Effect of ticagrelor monotherapy for 23 months following 1-month DAPT vs. standard DAPT for 12 months followed by 12 months of aspirin monotherapy in patients undergoing complex PCI

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On behalf of the Global Leaders investigators

*Steering committee of the Global Leaders study

Disclosure Statement of Financial Interest

Patrick W. Serruys, MD. PhD.

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support • Consulting Fees/Honoraria	• Abbott • Biosensors • Medtronic • Philips/Volcano • Sinomedical Sciences Technology • SMT • Xeltis

Why this study?

- **Data on optimal antiplatelet regimens in patients who underwent ESC-defined "complex PCI" are limited[1].**

- **A pooled patient-level analysis from six randomised trials has demonstrated that prolonged DAPT (>12 months), -**compared to abbreviated DAPT (3 or 6 months) **-, significantly reduced one-year MACE in patients who underwent "complex PCI",- but at the cost of an increased risk of BARC major bleeding[2].**

- **No previous study has evaluated the efficacy and safety of ticagrelor monotherapy following one-month DAPT in comparison to the standard 12-month DAPT in patients with "complex PCI". (the Global Leaders trial[3,4])**

1. Neumann et al. Eur Heart J. 2019 Jan 7;40(2):87-165.
2. Giustino et al. J Am Coll Cardiol 2016;68:1851-1864.
3. Vranckx et al. Lancet 2018; 392: 940–49
4. Serruys et al. EuroIntervention. 2019 Mar 19. pii: EIJ-D-19-00202.

Why this study?

ESC European Society of Cardiology
European Heart Journal (2019) 40, 87–165
doi:10.1093/eurheartj/ehy394

ESC/EACTS GUIDELINES

2018 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)

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Table 9. High-risk features for ischaemic events

Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
Diffuse multivessel disease, especially in diabetic patients
Chronic kidney disease
At least three stents implanted
At least three lesions treated
Bifurcation with two stents implanted
Total stented length >60 mm
Treatment of a chronic total occlusion
History of STEMI

Neumann et al. Eur Heart J. 2019 Jan 7;40(2):87-165.

GLOBAL LEADERS

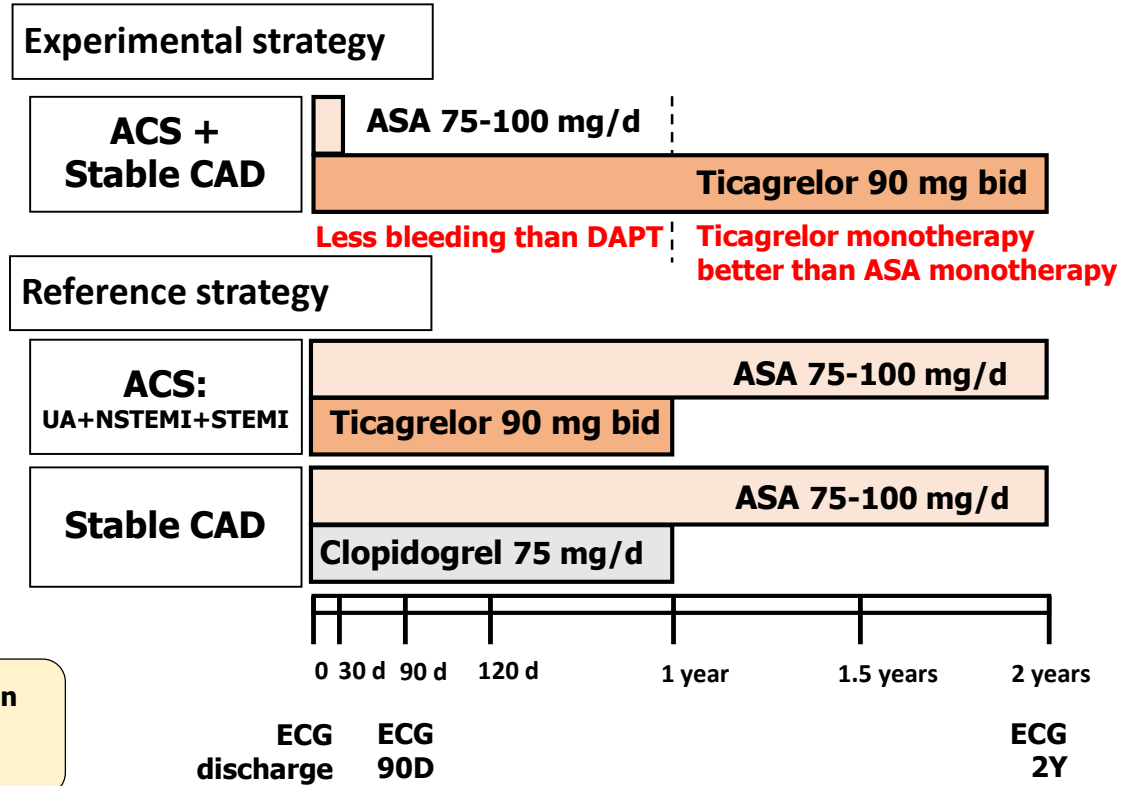
Study design

"All-comers" PCI population
N = 15,991
1:1 Randomisation, open-label design, 130 centers worldwide

- Any type of lesions: Left main, SVG, CTO bifurcation, ISR, etc.
- Unrestricted use of DES (number, length)

by default, Bivalirudine for anticoagulation

by default ,BioMatrix DES as stent



What did we study?

Primary endpoint

- **All-cause death (vital status known in 99.95.%) and non-fatal new Q wave MI at 2 years (Core Lab adjudication,Minessota code)**

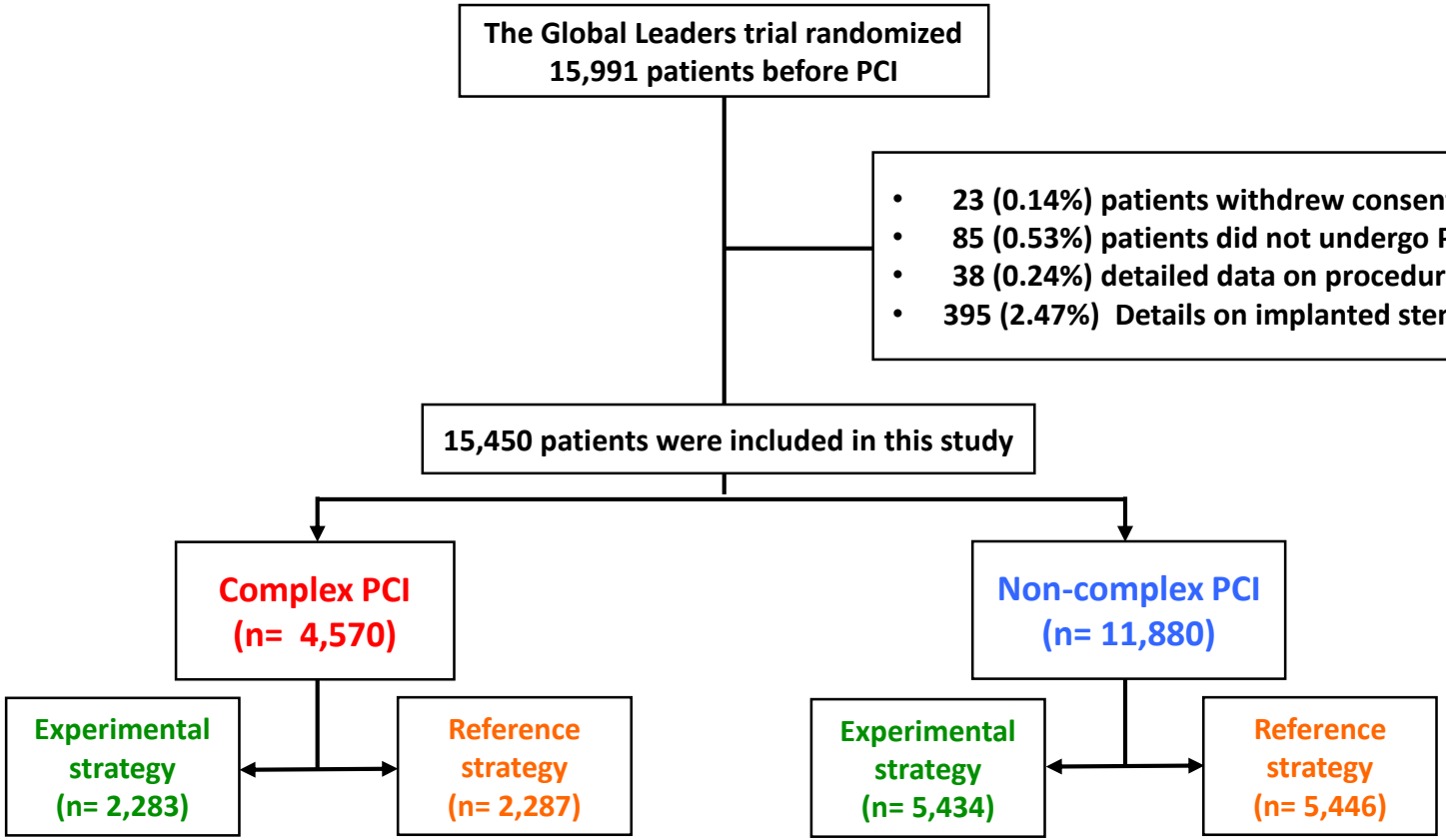
Secondary (safety) endpoints

- **The composite of BARC 3 or 5 bleeding up to 2 years post randomization**

Additional secondary endpoints

- **Investigator reported endpoints up to 2 years**
  - **Composite of all-cause mortality, stroke and non-fatal new Q-wave MI**
  - **All-cause death**
  - **Stroke: ischemic and/or hemorrhagic**
  - **Myocardial infarction (Third Universal Definition)**
  - **Coronary revascularization (Target vessel revascularization [TVR], Non-TVR)**
  - **Definite and/or probable stent thrombosis according to the Academic Research Consortium**
- **Patient oriented composite endpoints (POCE: all-cause death, any stroke, any MI, any revascularization) and Net adverse clinical events (NACE: POCE and BARC type 3 or 5 bleeding)**

Patient flow diagram of the present sub-study



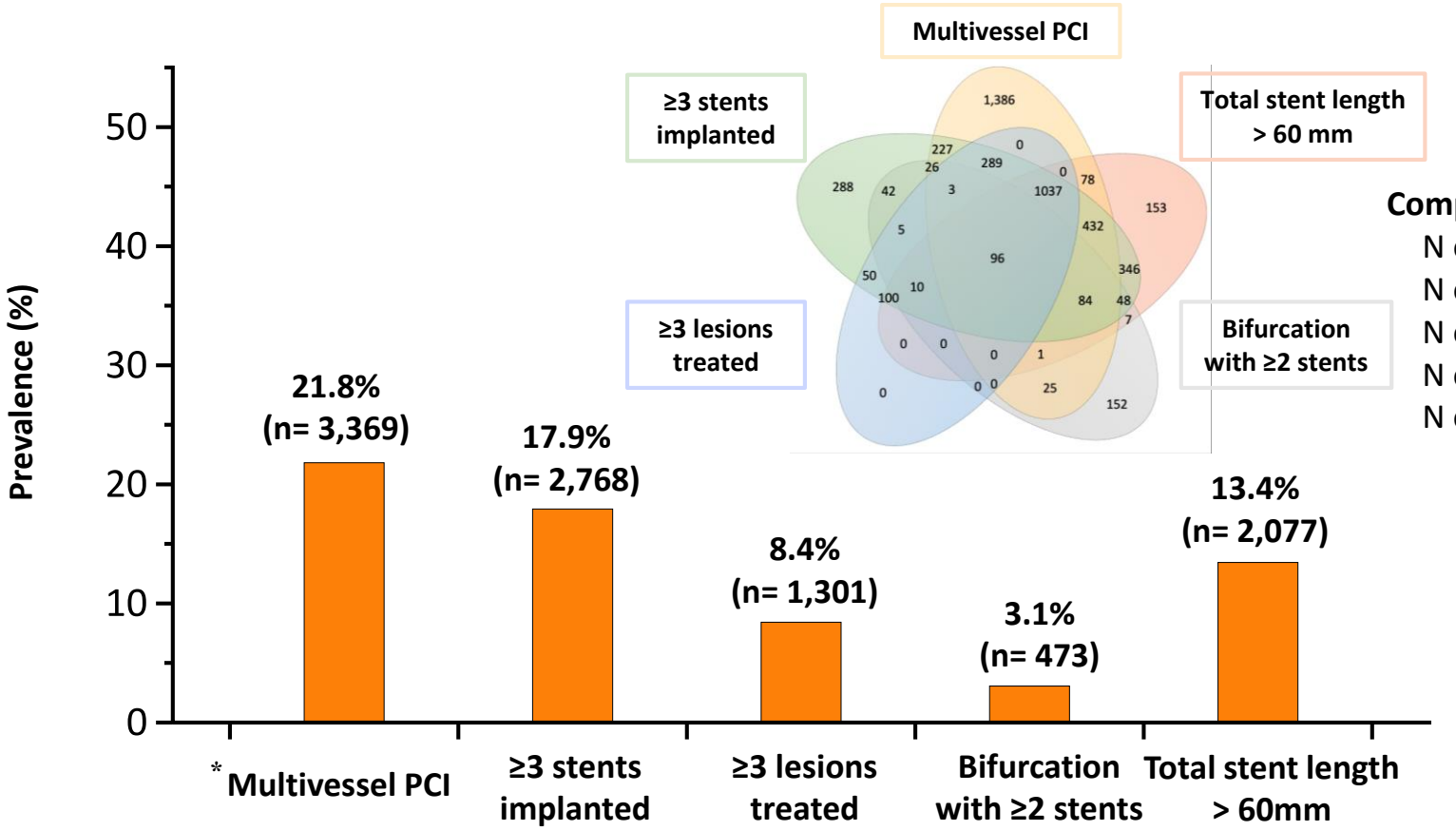
By randomized design, all baseline characteristics are equally distributed

Baseline characteristics

Complex PCI

Total number of patients	Experimental strategy N = 2,283	Reference strategy N = 2,287	p-value
Clinical presentation			
• Stable Coronary Artery Disease	51.4 %	51.4 %	0.975
• Acute Coronary Syndrome (ACS)	48.6 %	48.6 %	0.842
Unstable Angina	23.4 %	24.4 %	
Non-STEMI	48.1 %	47.1 %	
STEMI	28.6 %	28.5 %	
Treated lesions			
Left main	9.3 %	8.7 %	0.457
LAD	65.0 %	65.9 %	0.526
LCX	49.9 %	49.7 %	0.859
RCA	53.4 %	52.6 %	0.591
Bypass graft	1.3 %	1.1 %	0.250
Multivessel PCI	74.2 %	73.2 %	0.461
≥3 lesions treated	27.8 %	29.1 %	0.328
≥3 stents implanted	60.8 %	60.3 %	0.752
Bifurcation with ≥2 stents	10.1 %	10.6 %	0.607
Total stent length per patient > 60mm	44.5 %	46.4 %	0.180

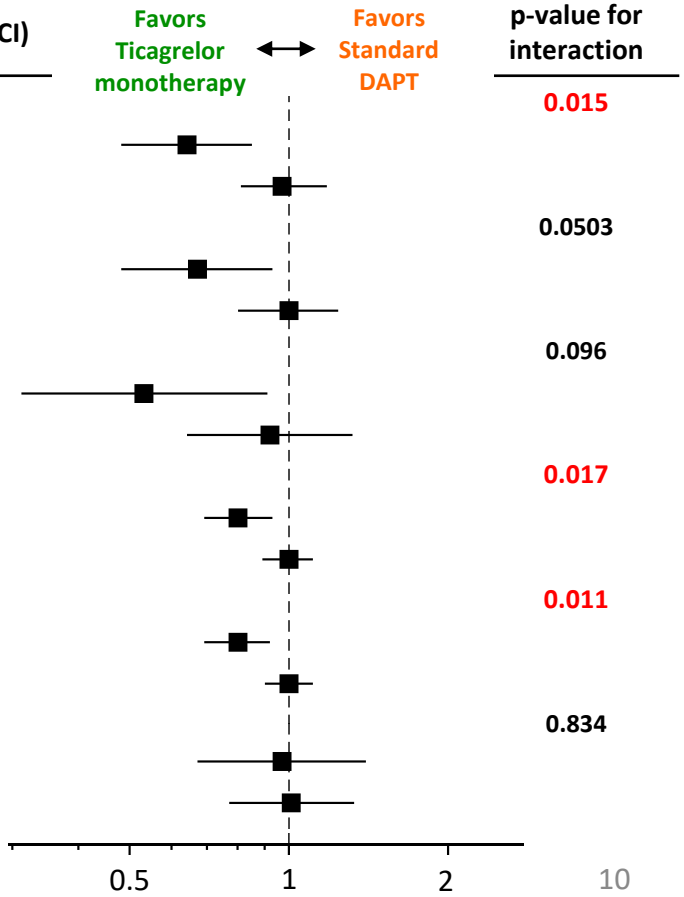
Prevalence of complex PCI features



* including left main PCI

Treatment effect of ticagrelor monotherapy vs. Standard DAPT according to PCI complexity

	Ticagrelor monotherapy	Standard DAPT	Hazard Ratio (95% CI)	p-value for interaction
Primary endpoint				0.015
Complex PCI	80/2283	124/2287	0.64 (0.48-0.85)	
Noncomplex PCI	211/5434	217/5446	0.97 (0.81-1.18)	
All-cause mortality				0.0503
Complex PCI	60/2283	89/2287	0.67 (0.48-0.93)	
Noncomplex PCI	156/5434	157/5446	1.00 (0.80-1.24)	
New Q-wave MI				0.096
Complex PCI	21/2283	39/2287	0.53 (0.31-0.91)	
Noncomplex PCI	57/5434	62/5446	0.92 (0.64-1.32)	
POCE				0.017
Complex PCI	316/2283	391/2287	0.80 (0.69-0.93)	
Noncomplex PCI	665/5434	672/5446	1.00 (0.89-1.11)	
NACE				0.011
Complex PCI	345/2283	427/2287	0.80 (0.69-0.92)	
Noncomplex PCI	730/5434	736/5446	1.00 (0.90-1.11)	
BARC type 3 or 5 bleeding				0.834
Complex PCI	55/2283	57/2287	0.97 (0.67-1.40)	
Noncomplex PCI	105/5434	104/5446	1.01 (0.77-1.33)	

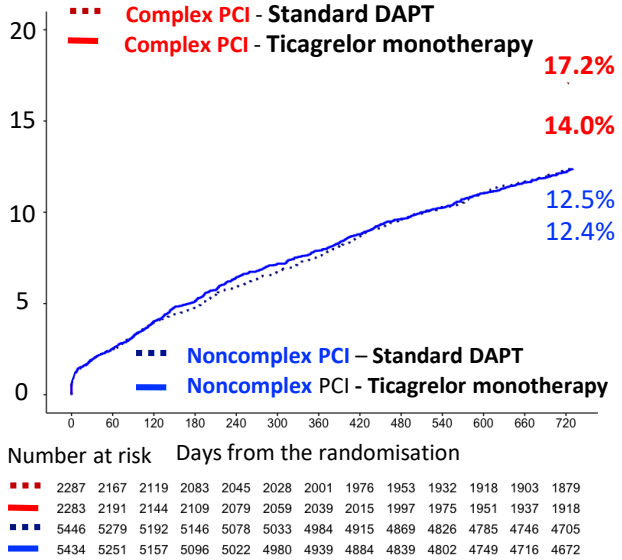


Impact of Ticagrelor monotherapy vs. Standard DAPT in patients with Non-Complex PCI and with complex PCI

POCE

Non-complex PCI - Ref. vs. Non-complex PCI - Exp.
HR (95% CI): 1.00 (0.89-1.11), p= 0.945
Complex PCI - Ref. vs. Complex PCI - Exp.
HR (95% CI): **0.79 (0.67-0.92)**, p= **0.003**

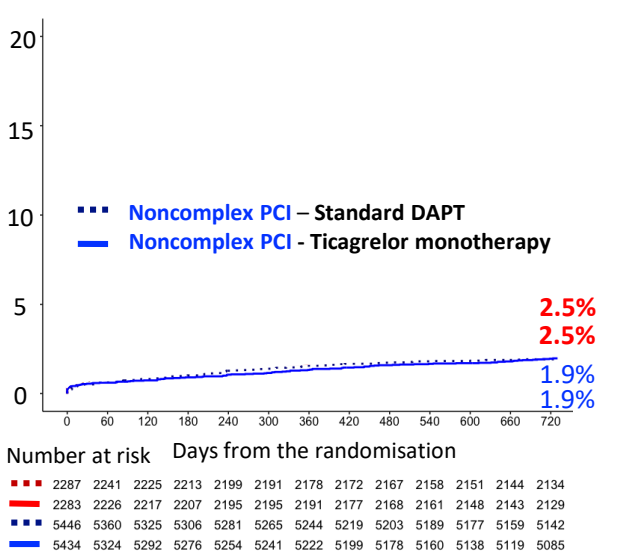
P_{int}= **0.017**



BARC type 3 or 5 bleeding

Non-complex PCI - Ref. vs. Non-complex PCI - Exp.
HR (95% CI): 1.01 (0.77-1.33), p= 0.915
Complex PCI - Ref. vs. Complex PCI - Exp.
HR (95% CI): 0.97 (0.67-1.40), p= 0.856

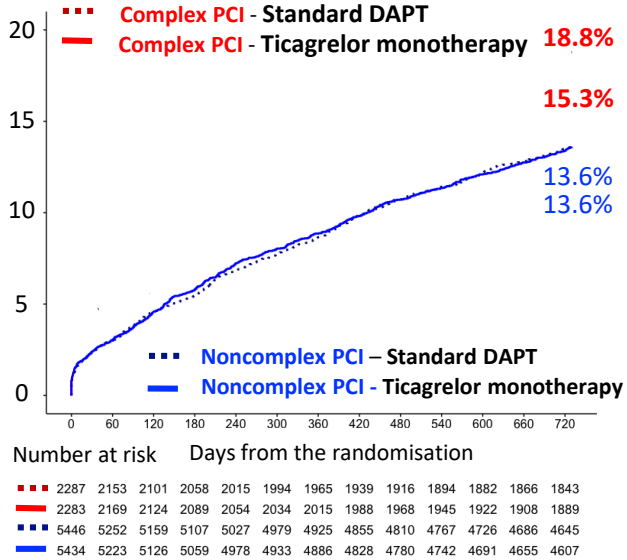
P_{int}= 0.834



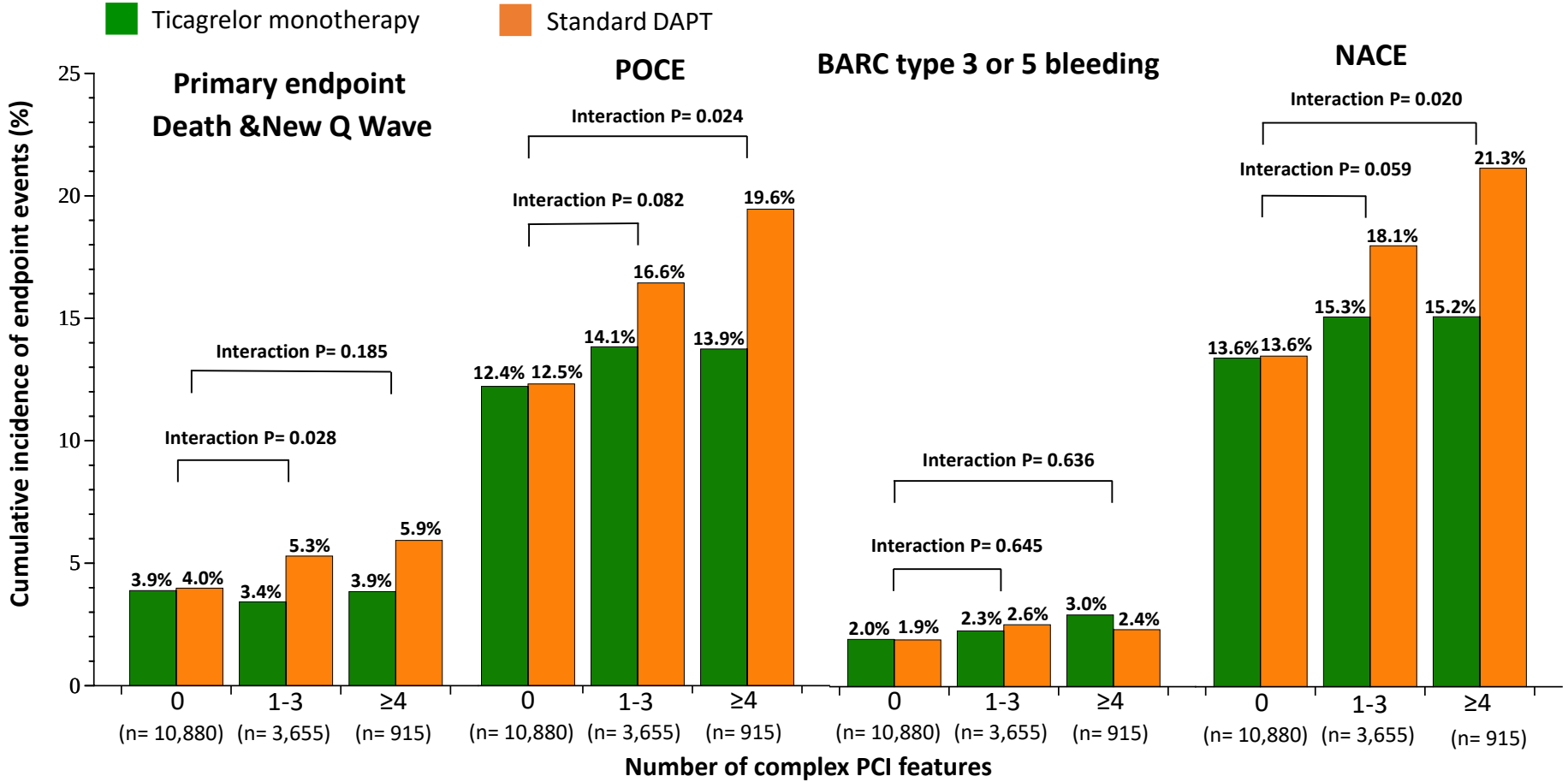
NACE

Non-complex PCI - Ref. vs. Non-complex PCI - Exp.
HR (95% CI): 1.00 (0.90-1.11), p= 0.973
Complex PCI - Ref. vs. Complex PCI - Exp.
HR (95% CI): **0.80 (0.69-0.92)**, p= **0.002**

P_{int}= **0.011**



Impact of ticagrelor monotherapy vs. standard DAPT on incidence of endpoint events in patients with complex PCI stratified according to high risk features of complex PCI



Limitations

- This analysis was **not pre-specified**, since high-risk features of complex PCI were first described in the 2018 guidelines of the ESC prior to the trial design (2013).
- All secondary endpoints were **site-reported**. However, seven on-site monitoring visits were performed in each participating center, and 20% of the reported events were checked according to source documents. In addition, the trial was monitored for event under-reporting and inconsistency in event definition.
- Our findings need to be interpreted as **hypothesis-generating** and call for confirmatory randomized trials.

Why is this important?

- Patients who underwent complex PCI had a higher risk of ischemic and bleeding events at two years, as compared to the non-complex PCI group.
- Ticagrelor monotherapy following 1-month DAPT was associated with a significantly lower risk of death/Q-wave MI (primary endpoint) and POCE, with a similar risk of BARC type 3 or 5 bleeding, thereby achieving a significant net clinical benefit, NACE in patients with complex PCI, but not in those with non-complex PCI.
- Importantly, the benefit of long-term ticagrelor monotherapy was greater as the number of high-risk features increased.
- Thus, ticagrelor monotherapy following 1-month ticagrelor and aspirin may be a better alternative to the standard DAPT in patients who underwent complex PCI.

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