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

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on behalf of the TWILIGHT Investigators
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ClinicalTrials.gov Number: NCT02270242

Declaration of Interest

The TWILIGHT Trial

Sponsoring organization: Icahn School of Medicine at Mount Sinai, NY

Funded by AstraZeneca

Coordinated by Icahn School of Medicine at Mount Sinai, NY

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Disclosures

Affiliation/Financial Relationship	Company
Consultant/ Exec committee/Advisory board/personal fees	Abbott Laboratories, Boston Scientific, Medscape, Siemens Medical Solutions, Phillips (Spectranetics), PLx Pharma, Roivant Sciences Inc, Volcano Corporation, Sanofi, Janssen,
Research Funding to Institution	Abbott Laboratories, Astra Zeneca, Bayer, Beth Israel Deaconess, BMS, CSL Behring, DSI, Medtronic, Boston Scientific, Novartis, OrbusNeich
Equity, <1%	Claret Medical, Elixir Medical
DSMB membership paid to the institution	Watermark Research Partners

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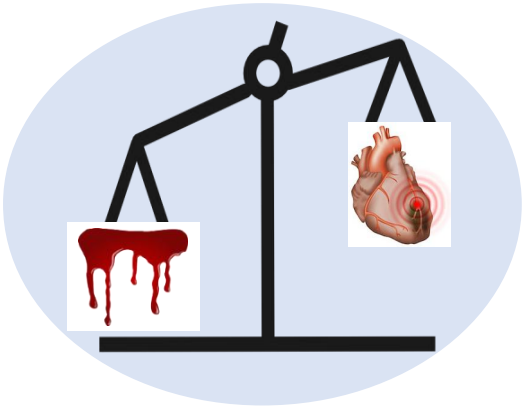
Background

- Balancing ischemic and bleeding complications post PCI is an important dilemma for clinicians.[1-3]
- Addressing the clinical imperatives of lowering bleeding while preserving ischemic benefit requires therapeutic strategies that decouple thrombotic from hemorrhagic risk.
- Reducing the duration of aspirin after PCI may allow for more prolonged use of potent $P2Y_{12}$ inhibitors while avoiding aspirin-related bleeding risk.[4]



1.Baber et al. *JACC Cardiovasc Interv* 2016;9:1349-57.
2.Genereux et al. *J Am Coll Cardiol* 2015;66:1036-45.
3.Valgimigli et al. *Eur Heart J* 2017;38:804-10.
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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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Methods

TWILIGHT was a randomized, double-blinded, placebo-controlled trial conducted in 187 sites across 11 countries.

Patients undergoing successful PCI with at least 1 locally-approved DES whom the treating clinician intended to discharge on ticagrelor plus aspirin were enrolled in the study

Trial inclusion required the presence of at least 1 additional clinical *and* angiographic feature associated with a high risk of ischemic or bleeding events.

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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

- x Under 18 years of age
- x Contraindication to aspirin or ticagrelor
- x Planned surgery within 90 days
- x Planned coronary revascularization (surgical or percutaneous) within 90 days
- x Need for chronic oral anticoagulation
- x Prior stroke
- x Dialysis-dependent renal failure
- x Active bleeding or extreme-risk for major bleeding
- x Salvage PCI or STEMI presentation

- x Liver cirrhosis
- x Life expectancy <1 year
- x Unable or unwilling to provide informed consent
- x Women of child-bearing potential

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Study Organization

Executive Committee

Roxana Mehran
Usman Baber
Dominick J. Angiolillo
David Cohen
George D. Dangas
Shamir Mehta
C. Michael Gibson
Adnan Kastrati
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Jerusa Altema	Project Manager
Samantha Sartori	Statistician

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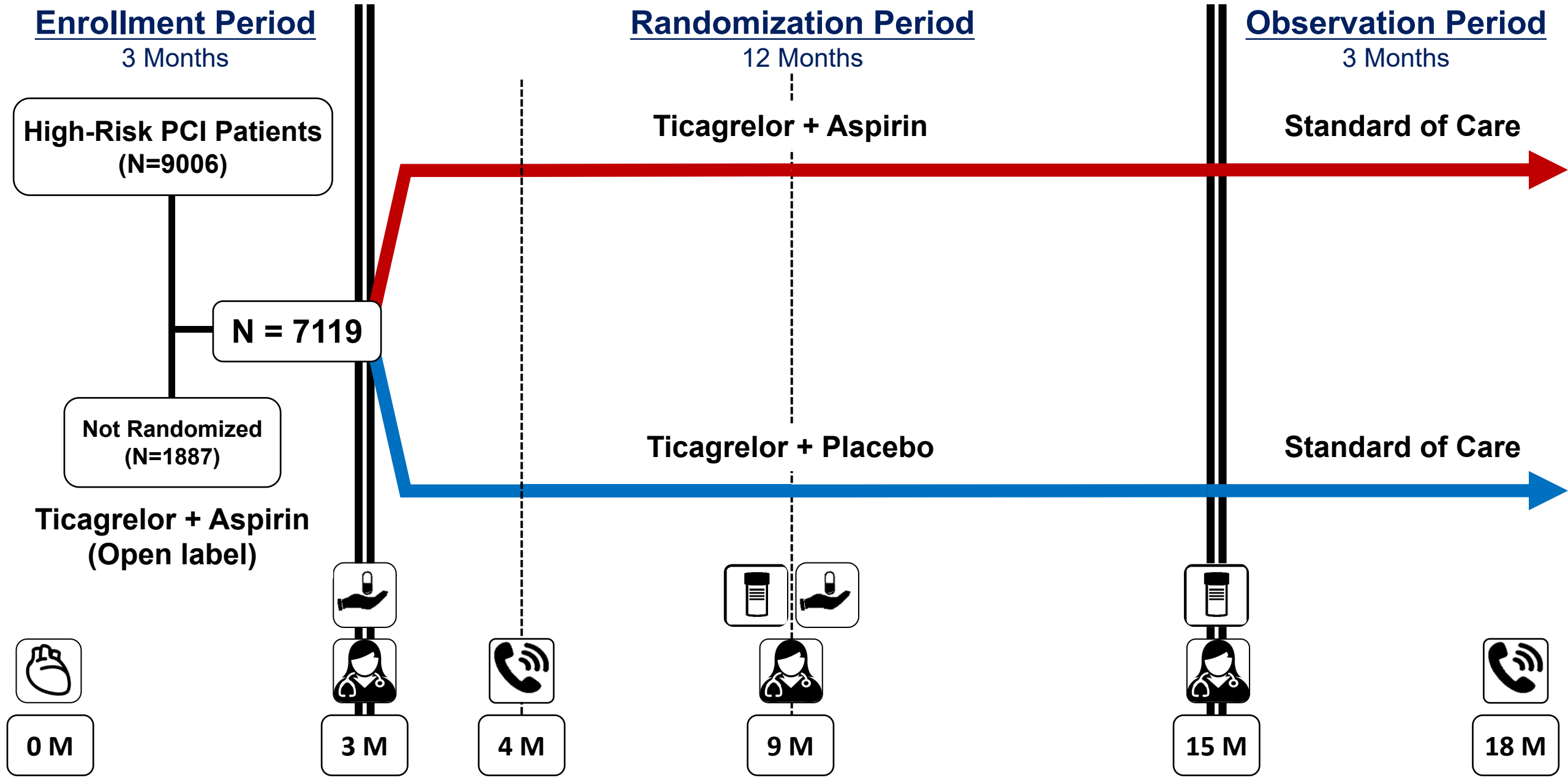
Sponsor: Icahn School of Medicine at Mount Sinai

Funding: AstraZeneca

Independent Data Analysis:

London School of Hygiene (Tim Collier)

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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Sample Size and Power Calculations

Assuming a one-year rate of BARC 2, 3 or 5 bleeding of 4.5% among patients receiving DAPT, a sample size of 8200 was chosen to detect a relative reduction of at least 28% with ticagrelor monotherapy and a type I error of 0.05.

Assuming a one-year rate of 8.0% for the key secondary endpoint, a sample size of 8200 provided 80% power to exclude an absolute non-inferiority margin of 1.6% with type I error 0.025.

An enrolled cohort of 9000 was chosen to accommodate an approximate 10% rate of randomization ineligibility.

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Statistical Analysis

The cumulative incidences of the primary and key secondary endpoints were expressed as Kaplan-Meier estimates by treatment group. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using Cox proportional hazards models with treatment allocation as a single covariate.

Treatment effects were also expressed as absolute risk differences using the one-year Kaplan-Meier estimates and Greenwood standard errors.

Superiority testing using a log-rank p-value was performed for the primary endpoint. For the key secondary endpoint a one-sided non-inferiority test was performed using the upper limit of the 95% CI for the absolute risk difference.

The primary endpoint was evaluated in the intention to treat (ITT) cohort while the key secondary endpoint was assessed in the per protocol cohort.

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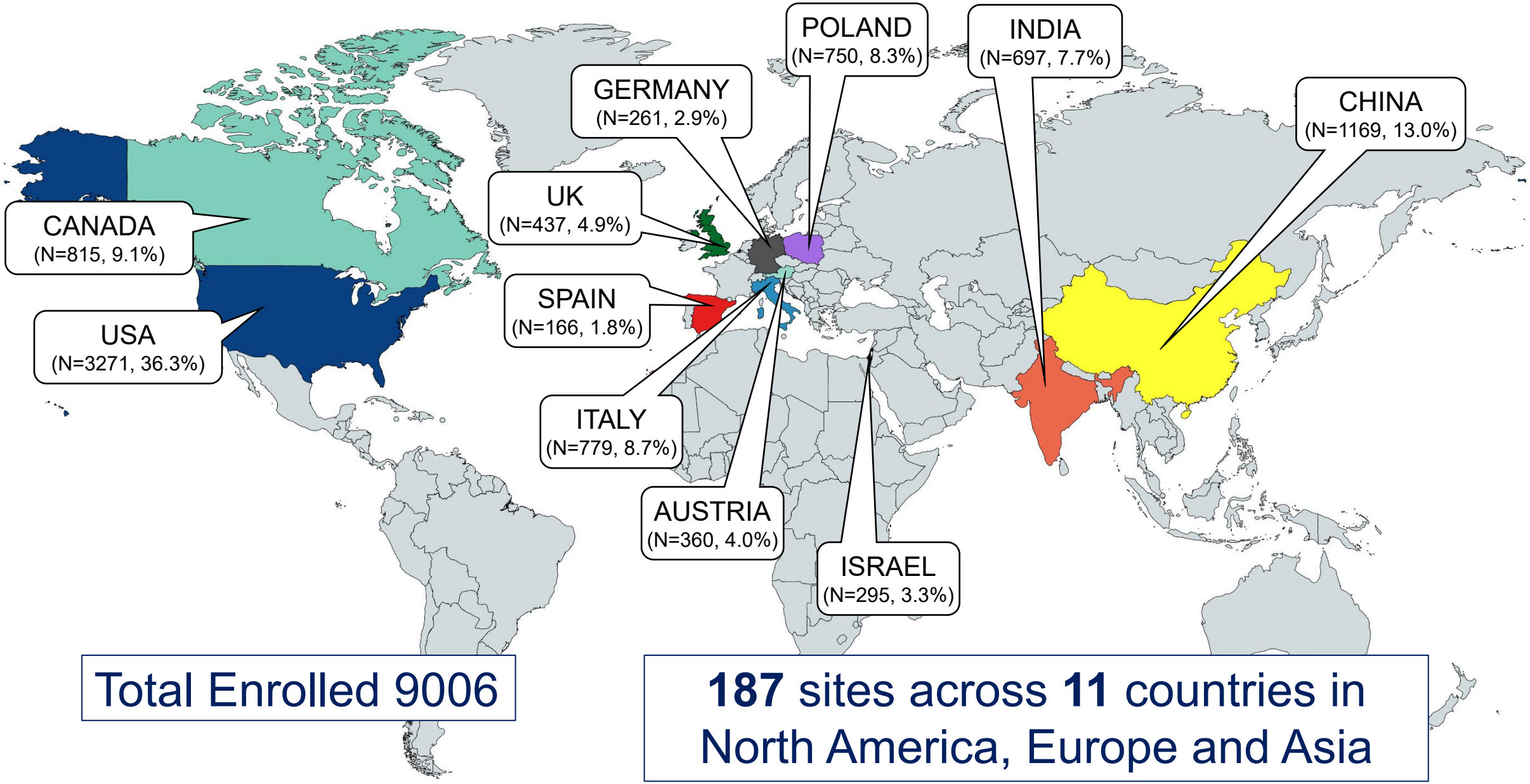
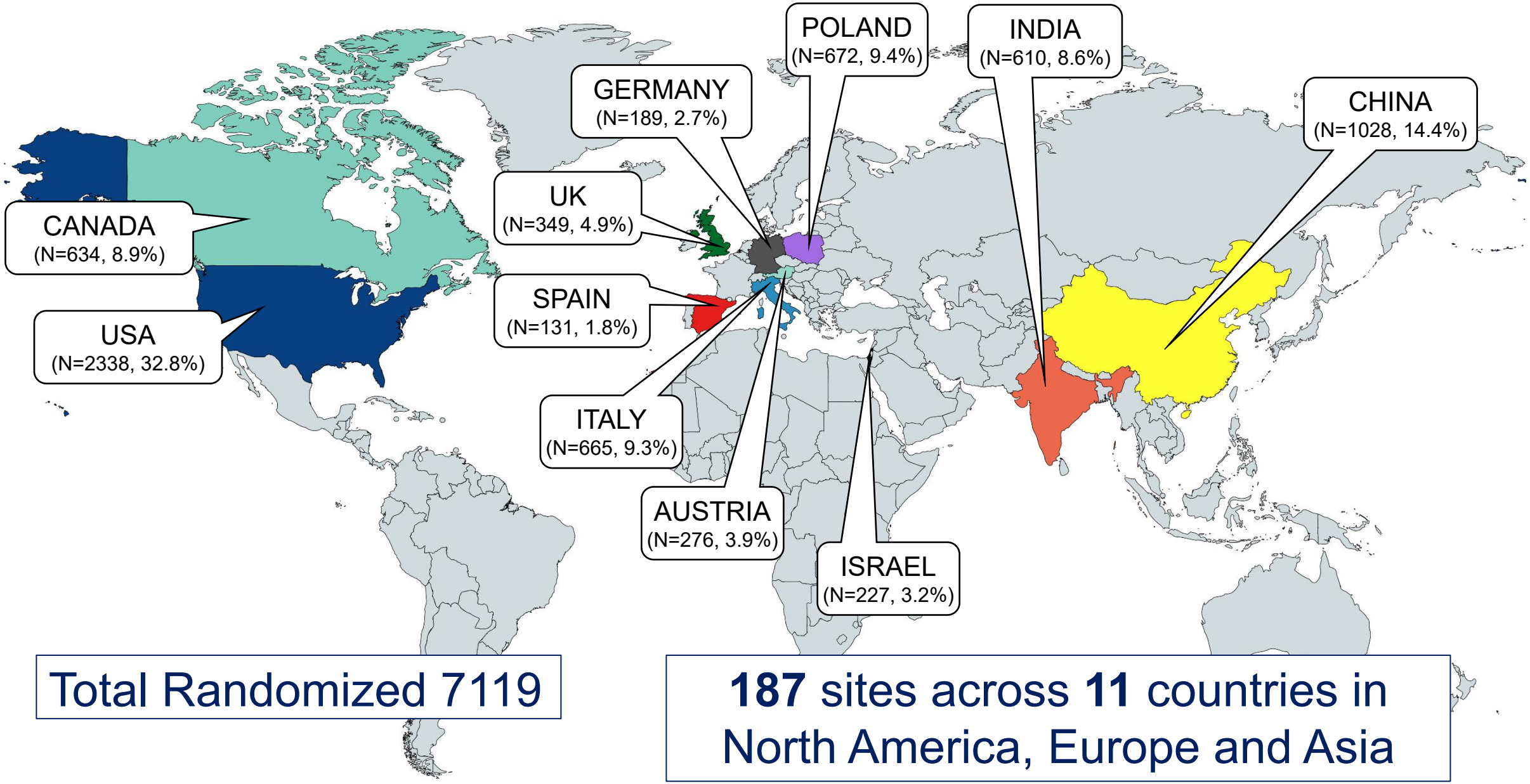
TWILIGHT Enrolled Population



Total Enrolled 9006

187 sites across **11** countries in North America, Europe and Asia

TWILIGHT Randomized Population



Total Randomized 7119

187 sites across **11** countries in North America, Europe and Asia

Top 10 Performing Sites

Site	Principal Investigator	Enrolled	Randomized	Follow-Up
1. General Hospital of Shenyang Military, China	Prof. Han Yaling	249	**240**	100%
2. Clinica Mediterranea, Italy	Prof. Carlo Briguori	250	**220**	100%
3. St. Francis Hospital, USA	Dr. Richard Shlofmitz	251	**158**	98%
4. Polsko-Amerykanskie Kliniki Serca II, Poland	Dr. Wojciech Fil	170	**152**	100%
5. Rex-UNC Hospital, USA	Dr. Deepak Pasi	196	**145**	98%
6. LeBauer-Cone Health, USA	Dr. Christopher McAlhany	159	**128**	98%
7. Clearwater Cardiovascular, USA	Dr. Douglas Spriggs	177	**126**	100%
8. Hamilton General Hospital, Canada	Dr. Shamir Mehta	182	**117**	99%
9. York PCI, Canada	Dr. Warren Cantor	149	**117**	98%
10. South Oklahoma Heart, USA	Dr. Naeem Tahirkheli	140	**113**	100%

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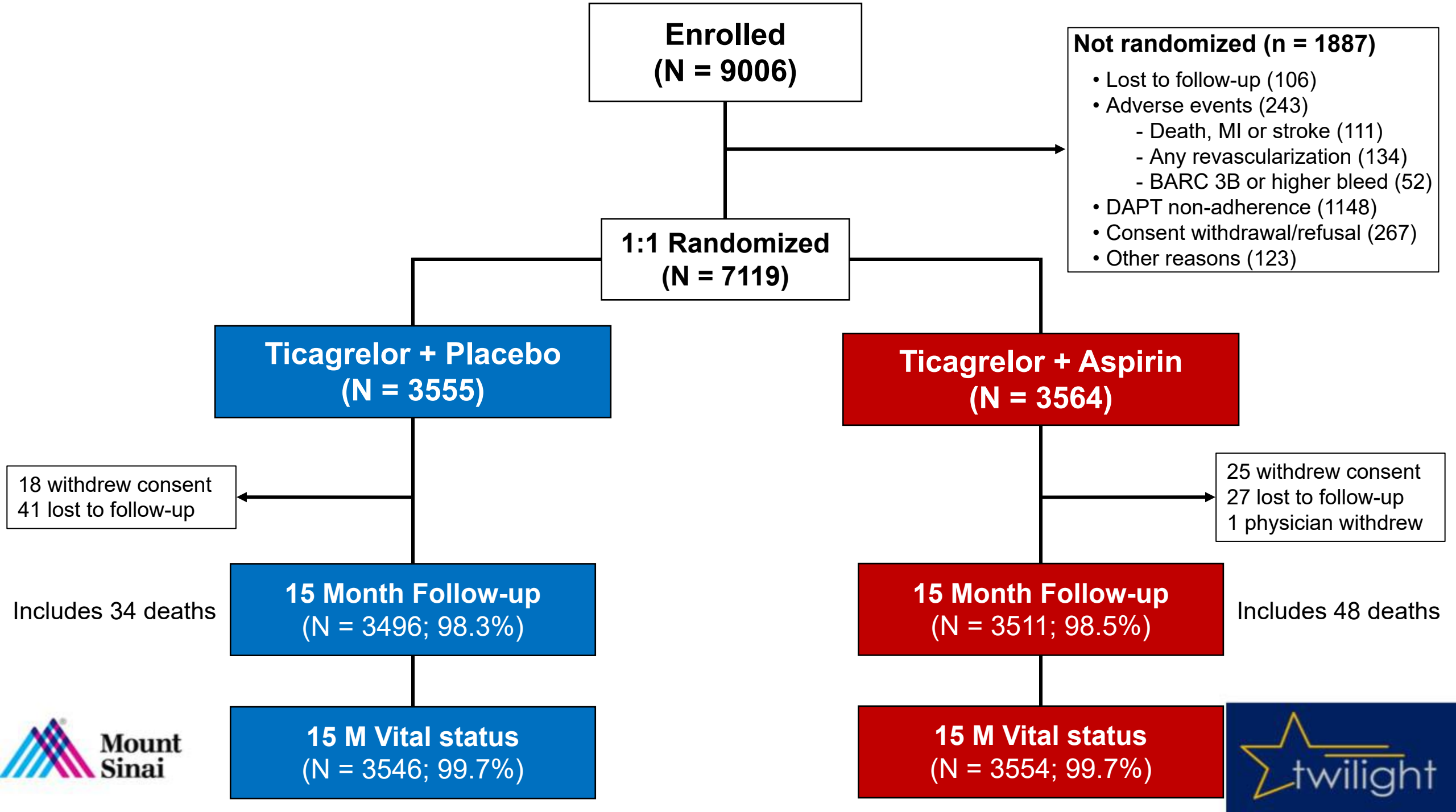
Enrolled
(N = 9006)
Not randomized (n = 1887)
• Lost to follow-up (106)
• Adverse events (243)
- Death, MI or stroke (111)
- Any revascularization (134)
- BARC 3B or higher bleed (52)
• DAPT non-adherence (1148)
• Consent withdrawal/refusal (267)
• Other reasons (123)
1:1 Randomized
(N = 7119)
Ticagrelor + 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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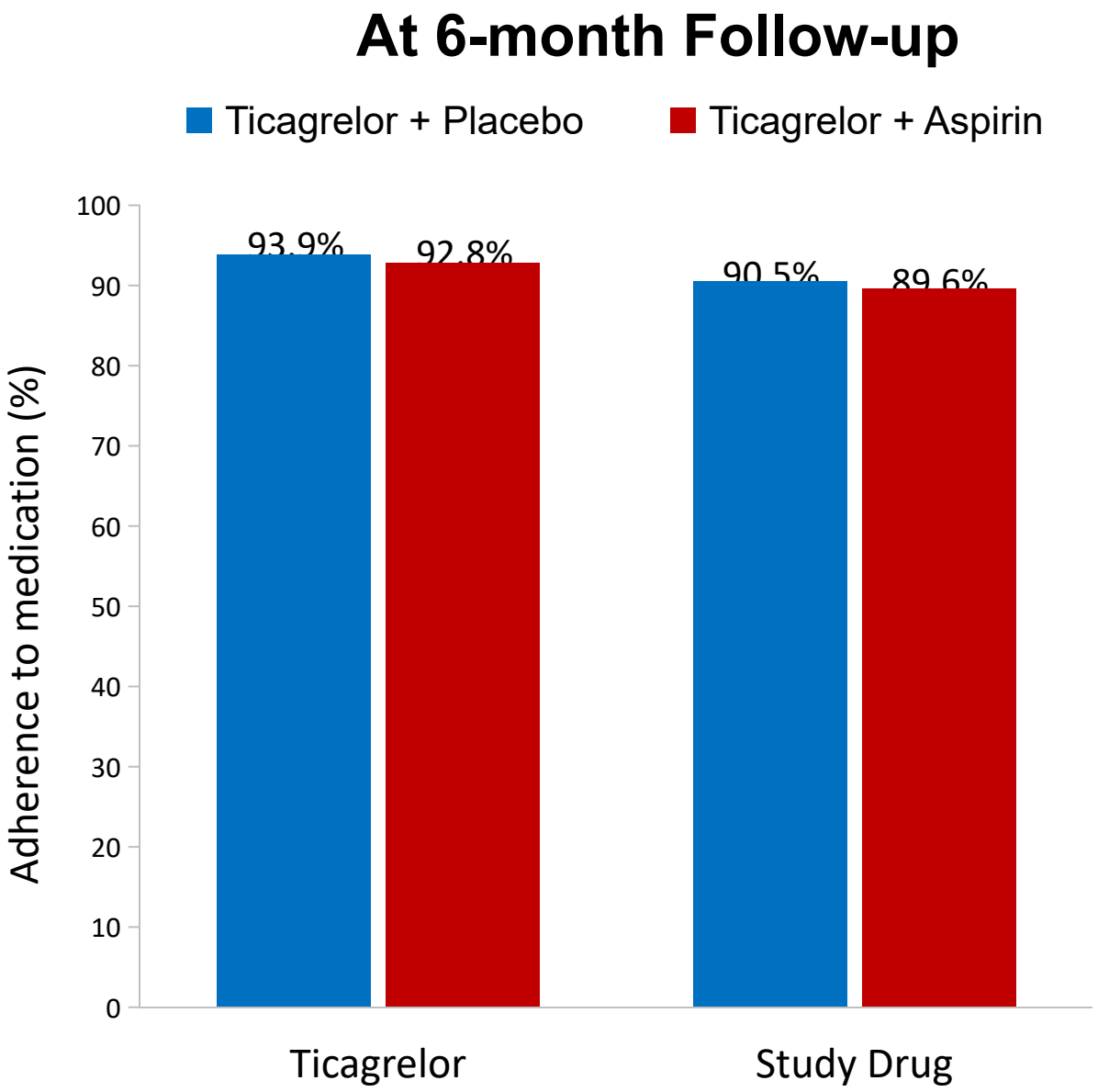
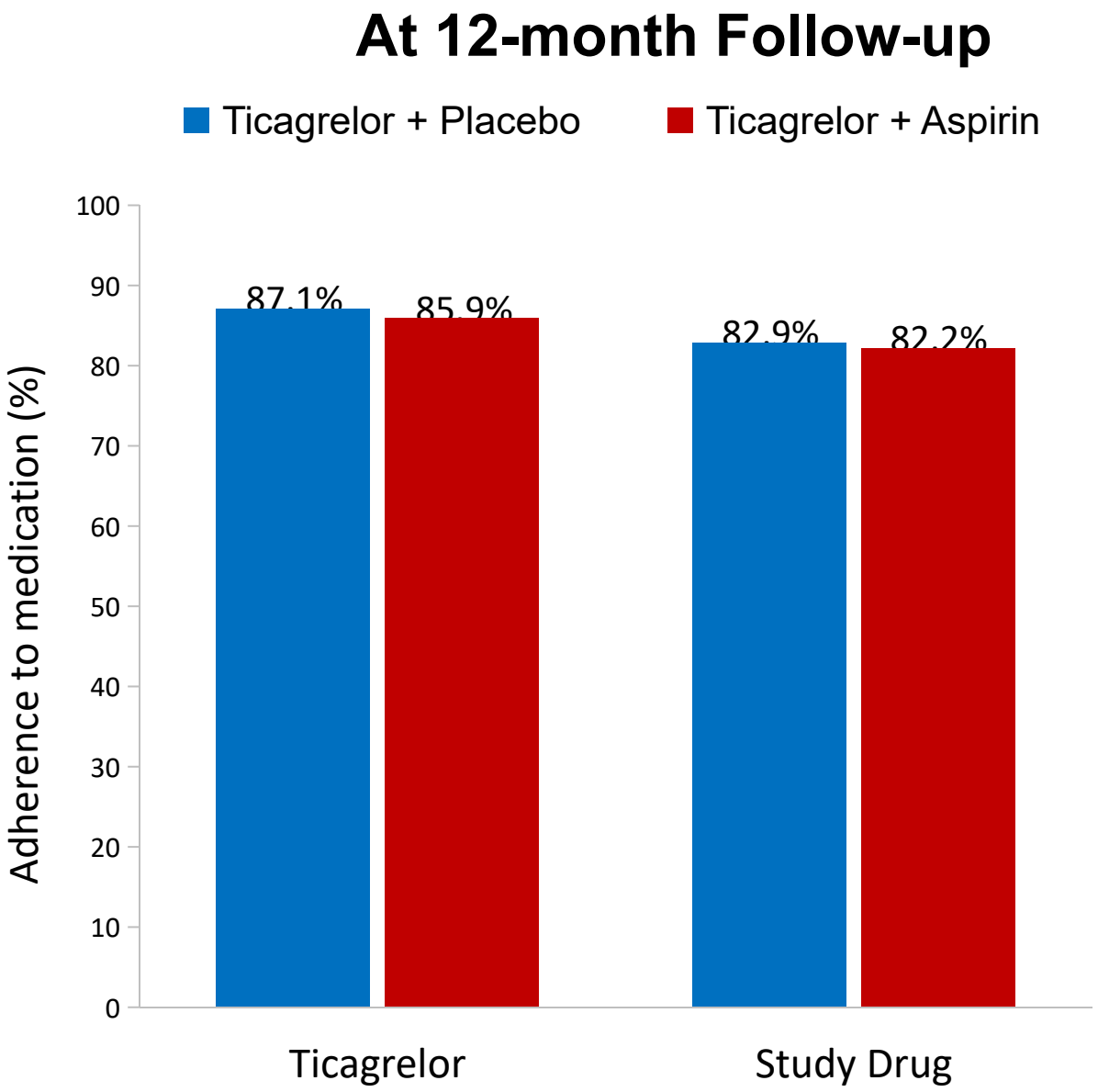
Adherence to Study Medications





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
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%
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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Patient Characteristics

Baseline Procedural Details

Variable	Tica + Placebo (N = 3555)	Tica + Aspirin (N = 3564)
Radial access	73.1%	72.6%
Multivessel CAD	63.9%	61.6%
Lesion morphology		
Thrombus	10.4%	10.7%
Calcification, moderate/severe	14.0%	13.7%
Any bifurcation	12.2%	12.1%
Chronic total occlusion	6.2%	6.3%
Total stent length	40.1 ± 24.2	39.7 ± 24.3

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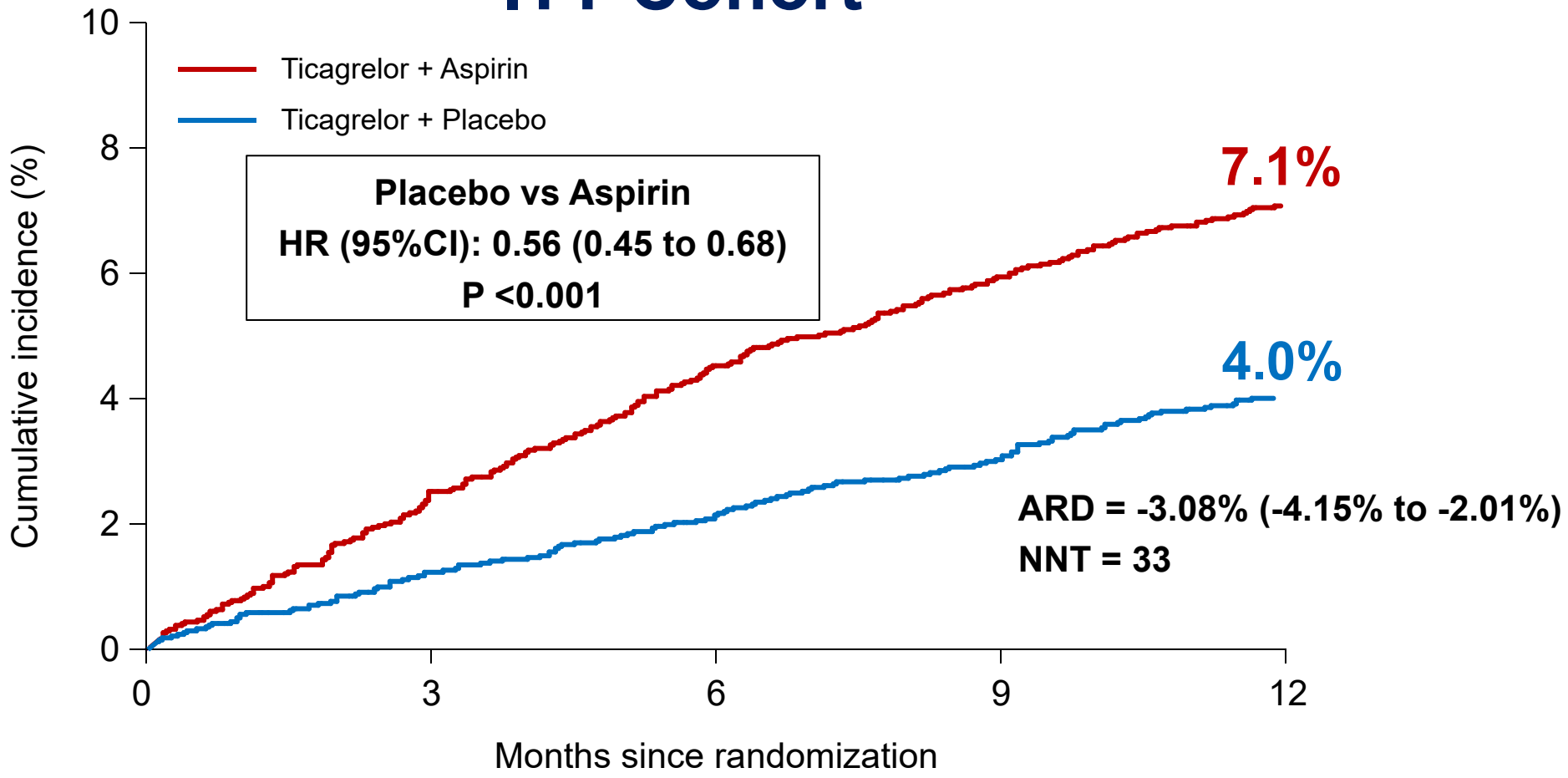
Primary Endpoint: BARC 2, 3 or 5 Bleeding

ITT Cohort



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

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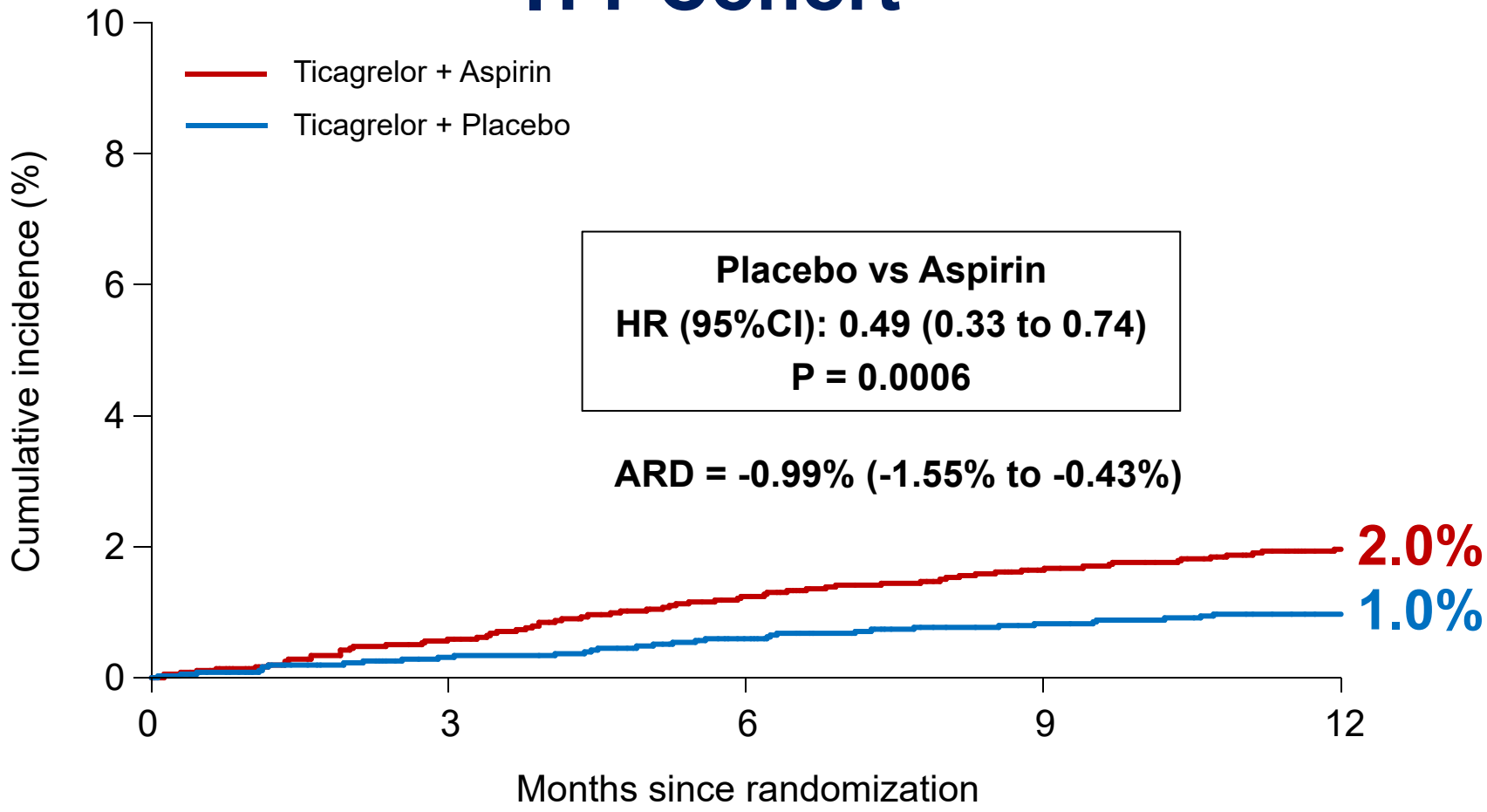
BARC 3 or 5 Bleeding

ITT Cohort



No. at risk					
Ticagrelor + Aspirin	3564	3516	3470	3426	3390
Ticagrelor + Placebo	3555	3504	3475	3440	3423

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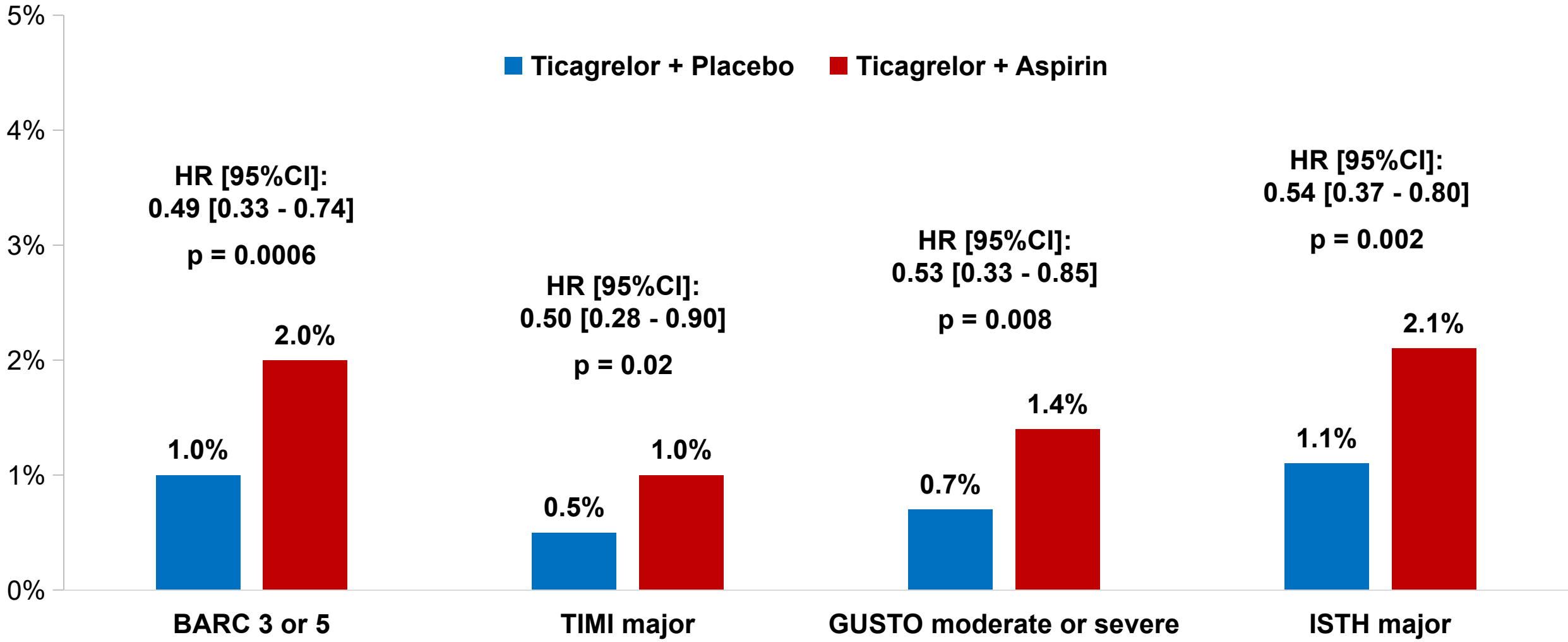
Prespecified Bleeding Endpoints (ITT Cohort)



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Prespecified Bleeding Endpoints (ITT Cohort)

Variable	Ticagrelor + Placebo (N = 3555)	Ticagrelor + Aspirin (N = 3564)	HR [95% CI]	p-value
BARC 3 or 5	34 (1.0%)	69 (2.0%)	**0.49 [0.33 - 0.74]**	0.0006
TIMI minor or major	141 (4.0%)	250 (7.1%)	**0.56 [0.45 - 0.68]**	<0.0001
TIMI major	17 (0.5%)	34 (1.0%)	**0.50 [0.28 - 0.90]**	0.02
GUSTO moderate or severe	26 (0.7%)	49 (1.4%)	**0.53 [0.33 - 0.85]**	0.008
ISTH major	39 (1.1%)	72 (2.1%)	**0.54 [0.37 - 0.80]**	0.002

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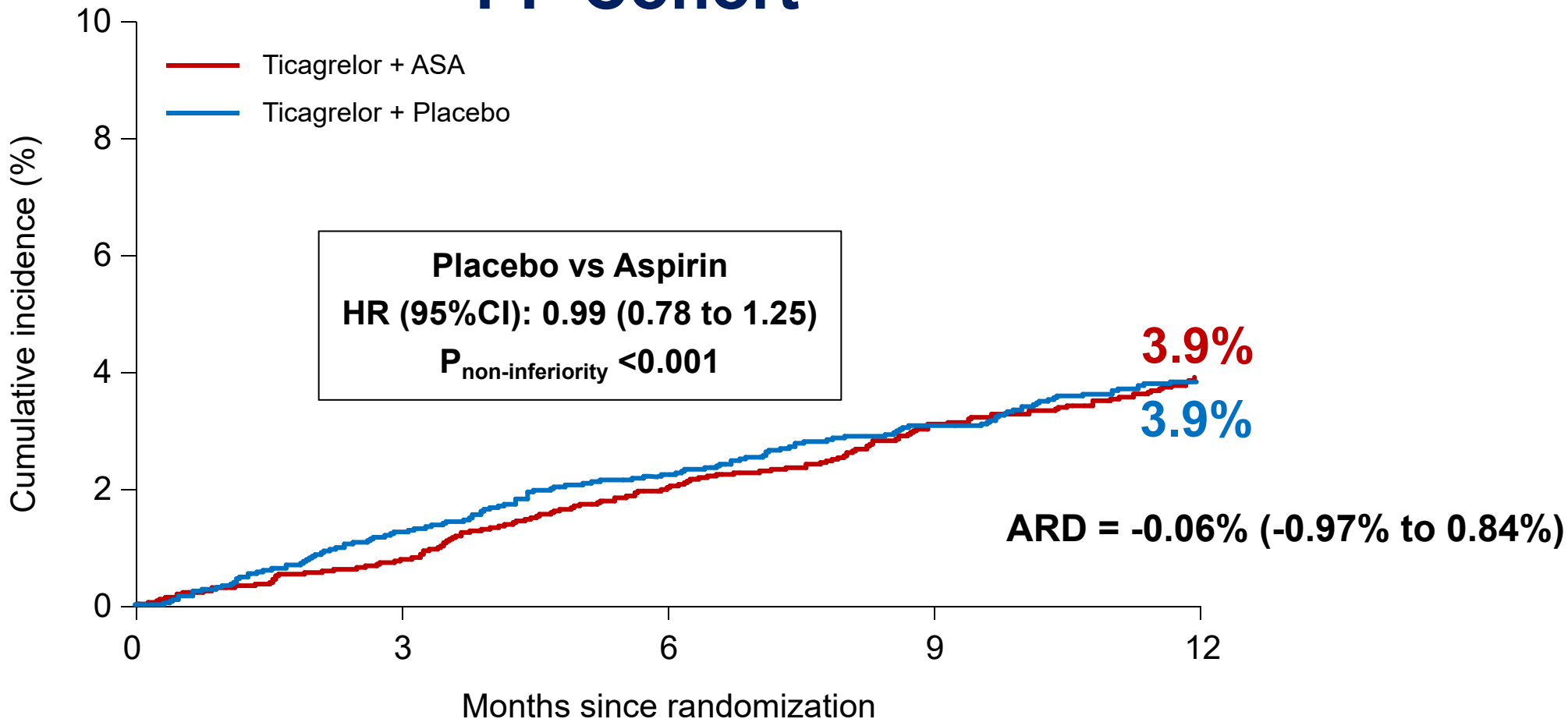
Key Secondary Endpoint: Death, MI or Stroke

PP Cohort



No. at risk					
Ticagrelor + Aspirin	3515	3466	3415	3361	3320
Ticagrelor + Placebo	3524	3457	3412	3365	3330

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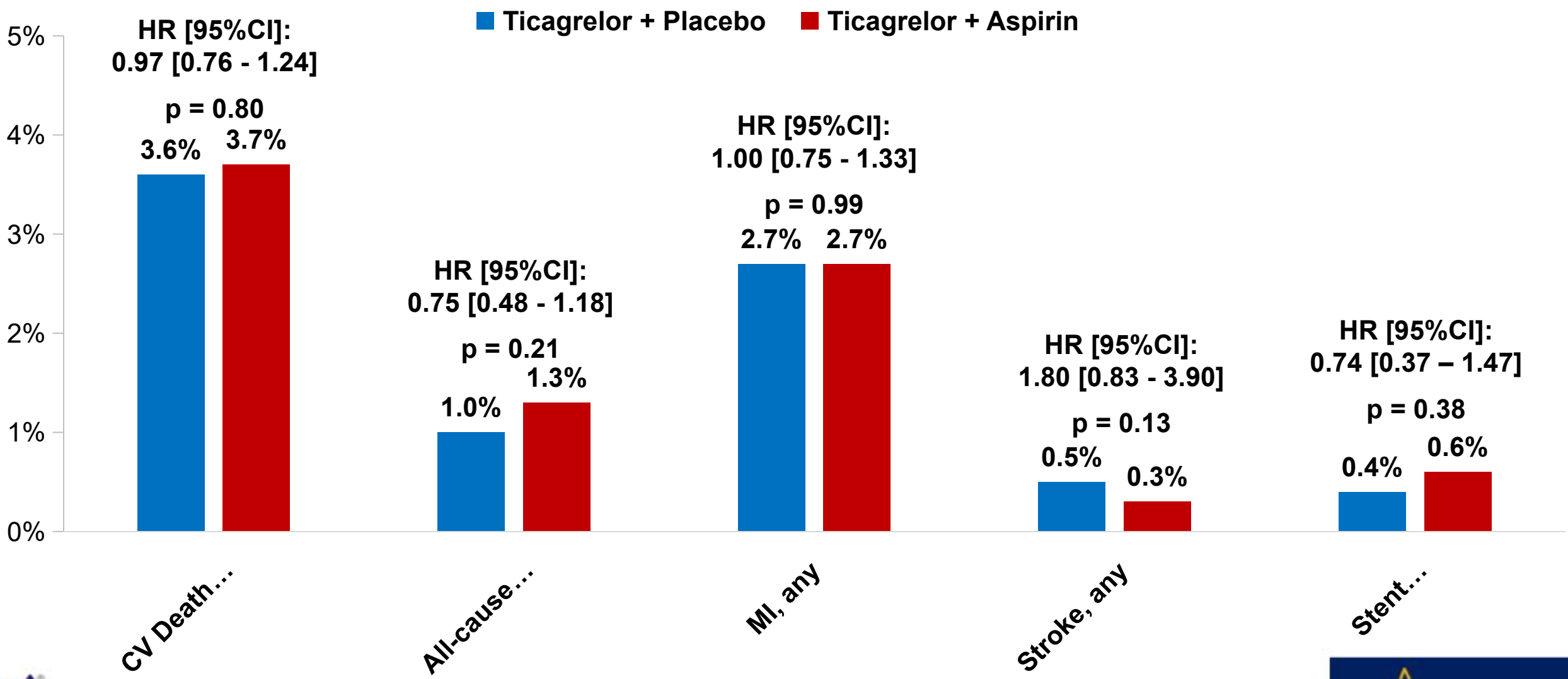
Prespecified Ischemic Endpoints (PP Cohort)



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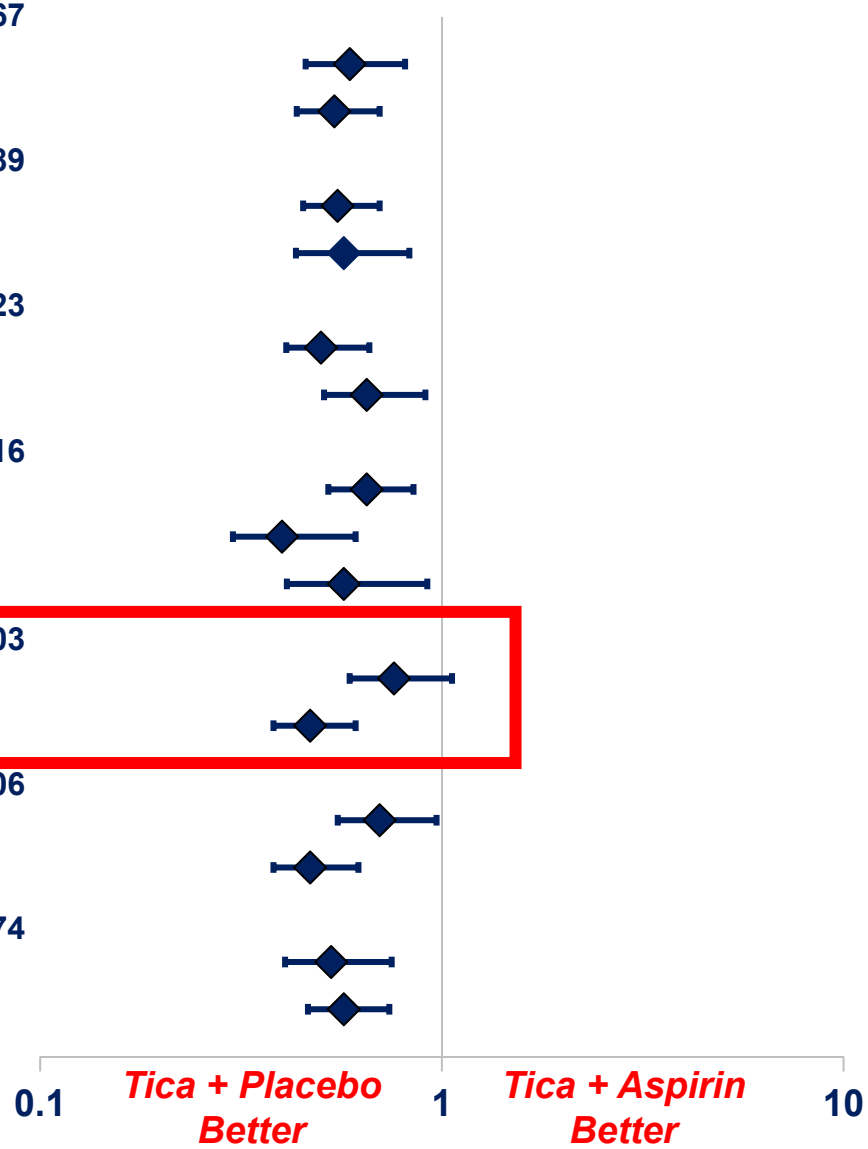
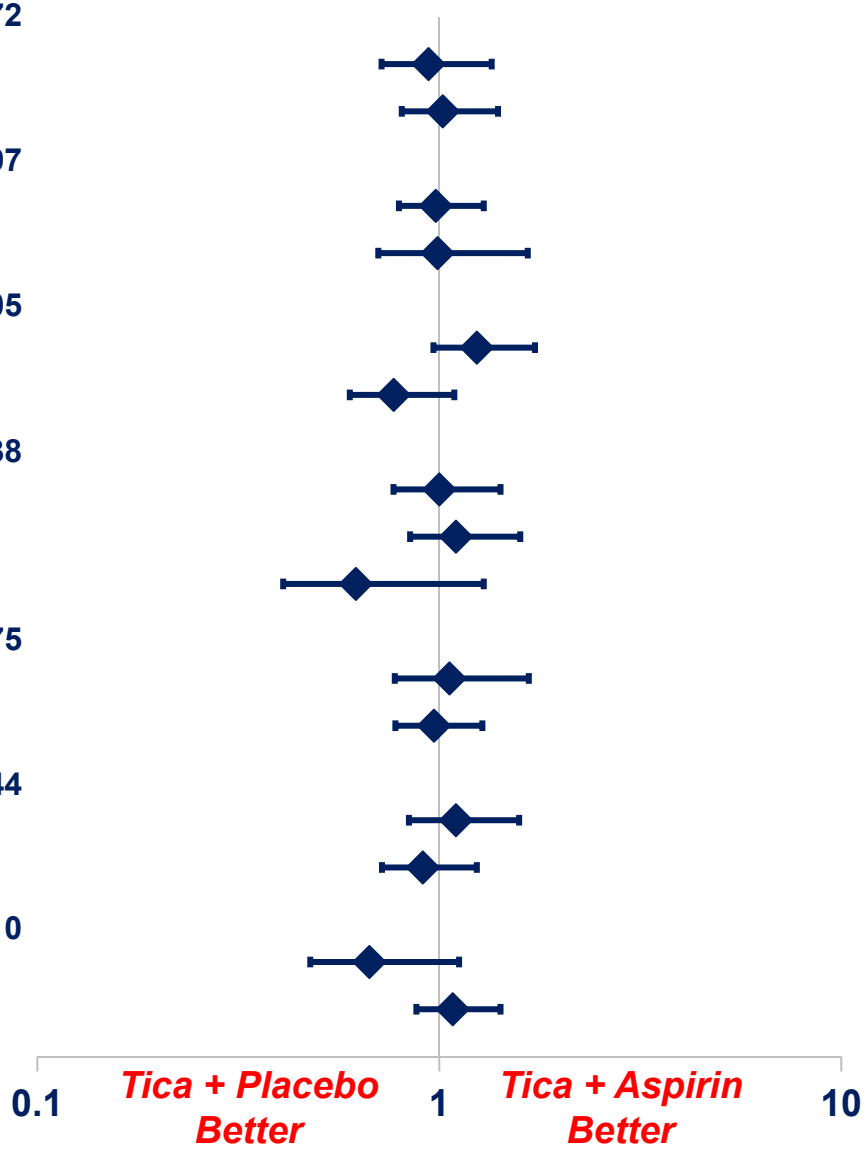
Subgroup Analysis for Primary Endpoint (ITT)

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]	



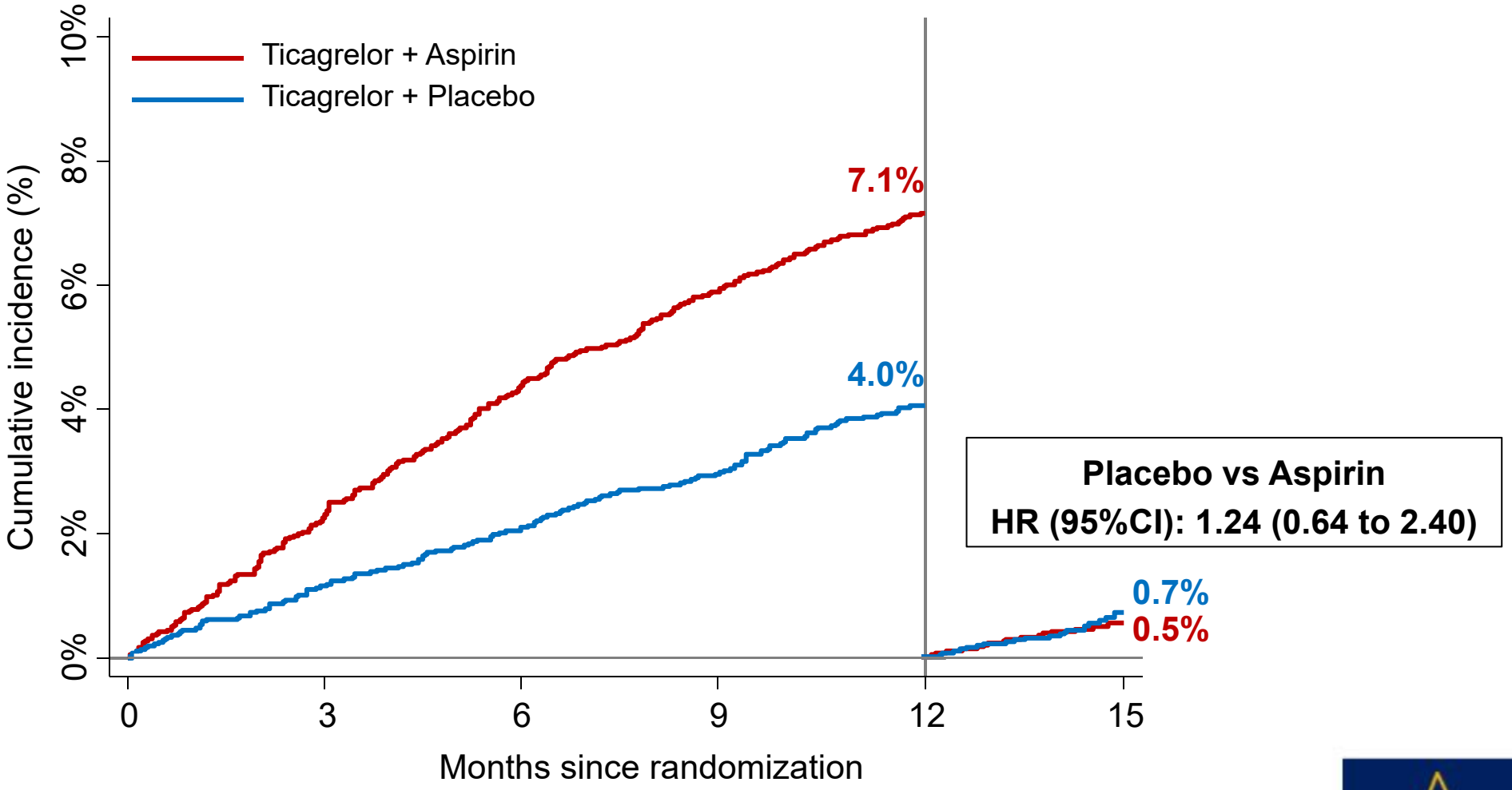
Subgroup Analysis for Key Secondary Endpoint (PP)

Subgroups	No. of patients	Tica + Placebo	Tica + Aspirin	HR [95% CI]	P Value for Interaction
		no. of events (% of patients)			
Age (years)					**0.72**
<65	3362	56 (3.4%)	60 (3.6%)	0.94 [0.65 – 1.35]	
≥65	3677	79 (4.3%)	77 (4.2%)	1.02 [0.75 – 1.40]	
Sex					**0.97**
Male	5363	106 (4.0%)	108 (4.1%)	0.98 [0.75 – 1.29]	
Female	1676	29 (3.5%)	29 (3.5%)	0.99 [0.59 – 1.66]	
Diabetes Mellitus					**0.05**
No	4446	76 (3.5%)	62 (2.8%)	1.24 [0.89 – 1.73]	
Yes	2593	59 (4.6%)	75 (5.9%)	0.77 [0.55 – 1.09]	
Region of Enrollment					**0.38**
North America	2939	62 (4.3%)	62 (4.3%)	1.00 [0.70 – 1.42]	
Europe	2487	61 (5.0%)	56 (4.5%)	1.10 [0.77 – 1.59]	
Asia	1613	12 (1.5%)	19 (2.4%)	0.62 [0.30 – 1.29]	
Indication for PCI					**0.75**
Stable	2472	39 (3.1%)	35 (2.9%)	1.06 [0.67 – 1.67]	
ACS	4565	96 (4.3%)	102 (4.5%)	0.97 [0.73 – 1.28]	
Total stent length (mm)					**0.44**
<30	3003	59 (4.0%)	56 (3.7%)	1.10 [0.76 – 1.58]	
≥30	4036	76 (3.8%)	81 (4.1%)	0.91 [0.67 – 1.24]	
Multivessel Disease					**0.10**
No	2392	23 (2.0%)	37 (3.0%)	0.67 [0.40 – 1.12]	
Yes	4647	112 (4.8%)	100 (4.4%)	1.08 [0.83 – 1.42]	



Landmark Analysis for Primary Endpoint

BARC 2, 3 or 5 Bleeding



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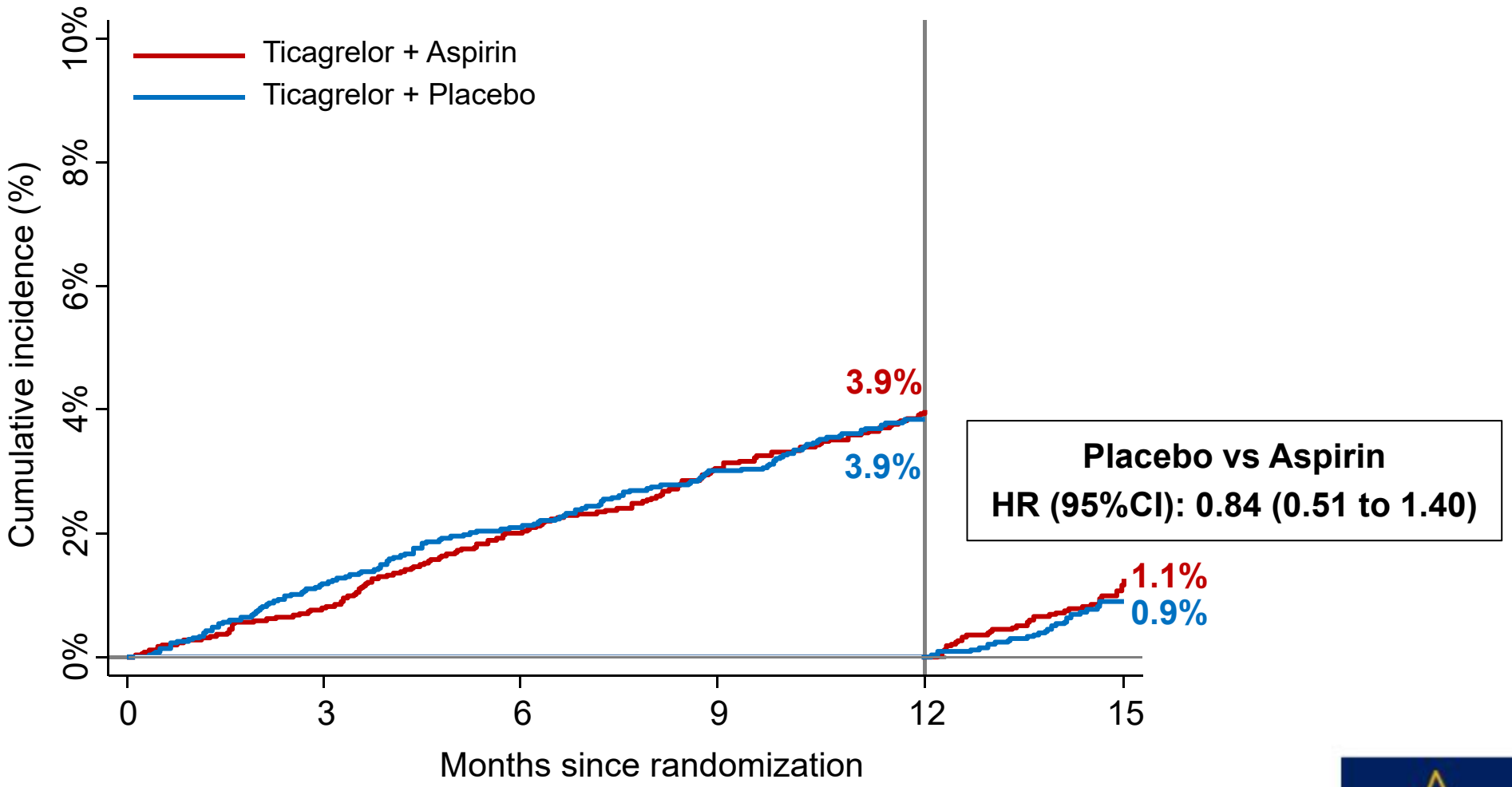
Landmark Analysis for Key Secondary Endpoint

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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The NEW ENGLAND JOURNAL of MEDICINE

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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Prespecified Ischemic Endpoints (PP Cohort)

Variable	Ticagrelor + Placebo (N = 3524)	Ticagrelor + Aspirin (N = 3515)	HR [95% CI]	p-value
CV Death, MI or Ischemic Stroke	126 (3.6%)	130 (3.7%)	**0.97 [0.76 - 1.24]**	0.80
All-cause death	34 (1.0%)	45 (1.3%)	**0.75 [0.48 - 1.18]**	0.21
CV Death	26 (0.8%)	37 (1.1%)	**0.70 [0.43 - 1.16]**	0.17
MI, any	95 (2.7%)	95 (2.7%)	**1.00 [0.75 - 1.33]**	0.99
Stroke, any	18 (0.5%)	10 (0.3%)	**1.80 [0.83 - 3.90]**	0.13
Ischemic	16 (0.5%)	8 (0.2%)	**2.00 [0.86 - 4.67]**	0.10
Stent thrombosis (definite/probable)	14 (0.4%)	19 (0.6%)	**0.74 [0.37 – 1.47]**	0.38
Clinically driven revascularization	246 (7.1%)	227 (6.6%)	**1.09 [0.91 - 1.30]**	0.36
Any hospitalization	601 (17.2%)	618 (17.8%)	**0.97 [0.87 - 1.09]**	0.60

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