Table 18: 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.

Prasugrel Efficacy Robustness

Because I have been asked to recommend approvability of prasugrel and labeling for it, I also performed some independent analyses of prasugrel efficacy in TAAL. I was interested in understanding the robustness of the prasugrel effect for comparison to the risk of cancer promotion. The sponsor's analyses of the TAAL use Clinical Endpoint Committee (CEC) adjudications of site-reported and lab value-triggered events. As a measure of robustness I analyzed the TAAL results using site-reported events only.

CEC Adjudication

The CEC adjudicated all important endpoint events, including MIs, strokes, and CV deaths as well as stent thromboses, and bleeding events for TAAL. What the study report and reviews do not state prominently is that there were two distinct paths for an event to be referred to the CEC: (1) by the site; and (2) "triggered" by a review of adverse events or lab values. (In addition, the CEC could find an event in a CRF or other documentation submitted for a different type of event, but such CEC-detected events were rare.) For MIs the majority of triggered events were peri-procedural MIs (PPMIs). There were far more potential PPMI events adjudicated by the CEC (2,583) than investigator reported MI events (483). However, because the CEC adjudicated the minority of potential PPMIs as MIs, the number of adjudicated MIs submitted in some fashion by the sites (705—in addition to MIs the sites also submitted other potential cardiac ischemic events) exceeded the number of adjudicated MIs based on PPMI triggers (512, with 11 additional MIs being otherwise triggered or CEC determined.)

The CEC adjudicated higher percentages of clopidogrel events as MIs than prasugrel events as shown in Table 19.

Table 19: CEC MI Adjudications by Type of Referring Event

	clopidogrel		prasugrel	
referring event	n	% MI	n	% MI
site MI event	303	80%	180	76%
site other ischemic event	984	19%	903	15%
triggered PPMI*	1022	21%	1049	19%

*PPMI = peri-procedural myocardial infarction

Note also that site referred MI events were substantially higher in the clopidogrel group than in the prasugrel while triggered potential PPMIs were equal between the two groups. However, there are problems with the determination of MI adverse events as I describe later.

Adjudication in a clinical study always raises at least three sets of issues: (1) whether the adjudication rules were pre-specified and appropriate; (2) whether referral for adjudication was comparable; and (3) whether the adjudication was performed fairly or, at least, how adjudication affects the results. Regarding the first set of issues, the criteria for the endpoint definitions, including the definition of an MI, were provided in the original protocol. One MI criterion was changed during the study as discussed in the primary clinical review: The original definition of peri-procedural myocardial infarction required an elevation of creatine kinase-myocardial band (CK-MB) to > 3x upper limit of normal (ULN) on a minimum of two samples within 48 hours of PCI. The modified definition, specified in Protocol Amendment (a) dated January 10, 2006, maintained the original definition but extended periprocedural myocardial infarctions to a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI. While this change does not appear to be problematic, there is an inconsistency in the PPMI definition that is: While the protocol and study report state the post-PCI and CABG CK-MB criteria without qualifications, the CEC Charter adds as a footnote that they "Cannot be determined within 12 hours of onset of qualifying STEMI." How PPMIs are adjudicated is critical because on day 0 there were 36 more PPMIs adjudicated for clopidogrel than for prasugrel. The first two PPMIs I checked (010003 10565 and 10966) had CEC Adjudication: Cardiac Ischemic Events forms with the type of event sections filled out but the Section A: Adjudication of Myocardial Infarction section not filled out and no signatures by CEC reviewers. How the PPMI cases were adjudicated is not well documented in the materials submitted to the NDA.

Regarding referral for adjudication, the CEC Charter includes an appendix describing the algorithms for Triggers for Identifying Events Not Reported by the Sites. The charter also describes the screening for triggered events being performed by the Contract Research Organization (CRO) but otherwise how or when the algorithms were developed and how they were implemented is not detailed. The referral of site-determined events is complicated by another problem: Sites were to assign an "AEID" (e.g., E01, E02, etc.) to each active medical problem at baseline and to each adverse event. Despite the AEIDs being required on many different forms filled out at many different times, the sites were not supposed to use the same AEID for different events or problems. Not surprisingly, sites made mistakes. In the original NDA submission for the adverse event data sets, if the sites erroneously re-used an AEID, the entries for the later event replaced those for the earlier ones. For cancer events we later obtained a file with both the original and final event data for every AEID and based our cancer analyses

on the more complete records of events. How this AEID problem affected referrals for adjudication I do not know, but I performed the following analyses to attempt to elucidate the impact.

In this first data set provided by the sponsor with initial and final values (AETERMCH), I counted 201 MI events for which the final value was not an MI. I counted 724 final MI events so that about 21% (201/925) of the MI events may have been lost. However, the potential loss does not appear to be biased because a similar percentage of the potential loss cases were clopidogrel (54%) as of the final value cases (56%). This first data set did not provide other details of the cases such as event dates so that further analysis of it is not helpful.

The sponsor submitted later more complete data sets of initial and final values (OEVENTSA and OVENTSB split because of size—I combined them into one data set OEVENTS). OEVENTS is the most complete description of adverse events for TAAL submitted by the sponsor. I classified MI and stroke events in OEVENTS by both the originally reported and final event terms. As a check of the completeness of the referral for adjudication of potential events, I cross-checked the MI events from OVENTS with the adjudicated events in the CEC adjudication dataset and with the investigator-reported events in CIE1. I found 62 MI events from OEVENTS that did not have records in CEC. Of these 62 events 61% were in clopidogrel patients, 85% had a flag set (CRF field) that they had been submitted for adjudication, and 25% of the prasugrel cases and 12.5% of the clopidogrel cases were not classified as having an MI based on another event. Hence the absolute number of cases that may have missed adjudication is small (10 cases for MIs by this analysis).

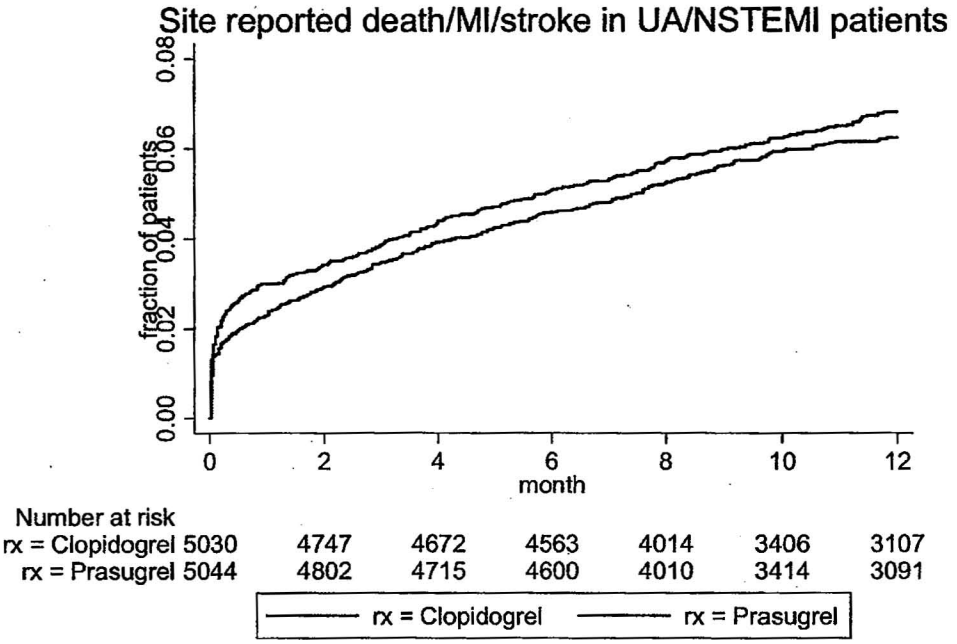
I also analyzed OEVENTS for an endpoint identical to the primary endpoint but not utilizing the CEC adjudications. I did the OEVENTS analyses as sensitivity analyses to determine the robustness of the results and to compare the site-reported results with the adjudicated results. The endpoint I tested was the composite of all-cause mortality, site-reported MIs, and site-reported strokes. I present the results below.

Site-Reported Endpoint Results

For the following analyses I accepted the site's description of the event as reported in the verbatim term, i.e., AEMODIFY in the SAS data sets. Sites reported many events as MIs and I counted them as such; however, for some cardiac events the sites described the events as "new Q wave", "acute coronary syndrome", "cardiac ischemia", or "LAD thrombosis". The CEC adjudicated the latter events and classified some of them as MIs; for the following analyses I counted the latter reports as not MIs (although note that vessel thrombosis reports were sometimes accompanied by a clinical event of MI.)

Based on site reports the endpoint most similar to the pre-specified primary endpoint (except avoiding adjudication—the composite of all cause mortality, site-reported MIs, and site-reported strokes) for the pre-specified primary analysis (time-to-event tested by the Gehan-Wilcoxon test for the unstable angina/non-ST elevation MI (UA/NSTEMI) subgroup (about 74% of the study population) shows early improvement but not a statistically significant benefit with prasugrel. I show the Kaplan-Meier (K-M) failure plot in Figure 15.

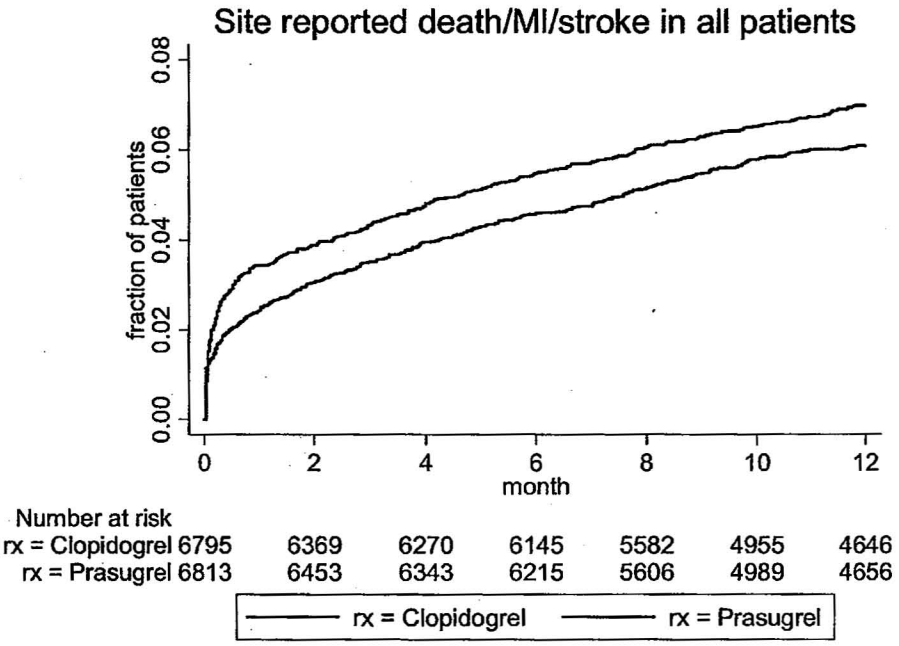
Figure 15: Site-reported Death/MI/Stroke in TAAL UA/NSTEMI Patients



p = 0.24 by Gehan test, 0.35 by log rank test

While the benefit with prasugrel is not statistically significant in this "noisy", site-reported and unadjudicated sensitivity analysis, there does appear to be a lower rate for early events. While the sponsor pre-specified the UA/NSTEMI subgroup as the primary analysis, the early lower rate of events is better shown in the whole study population in Figure 16.

Figure 16: Site-Reported Death/MI/Stroke in All TAAL Patientws

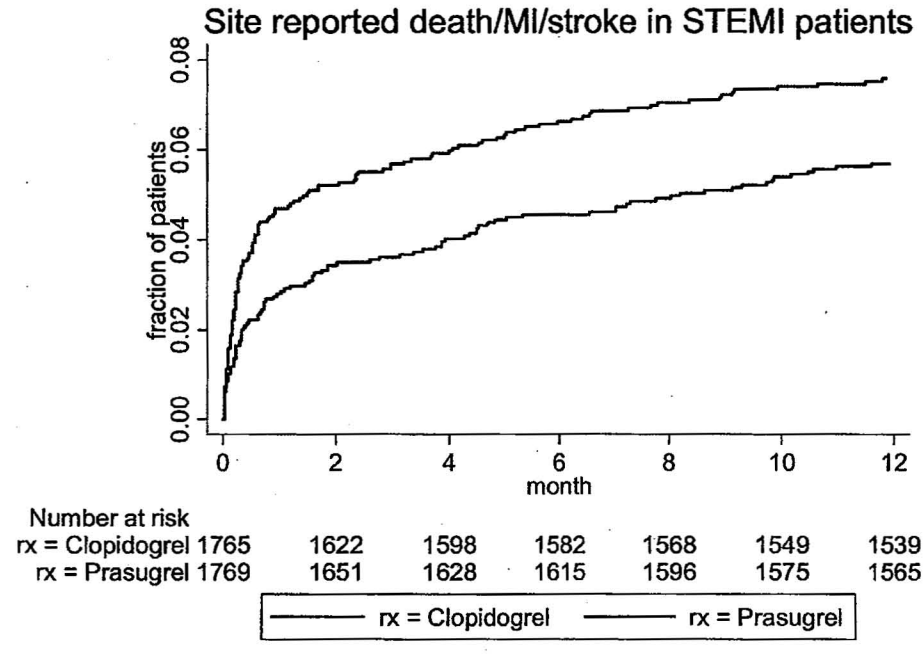


p = 0.12/0.04 (stratified/unstratified) by Gehan test, 0.08/0.07 by log rank test

The results for the primary site-reported endpoint are not statistically significant by the Gehan test stratified by ACS type, i.e., UA/NSTEMI vs. STEMI, or by the log rank test stratified or non-stratified. They are by the unstratified Gehan test. The Gehan test is more sensitive to the early part of the survival or failure curve compared to the log rank test. That event rates are highest immediately after an ACS event may be the reason the sponsor pre-specified using the Gehan rather than the log rank test. This pre-specification was accepted by the Division when the statistical analysis plan was submitted.

The prasugrel benefit appears greater for the STEMI subgroup as shown in Figure 17.

Figure 17: Site-Reported Death/MI/Stroke in TAAL STEMI Patients



p = 0.07 by Gehan test, 0.06 by log rank test

Note the much wider separation of the curves, still mainly early, in the STEMI subgroup. While the sponsor likely picked the UA/NSTEMI group as the group more likely to benefit based on the clopidogrel studies, prasugrel appears to show more benefit in the STEMI population.

The distribution of first site-reported event types is different from that for the CEC-adjudicated events. I show the site-reported first event types in Table 20.

Table 20: Site-Reported First Event Types

	UA/NSTEMI			STEMI			all		
	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ
MI	235	175	60	62	48	14	297	223	74
stroke	43	43	0	24	22	2	67	65	2
death	83	113	-30	58	49	9	141	162	-21

While prasugrel's benefit in all patients is due to a reduction in MIs, first events of all-cause deaths go in opposite directions in the two subgroups. Whether this latter dichotomy is a real difference or a subgroup variation due to chance is difficult to judge, but the dichotomy suggests that mortality differences should not be ignored.

The CEC-adjudicated events were the pre-specified primary endpoint and, if the adjudication really works, should be more discriminatory regarding risks. The latter can be evaluated

regarding risk of death, and I show the death rates for CEC-adjudicated and site reported MIs in Table 21.

Table 21: CEC-Adjudicated vs. Site-Reported MIs and Death Rates

		CEC-adjudicated			site-reported	
		no MI	PPMI only	MI event	no MI	MI event
clopidogrel	n	6,155	265	375	6,500	298
	% died	2.4%	4.5%	13.3%	2.4%	18.8%
prasugrel	n	6,327	231	255	6,588	226
	% died	2.8%	2.6%	11.4%	2.7%	14.2%

The site-reported MIs appear to be better predictors of death than the CEC-adjudicated MIs. The patients with only PPMIs in the prasugrel group actually had a rate of death comparable to those without MIs. While one might attribute these results to a benefit of prasugrel, the death rate for prasugrel patients without adjudicated MIs is not confirmatory of a prasugrel benefit.

Besides the overall assessment of benefit, the other question of critical importance for prasugrel use is the time course of the benefit. This question is critical because of the potential for tumor promotion, which should be related to duration of treatment. I show the cumulative difference in site-reported death/MI/stroke events per 100 patients in Figure 18. For comparison I show in Figure 19 the corresponding CEC-adjudicated results and in Figure 20 the results for the major adverse effect of bleeding.

Figure 18: Cumulative Site-Reported Death/MI/Stroke Difference in All TAAL Patients

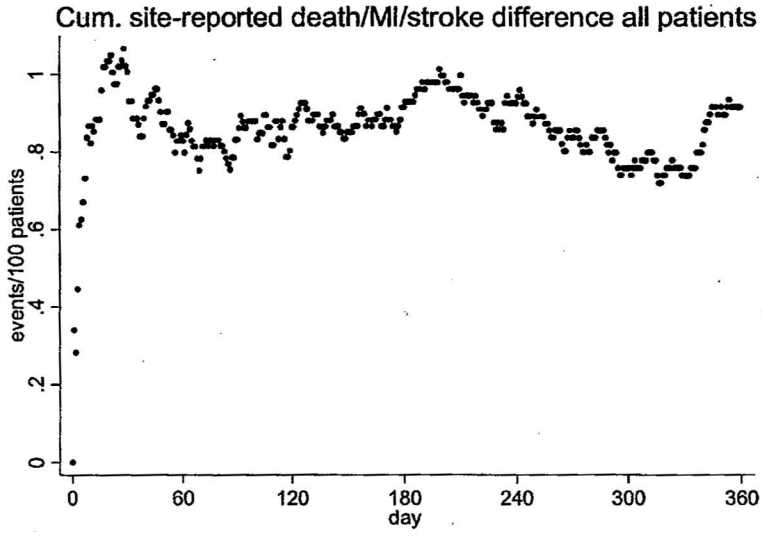


Figure 19: Cumulative CEC-Adjudicated CV Death/MI/Stroke Difference in All TAAL Patients

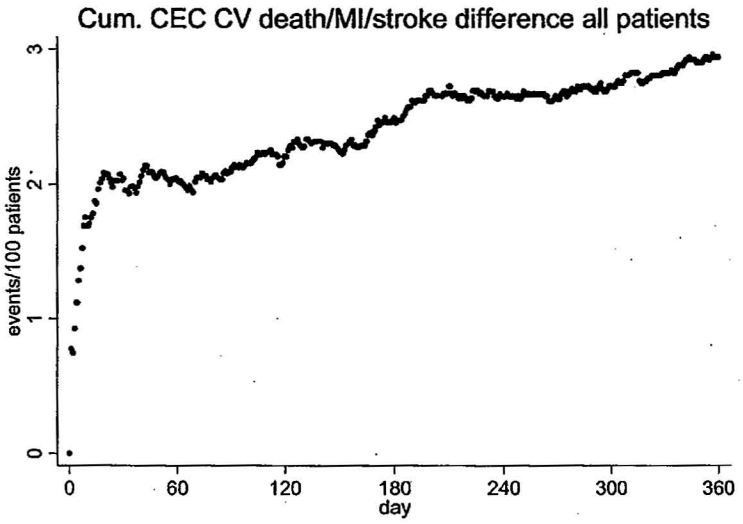
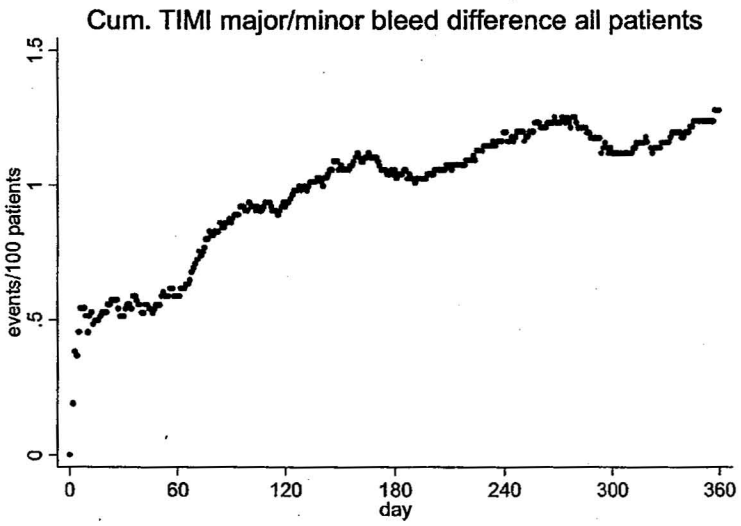


Figure 20: Cumulative TIMI Major/Minor Bleed Difference in All TAAL Patients

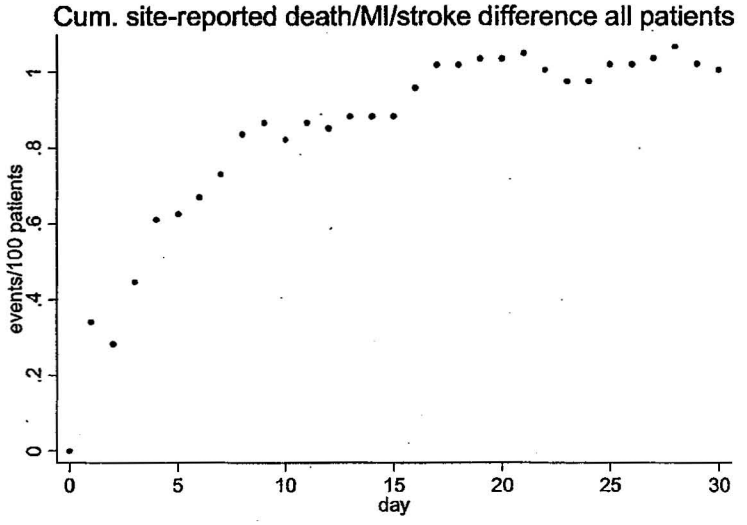


NOTE: The difference is reversed from the efficacy graphs:
There were more bleeds with prasugrel than with clopidogrel.
TIMI major/minor bleeding = hemoglobin drop of ≥ 3 gm/dL.

For site-reported events the benefit all appears to be early, i.e., within less than 30 days. Hence I show event differences through 30 days in Figure 21. The benefit appears to be close to maximal

at 3 weeks. Note also that the net efficacy benefit in site-reported events, about 1 event/100 patients, is matched by the net detriment in bleeding events between 2 and 4 months.

Figure 21: Cumulative Site-Reported Death/MI/Stroke Difference in All TAAL Patients



TAAL included two related but possibly distinct study populations: patients with UA/NSTEMI and those with STEMI. In fact, the sponsor pre-specified the primary efficacy analysis to be done in the UA/NSTEMI subgroup alone. Hence I show the site-reported composite endpoint results of UA/NSTEMI patients in Figure 22 and for STEMI patients in Figure 23. For all patients the MI benefit occurs early as shown in Figure 25.

Figure 22: Cumulative Site-Reported Death/MI/Stroke Difference in TAAL UA/NSTEMI Patients

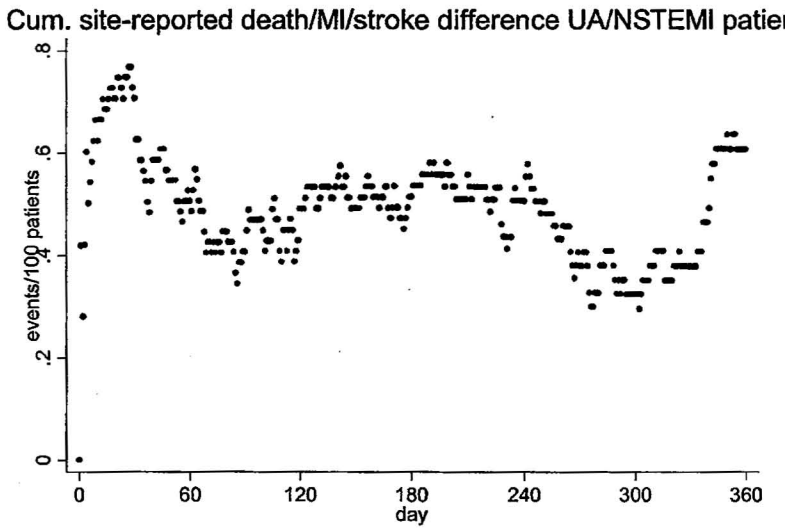
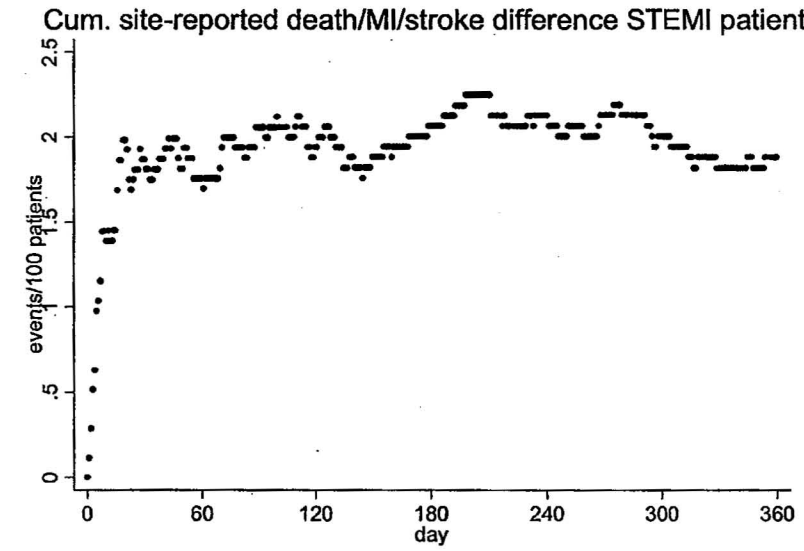


Figure 23: Cumulative Site-Reported Death/MI/Stroke Difference in TAAL STEMI Patients



For UA/NSTEMI patients there appears to be an early benefit that converts to a slight detriment as time progresses; for STEMI patients there appears to be a larger early benefit that improves

little with passing time. The late detriment for UA/NSTEMI patients occurs despite a continuing slight benefit for fewer MIs as shown in Figure 24.

Figure 24: Cumulative Site-Reported MI Difference in TAAL UA/NSTEMI Patients

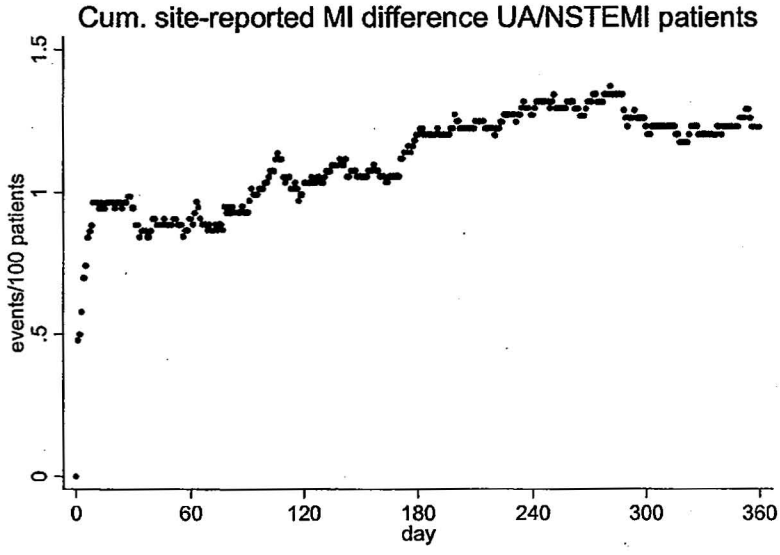


Figure 25: Cumulative Site-Reported MI Difference in All TAAL Patients