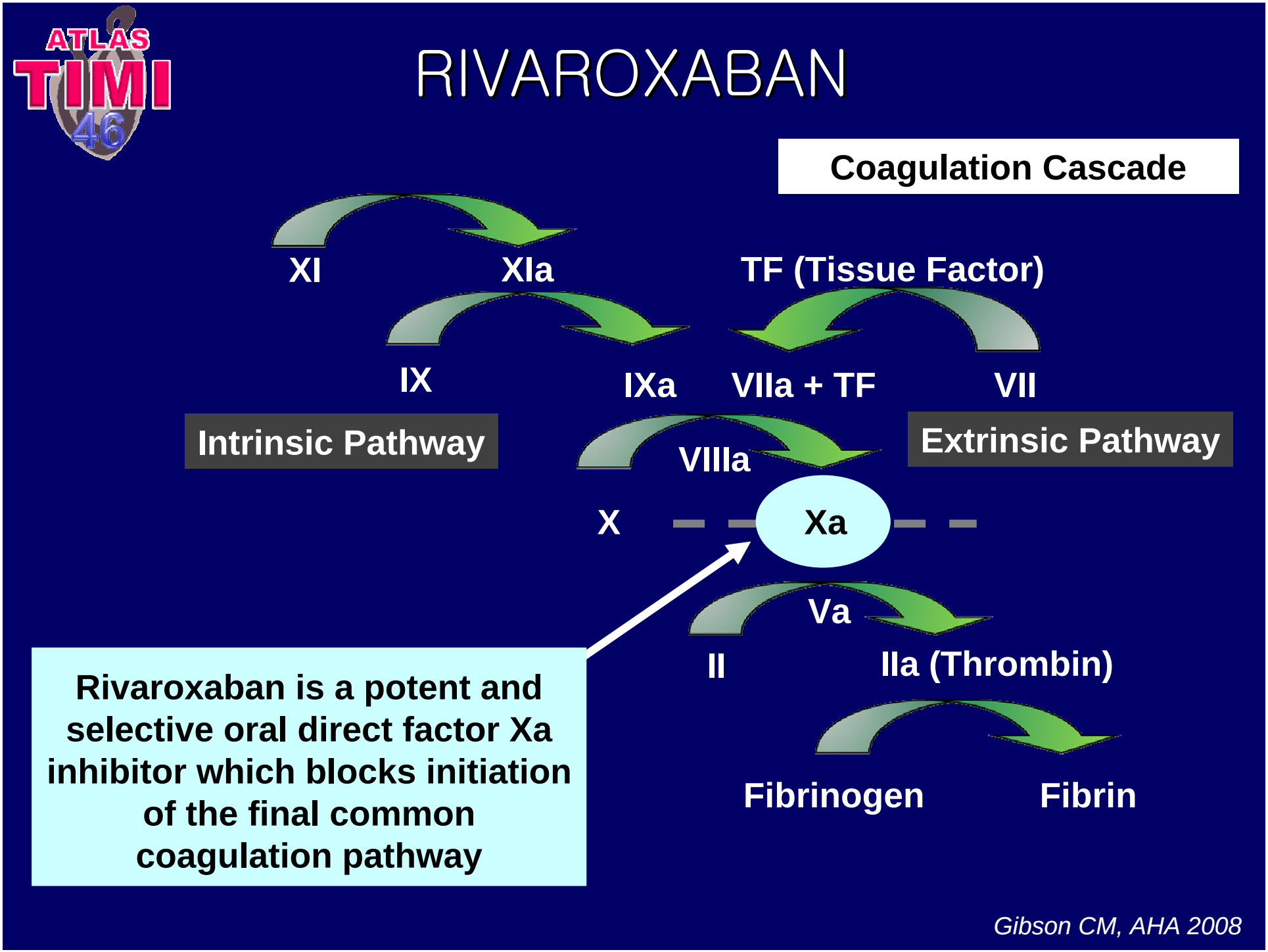
C. Michael Gibson, Jessica L. Mega, Christopher J. Hammett, Vasil Hricak, Pascual Bordes, Adam Witkowski, Valentin Markov, Paul Burton, and Eugene Braunwald for the TIMI 46 Study Group

Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 46 Trial

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

RIVAROXABAN



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GOALS of ATLAS ACS TIMI 46

Conduct a robust phase II dose ranging trial

Primary Goal – Safety:

- To identify tolerable doses of rivaroxaban in the treatment of ACS for evaluation in a large Phase III trial

Secondary Goal - Efficacy:

- To explore efficacy of rivaroxaban at tolerable doses

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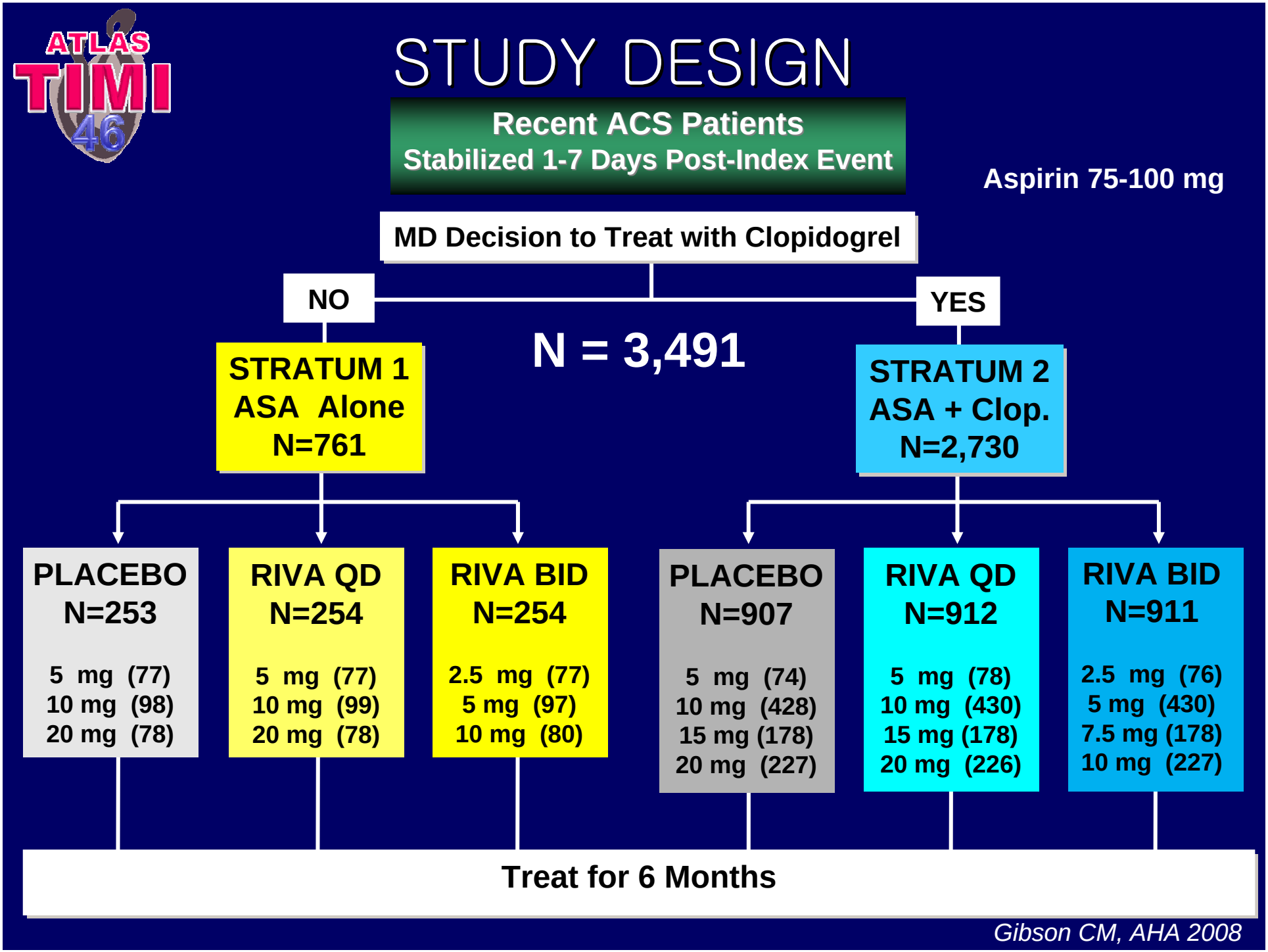
ATLAS TIMI 46
STUDY DESIGN
Recent ACS Patients
Stabilized 1-7 Days Post-Index Event
Aspirin 75-100 mg
MD Decision to Treat with Clopidogrel
NO
YES
N = 3,491
STRATUM 1
ASA Alone
N=761
STRATUM 2
ASA + Clop.
N=2,730
PLACEBO
N=253
5 mg (77)
10 mg (98)
20 mg (78)
RIVA QD
N=254
5 mg (77)
10 mg (99)
20 mg (78)
RIVA BID
N=254
2.5 mg (77)
5 mg (97)
10 mg (80)
PLACEBO
N=907
5 mg (74)
10 mg (428)
15 mg (178)
20 mg (227)
RIVA QD
N=912
5 mg (78)
10 mg (430)
15 mg (178)
20 mg (226)
RIVA BID
N=911
2.5 mg (76)
5 mg (430)
7.5 mg (178)
10 mg (227)
Treat for 6 Months
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SAFETY EVALUATION:

EXPANDED TIMI BLEEDING CLASSIFICATION

Clinically Significant Bleeding - *Any* of the following:

TIMI Major – Intracranial bleeding or clinically overt bleeding associated with a drop in Hgb of ≥ 5g/dl or absolute drop in Hct of ≥ 15%

TIMI Minor – Clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of ≥ 3 gm/dL but < 5 gm/dL from baseline

Bleeding Requiring Medical Attention – Bleeding requiring either medical attention, medical treatment, surgical treatment that does not meet the above criteria (e.g. a nosebleed)

* A transfusion is counted as 1 g/dl or 3% Hct

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EFFICACY EVALUATION

Primary Efficacy Endpoint:

- Death
- MI
- Stroke
- Severe Recurrent Ischemia Requiring Revascularization

Secondary Efficacy Endpoint:

- **Death**
- **MI**
- **Stroke**

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KEY ENROLLMENT CRITERIA

Inclusion Criteria

- ACS sx > 10 min at rest within 7 days of randomization
- STEMI or NSTEMI / UA with at least 1 of:
  - Elevated cardiac enzyme marker (CK-MB or Tn I or Tn T)
  - ≥ 1 mm ST-segment deviation
  - TIMI risk score ≥3

Exclusion Criteria

- Tx with warfarin
- GI bleeding within 6 mos.
- Increased bleeding risk
- H/o hemorrhagic stroke
- Ischemic stroke or TIA within 30 days
- Abciximab tx within 8 hrs, Eptifibatide or Tirofiban within 2 hrs

ACS=Acute Coronary Syndrome; NSTEMI=Non-ST-Elevation Myocardial Infarction; STEMI=ST-Elevation Myocardial Infarction; TIMI=Thrombolysis In Myocardial Infarction; UA=Unstable Angina

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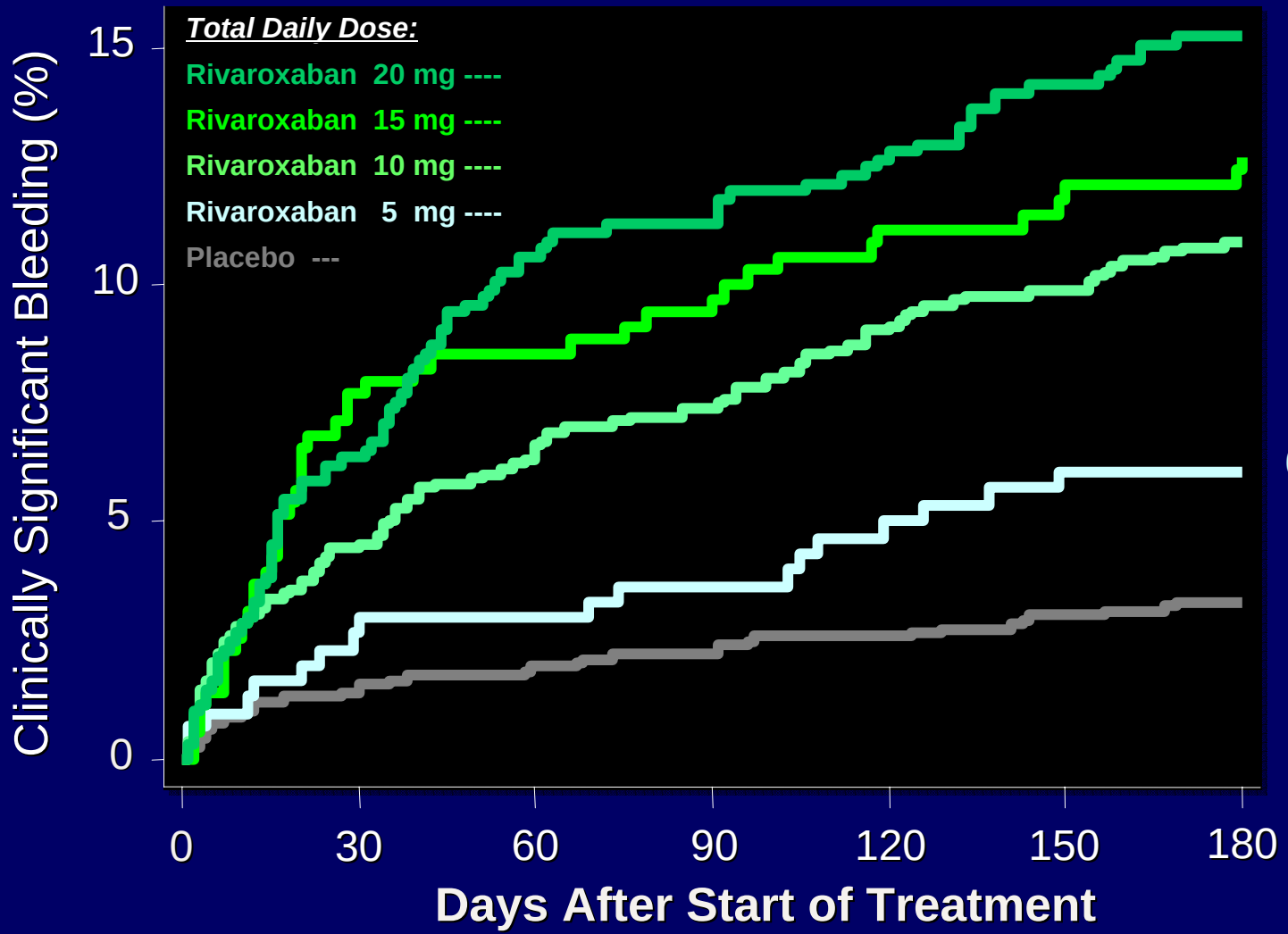
PRIMARY SAFETY ENDPOINT: CLINICALLY SIGNIFICANT BLEEDING

(= 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

Kaplan-Meier estimates for cumulative events, HR(CI), for bleeding rates during the 180 day period ; HR=Hazard Ratio; CI=Confidence Interval

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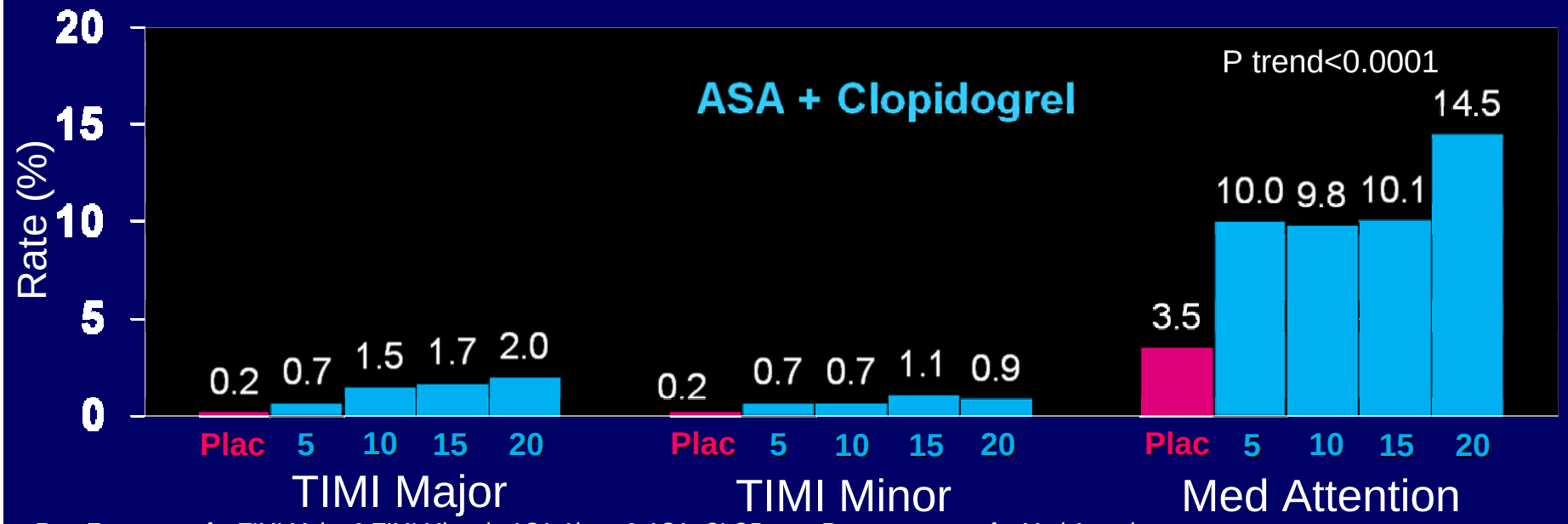
SAFETY ENDPOINTS:

TIMI Major, TIMI Minor and Bleeding Req. Med. Attn.



Raw Event rates for TIMI Major & TIMI Minor in ASA Alone & ASA+CLOP arm. Raw event rates for Med Attention in ASA alone. Kaplan-Meier estimate bleeding rate for medical attention in ASA+CLOP arm during 180 day period. P trend=p value for dose response over actual dose values.

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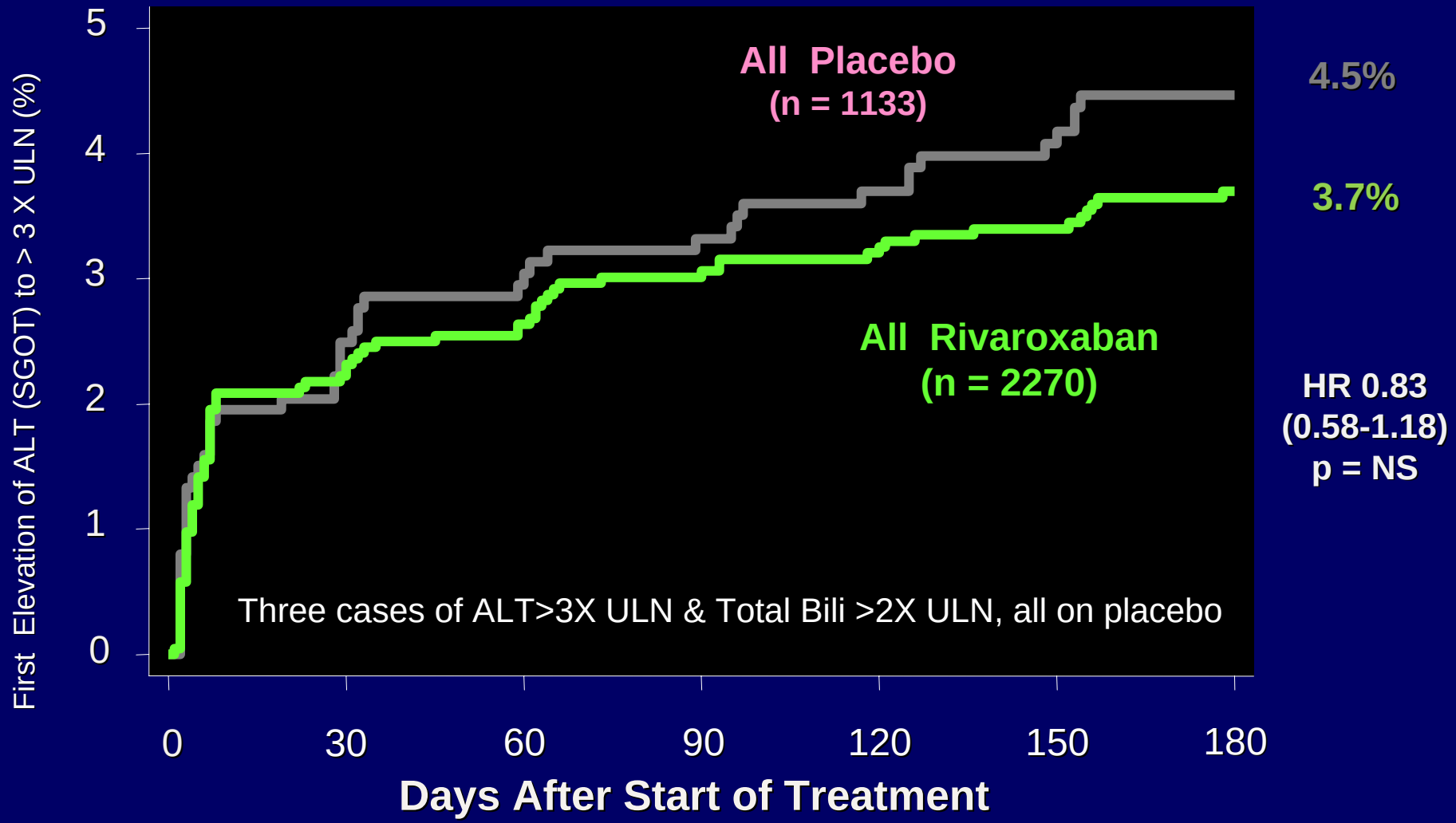
SAFETY EVALUATION: LIVER FUNCTION TEST ABNORMALITIES

First Elevation of ALT (SGPT) to > 3 X ULN



Kaplan-Meier estimates for cumulative events ,HR(CI), for rates of liver function test abnormalities during the 180 day period;HR=Hazard Ratio; CI=Confidence Interval; SGPT = Serum glutamate pyruvate transaminase; ALT = Alanine transaminase; Bili=Bilirubin; ULN= Upper Limit of Normal;

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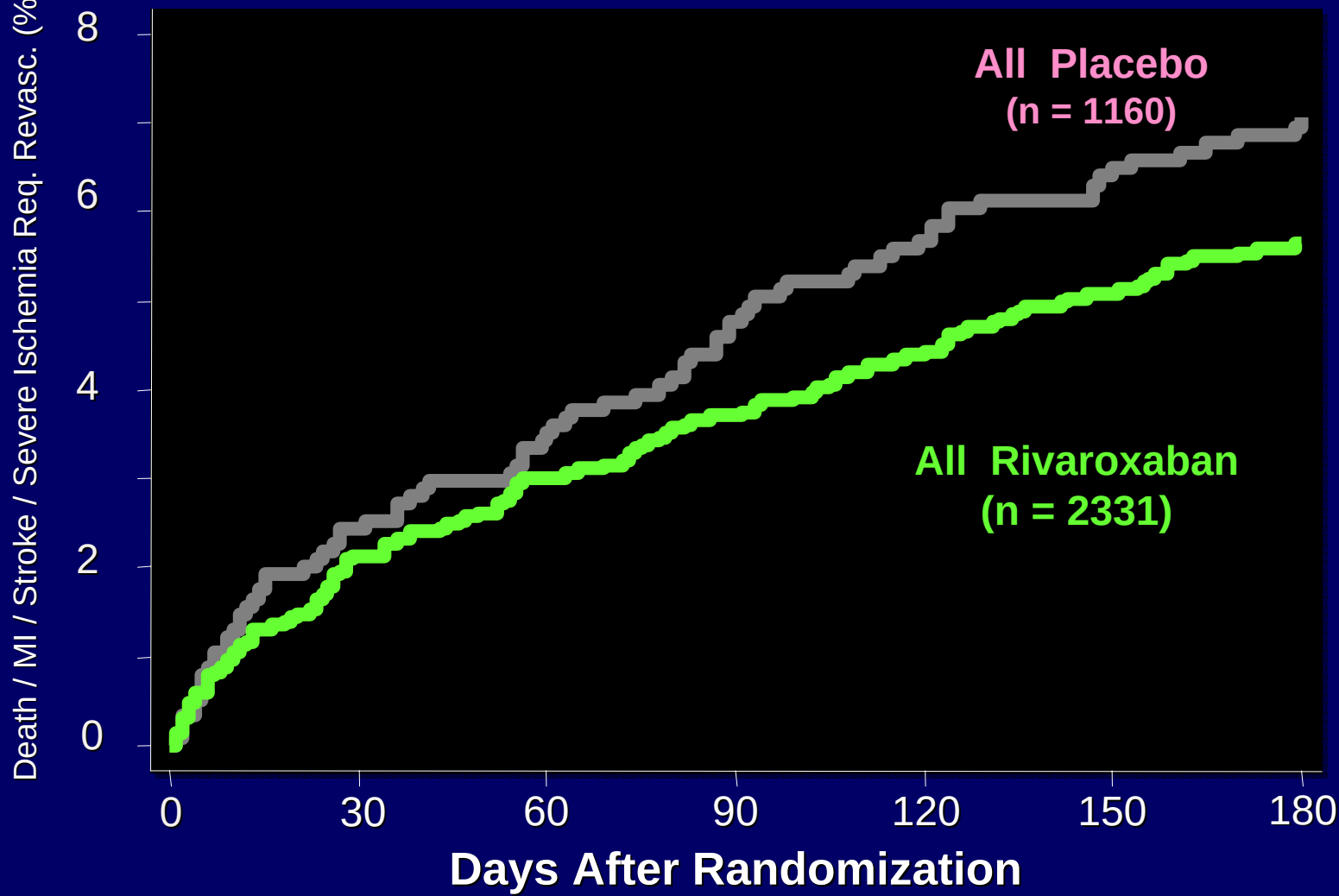
PRIMARY EFFICACY ENDPOINT: Death / MI / Stroke / Severe Ischemia Req. Revascularization



Cumulative Kaplan-Meier estimates of HR and the rates of key study end points during the 180 day period;
Death=All Cause Death ; HR=Hazard Ratio; MI=Myocardial Infarction;

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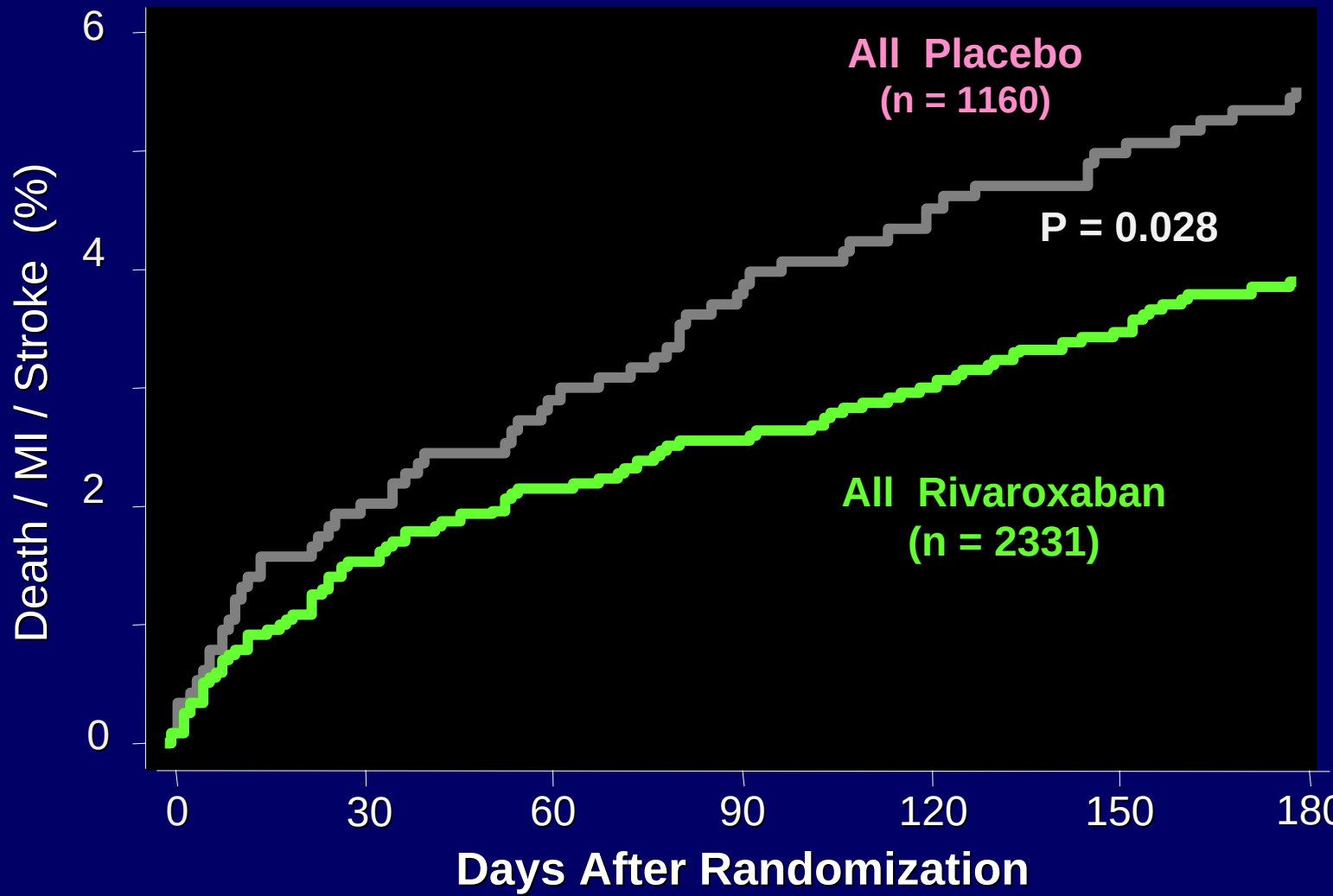
SECONDARY EFFICACY ENDPOINT: Incidence of Death / MI / Stroke



Kaplan-Meier estimates for cumulative events ,HR(CI), for rates of key study end points during the 180 day period; Death=All Cause Death; HR=Hazard Ratio; CI=Confidence Interval; MI=Myocardial Infarction; NNT=Number Needed to Treat per 6 months to prevent 1 event; ARR=Absolute Risk Reduction

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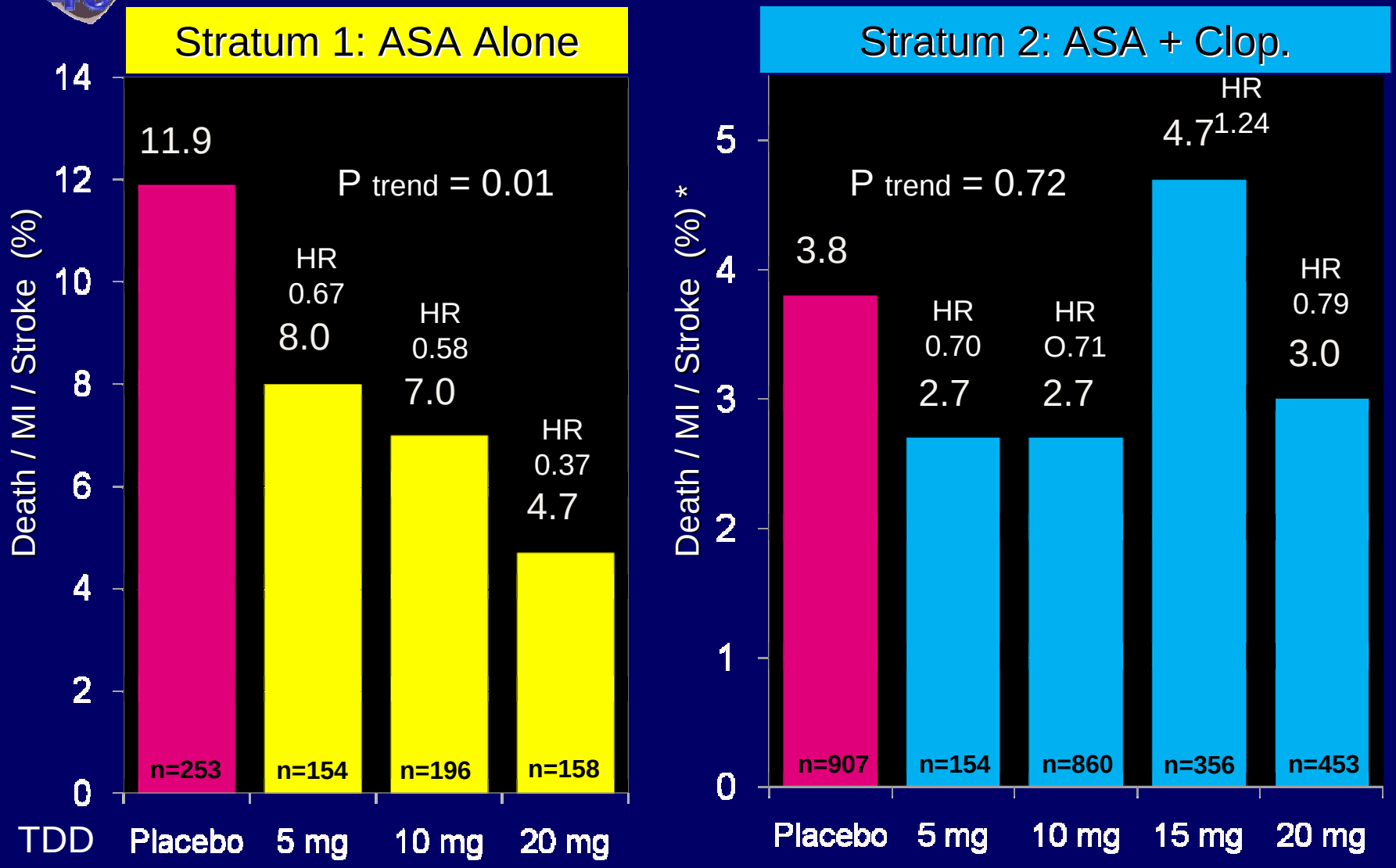
SECONDARY EFFICACY ENDPOINT: Incidence of Death / MI / Stroke



* Kaplan-Meier estimates for cumulative events, HR, for rates of key study end points during the 180 day period;
P trend=p value for dose response over actual dose values
Death=All Cause Death; HR=Hazard Ratio; MI=Myocardial Infarction. Note change in axis right hand panel.

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SUMMARY– SAFETY

- There was increased bleeding associated with higher doses of rivaroxaban.
- Most bleeding was bleeding requiring medical attention, rather than TIMI major or TIMI minor bleeding
- No evidence of drug induced liver injury

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SUMMARY–EFFICACY

1º Endpoint:
21% RRR (HR 0.79, p=0.10) in death, MI, stroke, or severe recurrent ischemia requiring revascularization

2º Endpoint:
31% RRR in the risk of death, MI, or stroke (HR 0.69, p=0.028)

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SELECTION OF DOSES FOR PHASE III

Based upon:

1. Efficacy at lower doses of rivaroxaban
2. Graded increase in bleeding at higher doses of rivaroxaban
3. A trend for BID doses of rivaroxaban to be safer and more efficacious than QD dosing of rivaroxaban in ACS

- Two low doses, 2.5 mg BID and 5 mg BID, have been selected for the Phase III trial

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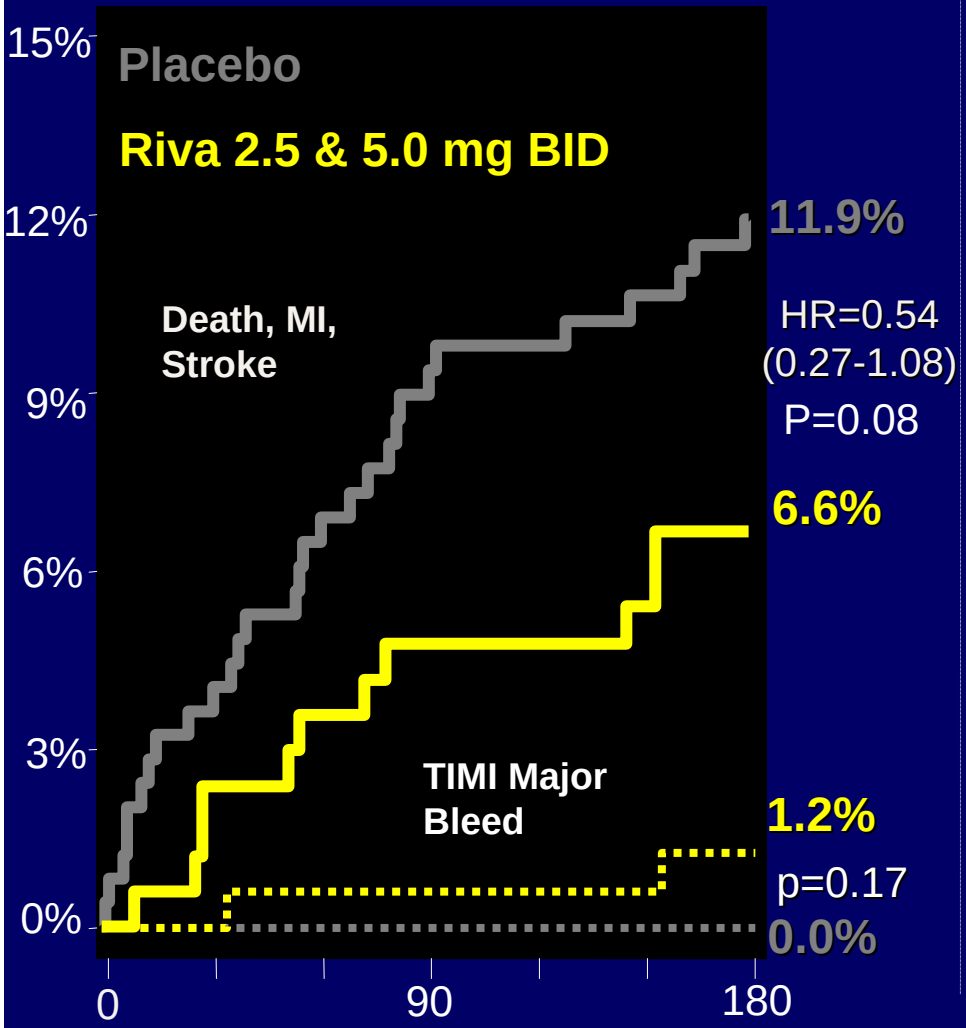
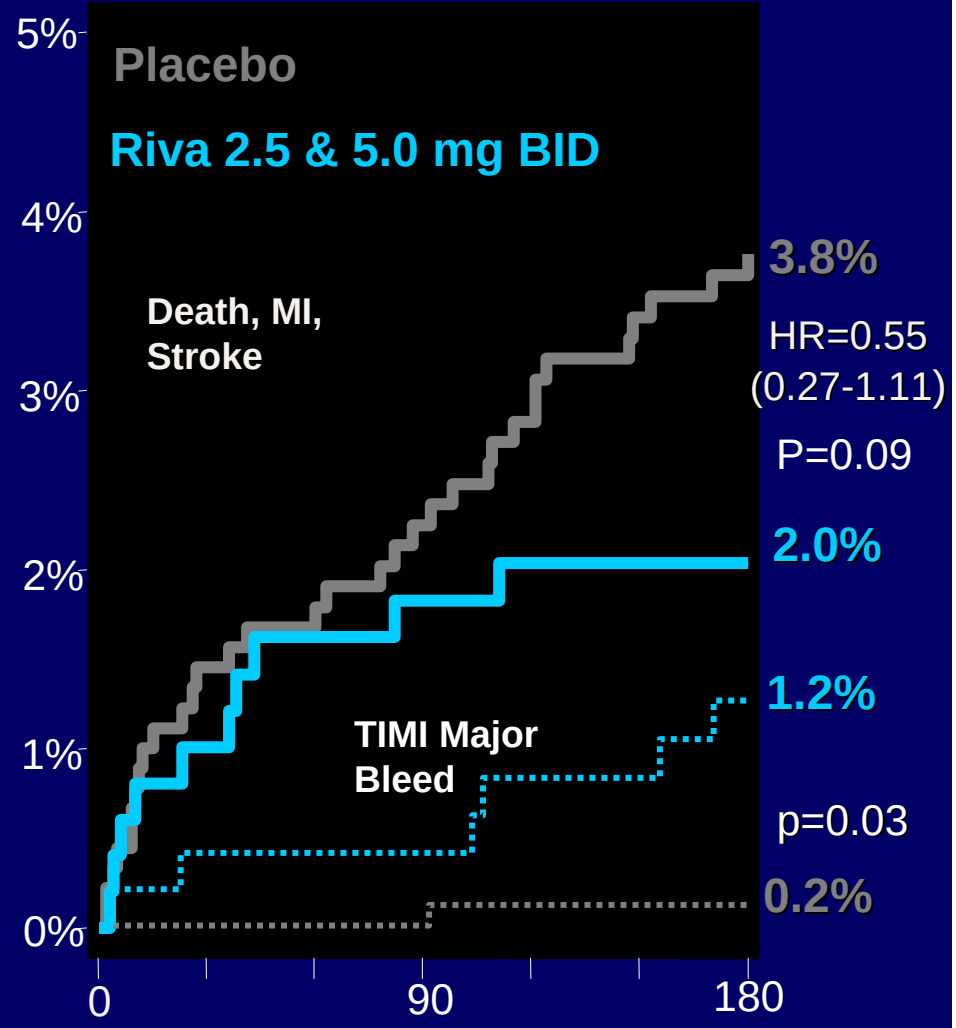
ATLAS 1 Outcomes in Doses to be Taken Forward in Phase 3 Trial

Stratum 1: ASA Alone



Stratum 2: ASA + Clop.



* If fewer than 5 events were present in a cell, raw event rates are reported and a Fisher's exact test was used, otherwise Kaplan-Meier(KM) estimates and a Hazard Ratio(HR) with confidene interval are provided for 180 day period. Raw event rates were reported for TIMI Major Bleed . KM estimates of HR and rates of secondary efficacy endpoints are provided. Death=All Cause Death; MI=Myocardial Infarction Note change in right hand panel.

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PHASE III DESIGN

Recent ACS Patients
(Event driven trial:
13,500 to16,000 pts)
Stabilized 1-7 Days Post-Index Event

Stratified by Thienopyridine use

PLACEBO	RIVAROXABAN 2.5 mg BID	RIVAROXABAN 5.0 mg BID

Study is event driven---expected duration is 33 months

PRIMARY EFFICACY ENDPOINT:
CV Death, MI, Stroke

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