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

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April 14, 2012

TABLE OF CONTENTS

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. ABBREVIATIONS AND ACRONYMS

ACS	Acute coronary syndrome
AAPI	Atlantic Anti-Platelet Initiative
bid	Twice daily
CABG	Coronary artery bypass grafting
GRACE	Global Registry of Acute Coronary Events
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
NSTEACS	Non-ST elevation acute coronary syndrome (i.e., non-ST elevation myocardial infarction or unstable angina)
NSTEMI	Non–ST-elevation myocardial infarction
od	Once daily
PCI	Percutaneous coronary intervention
PLATO	PLATelet inhibition and patient Outcomes
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
TRILOGY ACS	A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel
UA	Unstable angina

3. ACS CATEGORY DEFINITIONS

- **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.

- **STEMI or NSTEACS with planned medical management**

This is likely the largest ACS category in Atlantic Canada (see Section 5 [*Epidemiology and Treatment of ACS in Atlantic Canada*]) and 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. In medically managed patients who do undergo cardiac catheterization, the decision to manage medically may sometimes 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.

4. 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. The following document details 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]

5. EPIDEMIOLOGY AND TREATMENT OF ACS IN ATLANTIC CANADA

The Atlantic provinces comprise a population of approximately 2.3 million that, according to the 2006 Census, is the oldest in Canada (http://www.statcan.gc.ca). Nova Scotia, New

Brunswick, and Newfoundland and Labrador each have single cardiac catheterization and revascularization facilities in Halifax, Saint John, and St John's respectively. Prince Edward Island has no invasive facilities of its own and is served jointly by Nova Scotia and New Brunswick. Consequently, a common theme in Atlantic Canada is that ACS patients frequently have to travel long distances for invasive assessment and revascularization.

While some interprovincial variation exists, the AAPI Primary Panel agreed that ACS patient characteristics and treatment practices are likely very similar across the Atlantic region. Dual anti-platelet therapy with aspirin and clopidogrel is currently the standard of care in Atlantic Canada and is administered to the majority of ACS patients early after hospital presentation. Thus, ACS patients who subsequently undergo invasive assessment typically receive dual anti-platelet therapy well in advance of cardiac catheterization and revascularization.

Nova Scotia is the only Atlantic province with an established cardiovascular database and has been capturing detailed demographic, treatment and outcome data for every ACS hospitalization in the province since 1997. The following Nova Scotia ACS data were shared with the AAPI Primary Panel prior to guideline development and provide important context:

- In 2009, there were 3549 ACS hospitalizations in Nova Scotia:
  - 22% for STEMI
  - 51% for NSTEMI
  - 27% for UA
- For Nova Scotia residents hospitalized with NSTEACS (i.e., NSTEMI or UA):
  - ~50% undergo cardiac catheterization prior to discharge
  - ~50% of those who undergo catheterization have PCI prior to discharge
  - Only a small minority of very high risk patients undergo cardiac catheterization on the same day as admission; the median time to catheterization is 4 days

- For Nova Scotia residents with STEMI:
    - Thrombolysis is the most common acute reperfusion strategy; only 42% of the Nova Scotia population has access to PCI facilities within 90 minutes (the corresponding proportions in Prince Edward Island, New Brunswick, and Newfoundland and Labrador are 0%, 19% and 35% respectively)[4]
    - ~70% undergo cardiac catheterization prior to discharge
    - ~70% of those who undergo catheterization receive PCI prior to discharge
- For all ACS admissions in Nova Scotia in 2009:
    - 54% underwent cardiac catheterization prior to discharge
    - 31% had PCI and 6% had CABG prior to discharge
    - 63% received medical management alone

6. PRIORITY ACS CATEGORIES CONSIDERED BY THE AAPI PRIMARY PANEL

While there are multiple potential permutations of clinical presentation and subsequent management for patients with ACS, a priority for the AAPI Primary Panel was to reach consensus on the use of anti-platelet therapy in the following settings (see Section 3 for *ACS Category Definitions*):

- STEMI
    - Receiving thrombolytic therapy
    - Undergoing primary PCI
    - With planned medical management
- NSTEACS
    - Requiring urgent invasive assessment
    - With planned invasive assessment
    - With planned medical management
- Other ACS-related guidance
    - ACS patients undergoing early CABG
    - ACS sub-group considerations
    - Generic clopidogrel

7. AAPI PRIMARY PANEL RECOMMENDATIONS

7.1 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]**.[3,5]

7.2 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]**.[6,7]

7.3 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]**.[3,8,9] 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[10,11] (see Appendices 9.1 [*Prasugrel contraindications and cautions*] and 9.2 [*Ticagrelor contraindications and cautions*]), 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]**.[12-15] If there are no contraindications to either prasugrel[10] or ticagrelor,[11] 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.[14]

If a patient with STEMI undergoing primary PCI was administered clopidogrel prior to cardiac catheterization laboratory arrival and there are no contraindications[10,11] (see Appendices 9.1 [*Prasugrel contraindications and cautions*] and 9.2 [*Ticagrelor contraindications and cautions*]), 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.[12-15] (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*].) If there are no contraindications to either prasugrel[10] or ticagrelor,[11] 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.[14]

7.4 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]**.[3,6,7]

7.5 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]**.[3,8,16] 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]**.[14,17] 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[10,11] (see Appendices 9.1 [*Prasugrel contraindications and cautions*] and 9.2 [*Ticagrelor contraindications and cautions*]) 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.[12-15,18] (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*]). Switching to prasugrel should only be considered if PCI is going to be performed **[Conditional recommendation, very low-quality evidence]**.[12] If there are no contraindications to prasugrel[10] or ticagrelor,[11] 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.[14]

7.6 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].[3,16] For patients with high clinical risk (e.g., GRACE risk score >140 [see Appendix 9.5 (*GRACE risk score*)[19]] or TIMI risk score 5-7 [see Appendix 9.6 (*TIMI risk score*)[20]]), 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[10,11] (see Appendix 9.2 [*Ticagrelor contraindications and cautions*]) **[Conditional recommendation, moderate-quality evidence]**.[14,18]

For higher risk patients initially treated with clopidogrel, irrespective of whether they undergo PCI, a transition to ticagrelor 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]**.[14,18] The decision to transition to ticagrelor and the timing thereof will depend upon many factors and may occur at any time during hospitalization (see Appendix 9.4 [*Proposed algorithm for switching from clopidogrel to ticagrelor*]). 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]**.[12]

7.7 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]**.[3,16] For patients with high clinical risk (e.g., GRACE risk score >140 [see Appendix 9.5 (*GRACE risk score*)[19]] or TIMI risk score 5-7 [see Appendix 9.6 (*TIMI risk score*)[20]]), 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[10,11] (see Appendix 9.2 [*Ticagrelor contraindications and cautions*]) **[Conditional recommendation, moderate-quality evidence]**.[14]

For patients with NSTEACS likely to be medically managed who were initially treated with clopidogrel, subsequent transitioning to ticagrelor 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]**.[14] 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 (see Appendix 9.4 [*Proposed algorithm for switching from clopidogrel to ticagrelor*]).

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.[21]

7.8 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]**.[3,10-12,14,16,17,22-24]

Consistent with Canadian Cardiovascular Society guidelines and a separate position statement on anti-platelet 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]**.[3,16,17,22,23]

7.9 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]**.

7.10 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.[25-27] 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]**.

7.11 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]**.[3,12,14,16,28]

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.[29] 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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Appendix 9.1 Prasugrel contraindications and cautions[10]

Prasugrel is contraindicated in:

- Patients who are hypersensitive to the drug or any ingredient of the formulation
- Patients with a known history of transient ischemic attack or stroke
- Patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage
- Patients with severe hepatic impairment

Prasugrel is not recommended for:

- Patients ≥75 years of age because of an increased risk of fatal and intracranial bleeding
- Patients with body weight <60 kg because of an increased risk of major bleeding

Prasugrel should be used with caution in:

- Patients with a propensity to bleed (e.g., patients with recent trauma or surgery, recent or recurrent GI bleeding, active peptic ulcer, severe hepatic impairment)
- Patients taking other medications that may increase the risk of bleeding (e.g., oral anticoagulants, NSAIDs, fibrinolytics)

Appendix 9.2 Ticagrelor contraindications and cautions[11]

Ticagrelor is contraindicated in:

- Patients with hypersensitivity to ticagrelor or any ingredient in the formulation
- Patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage
- Patients with a history of intracranial hemorrhage
- Patients with moderate or severe hepatic impairment
- Patients taking strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir)

Ticagrelor should be used with caution in:

- Patients with a known increased risk of bleeding (e.g., recent trauma or surgery, active or recent GI bleeding, moderate hepatic impairment, oral anticoagulant use, concomitant NSAID administration)
- Patients at risk of bradycardic events (e.g., sick sinus syndrome, 2nd- or 3rd-degree AV block, bradycardia-related syncope with no pacemaker)

Appendix 9.3 Proposed algorithm for switching from clopidogrel to prasugrel

Switching after only a loading dose of clopidogrel

- *In the absence of relative or absolute contraindications to prasugrel (see Appendix 9.1)*: if only a 300-600–mg loading dose of clopidogrel has been given (e.g. a patient with STEMI undergoing primary PCI who has received 300 mg of clopidogrel in the Emergency Department prior to cardiac catheterization laboratory transfer), a 60–mg oral loading dose of prasugrel should generally be given, followed by prasugrel 10 mg orally od

Switching after a loading dose and ≥1 maintenance dose of clopidogrel

- *In the absence of relative or absolute contraindications to prasugrel (see Appendix 9.1):* if a 300-600–mg clopidogrel loading dose and at least one 75–mg clopidogrel maintenance dose have been given, prasugrel dosing options are as follows:

  ⇒ *If the clinical circumstances warrant a rapid and high level of platelet inhibition (e.g., a patient with NSTEACS receiving clopidogrel who is taken to the cardiac catheterization laboratory on day 3 because of recurrent ischemia and is found to have a thrombotic lesion requiring PCI)*, a 60–mg oral loading dose of prasugrel should generally be given, followed by prasugrel 10 mg orally od

  ⇒ *If the clinical circumstances do not warrant a rapid and high level of platelet inhibition (e.g., a patient with NSTEACS who has already undergone PCI and stenting while receiving clopidogrel but is felt to be at high risk of stent thrombosis and/or recurrent MI)*, a loading dose of prasugrel can be omitted and therapy with oral prasugrel 10 mg od can be started the day after receiving the last dose of clopidogrel

Appendix 9.4 Proposed algorithm for switching from clopidogrel to ticagrelor

Switching after only a loading dose of clopidogrel

- *In the absence of relative or absolute contraindications to ticagrelor (see Appendix 9.2)*: if only a 300-600–mg loading dose of clopidogrel has been given (e.g., a patient with STEMI undergoing primary PCI who has received 300 mg of clopidogrel in the Emergency Department prior to cardiac catheterization laboratory transfer), a 180–mg oral loading dose of ticagrelor should generally be given, followed by ticagrelor 90 mg orally bid

Switching after a loading dose and at least one maintenance dose of clopidogrel

- *In the absence of relative or absolute contraindications to ticagrelor (see Appendix 9.2)*: if a 300-600–mg clopidogrel loading dose and at least one 75–mg clopidogrel maintenance dose have been given, ticagrelor dosing options are as follows:

  ⇒ *If the clinical circumstances warrant a rapid and high level of platelet inhibition (e.g., a patient with NSTEACS receiving clopidogrel who is taken to the cardiac catheterization laboratory on day 3 because of recurrent ischemia and is found to have a thrombotic lesion requiring PCI)*, a 180–mg oral loading dose of ticagrelor should generally be given, followed by oral ticagrelor 90 mg bid

  ⇒ *If the clinical circumstances do not warrant a rapid and high level of platelet inhibition (e.g., a patient with NSTEACS being medically managed and currently receiving clopidogrel who has stabilized with initial treatment but is felt to be at increased risk of recurrent MI and death)*, a loading dose of ticagrelor can be omitted and patients can be started on oral ticagrelor 90 mg bid the day after receiving their last dose of clopidogrel

Appendix 9.5 GRACE risk score[19]

Risk Calculator for 6-Month Postdischarge Mortality After Hospitalization for Acute Coronary Syndrome

Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the total score on the x-axis of the nomogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 months.

Medical History

① Age in Years	Points
≤29	0
30–39	0
40–49	18
50–59	36
60–69	55
70–79	73
80–89	91
≥90	100

② History of Congestive Heart Failure	24
③ History of Myocardial Infarction	12

Findings at Initial Hospital Presentation

④ Resting Heart Rate, beats/min	Points
≤49.9	0
50–69.9	3
70–89.9	9
90–109.9	14
110–149.9	23
150–199.9	35
≥200	43

⑤ Systolic Blood Pressure, mm Hg	
≤79.9	24
80–99.9	22
100–119.9	18
120–139.9	14
140–159.9	10
160–199.9	4
≥200	0

⑥ ST-Segment Depression	11

Findings During Hospitalization

⑦ Initial Serum Creatinine, mg/dL	Points
0–0.39	1
0.4–0.79	3
0.8–1.19	5
1.2–1.59	7
1.6–1.99	9
2–3.99	15
≥4	20

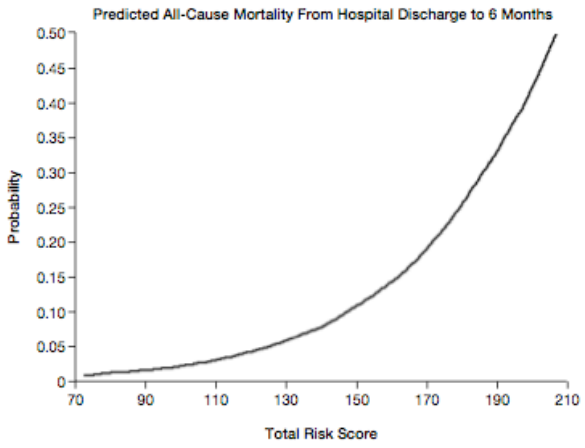
⑧ Elevated Cardiac Enzymes	15
⑨ No In-Hospital Percutaneous Coronary Invervention	14

Points

① _____
② _____
③ _____
④ _____
⑤ _____
⑥ _____
⑦ _____
⑧ _____
⑨ _____

Total Risk Score _____ (Sum of Points)

Mortality Risk _____ (From Plot)



Appendix 9.6 TIMI risk score[20]

One point each for:

- ≥65 years of age
- ≥3 risk factors for coronary artery disease[a]
- Significant coronary stenosis[b]
- ST deviation on presentation
- Severe anginal symptoms[c]
- Use of aspirin in last 7 days
- Elevated cardiac markers[d]

POINTS TOTAL = TIMI RISK SCORE

[a]Family history of coronary disease, hypertension, dyslipidemia, diabetes or current smoking.

[b]Prior coronary stenosis ≥50%.

[c]≥2 anginal episodes in last 24 hours.

[d]Troponin or creatine kinase MB.

Appendix 9.7 Cardiovascular Health Nova Scotia 2008 Guidelines for Acute Coronary Syndromes: recommended duration of clopidogrel therapy[28]

The duration of clopidogrel therapy should be tailored according to patient risk and the type of stent inserted in those who undergo PCI.

- Minimum one month of clopidogrel therapy in low-risk patients with STEMI who are managed medically or who undergo PCI with bare metal stent implantation
- Minimum three months of clopidogrel therapy in low-risk patients with NSTEACS who are managed medically or who undergo PCI with bare metal stent implantation
- Minimum of 12 months of clopidogrel therapy in all patients with ACS at increased risk of recurrent events (e.g., second ACS within 12 months, complex or extensive coronary artery disease, associated peripheral arterial or cerebrovascular disease) and/or who undergo PCI with implantation of ≥1 drug-eluting stent
- Consider prolonged (>12 months) clopidogrel therapy in all patients with ACS at very high risk of recurrent events (e.g., patients with degenerate saphenous vein bypass grafts or who also have peripheral vascular and cerebrovascular disease) or in some patients who undergo complex PCI (e.g., left main stenting)

Appendix 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[3]

- *For all patients with ACS who survive to hospital discharge,* indefinite therapy with low-dose aspirin (75-162 mg daily) is recommended (Class I, Level A). For patients allergic to or intolerant of aspirin, indefinite therapy with clopidogrel 75 mg daily is recommended (Class IIa, Level B).
- *For patients presenting with STEMI who are medically managed,* clopidogrel 75 mg daily is recommended in addition to aspirin 75-162 mg daily for at least 14 days (Class I, Level B) and up to 12 months in the absence of an excessive risk of bleeding (Class IIb, Level C).
- *For patients presenting with STEMI who are managed by PCI,* clopidogrel 75 mg daily is recommended in addition to aspirin 75-162 mg daily for 12 months (Class I, Level B). Continuation of combined therapy beyond 12 months may be considered in patients with a high risk of thrombosis and a low risk of bleeding (Class IIb, Level C).
- *For patients presenting with NSTEACS who are medically managed*, clopidogrel 75 mg daily is recommended in addition to aspirin 75-162 mg daily for at least 1 month (Class I, Level A) and up to 12 months in the absence of an excessive risk of bleeding (Class I, Level B).
- *For patients presenting with NSTEACS who are managed by PCI*, clopidogrel 75 mg daily is recommended in addition to ASA 75-162 mg daily for 12 months (Class I, Level A). Continuation of combined therapy beyond 12 months may be considered in patients with a high risk of thrombosis and a low risk of bleeding (Class IIb, Level C).
- *For patients presenting with NSTEACS who are managed by CABG*, clopidogrel 75 mg daily is recommended in addition to aspirin 75-162 mg daily for a minimum of 1 month and up to 12 months (Class I, Level B).
- *For patients with ACS who undergo stent implantation and have an increased risk of stent thrombosis* (e.g., STEMI, history of diabetes mellitus, or prior documented stent thrombosis), prasugrel 10 mg daily may be considered in addition to aspirin 75-162 mg

daily for 12 months (Class IIa, Level B). Prasugrel should be avoided in patients with an increased bleeding risk, likely to undergo CABG within 7 days, with a history of stroke or transient ischemic attack, aged ≥75 years, or weighing <60 kg (Class III, Level B).

- *For patients with ACS*, ticagrelor 90 mg twice daily may be added to aspirin 75-162 mg daily for 12 months (Class I, Level B).
- In general, the $P2Y_{12}$ inhibitor added to aspirin in the acute setting should be maintained for the duration of therapy (Class I, Level C).