CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 22-433 (0065)
Drug Name:	Brilinta (ticagrelor)
Indication(s):	Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)
Applicant:	Astra Zeneca
Date(s):	Date of Document: January 20, 2011
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Review Priority:	Standard
Biometrics Division:	Division of Biometrics I (HFD-710)
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Keywords:

Aspirin, treatment by ASA interaction, treatment by region interaction, regional heterogeneity

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1. EXECUTIVE SUMMARY

This review focused on the relationship between concurrent use of aspirin during the PLATO trial and the regional treatment effect of ticagrelor compared to clopidogrel.

In this resubmission, the sponsor appeared to provide sufficient details on algorithm, specific raw datasets and corresponding program that were used to derive the daily ASA dose as requested and dataset was reproducible, which is the base for all the calculations later on.

A total of 13 different ASA definitions and 6 imputations were proposed and analyses were performed in a number of Cox proportional hazards models under these scenarios. Almost all ASA definitions under worst case scenario failed to suggest a significant treatment-ASA interaction. ASA doses calculated based on the first 30 days of ASA did not show much of treatment-ASA interaction when only looking at the first 30-day primary events. There appeared some degrees of consistency as shown using certain definitions and imputations (A1-A7, A11, and A12, see **Table 2** and Table 4).

There appeared a consistently adverse trend for ticagrelor with high dose of ASA in US, while there did not in OUS.

An interesting finding is that the treatment effect of ticagrelor was not so adverse compared to clopidogrel in US during the first 30 days (HR=1.06 in US). The divergence between US and OUS became more obvious in the later events (HR=1.53 in US and HR=0.77 in OUS).

The reviewer examined the potential treatment-ASA interaction in TRITON study and did not find such an interaction between treatment effect and ASA.

In summary, imputation methods and whether to include the first day loading dose seem to have the most impact on suggesting whether there is a significant treatment-ASA interaction. Various ASA definitions appear to demonstrate some degrees of consistency in analyses. These analyses are still limited by the fact that there were only a small number of high ASA dose subjects in OUS. It remains a concern whether ASA is truly the only factor that might affect the ticagrelor effect, as there appeared no such an interaction in TRITON study.

2. INTRODUCTION

2.1 Overview

The application consists of a single phase III trial, PLATO. It is a randomized, double-blind, double-dummy, parallel group, international, multicentre trial which compared the efficacy and safety of ticagrelor 90 mg bid with clopidogrel 75 mg od for the prevention of CV death, MI, and stroke in patients with non-ST or ST elevation ACS. The original application was submitted on

November 13, 2009. One major issue in the application was the regional difference in the observed treatment effect between North America and the rest of the world (later referred as US versus OUS). Several possible explanations were proposed by the sponsor, including play of chance and concurrent use of aspirin (ASA). Potentially there may also be other covariate X that may contribute to the regional treatment difference; however, neither the reviewer nor the sponsor was able to identify any. The issue was further discussed in the Advisory Committee meeting on August 28, 2010. Please refer to the meeting transcript for detailed discussion at the meeting. The division subsequently issued a Complete Response Letter (CRL) on December 16, 2010 requesting additional analyses to examine the aspirin hypothesis.

This resubmission is the response to the FDA CRL on December 16, 2010. In the resubmission, the sponsor performed extensive analyses to examine the relationship between concurrent use of aspirin during the PLATO trial and the regional treatment effect of ticagrelor compared to clopidogrel on the primary endpoint as well as its three components.

2.2 Data Sources

The sponsor's electronic data is stored under the directory
\\Cdsesub1\evsprod\NDA022433\0065\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets

The reviewer also looked at aspirin information in TRITON study (prasugrel). The datasets are stored under directories
\\Cdsesub1\evsprod\NDA022307\0007\m5\datasets\h7t-mc-taal\listings (specifically, the aspirin information was taken from dataset ASPTHRPY.XPT) and
\\Cdsesub1\evsprod\NDA022307\0002\m5\datasets\h7t-mc-taal\analysis

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In the CRL, the division requested the sponsor to provide detailed algorithm, specific raw datasets and corresponding computer program that were used to derive the daily ASA dose for each subject. The sponsor did provide sufficient details on creation of the daily ASA dose datasets and imputation for missing records.

Specifically, antiplatelet medication dataset MED2 was used to derive the daily ASA dose datasets. The sponsor provided sufficient details on the algorithm and derivation of the daily ASA dataset from the original data source (MED2 taken from case report form). Six different imputation methods were also used when subjects had an incomplete or missing ASA record. The reviewer was able to reproduce the dataset used in the later analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Please refer to the statistical review filed on 6/29/2010 in DARRTS on the original NDA application.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Please refer to the statistical review filed on 6/29/2010 in DARRTS on the original NDA application.

3.2.3 Statistical Methodologies

Due to the various definitions of ASA doses used in the analyses, the sponsor created acronyms for each definition. The reviewer will use the same acronyms for consistency.

A1 = mean daily ASA doses taken in **the last 5 days** prior to the primary event/censoring date
A2 = mean daily ASA doses taken in **the last 10 days** prior to the primary event/censoring date
A3 = mean daily ASA doses taken in **the last 30 days** prior to the primary event/censoring date
A4 = median daily ASA doses taken in **the last 5 days** prior to the primary event/censoring date
A5 = median daily ASA doses taken in **the last 10 days** prior to the primary event/censoring date
A6 = median daily ASA doses taken in **the last 30 days** prior to the primary event/censoring date
A7 = the **last ASA dose taken within 30 days prior** to the primary event/censoring date

For primary events that occurred within 30 days of randomization:
A8 = mean ASA dose **from day 1 to the date of event/censoring or day 30,** whichever is sooner
A9 = median ASA dose **from day 1 to the date of event/censoring or day 30**, whichever is sooner
A10 = maximum ASA dose **from day 1 to the date of event/censoring or day 30**, whichever is sooner

For patients with a primary event/censoring that occurred after 30 days from randomization:
A11 = median daily ASA dose based on **day 31 to date event/**censoring
A12 = median daily ASA dose based on **day 2 to date event/**censoring
A13 = last daily ASA dose prior to primary event/censoring

The sponsor also used several imputation methods outlined in Table 1. There were 299 (1.6%) patients had no ASA records at all, ie, no day 1 loading or ASA maintenance dose records.

Table 1 Imputation Methods for Handling Subjects with Missing ASA Records

		For patients with ASA records but with at least 1 ASA daily dose not recorded	
		Impute zero	Impute as previous non-missing record
For patients with no ASA dose records	Impute country median	M1	M3
	Impute zero	M2	M4
	Impute as FDA 'worst case'	M5	M6

[Source: Table 6 in sponsor's response to FDA CRL]

Among these imputation methods, the FDA worst case imputation was suggested by the Division, specifically the method -
• impute a low dose (81 mg) of ASA for anyone who had an event while missing ASA data on ticagrelor
• impute a high dose (325 mg) of ASA for anyone who did not have an event while missing ASA data on ticagrelor
• impute a high dose of ASA for anyone who had an event while missing ASA data on clopidogrel
• impute a low dose of ASA for anyone who did not have an event while missing ASA data on clopidogrel

3.2.4 Results and Conclusions

3.2.4.1 PLATO Trial

As there were various ways to define ASA doses for analyses, with six different imputations to missing ASA records, the reviewer first examined the overall consistency of the results of the analyses based on these definitions and imputations. Table 2 summarizes the various ASA definitions that show significant treatment-ASA interaction. A significant treatment-ASA interaction is defined as the p-value of treatment-ASA interaction < 0.05 in the Cox proportional hazards model with terms of ASA, treatment, region, ASA-treatment interaction and region-treatment interaction (T+R+A+TA+TR). The cells highlighted in green are the corresponding ASA definitions and imputations, based on which a significant treatment-ASA interaction is suggested.

Table 2 Different ASA definitions with different imputation methods that suggest significant treatment-ASA interaction

	M1	M2	M3	M4	M5	M6
A1						
A2						
A3						
A4						
A5						
A6						
A7						
A8						
A9						
A10						
A11						
A12						
A13						

Almost all ASA definitions with worst case imputations (M5 and M6) failed to show a significant treatment-ASA interaction as displayed in Table 2.

The analyses (A8, A9, A10) looking at the primary events that occurred within 30 days of randomization did not suggest much of treatment-ASA interaction.

OUS subjects did display a trend of reduced treatment effect for later events occurred after 30 days with ticagrelor in the high ASA dose group by definition A13 (last ASA dose prior to primary event / censoring), however, ticagrelor remained nominally better than clopidogrel in the middle and high ASA groups. This is probably why A13 does not show any significant treatment-ASA interaction.

Forest plots are also used to compare different definitions of ASA and imputations. For example, Figure 1 and Figure 2 show the forest plot by mean and median ASA dose (A2 and A5) taken in the last 10 days prior to primary event or censoring, respectively. Overall, the subjects in US displayed a rather clear pattern suggesting a better effect with ticagrelor than with clopidogrel at a lower ASA dose by both definitions under all imputation methods (including worst case imputation). This is shown in Table 3, in which cells highlighted in blue are the ASA definition with specific imputation that shows reverse treatment effect on ticagrelor (HR>1). In contrast, due to the small number of high dose ASA subjects in OUS, the treatment-ASA relationship does not appear as stable as in US. Depending on the imputation methods used, the OUS subjects may or may not show the interaction between treatment effect and the ASA dose. Table 4 highlights the combinations (in blue) of different ASA definition and different imputation method, where a reversal against ticagrelor (i.e., HR>1 for ticagrelor versus clopidogrel) is observed in the high ASA group in OUS. Please also see appendix for additional graphs.

Table 3 Different ASA definitions with different imputation methods that show a less effect with ticagrelor than with clopidogrel in high ASA dose group in US subjects

	M1	M2	M3	M4	M5	M6
A1						
A2						
A3						
A4						
A5						
A6						
A7						
A8						
A9						
A10						
A11						
A12						
A13						

Table 4 Different ASA definitions with different imputation methods that show a less effect with ticagrelor than with clopidogrel in high ASA dose group in OUS subjects

	M1	M2	M3	M4	M5	M6
A1						
A2						
A3						
A4						
A5						
A6						
A7						
A8						
A9						
A10						
A11						
A12						
A13						

Other than ASA definitions A8, A9 and A10, OUS subjects did not show a reverse treatment effect (HR>1) in the high dose ASA group under definitions A4, A5 and A6 with M1 and M2 imputation, despite a significant treatment-ASA interaction was seen in the combined US and OUS (see Table 2). Also OUS subjects did not show a reverse treatment effect under all ASA definitions if the worst case imputations (M5 and M6) are used.

The primary endpoint was further analyzed by breaking down to events occurred within 30 days from randomization and beyond 30 days from randomization. Approximately half of the events occurred within 30 days from randomization. An interesting finding is that the treatment effect of ticagrelor was not so adverse compared to clopidogrel in US during the first 30 days (HR=1.06 in US). The divergence between US and OUS became more obvious in the later events

(HR=1.53 in US and HR=0.77 in OUS). This could be one of the reasons why definition A8, A9 and A10 did not show any treatment-ASA interaction since those three definitions are for analyses on the primary endpoints occurred within 30 days from randomization. Also these definitions included the first day loading dose in the calculation of ASA dose, which made a big impact on the extent of treatment by ASA interaction as suggested in the statistical reviews for the original NDA submission.

Table 5 Primary Endpoint Treatment Effects Pre- and Post-30 Days Follow-up

		Ticagrelor		Clopidogrel							
Events before	**Region**	**N**	**E**	**N**	**E**	**HR**	**Lower CL**	**Upper CL**	**p-value**	**Treat by region int χ^2**	**p-value**
All	All	9333	864	9291	1014	0.84	0.77	0.92	0.0003		
	US	707	84	706	67	1.27	0.92	1.75	0.1463	6.78	0.0092
	OUS	8626	780	8585	947	0.82	0.74	0.90	<0.0001		
≤30 days	All	9333	443	9291	502	0.88	0.77	1.00	0.0446		
	US	707	39	706	37	1.06	0.68	1.66	0.8005	0.75	0.3875
	OUS	8626	404	8585	465	0.86	0.76	0.99	0.0301		
>30 days	All	8763	421	8688	512	0.81	0.71	0.92	0.0016		
	US	654	45	658	30	1.53	0.96	2.43	0.0721	7.99	0.0047
	OUS	8109	376	8030	482	0.77	0.67	0.88	0.0001		

[Source: Sponsor's response on January 18 2011 to FDA CRL, confirmed by the reviewer]

Table 6, Table 7 and Table 8 explore the interactions terms in different Cox proportional hazards models.

- There is no treatment-region interaction under ASA definitions for early events, such as A8, A9 and A10. Most models do not show a treatment-ASA interaction under these definitions.
- There is no evidence of a significant three-way interaction under the full model for all definitions, except when the worst case imputation M6 was used, suggesting that there is no evidence that treatment-ASA interaction, if any, is different among regions.

In summary, which imputation method was used and whether the first day loading dose is included seem to have the most impact on analyses to possibly suggest a significant treatment-ASA interaction.

Figure 1 Forest Plot by Mean ASA Dose Taken in the Last 10 Days

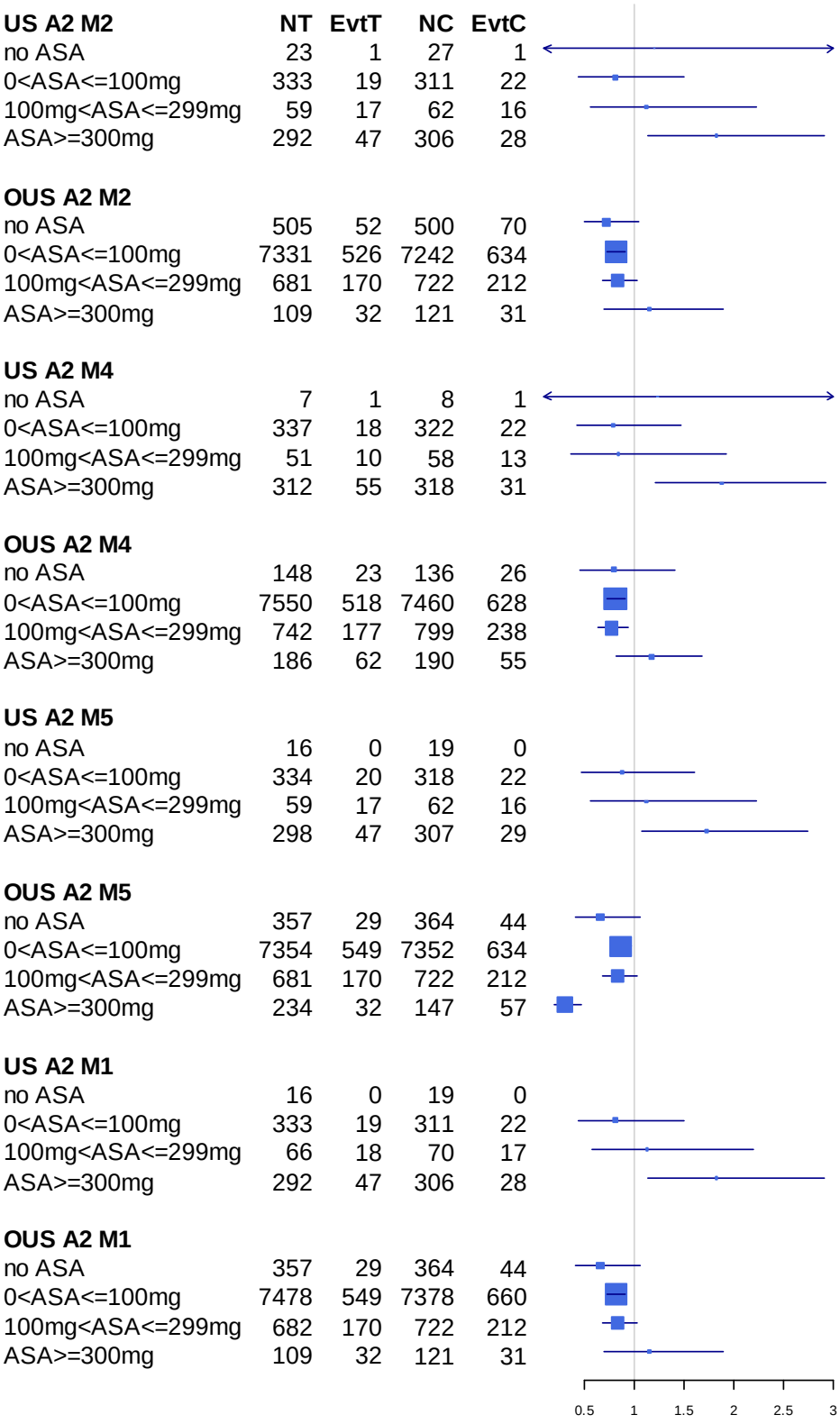


Figure 2 Forest Plot by Median ASA Dose Taken in the Last 10 Days

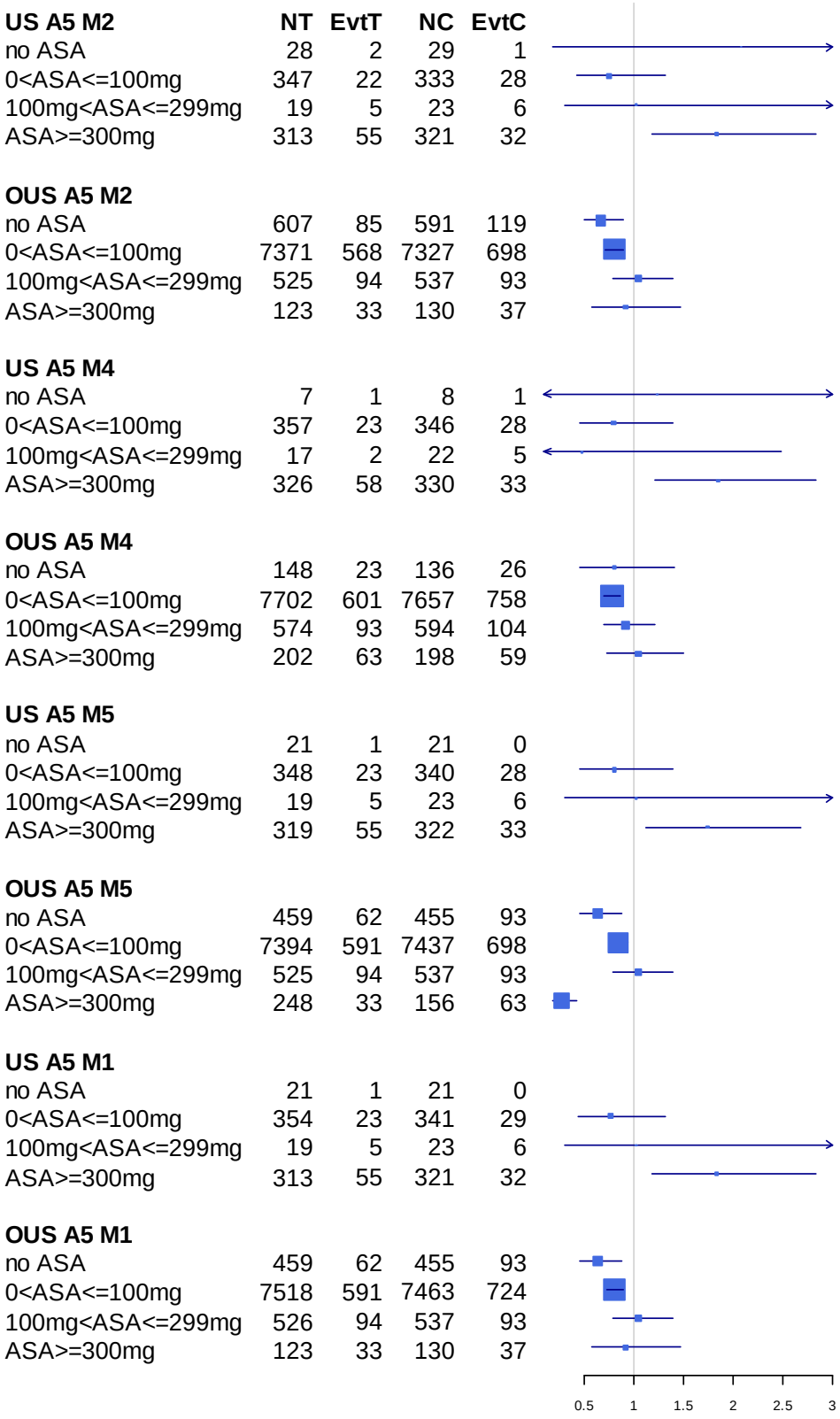


Figure 3 Forest Plot by the Median ASA Dose within 30 Days for Primary Event Occurred within 30 Days from Randomization

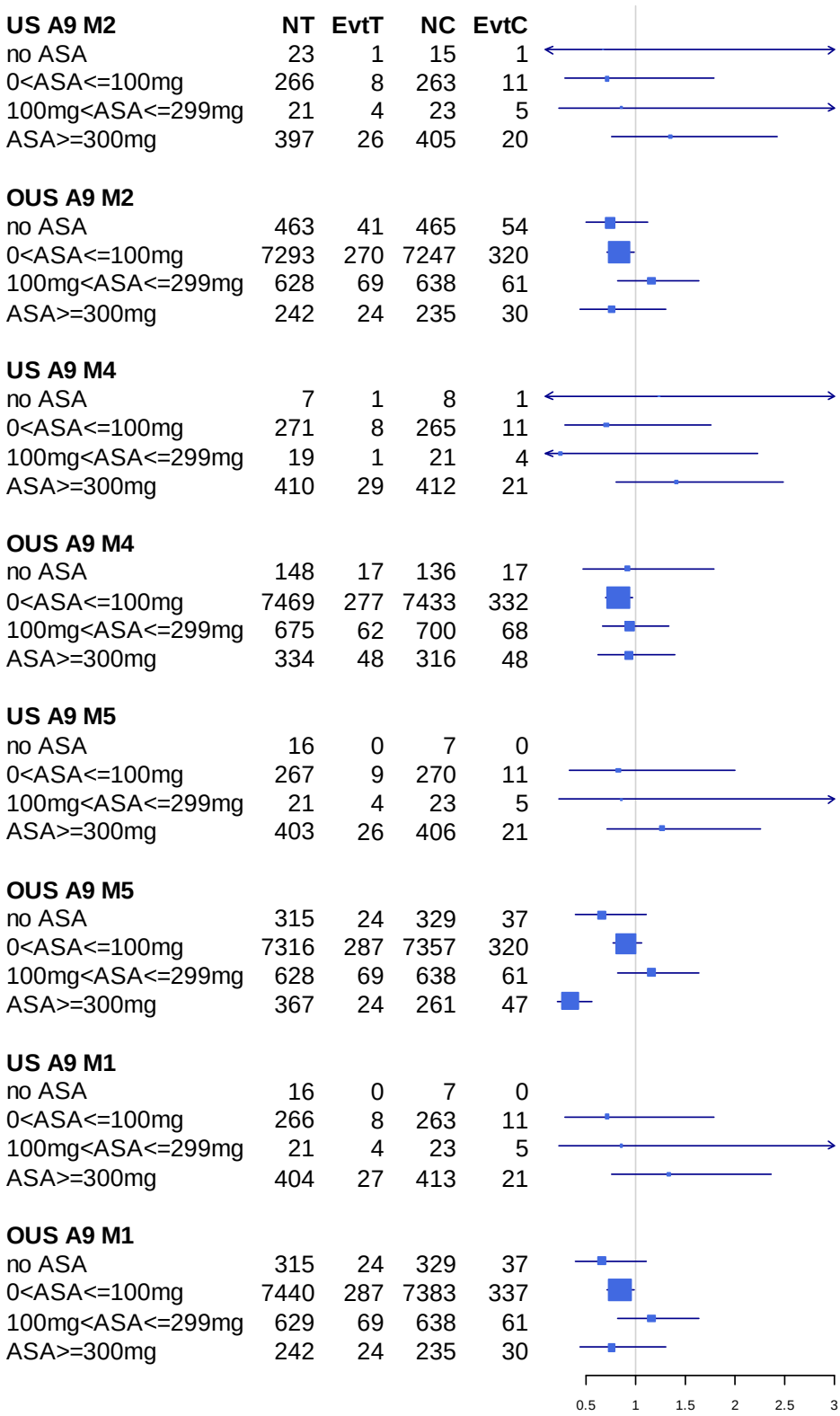


Figure 4 Forest Plot by the Median ASA Dose from Day 30 and Beyond for Primary Event Occurred after 30 Days from Randomization

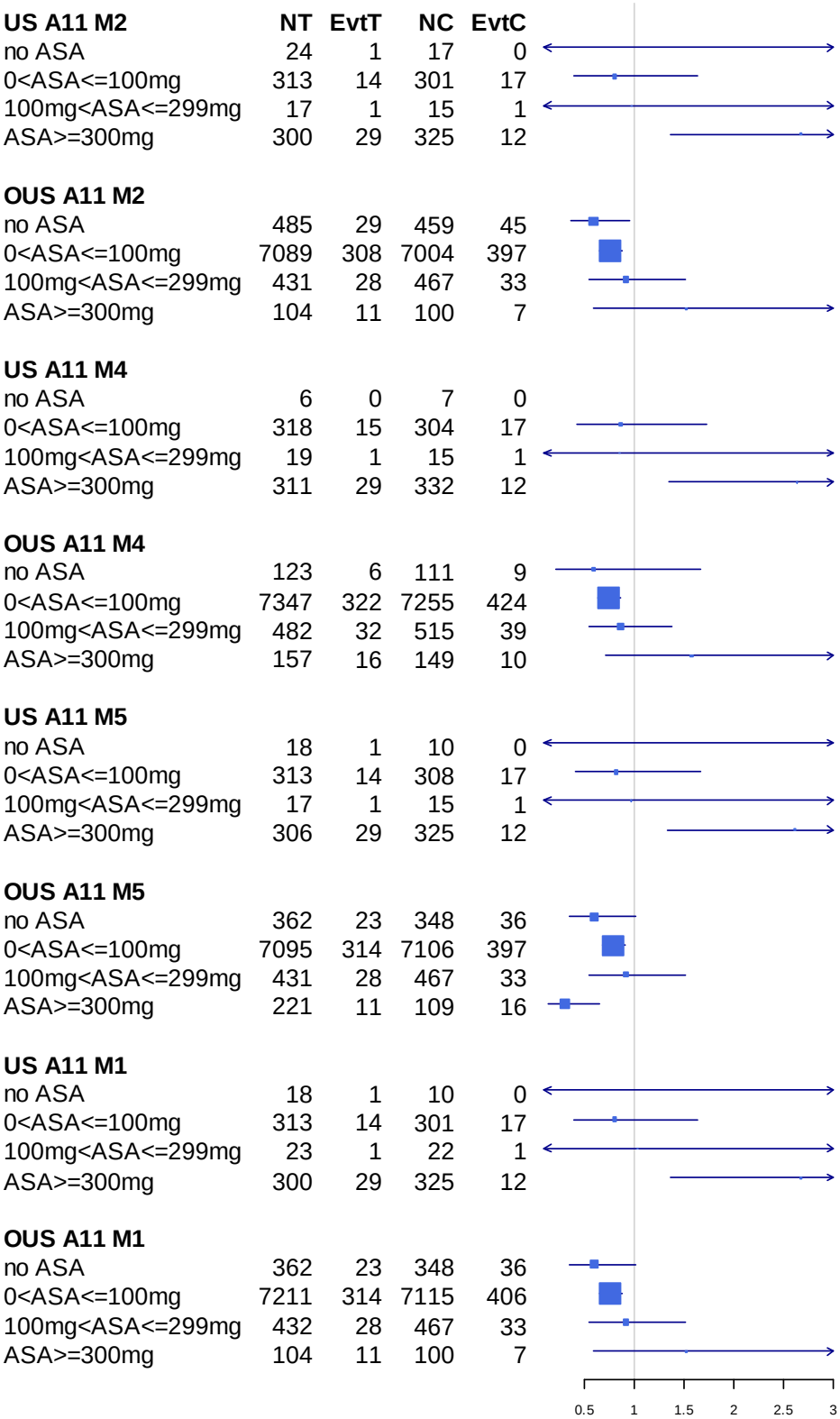


Table 6 Summary on Interactions in Various Models (1)

		T+R+A+TR		T+R+A+TR+AT				T+R+A+TR+AR+AT+ATR							
		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-region interaction		three-way interaction	
Imputation	ASA variable	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value
M1	A1	6.79	0.009	4.42	0.036	4.37	0.037	1.65	0.199	1.50	0.221	3.78	0.052	2.35	0.125
	A2	6.90	0.009	7.83	0.005	3.10	0.079	4.08	0.044	0.78	0.376	1.46	0.227	1.30	0.253
	A3	7.02	0.008	12.07	0.001	1.82	0.177	8.06	0.005	0.10	0.746	0.28	0.599	0.27	0.604
	A7	7.34	0.007	9.18	0.002	1.64	0.200	6.08	0.014	0.26	0.610	1.16	0.281	0.48	0.487
M2	A1	6.71	0.010	2.80	0.094	5.14	0.023	0.95	0.329	1.60	0.207	4.13	0.042	2.64	0.104
	A2	6.76	0.009	4.47	0.034	4.51	0.034	2.07	0.150	1.17	0.279	2.28	0.131	2.01	0.156
	A3	6.80	0.009	6.42	0.011	3.83	0.050	3.67	0.055	0.62	0.431	1.18	0.277	1.20	0.274
	A7	6.98	0.008	6.75	0.009	2.92	0.087	3.48	0.062	0.68	0.411	0.21	0.650	1.14	0.286
M3	A1	8.98	0.003	2.13	0.144	4.41	0.036	0.07	0.796	3.04	0.082	23.06	<.0001	4.18	0.041
	A2	9.45	0.002	2.56	0.110	4.35	0.037	0.04	0.852	3.19	0.074	26.48	<.0001	4.38	0.036
	A3	9.64	0.002	3.53	0.060	3.92	0.048	0.16	0.686	2.71	0.100	26.17	<.0001	3.79	0.052
	A7	7.34	0.007	9.18	0.002	1.64	0.200	6.08	0.014	0.26	0.610	1.16	0.281	0.48	0.487
M4	A1	7.49	0.006	4.87	0.027	2.31	0.128	1.80	0.180	1.32	0.250	5.34	0.021	1.90	0.168
	A2	7.52	0.006	4.59	0.032	2.37	0.124	1.53	0.216	1.42	0.233	6.85	0.009	2.04	0.153
	A3	7.50	0.006	5.17	0.023	2.19	0.139	2.00	0.157	1.08	0.298	6.43	0.011	1.62	0.204
	A7	6.98	0.008	6.75	0.009	2.92	0.087	3.48	0.062	0.68	0.411	0.21	0.650	1.14	0.286
M5	A1	6.82	0.009	0.12	0.728	6.16	0.013	0.13	0.717	1.84	0.175	2.85	0.091	3.02	0.082
	A2	6.97	0.008	0.40	0.530	5.70	0.017	0.01	0.939	1.57	0.210	0.65	0.421	2.62	0.106
	A3	7.15	0.008	0.70	0.402	5.22	0.022	0.03	0.853	1.09	0.296	0.00	0.974	1.93	0.165
	A7	7.73	0.005	0.43	0.511	7.90	0.005	2.05	0.152	2.79	0.095	3.78	0.052	4.22	0.040
M6	A1	9.65	0.002	4.80	0.029	13.91	<0.001	11.34	0.001	6.83	0.009	29.71	<.0001	9.44	0.002
	A2	10.05	0.002	4.23	0.040	13.96	<0.001	11.88	0.001	7.16	0.007	33.64	<.0001	9.87	0.002
	A3	10.18	0.001	3.19	0.074	13.26	<0.001	10.55	0.001	6.55	0.011	33.60	<.0001	9.12	0.003
	A7	7.73	0.005	0.43	0.511	7.90	0.005	2.05	0.152	2.79	0.095	3.78	0.052	4.22	0.040

Table 7 Summary on Interactions in Various Models (2)

		T+R+A+TR		T+R+A+TR+AT				T+R+A+TR+AR+AT+ATR							
		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-region interaction		three-way interaction	
Imputation	ASA variable	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value
M1	A4	6.67	0.010	5.16	0.023	4.86	0.028	2.35	0.126	1.92	0.166	6.66	0.010	2.98	0.084
	A5	6.69	0.010	9.55	0.002	4.10	0.043	5.69	0.017	0.86	0.354	6.96	0.008	1.49	0.222
	A6	6.73	0.009	12.11	0.001	3.42	0.064	7.76	0.005	0.60	0.438	4.94	0.026	1.08	0.299
M2	A4	6.70	0.010	4.02	0.045	5.24	0.022	1.82	0.177	1.80	0.179	6.46	0.011	2.96	0.085
	A5	6.69	0.010	7.19	0.007	4.69	0.030	4.25	0.039	0.93	0.334	6.75	0.009	1.70	0.192
	A6	6.72	0.010	8.54	0.003	4.33	0.038	5.39	0.020	0.79	0.375	5.10	0.024	1.46	0.227
M3	A4	8.51	0.004	9.50	0.002	1.49	0.223	3.30	0.069	2.15	0.142	15.81	0.000	2.86	0.091
	A5	8.29	0.004	9.31	0.002	1.43	0.232	3.75	0.053	1.26	0.261	12.63	0.000	1.80	0.180
	A6	8.19	0.004	9.44	0.002	1.36	0.244	3.94	0.047	1.23	0.268	12.14	0.000	1.74	0.187
M4	A4	7.13	0.008	9.52	0.002	1.74	0.187	4.07	0.044	1.33	0.248	0.94	0.333	1.82	0.177
	A5	7.04	0.008	9.35	0.002	1.71	0.191	4.61	0.032	0.69	0.405	0.31	0.581	1.04	0.307
	A6	7.02	0.008	9.01	0.003	1.77	0.183	4.29	0.038	0.77	0.381	0.26	0.609	1.14	0.286
M5	A4	6.65	0.010	1.06	0.303	5.73	0.017	0.13	0.714	1.88	0.170	6.12	0.013	3.08	0.079
	A5	6.69	0.010	3.02	0.082	5.12	0.024	1.23	0.268	0.92	0.337	6.34	0.012	1.70	0.193
	A6	6.75	0.009	3.70	0.054	4.76	0.029	1.75	0.186	0.80	0.371	4.21	0.040	1.49	0.222
M6	A4	8.94	0.003	0.63	0.426	9.22	0.002	5.03	0.025	7.49	0.006	24.02	<0.001	9.93	0.002
	A5	8.72	0.003	0.69	0.405	9.11	0.003	4.58	0.032	5.77	0.016	20.19	<0.001	7.92	0.005
	A6	8.62	0.003	0.68	0.410	8.99	0.003	4.47	0.035	5.78	0.016	19.64	<0.001	7.92	0.005

Table 8 Summary on Interactions in Various Models (3)

Imputation	ASA variable	T+R+A+TR		T+R+A+TR+AT				T+R+A+TR+AR+AT+ATR							
		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-region interaction		three-way interaction	
		Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value
M1	A8	1.02	0.313	1.63	0.201	0.11	0.742	0.76	0.385	0.17	0.682	2.16	0.142	0.22	0.643
	A9	0.73	0.393	5.89	0.015	0.04	0.849	4.07	0.044	0.35	0.557	1.51	0.218	0.38	0.539
	A10	0.75	0.387	0.18	0.676	0.64	0.424	0.07	0.790	0.25	0.620	0.10	0.753	0.34	0.561
M2	A8	0.77	0.381	0.32	0.573	0.45	0.502	0.10	0.755	0.22	0.641	0.07	0.793	0.33	0.565
	A9	0.68	0.410	2.88	0.090	0.23	0.634	1.86	0.172	0.37	0.544	1.11	0.292	0.48	0.490
	A10	0.73	0.393	0.00	0.947	0.73	0.392	0.03	0.864	0.10	0.751	0.03	0.861	0.20	0.658
M3	A8	2.23	0.136	0.31	0.580	1.28	0.257	1.12	0.290	1.63	0.201	15.68	<.0001	2.00	0.157
	A9	1.48	0.223	2.13	0.144	0.22	0.641	0.12	0.731	1.16	0.282	9.23	0.002	1.36	0.244
	A10	0.74	0.389	0.22	0.640	0.62	0.432	0.09	0.765	0.28	0.599	0.08	0.771	0.37	0.543
M4	A8	0.91	0.340	0.10	0.756	0.54	0.464	0.06	0.808	0.64	0.423	6.64	0.010	0.83	0.362
	A9	0.81	0.369	1.63	0.202	0.11	0.746	0.71	0.400	0.33	0.564	1.24	0.265	0.40	0.525
	A10	0.72	0.395	0.00	0.982	0.72	0.397	0.02	0.889	0.13	0.721	0.02	0.888	0.23	0.632
M5	A8	1.08	0.299	1.99	0.158	2.38	0.123	3.99	0.046	1.36	0.244	5.60	0.018	1.87	0.171
	A9	0.74	0.389	1.05	0.306	0.33	0.563	0.48	0.488	0.35	0.551	1.01	0.315	0.47	0.492
	A10	0.75	0.386	1.63	0.202	1.06	0.304	1.93	0.165	0.22	0.639	0.02	0.890	0.34	0.558
M6	A8	2.38	0.123	2.72	0.099	4.30	0.038	10.62	0.001	2.31	0.129	19.61	<.0001	3.01	0.083
	A9	1.60	0.206	1.04	0.307	2.48	0.115	4.83	0.028	2.32	0.127	13.85	<0.001	2.98	0.084
	A10	0.75	0.388	1.69	0.194	1.07	0.301	2.03	0.154	0.26	0.607	0.01	0.910	0.39	0.530

Table 9 Summary on Interactions in Various Models (4)

		T+R+A+TR		T+R+A+TR+AT				T+R+A+TR+AR+AT+ATR							
		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-treatment interaction		Treatment-region interaction		ASA-region interaction		three-way interaction	
Imputation	ASA variable	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value	Chi square	p-value
M1	A11	7.67	0.006	4.54	0.033	5.31	0.021	2.05	0.152	1.11	0.292	0.01	0.943	2.12	0.146
	A12	7.72	0.006	5.30	0.021	4.83	0.028	2.51	0.113	1.06	0.303	0.06	0.811	1.99	0.158
	A13	8.36	0.004	0.54	0.462	5.43	0.020	0.04	0.838	1.37	0.241	6.87	0.009	2.22	0.136
M2	A11	7.69	0.006	4.71	0.030	5.50	0.019	2.32	0.128	0.91	0.341	0.11	0.739	1.89	0.169
	A12	7.74	0.005	4.28	0.039	5.44	0.020	2.02	0.155	1.02	0.313	0.00	0.996	2.07	0.150
	A13	8.20	0.004	2.61	0.107	3.81	0.051	1.06	0.303	0.62	0.432	1.53	0.215	1.11	0.291
M3	A11	8.11	0.004	7.70	0.006	1.54	0.214	3.36	0.067	0.84	0.359	3.69	0.055	1.24	0.266
	A12	8.26	0.004	6.99	0.008	1.29	0.255	2.52	0.113	1.04	0.307	5.01	0.025	1.45	0.229
	A13	8.36	0.004	0.54	0.462	5.43	0.020	0.04	0.838	1.37	0.241	6.87	0.009	2.22	0.136
M4	A11	7.90	0.005	6.79	0.009	3.15	0.076	2.83	0.093	0.98	0.323	0.81	0.368	1.61	0.205
	A12	7.93	0.005	3.96	0.047	4.20	0.041	1.07	0.301	1.98	0.159	1.19	0.276	3.05	0.081
	A13	8.20	0.004	2.61	0.107	3.81	0.051	1.06	0.303	0.62	0.432	1.53	0.215	1.11	0.291
M5	A11	7.67	0.006	1.88	0.170	6.08	0.014	0.47	0.493	1.36	0.243	0.00	0.953	2.56	0.109
	A12	7.73	0.005	1.15	0.285	6.23	0.013	0.12	0.731	1.69	0.193	0.24	0.623	3.03	0.082
	A13	8.81	0.003	2.22	0.137	10.99	0.001	4.49	0.034	3.61	0.058	9.48	0.002	5.38	0.020
M6	A11	8.21	0.004	0.26	0.611	5.55	0.018	0.64	0.423	4.61	0.032	8.00	0.005	6.11	0.013
	A12	8.43	0.004	0.41	0.524	8.18	0.004	5.46	0.019	8.88	0.003	12.79	0.000	11.29	0.001
	A13	8.81	0.003	2.22	0.137	10.99	0.001	4.49	0.034	3.61	0.058	9.48	0.002	5.38	0.020

3.2.4.2 Results from TRITON Study

TRITON was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study. Clopidogrel was selected as the active comparator. A total of 13608 ACS subjects were enrolled to the study. Subjects were randomly assigned in a 1:1 ratio to receive either prasugrel or clopidogrel. The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The primary safety measure was the nonCABG TIMI major bleeding. Since subjects received aspirin during the 24 hours prior to PCI and continued throughout the study, the reviewer examined the potential interaction between treatment effect and aspirin.

The reviewer derived a daily aspirin dose dataset from the dataset that contains aspirin information (aspthrpy.xpt) and calculated the median ASA dose. The median ASA dose was calculated based on the period between randomization and primary efficacy event / censoring date. Out of 13608 ITT subjects, 1207 subjects did not have any ASA records. These 1207 subjects were not counted in the analyses below. For subjects who had at least 1 ASA record but with missing ASA doses, the reviewer imputed the missing ASA doses to be zero. The median ASA dose was divided into high and low dose ASA strata.

- Low Dose ASA: 0 mg < median ASA <=100mg
- High Dose ASA: median ASA > 100 mg

Figure 5 and Figure 6 show the distribution of median ASA over the whole trial period in US and OUS in TRITON study. The pattern is very similar to what the reviewer observed in PLATO study. Almost half of the US subjects took high dose ASA (325mg) while majority of OUS subjects took low dose ASA.

Figure 5 Distribution of Median ASA Dose in US (TRITON Study)

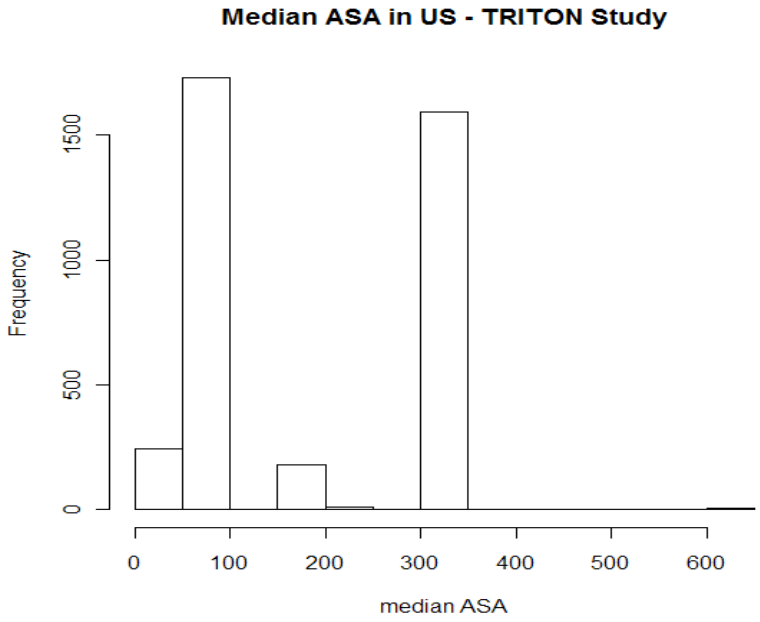
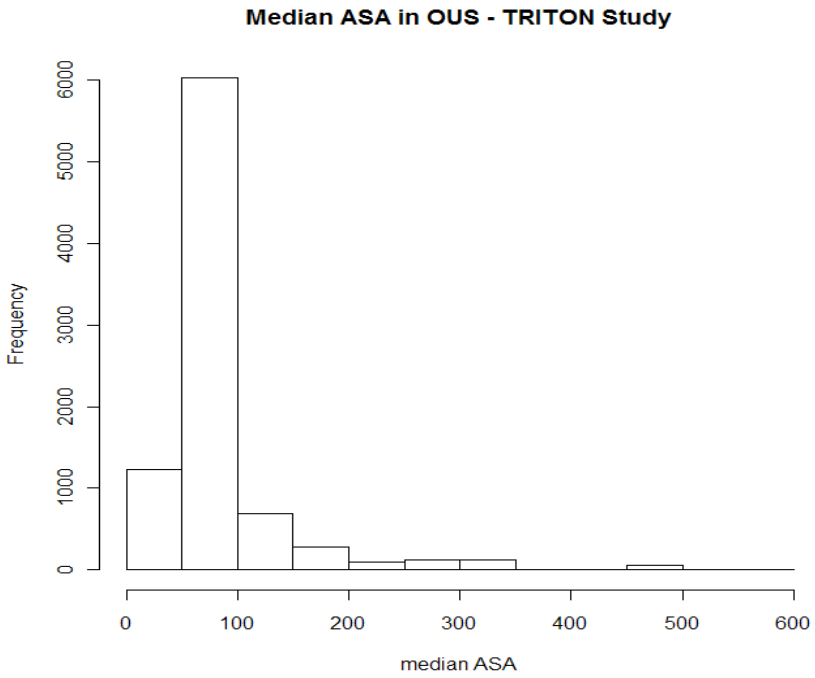


Figure 6 Distribution of Median ASA Dose in OUS (TRITON Study)



The reviewer further examined the relationship between the treatment effect of prasugrel and median ASA dose. In TRITON study, a large number of events occurred within the first 24 hours from randomization. The primary events were broken down by the timeline in the analyses. For example, the events occurred within the first 24 hours from randomization, the events occurred between 24 hours and 3 days from randomization, and et al. Analyses were performed within different median ASA strata based on different definition of ASA to examine the potential interaction between treatment and ASA. Median ASA below or equal to 100 mg was defined as low ASA dose and median ASA above 100 mg as high ASA dose. Specifically, the median ASA doses in different analyses were defined as follows:

For primary events that occurred within 24 hours from randomization:

- Median daily ASA doses taken in the first 24 hours (equivalent to the first day ASA dose)

For primary events that occurred between 24 hours and 3 days from randomization:

- Median daily ASA doses taken from Day 2 to Day 3 from randomization

For primary events that occurred between 3 days and 30 days from randomization:

- Median daily ASA doses taken from Day 4 to Day 30 from randomization

For patients with a primary event/censoring that occurred after 30 days from randomization:

- Median daily ASA dose based on Day 31 to the date of primary event/censoring

For overall patient population

- Median daily ASA dose based on Day 1 to the date of primary event/censoring
- Median daily ASA doses taken in the last 7 days prior to the primary event/censoring date
- Median daily ASA doses taken in the last 30 days prior to the primary event/censoring date
- The last ASA dose taken within 30 days prior to the primary event/censoring date

There appeared no heterogeneity in treatment effect (prasugrel versus clopidogrel) between the high and low ASA dose groups (Table 10).

Similar analyses were also performed on Non CABG TIMI major bleeding, which was the primary safety endpoint in the trial. The ASA doses were defined similarly except the calculations were based on the daily ASA dose up to the date of NCABG TIMI major bleeding / primary event / censoring, whichever occurred first. No trend of treatment effect in different ASA strata was found in these post-hoc bleeding analyses (**Table 11**).

Table 10 Analyses on Primary Efficacy Endpoint by Median ASA in TRITON

Median ASA	HR estimate	HR Lower Bound	HR Upper Bound	# of events	%	n	Analysis
low	0.734	0.553	0.975	195	4.1	4742	first 24 hours
high	0.845	0.689	1.036	371	4.8	7659	first 24 hours
low	0.645	0.35	1.189	43	0.6	7614	>24 hr and <=3 days
high	0.543	0.201	1.468	17	0.4	4196	>24 hr and <=3 days
low	0.594	0.419	0.841	134	1.6	8439	>3 days and <=30 days
high	0.559	0.309	1.01	48	1.5	3247	>3 days and <=30 days
low	0.891	0.724	1.097	357	4.1	8746	>30 days
high	0.799	0.573	1.114	141	5.3	2648	>30 days
low	0.759	0.655	0.88	718	7.8	9225	whole trial period
high	0.831	0.706	0.977	588	18.5	3176	whole trial period
low	0.792	0.666	0.941	521	5.7	9164	last 7 days from event
high	0.775	0.605	0.993	257	9.6	2686	last 7 days from event
low	0.789	0.664	0.938	522	5.7	9157	last 30 days from event
high	0.778	0.607	0.997	256	9.5	2693	last 30 days from event
low	0.757	0.654	0.877	725	7.7	9402	last dose within 30 days from event
high	0.852	0.724	1.004	581	19.4	2999	last dose within 30 days from event

Table 11 Analyses on Non CABG TIMI Major Bleeding by Median ASA in TRITON

Median ASA	HR estimate	HR Lower Bound	HR Upper Bound	# of events	%	Total	Analysis
low	1.27	0.557	2.896	23	0.5	4742	first 24 hours
high	1.271	0.706	2.289	45	0.6	7659	first 24 hours
low	2.011	0.687	5.882	15	0.2	8096	>24 hr and <=3 days
high	0.248	0.028	2.223	5	0.1	4190	>24 hr and <=3 days
low	0.932	0.461	1.884	31	0.3	8972	>3 days and <=30 days
high	2.025	0.371	11.053	6	0.2	3210	>3 days and <=30 days
low	1.638	1.094	2.453	100	1.1	9379	>30 days
high	1.218	0.614	2.416	33	1.3	2577	>30 days
low	1.448	1.06	1.976	164	1.7	9649	whole trial period
high	1.211	0.807	1.816	94	3.4	2752	whole trial period
low	1.479	1.06	2.064	144	1.5	9793	last 7 days from event
high	1.103	0.67	1.814	62	2.5	2515	last 7 days from event
low	1.48	1.061	2.065	144	1.5	9781	last 30 days from event
high	1.101	0.669	1.811	62	2.5	2527	last 30 days from event
low	1.408	1.051	1.884	186	1.9	9886	last dose within 30 days from event
high	1.232	0.775	1.959	72	2.9	2515	last dose within 30 days from event

In summary, there appears to have no obvious interaction between treatment effect and ASA in TRITON study based on the post-hoc analyses presented above.

3.3 Evaluation of Safety

Please refer to the clinical review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This whole NDA resubmission is to further examine the relationship between ASA and treatment and to seek potential explanation for the regional difference in the treatment effect, ticagrelor versus clopidogrel between US and OUS. All the analyses performed are subgroup analyses. Please refer to Section 3 for subgroup analyses on ASA doses. Please also refer to the statistical review filed on 6/29/2010 in DARRTS on analyses of other specific subgroup populations.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The reviewer considers the US-OUS regional difference a very important issue. The reviewer suggests that US-OUS subgroup analyses always be a pre-specified subgroup analysis in all NDA submissions. However, this resubmission and the whole ASA hypothesis are based on post-hoc subgroup analyses. All the conclusions and observations, including regional difference in treatment effect, are based on numerous subgroup analyses.

5.2 Conclusions and Recommendations

In summary, imputation methods and whether to include the first day loading dose seem to have the most impact on suggesting whether there is a significant treatment-ASA interaction. Various ASA definitions appear to demonstrate some degrees of consistency in analyses. These analyses are still limited by the fact that there were only a small number of high ASA dose subjects in OUS. It remains a concern whether ASA is truly the only factor that might affect the ticagrelor effect, as there appeared no such an interaction in TRITON study.

APPENDICES

Figure 7 Forest Plot by Mean ASA Dose Taken in the Last 5 Days

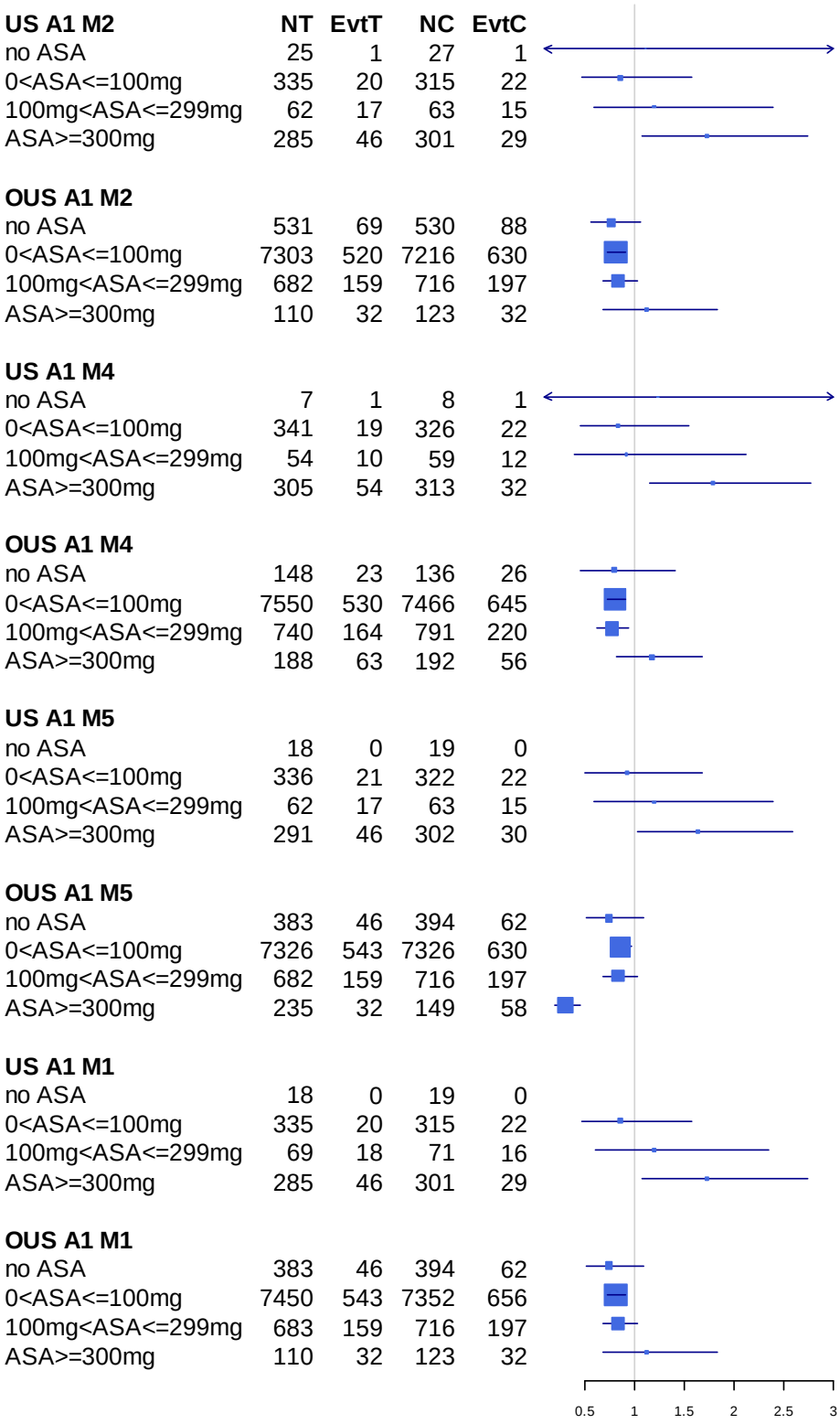


Figure 8 Forest Plot by Mean ASA Dose Taken in the Last 30 Days

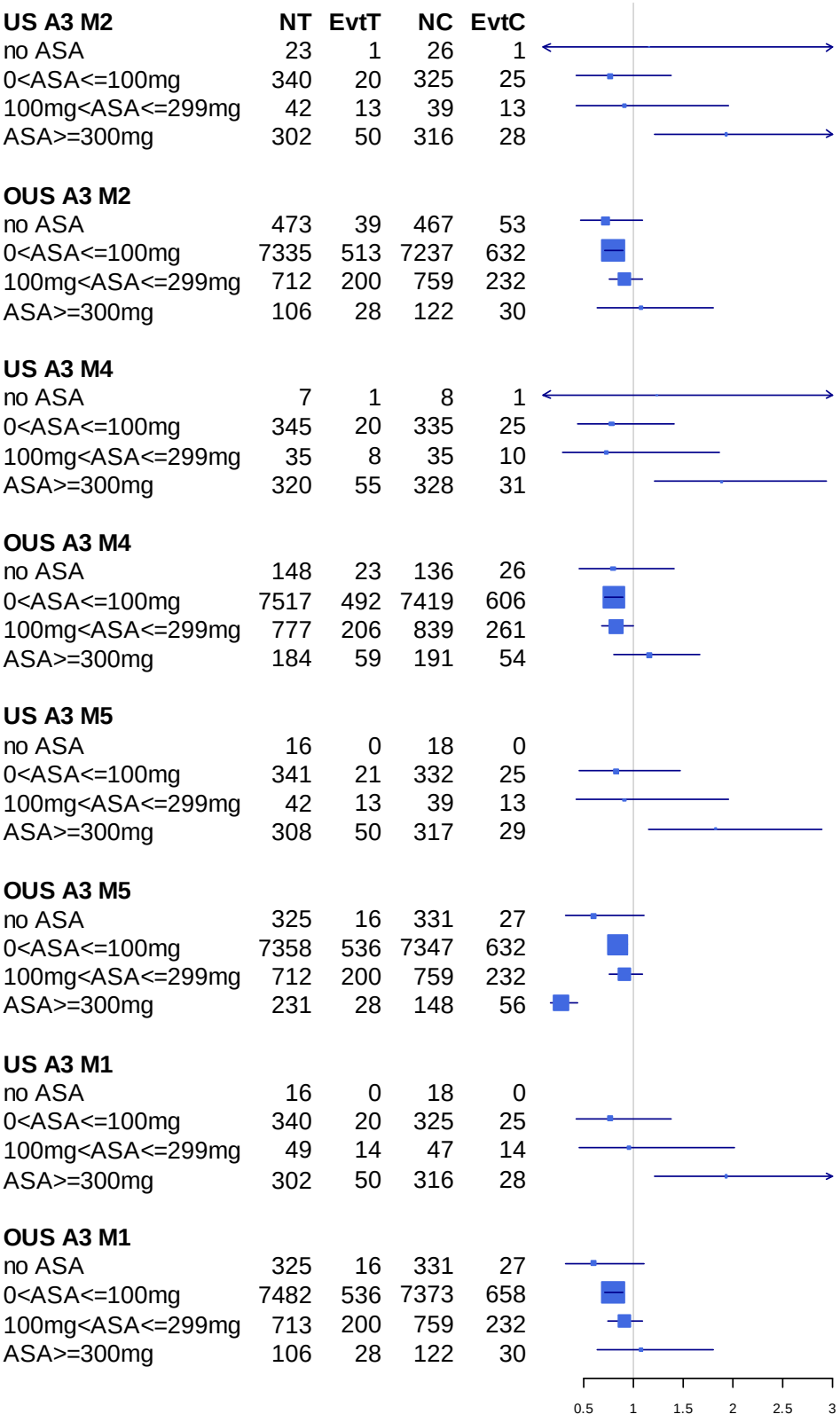


Figure 9 Forest Plot by Median ASA Dose Taken in the Last 5 Days

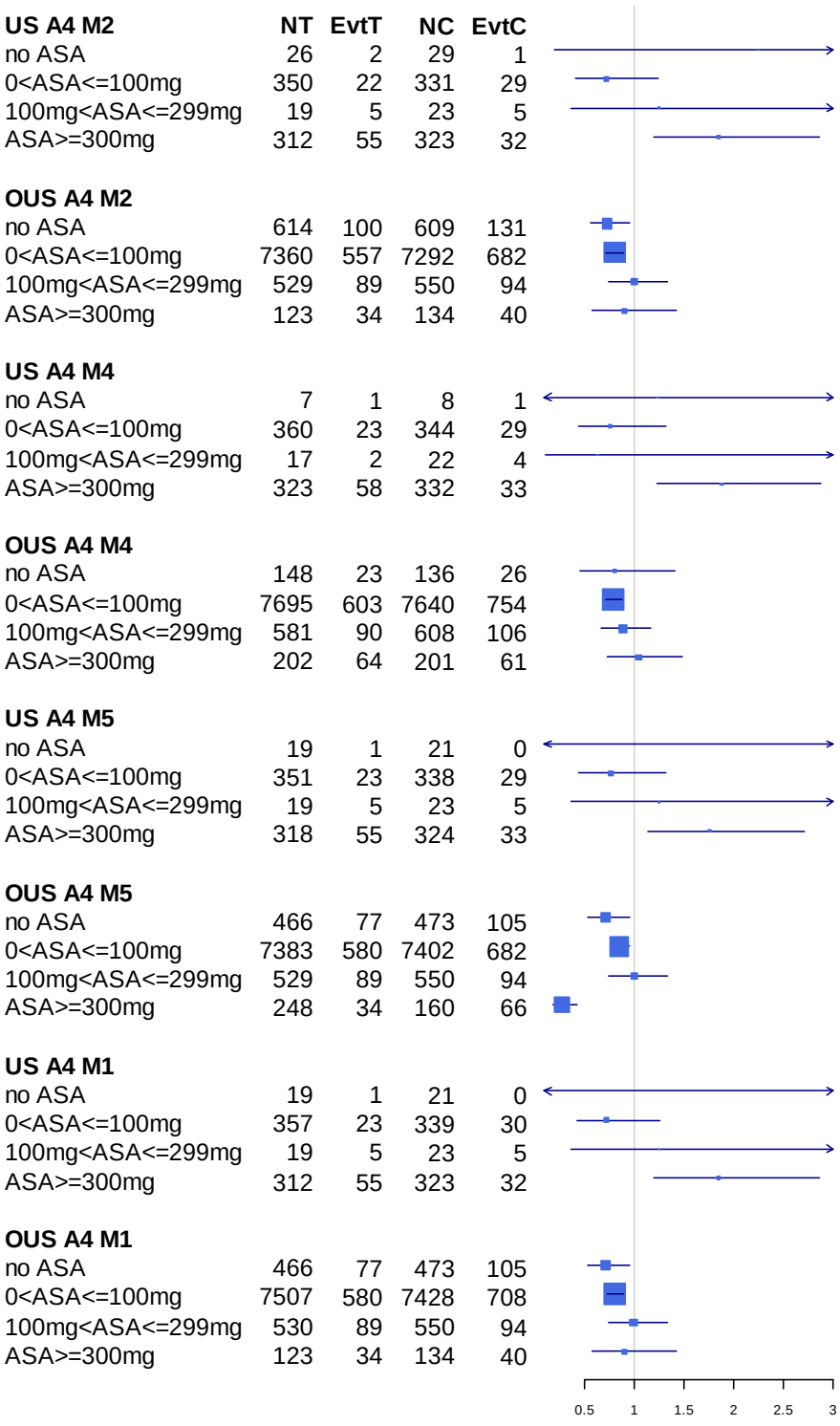


Figure 10 Forest Plot by Median ASA Dose Taken in the Last 30 Days

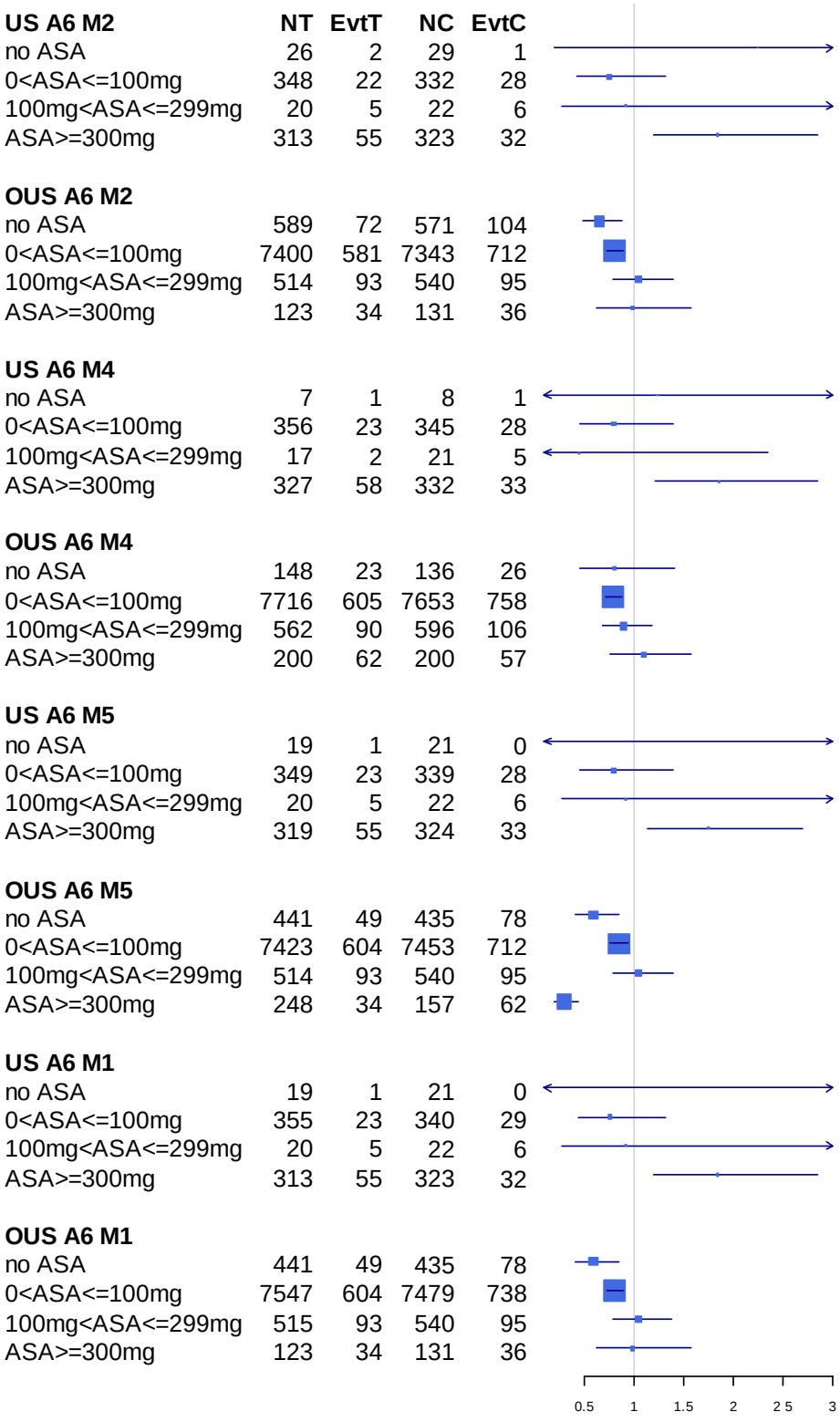


Figure 11 Forest Plot by the Last ASA Dose Taken within 30 Days Prior to Primary Event/Censoring

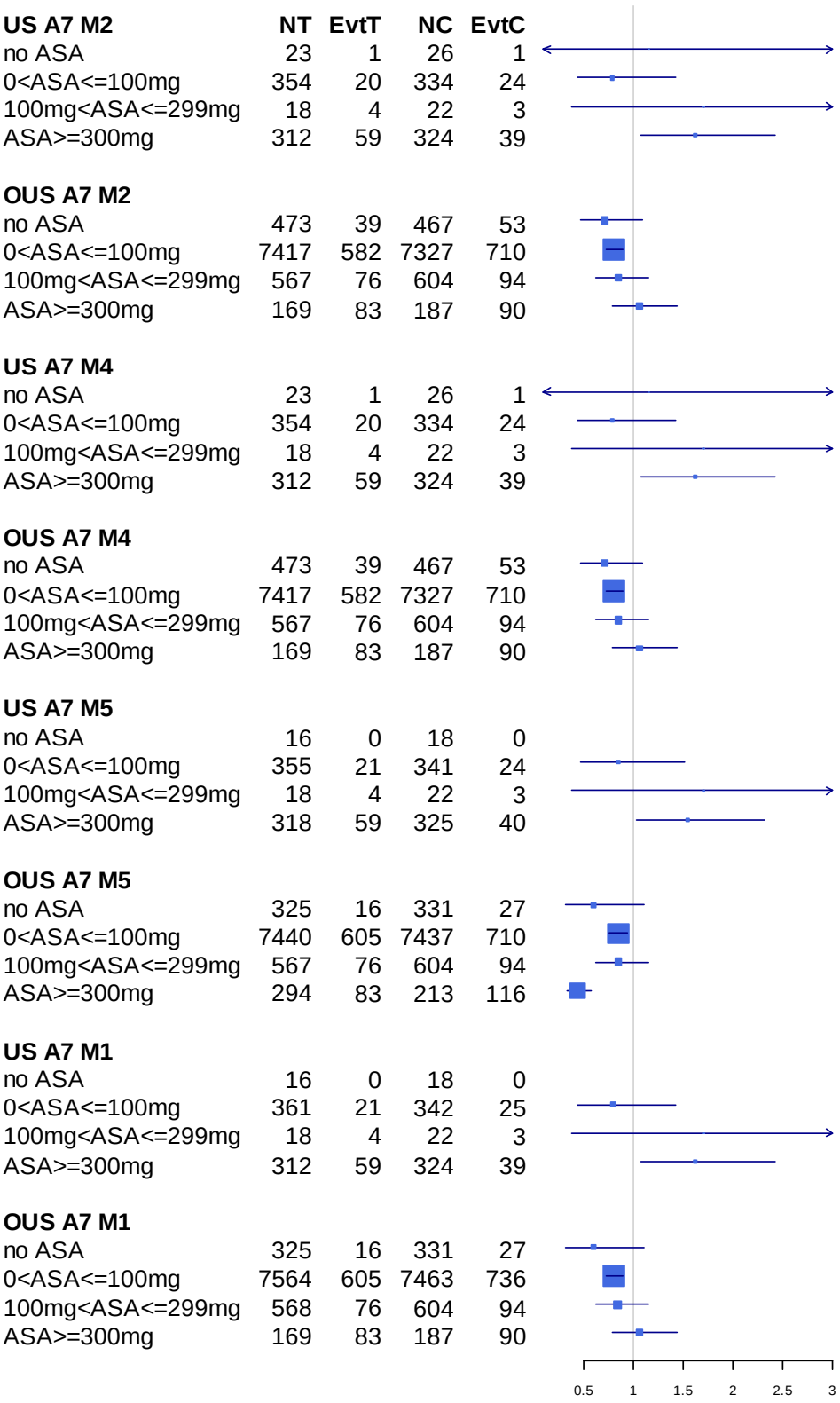


Figure 12 Forest Plot by the Mean ASA Dose Taken within 30 Days for Primary Event Occurred within 30 Days from Randomization

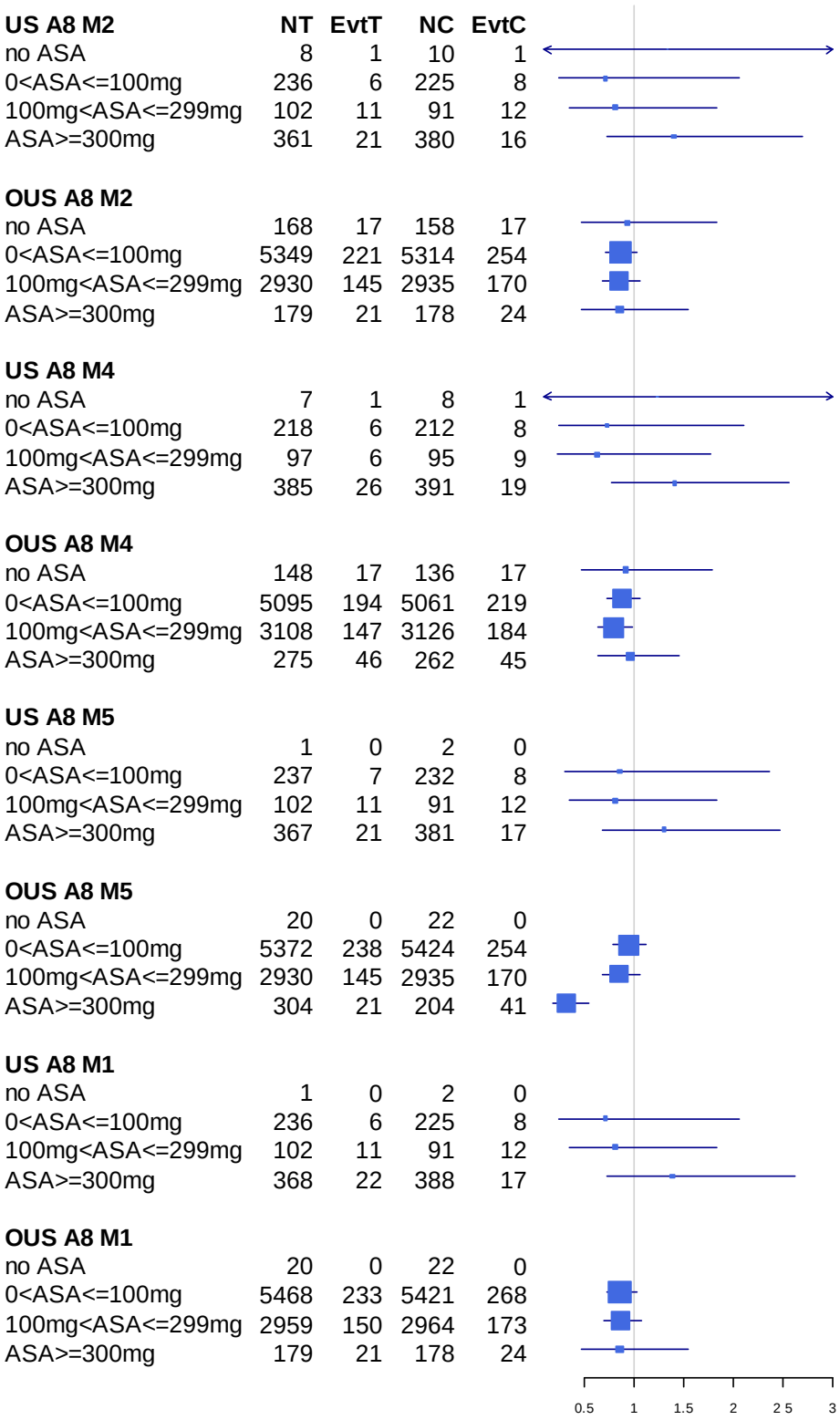


Figure 13 Forest Plot by the Maximum ASA Dose Taken within 30 Days for Primary Event Occurred within 30 Days from Randomization

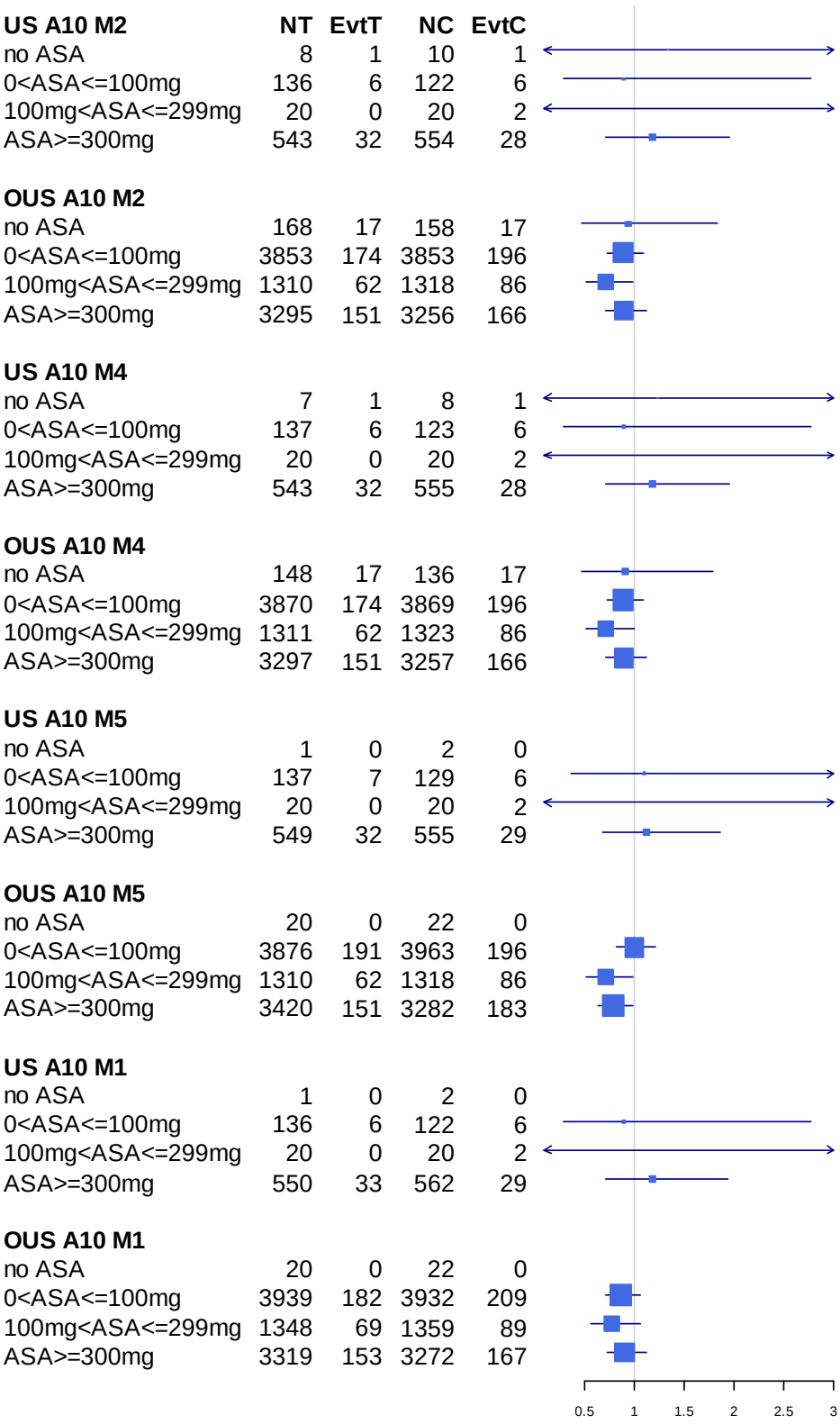


Figure 14 Forest Plot by the Median ASA Dose from Day 2 to Primary Event/Censoring for Primary Event Occurred after 30 Days from Randomization

	NT	EvtT	NC	EvtC
US A12 M2				
no ASA	23	1	17	0
0<ASA<=100mg	311	14	290	17
100mg<ASA<=299mg	17	1	16	1
ASA>=300mg	303	29	335	12
OUS A12 M2				
no ASA	474	26	440	39
0<ASA<=100mg	7097	310	7013	402
100mg<ASA<=299mg	434	29	473	34
ASA>=300mg	104	11	104	7
US A12 M4				
no ASA	8	0	8	0
0<ASA<=100mg	314	15	292	17
100mg<ASA<=299mg	19	1	16	1
ASA>=300mg	313	29	342	12
OUS A12 M4				
no ASA	184	9	171	12
0<ASA<=100mg	7339	324	7238	424
100mg<ASA<=299mg	466	29	504	38
ASA>=300mg	120	14	117	8
US A12 M5				
no ASA	15	1	9	0
0<ASA<=100mg	311	14	298	17
100mg<ASA<=299mg	17	1	16	1
ASA>=300mg	311	29	335	12
OUS A12 M5				
no ASA	290	17	269	27
0<ASA<=100mg	7106	319	7172	402
100mg<ASA<=299mg	434	29	473	34
ASA>=300mg	279	11	116	19
US A12 M1				
no ASA	15	1	9	0
0<ASA<=100mg	311	14	290	17
100mg<ASA<=299mg	25	1	24	1
ASA>=300mg	303	29	335	12
OUS A12 M1				
no ASA	290	17	269	27
0<ASA<=100mg	7279	319	7184	414
100mg<ASA<=299mg	436	29	473	34
ASA>=300mg	104	11	104	7

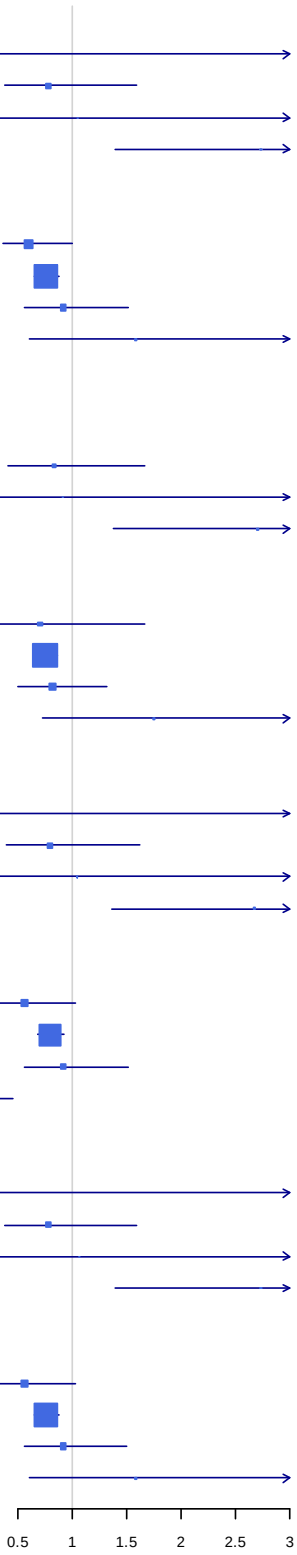
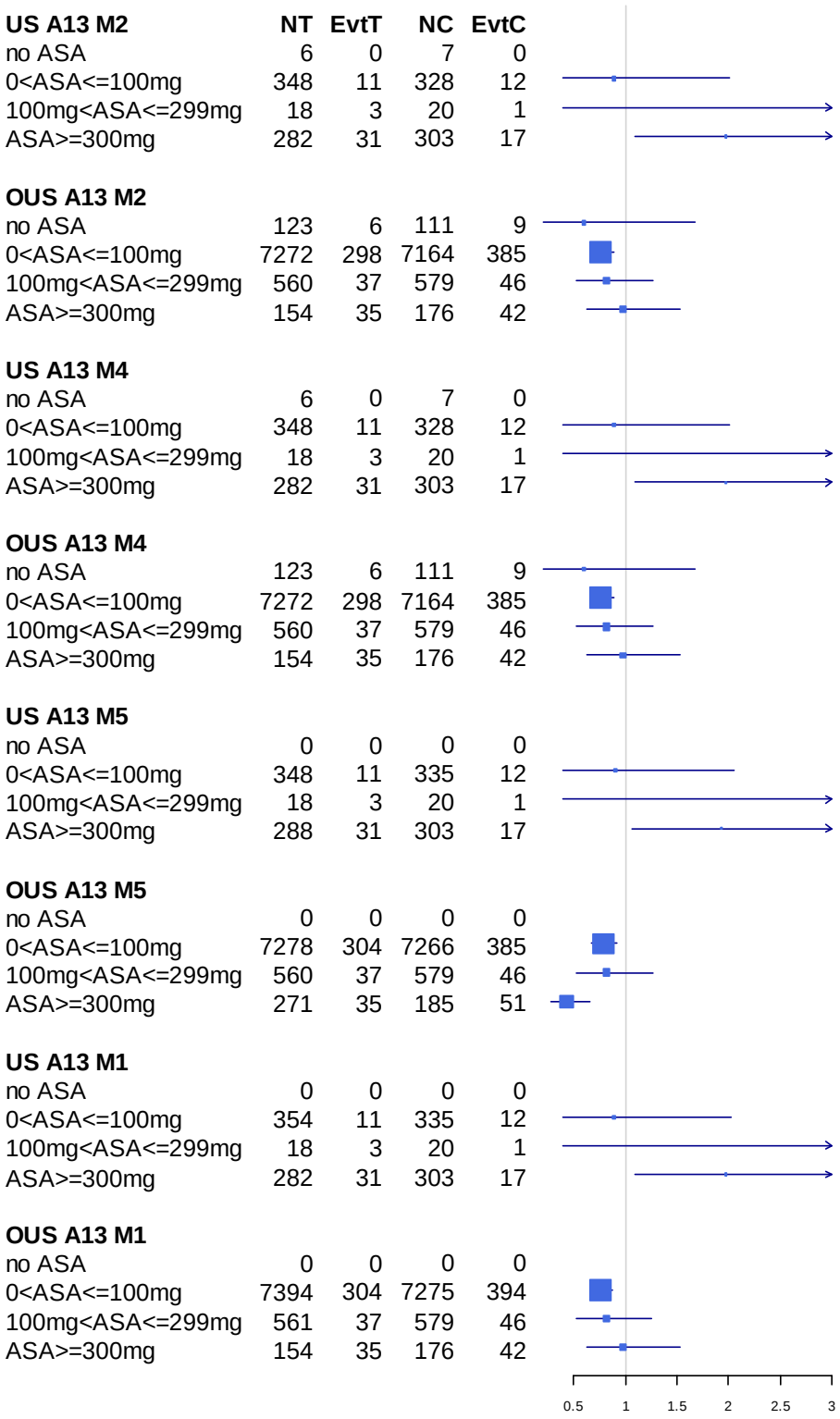


Figure 15 Forest Plot by the Last ASA Dose for Primary Event Occurred after 30 Days from Randomization



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/s/

JIALU ZHANG
04/28/2011

HSIEN MING J J HUNG
04/28/2011
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADDENDUM

NDA/Serial Number:	22-433 / N_000
Drug Name:	Brilinta (ticagrelor)
Indication(s):	Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)
Applicant:	AstraZeneca
Date(s):	Date of Document: November 17, 2009 PDUFA due date: September 16, 2010
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph. D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Robert Fiorentino, M.D.
Project Manager:	Michael Monteleone, Pharm.D.
Keywords:	Regional difference, aspirin

Executive Summary

This addendum provides additional analyses and results, some of which were presented in the Advisory Committee Meeting on July 29, 2010 but not included in the statistical review of June 29, 2010. Some other additional analyses were performed after the AC meeting. From the additional analyses, we continue to be troubled by the qualitative interaction between the region (US versus non-US) and treatment. In our view, neither play of chance nor concurrent use of ASA provides a satisfactory explanation for the US versus non-US disparity observed in this trial. Even though multiple factors have been screened for potential causes, the question remains unsolved. The disparity can still be caused by the difference in standard medical practice between US and the rest of the world, which is hard to quantify and has not been quantified. We ought to seek further data to either confirm or dismiss this disturbing finding. Without the data, we would recommend that this drug not be approved. Another study should be required if this drug is to be approved for use in US.

Background

This addendum is to further clarify the important issues on the US finding and provide additional analyses on PLATO trial. Please also refer to the statistical review filed in DARRTS on June 29, 2010 for further information.

NDA 22-433 (ticagrelor) was submitted by AstraZeneca on November 17, 2009. The application included a single phase III trial, PLATO, for indication of ticagrelor in reducing the rate of thrombotic events for patients with Acute Coronary Syndrome (ACS). The big issue in this application is the regional difference observed between US and non-US. The study reported a hazard ratio estimate of 0.84 [95% CI (0.77, 0.92)] for the overall population favoring ticagrelor. However, for US the hazard ratio estimate was 1.27 [95% CI (0.92, 1.75)]. The Advisory Committed meeting was held on July 29, 2010. AC members voted 7 yes and 1 no to approve ticagrelor.

Additional Analyses

This addendum includes additional analyses and results as a supplement to the primary statistical review. Some results below were shown during the Advisory Committee Meeting but not included in the primary review. In this addendum, we again examined three potential explanations for the US versus non-US differences.

- A play of chance
- Concurrent use of ASA
- Other factors

1. A play of chance

Though a play of chance can never be ruled out, such a big contrast between US and non-US was not seen before PLATO, according to our recollection.

If the total population is divided into 4 regions (North America, Central/South America, Asia/Australia, and Europe/Middle East/Africa), the region-treatment interaction has a nominal p-value of 0.045, suggesting possible heterogeneity in the primary endpoint results over the four regions. For the interest of US which is the focus of the Agency, the disparity between US and non-US is arguably more appropriate to examine. From our analysis, the disparity between US and non-US (as a whole) is quite concerning with p = 0.0095.

In PLATO US enrolled 1,413 subjects and had 151 primary endpoint events, which is the second largest country with enrollment out of the 43 countries. This ought to be factored into consideration.

If the hazard ratio 0.84 (i.e., risk reduction of 16%) of the overall population represents the true risk reduction in US, the probability of observing the hazard ratio 1.27 or greater is less than 0.01. As shown in Figure 1, even if a true hazard ratio is 1.0 (i.e., no difference between ticagrelor and clopidogrel), the chance of observing a hazard ratio of 1.27 in US is only 0.07. Though this calculation is post hoc and arguably does not take multiplicity into account, this is a focused subgroup analysis that is necessary for assessing the treatment effect in the US population rather than the controversial cherry-picking subgroup analyses for seeking an interesting subgroup finding. With the precision provided by the 151 events in US this calculation is sufficient to make the case that a play of chance cannot be the only basis for such disparity between US and non-US.

Figure 1. Probability of observing a hazard ratio estimate >= 1.27 in US

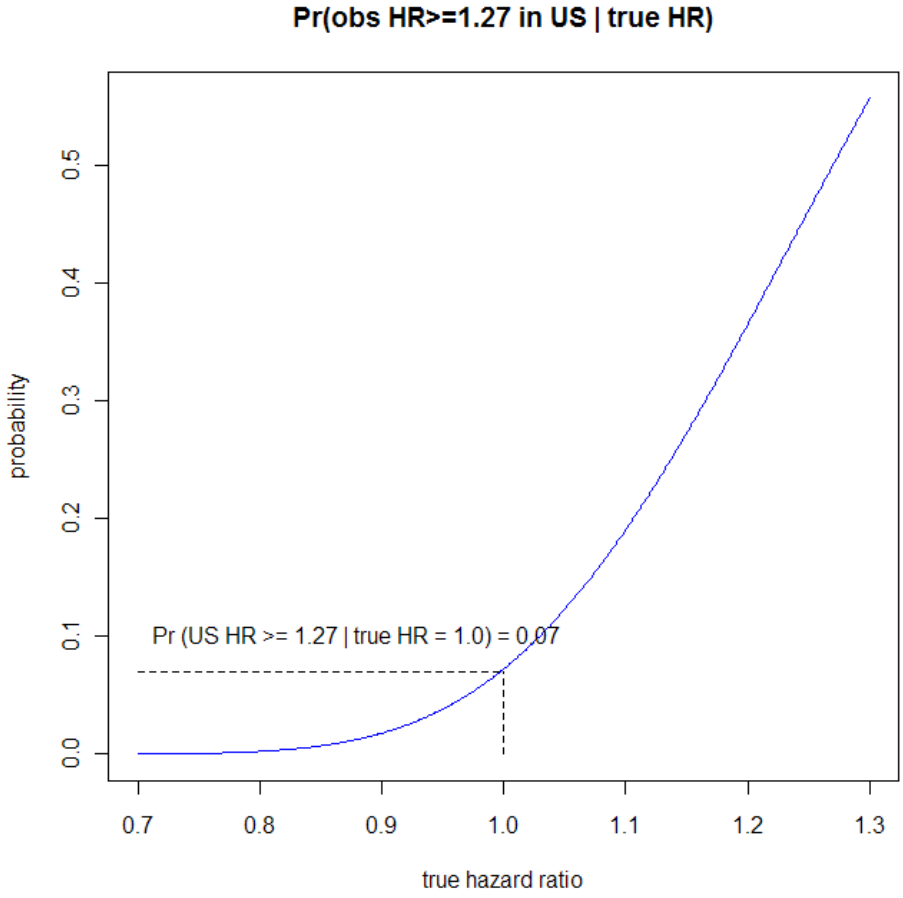


Table 1 shows the analyses on each individual component for the composite primary event. The hazard ratio estimates are based on time to the first event for each individual component. In each of the three components, US trends in the wrong direction (the number of strokes in US is quite small though). It is difficult to use "play of chance" to explain such a consistent adverse trend in all three components and the overall results in US.

Table 1 Analyses on components by region

	Characteristic	**Ticagrelor 90 mg bd**	**Clopidogrel 75 mg od**	**Hazard ratio (95% CI)**
Non-US	Composite of CV Death/MI (excl. silent MI)/Stroke	780	947	0.82 (0.74,0.90)
	CV death	329	423	0.77 (0.67, 0.89)
	MI (excl. silent MI)	440	546	0.80 (0.70, 0.90)
	Stroke	118	102	1.15 (0.88, 1.50)
US	Composite of CV Death/MI (excl. silent MI)/Stroke	84	67	1.27 (0.92,1.75)
	CV death	24	19	1.26 (0.69, 2.30)
	MI (excl. silent MI)	64	47	1.38 (0.94, 2.01)
	Stroke	7	4	1.73 (0.51, 5.92)

2. Concurrent use of ASA

Concurrent use of aspirin (ASA) was considered as a possible factor for such disparity. The Cox proportional hazards model with median ASA seems to explain the US versus non-US difference (p=0.003 for the median ASA-by-treatment interaction). However, in non-US, only a few subjects took a high dose ASA. These few subjects indeed had a large leverage on the robustness of the Cox model, as it is well known that the model fitting with covariate (i.e., dose in this case) is very sensitive to the disposition of a few events in the both ends of dose range fitted. By changing only 20 events in the high ASA dose group in non-US region, the relationship between ASA dose and hazard ratio changes dramatically (Table 2, Table 3, Figure 2, and Figure 3).

Table 2 Summary of primary events by region and median ASA

	Median ASA < 300 mg				Median ASA >= 300 mg			
	Ticagrelor		Clopidogrel		Ticagrelor		Clopidogrel	
	N	events	N	Events	N	events	N	events
US	383	44	354	40	324	40	352	27
Non-US	8486	752	8445	924	140	28	140	23

Table 3 Summary of primary events by region and median ASA after switching events

	Median ASA < 300 mg				Median ASA >= 300 mg			
	Ticagrelor		Clopidogrel		Ticagrelor		Clopidogrel	
	N	events	N	Events	N	events	N	Events
US	383	44	354	40	324	40	352	27
Non-US	8486	752	8445	924	140	18	140	33

Figure 2 The relationship between median ASA and hazard ratio based on original data

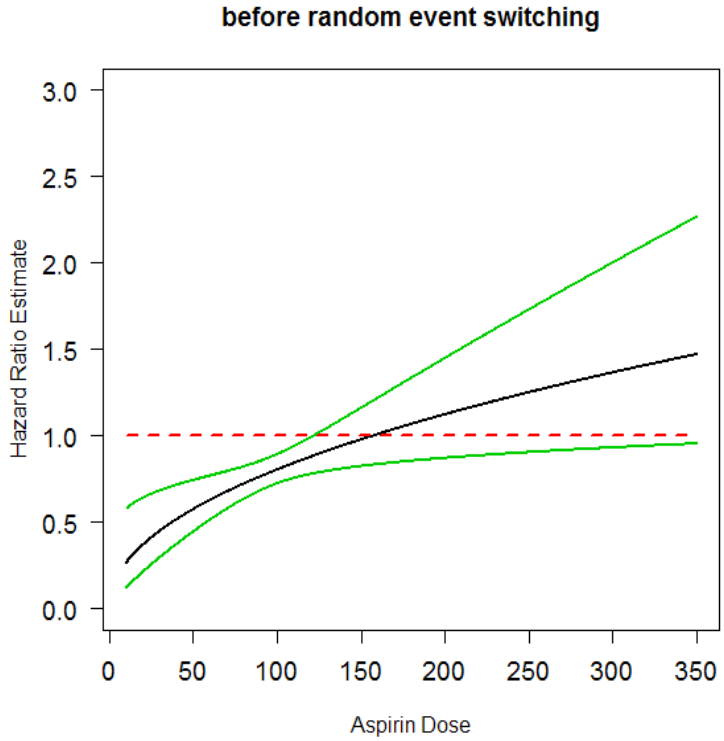


Figure 3 The relationship between median ASA and hazard ratio based on sensitivity analysis

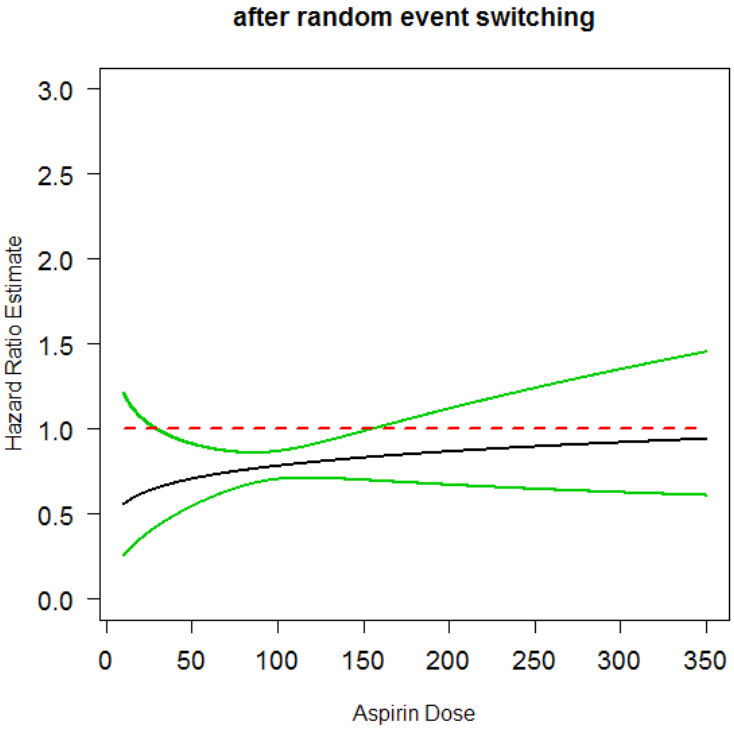


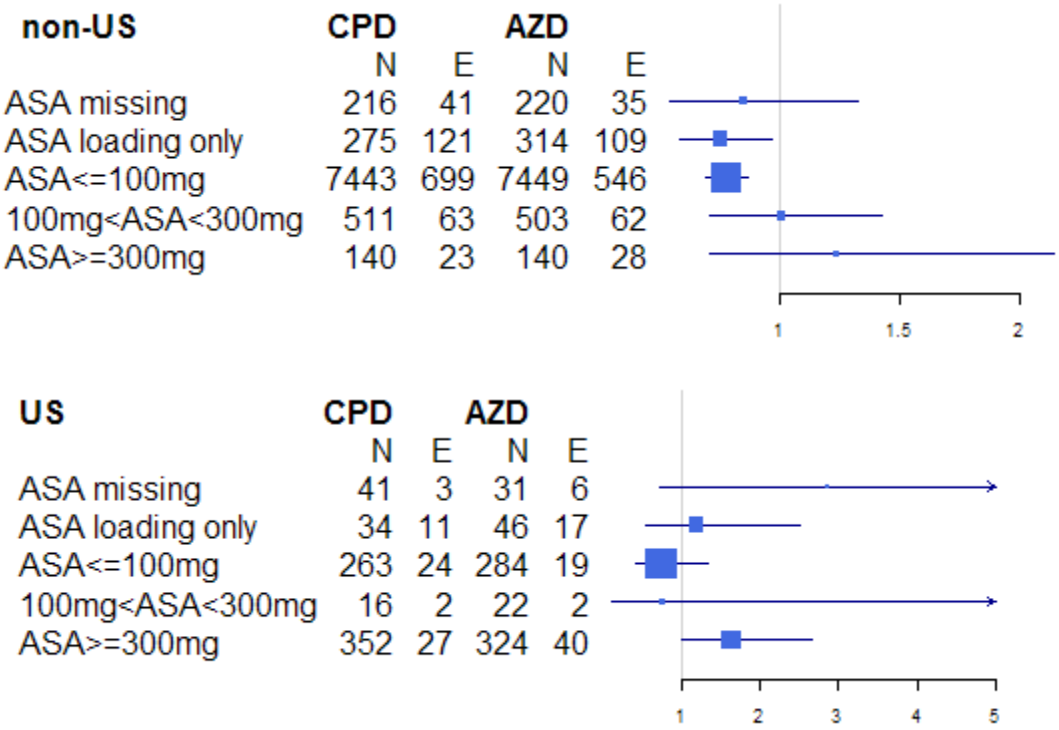
Table 4 shows the total number of subjects and events by each ASA subgroup. Also considered are the subjects who had ASA information missing (presumably those who did not take any ASA during the trial) and those who had only 1 day of ASA loading dose. These subjects are about 6% (N = 1,177) of the overall population.

Subjects who took only one day of ASA loading dose had a much higher rate of the primary event. Many subjects in this group had the primary event quickly (median time to event = 1.28 days). Nevertheless, from Figure 4, US still trends in the wrong direction favoring clopidogrel and non-US still shows consistent results favoring ticagrelor in these patients. Similar observations are made in those who had no ASA information recorded. Even though the numbers of these subjects are small in both US and non-US, we can still see a regional difference between US and non-US. This also casts doubts about the aspirin hypothesis that ticagrelor should benefit more than clopidogrel in the subjects who took low dose ASA.

Table 4 Total number of subjects and events in each ASA subgroup

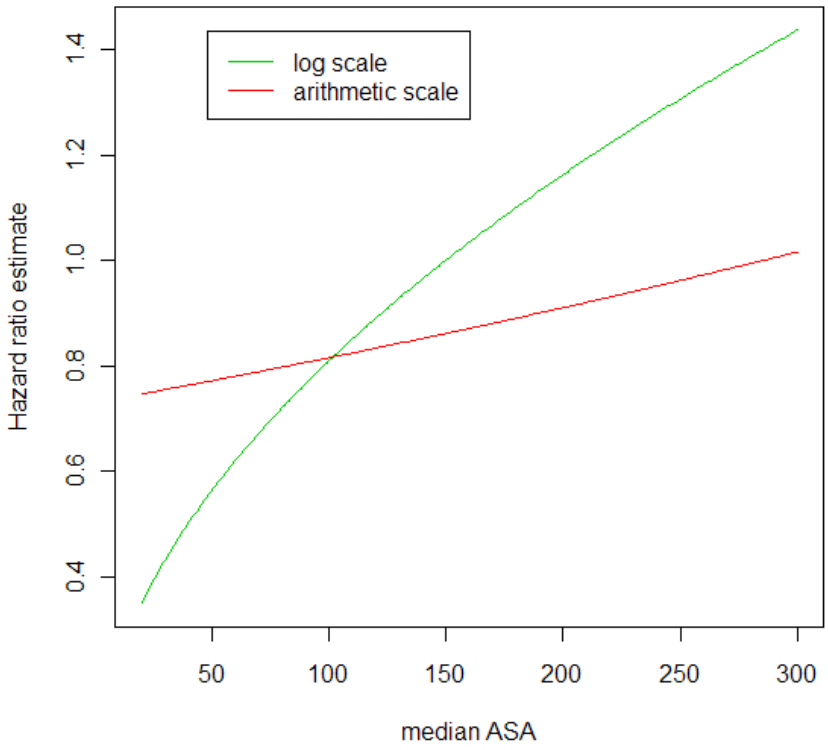
		US		Non-US	
Subgroup	**Treatment**	**N**	**Events**	**N**	**Events**
ASA info missing	clopidogrel	41	3	216	41
ASA info missing	ticagrelor	31	6	220	35
1 day ASA loading dose only	clopidogrel	34	11	275	121
1 day ASA loading dose only	ticagrelor	46	17	314	109
ASA<=100 mg	clopidogrel	263	24	7443	699
ASA<=100 mg	ticagrelor	284	19	7449	546
100mg<ASA<300mg	clopidogrel	16	2	511	63
100mg<ASA<300mg	ticagrelor	22	2	503	62
ASA>=300mg	clopidogrel	352	27	140	23
ASA>=300mg	ticagrelor	324	40	140	28

Figure 4 Forest plot on ASA subgroups by US and non-US



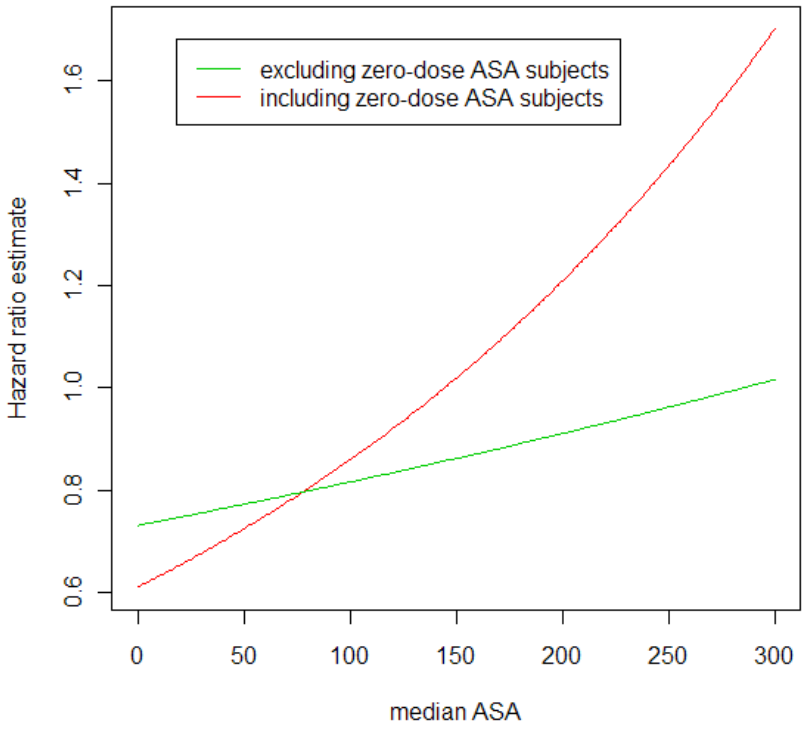
The sponsor presented sensitivity analyses by including the subjects who had only ASA loading dose or had missing information on ASA. However, since zero-dose ASA was included in the model, the analyses utilized arithmetic scale instead of logarithmic scale. This is in contrast to all other models in the sponsor's analyses in which the log scale was always used for ASA. As an example, the reviewer fit the original model using both the log scale and the arithmetic scale. The results are shown in Figure 5 and the models under two scales are very different. In this reviewer's opinion, using log scale seems to be a better approach. As mentioned in the primary review, there were subjects with extreme high median ASA values which may be a result of recording error. This can be managed by using the log scale for the median ASA.

Figure 5 Comparison of models under log scale and arithmetic scale



The reviewer also compared the models under arithmetic scale by either including or excluding the subjects with no ASA or only loading dose ASA. These subjects appear to have quite a large impact on the model (
Figure **6**). The relationship between hazard ratio and ASA appears to be strengthened by including those subjects who had no ASA or only the loading dose. However, both subgroups (subjects with missing ASA information and subjects who took only ASA loading dose) in US went in the wrong direction. This is contradictory to what the model suggests

Figure 6 ASA models under arithmetic scale



In essence, the subjects who had missing ASA information or who had only one day of loading dose on ASA should be taken into consideration. However, the sensitivity analyses presented by the sponsor during the AC remain problematic. As there is no satisfactory modeling for including all the data, the subgroup analysis shown in Figure 4 again casts doubts about the ASA hypothesis.

3. Other factors

The reviewer further examined some baseline characteristics by those ASA subgroups (Table 6 and Table 7 in Appendix). The selected baseline characteristics are all considerably imbalanced between US and non US subjects. Most of the selected baseline characteristics do not show much difference across ASA subgroups. Interestingly, it appears that higher dose ASA groups had higher percentage of subjects went through early PCI (highlighted in bold in Table 7). However, the indicator of early PCI alone does not appear to have a significant interaction with treatment.

The reviewer included some additional subgroups in Figure 7 and Figure 8.

Figure 7 Subgroup analysis (1)

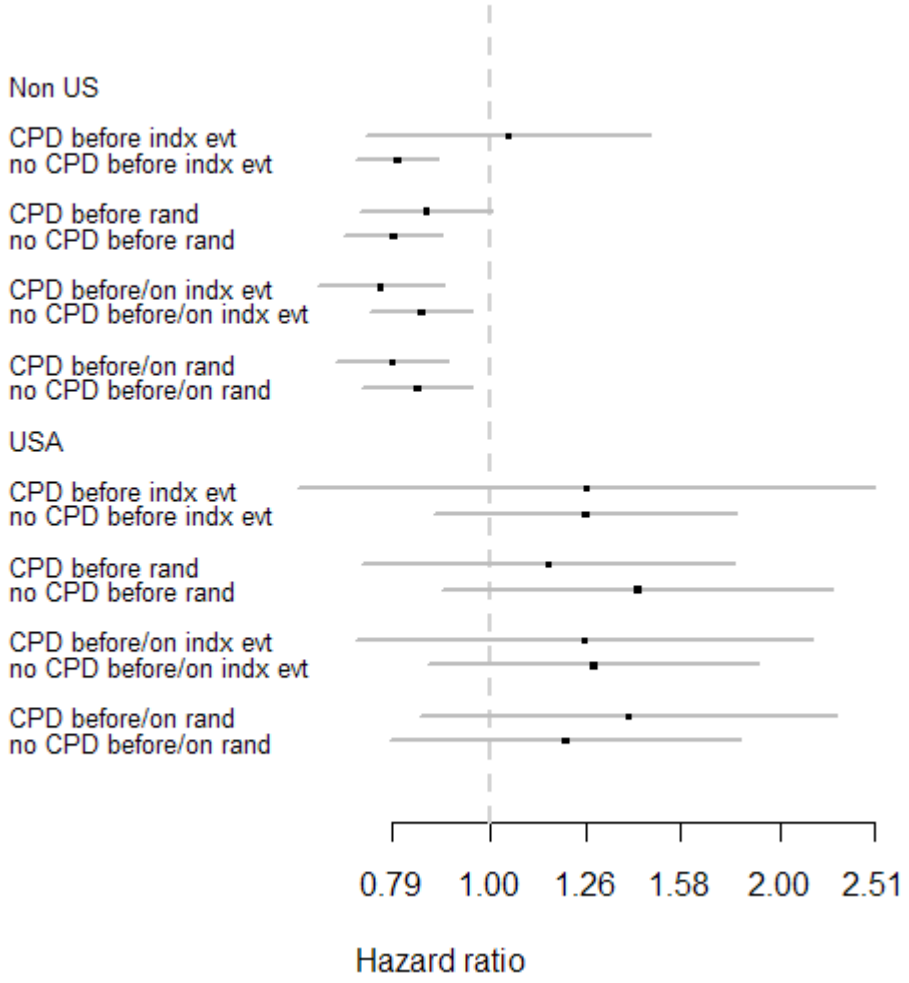
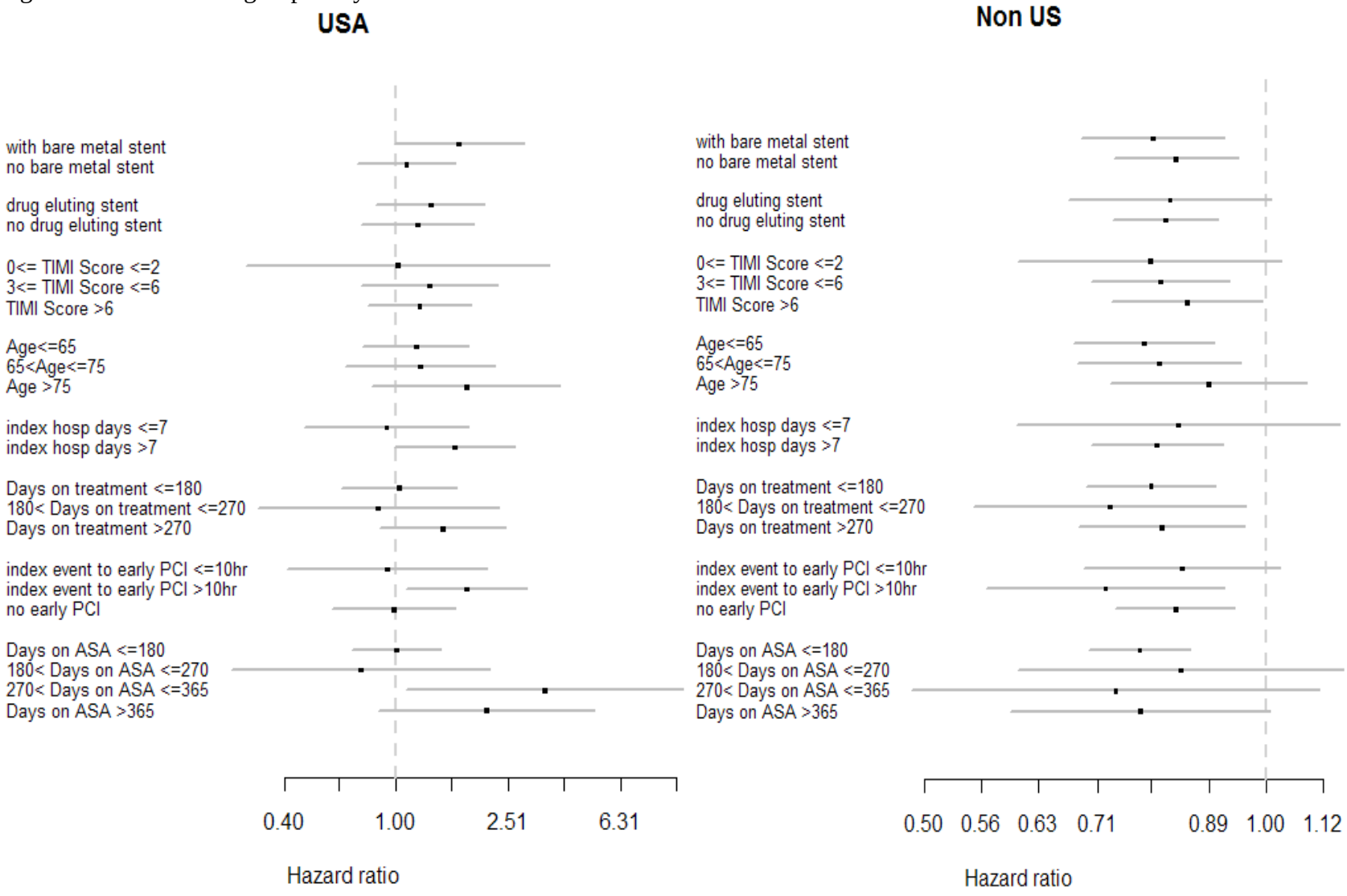


Figure 8 Additional subgroup analyses



4. Other analyses

To address the concern of lost to follow up, the sponsor performed additional sensitivity analyses. There were 1661 subjects (849 subjects in ticagrelor and 812 subjects in clopidogrel) who did not have the complete CV follow up. A subject with complete CV follow up was defined as a subject who died, or had a primary event before the scheduled final visit (the date randomized plus 365, 270 or 180 days depending on the randomization date) or reached scheduled final visit without a primary event.

For each subject who did not have complete CV follow up, the sponsor estimated the individual probability of observing a non-fatal CV event given that the subject survived up to the censoring time point. This was calculated by using the overall Kaplan-Meier estimate for non-fatal CV event and the Kaplan-Meier estimate at the censoring time point. The total number of missing CV events was then computed by summing the probabilities over all subjects who did not have complete CV follow up.

A simple approximation was used in calculating the new hazard ratio estimate and corresponding confidence interval if including the missing CV events (Table 5). By assigning different number of missing events to treatment groups, the potential influence of the subjects without complete CV follow up on the overall efficacy results was examined. It is reassuring to see that the overall efficacy result remains consistent in various scenarios. The reviewer verified the sensitivity analyses. The new hazard ratios calculated by the sponsor were in fact approximated by relative risk.

Table 5 Sensitivity Analysis on Incomplete CV Follow Up

new event in ticagrelor	new event in clopidogrel	Relative risk	overall relative risk	95% CI
40	20	1.9	0.87	(0.80,0.95)
60	0	infinity	0.91	(0.83,0.99)
80	20	3.8	0.91	(0.83,0.99)
100	0	infinity	0.95	(0.87,1.03)

Appendix

Table 6 Baseline Characteristics by ASA subgroup and region (1)

Covariates	ASA subgroup	Region	N	Mean	STD	Median
hours from index event to early pci	ASA missing	Non US	81	21.6	54.4	13.2
hours from index event to early pci	ASA missing	USA	12	11.8	7.9	10.1
hours from index event to early pci	ASA loading only	Non US	222	11.5	12.8	8.3
hours from index event to early pci	ASA loading only	USA	31	16.1	8.6	18.6
hours from index event to early pci	ASA<=100mg	Non US	7444	10.4	9.4	6.6
hours from index event to early pci	ASA<=100mg	USA	306	16.5	9.8	17.3
hours from index event to early pci	100mg<ASA<300mg	Non US	483	10.1	9.6	5.7
hours from index event to early pci	100mg<ASA<300mg	USA	26	15.3	10.8	13.0
hours from index event to early pci	ASA>=300mg	Non US	158	12.5	10.0	8.4
hours from index event to early pci	ASA>=300mg	USA	491	16.6	10.9	16.2
hours from index event to first dose study drug	ASA missing	Non US	288	19.6	39.5	15.8
hours from index event to first dose study drug	ASA missing	USA	16	58.6	96.7	17.5
hours from index event to first dose study drug	ASA loading only	Non US	588	12.5	15.5	9.6
hours from index event to first dose study drug	ASA loading only	USA	79	18.5	18.2	18.2
hours from index event to first dose study drug	ASA<=100mg	Non US	14885	12.6	22.0	10.8
hours from index event to first dose study drug	ASA<=100mg	USA	546	28.7	88.8	17.1
hours from index event to first dose study drug	100mg<ASA<300mg	Non US	1014	12.3	11.6	9.3
hours from index event to first dose study drug	100mg<ASA<300mg	USA	38	16.7	10.2	16.3
hours from index event to first dose study drug	ASA>=300mg	Non US	280	14.6	33.7	10.7
hours from index event to first dose study drug	ASA>=300mg	USA	676	24.0	72.3	16.3
hours from index event to randomization	ASA missing	Non US	428	14.6	24.6	13.9
hours from index event to randomization	ASA missing	USA	72	14.1	8.6	14.3
hours from index event to randomization	ASA loading only	Non US	589	11.5	10.5	9.1
hours from index event to randomization	ASA loading only	USA	79	16.3	10.0	16.9
hours from index event to randomization	ASA<=100mg	Non US	14891	11.5	8.1	10.1
hours from index event to randomization	ASA<=100mg	USA	547	14.7	8.3	15.3
hours from index event to randomization	100mg<ASA<300mg	Non US	1014	11.0	8.2	8.5
hours from index event to randomization	100mg<ASA<300mg	USA	38	15.6	10.0	14.7
hours from index event to randomization	ASA>=300mg	Non US	280	11.4	7.6	9.6
hours from index event to	ASA>=300mg	USA	676	14.6	8.7	15.0

randomization						
weight	ASA missing	Non US	416	76.4	14.2	75.0
weight	ASA missing	USA	72	91.4	24.8	88.0
weight	ASA loading only	Non US	580	78.9	15.0	79.0
weight	ASA loading only	USA	79	86.7	21.1	85.0
weight	ASA<=100mg	Non US	14868	80.2	15.3	80.0
weight	ASA<=100mg	USA	545	88.9	20.7	86.0
weight	100mg<ASA<300mg	Non US	1014	75.6	15.2	75.0
weight	100mg<ASA<300mg	USA	38	85.7	20.7	84.5
weight	ASA>=300mg	Non US	280	76.0	16.7	75.5
weight	ASA>=300mg	USA	676	89.8	19.9	88.0

Table 7 Baseline Characteristics by ASA subgroup and region (2)

ASA subroup	Region	Total N	Covariates		N	%
ASA missing	Non US	436	bare metal stent	Yes	88	20.2
ASA missing	USA	72	bare metal stent	Yes	5	6.9
ASA loading only	Non US	589	bare metal stent	Yes	189	32.1
ASA loading only	USA	80	bare metal stent	Yes	17	21.3
ASA<=100mg	Non US	14892	bare metal stent	Yes	7091	47.6
ASA<=100mg	USA	547	bare metal stent	Yes	101	18.5
100mg<ASA<300mg	Non US	1014	bare metal stent	Yes	481	47.4
100mg<ASA<300mg	USA	38	bare metal stent	Yes	11	28.9
ASA>=300mg	Non US	280	bare metal stent	Yes	144	51.4
ASA>=300mg	USA	676	bare metal stent	Yes	197	29.1
ASA missing	USA	72	black	Yes	8	11.1
ASA loading only	USA	80	black	Yes	13	16.3
ASA<=100mg	Non US	14892	black	Yes	75	0.5
ASA<=100mg	USA	547	black	Yes	50	9.1
100mg<ASA<300mg	Non US	1014	black	Yes	14	1.4
100mg<ASA<300mg	USA	38	black	Yes	4	10.5
ASA>=300mg	Non US	280	black	Yes	3	1.1
ASA>=300mg	USA	676	black	Yes	62	9.2
ASA missing	Non US	436	drug eluting stent	Yes	50	11.5
ASA missing	USA	72	drug eluting stent	Yes	9	12.5
ASA loading only	Non US	589	drug eluting stent	Yes	75	12.7
ASA loading only	USA	80	drug eluting stent	Yes	17	21.3
ASA<=100mg	Non US	14892	drug eluting stent	Yes	2933	19.7
ASA<=100mg	USA	547	drug eluting stent	Yes	244	44.6
100mg<ASA<300mg	Non US	1014	drug eluting stent	Yes	191	18.8
100mg<ASA<300mg	USA	38	drug eluting stent	Yes	23	60.5
ASA>=300mg	Non US	280	drug eluting stent	Yes	90	32.1
ASA>=300mg	USA	676	drug eluting stent	Yes	360	53.3
ASA missing	**Non US**	**431**	**early PCI**	**Yes**	**81**	**18.8**
ASA missing	**USA**	**72**	**early PCI**	**Yes**	**12**	**16.7**
ASA loading only	**Non US**	**589**	**early PCI**	**Yes**	**222**	**37.7**
ASA loading only	**USA**	**79**	**early PCI**	**Yes**	**31**	**39.2**
ASA<=100mg	**Non US**	**14892**	**early PCI**	**Yes**	**7444**	**50.0**
ASA<=100mg	**USA**	**547**	**early PCI**	**Yes**	**306**	**55.9**

100mg<ASA<300mg	**Non US**	**1014**	**early PCI**	**Yes**	**483**	**47.6**
100mg<ASA<300mg	**USA**	**38**	**early PCI**	**Yes**	**26**	**68.4**
ASA>=300mg	**Non US**	**280**	**early PCI**	**Yes**	**158**	**56.4**
ASA>=300mg	**USA**	**676**	**early PCI**	**Yes**	**491**	**72.6**
ASA missing	Non US	436	GPI during Index Hosp	Yes	53	12.2
ASA missing	USA	72	GPI during Index Hosp	Yes	22	30.6
ASA loading only	Non US	589	GPI during Index Hosp	Yes	159	27.0
ASA loading only	USA	80	GPI during Index Hosp	Yes	39	48.8
ASA<=100mg	Non US	14892	GPI during Index Hosp	Yes	3742	25.1
ASA<=100mg	USA	547	GPI during Index Hosp	Yes	243	44.4
100mg<ASA<300mg	Non US	1014	GPI during Index Hosp	Yes	280	27.6
100mg<ASA<300mg	USA	38	GPI during Index Hosp	Yes	21	55.3
ASA>=300mg	Non US	280	GPI during Index Hosp	Yes	119	42.5
ASA>=300mg	USA	676	GPI during Index Hosp	Yes	384	56.8
ASA missing	Non US	436	history of diabetes	Yes	101	23.2
ASA missing	USA	72	history of diabetes	Yes	19	26.4
ASA loading only	Non US	589	history of diabetes	Yes	144	24.4
ASA loading only	USA	80	history of diabetes	Yes	25	31.3
ASA<=100mg	Non US	14892	history of diabetes	Yes	3547	23.8
ASA<=100mg	USA	547	history of diabetes	Yes	186	34.0
100mg<ASA<300mg	Non US	1014	history of diabetes	Yes	320	31.6
100mg<ASA<300mg	USA	38	history of diabetes	Yes	13	34.2
ASA>=300mg	Non US	280	history of diabetes	Yes	78	27.9
ASA>=300mg	USA	676	history of diabetes	Yes	229	33.9
ASA missing	Non US	436	history of MI	Yes	92	21.1
ASA missing	USA	72	history of MI	Yes	14	19.4
ASA loading only	Non US	589	history of MI	Yes	113	19.2
ASA loading only	USA	80	history of MI	Yes	21	26.3
ASA<=100mg	Non US	14892	history of MI	Yes	2997	20.1
ASA<=100mg	USA	547	history of MI	Yes	148	27.1
100mg<ASA<300mg	Non US	1014	history of MI	Yes	190	18.7
100mg<ASA<300mg	USA	38	history of MI	Yes	9	23.7
ASA>=300mg	Non US	280	history of MI	Yes	45	16.1
ASA>=300mg	USA	676	history of MI	Yes	195	28.8
ASA missing	Non US	412	index event characteristics	UA	93	22.6
ASA missing	USA	71	index event characteristics	UA	8	11.3
ASA missing	Non US	412	index event characteristics	NSTEMI	176	42.7
ASA missing	USA	71	index event characteristics	NSTEMI	37	52.1
ASA missing	Non US	412	index event characteristics	STEMI	99	24.0
ASA missing	USA	71	index event characteristics	STEMI	8	11.3
ASA missing	Non US	412	index event characteristics	Other	44	10.7
ASA missing	USA	71	index event characteristics	Other	18	25.4
ASA loading only	Non US	582	index event characteristics	UA	80	13.7
ASA loading only	USA	79	index event characteristics	UA	6	7.6
ASA loading only	Non US	582	index event characteristics	NSTEMI	231	39.7
ASA loading only	USA	79	index event characteristics	NSTEMI	48	60.8
ASA loading only	Non US	582	index event characteristics	STEMI	186	32.0
ASA loading only	USA	79	index event characteristics	STEMI	12	15.2
ASA loading only	Non US	582	index event characteristics	Other	85	14.6
ASA loading only	USA	79	index event characteristics	Other	13	16.5

ASA<=100mg	Non US	14885	index event characteristics	UA	2557	17.2
ASA<=100mg	USA	547	index event characteristics	UA	62	11.3
ASA<=100mg	Non US	14885	index event characteristics	NSTEMI	6142	41.3
ASA<=100mg	USA	547	index event characteristics	NSTEMI	384	70.2
ASA<=100mg	Non US	14885	index event characteristics	STEMI	5957	40.0
ASA<=100mg	USA	547	index event characteristics	STEMI	71	13.0
ASA<=100mg	Non US	14885	index event characteristics	Other	229	1.5
ASA<=100mg	USA	547	index event characteristics	Other	30	5.5
100mg<ASA<300mg	Non US	1014	index event characteristics	UA	209	20.6
100mg<ASA<300mg	USA	38	index event characteristics	UA	4	10.5
100mg<ASA<300mg	Non US	1014	index event characteristics	NSTEMI	353	34.8
100mg<ASA<300mg	USA	38	index event characteristics	NSTEMI	26	68.4
100mg<ASA<300mg	Non US	1014	index event characteristics	STEMI	432	42.6
100mg<ASA<300mg	USA	38	index event characteristics	STEMI	7	18.4
100mg<ASA<300mg	Non US	1014	index event characteristics	Other	20	2.0
100mg<ASA<300mg	USA	38	index event characteristics	Other	1	2.6
ASA>=300mg	Non US	278	index event characteristics	UA	31	11.2
ASA>=300mg	USA	676	index event characteristics	UA	62	9.2
ASA>=300mg	Non US	278	index event characteristics	NSTEMI	104	37.4
ASA>=300mg	USA	676	index event characteristics	NSTEMI	454	67.2
ASA>=300mg	Non US	278	index event characteristics	STEMI	130	46.8
ASA>=300mg	USA	676	index event characteristics	STEMI	124	18.3
ASA>=300mg	Non US	278	index event characteristics	Other	13	4.7
ASA>=300mg	USA	676	index event characteristics	Other	36	5.3
ASA missing	Non US	436	intended invasive management at rand	Yes	268	61.5
ASA missing	USA	72	intended invasive management at rand	Yes	67	93.1
ASA loading only	Non US	589	intended invasive management at rand	Yes	487	82.7
ASA loading only	USA	80	intended invasive management at rand	Yes	78	97.5
ASA<=100mg	Non US	14892	intended invasive management at rand	Yes	10349	69.5
ASA<=100mg	USA	547	intended invasive management at rand	Yes	493	90.1
100mg<ASA<300mg	Non US	1014	intended invasive management at rand	Yes	749	73.9
100mg<ASA<300mg	USA	38	intended invasive management at rand	Yes	37	97.4
ASA>=300mg	Non US	280	intended invasive management at rand	Yes	232	82.9
ASA>=300mg	USA	676	intended invasive management at rand	Yes	648	95.9
ASA missing	Non US	436	prior CABG	Yes	28	6.4
ASA missing	USA	72	prior CABG	Yes	8	11.1
ASA loading only	Non US	589	prior CABG	Yes	26	4.4
ASA loading only	USA	80	prior CABG	Yes	8	10.0
ASA<=100mg	Non US	14892	prior CABG	Yes	748	5.0
ASA<=100mg	USA	547	prior CABG	Yes	100	18.3
100mg<ASA<300mg	Non US	1014	prior CABG	Yes	52	5.1
100mg<ASA<300mg	USA	38	prior CABG	Yes	8	21.1

ASA>=300mg	Non US	280	prior CABG	Yes	16	5.7
ASA>=300mg	USA	676	prior CABG	Yes	112	16.6
ASA missing	Non US	436	prior PCI	Yes	62	14.2
ASA missing	USA	72	prior PCI	Yes	16	22.2
ASA loading only	Non US	589	prior PCI	Yes	85	14.4
ASA loading only	USA	80	prior PCI	Yes	23	28.8
ASA<=100mg	Non US	14892	prior PCI	Yes	1797	12.1
ASA<=100mg	USA	547	prior PCI	Yes	153	28.0
100mg<ASA<300mg	Non US	1014	prior PCI	Yes	96	9.5
100mg<ASA<300mg	USA	38	prior PCI	Yes	11	28.9
ASA>=300mg	Non US	280	prior PCI	Yes	37	13.2
ASA>=300mg	USA	676	prior PCI	Yes	212	31.4
ASA missing	Non US	436	use of ACE at rand	Yes	212	48.6
ASA missing	USA	72	use of ACE at rand	Yes	33	45.8
ASA loading only	Non US	589	use of ACE at rand	Yes	318	54.0
ASA loading only	USA	80	use of ACE at rand	Yes	29	36.3
ASA<=100mg	Non US	14892	use of ACE at rand	Yes	8635	58.0
ASA<=100mg	USA	547	use of ACE at rand	Yes	267	48.8
100mg<ASA<300mg	Non US	1014	use of ACE at rand	Yes	529	52.2
100mg<ASA<300mg	USA	38	use of ACE at rand	Yes	19	50.0
ASA>=300mg	Non US	280	use of ACE at rand	Yes	153	54.6
ASA>=300mg	USA	676	use of ACE at rand	Yes	327	48.4
ASA missing	Non US	436	use of ARB at rand	Yes	45	10.3
ASA missing	USA	72	use of ARB at rand	Yes	5	6.9
ASA loading only	Non US	589	use of ARB at rand	Yes	51	8.7
ASA loading only	USA	80	use of ARB at rand	Yes	11	13.8
ASA<=100mg	Non US	14892	use of ARB at rand	Yes	1256	8.4
ASA<=100mg	USA	547	use of ARB at rand	Yes	67	12.2
100mg<ASA<300mg	Non US	1014	use of ARB at rand	Yes	87	8.6
100mg<ASA<300mg	USA	38	use of ARB at rand	Yes	6	15.8
ASA>=300mg	Non US	280	use of ARB at rand	Yes	21	7.5
ASA>=300mg	USA	676	use of ARB at rand	Yes	94	13.9
ASA missing	Non US	436	use of beta blocker at rand	Yes	293	67.2
ASA missing	USA	72	use of beta blocker at rand	Yes	55	76.4
ASA loading only	Non US	589	use of beta blocker at rand	Yes	430	73.0
ASA loading only	USA	80	use of beta blocker at rand	Yes	69	86.3
ASA<=100mg	Non US	14892	use of beta blocker at rand	Yes	11219	75.3
ASA<=100mg	USA	547	use of beta blocker at rand	Yes	482	88.1
100mg<ASA<300mg	Non US	1014	use of beta blocker at rand	Yes	708	69.8
100mg<ASA<300mg	USA	38	use of beta blocker at rand	Yes	33	86.8
ASA>=300mg	Non US	280	use of beta blocker at rand	Yes	184	65.7
ASA>=300mg	USA	676	use of beta blocker at rand	Yes	587	86.8

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

JIALU ZHANG
08/31/2010

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08/31/2010
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-433 / N_000
Drug Name:	Brilinta (ticagrelor)
Indication(s):	Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)
Applicant:	AstraZeneca
Date(s):	Date of Document: November 13, 2009
	PDUFA due date: September 13, 2010
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph. D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Robert Fiorentino, M.D.
Project Manager:	Michael Monteleone, Pharm.D.
Keywords:	Regional difference, aspirin

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The single phase III trial PLATO randomized 18,624 subjects to compare the efficacy and safety of ticagrelor 90 mg with clopidogrel 75 mg in the prevention of CV death, MI, and stroke in patients with non-ST or ST elevation ACS. One major issue is the regional difference observed between US and non-US. The study reported a hazard ratio estimate of 0.84 [95% CI (0.77, 0.92)] for the overall population favoring ticagrelor. However, for US the hazard ratio estimate was 1.27 [95% CI (0.92, 1.75)], which suggested a 27% greater risk of the clinical event with ticagrelor relative to clopidogrel. The magnitude of this point estimate of hazard ratio in US is quite concerning, especially since US had the second largest enrollment among 43 countries in this trial. The reviewer performed extensive analyses examining many factors or covariates but was not able to find a definitive explanation for the regional difference. However, the US population appeared different from the rest of the world in a number of ways based on the reviewer's analyses even though they did not seem to explain the regional difference. If US population differs sufficiently from the rest of the world, a US trial may be needed to further evaluate the efficacy of ticagrelor in US subjects.

Although play of chance can never be ruled out as a possible explanation, it seems to be a little overstretching, given the magnitude of the difference in hazard ratio estimates between US and non-US. The sponsor attributed the concurrent aspirin (ASA) use to the regional difference if it is not a play of chance. However, even though ASA seems to be the biggest contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the explanatory model used by the sponsor for explaining the regional difference does not appear robust since very few subjects outside US took high dose ASA. Thus, the interpretability of the results that the ASA dose may explain the regional difference remains very much uncertain.

1.2 Brief Overview of Clinical Studies

The application consists of a single phase III trial, PLATO. It was a randomized, double-blind, double-dummy, parallel group, international, multicenter study, compared the efficacy and safety of ticagrelor 90 mg bid with clopidogrel 75 mg od in the prevention of CV death, MI, and stroke in patients with non-ST or ST elevation ACS. The duration of treatment ranged from 6 to 12 months with planned study completion at 6, 9 and 12 months depending on date the patients entered the study.

The primary endpoint is time to composite endpoint of CV death, stroke and MI (excluding silent MI). The trial randomized 18624 subjects. A total of 1878 events were included in the primary analysis. The hazard ratio estimate for overall population is 0.84 [95% CI (0.77, 0.92)].

1.3 Statistical Issues and Findings

The big issue in this application is the regional difference observed between US and non-US. The magnitude of the point estimate of hazard ratio in US is quite concerning. The reviewer performed extensive analyses to search for potential explanations.

The hazard ratio estimates in US population stayed consistently above 1 throughout the trial. The probability of observing such results were calculated in several ways assuming that the true hazard ratio is 0.84. If taking the sample size as well as the magnitude of difference between the hazard ratio estimates into account, although play of chance can never be excluded from a possible explanation, it does seem to be a little overstretching if we observe a hazard ratio estimate of 1.27 in a country enrolled 1413 subjects while the rest of the world shows a clear benefit from ticagrelor (HR=0.84).

The sponsor attributed the concurrent ASA dose to the regional difference if it is not a play of chance. However, their finding remains questionable. First of all, most subjects taking 325 mg high dose ASA were from US. Use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US). Secondly, even though ASA seems to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. The Cox proportional hazards model appeared quite sensitive to the high ASA subjects in non-US region. The model also seemed to be sensitive to whether or not the first day ASA loading dose is included.

The reviewer was also unsuccessful in finding other potential covariates that may explain the regional difference between US and non-US. On the other hand, US population differed from non-US population in a number of ways even though they did seem to explain the regional difference. For example, it took much longer time on average for US subjects to receive first dose of study drug since occurrence of index. More US subjects enrolled in the trial were NSTEMI patients compared to the rest of the world. Other factors include prior history of PCI or MI, number of subjects who went through early PCI, pre-index event antiplatelet therapy, beta blocker usage at randomization, planned treatment approach at randomization, GPI during index hospitalization, and many more.

2. INTRODUCTION

2.1 Overview

The application consists of a single phase III trial, PLATO. It is a randomized, double-blind, double-dummy, parallel group, international, multicentre trial which compared the efficacy and safety of ticagrelor 90 mg bid with clopidogrel 75 mg od for the prevention of CV death, MI, and

stroke in patients with non-ST or ST elevation ACS. The duration of treatment ranged from 6 to 12 months with planned study completion at 6, 9 and 12 months depending on date the patients entered the study (e.g., patients that entered towards the end of the enrolment period would have the shortest duration of treatment).

The primary endpoint is time to composite endpoint of CV death, stroke and MI (excluding silent MI). The trial randomized 18,624 subjects. A total of 1,878 events were included in the primary analysis. The hazard ratio estimate for overall population is 0.84 [95% CI (0.77, 0.92)].

2.2 Data Sources

The sponsor's electronic data is stored under the directory \\Cdsesub1\evsprod\NDA022433\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets\.

The sponsor also submitted an updated aspirin data on June 10, 2010 and it is stored under the directory \\Cdsesub1\evsprod\NDA022433\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets\.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY PLATO

3.1.1.1 Study Objectives

The primary objective is to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with non-ST or ST elevation ACS. The study also assessed the safety and tolerability of ticagrelor compared to clopidogrel.

3.1.1.2 Study Design

The trial is a randomized, double-blind, double-dummy, parallel group, international, multicentre study. A total of 18,624 patients were randomized in a ratio of 1:1 to either ticagrelor group or clopidogrel group. Patients were randomized within 24 hours of the index event to either ticagrelor (N=9333) or clopidogrel (N=9291) against a background ASA therapy. Patients treated with ticagrelor received a loading dose of 180 mg (with an additional 90 mg if PCI occurred >24 hours after randomization) followed by 90 mg bid. Patients treated with clopidogrel received a loading dose of clopidogrel 300 mg (with an additional 300 mg at PCI at the investigator's discretion) followed by 75 mg od.

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary variable is time to first occurrence of any event from composite of CV death, MI, and stroke.

(2) Secondary Efficacy Endpoints

The following secondary efficacy endpoints were analyzed in the order presented using a hierarchical procedure:

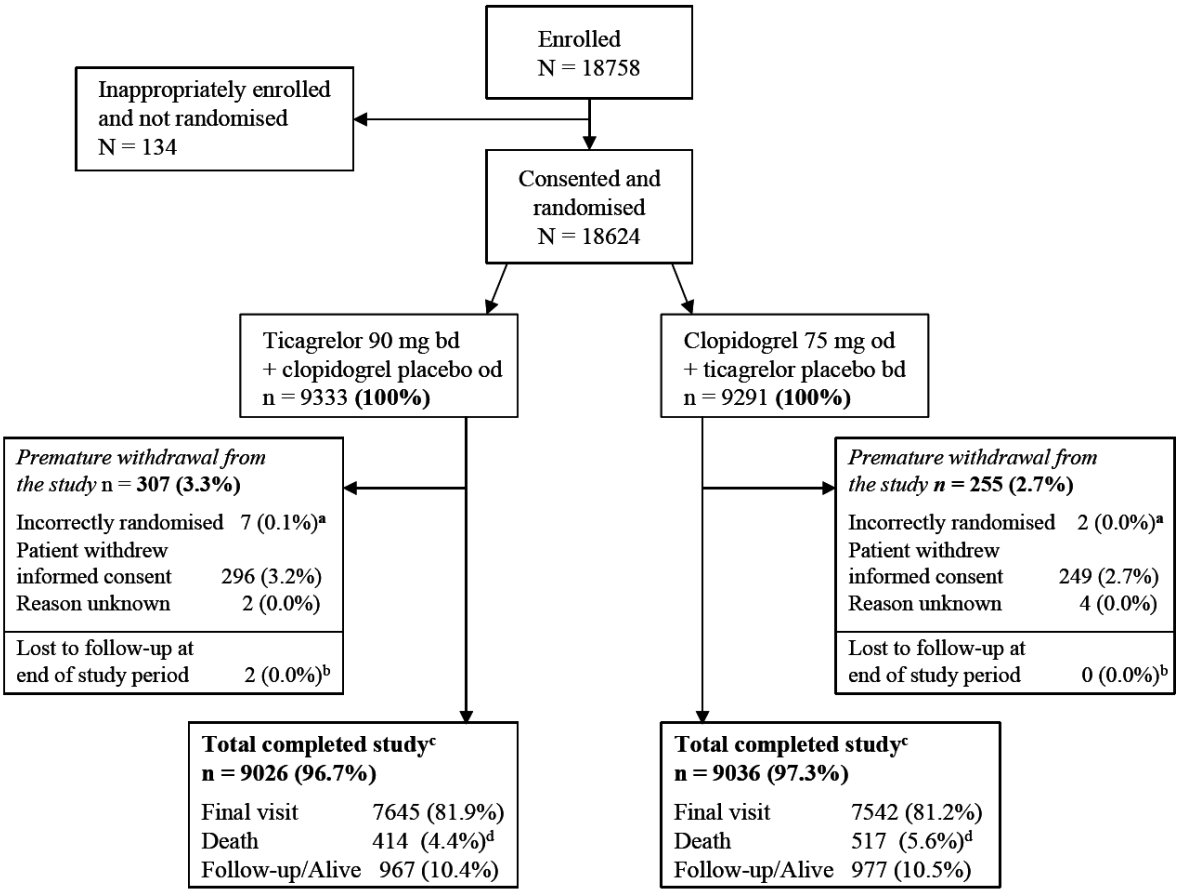
(i) Time to first occurrence of any event from the composite of CV death, MI and stroke for the subgroup of patients with intent for invasive management at randomization
(ii) Time to first occurrence of any event from the composite of all-cause mortality, MI, and stroke
(iii) Time to first occurrence of any event from the composite of CV death, MI (including silent MI), stroke, severe recurrent cardiac ischaemia (SRI), recurrent cardiac ischaemia (RI), transient ischaemic attack (TIA) and other arterial thrombotic events (ATEs)
(iv) Time to first occurrence of each component of the primary composite efficacy endpoint individually in the order of MI, CV death and then stroke
(v) Time to occurrence of all-cause mortality.

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

In total, 18758 subjects enrolled into the study from 43 countries in North America, South America and Central America, Asia and Australia, as well as Europe, the Middle East, and Africa. 18624 subjects were randomized. The first patient enrolled on 11 October 2006 and the last patient completed the study on 27 February 2009.

Patient disposition was similar across the ticagrelor and clopidogrel treatment groups.

Figure 1 Patient disposition



[Source: Figure 5 in sponsor's clinical study report on page 90]

Table 1 summarizes demographic and baseline characteristics of study subjects. There were more male than female subjects in the study. Majority of subjects were Caucasian.

Table 1 Demographic and baseline characteristics at enrollment

Characteristic	Statistic or category	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	Total N=18624
Age (years)	N	9332	9290	18622
	Mean (SD)	62.1 (11.21)	62.3 (11.21)	62.2 (11.21)
Sex	Total	9333	9291	18624
	Male	6678 (71.6%)	6658 (71.7%)	13336 (71.6%)
	Female	2655 (28.4%)	2633 (28.3%)	5288 (28.4%)
Race	Total	9332	9291	18623
	Caucasian	8566 (91.8%)	8511 (91.6%)	17077 (91.7%)
	Black	115 (1.2%)	114 (1.2%)	229 (1.2%)
	Asian	542 (5.8%)	554 (6.0%)	1096 (5.9%)
	Other	109 (1.2%)	112 (1.2%)	221 (1.2%)
	Unknown	1 (0.0%)	0	1 (0.0%)
Weight (kg)	N	9305	9263	18568
	Mean (SD)	80.6 (15.97)	80.3 (16.01)	80.4 (15.99)
BMI (kg/m2)	Total	9291	9241	18532
		27.9 (4.68)	27.8 (4.73)	27.9 (4.70)
Smoking status	Total	9325	9285	18610
	Non-smoker	3592 (38.5%)	3664 (39.5%)	7256 (39.0%)
	Ex-smoker	2373 (25.4%)	2303 (24.8%)	4676 (25.1%)
	Habitual smoker	3360 (36.0%)	3318 (35.7%)	6678 (35.9%)

[Source: Sponsor's clinical study report, confirmed by the reviewer]

3.1.1.5 Sponsor's Primary Efficacy Results

The primary analysis compared the time from randomization to the first occurrence of any event in the composite endpoint using the Cox proportional hazards model with a factor for treatment group. All efficacy variables were analyzed using the full analysis set.

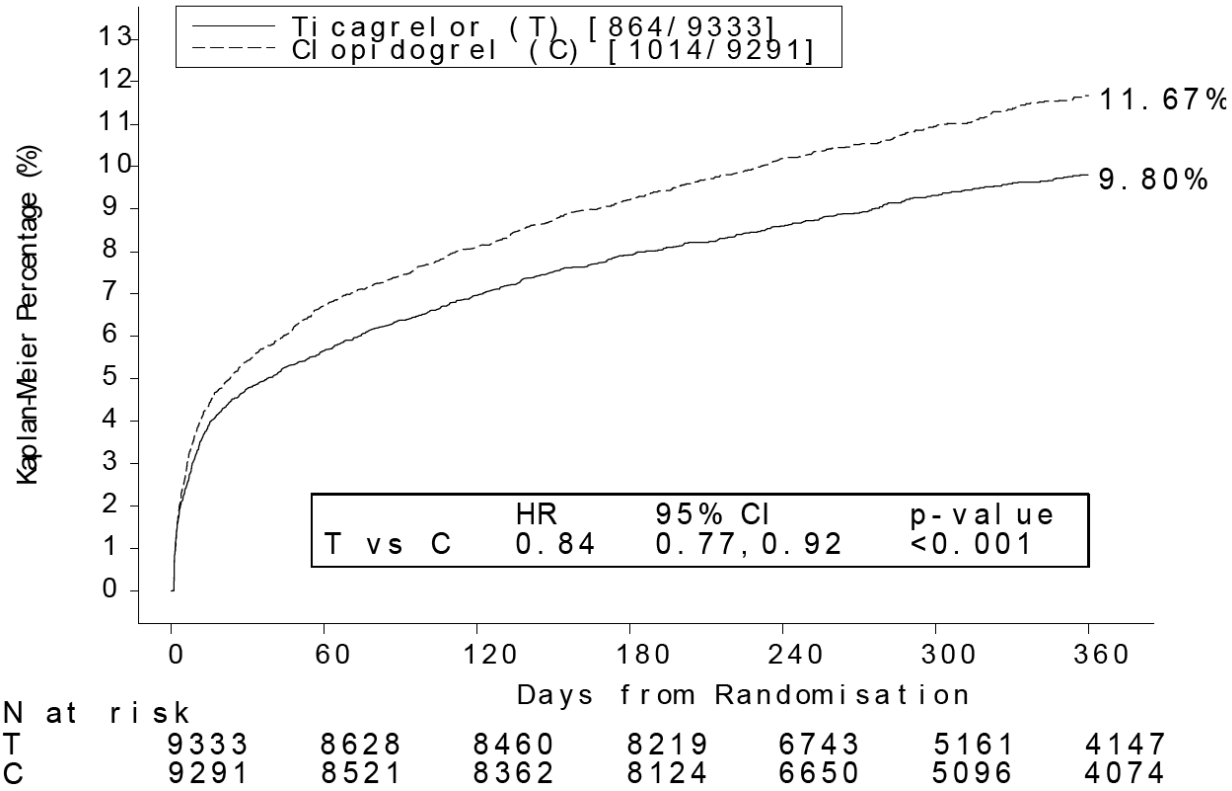
One interim analysis of the primary composite efficacy endpoint was performed when approximately 1200 adjudicated events (2/3rds of the total target number of 1780 events) were observed. The Peto-Haybittle group sequential boundary was used with a critical p-value of 0.001. The critical p-value at the final analysis was 0.0497.

Table 2 Primary efficacy endpoint and its components

Characteristic	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291	Hazard ratio (95% CI)	p-value
Composite of CV Death/MI (excl. silent MI)/Stroke	864 (9.3%)	1014 (10.9%)	0.84 (0.77, 0.92)	0.0003
CV death	353 (3.8%)	442 (4.8%)	0.79 (0.69, 0.91)	0.0013
MI (excl. silent MI)	504 (5.4%)	593 (6.4%)	0.84 (0.75, 0.95)	0.0045
Stroke	125 (1.3%)	106 (1.1%)	1.17 (0.91, 1.52)	0.2249

[Source: Sponsor's results, confirmed by the reviewer]

Figure 2 Kaplan-Meier Curve of the primary efficacy endpoint



[Source: Figure 13 from sponsor's clinical study report]

3.1.1.6 Sponsor's Secondary Efficacy Results

The results of secondary analyses are shown in Table 3. In subjects intended to have invasive procedures (coronary angiography followed by PCI and CABG if indicated), ticagrelor treatment was superior in the primary composite endpoint, compared to clopidogrel. Ticagrelor showed a statistically significant reduction in events for the composite of all-cause mortality, MI, and stroke compared to clopidogrel. Ticagrelor also demonstrated superiority on the composite of CV death, total MI (including silent MI), stroke, SRI and RI, TIA, and other ATEs.

Ticagrelor also showed statistical significance to clopidogrel in primary endpoint components MI (excluding silent MI) and CV death. No statistically significant difference was observed between ticagrelor and clopidogrel for the efficacy component stroke. Thus further formal testing of secondary endpoints was stopped. However, ticagrelor did show a nominally significant reduction in all-cause mortality compared to clopidogrel (nominal p-value=0.0003).

Table 3 Summary of Secondary Endpoints in PLATO

Secondary objective	Ticagrelor 90 mg bd (N = 9333)	Clopidogrel 75 mg od (N = 9291)	Hazard ratio (95% CI)	p-value
(i) Composite of CV death/MI (excl. silent MI)/stroke - intent to invasively manage	569 (8.5%)	668 (10.0%)	0.84 (0.75, 0.94)	0.0025
(ii) Composite of all-cause mortality/MI (excl. silent MI)/stroke	901 (9.7%)	1065 (11.5%)	0.84 (0.77, 0.92)	0.0001
(iii) Composite of CV Death/Total MI/Stroke /SRI/RI/TIA/Other ATE	1290 (13.8%)	1456 (15.7%)	0.88 (0.81, 0.95)	0.0006
(iv) Each component of primary efficacy endpoint:				
MI (excl. silent MI)	504 (5.4%)	593 (6.4%)	0.84 (0.75, 0.95)	0.0045
CV death	353 (3.8%)	442 (4.8%)	0.79 (0.69, 0.91)	0.0013
Stroke	125 (1.3%)	106 (1.1%)	1.17 (0.91, 1.52)	0.2249
(v) All-cause mortality	399 (4.3%)	506 (5.4%)	0.78 (0.69, 0.89)	0.0003

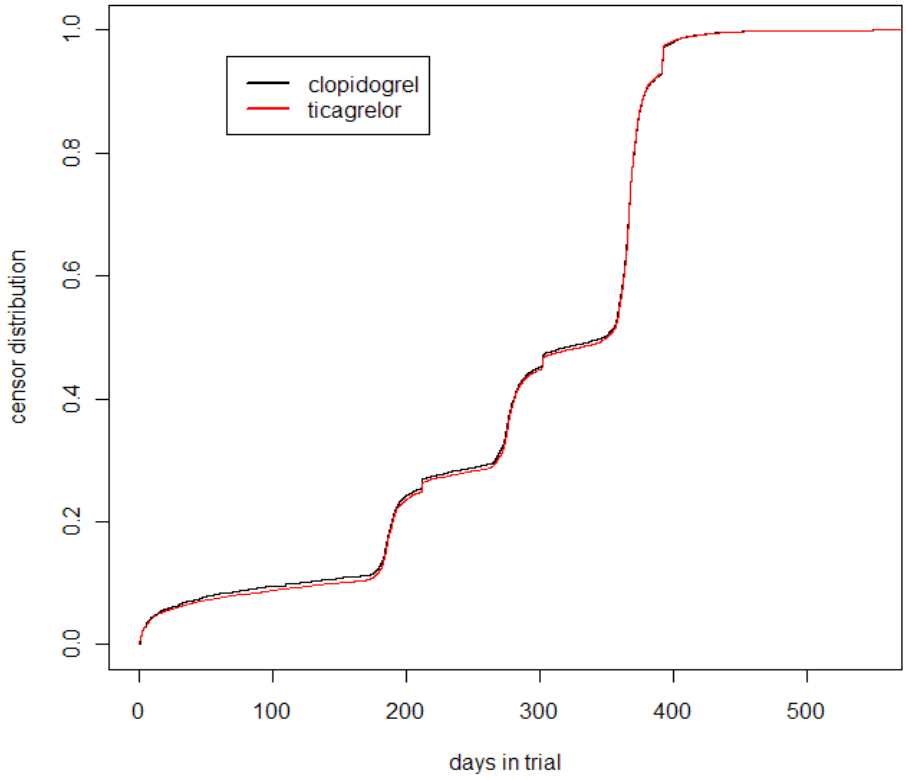
[Source: Sponsor's results, confirmed by the reviewer]

3.1.1.7 Reviewer's Results

During the review, question was brought up with regard to the censoring rules. Subject who discontinued the study early but did not withdraw consent was censored 30 days after the date when the End of Treatment visit should have occurred. In other words, the censoring dates of those subjects were projected. The sponsor clarified that "censoring rules were needed to allow counting events that were discovered following the final patient contact." Figure 3 shows the cumulative distribution of censored subjects; there are three sharp increments during the trial. This is consistent with the fact that majority of subjects finished the treatment within 6-month, 9-month or 12-month periods. The length of the treatment was determined by the time when the subject was enrolled in the study. Subjects that entered towards the end of the enrolment period would have the shortest duration of treatment. Figure 3 also showed three vertical "jumps" in the

middle of the three increments. Those "jumps" represent the patients who had projected censoring dates. The censoring distribution of subjects in clopidogrel group overlaps very well with the censoring distribution of subjects in ticagrelor group. Therefore, although the projected censoring dates may still be a concern, it is reassuring to see that the two groups are well balanced in this aspect.

Figure 3. Censor distribution for all subjects



The reviewer also performed a sensitivity analysis on the primary endpoint. In the sensitivity analysis, subjects no longer have the projected censor dates. Subjects who did not have a primary event were censored at the last real visit. HR estimate came out to be 0.86 with 95% CI (0.78, 0.94) in overall population in the sensitivity analysis. US population had HR=1.21 with 95% CI (0.88, 1.67). So the conclusion remains unchanged by different censoring rule. Figure 4 shows the cumulative percentage of subjects who did not make it to the expected last visit (excluding subjects who died).

Figure 4 Cumulative percentage of subjects who lost to follow up

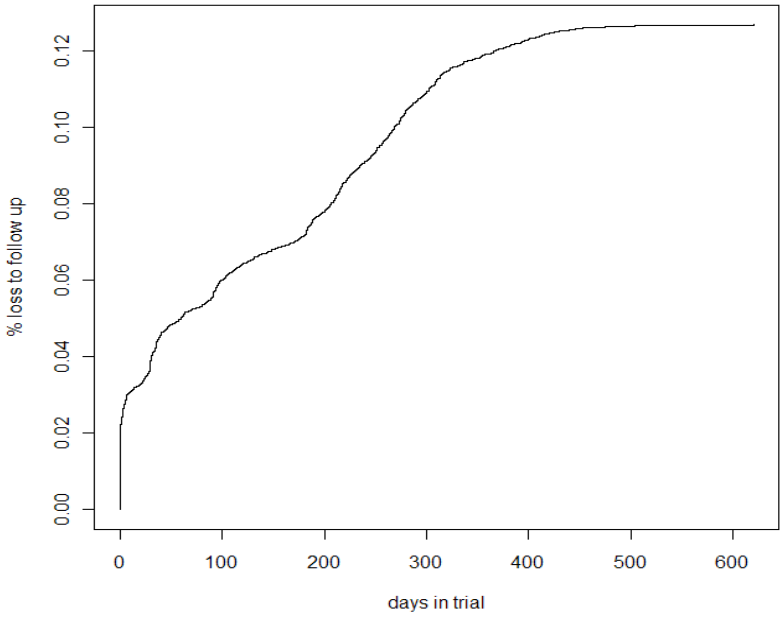
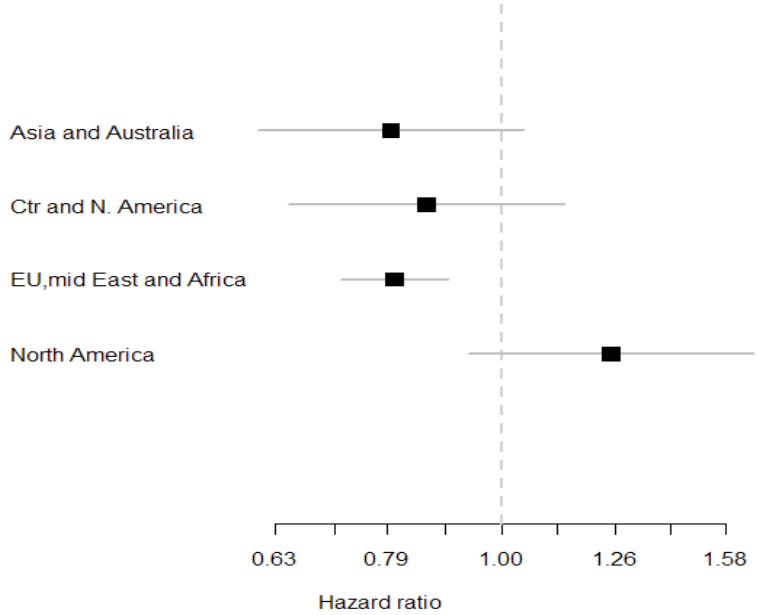


Figure 5 shows the hazard ratio estimates by region. Region was prospectively defined as Europe, Middle East and Africa; North America; Asia and Australia; and Central and South America. The hazard ratio point estimate for the primary endpoint numerically favored clopidogrel in the North America region and favored ticagrelor in the rest of 3 other regions.

Figure 5 Hazard ratio estimates by region



The major issue in this application is the regional difference observed between US and non-US. It is even more concerning that ticagrelor treatment appears to have a nominally negative effect on US subjects that almost reached nominal statistical significance itself (HR=1.27 with 95% CI (0.92, 1.75)).

In the following analyses, the reviewer performed extensive analyses to search for all potential explanations for the regional difference between US and non-US. For clarification, the treatment-by-region interaction referred below by the reviewer is based on models comparing US versus non-US (by combining all non-US countries into one region).

Table 4 Primary event rate in countries with top 10 largest enrollments

	ticagrelor			clopidogrel		
COUNTRY	N	event	rate (%)	N	event	rate (%)
Poland	1337	96	7.2	1329	137	10.3
USA	707	84	11.9	706	67	9.5
Hungary	632	42	6.6	635	70	11.0
Germany	580	55	9.5	576	62	10.8
Czech Republic	510	41	8.0	511	49	9.6
Netherlands	457	33	7.2	456	48	10.5
Brazil	347	49	14.1	343	62	18.1
Russia	340	37	10.9	338	35	10.4
Israel	320	25	7.8	316	24	7.6
Italy	312	20	6.4	313	21	6.7

Table 4 shows the primary event rate in each treatment group for the countries with top 10 largest enrollments. The overall event rates are 10.9% for clopidogrel group and 9.3% for ticagrelor group. Looking at the primary event rate in US, the ticagrelor group appeared to have a higher event rate while the clopidogrel group had a lower event rate than average.

Due to the observed treatment-by-region interaction, the reviewer focused on exploratory analyses in this section to examine any potential factors (such as play of chance, baseline factors, trial conduct matters, and patient characteristics, etc) that may explain the observed regional difference between US and non-US.

The reviewer examined the data from three aspects:

1. Is the difference between US and non-US a play of chance?
2. Is the difference between US and non-US caused by aspirin?
3. Is the difference between US and non-US caused by some other factors?

1. Is the regional difference due to a play of chance?

Figure 6 Funnel Plot

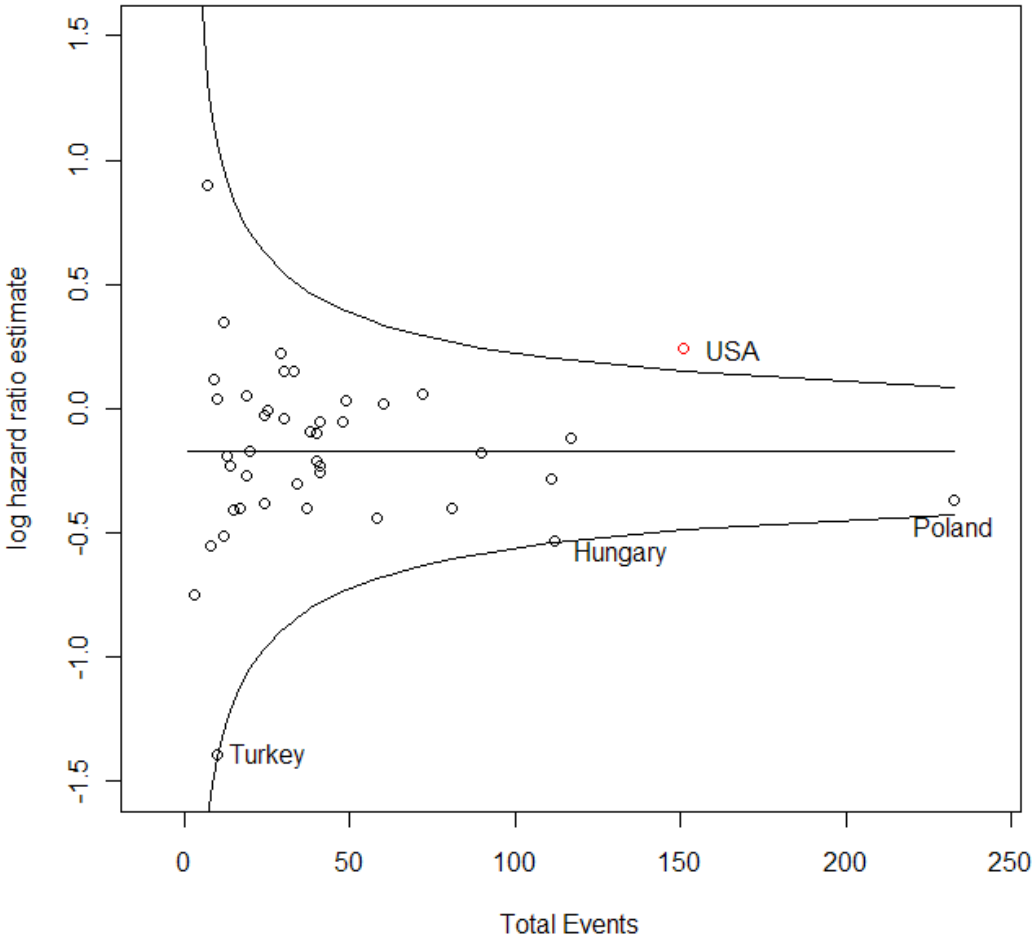


Figure 6 is a funnel plot to show potential outliers. USA is the only country out of the approximated 95% CI boundary. Hungary, Poland and Turkey are close to the bound. In fact, given that there are 43 countries in the trial, observing one country lying outside the bound should not be too surprising.

Since both Hungary and Poland enrolled large number of subjects, they may drive the study result to favor ticagrelor. The reviewer excluded all three countries (Turkey, Hungary and Poland) and re-analyzed the primary endpoint as a sensitivity analysis. The hazard ratio estimate is 0.90 with 95% confidence interval (0.81, 0.99). Even by excluding the big centers which showed big treatment effect favoring ticagrelor over clopidogrel (Poland and Hungary), the overall result still favors ticagrelor. The efficacy results seem robust.

The reviewer examined the data by plotting the hazard ratio estimate along the time (Figure 7). The hazard ratio estimate was calculated after every 10 events occurred in the trial. The grey area shows how the primary events accumulated in the ITT population. As more subjects enrolled into the trial, more events occurred and the confidence interval of the hazard ratio estimate became narrower as shown in the plot. It is noteworthy that the hazard ratio estimate stayed under 1 throughout the trial and the upper bound of the confidence interval was below 1 and

stayed below 1 in the second half of the trial. This result again showed the robustness and consistence of the overall efficacy results.

Figure 8 is the plot on nominal p-value corresponding to the hazard ratio estimates in Figure 7.

On the other hand,
Figure 9 and Figure 10 showed similar plot but this time based on US subjects only. Contrary to the hazard ratio plot in overall population, the hazard ratio estimates in US population stayed consistently above 1 throughout the trial. Although the hazard ratio estimates decreased gradually toward one, the estimates seemed to be stabilized after June 2008. The result in US subjects itself seemed consistent as well.

Figure 7 Hazard Ratio Plot for All Subjects in the Trial

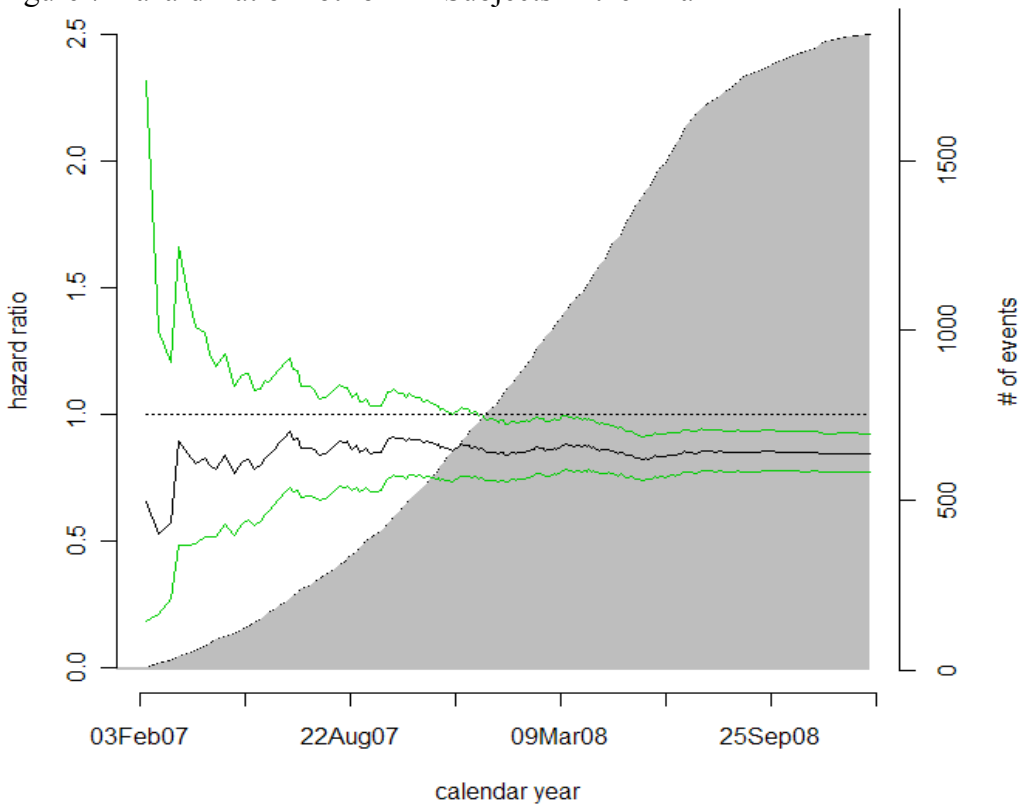


Figure 8 P-value Plot for All Subjects in the Trial

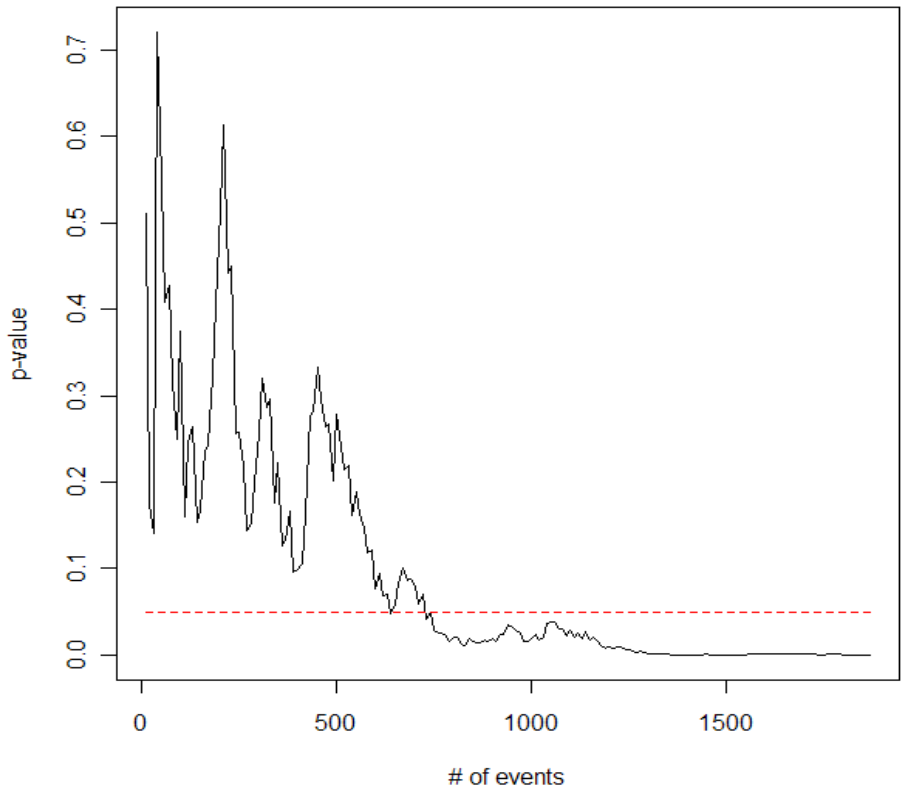


Figure 9 Hazard Ratio Plot for Subjects in US only

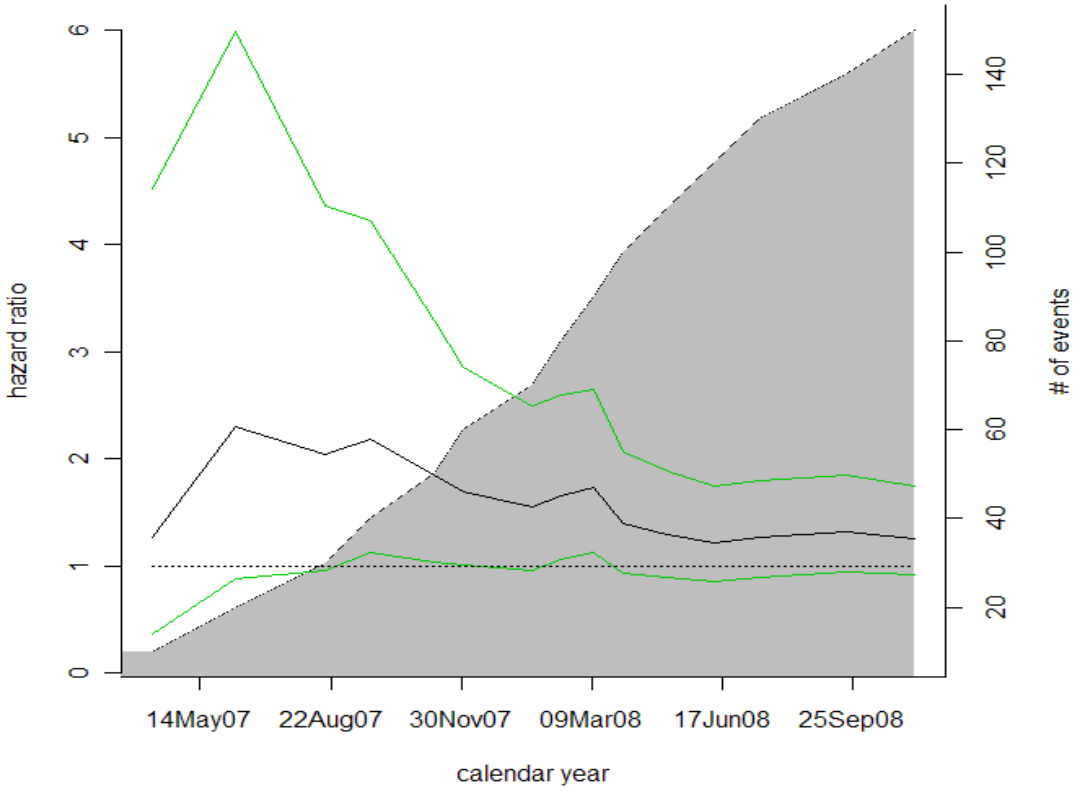
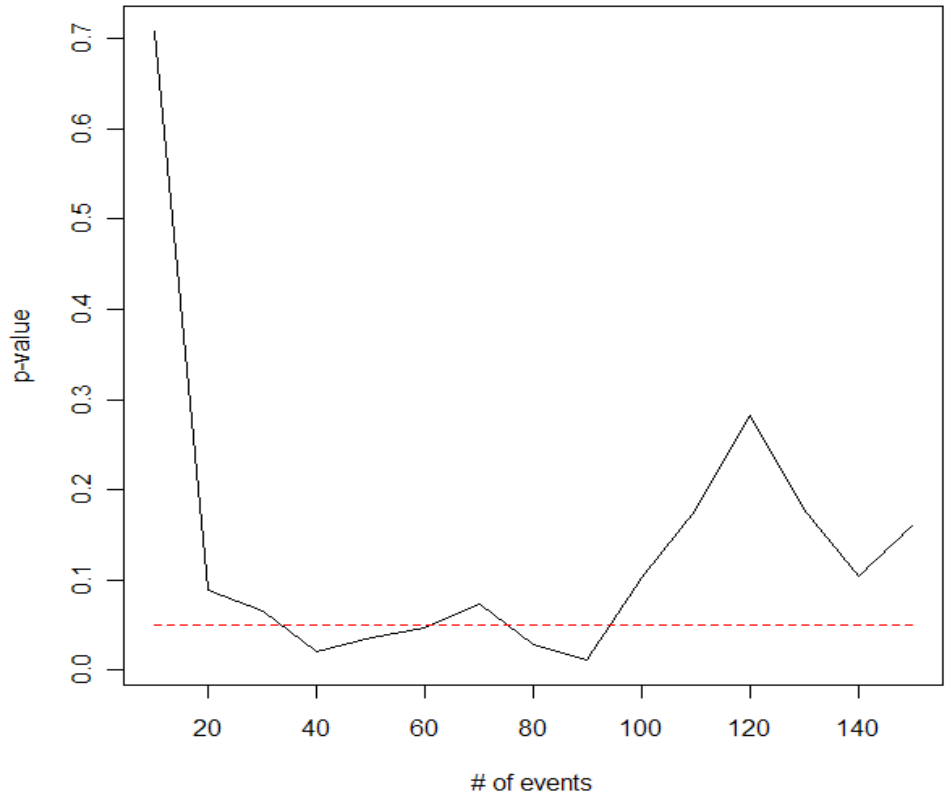


Figure 10 P-value plot for Subjects in US Only



The sponsor calculated the probability of observing such results in several ways, which were confirmed by the reviewer.

First of all, given the distribution of patients and events across the 4 pre-specified regions and assuming a common overall HR across regions of 0.84 as observed in PLATO, the probability of observing a result numerically favoring clopidogrel in the North America region while numerically favoring ticagrelor in the other 3 regions is 10%. However, this did not take into the account of the magnitude of the difference observed in hazard ratio estimates between US and non-US.

Secondly, 12 countries were found to have a HR >1 and 3 countries to have a HR >1.25. While it is not uncommon to observe a country with HR estimate going to the opposite direction from the overall HR in multi-regional trial with such large scale, the magnitude of difference in the HR estimate (HR=1.25 in US versus HR=0.84 in the rest of the world) is concerning, especially when US had the largest number of subjects enrolled among the 12 countries which had HR estimate above 1. Two other countries which had HR>1.25 are Australia (N=92) and Taiwan (N=83).

Another calculation was to compute the probability of observing a HR >1.25 if the true HR across all regions was 0.84. It was estimated to be <1% given the number of events in the US.

These calculations in general oversimplify the real situation. Nevertheless, it can shed some light on how likely the difference between US and non-US is due to a play of chance.

In the three calculations mentioned above, only the last one took the number of events in the US as well as the magnitude of difference between the hazard ratio estimates into account. Even though it may underestimate the probability of observing such a HR estimate in US due to the post-hoc nature of this calculation that does not account for multiplicity in the analyses, the estimate may be relatively closer to real probability in this reviewer's point of view. In other words, although play of chance can never be ruled out of possible explanations, it seems a little overstretching if we observed a hazard ratio estimate of 1.25 in a center enrolled 1413 subjects while the rest of the world showed a clear benefit from ticagrelor (HR=0.84).

2. Can the regional difference be explained by the aspirin usage?

The sponsor analyzed over 30 factors including pre-specified covariates and post-hoc covariates and discovered that the concurrent ASA use contributed significantly to the observed treatment-by-region interaction. So the concurrent ASA dose was considered a strong candidate for explaining the regional difference if it is not due to a play of chance. However, the sponsor also acknowledged that "there are no data from preclinical pharmacology studies that could explain why specifically ticagrelor could be less effective than clopidogrel with concomitant administration of high dose ASA".

Figure 11 and Figure 12 show the distribution of median aspirin dose for non US subjects and US subjects in the trial, respectively. As shown in the figures, most subjects taking high dose

ASA (median ASA dose>=300mg) were from US. A total of 676 subjects in US took high ASA dose, while only 280 subjects in the rest of the world took high ASA dose (the numbers are based on variable MEDIAN55, a derived median ASA dose by the sponsor). So use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US).

Figure 11 Distribution of Median Aspirin Dose for Non-US Subjects

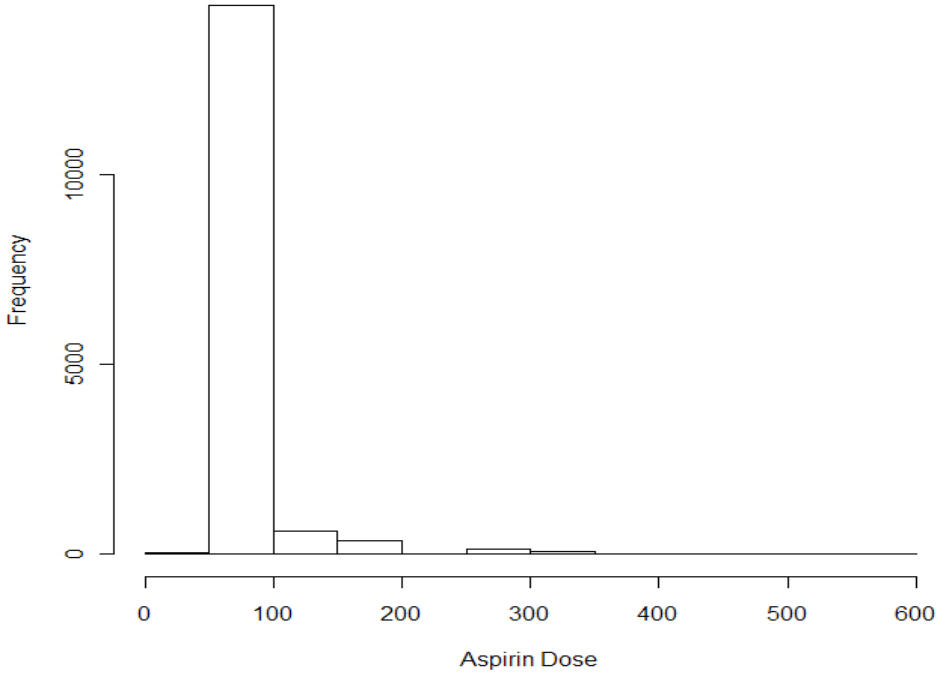
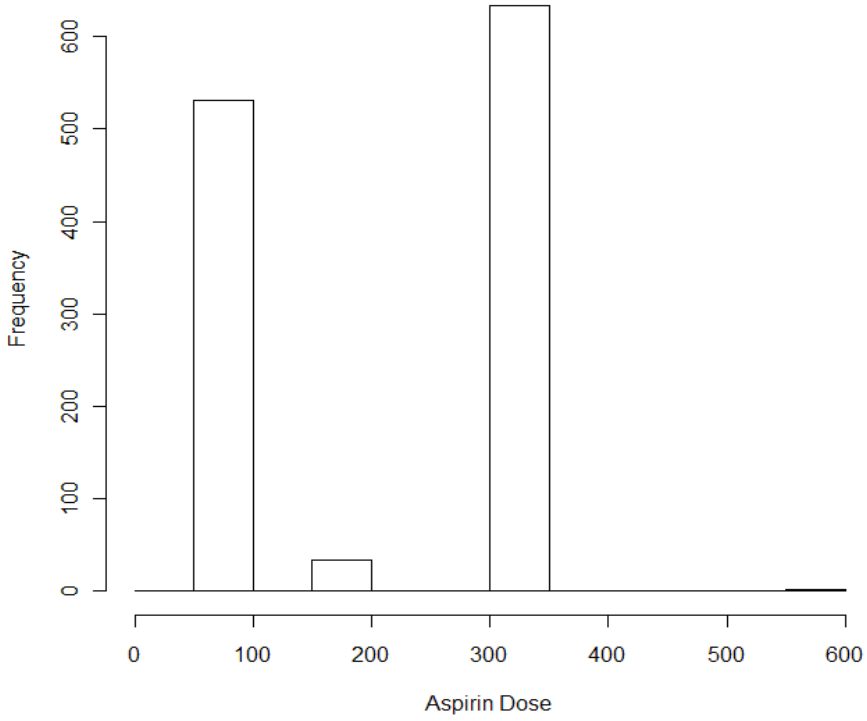


Figure 12 Distribution of Median Aspirin Dose for US Subjects

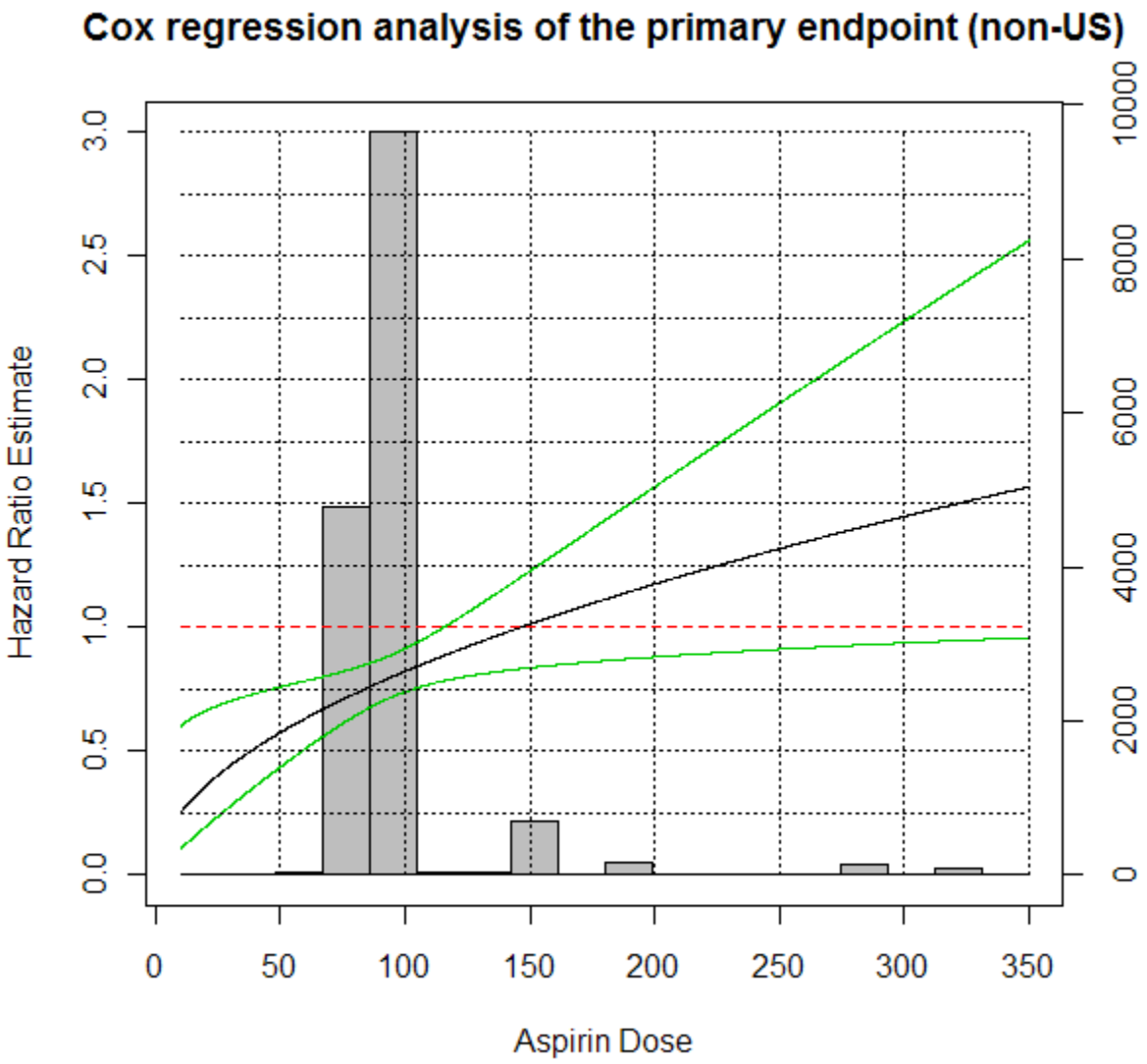


The sponsor also performed analysis using Cox Proportional Hazards model in the non-US population. The model included treatment, log(median ASA dose) and interaction between treatment and log(median aspirin dose) as shown in Figure 13. The black curve is the estimate of hazard ratio of ticagrelor over clopidogrel and the confidence interval boundaries are marked in green. It appears that the hazard ratio estimate increases as the ASA dose increases.

This is further verified by using the average of the median ASA doses in US subjects in the model to calculate a "hypothetical" hazard ratio estimate for US. The average of the median ASA dose in US subjects is 217.6 mg. Based on the covariate coefficient estimates in the Cox proportional hazard model from the non-US region as shown in Figure 13, the corresponding "hypothetical" hazard ratio estimate for US is 1.23 with 95% CI (0.89, 1.69). This is quite close to the hazard ratio estimate in US based on real data (1.27 with 95% CI (0.92, 1.75)).

However, the reviewer has some concerns on the analysis. The most important one is that the majority of subjects in the non-US region took either 75mg or 100 mg ASA so the model may not be robust due to the limited data on the high end of ASA dose in the non-US region. This can also be seen in the widening confidence band as the ASA dose increases.

Figure 13 Hazard Ratio Estimate Using Cox Proportional Hazards Model Including Aspirin-Treatment Interaction



It is unknown whether the median ASA dose is sufficient to capture the information. After all, each subject used a single value to represent the whole course of ASA treatment during the trial in these analyses.

Table 5 lists all subjects who took any daily ASA dose >= 1000 mg. Some doses taken are very large. According to the sponsor, "a further review of the database revealed 33 patients whose recorded aspirin dose was something other than 'mg': namely 'µg', 'g', 'mL' or 'IU'; and the dose was equal to the subject's median aspirin dose. In most of the cases, the dose appears to be a valid aspirin dose or a multiple of a valid dose." Since the number of subjects is small and the median ASA dose is not sensitive to extreme values, it is probably not a big concern.

Table 5 Subjects with daily dose of ASA >= 1000mg

SUBJECT	Days with ASA>=1000mg	Minimum (mg)	Maximum (mg)
E1202063	1	2500	2500
E1317013	30	1500	1500
E1417031	2	1500	1600
E1421021	6	3000	3000
E1639007	12	1950	2600
E1639012	6	2600	2600
E1643005	1	1850	1850
E1643006	1	1950	1950
E1710002	1	10000	10000
E2115005	32	3000	3000
E2132005	5	2250	3000
E2133021	1	3000	3000
E2133033	1	3000	3000
E2309031	1	1500	1500
E2309059	1	1500	1500
E2309130	1	1500	1500
E2309165	1	1500	1500
E2309196	1	1500	1500
E2309249	1	1500	1500
E2309261	1	1500	1500
E2309274	1	1500	1500
E2313049	1	1500	1500
E2318008	27	1100	3000
E2341001	1	1500	1500
E2341004	1	1500	1500
E2349005	1	1200	1200
E2610032	1	5000	5000
E2901083	5	1200	1800
E3318002	30	2400	2400
E3340007	1	1200	1200
E3604043	7	1800	1800
E3624100	1	3000	3000
E3706016	1	1500	1500
E3913022	1	2050	2050
E4208050	1	1600	1600
E4404004	2	1200	1200
E4409025	2	1300	1500
E4414004	5	3000	3000
E5335001	367	6325	6325
E5514004	37	25200	25200

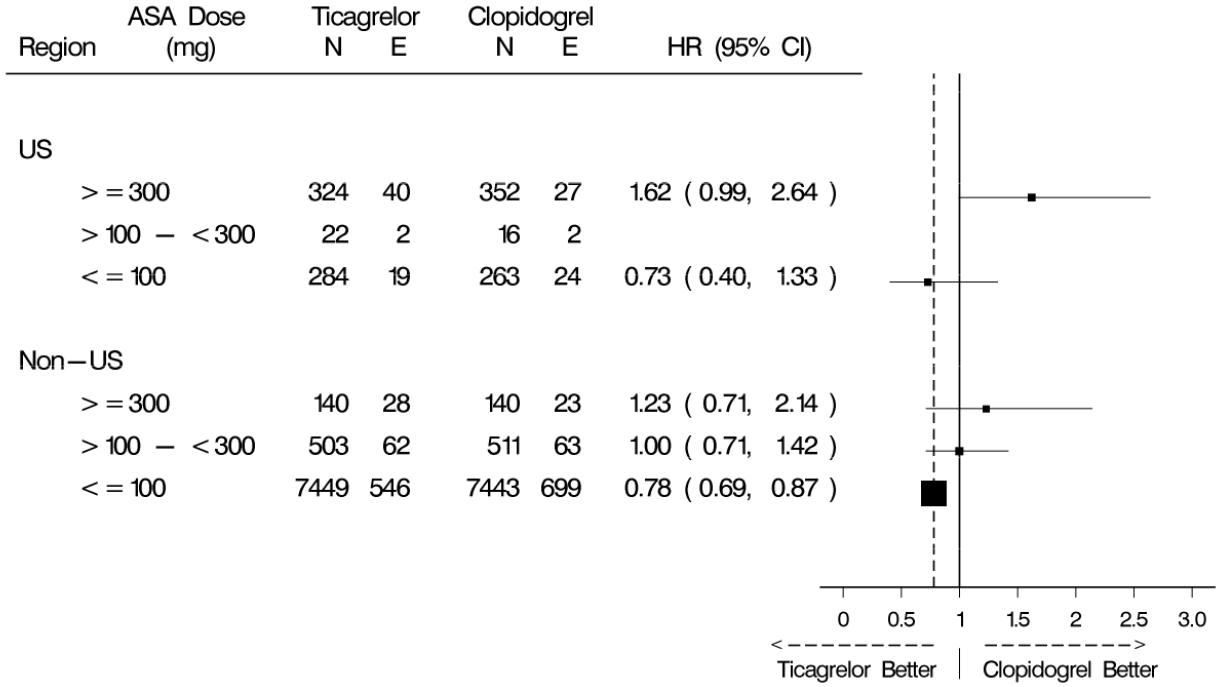
The sponsor also performed sensitivity analyses with regard to the median ASA dose. Median ASA dose was originally defined as the median of all of a patient's aspirin doses taken during the study drug period, regardless of whether and when the patient had an event. In addition, the original definition excluded patients who took less than 5 doses of aspirin. This is to avoid the possibly confounding influence of high ASA loading dose following the index event since some

patients took high dose for 1 day and had an immediate event. Taking the feedback from outside experts into consideration, the sponsor conducted a number of sensitivity analyses. They reported that "both analyses (MEDIAN24 and MEDIAN55) lead to similar conclusions, supporting a potential role for ASA maintenance dose in the treatment-by-region interaction observed in PLATO."

The sponsor defined in a number of ways to calculate the median. MEDIAN55 excludes the loading dose of ASA in the calculation completely. MEDIAN24 excludes subjects who had only 1 day of ASA (presumably, only the loading dose). MEDIAN20 excludes subjects who had less than 5 days of ASA and MEDIAN25 includes all doses (loading dose as well) in the calculation. Nevertheless, the sponsor tried to assess how sensitivity the model is to the different definition of the median ASA. It appears reasonable to this reviewer that the ASA doses after a subject had a primary event should be excluded in calculating the median ASA dose.

In the sensitivity analysis, the variable MEDIAN55 represents the median summary of ASA doses, excluding Day 1 loading dose, and up until the day of the event. Given the fact that all the sensitivity analyses are exploratory, MEDIAN55 was preferred by the sponsor because it "appears more relevant in addressing the input of clinical experts and the FDA, and in separating maintenance dosing from loading dose". Interestingly, HR point estimate in US subjects decreased to 0.73 for low dose ASA (below 100 mg) by the new definition MEDIAN55 shown in Figure 14. In the sponsor's original analysis, the hazard ratio estimate in subjects who took low ASA dose (<=100mg) in US was 0.99.

Figure 14 Hazard ratio estimates by different ASA dose using MEDIAN55

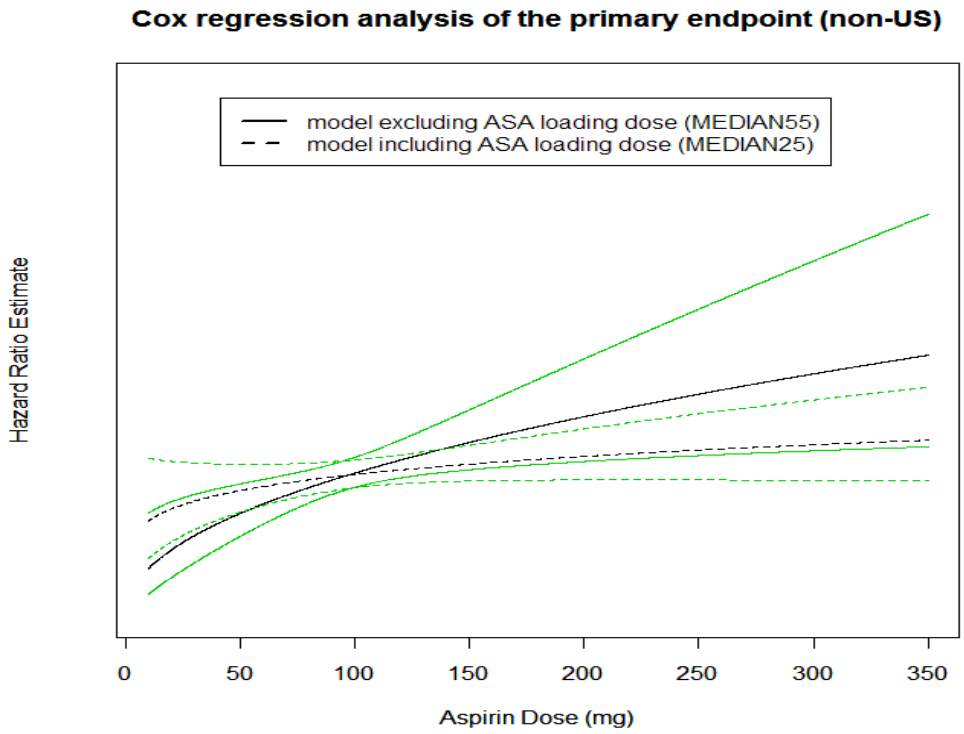


[Source: Figure 9 on sponsor's correspondence submitted on 6/16/2010]

MEDIAN24 represents the median summary of ASA doses, excluding patients with less than 2 days of aspirin. It includes all aspirin during the study drug period for patients who did not have an event. The results are similar to MEDIAN55.
The sponsor also used MEDIAN25 which included all aspirin during the study drug period for patients who did not have an event. It includes all aspirin up to the time of the event for subjects who had a primary event.

The Cox proportional hazards model seems to be sensitive to whether or not the first day ASA loading dose is included. Just by including the first day loading dose, the relationship between the hazard ration estimate and median ASA dose becomes much flatter (Figure 15). It is also interesting to find that the treatment*region interaction does not seem to be affected by the total ASA dose taken during the trial.

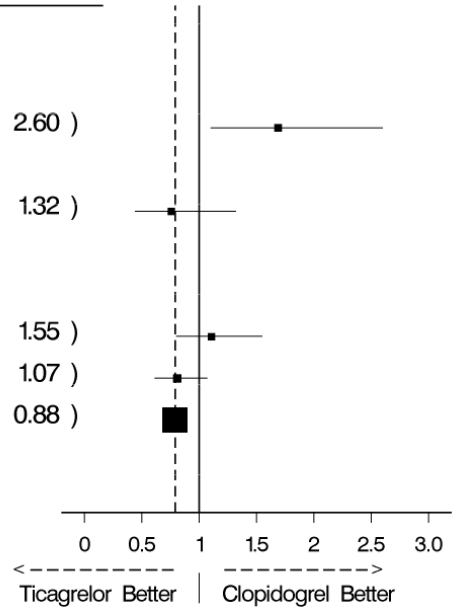
Figure 15 Comparison of models excluding or including 1st day ASA loading dose



Looking further to compare Figure 14 and Figure 16, which show the subgroups by region and by median ASA dose using different median ASA measurements, the biggest difference between the two is that there are considerably more subjects in the high ASA dose group in the non-US region if the calculation of median ASA includes the loading dose. It again puts the small number of high dose ASA subjects in the non-US region into a crucial position. Those subjects appeared to have a huge leverage on the Cox proportional hazards model.

Figure 16 Hazard ratio estimates by different ASA dose using MEDIAN25

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US						
	>=300	359	53	377	34	1.69 (1.10, 2.60)
	>100 – <300	25	2	17	2	
	<=100	292	23	271	28	0.76 (0.44, 1.32)
Non–US						
	>=300	290	75	274	66	1.11 (0.80, 1.55)
	>100 – <300	588	86	602	106	0.81 (0.61, 1.07)
	<=100	7528	584	7493	734	0.79 (0.71, 0.88)



[Source: Figure 7 on sponsor's correspondence submitted on 6/16/2010]

The reviewer went further to investigate how sensitivity the model is to the high dose ASA data. The reviewer simply used the median ASA variable MEDIAN55 preferred by the sponsor in the following sensitivity analyses. In fact, there were only 472 subjects whose median daily ASA dose were above 200 mg out of a total of 16186 subjects in non-US region took at least two days of ASA during the study period. Among those 472 subjects, 280 subjects had median daily ASA dose equal or above 300 mg. In order to show how much leverage those 472 subjects had on the Cox proportional hazards model, the reviewer applied the same model in the non-US excluding these subjects with high median ASA dose. Although the relationship between ASA dose and hazard ratio estimate still seemed to exist, the model appeared quite sensitive to these subjects (Figure 17 and Figure 18). The curve can swing up and down considerably by excluding either all subjects who had median ASA no less than 300 mg or subjects who had median ASA no less than 200 mg. It casts doubt on how real the relationship is since less than 3% subjects can make such big impact on the model.

There are a number of other factors which showed a significant interaction with treatment within US population and differed between US and non-US populations, for example, use of GPI during index hospitalization and whether subjects went through early PCI. However, these factors did not show any significant interaction with treatment in the non-US populations and were not considered as important contributors to the regional difference. Therefore the robustness of the Cox proportional model on the non-US population is crucial. A few more or less events in that high ASA dose subpopulation in the non-US region may make a huge impact on the Cox proportional hazards model and therefore influence the interpretation.

Figure 17 Sensitivity analyses on median ASA dose (1)

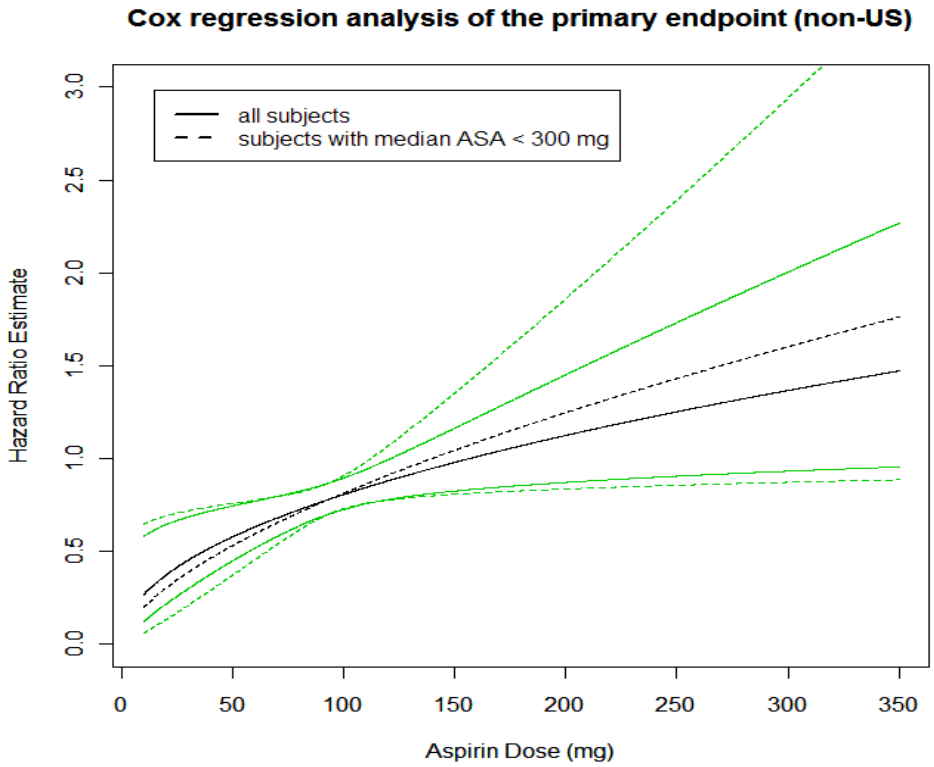
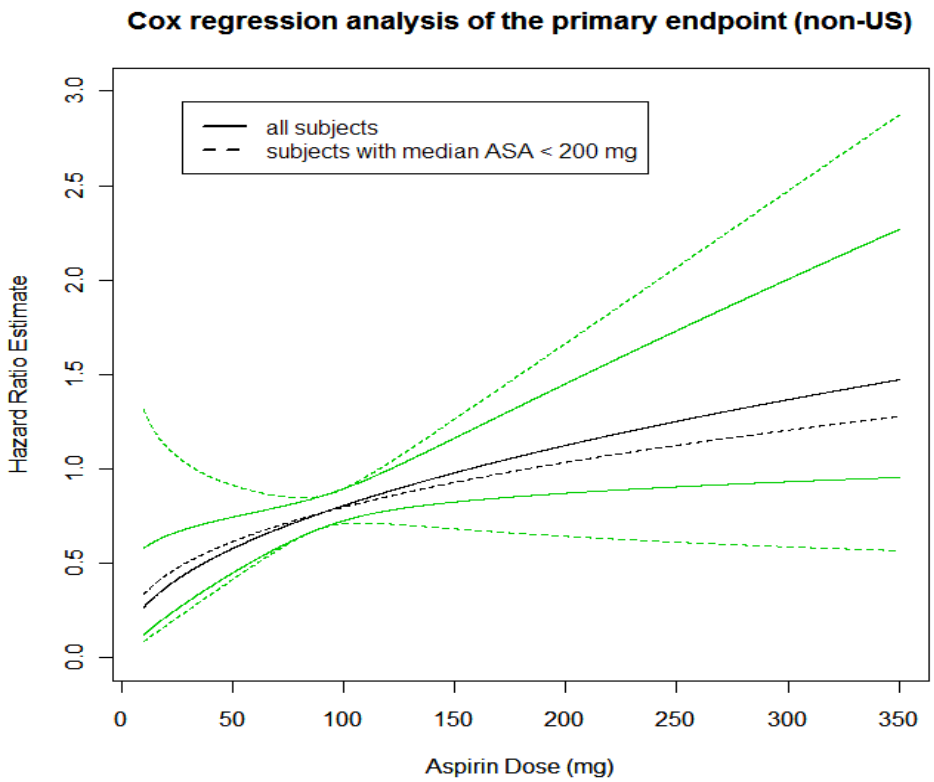


Figure 18 Sensitivity analyses on median ASA dose (2)



Therefore, the finding that ASA may contribute to the regional difference remains questionable. First of all, as the reviewer mentioned before, as most subjects taking high dose ASA were from US, high dose ASA may simply be a confounding variable. Even though ASA seemed to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. A few more or less events in that subpopulation in the non-US region can make a huge impact on the Cox proportional hazards model and therefore influence the interpretation.

3. Is the difference caused by other factors?

While the sponsor performed pre-specified analyses of 31 baseline factors to explore interactions with treatment for the primary efficacy endpoint, the reviewer also explored certain other factors as well as models.

Here is a list of pre-specified factors explored by the sponsor.

1. Gender (male, female)
2. Race (Caucasian, Black, Oriental, Other)
3. Waist circumference (<100 cm, ≥100 cm)
4. Troponin I (positive, negative)
5. Index event characteristic (unstable angina; NSTEMI; STEMI; other)
6. Pre-index event antiplatelet therapy (none, clopidogrel, ASA, clopidogrel + ASA, other)
7. ASA on day of randomization (yes, no)
8. History of diabetes (yes, no)
9. Prior MI (yes, no)
10. Prior PCI (yes, no)
11. Prior CABG (yes, no)
12. Intent at time of randomization for medical management versus invasive management (yes, no)
13. Moderate CYP3A inhibitor usage at randomization (yes, no)
14. Any use of GP IIb/IIIa inhibitor between index event and end of index hospitalisation (yes, no)
15. Unfractionated heparin, low molecular weight heparin, fondiparinux (fondaparin), or bivalirudin between index event and end of index hospitalisation (yes, no)
16. Lipid-lowering drugs on day of randomization (yes, no)
17. β-blockers on day of randomization (yes, no)
18. ACE inhibitors on day of randomization (yes, no)
19. ARBs on day of randomization (yes, no)
20. Calcium channel blockers on day of randomization (yes, no)
21. Age (years) as a continuous factor
22. Weight (kg) as a continuous factor
23. BMI as a continuous factor
24. Time from start of index event to initiation of study therapy as a continuous factor
25. At least 80% compliance with assigned study medication at all visits (yes, no)

26. Concomitant median ASA dose (mg) as a continuous variable
27. Having PCI (yes, no)
28. Use of DES or BMS (yes, no)
29. PPI use on day of randomization (yes, no)
30. Angiography quartiles in terms of access to catheterisation laboratory (high access, medium-high access, medium-low access, low access)
31. Randomized treatment

Nine more factors were identified and included in the analyses by the sponsor.

The following additions or changes in definitions of factors were adopted for some analyses.
1. Age as a continuous factor
2. Weight as a continuous factor
3. BMI as a continuous factor
4. Geographic region was categorized as US and non-US. The analyses were also conducted for NA (United States and Canada) and ROW
5. Time from start of index event to initiation of study therapy as a continuous factor
6. In addition to the use (yes/no) of GP IIb/IIIa, the type of GP IIb/IIIa was analysed, if available in the dataset.
7. At least 80% compliance with assigned study medication at all visits (yes/no)
8. Cumulative 24-hour clopidogrel loading dose instead of the dose within a 4-hour window: none, 1 to 450 mg, >450 mg
9. Angiography for non-ST elevation myocardial infarction (NSTEMI) patients

The reviewer also examined a number of variables by US and Non US as shown in Table 6 and Table 7.

Table 6 Comparisons of categorical covariates in US and non-US

Factors		Non-US		US	
		N	Percentage	N	Percentage
ACE use at randomization	No	7364	42.8	738	52.2
	Yes	9847	57.2	675	47.8
pre-index event antiplatelet therapy	None	11403	66.3	744	52.7
	clopidogrel	254	1.5	35	2.5
	ASA	4542	26.4	482	34.1
	clopidogrel+ASA	956	5.6	152	10.8
	Other	56	0.3		
ARB use at randomization	No	15751	91.5	1230	87.0
	Yes	1460	8.5	183	13.0
ASA use at randomization	No	839	4.9	88	6.2
	Yes	16372	95.1	1325	93.8
Beta blocker at randomization	No	4377	25.4	187	13.2
	Yes	12834	74.6	1226	86.8
Prior CABG	No	16341	94.9	1177	83.3
	Yes	870	5.1	236	16.7
CCB use at randomization	No	14684	85.3	1204	85.2

	Yes	2527	14.7	209	14.8
History of diabetes	No	13021	75.7	941	66.6
	Yes	4190	24.3	472	33.4
Index event characteristic	Unstable Angina	2970	17.3	142	10.1
	NSTEMI	7006	40.8	949	67.3
	STEMI	6804	39.6	222	15.7
	Other	391	2.3	98	6.9
GPI during index hospitalization	No	12858	74.7	704	49.8
	Yes	4353	25.3	709	50.2
Heparin during index hospitalization	No	6222	36.2	474	33.5
	Yes	10989	63.8	939	66.5
Prior PCI	No	15134	87.9	998	70.6
	Yes	2077	12.1	415	29.4
Lipid lowering agent at randomization	No	3459	20.1	309	21.9
	Yes	13752	79.9	1104	78.1
Previous MI	No	13774	80.0	1026	72.6
	Yes	3437	20.0	387	27.4
Race	caucasian	15815	91.9	1262	89.3
	Black	92	0.5	137	9.7
	Oriental	1087	6.3	9	0.6
	Other	216	1.3	5	0.4
Gender	Male	12329	71.6	1007	71.3
	Female	4882	28.4	406	28.7
Early PCI	No	8818	51.2	546	38.7
	Yes	8388	48.8	866	61.3
Habitual smoker	No	11048	64.2	898	63.6
	Yes	6163	35.8	515	36.4
Use of DES or BMS	No	6810	39.6	525	37.2
	Yes	10401	60.4	888	62.8
Indicator of 1st PCI	No	6281	36.5	482	34.1
	Yes	10925	63.5	930	65.9
Prior stroke?	No	16991	98.7	1402	99.2
	Yes	220	1.3	11	0.8
Troponin I>ULN 24 hr Post Index Event	Positive	13913	80.8	1176	83.2
	Negative	2797	16.3	171	12.1
	missing	501	2.9	66	4.7
Waist circumference	<100cm	9067	52.7	560	39.6
	>=100cm	7289	42.4	689	48.8
	unknown	855	5.0	164	11.6
Cyp3A strong inducer	No	17057	99.2	1398	99.1
	Yes	133	0.8	13	0.9
Cyp3A strong inhibitor	No	16947	98.6	1390	98.5
	Yes	243	1.4	21	1.5
Subject flag	NSTEMI	9976	59.5	1091	83.1
	STEMI	6804	40.5	222	16.9
Planned treatment approach at randomization	medical management	5126	29.8	90	6.4

	invasive management	12085	70.2	1323	93.6
TIMI risk score(STEMI)	0-2	3755	55.2	134	60.4
	3-6	2799	41.1	85	38.3
	>6	250	3.7	3	1.4
TIMI risk score(NSTEMI)	0-2	685	6.9	45	4.1
	3-6	4987	50.0	501	45.9
	>6	4304	43.1	545	50.0

Table 7 Comparisons of continuous covariates in US and non-US

	US				Non US			
	N	Median	Mean	STD	N	Median	Mean	STD
hours between hosp admission to early PCI	702	11.1	12.0	9.9	7663	1.8	5.6	8.4
hours between index event to early PCI	866	16.8	16.5	10.4	8388	6.6	10.5	10.9
hours between index event to randomization	1412	15.3	14.7	8.7	17202	10.1	11.5	9.0
hours between index event to hospitalization	1141	2.8	4.4	4.8	15052	2.8	4.5	4.9
hours between 1st dose IP to early PCI	858	0.2	1.3	9.1	8376	0.3	1.5	5.9
hours between randomization to early PCI	866	1.0	2.7	4.9	8388	0.6	2.1	4.7
hours between randomization to 1st IP	1356	0.6	11.0	76.1	17064	0.3	1.2	20.1
hours from Index Event to 1st Study Drug	1355	16.7	25.8	77.0	17055	10.8	12.7	22.0
hours between hospital admission and 1st dose	1096	12.5	21.9	78.9	14931	3.8	12.8	495.9
days on ASA	1342	272.0	229.0	141.5	16780	275.0	243.3	132.6
mean ASA dose (mg)	1342	268.3	227.1	274.7	16779	100.0	108.2	97.1
median ASA dose (mg)	1203	325.0	217.6	213.6	15656	100.0	99.3	43.3
ticagrelor study drug (mg) before 1st PCI	406	180.0	180.0	24.5	3964	180.0	179.5	15.1
clopidogrel study drug (mg) before 1st PCI	425	300.0	288.5	163.1	4176	300.0	230.6	160.6
clopidogrel open label (mg) before 1st PCI	314	300.0	291.5	213.2	4325	375.0	418.2	187.4
clopidogrel total dose (mg) before 1st PCI	595	300.0	359.9	194.4	6409	375.0	432.5	185.0
Clop Load Cumulative between IE and Rand+24h	920	300.0	348.8	191.3	12613	300.0	388.2	181.2
Clop Load Max in Any 4h IE to Rand+24h	920	300.0	306.5	173.0	12613	300.0	351.7	165.8
weight (KG)	1410	87.0	89.2	20.6	17158	80.0	79.7	15.3
Age	1413	61.0	61.1	11.6	17209	62.0	62.3	11.2
number of BMS stent	1413	0.0	0.4	0.8	17211	0.0	0.7	0.9
number of DES stent	1413	0.0	0.8	1.2	17211	0.0	0.3	0.8

US population differs from non-US population in a number of ways. For example, it took much longer time on average for US subjects to receive first dose of study drug since occurrence of index events (median=16.7 hours in US, median =10.8 hours in non-US). More US subjects enrolled in the trial were NSTEMI patients compared to the rest of the world (67.3% in US and 40.8% in non-US). If a subject had stents inserted, US subjects tended to have drug eluting stents and non-US subjects tended to have bare metal stents. Other factors including prior history of PCI or MI, number of subjects who went through early PCI, pre-index event antiplatelet therapy, beta blocker usage at randomization, planned treatment approach at randomization, GPI during index hospitalization, and many more (Table 8). So it appears that the US population in the trial

differs from the population outside of US in many ways. The reviewer further broke down the US population and non-US population by each covariate and looked at the hazard ratio estimate by each subgroup. Figure 19, Figure 20 and Figure 21 shows the subgroup analyses in US and non-US populations side by side.

Table 8 Comparison of US and Non-US characteristics

	US			non-US		
	N	# of subjects	Percentage	N	# of subjects	Percentage
Use of ACE at randomization	1413	675	47.8	17211	9847	57.2
Use of ARB at randomization	1413	183	13	17211	1460	8.5
beta blocker use at randomization	1413	1226	86.8	17211	12834	74.6
Prior CABG	1413	236	16.7	17211	870	5.1
History of diabetes	1413	472	33.4	17211	4190	24.3
Index event (NSTEMI)	1413	949	67.3	17211	7006	40.8
GPI during index hospitalization	1413	709	50.2	17211	4353	25.3
Prior PCI	1413	415	29.4	17211	2077	12.1
Prior MI	1413	387	27.4	17211	3437	20
Black	1413	137	9.7	17211	92	0.5
early PCI	1413	866	61.3	17211	8388	48.8
Planned invasive management at randomization	1413	1323	93.6	17211	12085	70.2
Use of bare metal stents	1413	331	23.4	17211	7993	46.4
Use of drug eluting stents	1413	653	46.2	17211	3339	19.4
	N	Mean	Median	N	Mean	Median
weight (KG)	1413	89.2	87	17158	79.7	80
median ASA dose (mg)	1261	219	325	16186	100.1	100
hours from index event to 1st study drug	1355	25.8	16.7	17055	12.7	10.8
hours from index event to early PCI	866	16.5	16.8	8388	10.5	6.6
hours from index event to randomization	1412	14.7	15.3	17202	11.5	10.1

US and non-US populations appear to be affected differently by some covariates as shown in the forest plots. The reviewer then included each individual covariate and covariate*treatment interaction into the Cox proportional hazards model with presence of treatment*region interaction term. However, not a single covariate seems to contribute much to the treatment*region interaction.

Figure 19 Analysis by various subgroups (1)

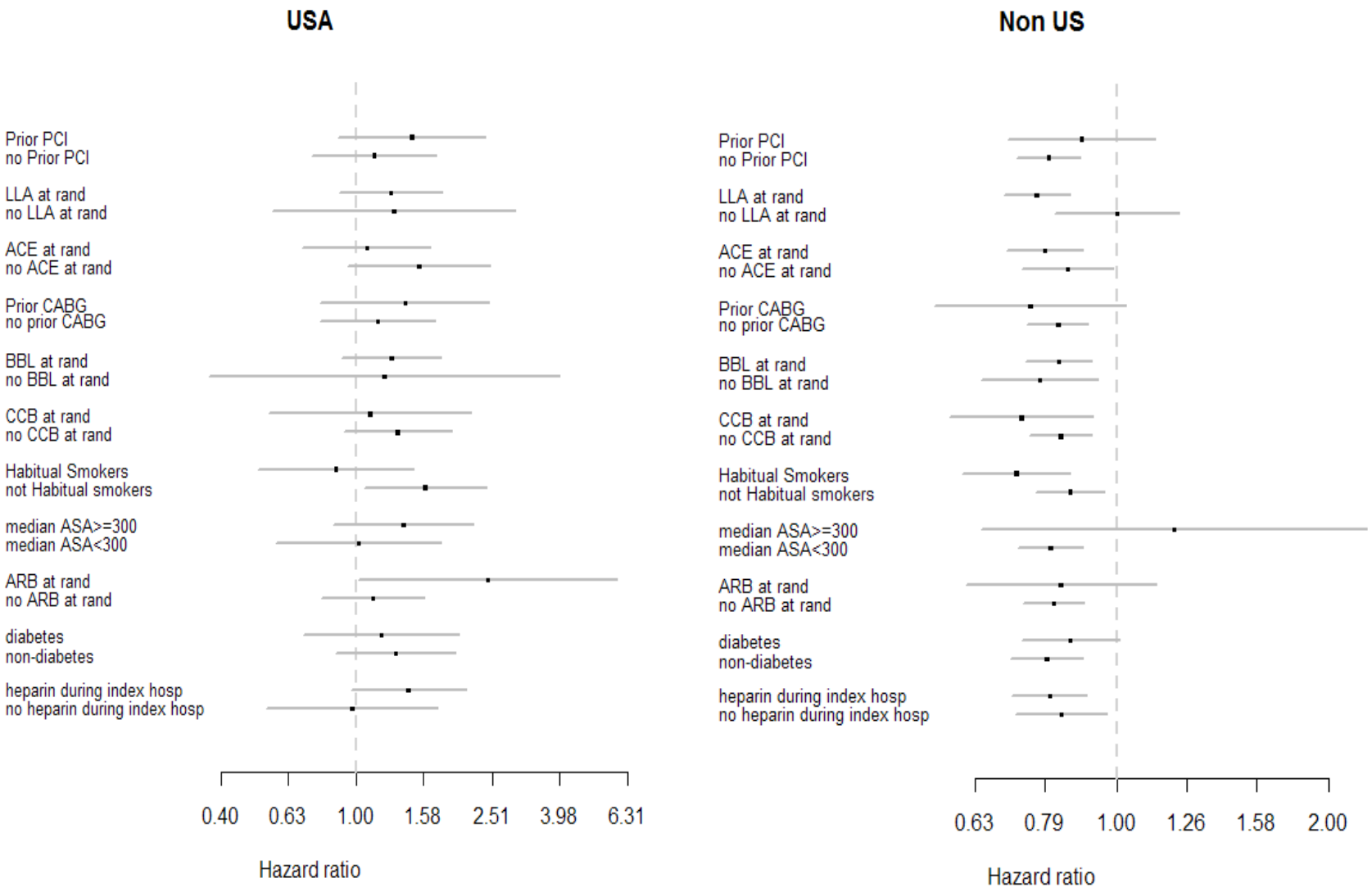


Figure 20 Analysis by various subgroups (2)

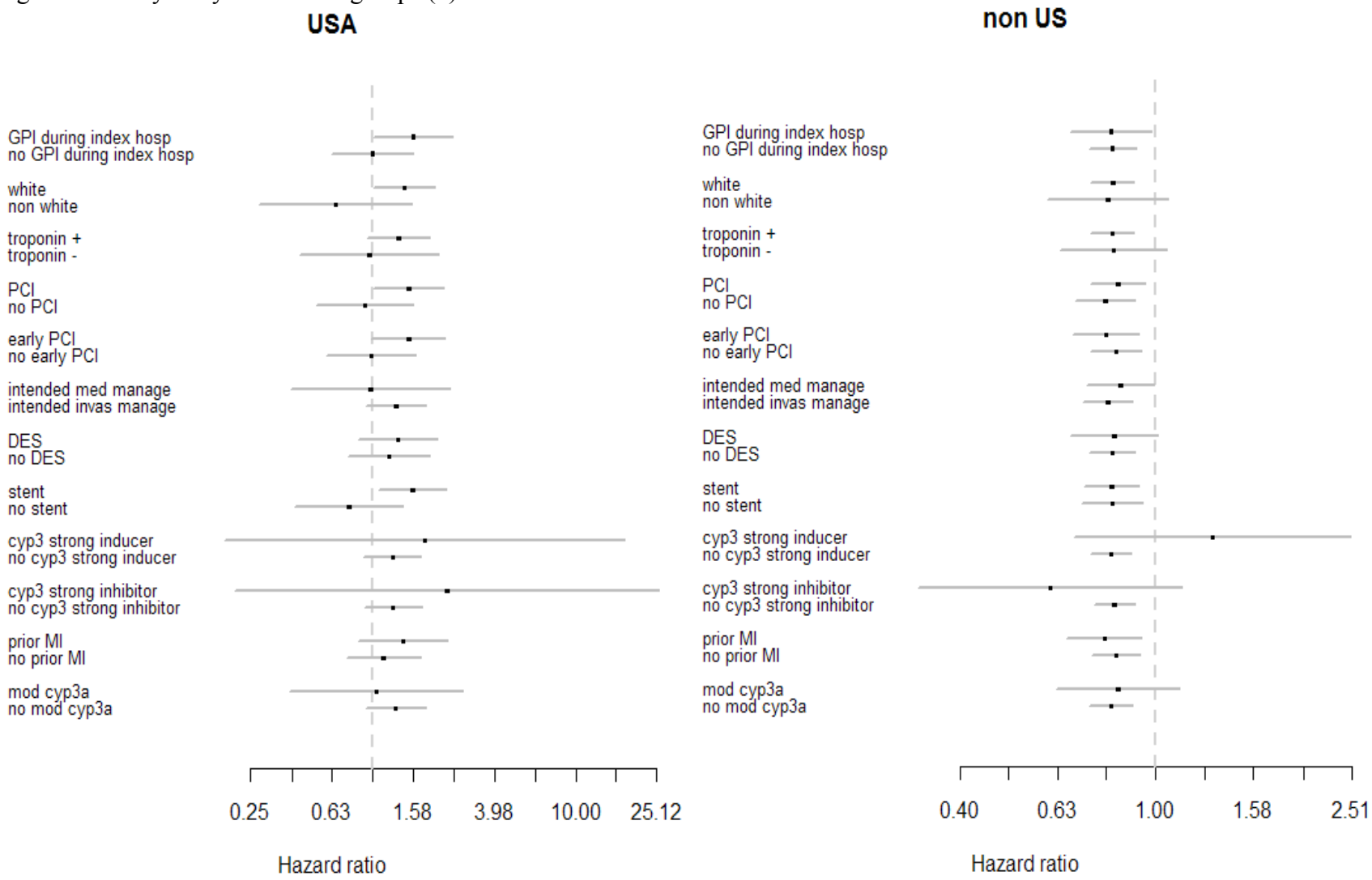
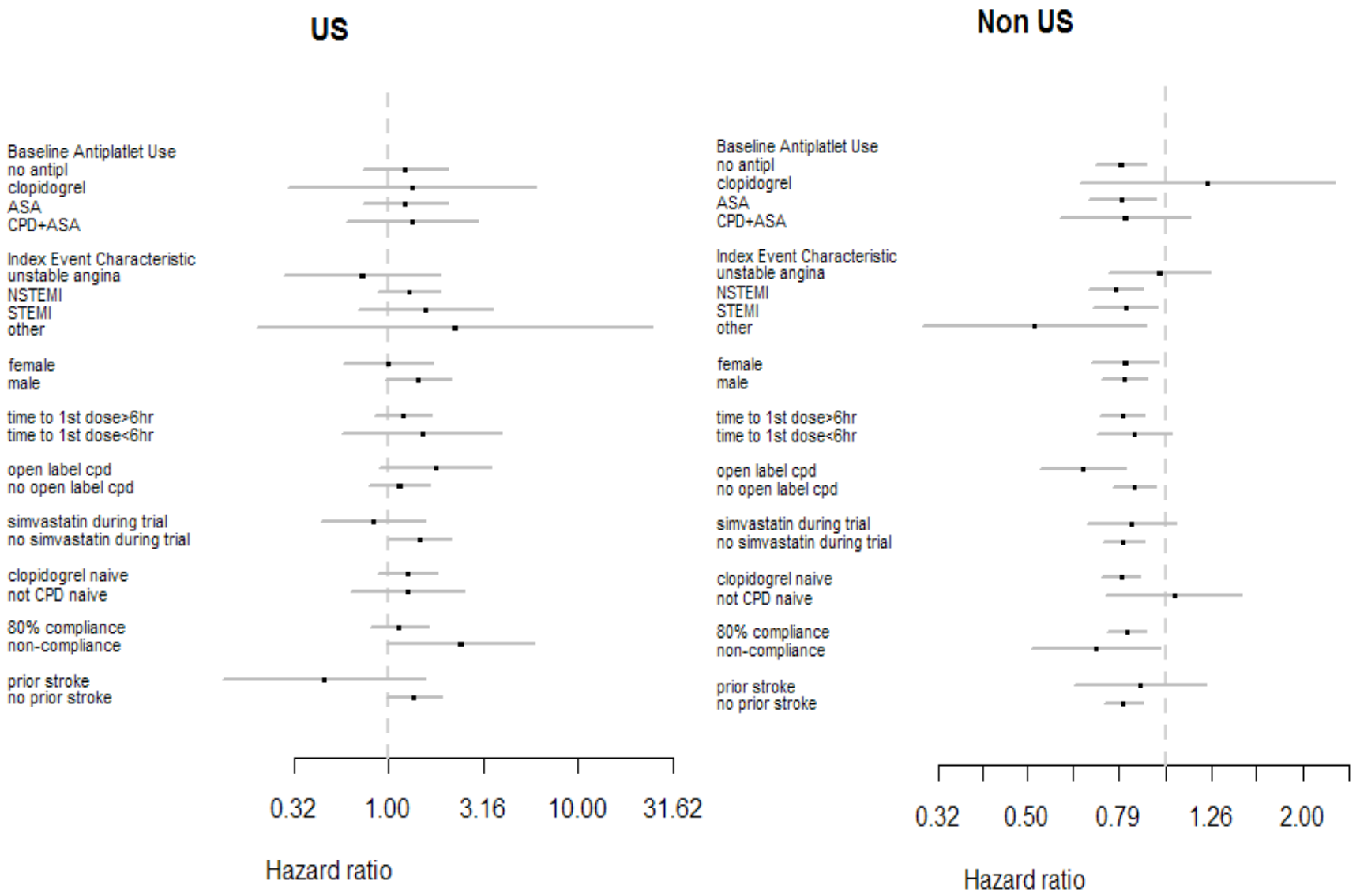


Figure 21 Analysis by various subgroups (3)



The reviewer also performed multivariate analyses based on the non-US population and compute the estimates of covariate coefficients. Due to some missing values, only 14258 subjects were included in the model. The covariates include

1. age
2. use of ARB at randomization
3. use of ASA at randomization
4. use of beta blocker at randomization
5. BMI
6. history of previous CABG
7. use of calcium channel blocker at randomization
8. use of modest CYP3A at randomization
9. history of diabetes
10. use of GPI during index hospitalization
11. use of heparin during index hospitalization
12. history of previous MI
13. race (white versus non-white)
14. use of DES or BMS
15. weight (kg)
16. planned treatment approach at randomization
17. use of CYP3A strong inducer during the study
18. use of CYP3A strong inhibitor during the study
19. PCI received during the study
20. habitual smoker
21. hours between index event to the first dose of study drug
22. statin use during the study
23. total number of bare metal stents inserted
24. total number of drug eluting stents inserted
25. early PCI received during the study
26. use of simvastatin during the study
27. whether took clopidogrel before index event (clopidogrel naïve)
28. use of lipid lowering agents at randomization
29. index event characteristic (NSTEMI, unstable angina, or other)
30. use of antiplatelet at randomization (ASA, clopidogrel or other)
31. days in hospital
32. hours between index event to hospital admission
33. history of previous stroke
34. 80% compliance

The treatment, covariates and covariate*treatment interactions were included in the model for the non-US population. Then a "hypothetical" estimate of hazard ratio on the US population was calculated based on the covariate coefficient estimates from the non-US model using the average of the corresponding covariates in the US population. If this multivariate model includes some factors contributing to the difference in treatment effect between US and non-US, the "hypothetical" hazard ratio estimate for US would be close to the hazard ratio estimate we

observed in the study for US population. The "hypothetical" hazard ratio estimate comes out to be 0.794. From this prospective, the covariates listed above do not seem to contribute significantly to the regional difference we observed.

3.1.1.8 Conclusions

The big issue in this application is the regional difference observed between US and non-US. The magnitude of the point estimate of hazard ratio in US is quite concerning. The reviewer performed extensive analyses to search for potential explanations.

Although play of chance can never be ruled out as a possible explanation, it seems to be a little overstretching if we observe a hazard ratio estimate of 1.25 in the US with 1413 subjects randomized while the rest of the world shows a clear benefit from ticagrelor (HR=0.84).

The sponsor attributed the concurrent ASA dose to the regional difference if it is not a play of chance. However, their finding remains questionable. First of all, most subjects taking 325 mg high dose ASA were from US. Use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US). Secondly, even though ASA seems to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. A few more or less events in that subpopulation in the non-US region can make a huge impact on the Cox proportional hazards model and therefore influence the interpretation.

The reviewer was also unsuccessful in finding other potential covariates that may explain the regional difference between US and non-US.

3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

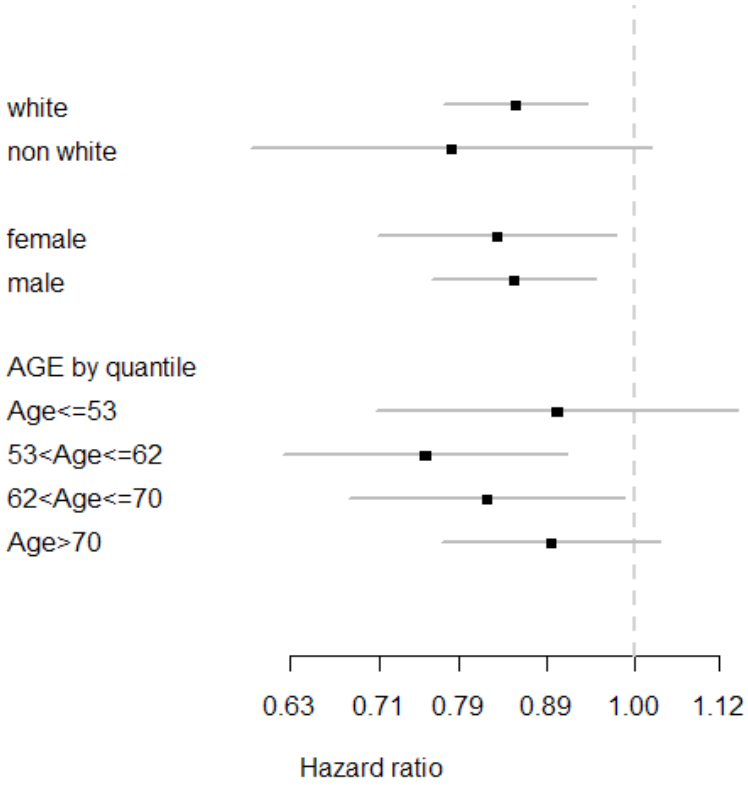
Over 90% subjects enrolled in the study are Caucasian. Gender, age and ethnic group are all well balanced between the two treatment groups (Table 9).

Table 9 Demographic Information on Age, Gender and Ethnic Group

Characteristic	Statistic or category	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	Total N=18624
Age (years)	N	9332	9290	18622
	Mean (SD)	62.1 (11.21)	62.3 (11.21)	62.2 (11.21)
Sex	Total	9333	9291	18624
	Male	6678 (71.6%)	6658 (71.7%)	13336 (71.6%)
	Female	2655 (28.4%)	2633 (28.3%)	5288 (28.4%)
Race	Total	9332	9291	18623
	Caucasian	8566 (91.8%)	8511 (91.6%)	17077 (91.7%)
	Black	115 (1.2%)	114 (1.2%)	229 (1.2%)
	Asian	542 (5.8%)	554 (6.0%)	1096 (5.9%)
	Other	109 (1.2%)	112 (1.2%)	221 (1.2%)
	Unknown	1 (0.0%)	0	1 (0.0%)

Figure 22 shows the hazard ratio estimates by the individual subgroups. Numerically, treatment effect of ticagrelor appears to be consistent across gender, race and age.

Figure 22 Hazard ratio estimates by race, gender and age



4.2 Other Subgroup Populations

Please refer to Section 3.1.1.7 for reviewer's analyses on regional difference.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The big issue in this application is the regional difference observed between US and non-US. The magnitude of the point estimate of hazard ratio in US is quite concerning. The reviewer performed extensive analyses to search for potential explanations.

The hazard ratio estimates in US population stayed consistently above 1 throughout the trial. The probability of observing such results were calculated in several ways assuming that the true hazard ratio is 0.84. If taking the sample size as well as the magnitude of difference between the hazard ratio estimates into account, although play of chance can never be excluded from a possible explanation, it does seem to be a little overstretching if we observe a hazard ratio estimate of 1.27 in a country enrolled 1413 subjects while the rest of the world shows a clear benefit from ticagrelor (HR=0.84).

The sponsor attributed the concurrent ASA dose to the regional difference if it is not a play of chance. However, their finding remains questionable. First of all, most subjects taking 325 mg high dose ASA were from US. Use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US). Secondly, even though ASA seems to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. The Cox proportional hazards model appeared quite sensitive to the high ASA subjects in non-US region. The model also seemed to be sensitive to whether or not the first day ASA loading dose is included.

The reviewer was also unsuccessful in finding other potential covariates that may explain the regional difference between US and non-US. On the other hand, US population differed from non-US population in a number of ways even though they did seem to explain the regional difference. For example, it took much longer time on average for US subjects to receive first dose of study drug since occurrence of index. More US subjects enrolled in the trial were NSTEMI patients compared to the rest of the world. Other factors include prior history of PCI or MI, number of subjects who went through early PCI, pre-index event antiplatelet therapy, beta blocker usage at randomization, planned treatment approach at randomization, GPI during index hospitalization, and many more.

5.2 Conclusions and Recommendations

The single phase III trial PLATO randomized 18,624 subjects to compare the efficacy and safety of ticagrelor 90 mg with clopidogrel 75 mg in the prevention of CV death, MI, and stroke in patients with non-ST or ST elevation ACS. One major issue is the regional difference observed between US and non-US. The study reported a hazard ratio estimate of 0.84 [95% CI (0.77, 0.92)] for the overall population favoring ticagrelor. However, for US the hazard ratio estimate was 1.27 [95% CI (0.92, 1.75)], which suggested a 27% greater risk of the clinical event with ticagrelor relative to clopidogrel. The magnitude of this point estimate of hazard ratio in US is quite concerning, especially since US had the second largest enrollment among 43 countries in this trial. The reviewer performed extensive analyses examining many factors or covariates but was not able to find a definitive explanation for the regional difference. However, the US population appeared different from the rest of the world in a number of ways based on the reviewer's analyses even though they did not seem to explain the regional difference. If US population differs sufficiently from the rest of the world, a US trial may be needed to further evaluate the efficacy of ticagrelor in US subjects.

Although play of chance can never be ruled out as a possible explanation, it seems to be a little overstretching, given the magnitude of the difference in hazard ratio estimates between US and non-US. The sponsor attributed the concurrent aspirin (ASA) use to the regional difference if it is not a play of chance. However, even though ASA seems to be the biggest contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the explanatory model used by the sponsor for explaining the regional difference does not appear robust since

very few subjects outside US took high dose ASA. Thus, the interpretability of the results that the ASA dose may explain the regional difference remains very much uncertain.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

JIALU ZHANG
06/29/2010

HSIEN MING J J HUNG
06/29/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-433 **Applicant: AstraZeneca** **Stamp Date: 11/16/2009**

Drug Name: Brilinta **NDA/BLA Type: priority**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	x			
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			x	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician	Date
Supervisor/Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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JIALU ZHANG
12/30/2009

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12/30/2009