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# New normal of SAPT : Aspirin drop era

**Kosin University Gospel Hospital**  
**Division of Cardiology**  
**Jung Ho Heo**

WE are living in the New Normal Era

in the days with Covid -19      In the days with Vaccinations

In the days with DAPT

In the days with SAPT



# Contents

01

## Guidelines recommendations on DAPT

02

## Controversy about Aspirin

– Primary prevention, GI toxicity

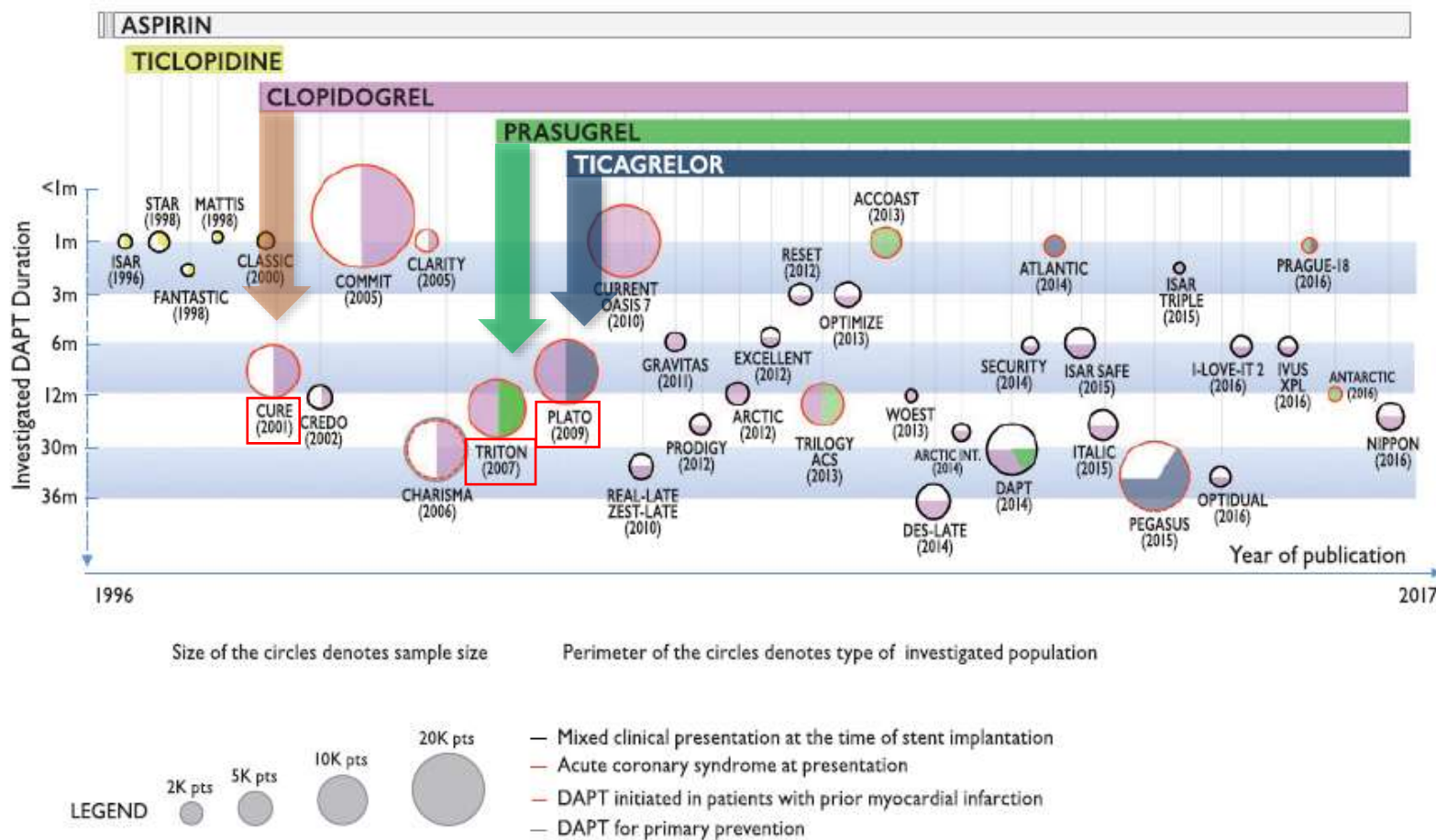
03

## P2Y<sub>12</sub> inhibitor trials exploring dropping Aspirin

– Ticagrelor  
– Clopidogrel

# After landmark studies about DAPT with P2Y<sub>12</sub> receptor antagonists released, DAPT has been conveying global patient protection.

## History of DAPT in patients with coronary artery disease



The size of the circles denotes sample size. The colours of perimeters identify the type of included patient populations within each study. The colours within each circle identify the antiplatelet agent(s) investigated.

# EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS\*

## CURE Trial

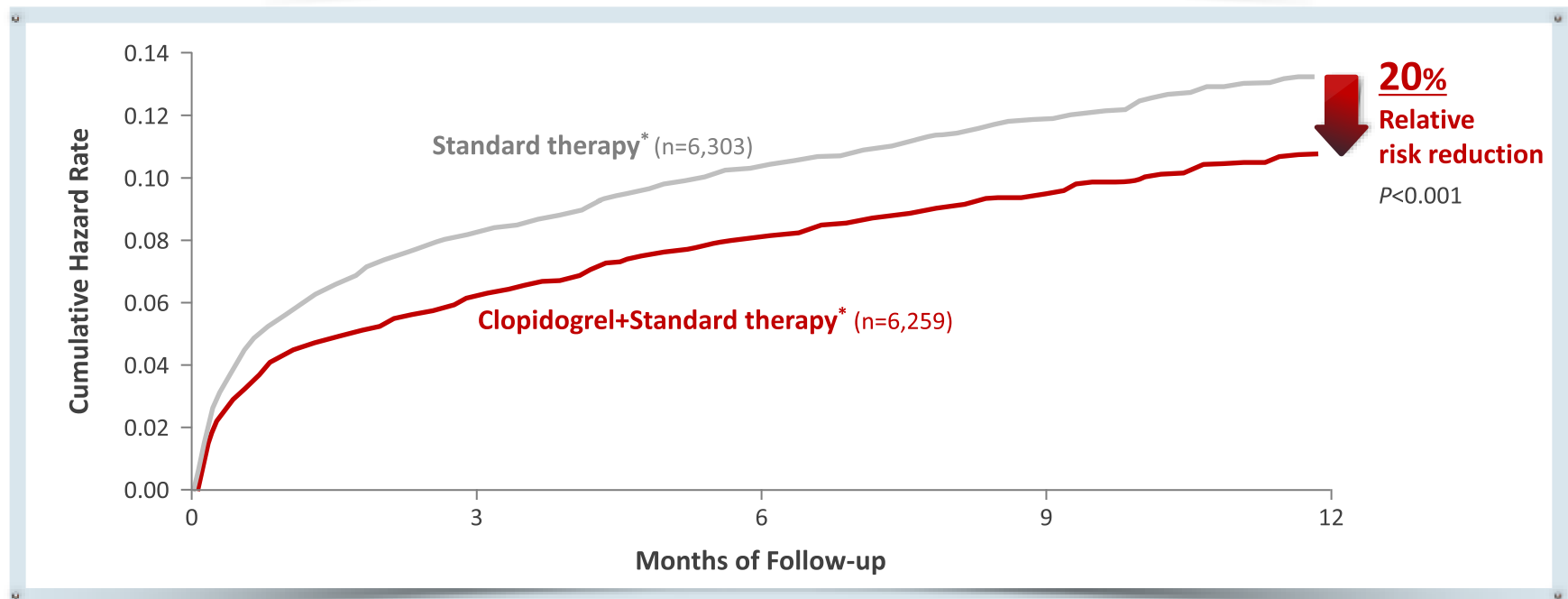
- 12,562 patients with NSTEMI-ACS
- Randomized to clopidogrel (300 mg loading dose and 75 mg daily maintenance dose) or placebo; background ASA
- Treatment at the discretion of the treating physician

# CURE:

## Establishing the long-term efficacy of clopidogrel DAPT

- **The first primary outcome occurred in 582 of the 6,259 patients in the clopidogrel group (9.3%) as compared with 719 of the 6,303 patients in the placebo group (11.4%); (relative risk, 0.80 95% CI, 0.72 to 0.90;  $P < 0.001$ )**

### Cumulative Events (Myocardial Infarction, Stroke, or Cardiovascular Death)



#### Study Design

We randomly assigned 12,562 patients who had presented within 24 hours after acute coronary syndromes without ST-segment elevation to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) (6,259 patients) or placebo (6,303 patients) in addition to aspirin for 3 to 12 months.

\*including ASA Time from onset to randomization=14.2h

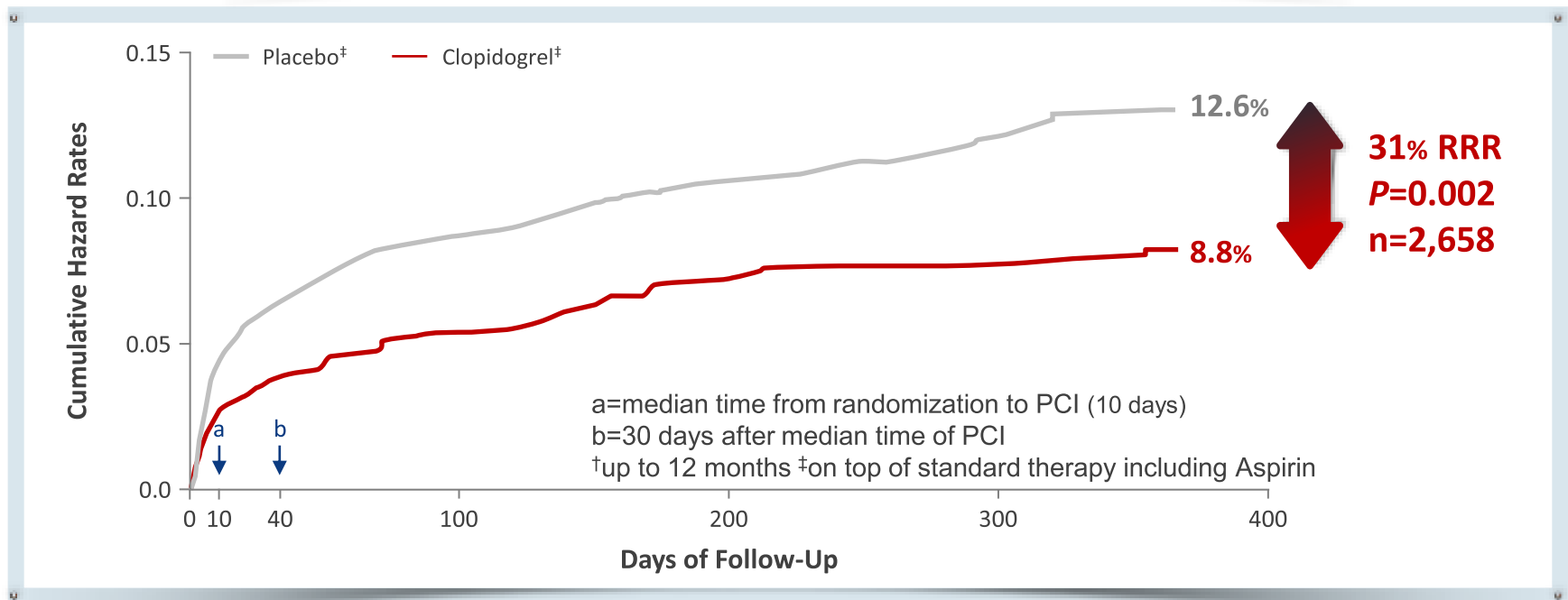
1. The CURE Trial Investigators. *N Engl J Med* 2001;345:494–502.

# PCI-CURE:

## Establishing the long-term efficacy of clopidogrel DAPT

- **For the endpoint of myocardial infarction (MI) or cardiovascular death from time of randomization to end of follow-up, treatment with clopidogrel\* resulted in a 31% relative risk reduction (8.8% clopidogrel vs 12.6% placebo;  $P=0.002$ )<sup>‡</sup>**

### Composite of CV-Death or MI from Randomization to End of Follow-Up<sup>†</sup>



Population: 2,658 patients with non-ST-elevation acute coronary syndrome undergoing PCI in the CURE study; Design: Randomized, double-blind, placebo-controlled trial; Treatment: Clopidogrel or placebo

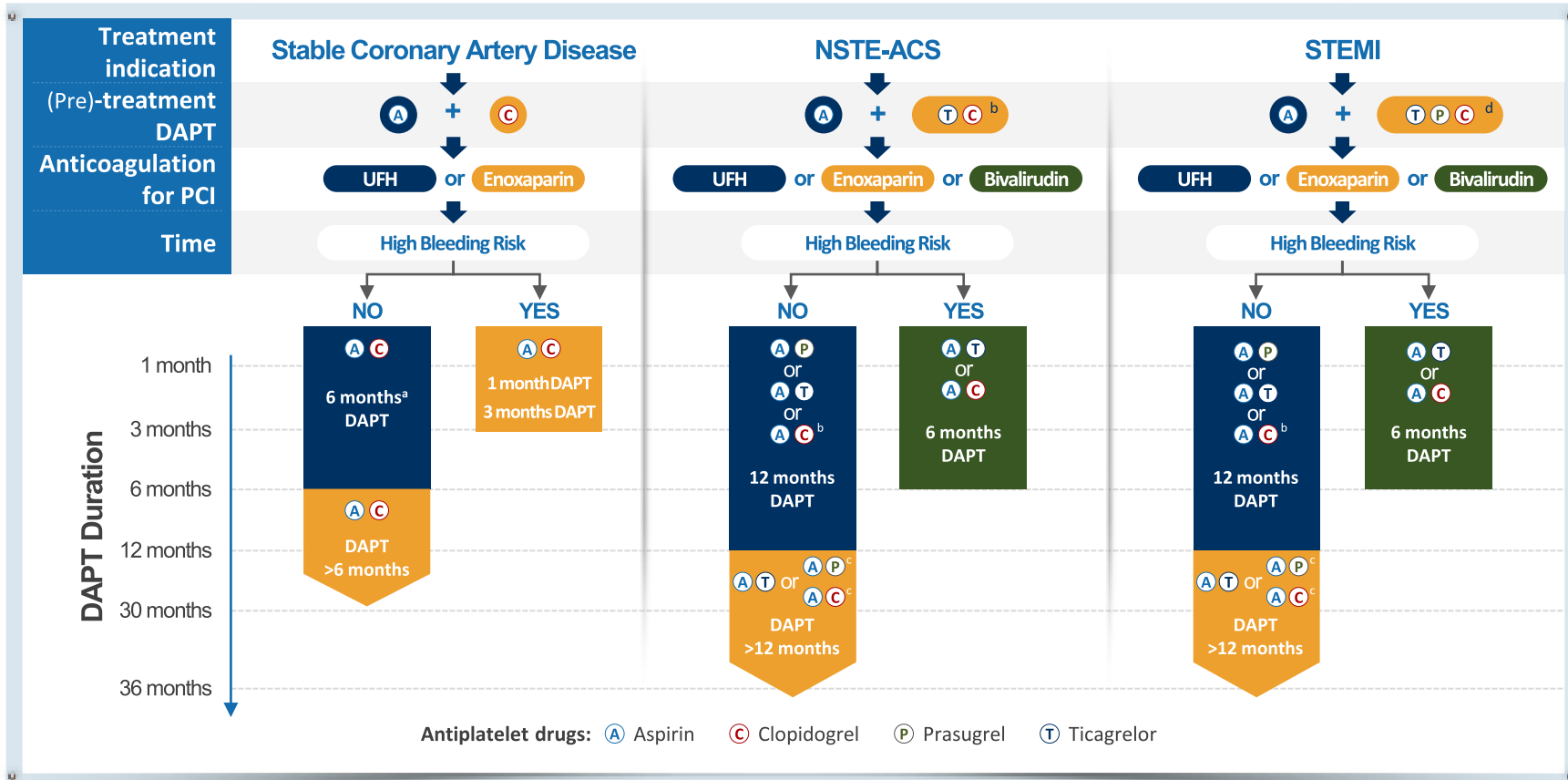
Primary endpoint: The composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI; Conclusion: In patients with acute coronary syndrome receiving aspirin, a strategy of clopidogrel pretreatment followed by long-term therapy is beneficial in reducing major cardiovascular events, compared with placebo





# 2018 ESC/EACTS Guideline: Algorithm for the use of antithrombotic drugs in patients undergoing PCI

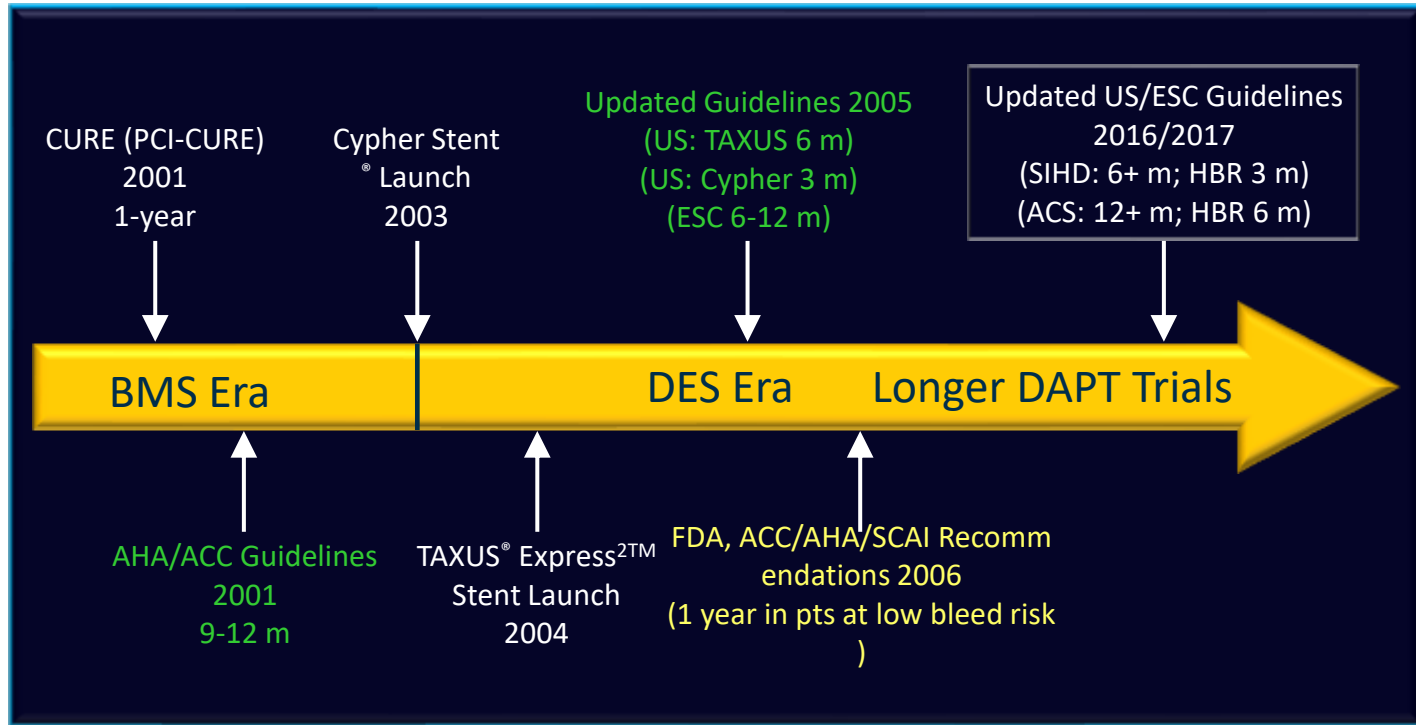
## Antithrombotic Treatment in Patients Undergoing Percutaneous Coronary Intervention



DAPT: DUAL ANTIPLATELET THERAPY  
 PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subseQuent Dual Anti Platelet Therapy, STEMI: ST-elevation myocardial infarction  
 High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score  $\geq 25$ ). Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb). Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.

a: After PCI with DCB 6 months. DAPT should be considered (Class IIa B). b: Clopidogrel if patient is not eligible for a treatment with prasugrel or ticagrelor. c: Clopidogrel or prasugrel if patient is not eligible for a treatment with ticagrelor. d: Pretreatment before PCI (or at the latest at the time of PCI), clopidogrel if potent P2Y<sub>12</sub> inhibitors are contraindicated or not available.

# Evolution of Optimal DAPT Post DES: Still Unclear?



# 2018 ESC/ EACTS Guideline: In SCAD patients undergoing PCI

## Recommendations for platelet inhibition

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Pre-treatment and antiplatelet therapy</b>		
Treatment with 600 mg clopidogrel is recommended in elective PCI patients once the coronary anatomy is known and a decision is made to proceed with PCI.	I	A
Pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C
In patients on a maintenance dose of 75 mg clopidogrel, a new loading dose of 600 mg may be considered once the indication for PCI is confirmed.	IIb	C
<b>Peri-interventional treatment</b>		
Aspirin is indicated before elective stenting.	I	A
An oral loading dose of aspirin (150-300 mg p.o. or 75-250 mg i.v.) is recommended if the patient is not pre-treated.	I	C
Clopidogrel (600 mg loading dose, 75 mg daily maintenance dose) is recommended for elective stenting.	I	A

ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; NSTEMI-ACS = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREDicting bleeding Complications In patients undergoing Stent implantation and subSEquent Dual Anti Platelet Therapy; SCAD = stable coronary artery disease;

STEMI = ST-elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

<sup>a</sup>Class of recommendation.; <sup>b</sup>Level of evidence

# 2018 ESC/ EACTS Guideline: In SCAD patients undergoing PCI

## Recommendations for platelet inhibition

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Post-interventional and maintenance treatment</b>		
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. <sup>c</sup>	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 $\geq 25$ ), DAPT should be considered for 3 months. <sup>d</sup>	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

ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; NSTEMI-ACS = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREDicting bleeding Complications In patients undergoing Stent implantation and subSEquent Dual Anti Platelet Therapy; SCAD = stable coronary artery disease;

STEMI = ST-elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.; <sup>a</sup>Class of recommendation.; <sup>b</sup>Level of evidence.; <sup>c</sup>These recommendations refer to stents that are supported by large-scale randomized trials with clinical endpoint evaluation leading to an unconditional CE mark.; <sup>d</sup>The evidence supporting this recommendation comes from two studies where the zotarolimus-eluting Endeavour stent was investigated in conjunction with a 3 month DAPT regimen.

# 2018 ESC/ EACTS Guideline: In NSTEMI-ACS patients undergoing PCI

## Recommendations for platelet inhibition

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Pre-treatment and antiplatelet therapy</b>		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 75-250 mg i.v.), and at a maintenance dose of 75-100 mg daily long-term.	I	A
A P2Y <sub>12</sub> inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding. Options are:	I	A
• Prasugrel in P2Y <sub>12</sub> -inhibitor naïve patients who proceed to PCI (60 mg loading dose, 10 mg daily dose).	I	B
• Ticagrelor irrespective of the preceding P2Y <sub>12</sub> inhibitor regimen (180 mg loading dose, 90 mg b.i.d).	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
For pre-treatment in patients with NSTEMI-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg b.i.d.), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
<b>Peri-interventional therapy</b>		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy.	I	A
It is recommended that anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent.	I	C

ACS = acute coronary syndrome; b.i.d. = twice daily; NSTEMI-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention;.

<sup>a</sup>Class of recommendation.; <sup>b</sup>Level of evidence

# 2018 ESC/ EACTS Guideline: In STEMI patients undergoing PCI

## Recommendations for platelet inhibition

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Pre-treatment and antiplatelet therapy</b>		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 75-250 mg i.v.), and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy	I	A
A potent P2Y <sub>12</sub> inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
<b>Peri-interventional therapy</b>		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A

ACS = acute coronary syndrome; b.i.d. = twice daily; PCI = percutaneous coronary intervention; STEMI= ST-elevation myocardial infarction  
<sup>a</sup>Class of recommendation.; <sup>b</sup>Level of evidence

# 2018 ESC Guidelines recommended considering de-escalation P2Y<sub>12</sub> inhibitor

- **Recommendations for post-interventional and maintenance treatment in patients with non-ST-elevation acute coronary syndromes and ST-elevation myocardial infarction undergoing percutaneous coronary intervention**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<p><b>De-escalation of P2Y<sub>12</sub> inhibitor treatment</b>            (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for 12-month potent platelet inhibition</p>	<p><b>IIb</b></p>	<p><b>B</b></p>

# Modalities of de-escalation

- Safety concerns associated with switching between antiplatelet agents, has prompted the use of clopidogrel for patients with ACS especially after PCI as a de-escalation strategy.

## De-escalation modalities in patients with ACS

De-escalation	When	How
Switching from ticagrelor to clopidogrel	<ul style="list-style-type: none"> <li>- Major bleeding events</li> <li>- Adverse reactions (such as dyspnea)</li> <li>- Need for oral anticoagulation</li> </ul>	Clopidogrel 600 mg LD then 75 mg/d* Or clopidogrel 75 mg/d directly*
From prasugrel to clopidogrel	<ul style="list-style-type: none"> <li>- Major bleeding events</li> <li>- Need for oral anticoagulation</li> </ul>	Clopidogrel 600 mg LD then 75 mg/d*
Early stage potent P2Y <sub>12</sub> receptor inhibitor monotherapy	<ul style="list-style-type: none"> <li>- Increased atherothrombotic risk</li> <li>- Increased bleeding risk</li> </ul>	1 to 3 months DAPT followed by P2Y <sub>12</sub> receptor inhibitor Monotherapy
Reducing the dose of P2Y <sub>12</sub> receptor inhibitors	- Stable period after myocardial infarction, with at least one additional atherothrombotic risk factor	Ticagrelor 90 mg bid 1 year then 60 mg bid*
Shortening the duration of dual antiplatelet therapy	- Stable CAD or low-risk ACS (unstable angina) patients with newer generation DES	3 or 6 months of DAPT then aspirin or P2Y <sub>12</sub> receptor inhibitor monotherapy

\* Combined with aspirin. ACS, acute coronary syndrome; CAD, coronary artery disease; DES, drug-eluting stent; DAPT, dual antiplatelet therapy; LD: loading dose.



# Contents

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on DAPT**

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Aspirin**

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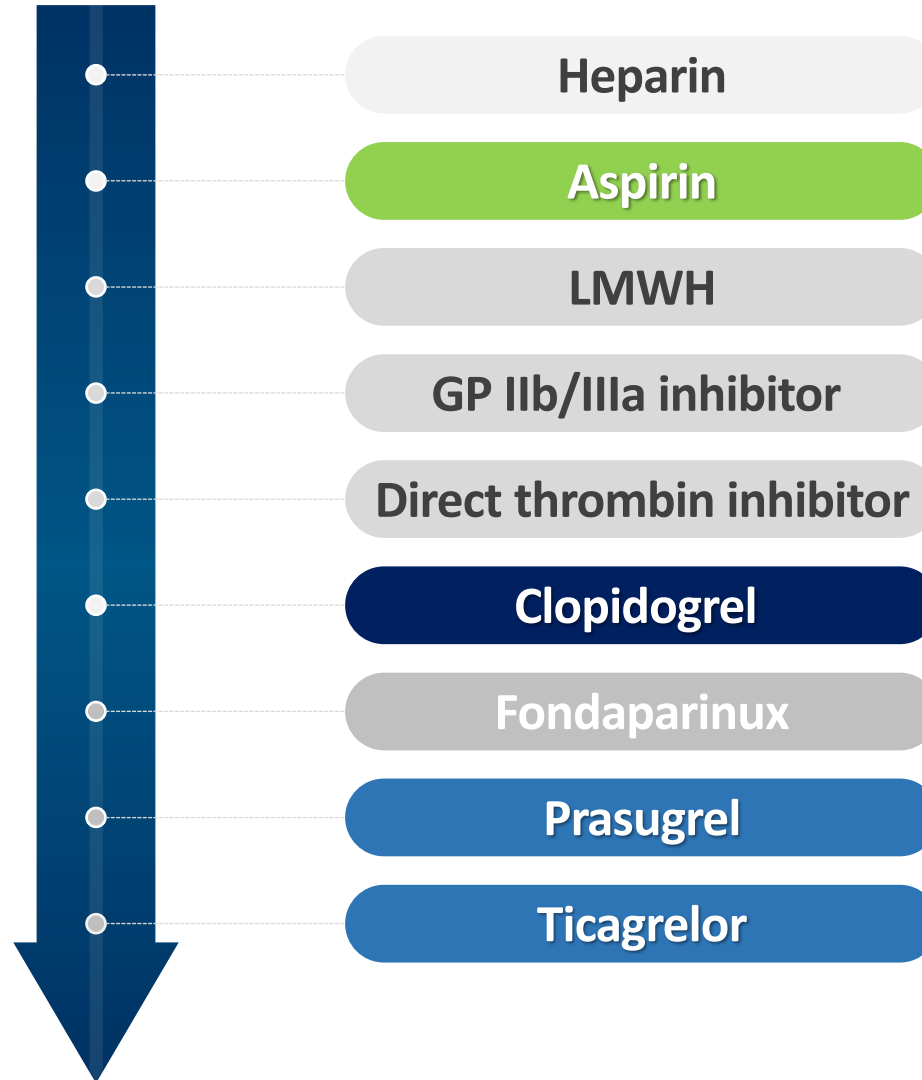
**P2Y<sub>12</sub> inhibitor trials  
exploring dropping Aspirin**

– Ticagrelor

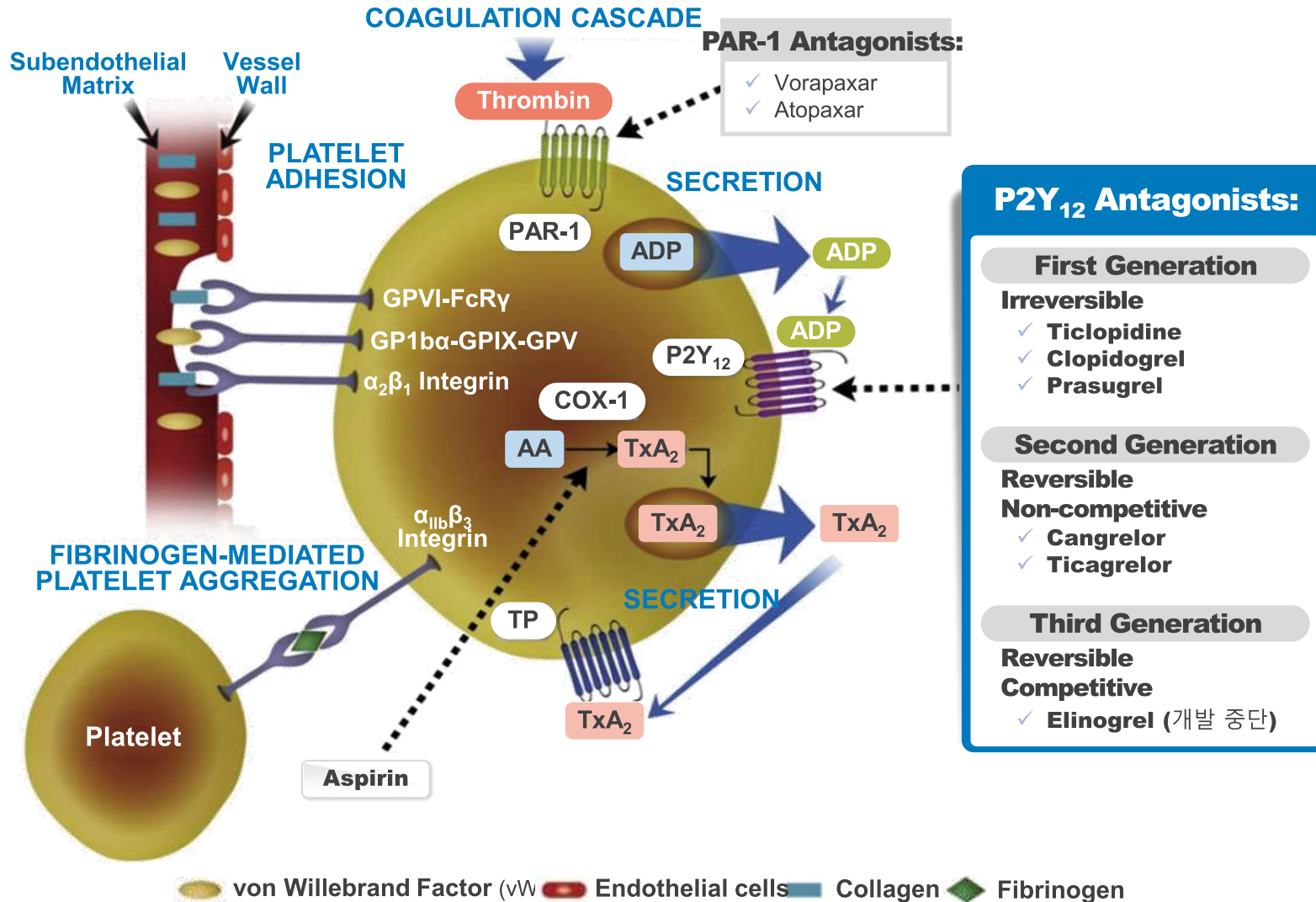
– Clopidogrel

# Antithrombotics for Acute Coronary Syndrome(ACS)

FDA Approval

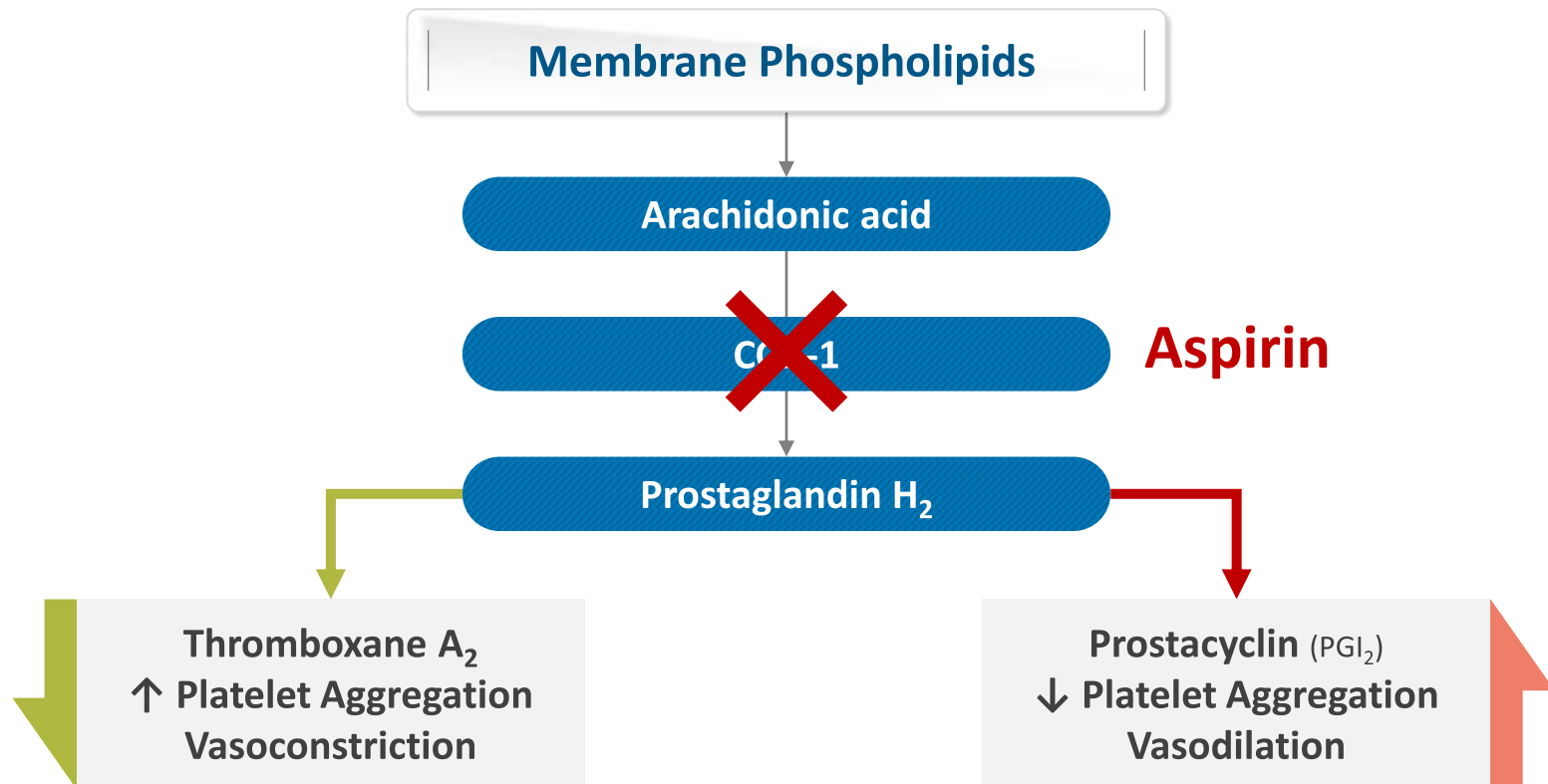


# P2Y<sub>12</sub> Receptor Antagonists: Mode of action



# Mechanism of Action: Aspirin

- Irreversible inhibition of cyclooxygenase enzyme (COX-1) via acetylation
- Small dose of aspirin inhibits thromboxane (TXA<sub>2</sub>) synthesis in platelets but not inhibit prostacyclin (PGI<sub>2</sub>) synthesis in endothelium (larger dose)



# Uses of Aspirin



- **Prophylaxis of thromboembolism e.g.** prevention of TIA, ischemic stroke and MI
  - **Prevention of ischemic events** in patients with unstable angina pectoris
- **Aspirin can be combined with other antiplatelet drugs** (clopidogrel, etc.) **or anticoagulants** (heparin, etc.)

# Low-Dose Aspirin Is Now Out of Favor with the Medical Establishment

*No significant effect in primary prevention  
But clear gastrotoxicity*

"스텐트 시술받은 환자에 아스피린 안 써도 출혈관리 가능"

♾️ 고종관 기자 | ⌚ 승인 2019.07.25 16:08

| 삼성서울병원 권현철 교수팀, 대규모 환자 대상으로 항혈소판 단독요법과

FEATURE | TCT 2019

## Off Script: The TWILIGHT of Aspirin? A Brief History of ASA's Rise and Fall

The TCT 2019 late breaker speaks to the slow erosion of aspirin's position in the pantheon of cardiovascular pharmacology



By [Kwan S. Lee](#) | September 29, 2019

THE LANCET

REVIEW | VOLUME 393, ISSUE 10196, P2156-2167, MAY 25, 2019

### The rise and fall of aspirin in the primary prevention of cardiovascular disease

[Inbar Raber, MD](#) · [Cian P McCarthy, MB](#) · [Muthiah Vaduganathan, MD](#) · [Prof Deepak L Bhatt, MD](#) · [Prof David A Wood, MSc](#) · [Prof John G F Cleland, MD](#) · et al. [Show all authors](#)

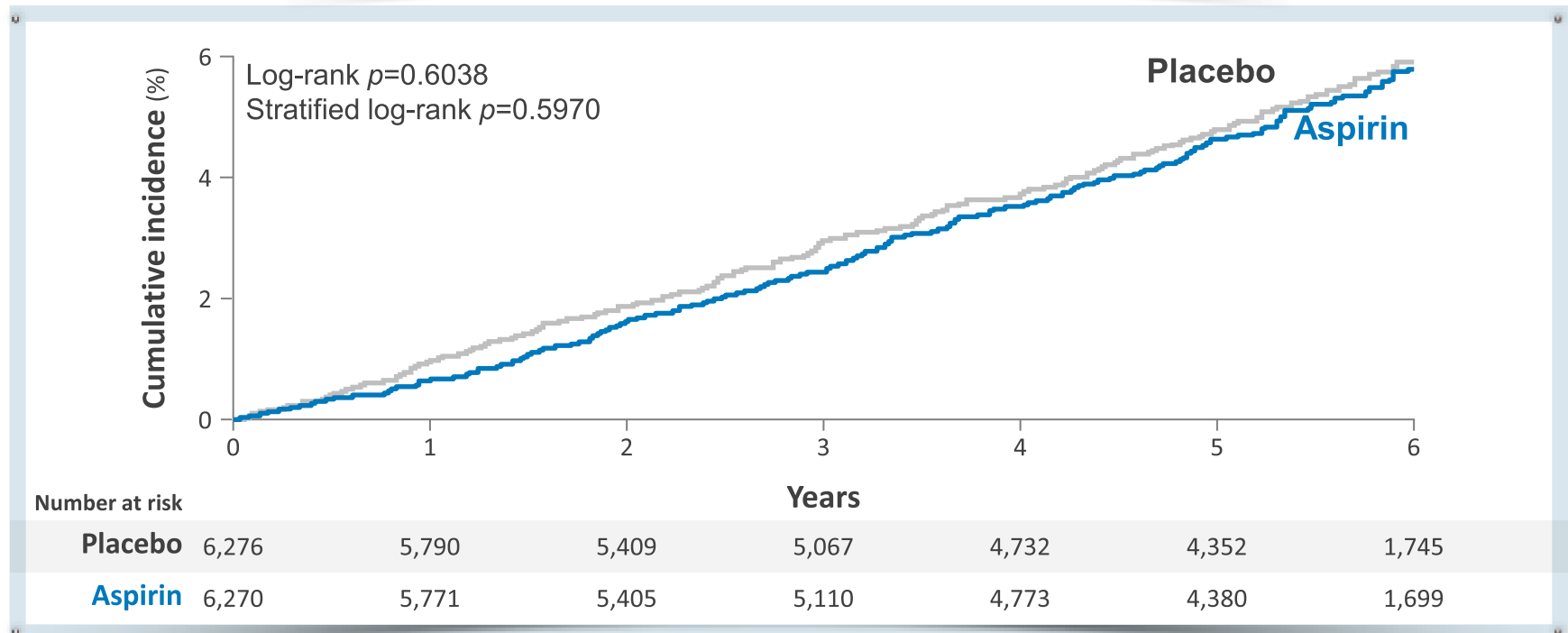
Published: May 25, 2019 · DOI: [https://doi.org/10.1016/S0140-6736\(19\)30541-0](https://doi.org/10.1016/S0140-6736(19)30541-0)

# Aspirin Evidence: ARRIVE

No significant effect in primary prevention in patients at moderate risk of CVD

- Aspirin treatment **did not lower risk of major cardiovascular events in patients at moderate risk of cardiovascular disease**

## Kaplan-Meier cumulative incidence of primary outcome



ARRIVE is a randomised, double-blind, placebo-controlled, multicentre study done in seven countries. Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate on the basis of the number of specific risk factors. Median follow-up was 60 months

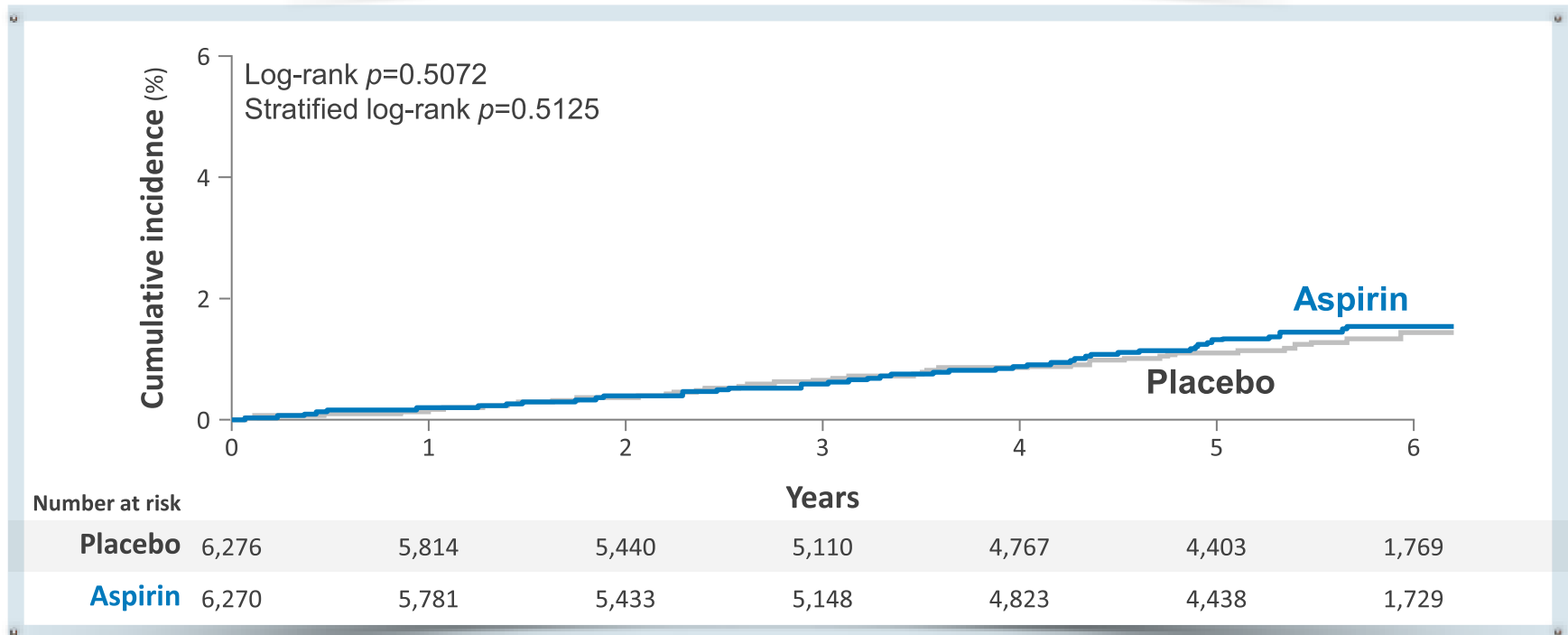
CVD: cardiovascular disease

# Aspirin Evidence: ARRIVE

No significant effect in primary prevention in patients at moderate risk of CVD

- Aspirin treatment **did not lower risk of stroke** in patients at moderate risk of cardiovascular disease.

## Kaplan-Meier cumulative incidence of stroke



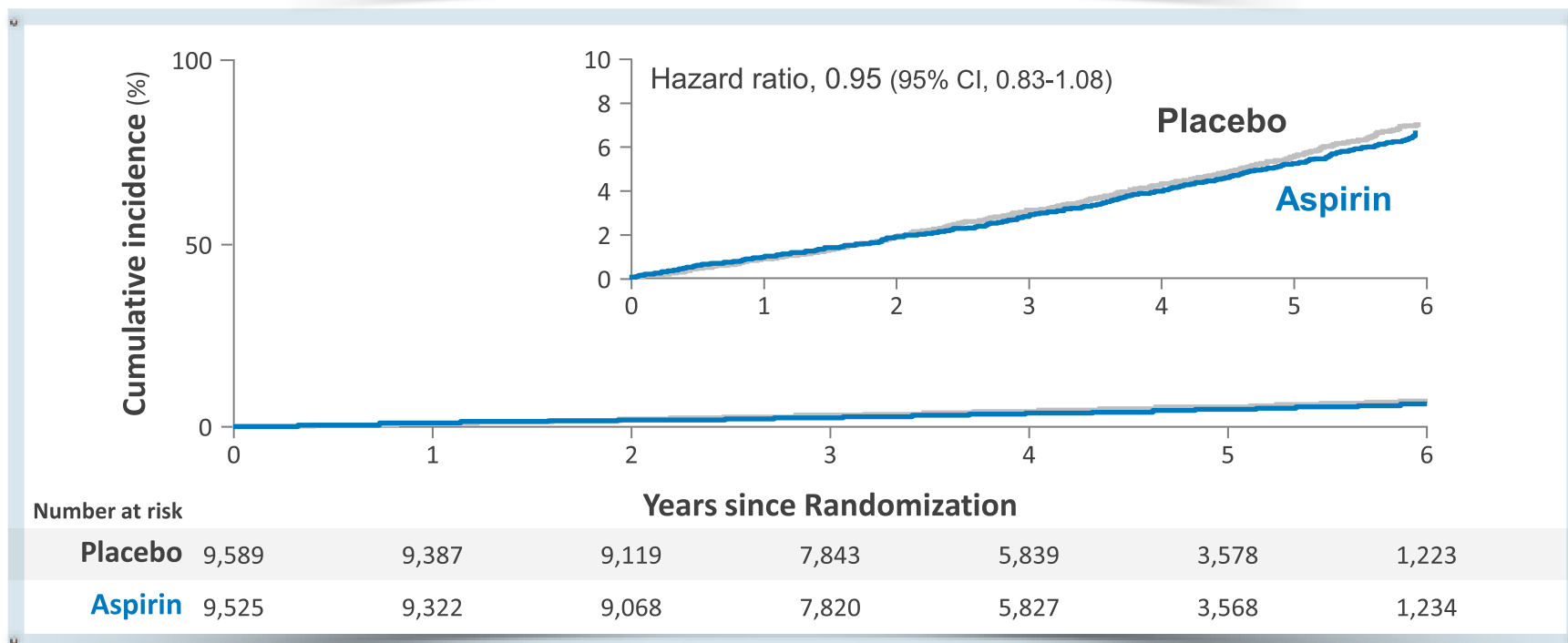


# Aspirin Evidence: ASPREE

No significant effect in primary prevention in the healthy elderly

- In **ASPREE** study, the use of low-dose aspirin as a primary prevention strategy in older adults did **not result in a significantly lower risk of cardiovascular disease than placebo**

Cumulative incidence of cardiovascular disease\*



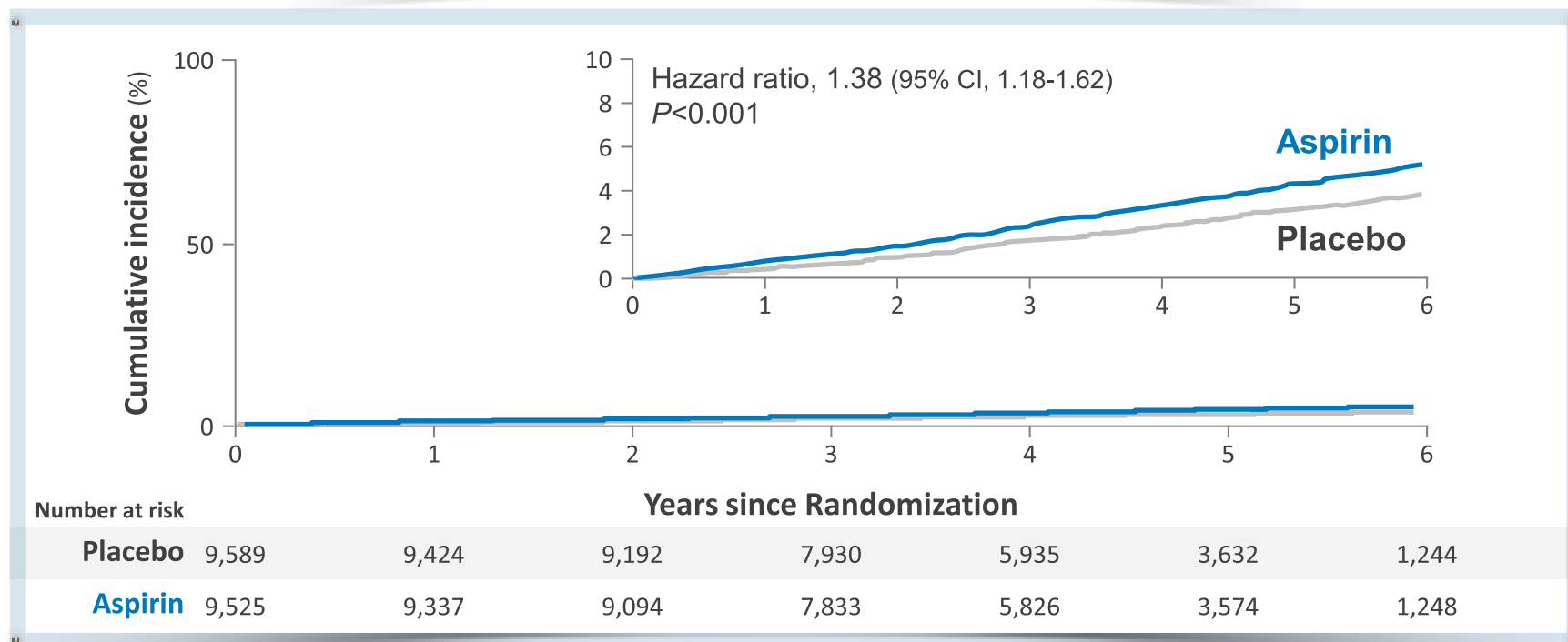
\*A composite of fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure  
Community-dwelling men and women in Australia and the United States who were 70 years of age or older (or  $\geq 65$  years of age among blacks and Hispanics in the United States) and did not have cardiovascular disease, dementia, or disability were enrolled. Participants were randomly assigned to receive 100 mg of enteric-coated aspirin or placebo.

# Aspirin Evidence: ASPREE

## Higher risk of major hemorrhage in the healthy elderly

- In ASPREE study, the use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage than placebo**

### Cumulative incidence of major hemorrhage\*



\*Major hemorrhage (a composite of hemorrhagic stroke, symptomatic intracranial bleeding, or extracranial bleeding that led to transfusion, hospitalization, prolongation of hospitalization, surgery, or death)

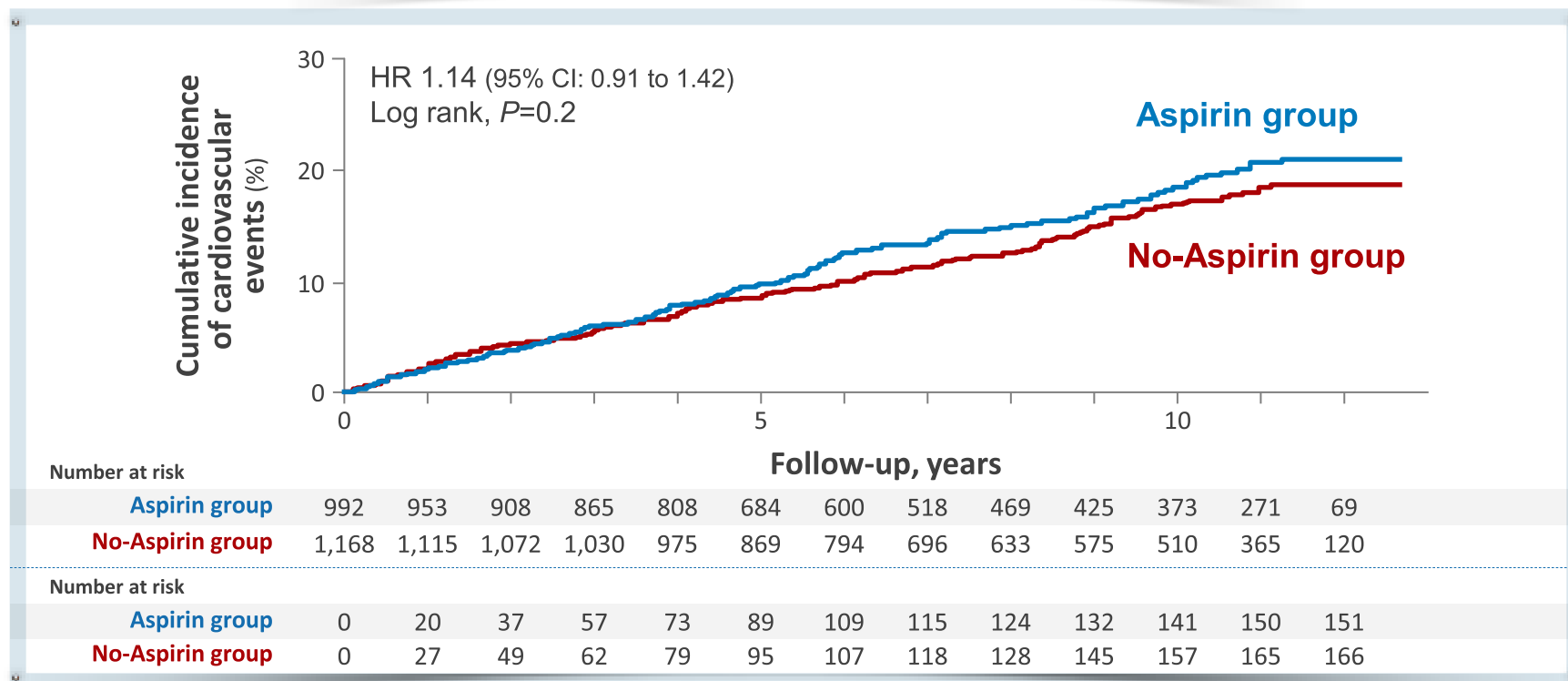
Community-dwelling men and women in Australia and the United States who were 70 years of age or older (or  $\geq 65$  years of age among blacks and Hispanics in the United States) and did not have cardiovascular disease, dementia, or disability were enrolled. Participants were randomly assigned to receive 100 mg of enteric-coated aspirin or placebo.

# Aspirin Evidence: JPAD

No significant effect in primary prevention in patients with T2DM

- **Low-dose aspirin did not affect the risk for cardiovascular events in patients with **type 2 diabetes mellitus** in a primary prevention setting.**

## The incidence of the primary end point



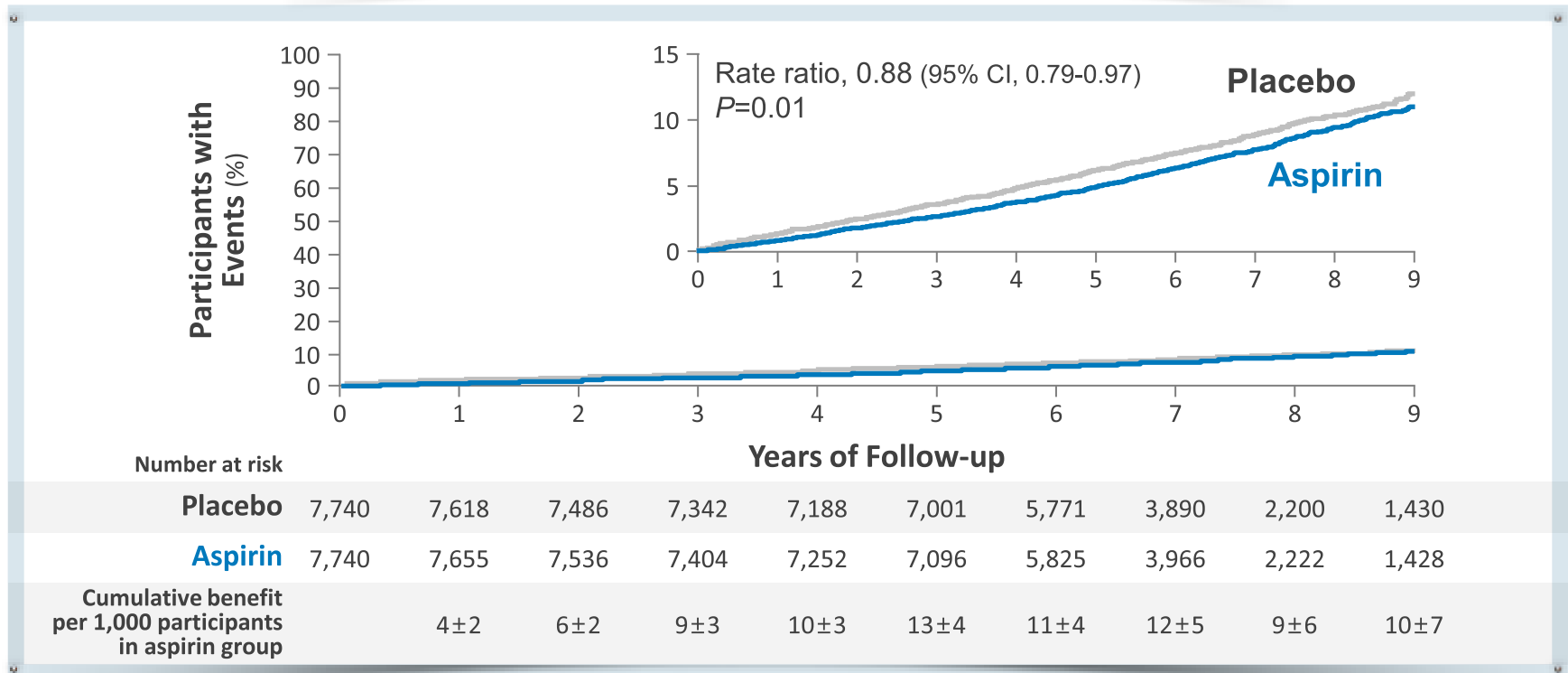
The JPAD trial (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) was a randomized, open-label, standard care-controlled trial examining whether low-dose aspirin affected cardiovascular events in 2539 Japanese patients with type 2 diabetes mellitus and without preexisting cardiovascular disease.; Primary end points were cardiovascular events, including sudden death, fatal or nonfatal coronary artery disease, fatal or nonfatal stroke, and peripheral vascular disease. T2DM, type 2 diabetes mellitus

# Aspirin Evidence: ASCEND

## Effects for Primary Prevention in Persons with Diabetes Mellitus

- In ASCEND Study, the low-dose aspirin led to a lower risk of serious vascular events than placebo among persons with diabetes who did not have evident cardiovascular disease at trial entry.

### First serious vascular event



15,480 adults who had diabetes but no evident cardiovascular disease were randomly assigned to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding).

# Aspirin Evidence: ASCEND

## Effects for Primary Prevention in Persons with Diabetes Mellitus

- In ASCEND Study, aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events.**

### Effect of aspirin on vascular outcome and major bleeding

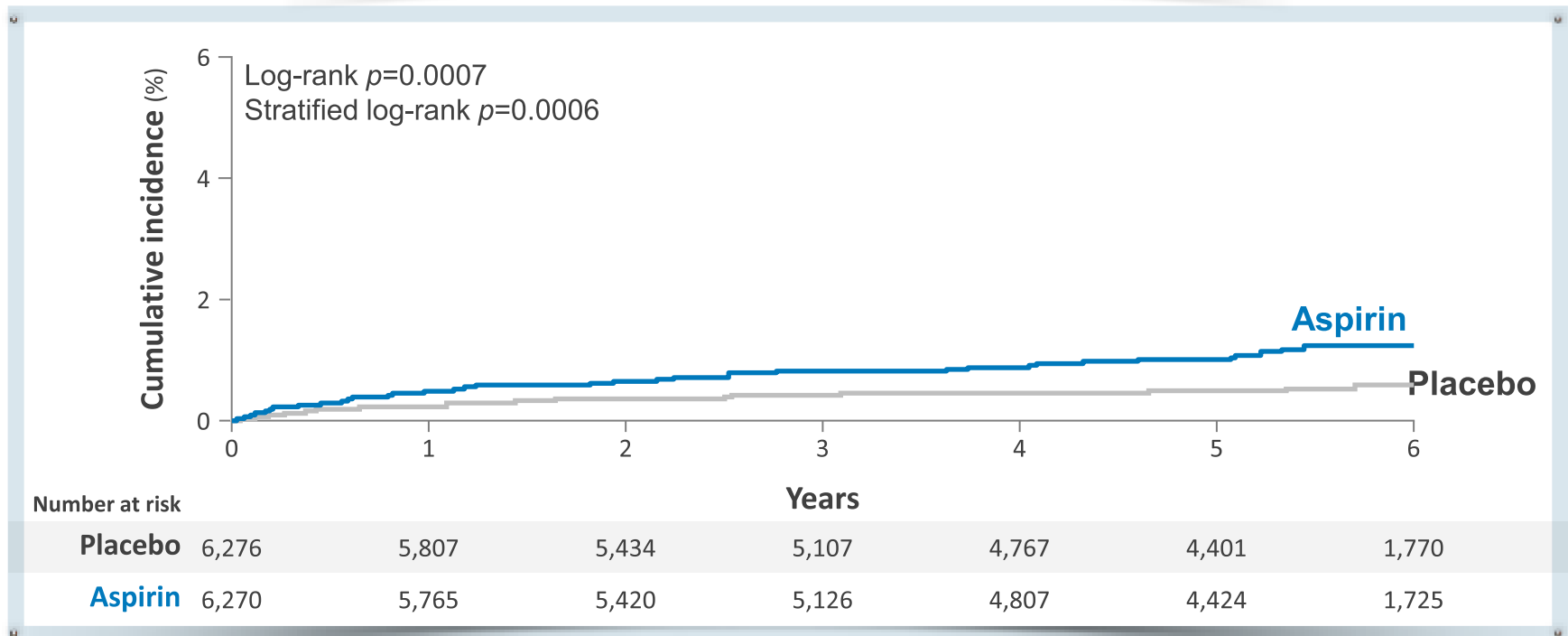
Type of Event	Aspirin Group (N=7,740)	Placebo Group (N=7,740)	Rate Ratio (95% CI)	P Value
	<i>no. of participants with event (%)</i>			
<b>Vascular Outcomes</b>				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80-1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73-1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75-1.10)	
<b>Any serious vascular event excluding TIA</b>	<b>542 (7.0)</b>	<b>587 (7.6)</b>	<b>0.92 (0.82-1.03)</b>	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69-1.04)	
<b>Any serious vascular event including TIA</b>	<b>658 (8.5)</b>	<b>743 (9.6)</b>	<b>0.88 (0.79-0.97)</b>	<b>0.01</b>
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76-1.02)	
<b>Any serious vascular event or revascularization</b>	<b>833 (10.8)</b>	<b>936 (12.1)</b>	<b>0.88 (0.80-0.97)</b>	
<b>Major Bleeding</b>				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82-1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62-1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05-1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18-2.44)	
<b>Any major bleeding</b>	<b>314 (4.1)</b>	<b>245 (3.1)</b>	<b>1.36 (1.09-1.52)</b>	<b>0.003</b>

# Risk of GI Bleeding

Higher risk of gastrointestinal bleeding in patients at moderate risk of CVD

- In ARRIVE, rates of gastrointestinal bleeding events were higher in the aspirin treatment group.

## Kaplan-Meier cumulative incidence of gastrointestinal bleeding



ARRIVE is a randomised, double-blind, placebo-controlled, multicentre study done in seven countries. Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate on the basis of the number of specific risk factors. Median follow-up was 60 months  
CVD, cardiovascular disease

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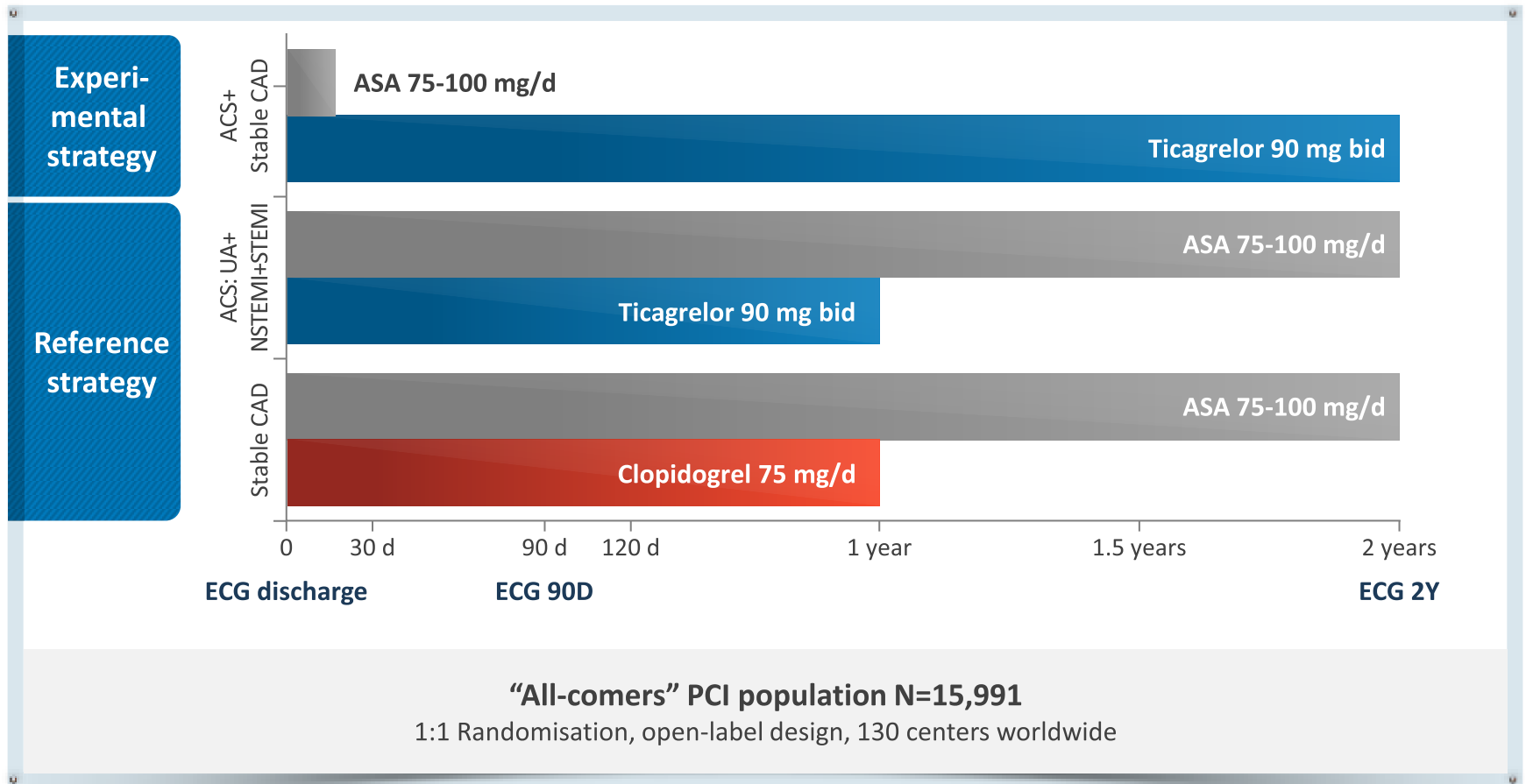
**P2Y<sub>12</sub> inhibitor trials  
exploring dropping Aspirin**

– Ticagrelor

– Clopidogrel

# GLOBAL-LEADERS :

## Ticagrelor monotherapy not superior to Aspirin monotherapy



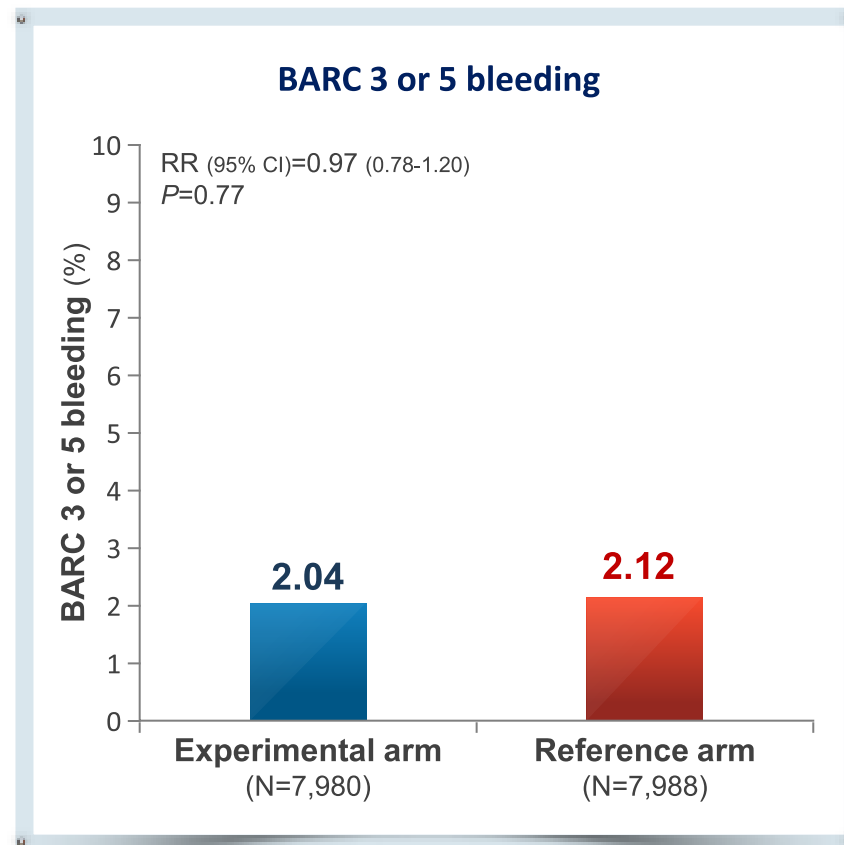
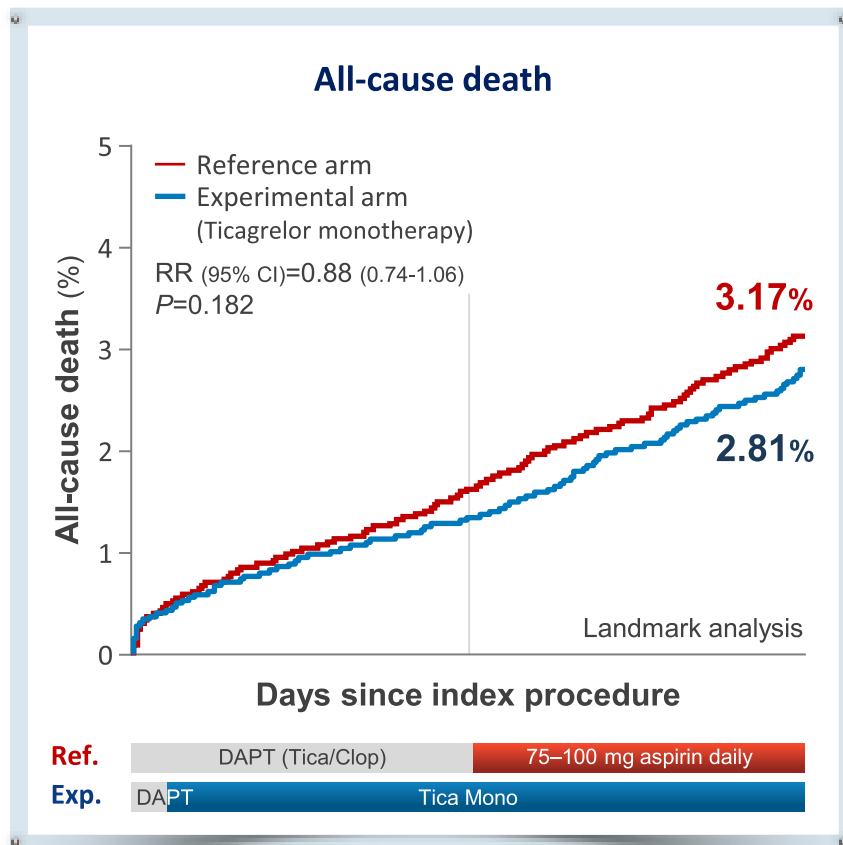
- **Primary endpoint: Composite of all-cause mortality or non-fatal new Q-wave MI up to 2 years post randomization**
- **Safety endpoint: Investigator-reported BARC 3 or 5 bleeding up to 2 years**



# GLOBAL-LEADERS :

## Ticagrelor monotherapy not superior to Aspirin monotherapy

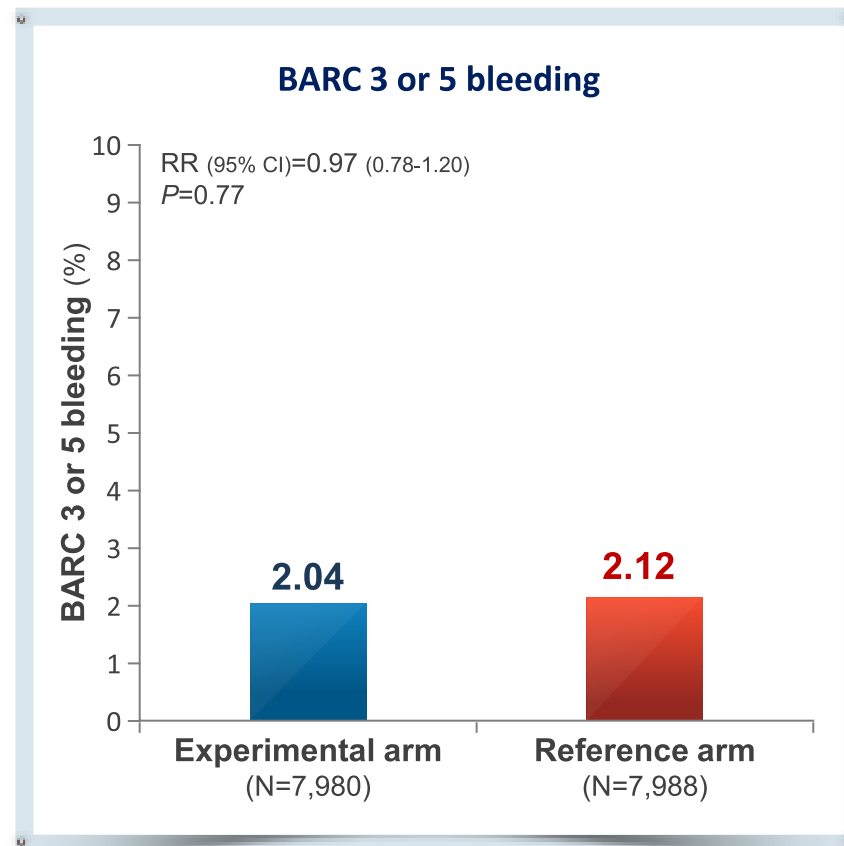
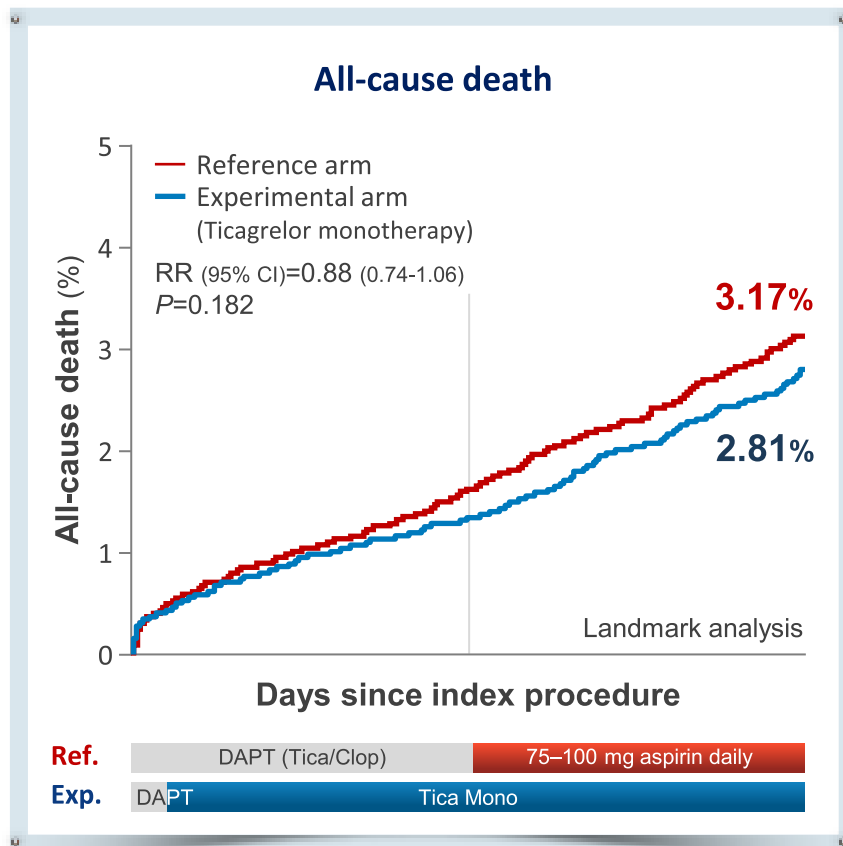
### Kaplan Meier estimate of mortality and safety outcome at 2 years



# GLOBAL-LEADERS :

## Ticagrelor monotherapy not superior to Aspirin monotherapy

### Kaplan Meier estimate of mortality and safety outcome at 2 years



# TWILIGHT study

## Objective

To determine whether switching to ticagrelor monotherapy after 3 months of DAPT we examined the effect of ticagrelor alone as compared with ticagrelor plus aspirin regarding clinically relevant bleeding among patients who were at high risk for bleeding or an ischemic event and had undergone PCI

## Study Design

After 3 months of treatment with ticagrelor plus aspirin, patients who had not had a major bleeding event or ischemic event continued to take ticagrelor and were randomly assigned to receive aspirin or placebo for 1 year.

R  
N=7,119

Ticagrelor mono

DAPT with ASA+Ticagrelor

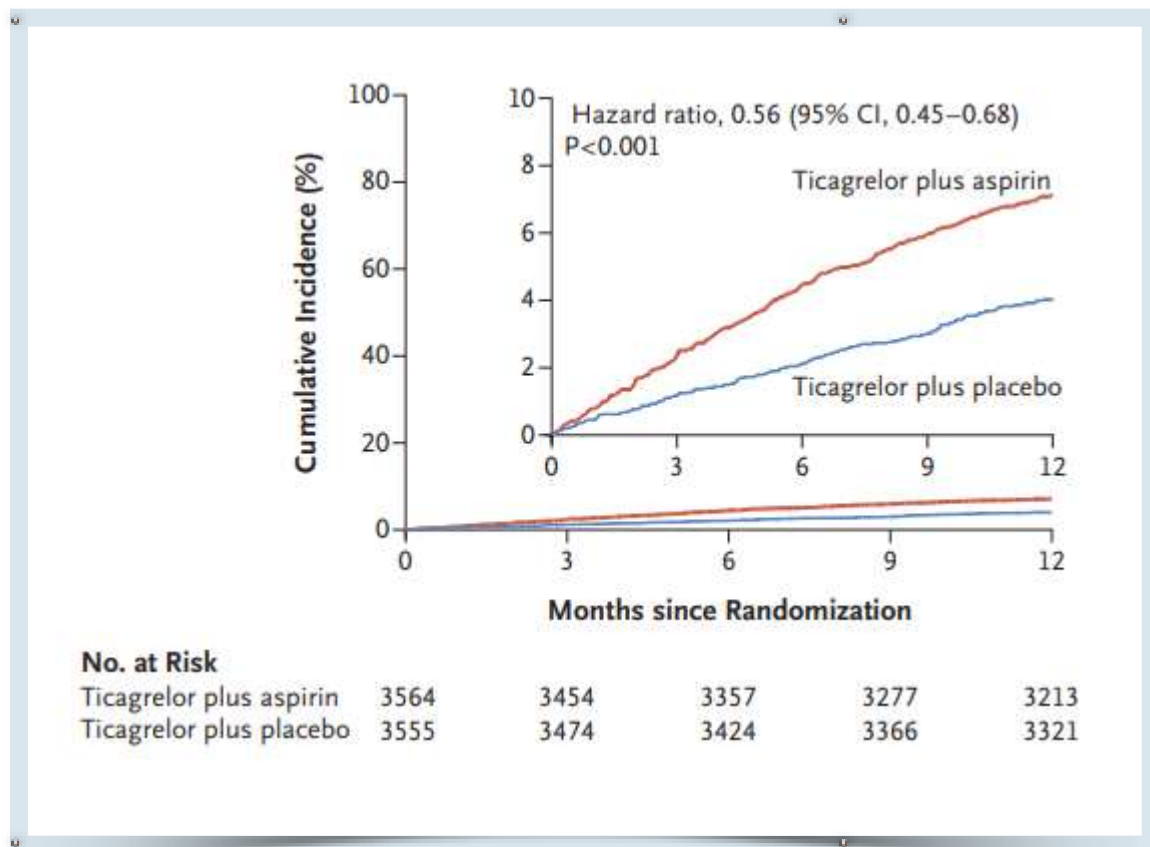
Treatment  
Duration :  
12 months

## Endpoint

- Primary outcome: Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding
- Secondary outcome: composite end point of death from any cause, nonfatal myocardial infarction, or nonfatal stroke, using a noninferiority hypothesis with an absolute margin of 1.6 percentage points

# TWILIGHT study

## Kaplan–Meier Estimates of the Incidence

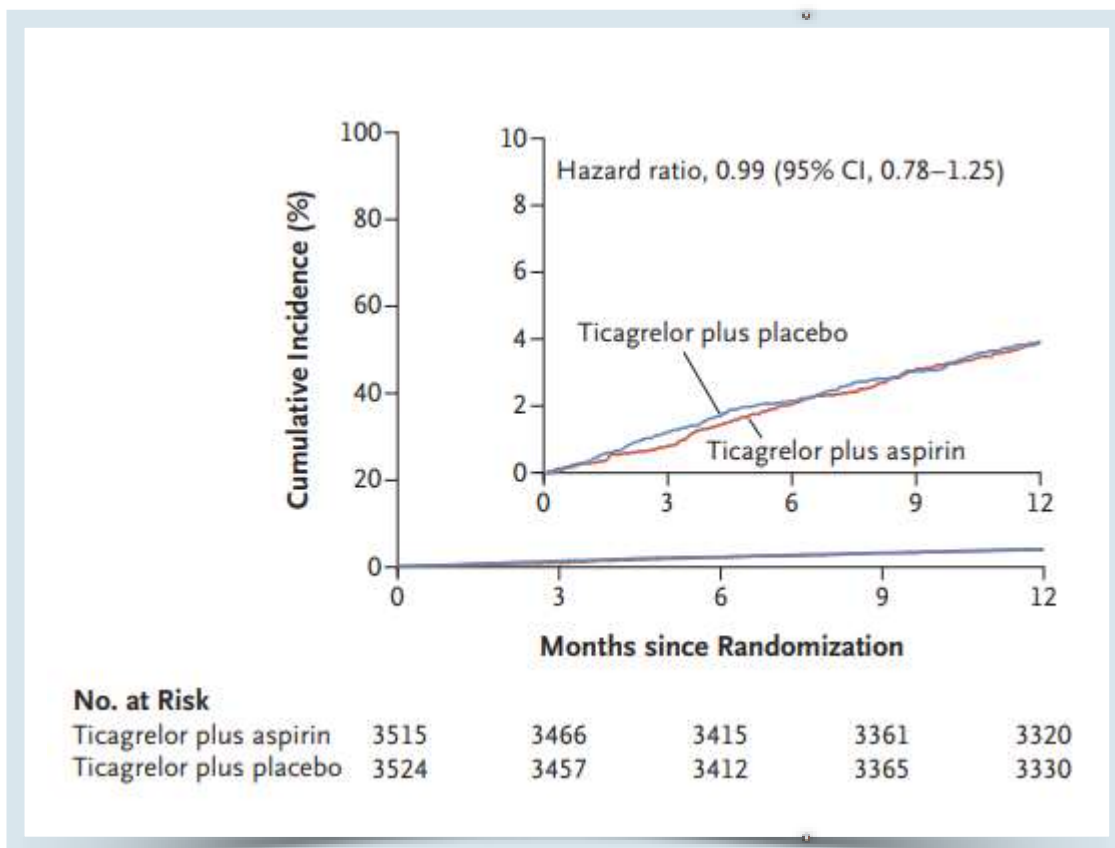


**Primary endpoint:**  
**BARC Type 2, 3, or 5 Bleeding 1 Year**  
**after Randomization (Intention-to-Treat**  
**Population)**

the incidence of the primary end point was 4.0% among patients randomly assigned to receive ticagrelor plus placebo and 7.1% among patients assigned to receive ticagrelor plus aspirin (hazard ratio, 0.56; 95% confidence interval [CI], 0.45 to 0.68; P<0.001)

# TWILIGHT study

## Kaplan Meier estimate of mortality and safety outcome at 2 years



**Key secondary endpoint:  
Incidence of Death from Any Cause,  
Nonfatal Myocardial Infarction, or  
Nonfatal Stroke 1 Year after  
Randomization  
(Per-Protocol Population).**

The key secondary composite end point of death from any cause, nonfatal myocardial infarction, or nonfatal stroke occurred in 135 patients (3.9%) who received ticagrelor plus placebo and in 137 patients (3.9%) who received ticagrelor plus aspirin (hazard ratio, 0.99; 95% CI, 0.78 to 1.25), for a difference in risk of  $-0.06$  percentage points (95% CI,  $-0.97$  to  $0.84$ )

# TICO randomized trial : Ticagrelor monotherapy vs. DAPT in ACS

## Objective

To determine whether switching to ticagrelor monotherapy after 3 months of DAPT reduces net adverse clinical events compared with ticagrelor-based 12-month DAPT in patients with ACS treated with drug-eluting stents.

## Study Design

A randomized multicenter trial was conducted in **3056 patients with ACS treated with drug-eluting stents** between August 2015 and October 2018 at 38 centers in South Korea. Follow-up was completed in October 2019



3month  
DAPT

Ticagrelor mono  
(n=1,527)

DAPT with ASA+Tcagrelor  
(n=1,529)

Treatment  
Duration :  
12 months

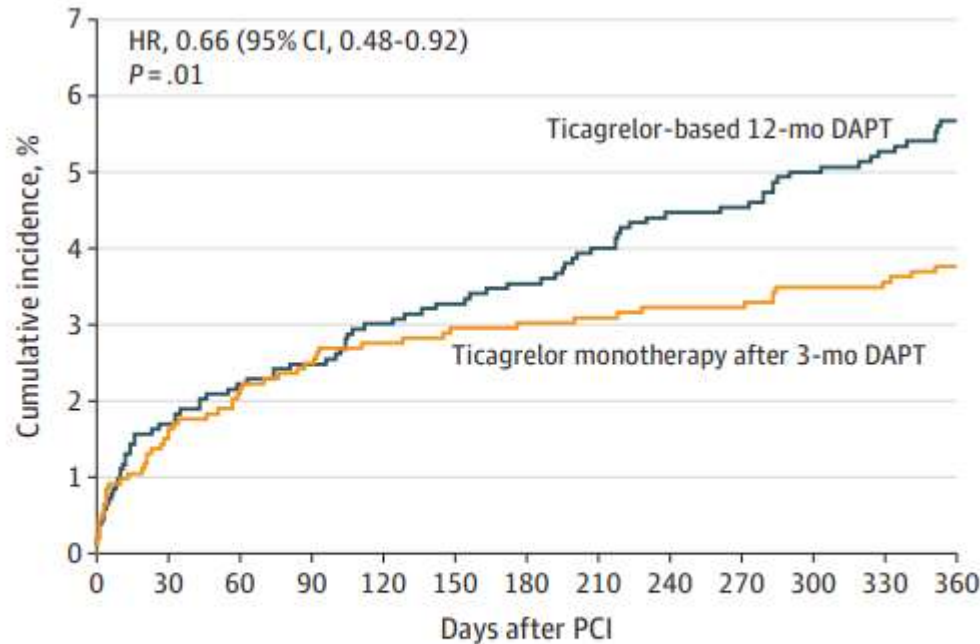
## EndPoints

- Primary outcome: 1-year net adverse clinical event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events (death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization).
- Secondary outcome: major bleeding and major adverse cardiac and cerebrovascular events.

# TICO randomized trial : Ticagrelor monotherapy vs. DAPT in ACS

## Time-to-Event Curves for the Primary Outcome and Landmark Analysis at 3 Months

Primary outcome of the net adverse clinical event



No. at risk

12-mo DAPT	1529	1500	1489	1481	1466	1460	1455	1442	1432	1430	1423	1418	1407
3-mo DAPT	1527	1498	1483	1471	1462	1456	1452	1442	1437	1437	1432	1430	1424

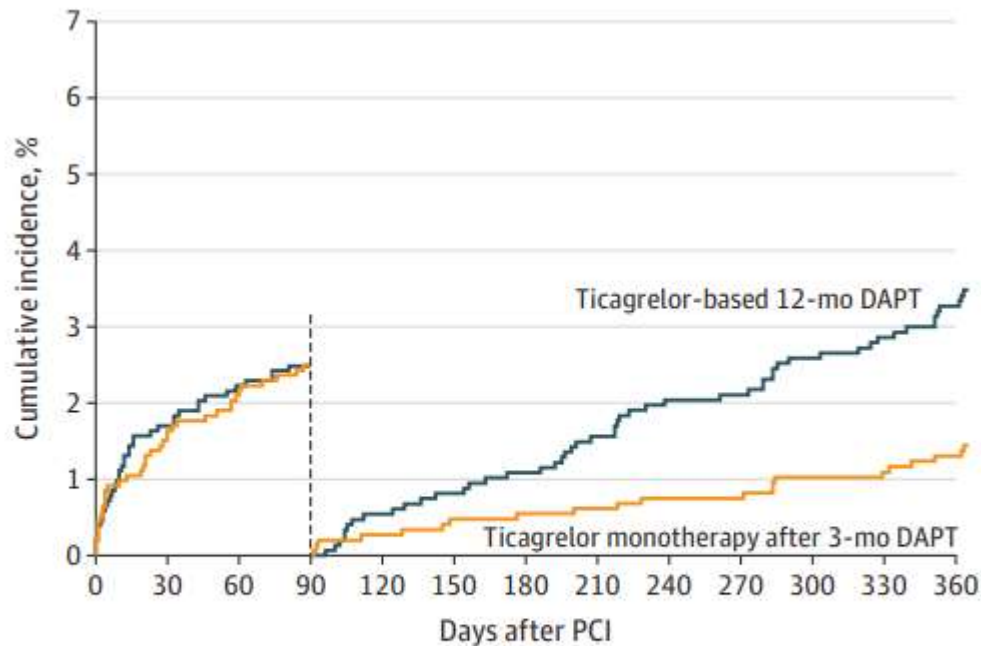
**Ticagrelor-based 12-month DAPT, resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and cardiovascular events at 1 year.**

A net adverse clinical event was defined as a composite of major bleeding by the Thrombolysis in Myocardial Infarction criteria or major adverse cardiac and cerebrovascular event. Between 3 and 12 months, the hazard ratio (HR) was 0.41 (95% CI, 0.25-0.68; P = .001). Reported HRs are for the patients with ticagrelor monotherapy after 3-month dual antiplatelet therapy (DAPT). The median observation periods were 365 days (interquartile range, 365-365) for both study groups.

# TICO randomized trial : Ticagrelor monotherapy vs. DAPT in ACS

## Time-to-Event Curves for the Primary Outcome and Landmark Analysis at 3 Months

Landmark analysis at 3 months for the net adverse clinical event



1529 1500 1489 1481 1466 1460 1455 1442 1432 1430 1423 1418 1407  
1527 1498 1483 1471 1462 1456 1452 1442 1437 1437 1432 1430 1424

**Ticagrelor-based 12-month DAPT, resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and cardiovascular events at 1 year.**

A net adverse clinical event was defined as a composite of major bleeding by the Thrombolysis in Myocardial Infarction criteria or major adverse cardiac and cerebrovascular event. Between 3 and 12 months, the hazard ratio (HR) was 0.41 (95% CI, 0.25-0.68;  $P = .001$ ). Reported HRs are for the patients with ticagrelor monotherapy after 3-month dual antiplatelet therapy (DAPT). The median observation periods were 365 days (interquartile range, 365-365) for both study groups.



# TICO randomized trial : Ticagrelor monotherapy vs. DAPT in ACS

## Clinical Outcomes at 1 Years

Outcomes	No. of patients with event (% cumulative incidence) <sup>a</sup>		Absolute difference, % (95% CI)	Hazard ratio (95% CI)	P value <sup>b</sup>
	Ticagrelor monotherapy after 3-mo DAPT (n = 1527)	Ticagrelor-based 12-mo DAPT (n = 1529)			
<b>Primary outcome</b>					
Net adverse clinical event <sup>c</sup>	59 (3.9)	89 (5.9)	-1.98 (-3.50 to -0.45)	0.66 (0.48 to 0.92)	.01
<b>Secondary outcomes</b>					
<b>TIMI</b>					
Major bleeding	25 (1.7)	45 (3.0)	-1.33 (-2.40 to -0.27)	0.56 (0.34 to 0.91)	.02
Major or minor bleeding	53 (3.6)	83 (5.5)	-2.06 (-3.52 to -0.60)	0.64 (0.45 to 0.90)	.01
Major adverse cardiac and cerebrovascular event <sup>d</sup>	35 (2.3)	51 (3.4)	-1.05 (-2.23 to 0.13)	0.69 (0.45 to 1.06)	.09
Cardiac death or acute MI	13 (0.9)	22 (1.5)	-0.59 (-1.35 to 0.16)	0.59 (0.30 to 1.18)	.14
Cardiac death, acute MI, stent thrombosis, or target-vessel revascularization	18 (1.2)	30 (2.0)	-0.79 (-1.68 to 0.10)	0.60 (0.34 to 1.08)	.09
Death	16 (1.1)	23 (1.5)	-0.46 (-1.26 to 0.35)	0.70 (0.37 to 1.32)	.27
Cardiac	7	12			
Noncardiac	9	11			
Acute MI	6 (0.4)	11 (0.7)	-0.34 (-0.87 to 0.19)	0.55 (0.20 to 1.48)	.24
Stent thrombosis	6 (0.4)	4 (0.3)	0.13 (-0.27 to 0.54)	1.51 (0.43 to 5.33)	.53
Subacute	4	2			
Late	2	2			
Stroke	8 (0.5)	11 (0.7)	-0.20 (-0.76 to 0.37)	0.73 (0.29 to 1.81)	.50
Ischemic	5	9			
Hemorrhagic	3	2			
Target-vessel revascularization	8 (0.5)	10 (0.7)	-0.13 (-0.69 to 0.42)	0.80 (0.32 to 2.03)	.64

**Mainly driven by a reduction in bleeding**

NEWS | ACC 2019

## Dropping Aspirin: Two Trials Explore P2Y12 Monotherapy After Short-term DAPT Post-PCI

The findings could “change the paradigm” of post-PCI antiplatelet therapy choices in noncomplex patients, experts say.



By [Yael L. Maxwell](#) | March 18, 2019

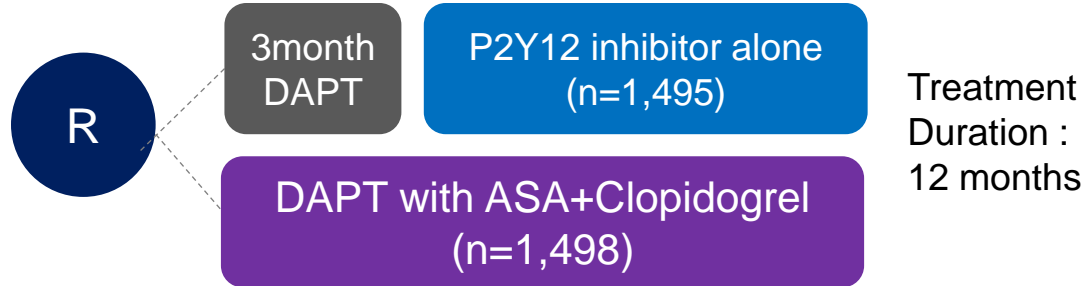
## Overview

### Objective

To determine whether P2Y12 inhibitor monotherapy after 3 months of DAPT is noninferior to 12 months of DAPT in patients undergoing PCI.

### Study Design

an open-label, noninferiority, randomized study conducted in 33 hospitals in Korea included 2,993 patients undergoing DES PCI



P2Y12 inhibitor	Monotherapy (n= 1,495)	DAPT (n= 1,498)
<b>Clopidogrel</b>	<b>1,149 (76.9%)</b>	1,163 (77.6%)
Prasugrel or ticagrelor	346 (23.1%)	335 (22.4%)

### EndPoints

- Primary Outcome: a composite of all-cause death, MI, or stroke
- Secondary Outcome: components of the primary end point and bleeding defined as BARC type 2 ~ 5

# SMART CHOICE:

## P2Y12 inhibitor monotherapy was non-inferior to DAPT

- There were **no significant differences** in the cumulative rates of the components of the primary end point at 12 months for all-cause death, MI, and stroke
- The rate of **bleeding was significantly lower in the P2Y<sub>12</sub> inhibitor monotherapy group than in the DAPT group (2.0% vs 3.4%; HR 0.58; 95% CI 0.36-0.92; P = .02)**

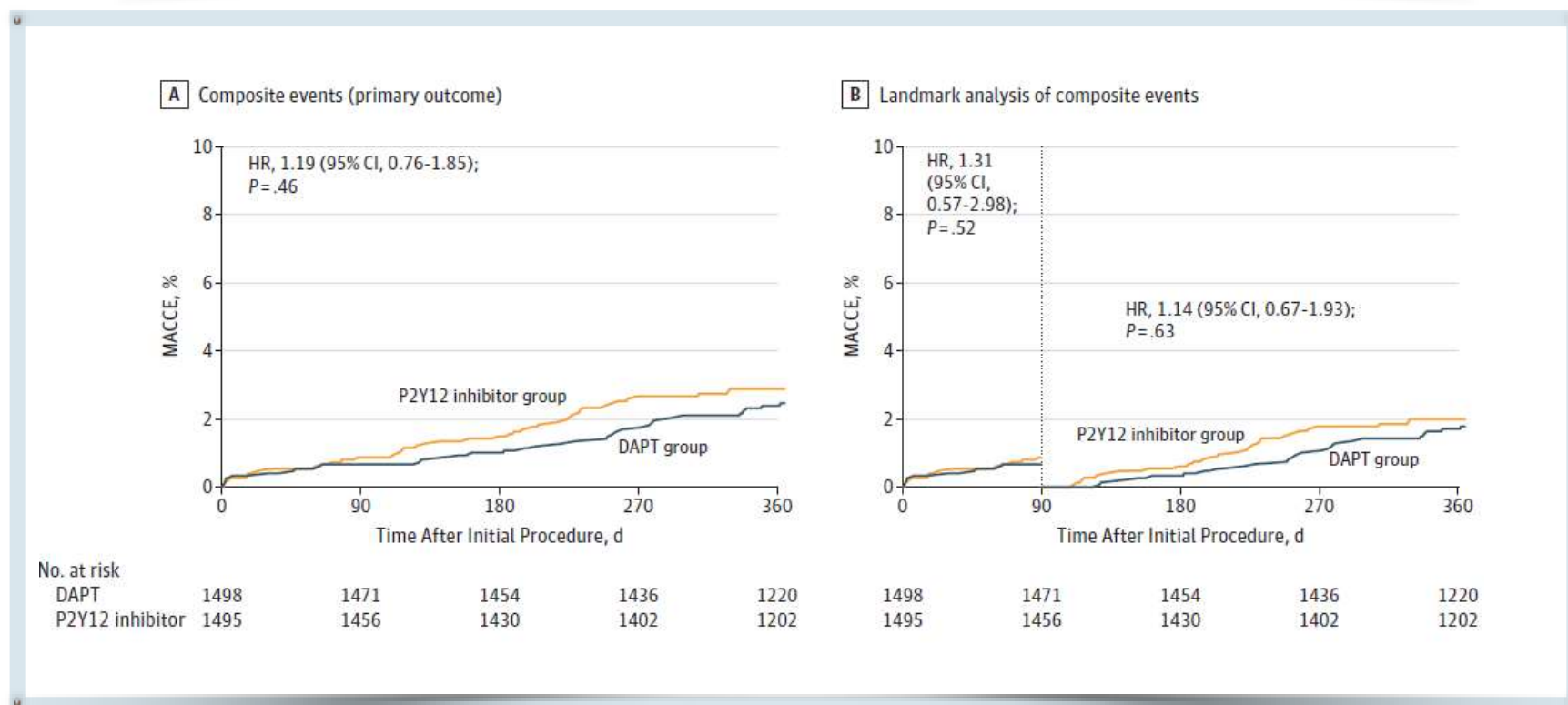
Outcome	No. (%)		Estimate of Difference, % (95% 1-Sided CI)	P Value
	P2Y12 Inhibitor Monotherapy (n = 1495) <sup>a</sup>	Dual Antiplatelet Therapy (n = 1498) <sup>a</sup>		
<b>Primary End Point</b>				
MACCE <sup>b</sup>	42 (2.9)	36 (2.5)	0.4 (-∞ to 1.3)	.007 (noninferiority)
<b>Secondary End Points</b>			<b>Hazard Ratio (95% CI)</b>	
All-cause death	21 (1.4)	18 (1.2)	1.18 (0.63 to 2.21)	.61
Myocardial infarction	11 (0.8)	17 (1.2)	0.66 (0.31 to 1.40)	.28
Stroke	11 (0.8)	5 (0.3)	2.23 (0.78 to 6.43)	.14
Cardiac death	11 (0.8)	13 (0.9)	0.86 (0.38 to 1.91)	.70
Stent thrombosis	3 (0.2)	2 (0.1)	1.51 (0.25 to 9.02)	.65
Bleeding BARC type 2-5	28 (2.0)	49 (3.4)	0.58 (0.36 to 0.92)	.02
Major bleeding <sup>c</sup>	12 (0.8)	14 (1.0)	0.87 (0.40 to 1.88)	.72
<b>Post Hoc Analysis</b>				
Death or myocardial infarction	31 (2.1)	32 (2.2)	0.98 (0.60 to 1.61)	.94
Cardiac death or myocardial infarction	21 (1.5)	27 (1.9)	0.79 (0.45 to 1.39)	.50
Net adverse clinical and cerebral events <sup>d</sup>	65 (4.5)	81 (5.6)	0.81 (0.58 to 1.12)	.20

# SMART CHOICE:

## P2Y12 inhibitor monotherapy was non-inferior to DAPT

- A post hoc landmark analysis showed that the risk of major adverse cardiac and cerebrovascular events between 3 and 12 months was **not significantly different** between the groups (HR 1.14; 95% CI 0.67-1.93; P = .63)

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

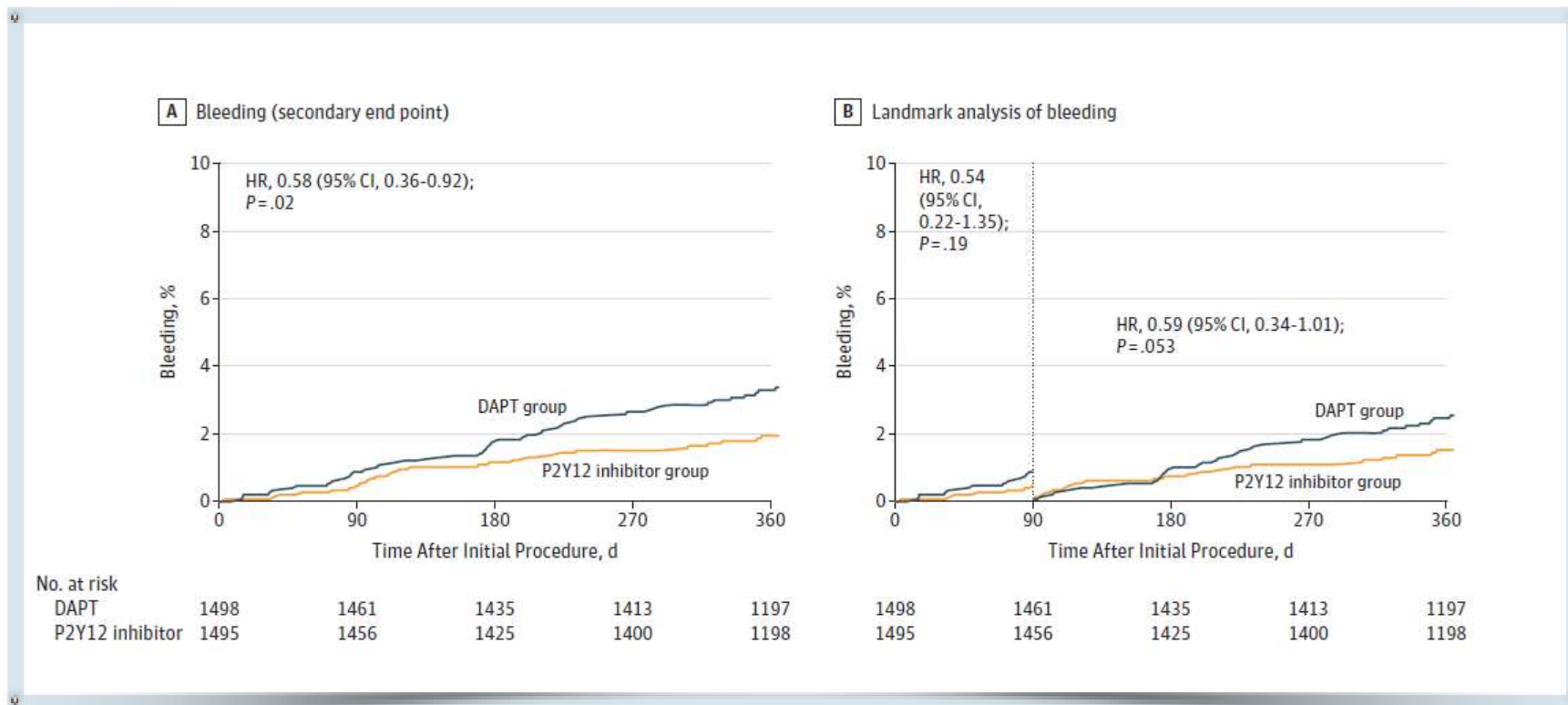


# SMART CHOICE:

bleeding was lower in the P2Y12 inhibitor monotherapy

- The rate of **bleeding** was significantly lower in the **P2Y12 inhibitor monotherapy group** than in the **DAPT group** (2.0% vs 3.4%; HR 0.58; 95% CI 0.36-0.92; P = .02)

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



### Objective

To test the hypothesis of noninferiority of 1 month of DAPT vs. standard 12 months of DAPT for a composite end point of CV and bleeding events.

### Study Design

Multicenter, open-label, randomized clinical trial enrolling 3045 patients who underwent PCI



1 month  
DAPT

Clopidogrel  
monotherapy  
(n=1,523)

DAPT with ASA + Clopidogrel  
(n=1,522)

Treatment  
Duration :  
12 months

### EndPoints

- Primary Outcome:
  - a composite of CV death, MI, stroke, stent thrombosis, or major or minor bleeding
- Secondary Outcome:
  - CV: a composite of CV death, MI, stroke, stent thrombosis
  - Major or minor bleeding

# STOP DAPT 2

1 month DAPT followed by Clo mono was noninferior to 12 month DAPT

## Clinical outcomes at 1 Year

Outcomes	No. of Patients With Event (Cumulative Incidence, %) <sup>a</sup>		Hazard Ratio (95% CI)	P Value <sup>b</sup>	
	1-Month DAPT (n = 1500)	12-Month DAPT (n = 1509)		Noninferiority	Superiority
<b>Primary End Point</b>					
Composite of cardiovascular death, myocardial infarction, definite stent thrombosis, ischemic or hemorrhagic stroke, or TIMI major or minor bleeding	35 (2.36)	55 (3.70)	0.64 (0.42-0.98)	<.001	.04
<b>Major Secondary End Points</b>					
Cardiovascular end point: composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or ischemic or hemorrhagic stroke	29 (1.96)	37 (2.51)	0.79 (0.49-1.29)	.005	.34
Bleeding end point: TIMI major or minor bleeding	6 (0.41)	23 (1.54)	0.26 (0.11-0.64)		.004

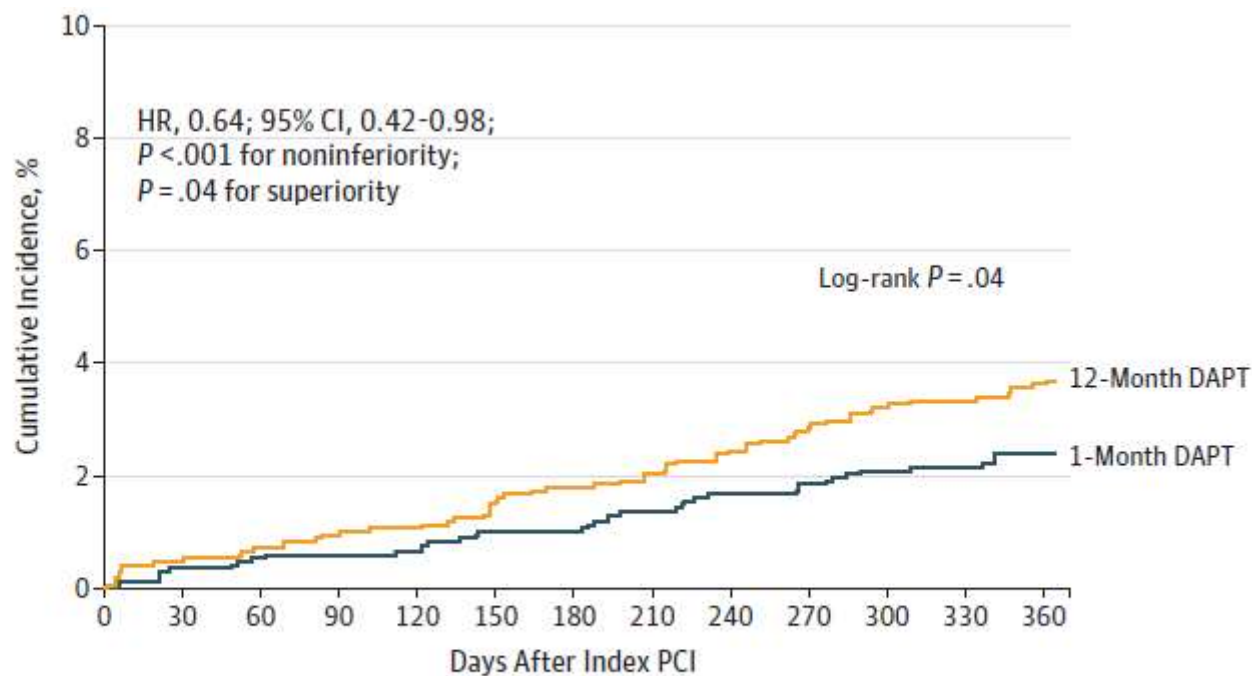
- **1 month DAPT followed by Clo mono was noninferior to 12 month DAPT and associated with a net clinical benefit for the primary end point**
- **1 month of DAPT was noninferior for the CV composite secondary end point and superior for the major secondary bleeding end point compared with 12 months of DAPT.**



# STOP DAPT 2

1 Month DAPT followed by Clo mono was noninferior to 12 month DAPT

## One-Year Time to Events for the Primary End Point



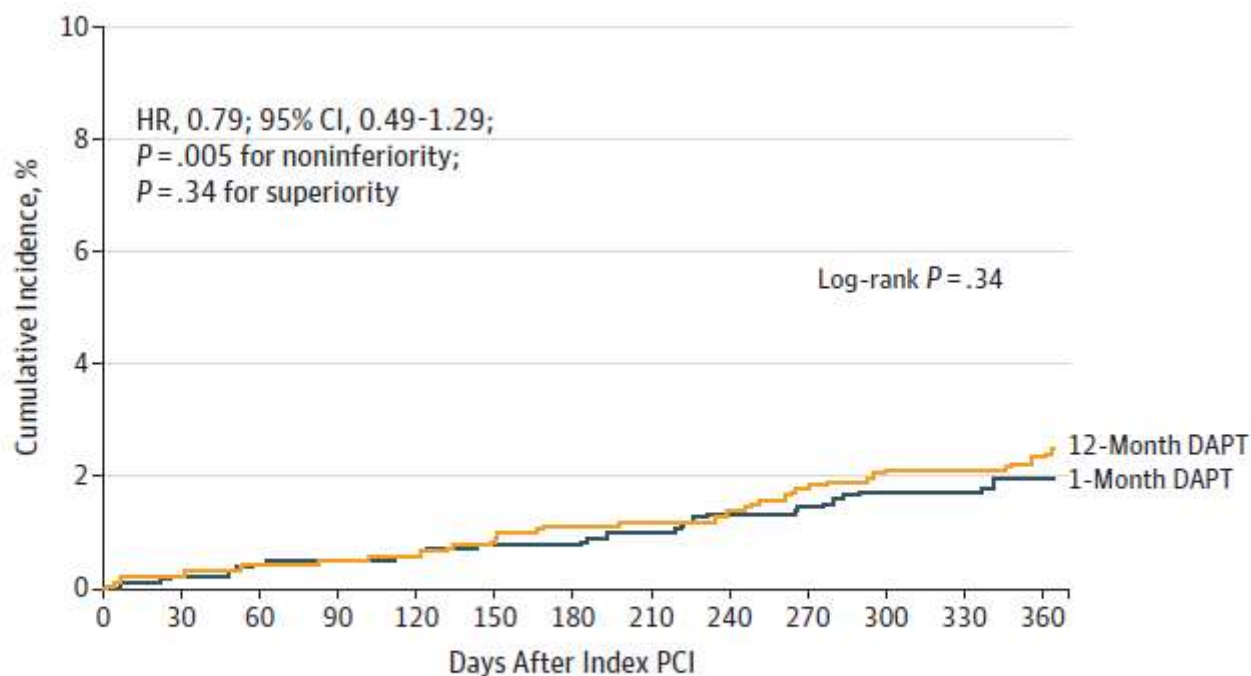
No. at risk	0	30	60	90	120	150	180	210	240	270	300	330	360
12-Month DAPT	1509	1501	1486		1481	1469	1458	1442	1159				
1-Month DAPT	1500	1494	1479		1475	1468	1453	1441	1151				

Primary end point (Composite of cardiovascular death, MI, definite stent thrombosis, ischemic and hemorrhagic stroke, or TIMI major or minor bleeding)

# STOP DAPT 2

The benefit was driven by a significant ▼ of bleeding without an ▲ in CV events

## One-Year Time to Events for the Secondary End Point



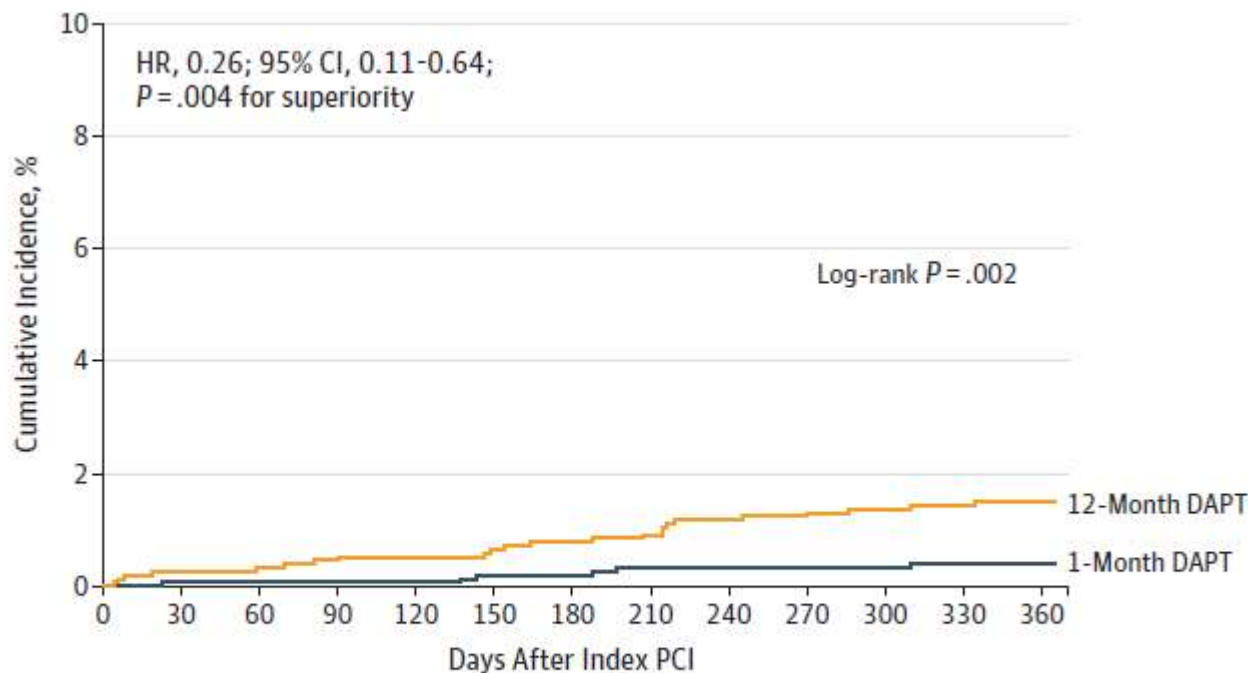
No. at risk	0	30	60	90	120	150	180	210	240	270	300	330	360
12-month DAPT	1509	1504	1490		1488	1479	1473	1458	1172				
1-month DAPT	1500	1495	1480		1476	1471	1458	1446	1157				

Composite of cardiovascular death, MI, definite stent thrombosis, or ischemic and hemorrhagic stroke

# STOP DAPT 2

The benefit was driven by a significant ▼ of bleeding without an ▲ in CV events

## One-Year Time to Events for the Secondary End Point



No. at risk	0	30	60	90	120	150	180	210	240	270	300	330	360
12-month DAPT	1509	1504	1491		1487	1480	1471	1462	1462	1462	1462	1462	1180
1-month DAPT	1500	1495	1483		1481	1477	1467	1457	1457	1457	1457	1457	1166

TIMI major/minor bleeding

# STOP DAPT 2

The lower risk of 1 month DAPT was consistent in subgroups except for the severe CKD

## Subgroup Analyses for the Effect of 1-Month DAPT on the Primary End Point

	No./Total (%)		HR (95% CI)	Favors 1-Month DAPT	Favors 12-Month DAPT	P Value	P Value for Interaction
	1-Month DAPT (n=1500)	12-Month DAPT (n=1509)					
Age, y							
≥75	10/448 (2.26)	25/499 (5.08)	0.44 (0.21-0.92)	■		.03	.20
<75	25/1052 (2.41)	30/1010 (3.02)	0.80 (0.47-1.36)	■		.41	
Acute coronary syndrome							
Yes	16/565 (2.88)	23/583 (4.02)	0.72 (0.38-1.36)	■		.44	.64
No	19/935 (2.05)	32/926 (3.49)	0.59 (0.33-1.03)	■		.06	
STEMI							
Yes	9/291 (3.15)	14/270 (5.26)	0.60 (0.26-1.38)	■		.23	.87
No	26/1209 (2.18)	41/1239 (3.36)	0.65 (0.40-1.06)	■		.08	
Severe chronic kidney disease							
Yes	9/82 (11.22)	5/84 (5.97)	1.93 (0.65-5.75)		■	.24	.03
No	26/1418 (1.86)	50/1425 (3.56)	0.52 (0.32-0.84)	■		.007	
Diabetes							
Yes	18/585 (3.12)	25/574 (4.45)	0.70 (0.38-1.29)	■		.26	.65
No	17/915 (1.88)	30/935 (3.24)	0.58 (0.32-1.05)	■		.07	
Total stent length ≥28 mm							
Yes	19/742 (2.60)	33/787 (4.23)	0.61 (0.35-1.07)	■		.08	.76
No	16/758 (2.14)	22/722 (3.12)	0.69 (0.36-1.32)	■		.26	
≥2 Target vessels							
Yes	4/100 (4.14)	8/116 (6.94)	0.58 (0.17-1.92)	■		.37	.85
No	31/1400 (2.24)	47/1393 (3.43)	0.66 (0.42-1.03)	■		.07	

In the subgroup analysis, the lower risk of 1 month of DAPT compared with 12 months of DAPT for the primary end point was consistently seen across subgroups except for the small subgroup of patients with severe CKD.

# Key Implication from SMART CHOICE & STOP DAPT 2

1

Aspirin might provide little additional inhibition of platelet aggregation in the presence of a P2Y12 inhibitor. P2Y12 receptor activation is important to platelet TXA2 production.

2

Reduction of bleeding after PCI is of great importance because it has a strong relationship with mortality and major events. Also, interruption of antiplatelet therapy because of bleeding may be associated with an increase in thrombotic events.

3

Shorter DAPT followed by clopidogrel monotherapy might be adequate to prevent stent thrombosis after implantation of current-generation drug-eluting stents.

4

Short DAPT in a population at high bleeding risk may be a viable option but needs further study because of the high ischemic risk of this population.

# HOST-EXAM

(**H**armonizing **O**ptimal **S**trategy for **T**reatment of coronary artery stenosis – **EX**tended **A**ntiplatelet **M**onotherapy)

약물 용출 스텐트 이식 후 항혈소판제 병합요법을 시행한 환자를 대상으로  
향후 2년 동안 Clopidogrel 또는 Aspirin의 단일 치료 요법의 효과 비교

Comparison of Clopidogrel vs. Aspirin monotherapy  
beyond two year after drug-eluting stent implantation

# Design

## Assumption

: 12% vs. 9.6%

Superiority Design

Sampling ratio: 1:1

Alpha: 1-sided 5%

Power 80%

5,530 pts needed

5,530 Patients that received  
PCI with DES without events  
for 12 ( $\pm$  6) months

43 centers in Korea

**Aspirin  
Monotherapy**

**N=2765**

Randomization  
1:1

**Clopidogrel  
Monotherapy**

**N=2765**

Outpatient Clinic-based Clinical Trial

Baseline PCI

Randomization

12mo

Post-rand  
1 year

Post-rand  
2 year

3yr

Primary Endpoint

Composite of  
All cause death, MI, stroke,  
readmission due to ACS, u  
rgent revascularization, b  
leeding

# Conclusion

**1**

**Guidelines recommendations on DAPT is changing based on the well designed randomized trials.**

**2**

**The effectiveness of aspirin in the field of IHD is weakened and attacked by some randomized trials.**

**3**

**SAPT instead of DAPT is gaining the Evidences.**

**4**

**New Era of SAPT is coming?**