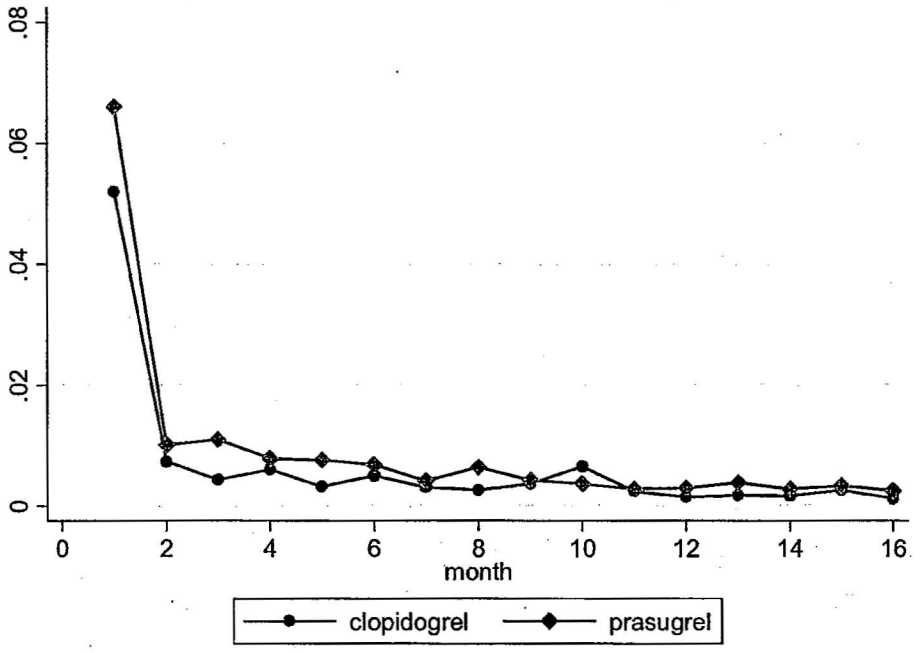
Figure 6: Bleeding Event Rates by Treatment and Month in TRITON



"The last statistics worth noting regarding cancer in TRITON 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. We adjudicated 24 cancer deaths to prasugrel and 15 to clopidogrel. There does appear to be an excess of cancer deaths with prasugrel."

"Because a good question is whether carcinogenicity could be a class effect, we also examined the data we have available for large outcome trials using clopidogrel. At this time we have done preliminary analyses for CREDO, CURE and CHARISMA data; we do not currently have data for the oldest study, CAPRIE. For reference we show the study features in Table 8."

Table 5: Clopidogrel Studies

Study	Population	Aspirin	Median age	n	Median months
CAPRIE	high CV risk	325 control	62.5*	19,185	23*
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

* mean

"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."

"We present tabulations of cancers in CURE in Table 9, CREDO in Table 10, and CHARISMA in Table 11."

Table 6: Numbers of Cancers by Site and Treatment in CURE

	clopidogrel	placebo
patients	6,259	6,303
bladder	1	3
breast	1	2
cervix	1	0
colorectal	16	8
esophagus	3	1
gall bladder	0	1
kidney	1	1
leukemia	2	2
liver	2	0
lung	12	8
lymphoma	1	4
melanoma	2	1
metastatic	0	2
myelopro	2	1
other	2	0
ovary	2	2
pancreas	1	1
prostate	4	7
unknown	1	5
uterus	1	0
total nonskin/ nonbrain	55	49
brain	1	2
skin	9	11

Table 7: Numbers of Cancers by Site and Treatment in CREDO

	clopidogrel	placebo
patients	1,054	1,064
bladder	2	3
breast	2	1
colorectal	3	3
esophagus	0	1
kidney	0	1
liver	1	0
lung	5	0
melanoma	1	0
other	1	0
prostate	2	2
stomach	3	0
uterus	0	1
total nonskin/ nonbrain	20	12
skin	8	6

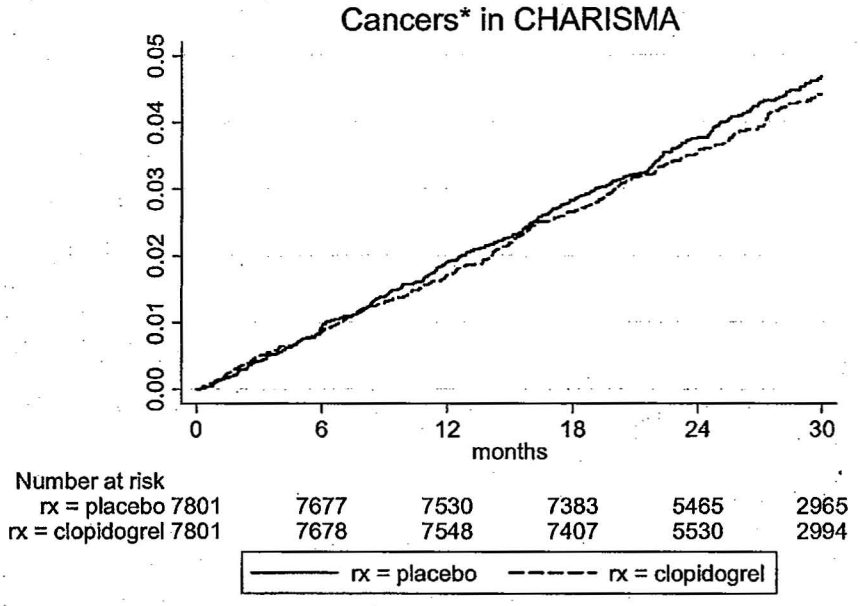
	clopidogrel	placebo
brain	1	2

Table 8: 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
gi	2	0
head & neck	16	22
kidney	11	13
leukemia	9	4
liver	5	7
lung	70	63
lymphoma	4	15
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 nonskin /nonbrain	310	330
brain	7	3

"Note that CURE and CREDO studies show a higher rate of lung cancers with clopidogrel than placebo ($p = 0.03$ for the 5:0 lung cancers in CREDO—commented upon in the study report without a conclusion) and CURE also shows a higher rate of colorectal cancer with clopidogrel. CHARISMA shows only a slight excess for lung cancers and differences in specific sites appear to be randomly distributed—for all sites combined clopidogrel shows a small deficit compared to placebo (as do cancer deaths: 77 to 67 favoring clopidogrel). The K-M incidence plot (Figure 6)confirms that the cancer rates for placebo and clopidogrel in CHARISMA are similar."

Figure 7: K-M Incidence Plot for Cancers in CHARISMA



*excluding non-melanoma skin but including all brain tumors; p = 0.6 by log rank

One final comment about CHARISMA: bleeding rates were high in the clopidogrel group as shown in Table 11.

Table 9: 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: We interpret all of these results as follows: The preclinical studies suggest that prasugrel is a tumor promoter in mice. The clinical results in TRITON are also suggestive of a promoter effect. While it is tempting to dismiss the clinical findings as due to ascertainment bias, the delay in the divergence of the incidence plots for four+ months, the continued convergence of most plots through 16 months, the lack of evidence for an ascertainment bias for solid tumors other than GU, and cancer deaths leaning in the wrong direction do not support the ascertainment bias hypothesis. The consistent deviations in all of the studies (except colorectal in the small CREDO study) are for lung and colorectal cancers; there is also some suggestion of activity in the mouse study for these sites. We need convincing demonstration of an

ascertainment bias or other non-promoter mechanism for lung, breast, and colorectal cancer to negate the conclusion that prasugrel is a tumor promoter in humans."

"While the findings with clopidogrel in CURE and CREDO are slightly suggestive of a similar effect with clopidogrel, CHARISMA, the study with the highest exposure, does not suggest that clopidogrel has any worrisome carcinogenic effect. The CHARISMA results also suggest that increased bleeding rates with a detection bias may not explain the differences in cancer rates in TRITON because there is no suggestion of a detection bias in CHARISMA despite the higher bleeding rates with clopidogrel. CAPRIE should be very helpful in confirming the lack of carcinogenicity for clopidogrel—what to do about prasugrel is a challenge."

DDOP responses to the questions (please also see the DDOP reviewer comments after the questions):

1. Do you agree that there is a statistically significant difference in the development of new malignancies in Study TAAL between the prasugrel and clopidogrel treatment groups?

DDOP: Agree that when the incidences of "all cancers" between the two Triton study arms are compared, a p value of < 0.05 is obtained. However we are not certain of the statistical or clinical significance of this finding. The study was not designed to compare the cancer incidences between the study arms, so the Type I error rate (α level) for this exploratory significance testing is essentially unknown. Clinical significance of the statistical findings obtained by combining of "different cancers" in the comparisons is hard to interpret given differing etiologies and natural histories of the diverse types of cancers.

2. Do you agree that cancers in women are driving this statistically significant difference?

DDOP: Please see the response to question 1 above.

3. Do you believe that prasugrel is a "promoter"?

DDOP: No, there are no data in the Triton trial to support a belief that prasugrel is a "promoter" in humans. No data from the Triton study are available to address this question. Given the absence of a well defined cancer screening at Triton study entry, short drug exposure to the study drugs (6 to 15 months), and no specified follow up to detect specific cancers, the cancers diagnosed on study are more likely to be incidental.

4. There were a number of patients who had a history of cancer and developed worsening cancer in Study TAAL. Please comment on whether or not you believe this worsening of cancer (or development of metastatic disease) was related to the study drug, underlying malignancy, or both.

DDOP: Cancers progress in the absence of definitive treatment. Given the absence of a well defined cancer screening at Triton study entry and short drug exposure to the study drugs (6 to 15 months) the cancers diagnosed on this study are more likely to be incidental. At the minimum, one would need to study the progress of known cancers when exposed to the study drugs and a placebo to address whether worsening of cancer was related to study drugs or was spontaneous. Such trials are not possible in humans for clinical, statistical, and ethical reasons.

5. Please advise us on recommendations we can make to the sponsor regarding additional analyses (or studies) to be performed to further evaluate the possible carcinogenicity of prasugrel.

DDOP: Consult with OSE may be useful for additional suggestions; DDOP suggestions follow:

For the available data:

1. Addressing the issue of ascertainment bias

The best use of the available data from Triton study may be to make or refute a case for ascertainment bias, but no analyses based on the available data assessing cancer incidence can be conclusive. In defining the ascertainment bias, the interest is in cancer discovery during work up for bleeding while on the study drugs. A table capturing the age, sex, date of cancer diagnosis, date of start of study treatment, presence or absence of bleeding may be helpful. In how many patients the cancer diagnosis was led to by the work up initiated by a bleeding episode will be of interest. For the colon cancers this has been done by the sponsor.

2. Epidemiologic analyses of observed cancer incidence

Epidemiologic comparison with the SEER data may be helpful; however, the results are of very limited value and likely to be inconclusive and possibly misleading as the study population in Triton is drawn from several different (thirty) countries. SEER data come from the US populations from selected cities/regions.

Obtaining further data on cancer incidence in patients on prasugrel

1. Suggestion for further safety studies to address the higher cancer incidence question

- A definitive study would require a screened population (cancer free) of adequate size randomly assigned to the study treatments and followed up for new cancers for an adequate length of time. Follow up will have to be long enough to discover the cancers that may appear long after the study drug exposure has stopped.

2. A registry to track the incidence of cancer on prasugrel may be useful

- This population will be more representative of the US population if the registry is established within the US; however, all steps to minimize missing data will be important.

Inclusion of Colon cancer findings in Prasugrel Label

As colon cancer incidence was statistically significant, an appropriately worded inclusion of colon cancer incidence findings in the prasugrel label may be appropriate, eg, a need for prompt workup of GI bleeding as it may indicate an underlying colon cancer.

Note that the study investigators have published the colon cancer findings.

"The adverse events reported included severe thrombocytopenia in 17 patients in the prasugrel group (0.3%) and 18 patients in the clopidogrel group (0.3%) (P = 0.86); neutropenia in 2 patients (<0.1%) and 10 patients (0.2%) (P = 0.02), respectively; and colonic neoplasms in 13 patients (0.2%) and 4 patients (0.1%) (P = 0.03). Known gastrointestinal bleeding preceded the diagnosis of colonic neoplasms in nine patients (seven in the prasugrel group and two in the clopidogrel group).

"In addition to the results of our key prespecified safety analyses, we noted a higher rate of adverse events related to colonic cancer in the prasugrel group than in the clopidogrel group. Though we cannot fully rule out either a possible causative effect or the play of chance, this imbalance may have resulted from the more potent antiplatelet effect of prasugrel bringing more events to medical attention, a phenomenon seen with other anticoagulant agents, including warfarin."

(Source: *N Engl J Med 2007;357:2001-15*).

DDOP Reviewer Comments:

Suitability of Triton to assess and compare cancer incidence:

This is the most important flaw in the study design if one is to study the cancer incidence in Triton; it was not designed to evaluate the effect of study drug on cancer incidence. Analyses of new cancer diagnoses are not reliable as Triton was not designed to study and compare the incidences of new cancers between the two treatment arms. Absence of cancers at entry by screening for cancers was not a requirement. No baseline evaluation of the study patients to detect cancers present at the time of enrollment was conducted. This is a serious limitation of all the findings regarding cancer incidence from Triton study. Findings are not conclusive.

Notably the cancers that are found to be at a higher rate are the common cancers in population at large. Patients should have had evaluations to rule out the common cancers present at the baseline if their incidences were to be evaluated, eg, bilateral mammograms for breast cancer, colonoscopy for colorectal cancers, and perhaps CXR or CT scan to rule out lung cancers.

Incidence of bleeding and possibility of ascertainment bias

Incidence of non CABG related bleeding is higher in prasugrel arm. Among patients treated with prasugrel, about 2.4% of the patients had at least one TIMI major hemorrhage that was not related to CABG, as compared with 1.8% treated with clopidogrel.

Triton is inadequate to address the question whether prasugrel is a tumor promoter

Whether prasugrel is a tumor promoter is impossible to decide based on Triton. In the absence of definitive cancer treatment, cancer is expected to progress. To assess a "promoter" effect one would need to expose patients with premalignant or malignant lesions to the study drug—this is an impossible study to do in humans for multiple reasons.

Combining incidences of all cancers (increase the study power)

Combining of all cancers for comparison between the two study arms may be misleading. Statistical and clinical significance of the finding of higher incidence of all cancers combined together is arguable. Combining of diverse cancers is not justifiable based on the known differences in biologies of different cancers and their clinical courses.

Possibility of further addressing the issue of ascertainment bias

The best use of the available data from Triton study may be to make or refute a case for ascertainment bias, but no analyses based on the available data assessing cancer incidence can be conclusive. Interest is in cancer discovery during work up for bleeding while on the study drugs. A table capturing the age, sex, date of cancer diagnosis, date of start of study treatment, presence or absence of bleeding may be helpful.

Possibility of epidemiological analyses of observed cancer incidence

Epidemiologic comparison with the SEER data may be helpful; however, the results are of limited value and likely to be inconclusive as the study population in Triton is drawn from several different countries. SEER data come from US populations from selected cities/regions.

Suggestion for further safety studies to address the higher cancer incidence question

- Consult with OSE might be useful.
- Definitive study would require a screened population (cancer free) of adequate size randomly assigned to the study treatments and followed up for adequate time.

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/s/

Bhupinder Mann
4/24/2008 02:28:28 PM
MEDICAL OFFICER
Label comments as discussed are on page 20 or 21

Patricia Cortazar
5/27/2008 12:19:57 PM
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