ONTARIO PHARMACISTS ASSOCIATION
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Therapeutic Options

FOCUS ON ACUTE MYOCARDIAL INFARCTION

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BACKGROUND

Ischemic heart disease, defined as a buildup of plaque in the arteries of the heart, is a significant cause of morbidity and mortality to Canadians, second only to cancer as a leading cause of death. As a subset of ischemic heart disease, acute myocardial infarction (AMI) is often the first indication of heart disease, with an average of 62,000 Canadians annually experiencing a first AMI.[22] The Canadian Chronic Disease Surveillance System examined population data related to ischemic heart disease, including AMI, over a 12 year period (2000-2001 to 2012-2013). In Canadian adults >20 years old, the prevalence of ischemic heart disease initially increased then stabilized over the 12 years, while the number of Canadians with a history of AMI increased from 1.2% to 2.0% (578,000 people). However, the age-standardized incidence rate of AMI decreased by 17%. This increase in prevalence concurrent with a decline in incidence may indicate that fewer people are having AMIs and that more people are surviving them. In people with an AMI, the overall mortality rate from any cause decreased by 35% over the twelve years; however, this rate is still four times greater compared to those with no history of AMI.[1]

Although AMI risk increases with age in both sexes, in Canada, the rate of AMI is 2.5 times more prevalent in men than women. Heart disease, including AMI, occurs 10 years later in women compared with men, likely due to a cardioprotective effect of estrogen in pre-menopausal females.[1] The average age of first AMI is 65 years in men and 72 years in women.[2] After menopause, risk factors such as high cholesterol, hypertension and diabetes become more significant. Among those with a history of AMI, women <75 years of age are more likely to die from any cause compared with men of the same age.[1] Women between 35 to 84 years of age also have a higher in-hospital mortality rate after AMI.[3]

Patients who experience an AMI have a reduced overall long-term survival and quality of life, compared with the general population. A Canadian study found that 7.7% of AMI patients were readmitted within one year for a second AMI, 12.5% for angina and 7.5% for heart failure.[3] Post-discharge medication and rehabilitation are critically important in secondary prevention and ongoing health of the AMI patient.

ETIOLOGY AND PATHOPHYSIOLOGY

Acute coronary syndromes (ACS) represent a spectrum of coronary disease that includes AMI and unstable angina. AMI is subdivided into two types depending on electrocardiograph (ECG) characteristics: ST-elevated myocardial infarction (STEMI), or non-ST-elevated myocardial infarction (NSTEMI). Unstable angina traditionally referred to patients with clinical and ECG evidence of myocardial ischemia in the absence of elevated cardiac enzymes, but more universal utilization of high-sensitivity troponin testing has reclassified the majority of unstable angina cases to NSTEMI, and both are now designated under the term NSTE-ACS.[4] The classification of STEMI versus NSTE-ACS is important as that will determine initial treatment.[5]

A classification system[i] further delineates AMI into five types based on cause. The minority of AMI cases (types 2 through 5) may be caused by coronary dissection, vasospasm, emboli, microvascular dysfunction, or as a result of a cardiac procedure or surgery.[6] The majority of AMI is type 1, caused by atherosclerotic plaque disruption (either rupture or erosion) leading to thrombus development that partially or completely occludes a coronary blood vessel.[4,7] When a vulnerable plaque ruptures, platelets are activated and the coagulation cascade begins. A thrombus forms, and atherosclerotic debris travel downstream potentially causing additional emboli. More vulnerable plaques may be disrupted in this hypercoagulation environment, resulting in multiple intra-arterial lesions. Myocyte death occurs, the severity of which depends on the extent of occlusion of the vessel, duration and number of blockages, volume of heart tissue impacted, and the time to adequate reperfusion.[4] If there is insufficient collateral supply of blood to the tissues, myocyte necrosis begins within 15 minutes.[7]

Patients with STEMI have significantly higher vessel occlusion and consequential left ventricular remodelling with changes in the size, thickness and shape of the left ventricle. Extra load is placed on the remaining functioning myocardium and may lead to additional hypertrophy. Pathophysiological changes in the

i Developed by the Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation (ESC/ACCF/AHA/WHF) in 2018.

Table 1: Risk Factors for Ischemic Heart Disease[11,12]

Non modifiable:
Age - Adults 40 to 75 years
Male sex
Family history of early heart disease - Males <55 years; females <65 years
Post-menopause - Especially premature menopause <40 years
History of pregnancy-associated conditions - Preeclampsia, pre-term delivery
High-risk ethnicity/race - e.g. South Asian ancestry
Modifiable:
Diabetes
Dyslipidemia - LDL-C 4.1-4.8 mmol/L; non-HDL-C 4.9-5.6 mmol/L (primary prevention)
Obesity/Metabolic syndrome - At least three of: elevated triglycerides (>1.7 mmol/DL), abdominal obesity, hypertension, elevated glucose, low HDL-C (<40mg/dL [1.0 mmol/L] men or <50mg/dL [1.3 mmol/L] women)†
Hypertension
Chronic kidney disease - eGFR 15–59 mL/min/1.73 m^2‡
Chronic inflammatory disease - RA, lupus, HIV/AIDS, psoriasis
Psychosocial disorders - Stress, depression
Sedentary lifestyle
Excessive alcohol consumption
Diet low in fruits and vegetables
Smoking

AIDS = Acquired Immunodeficiency Syndrome; eGFR = estimated Glomerular Filtration Rate; HDL=high-density lipoprotein; HIV = Human Immunodeficiency Virus; LDL-C=low-density lipoprotein cholesterol; RA = Rheumatoid Arthritis

† mg/dL was converted to mmol/L using a conversion factor from http://www.scymed.com/en/smnxpb/pbxhb016_c.htm

‡ not on dialysis or post kidney transplantation

heart such as electrical instability and subsequent cardiac arrythmias, pump failure, extra sympathetic stimulation, changes to myocardial structures, aneurysm formation, and/or wall rupture will inform the treatment (pharmacological, catheter-based, surgical) plan.[7]

In contrast to STEMI, angina results from severe stenosis of a vessel of ≥ 70%. These stenoses are generally less susceptible to rupture and usually do not lead to type 1 AMI.[6] A thrombus forms in 35% to 75% of unstable angina or NSTEMI patients; immediate reperfusion is less urgent compared with STEMI patients where thrombus formation is present in 90% of cases.[7]

RISK FACTORS

Modifiable factors account for approximately 90% of the overall risk of ACS. Lifestyle and medical intervention (drug or procedural) have likely equally contributed to the decline in mortality from coronary disease over the past several decades.[8] People with diabetes in particular have three times the risk of ACS and will experience acute coronary events 15 years earlier, on average, compared to those without diabetes.[9] Women with diabetes have a four-fold increased risk of initial ACS compared to women without diabetes. Women with ACS more frequently have comorbidities such as obesity, smoking, depression, kidney disease, and hypertension than their male counterparts.[10]

SIGNS AND SYMPTOMS

Early recognition of common symptoms of AMI results in faster treatment, and better health and survival outcomes.[7,13] However, ACS clinical presentation can be variable.[8,10] Ischemia-induced chest pain, pressure, or tightness are the most common presenting symptoms in men and women. The pain may also present in the shoulder, jaw, or arm.[10] Low grade fever related to inflammation may be present, while tachycardia and sweating may be due to sympathetic activation. Vagal activation causes nausea, vomiting, and bradycardia.[8] Individuals may also experience shortness of breath, anxiety, and weakness. Some individuals may present with cardiac arrest. Atypical presentation without chest pain but some or all of the aforementioned symptoms may occur in as many as one third of AMIs and is more frequent in women, people with diabetes, and older individuals.[6]

An elevated cardiac troponin level is indicative of injury to myocytes; a higher level correlates with increased mortality and AMI recurrence.[8,10] Elevated leucocytes and inflammatory markers such as creatine kinase indicate inflammation. ECG changes will assist in differentiating between STEMI, NSTE-ACS, or undifferentiated chest pain.[8] Elevated cardiac troponin alone is not indicative of AMI but must be considered in combination with symptoms, ECG changes, imaging or angiography for a confirmational diagnosis. In patients with a history of angina, chest pain that is longer in duration than 20 minutes, occurs with limited physical activity, or is a change in duration, severity, or onset, may indicate AMI.[6]

NONPHARMACOLOGIC INTERVENTIONS/PREVENTION

The ACS patient requires significant support with a comprehensive cardiac rehabilitation program to optimize recovery and prevention of subsequent cardiovascular events, particularly recurrent AMI.[17] This strategy includes a gradual return to exercise with an individual plan that considers age, weight, level of fitness, and physical capability.[4] Depression and anxiety are common after AMI, and should be addressed along with any underlying psychosocial issues such as stress.[7,10] Adherence to prescribed drug therapy is critical in the prevention of secondary cardiac events. If applicable, a smoking cessation treatment plan should be started and can reduce the risk of major adverse cardiovascular events by 40%.[8] As well, a target body mass index (BMI) of 18.5-25 and a waist circumference of <100cm (male) or <90cm (female) is ideal. Counselling by a nutritionist can facilitate weight loss goals.[17] Finally, controlling comorbidities such as hypertension and diabetes are important measures in secondary prevention.

PHARMACOTHERAPY

Individuals diagnosed with STEMI or NSTE-ACS are managed differently. For a suspected STEMI, timely revascularization treatment with percutaneous coronary intervention (PCI) is the main treatment goal and should occur within ≤ 120 minutes (ideally ≤ 90 minutes in urban centres) from first medical contact. PCI

Table 2: Therapeutic Options for STEMI/NSTE-ACS[2,4,11,14,16,17,18 ,19,20,21]

Anti-platelet agents

Upon first recognition of ACS symptoms, an individual should chew 162mg to 325mg of non-enteric coated **ASA**. Dual anti-platelet therapy (DAPT) is the combination of aspirin and a $P2Y_{12}$ inhibitor and is recommended for at least one year after AMI, regardless of initial management (medical or PCI) or stent type. **Ticagrelor** has become the preferred $P2Y_{12}$ inhibitor and is considered the standard of care; **clopidogrel** is an alternate choice. A loading dose is administered prior to reperfusion with PCI or fibrinolysis followed by a maintenance dose of ticagrelor 90mg twice daily or clopidogrel 75mg daily for one year.

Recent studies have demonstrated a reduction in recurrent AMI and major adverse cardiovascular and cerebrovascular events when the duration of DAPT was extended beyond 1 year in the PEGASUS-TIMI-54 study using ticagrelor. This benefit was offset by increased bleeding events. The Canadian Cardiovascular Society guidelines recommend extending DAPT up to three years in those patients who tolerate it well for one year post PCI without a major bleeding event, and who are at low risk for bleeding.

If DAPT is extended beyond 1 year, a dose of ticagrelor 60mg twice daily or clopidogrel 75mg daily is recommended. ASA is continued indefinitely.

Anticoagulants

Unfractionated heparin (UFH), **enoxaparin** (LMWH), or **bivalirudin** are recommended for procedural anticoagulation in patients undergoing PCI to reduce the risk of thrombosis.

Dual pathway therapy with ASA 100mg daily and **rivaroxaban** 2.5mg twice daily decreased the cardiovascular composite outcome of death, stroke, or MI in patients with chronic stable coronary artery disease, including those with AMI history, over 23 months. The benefit was at the expense of increased nonfatal bleeding. As an alternative to extended DAPT, dual pathway treatment starting one year after MI may provide a treatment option in patients who are at high risk of ischemic events, particularly stroke, and who have a low risk of bleeding.

In patients with atrial fibrillation (AF), or a left ventricular thrombus, an oral anticoagulant is recommended. Evidence supports the use of **warfarin** for LV thrombus, or a **direct acting oral anticoagulant** (DOAC) in AF. As bleeding risk is increased when a $P2Y_{12}$ inhibitor is combined with an anti-coagulant, careful consideration must be given to the individual clinical situation. It may be prudent to discontinue the ASA early when dual pathway is used.

Beta-blockers

Early administration of a beta-blocker reduces early mortality, infarct size and left ventricular remodelling. Although less evidence is available to support beta-blocker use in NSTE-ACS, generally beta-blockers should be considered for all AMI patients. Preference is to start with an oral (rather than intravenous), short-acting beta-blocker to allow for dose adjustment, and upon hospital discharge, switch to a long-acting formulation for adherence. A cardio-selective agent such as **atenolol** or **metoprolol** is preferred for post-AMI; patients with heart-failure or low ejection fraction should be treated with **carvedilol** or **bisoprolol**. Long-term beta-blocker therapy is recommended for all AMI patients, but optimal duration is unknown. Patients with comorbid conditions such as COPD/asthma, reduced left ventricular ejection fraction, treated heart failure, diabetes, and peripheral artery disease may also gain a survival benefit from beta-blockers despite potential contraindications. A reasonable target heart rate is 55 to 70 beats per minute with a systolic pressure > 90 mmHg.

Lipid-Lowering agents

Aggressive lipid lowering activity with intensive statin therapy has demonstrated a significant reduction in outcomes such as cardiovascular death, nonfatal MI, ischemic stroke, and coronary revascularization, regardless of pre-existing lipid levels. The LDL-C treatment goal is <1.8 mmol/L (Canadian dyslipidemia guidelines 2021). If lipid targets cannot be achieved with a maximum **statin** dose (atorvastatin 80mg or equivalent), **ezetimibe** 10mg should be added. Alternately, a **bile acid sequestrant** may be added if lipid targets are not met, although robust outcome data is not available for this strategy. Lastly, **PCSK9 inhibitors** may further reduce LDL-C by 50% to 60% when added to a statin. Short-term studies have shown improved cardiovascular outcomes with this combination; however, the parenteral format and high cost limit the use of these drugs.

Angiotensin inhibition

ACEIs are recommended in patients with HF or LVEF<40% and in patients with hypertension, diabetes or stable chronic kidney disease. **ARBs** are recommended in patients with HF or LVEF<40% and when ACEIs are not tolerated.

Aldosterone blockade

Aldosterone blockade is beneficial in individuals with HF. **Eplerenone** 25mg to 50mg daily reduced mortality by 15% when given to individuals with HF and LVEF<40% or with diabetes and poor LV function. **Spironolactone** is beneficial when combined with an ACEI and a diuretic.

ACEI=Angiotensin-converting enzyme inhibitor; ACS=acute coronary syndrome; AMI=acute myocardial infarction; ARB=Angiotensin II receptor blocker; HF= Heart failure; LDL-C=low density lipoprotein cholesterol; LMWH=low molecular weight heparin; LV=Left ventricle; LVEF=Left ventricular ejection fraction; PCI=percutaneous coronary intervention; PCSK9=proprotein convertase subtilisin kexin 9

refers to coronary angioplasty with insertion of a balloon or stent to open the artery. If PCI is not available, reperfusion with a fibrinolytic such as tenecteplase, reteplase, alteplase, or streptokinase is recommended at the nearest hospital. The algorithm for pre-hospital and hospital treatment of these patients is multi-faceted and dependent on various elements (such as patient risk factors, time to intervention, availability of PCI, single versus multi-vessel disease) and is beyond the scope of this review. [14] For the majority of patients presenting with NSTE-ACS, PCI treatment is used for reperfusion if available; however, these patients are stratified by risk to determine the urgency of the intervention.[15]

In general, pharmacotherapy may involve a combination of an anti-platelet, an anticoagulant, a beta blocker, a lipid-lowering agent, and an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB). Presented in the table below is the pharmacotherapy typically implemented during hospital stay and continued after discharge for STEMI and NSTE-ACS patients.

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