6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomized, open-label, non-inferiority trial

ACC.18 Late-Breaking Clinical Trials

Hyeon-Cheol Gwon,

On the behalf of SMART-DATE trial investigators

Disclosure Statement of Financial Interest

- Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.
  - CONSULTING FEES/HONORARIA:
    - Medtronic Asia Pacific
  - RESEARCH/RESEARCH GRANTS:
    - Abbott Korea
    - Boston Scientific Korea
    - Medtronic Korea

Background

- Patients with acute coronary syndrome (ACS) carry a higher risk of recurrent ischemic events than those with stable ischemic heart disease.
- Current guidelines recommend dual antiplatelet therapy (DAPT) for 12 months or longer in these patients, unless there are no excessive risk of bleeding. These recommendations, however, were not based on randomized controlled trials dedicated to the optimal duration of DAPT in ACS population.

Primary objective of study

To investigate whether a 6-month duration of DAPT would be non-inferior to the conventional 12-month or longer duration of DAPT after implantation of drug-eluting stents (DES) in ACS patients.

Working hypothesis

After implantation of DES in ACS patients, the reduced 6-month duration of DAPT is non-inferior to the conventional 12-month or longer duration of DAPT to prevent major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause mortality, myocardial infarction (MI), and cerebrovascular event at 18 months after index procedure.

Patient selection criteria

- Key inclusion criteria

  Patients with ACS (unstable angina, non-ST or ST elevation myocardial infarction) with target lesion(s) in native coronary artery(s), amenable for PCI with DES implantation

- Key exclusion criteria

  Recent major bleeding, bleeding diathesis, DES implantation within 12 months, life expectancy < 2 years, planned elective surgery within 12 months

* The specific definitions of ACS

1) ST-segment elevation MI: elevation of ST-segment ≥ 0.1 mV in 2 or more contiguous ECG leads or new LBBB with elevated biomarkers of myocardial necrosis
2) Non-ST-segment elevation MI: elevated biomarkers of myocardial necrosis (troponin or CK-MB ≥ upper reference limit) with one of the following:
   (a) Transient ST-segment elevation or depression, or T-wave changes consistent with myocardial ischemia
   (b) Identification of a culprit lesion at coronary angiography
3) Unstable angina: an accelerating pattern or recurrent episodes of chest pain at rest or with minimal effort and new ST-segment depression of at least 0.05 mV, or T-wave inversion of at least 0.3 mV in at least 2 leads. The ECG criteria for unstable angina were based on the TACTICS-TIMI 18 trial.

Study endpoints

- **Primary endpoint**
  - Major adverse cardiac and cerebrovascular events (MACCE) at 18 months after the index procedure (a composite of all-cause mortality, myocardial infarction, or cerebrovascular events)
- **Secondary endpoints**
  - The individual components of the primary endpoint
  - Definite/probable stent thrombosis
  - Bleeding Academic Research Consortium (BARC) type 2 to 5 bleeding

** Definitions follow the ARC recommendations, if not described.*

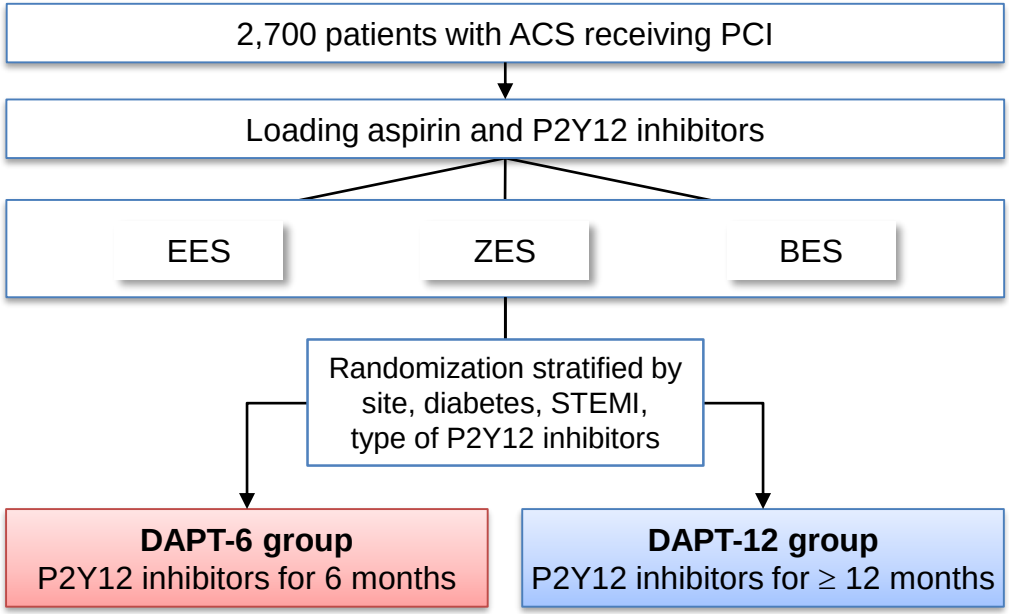
Sample size calculation

- **Primary Endpoint: 18-month MACCE**
- Estimated event rates for 18 months: 4.5%
- Non-inferiority margin: 2.0%
- Sampling ratio of 1:1
- Follow-up loss for 18 months: 2%
- Study power: 80%
- An one-sided α error: 5%.

- **2,700 patients would be required**

Study design

A prospective, multicenter, randomized, and open-label trial



Primary endpoint: 18-month MACCE
a composite of all-cause mortality, MI, and cerebrovascular events

- PCI=percutaneous coronary intervention
- EES = everolimus eluting stent (Xience Prime)
- ZES = zotarolimus eluting stent (Resolute Integrity)
- BES = biolimus eluting stent (Biomatrix Flex)
- STEMI = ST elevation myocardial infarction
- MI = myocardial infarction

Participating centers

31 centers in South Korea

Cheju Halla General Hospital	Konyang University Hospital
Chonnam National university hospital	Korean University Guro Hospital
Chung-Ang University Hospital	Kyimyung University Dongsan Medical Center
Chungnam National University Hospital	Kyungpook national university hospital
Daegu Catholic University Medical Center	Myeongji Hospital
Daejeon Eulji Medical Center	Pusan National University Hospital
Dankook University Hospital	Sam Hospital
Dong-A University Hospital	Samsung Changwon Hospital
Gwangju Veterans Hospital	Samsung Medical Center
Gyeongsang National University Hospital	Sejong Hospital
Hanil General Hospital	Seoul National University Boramae Medical Center
Inje University Haeundae Paik Hospital	Seoul National University Bundang Hospital
Inje University Ilsan Paik Hospital	St. Carollo Hospital
Inje University Sanggye Paik Hospital	VHS Medical Center
Kangbuk Samsung Hospital	Yeungnam University Medical Center
Konkuk University Chungju Hospital	

Trial coordination

P.I. Hyeon-Cheol Gwon

Trial Center

Academic Clinical Research Organization

DSMB

Data Safety Monitoring Board

CEAC

Clinical Event Adjudication Committee

Steering Committee

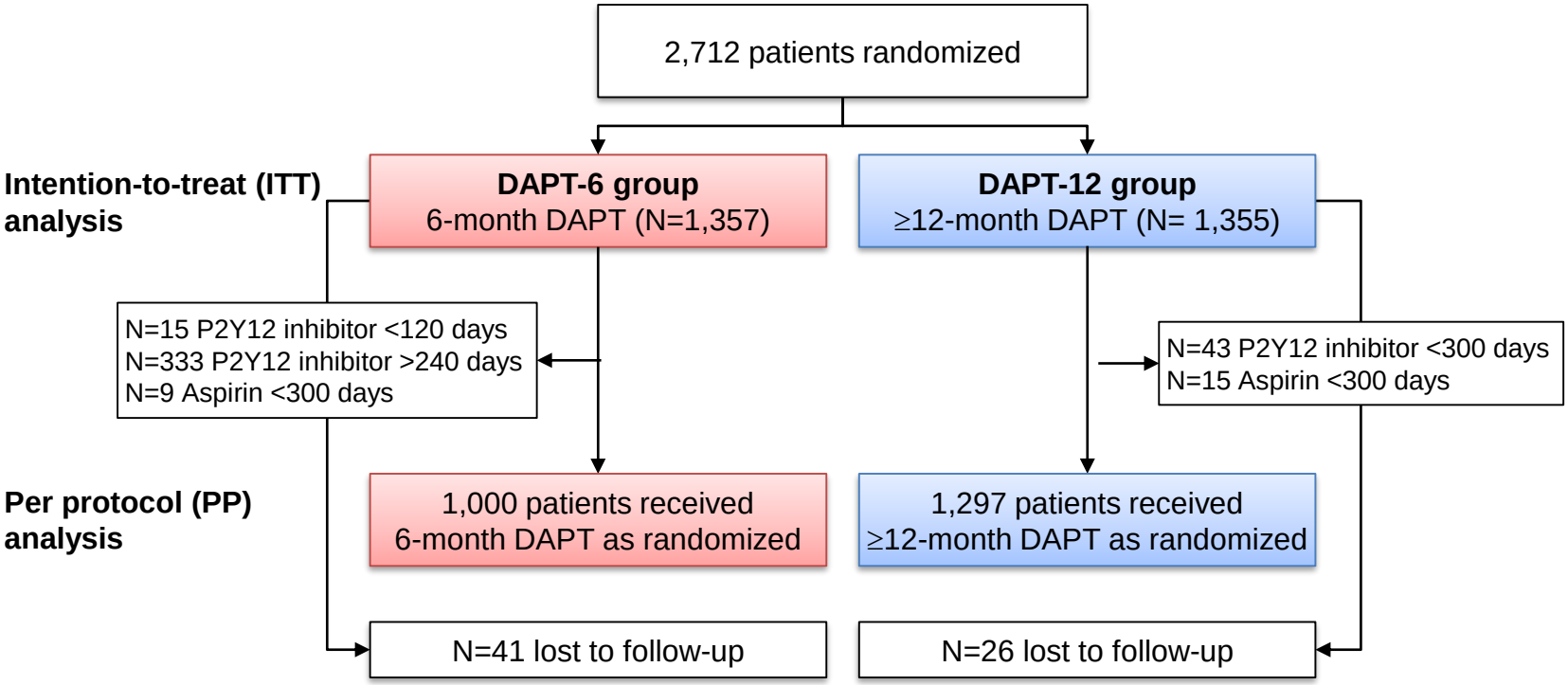
31 study investigators

Grant Support

Abbott Vascular Korea, Medtronic Korea, Biosensors Korea, Dong-A ST

The sponsors were not involved with the protocol development or the study process, including site selection, management, and data collection and analysis.

Study flow



18 months FU rate 97.5%

Clinical characteristics

	DAPT-6 group (n=1357)	DAPT-12 group (n=1355)
Age, median (years)	62 [54-71]	63 [53-71]
Male	1016 (74.9%)	1028 (75.9%)
Diabetes mellitus	365/1355 (26.9%)	379/1350 (28.1%)
Hypertension	669/1340 (49.9%)	654/1342 (48.7%)
Dyslipidemia	322/1329 (24.2%)	336/1332 (25.2%)
Current smoking	506/1333 (38.0%)	536/1335 (40.1%)
Previous MI	30/1328 (2.3%)	23/1334 (1.7%)
Previous revascularization	65/1320 (4.9%)	52/1328 (3.9%)
Cerebrovascular disease	52/1330 (3.9%)	58/1332 (4.4%)
Chronic renal failure	13/1327 (1.0%)	6/1328 (0.5%)
Ejection fraction (%)	55.5±11.0	55.4±10.5

	DAPT-6 group (n=1357)	DAPT-12 group (n=1355)
Clinical presentation		
ST-elevation MI	509 (37.5%)	514 (37.9%)
Non-ST-elevation MI	428 (31.5%)	425 (31.4%)
Unstable angina	420 (31.0%)	416 (30.7%)
Discharge medication		
Aspirin	1353 (99.7%)	1354 (99.9%)
P2Y12 receptor inhibitor	1352 (99.6%)	1350 (99.6%)
Clopidogrel	1082 (79.7%)	1109 (81.8%)
Statin	1212 (89.3%)	1238 (91.4%)
ACE inhibitor	529 (39.0%)	557 (41.1%)
ARB	416 (30.7%)	390 (28.8%)
β-blocker	961 (70.8%)	999 (73.7%)

MI = myocardial infarction, ACE = angiotensin converting enzyme,
ARB = angiotensin receptor blocker

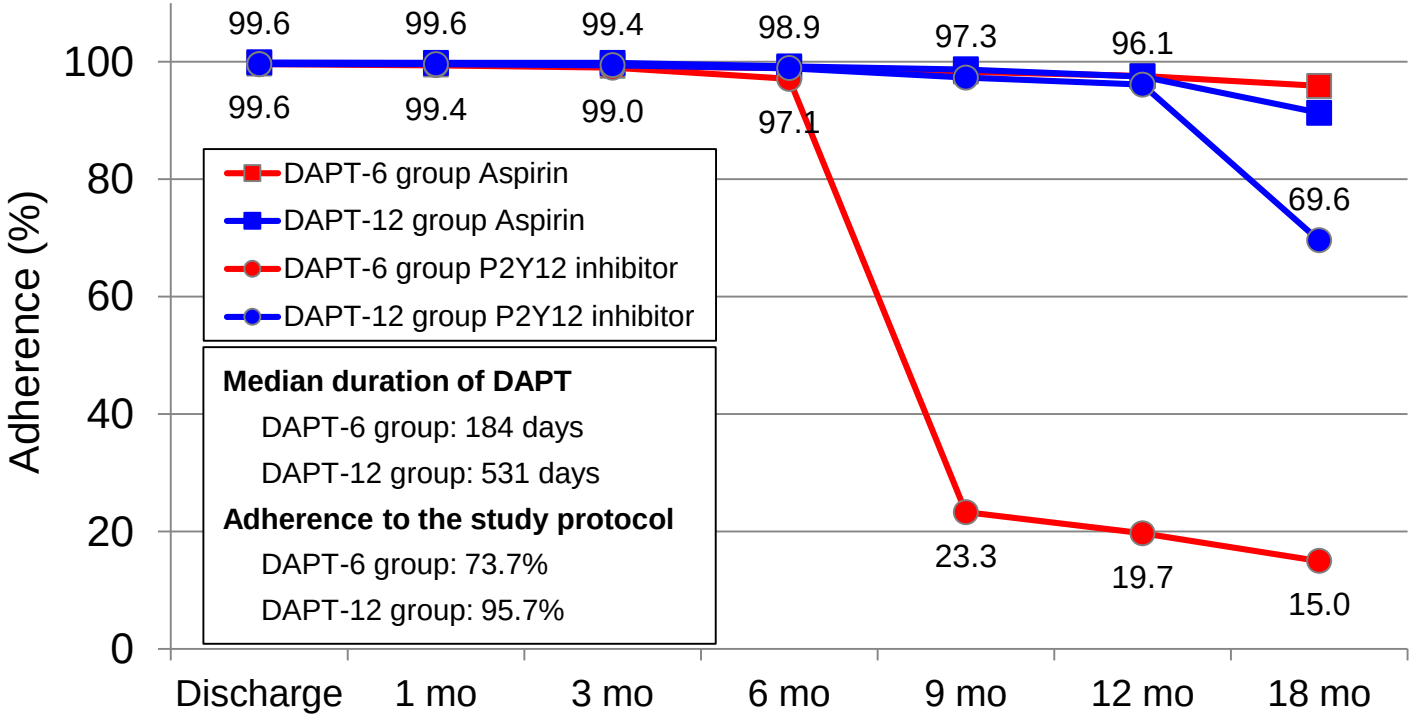
Lesion and procedural characteristics

	DAPT-6 group (n=1357)	DAPT-12 group (n=1355)
Transradial approach	637/1354 (47·0%)	632/1354 (46·7%)
Multiple vessels disease	591/1356 (43·6%)	631/1355 (46·6%)
Location of lesion treated		
LM	29/1356 (2·1%)	17/1355 (1·3%)
LAD	767/1356 (56·6%)	826/1355 (61·0%)
LCX	331/1356 (24·4%)	340/1355 (25·1%)
RCA	504/1356 (37·2%)	490/1355 (36·2%)
Calcified lesion	165/1355 (12·2%)	178/1353 (13·2%)
Bifurcation lesion	124/1355 (9·2%)	123/1353 (9·1%)
Thrombotic lesion	325/1355 (24·0%)	330/1353 (24·4%)
Glycoprotein IIb/IIIa inhibitors	62/1349 (4·6%)	81/1350 (6·0%)
Use of intravascular ultrasound	311/1355 (23·0%)	331/1353 (24·5%)

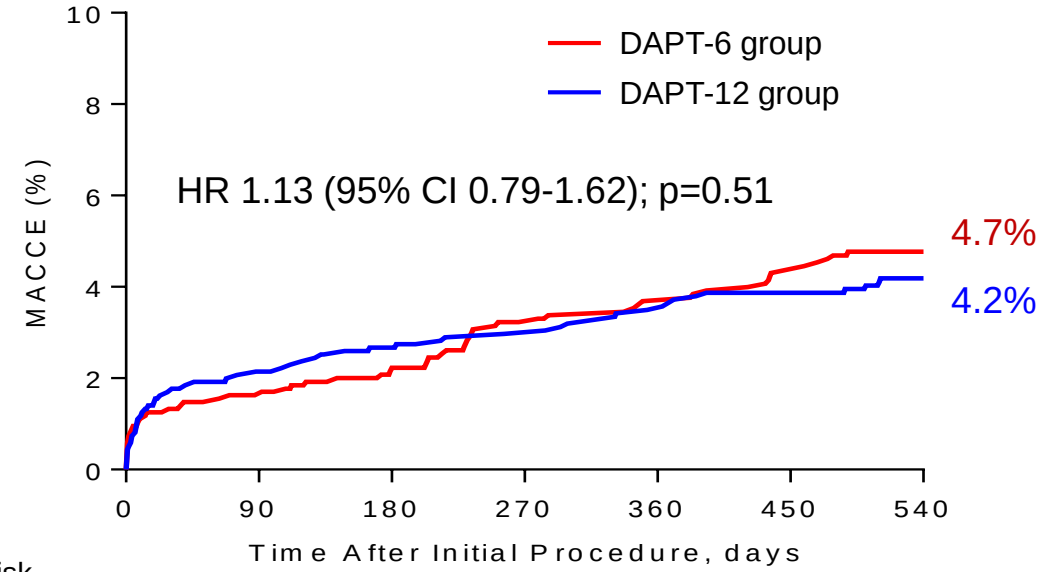
	DAPT-6 group (n=1357)	DAPT-12 group (n=1355)
Treated lesions per patient	1·3±0·6	1·4±0·7
Multi-lesion intervention	339/1356 (25·0%)	367/1355 (27·1%)
Multi-vessel intervention	263/1356 (19·4%)	281/1355 (20·7%)
Stents per patient	1·4±0·8	1·5±0·8
Stents per lesion	1·1±0·3	1·1±0·3
Stent length per lesion, mm	26·1±10·1	26·3±10·3
Type of drug-eluting stents		
No stent	9 (0·7%)	5 (0·4%)
Everolimus-eluting stents	476 (35·1%)	462 (34·1%)
Zotarolimus-eluting stents	459 (33·8%)	459 (33·9%)
Biolimus-eluting stents	406 (29·9%)	419 (30·9%)
Other stents	7 (0·5%)	10 (0·7%)
Procedural success	1299/1355 (95·9%)	1280/1353 (94·6%)

LM=left main, LAD = left anterior descending, IVUS =intravascular ultrasound,
EES=everolimus eluting stent, ZES=zotarolimus eluting Stent, BES=biolimus eluting stent,

Adherence of antiplatelet therapy



Primary endpoint (MACCE)



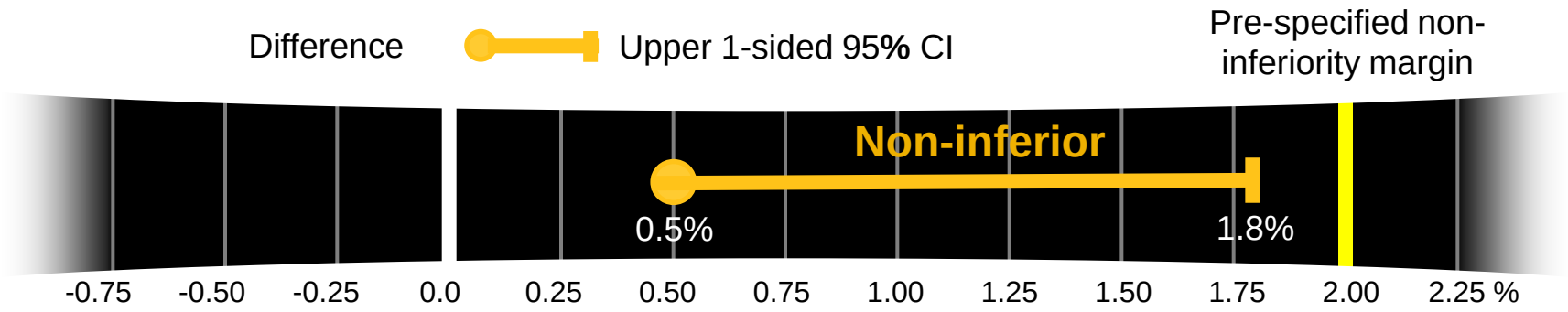
No. at risk							
Long-term	1355	1312	1299	1290	1283	1278	1043
Short-term	1357	1318	1296	1271	1264	1255	1032

* MACCE = A composite of all-cause mortality, myocardial infarction, and cerebrovascular events

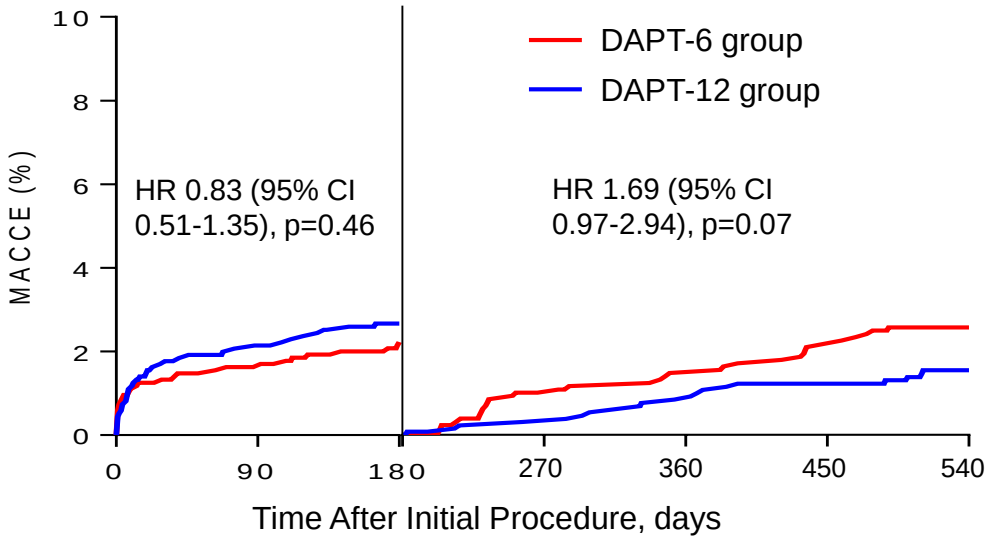
Primary endpoint (MACCE)

Cumulative proportional MACCE estimate at 18 months (Kaplan-Meier analysis)

DAPT-6 (N=1,357)	DAPT-12 (N=1,355)	Difference of event rate	Pre-specified non-inferiority margin	Upper margin of 1-sided 95% CI	Non-inferiority
4.7%	4.2%	0.5%	2.0%	1.8%	p=0.027

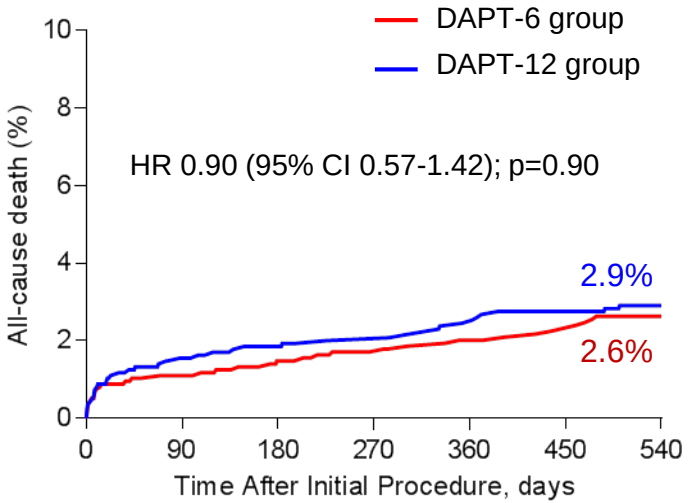


MACCE (Landmark analysis)

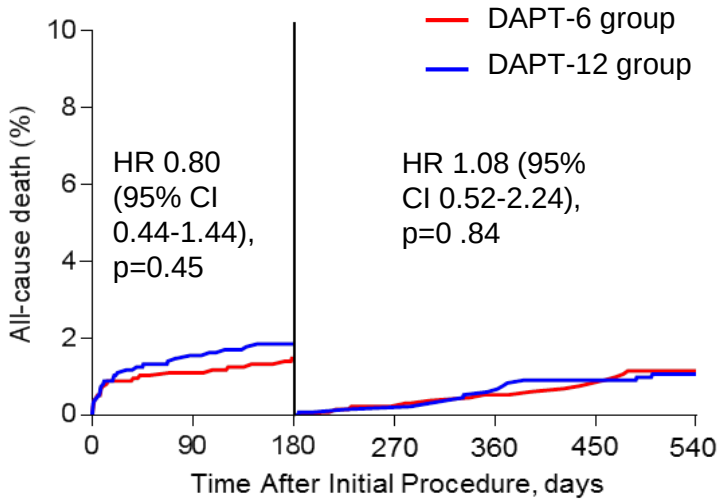


No. at risk							
Long-term	1355	1312	1299	1290	1283	1278	1043
Short-term	1357	1318	1296	1271	1264	1255	1032

All-cause death (ITT)

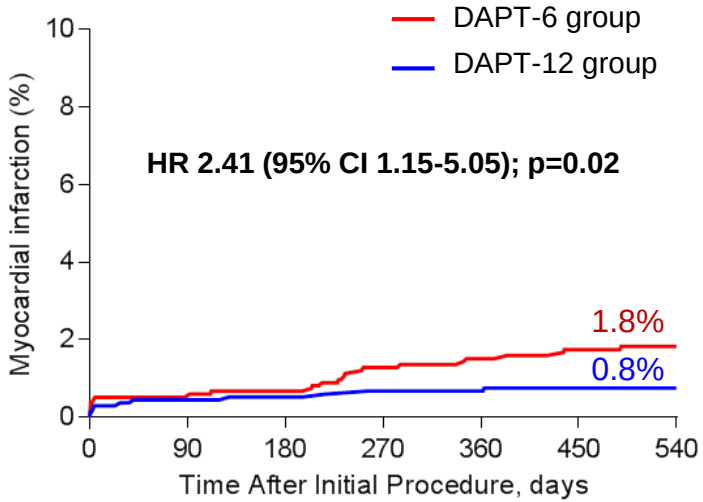


No. at risk							
Long-term	1355	1320	1309	1302	1296	1292	1056
Short-term	1357	1325	1306	1290	1285	1281	1055



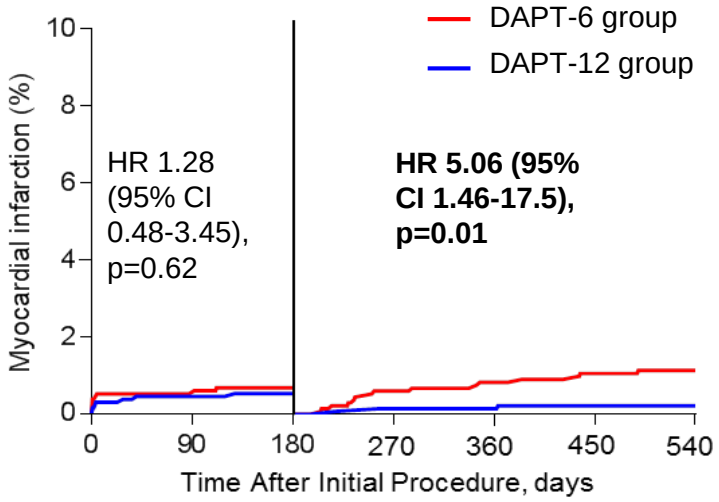
No. at risk							
Long-term	1355	1320	1309	1302	1296	1292	1056
Short-term	1357	1325	1306	1290	1285	1281	1055

Myocardial infarction (ITT)



No. at risk

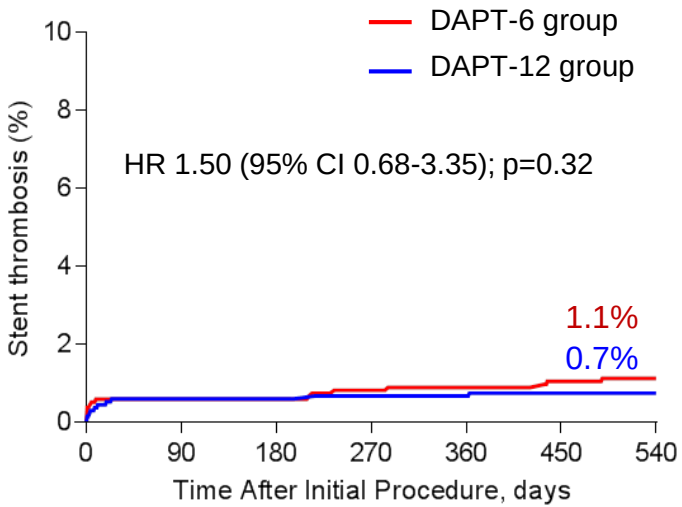
Long-term	1355	1315	1303	1295	1289	1284	1049
Short-term	1357	1321	1300	1277	1270	1263	1039



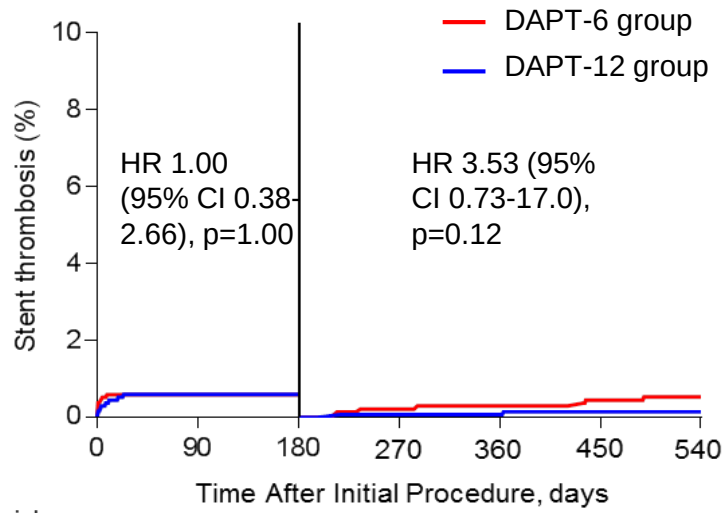
No. at risk

Long-term	1355	1315	1303	1295	1289	1284	1049
Short-term	1357	1321	1300	1277	1270	1263	1039

Stent thrombosis (ITT)

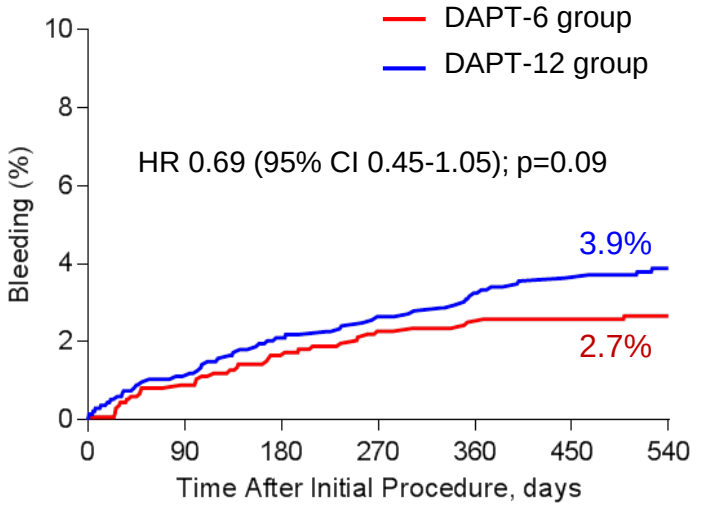


No. at risk							
Long-term	1355	1316	1305	1298	1292	1287	1051
Short-term	1357	1321	1302	1284	1279	1273	1047

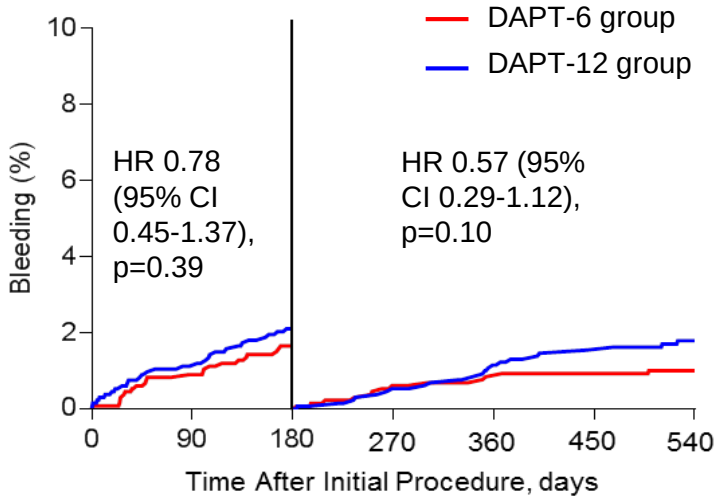


No. at risk							
Long-term	1355	1316	1305	1298	1292	1287	1051
Short-term	1357	1321	1302	1284	1279	1273	1047

BARC 2-5 Bleeding (ITT)



No. at risk							
Long-term	1355	1307	1285	1271	1260	1251	1023
Short-term	1357	1314	1286	1263	1257	1252	1034



No. at risk							
Long-term	1355	1307	1285	1271	1260	1251	1023
Short-term	1357	1314	1286	1263	1257	1252	1034

Clinical outcomes at 18 months

Intention-to-treat (ITT)

	DAPT-6 group (n=1357)	DAPT-12 group (n=1355)	**HR (95% CI)**	**p value**
MACCE	63 (4.7%)	56 (4.2%)	1.13 (0.79-1.62)	0.51
Death	35 (2.6%)	39 (2.9%)	0.90 (0.57-1.42)	0.90
Myocardial infarction	24 (1.8%)	10 (0.8%)	2.41 (1.15-5.05)	0.02
Target vessel MI	14 (1.1%)	7 (0.5%)	2.01 (0.81-4.97)	0.13
Non-target vessel MI	10 (0.8%)	3 (0.2%)	3.35 (0.92-12.2)	0.07
Cerebrovascular accident	11 (0.8%)	12 (0.9%)	0.·92 (0.41-2.08)	0.84
Cardiac death	18 (1.4%)	24 (1.8%)	0.75 (0.41-1.38)	0.36
Cardiac death or MI	39 (2.9%)	32 (2.4%)	1.22 (0.77-1.95)	0.40
Stent thrombosis	15 (1.1%)	10 (0.7%)	1.50 (0.68-3.35)	0.32
Bleeding BARC type 2-5	35 (2.7%)	51 (3.9%)	0.69 (0.45-1.05)	0.09
Major bleeding (BARC type 3,4,or 5)	6 (0.5%)	10 (0.8%)	0.60 (0.22-1.65)	0.33
Net adverse clinical and cerebral events	96 (7.2%)	99 (7.4%)	0.97 (0.73-1.29)	0.84

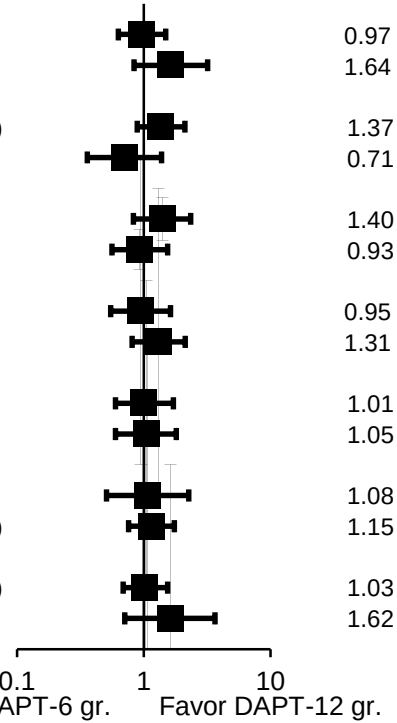
Clinical outcomes at 18 months

Per protocol (PP)

	DAPT-6 group (n=1000)	DAPT-12 group (n=1297)	**HR (95% CI)**	**p value**
MACCE	44 (4.5%)	52 (4.1%)	1.11 (0.74-1.66)	0.61
Death	29 (3.0%)	37 (2.9%)	1.03 (0.63-1.67)	0.92
Myocardial infarction	15 (1.6%)	10 (0.8%)	1.97 (0.88-4.38)	0.10
Target vessel MI	11 (1.1%)	7 (0.5%)	2.06 (0.80-5.31)	0.14
Non-target vessel MI	4 (0.4%)	3 (0.2%)	1.75 (0.39-7.81)	0.47
Cerebrovascular accident	6 (0.6%)	10 (0.8%)	0.79 (0.29-2.17)	0.64
Cardiac death	15 (1.5%)	22 (1.7%)	0.89 (0.46-1.72)	0.73
Cardiac death or MI	27 (2.8%)	30 (2.3%)	1.18 (0.70-1.98)	0.54
Stent thrombosis	13 (1.3%)	10 (0.8%)	1.70 (0.75-3.88)	0.21
Bleeding BARC type 2-5	22 (2.3%)	48 (3.8%)	0.60 (0.36-0.99)	0.046
Major bleeding (BARC type 3,4,or 5)	4 (0.4%)	10 (0.8%)	0.53 (0.17-1.68)	0.28
Net adverse clinical and cerebral events	65 (6.6%)	92 (7.2%)	0.92 (0.67-1.27)	0.62

Subgroup analysis: MACCE (ITT)

Subgroup	N	DAPT-6 group	DAPT-12 group	Hazard ratio (95% CI)	p for interaction
Age					0.19
≥65 years	1199	40/596 (6.9)	42/603 (7.1)	0.97 (0.63–1.49)	
<65 years	1513	23/761 (3.1)	14/752 (1.9)	1.64 (0.84–3.19)	
Sex					0.11
Male	2044	48/1016 (4.8)	36/1028 (3.5)	1.37 (0.89-2.11)	
Female	668	15/341 (4.5)	20/327 (6.2)	0.71 (0.36-1.38)	
STEMI					0.27
Yes	1023	34/509 (6.8)	25/514 (4.9)	1.40 (0.83-2.34)	
No	1689	29/848 (3.5)	31/841 (3.7)	0.93 (0.56-1.54)	
Diabetes					0.38
Yes	744	25/365 (7.0)	27/379 (7.2)	0.95 (0.55–1.63)	
No	1968	38/992 (3.9)	29/976 (3.0)	1.31 (0.81–2.13)	
LVEF					0.93
<50%	743	28/378 (7.6)	27/365 (7.5)	1.01 (0.60-1.71)	
≥50%	1766	26/881 (3.0)	25/885 (2.9)	1.05 (0.60-1.81)	
Multi-vessel PCI					0.87
Yes	544	14/263 (5.4)	14/281 (5.0)	1.08 (0.51-2.26)	
No	2168	49/1094 (4.6)	42/1074 (4.0)	1.15 (0.76-1.74)	
P2Y12 inhibitor					0.34
Clopidogrel	2191	47/1082 (4.4)	47/1109 (4.3)	1.03 (0.69-1.54)	
New P2Y12 inhibitor	521	16/275 (5.9)	9/246 (3.7)	1.62 (0.71-3.66)	



STEMI = ST elevation myocardial infarction, LVEF=left ventricular ejection fraction, PCI = percutaneous coronary intervention

Study Limitations

1. Randomization at the index procedure
2. Open label trial (not placebo-controlled)
3. A considerable cross-over rate in in the 6-month DAPT group
4. Clopidogrel was predominantly used as a P2Y12 inhibitor.
5. Our findings apply only to ACS patients undergoing PCI with DES.

Conclusions

- Although the non-inferiority of the 6-month DAPT to 12-month or longer DAPT was met, the increased MI risk with 6-month DAPT prevent us from concluding that short-term DAPT is safe in ACS patients undergoing PCI with current-generation DES.
- Prolonged DAPT in ACS patients without excessive risk of bleeding should remain the standard of care.

This study is published online in The Lancet, today

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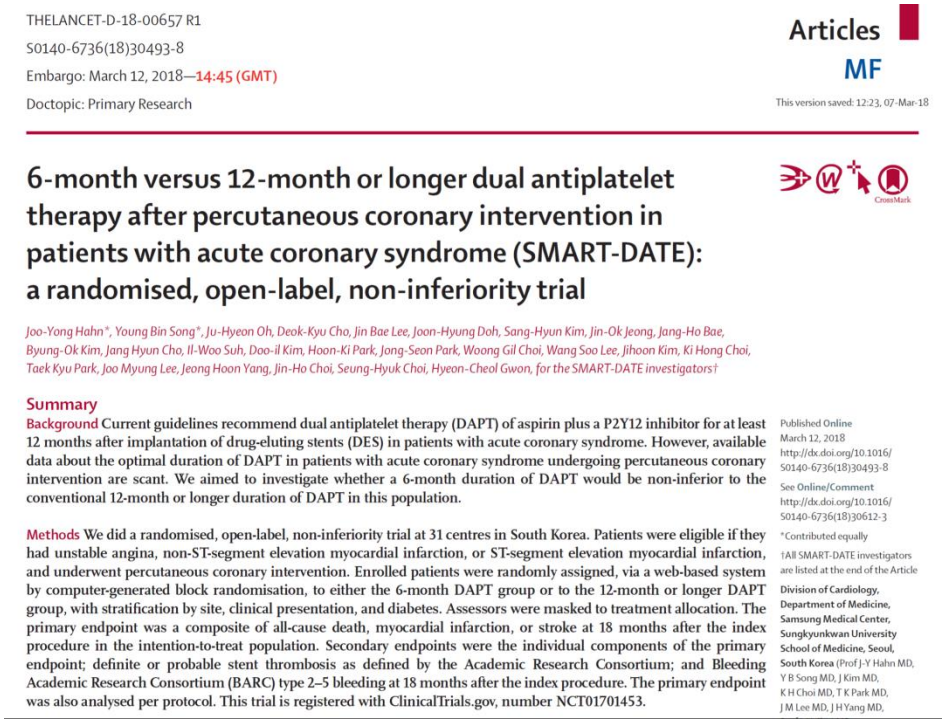
I would like to express many thanks

to all investigators of SMART-DATE trial



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Articles
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6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial

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Summary

Background Current guidelines recommend dual antiplatelet therapy (DAPT) of aspirin plus a P2Y12 inhibitor for at least 12 months after implantation of drug-eluting stents (DES) in patients with acute coronary syndrome. However, available data about the optimal duration of DAPT in patients with acute coronary syndrome undergoing percutaneous coronary intervention are scant. We aimed to investigate whether a 6-month duration of DAPT would be non-inferior to the conventional 12-month or longer duration of DAPT in this population.

Methods We did a randomised, open-label, non-inferiority trial at 31 centres in South Korea. Patients were eligible if they had unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction, and underwent percutaneous coronary intervention. Enrolled patients were randomly assigned, via a web-based system by computer-generated block randomisation, to either the 6-month DAPT group or to the 12-month or longer DAPT group, with stratification by site, clinical presentation, and diabetes. Assessors were masked to treatment allocation. The primary endpoint was a composite of all-cause death, myocardial infarction, or stroke at 18 months after the index procedure in the intention-to-treat population. Secondary endpoints were the individual components of the primary endpoint; definite or probable stent thrombosis as defined by the Academic Research Consortium; and Bleeding Academic Research Consortium (BARC) type 2–5 bleeding at 18 months after the index procedure. The primary endpoint was also analysed per protocol. This trial is registered with ClinicalTrials.gov, number NCT01701453.

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Thank you for your attention