7.1.2.1.3 Intracranial Hemorrhage

In Study TAAL, there were 20 (0.29%) and 16 (0.24%) CEC-adjudicated intracranial hemorrhages (ICH) in the prasugrel and clopidogrel treatment groups, respectively.

However, in several of the sponsor's analyses, the number of intracranial hemorrhages reported is slightly different (19-prasugrel; 17-clopidogrel), given the fact that there was separate CEC adjudication of efficacy (stroke) and bleeding (ICH) endpoints. A summary of CEC-adjudicated intracranial hemorrhages occurring 'while at risk" is displayed in Table 25. "While at risk" included safety events occurring from the first dose of study drug up to the date of the close-out visit, within 7 days after the permanent study drug discontinuation, or 464 days from randomization, whichever was earlier. In both treatment groups, most of the intracranial hemorrhages occurred between 30 and 180 days, inclusive. Intracranial hemorrhages in the prasugrel treatment group were more severe and recovery from these events was lower than in the clopidogrel treatment group. Compared to clopidogrel, almost twice as many subjects treated with prasugrel died from intracranial hemorrhages.

Table 25. Summary of Intracranial Hemorrhages While at Risk (CEC Adjudicated) (All Treated All ACS Subjects) (TAAL)

	Prasugrel n/N (%)	Clopidogrel n/N (%)	Total n/N (%)
Number of Treated Subjects	**6741**	**6716**	**13457**
Total ICH Cases	**19/6741 (0.28)**	**17 (6716) (0.25)**	**36/13457 (0.27)**
Time to Bleeding Event			
≤ 3 days	1	1	2
> 3 days, ≤ 30 days	2	2	4
> 30 days, ≤ 180 days	9	9	18
> 180 days, ≤ 365 days	3	4	7
> 365 days, ≤ 464 days	4	1	5
Age			
≥ 75 years old	7/891 (0.79)	3/894 (0.34)	10/1785 (0.56)
< 75 years old	12/5850 (0.21)	14/5822 (0.24)	26/11672 (0.22)
Sex			
Female	5/1684 (0.30)	7/1798 (0.39)	12/3482 (0.34)
Male	14/5057 (0.28)	10/4918 (0.20)	24/9975 (0.24)
Body Weight			
< 50 kg	0/45 (0.00)	1/45 (2.22)	1/90 (1.11)
50 - < 70 kg	3/1133 (0.26)	6/1232 (0.49)	9/2365 (0.38)
70- < 90 kg	14/3378 (0.41)	9/3297 (0.27)	23/6675 (0.34)
≥ 90 kg	2/2125 (0.09)	1/2081 (0.05)	3/4206 (0.07)
History of Prior TIA or Stroke			
Yes	6/257 (2.33)	0/252 (0.00)	6/509 (1.18)
No	13/6484 (0.20)	17/6464 (0.26)	30/12948 (0.23)
Prior History of Hypertension			
Yes	14/4321 (0.32)	16/4324 (0.37)	30/8645 (0.35)
No	5/2420 (0.21)	1/2392 (0.04)	6/4812 (0.12)
Maximum Severity			
Mild	0	1/17 (5.88)	-
Moderate	2/19 (10.53)	5/17 (29.41)	-
Severe	17/19 (89.47)	11/17 (64.71)	-
Outcome			
Recovered	4/19 (21.05)	8/17 (47.06)	-
Recovering/Resolving	3/19 (15.79)	2/17 (11.76)	-
Not Recovered	1/19 (5.26)	0	-
Recovered with Sequelae	1/19 (5.26)	1/17 (5.88)	-
Died	9/19 (47.37)	5/17 (29.41)	-
Missing Data	1/19 (5.26)	1/17 (5.88)	-

ICH=intracranial hemorrhage; TIA=transient ischemic attack
Reproduced from Sponsor, TAAL Clinical Study Report, TAAL.12.15, page 601, and from Risk Management Plan, Table 1.9, page 23..

Over 2.0% of patients in the prasugrel treatment group who experienced intracranial hemorrhage had a prior history of TIA/CVA. In the prasugrel treatment group, three out of the nine subjects who died as a result of intracranial

hemorrhage had a history of atrial fibrillation and were not taking warfarin. All three subjects were > 75 years of age, and one subject had a history of prior TIA/CVA.

7.1.2.1.4 FDA Bleeding Analysis (TAAL)

In TAAL, we analyzed all bleeding events in treated subjects (n = 13,457), including 6741 subjects in the prasugrel treatment group and 6716 subjects in the clopidogrel treatment group. We determined the number and percentage of subjects in each treatment group who experienced particular bleeding events. Additionally, we analyzed the following variables and calculated the relative risk of bleeding on prasugrel compared to clopidogrel:

- Age
- Sex
- Ethnicity
- Weight
- Glomerular Filtration Rate
- History of a Prior TIA/CVA
- Stent Type (BMS vs. DES)
- Killip Class
- TIMI Risk Score
- TIMI Risk Index
- Maximum activated clotting time (ACT) during PCI
- Timing of Loading Dose
- Varying Aspirin Doses at Different time points in the study
- Use of unfractionated heparin, glycoprotein IIb/IIIa inhibitors, low molecular weight heparin, bivalirudin, or fondaparinux during PCI
- Use of multiple antithrombotic agents during PCI
- Glycoprotein IIb/IIIa inhibitor use up to 3 days
- Bivalirudin use to hospital discharge
- Warfarin and other coumarin use after randomization
- Argatroban use from symptom onset $\leq$ 3 days
- Proton pump inhibitors
- Hormone replacement therapy
- Statin use
- Sheath size
- Sheath site
- Use of closure device
- Type of closure device used

Pertinent findings are presented below.

7.1.2.1.4.1 Number and Percentage of Bleeding Events (TAAL)

The number and percentage of subjects developing particular types of bleeding events in TAAL is summarized by treatment group in Table 26 and Table 27. With the exception of pulmonary bleeding, a greater percentage of subjects in the prasugrel treatment group experienced bleeding events compared to clopidogrel.

Table 26. FDA Analysis: Number and Percentage of Subjects with Bleeding Events (TAAL)

All (N=13,457)	N	Any Bleed?	Moderate/Severe Bleed?	Severe Bleed?	Serious Bleed?
Prasugrel	6741	1926 (28.6%)	732 (10.9%)	196 (5.5%)	370 (5.5%)
Clopidogrel	6716	1412 (21.0%)	535 (8.0%)	144 (2.1%)	252 (3.8%)
Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.					

Table 27. Number and Percentage of Subjects with Bleeding by Organ System (TAAL)

All (n=13,457)	N	Gastrointestinal Bleed	Hematuria	Uterine/Vaginal/Male Reproductive Bleed	Intracranial Hemorrhage	Pulmonary Bleed	Retroperitoneal Bleed
Prasugrel	6741	261 (3.9%)	99 (1.5%)	29 (0.4%)	20 (0.3%)	34 (0.5%)	23 (0.3%)
Clopidogrel	6716	197 (2.9%)	85 (1.3%)	22 (0.3%)	16 (0.2%)	31 (0.5%)	14 (0.2%)
Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.							

7.1.2.1.4.2 Relative Risk of Bleeding on Prasugrel Compared to Clopidogrel

The relative risk of bleeding on prasugrel compared to clopidogrel is displayed in Table 28 and Table 29. Overall, there was a 36% increased risk of experiencing any bleed and a 46% increased risk of experiencing a serious bleed on prasugrel, compared to clopidogrel. In general, the risk of bleeding on prasugrel was higher in subjects ≥ 75 years of age, subjects with a prior history of a transient ischemic attack or cerebrovascular accident, and subjects who were not on a proton pump inhibitor.

Since the risk of bleeding on prasugrel was reduced in all organ systems on proton pump inhibitors, we are concerned that subjects may be receiving less drug product due to varying degrees of absorption from the salt to base conversion. At higher pH, prasugrel HCl has higher solubility and is absorbed more quickly than prasugrel base.

With respect to the timing of the loading dose, subjects on prasugrel had a greater risk of bleeding at all time points, compared to clopidogrel. While previous analyses have shown that if the prasugrel loading dose was given during PCI or within 30 minutes of the start of PCI, there was a reduction in the primary endpoint, the comparative bleeding risk on prasugrel did not seem to be higher when given during that time frame, except for severe bleeding events. In the setting of a retroperitoneal bleed when the loading dose was given prior to PCI, there was a two-fold increase in the risk of bleeding on prasugrel compared to clopidogrel.

Table 28. FDA Analysis: Relative Risk (95% CI) of Bleeding on Prasugrel Compared to Clopidogrel (TAAL)

	Any Bleed?	Moderate/Severe Bleed?	Severe Bleed?	Serious Bleed?
All Subjects	**1.36 (1.28, 1.44)**	**1.36 (1.23, 1.52)**	**1.36 (1.1, 1.68)**	**1.46 (1.25, 1.71)**
Age (years)				
< 65	1.35 (1.24, 1.46)	1.35 (1.16, 1.57)	1.3 (0.95, 1.79)	1.58 (1.24, 2.01)
65 - < 75	1.34 (1.19, 1.5)	1.31 (1.07, 1.59)	1.28 (0.86, 1.91)	1.51 (1.13, 2.02)
≥ 75	1.44 (1.27, 1.65)	1.48 (1.19, 1.84)	1.56 (1.04, 2.35)	1.27 (0.95, 1.7)
Prior TIA/CVA				
Yes	1.36 (1.28, 1.45)	1.35 (1.21, 1.51)	1.34 (1.08, 1.67)	1.46 (1.24, 1.71)
No	1.34 (1.02, 1.77)	1.7 (1, 2.91)	1.68 (0.67, 4.2)	1.51 (0.77, 2.97)
Proton Pump Inhibitors				
Yes	1.28 (1.19, 1.39)	1.19 (1.04, 1.36)	1.26 (0.97, 1.62)	1.36 (1.12, 1.63)
No	1.45 (1.33, 1.59)	1.68 (1.41, 2)	1.58 (1.08, 2.32)	1.71 (1.29, 2.27)
Timing of Loading Dose				
Pre-PCI	1.36 (1.2, 1.55)	1.38 (1.09, 1.76)	1.04 (0.68, 1.6)	1.64 (1.2, 2.25)
During PCI	1.36 (1.27, 1.46)	1.37 (1.22, 1.55)	1.49 (1.16, 1.91)	1.43 (1.19, 1.72)
Post-PCI	1.27 (0.82, 1.96)	1.00 (0.49, 2.02)	1.08 (0.23, 5.15)	1.44 (0.34, 6.18)
CI=confidence interval; CVA=cerebrovascular accident; TIA=transient ischemic attack Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.				

Table 29. Relative Risk (95% CI) of Bleeding on Prasugrel Compared to Clopidogrel (TAAL)

	Gastrointestinal Bleed	Hematuria	Uterine/Vaginal/ Male Reproductive Bleed	Intracranial Hemorrhage	Pulmonary Bleed	Retroperitoneal Bleed
All Subjects	**1.32 (1.1, 1.58)**	**1.16 (0.87, 1.55**	**1.31 (0.76, 2.28)**	**1.14 (0.56, 2.33)**	**1.09 (0.67, 1.78)**	**1.64 (0.84, 3.18)**
Age (years)						
< 65	1.33 (1.03, 1.74)	0.80 (0.49, 1.29)	1.28 (0.68, 2.40)	1.97 (0.49, 7.89)	0.85 (0.39, 1.83)	1.38 (0.61, 3.11)
65 - < 75	1.51 (1.04, 2.19)	1.25 (0.75, 2.09)	0.61 (0.15, 2.54)	0.58 (0.17, 1.98)	1.42 (0.63, 3.19)	2.54 (0.49, 13.06)
≥ 75	1.16 (0.83, 1.63)	1.66 (1.00, 2.76)	-	1.51 (0.43, 5.32)	1.15 (0.42, 3.15)	2.01 (0.37, 10.93)
Prior TIA/CVA						
Yes	0.91 (0.42, 1.95)	1.47 (0.25, 8.73)	-	-	0.98 (0.06, 15.59)	-
No	1.35 (1.12, 1.63)	1.15 (0.86, 1.54)	1.22 (0.7, 2.15)	0.78 (0.36, 1.72)	1.1 (0.67, 1.8)	1.57 (0.8, 3.06)
Proton Pump Inhibitors						
Yes	1.21 (0.98, 1.49)	1.17 (0.8, 1.71)	1.15 (0.53, 2.48)	1.11 (0.43, 2.87)	0.94 (0.53, 1.69)	1.69 (0.67, 4.29)
No	1.68 (1.16, 2.42)	1.14 (0.74, 1.77)	1.51 (0.68, 3.36)	1.17 (0.40, 3.49)	1.51 (0.62, 3.69)	1.58 (0.61, 4.08)
Timing of Loading Dose						
Pre-PCI	1.43 (0.94, 2.17)	1.49 (0.74, 2.99)	0.65 (0.18, 2.28)	-	0.87 (0.36, 2.14)	2.26 (0.59, 8.72)
During PCI	1.30 (1.06, 1.59)	1.14 (0.82, 1.57)	1.44 (0.76, 2.72)	0.86 (0.40, 1.85)	1.26 (0.69, 2.3)	1.36 (0.63, 2.97)
Post-PCI	1.62 (0.28, 9.37)	1.62 (0.28, 9.37)	-	-	-	-

CI=confidence interval; CVA=cerebrovascular accident; TIA=transient ischemic attack; - = not evaluated due to insufficient data
Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.

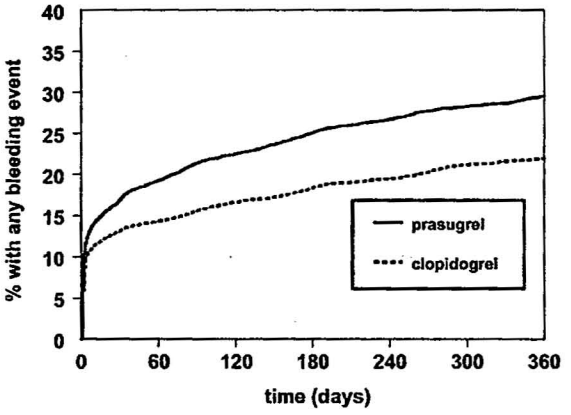
Kaplan-Meier Plots for Bleeding

Kaplan-Meier time-to-event analyses for bleeding events are presented in the figures below. These analyses were performed by Karen Hicks, M.D. and Ellis Unger, M.D..

Time to Any Bleed

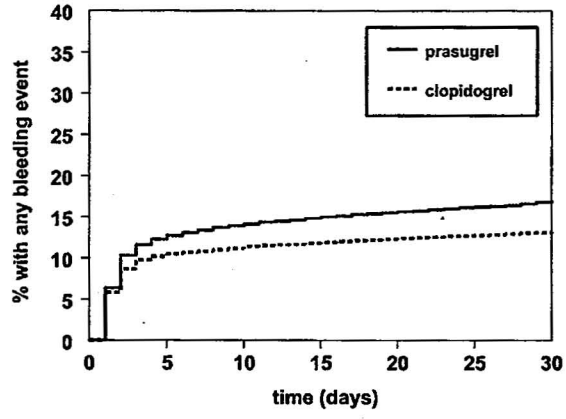
The percentage of subjects in each treatment group experiencing any bleeding event over time is displayed in Figure 12. Approximately 29% of subjects on prasugrel and 21% of subjects on clopidogrel experienced a bleeding event in TAAL. In both treatment groups, many of the bleeding events occurred within the first 3 to 5 days of the index procedure, as seen in Figure 13. However, the percentage of subjects experiencing any bleeding event on prasugrel or clopidogrel increased over time, with divergent curves at the 45 to 60 day time point.

Figure 12. FDA Analysis: Kaplan-Meier Plot for Any Bleeding Event (Day 0 to 360) (TAAL)



(p < 0.0001 by log rank)

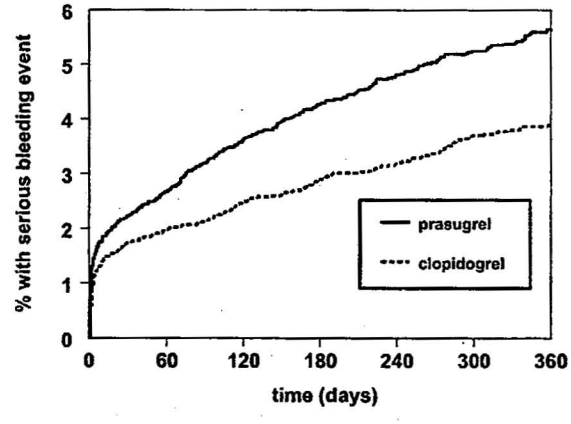
Figure 13. FDA Analysis: Kaplan-Meier Plot for Any Bleeding Event (Day 0 to 30) (TAAL)



Time to Serious Bleeding

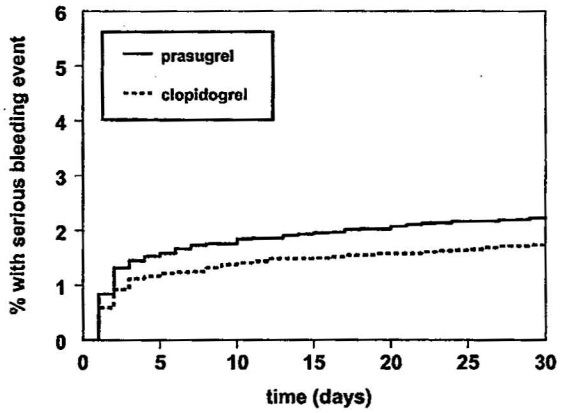
The percentage of subjects in each treatment group experiencing a serious bleeding event over time is displayed in Figure 14. Approximately 5.5% of subjects in the prasugrel treatment group experienced serious bleeding events, compared to 3.8% of subjects in the clopidogrel treatment group. Many of the serious bleeding events also occurred within the first 3 to 5 days of the index procedure. However, the percentage of subjects experiencing a serious bleeding event in both treatment groups increased over time, with divergent curves at the 45 to 60 day time point, as shown in Figure 15.

Figure 14. FDA Analysis: Kaplan-Meier Plot for Serious Bleeding Events (Day 0 to 360)



(p < 0.0001 by log rank)

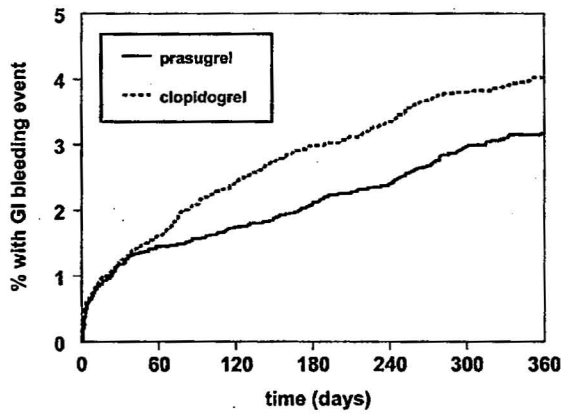
Figure 15. Kaplan-Meier Plot for Serious Bleeding Events (Day 0 to 30)



Time to Gastrointestinal Bleeding

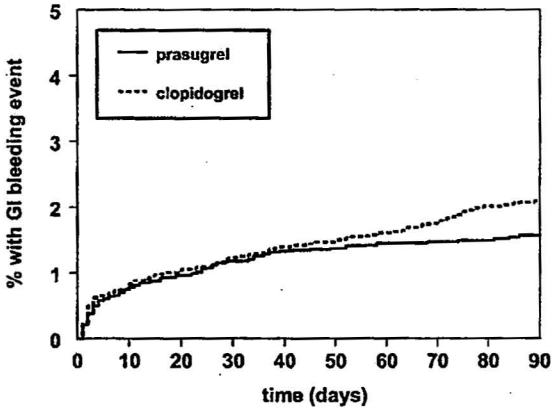
The percentage of subjects in each treatment group experiencing a gastrointestinal bleeding event over time is displayed in Figure 16. Approximately 3.9% of subjects in the prasugrel treatment group experienced gastrointestinal bleeding events, compared to 2.9% of subjects in the clopidogrel treatment group. The bleeding curves diverged at 40-60 days, as shown in Figure 17.

Figure 16. Kaplan-Meier Plot for Gastrointestinal Bleeding Events (Day 0 to 360)



(p = 0.0030 by log rank)

Figure 17. Kaplan-Meier Plot for Gastrointestinal Bleeding (Day 0 to 90)



7.1.2.2 Neoplasms

In TAAL, there was an increased rate of all neoplasms, particularly the solid tumors, in the prasugrel treatment group compared to clopidogrel (p = 0.006). In the prasugrel treatment group, there were 104 nonskin, nonbrain cancers, compared to 69 in the clopidogrel group. The neoplasms are summarized in Table 30.

Table 30. Number of New First Cancers by Site and Treatment (TAAL)

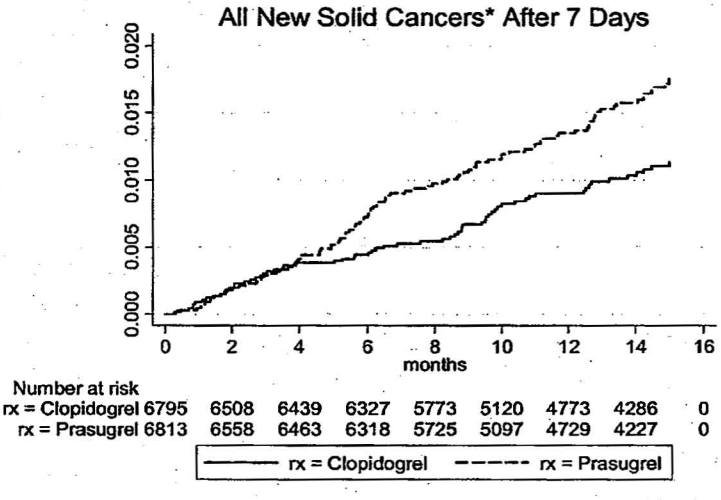
	clopidogrel	prasugrel
patients	6,696	6,682
bladder	8	7
breast	1	5
cervix	0	1
colorectal	8	19
esophagus	2	5
gall bladder	0	2
gastrointestinal	1	0
head & neck	2	2
kidney	4	4
leukemia	2	1
liver	1	0
lung	13	21
lymphoma	2	2
melanoma	3	3
mesothelioma	0	1
myelodysplastic	1	2
ovary	0	1
pancreas	3	2
prostate	8	10
sarcoma	0	2
stomach	7	6

	clopidogrel	prasugrel
thyroid	0	1
unknown/other	2	7
uterus	1	0
all nonskin/ nonbrain	69	104
brain	0	2 (pituitary)
skin	14	10
squamous	4	5

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Since tumor findings were sometimes noted at screening but not further evaluated until after enrollment, initial FDA analyses excluded cancers diagnosed during Days 0 to 7. The Kaplan-Meier incidence plot for all new solid cancers demonstrates a divergence in incidence between the prasugrel and clopidogrel treatment groups at 4 months, with continuing divergence through the duration of the study, as shown in Figure 18.

Figure 18. Kaplan-Meier (K-M) Incidence Plot for All New Solid Cancers Diagnosed After 7 Days in TRITON

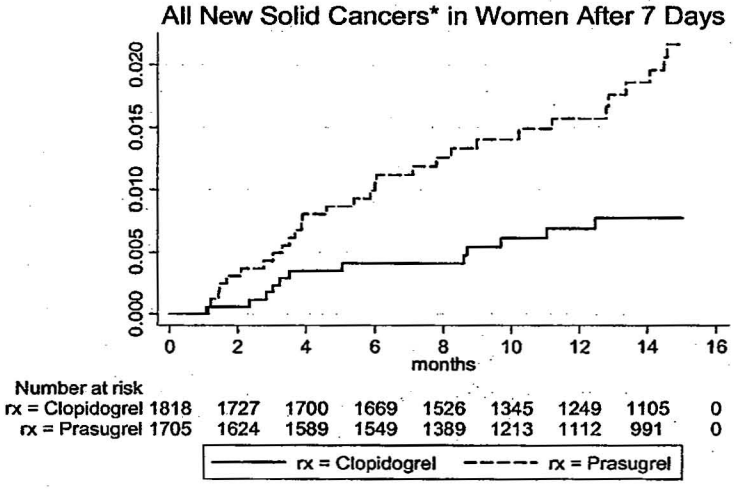


***excluding non-melanoma skin cancers and brain tumors; p = 0.006 by log rank**

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

If the neoplasms are analyzed by sex, there are 18 excess neoplasms in women and 17 excess neoplasms in men in the prasugrel treatment group, compared to clopidogrel. The incidence of new solid cancers in women after 7 days is significant between treatment groups (p = 0.0024) while the incidence in men is not (p = 0.16). The Kaplan-Meier Incidence plots for these analyses are displayed in Figure 19 and Figure 20.

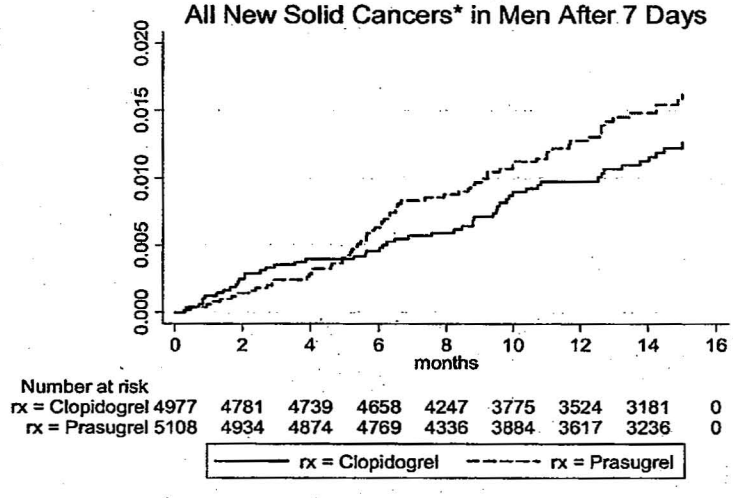
Figure 19. Kaplan-Meier Incidence Plot for All New Solid Cancers in Women After 7 Days



***excluding non-melanoma skin cancers and brain tumors; p = 0.0024 by log rank**

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Figure 20. Kaplan-Meier Incidence Plot for All New Solid Cancers in Men After 7 Days

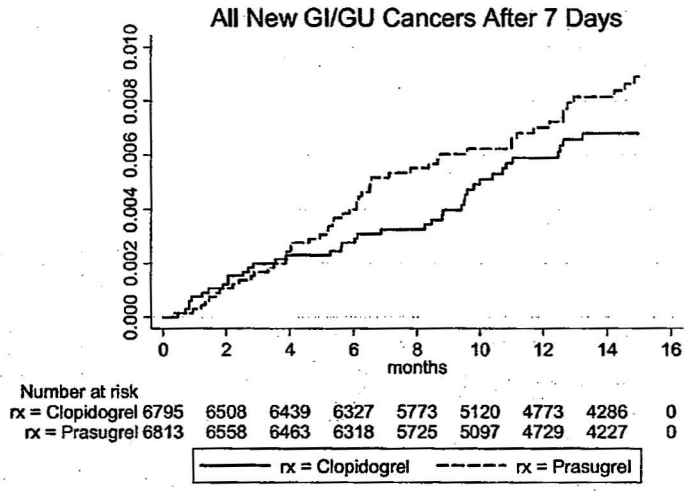


***excluding non-melanoma skin cancers and brain tumors; p = 0.16 by log rank**

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

The incidence of new gastrointestinal/genitourinary cancers diagnosed after 7 days was not significantly different between treatment groups (p = 0.2 by log-rank), as seen in Figure 21.

Figure 21. Kaplan-Meier Incidence Plot for New Gastrointestinal/Genitourinary Cancers Diagnosed After 7 Days in TRITON

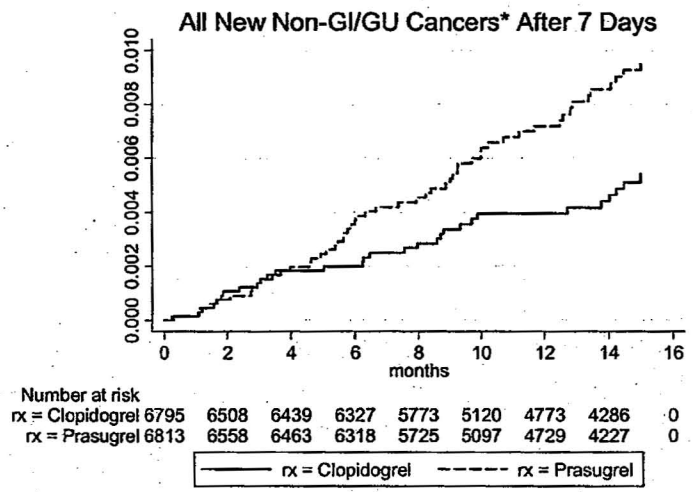


***excluding non-melanoma skin cancers and brain tumors; p = 0.2 by log rank**

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Examined separately, new gastrointestinal or genitourinary cancers were also not significantly different between treatment groups. However, new non-gastrointestinal or non-genitourinary cancers were significantly different between the prasugrel and clopidogrel treatment groups (p = 0.01), as displayed in Figure 22.

Figure 22. Kaplan-Meier Incidence Plot for New Non-Gastrointestinal/Genitourinary Cancers Diagnosed After 7 Days in TRITON



*** excluding non-melanoma skin cancers and brain tumors; p = 0.01 by log rank**

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)