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Lifelong APT

Lifelong Antiplatelet Therapy After PCI for Prevention of Ischemic Events

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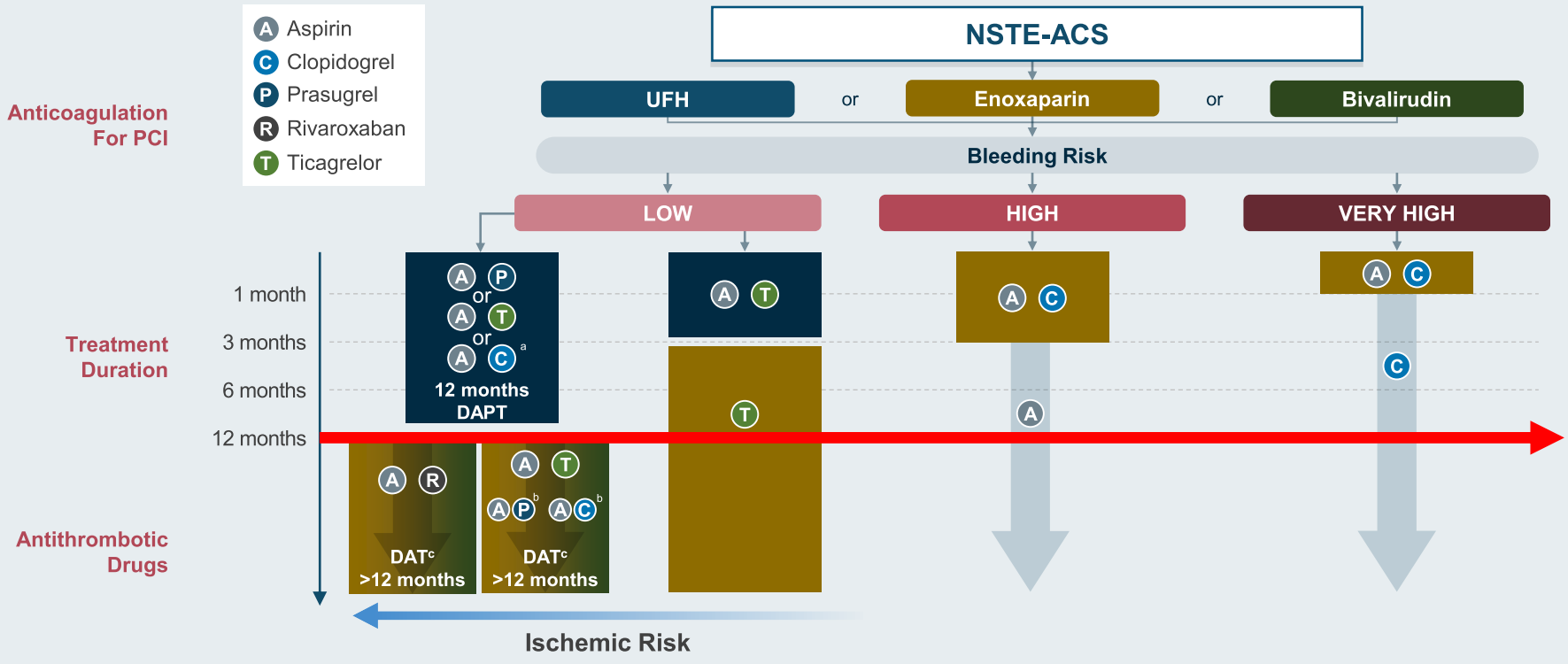
MAT-KR-2102401-1.0-01/2022

Lack of clear evidence about Antiplatelet therapy strategy in maintenance phase

Contents

2020 ESC Guidelines of NSTE-ACS

Algorithm for antithrombotic therapy in NSTE-ACS patients without AF undergoing PCI



Study Design

Post hoc subgroup analysis regarding the effect of very short DAPT for HBR patients in STOPDAPT- 2 trial. were conducted . The primary endpoint was a 1-year composite of cardiovascular (cardiovascular death, myocardial infarction, definite stent thrombosis, or stroke) and bleeding (TIMI major/minor bleeding) outcomes.

HBR is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25 or ARC-HBR) Very HBR is defined as recent bleeding in the past month and/or not deferrable planned surgery. Colour-coding refers to the ESC classes of recommendations (green=class I; yellow = IIa; orange = Class IIb)
A=aspirin; ARC-HBR=Academic Research Consortium High Bleeding Risk; C=clopidogrel; DAPT=dual antiplatelet therapy; DAT=dual antithrombotic therapy (here: aspirin þ rivaroxaban); eGFR=estimated glomerular filtration rate; ESC=European Society of Cardiology; HBR=high bleeding risk; NSTE-ACS=non-ST-segment elevation acute coronary syndrome; P=prasugrel; PCI=percutaneous coronary intervention; PRECISE-DAPT=PRE dicting bleeding Complications In patients undergoing Stent implantation and subs Equent Dual Anti Platelet Therapy; R=rivaroxaban; T=ticagrelor; UFH=unfractionated heparin. a Clopidogrel during 12 months DAPT if patient is not eligible for treatment with prasugrel or ticagrelor or in a setting of DAPT de-escalation with a switch to clopidogrel (class IIb). B Clopidogrel or prasugrel if patient is not eligible for treatment with ticagrelor. C Class IIa indication for DAT or DAPT >12 months in patients at high risk for is chaemic events and without increased risk of major bleeding (=prior history of intracranial haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, renal failure requiring dialysis, or with eGFR <15 mL/ min/1.73 m^2); Class IIb indication for DAT or DAPT>12 months in patients with moderately increased risk of ischaemic events and without increased risk of major bleeding.

1. Collet JP, *et al.* Eur Heart J. 2020 ;42(14):1289-1367

2018 ESC/EACTS Guideline:
In SCAD patients undergoing PCI

Recommendations for platelet inhibition

Recommendations	Class[a]	Level[b]
Post-interventional and maintenance treatment		
Life-long single antiplatelet therapy, usually aspirin, is recommended.	I	A
Instruction of patients about the importance of complying with antiplatelet therapy is recommended.	I	C
In patients with SCAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type.[c]	I	A
In patients with SCAD treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.	IIa	C
In patients with SCAD treated with DCB, DAPT should be considered for 6 months.	IIa	B
In patients with SCAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT should be considered for 3 months.[d]	IIa	A
In patients with SCAD who have tolerated DAPT without a bleeding complication and who are at low bleeding risk but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and up to 30 months may be considered.	IIb	A
In patients with SCAD in whom 3 month DAPT poses safety concerns, DAPT may be considered for 1 month.	IIb	C

[a]Class of recommendation.; [b]Level of evidence

1. Neumann FJ, *et al*. Eur Heart J. 2018. ;40(2):87-165.

AHA Scientific Statement 2020

Antithrombotics in stable patients with T2DM and CAD

Clopidogrel alone may be a reasonable option compared with aspirin in stable patients with T2DM and CAD (ie, no stent or acute coronary syndrome in the prior year).

Management of Stable CAD: Antithrombotics

Underlying issue: T2DM is a generalized prothrombotic state caused by both altered coagulation and altered platelet function.

Aspirin alone	Lowest risk of bleeding but high residual platelet reactivity increases cardiovascular risk
Clopidogrel alone	Decreased cardiovascular risk **without** meaningfully increased risk of bleeding vs aspirin alone
Aspirin+clopidogrel/tica	Decreased cardiovascular risk with increased risk of bleeding; targets patients with additional risk factor and low risk of bleeding (use risk scores)
Aspirin+low-dose rivaroxaban	Decreased cardiovascular risk with increased risk of bleeding; targets the aberrant coagulation with T2DM

1. Arnold SV, *et al.* Circulation. 2020; 141(19):e779-e806

2021 ESC Guidelines of CVD Prevention

Recommendations for antithrombotic therapy

RECOMMENDATIONS	Class[a]	Level[b]
Aspirin 75-100 mg daily is recommended for secondary prevention of CVD.	**I**	**A**
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.	**I**	**B**
Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD.	IIb	**A**
Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal Bleeding	**I**	**A**
In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications	**IIb**	**A**

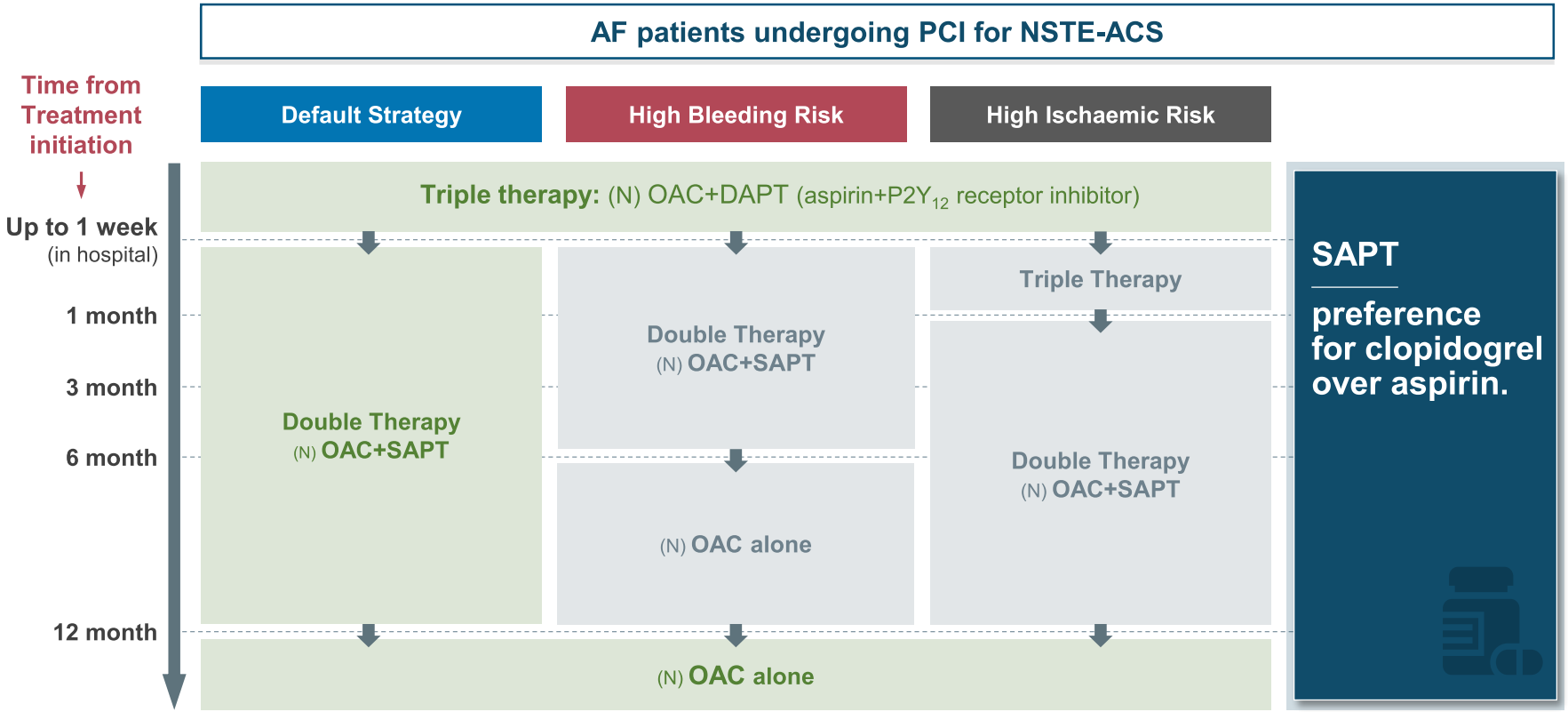
[a]Classes of recommendations: I, recommended/indicated; IIa, should be considered; IIb, may be considered
[b]Level of evidence; A, Data derived from multiple randomized clinical trials or meta-analyses; B, Data derived from a single randomized clinical trial or large non-randomized studies
[c]Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds; prasugrel is not recommended for patients ≥75 years of age or with a body weight <60 kg.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DM, diabetes mellitus

1. Visseren FLJ, *et al.* Eur Heart J. 2021;42(34):3227-3337

2020 ESC Guidelines of NSTE-ACS

Antithrombotic therapy with AF undergoing PCI

Algorithm for antithrombotic therapy in NSTE-ACS patients with AF undergoing PCI or medical management



Study Design

Green (class I) and yellow (class IIa) colours denote the classes of recommendation,
OAC: preference for a NOAC over VKA for the default strategy and in all other scenarios if no contraindications.
Ticagrelor may be considered in patients with high ischaemic risk and low bleeding risk. Treatment >1 month:OAC þ DAPT (TAT) may be considered for up to 6 months in selected patients with high ischaemic risk (IIa C).
Treatment >12 months: OAC þ SAPT may be considered in selected patients with high ischaemic risk. ARC-HBR=PRECISE-DAPT score of≥25. AF=atrial fibrillation; ARC-HBR=Academic Research Consortium High Bleeding Risk; b.i.d.=bis in die (twice a day); DAPT=dual antiplatelet therapy; DAT=dual antithrombotic therapy; NOAC=non-vitamin K antagonist oral anticoagulant; NSTEACS=non-ST-segment elevation acute coronary syndrome; OAC=oral anticoagulation/anticoagulant; PCI=percutaneous coronary intervention; PRECISE-DAPT=PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; SAPT=single antiplatelet therapy; TAT=triple antithrombotic therapy; VKA=vitamin K antagonist.

1. Collet JP, *et al.* Eur Heart J. 2020 ;42 (14):1289-1367

Current guidelines recommendation

Insights and limitations

Summary

- Aspirin is recommended as the standard strategy, however, there's **limited clinical evidence** directly comparing clopidogrel and aspirin after PCI updated guidelines.[1-3]
- In symptomatic PAD, CAD with **T2DM** and in patients with established ASCVD, **clopidogrel** is more recommended compared to aspirin in guidelines.[4-6]
- From recent guideline about **AF-PCI patient**, **clopidogrel** is preferred over aspirin.[3]

1. Neumann FJ, *et al*. Eur Heart J. 2018. ;40(2):87-165. **2.** Knuuti J, *et al*. Eur Heart J. 2020;41(3):407-477
3. Collet JP, *et al*. Eur Heart J . 2020 ;42(14):1289-1367 **4.** Arnold SV, *et al*. Circulation. 2020 ;141(19):e779-e806
5. Aboyans V, *et al*. Eur Heart J. 2018 ;39(9):763-816. **6.** Visseren FLJ, *et al*. Eur Heart J. 2021;42(34):3227-3337

Contents

Odds Ratio of Upper GI Bleeding in Patients Taking NSAIDS

FACTOR	Patients (N=317)	Controls (N=187)	Adjusted OR (95% CI)	*P* Value
	Number (%)			
History of GI bleeding	37 (11.7)	6 (3.2)	3.7 (1.2-11)	0.01
History of ulcer	69 (21.8)	18 (9.6)	1.8 (0.9-3.6)	0.09
Aspirin at any dose	73 (23.0)	18 (9.6)	**3.1 (1.7-5.9)**	<0.001
Nitrovasodilator	11 (3.5)	11 (5.9)	0.3 (0.1-0.9)	0.04
Anti-secretory medication	29 (9.1)	37 (19.8)	0.4 (0.2-0.7)	0.001

✓ The case group was made of 1,122 consecutive patients admitted to one of four hospitals with bleeding from a peptic lesion.
✓ The 2,231 control subjects were 1,109 patients hospitalized for other reasons and 1,122 outpatients from the same geographic area.

Study Design
We performed a case-control study to determine the risk of bleeding in patients taking nitrovasodilators, low-dose aspirin, or other nonsteroidal antiinflammatory drugs.

1. Lanas A, *et al*. N Engl J Med 2000;343: 834-839.

Comparison of the Ulcerogenic Drug History in Patients with Bleeding Peptic Ulcer

Comparison of the Ulcerogenic Drug History between the Geriatric and Non-geriatric Patients with Bleeding Peptic Ulcer

Usage of Drug	No (%) (n=88)	Age ≥65 (%) (n=34)	Age <65 (%) (n=54)	*P*-Value
Total	40/88 (45.5)	23/34 (64.7)	18/54 (33.3)	<0.05
Aspirin+Clopidogrel	**15** (17.0)	**8** (23.6)	**7** (13.0)	
Aspirin	**13** (14.9)	**7** (20.6)	**6** (11.0)	
NSAID	6 (6.9)	3 (8.9)	3 (5.5)	
Steroid	2 (2.3)	1 (2.9)	1 (1.9)	
Coumadine	1 (1.1)	1 (2.9)	0 (0.0)	
Clopidogrel	**1** (1.1)	**0** (0.0)	**1** (1.9)	
Aspirin+Coumadine	1 (1.1)	1 (2.9)	0 (0.0)	
Aspirin+NSAID	1 (1.1)	1 (2.9)	0 (0.0)	

Methods

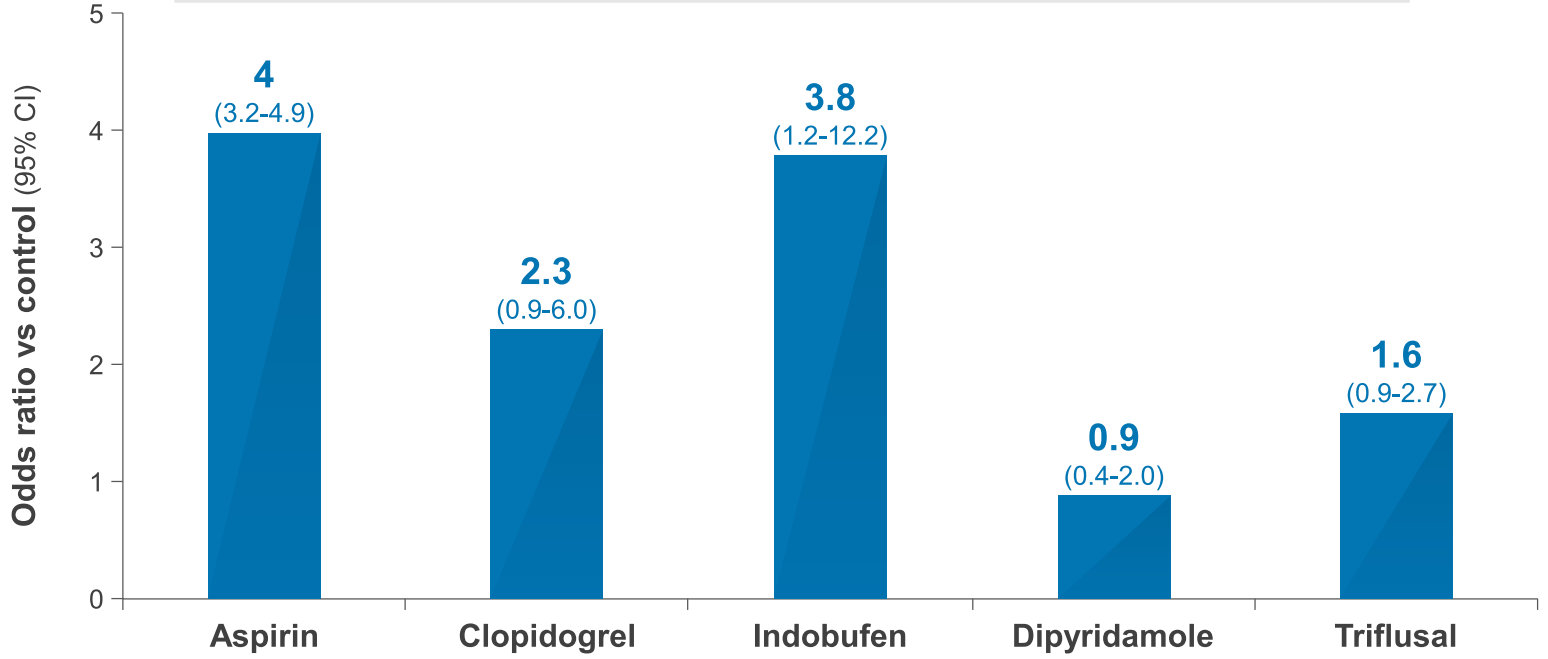
This study was a retrospective study of 88 patients with peptic ulcer bleeding treated with therapeutic endoscopy from January 2006 to December 2006. The clinical characteristics and outcomes of geriatric patients (n=34, 38.6%) with those of non-geriatric patients (n=54, 61.4%) were compared.

1. 나윤주 외. 대한소화기학회지 2009;53: 297-304.

Bleeding from Antiplatelet Drugs

- UGIB risk associated with various antiplatelet drugs suggested a weaker association for clopidogrel than aspirin.

UGIB risk associated with various antiplatelet drugs in week before the index day, by all dose



Study Design

In a case-control study, we compared all cases of upper gastrointestinal bleeding from a gastric or duodenal lesion in patients over 18 years of age (2,813 cases) to estimate the risk of upper gastrointestinal bleeding associated with the use of antiplatelet drugs and its prevention by gastroprotective agents, with 7,193 matched controls. Odds ratios of upper gastrointestinal bleeding for individual antiplatelet drugs with adjustment for potential confounders were estimated.

Index day, the day on which UGIB started

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; TIMI, Thrombolysis in myocardial infarction; UGIB, upper gastrointestinal bleeding

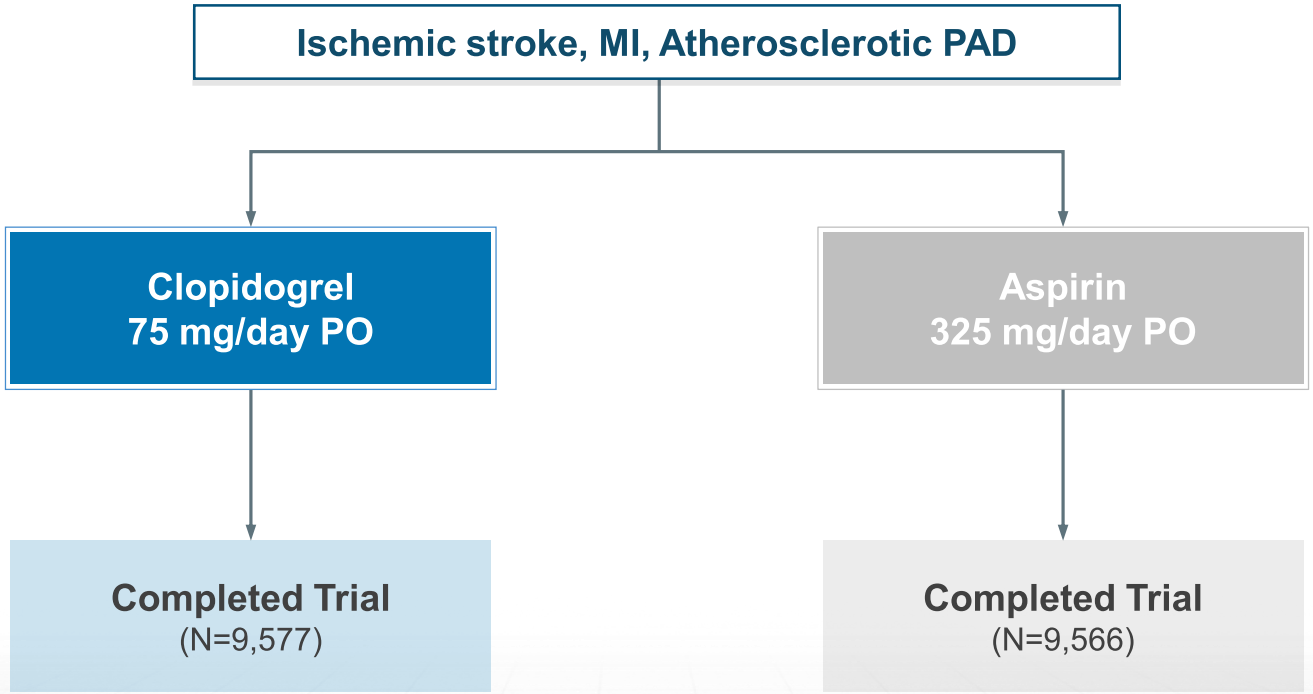
1. Ibáñez L, *et al.* Aliment Pharmacol Ther 2006;23: 235-242

Contents

CAPRIE
Head to Head Design

- **Design:** Multicenter, multinational, randomized, double-blind, parallel group

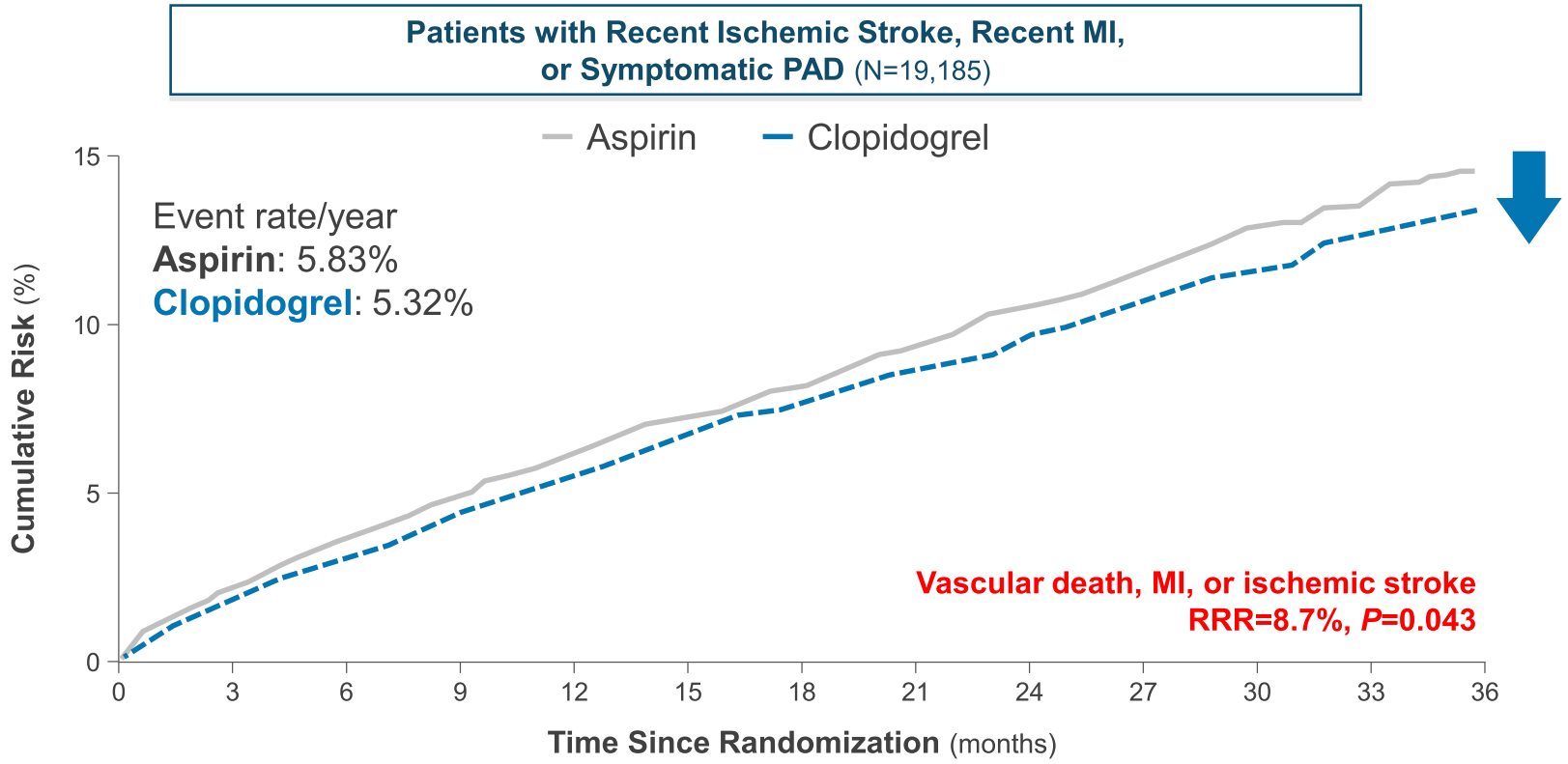
- **Patients:** 19,185 patients with atherosclerotic vascular disease
  (either recent ischemic stroke, recent MI or symptomatic peripheral arterial disease)



1. CAPRIE Steering Committee. Lancet 1996;348: 1329-1339.

CAPRIE
Efficacy of Clopidogrel

Clopidogrel reduced the long-term risk of ischemic events compared with ASA in a wide population of atherothrombotic patients (n=19,185)



Patients At Risk

Aspirin	9,586	9,190	8,087	6,139	3,979	2,143	542
Clopidogrel	9,599	9,247	8,131	6,160	4,053	2,170	539

1. CAPRIE Steering Committee. Lancet 1996;348: 1329-1339.

CAPRIE

Comparative Benefits of Clopidogrel in High-Risk Patient Populations

- **High-risk groups in the CAPRIE studies derived enhanced benefit with clopidogrel than with ASA.**

Enhanced Risk Reduction with Clopidogrel Therapy in High-Risk Patients in the CAPRIE Study

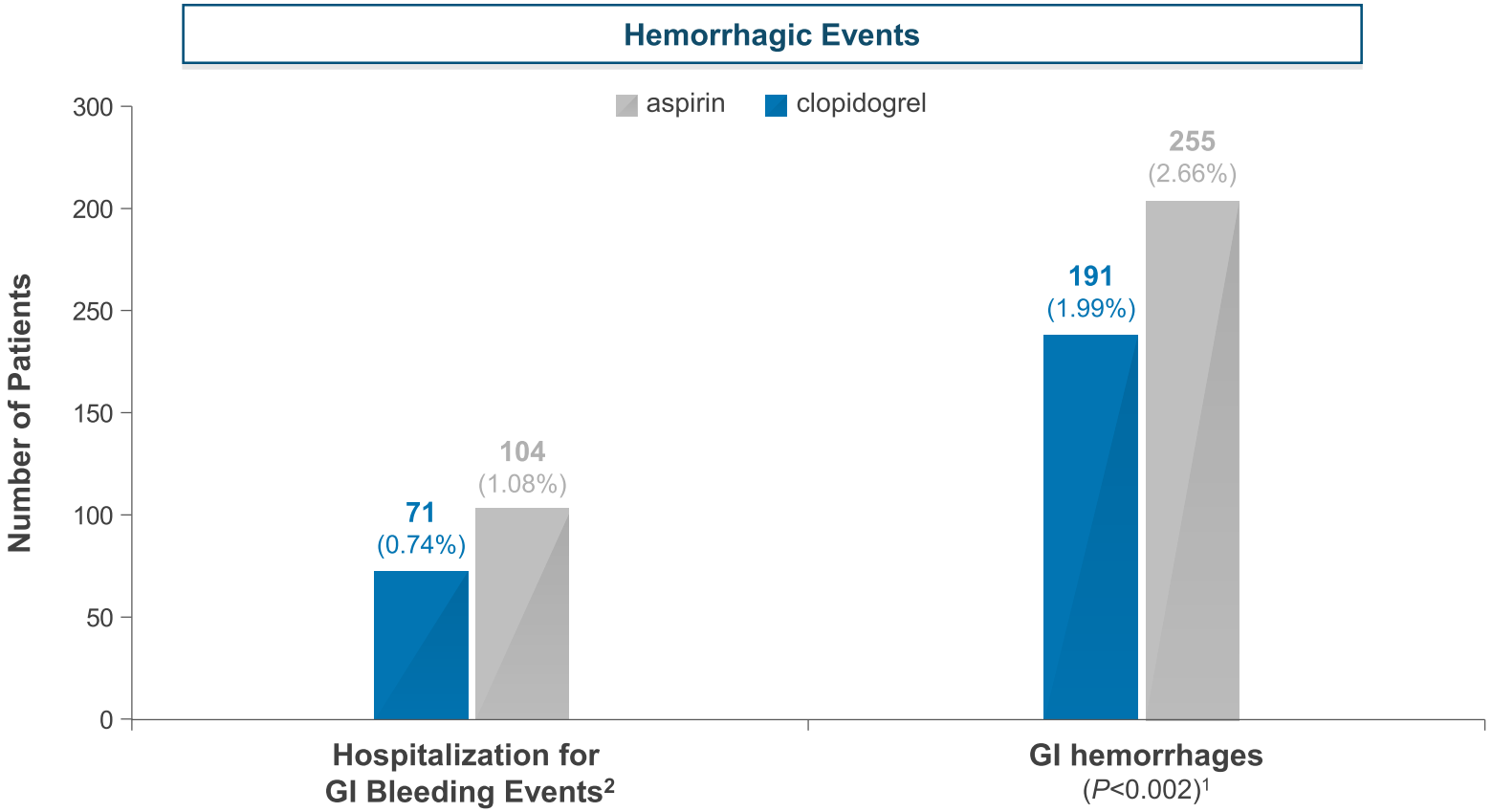
High-risk Population	Clopidogrel: ER, %	ASA: ER, %	Clopidogrel		
			RRR, %	ARR, %	NNT
Total CAPRIE population	12.57	13.67	7.9	1.1	91
Patients with previous CABG	15.9	22.3	**28.9**	6.4	16
Patients with a history of ≥1 ischemic event	18.4	20.4	**10.0**	2.0	50
Patients with involvement of multiple vascular beds	17.39	19.84	**12.4**	2.45	41
Patients with diabetes	15.6	17.7	**12.5**	2.1	48
Patients with hypercholesterolemia	12.3	13.6	9.7	1.3	77

ARR, absolute risk reduction, ER, event rate; NNT, number of patients needed to treat to prevent an event; RRR, relative risk reduction.

1. Hirsh J, Bhatt DL. Arch Intern Med 2004;164: 2106-10.

CAPRIE
Safety Profile

- **Trend to less cerebral hemorrhages, fatal or non-fatal, and less hemorrhagic deaths in clopidogrel group:** clopidogrel 37 compared to aspirin 51 (0.39% vs. 0.53%)[1]



1. CAPRIE Steering Committee. Lancet 1996;348: 1329-1339. **2.** Harker LA, *et al.* Drug Saf. 1999;21 (4):325-335

CAPRIE
Safety Profile

Adverse experiences†	Aspirin (n=9,586)	Clopidogrel (n=9,599)	*P*-value
Diarrhoea (severe)	0.11%	0.23%	NS
Gastritis	1.32%	0.75%	<0.001
GI ulcer	**1.15%**	**0.68%**	**<0.001**
GI hemorrhage (severe)	**0.71%**	**0.49%**	**<0.05**
Intracranial hemorrhage	0.49%	0.35%	NS
Rash (severe)	0.10%	0.26%	<0.05
Neutropenia	0.17%	0.10%	NS

*Patients with ASA intolerance were excluded
†Clinically severe or resulting in early drug discontinuation

1. CAPRIE Steering Committee. Lancet 1996;348: 1329-1339.
2. Harker LA, *et al*. Drug Safety 1992;21: 325-335.

CAPRIE
Limitations

CAPRIE trial showed the superiority of clopidogrel over aspirin in the pre-DES era

- ✓ No PCI patients was enrolled.
- ✓ No de-escalation from DAPT to SAPT

CAPRIE trial compared clopidogrel 75 mg vs. Aspirin 325 mg.

- ✓ Aspirin 100 mg is prescribed generally these days

Caucasian population mostly included.

- ✓ Genetic phenotype might affect the clinical outcomes of clopidogrel.

1. Levine GN, *et al.* J Am Coll Cardiol 2016;68: 1082-1115.
2. CAPRIE Steering Committee. Lancet 1996;348: 1329-1339.

Lifelong SAPT after PCI

1. Samsung Medical Center Registry
2. HOST-EXAM

Samsung Medical Center Registry Study

Clopidogrel compared to Aspirin after DAPT

Background

- The use of dual-antiplatelet therapy (DAPT) exceeding 12 months may increase a bleeding risk despite a lower risk of ischemic events.
- There is no study to compare clinical outcomes in patients treated with a single-antiplatelet drug after DAPT in the era of drug-eluting stents (DES).

Objective

- To investigate the efficacy and safety of clopidogrel versus aspirin monotherapy after 12-month DAPT after DES implantation using an institutional registry

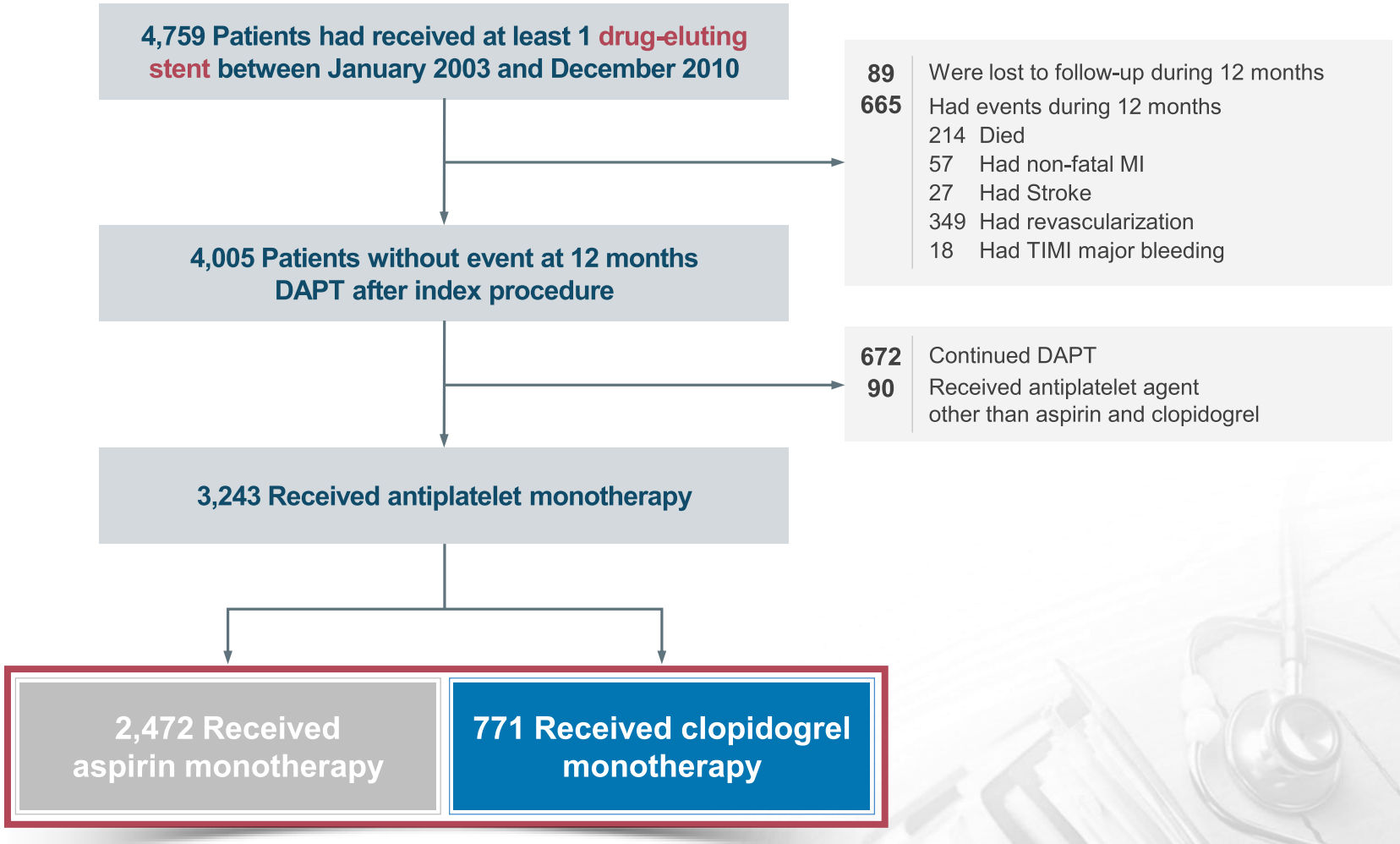
Method

- **Observational study**
- A total of 3,243 patients receiving 12-month DAPT after DES implantation without adverse clinical outcomes were divided into 2 groups based on prescribed antiplatelet status: aspirin (n=2,472) and clopidogrel (n=771)
- **Assessment conducted at 36 months after initiation**

1. Park TK, *et al*. Circ Cardiovasc Interv. 2016;9: e002816.

Samsung Medical Center Registry Study

Single Center, Observational Study



1. Park TK, *et al.* Circ Cardiovasc Interv. 2016;9: e002816.

Samsung Medical Center Registry Study

Baseline Clinical Characteristics between the 2 Groups

- **The clopidogrel group had a higher prevalence of old age, diabetes mellitus, hypertension, dyslipidemia, current smoking, chronic kidney disease, previous PCI, and previous stroke than the aspirin group**

	Aspirin (n=2,472)	Clopidogrel (n=771)	SMD, %	SMD, %, after IPTW
Age, y	**62** (53-69)	**64** (56-71)	19.9	7.0
Men	1,811 (73.3)	570 (73.9)	1.5	-2.0
Diabetes mellitus	**834** (33.7)	**325** (42.2)	17.0	5.6
Hypertension	**1,315** (53.2)	**497** (64.5)	23.5	2.7
Dyslipidemia	**705** (28.5)	**258** (33.5)	10.5	-2.2
Current smoking	429 (17.4)	174 (22.6)	12.5	-1.2
Chronic kidney disease	**199** (8.1)	**79** (10.2)	7.2	6.5
Previous myocardial infarction	469 (19.0)	142 (18.4)	-1.4	1.5
Previous PCI	243 (9.8)	109 (14.1)	12.4	1.1
Previous bypass surgery	63 (2.5)	26 (3.4)	4.6	1.7
Previous stroke	**79** (3.2)	**47** (6.1)	12.1	0.1
Clinical presentation				
Silent ischemia/stable angina	1,455 (58.9)	447 (58.0)	-1.8	6.3
UA/NSTEMI	654 (26.5)	241 (31.3)	10.4	-2.1
STEMI	363 (14.7)	83 (10.8)	-12.6	-6.9
LVEF, %*	62 (55-67)	62 (56-68)	6.3	9.4

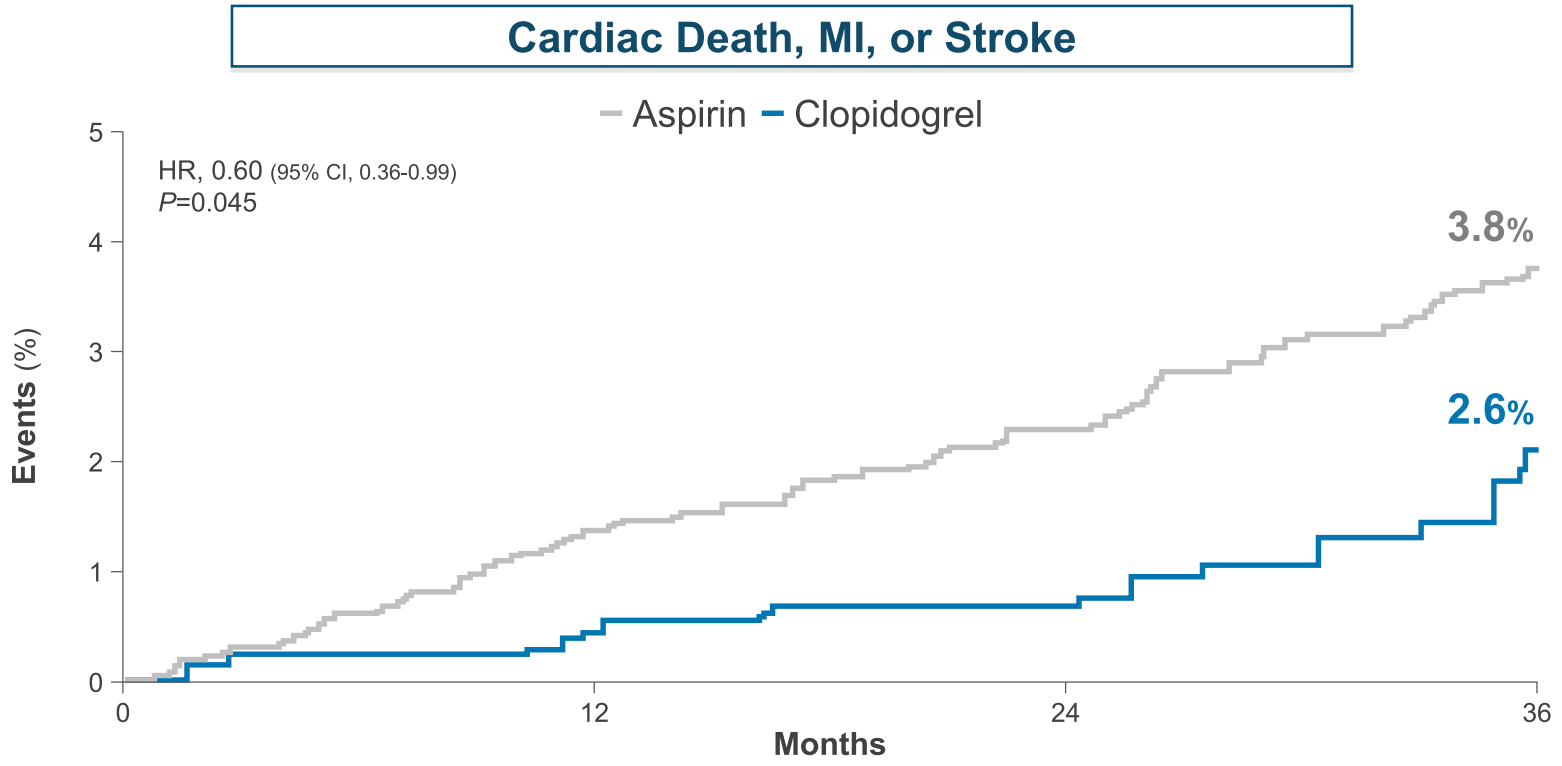
Data are median (25th-75th percentiles) or number of patients (%). IPTW indicates inverse probability of treatment weighting; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; SMD, standardized mean difference; STEMI, ST-segment- elevation myocardial infarction; and UA, unstable angina. *LVEF was available in 2,165 (87.6%) patients treated with aspirin and 699 (90.7%) patients treated with clopidogrel

1. Park TK, *et al.* Circ Cardiovasc Interv. 2016;9: e002816.

Samsung Medical Center Registry Study

Primary efficacy endpoint

- **At 36 months after initiation of antiplatelet monotherapy, the risk for a composite of Cardiac death, MI, or stroke was significantly lower in the clopidogrel group than in the aspirin group** (HR, 0.60; 95% CI, 0.36-0.99; *P*=0.045)



No. At Risk				
Aspirin	2,472	2,420	2,377	2,235
Clopidogrel	771	760	747	684

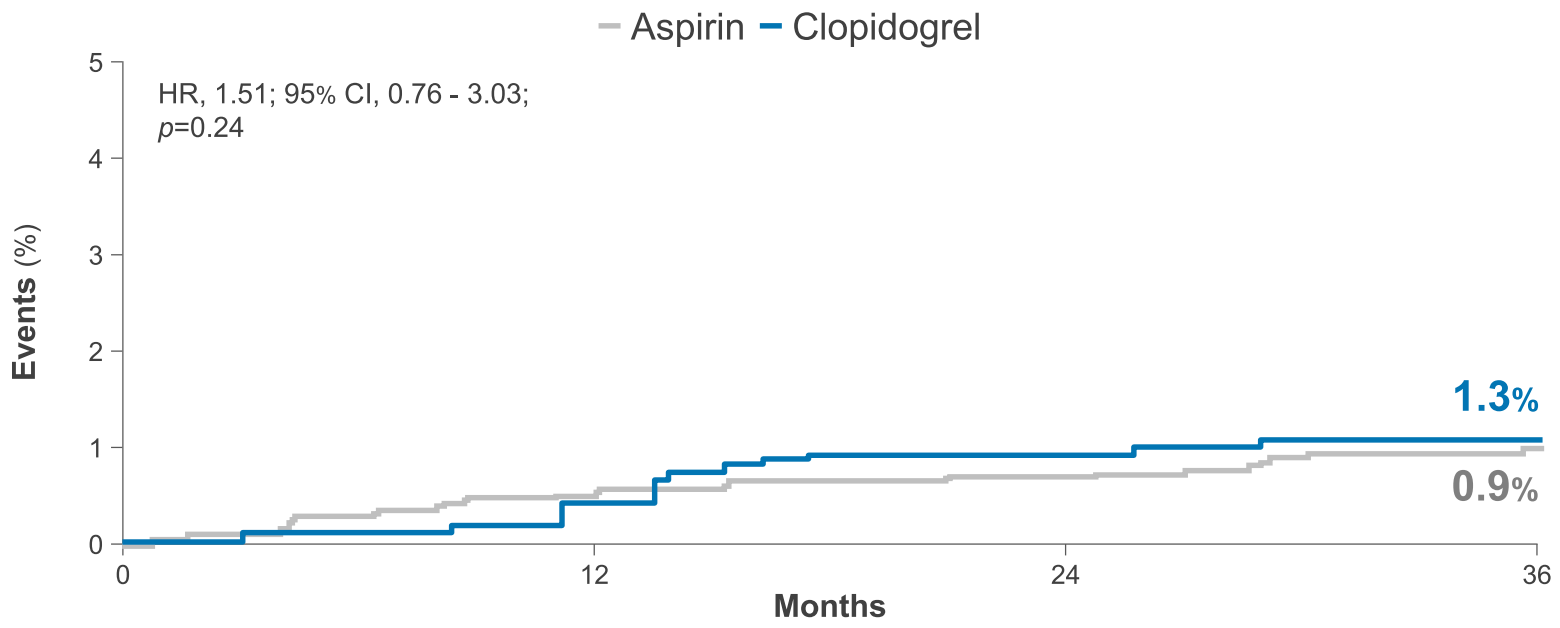
1. Park TK, *et al*. Circ Cardiovasc Interv. 2016;9: e002816.

Samsung Medical Center Registry Study

Bleeding End Points

- **Safety concerns on late bleeding should be considered when we select antiplatelet monotherapy. We observed no significant difference between aspirin and clopidogrel monotherapy in terms of TIMI major bleeding including fatal bleeding or intracranial bleeding. BARC type 3 or 5 bleeding also was simila between 2 groups.**

TIMI major bleeding



No. At Risk				
Aspirin	2,472	2,435	2,405	2,274
Clopidogrel	771	763	748	693

1. Park TK, *et al.* Circ Cardiovasc Interv. 2016;9: e002816.

Samsung Medical Center Registry Study

Clopidogrel with better efficacy was consistent across subgroups

There were no significant interactions between primary efficacy end point and several subgroups regardless of age, acute coronary syndrome, diabetes, current smoking status, stroke, multi-vessel disease, stent type, and PCI year.

Subgroup analysis

Subgroup	Patients	Cardiac death, MI, or Stroke (%)		Favor Clopidogrel	Favor Aspirin	Adjusted HR (95% CI)	*p* Value	*p* for Interaction
		Aspirin	Clopidogrel					
Age								
≥ 65 years	1,383	53/1,012 (5.2)	13/371 (3.5)			0.73 (0.40-1.34)	0.31	0.32
< 65 years	1,860	42/1,460 (2.9)	7/400 (1.8)			0.43 (0.15-1.27)	0.13	
ACS								
Yes	1,341	44/1,017 (4.3)	7/324 (2.2)			0.37 (0.14-1.03)	0.06	0.21
No	1,902	51/1,455 (3.5)	13/447 (2.9)			0.68 (0.35-1.33)	0.26	
DM								
Yes	1,159	45/834 (5.4)	9/325 (2.8)			0.63 (0.31-1.27)	0.19	0.78
No	2,084	50/1,638 (3.1)	11/446 (2.5)			0.61 (0.29-1.31)	0.21	
Current smoking								
Yes	603	12/429 (2,8)	2/174 (1.2)			0.41 (0.08-2.06)	0.28	0.56
No	2,640	83/2,043 (4.1)	18/597 (3.0)			0.62 (0.35-1.12)	0.11	
Stroke								
Yes	126	8/79 (10.1)	2/47 (4.3)			0.91 (0.25-3.26)	0.88	0.91
No	3,117	87/2,393 (3.6)	18/724(2.5)			0.60 (0.34-1.07)	0.08	
Multi-vessel disease								
Yes	1,833	64/1,363 (4.7)	13/470 (2.8)			0.67 (0.36-1.25)	0.21	0.78
No	1,410	31/1,109 (2.8)	7/301 (2.3)			0.45 (0.15-1.34)	0.15	
Type of stent								
SES/PES	1,835	73/1,590 (4.6)	7/245 (2.9)			0.33 (0.11-0.97)	0.04	0.19
EES/ZES/BES	1,408	22/882 (2.5)	13/526 (2.5)			1.03 (0.51-2.08)	0.94	
PCI year								
2003-2006	1,408	65/1,287 (5.1)	4/121 (3.3)			0.32 (0.08-1.28)	0.11	0.13
2007-2008	1,835	30/1,185 (2.5)	16/650 (2.5)			0.92 (0.50-1.71)	0.80	

1. Park TK, *et al*. Circ Cardiovasc Interv. 2016;9: e002816.

Samsung Medical Center Registry Study

Limitations

1

✓ A **retrospective analysis** of **observational data**.

✓ The choice of antiplatelet agent was **not randomly assigned** but was **selected** at the discretion of the attending physician.

2

✓ **Clinical events** were identified by the attending physicians, not assessed by an independent clinical events adjudication committee.

3

✓ **Statistical power** of this study might be low because of the **low event rates**. The rates of MI and ST were low when compared with adequately powered DAPT trial

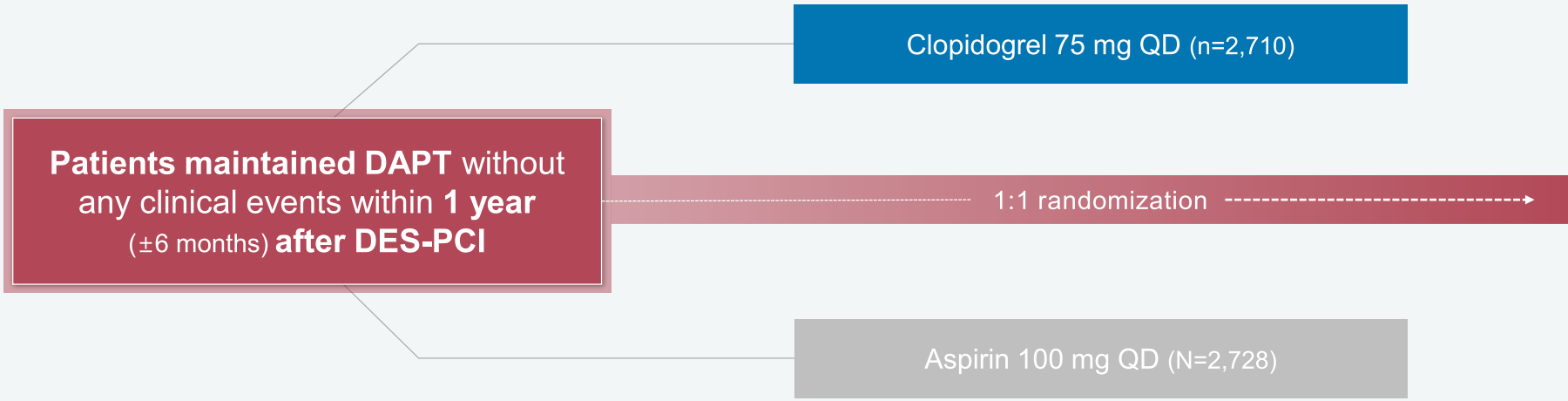
1. Park TK, *et al*. Circ Cardiovasc Interv. 2016;9: e002816.

HOST-EXAM

Aspirin versus clopidogrel for chronic maintenance monotherapy after PCI

Study Start Date: Feb 2014

- **Study design**: Investigator-initiated, prospective, randomized, open-label, multicenter trial
- **Objectives**:
  To compare the efficacy and safety **of clopidogrel monotherapy** with **aspirin monotherapy** in patients **who received dual antiplatelet therapy for 1 year** (±6 months) **after DES implantation** for coronary artery disease
- **Patient Enrollment**: 5,530 patients enrolled at 37 centers in Korea



DAPT, dual antiplatelet therapy; DES, drug-eluting stents; HOST-EXAM, Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; PCI, percutaneous coronary intervention; QD, once daily

1. Lee H, *et al*. Am Heart J. 2017;185:17-25
2. Koo BK *et al*. Lancet . 2021 May 14;S0140-6736 (21)01063-1

HOST-EXAM
Method

- **Patients aged 20 years or older who underwent PCI with DES and maintained DAPT without any clinical events within 6-18 months after PCI were eligible for this study.**
- **Patients with any ischemic and major bleeding complications** (ie, non-fatal MI, Any repeat revascularization, readmission due to a cardiovascular cause, and major bleeding) **were Excluded from randomization.**
- **Antiplatelet therapy before enrolment was composed of aspirin plus any $P2Y_{12}$ inhibitor.**

Primary Endpoint
- A composite of all-cause death, non-fatal MI, stroke, readmission due to ACS, and major bleeding complications during the 24-month follow-up period.
  Major bleeding was defined as BARC type bleeding of ≥3.

Secondary Endpoint
- The individual components of the primary endpoint, revascularization, and minor gastrointestinal complications were analyzed at 24 months

Post-hoc secondary composite endpoints
- The thrombotic composite endpoint (defined as cardiac death, non-fatal myocardial infarction, ischamic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis) and any bleeding (defined as BARC type ≥2 bleeding), were analysed.

DAPT, dual antiplatelet therapy; DES, drug-eluting stents; HOST-EXAM, Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; PCI, percutaneous coronary intervention

1. Lee H, *et al*. Am Heart J. 2017;185:17-25
2. Koo BK *et al*. Lancet . 2021 May 14;S0140-6736 (21)01063-1

HOST-EXAM

Baseline characteristics of the population

- **The two groups were well balanced for demographic, clinical, and procedural characteristics, and non-trial-related medications.**
- **The DAPT regimen before randomization was mainly aspirin plus clopidogrel** (4,430 [81.5%])**.**

Baseline characteristics of population by DAPT regimen and angiographic data per patient

		Clopidogrel (n=2,710)	**Aspirin** (n=2,728)
DAPT at the randomisation			
Aspirin plus clopidogrel		2,218 (81.8%)	2,212 (81.1%)
Aspirin plus ticagrelor		226 (9.8%)	268 (9.8%)
Aspirin plus prasugrel		212 (7.8%)	235 (8.6%)
Aspirin plus clopidogrel plus cilostazol		14 (0.5%)	13 (0.5%)
Angiographic data per patient			
Extent of CAD	One-vessel disease	1,367 (50.4%)	1,376 (50.4%)
	Two-vessel disease	855 (31.5%)	844 (30.9%)
	Three-vessel disease	488 (18.0%)	507 (18.6%)
Generation of DES	First generation DES	54 (2.0%)	52 (1.9%)
	Second generation DES	2,627 (96.9%)	2,651 (97.2%)
	Unknown generation	29 (1.1%)	25 (0.9%)

CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stents

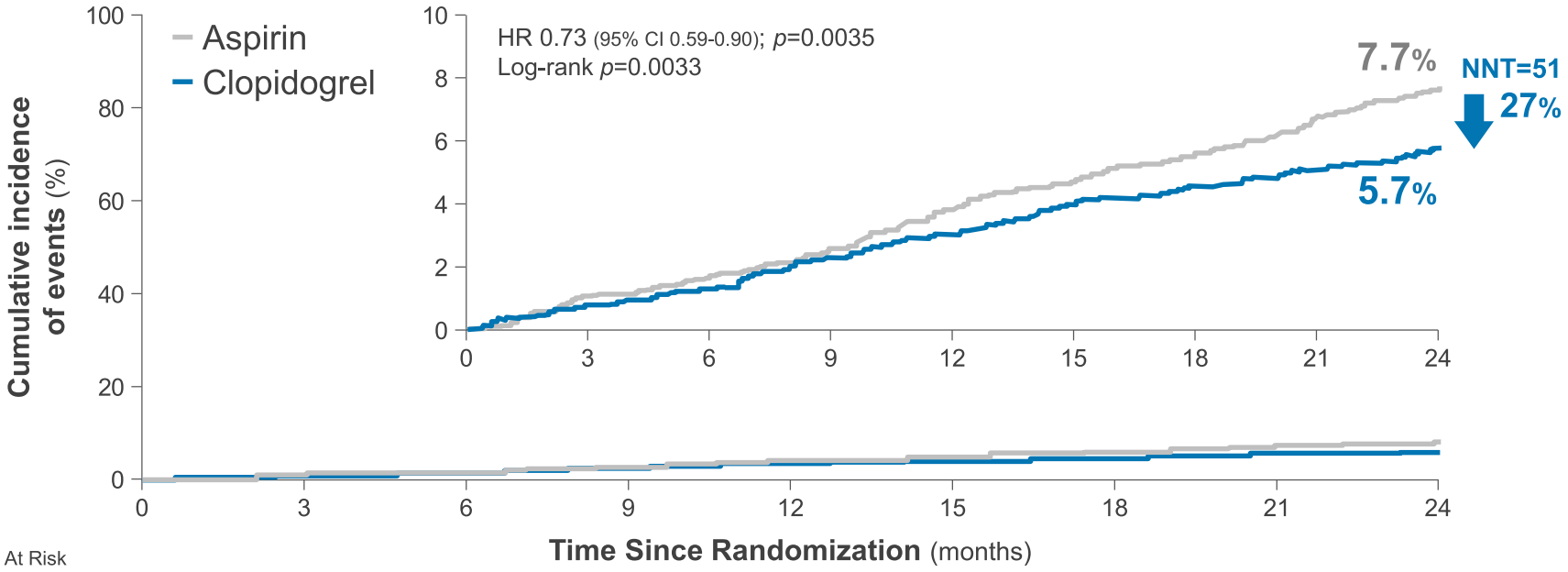
1. Koo BK *et al.* Lancet . 2021 May 14;S0140-6736 (21)01063-1

HOST-EXAM
Primary endpoint

During the 24-month follow-up, the primary endpoint occurred in 152 patients (5.7%) **who received clopidogrel monotherapy and in 207 patients** (7.7%) **who received aspirin monotherapy** (hazard ratio [HR] 0.73 [95% CI 0.59-0.90]; *p*=0.0035) **with an absolute risk reduction of 2.0%** (95% CI 0.6-3.3)**.**

The cumulative incidence of the secondary composite thrombotic endpoint

(All-cause death, non-fatal MI, stroke, readmission due to ACS, and major bleeding (BARC ≥3) complications)



No. At Risk (number censored)									
Aspirin	2,728 (0)	2,677 (22)	2,657 (22)	2,629 (24)	2,585 (40)	2,555 (48)	2,531 (49)	2,493 (64)	2,456 (66)
Clopidogrel	2,710 (0)	2,667 (23)	2,654 (26)	2,626 (24)	2,597 (33)	2,565 (41)	2,549 (43)	2,521(54)	2,500 (58)

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat

1. Koo BK *et al*. Lancet . 2021 May 14;S0140-6736(21)01063-1

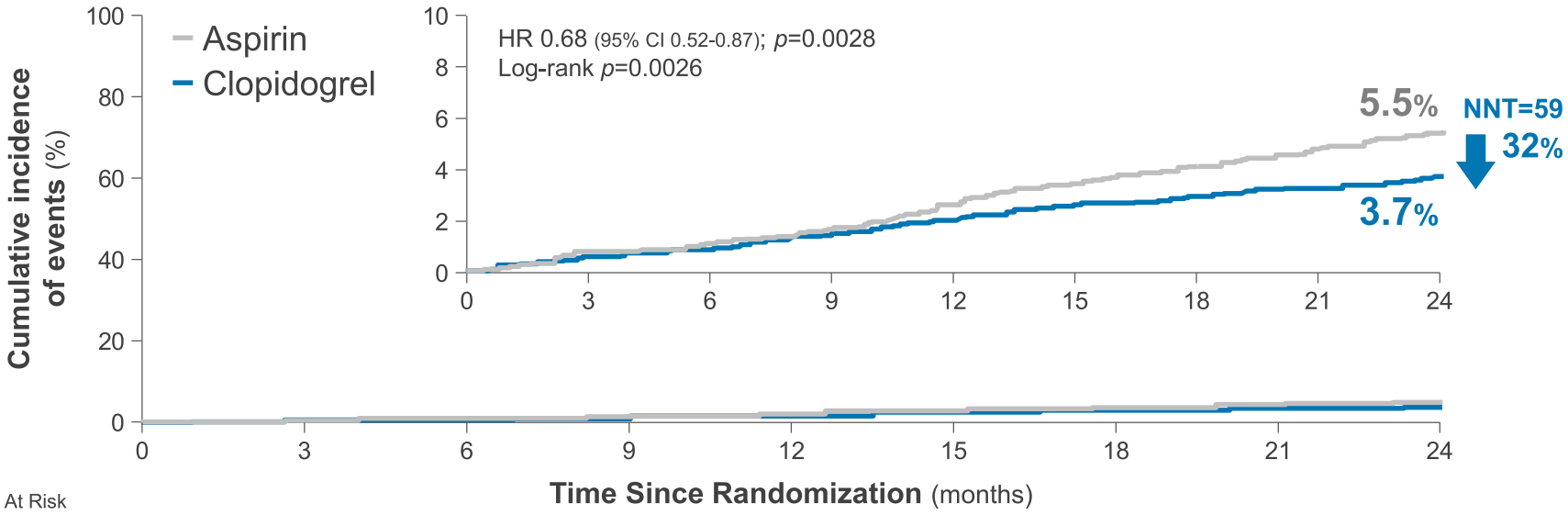
HOST-EXAM

Secondary composite thrombotic endpoint

The composite thrombotic endpoint of cardiac death, non-fatal MI, stroke, readmission due to ACS, or definite or probable ST occurred in 99 (3.7%) **patients in the clopidogrel group and 146** (5.5%) **patients in the aspirin group** (HR 0.68 [95% CI 0.52-0.87]; *p*=0.0028)**, for a difference in risk of 1.7%** (95% CI 0.6-2.8)**.**

The cumulative incidence of the secondary composite thrombotic endpoint

(Cardiac death, non-fatal MI, ischemic stroke, readmission due to ACS, or definite or probable ST)



No. At Risk (number censored)									
Aspirin	2,728 (0)	2,685 (23)	2,670 (28)	2,649 (35)	2,608 (49)	2,577 (59)	2,557 (64)	2,525 (82)	2,495 (87)
Clopidogrel	2,710 (0)	2,670 (25)	2,661 (26)	2,639 (34)	2,612 (46)	2,584 (58)	2,569 (64)	2,545 (79)	2,524 (86)

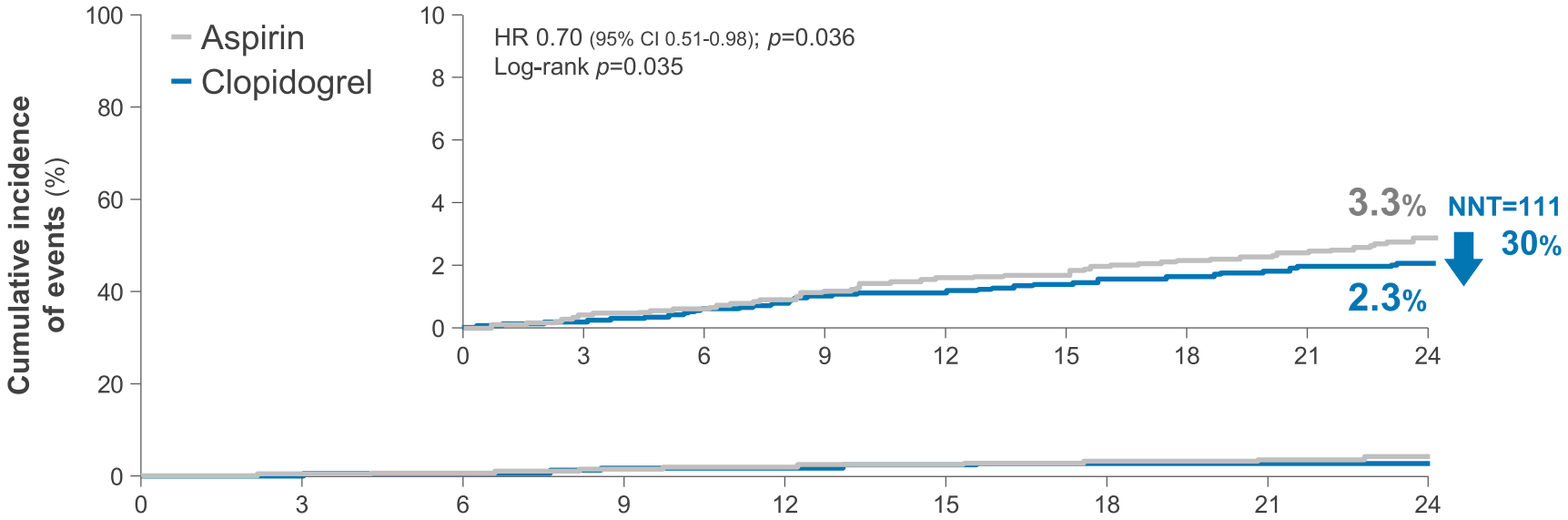
CI, confidence interval; HR, hazard ratio; NNT, number needed to treat

1. Koo BK *et al*. Lancet . 2021 May 14;S0140-6736(21)01063-1

HOST-EXAM
Any bleeding events

Any bleeding (BARC type ≥2) **occurred in 61** (2.3%) **patients in the clopidogrel group and 87** (3.3%) **patients in the aspirin group** (HR 0.70 [0.51-0.98]; *p*=0.036)**, for a difference in risk of 0.9%** (0.0-1.8)**.**

The cumulative incidence of any bleeding events (BARC type ≥2)



No. At Risk (number censored)

Aspirin	2,728 (0)	2,690 (26)	2,677 (31)	2,653 (39)	2,626 (54)	2,610 (65)	2,595 (67)	2,572 (85)	2,547 (93)
Clopidogrel	2,710 (0)	2,676 (28)	2,664 (29)	2,643 (37)	2,621 (56)	2,597 (72)	2,585 (77)	2,556 (98)	2,542 (105)

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat

1. Koo BK *et al*. Lancet . 2021 May 14;S0140-6736(21)01063-1

HOST-EXAM
Detailed Clinical Outcomes

	Clopidogrel (n=2,710)	**Aspirin** (n=2,728)
Primary composite endpoint	5·7% (152)	7·7% (207)
Thrombotic composite endpoint	3·7% (99)	5·5% (146)
Any bleeding (BARC type ≥2)	2·3% (61)	3·3% (87)
All-cause death	1·9% (51)	1·3% (36)
Cardiac death	0·7% (19)	0·5% (14)
Non-cardiac death	1·2% (32)	0·8% (22)
Non-fatal myocardial infarction	0·7% (18)	1·0% (28)
Stroke	0·7% (18)	1·6% (43)
Ischemic stroke	0·5% (14)	1·0% (26)
Hemorrhagic stroke	0·2% (4)	0·6% (17)
Readmission due to ACS	2·5% (66)	4·1% (109)
Unstable angina	1·8% (47)	3·0% (79)
Urgent revascularization	1·7% (44)	2·2% (58)
Major bleeding (BARC type ≥3)	1·2% (33)	2·0% (53)
Minor bleeding (BARC type 2)	1·1% (28)	1·3% (34)

1. Koo BK *et al*. Lancet. 2021 May 14;S0140-6736(21)01063-1

HOST-EXAM
Discussion

- The HOST-EXAM trial is **the first large-scale randomized controlled trial to compare clopidogrel with aspirin monotherapy** during the chronic maintenance period in patients who received stenting with DES and had successfully completed 6-18 months of DAPT without events.
- Compared with aspirin, **clopidogrel monotherapy was associated with a lower risk of the composite** of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding during the 24-month follow-up period.
- The benefit of clopidogrel monotherapy was obvious in **both thrombotic and bleeding endpoints.**
- The results were **consistent across major patient subgroups**, regardless of baseline clinical and angiographic characteristics.
- **Post-hoc subgroup analyses reported no significant interaction** between the treatment effect and various subgroups, such as the DES generation, duration from index PCI to randomization, and concomitant medications.
- Collectively, our results show that **clopidogrel monotherapy** compared with aspirin monotherapy provides **clinical benefit with fewer thrombotic and bleeding events**, when given in **the chronic maintenance period** for patients who received PCI with DES.

DAPT, dual antiplatelet therapy; DES, drug-eluting stents; PCI, percutaneous coronary intervention

1. Koo BK *et al*. Lancet. 2021 May 14;S0140-6736(21)01063-1

HOST-EXAM
Conclusions

- **Clopidogrel monotherapy, compared with aspirin monotherapy during the chronic maintenance period after PCI with DES significantly reduced the risk of the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC bleeding type ≥3.**
- **The benefit of clopidogrel monotherapy was observed in both thrombotic and bleeding endpoints.**
- **In patients requiring lifelong antiplatelet therapy after PCI, clopidogrel monotherapy was superior to aspirin monotherapy in preventing future adverse clinical events.**

BARC, Bleeding Academic Research Consortium; DES, drug-eluting stents; PCI, percutaneous coronary intervention

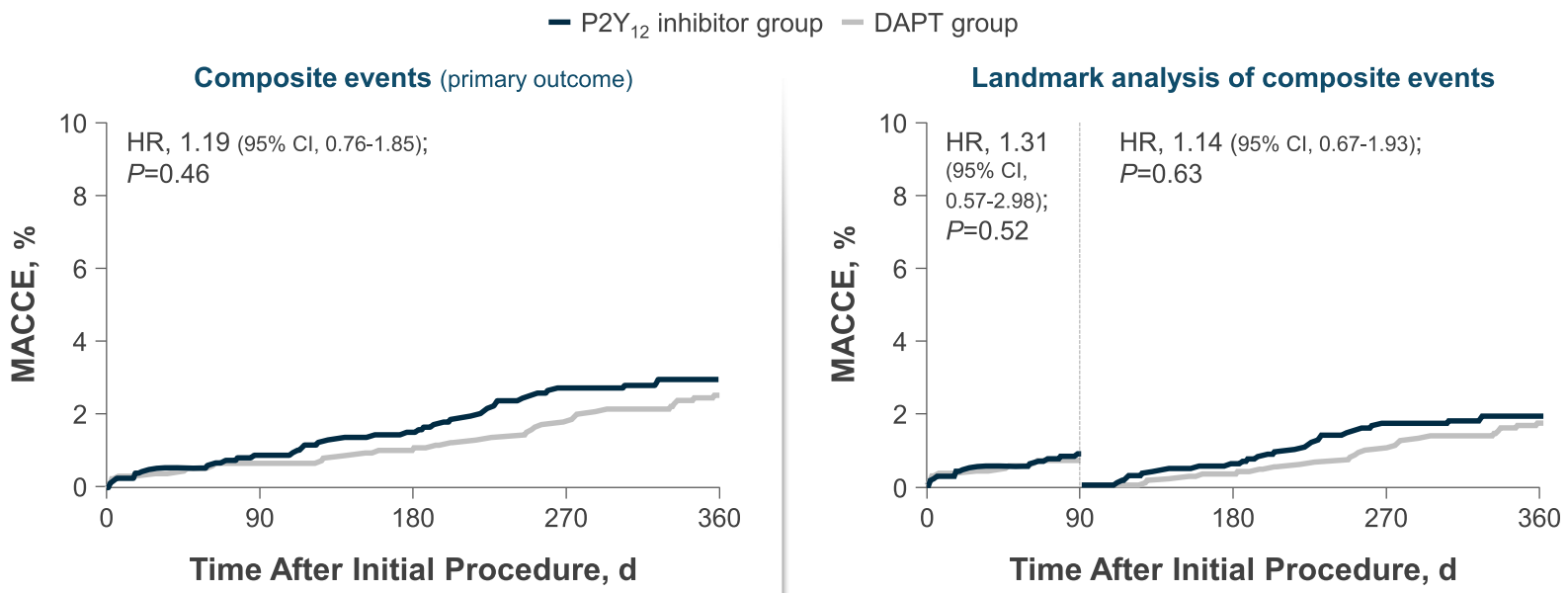
1. Koo BK *et al.* Lancet . 2021 ;S0140-6736(21)01063-1

SMART-CHOICE

Primary endpoint (A composite of all-cause death, myocardial infarction, or stroke)

- **At 12 months, MACCE occurred in 42 patients in the $P2Y_{12}$ inhibitor monotherapy group and in 36 patients in the DAPT group** (2.9% and 2.5%; 1-sided 95% CI, -∞%to 1.3%; *P*=0.007 for non-inferiority).

Time-to-Event Curves for the Major Adverse CV and CeV Events and Landmark Analysis at 3 Months



No. At Risk

DAPT	1,498	1,471	1,454	1,436	1,220	1,498	1,471	1,454	1,436	1,220
$P2Y_{12}$ inhibitor group	1,495	1,456	1,430	1,402	1,202	1,495	1,456	1,430	1,402	1,202

Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses. Hazard ratios are for the patients in the $P2Y_{12}$ inhibitor monotherapy group.; MACCE was defined as a composite of all-cause death, myocardial infarction, or stroke. Landmark analysis were performed at 3 months (the point after which one group received $P2Y_{12}$ inhibitor only and the other received DAPT). DAPT, dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events.

1. Hahn JY, *et al*. JAMA. 2019;321(24):2428-2437

Summary

- **Aspirin** is recommended as the **standard strategy**, however, there's **limited clinical evidence** directly comparing clopidogrel and aspirin after PCI updated guidelines.[1-3]
- The latest evidences showed that **clopidogrel** was associated with a better efficacy in reducing **thrombotic events** and the risk of **major bleeding** events than aspirin [4,5]

Given the favorable efficacy/safety ratio, clopidogrel can be considered as an antiplatelet agent for long-term use in patients after PCI[4,5]

1. Neumann FJ, *et al*. Eur Heart J. 2018. ;40(2):87-165. **2.** Knuuti J, *et al*. Eur Heart J. 2020;41(3):407-477 **3.** Collet JP, *et al*. Eur Heart J . 2020 ;42(14):1289-1367
4. CAPRIE Steering Committee. Lancet 1996;348: 1329-1339 **5.** Koo BK *et al*. Lancet. 2021 ;S0140-6736(21)01063-1.

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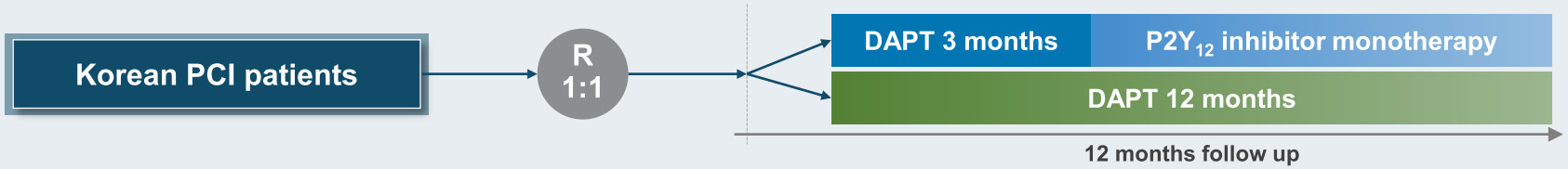
Thank You.

MAT-KR-2102401-1.0-01/2022

SMART-CHOICE

- An open-label, non-inferiority, randomized study that was conducted in 33 hospitals in Korea
- 2,993 patients undergoing PCI with drug-eluting stents.
- Patients were randomly assigned to receive aspirin plus a $P2Y_{12}$ inhibitor for 3 months and thereafter $P2Y_{12}$ inhibitor alone (n=1,495) or DAPT for 12 months (n=1,498).



- The primary end point was major adverse cardiac and cerebrovascular events (a composite of all-cause death, myocardial infarction, or stroke) at 12 months after the index procedure.
- Secondary end points included the components of the primary end point and bleeding defined as Bleeding Academic Research Consortium type 2 to 5.
- Adherence to the study protocol was 79.3% of the $P2Y_{12}$ inhibitor monotherapy group and 95.2% of the DAPT group.

Discharge $P2Y_{12}$ inhibitor

	$P2Y_{12}$ inhibitor monotherapy (n=1,495)	DAPT (n=1,498)
$P2Y_{12}$ receptor inhibitor	1,493/1,495 (99.9)	1,496/1,498 (99.9)
Clopidogrel	1,149/1,495 (76.9)	1,163/1,498 (77.6)
Prasugrel	62/1,495 (4.1)	67/1,498 (4.5)
Ticagrelor	284/1,495 (19.0)	268/1,498 (17.9)

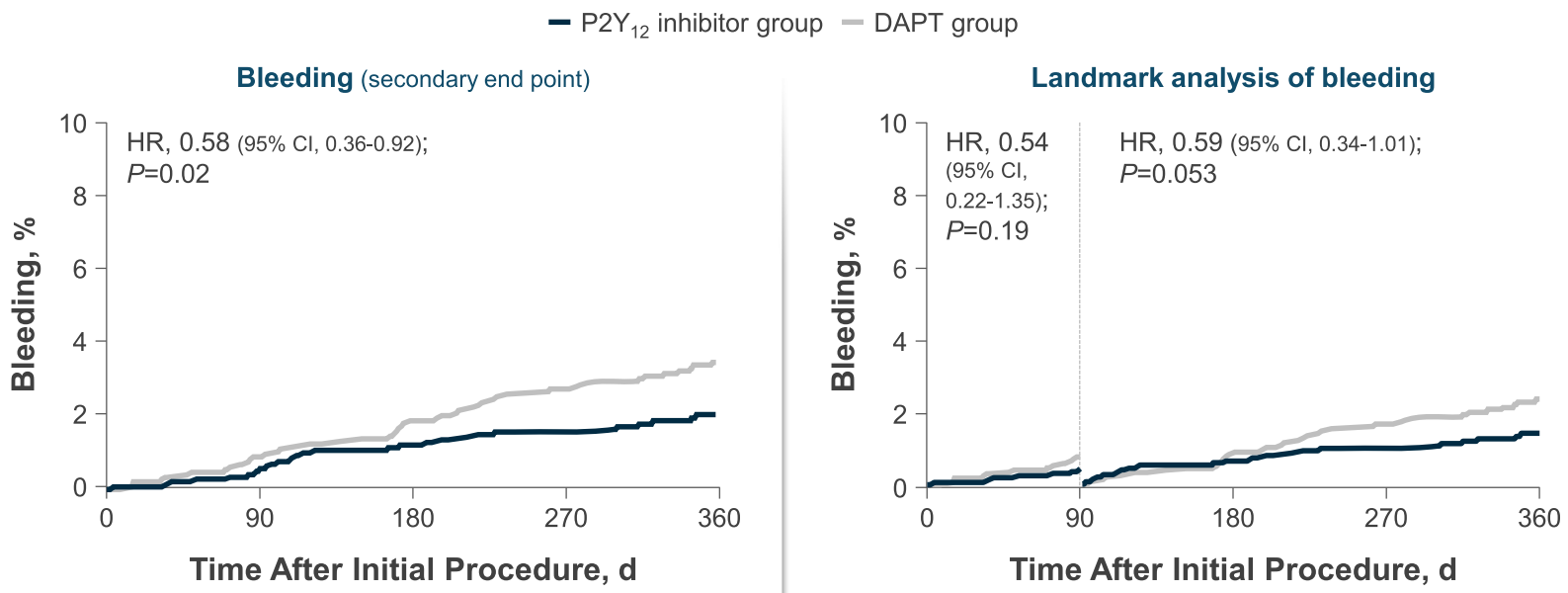
DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention

1. Hahn JY, *et al*. JAMA. 2019;321(24):2428-2437 and suppl.

SMART-CHOICE
Secondary end point

The rate of bleeding was significantly lower in the $P2Y_{12}$ inhibitor monotherapy group than in the 12-month DAPT group (2.0% and 3.4%; HR, 0.58; 95%CI, 0.36-0.92; *P*=0.02).

Time-to-Event Curves for the Bleeding and Landmark Analysis at 3 Months



No. At Risk

DAPT	1,498	1,461	1,435	1,413	1,197	1,498	1,461	1,435	1,413	1,197
$P2Y_{12}$ inhibitor group	1,495	1,456	1,425	1,400	1,198	1,495	1,456	1,425	1,400	1,198

Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses. Hazard ratios are for the patients in the $P2Y_{12}$ inhibitor monotherapy group. Landmark analysis were performed at 3 months (the point after which one group received $P2Y_{12}$ inhibitor only and the other received DAPT.; DAPT, dual antiplatelet therapy; HR, hazard ratio

1. Hahn JY, *et al.* JAMA. 2019;321(24):2428-2437