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

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ClinicalTrials.gov Number: NCT02270242

Trial Hypothesis

In patients undergoing PCI who are at high risk for ischemic or hemorrhagic complications and who have completed a 3-month course of dual antiplatelet therapy with ticagrelor plus aspirin, continued treatment with ticagrelor monotherapy would be ***superior*** to ticagrelor plus aspirin with respect to clinically relevant bleeding and would not lead to ischemic harm.

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Trial Objectives

Primary Objective:

To determine the impact of SAPT (ticagrelor monotherapy) *versus* DAPT (ticagrelor plus aspirin) for 12 months in reducing **clinically relevant bleeding** (BARC 2, 3 or 5) among high-risk patients who have undergone successful PCI.

Secondary Objective:

To determine the impact of SAPT (ticagrelor monotherapy) *versus* DAPT (ticagrelor plus aspirin) for 12 months on **major ischemic adverse events** (all-cause death, non-fatal MI or stroke) among high-risk patients who have undergone successful PCI.

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TWILIGHT Inclusion Criteria

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

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TWILIGHT Exclusion Criteria

- Under 18 years of age
- Contraindication to aspirin or ticagrelor
- Planned surgery within 90 days
- Planned coronary revascularization (surgical or percutaneous) within 90 days
- Need for chronic oral anticoagulation
- Prior stroke
- Dialysis-dependent renal failure
- Active bleeding or extreme-risk for major bleeding
- Salvage PCI or STEMI presentation
- Liver cirrhosis
- Life expectancy <1 year
- Unable or unwilling to provide informed consent
- Women of child bearing potential
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
- Platelet count <100,000 mm^3
- Requiring ongoing treatment with aspirin ≥325 mg daily

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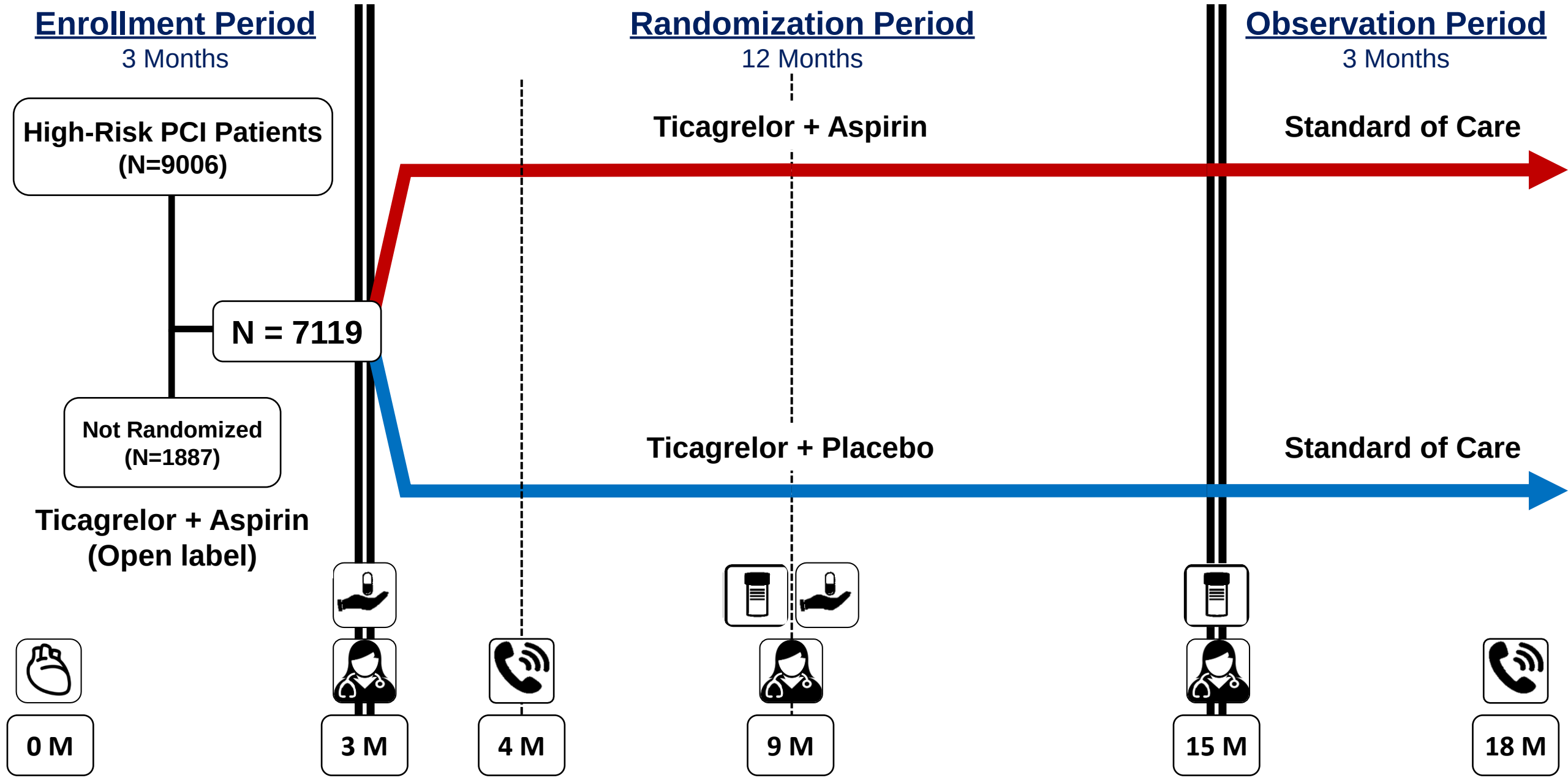
Study Design



Study Endpoint

Primary Endpoint (Bleeding): Superiority Hypothesis

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

Key Secondary Endpoint (Ischemic): Non-inferiority Hypothesis

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

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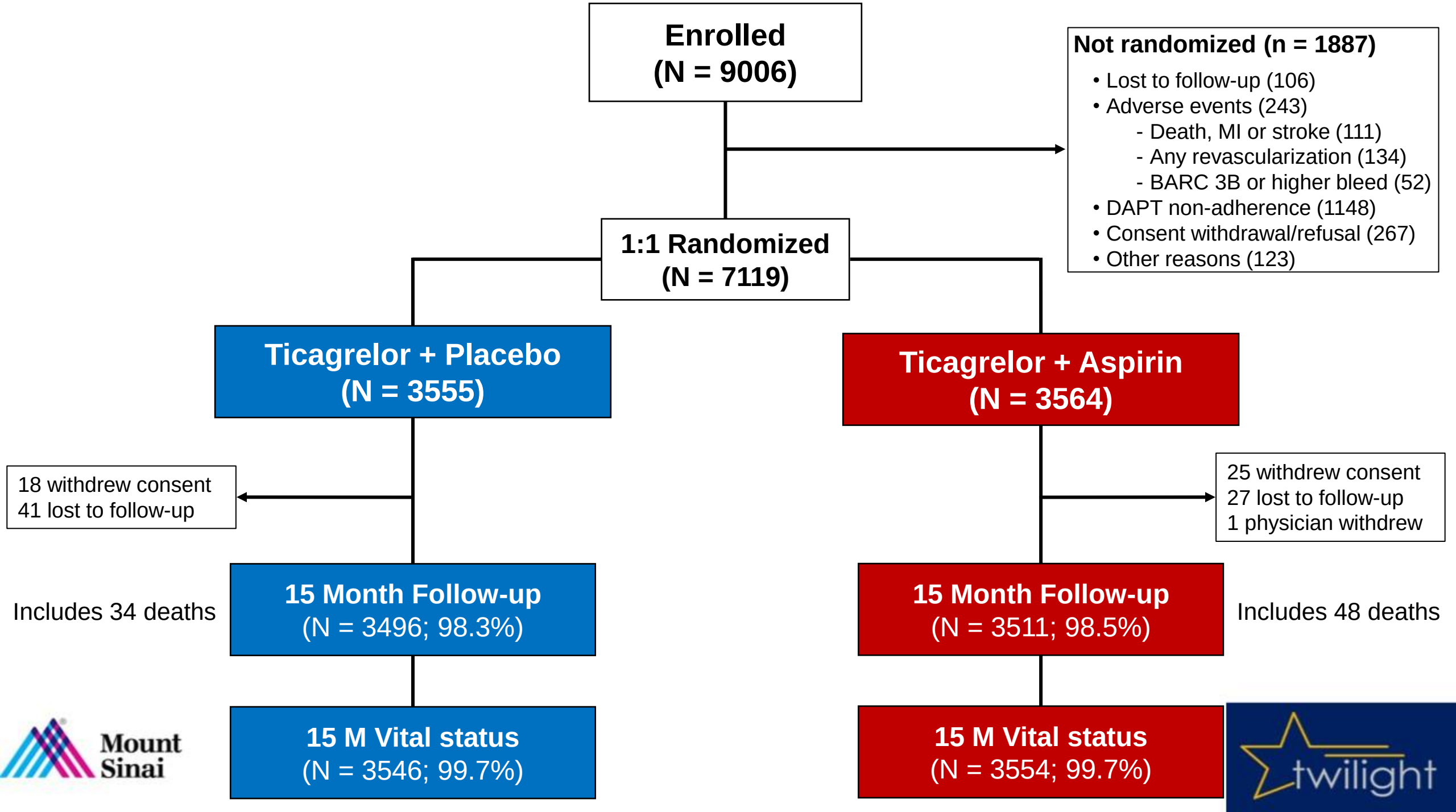
Enrolled
(N = 9006)
Not randomized (n = 1887)
• Lost to follow-up (106)
• Adverse events (243)
- Death, MI or stroke (111)
- Any revascularization (134)
- BARC 3B or higher bleed (52)
• DAPT non-adherence (1148)
• Consent withdrawal/refusal (267)
• Other reasons (123)
1:1 Randomized
(N = 7119)
Ticagrelor + Placebo
(N = 3555)
Ticagrelor + Aspirin
(N = 3564)
18 withdrew consent
41 lost to follow-up
25 withdrew consent
27 lost to follow-up
1 physician withdrew
Includes 34 deaths
15 Month Follow-up
(N = 3496; 98.3%)
15 Month Follow-up
(N = 3511; 98.5%)
Includes 48 deaths
15 M Vital status
(N = 3546; 99.7%)
15 M Vital status
(N = 3554; 99.7%)
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Patient Characteristics

Baseline Demographics

Variable	Tica + Placebo (N = 3555)	Tica + Aspirin (N = 3564)
Age, years [Mean ± SD]	65.2 ± 10.3	65.1 ± 10.4
Female sex	23.8%	23.9%
Nonwhite race	31.2%	30.5%
BMI, kg/m^2	28.6 ± 5.5	28.5 ± 5.6
Diabetes Mellitus	37.1%	36.5%
Insulin requiring	9.4%	10.5%
Chronic Kidney Disease	16.8%	16.8%
Anemia	19.8%	19.1%
ACS presentation	64.0%	65.7%
Current Smoker	20.4%	23.1%
Previous MI	28.7%	28.6%
Previous PCI	42.3%	42.0%
Previous CABG	10.2%	9.8%
Previous major bleed	0.9%	0.9%

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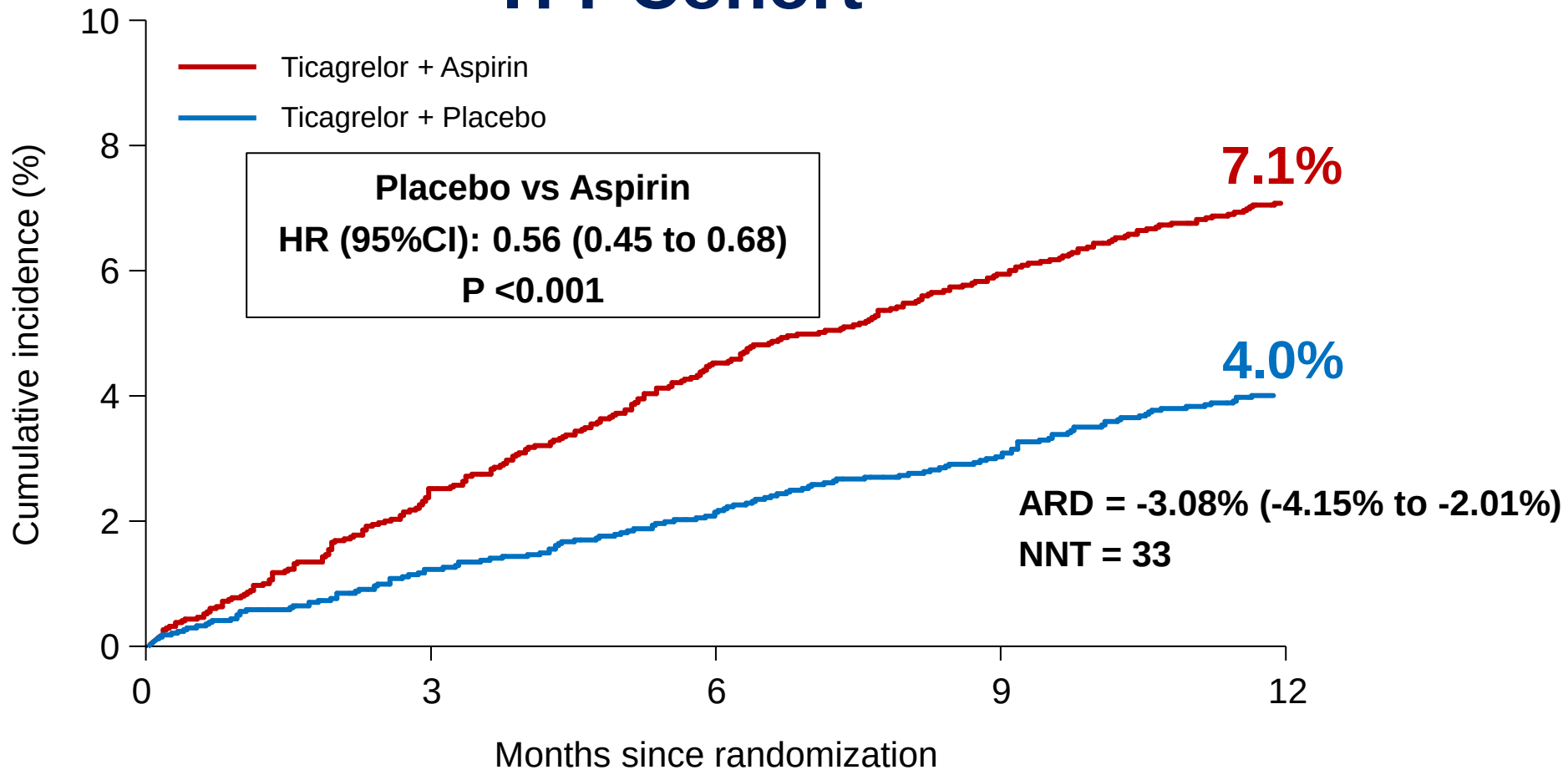
Primary Endpoint: BARC 2, 3 or 5 Bleeding

ITT Cohort



No. at risk					
Ticagrelor + Aspirin	3564	3454	3357	3277	3213
Ticagrelor + Placebo	3555	3474	3424	3366	3321

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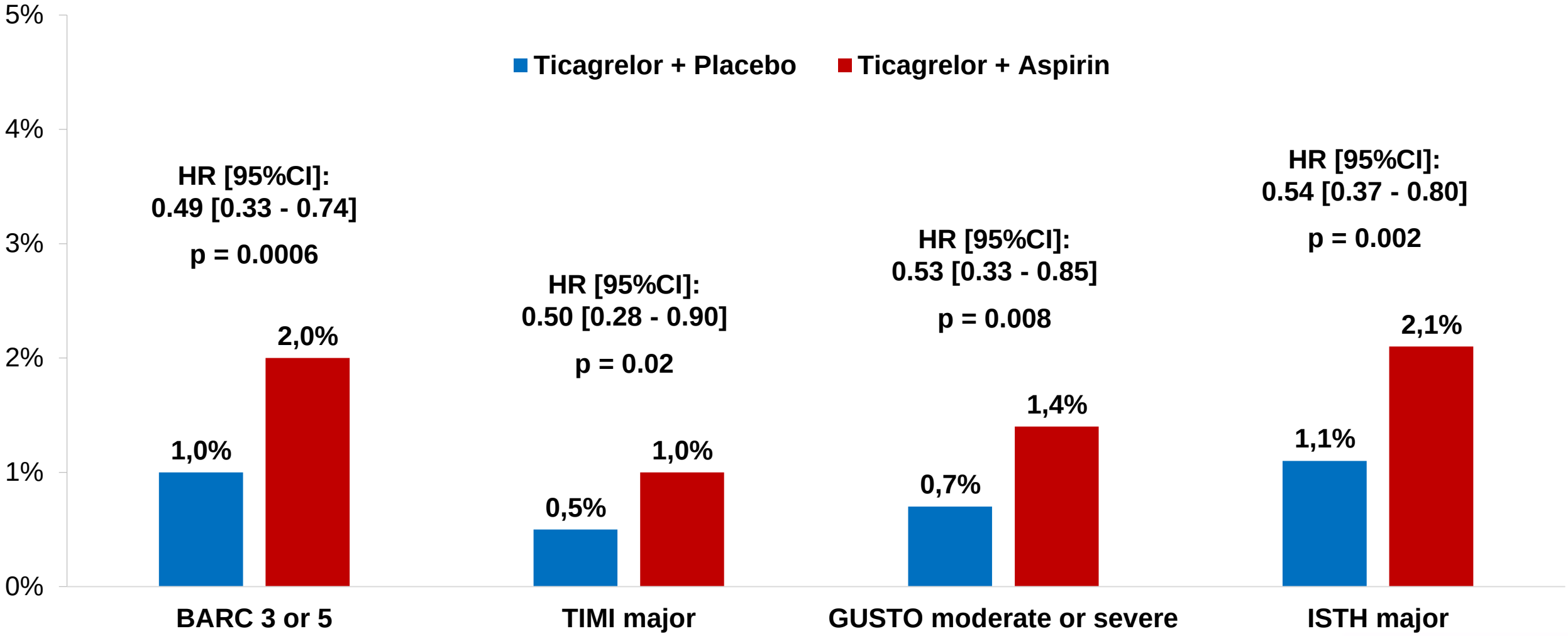
Prespecified Bleeding Endpoints (ITT Cohort)



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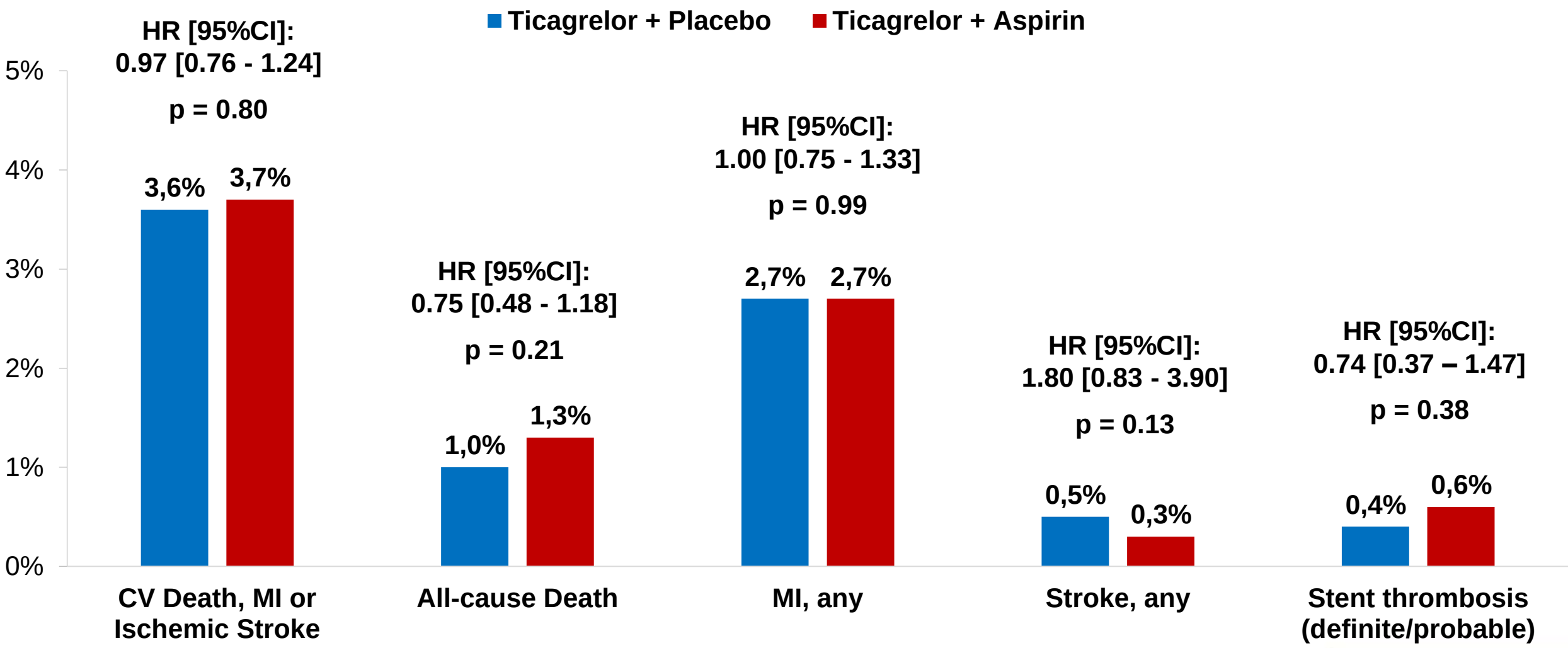
Prespecified Ischemic Endpoints (PP Cohort)



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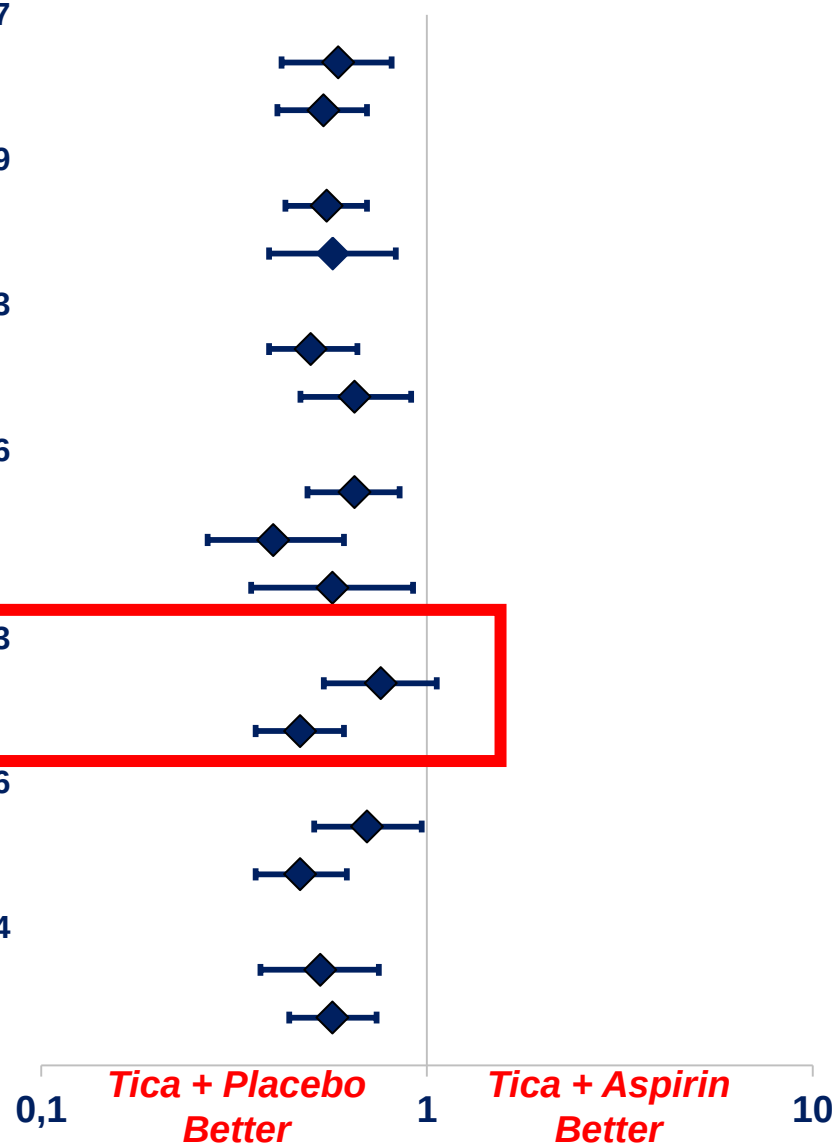
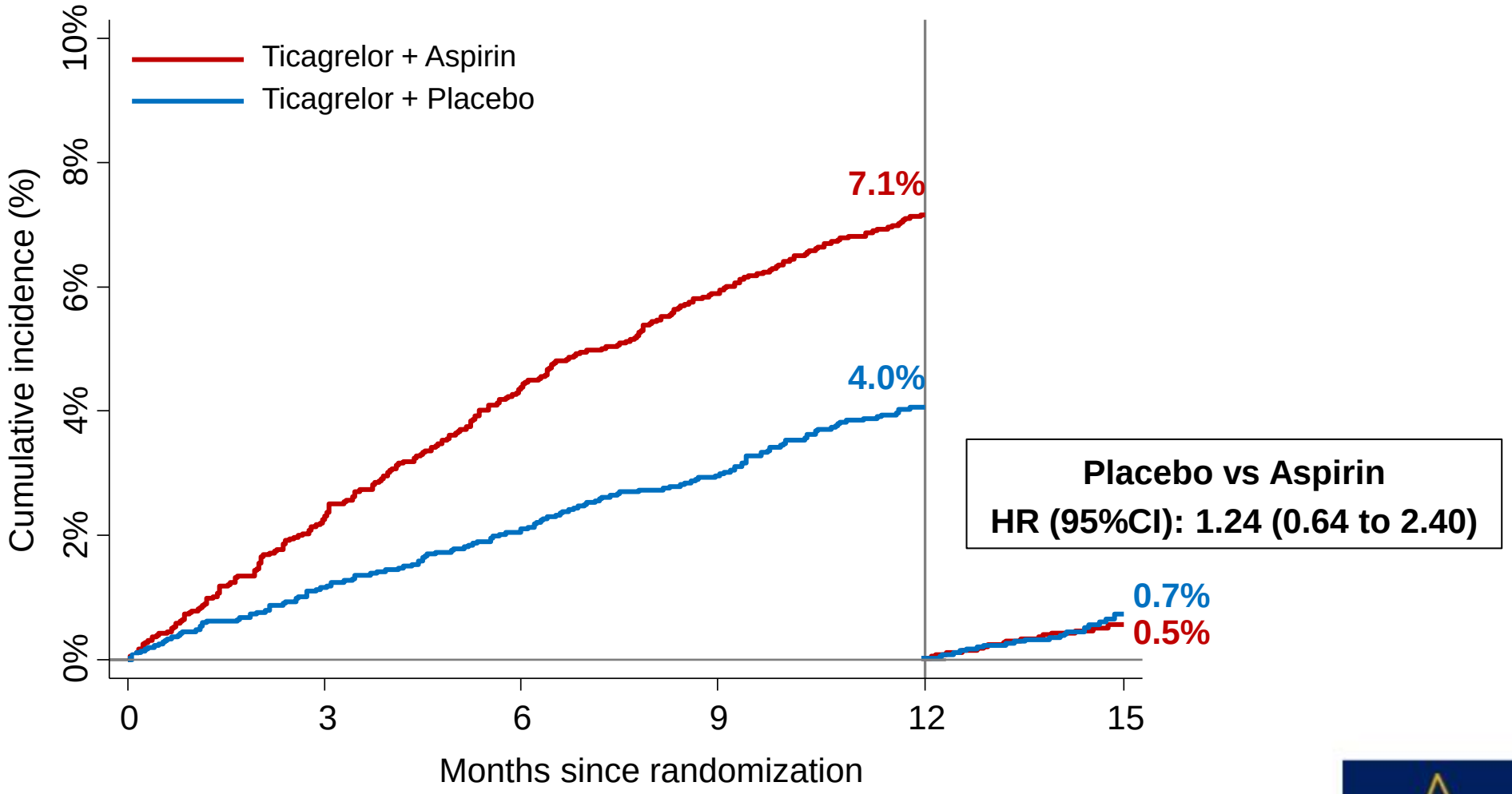
Subgroup Analysis for Primary Endpoint (ITT)

Subgroups	No. of patients	Tica + Placebo	Tica + Aspirin	HR [95% CI]	P Value for Interaction
		no. of events (% of patients)			
Age (years)					**0.67**
<65	3400	59 (3.5%)	100 (6.0%)	0.59 [0.42 – 0.81]	
≥65	3719	82 (4.5%)	150 (8.2%)	0.54 [0.41 – 0.70]	
Sex					**0.89**
Male	5421	99 (3.7%)	178 (6.7%)	0.55 [0.43 – 0.70]	
Female	1698	42 (5.0%)	72 (8.6%)	0.57 [0.39 – 0.83]	
Diabetes Mellitus					**0.23**
No	4499	83 (3.8%)	164 (7.3%)	0.50 [0.39 – 0.66]	
Yes	2620	58 (4.5%)	86 (6.6%)	0.65 [0.47 – 0.91]	
Region of Enrollment					**0.16**
North America	2972	83 (5.7%)	126 (8.7%)	0.65 [0.49 – 0.85]	
Europe	2509	32 (2.6%)	79 (6.3%)	0.40 [0.27 – 0.61]	
Asia	1638	26 (3.2%)	45 (5.5%)	0.57 [0.35 – 0.92]	
Indication for PCI					**0.03**
Stable	2503	60 (4.8%)	75 (6.2%)	0.76 [0.54 – 1.06]	
ACS	4614	81 (3.6%)	175 (7.6%)	0.47 [0.36 – 0.61]	
Total stent length (mm)					**0.06**
<30	3036	64 (4.4%)	93 (6.1%)	0.70 [0.51 – 0.97]	
≥30	4082	77 (3.8%)	157 (7.9%)	0.47 [0.36 – 0.62]	
Multivessel Disease					**0.74**
No	2422	47 (4.1%)	94 (7.6%)	0.53 [0.37 – 0.75]	
Yes	4697	94 (4.0%)	156 (6.9%)	0.57 [0.44 – 0.74]	



Landmark Analysis for Primary Endpoint

BARC 2, 3 or 5 Bleeding



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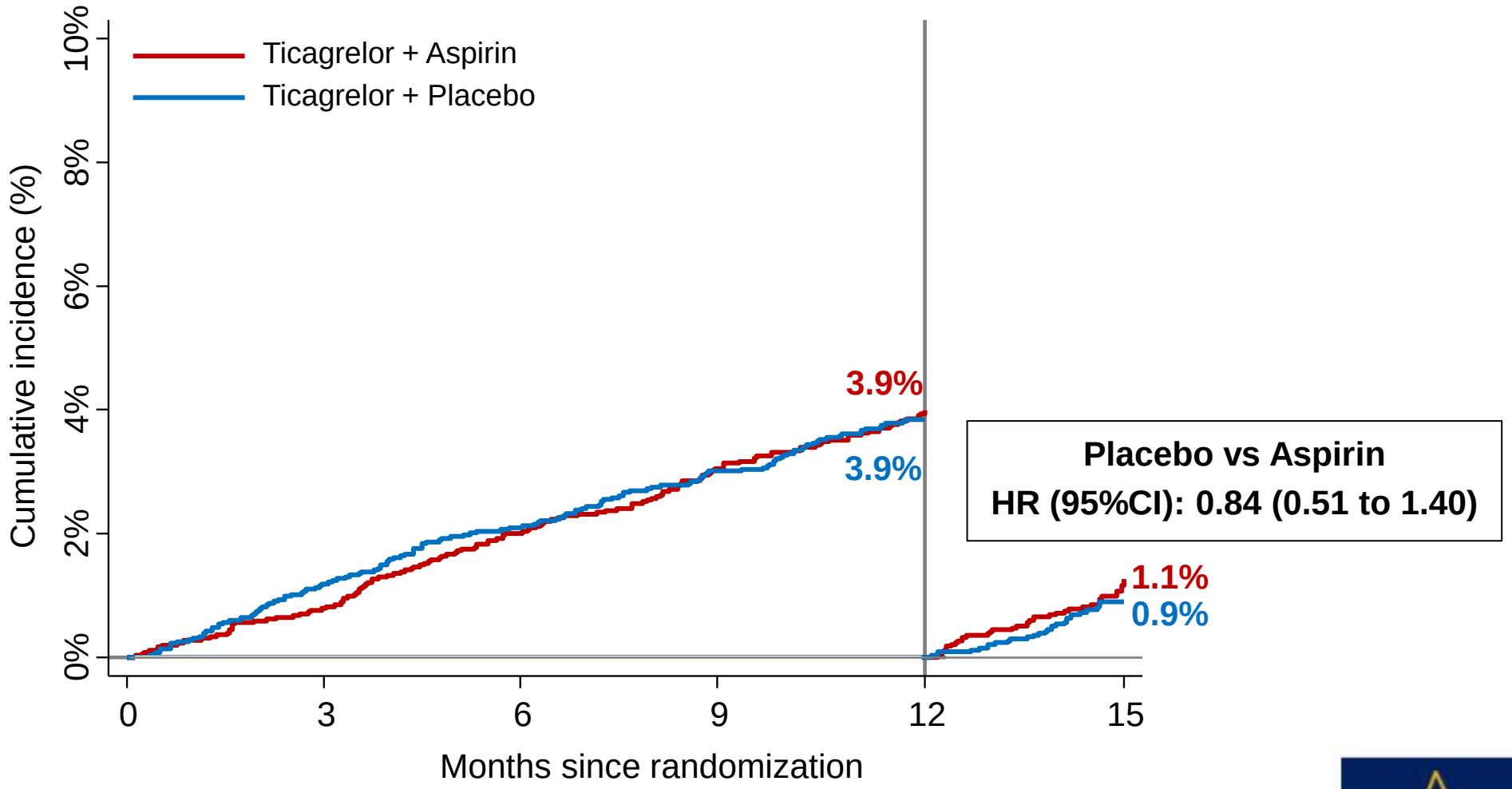
Landmark Analysis for Key Secondary Endpoint

Death, MI or Stroke



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Limitations

- These results may not be generalizable to
  - all patients undergoing PCI, given the requirement in our trial for both high-risk (clinical and angiographic) features, and
  - patients receiving background therapy with other $P2Y_{12}$ inhibitors.
- Observed treatment effects do not apply to all enrolled participants but rather to those patients who were able to take 3 months of dual antiplatelet therapy without any major adverse events.
- A lower-than expected incidence of the composite end point of death, MI, or stroke may have biased our results for this key secondary end point toward the null.
- Lack of power to detect differences in the risk of important yet rare clinical events, such as stent thrombosis and stroke.

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Conclusions

In *high-risk* patients who underwent PCI and were treated with ticagrelor and aspirin for 3 months without any major adverse (bleeding or ischemic) events, an antiplatelet strategy of continuing ticagrelor monotherapy resulted in:

- **substantially *less bleeding* than ticagrelor plus aspirin**
- **without increasing ischemic events over a period of *1 year***

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ORIGINAL ARTICLE

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

R. Mehran, U. Baber, S.K. Sharma, D.J. Cohen, D.J. Angiolillo, C. Briguori, J.Y. Cha, T. Collier, G. Dangas, D. Dudek, V. Džavík, J. Escaned, R. Gil, P. Gurbel, C.W. Hamm, T. Henry, K. Huber, A. Kastrati, U. Kaul, R. Kornowski, M. Krucoff, V. Kunadian, S.O. Marx, S.R. Mehta, D. Moliterno, E.M. Ohman, K. Oldroyd, G. Sardella, S. Sartori, R. Shlofmitz, P.G. Steg, G. Weisz, B. Witzenbichler, Y. Han, S. Pocock, and C.M. Gibson

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