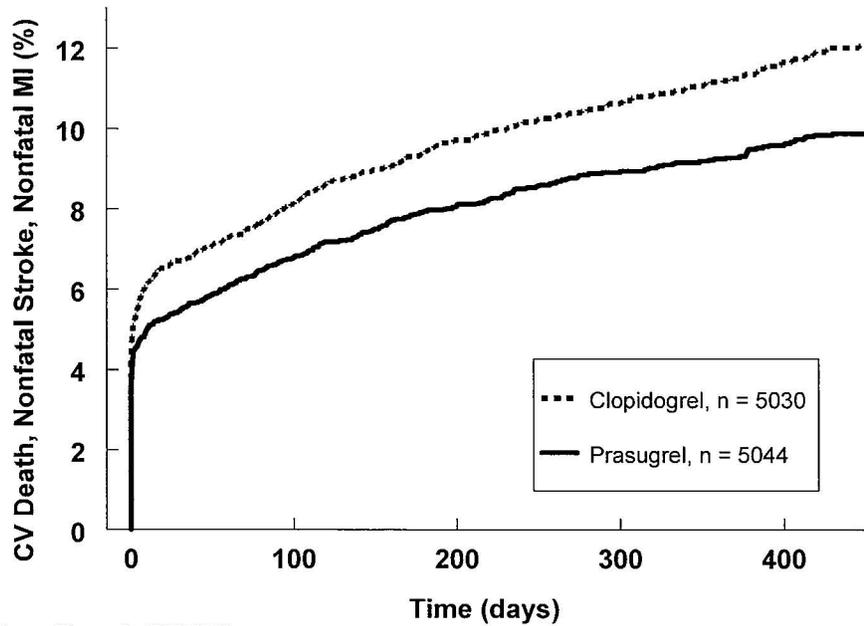


Figure 5: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke

Top Panel: NSTEMI/UA



Bottom Panel: STEMI

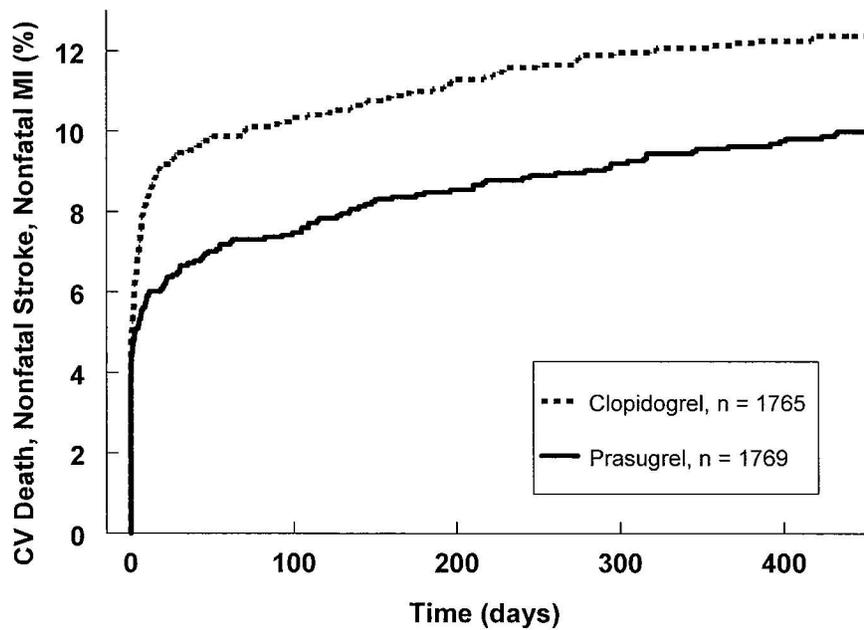
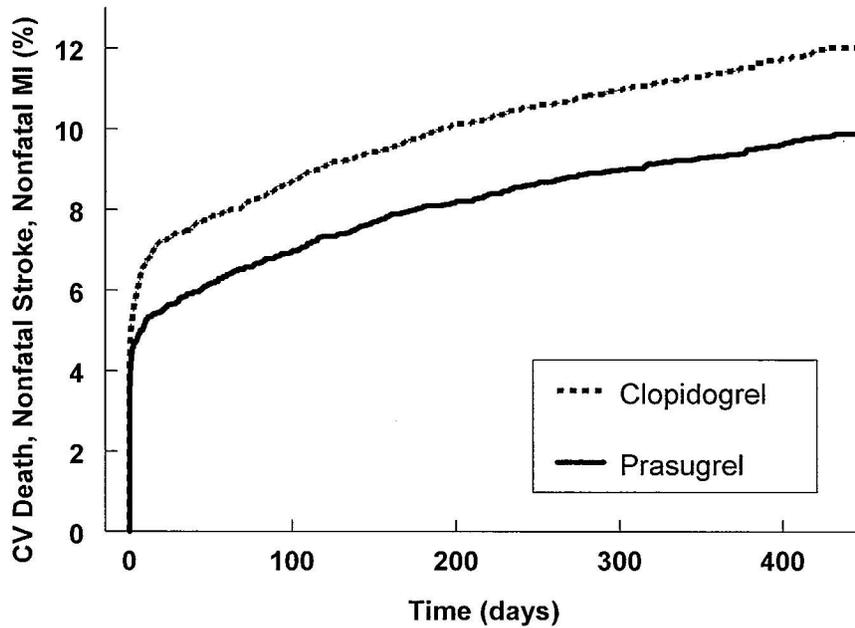
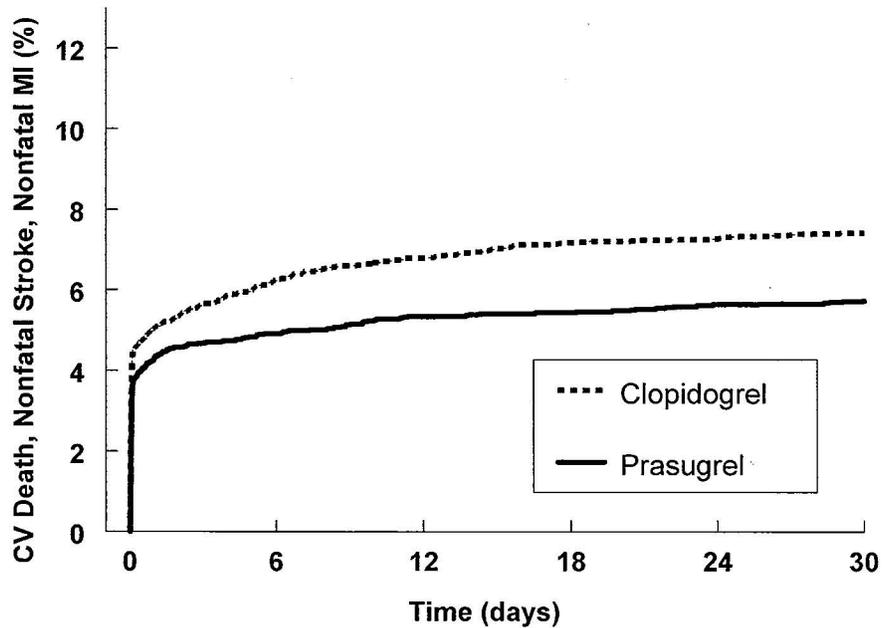


Figure 6: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke, All ACS Subjects

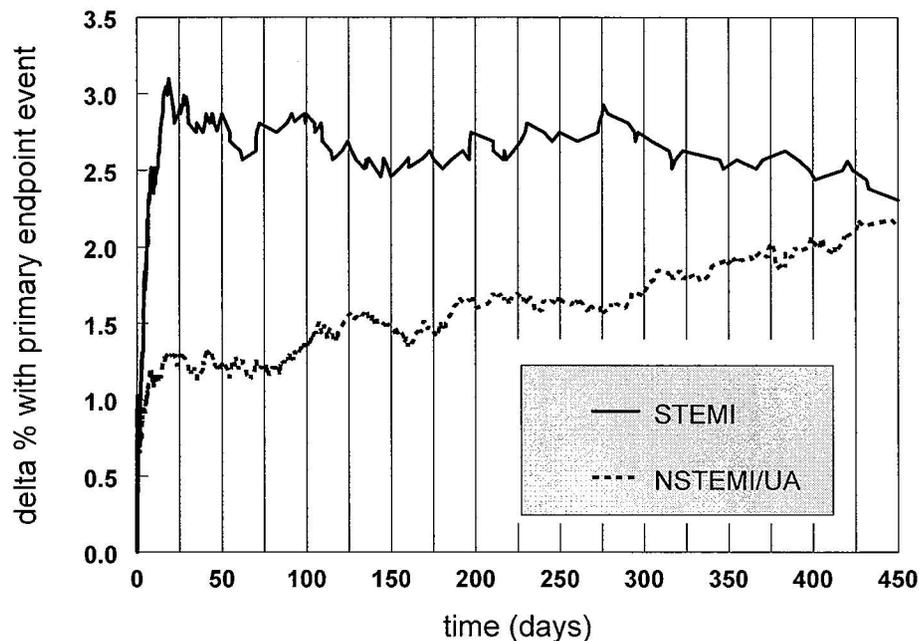
Top Panel: 0 – 450 Days;



Bottom Panel: 0 – 30 Days:



**Figure 7: Kaplan-Meier Estimates of the 1° Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations**



### 7.3.1. Explorations on the Primary Endpoint

#### Sponsor's Sensitivity Analyses:

The sponsor conducted sensitivity analyses, restricting the analysis of the 1° endpoint to subjects on treatment, and subjects on treatment and compliant to study drug. For both analyses, the results were consistent with the study results on the whole.

#### Individual Components of the Endpoint:

The individual components of the 1° endpoint are shown for the UA/NSTEMI, STEMI, and the All ACS populations in Table 7, as reported by the sponsor and confirmed by the statistical reviewer. The incidence of nonfatal MI is statistically significantly lower in the prasugrel group in both the UA/NSTEMI and STEMI populations, and in the ACS population overall; this component of the composite endpoint is what drives the overall study results. The CV death component shows a trend in favor of prasugrel in the STEMI population (hazard ratio = 0.74,  $p = 0.13$ ), and neutrality for the UA/NSTEMI population (representing roughly three-quarters of the overall study population), with only a very weak trend in the overall population ( $p=0.307$ ). The effect of prasugrel on nonfatal stroke was neutral. The statistical reviewer noted that prasugrel was associated with a higher incidence of nonfatal stroke in the All ACS and STEMI populations, but the numbers of events were small, with a hazard ratio fairly close to unity (Table 7).

**Table 7: Components of 1° Efficacy Endpoint (from table 11.7 in TAAL Study Report)**

endpoint	Patient population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
CV Death	UA/NSTEMI	5044	90	1.8	5030	92	1.8	10074	182	1.8	0.98 (0.73,1.31)	0.885
	STEMI	1769	43	2.4	1765	58	3.3	3534	101	2.9	0.74 (0.50,1.09)	0.129
	All ACS	6813	133	2.0	6795	150	2.2	13608	283	2.1	0.89 (0.70,1.12)	0.307
Nonfatal MI	UA/NSTEMI	5044	357	7.1	5030	464	9.2	10074	821	8.1	0.76 (0.66,0.87)	<0.001
	STEMI	1769	118	6.7	1765	156	8.8	3534	274	7.8	0.75 (0.59,0.95)	0.016
	All ACS	6813	475	7.0	6795	620	9.1	13608	1095	8.0	0.76 (0.67,0.85)	<0.001
Nonfatal Stroke	UA/NSTEMI	5044	40	0.8	5030	41	0.8	10074	81	0.8	0.98 (0.63,1.51)	0.922
	STEMI	1769	21	1.2	1765	19	1.1	3534	40	1.1	1.10 (0.59,2.04)	0.77
	All ACS	6813	61	0.9	6795	60	0.9	13608	121	0.9	1.02 (0.71,1.45)	0.93

**Definition of MI:**

The protocol's original definition of peri-procedural MI required an elevation of CK-MB to >3X ULN on at least two samples within 48 hours of PCI. A modified definition, specified in protocol amendment "A" dated January 10, 2006, extended the definition of peri-procedural MI to a CK-MB >5X ULN on a single sample if it was the last available sample drawn and obtained ≥12 hours after PCI. This change resulted in the addition of 38 and 44 endpoint events to the prasugrel and clopidogrel groups, respectively, with no substantive change in the overall findings.

**Statistical Assumptions of the Cox Model:**

Non-informative censoring is a key assumption of the Cox model; the study design must ensure that mechanisms leading to the censoring of subjects are not related to the probability of an event. Dr. Liu, the statistical reviewer, examined the censoring distributions between the two treatment groups in all three subject populations and found them to be similar. Another key assumption of the Cox's regression analysis is the assumption of proportionality of the hazard ratio over time. Dr. Liu created log(-log survivor) plots for the UA/NSTEMI, STEMI, and overall ACS populations. For all 3 populations, the two relations were reasonably parallel over time, supporting the concept that the hazard ratio was fairly constant over time. Thus, the statistical reviewer found no important issues with the statistical assumptions of the Cox Model.

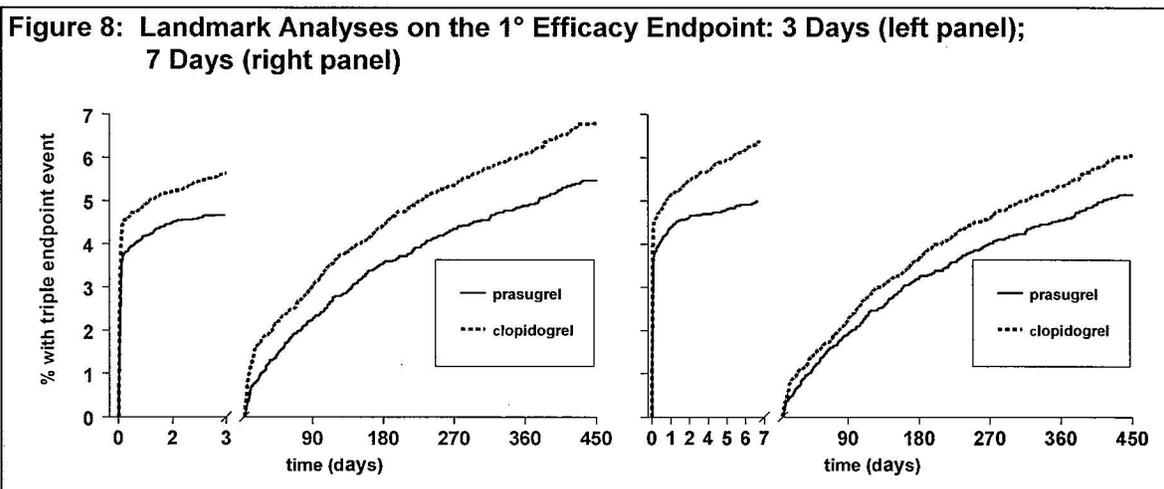
**Landmark Analyses:**

There is support for the concept that a clopidogrel LD of 600-mg is associated with more rapid inhibition of platelet aggregation than the standard LD of 300-mg (used in TAAL), and OASIS7 is being conducted to examine this hypothesis in a randomized controlled trial (ClinicalTrials.gov Identifier: NCT00335452). Thus, some have argued that in TAAL, an inadequate clopidogrel LD provided prasugrel with an advantage during the initial hours of therapy, during the interval when patients were subjected to PCI and at risk of peri-procedural myocardial infarctions.<sup>1</sup>

This reviewer conducted landmark analyses, in essence time-to-event analyses before and after cut-points of 3 days (Figure 8, left panel) and 7 days (Figure 8, right panel). These consider event-free survival beginning at points in time beyond which the adequacy of the LD would be

<sup>1</sup> *N Engl J Med.* 2008;358:1298-9

expected to influence events, and beyond which peri-procedural events are likely to occur. The landmark analyses have limitations in that the original randomization is not preserved; therefore, the analyses are somewhat observational in nature. The point can also be argued that events occurring at the beginning of the study might influence events later on; however, it is also true that subjects at the highest risk experience events early in the study. As such, the clopidogrel group is “de-enriched” through removal of subjects at highest risk. Although interpretation is not straightforward, the analyses show a treatment effect of prasugrel from both Day 3 and Day 7 forward, and are consistent with the concept that the superiority of prasugrel is not merely a function of the LD, or simply a reduction in early peri-procedural events.



Multiplicity:

Given the nature and interrelations of the indications supported by the study, multiplicity is a complex issue. Although the statistical reviewer noted that a number of reviewers had comments on multiplicity in their reviews of the study protocol, she opined that the pre-specified strategy for dealing with multiplicity was reasonable. She noted also that adjustment of multiplicity is a moot issue, given the very small nominal p-values for the 1° composite endpoint and the pre-specified 2° endpoints.

Site-Reported Endpoint Events:

Dr. Marciniak performed a number of exploratory analyses to assess the robustness of the 1° efficacy endpoints. In light of his concerns regarding neoplasia (see section 7.4.15), the strength of the efficacy findings are particularly important to the risk-benefit profile.

In TAAL, events could be referred to the CEC by site, or triggered by a review of laboratory values. Dr. Marciniak noted (page 28 of his review): “The CEC adjudicated higher percentages of clopidogrel events as MIs than prasugrel events, as shown in Table 19.” (reproduced here):

**Table 19: CEC MI Adjudications by Type of Referring Event**

referring event	clopidogrel		prasugrel	
	n	% MI	n	% MI
site MI event	303	80%	180	76%
site other ischemic event	984	19%	903	15%
triggered PPMI*	1022	21%	1049	19%

\*PPMI = peri-procedural myocardial infarction

He concluded that site reported MI's appear to be better predictors of death than the CEC-adjudicated MI's, and noted, therefore, that site-reported events are clinically more important than those that are not site-reported. He went on to assess the efficacy endpoint (death, non-fatal MI, non-fatal stroke) in the UA/NSTEMI, STEMI, and overall ACS populations, counting only site-reported events. (Site-reported events represented approximately 60-70% of the total events; therefore, some 30-40% of events were not included in his sensitivity analyses.) With omission of these events, results were not statistically significant. He also noted that there is no substantial treatment effect after 30 days, when considering site-reported events. This is essentially in line with the standard analysis, where the treatment effect waned after 18 days (in STEMI subjects), and waned more gradually in STEMI subjects (Figure 7). Dr. Marciniak has also emphasized that the numbers of events decrease greatly after 30 days. Thus, if there is ongoing risk, it must be considered against a background of diminishing benefit.

This reviewer strongly agrees with the latter point, that is, that the treatment effect is front-loaded. In the opinion of this reviewer, however, these sensitivity analyses do not raise important questions regarding the validity or persuasiveness of the results. My rationale can be summarized as follows:

- 1) Based on Table 19, above, there was essentially no evidence of differential reporting or biased adjudication for the two treatment groups.
- 2) "Enzyme leaks" are widely believed to be of clinical importance. TAAL was designed with the knowledge that many non-fatal myocardial infarctions would be asymptomatic, manifested only as "chemical MIs" or "enzyme leaks." However, because these "events" are believed to have clinical significance,<sup>2</sup> the trial was designed in such a way as to attempt to ensure that they would be detected and included in efficacy analyses.
- 3) The Division prospectively agreed with the protocol design, to ensure that these events would be counted.

In some clinical trials, it can be important to assess the adjudication of events by a central committee. This is particularly true in studies where there is the potential for unblinding of subjects or investigators (e.g., because of side effects, changes in laboratory values, injection site reactions, etc.), and ascertainment bias is suspected or possible. In such cases, a disparity between treatment groups in terms of the percentages of events adjudicated as positive (versus negative) might suggest that bias was operational. In TAAL, adjudication seems less critical, considering that unblinding would be unlikely, and given that strict criteria were used to analyze laboratory data. (Although these criteria were revised at one point during the study, there is no reason to suspect a differential effect by treatment group.)

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<sup>2</sup> *Eur Heart J.* 2004;25:313-21

#### Results of the Study by Half:

This reviewer assessed the overall study results by median time of enrollment (first and second halves of study). A trend in favor of a more robust treatment effect in the second half of a study versus the first half would support (but by no means prove) the concept that knowledge gained during the course of the study was used improperly as a basis to alter the study design, enrollment pattern, or analytic plan, in order to increase the apparent (or real) treatment effect. In TAAL, the opposite trend occurred. That is, for the triple composite endpoint over the entire ACS population, the log-rank for prasugrel versus clopidogrel was 0.0013 for the first study half (subjects enrolled through December 20, 2005), and 0.0213 for the second. The less robust treatment effect in the second half of the study suggests that the study was “honest:” that is, there is no suggestion that knowledge gained during the conduct of the study was used improperly to influence study conduct or analysis.

In summary, the results for the 1° efficacy endpoint are persuasive and robust to exploration. The overall treatment effect was driven by nonfatal MI. The CV death component shows a trend in favor of prasugrel in the STEMI population, but only a very weak trend in the overall population. The effect of prasugrel versus clopidogrel on nonfatal stroke was neutral. In light of these findings, the indication in labeling should be restricted to prevention of MI.

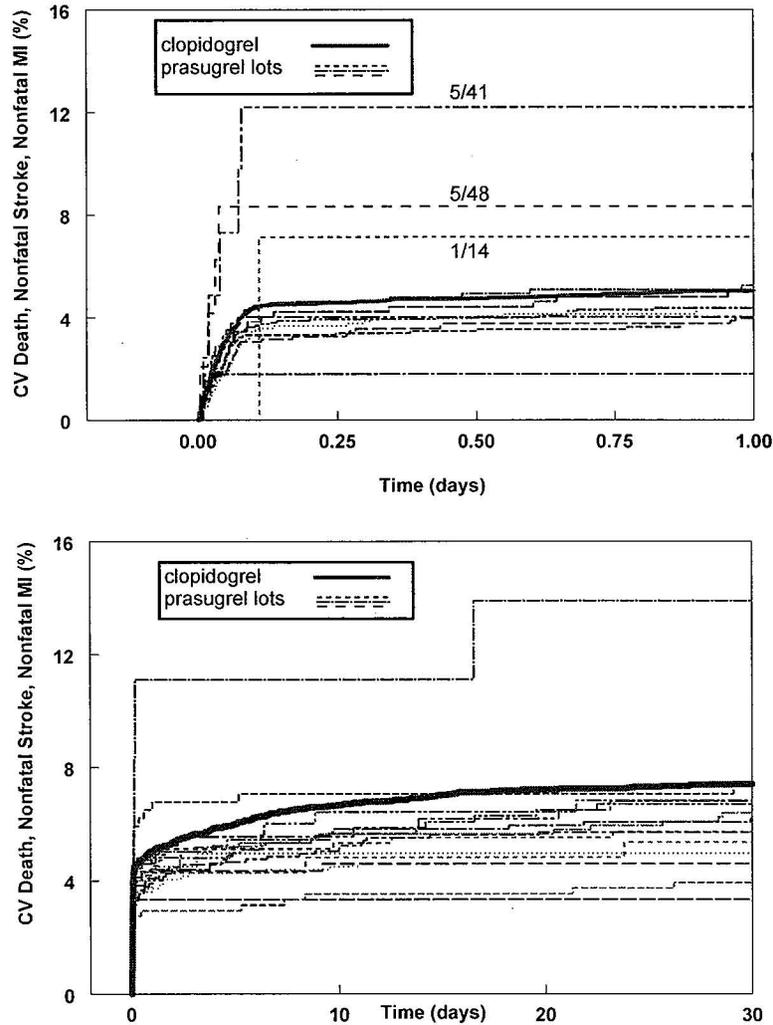
#### Drug Quality:

The sponsor initiated drug development using the free base of the drug substance, but switched to a hydrochloride (HCl) salt because of greater bioavailability in patients with higher gastric pH. Near the time when TAAL completed enrollment, the sponsor discovered a reaction between the HCl salt and an excipient that converted up to 86% of the salt to the free base. Although lots with low, intermediate, and high conversion to base were found to be bioequivalent at normal gastric pH, prasugrel lots with differing salt to base conversion were bio-inequivalent when administered in the presence of PPI. This is salient because PPI use is common in patients with ACS.

Ideally, one might estimate the clinical importance of salt-to-base conversion by estimating efficacy (and safety) in TAAL by the extent of salt-to-base conversion for the prasugrel administered to each subject. Practically speaking, however, this was problematic for two reasons: First, the lots were batch-tested for salt-to-base conversion at only a few points in time. Conversion was not assessed near the time of administration, and was not assessed serially (serial data might have been used to estimate the extent of conversion at the time of administration). Second, subjects obtained prasugrel from several lots during the course of TAAL.

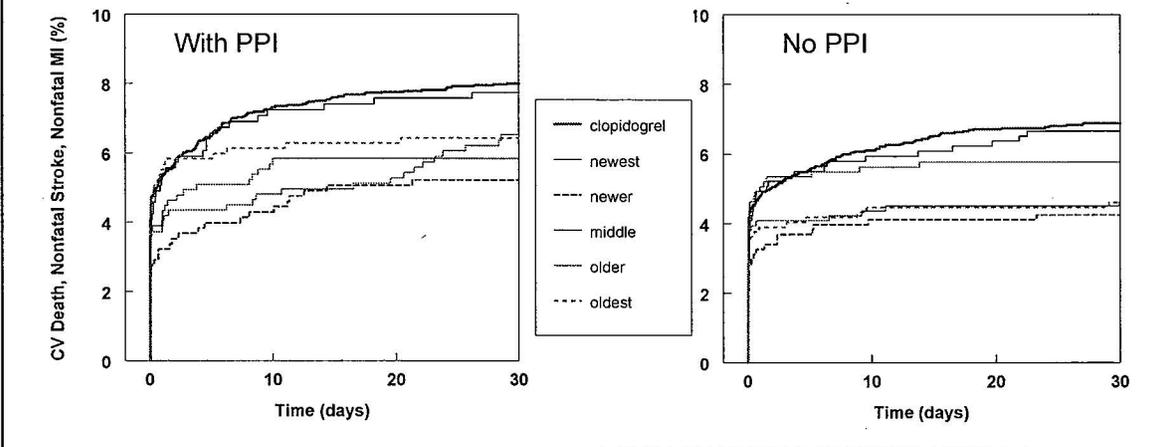
These issues notwithstanding, some estimate of the clinical importance of conversion can be gleaned through the following analyses: Although subjects obtained prasugrel from several lots during the course of the study, the loading dose (6 pills) was obtained from a single lot, and the initial month's supply (Days 2-30) was obtained from a single (but generally different) lot as well. Because more than half of all events occurred between Days 0 and 30, and because the majority of prasugrel's treatment effect was evident during this period, this reviewer analyzed efficacy on the triple composite endpoint as a function of prasugrel lot used for the loading dose (Figure 9, top) and the lot administered Day 2 to 30 (Figure 9, bottom). Although the salt-to-base conversion at the time of actual use cannot be estimated for the disparate prasugrel lots, it is difficult to interpret event-free survival as importantly different from clopidogrel for any prasugrel lot subgroup with a sizable number of subjects. (Note that the subgroups associated with higher event rates tend to be small in size; fractions indicate N with events/ N at risk.)

**Figure 9: 1° Efficacy Endpoint by Prasugrel Lot Administered Through Day 30:  
Top – Loading Dose Through Day 1; Bottom – Maintenance Dose Through Day 30**



Because the sponsor asserts that there was at least some conversion of salt to base during storage, this reviewer also assessed efficacy as a function of the age of the prasugrel lot used to supply each subject with their initial 30 day supply, in the presence and absence of PPI use (age = date administered minus date of manufacture). Of note, use of PPIs was transient or intermittent in some subjects; subjects with recorded PPI use at any time were considered PPI users for the purpose of this analysis. In both the presence and absence of PPIs, there was no relation between age of lot administered during the initial 30 days and efficacy (Figure 10).

**Figure 10: 1° Efficacy Endpoint by Age of Prasugrel Lot Administered Through Day 30**



These analyses suggest that prasugrel's efficacy was at least similar to clopidogrel for the vast majority of lots, and efficacy was not importantly affected by pill age. (The lot with the highest event rate included only 36 subjects.)

Both of these analyses support the concept that neither disparate salt to base conversion nor pill age had an important bearing on efficacy.

### 7.3.2. Subgroup Analyses

#### Body Weight:

Given that the study employed a fixed dosing regimen (non-weight-adjusted), there is concern that subjects at higher weights may have received an insufficient dose of prasugrel. (There is also the concern that subjects at the lower fringes of weight may have received excess drug, but this is more an issue for safety.) The Clinical Pharmacology Review considered the relationship between body weight and efficacy. Using an exploratory univariate Cox model, the results were inconsistent for the impact of body weight on efficacy, depending on whether it was used as a continuous or categorical variable. Multivariate analyses did not show body weight to be a significant predictor of efficacy.

Dr. Liu, the statistical reviewer, provided a number of analyses of the 1° endpoint by patient weight. The odds ratio was statistically significantly <1 for subjects in the  $\geq 50$  to <70 kg weight group, as well as for subjects in the  $\geq 70$  kg, 70-90 kg, and <60 kg weight groups. Only for subjects weighing <50 kg (n=50 for the entire study, or 0.4% of the study population) was the odds ratio >1 (1.05; with 95% C.I. 0.60 – 1.82).

Because weight is confounded by sex, this reviewer assessed the 1° efficacy endpoint by weight quintiles, for male and female subjects separately (Figure 11). No trends emerged to suggest that subjects with higher body weights received insufficient drug. The probability of experiencing an endpoint event did not tend to increase with increasing subject weight.

Figure 12 shows the results on the 1° endpoint for the overall ACS population by weight. The upper left panel shows the results for subjects weighing <60 kg. The effect of prasugrel was neutral in this small subgroup, comprising 6% of the overall subject population. The remaining panels show results for weight quintiles 1 through 5. Weights for the 5 quintiles broke down as follows: Q1: weight  $\leq 70$  kg, Q2: >70 to  $\leq 78$  kg, Q3: >78 to  $\leq 85$  kg, Q4: >85 to  $\leq 95.24$  kg, and Q5: >95.24 kg.