NDA 22-433 Brilinta® (ticagrelor)

Efficacy Review

Cardio-Renal Advisory Committee Meeting

July 28, 2010

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CDER, DCRP

Proposed Indication:

Reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be:

- **managed medically**
- **managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG**

BRILINTA as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes. BRILINTA as compared to clopidogrel has also been shown separately to reduce the rate of:

- CV death
- MI

Outline

- **Regulatory context of PLATO**
- **Subgroups relevant to the proposed indication**
  - Outcome by Index ACS Event
  - Outcome by Medical *vs.* Invasive Management
  - Accrual & Timing of benefit compared to clopidogrel
- **Regional Differences (US *vs.* non-US)**
- **ASA-ticagrelor treatment interaction hypothesis**

PLATO

- One strength of PLATO was that subjects were to take the first dose of study medication as soon as possible after randomization and before any PCI
- Subjects could also be medically managed without a planned intervention (PCI) for the index event
- Goal was to reflect current clinical management of ACS, with early initiation of dual antiplatelet therapy, irrespective of whether patients are medically managed or invasively managed
- PLATO enrolled STEMI, NSTEMI and UA (without stratification)

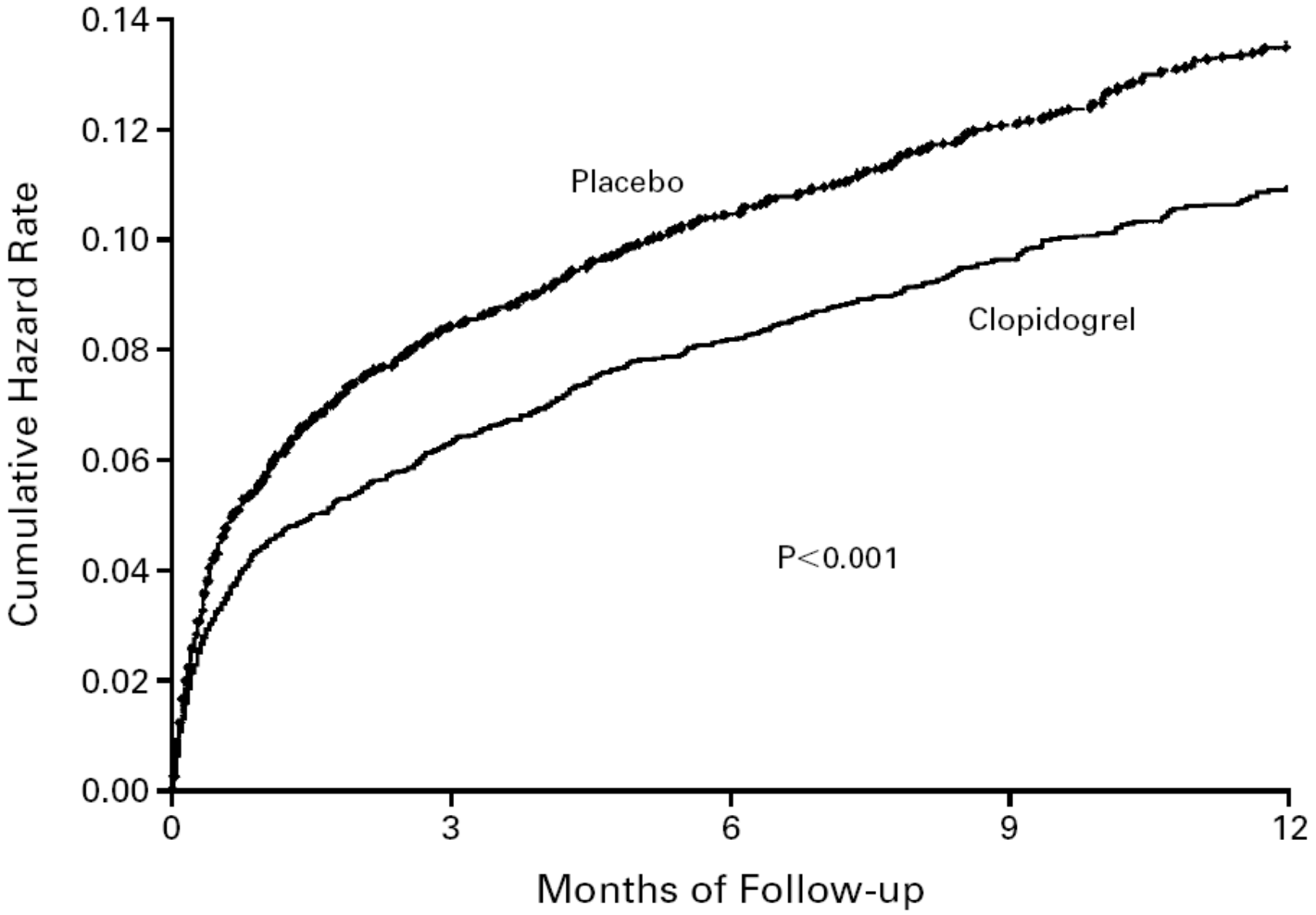
Prior Antiplatelet Studies: Clopidogrel & Prasugrel

CURE (clopidogrel)

- ACS within 24 hours after the onset of symptoms
- No STEMI
- *Some without ECG changes*
- …*vs.* placebo (ASA background)
- Primary Endpoint: CV death, nonfatal MI, or stroke

TRITON-TIMI 38 (prasugrel)

- ACS with scheduled percutaneous coronary intervention
- UA/NSTEMI & STEMI
- IP delayed until after angiography (except STEMI ≤12hr)
- …*vs.* clopidogrel (ASA background)
- Primary endpoint: CV death, nonfatal MI, or stroke



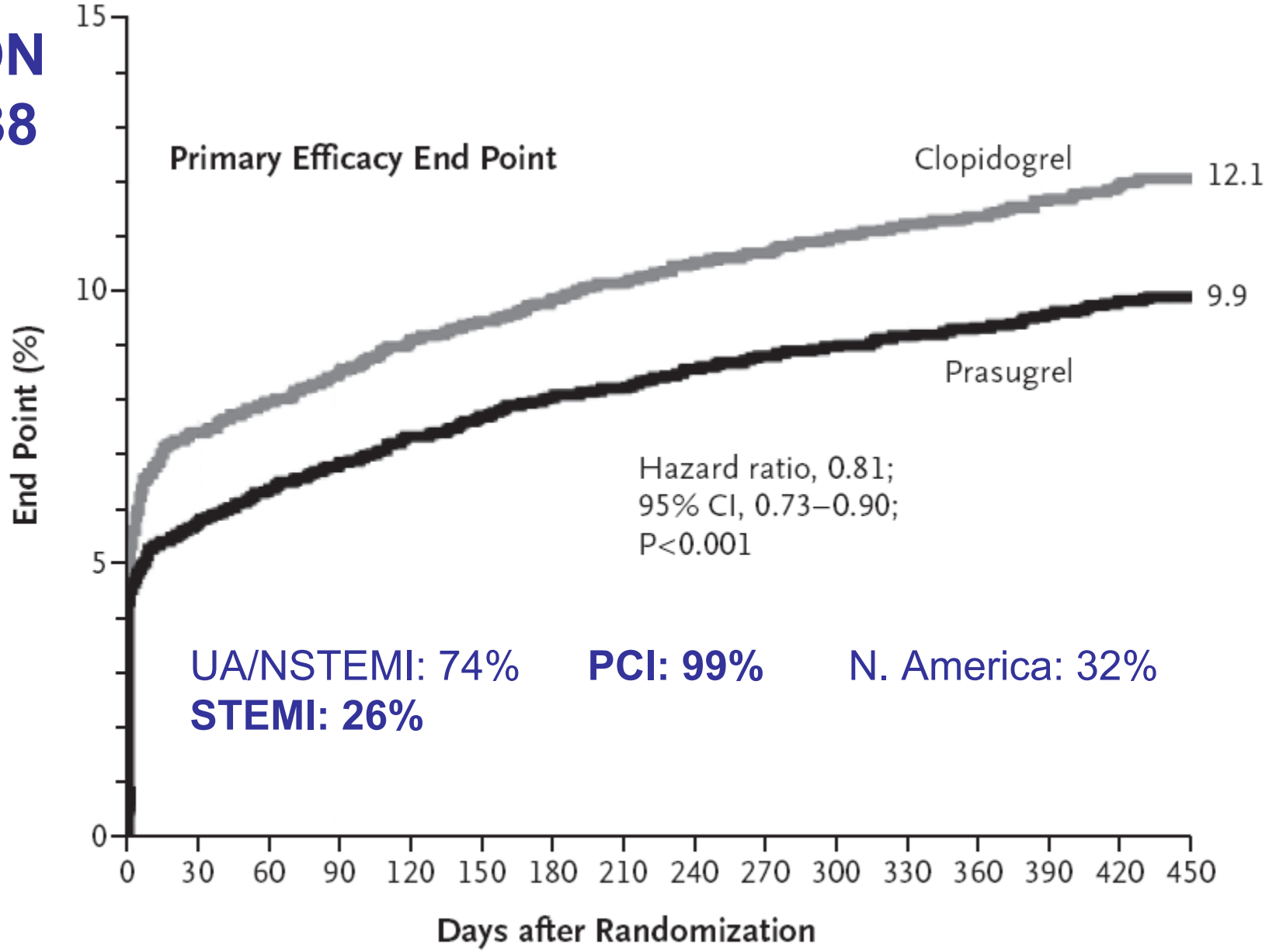
No. at Risk

Placebo	6303	5780	4664	3600	2388
Clopidogrel	6259	5866	4779	3644	2418

Figure 1. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study.

The results demonstrate the sustained effect of clopidogrel.

TRITON TIMI-38

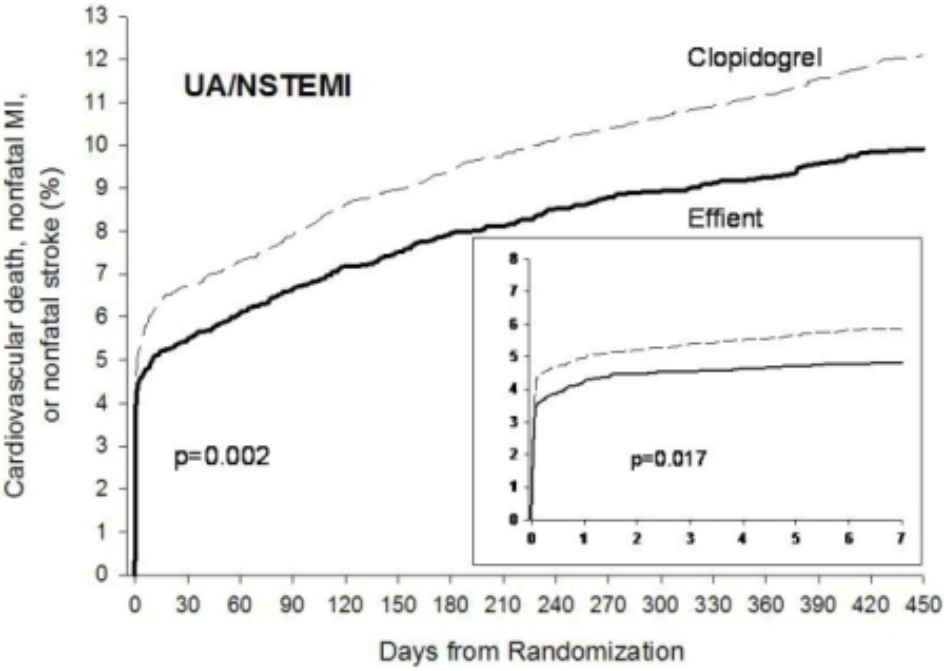


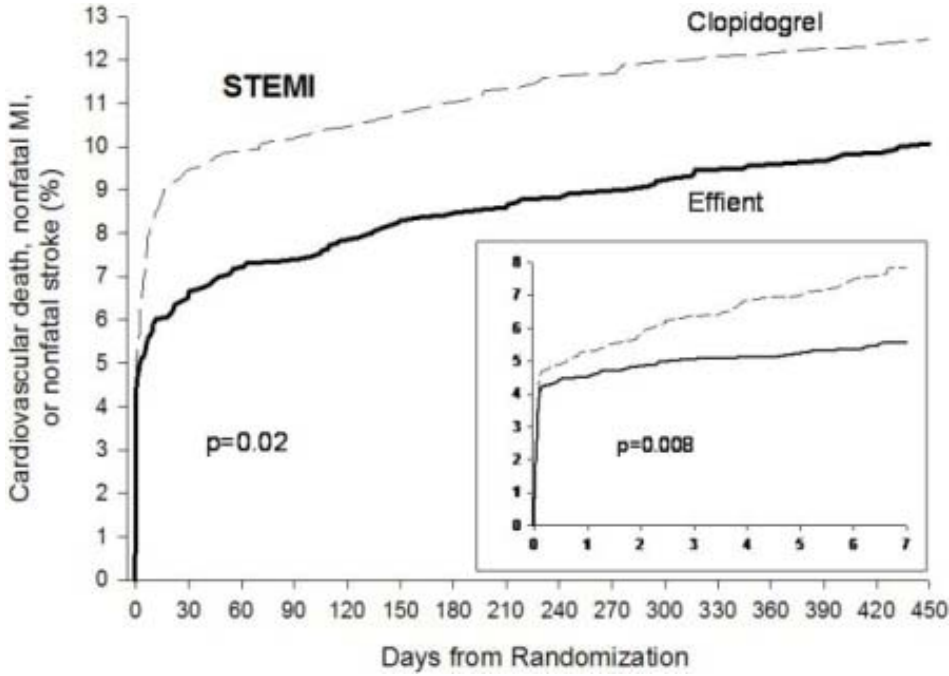
UA/NSTEMI: 74% **PCI: 99%** N. America: 32%
STEMI: 26%

No. at Risk

Clopidogrel	6795 6169	6036	5835	5043	4369	3017
Prasugrel	6813 6305	6177	5951	5119	4445	3085

TRITON TIMI-38: Index ACS Event



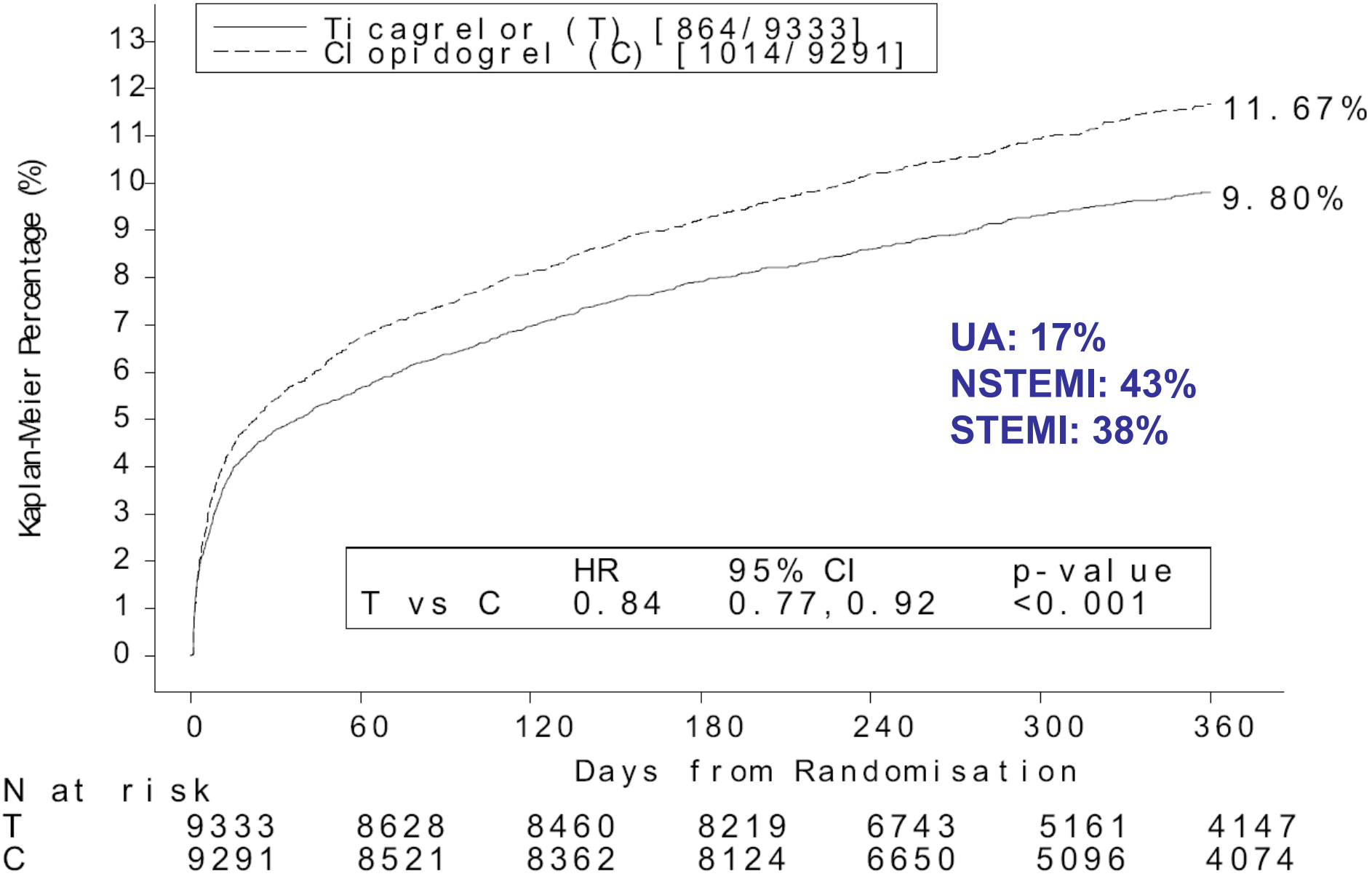


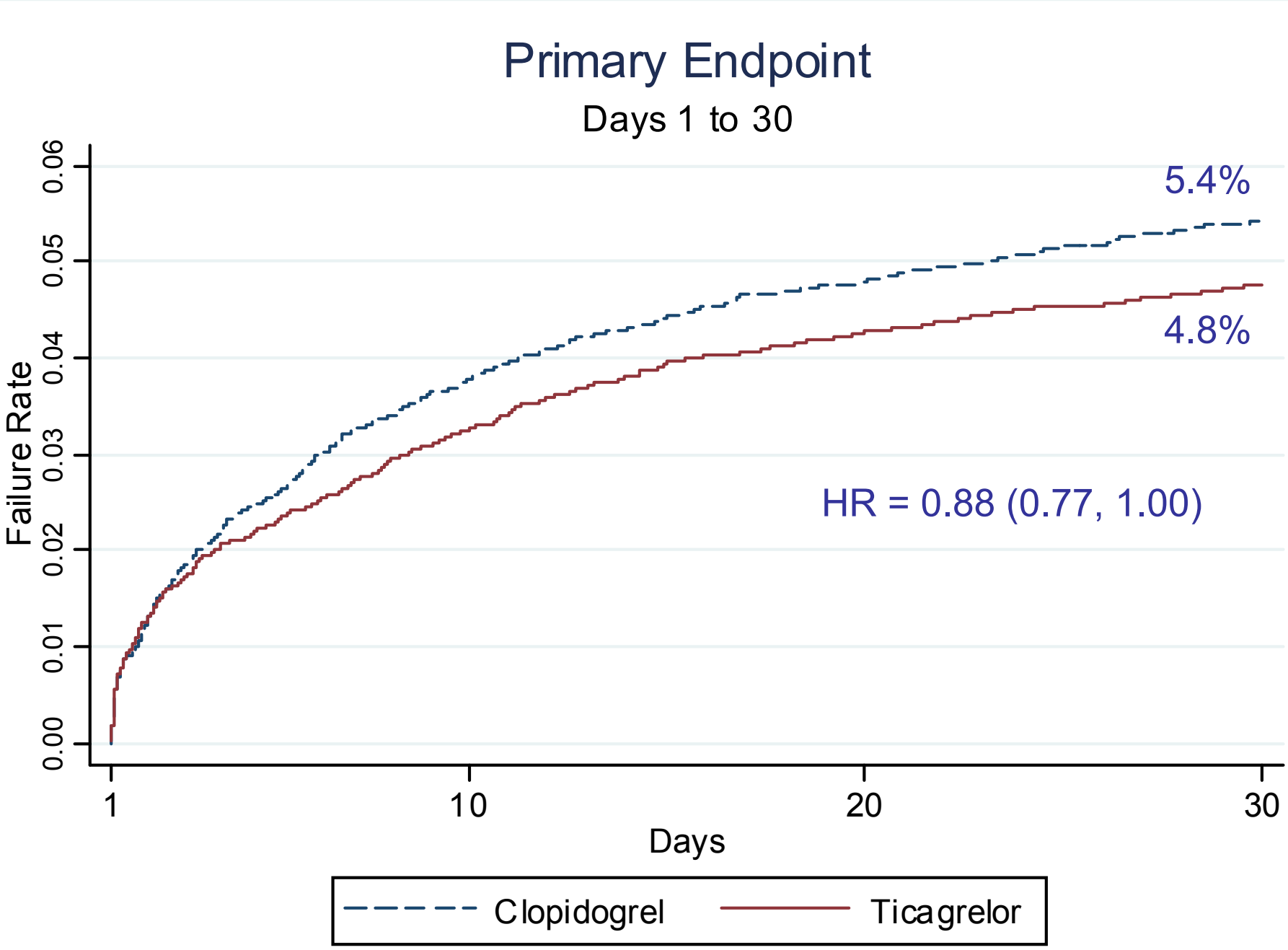
The KM curves show the adjudicated primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time in the UA/NSTEMI and STEMI populations.

In the **UA/NSTEMI** population, the curves continue to diverge throughout the 15 month follow-up period.

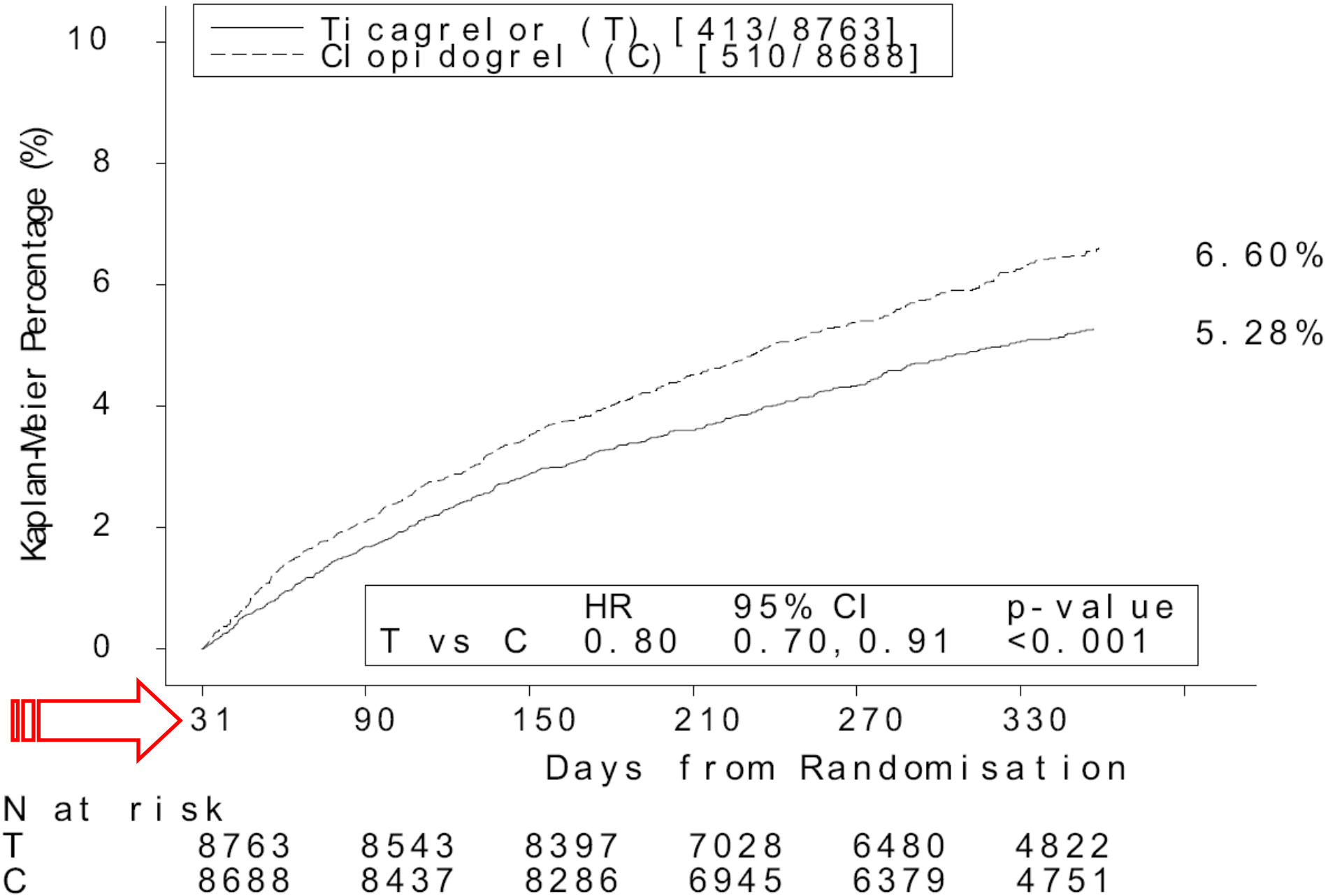
In the **STEMI** population, the early separation was maintained throughout the 15 month follow-up period, but there was no progressive divergence after the first few weeks.

PLATO


Ticagrelor (T) [864/9333]
Clopidogrel (C) [1014/9291]
11.67%
9.80%
UA: 17%
NSTEMI: 43%
STEMI: 38%
HR 95% CI p-value
T vs C 0.84 0.77, 0.92 <0.001
Kaplan-Meier Percentage (%)
0 1 2 3 4 5 6 7 8 9 10 11 12 13
0 60 120 180 240 300 360
Days from Randomisation
N at risk
T 9333 8628 8460 8219 6743 5161 4147
C 9291 8521 8362 8124 6650 5096 4074


Primary Endpoint
Days 1 to 30
Failure Rate
0.00
0.01
0.02
0.03
0.04
0.05
0.06
5.4%
4.8%
HR = 0.88 (0.77, 1.00)
1
10
20
30
Days
Clopidogrel
Ticagrelor

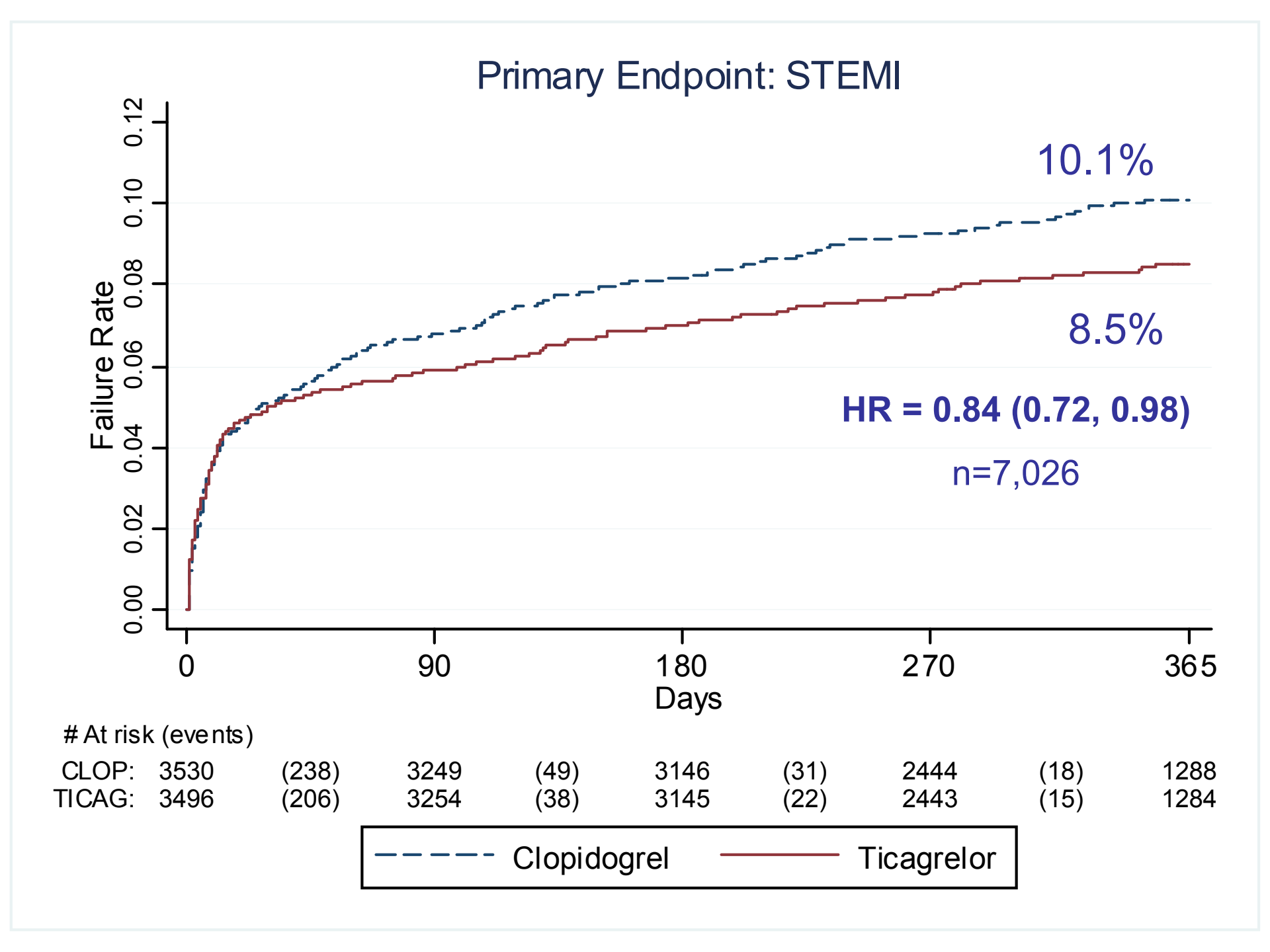
Primary Endpoint: 30-day landmark

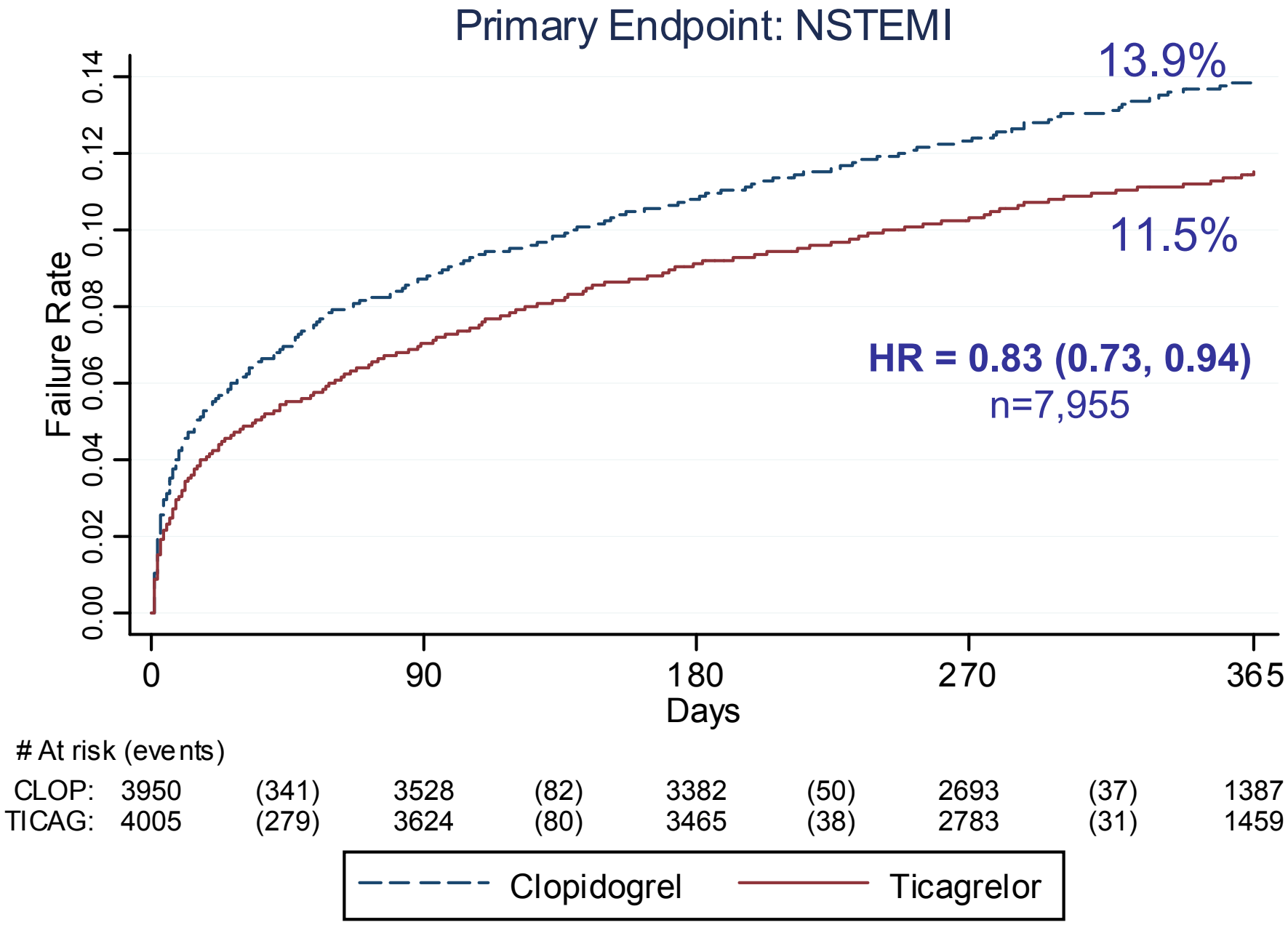


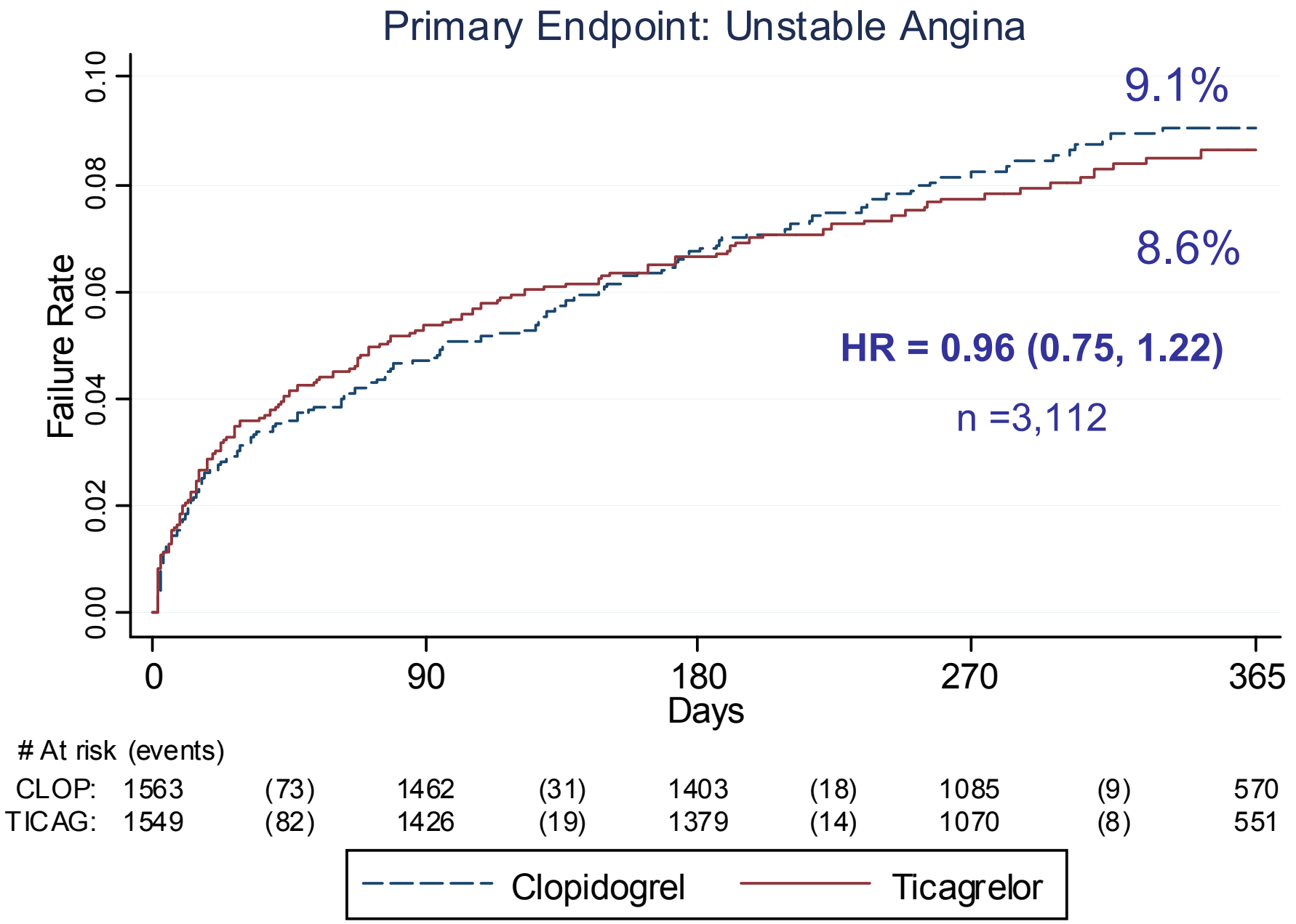
Final Diagnosis of Index Event

"At enrolment, a preliminary diagnosis of non-ST or ST segment elevation ACS was made based on initial ECG.

By the end of the initial hospitalisation (Visit 1 discharge), the availability of laboratory data allowed the index event to be classified as UA, NSTEMI, or STEMI."


Primary Endpoint: STEMI
Failure Rate
0.00
0.02
0.04
0.06
0.08
0.10
0.12
10.1%
8.5%
HR = 0.84 (0.72, 0.98)
n=7,026
0
90
180
270
365
Days
At risk (events)
CLOP: 3530 (238) 3249 (49) 3146 (31) 2444 (18) 1288
TICAG: 3496 (206) 3254 (38) 3145 (22) 2443 (15) 1284
Clopidogrel
Ticagrelor


Primary Endpoint: NSTEMI
13.9%
11.5%
HR = 0.83 (0.73, 0.94)
n=7,955
Failure Rate
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0
90
180
270
365
Days
At risk (events)
CLOP: 3950 (341) 3528 (82) 3382 (50) 2693 (37) 1387
TICAG: 4005 (279) 3624 (80) 3465 (38) 2783 (31) 1459
Clopidogrel
Ticagrelor


Primary Endpoint: Unstable Angina
Failure Rate
0.00
0.02
0.04
0.06
0.08
0.10
9.1%
8.6%
HR = 0.96 (0.75, 1.22)
n =3,112
0
90
180
270
365
Days
At risk (events)
CLOP: 1563 (73) 1462 (31) 1403 (18) 1085 (9) 570
TICAG: 1549 (82) 1426 (19) 1379 (14) 1070 (8) 551
Clopidogrel
Ticagrelor

PLATO: Unstable Angina Population

ACS within 24 hours before randomization and documented cardiac ischemic symptoms of ≥10 minutes duration at rest.

If ST segment changes on ECG indicative of ischemia, but no STEMI or NSTEMI, had to have at least 1 of the following risk factors:

- Aged 60 or over
- Previous MI or CABG
- Known multi-vessel coronary artery disease (CAD)
- Previous ischemic stroke, TIA, carotid stenosis (≥ 50%) or cerebral revascularization
- Diabetes mellitus
- Peripheral arterial disease
- Chronic renal dysfunction

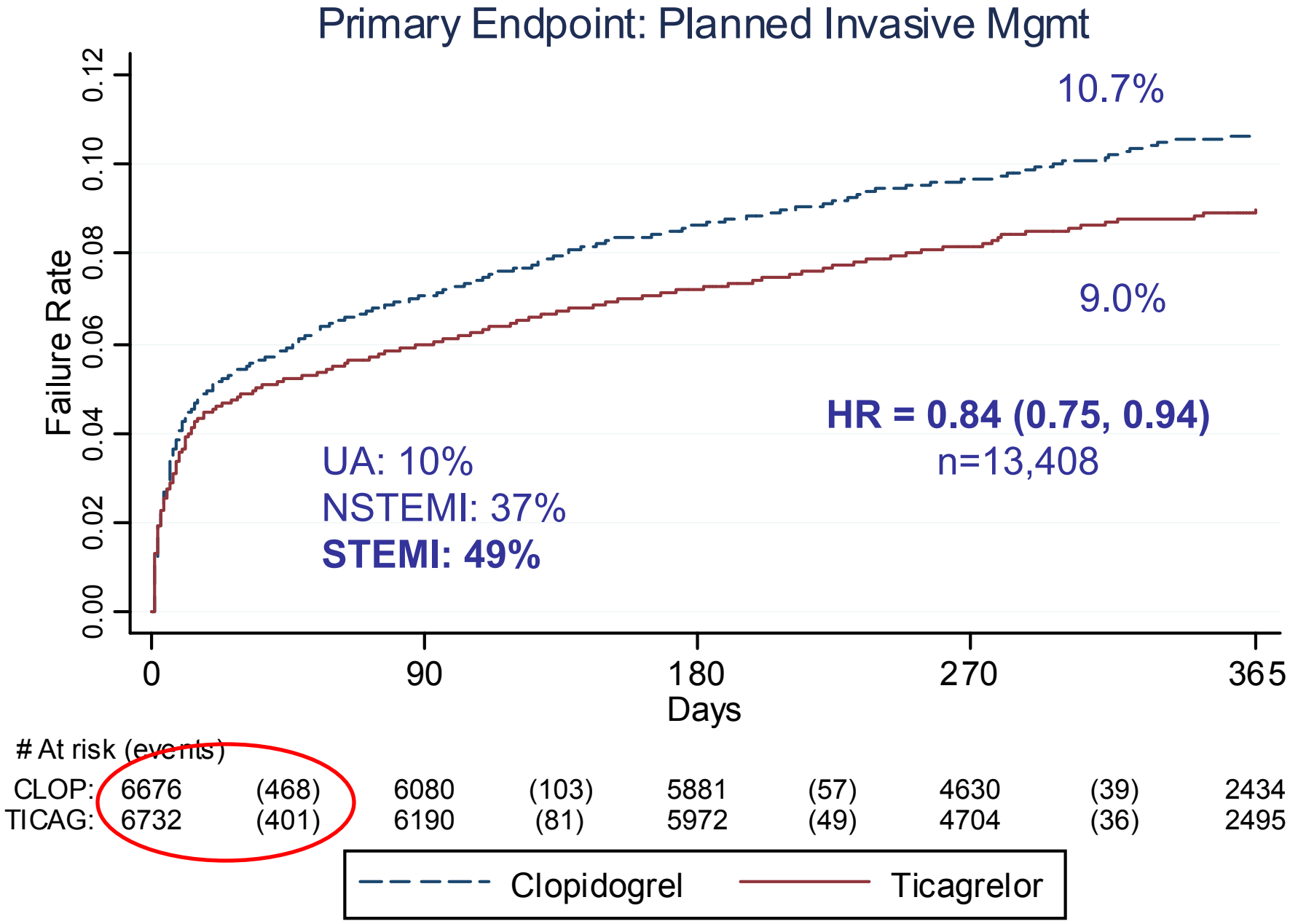
Outcome by Index ACS Event

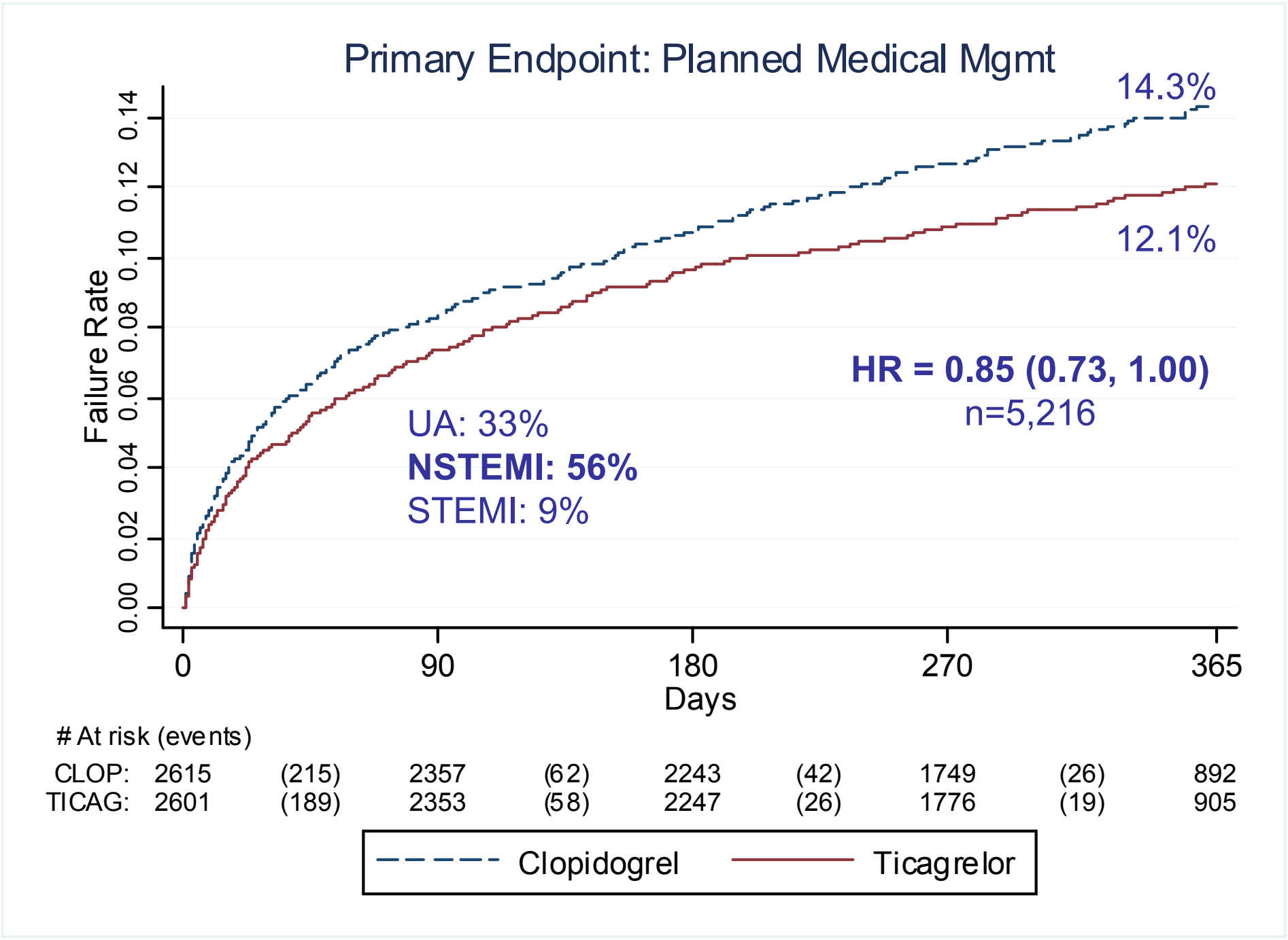
- There was no relative benefit in subjects with Unstable Angina
  - *What is the clinical significance in an ACS population?*
- The index ACS event itself was associated with planned (and actual) treatment strategy at randomization

Invasive vs. Medical Management

- IP + ASA given irrespective of whether patients were medically managed or invasively managed (with PCI or CABG)

- Reflecting current guidelines, initiation of treatment in PLATO was to occur as soon as possible after symptom onset, prior to the assessment of coronary anatomy by angiography


Primary Endpoint: Planned Invasive Mgmt
Failure Rate
0.00
0.02
0.04
0.06
0.08
0.10
0.12
10.7%
9.0%
HR = 0.84 (0.75, 0.94)
n=13,408
UA: 10%
NSTEMI: 37%
STEMI: 49%
0
90
180
270
365
Days
At risk (events)
CLOP: 6676 (468) 6080 (103) 5881 (57) 4630 (39) 2434
TICAG: 6732 (401) 6190 (81) 5972 (49) 4704 (36) 2495
Clopidogrel
Ticagrelor


Primary Endpoint: Planned Medical Mgmt
14.3%
12.1%
HR = 0.85 (0.73, 1.00)
n=5,216
UA: 33%
NSTEMI: 56%
STEMI: 9%
Failure Rate
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0
90
180
270
365
Days
At risk (events)
CLOP: 2615 (215) 2357 (62) 2243 (42) 1749 (26) 892
TICAG: 2601 (189) 2353 (58) 2247 (26) 1776 (19) 905
Clopidogrel
Ticagrelor

Primary Endpoint:
Planned Treatment Approach at Randomization *vs.* Index ACS Event

	STEMI		NSTEMI		UA	
Medical Mgmt	T: 14.7% (31/218) C: 19.5% (44/233)	**0.73** (0.46, 1.16)	T: 14.0% (190/1441) C: 16.6% (226/1469)	**0.85** (0.70, 1.02)	T: 8.1% (65/873) C: 8.6% (67/853)	**0.97** (0.69, 1.37)
Invasive Mgmt	T: 8.1% (250/3278) C: 9.5% (293/3297)	**0.86** (0.72, 1.01)	T: 10.2% (242/2564) C: 12.2% (284/2481)	**0.82** (0.70, 0.97)	T: 9.3% (59/676) C: 9.7% (65/710)	**0.95** (0.67, 1.35)

T = ticagrelor, C = clopidogrel; % are KM% at 365 days; HR (95%CI)

Are there 6 subgroups in the proposed indication?

US v. non-US Outcomes

	Ticagrelor (n/N)	Clopidogrel (n/N)	HR (95% CI)
PLATO Overall N=18,624	9.8% (864/9333)	11.7% (1014/9291)	**0.84** (0.77, 0.93)
Non-US n=17,211	9.6% (780/8626)	11.8% (947/8585)	**0.81** (0.74, **0.90**)
US n=1,413	12.6% (84/707)	10.1% (67/706)	**1.27** (**0.92**, 1.75)

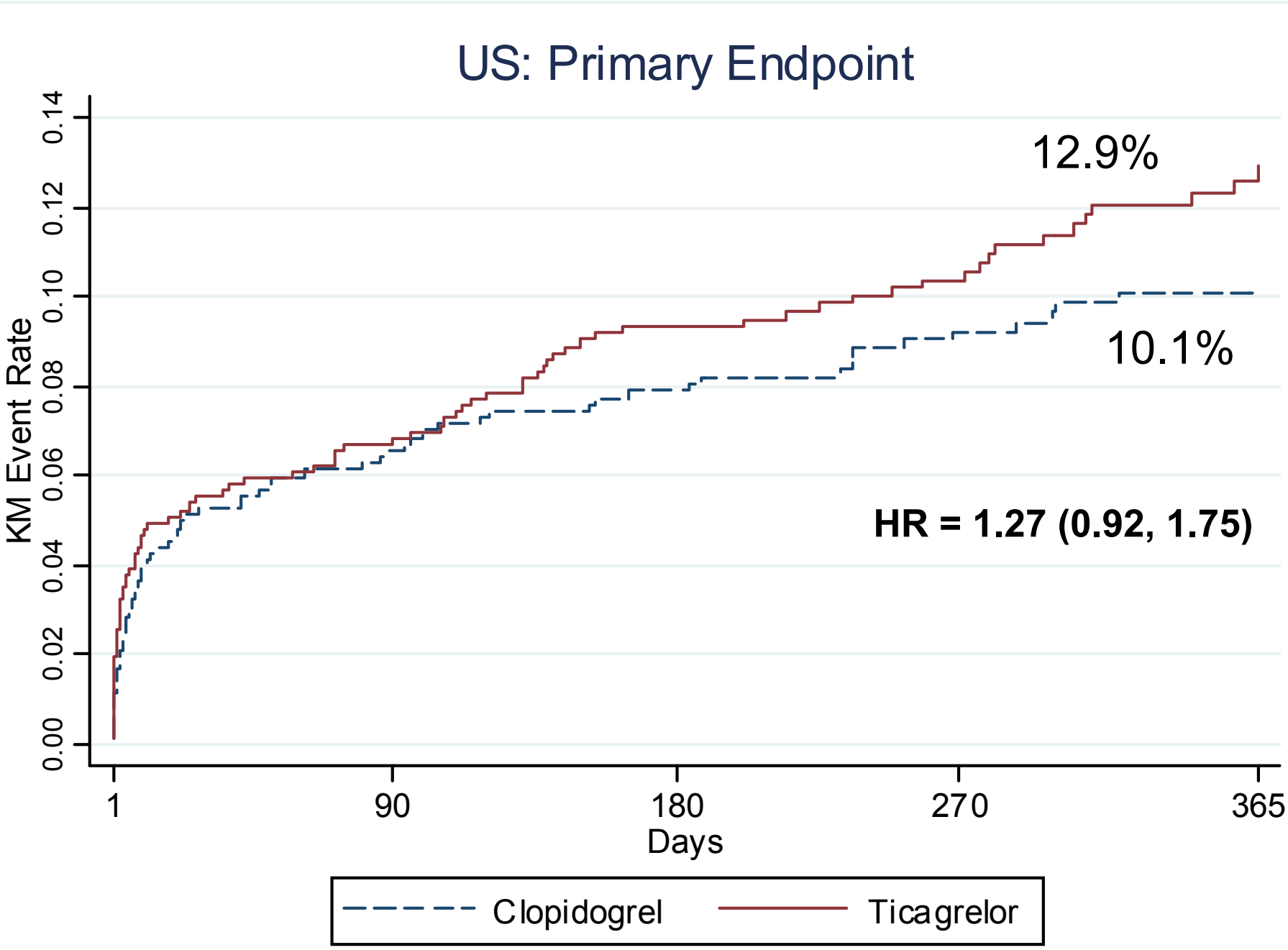
- 95% CIs of the US and non-US subgroups do not overlap
- In the US, clopidogrel did 'better' and ticagrelor did 'worse'

US *vs.* non-US

- Significant interaction between region and treatment (p=0.045) due to “North America”
- The United States comprised 78% of subjects in North America
- Both US and Canada had primary outcomes unfavorable towards ticagrelor

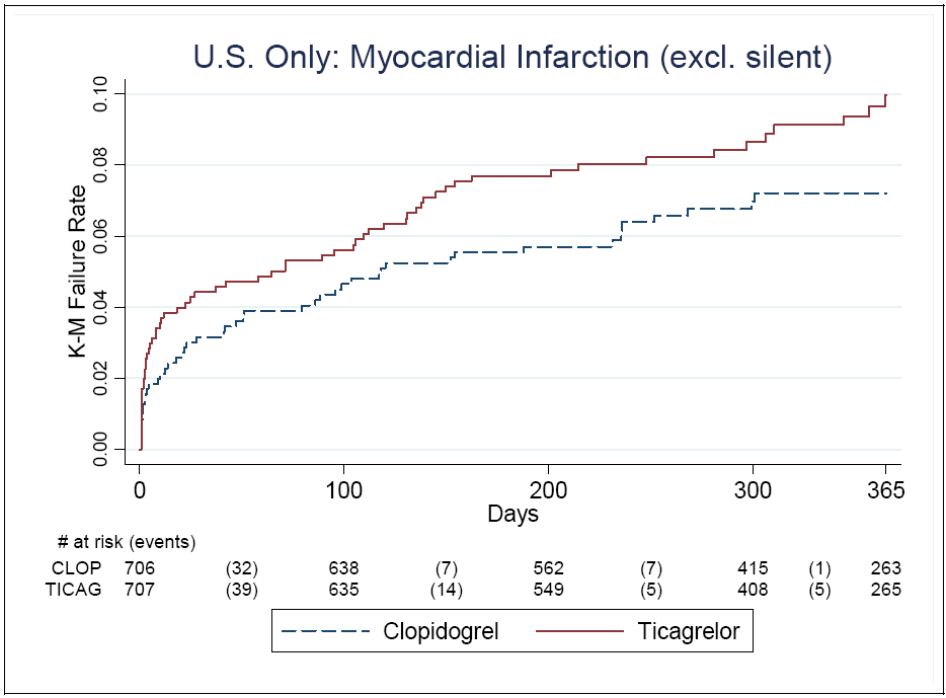
  US: HR = 1.27 (0.92, 1.75), n=1,413

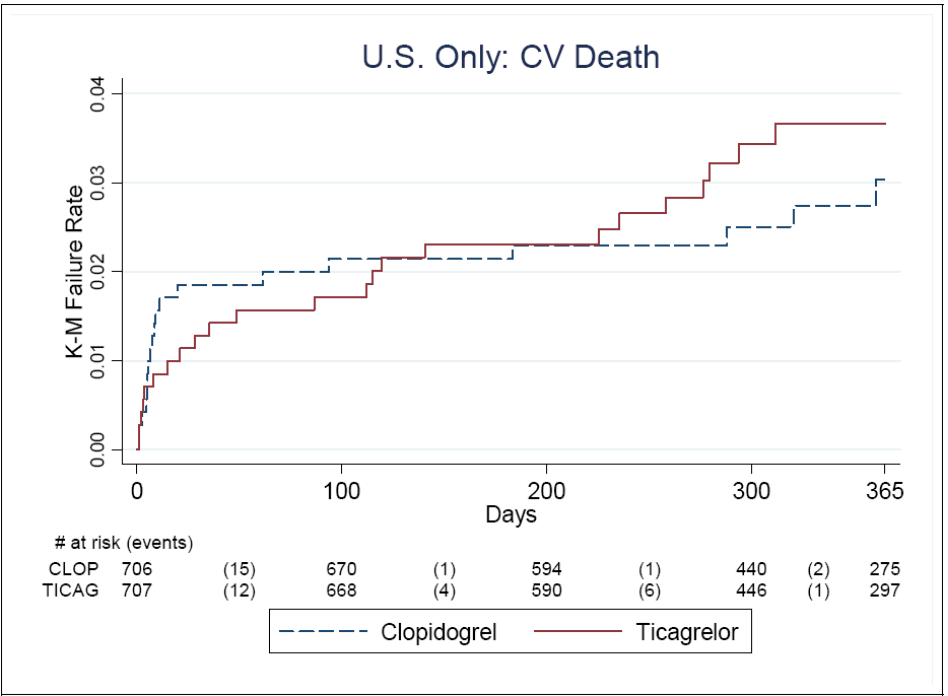
  Canada: HR=1.17 (0.59, 2.31), n=401

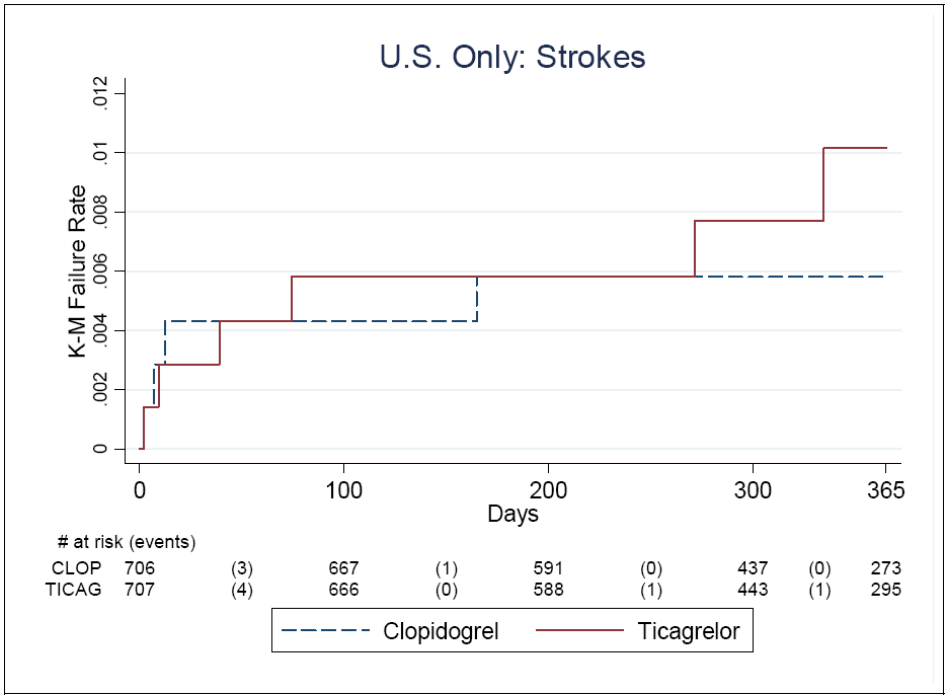

US: Primary Endpoint
KM Event Rate
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
12.9%
10.1%
HR = 1.27 (0.92, 1.75)
1
90
180
270
365
Days
Clopidogrel
Ticagrelor

US ONLY

MI: 1.38 (0.95, 2.01)
CV Death: 1.26 (0.69, 2.31)
Strokes: 1.75 (0.51, 5.97)







Factor	US	Non-US
Weight (median)	87kg	80kg
Diabetes	33%	24%
Prior MI	27%	20%
Prior PCI	29%	12%
Prior CABG	17%	5%
STEMI	16%	40%
NSTEMI	67%	41%
UA	10%	17%
≥ 12 hrs index event to study drug	63%	46%
Planned Invasive Mgmt	94%	70%
PCI < 24hr after randomization	62%	50%
PCI w/ Drug eluting stent Ave. # DES implanted	46% 1.8	19% 1.6
PCI w/ Bare Metal stent Ave. # BMS implanted	23% 1.5	46% 1.5
ASA dose, mg Median Mean	325 217	100 99
Compliance	86%	95%

- The US population had different baseline factors at the time of enrollment and subsequently underwent different treatment strategies compared to the general non-US population

- …including the use of concomitant higher-dose aspirin

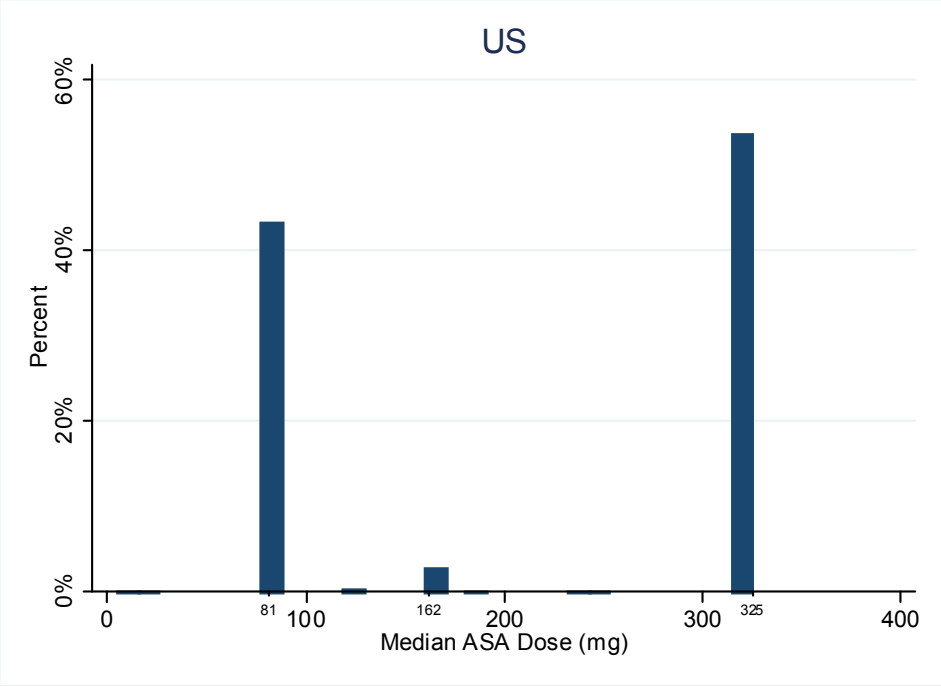
ASA Interaction

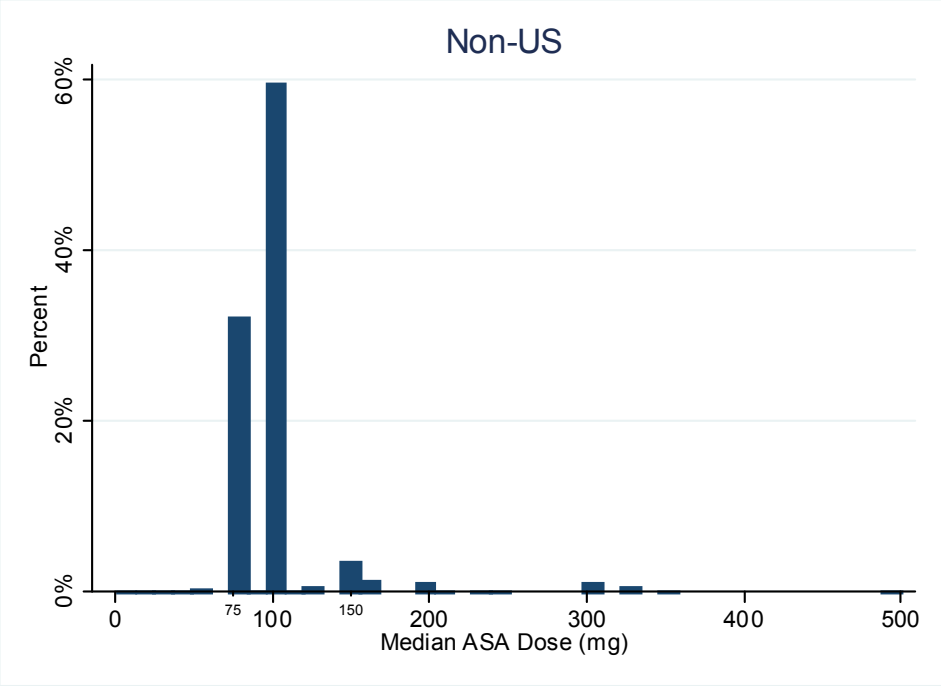
- The most pronounced initial observation explaining the regional differences in outcome was that of a potential treatment interaction between aspirin (ASA) and study treatment, such that higher-dose aspirin was associated with comparatively unfavorable outcomes for ticagrelor.

ASA Interaction

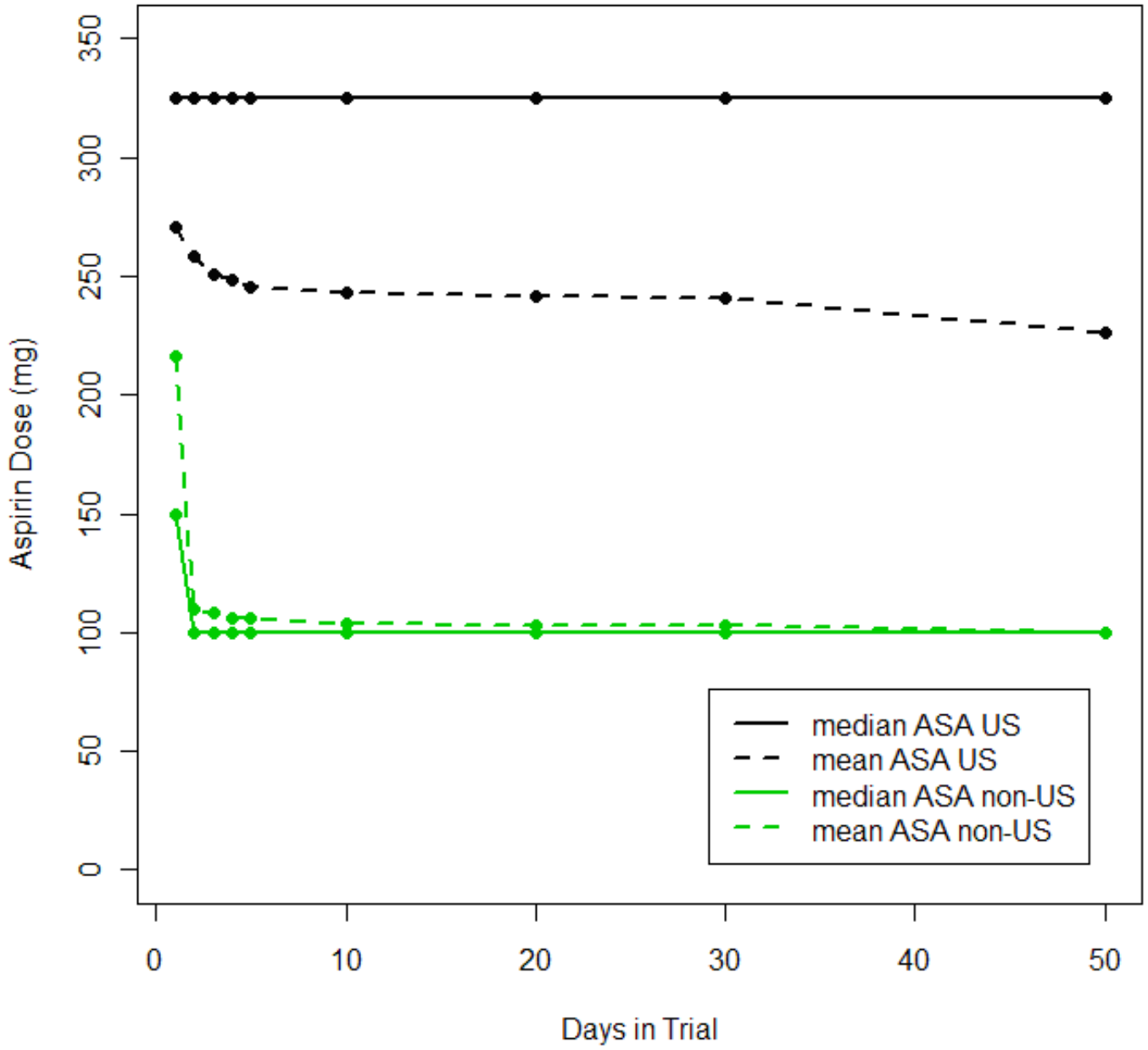
- On average, the US took a substantially higher dose of concomitant aspirin compared to the rest of the world
- Avg. ~220mg US vs. ~100mg non-US
- Over half of the US study population received concomitant median daily doses of 325mg aspirin, with a lesser number receiving 81mg

Median ASA Dose: US vs. non-US





ASA Dose over time



US

Non-US

ASA Interaction

- Further analyses suggested that US subjects who received ASA 81mg had numerically better outcomes than those on 325mg
- It was not clear if effect modifiers related to higher dose aspirin could explain these differences *independently*

ASA Interaction (cont'd)

- US subjects who received higher-dose, 325mg ASA (n=667) when compared to those with 81mg (n=545), were more likely to have:
  - PCI on-study (77% vs. 61%)
  - More stents implanted (74% vs. 58%)
  - More frequent use of GPIIb/IIIa inhibitors during index hospitalization (57% vs. 45%)

ASA Interaction (cont'd)

- However, no specific factor was highly correlated with higher ASA dose in the US
- Overall, there was no other single factor identified that appeared to be acting as a *surrogate* for higher-dose ASA that was the true causal factor for the regional interaction
- Possible that the baseline and treatment characteristics of US population, including the use of higher-dose aspirin, were confounded with outcome in a manner that could not be teased apart by *post hoc* multivariate analyses *(multicollinearity)*

Conclusion

- There are potentially multiple confounders and/or effect modifiers that complicate these post hoc analyses
- Imbalances in study populations may create fertile ground for an as yet uncharacterized effect modification
- It seems unlikely that the unfavorable US outcome can be explained entirely by any single factor alone, including aspirin
- The possibility of a chance outcome cannot be excluded

Conclusion (cont'd)

- No clear biological or pathophysiological explanation for a ticagrelor effect modifier, ASA or otherwise, has been indentified…

- But there has been speculation

Thank you

NDA 22-433 Brilinta®
(ticagrelor)

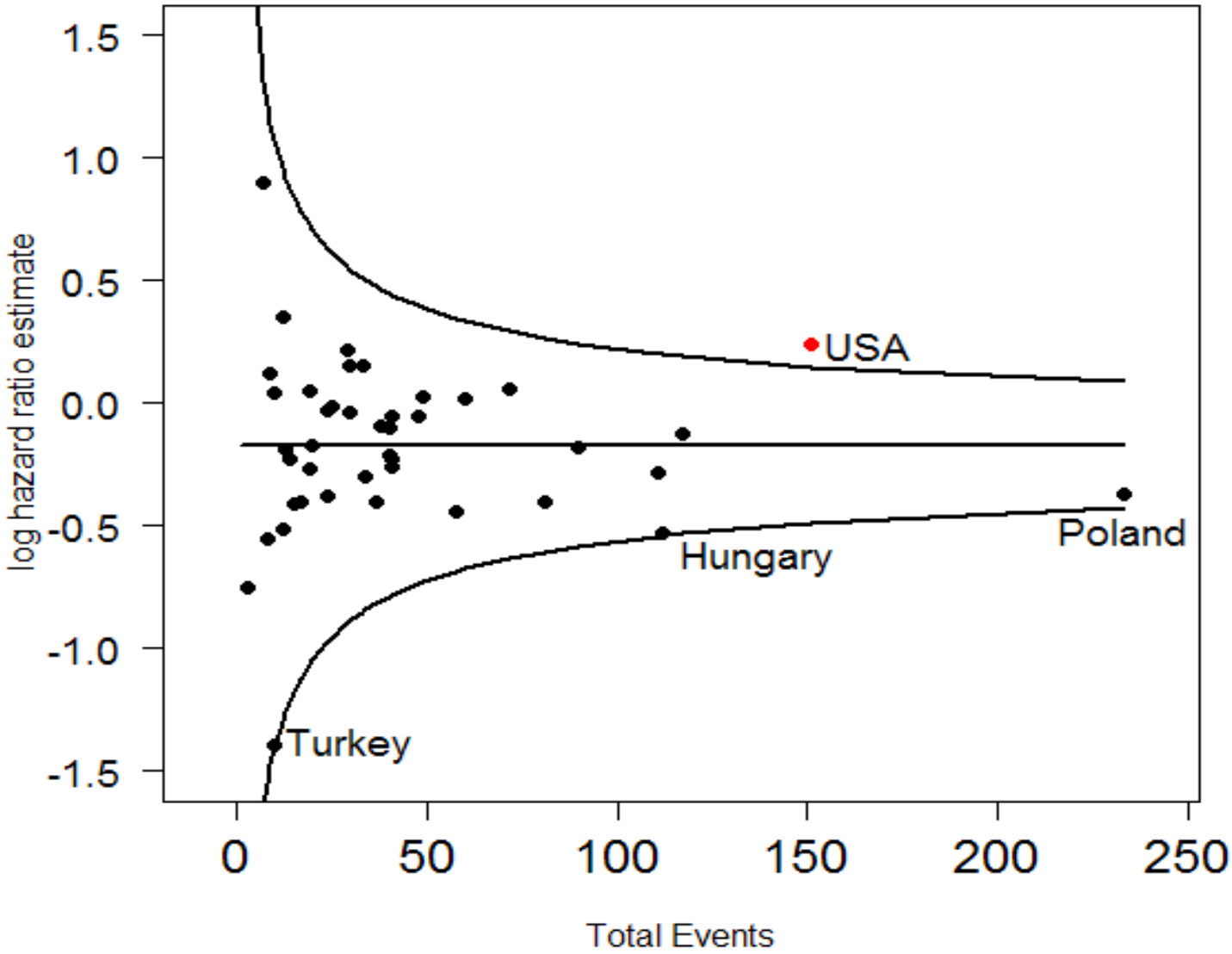
Cardio-Renal Advisory Committee Meeting
July 28, 2010

Jialu Zhang, Ph.D.

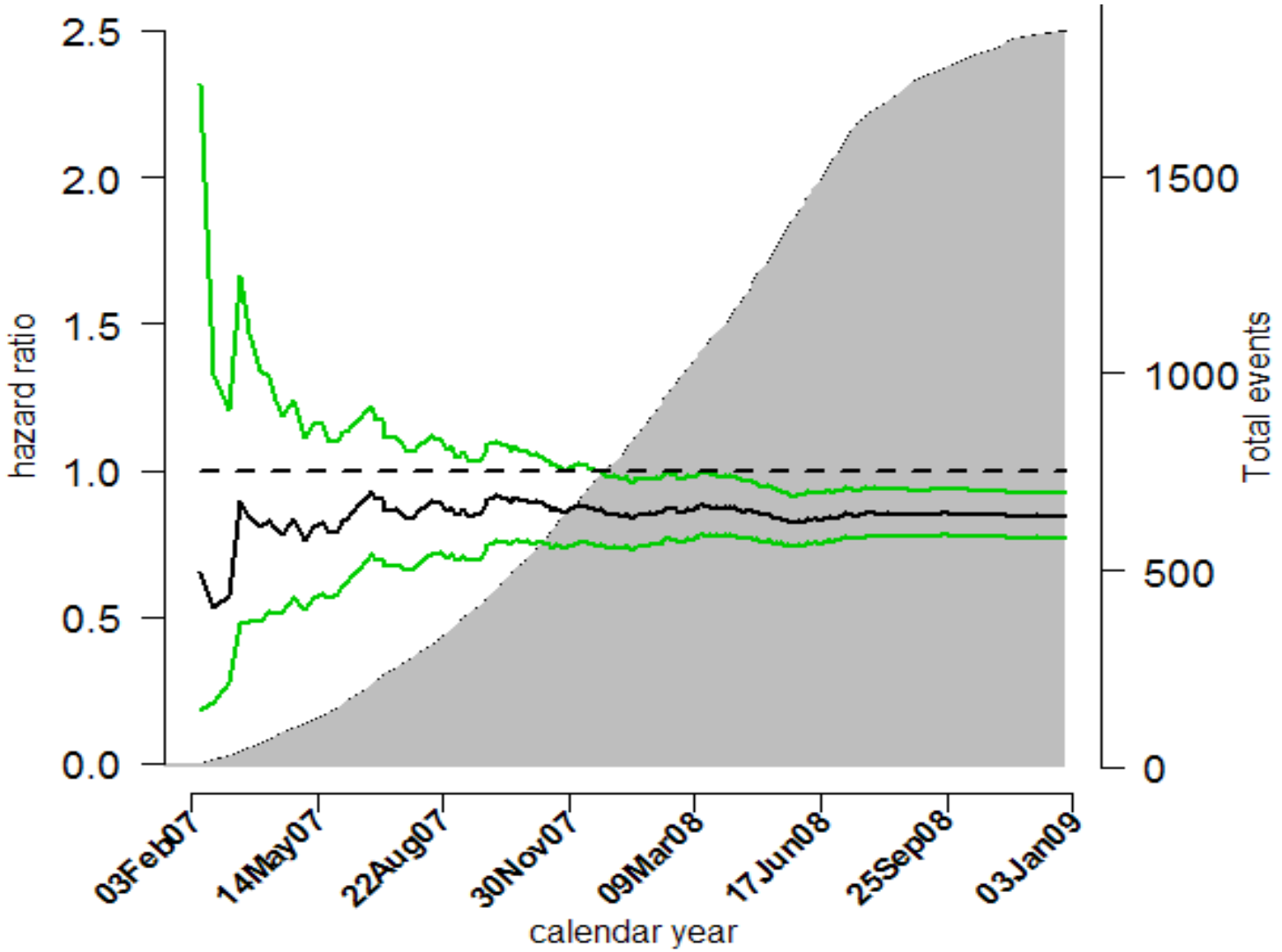
Possible Explanations for US versus Non-US Difference

- Play of chance
- Concurrent ASA
- Other factors

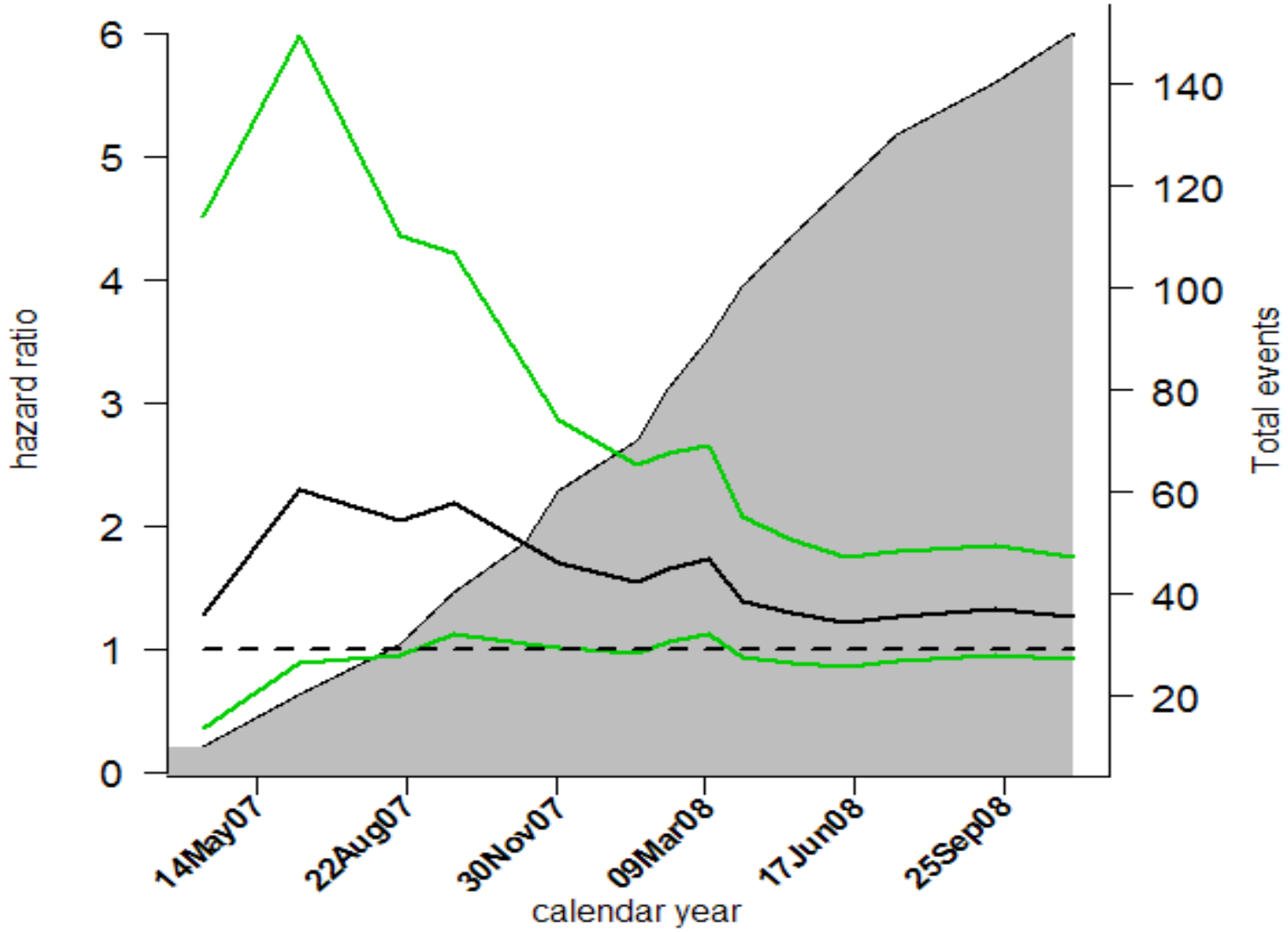
Funnel Plot: US is an outlier



Hazard Ratio Plot for All Subjects: Consistent Results Favoring Ticagrelor



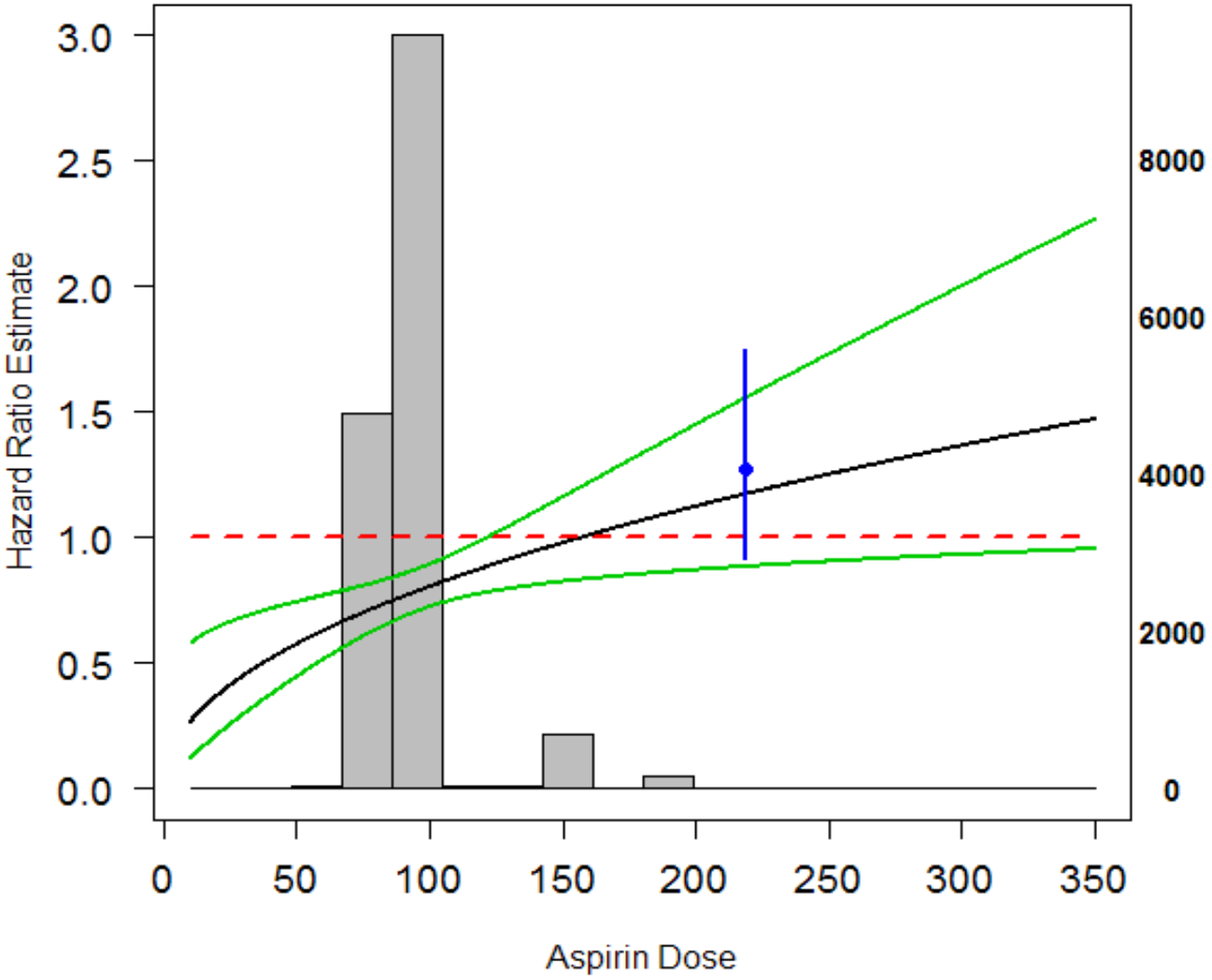
Hazard Ratio Plot for US Subjects: Hazard Ratio Estimate Stayed above 1



A Play of Chance?

- Total primary events: 1878 (151 in US)
- Treatment-by-US interaction is significant (p=0.0095)
- 3 countries had estimated HR ≥ 1.27
  - Australia (N=92), Taiwan (N=83) and US (N=1413)
- P(HR≥1.27 in US | true HR=0.84) < 0.006

Cox regression analysis of the primary endpoint (non-US)



Very Few Subjects Had High Dose ASA in Non-US Region

	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

* Median ASA dose is calculated by excluding the first day loading dose

An Example of Sensitivity Analysis

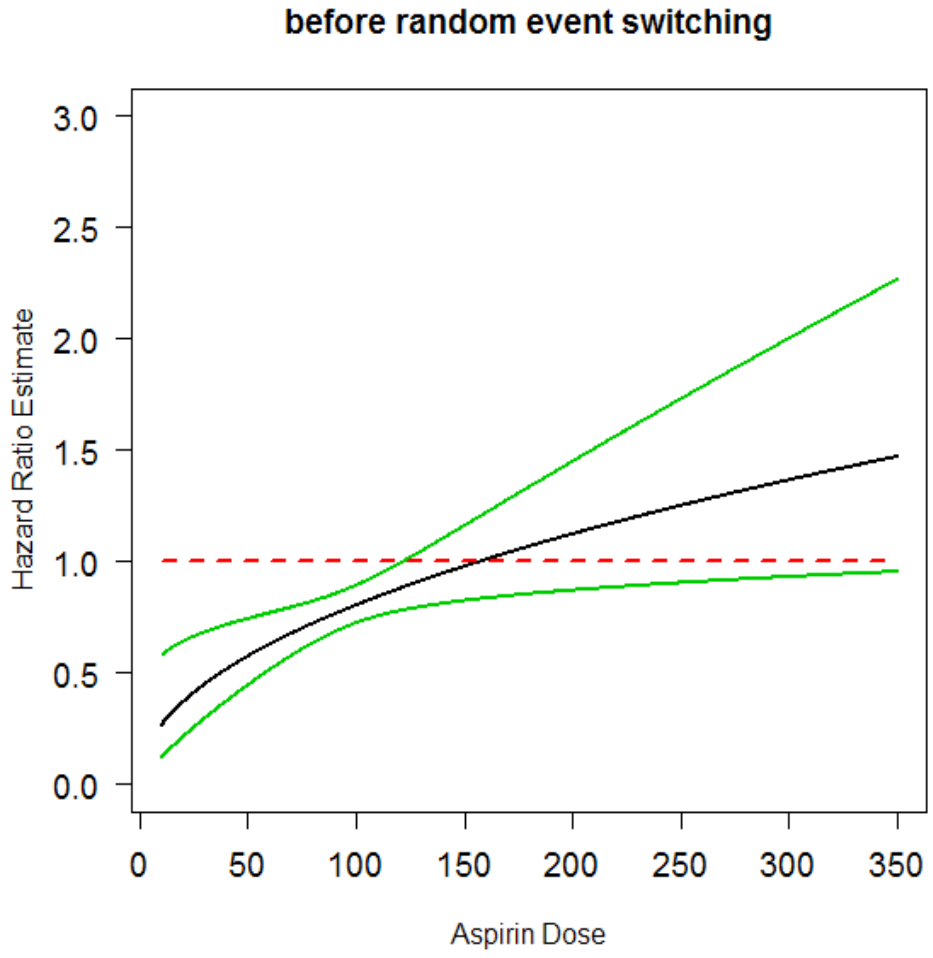
	Median ASA < 300 mg				Median ASA >= 300 mg			
	Ticagrelor		Clopidogrel		Ticagrelor		Clopidogrel	
	N	events	N	events	N	events	N	events
US	383	44	354	40	324	40	352	27
Non-US	8486	752	8445	924	140	18	140	33

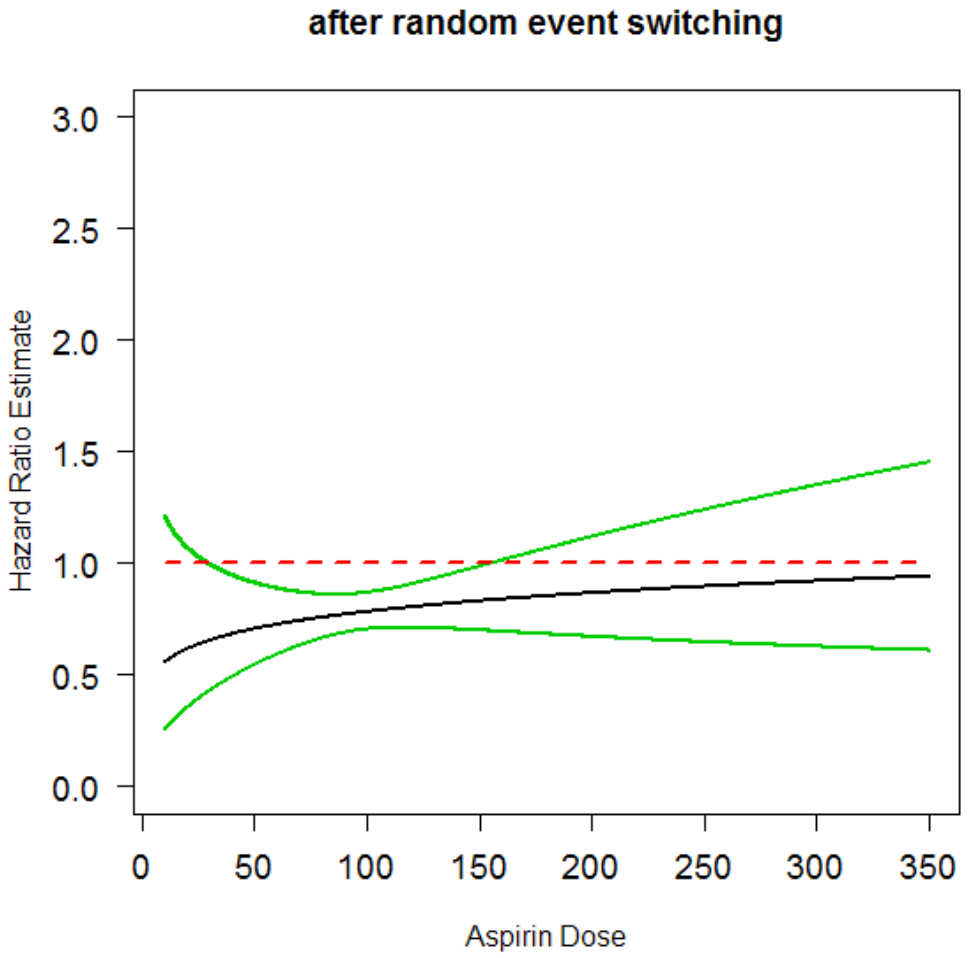
Among the high dose ASA subjects from non-US

- Randomly select 10 subjects with events in ticagrelor group and make them censored with no events
- Randomly select 10 subjects without events in clopidogrel group and assign them primary events

A change of 20 events out of 1878 primary events

The Cox Proportional Hazards Model is Sensitive to the Few Events in High ASA Subjects from Non-US





Other Covariates

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

Conclusions

- Although play of chance can never be ruled out as a possible explanation, the probability of play of chance seems low.
- Concurrent use of aspirin is shown to be the single best factor for explaining the geographic disparity; however, the robustness of the explanatory model is in question.
- The reviewer was not able to find a definitive explanation by looking at other available covariates.

Ticagrelor (Brilinta) Safety Review

Melanie Blank, MD
Medical Officer
Safety Reviewer for this NDA

July 28, 2010

Pre-phase 3 safety concerns

- Bleeding
- Ventricular Pauses*
- Dyspnea*
- Hormonal effects (preclinical findings on female gynecological tumors)

***Evaluated in sub-studies**

Disposition

	Ticagrelor N	Clopidogrel N
Randomization	9333	9291
Treated	9235 (98.9)	9186 (98.9)
Permanent Discontinuation	2186 (23.7)	1999 (21.8)
Adverse event	690 (7.5)	556 (6.1)
Index criteria not met	22 (0.2)	16 (0.2)
Unwilling to continue	946 (10.2)	859 (9.4)
Severe noncompliance	41 (0.4)	47 (0.5)
Other	479 (5.2)	518 (5.6)
Unknown	4 (0)	1 (0)
Lost to follow up	4 (0)	4 (0)
Patients Completed	7049 (76.3)	7187 (78.3)

BLEEDS

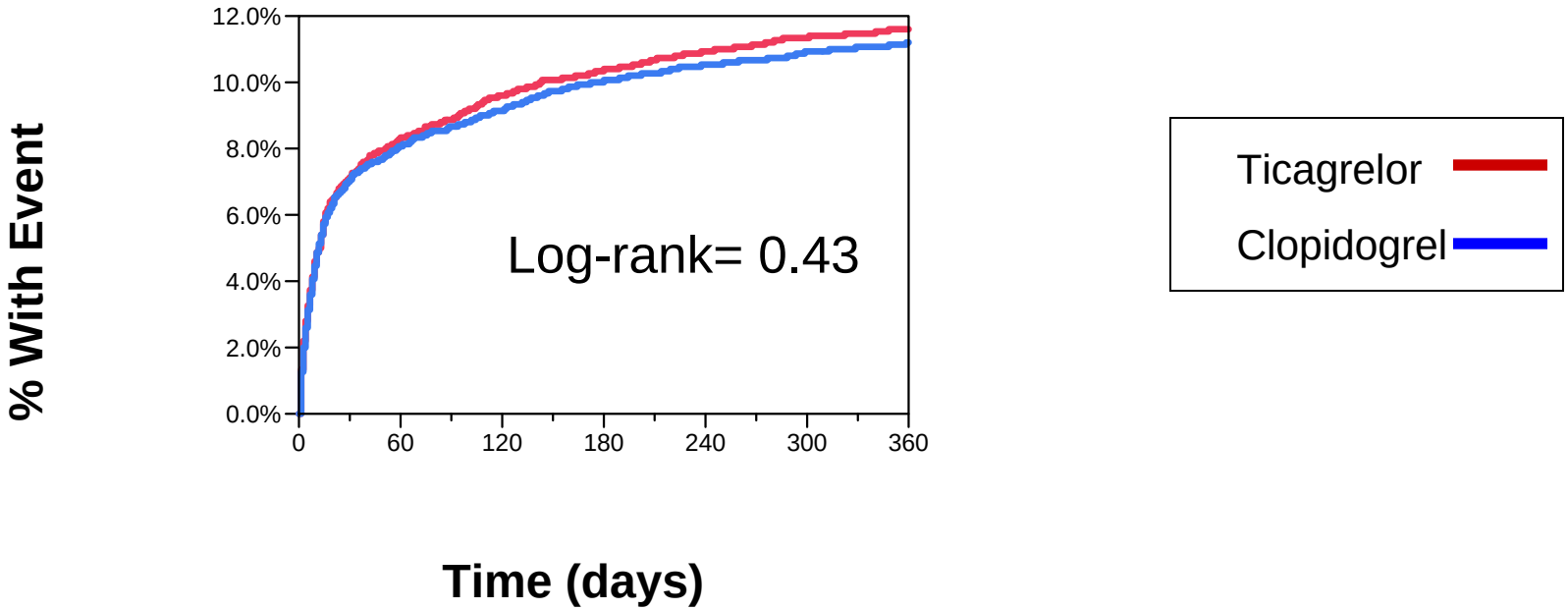
Definitions of Major Bleeding in PLATO

- TIMI Major = Intracranial, or overt hemorrhage with a drop in Hb of > 5 g/dL (not all fatal bleeds are TIMI-Major)
- PLATO Major Fatal/Life threatening = TIMI-Major + any fatal bleed, + intrapericardial bleed with cardiac tamponade or transfusion of 4 or more units whole blood or PRBCs for bleeding
- PLATO “Major” = Major Fatal/Life threatening included and “Major Other” (disabling, drop in Hb of 3-5 g/dL, and transfusion of 2-3 units blood for bleeding)

Primary Prespecified Safety Analysis

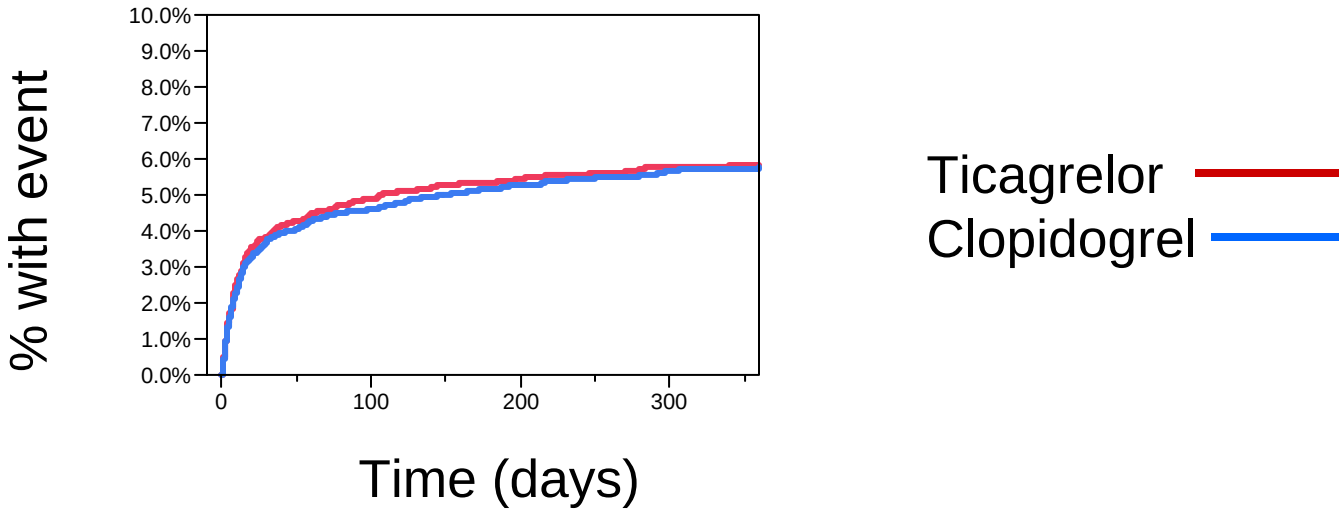
Time to first major (or life threatening/fatal) or “major other” adjudicated bleed

K-M: Adjudicated Major Bleeds by Actual Treatment (only one adjudicated major bleed counted per patient)



Group	Number failed	Number censored	KM% failed
Ticagrelor	961	8274	10.4%
Clopidogrel	929	8257	10.1%

K-M: Adjudicated Life-threatening/Fatal Bleeds by Actual Treatment (only one L-T/F bleed counted per patient)



Group	# failed	# censored	KM% failed
Ticagrelor	491	8744	5.3%
Clopidogrel	482	8704	5.2%

Delta Events per 1000 patients treated (negative = favorable for ticagrelor)

	Ticagrelor N=9333 patients with events	Clopidogrel N=9291 patients with events	RR	Increase or decrease in events/ 1000 patients treated
Composite CV Death/ MI/ Stroke	864 (9.3%)	1014 (10.9%)	0.84 (0.77,0.92)	-17
CV Death	353 (3.8%)	442 (4.8%)	0.79 (0.69,0.91)	-10
MI	504 (5.4%)	593 (6.4%)	0.84 (0.75,0.95)	-10
Stroke	125 (1.3%)	106 (1.1%)	1.17 (0.91,1.52)	2

Delta Events per 1000 patients treated (negative = favorable for ticagrelor)

	Ticagrelor N=9235 patients with events	Clopidogrel N=9186 patients with events	RR	Increase or decrease in events/ 1000 patients treated
Death (All-cause)	408 (4.4%)	505(5.5%)	0.8	-10
Major Bleed	961 (10.4%)	929 (10.1%)	1.03	3
Major Fatal/Life-threatening	491 (5.3%)	480 (5.2%)	1.02	1
Fatal Bleed	21 (0.2%)	23 (0.3%)	0.91	0
TIMI defined Major Bleed	657 (7.1%)	638 (6.9%)	1.02	2
Non-procedural Major Bleed	235 (2.5%)	180 (2.0%)	1.3	6
Intracranial Bleed	27(0.3%)	14 (0.2)	1.9	1
Deaths from Intracranial Bleed	11 (0.1)	2 (0.0)	5.47	1
CABG	**N= 770**	**N=814**		
CABG-related bleed Major Bleed	619 (80.4%)	654 (80.3%)	1	0
CABG-related fatal Bleed	6 (0.8%)	6 (0.7%)	0	0

Non-adjudicated major bleed by different definition

MAJOR BLEEDS Description	Ticagrelor N=9235	Clopidogrel N=9186	HR	CI
Fatal, intracranial, intrapericardial bleed with tamponade, shock/hypotension from bleeding, hb decrease >5	191 (2.1%)	168 (1.8%)	1.13	(0.92, 1.39)

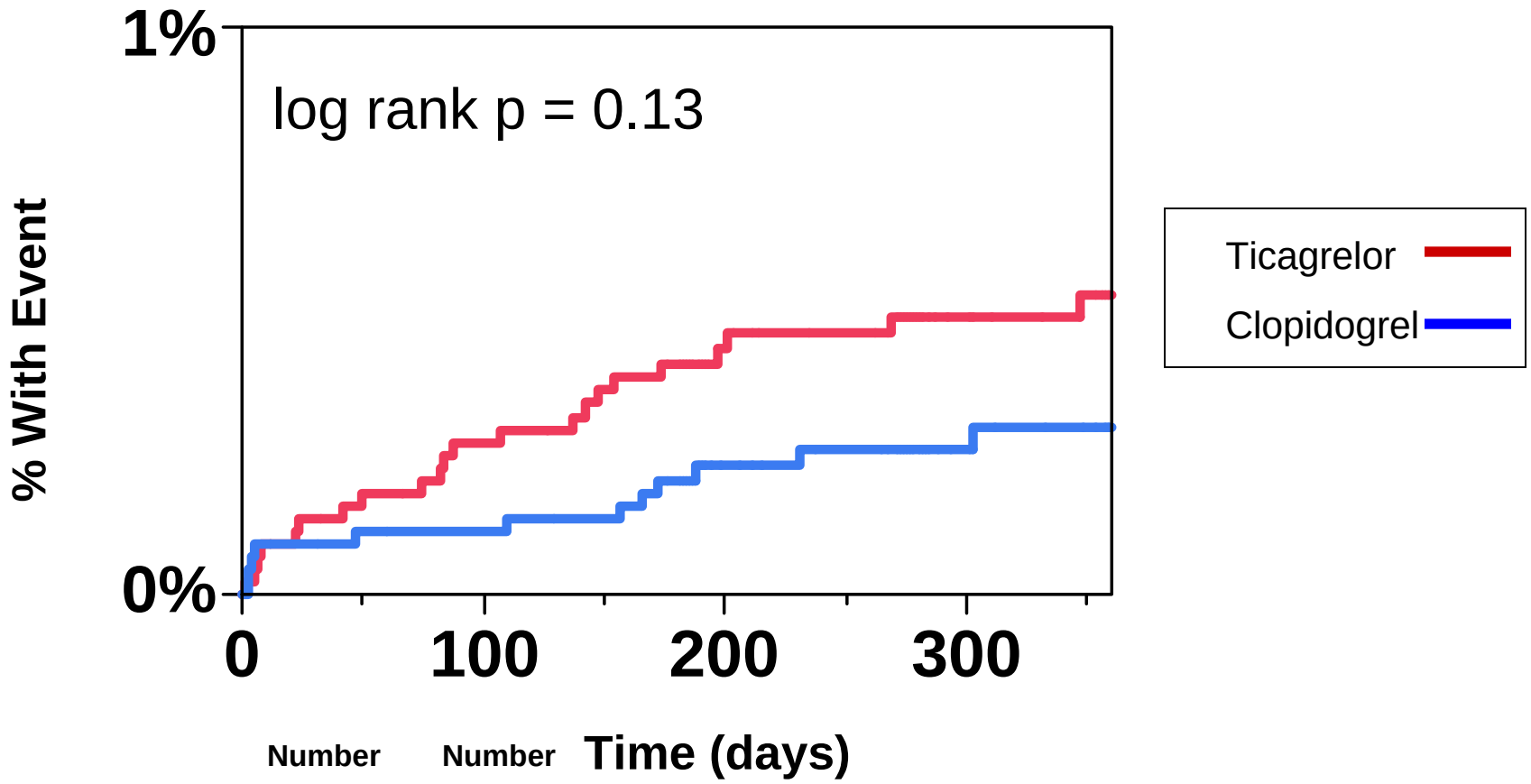
Adjudicated bleeds for North America (N.A.) and Outside N.A. (patients received at least one dose of treatment)

All Bleeds	Treatment	At Risk N	PLATO Major (K-M%)	PLATO Lifethreatening/ Fatal (K-M%)	PLATO Fatal (K-M%)
Outside NA	Ticagrelor	8350	858 (10.3)	441 (5.3)	18 (0.2)
	Clopidogrel	8319	831 (10.0)	438 (5.3)	21 (0.3)
NA	Ticagrelor	885	103 (11.6)	50 (5.6)	2 (0.2)
	Clopidogrel	867	98 (11.3)	44 (5.1)	2 (0.2)

Frequency of Major Bleeds, Life-threatening/Fatal Bleeds, and Fatal Bleeds by Aspirin (ASA) Dose per Patient

ASA dose	Major		Lifethreatening/Fatal		Fatal	
	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel
<100 mg	N=7506 n (%) 732 (9.8)	N=7482 n (%) 684 (9.1)	N=7506 n (%) 360 (4.8)	N=7482 n (%) 340 (4.5)	N=7506 n (%) 17 (0.2)	N=7482 n (%) 13 (0.2)
>=100 -< 300 mg	N=497 n (%) 62 (12.5)	N=498 n (%) 60 (12.0)	N=497 n (%) 31 (6.2)	N=498 n (%) 32 (6.4)	N=497 n (%) 0 (0)	N=498 n (%) 0 (0)
>= 300mg	N=422 n (%) 40 (9.5)	N=454 n (%) 39 (8.6)	N=422 n (%) 20 (4.7)	N=454 n (%) 16 (3.5)	N=422 n (%) 0 (0)	N=454 n (%) 1 (0.2)
Unknown	N=810 n (%) 127 (15.7)	N=752 n (%) 146 (19.4)	N=810 n (%) 80 (9.9)	N=752 n (%) 92 (12.2)	N=810 n (%) 3 (0.4)	N=752 n (%) 9 (1.2)

K-M: Hemorrhagic Stroke



Group	Number failed	Number censored
AZD6140 BD	22	9213
CLOPIDOGREL 75 MG OD	13	9173
Combined	35	18386

Coronary Artery Bypass Graft Surgery (CABG) and Bleeding

CABG Bleeds

Characteristic/Bleed Severity	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
Patients with CABG procedures	770 (100%)	814 (100%)
No bleeding event	33 (4.3%)	31 (3.8%)
Any bleeding event	737 (95.7%)	783 (96.2%)
Major	619 (80.4%)	654 (80.3%)
Major Fatal/Life-threatening	329 (42.7%)	341 (41.9%)
Fatal	6 (0.8%)	6 (0.7%)
Major Other	290 (37.7%)	313 (38.5%)
Minor	47 (6.1%)	58 (7.1%)
Minimal	71 (9.2%)	71 (8.7%)

Major CABG Bleeds by definition

MAJOR CABG BLEEDS Description	Ticagrelor N=770	Clopidogrel N=814	HR	CI
Fatal, intracranial, intrapericardial bleed with tamponade, shock/hypotension from bleeding, hb decrease >5	86 (11.2%)	74 (9.1%)	1.23	(0.91, 1.65)
Fatal, intracranial, intrapericardial bleed with tamponade, shock/hypotension from bleeding	21 (2.7%)	18 (2.2%)	1.23	(0.66, 2.3)

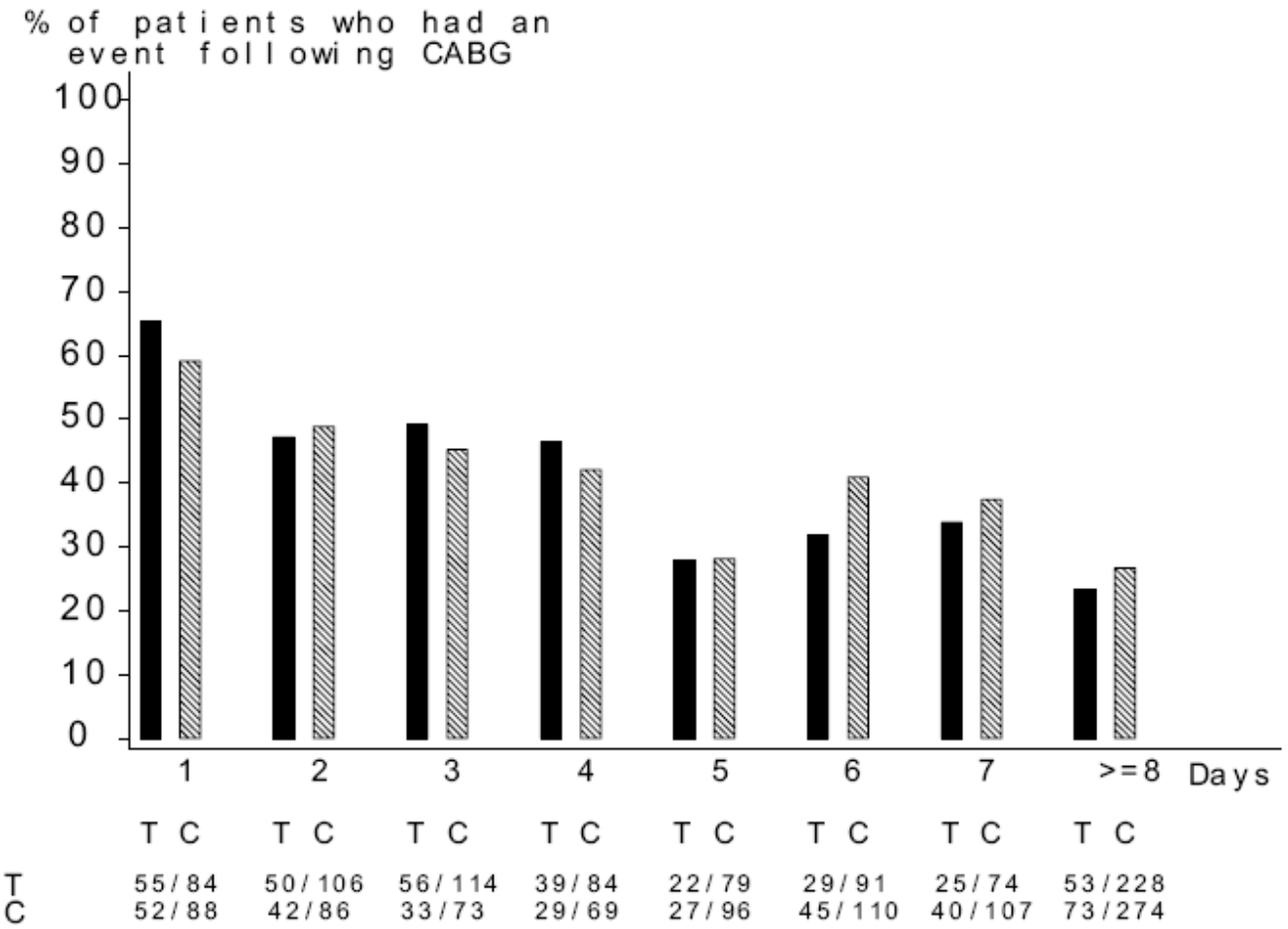
CABG-related adjudicated bleeds for North America and Outside North America (patients received at least one dose of treatment)

CABG-related bleeds	Treatment	At Risk N	PLATO Major (K-M%)	PLATO Lifethreatening/ Fatal (K-M%)	PLATO Fatal (K-M%)
Outside N.A.	Ticagrelor	654	487 (74.5)	257 (39.3)	6 (0.9)
	Clopidogrel	705	514 (72.9)	277 (39.3)	6 (0.7)
N.A	Ticagrelor	116	66 (56.9)	36 (31.0)	0 (0)
	Clopidogrel	109	70 (64.2)	32 (29.4)	0 (0)

Frequency of Major Bleeds, Life-threatening/Fatal Bleeds, and Fatal Bleeds by Aspirin (ASA) Dose per CABG Patient

ASA Dose	Major		Lifethreatening/Fatal		Fatal	
	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel
<100 mg	N=653 n (%) 463 (70.9)	N=692 n (%) 481 (69.5)	N=653 n (%) 239 (36.6)	N=692 n (%) 237 (34.2)	N=653 n (%) 5 (0.8)	N=692 n (%) 2 (0.3)
>=100 -< 300 mg	N=65 n (%) 51 (78.5)	N=57 n (%) 43 (75.4)	N=65 n (%) 25 (38.5)	N=57 n (%) 23 (40.4)	N=65 n (%) 0 (0)	N=57 n (%) 0 (0)
>= 300mg	N=44 n (%) 22 (50.0)	N=34 n (%) 24 (70.6)	N=44 n (%) 14 (32.8)	N=34 n (%) 10 (29.4)	N=44 n (%) 0 (0)	N=34 n (%) 0 (0)
Unknown	N=143 n (%) 83 (58.0)	N=161 n (%) 106 (65.8)	N=143 n (%) 51 (35.7)	N=161 n (%) 71 (44.1)	N=143 n (%) 1 (0.7)	N=161 n (%) 4 (2.5)

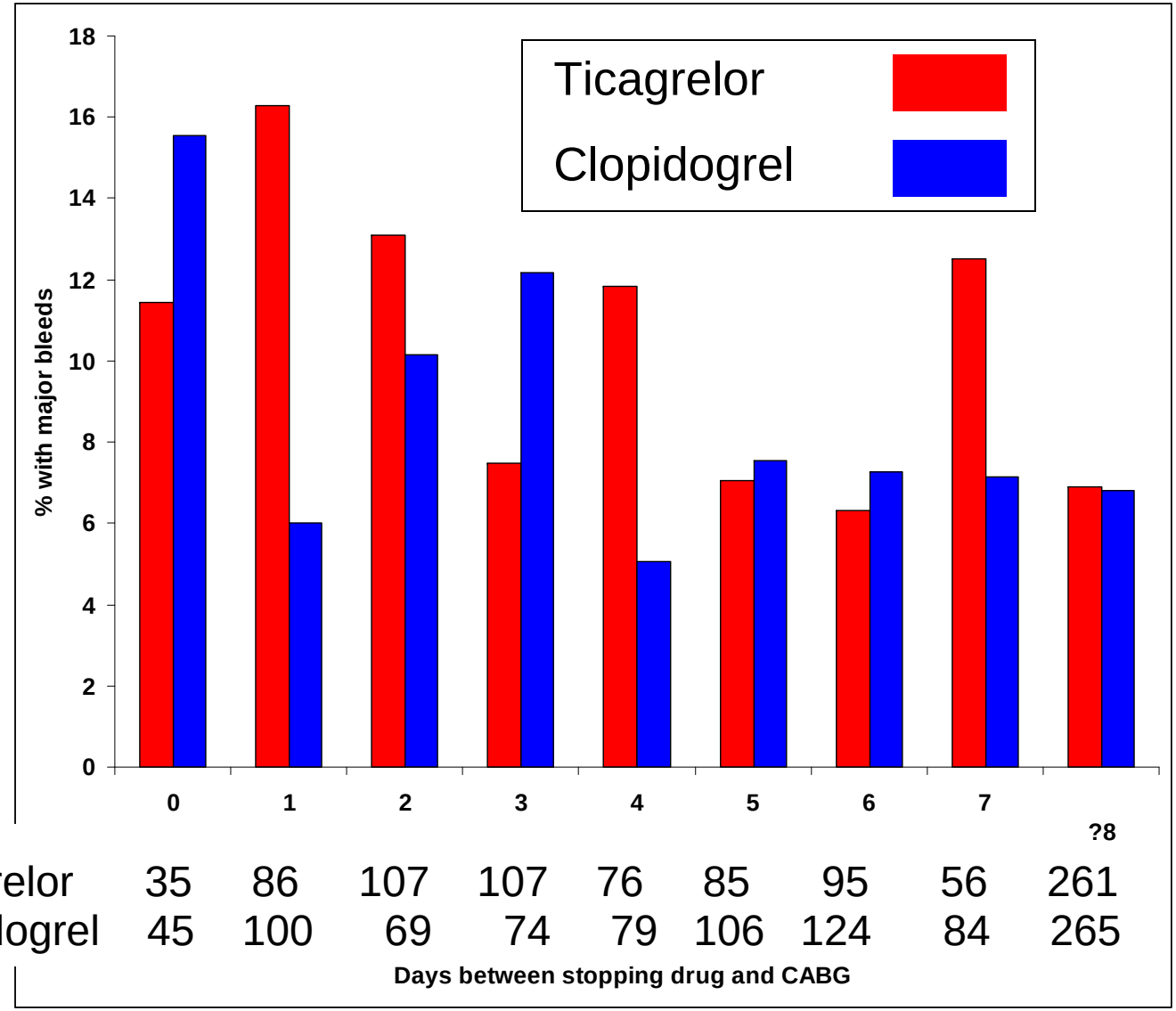
Major Fatal/ Life-threatening bleeding by days from last dose of treatment to CABG procedure



Source: PLATO study report p. 3674

Major CABG Bleed (not adjudicated):

Fatal, intracranial, intrapericardial bleed with tamponade, shock/ hypotension from bleeding, hgb decrease >5.0 g/dL



DYSPNEA

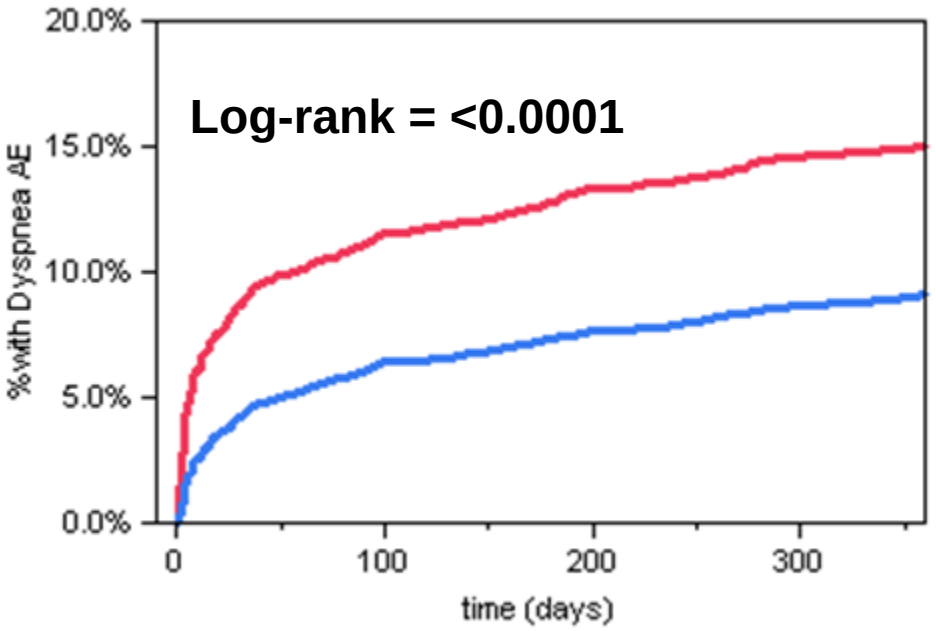
Dyspnea

Dyspnea Adverse Event*

	Ticagrelor	Clopidogrel	RR
All subjects			
N	**9235**	**9186**	
adverse event	1344 (14.6%)	803 (8.7%)	1.7
serious adverse event	79 (0.9%)	53 (0.6%)	1.5
adverse event, drug stopped	108 (1.2%)	25 (0.3%)	4.3
Subjects with baseline asthma or COPD			
N	**759**	**718**	
adverse event	177 (23.3%)	102 (14.2%)	1.6
serious adverse event	17 (2.2%)	10 (1.4%)	1.6
adverse event, drug stopped	19 (2.5%)	3 (0.4%)	6.0

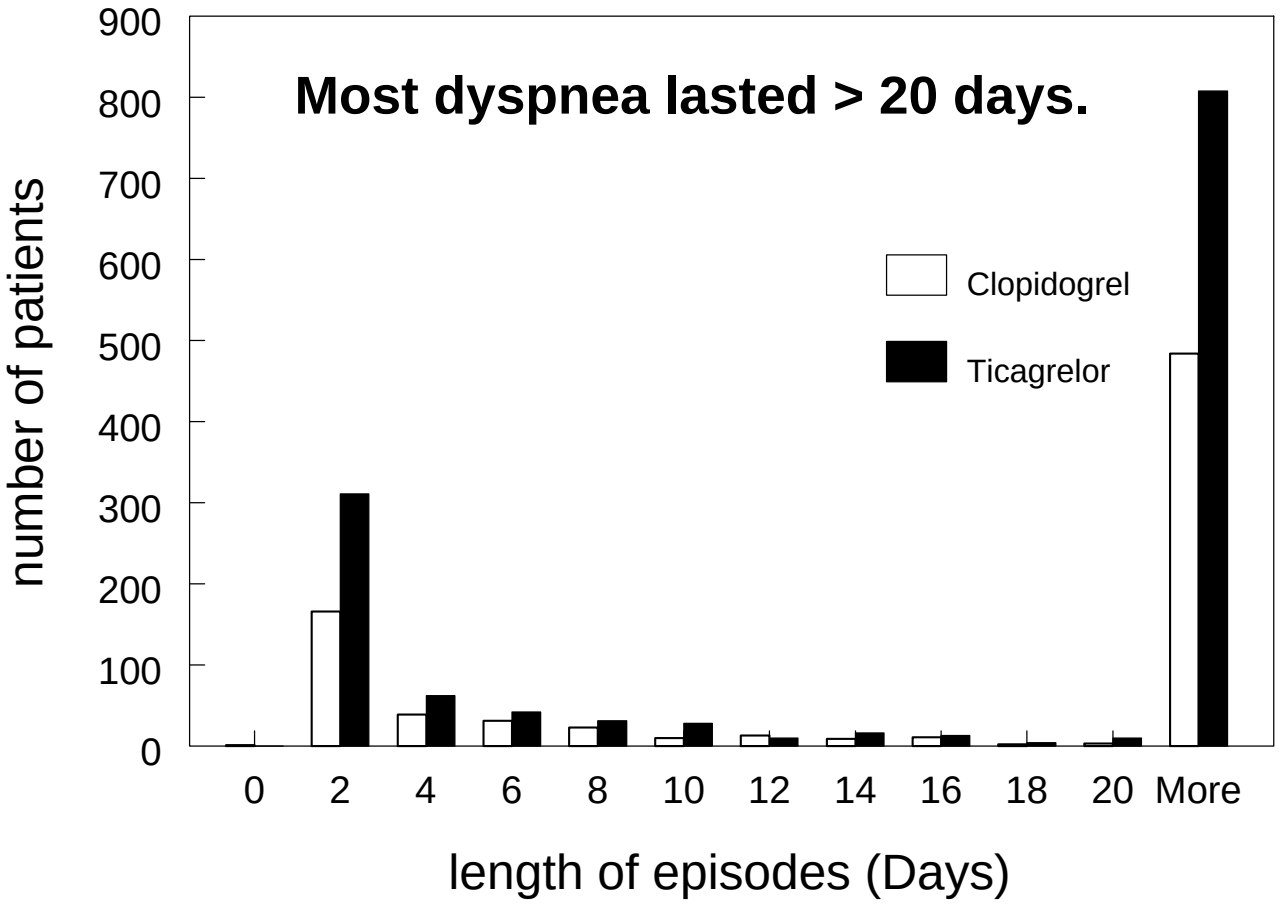
* **Preferred Terms:** dyspnea, dyspnea at rest, dyspnea exertional, dyspnea paroxysmal nocturnal, nocturnal dyspnea, orthopnea, and painful respiration.

Dyspnea time to event analysis



Group	# failed	# censored	KM% failed
Ticagrelor	1344	7891	14.6%
Clopidogrel	803	8383	8.7%

Dyspnea


Most dyspnea lasted > 20 days.
number of patients
900
800
700
600
500
400
300
200
100
0
Clopidogrel
Ticagrelor
0
2
4
6
8
10
12
14
16
18
20
More
length of episodes (Days)

SEX HORMONE EFFECTS

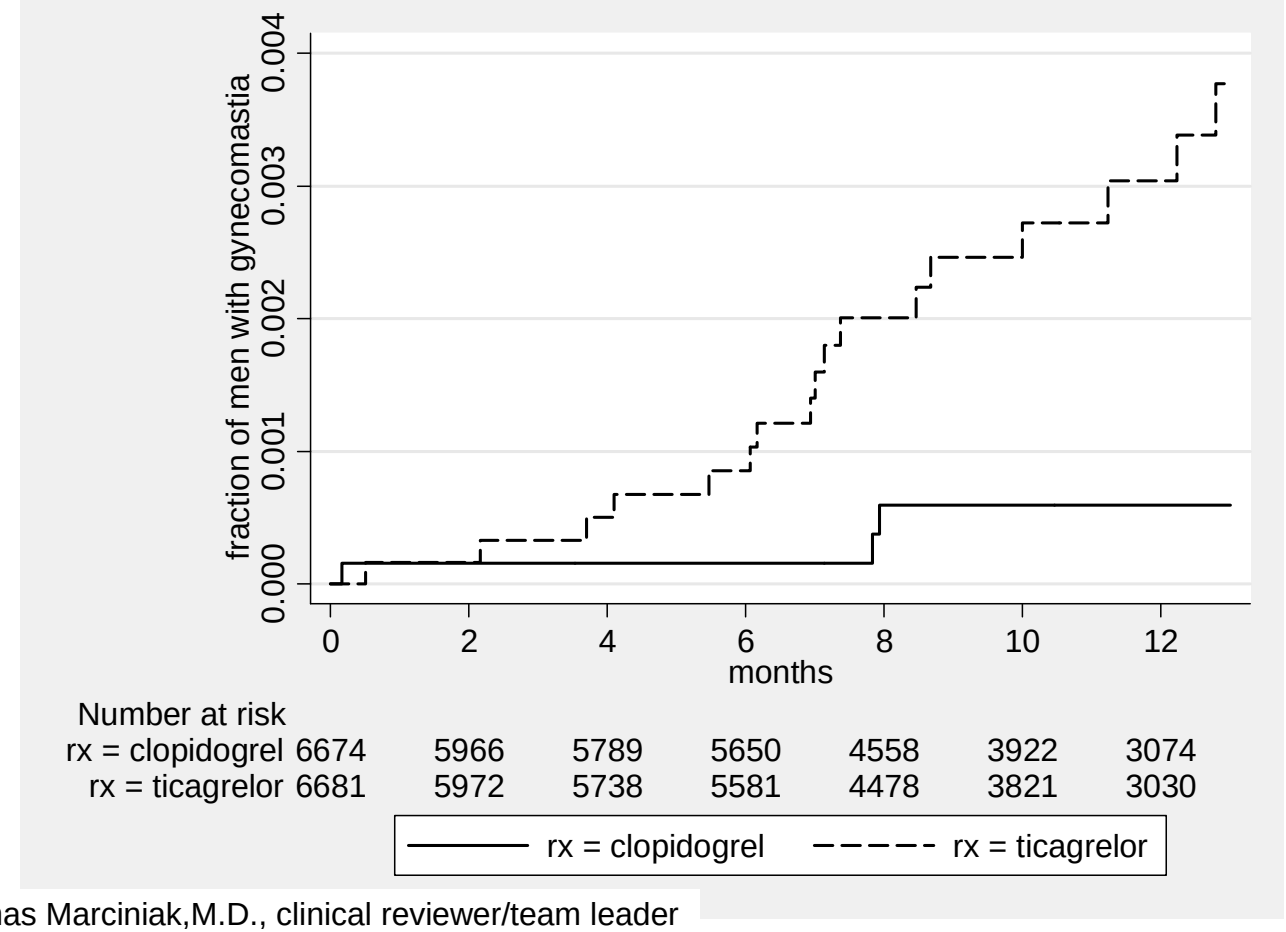
Non-Clinical Issues

- Impurity: Data has been requested for one potentially genotoxic impurity to support the proposed specification limit of 0.1%
- 2 Year rodent carcinogenicity studies showed an increased incidence of uterine malignancies in the high dose rats.
  - Plasma levels of ticagrelor >25X human levels

Evidence of Sex Hormone Mediated Effects

- Gynecomastia and breast swelling/ mass were observed more frequently 17 (0.26%) in ticagrelor-treated males vs. 3 (0.05%) in clopidogrel-treated males (RR=5.2)

Gynecomastia, breast swelling or breast mass



Thomas Marciniak,M.D., clinical reviewer/team leader

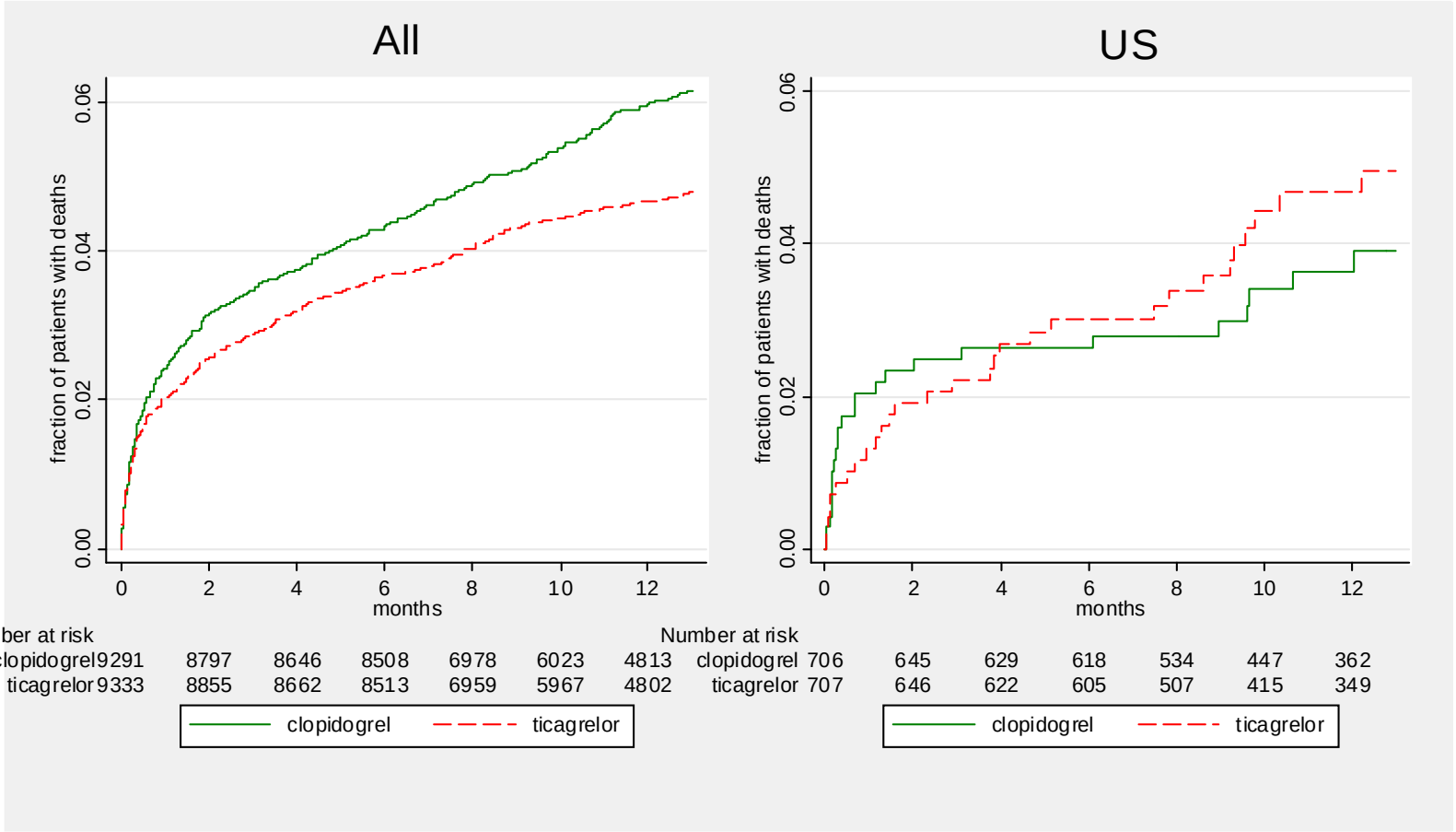
Hormonally-related AEs

Characteristic	Ticagrelor	Clopidogrel	RR
All patients	N= 9235	N= 9186	
Females only	N= 2634	N= 2603	
Males only	N= 6601	N= 6583	
	n(percent)	n(percent)	
Vaginal bleeding (females)	22 (0.84)	17 (0.65)	1.3
Gynecomastia/ swelling/ mass (males)	17 (0.26)	3 (0. 05)	5.2
Prostate cancer (males)	13 (0.19)	12 (0.18)	1.1
BPH (males)	10 (0.15)	8 (0.12)	1.3
Breast Cancer (females)	4 (0.15)	10 (0.38)	0.4
Sexual Dysfunction (males)	3 (0.05)	11 (0.17)	0.3
Cervical/ uterine malignancy (females)	1 (0)	0 (0)	0

PLATOnic Relationships

Thomas A. Marciniak, M.D.
Division of Cardiovascular and Renal Products
FDA

Deaths



Hazard ratio 0.78

(95% CI 0.69 to 0.89)

Hazard ratio 1.2

(not significant – small subgroup)

Outline of Presentation

- The ideal trial vs. PLATO reality
- Patterns in prior $P2Y_{12}$ inhibitor trials
- PLATO the early days
  - Does lack of early benefit explain the US vs. OUS discrepancy?
- Deaths and PCIs
  - Do deaths dictate differently?
- Follow-up issues

The Ideal Outcomes Trial

arm	events
drug	e_d
control	e_c

If e_d is significantly less than e_c, drug wins!

The PLATO Outcomes Trial

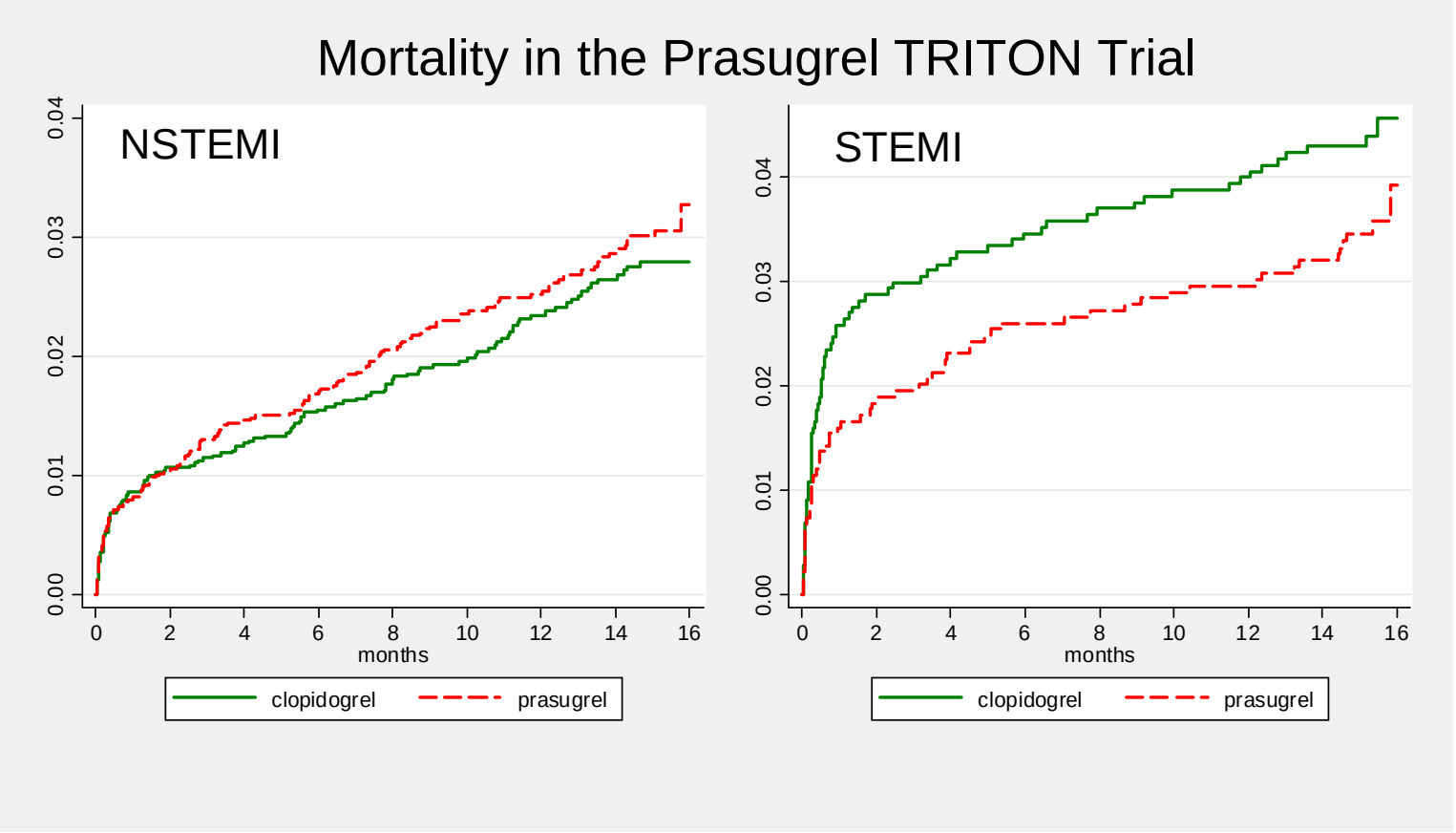
A-Z Endpoint Events by "Arm"

arm	prior/day 1 clopidogrel	region	NSTEMI/UA		STEMI	
			medical	invasive	medical	invasive
clopidogrel	no	OUS	244	86	46	111
		US	11	20	0	3
	yes	OUS	214	76	56	114
		US	14	12	3	4
ticagrelor	no	OUS	204	54	36	109
		US	16	19	1	10
	yes	OUS	197	58	31	91
		US	12	23	0	3

48%

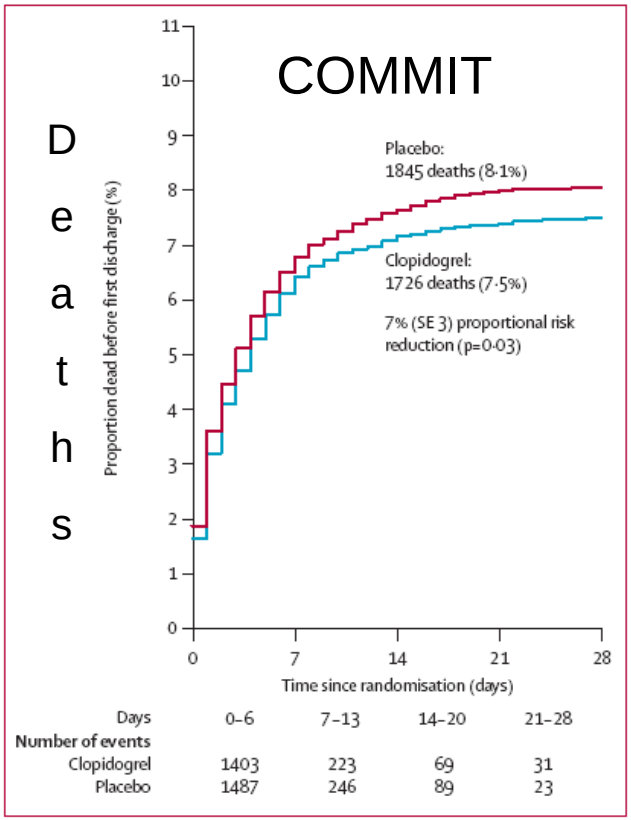
Not 2x1 but 8x4 with low event #s in many cells

Do STEMI & NSTEMI behave differently with $P2Y_{12}$ inhibitors?



Note: Prasugrel TRITON was all <u>invasive</u>.

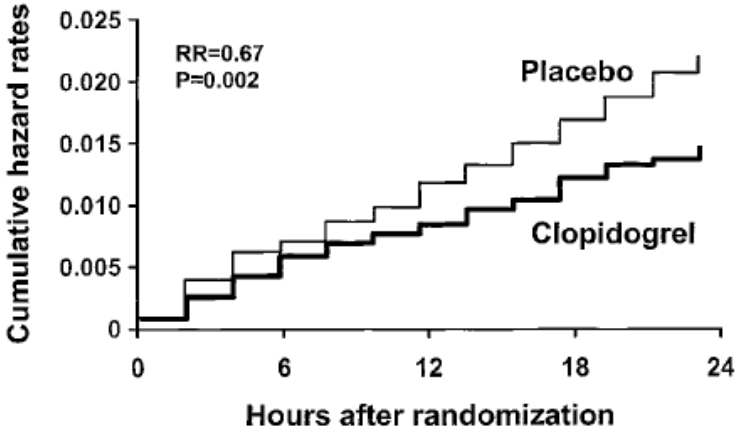
Can a $P2Y_{12}$ inhibitor also show an immediate benefit in STEMI managed medically?

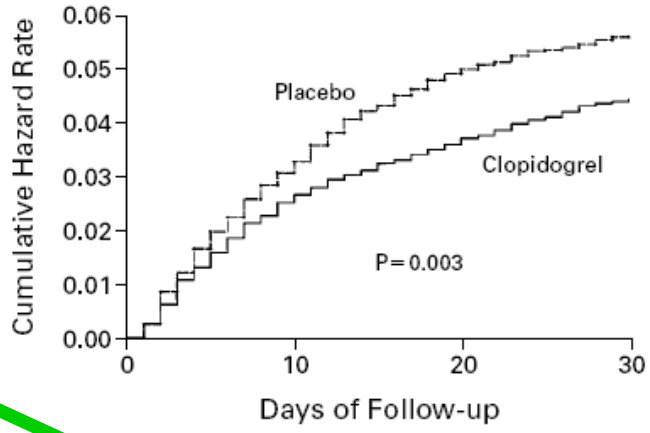


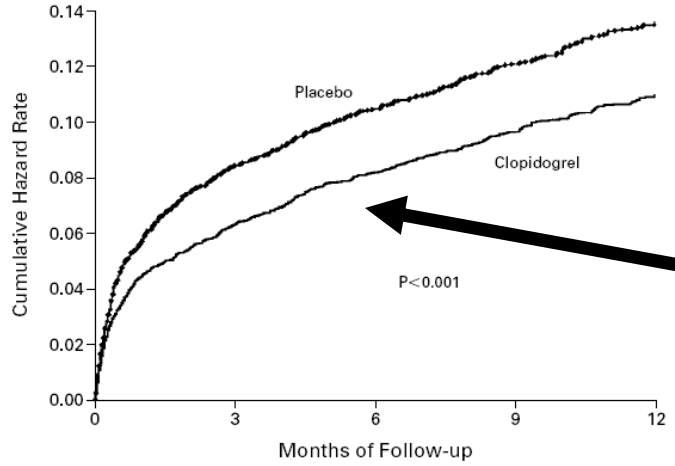
Note: Thrombolytic in 54%;

PCI in 3% led to discontinuation.

Does P2Y12 benefit accrue rapidly or slowly in UA/NSTEMI?
MACE in CURE





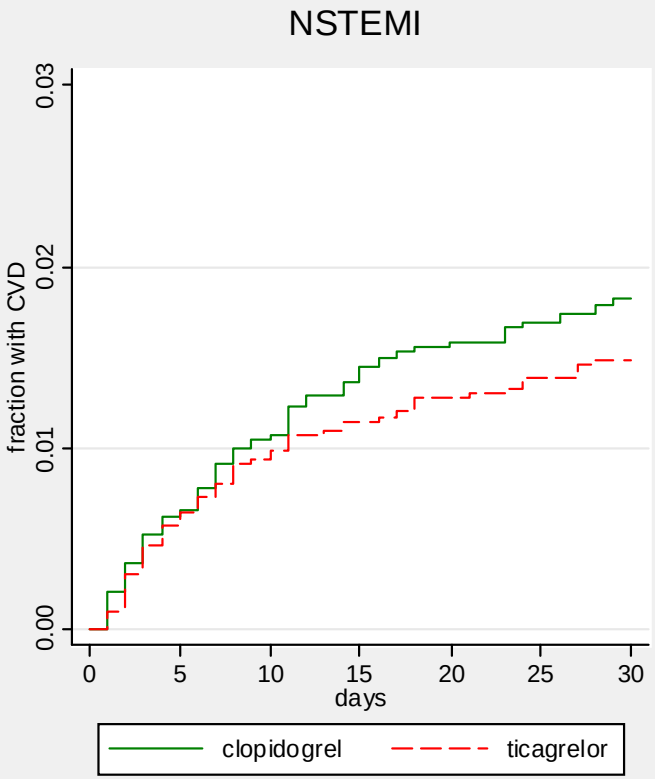


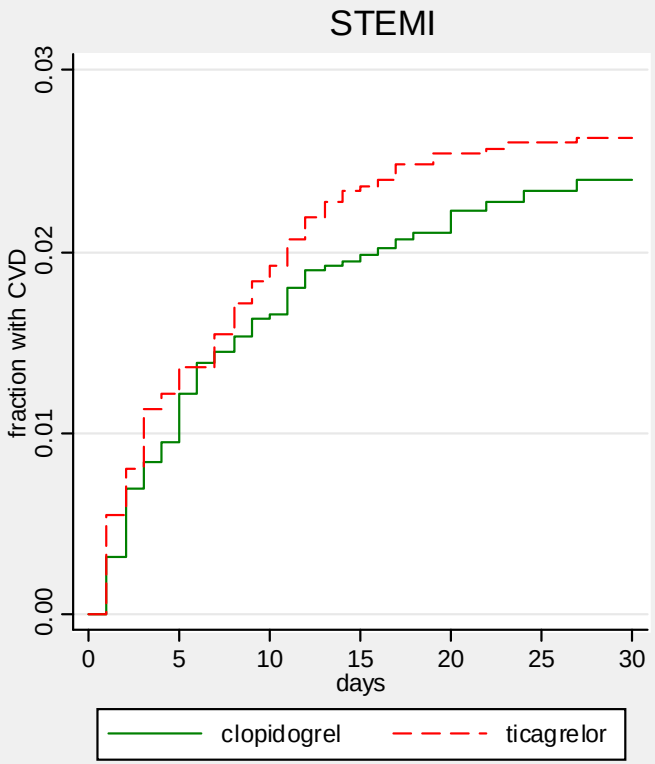
Rapid benefit

But little after 3 months

Do PLATO results in the early days vary by index MI type?

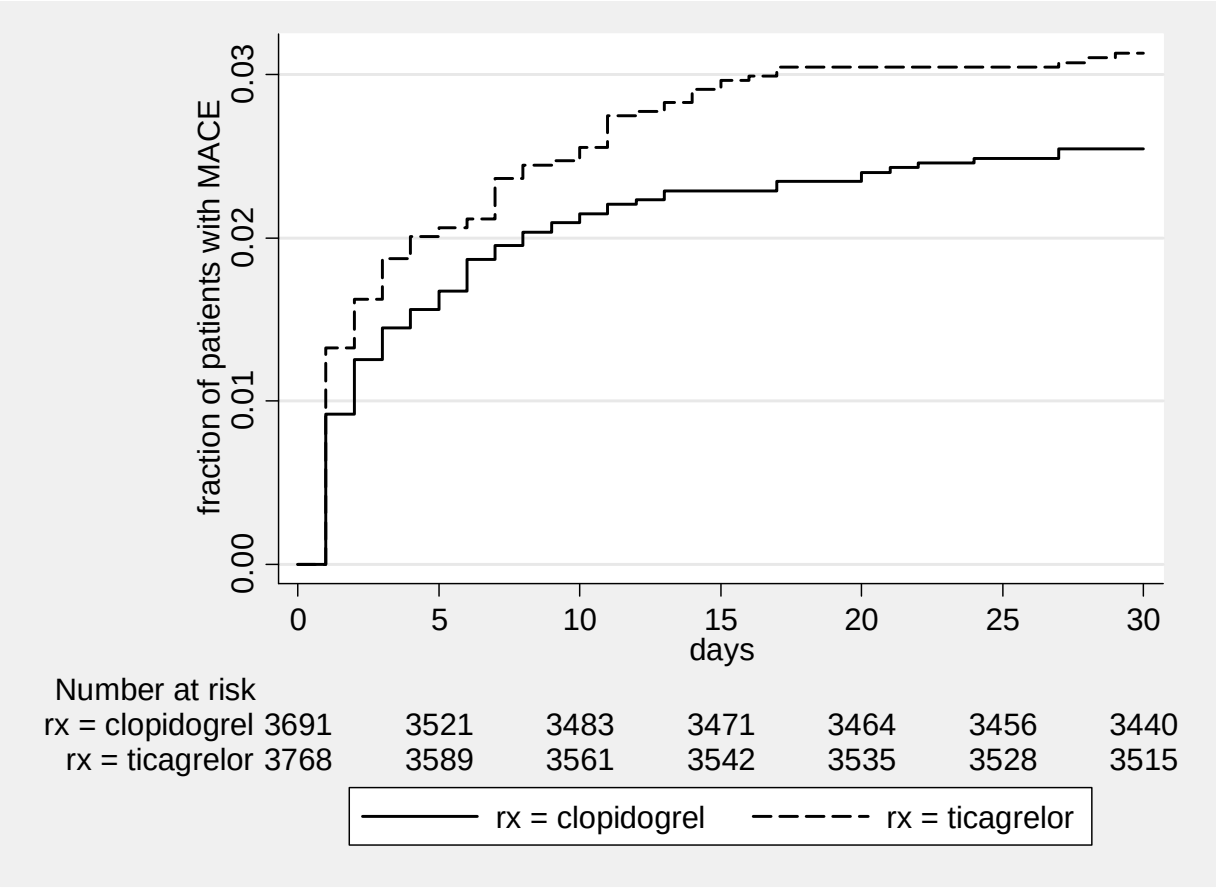
FDA CV Death (Not Including Bleeds)





Do results vary by invasiveness?

FDA MACE after PCI Day 1 But No Later PCI



(Note: Like the aspirin analyses, not a randomized comparison.)

Do results vary by invasiveness?

MI/CVD within 30d by PCI <10h & Region

OUS & US are more consistent

region	pci<10h	clopidogrel	ticagrelor	RR
OUS	no	4.3%	3.5%	0.8
	yes	2.7%	2.8%	1.0
US	no	2.7%	2.3%	0.9
	yes	2.2%	3.0%	1.4

(Note: Not strictly a randomized comparison but less confounded than prior analysis.)

Do results vary by invasiveness?

MI/CVD within 30d by PCI <10h, Region, & Prior Clopidogrel

Ticagrelor patients do better with prior clopidogrel

prior/day 1 clopidogrel*	region	pci<10h	clopidogrel	ticagrelor	RR
yes	OUS	no	4.3%	3.2%	0.76
		yes	2.7%	2.4%	0.9
	US	no	2.7%	1.8%	0.7
		yes	2.2%	2.6%	1.2
no	OUS	no	4.3%	3.6%	0.83
		yes	2.7%	3.2%	1.2
	US	no	2.7%	2.6%	1.0
		yes	2.2%	3.2%	1.5

*ticagrelor arm only

Do results vary by ASA dose?

MI/CVD within 30d by ASA Dose, Arm, Prior Clopidogrel, Index MI Type, & PCI <10h

Higher ASA dose is a marker for risk particularly in STEMI patients

arm	prior/day 1 clopidogrel	ASA ≥ 300	NSTEMI/UA		STEMI	
			medical	invasive	medical	invasive
ticagrelor	no	no	3.3%	2.1%	5.0%	2.9%
		yes	0.9%	3.7%	0.0%	18.4%
	yes	no	2.6%	0.7%	5.3%	2.3%
		yes	3.8%	2.2%	12.5%	25.6%
clopidogrel		no	3.3%	2.0%	7.6%	2.6%
		yes	3.9%	3.9%	22.2%	4.0%

Clopidogrel results also suggest higher ASA dose, higher risk

Higher ASA dose is associated with urgent CABG OUS

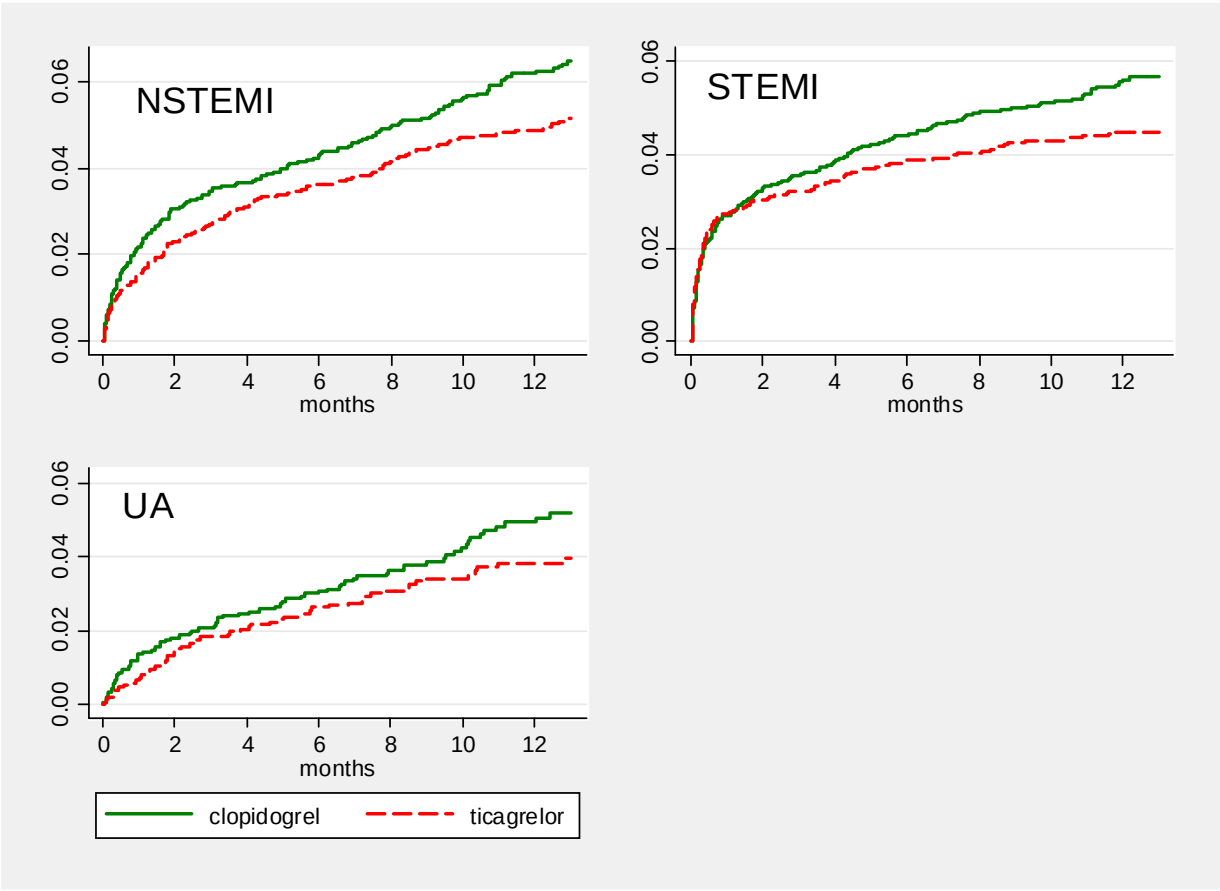
Median ASA dose ≥ 300 mg by CABG type

CABG	OUS	US
none	1%	56%
routine	2%	52%
urgent	5%	46%

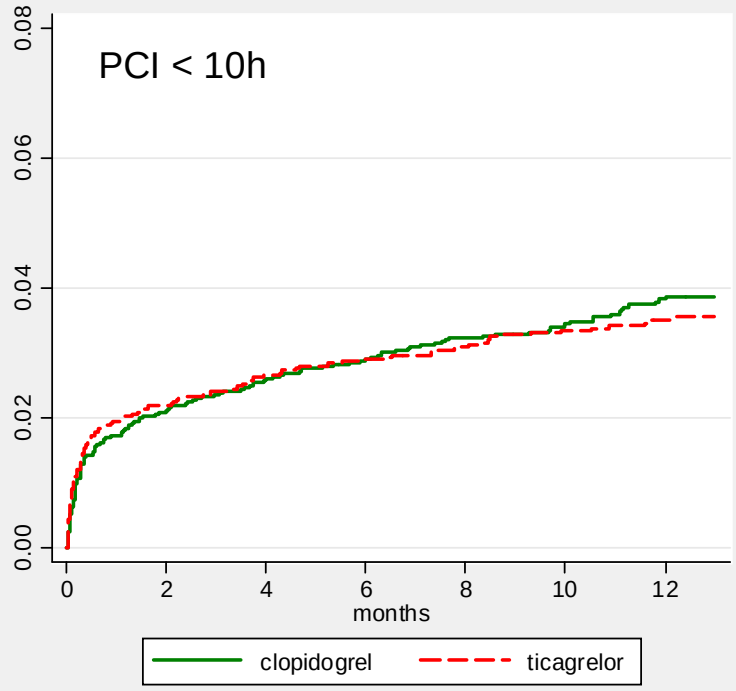
Why not examine timing of study drug administration?

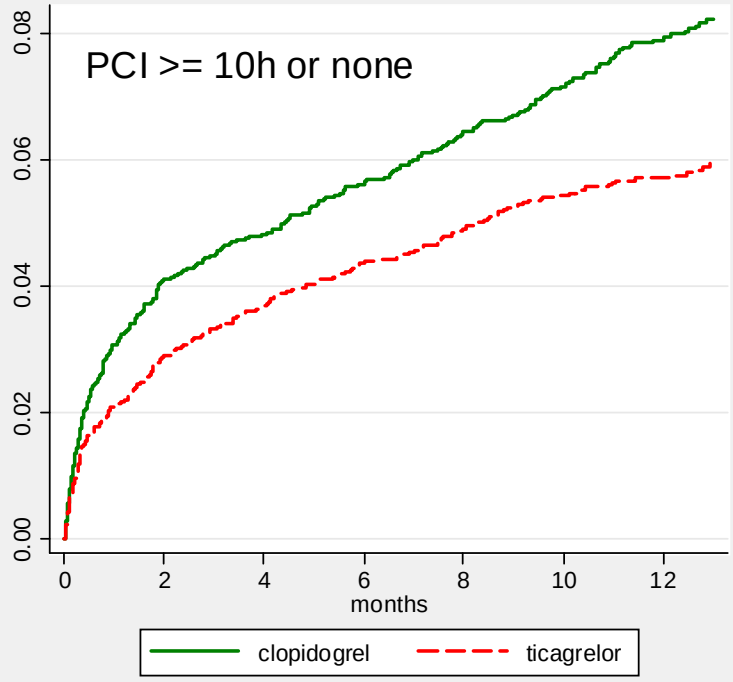
- Only the date, not the time, of starting non-study drug anti-thrombotic was captured
  - E.g., non-study clopidogrel, GP IIb/IIIa inhibitor
- Substantial errors in times
  - 725 cases study drug prior to randomization
  - 335 PCIs prior to randomization
    - Protocol violation vs. time error
  - 730 PCIs prior to study drug

Deaths by Index Event

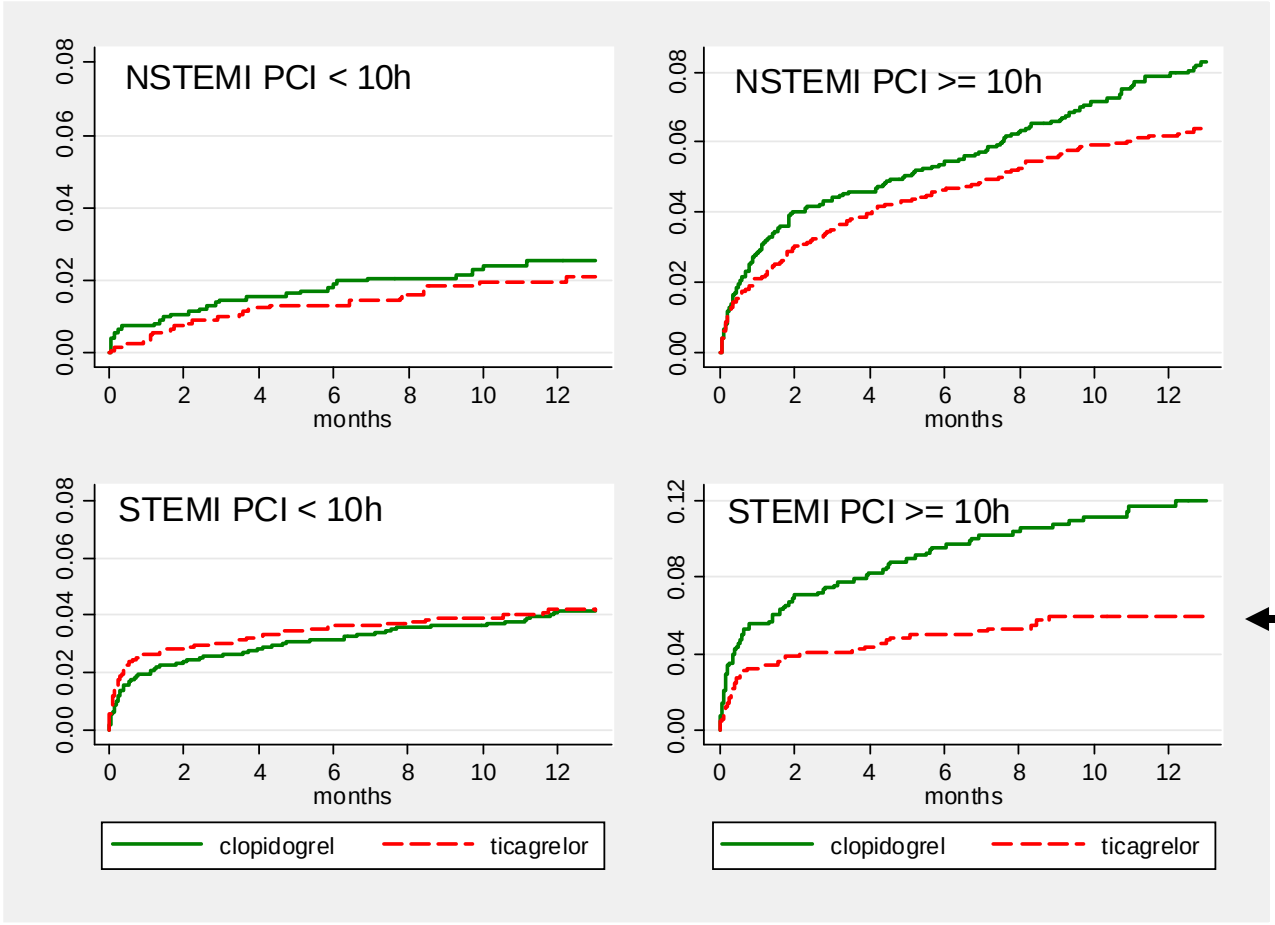


Deaths by PCI within 10h



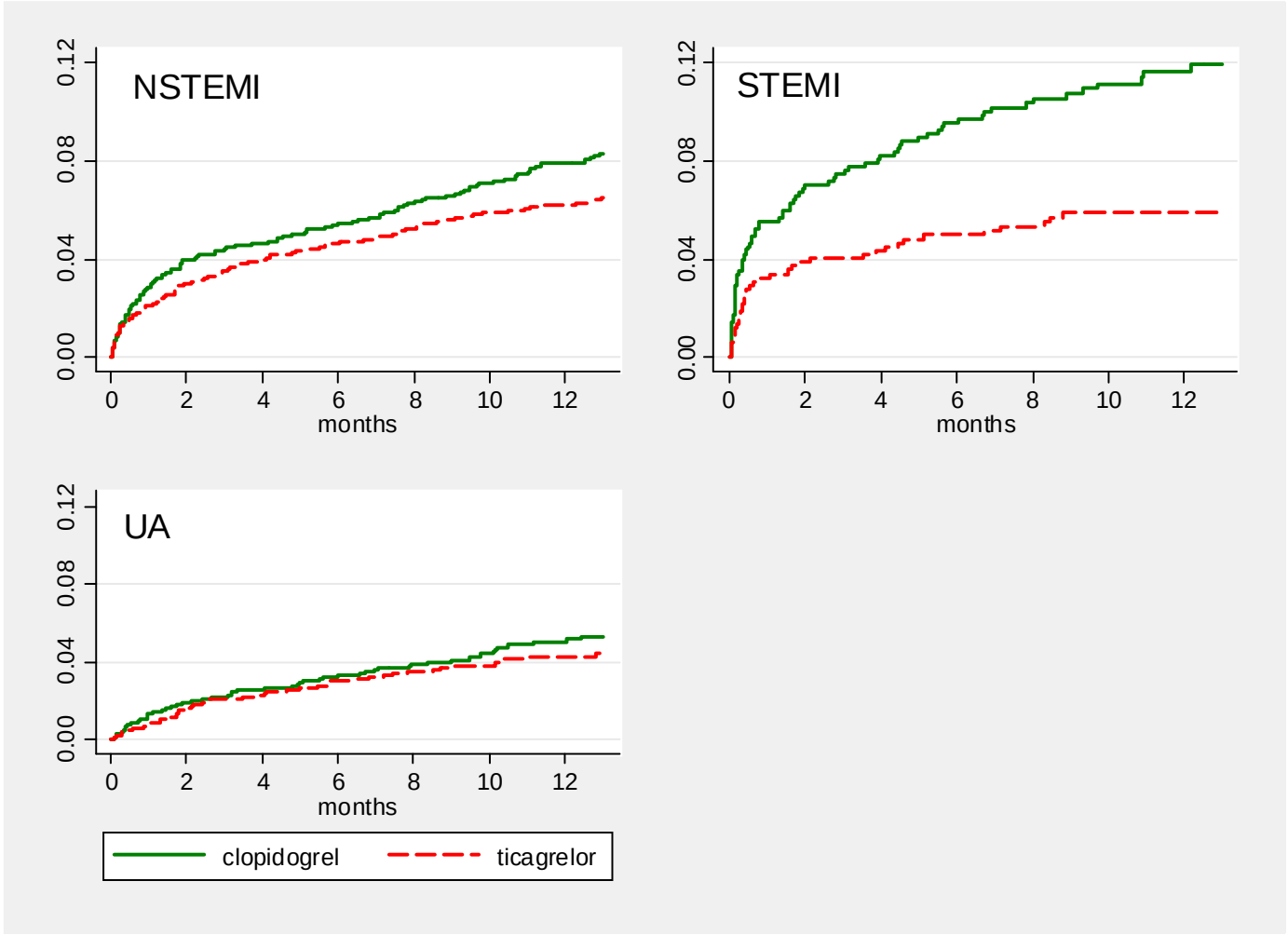


Deaths by PCI within 10h & MI Type



Note different scale

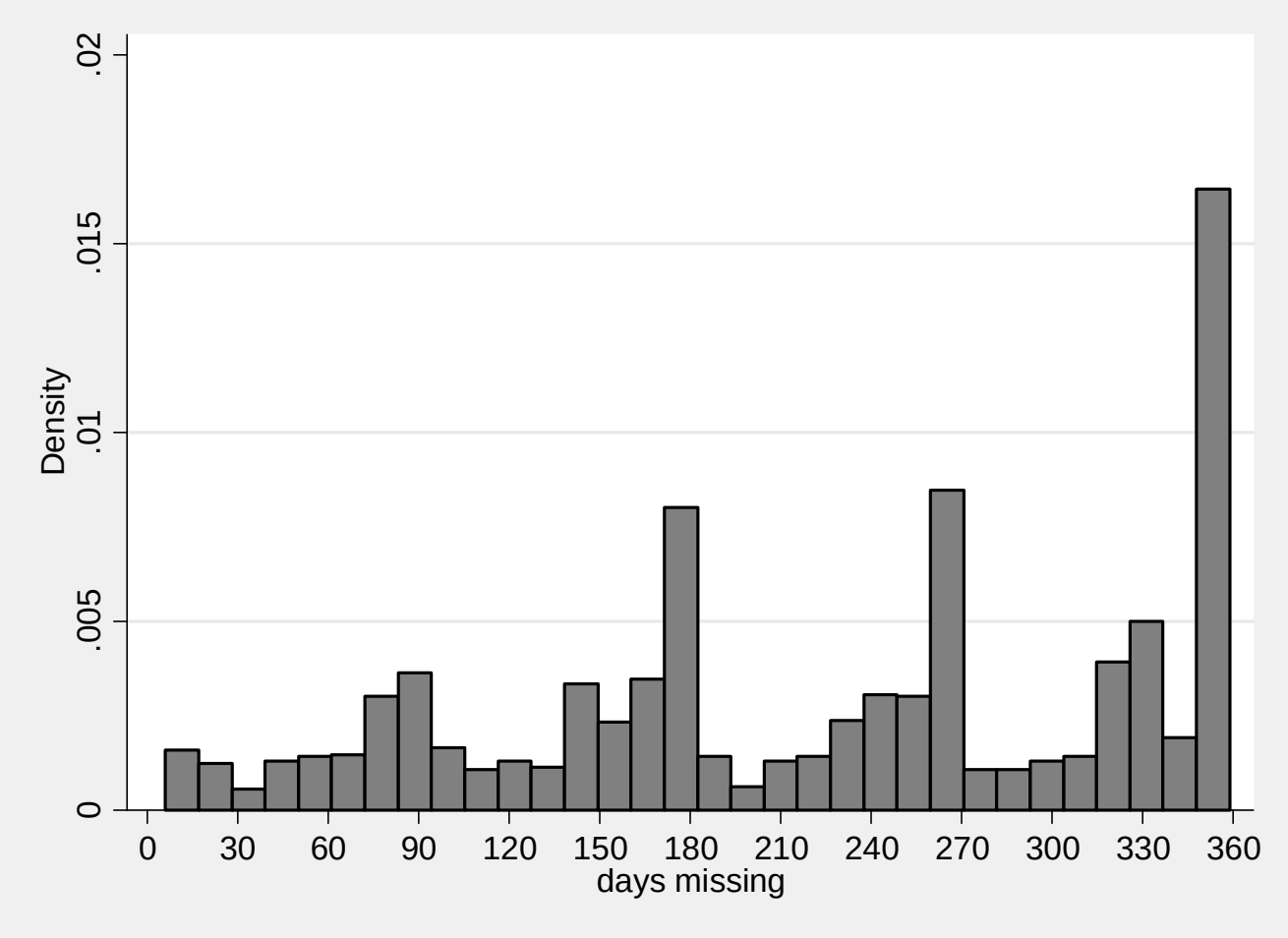
Deaths by Index Event & No PCI < 10h



Follow-up Issues

- CV follow-up limited in this 1-year study
  - 15.9% ticagrelor vs. 14.7% clopidogrel did not have a final clinic visit
  - 8.6% in each arm did not have a final contact at which CV events were documented
- Vital status follow-up also limited
  - 3.1% ticagrelor vs. 2.6% clopidogrel did not have vital status contact after Oct. 8, 2008

Days of CV Follow-up Missing



Median 241 days, 86% missing

Number 1 Outcome Trial Problem

- Missing follow-up and missing data are becoming increasingly problematic
  - "Withdrew consent" hit 16% in one recent trial
  - Interpretability of trials is threatened
- One response (FDA sponsored):

The Prevention and Treatment of Missing Data in Clinical Trials

Panel on Handling Missing Data in Clinical Trials; National Research Council

http://www.nap.edu/catalog/12955.html