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.

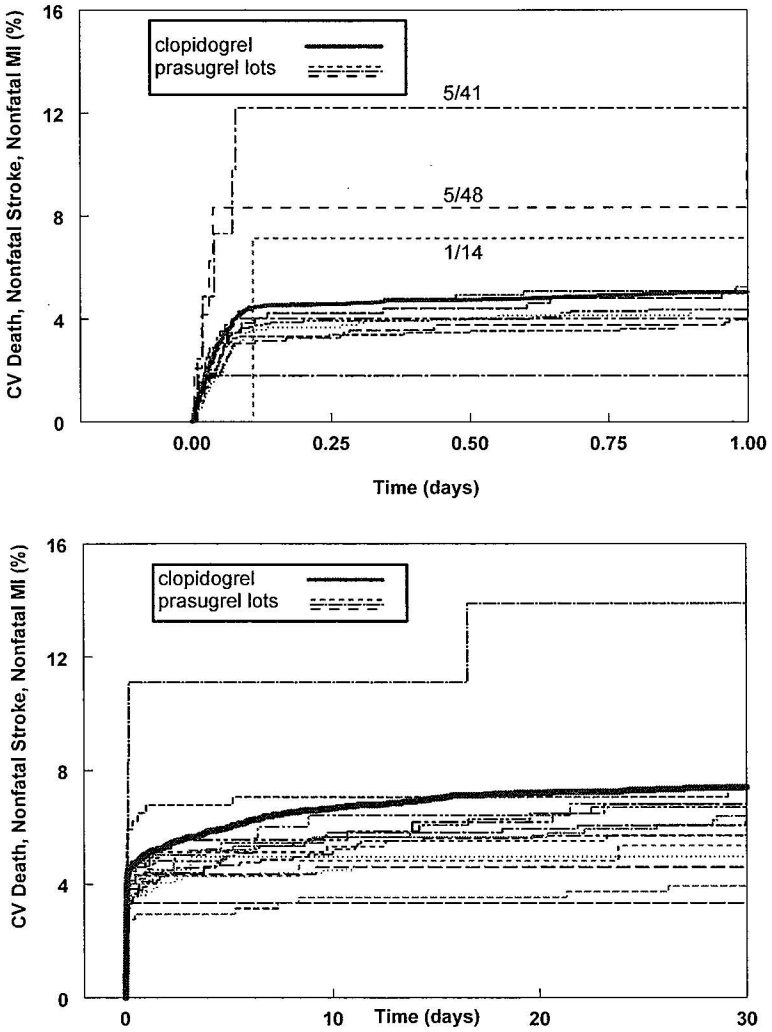
In summary, the results for the 1° efficacy endpoint are persuasive and robust to exploration. The overall treatment effect was driven by nonfatal MI. The CV death component shows a trend in favor of prasugrel in the STEMI population, but only a very weak trend in the overall population. The effect of 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.

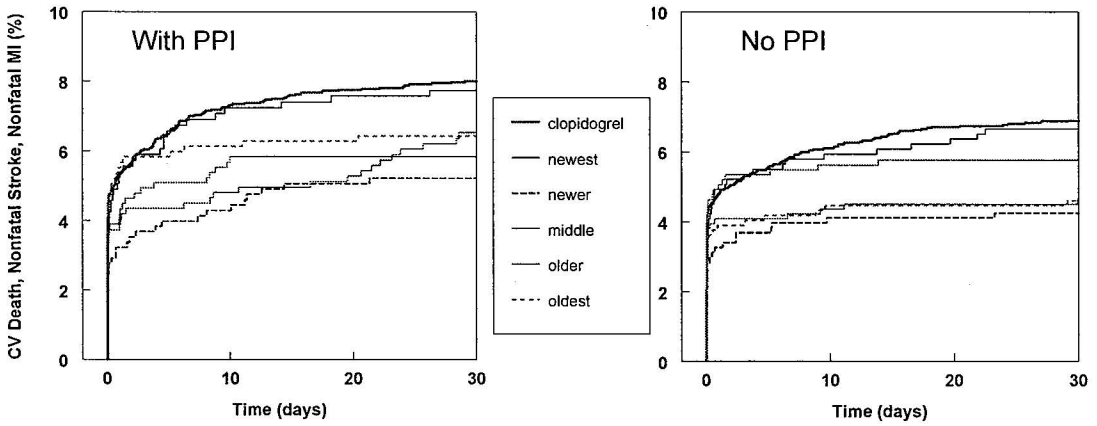
These issues notwithstanding, some estimate of the clinical importance of conversion can be gleaned through the following analyses: Although subjects obtained prasugrel from several lots during the course of the study, the loading dose (6 pills) was obtained from a single lot, and the initial month's 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:

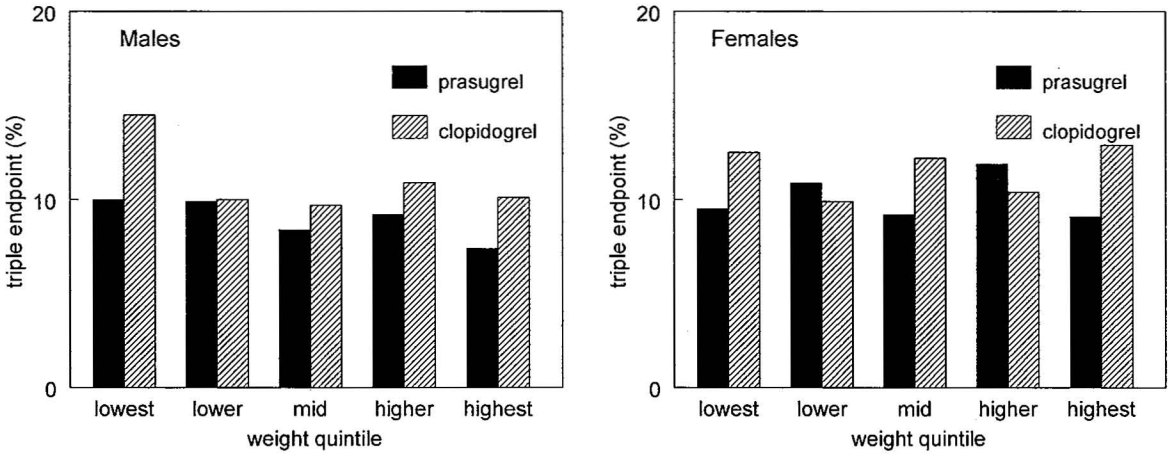
Given that the study employed a fixed dosing regimen (non-weight-adjusted), there is concern that subjects at higher weights may have received an insufficient dose of prasugrel. (There is also the concern that subjects at the lower fringes of weight may have received excess drug, but this is more an 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 ≥50 to <70 kg weight group, as well as for subjects in the ≥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.

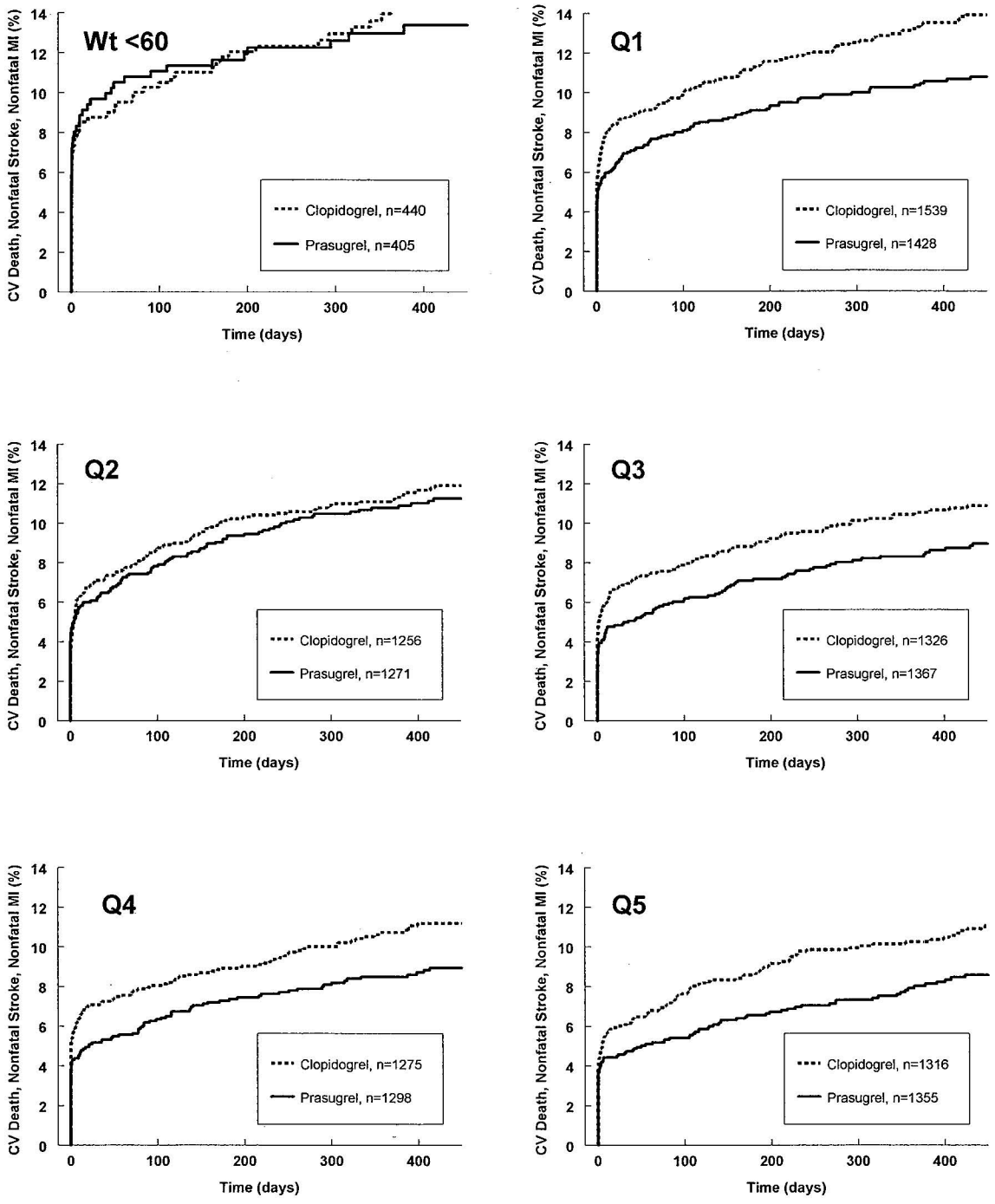
Figure 12 shows the results on the 1° endpoint for the overall ACS population by weight. The upper left panel shows the results for subjects weighing <60 kg. The effect of prasugrel was neutral in this small subgroup, comprising 6% of the overall subject population. The remaining panels show results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

Figure 11: Triple Efficacy Endpoint by Weight Quintiles and Sex



In short, prasugrel appears effective over the range of weights studied. For the small subgroup of subjects weighing <60 kg, prasugrel appears similar, and not superior, to the comparator on the 1° efficacy endpoint.

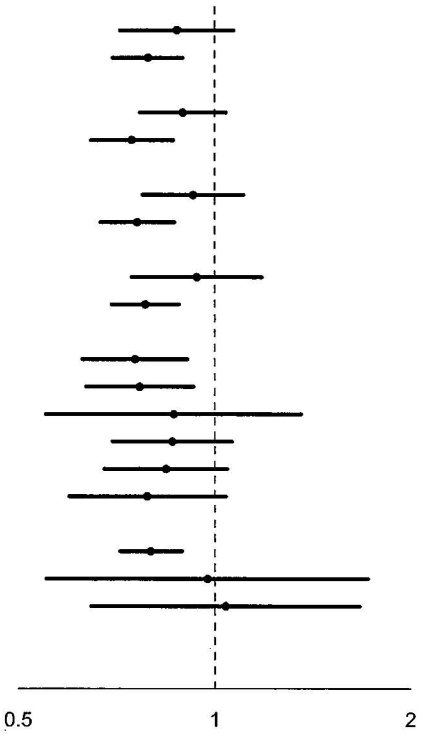
Figure 12: Primary Triple Composite Endpoint by Weight



Subgroups on Sex, Age, and Geographic Location:
Hazard ratios and 95% confidence intervals are shown for the 1° efficacy endpoint for the overall All ACS population across subgroups of sex, age, and geographic location (Figure 13). The treatment benefit of prasugrel tended to be greater in younger versus older populations. Event rates in subjects of African descent tended to be higher than those in Caucasians and the effect of prasugrel was essentially neutral compared to clopidogrel in this population, although the strength of this conclusion is limited given the small number of subjects of African descent studied (less than 3% of the total study population). The numbers of subjects of Asian descent, and numbers of events, were small, and are not shown (1/60 in the prasugrel group; 4/64 in the clopidogrel group). Exposure may be higher in patients of Asian descent (see section 5.2.5).

Figure 13: Results for Triple Composite Endpoint – All ACS Population – Subgroups of Sex, Age, Geographic Location, and Ethnicity

	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
female	1705	178	10.4	1818	215	11.8
male	5108	465	9.1	4977	566	11.4
age ≥ 65	2625	321	12.2	2661	361	13.6
age <65	4188	322	7.7	4134	420	10.2
age ≥ 70	1668	235	14.1	1699	257	15.1
age <70	5145	408	7.9	5096	524	10.3
age ≥ 75	901	144	16.0	908	154	17.0
age <75	5912	499	8.4	5887	627	10.7
North America	2164	199	9.2	2146	258	12.0
U.S.	2039	191	9.4	2020	244	12.1
South America	270	36	13.3	264	40	15.2
Western Europe	1779	164	9.2	1774	188	10.6
Eastern Europe	1657	153	9.2	1665	181	10.9
rest of world	943	91	9.7	946	114	12.1
Caucasian	6263	581	9.3	6274	720	11.5
African	205	25	12.2	187	23	12.3
Hispanic	269	36	13.4	256	33	12.9

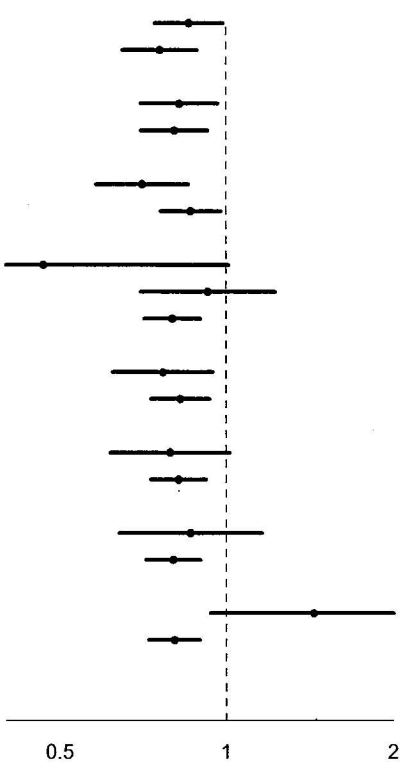


Event rates were fairly similar across geographic regions, except for South America, where event rates were higher. There, too, the odds ratio trended favorable for prasugrel.

Figure 14 shows the results for subgroups of prior (known) vascular disease, metabolic syndrome, diabetes, creatinine clearance (Ccr), prior MI, prior PCI, prior CABG, and history of stroke or TIA. The results trend consistently in favor of prasugrel, with the exception of subjects with a prior history of TIA or stroke.

Figure 14: Results for Triple Composite Endpoint – All ACS Population – Subgroups of Preexisting Medical Conditions, Coronary Disease, Procedures, TIA, and CVA

	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
Hx vascular disease	2907	358	12.3	2848	405	14.2
No Hx vascular disease	3906	285	7.3	3947	376	9.5
Metabolic syndrome	2966	279	9.4	2938	333	11.3
No metabolic syndrome	3847	364	9.5	3857	448	11.6
Diabetes	1576	180	11.4	1570	248	15.8
No dibetes	5237	463	8.8	5225	533	10.2
Ccr <30	51	11	21.6	54	21	38.9
Ccr 30-60	666	92	13.8	720	106	14.7
Ccr >60	5982	515	8.6	5907	630	10.7
Prior MI	1226	161	13.1	1208	201	16.6
No prior MI	5587	482	8.6	5587	580	10.4
Prior PCI	904	112	12.4	926	143	15.4
No prior PCI	5909	531	9.0	5869	638	10.9
Prior CABG	541	86	15.9	497	90	18.1
No prior CABG	6272	557	8.9	6298	691	11.0
Prior TIA or CVA	262	50	19.1	256	36	14.1
No prior TIA or CVA	6551	642	9.8	6539	786	12.0



Subjects with Prior History of Transient Ischemic Attack or Stroke:
The clinical outcomes were particularly poor for prasugrel-treated subjects with a prior history of transient ischemic attack (TIA) or non-hemorrhagic stroke. Because of the risk of ICH, potential subjects with a history of hemorrhagic stroke, ischemic stroke ≤3 months prior to screening, intracranial neoplasm, arteriovenous malformation, or aneurysm were excluded from participation in TAAL. These criteria allowed entry to patients with a history of ischemic stroke >3 months prior to screening, as well as patients with a history of TIA.

For subjects with a prior history of TIA or non-hemorrhagic stroke, the HR for the composite efficacy endpoint was unfavorable for prasugrel, going against the grain of the study as a whole. The HR was 1.38 in favor of *clopidogrel*: 47 of 262 prasugrel treated subjects (17.9%) experienced an endpoint event, compared to 35 of 256 clopidogrel-treated subjects (13.7%). Table 8 breaks down the components of the triple endpoint for subjects with and without a prior history of TIA or stroke, and shows "All Stroke" as well. Of note, approximately 1/3 of the endpoint events in the prasugrel group were stroke. Specifically, 6.5% of subjects in the prasugrel treatment group experienced a stroke on study (2.3% ICH; 4.2% thrombotic) compared to 1.2% in the clopidogrel treatment group (0% ICH; 1.2% thrombotic), for a HR of

5.64. In patients with no prior history of TIA or non-hemorrhagic stroke, the incidence of stroke was 0.9% (0.2% ICH) in the prasugrel treatment group and 1.0% (0.3%) in the clopidogrel treatment group.

It is striking that more than one-quarter of the non-fatal stokes in the prasugrel treatment group (17 of 61) occurred in the sub-population of subjects with a history of prior TIA or non-hemorrhagic stroke, a sub-population encompassing only 3.8% of the total subject population. Moreover, it should be re-emphasized that subjects with a history of ischemic stroke within 3 months of randomization, as well as subjects with a history of hemorrhagic stroke at any time, were excluded from the study. (It is possible that such patients would have fared even worse.)

Based on these concerns, the clinical reviewer recommended a contraindication for prasugrel in patients with a prior history of TIA or stroke. This reviewer supports that recommendation.

Table 8: Cardiovascular Death, Nonfatal MI, Nonfatal Stroke, and All Stroke in Subjects With and Without a Prior History of Stroke or TIA

Endpoint	Prior TIA or Stroke?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
Triple Composite	Yes	262	47	17.9	256	35	13.7	1.38 (0.89, 2.13)	0.15
	No	6551	596	9.1	6539	746	11.4	0.79 (0.71, 0.88)	<0.001
CV Death	Yes	262	9	3.4	256	15	5.9	0.63 (0.28, 1.44)	0.27
	No	6551	124	1.9	6539	135	2.1	0.92 (0.72, 1.17)	0.48
Nonfatal MI	Yes	262	29	11.1	256	25	9.8	1.15 (0.67, 1.97)	0.61
	No	6551	446	6.8	6539	595	9.1	0.74 (0.66, 0.84)	<0.001
Nonfatal Stroke	Yes	262	15	5.7	256	2	0.8	7.39 (1.69, 32.3)	0.002
	No	6551	46	0.7	6539	58	0.9	0.79 (0.54, 1.17)	0.23
All Stroke	Yes	262	17	6.5	256	3	1.2	5.64 (1.65, 19.3)	0.002
	No	6551	58	0.9	6539	68	1.0	0.85 (0.60, 1.21)	0.36

Concomitant Therapies:

- Stents

In the All ACS population, the hazard ratio for prasugrel compared to clopidogrel was essentially the same in subjects receiving any stent (0.81), no stent (0.82), any drug-eluting stent (0.79), and any bare metal stent (0.80).

- GPIIb/IIIa Inhibitors

In the All ACS population, the hazard ratio for prasugrel compared to clopidogrel was similar in subjects receiving a GPIIb/IIIa inhibitor during the index procedure (0.79) compared to subjects not receiving a GPIIb/IIIa inhibitor during the index procedure (0.83). A similar pattern was observed for the UA/NSTEMI and STEMI populations.

- Statins

For the overall ACS population, the hazard ratio in favor of prasugrel was similar in subjects treated and not treated with a statin, 0.81 and 0.83, respectively. Hazard ratios were similar for the UA/NSTEMI and STEMI populations.

- Aspirin

According to the sponsor's analyses, the relative risk reduction with prasugrel compared to clopidogrel in the all ACS population was not influenced by the maximum aspirin dose (>0 to <100, 100 to 200, >200-mg/day) administered through 3 days after randomization and more than 3 days from randomization. These observations were similar for the UA/NSTEMI and STEMI populations.

- Proton Pump Inhibitors

If PPI had importantly diminished prasugrel's pharmacodynamic effects in the setting of salt-to-base conversion, one would expect diminished efficacy in subjects who were receiving PPI. Approximately 40% of the subjects in each treatment group reported use of PPI as a concomitant medication. The Cox proportional hazard ratio favored prasugrel over clopidogrel in subsets of subjects who received and did not receive PPI, and was virtually the same in both subsets. Hazard ratios were 0.82 and 0.80 in subjects who reported and did not report use of PPI, respectively.

- CABG

In the All ACS population undergoing CABG, the hazard ratio was favorable for prasugrel (0.71).

Time from First Symptom to Randomization:

For the UA/NSTEMI population, the hazard ratios were favorable for prasugrel in subjects randomized ≤24 hours and >24 hours after symptom onset (hazard ratios 0.75 and 0.87, respectively).

For the STEMI population, the hazard ratios were favorable for prasugrel in subjects randomized >12 hours after symptom onset and ≤12 hours after symptom onset (hazard ratios 0.65 and 0.87, respectively).

Time from Loading Dose to PCI:

Dr. Raj Madabushi explored the relation between the triple-endpoint outcome and the time interval between LD and start of PCI. He divided subjects in octiles based on time between LD and start of PCI, and computed the proportion of triple endpoint events for each octile, by treatment arm. Within each octile, there were fewer numbers of events in prasugrel-treated subjects, demonstrating a consistent advantage of prasugrel over clopidogrel, irrespective of the timing of the LD relative to PCI.

Interestingly, in both treatment arms, the lowest numbers of endpoint events were observed when the loading dose was administered at the start of PCI or within 30 minutes thereof. With increasing time between the LD and start of PCI (earlier or later), the proportion of endpoint events increased. Dr. Madabushi concluded that the LD (for either prasugrel or clopidogrel) should be administered within 30 minutes of the start of PCI.

This conclusion is subject to interpretation. The finding of an association between outcome and timing of the LD relative to PCI does not prove causality. For example, administration of the LD >1 hour after leaving the catheterization laboratory was a protocol violation, and could be related to a subject's medical instability. Prolonged intervals between administration of the LD and subsequent PCI were interpreted as "early" administration of the LD, but may in fact represent delayed PCI, due to difficult vascular access, complex anatomy, clinical instability, etc., which might be associated with worse outcomes. Thus, although these analyses are