criteria) lasting for at least 20 minutes and accompanied by ischemic chest pain or hemodynamic decompensation.

Five major sets of criteria were used for diagnosis of nonfatal MI:

1. ST elevation or re-elevation, and either ischemic chest pain ≥20 minutes in duration or hemodynamic decompensation.

2. Spontaneous CK-MB or troponin >ULN, and ischemic chest pain (or anginal equivalent) ≥20 minutes in duration or ST segment deviation ≥1 mm in one or more leads

3. CK-MB >3X ULN on ≥2 samples following PCI

4. CK-MB >10X ULN on one sample following CABG

5. New Q waves ≥0.04 seconds, or pathology distinct from prior MI

ECGs and other supporting clinical tests and evaluations were to be centrally adjudicated by a Clinical Endpoints Committee (CEC).

- Nonfatal Stroke ≡ the acute onset of new-persistent neurologic deficit lasting >24 hours. Head computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging was strongly recommended. CT or MRI scans were to be considered by the CEC to support the clinical impression. Nonfatal stroke was to be classified as either ischemic or hemorrhagic based on imaging data, if available, or uncertain cause if imaging data were not available.

- Urgent target vessel revascularization (UTVR) ≡ PCI or CABG for recurrent ischemia that, in the investigator's opinion, is non-elective and cannot be delayed for more than 24 hours. UTVR must include the vessel(s) dilated at initial PCI.

Safety objectives were primarily focused on bleeding, designed to compare prasugrel with clopidogrel with respect to:

- TIMI Study Group (TIMI) major bleeding ≡ any intracranial hemorrhage (ICH) or overt bleeding associated with a hemoglobin (Hgb) decrease ≥5 g/dL from baseline
- TIMI life-threatening bleeding (a subset of the above). "Life-threatening" ≡ fatal, causes hypotension that requires IV inotropic agents, surgical intervention, ≥4 units blood or packed RBCs within 48 hours, or symptomatic ICH.
- TIMI minor bleeding ≡ clinically overt bleeding associated with a decrease in Hgb of ≥3 g/dL but <5 g/dL from baseline

Bleeding was categorized as related to, or not related to, coronary artery bypass graft (CABG) surgery.

- assessments of clinical findings, laboratory values, and adverse events (AEs)

Safety Endpoints:
• Non-CABG related TIMI major bleeding

• Non-CABG-related TIMI life-threatening bleeding (any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension, requires surgical intervention, or necessitates transfusion of ≥4 units blood products; or any symptomatic ICH)

• Non-CABG-related fatal bleeding

• Non-CABG-related TIMI minor bleeding (clinically overt bleeding associated with a fall in Hgb of ≥ 3 g/dL but < 5 g/dL)

• CABG related bleeding

Analytic Methodology:
The statistical analysis plan was finalized on September 18, 2007. The analyses of the primary and secondary endpoints are discussed below.

Efficacy endpoints:
An independent CEC performed blinded adjudicated all efficacy events reported by investigators. Per protocol, the 1°, 2°, and other efficacy endpoint analyses were based on the determinations of events as adjudicated by the CEC.

Primary endpoint: Due to a potentially varying hazard ratio, the analysis for the 1° efficacy endpoint was based on the time from randomization to the first primary outcome using the Gehan-Wilcoxon test. Primary analyses were carried out in a hierarchical manner. At the first step, time-to-first primary outcome was carried out at a one-sided significance level of 0.025 (equivalent to a two-sided test at 0.05) in the UA/NSTEMI subject population. If superiority of prasugrel was established in the UA/NSTEMI population, then time-to-first primary outcome was to be carried out at a one-sided significance level of 0.025 in the All ACS population. For the latter analysis, ACS classification (UA/NSTEMI or STEMI) was to be used as a stratification factor. No adjustment for multiplicity was applied, because of the closed nature of hypothesis testing.

Secondary endpoints:
- Plan for evaluating secondary endpoints in UA/NSTEMI subject population

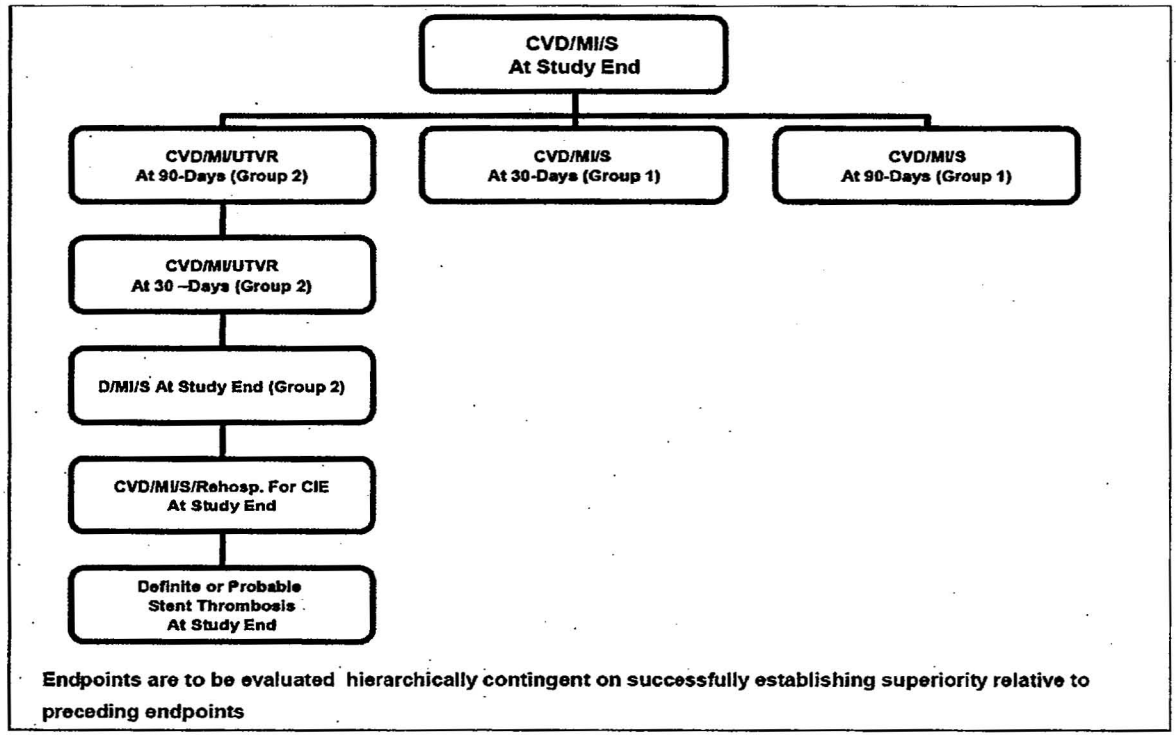
Following the establishment of the superiority of prasugrel over clopidogrel relative to the primary endpoint, additional analyses for secondary efficacy endpoints were performed using the log-rank test. Per agreement with FDA, the secondary endpoints were comprised of two groups: the first (Group 1) are those endpoints that do not require adjustment for multiplicity; the second (Group 2) are those that need to be predefined in a hierarchical manner (see Figure 3).

Group 1 secondary endpoints were each evaluated at a one-sided 0.025 alpha level (i.e., equivalent to a two-sided 0.05 level).

- Triple endpoint at Day 90
- Triple endpoint at Day 30

Both 2° endpoints in Group 1 were to be eligible for inclusion in labeling if the results were statistically significant.

Figure 3: Hierarchical plan for secondary endpoints



(Source: Sponsor's Figure 9.2, page 9169 of H7T-MC-TAAL Study Report. Abbreviations: CVD = cardiovascular death, D = death, Rehosp. = rehospitalization, S = stroke)

The evaluations of Group 2 endpoints were dependent on demonstration of superiority of prasugrel on the 1° endpoint in the UA/NSTEMI population. To protect the overall type 1 error rate at a level of 0.05, the 5 remaining secondary endpoints were evaluated hierarchically, each at a one-sided 0.025 alpha level:

- CVD, nonfatal MI, or UTVR at 90 days post-randomization
- CVD, nonfatal MI, or UTVR at 30 days post-randomization
- All cause mortality, nonfatal MI, or nonfatal stroke at study end
- CVD, nonfatal MI, nonfatal stroke, or rehospitalization for cardiac ischemic event at study end
- Definite or probable stent thrombosis.

Numerous exploratory endpoints included components of the above composite endpoints at various timepoints.

- Plan for evaluating secondary endpoints in All ACS subject population

Contingent on a demonstration of superiority of prasugrel for the 1° endpoint in the All ACS population, each of the 7 secondary endpoints was evaluated in the hierarchical method described above in All ACS population. The log-rank test was used for each analysis at a one-

sided 0.025 significance level. The clinical presentation (UA/NSTEMI or STEMI) was used as the stratification factor in these analyses.

Power and Sample Size:
For UA/NSTEMI subjects, the study was planned to provide 90% power to establish superiority on the triple endpoint based on the following assumptions:

- 10.5% of subjects in the clopidogrel group would reach the triple endpoint within 1 year of PCI, based on event rates of the "Clopidogrel in Unstable Angina to Prevent Recurrent Events" (CURE) trial, for the subset of subjects with a TIMI risk score ≥3
- A mean hazard ratio of 0.80 for prasugrel versus clopidogrel relative to the primary endpoint, and
- The time-to-first event analysis based on a two-sided log-rank test used a two-sided significance level (alpha) of 0.05 to assess superiority relative to the triple endpoint.

The proposed sample size was 13,000 subjects, assuming that ≥95% of subjects would be evaluable for the primary endpoint and that STEMI subjects would comprise 20 to 30% of the total enrollment (with a cap of 3500 subjects).

The study was to continue until 875 UA/NSTEMI subjects experienced a triple endpoint event, a median duration of therapy of 12 months, and a minimum follow-up of 6 months.

The blinded event rate was to be evaluated when 650 UA/NSTEMI subjects had reached the primary endpoint. However, the Study Operations Committee conducted a blinded review of the aggregated event rate when 589 subjects with UA/NSTEMI reached the primary endpoint and determined there was a slightly lower than anticipated aggregated event rate. Thus, the size of the UA/NSTEMI population was expanded to 10,100 subjects to achieve a target of 875 events.

Results:

Conduct:
TAAL was conducted from November 5, 2004 through July 22, 2007. A total of 13,619 subjects were enrolled over a period of approximately 26 months, with entrance of the final subject on January 14, 2007. The study involved 725 centers in 30 countries, for an overall average of approximately 19 subjects enrolled per site. The database was locked on September 20, 2007.

Reviewer's Comments: In light of the rapid enrollment of the study, and the fact that the study was concluded only within the past year, the data are very much representative of contemporary medical practice. Beyond this, the requirement for all subjects to undergo PCI ensured a fair degree of consistency in medical management of ACS, consistency that could be lacking in studies where PCI is only optional.

Protocol violations, identified from both the clinical database and site monitoring, were relatively unimportant, low in number, and similar in frequency between treatment groups. As such, they are deemed unlikely to influence the study results.

Disposition of subjects:
Overall, 18,357 potential subjects were screened, in order to enroll 13,619 subjects (approximately 25% were screening failures). Of the 13,619 subjects enrolled, 11 had an incomplete informed consent document, and were not included in the analyses. Thus, the intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to

prasugrel and 6,795 subjects were randomized to clopidogrel. Approximately 98.8% of randomized subjects received the study agent (13,457), and comprise the safety population. Median length of follow-up was 450 days (mean 380 ± 121 days). Nineteen percent (19%) of subjects had unstable angina, 55% had NSTEMI, and 26% had STEMI (18% treated within 12 hours, 8% beyond 12 hours).

Baseline characteristics:
As expected in a study of this size, there were no important imbalances in baseline demographic or disease characteristics (Table 1). From the standpoint of generalizability of the results, however, several points are worth noting. Roughly a quarter of the subjects were female; only 3% of subjects were of African ancestry. Approximately 30% of subjects were from the U.S.; eastern and western Europe each accounted for approximately 25% of subjects. The median (and mean) age was 61, with 13% of subjects age 75 or older. Concomitant medical history (Table 2) and pharmacotherapy (Table 3) were typical of an ACS population. The majority of subjects were taking statins and beta blockers; about half of the subjects were taking GPIIb/IIIa inhibitors and ACE inhibitors.

Table 1: Demographic Characteristics in TAAL

	Prasugrel n=6813	Clopidogrel n=6795
Age (years)		
mean ± SD	60.9 ± 11.2	60.9 ± 11.4
median	61	61
25th, 75th percentile	53, 69	53, 70
≥ 75 yrs	13.2	13.4
Female sex	25.0	26.8
Ethnicity		
Caucasian	91.9	92.3
African	3.0	2.8
Hispanic	3.9	3.8
Asian	0.9	0.9
Other	0.2	0.2
Region of enrollment		
U.S.	29.9	29.7
North America, non-U.S.	1.9	1.9
South America	4.0	3.9
Western Europe	26.1	26.1
Eastern Europe	24.3	24.5
Rest of world	13.8	13.9
Body Mass Index (kg/m^2)		
mean ± SD	28.5 ± 5.0	28.5 ± 5.1
median	27.8	27.8
25th, 75th percentile	25.1, 31.1	25.1, 31.1
Weight (kg)		
mean ± SD	83.6 ± 16.8	83.2 ± 16.9
median	82.0	81.0
25th, 75th percentile	72.6, 93.0	72.0, 92.1

Index Procedure:
Essentially all subjects (98.6% in each treatment group) underwent PCI as directed per protocol, and 94% received at least one stent, divided fairly equally between bare metal stents (47%) and drug eluting stents (42%) (Table 4). Of the 1.4% of subjects who did not undergo PCI, one-fourth (0.35% overall) underwent CABG and three-fourths (1.1% overall) were managed medically without revascularization.

Primary Efficacy Endpoint:

For the study as a whole (All ACS), 643 subjects (9.4%) in the prasugrel group and 781 subjects (11.5%) in the clopidogrel group experienced a 1° triple endpoint event of cardiovascular death, nonfatal MI, or nonfatal stroke. Treatment with prasugrel was associated with a statistically significant reduction in the triple composite endpoint in the UA/NSTEMI population (Cox proportional hazard ratio in favor of prasugrel 0.82, 95% C.I. 0.73 to 0.93, p=0.002, Table 5, Figure 4, top panel). Therefore, as prospectively specified in the analytic plan, the analysis was carried out in the overall ACS patient population (Figure 5). Prasugrel was associated with a statistically significant treatment effect, with a hazard ratio of 0.81 (95% C.I. 0.73 to 0.90,

Table 2: Medical History (%)

	Prasugrel n=6813	Clopidogrel n=6795
Hypertension	64.1	64.3
Hypercholesterolemia	55.6	55.8
Diabetes	23.1	23.1
treated with insulin	5.6	5.8
not treated with insulin	17.5	17.3
Metabolic syndrome	43.5	43.2
Tobacco use		
ever	65.5	66.1
current	38.3	38.0
Hepatic impairment	0.5	0.6
Renal impairmant		
Ccr ≤ 60 mL/min	10.7	11.6
Ccr ≤ 30 mL/min	0.8	0.8
Prior MI	18.0	17.8
Prior PCI	13.3	13.6
Prior CABG	7.9	7.3
History of CHF	3.9	3.6
Atrial fibrillation	3.1	3.1
History of carotid/vertebral artery disease	2.8	2.9
Prior Stroke	2.6	2.4
Prior TIA	1.4	1.7
History of peripheral vascular disease	5.1	5.3
Peptic ulcer disease	5.9	6.1

Table 3: Concomitant Pharmacotherapy (%)

	Prasugrel n=6813	Clopidogrel n=6795
Statins	78.8	78.6
ACE inhibitor	52.0	49.4
Beta blocker	74.0	73.9
Calcium channel blocker	14.7	14.2
Aspirin within 7 days prior to symptom onset	34.1	34.3
GPIIb/IIIa use through 3 days	53.4	54.9

Table 4: Index Procedure (%)

	Prasugrel n=6813	Clopidogrel n=6795
PCI	98.6	98.6
no stent	4.0	3.6
bare metal stent only	46.8	46.9
≥ 1 drug-eluting stent	42.0	42.3
CABG	0.4	0.3
Medically managed	1.1	1.1

p<0.001, Table 5, Figure 5). Results were also statistically significant for prasugrel in the STEMI population alone (Table 5, Figure 4, bottom panel). The efficacy results for the 1° endpoint were verified by Dr. Ququan Liu in her statistical review.

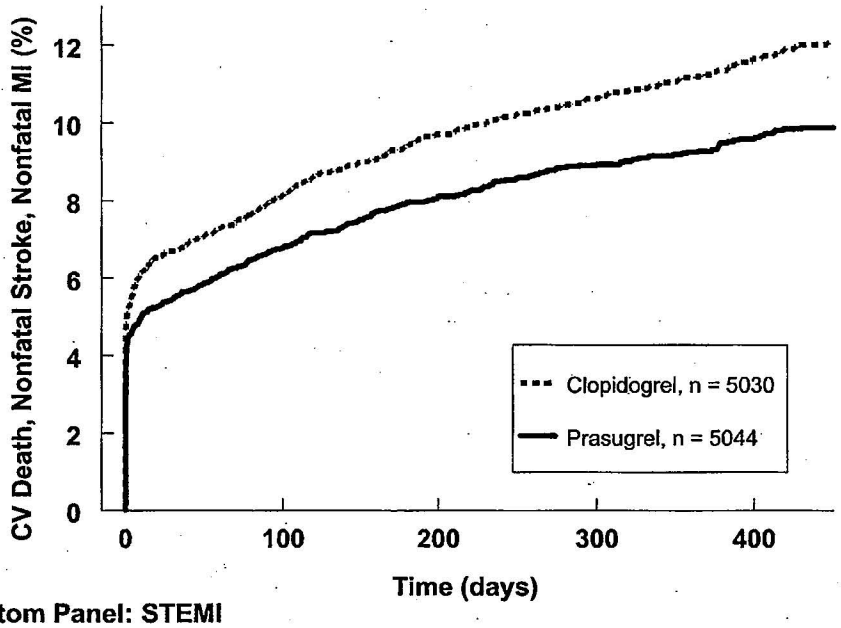
Table 5: Number and % of Subjects Reaching Composite Endpoint

	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
subject population	N	n	(%)	N	n	(%)	N	n	(%)		
UA or NSTEMI	5044	469	9.3	5030	565	11.2	10074	1034	10.3	0.82 (0.73, 0.93)	0.002
STEMI	1769	174	9.8	1765	216	12.2	3534	390	11.0	0.79 (0.65, 0.97)	0.019
Overall	6813	643	9.4	6795	781	11.5	13608	1424	10.5	0.81 (0.73, 0.90)	<0.001

For the entire ACS population, Figure 5 shows the Kaplan-Meier estimates for the composite triple endpoint. The top panel shows the events over the full 450 days; the bottom panel displays the same data but is limited to the first 30 days only. In order to better delineate how prasugrel's treatment advantage is manifested with respect to time, Figure 6 shows the *delta %* with a primary endpoint event as a function of time for both the STEMI and NSTEMI/UA populations. In essence, the Kaplan Meier time-to-event lines in Figure 4 are subtracted to produce Figure 6, and the delta % of Figure 6 represents the distance between the curves in Figure 4, the *cumulative* difference in event rates. For STEMI, the advantage begins immediately, reaches its maximum at 18 days, and remains unchanged thereafter. In the NSTEMI/UA population, approximately 60% of the cumulative treatment advantage occurred within 3 weeks, but the delta continues to increase fairly linearly through 450 days, supporting the concept that prasugrel's treatment advantage persists throughout the entire study.

Figure 4: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke

Top Panel: NSTEMI/UA



Bottom Panel: STEMI