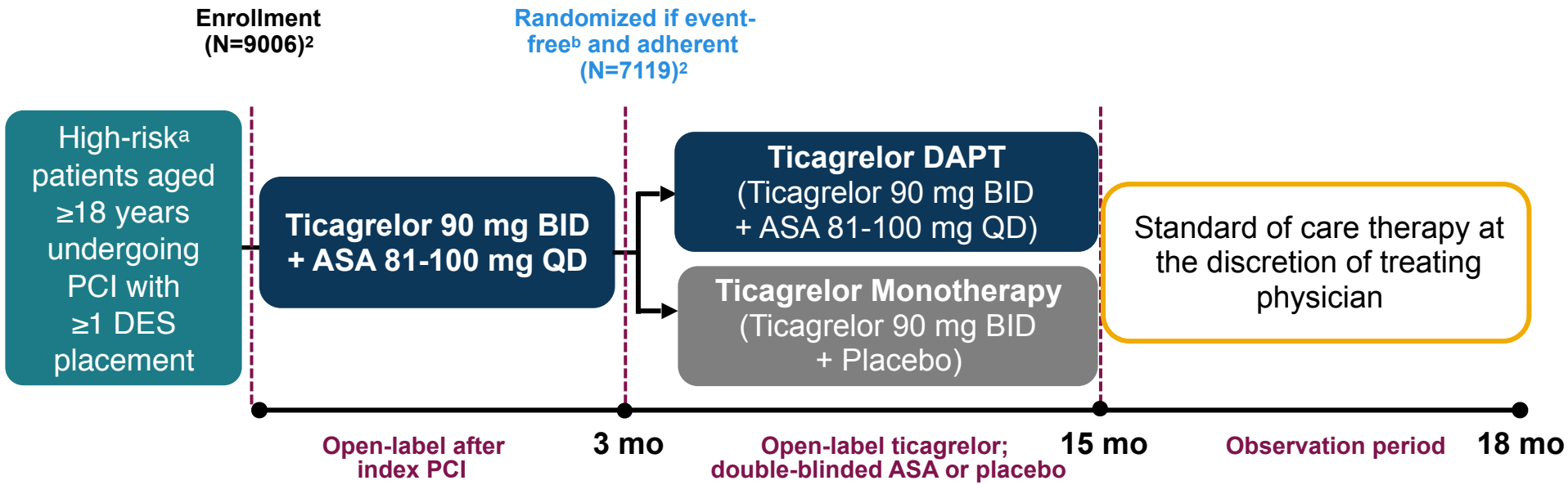
TWILIGHT

Ticagrelor With asplrin or aLone In hiGH-risk patients after coronary inTervention

TWILIGHT: Study Design Overview[1]



Primary composite endpoint (ITT):
Clinically relevant (BARC type 2, 3, or 5) bleeding during months 3-15

Key secondary endpoint (per protocol):
Composite of all-cause death, non-fatal MI, stroke during months 3-15[c]

[a]**High-risk patients must meet ≥1 criteria from both clinical and angiographic criteria (Inclusion criteria):**
- **Clinical:** ≥65 years of age, female, troponin positive ACS, established vascular disease (previous MI, documented PAD or CAD/PAD revascularization), DM treated with medications, CKD (eGFR <60 mL/min/1.73 m^2 or CrCl <60 mLmin)
- **Angiographic:** multivessel CAD, target lesion total stent length >30 mm, thrombotic target lesion, bifurcation lesions with Medina X, 1, 1 classification requiring ≥2 stents, left main ≥50% or proximal LAD ≥70% lesion, calcified target lesion requiring atherectomy

Exclusion Criteria

[b]**Event-free if none of the following:**
- Major bleeding (≥BARC type 3b); ischemic event after PCI (eg, non-fatal MI, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with DES); no longer taking DAPT with ticagrelor + ASA; non physician-guided cessation of ASA or ticagrelor of ≥5 consecutive days; current indication for oral anticoagulation or high dose ASA; renal failure requiring dialysis; woman of child bearing potential; refusal of randomization by patient or treating physician; withdrawal of consent; lost to follow-up

[c]Other secondary ischemic endpoints included time to first occurrence of: (i) CV death, non-fatal MI, ischemic stroke or clinically-driven revascularization; (ii) CV death, non-fatal MI or ischemic stroke; (iii) definite or probable stent thrombosis; (iv) CV death.

1. Baber U et al. *Am Heart J.* 2016;182:125-134; 2. Mehran R et al. *N Engl J Med*. 2019.

TWILIGHT: Inclusion and Exclusion Criteria

Inclusion Criteria

Clinical Criteria (must meet ≥ 1):

- ≥65 years of age
- Female
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revascularization)
- DM treated with medications
- CKD (eGFR <60mL/min/1.73m^2 or CrCl <60mL/min)

Angiographic Criteria (must meet ≥ 1):

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

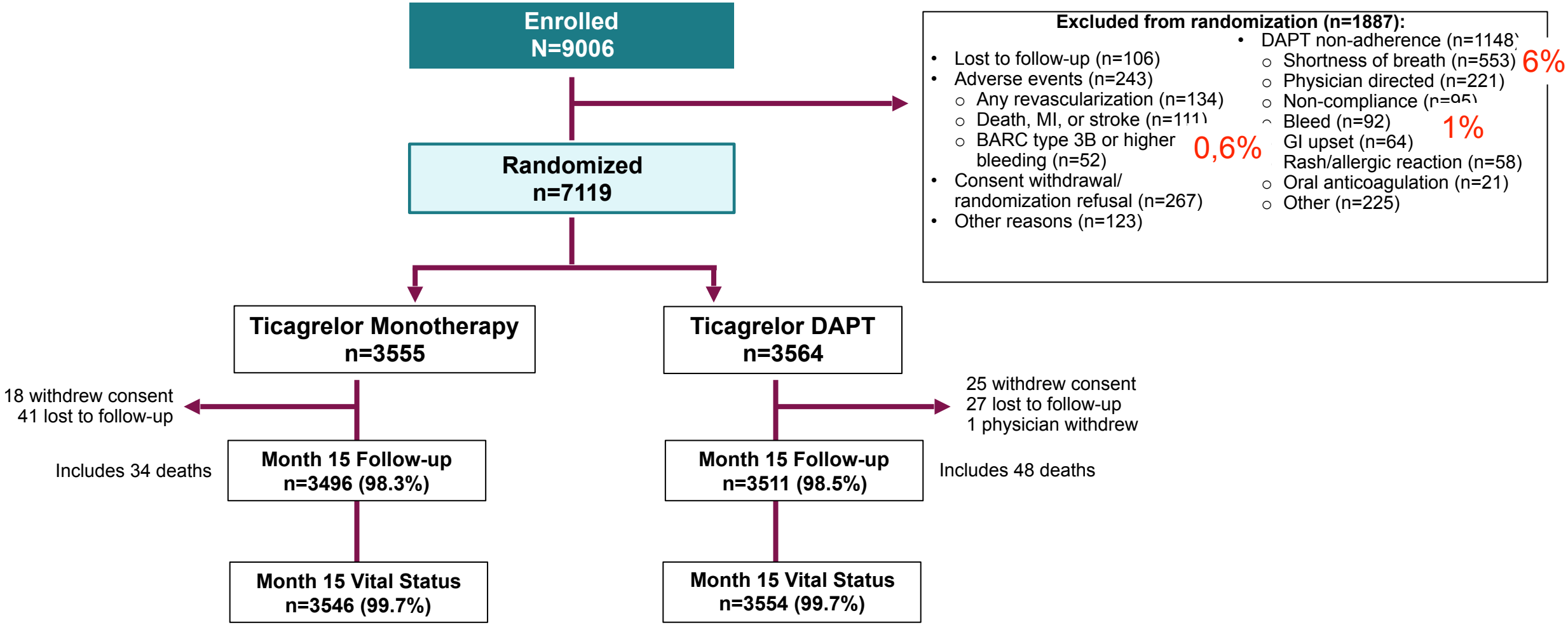
Exclusion Criteria

- <18 years of age
- Contraindication to ASA or ticagrelor
- Planned surgery or coronary revascularization within 90 days
- Need for chronic oral anticoagulation or ongoing ASA ≥325 mg
- Prior stroke
- Dialysis-dependent renal failure or liver cirrhosis
- Active bleeding or extreme-risk for major bleeding
- Salvage PCI or STEMI presentation
- Life expectancy <1 year
- Women of child bearing potential
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P450 3A inhibitor/ inducer
- Platelet count <100,000 mm^3

ACS = acute coronary syndrome; ASA = aspirin; CAD = coronary artery disease; CKD = chronic kidney disease; CrCl = creatinine clearance; DM = diabetes mellitus; eGFR = estimated glomerular filtration; LAD = left anterior descending; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Patient Distribution



BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GI = gastrointestinal; MI = myocardial infarction.

Mehran R et al. Article and supplementary appendix online ahead of print. *N Engl J Med*. 2019.

TWILIGHT: Baseline Demographics of the Randomized Population

Characteristic[a]	Ticagrelor Monotherapy (n=3555)	Ticagrelor DAPT (n=3564)
Clinical parameters		
Age, years (mean ± SD)	65.2 ± 10.3	65.1 ± 10.4
Female	846 (23.8)	852 (23.9)
Nonwhite race	1110 (31.2)	1086 (30.5)
BMI, kg/m^2 (mean ± SD)	28.6 ± 5.5	28.5 ± 5.6
Medical history		
Diabetes mellitus	1319 (37.1)	1301 (36.5)
Chronic kidney disease (eGFR <60mL/1.73m^2)	572/3410 (16.8)	573/3425 (16.7)
Anemia	675/3405 (19.8)	654/3423 (19.1)
Current smoker	726/3553 (20.4)	822/3562 (23.1)
Hypercholesterolemia	2157 (60.7)	2146 (60.2)
Hypertension	2580/3555 (72.6)	2574/3563 (72.2)
Peripheral arterial disease	245 (6.9)	244 (6.8)
Previous MI	1020 (28.7)	1020 (28.6)
Previous PCI	1502 (42.3)	1496 (42.0)
Previous CABG	362/3554 (10.2)	348/3564 (9.8)
Multivessel CAD	2272 (63.9)	2194 (61.6)
Previous major bleeding event	31 (0.9)	32 (0.9)
Indication for PCI		
Asymptomatic	234/3554 (6.6)	223/3563 (6.3)
Stable angina	1047/3554 (29.5)	999/3563 (28.0)
Unstable angina	1249/3554 (35.1)	1245/3563 (34.9)
NSTEMI	1024/3554 (28.8)	1096/3563 (30.8)

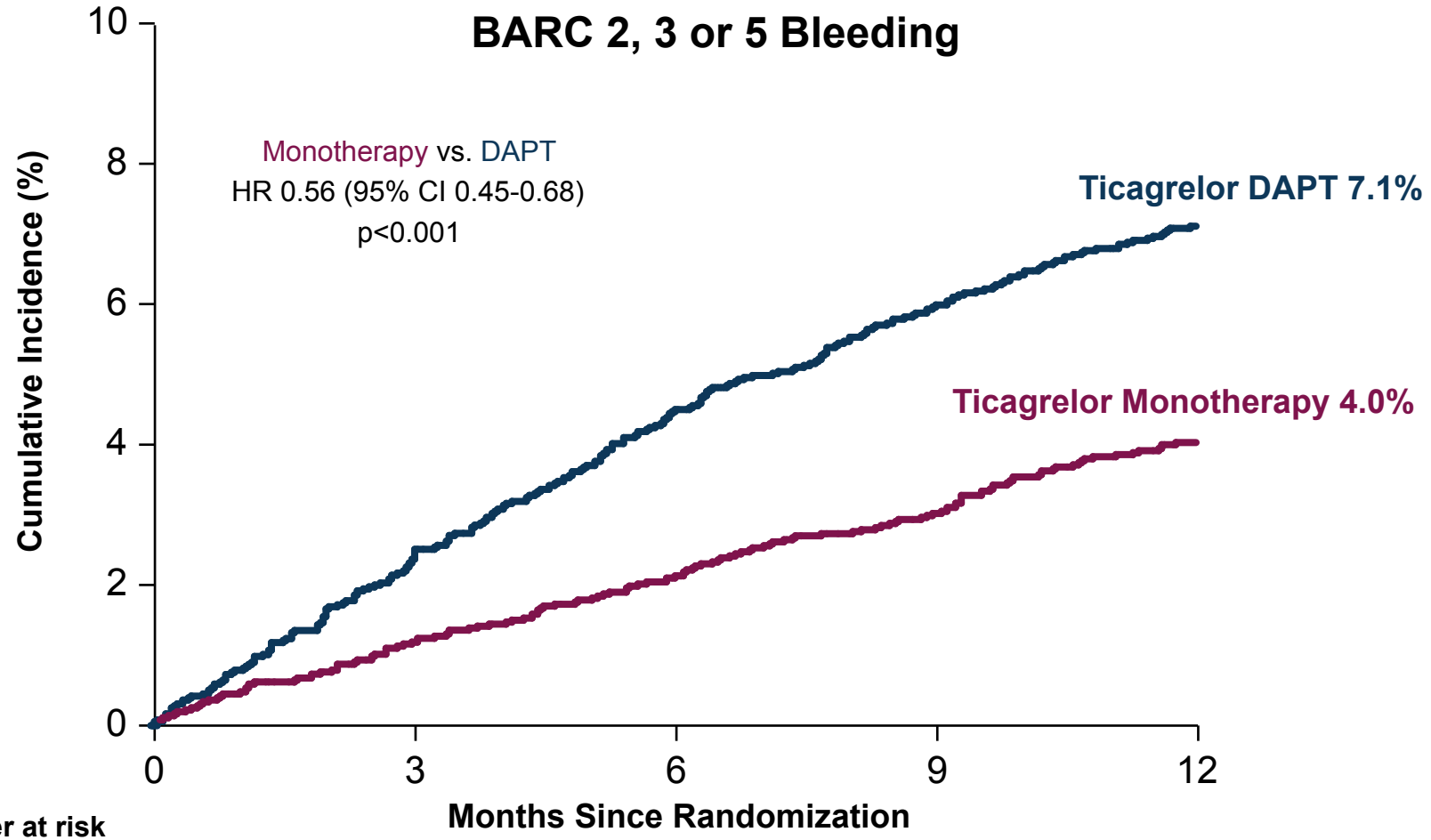
[a]Data presented as number (%) or number/total number of patients (%) unless otherwise noted.

Mehran R et al. Online ahead of print. *N Engl J Med*. 2019.

Procedural Characteristics of the Randomized Population

Baseline Characteristics of the Enrolled Cohort

TWILIGHT: Primary Endpoint[1]



Definitions of BARC Bleeding

Note: The primary endpoint analysis was performed in the ITT cohort, including those who were successfully randomized at the 3-month visit.[2]

1. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J*. 2016;182:125-134.

TWILIGHT: Primary and Pre-Specified Secondary Bleeding Outcomes[1]

Endpoint, n (K-M%)	Ticagrelor Monotherapy (n=3555)	Ticagrelor DAPT (n=3564)	HR (95% CI)	p-value
Primary endpoint				
BARC 2, 3, or 5	141 (4.0)	250 (7.1)	0.56 (0.45-0.68)	<0.001[a]
Secondary bleeding endpoints				
BARC 3 or 5	34 (1.0)	69 (2.0)	0.49 (0.33-0.74)	---
TIMI major or minor	141 (4.0)	250 (7.1)	0.56 (0.45-0.68)	---
GUSTO moderate or severe	26 (0.7)	49 (1.4)	0.53 (0.33-0.85)	---
ISTH major	39 (1.1)	72 (2.1)	0.54 (0.37-0.80)	---

Note: Bleeding analyses were performed in the ITT cohort, including those who were successfully randomized at the 3-month visit.[2]

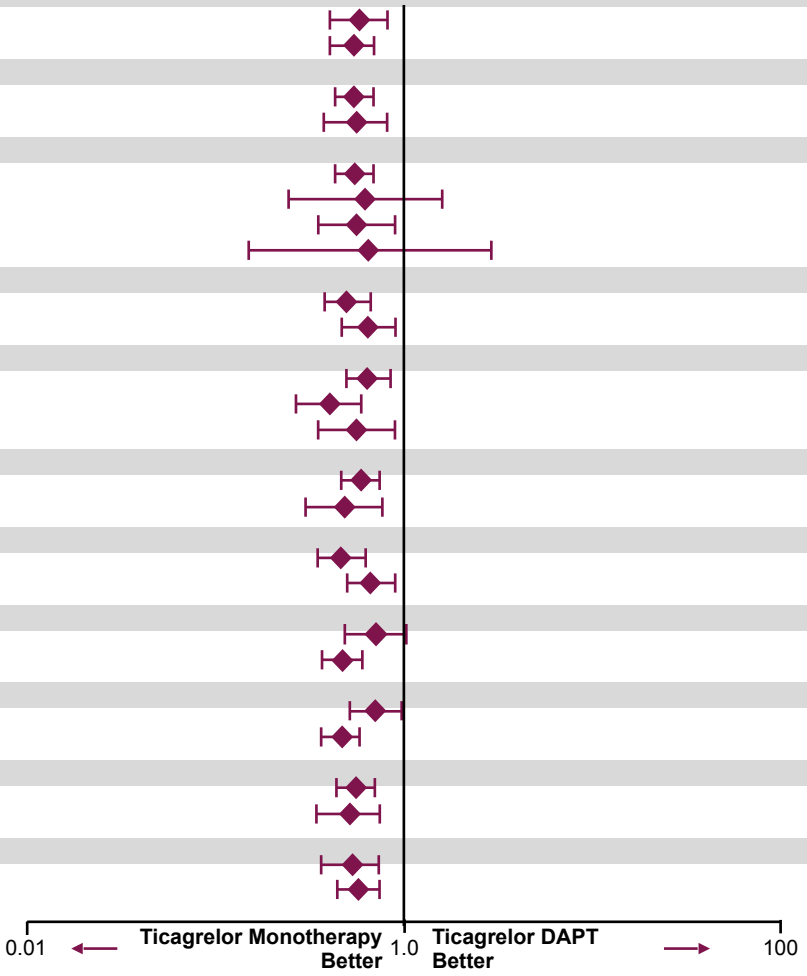
[a]Risk difference, -3.08%; 95% CI, -4.15% to -2.01%.

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and TPA for Occluded Arteries; HR = hazard ratio; ISTH = International Society of Thrombosis and Hemostasis; K-M = Kaplan-Meier; TIMI = Thrombolysis in Myocardial Infarction.

1. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Primary Endpoint of BARC 2, 3, or 5 Bleeding in Pre-specified Patient Subgroups[1]

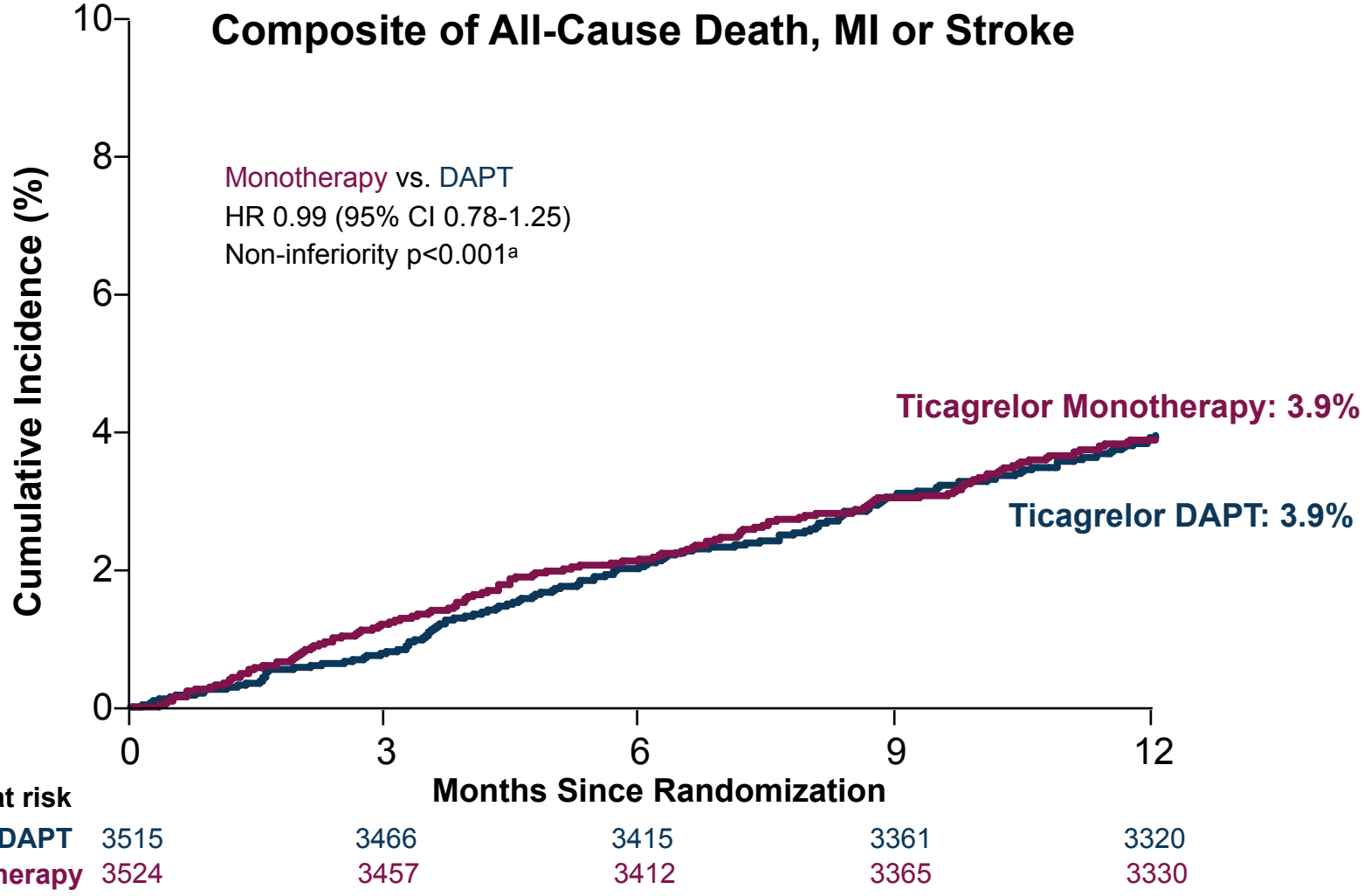
		n (%)		
Subgroups	**# of Patients**	**Ticagrelor Monotherapy**	**Ticagrelor DAPT**	**HR (95% CI)**
Age (years)				
<65	3400	59 (3.5)	100 (6.0)	0.59 (0.42-0.81)
≥65	3719	82 (4.5)	150 (8.2)	0.54 (0.41-0.70)
Sex				
Male	5421	99 (3.7)	178 (6.7)	0.55 (0.43-0.70)
Female	1698	42 (5.0)	72 (8.6)	0.57 (0.39-0.83)
Race/Ethnicity				
White	4923	104 (4.3)	189 (7.7)	0.55 (0.43-0.70)
Black	269	7 (5.5)	11 (8.3)	0.63 (0.24-1.62)
Asian	1784	27 (3.0)	46 (5.2)	0.57 (0.35-0.92)
Other	143	3 (4.0)	4 (6.2)	0.65 (0.15-2.90)
Diabetes Mellitus				
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				
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)
CKD (eGFR <60 mL/min)				
No	5690	113 (4.0)	188 (6.7)	0.60 (0.47-0.75)
Yes	1145	25 (4.5)	50 (8.9)	0.48 (0.30-0.78)
BMI (kg/m²)				
Below Median	3559	64 (3.7)	135 (7.7)	0.47 (0.35-0.63)
Above Median	3531	77 (4.4)	113 (6.5)	0.67 (0.50-0.90)
Indication for PCI				
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)				
<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)
Prior MI				
No	5079	104 (4.2)	179 (7.1)	0.57 (0.45-0.73)
Yes	2040	37 (3.7)	71 (7.1)	0.51 (0.34-0.76)
Multivessel Disease				
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)



Note: The primary endpoint analysis was performed in the ITT cohort, including those who were successfully randomized at the 3-month visit.[2]

1. Mehran R et al. Supplementary appendix. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Key Secondary Endpoint[1]



Note: The key secondary endpoint was performed in the per protocol cohort, including those who were randomized and completed all study-related contacts without any major protocol deviations.[2]
[a]Non-inferiority was tested at a one-sided alpha level of 0.025 using 1.6% as the absolute upper limit of the 95% CI.[2]
1. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

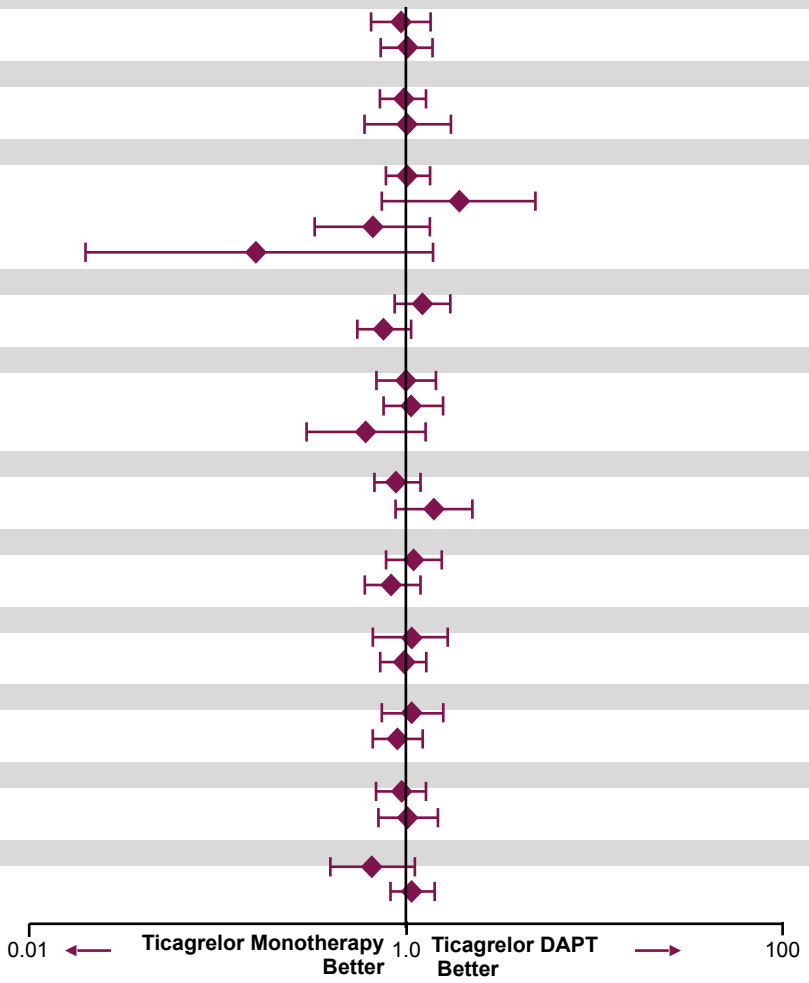
TWILIGHT: Secondary Ischemic Outcomes[1]

Endpoint, n (K-M%)	Ticagrelor Monotherapy (n=3524)	Ticagrelor DAPT (n=3515)	HR (95% CI)	Non-inferiority p-value
Key secondary ischemic outcome				
Composite of all-cause death, MI or stroke	135 (3.9)	137 (3.9)	0.99 (0.78-1.25)	<0.001[a]
Other ischemic endpoints				
Composite of CV death, MI or ischemic stroke	126 (3.6)	130 (3.7)	0.97 (0.76-1.24)	---
All-cause death	34 (1.0)	45 (1.3)	0.75 (0.48-1.18)	---
CV death	26 (0.8)	37 (1.1)	0.70 (0.43-1.16)	---
MI	95 (2.7)	95 (2.7)	1.00 (0.75-1.33)	---
Ischemic stroke	16 (0.5)	8 (0.2)	2.00 (0.86-4.67)	---
Stent thrombosis (definite or probable)	14 (0.4)	19 (0.6)	0.74 (0.37-1.47)	---

Note: Ischemic endpoints were performed in the per protocol cohort, including those who were randomized and completed all study contact visits without any major protocol deviations.[2]
[a]Non-inferiority was tested at a one-sided alpha level of 0.025 using 1.6% as the absolute upper limit of the 95% CI;[2] Risk difference,-0.06%; 95% CI, -0.97% to 0.84%.[1]
CV = cardiovascular; DAPT = dual antiplatelet therapy; HR = hazard ratio; K-M = Kaplan-Meier; MI = myocardial infarction.
1. Mehran R et al. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Key Secondary Endpoint (Composite of All-cause Death, MI or Stroke) in Pre-specified Patient Subgroups[1]

		n (%)		
Subgroups	**# of Patients**	**Ticagrelor Monotherapy**	**Ticagrelor DAPT**	**HR (95% CI)**
Age (years)				
<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				
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)
Race/Ethnicity				
White	4874	108 (4.5)	106 (4.4)	1.03 (0.79-1.35)
Black	267	13 (10.2)	7 (5.4)	1.91 (0.76-4.79)
Asian	1757	13 (1.5)	19 (2.2)	0.67 (0.33-1.35)
Other	141	1 (1.3)	5 (7.8)	0.16 (0.02-1.41)
Diabetes Mellitus				
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				
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)
CKD (eGFR <60 ml/min)				
No	5629	90 (3.2)	100 (3.6)	0.90 (0.68-1.20)
Yes	1133	43 (7.7)	31 (5.5)	1.40 (0.88-2.22)
BMI (kg/m²)				
Below Median	3520	72 (4.1)	65 (3.7)	1.11 (0.80-1.56)
Above Median	3490	62 (3.6)	72 (4.2)	0.85 (0.61-1.20)
Indication for PCI				
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)				
<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)
Prior MI				
No	5020	77 (3.1)	81 (3.3)	0.95 (0.70-1.30)
Yes	2019	58 (5.8)	56 (5.6)	1.03 (0.72-1.49)
Multivessel Disease				
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)

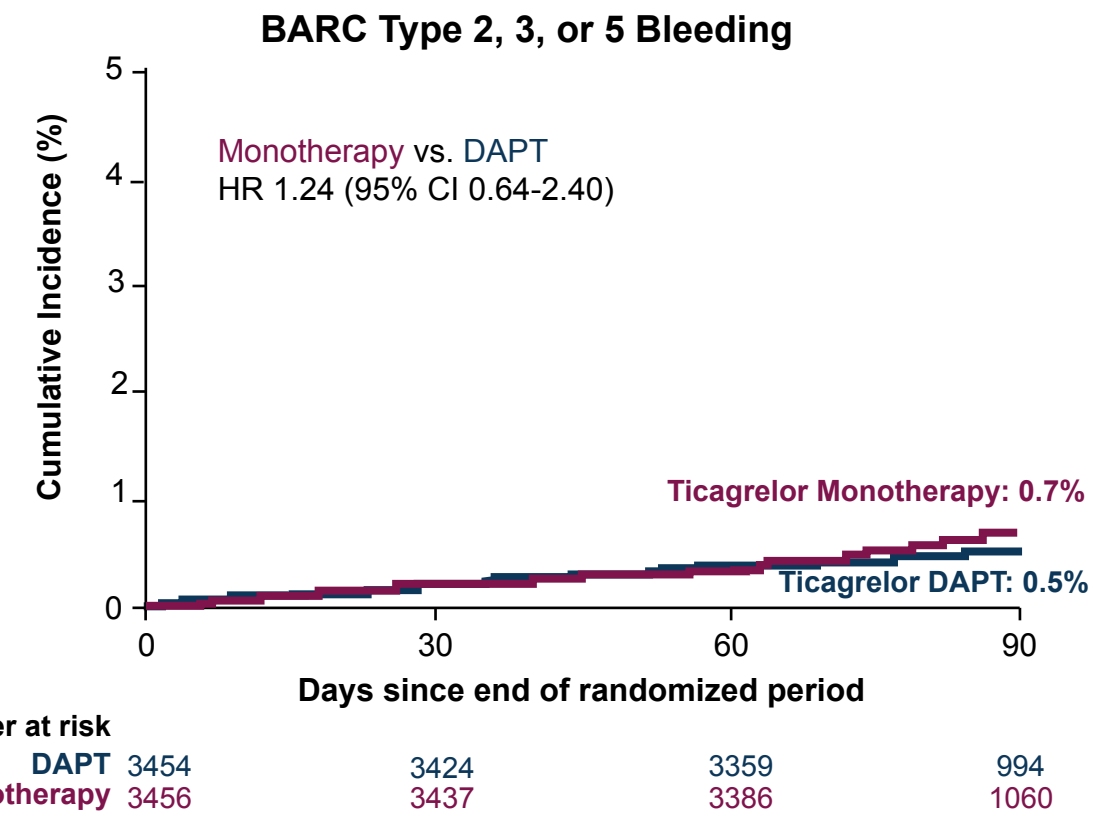


Note: Ischemic endpoints were performed in the per protocol cohort, including those who were randomized and completed all study contact visits.[2]

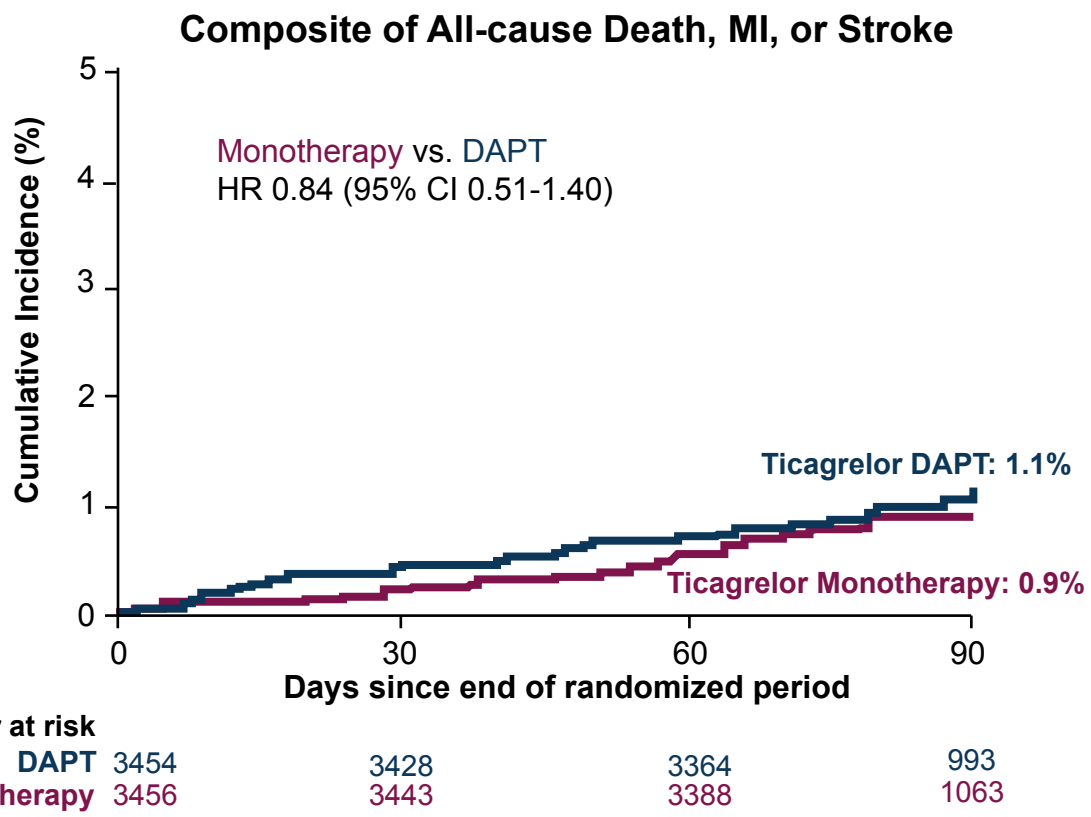
1. Mehran R et al. Supplementary appendix. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT: Landmark Analyses Between 15 and 18 Months After PCI (Observational Period)

Low bleeding event rate overall; no difference in BARC 2, 3 or 5 bleeding during the observational period



No difference in composite ischemic events during the observational period



BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Mehran R et al. Supplementary appendix. *N Engl J Med*. 2019.

TWILIGHT: Limitations

- Enrolled population of high-risk PCI patients that were chosen by a provider to receive ticagrelor 90 mg plus ASA DAPT, and those randomized had tolerated a 3 month DAPT run-in period, limiting generalizability
- Lack of power to detect differences in individual ischemic endpoints
- Lower than expected event rate for the key secondary ischemic endpoint

ASA = aspirin; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention.

Mehran R et al. *N Engl J Med*. 2019.

TWILIGHT: Conclusions

- In a population of PCI patients at high-risk for bleeding and ischemic events who had tolerated ticagrelor DAPT for 3 months, ticagrelor monotherapy significantly reduced BARC type 2, 3, or 5 bleeding by 44% compared to a ticagrelor DAPT regimen
  - The rate of BARC type 3 or 5 bleeding was reduced 51% with ticagrelor monotherapy compared to ticagrelor DAPT
- Ticagrelor monotherapy was non-inferior to ticagrelor DAPT for the composite endpoint of all-cause death, MI or stroke
- In patients who have undergone PCI with clinical and angiographic characteristics consistent with the TWILIGHT enrollment criteria, ticagrelor monotherapy after a 3-month course of ticagrelor DAPT, may be an option to reduce the risk of bleeding without ischemic harm

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Mehran R et al. Online ahead of print. *N Engl J Med*. 2019.