

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 (component 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 related to CABG or PCI	31	0.46	30	0.44	-0.1
dysrhythmia	15	0.22	16	0.24	0.2
pulmonary embolism	4	0.06	7	0.1	0.4
acute MI	3	0.04	0	0	-0.4
sudden or unwitnessed ICH	24	0.35	36	0.53	1.8
non-hemorrhagic stroke	36	0.53	42	0.62	0.9
other cardiovascular	9	0.13	5	0.07	-0.6
Non-Cardiovascular	55	0.81	47	0.69	-1.2
accident/trauma	5	0.07	6	0.09	0.1
hemorrhage, non-ICH	6	0.09	5	0.07	-0.1
infection	4	0.06	4	0.06	0.0
malignancy	9	0.13	1	0.01	-1.2
suicide	11	0.16	10	0.15	-0.1
other	21	0.31	17	0.25	-0.6
	3	0.04	2	0.03	-0.1
	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.

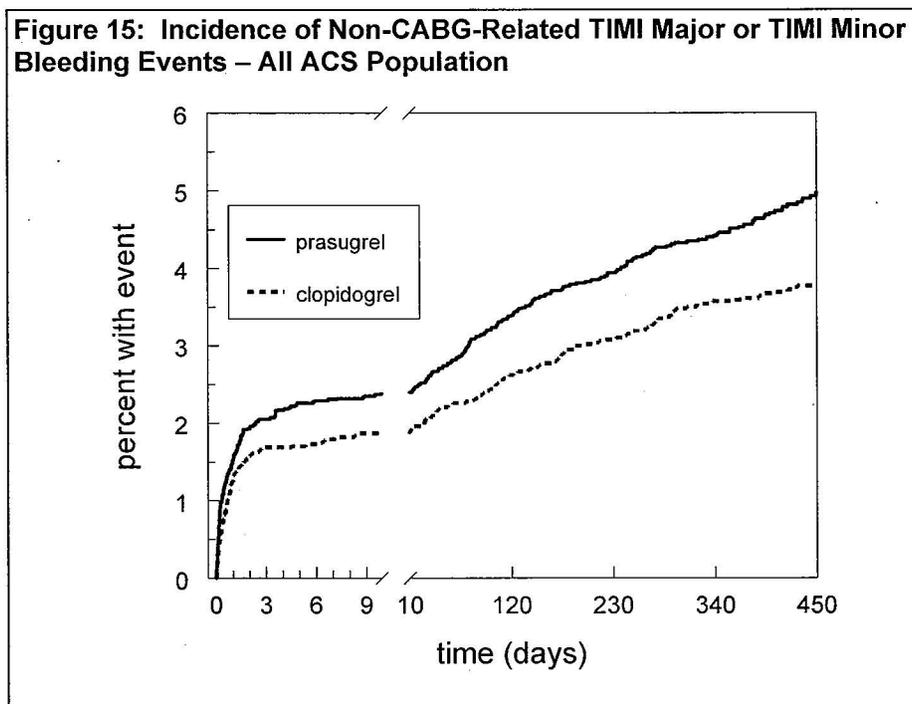


Table 11 summarizes the various categories of bleeding events in TAAL. Because some subjects experienced more than one bleeding event, they appear in more than one category. The last two categories of the upper section, “Worst: TIMI Minor” and “Worst: TIMI Minimal,” represent the subjects in whom the 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 ≥ 3 g/dL, and 5.1 bleeding events associated with a decrease in hemoglobin of ≥ 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

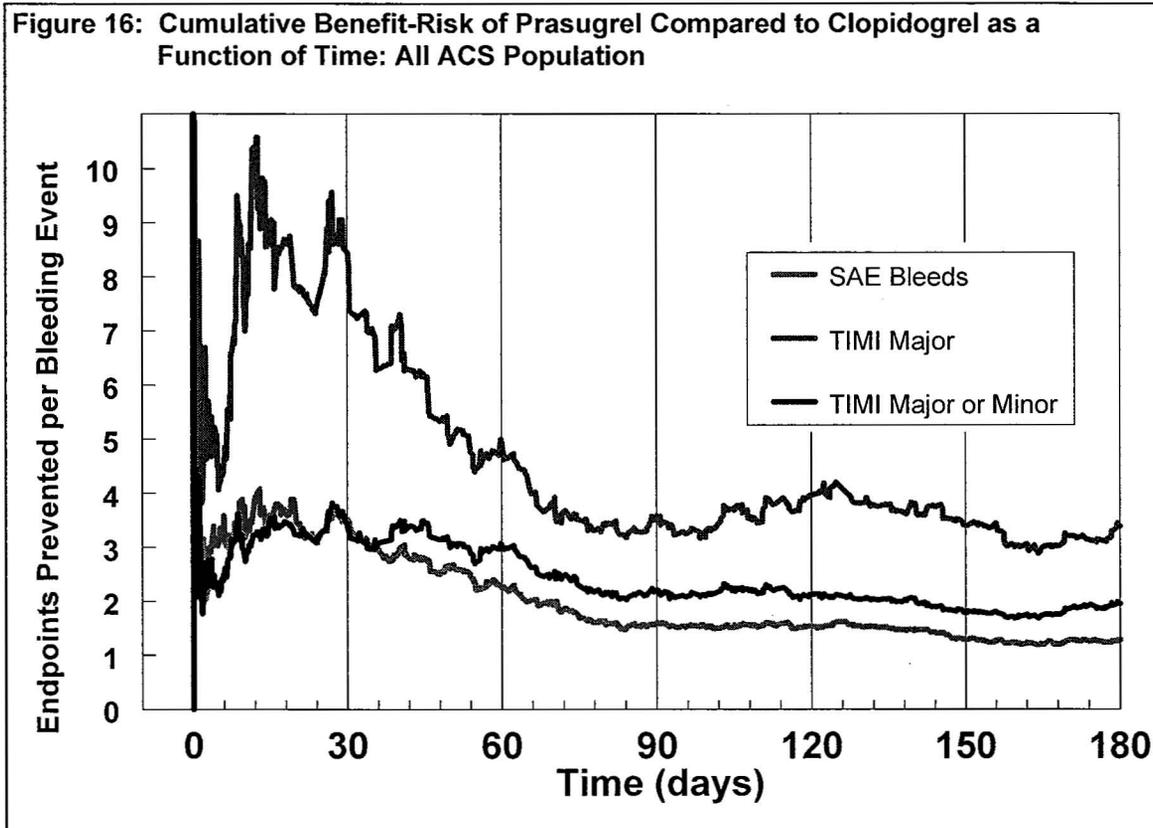
Non-CABG-Related								
bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	6741	21	0.3	6716	5	0.1	4.19 (1.58,11.1)	0.002
TIMI Life-Threatening	6741	85	1.3	6716	56	0.8	1.52 (1.08,2.13)	0.015
TIMI Major	6741	146	2.2	6716	111	1.7	1.32 (1.03,1.68)	0.029
TIMI Minor	6741	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).



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.

7.4.9. Bleeding Events: Subgroup Analyses

Table 12 shows the incidence of non-CABG-related TIMI major or minor bleeding events in subgroups based on demographic characteristics and weight. The data reflect bleeding events while at risk, i.e., events from the first dose of study drug through 7 days after permanent study drug discontinuation. The top portion of the table shows pre-specified subgroups, as adapted from TAAL Table 12.18. The analysis by weight quintiles (bottom) was performed by this reviewer, and is based on the sponsor's CECBLDF.xpt dataset, variable "C_TAIALL."

The sponsor found no significant treatment-by-demographic characteristic interactions. None of the subgroups distinguished themselves as being associated with a particularly high RR for prasugrel, although RR trended slightly higher in females. Relative risk was higher (1.72) for subjects weighing <60 kg; however, this is an arbitrary weight cutoff with relatively few subjects in this subgroup. The overall analysis of RR of bleeding by quintile does not suggest a particular issue with subjects of lower weight. 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. A few other factors deserve special consideration, and they are discussed below.

parameter	Prasugrel			Clopidogrel			RR (95% C.I.)	p	
	N	n	%	N	n	%			
overall	6741	303	4.5	6716	231	3.4	1.31 (1.11, 1.56)	0.002	
sex	female	1684	123	7.3	1798	97	5.4	1.38 (1.06, 1.80)	0.017
	male	5057	180	3.6	4918	134	2.7	1.31 (1.05, 1.64)	0.018
age	<65	4149	141	3.4	4096	99	2.4	1.41 (1.09, 1.83)	0.008
	>=65	2592	162	6.3	2620	132	5.0	1.26 (1.00, 1.59)	0.046
	<70	5095	182	3.6	5041	138	2.7	1.31 (1.05, 1.64)	0.016
	>=70	1646	121	7.4	1675	93	5.6	1.35 (1.03, 1.76)	0.03
ethnicity	<75	5850	223	3.8	5822	169	2.9	1.32 (1.08, 1.61)	0.006
	>=75	891	80	9.0	894	62	6.9	1.35 (0.97, 1.88)	0.078
	Caucasian	6196	281	4.5	6200	217	3.5	1.30 (1.09, 1.56)	0.003
	African	201	10	5.0	185	7	3.8	1.34 (0.51, 3.53)	0.551
weight quintile; range (kg)	Hispanic	269	10	3.7	255	6	2.4	1.55 (0.56, 4.27)	0.393
	Asian	60	2	3.3	63	1	1.6	-	-
weight <60 kg *	1 (32 - 70)	1416	96	6.8	1526	75	4.9	1.38 (1.03, 1.85)	<0.05
	2 (>70 - 78)	1265	61	4.8	1245	43	3.5	1.40 (0.95, 2.05)	NS
	3 (>78 - 85)	1365	49	3.6	1315	39	3.0	1.21 (0.80, 1.83)	NS
	4 (>85 - 95.2)	1291	50	3.9	1265	42	3.3	1.17 (0.78, 1.75)	NS
	5 (>95.2)	1344	43	3.2	1304	30	2.3	1.39 (0.88, 2.2)	NS
weight unknown	60	4	6.7	61	2	3.3	2.03 (0.39, 10.7)	NS	
weight <60 kg *	412	40	9.7	444	25	5.6	1.72 (1.07, 2.79)	<0.05	

* Weight <60 kg is a subset of quintile #1.

7.4.10. Bleeding and Advanced Age

For the study overall, there was a striking increase in bleeding with advancing age; however, the HR for prasugrel compared to clopidogrel was consistent across age strata. Specifically, the HR for TIMI Major/Minor bleeding for the overall study was 1.31 (worse for prasugrel). Similarly, the HR for subjects over 70 years of age was 1.35, as was the HR for subjects over 75. Thus, based on a comparison to clopidogrel, prasugrel's risk of bleeding in subjects over 75 seems similar to that in younger patients.

However, the *outcomes* secondary to bleeding in prasugrel-treated subjects over 75 years of age were of particular concern. Specifically, the frequency of fatal hemorrhage was 9/891 (1.0%) for prasugrel-treated subjects, versus 1/894 (0.1%) for clopidogrel-treated subjects. For symptomatic intracranial hemorrhage (ICH), there were 7 (0.8%) versus 3 (0.3%) cases associated with prasugrel and clopidogrel, respectively.

Moreover, prasugrel's efficacy is less certain in patients age 75 or greater. First, In TAAL, the percentages of subjects over the age of 75 experiencing a 1° endpoint event were closer for the prasugrel and clopidogrel groups (16.0% versus 17.0%, respectively) than in the overall study, where the difference was about 2%. Second, the efficacy of *clopidogrel* is less well-established in patients over the age of 75. In CURE, the registrational study of clopidogrel that compared clopidogrel and placebo in the setting of ACS, the frequencies of experiencing the triple endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke were 9.3% and 11.4% for clopidogrel and placebo, respectively. However, in subjects age 75 and over, the respective

frequencies were 17.8% and 19.2%. Thus, efficacy is modest for clopidogrel in the over-75 age group, and by extension, for prasugrel.

In summary, therefore, prasugrel was associated with malignant bleeding outcomes in patients ≥ 75 years of age. Given that prasugrel's efficacy is less clear in this subgroup of patients, the review team opined that use of prasugrel should be discouraged in patients ≥ 75 years of age, and I agree with their reasoning and recommendation.

7.4.11. Concomitant Medication Use

The sponsor conducted subgroup analyses to assess the effects of concomitant medications on the incidence of non-CABG-related bleeding events. The purpose was to investigate the relationship between these medications and the incidence of bleeding during the index hospitalization; therefore, the analysis was limited to medications administered and bleeding events experienced during first 3 days after the LD of study drug.

Medication	Use?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)
		N	n	%	N	n	%	
Overall		6741		4.5	6716	0	3.4	
GPIIb/IIIa	any	3652	22	0.6	3697	17	0.5	1.31 (0.70, 2.47)
	never	3089	12	0.4	3019	7	0.2	1.68 (0.66, 4.27)
Antithrombin	UFH	3455	21	0.6	3436	9	0.3	2.32 (1.06, 5.07)
	UFH+LMWH	2101	8	0.4	2161	14	0.6	0.58 (0.24, 1.39)
Fibrinolytic	yes	210	0	0.0	218	0	0.0	
	no	6531	34	0.5	6498	24	0.4	1.41 (0.84, 2.38)
Aspirin	>0 - <100 mg	689	7	1.0	672	3	0.4	2.28 (0.59, 8.80)
	100 - 200 mg	1703	10	0.6	1741	8	0.5	1.28 (0.51, 3.24)
	>200 mg	4328	16	0.4	4276	11	0.3	1.44 (0.67, 3.10)
	none	21	1	4.8	27	2	7.4	

Table 13 provides a summary of subgroup analyses of spontaneous (non-instrumented) non-CABG-related TIMI major or minor bleeding events by the use or non-use of a GPIIb/IIIa inhibitor, antithrombin agent, fibrinolytic, and aspirin, from symptom onset through Day 3 (from sponsor's Table 12.24.). For all of these subgroups, the data are somewhat difficult to interpret because the numbers of events are small (the analyses are through Day 3, only). There was a significant treatment-by-subgroup interaction for anti-thrombin monotherapy, unfractionated heparin (UFH), compared to UFH plus low molecular weight heparin (LMWH). In subjects receiving only UFH, the RR for spontaneous non-CABG-related TIMI major or minor bleeding events was 2.32 (worse with prasugrel). Conversely, in subjects receiving UFH plus LMWH, the RR strongly favored prasugrel (RR=0.58). There was higher incidence of bleeding events through 3 days while at risk in subjects receiving a GPIIb/IIIa inhibitor compared to subjects not receiving a GPIIb/IIIa inhibitor in each treatment group. For subjects who received GPIIb/IIIa inhibitors, the RR (1.31, unfavorable for prasugrel) is identical to the RR for the study as a

whole, suggesting that GPIIb/IIIa inhibitors do not pose a particular risk for patients who receive prasugrel.

Proton Pump Inhibitors:

Use of PPI deserves special mention. The clinical pharmacology reviewer (Dr. Mishina) noted that concomitant lansoprazole administration (a PPI) reduced the Cmax of prasugrel's active metabolite by nearly 30% (Study TAAI). This interaction is thought to be a function of conversion of the product from the hydrochloride salt form to the free base form, i.e., the PPI interaction is important for the free base, but not the salt. The prasugrel used in TAAI was predominantly free base.

Table 14 shows the incidence of TIMI Major and Minor bleeding events through 3 days, dichotomized by PPI use or non-use (top) and H2 receptor antagonist use or non-use (bottom) through 3 days. For both treatment groups, the table also shows the relative risk of using PPI and H2 receptor antagonists, relative to not using them.

Table 14: Non-CABG-Related TIMI Major or Minor Bleeding Events from Symptom Onset Through Day 3, by PPI and H2 Receptor Antagonist Use Through Day 3

Medication	Use?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)
		N	n	%	N	n	%	
PPI	yes	2760	70	2.5	2719	62	2.3	1.11 (0.79, 1.56)
	no	3981	68	1.7	3997	51	1.3	1.35 (0.94, 1.94)
RR of using PPI:				1.5			1.8	
H2 Antagonist	yes	1027	30	2.9	1017	25	2.5	1.19 (0.70, 2.02)
	no	5714	108	1.9	5699	88	1.5	1.23 (0.93, 1.63)
RR of using H2 Antagonist:				1.5			1.6	

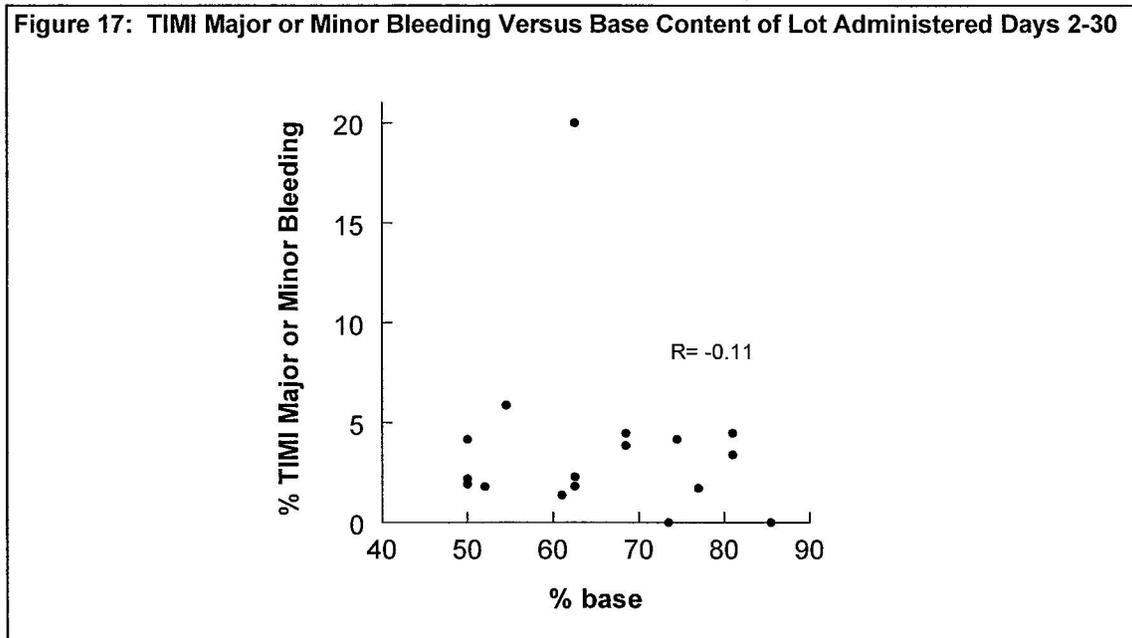
For both treatment groups, the incidence of bleeding was higher in subjects who received gastric pH-raising drugs than in those who did not. This may be related, in part, to the fact that PPI and H2 antagonist use was discretionary, and physicians may have been more willing to prescribe them for patients perceived to be at higher risk of bleeding events.

If prasugrel's salt-to-base conversion led to an important interaction between gastric pH and bleeding (and absent a similar interaction with clopidogrel), use of these medications would be expected to influence prasugrel's bleeding rates to a greater extent than those of clopidogrel. Although this is not a randomized comparison and the numbers of bleeding events are relatively small (through only Day 3), the data do not suggest an interaction that exists for prasugrel but not for clopidogrel. They do suggest that prasugrel's bleeding risk, with or without PPIs or H2 receptor antagonists, is fairly consistent with the study as a whole.

7.4.12. Bleeding by Lot

This reviewer assessed TIMI Major or Minor bleeding rates by lot administered during Days 2-30, and found no relation between salt-to-base conversion and bleeding (Figure 17).

Figure 17: TIMI Major or Minor Bleeding Versus Base Content of Lot Administered Days 2-30



7.4.13. Timing of Drug Discontinuation and CABG-Related Bleeding

Table 15 shows the incidence of TIMI Major/Minor bleeding events as a function of time of discontinuation of study agent relative to subsequent CABG. The frequency of CABG-related bleeding was substantially higher in subjects treated with prasugrel compared to subjects treated with clopidogrel. For prasugrel, the length of time of discontinuation of the drug in advance of CABG was an important determinant of bleeding frequency. When CABG was performed within 3 days of discontinuing prasugrel, the frequency of TIMI Major or Minor bleeding was 12/45 = 27%. For clopidogrel, the corresponding frequency was 3/60 = 5%. The respective frequencies for discontinuation of prasugrel and clopidogrel >3 to ≤7 days prior to CABG were 11% and 3%, respectively. Between 7 and 14 days, the respective frequencies were 10% and 7%. Thus, for prasugrel, it is clear that a longer period of discontinuation will result in less bleeding, and that the risk of bleeding within 3 days of discontinuing prasugrel is particularly high.

The primary clinical reviewer concluded that prasugrel should be discontinued at least 7 days prior to undergoing CABG, if possible. This advice seems reasonable, given that the frequency of TIMI major bleeding was 12.7% when CABG was performed within 7 days of the last dose of prasugrel. However, the risk of bleeding when prasugrel was stopped >7 days prior to surgery is not much lower than 12.7% (it is 8.9%), and is based on only 7 events in 79 subjects.

Figure 18 is adapted from the data at the bottom of Table 15, and shows the cumulative TIMI Major or Minor bleeding frequencies through each day of discontinuation, prior to CABG. Thus, the percentages of events at Day 6 correspond to cumulative bleeding frequencies when the drugs were discontinued ≤ 6 days prior to CABG. For prasugrel, there is little reduction in frequency after Days 7-8. Thus, advice to discontinue prasugrel 7 or more days prior to elective surgery seems fairly reasonable. For clopidogrel, the risk is far lower, and little affected by timing of discontinuation.