Changing Course: Anticoagulation in Secondary Prevention of Cardiovascular Disease Events

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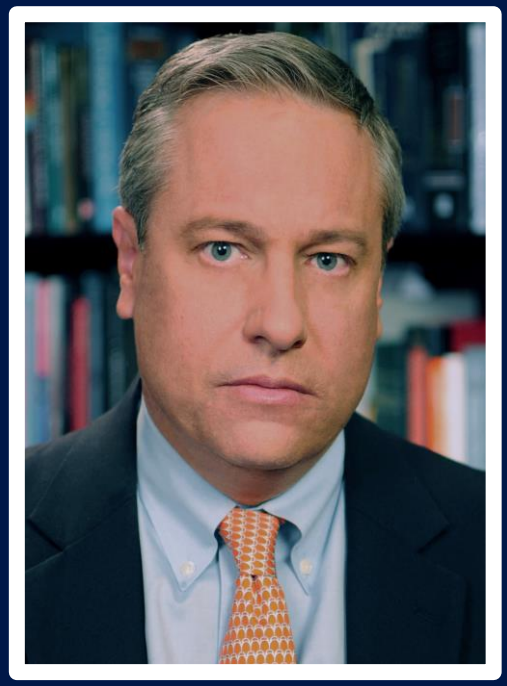

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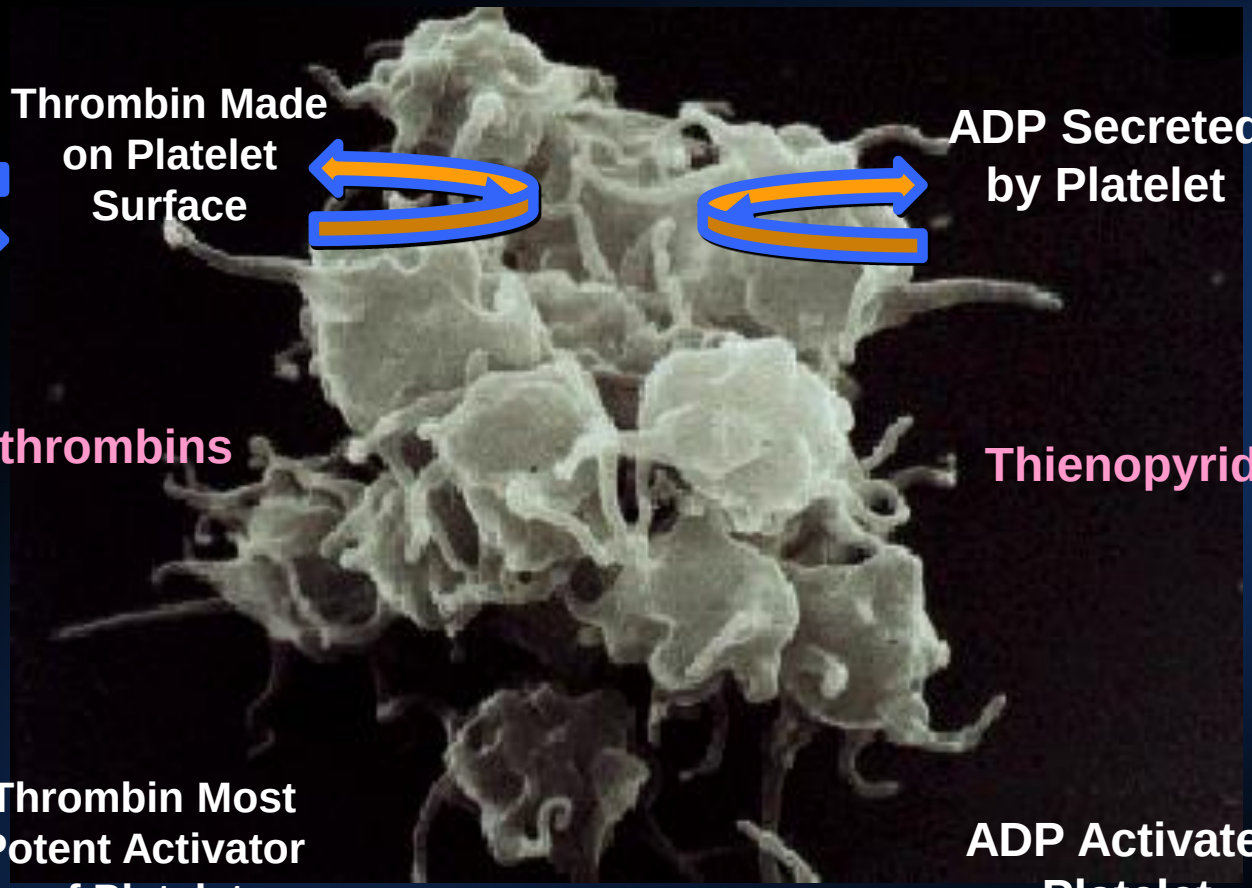
This activity discusses an off-label use for rivaroxaban.

Platelet Amplification
Two Positive Feedback Loops



Thrombin Made on Platelet Surface

ADP Secreted by Platelet

Antithrombins

Thienopyridines

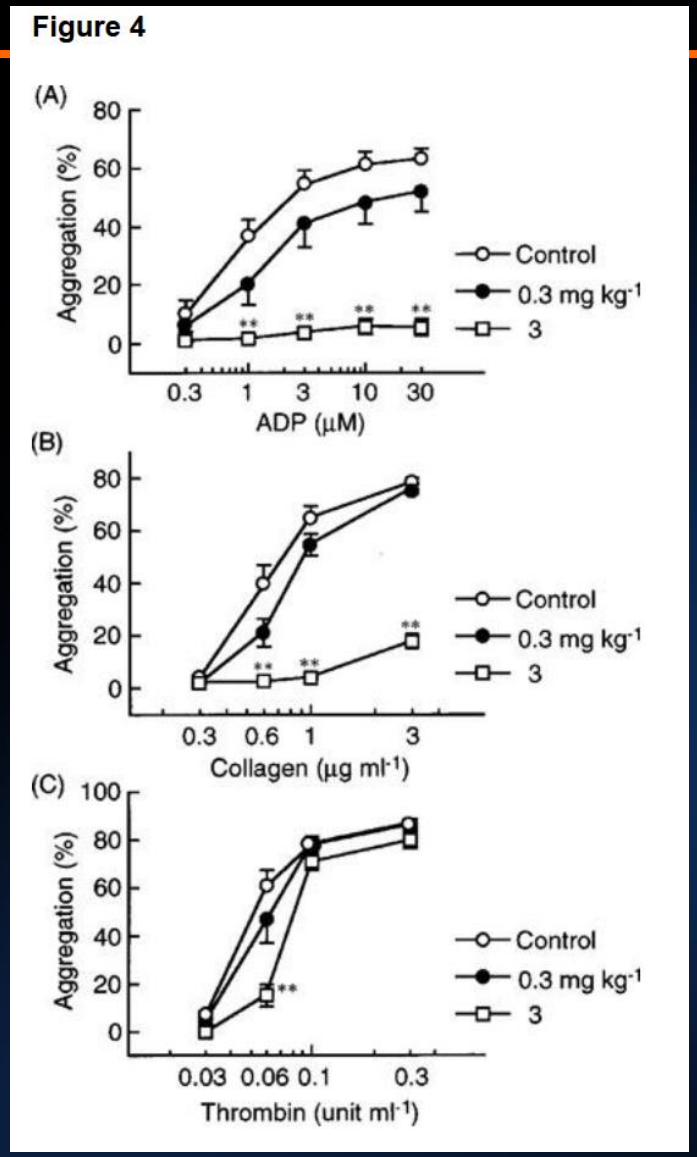
Thrombin Most Potent Activator of Platelet

ADP Activates Platelet

"Amplification"
"Burst"
"Activation"
"Growth of Thrombus"

Slide by C. Michael Gibson, M.S., M.D.

Novel Thienopyridines Do Not Block Activation by Thrombin



Ex vivo **effects of single administration of CS-747 on washed platelet aggregation induced by ADP (A), collagen (B), and thrombin (C) in rats. CS-747 was orally administered once to rats at doses of 0.3 and 3 mg kg^{-1}. The aggregation was measured 4 h after the dosing. Results are presented as the mean±s.e.mean (*n*=6). $^{**}P<0.01$ vs control (vehicle-treated group).**

"Treatment with CS-747 (Prasugrel) inhibited ex vivo washed platelet aggregation in response to ADP but not to thrombin. This is consistent with the hypothesis that the antiaggregative action of CS-747 (Prasugrel) is due to its specific inhibition of the G_i-linked P2T receptor rather than its interference with the fibrinogen receptors."

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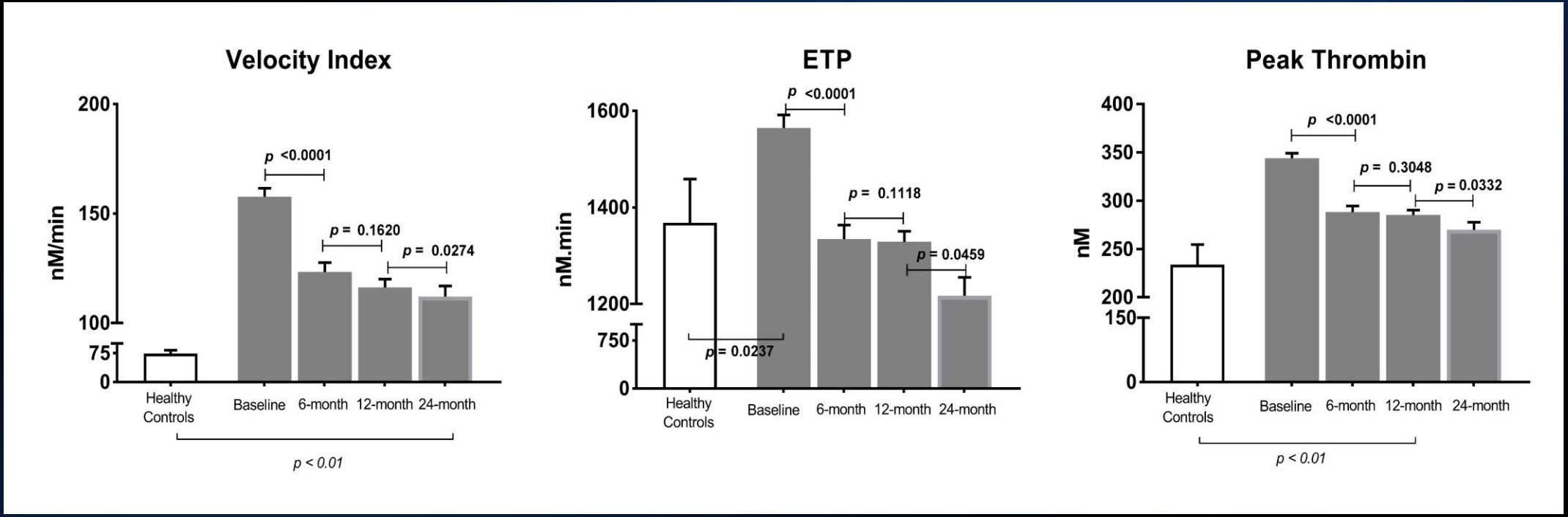
Sugidachi A et al; Br J Pharmacol. Apr 2000; 129(7): 1439–1446.

ACS Is Associated With Long Term Abnormalities in Coagulation

Christina Yip[1*], Aruni Seneviratna[2*], Sock Hwee Tan[2], Sock Cheng Poh[2], Zhen Long Teo[3], Joshua Loh[2], Eng Soo Yap[1,4] , E. Magnus Ohman[5], C. Michael Gibson[6], Mark Richards[2,3] and Mark Chan[2,3]



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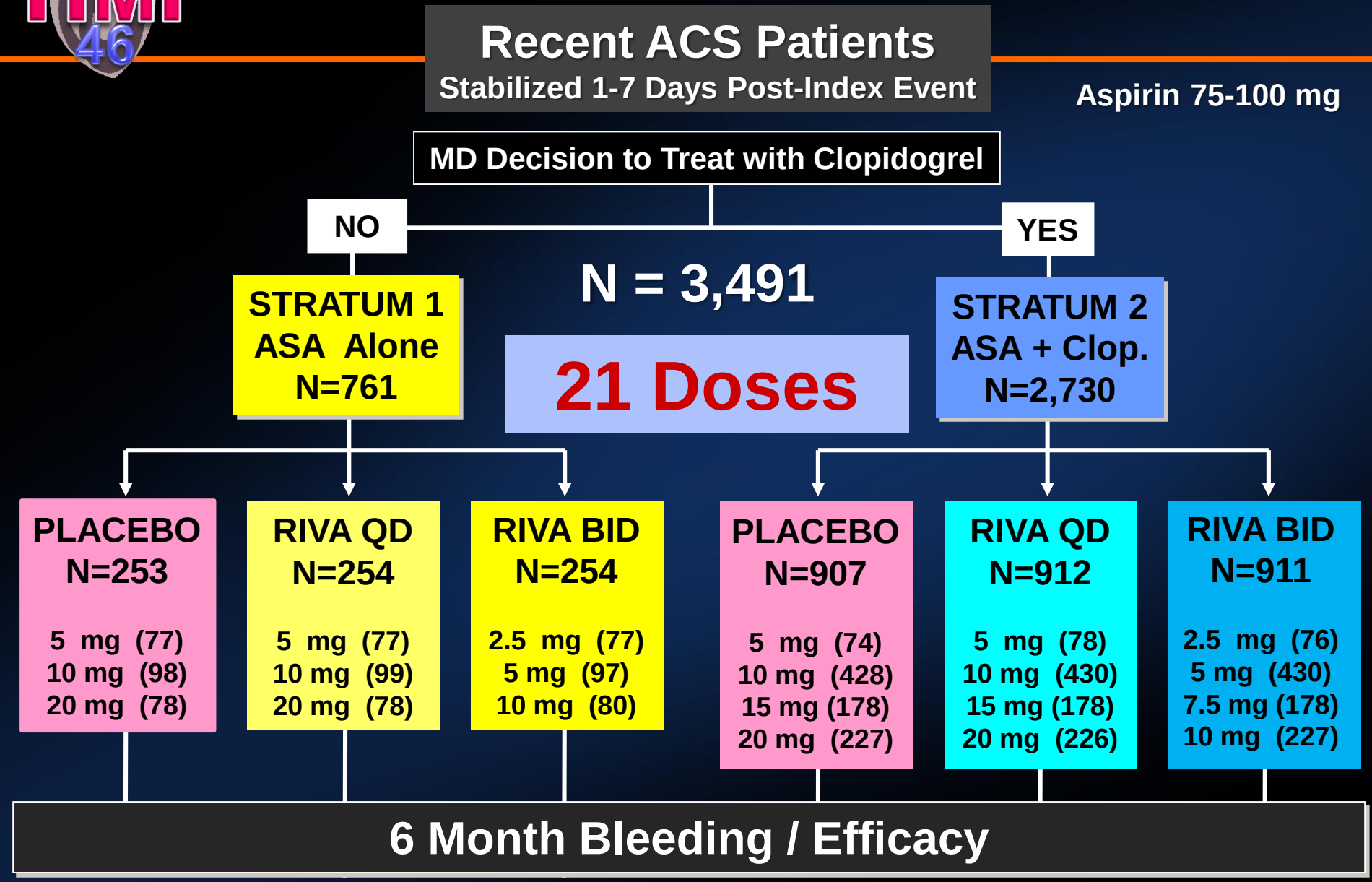
PHASE 2 STUDY DESIGN



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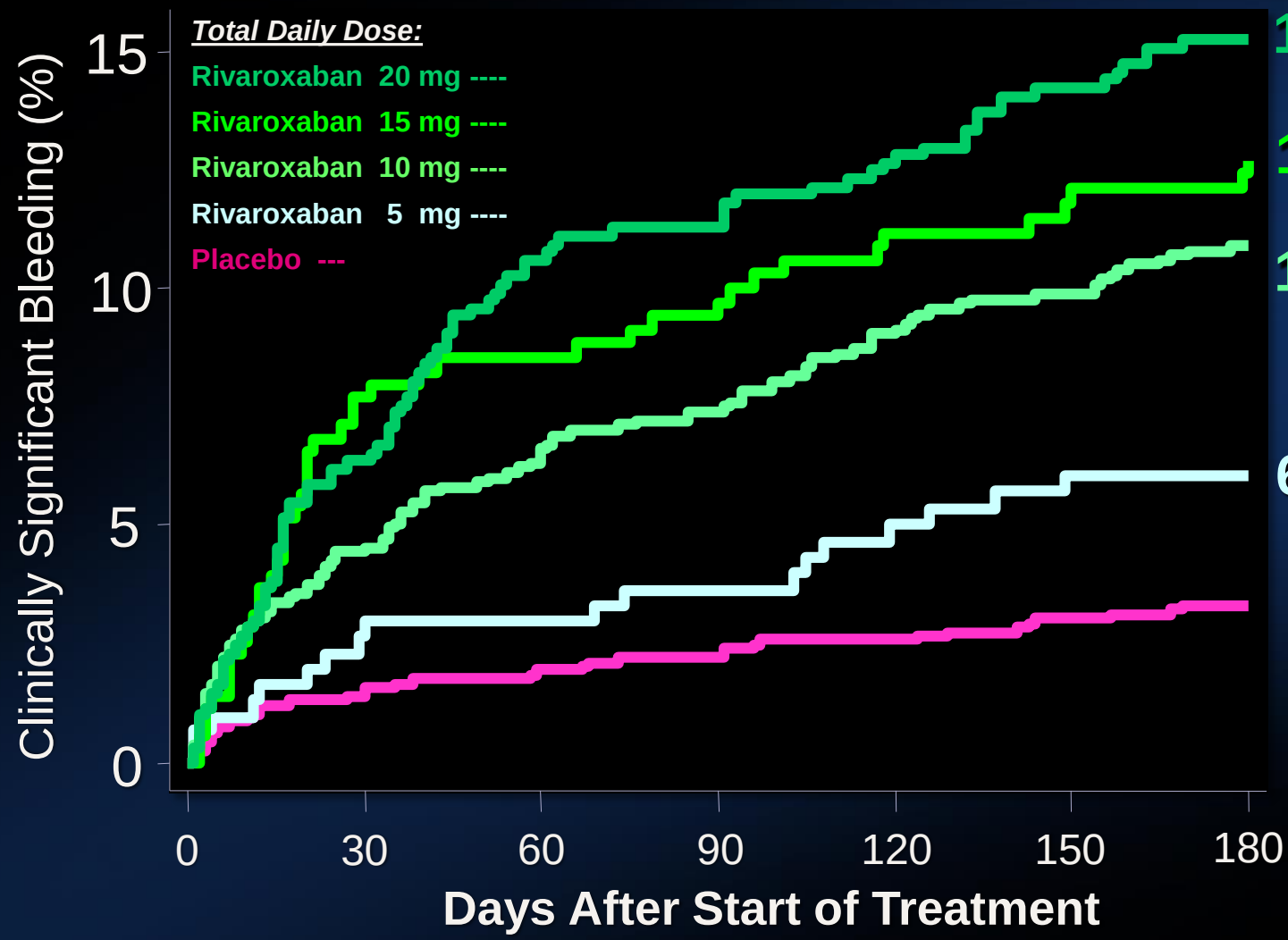
Gibson CM, AHA 2008

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

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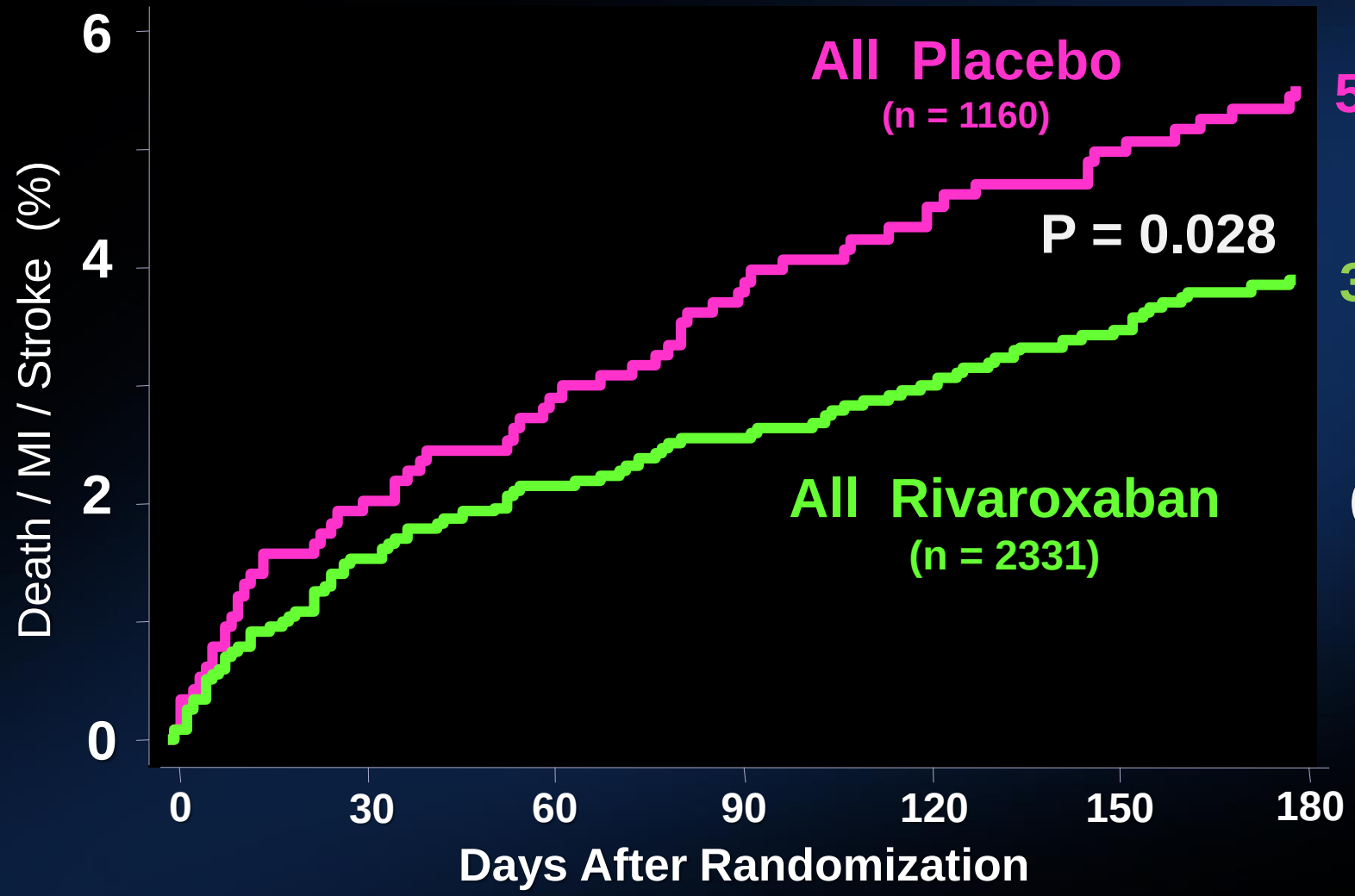
Gibson CM, AHA 2008

SECONDARY EFFICACY ENDPOINT:

Incidence of Death / MI / Stroke



HR 0.69
(0.50-0.96)

P=0.028

ARR = 1.6%
NNT = 63

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Gibson CM, AHA 2008

ATLAS ACS 2 TIMI 51

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

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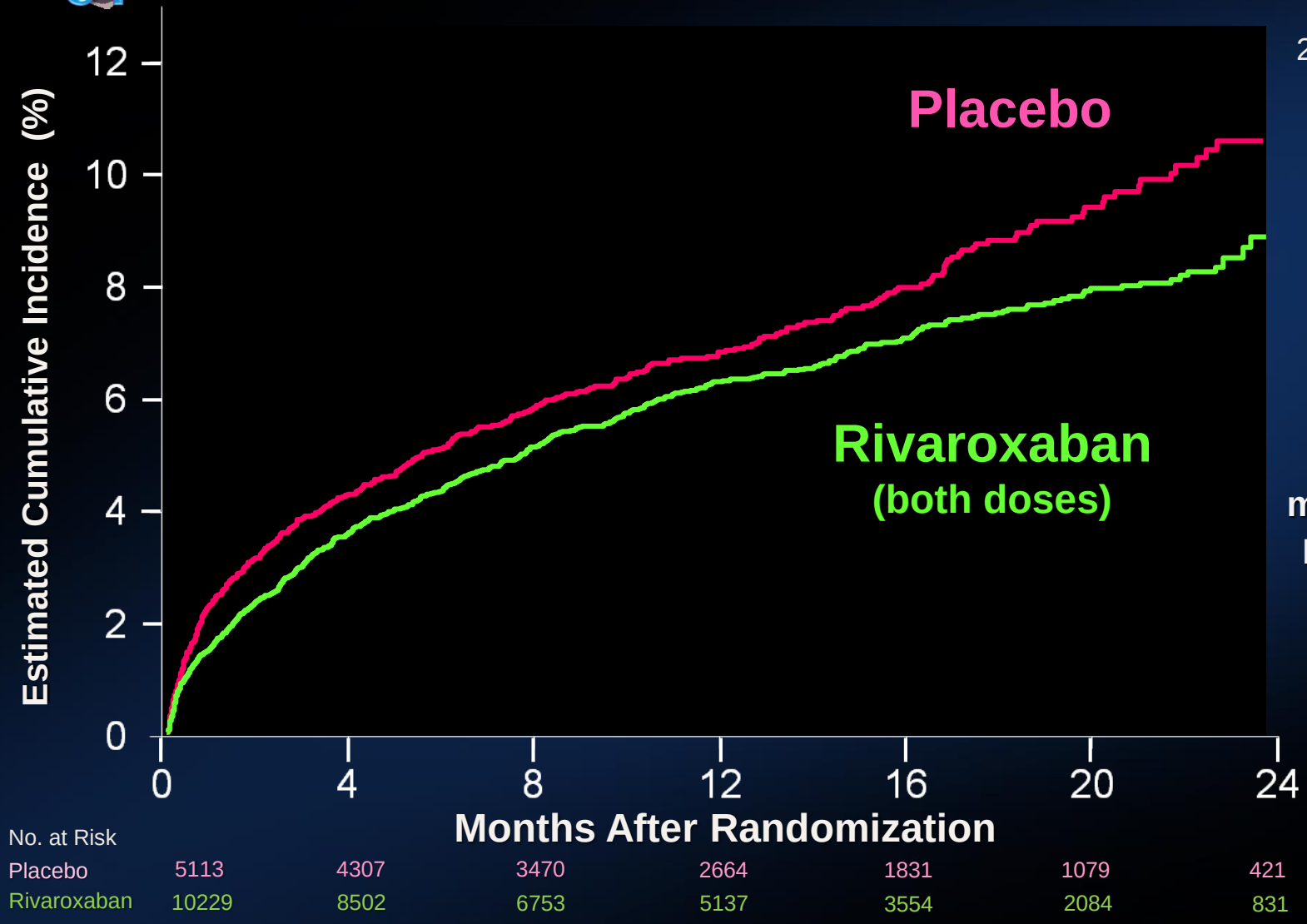
Gibson CM, AHA 2011

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

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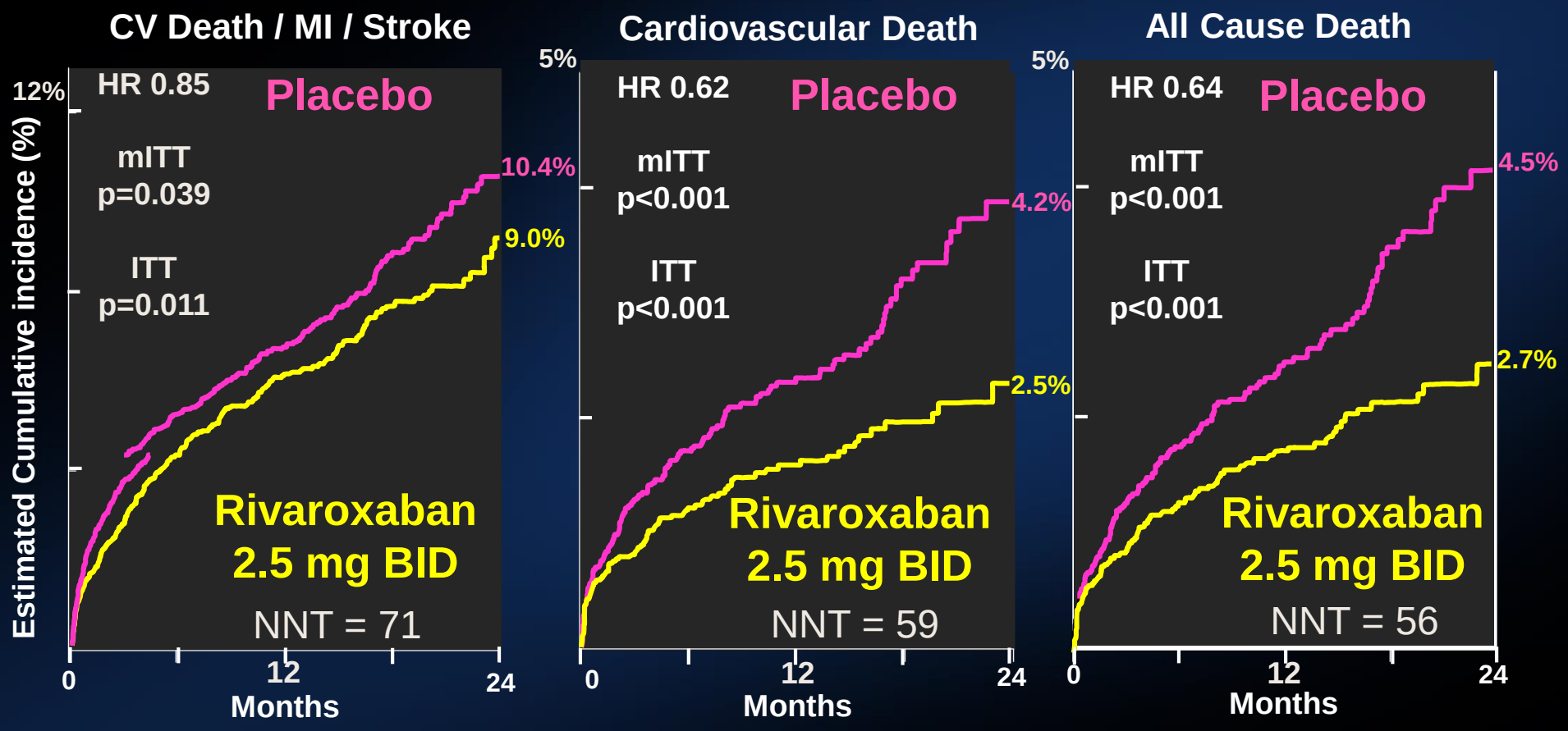
Gibson CM, AHA 2011

ATLAS ACS 2 TIMI 51

EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID

Patients Treated with ASA + Thienopyridine



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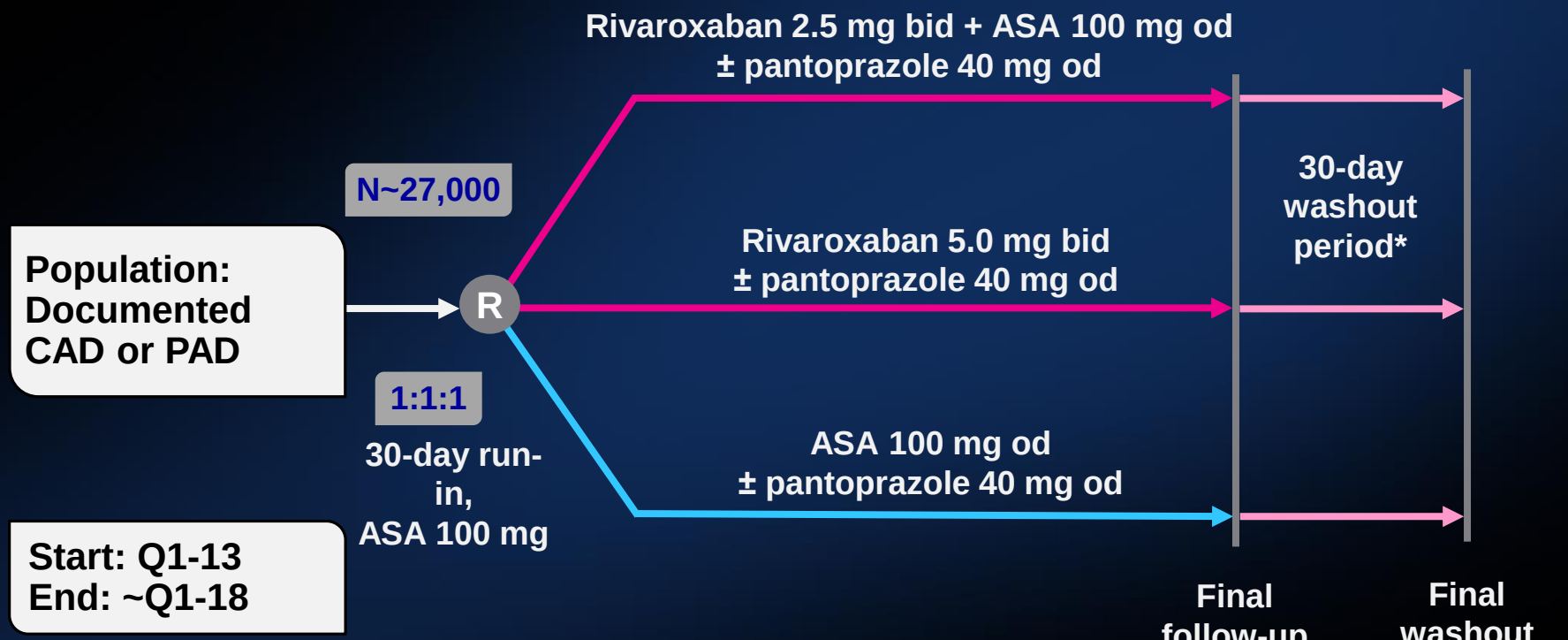
Gibson CM, AHA 2011

COMPASS: Rivaroxaban in CAD or PAD

Objective: efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in CAD or PAD



*Patients treated according to local standard of care
#≤30 days of the required pre-specified number of events having occurred

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www.clinicaltrials.gov/show/NCT01776424

Primary: CV death, stroke, MI

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + aspirin vs. aspirin		Rivaroxaban vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	p	HR (95% CI)	p
CV death, stroke, MI	379 (4.1%)	448 (4.9%)	496 (5.4%)	0.76 (0.66-0.86)	<0.0001	0.90 (0.79-1.03)	0.12

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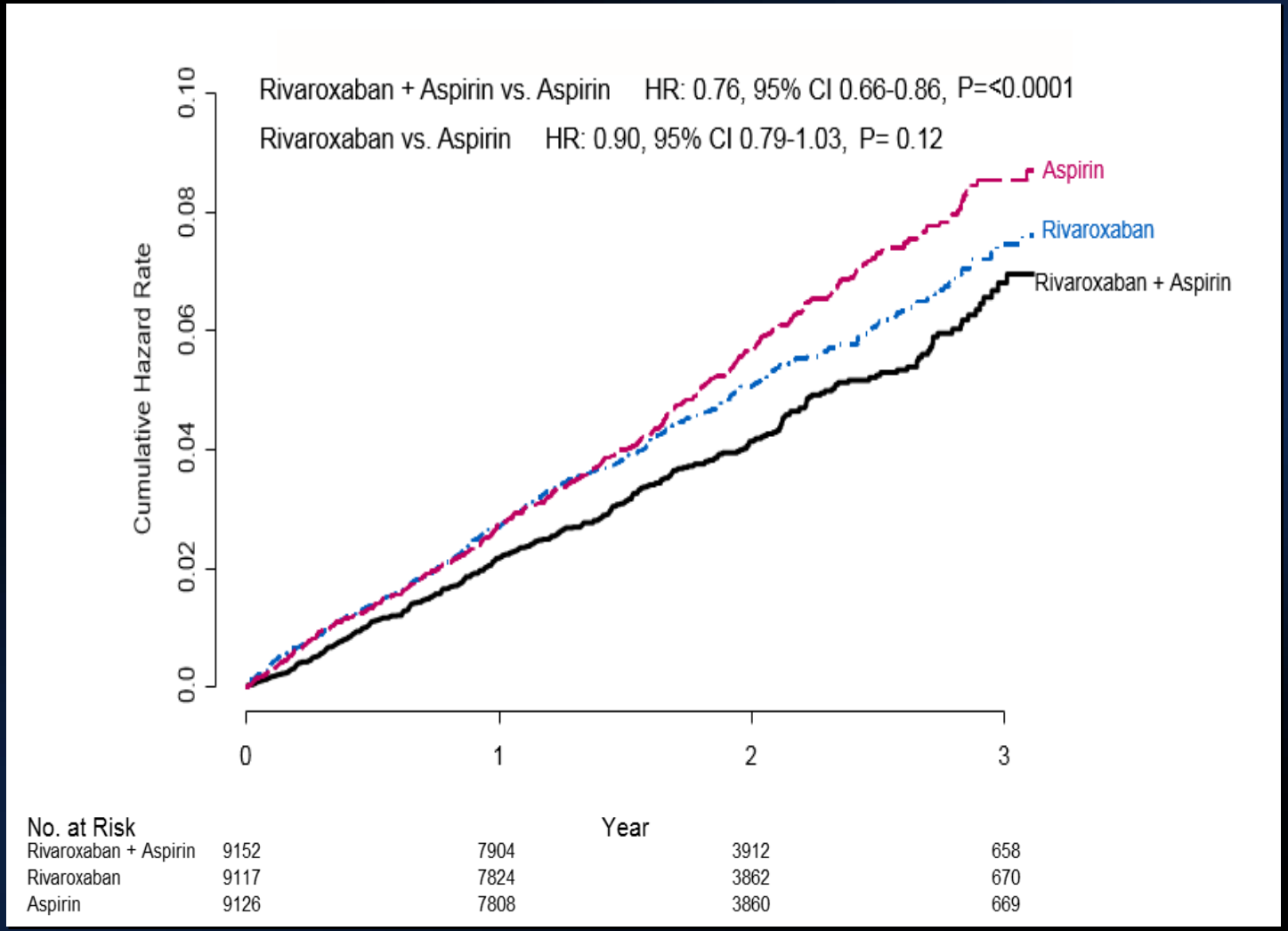
Primary: CV death, stroke, MI



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Secondary outcomes

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P*
CHD death, IS, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63-0.83)	<0.0001
CV death, IS, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65-0.85)	<0.0001
Mortality	313 (3.4%)	378 (4.1%)	0.82 (0.71-0.96)	0.01

*** pre-specified threshold P=0.0025**

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CAD and PAD
Subgroups for primary outcome

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin
	N (%)	N (%)	HR (95% CI)
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

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Major bleeding

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

*** symptomatic**

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Net clinical benefit

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

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Rivaroxaban 2.5 mg: Efficacy

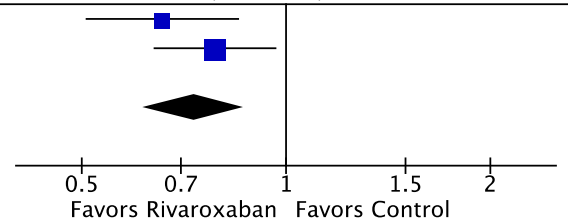
Pooled Analysis of ATLAS ACS 2–TIMI 51 and COMPASS

- **CV Death**

Study or Subgroup	Rivaroxaban Events	Rivaroxaban Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Rivaroxaban 2.5 mg BID (ATLAS ACS 2-TIMI 51)	94	5114	143	5113	40.2%	0.66 [0.51, 0.85]
Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)	160	9152	203	9126	59.8%	0.79 [0.64, 0.96]
Total (95% CI)		**14266**		**14239**	**100.0%**	**0.73 [0.62, 0.87]**
Total events	254		346			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.13, df = 1 (P = 0.29); I^2 = 12%

Test for overall effect: Z = 3.57 (P = 0.0004)

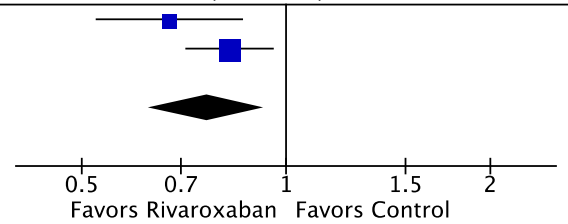


- **All-Cause Death**

Study or Subgroup	Rivaroxaban Events	Rivaroxaban Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Rivaroxaban 2.5 mg BID (ATLAS ACS 2-TIMI 51)	103	5114	153	5113	37.8%	0.67 [0.53, 0.86]
Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)	313	9152	378	9126	62.2%	0.83 [0.71, 0.96]
Total (95% CI)		**14266**		**14239**	**100.0%**	**0.76 [0.63, 0.93]**
Total events	416		531			

Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.95, df = 1 (P = 0.16); I^2 = 49%

Test for overall effect: Z = 2.71 (P = 0.007)



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Bewildering Number of Strategies in the ACS Patient with Atrial Fibrillation

- ASA Dose: None Low High 2
- ASA Duration (mos): 1 3 6 12 4
- Thineopyridine: None Clop Ticlid Pras Ticag 4
- Thienopyridine duration (mos): 1 3 6 12 4
- AC: None Warf Dabi Riva Apix Edox 5
- AC INR/Dose: Low High 2

1+8 = 9 ASA

1+16 = 17 Thieno

1+10 = 11 ACs

Permutations of Single, Dual or Triple Therapy as *Early Initial Therapy* (0,1,3,6 mos) following ACS: 9 X 17 X 11 = 1,683

Permutations of Single or Dual Therapy *Late After Early Therapy (0,1,3,6 mos)* following ACS: 1,683

Total Permutations *throughout one year:* 2.8 Million

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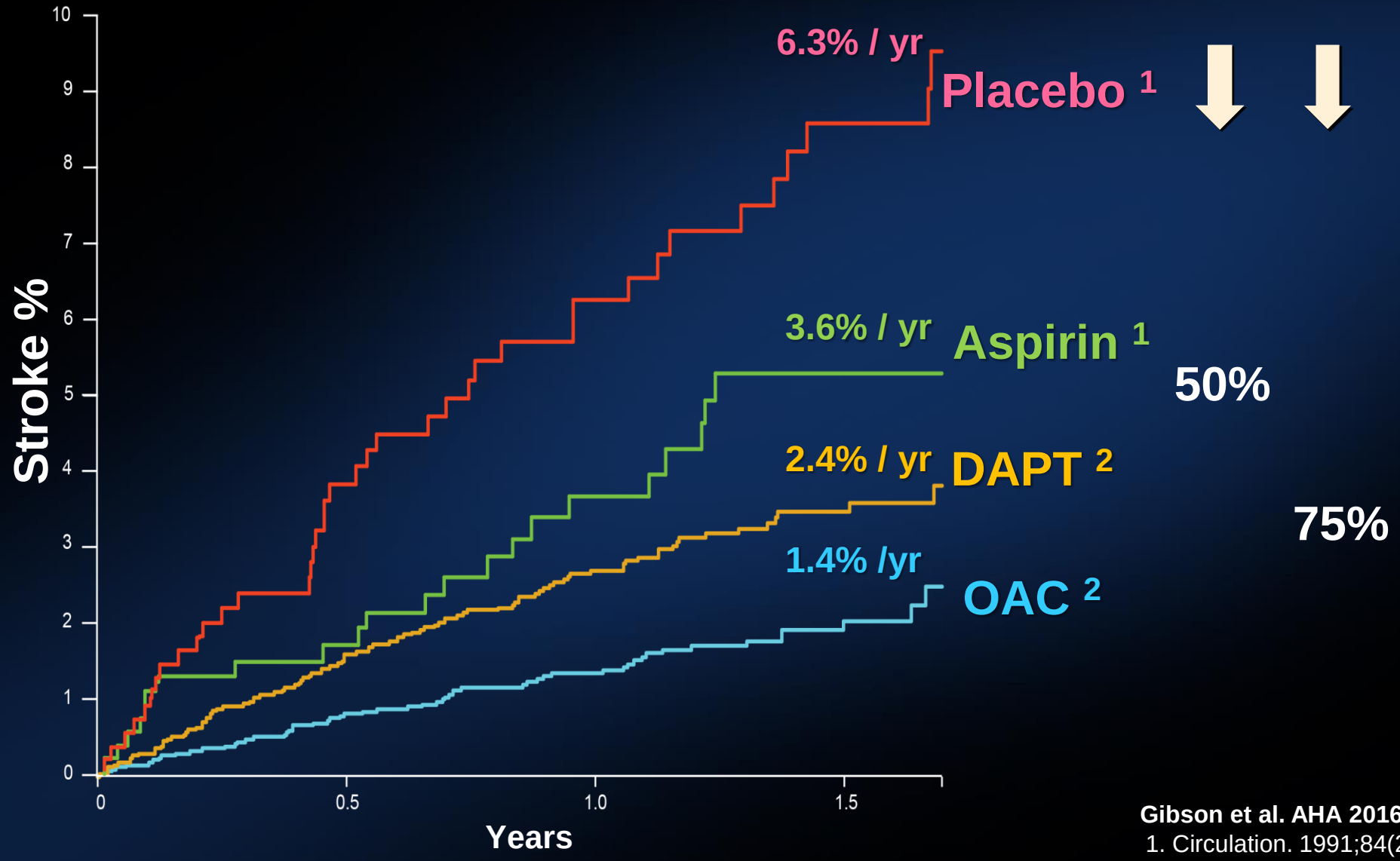
Gibson et al. AHA 2016

Gibson CM, J Am Coll Cardiol 2016

Aspirin and DAPT Do Reduce Risk Of Stroke Among Patients With Atrial Fibrillation



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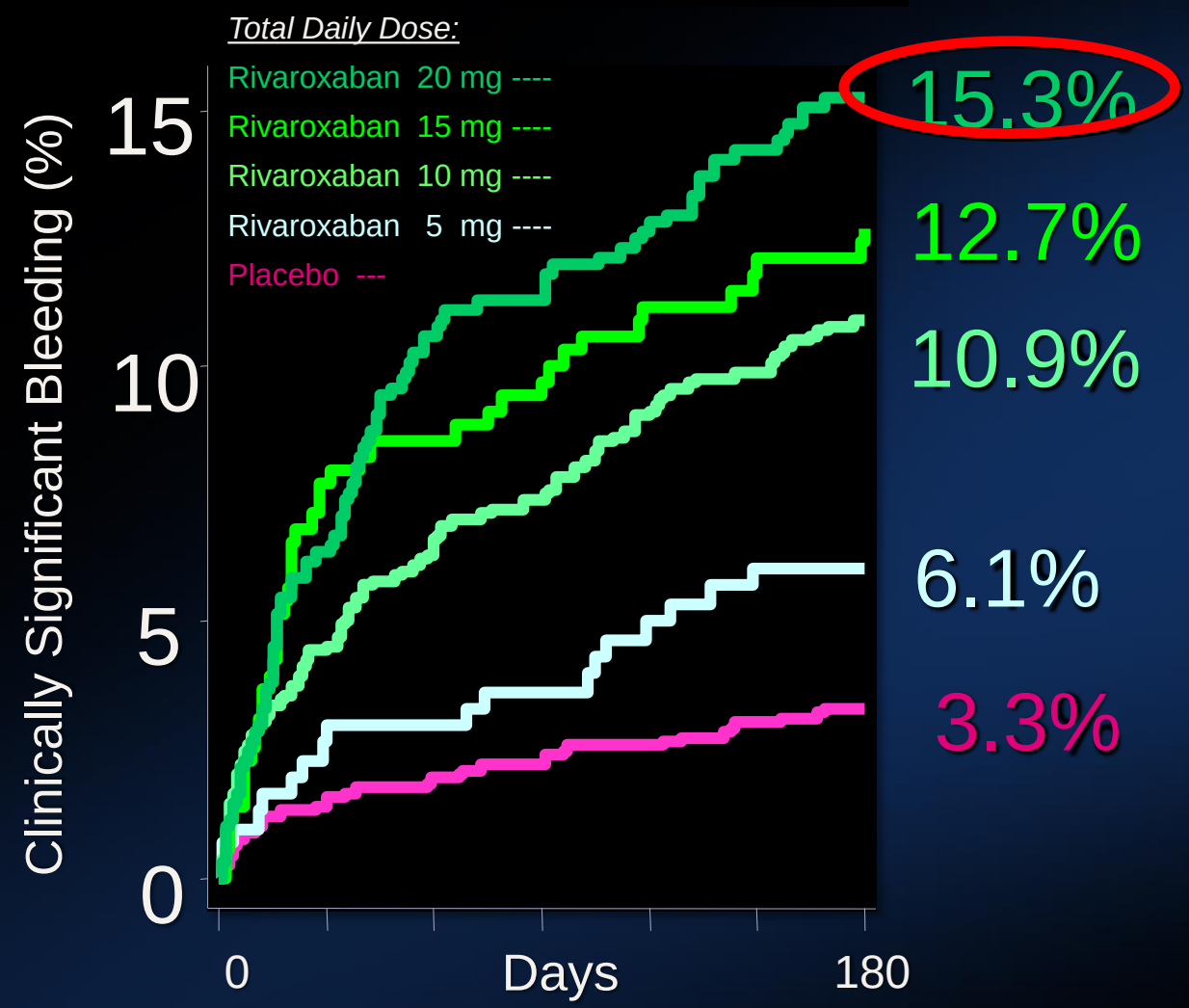
Gibson et al. AHA 2016

1. Circulation. 1991;84(2):527-39.
2. Lancet 2006;367(9526):1903-12.

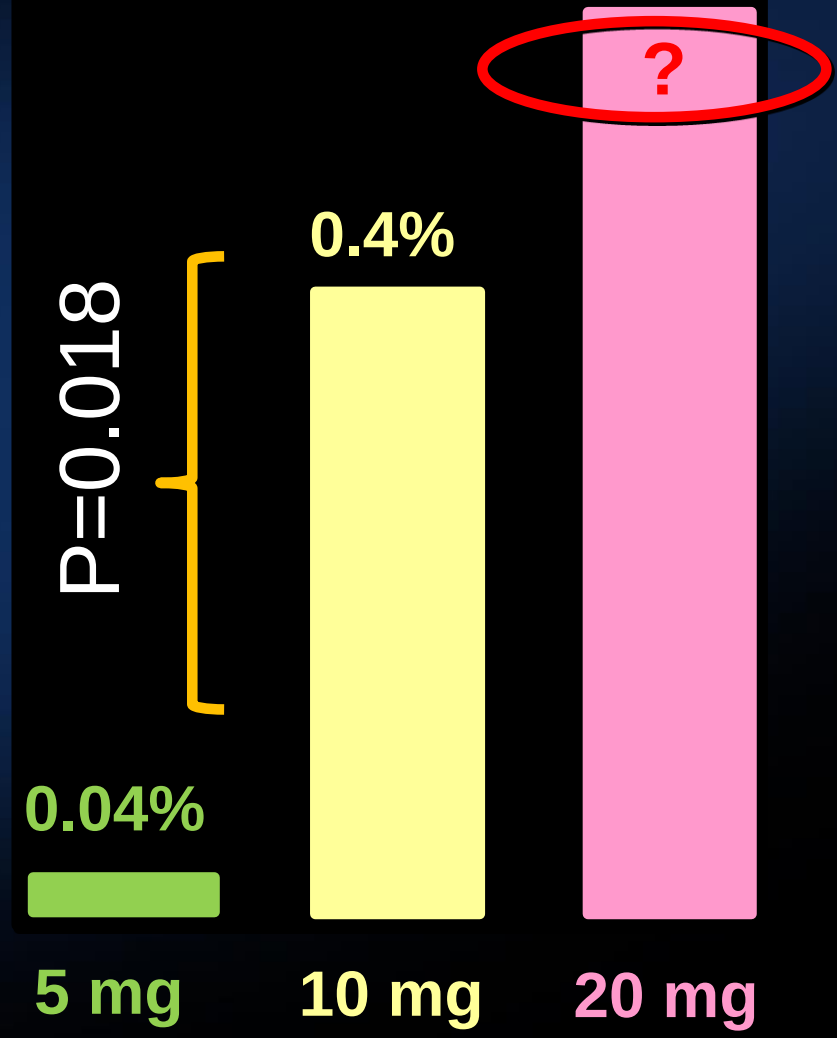
Rivaroxaban + DAPT Bleeding

TIMI Major, TIMI Minor, Bleed Req. Med. Attn.



Gibson CM, AHA 2008

Fatal Bleeding



Gibson CM, AHA 2011
STEMI cohort, p=0.044 in all ACS

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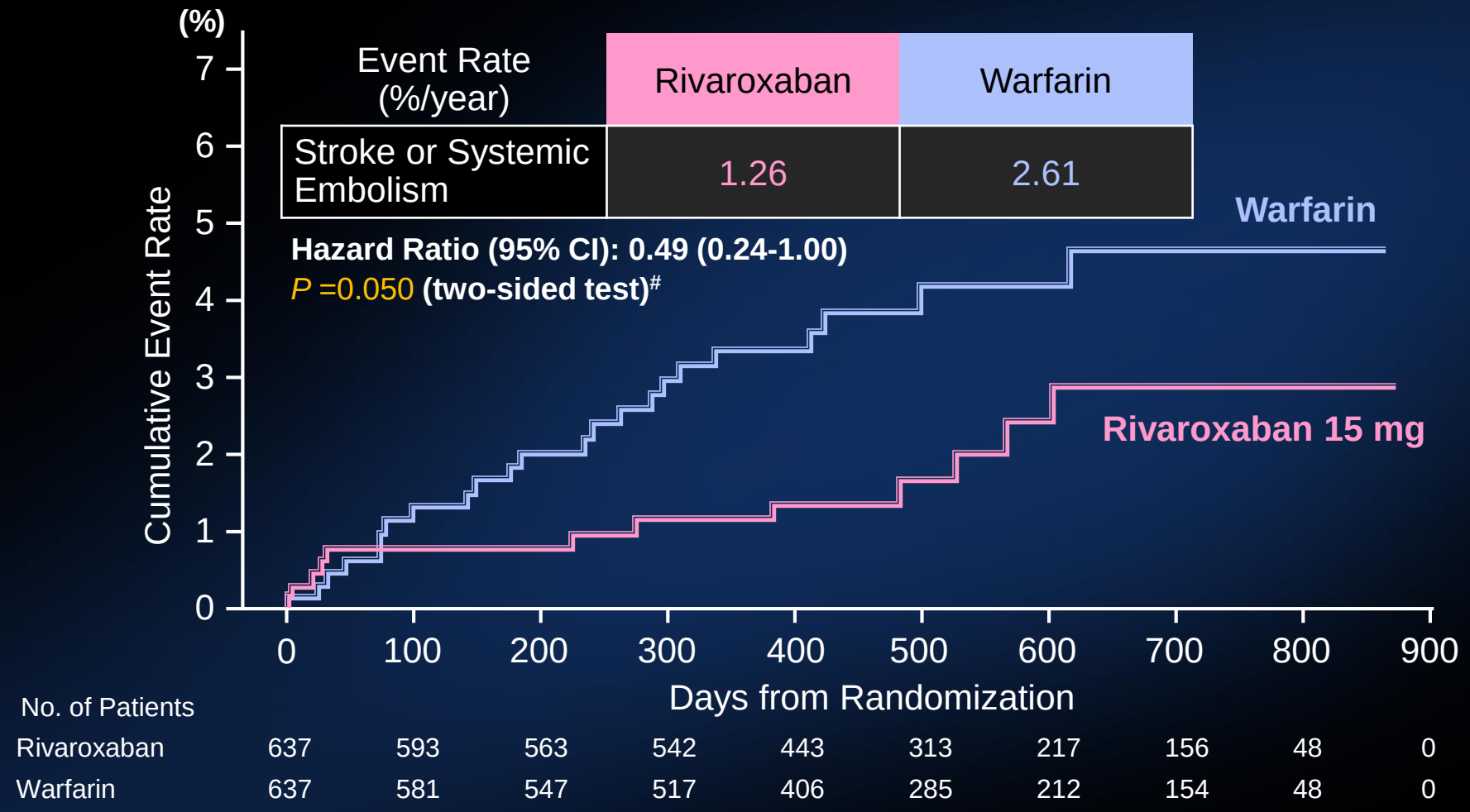
J-ROCKET AF: Primary Efficacy Endpoint

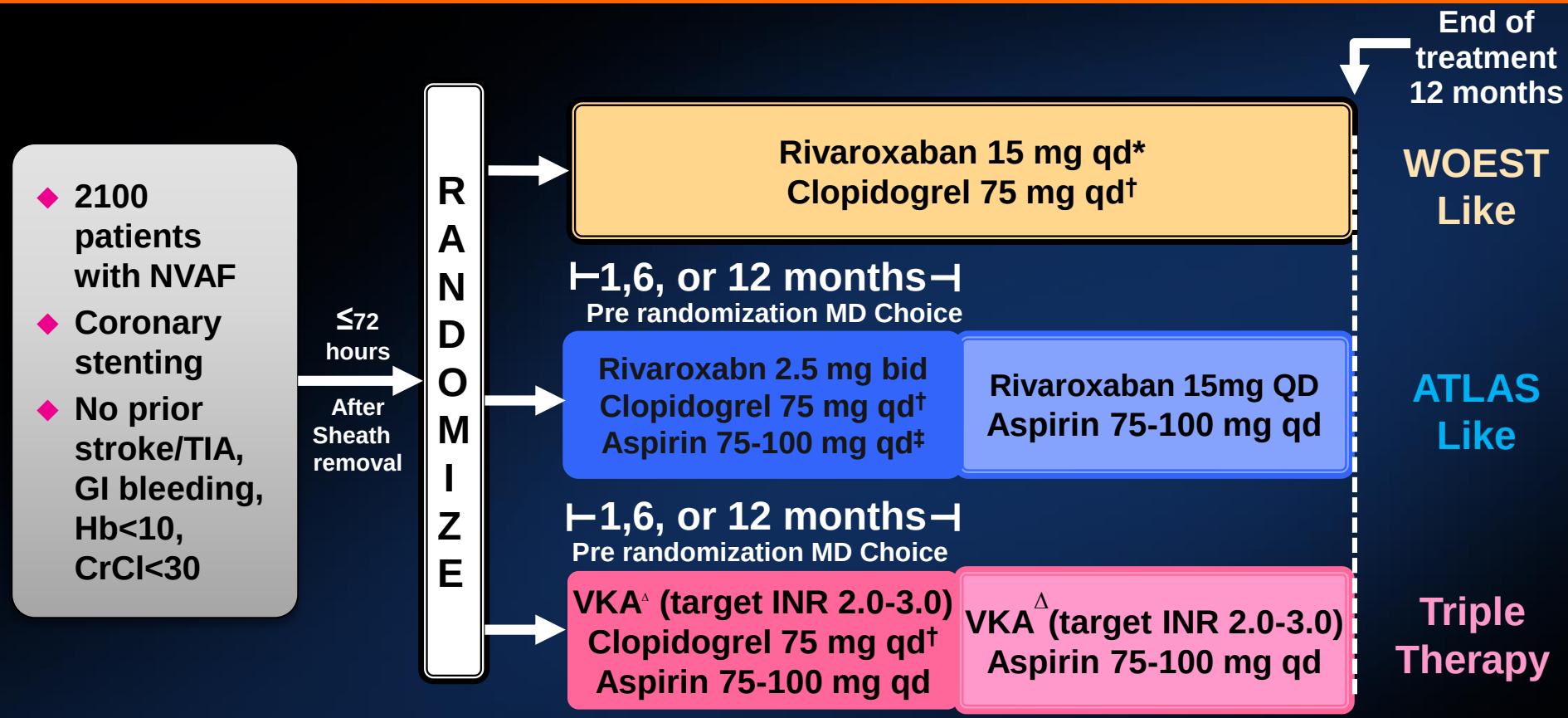


CI, confidence interval.
Per-protocol, on-treatment population
Analysis method: Cox proportional hazard model

Gibson et al. AHA 2016

Hori M et al. Circ J 2012; 76: 2104-2111

Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

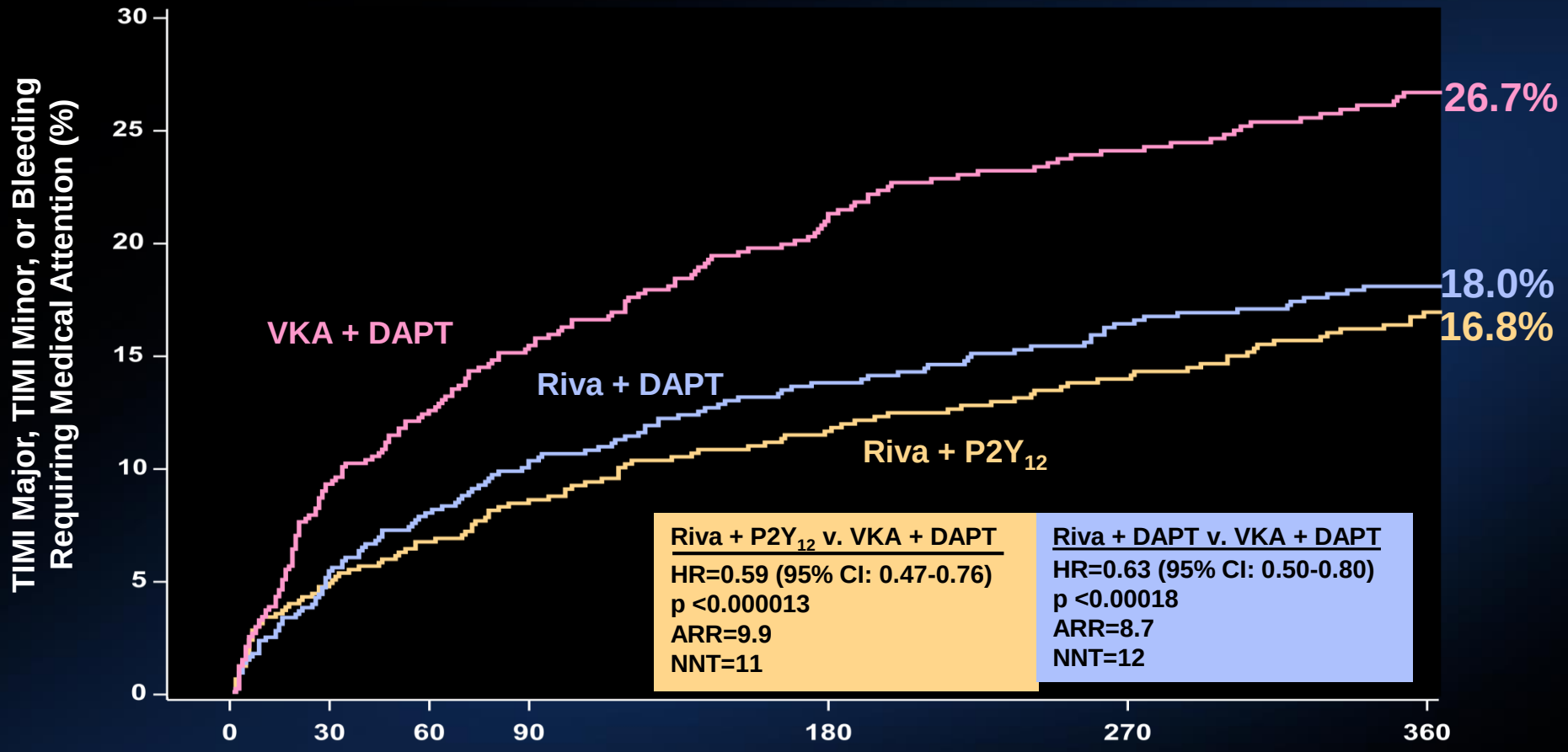
*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.

†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

‡Low-dose aspirin (75-100 mg/d). ∆ Open label VKA

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



No. at risk							
Riva + P2Y12	696	628	606	585	543	510	383
Riva + DAPT	706	636	600	579	543	509	409
VKA + DAPT	697	593	555	521	461	426	329

Gibson et al. AHA 2016

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA. Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model. Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

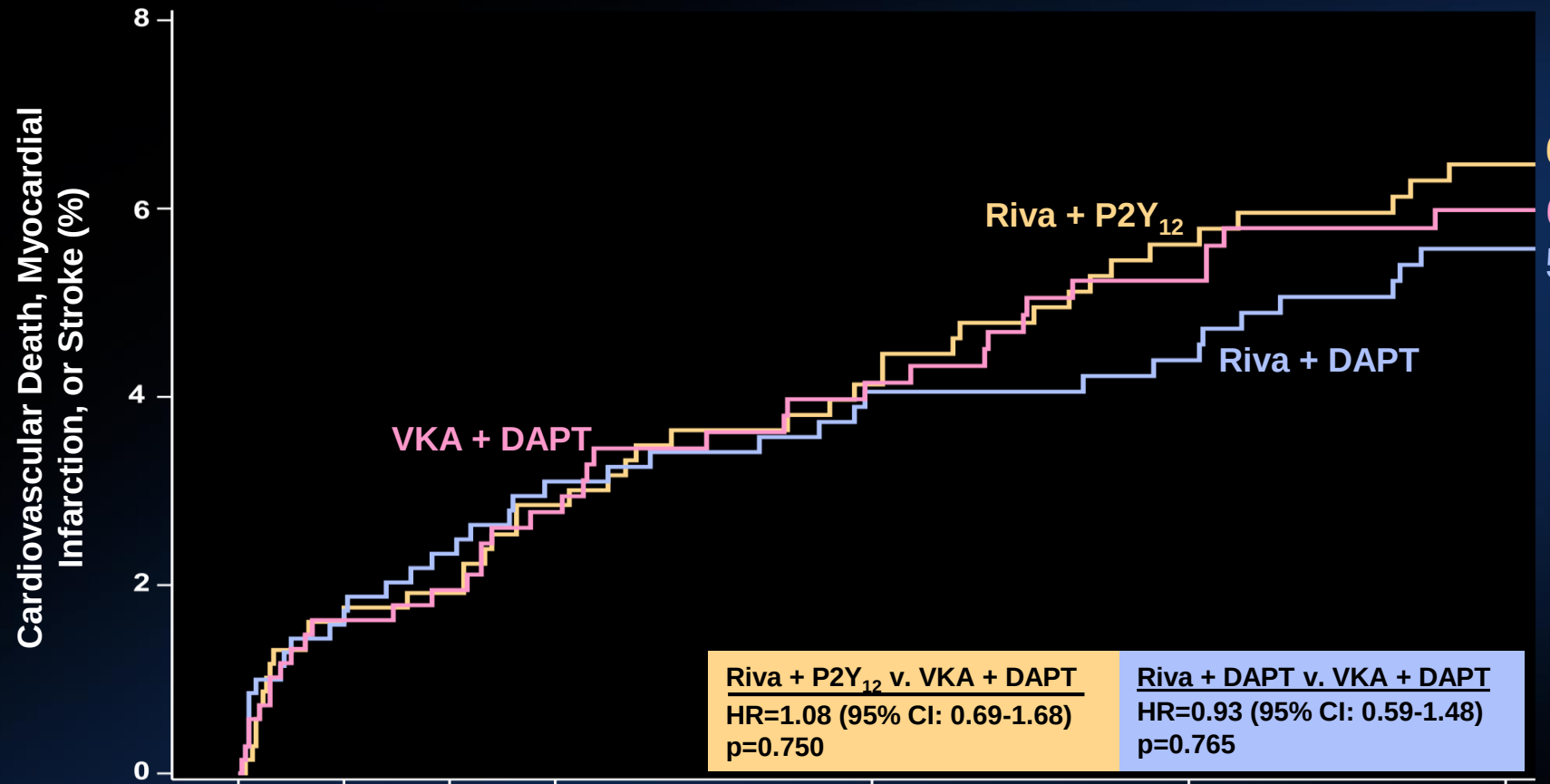
Bleeding Events Using GUSTO & BARC Scales (Pre-Specified Secondary Analyses)

	Riva + $P2Y_{12}$ (N = 696)	Riva + DAPT (N = 706)	Combined Riva (N = 1402)	VKA + DAPT (N = 697)	Group 1 vs Group 3 p-value	Group 2 vs Group 3 p-value	Combined vs Group 3 p-value
GUSTO classification							
Severe	7 (1.0%)	10 (1.4%)	17 (1.2%)	20 (2.9%)	**0.012**	0.060	**0.007**
Moderate	13 (1.9%)	10 (1.4%)	23 (1.6%)	9 (1.3%)	0.388	0.839	0.539
Mild	193 (27.7%)	214 (30.3%)	407 (29.0%)	255 (36.6%)	**<0.001**	**0.013**	**<0.001**
BARC classification							
Type 0	9 (1.3%)	14 (2.0%)	23 (1.6%)	10 (1.4%)	0.820	0.428	0.721
Type 1 (minimal)	125 (18.0%)	153 (21.7%)	278 (19.8%)	167 (24.0%)	**0.006**	0.307	**0.029**
Type 2 (actionable)	92 (13.2%)	91 (12.9%)	183 (13.1%)	126 (18.1%)	**0.013**	**0.007**	**0.002**
Type 3a	8 (1.2%)	7 (1.0%)	15 (1.1%)	12 (1.7%)	0.369	0.237	0.212
Type 3b (>5g, pressors)	13 (1.9%)	16 (2.3%)	29 (2.1%)	26 (3.7%)	**0.035**	0.108	**0.025**
Type 3c	2 (0.3%)	5 (0.7%)	7 (0.5%)	4 (0.6%)	0.687	>0.999	0.760
Type 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-
Type 5a	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	>0.999	0.497	.554
Type 5b (Definite Fatal)	1 (0.1%)	2 (0.3%)	3 (0.2%)	7 (1.0%)	0.070	0.106	**0.019**

BARC denotes Bleeding Academic Research Consortium, GUSTO Global Utilization Of Streptokinase and Tpa For Occluded Arteries
Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy.
Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke



No. at risk							
Riva + P2Y$_{12}$	694	648	633	621	590	562	430
Riva + DAPT	704	662	640	628	596	570	457
VKA + DAPT	695	635	607	579	543	514	408

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Composite of adverse CV events is composite of CV death, MI, and stroke.
Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.
6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines

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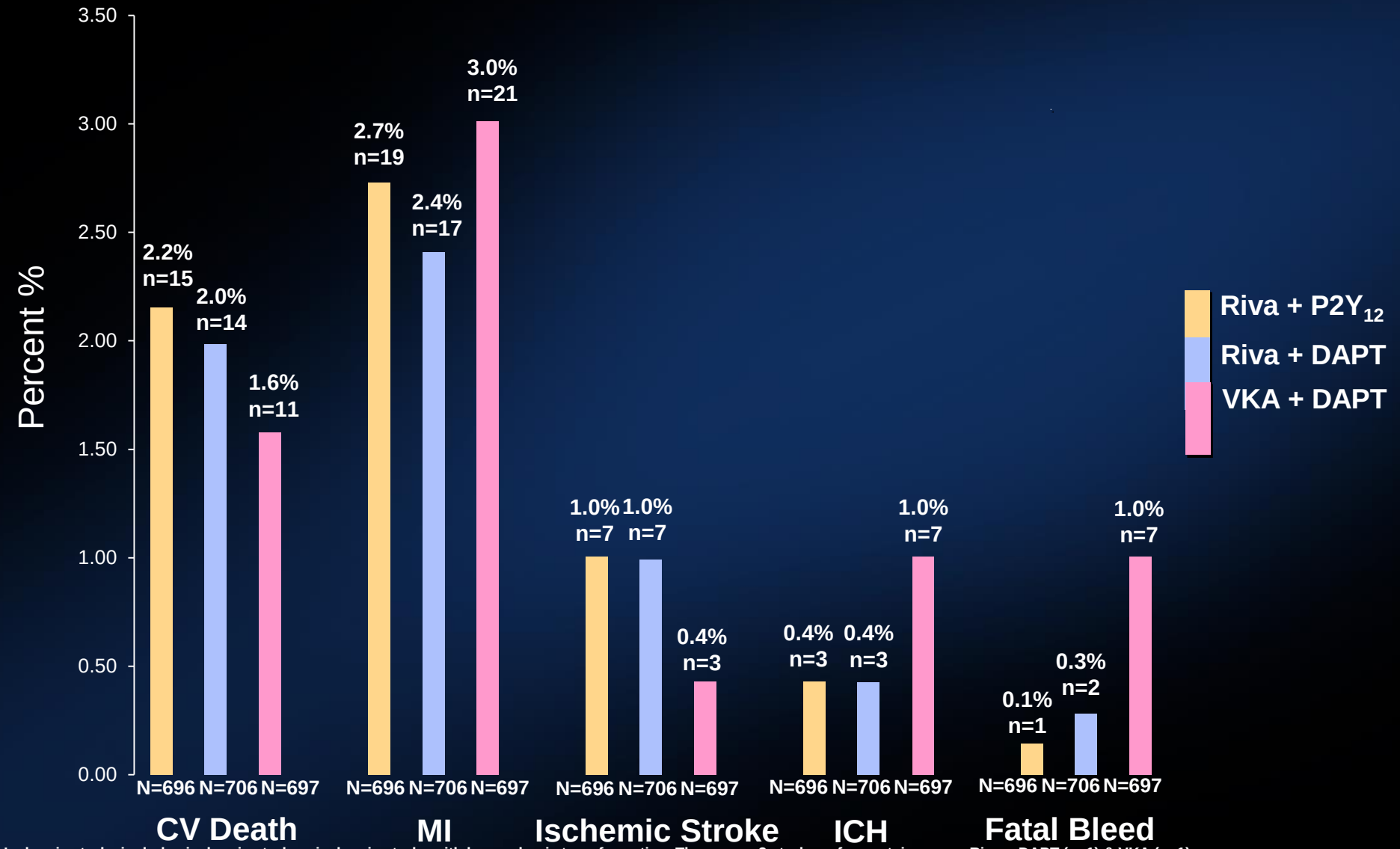
CV Death, MI, Ischemic Stroke, ICH or Fatal Bleed

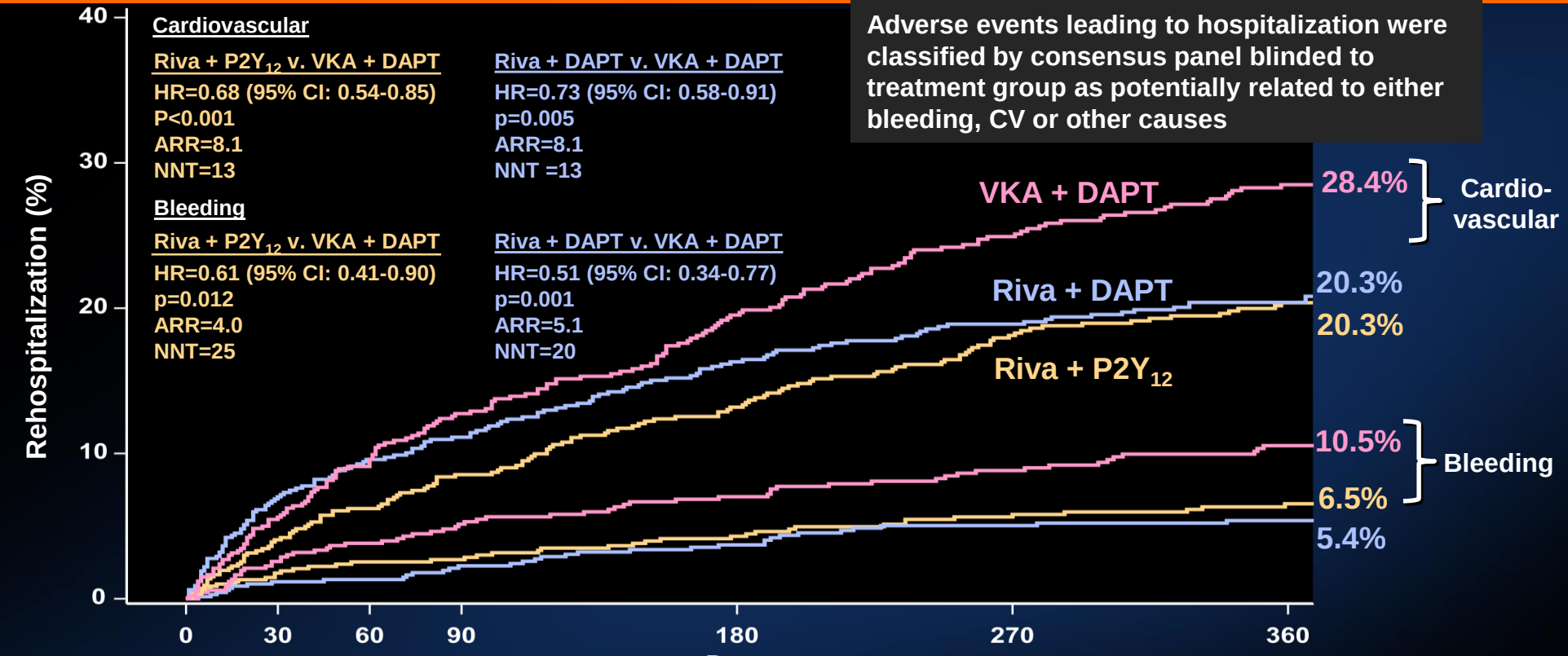


Ischemic stroke includes ischemic stroke + ischemic stroke with hemorrhagic transformation. There were 2 strokes of uncertain cause: Riva + DAPT (n=1) & VKA (n=1).
Fatal bleed was defined as BARC Type 5B bleeds

Gibson et al. AHA 2016

Hospitalization Related to Cardiovascular or Bleeding Event

Adverse events leading to hospitalization were classified by consensus panel blinded to treatment group as potentially related to either bleeding, CV or other causes



No. at risk cardiovascular							
Riva + P2Y12	696	632	607	586	537	491	367
Riva + DAPT	706	627	595	576	525	495	400
VKA + DAPT	697	609	560	517	457	410	314
No. at risk bleeding							
Riva + P2Y12	696	645	630	618	585	553	421
Riva + DAPT	706	659	636	621	590	560	453
VKA + DAPT	697	630	601	568	528	494	386

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Rehospitalizations do not include the index event and include the first rehospitalization after the index event.
Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.

Gibson et al. AHA 2016

Results of PIONEER & ReDual PCI

	Treatment n/N (%)	Control n/N (%)	RR (95% CI)
PIONEER AF-PCI (Riva combined) [1]	127/1398 (9.08)	64/695 (9.21)	0.99 (0.74–1.31)
Rivaroxaban 15 mg QD + $P2Y_{12}$ inhibitor	63/694 (9.08)	64/695 (9.21)	0.99 (0.71–1.37)
Rivaroxaban 2.5 mg BID + $P2Y_{12}$ inhibitor + ASA	64/704 (9.09)	64/695 (9.21)	0.99 (0.71–1.37)
RE-DUAL PCI (Dabi combined) [2]	239/1744 (13.70)	131/981 (13.35)	1.03 (0.84–1.25)
Dabigatran 110 mg BID + $P2Y_{12}$ inhibitor	149/981 (15.19)	131/981 (13.35)	1.14 (0.92–1.41)
Dabigatran 150 mg BID + $P2Y_{12}$ inhibitor	90/763 (11.80)	98/764 (12.83)	0.92 (0.70–1.20)

Data on file PERFUSE Study Group

1. *N Engl J Med 2016; 375:2423-2434. DOI:*
2. *10.1056/NEJMoa1708454*

2017 ESC Guidelines Update: Use of NOACs

When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AF trials should be considered.[c]	IIa	C
When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg *q.d.* may be used instead of rivaroxaban 20 mg *q.d.*[191]	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

Valgimigli M. ESC 2017, Updated Guidelines