Review Article

Expert Consensus on Dual Antiplatelet Therapy (DAPT) for Acute Coronary Syndrome in Thailand: Review Article

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Acute coronary syndrome (ACS) is an emergency condition that may lead to severe morbidity or mortality. One factor that may improve mortality in ACS is dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor blocker on top of aspirin. Recently, several guidelines recommended DAPT in ACS patients. This consensus aimed to summarize how to choose the appropriate DAPT for ACS patients based on guidelines and clinical trials to ensure the best patient outcomes. The recommendations of DAPT for the eight settings of ACS, which are STEMI with primary percutaneous coronary intervention (PCI), ST elevation myocardial infarction (STEMI) with fibrinolytics, STEMI without reperfusion therapy, non-ST elevation acute coronary syndrome (NSTE-ACS) with PCI, medically managed NSTE-ACS, maintenance DAPT in ACS, recurrent ACS, and ACS in the elderly, are reported.

Keywords: Acute coronary syndrome, Dual antiplatelet therapy, $P2Y_{12}$ receptor blocker, ST elevation myocardial infarction, Non-ST elevation acute coronary syndrome

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Acute coronary syndrome (ACS) is an emergency condition that may lead to severe morbidity or mortality. Worldwide deaths from cardiovascular diseases are predicted to be 23.4 million in 2030 [(1)]. The mortality rates in ACS in Thailand tended to be lower from the two national surveys where the mortality rate in ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTE-ACS) were lowered from 17.0% in 2004 to 5.3% in 2008 and 13.1% to 5.1%, respectively[(2)]. However, these surveys were conducted only in secondary and tertiary care.

Even though aspirin is effective in reducing vascular events, 54% of patients still have future coronary events[(3)]. Dual antiplatelet therapy (DAPT) such as clopidogrel, a $P2Y_{12}$ receptor blocker, showed better reduction in cardiovascular events (9.3% versus 11.4%; $p<0.001$) compared with aspirin alone[(3)]. Despite better outcomes, DAPT had significantly increase in major bleeding compared with aspirin (3.7% versus 2.7%; $p=0.001$)[(3)]. There are four available $P2Y_{12}$ receptor blockers in ACS, including clopidogrel, ticagrelor, prasugrel, and cangrelor. The first three agents are oral form and available in Thailand, while cangrelor is an intravenous medication and not available in Thailand. Clopidogrel and ticagrelor have been listed in the national drug list that can be reimbursed under specific conditions[(4)]. Even though all agents block adenosine diphosphate receptor in platelet, they have different properties as shown in Table 1, and can be used in different setting of ACS[(5)]. Both ticagrelor and prasugrel are considered as potent $P2Y_{12}$ receptor blockers. Several guidelines recommended DAPT in ACS patient such as the 2018 ESC/EACTS Guidelines on myocardial revascularization[(6)], the 2017 ESC, which updated the

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Table 1. Properties of available $P2Y_{12}$ receptor blockers in Thailand[5]

Properties	Clopidogrel	Ticagrelor	Prasugrel
Dosing	Loading 300 to 600 mg Maintenance 75 mg daily	Loading 180 mg Maintenance 90 mg bid	Loading 60 mg Maintenance 10 mg daily
Class	Thienopyridine (prodrug)	Cyclopentyltria-zolopyrimidines (active drug)	Thienopyridine (prodrug)
Oral bioavailability	>50% (active metabolite)	30% to 42%	>78% (active metabolite)
Onset	2 to 4 hours with IPA	0.5 hour with IPA	1 hour with IPA 90%
	50% to 70%	90%	
Half life	0.5 hours	9 hours	7 hours
Elimination	Esterases; Metabolism by CYP-450 enzymes (CYP2C19)	Metabolism by CYP-450 enzymes (CYP3A4/5)	Esterases; Metabolism by CYP-450 enzymes (CYP3A4, CYP2B6)
Off set (when to stop before surgery)	5 to 7 days	5 days	7 days

IPA=inhibition of platelet aggregation

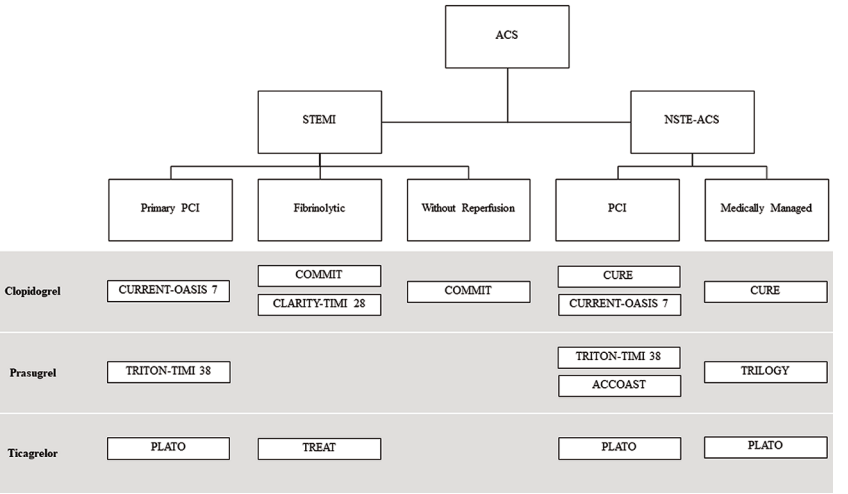

Figure 1. Summary of clinical evidences in ACS setting.

DAPT in coronary artery disease and was developed in collaboration with EACTS[7], and the 2016 ACC/AHA Guideline, which updated the duration of DAPT in patients with coronary artery disease[8].

This consensus aimed to summarize how to choose the appropriate DAPT for ACS patients based on the guidelines and clinical trials to ensure the best patient outcome for health care provider and a suitable economic outcome for Thailand. Relevant trials or guidelines up to December 2018 were reviewed to conclude DAPT in these eight settings, STEMI with primary percutaneous coronary intervention (PCI), STEMI with fibrinolytics, STEMI without reperfusion therapy, NSTE-ACS with PCI, medically managed NSTE-ACS, maintenance DAPT in ACS, recurrent ACS, and ACS in the elderly. Summary of clinical evidences were reviewed in each ACS setting (except maintenance DAPT in ACS, recurrent ACS, and ACS in the elderly) as shown in Figure 1.

Two large studies compared the potent $P2Y_{12}$ receptor blockers and the clopidogrel, which was ticagrelor versus clopidogrel (Platelet Inhibition and Patient Outcomes [PLATO] study), and prasugrel versus clopidogrel on top of aspirin in all treatment arms (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 [TRITON-TIMI 38] study)[9,10]. Both studies were conducted in ACS patients with a ratio of STEMI in 37.5% to 38.0% in the PLATO study and 26%

Table 2. Summary of two studies compared ticagrelor or prasugrel with clopidogrel in acute coronary syndrome

Factors	PLATO[9]		TRITON-TIMI 38[10]	
	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	Prasugrel (n=6,813)	Clopidogrel (n=6,795)
STEMI, n (%)	3,496 (37.5)	3,530 (38.0)	26%	26%
PCI index hospitalization, n (%)	5,687 (60.9)	5,676 (61.1)	99%	99%
Treatment	180 mg loading, 90 mg bid	300 to 600 mg loading, 75 mg daily	60 mg loading, 10 mg daily dose	300 mg loading, 75 mg daily
Follow-up	12 months		15 months	
Primary efficacy endpoint (death from vascular causes, MI, or stroke), n (%)	864 (9.8)	1,014 (11.7)*	643 (9.9)	781 (12.1)*
Secondary endpoint (death from any cause, MI, or stroke), n (%)	901 (10.2)	1,065 (12.3)*	692 (10.7)	822 (12.7)*
MI	504 (5.8)	593 (6.9)*	475 (7.3)	620 (9.5)*
Death from vascular causes	353 (4.0)	442 (5.1)*	133 (2.1)	150 (2.4)
Stroke	125 (1.5)	106 (1.3)	61 (1.0)	60 (1.0)
Stent thrombosis	71 (1.3)	106 (1.9)*	68 (1.1)	142 (2.4)*
Primary safety endpoint				
Major bleeding	961 (11.6)[a]	929 (11.2)[a]	146 (2.4)[b]	111 (1.8)[b]*
Fatal bleeding	20 (0.3)	23 (0.3)	21 (0.4)	5 (0.1)*
Intracranial bleeding	26 (0.3)	14 (0.2)	19 (0.3)	17 (0.3)

STEMI=ST elevation myocardial infarction; MI=myocardial infarction; PCI=percutaneous coronary intervention

[a] Fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells; [b] Key safety endpoint or non-CABG-related TIMI major bleeding

* $p<0.05$

in the TRITON-TIMI 38. The PCI was performed during index hospitalization in approximately 61% in the PLATO study and 99% in the TRITON-TIMI 38 study. The treatment time of prasugrel was longer in the TRITON-TIMI 38 study than ticagrelor in the PLATO study (15 versus 12 months). Note that the median duration of prasugrel treatment was 14.5 months in the TRITON-TIMI 38 study, and 9.2 months in the PLATO study. Both studies showed that DAPT with potent $P2Y_{12}$ receptor blockers on top of aspirin had significant improvement of the primary efficacy endpoint, which is a composite of the rate of death from cardiovascular causes, myocardial infarction (MI), or stroke as opposed to clopidogrel on top of aspirin. The hazard ratio (HR) for a primary efficacy endpoint by ticagrelor was 0.84 with 95% confidence interval (CI) of 0.77 to 0.92, while the HR by prasugrel was 0.81 with 95% CI of 0.73 to 0.90, which both compared with clopidogrel. Both ticagrelor and prasugrel had lower rate of MI but only ticagrelor had significant lower rate of death from cardiovascular causes with the HR as 0.79 with 95% CI of 0.69 to 0.91. Regarding the primary safety end points, in the PLATO study, the primary safety end points were major bleeding, and ticagrelor had comparable major bleeding rate as clopidogrel, both in the study criteria (11.6% versus 11.2%; HR 1.04; 95% CI 0.95 to 1.13) and in the thrombolysis in myocardial infarction (TIMI) criteria (7.9% versus 7.7%; HR 1.03; 95% CI 0.93 to 1.15). However, in the TRITON-TIMI 38, the key safety endpoint was non-coronary artery bypass surgery (CABG)-related TIMI major bleeding. Prasugrel was significantly higher than clopidogrel (2.4% versus 1.8%; HR 1.32; 95% CI 1.03 to 1.68). Other details on bleeding from both ticagrelor and prasugrel are shown in Table 2.

Recommendation

STEMI with primary PCI

PLATO and TRITON-TIMI 38 were conducted in ACS patients with a ratio of STEMI in 37.5% to 38.0% and 26%, respectively. The PCI was performed

during index hospitalization in approximately 61% in PLATO study and 99% in the TRITON-TIMI 38 study. For ticagrelor[11], the STEMI with primary PCI subgroup analysis of the PLATO trial in patients with STE-ACS intended for reperfusion with primary PCI showed benefit on primary efficacy endpoint in STEMI with primary PCI group and almost reached statistical significance (HR 0.87; 95% CI 0.75 to 1.01). However, if STEMI was defined as those with ST elevation at presentation, left bundle branch block (LBBB) at presentation, or patients with a final diagnosis (n=8,430), ticagrelor showed significant benefit on primary efficacy endpoint when compared to clopidogrel with HR of 0.85 (95% CI 0.74 to 0.97). For primary safety endpoint in STEMI with primary PCI group, ticagrelor had comparable major bleeding rate as clopidogrel by both study criteria (9.0% versus 9.2%; p=0.43; HR 0.98; 95% CI 0.83 to 1.14) and TIMI major bleeding criteria (6.1% versus 6.4%; HR 0.96; 95% CI 0.79 to 1.16). Both primary efficacy and safety endpoints were consistent with the overall PLATO results.

For prasugrel, there was results for STEMI with PCI population[12]. In STEMI with primary PCI population, prasugrel had a lower rate of primary efficacy endpoint when compared with clopidogrel (6.6% versus 8.2%) without statistical significance (HR 0.80; 95% CI 0.60 to 1.08). However, the HR was significant in all STEMI cohort (HR 0.68; 95% CI 0.54 to 0.87). For safety endpoint defined as TIMI major bleeding unrelated to CABG surgery, prasugrel treatment had comparable bleeding outcomes as clopidogrel treatment (1.2% versus 1.5%; HR 0.80; 95% CI 0.40 to 1.60) in STEMI with primary PCI population.

There was no large clopidogrel study in STEMI with primary PCI, but a 2×2 factorial design study was conducted to compare double-dose versus standard dose of clopidogrel in ACS undergoing PCI or the CURRENT-OASIS 7 trial[13]. It is important to note that each arm comprised of STEMI between 36.6% to 37.2%. A 600 mg clopidogrel on day 1, 150 mg once daily on day 2 to 7, and then 75 mg daily regimen was used, while the standard dose used 300 mg loading dose of clopidogrel on day 1 and then 75 mg daily. The double-dose clopidogrel regimen significantly lowered the primary outcome, which is the composite of cardiovascular death, MI, or stroke at 30 days, compared to the standard dose clopidogrel with adjusted HR of 0.86 (95% CI 0.74 to 0.99; p=0.039). However, the major bleeding, defined as study criteria, increased by 41% when using the double-dose regimen as compared to the standard dose regimen (adjusted HR 1.41; 95% CI 1.09 to 1.83; p=0.009). In summary, clopidogrel with 600 mg loading on day 1 prior to PCI reduced cardiovascular events but may increase major bleeding.

Both the European Society of Cardiology (ESC)[7] and the American College of Cardiology (ACC)[8] guidelines recommended potent $P2Y_{12}$ receptor blockers in STEMI with primary PCI over clopidogrel. Clopidogrel may be an optional treatment when $P2Y_{12}$ receptor blockers are contraindicated or not available.

Based on clinical evidences and guideline recommendation, the expert consensus group recommended DAPT with potent $P2Y_{12}$ receptor blockers for at least 12 months in STEMI with primary PCI patients. If potent $P2Y_{12}$ receptor blockers are not available or contraindicated, clopidogrel can be an alternative treatment. Generic clopidogrel should be used only if met with the standard quality control.

STEMI with fibrinolytics

Both the TRITON-TIMI 38 and the PLATO study excluded those patients that received fibrinolytic therapy within 24 to 48 hours[9,10], but there were three randomized placebo controlled trials adding clopidogrel and ticagrelor to aspirin in STEMI patients who received fibrinolytic therapy, CLARITY-TIMI 28, Clopidogrel, and Metoprolol in Myocardial Infarction Trial (COMMIT), and TREAT study[14-16].

In CLARITY-TIMI 28[14], all STEMI patients were treated with a fibrinolytic agent and tenecteplase was used in approximately 50% of the patients. In addition to clopidogrel and aspirin, a fibrinolytic agent showed significant reduction of primary efficacy endpoint (the composite of an occluded infarct-related artery defined by a TIMI flow grade of 0 or 1) on angiography, death from any cause before angiography could be performed, or recurrent MI before angiography with odds ratio 0.64 (95% CI 0.53, 0.76) over placebo. For the primary safety endpoint defined as TIMI, major bleeding was comparable between the clopidogrel and the placebo group (1.3% versus 1.1%, p=0.64). Another clopidogrel study was the COMMIT study that compared clopidogrel 75 mg versus placebo in addition to aspirin 162 mg daily for four weeks in acute MI patients[15]. In that study, about 54% of patients received fibrinolytic agent. Adding clopidogrel to aspirin had a lower primary outcome than placebo (9.2% versus 10.1%, odd ratio 0.91, 95% CI 0.86 to 0.97).

In TREAT, a multicenter, randomized, open-label with blinded bleeding endpoint was conducted

to compare ticagrelor and clopidogrel as DAPT in STEMI patients after fibrinolytic therapy who had 24 hours of symptom onset[16]. There were 3,799 eligible patients, younger than 75 years, that enrolled in the study. The treatments were either ticagrelor (180 mg loading, 90 mg twice daily) or clopidogrel (300 to 600 mg loading, 75 mg daily). The primary outcome or major TIMI bleeding at 30 days was comparable between the two groups (0.73% in ticagrelor and 0.69% in clopidogrel group; p for non-inferiority <0.001). The composite of death from vascular causes, MI, or stroke was also not significantly different between the two groups (4.0% in ticagrelor versus 4.3% in clopidogrel group; p=0.57). It is important to note that the majority of fibrinolytic was tenecteplase (40%) while streptokinase was only 5.7%. In conclusion, ticagrelor was non-inferior to clopidogrel in terms of the rate of major bleeding at 30 days, regardless of the bleeding classification used (TIMI, PLATO, BARC), and could be used within the first 24 hours after fibrinolysis, even when a patient had been pre-treated with clopidogrel.

Both 2017 ESC[7] and 2016 ACC[8] guidelines recommended clopidogrel as co-adjuvant and after fibrinolysis. However, the 2017 ESC Guidelines for the management of acute MI in patients presenting with ST-segment elevation[17] recommended that switching to prasugrel or ticagrelor 48 hours after fibrinolysis might be considered in patients who underwent PCI.

Based on clinical evidences and guideline recommendation, the expert consensus group recommended clopidogrel as the $P2Y_{12}$ receptor blocker of choice as co-adjuvant or after streptokinase. It should be loaded only to 75 mg in patients of 75 years or older. Ticagrelor may be an option in patient receiving tenecteplase within 24 hours. Potent $P2Y_{12}$ receptor blockers might be considered 48 hours after streptokinase.

STEMI without reperfusion therapy

The COMMIT study[15] showed that the addition of clopidogrel to aspirin was safe and reduced mortality and major vascular events in hospital. In the study, some patients did not receive fibrinolytic agents. In the pre-specified sub-categories of enrolled patients, clopidogrel had the benefit irrespective of the use of fibrinolytic therapy (heterogeneity p=0.4).

Since there is no clinical data of potent $P2Y_{12}$ receptor blockers in STEMI without reperfusion therapy, the expert consensus group recommended clopidogrel 75 mg per day in STEMI patients who did not have any reperfusion therapy.

NSTE-ACS with PCI

From the PLATO trial, ticagrelor significantly reduced the primary endpoint, which is deaths from cardiovascular causes, compared with clopidogrel[9]. There was a ticagrelor sub-analysis to explore the effect of ticagrelor versus clopidogrel in the total NSTE-ACS subgroup of the PLATO trial[18]. In that study, NSTE-ACS accounted for 59.49% (11,080 patients from PLATO study where 5,581 NSTE-ACS were randomized to ticagrelor and 5,499 to clopidogrel). In each treatment arm, about 80% of the patients had troponin positive, almost 60% of patients had ST segment depression of 0.1 mm or greater, and almost 90% of patients had TIMI risk score 2 or more. From the subgroup analysis in those with NSTE-ACS, ticagrelor had positive benefit over clopidogrel in the efficacy endpoint, which is composite of cardiovascular death, MI, and stroke with HR of 0.83 (95% CI 0.74 to 0.93). Moreover, ticagrelor had lower deaths from all causes than clopidogrel with HR of 0.76 (95% CI 0.64 to 0.90). In the safety endpoint, classified as major bleeding (study criteria), ticagrelor was not significantly different than clopidogrel with HR of 1.07 (95% CI 0.95 to 1.19). The present study also had an analysis on the effect of ticagrelor in NSTE-ACS with early revascularization. There were 2,873 NSTE-ACS with revascularization in the ticagrelor group and 2,841 in the clopidogrel group. Approximately 90% of the patients in both treatment arms had PCI during the first 10 days. In the efficacy endpoint, ticagrelor showed the benefit over clopidogrel with HR of 0.86 (95% CI 0.68 to 1.09) without significant increase in major bleeding defined by study criteria with HR 1.10 (95% CI 0.84 to 1.44).

Two studies were conducted on using prasugrel as DAPT in NSTE-ACS. They were TRITON-TIMI 38[10] and the comparison of prasugrel at the time of PCI or as pre-treatment at the time of diagnosis in patients with non-ST elevation myocardial infarction (ACCOAST)[19]. In the TRITON-TIMI 38 trial[20], prasugrel showed benefit over clopidogrel in all ACS with scheduled PCI population. There was an analysis from TRITON-TIMI 38 trial in patient with unstable angina (UA) or NSTE-ACS. There were 10,074 NSTE-ACS patients categorized as NSTEMI in 7,541 patients, UA in 2,528 patients, and undetermined in five patients. The PCI was performed in 99.1% of NSTE-ACS patients in this trial. The primary endpoint comprised of cardiovascular death, non-fatal MI, and non-fatal stroke. In that study,

prasugrel had significant lower rate than clopidogrel (9.3% versus 11.2%) with HR of 0.82 (95% CI 0.73 to 0.93). However, risks of TIMI major bleeding not related to CABG was increased in the prasugrel arm (2.2%) compared to the clopidogrel arm (1.6%) with HR 1.40 (95% CI 1.05 to 1.88). In the present study, 60 mg of prasugrel was loaded at any time between randomization and one hour after leaving the cardiac catheterization laboratory and received prasugrel 10 mg as maintenance doses.

The ACCOAST study, a phase 3, randomized, double-blind, event-driven study, compared between prasugrel pre-treatment group and no pre-treatment group. The pre-treatment group was given prasugrel at the time of diagnosis, while the no pre-treatment group received prasugrel after coronary angiography in NSTE-ACS patients[19]. There were 4,033 eligible patients, randomized to pre-treatment group (2,037 patients) and no pre-treatment group (1,996 patients). All patients were planned to have coronary angiogram within 2 to 48 hours after randomization. The pre-treatment group received 30 mg of prasugrel before coronary angiogram plus 30 mg of prasugrel at the time of PCI. For the no pre-treatment group, 60 mg of prasugrel was given after angiography in patients who underwent PCI, which is similar to the TRITON-TIMI 38 trial. The primary efficacy endpoint, which is death from cardiovascular causes, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor bailout, was not statistically different between both groups at day 7 (10.0% versus 9.8%; HR 1.02; 95% CI 0.84 to 1.25) and at day 30 (10.8% versus 10.8%; HR 0.997; 95% CI 0.83 to 1.20). The key safety endpoint classified as all CABG-related or non-CABG-related TIMI major bleeding was significantly higher in the pre-treatment group than the no pre-treatment group at day 7 (2.6% versus 1.4%; HR 1.90; 95% CI 1.19 to 3.02) and day 30 (2.9% versus 1.5%; HR 1.97; 95% CI 1.26 to 3.08).

Clopidogrel may be an option in NSTE-ACS with PCI. The Clopidogrel in UA to Prevent Recurrent Events (CURE) study was conducted to evaluate the effects of clopidogrel in addition to aspirin in NSTE-ACS group[21]. Twelve thousand five hundred sixty-two NSTE-ACS patients received clopidogrel 300 mg immediately and followed by 75 mg once daily or placebo in addition to aspirin. The first primary outcome (death from cardiovascular causes, non-fatal MI, or stroke) was lower in the clopidogrel group than the placebo group (9.3% versus 11.4%, relative risk 0.80 with 95% CI 0.72 to 0.90). However, major bleeding was significantly higher in the clopidogrel group compared with the placebo (3.7% versus 2.7%; relative risk 1.38 with 95% CI 1.13 to 1.67). There was an analysis in NSTE-ACS with PCI in CURE study (the PCI-CURE study)[22]. Two thousand six hundred fifty-eight NSTE patients with PCI patients were randomized to either clopidogrel (n=1,313) or placebo (n=1,345). The rate of primary endpoint from PCI to 30 days was significantly lower in the clopidogrel than in the placebo group (4.5% versus 6.4%; relative risk 0.70 with 95% CI 0.50 to 0.97) with comparable rates of major bleeding (1.6% versus 1.4%; relative risk 1.13 with 95% CI 0.61 to 2.10).

Both ESC[7] and ACC[8] guidelines recommended potent $P2Y_{12}$ receptor blockers in NSTE-ACS with PCI over clopidogrel. Ticagrelor with aspirin is recommended in NSTE-ACS undergoing invasive management, regardless of initial treatment strategy, including patients pre-treated with clopidogrel. While prasugrel is recommended for $P2Y_{12}$ receptor blocker-naive patients, it is not recommended if coronary anatomy is unknown. Clopidogrel may be an optional treatment when $P2Y_{12}$ receptor blockers are contraindicated or not available.

Based on clinical evidences and guideline recommendation, the expert consensus group recommended DAPT with potent $P2Y_{12}$ receptor blockers for at least 12 months in NSTE-ACS with PCI patients. Ticagrelor is preferred in moderate to high risk patients regardless of clopidogrel pre-treatment[9,18]. Prasugrel can be initiated if coronary anatomy was known and planned to have an invasive strategy[19,20]. If potent $P2Y_{12}$ receptor blockers were not available or contraindicated or patients with high risk of bleeding, clopidogrel could be an alternative treatment[21,22]. Again, generic clopidogrel should be used only if met with the standard quality control.

Medically managed NSTE-ACS

A randomized controlled trial, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study, compared prasugrel versus clopidogrel in UA/NSTEMI patients who did not perform revascularization[23]. The study had two study populations, age under 75 years and overall population, which included patients 75 years or older. The prasugrel dose was 10 mg in patients under 75 years and 5 mg in patients 75 years or older or who weighed less than 60 kg. Clopidogrel was given 75 mg in all patients. The primary endpoint was a composite of death from cardiovascular diseases, non-fatal MI, or non-fatal stroke at 30 months. There

were 7,243 patients in the analyses of patients under 75 years and 2,083 patients at 75 years or older. The median follow-up was 17 months. There was no statistical different on primary endpoint and bleeding risk between both groups of treatment and in both study populations. The primary efficacy outcome at 30 months in prasugrel and clopidogrel group were 13.9% and 16.0%, respectively (HR 0.91; 95% CI 0.79 to 1.05). In the present study, prasugrel did not show a superior outcome when compared with clopidogrel.

In NSTE-ACS subgroup of the PLATO trial[18], there was an analysis of both efficacy and safety according to treatment strategy. The treatment strategy was either initially underwent revascularization or no early revascularization for either PCI or CABG with or without angiography within the first 10 days. Ticagrelor had better benefits over clopidogrel regardless of revascularization strategy (HR of 0.86 in NSTE-ACS revascularization group and HR of 0.85 in NSTE-ACS without revascularization group, interaction p=0.93) without significant difference in overall major bleeding defined by study criteria (HR of 1.10 in NSTE-ACS revascularization group versus 1.05 in NSTE-ACS without revascularization group, interaction p=0.82).

Both ESC[7] and ACC[8] guidelines recommended ticagrelor over clopidogrel in this setting unless the risk of bleeding is more than the benefit to prevent ischemic event. Prasugrel is not recommended in this setting.

Based on clinical evidences and guideline recommendation, the expert consensus group recommended ticagrelor over clopidogrel in medically managed NSTE-ACS. Clopidogrel may be an optional treatment when ticagrelor is not available or contraindicated or high bleeding risk patients. Prasugrel is not recommended in this setting based on the negative results of the TRILOGY[23] and the present study population was excluded in the TRITON-TIMI 38 study[10].

Maintenance DAPT in ACS

From the results of PLATO and TRITON-TIMI 38 study (Table 2), the potent $P2Y_{12}$ receptor blockers should be given to all ACS patients for at least 12 months[9,10].

For those ACS patients with high risk for bleeding or when potent $P2Y_{12}$ receptor blockers are not available or are contraindicated, clopidogrel treatment may be an optional treatment. An open labeled, randomized trial was conducted and compared potent $P2Y_{12}$ receptor blockers versus aspirin plus clopidogrel treatment[24]. The switching regimen started at one month with 75 mg of aspirin plus 75 mg of clopidogrel in ACS patients who underwent PCI. Both treatment regimens were scheduled for one year when outcomes were evaluated. The dosage of clopidogrel was between 300 to 675 mg. Out of 646 eligible patients, 257 (40%) patients were diagnosed as STEMI. The primary outcome, composite of cardiovascular death, urgent revascularization, stroke, and bleeding, was significantly lower in switching DAPT group than unchanged DAPT group (13.4% versus 26.3%) with HR of 0.48 (95% CI 0.34 to 0.68; p<0.01). Major bleeding was also significantly lower in switched DAPT group (4.0% versus 14.9%; HR 0.30; 95% CI 0.18 to 0.50; p<0.01). All ischemic outcomes were comparable between the two groups (9.3% versus 11.5%; p=0.36). The compliance rate in the switched DAPT group was significantly higher than the unchanged DAPT group at the end of study (86.0% versus 74.9%; p<0.01).

A maintenance DAPT therapy of clopidogrel with an early de-escalation strategy guided by a platelet function testing (PFT) is an optional treatment[25]. This regimen may be feasible for those with medical contraindicated or due to socioeconomic reason for potent DAPT. An investigator-initiated, randomized, open-label, assessor-blinded, multicenter trial (TROPICAL-ACS) was conducted in Europe. The inclusion criteria were ACS patients with positive-biomarker, successful PCI, and a planned treatment of 12-month DAPT. The early guided de-escalation group received one week of prasugrel treatment, then one week of clopidogrel treatment, then the 11.5-month therapy of DAPT with either prasugrel or clopidogrel by evidence of high on-treatment platelet reactivity (HPR). Those with sufficient platelet inhibition or no HPR continued with clopidogrel. Two thousand six hundred ten patients were included in the study with 1,304 to guided de-escalation group and 1,306 to the control group. HPR was detected in 511 patients (39% of the intention-to-treat population) in the intervention group. The guided de-escalation of DAPT with clopidogrel was non-inferior to prasugrel at one year for primary outcome, the net clinical benefit [cardiovascular death, MI, stroke, or bleeding grade 2 or higher according to the Bleeding Academic Research Consortium (BARC) criteria] with a margin of non-inferiority at 30%. Ninety-five patients (7%) and 118 patients (9%) in the guided de-escalation and standard group had the primary endpoint [$p_{non\text{-}inferiority}$=0.0004; HR 0.81 (95% CI 0.62 to 1.06), $p_{superiority}$=0.12]. The guided de-escalation treatment

may be more beneficial in those with STEMI than NSTE-ACS (HR 0.54; 95% CI 0.35 to 0.83) with a p for interaction of 0.0116, but not for gender (p for interaction 0.60), age (p for interaction 0.11), or diabetes (p for interaction 0.10).

There are additional studies to continue DAPT longer than 12 months after ACS period. There were two studies conducted by using potent $P2Y_{12}$ receptor blockers, ticagrelor (PEGASUS-TIMI 54 trial) and prasugrel (DAPT trial), as DAPT for more than 12 months[26,27]. Both studies showed significant reduction in primary composite endpoint of cardiovascular death, MI, or stroke. The treatment of ticagrelor of 60 and 90 mg for three years (median follow up of 33 months) had HR (95% CI) over placebo of 0.84 (0.74 to 0.95); p=0.004 and 0.84 (0.75 to 0.96); p=0.008, respectively. The DAPT trial showed that thienopyridine treatment for 30 months compared with placebo had lower major adverse cardiovascular and cerebrovascular events with HR (95% CI) of 0.71 (0.59 to 0.85); p<0.001. The DAPT trial also showed significant reduction in stent thrombosis with HR (95% CI) of 0.29 (0.17 to 0.48); p<0.001. The rate of stent thrombosis in the treatment arm was 0.4% compared with 1.4% in placebo arm. However, both studies showed that long term DAPT treatment with potent $P2Y_{12}$ receptor blockers increased the risk of bleeding. The PEGASUS-TIMI 54 study had TIMI major bleeding rate of 2.30% and 2.60% in 60- and 90-mg of ticagrelor compared with 1.06% of placebo (p<0.001). Similarly, long term thienopyridine treatment in the DAPT trial increased moderate or severe bleeding compared with the placebo (2.5% versus 1.6%; p=0.001).

Both PEGASUS-TIMI 54 and DAPT trial had different settings. First, the PEGASUS-TIMI 54 trial enrolled previous MI one to three years, age over 50 years, with one high risk feature or age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic kidney disease stage 3 or more. The DAPT trial enrolled patients older than 18 years, treated with FDA-approved drug-eluting or bare-metal stents, and eligible for DAPT. Additionally, patients should not have any major cardiovascular or cerebrovascular event, repeat revascularization, or moderate or severe bleeding and have been adherent to thienopyridine therapy (defined as having taken 80% to 120% of the drug without an interruption of longer than 14 days) at 12 months after DAPT[27]. Note that approximately 80% of the patients in the PEGASUS-TIMI 54 study had history of PCI, and 96.5% of these patients underwent PCI with stenting. Second, the PEGASUS-TIMI 54 is a randomized study on either ticagrelor or placebo. Whereas, only 34% of patients received prasugrel therapy in the DAPT trial. The rest of the patients were treated with clopidogrel. These data suggested that the results of the PEGASUS-TIMI 54 trial were from ticagrelor only, while the results of DAPT trial may be the effects of clopidogrel in two-third of the patients. In other words, clopidogrel may be an optional DAPT in drug-eluting stent. Third, the DAPT trial had results on stent thrombosis, but not the PEGASUS-TIMI 54 trial. Neither studies showed the net clinical benefit between reduction of cardiovascular risks and increasing bleeding risks.

Both ESC[7] and ACC[8] guidelines recommended DAPT duration in all ACS settings at least 12 months if patients can tolerate and have no bleeding. The ESC guideline[7] recommended ticagrelor or clopidogrel in ACS with PCI who are at high risk of bleeding and should be considered discontinuation DAPT therapy after 6 months. However, MI patients with high ischemic risk who have no bleeding complication from DAPT, the DAPT treatment may be longer than 12 months.

Based on clinical evidences and guideline recommendation, the expert consensus group recommended DAPT duration in all ACS setting for at least 12 months. It should be a DAPT regimen with potent $P2Y_{12}$ receptor blockers. Clopidogrel is an optional treatment if potent $P2Y_{12}$ receptor blockers were not available or bleeding occurred. The dosage for clopidogrel reloading is 300 mg and 75 mg of clopidogrel should be given on a daily basis. Judgement may be made individually, weighing between cardiovascular benefit and bleeding risk.

Recurrent ACS

There is no available clinical data on DAPT in recurrent ACS within the first 12 months. From the PLATO study[9], the rate of MI after DAPT in ticagrelor and clopidogrel group were 5.8% and 6.9%, respectively, as shown in Table 2. These data also demonstrated the reduction of recurrent MI using ticagrelor by 16% (HR 0.84; 95% CI 0.75 to 0.95). Prasugrel also reduced the rate of non-fatal MI compared with clopidogrel by 24% (HR 0.76; 95% CI 0.67 to 0.85)[10]. Both DAPT regimens with ticagrelor and prasugrel significantly reduced the chances of stent thrombosis compared with clopidogrel by 33% and 52%, respectively. The HR (95% CI; p-value) for ticagrelor and prasugrel regimen were 0.67 (0.50 to 0.91; p=0.009) and 0.48 (0.36 to 0.64; p<0.001),

Table 3. Outcome of ticagrelor versus clopidogrel in elderly patients with ACS: sub study from PLATO trial[28]

Outcomes	Age group (years)	Number of events	Rate in ticagrelor group	Rate in clopidogrel group	Adjusted hazard ratio	95% CI	p value (interaction)
CV death, MI, or stroke	≥75	471	17.2	18.3	0.89	0.74 to 1.08	0.56
	<75	1,399	8.6	10.4	0.84	0.75 to 0.93	
Overall major bleeding	≥75	341	14.2	13.5	1.02	0.82 to 1.27	0.89
	<75	1,545	11.2	10.8	1.04	0.94 to 1.15	

CI=confidence interval; CV=cardiovascular

Table 4. $P2Y_{12}$ receptor blockers recommendation in DAPT regimen from expert consensus group in ACS setting

ACS setting	$P2Y_{12}$ receptor blockers of choice		
STEMI with primary PCI	Ticagrelor[A]	Prasugrel*[A]	Clopidogrel[B]
	180 mg loading dose followed by 90 mg twice a day	60 mg loading dose followed by 10 mg once daily	300 to 600 mg loading dose, followed by 75 mg once daily
	Clopidogrel is an option when prasugrel or ticagrelor are contraindicated or are not available		
STEMI with fibrinolytics	Clopidogrel[A]	Ticagrelor[B]	Prasugrel[D]*
	300 mg loading dose followed by 75 mg once daily	180 mg loading dose followed by 90 mg twice a day	No evidence
	(without loading dose in patients who age 75 year or older)		
	Clopidogrel is a $P2Y_{12}$ receptor blocker of choice but after 48 hours may be considered switching to prasugrel or ticagrelor who underwent PCI. ticagrelor may be considered if fibrinolytic is tenecteplase		
STEMI without reperfusion therapy	Clopidogrel[A]	Ticagrelor[D]	Prasugrel[D]*
	300 mg loading dose followed by 75 mg once daily	No evidence	No evidence
	No data for ticagrelor and prasugrel		
NSTE-ACS with PCI	Ticagrelor[A]	Prasugrel[A]*	Clopidogrel[B]
	180 mg loading dose followed by 90 mg twice a day	60 mg loading dose followed by 10 mg once daily	300 to 600 mg loading dose, followed by 75 mg once daily
		(not recommended in whom coronary anatomy is not known)	
	Clopidogrel is an option when prasugrel or ticagrelor are contraindicated or are not available		
Medically managed NSTE-ACS	Ticagrelor[A]	Clopidogrel[B]	Prasugrel[C]*
	180 mg loading dose followed by 90 mg twice a day	300 to 600 mg loading dose, followed by 75 mg once daily	Not recommended
	300 to 600 mg loading dose, followed by 75 mg once daily		
	Clopidogrel is an option when ticagrelor is contraindicated or is not available		
Maintenance DAPT in ACS	At least 12 months (All $P2Y_{12}$ receptor blockers)		
Recurrent ACS	Ticagrelor[A]	Prasugrel[A]*	Clopidogrel[B]
	180 mg loading dose followed by 90 mg twice a day	60 mg loading dose followed by 10 mg once daily	300 to 600 mg loading dose, followed by 75 mg once daily
	Ticagrelor or prasugrel may be considered in recurrent ACS or stent thrombosis setting		
ACS in the elderly	Ticagrelor[A]	Clopidogrel[A]	Prasugrel[C]*
	180 mg loading dose followed by 90 mg twice a day	75 mg once daily without loading dose	Not recommended in 75 years or older
	Ticagrelor is preferable as DAPT in elderly ACS patients regardless of age		

ACS=acute coronary syndrome; STEMI=ST elevation myocardial infarction; PCI=percutaneous coronary intervention; NTSE=non-ST elevation acute coronary syndrome; DAPT=dual antiplatelet therapy

[A] First choice recommendation, [B] Second choice recommendation, [C] Not recommended in that setting, [D] No data available

* Not recommended in patients ≥75 years old or weighing <60 kg

respectively.

Based on clinical evidences, DAPT regimen with clopidogrel in ACS patients had higher risk of having recurrent ACS compared with DAPT regimen with either ticagrelor or prasugrel. There is no current clinical data on DAPT regimen in the outcome of recurrent ACS. However, the expert consensus group recommended DAPT regimen with either ticagrelor or prasugrel in recurrent ACS or stent thrombosis setting.

ACS in the elderly

A subgroup analysis of the PLATO trial or PLATO in the elderly[28] showed that there was no difference on primary efficacy endpoint (cardiovascular deaths, MI, or stroke) or overall major bleeding between the age of 75 years as a cutoff point by ticagrelor versus clopidogrel as shown in Table 3.

In TRITON-TIMI 38 study, 13% of the patients (out of 13,608 patients) had moderate-to-high-risk ACS with scheduled PCI and were 75 years or older[10]. For subgroup analysis with 75 years or older, body weight less than 60 kg, or history of stroke or TIA, the net benefit between deaths from any causes or non-CABG-related non-fatal TIMI major bleeding was not different between prasugrel and clopidogrel (20.2% versus 19.0%) with HR of 1.07 (95% CI 0.90 to 1.28). Patients 75 years or older had no net benefit from prasugrel (HR 0.99; 95% CI 0.81 to 1.21). The unadjusted HR of prasugrel in primary outcome reduction compared with clopidogrel was significant only in age group under 65 years (8.1% versus 10.6 or 25% reduction with sample size of 8,322 patients; $p<0.05$). Whereas, prasugrel had non-significant benefits over clopidogrel in those with age. Therefore, prasugrel did not show positive impact in ACS patients with age over 65 years.

Based on clinical evidences, the expert consensus group recommended ticagrelor and clopidogrel in patients 75 years or older. Ticagrelor is preferable as DAPT in elderly ACS patients regardless of age. Prasugrel is not recommended for the elderly patients with ACS.

Conclusion

DAPT regimens had shown the benefit in all ACS settings in thrombotic events prevention. Based on clinical studies of potent $P2Y_{12}$ receptor blockers that showed the benefit over clopidogrel across ACS population, potent $P2Y_{12}$ receptor blockers are preferred and recommended by guidelines over clopidogrel in ACS setting. Although, there are lack of evidences of $P2Y_{12}$ receptor blockers in Thai population, the expert consensus group summarized how to choose the appropriate DAPT for ACS patients (Table 4) based on latest guidelines and clinical trials until December 2018 for health care provider to ensure the best patient outcome and improve ACS treatment in Thailand.

What is already known on this topic?

A DAPT with a $P2Y_{12}$ receptor blocker on top of aspirin can be used in various conditions of ACS.

What this study adds?

Recommendations of DAPT in eight various topics are summarized including STEMI with primary PCI, STEMI with fibrinolytics, STEMI without reperfusion therapy, NSTE-ACS with PCI, medically managed NSTE-ACS, maintenance DAPT in ACS, recurrent ACS, and ACS in the elderly.

Conflicts of interest

The authors declare no conflict of interest.

References

1. World Health Organization. The global burden of disease [Internet]. 2008 [cited 2013 May 25]. Available from: https://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf.
2. Srimahachota S, Boonyaratavej S, Kanjanavanit R, Sritara P, Krittayaphong R, Kunjara-Na-ayudhya R, et al. Thai registry in acute coronary syndrome (tracs)--an extension of thai acute coronary syndrome registry (tacs) group: Lower in-hospital but still high mortality at one-year. J Med Assoc Thai 2012;95:508-18.
3. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-660.
4. National Drug Information [Internet]. 2016 [cited 2013 May 25]. Available from: http://ndi.fda.moph.go.th/drug_national/drugs_current.
5. Kubisa MJ, Jezewski MP, Gasecka A, Siller-Matula JM, Postula M. Ticagrelor - toward more efficient platelet inhibition and beyond. Ther Clin Risk Manag 2018;14:129-40.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
7. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease

developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-60.
8. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An update of the 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention, 2011 ACCF/AHA Guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123-55.
9. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
10. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
11. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131-41.
12. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723-31.
13. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010;376:1233-43.
14. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-89.
15. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21.
16. Berwanger O, Nicolau JC, Carvalho AC, Jiang L, Goodman SG, Nicholls SJ, et al. Ticagrelor vs clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: A randomized clinical trial. JAMA Cardiol 2018;3:391-9.
17. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
18. Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, et al. Ticagrelor versus clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J 2014;35:2083-93.
19. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999-1010.
20. De Servi S, Goedicke J, Schirmer A, Widimsky P. Clinical outcomes for prasugrel versus clopidogrel in patients with unstable angina or non-ST-elevation myocardial infarction: an analysis from the TRITON-TIMI 38 trial. Eur Heart J Acute Cardiovasc Care 2014;3:363-72.
21. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
22. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.
23. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012;367:1297-309.
24. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J 2017;38:3070-8.
25. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747-57.

26. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800.
27. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.
28. Husted S, James S, Becker RC, Horrow J, Katus H, Storey RF, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes 2012;5:680-8.