NDA 202-439
Rivaroxaban for
Acute Coronary Syndromes

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Food & Drug Administration

May 23, 2012

ATLAS Challenge:

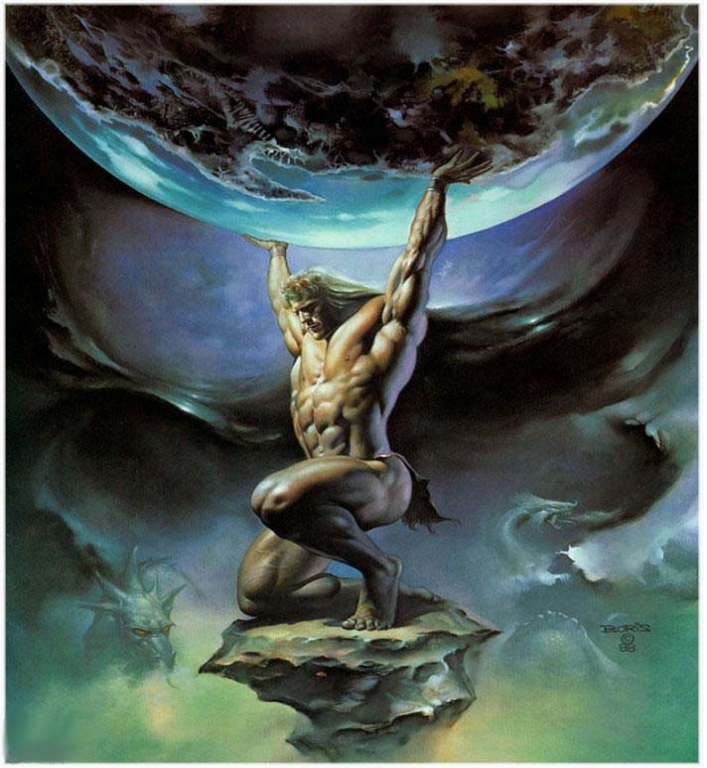
Missing Data & Questionable Quality

Is it:

Atlas shrugged?

or

The weight of the world is too great today?

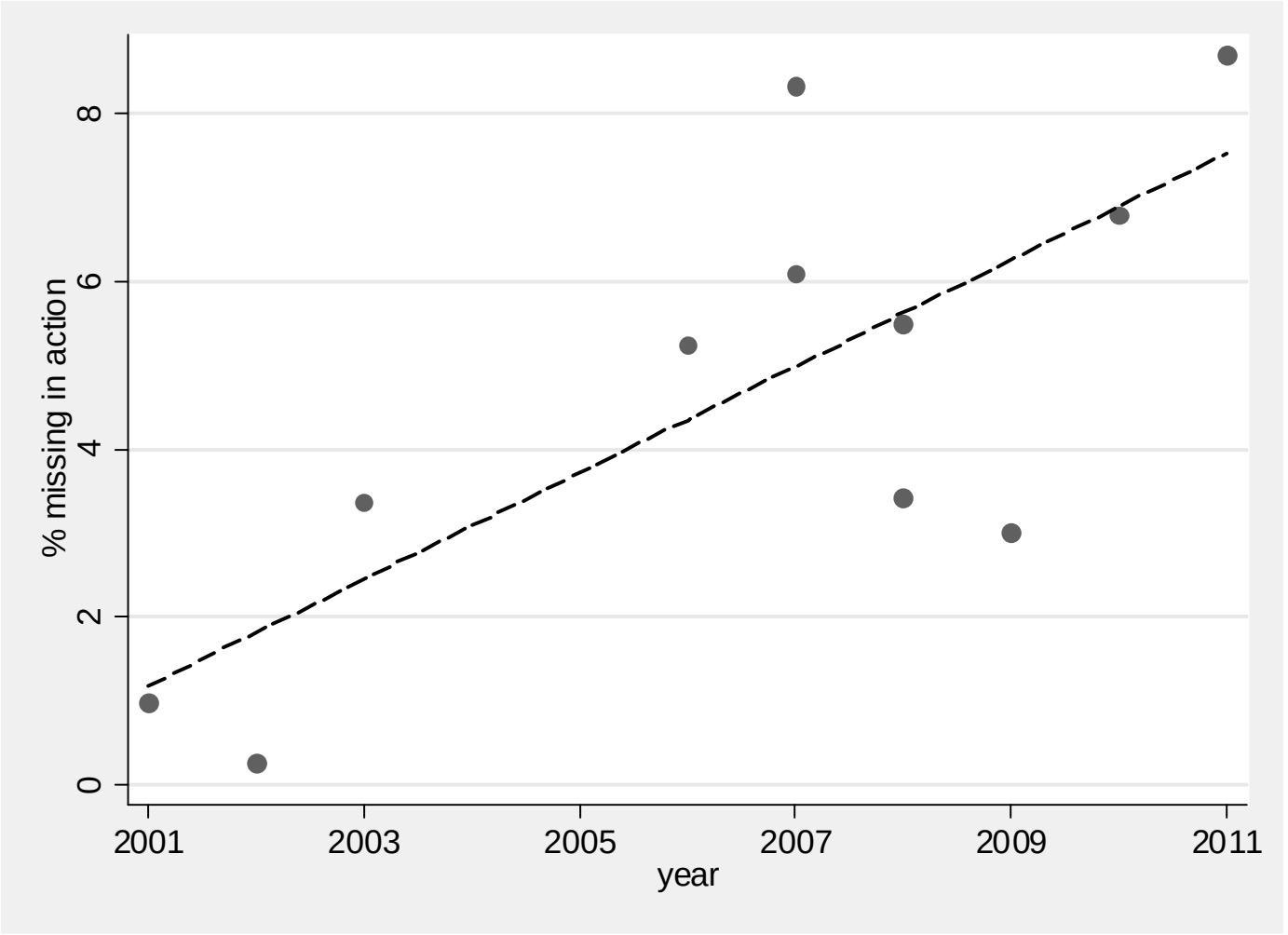


Patient Status at ATLAS End

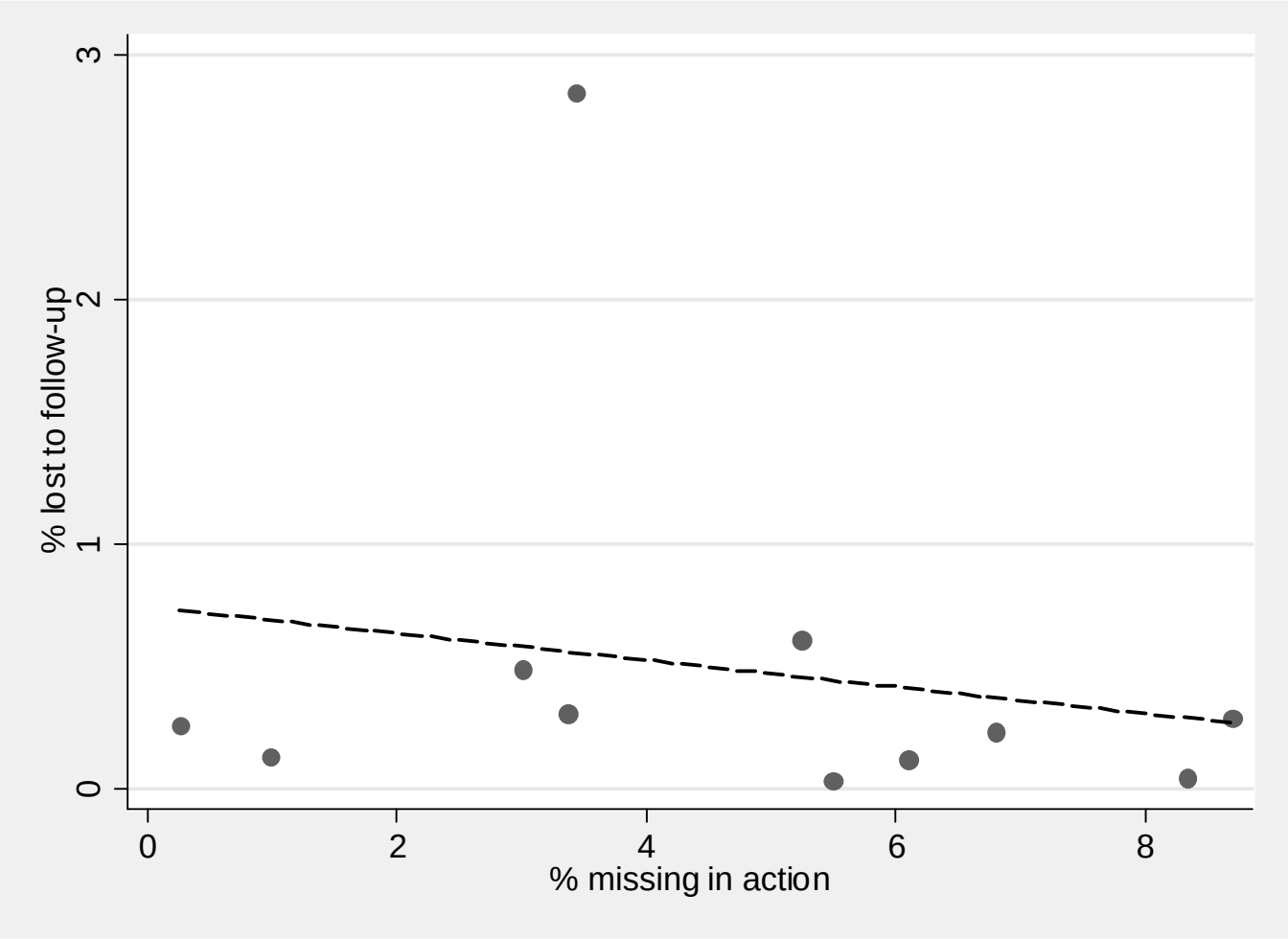
	placebo	2.5	5
complete	85%	85%	84%
death	4%	3%	4%
good f/u	89%	88%	87%
consent withdrawn	8%	9%	9%
lost	0.3%	0.2%	0.3%
other	3%	3%	4%
bad f/u	11%	12%	13%

Source: Sponsor's TRLSTAT (Status at End of Study) in ADSL.XPT

Missing Vital Status for Major CV Outcome Trials

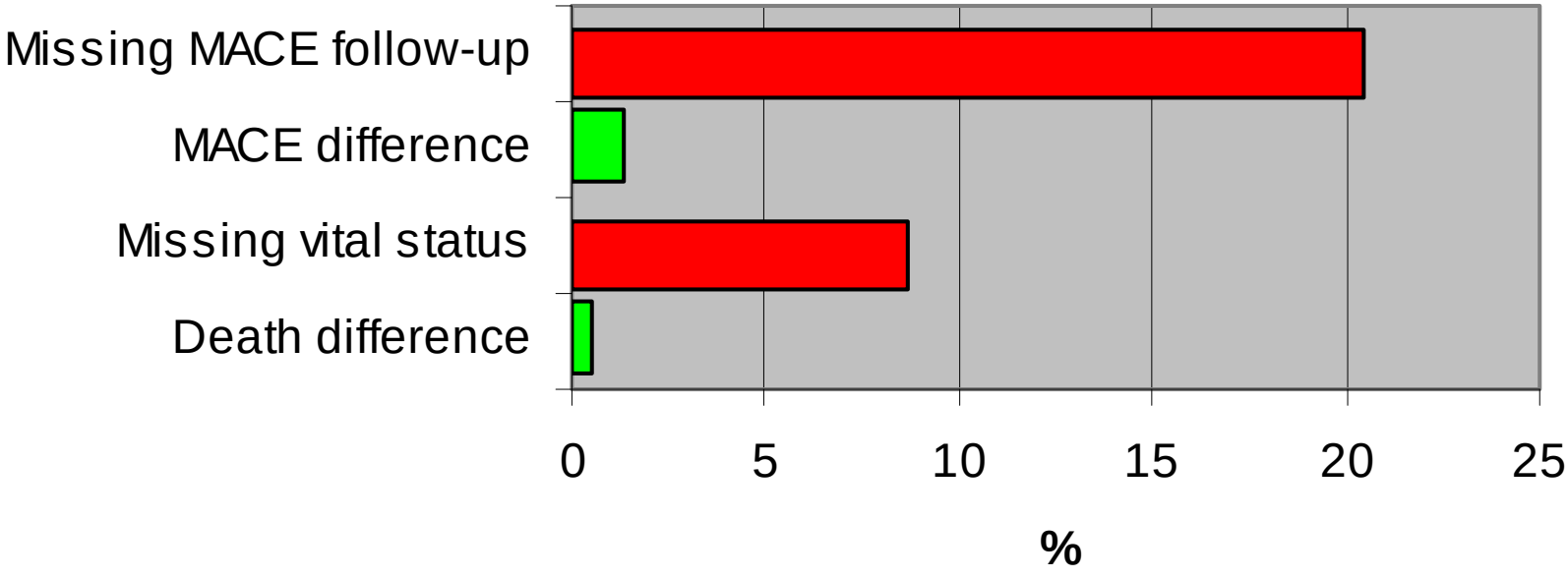


Lost to Follow-up vs. Missing Vital Status



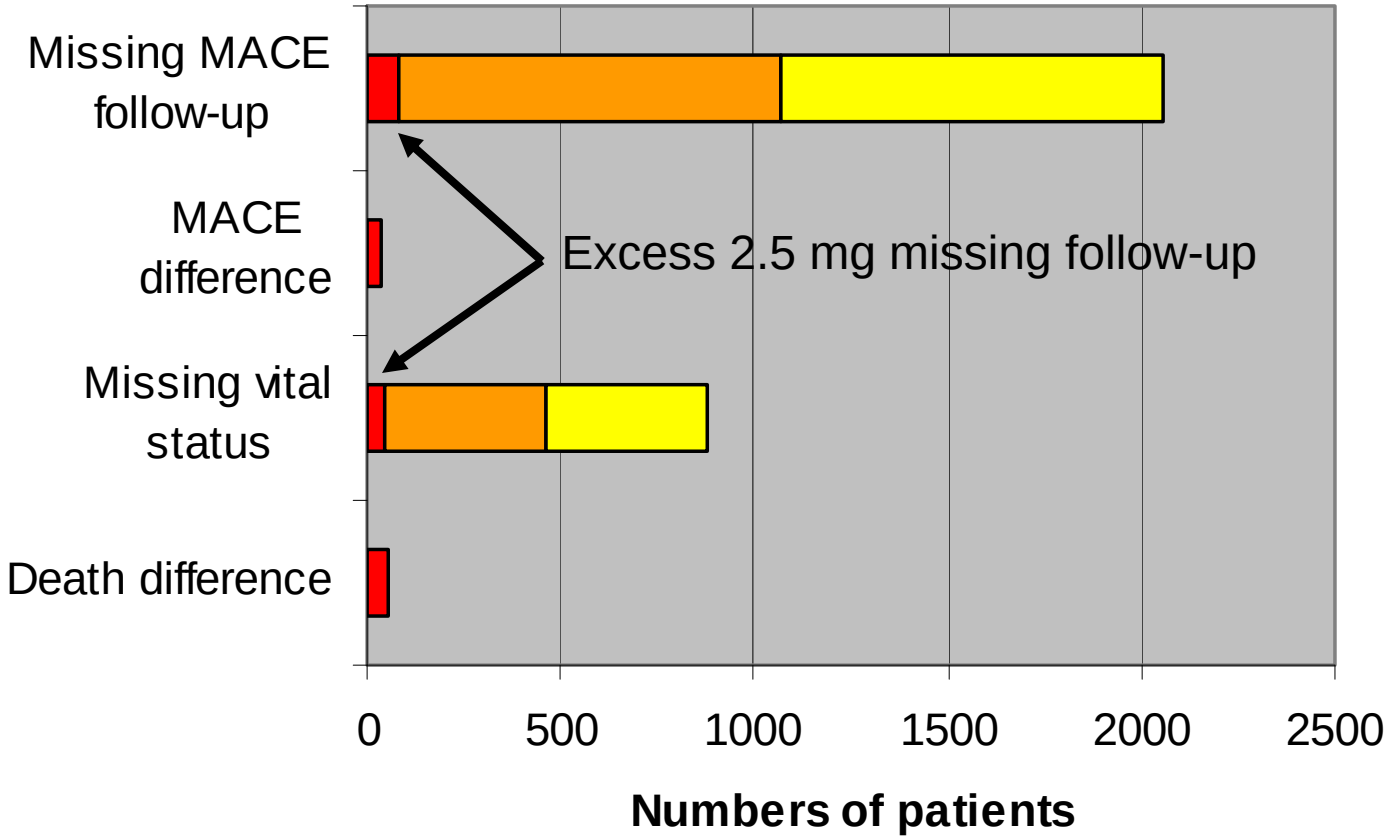
Missing Follow-up vs. Endpoint Differences

Both rivaroxaban doses vs. placebo, ITT



Missing Follow-up vs. Endpoint Differences

Rivaroxaban 2.5 mg vs. placebo, ITT



mITT – NOT!

- Sponsor's "mITT" = on treatment plus 30 days
  - Modified on treatment
  - "Agreement" with FDA for primary analysis only
- ITT: as randomized plus
  - Follow-up through global study treatment end date = 3June2011
  - But NO ATLAS analyses are true ITT because of the vast missing data!

Q: Why push for on treatment analysis?

A: Rivaroxaban causes more bleeding & bleeding leads to more CV events & death.

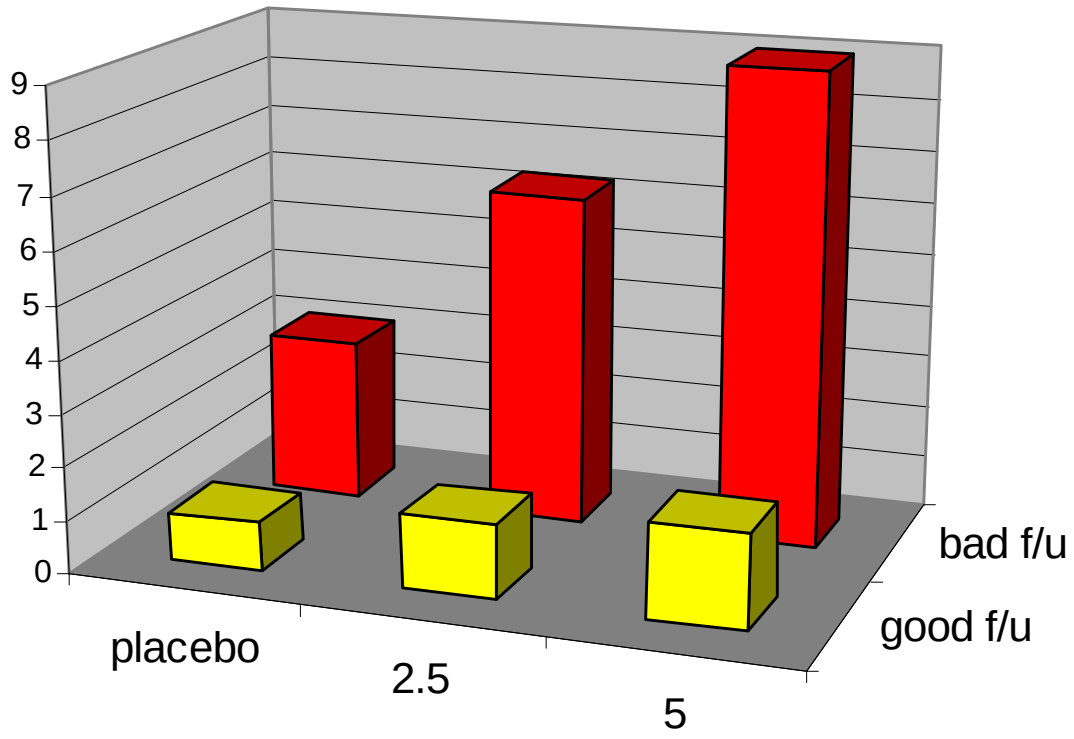
Eikelboom, J. W., S. R. Mehta, et al. (2006). "Adverse impact of bleeding on prognosis in patients with acute coronary syndromes." Circulation **114**(8): 774-82.

Spencer, F. A., M. Moscucci, et al. (2007). "Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction?" Circulation **116**(24): 2793-801.

Ndrepepa, G., T. Schuster, et al. (2012). "Validation of the Bleeding Academic Research Consortium Definition of Bleeding in Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention / Clinical Perspective." Circulation **125**(11): 1424-1431.

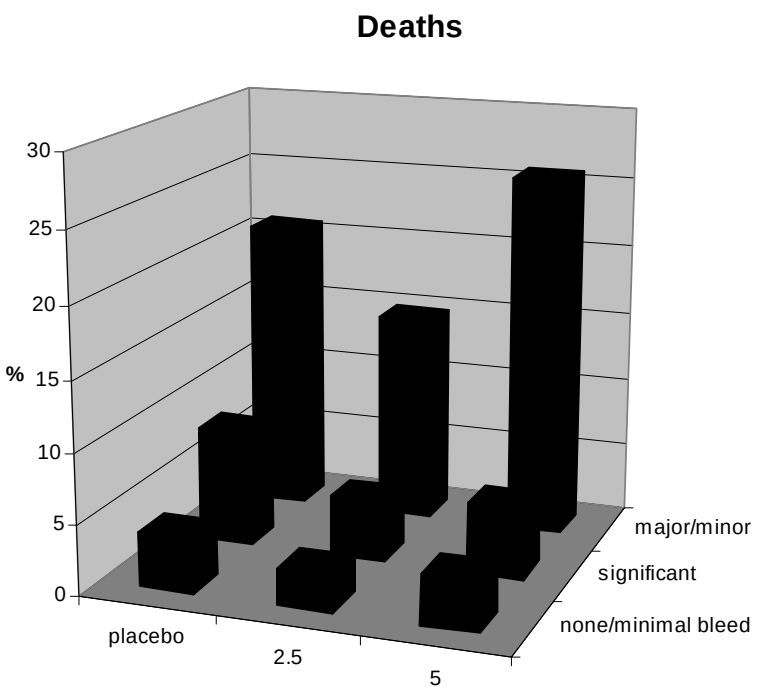
ATLAS bleeding rates were higher with incomplete follow-up

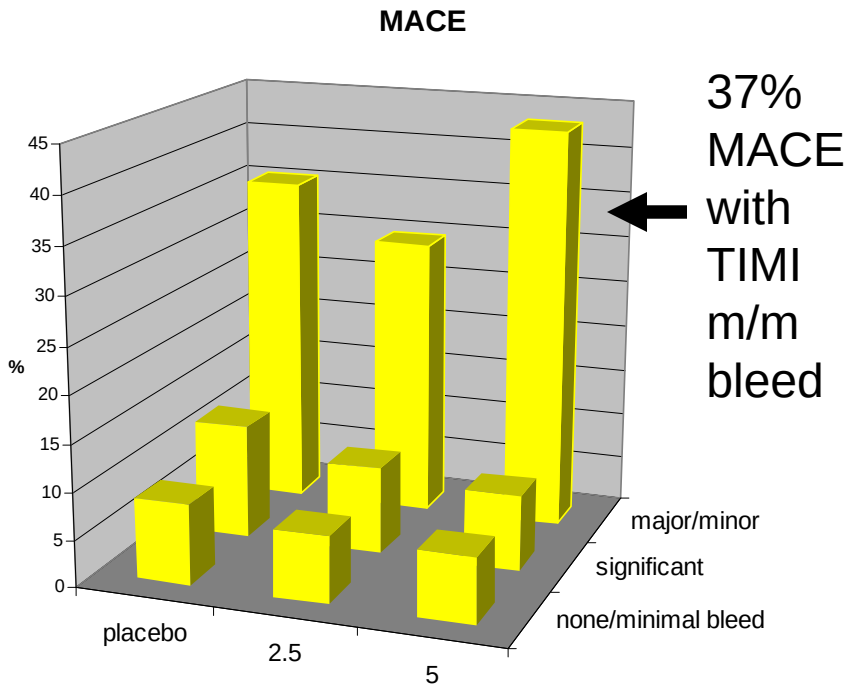
TIMI major/ minor bleeds per 100 PEY*



*PEY = person exposure year

ATLAS death & MACE rates were higher with bleeding





37% MACE with TIMI m/m bleed

Q: Can more bleeds with riv & incomplete f/u explain the endpoint differences?

# incomplete follow-up for riv:	2192
# more riv MACE for p>0.05:	36
# more TIMI m/m bleeds to yield 36 more MACE = 36/0.37 =	97
# riv incomplete f/u, no MACE, but TIMI major/minor bleed:	98

(And this analysis ignores the incomplete ascertainment of bleeding.)

A: Yes!

Uncounted Deaths
Chronology

12/29/11	CSR Fig. 3: 537 deaths (except one more in "other" category = 538)
02/16/12	One more death not counted because after consent withdrawal; Sponsor: no other efficacy events deleted
04/05/12	Two more uncounted deaths after consent withdrawal found by FDA and confirmed by sponsor

(all rivaroxaban)

Uncounted Deaths
Dates

dose	withdrew consent	died*	sponsor's censored	sponsor's status
5	06/14/10	after censored	08/30/10	alive
2.5	01/16/11	between	07/17/11	alive
5	12/23/09	between	07/17/11	alive

*exact dates redacted for privacy reasons

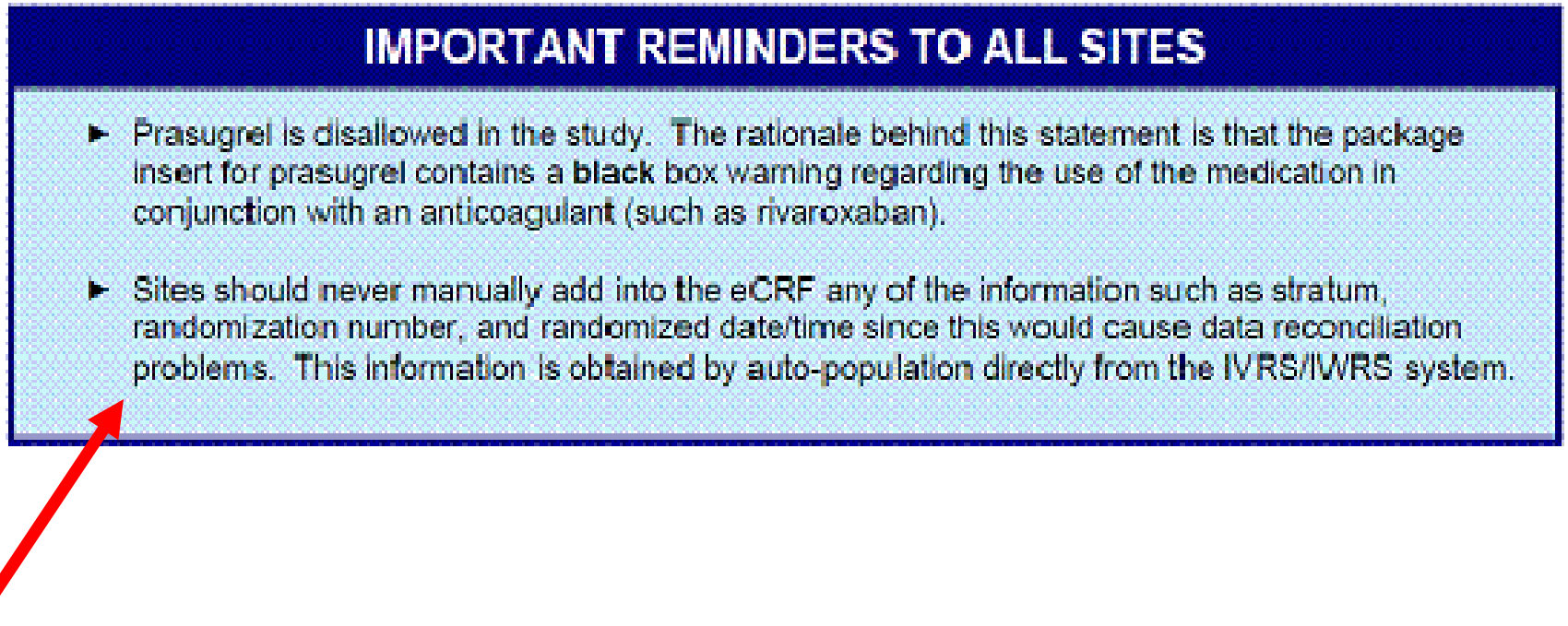
Uncounted Deaths (& Sites)
Impacts on Cox Mortality Regressions

censor	strata:	both			
	exclude 3 deaths:	yes		no	
	exclude 3 sites	yes	no	yes	no
JNJ	"mITT" (on rx + 30d)	0.044	0.055	0.055	0.071
	ITT	0.082	0.097	0.102	0.119
FDA	ITT	0.081	0.096	0.101	0.118

P values

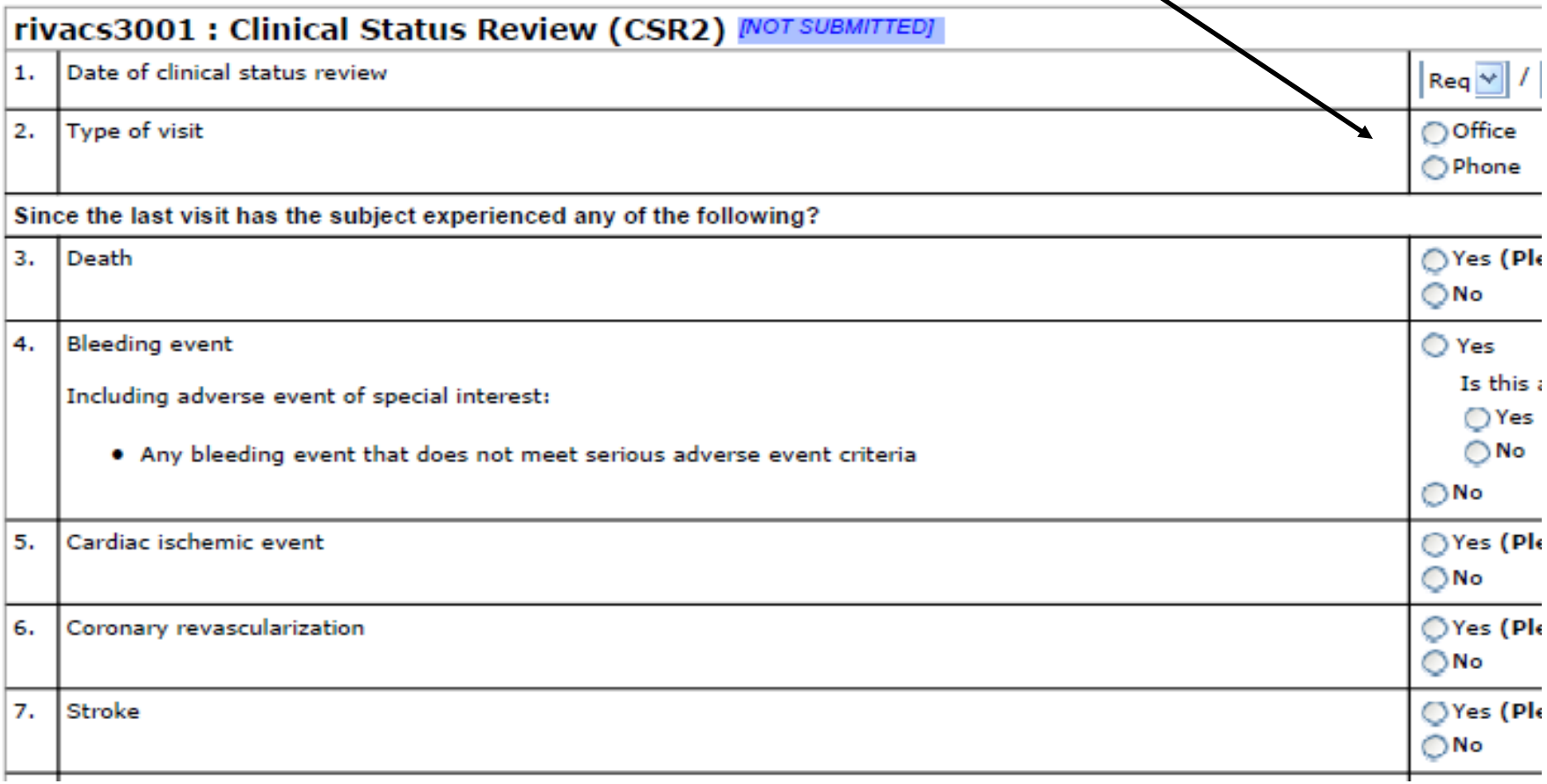
Data Limitations at Trial Start

From the ATLAS November 2009 newsletter to sites:



Data Limitations During Trial

(Only CRF to record type of visit)



rivacs3001 : Clinical Status Review (CSR2) *[NOT SUBMITTED]*

1.	Date of clinical status review	Req /
2.	Type of visit	○ Office ○ Phone
Since the last visit has the subject experienced any of the following?		
3.	Death	○ Yes (Ple ○ No
4.	Bleeding event Including adverse event of special interest: • Any bleeding event that does not meet serious adverse event criteria	○ Yes Is this a ○ Yes ○ No ○ No
5.	Cardiac ischemic event	○ Yes (Ple ○ No
6.	Coronary revascularization	○ Yes (Ple ○ No
7.	Stroke	○ Yes (Ple ○ No

Clinical Status Review Intent?

- CEC Charter June 2009, Overview: “The adjudication process will begin by the sites submitting data indicators that a suspected safety or efficacy endpoint occurred utilizing the electronic case report form (eCRF).”

- 17Apr12: “The purpose of these CSR pages (intentionally and solely) was to serve as a reminder to the site staff of the necessity to perform a patient evaluation, and as such, it was determined at the start of the study that data on these CSR pages, would not be used for data abstraction, nor be combined into the clinical database.”

Clinical Status Review Problems

- 309 “office” visits for “death” since last visit
  - 46 were patients otherwise reported alive
- 61 patients counted as living had at least one CSR reporting death
- Imbalanced by arm:
  - 11 in placebo arm
  - 23 in 2.5 mg arm
  - 27 in 5 mg arm

Odds Ratios of Potential Events from Clinical Status Reviews

	both doses vs. placebo			
	entire study		thienopyridine stratum	
	OR	p	OR	p
death	0.95	0.5	0.91	0.29
cardiac ischemic event	0.94	0.17	0.94	0.22
revascularization	0.97	0.6	1.0	>0.9
stroke	1.0	>0.9	1.0	>0.9

OR = odds ratio by logistic regression

Independent (?) Clinical Events Committee

- CEC Charter:
  - "Subject source documents pertaining to endpoints will be collected and tracked by JNJ PRD."
  - "The CEC coordinator and members will not correspond directly with a site for questions about endpoint-related issues. All requests for additional information will be directed to JNJ PRD, who will obtain the necessary information from the sites."

Hazard Ratios of Site-Reported Endpoints and FDA CV Death

	both doses vs. placebo			
	entire study		thienopyridine stratum	
	HR	p	HR	p
MACE	0.89	0.093	0.89	0.11
CV death	0.83	0.065	0.80	0.028
myocardial infarction	0.91	0.33	0.93	0.4
stroke	1.2	0.3	1.3	0.2

HR = hazard ratio by Cox regression

Data Limitations at Trial End

1.	Did the subject complete the follow-up period?	No Reason for not completing: Other Specify: Pt did not return for follow up visit. Calls were not returned. Letter sent in Oct. no response. Certified letter sent 1/14/2010. Signed by 3rd party on 1/19/10. Survival status was obtained 6/28/11.
2.	Subject survival status	Confirmed as alive Date of last contact: 28/Jun/2011 Type of contact: Patient

Sponsor censor date: 01/14/10--date certified letter sent!
Placebo patient, status “other”

Sponsor’s Last Contact Date

Last contact date will be the maximum of all available dates from the following datasets: AE, CF, CM, DS (imputed, excluding DSCAT=’OTHER EVENT’ and ‘CODE BROKEN’ record), EX (imputed), LB, RA, and SV, and the calculated date should be bounded by raw death date (see death.pdf).

If both of DSDTC [disposition event date] and DSSTDTC [collection date] is partial dataset or one is partial while another is totally missing, if month is missing, replace with 12-31, if day is missing, replaced with end day of that month. Time make up with 23:59:59.

ATLAS Conclusion

ATLAS failed, not shrugged.

The missing data and quality problems preclude ATLAS from providing substantial evidence of effectiveness.

NDA 202439
XARELTO®
Rivaroxaban
Statistical Presentation

Steve Bai, Ph.D.

Statistician

Outline

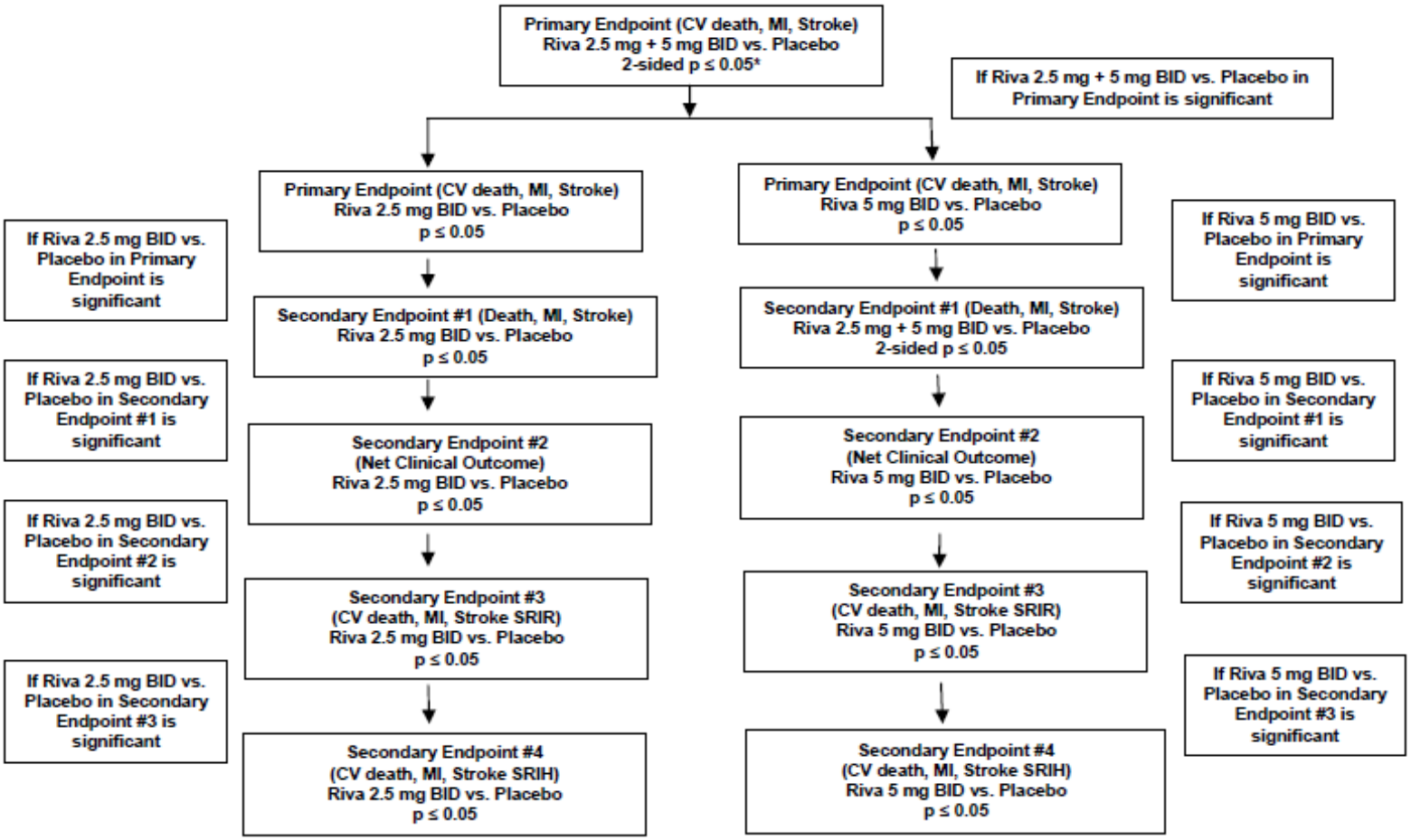
- Study Populations and Multiplicity
- Missing Data Issues
  - Distributions
  - Various Sensitive Analyses
- Assessment of Robustness
  - Cox Model across the trial calendar date

All Strata vs. Stratum 2 (Per Q1.1.2)

Stratum	Rivaroxaban			Placebo					
	2.5 mg	5.0 mg	Combined		2.5 mg vs. Placebo		5.0 mg vs. Placebo		Combined vs. Placebo	
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value	HR (95% CI)	Log-Rank P-Value
ALL Strata	313/5114 (6.1)	313/5115 (6.1)	626/10229 (6.1)	376/5113 (7.4)	0.84 (0.72, 0.97)	0.02	0.85 (0.73, 0.98)	0.028	0.84 (0.74, 0.96)	0.008
ASA + Thieno	286/4765 (6.0)	289/4767 (6.1)	575/9532 (6.0)	340/4760 (7.1)	0.85 (0.72, 0.992)	0.039	0.87 (0.74, 1.02)	0.076	0.86 (0.75, 0.98)	.0245

- Sponsor and FDA had agreement on: Two simultaneous evaluation strategies were selected on the basis of differing regulatory requirements. The primary evaluation strategy was based on data combined across both strata (i.e., All Strata). A second evaluation strategy was based on the FDA-recommended approach of combined analyses across both dose regimens in subjects in Stratum 2 (ASA+Thienopyridine) only.

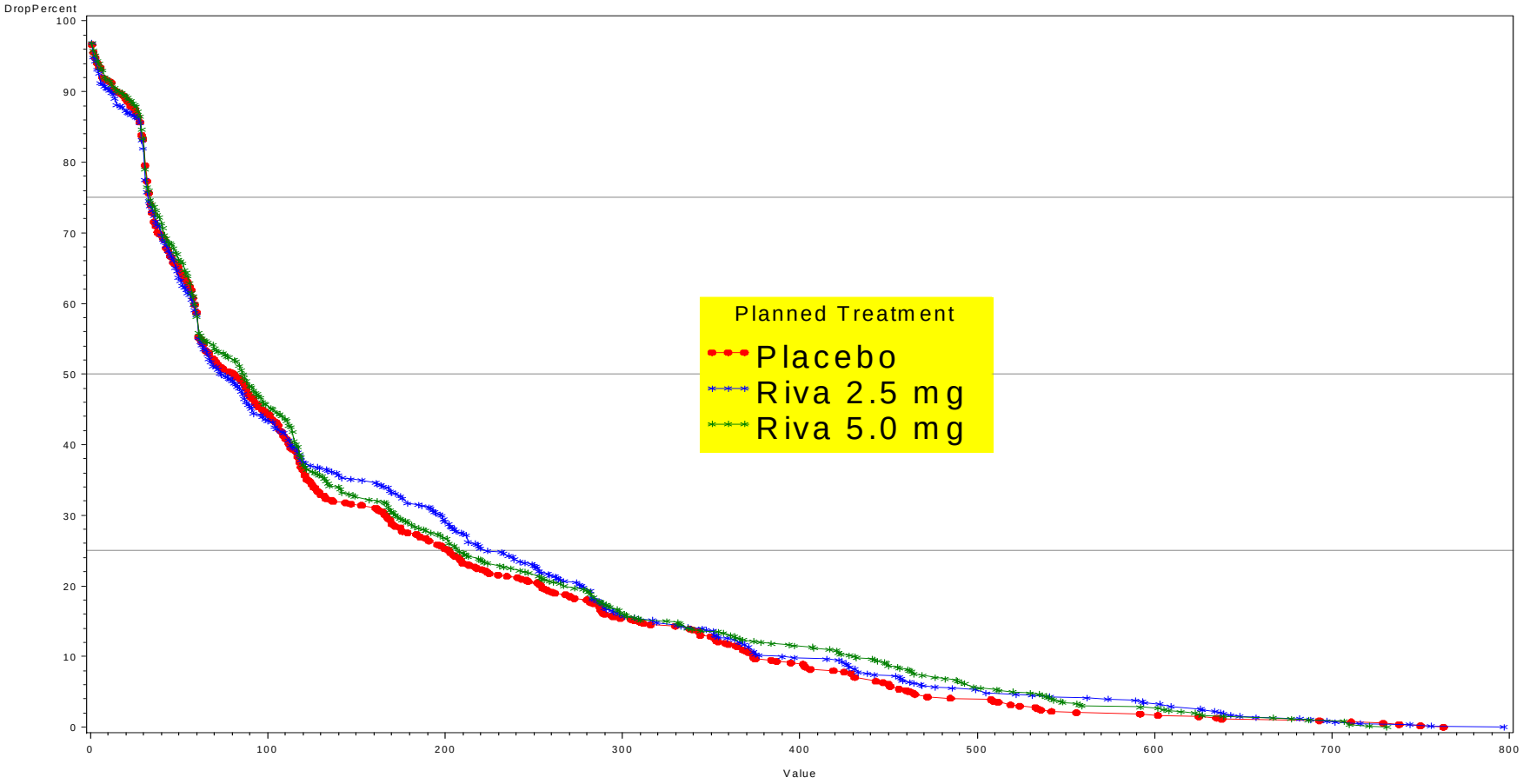
Multiplicity Issues (Per Q1.3)



Reasons for Discontinuation (mITT) ATLAS

ALL STRATA Standard Disposition Term Reason	Rivaroxaban			Placebo (N=5113) n (%)	Total (N=15,342) n (%)
	2.5 mg BID (N=5114) n (%)	5.0 mg BID (N=5115) n (%)	Combined (N=10,229) n (%)		
Prematurely Discontinued from study	581 (11.4)	600 (11.8)	1181 (11.5)	538 (10.5)	1719 (11.2)
Consent withdrawn	441 (8.6)	434 (8.5)	875 (8.6)	396 (7.7)	1271 (8.3)
Lost to follow-up	8 (0.2)	16 (0.3)	24 (0.2)	13 (0.3)	37 (0.2)
Other	132 (2.6)	150 (2.9)	282 (2.8)	129 (2.5)	411 (2.7)
Occurrence of Events					
Yes	27 (0.5)	26 (0.5)	53 (0.5)	24 (0.5)	77 (0.5)
No	554 (10.8)	574 (11.2)	1128 (11.0)	514 (10.0)	1642 (10.7)

Distribution Function of Time to Dropout for Subjects Discontinued from Study



Sensitivity Analyses

mITT

All Strata

Stratumn 2

All Missing as Events

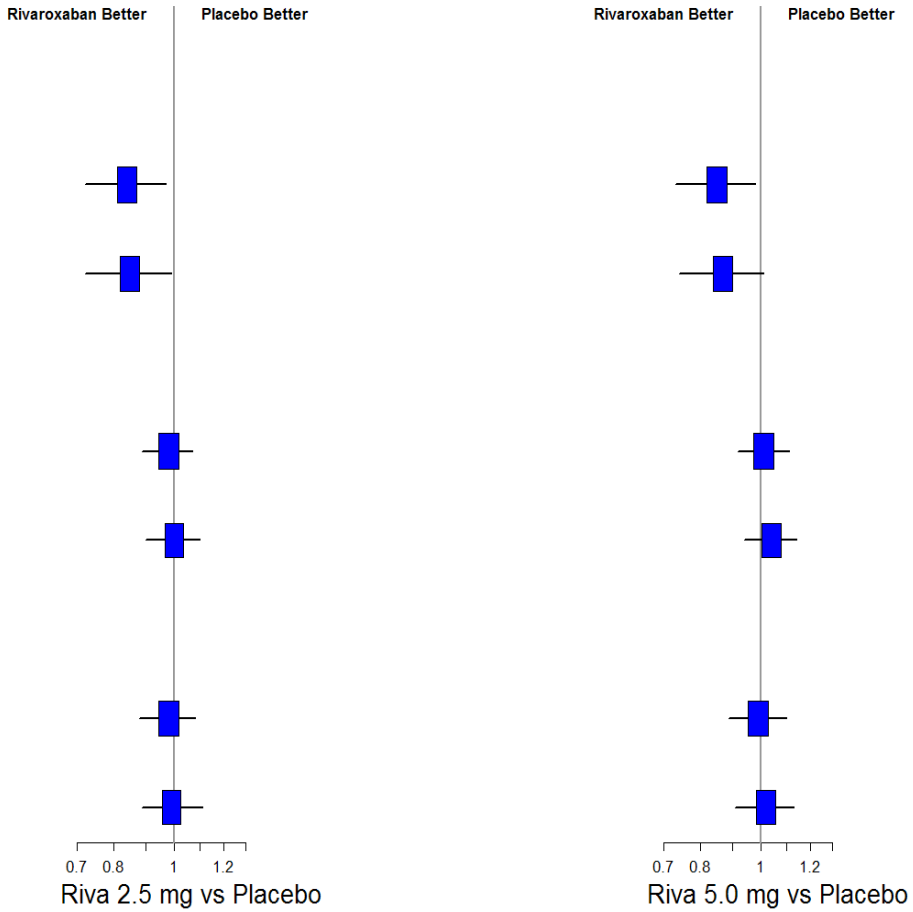
All Strata

Stratumn 2

All CW Missing as Events

All Strata

Stratumn 2

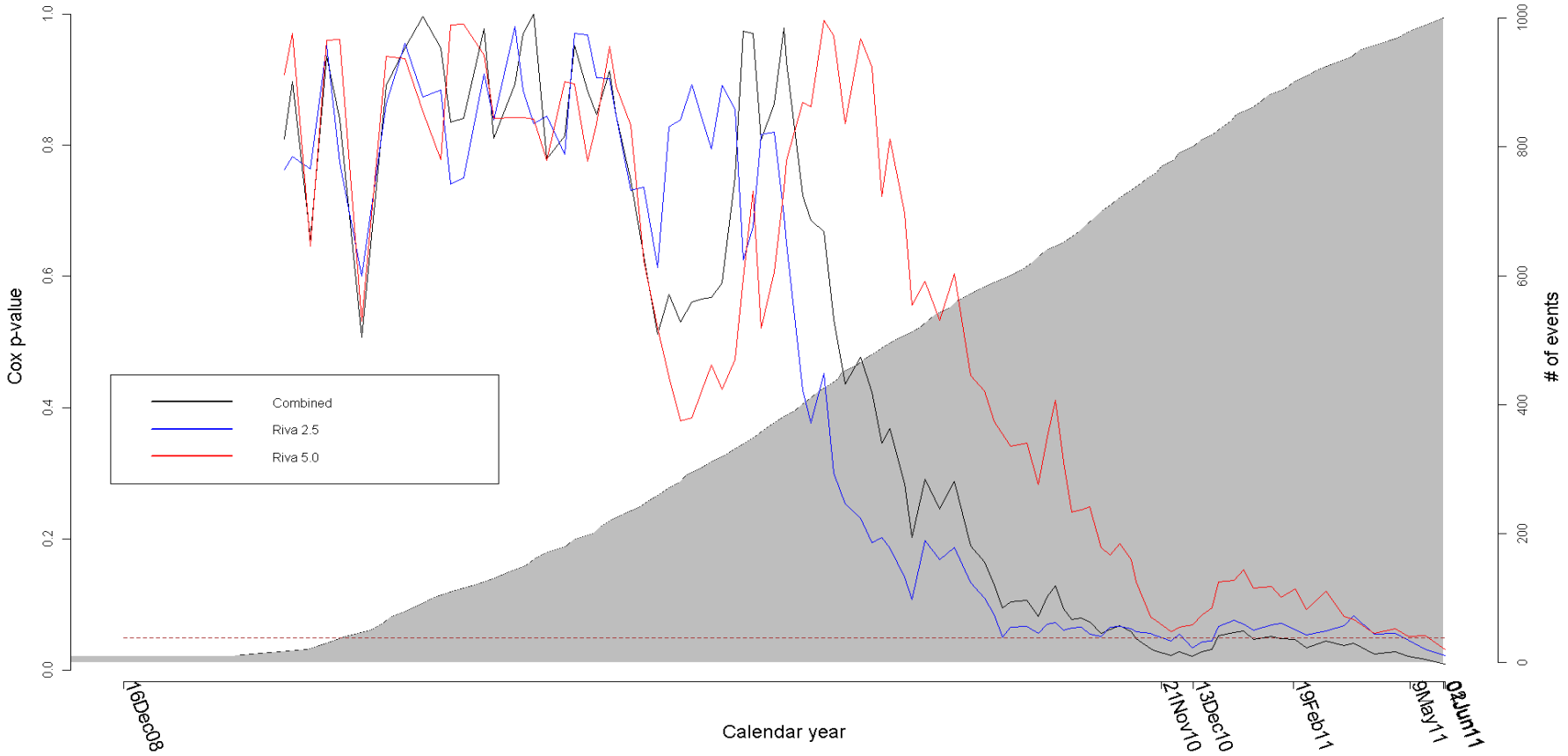


ATLAS – Sensitivity Analyses

Primary Endpoint, mTT		Additional events needed in Rivaroxaban arms (fix Placebo) to nullify the finding	Additional events needed to nullify the finding
Stratums and Rivaroxaban Dose		Relative Risk	Relative Risk
ALL STRATA	Combined Dose	626→666 =↑40	
	Placebo	N/A[1]	
	2.5 mg	313→326= ↑13	313→554= ↑241
	Placebo	N/A[1]	376→617= ↑241
	5.0 mg	313→326= ↑13	313→556= ↑243
	Placebo	N/A[1]	376→619= ↑243
ASA+Thieno	Combined Dose	575→599 =↑24	
	Placebo	N/A[1]	
	2.5 mg	286→293= ↑7	286→396= ↑110
	Placebo	N/A[1]	340→450=↑110
	5.0 mg	N/A[2]	N/A[2]
	Placebo	N/A[2]	N/A[2]

1. The number of Placebo Events are fixed
2. Did not apply due to insignificance findings based on the Cox Model

Cox Model P-values of the primary endpoint across trial calendar date (All Strata MITT Exclude 3 sites)



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Cardiovascular and Renal Drugs Advisory Committee Meeting
May 23, 2012

Karen A. Hicks, M.D., FACC
Medical Officer
Division of Cardiovascular and Renal Products

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Biometrics Reviewer:	Steve Bai, Ph.D.
Non-Clinical Reviewer:	Patricia P. Harlow, Ph.D.
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Clinical Pharmacology Reviewers:	Divya Menon-Andersen, Ph.D. Dhananjay Marathe, Ph.D.
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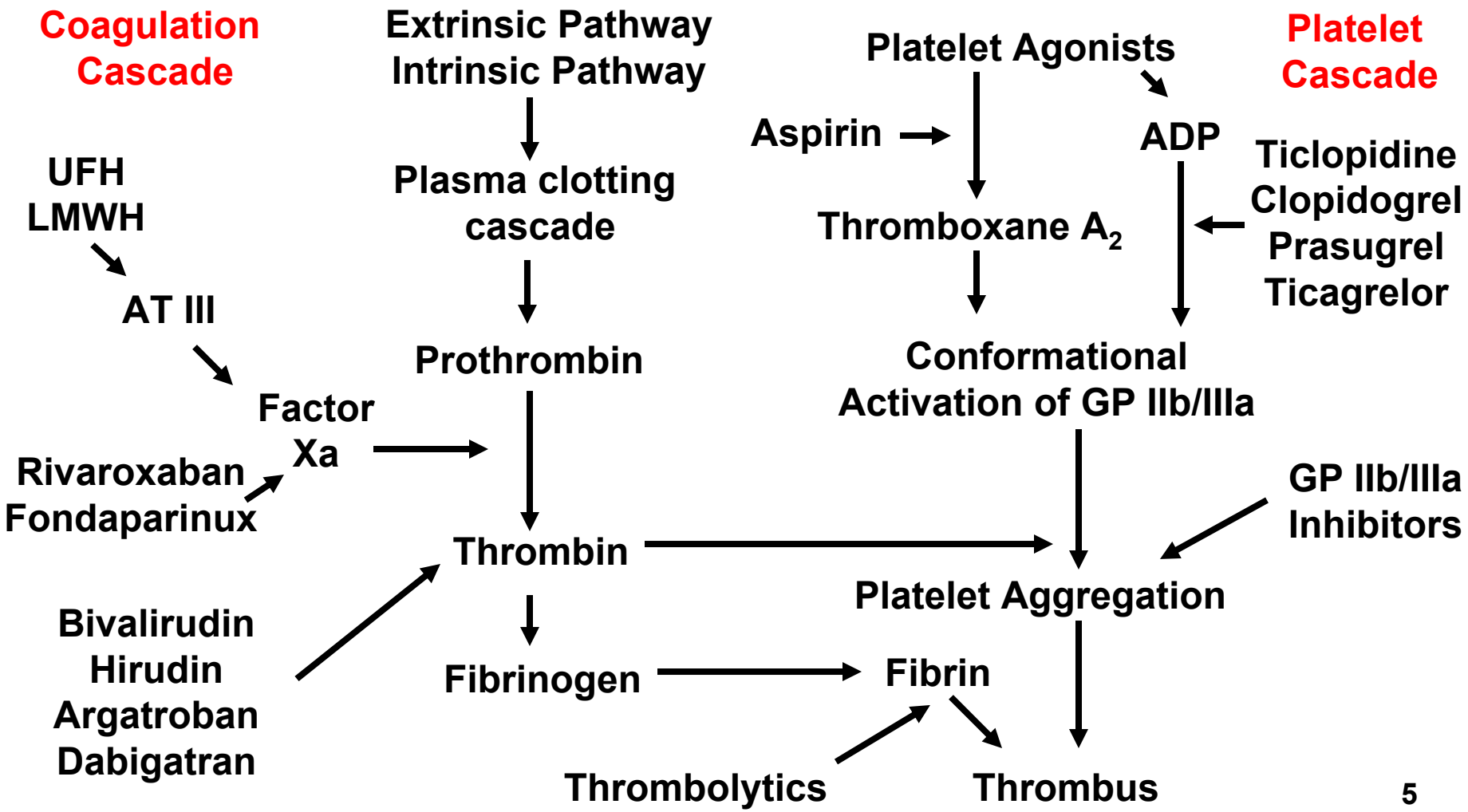
Patient Labeling Reviewer:	Latonia Ford, MBA, BSN, RN
Regulatory Project Manager:	Michael Monteleone, MS, RAC

Outline

- Background
- Patient Selection
- Net Clinical Benefit

BACKGROUND

Sites of Anti-Thrombotic Drug Action



Anticoagulants

Anti-Platelets

- Aspirin
- Thienopyridines
  - Ticlopidine
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
- GP IIb/IIIa Inhibitors
  - Abciximab
  - Eptifibatide
  - Tirofiban

Vitamin K Antagonist

- Warfarin

Anti-thrombins

- Heparin
- LMWH
  - Dalteparin
  - Enoxaparin
- Factor Xa Inhibitors
  - Fondaparinux
  - Rivaroxaban
- Direct Thrombin Inhibitors (DTI)
  - Argatroban
  - Bivalirudin
  - Lepirudin
  - Dabigatran

Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2)

- Double-blind, placebo-controlled, randomized clinical trial
- 858 sites in 39 countries
- Inclusion criteria:
  - ACS within 7 days
  - 2 or more high risk characteristics:
    - Age ≥ 65 years
    - Diabetes mellitus
    - MI within the prior 5 years
    - Cerebrovascular disease
    - Peripheral vascular disease
    - Clinical heart failure or LVEF < 40% with index event
    - Impaired renal function (CrCl < 60 ml/min)
    - No revascularization after index event

APPRAISE-2

- **Primary Efficacy Outcome: composite of CV death, MI, or ischemic stroke**
- **Primary Safety Outcome: TIMI Major bleeding**
- **7392 subjects randomized from March 17, 2009 to November 18, 2010**
  - **1:1 ratio (apixaban 5 mg BID or matching placebo)**
    - **If CrCl < 40 ml/min, then apixaban 2.5 mg BID / placebo**
- **Trial terminated prematurely**
  - **Median duration of f/u: 240 days**

Baseline Demographics: APPRAISE-2 versus ATLAS

Variable	Apixaban (N = 3705) n (%)	Rivaroxaban (N = 10350) n (%)
Demographic Characteristics		
Age (years)		
Median	67	61
Interquartile Range	59, 73	56, 68
Female sex (n, %)	1209 (32.6)	2632 (25.4)
Risk Factors		
Age ≥ 65	2179 (58.8)	3826 (37.0)
Diabetes	1804 (48.7)	3317 (32.0)
Prior MI	923 (24.9)	2766 (26.7)
History of Stroke/TIA	378 (10.2)	292 (2.8)
History of Impaired Renal Function (CrCl < 60 mL/min)	1048 (28.3)	1554 (15.0)
No revascularization for index event	2061 (55.6)	4089 (39.5)
Other Medical History		
Heart Failure	1023 (27.6)	1136 (11.0)
Index ACS Event		
Time from Event to Randomization (days)	6.0	4.7
Type of Event		
STEMI	1474 (39.8)	5185 (50.1)
NSTEMI	1533 (41.4)	2656 (25.7)
Unstable Angina	673 (18.2)	2509 (24.2)
Management of Event		
PCI	1624 (43.8)	6223 (60.1)
CABG	22 (0.6)	38 (0.4)

CABG: Coronary artery bypass graft surgery; CrCL: creatinine clearance; PCI: percutaneous coronary intervention; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction
N Engl J Med 2011; 365:699-708.

APPRAISE-2 – Efficacy Results

Outcome	Apixaban		Placebo		Hazard Ratio with Apixaban (95% CI)	P-value
	Total	Event Rate	Total	Event Rate		
	No. of patients (%)	No. of Events/ 100 patient-yr	No. of patients (%)	No. of Events/ 100 patient-yr		
Efficacy	3705 (100)		3687 (100)			
CV death, MI, or ischemic stroke	279 (7.5)	13.2	293 (7.9)	14.0	0.95 (0.80, 1.11)	0.51
Death	155 (4.2)	7.1	143 (3.9)	6.6	1.08 (0.86-1.35)	0.51
CV death	105 (2.8)	4.8	109 (3.0)	5.0	0.96 (0.73, 1.25)	0.76
MI	182 (4.9)	8.6	194 (5.3)	9.2	0.93 (0.76-1.14)	0.51
Ischemic Stroke	23 (0.6)	1.1	34 (0.9)	1.6	0.68 (0.40, 1.15)	0.14
N Engl J Med 2011; 365:699-708.						

APPRAISE-2: Safety Results

Outcome	Apixaban		Placebo		Hazard Ratio with Apixaban (95% CI)	P-value
	Total	Event Rate	Total	Event Rate		
	No. of patients (%)	No. of Events/ 100 patient-yr	No. of patients (%)	No. of Events/ 100 patient-yr		
Safety: bleeding	3673 (100)		3642 (100)			
TIMI Major	46 (1.3)	2.4	18 (0.5)	0.9	2.59 (1.50, 4.46)	0.001
TIMI Major or Minor	80 (2.2)	4.2	29 (0.8)	1.5	2.79 (1.83, 4.27)	< 0.001
Fatal Bleeding	5 (0.1)	0.3	0	NA	NA	NA
Intracranial Bleeding	12 (0.3)	0.6	3 (0.1)	0.2	4.06 (1.15, 14.38)	0.03

N Engl J Med 2011; 365:699-708.

APPRAISE-2: Net Clinical Outcome

Outcome	Apixaban		Placebo		Hazard Ratio with Apixaban (95% CI)	P-value
	Total	Event Rate	Total	Event Rate		
	No. of patients (%)	No. of Events/ 100 patient-yr	No. of patients (%)	No. of Events/ 100 patient-yr		
Net Clinical Outcomes	3705 (100)		3687 (100)			
CV death, MI, ischemic or hemorrhagic stroke, or fatal bleeding	295 (8.0)	14.0	299 (8.1)	14.3	0.98 (0.83, 1.15)	0.80
Death, MI, or ischemic or hemorrhagic stroke	327 (8.8)	15.5	328 (8.9)	15.6	0.99 (0.85, 1.15)	0.90

N Engl J Med 2011; 365:699-708.

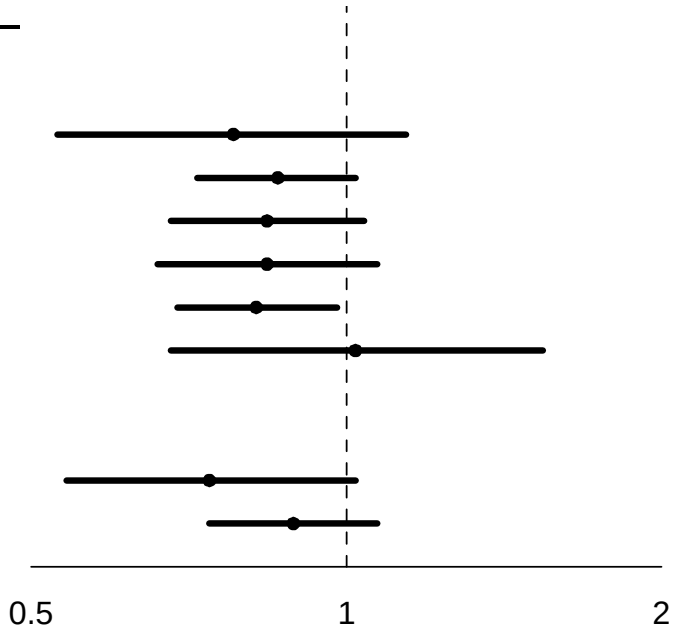
APPRAISE-2: Summary

- Premature termination after enrollment of 7392 subjects
- No statistically significant reduction in the primary endpoint (composite of CV death, MI, or ischemic stroke)
- Safety Results
  - 2.6-fold increase in TIMI Major bleeding (p = 0.001)
  - 4-fold increase in Intracranial bleeding (p = 0.03)
  - Increase in fatal bleeding
- No significant improvement in net clinical outcome

Patient Selection (ATLAS)
(Stratum 2, Rivaroxaban 2.5 mg BID)

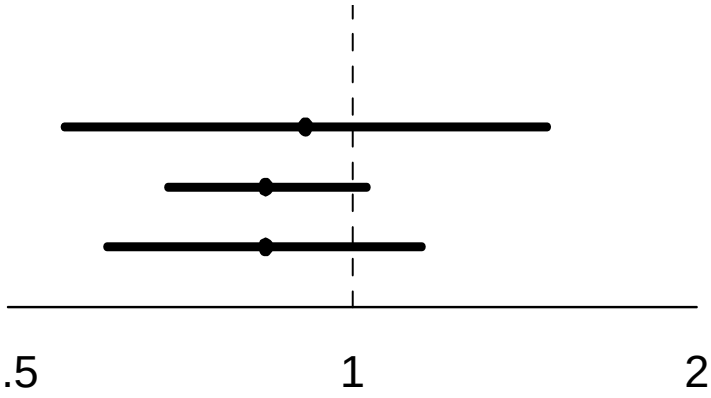
Primary Efficacy End Point by Age and Sex (Stratum 2, Rivaroxaban 2.5 mg BID)

	HR	95% CI	p-value
Age			
< 55	0.78	(0.53, 1.14)	0.2
≥ 55	0.86	(0.72, 1.02)	0.09
< 65	0.84	(0.68, 1.04)	0.11
≥ 65	0.84	(0.66, 1.07)	0.15
< 75	0.82	(0.69, 0.98)	0.03
≥ 75	1.02	(0.68, 1.54)	0.93
Sex			
F	0.74	(0.54, 1.02)	0.06
M	0.89	(0.74, 1.07)	0.2



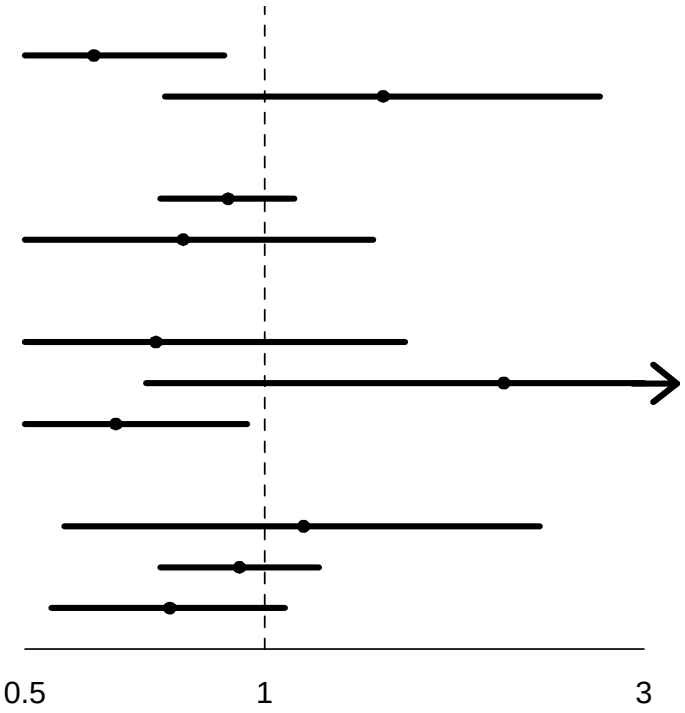
Primary Efficacy End Point by Weight: Stratum 2, Rivaroxaban 2.5 mg BID

	HR	95% CI	p-value
Weight			
< 60 kg	0.91	(0.56, 1.48)	0.7
60-90 kg	0.84	(0.69, 1.03)	0.09
≥ 90 kg	0.84	(0.61, 1.15)	0.28



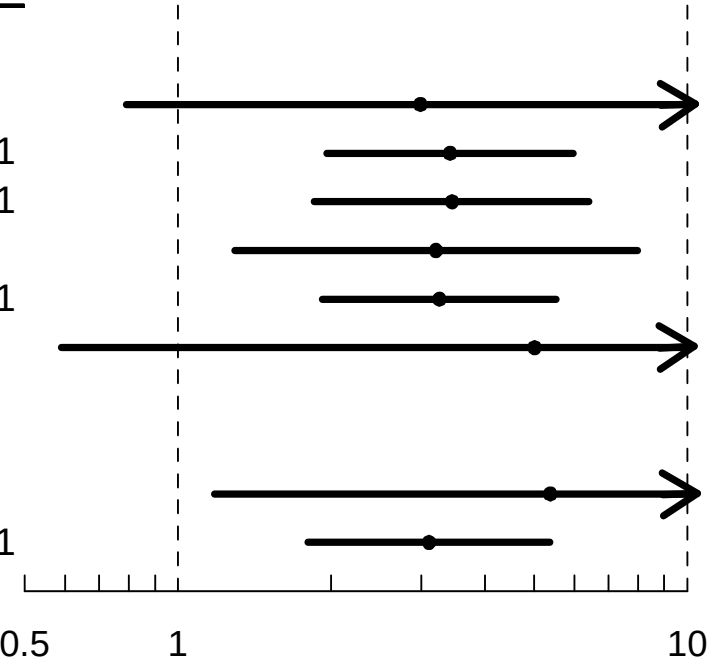
Primary Efficacy End Point by Age, Sex, and Weight (Stratum 2, Rivaroxaban 2.5 mg BID)

	HR	95% CI	p-value
Women			
< 75 years	0.61	(0.42, 0.89)	0.01
≥ 75 years	1.41	(0.75, 2.64)	0.29
Men			
< 75 years	0.9	(0.74, 1.09)	0.27
≥ 75 years	0.79	(0.46, 1.37)	0.41
Women			
< 60 kg	0.73	(0.36, 1.50)	0.4
60 - 90 kg	2	(0.71, 5.69)	0.19
≥ 90 kg	0.65	(0.44, 0.95)	0.03
Men			
< 60 kg	1.12	(0.56, 2.22)	0.75
60 - 90 kg	0.93	(0.74, 1.17)	0.53
≥ 90 kg	0.76	(0.54, 1.06)	0.11



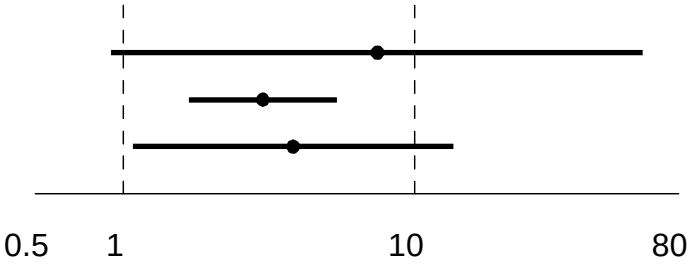
Non-CABG-Related TIMI Major Bleeding Event by Age and Sex (Stratum 2, Rivaroxaban 2.5 mg BID)

	HR	95% CI	p-value
Age			
< 55	2.99	(0.79, 11.25)	0.11
≥ 55	3.42	(1.96, 5.96)	< 0.001
< 65	3.45	(1.85, 6.41)	< 0.001
≥ 65	3.21	(1.29, 7.99)	0.01
< 75	3.26	(1.92, 5.53)	< 0.001
≥ 75	5.01	(0.59, 42.93)	0.14
Sex			
F	5.38	(1.18, 24.54)	0.03
M	3.11	(1.80, 5.37)	< 0.001



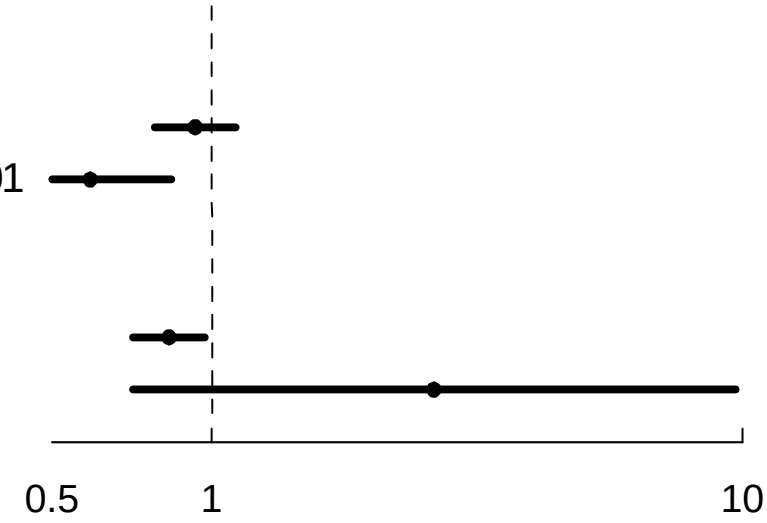
Non-CABG-Related TIMI Major Bleeding Event by Weight (Stratum 2, Rivaroxaban 2.5 mg BID)

	HR	95% CI	p-value
Weight			
< 60 kg	7.43	(0.91, 60.42)	0.061
60-90 kg	3.01	(1.68, 5.41)	< 0.001
≥ 90 kg	3.82	(1.08, 13.54)	0.04



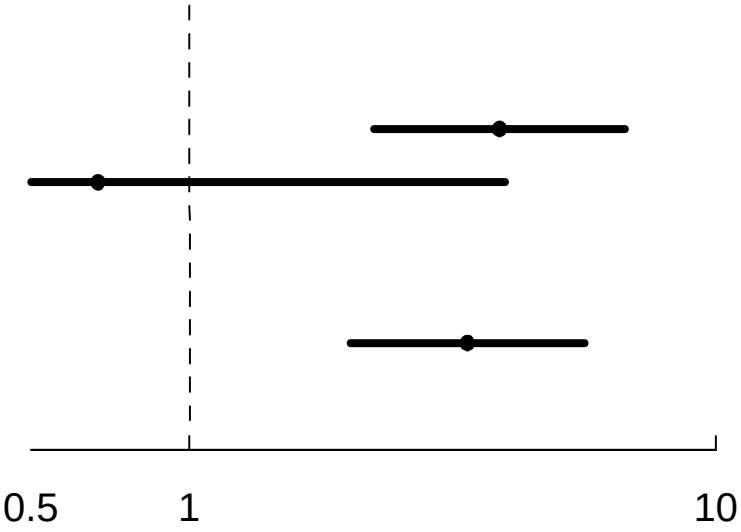
Primary Efficacy End Point: Subjects with a History of CHF or Ischemic Stroke/TIA (Stratum 2, Rivaroxaban 2.5 mg BID)

	HR	95% CI	p-value
Hx of CHF			
No	0.93	(0.78, 1.11)	0.41
Yes	0.59	(0.41, 0.84)	< 0.001
Hx of Ischemic Stroke/TIA			
No	0.83	(0.71, 0.97)	0.02
Yes	2.62	(0.71, 9.73)	0.15



Non-CABG TIMI Major Bleeding Event: Subjects with a History of CHF or Ischemic Stroke/TIA (Stratum 2, Rivaroxaban 2.5 mg BID)

	HR	95% CI	p-value
Hx of CHF			
No	3.88	(2.24, 6.72)	< 0.001
Yes	0.67	(0.11, 3.98)	0.66
Hx of Ischemic Stroke/TIA			
No	3.37	(2.02, 5.63)	< 0.001
Yes	-	-	-



Box Warnings for Bleeding Risk

- Warfarin sodium
- Prasugrel
- Ticagrelor

Bleeding Risk in Warnings and Precautions

- Abciximab
- Eptifibatide
- Tirofiban
- Bivalirudin
- Ticlopidine
- Dalteparin
- Argatroban
- Lepirudin
- Dabigatran

Other Box Warnings

- **Rivaroxaban**
  - **Increased risk of thrombotic events in patients with nonvalvular atrial fibrillation discontinuing rivaroxaban**
  - **Spinal/epidural hematoma (neuraxial anesthesia/spinal puncture)**
- **Dalteparin**
  - **Spinal/epidural hematoma**
- **Fondaparinux**
  - **Spinal/epidural hematoma**
- **Lovenox**
  - **Spinal/epidural hematoma**
- **Ticlopidine**
  - **Neutropenia/agranulocytosis; thrombotic thrombocytopenic purpura (TTP); aplastic anemia**

Subgroup Analysis Summary - 1 (Stratum 2, Rivaroxaban 2.5 mg BID)

- **Overall, Rivaroxaban was effective in reducing the risk of the primary endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) in men and women**
  - **Rivaroxaban increased the risk of the primary end point in women ≥ 75 years of age (HR 1.41 (95% CI: 0.75, 2.64))**
- **Rivaroxaban increased the risk of the primary end point in subjects with a history of ischemic stroke/TIA (HR 2.62 (95% CI: 0.71, 9.73)**

Subgroup Analysis Summary - 2 (Stratum 2, Rivaroxaban 2.5 mg BID)

- **Rivaroxaban increased the risk of NCABG-Related TIMI Major Bleeding in all subgroups except those with a history of CHF**
  - **Those at higher risk may include subjects ≥ 75 years of age (HR 5.01 (0.59, 42.93)), subjects weighing < 60 kg (HR 7.43 (95% CI: 0.91, 60.42)) or ≥ 90 kg (HR 3.82 (95% CI: 1.08, 13.54), subjects with moderate renal impairment, and women (HR 5.38 (1.18, 24.54))**

Subgroup Analysis Summary - 3 (Stratum 2, Rivaroxaban 2.5 mg BID)

- Rivaroxaban was effective in reducing the risk of the primary end point in subjects with a history of CHF (HR 0.59 (95% CI: 0.41, 0.84)) and did not increase the risk of NCABG-Related TIMI Major Bleeding at the 2.5 mg BID dose in Stratum 2 (HR 0.67 (95% CI: 0.11, 3.98))
- Box warnings can be an effective communication tool for bleeding risk

Net Clinical Benefit

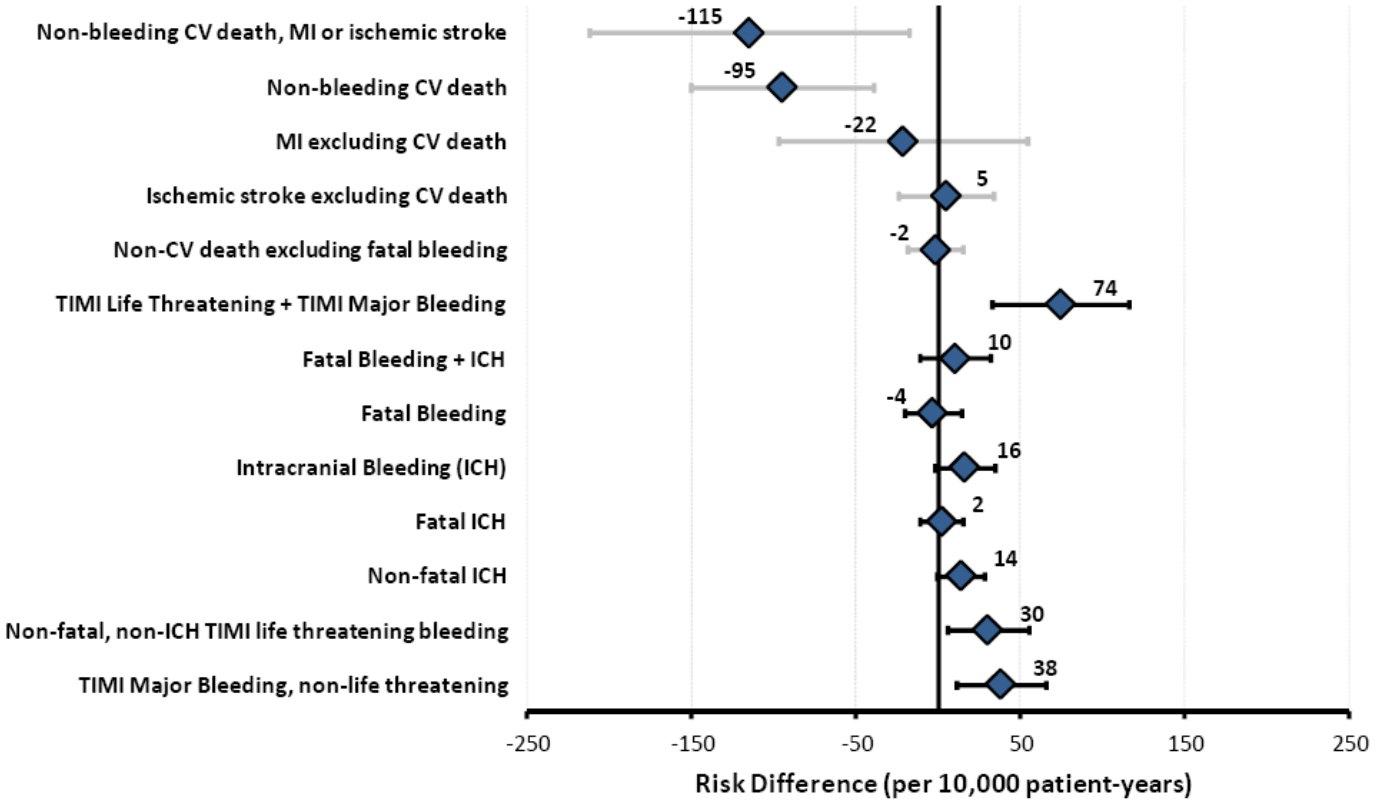
Net Clinical Outcome

- Composite of
  - CV death
  - MI
  - Ischemic Stroke
  - Non-CABG-Related TIMI Major Bleeding Event

Net Clinical Outcome

Subject Stratum Parameter	Rivaroxaban			Placebo	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
	2.5 mg BID	5 mg BID	Combined							
ALL STRATA	N = 5114 n (%)	N = 5115 n (%)	N = 10229 n (%)	N = 5113 n (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Net Clinical Outcome	361 (7.1)	366 (7.2)	727 (7.1)	391 (7.6)	0.93 (0.81, 1.07)	0.320	0.95 (0.83, 1.10)	0.508	0.94 (0.83, 1.06)	0.337
CV Death	94 (1.8)	132 (2.6)	226 (2.2)	143 (2.8)	0.66 (0.51, 0.86)	0.002	0.94 (0.75, 1.20)	0.633	0.80 (0.65, 0.99)	0.038
MI	205 (4.0)	179 (3.5)	384 (3.8)	229 (4.5)	0.90 (0.75, 1.09)	0.270	0.79 (0.65, 0.97)	0.020	0.85 (0.72, 1.00)	0.047
Ischemic Stroke	30 (0.6)	35 (0.7)	65 (0.6)	34 (0.7)	0.89 (0.55, 1.45)	0.643	1.05 (0.65, 1.68)	0.844	0.97 (0.64, 1.47)	0.886
Non-CABG TIMI Major	68 (1.3)	85 (1.7)	153 (1.5)	23 (0.4)	2.99 (1.86, 4.80)	<0.001	3.81 (2.40, 6.04)	<0.001	3.40 (2.19, 5.26)	<0.001

Risk Differences (per 10,000 patient years) (Stratum 2, Rivaroxaban 2.5 mg BID, mITT excluding 3 sites) (Sponsor)



Note: Diamonds indicate point estimates. Grey and black bars show 95% CIs for ischemic and hemorrhagic endpoints respectively.
Data source: RNCB055.

Risk Differences

- **516 additional Clinically Significant Bleeding events**
  - **Including 423 TIMI Medical Attention Bleeding events per 10,000 patient-years**
- **1 additional Clinically Significant Bleeding event every 19 patient-years**
  - **1 additional TIMI Medical Attention Bleeding event every 24 patient-years**

Summary (ATLAS)
(Stratum 2, Rivaroxaban 2.5 mg BID)

Summary - 1

- **Overall, Rivaroxaban was effective in reducing the risk of the primary endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) in men and women**
  - **Rivaroxaban increased the risk of the primary end point in women ≥ 75 years of age (HR 1.41 (95% CI: 0.75, 2.64))**
- **Rivaroxaban increased the risk of the primary end point in subjects with a history of ischemic stroke/TIA (HR 2.62 (95% CI: 0.71, 9.73))**

Summary - 2

- Box warnings can be an effective communication tool for bleeding risk
- Patients and Health Care Providers (HCPs) need to know the risks associated with rivaroxaban and HCPs must communicate these risks effectively to the patient
- There are numerous ways to assess net clinical benefit

Summary - 3

- **Rivaroxaban increased the risk of NCABG-Related TIMI Major Bleeding in all subgroups except those with a history of CHF in Stratum 2 on Rivaroxaban 2.5 mg BID**
  - **Those at higher risk of bleeding:**
    - **subjects ≥ 75 years of age**
    - **subjects weighing < 60 kg or ≥ 90 kg**
    - **subjects with moderate renal impairment**
    - **women**