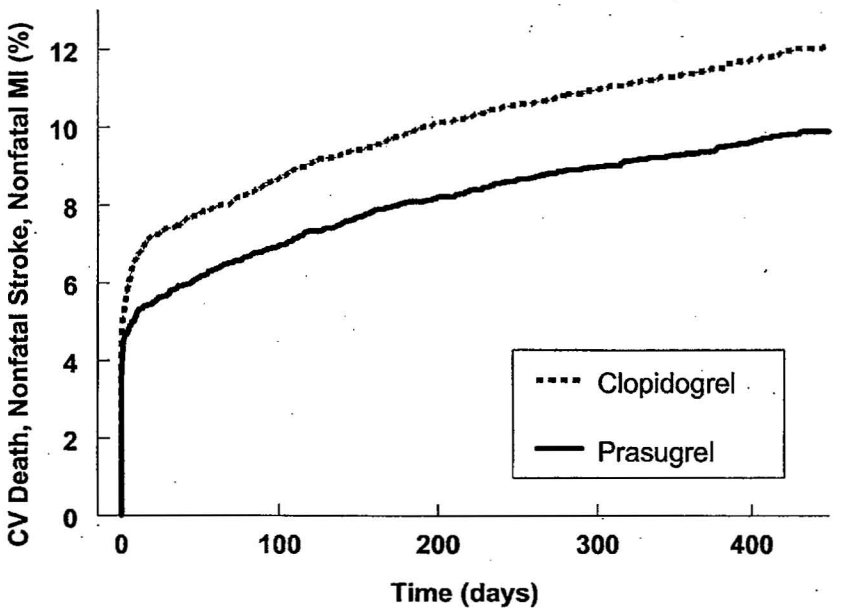
**Figure 5: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke, All ACS Subjects**

**Top Panel: 0 – 450 Days;**




**Bottom Panel: 0 – 30 Days:**

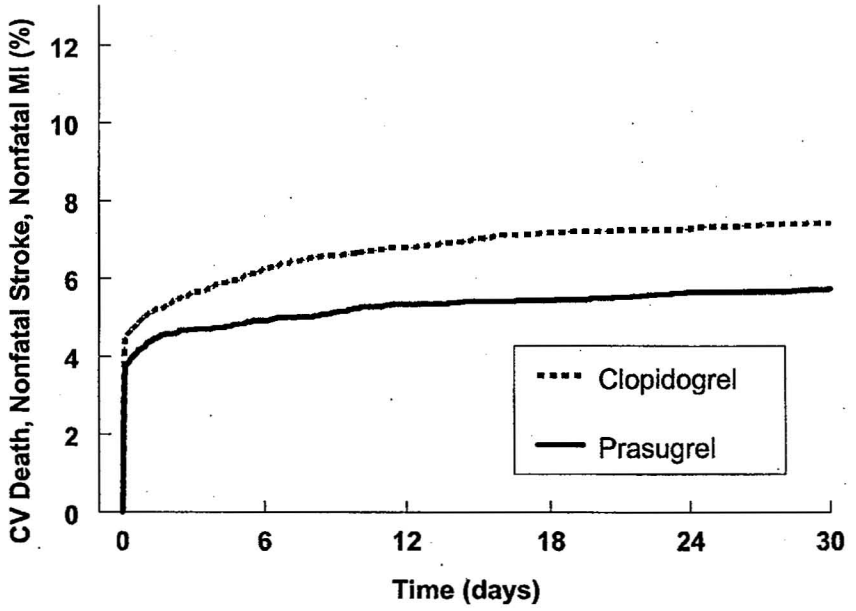
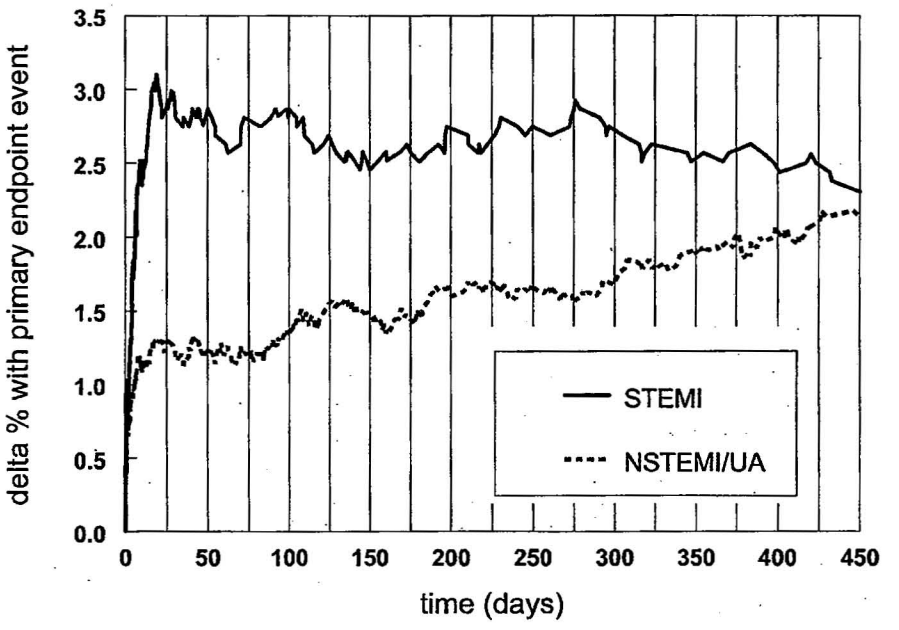


**Figure 6: Kaplan-Meier Estimates of the 1° Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations**




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 6, 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 6).

**Table 6: 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 within 12 hours of PCI. This change resulted in the addition of 38 and 44 endpoint events to the prasugrel and clopidogrel groups, respectively, with no substantive change on 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.

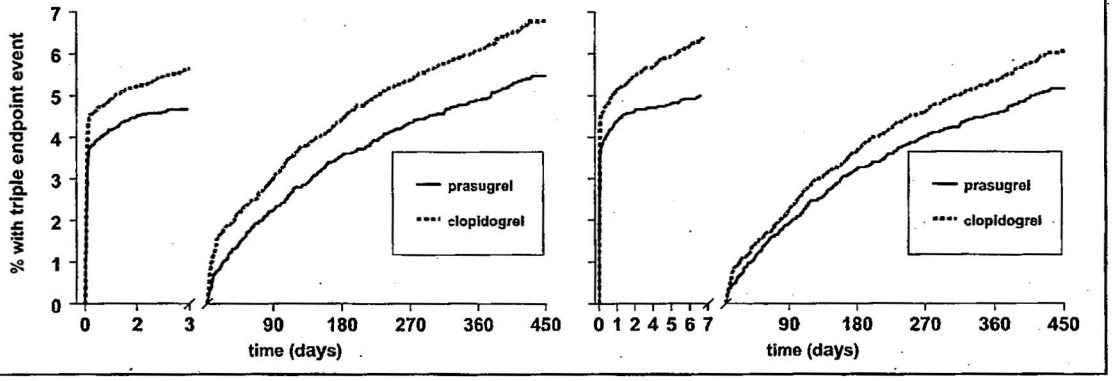
Landmark Analyses:
There is support for the concept that a clopidogrel LD of 600-mg is associated with more rapid inhibition of platelet aggregation than the standard LD of 300-mg (used in TAAL), and OASIS7 is being conducted to examine this hypothesis in a randomized controlled trial (ClinicalTrials.gov 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.[1]

This reviewer conducted landmark analyses, in essence time-to-event analyses before and after cut-points of 3 days (Figure 7, left panel) and 7 days (Figure 7, right panel). These consider

[1] *N Engl J Med.* 2008;358:1298-9

event-free survival beginning at points in time beyond which the adequacy of the LD would be 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.

**Figure 7: Landmark Analyses on the 1° Efficacy Endpoint: 3 Days (left panel); 7 Days (right panel)**




Multiplicity:
Given the nature an 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.

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.

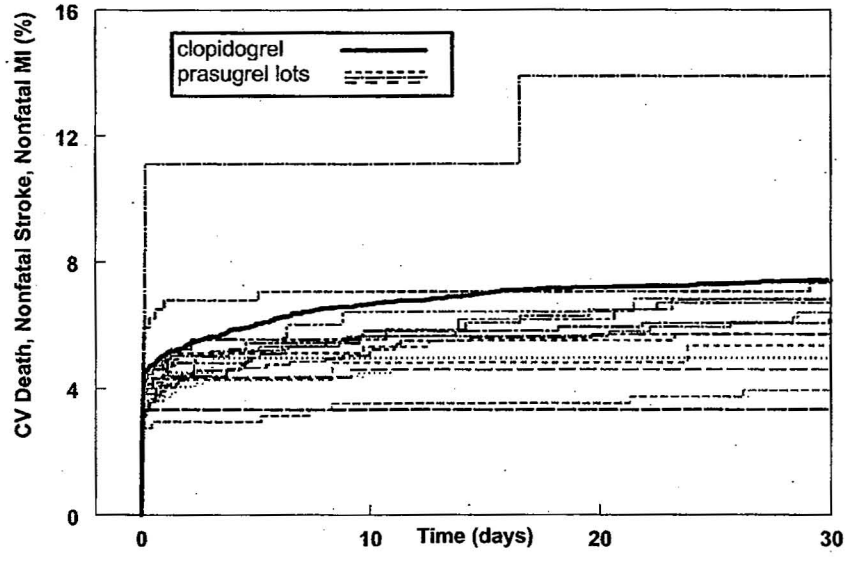
In summary, the results for the 1° efficacy endpoint are persuasive and robust to exploration. The overall treatment effect was driven by nonfatal MI. The CV death component shows a trend

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 70% 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, the clinical pharmacology reviewers found lots of prasugrel with differing salt to base conversion to be bio-inequivalent in the presence of PPI. This is salient because a large fraction of patients who are treated with anti-platelet agents also take PPI.

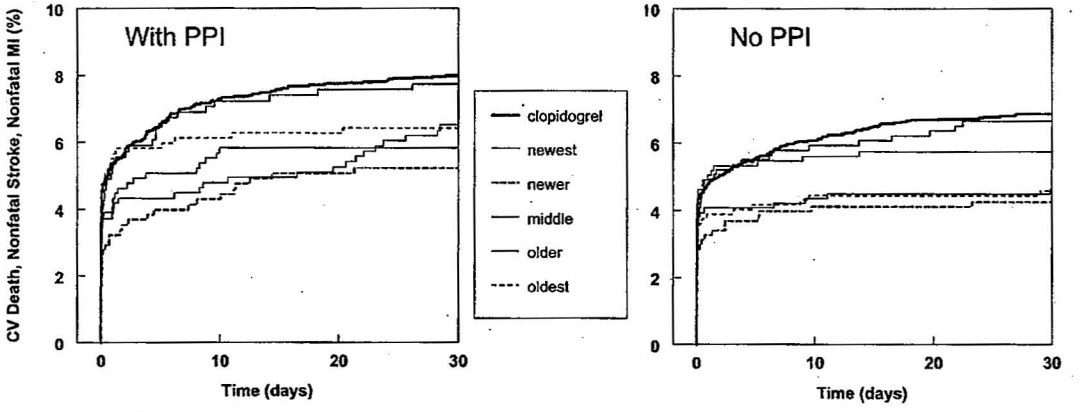
Although most subjects obtained prasugrel from a several lots during the course of the study, the initial 30-day supply was dispensed from a single lot. (The LD administered on Day 0 was generally NOT from the same lot used for the MD on Days 1-30, but a single lot was dispensed for Days 1-30.) Because 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 by prasugrel lot (Figure 8). The vast majority of prasugrel lots appeared at least non-inferior to clopidogrel. (The numbers of subjects who received some lots were limited, and it is difficult to interpret event-free survival as importantly different from clopidogrel.)

**Figure 8: 1° Efficacy Endpoint by Prasugrel Lot Administered Through Day 30**




Because salt to base conversion proceeded with time, 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, subjects with any recorded PPI use at any time were considered PPI

**Figure 9: 1° Efficacy Endpoint by Age of Prasugrel Lot Administered Through Day 30**




users for the purpose of this analysis. In both the presence and absence of PPIs, there was no relation between age of pills administered during the initial 30 days and efficacy (Figure 9).

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

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 gender, this reviewer assessed the 1° efficacy endpoint by weight quintiles, for male and female subjects separately (Figure 10). 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 10: Triple Efficacy Endpoint by Weight Quintiles and Sex**

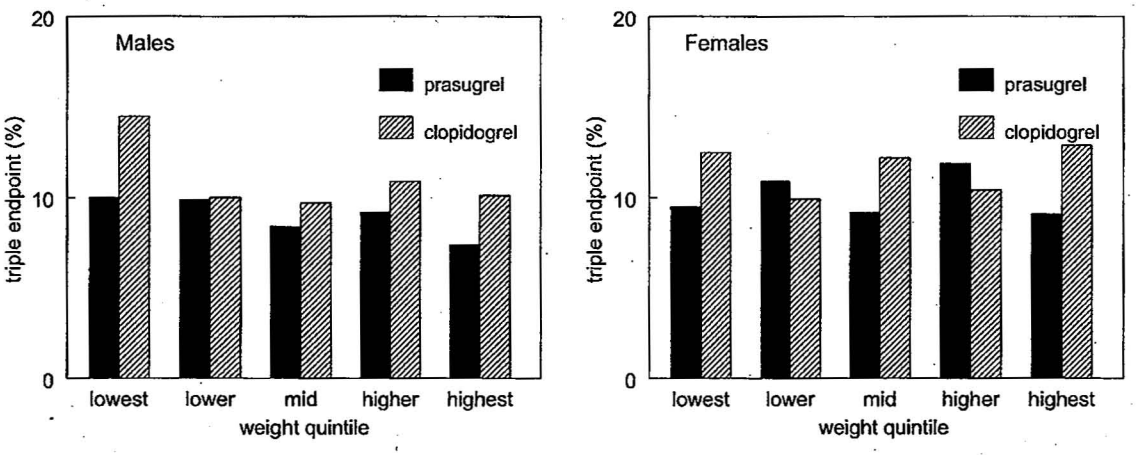
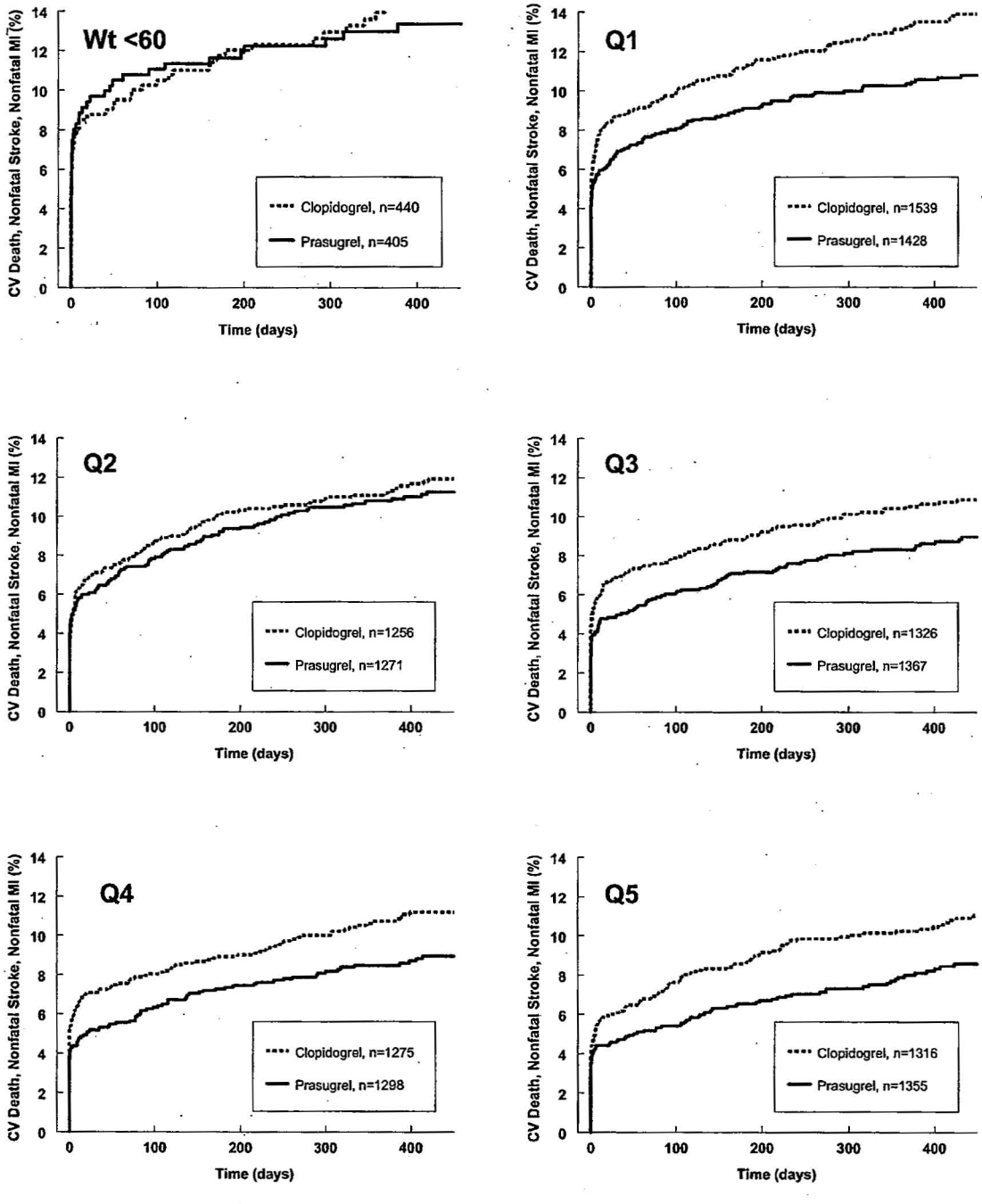



Figure 11 shows the results on the 1° endpoint for the overall ACS population by weight. The upper left panel shows the results for subjects weighing <60 kg. The effect of prasugrel was neutral in this small subgroup, comprising 6% of the overall subject population. The remaining panels show results 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.

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.

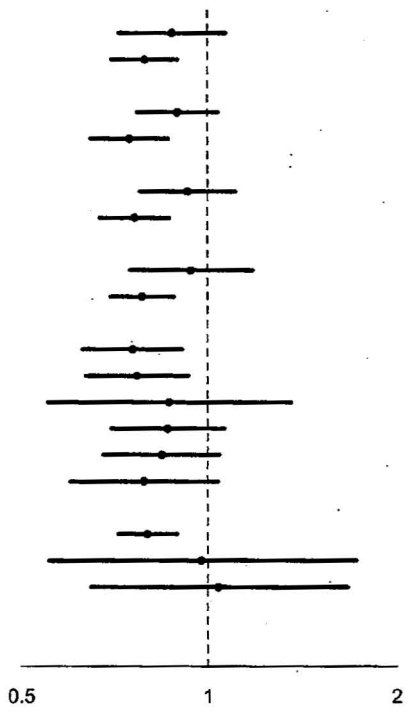
**Figure 11: Primary Triple Composite Endpoint by Weight**



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 12). 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).

**Figure 12: 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 13 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. In the latter subgroup (comprising 3.8% of the total study population), the hazard ratio was 1.44, with 95% C.I. 0.94 to 2.2. Table 7 breaks down the