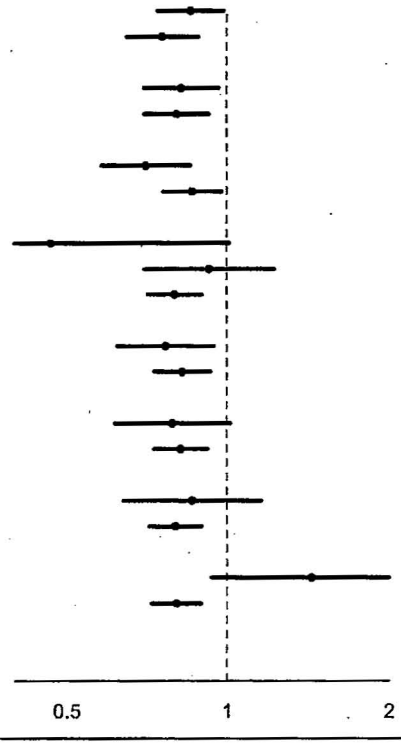
components of the triple endpoint for subjects with and without a prior history of TIA or stroke, and shows "All Stroke" as well.

Figure 13: 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



For patients with a prior history of TIA or stroke, 6.5% of subjects in the prasugrel treatment group experienced a stroke (2.3% intracranial hemorrhage [ICH]), compared to 1.2% (0% ICH) in the clopidogrel treatment group, for a hazard ratio of 5.64 (95% C.I.: 1.65, 19.3). In patients with no prior history of TIA or 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. With respect to both nonfatal stroke and all-stroke, it is remarkable that approximately one-quarter of all events in the prasugrel treatment group occurred in subjects with a history of prior TIA or stroke, yet this subgroup encompassed only 3.8% of the total subject population. Moreover, it must be 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.

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 7: 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

Approximately half of the subjects in each treatment group reported use of PPI as a concomitant medication. The hazard ratio favored prasugrel and was virtually the same, both in subjects who reported and did not report use of PPI (hazard ratios 0.82, 0.80, 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:

The pharmacometrics consultant (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 interesting and merit consideration, this secondary reviewer is not convinced that the association should be used to provide advice to practitioners in labeling.

Secondary Endpoints:

Results from the 2° endpoints are shown in Table 8. The triple composite endpoint was statistically significant in favor of prasugrel at Days 30 and 90. (Although these were denoted as 2° endpoints, they are, in fact, sensitivity analyses on the 1° endpoint.)

The other 2° endpoints were statistically significantly in favor of prasugrel for the All ACS population, and to lesser extents, for the UA/NSTEMI and STEMI populations individually.

The clinical reviewer (Dr. Karen Hicks) raised serious questions regarding the validity of the stent thrombosis endpoint. Although the data, as reported by the sponsor, show a highly statistically significant hazard ratio of 0.5 in favor of prasugrel, the reviewer noted that the CEC reviewed only *reports* of coronary angiograms and other clinical reports when making determinations of stent thrombosis, and not the actual angiographic images. She expressed the opinion that the findings be construed as preliminary, and suggested that the sponsor "...participate in a randomized, prospective clinical trial to further evaluate these preliminary findings." If the angiograms can be collected by the investigators and sponsor, it is the view of this secondary reviewer that the endpoint can be appropriately adjudicated by a blinded endpoint committee. This committee would not necessarily have to be the original TAAL CEC. Thus, the stent thrombosis claim should be withheld from labeling, but may be appropriate eventually, depending on the feasibility and results of a central, blinded adjudication of the angiographic images.

Efficacy Conclusions:
Treatment with prasugrel was associated with a statistically significant reduction in the composite triple endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke. These findings were statistically persuasive across the UA/NSTEMI population, the STEMI population, and the overall ACS population, and robust to exploration. The effect of prasugrel on the 1° endpoint was evident across the spectrum of subject weight, age, and sex, and in the presence

Table 8: TAAL – Secondary Endpoints

endpoint	Patient population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
Composite of CV death, nonfatal MI, or UTVR at Day 30												
	UA/NSTEMI	5044	281	5.57	5030	349	6.94	10074	630	6.25	0.80 (0.68, 0.93)	0.005
	STEMI	1769	118	6.67	1765	155	8.78	3534	273	7.72	0.75 (0.59, 0.96)	0.02
	All ACS	6813	399	5.86	6795	504	7.42	13608	903	6.64	0.78 (0.69, 0.89)	<0.001
Composite triple endpoint at Day 30												
	UA/NSTEMI	5044	274	5.43	5030	336	6.68	10074	610	6.06	0.81 (0.69, 0.95)	0.009
	STEMI	1769	115	6.50	1765	166	9.41	3534	281	7.95	0.68 (0.54, 0.87)	0.002
	All ACS	6813	389	5.71	6795	502	7.39	13608	891	6.55	0.77 (0.67, 0.88)	<0.001
Composite of CV death, nonfatal MI, or UTVR at Day 90												
	UA/NSTEMI	5044	345	6.84	5030	420	8.35	10074	765	7.59	0.81 (0.70, 0.94)	0.004
	STEMI	1769	127	7.18	1765	168	9.52	3534	295	8.35	0.75 (0.59, 0.94)	0.013
	All ACS	6813	472	6.93	6795	588	8.65	13608	1060	7.79	0.79 (0.70, 0.90)	<0.001
Composite triple endpoint at Day 90												
	UA/NSTEMI	5044	333	6.60	5030	395	7.85	10074	728	7.23	0.83 (0.72, 0.97)	0.015
	STEMI	1769	129	7.29	1765	178	10.08	3534	307	8.69	0.72 (0.57, 0.90)	0.004
	All ACS	6813	462	6.78	6795	573	8.43	13608	1035	7.61	0.80 (0.71, 0.90)	<0.001
Composite triple endpoint or re-hospitalization for cardiac ischemic events												
	UA/NSTEMI	5044	598	11.86	5030	688	13.68	10074	1286	12.77	0.86 (0.77, 0.96)	0.006
	STEMI	1769	199	11.25	1765	250	14.16	3534	449	12.71	0.78 (0.65, 0.94)	0.009
	All ACS	6813	797	11.70	6795	938	13.80	13608	1735	12.75	0.84 (0.76, 0.92)	<0.001
Composite of all-cause mortality, nonfatal MI, or nonfatal stroke												
	UA/NSTEMI	5044	504	9.99	5030	590	11.73	10074	1094	10.86	0.84 (0.75, 0.95)	0.005
	STEMI	1769	188	10.63	1765	232	13.14	3534	420	11.88	0.80 (0.66, 0.97)	0.02
	All ACS	6813	692	10.16	6795	822	12.10	13608	1514	11.13	0.83 (0.75, 0.92)	<0.001
Definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end												
	UA/NSTEMI	4798	39	0.81	4789	80	1.67	9587	119	1.24	0.49 (0.34, 0.72)	<0.001
	STEMI	1624	19	1.17	1633	40	2.45	3257	59	1.81	0.50 (0.29, 0.87)	0.011
	All ACS	6422	58	0.90	6422	120	1.87	12844	178	1.39	0.49 (0.36, 0.68)	<0.001

and absence of concomitant diseases and medications that are common in the ACS population. Results were similar whether or not subjects received a stent, and irrespective of whether a bare metal stent or drug-eluting stent was deployed.

Efficacy was driven by a reduction in non-fatal MI, which was statistically significant in both the STEMI and UA/NSTEMI populations. There was a positive trend in mortality in favor of prasugrel in the STEMI population, but not in the larger UA/NSTEMI population. Stroke was similar in the two groups. In exploratory analyses, variability in salt to base conversion had no demonstrable effect on prasugrel's efficacy.

The following weaknesses and concerns were identified:

1) Stent thrombosis: The clinical reviewer levied serious criticism regarding the claim for prasugrel in preventing stent thrombosis. Because *reports* of angiograms, and not the original angiographic images per se, were utilized in adjudicating the endpoint, the reliability of the data is not sufficient to support a labeling claim.

2) Prevention of stroke: Importantly, the efficacy of clopidogrel was established in CURE, where clopidogrel was compared to placebo on a background of aspirin in subjects presenting with UA/NSTEMI. The study utilized a triple composite endpoint similar to that used in TAAL. In CURE, clopidogrel was associated with a 20% relative risk reduction on the triple endpoint, but was essentially neutral on the stroke component of the endpoint. Specifically, rates of stroke were 1.2% and 1.4% for the clopidogrel and placebo groups, respectively, for a non-statistically significant relative risk reduction of 14% (95% C.I. -17.7% to 36.6%). In TAAL, prasugrel's effect on stroke was neutral with respect to clopidogrel (hazard ratio 1.02 in favor of clopidogrel, 95% C.I. 0.71 to 1.45). Therefore, in estimating what prasugrel's effect on stroke would have been relative to placebo, the neutral effects in CURE and TAAL are chained, and the evidence of effectiveness is nil.

Moreover, in TAAL, in the subgroup of subjects with a prior history of TIA or stroke, the overall effect of prasugrel was negative, driven by a striking *increase* in strokes (hazard ratio of 5.64, 95% C.I. 1.65 to 19.3). (Of note, subjects with a history of hemorrhagic stroke were excluded from participation, and it is possible that inclusion of such patients might have driven the risk of recurrent stroke even higher.) *Presently, the evidence that prasugrel causes stroke in patients with a prior TIA or stroke seems more persuasive than the evidence that prasugrel prevents stroke in those without such a history.* As such, it would not be appropriate to give prasugrel an indication for stroke, based on extant data. On the contrary, risk management should include a contraindication for patients with a prior history of TIA or stroke.

3) Subjects of African descent: Subjects of African descent accounted for less than 3% of the subject population in TAAL. At this point, there is no reason to believe that results from Caucasians can not be extrapolated to patients of African descent, but the size of the subgroup was too limited to be very informative in its own right.

6.2 Safety

6.2.1. Exposure:

TALL included 6741 subjects in the prasugrel treated population and 6716 subjects in the clopidogrel treated population (13,457 in total). Taking into consideration temporary drug discontinuations, median exposure was 442 days in the prasugrel group and 444 days in the

clopidogrel group. Over 4200 subjects in each treatment group were exposed for greater than one year.

Although TAAL was a large cardiovascular outcome study, it was by no means a large "simple" trial. Subjects were evaluated at hospital discharge, Days 30, 90, 180, 270, 360, and 450 (or last visit) for adverse events and concomitant medications. In addition, vital signs, ECG, complete blood count, platelet count, and clinical chemistries were performed at each visit. Thus, the safety database is quite robust.

Because 98.8% of randomized subjects received the study agent, the safety population is not importantly different from the ITT efficacy population. As such, the reader is referred back to Table 1 and Table 2 for a breakdown of demographic and historical characteristics, respectively.

The following weaknesses are identifiable in terms of exposure: the database included few subjects with hepatic and renal impairment. Approximately 0.5% of subjects in each group had pre-existing hepatic impairment; approximately 0.8% had severe renal impairment (calculated creatinine clearance < 30 mL/min). Approximately 10% of subjects had calculated creatinine clearance between 30-60 mL/min. Thus, experience is extremely limited in subjects with severe hepatic and renal dysfunction, and this should be pointed out in labeling.

6.2.2. Deaths:

Cardiovascular deaths were considered within the composite endpoint of TAAL (Table 6), and are not further considered in the safety analysis. There were no significant differences in all-cause mortality between treatment groups. In the overall ACS population, the frequencies of CEC-adjudicated all-cause mortality were 2.76% and 2.90% in the prasugrel and clopidogrel treatment groups, respectively. In the UA/NSTEMI population, the respective frequencies were 2.58% and 2.41%; in the STEMI population, the respective frequencies were 3.28% and 4.31%.

Twenty-two (22) subjects in the prasugrel group succumbed to TIMI fatal hemorrhage, compared with 5 in the clopidogrel group (0.32% versus 0.07%, respectively, RR=4.4, 95% C.I. 1.7 to 12). Nine of the 22 deaths in the prasugrel group were attributed to intracranial hemorrhage (ICH); all 5 deaths in the clopidogrel group were attributed to ICH (P=NS).

Because of the Division's concerns regarding disproportionate numbers of malignancies in the prasugrel and clopidogrel groups (discussed below), the sponsor was asked to obtain additional information on subjects with neoplasms, to determine, for each neoplasm, whether it was pre-existing or new, whether bleeding or anemia might have led to its diagnosis, and whether it was fatal.

The sponsor's "Supplemental Regulatory Response Concerning Neoplasms" of May 9, 2008 summarized cancer deaths, as follows: For subjects with non-benign neoplasms that the sponsor considered pre-existing (n=28 for prasugrel; n=10 for clopidogrel), there were 6 and 2 deaths due to malignancy in the prasugrel and clopidogrel groups, respectively (Table 8 of sponsor's Supplemental Response). For subjects with non-benign neoplasms that were considered to be new, there were 27 and 19 deaths due to malignancy in the prasugrel and clopidogrel groups, respectively (Table 14 of sponsor's Supplemental Response). Overall, therefore, for subjects with non-benign neoplasms (new or pre-existing), there were 33 and 21 cancer deaths in the prasugrel and clopidogrel groups, respectively (RR=1.57, 95% C.I. 0.91 to 2.71). Cancer is addressed more fully, below.

Discontinuations:

The most commonly cited reason given for discontinuation was "subject decision," reported in approximately 9% of subjects in each treatment group. The second most common reason for discontinuation was an adverse event, with 7.2% and 6.3% of subjects discontinuing in the prasugrel and clopidogrel groups, respectively (Table TAAL 12.2, TAAL Clinical Study Report). Hemorrhagic adverse events accounted for essentially all of the disparity: the percentages of subjects discontinuing study drug due to a serious hemorrhagic event were 1.6% and 0.9% in the prasugrel and clopidogrel groups, respectively. For non-serious hemorrhagic events, the respective percentages were 0.9% and 0.5%. The numbers of discontinuations for non-hemorrhagic adverse events were similar in the two groups.

6.2.3. Adverse Events of Interest:

6.2.3.1. Bleeding

Non-CABG-Related Bleeding

The risk of bleeding was well-considered in the review by Dr. Hicks. Prasugrel was associated with excess bleeding, irrespective of bleeding definition, seriousness, or location, and across most subgroups assessed. Table 9 summarizes the bleeding events in TAAL. Because some subjects experienced more than one bleeding event, they appear in more than one category. The last two categories of the upper section, "Worst: TIMI Minor" and "Worst: TIMI Minimal," represent the subjects in whom the most significant bleeding event was a TIMI minor or TIMI minimal bleeding event, respectively.

There were 21 and 5 fatal bleeding events in the prasugrel and clopidogrel groups, respectively (RR = 4.19, 95% C.I.: 1.58, 11.1, p=0.002), Table 9. For the clopidogrel group, all 5 fatal bleeding events were intracranial in location. For the prasugrel group, 9 bleeding events were intracranial, 5 were gastrointestinal (GI), 2 originated from puncture sites, 2 from surgical sites, 2 from retroperitoneal locations, and 1 from an intra-abdominal location. Considering that it is virtually impossible to establish hemostasis for a massive intracranial hemorrhage, but generally feasible to achieve hemostasis at extra-cranial sites, it is worth emphasizing that none of the deaths in the clopidogrel group, but over half the deaths in the prasugrel group, were attributed to extra-cranial sites of hemorrhage.

The RR was 1.52 for TIMI life-threatening bleeding events, and this was also statistically significant (Table 9). For TIMI major and TIMI minor bleeding, the relative risks were 1.32 and 1.31, respectively, and the differences were statistically significant.

From these data, it is possible to characterize bleeding in terms of excess bleeding events per 1000 patients treated. Comparing prasugrel to clopidogrel, the absolute risks predict 2.4 additional fatal bleeding events, 4.3 additional TIMI life-threatening bleeds, 5.1 additional TIMI major bleeds (which include fatal and life-threatening bleeds), 5.4 additional TIMI minor bleeds, and 19.4 additional TIMI minimal bleeds per 1000 patients treated. In total, per 1000 patients treated, these calculate to 30 excess TIMI bleeding events of any magnitude, 10.5 bleeding events associated with a decrease in hemoglobin of $\geq$ 3 g/dL, and 5.1 bleeding events associated with a decrease in hemoglobin of $\geq$ 5 g/dL.

CABG-Related Bleeding

The prasugrel-associated bleeding risk was particularly malignant in subjects who underwent CABG (Table 9, bottom). In the prasugrel group, there were 24 TIMI major bleeding events in

213 total ACS subjects (11.3%, RR=3.50), of which 2 were fatal (0.9%). In the clopidogrel group, there were 8 TIMI major bleeds, and none were fatal. There are additional analyses of CABG-related bleeding on page 43.

Reviewer's Comments: Prasugrel should not be the drug of choice for patients in whom CABG surgery is anticipated. From a practical standpoint, prasugrel is not well-suited for pre-treatment of patients in whom coronary anatomy is unknown.

CDER undertook independent analyses of bleeding adverse events, characterized as "mild," "moderate," or "severe," as well as those meeting the regulatory definition of a serious adverse event (see primary clinical review). For all categories of bleeding events, the RR was approximately 1.4, and the difference between treatment groups was statistically significant. The frequencies of bleeding events meeting the regulatory definition of a serious adverse event were 5.5 and 3.8% in the prasugrel and clopidogrel groups, respectively (RR 1.46, 95% C.I. 1.25, 1.71).

Table 9: CEC Adjudicated Bleeding

Non-CABG-Related

endpoint	Patient population	Prasugrel			Clopidogrel			Total			HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
TIMI Fatal	UA/NSTEMI	5001	14	0.3	4980	3	0.1	9981	17	0.2	4.66 (1.34,16.2)	0.008
	STEMI	1740	7	0.4	1736	2	0.1	3476	9	0.3		
	All ACS	6741	21	0.3	6716	5	0.1	13457	26	0.2	4.19 (1.58,11.1)	0.002
TIMI Life-Threatening	UA/NSTEMI	5001	65	1.3	4980	38	0.8	9981	103	1.0	1.71 (1.15,2.55)	0.008
	STEMI	1740	20	1.1	1736	18	1.0	3476	38	1.1	1.11 (0.59,2.10)	0.75
	All ACS	6741	85	1.3	6716	56	0.8	13457	141	1.0	1.52 (1.08,2.13)	0.015
TIMI Major	UA/NSTEMI	5001	108	2.2	4980	77	1.5	9981	185	1.9	1.40 (1.05,1.88)	0.022
	STEMI	1740	38	2.2	1736	34	2.0	3476	72	2.1	1.12 (0.70,1.77)	0.65
	All ACS	6741	146	2.2	6716	111	1.7	13457	257	1.9	1.32 (1.03,1.68)	0.029
TIMI Minor	UA/NSTEMI	5001	117	2.3	4980	80	1.6	9981	197	2.0	1.46 (1.10,1.95)	0.008
	STEMI	1740	47	2.7	1736	45	2.6	3476	92	2.6	1.04 (0.69,1.57)	0.85
	All ACS	6741	164	2.4	6716	125	1.9	13457	289	2.1	1.31 (1.04,1.66)	0.022
TIMI Minimal	UA/NSTEMI	5001	358	7.2	4980	251	5.0	9981	609	6.1	1.44 (1.22,1.69)	0.008
	STEMI	1740	102	5.9	1736	63	3.6	3476	165	4.7	1.63 (1.19,2.23)	0.85
	All ACS	6741	460	6.8	6716	314	4.7	13457	774	5.8	1.47 (1.28,1.70)	0.022
Worst: TIMI Minor	All ACS	6741	157	2.3	6716	120	1.8	13457	277	2.1		
Worst: TIMI Minimal	All ACS	6741	429	6.4	6716	297	4.4	13457	726	5.4		

CABG-Related

endpoint	Patient population	Prasugrel			Clopidogrel			Total			HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
TIMI Fatal	UA/NSTEMI	138	0	0.0	141	0	0.0	279	0	0.0		
	STEMI	75	2	2.7	83	0	0.0	158	2	1.3		
	All ACS	213	2	0.9	224	0	0.0	437	2	0.5		
TIMI Major	UA/NSTEMI	138	12	8.7	141	4	2.8	279	16	5.7	3.26 (1.03,10.4)	0.035
	STEMI	75	12	16.0	83	4	4.8	158	16	10.1	3.76 (1.16,12.2)	0.02
	All ACS	213	24	11.3	224	8	3.6	437	32	7.3	3.50 (1.53,7.99)	0.002

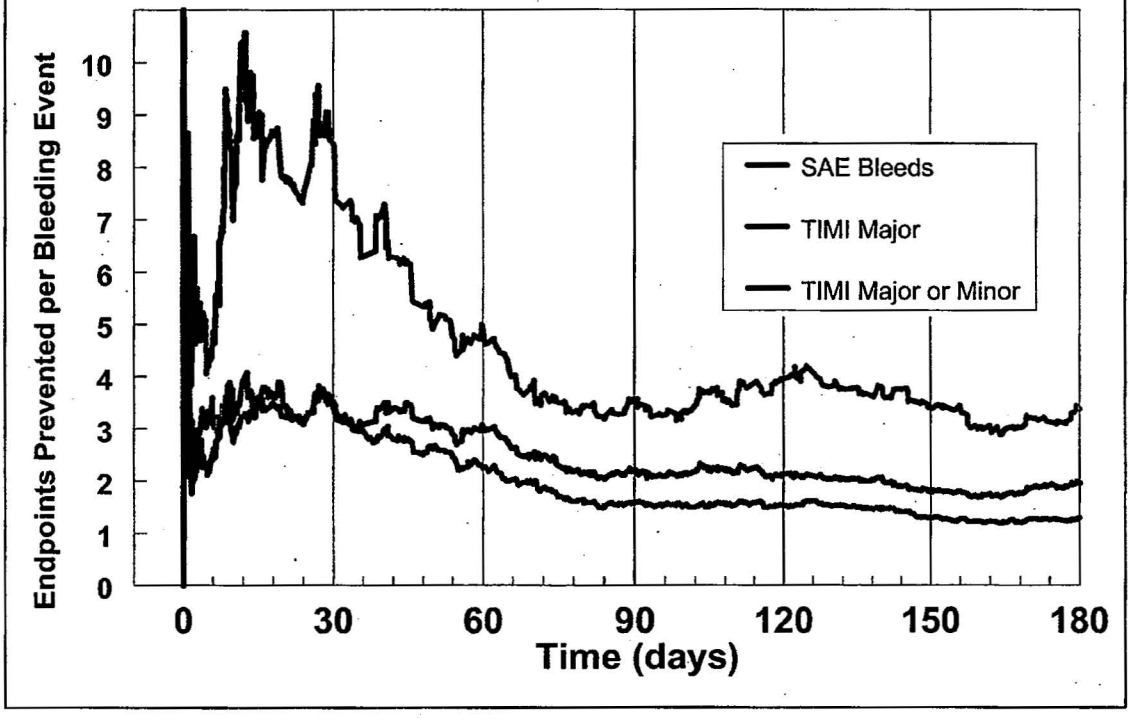
The fatality rate for intracranial hemorrhages was twice as high in the prasugrel treatment group compared to the clopidogrel treatment group.

Risk-Benefit Analysis: Bleeding as a Function of Time

Relative to clopidogrel, the principal risk associated with prasugrel is the risk of bleeding, and the principal benefit is the prevention of non-fatal myocardial infarction. By considering the endpoint events prevented by prasugrel relative to the bleeding events attributed to prasugrel, an actual cumulative benefit-risk *ratio* can be calculated cumulatively over time. The cumulative percentage of endpoint events prevented was calculated by subtracting the event rates for prasugrel and clopidogrel in the Kaplan-Meier analysis for the overall ACS population (i.e., the method used to generate Figure 6). The same approach was used for bleeding events that met the regulatory definition of a serious adverse event (SAE), TIMI major, and TIMI major or minor bleeds. For each bleeding category, the cumulative delta percent was calculated over time. Finally, at each time point, the percentage of endpoint events prevented was divided by the percentage of excess bleeding events. The resulting functions represent the cumulative number of endpoint events prevented per excess bleeding event, as a function of time (Figure 14).

The general shapes of the relations are similar for all the 3 categories of bleeding events. The tradeoff between efficacy and bleeding is most favorable around day 12, exhibits a gentle "plateau" through approximately Day 30, and declines through day 80, as the numbers of attributable bleeding events outpace the number of endpoint events prevented. After day 80, the benefit-risk relation is fairly constant (Figure 14, data shown through Day 180).

Figure 14: Cumulative Benefit-Risk of Prasugrel Compared to Clopidogrel as a Function of Time: All ACS Population



Although the *y*-axis scaling factor depends on the particular definition of bleeding used for the analysis, it is important to note that the *shape* of the curve is largely independent of the definition of bleeding used, and shows how benefit and risk relate through time. It is also important to emphasize that the relation approximates the benefit-risk for prasugrel relative to clopidogrel, and not to placebo.

Bleeding Events: Subgroup Analyses

Table 10 displays pre-specified subgroup analyses to assess the effect of demographics and baseline characteristics on the incidence of non-CABG-related TIMI major or minor bleeding events (from TAAL Table 12.18). The sponsor found no significant treatment-by-demographic characteristic interactions. With respect to the RR of bleeding for prasugrel compared to clopidogrel, none of the subgroups distinguished themselves as being associated with a particularly high RR for prasugrel, although there were trends for higher RR in females and those of lower weight. For both treatment groups, the frequency of bleeding was far higher in older subjects; however, the RR was fairly consistent across all age strata. The RR for subjects of African descent was similar to the RR for Caucasians; the RR was less favorable for prasugrel in Hispanic and Asian subjects, although the sample size in both of these subgroups was small.

For subjects ≥ 75 years of age, the RR of TIMI major or minor bleeding events was 1.35, which is similar to the RR in younger subsets (Table 10). However, subjects ≥ 75 years of age had a higher frequency of fatal and life-threatening bleeding events, and the RR was very unfavorable