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May 8, 2023

Updated antiplatelet approaches for ACS patients
: Tailored DAPT strategy in De-escalation era

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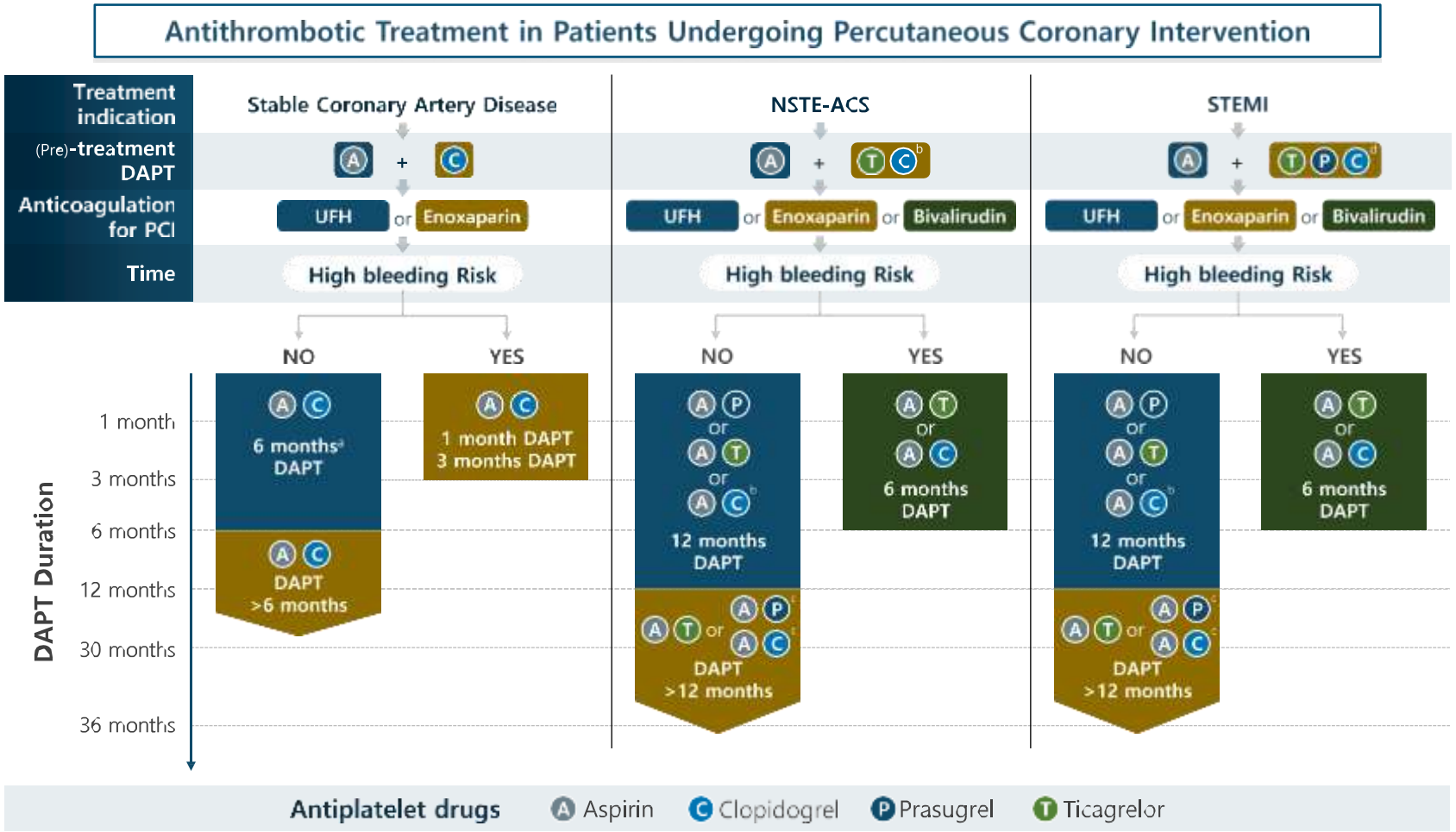
Contents

2018 ESC GUIDELINES ON MYOCARDIAL REVASCULARIZATION

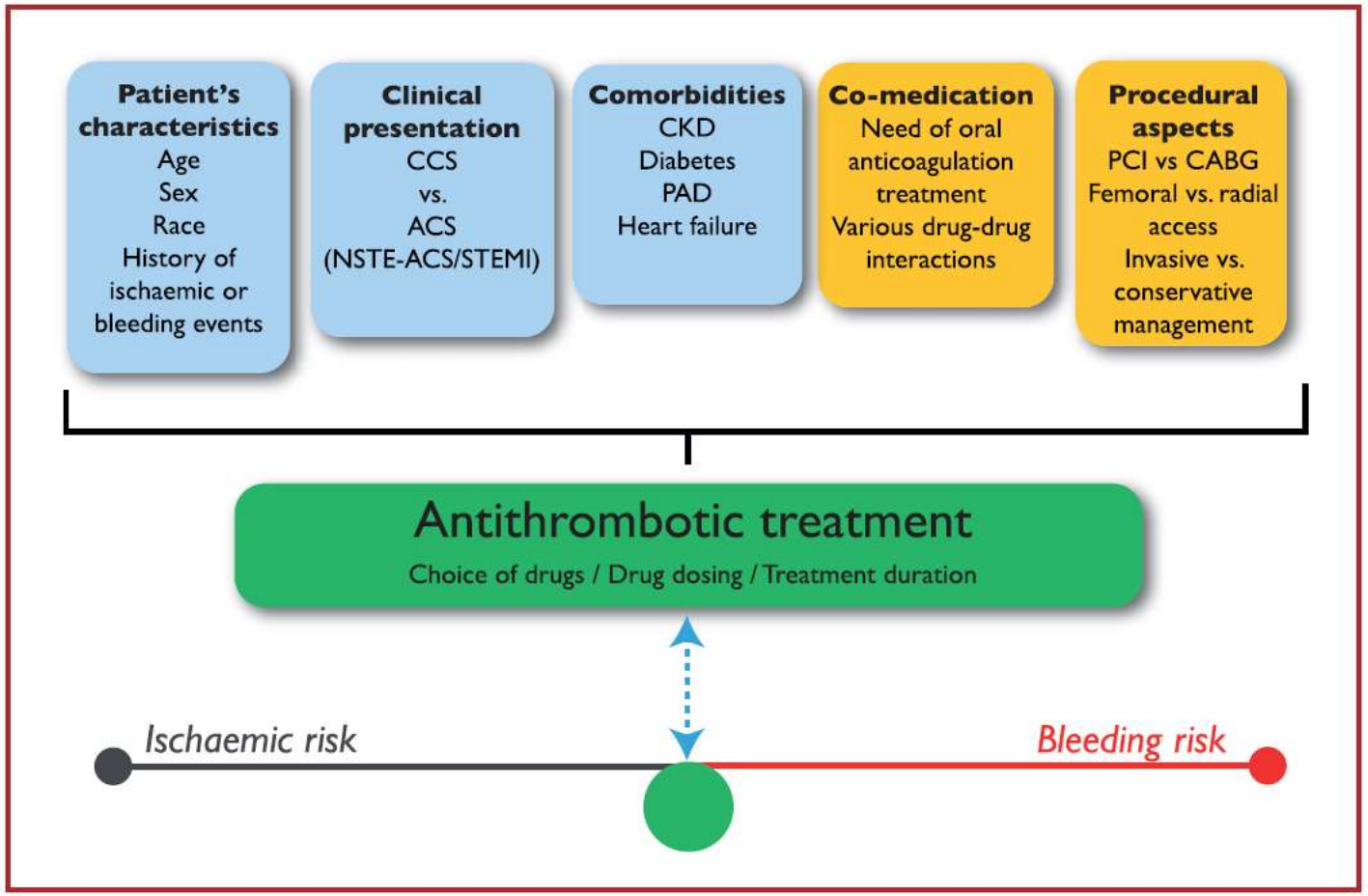
- The choice of treatment, the combination, the time point of initiation, and the duration of APT depend on the **patient's characteristics, comorbidities, and the clinical setting (elective revascularization vs. ACS).**



Nuemann FJ, et al. European Heart Journal (2019) 40, 87–165

2020 ESC GUIDELINES OF NSTE ACS:
Determinants of antithrombotic treatment in coronary artery disease

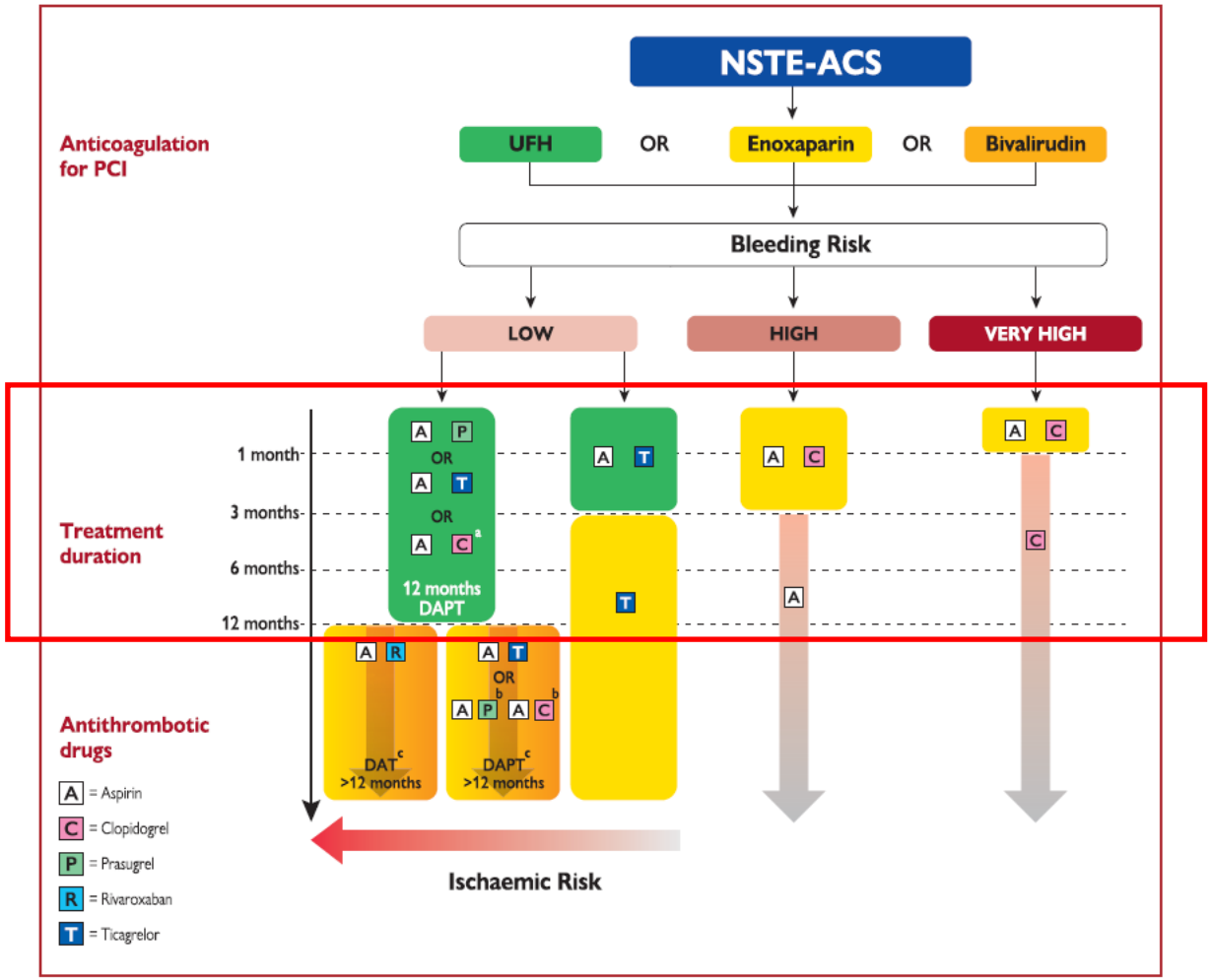
- **Intrinsic (in blue) and extrinsic (in yellow) variables** be considered on the choice, dosing, and duration of antithrombotic treatment.



Collet JP, et al. European Heart Journal (2021) 42, 1289-136

2020 ESC GUIDELINES OF NSTE ACS:
Algorithm for antithrombotic therapy in NSTE ACS patients without AF undergoing PCI

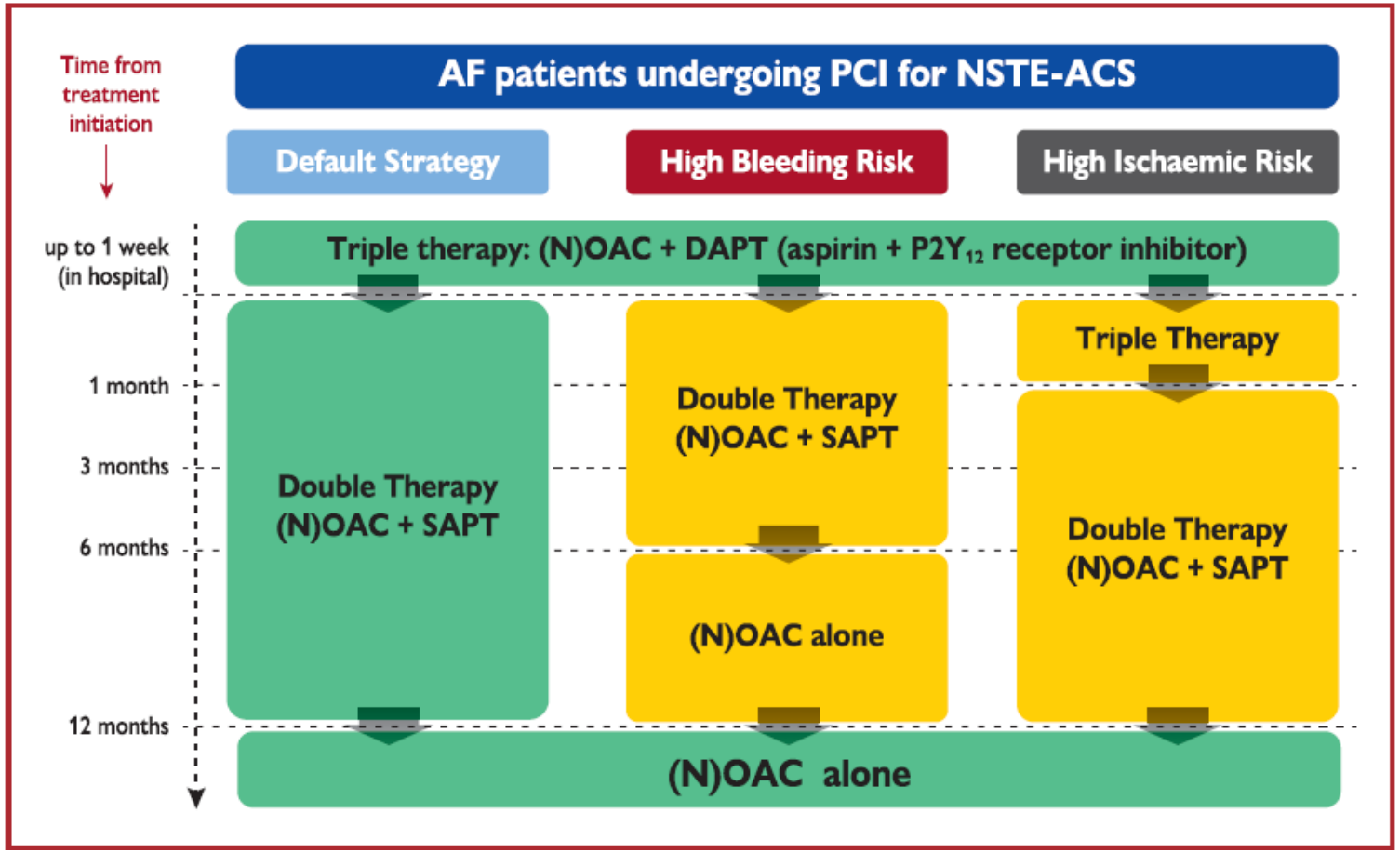
- **DAPT duration** may vary from 12 months to 1 month, which can be decided **mainly depending on the patient's ischaemic and bleeding risk**. In patients at high bleeding risk, clopidogrel is recommended than potent P2Y12 inhibitor.



Collet JP, et al. European Heart Journal (2021) 42, 1289-136

2020 ESC GUIDELINES OF NSTE ACS:
Algorithm for antithrombotic therapy in NSTE ACS patients with AF undergoing PCI

- **DAT with a NOAC and single antiplatelet therapy (preferably clopidogrel)** is recommended as the **default strategy up to 12 months** after a short period (up to 1 week) of triple antithrombotic therapy (with NOAC and DAPT).



Collet JP, et al. European Heart Journal (2021) 42, 1289-136

Contents

Decision Making for DAPT Choice and Duration: Ischemic risk vs. Bleeding risk

Drug-eluting coronary stent implantation

↓

Mandatory period of DAPT

↓

Comprehensive clinical evaluation

UNFAVORABLE PROFILE

Clinical considerations

- Short life expectancy
- Poor socio-economic status
- Poor expected DAPT adherence
- Poor mental status
- Malignancy
- End stage renal failure
- Smoker

BLEEDING RISK OUTWEIGHS ISCHEMIC RISK

Patient presentation

- Clinically significant bleeding on DAPT
- Advanced age
- Female
- Liver disease
- Peptic ulcer disease
- Chronic oral NSAID therapy
- Anemia and/or thrombocytopenia
- Uncontrolled hypertension
- Bleeding diathesis
- Prior major bleeding/ prior hemorrhagic stroke
- Atrial fibrillation/chronic anticoagulation therapy
- High bleeding risk score

ISCHEMIC RISK OUTWEIGHS BLEEDING RISK

Patient presentation

- Recurrent ischemic event on DAPT
- Stent-related complications
- Acute coronary syndrome
- Male
- Diabetes mellitus
- Left ventricular dysfunction
- Chronic kidney disease
- Peripheral vascular disease
- Prior ischemic stroke
- Clopidogrel nonresponsiveness
- Prior myocardial infarction
- Lesion complexity
- Incomplete stent apposition
- Stent undersizing/ underexpansion
- Residual edge dissection
- Stent deployment in necrotic core
- Stent overlap

✖ **STOP DAPT AFTER MANDATORY PERIOD**

✔ **CONTINUE WITH DAPT**

NSAID, nonsteroidal anti-inflammatory drug

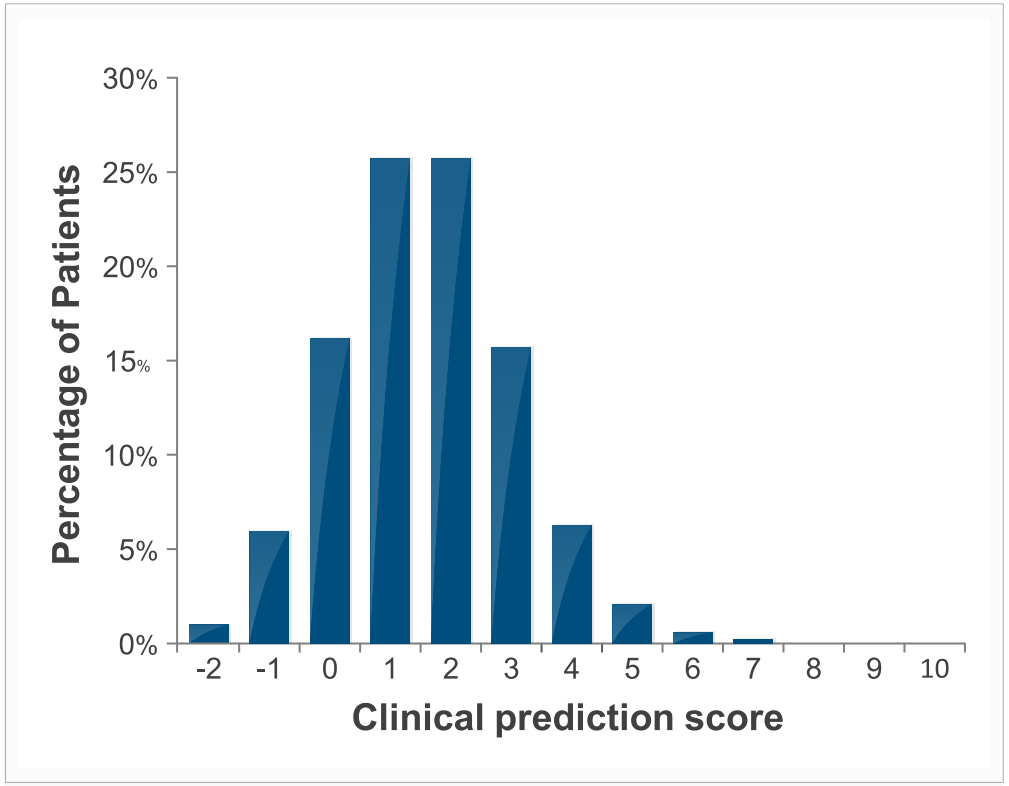
1. Montalescot, G. *et al J Am Coll Cardiol* 2015; 66(7):832–47.

The DAPT Score

Variable Patient Characteristic		Points
Age	≥ 75	-2
	65 - <75	-1
	< 65	0
Diabetes Mellitus		1
Current Cigarette Smoker		1
Prior PCI or Prior MI		1
CHF or LVEF < 30%		2

Index Procedure Characteristic	Points
MI at Presentation	1
Vein Graft stent	2
Stent Diameter < 3 mm	1

Distribution of DAPT Scores among All Randomized Subjects in the DAPT Study



Study Design

Among 11,648 randomized DAPT Study patients from 11 countries (August 2009-May 2014), a prediction rule was derived stratifying patients into groups to distinguish ischemic and bleeding risk 12 to 30 months after PCI.

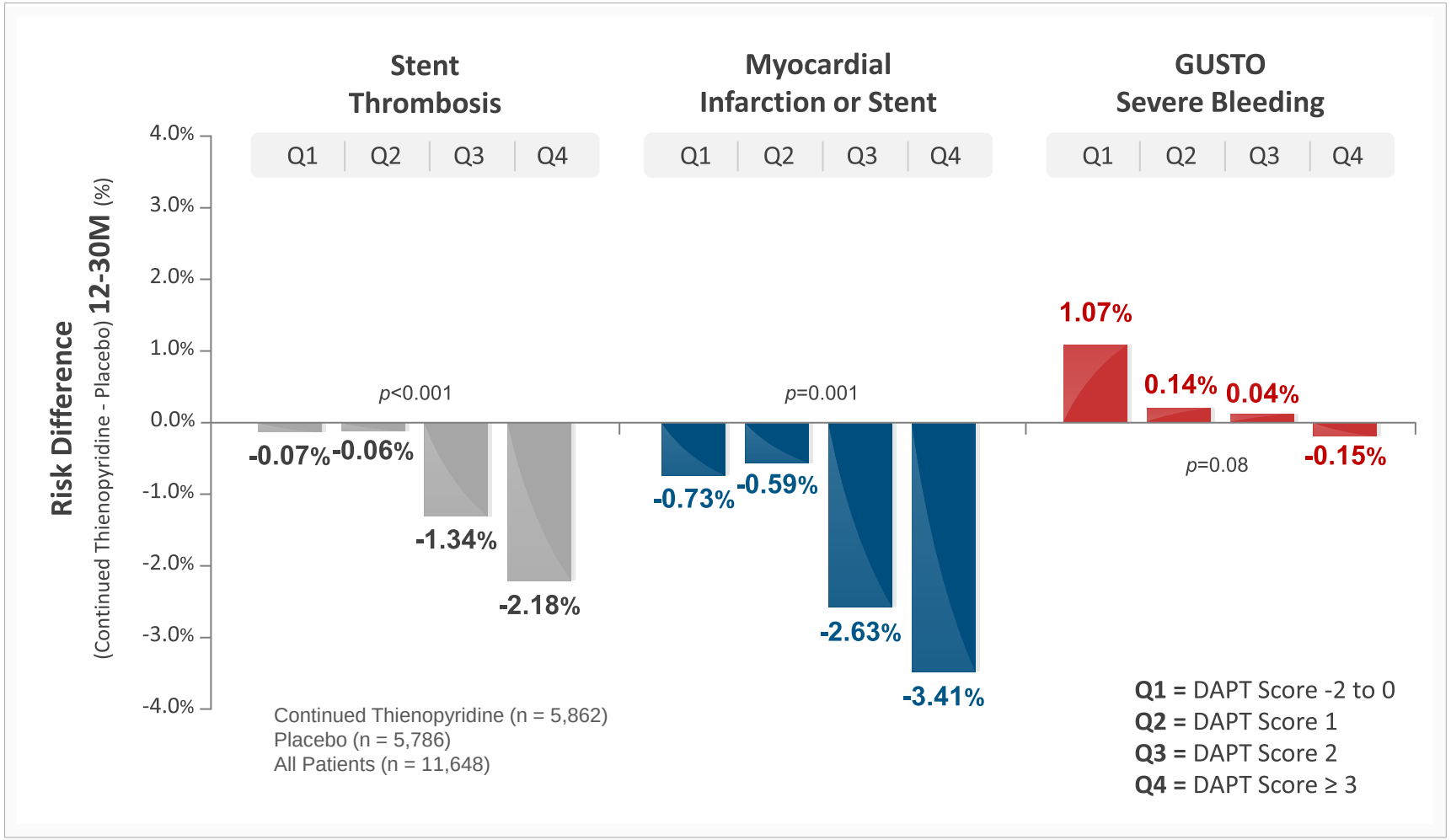
CHF, congestive heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary interventions

1. Yeh RW, *et al. JAMA* 2016;315:1735-1749.

Secondary analysis of the DAPT Study

Observed Outcomes by Treatment Group from 12 through 30 Months:

Continued thienopyridine vs. placebo treatment effect by DAPT score quartile



GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries

1. Yeh RW, *et al. JAMA* 2016;315:1735-1749.

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2017 ESC Guideline propose PRECISE-DAPT or DAPT score for bleeding risk stratification

- **The PRECISE-DAPT score:** a simple five-item risk score, which provides a standardized tool for the prediction of out-of-hospital bleeding during DAPT.
- **Shorter than 12-month treatment in patients at high bleeding risk may prevent excessive bleeding hazard. In turn, patients at non-high bleeding risk might receive a standard or prolonged course of treatment if tolerated.**

Risk scores validated for dual antiplatelet therapy duration decision-making

	PRECISE-DAPT score		DAPT score	
Time of use	At the time of coronary stenting		After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3-6 months) vs. Standard/long DAPT (12-24 months)		Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]	HB	≥12 11-5 11 10-5 ≤10	Age	
	WBC	≤5 8 10 12 14 16 18 ≥20	≥75	-2 pt
	Age	≤50 60 70 80 ≥90	65 to <75	-1 pt
	CrCl	≥100 80 60 40 20 0	<65	0 pt
	Prior Bleeding	No Yes	Cigarette smoking	+1 pt
	Score Points	0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	Diabetes mellitus	+1 pt
			MI at presentation	+1 pt
			Prior PCI or prior MI	+1 pt
			Paclitaxel-eluting stent	+1 pt
			Stent diameter <3 mm	+1 pt
			CHF or LVEF <30%	+2 pt
			Vein graft stent	+2 pt
Score range	0 to 100 points		-2 to 10 points	
Decision making cut-off suggested	**Score ≥25→Short DAPT**	**Score <25→Standard/long DAPT**	**Score ≥2→Long DAPT**	**Score <2→Standard DAPT**
Calculator	www.precisedaptscore.com		www.daptstudy.org	

CHF: congestive heart failure; CrCl=creatinine clearance; DAPT: dual antiplatelet therapy; Hb: haemoglobin; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; WBC: white blood cell count.

1. Valgimigli M, *et al.* Eur Heart J. 2018 ;39:213-260

New potent $P2Y_{12}$ inhibitors

- **Ticagrelor significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke**

  (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001 vs clopidogrel at 12 months)**.**[1]

- **Prasugrel showed the clinical benefit compared with clopidogrel for ischaemic events of myocardial infarction** (MI)**, stent thrombosis** (ST)**, and urgent target vessel revascularization.**[2]

- **However, the greater reduction in ischaemic recurrence after ACS was observed during the initial 30 days following the treatment initiation, and a significant increase in the bleeding risk after the first month was also reported**

  (Ticagrelor vs clopidogrel in non-CABG-related major or minor bleeding: 3.98 vs. 2.97%; HR 1.35; 95% CI 1.09-1.67; *P*=0.006)

  in PLATO, phase 3 clinical trial in patients with acute ST elevation and non-ST-segment elevation ACS.[3]

Study Design

Ref1. ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) were compared in a multicenter, double-blind, randomized trial for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation; Ref2. A total of 13,608 patients with an ACS (both unstable angina/non-ST-segment myocardial infarction and ST-segment myocardial infarction were randomized in TRITON-TIMI 38. Landmark analyses for efficacy, safety, and net clinical benefit with the prasugrel and clopidogrel groups were performed from randomization to day 3 and from day 3 to the end of the trial; Ref3. PLATO was a randomized, double-blind, active control international, phase 3 clinical trial in patients with acute ST elevation and non-ST-segment elevation ACS. A total of 18 624 patients were randomized to either ticagrelor, a nonthienopyridine, reversibly binding platelet $P2Y_{12}$ receptor antagonist, or clopidogrel in addition to aspirin. The primary safety endpoint was PLATO total major bleeding. Secondary safety endpoints were the categories of major bleeding and minor bleeding combined, as well as TIMI (Thrombolysis In Myocardial Infarction) and GUSTO (Global Use of Streptokinase and Tissue plasminogen activator to Open occluded coronary arteries) bleeding scales and transfusion of blood products (packed red blood cells or whole blood).

1. Wallentin L, *N Engl J Med* 2009;36:1045-1057 **2.** Antman EM *et al. J Am Coll Cardiol* 2008;51:2028-2033 **3.** Becker RC *et al. Eur Heart J* 2011;32:2933-2944.

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Bleeding Risk:
Potent P2Y12 Inhibitors vs. Clopidogrel

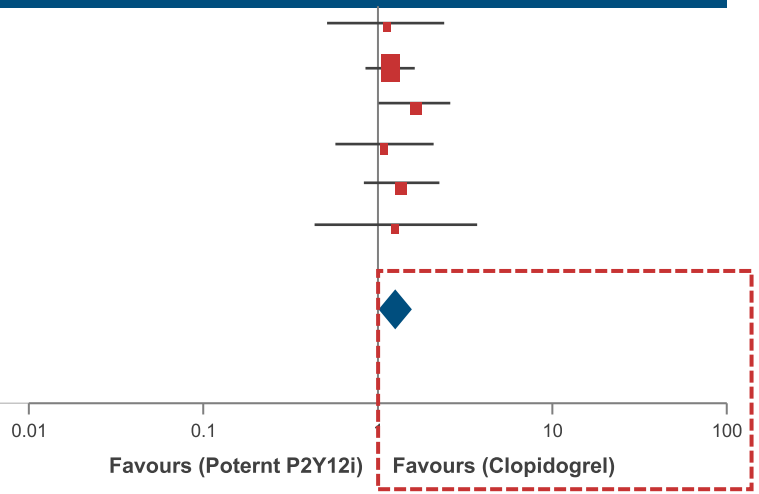
- In **systematic review and meta-analysis to investigate the efficacy and safety of potent P2Y12 inhibitors** versus clopidogrel **in elderly patients with ACS**, potent P2Y12 inhibitors had similar risk of MACE*, all-cause mortality**, reduced the risk of CV death¶ comparing with clopidogrel.

- With regards to the safety endpoint, **potent P2Y12 inhibitors significantly increased major bleeding compared with clopidogrel**.

Effect of antiplatelet therapy on safety endpoint

Study or Subgroup	Potent P2YI2i Events/Total	Clopidogerl Events/Total	Weight	Hazard Ratio IV, Random, 95% CI
Elderly ACS II	13/713	12/730	6.9%	1.11 [0.51, 2.42]
PLATO	NA/NA	NA/NA	44.8%	1.18 [0.87, 1.60]
POPULAR AGE	46/502	28/500	18.5%	1.64 [1.02, 2.63]
TRILOGY-ACS	19/1043	18/1040	9.9%	1.09 [0.57, 2.08]
TRITON-TIMI38	34/889	26/893	16.3%	1.36 [0.82, 2.26]
Wang et al. 2016	8/100	6/100	3.7%	1.25 [0.43, 3.63]
Total (95% CI)			**100.0%**	**1.27 [1.04, 1.56]**

Heterogeneity: Tau2 = I = 0.88; I^2 = 0%
Test for overall effect: Z = 2.30 (P = 0.02)



*MACE (HR: 0.94; 95%CI [0.85-1.06], P=0.31, I2=9%), **all-cause mortality (HR: 0.89; 95%CI [0.74-1.07] ¶risk of CV death(HR: 0.82; 95%CI [0.68-0.98], P=0.03, I2=16%)

ACS, acute coronary syndrome; CI, confidence interval; HR, hazard ratio; IV, inverse variance; MACE, major adverse cardiovascular events; NA, not available; SE, standard error

Study design

This study aimed to investigate the efficacy and safety of potent P2Y12 inhibitors versus clopidogrel in elderly patients with ACS. PUBMED and EMBASE were searched through July 2020 for randomized control trials (RCTs) or subgroup analyses of RCTs investigating potent P2Y12 inhibitors (prasugrel or ticagrelor) or clopidogrel in elderly (age ≥ 65 years) patients with ACS. The primary endpoint was trial defined MACE defined as a composite of cardiovascular death, myocardial infarction, and stroke if available, but a composite of death, myocardial infarction and stroke could be an alternative. The secondary endpoints were all-cause mortality, cardiovascular death, myocardial infarction, stroke, stent thrombosis, and trial defined major bleeding. This study identified 9 eligible RCTs (6 subgroup analyses of RCTs) including a total of 10,792 elderly patients

1. Fujisaki T, et al. Am Heart J. 2021;237:34-44.

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Ethnicity-tailored antithrombotic strategy
in East Asians

- **East Asians have shown low risk of atherothrombotic events including cardiovascular** (CV) **morality:** potential role of inflammation and coagulation activity.
- **East Asians also have increased tendency for gastrointestinal** (GI) **and intracranial bleeding events:** different prevalence of intracranial atherosclerosis or Helicobacter pylori infection.

Unique features of East Asian patients during antithrombotic treatment

Unique characteristics of East Asians in CV events and pharmacokinetics

Low ischaemic risk

- ↓ CV death, Myocardial infarction
- ↓ Stent thrombosis
  - ↓ Inflammation
  - ↓ Coagulation activity
  - Genetic factors
  - Epigenetic factors (e.g., obesity, diet)

Differemt response to antithrombotic agents:
Active metabolite concentration in East Asians vs. Caucasians

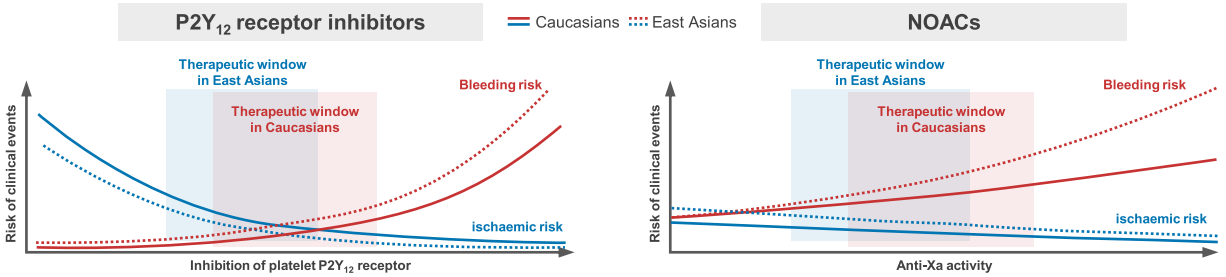
$P2Y_{12}$ receptor inhibitors		NOACs	
Clopidogrel	↓	*Dabigatran*	↑ (20-30%)
Prasugrel	↑↑ (30-47%)	*Rivaroxaban*	↑ (20-30%)
Ticagrelor	↑↑ (40-48%)	*Apixaban*	↔
		Edoxaban	↓ (20-25%)

High bleeding risk

- ↑ Intracranial haemorrhage
  - ↑ ICAS
  - ↑ Haemorrhagic transformation
  - Poor control of blood pressure
- ↑ GI bleeding
  - ↑ Helicobacter pyiori infection

Ischaemia/ bleeding trade-off

Different therapeutic window of antithrombotic effect in East Asians vs. Caucasians



Ethnicity-tailored antithrombotic strategy in East Asians

- Reduced dose regimen of $P2Y_{12}$ receptor inhibitor and NOACs
- Optimal DAPT duration after PCI
- GI bleeding avoidance

DOACs, direct oral anticoagulants; HIV, human immunodeficiency virus; VTE, venous thromboembolism; vWF, vonWillebrand factor

1. Kim HK, *et al*. Thromb Haemost. 2021;121(4):422-432

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Contents

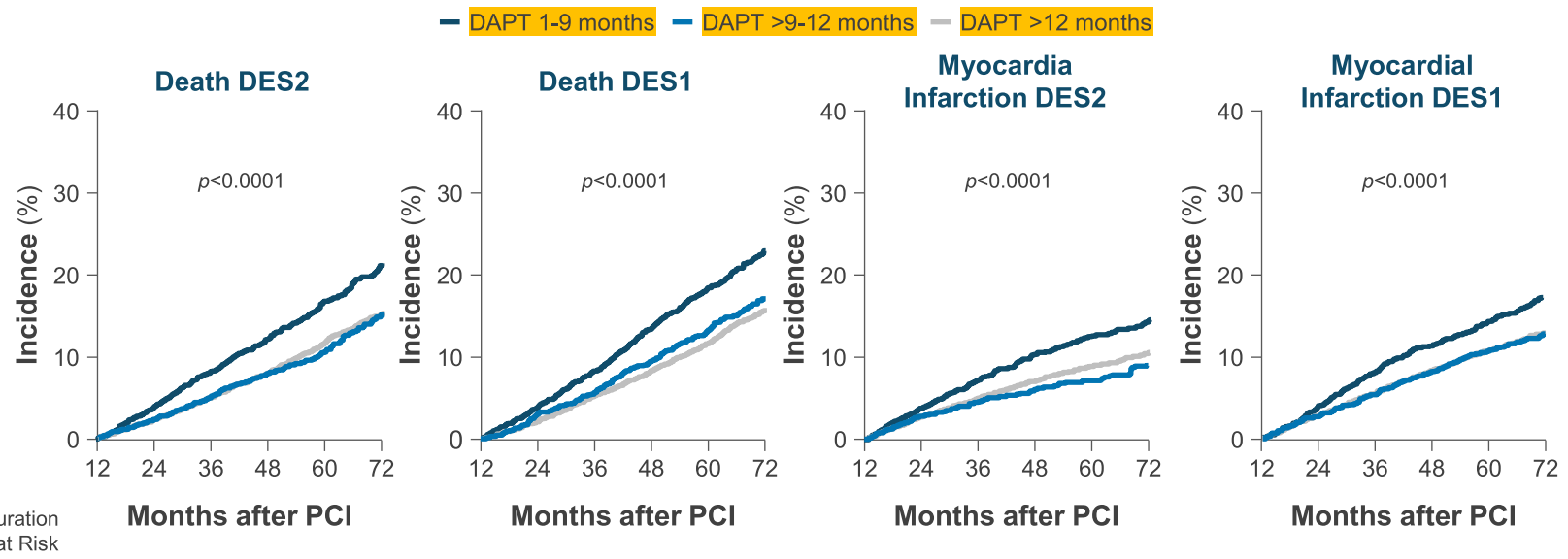
Veterans Affairs Healthcare System

Premature Discontinuation of DAPT After Coronary Stenting

Patients who were free of major ischemic or bleeding events in the first 12 months

Patients who discontinue DAPT prematurely have a persistently high long-term risk of ischemic events over an average of 5 years.

Event curves for death and myocardial infarction occurring >12 months after PCI by DAPT duration



DAPT Duration No. at Risk	Death DES2			Death DES1			Myocardia Infarction DES2			Myocardial Infarction DES1		
<9 months	3,467	3,129	1,221	2,233	2,040	1,526	3,467	2,934	1,105	2,233	1,889	1,341
>9-12 months	2,766	2,599	1,002	1,562	1,470	1,140	2,766	2,476	838	1,562	1,394	1,015
>12 months	8,003	7,522	3,099	4,785	4,523	3,602	8,003	7,189	2,840	4,785	4,297	3,247

Study Design

We assessed all patients having percutaneous coronary intervention with coronary second-or first-generation drug-eluting stents in the Veterans Affairs healthcare system **between 2006 and 2012 who were free of major ischemic or bleeding events in the first 12 months**. The characteristics of patients who stopped DAPT prematurely (1-9 months duration), compared with >9 to 12 months, or extended duration (>12 months) were assessed by odds ratios (ORs) from multivariable logistic models. The risk of adverse clinical outcomes over a mean 5.1 years in patients who stopped DAPT prematurely was assessed by hazard ratios (HRs) and 95% CIs from Cox regression models. A total of 14,239 had second-generation drug-eluting stents, and 8,583 had first-generation drug-eluting stents.

DAPT, dual antiplatelet therapy; DES 2, second-generation drug-eluting stents; DES 1, first-generation drug-eluting stents

1. Kinlay S, *et al*. J Am Heart Assoc. 2021;10:e018481.

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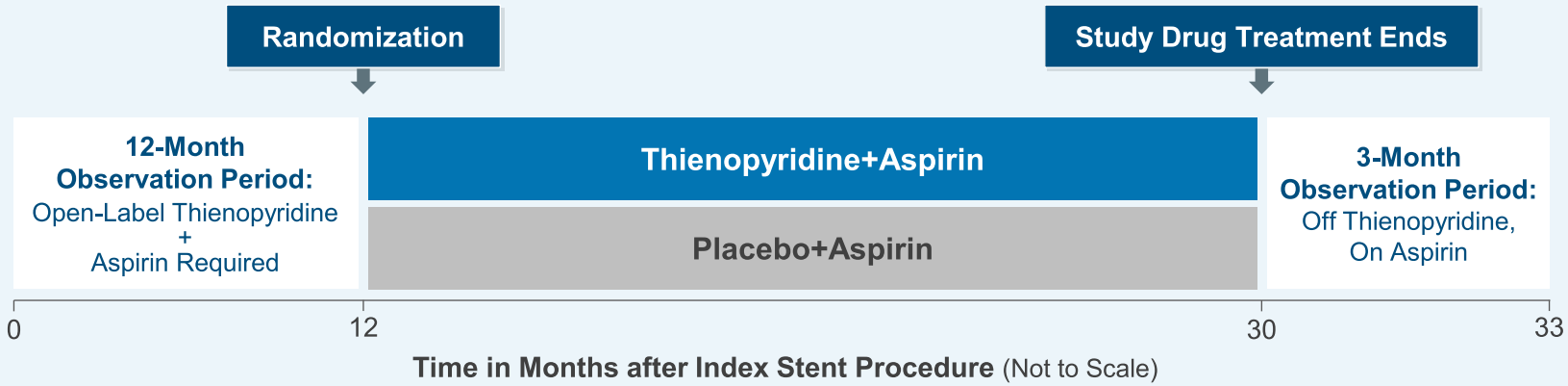
DAPT (2014)

Comparing aspirin alone (n=4,941) and Continued DAPT (n=5,020) for an additional 18 months
Patients who received 12 months DAPT and free from major ischemic or bleeding events

- **Multicenter, randomized, international, placebo-controlled** (N=9,961)



- **Enrolled:** Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expextancy <3 years excluded

- **Randomized:** Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption >14 days)

Study Design

Patients were enrolled after they had undergone a coronary stent procedure in which a drug-eluting stent was placed. After 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin, patients were **randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months**; all patients continued receiving aspirin. The coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months.

BMS, bare-metal stents; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MI, myocardial infarction

1. Mauri L, *et al*. *N Engl J Med* 2014; 371:2155-2166.

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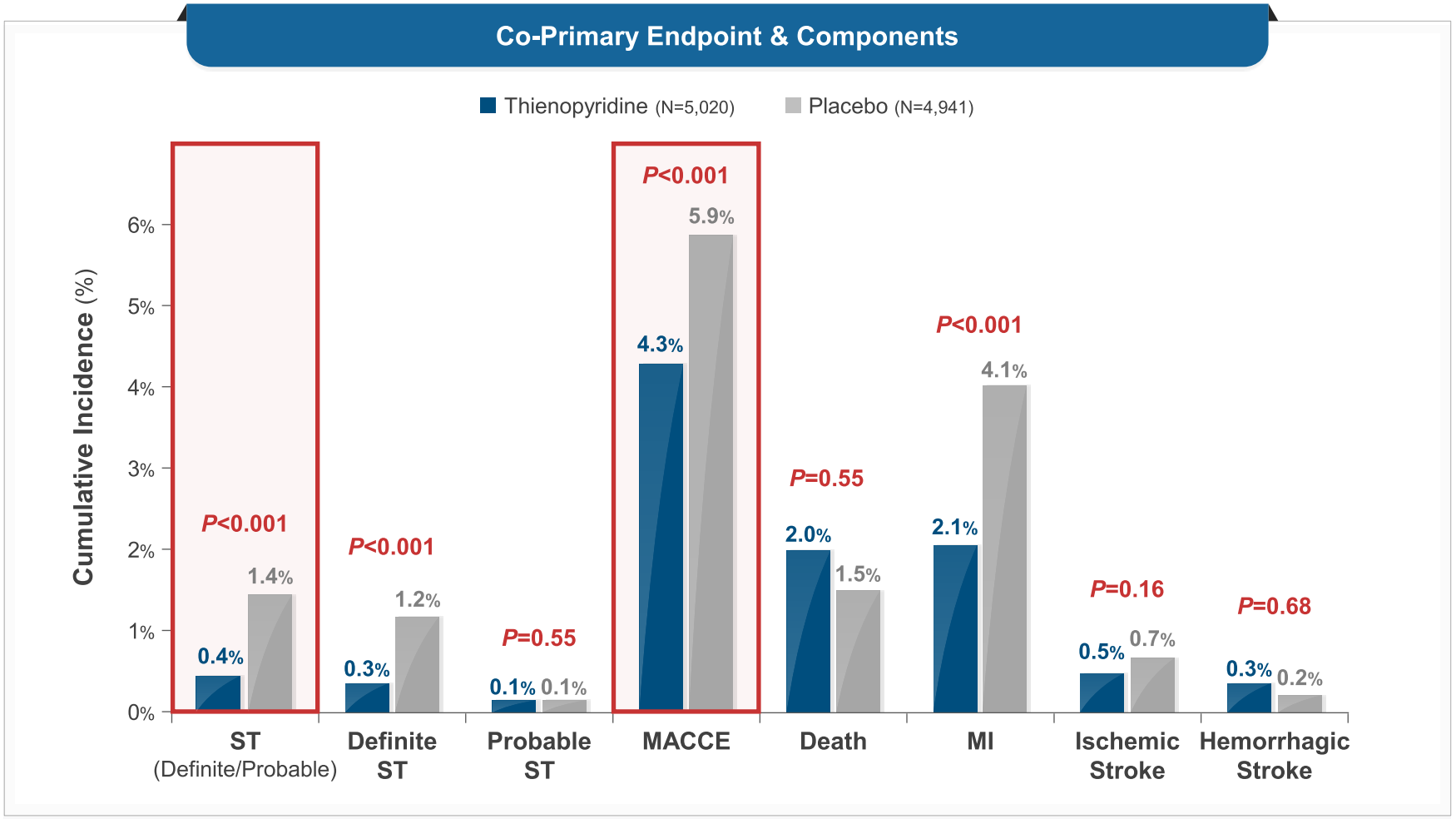
DAPT (2014)
Co-Primary Endpoint & Components

- Patients who received long-term DAPT had a lower incidence of MACCE or ST.



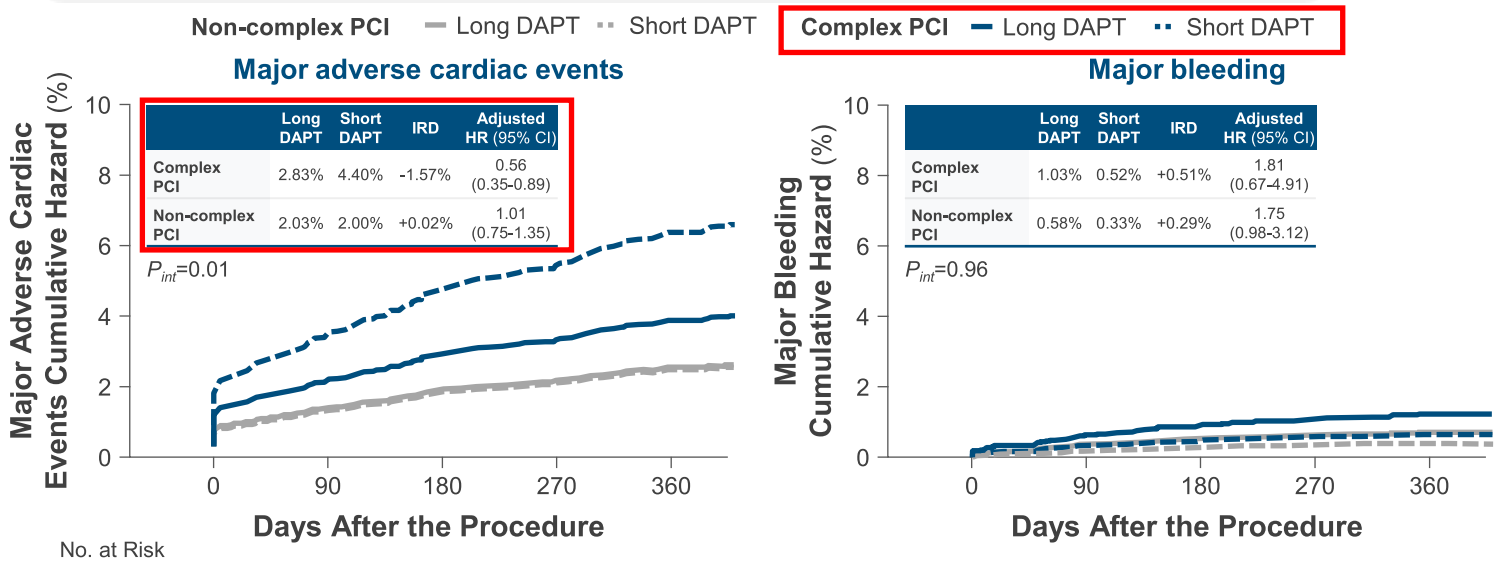
DAPT, dual antiplatelet therapy; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; ST, stent thrombosis

1. Mauri L, *et al. N Engl J Med* 2014;371:2155-2166.

DAPT duration according to PCI complexity

- **Long-term DAPT** (≥1 year) **significantly reduced** (Pint=0.01) **the risk of cardiac ischemic events with a magnitude that was greater for higher procedural complexity.**

Cumulative hazard curves for long-term DAPT versus short-term DAPT



No. at Risk

Non-complex PCI-Long DAPT	3,932	3,874	3,824	3,794	3,520	3,941	3,892	3,844	3,811	3,540
Non-complex PCI-Short DAPT	3,938	3,875	3,816	3,782	3,511	3,947	3,900	3,849	3,814	3,550
Complex PCI-Long DAPT	840	816	805	796	668	846	826	815	808	706
Complex PCI-Short DAPT	802	777	768	759	693	816	801	794	787	692

Study Design

The authors pooled patient-level data from 6 randomized controlled trials investigating DAPT durations after PCI. Complex PCI was defined as having at least 1 of the following features: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion. The primary efficacy endpoint was major adverse cardiac events (MACE), defined as the composite of cardiac death, myocardial infarction, or stent thrombosis. The primary safety endpoint was major bleeding. Of 9,577 patients included in the pooled dataset for whom procedural variables were available, 1,680 (17.5%) underwent complex PCI.

DAPT, dual-antiplatelet therap; int, interaction; PCI, percutaneous coronary intervention
Intention-to-Treat Analysis. Incidence rates are expressed as 100 patient-years of follow-up.

1. Giustino G, *et al*. J Am Coll Cardiol. 2016;68(17):1851-1864.

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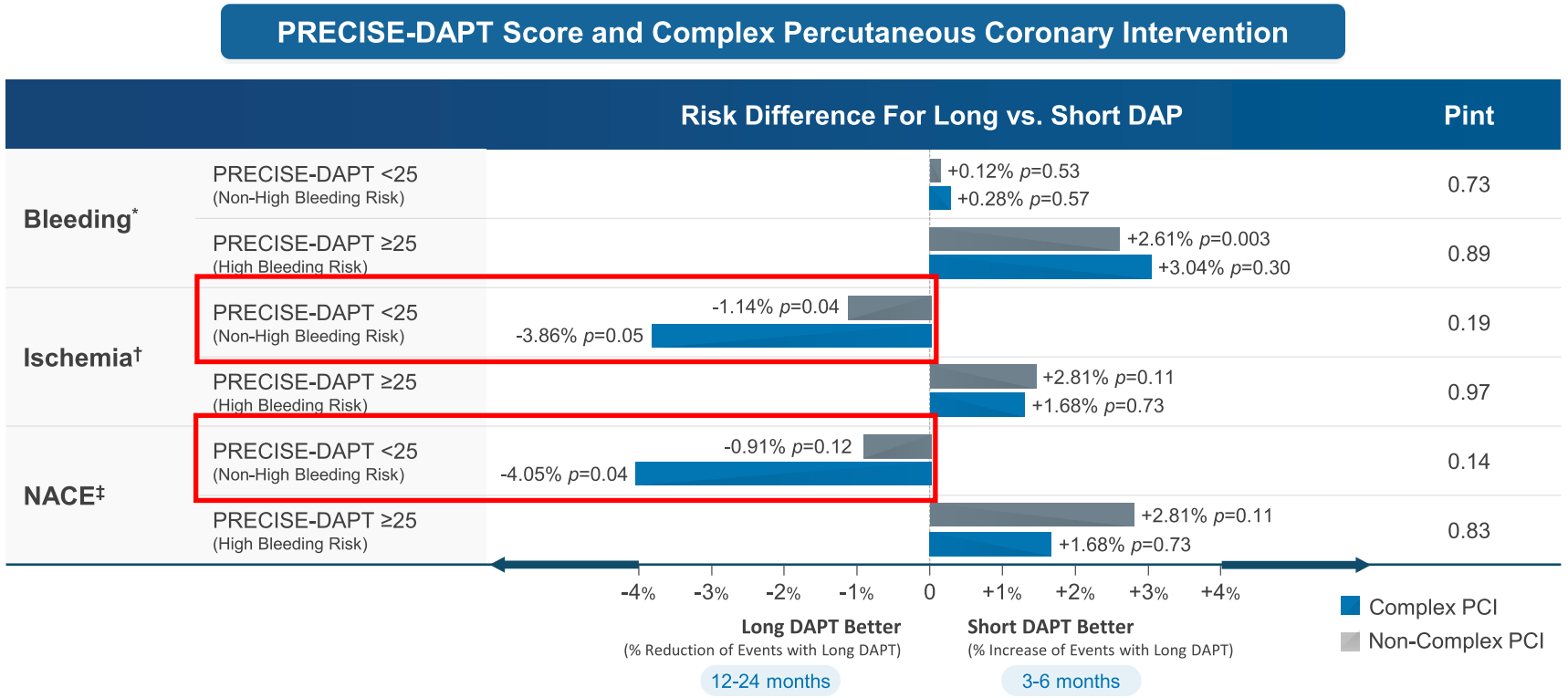
DAPT duration according to PCI complexity

- **Patients who underwent complex PCI had a higher risk of ischemic events, but benefitted from long-term DAPT only if HBR features were not present.**



Study Design

The study population, which consisted of a total of 14,963 patients treated with percutaneous coronary intervention (PCI) and subsequent DAPT was previously described. In brief, patients treated with coronary stenting in an elective, urgent, or emergent setting were pooled at an individual level from 8 randomized controlled trials. The duration of DAPT with aspirin and a $P2Y_{12}$ inhibitor was randomly assigned to short- (3 or 6 months) or long-term (12 or 24 months) treatment in 10,081 patients in 5 of the 8 included studies

*Complex PCI is defined as the presence of a PCI with ≥3 stents implanted, ≥3 lesions treated, 3 coronary vessels treated, bifurcation with 2 stents implanted, total stent length >60 mm, and/or treatment of a chronic total occlusion. **Bleeding endpoint defined according to the TIMI major/minor bleeding definition. †Ischemic endpoint defined according to the composite of myocardial infarction, definite stent thrombosis, stroke or target vessel revascularization. ‡Net adverse clinical events defined according to the composite of myocardial infarction, definite stent thrombosis, stroke, target vessel revascularization or TIMI major/minor bleeding. DAPT, dual antiplatelet therapy; HBR, high bleeding risk; NACE, net adverse clinical events

1. Costa F, *et al.* J Am Coll Cardiol. 2019 ;73(7):741-754

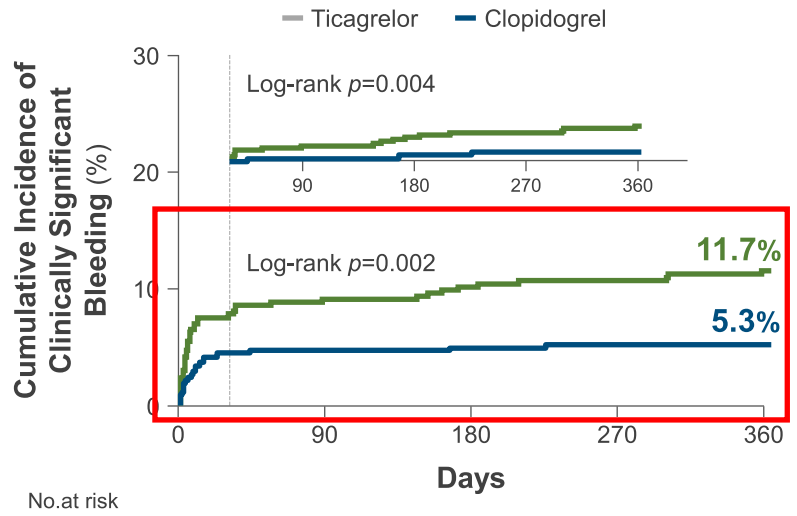
Contents

TICAKOREA

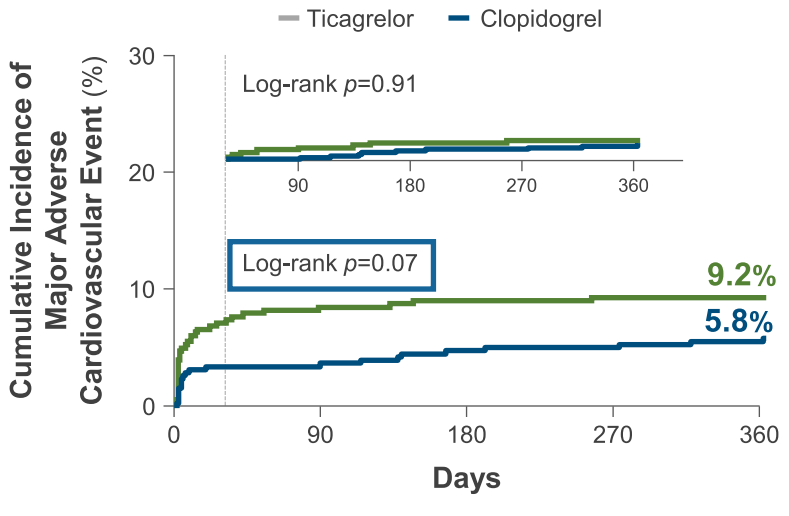
An open-label RCT, 800 Korean patients hospitalized for acute coronary syndromes

- **Standard-dose ticagrelor as compared with clopidogrel was associated with a higher incidence of clinically significant bleeding.**
- **The numerically higher incidence of ischemic events should be interpreted with caution, given the present trial was underpowered to draw any conclusion regarding efficacy.**

Cumulative incidence of the primary safety end point
(a composite of major bleeding or minor bleeding according to PLATO criteria)



Cumulative incidence of the secondary efficacy end point
(a composite of death from cardiovascular causes, myocardial infarction, or stroke)



No.at risk										
Ticagrelor	400	341	337	334	324	400	354	352	351	345
Clopidogrel	400	372	371	369	361	400	380	375	373	362

All patients received aspirin 100 mg daily during the entire follow-up, unless they were intolerant.
CI, confidence interval; HR, hazard ratio; TICAKOREA, (Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Mmanagement

1. Park DW, *et al*. Circulation. 2019;140(23):1865-1877

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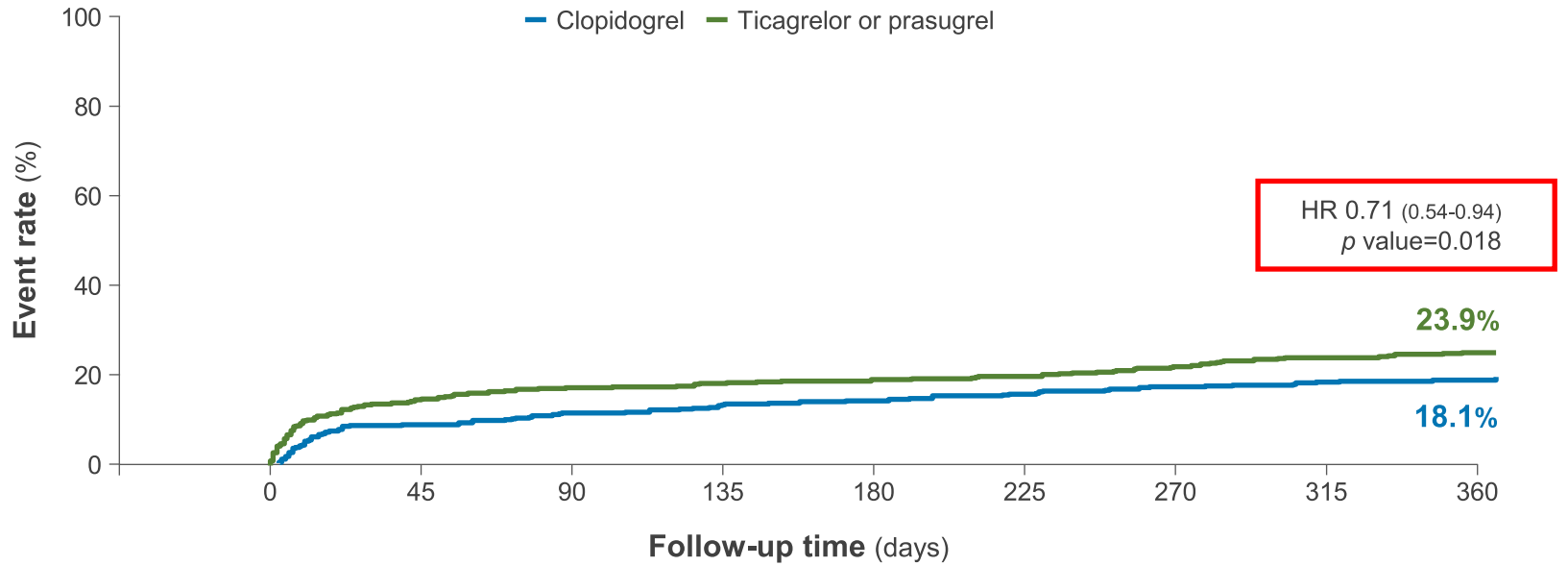
POPULAR AGE

Open-label independent, blinded clinical trial
1,003 patients ≥70 years of age with an NSTE-ACS

Among elderly patients (≥70 years of age) **being treated for an NSTE-ACS, primary bleeding outcome was significantly lower in the clopidogrel group** (88 [**18%**] of 500 patients) **than in the ticagrelor group** (118 [**24%**] of 502; hazard ratio 0.71, 95% CI 0.54 to 0.94; *p*=0.02 for superiority).

Kaplan-Meier curve for the primary bleeding outcome



No. At Risk									
Ticagrelor or prasugrel	502	422	408	404	398	394	383	372	366
Clopidogrel	500	452	438	422	419	408	399	391	387
Ticagrelor or prasugrel discontinuation	502	346	312	295	285	276	264	253	242
Clopidogrel discontinuation	500	424	402	392	388	379	369	362	356

ACS, acute coronary syndrome; HR, hazard ratio; NSTE, non-ST-elevation acute coronary syndrome

1. Gimbel ME *et al.* Lancet. 2020;395:1374-1381

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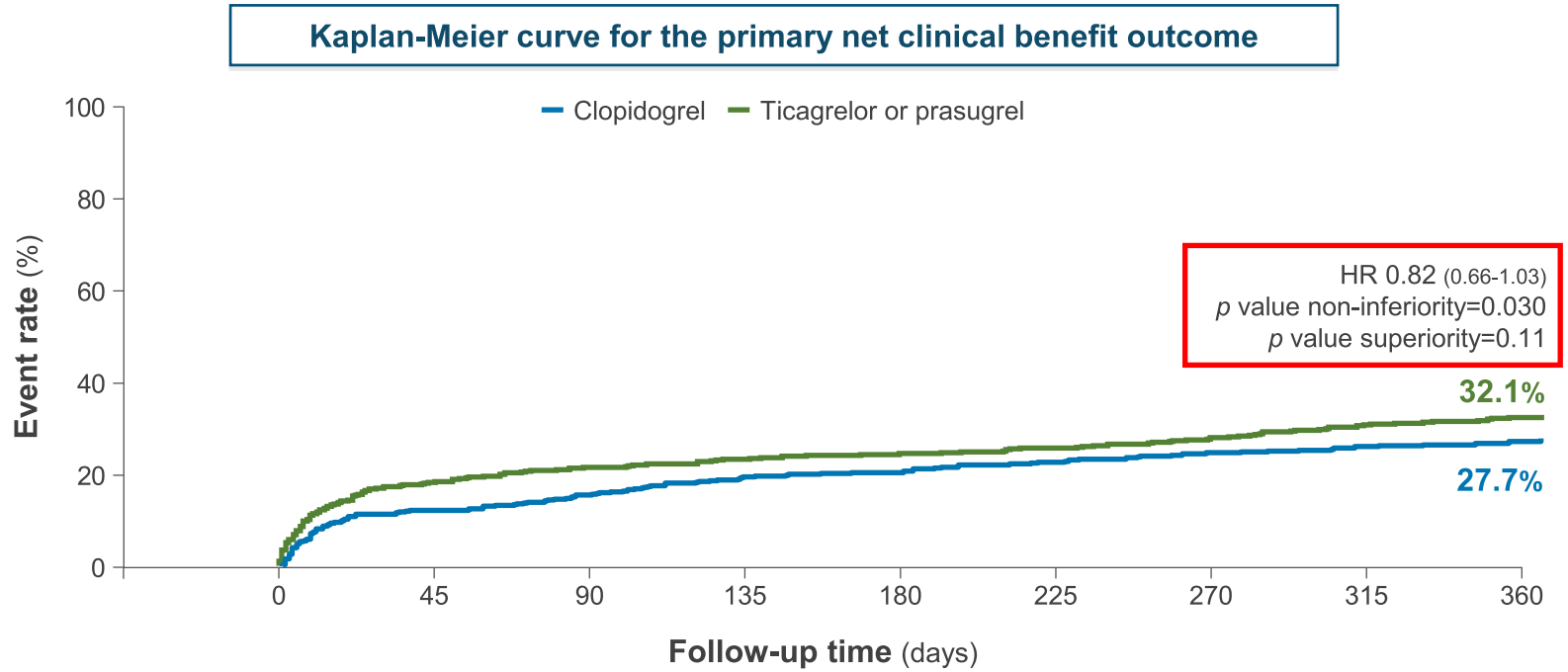
POPULAR AGE

The co-primary net clinical benefit outcome

Co-primary net clinical benefit outcome was non-inferior for the use of clopidogrel (139 [28%]) **versus ticagrelor** (161 [**32%**]; absolute risk difference -4%, 95% CI -10.0 to 1.4; *p*=0.03 for non-inferiority).



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HR, hazard ratio

1. Gimbel ME *et al.* Lancet. 2020;395:1374-1381

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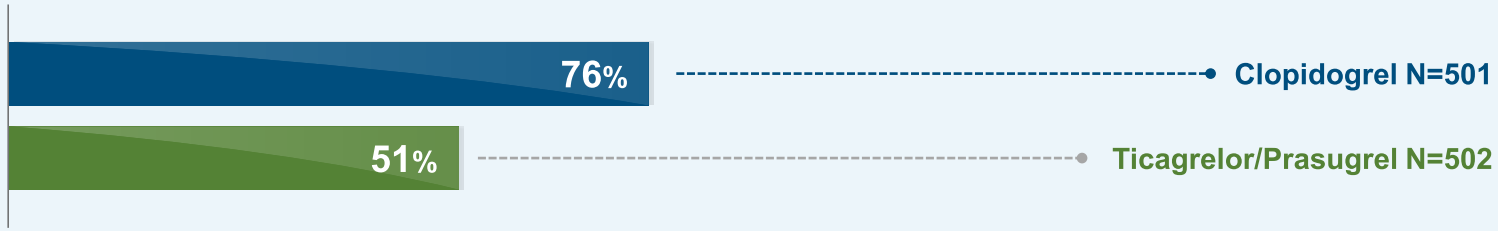
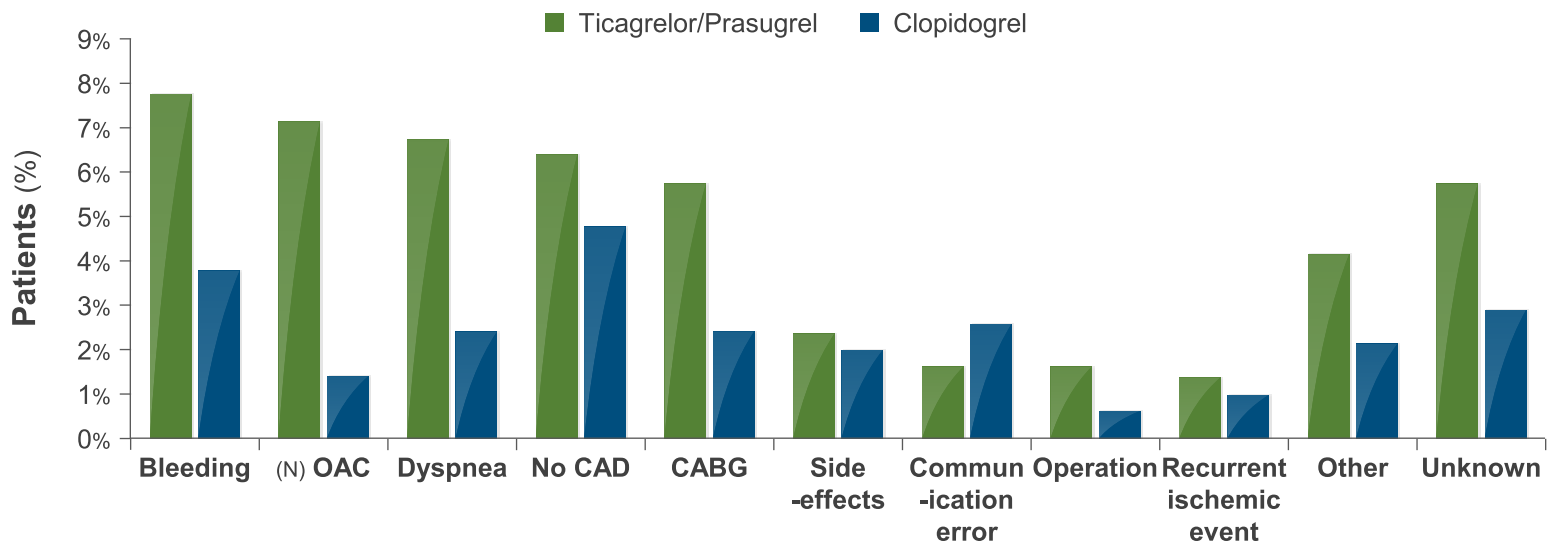
POPULAR AGE

Adherence

Adherence



Reasons for switching and discontinuing study medication



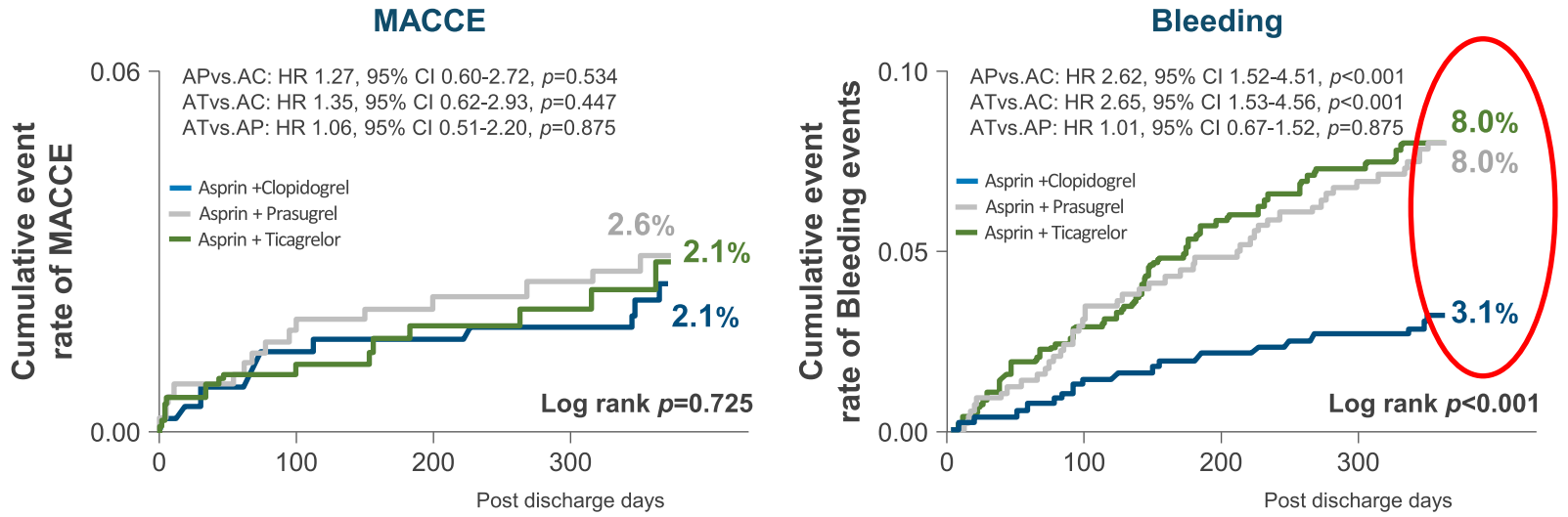
1. Gimbel ME Lancet 2020, 395, 1374–1381

KAMIR NIH

Clopidogrel vs prasugrel and ticagrelor

Prasugrel and ticagrelor showed similar rates of 1-year MACCE, but a higher rate of bleeding events, compared with clopidogrel in Korean AMI patients

Cumulative incidence of 1-year clinical outcomes of the propensity score-matched population



No at risk								
Asprin+Clopidogrel	572	565	505	478	572	560	543	539
Asprin+Ticagrelor	572	566	338	321	572	554	508	500
Asprin+Prasugrel	572	562	479	459	572	551	523	511

Study Design

From the Korean AMI Registry, 9,355 patients who received dual antiplatelet agent (aspirin with clopidogrel [AC], 6,444 [70.5%] patients; aspirin with prasugrel [AP], 1,100 [11.8%] patients; or aspirin with ticagrelor [AT], 1,811 [19.4%] patients) were analysed. In-hospital endpoints were all-cause mortality or bleeding events during admission and 1-year endpoints were major adverse cardiac and cerebrovascular events (MACCE) and major bleeding events

MACCE, which was defined as a composite of cardiac death, non-fatal recurrent myocardial infarction (MI), stent thrombosis and stroke
A, aspirin; C, clopidogrel; KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institute of Health; P, prasugrel; T, ticagrelor

1. Kang J, *et al*. Thromb Haemost 2018;118:591-600.

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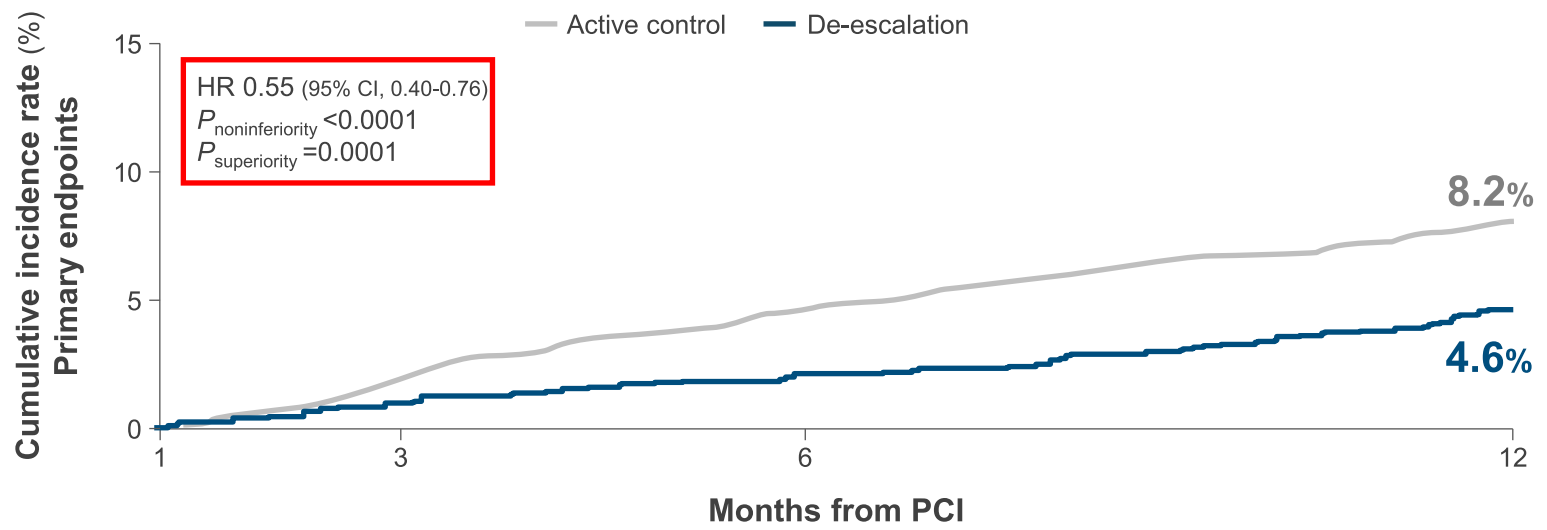
TALOS-AMI

A multicenter, randomized, and open-label study conducted in South Korea

- **N=2,697, AMI patients receiving ticagrelor+ASA and without major events in the first month after index PCI were randomized to the de-escalation group (clopidogrel+aspirin,** N=1,349**) or continuing ticagrelor+ASA** (N=1,348)**. Patients were followed up until 12 months after PCI.**
- **Primary endpoint:** Net adverse clinical events
  (composite of cardiovascular death, MI. stroke & BARC 2, 3 or 5 bleeding from 1 to 12 months after PCI)

Composite cardiovascular death, MI, stroke and BARC bleeding (type 2,3 or 5)



Number at risk				
Active control	1,348	1,273	1,191	1,099
De-escalation	1,349	1,291	1,247	1,172

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR,hazard ratio; CV, cardiovascular; PCI, percutaneous coronary intervention; TALOS-AMI, The Ticagrelor versus Clopidogrel in Stabilized Patients with acute myocardial infarction

1. Kim CJ, *et al.* Lancet 2021; 398(10308):1305–16

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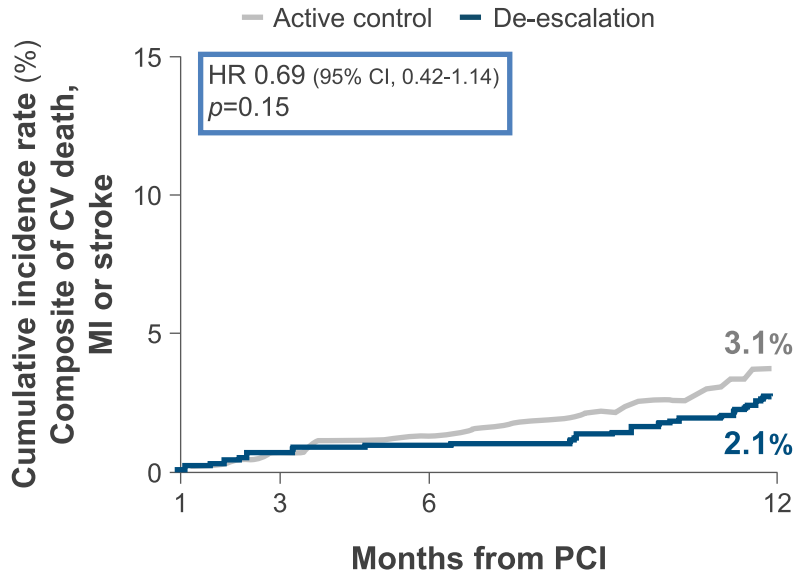
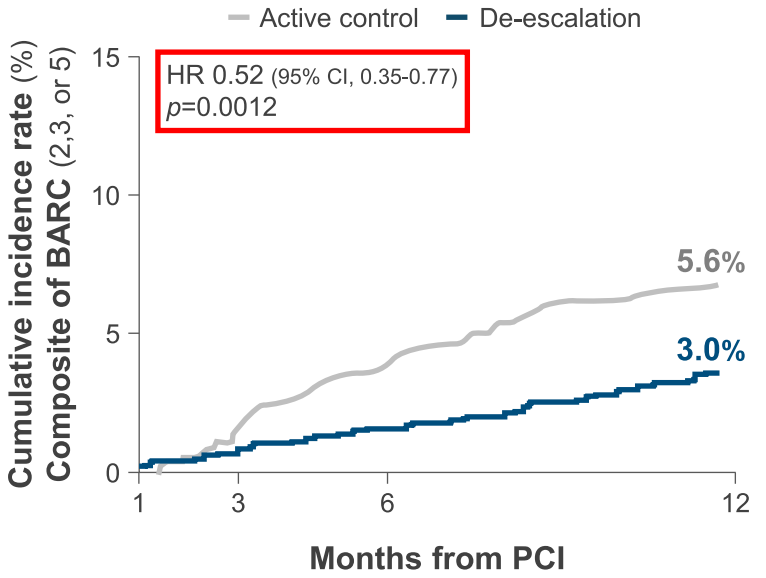
TALOS-AMI

Ischemic and Bleeding Events

Composite of cardiovascular death, MI, and stroke



Composite of BARC bleeding (type 2,3, or 5)



Number at risk

De-escalation	1,349	1,299	1,264	1,201	1,349	1,293	1,251	1,180
Active control	1,348	1,288	1,226	1,147	1,348	1,276	1,197	1,120

Conclusion

In AMI patients who had no major adverse events during the 1st month after PCI, a uniform, unguided de-escalation DAPT strategy switching from ticagrelor to clopidogrel was superior to the ticagrelor-based continuing DAPT strategy, in terms of ***net clinical benefit with a significant decrease in bleeding risk and no increase in ischemic risk***.

BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR,hazard ratio; CV, cardiovascular; PCI, percutaneous coronary intervention; TALOS-AMI, The Ticagrelor versus Clopidogrel in Stabilized Patients with acute myocardial infarction

1. Kim CJ, *et al.* Lancet 2021; 398(10308):1305–16

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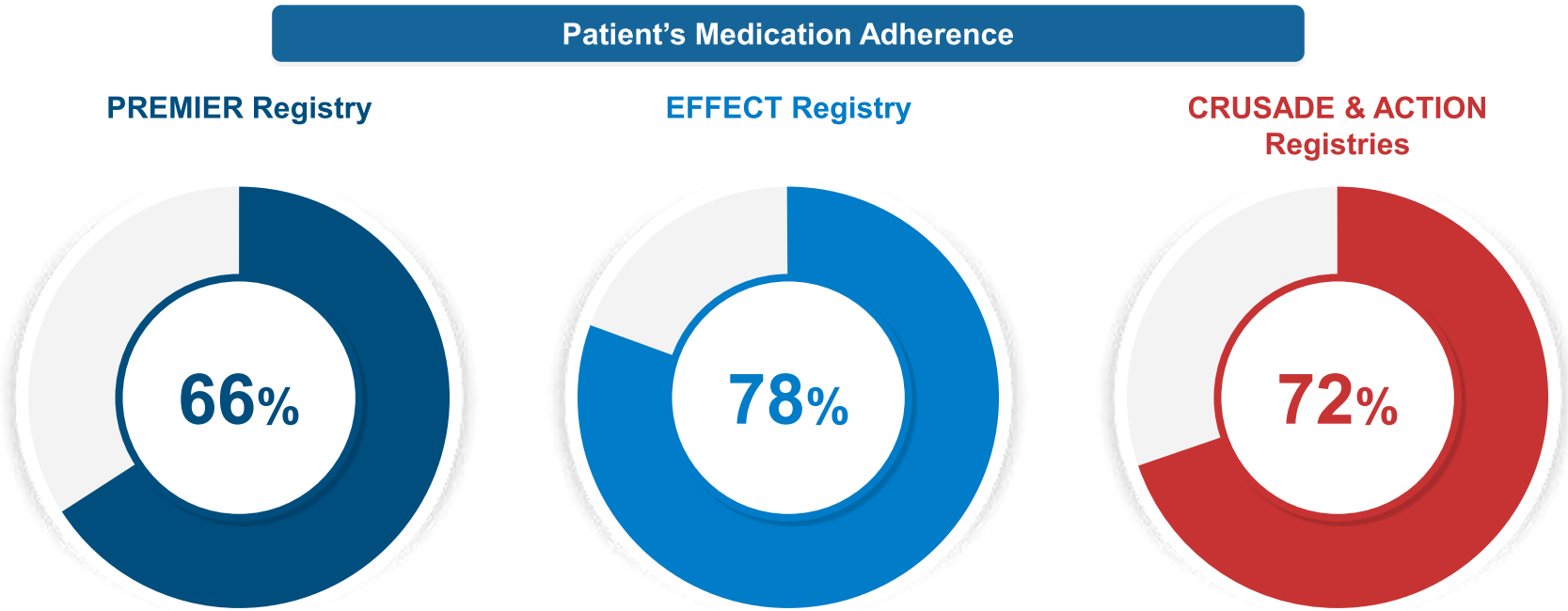
Contents

The Non-adherence Pandemic:

Non-adherence to cardiovascular medications is a Global Threat

- Even following acute MI, only 66% of patients in the PREMIER Registry reported taking key medications
- In the Ontario-based EFFECT Registry, only 78% of patients filled prescriptions within 120 days of an AMI
- Similarly, within 3 months of AMI discharge, only 72% reported taking prescribed medications in the CRUSADE and ACTION Registries



AMI, acute Myocardial infarction; MI, myocardial infarction

1. Kolandaivelu K, *et al. Eur Heart J* 2014;35:3267-3276.

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2021 ACC/AHA/SCAI Guideline

Early DAPT interruption (for bleeding, procedures, or nonadherence) is a reversible risk factor that is strongly **associated with stent thrombosis, particularly early after PCI, with the relative increase in stent thrombosis** rates between 2-fold and >20-fold.

Nonrandomized trials, observational studies, and/or registries of DAPT compliance[2]

Study Acronym; Author (year)	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Silber S et al., 2014	Study type: pooled analysis of 4 randomized trials Size: 4896	Inclusion criteria: patients receiving PCI with zotarolumus eluting stent Exclusion criteria: N/A	1° endpoint: stent thrombosis Results: 21.8% of patients had interruption of DAPT. Rate of stent thrombosis was 0.8% in patients with continued DAPT versus 3.6% among patients who interrupted DAPT within the first month after PCI	**Interruption of dual antiplatelet therapy within the first month after PCI is associated with higher risk of stent thrombosis** and **increased risk of poor cardiovascular outcomes.**
Brodie et al., 2015	Study type: cohort study Size: 8582	Inclusion criteria: successful drug-eluting stent placement Exclusion criteria: planned bypass surgery or significant anemia	1° endpoint: stent thrombosis Results: Premature cessation of DAPT was associated with 2.67 fold increased risk of stent thrombosis	**Premature cessation of DAPT was associated with increased risk of stent thrombosis**
Genereaux et al., 2015	Study type: pooled analysis of 3 randomized trials and 4 registries Size: 11219	Inclusion criteria: enrollment of 3 trials and 4 registries of PCI with everolimus eluting stents Exclusion criteria: incomplete data in the database for DAPT usage	1° endpoint: Stent thrombosis Results: premature cessation of DAPT within 30 days was associated with increased risk of stent thrombosis (HR 26.8, 95% CI 8.4-85.4)	**DAPT cessation within 30 days of PCI was associated with substantially increased risk of stent thrombosis**
Rozemeijer R et al., 2019	Study type: cohort study Size: 6545	Inclusion criteria: consecutive patents undergoing PCI Exclusion criteria: N/A	1° endpoint: stent thrombosis Results: DAPT non-use was associated with increased risk of stent thrombosis (OR 10.9, 95% CI 2.47-48.5). Stent thrombosis was associated with mortality (HR 2.29, 95% CI 1.03-5.1)	**DAPT non-use is associated with stent thrombosis and stent thrombosis associated with mortality.**

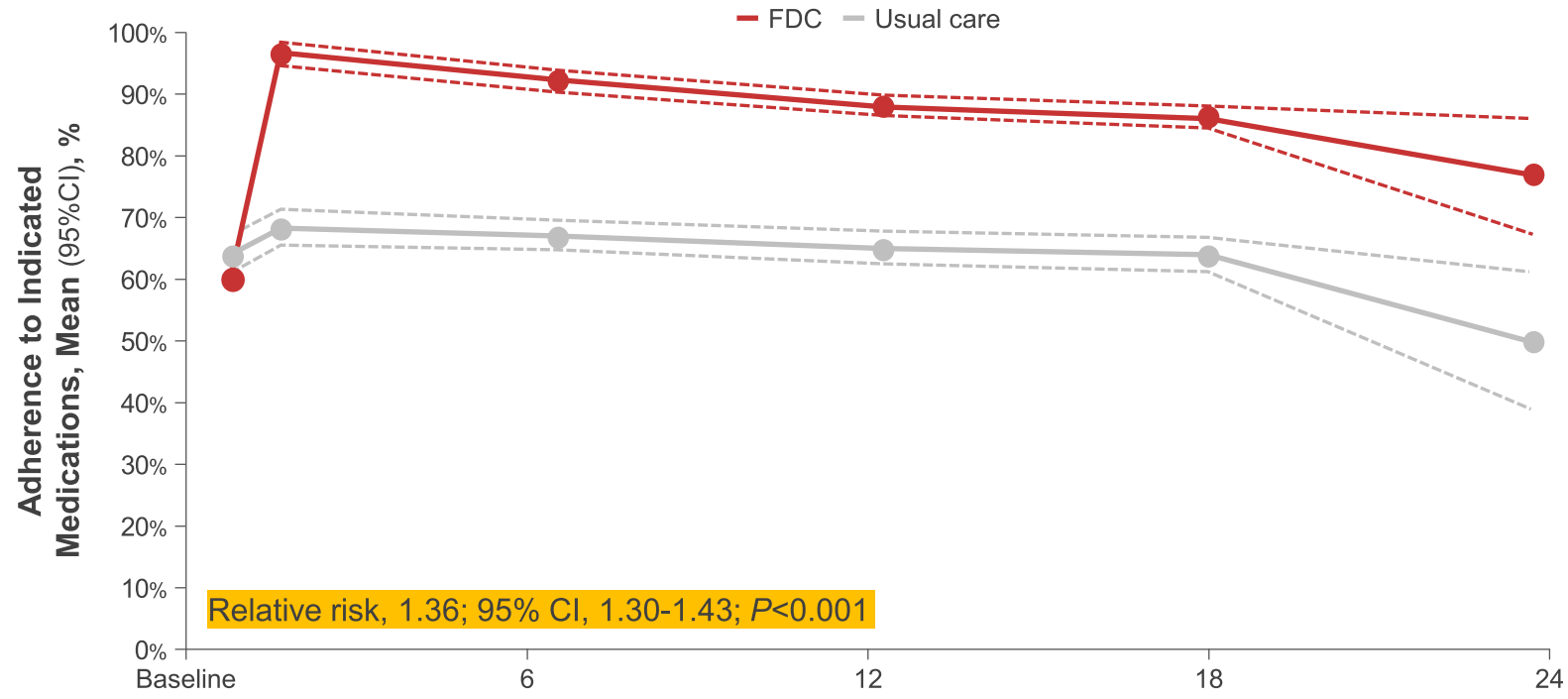
DAPT; dual antiplatelet therapy; PCI, percutaneous coronary intervention; N/A, not available

1. Lawton JS, et al. J Am Coll Cardiol. 2022;79 (2):e21–e129. 2. Lawton JS, et al. J Am Coll Cardiol. 2022;79 (2):e21–e129[Suppl]

Effect of FDC Treatment on Adherence:

By reducing pill burden, FDCs may improve adherence

- **Fixed-Dose combination** (FDC) **delivery of statin, aspirin, and 2 BP-lowering medications vs. Usual care improved long-term adherence to indicated therapy**

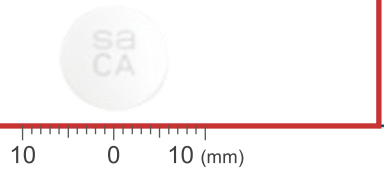


No. of events/total No.					
FDC	598/1,002	899/977	827/935	452/524	26/34
Usual care	635/1,002	657/978	602/925	334/522	18/36

BP, blood pressure

1. Thom S, *et al. JAMA* 2013;310(9):918-29.

Previously Approved Clopidogrel-ASA FDC in Korea: All capsule formulation

제품	Price**	제형	Size†
A	1,190	캡슐제 ▪ 장용코팅 아스피린 펠렛 ▪ 클로피도그렐 펠렛	
B	1,199		
C	1,205		
D	1,202		
플라빅스에이 (사노피)	1,158	정제	

10 0 10 (mm)

**as of Jan 01, 2021 †실 사이즈 기준

1. 보건복지부 고시 제2021-317호 약제급여목록및급여상한금액표_(2022.1.1.)

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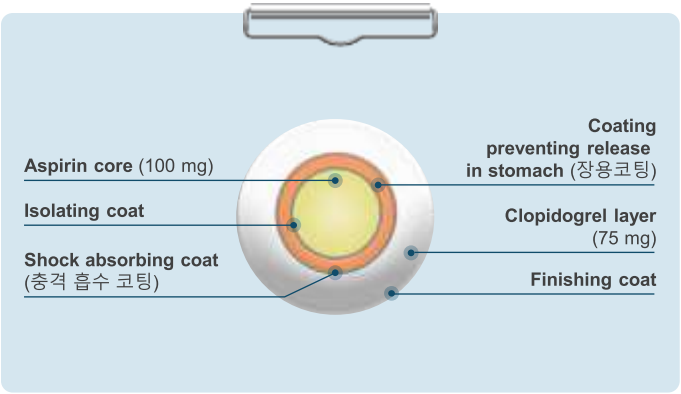
Product Development History:
Clopidogrel/Aspirin FDC in Korea

Early investigation on technology
- **Tab in Tab** (유핵정)은 아스피린으로 인한 **위장장애를 최소화하기에 적합**
- 플라빅스와 동일하게 정제로 개발

Two key points for FDC development
- **Incompatibility of both drug substances**
  - Separation of two substances
- **The necessity for no release of aspirin in the stomach**
  - Gastro resistant protection & tab in tab technology



Enteric coated tablet (장용정)
- 강산의 환경인 위 내에서는 용해되지 않고 상대적으로 **알칼리성 환경인 장내에서 쉽게 용해되는 코팅제로 피복한 정제**
- 약물이 위산에 의해 쉽게 분해되거나 **위점막을 자극하는 경우** (e.g. aspirin, naproxen 등의 NSAIDs) 또는 위를 우회하면 장관에서 효율적으로 흡수가 증대되는 약물에 적합

Tab in Tab (유핵정)
- 안쪽의 정제가 핵 (core)이 되고 바깥쪽의 껍질 (shell)로 구성되는 정제
- **장용화에 유리**한 제형

1. Data from Ambares PSO Development Center

Summary

- Recent Guidelines recommend that the choice and duration of DAPT should be decided according to the ischemic and bleeding risk of patients with ACS.
- DAPT Score and PRECISE-DAPT score may help clinicians decide who should be treated with shorter or extended DAPT considering ischemic and bleeding risk.
- The use of clopidogrel and aspirin can be considered as the first choice of DAPT for patients ≥70 years with NSTE-ACS or East Asian patients with ACS without definitive increased risk of early ischemic events.
- De-escalation DAPT strategy switching from ticagrelor to clopidogrel can be considered in East Asian patients with ACS.
- Simplification of drug regimen can improve adherence in patients with ACS.
- PlavixA is developed as advanced formula, 'tab in tab' for less release aspirin in stomach and for improving adherence.