
# Atlantic Canadian Guidelines for the Acute Use of Oral Anti-Platelet Therapy in Patients With Acute Coronary Syndromes: Executive Summary



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## 1. GUIDE TO RATING OF RECOMMENDATIONS

Recommendations are rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system of evaluation.[1,2]

**Factors determining the strength of recommendations**

| FACTOR | COMMENTS |
|---|---|
| Quality of evidence | The higher the quality of evidence, the greater the probability that a strong recommendation is indicated |
| Difference between desirable and undesirable effects | The greater the difference between desirable and undesirable effects, the greater the probability that a strong recommendation is indicated |
| Values and preferences | The greater the variation or uncertainty in values and preferences, the higher the probability that a conditional recommendation is indicated |
| Cost | The higher the cost, the lower the likelihood that a strong recommendation is indicated |

**Rating of quality of evidence**

| GRADE | COMMENTS |
|---|---|
| High | Future research unlikely to change confidence in estimate of effect (e.g., multiple well-designed, well-conducted clinical trials) |
| Moderate | Further research likely to have an important impact on confidence in estimate of effect and may change the estimate (e.g., limited clinical trials, inconsistency of results or study limitations) |
| Low | Further research very likely to have a significant impact on the estimate of effect and is likely to change the estimate (e.g., small number of clinical studies or cohort observations) |
| Very low | The estimate of effect is very uncertain (e.g., case studies, consensus opinion) |

## 2. ACUTE CORONARY SYNDROME (ACS) CATEGORY DEFINITIONS

- **Non-ST-elevation acute coronary syndrome (NSTEACS) requiring urgent invasive assessment**

Patients with very high-risk features (e.g., hemodynamic instability, refractory ischemia despite initial medical therapy, recurrent ventricular arrhythmias, etc.) who are taken directly to the cardiac catheterization laboratory from the Emergency Department or within a few hours of hospital admission.

- **NSTEACS with planned invasive assessment**

Patients without very high-risk features who stabilize with initial medical therapy but in whom risk stratification justifies non-urgent cardiac catheterization and revascularization as indicated prior to discharge.

- **ST-elevation myocardial infarction (STEMI) or NSTEACS with planned medical management**

This ACS category spans a spectrum of very low to very high risk. The decision to manage medically will sometimes be based upon patient/clinical characteristics alone without performing cardiac catheterization. If cardiac catheterization is performed, the decision to manage medically may be because of perceived low risk (e.g., catheterization showed no or only minor coronary artery disease) or because cardiac catheterization identified coronary disease unsuitable or too high risk for revascularization.

## 3. INTRODUCTION

The primary goal of the *Atlantic Anti-Platelet Initiative* (AAPI) was to develop evidence-based guidelines for the acute administration of oral anti-platelet therapy in patients presenting with ACS in Atlantic Canada. Although dual anti-platelet therapy with aspirin and clopidogrel is well established as the regional standard of care, there is currently significant uncertainty in Atlantic Canada about how the novel $P2Y_{12}$ inhibitors prasugrel and ticagrelor should be incorporated into clinical practice. Furthermore, although Canadian Cardiovascular Society™ anti-platelet guidelines were recently published,[3] they focus on anti-platelet therapy in the outpatient setting and do not address the acute phase of ACS care.

In collaboration with the Atlantic Cardiovascular Society, a Primary Panel representing key stakeholders from Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland and Labrador was convened and met in Halifax on August 27, 2011. Key stakeholder groups represented included emergency medicine, internal medicine, invasive and non-invasive cardiology, pharmacy, patients, the Atlantic Cardiovascular Society and Cardiovascular Health Nova Scotia. The Primary Panel unanimously agreed that the guidance developed needed to be practical and easy to integrate with existing ACS management protocols. This executive summary highlights the key recommendations of the AAPI Primary Panel. Consistent with Canadian Cardiovascular Society policy, the recommendations of the Panel have been rated using the GRADE rating system.[1,2]

## 4. AAPI PRIMARY PANEL RECOMMENDATIONS

### 4.1 Aspirin

Aspirin should be administered to all patients with definite or suspected ACS who do not have contraindications to therapy and who have not been taking aspirin previously (160-325–mg non-enteric coated oral loading dose followed by 81 mg od) **[Strong recommendation, high-quality evidence]**.[3,4]

### 4.2 STEMI receiving thrombolytic therapy

In the absence of any clinical trial evidence supporting the use of prasugrel or ticagrelor in patients with STEMI receiving thrombolytic therapy, clopidogrel should continue to be the preferred $P2Y_{12}$ inhibitor in this setting (300–mg oral loading dose followed by 75 mg od; loading dose should be omitted in patients aged >75 years) **[Strong recommendation, high-quality evidence]**.[5,6]

### 4.3 STEMI undergoing primary PCI

If a patient with STEMI undergoing primary PCI is administered a $P2Y_{12}$ inhibitor prior to cardiac catheterization laboratory arrival, clopidogrel should continue to be the preferred agent; the dose of clopidogrel administered should be according to existing local protocols (typically 300-600–mg oral loading dose followed by 75 mg od) **[Strong recommendation, high-quality evidence]**.[3,7,8] Pre-hospital or Emergency Department administration of prasugrel or ticagrelor in this setting is not recommended at the present time **[Conditional recommendation, very low-quality evidence]**.

If a patient with STEMI undergoing primary PCI is first administered a $P2Y_{12}$ inhibitor in the cardiac catheterization laboratory and there are no contraindications[9,10] (see Appendices 9.1 [*Prasugrel contraindications and cautions*] and 9.2 [*Ticagrelor contraindications and cautions*] of the full document), prasugrel (60–mg oral loading dose followed by 10 mg od) or ticagrelor (180–mg oral loading dose followed by 90 mg bid) should be considered instead of clopidogrel **[Strong recommendation, moderate-quality evidence]**.[11-14] If there are no contraindications to either prasugrel[9] or ticagrelor,[10] ticagrelor should generally be the preferred agent **[Conditional recommendation, moderate-quality evidence]**; this recommendation is based primarily upon the significant reduction in mortality observed with extended ticagrelor therapy in the overall PLATO study population.[13]

If a patient with STEMI undergoing primary PCI was administered clopidogrel prior to cardiac catheterization laboratory arrival and there are no contraindications[9,10] (see Appendices 9.1 [*Prasugrel contraindications and cautions*] and 9.2 [*Ticagrelor contraindications and cautions*] of the full document), switching to prasugrel **[Conditional recommendation, very low-quality evidence]** or ticagrelor **[Strong recommendation, moderate-quality evidence]** during or after cardiac catheterization can be considered if a higher degree of platelet inhibition is desired.[11-14] (For switching algorithms, see Appendices 9.3 [*Proposed algorithm for switching from clopidogrel to prasugrel*] and 9.4 [*Proposed algorithm for switching from clopidogrel to ticagrelor*] of the full document.) If there are no contraindications to either prasugrel[9] or ticagrelor,[10] ticagrelor should generally be the preferred agent **[Conditional recommendation, moderate-quality evidence]**; this recommendation is based upon the stronger evidence

provided by the overall PLATO study to support the safety and efficacy of switching and the mortality benefit observed with extended ticagrelor therapy.[13]

### 4.4 STEMI with planned medical management

In the absence of clinical trial evidence supporting the use of prasugrel or ticagrelor in the setting of STEMI with planned medical management, clopidogrel should be the preferred $P2Y_{12}$ inhibitor if the clinical circumstances are felt to warrant dual anti-platelet therapy (300–mg oral loading dose followed by 75 mg od; loading dose should be omitted in patients aged >75 years who also receive thrombolytic therapy) **[Strong recommendation, moderate-quality evidence]**.[3,5,6]

### 4.5 NSTEACS requiring urgent invasive assessment

Unless there are clinical features that predict an increased likelihood of urgent cardiac surgery (e.g., cardiogenic shock, pre-existing left main disease of >50%, or known triple-vessel coronary disease with poor left ventricular systolic function), a $P2Y_{12}$ inhibitor should be administered prior to cardiac catheterization in the majority of patients with NSTEACS requiring urgent invasive assessment. Clopidogrel should be the preferred agent, with dosing according to existing local protocols (typically 300-600–mg oral loading dose followed by 75 mg od) **[Strong recommendation, high-quality evidence]**.[3,7,15] Ticagrelor should generally not be administered prior to cardiac catheterization in this setting due to the increased risk of major bleeding should urgent cardiac surgery be required **[Conditional recommendation, very low-quality evidence]**.[13,16] Prasugrel should not be administered prior to cardiac catheterization in

this setting due to a lack of evidence supporting this approach **[Conditional recommendation, very low-quality evidence]**.

In patients with very high-risk NSTEACS who receive clopidogrel prior to cardiac catheterization laboratory arrival, switching to prasugrel **[Conditional recommendation, very low-quality evidence]** or ticagrelor **[Strong recommendation, moderate-quality evidence]** can be considered in the absence of contraindications[9,10] (see Appendices 9.1 [*Prasugrel contraindications and cautions*] and 9.2 [*Ticagrelor contraindications and cautions*] of the full document) during or after cardiac catheterization if a higher degree of platelet inhibition is desired and the need for urgent cardiac surgery has been ruled out.[11-14,17] (For switching algorithms, see Appendices 9.3 [*Proposed algorithm for switching from clopidogrel to prasugrel*] and 9.4 [*Proposed algorithm for switching from clopidogrel to ticagrelor*] of the full document). Switching to prasugrel should only be considered if PCI is going to be performed **[Conditional recommendation, very low-quality evidence]**.[11] If there are no contraindications to prasugrel[9] or ticagrelor,[10] ticagrelor should generally be the preferred agent **[Conditional recommendation, moderate-quality evidence]**. This recommendation is based upon the stronger evidence provided by the overall PLATO study to support the safety and efficacy of switching therapy and the mortality benefit observed with extended ticagrelor therapy.[13]



**4.6 NSTEACS with planned invasive assessment**

For the majority of patients with definite NSTEACS likely to undergo cardiac catheterization and possible revascularization prior to discharge, the preferred $P2Y_{12}$ inhibitor for acute administration should be clopidogrel (300–mg oral loading dose followed by 75 mg od) **[Strong**

**recommendation, high-quality evidence]**.[3,15] For patients with high clinical risk (e.g., GRACE risk score >140 [see Appendix 9.5 of the full document][18] or TIMI risk score 5-7 [see Appendix 9.6 of the full document][19]), acute administration of ticagrelor (180–mg oral loading dose followed by 90 mg bid) instead of clopidogrel can be considered in the absence of contraindications (see Appendix 9.7 of the full document) **[Conditional recommendation, moderate-quality evidence]**.[13,17]

For higher risk patients initially treated with clopidogrel, irrespective of whether they undergo PCI, a transition to ticagrelor (see Appendix 9.4 of the full document) should be considered once more is known about the patient's clinical characteristics, coronary anatomy and anticipated ability to tolerate/comply with therapy **[Strong recommendation, moderate-quality evidence]**.[13,17] The decision to transition to ticagrelor and the timing thereof will depend upon many factors and may occur at any time during hospitalization. Transitioning from clopidogrel to prasugrel is generally not recommended in this setting because TRITON-TIMI 38 did not establish the safety or efficacy of this approach **[Conditional recommendation, very low-quality evidence]**.[11]



**4.7 NSTEACS with planned medical management**

For the majority of patients with definite NSTEACS likely to be medically managed, the preferred $P2Y_{12}$ inhibitor for acute administration should be clopidogrel (300–mg oral loading dose followed by 75 mg od) **[Strong recommendation, high-quality evidence]**.[3,15] For patients with high clinical risk (e.g., GRACE risk score >140 [see Appendix 9.5 of the full document][18] or TIMI risk score 5-7 [see Appendix 9.5 of the full document][19]), acute administration of ticagrelor

(180–mg oral loading dose followed by 90 mg bid) instead of clopidogrel can be considered in the absence of contraindications (see Appendix 9.2 [*Ticagrelor contraindications and cautions*] of the full document) **[Conditional recommendation, moderate-quality evidence]**.[10,13]

For patients with NSTEACS likely to be medically managed who were initially treated with clopidogrel, subsequent transitioning to ticagrelor (see Appendix 9.4 of the full document) should be considered in higher risk patients once more is known about their clinical characteristics, coronary anatomy (if cardiac catheterization performed) and anticipated ability to tolerate/comply with therapy **[Strong recommendation, moderate-quality evidence]**.[13] The decision to transition to ticagrelor and the timing of such a change will depend upon many factors and may occur at any time during hospitalization.

Due to a lack of evidence, prasugrel is currently not recommended for patients with NSTEACS likely to be medically managed **[Conditional recommendation, very low-quality evidence]**. The ongoing TRILOGY-ACS may provide evidence for the use of prasugrel in this population.[20]



### 4.8 Patients with ACS undergoing early CABG

In patients with very high-risk ACS who have clinical features that predict an increased likelihood of the need for urgent cardiac surgery (e.g., cardiogenic shock, pre-existing left main disease of >50%, or known triple-vessel coronary disease with poor left ventricular systolic function), it is recommended that a $P2Y_{12}$ inhibitor should generally not be administered prior to cardiac catheterization **[Conditional recommendation, low-quality evidence]**.

In patients with ACS who have received a $P2Y_{12}$ inhibitor and require urgent CABG, the timing of surgery should be determined by weighing the risk of bleeding associated with immediate surgery versus the ischemic risk associated with deferred surgery. Consistent with current Health Canada labeling and if clinical circumstances permit, $P2Y_{12}$ inhibitor therapy should be discontinued 5 days before surgery in patients who have received clopidogrel or ticagrelor and 7 days before surgery in patients who have received prasugrel **[Strong recommendation, moderate-quality evidence]**.[3,9-11,13,15,17,21-23]

Consistent with Canadian Cardiovascular Society guidelines and a separate position statement on antiplatelet therapy in the setting of CABG, it is recommended that $P2Y_{12}$ inhibitor therapy be restarted after surgery in patients with ACS who undergo CABG; patients should generally be restarted on the same $P2Y_{12}$ inhibitor that was administered pre-operatively **[Conditional recommendation, low-quality evidence]**.[3,15,16,21,22]

**4.9 ACS sub-group considerations**

In principle, it is recommended that the subgroup findings of major ACS anti-platelet trials be interpreted with caution and that the greatest emphasis be placed upon the overall trial results. Contemporary risk stratification and prediction of bleeding typically requires consideration of multiple clinical and patient factors. Consequently, the choice of $P2Y_{12}$ inhibitor should generally not be based on the presence or absence of isolated clinical features **[Conditional recommendation, moderate-quality evidence]**.

### 4.10 Generic clopidogrel

Generic clopidogrel became available in Canada in early 2012 at a significantly lower cost than branded Plavix® (Sanofi-aventis Canada Inc.). Despite some concerns about the potential clinical implications of generic substitution, there is currently no clinical evidence to justify preferential use of branded Plavix over generic clopidogrel in the ACS setting.[24-26] Consequently, either generic clopidogrel or branded Plavix can be prescribed in both the emergent and non-emergent ACS settings. Repeated switching between different clopidogrel preparations in either the acute or chronic phase of ACS care should be avoided if possible **[Conditional recommendation, low-quality evidence]**.

### 4.11 Duration of $P2Y_{12}$ inhibitor therapy

Following hospital discharge for ACS, it is recommended that the duration of $P2Y_{12}$ inhibitor therapy be as directed by existing provincial and national guidelines (see Appendices 9.7 [*Cardiovascular Health Nova Scotia 2008 Guidelines for Acute Coronary Syndromes: recommended duration of clopidogrel therapy*] and 9.8 [*Canadian Cardiovascular Society 2011 Guidelines for the Use of Anti-Platelet Therapy in the Outpatient Setting: anti-platelet therapy for secondary prevention in the first year following an ACS*]) **[Strong recommendation, moderate-quality evidence]**.[3,11,13,15,27]

### 7.12 Risk factors for bleeding in ACS

Patients with ACS who develop major bleeding complications are at a substantially increased risk of adverse outcomes, including death. Therefore, the benefits of anti-platelet

therapy should always be weighed carefully against the risk of bleeding.[28] Clinical trials and patient registries have identified a number of key risk factors for bleeding, including older age, female sex, lower body weight, renal insufficiency, history of previous bleeding, anemia, use of invasive procedures and greater intensity of anti-platelet and anti-thrombotic therapy.

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