Lifelong Antiplatelet Therapy after PCI for Prevention of Ischemic Events

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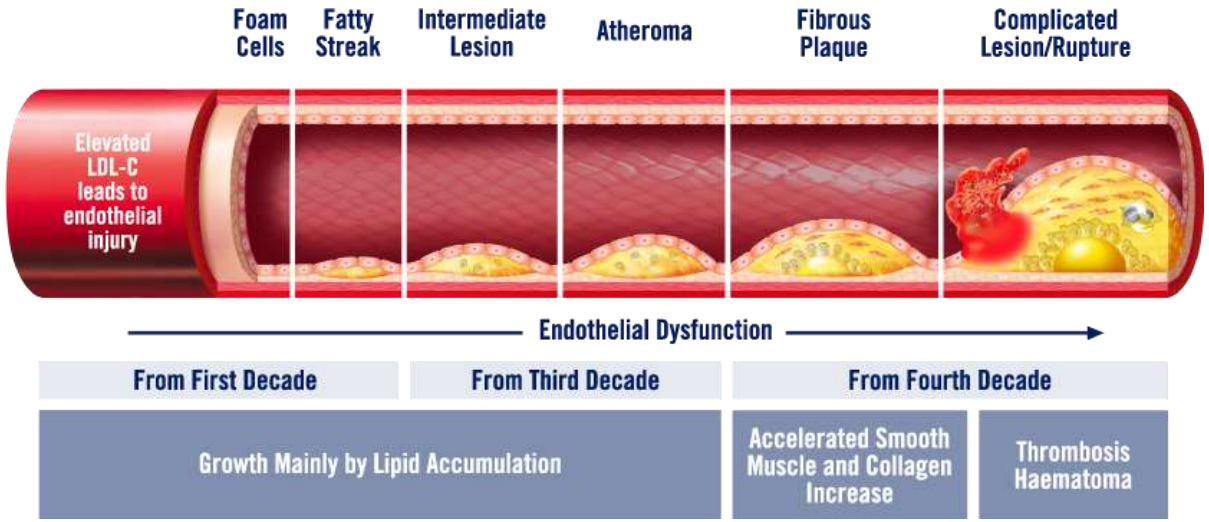
PCI and antiplatelet therapy, and the bleeding risk

- **PCI for Coronary artery disease**
  - Treating ***thrombotic lesions*** with a potentially ***thrombotic material***

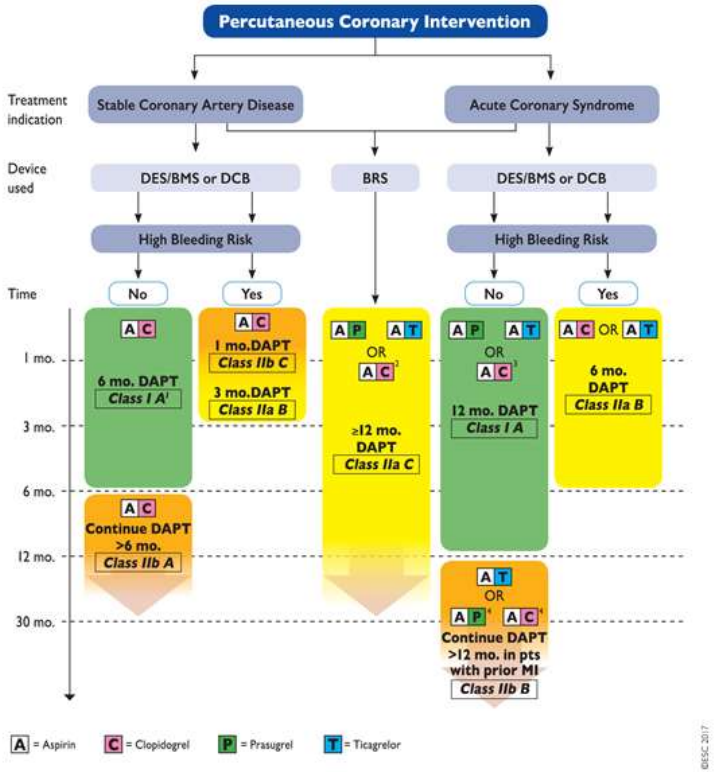


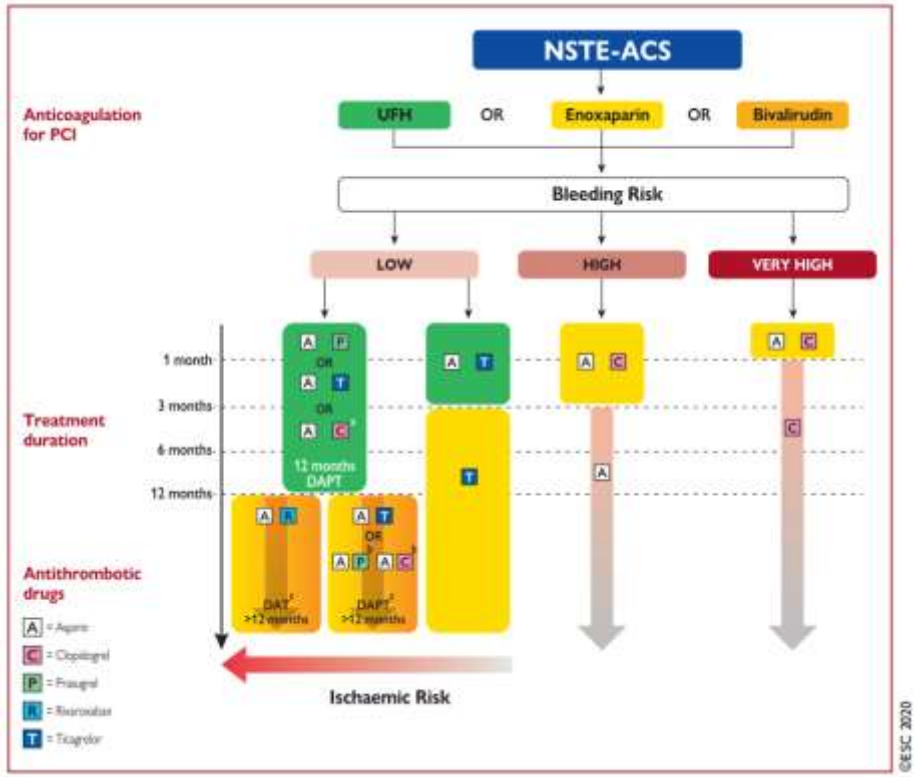
  - Antiplatelets are used to inhibit peri-procedural thrombosis formation
- Historical trials mainly focused on the thrombotic risk.
  - *The* **main purpose** *of antiplatelets*

2018 ESC/EACTS Guidelines on myocardial revascularization
2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention

Introduction – Long term management of PCI pts

- **Current trends**
  - Most DAPT studies focus on the ***acute phase (<1 year post PCI)***
  - The **Bleeding risk** is the main contributor of antiplatelet intensity
  - Limited evidence in how should we treat patients 1-year post-PCI?





2018 ESC/EACTS Guidelines on myocardial revascularization, 2021 ESC Guidelines of CVD Prevention

Introduction – Long term management of PCI pts

- **Current trends**
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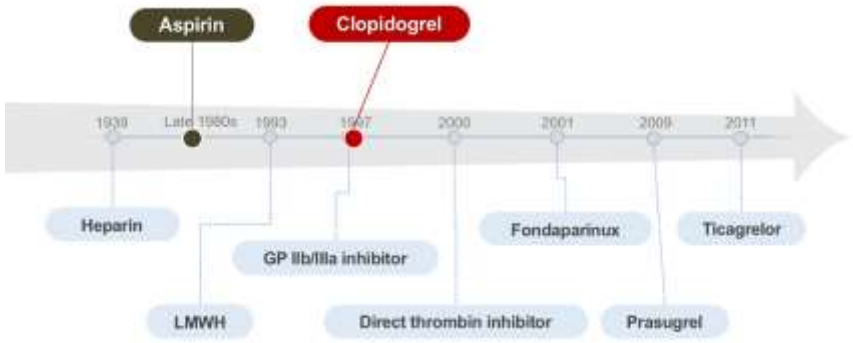
  - The Bleeding risk is the main contributor of antiplatelet intensity
  - Limited evidence in how should we treat patients 1-year post-PCI?

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



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

Levels of Evidence

- Level 1a: Meta-analysis of well-designed randomized control trials
- Level 1b: Well-designed randomized control trials
- Level 2a: Well-designed controlled study without randomization
- Level 2b: Well-designed quasi-experimental study
- Level 3: Well-designed non-experimental study (case studies)
- Level 4: Expert opinion or consensus statement

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Aspirin for 1’ and 2’ prevention

Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials

*Antithrombotic Trialists' (ATT) Collaboration**

Summary

Background Low-dose aspirin is of definite and substantial net benefit for many people who already have occlusiv vascular disease. We have assessed the benefits and risks in primary prevention.

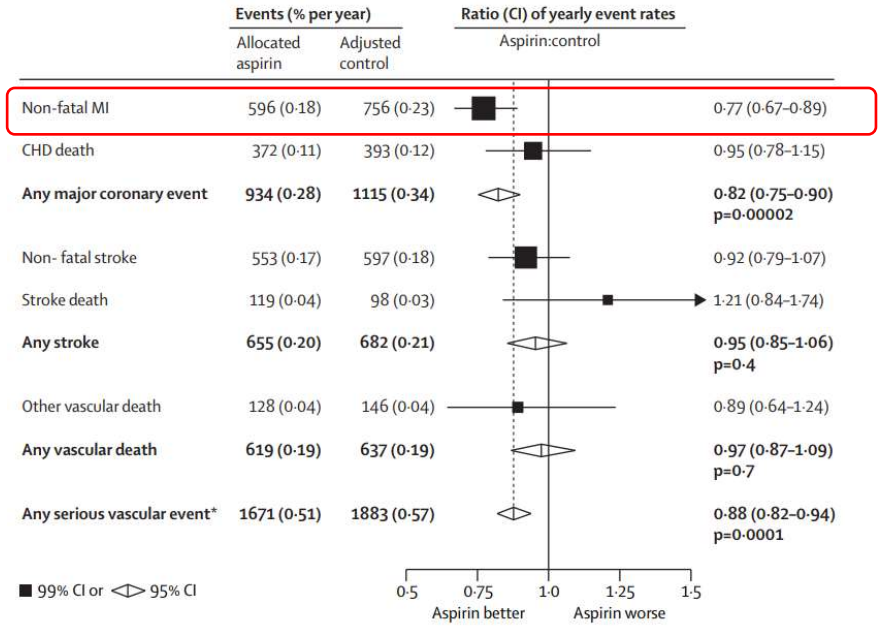
Methods We undertook meta-analyses of serious vascular events (myocardial infarction, stroke, or vascular death and major bleeds in six primary prevention trials (95 000 individuals at low average risk, 660 000 person-years 3554 serious vascular events) and 16 secondary prevention trials (17 000 individuals at high average risk 43 000 person-years, 3306 serious vascular events) that compared long-term aspirin versus control. We repor intention-to-treat analyses of first events during the scheduled treatment period.

Findings In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0·51% aspirin *vs* 0·57% control per year, p=0·0001), due mainly to a reduction of about a fifth in non-fatal myocardial infarction (0·18% *vs* 0·23% per year, p<0·0001). The net effect on stroke was not significant (0·20% *vs* 0·21% per year, p=0·4: haemorrhagic stroke 0·04% *vs* 0·03%, p=0·05; other stroke 0·16% *vs* 0·18% per year, p=0·08). Vascular mortality did not differ significantly (0·19% *vs* 0·19% per year, p=0·7). Aspirin allocation increased major gastrointestinal and extracranial bleeds (0·10% *vs* 0·07% per year, p<0·0001), and the main risk factors for coronary disease were also risk factors for bleeding. In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6·7% *vs* 8·2% per year, p<0.0001), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (2·08% *vs* 2·54% per year, p=0·002) and in coronary events (4·3% *vs* 5·3% per year, p<0·0001). In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women.

	Dates of recruitment	Participating countries	Year of main publication	Number of participants	Mean duration of follow-up (years)	Target population	Eligible age range (years) at entry	Aspirin regimen	Randomised factorial comparison	Placebo control
British Doctors' Study[10]	Nov 1978–Nov 1979	UK	1988	5139	5·6	Male doctors	19–90	500 mg daily	None	No
US Physicians' Health Study[11]	Aug 1981–Apr 1984	USA	1988	22071	5·0	Male doctors	45–73	325 mg alternate days	β carotene *vs* placebo	Yes
Thrombosis Prevention Trial[9]	Feb 1989–May 1994	UK	1998	5085	6·7	Men with risk factors for CHD	45–69	75 mg daily	Warfarin *vs* placebo	Yes
Hypertension Optimal Treatment Trial[12]	Oct 1992–May 1994	Europe, North and South America, Asia	1998	18790	3·8	Men and women with DBP 100–115 mm Hg	50–80	75 mg daily	Three blood pressure regimens	Yes
Primary Prevention Project[13]	June 1993–Apr 1998	Italy	2001	4495	3·7	Men and women with one or more risk factors for CHD	45–94	100 mg daily	Vitamin E *vs* open control	No
Women's Health Study[14]	Sep 1992–May 1995	USA	2005	39876	10·0	Female health professionals	≥45	100 mg alternate days	Vitamin E *vs* placebo	Yes

CHD=coronary heart disease. DBP=diastolic blood pressure.

Table 1: **Design and eligibility criteria of primary prevention trials**



Lancet 2009;373:1849

Aspirin for 1’ and 2’ prevention

Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant

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Evidence from those who lived 3-4 decades ago.

p=0·0001

■ 99% CI or ◁▷ 95% CI

0·5 0·75 1·0 1·25 1·5

Aspirin better Aspirin worse

Lancet 2009;373:1849

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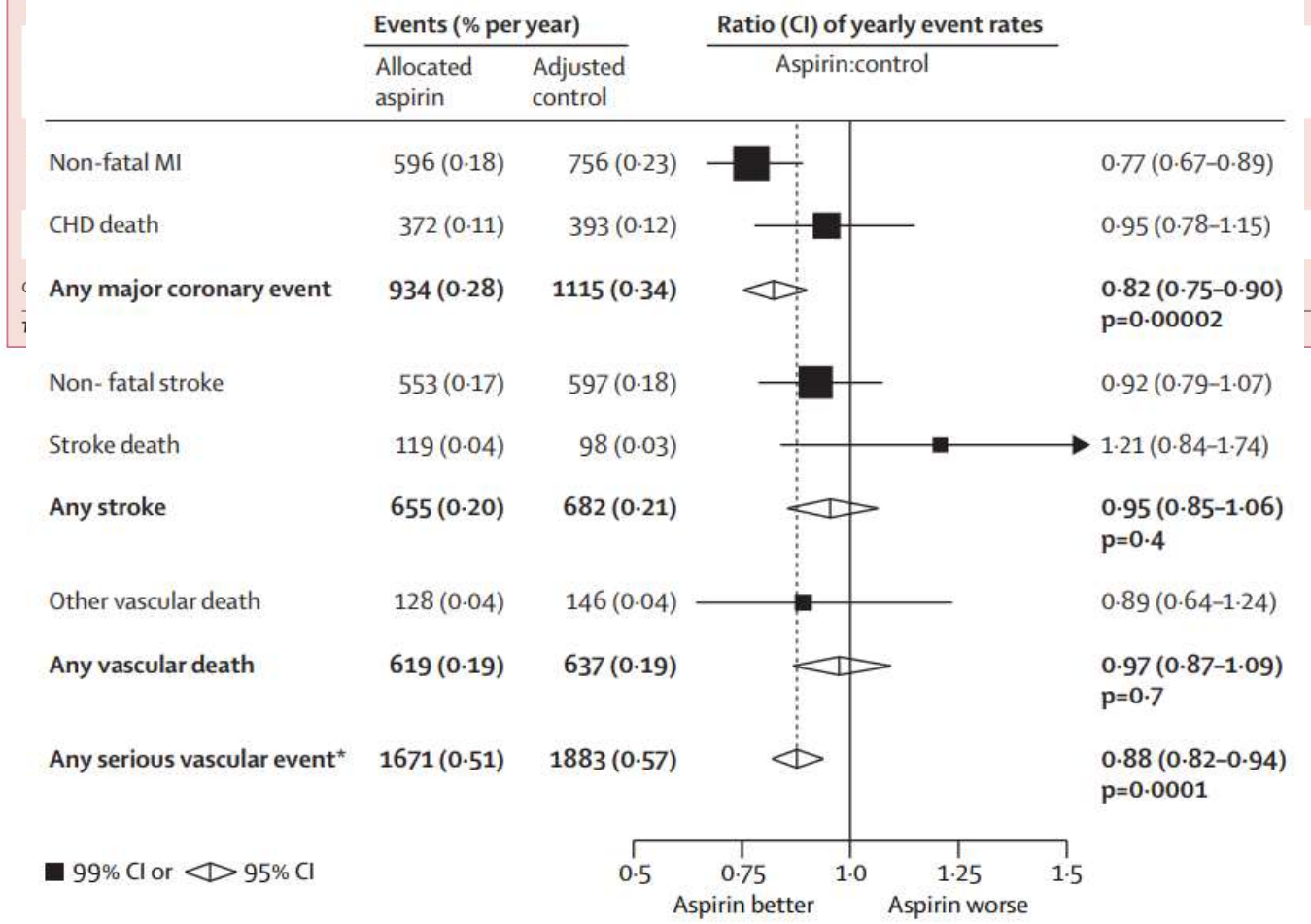

- ✓ ***Medically treated MI (non-PCI treated)***
- ✓ ***The main benefit of aspirin vs. (no aspirin) is decreased non-fatal MI.***

Lancet 2009;373:1849

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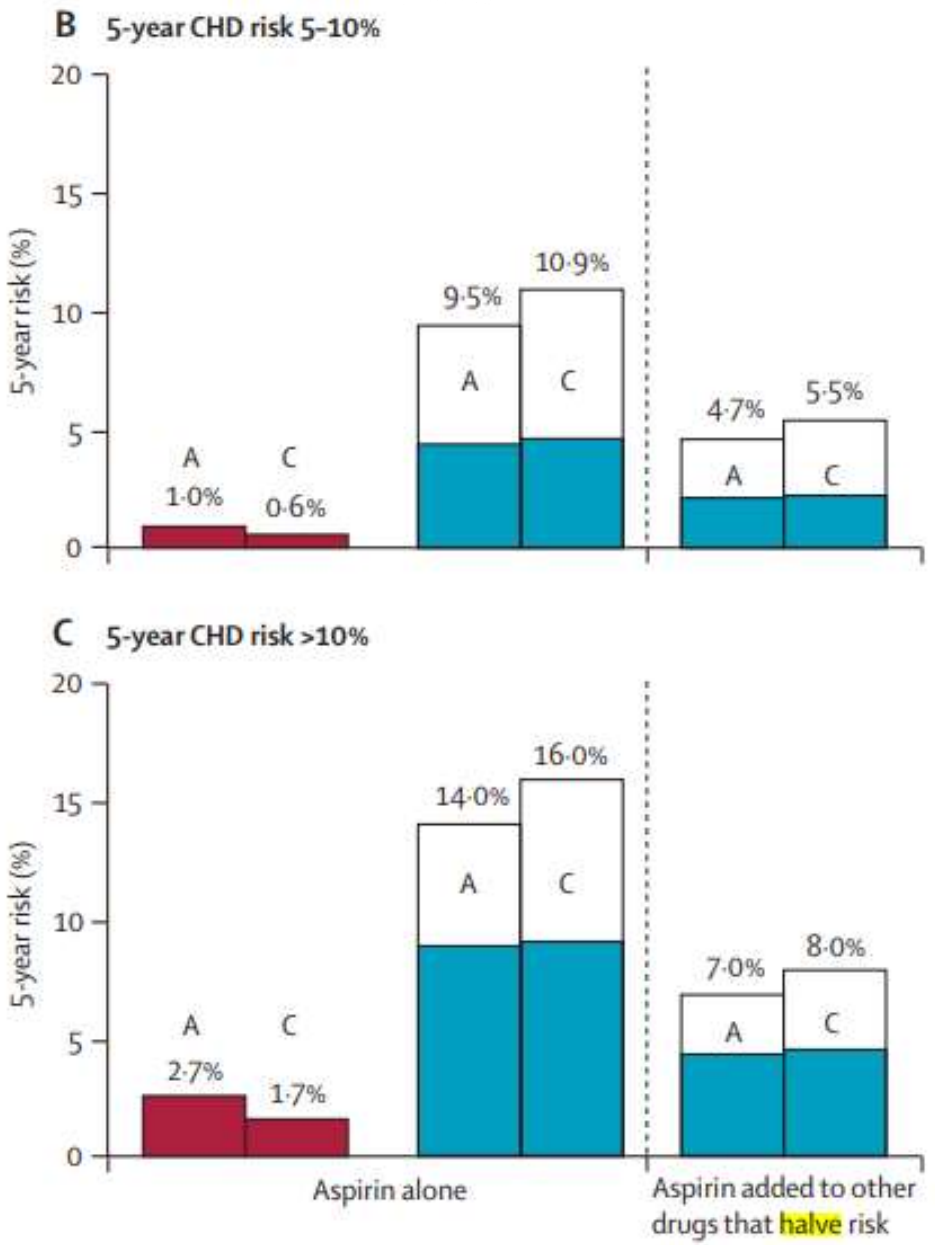
Antithrombotic Trialists' (ATT) Collaboration*

prevention only by aspirin. If so, then one of the main questions for aspirin in primary prevention nowadays is whether it is worthwhile to add it to a statin (or to some statin-based combination of measures). If the risk of occlusive vascular disease is already approximately halved by statins or other measures, then the further absolute benefit of adding aspirin could well be only about half as large as was suggested by these primary prevention trials, but the main bleeding hazards could well remain. In that case, the benefits and hazards of adding long-term aspirin in people without pre-existing disease might be of approximately similar magnitude.



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Why is the position of Aspirin under controversy?

- ***In terms off efficacy***
  - Can aspirin decrease thrombotic adverse events?

- ***In terms of safety***
  - Are the side effects of aspirin well-tolerated? Or are they worth it?

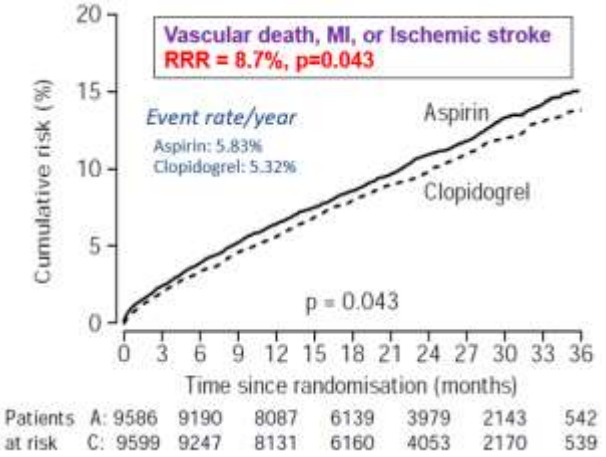
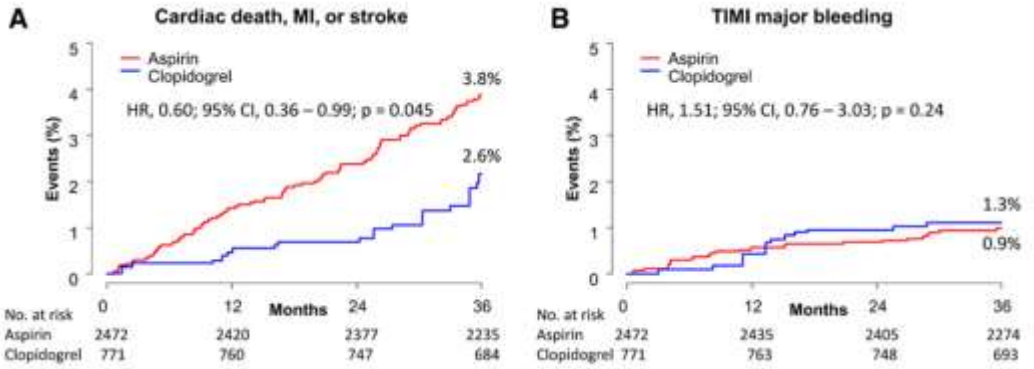


Table 1: Summary of the Three Aspirin Trials for Primary Prevention of Cardiovascular Disease

	ARRIVE	ASCEND	ASPREE
Sample Size	12,546	15,480	19,114
Inclusion Criteria	Multiple risk factors without established CVD	Diabetes without established CVD	Age ≥ 70 years without established CVD
Mean Age	64 years	63 years	74 years
Mean Follow-up	5 years	7.4 years	4.7 years
Aspirin Dose	100 mg	100 mg	100 mg
Ratio for CVD Benefit	0.96 (95% CI 0.81-1.13)	0.88 (95% CI 0.79-0.97)	0.95 (95% CI 0.83-1.08)
Bleeding Risk	2.11 (95% CI 1.36-3.28)	1.29 (95% CI 1.09-1.52)	1.38 (95% CI 1.18-1.62)

Clopidogrel Versus Aspirin as an Antiplatelet Monotherapy After 12-Month Dual-Antiplatelet Therapy in the Era of Drug-Eluting Stents

Taek Kyu Park, MD; Young Bin Song, MD, PhD; Joonghyun Ahn, MS; K.C. Carriere, PhD; Joo-Yong Hahn, MD, PhD; Jeong Hoon Yang, MD, PhD; Seung-Hyuk Choi, MD, PhD; Jin-Ho Choi, MD, PhD; Sang Hoon Lee, MD, PhD; Hyeon-Cheol Gwon, MD, PhD

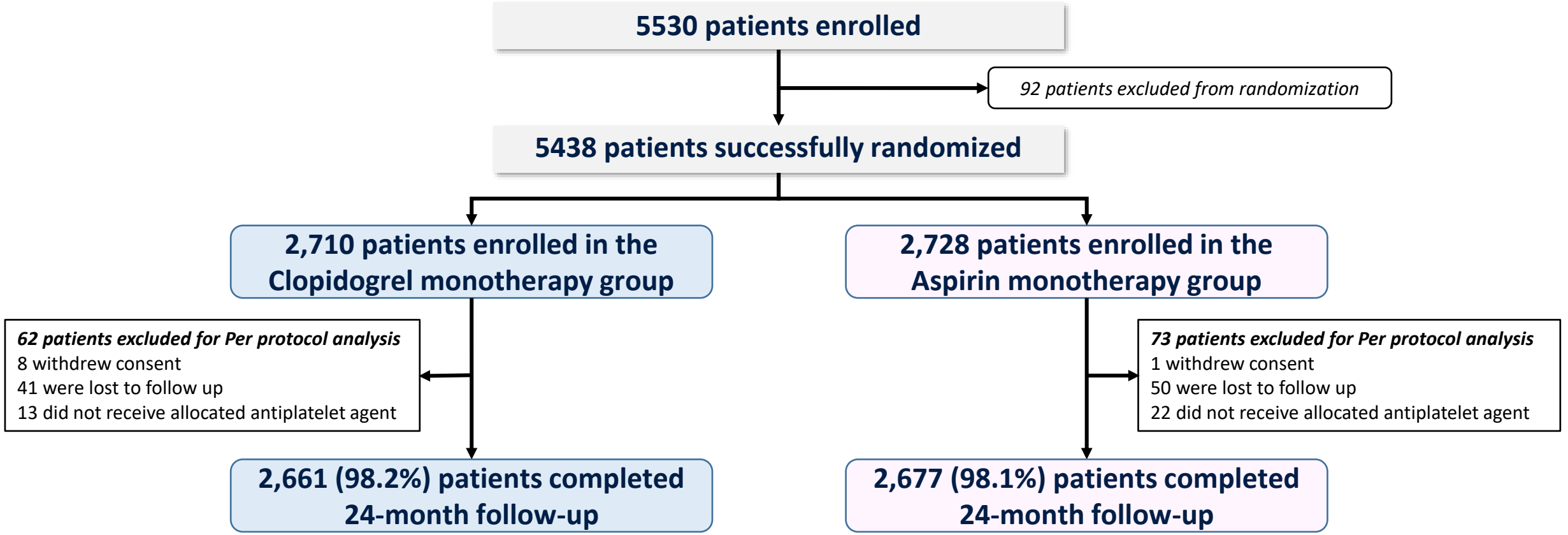


The HOST-EXAM trial

HOST EXAM
EXtended Antiplatelet Monotherapy

Working Hypothesis

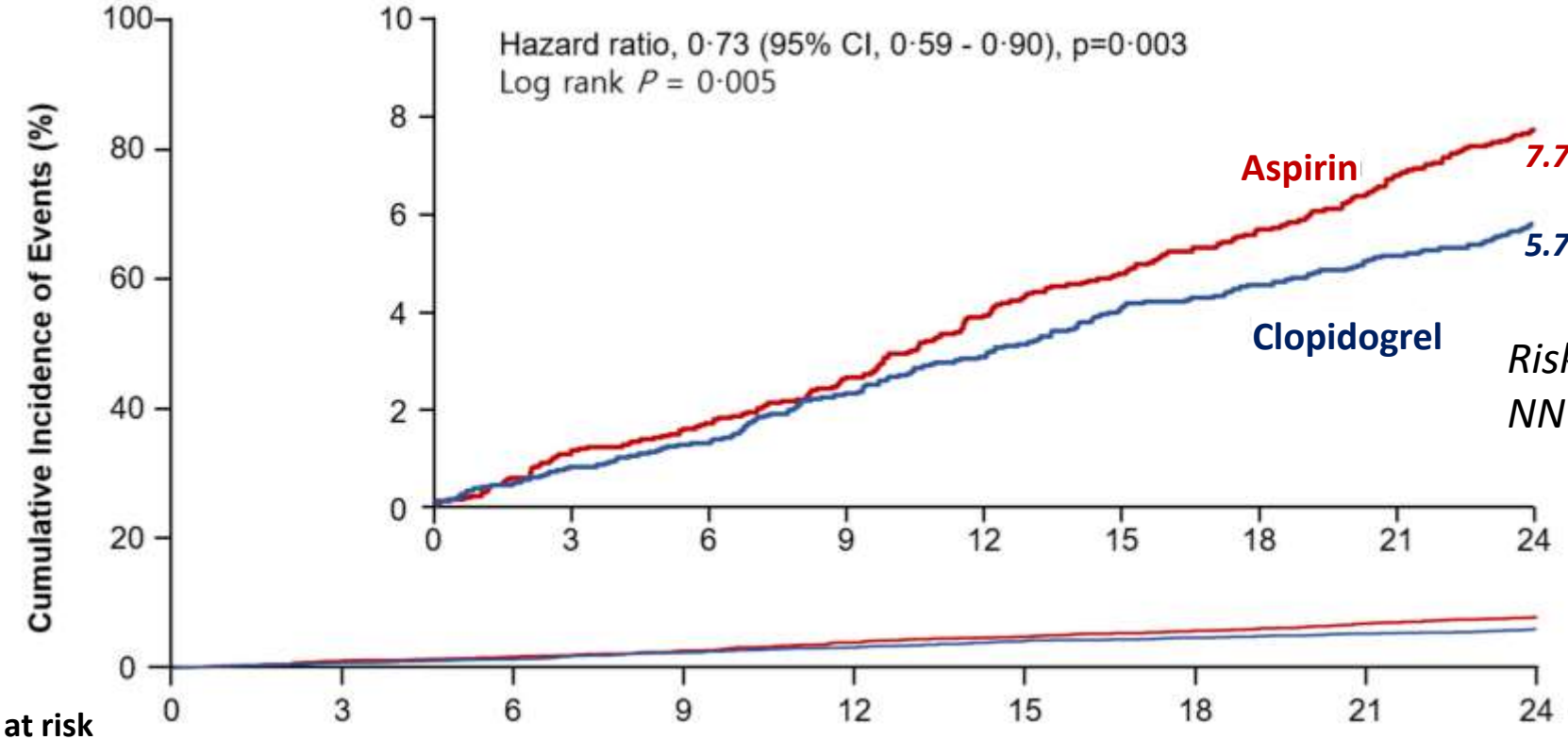
In the chronic maintenance period of a **PCI population**, ***Clopidogrel will be superior to Aspirin***,
In terms of patient oriented composite outcomes (POCO)



The HOST-EXAM trial

- ***Primary Outcome***

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



Risk difference : -2.0% (-3.3% - 0.6%)
NNT : 50.6 (30.0 – 161.9)

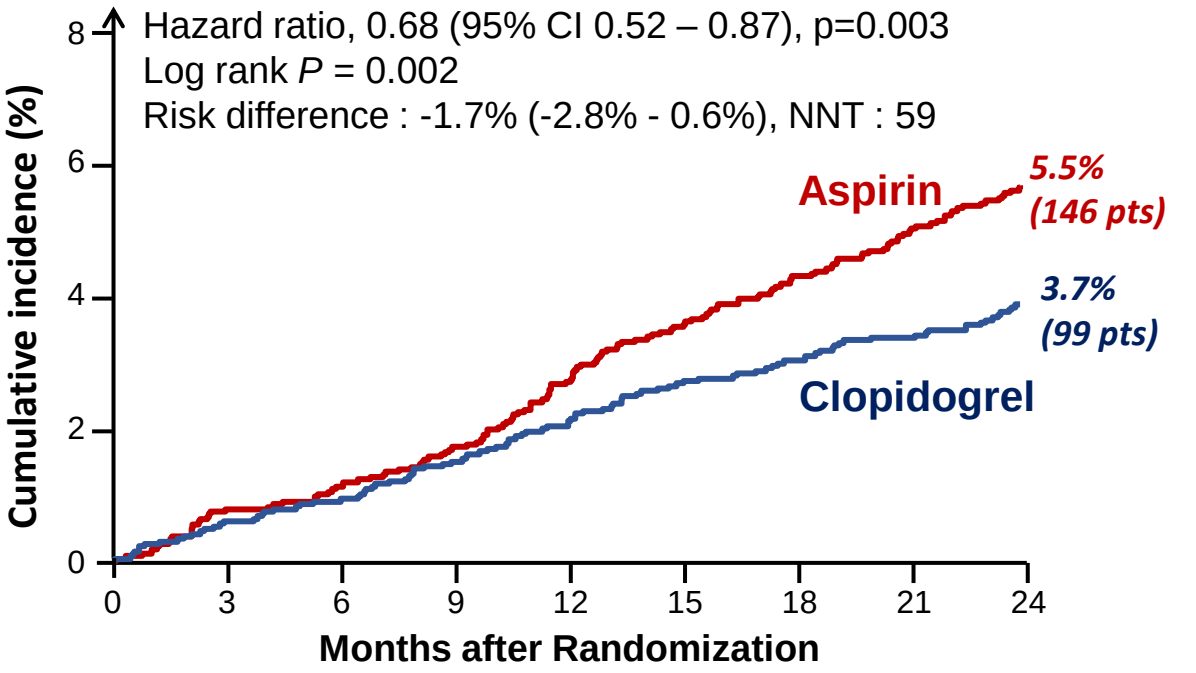
Number at risk									
Clopidogrel	2710	2667	2654	2626	2597	2565	2549	2521	2500
Aspirin	2728	2667	2657	2629	2585	2555	2531	2493	2456

BK Koo, J Kang, KW Park, HS Kim et al. Lancet 2021

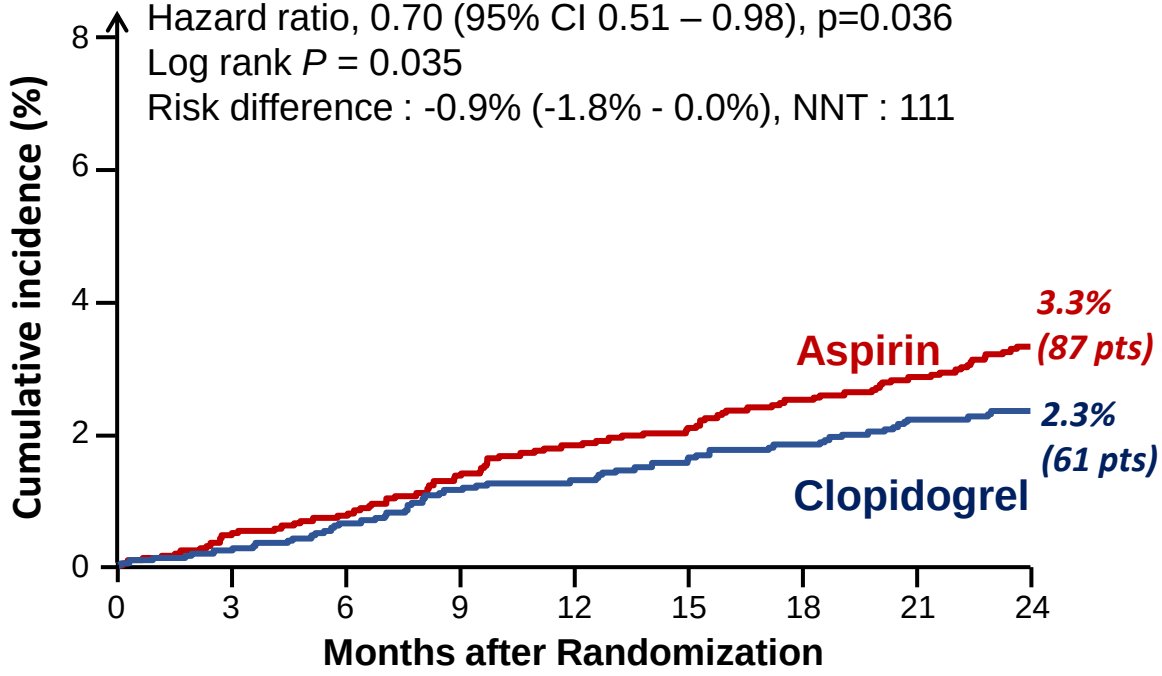
The HOST-EXAM trial

- ***Secondary Outcomes***

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)



In patients who received ***PCI with a DES***, and who were ***event-free*** for 6~18 months post-PCI,

Clopidogrel monotherapy as compared with ***Aspirin monotherapy*** significantly reduced the risk of the POCO. The beneficial effect of clopidogrel was observed in ***thrombotic composite endpoints*** as well as ***any bleeding endpoint.***

The HOST-EXAM trial….But…

- ***The Mortality Issue***

	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
Definite or probable ST	0.4% (10)	0.6% (16)	0.63 (0.29-1.39)	0.251
Any minor GI complications	10.2% (272)	11.9% (320)	0.85 (0.72-1.00)	0.048

- "I wonder whether the authors could comment on if they have any reasoning-other than the inevitable lack of power-for why **CV death trends in the opposite direction to the non-fatal CV outcomes**."

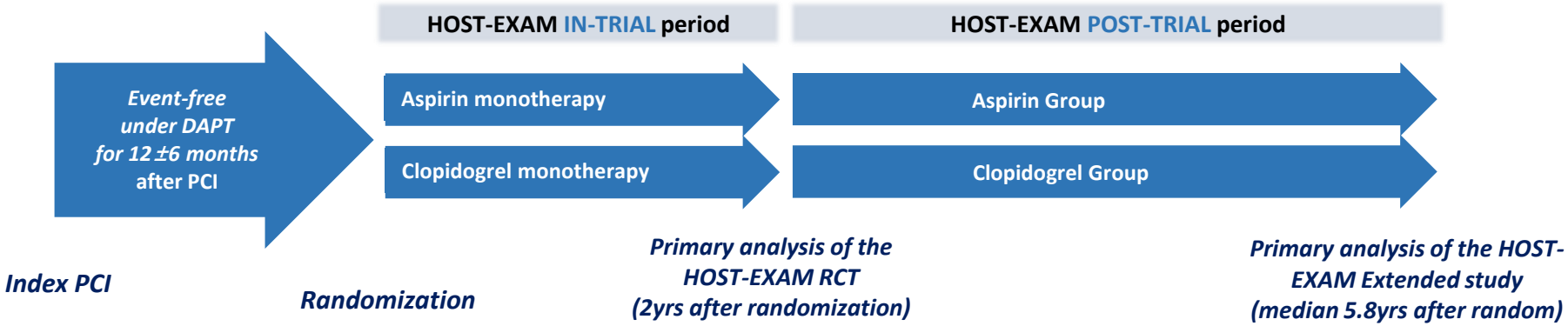
- "the **follow-up duration of 2 years might be too short**, considering the fact that maintenance antiplatelet therapy is basically administered permanently."

No. of patients	Total	Clopidogrel	Aspirin	P value
Cardiovascular cause	43	25	18	0·274
- **Cardiac arrest**	18	11	7	0·338
- **Cerebrovascular accident**	10	6	4	0·520
- **Unknown origin of death**	15	8	7	0·786

BK Koo, J Kang, KW Park, HS Kim et al. Lancet 2021

The HOST-EXAM, Extended trial

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



Clinical events and final clinical status ascertained at March, 2022.
The vital status of all patients cross-checked via the National Health Insurance Service system.

- **Primary Endpoint: POCO (Patient Oriented Composite outcome)**
  - All-cause death, nonfatal MI, stroke, readmission due to ACS, and major bleeding complications (BARC type ≥3 bleeding)
- **Key Secondary Endpoints**
  - **Thrombotic composite endpoint, Bleeding endpoint**

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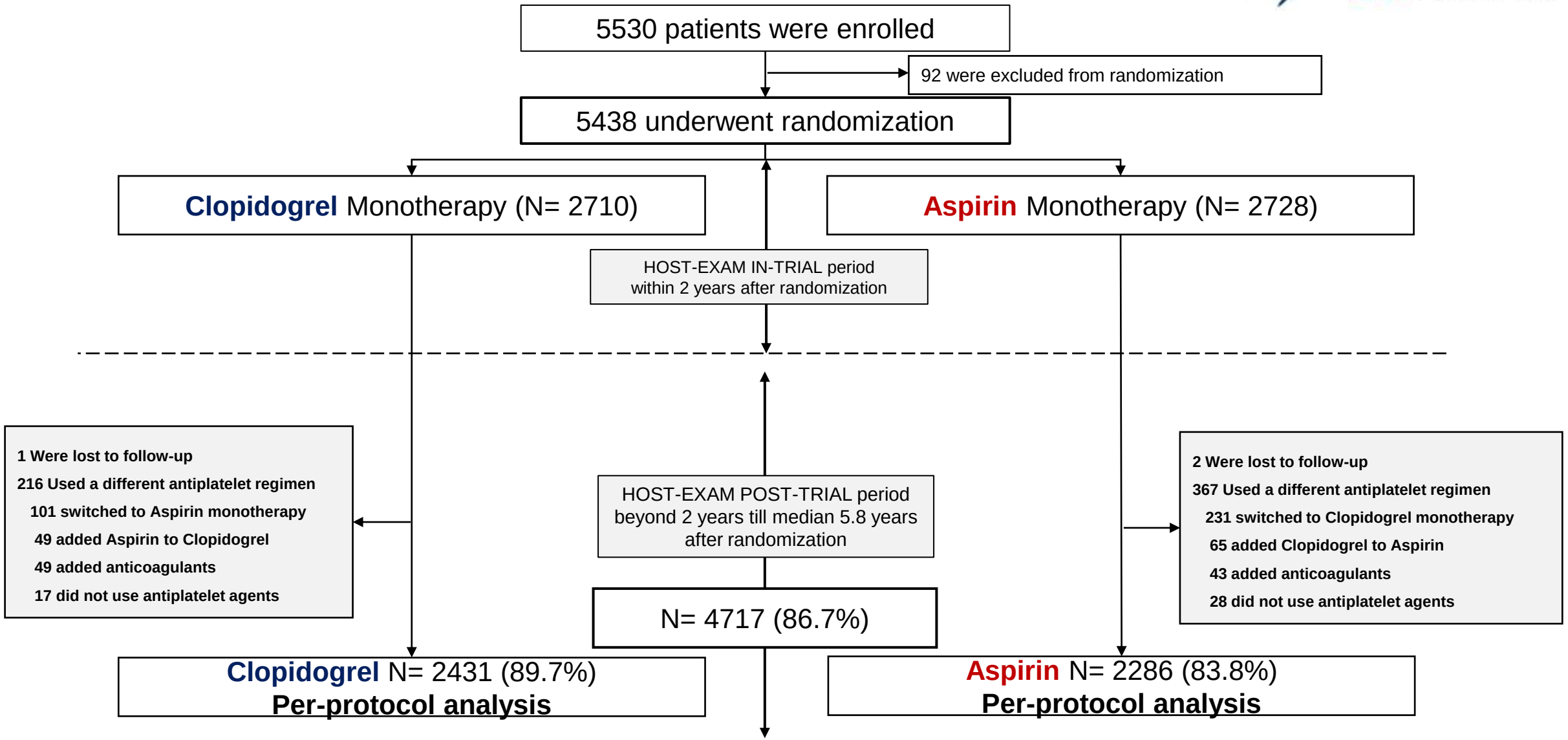
The HOST-EXAM, Extended trial



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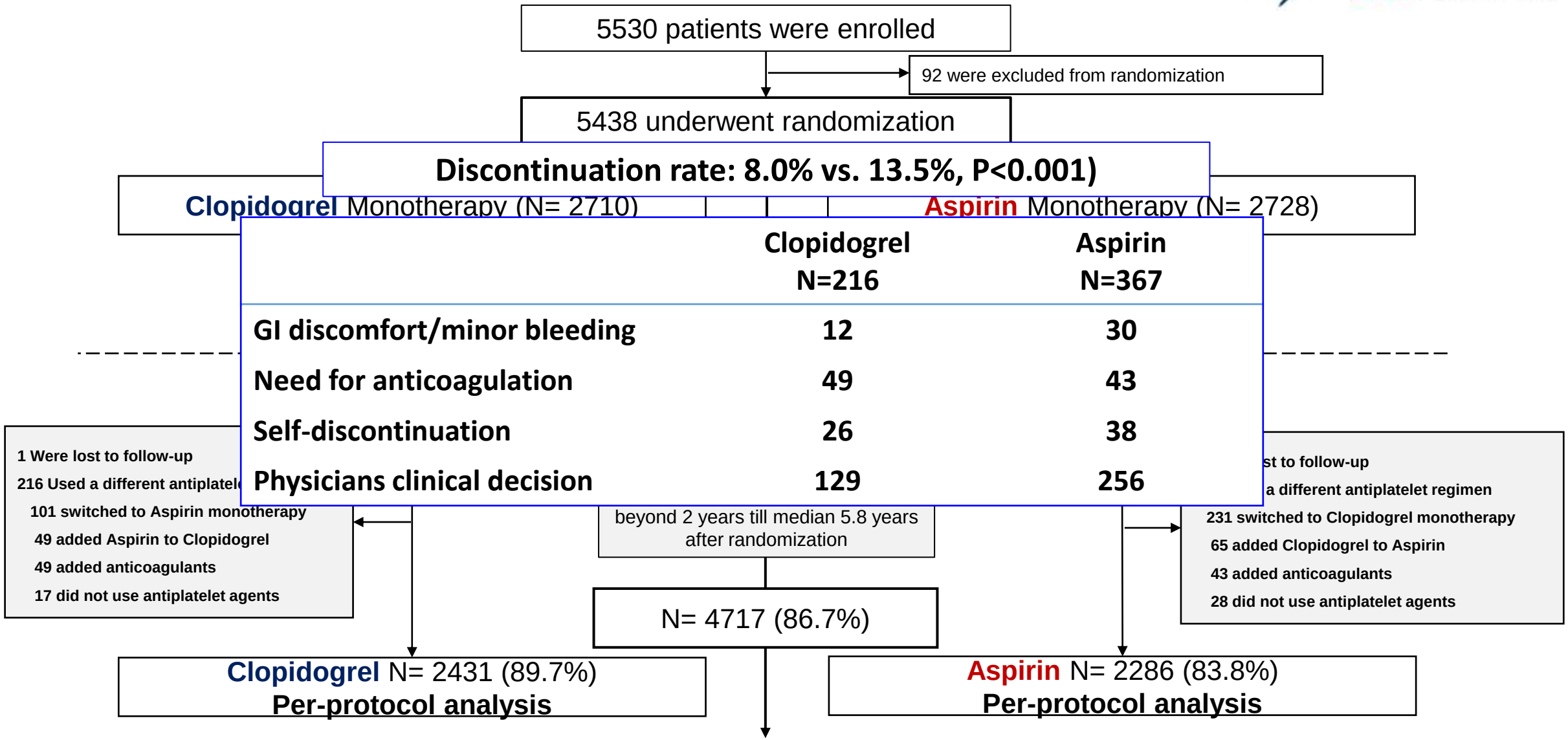

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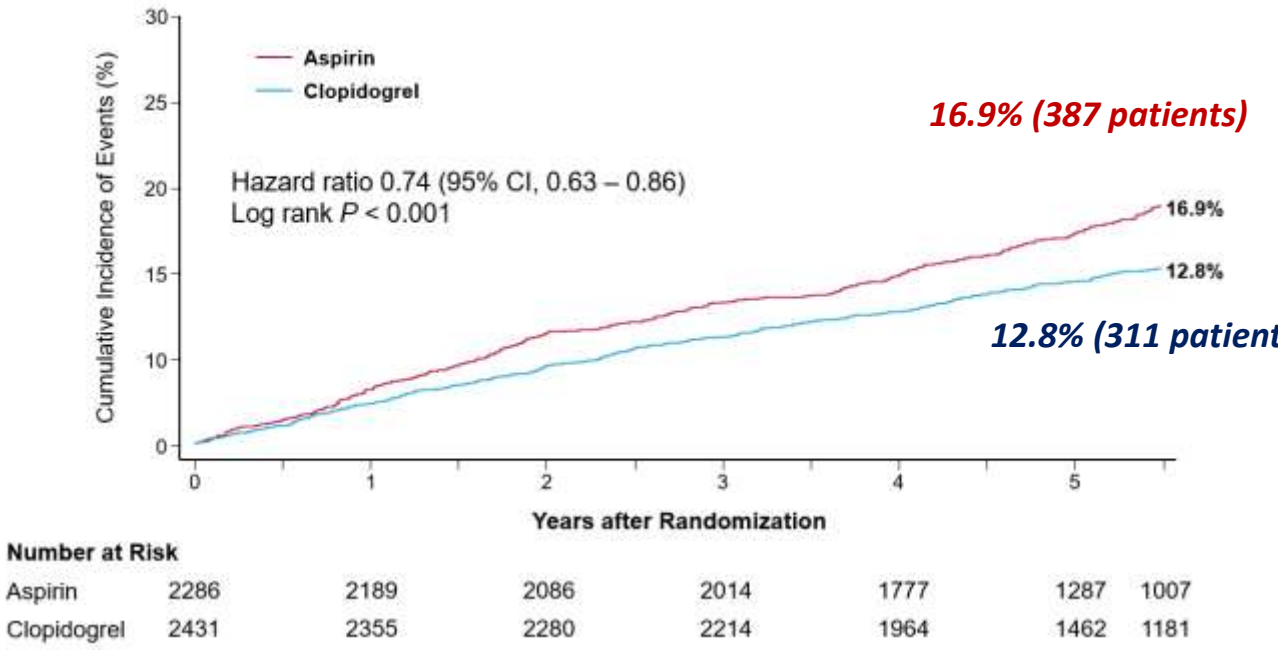
The HOST-EXAM, Extended trial

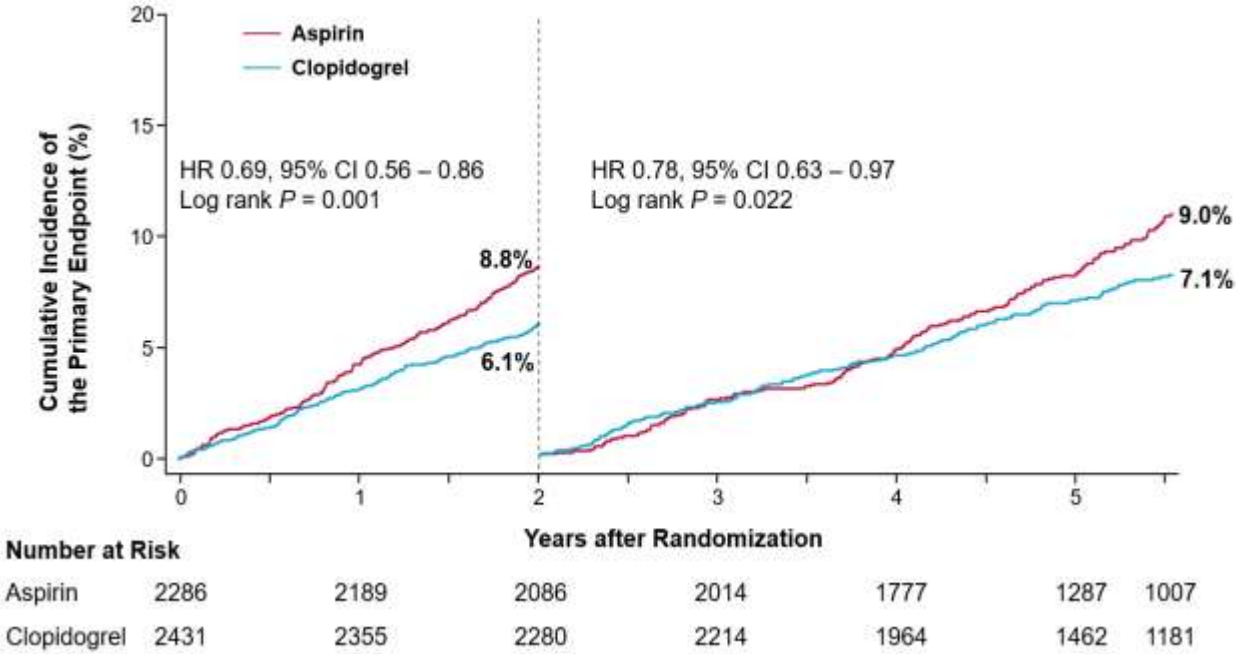
- ***Primary Outcome***

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



16.9% (387 patients)

12.8% (311 patient



Risk difference : 4.1% (2.1% - 6.2%)
Number needed to treat : 24

Upto 2 years:

Hazard ratio, 0·73 (95% CI, 0·59 - 0·90), p=0·003
Log rank *P* = 0·005

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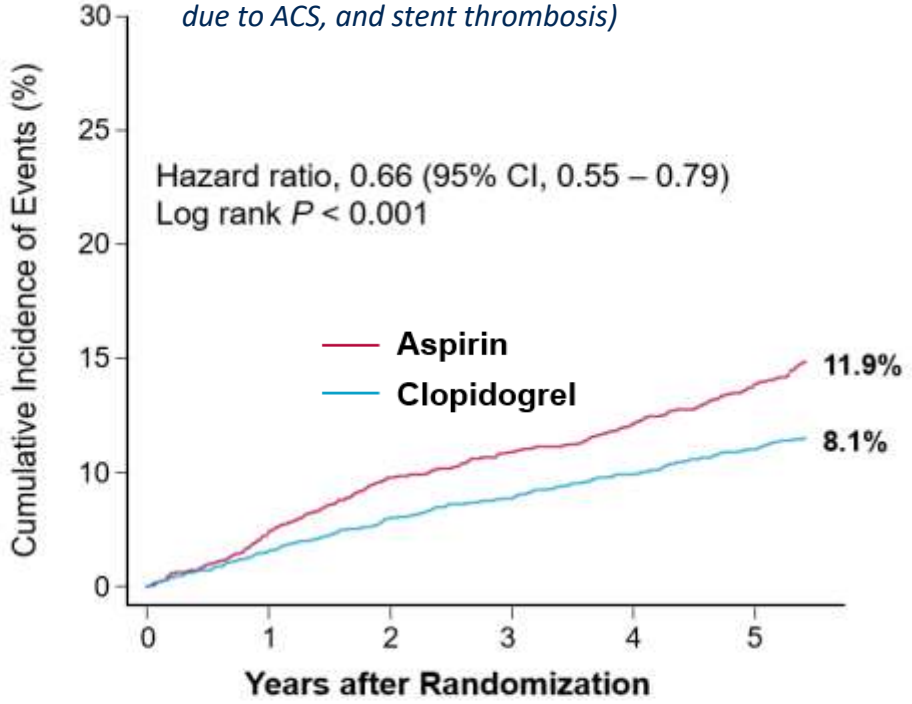
The HOST-EXAM, Extended trial

- ***Key Secondary Outcomes***

Thrombotic composite outcome
(cardiac death, non-fatal MI, ischemic stroke, readmission due to ACS, and stent thrombosis)

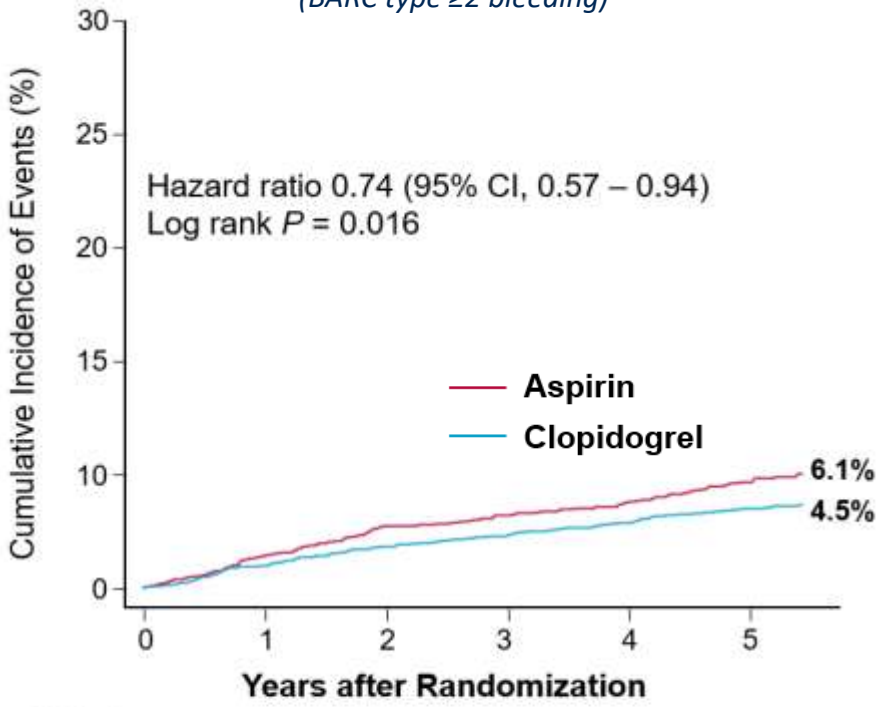


Number at Risk

Aspirin	2286	2120	1819	1040
Clopidogrel	2431	2304	1992	1202

Upto 2 years: Hazard ratio, 0.68 (95% CI 0.52 – 0.87), p=0.003
Log rank *P* = 0.002

Any bleeding
(BARC type ≥2 bleeding)



Number at Risk

Aspirin	2286	2175	1888	1104
Clopidogrel	2431	2323	2028	1238

Upto 2 years: Hazard ratio, 0.70 (95% CI 0.51 – 0.98), p=0.036
Log rank *P* = 0.035

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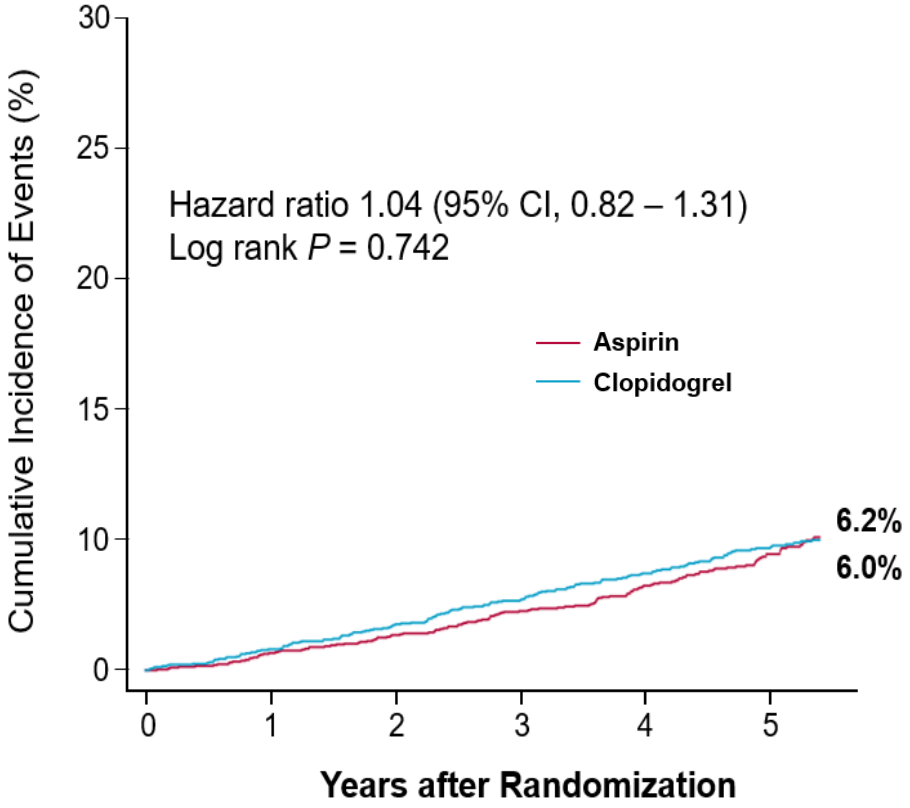
The HOST-EXAM, Extended trial

- ***Mortality Issue***



Number at Risk

Aspirin	2286	2244	1971	1165
Clopidogrel	2431	2374	2088	1285

No. of patients	Clopidogrel (N=2431)	Aspirin (N=2286)	P value
Total mortality	150 (6.2%)	136 (6.0%)	0.753
Cardiovascular cause	69 (2.8%)	71 (3.1%)	0.587
Cardiac arrest	21	22	
Heart failure aggravation	5	3	
Cerebrovascular accident	7	3	
Unknown origin of death	36	43	
Non-cardiovascular cause	81 (3.3%)	65 (2.8%)	0.334
Malignancy	34	29	
- Gastrointestinal origin	15	12	
- Respiratory origin	8	11	
- Endocrinology origin	1	1	
- Genitourinary origin	4	3	
- Other	3	2	
- Unknown primary	3	0	
Infectious disease	4	5	
Suicide or Trauma	8	3	
Others	20	16	

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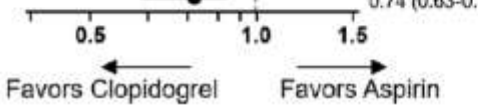
The HOST-EXAM, Extended trial

	Clopidogrel group (events/patients)	Aspirin group (events/patients)	Hazard Ratio (95% CI)	P value	Interaction P
Age (years)					
≥65	200/1040	232/992	0.80 (0.66-0.96)	0.019	0.176
<65	110/1390	155/1294	0.65 (0.51-0.83)	<0.001	
Sex					
Male	222/1807	287/1723	0.72 (0.60-0.85)	<0.001	0.563
Female	89/624	100/563	0.79 (0.59-1.05)	0.107	
Body Mass Index ≥ 25 kg/m²					
Yes	119/1103	140/976	0.74 (0.58-0.94)	0.014	0.936
No	179/1244	231/1233	0.75 (0.61-0.91)	0.003	
Diabetes Mellitus					
Yes	128/817	165/776	0.71 (0.57-0.90)	0.004	0.764
No	182/1613	222/1510	0.75 (0.62-0.91)	0.004	
Chronic Kidney Disease					
Yes	77/313	95/274	0.67 (0.50-0.90)	0.009	0.614
No	233/2117	292/2012	0.74 (0.62-0.88)	0.001	
Multivessel Disease					
Yes	170/1201	227/1145	0.69 (0.57-0.85)	0.002	0.356
No	140/1229	159/1140	0.80 (0.64-1.00)	0.054	
Acute Myocardial Infarction					
Yes	116/888	143/858	0.77 (0.60-0.98)	0.036	0.756
No	194/1542	244/1428	0.72 (0.59-0.86)	<0.001	
Acute Coronary Syndrome					
Yes	219/1758	274/1631	0.72 (0.61-0.86)	<0.001	0.556
No	91/672	113/655	0.76 (0.58-1.00)	0.053	
Complex PCI†					
Yes	60/530	92/499	0.59 (0.43-0.82)	0.002	0.138
No	249/1882	294/1769	0.78 (0.66-0.92)	0.004	
High Bleeding Risk‡					
Yes	113/461	126/390	0.71 (0.55-0.92)	0.009	0.860
No	161/1616	204/1536	0.74 (0.60-0.90)	0.004	
Proton Pump Inhibitor usage					
Yes	39/251	56/266	0.72 (0.48-1.08)	0.113	0.888
No	272/2180	331/2020	0.74 (0.63-0.87)	<0.001	



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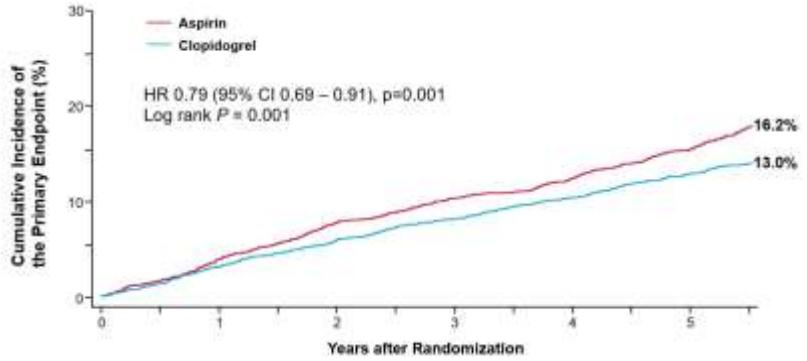
The HOST-EXAM, Extended trial - ITT

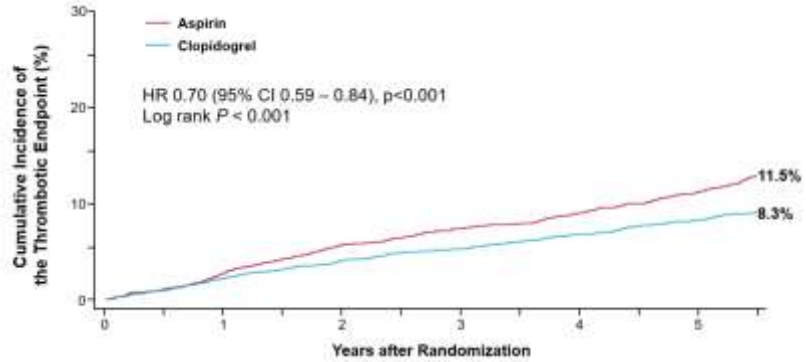
- ***If most violations were due to the physicians decision, how should the PP and ITT results differ?***

Primary endpoint



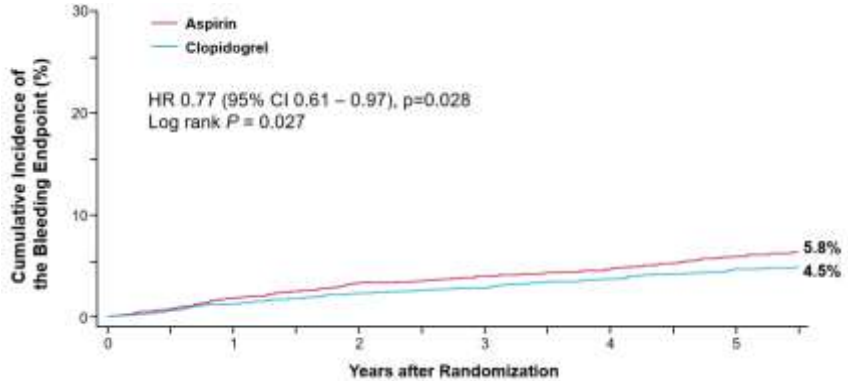
> Hazard ratio 0.74 (95% CI, 0.63 – 0.86)
> Log rank $P < 0.001$

Thrombotic composite outcome



> Hazard ratio, 0.66 (95% CI, 0.55 – 0.79)
> Log rank $P < 0.001$

Any bleeding
(BARC type ≥2 bleeding)



> Hazard ratio 0.74 (95% CI, 0.57 – 0.94)
> Log rank $P = 0.016$

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The HOST-EXAM, Extended trial

- ***Conclusion***

  - In the extended 6 years' follow-up of patients who were event-free under DAPT for 12±6 months after PCI with DES,
    - Clopidogrel monotherapy as compared with Aspirin monotherapy significantly reduced the risk of the composite of all-cause death, nonfatal myocardial infarction, 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.
    - The mortality risk was similar between the two groups.

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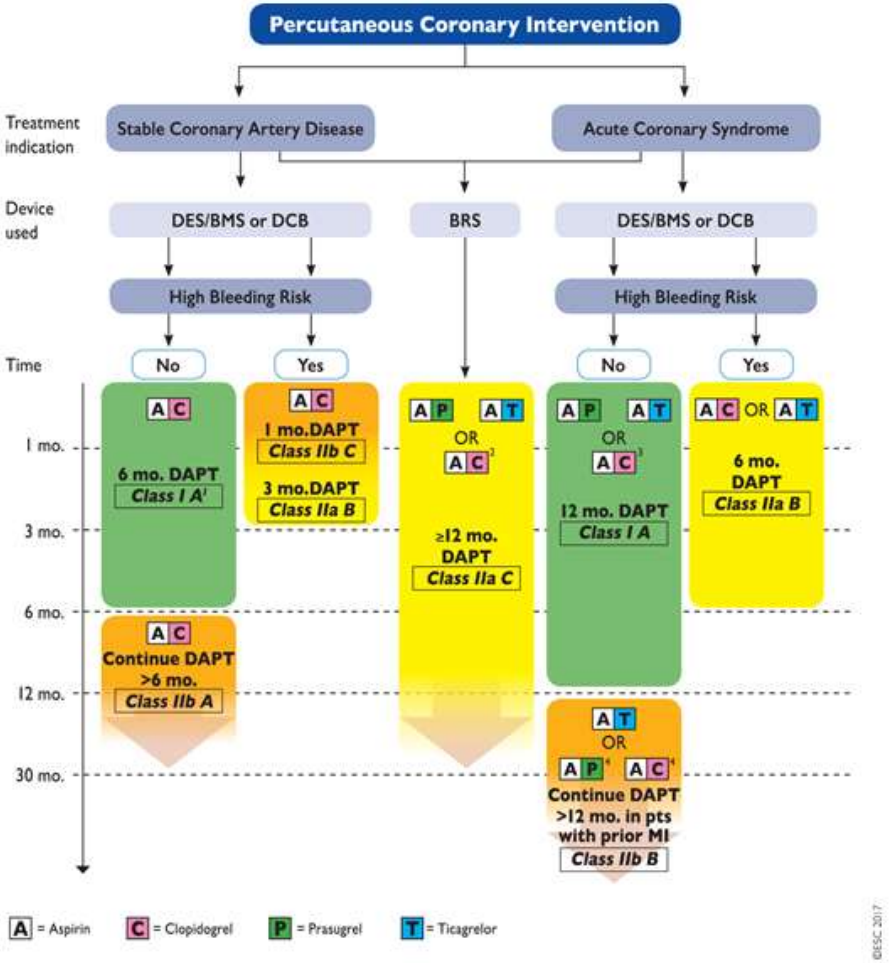
The HOST-EXAM, Extended trial

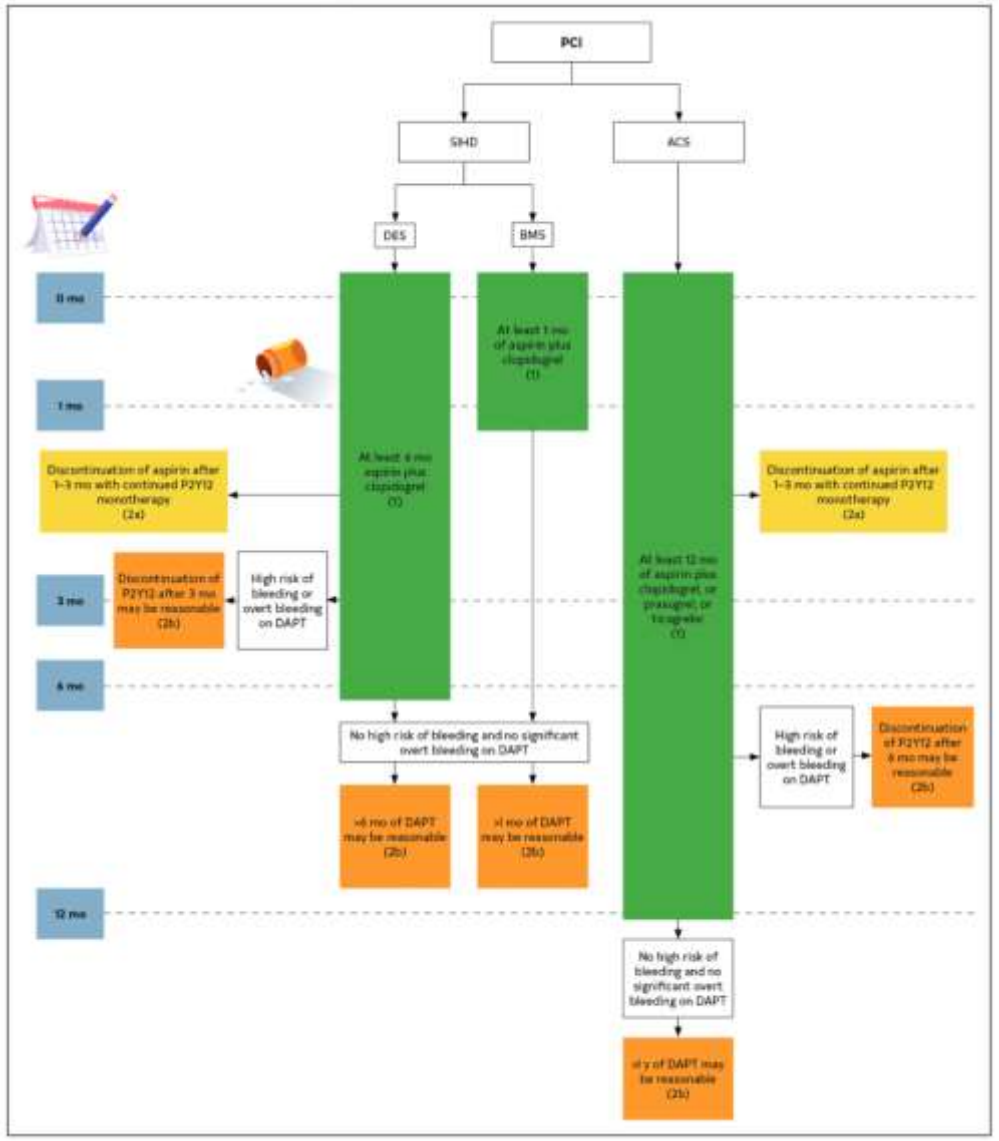
- ***Why is there NO mortality reduction by a medication that reduced both thrombotic and bleeding outcomes after PCI ?***

- ***Is CAD a 'life and death' related disease?***
- ***Is a 6-year follow-up period sufficient to determine mortality in Stable CAD?***
- ***How much can antiplatelet agents determine of mortality?***
- ***Does a medication HAVE to reduce mortality?***

What should be done next?

- **Antiplatelet therapy after PCI**





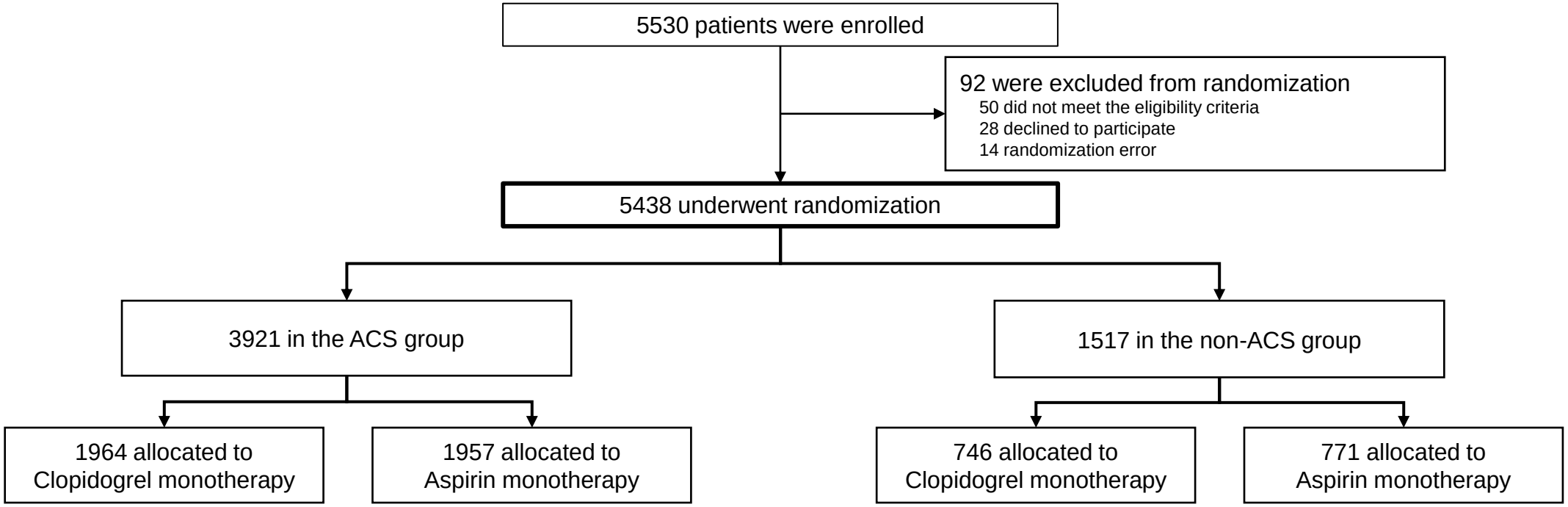
2017 ESC focused update on dual antiplatelet therapy in CAD; 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization

Subgroup analysis: By ACS

HOST EXAM
EXtended Antiplatelet Monotherapy

- **The initial presentation as ACS is a major determinant of antiplatelet strategy. How should we prescribe chronic antiplatelet agents according to the initial clinical presentation?**

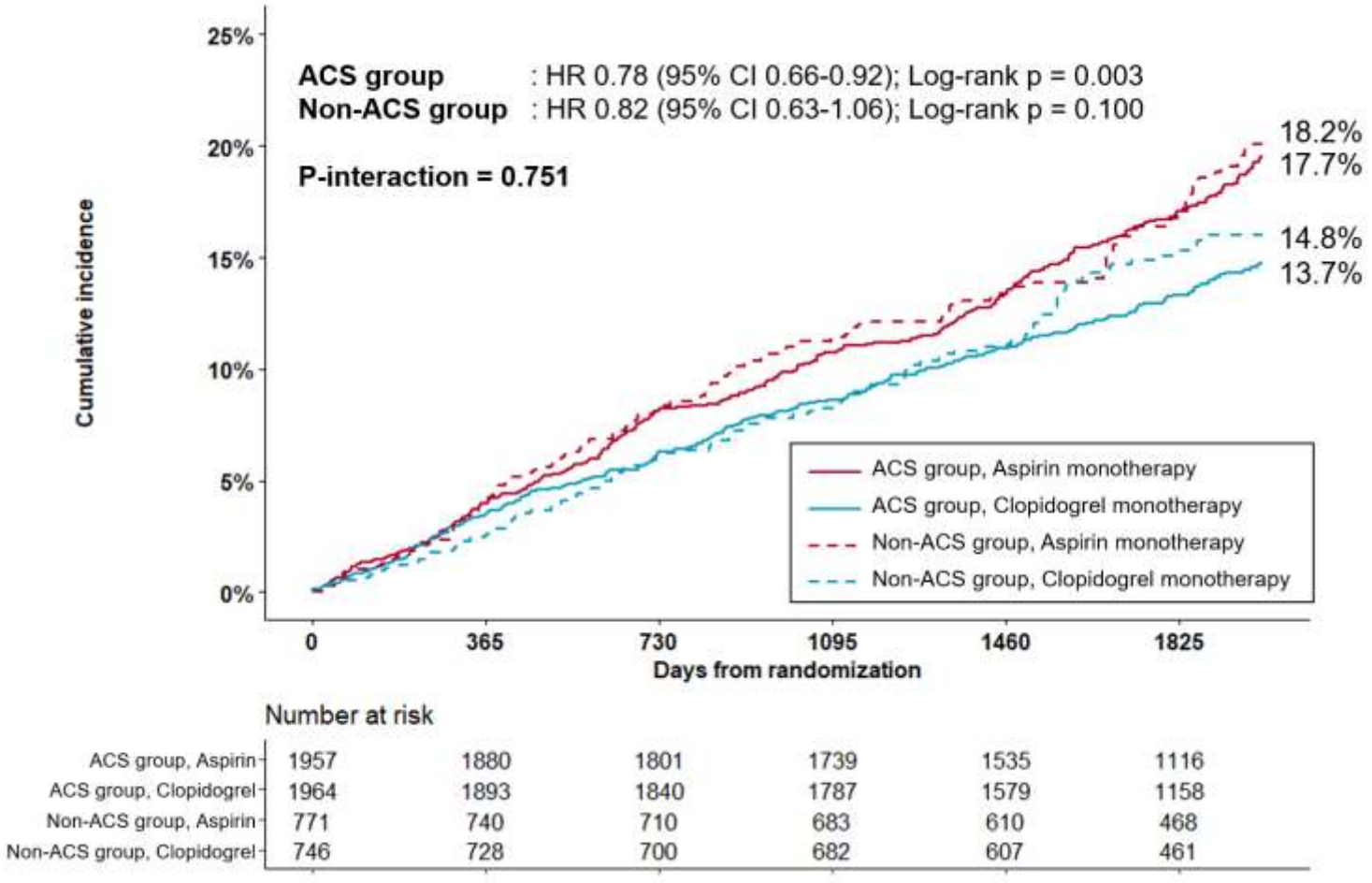
- ***ACS is a well-known risk factor for thrombotic risk. Does this have impact in the long term antiplatelet agent?***



Subgroup analysis: By ACS

- ***Primary Outcome***

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



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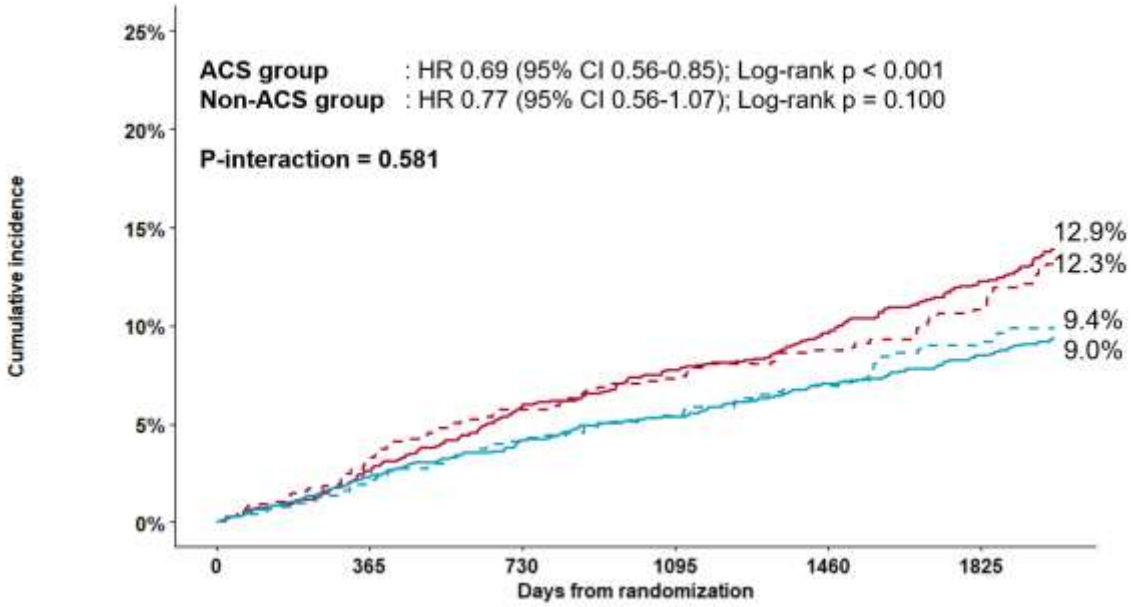
Subgroup analysis: By ACS

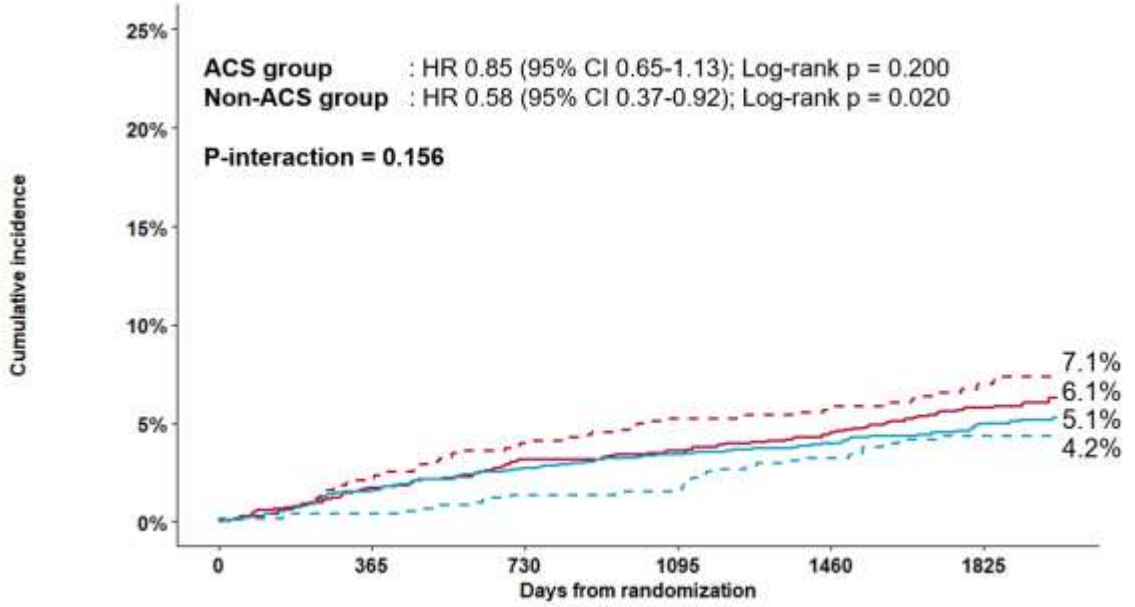
HOST EXAM
EXtended Antiplatelet Monotherapy

- ***Key Secondary Outcomes***

Thrombotic composite outcome
(cardiac death, non-fatal MI, ischemic stroke, readmission due to ACS, and stent thrombosis)



Any bleeding
(BARC type ≥2 bleeding)



The clinical benefit of clopidogrel over aspirin was consistent in patients with or without ACS.
The beneficial effect in bleeding event reduction was prominent in non-ACS patients.

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Subgroup analysis: By ACS

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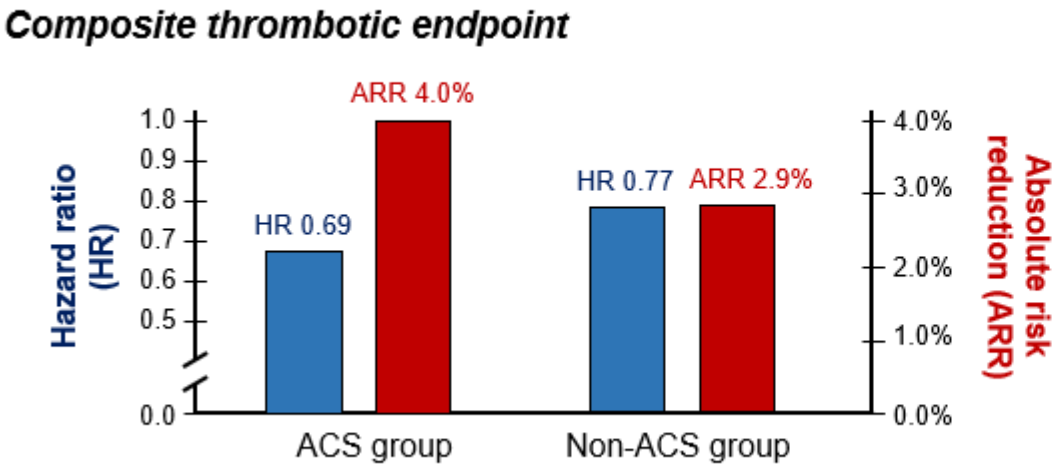

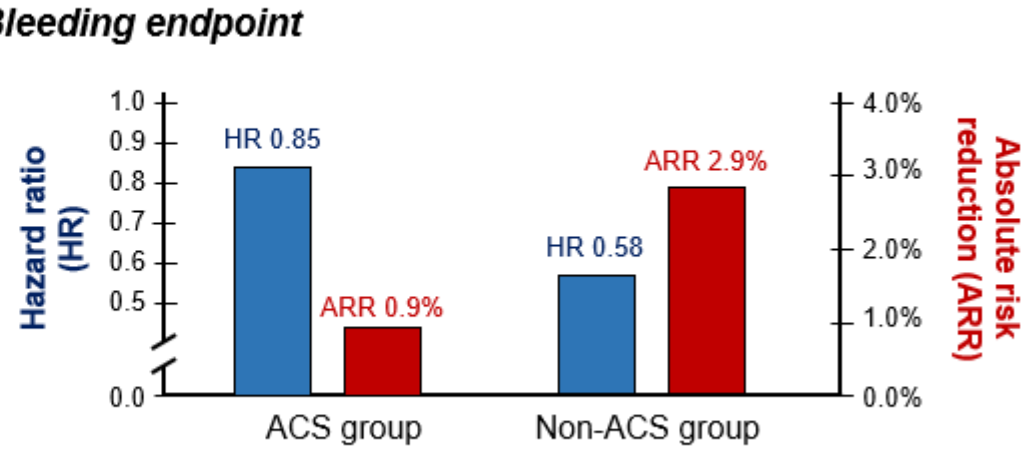

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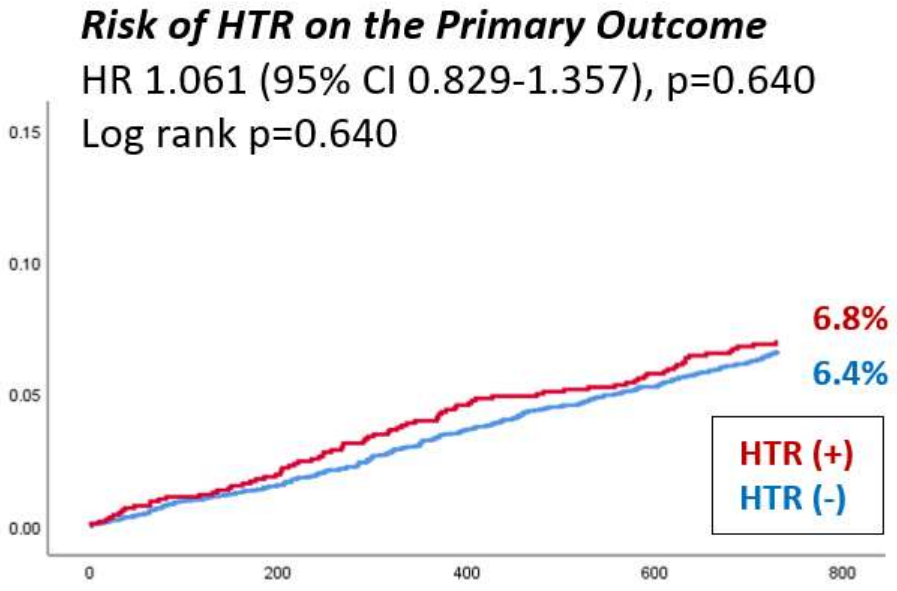
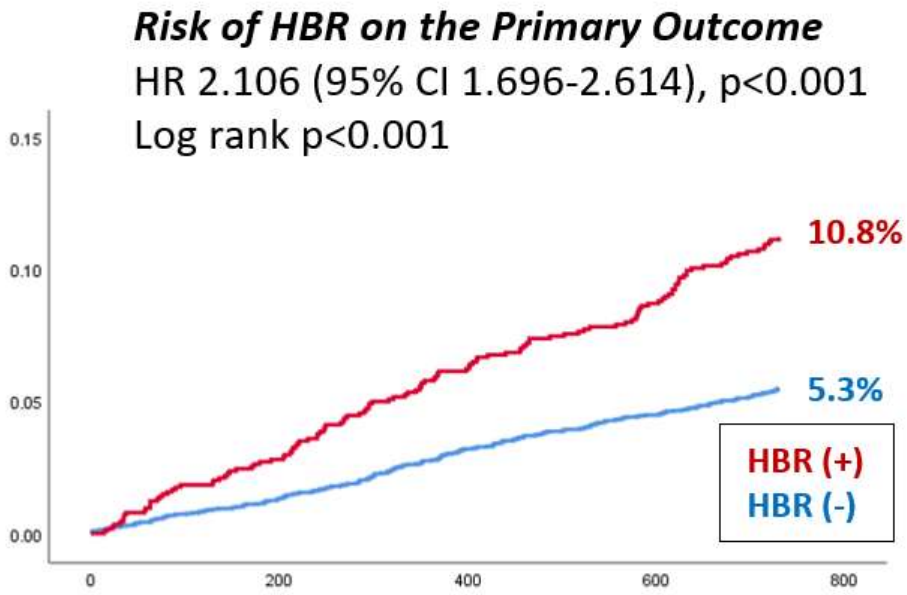
Subgroup analysis: By HBR…and HTR

- In patients with ***High Thrombotic Risk*** **[HTR]** *: defined by the Complex PCI criteria*
- In patients with ***High Bleeding Risk*** **[HBR]** *: defined by the HBR criteria*

- **Risk of HTR and HBR for the primary outcome [In the chronic phase after PCI]**



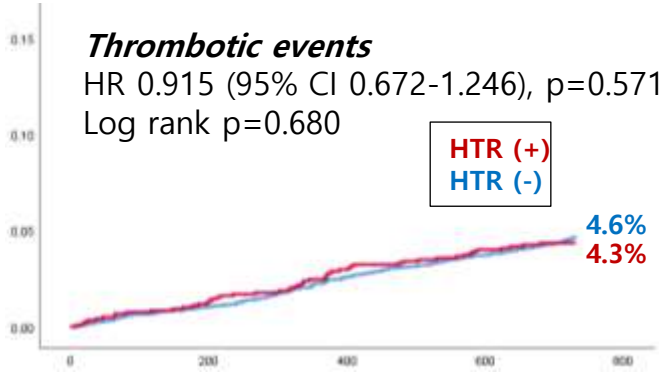


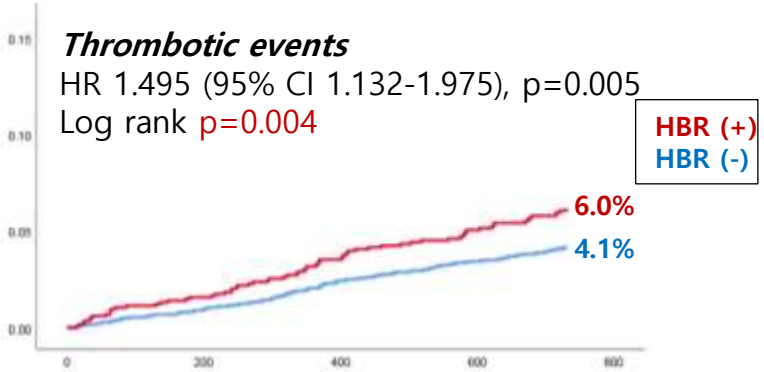
Subgroup analysis: By HBR…and HTR

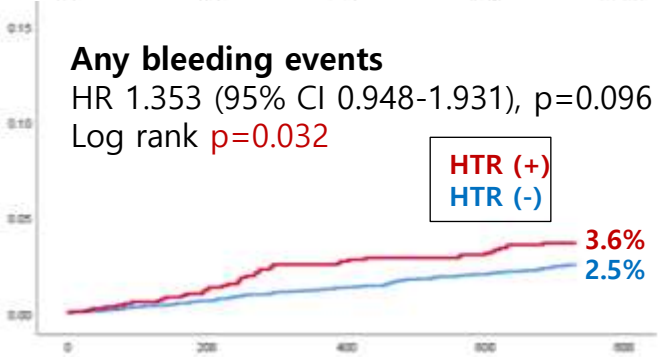
HOST EXAM
EXtended Antiplatelet Monotherapy

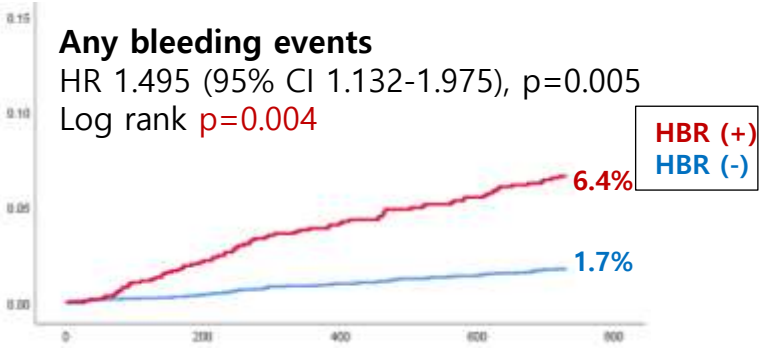
- **In patients with *High Thrombotic Risk* [HTR]** *: defined by the Complex PCI criteria*
- **In patients with *High Bleeding Risk* [HBR]** *: defined by the HBR criteria*

- **Risk of HTR and HBR for the secondary outcome [In the chronic phase after PCI]**





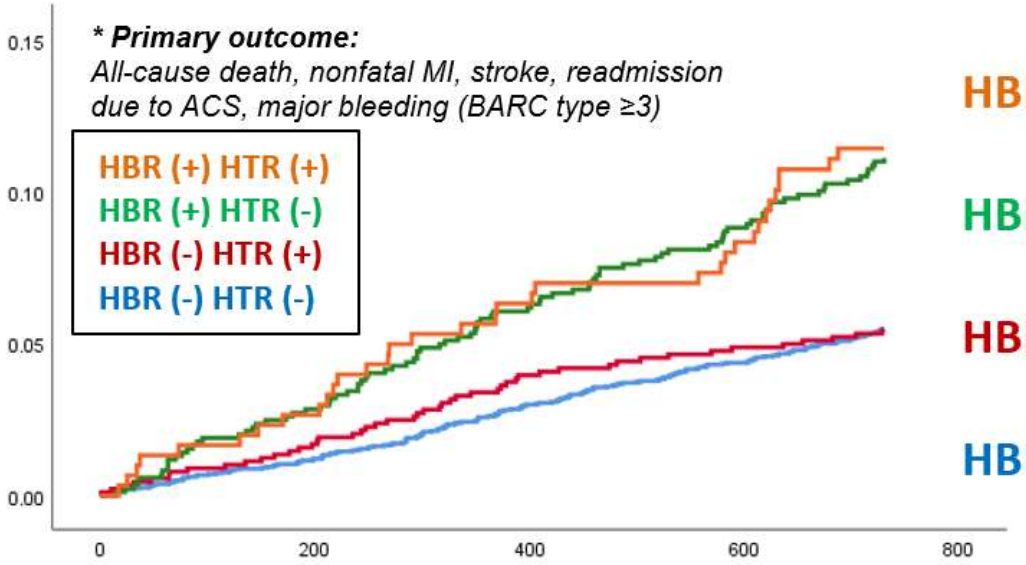


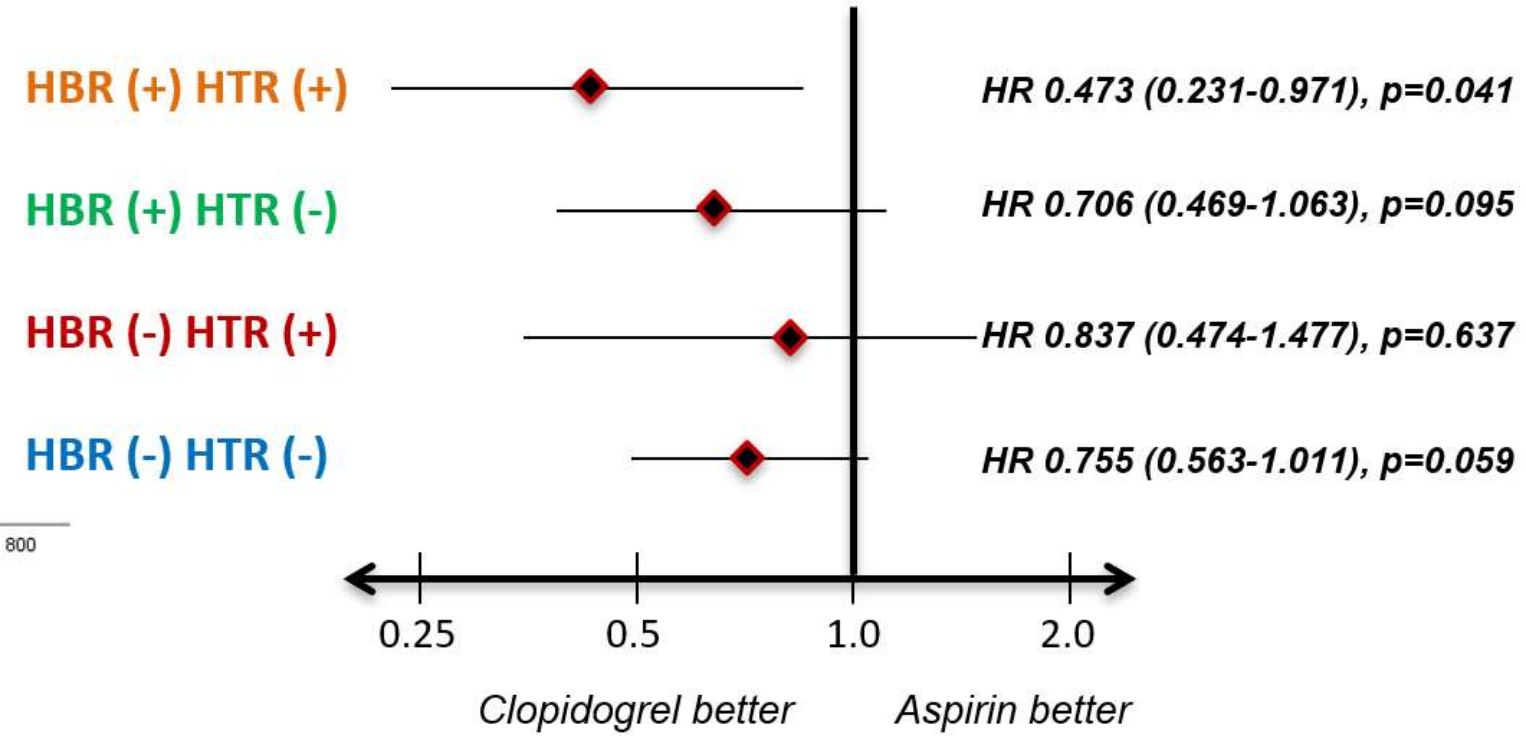


Subgroup analysis: By HBR…and HTR

HOST EXAM
EXtended Antiplatelet Monotherapy

- **Cumulative event curve of the primary outcome & Impact of Clopidogrel vs. Aspirin**





The clinical benefit of clopidogrel over aspirin was consistent in patients with or without HTR/HBR.

Patients with both HTR and HBR accounted for 5.5% of the total population and showed higher risk of clinical events. The benefit of clopidogrel over aspirin was prominent in this high-risk subset.

Conclusion and Summary

- The HOST-EXAM study and HOST-EXAM-extended study proved safety of clopidogrel monotherapy in **Stable CAD** patients.

- The point would be “how can we stabilize a CAD patient (including ACS patients and complex patients) to a “**Stable CAD**” patient?”.
  - ***As is****: After 1 year vs. Within 1 year*
  - **To be**: After stabilization vs. Before stabilization

- In whom should we consider a different strategy?
  - Afib-PCI, or polyvascular disease patients
  - Who may benefit from a stronger anti-thrombotic strategy?