Rivaroxaban in Acute Coronary Syndromes

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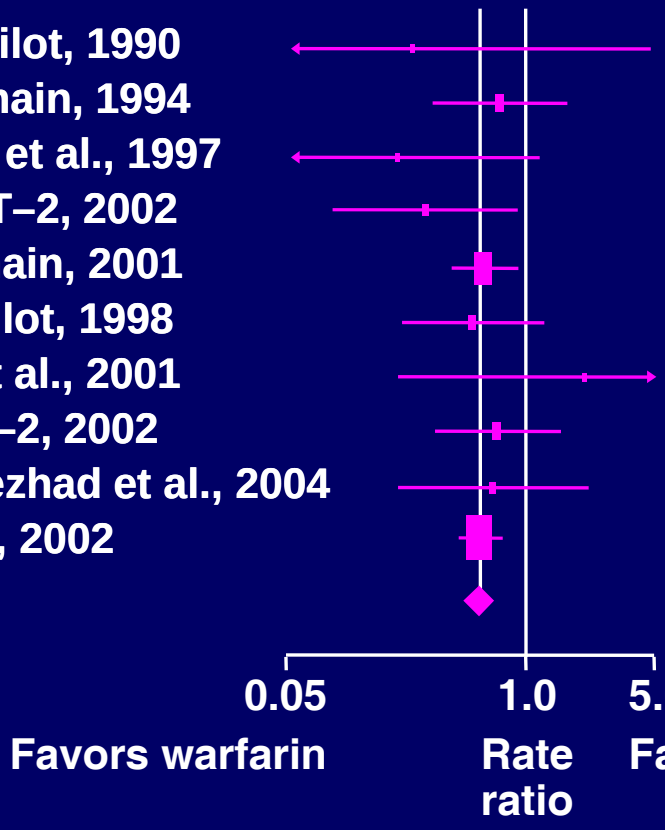
Meta-Analysis of Anticoagulation: Efficacy – Recurrent MI



Study, year	Rate ratio (95% CI)	Weight (%)	Events/ patient-years: Warfarin	Events/ patient-years: ASA
ATACS pilot, 1990	0.22 (0.01 – 4.66)	0.5	0/9	1/7
ATACS main, 1994	0.69 (0.29 – 1.65)	5.7	6/24	9/25
Williams et al., 1997	0.19 (0.03 – 1.16)	1.3	1/6	5/5
APRICOT–2, 2002	0.28 (0.09 – 0.92)	3.1	3/34	11/35
OASIS main, 2001	0.58 (0.38 – 0.98)	23.9	30/373	52/375
OASIS pilot, 1998	0.51 (0.20 – 1.26)	5.2	5/25	10/25
Huynh et al., 2001	2.07 (0.20 – 21.85)	0.8	2/38	1/39
ASPECT–2, 2002	0.69 (0.31 – 1.53)	6.8	10/298	14/289
Zibaeenezhad et al., 2004	0.87 (0.20 – 2.28)	2.9	4/70	6/70
WARIS II, 2002	0.56 (0.42 – 0.75)	49.8	69/4,927	117/4,669
Overall	0.56 (0.48 – 0.69)	100.0	130/5,834	228/5,539

Prevent 19 MIs per 1,000 pt-years

Rothberg MB, et al. *Ann Int Med.* 2005;143:241-250.

Search for Better Anticoagulants

INTRINSIC PATHWAY
(FXII, FXI, FIX, FVIII, PL, Ca^{2+})

EXTRINSIC PATHWAY
(TF, FVII)

Otamixaban (IV)
Rivaroxaban (PO)
Apixaban (PO)
Edoxaban (PO)

Factor X → Factor Xa

ATIII **Fondaparinux**

ATIII **LMWH**

ATIII **UFH**

Common Pathway

Prothombinase Complex
(PL, FVIII, FV, **FXa,** FII, Ca^{2+})

F1+2

Prothrombin (F II)

Thrombin (F IIa)

Fibrin Formation

Bivalirudin (IV)
Dabigatran (PO)

Factor XIIIa Activation

Platelet Aggregation

PHASE 2 STUDY DESIGN

ATLAS TIMI 46

Recent ACS Patients

Stabilized 1-7 Days Post-Index Event

Aspirin 75-100 mg

MD Decision to Treat with Clopidogrel

N = 3,491

NO

STRATUM 1
ASA Alone
N=761

PLACEBO N=253	RIVA QD N=254	RIVA BID N=254
5 mg (77)	5 mg (77)	2.5 mg (77)
10 mg (98)	10 mg (99)	5 mg (97)
20 mg (78)	20 mg (78)	10 mg (80)

YES

STRATUM 2
ASA + Clop.
N=2,730

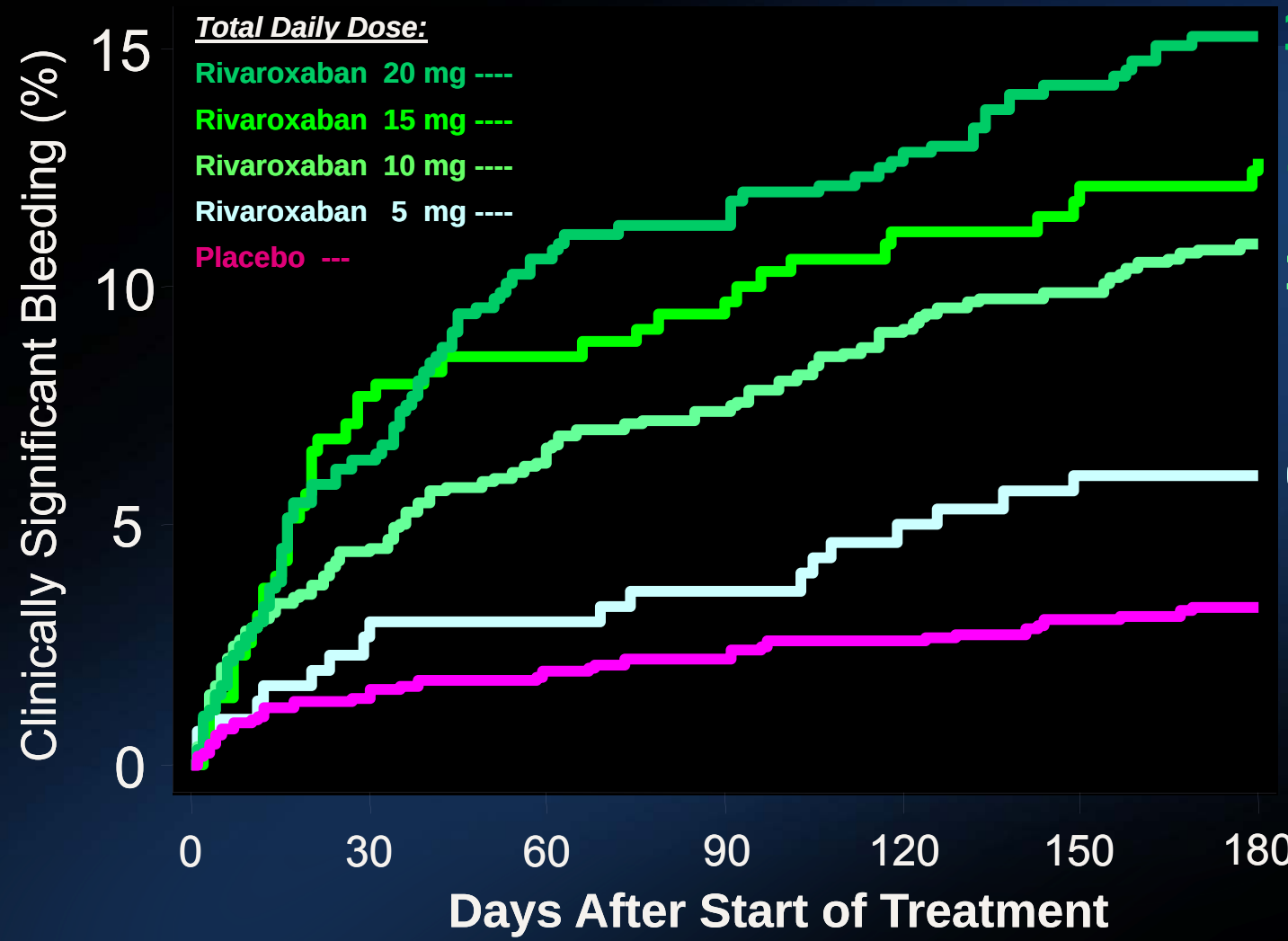
PLACEBO N=907	RIVA QD N=912	RIVA BID N=911
5 mg (74)	5 mg (78)	2.5 mg (76)
10 mg (428)	10 mg (430)	5 mg (430)
15 mg (178)	15 mg (178)	7.5 mg (178)
20 mg (227)	20 mg (226)	10 mg (227)

6 Month Bleeding / Efficacy

Mega JL et al. *Lancet* 2009;374:29-38.

PRIMARY SAFETY ENDPOINT: CLINICALLY SIGNIFICANT BLEEDING

(= TIMI Major, TIMI Minor, Bleed Req. Med. Attn.)



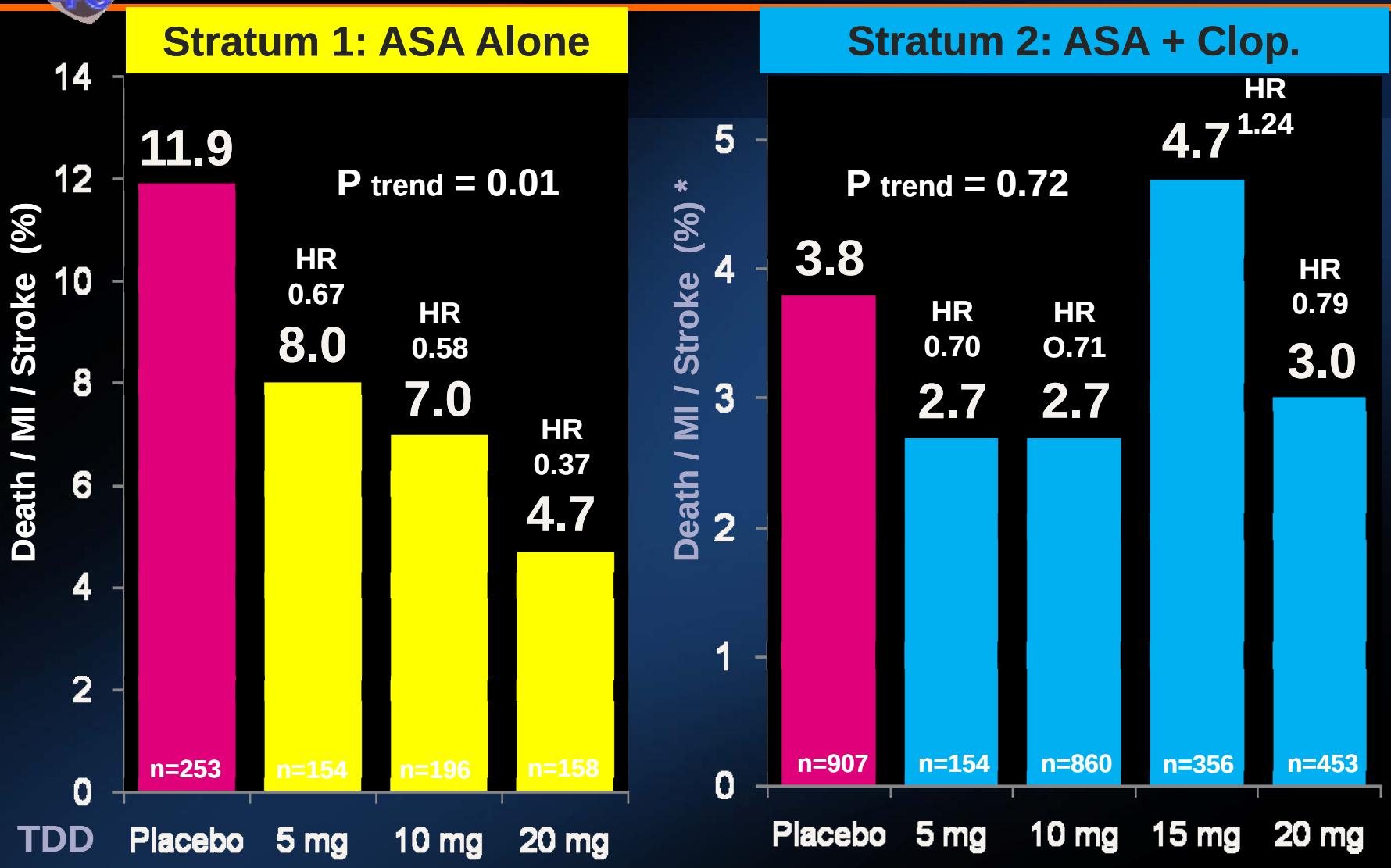
	HR
15.3%	5.1 (3.4-7.4)
12.7%	3.6 (2.3-5.6)
10.9%	3.4 (2.3-4.9)
6.1%	2.2 (1.25-3.91)
3.3%	

*p<0.01 for placebo Vs Riva 5mg. p<0.001 for Riva 10,15,20mg vs placebo

Mega JL et al. *Lancet* 2009;374:29-38.

SECONDARY EFFICACY ENDPOINT:

Incidence of Death / MI / Stroke



Mega JL et al. *Lancet* 2009;374:29-38.

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	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID
n=5,176	n=5,174	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

Mega JL et al. *NEJM* 2012;366:9-19

ATLAS ACS 2 TIMI 51

BASELINE CHARACTERISTICS

	Placebo	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID
PRE HOSPITAL			
Age, mean (SD)	61.5 (± 9.4)	61.8 (± 9.2)	61.9 (± 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, (%)	60.4	60.6	60.3
ASA+Thienopyridine, (%)	93.1	93.3	93.3

Mega JL et al. *NEJM* 2012;366:9-19

ATLAS, PLATO, and TRITON
Risk at Baseline

	ATLAS[3]	PLATO[2]	TRITON[1]	ACTION Registry STEMI*	ACTION Registry NSTEMI*
Age, mean	62	61	62	62	67
Sex, female	27	28	26	30	39
Prior MI, (%)	27	20	18	19	27
Diabetes, (%)	32	25	23	22	34
STEMI, (%)	50	38	26	N/A	N/A
PCI, (%)	60	60	99	77	53

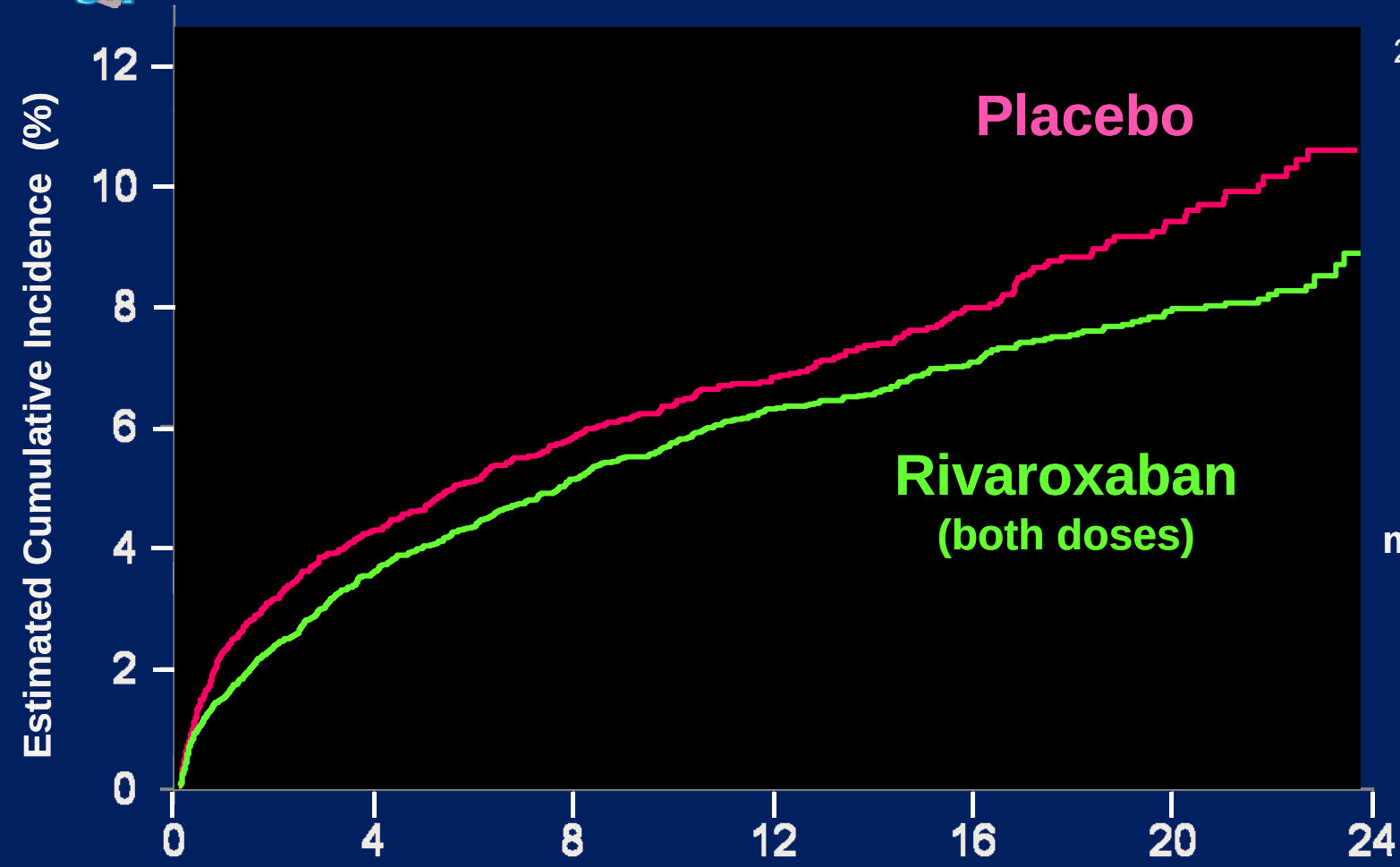
*ACTION data July 2007 – June 2008 (PCI rates from CRUSADE 2006)

1. NEJM 2007;357:2001-2015
2. NEJM 2009;361:1045-1057.
3. NEJM 2012;366:9-19

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke



2 Yr KM Estimate

10.7%

8.9%

HR 0.84
(0.74-0.96)

mITT p = 0.008
ITT p = 0.002

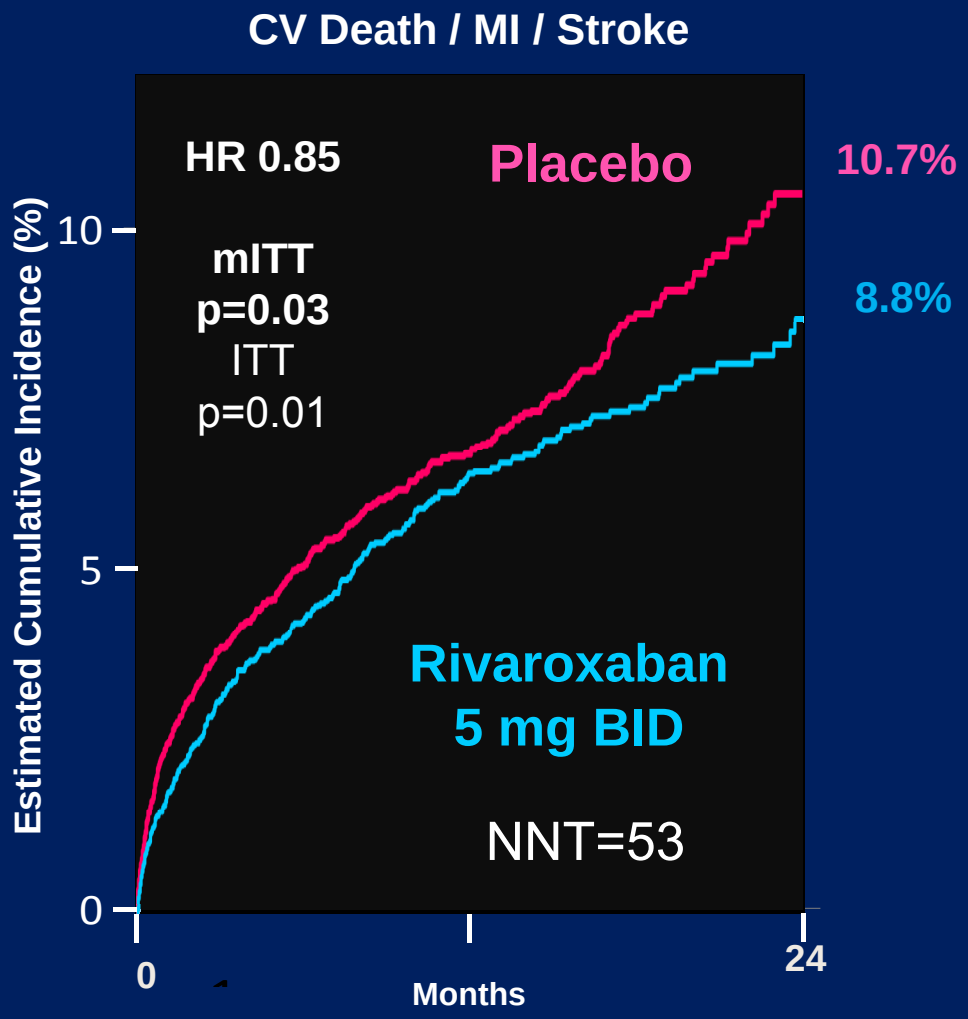
ARR 1.8%
NNT = 56

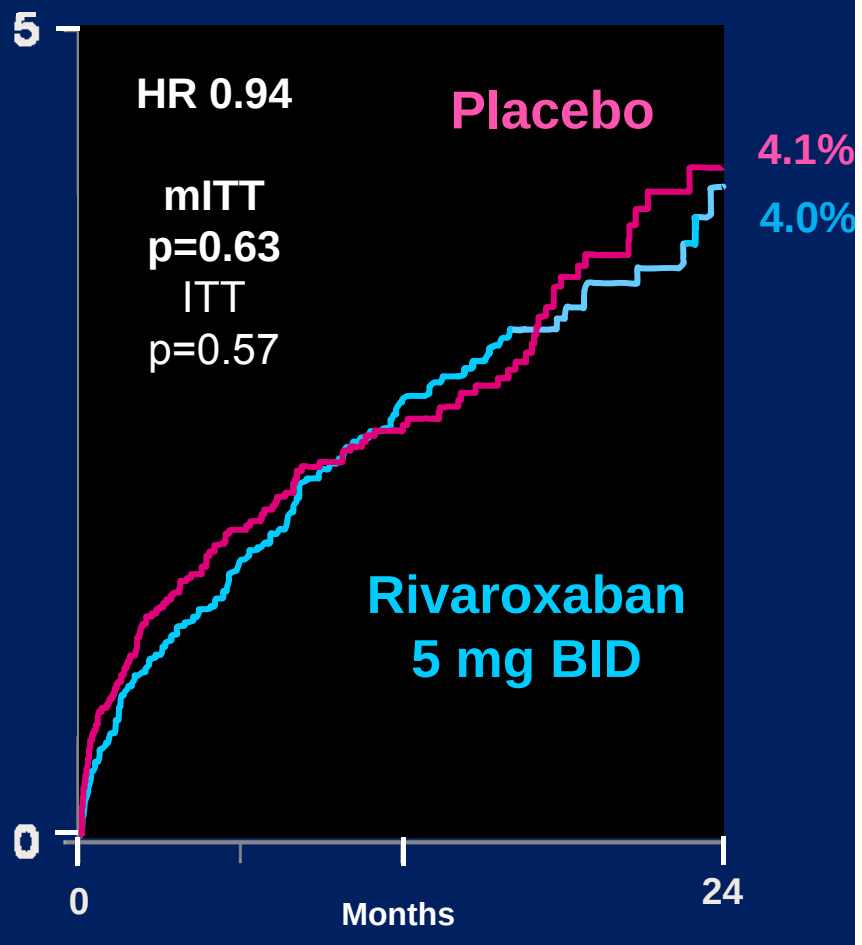
No. at Risk							
Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

HR and 95% CI 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.

Mega JL et al. *NEJM* 2012;366:9-19

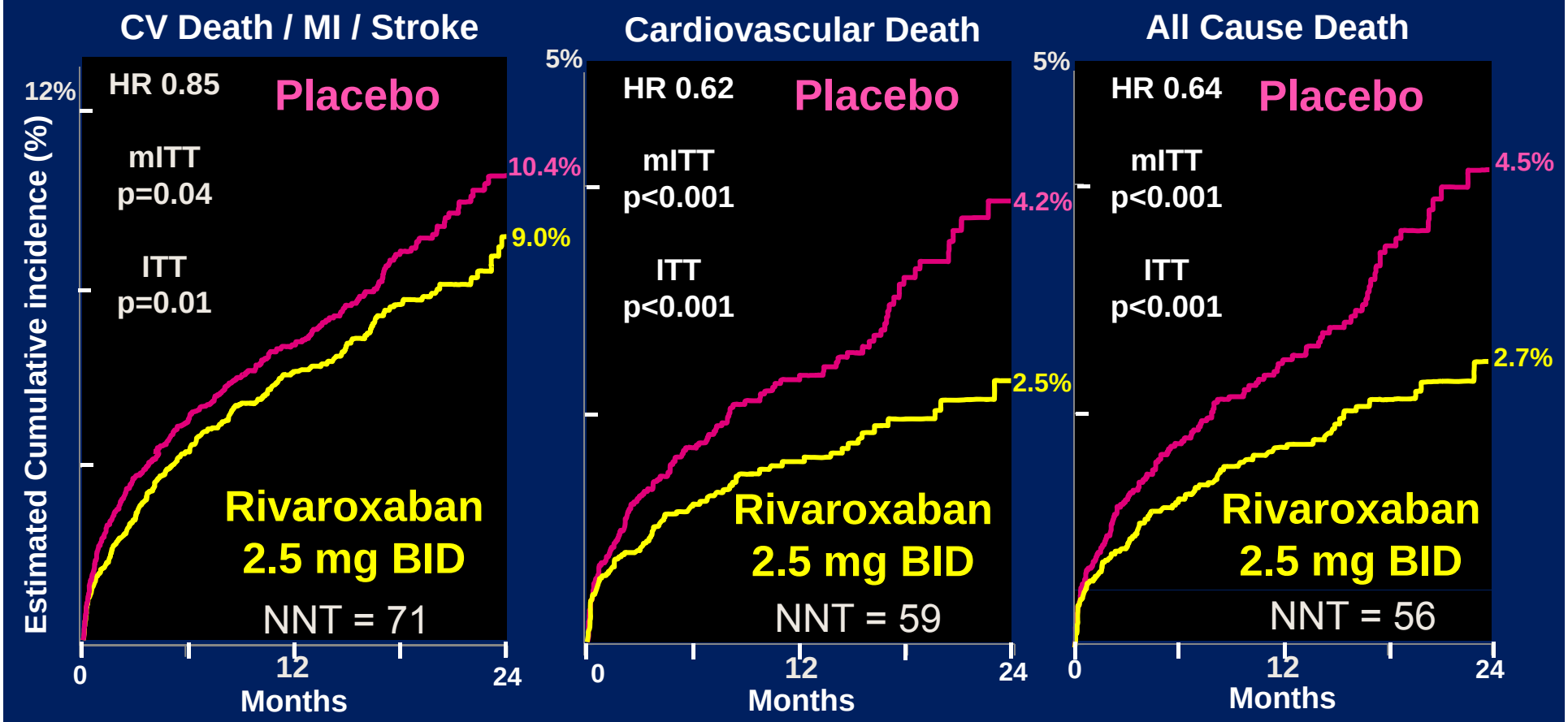
EFFICACY ENDPOINTS: Low Dose 5.0 mg BID





Mega JL et al. *NEJM* 2012;366:9-19

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



Mega JL et al. *NEJM* 2012;366:9-19

Anatomic Features in Victims of Sudden Coronary Death

Coronary Artery Pathology

Michael J. Davies, MD, FACC

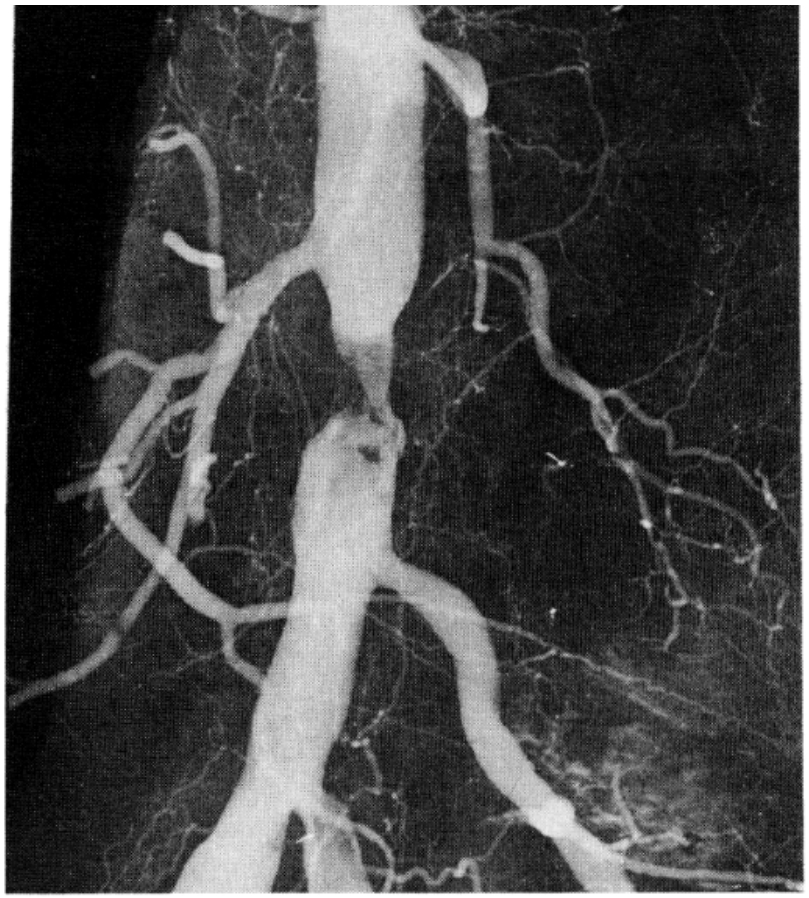
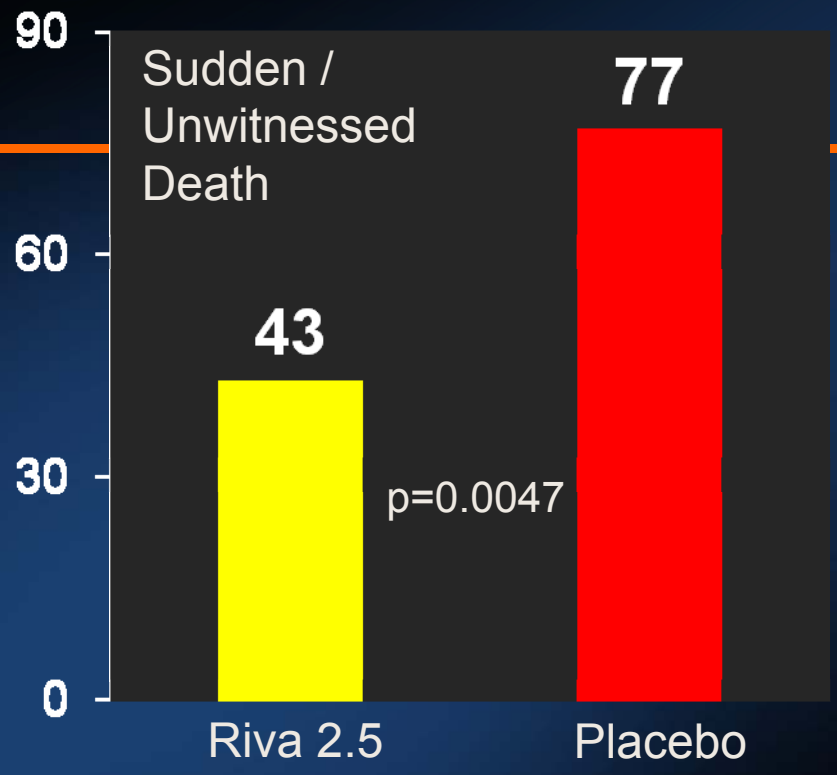


FIGURE 1. *Postmortem angiogram showing the characteristic sudden coronary death lesion. There is an eccentric stenosis with a ragged edge associated with an intraluminal filling defect.*



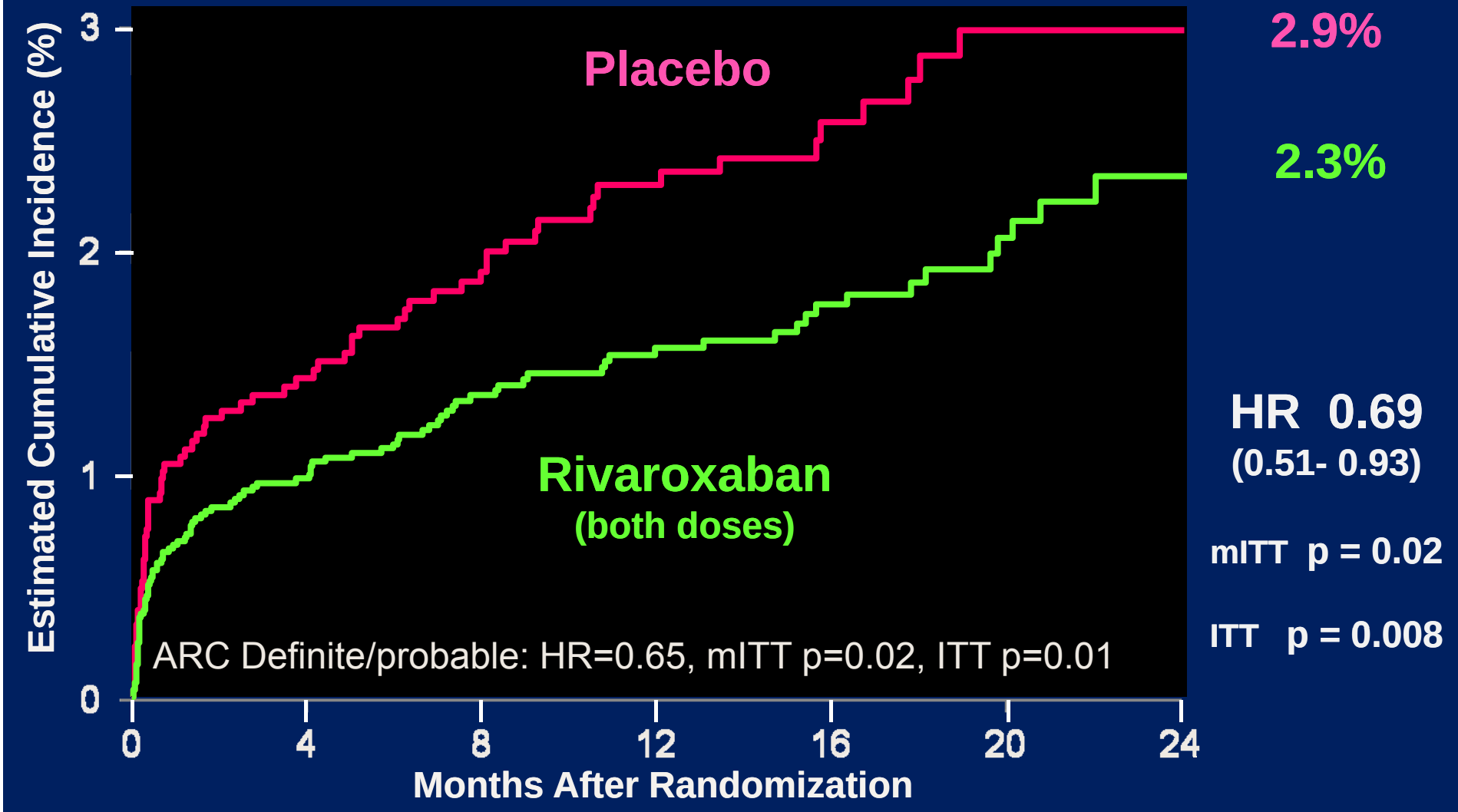
"A study of 168 consecutive cases of sudden coronary death showed 73.3% to have had a recent coronary thrombotic lesion"

Circulation 1992;85 [suppl 11:1-19-1-24.

ATLAS ACS 2 TIMI 51

STENT THROMBOSIS

ARC Definite / Probable / Possible

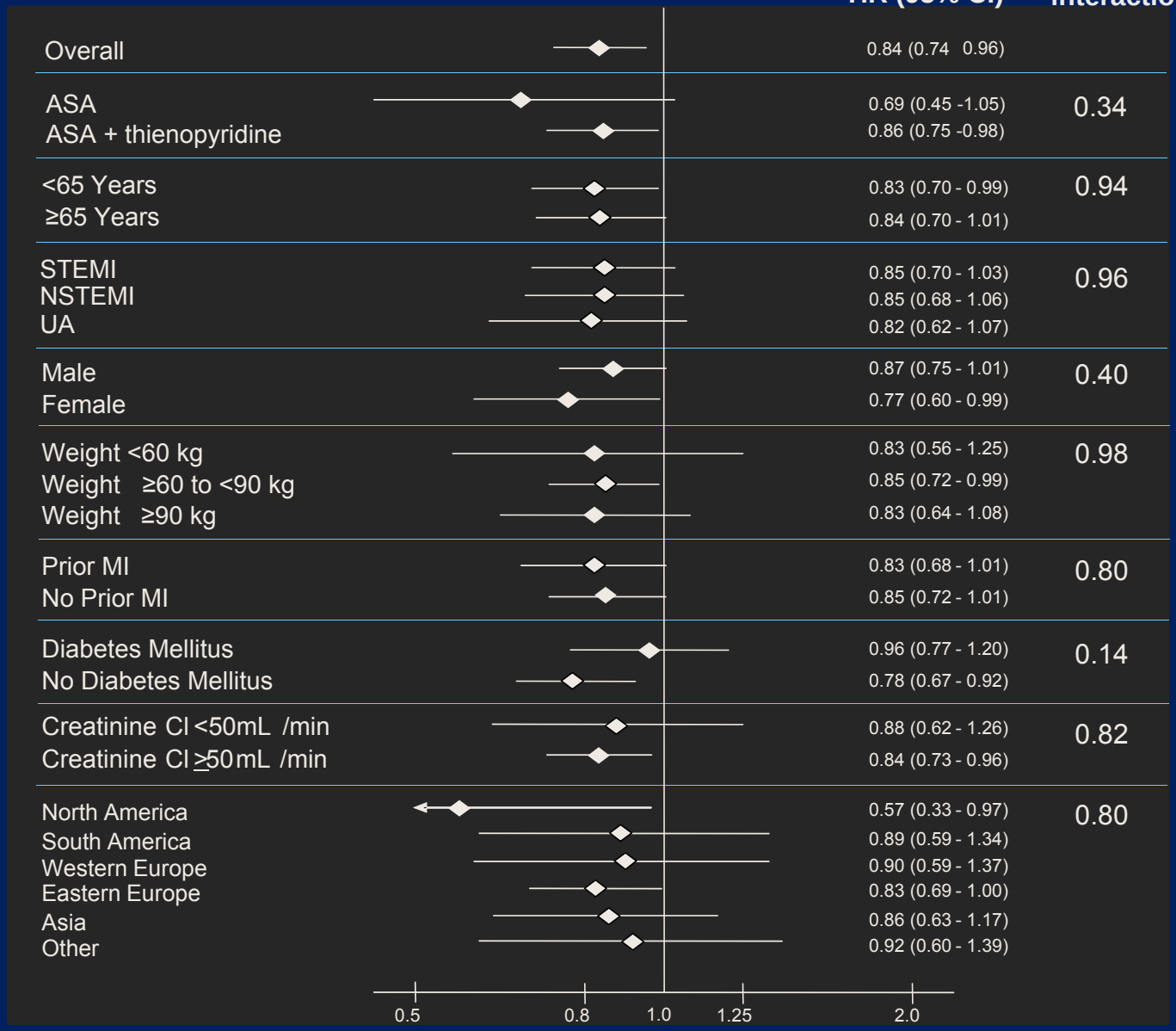


Mega JL et al. *NEJM* 2012;366:9-19

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY SUBGROUP RESULTS

All Rivaroxaban vs. Placebo



NEJM 2012;366:9-19

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

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.

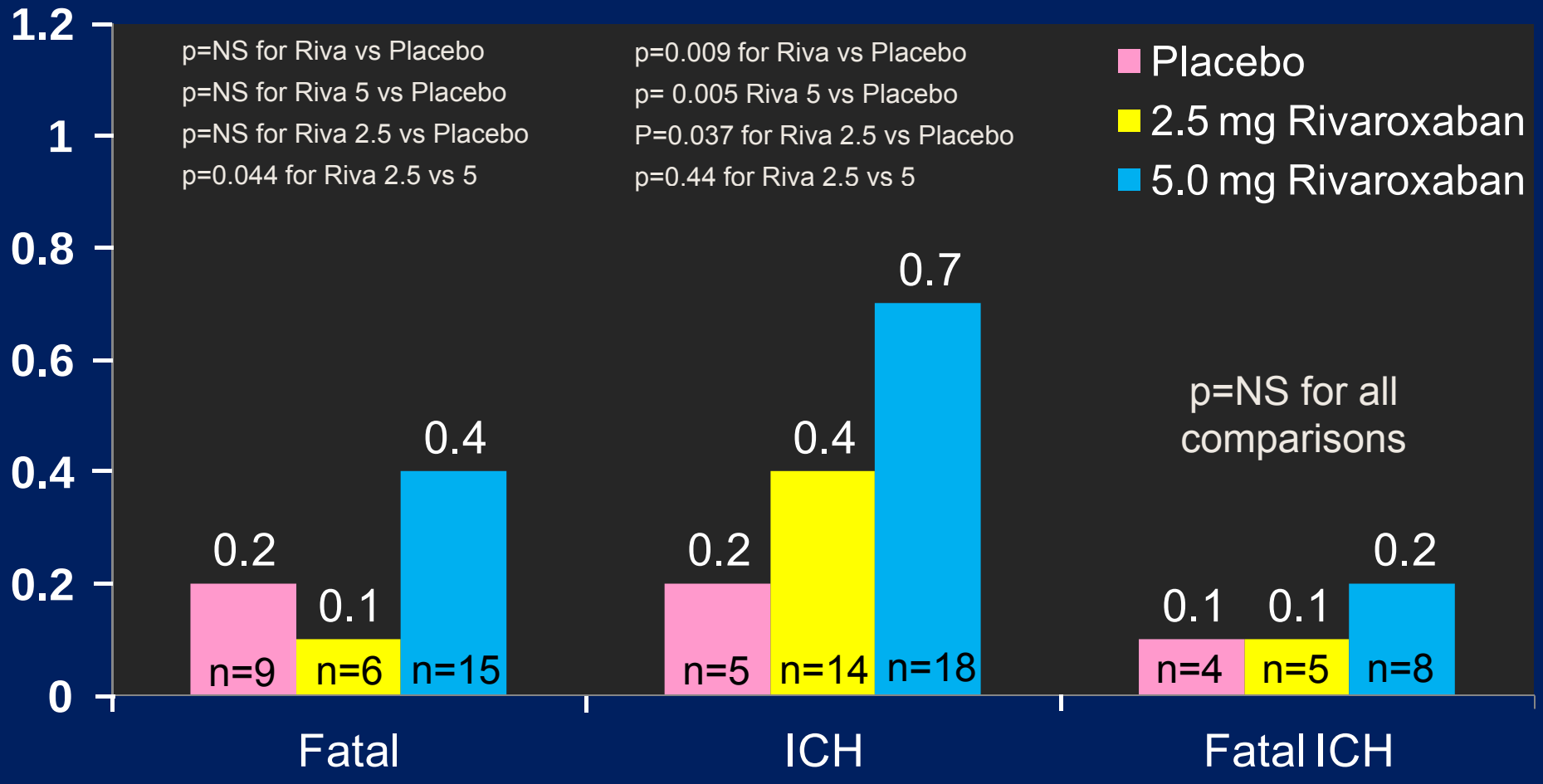
Post-Treatment CVD / MI / Stroke##

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

*: 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, HRs 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.

Mega JL et al. *NEJM* 2012;366:9-19

TREATMENT-EMERGENT FATAL BLEEDS AND ICH



Mega JL et al. *NEJM* 2012;366:9-19

Putting Bleeding Into Context of Other New Drugs

TIMI Major Non-CABG Bleeding

- **Prasugrel: 2.4% vs 1.8% over one year = 0.6% annually[1]**
- **Ticagrelor: 2.8% vs 2.2% over one year = 0.6% annually[2]**
- **Rivaroxaban: 1.8% vs 0.6% over two years = 0.6% annually[3]**

0.6% per year for all 3 agents
(rivaroxaban, ticagrelor, prasugrel)

Fatal Bleeding or ICH

- **Prasugrel: Increase in fatal bleeding (0.4% vs 0.1%, 21 vs 5 events, p=0.002)[1]**
- **Ticagrelor: Increase in fatal ICH (11 vs 1, p = 0.02)[2]**
- **Rivaroxaban: No increase in either fatal bleeding or fatal ICH[3]**

1. NEJM 2007;357:2001-2015
2. NEJM 2009;361:1045-1057.
3. NEJM 2012;366:9-19

ATLAS ACS 2 TIMI 51

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.