- *Some carcinogens cause skin cancers and some skin tumors are sensitive to some promoters.* But most carcinogens are site-specific, as a perusal of the Carcinogenic Potency Database will confirm. (Carcinogenic_Potency_Project 2008) Ideally we would like to know in advance exactly what cancers a carcinogen or promoter affects. In the case of prasugrel we can look to the animal data for some hints—which is what I did.

- *Skin would be a good signal tumor to detect tumor promotion because skin is an active mitotic organ and skin tumors are likely to have a lower probability of providing false negatives.* No data are presented to support these assertions. Because skin cancers are not as serious as other cancers and are usually handled without hospitalizations, reporting of them is more erratic than for other cancers. (Karagas 1994) Skin cancer data are noisy and may mask real effects.

- *Recent assessment of the role of drugs in cancer promotion include melanotic and nonmelanotic skin cancers (ezetimibe/Vytorin – Peto et al, 2008)* For ezetimibe there are no pre-clinical studies suggesting sites to examine, so inclusion in skin is reasonable. However, it may also illustrate my contention that skin cancer data are noisy because the greatest difference in rates in the one study (SEAS) in which more cancers were reported in the ezetimibe group was for skin cancers, and the difference for skin cancer rates favors ezetimibe in the other studies. (Peto, Emberson et al. 2008) Regardless, a signal of increased cancers with or without skin cancers is highly concerning. The ezetimibe SEAS data are of low concern only because there are other large trials with ezetimibe that do not show increased cancer rates. Prasugrel, too, needs other large trials (or at least one) not showing increased cancer rates.

COMMENT: I believe I have excellent justification for excluding skin cancers. I discuss cancer and bleeding next.

Cancer and Bleeding

Bleeding reporting is complicated because there were three sources for capturing bleeds: (1) the adverse event CRFs; (2) the bleeding endpoint CRFs; and (3) Clinical Endpoint Committee (CEC) added bleeds that are not recorded on the AE or bleeding endpoint CRFs but were mentioned on other documents provided to the CEC. For the following analyses I have used the data for bleeding events from all three sources. Because most common bleeds (epistaxis, bruises, etc.) would not initiate a cancer workup, I analyzed bleeds that would be likely to initiate a cancer workup (GI, hemoptysis, hematuria, vaginal, breast) as well as all bleeds and site-specific bleeds.

For patients with new solid cancers, 54% of the prasugrel and 41% of the clopidogrel patients had a preceding bleed of any type. About 33% in each group had a preceding bleed of a type likely to lead to a cancer workup. I show the rates of site-specific prior bleeds for the solid cancers for which bleeding is a common presentation, plus breast cancer because its rates are different in the two treatment groups, in Table 12.

Table 12: New Solid Cancers and Site-Specific Prior Bleeds in TAAL

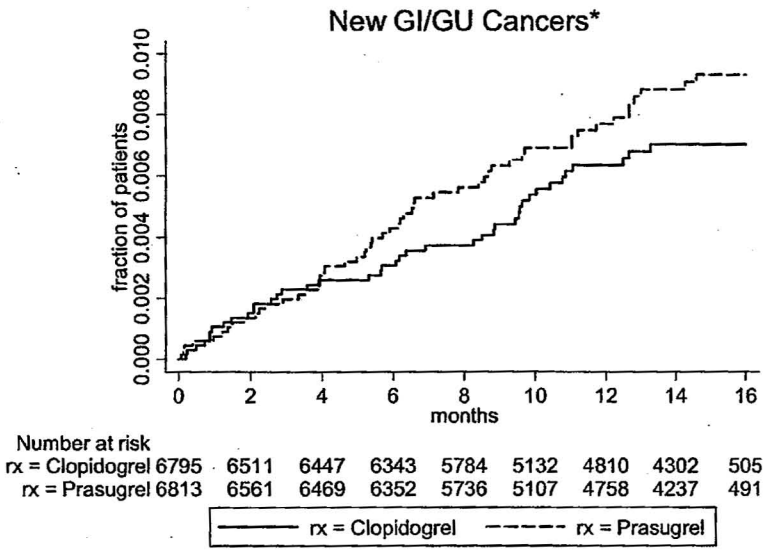
	new cancers		# with prior site specific bleed		% with prior site specific bleed	
	clopidogrel	prasugrel	clopidogrel	prasugrel	clopidogrel	prasugrel
breast	1	4	0	0	0%	0%
colorectal	10	22	6	12	60%	55%
gi*	20	33	11	16	55%	49%
lung	12	15	0	2	0%	13%
kidney/bladder	11	12	7	5	64%	42%
cervix/uterus	1	1	1	1	100%	100%

*includes colorectal, stomach, esophagus but not pancreas, liver, gall bladder

COMMENT: For the site (colorectal) with the largest difference in cancers and the one the sponsor argues that the difference is due to a detection bias, there is no difference in preceding site-specific bleeding. For kidney and bladder the prior bleeding also leans towards clopidogrel. The sponsor's analyses that suggest such a bias include neoplasms other than solid cancers and benign tumors and the common bleeds such as epistaxis, ecchymoses, and superficial hematomas that are unlikely to lead to a cancer search. Regardless, demonstrating more bleeding prior to cancer detection is not very reassuring: I would expect cancers stimulated to grow would bleed more readily, so we can not be certain that more bleeding is due to some cancer effect, e.g., increased angiogenesis, or platelet inhibition or both. The appropriate criterion for whether a cancer is serious is not whether it is preceded by bleeding but whether it is followed by serious consequences, e.g., death. The excess prasugrel cancers are serious by this latter, vital criterion.

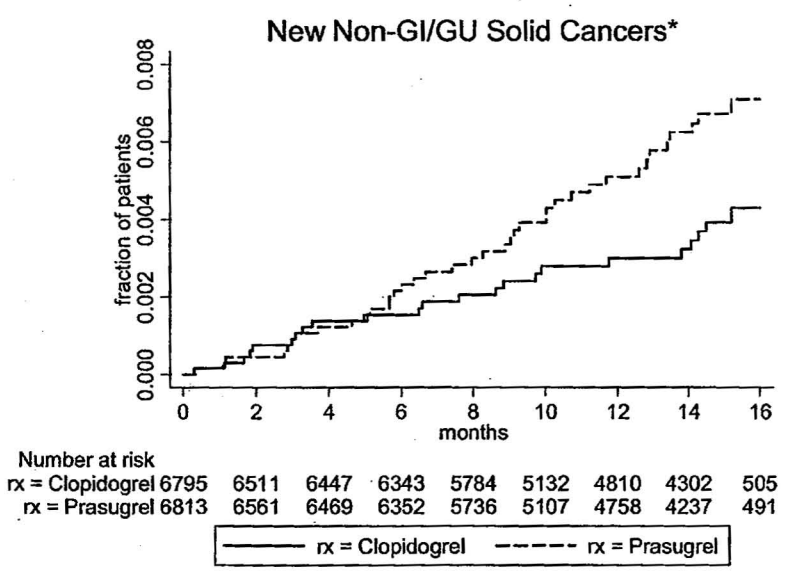
To explore further the hypothesis of ascertainment bias due to bleeding, I examined the incidence curves for cancers that commonly present with bleeding. I show the K-M incident plot for GI/GU cancers in
Figure 7, for non-GI/GU cancers in Figure 8, for GI cancers alone in Figure 9, and for GU cancers alone in Figure 10. (For these analyses I have not counted ovarian or testicular cancers as GU cancers or pancreas, gall bladder, or liver cancers as GI cancers because they do not usually present by bleeding.) For comparison, I show the bleeding rates by month in TAAL in Figure 11.

Figure 7: K-M Incidence Plot for New GI/GU Cancers in TAAL



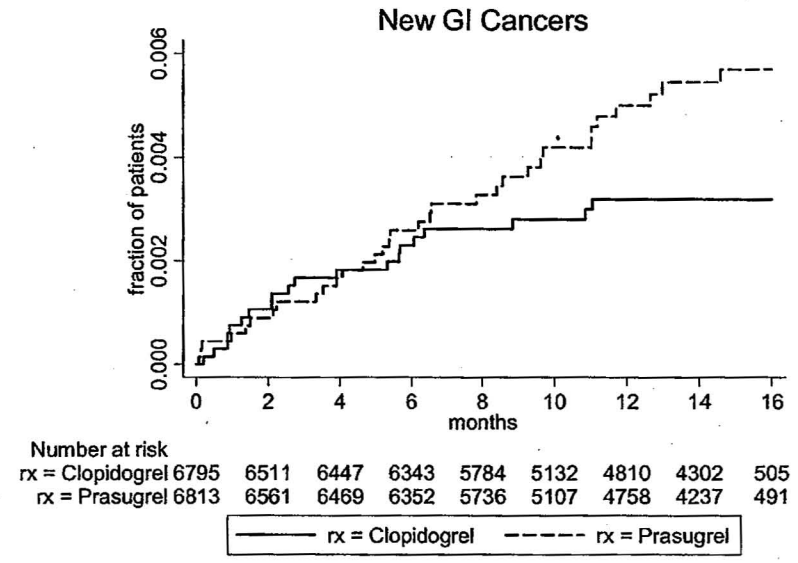
*ovarian, testicular, hepatic, GB, and pancreatic cancers excluded; p = 0.18 by log rank

Figure 8: K-M Incidence Plot for New Non-GI/GU Solid Cancers in TAAL



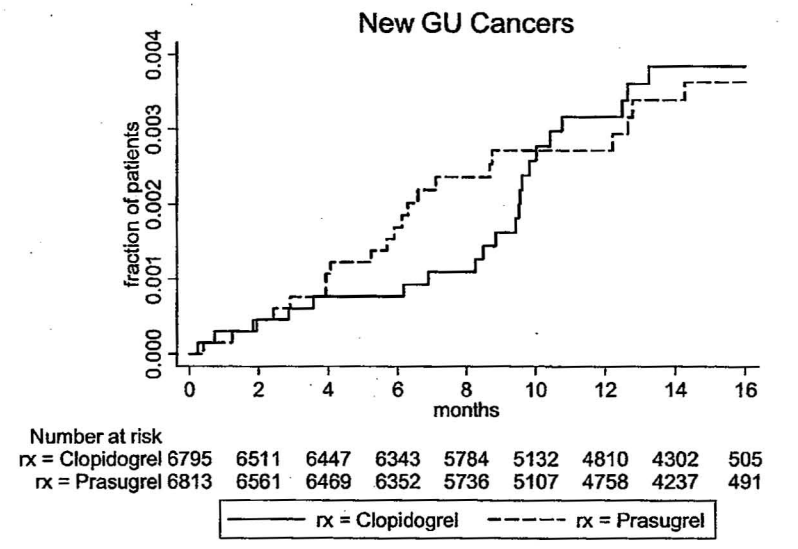
*excluding non-melanoma skin cancers and brain tumors; p = 0.053 by log rank

Figure 9: K-M Incidence Plot for New GI Solid Cancers in TAAL



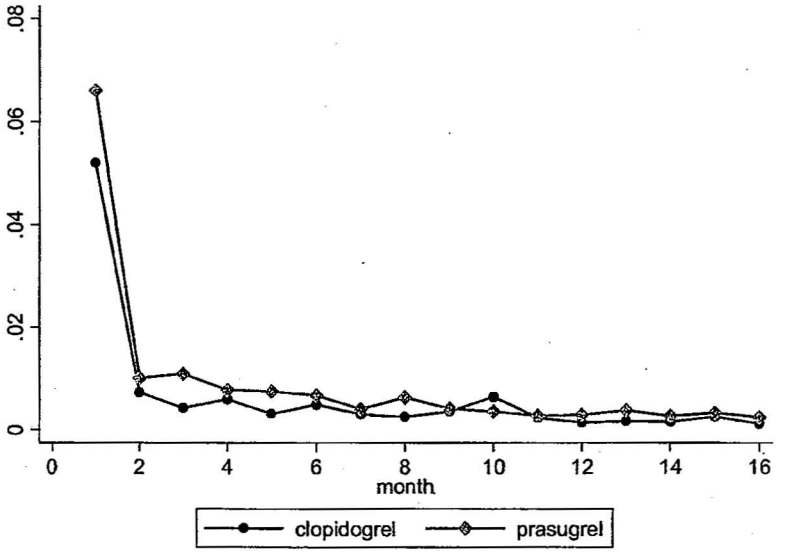
p = 0.074 by log rank

Figure 10: K-M Incidence Plot for New GU Cancers in TAAL



p = 0.99 by log rank

Figure 11: Bleeding Event Rates by Treatment and Month in TAAL



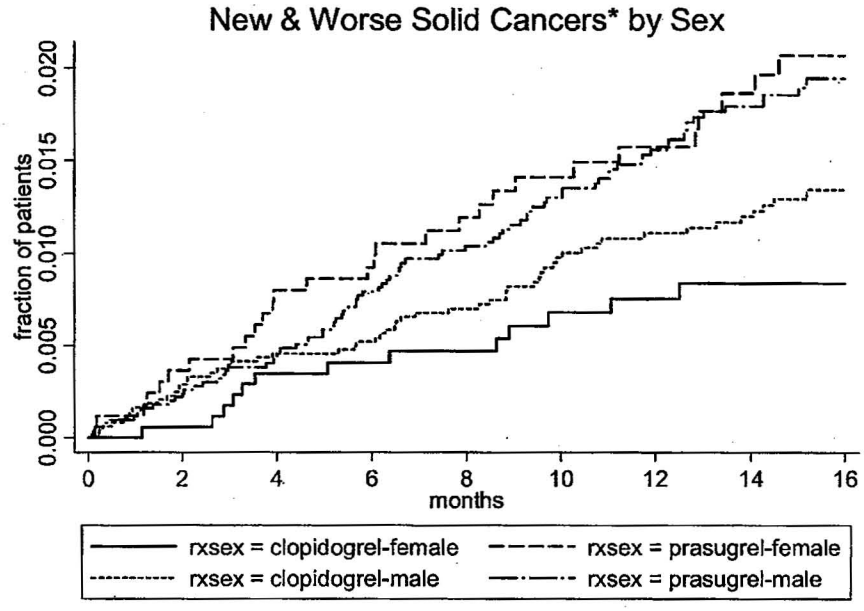
COMMENT: The site-specific incidence plots for GI/GU cancers diverge at four months and then almost converge at about 12 months. However, they do not diverge early when many bleeding events occur (as shown in Figure 11.*) Non-GI/GU cancers show a continuing divergence as do GI cancers, leaving only GU cancers for which the ascertainment bias due to bleeding remains plausible. Both the incidence plots for GI solid cancers (Figure 9) and for non-GI/GU cancers (Figure 8) suggest that the diagnosis rates for non-GU cancers were higher in the first four months than later, particularly for clopidogrel. I would speculate that this difference is due to the increased surveillance initially due to the hospitalization for the ACS event.*

Other Cancer Issues

Cancer and Gender

Based on preliminary analyses of all solid cancers by sex, the primary clinical reviewer has noted that increases in new solid cancers with prasugrel were greater in women than in men. I show the incidence plots for new and worse cancers by sex in Figure 12. Note that TAAL patients were predominantly male (74%).

Figure 12: K-M Incidence Plot for New and Worse Solid Cancers (Excluding Skin and Brain) by Sex in TAAL



*excluding non-melanoma skin cancers and brain tumors

COMMENT: There is some variation in new and worse cancer rates by sex, with females on clopidogrel having the lowest rate and females on prasugrel having the highest. However, for each sex cancer rates are higher with prasugrel. I attribute the variations to the smaller numbers of female patients in TAAL.

Early Cancers

There is no biologic plausibility for cancers diagnosed shortly after randomization to be causally related to study drug. There were reasonable numbers of cancer AEs in TAAL in the immediate months following randomization as shown in the incidence plots above. During internal discussions within the Division of the cancer findings in TAAL, we discussed excluding cancers for some short, arbitrary period after randomization to eliminate biologically implausible incident cancers. I show the effects of varying early cancer diagnosis exclusions in Table 13.

Table 13: New Solid Cancers (excluding Non-Melanoma Skin and Brain) in TAAL Excluding Early Diagnoses

cutoff	clopidogrel	prasugrel	RR*	p†
none	64	92	1.44	0.024
>7 days	62	89	1.44	0.027
>14 days	60	87	1.45	0.025
> 30 days	56	86	1.54	0.011

*RR = relative risk prasugrel/clopidogrel; † by log rank

COMMENT: Not surprisingly, given the superimposed incident curves for the first four months, whether one excludes or includes very early solid cancers makes little difference in the analysis. Because a 7-day (or 14-day, or any length) exclusion is arbitrary, the occurrences of non-study drug related cancers should be reasonably balanced by the randomization, and handling these cases differently breaks the randomization, I would not exclude early cancers from the analyses. The one complicating factor is the possible effect of bleeding that I address next.

Cancer by Region

The sponsor has also argued that the cancer results are inconsistent in subgroups, e.g., by country. I have classified the geographic sources of patients into four regions (US, Eastern and Western Europe, and other) yielding reasonable number of patients in each region. I show the rates of new solid cancers by region in Table 14.

Table 14: Rates of New Solid Cancers by Region in TAAL

Region	Patients		New solid cancers	
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel
E Europe	1,665	1,657	0.8%	1.4%
Other	1,342	1,342	0.7%	1.3%
US	2,020	2,039	1.0%	1.4%
W Europe	1,768	1,775	1.1%	1.2%
Total	6,795	6,813	0.9%	1.4%

COMMENT: New solid cancer rates with prasugrel are higher in all regions, with only Western Europe showing a small effect size. The US, the region of greatest interest to us, show rates very similar to the entire study. Overall the variations in this table are consistent with random subgroup variations. I did not find convincing evidence for subgroup inconsistencies either by region or by sex.

Clopidogrel and Cancer

Because an excellent and critical question is whether carcinogenicity could be a class effect, I also examined the data we have available for large outcome trials using clopidogrel. For reference I have summarized the study features in Table 15.

Table 15: Clopidogrel Studies

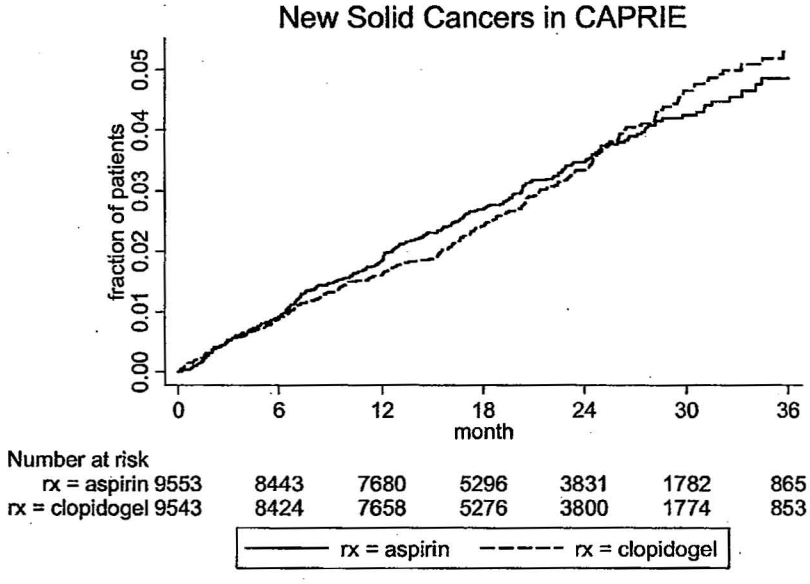
Study	Population	Aspirin	Median age	n	Median months
CAPRIE	high CV risk	325 control	63	19,185	20
CREDO	PCI	325 then 81-325	61	2,116	12
CURE	ACS NSTEMI	75-325	65	12,562	9
CHARISMA	high CV risk	75-162	64	15,603	28

Note that CAPRIE used aspirin only in the control group, while the other studies involved adding clopidogrel to background aspirin at dosages selected by the investigators. CURE and CREDO are the smaller studies with more limited follow-up, so I will summarize briefly their findings but present CAPRIE and CHARISMA in more detail.

In CURE there was a slight excess of solid cancers (48 vs. 42) with clopidogrel due to higher rates of colorectal (16 vs. 8) and lung (12 vs. 7) but slightly higher rates for breast, prostate, bladder, and unknown in the placebo group. In CREDO there was a 5 vs. 0 excess of lung cancers (*post hoc* p = 0.03 commented upon in the study report) but overall new solid cancers were less frequent with clopidogrel (20 vs. 12). Hematologic malignancies and brain tumors did not show any noteworthy variations except a 4 vs. 1 excess of lymphomas in the placebo group in CURE.

I show the new solid cancer incidence plots for CAPRIE in Figure 13 and for CHARISMA in Figure 14; I show the types of cancers for CAPRIE in Table 16 and for CHARISMA in Table 17.

Figure 13: K-M Incidence Plot of New Solid Cancers in CAPRIE



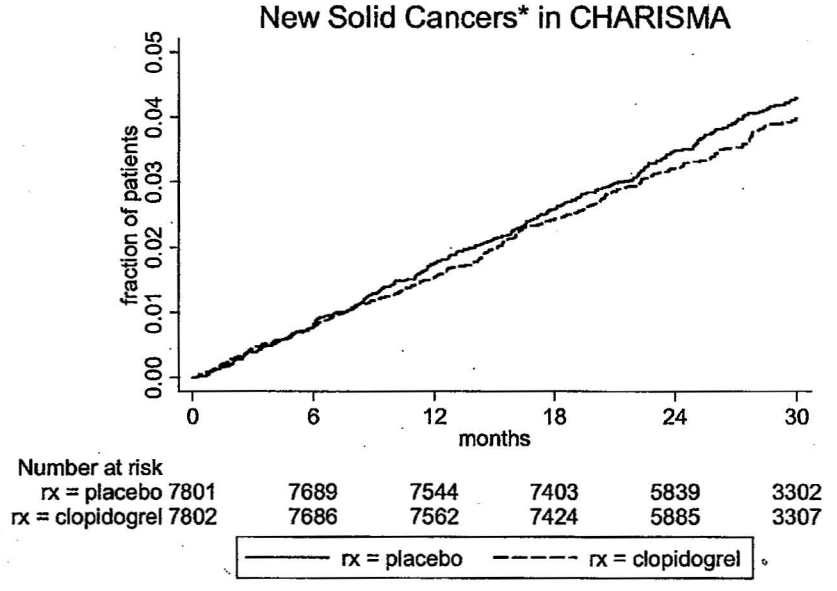
*excluding non-melanoma skin cancers and brain tumors; p = 0.9 by log rank

Table 16: Numbers of Cancers by Site and Treatment in CAPRIE

	aspirin	clopidogrel
patients	9599	9586
bladder	28	26
breast	15	11
cervix	2	2
colorectal	40	33
esophagus	4	4
gall bladder	3	0
head & neck	11	16
kidney	10	10
liver	4	3
lung	74	72
melanoma	13	11

	aspirin	clopidogrel
mesothelioma	0	1
ovary	1	3
pancreas	11	3
prostate	46	61
sarcoma	1	4
stomach	5	13
unknown	11	8
uterus	5	1
total new solid cancers	284	282
skin	71	76
pituitary	4	0
brain	3	9
leukemia	4	5
lymphoma	12	7
myeloma	0	4
polycythemia	4	3

Figure 14: K-M Incidence Plot for New Solid Cancers in CHARISMA



*excluding non-melanoma skin and brain; p = 0.35 by log rank

Table 17: Numbers of Cancers by Site and Treatment in CHARISMA

	clopidogrel	placebo
patients	7,802	7,801
bile duct	3	1
bladder	26	19
breast	13	22

	clopidogrel	placebo
cervix	0	2
colon	0	1
colorectal	41	39
esophagus	6	5
gall bladder	0	1
gi	2	0
head & neck	16	22
kidney	11	13
liver	5	7
lung	70	63
melanoma	9	13
mesothelioma	2	1
myeloma	4	2
other	2	1
ovary	1	3
pancreas	5	10
pelvis	2	1
prostate	52	52
sarcoma	1	0
small intestine	3	2
stomach	8	10
testis	2	0
thyroid	1	1
unknown	9	15
uterus	3	4
vagina	0	1
total new solid cancers	297	311
brain	7	3
leukemia	9	4
lymphoma	4	15

The K-M incidence plots show no significant differences in the rates of new solid cancers in either CAPRIE or CHARISMA. The plot for CAPRIE looks like it might be starting to trend unfavorably for clopidogrel but the plot for CHARISMA looks like it might be trending favorably for clopidogrel. The distributions of cancer types by treatment group also show random differences in the rates, e.g., slightly more prostate and stomach cancers with clopidogrel in CAPRIE but less colorectal cancer; more bladder and lung cancers with clopidogrel in CHARISMA but less breast cancer.

One final comment about CHARISMA: bleeding rates were higher in the clopidogrel group as shown in Table 18.