# Antiplatelet Therapy for Non ST-segment Elevation Acute Coronary Syndrome: Highlight of the 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the Management of Non ST-segment Elevation Acute Coronary Syndrome

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## Abstract

Antiplatelet therapy is the cornerstone in the management of non ST-segment elevation acute coronary syndrome (NSTE-ACS). The 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the Management of NSTE-ACS was recently published. This guideline suggests that administration of dual antiplatelet therapy with aspirin and P2Y12 inhibitor is necessary for NSTE-ACS to reduce recurrent ischemic events. Regarding the choice of P2Y12 inhibitor, ticagrelor is indicated for NSTE-ACS patients treated with either invasive or medical treatment; while prasugrel is only recommended in patients undergoing percutaneous coronary intervention (PCI). For patients with high bleeding risk features, clopidogrel or decreased dose of prasugrel might be considered to reduce the bleeding risk. Glycoprotein IIb/IIIa inhibitor is only recommended as adjunctive therapy during PCI for large thrombus burden or as bailout for thrombotic complications. We hope the implementation of this guideline's recommendations can lead to the improvement of clinical outcomes for NSTE-ACS patients in Taiwan.

**Keywords:** acute coronary syndrome, antiplatelet therapy, guideline

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## Introduction

The onset of acute coronary syndrome (ACS) is closely linked to vulnerable coronary plaque rupture, which induces a cascade of platelet adhesion, activation, and aggregation, and subsequently leads to the formation of occlusive thrombus in the coronary artery.[1] Antiplatelet therapy is recognized as a cornerstone of treatment for ACS. In past decades, dual antiplatelet therapy (DAPT) has been proven to improve the clinical outcomes in ACS patients. In the Taiwan ACute CORonary Syndrome Descriptive (T-ACCORD) registry, 1331 non-ST segment elevation acute coronary syndrome (NSTE-ACS) patients were enrolled from 27 hospitals in Taiwan. DAPT for more than 9 months was associated with a higher survival rate in this observational study.[2] The Taiwan ACS Full Spectrum Registry recruited 3131 ACS patients, of whom 46.8% were NSTE-ACS subjects. It demonstrated that DAPT for less than 9 months was associated with an increased risk of composite ischemic outcome.[3] Compared with clopidogrel, new generation P2Y12 inhibitors including prasugrel and ticagrelor have been shown to further reduce ischemic events in ACS patients. Since these new drugs are more potent in platelet inhibition, the trade-off between ischemic and bleeding risk becomes a challenge in ACS management. The 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the management of NSTE-ACS was recently published.[4] The purpose of this article is to highlight the recommendations for antiplatelet therapy proposed in the guidelines. We sought to summarize these recommendations and provide a brief overview of the most important scientific background evidence.

## Aspirin

Aspirin has been well studied before in both randomized control trials[5-8] and meta-analysis[9,10] to reduce recurrent myocardial infarction (MI) or mortality in NSTE-ACS patients. Aspirin should be prescribed in all ACS patients unless there are contraindications. In Taiwan, for rapid absorption, 300 mg aspirin with non-enteric coated chewable form is recommended as the initial loading dose. Aspirin 100 mg/day is suggested as the long-term maintenance dose. The recommendation for aspirin in this guideline is:

- **For patients with NSTE-ACS, aspirin should be given at an initial oral loading dose of 300 mg (in aspirin-naive patients) and a maintenance dose of 100 mg/day if there are no contraindications.**

## P2Y12 inhibitor

### 1. Clopidogrel

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study showed that DAPT with clopidogrel and aspirin reduced major cardiovascular (CV) events compared with aspirin monotherapy in NSTE-ACS patients.[8] This benefit was consistently demonstrated in ACS patients undergoing percutaneous coronary intervention (PCI).[11] Two large multicenter registries in Taiwan showed DAPT with aspirin and clopidogrel longer than 9 months was associated with better clinical outcomes.[2,3] Higher clopidogrel loading dose of 600 mg was associated with higher and faster platelet inhibition than with 300 mg loading dose in patients undergoing elective PCI.[12,13] The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Symptoms (CURRENT–OASIS 7) trial demonstrated that high clopidogrel loading dose (600 mg) was associated with similar rate of primary outcome (CV death, MI, or stroke) and higher risk of major bleeding compared with 300 mg loading dose. But in the subgroup of patients who received PCI, clopidogrel 600 mg loading was associated with significant risk reductions in both primary outcome and stent thrombosis.[14] A meta-analysis showed the 600 mg

clopidogrel loading regimen was associated with lower major CV events and similar major bleeding risk compared with the 300 mg loading regimen in patients undergoing PCI.[15] Hence, based on this evidence, a loading dose of 300 mg to 600 mg is recommended in patients with NSTE-ACS in Taiwan. One of the drawbacks of clopidogrel is its drug response variability due to genetic polymorphisms. This may cause clopidogrel resistance and increase the CV risk in some patients.[16,17] As an inactive prodrug, clopidogrel requires a 2-step metabolism to become an active metabolite. This results in a slower onset of action because of the time needed to reach sufficient therapeutic drug level.[18] Therefore, new generation P2Y12 inhibitors including prasugrel and ticagrelor have been developed to overcome unmet clinical needs.

## 2. Prasugrel

Prasugrel (60 mg loading and 10 mg/day maintenance dose) achieves a faster and greater platelet inhibition than clopidogrel in patients receiving PCI.[19] The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 trial randomized ACS patients with scheduled PCI to be treated with either prasugrel or clopidogrel. Overall, prasugrel reduced more ischemic events compared with clopidogrel, but also increased the risk of major bleeding. Post hoc analyses revealed patients weighing less than 60 kg and patients 75 years of age or older had no net benefit from prasugrel. Patients with previous stroke or transient ischemic attack (TIA) had net harm from prasugrel due to a trend toward more major bleeding ($p = 0.06$).[20] The results were consistent among the NSTE-ACS subgroup analysis showing reduced primary endpoint but increased major bleeding with prasugrel. However, after excluding patients with previous stroke/TIA, weight less than 60 kg, and aged 75 or older, prasugrel was shown to be superior to clopidogrel regarding the primary endpoint and without significant increase of major bleeding in NSTE-ACS patients.[21] As a consequence, prasugrel is not recommended in patients with prior history of stroke/TIA and should be used with caution in patients with low body weight or old age. In NSTE-ACS patients who only received medical control, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study showed that the ischemic and bleeding events were similar between prasugrel and clopidogrel groups.[22] In addition, the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) study demonstrated that the pretreatment with prasugrel before coronary angiography in NSTE-ACS patients not only had no benefit in reducing ischemic events, but further increased major bleeding complications.[23] Prasugrel should only be prescribed when PCI is indicated after coronary angiography.

In Japan, prasugrel is used with lower loading and maintenance dose (20/3.75 mg) to avoid bleeding events. The lower dose regimen was tested in the PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI (PRASFIT-ACS) study.[24] After excluding patients with prior ischemic stroke/TIA, the lower dose prasugrel was associated with a trend of 23% reduction in adverse CV events and similar major bleeding risk compared with clopidogrel in Japanese ACS patients undergoing PCI.

## 3. Ticagrelor

Ticagrelor is an active drug and does not require hepatic metabolism for activation. The maximal platelet inhibition can be achieved more extensively and rapidly than with clopidogrel. In addition, ticagrelor reversibly binds to P2Y12 receptors, resulting in a faster platelet inhibition offset after drug discontinuation when compared with clopidogrel.[25] The major CV outcome trial of ticagrelor was the Platelet Inhibition and Patient

Outcomes (PLATO) study, which tested the efficacy and safety of ticagrelor (180 mg loading and 90 mg twice daily maintenance dose) in ACS patients. Compared with clopidogrel, ticagrelor significantly reduced the combined risk of CV death, MI, or stroke. However, ticagrelor was associated with a significantly higher rate of major bleeding not related to coronary artery bypass grafting (CABG).[26] The benefits of ticagrelor versus clopidogrel in the overall PLATO trial were consistent with patients initially treated with invasive or non-invasive strategies.[27,28] The subgroup analysis of the PLATO study for NSTE-ACS patients showed similar results as the overall PLATO populations.[29]

The data from small sized randomized control trials and observational studies in Asia revealed controversial and conflicting results for ticagrelor. The PHILO study included 801 Asian ACS patients (Japanese, n = 721; Taiwanese, n = 35; South Korean, n = 44; unknown ethnicity, n = 1) that were scheduled to receive PCI.[30] It demonstrated that ticagrelor was not superior to clopidogrel regarding the primary efficacy endpoint but carried a trend to higher bleeding risk. The small sample size, low event rate, and imbalance in clinical characteristics in this study may have contributed to the discrepancy in results between the PLATO and PHILO studies. In Taiwan, there were two retrospective observation studies comparing ticagrelor and clopidogrel in ACS patients. Both studies showed that patients treated with ticagrelor were associated with lower ischemic events and similar major bleeding risks when compared to clopidogrel-treated patients.[31, 32]

Based on currently available evidence, ticagrelor should be the first-line P2Y12 inhibitor for NSTE-ACS patients in Taiwan regardless of the initial treatment strategies (invasive or ischemia-guided). But if concerns about bleeding prevail over ischemia, clopidogrel or reduced dose of prasugrel (only for patients receiving PCI) are reasonable alternative choices. The common bleeding risk features include old age, low body weight, anemia, chronic kidney disease, concomitant use of oral anticoagulant, prior intracranial hemorrhage, or other major bleeding history. The selection of P2Y12 inhibitors and the trade-off between ischemic and bleeding risk should be individualized to get the greatest net clinical benefit for NSTE-ACS patients in Taiwan.

The recommendation for the use of P2Y12 inhibitors in this guideline is:

- **Ticagrelor (180 mg loading dose then 90 mg twice daily) or clopidogrel (300-600mg loading dose, 75 mg daily dose) are recommended in NSTE-ACS patients treated with either invasive or medical treatment unless contraindicated and ticagrelor is preferred to clopidogrel. (COR I, LOE B)**
- **Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended only in NSTE-ACS patients undergoing PCI without contraindication. (COR I, LOE B)**
- **Clopidogrel rather than ticagrelor or prasugrel may be considered in patients with increased bleeding risk features. (COR IIa, LOE C)**
- **Reduced dose of prasugrel (20 mg loading dose, 3.75 mg daily dose) may be considered in NSTE-ACS patients undergoing PCI if there are increased bleeding risk features. (COR IIb, LOE B)**
- **Pretreatment with prasugrel before diagnostic angiography is not recommended for NSTE-ACS patients. (COR III, LOE B)**

## Glycoprotein IIb/IIIa receptor inhibitors

Glycoprotein (GP) IIb/IIIa inhibitor has been shown to reduce ischemic events in NSTE-ACS patients undergoing PCI.[33-35] A meta-analysis indicated that GP IIb/IIIa inhibitor was associated with a significant reduction of death or non-fatal MI at 30 days in NSTE-ACS patients. The

benefits were more prominent in patients receiving PCI than in patients who received medical treatment only.[36] The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial compared NSTE-ACS patients receiving invasive treatment with three antithrombotic regimens: bivalirudin alone, unfractionated heparin or enoxaparin plus a GP IIb/IIIa inhibitor, or bivalirudin plus a GP IIb/IIIa inhibitor. Compared with heparin plus GP IIb/IIIa inhibitor, bivalirudin was associated with significantly reduced risk of major bleeding and similar ischemic endpoints.[37] Routine upstream use of GP IIb/IIIa inhibitor before invasive treatment could not reduce ischemic events, but increased the risk of major bleeding.[38,39] There have not been prospective studies about the efficacy and safety of combination therapy with GP IIb/IIIa inhibitor and new generation P2Y12 inhibitors such as prasugrel or ticagrelor. DAPT with potent P2Y12 inhibitor is the current standard therapy in NSTE-ACS patients. GP IIb/IIIa inhibitor is now only indicated provisionally during PCI for coronary thrombotic lesions or thrombotic complications bailout after PCI.

The recommendation for the use of GP IIb/IIIa inhibitors in this guideline is:

- **Use of GP IIb/IIIa inhibitors in patients with NSTE-ACS as adjunctive therapy during PCI may be indicated for large thrombus burden or as bailout for thrombotic complications. (COR IIa, LOE B)**
- **Routine use of GP IIb/IIIa inhibitors in patients with NSTE-ACS is not recommended before coronary angiography. (COR III, LOE A)**

## Conclusions

Overall, the 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the management of NSTE-ACS provide several recommendations for antiplatelet therapy in NSTE-ACS patients. Based on current evidence, DAPT with aspirin and new generation P2Y12 inhibitor is preferred for further ischemic risk reduction and better clinical outcomes. However, the most appropriate regimen should still be individualized to balance the ischemic and bleeding risks in NSTE-ACS patients in Taiwan.

## References


1. Meadows TA, DL Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. *Circ Res* 2007;100:1261-75.
2. Cheng CI, Chen CP, Kuan PL, et al. The causes and outcomes of inadequate implementation of existing guidelines for antiplatelet treatment in patients with acute coronary syndrome: the experience from Taiwan Acute Coronary Syndrome Descriptive Registry (T-ACCORD Registry). *Clin Cardiol* 2010;33:E40-8.
3. Chiang FT, Shyu KG, Wu CJ, et al. Predictors of 1-year outcomes in the Taiwan Acute Coronary Syndrome Full Spectrum Registry. *J Formos Med Assoc* 2014;113:794-802.
4. Li YH, Wang YC, Wang YC, et al. 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the management of non ST-segment elevation acute coronary syndrome. *J Formos Med Assoc* 2018;117:766-90.
5. The RISC group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827-30.
6. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration cooperative study. *N Engl J Med* 1983;309:396-403.
7. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
8. 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.
9. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-

60.
10. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
11. Mehta SR, Yusuf S, Peters RJ, 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.
12. Gurbel PA, Bliden KP, Zaman KA, Yoho JA, Hayes KM, Tantry US. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation* 2005;111:1153-9.
13. von Beckerath N, Taubert D, Pogatsa-Murray G, Schömig E, Kastrati A, Schömig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. *Circulation* 2005;112:2946-50.
14. Mehta SR, Tanguay JF, Eikelboom JW, 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.
15. Siller-Matula JM, Huber K, Christ G, et al. Impact of clopidogrel loading dose on clinical outcome in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Heart* 2011;97:98-105.
16. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109:3171-5.
17. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet* 2009;373:309-17.
18. Schömig A. Ticagrelor - is there need for a new player in the antiplatelet-therapy field? *N Engl J Med* 2009;361:1108-11.
19. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;116:2923-32.
20. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.
21. 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.
22. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012;367: 1297-309.
23. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 2013;369:999-1010.
24. Saito S, Isshiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. *Circ J* 2014;78:1684-92.
25. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120:2577-85.
26. Wallentin L, Becker RC, Budaj A , et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
27. Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010;375:283-93.
28. James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *BMJ* 2011;342:d3527.
29. Lindholm D, Varenhorst C, Cannon CP, et al. Ticagrelor vs. 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.
30. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. *Circ J* 2015;79:2452-60.

31. Chen IC, Lee CH, Fang CC, et al. Efficacy and safety of ticagrelor versus clopidogrel in acute coronary syndrome in Taiwan: A multicenter retrospective pilot study. *J Chin Med Assoc* 2016;79:521-30.
32. Lee CH, Cheng CL, Yang KYH, Chao TH, Chen JY, Li YH. Cardiovascular and bleeding risks in acute myocardial infarction newly treated with ticagrelor vs. clopidogrel in Taiwan. *Circ J* 2018;82:747-56.
33. EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689-96.
34. Valgimigli M, Percoco G, Barbieri D, et al. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004;44:14-9.
35. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006;295:1531-8.
36. Roffi M, Chew DP, Mukherjee D, et al. Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes. Gradient of benefit related to the revascularization strategy. *Eur Heart J* 2002;23:1441-8.
37. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203-16.
38. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. *JAMA* 2007;297:591-602.
39. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 2009;360:2176-90.