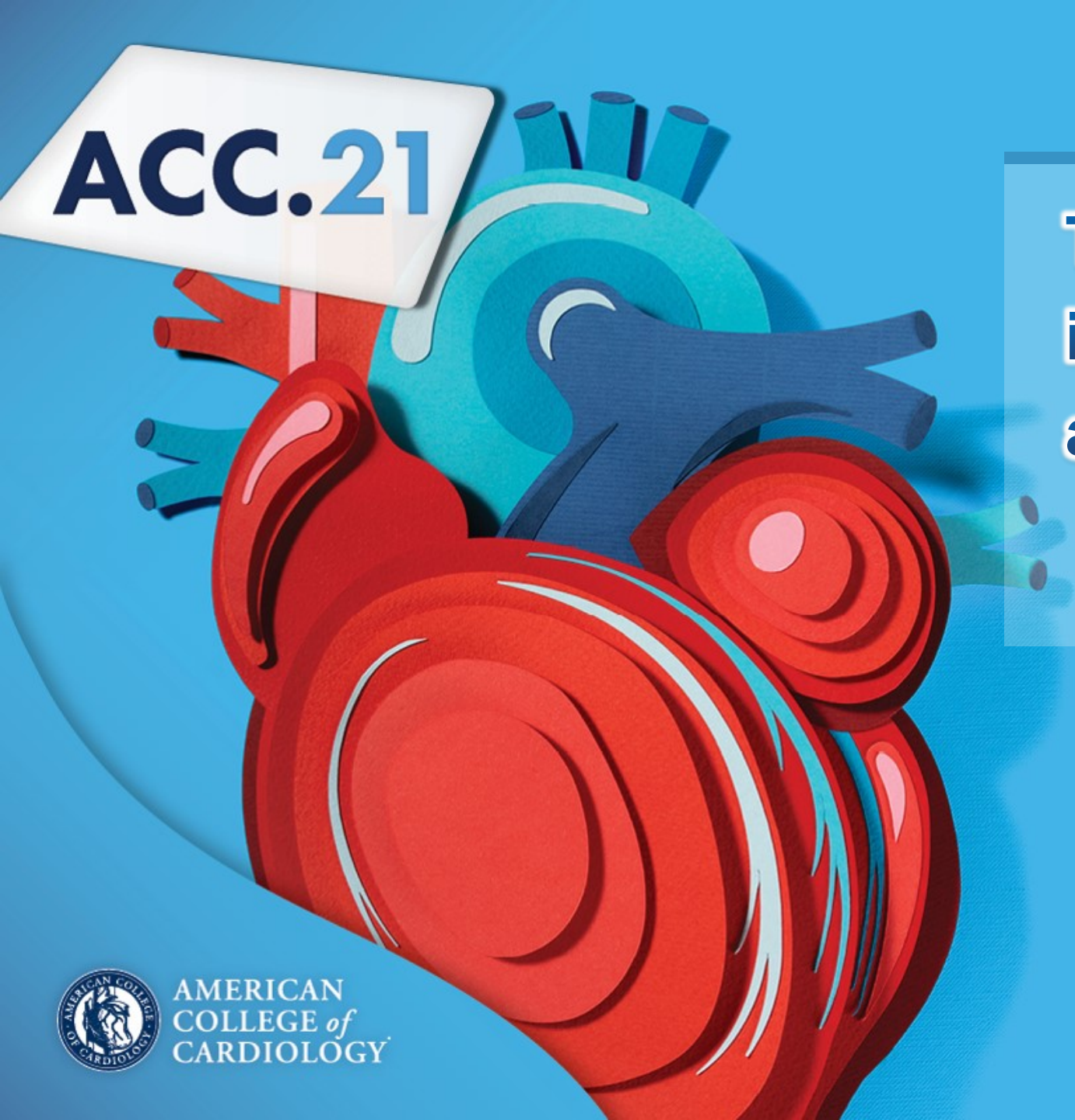


Ticagrelor vs. Clopidogrel in Stabilized Patients after AMI

: TALOS-AMI trial

A Multicenter, Randomized, Open-label trial

Kiyuk Chang

MD, Ph.D

On behalf of the TALOS-AMI trial investigators

AMERICAN COLLEGE of CARDIOLOGY

Disclosure Statement of Financial Interest

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

CONSULTING FEES/HONORARIA

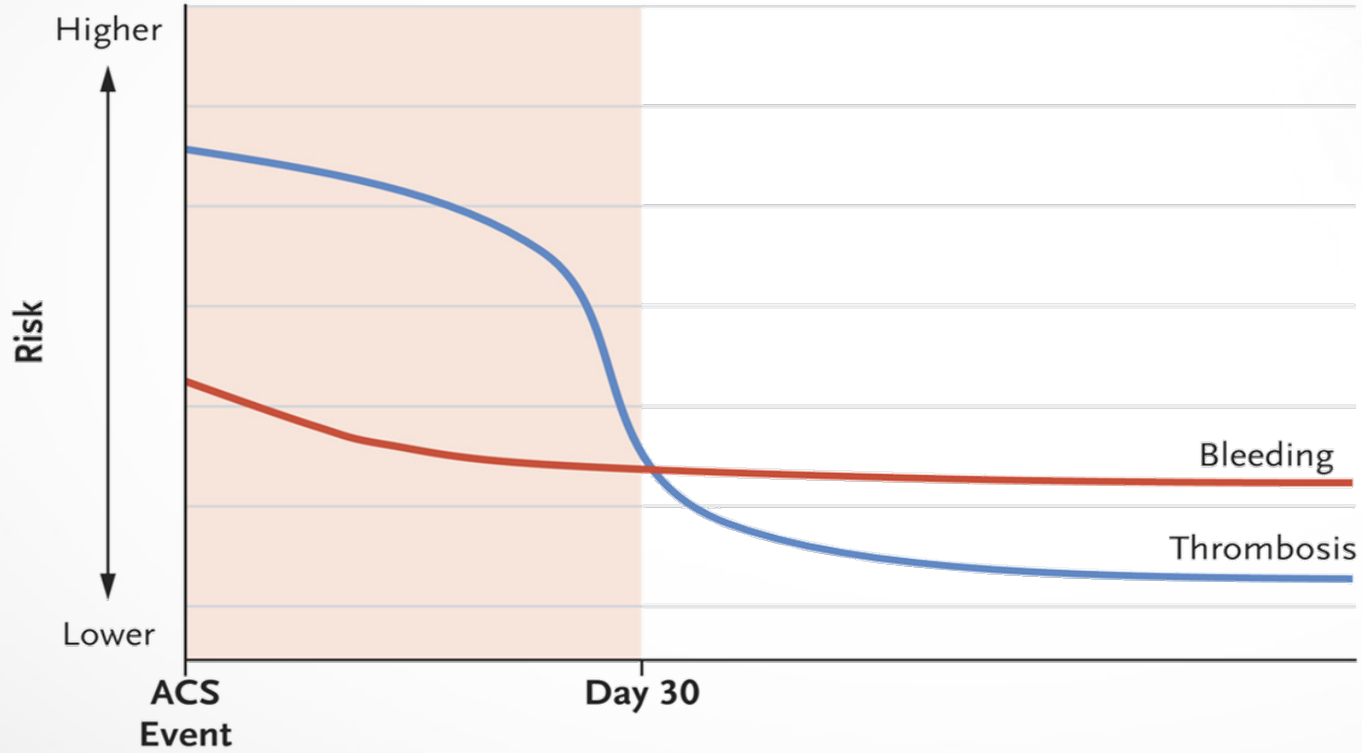
- Chong Kun Dang Pharm
- Medtronic Korea
- Edwards Korea

RESEARCH GRANTS

- Abbott Korea
- Medtronic Korea
- Boston Korea

Background

Risks of thrombosis & bleeding after acute myocardial infarction (AMI)



F Rodriguez, RA Harrington.
N Engl J Med
2021;384:452-460.

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Background

Large-scale data are lacking

on unguided stepwise de-escalation of dual antiplatelet therapy (DAPT) strategy

Potent P2Y12 inhibitor

in the acute phase

(<30 days after AMI)

Less potent clopidogrel

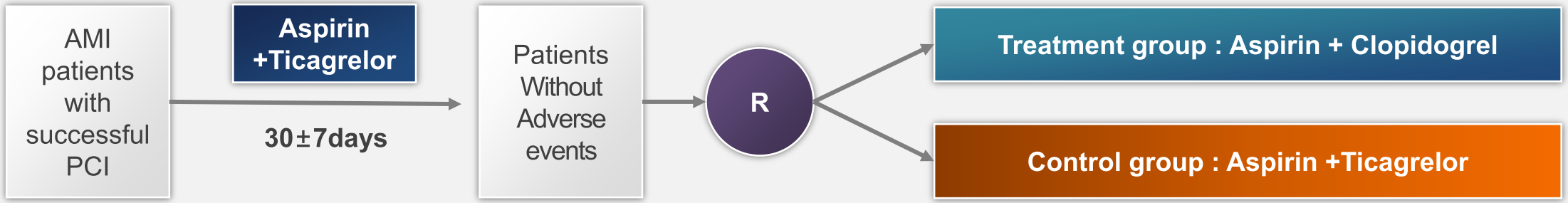
during the maintenance phase

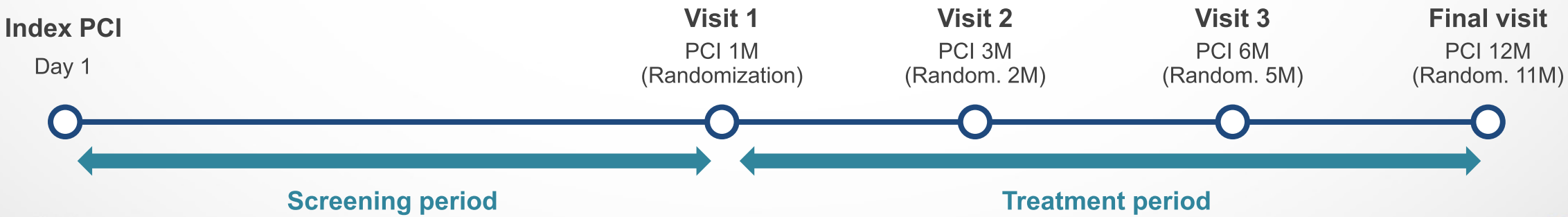
Hypothesis

De-escalating DAPT with clopidogrel may be non-inferior to ticagrelor in terms of net clinical benefit in stabilized patients with AMI who did not experience major adverse events during the first month after an index PCI.

Study Design

A multicenter, randomized, and open-label study





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De-escalation Protocol (ticagrelor to clopidogrel)

Uniform, unguided de-escalation

:no PFT, no genotype-guided

After final dose of ticagrelor,

clopidogrel 75mg

without loading dose

(approximately 12 hours from the last dose of ticagrelor)

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Study Organization

CI	Kiyuk Chang
Steering Committee	Kiyuk Chang, Chan Joon Kim, Mahn-Won Park, Youngkeun Ahn, Min-Chul Kim
DSMB	Cheol Whan Lee (Chair), Joo-Yong Hahn, Hyeon Woo Yim
CEAC	Hyun Kuk Kim (Chair), Seung-Woon Rha, Keun Ho Park
CRO	A-CRO, Seoul, Korea
Centers	32 centers in Korea
Sponsor	Chong Keun Dang Pharm, Abbott Vascular, Medtronic, and Boston Scientific

Study Endpoints: Primary Endpoint

Net adverse clinical events

Composite of cardiovascular death, MI,

stroke & BARC bleeding type 2, 3 or 5

from 1 to 12 months after an index PCI

Study Endpoints: Main Secondary Endpoints

Composite of CV death, MI or stroke (ischemic event)

Composite of BARC bleeding type 2, 3 or 5 (safety)

Composite of CV death, MI, stroke or BARC bleeding type 3 or 5 between 1 and 12 months after an index PCI

Sample size calculation

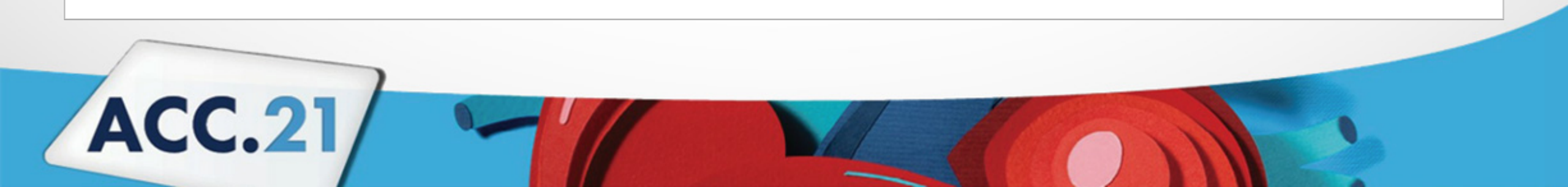
Expected event rates of the primary endpoint from 1 to 12 months

- Active control group (ticagrelor+aspirin): **9.35%**
- De-escalation group (clopidogrel+aspirin): **9.59%**

Non-inferiority margin: 3.0%, Follow-up loss rate 10%

80% power at a one-sided type I error of 5%

A total of 2590 patients (1295 per group)



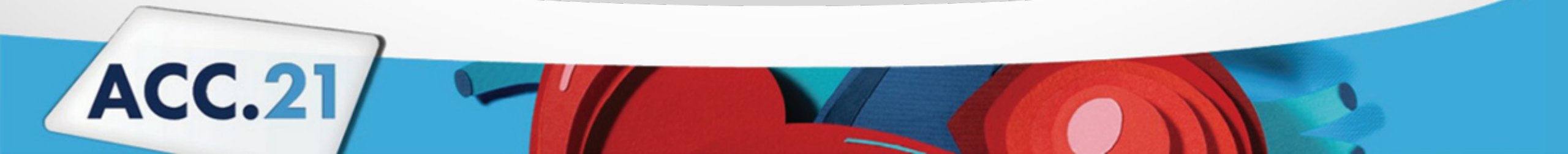
Statistical Analyses

Analyses 01

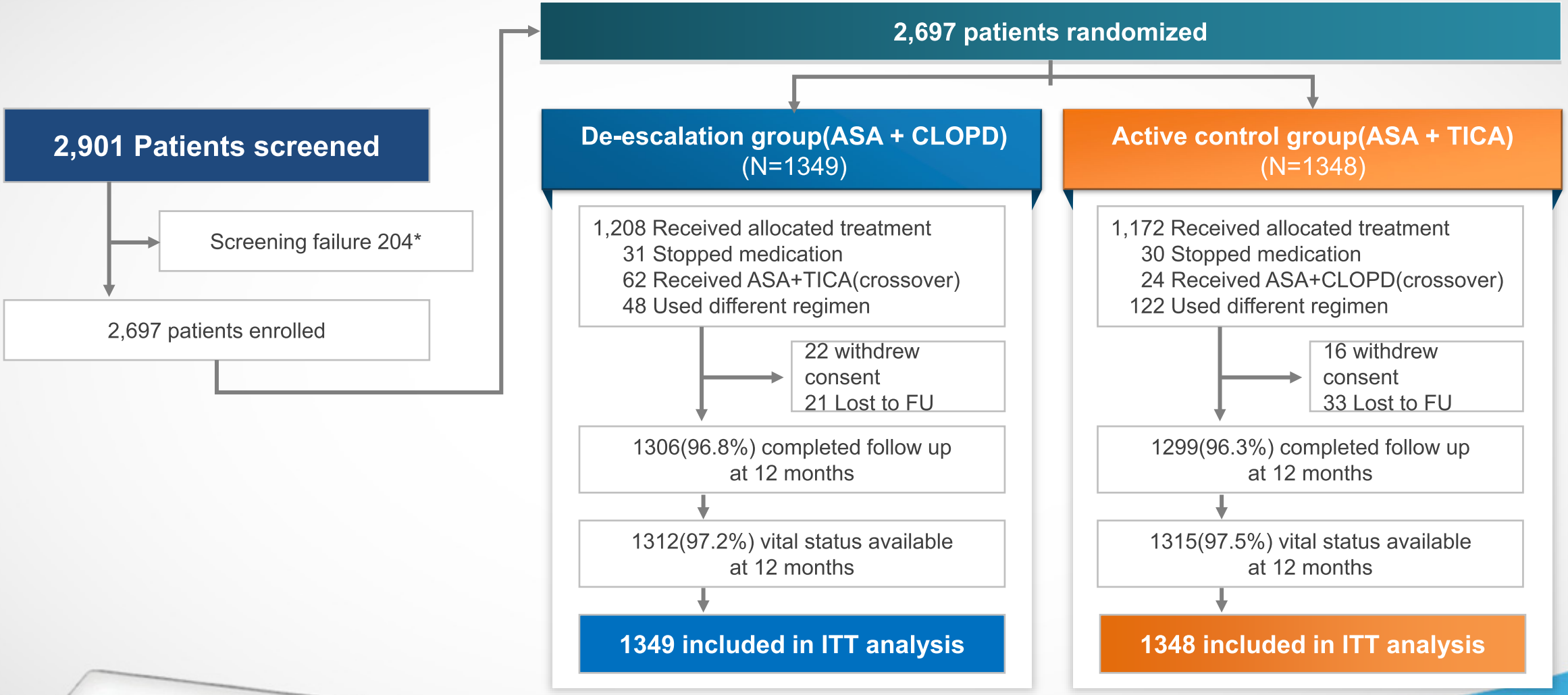
Primary analysis was performed in the intention-to -treat population.

Analyses 02

If the requirement for noninferiority was met, testing for the superiority was subsequently performed.



Enrollment, Randomization, and Follow-up



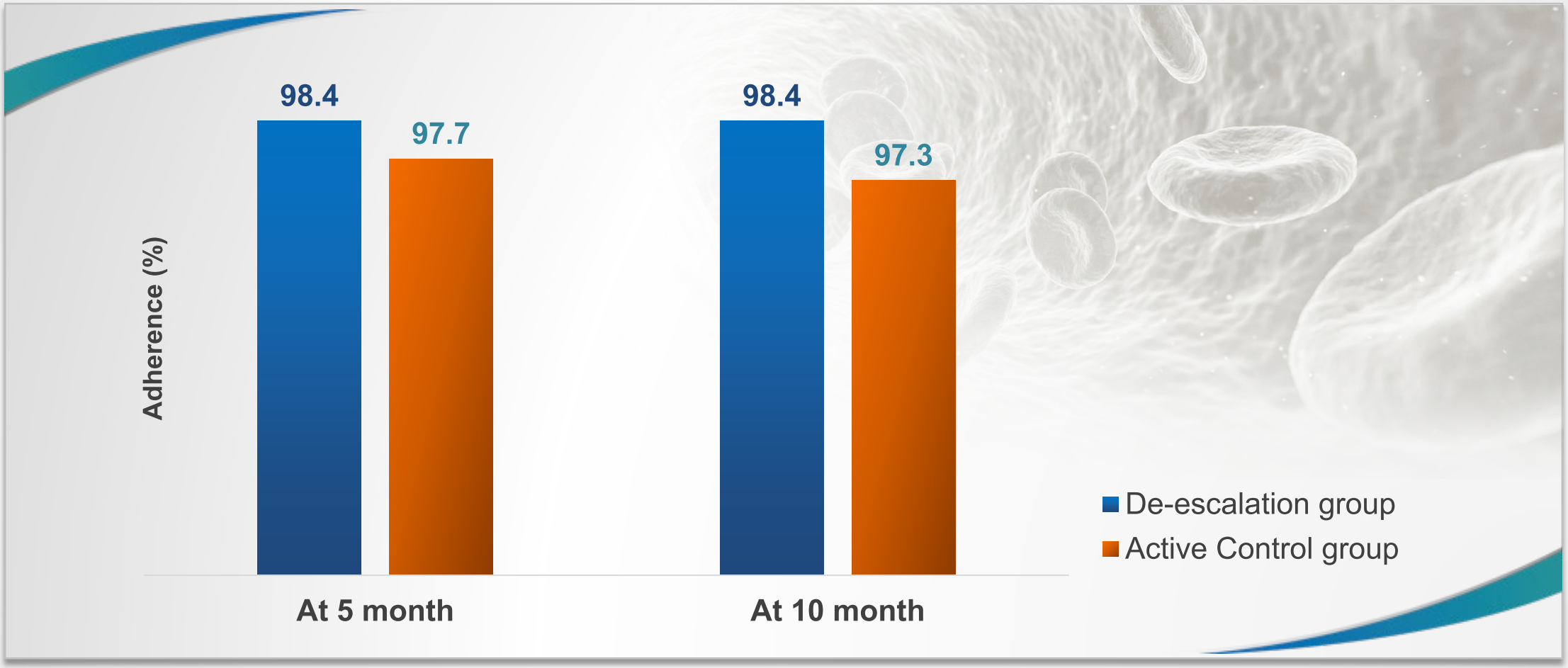
Clinical Characteristics

Characteristics	De-escalation (n=1349)	Active Control (n=1348)
Age-yr		
mean±SD	60.1±11.3	59.9±11.4
Female sex - no. (%)	217 (16.1)	237 (17.6)
Hypertension - no. (%)	655 (48.6)	663 (49.2)
Diabetes mellitus – no. (%)	362 (26.8)	369 (27.4)
Clinical Presentation		
STEMI - no. (%)	734 (54.4)	721 (53.5)
NSTEMI- no. (%)	615 (45.6)	627 (46.5)

Lesion and procedural characteristics

Characteristics	De-escalation (n=1349)	Active Control (n=1348)
Access site		
Radial – no. (%)	666 (49.4)	686 (51.0)
Femoral – no. (%)	667 (49.4)	644 (47.8)
Infarct related artery (Culprit)		
LM – no. (%)	21 (1.6)	24 (1.8)
LAD – no. (%)	685 (50.8)	634 (47.1)
Number of treated vessels	1.3±0.6	1.3±0.6
Multivessel treatment		
2 vessels – no. (%)	300 (22.2)	322 (23.9)
3 vessels – no. (%)	71 (5.3)	61 (4.5)
Total stent length of infarct related artery	29.8±13.2	29.6±13.8
Stent diameter of infarct related artery	3.2±0.4	3.2±0.5

Adherence of antiplatelet therapy



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Safety of switching from ticagrelor to clopidogrel without loading dose

Within 2 weeks after randomization

De-escalation group

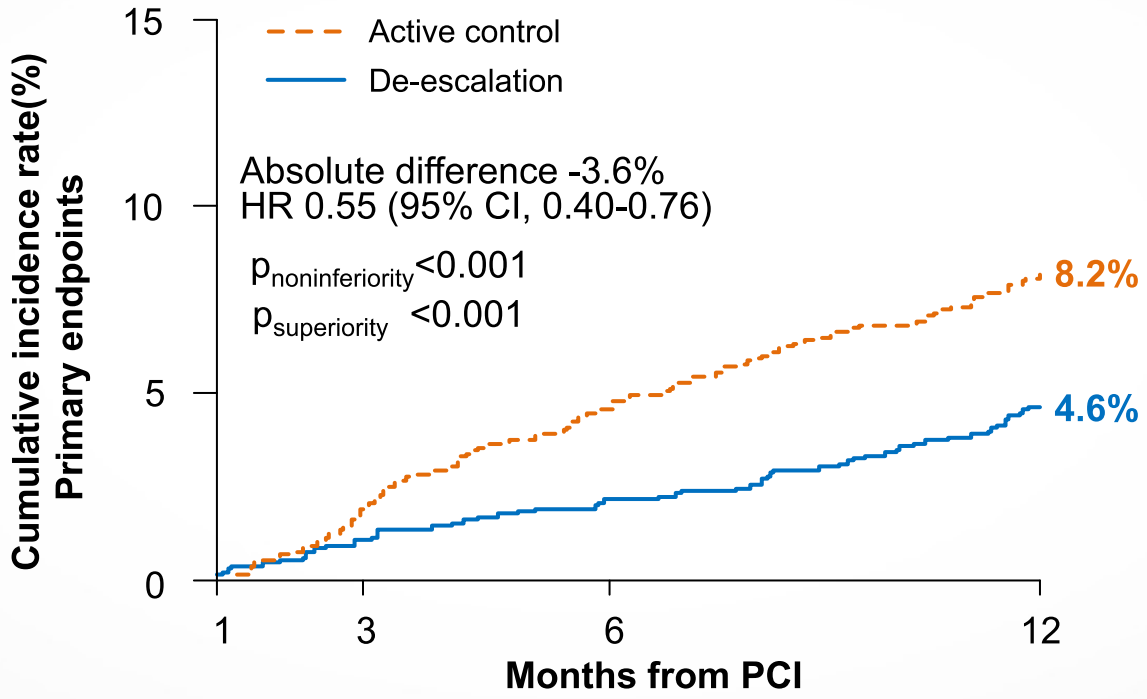
- No death or no stent thrombosis
- Only one case of non-target lesion MI (not related to stent thrombosis) 5 days after switching

Active control group

- no ischemic events

Primary Endpoint

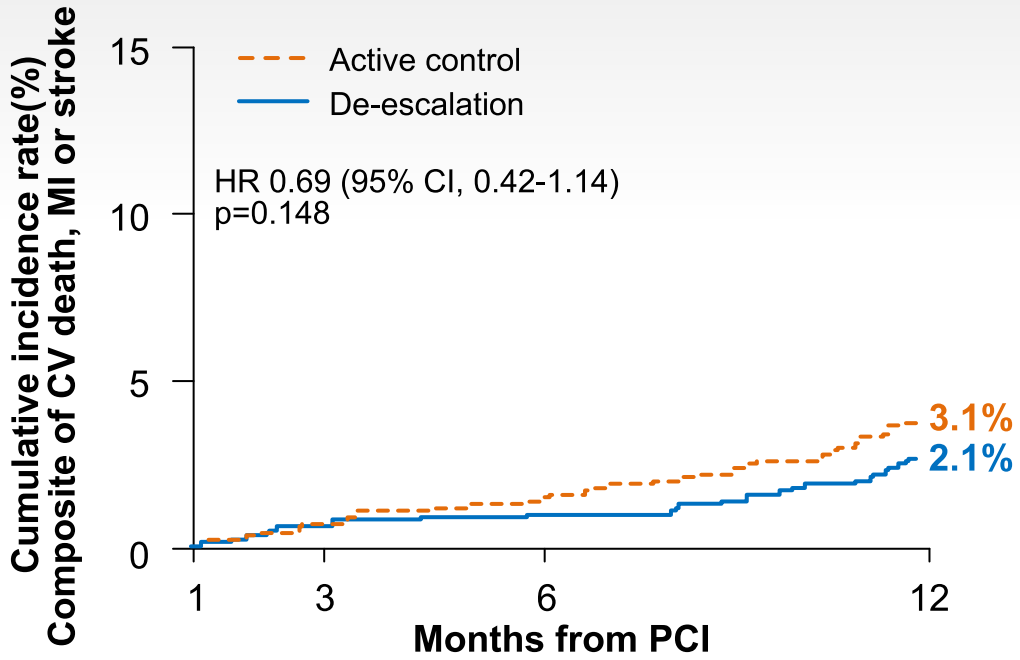
Composite of cardiovascular death, MI, stroke and
BARC bleeding (type 2,3, or 5)



Number at risk				
De-escalation	1349	1291	1247	1172
Active control	1348	1273	1191	1099

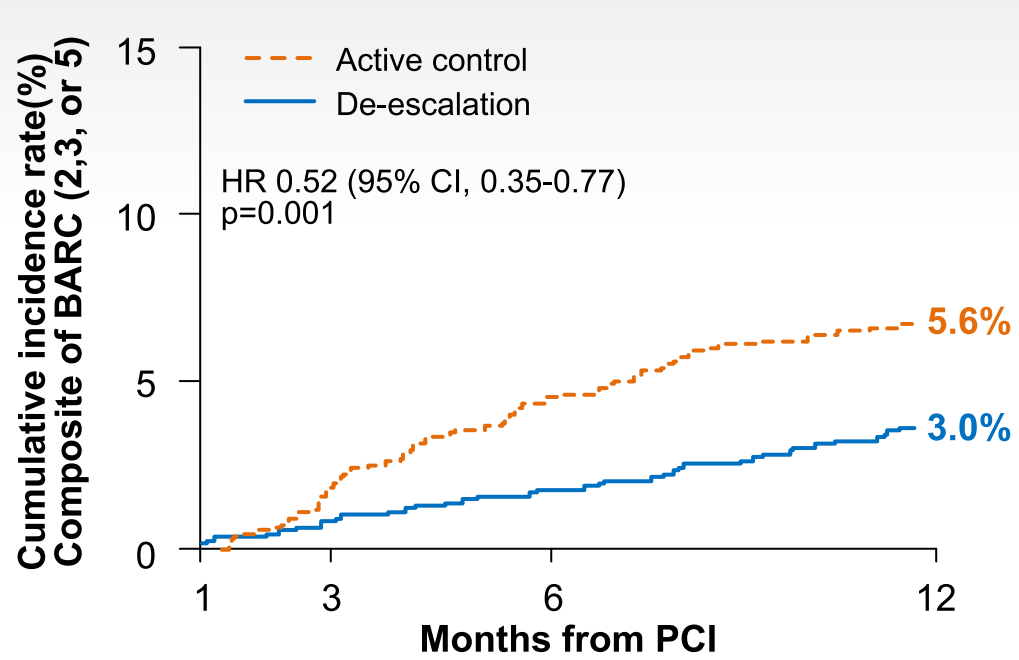
Main Secondary Endpoints

Composite of cardiovascular death, MI, and stroke



Number at risk				
De-escalation	1349	1299	1264	1201
Active control	1348	1288	1226	1147

Composite of BARC bleeding (type 2,3, or 5)



Number at risk				
De-escalation	1349	1293	1251	1180
Active control	1348	1276	1197	1120

Primary & Secondary Outcomes (ITT population)

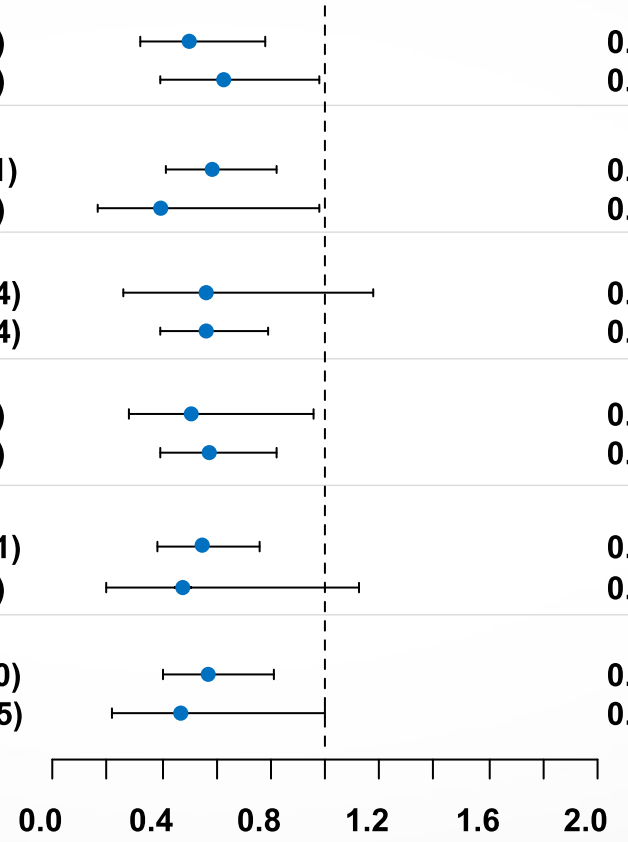
Variables	De-escalation (n=1349)	Active Control (n=1348)	HR (95% CI)	P value
Composite of BARC (2, 3, or 5)	38 (3.0)	71 (5.6)	0.52(0.35-0.77)	0.001
Compisite of BARC 3 or 5 bleeding	15 (1.2)	28 (2.3)	0.53(0.28-0.99)	0.046
BARC 2	27 (2.1)	50 (3.9)	0.53(0.33-0.85)	0.008
BARC 3	15 (1.2)	28 (2.3)	0.53(0.28-0.99)	0.046
BARC 5	1 (0.1)	0 (0.0)	2.95(0.03-271.44)	0.640
Composite of CV death, MI, stroke or BARC bleeding (type 3 or 5)	36 (2.8)	61 (4.9)	0.58(0.38-0.87)	0.009

Primary & Secondary Outcomes (ITT population)

Variables	De-escalation (n=1349)	Active Control (n=1348)	HR (95% CI)	P value
All cause death	11 (0.9)	10 (0.8)	1.07(0.45-2.52)	0.877
CV death	6 (0.5)	6 (0.5)	0.98(0.32-3.03)	0.970
Any myocardial infarction	12 (1.0)	20 (1.6)	0.59(0.29-1.21)	0.150
Spontaneous	9 (0.7)	14 (1.1)	0.64(0.28-1.47)	0.290
Periprocedural	3 (0.2)	6 (0.5)	0.52(0.13-2.06)	0.354
Target vessel MI	7 (0.6)	8 (0.7)	0.86(0.31-2.36)	0.764
Stroke	9 (0.7)	13 (1.0)	0.69(0.29-1.61)	0.389
Target lesion revascularization	14 (1.1)	9 (0.7)	1.48(0.64-3.42)	0.357
Target vessel revascularization	17 (1.4)	17 (1.4)	0.97(0.50-1.90)	0.929
Any revascularization	32 (2.6)	39 (3.2)	0.80(0.50-1.27)	0.342
Stent thrombosis**	3 (0.2)	3 (0.2)	0.97(0.20-4.80)	0.969

Subgroup Analysis

	De-escalation	Active control	HR (95% CI)	Interaction p value
Clinical presentation				
STEMI	4.1(30/734)	8.0(58/721)	0.50(0.32-0.78)	0.531
NSTEMI	4.7(29/615)	7.3(46/627)	0.62(0.39-0.98)	
Gender				
Male	4.7(53/1132)	7.8(87/1111)	0.58(0.41-0.82)	0.433
Female	2.8(6/217)	7.2(17/237)	0.39(0.16-0.98)	
Age				
≥ 75 years	6.4(10/157)	11.6(19/164)	0.55(0.26-1.18)	0.976
< 75 years	4.1(49/1192)	7.2(85/1184)	0.56(0.39-0.79)	
Diabetes				
yes	4.1(15/362)	7.9(29/369)	0.51(0.27-0.95)	0.780
no	4.5(44/987)	7.7(75/978)	0.57(0.39-0.82)	
LVEF				
≥ 40 %	4.1(50/1222)	7.3(89/1211)	0.54(0.38-0.76)	0.792
< 40 %	7.8(8/103)	16.1(15/93)	0.48(0.20-1.12)	
eGFR				
≥ 60	4.0(47/1161)	6.9(82/1180)	0.57(0.40-0.81)	0.643
< 60	6.3(10/160)	13.1(19/145)	0.47(0.22-1.00)	



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Study Limitations

Open-label and not placebo-controlled

Conducted only in South Korea

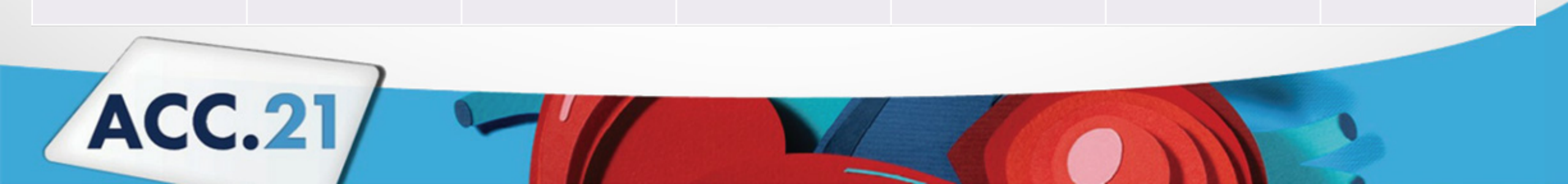
- Prevalence of CYP2C19 LOF alleles high in Koreans
- Potential of applying this de-escalation strategy to other ethnicities

Incidences of primary endpoints: slightly lower than estimated

- De-escalation group: 4.6% vs. 9.59% // Active control group: 8.2% vs. 9.35%

Event Rates Comparison of Major De-escalation Trials

	TALOS-AMI	TICO	Twilight-ACS	TROPICAL-ACS	POPular Genetics	HOST-REDUCE-POLYTECH-ACS
De-escalation method	A+clopidogrel from 1 month	Ticagrelor mono from 3 months	Ticagrelor mono from 3 months	PFT-guided from 2 weeks	Genotype-guided from 48 h	A+Prasugrel 5mg from 1 month
Primary Ischemic Outcome	1-12 mo incidence of CV death, MI or stroke	1-Yr incidence of CV death, MI,ST or TVR	1-Yr incidence of All-cause mortality, MI, stroke	1-Yr incidence of CV death, MI or stroke	I-Yr incidence of Vascular death, MI, ST or stroke	1-Yr incidence of CV death, MI, ST or stroke
de-escalation	**2.1%**	1.2%	4.3%	3.0%	2.7%	1.4%
standard	**3.1%**	2.0%	4.4%	3.0%	3.3%	1.8%
Primary Bleeding Outcome	BARC 2, 3, or 5	TIMI Major + Minor	BARC 2, 3 or 5	BARC 2, 3, or 5	PLATO major + minor	BARC 2, 3, or 5
de-escalation	**3.0%**	3.6%	4.0%	5.0%	10.1%	2.9%
standard	**5.6%**	5.5%	7.1%	6.0%	13.1%	5.9%



Sensitivity Analysis

A sensitivity analysis was performed which included a complete case (only for subjects who status was known at 1 year), a best-case (assuming missing subjects of the de-escalation group were event free and missing subjects of the active control group had event at 1 year), and a worst case (assuming missing subjects of the de-escalation groups had event and missing subjects of the active control group were event free)

ITT	De-escalation	Active Control
Withdrew consent/ Lost to FU	43	49

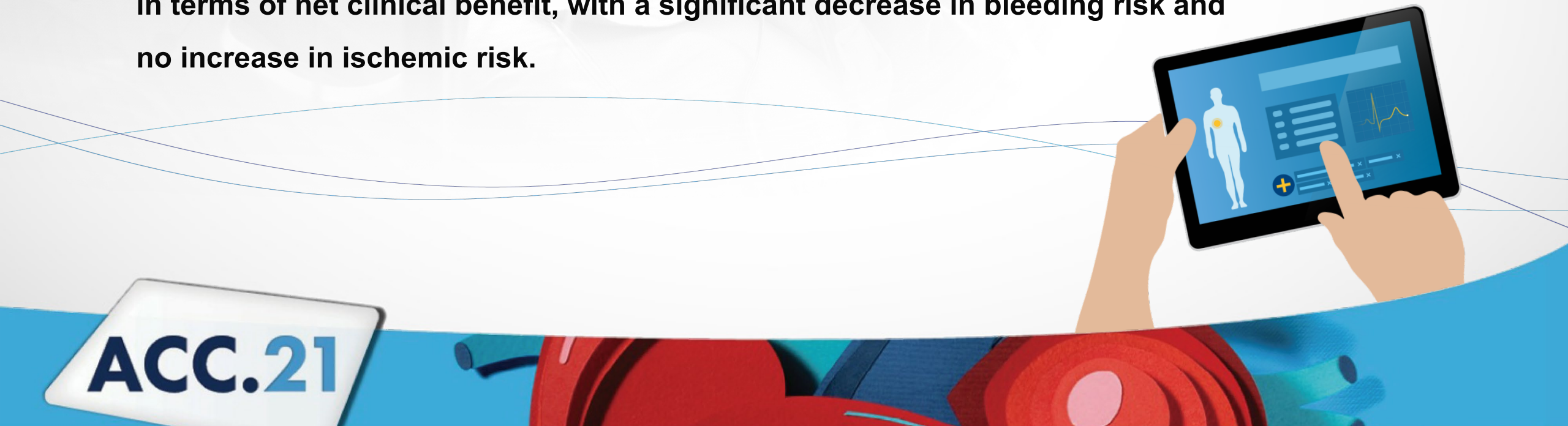
Primary endpoints :Composite of CV death, MI, stroke and BARC bleeding type 2,3, or 5	De-escalation	Active Control	Difference (95% CI)	non-inferiority test, p value	HR (95%CI)	p value
	n=1306	n=1299				
complete case (n=2605)	59 (4.7)	104 (8.3)	-3.7(-5.6, -1.7)	<0.001	0.55(0.40-0.75)	<0.001
	n=1349	n=1348				
best-case (n=2697)	59 (4.5)	153 (12.0)	-7.5(-9.6, -5.3)	<0.001	0.37(0.28-0.50)	<0.001
	n=1349	n=1348				
a worst-case (n=2697)	102 (7.9)	104 (8.0)	-0.1(-2.2, 2.0)	0.002	0.94(0.72-1.24)	0.675

Conclusions

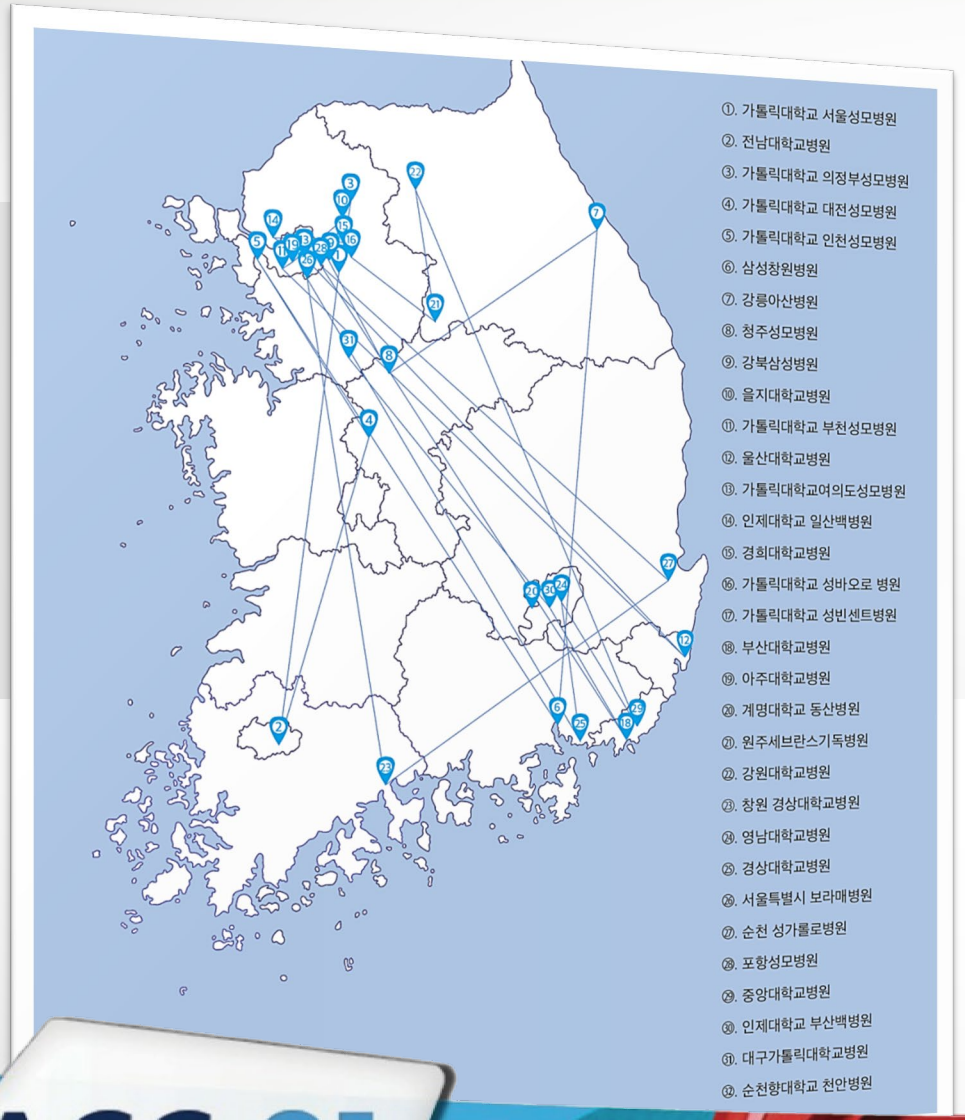
In AMI patients who had no major adverse events during the first month after an index PCI,

a uniform, unguided de-escalation DAPT strategy switching from ticagrelor to clopidogrel was superior to the ticagrelor-based continuing DAPT strategy

in terms of net clinical benefit, with a significant decrease in bleeding risk and no increase in ischemic risk.



Acknowledgement



I would like to thank

patients enrolled, research nurses, study coordinators and participating investigators.

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