Ticagrelor With AspIrin or ALone In HiGH-Risk PaTients After Complex Percutaneous Coronary Intervention: *The TWILIGHT-COMPLEX Study*

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on behalf of the TWILIGHT Investigators

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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

Presenter Disclosure Information

Name: George D. Dangas

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

I/my spouse received payment as an individual for:
a) Abbott Vascular: consultant, advisory board
b) Boston Scientific: consultant, advisory board
c) Sanofi-Aventis: consultant, advisory board

Common stock (entirely divested): Medtronic

Institutional payments for research grants:
a) Astra Zeneca
b) Bayer
c) Daiichi-Sankyo
d) Abbott Vascular
e) Boston Scientific

Background

- Patients who undergo complex PCI are at high risk of ischemic events [1,2]. This risk is higher with increments in PCI complexity and may be reduced by extending DAPT [3].

- On the other hand (regardless of PCI complexity) extension of DAPT duration is associated with increased risk for major bleeding, which is in turn associated with increased morbidity, mortality and healthcare cost [4].

- A strategy of withdrawing aspirin and maintaining $P2Y_{12}$ inhibitor monotherapy after a brief period of DAPT has emerged a potential bleeding reduction strategy [5]. In particular, the TWILIGHT study showed that monotherapy with the potent $P2Y_{12}$-receptor inhibitor ticagrelor after 3 months of DAPT was associated with a lower incidence of clinically relevant bleeding, without increasing the risk of ischemic events compared to continuing DAPT [6].

- Whether such an approach mitigates bleeding complications, without increasing ischemic risk in patients who undergo complex PCI is unknown.

1. Giustino et al. J Am Coll Cardiol 2016;68:1851-1864.
2. Genereux et al. Int J Cardiol 2018;268:61-67.
3. Serruys et al. Eur Heart J 2019;40:2595-2604.
4. Baber et al. JACC Cardiovasc Interv 2016;9:1349-57.
5. Capodanno et al. Nature Reviews Cardiology 2018;15:480-496.
6. Mehran et al. N Engl J Med 2019;381:2032-2042.

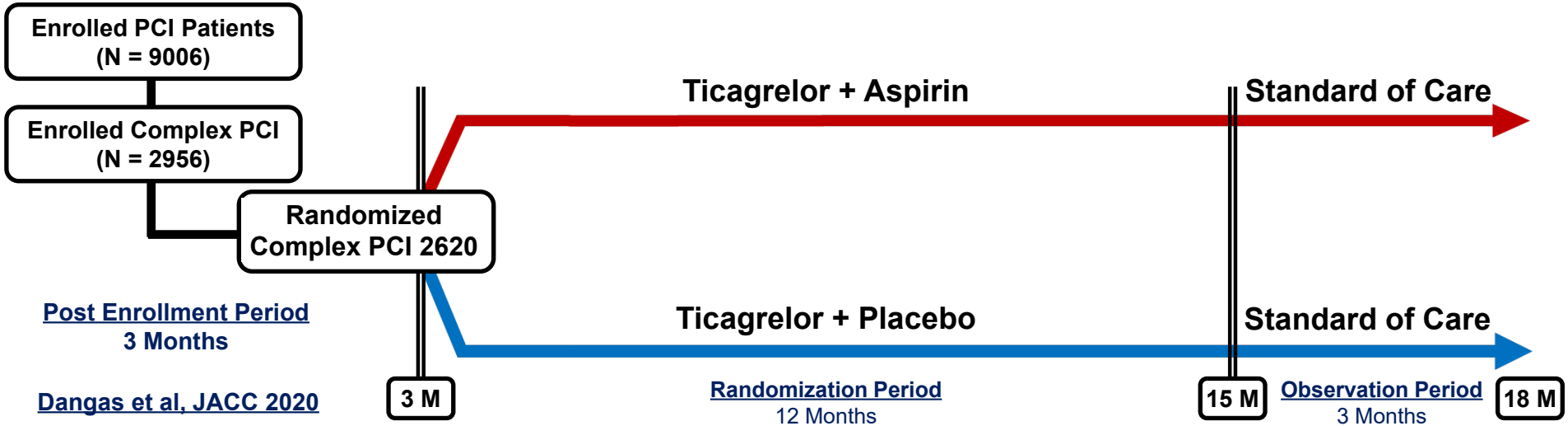
TWILIGHT-Complex: Study Objective

Post-hoc analysis of the TWILIGHT trial

To evaluate the safety and efficacy of a regimen of ticagrelor monotherapy versus ticagrelor plus aspirin, in patients who initially completed 3 months of DAPT after **complex** PCI.

TWILIGHT-Complex: Study Design

- Randomized, double-blind placebo-controlled trial in 187 sites and 11 countries.
- High-risk PCI patients 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 12 months.



TWILIGHT Inclusion/Exclusion Criteria

Patients Must meet at least 1 clinical AND 1 angiographic criterion

Clinical criteria

- Age ≥65 years
- Female gender
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revascularization)
- 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 repeat coronary revascularization

TWILIGHT-Complex: Methods

Target Population

Randomized TWILIGHT participants undergoing *complex* PCI, as defined below.

Complex PCI included PCI with at least 1 of the following characteristics:

- 3 vessels treated
- ≥3 lesions treated
- total stent length >60 mm
- bifurcation with 2 stents implanted
- use of any atherectomy device
- left main as target vessel
- venous or arterial bypass graft as target lesion
- chronic total occlusion of target lesion

Endpoints

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

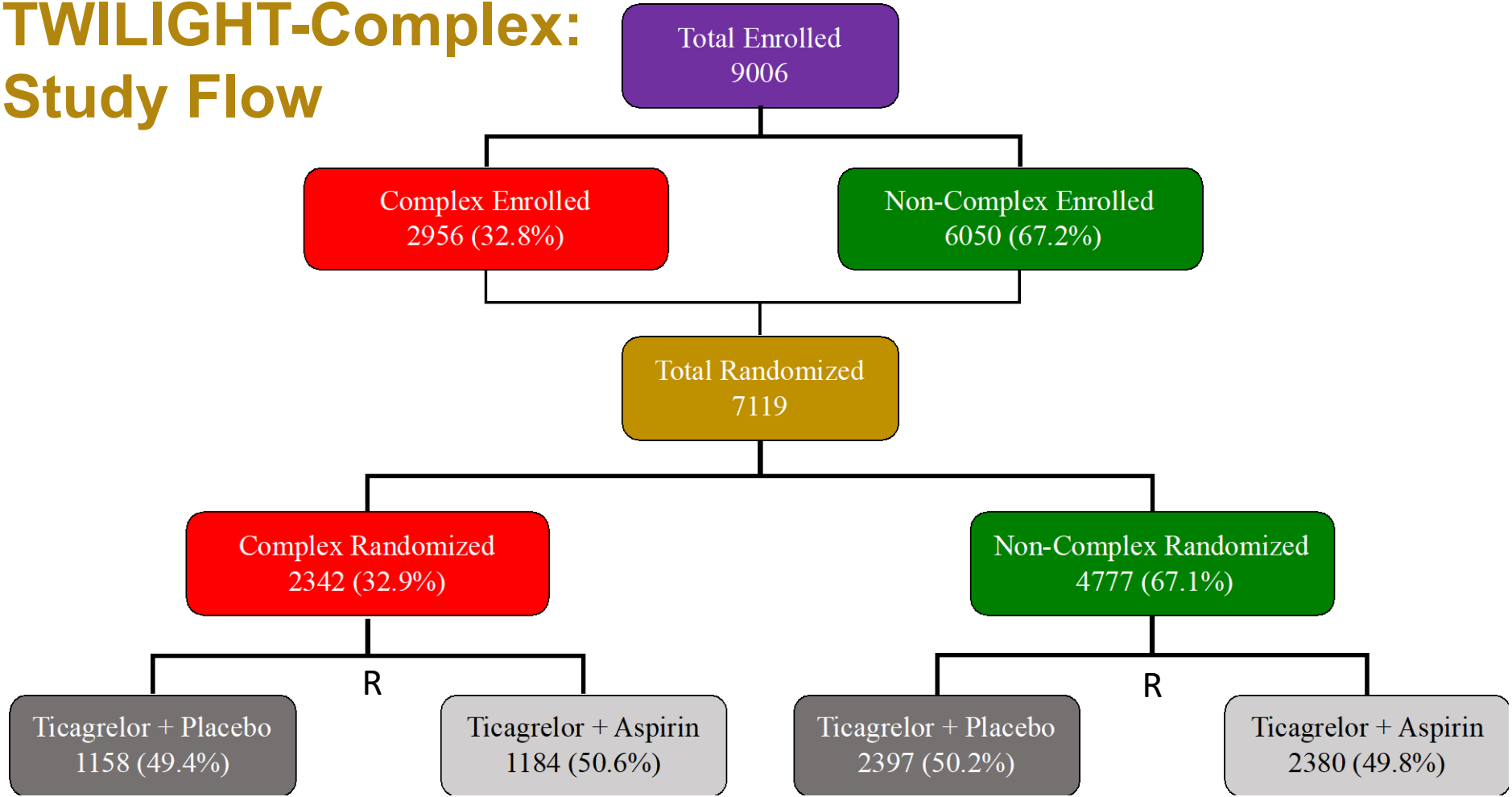
Secondary: All-cause death, non-fatal MI or stroke between 0 - 12 months after randomization

TWILIGHT-Complex: Methods

Statistical Analysis

- Analyses were performed in the intention-to-treat population for bleeding endpoints and in the per-protocol population for ischemic endpoints.
- The cumulative incidence of the primary and secondary endpoints was estimated by Kaplan–Meier methods.
- Hazard ratios (HR) and 95% confidence intervals were generated with Cox proportional-hazards models.
- The consistency of the treatment effects of ticagrelor monotherapy versus ticagrelor plus aspirin between the complex and non-complex PCI subgroups was evaluated with formal interaction testing.

TWILIGHT-Complex: Study Flow



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TWILIGHT-Complex: Patient Characteristics

Baseline Demographics

Variable	Complex PCI (N = 2342)	Non-Complex PCI (N = 4777)	p-value
Age, years [Mean ± SD]	66.0 ± 10.4	64.7 ± 10.3	<0.0001
Female sex	498 (21.3%)	1200 (25.1%)	<0.0001
Non-white race	803 (34.3%)	1393 (29.2%)	<0.0001
BMI, kg/m^2 [Mean ± SD]	28.1 ± 5.3	28.8 ± 5.7	<0.0001
Enrolling region			<0.0001
North America	916 (39.1%)	2056 (43.0%)	
Europe	796 (34.0%)	1713 (35.9%)	
Asia	630 (26.9%)	1008 (21.1%)	
Chronic Kidney Disease	405 (18.1%)	740 (16.1%)	0.04
Anemia	479 (21.4%)	850 (18.5%)	0.004
Acute Coronary Syndrome presentation	1488 (63.6%)	3126 (65.4%)	<0.0001
Current Smoker	483 (20.6%)	1065 (22.3%)	0.11
Previous Myocardial Infarction	672 (28.7%)	1368 (28.6%)	0.96
Previous PCI	971 (41.5%)	2027 (42.4%)	0.44
Previous CABG	361 (15.4%)	349 (7.3%)	<0.0001
Previous major bleeding episode	23 (1.0%)	40 (0.8%)	0.54

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TWILIGHT-Complex: Patient Characteristics

Baseline Angiographic & Procedural Details

Variable	Complex PCI (N = 2342)	Non-Complex PCI (N = 4777)	p-value
Multivessel CAD	1734 (74.0%)	2732 (57.2%)	<0.0001
Number of vessels treated	1.6 ± 0.7	1.2 ± 0.4	<0.0001
Target vessel			
LAD	1429 (61.0%)	2574 (53.9%)	<0.0001
RCA	996 (42.5%)	1504 (31.5%)	<0.0001
LCX	874 (37.3%)	1423 (29.8%)	<0.0001
Venous or arterial bypass graft	161 (6.9%)	0 (0.0%)	<0.0001
Left Main Disease ≥50%	353 (15.1%)	0 (0.0%)	0.14
Number of lesions treated [Mean ± SD]	2.1 ± 0.9	1.3 ± 0.4	<0.0001
Lesion morphology			
Calcification, moderate/severe	506 (21.6%)	481 (10.1%)	<0.0001
Any bifurcation	502 (21.4%)	364 (7.6%)	<0.0001
Chronic total occlusion	446 (19.0%)	0 (0.0%)	<0.0001
Total stent length [Mean ± SD]	59.6 ± 29.4	30.2 ± 13.1	<0.0001

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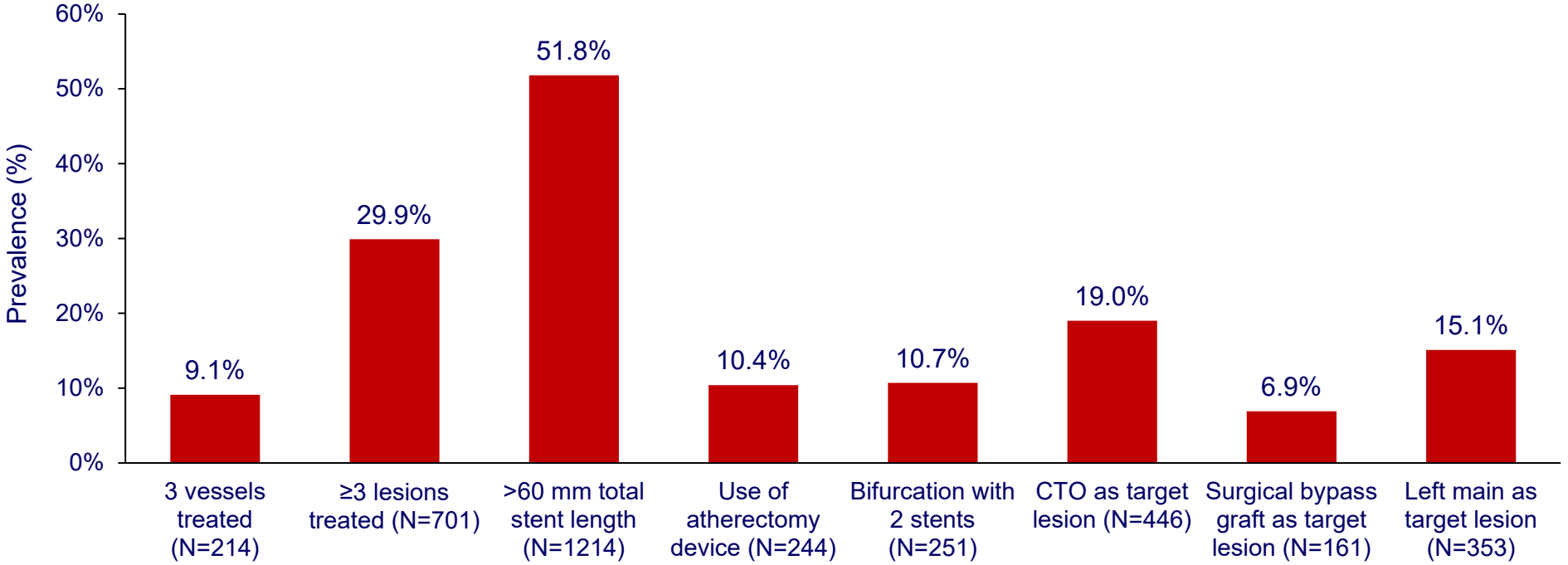
TWILIGHT: Components of Complex PCI



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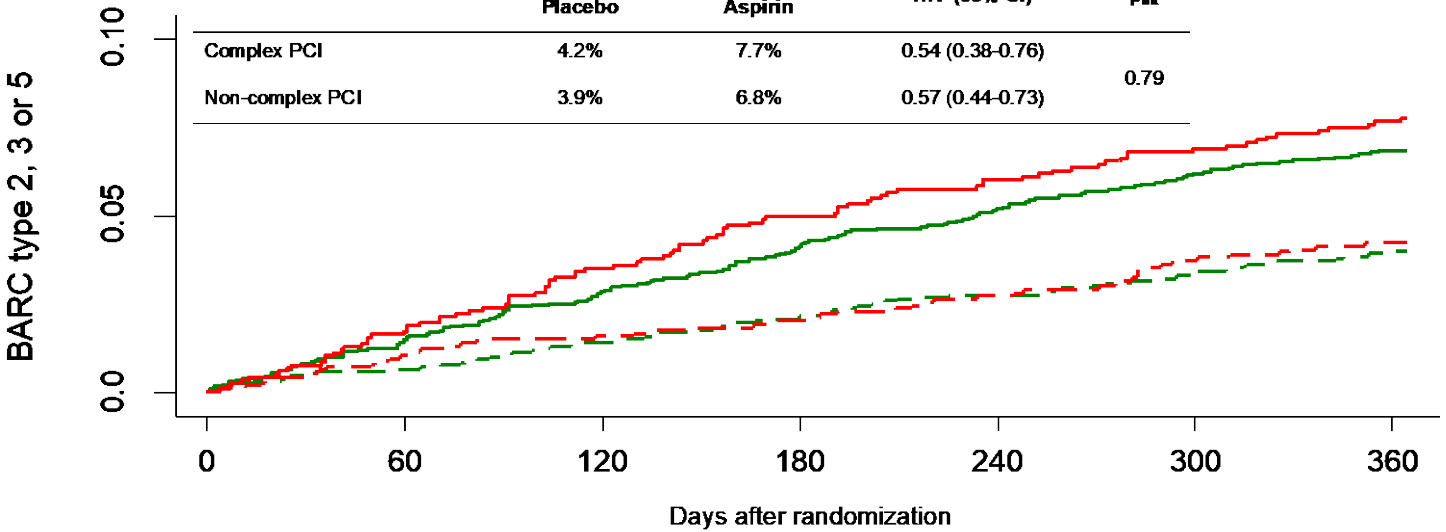
TWILIGHT-Complex: BARC 2, 3 or 5 Bleeding

Intention-To-Treat Cohort

	Ticagrelor + Placebo	Ticagrelor + Aspirin	HR (95% CI)	p_{int}
Complex PCI	4.2%	7.7%	0.54 (0.38-0.76)	0.79
Non-complex PCI	3.9%	6.8%	0.57 (0.44-0.73)	



Number at risk

Ticagrelor + Aspirin - Non-Complex	2380	2331	2291	2256	2216	2184	2154
Ticagrelor + Placebo - Non-Complex	2397	2365	2340	2314	2282	2263	2244
Ticagrelor + Aspirin - Complex	1184	1157	1130	1107	1090	1077	1061
Ticagrelor + Placebo - Complex	1158	1133	1123	1115	1098	1086	1077

Ticagrelor + Aspirin – Complex PCI

Ticagrelor + Placebo – Complex PCI

Ticagrelor + Aspirin – Non-complex PCI

Ticagrelor + Placebo – Non-complex PCI

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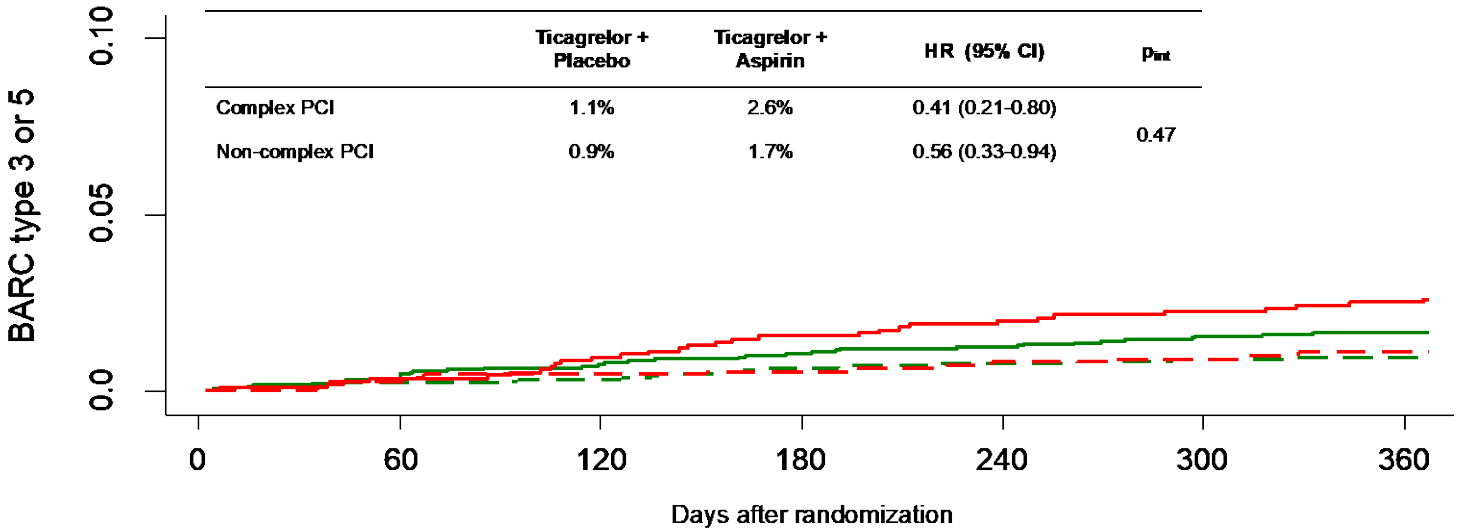
TWILIGHT-Complex: BARC 3 or 5 Bleeding

Intention-To-Treat Cohort



	Ticagrelor + Placebo	Ticagrelor + Aspirin	HR (95% CI)	p_{int}
Complex PCI	1.1%	2.6%	0.41 (0.21-0.80)	0.47
Non-complex PCI	0.9%	1.7%	0.56 (0.33-0.94)	

Number at risk

Ticagrelor + Aspirin - Non-Complex	2380	2353	2338	2328	2307	2290	2273
Ticagrelor + Placebo - Non-Complex	2397	2376	2366	2347	2328	2320	2313
Ticagrelor + Aspirin - Complex	1184	1172	1159	1146	1136	1129	1120
Ticagrelor + Placebo - Complex	1158	1140	1135	1131	1118	1116	1110

Ticagrelor + Aspirin – Complex PCI

Ticagrelor + Placebo – Complex PCI

Ticagrelor + Aspirin – Non-complex PCI

Ticagrelor + Placebo – Non-complex PCI

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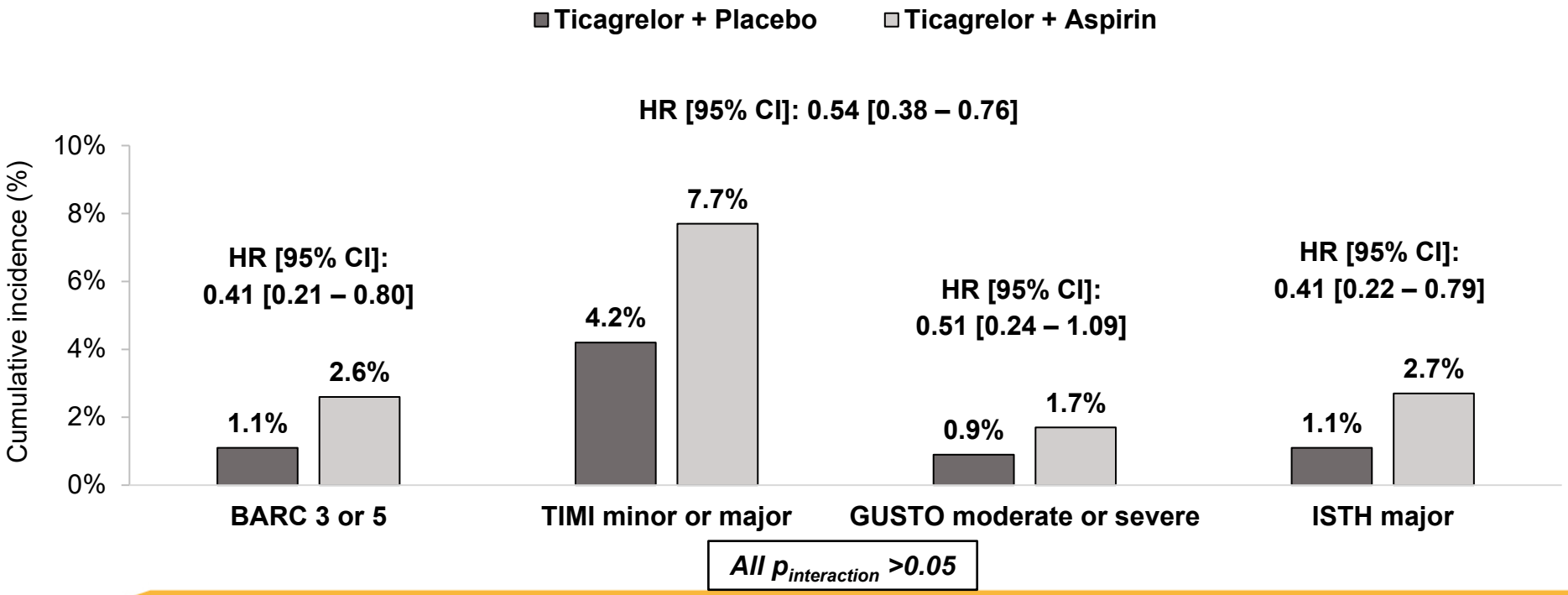
Prespecified Bleeding Endpoints (ITT)

TWILIGHT Complex PCI Patients



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Bleeding Events With and Without Complex PCI

Variable	Complex PCI patients (N = 2342)			Non-Complex PCI patients (N = 4777)			Interaction p-value
	Tica + Placebo (N = 1158)	Tica + Aspirin (N = 1184)	HR (95% CI)	Tica + Placebo (N = 2397)	Tica + Aspirin (N = 2380)	HR (95% CI)	
	no. of patients (%)			*no. of patients (%)*			
BARC 2, 3 or 5	48 (4.2%)	90 (7.7%)	0.54 (0.38 – 0.76)	93 (3.9%)	160 (6.8%)	0.57 (0.44 – 0.73)	0.79
BARC 3 or 5	12 (1.1%)	30 (2.6%)	0.41 (0.21 – 0.80)	22 (0.9%)	39 (1.7%)	0.56 (0.33 – 0.94)	0.47
TIMI minor or major	48 (4.2%)	90 (7.7%)	0.54 (0.38 – 0.76)	93 (3.9%)	160 (6.8%)	0.57 (0.44 – 0.73)	0.79
GUSTO moderate or severe	10 (0.9%)	20 (1.7%)	0.51 (0.24 – 1.09)	16 (0.7%)	29 (1.2%)	0.55 (0.30 – 1.01)	0.89
ISTH major	13 (1.1%)	32 (2.7%)	0.41 (0.22 – 0.79)	26 (1.1%)	40 (1.7%)	0.64 (0.39 – 1.05)	0.29

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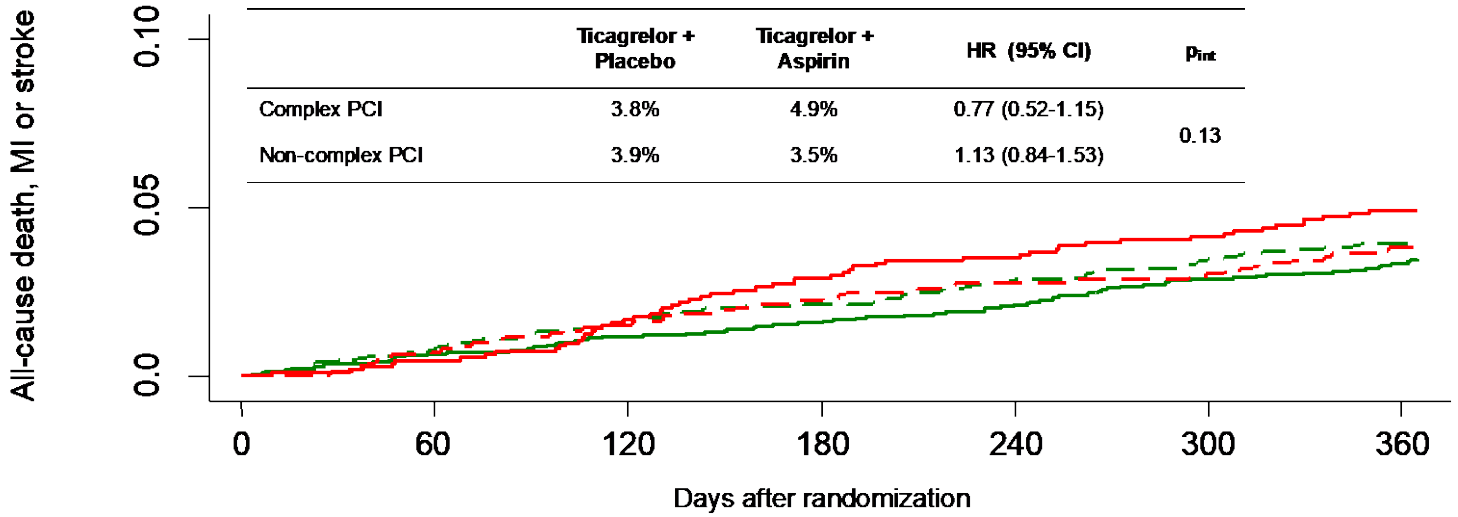
TWILIGHT-Complex: Death, MI or Stroke

Per-Protocol Cohort



	Ticagrelor + Placebo	Ticagrelor + Aspirin	HR (95% CI)	p_{int}
Complex PCI	3.8%	4.9%	0.77 (0.52-1.15)	0.13
Non-complex PCI	3.9%	3.5%	1.13 (0.84-1.53)	

Number at risk

Ticagrelor + Aspirin - Non-Complex	2356	2327	2314	2300	2275	2256	2238
Ticagrelor + Placebo - Non-Complex	2372	2342	2321	2302	2276	2260	2246
Ticagrelor + Aspirin - Complex	1159	1147	1132	1118	1107	1099	1085
Ticagrelor + Placebo - Complex	1152	1133	1123	1114	1099	1096	1084

Ticagrelor + Aspirin – Complex PCI

Ticagrelor + Placebo – Complex PCI

Ticagrelor + Aspirin – Non-complex PCI

Ticagrelor + Placebo – Non-complex PCI

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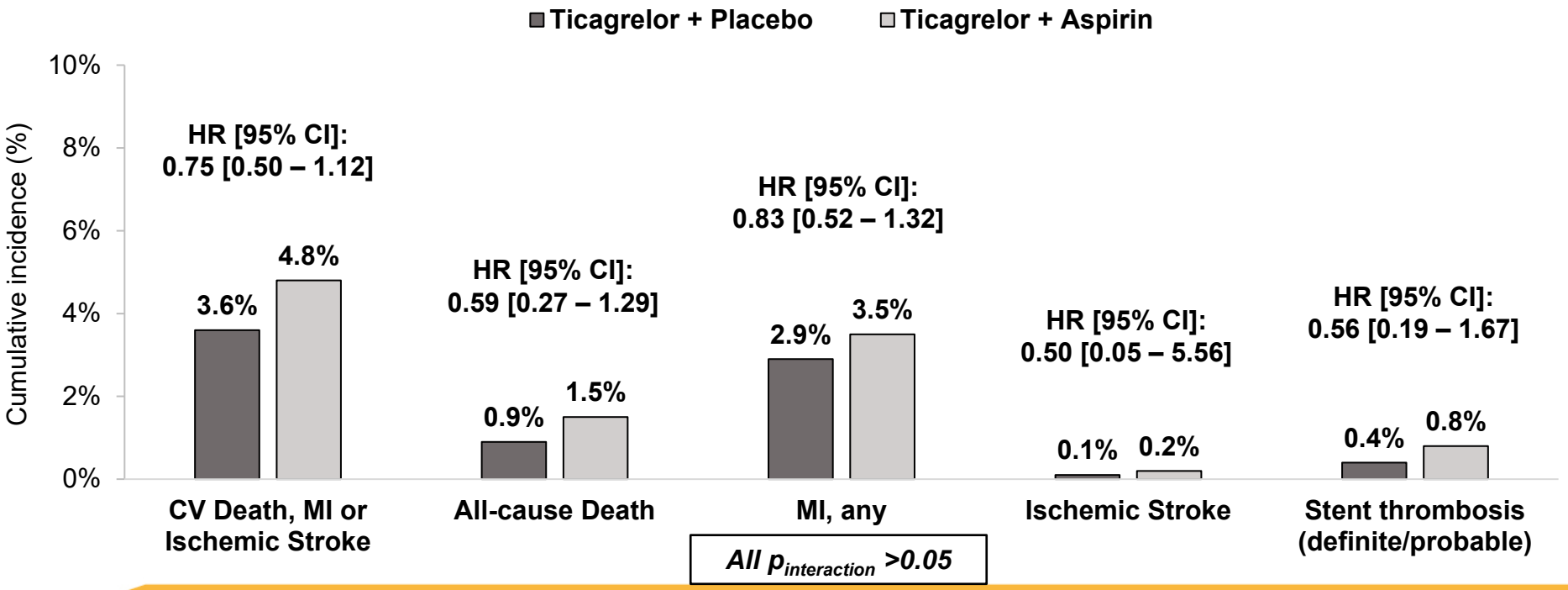
Prespecified Ischemic Endpoints (PP)

Complex PCI Patients



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Ischemic Events With and Without Complex PCI

Variable	Complex PCI patients (N = 2342)			Non-Complex PCI patients (N = 4777)			Interaction p-value
	Tica + Placebo (N = 1158)	Tica + Aspirin (N = 1184)	HR (95% CI)	Tica + Placebo (N = 2397)	Tica + Aspirin (N = 2380)	HR (95% CI)	
	no. of patients (%)			*no. of patients (%)*			
Death, MI or stroke	43 (3.8%)	56 (4.9%)	0.77 (0.52 – 1.15)	92 (3.9%)	81 (3.5%)	1.13 (0.84 – 1.53)	0.13
Cardiovascular death, MI or ischemic stroke	41 (3.6%)	55 (4.8%)	0.75 (0.50 – 1.12)	85 (3.6%)	75 (3.2%)	1.13 (0.83 – 1.54)	0.12
All-cause death	10 (0.9%)	17 (1.5%)	0.59 (0.27 – 1.29)	24 (1.0%)	28 (1.2%)	0.85 (0.49 – 1.47)	0.45
Cardiovascular death	9 (0.8%)	17 (1.5%)	0.53 (0.24 – 1.20)	17 (0.7%)	20 (0.9%)	0.84 (0.44 – 1.61)	0.39
MI	33 (2.9%)	40 (3.5%)	0.83 (0.52 – 1.32)	62 (2.6%)	55 (2.4%)	1.12 (0.78 – 1.61)	0.32
Ischemic stroke	1 (0.1%)	2 (0.2%)	0.50 (0.05 – 5.56)	15 (0.6%)	6 (0.3%)	2.49 (0.97 – 6.42)	0.23
Stent thrombosis (definite/probable)	5 (0.4%)	9 (0.8%)	0.56 (0.19 – 1.67)	9 (0.4%)	10 (0.4%)	0.89 (0.36 – 2.20)	0.52

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Limitations

- As a post-hoc analysis, randomization was not stratified by complex PCI status and we did not account for multiplicity thereby increasing the chance for a type 1 error.
- The complex PCI and the non-complex PCI groups were not individually powered to draw definite conclusions on the effect of a regimen of ticagrelor monotherapy on the bleeding and ischemic endpoints. However, the magnitude and direction of the effect were largely consistent with the overall trial findings.
- These results are not generalizable to all patients who undergo PCI due to the inclusion and exclusion criteria applied in the TWILIGHT trial.
- The observed treatment effects are applicable only to patients who tolerated an initial 3 months of DAPT with ticagrelor plus aspirin without any major adverse events. Whether the ticagrelor monotherapy findings are generalizable to a regimen of clopidogrel or prasugrel monotherapy remains unknown.

Conclusions

- Among patients who underwent complex PCI as defined by a combination of high-risk angiographic and procedural features, a regimen of ticagrelor monotherapy (after an initial 3 months of DAPT with ticagrelor plus aspirin) was associated with significantly lower clinically-relevant bleeding without increasing the risk of ischemic events compared to continuing the DAPT.

- This effect was consistent across the individual components of the complex PCI definition.

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Acknowledgement

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

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THANK YOU!