ACC.24

One-month Ticagrelor Monotherapy After PCI in Acute Coronary Syndromes: **Principal Results From the Double-blind, Placebo-controlled ULTIMATE-DAPT Trial**

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AMERICAN COLLEGE of CARDIOLOGY

Background

- International guidelines currently recommend DAPT with aspirin plus a potent $P2Y_{12}$ receptor inhibitor for 12 months in most patients presenting with an ACS treated with PCI to prevent MI and stent thrombosis

- Limited data exist regarding the use of single antiplatelet therapy with a potent $P2Y_{12}$ inhibitor starting 1 month after PCI in ACS, and no such trials have been placebo-controlled

Objectives

- We therefore performed a large-scale, international, multicenter, placebo-controlled, double-blind randomized trial to determine whether the use of ticagrelor alone beginning 30 days after PCI in pts with ACS could reduce clinically-relevant bleeding without an accompanying increase in major adverse cardiovascular or cerebrovascular events (MACCE) compared with ticagrelor plus aspirin

Inclusion Criteria

Patients presenting with ACS within 30 days before randomization

- ≥18 years of age
- With either:
  - Biomarker pos NSTEMI or STEMI, or
  - Biomarker neg unstable angina → 1) DS ≥90%, *or* 2) Ruptured plaque, *or* 3) Thrombotic lesion
- Had been randomized in the IVUS-ACS trial of IVUS-guided vs. angio-guided PCI
- Remained event-free after PCI with contemporary drug-eluting stents (DES) for one month on ticagrelor (90 mg bid) plus aspirin (100 mg qd)

Key Exclusion Criteria

- ✓ Stroke within 3 months or any permanent neurologic deficit
- ✓ Previous CABG
- ✓ Any planned surgery within 12 months
- ✓ eGFR <20 ml/min/1.73 m^2
- ✓ Need for chronic oral anticoagulation
- ✓ Life expectancy <1 year
- ✓ Any condition likely to interfere with study processes

Primary Endpoints

- Assessed between 1- and 12-months post-PCI -

1. **Effectiveness:** Clinically-relevant bleeding (BARC types 2, 3, or 5), powered for superiority testing

2. **Safety:** Composite MACCE, including cardiac death, MI, ischemic stroke, definite stent thrombosis, or clinically-driven TVR, powered for non-inferiority testing

Assumptions and Sample Size Calculations

1. **Effectiveness:** Assuming a 3.0% rate of clinically-relevant bleeding between 1 and 12 months on ticagrelor plus aspirin, randomizing 3400 patients provided 80% power to detect a 50% reduction with ticagrelor monotherapy with 2-sided alpha 0.05

2. **Safety:** Assuming a 6.2% rate of MACCE between 1 and 12 months on ticagrelor plus aspirin, randomizing 3068 patients provided 80% power to demonstrate noninferiority of ticagrelor monotherapy with an absolute margin of 2.5% with 1-sided alpha 0.025

Tested hierarchically to preserve alpha: Effectiveness had to pass for safety to be tested

Sponsorship, Funding and Study Leadership

Investigator-sponsored study

Shao-Liang Chen, MD, Nanjing First Hospital, China

Executive Committee

Shao-Liang Chen, MD (Study chair and PI)

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Funding

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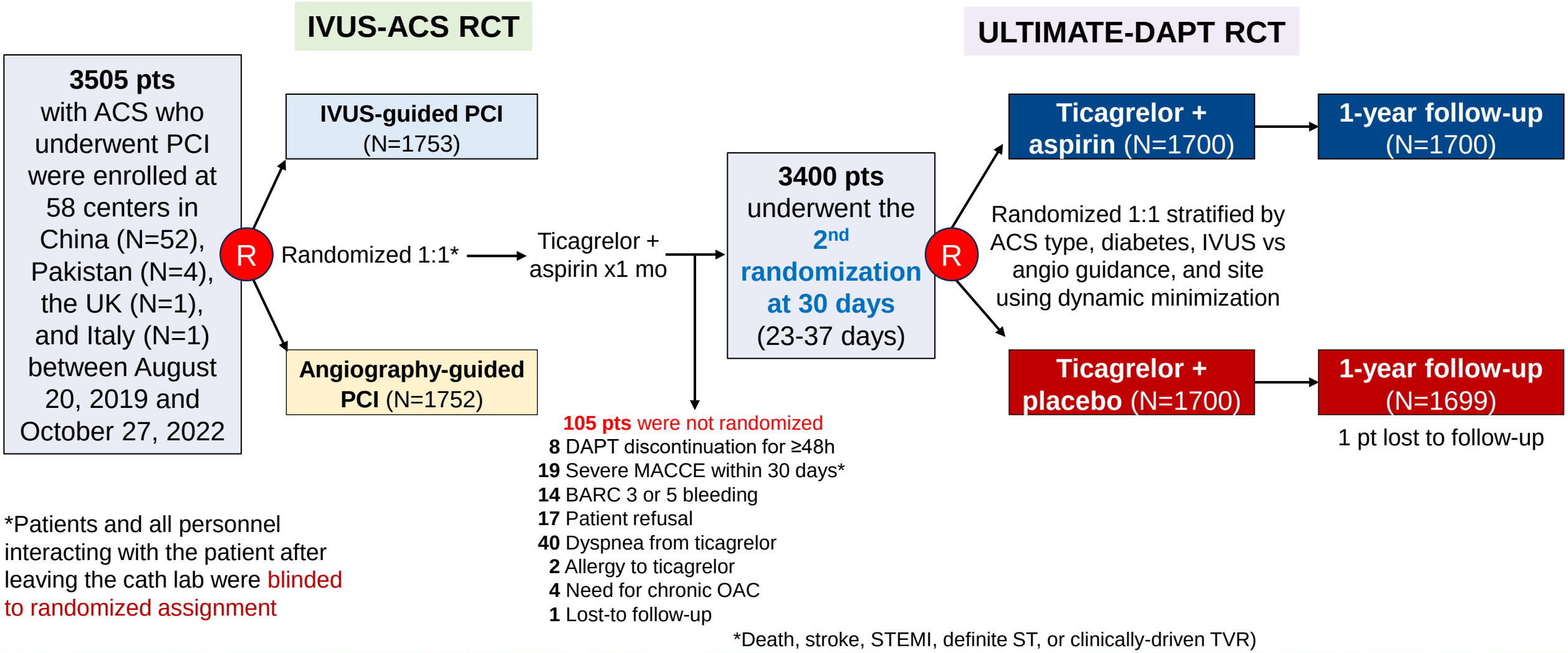
2x2 Randomization and Study Flowchart



Baseline Characteristics

	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)
Age, years, median (IQR)	62 (54, 70)	63 (54, 69)
Male sex	1264 (74.4%)	1257 (73.9%)
Race, Chinese	1476 (86.8%)	1519 (89.4%)
Hypertension	1058 (62.2%)	1063 (62.5%)
Diabetes mellitus	540 (31.8%)	535 (31.5%)
Dyslipidemia	1178 (69.3%)	1157 (68.1%)
Current smoking	486 (28.6%)	482 (28.4%)
CKD (eGFR <60 mL/min/1.73m^2)	119 (7.0%)	129 (7.6%)
Previous PCI	171 (10.1%)	174 (10.2%)
Previous CABG	2 (0.1%)	4 (0.2%)
Previous MI	143 (8.4%)	156 (9.2%)
Previous stroke	154 (9.1%)	147 (8.7%)
Initial clinical presentation		
Unstable angina	668 (39.3%)	708 (41.7%)
With ischemic ECG changes	650/668 (97.3%)	685/708 (96.8%)
Non-STEMI	545 (32.1%)	531 (31.2%)
STEMI	487 (28.7%)	461 (27.1%)
LVEF (TTE), %	62 (55, 65)	63 (56, 65)

Culprit Lesion Characteristics (site-assessed)

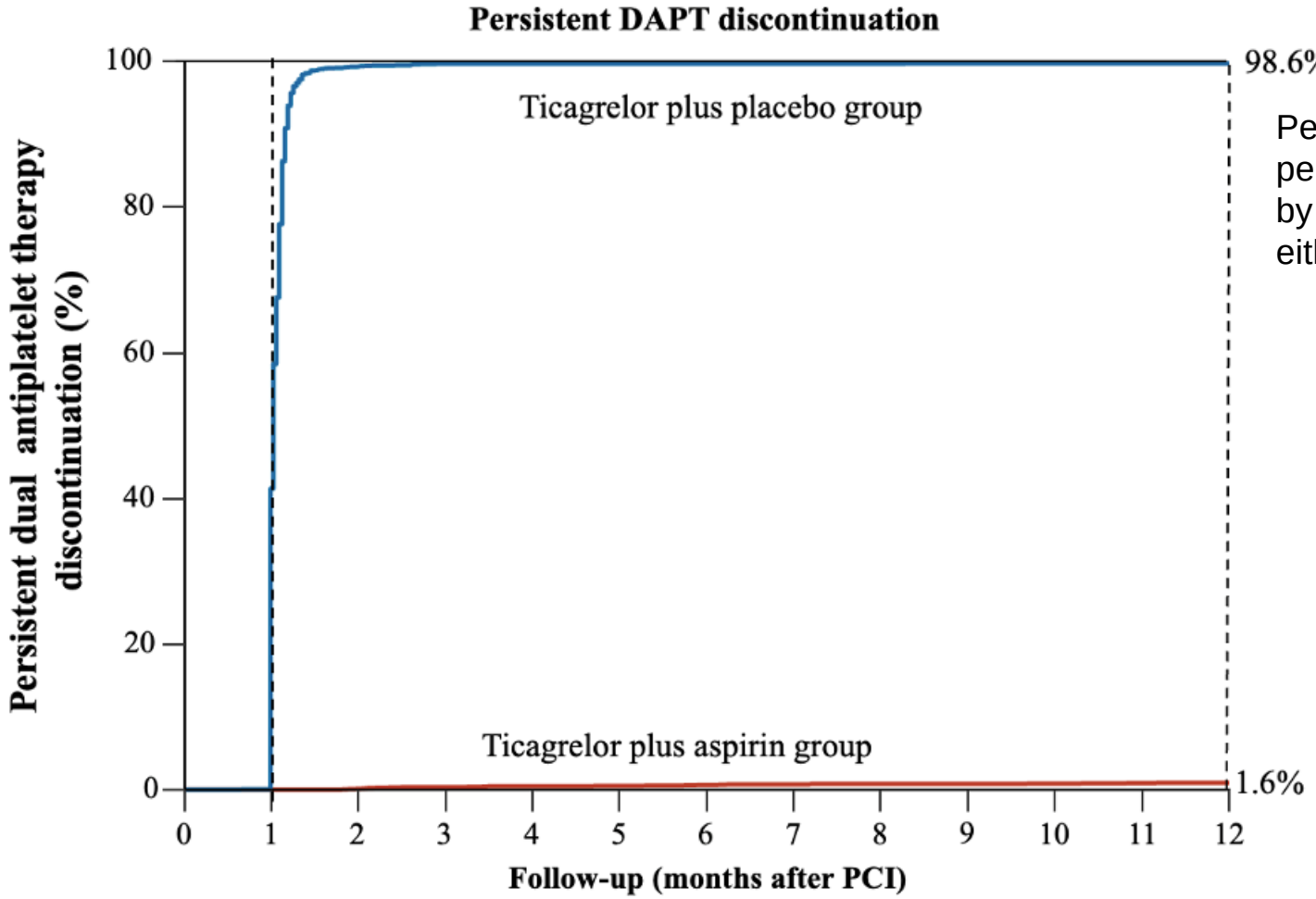
	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)
Number of diseased vessels		
One	1199 (70.5%)	1171 (68.9%)
Two	397 (23.4%)	393 (23.1%)
Three	104 (6.1%)	136 (8.0%)
Total number of lesions treated	1.3 ± 0.6	1.3 ± 0.6
Culprit lesion location		
Unprotected left main	86 (5.1%)	60 (3.5%)
Left anterior descending	956 (56.2%)	956 (56.2%)
Left circumflex	237 (13.9%)	258 (15.2%)
Right	421 (24.8%)	426 (25.1%)
Culprit lesion types		
True bifurcation (Medina 1,1,1 or 0,1,1)	265 (15.6%)	255 (15.0%)
Long or diffuse (≥30 mm)	1256 (73.9%)	1205 (70.9%)
Moderate or severe calcification (encircling)	120 (7.1%)	133 (7.8%)
Thrombus (filling defect in multiple views)	158 (9.3%)	147 (8.7%)
TIMI flow at baseline		
0/1	333 (19.6%)	326 (19.2%)
2	88 (5.2%)	88 (5.2%)
3	1279 (75.2%)	1286 (75.6%)

Procedural Characteristics

	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)
Transradial access	1645 (96.8%)	1630 (95.9%)
Intravascular imaging guidance	854 (50.2%)	857 (50.4%)
Aspiration thrombectomy used	23 (1.4%)	24 (1.4%)
Rotational atherectomy used	3 (0.2%)	10 (0.6%)
Number of stents implanted	1.5 ± 0.7	1.4 ± 0.7
Type of DES implanted		
Firehawk family	874 (51.4%)	888 (52.2%)
Resolute family	717 (42.2%)	706 (41.5%)
Mixed	103 (6.1%)	98 (5.8%)
Maximum stent diameter, mm	3.17 ± 0.43	3.16 ± 0.46
Total stent length, mm	33 (23 - 51)	32 (23 - 48)
Post-dilation performed	1625 (95.6%)	1608 (94.6%)
Maximum balloon pressure, atm	17.3 ± 3.1	17.2 ± 2.9
Contrast media used, mL	150 (120 - 180)	150 (120 - 180)
Procedural time, min	40 (25 - 60)	40 (27 - 60)
Complete revascularization	1493 (87.8%)	1496 (88.0%)
Procedural success*	1688 (99.3%)	1686 (99.2%)

*TIMI 3 flow, residual DS <20%, absence of ≥type B dissection, no intra-procedural complications

DAPT Adherence During Follow-up

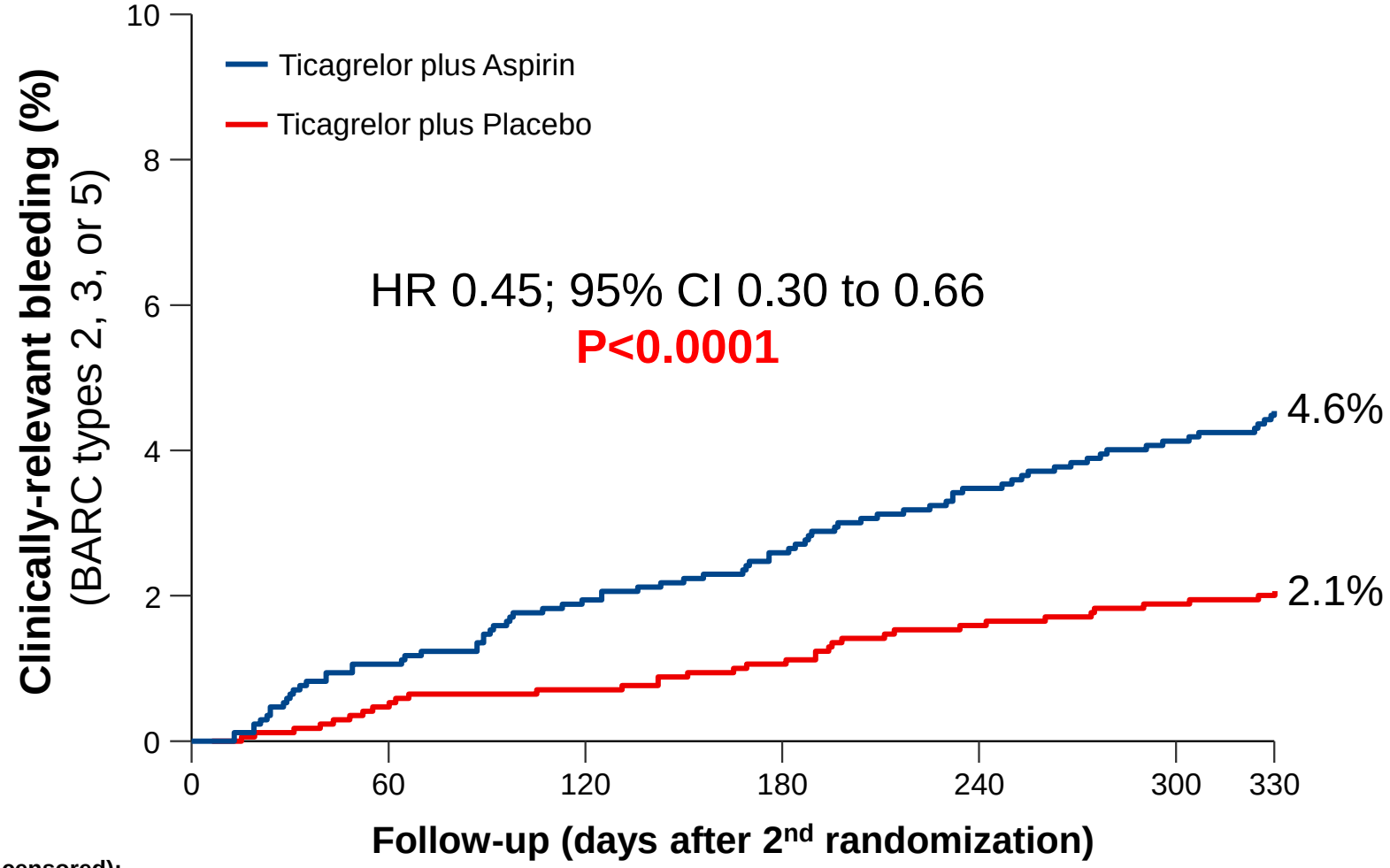


No. at risk													
Ticagrelor plus placebo	1700	1002	13	6	6	6	6	6	6	6	6	6	6
Ticagrelor plus aspirin	1700	1700	1697	1692	1688	1686	1683	1679	1676	1676	1673	1672	1672

Persistent DAPT discontinuation was defined as permanent discontinuation of either aspirin as dictated by the study protocol or non-directed discontinuation of either aspirin or ticagrelor for >60 days.

During FU a reduction in ticagrelor from 90 mg to 60 mg bid was required in 12 pts (0.7%) treated with ticagrelor plus placebo and 16 pts (0.9%) treated with ticagrelor plus aspirin. Conversion from ticagrelor to clopidogrel was required in 22 (1.3%) and 19 (1.1%) pts respectively. Unblinding was required during follow-up in 39 pts (1.1%) who had a BARC 3 or 5 bleed (11 in the ticagrelor alone group and 28 in the ticagrelor plus aspirin group) and in 8 pts (0.2%) who had a stent thrombosis (3 in the ticagrelor alone group and 5 in the ticagrelor plus aspirin group).

Primary Effectiveness Endpoint: BARC types 2, 3 or 5 bleeding



Number at risk (number censored):

Ticagrelor plus Aspirin	1700 (0)	1681 (1)	1664 (2)	1652 (1)	1634 (3)	1622 (2)	1615 (2)
Ticagrelor plus Placebo	1700 (0)	1688 (2)	1684 (2)	1676 (2)	1665 (2)	1657 (3)	1654 (3)

Bleeding Endpoints

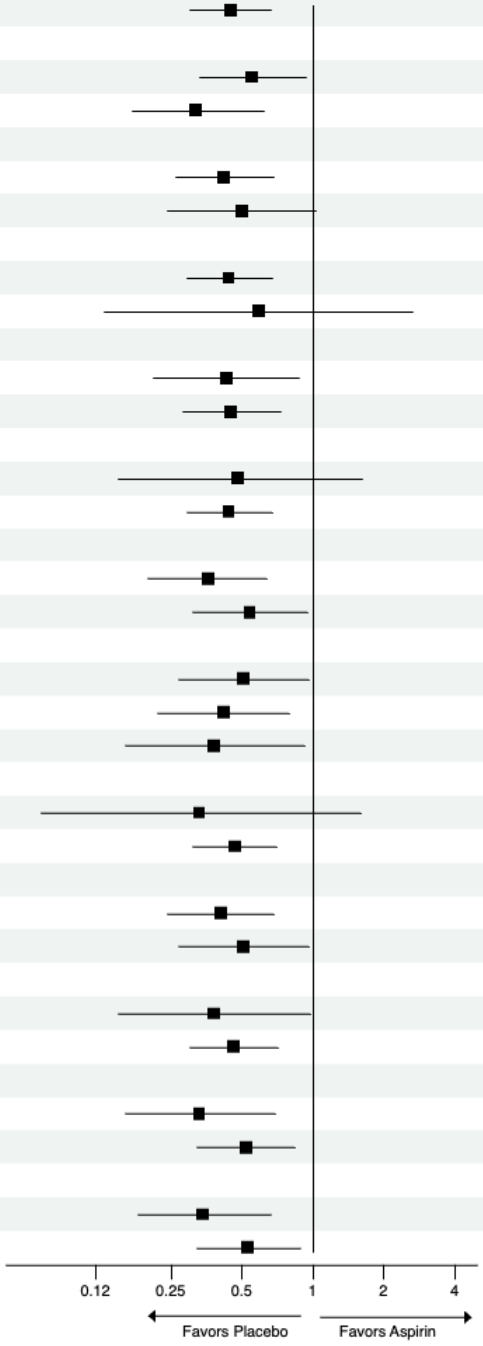
Between 1- and 12-months post-PCI	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)	Hazard ratio (95% CI)	P-value
Primary endpoint: Clinically-relevant bleeding (BARC types 2, 3, or 5)	35 (2.1%)	78 (4.6%)	0.45 (0.30 – 0.66)	**<0.0001**
Major bleeding				
BARC types 3 or 5	11 (0.7%)	28 (1.7%)	0.39 (0.19 – 0.79)	**0.009**
TIMI major or minor	11 (0.7%)	27 (1.6%)	0.41 (0.20 – 0.82)	**0.01**
Major	8 (0.5%)	19 (1.1%)	0.42 (0.18 – 0.96)	**0.04**
Minor	3 (0.2%)	8 (0.5%)	0.39 (0.10 – 1.46)	0.16
GUSTO moderate, severe or life-threatening	8 (0.5%)	19 (1.1%)	0.42 (0.18 – 0.96)	**0.04**
Moderate	3 (0.2%)	10 (0.6%)	0.30 (0.08 – 1.10)	0.07
Severe or life-threatening	5 (0.3%)	9 (0.5%)	0.56 (0.19 – 1.66)	0.29
ISTH major bleeding	8 (0.5%)	21 (1.2%)	0.38 (0.17 – 0.86)	**0.02**
BARC types 1-5				
1	8 (0.5%)	12 (0.7%)	0.67 (0.27 – 1.63)	0.37
2	24 (1.4%)	50 (2.9%)	0.48 (0.29 – 0.78)	**0.003**
3	10 (0.6%)	24 (1.4%)	0.42 (0.20 – 0.88)	**0.02**
5	1 (0.1%)	4 (0.2%)	0.25 (0.03 – 1.98)	0.20

Clinically-Relevant Bleeding (BARC types 2, 3, 5)

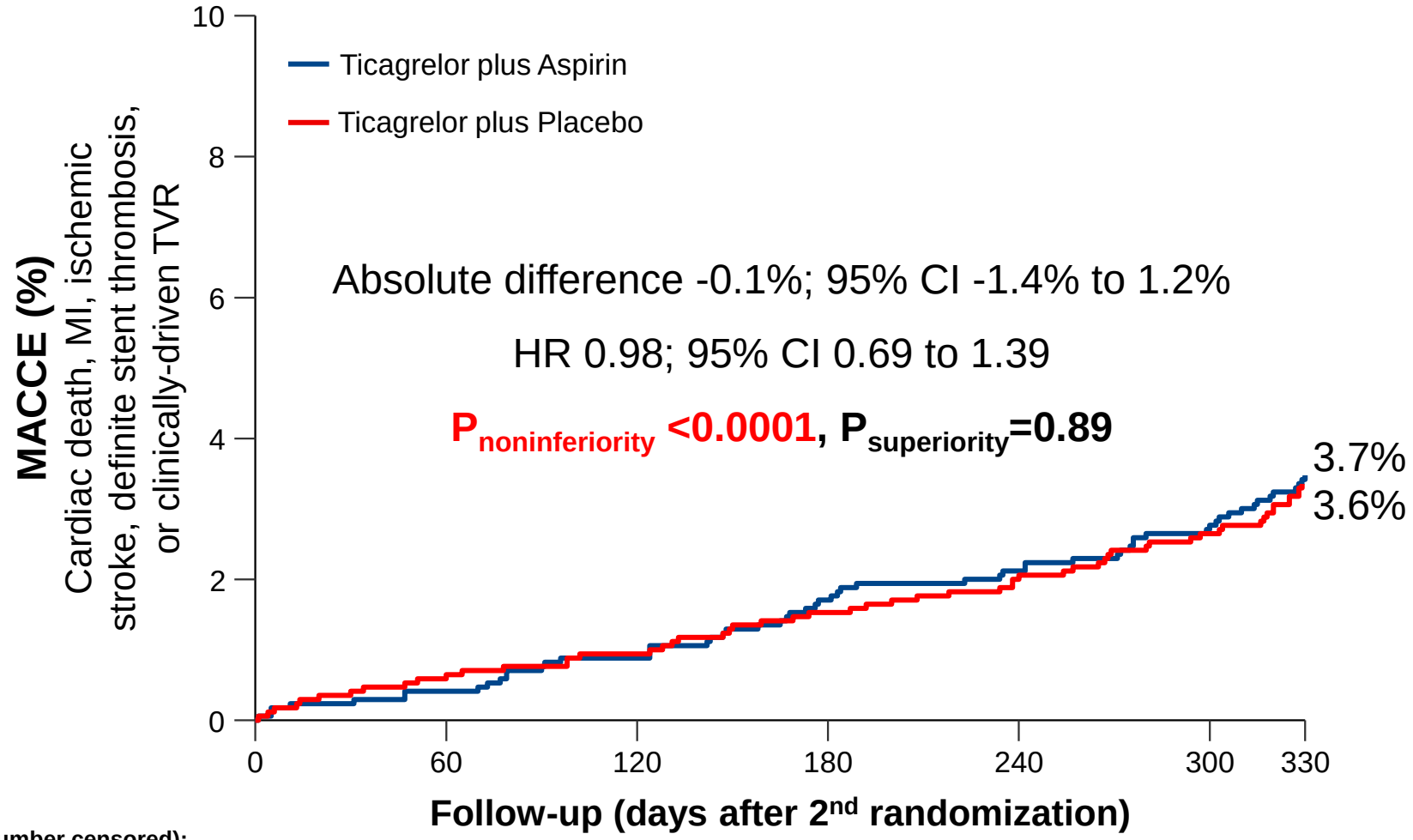
- Subgroup analysis -

No significant interactions were present in 12 pre-specified subgroups

	Clinically-relevant bleeding, n/N (%)				
	Ticagrelor Plus Placebo	Ticagrelor Plus Aspirin	Hazard ratio (95%CI)	Hazard ratio (95%CI)	$P_{interaction}$
Overall	35/1700 (2.1%)	78/1700 (4.6%)		0.45 (0.30-0.66)	
Age, years					0.30
≥65	23/729 (3.2%)	40/703 (5.7%)		0.55 (0.33-0.93)	
<65	12/971 (1.2%)	38/997 (3.8%)		0.32 (0.17-0.62)	
Sex					0.73
Male	24/1264 (1.9%)	56/1257 (4.5%)		0.42 (0.26-0.68)	
Female	11/436 (2.5%)	22/443 (5.0%)		0.50 (0.24-1.03)	
Race					0.69
Chinese	32/1476 (2.2%)	74/1519 (4.9%)		0.44 (0.29-0.67)	
Non-Chinese	3/224 (1.3%)	4/181 (2.2%)		0.59 (0.13-2.64)	
Diabetes mellitus					0.92
Yes	11/540 (2.0%)	25/535 (4.7%)		0.43 (0.21-0.87)	
No	24/1160 (2.1%)	53/1165 (4.6%)		0.45 (0.28-0.73)	
Renal dysfunction					0.82
Yes	4/119 (3.4%)	8/129 (6.2%)		0.48 (0.15-1.61)	
No	31/1581 (2.0%)	70/1571 (4.5%)		0.44 (0.29-0.67)	
BMI, Kg/m²					0.28
≤25	16/845 (1.9%)	43/842 (5.1%)		0.36 (0.20-0.64)	
>25	19/855 (2.2%)	35/858 (4.1%)		0.54 (0.31-0.95)	
Initial presentation					0.59
Unstable angina	14/668 (2.1%)	29/708 (4.1%)		0.51 (0.27-0.96)	
Non-STEMI	14/545 (2.6%)	32/531 (6.0%)		0.42 (0.22-0.79)	
STEMI	7/487 (1.4%)	17/461 (3.7%)		0.38 (0.16-0.92)	
History of prior MI					0.85
Yes	2/143 (1.4%)	8/156 (5.1%)		0.33 (0.07-1.59)	
No	33/1557 (2.1%)	70/1544 (4.5%)		0.47 (0.31-0.70)	
Biomarker positive					0.60
Yes	21/1032 (2.0%)	49/992 (4.9%)		0.41 (0.24-0.68)	
No	14/668 (2.1%)	29/708 (4.1%)		0.51 (0.27-0.96)	
Stent length (mm)					0.69
≥60	6/258 (2.3%)	15/245 (6.1%)		0.38 (0.15-0.98)	
<60	29/1441 (2.0%)	63/1454 (4.3%)		0.46 (0.30-0.71)	
Multivessel disease					0.32
Yes	10/534 (1.9%)	30/545 (5.5%)		0.33 (0.16-0.69)	
No	25/1166 (2.1%)	48/1155 (4.2%)		0.52 (0.32-0.84)	
IVUS-guided PCI					0.27
Yes	12/856 (1.4%)	35/857 (4.1%)		0.34 (0.18-0.66)	
No	23/844 (2.7%)	43/843 (4.2%)		0.53 (0.32-0.88)	



Primary Safety Endpoint: MACCE



Number at risk (number censored):

Ticagrelor plus Aspirin	1700 (0)	1693 (0)	1684 (1)	1669 (2)	1659 (2)	1648 (2)	1636 (2)
Ticagrelor plus Placebo	1700 (0)	1690 (0)	1684 (0)	1673 (1)	1664 (1)	1652 (2)	1640 (2)

MACCE and NACE Endpoints

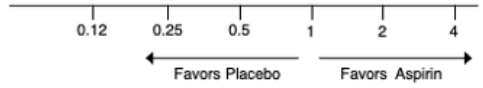
Between 1- and 12-months post-PCI	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)	Hazard ratio (95% CI)	P-value
Primary endpoint: MACCE	61 (3.6%)	63 (3.7%)	0.98 (0.69 – 1.39)	0.89
Secondary endpoints				
All-cause death	12 (0.7%)	13 (0.8%)	0.93 (0.42 – 2.03)	0.84
Cardiac death	8 (0.5%)	7 (0.4%)	1.15 (0.42 – 3.18)	0.46
Stroke	20 (1.2%)	24 (1.4%)	0.83 (0.46 – 1.50)	0.54
Myocardial infarction	17 (1.0%)	11 (0.7%)	1.45 (0.67 – 3.23)	0.27
Procedural MI	1 (0.05%)	1 (0.05%)	-	0.88
Non-procedural MI	16 (0.9%)	11 (0.7%)	1.42 (0.66 – 3.03)	0.29
Repeat revascularization	40 (2.4%)	41 (2.4%)	0.99 (0.64 – 1.53)	0.95
TVR	33 (2.0%)	36 (2.1%)	0.93 (0.58 – 1.49)	0.75
TLR	27 (1.6%)	28 (1.7%)	0.97 (0.57 – 1.65)	0.92
Stent thrombosis, definite or probable	5 (0.3%)	5 (0.3%)	0.97 (0.28 – 3.40)	0.96
Definite	3 (0.2%)	5 (0.3%)	0.59 (0.14 – 2.51)	0.47
Probable	2 (0.1%)	0 (0.0%)	-	-
Net adverse clinical events (NACE): MACCE or BARC types 1-5 bleeding	97 (5.7%)	140 (8.2%)	0.68 (0.53 – 0.88)	**0.007**

MACCE

- Subgroup analysis -

No significant interactions were present in 12 pre-specified subgroups, except possibly for age

	MACCE , n/N (%)				
	Ticagrelor Plus Placebo	Ticagrelor Plus Aspirin	Hazard ratio (95%CI)	Hazard ratio (95%CI)	$P_{interaction}$
Overall	61/1700 (3.6%)	63/1700 (3.7%)		0.98 (0.69-1.39)	
Age, years					0.02
≥65	39/729 (5%)	26/703 (4%)		1.48 (0.90-2.43)	
<65	22/971 (2%)	37/997 (4%)		0.61 (0.36-1.03)	
Sex					0.48
Male	48/1264 (4%)	46/1257 (4%)		1.05 (0.70-1.57)	
Female	13/436 (3%)	17/443 (4%)		0.77 (0.37-1.58)	
Race					0.28
Chinese	59/1476 (4%)	59/1519 (4%)		1.03 (0.72-1.48)	
Non-Chinese	2/224 (1%)	4/181 (2%)		0.38 (0.07-2.06)	
Diabetes mellitus					0.09
Yes	28/540 (5%)	20/535 (4%)		1.43 (0.80-2.53)	
No	33/1160 (3%)	43/1165 (4%)		0.77 (0.49-1.21)	
Renal dysfunction					0.43
Yes	6/119 (5%)	4/129 (3%)		1.64 (0.45-5.95)	
No	55/1581 (4%)	59/1571 (4%)		0.93 (0.65-1.35)	
BMI, Kg/m²					0.07
≤25	32/845 (4%)	23/842 (3%)		1.42 (0.83-2.43)	
>25	29/855 (3%)	40/858 (5%)		0.73 (0.45-1.18)	
Initial presentation					0.39
Unstable angina	28/668 (4%)	29/708 (4%)		1.03 (0.61-1.74)	
Non-STEMI	12/545 (2%)	23/531 (4%)		0.51 (0.25-1.03)	
STEMI	21/487 (4%)	11/461 (3%)		1.76 (0.85-3.68)	
History of prior MI					0.16
Yes	9/143 (6%)	5/156 (3%)		2.11 (0.70-6.34)	
No	52/1557 (3%)	58/1544 (4%)		0.89 (0.61-1.30)	
Biomarker positive					0.78
Yes	33/1032 (3%)	34/992 (3%)		0.93 (0.58-1.50)	
No	28/668 (4%)	29/708 (4%)		1.03 (0.61-1.74)	
Stent length, mm					0.61
≥60	12/258 (5%)	10/245 (4%)		1.21 (0.52-2.81)	
<60	49/1441 (3%)	53/1454 (4%)		0.94 (0.64-1.39)	
Multivessel disease					0.50
Yes	25/534 (5%)	30/545 (6%)		0.84 (0.49-1.42)	
No	36/1166 (3%)	33/1155 (3%)		1.09 (0.68-1.74)	
IVUS-guided PCI (first randomization)					0.10
Yes	16/856 (2%)	25/857 (3%)		0.65 (0.35-1.22)	
No	45/844 (5%)	38/843 (5%)		1.20 (0.78-1.85)	



Limitations

1. The primary efficacy endpoint included minor bleeding (BARC type 2)
   - However, major bleeding was also significantly reduced with ticagrelor monotherapy (BARC types 3 or 5, TIMI major or minor, GUSTO and ISTH)
2. Non-inferiority for MACCE was tested with an absolute margin of 2.5%. Given the lower observed ischemic event rate in the control group than anticipated (3.7% vs. 6.2%), this relative margin is wide
   - Given the 95% CI of the observed difference, it is likely that the absolute MACCE rate with ticagrelor monotherapy is <1.2% greater than with ticagrelor + aspirin
3. ~40% of pts had biomarker-negative unstable angina
   - hs-troponin assays were not widely available in China and Pakistan during the enrollment period, and it is likely that many of these pts had NSTEMI
4. 88.1% of pts were from China, possibly affecting the generalizability of the results

Conclusions and Clinical Implications

- The present results demonstrate that in pts with ACS treated with PCI with contemporary DES who are free from major adverse ischemic and bleeding events after 1 month on DAPT, treatment with ticagrelor alone between 1 and 12 months will decrease clinically-relevant and major bleeding while providing similar protection from MACCE compared with ticagrelor plus aspirin

- These results, in concert with prior trials, warrant updating the guidelines and change in practice to treat most pts with ACS after PCI with 1-month DAPT only followed by conversion to SAPT with a potent $P2Y_{12}$ inhibitor (with the strongest evidence to date supporting ticagrelor)

The Lancet, April 7, 2024

Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomised, placebo-controlled, double-blind clinical trial

Zhen Ge, Jing Kan*, Xiaofei Gao*, Afsar Raza, Jun-Jie Zhang, Bilal S Mohydin, Fentang Gao, Yibing Shao, Yan Wang, Hesong Zeng, Feng Li, Hamid Sharif Khan, Naeem Mengal, Hongliang Cong, Mingliang Wang, Lianglong Chen, Yongyue Wei, Feng Chen, Gregg W Stone, Shao-Liang Chen, for the ULTIMATE-DAPT investigators†*

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