TICO-STEMI: A Randomized Trial of Ticagrelor Monotherapy vs. Ticagrelor With Aspirin in STEMI

Late-Breaking Clinical Trial at 2020 TCT Connect

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On the behalf of the TICO trial investigators

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Disclosure Statement of Financial Interest

I, Byeong-Keuk Kim DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Background

- **From the randomized trials,[1-3] the *potent P2Y12 inhibitor monotherapy after brief period of DAPT* has been considered as the optimal treatment strategy for high-risk patients balancing the ischemic and bleeding risks.**

1. *Vranckx P, et al. GLOBAL-LEADERS. Lancet 2018;392:940-9.*
2. *Mehran R,, et al. TWILIGHT. N Engl J Med 2019;381:2032-42.*
3. *Kim BK, et al. TICO. JAMA 2020;323:2407-16.*

- **Of these, *TICO trial*** (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome) **was targeted for *ACS patients including all subsets of ACS;* patients with *STEMI*, which was regarded as a highest risk for recurrent thrombotic events, was enrolled.[3]**

Research

JAMA | Original Investigation

Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome

The TICO Randomized Clinical Trial

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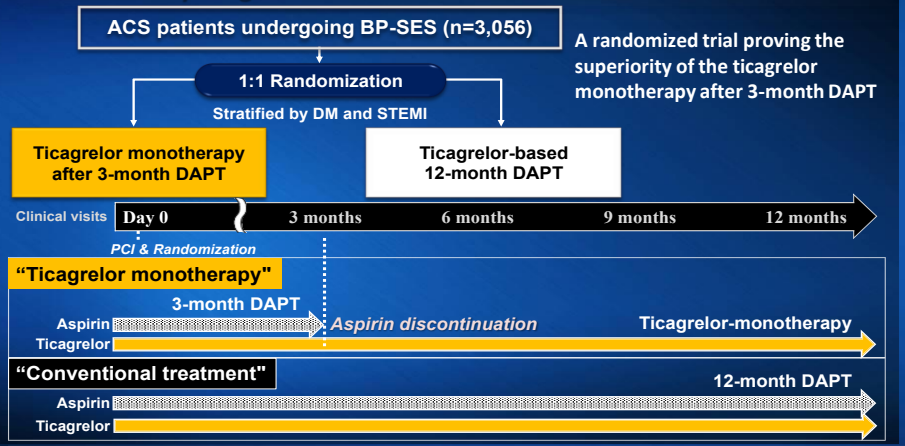
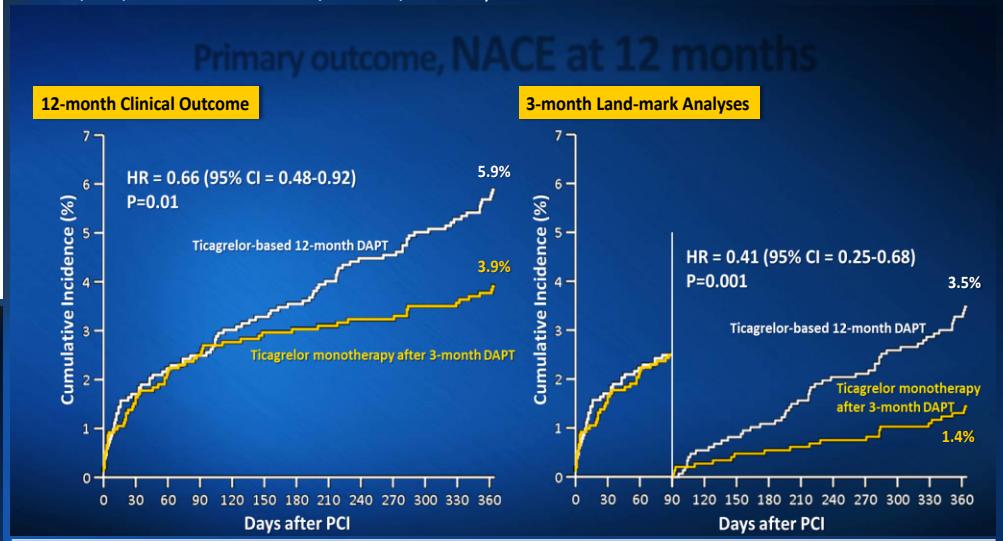
Schematic study design of the TICO trial

Clinicaltrials.gov Identifier: NCT02494895 Kim C,...& Kim BK. Am Heart J. 2019 ;212:45-52



Primary outcome: **Net adverse clinical event (NACE)**, defined as a composite of major bleeding (TIMI-major) and major adverse cardiac and cerebrovascular events (all-cause death, MI, stent thrombosis, stroke, or TVR)



Outcomes	Ticagrelor Monotherapy after 3-m DAPT (N=1527)	Ticagrelor-based 12-m DAPT (N=1529)	Hazard Ratio (95% CI)	*P* Value
Primary outcome				
Net adverse clinical event	59 (3.9%)	89 (5.9%)	0.66 (0.48 to 0.92)	.01
Secondary outcome				
TIMI major bleeding	25 (1.7%)	45 (3.0%)	0.56 (0.34 to 0.91)	.02
MACCE	35 (2.3%)	51 (3.4%)	0.69 (0.45 to 1.06)	.09

Conclusion. ***Among ACS patients treated with DESs, Ticagrelor monotherapy after 3-month DAPT showed a significantly lower risk of NACE than the ticagrelor-based 12-month DAPT; Reduced risk was mainly due to decreased major bleeding without increasing risk of MACCE).***

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Kim et al. *JAMA*. 2020;323(23):2407-16

TICO trial for patients with ACS

- **TICO trial targeted all subsets of ACS, including STEMI (with random stratification).**

	Ticagrelor Monotherapy after 3-M DAPT (N=1527)	Ticagrelor-based 12-M DAPT (N=1529)
Clinical presentation		
Unstable angina	442 (29%)	484 (32%)
Non-ST-elevation MI	539 (35%)	488 (32%)
ST-elevation MI	546 (36%)	557 (36%)

- **Randomized trials evaluating *potent P2Y12 inhibitor monotherapy after short-term DAPT* following DES implantation**

	GLOBEAL LEADERS[1]	TWILIGHT[2]	TICO[3]
Year of publication	2018	2019	2020
ACS, %	47%	65%	**100%**
STEMI, %	0% (excluded)	0% (excluded)	**36% (included)**
DAPT duration after PCI	1 M	3 M	3 M
Primary Endpoint	All-cause mortality or new Q-MI	BARC type 2, 3, or 5 bleeding	Net adverse clinical event; (TIMI major bleeding + MACCE)

1. Vranckx P, et al. GLOBAL-LEADERS. Lancet 2018;392:940-9.
2. Mehran R,, et al. TWILIGHT. N Engl J Med 2019;381:2032-42.
3. Kim BK, et al. TICO. JAMA 2020;323:2407-16.

Objective of the TICO-STEMI study

- To assess the safety and feasibility of **ticagrelor monotherapy after 3 months of DAPT in STEMI patients** treated with ultrathin bioresorbable polymer sirolimus-eluting stents, using a prespecified subgroup analyses of the STEMI cohort of the TICO trial

TICO trial …
- A prospective, randomized, multi-center trial conducted at 38 centers in South Korea
- All types of ACS (UA, 30.3%; NSTEMI, 33.6%; and STEMI, 36.1%) were enrolled.
- According to the presence of STEMI, stratified randomization was performed.

Key inclusion criteria	Key exclusion criteria
1. Age ≥19 years 2. Patients with **ACS (UA, NSTEMI, STEMI)** who received bioresorbable polymer sirolimus-eluting stent implantation	1. Age >80 years 2. Any prior hemorrhagic stroke 3. Ischemic stroke, dementia, or impairment of CNS within a year 4. Documented or suspected aortic dissection 5. Internal bleeding within the past 6 weeks and active bleeding 6. Anemia (Hb ≤8 g/dL) or thrombocytopenia (Plt <100,000/μL); 7. Need for oral anticoagulation therapy

Outcomes

- **Primary outcome:**

  Net adverse clinical event (NACE) at 12 months including bleeding and ischemic outcomes

  - **Bleeding outcomes – TIMI major bleeding**
  - **Ischemic outcomes – Major adverse cardiac & cerebrovascular event (MACCE); all-cause death, MI, stent thrombosis, stroke, or TVR**

- Primary analysis: **Intention-to-treat manner**
  - Prespecified 3-month landmark analyses
  - Post-hoc analyses for the as-treated population considering the actual treatments received
  - Kaplan-Meier estimates for the comparisons of the outcomes
  - Hazard ratios (HR) and 95% confidence intervals (CI) generated with Cox proportional-hazards models

Post-hoc analyses in patients/ lesions with high risks

- **High bleeding risk (+); PRECISE-DAPT score ≥ 25**

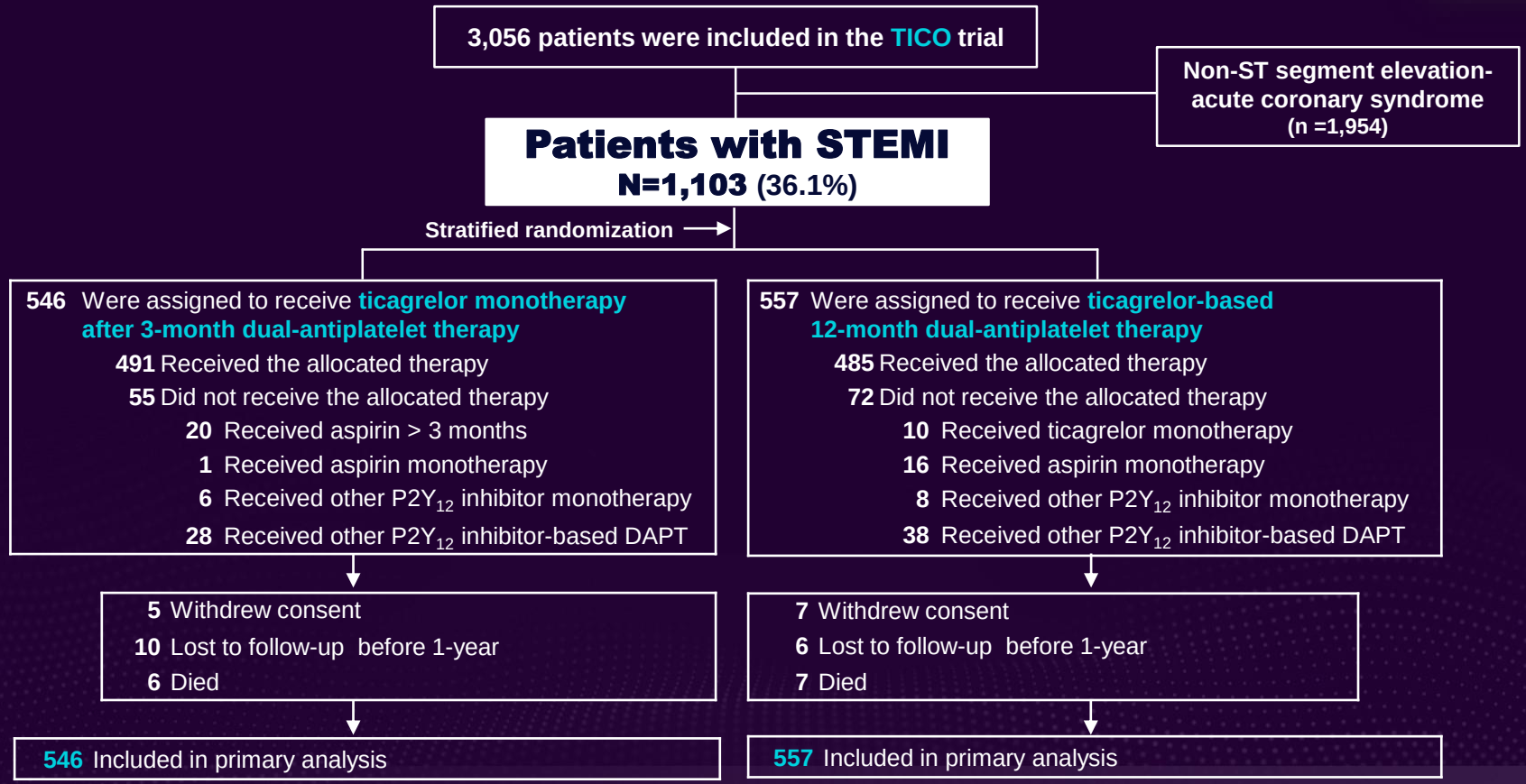
  Derived from the 5 clinical variables: 1) age, 2) creatinine clearance, 3) hemoglobin level, 4) white blood cell count, and 5) history of previous spontaneous bleeding.

  Costa F, et al. Lancet 2017;389:1025-34.

- **Complex PCI (+);** defined as any of the following:
  1) **3 vessels treated,**
  2) **≥3 lesions treated,**
  3) **total stent length >60 mm,**
  4) **bifurcation with 2 stents implanted,**
  5) **left main PCI,**
  6) **CTO as target lesions**

Giustino G, et al. J Am Coll Cardiol 2016;68:1851-64.
Dangas G, et al. J Am Coll Cardiol 2020;75:2414-24.

Study Flow of the *TICO-STEMI* study



Baseline Characteristics (1)

Characteristics	Ticagrelor Monotherapy after 3-m DAPT (N=546)	Ticagrelor-based 12-m DAPT (N=557)	*P* value
Age, yrs	59 ± 11	59 ± 11	0.47
Women	87 (16%)	82 (15%)	0.64
Body mass index, kg/m^2	24.7 ± 3.1	24.9 ± 3.3	0.27
Hypertension	252 (46%)	242 (43%)	0.84
Diabetes mellitus	113 (21%)	119 (21%)	0.84
Chronic kidney disease	120 (22%)	130 (23%)	0.64
Current smoker	246 (45%)	272 (49%)	0.23
Prior myocardial infarction	21 (4%)	14 (3%)	0.28
Prior percutaneous coronary intervention	35 (6%)	23 (4%)	0.12
Prior coronary bypass surgery	3 (0.5%)	1 (0.2%)	0.60
Prior stroke	11 (2%)	19 (3%)	0.22

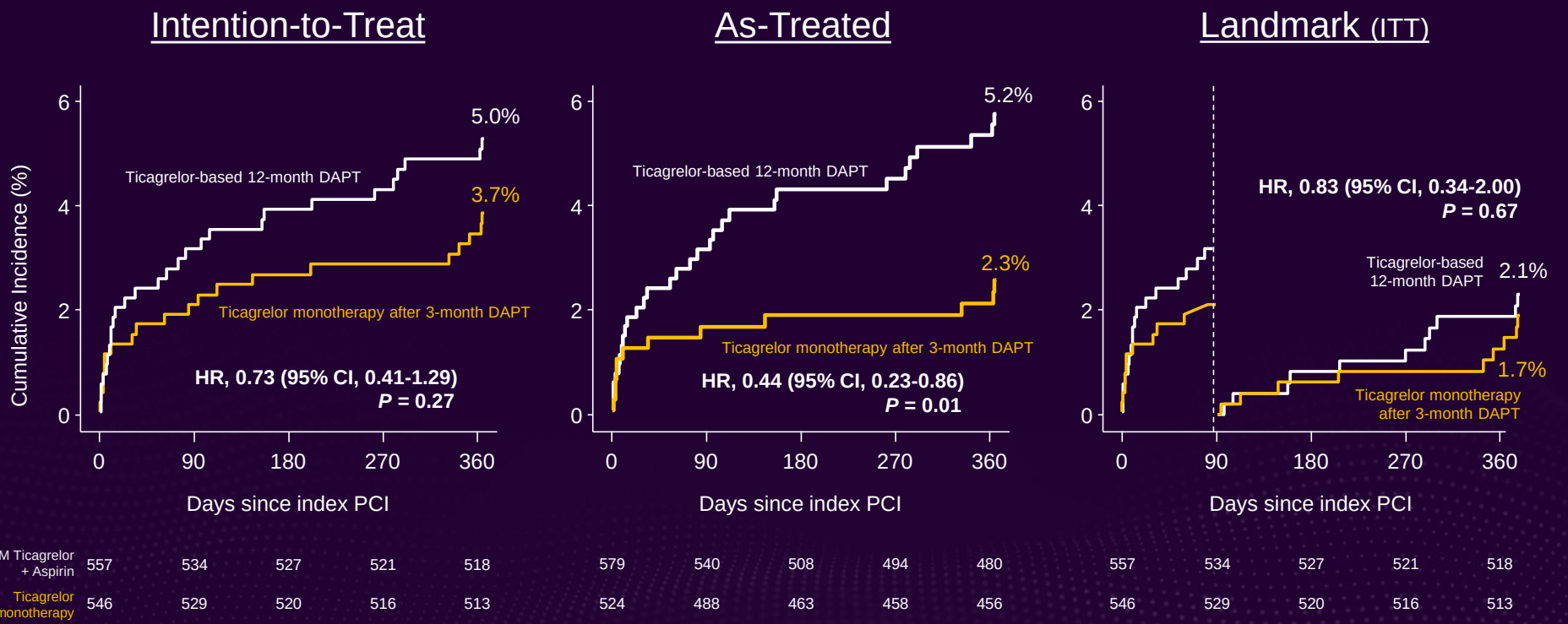
Baseline Characteristics (2)

Characteristics	Ticagrelor Monotherapy after 3-m DAPT (N=546)	Ticagrelor-based 12-m DAPT (N=557)	*P* value
Admission via emergency room	523 (96%)	538 (97%)	0.59
Antithrombotic drug before intervention			
Unfractionated heparin	410 (75%)	409 (73%)	0.57
Low-molecular-weight heparin	44 (8%)	52 (9%)	0.52
Glycoprotein IIb/IIIa inhibitors	69 (13%)	71 (13%)	0.99
Transradial approach	183 (34%)	192 (35%)	0.79
2- or 3-vessel diseases	285 (52%)	290 (52%)	0.99
Multi-lesion intervention	89 (16%)	75 (14%)	0.22
Multi-vessel intervention	65 (12%)	55 (10%)	0.32
Treated lesions per patient, n	1.2 ± 0.5	1.2 ± 0.4	0.21
Total number of stents per patient, n	1.3 ± 0.6	1.3 ± 0.5	0.31
Total stent length per patient, mm	33 ± 18	32 ± 17	0.50

Various ischemic outcomes at 12 months

Outcomes	Ticagrelor-monotherapy after 3-m DAPT (N=546)	Ticagrelor-based 12-m DAPT (N=557)	HR (95% CI)	*P* value
MACCE	15 (2.7)	14 (2.5)	1.10 (0.53-2.27)	0.81
Cardiac death, MI, or stent thrombosis	6 (1.1)	8 (1.4)	0.77 (0.27-2.21)	0.62
Death	6 (1.1)	7 (1.3)	0.88 (0.29-2.61)	0.81
Cardiac	4	5		
Non-cardiac	2	2		
Myocardial infarction	2 (0.4)	3 (0.5)	0.68 (0.11-4.07)	0.67
Stent thrombosis	4 (0.7)	1 (0.2)	4.09 (0.46-36.61)	0.21
Subacute	3	1		
Late	1	0		
Stroke	2 (0.4)	3 (0.5)	0.68 (0.11-4.07)	0.67
Target-vessel revascularization	6 (1.1)	2 (0.4)	3.07 (0.62-15.21)	0.17

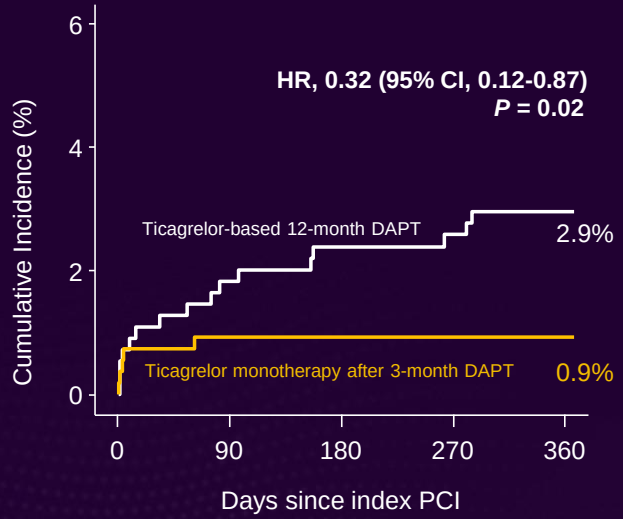
Primary outcome, *NACE* at 12-months



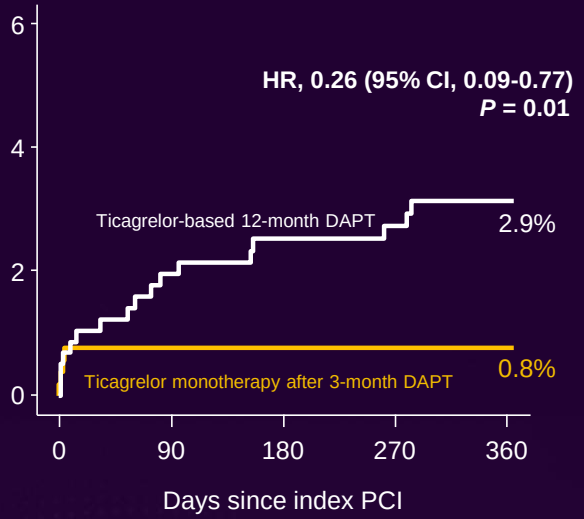
Bleeding outcome;

TIMI Major bleeding at 12 months

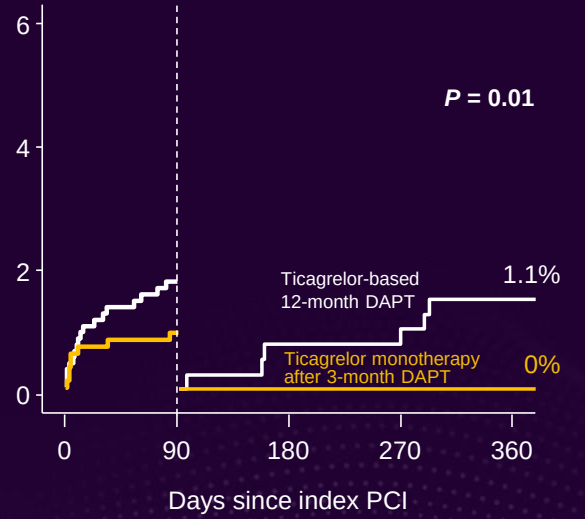
Intention-to-Treat



As-Treated

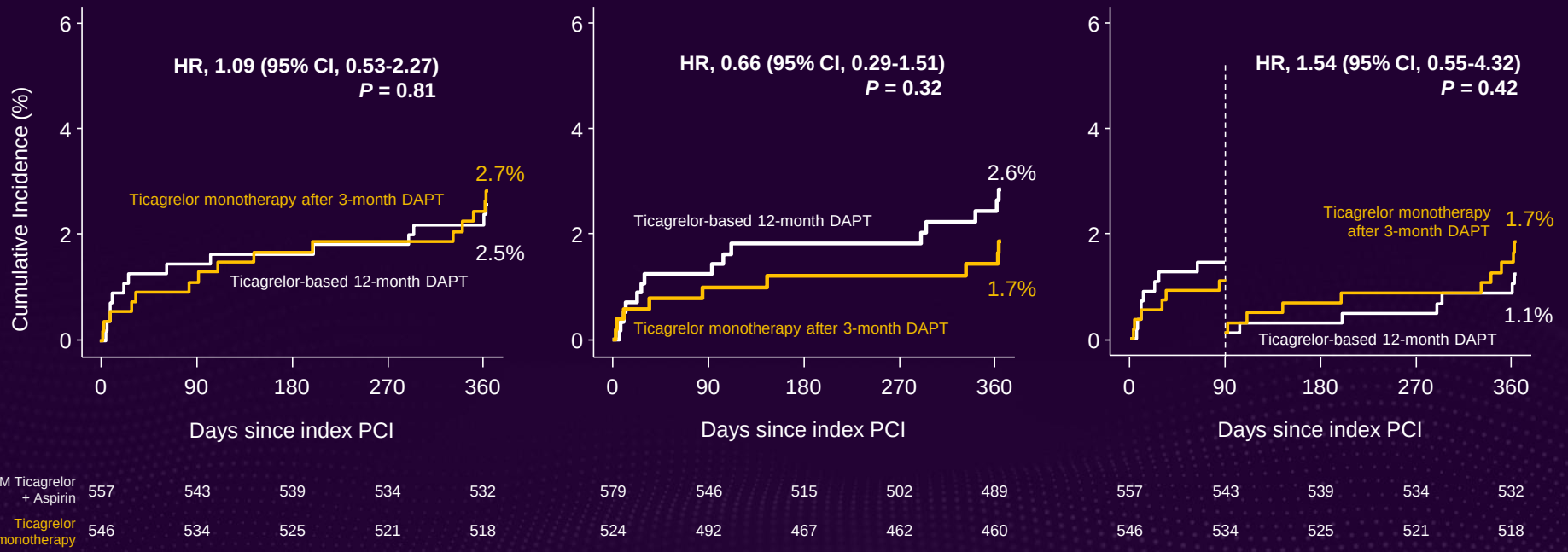


Landmark (ITT)



12M Ticagrelor + Aspirin	557	536	530	525	523	579	542	513	499	487	557	536	530	525	523
Ticagrelor monotherapy	546	532	525	521	520	524	490	465	460	458	546	532	525	521	520

Ischemic outcome;
Major Adverse Cardiac and Cerebrovascular Event at 12 months



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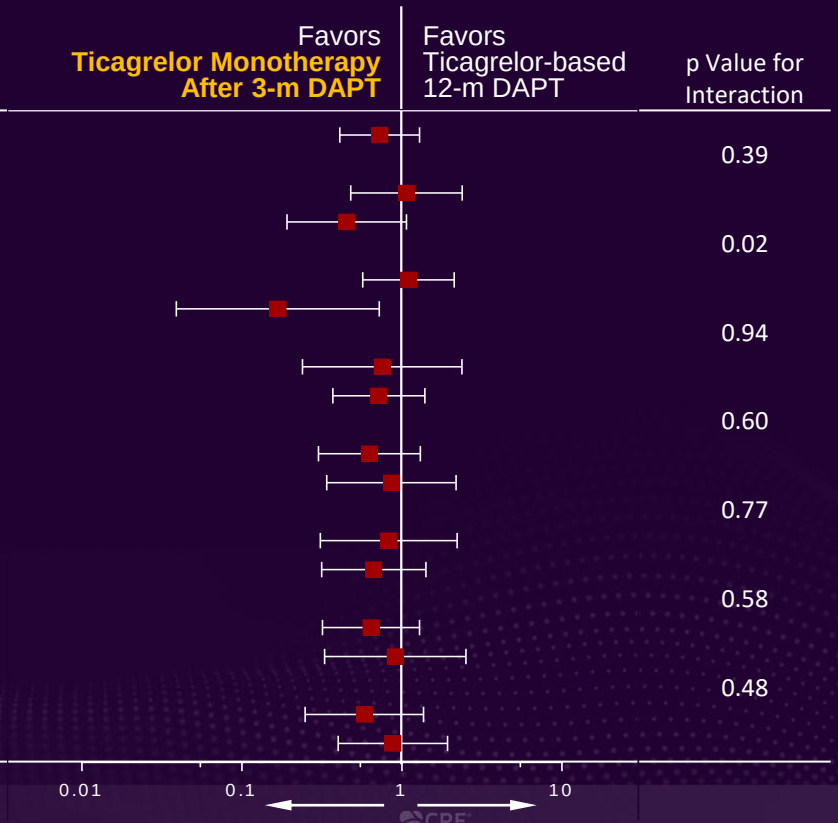
Subgroup analysis for primary outcome

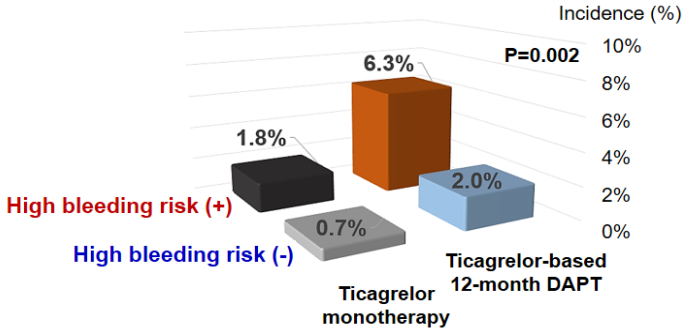
Subgroup	No. / Total (%) Ticagrelor Monotherapy After 3-m DAPT	Ticagrelor-based 12-m DAPT	HR (95% CI)	p Value for Interaction
All patients	20/546 (3.7)	28/557 (5.0)	0.73 [0.41;1.29]	
Age, years				0.39
<65	12/361 (3.3)	12/388 (3.1)	1.07 [0.48;2.38]	
≥65	8/185 (4.3)	16/169 (9.5)	0.46 [0.19;1.06]	
Sex				0.02
Men	18/459 (3.9)	17/475 (3.6)	1.10 [0.57;2.13]	
Women	2/87 (2.3)	11/82 (13.4)	0.16 [0.04;0.74]	
Diabetes mellitus				0.94
Yes	5/113 (4.4)	7/119 (5.9)	0.75 [0.24;2.38]	
No	15/433 (3.5)	21/438 (4.8)	0.72 [0.37;1.39]	
Hypertension				0.60
Yes	12/252 (4.8)	18/242 (7.4)	0.63 [0.30;1.30]	
No	8/294 (2.7)	10/315 (3.2)	0.86 [0.34;2.19]	
Chronic kidney disease				0.77
Yes	7/120 (5.8)	9/130 (6.9)	0.83 [0.31;2.22]	
No	13/426 (3.1)	19/427 (4.4)	0.69 [0.34;1.39]	
Body mass index, kg/m^2				0.58
<25	13/294 (4.4)	20/298 (6.7)	0.64 [0.32;1.29]	
≥25	7/252 (2.8)	8/259 (3.1)	0.91 [0.33;2.52]	
Current smoking				0.48
Yes	8/246 (3.3)	15/272 (5.5)	0.58 [0.25;1.37]	
No	12/300 (4.0)	13/285 (4.6)	0.88 [0.40;1.93]	

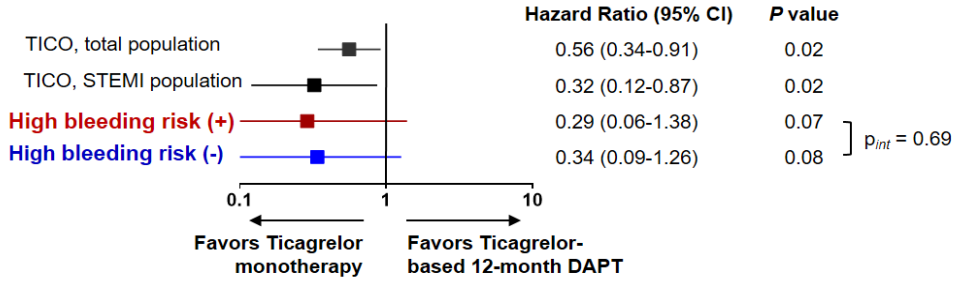


Post-hoc analyses in patients/ lesions with high risks

Major bleeding

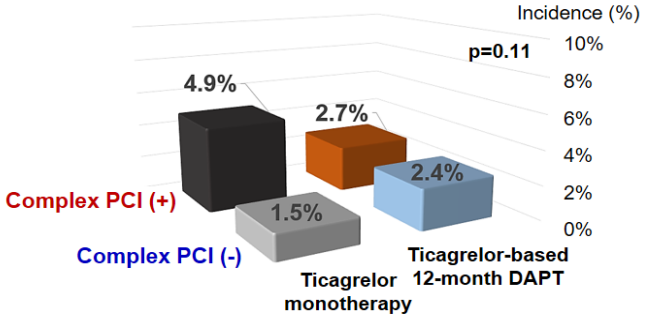
- High bleeding risk (+) PRECISE-DAPT score ≥ 25

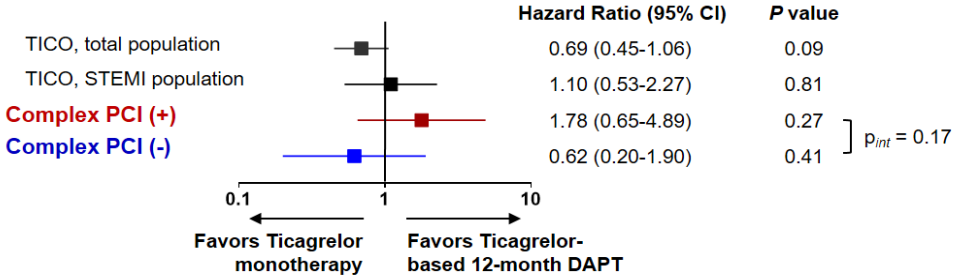




Major adverse cardiac and cerebrovascular event

- Complex PCI (+) 3 vessels treated; ≥3 lesions treated; total stent length >60 mm; bifurcation c 2 stents; left main PCI; or CTO as target lesions





Limitations

- Although this was a prespecified, randomly stratified subgroup analysis, the presentation of STEMI was not individually powered to draw definite conclusions.
- This study would be underpowered for each component of primary outcome.
- The TICO trial was an open-label trial (not placebo controlled).
- Despite of the superior effect of ticagrelor monotherapy in the main TICO trial, the lower-than-expected rate of adverse events could have limited the power of our analyses.

→ *Our findings should be interpreted with caution and call for confirmatory randomized trials.*

Conclusions

This is the first report assessing the feasibility of the ticagrelor monotherapy after short-term DAPT for STEMI patients with DES.

Among patients with *STEMI* *treated with ultrathin bioresorbable polymer sirolimus-eluting stents*,

- ***Ticagrelor monotherapy after 3-month DAPT*, compared with ticagrelor-based 12-month DAPT, resulted in a reduced risk of major bleeding.**
- **As for MACCE, there were no significant differences between the two treatment groups, without significant interaction with clinical presentation in this study.**
- **However, care should be taken in applying these results to the overall STEMI population, especially those at high risk for ischemia.**


Severance
TICO
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