Safety and Efficacy of Ticagrelor versus Clopidogrel in Korean Patients with Acute Coronary Syndromes Intended for Invasive Management: A Randomized Clinical Trial

TICAKOREA

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Disclosure

- I have nothing to disclosure

Background

- Ticagrelor is an oral, reversible, direct-acting, P2Y12 inhibitor that provides faster, greater, and more consistent P2Y12 inhibition compared to clopidogrel.

- European and U.S. guidelines recommend that ticagrelor should be preferred to clopidogrel as a P2Y12 antagonist in ACS patients with or without PCI.

East Asian paradox

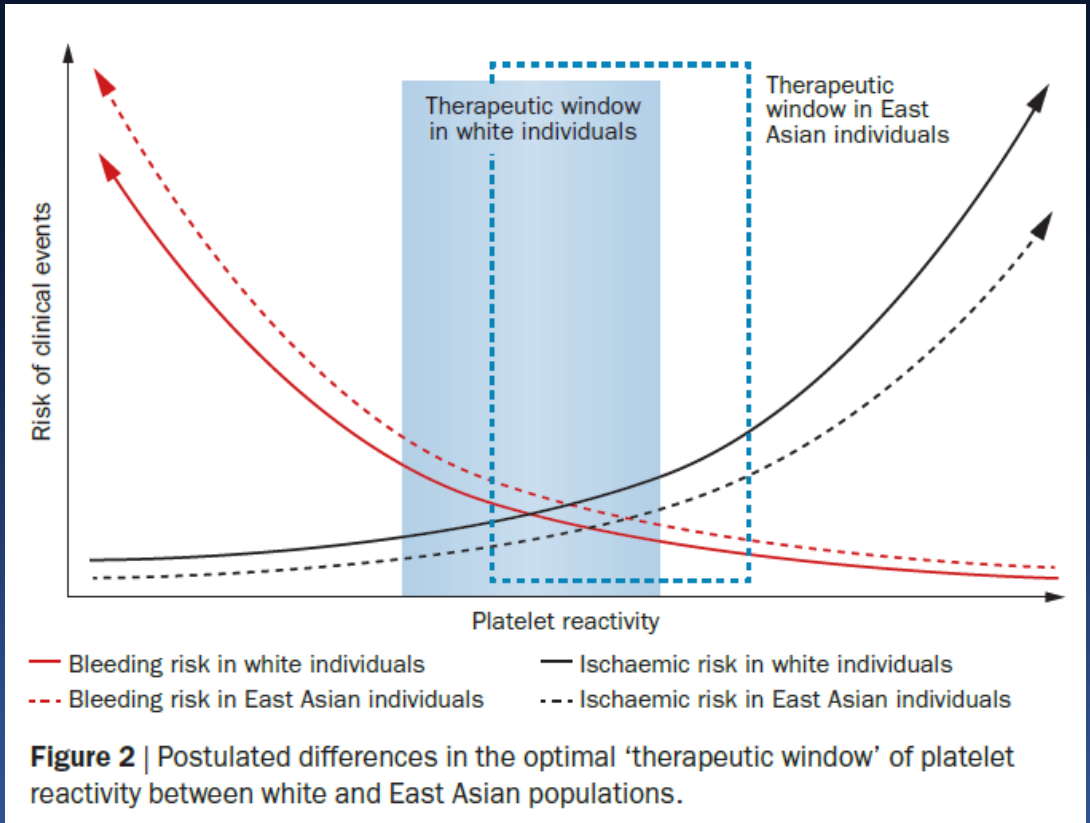


Figure 2 | Postulated differences in the optimal 'therapeutic window' of platelet reactivity between white and East Asian populations.

Levine, G. N. et al. Nat. Rev. Cardiol. 11, 597–606 (2014)

Compared to Caucasians, East Asian patients are regarded as more susceptible to bleeding events, but relatively resistant to thromboembolic events, even on a higher prevalence of high on-treatment reactivity, a phenomenon that is referred to as "East Asian paradox."

PHILO trial with ticagrelor

	Ticagrelor	Clopidogrel	OR (95%CI)	P-value
	N=401	N=400		
Composite end point	43	28	1.60(0.97-2.62)	0.08
Death	10	7	1.44(0.54-4.25)	0.63
Stroke	9	6	1.51(0.54-4.25)	0.60
MI	24	15	1.63(0.85-3.15)	0.19
Bleeding*	92	56	1.83(1.27-2.63)	0.001
Net clinical Benefit**	76	51	1.6(1.09-2.35)	0.02

*MI (excluding silent), * PLATO defined, ** PLATO defined as CV death, MI, stroke, or CABG related or non CABG related major bleeding.*

In the PHILO trial targeting East Asian (Japanese, Korean, and Chinese) patients, ticagrelor was associated with a higher rate of bleeding events and a non-significant higher risk of ischemic events compared to clopidogrel.

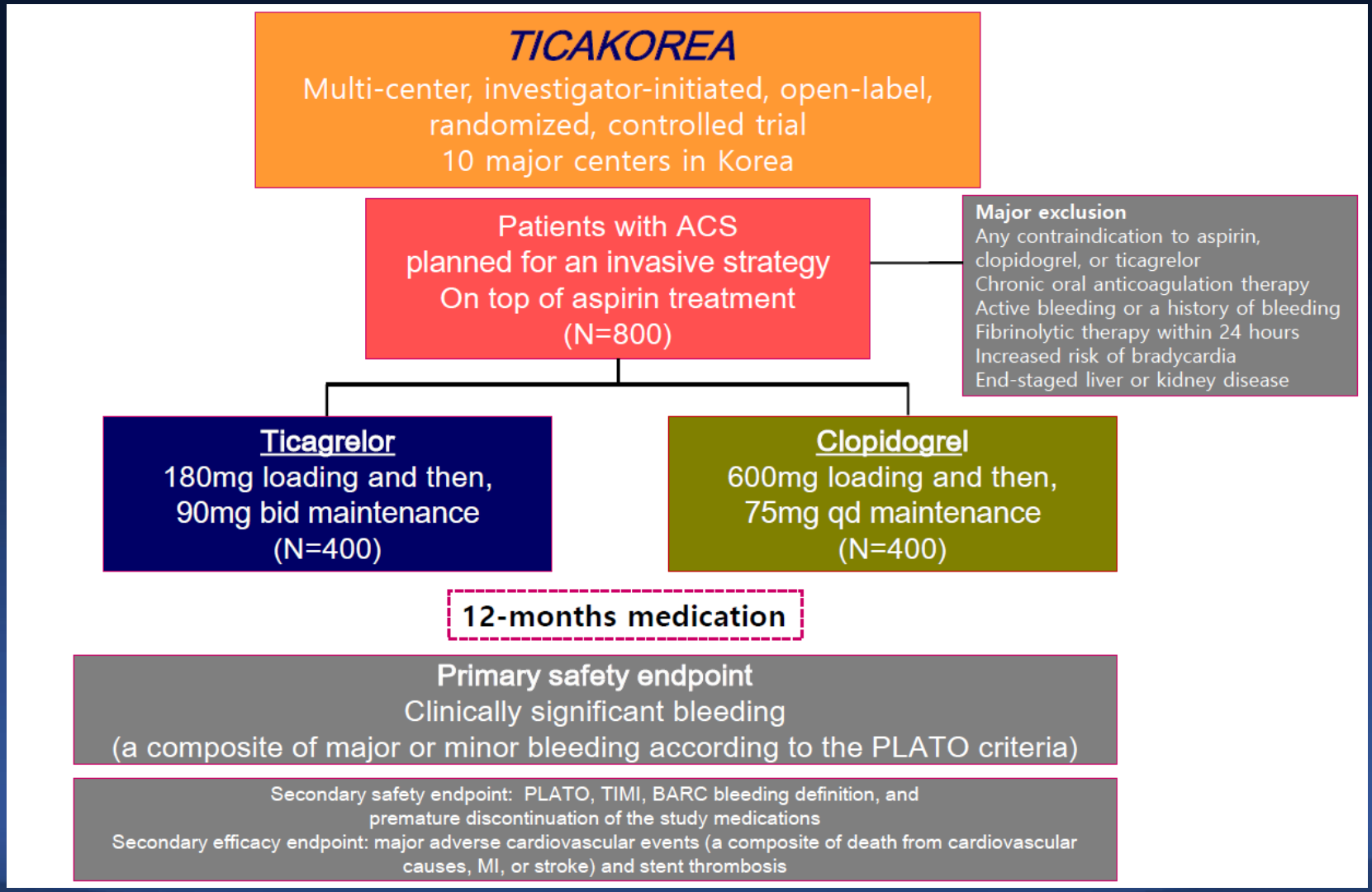
Shinya Goto, et al., Circ J 2015; 79: 2452 – 2460
DW Park TCT2018

Background

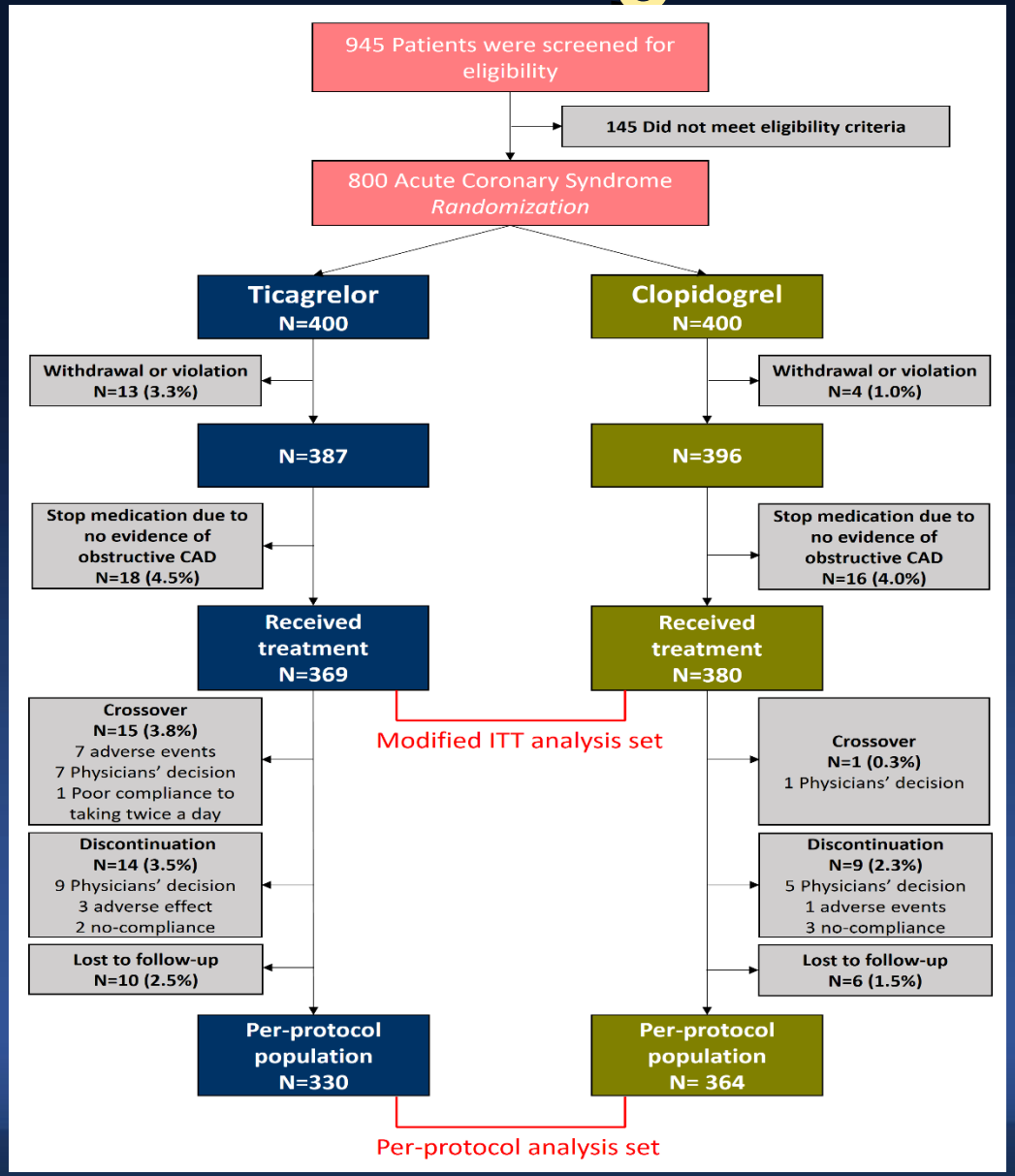
- The superior efficacy of ticagrelor, as observed in the PLATO trial, was questioned in East Asian patients, and more alarmingly, the pronounced bleeding risk with ticagrelor use was of concern.

- We conducted a practical randomized trial to compare the safety and efficacy of ticagrelor with those of clopidogrel in Korean patients with ACS who were planned for an invasive strategy.

Study design



Flow Diagram



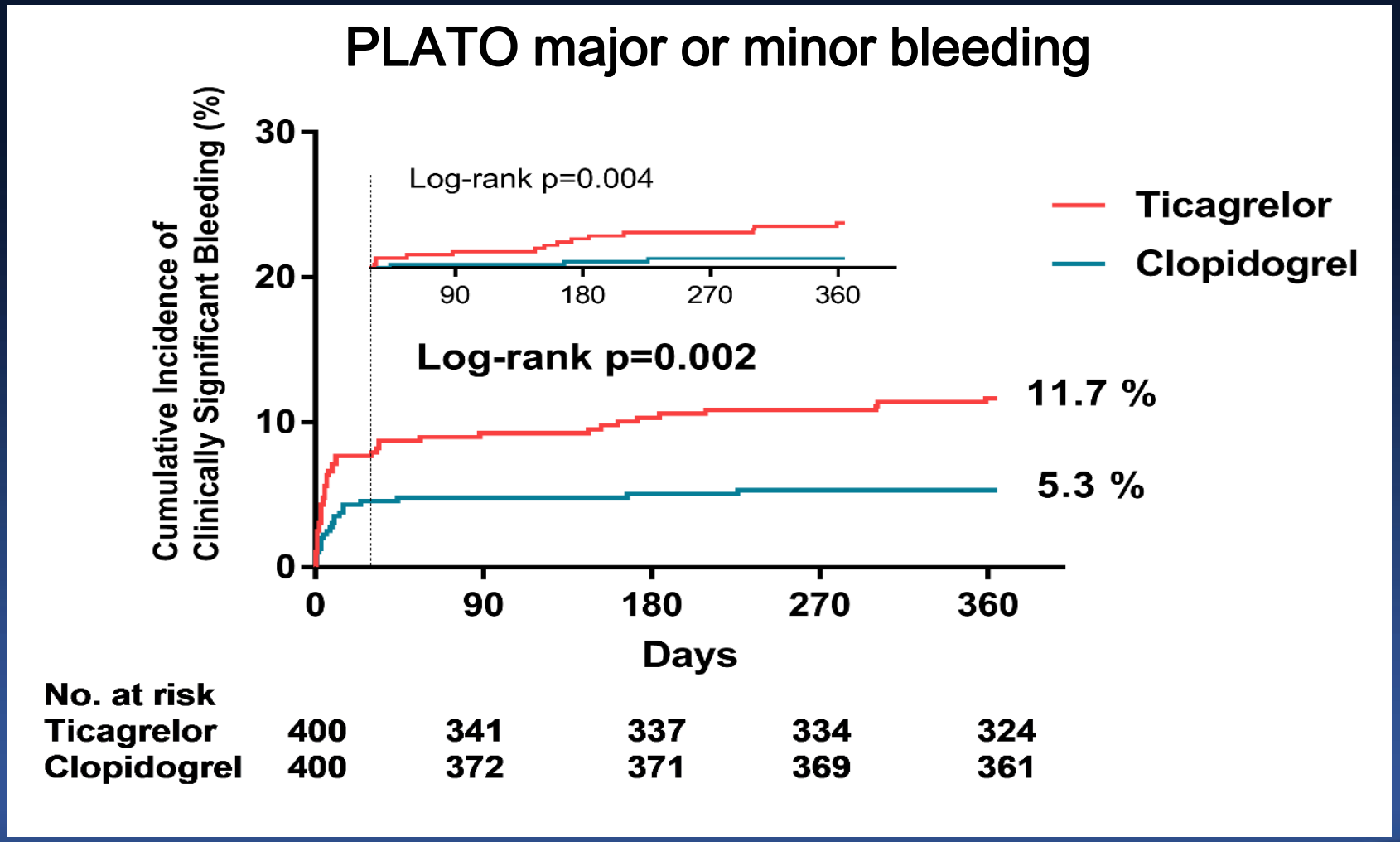
Baseline Characteristics

Characteristic	All population (N=800)	Ticagrelor (N=400)	Clopidogrel (N=400)	P value
Age, years	62.4 ± 11.	62.5 ± 11.3	62.3 ± 11.5	0.86
Age ≥ 75 years	122 (15.3)	64 (16.0)	58 (14.5)	0.55
Male sex	599 (74.8)	297 (74.2)	302 (75.5)	0.74
Body mass index, kg/m^2	24.7 ± 3.1	24.6 ± 3.0	24.9 ± 3.2	0.33
Body mass index < 20 kg/m^2	41 (5.1)	20 (5.0)	21 (5.3)	0.87
Hypertension	416 (51.9)	223 (55.8)	193 (48.2)	**0.04**
Diabetic mellitus	216 (27.0)	116 (29.0)	100 (25.0)	0.23
Insulin use	16 (2.0)	8 (2.0)	8 (2.0)	>0.99
Current smoker	285 (35.6)	146 (36.5)	139 (34.8)	0.61
Hyperlipidemia	402 (50.2)	208 (52.0)	194 (48.5)	0.36
History of myocardial infarction	45 (5.6)	25 (6.2)	20 (5.0)	0.54
Prior PCI	72 (9.0)	41 (10.2)	31 (7.8)	0.27
Prior CABG	7 (0.9)	4 (1.0)	3 (0.8)	>0.99
History of stroke	40 (5.0)	24 (6.0)	16 (4.0)	0.26
History of heart failure	16 (2.0)	10 (2.5)	6 (1.5)	0.45
Peripheral artery disease	6 (0.7)	4 (1.0)	2 (0.5)	0.68
Chronic renal disease	7 (0.9)	6 (1.5)	1 (0.2)	0.13
Chronic lung disease	15 (1.9)	12 (3.0)	3 (0.8)	**0.04**
History of gout	9 (1.1)	5 (1.2)	4 (1.0)	>0.99
Previous GI bleeding	1 (0.1)	1 (0.2)	0 (0.0)	>0.99

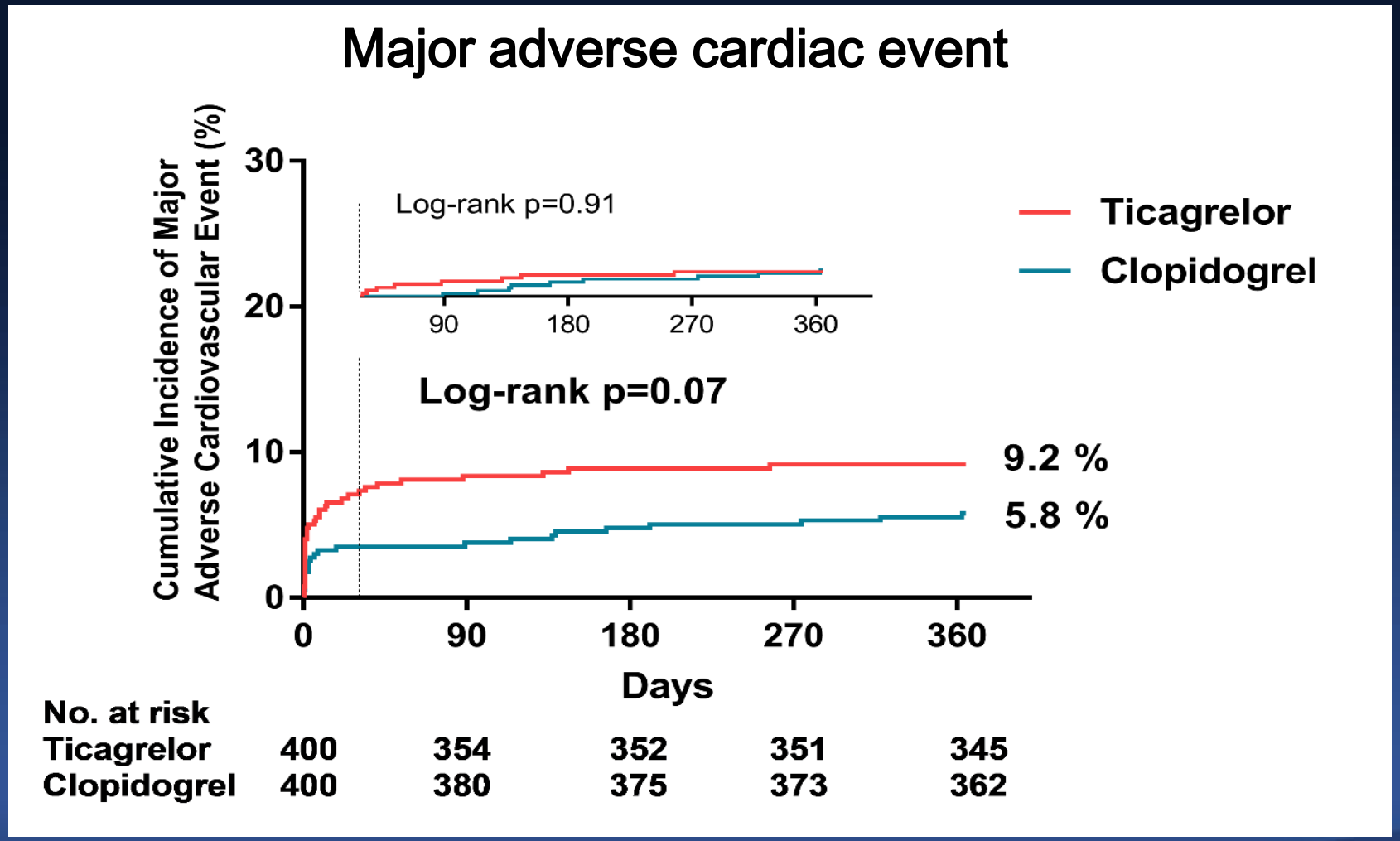
Baseline Characteristics

Characteristic	All population (N=800)	Ticagrelor (N=400)	Clopidogrel (N=400)	P value
Clinical presentation				0.59
Unstable angina	171 (21.3)	82 (20.5)	89 (22.2)	
NSTEMI	303 (37.8)	148 (37.0)	155 (38.8)	
STEMI	326 (40.7)	170 (42.5)	156 (39.0)	
Killip class > 2	21 (2.6)	10 (2.5)	11 (2.8)	0.83
Positive Troponin I or T at inclusion	671 (83.9)	338 (84.5)	333 (83.3)	0.63
Final treatment				0.32
PCI with stenting	620 (77.5)	300 (75.0)	320 (80.0)	
PCI with ballooning	48 (6.0)	26 (6.5)	22 (5.5)	
CABG	17 (2.1)	11 (2.8)	6 (1.5)	
Medical treatment only	115 (14.4)	63 (15.8)	52 (13.0)	
Glycoprotein IIb/IIIa inhibitors	22 (2.8)	8 (2.0)	14 (3.5)	0.20
Discharge medications				
β-blocker	572 (71.5)	275 (68.8)	297 (74.2)	0.10
Calcium channel blocker	180 (22.5)	90 (22.5)	90 (22.5)	>0.99
ACE inhibitor or ARB	334 (41.8)	163 (40.8)	171 (42.8)	0.62
Statin	723 (90.4)	354 (88.5)	369 (92.2)	0.09
Proton-pump inhibitors	20 (2.5)	12 (3.0)	8 (2.0)	0.50

Primary Safety Endpoint



Secondary Efficacy Endpoint



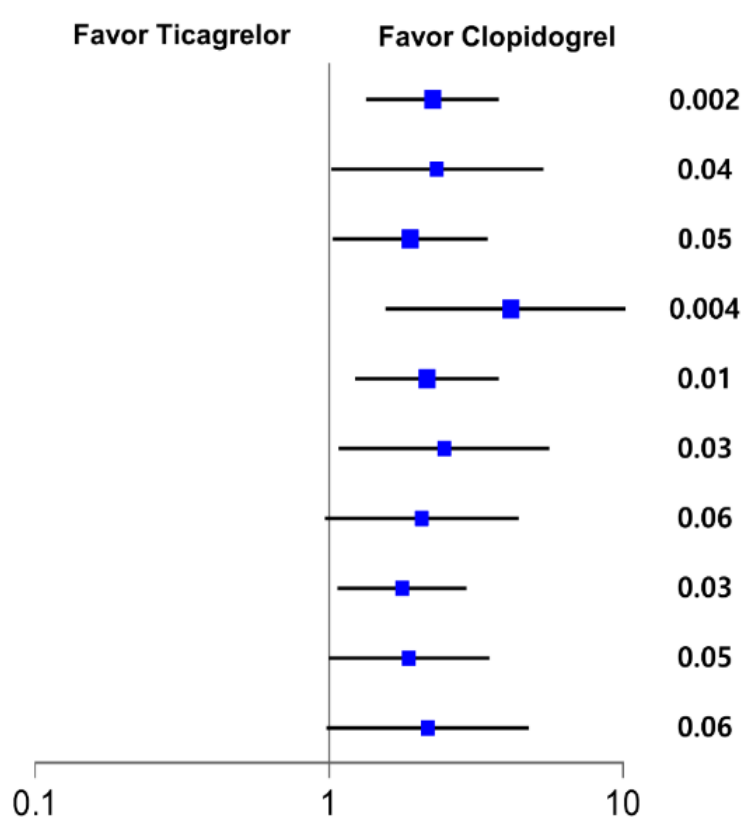
Primary Safety Endpoint and Its Components

End point number (%)*	Ticagrelor (N=400)	Clopidogrel (N=400)	Hazard Ratio for Ticagrelor Group (95% CI)	P value†
Clinically significant bleeding (PLATO major or minor bleeding)	45 (11.7)	21 (5.3)	2.26 (1.34–3.79)	**0.002**
Procedure-related	11 (2.8)	7 (1.8)	1.59 (0.62–4.11)	0.34
CABG-related	11 (2.8)	4 (1.0)	2.85 (0.91–8.94)	0.07
Non-procedure or CABG-related	23 (6.0)	10 (2.5)	2.39 (1.14–5.02)	**0.02**
PLATO major bleeding	29 (7.5)	16 (4.1)	1.89 (1.03–3.48)	**0.04**
Procedure-related	4 (1.0)	5 (1.3)	0.81 (0.22–3.01)	0.75
CABG-related	11 (2.8)‡	4 (1.0)	2.85 (0.91–8.94)	0.07
Non-procedure or CABG-related	14 (3.7)	7 (1.8)	2.07 (0.84–5.13)	0.12
PLATO minor bleeding	20 (5.2)	5 (1.3)	4.16 (1.56–11.1)	**0.002**
Procedure-related	8 (2.0)	2 (0.5)	4.05 (0.86–19.07)	0.06
CABG-related	0 (0.0)	0 (0.0)	NA	NA
Non-procedure or CABG-related	12 (3.2)	3 (0.8)	4.17 (1.18–14.79)	0.02
Fatal bleeding	4 (1.0)§	0 (0.0)	NA	0.04¶

Data are presented as number (%). The percentages are Kaplan-Meier estimates of the rates of the indicated events at 12 months, †P values were obtained by means of Cox regression analysis,
‡Two cases of CABG were electively performed during the follow-up period after the index treatment of balloon angioplasty,
§Fatal bleeding included 1 GI bleeding, 1 hemorrhagic pericarditis, 1 intracranial bleeding, and 1 adrenal hemorrhage
¶P value was calculated with the use of the log-rank test, Abbreviation: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NA, not available

Safety Endpoints according to the different Bleeding Criteria

	Ticagrelor (N=400)	Clopidogrel (N=400)	Hazard ratio for Ticagrelor (95% CI)	P value
PLATO major or minor	45 (11.7)	21 (5.3)	2.26 (1.34 - 3.79)	0.002
PLATO major	29 (7.5)	16 (4.1)	1.89 (1.03 - 3.48)	0.04
PLATO life-threatening	18 (4.6)	8 (2.0)	2.33 (1.02 – 5.37)	0.05
PLATO minor	20 (5.2)	5 (1.3)	4.16 (1.56 - 11.1)	0.004
TIMI major or minor	37 (9.6)	18 (4.6)	2.16 (1.23 - 3.79)	0.01
TIMI major	19 (4.9)	8 (2.0)	2.47 (1.08 - 5.64)	0.03
TIMI minor	20 (5.2)	10 (2.5)	2.07 (0.97 - 4.42)	0.06
BARC 2,3,4 or 5	41 (10.6)	24 (6.1)	1.78 (1.07 - 2.94)	0.03
BARC 3,4 or 5	27 (7.0)	15 (3.8)	1.87 (1.00 - 3.52)	0.05
BARC 2	19 (5.0)	9 (2.3)	2.17 (0.98 - 4.80)	0.06

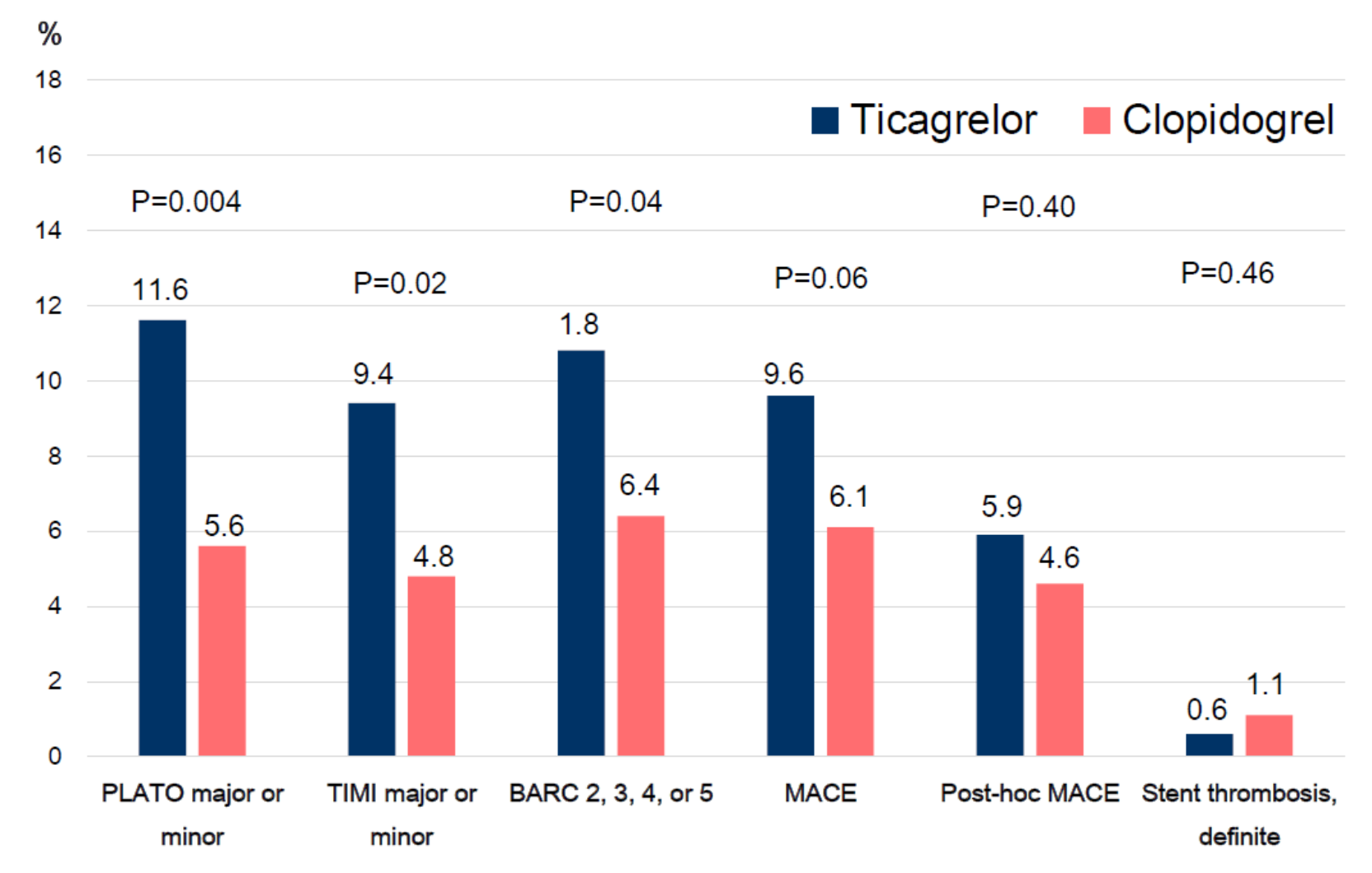


Secondary Efficacy Endpoint and Its Components

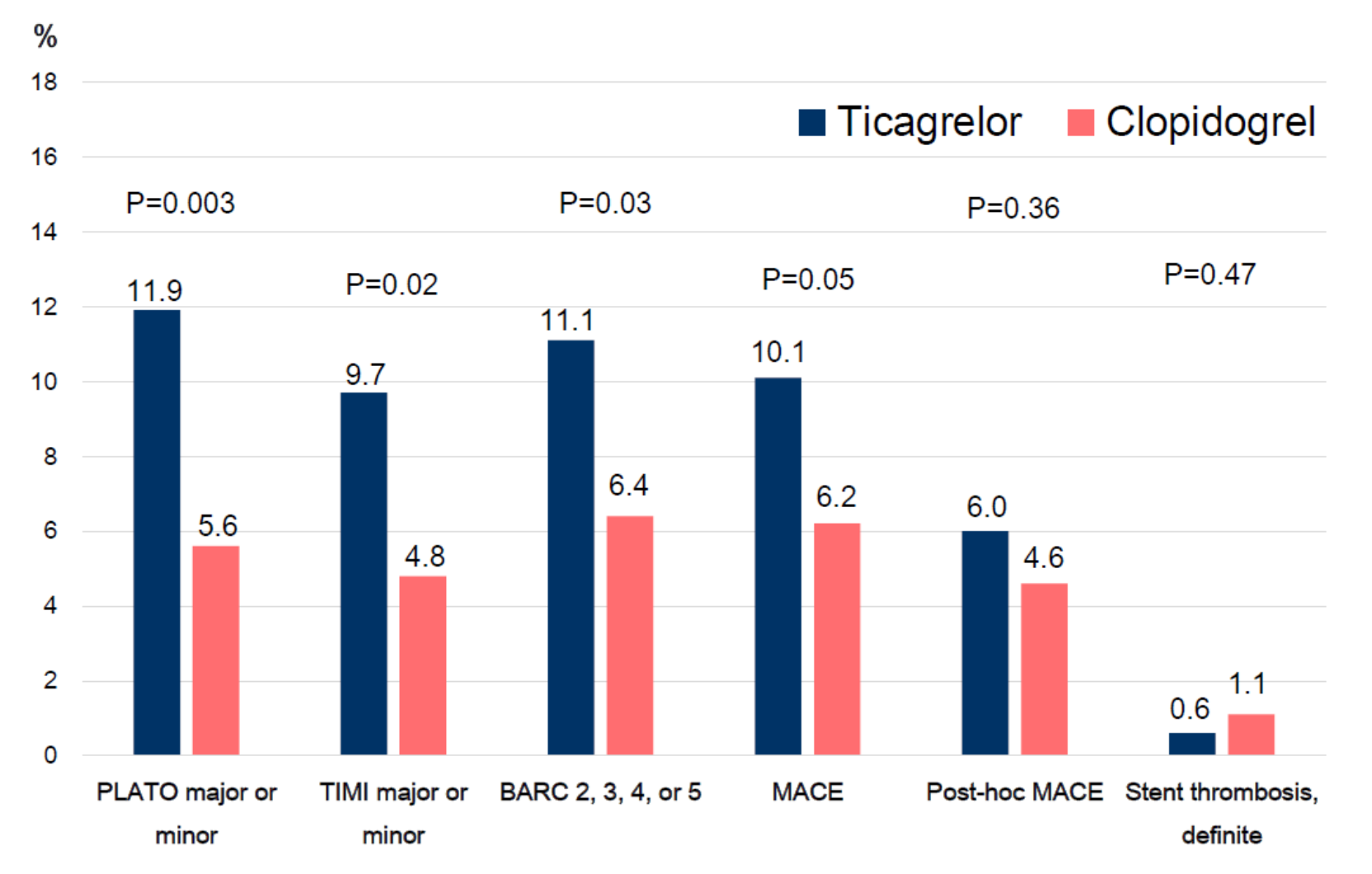
End point number (%)*	Ticagrelor (N=400)	Clopidogrel (N=400)	Hazard Ratio for Ticagrelor Group (95% CI)	P value†
Major adverse cardiovascular event				
Composite of cardiovascular death, MI or stroke	36 (9.2)	23 (5.8)	1.62 (0.96–2.74)	0.07
Post-hoc: composite of cardiovascular death, spontaneous MI, or stroke	21 (5.4)	17 (4.3)	1.27 (0.67–2.40)	0.47
Other secondary efficacy endpoints				
Composite of all-cause death, MI or stroke	37 (9.4)	27 (6.8)	1.42 (0.86–2.33)	0.17
All-cause death	16 (4.1)	10 (2.5)	1.65 (0.75–3.63)	0.22
Cardiovascular death	15 (3.8)	6 (1.5)	2.61 (1.01–6.72)	**0.05**
Non-cardiovascular death	1 (0.3)	4 (1.0)	0.26 (0.03–2.31)	0.23
Myocardial infarction	20 (5.1)	16 (4.0)	1.28 (0.66–2.47)	0.46
Periprocedural MI	16 (4.0)	7 (1.7)	2.30 (0.95–5.60)	0.07
Spontaneous MI	4 (1.1)	9 (2.3)	0.45 (0.14–1.47)	0.19
Stroke	6 (1.6)	5 (1.3)	1.25 (0.38–4.09)	0.72
Repeat revascularization	10 (2.7)	12 (3.1)	0.86 (0.37–2.00)	0.73
Target-vessel	5 (1.3)	8 (2.0)	0.65 (0.21–1.97)	0.44
Target-lesion	4 (1.1)	4 (1.0)	1.03 (0.26–4.13)	0.96
Non-target vessel	6 (1.6)	3 (0.8)	2.09 (0.52–8.35)	0.30
Stent thrombosis, definite	2 (0.5)	4 (1.0)	0.51 (0.09–2.79)	0.44

Data are presented as number (%), *The percentages are Kaplan-Meier estimates of the rates of the end points at 12 months, †P values were calculated by means of Cox regression analysis
Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction

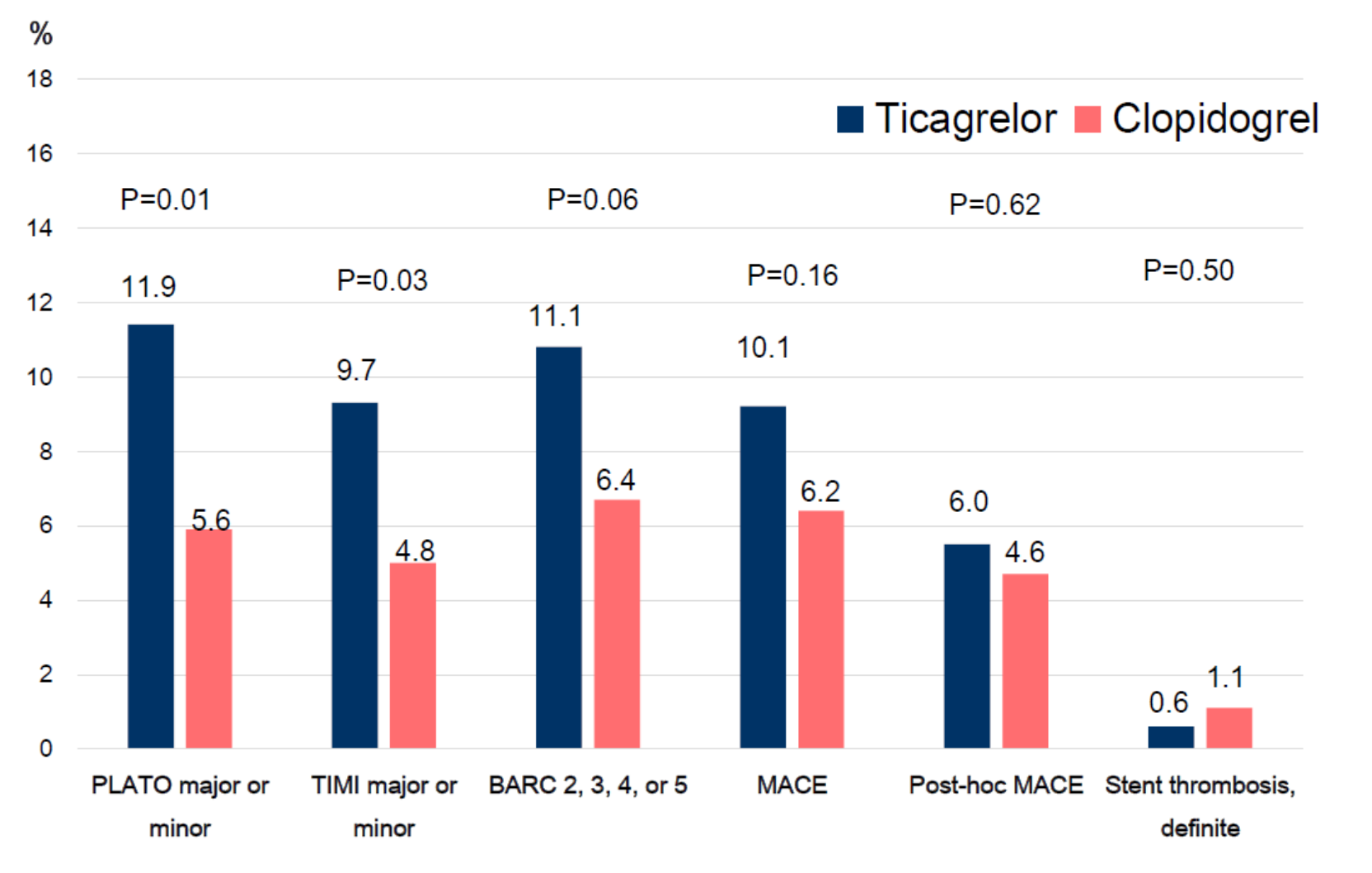
Safety and Efficacy Endpoints According to the Lag-Censoring Analysis



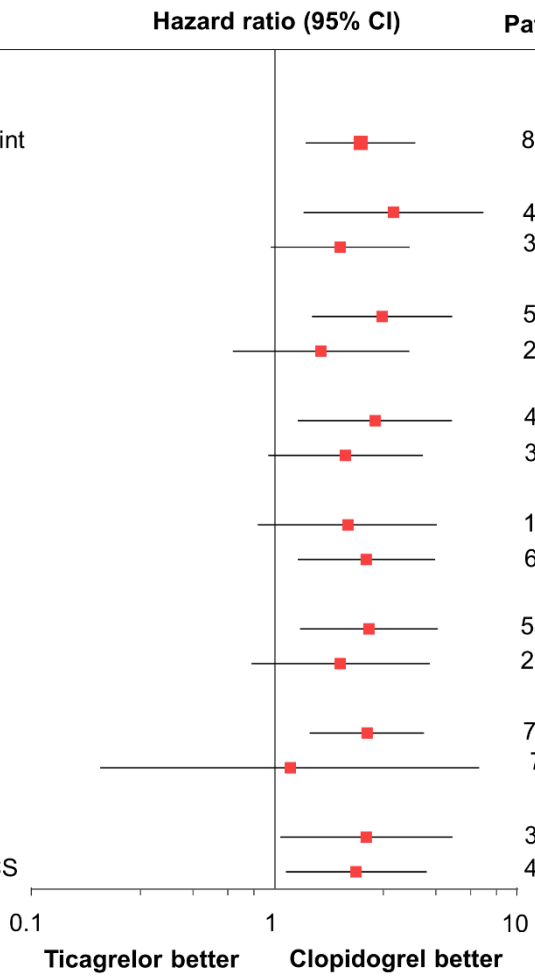
Safety and Efficacy Endpoints According to the Modified Intention-to-Treat Analysis and its Lag-Censoring Analysis



Safety and Efficacy End Points According to the Per-Protocol Analysis and its Lag-Censoring Analysis

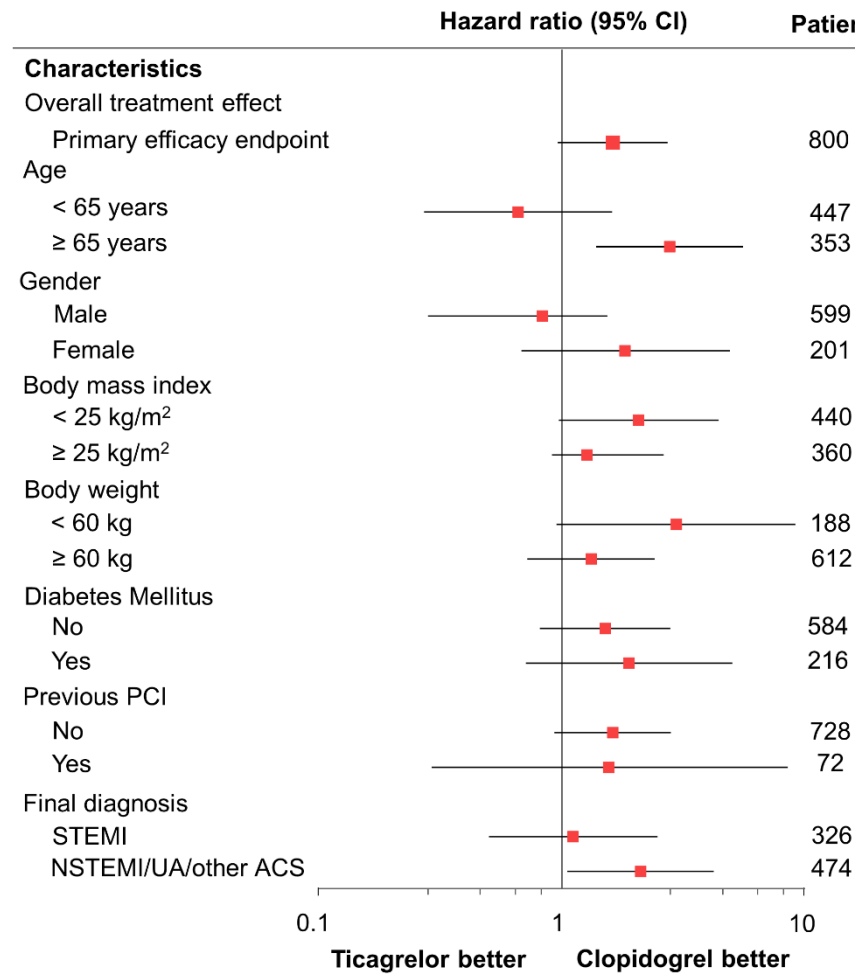


Primary Safety Endpoint According to Patient Key Subgroups



Characteristics	Patients	Ticagrelor	Clopidogrel	Hazard ratio (95% CI)	p value (interaction)
Overall treatment effect					
Primary safety endpoint	800	45 (11.7%)	21 (5.3%)	2.26 (1.34 – 3.79)	
Age					0.37
< 65 years	447	21 (9.6%)	7 (3.3%)	3.08 (1.31 – 7.25)	
≥ 65 years	353	24 (14.3%)	14 (7.8%)	1.86 (0.96 – 3.59)	
Gender					0.29
Male	599	31 (10.8%)	12 (4.0%)	2.77 (1.42 – 5.39)	
Female	201	14 (14.2%)	9 (9.2%)	1.55 (0.67 – 3.58)	
Body mass index					0.59
< 25 kg/m^2	440	25 (11.8%)	10 (4.6%)	2.59 (1.24 – 5.38)	
≥ 25 kg/m^2	360	20 (11.5%)	11 (6.1%)	1.95 (0.94 – 4.07)	
Body weight					0.76
< 60 kg	188	16 (17.2%)	8 (8.9%)	2.00 (0.85 – 4.66)	
≥ 60 kg	612	29 (9.9%)	13 (4.3%)	2.38 (1.24 – 4.58)	
Diabetes Mellitus					0.64
No	584	29 (10.5%)	13 (4.4%)	2.44 (1.27 – 4.70)	
Yes	216	16 (14.4%)	8 (8.0%)	1.86 (0.80 – 4.35)	
Previous PCI					0.45
No	728	42 (12.2%)	19 (5.2%)	2.40 (1.39 – 4.12)	
Yes	72	3 (7.4%)	2 (6.5%)	1.16 (0.19 – 6.96)	
Final diagnosis					0.85
STEMI	326	20 (12.0%)	8 (5.2%)	2.38 (1.05 – 5.40)	
NSTEMI/UA/other ACS	474	25 (11.4%)	13 (5.4%)	2.16 (1.11 – 4.23)	

Secondary Efficacy Endpoint According to Patient Key Subgroups



Characteristics	Patients	Ticagrelor	Clopidogrel	Hazard ratio (95% CI)	p value (interaction)
Overall treatment effect					
Primary efficacy endpoint	800	36 (9.2%)	23 (5.8%)	1.62 (0.96 – 2.73)	
Age					0.01
< 65 years	447	8 (3.6%)	12 (5.6%)	0.66 (0.27 – 1.61)	
≥ 65 years	353	28 (16.2%)	11 (6.2%)	2.78 (1.38 – 5.59)	
Gender					0.78
Male	599	25 (8.5%)	17 (5.7%)	1.54 (0.83 – 2.85)	
Female	201	11 (11.0%)	6 (6.2%)	1.82 (0.68 – 4.93)	
Body mass index					0.37
< 25 kg/m^2	440	20 (9.2%)	10 (4.7%)	2.07 (0.97 – 4.42)	
≥ 25 kg/m^2	360	16 (9.1%)	13 (7.2%)	1.27 (0.91 – 2.63)	
Body weight					0.22
< 60 kg	188	12 (12.6%)	4 (4.5%)	2.96 (0.95 – 9.17)	
≥ 60 kg	612	24 (8.1%)	19 (6.2%)	1.32 (0.72 – 2.41)	
Diabetes Mellitus					0.71
No	584	24 (8.5%)	17 (5.7%)	1.51 (0.81 – 2.80)	
Yes	216	12 (10.7%)	6 (6.0%)	1.89 (0.71 – 5.05)	
Previous PCI					0.97
No	728	32 (9.1%)	21 (5.8%)	1.62 (0.93 – 2.81)	
Yes	72	4 (9.9%)	2 (6.5%)	1.56 (0.29 – 8.54)	
Final diagnosis					0.23
STEMI	326	13 (7.7%)	11 (7.1%)	1.11 (0.50 – 2.48)	
NSTEMI/UA/other ACS	474	23 (10.2%)	12 (5.0%)	2.11 (1.05 – 4.23)	

Premature Discontinuation of the Medications

	All population (N=800)	Ticagrelor (N=400)	Clopidogrel (N=400)	P value*
Bleeding events	9 (1.1)	8 (2.0)	1 (0.3)	0.02
Adverse event other than bleeding	10 (1.3)	9 (2.3)	1 (0.3)	0.01
Dyspnea†	7 (0.9)	7 (1.8)	0 (0.0)	0.02
Gout	1 (0.1)	1 (0.3)	0 (0.0)	>0.99
Impotence	1 (0.1)	1 (0.3)	0 (0.0)	>0.99
GI trouble	1 (0.1)	0 (0.0)	1 (0.3)	>0.99
Physicians' decision	24 (3.0)	16 (4.0)	8 (2.0)	0.15
High bleeding risk†	7 (0.9)	7 (1.8)	0 (0.0)	0.02
High thrombotic burden‡	1 (0.5)	0 (0.0)	1 (1.0)	>0.99
Thrombotic event (MI)‡	2 (0.3)	0 (0.0)	2 (0.5)	0.50
Short duration of DAPT	11 (1.4)	6 (1.5)	5 (1.3)	>0.99
Requiring concomitant anticoagulation	3 (0.4)	3 (0.8)	0 (0.0)	0.25
Poor compliance to taking twice a day†	1 (0.1)	1 (0.3)	0 (0.0)	>0.99
Non-compliance	5 (0.6)	2 (0.5)	3 (0.8)	>0.99
Lost to follow-up	16 (2.0)	10 (2.5)	6 (1.5)	0.45

Data are presented as number (%), *P values were calculated with the use of Fisher's exact test, †The study medication was switched from ticagrelor to clopidogrel
‡The study medication was switched from clopidogrel to ticagrelor
Abbreviations: DAPT, dual antiplatelet therapy; GI, gastrointestinal; MI, myocardial infarction

Conclusion

- Among Korean ACS patients with or without ST-elevation who are intended for an invasive strategy, use of ticagrelor was associated with a higher rate of clinically significant bleeding at 12 months than was clopidogrel therapy.
- A non-significant higher rate of MACE was observed with ticagrelor use, although the present trial was underpowered to draw any conclusion regarding efficacy.
- A larger, adequately powered trial would be required to definitively assess the efficacy and safety of potent P2Y12 inhibitor ticagrelor in East Asian population.

Thank you for your attention.

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The PLATO trial

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria‡	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)	1.00 (0.91–1.11)	0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33

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Table 3. Adverse Events for All Patients

	Ticagrelor 90 mg b.i.d.	Clopidogrel 75 mg o.d.	HR for ticagrelor (95% CI)
Major bleeding (PLATO-defined)	40 (10.3)	26 (6.8)	1.54 (0.94–2.53)
CABG-related	8 (2.1)	5 (1.3)	1.57 (0.51–4.81)
Non-CABG-related	32 (8.3)	22 (5.8)	1.45 (0.84–2.50)
Coronary procedural	14 (3.6)	11 (2.9)	1.25 (0.57–2.77)
Non-coronary procedural	2 (0.5)	3 (0.8)	0.66 (0.11–3.93)
Minor bleeding (PLATO-defined)	59 (15.2)	35 (9.2)	1.75 (1.15–2.67)
CABG-related	0	1 (0.3)	
Non-CABG-related	59 (15.2)	34 (8.9)	1.81 (1.18–2.76)
Coronary procedural	31 (8.0)	22 (5.8)	1.43 (0.82–2.48)
Non-coronary procedural	10 (2.6)	4 (1.1)	2.51 (0.79–8.01)
Composite of major and minor bleeding	92 (23.8)	56 (14.7)	1.72 (1.23–2.40)
CABG-related	8 (2.1)	5 (1.3)	1.57 (0.51–4.81)
Non-CABG-related	85 (22.0)	52 (13.7)	1.71 (1.20–2.41)
Coronary procedural	44 (11.4)	31 (8.2)	1.44 (0.91–2.29)
Non-coronary procedural	12 (3.1)	7 (1.8)	1.72 (0.68–4.36)
Any adverse event (excluding bleeding)	327 (84.5)	337 (88.7)	
Mild	321 (82.9)	322 (84.7)	
Moderate	67 (17.3)	83 (21.8)	
Severe	30 (7.8)	38 (10.0)	
Dyspnea	22 (5.7)	9 (2.4)	
Bradycardia	11 (2.8)	8 (2.1)	
Ventricular extrasystoles	7 (1.8)	6 (1.6)	
Ventricular pauses ≥3 s on Holter monitoring	0	1 (1.9)	
Increase in serum creatinine >30% (on treatment)	75 (19.4)	60 (15.8)	
Increase in serum uric acid from baseline to end of treatment (μmol/L)	34±87	9±80	
Any uric acid adverse event†	26 (6.7)	20 (5.3)	

Data given as mean±SD or n (%). †Includes hyperuricemia, blood uric acid increase, gout, blood urine present, calculus ureteric, joint swelling. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

End point number (%)*	Ticagrelor (N=400)	Clopidogrel (N=400)	Hazard Ratio for Ticagrelor Group (95% CI)	P value†
Clinically significant bleeding (PLATO major or minor bleeding)	45 (11.7)	21 (5.3)	2.26 (1.34–3.79)	0.002
Procedure-related	11 (2.8)	7 (1.8)	1.59 (0.62–4.11)	0.34
CABG-related	11 (2.8)	4 (1.0)	2.85 (0.91–8.94)	0.07
Non-procedure or CABG-related	23 (6.0)	10 (2.5)	2.39 (1.14–5.02)	0.02
PLATO major bleeding	29 (7.5)	16 (4.1)	1.89 (1.03–3.48)	0.04
Procedure-related	4 (1.0)	5 (1.3)	0.81 (0.22–3.01)	0.75
CABG-related	11 (2.8)‡	4 (1.0)	2.85 (0.91–8.94)	0.07
Non-procedure or CABG-related	14 (3.7)	7 (1.8)	2.07 (0.84–5.13)	0.12
Intracranial	4	1		
Gastrointestinal	6	1		
Genitourinary	0	1		
Pulmonary	1	2		
Surgery-related	0	2		
Skin	2	0		
Pericarditis, hemorrhagic	1	0		
PLATO minor bleeding	20 (5.2)	5 (1.3)	4.16 (1.56–11.1)	0.002
Procedure-related	8 (2.0)	2 (0.5)	4.05 (0.86–19.07)	0.06
CABG-related	0 (0.0)	0 (0.0)	NA	NA
Non-procedure or CABG-related	12 (3.2)	3 (0.8)	4.17 (1.18–14.79)	0.02
Gastrointestinal	5	1		
Genitourinary	2	1		
Pulmonary	1	0		
Genitourinary	2	1		
Epistaxis	2	0		
Fatal bleeding	4 (1.0)§	0 (0.0)	NA	0.04¶