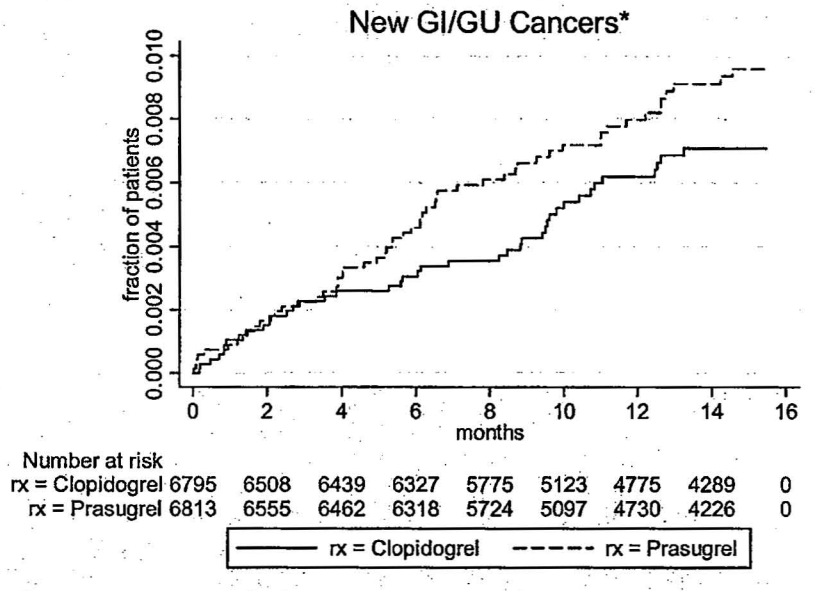
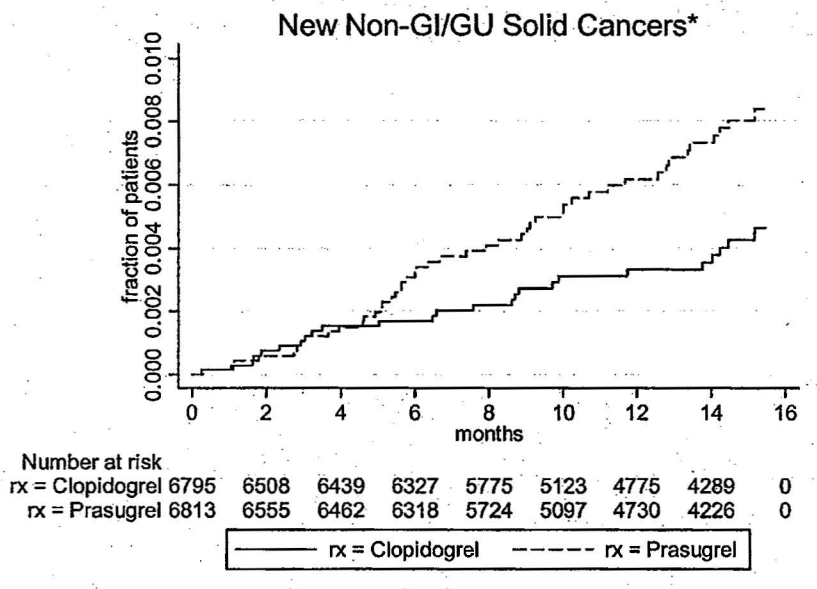
Figure 9: K-M Incidence Plot for New GI/GU Cancers in TAAL



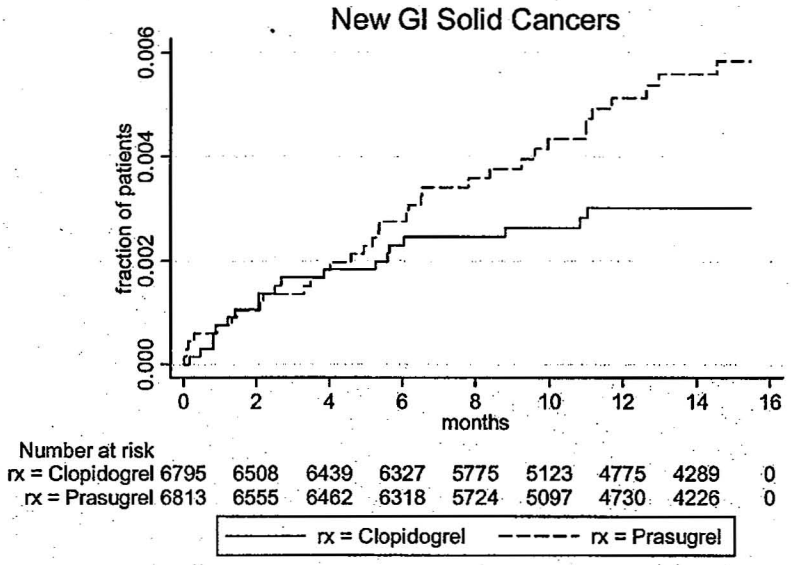
*ovarian, testicular, hepatic, GB, and pancreatic cancers excluded; p = 0.13 by log rank

Figure 10: K-M Incidence Plot for New Non-GI/GU Solid Cancers in TAAL



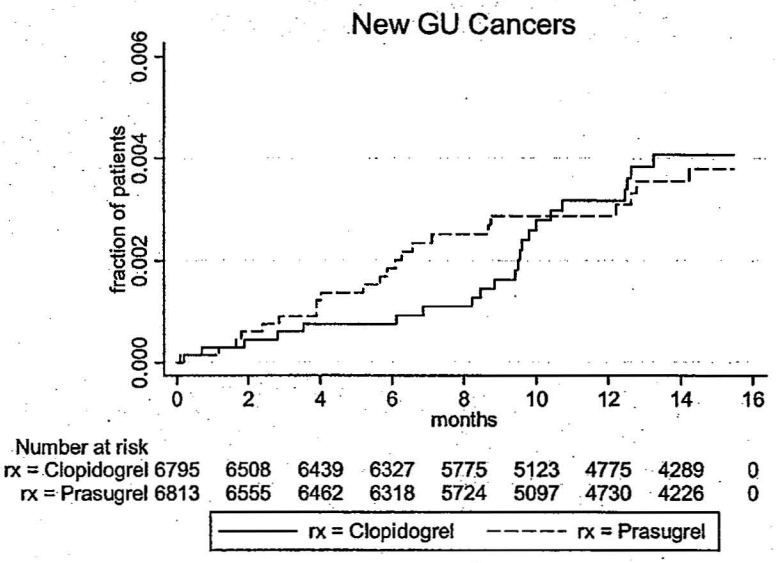
*excluding non-melanoma skin cancers and brain tumors; p = 0.012 by log rank

Figure 11: K-M Incidence Plot for New GI Solid Cancers in TAAL



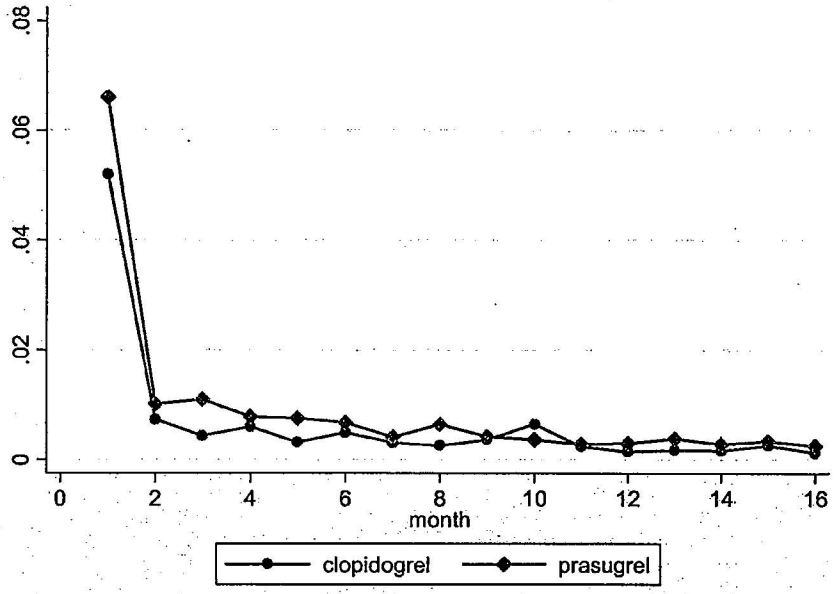
p = 0.04 by log rank

Figure 12: K-M Incidence Plot for New GU Cancers in TAAL



p = 0.99 by log rank

Figure 13: Bleeding Event Rates by Treatment and Month in TAAL



COMMENT: The preceding bleeds statistics for GI and GU cancers are similar for clopidogrel and prasugrel and do not support a hypothesis that more bleeding with prasugrel led to more cancer detection. Regarding the site-specific incidence plots, there is a suggestion that GI/GU cancers diverge at four months and then may converge at about 12 months. However, they do not diverge early when many bleeding events occur (as shown in Figure 13.*) 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 11) and for non-GI/GU cancers (Figure 10) 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.*

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 12.

Table 12: 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%	1.5%
Other	1,342	1,342	0.7%	1.4%
US	2,020	2,039	1.1%	1.8%
W Europe	1,768	1,775	1.1%	1.2%
Total	6,795	6,813	1.0%	1.5%

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, is tied for the largest absolute effect size, a difference of 0.7%. However, 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.

The last statistics worth noting regarding cancer in TAAL are cancer deaths. Investigators reported cancer deaths in 19 prasugrel vs. 11 clopidogrel patients. The Clinical Endpoints Committee adjudicated 21 cancer deaths for prasugrel vs. 17 for clopidogrel. I adjudicated 24 cancer deaths to prasugrel and 15 to clopidogrel. Of these, most were in patients with new solid cancers (22 and 14 respectively). The sponsor obtained further follow-up on most of the cancer patients. With the additional follow-up 22 (33%) of the clopidogrel and 39 (38%) of the prasugrel patients with new solid cancers have died (all causes). Among the patients with new or worse solid cancers, 24 (34%) of the clopidogrel and 42 (36%) of the prasugrel patients have died.

COMMENT: The new solid cancers with prasugrel appear to be at least as lethal as those with clopidogrel, and the new and worse solid cancers are comparable lethal. These findings argue against there being an early detection bias.

Because a good 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 show the study features in Table 13.

Table 13: Clopidogrel Studies

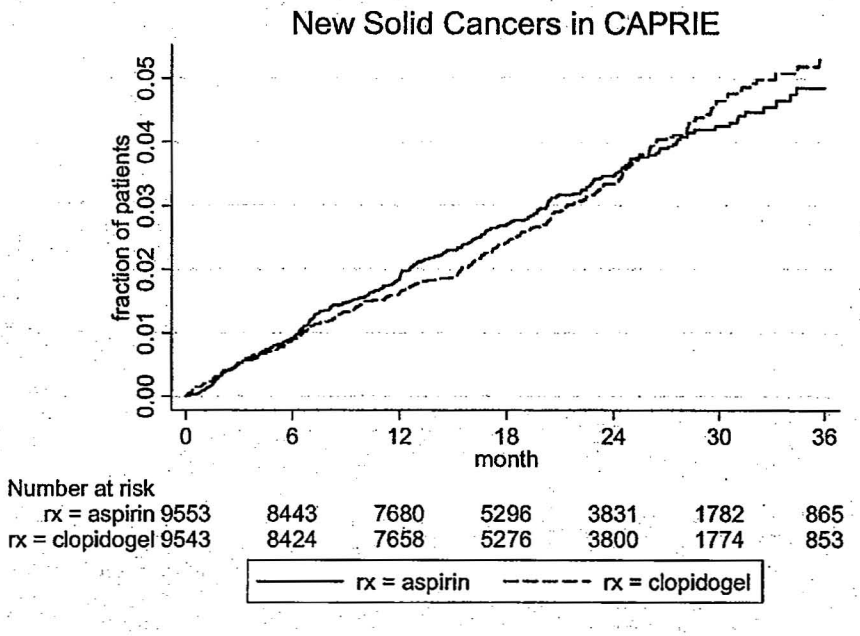
Study	Population	Aspirin	Median age	n	Median months
CAPRIE	high CV risk	325 control	63	19,185	20
CREDO	PCI	325 then 81-325	61	2,116	12
CURE	ACS NSTEMI	75-325	65	12,562	9
CHARISMA	high CV risk	75-162	64	15,603	28

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 14 and for CHARISMA in Figure 15; I show the types of cancers for CAPRIE in Table 14 and for CHARISMA in Table 15.

Figure 14: K-M Incidence Plot of New Solid Cancers in CAPRIE



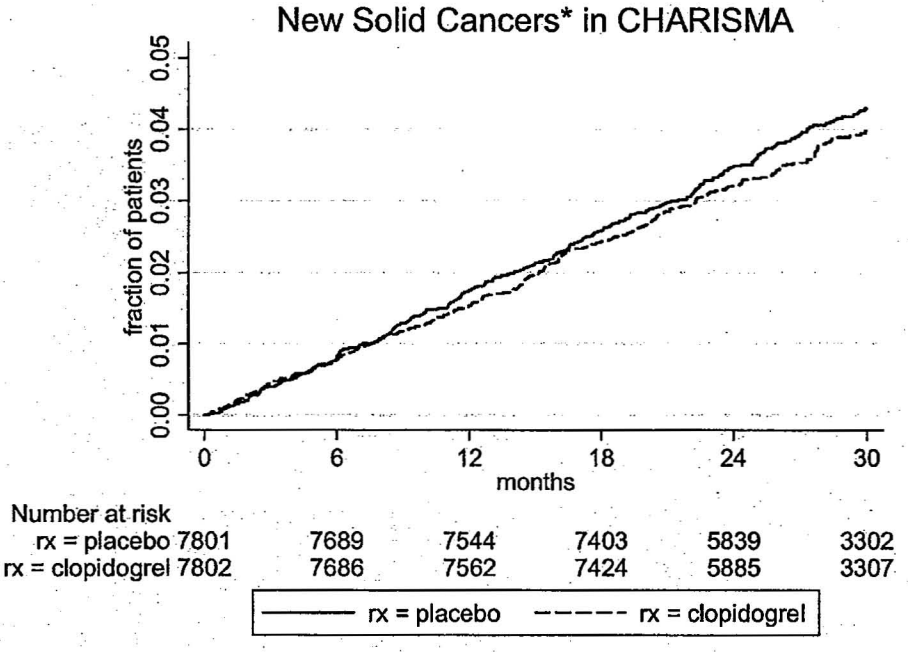
*excluding non-melanoma skin cancers and brain tumors; p = 0.9 by log rank

Table 14: 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
mesothelioma	0	1
ovary	1	3
pancreas	11	3
prostate	46	61
sarcoma	1	4
stomach	5	13
unknown	11	8

	aspirin	clopidogrel
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 15: K-M Incidence Plot for New Solid Cancers in CHARISMA



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

Table 15: 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
cervix	0	2
colon	0	1
colorectal	41	39
esophagus	6	5
gall bladder	0	1

	clopidogrel	placebo
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 16.

Table 16: Bleeding in CHARISMA

Type of Bleeding (GUSTO)	No. % With Event		Difference Clopidogrel - Placebo (%) (95% CI)	p-Value
	Clopidogrel (N=7802)	Placebo (N=7801)		
Any	2827 (36.23)	1616 (20.72)	15.52 (14.12,16.91)	<0.001
Severe/Moderate [a]	290 (3.72)	197 (2.53)	1.19 (0.65,1.74)	<0.001
Severe [a]	130 (1.67)	104 (1.33)	0.33 (-0.05,0.71)	0.087
Moderate [ab]	164 (2.10)	101 (1.29)	0.81 (0.40,1.21)	<0.001
Other bleeding [c]	2646 (33.91)	1487 (19.06)	14.85 (13.49,16.22)	<0.001

COMMENT: Clopidogrel does not appear to have an appreciable effect upon cancer rates. The exposure in the clopidogrel studies is much higher than that for prasugrel in TAAL and should be sufficient for detecting an effect comparable to that seen in TAAL. I believe the clopidogrel studies are good examples of what variations in results to expect when analyses like those I performed for TAAL are done for a drug that has good substantiation of a lack of carcinogenic potential. Furthermore, the fact that in CHARISMA there was substantially more bleeding in the clopidogrel group than in the control group but similar cancer rates does not support the hypothesis that increased bleeding leads to a cancer ascertainment bias.

Discussion

I interpret all of these results as follows: The preclinical studies suggest, but are not conclusive, that prasugrel is a tumor promoter in mice. The clinical results in TAAL are also suggestive of a promoter effect. While it is tempting to dismiss the clinical findings as due to ascertainment bias due to increased bleeding with prasugrel, the delay in the divergence of the incidence plots for four+ months, the continued divergence of most plots through 16 months, the lack of evidence for an ascertainment bias for solid tumors other than GU, the cancer deaths leaning in the wrong direction, and the lack of a similar ascertainment bias in CHARISMA do not support the ascertainment bias hypothesis.

Besides drug effect, one other possible explanation is a play of chance resulting in more cancer prone individuals ending up in the prasugrel group. While this remains possible, I think it is unlikely because of the size of TAAL and the reasonably extreme p values for the most relevant comparisons (0.005 and 0.0005). While these p values do not have the same strength of evidence as that of a pre-specified primary efficacy endpoint, neither were they picked as unusual from data dredging the trial results. The p value of 0.005 is generated by the initial analysis I had envisioned based on my review of the pre-clinical data.

One limitation of TAAL is the quality of the data. TAAL was not pre-specified to examine cancer rates, although cancer events are routinely captured in most CV trials and were captured prospectively in TAAL. TAAL did not capture prospectively a complete history of all cancers. However, from a patient perspective, a cancer recurrence is as deadly as or usually more deadly than a new cancer—prasugrel looks as bad for new and worse solid cancers as it does for new solid cancers. So the data quality issue (the lack of cancer histories) that some reviewers have viewed as insurmountable does not make the TAAL cancer results uninterpretable. TAAL raises a serious safety concern. I don't think that safety concern can be put to rest by TAAL; another study is needed.

I am not impressed at all by the counterargument that the finding lacks biologic plausibility because we have never seen a similar pattern before. We have no large randomized trials of documented tumor promoters in humans. We should not assume that we know exactly what to expect based on animal studies. The evidence for a problem is far stronger in TAAL than it was at NDA submission times for the recent withdrawals from market, such as Vioxx and Zelnorm.

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Thomas Marciniak
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MEDICAL OFFICER