Review

Assessment and Management of Acute Coronary Syndromes (ACS): A Canadian Perspective on Current Guideline-Recommended Treatment – Part 1: Non-ST–Segment Elevation ACS

David H. Fitchett, MD,a,b,c Pierre Theroux, MD,d,e James M. Brophy, MD, PhD,f,g Warren J. Cantor, MD,b,h Jafna L. Cox, MD,i,j Milan Gupta, MD,k,l,m Heather Kertland, PharmD,a,b Shamir R. Mehta, MD, MSc,m,n Robert C. Welsh, MD,o,p and Shaun G. Goodman, MD, MSca,b,c

a St Michael’s Hospital, Toronto, Ontario, Canada
b University of Toronto, Toronto, Ontario, Canada
c Canadian Heart Research Centre, Toronto, Ontario, Canada
d Montreal Heart Institute, Montreal, Quebec, Canada
e University of Montreal, Montreal, Quebec, Canada
f McGill University Health Centre, Montreal, Quebec, Canada
g McGill University, Montreal, Quebec, Canada
h Southlake Regional Health Centre, Newmarket, Ontario, Canada
i Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada
j Dalhousie University, Halifax, Nova Scotia, Canada
k William Osler Health Centre, Brampton, Ontario, Canada
l Canadian Cardiovascular Research Network, Hamilton, Ontario, Canada
m McMaster University, Hamilton, Ontario, Canada
n Hamilton Health Sciences Centre, Hamilton, Ontario, Canada
o Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada
p University of Alberta, Edmonton, Alberta, Canada

ABSTRACT

Despite the reduction of coronary heart disease mortality over the past 40 years, hospital admissions for acute coronary syndromes (ACS) continue to increase. The goal of this 2-part article is to review the issues at each stage of assessment and management of the ACS.

Coronary heart disease remains a major cause of mortality and morbidity. Despite a marked reduction in cardiovascular (CV) mortality over the past 40 years, the rates of myocardial infarction (MI) continue to increase. Approximately 70,000 acute myocardial infarction (AMI) occur each year in Canada and some 19,000 Canadians die from this condition.1,2 More than half of 30-day MI mortality occurs prior to hospital arrival, mostly within 1 hour of symptom onset.3 About 12% of initial survivors will die in hospital.1 Furthermore, there is considerable regional variation, with the far north and Atlantic Canada recording a disproportionately higher event rate.1,3,4 This regional variation in mortality, in turn, likely reflects the differential distribution of CV risk across the country.5,6

RÉSUMÉ

En dépit de la diminution de mortalité liée à la maladie coronarienne depuis les 40 dernières années, les admissions à l’hôpital pour des syndromes coronariens aigu (SCA) continuent d’augmenter. Le but de cet article en deux parties est de revoir les enjeux de chacune des...
patient, and to propose an optimal treatment strategy for the individual patient in the context of the realities, culture, and delivery of healthcare in Canada.

ACS patients are categorized as either ST segment elevation myocardial infarction (STEMI) or non-ST–elevation ACS (NSTE-ACS). For the patients with NSTE-ACS, prevention of recurrent ischemic events is the primary goal. Assessment of risk for recurrent ischemic and bleeding events helps to determine the net benefit of early cardiac catheterization and percutaneous coronary intervention (PCI) and intensive antiplatelet and anticoagulant treatment. Those with higher ischemic risk features should be considered for an early invasive strategy and receive both dual antiplatelet therapy and an anticoagulant at the time of first medical assessment. Patients without high-risk features could be considered for medical treatment and a selectively invasive strategy; with coronary angiography and revascularization only if high-risk features become apparent.

Long-term vascular protection with lifestyle modification (especially smoking cessation), lipid lowering, blood pressure and glycemic control, and the use of renin angiotensin aldosterone system (RAAS) blockade to prevent recurrent ischemic events, is important in all patients with ACS.

The assessment and management of acute coronary syndromes (ACS) has evolved over the past 35 years due to a wealth of knowledge gained from basic research, clinical trials, registry data, and clinical expertise leading to the development of new technologies. Consequent to improved risk factor modification and management innovations, both short- and longer-term mortality from ACS have fallen substantially. In Ontario, age-adjusted coronary heart disease mortality fell by 35% between 1994 and 2005, with trends in risk factors and improvements in medical management, each explaining about half of the decrease. Canadian hospital admissions for MI decreased by 9%-30% between 1994 and 2004, and age-adjusted coronary heart disease mortality fell by one-third.8,9

The ACS spectrum includes patients with ST-elevation myocardial infarction (STEMI) and non-ST–elevation ACS (NSTE-ACS), which is comprised of non-STEMI (NSTEIM) and unstable angina. The initial difference in pathophysiology and early outcomes between STEMI and NSTE-ACS lead to contrasted early treatment strategies. In STEMI, prompt reopening of the occluded artery is the therapeutic priority that limits the extent of myocardial injury and saves lives (see Part 2 article). In contrast, the therapeutic goals in NSTE-ACS management are to prevent progression of the thrombus to total occlusion, plaque thromboembolization, and recurrent infarction. In-hospital mortality rates in STEMI remain 50% higher than for NSTEIM patients. However, the high rates of recurrent ischemic events in NSTE-ACS patients result in similar 1-year mortality rates in the 2 conditions, emphasizing the need for selecting appropriate early management strategies and secondary prevention measures.

Older data have suggested suboptimal use of certain acute treatments for STEMI across Canada including, again, some interregional variation.9,11 Comparable data for NSTE-ACS are not available but similar variation in care doubtless exists with this condition as well. More remarkable have been the differences noted across provinces in secondary prevention following hospitalization for the index MI, regardless of type12 as well as the differential access to invasive cardiac procedures after an acute MI.13 Not only do treatment patterns for ACS differ across the country, and on the whole remain somewhat suboptimal,14-17 but varying provincial health policies lead to regional differences in treatment access in general.18,20 These policies have directly impacted the timing of initiation and duration of coverage of certain key ACS drugs with adverse impact on patient outcomes.18,21-22

The closer the adherence to guideline recommendations for treatment of ACS, the better are clinical outcomes.23 However, the leading unstable angina/NSTEMI treatment guidelines of the American Heart Association (AHA)/American College of Cardiology (ACC)24 with 2011 focused update,25 and the European Society of Cardiology (ESC)26 are comprehensive but complex, and perhaps as a result they often are not followed.27 There is no single recipe for all patients, nor does one algorithm fit the requirements of all communities and their populations. Yet a clear and more easily applied set of guideline recommendations is likely to result in a larger proportion of patients receiving optimal recommended treatment. Indeed, it is hoped that at some time in the near future standard approaches to treatment, including the timing of access to investigations and invasive procedures, might be adopted across Canada in order to attenuate the variation in management and potentially the differences in outcome that have been previously documented on a regional basis.

The goal of this report is to review the issues at each stage of assessment and management of the ACS patient, from presentation to long-term care, and to identify optimal treatment for the individual patient in the context of the realities, culture, and delivery of healthcare in Canada based upon guideline
Table 1. Signs and symptoms of ACS

<table>
<thead>
<tr>
<th>Chest pain or discomfort</th>
<th>● Central or substernal, upper abdominal, or epigastric discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● Pain radiating to neck, jaw, shoulders, back, 1 or both arms</td>
</tr>
<tr>
<td></td>
<td>● Sensation of pressure, crushing, tightness, heaviness, cramping, burning, aching</td>
</tr>
<tr>
<td></td>
<td>● Accompanying dyspnea, indigestion, nausea, vomiting, diaphoresis</td>
</tr>
<tr>
<td></td>
<td>● Associated hypotension or ventricular arrhythmias</td>
</tr>
</tbody>
</table>

Other symptoms associated with myocardial ischemia

| ● Isolated dyspnea |
| ● Weakness |
| ● Diaphoresis |
| ● Light-headedness and/or syncope |
| ● Nausea |
| ● The elderly, women, and individuals with diabetes may present with ‘anginal equivalents’ or symptoms that are not typical for myocardial ischemia. This occurs in approximately 30% of ACS patients and is associated with a worse prognosis. |

Symptoms of clinical instability

| ● Progressive angina (ie, new onset angina with progressive symptoms or exacerbation of pervious angina with more frequent, severe, or prolonged pain occurring at a lower exercise threshold or at rest) |
| ● Prolonged chest pain (ie, ≥ 20 minutes) |

ACS, acute coronary syndromes.

recommendations from the AHA/ACC, ESC, and the recent Canadian Cardiovascular Society Antithrombotic Guideline in the outpatient setting. In addition, it provides an algorithm for ACS risk assessment and management that is potentially simple to follow and easy to implement.

The initial ECG is crucial for immediate triage. In the presence of ST-segment elevation or new or presumably new left bundle branch block, immediate reperfusion with either fibrinolytic or primary PCI should be considered (see Part 2 article). Consequently, it is important that the earliest medical contact, including emergency transportation services, has the ability to record and interpret or transmit ECGs in order to triage patients rapidly to the most appropriate care. Other ECG abnormalities such as ST-segment depression or deep T wave inversion indicate a higher risk NSTE-ACS and support an early invasive management strategy together with dual antiplatelet therapy and parenteral anticoagulation.

A rise and fall of troponin, in association with symptoms compatible with ACS is associated with an increased risk of recurrent ischemic and fatal events. If the first troponin is below the reference threshold, the test should be repeated 6 hours later. The universal definition of MI requires the detection of a rise and/or fall of a cardiac biomarker with at least 1 value above the 99th percentile reference level (at this level the assay has a coefficient of variation of less than 10%), accompanied by 1 of the following: symptoms consistent with ischemia, ECG changes indicative of new ischemia, new pathological Q waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. Troponin levels can remain elevated for 10-14 days after ACS; thus elevated levels within 2 weeks of an ACS may not be due to a new event. Extension of an infarction may then be best recognized by a new elevation in CK-MB levels.

With the development of ultrasensitive troponin assays, the diagnosis of ACS is being made earlier and more frequently. Whether a diagnosis of MI should apply to patients with ACS and a rise and fall of troponin to above the very low reference threshold of the ultrasensitive assay, remains controversial and requires further study. Regardless, such individuals do have an increased risk of recurrent ischemic events and need long-term measures to reduce further events (including ASA, statins, and blood pressure control), whether or not they undergo early invasive assessment. Troponin is a highly specific and sensitive marker of myocardial cell injury, but is not a specific marker for plaque rupture, erosion, and/or ulceration and thrombosis precipitating ACS. Indeed, circulating troponin can be increased by many non-ACS causes of cardiomyocyte damage (Table 3). Evaluation of a patient in the emergency department found to have a troponin level above the reference threshold includes assessment of the likelihood of an acute coronary ischemic event.

Table 2. Other conditions to consider in the patient with a suspected acute coronary syndrome

| ● Aortic dissection |
| ● Pulmonary embolism |
| ● Pneumothorax |
| ● Pericarditis |
| ● Esophageal rupture |
| ● Pneumonia |
| ● Pancreatitis |
| ● Cholecystitis |
| ● Peptic ulcer with or without perforation |
| ● Gastroesophageal reflux |

The time of first medical contact through hospital discharge to long-term care. The secondary prevention measures initiated at triage, and undergo a rapid yet comprehensive evaluation of their demographics, past medical history, medications, symptoms, and signs. An ECG should be taken and evaluated within 10 minutes of arrival. Continuous ECG monitoring and an adequate intravenous access should be initiated. Immediate treatment should include aspirin (ASA) 162-325 mg chewed, sublingual nitroglycerin spray (for ongoing symptoms without hypotension or recent use of a phosphodiesterase inhibitor), supplemental oxygen when hypoxic or dyspneic, and morphine for pain control. Other conditions in the differential diagnosis should be considered (Table 2) as well as other medical conditions that could indirectly precipitate a secondary form of accelerated angina such as severe anemia, thyrotoxicosis, or tachyarrhythmia.

Assessment and Diagnosis

Assessment begins at first contact with medical services, which is the emergency medical systems teams should obtain a 12-lead electrocardiogram (ECG) to identify the presence of ST-T deviation; most important to recognize ST-segment elevation promptly in order to facilitate immediate access to timely reperfusion.

Patients arriving at an emergency department with chest discomfort or other symptoms suggestive of ACS (Table 1) should receive high priority at triage, and undergo a rapid yet comprehensive evaluation of their demographics, past medical history, medications, symptoms, and signs. An ECG should be taken and evaluated within 10 minutes of arrival. Continuous ECG monitoring and an adequate intravenous access should be initiated. Immediate treatment should include aspirin (ASA) 162-325 mg chewed, sublingual nitroglycerin spray (for ongoing symptoms without hypotension or recent use of a phosphodiesterase inhibitor), supplemental oxygen when hypoxic or dyspneic, and morphine for pain control. Other conditions in the differential diagnosis should be considered (Table 2) as well as other medical conditions that could indirectly precipitate a secondary form of accelerated angina such as severe anemia, thyrotoxicosis, or tachyarrhythmia.

The initial ECG is crucial for immediate triage. In the presence of ST-segment elevation or new or presumably new left bundle branch block, immediate reperfusion with either fibrinolytic or primary PCI should be considered (see Part 2 article). Consequently, it is important that the earliest medical contact, including emergency transportation services, has the ability to record and interpret or transmit ECGs in order to triage patients rapidly to the most appropriate care. Other ECG abnormalities such as ST-segment depression or deep T wave inversion indicate a higher risk NSTE-ACS and support an early invasive management strategy together with dual antiplatelet therapy and parenteral anticoagulation.

A rise and fall of troponin, in association with symptoms compatible with ACS is associated with an increased risk of recurrent ischemic and fatal events. If the first troponin is below the reference threshold, the test should be repeated 6 hours later. The universal definition of MI requires the detection of a rise and/or fall of a cardiac biomarker with at least 1 value above the 99th percentile reference level (at this level the assay has a coefficient of variation of less than 10%), accompanied by 1 of the following: symptoms consistent with ischemia, ECG changes indicative of new ischemia, new pathological Q waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. Troponin levels can remain elevated for 10-14 days after ACS; thus elevated levels within 2 weeks of an ACS may not be due to a new event. Extension of an infarction may then be best recognized by a new elevation in CK-MB levels.

With the development of ultrasensitive troponin assays, the diagnosis of ACS is being made earlier and more frequently. Whether a diagnosis of MI should apply to patients with ACS and a rise and fall of troponin to above the very low reference threshold of the ultrasensitive assay, remains controversial and requires further study. Regardless, such individuals do have an increased risk of recurrent ischemic events and need long-term measures to reduce further events (including ASA, statins, and blood pressure control), whether or not they undergo early invasive assessment. Troponin is a highly specific and sensitive marker of myocardial cell injury, but is not a specific marker for plaque rupture, erosion, and/or ulceration and thrombosis precipitating ACS. Indeed, circulating troponin can be increased by many non-ACS causes of cardiomyocyte damage (Table 3). Evaluation of a patient in the emergency department found to have a troponin level above the reference threshold includes assessment of the likelihood of an acute coronary ischemic event.
Table 4. Increased troponin is a marker of myocardial necrosis, but not necessarily a consequence of an ACS

<table>
<thead>
<tr>
<th>ACS</th>
<th>Cardiac but non-ACS</th>
<th>Iatrogenic</th>
<th>Analytical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>Myocarditis</td>
<td>Coronary angioplasty</td>
<td>Heterophile antibodies</td>
</tr>
<tr>
<td></td>
<td>Pulmonary emboli</td>
<td>Cardiac surgery</td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
<td>Balloon valvuloplasty</td>
<td>Fibrin strands</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>Cardioversion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supraventricular tachycardia</td>
<td>EP ablation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subarachnoid hemorrhage</td>
<td>Cardiotoxic chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart transplant rejection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac contusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aortic valve disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhabdomyolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac amyloid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scorpion venom</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prolonged strenuous exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary spasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS, acute coronary syndromes; EP, electrophysiology.

Early Risk Stratification

Early risk assessment, for both recurrent ischemic events and the risk of bleeding, allows selection of the most appropriate treatment strategy. It is an essential part of the early evaluation of the patient with ACS. Treatments such as an early invasive strategy and anticoagulant and/or antiplatelet agents offer the greatest benefit in the higher risk patient; in contrast, harm from these therapies could outweigh the potential benefits in a low risk patient.

Clinical observations available at the time of initial evaluation permit an assessment of the risk for recurrent ischemic events (Table 4). The presence of ST-segment depression and elevated troponin levels identify patients at greater risk for recurrent ischemic events. However, even in the absence of ECG abnormalities or elevated biomarkers, patients with typical ischemic cardiac discomfort who have diabetes, renal failure, heart failure, or a history of previous coronary artery bypass graft (CABG), should be carefully evaluated as they may be at high risk for potentially fatal events over the next year.32 Outcome after an ACS is determined by an interaction between the patient’s pre-event status (eg, age, diabetes, renal function, pre-existing coronary disease, left ventricular function, and prior treatment), and the impact of the acute event (as indicated by low blood pressure, increased heart rate, higher Killip class, ECG ST deviation, and troponin elevation).

The initial risk assessment helps to select patients who potentially benefit the most from early cardiac catheterization and intensified antithrombotic therapy. Most clinical trials that compared an early invasive with a conservative strategy selected patients with ECG ST-segment depression and/or an elevated biomarker. However, a wide gradient of risk is known to exist amongst these patients. Consequently, some patients selected either on the basis of an ECG abnormality, or elevated biomarkers may not be truly high risk and hence would not necessarily benefit from an early invasive strategy. Indeed, the 2007 ACC/AHA NSTE-ACS Guidelines24 have a grade IIb, evidence level C recommendation for conservative management of initially stabilized patients including some with elevated troponin based on the results of the Invasive vs Conservative Treatment in Unstable Coronary Syndromes (ICTUS) study.33 Yet the same guidelines have a grade 1, evidence level A recommendation for an early invasive approach in patients at high risk for recurrent ischemic events identified by factors that include an elevated troponin. In this document we have kept to the ACC/AHA grade 1 recommendation and as indicated in the algorithm, recommend an early invasive approach for most patients with NSTE-ACS and elevated troponin. Furthermore, it should be recognized that some patients who are biomarker-negative may still have a high mortality risk.34 For this reason, the 2011 ACC/AHA NSTE-ACS guideline update25 recommend that patients with NSTE-ACS and diabetes, irrespective of troponin status, be considered for an early invasive strategy.

The application of risk scores such as Thrombolysis in Myocardial Infarction (TIMI)35 (available at http://www.mdcalc.com/timi-risk-score-for-unicostemi) or Global Registry of Acute Coronary Events (GRACE)36 (available at http://www.outcomes-umassmed.org/grace) may provide a better estimate of benefit.

Table 4. High-risk features for recurrent ischemic events after NSTE-ACS

<table>
<thead>
<tr>
<th>Clinical</th>
<th>ECG</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple episodes of pain (or documented ischemia)</td>
<td>• ST-segment depression &gt; 0.5 mm</td>
<td>• Troponin &gt; 99th percentile reference level (with a troponin test with &lt; 10% variation)</td>
</tr>
<tr>
<td>• Associated heart failure, hypotension, or tachycardia</td>
<td>• Transient ST-segment elevation</td>
<td>• Mortality associated with higher levels</td>
</tr>
<tr>
<td>• Refractory ischemia with ECG changes despite treatment</td>
<td>• Outcome relates to degree of ST depression</td>
<td>• Lower level increase associated with increased risk for recurrent ischemia and/or MI</td>
</tr>
<tr>
<td>• Renal dysfunction, type 2 diabetes, prior revascularization</td>
<td>• T-wave inversion &gt; 2 mm in multiple precordial leads</td>
<td></td>
</tr>
<tr>
<td>• Sustained ventricular tachycardia</td>
<td>• New left bundle branch block</td>
<td></td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; MI, myocardial infarction; NSTE-ACS, non-ST–elevation acute coronary syndromes.
from an invasive strategy. Although these scores have been validated in other populations, they have never been thoroughly evaluated prospectively. However, despite the perception that they might be cumbersome to routinely use at the bedside, it is clear that the alternative (ie, physician “impression” of risk) is suboptimal in many cases. Risk assessment is an ongoing process and must be updated with repeated clinical assessment, ECGs, and troponin levels during the first 12-24 hours. Key clinical characteristics to assess include signs or symptoms of recurrent ischemia, heart failure, hemodynamic instability, as well as levels of hemoglobin, electrolytes, blood sugar, and renal function.

Canadian perspective

In Canada today, the majority of patients with NSTE-ACS who have either ST depression and or elevated troponin undergo early cardiac catheterization. Most high-risk patients should ideally undergo catheterization within the first 24-48 hours from symptom onset. To ensure the majority of patients at high risk are identified and managed appropriately, a Canadian group published a simplified algorithm of risk stratification (Fig. 1). Patients with symptoms, but no ECG changes or biomarker elevation, are classified as having an indeterminate risk and require observation for at least 12 hours so that their actual risk can be better clarified. Determining the TIMI or GRACE risk score in this indeterminate risk group may also help to direct management, especially related to the need for coronary angiography. Early stress testing should be considered in patients with symptoms compatible with myocardial ischemia, but no high-risk features.

Figure 1. Algorithm for management of non-ST–elevation ACS. ACS, acute coronary syndromes; ASA, aspirin; bid, twice daily; BP, blood pressure; ECG, electrocardiogram; IACBP, intra-aortic counterpulsation balloon pump; od, once daily; q, every; SC, subcutaneous; stat, immediately; UFH, unfractionated heparin. *Refers to high-risk features indicated in the shaded rectangle. †Refers to high-risk features indicated in the shaded circle.
Table 5. Clinical factors associated with increased bleeding risk

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Management factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Use of glycoprotein IIb/IIIa inhibitors</td>
</tr>
<tr>
<td>Female gender</td>
<td>Catheterization/PCI in first 24 h</td>
</tr>
<tr>
<td>Low body weight</td>
<td>Excessive antiplatelet and/or antithrombotic dosing</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Triple therapy (ASA, clopidogrel, and warfarin)</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td></td>
</tr>
<tr>
<td>Increased risk of ischemic event</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency (CrCl &lt; 60 ml per min)</td>
<td></td>
</tr>
</tbody>
</table>

ASA, aspirin; PCI, percutaneous coronary intervention.

Table 6. Prevention of bleeding

- Careful patient history, physical examination, and assignment to therapy
- Appropriate dosing of antithrombotic drugs (consider age, renal function, weight)
- Shorten duration of exposure to antithrombotic agents (if early invasive strategy is selected, early catheterization)
- Use fondaparinux or UFH in patients at higher risk
- Use a proton pump inhibitor for gastric protection in patients at high risk
- At the time of angiography/angioplasty radial artery access may be preferred; catheter size should be minimized; sheaths should be removed as soon as possible
- Respond to bleeding early: reduce medications and consider reversing anticoagulation with high-risk bleed. Identify retroperitoneal bleeding (perform CT scan in patients with back or leg pain, hypotension, or progressive anemia)

CT, computed tomography; UFH, unfractionated heparin.
Table 7. Management of bleeding

<table>
<thead>
<tr>
<th>Local hemostasis when possible</th>
<th>Minor bleeding</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Maintain volume status</td>
<td>- Discontinue IV anticoagulation, GP IIb/IIIa inhibitor</td>
<td>- Maintain volume status</td>
</tr>
<tr>
<td>- Avoid transfusion if possible (transfuse only when Hb &lt; 80 g/L or Hct &lt; 25%)</td>
<td>- Discontinue IV anticoagulation, GP IIb/IIIa inhibitor</td>
<td>- Avoid transfusion if possible (transfuse only when Hb &lt; 80 g/L or Hct &lt; 25%)</td>
</tr>
<tr>
<td>- Consider platelet transfusion; protamine for UFH/enoxaparin</td>
<td>- Maintain volume status</td>
<td>- Avoid transfusion if possible (transfuse only when Hb &lt; 80 g/L or Hct &lt; 25%)</td>
</tr>
<tr>
<td>- Give Octaplex (prothrombin complex concentrate) if high INR on warfarin</td>
<td>- Consider platelet transfusion; protamine for UFH/enoxaparin</td>
<td>- Give Octaplex (prothrombin complex concentrate) if high INR on warfarin</td>
</tr>
<tr>
<td>- rFactor VII only if bleeding is severe, life-threatening</td>
<td>- Give Octaplex (prothrombin complex concentrate) if high INR on warfarin</td>
<td>- rFactor VII only if bleeding is severe, life-threatening</td>
</tr>
</tbody>
</table>

GP, glycoprotein; Hb, hemoglobin; Hct, hematocrit; INR, international normalized ratio; IV, intravenous; UFH, unfractionated heparin.

toma) were less when the radial arterial approach was used. Furthermore, in the STEMI subgroup there was a 40% reduction of the combined primary outcome and a 61% reduction of mortality in the patients who had radial arterial access. In centres with high volume use of radial arterial access, the radial arterial approach was associated with a 51% reduction of the primary combined end point. Smaller sheaths, radial access, and timely sheath removal likely reduce the bleeding risk even when potent antithrombotic and/or antiplatelet therapy is used. In high-risk individuals who require anticoagulation for several days, choosing fondaparinux rather than enoxaparin reduces bleeding. Management of bleeding depends upon the site and severity of bleeding (Table 7).

Therapeutic dual oral antiplatelet therapy at the time of major surgery significantly increases bleeding risk. Clopidogrel taken within 5 days of coronary artery bypass surgery is associated with a 50% increase in major bleeding. For the 8%-15% of ACS patients that require coronary bypass surgery during the index hospitalization, the majority can wait for 5 days after discontinuation of clopidogrel before undergoing the operation. For prasugrel (which should not be administered in patients with NSTE-ACS until after the coronary artery anatomy has been defined, to conform with the protocol of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel [TRITON] study), it is recommended that most patients discontinue the agent 7 days prior to surgery. Small numbers of very high-risk unstable patients require surgery earlier, and they should not be denied life-saving surgery because of an increased bleeding risk. The recently reported analysis of the Platelet Inhibition and Patient Outcomes (PLATO) study suggests that patients undergoing CABG who had received ticagrelor within 7 days of surgery had a lower mortality than the patients receiving clopidogrel, without any increase in perioperative bleeding.

Canadian perspective

The radial arterial approach to coronary arterial procedures is advocated by many Canadian centres and is currently used in an increasing proportion of patients undergoing both coronary angiography and PCI. Although the recently reported RIVAL trial showed no difference for major outcomes in the overall trial, patient preferences, the results with high volume use of the radial access, and the reduced vascular complication rate, favour the radial approach in many Canadian centres.

Clopidogrel is routinely administered in the emergency department to most patients with NSTE-ACS. For patients requiring urgent CABG who have received clopidogrel, there is a range of practice standards in Canada. Some surgeons delay surgery for at least 5 days, and others operate promptly and use a variety of techniques to minimize bleeding. A consistent approach by cardiac surgeons in assessing the benefits and risks of early surgery has been encouraged by the recent publication of a Canadian position paper. While the Canadian product monograph recommendation for delaying bypass surgery (where possible) in ticagrelor-treated patients is also 5 days, unique properties of this adenosine diphosphate-receptor antagonist (ie, reversible binding with restoration of platelet function as plasma drug levels fall) may allow proceeding to CABG slightly earlier (eg, 72-96 hours after the last dose).

Selection of Management Strategy

The choice of either an early invasive strategy (with elective coronary angiography within the first 24-48 hours) or a more conservative selective invasive strategy (with medical treatment and coronary angiography only in response to recurrent symptoms, development of other high-risk clinical features, or high risk noninvasive testing) is made after weighing the balance of expected benefits and risks (Table 8). Consider the risk of complications from an invasive procedure, especially bleeding, as low-risk patients may have limited benefit from an invasive approach, or may even be harmed.

A meta-analysis of major clinical trials to date comparing an invasive strategy to a selective invasive approach in higher risk NSTE-ACS patients showed that an invasive strategy led to:

- A significant 25% reduction in mortality over a mean follow-up period of 2 years;
- An 18% reduction in nonfatal MI over the period of follow-up;
- A 31% reduction in recurrent unstable angina requiring hospitalization.

A recent meta-analysis shows that an early invasive strategy in high-risk patients reduces the 5-year absolute risk of death and/or MI by 11%.

Table 8. Advantages and disadvantages of an early invasive management strategy

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Easy risk stratification approach</td>
<td>- Complications from invasive procedure (MI, bleeding)</td>
</tr>
<tr>
<td>- Rapid, accurate diagnosis and risk stratification</td>
<td>- Patients without higher risk features have no prognostic benefit and may delay early intervention for high-risk patients</td>
</tr>
<tr>
<td>- Approximately 20% with no angiographically significant CAD</td>
<td>- Cost, impact on resources</td>
</tr>
<tr>
<td>- Approximately 15% with left main stenosis</td>
<td></td>
</tr>
<tr>
<td>- Improved outcomes from early revascularization in high-risk patients</td>
<td></td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; MI, myocardial infarction.
The clinical trials published between 1994 and 2005 have a wide range of entry criteria, management, and treatment strategies (including time to catheterization and revascularization, mode of revascularization, adjunctive antithrombotic therapy, and definition of ischemic end points) precluding any precise estimate of benefit. However, a common finding is that only the higher-risk patients benefit from the early invasive strategy.65

The Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI) 18 trial66 indicated the optimal timing of coronary angiography in the ACS patient selected for an invasive strategy was within the first 48 hours. The CRUSADE registry67 suggested there was no harm delaying investigation by 1 day in most patients. The Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial168 showed that for the majority of patients with NSTE-ACS early (< 24 hours) coronary angiography was no better than delayed (> 36 hours) investigation. However, for high-risk patients (approximately 30%) with a high GRACE risk score (> 141), early coronary angiography (median 16 hours) resulted in a significantly lower rate of death, MI, or stroke compared with later investigation (median 50 hours). Consequently, the majority of patients with NSTE-ACS selected for an early invasive management strategy can wait 24-72 hours, and only the highest risk should be considered for an early emergent procedure (Table 9).

Anticoagulant and Antiplatelet Therapy
Both antiplatelet and anticoagulation therapies are required to reduce thrombotic and recurrent ischemic events in patients with ACS whether or not the patient is destined for an early invasive or selectively invasive strategy.

Anticoagulation
Currently available agents are UFH, low molecular weight heparin (usually enoxaparin), fondaparinux, and bivalrudin (see Table 10). The choice of individual agents depends upon the risk of an ischemic event, the management strategy (early invasive vs conservative), the time to cardiac catheterization (very early vs later), renal function, and the bleeding risk. For patients with severe renal dysfunction, enoxaparin, fondaparinux, and bivalrudin are contraindicated.68 Although enoxaparin prescribing information recommends dose adjustments when eGFR is less than 30mL per minute, there are no safety data to support this strategy. Fondaparinux is renally excreted, but is safer than enoxaparin in patients with creatinine < 265 μmol/L or eGFR > 30mL per minute.69

Enoxaparin was shown to be superior to UFH in ACS trials when the agents were compared with treatment durations of at least 48-72 hours.69 In the Superior Yield of the New Strategy of Enoxaparin, Revascularisation and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial,70 enoxaparin in patients managed with very early (median 22 hours) coronary angiography was not superior to UFH for efficacy, but major bleeding was increased. Fondaparinux was compared with enoxaparin in the Organization to Assess Strategies in Ischemic Syndromes (OASIS) 5 trial and was associated with similar early (9-day) ischemic events yet bleeding rates were halved.71 By 30 days, there was a significant reduction in mortality in the fondaparinux group that was closely associated with the reduced bleeding. Bivalrudin monotherapy in the ACUITY trial,71 when compared with UFH or enoxaparin combined with a GP IIb/IIIa inhibitor, showed no reduction of ischemic events yet bleeding was reduced. Interpretation of the ACUITY trial results is confounded by the fact that almost two-thirds of patients receiving enoxaparin or UFH prior to randomization, and then received study drug anticoagulation for only 4-5 hours subsequently. As most NSTE-ACS patients in Canada would require bivalirudin treatment for more than 24 hours prior to catheterization, it is unlikely that bivalirudin would be a cost-effective alternative to either UFH or enoxaparin when administered over this longer time period. Presently, the use of bivalirudin in Canada is confined to patients in the catheterization laboratory undergoing PCI.

The ESC and AHA/ACC recommendations on the tailored use of anticoagulation differ. Table 11 shows a suggested Canadian approach (that is closer to the ESC recommendations than the US guidelines). The choice of either fondaparinux or enoxaparin depends upon local practice and may be influenced by the opinions of local cardiologists.

Antiplatelet therapy
ASA and clopidogrel are currently the antiplatelet agents most frequently used in the early management of ACS. ASA was introduced for the management of ACS in the mid-1980’s after 4 trials

---

**Table 9. Characteristics in favour and against early invasive strategy: Levels of recommendation**

<table>
<thead>
<tr>
<th>Grade 1; strong recommendation</th>
<th>Grade 2; need to assess benefits and risks in individual patient</th>
<th>Grade 3; not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Refractory angina and/or ischemia (1B)</td>
<td>● Chronic renal insufficiency</td>
<td>● Competing comorbidities, high risk of revascularization and comorbid conditions outweigh benefits of revascularization</td>
</tr>
<tr>
<td>● Clinical instability (1B)</td>
<td>● Diabetes (consider as indication for early invasive strategy)</td>
<td>● Acute chest pain with low likelihood of ACS</td>
</tr>
<tr>
<td>● Elevated risk for ischemic event (1A)</td>
<td></td>
<td>● No patient consent to undergo revascularization whatever the findings</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome.

---

**Table 10. Anticoagulant properties**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Monitoring</th>
<th>Causes HIT</th>
<th>Impact of renal dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>Frequent aPTT</td>
<td>+ + +</td>
<td>–</td>
</tr>
<tr>
<td>Low molecular weight</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>None</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>+</td>
<td>+ + +</td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>+</td>
<td>+ + +</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>None</td>
<td>–</td>
<td>+ + +</td>
</tr>
<tr>
<td>Bivalrudin</td>
<td>None</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

+ to + + + indicates increasing impact. – indicates no impact.

aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombosis; UFH, unfractionated heparin.
showed a greater than 50% reduction of death or MI in short- and long-term administration. Yet the optimal dose of ASA remains controversial because until recently, there was no large-scale comparison of ASA dose in ACS. Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events: Organizing to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) trial was a Canadian-led, international trial evaluating higher-dose (300-325 mg daily) vs low-dose (75 mg daily) loading and maintenance dose for the first week (instead of the usual 75 mg) in patients undergoing PCI. Fonodaparinux preferable to enoxaparin, or UFH. If increased bleeding risk consider fonodaparinux.

Selectively invasive and/or delayed intervention
ASA, ticagrelor (180 mg loading dose followed by 90 mg twice daily; consider additional 90 mg at the time of PCI) or clopidogrel (300 mg loading dose followed by 75 mg daily; consider additional 300 mg load at the time of PCI, and 150 mg for days 2-7, followed by 75 mg daily in patients undergoing PCI)
Fondaparinux, enoxaparin, or UFH. If increased bleeding risk consider fonodaparinux

Table 11. Suggested antithrombotic approach for the Canadian setting

<table>
<thead>
<tr>
<th>Approach</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urgent invasive approach</strong></td>
<td>ASA, ticagrelor (180 mg loading dose) or clopidogrel (600 mg loading dose)</td>
</tr>
<tr>
<td></td>
<td>Consider a GP IIb/IIIa antagonist in patients with refractory symptoms or clinical instability</td>
</tr>
<tr>
<td></td>
<td>Use UFH.</td>
</tr>
<tr>
<td><strong>Early invasive approach (within 48 h)</strong></td>
<td>ASA, ticagrelor (180 mg loading dose followed by 90 mg twice daily; consider additional 90 mg at the time of PCI) or clopidogrel (300 mg loading dose followed by 75 mg daily; consider additional 300 mg load at the time of PCI, and 150 mg for days 2-7, followed by 75 mg daily in patients undergoing PCI)</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux, enoxaparin, or UFH. If increased bleeding risk consider fonodaparinux</td>
</tr>
<tr>
<td><strong>Selective invasive and/or delayed approach</strong></td>
<td>ASA, ticagrelor (180 mg loading dose followed by 90 mg twice daily; consider additional 90 mg at the time of PCI) or clopidogrel (300 mg loading dose followed by 75 mg daily; consider additional 300 mg load at the time of PCI, and 150 mg for days 2-7, followed by 75 mg daily in patients undergoing PCI)</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux preferable to enoxaparin, especially if bleeding risk is high.</td>
</tr>
<tr>
<td></td>
<td>Continue to hospital discharge.</td>
</tr>
</tbody>
</table>

ASA, aspirin; GP, glycoprotein; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

Table 12. Recommendations for use of clopidogrel in NSTE-ACS

**Loading dose**
- Clopidogrel 300 mg followed by 75 mg daily
- Clopidogrel 600 mg followed by clopidogrel 150 mg daily for 7 d is preferred if likely to undergo urgent or early angiography and PCI

**Reloading**
- A reloading dose of 300 mg (or 600 mg) is recommended in patients already using clopidogrel who will likely undergo PCI

**Allergy or intolerance**
- Cutaneous rash may develop after PCI in relation with administration of contrast agents and other drugs including clopidogrel. The allergic reaction is treated with antihistaminic drugs and corticosteroids if required. If the rash disappears after 2 to 3 d, clopidogrel is continued; if it persists, clopidogrel is stopped and replaced with an alternative

**Alternative therapy**
- Ticlopidine has been the replacement agent for patients who could not tolerate clopidogrel, however, adverse effects and the need for close hematological monitoring make it an unattractive agent today

- Prasugrel is suitable for administration to patients about to undergo PCI in whom the coronary anatomy is known and have not already received clopidogrel. Cross-reactivity with prasugrel is reported in patients with clopidogrel sensitivity

- Ticagrelor is likely the best replacement for patients with clopidogrel allergy

**Duration of therapy**
- The ACC/AHA and ESC recommend 12 mo of therapy after ACS, whether in medically treated patients, or those undergoing a revascularization procedure (placement of a drug-eluting- or bare-metal stent)

ACC, American College of Cardiology; ACS, acute coronary syndromes; AHA, American Heart Association; ESC, European Society of Cardiology; NSTE-ACS, non-ST–elevation ACS; PCI, percutaneous coronary intervention.
inhibitor in the catheterization laboratory was associated with significantly fewer bleeding events, but with the same rates of clinical outcomes at 30 days as with the upstream use.

Consequently, the use of GP IIb/IIIa inhibitors (epifibatide, tirofiban, and abciximab) should be mainly restricted to those patients undergoing PCI, but could also be considered prior to the procedure (ie, upstream use) in patients with ongoing and/or recurrent ischemia despite dual antiplatelet therapy and an anticoagulant, and those with heart failure, serious arrhythmias, or cardiogenic shock who are scheduled for urgent coronary angiography.

**Alternative antiplatelet agents**

In vitro studies have shown considerable variability of clopidogrel inhibition of platelet aggregation. Recent studies have demonstrated genetic polymorphisms of cytochrome enzymes responsible for clopidogrel metabolism to the active metabolite that are responsible for reduced clopidogrel-induced inhibition of platelet aggregation and an associated increase of ischemic cardiac events in patients with recent ACS. Clopidogrel has a slow onset of action and achieves only 50%-60% inhibition of platelet aggregation. However, it is unclear as yet what is the optimal level of platelet inhibition with oral antiplatelet agents for acute and long-term ACS management.

Two new antiplatelet agents, prasugrel and ticagrelor have recently been approved for use in Canada. Prasugrel is a third generation thienopyridine irreversible platelet P2Y12-receptor inhibitor. Compared with clopidogrel, prasugrel requires 1 rather than 2 metabolic steps to generate the active metabolite, resulting in more rapid, potent, and consistent platelet inhibition, and is not affected by genetic polymorphisms of cytochrome P450 (CYP) enzymes responsible for metabolic activation of clopidogrel (eg, CYP3A4 and CYP2C19). In the Triptolemy Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study of thienopyridine-naive patients with an acute or recent ACS undergoing PCI (and where the coronary anatomy had been defined unless the patient was going to primary PCI for STEMI), prasugrel was shown to be superior to clopidogrel for the reduction of ischemic events and early stent thrombosis. Major bleeding, including fatal bleeding unrelated to CABG surgery, was significantly higher in prasugrel-treated patients. Thus, for Canadian ACS patients with identified coronary anatomy warranting PCI, prasugrel 60 mg administered immediately before PCI, followed by 10 mg daily, offers better protection from recurrent ischemic events (including MI) and stent thrombosis than clopidogrel 300 mg followed by 75 mg daily. The consistency of the observed benefit of prasugrel over clopidogrel was observed in subgroups of patients, such as those with STEMI and with a history of diabetes.

Current Canadian practice, based on the results of the CURE trial, is to administer clopidogrel 300 mg in the emergency department, and not to wait until coronary angiography has been performed. The strategy of up-front loading of prasugrel in a medically managed patient population is currently being tested in a large clinical trial with prasugrel [Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRITLOGY ACS); ClinicalTrials.gov Identifier: NCT00699998]. The recent Canadian Cardiovascular Society Antiplatelet Therapy Guidelines 2010 recommend that in patients with ACS who undergo stent implantation and have an increased risk of stent thrombosis (eg, STEMI, history of diabetes, or prior documented stent thrombosis), prasugrel may be preferred over clopidogrel, in addition to ASA for 12 months. However, the recommendations state that prasugrel should be avoided in patients with an increased bleeding risk, likely to undergo CABG within 7 days, and with a history of stroke or transient ischemic attack (absolute contraindication). The 2011 ACC Foundation (ACCF)/AHA-focused unstable angina/NSTEMI update indicates that for patients aged >75 years, or with weight <60 kg, prasugrel had no net benefit and probably should only be used when there are other high-risk features (ie with diabetes or a history of prior MI), in which case, the net benefit appears to be greater.

Ticagrelor is a nonthienopyridine, reversible direct platelet P2Y12 inhibitor not requiring metabolic activation, with a more rapid onset, and more pronounced platelet inhibition than clopidogrel. Ticagrelor is administered twice daily, whereas clopidogrel and prasugrel are administered once daily. In the PLATO study, ticagrelor was superior to clopidogrel in patients across the spectrum of ACS, including NSTEMI patients and those not undergoing revascularization. Either ticagrelor 180 mg (followed by 90 mg twice daily), or clopidogrel 300 mg (followed by 75 mg daily) was administered at the time of randomization (11 hours after symptom onset and 4 hours after hospitalization), which was approximately 4 hours before coronary angiography. In contrast to the TRITON-TIMI 38 study evaluating prasugrel, in the PLATO study patients were allowed to have received clopidogrel prior to study drug randomization (46%), including up to a 600 mg load. Ticagrelor reduced recurrent ischemic events (CV death, MI, stroke) by 16% with no increase in major bleeding or the need for blood transfusion. There was a significant 21% reduction in CV mortality alone, as well as a reduction of in-stent thrombosis, balanced by a significant increase in non-CABG bleeding, and no difference in CABG-related bleeding. Ticagrelor was also superior to clopidogrel in patients undergoing either an invasive or a non-invasive strategy. Due to apparent “off-target” effects, ticagrelor was associated with an increased incidence of dyspnea. However, the dyspnea appears to be transient, self-limited in most cases, and benign (ie, unrelated to changes in cardiorespiratory function). For patients requiring early CABG, discontinuation of ticagrelor returns platelet aggregation to almost normal levels within 4-5 days, in comparison to 5-7 days with clopidogrel, although levels of platelet inhibition remain significantly higher than with clopidogrel in the first 48 hours after stopping the antiplatelet agents. Ticagrelor therapy overcomes nonresponsiveness to platelet inhibition with clopidogrel, and its antiplatelet effect is the same in clopidogrel responders and nonresponders, as defined by various tests measuring platelet aggregation.

For NSTEMI patients, prasugrel use should be restricted to patients who have not received clopidogrel prior to coronary angiography and who require PCI. Ticagrelor, recently approved for use in Canada, is an attractive alternative to clopidogrel in high-risk patients with NSTEMI at the time of first medical contact, as was the case for nearly half the PLATO population. Furthermore, ticagrelor can be used in most ACS situations, except concomitantly with fibrinolysis where it has not yet been tested. However, provincial reimbursement varies widely and currently limits access to new agents such as prasugrel and ticagrelor for many Canadians. An initial Swedish analysis based on the PLATO study showed treatment with ticagrelor compared with generic clopidogrel to be cost-effective. Ticagrelor was associated with a cost per quality-adjusted life years gained in the range of...
ASA, all patients with ACS unless contraindicated
Aldosterone antagonist, Spironolactone or eplerenone
Influenza vaccine, Almost negligible

Table 13. In-hospital and/or discharge medications following ACS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Warnings</th>
<th>Duration</th>
<th>Controversial issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers(^\text{91})</td>
<td>Most patients post ACS; especially with LV dysfunction or residual coronary stenoses</td>
<td>Signs of heart failure</td>
<td>Uncertain; Up to 3 to 4 y based on clinical trial duration; Indefinite with moderate to severe LV dysfunction</td>
</tr>
<tr>
<td>ASA(^\text{92,93})</td>
<td>All patients with ACS unless contraindicated</td>
<td>Active asthma</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel(^\text{74})</td>
<td>Most patients with ACS; alternatives are prasugrel or ticagrelor</td>
<td>Clopidogrel allergy (see text) Platelet genetic polymorphisms Interaction with PPI not conclusive; probably better to use pantoprazole</td>
<td>Post ACS no stent or BMS 12 mo Post ACS DES at least 12 mo</td>
</tr>
<tr>
<td>Prasugrel(^\text{59})</td>
<td>ACS patients. Prasugrel initiated after coronary anatomy defined</td>
<td>Allergy (cross reacts with clopidogrel)</td>
<td>12-15 mo</td>
</tr>
<tr>
<td>Ticagrelor(^\text{76})</td>
<td>ACS patients (not post-thrombolysis)</td>
<td>Dyspnea Ventricular pauses</td>
<td>12 mo</td>
</tr>
<tr>
<td>Statin(^\text{94-96})</td>
<td>ACS independent of lipid profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE(^\text{97-100})</td>
<td>ACS patients with LVEF &lt; 40% Consider for all ACS patients to prevent recurrent MI</td>
<td>Hyperkalemia Hypotension</td>
<td>Lifetime Agreement for LV protection HOPE and EUROPA support use with normal LV function Routine replacement of ACEi for vascular protection Spironolactone or eplerenone</td>
</tr>
<tr>
<td>ARB(^\text{101,102})</td>
<td>ACS patients intolerant of ACEi with LVEF &lt; 40%</td>
<td>Hyperkalemia Hypotension</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Aldosterone antagonist(^\text{105})</td>
<td>ACS with LVEF &lt; 40%</td>
<td>Hyperkalemia Hypotension</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Influenza vaccine(^\text{104})</td>
<td>All ACS patients</td>
<td>Almost negligible</td>
<td>Yearly</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; ACEi, ACE inhibitor; ACS, acute coronary syndromes; ARB, angiotensin receptor blocker; ASA, aspirin; BMS, bare-metal stent; DES, drug-eluting stent; EUROPA, European Trial of Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease; HOPE, Heart Outcomes Prevention Evaluation study; HR, heart rate; LDL, low-density lipoprotein; LV, left ventricular; LVEF, LV ejection fraction; MI, myocardial infarction; PPI, proton pump inhibitor; SBP, systolic blood pressure.

In-Hospital and Discharge Therapy

Patients with ACS are at high risk for recurrent ischemic events especially in the first 30-45 days following their index event, but also over the long-term. Strategies for CV risk reduction with the aim of preventing recurrent ischemic events and heart failure must start early following an ACS. Lifestyle modification (smoking cessation, weight control, exercise, and diet) plays a crucial role in long-term management. Teaching is initiated and strategies discussed to achieve these adjustments while the patient is in-hospital. Referral to a cardiac rehabilitation clinic allows continued reinforcement and support for lifestyle change as well as optimization of treatment goals. The role of allied healthcare professionals including nurses, pharmacists, and dieticians is crucial not only for patient education, but also to ensure consistent adherence to discharge planning strategies.

Medications for long-term risk reduction are shown in Table 13. In addition, blood pressure control and glycemic management remain important. For ACS patients with diabetes and established coronary artery disease, the target for glycemic control is HbA1c < 7%. Recommended blood pressure targets are < 140/90 for most patients and < 130/80 for patients with diabetes and/or chronic kidney disease. A recent study\(^\text{103}\) suggests that influenza vaccine reduces major CV events in patients with ACS.

Acknowledgements


Funding Sources

Publication of this article was supported by AstraZeneca Canada Inc. and Bristol-Myers Squibb Canada and sanofi-aventis Canada.

Disclosures

David Fitchett has received speaker honoraria from and served on advisory boards for Astra Zeneca, sanofi-aventis, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Servier, Boehringer Ingelheim, Abbott, and Roche.

Pierre Theroux has served as a consultant for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Merck, and sanofi-aventis. Dr
Theroux has also received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, and sanofi-aventis, and he has received a research grant from Merck.

James Brophy has no conflicts of interest to disclose.

Warren Cantor has received speaker honoraria from and served on the advisory boards for AstraZeneca, Eli Lilly, and sanofi-aventis.

Jafna Cox has received speaker honoraria from AstraZeneca and served on advisory boards for AstraZeneca and Bristol-Myers Squibb/sanofi-aventis. Dr Cox has also had research funded by Pfizer, served as an expert consultant on the review of ticagrelor/Brillinta by the Canadian Agency for Drugs and Technologies in Health, and served as a scientific advisor to Cardiovascular Health Nova Scotia.

Milan Gupta has received research grants and speaker honoraria from and served on advisory boards for AstraZeneca, Merck, Eli Lilly, Boehringer Ingelheim, sanofi-aventis, Roche, Servier, Abbott, and Bayer.

Heather Kertland has received honoraria or consulting fees from sanofi-aventis, Astra Zeneca, and Eli Lilly.

Shamir Mehta has served as an advisor or consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Portola, and sanofi-aventis. Dr Mehta has also received clinical trial funding from Astellas, Bristol-Myers Squibb, and sanofi-aventis.

Robert Welsh has received research grant support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Portola, and sanofi-aventis. Dr Welsh has also served as a consultant/advisory board member for or speaker honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Medtronic, Roche, and sanofi-aventis.

Shaun Goodman has received research grant support and/or honoraria for consulting/speaking from Actelion, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, Gilead, Glaxo Smith Kline, Johnson & Johnson, KI Pharmaceuticals, Lilly, Merck, Novartis, Pfizer, Roche, sanofi-aventis, Servier, and The Medicines Company.

References


