Ticagrelor With AspIrin or ALone In HiGH-Risk Patients After Coronary InTervention for Acute Coronary Syndrome

TWILIGHT-ACS

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Disclosures

Affiliation/Financial Relationship	Company
Advisory board/personal fees	Amgen; AstraZeneca; Boston Scientific
Research Funding to Institution	AstraZeneca

Background

- The prevailing construct of dual antiplatelet therapy (DAPT) as the preferred treatment for patients with acute coronary syndromes (ACS) originated from clinical trials showing that the addition of an oral $P2Y_{12}$ inhibitor to aspirin significantly lowers recurrent ischemic events as compared with aspirin alone.[1,2]

- The benefits, or harms, of maintaining aspirin as a long-term component of DAPT in the setting of ACS remains unknown, however, as aspirin served as a background agent in earlier studies.

- Recent studies have suggested that aspirin-free strategies lower bleeding without increasing ischemic risk as compared with conventional DAPT in select patients undergoing percutaneous coronary intervention (PCI).[3,4,5]

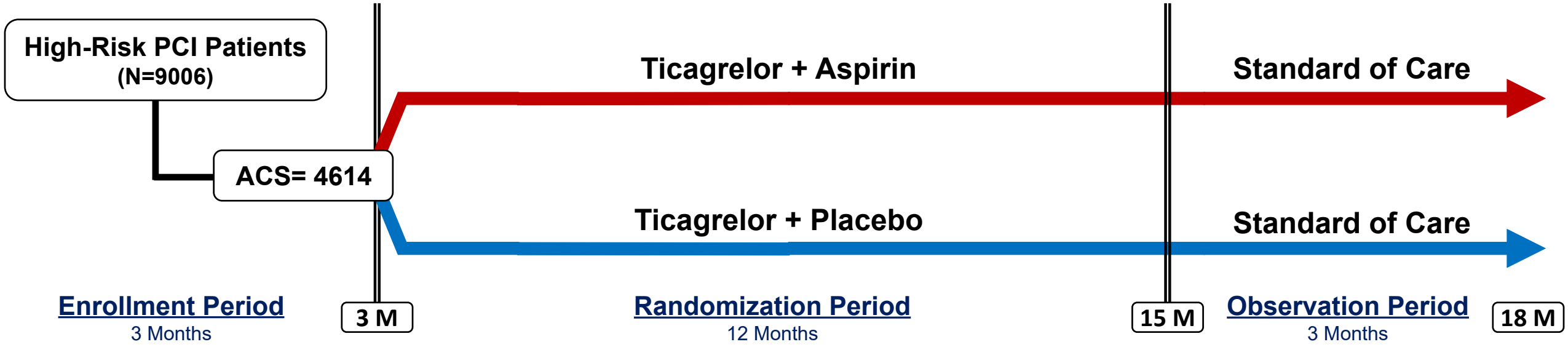
[1]Mehta et al., Lancet 2001; [2]Levine et al., JACC 2016; [3]Mehran et al., NEJM 2019; [4]Watanabe et al., JAMA 2019; [5]Hahn et al., JAMA 2019

Study Objective

To examine the effect of antiplatelet monotherapy with ticagrelor alone versus ticagrelor plus aspirin among patients with non-ST elevation acute coronary syndromes (NSTE-ACS) undergoing PCI with drug eluting stents who had already completed a 3-month course of DAPT

Study Design

- Randomized, double-blind placebo controlled trial in 187 sites and 11 countries
- High-risk patients underwent PCI and were treated with ticagrelor plus aspirin for 3 months
- Event-free and adherent patients were randomized to aspirin versus placebo and continued ticagrelor for an additional year



Inclusion/Exclusion Criteria

Must meet at least one clinical AND one angiographic criterion

Clinical criteria

- Age ≥65 years
- Female gender
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revasc)
- DM treated with medications or insulin
- CKD (eGFR <60ml/min/1.73m^2 or CrCl <60ml/min)

Angiographic criteria

- Multivessel CAD
- Target lesion requiring total stent length >30mm
- Thrombotic target lesion
- Bifurcation lesion(s) with Medina X,1,1 classification requiring ≥2 stents
- Left main (≥50%) or proximal LAD (≥70%) lesions
- Calcified target lesion(s) requiring atherectomy

Key Exclusions: STEMI; Salvage PCI; need for chronic oral anticoagulation; planned coronary revascularization

TWILIGHT-ACS: Methods

Target Population

Randomized TWILIGHT participants presenting with unstable angina or non-ST elevation MI (NSTE-ACS)

Endpoints

Primary: BARC 2, 3 or 5 bleeding between 0 - 12 months after randomization

Secondary: Non-fatal MI, stroke or all-cause death between 0 - 12 months after randomization

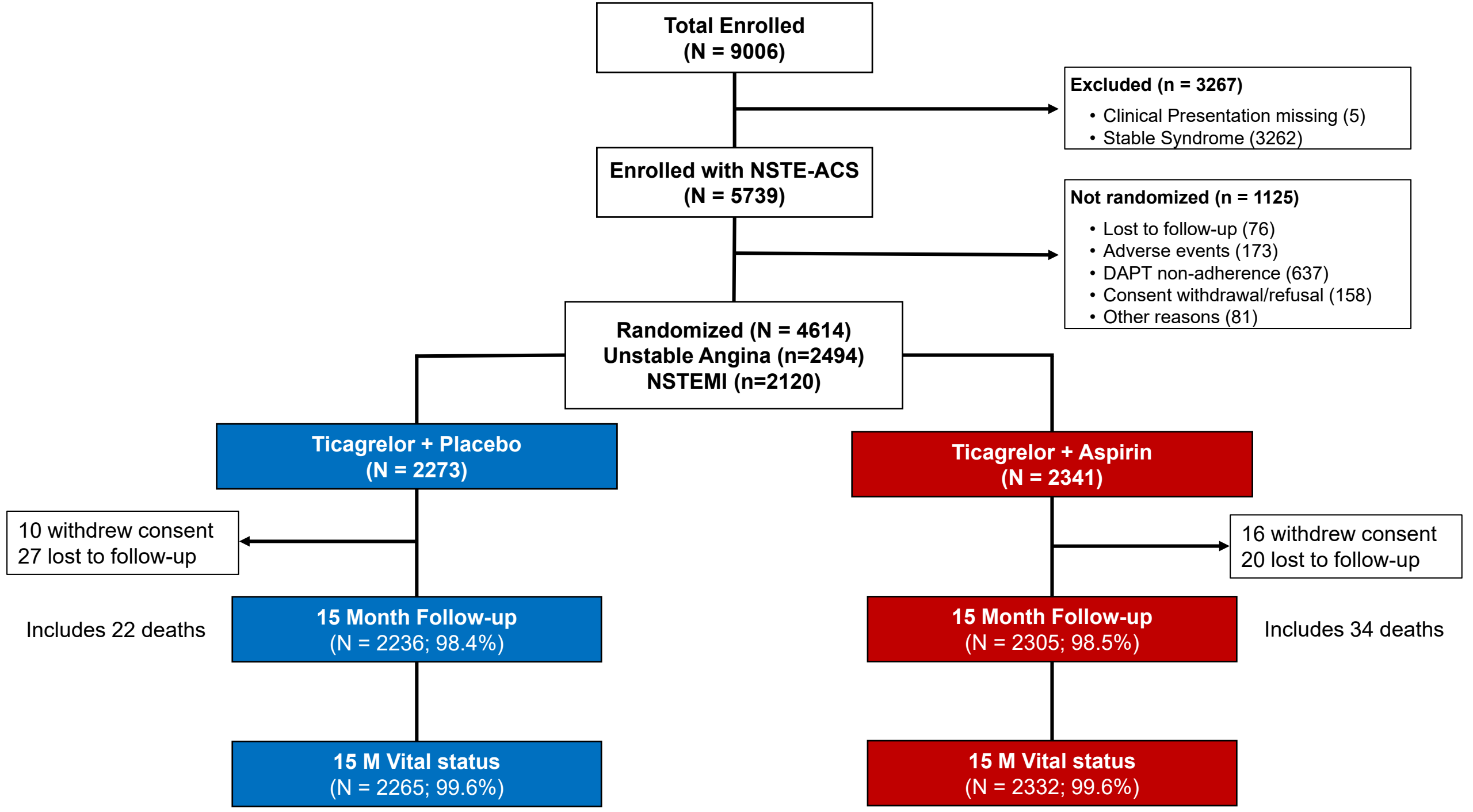
Analytic Approach

Survival analyses using the Kaplan-Meier method

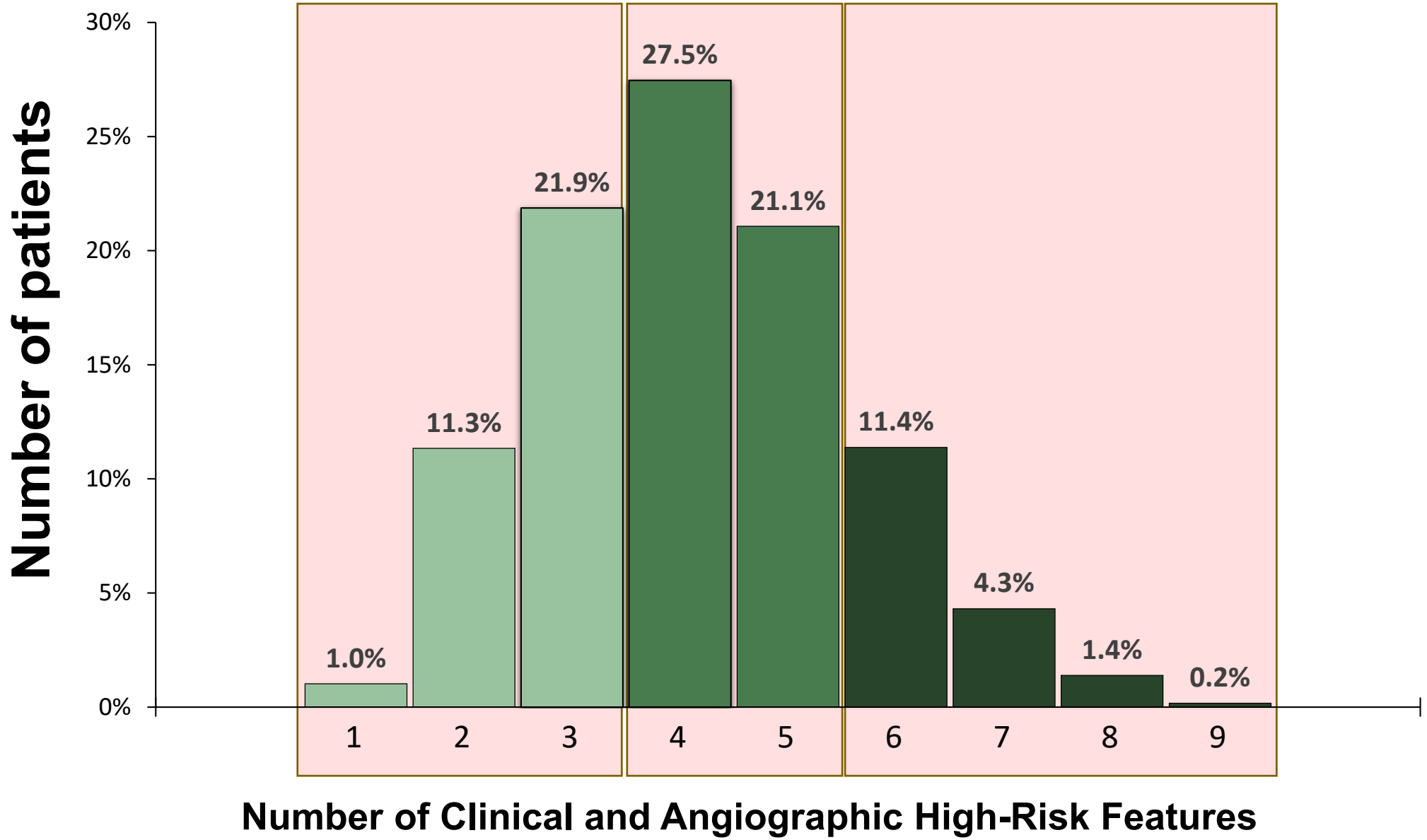
Hazard ratios and 95% confidence intervals (CI) generated using Cox regression

Treatment effect examined in relation to number of clinical and angiographic risk factors

Stratified analyses among those with unstable angina or NSTEMI


Total Enrolled
(N = 9006)
Excluded (n = 3267)
• Clinical Presentation missing (5)
• Stable Syndrome (3262)
Enrolled with NSTE-ACS
(N = 5739)
Not randomized (n = 1125)
• Lost to follow-up (76)
• Adverse events (173)
• DAPT non-adherence (637)
• Consent withdrawal/refusal (158)
• Other reasons (81)
Randomized (N = 4614)
Unstable Angina (n=2494)
NSTEMI (n=2120)
Ticagrelor + Placebo
(N = 2273)
Ticagrelor + Aspirin
(N = 2341)
10 withdrew consent
27 lost to follow-up
16 withdrew consent
20 lost to follow-up
Includes 22 deaths
15 Month Follow-up
(N = 2236; 98.4%)
15 Month Follow-up
(N = 2305; 98.5%)
Includes 34 deaths
15 M Vital status
(N = 2265; 99.6%)
15 M Vital status
(N = 2332; 99.6%)

TWILIGHT-ACS: Distribution of Pre-Specified Clinical and Angiographic High-Risk Features



TWILIGHT-ACS: Patient Characteristics

Baseline Demographics

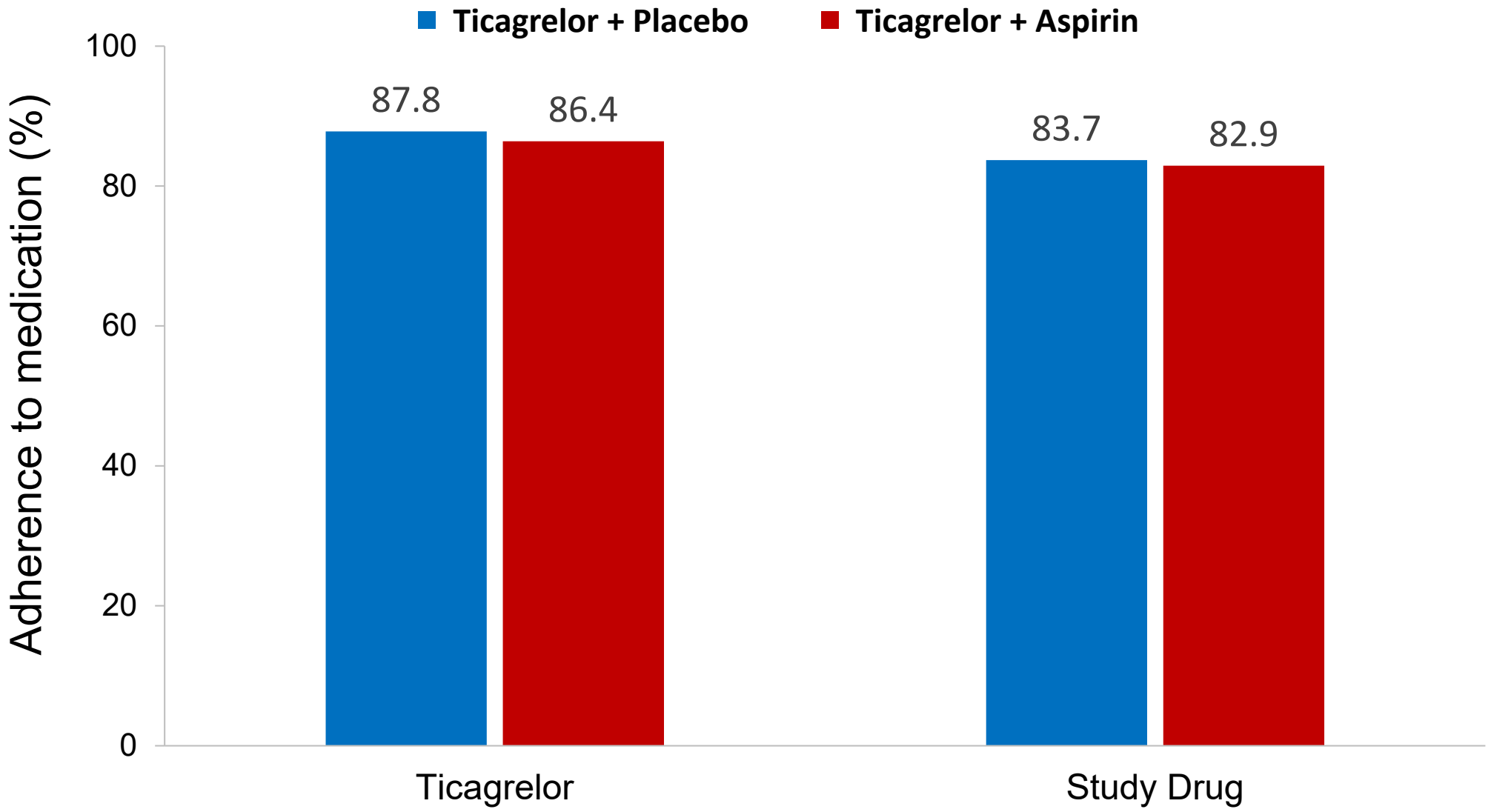
Variable	Tica + Placebo (n=2273)	Tica + Aspirin (n=2341)	p-value
Age, years [Mean ± SD]	64.2 ± 10.5	64.2 ± 10.6	0.99
Female sex	25.5%	24.8%	0.56
Age, years [Mean ± SD]	64.2 ± 10.5	64.2 ± 10.6	0.99
Diabetes Mellitus	35.6%	34.3%	0.36
Current Smoker	23.3%	26.6%	0.02
Previous MI	25.4%	25.2%	0.83
Anemia	19.9%	19.5%	0.76
Current Smoker	23.3%	26.6%	0.02
Previous MI	25.4%	25.2%	0.83
Previous PCI	34.2%	34.4%	0.91
Previous CABG	8.8%	8.5%	0.68

TWILIGHT-ACS: Patient Characteristics

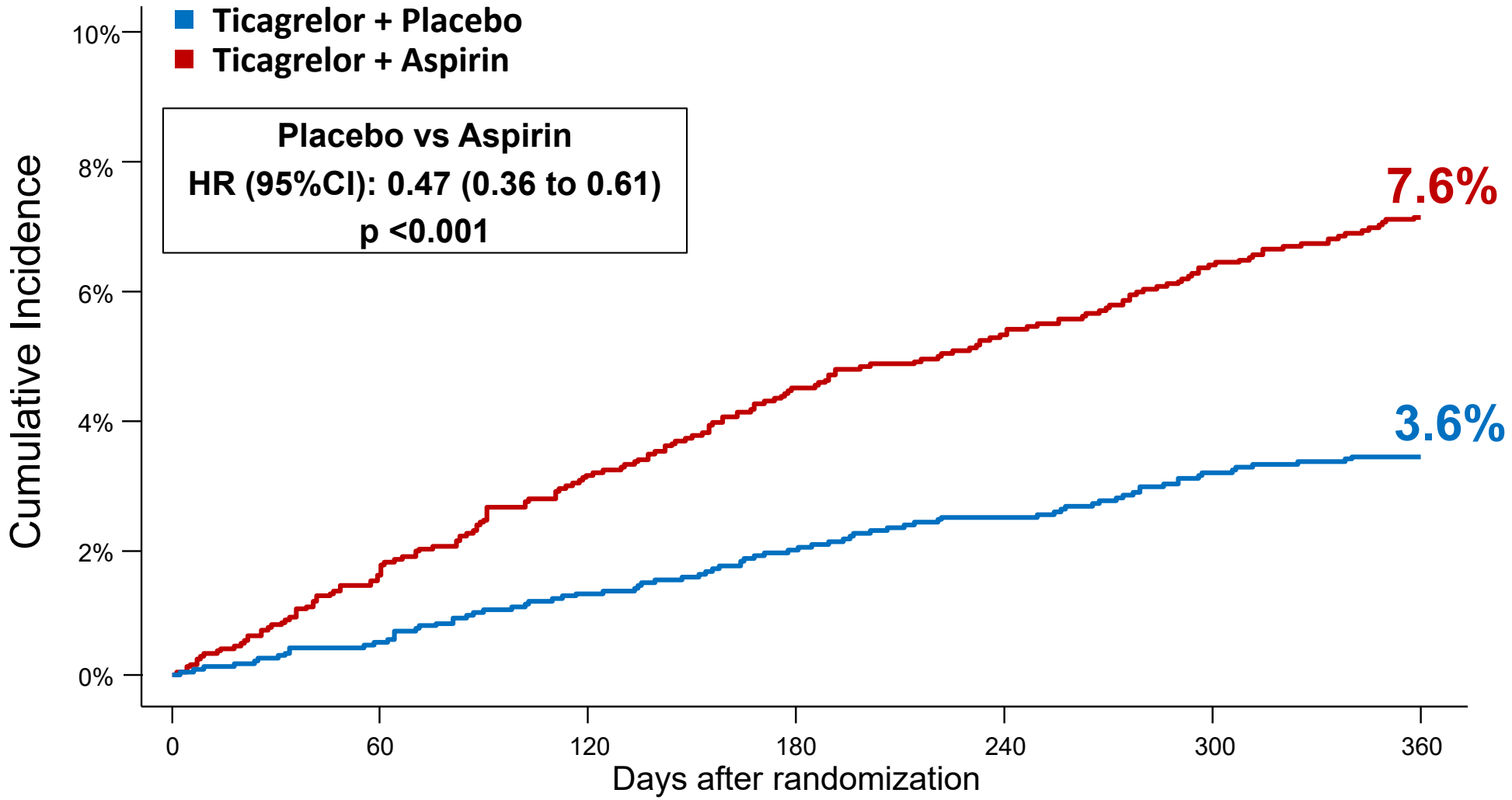
Procedural Details

Variable	Tica + Placebo (n=2273)	Tica + Aspirin (n=2341)	p-value
Radial access	76.7%	76.3%	0.78
Multivessel CAD	61.9%	59.5%	0.08
Multivessel CAD	61.9%	59.5%	0.08
Lesion morphology			
Thrombus	14.9%	15.4%	0.60
Calcification (Moderate/Severe)	12.0%	11.9%	0.92
Total stent length	40.5 ± 24.5	39.8 ± 24.6	0.35
Calcification (Moderate/Severe)	12.0%	11.9%	0.92
Any bifurcation	12.5%	12.6%	0.98
Chronic total occlusion	5.6%	6.1%	0.49
Total stent length	40.5 ± 24.5	39.8 ± 24.6	0.35

TWILIGHT-ACS: Adherence by Treatment Allocation



TWILIGHT-ACS: BARC 2, 3 or 5

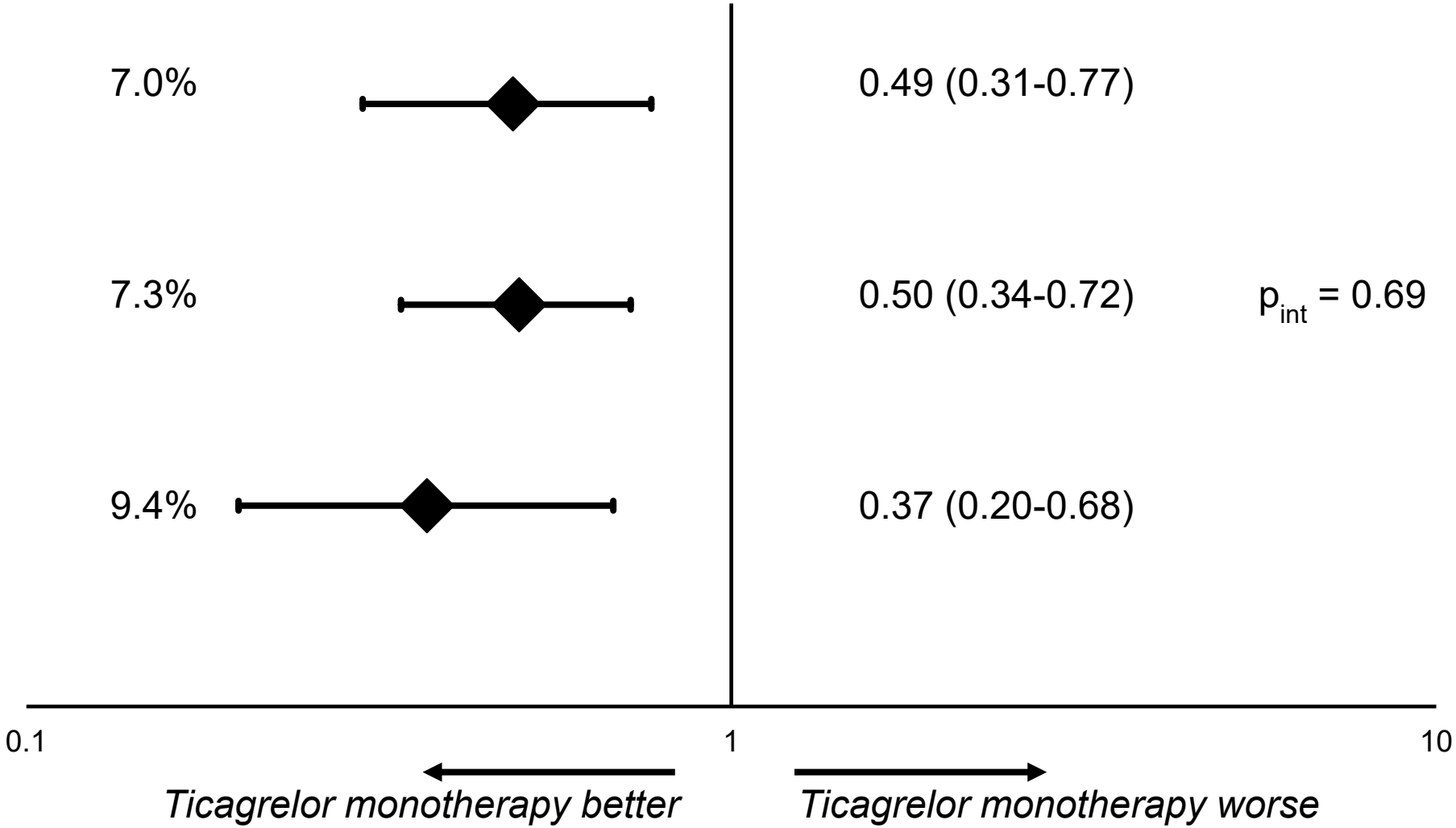


Number at risk

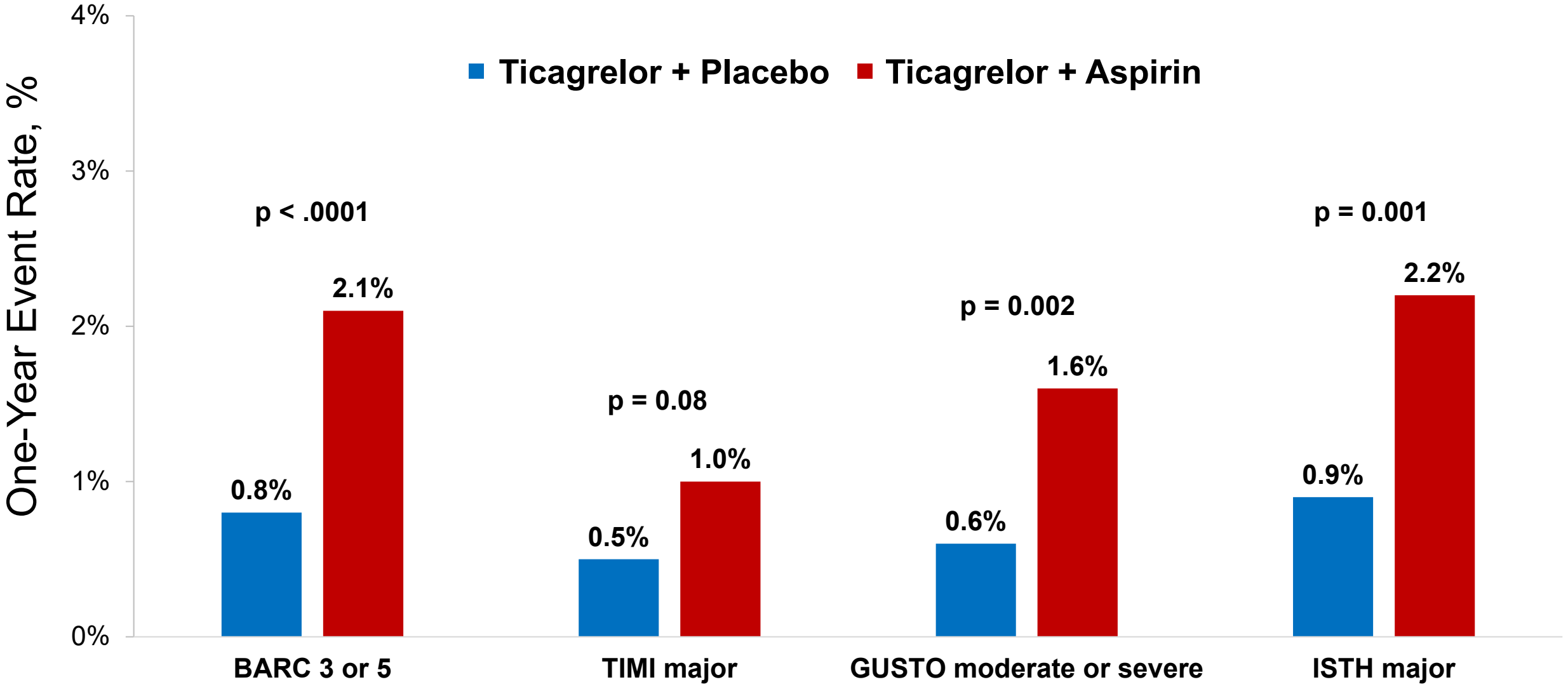
Ticagrelor plus Aspirin	2338	2285	2240	2197	2160	2129	2095
Ticagrelor plus Placebo	2269	2238	2215	2190	2159	2142	2130

TWILIGHT-ACS: BARC 2, 3 or 5 in Relation to Risk Factor Burden

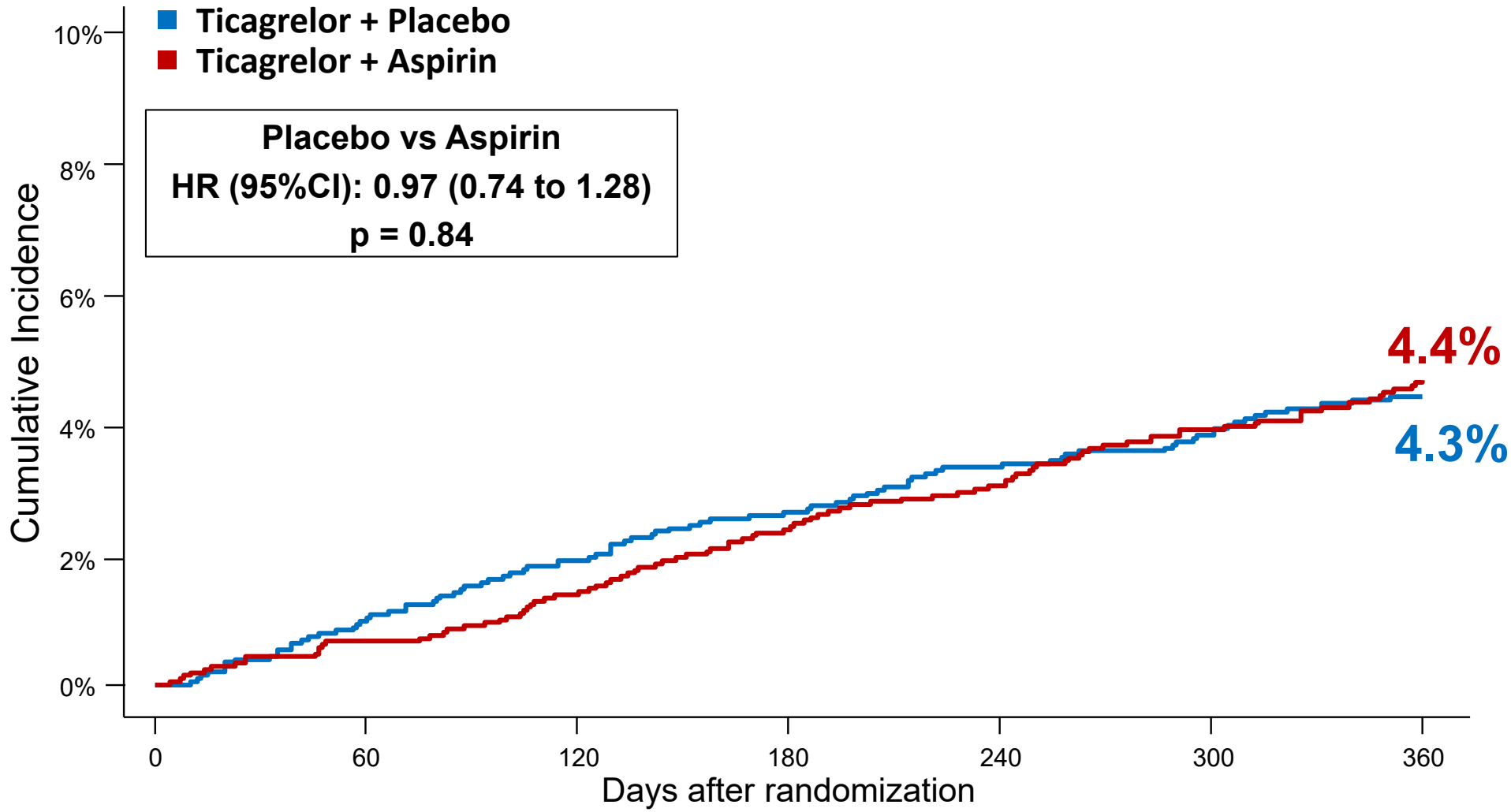
Number of Risk Factors	One-year rate (%) T+P	One-year rate (%) T+A	Hazard ratio (95% CI)	
1 – 3 (n=1579)	3.5%	7.0%	0.49 (0.31-0.77)	
4, 5 (n=2239)	3.7%	7.3%	0.50 (0.34-0.72)	p_{int} = 0.69
6 – 9 (n=796)	3.6%	9.4%	0.37 (0.20-0.68)	



TWILIGHT-ACS: Pre-Specified Bleeding Endpoints



TWILIGHT-ACS: Death, MI or Stroke

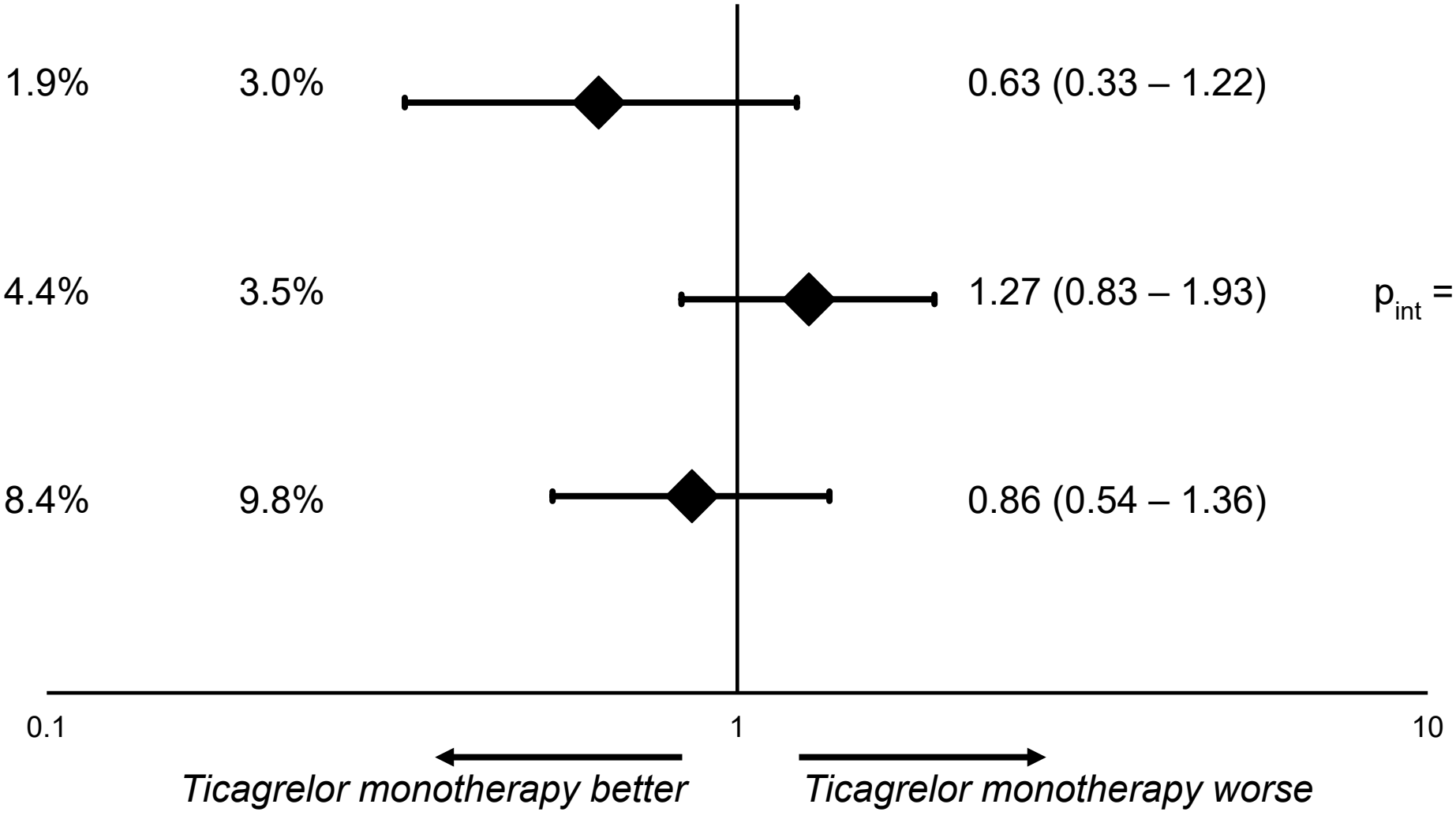


Number at risk

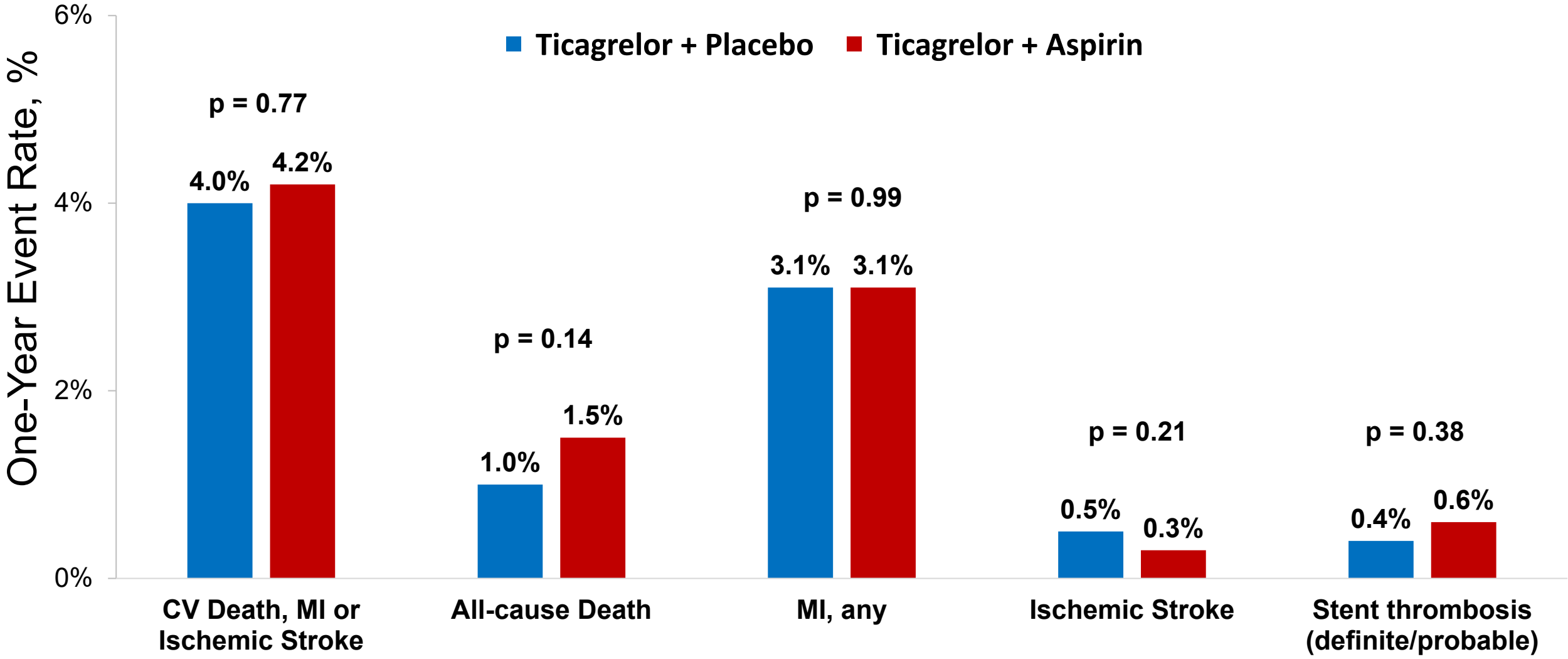
Ticagrelor plus Aspirin	2338	2208	2292	2169	2242	2223	2201
Ticagrelor plus Placebo	2269	2235	2215	2195	2167	2158	2143

TWILIGHT-ACS: Death, MI or Stroke in Relation to Risk Factor Burden

Number of Risk Factors	One-year rate (%) T+P	One-year rate (%) T+A	Hazard ratio (95% CI)	
1 – 3 (n=1579)	1.9%	3.0%	0.63 (0.33 – 1.22)	
4, 5 (n=2239)	4.4%	3.5%	1.27 (0.83 – 1.93)	p_{int} = 0.18
6 – 9 (n=796)	8.4%	9.8%	0.86 (0.54 – 1.36)	



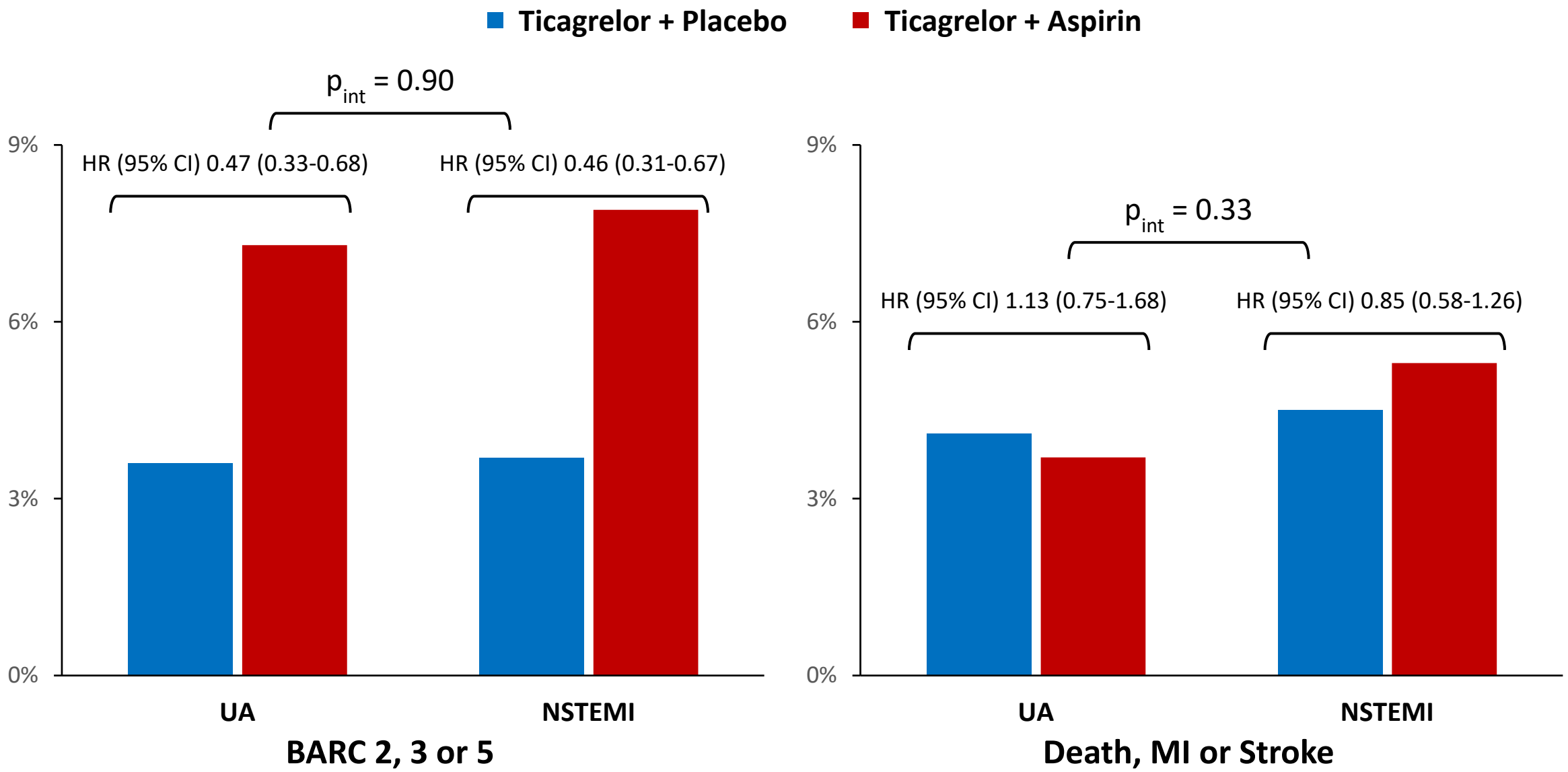
TWILIGHT-ACS: Pre-specified Ischemic Endpoints



TWILIGHT-ACS: Adjusted Hazards for Death, MI, Stroke

Variable	HR (95% CI)
Ticagrelor plus Placebo	1.02 (0.74-1.41)
Age, per year increase	1.01 (0.99-1.03)
Female sex	0.92 (0.62-1.36)
Troponin (+)	1.77 (1.23-2.55)
Established vascular disease	2.77 (1.94-3.97)
Atherectomy use	2.46 (1.19-5.1)
BARC type 3 or 5 Bleeding (time-updated covariate)	6.7 (3.1-14.6)
Bifurcation requiring 2 stents	1.32 (0.61-2.83)
Atherectomy use	2.46 (1.19-5.1)
Thrombotic lesion	1.09 (0.67-1.77)
Left main or LAD lesion	0.90 (0.61-1.34)
BARC type 3 or 5 Bleeding (time-updated covariate)	6.7 (3.1-14.6)

TWILIGHT-ACS: Stratified Analysis According to UA or NSTEMI



Limitations

- Extrapolating results to STEMI patients not possible given trial design.
- Generalizing to broader population of PCI patients without high-risk features pre-specified in TWILIGHT is limited.
- Use of ticagrelor as background antiplatelet agent thereby precluding inference for other $P2Y_{12}$ inhibitors.
- Lack of power to detect differences in the risk of important yet rare clinical events, such as stent thrombosis and stroke.

Conclusions

- Among patients with NSTE-ACS undergoing PCI with DES and who have completed a 3-month course of DAPT with ticagrelor plus aspirin, continued treatment with ticagrelor alone significantly lowers clinically relevant and major bleeding without increasing risk for ischemic events over one year.
- The effect of ticagrelor monotherapy with respect to bleeding and ischemic events is uniform across different levels of risk.
- Results are unchanged for patients presenting with UA or NSTEMI.
- Overall findings are concordant with the results of the primary trial.

Acknowledgement

We thank all country leaders, investigators, coordinators and study participants who made ***TWILIGHT*** possible!

Thank you!

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