



Anti-Xa Therapy to Lower

**Cardiovascular Events in Addition to Standard Therapy in
Subjects with Acute Coronary Syndrome - Thrombolysis in
Myocardial Infarction 51 Trial (ATLAS ACS 2 - TIMI 51):**

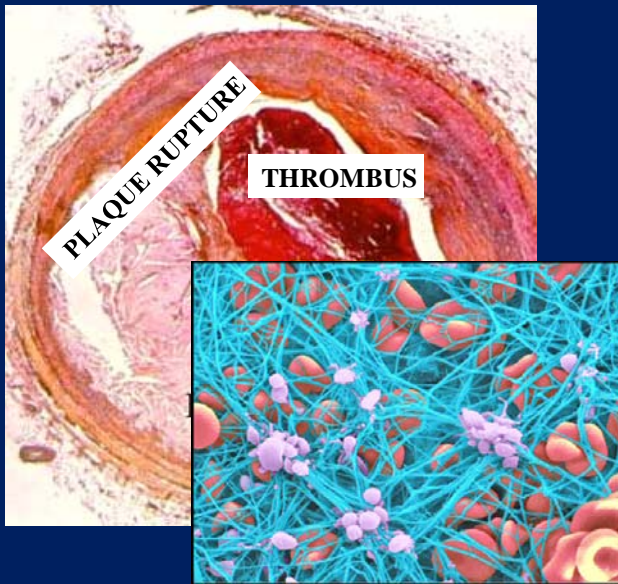
**A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of
Rivaroxaban in Subjects with Acute Coronary Syndrome**

C. Michael Gibson, MS, MD

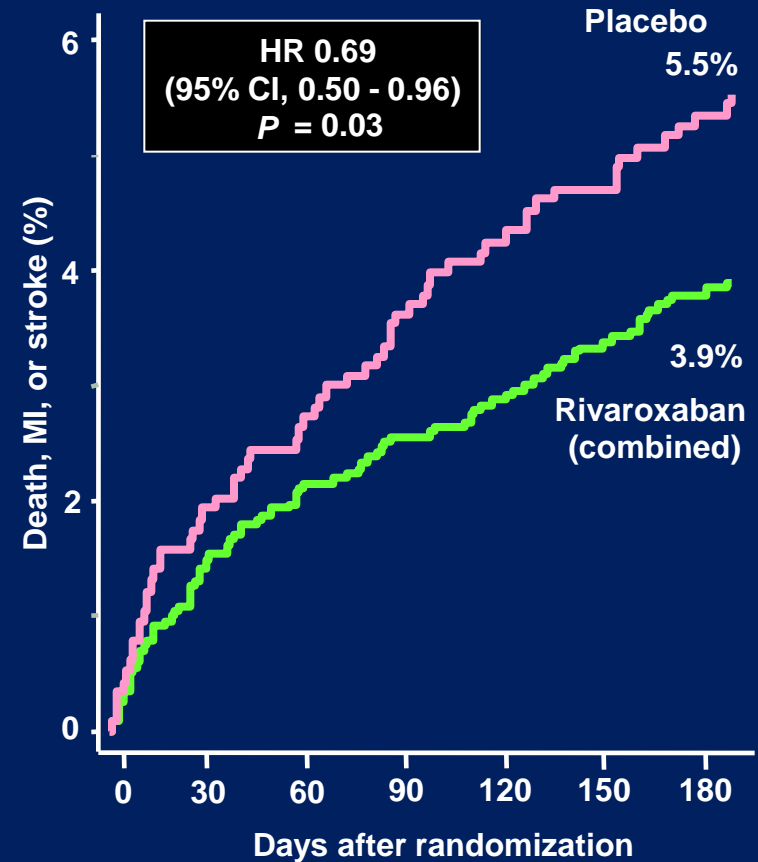
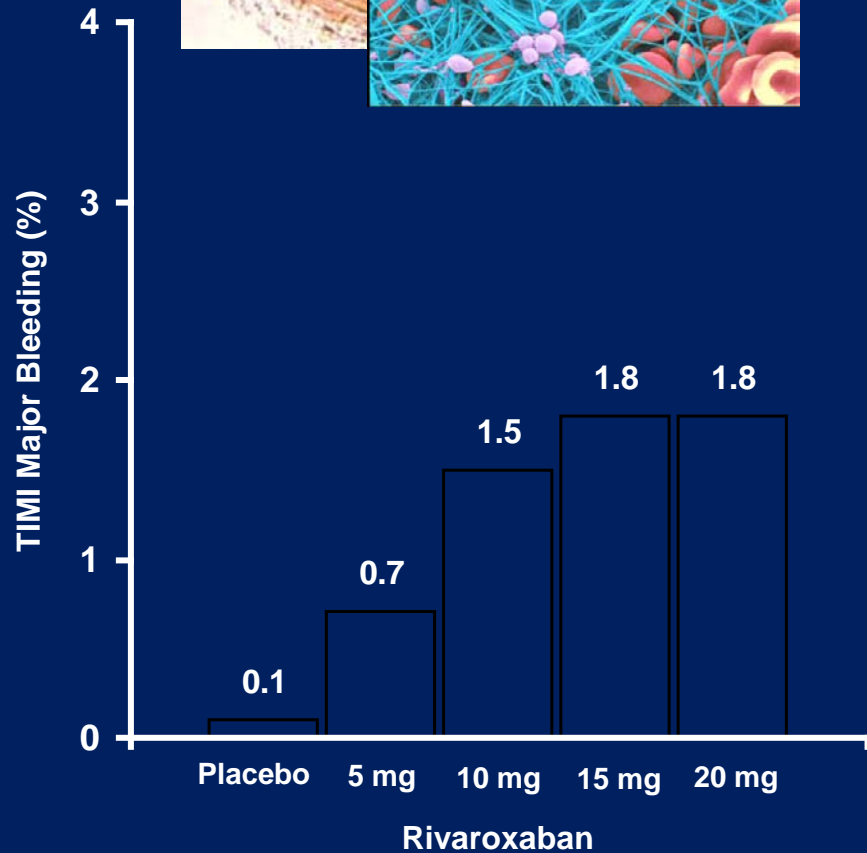
on behalf of the ATLAS ACS 2 TIMI 51 Investigators

Funded by a research grant from Johnson and Johnson and Bayer to Brigham & Women's Hospital. Dr. Gibson has received honoraria & consulting fees from J&J and Bayer.

BACKGROUND



ATLAS ACS-TIMI 46 N = 3,491





TRIAL ORGANIZATION

Trial Leadership: TIMI Study Group

Chairman: Eugene Braunwald, Principal Investigator: C. Michael Gibson

Investigator: Jessica Mega, Statisticians: Sabina Murphy, Charles Contant

Executive Committee

Jean-Pierre Bassand, Deepak Bhatt, Christoph Bode, Keith Fox, Marc Cohen, Shinya Goto, David Schneider, Freek Verheugt

Sponsors: Johnson & Johnson and Bayer Health Care

J&J: Paul Burton, Peter DiBattiste, Alexei N. Plotnikov, Linda DeCaprio, Xiang Sun

Bayer: Nancy Cook Bruns, Scott Berkowitz, Frank Misselwitz

Data Safety Monitoring Board

Douglas Weaver (Chair) , Christian Hamm, Judith S. Hochman, Jeffrey Anderson, Hiroyuki Daida, Statistician: Allan Skene

Recent ACS: STEMI, NSTEMI, UA

Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH,
prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo

n=5,176

Rivaroxaban

2.5 mg BID

n=5,174

Rivaroxaban

5.0 mg BID

n=5,176

PRIMARY ENDPOINTS:

EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

SAFETY: TIMI major bleeding not associated with CABG

Event driven trial with 1,002 primary efficacy events

NATIONAL LEAD INVESTIGATORS



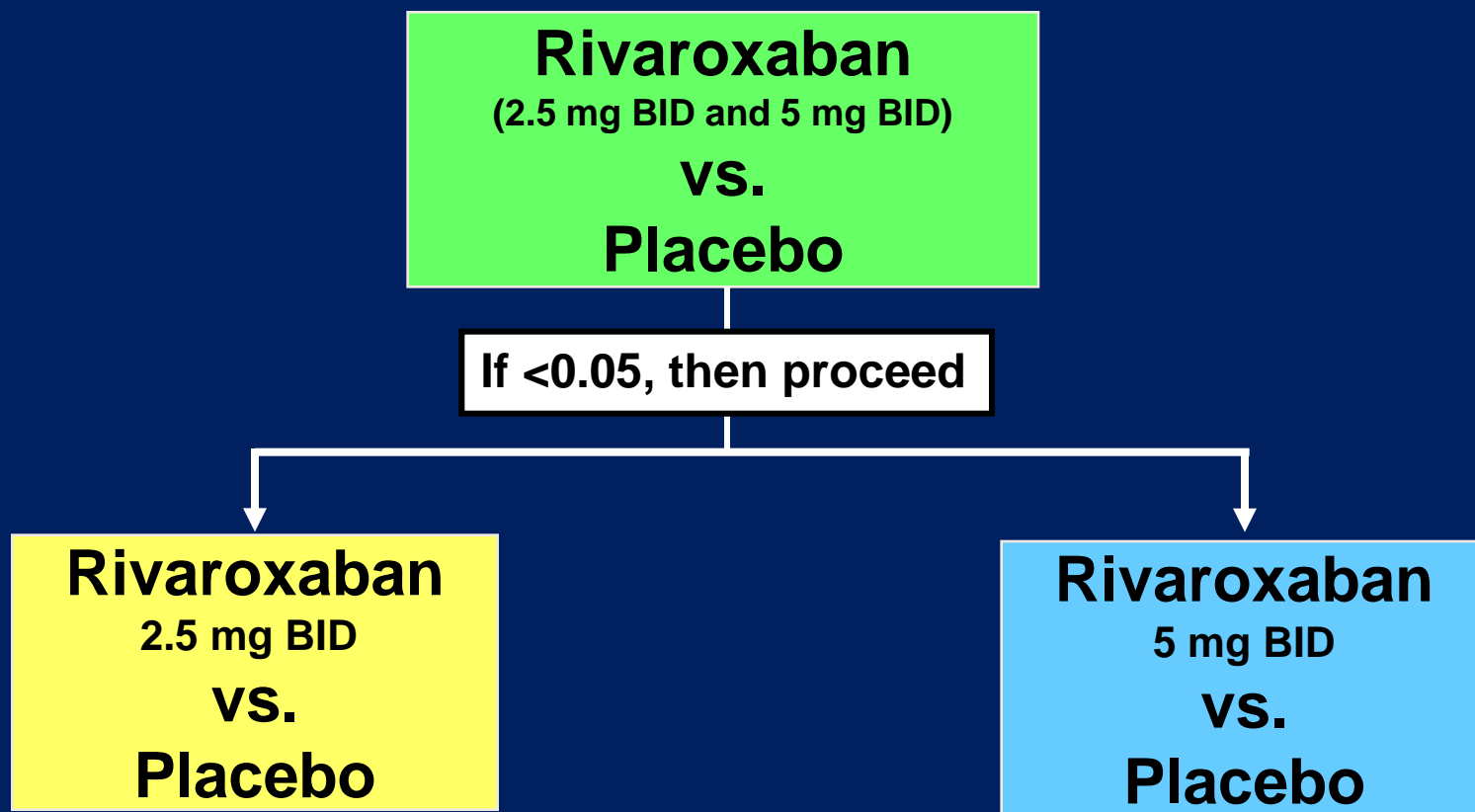
44 Countries 766 Sites

BASELINE CHARACTERISTICS

	Placebo	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID
PRE HOSPITAL			
Age, mean (SD)	61.5 (\pm 9.4)	61.8 (\pm 9.2)	61.9 (\pm 9.0)
Sex, male (%)	75.0	74.9	74.2
Prior MI, (%)	27.3	26.3	27.1
Diabetes, (%)	31.8	32.3	31.8
HOSPITAL			
STEMI, (%)	50.9	50.3	49.9
NSTEMI, (%)	25.6	25.5	25.8
UA, (%)	23.6	24.2	24.3
Revasc at Index, (%)	60.7	60.4	60.4
ASA+Thienopyridine, (%)	93.1	93.3	93.3

STATISTICAL ANALYSIS

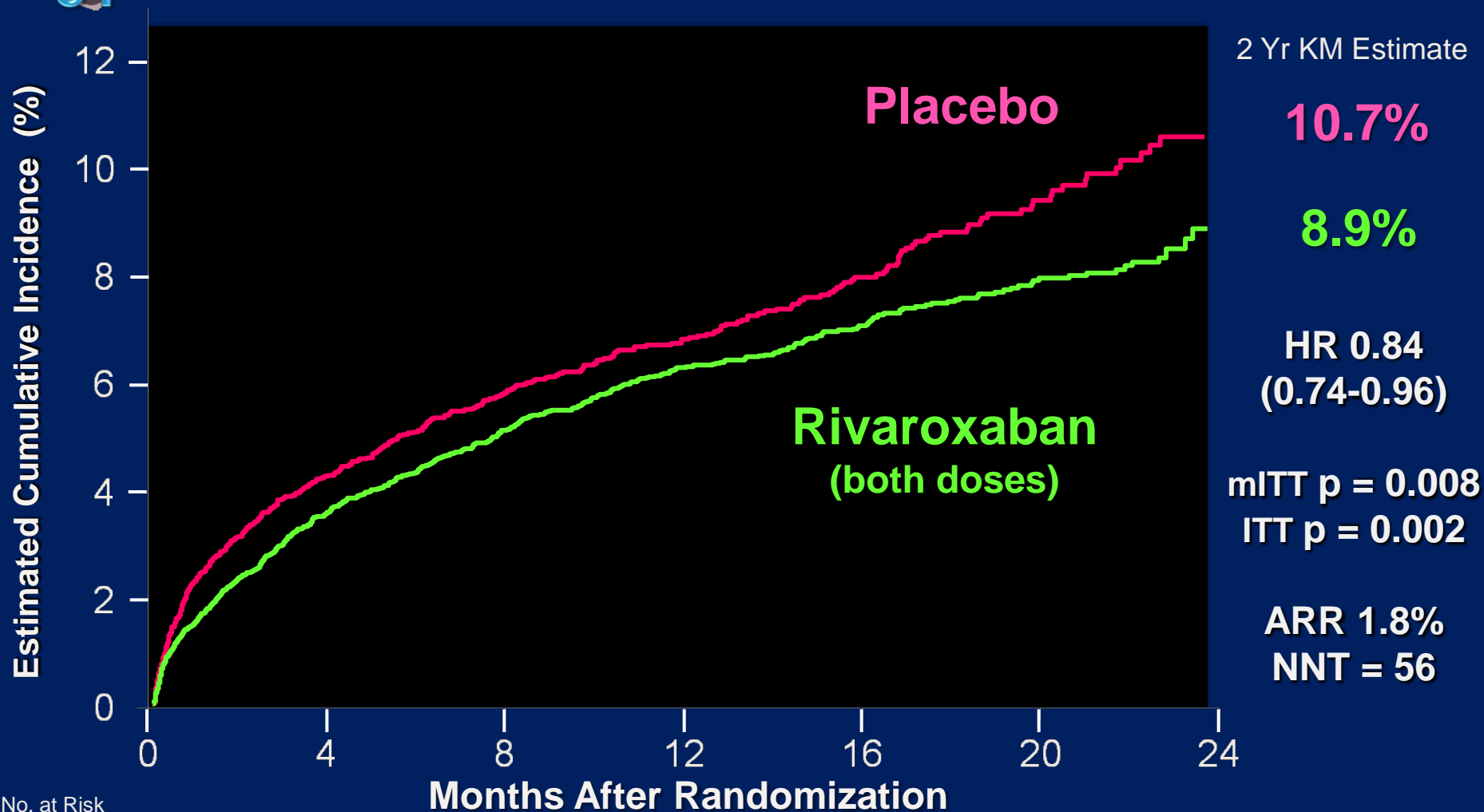
Pre-specified Primary Efficacy Analysis



- The primary method of analysis was a log rank test stratified by thienopyridine use in the mITT population with confirmation in an ITT analysis

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke



No. at Risk

Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

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.

STENT THROMBOSIS

ARC Definite / Probable / Possible

2 Yr KM Estimate

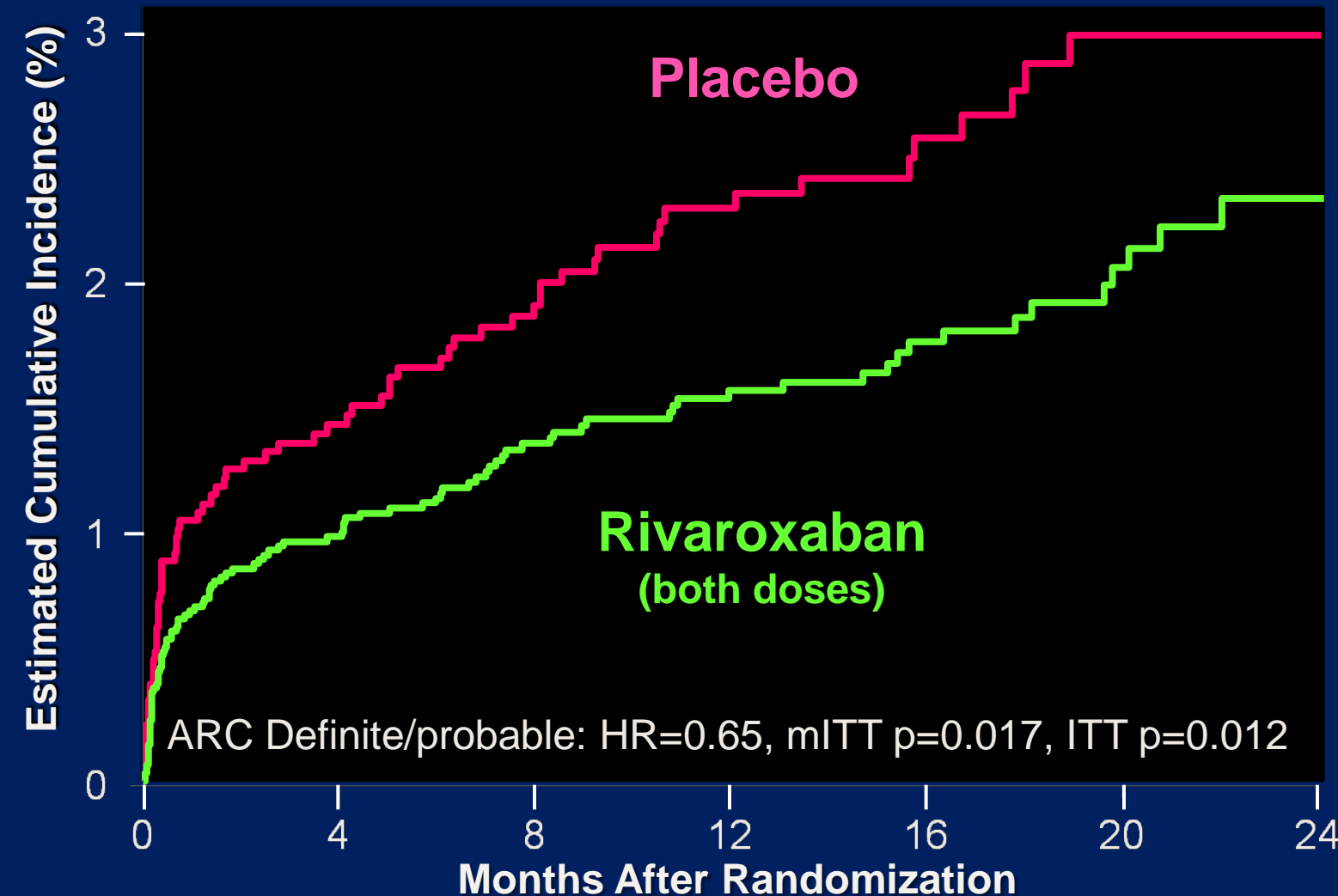
2.9%

2.3%

HR 0.69
(0.51- 0.93)

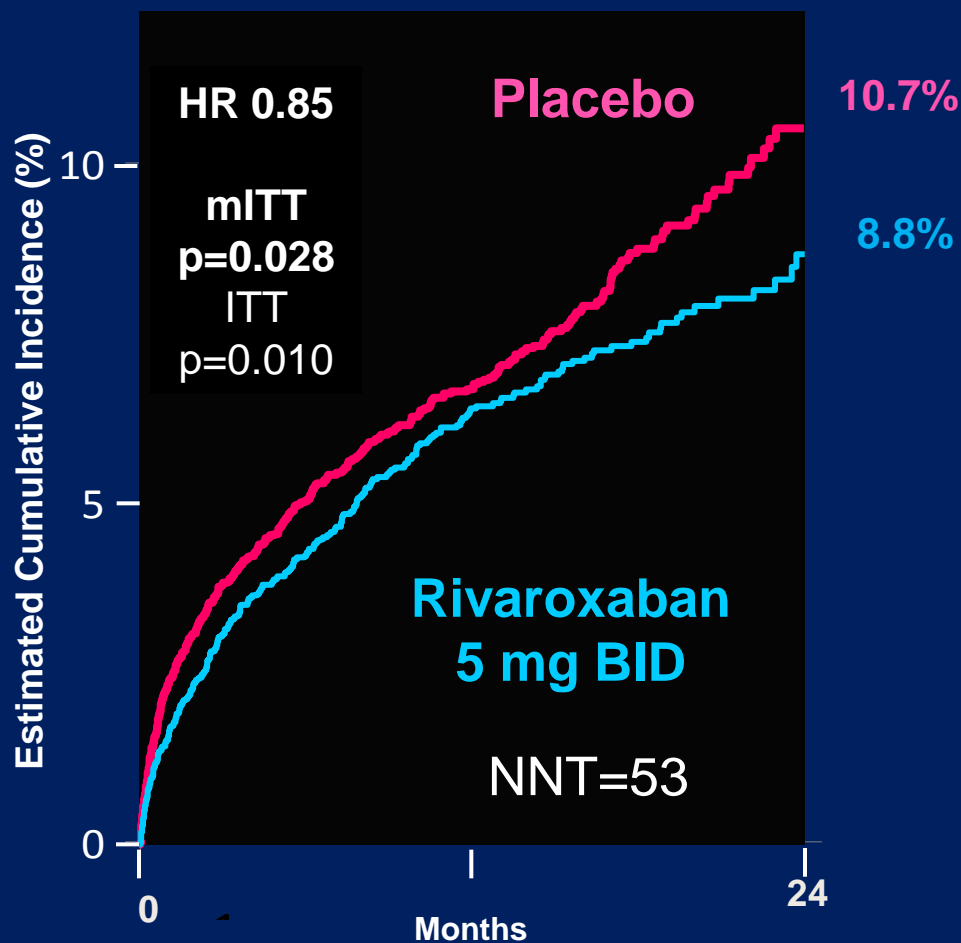
mITT p = 0.016

ITT p = 0.008

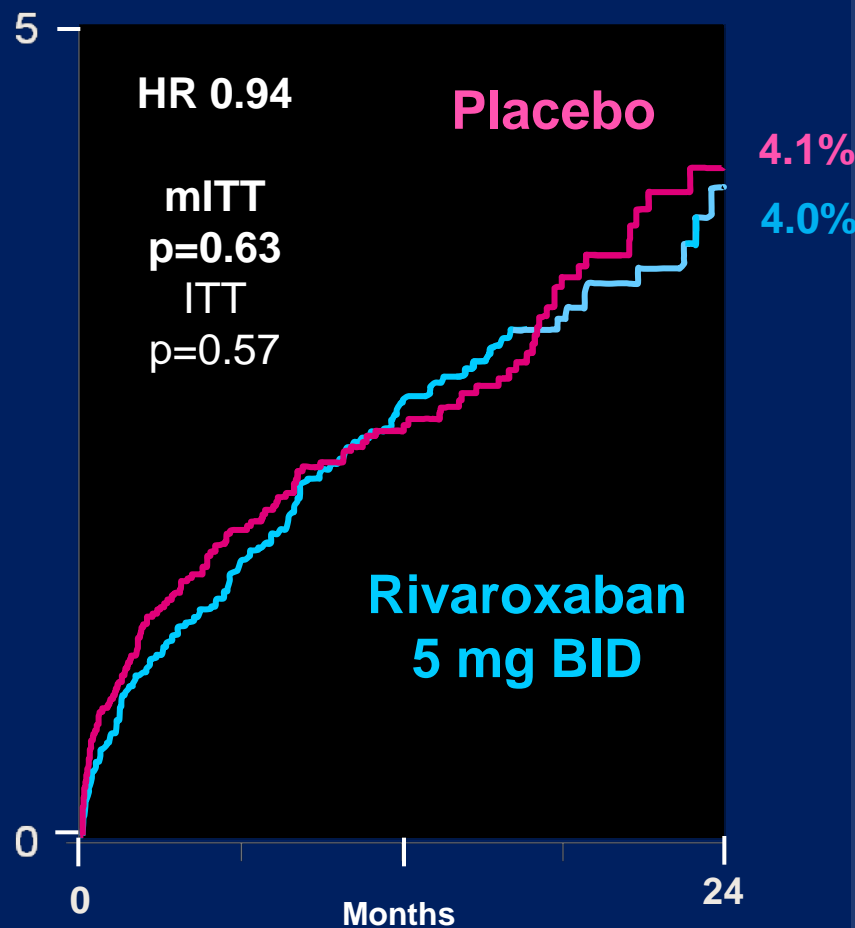


EFFICACY ENDPOINTS: Low Dose 5.0 mg BID

CV Death / MI / Stroke

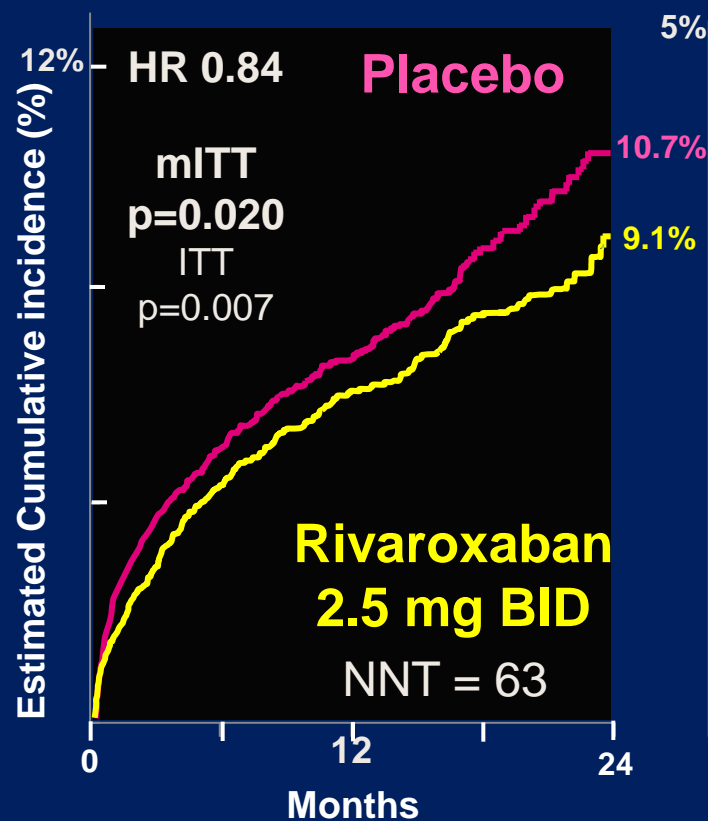


Cardiovascular Death

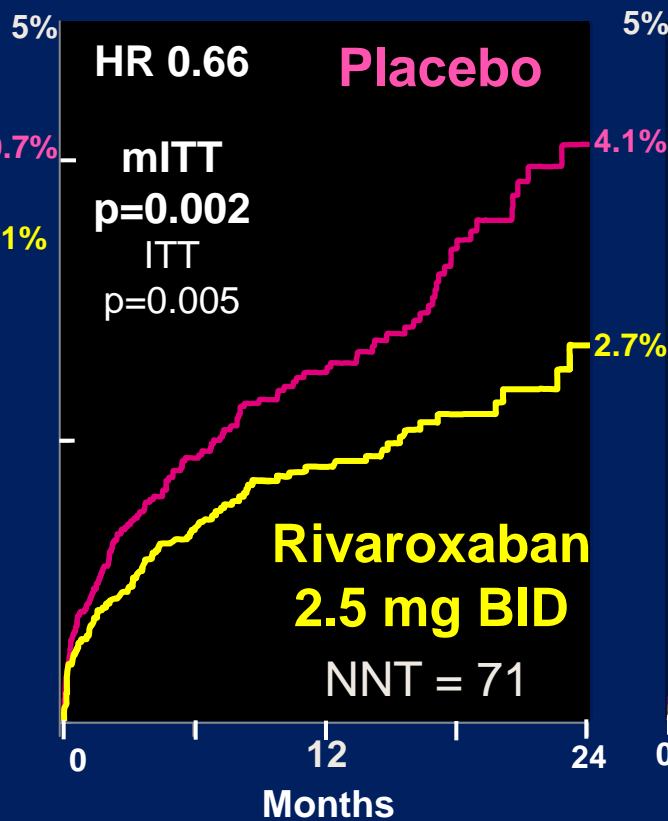


EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID

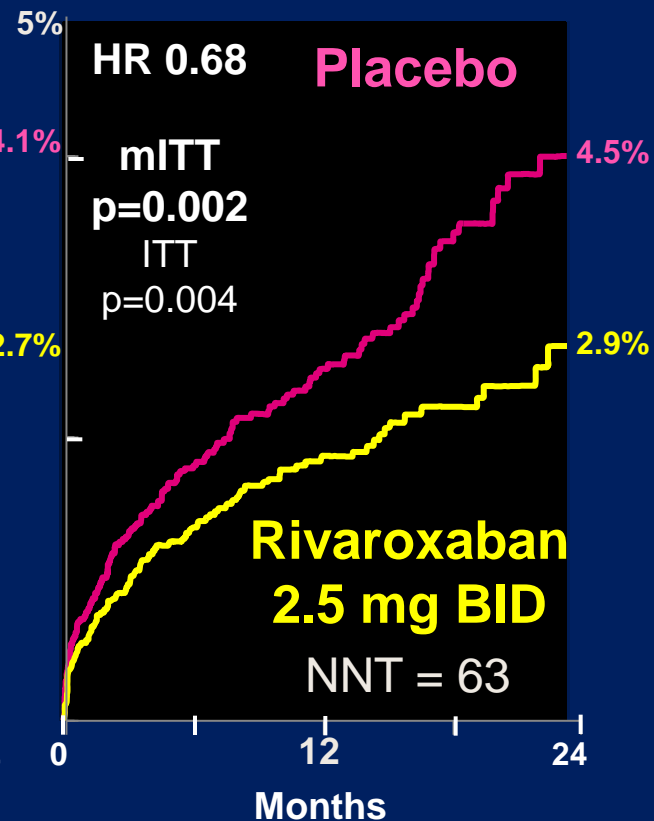
CV Death / MI / Stroke



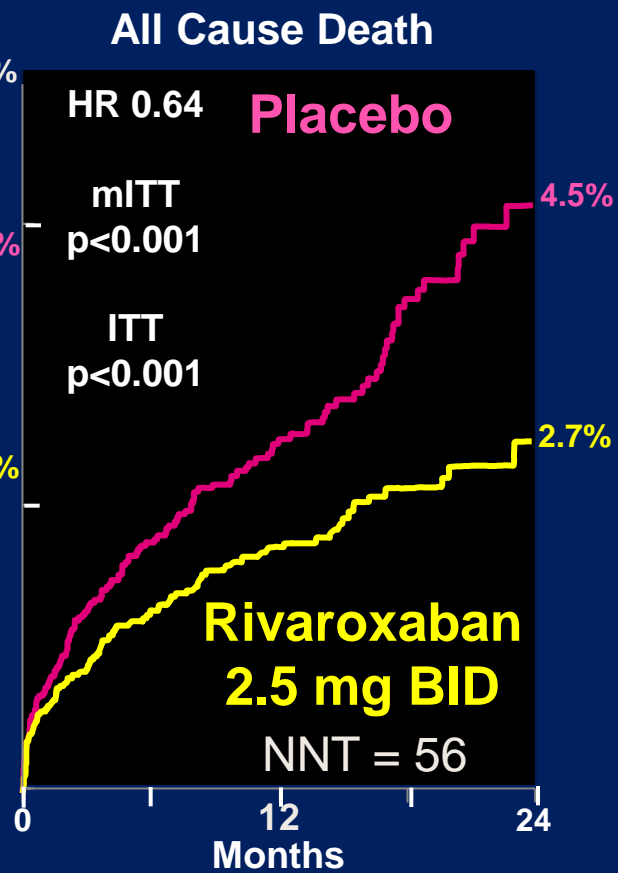
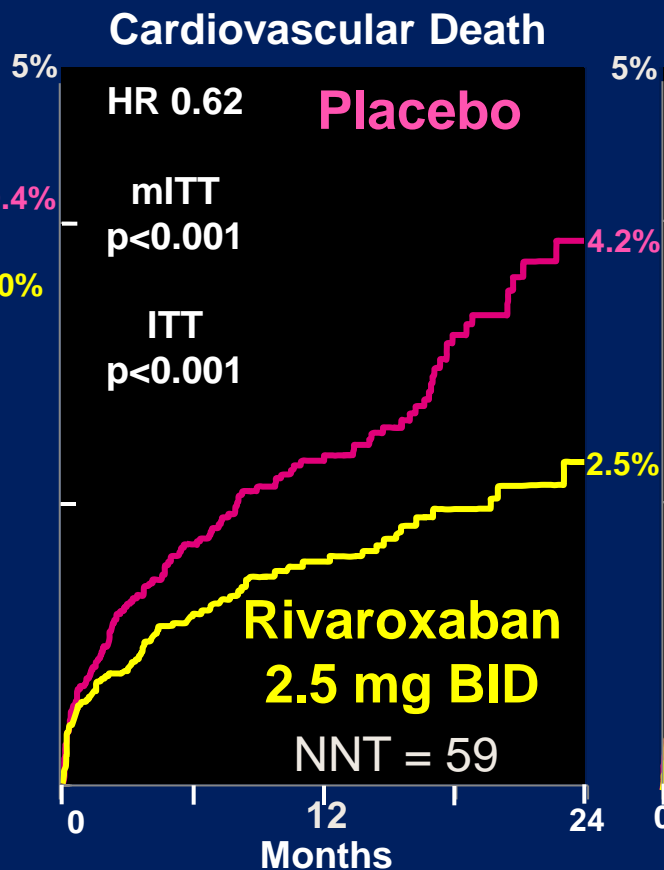
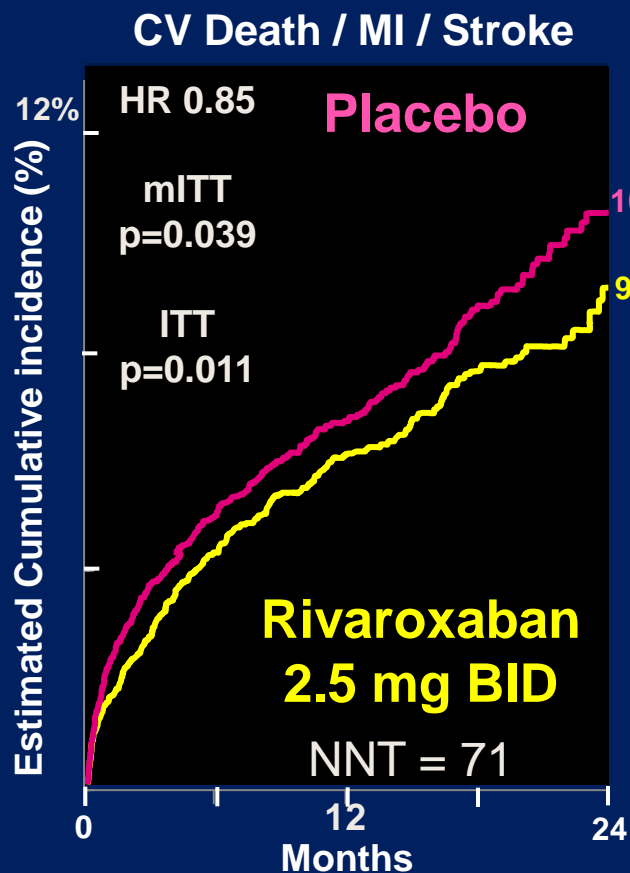
Cardiovascular Death



All Cause Death



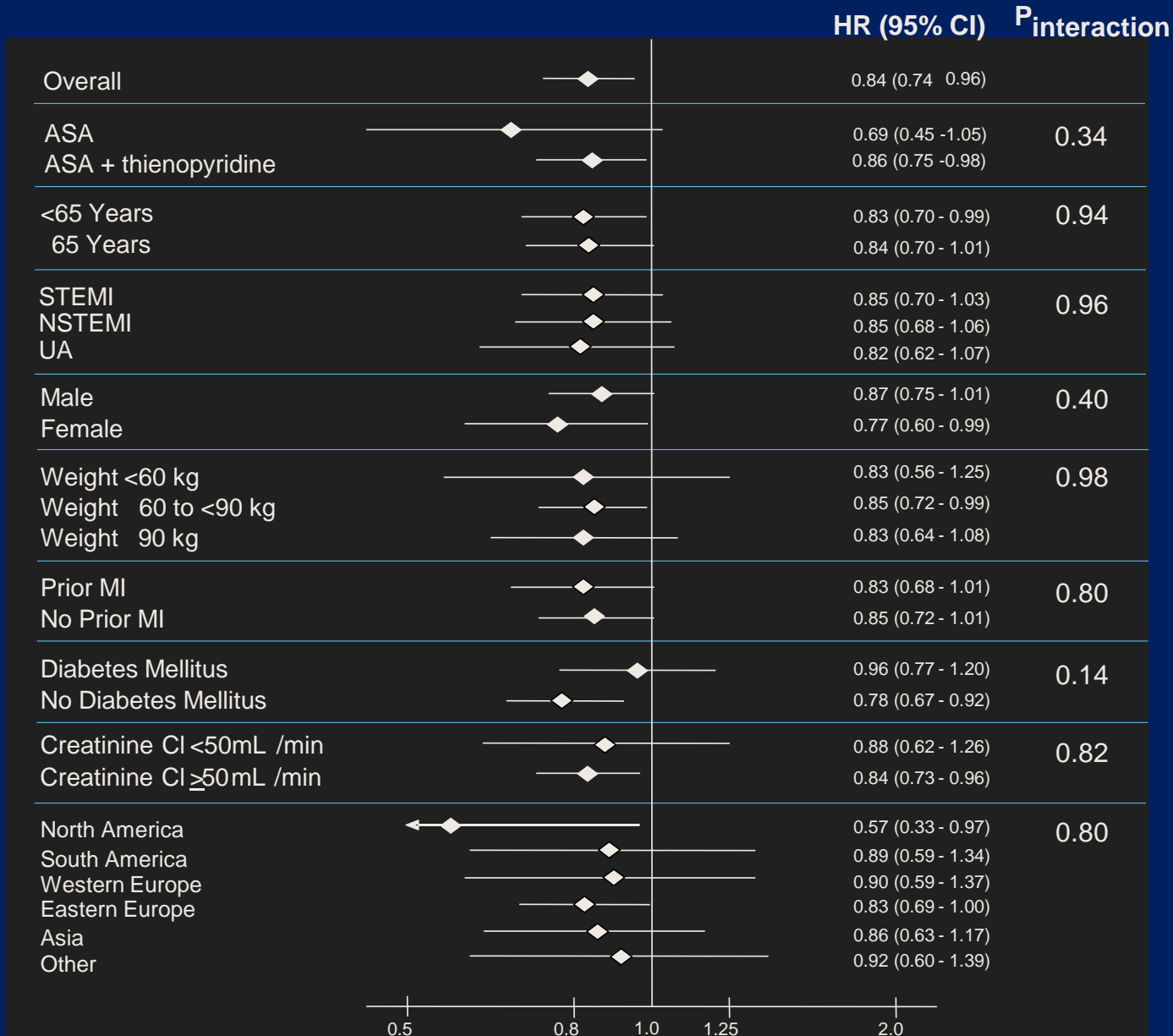
EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID Patients Treated with ASA + Thienopyridine





PRIMARY EFFICACY SUBGROUP RESULTS

All Rivaroxaban vs. Placebo



Rivaroxaban Better

Placebo Better

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
<div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> <p>p<0.001</p> </div> <p>p<0.001</p>			

Liver Function Test (ALT > 3xULN)

ALT > 3X ULN	1.6%	1.3% p=NS	1.4% p=NS
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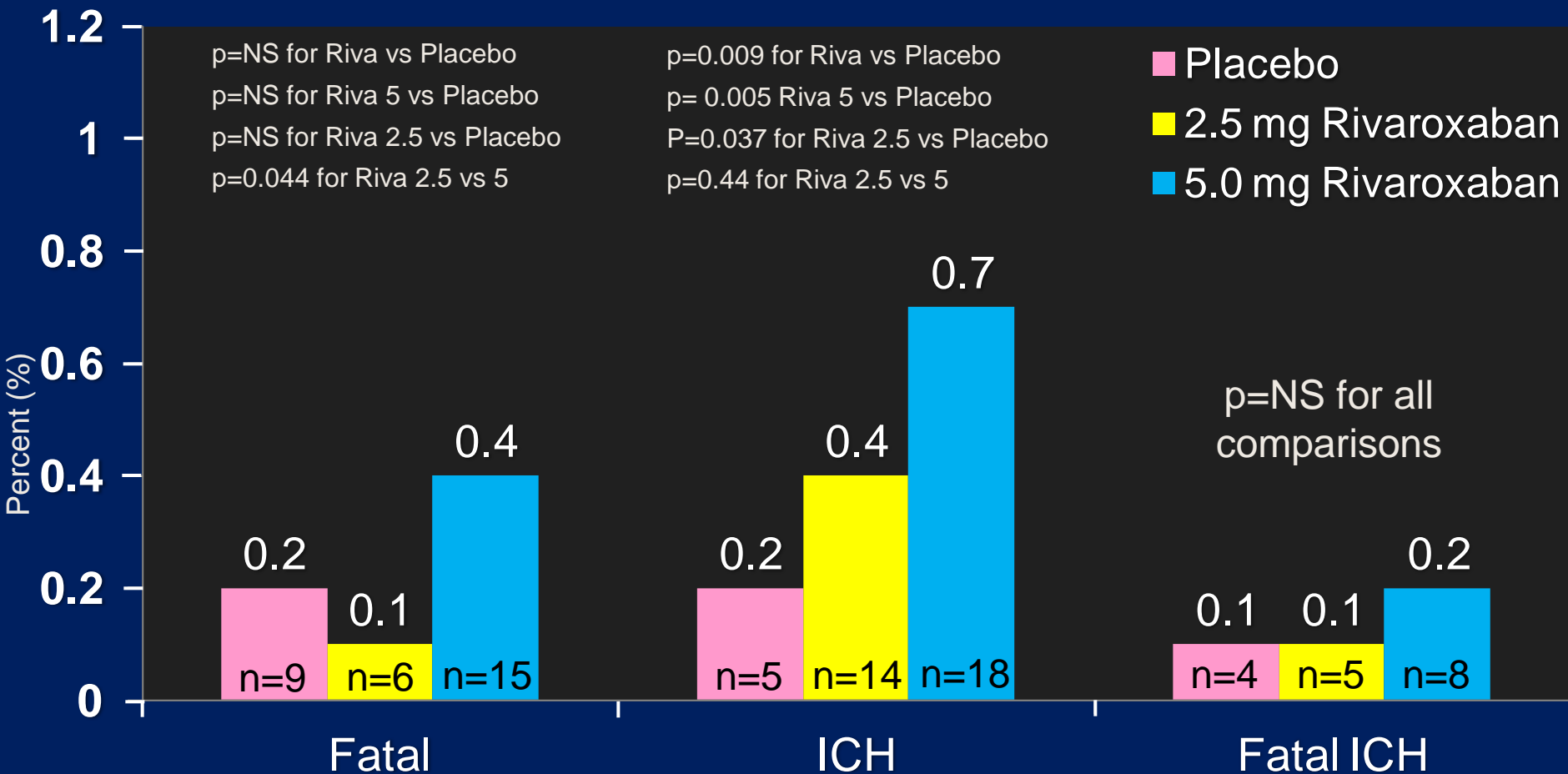
There was no excess of either combined ALT > 3x ULN and Total Bilirubin > 2x ULN cases among patients treated with Rivaroxaban, or SAEs.

Post-Treatment CVD / MI / Stroke##

1-10 Days After Last Dose	1.8%	1.4% p=NS	2.2% p=NS
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*: 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 of subjects with abnormal value measured between first dose to 2 days post last dose among subjects with normal baseline measurement; ##: Raw percentage.

TREATMENT-EMERGENT FATAL BLEEDS AND ICH



SUMMARY

- Rivaroxaban reduced the risk of cardiovascular death, myocardial infarction, or stroke in patients across the spectrum of ACS.
- Rates of major bleeding and ICH were higher with rivaroxaban; however, there was no excess risk of fatal ICH or fatal bleeding with rivaroxaban compared to placebo (particularly with 2.5 mg BID).
- One death would be prevented if 56 patients on antiplatelet therapies were treated for two years with rivaroxaban 2.5 mg BID.

CONCLUSION

- Very low dose anticoagulation with rivaroxaban (2.5 mg BID), in addition to antiplatelet therapies, represents an effective strategy to reduce cardiovascular events in patients with a recent ACS.

ORIGINAL ARTICLE

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., Alexei N. Plotnikov, M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D., and C. Michael Gibson, M.D.,
for the ATLAS ACS 2–TIMI 51 Investigators*

The full article is available online at www.nejm.org.



A New Era in Secondary Prevention after Acute Coronary Syndrome

Matthew T. Roe, M.D., and E. Magnus Ohman, M.B., F.R.C.P.I.