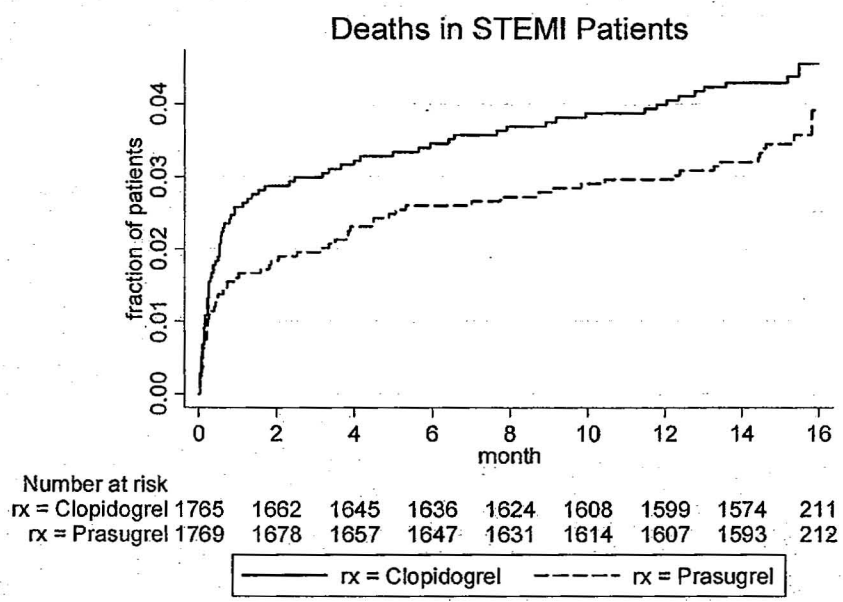


Figure 20: Deaths in STEMI Patients in TAAL



The CEC-adjudicated events were the pre-specified primary endpoint and, if the adjudication really works, should be more discriminatory regarding risks. The latter can be evaluated

regarding risk of death, and I show the death rates for CEC-adjudicated and site reported MIs in Table 25.

Table 25: CEC-Adjudicated vs. Site-Reported MIs and Death Rates

		CEC-adjudicated			site-reported	
		no MI	PPMI only	MI event	no MI	MI event
clopidogrel	n	6,155	265	375	6,500	298
	% died	2.2%	4.2%	13.5%	2.4%	18.8%
prasugrel	n	6,327	231	255	6,588	226
	% died	2.5%	2.6%	11.2%	2.7%	14.2%

The site-reported MIs appear to be better predictors of death than the CEC-adjudicated MIs. The patients with only PPMIs in the prasugrel group actually had a rate of death comparable to those without MIs, although, for any PPMI ignoring subsequent MI events, the death rates were very similar in both groups (about 4.1%).

COMMENT: PPMIs as adjudicated in TAAL appear to convey a risk much lower than that of having a second MI event, particularly as reported by the sites. PPMIs as adjudicated in TAAL should not be considered equivalent to the other components of the primary composite endpoint (MI events, strokes, and CV death). This issue, that "chemical" MIs are not equivalent to the MI events used in past CV trial endpoints, is not limited to TAAL: All new trials that use the universal definition of MI (with its MI criterion of a troponin exceeding the 99th percentile) must prospectively define how chemical MIs and MI events will be incorporated into their endpoints.

Besides the overall assessment of benefit, the other question of critical importance for prasugrel use is the time course of the benefit. This question is critical because of the potential for tumor promotion, which should be related to duration of treatment. I show the cumulative difference in site-reported death/MI/stroke events per 100 patients in Figure 21. For comparison I show in Figure 22 the corresponding CEC-adjudicated results and in Figure 23 the results for the major adverse effect of bleeding.

Figure 21: Cumulative Site-Reported Death/MI/Stroke Difference in All TAAL Patients

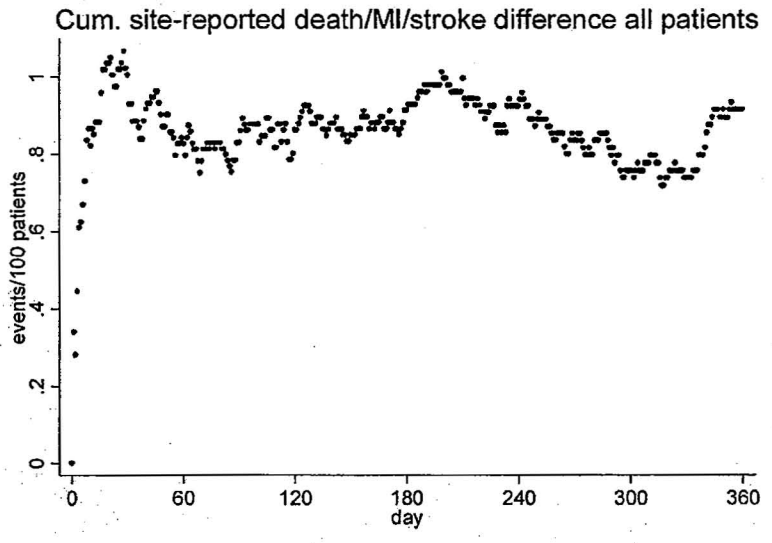


Figure 22: Cumulative CEC-Adjudicated CV Death/MI/Stroke Difference in All TAAL Patients

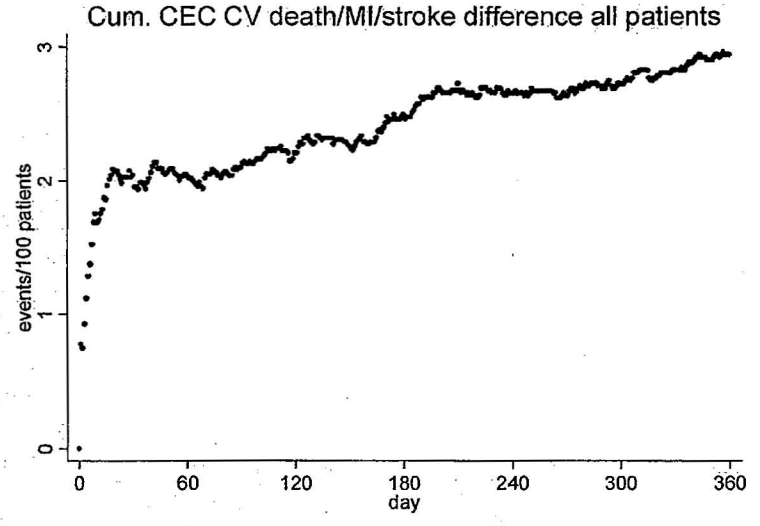
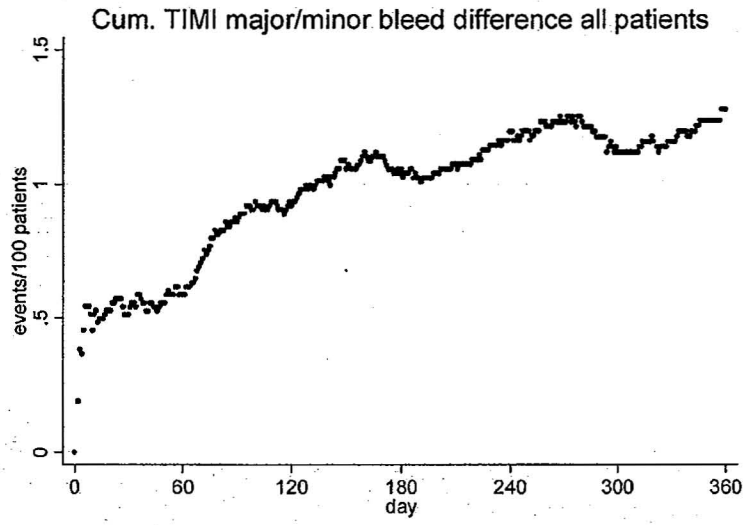


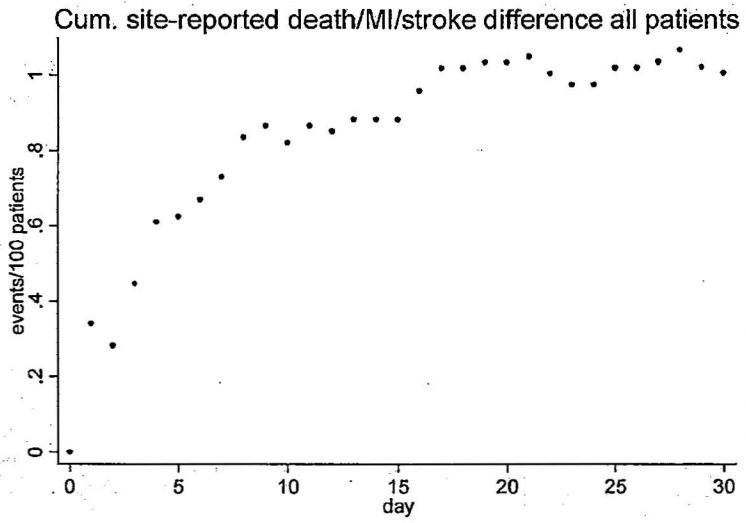
Figure 23: Cumulative TIMI Major/Minor Bleed Difference in All TAAL Patients



NOTE: The difference is reversed from the efficacy graphs:
There were more bleeds with prasugrel than with clopidogrel.
TIMI major/minor bleeding = hemoglobin drop of ≥ 3 gm/dL.

For site-reported events the benefit all appears to be early, i.e., within less than 30 days. Hence I show event differences through 30 days in Figure 24. The benefit appears to be close to maximal at 3 weeks. Note also that the net efficacy benefit in site-reported events, about 1 event/100 patients, is matched by the net detriment in bleeding events between 2 and 4 months.

Figure 24: Cumulative Site-Reported Death/MI/Stroke Difference in All TAAL Patients



TAAL included two related but distinct study populations: patients with UA/NSTEMI and those with STEMI. In fact, the sponsor pre-specified the primary efficacy analysis to be done in the UA/NSTEMI subgroup alone. Hence I show the site-reported composite endpoint results of UA/NSTEMI patients in Figure 25 and for STEMI patients in Figure 26. For all patients the MI benefit occurs early as shown in Figure 28.

Figure 25: Cumulative Site-Reported Death/MI/Stroke Difference in TAAL UA/NSTEMI Patients

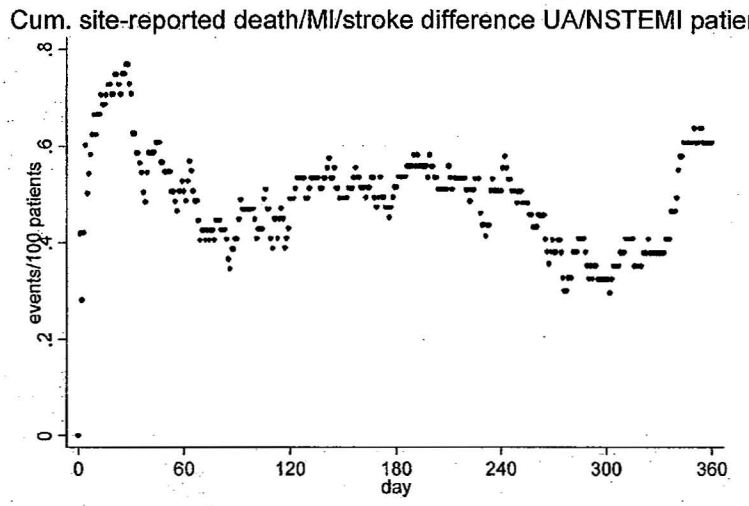
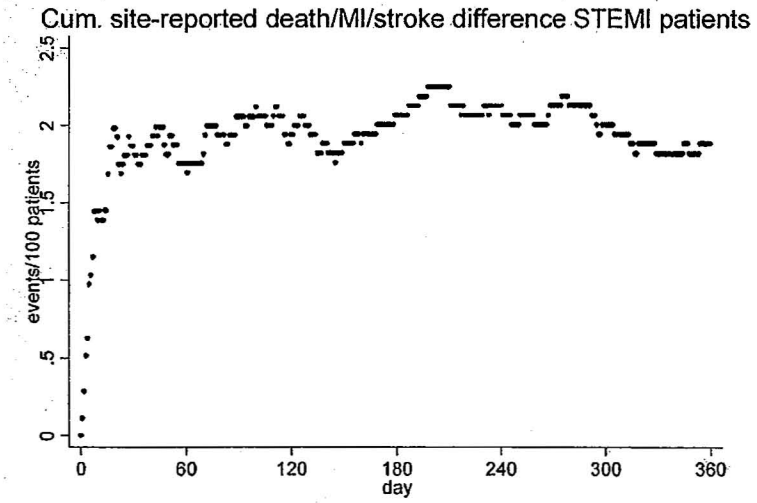


Figure 26: Cumulative Site-Reported Death/MI/Stroke Difference in TAAL STEMI Patients



For UA/NSTEMI patients there appears to be an early benefit that converts to a slight detriment as time progresses; for STEMI patients there appears to be a larger early benefit that improves little with passing time. The late detriment for UA/NSTEMI patients occurs despite a continuing slight benefit for fewer MIs as shown in Figure 27.

Figure 27: Cumulative Site-Reported MI Difference in TAAL UA/NSTEMI Patients

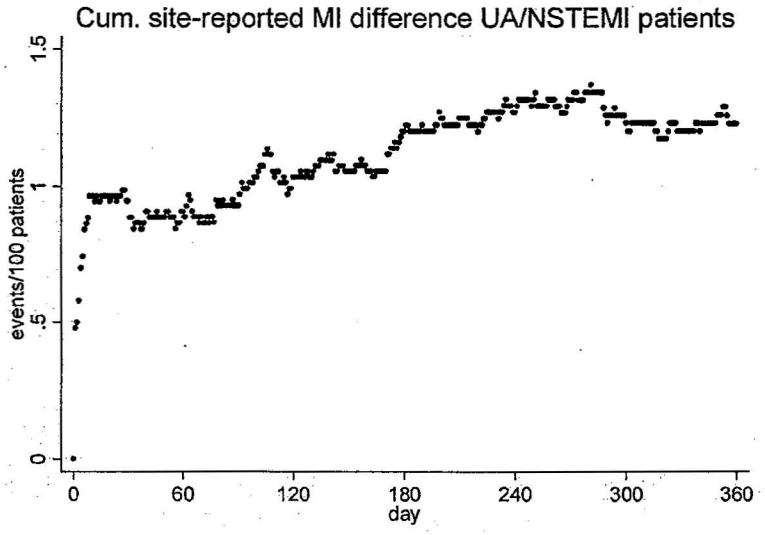
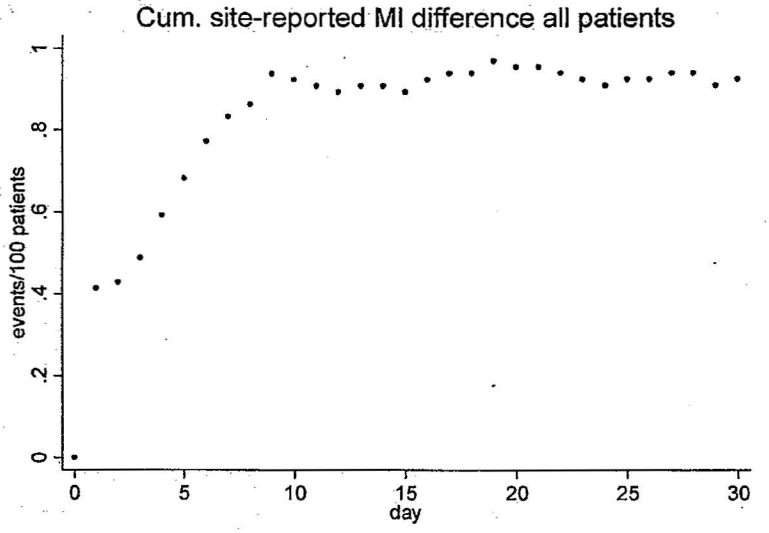


Figure 28: Cumulative Site-Reported MI Difference in All TAAL Patients



Heart failure events roughly follow the pattern for deaths and MIs: Prasugrel has an early benefit that is not sustained after 30 days. Heart failure events after 30 days were virtually equal in the two groups (119 clopidogrel vs. 118 prasugrel).

COMMENT: The site-reported events portray a slightly different picture of prasugrel benefit than the CEC adjudications. For the composite site-reported endpoint (all cause death/MI/stroke) corresponding to the CEC-adjudicated primary endpoint (CV death/MI/stroke), the TAAL results are not statistically significant for the pre-specified primary analysis in UA/NSTEMI patients. However, in the UA/NSTEMI patients the point estimate is beneficial for prasugrel and in all patients there is a statistically significant improvement in the site-reported death/MI/stroke endpoint by unstratified analysis. The benefit in all analyses appears to be a reduction in MIs. However, the site-reported events show a lower absolute benefit, a suggestion that deaths may be problematic, and little evidence of benefit beyond 15-30 days.

I interpret these efficacy results as showing that prasugrel has a small (in the order of one event/100 patients) early (< 30 days) benefit related to reduction in MIs. Whether the benefit increases beyond 30 days is less clear but it is very clear that significant bleeding increases continuously with time and the potential for tumor promotion remains a serious question for long term use.

Timing of Loading Dose

The early nature of the benefit raises another efficacy issue: The loading dose was not administered immediately in TAAL, as was the case in the clopidogrel trials and recommended in guidelines, but was delayed by protocol until after angiography was performed for UA/NSTEMI patients and not specified as immediate for STEMI patients. The article reporting the TAAL main results has this summary of the timing of the loading dose: "The study drug was administered before the first coronary guidewire was placed in 25% of patients, after the first coronary guidewire was placed and during the PCI or within 1 hour after PCI in 74%, and more than 1 hour after PCI in 1%." (Wiviott, Braunwald et al. 2007) I analyzed the times for PCI start and loading dose administration by ACS type to generate Table 26.

Table 26: Timing of Loading Dose Relative to PCI in TAAL by ACS Type

	before PCI	during or after PCI
STEMI	25%	75%
UA/NSTEMI	22%	78%

Note that, even though study drug could be given immediately in STEMI patients, it was usually delayed until during or after the PCI similar to the mandatory delay in UA/NSTEMI patients. The delay in administering the loading dose was actually worst in the US (about 87%) and better in Eastern Europe (about 59%). The delays were similar in both treatment groups.

The other critical timing issue is the time from onset of symptoms to study drug administration. (Determining timing relative to hospital presentation—i.e., door to administration time—is not possible because time of first contact was not recorded.) I show the time from symptom onset to loading dose administration in TAAL in Table 27.

Table 27: Hours from Symptom Onset to Loading Dose Administration in TAAL by ACS Type

	median	interquartile range
STEMI	7	3.7 - 28.5
UA/NSTEMI	29.7	17.4 - 49.8

The delay in administering study drug was worst in the US, with a median time of about 11 hours in STEMI patients and 31.5 hours in UA/NSTEMI patients.

The numbers in Table 26 and Table 27 for thienopyridine use in TAAL are substantially different from those in the clopidogrel trials. I show in Table 28 comparable information for the relevant clopidogrel trials with PCI. (Yusuf, Zhao et al. 2001; Steinhubl, Berger et al. 2002; Sabatine, Cannon et al. 2005)

Table 28: Timing of Loading Dose in Clopidogrel Trials with PCI

study	date published	population	dosing	time from onset	drug to PCI
PCI-CURE	2001 August	UA/NSTEMI with PCI	immediate	mean 14.1h	median 10d
CREDO	2002 November	elective PCI	immediate	(not applicable)	mean 9.8h
CLARITY	2005 March	STEMI fibrinolysis followed by PCI	immediate	median 2.9h	median 84h

Note that in the clopidogrel trials dosing was immediately after randomization, the time from onset of symptoms to dosing was shorter than in TAAL, and the time from clopidogrel dosing to PCI was long, ranging from 10 hours to 10 days. Two of the three trials in Table 28 well preceded TAAL and for the third (CLARITY), while its formal publication is dated March 2005 (4 months after enrollment began in TAAL), the TIMI Group provided the scientific oversight for both it and TAAL. That pretreatment with clopidogrel prior to PCI is beneficial and safe has also been suggested by a meta-analysis combining the results from these three trials. (Sabatine, Hamdalla et al. 2008)

COMMENT: Patients were enrolled at substantially later times from start of symptoms and the loading dose of thienopyridine was delayed in TAAL compared to the clopidogrel trials. Clopidogrel was not used in the most efficacious manner in TAAL. The delay in use affecting efficacy and the higher rates of bleeding preclude prasugrel being described as superior to clopidogrel for either efficacy or safety.

The sponsor discussed the timing of the loading dose in TAAL with the Division at an end-of-phase 2 meeting on August 4, 2004. The sponsor proposed the timing as acceptable because there were (and still are) no outcome trials comparing early with delayed treatment, ignoring the fact that all clopidogrel outcome trials involved immediate treatment. The Division judged the timing to be acceptable. In retrospect the issue of timing of loading dose should have been handled differently, e.g., either immediate treatment or a factorial study comparing immediate with delayed treatment should have been employed in TAAL. Regardless, acceptability for supporting approval does not equate to acceptability for a superiority claim and, in 2009, immediate use of clopidogrel is the appropriate comparator for a superiority claim.

We can attempt to examine event rates relative to the delay in thienopyridine initiation in TAAL. However, before doing so, I note one major limiting factor for interpretation of such analyses: TAAL did not randomize patients to varying delays. There likely are patient and investigator characteristics that influenced the delays. Investigators could have administered thienopyridine earlier to patients that had more severe presentations—or the investigators could have been distracted by performing other therapeutic measures in the more severe patients and delayed thienopyridine administration. While earlier administration in severe patients seems more likely, I am unaware of any studies that report the characteristics associated with delayed use.

The FDA pharmacometrics reviewer has performed analyses of the primary endpoint relative to the timing of thienopyridine use, and some of his analyses are summarized in the FDA primary clinical review. However, he used the primary endpoint results for the entire study. I would expect that endpoint results over the entire study would be more reflective of the relative efficacy of the two drugs; endpoint results for the start of the study should be more reflective of delays in the loading dose. Additionally, I believe that for these analyses it is critical to analyze results separately for the STEMI and UA/NSTEMI groups because of the stratification, the different specification for the timing of the loading dose, and the greater severity of the STEMI patients.

Besides the non-random nature of the loading dose delays, another limitation of the TAAL data is that most patients did have their loading doses at the start of the PCI or shortly thereafter. I show in Table 29 the numbers of patients by hour from PCI start for the hours with more than a few patients.

Table 29: Numbers of Patients by Hour from PCI Start in TAAL

hour from PCI start	UA/NSTEMI		STEMI	
	clopidogrel	prasugrel	clopidogrel	prasugrel
-2	31	33	7	6
-1	81	75	81	86
0	2,353	2,378	768	770
1	2,024	2,026	707	709
2	234	247	98	81
3	22	11	3	5

Because other hours have few data, I believe the maximum range of hours for which rates should be calculated are hours -2 to 3 for UA/NSTEMI patients and -1 to 2 for STEMI patients. I show the rates of primary endpoint events in the first 10 days by timing of loading dose for UA/NSTEMI patients in Figure 29 and for STEM patients in Figure 30.

Figure 29: Rates of UA/NSTEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TAAL

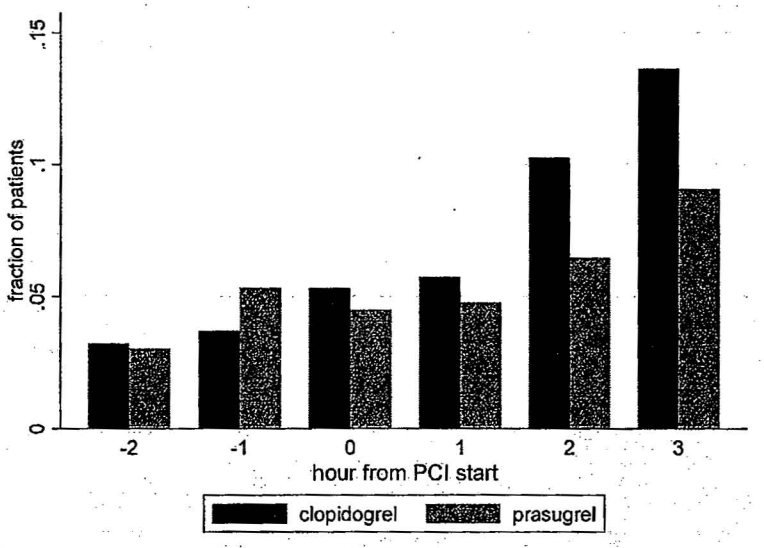


Figure 30: Rates of STEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TAAL