Less than 1-month dual anti-platelet therapy followed by ticagrelor monotherapy after coronary drug-eluting stent implantation for acute coronary syndrome: A randomized T-PASS trial

Myeong-Ki Hong, MD

on behalf of the T-PASS trial investigators

Professor, Yonsei University College of Medicine,
Severance Hospital, Seoul, Korea

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Background

- To achieve an optimal balance between ischemic and bleeding risks, various DAPT regimens have been studied in patients with acute coronary syndrome (ACS) who underwent PCI with DES implantation.

- The TICO[1] and TWILIGHT[2] trials have demonstrated that ticagrelor monotherapy after 3 months of DAPT significantly reduces bleeding risk without increasing ischemic events after PCI in ACS or high-risk PCI patients

- However, stopping aspirin less than 1 month after DES implantation for ticagrelor monotherapy has not been sufficiently evaluated for ACS patients

1. Kim BK & Hong SJ et al. *JAMA* 2020; 2. R Mehran et al. *N Engl J Med* 2019

Objective

- The aim of this study was to investigate whether ticagrelor monotherapy after <1 month of DAPT is noninferior to 12-month of ticagrelor-based DAPT for adverse cardiovascular and bleeding events (net adverse cardiovascular events, NACE) in patients with ACS who underwent PCI with DES implantation

Hypothesis

- The NACE of ticagrelor monotherapy after <1 month of DAPT would be noninferior to 12-month of ticagrelor-based DAPT after DES implantation in ACS patients. If significant, the superiority hypothesis would then be evaluated.

Study Design

- **A prospective, randomized, multi-center trial**
- **At 24 centers in Korea**
- **Enrollment period: Apr 2019 and May 2022**

Key inclusion criteria	Key exclusion criteria
1. Age ≥19 years 2. Patients who received bioresorbable polymer sirolimus-eluting stent implantation to treat **ACS** 3. Provision of informed consent	1. Age >80 years 2. Increased risk of bleeding due to: Any prior event of hemorrhagic stroke; Ischemic stroke, dementia, or impairment of CNS within a year; Traumatic brain injury or surgery within the past 6 months; Known intracranial tumor; Documented or suspected aortic dissection; Internal bleeding within the past 6 weeks; Active bleeding or bleeding diathesis; Anemia (Hb ≤8 g/dL) or thrombocytopenia (Plt <100,000/μL); Surgery or injury resulting in physical activity impairment <3 wks 3. Need for oral anticoagulation therapy 4. Current or potential pregnancy 5. Life expectancy <1 year

Schematic Study Design

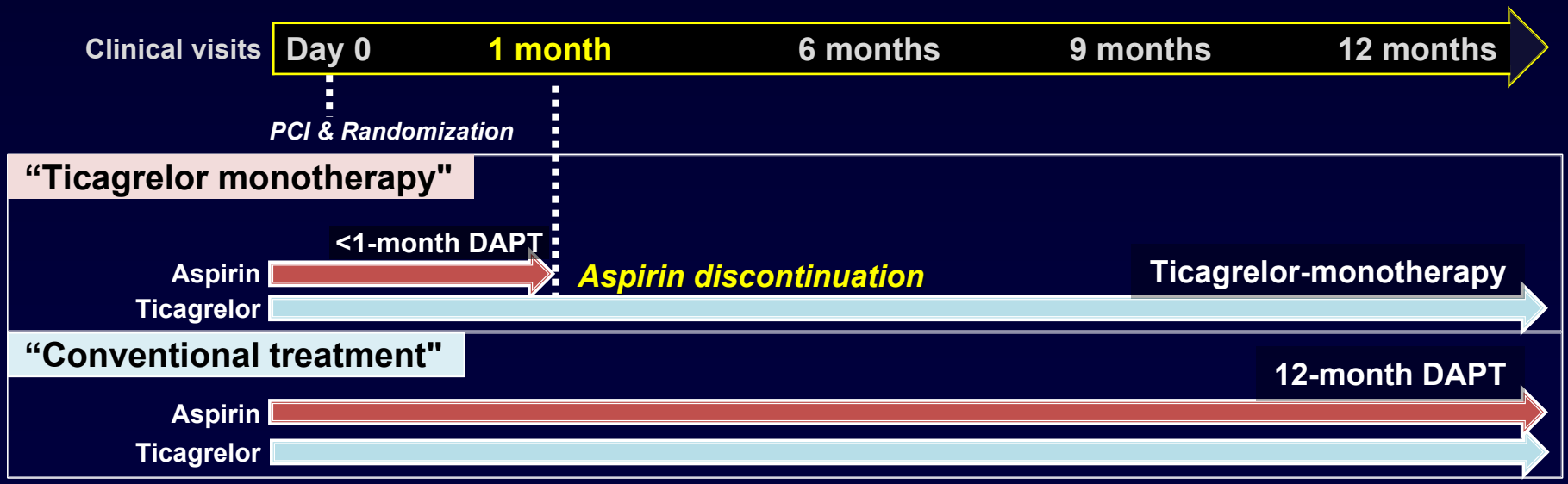
ACS patients undergoing BP-SES (Orsiro, Biotronik, Switzerland)

1:1 Randomization

Stratified by *DM* and *STEMI*

Primary endpoint: Net clinical adverse events at 12M
- A composite of death, MI, stent thrombosis, stroke or major bleeding (BARC type 3 or 5)

Ticagrelor monotherapy after <1-month DAPT	Ticagrelor-based 12-month DAPT



Clinicaltrials.gov Identifier: NCT03797651

Outcomes

- **Primary outcome:**

Net adverse clinical event (NACE) at 12 months

- **Major Bleeding (BARC type 3 or 5)**

+

- **Major Adverse Cardiovascular Events**

  All-cause death, MI, stent thrombosis, or stroke

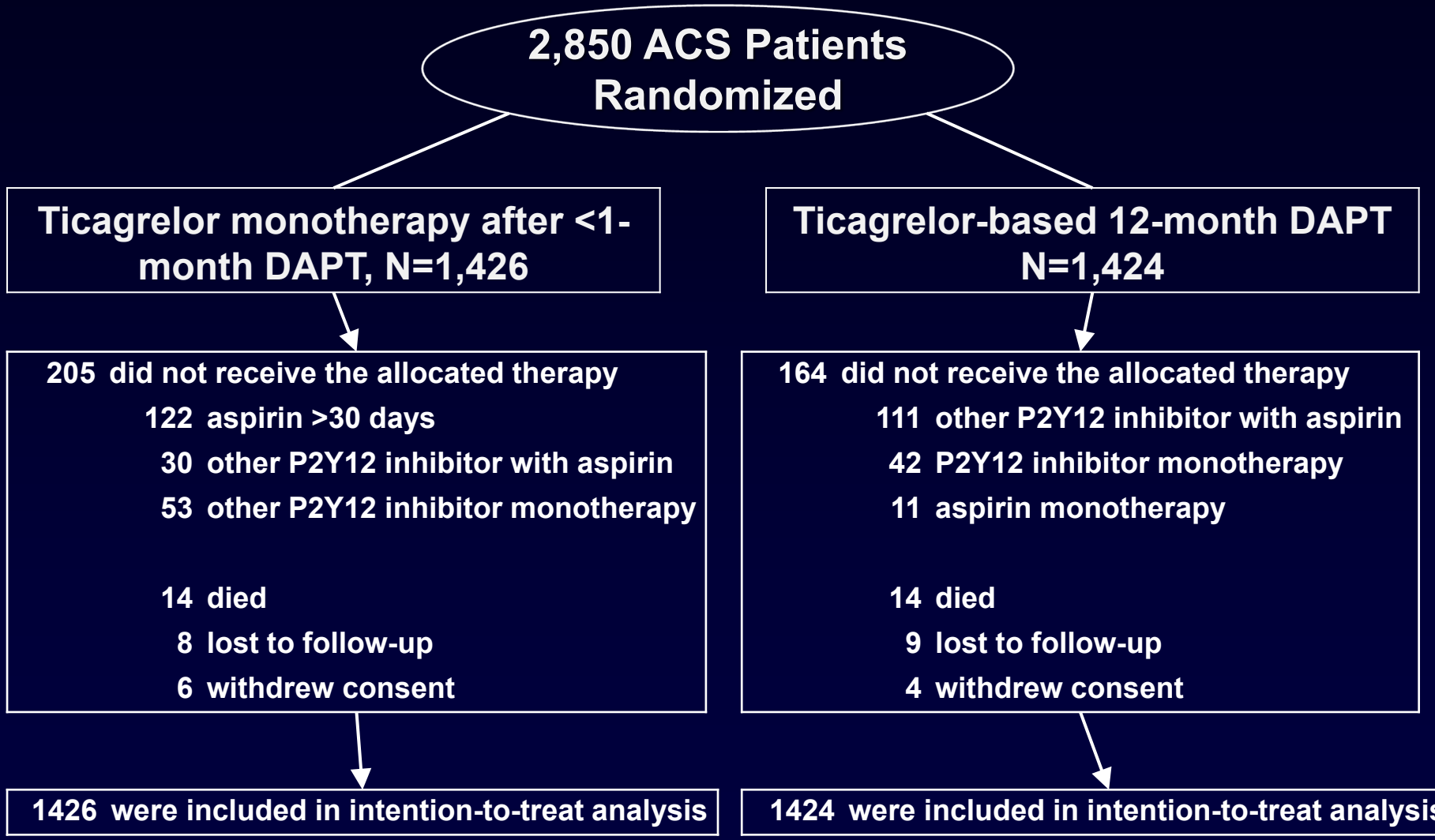
Statistical Analysis

- **Sample size calculation**
  - Power calculations were based on a non-inferiority assumption
    - Non-inferiority margin: hazard ratio (HR) of 1.3
    - Expected clinical event rates : 14% in both groups
    - Expected follow-up loss rate: 10%

    → A total of 2,850 patients was required, with a 5% one-sided α error rate and 80% statistical power

- **Primary analysis**
  - Intention-to-treat population
  - Kaplan-Meier estimates for the comparisons of the study outcomes
  - HR and 95% CI generated with Cox proportional-hazards models

Study Flow


2,850 ACS Patients Randomized
Ticagrelor monotherapy after <1-month DAPT, N=1,426
Ticagrelor-based 12-month DAPT N=1,424
205 did not receive the allocated therapy
122 aspirin >30 days
30 other P2Y12 inhibitor with aspirin
53 other P2Y12 inhibitor monotherapy
14 died
8 lost to follow-up
6 withdrew consent
164 did not receive the allocated therapy
111 other P2Y12 inhibitor with aspirin
42 P2Y12 inhibitor monotherapy
11 aspirin monotherapy
14 died
9 lost to follow-up
4 withdrew consent
1426 were included in intention-to-treat analysis
1424 were included in intention-to-treat analysis

Baseline Characteristics (1)

*Characteristics	Ticagrelor Monotherapy after <1-m DAPT (N=1426)	Ticagrelor-based 12-m DAPT (N=1424)
Age, yrs	61 ± 10	61 ± 10
Men	1193 (84%)	1181 (83%)
Body mass index, kg/m^2	25.1 ± 3.6	25.0 ± 3.5
Hypertension	669 (47%)	679 (48%)
Diabetes mellitus	422 (30%)	408 (29%)
Diabetes treated by insulin	40 (3%)	32 (2%)
Chronic kidney disease	292 (19%)	328 (22%)
Current smoker	557 (39%)	537 (38%)
Prior myocardial infarction	27 (2%)	25 (2%)
Prior percutaneous coronary intervention	92 (7%)	92 (7%)
Prior coronary bypass graft	4 (<1%)	2 (<1%)
Prior stroke	43 (3%)	49 (3%)

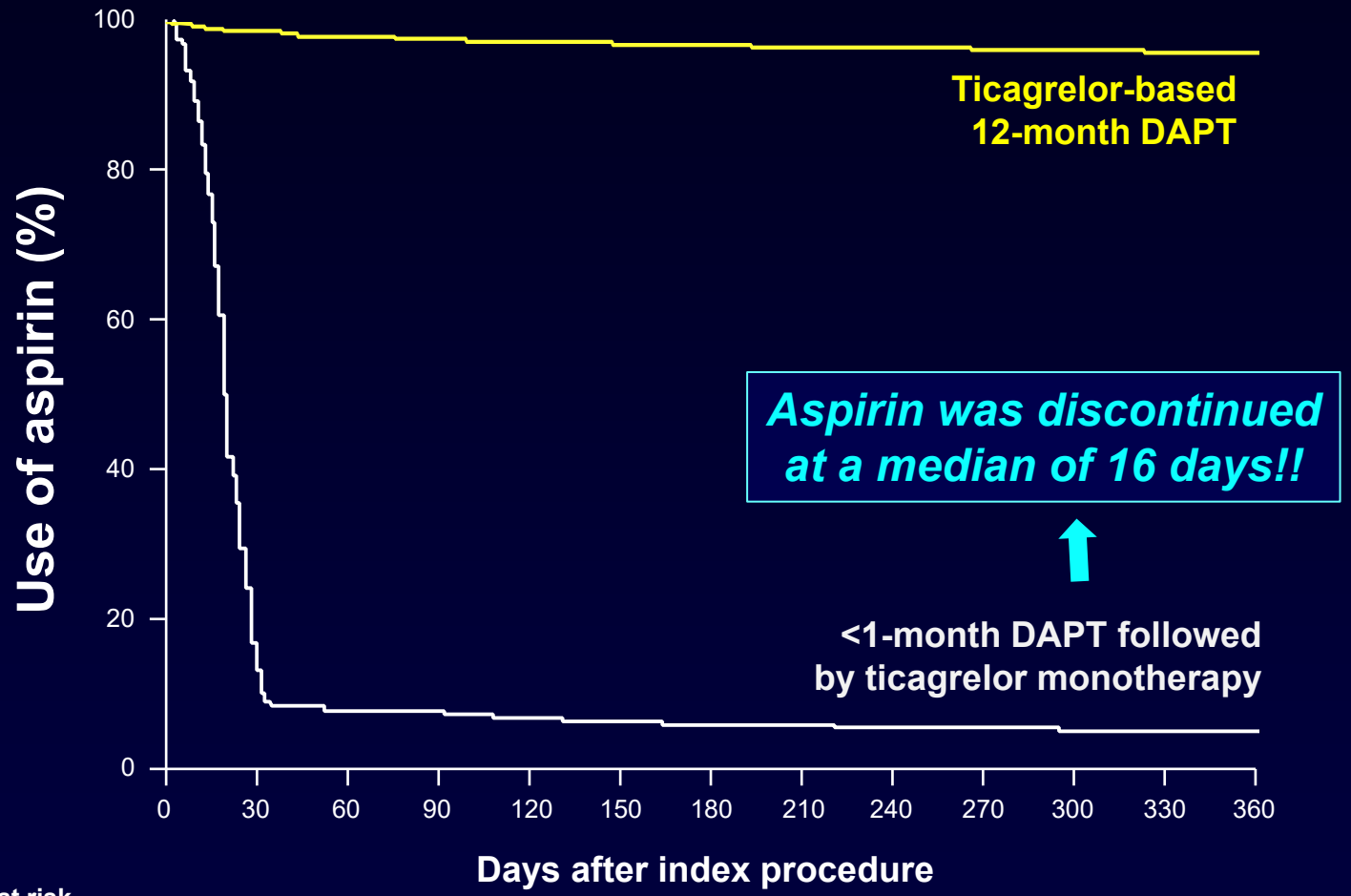
*Baseline characteristics were equal between the two groups.

Baseline Characteristics (2)

*Characteristics	Ticagrelor Monotherapy after <1-m DAPT (N=1426)	Ticagrelor-based 12-m DAPT (N=1424)
Admission via emergency room	1056 (74%)	1050 (74%)
Clinical presentation		
Unstable angina	347 (24%)	361 (25%)
Non-ST-elevation MI	507 (36%)	485 (34%)
ST-elevation MI	**572 (40%)**	**578 (41%)**
Transfemoral approach	467 (33%)	470 (33%)
Bifurcation lesion	219 (15%)	215 (15%)
2- or 3-vessel diseases	749 (53%)	738 (52%)
Multi-lesion intervention	299 (21%)	279 (20%)
Multi-vessel intervention	233 (16%)	231 (16%)
Treated lesions per patient, n	1.3 ± 0.5	1.2 ± 0.5
Total number of stents per patient, n	1.4 ± 0.8	1.4 ± 0.7
Total stent length per patient, mm	38 ± 23	37 ± 22

*Baseline characteristics were equal between the two groups.

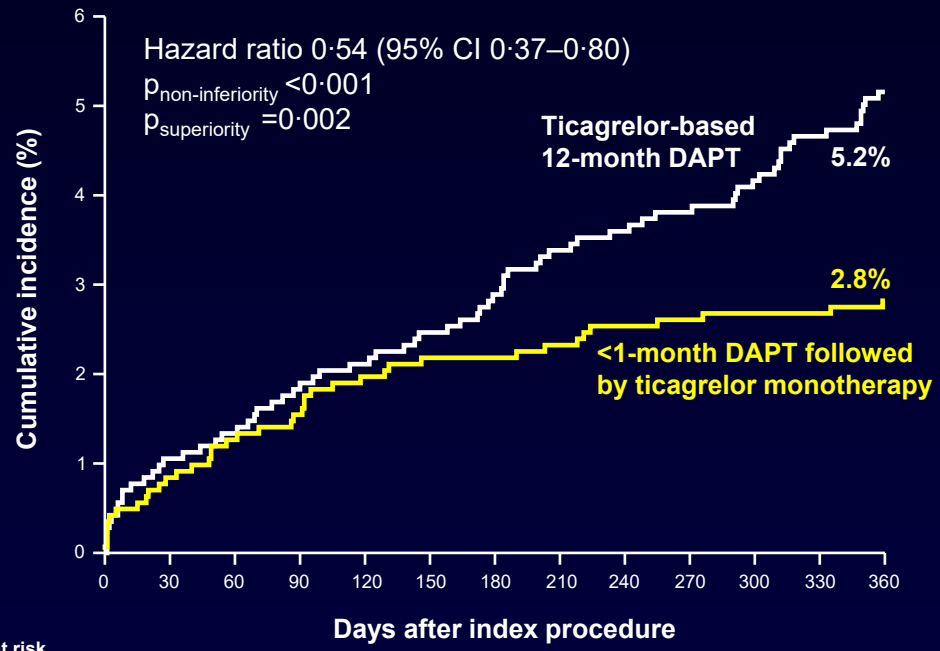
Proportion of use of aspirin



No. at risk						
12-m DAPT	1424	1404	1382	1367	1362	1357
<1-m DAPT	1426	138	101	87	80	77

Primary Outcome (NACE)

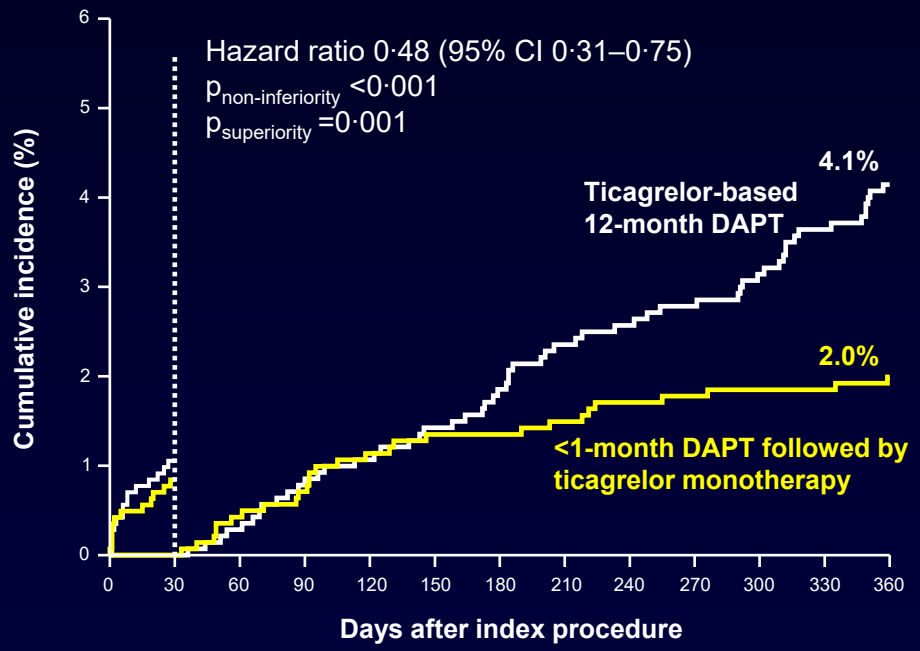
12-month Clinical Outcome



No. at risk

12-m DAPT	1424	1406	1401	1393	1384	1379	1373	1365	1361	1358	1353	1346	1338
<1-m DAPT	1426	1410	1401	1397	1388	1383	1382	1380	1377	1375	1374	1374	1372

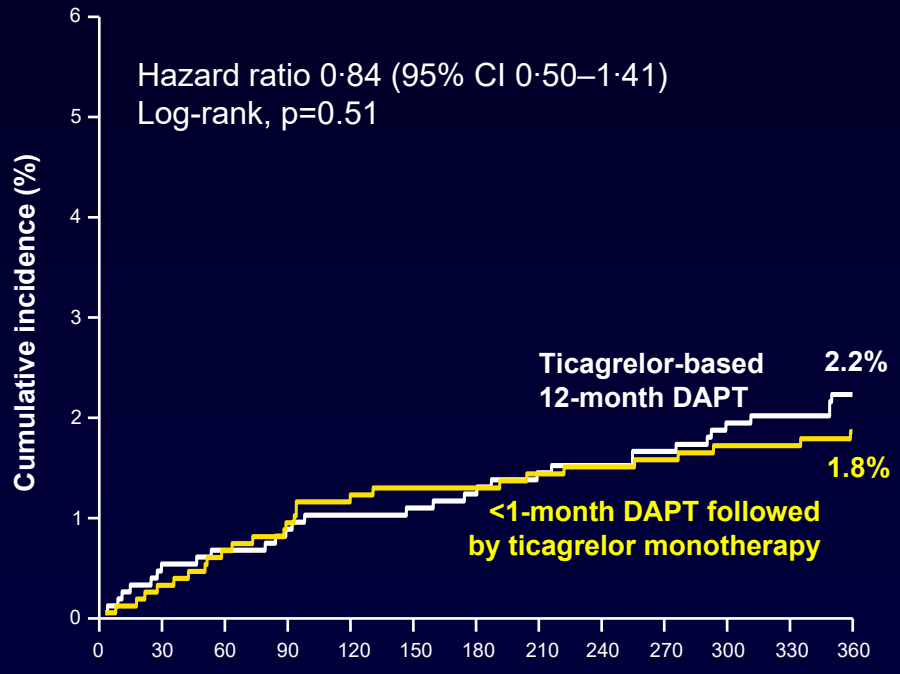
1-month Land-mark Analyses



1406	1401	1393	1384	1379	1373	1365	1361	1358	1353	1346	1338
1409	1401	1397	1388	1383	1382	1380	1377	1375	1374	1374	1372

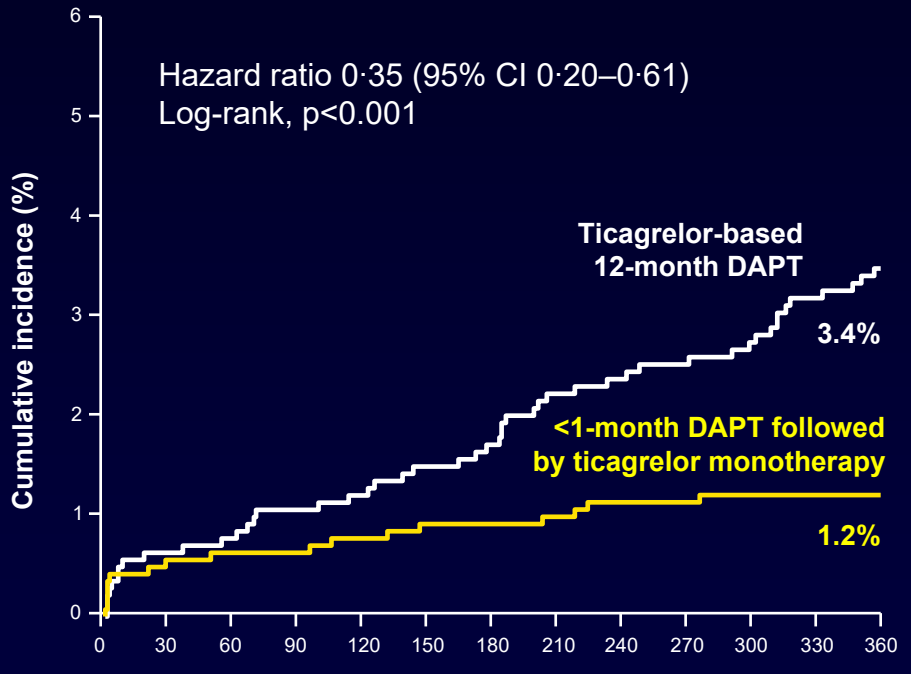
MACCE and Major Bleeding

Death, MI, Stent thrombosis or Stroke



No. at risk													
12-m DAPT	1424	1414	1411	1407	1400	1399	1396	1393	1391	1389	1385	1384	1380
<1-m DAPT	1426	1418	1410	1406	1399	1396	1395	1393	1392	1390	1388	1388	1386

Major bleeding



	1424	1411	1406	1400	1392	1387	1383	1375	1371	1369	1365	1358	1352
	1426	1412	1406	1404	1397	1392	1391	1389	1386	1385	1384	1384	1384

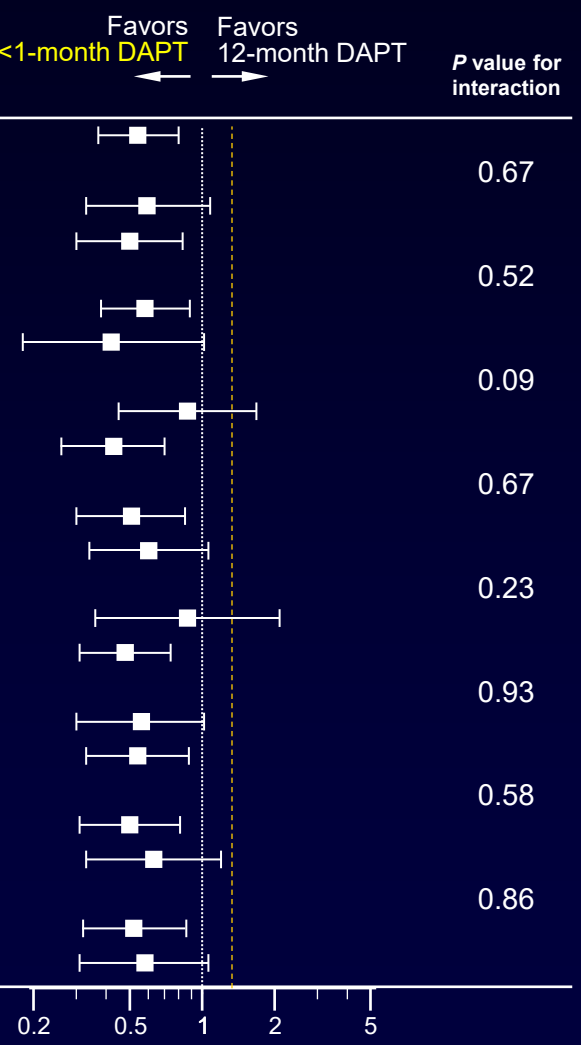
Clinical Outcomes at 12 months

Outcomes	Ticagrelor Monotherapy after 1-m DAPT (N=1426)	Ticagrelor-based 12-m DAPT (N=1424)	Hazard Ratio (95% CI)	*P* Value
Primary outcome				
Net adverse clinical event	40 (2.8%)	73 (5.2%)	0.54 (0.37 to 0.80)	0.002†
Secondary outcome				
Major bleeding (BARC type 3 or 5)	25 (1.7%)	45 (3.0%)	0.35 (0.20 to 0.61)	<0.001
Any bleeding (BARC type ≥2)	28 (2.0%)	64 (4.5%)	0.43 (0.28 to 0.68)	<0.001
Major adverse cardiac events	21 (1.5%)	32 (2.2%)	0.68 (0.39 to 1.18)	0.17
Death	14 (1.0%)	14 (1.0%)	1.00 (0.48 to 2.10)	>0.99
Cardiac	6	9		
Acute MI	7 (0.5%)	8 (0.6%)	0.88 (0.32 to 2.41)	0.80
Stent thrombosis	2 (0.1%)	2 (0.1%)	1.00 (0.14 to 7.09)	>0.99
Stroke	8 (0.6%)	11 (0.8%)	0.73 (0.29 to 1.81)	0.49
Ischemic	6	8		
Hemorrhagic	2	3		
Target-vessel revascularization	11 (0.8%)	18 (1.3%)	0.61 (0.29 to 1.29)	0.20

†P values for superiority test were derived from the log-rank test.

Subgroup analysis for primary outcome

Subgroup	No. /Total (%) Ticagrelor monotherapy after <1-month DAPT	No. /Total (%) Ticagrelor-based 12-month DAPT	HR (95% CI)	*P* value for interaction
All patients	40/1426 (2.8)	73/1424 (5.2)	0.54 (0.37-0.80)	
Age, years				0.67
<65	17/888 (1.9)	29/901 (3.2)	0.59 (0.33-1.08)	
≥65	23/538 (4.3)	44/523 (8.5)	0.50 (0.30-0.83)	
Sex				0.52
Men	33/1193 (2.8)	56/1181 (4.8)	0.58 (0.38-0.89)	
Women	7/233 (3.0)	17/243 (7.1)	0.42 (0.18-1.02)	
Diabetes mellitus				0.09
Yes	17/422 (4.1)	19/408 (4.7)	0.87 (0.45-1.68)	
No	23/1004 (2.3)	54/1016 (5.3)	0.43 (0.26-0.70)	
Hypertension				0.67
Yes	21/669 (3.2)	42/679 (6.2)	0.51 (0.30-0.85)	
No	19/757 (2.5)	31/745 (4.2)	0.60 (0.34-1.06)	
Chronic kidney disease				0.23
Yes	10/118 (8.6)	10/104 (9.7)	0.87 (0.36-2.10)	
No	30/1308 (2.3)	63/1320 (4.8)	0.48 (0.31-0.74)	
ST-elevation MI				0.93
Yes	16/572 (2.8)	29/578 (5.0)	0.56 (0.30-1.02)	
No	24/854 (2.8)	44/846 (5.2)	0.54 (0.33-0.88)	
Multivessel disease				0.58
Yes	25/749 (3.4)	49/738 (6.7)	0.50 (0.31-0.81)	
No	15/677 (2.2)	24/686 (3.5)	0.63 (0.33-1.20)	
Total stent length, mm				0.86
≥30	24/791 (3.1)	45/788 (5.7)	0.53 (0.32-0.87)	
<30	16/635 (2.5)	28/636 (4.4)	0.57 (0.31-1.05)	



Limitations

- Study power was calculated by estimating the occurrence of NACE.
  - Thus, comparisons of the occurrence of each component, particularly MACE, could be underpowered.
- Our study was an open-label trial and not placebo-controlled.
  - All clinical outcomes were assessed by members of an independent clinical event adjudication committee.
- The event rates were lower than the previous trials used in sample size calculation
  - The primary outcome satisfied the noninferiority and the subsequent superiority test.

Conclusions

Among patients treated with ultrathin biodegradable polymer sirolimus eluting stents for ACS,

- <1 month of DAPT followed by ticagrelor monotherapy met a noninferiority threshold and provided evidence of superiority to 12 months of ticagrelor-based DAPT for a 1-year composite outcome of death, myocardial infarction, stent thrombosis, stroke, and major bleeding, primarily due to a significant reduction in bleeding events.
- This study provides evidence that stopping aspirin within 1 month after implantation of drug-eluting stents for ticagrelor monotherapy is a reasonable alternative to 12-month DAPT as for adverse cardiovascular and bleeding events.


Dreams will
come true