Aspirin vs. Clopidogrel for Chronic Maintenance Monotherapy after Percutaneous Coronary Intervention

The HOST-EXAM trial

Session of Late Breaking Clinical Trials Session III

ACC.21 Congress

Hyo-Soo Kim, MD/PhD
Cardiovascular Center,
Seoul National University Hospital, Korea

Disclosures

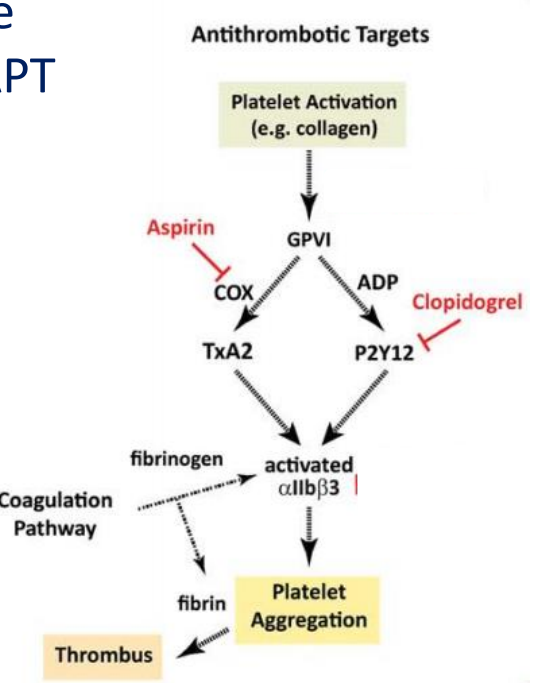
- *The **HOST-EXAM** trial,*
  - (***H**armonizing **O**ptimal **S**trategy for **T**reatment of coronary artery diseases – **EX**tended **A**ntiplatelet **M**onotherapy)*
  - *is an investigator-initiated, randomized, open-label, multicenter trial sponsored by Seoul National University Hospital*

- *The **HOST-EXAM** trial has received research funds from,*
  - *A consortium of four Pharmaceutical Companies*
    - *ChongKunDang, SamJin, HanMi, and DaeWoong*
  - *The Ministry of Health & Welfare, Republic of Korea*

Background

- After PCI (percutaneous coronary intervention), guidelines recommend indefinite maintenance of single antiplatelet therapy after the initial 6- to 12-months of DAPT (dual antiplatelet therapy).
- ***Aspirin*** is the most widely used, standard antiplatelet agent (LOE 1A).

Post-interventional and maintenance treatment		
Life-long single antiplatelet therapy, usually aspirin, is recommended.[681,683]	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 690–694]	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



- ***Clopidogrel*** is recommended as an alternative strategy.
  - Previous trials have shown that clopidogrel may have potential benefits **in patients with atherosclerotic vascular disease**.
- However, no trial has addressed which antiplatelet agent may be the optimal choice during the chronic maintenance period after PCI with DES.

Objective

- To compare the efficacy and safety between aspirin versus clopidogrel monotherapy as chronic maintenance therapy in patients who received PCI with a DES.

- **The HOST-EXAM trial**
  - ***H***armonizing ***O***ptimal ***S***trategy for ***T***reatment of coronary artery diseases
  - – ***EX***tended ***A***ntiplatelet ***M***onotherapy

Working Hypothesis

In the chronic maintenance period after PCI,
Clopidogrel will be superior to Aspirin,
In terms of patient oriented composite outcomes (POCO)

Endpoints and Sample Size Calculation

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- ***Endpoints***
  - ***Primary Endpoint: POCO (Patient Oriented Composite outcome) at 24 months***
    - All-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding complications (defined as Bleeding Academic Research Consortium (BARC) type ≥3 bleeding)
  - ***Key Secondary Endpoints***
    - ***Thrombotic composite endpoint***: Cardiac death, nonfatal myocardial infarction, ischemic stroke, readmission due to acute coronary syndrome and stent thrombosis
    - ***Any Bleeding endpoint***: BARC type ≥2 bleeding
- ***Sample size calculation***
  - Assumed 24-month POCO in the aspirin monotherapy group: 12.0%
  - Assumed 24-month POCO in the clopidogrel monotherapy group: 9.6%
  - Type I error: 0.05, Power: 80%
  - Estimated withdrawal rate: 5%

A total of 5,530 patients was needed to prove superiority of clopidogrel

Study Design and Patient Population

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- ***5,530 eligible patients screened, from 37 centers in Korea***

✓ ***Key criterias***

Patients who recieved PCI with a drug-eluting stent (DES) and maintained DAPT without any clinical event during 12 ± 6 months after PCI.

No exclusion criteria of the clinical risk factors / clinical diagnosis / complexity of the PCI

Inclusion Criteria
a) Subject must be ≥ 20 years b) Maintenance of DAPT for at least 12 ± 6 months after PCI with DES c) No history of clinical event after PCI with DES before enrollment d) Agreement to give written informed consent
Exclusion Criteria
a) Known hypersensitivity or contraindication to key medications b) Patients with active pathologic bleeding c) Female of childbearing potential, unless a pregnancy test is negative d) History of bleeding diathesis, known coagulopathy e) Non-cardiac co-morbid conditions with life expectancy <1 year

Randomization and Data Collection

- ***Randomization***
  - Eligible patients were centrally randomized, via a web-based randomization sequence (MRCC IWRS System) developed by the Medical Research Collaborating Center (Seoul, South Korea).
  - No blocking or stratification methods were applied.

- ***Data collection and management***
  - Data collected by a web-based electronic case report form (eCRF)
  - All clinical events were adjudicated by an independent event adjudication committee, who did not know the treatment allocations.

- ***Role of funding source***
  - The funders of this study had no role in study design, collection of data and data analysis, or writing of the manuscript.

Study Organization

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Principle Investigator

Hyo-Soo Kim

Steering Committee

Hyo-Soo Kim
Bon Kwon Koo
Eun-Seok Shin
Jung-Kyu Han

Clinical event adjudication committee

Woo Jin Jang
Ki-Hyun Jeon

Publication Committee

Hyo-Soo Kim
Bon Kwon Koo
Eun-Seok Shin
Seung-Woon Rha
Jang-Whan Bae
Kyung Woo Park
Jung-Kyu Han
Jeehoon Kang

Primary Statisticians

Jeehoon Kang
Jayoun Kim
Tae-Min Rhee

Data coordination and management

Medical Research Collaborating Center of Seoul National University Hospital

Sponsor: Seoul National University Hospital

Trial Flow

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Index PCI

Randomization

Primary outcome

All-cause death, nonfatal MI, stroke,
readmission due to ACS,
major bleeding (BARC type ≥3)

5530 patients enrolled

92 patients excluded from randomization
50 did not meet the eligibility criteria
28 declined participation
14 randomization error

5438 patients successfully randomized

2,710 patients enrolled in the Clopidogrel monotherapy group

2,728 patients enrolled in the Aspirin monotherapy group

62 patients excluded for Per protocol analysis
8 withdrew consent
41 were lost to follow up
13 did not receive allocated antiplatelet agent

73 patients excluded for Per protocol analysis
1 withdrew consent
50 were lost to follow up
22 did not receive allocated antiplatelet agent

2,661 (98.2%) patients completed 24-month follow-up

2,677 (98.1%) patients completed 24-month follow-up

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Baseline Profiles

		Clopidogrel (N = 2710)	Aspirin (N = 2728)
Demographics	Age, years	63.5 ± 10.7	63.4 ± 10.7
	Men	74.4% (2015)	74.7% (2039)
Comorbidities	Diabetes mellitus	34.1% (925)	34.3% (935)
	Hypertension	61.4% (1664)	61.4% (1674)
	Dyslipidemia	69.5% (1884)	69.0% (1883)
	Current smoker	20.1% (545)	21.3% (581)
	Chronic renal failure	13.1% (356)	12.4% (337)
	Previous MI	16.1% (437)	15.9% (435)
	Previous CVA	4.4% (120)	4.9% (133)
Clinical indication of PCI *(performed 6-18 months before randomization)*	Silent ischemia	2.1% (58)	2.6% (70)
	Stable angina	25.4% (688)	25.7% (701)
	Unstable angina	36.0% (975)	35.2% (959)
	Non-ST elevation MI	19.4% (526)	19.4% (528)
	ST elevation	17.1% (463)	17.2% (470)

Baseline Profiles

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		Clopidogrel (N = 2710)	Aspirin (N = 2728)
Days from PCI to randomization		383.0 (357.0-424.0)	380.0 (358.0-421.0)
DAPT just before Randomization	Aspirin plus clopidogrel	81.8% (2218)	81.1% (2212)
	Aspirin plus ticagrelor	9.8% (266)	9.8% (268)
	Aspirin plus prasugrel	7.8% (212)	8.6% (235)
	Others	0.5% (14)	0.5% (13)
Angiographic data per patient	1-vessel disease	50.4% (1367)	50.4% (1376)
	2-vessel disease	31.5% (855)	30.9% (844)
	3-vessel disease	18.0% (488)	18.6% (507)
	Left main disease	5.2% (142)	4.8% (130)
	PCI for bifurcation lesion	10.5% (285)	10.8% (295)
	PCI for CTO lesion	9.5% (257)	9.3% (254)
	Total length of implanted stents	36.1 ± 24.2	35.7 ± 23.6
	Total number of implanted stents	1.5 ± 0.8	1.5 ± 0.8

Primary Outcome

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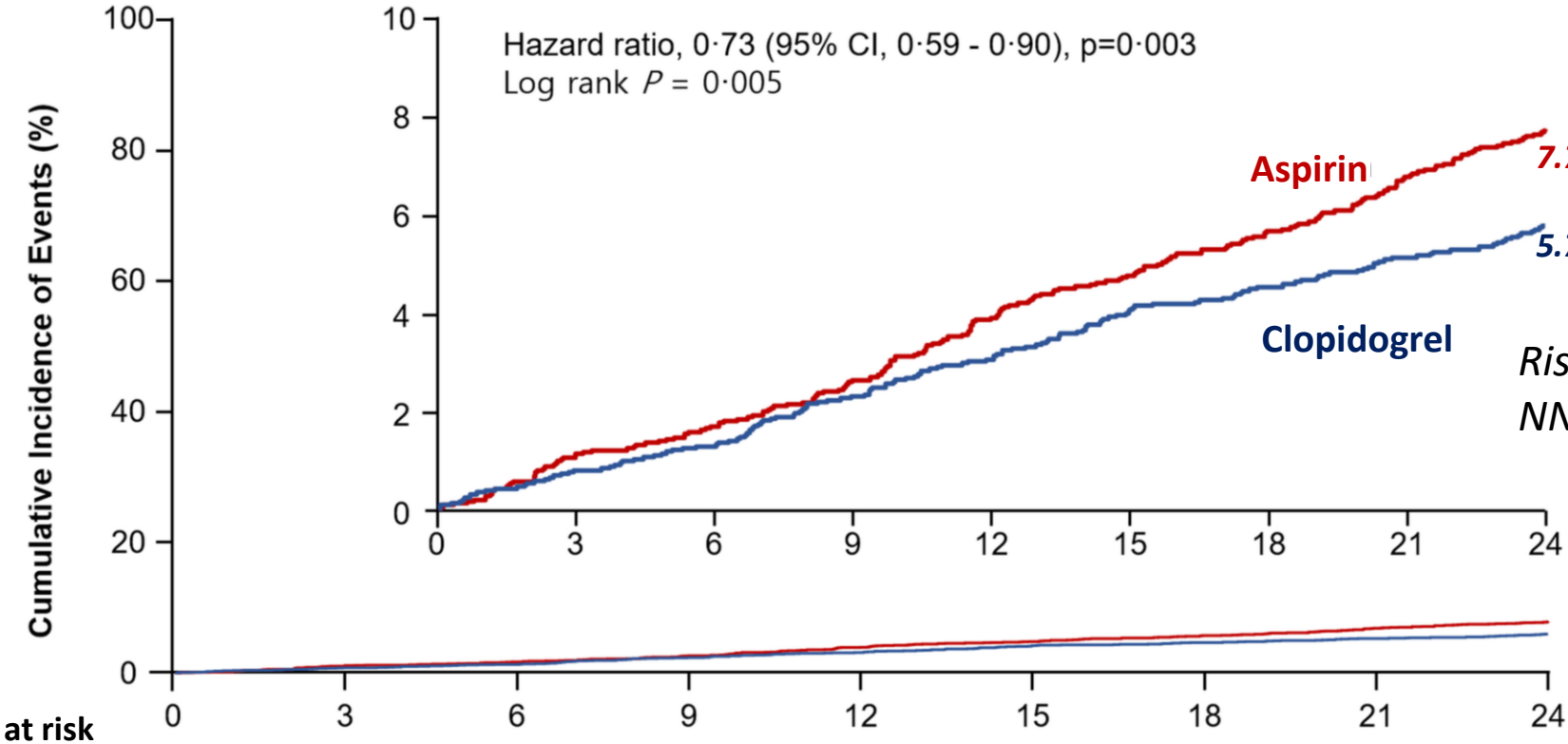
All-cause death, nonfatal MI, stroke, readmission due to ACS, major bleeding (BARC type ≥3)



7.7% (207 patients)

5.7% (152 patients)

Risk difference : -2.0% (-3.3% - 0.6%)

NNT : 50.6 (30.0 – 161.9)

Number at risk

Clopidogrel	2710	2667	2654	2626	2597	2565	2549	2521	2500
Aspirin	2728	2667	2657	2629	2585	2555	2531	2493	2456

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Secondary Outcomes

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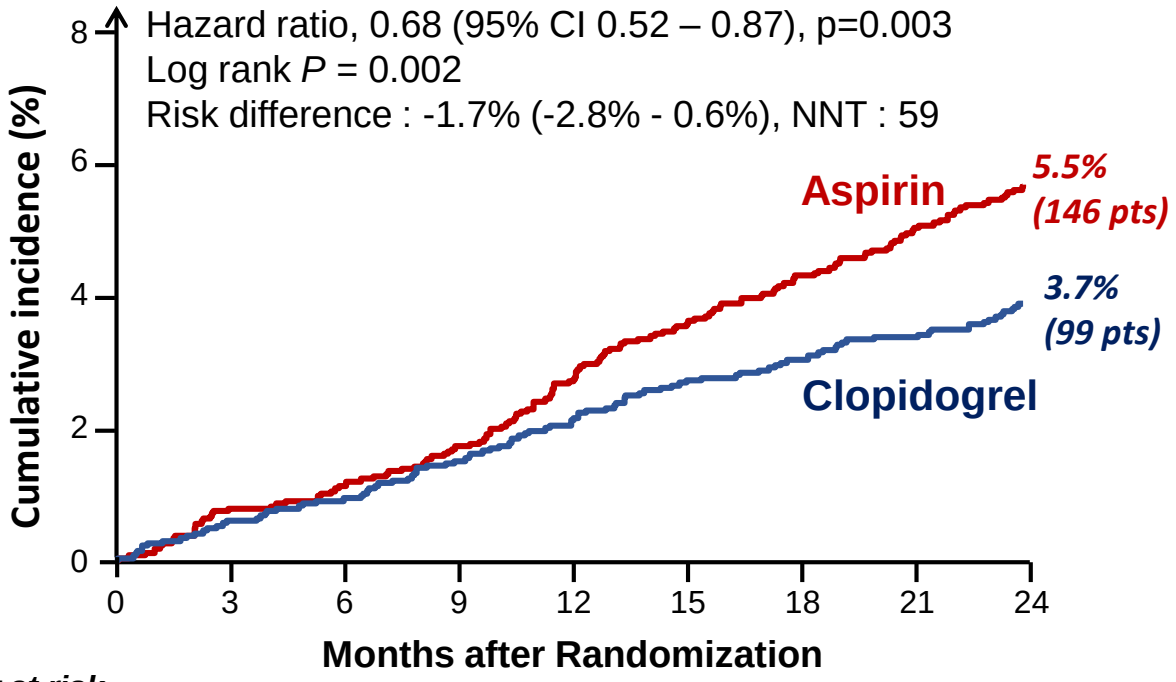
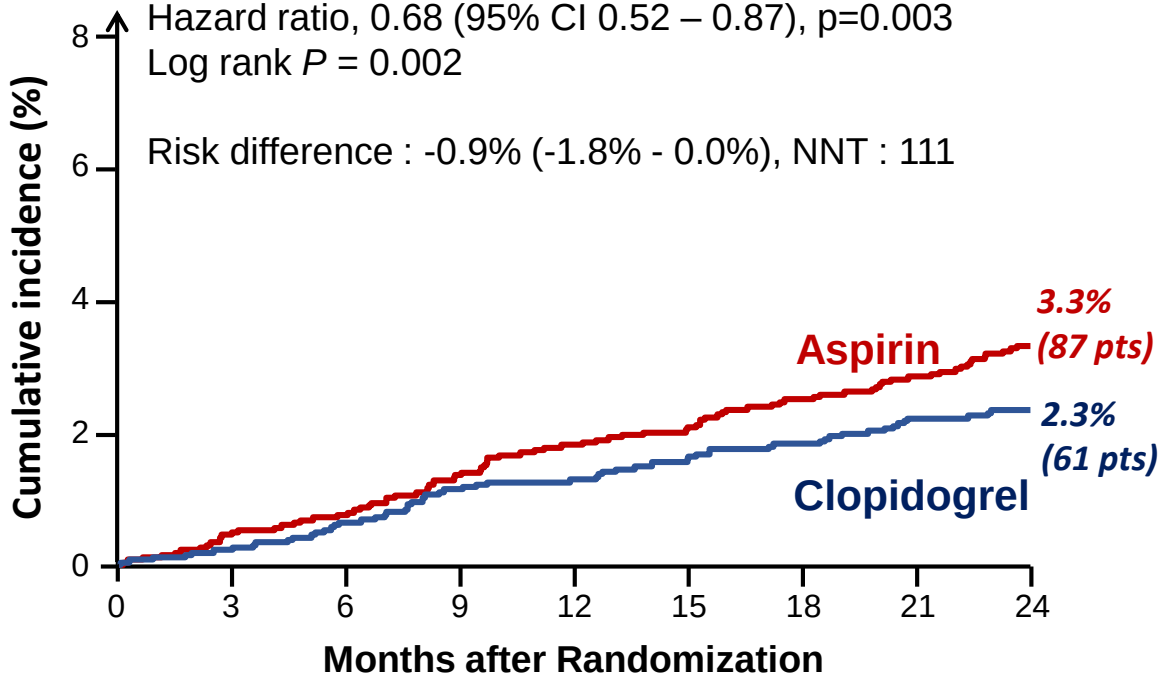
Thrombotic composite outcome

(cardiac death, non-fatal MI, ischemic stroke, readmission due to ACS, and definite or probable stent thrombosis)



Any bleeding

(BARC type ≥2 bleeding)



Number at risk

Clopidogrel	2710	2661	2612	2569	2524	2710	2664	2621	2585	2542
Aspirin	2728	2670	2608	2557	2495	2728	2677	2626	2595	2547

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Component of Outcomes for 2 years

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	Clopidogrel (n=2710)	Aspirin (n=2728)	Hazard Ratio (95% CI)	P value
	No. of patients (%)			
All-cause death	1.9% (51)	1.3% (36)	1.43 (0.93-2.19)	0.101
Cardiac death	0.7% (19)	0.5% (14)	1.37 (0.69-2.73)	0.374
Non-cardiac death	1.2% (32)	0.8% (22)	1.47 (0.85-2.52)	0.167
Non-fatal myocardial infarction	0.7% (18)	1.0% (28)	0.65 (0.36-1.17)	0.150
Stroke	0.7% (18)	1.6% (43)	0.42 (0.24-0.73)	0.002
Ischemic stroke	0.5% (14)	1.0% (26)	0.54 (0.28-1.04)	0.064
Hemorrhagic stroke	0.2% (4)	0.6% (17)	0.24 (0.08-0.70)	0.010
Readmission due to ACS	2.5% (66)	4.1% (109)	0.61 (0.45-0.82)	0.001
Major bleeding (BARC type ≥3)	1.2% (33)	2.0% (53)	0.63 (0.41-0.97)	0.035
Any revascularization	2.1% (56)	2.6% (69)	0.82 (0.57-1.16)	0.261
Target lesion revascularization	0.9% (24)	1.4% (36)	0.67 (0.40-1.12)	0.130
Target vessel revascularization	1.4% (37)	1.8% (48)	0.78 (0.50-1.19)	0.245
Definite or probable stent thrombosis	0.4% (10)	0.6% (16)	0.63 (0.29-1.39)	0.251
Any minor GI complaints	10.2% (272)	11.9% (320)	0.85 (0.72-1.00)	0.048

Cause of Mortality for 2 years

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(No. of patients)	Total	Clopidogrel group	Aspirin group	P value
Cardiac cause	33	19	14	0.374
- Cardiac arrest	18	11	7	0.338
- Unknown origin of death	15	8	7	0.786
Non-cardiac cause	54	32	22	0.217
- Cerebrovascular accident	10	6	4	0.520
- Malignancy	**29**	**18**	**11**	**0.186**
Gastrointestinal origin	12	8	4	
Respiratory origin	8	4	4	
Endocrinology origin	2	1	1	
Genitourinary origin	4	2	2	
Other	3	3	0	
- Infectious disease	9	4	5	0.746
- Suicide or Trauma	3	2	1	0.560
- Others	3	2	1	0.560

No significant interaction between the treatment effect and subgroups

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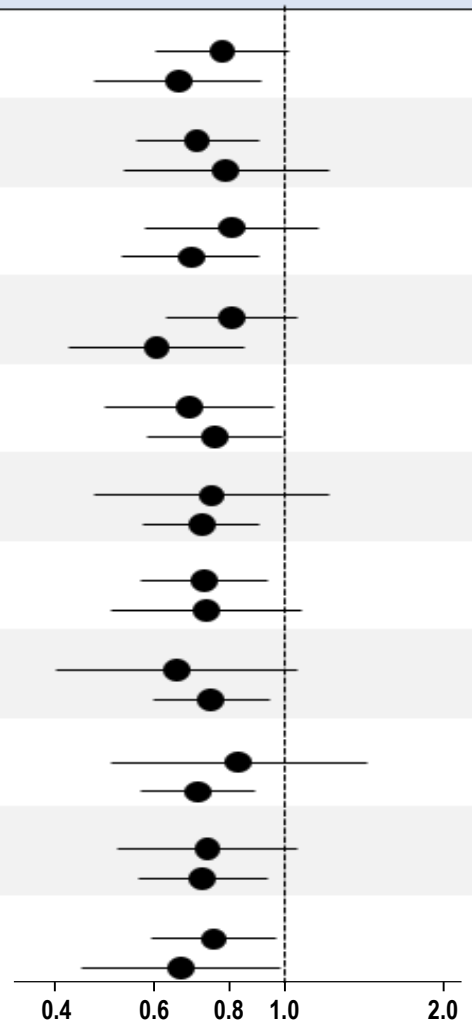
Subgroup	Clopidogrel (n=2710)	Aspirin (n=2728)	Hazard Ratio (95% CI)	P	Interaction P
	no. of events / total no. of patients				
Age (years)					
≥65	95/1177	121/1186	0.79 (0.60-1.03)	0.077	0.423
<65	57/1533	86/1542	0.66 (0.47-0.92)	0.015	
Sex					
Men	110/2015	155/2039	0.71 (0.56-0.91)	0.006	0.632
Women	42/695	52/689	0.80 (0.53-1.20)	0.275	
Body Mass Index					
≥25 kg/m²	60/1221	71/1178	0.81 (0.58-1.15)	0.239	0.477
<25 kg/m²	86/1391	127/1445	0.69 (0.53-0.91)	0.009	
Hypertension					
Yes	102/1664	125/1674	0.82 (0.63-1.06)	0.130	0.175
No	50/1046	82/1054	0.60 (0.42-0.86)	0.005	
Diabetes Mellitus					
Yes	58/925	84/935	0.69 (0.49-0.96)	0.030	0.651
No	94/1785	123/1793	0.76 (0.58-1.00)	0.046	
Chronic Kidney Disease					
Yes	31/356	39/337	0.75 (0.47-1.21)	0.237	0.885
No	121/2354	168/2391	0.72 (0.57-0.91)	0.007	
Dyslipidemia					
Yes	106/1884	144/1883	0.73 (0.57-0.94)	0.014	0.965
No	46/826	63/845	0.74 (0.50-1.08)	0.115	
Smoking					
Current smoker	27/545	43/581	0.66 (0.41-1.06)	0.086	0.619
Non-/Ex-smoker	125/2165	164/2147	0.75 (0.59-0.95)	0.016	
Previous history of MI					
Yes	27/437	32/435	0.84 (0.50-1.40)	0.499	0.573
No	125/2273	175/2293	0.71 (0.57-0.90)	0.004	
Acute Myocardial Infarction					
Yes	53/989	72/998	0.74 (0.52-1.06)	0.096	0.940
No	99/1721	135/1730	0.73 (0.56-0.94)	0.016	
Acute Coronary Syndrome					
Yes	112/1964	146/1957	0.76 (0.59-0.97)	0.028	0.584
No	40/746	61/771	0.67 (0.45-0.99)	0.045	



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No significant interaction between the treatment effect and subgroups

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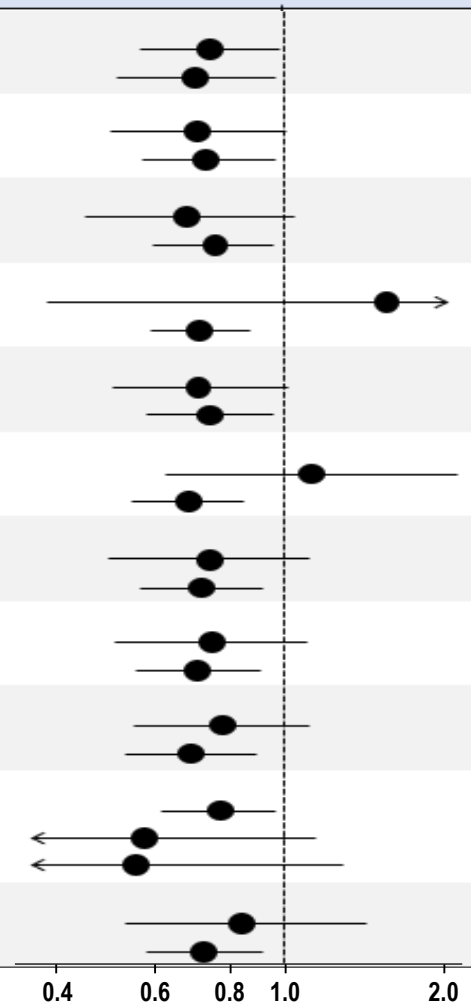
Subgroup	Clopidogrel (n=2710) no. of events / total no. of patients	Aspirin (n=2728) no. of events / total no. of patients	Hazard Ratio (95% CI)	P	Interaction P
Multivessel Disease					
Yes	86/1343	114/1351	0.75 (0.57-0.99)	0.045	0.785
No	66/1367	93/1376	0.71 (0.52-0.97)	0.032	
Complex PCI					
Yes	33/598	49/595	0.71 (0.50-1.02)	0.063	0.854
No	118/2091	109/1832	0.74 (0.57-0.96)	0.024	
High bleeding risk					
Yes	46/521	66/467	0.67 (0.43-1.04)	0.072	0.655
No	118/2091	158/2114	0.75 (0.59-0.95)	0.016	
Generation of DES					
1st generation DES	5/54	3/52	1.63 (0.39-6.84)	0.502	0.254
2nd generation DES	146/2627	204/1376	0.71 (0.58-0.88)	0.002	
Time from index PCI					
< 365 days	51/852	73/882	0.71 (0.50-1.02)	0.063	0.854
≥ 365 days	101/1857	134/1844	0.74 (0.57-0.96)	0.024	
PCI for Bifurcation Lesion					
Yes	24/285	22/295	1.12 (0.63-2.00)	0.692	0.120
No	128/2425	185/2433	0.69 (0.55-0.86)	0.001	
Number of treated lesions					
≥2 treated lesions	42/692	56/691	0.75 (0.50-1.12)	0.155	0.896
<2 treated lesions	110/2018	151/2035	0.73 (0.57-0.93)	0.010	
Total length of stents					
>40 mm	47/749	59/713	0.75 (0.51-1.11)	0.149	0.818
≤40 mm	104/1940	148/1995	0.71 (0.56-0.92)	0.009	
Total number of stents					
≥2 stents	56/907	69/879	0.79 (0.55-1.12)	0.180	0.589
<2 stents	95/1783	138/1829	0.70 (0.54-0.90)	0.007	
P2Y12 inhibitor usage before randomization					
Clopidogrel	132/2218	169/2212	0.77 (0.61-0.97)	0.026	0.430
Ticagrelor	12/266	21/268	0.57 (0.28-1.16)	0.122	
Prasugrel	8/212	16/235	0.55 (0.23-1.27)	0.162	
PPI usage					
Yes	29/290	39/331	0.84 (0.52-1.35)	0.463	0.580
No	123/2420	168/2397	0.72 (0.57-0.91)	0.005	



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Per-protocol Analysis

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5438 patients successfully randomized

2,710 patients in the Clopidogrel group

2,728 patients in the Aspirin group

62 patients excluded for Per protocol analysis
8 withdrew consent
41 were lost to follow up
13 did not receive allocated antiplatelet agent

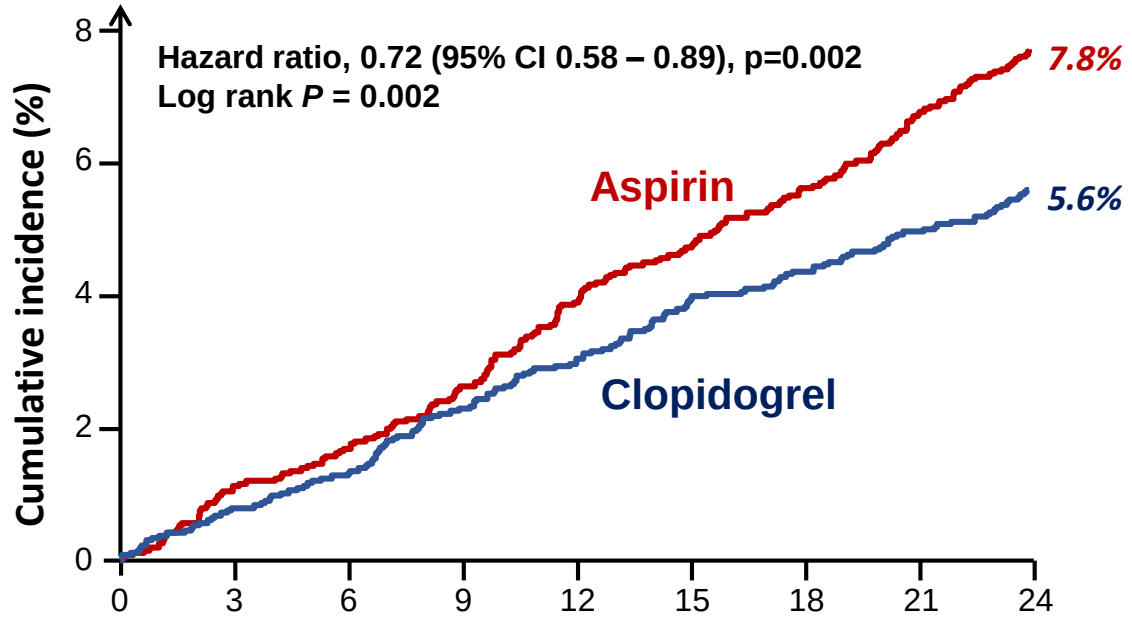
73 patients excluded for Per protocol analysis
1 withdrew consent
50 were lost to follow up
22 did not receive allocated antiplatelet agent

2,648 in the per-protocol analysis

2,655 in the per-protocol analysis

Primary Outcome

All-cause death, nonfatal MI, stroke, readmission due to ACS, major bleeding (BARC type ≥3)



Number at risk

Clopidogrel	2648	2614	2570	2532	2498
Aspirin	2655	2610	2551	2507	2448

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Limitation

- ✓ ***The open-label design***: potential for bias in outcome reporting and ascertainment
  - ✓ All clinical events were adjudicated by an CEAC that was unaware of the treatment group.
  - ✓ Periodic monitoring was performed in more than 80%, and the Vital status was double-checked based on national databases.
- ✓ ***Phenotypic and genetic testing for clopidogrel*** was not performed
  - ✓ Despite the high prevalence of LOF mutations of the CYP2C19 gene, thrombotic event rates are lower in East Asians (East Asian paradox).
- ✓ ***A follow-up duration of 24 months*** may be too short to give a concrete conclusion
  - ✓ We have launched the "***HOST-EXAM Extended study***" for extending follow-up to median 10 years.
- ✓ Enrolled patients were ***event-free*** under DAPT for around one year after PCI
  - ✓ Difficult to extrapolate the result to those who use a shorter DAPT (i.e. 1 month or 3 months DAPT).
  - ✓ Difficult to extrapolate the result to oral anticoagulants users

Conclusion

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EXtended Antiplatelet Monotherapy

In patients who were ***event-free*** under DAPT for 6~18 months after ***PCI with DES***,

- ***Clopidogrel monotherapy,*** as compared with ***Aspirin monotherapy,*** significantly reduced the risk of the composite of all-cause death, nonfatal MI, stroke, readmission due to ACS, and BARC type ≥3 bleeding.

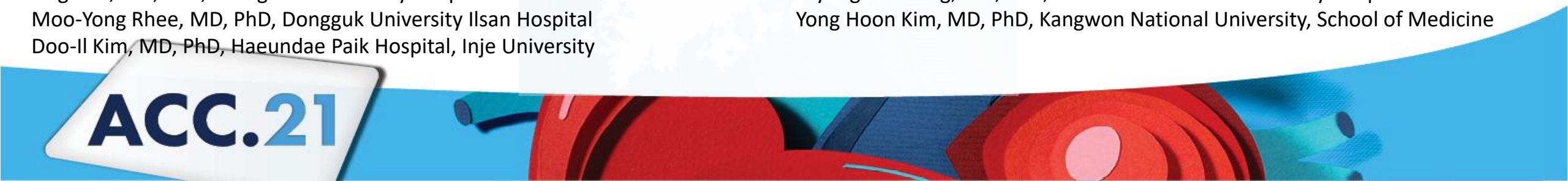
- The beneficial effect of clopidogrel was observed in ***thrombotic composite endpoints*** as well as ***any bleeding endpoint.***

- ***Long-term follow-up of this cohort*** will give us the concrete conclusion on the optimal single agent during the chronic maintenance period after PCI with DES.

Thank you for your kind attention

We thank all investigators of **the HOST-EXAM RCT**

Ki-Bum Won, MD, PhD, Ulsan University Hospital
Eun-Seok Shin, MD, PhD, Ulsan University Hospital
Seung-Woon Rha, MD, PhD, Korea University Guro Hospital
Jang-Whan Bae, MD, PhD, Chungbuk National University College of Medicine
Nam Ho Lee, MD, PhD, Kangnam Sacred Heart Hospital, Hallym University
Seung-Ho Hur, MD, PhD, Keimyung University Dongsan Hospital
Junghan Yoon, MD, PhD, Yonsei University Wonju Severance Christian Hospital
Tae-Ho Park, MD, PhD, Dong-A University Hospital
Bum Soo Kim, MD, PhD, Kangbuk Samsung Hospital, Sungkyunkwan University
Sang Wook Lim, MD, PhD, CHA Bundang Medical Center, CHA University
Yoon Haeng Cho, MD, PhD, Soonchunhyang University Bucheon Hospital
Dong Woon Jeon, MD, PhD, National Health Insurance Service Ilsan Hospital
Sang-Hyun Kim, MD, PhD, Boramae Medical Center
Kyoo-Rok Han, MD, PhD, Kangdong Sacred Heart Hospital, Hallym University
Keon-Woong Moon, MD, PhD, St.Vincent's Hospital, The Catholic University
Seok Kyu Oh, MD, PhD, Wonkwang University Hospital
Ung Kim, MD, PhD, Yeungnam University Hospital
Moo-Yong Rhee, MD, PhD, Dongguk University Ilsan Hospital
Doo-Il Kim, MD, PhD, Haeundae Paik Hospital, Inje University
Song-Yi Kim, MD, PhD, College of Medicine, Jeju National University
Sung-Yun Lee, MD, PhD, Ilsan Paik Hospital, Inje University, Ilsan
Seung Uk Lee, MD, PhD, Kwangju Christian Hospital
Sang-Wook Kim, MD, PhD, Chung-Ang University Hospital
Seok Yeon Kim, MD, PhD, Seoul Medical Center
Hui-Kyung Jeon, MD, PhD, Uijeongbu St. Mary's Hospital
Kwang Soo Cha, MD, PhD, Pusan National University School of Medicine
Sang-Ho Jo, MD, PhD, Hallym University Sacred Heart Hospital
Jae Kean Ryu, MD, PhD, Daegu Catholic University Medical Center
Il-Woo Suh, MD, PhD, Anyang SAM Medical Center
Hyun-Hee Choi, MD, PhD, Chuncheon Sacred Heart Hospital, Hallym University
Seoung-Il Woo, MD, PhD, Inha University Hospital
In-Ho Chae, MD, PhD, Seoul National University Bundang Hospital
Won-Yong Shin, MD, PhD, Soonchunhyang University Cheonan Hospital
Dae-Kyeong Kim, MD, PhD, Busan Paik Hospital, Inje University
Ju Hyeon Oh, MD, PhD, Samsung Changwon Hospital, Sungkyunkwan University
Myung Ho Jeong, MD, PhD, Chonnam National University Hospital
Yong Hoon Kim, MD, PhD, Kangwon National University, School of Medicine



Aspirin vs. Clopidogrel for Chronic Maintenance Monotherapy after Percutaneous Coronary Intervention

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Hyo-Soo Kim, MD/PhD
Cardiovascular Center,
Seoul National University Hospital, Korea

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