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

7.3.3. Secondary Endpoints

Results from the 2° endpoints are shown in Table 9. 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 stent thrombosis endpoint is robust (0.49 RR in favor of prasugrel, 95% CI 0.36, 0.68, for the overall ACS population, p<0.001). Initially, the clinical reviewer (Dr. Karen Hicks) raised concerns regarding the validity of the stent thrombosis endpoint, because the CEC review did not meet the diagnostic standards for stent thrombosis developed recently by the Academic Research Consortium (2007). These standards require angiographic confirmation of stent thrombosis, generally determined by an angiographic core laboratory or pathological confirmation: evidence of recent thrombus within the stent or direct examination of tissue retrieved following thrombectomy. In TAAL, there was no review of angiograms by an angiographic core laboratory, and there was limited pathological confirmation; only *reports* of coronary angiograms and other clinical reports were use to make determinations of stent

Table 9: 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

thrombosis.

The sponsor argued (regulatory response of August 22, 2008) that according to FDA draft guidance, an angiographic core laboratory is not *required*: "FDA strongly recommends that interpretation of data from tests such as angiograms, IVUS, and ECGs be performed by independent core labs and that blinded adjudication of clinical events be conducted by a clinical events committee (CEC Clinical adjudication committees should be independent of core lab analysis centers to avoid potential bias)."[3]

Ultimately, Dr. Hicks selected a number of cases for review by an independent core laboratory, and requested details regarding the adjudication process. The independent review appeared to support the reliability of the original results.

7.3.4. 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 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 have been identified:

1) 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.

2) For 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*

[3] Guidance for Industry: "Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies," draft, March 2008. http://www.fda.gov/cdrh/ode/guidance/6255.html

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.

7.4. Safety

7.4.1. 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 2 and Table 3 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.

7.4.2. All-Cause Mortality

Table 10 displays the sponsor's summary breakdown of deaths in TAAL, adapted from Table TAAL.11.10 of the TAAL study report. The right-most column provides point estimates for the numbers of events that prasugrel would be expected to prevent (if >0) or cause (if <0), relative to clopidogrel, per 1000 patients treated.

There was no significant difference in all-cause death between treatment groups; the frequencies of CEC-adjudicated all-cause mortality were 2.76% and 2.90% in the prasugrel and clopidogrel treatment groups, respectively (p=0.64, Table 10). Differences in mortality in the various categories are not statistically significant, but the most favorable trends for prasugrel (fewer deaths) are in those classified as related to acute MI and sudden/unwitnessed. The most unfavorable trends for prasugrel are in deaths classified as hemorrhagic/non-ICH, ICH, and malignancy.

Deaths due to bleeding and malignancy are addressed more fully in sections below.

Table 10: Summary of Deaths in TAAL (adapter from sponsor's Table TAAL.11.10)

	Prasugrel n=6813		Clopidogrel n=6795		delta events per 1000 patients treated (positive = favorable for prasugrel)
	n	%	n	%	
All Cause Death	**188**	**2.76**	**197**	**2.9**	**1.4**
Cardiovascular (conponent of 1° efficacy endpoint)	**133**	**1.95**	**150**	**2.21**	**2.6**
atherosclerotic vascular disease (excluding coronary)	0	0	3	0.04	0.4
CHF/cardiogenic shock	31	0.46	30	0.44	-0.1
related to CABG or PCI	15	0.22	16	0.24	0.2
dysrhythmia	4	0.06	7	0.1	0.4
pulmonary embolism	3	0.04	0	0	-0.4
acute MI	24	0.35	36	0.53	1.8
sudden or unwitnessed	36	0.53	42	0.62	0.9
ICH	9	0.13	5	0.07	-0.6
non-hemorrhagic stroke	5	0.07	6	0.09	0.1
other cardiovascular	6	0.09	5	0.07	-0.1
Non-Cardiovascular	**55**	**0.81**	**47**	**0.69**	**-1.2**
accident/trauma	4	0.06	4	0.06	0.0
hemorrhage, non-ICH	9	0.13	1	0.01	-1.2
infection	11	0.16	10	0.15	-0.1
malignancy	21	0.31	17	0.25	-0.6
suicide	3	0.04	2	0.03	-0.1
other	7	0.1	13	0.19	0.9

7.4.3. 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.

7.4.4. Intracranial Hemorrhage (ICH)

In TAAL, ICH was reported in 20 (0.29%) and 16 (0.24%) subjects in the prasugrel and clopidogrel groups, respectively. In both groups, the majority of events occurred between 30 and 180 days post-randomization. Intracranial hemorrhages in the prasugrel group were more severe and recovery from these events was lower than in the clopidogrel group. Compared to clopidogrel, twice as many prasugrel-treated subjects died from ICH.

7.4.5. Non-ICH Bleeding

The sponsor categorized bleeding events as related or unrelated to coronary artery bypass graft (CABG) surgery. Events within 7 days of completion of the CABG surgery were classified as CABG-related by the central adjudication committee.

7.4.6. Non-CABG-Related Bleeding

The risk of bleeding was well-considered in the review by Dr. Hicks. Prasugrel was associated with excess bleeding relative to clopidogrel, irrespective of bleeding definition, seriousness, or location, and across most subgroups assessed. The time course of CEC-adjudicated TIMI major or minor bleeding is shown Figure 15. Note that approximately one-third of all bleeding events were recorded in the first day; nearly half of all bleeding events were reported in the initial 10 days.

Figure 15: Incidence of Non-CABG-Related TIMI Major or TIMI Minor Bleeding Events – All ACS Population

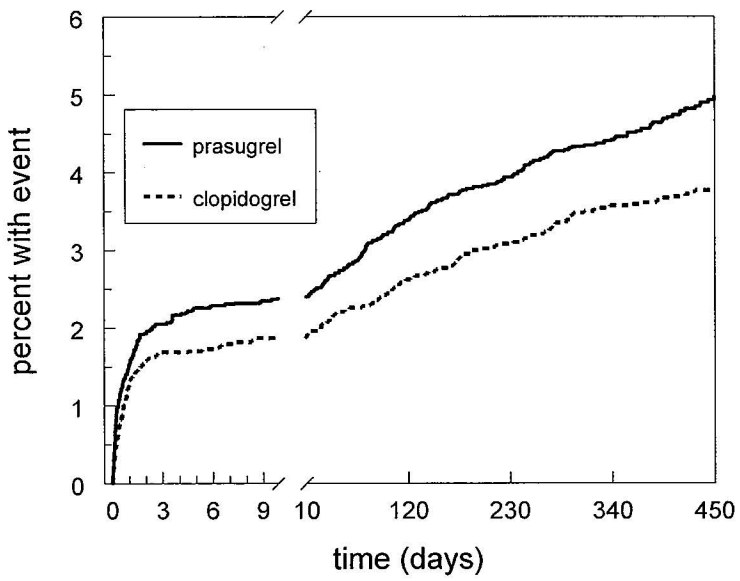

Table 11 summarizes the various categories of bleeding events in TAAL. Because some subjects experienced more than one bleeding event, they appear in more than one category. The last two categories of the upper section, "Worst: TIMI Minor" and "Worst: TIMI Minimal," represent the subjects in whom the 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 11. All 5 of the fatal bleeding events in the clopidogrel group were intracranial in location. For the prasugrel group, 9 of 21 fatal bleeding events were intracranial, and 12 were not (5 were gastrointestinal [GI], 2 originated from puncture sites, 2 from surgical sites, 2 from retroperitoneal locations, and 1 from an intra-abdominal location). Given that it is generally more feasible to manage bleeding at extra-cranial sites than at intracranial 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 disparity in deaths from extracranial hemorrhage between the prasugrel and clopidogrel groups suggests that severe bleeding may be more difficult manage in patients who received prasugrel.

The RR was 1.52 for TIMI life-threatening bleeding events, and this was also statistically significant (Table 11). 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.

7.4.7. CABG-Related Bleeding

The prasugrel-associated bleeding risk was particularly malignant in subjects who underwent CABG (Table 11, 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 11: CEC Adjudicated Bleeding

Non-CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	6741	21	0.3	6716	5	0.1	4.19 (1.58,11.1)	0.002
TIMI Life-Threatening	6741	85	1.3	6716	56	0.8	1.52 (1.08,2.13)	0.015
TIMI Major	6741	146	2.2	6716	111	1.7	1.32 (1.03,1.68)	0.029
TIMI Minor	6741	164	2.4	6716	125	1.9	1.31 (1.04,1.66)	0.022
TIMI Minimal	6741	460	6.8	6716	314	4.7	1.47 (1.28,1.70)	0.022

CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	213	2	0.9	224	0	0.0		
TIMI Major	213	24	11.3	224	8	3.6	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.

7.4.8. 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 7). 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 16).

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 16, data shown through Day 180).