investigator's discretion. Although daily doses of ASA ranging from 75 to 162 mg were recommended after discharge, the aspirin dose was left to the investigator's discretion.

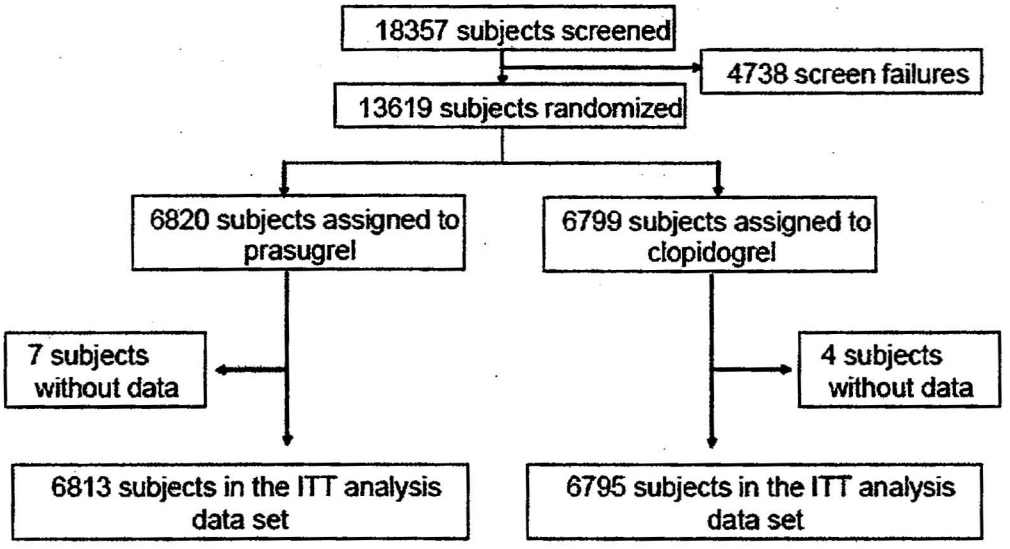
Subjects were to be followed for a maximum of 15 months. They were to return on Days 30, 90, and 180 for clinic visits and if enrolled in the study over 180 days were also to return on Days 270, 360, and 450.

6.1.3.1.1 Disposition of Subjects

A total of 13,619 subjects with ACS were randomized, including 6,799 subjects to clopidogrel (300 mg loading dose followed by once-daily 75 mg maintenance dose) and 6,820 subjects to prasugrel (60 mg loading dose followed by once-daily 10 mg maintenance dose). Subjects were treated until the subject's termination or 464 days from randomization, whichever was earlier. The maximum follow-up was 15 months.

Seven subjects randomly assigned to prasugrel and four subjects randomly assigned to clopidogrel were not included in the final analysis dataset due to an incomplete informed consent document. The remaining 13,608 subjects, including 6813 subjects in the prasugrel treatment group and 6795 subjects in the clopidogrel treatment group, comprised the intent-to-treat (ITT) analysis data set and were referred to as "All Randomized Subjects." Enrollment is summarized in Figure 26.

Figure 8. Enrollment of Subjects (TAAL)



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Out of the 13,608 randomized patients, 13,457 subjects were treated, including 6741 in the prasugrel treatment group and 6716 subjects in the clopidogrel treatment group.

At the time of the index hospitalization, 6715 (98.56%) subjects underwent PCI in the prasugrel treatment group, including 5004 (99.21%) in the UA/NSTEMI population and 1711 (96.72%) in the STEMI population. In the clopidogrel treatment group, 6698 (98.57%) underwent PCI, including 4984 (99.09%) in the UA/NSTEMI population and 1714 (97.11%) in the STEMI population.

During the index hospitalization, 25 (0.37%) subjects in the prasugrel treatment group underwent CABG, including 16 (0.32%) in the UA/NSTEMI population and 9 (0.51%) in the STEMI population. In the clopidogrel treatment

group, 23 (0.34%) subjects underwent CABG, including 12 (0.24%) in the UA/NSTEMI population and 11 (0.62%) in the STEMI population.

A total of 73 (1.07%) subjects in the prasugrel treatment group and 74 (1.09%) subjects in the clopidogrel treatment group were medically managed during the index hospitalization. In the UA/NSTEMI population, 24 (0.48%) and 34 (0.68%) subjects in the prasugrel and clopidogrel treatment groups, respectively, did not undergo revascularization. In the STEMI population, 49 (2.77%) and 40 (2.27%) in the prasugrel and clopidogrel treatment groups, respectively, did not undergo revascularization.

From index hospitalization to study end, 213 subjects in the prasugrel treatment group underwent CABG, including 180 elective and 33 urgent surgeries. In the clopidogrel treatment group, 224 subjects underwent CABG, including 186 elective and 38 urgent surgeries.

6.1.4 Efficacy Findings

6.1.4.1 Primary Efficacy Endpoint

In TAAL, prasugrel significantly reduced the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction, or nonfatal stroke at a median of twelve months of follow-up using the original and expanded definitions of peri-procedural myocardial infarction, as displayed in Table 1 and Table 2, respectively. The original definition of peri-procedural myocardial infarction required an elevation of creatine kinase-myocardial band (CK-MB) to > 3x upper limit of normal (ULN) on a minimum of two samples within 48 hours of PCI. The modified definition, specified in Protocol Amendment (a) dated January 10, 2006, maintained the original definition but extended periprocedural myocardial infarctions to a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI. Since there was no difference in cardiovascular death and nonfatal stroke between treatment groups, the difference in the primary endpoint was driven by the difference in nonfatal myocardial infarctions.

Table 8. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI or Nonfatal Stroke Using the Definition of Peri-Procedural Myocardial Infarction Prior to Protocol Amendment (CEC Adjudicated) (All Randomized Subjects) (TAAL)

	Prasugrel			Clopidogrel			Total					
Subject Population	N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]	HR	(95% CI)[b]	p-value[c]
UA/NSTEMI	5044	443	(8.78)	5030	536	(10.66)	10074	979	(9.72)	0.817	(0.720, 0.926)	0.002
STEMI	1769	162	(9.16)	1765	201	(11.39)	3534	363	(10.27)	0.793	(0.645, 0.976)	0.024
All ACS	6813	605	(8.88)	6795	737	10.85)	13608	1342	(9.86)	0.810	(0.727, 0.902)	<0.001

CI=confidence interval, CV=cardiovascular, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
[a]% is percentage of randomized subjects reaching the primary endpoint.
[b]HR and two-sided 95% CI derived using Cox proportional hazards model.
[c]Two-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions of Prasugrel and Clopidogrel Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.
(Reproduced from Sponsor, Table TAAL.14.20, page 1407 of 27,024)
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Table 9. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke Using the Expanded Definition of Peri-Procedural Myocardial Infarction After Protocol Amendment (CEC Adjudicated) (All Randomized Subjects) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)[b]	p-value[c]
	N	n	(%)[a]	N	n	(%)[a]	N	n	(%)[a]			
UA/NSTEMI	5044	469	(9.30)	5030	565	(11.23)	10074	1034	(10.26)	0.820	(0.726, 0.927)	0.002
STEMI	1769	174	(9.84)	1765	216	(12.24)	3534	390	(11.04)	0.793	(0.649, 0.968)	0.019
All ACS	6813	643	(9.44)	6795	781	(11.49)	13608	1424	(10.46)	0.812	(0.732, 0.902)	<0.001

CI=confidence interval, CV=cardiovascular, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
[a]% is percentage of randomized subjects reaching the primary endpoint.
[b]HR and two-sided 95% CI used as an estimate of overall relative risk, Prasugrel versus Clopidogrel, over the course of the study.
[c]Two-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions of Prasugrel and Clopidogrel Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.
(Reproduced from Sponsor, Table TAAL.11.5, page 202 of 27,024).
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Using the original definition, there were 437 nonfatal myocardial infarctions in the prasugrel treatment group and 576 nonfatal myocardial infarctions in the clopidogrel treatment group for a total of 1013 nonfatal myocardial infarctions. Using the expanded definition, there were 475 nonfatal myocardial infarctions in the prasugrel treatment group and 620 nonfatal myocardial infarctions in the clopidogrel treatment group for a total of 1095 nonfatal myocardial infarctions. These results are displayed by treatment group and by population in Table 10.

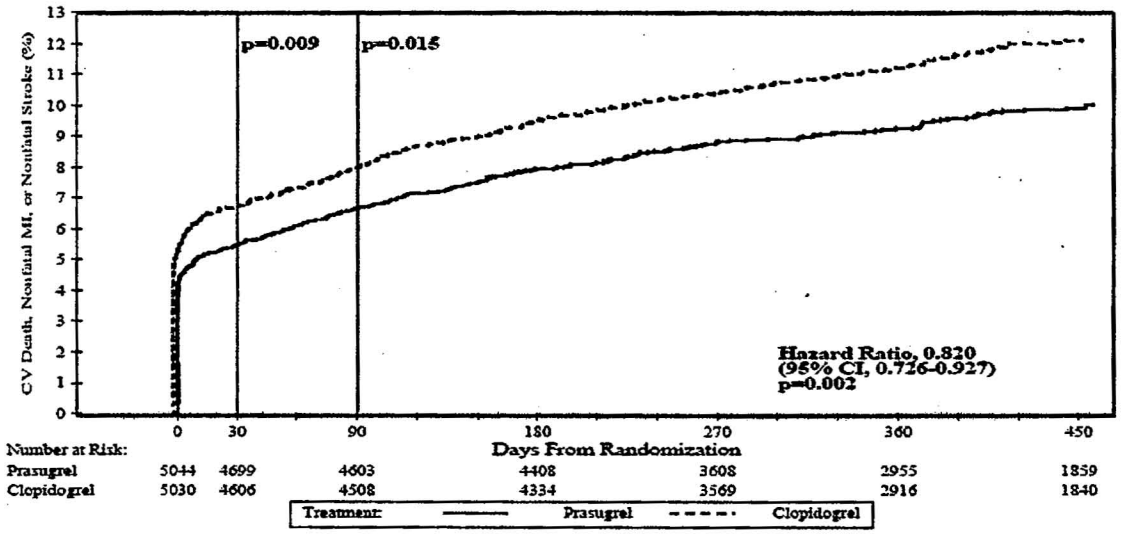
Table 10. Sponsor's Analysis: Nonfatal MI (TAAL)

Myocardial Infarction		Prasugrel N, n, (%)	Clopidogrel N, n, (%)	p-value
Original Definition	UA/NSTEMI	5044, 331, (6.56)	5030, 435, (8.65)	< 0.001
	STEMI	1769, 106, (5.99)	1765, 141, (7.99)	0.020
	All ACS	6813, **437**, (6.41)	6795, **576** (8.48)	<0.001
Expanded Definition	UA/NSTEMI	5044, 357, (7.08)	5030, 464, (9.22)	<0.001
	STEMI	1769, 118, (6.67)	1765, 156, (8.84)	0.016
	All ACS	6813, **475**, (6.97)	6795, **620**, (9.12)	<0.001

N=number of subjects; n=number of subjects experiencing a nonfatal MI.

In all three study populations, most of the treatment effect with prasugrel was realized early, within 24 to 72 hours of study drug administration. The Kaplan-Meier estimate of the incidence of the CEC-adjudicated composite endpoint of CV death, nonfatal MI, or nonfatal stroke in the UA/NSTEMI population at a median of 12 months of follow-up is shown in Figure 9.

Figure 9. Kaplan-Meier Estimate of the Incidence of the Composite Endpoint of Cardiovascular Death, Nonfatal MI, or Nonfatal Stroke (CEC Adjudicated) (All Randomized UA/NSTEMI Subjects) (TAAL)



(Reproduced from Sponsor, Clinical Study Report, Figure TAAL.11.6a, page 218)

A total of 961 nonfatal myocardial infarctions occurred outside the setting of stent thrombosis, including 529 in the clopidogrel treatment group and 432 in the prasugrel treatment group. In both treatment groups, most of these nonfatal MIs occurred either within 24 hours of PCI or from > 30 days to 1 year.

In the setting of stent thrombosis, there were 91 nonfatal myocardial infarctions in the clopidogrel treatment group and 43 nonfatal myocardial infarctions in the prasugrel treatment group. The timing of the nonfatal MIs is displayed in Table 11. Outside the setting of stent thrombosis, most nonfatal MIs in both treatment groups occurred periprocedurally (≤ 24 hours) or > 30 days to 1 year. In the setting of stent thrombosis, most nonfatal MIs in the clopidogrel treatment group occurred > 24 hours to 30 days post index PCI while most nonfatal MIs in the prasugrel treatment group occurred > 30 days to 1 year.

Table 11. Sponsor's Analysis: Summary of Nonfatal Myocardial Infarction

Time Interval	Nonfatal MI Not Associated with Stent Thrombosis		Nonfatal MI Associated with Stent Thrombosis	
	Clopidogrel N[a] (%)[b]	Prasugrel N[a] (%)[b]	Clopidogrel N[a](%)[b]	Prasugrel N[a] (%)[b]
≤ 24 hours	308 (58.2%)	266 (61.6%)	19 (20.9%)	13 (28.6%)
> 24 hours – 30 days	48 (9.1%)	34 (7.9%)	47 (51.6%)	5 (11.9%)
> 30 days to 1 year	154 (29.1%)	119 (27.5%)	19 (20.9%)	22 (52.4%)
> 1 year	16 (3.0%)	10 (2.3%)	6 (6.6%)	3 (7.1%)
Unknown	3 (0.6%)	3 (0.7%)	0	0
Total	529	432	91	43

[a]N=Number of subjects experiencing the indicated event.
[b]%=N divided by the column total.

6.1.4.2 Subgroup Analyses of the Primary Endpoint

6.1.4.2.1 Age

In the UA/NSTEMI, STEMI, and All ACS populations, patients ≥ 75 years of age appeared to receive less benefit with prasugrel, compared to patients < 75 years of age, as shown in Table 12.

Table 12. FDA Subgroup Analysis of Primary Endpoint by Age (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Age (yr)									
<75 N	4328	4344	0.78	1584	1543	0.80	5912	5887	0.78
n	356	454	0.68, 0.90	143	173	0.64, 0.99	499	627	0.70, 0.88
%	8.23	10.45	0.0006	9.02	11.21	0.0370	8.44	10.65	<.0001
≥75 N	716	686	0.97	185	222	0.85	901	908	0.94
n	113	111	0.75, 1.26	31	43	0.54, 1.35	144	154	0.75, 1.18
%	15.78	16.18	0.8539	16.76	19.37	0.4478	15.98	16.96	0.5329
≥75 Female N	292	309	0.98	79	96	0.71	371	405	0.91
n	43	46	0.65, 1.49	12	20	0.35, 1.46	55	66	0.63, 1.29
%	14.73	14.89	0.9723	15.19	20.83	0.3637	14.82	16.30	0.5891
≥75 Male N	424	377	0.96	106	126	0.97	530	503	0.96
n	70	65	0.68, 1.34	19	23	0.53, 1.79	89	88	0.72, 1.29
%	16.51	17.24	0.7598	17.92	18.25	0.8197	16.79	17.50	0.6908

ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

6.1.4.2.2 Sex

Approximately 27% of the patients randomized in TAAL were women. Women appeared to receive less benefit from prasugrel compared to men, as displayed in Table 13.

Table 13. FDA Subgroup Analysis of Primary Endpoint by Sex (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Sex									
Female N	1325	1399	0.91	380	419	0.79	1705	1818	0.88
n	137	159	0.72, 1.14	41	56	0.53, 1.19	178	215	0.73,1.07
%	10.34	11.37	0.5150	10.79	13.37	0.2107	10.44	11.83	0.1962
Male N	3719	3631	0.79	1389	1346	0.80	5108	4977	0.79
n	332	406	0.68, 0.91	133	160	0.63, 1.00	465	566	0.7, 0.9
%	8.93	11.18	0.0014	9.58	11.89	0.0503	9.10	11.37	0.0002

ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

6.1.4.2.3 Ethnicity

Ninety-two percent of patients enrolled in TAAL were Caucasian. Other ethnicities were poorly represented, limiting any conclusions from this subgroup analysis. Prasugrel significantly decreased the primary endpoint in Caucasians.

Table 14. FDA Subgroup Analysis of Primary Endpoint by Ethnicity (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Ethnicity									
Caucasian									
N	4575	4569	0.80	1688	1705	0.80	6263	6274	0.80
n	414	511	0.70, 0.91	167	209	0.65, 0.98	581	720	0.72, 0.89
%	9.05	11.18	0.0011	9.89	12.26	0.0242	9.28	11.48	<.0001
African									
N	177	168	1.03	28	19	0.66	205	187	0.98
n	22	20	0.56, 1.89	3	3	0.13, 3.25	25	23	0.55, 1.72
%	12.43	11.91	0.8896	10.71	15.79	0.5967	12.20	12.30	0.9647
Hispanic									
N	242	237	1.08	27	19	0.70	269	256	1.04
n	33	30	0.66, 1.77	3	3	0.14, 3.46	36	33	0.65, 1.67
%	13.64	12.66	0.7287	11.11	15.79	0.6436	13.38	12.89	0.8737
Asian									
N	37	42	NE	23	22	NE	60	64	NE
n	0	3		1	1		1	4	
%	-	7.14		4.35	4.55		1.67	6.25	
Other									
N	13	14	NE	3	0	NE	16	14	NE
n	0	1		0	0		0	1	
%	-	7.14					-	7.14	

ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; NE=not evaluated due to insufficient data; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

6.1.4.2.4 Prior History of Transient Ischemic Attack/Stroke

In All ACS subjects with a prior history of transient ischemic attack or stroke, there was a 38% increased risk of experiencing death, nonfatal myocardial infarction, or nonfatal stroke at a median of 12 months of follow-up on prasugrel, compared to clopidogrel (p = 0.1382).

Table 15. FDA Subgroup Analysis of Primary Endpoint by Prior History of Transient Ischemic Attack or Stroke (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Prior History of Transient Ischemic Attack/Stroke									
Yes									
N	213	192	1.53	49	64	0.98	262	256	1.38
n	39	24	0.92, 2.55	8	11	0.39, 2.42	47	35	0.89, 2.13
%	18.31	12.50	0.0677	16.33	17.19	0.9127	17.94	13.67	0.1382
No									
N	4831	4838	0.79	1720	1701	0.79	6551	6539	0.79
n	430	541	0.69, 0.89	166	205	0.64, 0.97	596	746	0.71, 0.88
%	8.90	11.18	0.0003	9.65	12.05	0.020	9.10	11.41	<.0001

ACS=acute coronary syndrome; CI=confidence interval,; CV=cardiovascular; HR=hazard ratio; NE=not evaluated; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

6.1.4.2.5 Timing of Loading Dose

In TAAL, 73% of the loading doses were given during PCI and 26% of the loading doses were given 0-2 hours prior to PCI. Only 1% of subjects received the loading dose post PCI. However, the timing of the loading dose appears to be important and suggests that prasugrel should be given during PCI. Unfortunately, the number of patients in the post PCI treatment group is too small to draw a definitive conclusion about the post PCI timing of the loading dose. With regard to timing of loading dose and efficacy, our FDA analysis is presented in Table 16 and is consistent with the findings of the sponsor.

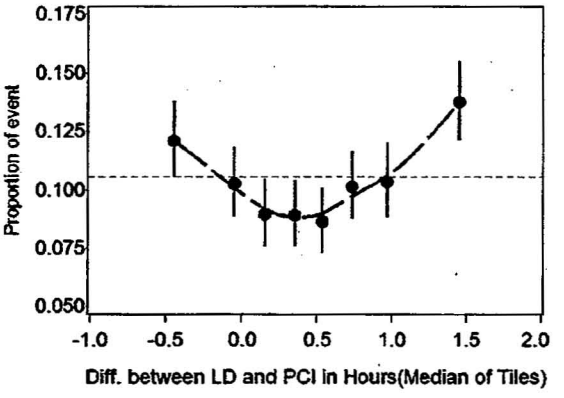
Table 16. FDA Subgroup Analysis of Primary Endpoint by Timing of Loading Dose (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

Timing of Loading Dose	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
0-2 hrs prior to PCI	N=1078 n=103	N=1045 n=117	0.85 0.65, 1.11 0.3212	N=432 n=52	N=440 n=59	0.90 0.62, 1.30 0.5843	N=1510 n=155	N=1485 n=176	0.86 0.70, 1.08 0.2340
2-6 hrs prior to PCI	N=61 n=4	N=67 n=5	0.9191	N=9 n=1	N=7 n=1	NE	N=70 n=5	N=74 n=6	0.90 0.28, 2.95 0.8927
6-12 hrs prior to PCI	N=16 n=3	N=9 n=2	0.84 0.14, 5.08 0.8530	N=4 n=0	N=1 n=1	NE	N=20 n=3	N=10 n=3	0.46 0.09, 2.30 0.3263
≥12 hrs prior to PCI	N=102 n=15	84 12	1.01 0.47, 2.16 0.9651	N=10 n=1	N=5 n=1	NE-	N=112 n=16	N=89 n=13	1.01 0.47, 2.16 0.8358
During PCI	**N=3660 n=329**	**3671 400**	**0.82 0.71, 0.95 0.0081**	**N=1221 n=110**	**N=1213 n=143**	**0.75 0.59, 0.97 0.0209**	**N=4881 n=439**	**N=4884 n=543**	**0.80 0.71, 0.91 0. 0005**
Post PCI	N=1078 n=103	1045 117	0.85 0.65, 1.11 0.3212	N=15 n=2	N=21 n=2	NE	N=63 n=7	N=68 n=16	0.43 0.18, 1.04 0.0391

ACS=acute coronary syndrome; CI=confidence interval, CV=cardiovascular, HR=hazard ratio; NE=not evaluated; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

Dividing the timing of the loading dose into octiles, maximum effectiveness with prasugrel and the lowest incidence of cardiovascular death, nonfatal MI, or nonfatal stroke was achieved when the loading dose was administered at the start or within 30 minutes of the start of PCI, as shown in Figure 10.

Figure 10. Incidence of Cardiovascular Death, Nonfatal MI, or Nonfatal Stroke (TAAL) Based on Timing of Loading Dose

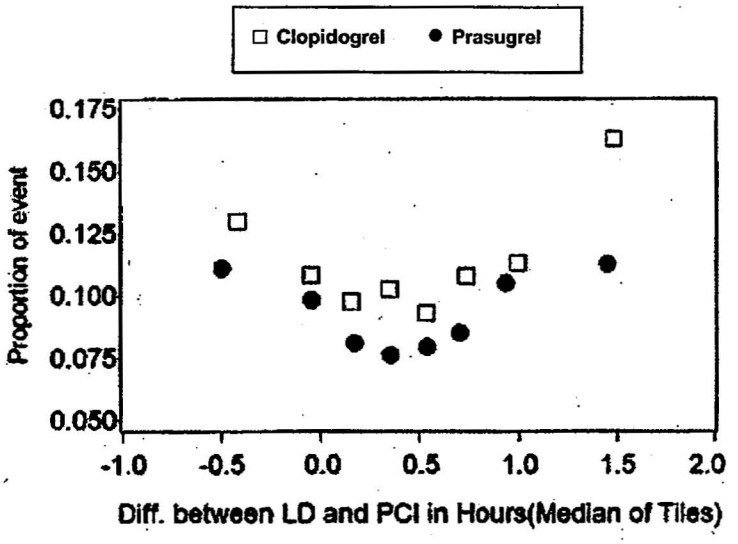


(Dots: represent proportion of events corresponding to the midpoints of the octiles; Bars: 95% Confidence interval; Black line: smooth trend line; Dotted line: lowest confidence limit of the extremes)

(Analysis by Rajanikanth Madabushi, Ph.D., Pharmacometrics, FDA)

The timing of loading dose was important for both prasugrel and clopidogrel. When the loading dose was given during PCI or within 30 minutes of the start of PCI, both treatments resulted in a decreased incidence of the primary endpoint over the course of the study, as shown in Figure 11.

Figure 11. Timing of Loading Dose and Effect on Primary Endpoint (TAAL)



(Analysis by Rajanikanth Madabushi, Ph.D., Pharmacometrics, FDA)

6.1.4.2.6 Proton Pump Inhibitors

Approximately 50% of the All ACS population received proton pump inhibitors in TAAL. The use of proton pump inhibitors did not appear to affect the efficacy of prasugrel for the primary endpoint.

Table 17. FDA Subgroup Analysis of Primary Endpoint by Use of Proton Pump Inhibitors (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Use of Proton Pump Inhibitors									
Yes									
N	2474	2463	0.83	916	882	0.80	3390	3345	0.82
n	262	310	0.70, 0.98	103	122	0.62, 1.05	365	432	0.72, 0.95
%	10.59	12.59	0.0319	11.24	13.83	0.0857	10.77	12.91	0.0056
No									
N	2570	2567	0.81	853	883	0.77	3423	3450	0.80
n	207	255	0.67, 0.97	71	94	0.57, 1.05	278	349	0.68, 0.93
%	8.05	9.93	0.0248	8.32	10.65	0.0986	8.12	10.12	0.0046

ACS=acute coronary syndrome; CI=confidence interval; HR=hazard ratio; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

6.1.4.2.7 Weight

Except for the weight category < 50 kg which demonstrated a 5% increased risk (p=0.83) of the primary endpoint, prasugrel significantly reduced the risk of the composite endpoint of death, nonfatal MI, and nonfatal stroke at a median follow-up of 12 months in all other weight categories, compared to clopidogrel.

Table 18. FDA Subgroup Analysis of Primary Endpoint by Weight (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Weight (kg)									
< 50									
N	92	86	1.14	45	39	0.90	137	125	1.05
n	17	15	0.57, 2.29	9	9	0.36, 2.28	26	24	0.60, 1.82
%	18.48	17.44	0.7713	20.00	23.08	0.9671	18.98	19.2	0.8318
< 60									
N	5044	5030	0.82	1769	1765	0.79	6813	6795	0.81
n	469	565	0.73, 0.93	174	216	0.65, 0.97	643	781	0.73, 0.90
%	9.30	11.23	0.0021	9.84	12.24	0.0192	9.44	11.49	<0.0001
≥ 50 < 70									
N	844	910	0.86	298	333	0.66	1142	1243	0.79
n	83	103	0.64, 1.14	34	56	0.43, 1.00	117	159	0.62, 1.00
%	9.83	11.32	0.3270	11.41	16.82	0.0388	10.25	12.79	0.0436
≥ 70									
N	2451	2433	0.84	942	895	0.78	3393	3328	0.83
n	234	275	0.70, 1.00	85	100	0.60, 1.06	319	375	0.71, 0.96
%	9.55	11.30	0.0549	9.02	11.17	0.1138	9.40	11.27	0.0119
≥ 70 < 90									
N	1657	1601	0.75	484	498	0.93	2141	2099	0.79
n	135	172	0.60, 0.94	46	51	0.62, 1.38	181	223	0.65, 0.96
%	8.15	10.74	0.0112	9.50	10.24	0.6796	8.45	10.62	0.0138

ACS=acute coronary syndrome; CI=confidence interval; HR=hazard ratio; NE=not evaluated; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

6.1.4.2.8 Additional Subgroup Analyses of the Primary Endpoint

Please see the Appendix under Study TAAL for further subgroup analyses of the primary endpoint.

6.1.4.3 Secondary Composite Endpoints

Compared to clopidogrel, prasugrel significantly reduced the following CEC adjudicated secondary composite endpoints in all study populations:

- CV death, nonfatal MI or nonfatal stroke through 90 days, compared to clopidogrel
- CV death, nonfatal MI or nonfatal stroke through 30 days, compared to clopidogrel
- CV death, nonfatal MI, or urgent target vessel revascularization through 90 days
- CV death, nonfatal MI, or urgent target vessel revascularization through 30 days
- All cause death, nonfatal MI, or nonfatal stroke through study end
- CV death, nonfatal MI, nonfatal stroke or rehospitalization for cardiac ischemic events through study end

These results are summarized in Table 19.

6.1.4.3.1 Secondary and Other Efficacy Endpoints

Prasugrel, compared to clopidogrel, did not significantly decrease CV death, all cause death, nonfatal stroke, all stroke, or rehospitalization due to an ischemic event. However, compared to clopidogrel, prasugrel reduced the incidence of the following endpoints:

- CV death or nonfatal MI
- Nonfatal MI
- All MI
- Urgent target vessel revascularization (in the UA/NSTEMI and All ACS populations)

The results of these secondary and other efficacy endpoints are presented in Table 20.