Emerging New Oral Anticoagulants

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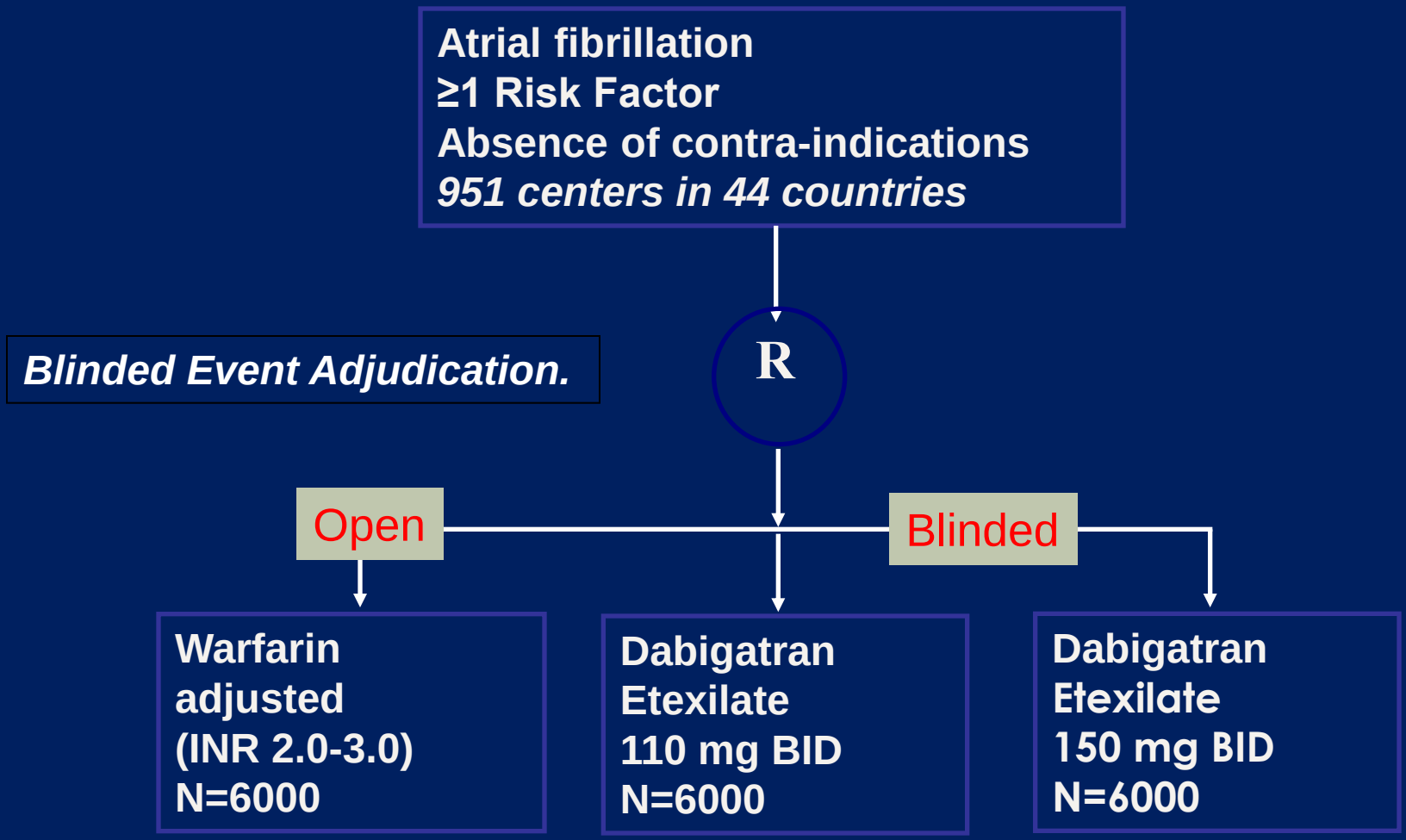
Atrial Fibrillation and Stroke

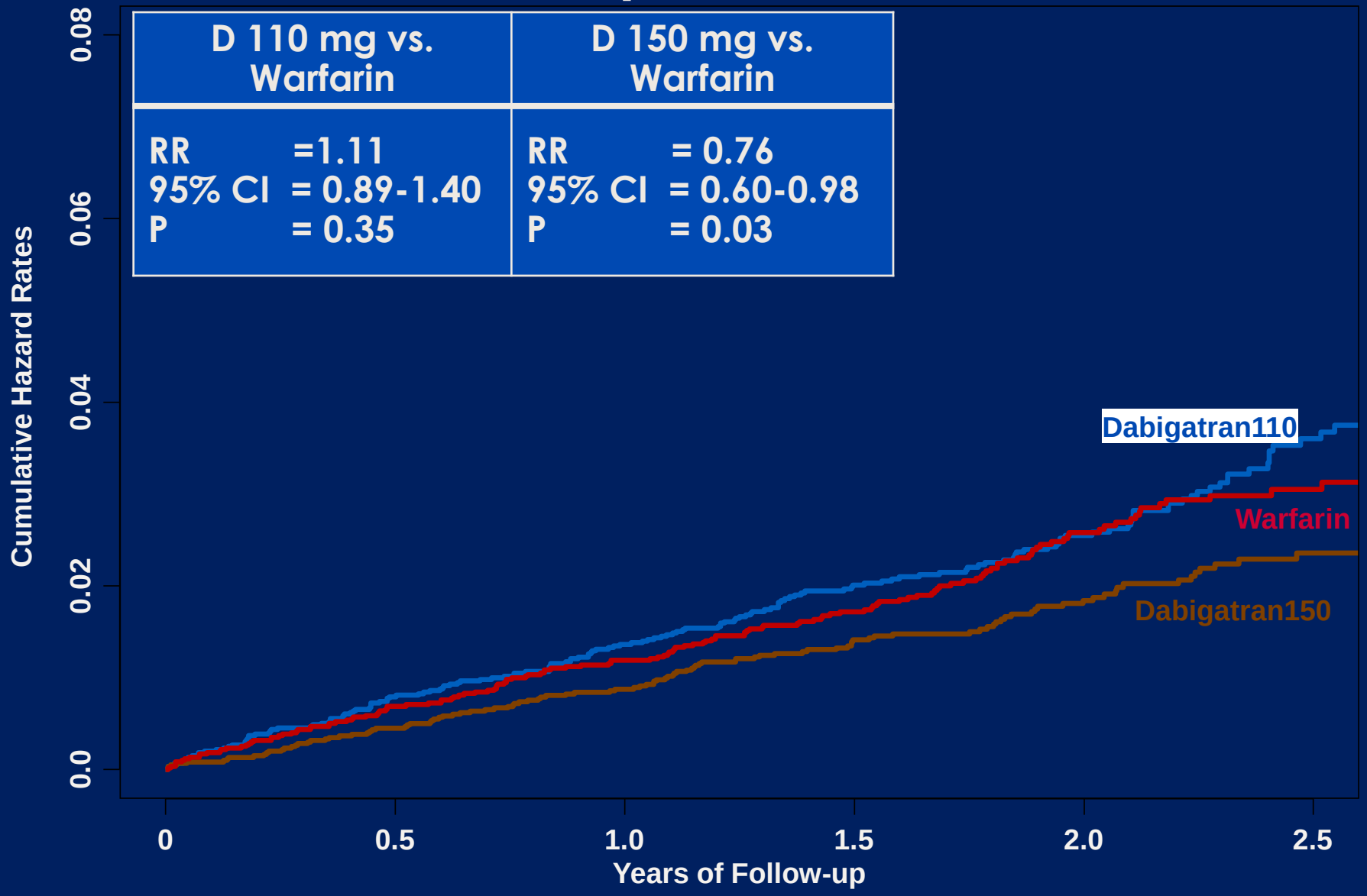
- AF responsible for 1/6 of all strokes
- Warfarin reduces stroke in AF by 64%
  - significant increase in intracranial and other hemorrhage
  - Difficult to use
- Only 50% of eligible patients receive warfarin
- An alternative treatment is needed

RE-LY: A Non-inferiority Trial



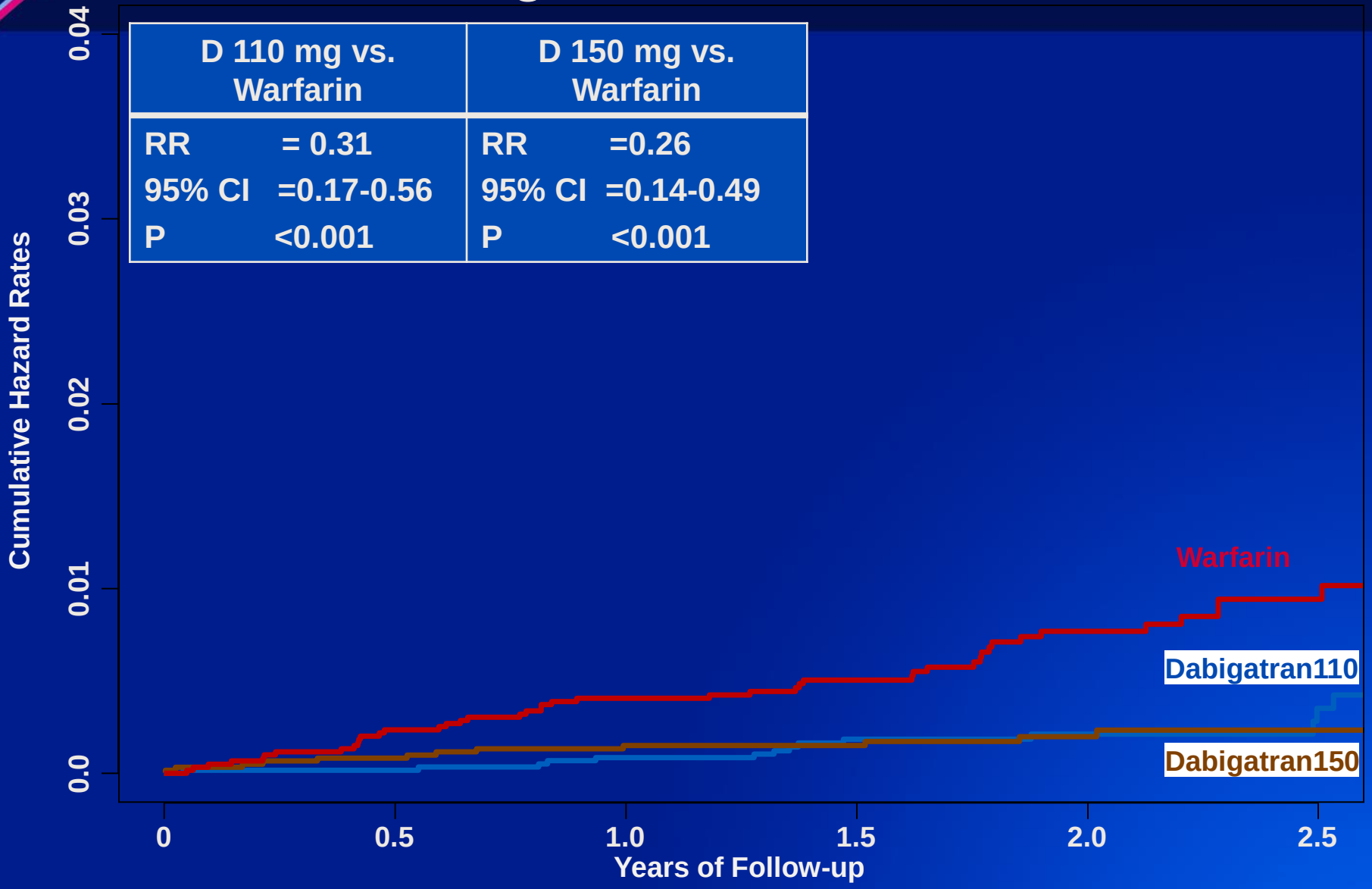
Ischemic/Unspecified Stroke

D 110 mg vs. Warfarin	D 150 mg vs. Warfarin
RR =1.11 95% CI = 0.89-1.40 P = 0.35	RR = 0.76 95% CI = 0.60-0.98 P = 0.03



Hemorrhagic Stroke

D 110 mg vs. Warfarin	D 150 mg vs. Warfarin
RR = 0.31	RR =0.26
95% CI =0.17-0.56	95% CI =0.14-0.49
P <0.001	P <0.001



Bleeding

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Total	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life-Threatening major	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Gastro-intestinal Major	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

MI, Death and Net clinical Benefit

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
MI	0.7%	0.7 %	0.5 %	1.35 0.98-1.87	0.07	1.38 1.00-1.91	0.048
Death	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.05
Net Clinical Benefit	7.1 %	6.9 %	7.6 %	0.92 0.84-1.02	0.10	0.91 0.82-1.00	0.04

Net Clinical Benefit includes vascular events, death and major bleed

Common Adverse Events

Adverse events occurring in >5% of any group	Dabigatran 110 mg %	Dabigatran 150 mg %	Warfarin %
Dyspepsia *	11.8	11.3	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

*Occurred more commonly on dabigatran $p<0.001$

Summary

- Dabigatran 150 mg significantly reduced stroke compared to warfarin with similar risk of major bleeding
- Dabigatran 110 mg had a similar rate of stroke as warfarin with significantly reduced major bleeding
- Both doses markedly reduced intra-cerebral, life-threatening and total bleeding
- Dabigatran had no major toxicity, but did increase dyspepsia and GI bleeding

Apixaban versus Warfarin in Patients with Atrial Fibrillation
Results of the ARISTOTLE Trial

Presented on behalf of the ARISTOTLE Investigators and Committees

Sponsored by Bristol-Myers Squibb and Pfizer

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

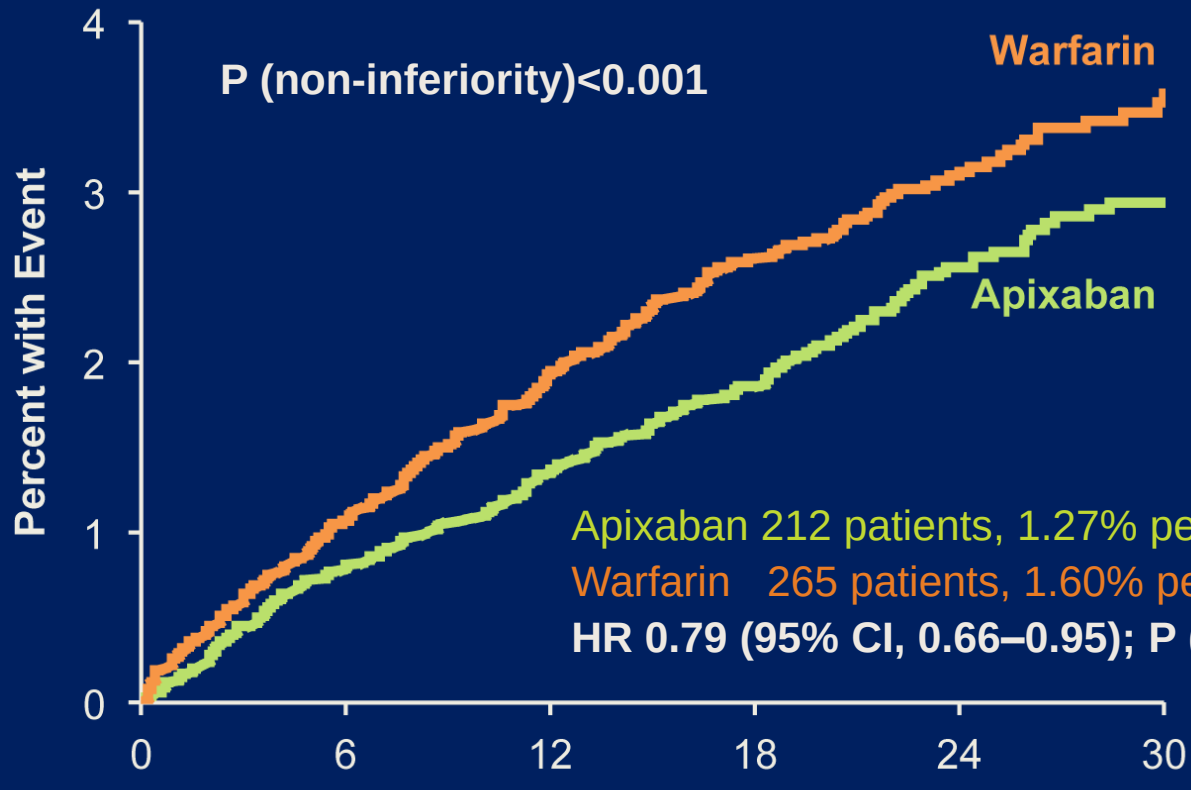
Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Primary Outcome

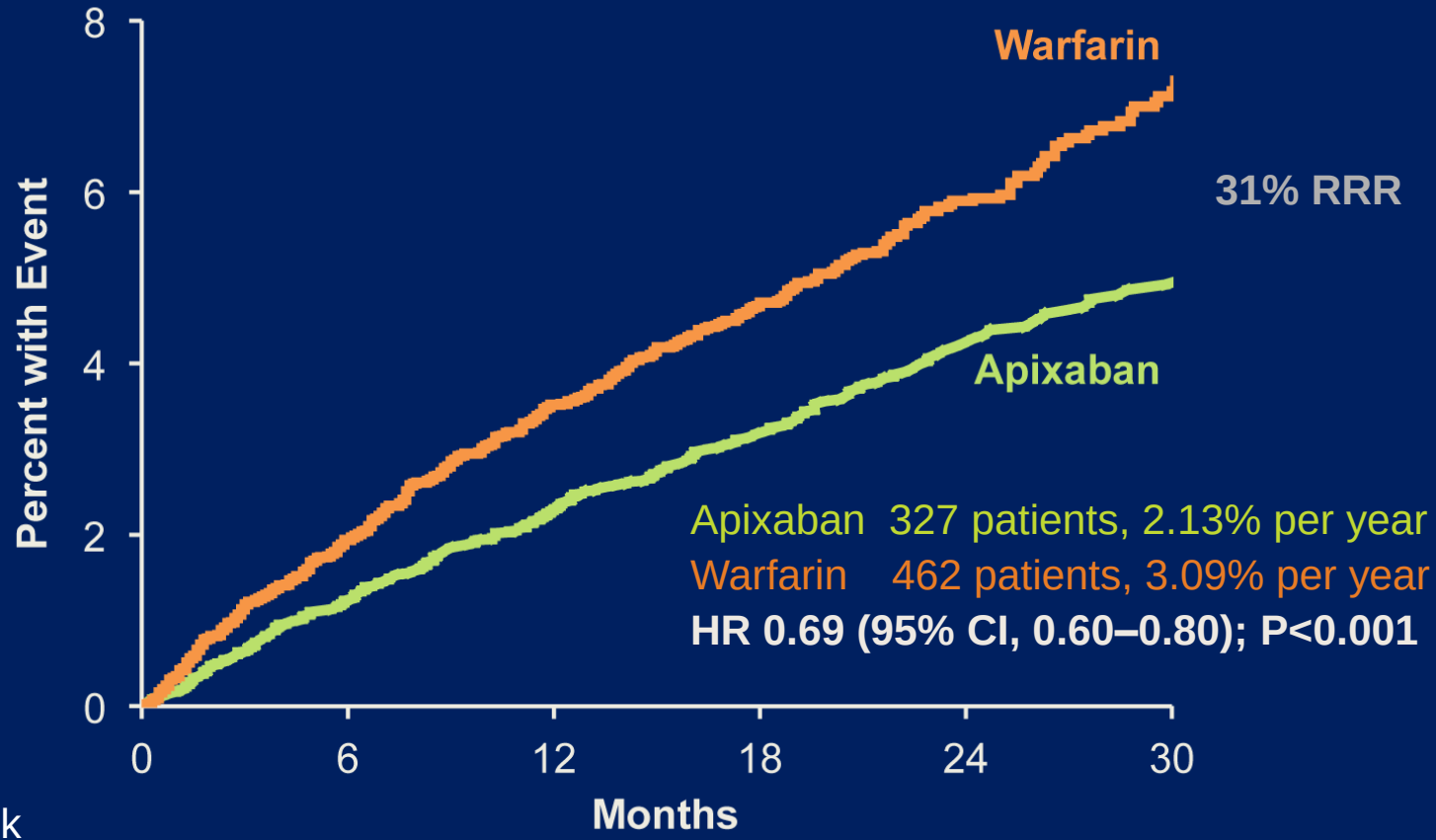
Stroke (ischemic or hemorrhagic) or systemic embolism



No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Major Bleeding

ISTH definition



No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

Compared with warfarin, apixaban (over 1.8 years) prevented

- 6 Strokes
  - 4 hemorrhagic
  - 2 ischemic/uncertain type
- 15 Major bleeds
- 8 Deaths

per 1000 patients treated.

Summary

Treatment with apixaban as compared to warfarin in patients with AF and at least one additional risk factor for stroke:

- Reduces stroke and systemic embolism by 21% ($p=0.01$)
- Reduces major bleeding by 31% ($p<0.001$)
- Reduces mortality by 11% ($p=0.047$)

ROCKET AF

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Atrial Fibrillation

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind /
Double Dummy
(n ~ 14,000)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

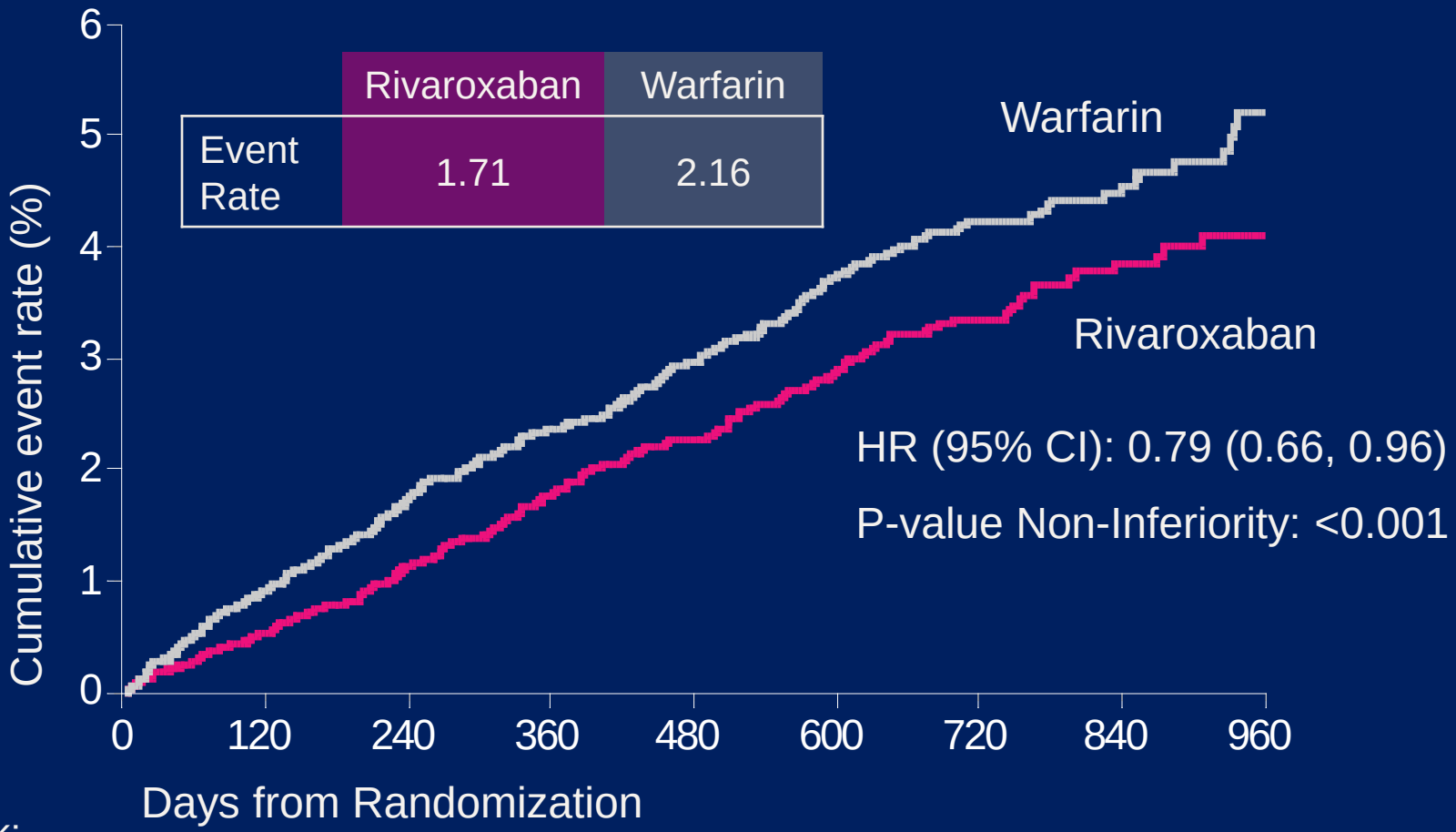
Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Primary Efficacy Outcome

Stroke and non-CNS Embolism



No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion (> 2 units)	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

Summary

- **Efficacy**:
  - Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism.
  - Rivaroxaban was superior to warfarin while patients were taking study drug.
  - By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.
- **Safety**:
  - Similar rates of bleeding and adverse events.
  - Less ICH and fatal bleeding with rivaroxaban.
- **Conclusion**:
  - Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF.

BACKGROUND: Thrombin In ACS

- There is excess thrombin generation that persists for 6 months following an index ACS event.[1]
- Thrombin is the most potent stimulant of platelet aggregation.[2]
- Reduction of thrombin generation by warfarin reduces recurrent MI by 44% in a meta-analysis of 10 ACS trials.[3]
- Rivaroxaban is a direct factor Xa inhibitor which blocks initiation of the final common pathway leading to thrombin generation.
- Based upon safety and efficacy in Phase II, 5.0 mg bid and 2.5 mg bid doses of Rivaroxaban were chosen for Phase III evaluation in ATLAS TIMI 51.[4]

1. Merlini PA et al. *Circulation.* 1994;90:61-68. 2. Coughlin S. Thrombin signaling and protease-activated receptors. Nature 2000;407(6801):258-64. 3. Rothberg MB et al *Ann Intern Med*. 2005 Aug 16;143(4):241-50. 4. *Lancet. 2009;374(9683):29-38.*

ATLAS ACS 2 TIMI 51

Recent ACS: STEMI, NSTEMI, UA

No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine

Stabilized 1-7 Days Post-Index Event

Stratified by Thienopyridine use at MD Discretion

+ ASA 75 to 100 mg/day

Placebo
N=5,176
ASA + Thieno, n=4,821
ASA, n=355

RIVAROXABAN
2.5 mg BID
n=5,174
ASA + Thieno, n=4,825
ASA, n=349

RIVAROXABAN
5.0 mg BID
N=5,176
ASA + Thieno, n=4,827
ASA, n=349

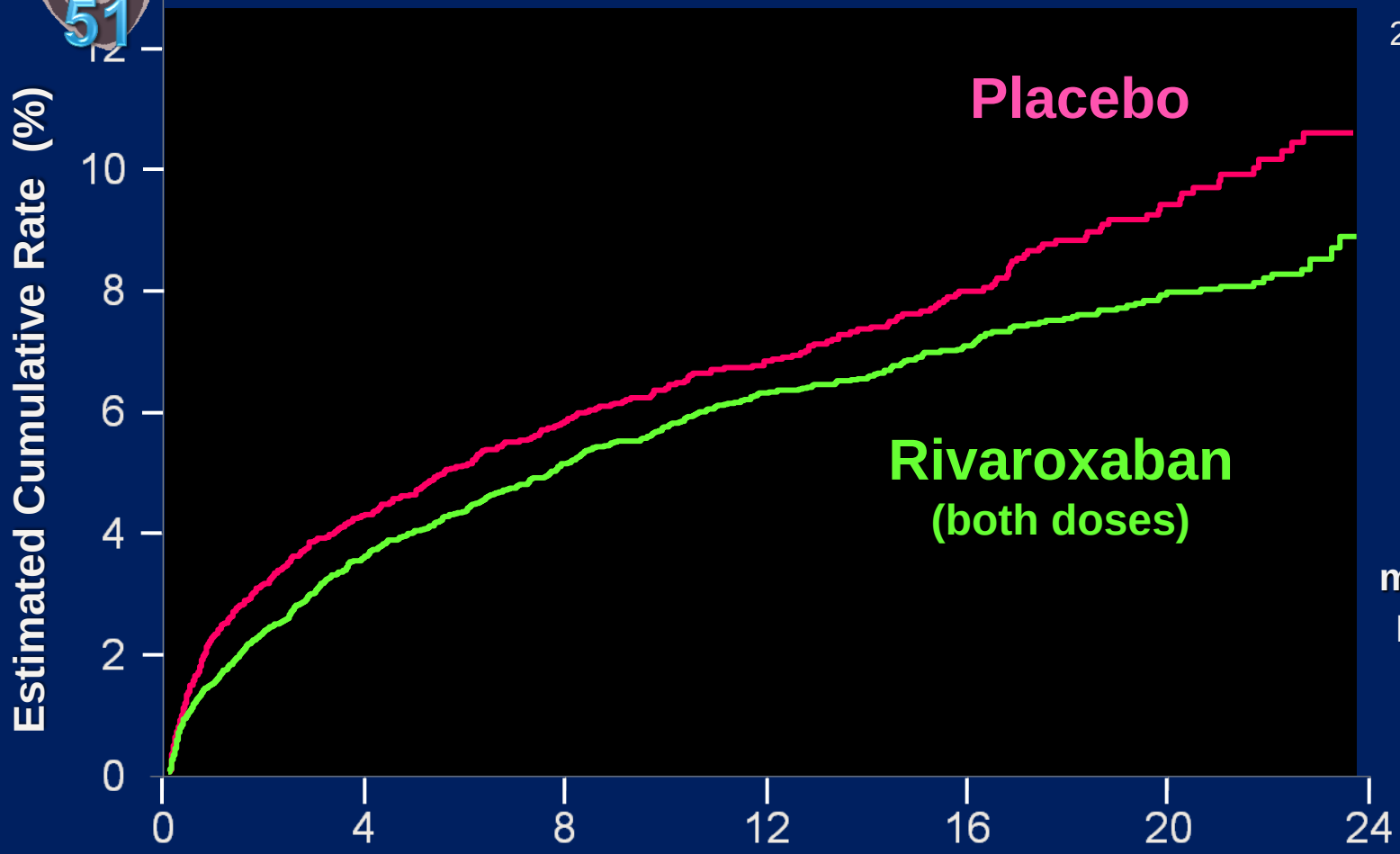
PRIMARY ENDPOINT:
EFFICACY: CV Death, MI, Stroke* (Ischemic + Hemg.)
SAFETY: TIMI major bleeding not associated with CABG
Event driven trial of 1,002 events in 15,342 patients**

* Stroke includes ischemic stroke, hemorrhagic stroke, and uncertain stroke
** 184 subjects were excluded from the efficacy analyses prior to unblinding

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke* (Ischemic + Hemg.)



2 Yr KM Estimate

10.7%

8.9%

HR 0.84
(0.74-0.96)
ARR 1.7%

mITT p = 0.008
ITT p = 0.002

NNT = 59

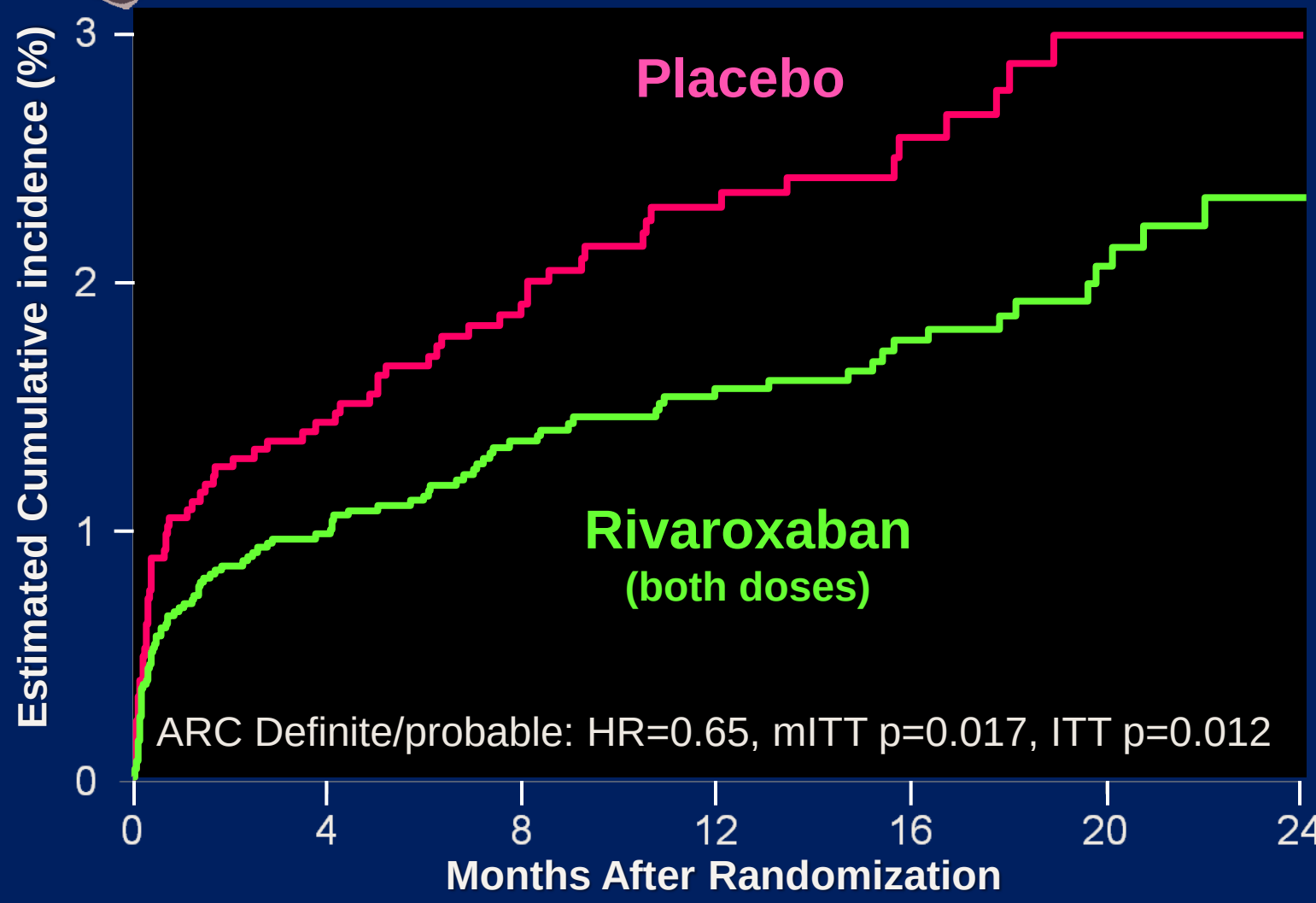
No. at Risk							
Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; ARR=Absolute Relative Reduction; NNT=Number needed to treat; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.

ATLAS ACS 2 TIMI 51

STENT THROMBOSIS*

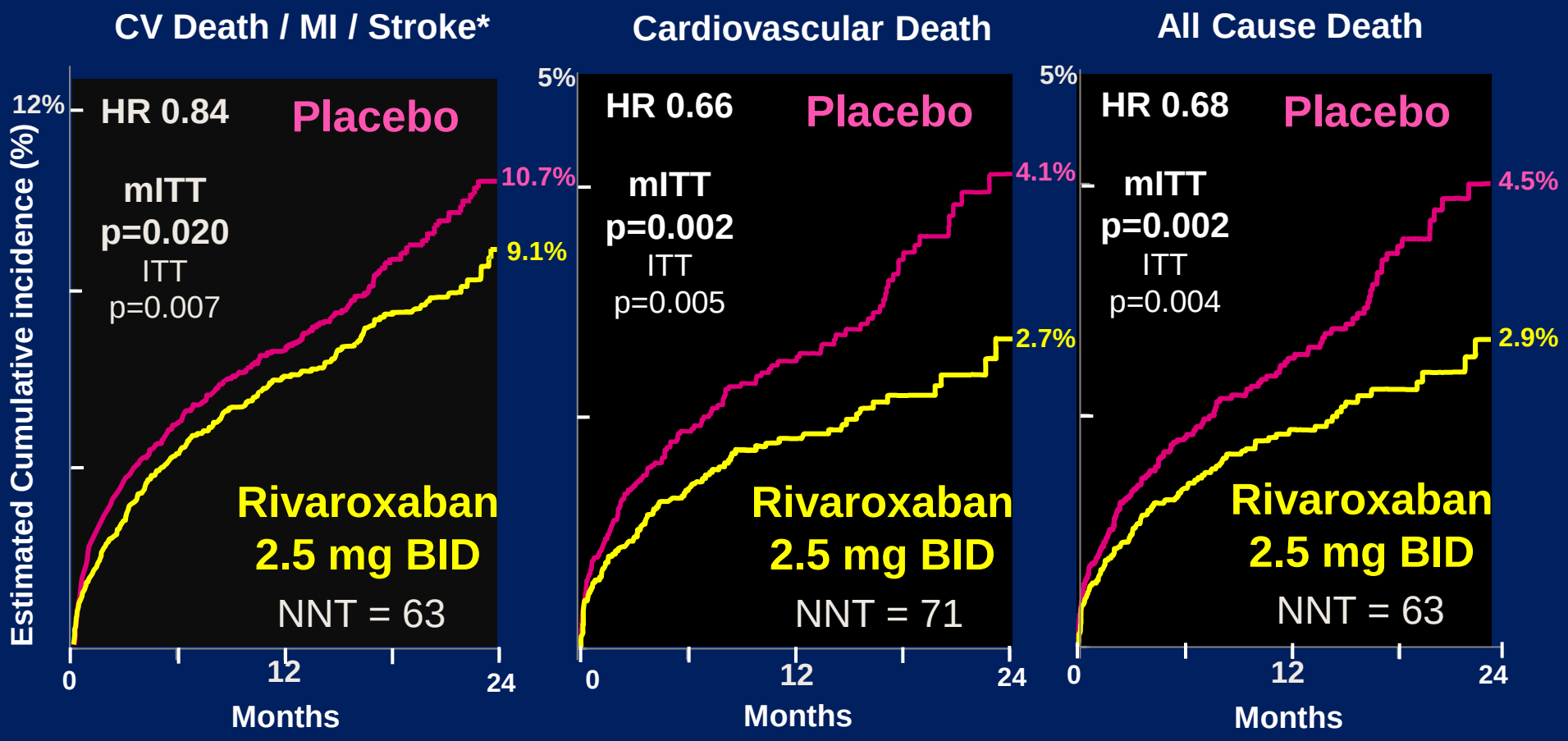
ARC Definite, Probable, Possible



* End point events are as adjudicated by the CEC across thienopyridine use strata

Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.

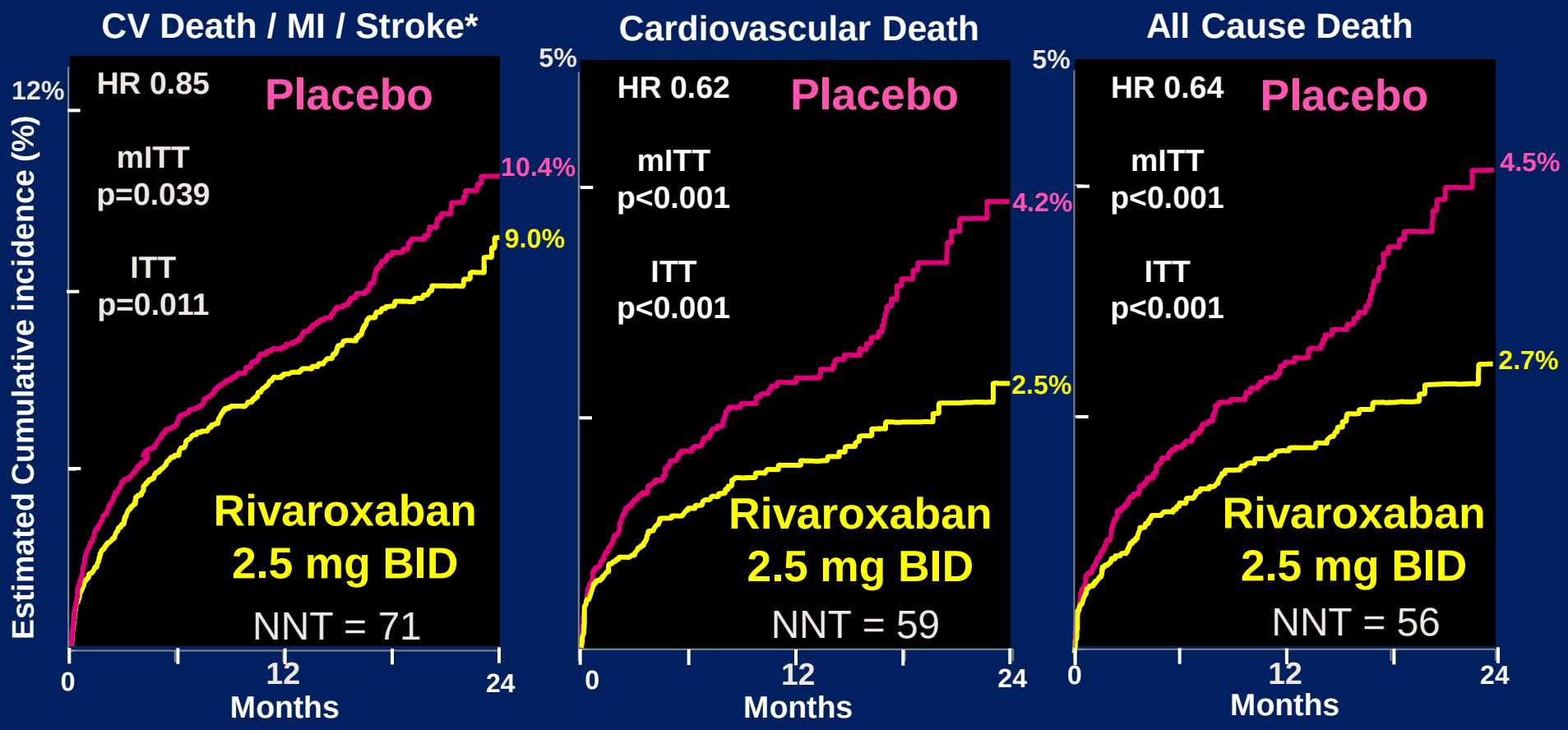
PRIMARY EFFICACY ENDPOINT*: 2.5 mg PO BID



* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINTS: 2.5 mg PO BID In Patients Treated with ASA + Thienopyridine



*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

ATLAS ACS 2 TIMI 51

SAFETY ENDPOINTS

Treatment-Emergent Non CABG TIMI Major Bleeding*

Analysis	Placebo	2.5 mg Rivaroxaban	5.0 mg Rivaroxaban
2 Yr KM Estimate	0.6%	1.8% HR 3.46	2.4% HR 4.47

p<0.001

p<0.001

Post-Treatment Ischemic Events#

1-10 Days After Last Dose	1.8%	1.4% p=NS	2.2% p=NS

Liver Function Test (ALT > 3xULN)

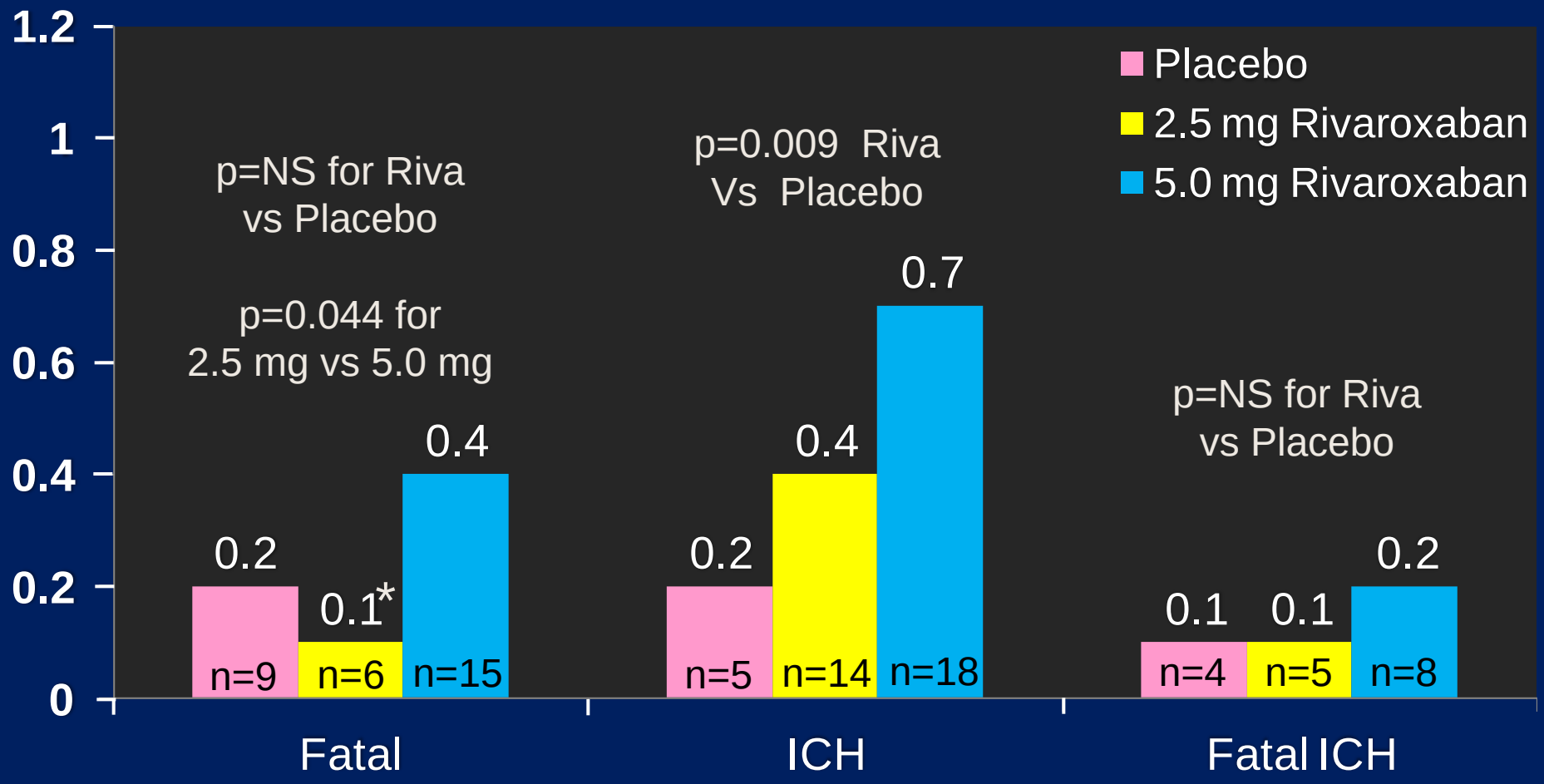
Treatment-Emergent	1.6%	1.3% p=NS	1.4% p=NS

There was no excess of either combined ALT > 3x ULN and Total Bilirubin > 2x ULN cases among patients treated with Rivaroxaban, or SAEs.

*: First occurrence of Non-CABG TIMI major bleeding events occurred between first dose to 2 days post last dose as adjudicated by the CEC across thienopyridine use strata; Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine are provided; Stratified log-rank p-values are provided; #: Raw percentage for CV death/MI/stroke (ischemic, hemorrhagic, uncertain) ; ##: Raw percentage of subjects with abnormal value measured between first dose to 2 days post last dose among subjects with normal baseline measurement.

ATLAS ACS 2 TIMI 51

TREATMENT-EMERGENT FATAL BLEEDS AND ICH



*Among patients treated with aspirin + thienopyridine, there was an increase in fatal bleeding among patients treated with 5.0 mg of Rivaroxaban (15/5110) vs 2.5 mg of Rivaroxaban (5/5115) (p=0.02)

ATLAS ACS 2 TIMI 51

SUMMARY- SAFETY

- There was a dose dependent increase in bleeding associated with rivaroxaban (2.5 mg ↓ 5.0 mg).

- Although ICH was increased with rivaroxaban, there was no excess risk of fatal ICH or fatal bleeding associated with rivaroxaban compared to placebo.

- No evidence of drug induced liver injury or rebound (post-treatment) ischemic events

SUMMARY-EFFICACY

- The primary efficacy endpoint of CV death, MI and stroke was reduced when added to standard therapy for both rivaroxaban doses combined, and for the 2.5 and 5.0 mg BID doses separately

- CV and all cause death were reduced for both rivaroxaban doses combined, and for the 2.5 mg BID dose in both mITT and ITT analyses

ATLAS ACS 2 TIMI 51

SUMMARY-EFFICACY (cont.)

- When 2.5 mg PO BID of rivaroxaban was added to ASA + thienopyridine, cardiovascular death was reduced by 38% and all cause death by 36%

- One death prevented if 56 patients treated for two years with 2.5 mg BID of Rivaroxaban

Thank you