Prolonged DAPT in ACS patients:
DATA from RCT and recommendation from 2017 ESC Guideline

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Disclosure

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  - Ministry of Health & Welfare, Republic of Korea
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  - Abbott Vascular, Astra Zeneca, Biotronik, Boston Scientific, Daiichi Sankyo, MSD Korea, Pfizer, and Sanofi-Aventis

Contents

- Duration of DAPT in patients with acute coronary syndrome (ACS)
  - SMART-DATE trial
  - PEGASUS-TIMI 54 trial

- ESC guidelines and reimbursement in Korea

ACC/AHA DAPT guideline 2016

COR	LOE	Recommendations
I	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months (16,50-55,72,96-98).
I	B-NR	In patients treated with DAPT, the recommended daily dose of aspirin is 81 mg (range, 75 mg to 100 mg) (56-60,75-78).
IIb	A^{SR}	In patients with ACS (NSTE-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable (16,22-26,28,30,40,41,43,53,54,72).
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable (17-21,34,36,37).
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA (54).

SR indicates systematic review.

SMART-DATE trial

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.

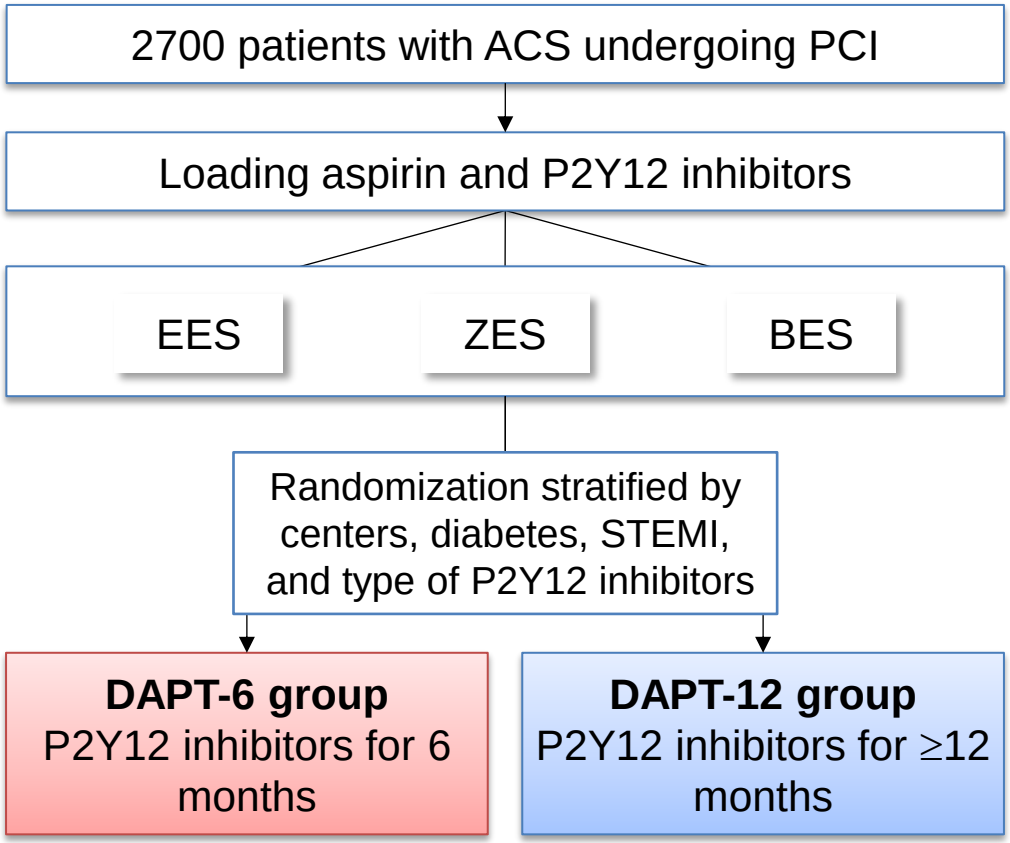
Working hypothesis

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.

Study design

ClinicalTrials.gov NCT01701453

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



Primary endpoint: 18-month MACCE
a composite of all-cause mortality, MI, or stroke

- 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

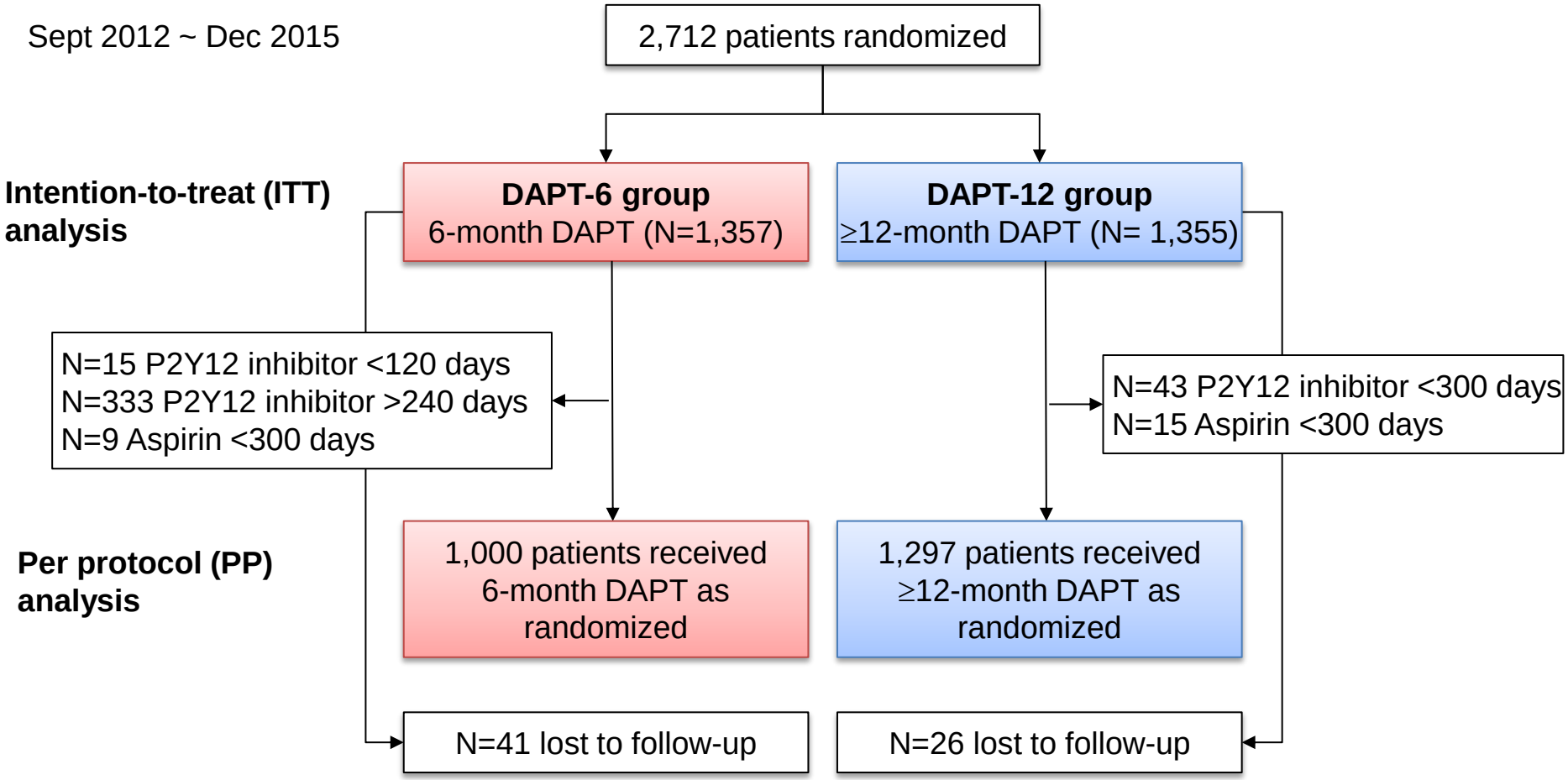
Lee JM, Hahn JY, …, Gwon HC. Am Heart J 2016

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 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

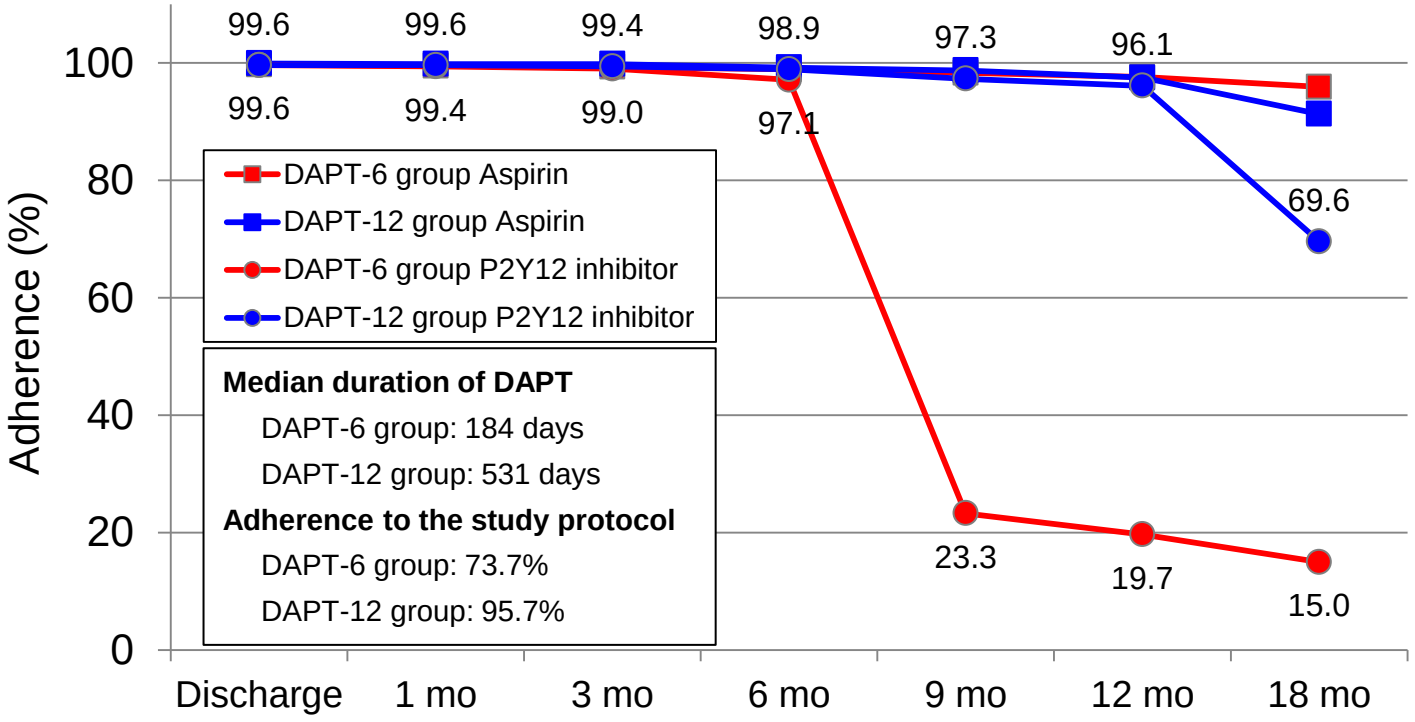
Lesion and procedural characteristics

	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,

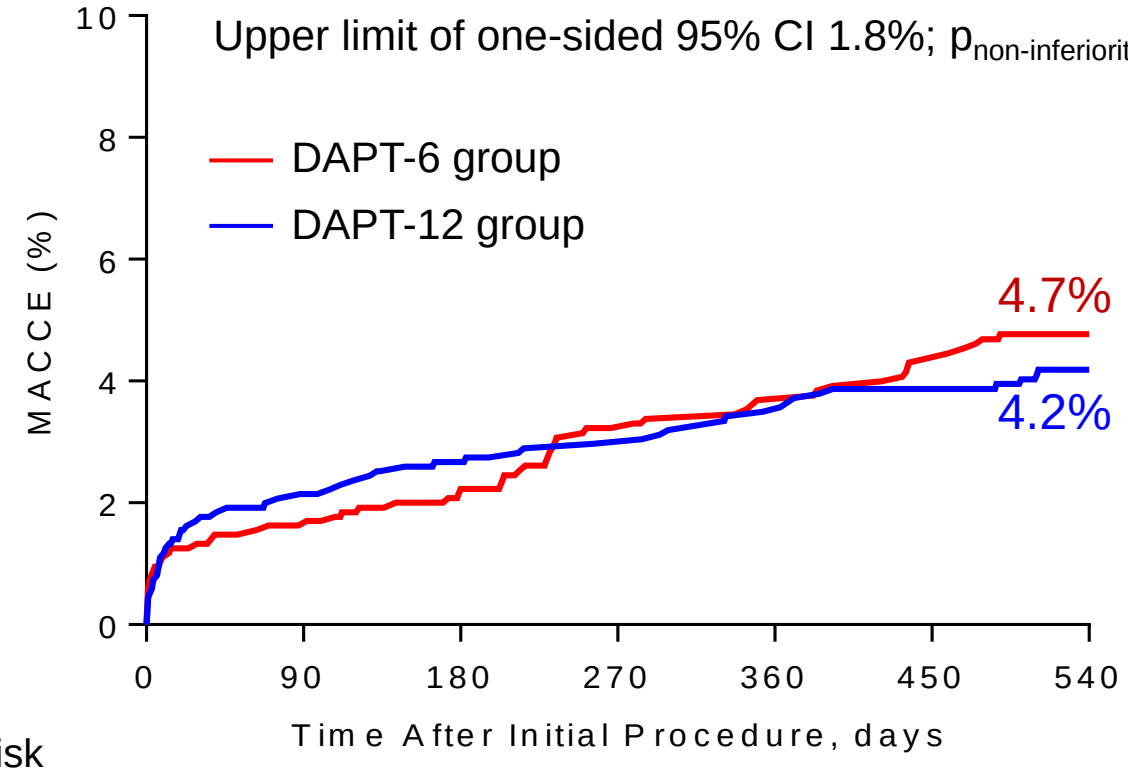
Adherence of antiplatelet therapy



Primary endpoint (MACCE)

HR 1.13 (95% CI 0.79-1.62); p=0.51

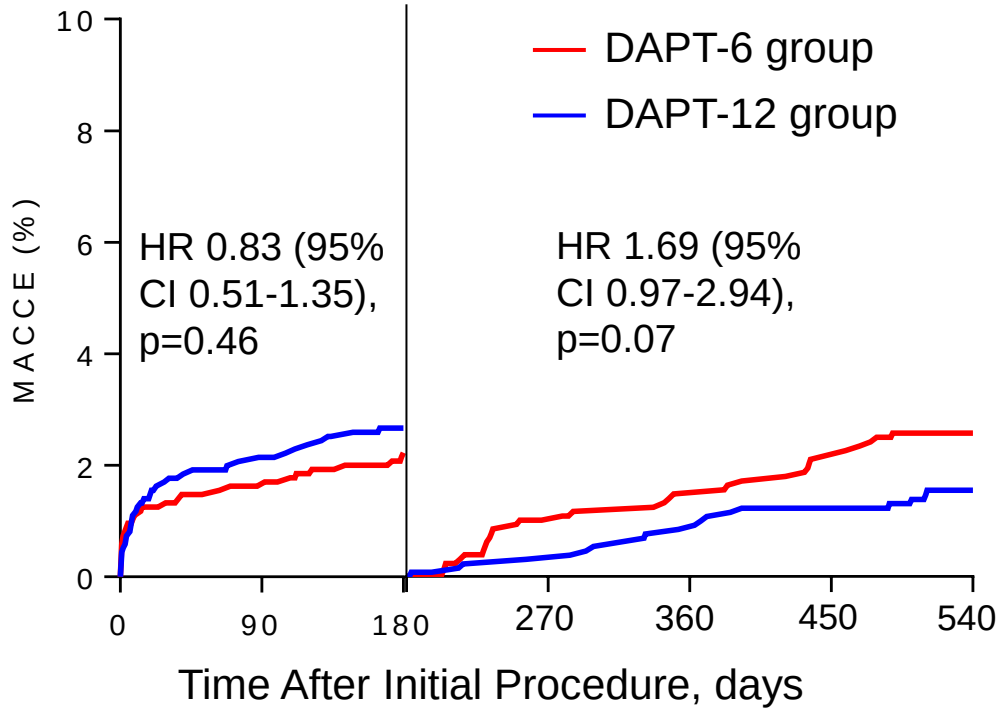
Upper limit of one-sided 95% CI 1.8%; $p_{non\text{-}inferiority}$=0.03



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, or stroke

MACCE (Landmark analysis)



No. at risk

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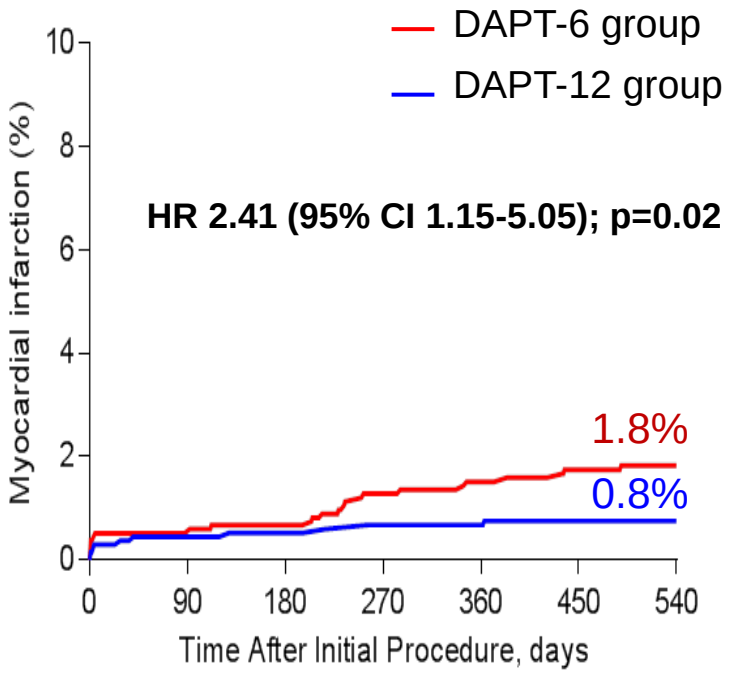
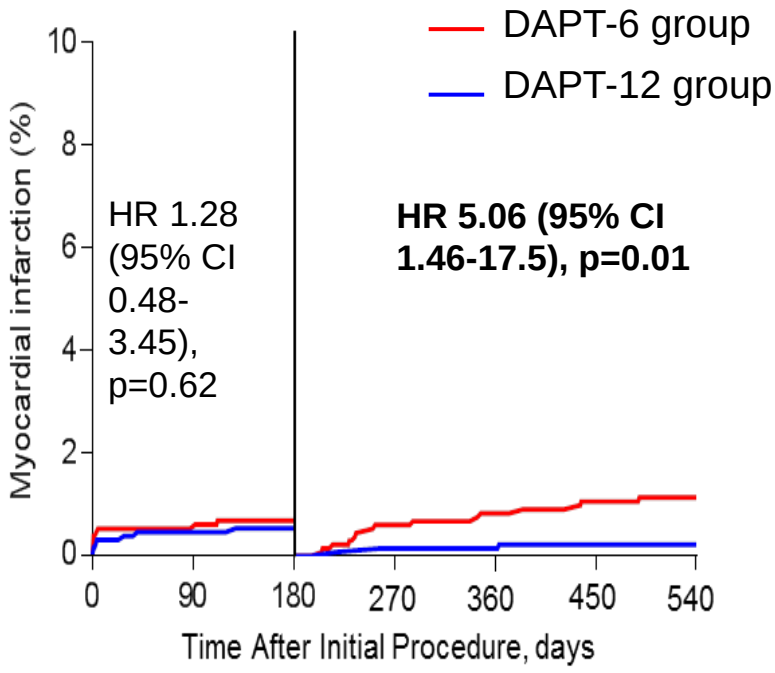
Hahn JY, Song YB,…, Gwon HC. Lancet 2018

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

Hahn JY, Song YB,…, Gwon HC. Lancet 2018

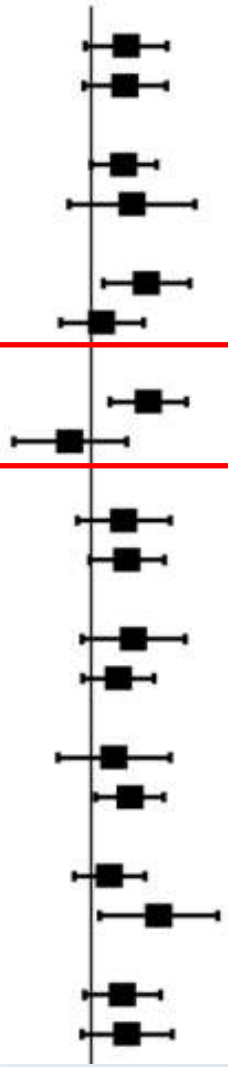
Clinical outcomes at 18 months
Intention-to-treat (ITT)

	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 (stroke)	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

Hahn JY, Song YB,…, Gwon HC. Lancet 2018

Subgroup analyses of myocardial infarction

Subgroup	Patients	Myocardial infarction (%) 6-month DAPT	Myocardial infarction (%) 12-month or longer DAPT	Hazard ratio (95% CI)	p for interaction
Age					0.98
≥65 years	1199	12/596 (2·1)	5/603 (0·9)	2·44 (0·86–6·92)	
<65 years	1513	12/761 (1·6)	5/752 (0·7)	2·39 (0·84–6·79)	
Sex					0.82
Male	2044	18/1016 (1·8)	8/1028 (0·8)	2·30 (1·00-5·30)	
Female	668	6/341 (1·8)	2/327 (0·6)	2·83 (0·57-14·03)	
STEMI					0.14
Yes	1023	16/509 (3·2)	4/514 (0·8)	4·10 (1·37-12·27)	
No	1689	8/848 (1·0)	6/841 (0·7)	1·32 (0·46-3·81)	
AMI					0.025
Yes	1876	21/937 (2·3)	5/939 (0·5)	4·27 (1·61-11·32)	
No	836	3/420 (0·7)	5/416 (1·2)	0·59 (0·14-2·46)	
Diabetes					0.91
Yes	744	9/365 (2·6)	4/379 (1·1)	2·29 (0·71–7·44)	
No	1961	15/990 (1·6)	6/971 (0·6)	2·49 (0·97–6·42)	
LV ejection fraction					0.64
<50%	743	9/378 (2·5)	3/365 (0·9)	2·94 (0·80-10·85)	
≥50%	1766	14/881 (1·6)	7/885 (0·8)	2·01 (0·81-4·98)	
Multivessel PCI					0.64
Yes	544	5/263 (2·0)	3/281 (1·1)	1·79 (0·43-7·50)	
No	2168	19/1094 (1·8)	7/1074 (0·7)	2·68 (1·13-6·38)	
LM or LAD lesion					0.16
Yes	1619	12/786 (1·6)	8/833 (1·0)	1·59 (0·65-3·90)	
No	1092	12/570 (2·2)	2/522 (0·4)	5·57 (1·25-24·90)	
P2Y12 inhibitor					0.89
Clopidogrel	2191	13/1082 (1·2)	6/1109 (0·5)	2·23 (0·85-5·87)	
New P2Y12 inhibitor	521	11/275 (4·1)	4/246 (1·7)	2·49 (0·79-7·83)	



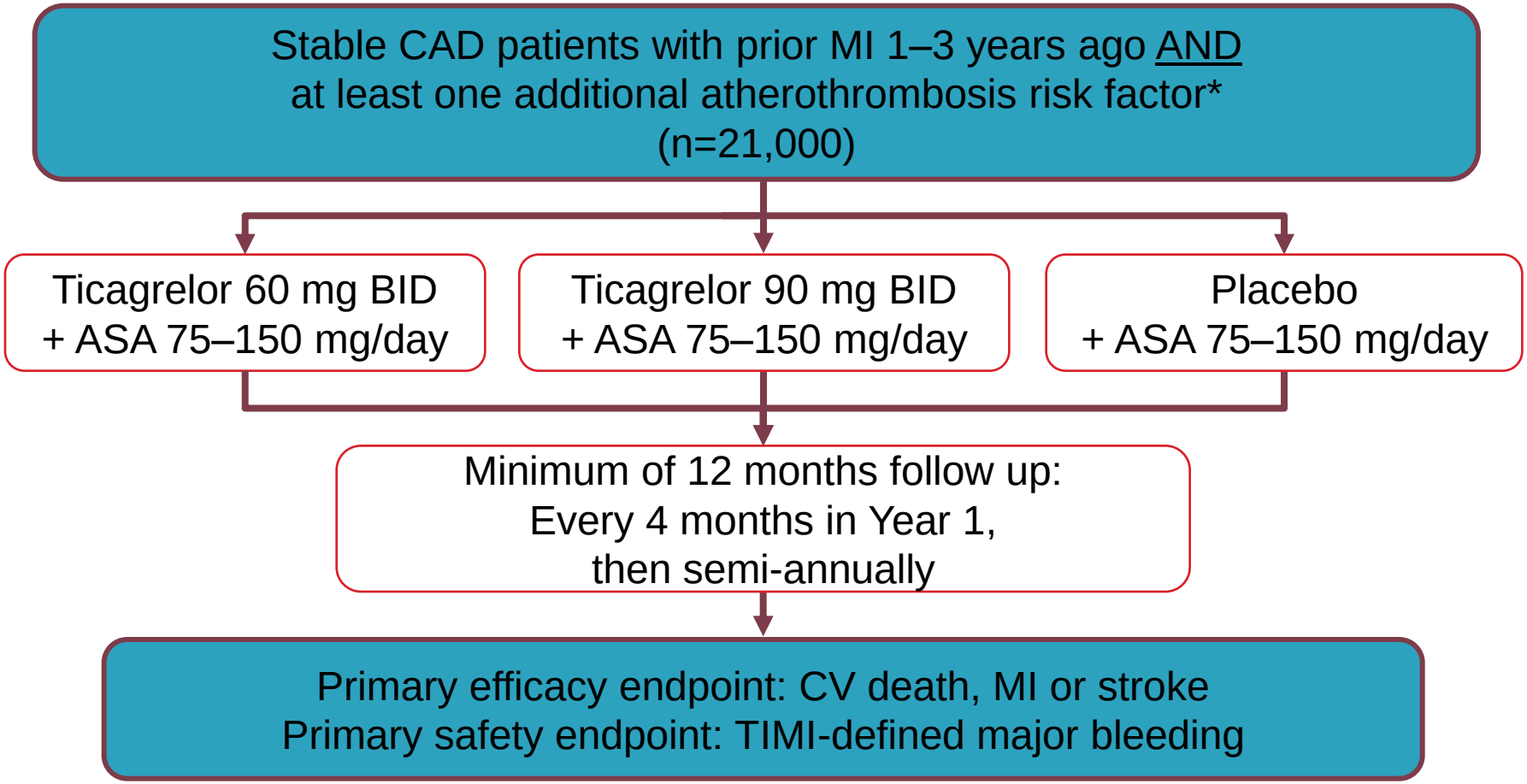
Conclusions

- 6-month DAPT was non-inferior to 12-month or longer DAPT for the primary end point of MACCE at 18 months after the index procedure in patients with ACS undergoing PCI with DES.

- However, the increased risk of myocardial infarction with 6-month DAPT and the wide non-inferiority margin prevent us from concluding that short-term DAPT is safe in this population.

- Prolonged 12 months or longer DAPT in patients with acute coronary syndrome without excessive risk of bleeding should remain the standard of care.

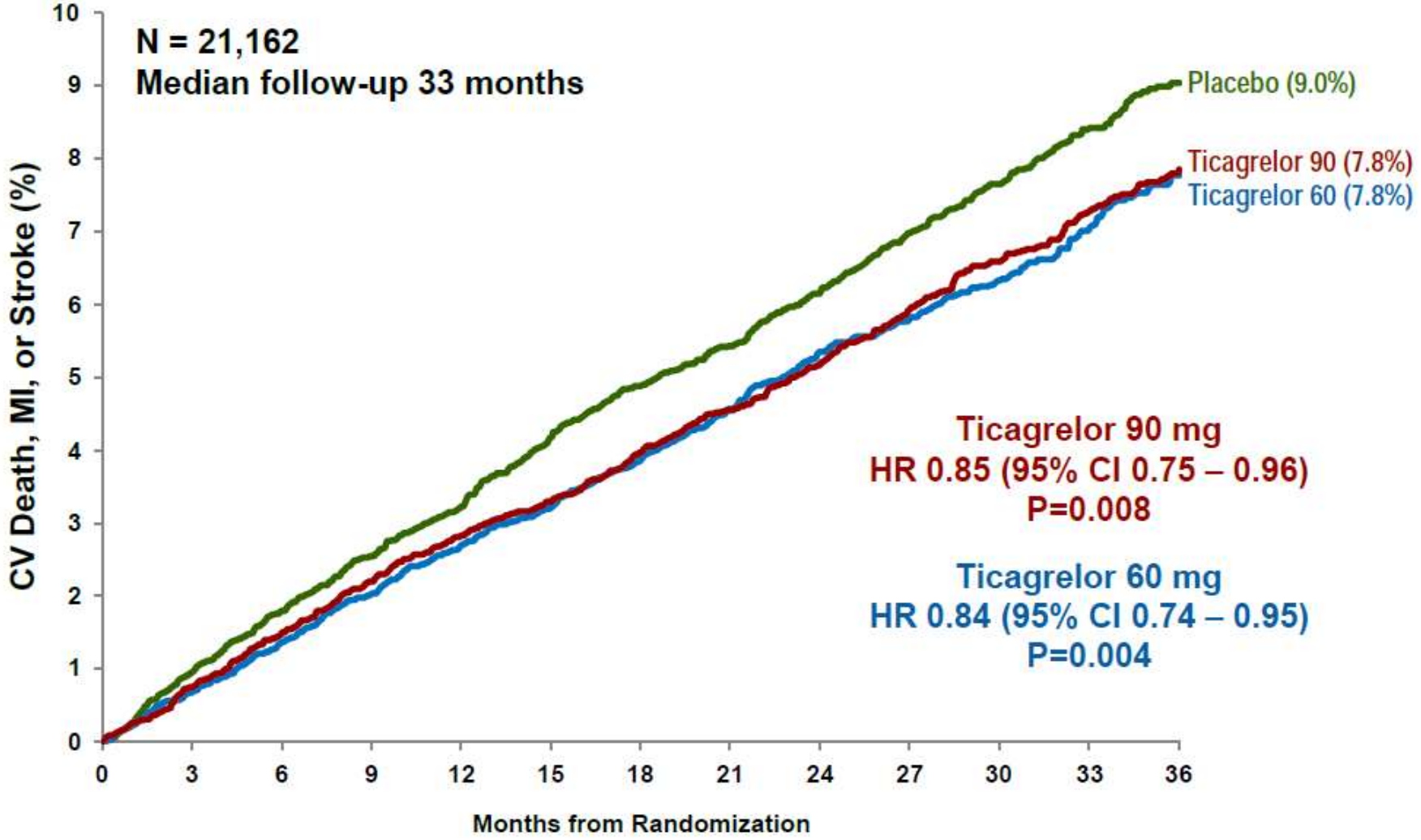
PEGASUS-TIMI 54: Study design



*Age ≥65 years, diabetAtherothrombotic risk factors defined as age ≥65 years, diabetes, a second prior MI, evidence of multivess el CAD or chronic non-end-stage renal dysfunction. Bonaca MP, et al. *Am Heart J* 2014

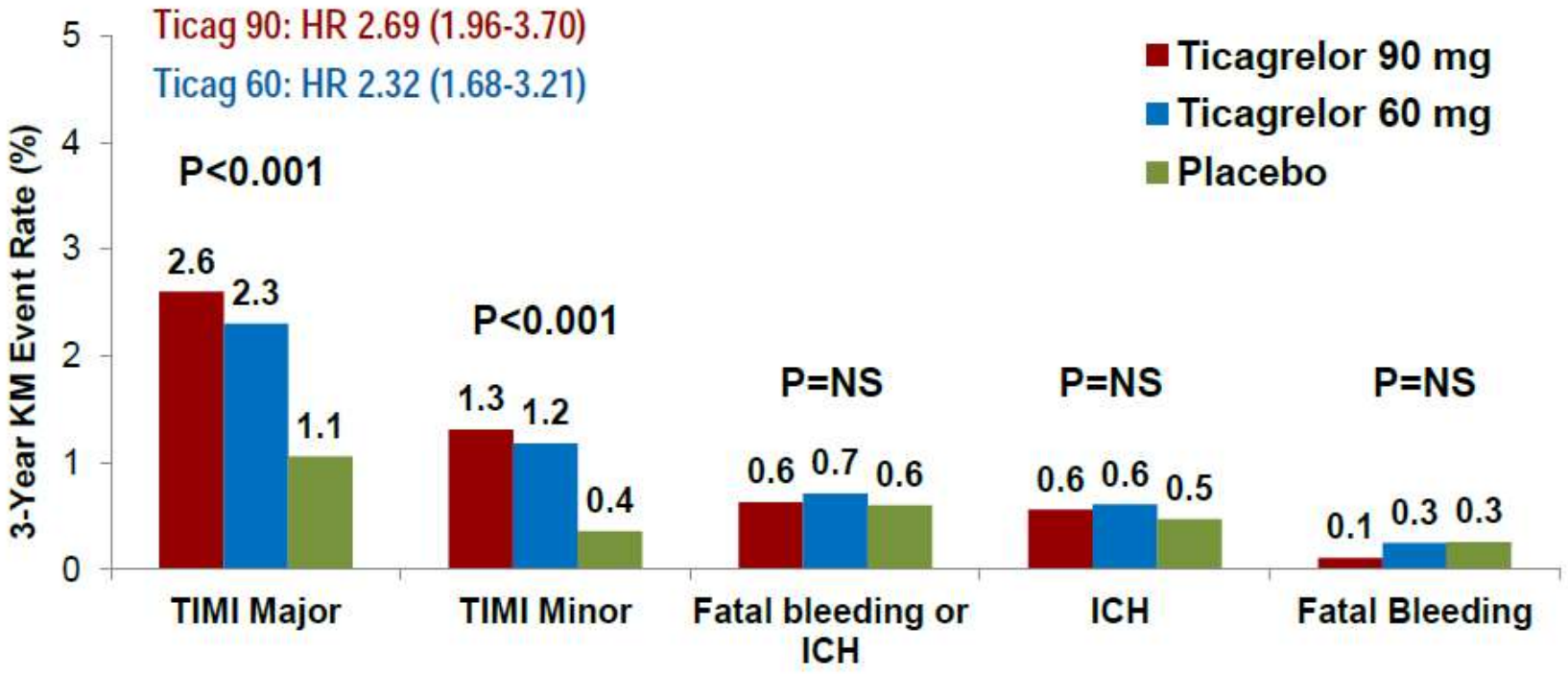
PEGASUS TIMI 54

Primary Endpoint

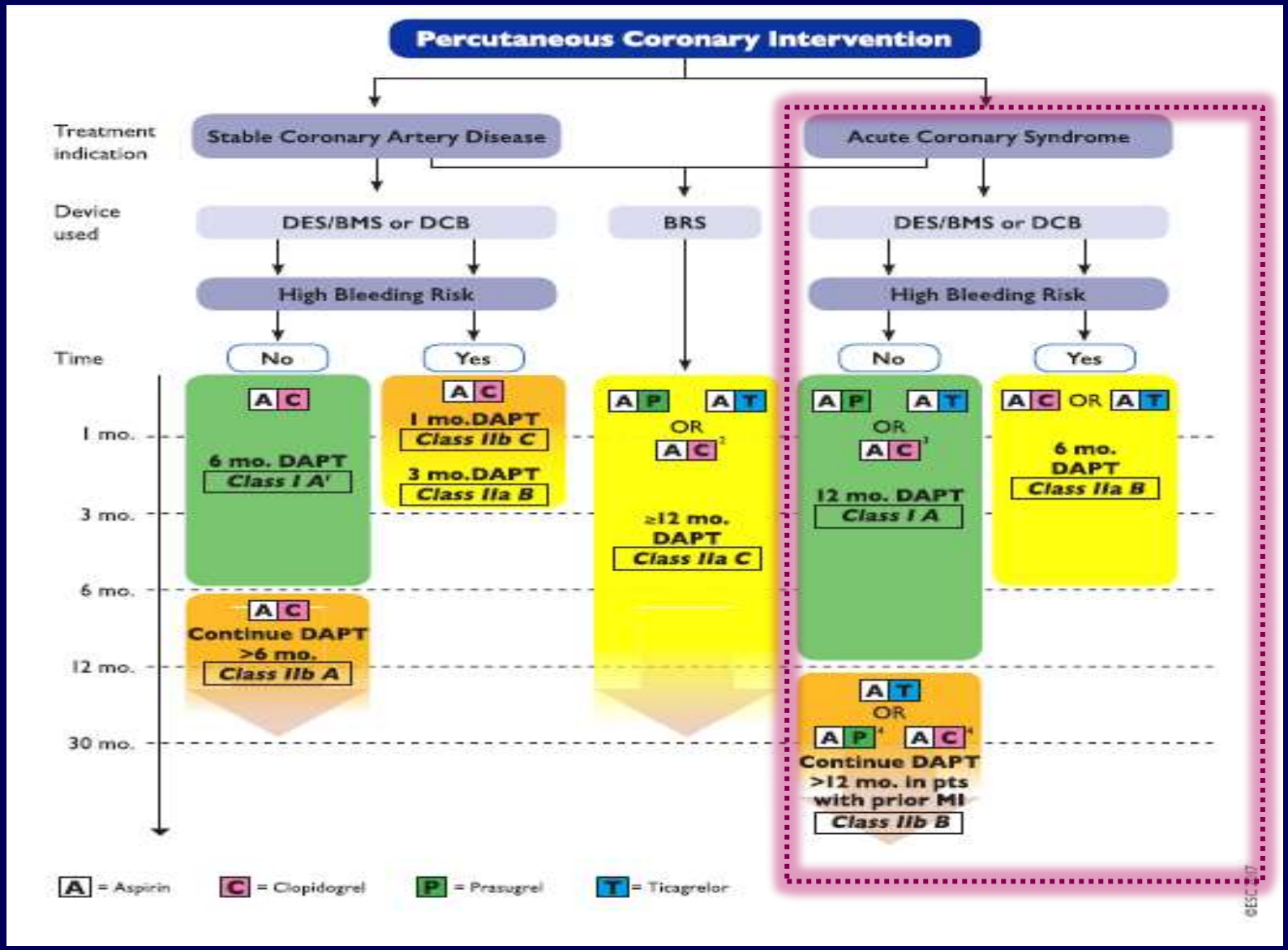


PEGASUS TIMI 54

Bleeding



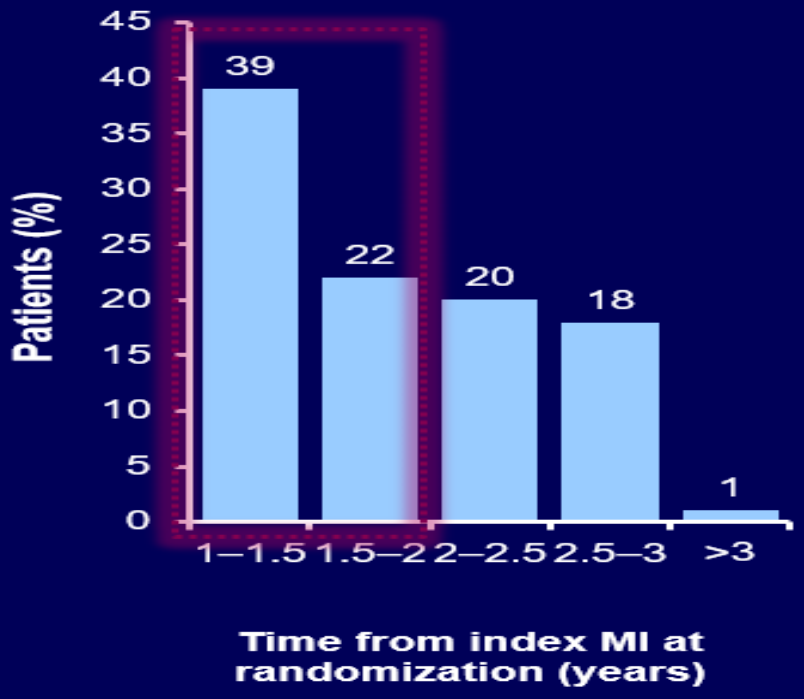
Updated ESC guideline Place ticagrelor in a preferred position in acute and long term therapy



European Heart Journal (2017) 0, 1–48. doi:10.1093/eurheartj/ehx419

PEGASUS EU label sub study method

- Patients with <= 2 years from qualifying MI or <= 1 year from prior ADP receptor inhibitor treatment.
- 5388 were in the ticagrelor 60 mg and 5391 in the placebo group.
- Hazard ratios, 95% confidence intervals and two-sided p-values were generated using the Cox proportional hazards model.
- The cumulative proportions of patients with events at 36 months were calculated by the Kaplan–Meier (KM) method.



Reasons for $P2Y_{12}$ discontinuation prior to randomization	Timing unknown or not applicable* N=2401 n (%)	≤ 30 days N=7181 n (%)	> 30 days to 1 year N=6501 n (%)	> 1 year N=5079 n (%)
Recommendation by treating physician	64 (2.7)	6753 (94.0)	6124 (94.2)	4756 (93.6)
Patient preference	7 (0.3)	373 (5.2)	349 (5.4)	287 (5.7)
Bleeding	0 (0.0)	0 (0.0)	14 (0.2)	13 (0.3)
Non-bleeding adverse reaction	0 (0.0)	2 (<0.1)	3 (<0.1)	18 (0.4)
Other	0 (0.0)	4 (<0.1)	6 (<0.1)	3 (0.1)
Unknown	2330 (97)	49 (0.7)	5 (<0.1)	2 (<0.1)

*Patients in this category may have no prior $P2Y_{12}$ inhibitor recorded or have a $P2Y_{12}$ inhibitor recorded but with a missing withdrawal date

1. Mikael Dellborg et al. ESC 2017. Poster session 4: Acute coronary syndromes.

PEGASUS EU label sub study result : CV mortality 29% reduction and improved efficacy benefit vs overall result

Table 2: Primary and secondary outcomes; patients with <= 2 years from qualifying MI or <= 1 year from prior ADP receptor inhibitor treatment (efficacy cohort)

Outcome	Ticagrelor 60 mg bd (N=5388)		Placebo (N=5391)		Hazard ratio (95% CI)	P value
	n	3-yr KM%	n	3-yr KM%		
Composite of CV death, MI or Stroke	373	7.9	463	9.6	0.80 (0.70, 0.91)	0.001
CV death	119	2.6	167	3.6	0.71 (0.56, 0.90)	0.0041
MI	230	4.8	274	5.6	0.83 (0.70, 0.99)	0.041
Stroke	71	1.5	95	2.0	0.74 (0.55, 1.01)	0.058
All-cause mortality	206	4.4	256	5.4	0.80 (0.67, 0.96)	0.018

- 4% additional benefit vs overall

-12% additional benefit vs overall

1. Mikael Dellborg et al. ESC 2017. Poster session 4: Acute coronary syndromes. 2. Bonaca MP et al. N Engl J Med 2015;372:1791–1800

Efficacy and safety with Ticagrelor in Patients with Prior Myocardial Infarction in the approved European label: Insights from PEGASUS-TIMI 54

Mikael Dellborg[1], Marc P. Bonaca[2], Robert F. Storey[3], P. Gabriel Steg[4], KyungAh Im[2], Marc Cohen[5], Deepak L. Bhatt[2], Per Johanson[6], Olof Bengtsson[6], Anders Himmelmann[6], Eugene Braunwald[2], Marc S. Sabatine[2]

[1]Sahlgrenska University Hospital, Gothenburg, Sweden; [2]TIMI Study Group, Brigham and Women's Hospital, Harvard Medical School, Boston; [3]University of Sheffield, Sheffield, United Kingdom; [4]INSERM Unité 1148, Assistance Publique–Hôpitaux de Paris and Université Paris Diderot, Paris, France; [5]Newark Beth Israel Medical Center, Rutgers-New Jersey Medical School, Newark MA; [6]AstraZeneca, Mölndal, Sweden.

ClinicalTrials.gov, NCT01225562

Summary

- In PEGASUS-TIMI 54, long-term treatment with ticagrelor 60 mg in patients closer to their MI or to ADP receptor blocker discontinuation, as recommended in the European label, was associated with a relative risk reduction of 20% in CV death, MI or stroke, 29% in CV death, and 20% in all-cause mortality.

- Overall TIMI major bleeding was increased, but fatal or intracranial bleeding was similar to placebo.

- **There is a very favorable benefit-risk ratio** for long-term ticagrelor 60 mg in patients with prior MI in the CHMP-EMA approved population of patients.

PEGASUS TIMI 54

Efficacy and safety with Ticagrelor in Patients with Prior Myocardial Infarction in the approved European label: Insights from PEGASUS-TIMI 54

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- The CHMP-EMA approved European label recommends that after the initial one-year treatment with ticagrelor 90 mg bid in ACS patients, treatment with ticagrelor 60 mg bid may be started without interruption as continuation therapy;
  - Treatment can also be initiated **up to 2 years from the MI**, or **within one year after stopping previous ADP receptor inhibitor treatment.**
- Brilinta 60mg label in Korea. (Similar with EU label)

- 심근경색 발생 후 초기 1년간 이 약 90mg 또는 다른 ADP 수용체 저해제(티클로피딘, 클로피도그렐, 프라수그렐)를 복용하던 환자는 이 약 60mg으로 투여를 계속할 수 있다.
- 이 약은 심근경색 후 2년 이내 또는 이전 ADP 수용체 저해제(티클로피딘, 클로피도그렐, 프라수그렐)를 중단한지 1년 이내의 환자에게도 투여를 시작할 수 있다.

1. Mikael Dellborg et al. ESC 2017. Poster session 4: Acute coronary syndromes. 2. Brilinta Prescribing information in Korea

Conclusion

- In patients with MI, the risk of a recurrent atherothrombotic event is high and persistent; therefore, patients need protection from CV events in both the short and long term.
- Prolonged DAPT in patients with acute coronary syndrome without excessive risk of bleeding should remain the standard of care (SMART-DATE trial).
- BRILINTA 90 mg delivers a 16% RRR (ARR 1.9%) in the composite endpoint of CV mortality, MI or stroke vs clopidogrel that accrues over 12 months, with an increase in minor and minimal bleeding but without a significant increase in overall major or fatal bleeding (PLATO trial).
- BRILINTA 60 mg is the only $P2Y_{12}$ inhibitor proven to reduce atherothrombotic events over 3 years in higher-risk post-MI patients vs ASA alone, with an expected increase in TIMI major bleeding but without significantly increasing intracranial haemorrhage or fatal bleeding (PEGASUS-TIMI 54 trial).
- **Maximize BRILINTA 60 mg's benefits through continuation therapy following 12 months with BRILINTA 90 mg in post-MI patients.**
  - Patients continuing $P2Y_{12}$ inhibitor treatment, or restarting ≤30 days from discontinuation, experienced the greatest benefit with BRILINTA 60 mg vs ASA alone.
  - Among patients who completed 1 year of treatment with ticagrelor 60mg the subsequent rate of discontinuation because of an adverse event was low.

감사합니다.
Thank you for your attention.

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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, amenable for PCI with DES implantation

- Key exclusion criteria

  Recent major bleeding, bleeding diathesis, DES implantation within 12 months, life expectancy <1 year, 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

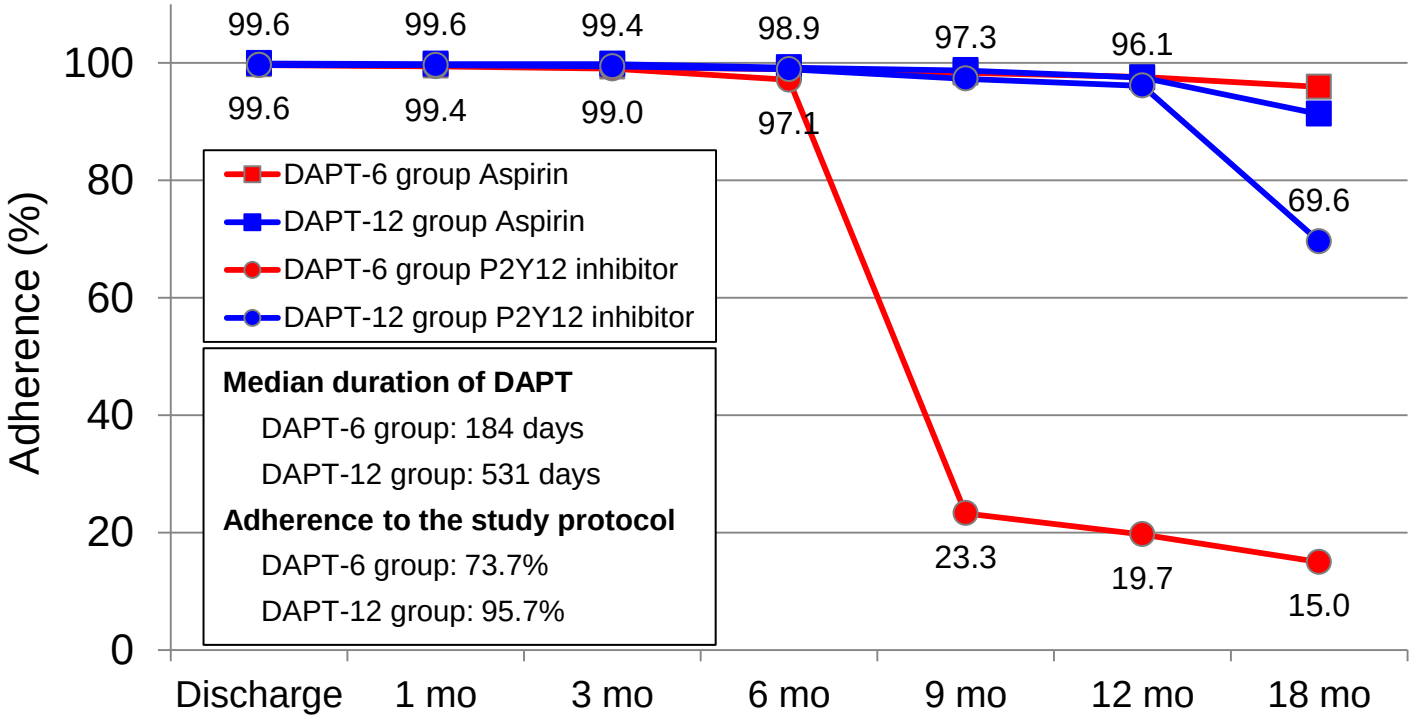
  2) Non-ST-segment elevation MI: elevated biomarkers of myocardial necrosis (troponin or CK-MB ≥ upper reference limit) with one of the following:

  (a) Transient ST-segment elevation or depression, or T-wave changes consistent with myocardial ischemia

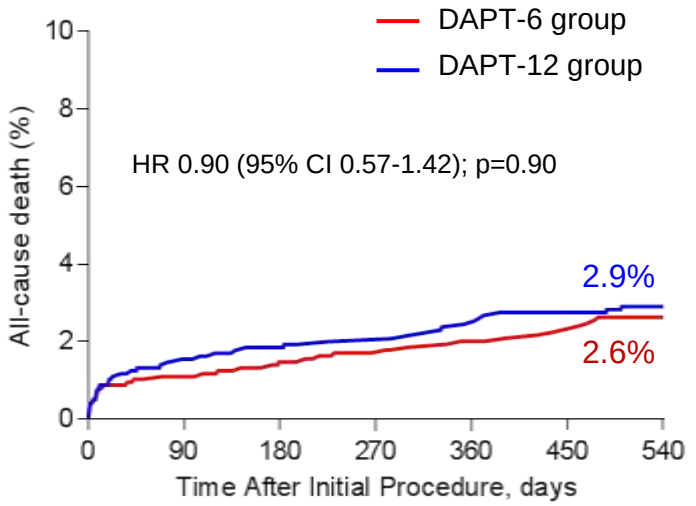
  (b) Identification of a culprit lesion at coronary angiography

  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.

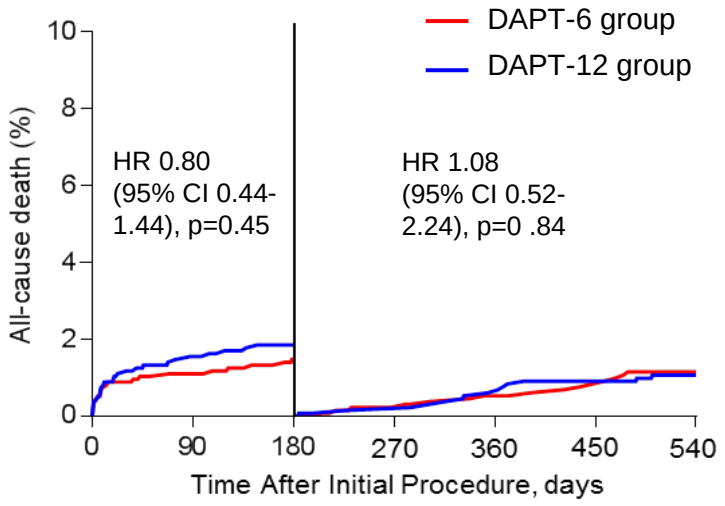
Adherence of antiplatelet therapy



All-cause death (ITT)

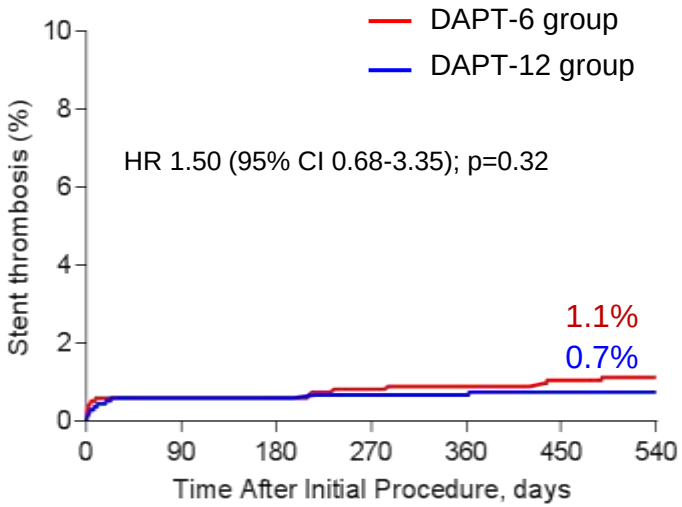


No. at risk							
Long-term	1355	1320	1309	1302	1296	1292	1056
Short-term	1357	1325	1306	1290	1285	1281	1055



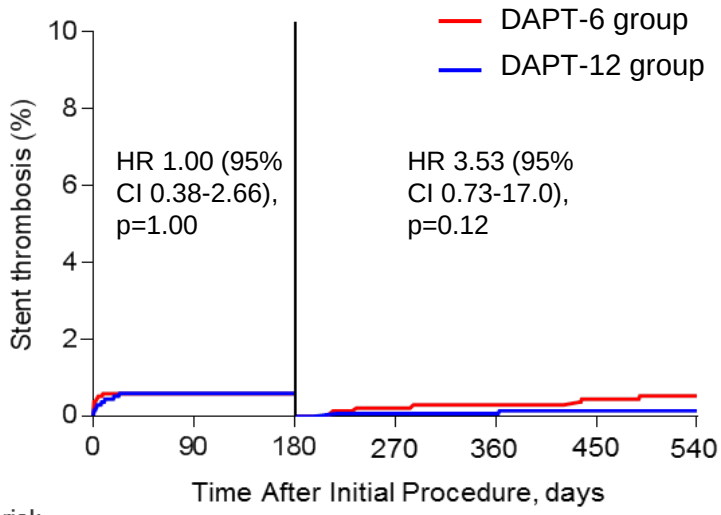
No. at risk							
Long-term	1355	1320	1309	1302	1296	1292	1056
Short-term	1357	1325	1306	1290	1285	1281	1055

Stent thrombosis (ITT)



No. at risk

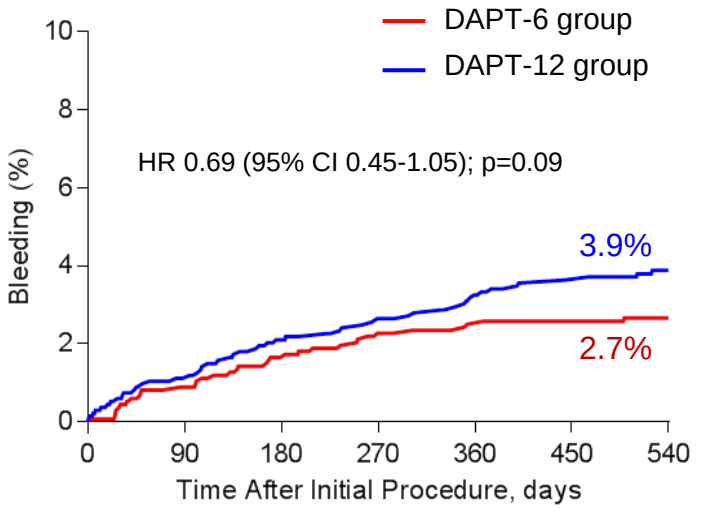
Long-term	1355	1316	1305	1298	1292	1287	1051
Short-term	1357	1321	1302	1284	1279	1273	1047



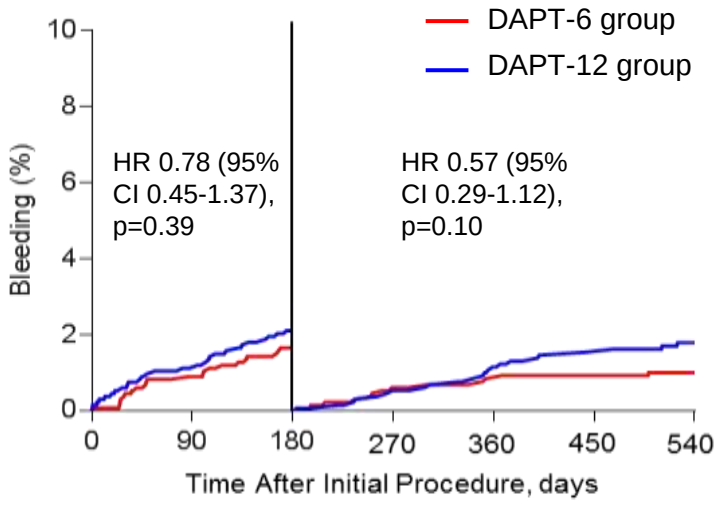
No. at risk

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