2013

Acute Coronary Syndromes: Current Treatment Guidelines and Updates

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Recommended Citation

Lau B, Lee M, Tran T, Tsu LV. Acute coronary syndromes: current treatment guidelines and updates. *Arizona Journal of Pharmacy* 2013;40-49.

Acute Coronary Syndromes: Current Treatment Guidelines and Updates

Acute Coronary Syndromes: Current Treatment Guidelines and Updates

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Goal:
This home-study CPE activity has been developed to educate pharmacists on acute coronary syndrome (ACS) and its medical management.

Objectives: At the conclusion of this CPE activity, successful participants should be able to:

1. Identify the type of ACS (STEMI, NSTEMI, or UA) based on imaging and laboratory values.
2. List the recommendations for emergency department management for ACS.
3. Assess the eligibility of patients (STEMI or NSTEMI/UA) for PCI or fibrinolytic therapy.
4. Develop an appropriate pharmacotherapy treatment plan in patients admitted into hospital with ACS (STEMI or NSTEMI/UA).
5. Discuss the medication management for discharge in the patient with ACS.

Introduction

Cardiovascular disease (CVD) is a major leading cause of death worldwide. Acute coronary syndromes (ACS) make up the majority of CVD related mortalities, with more than 1.2 million Americans suffering from some sort of ACS every year.[1] ACS, a result of having coronary heart disease, is very costly to health care and the economy, with direct and indirect costs totaling more than $177 billion in 2010.

Etiology

ACS is a result of occlusion and rupturing of atherosclerotic plaques in the vasculature of the heart.[1] Atherosclerosis is a narrowing of the arteries that involves excess cholesterol and inflammation. The initial stage of this disease begins with an atherosclerotic plaque, or atheroma. These plaques normally occur in humans starting in the adolescent years. They are composed of macrophages that have taken up oxidized low density lipoproteins (LDL). Over time, these macrophages become foam cells, which subsequently become calcified as they become older and less metabolically active. The calcified plaque causes the artery to become stiff, which induces more stress on the arteries when blood flows through them as they are less compliant. As a result, gene regulation is altered and the endothelial cells lining the blood vessels decrease their production of nitric oxide, a potent endogenous vasodilator. The alteration in gene regulation also causes an increase in the rate of oxidation of LDL and enables them to enter the arterial wall. Monocytes also become more adhesive to the arterial wall, which causes smooth cell proliferation and the release of local vasoconstrictors and prothrombotic substances into the blood, resulting in an inflammatory response.

Pathophysiology

The leading cause of ACS in most patients is rupture of an unstable atherosclerotic plaque with subsequent thrombus development resulting in the limitation or interruption of coronary blood flow.[1] In contrast to a stable plaque, an unstable plaque has an irregular shape, a thin fibrous cap, minimal amount of smooth muscle cells and a large lipid core that is highly populated with inflammatory cells such as macrophages and lymphocytes. These inflammatory cells release proteolytic enzymes and cause the thinning of the fibrous cap resulting in a plaque that is more susceptible to tear under constant shear stress. It is also noted that plaques that occlude less than 50% of the diameter of the coronary artery are more likely to rupture than those with a higher degree of occlusion. Following plaque rupture, tissue factor and subendothelial collagen are exposed to the blood components at the site of rupture, leading to platelet adhesion and activation. Activated platelets release thromboxane A2, adenosine diphosphate (ADP), and other vasoactive and prothrombotic substances that further intensify platelet recruitment and aggregation. Additionally, during platelet activation, ADP binds to the $P2Y_{12}$ receptors and induces a conformational change in the glycoprotein (GP) IIb/IIIa receptors located on the surface of platelets, thereby facilitating the binding of fibrinogens responsible for cross-linking other platelets to form a preliminary clot. At the same time, the extrinsic coagulation cascade pathway is also activated by the exposed tissue elements at the site of injury. Thrombin (factor IIa), the final product of this cascade and a potent platelet aggregation agonist, stabilizes the cross-linked platelets by converting the fibrinogen bridges to fibrin, thus trapping the red blood cells to form a stable clot. Other clotting factors also contribute to clot extension by gathering on the anionic surface of activated platelets and promoting more thrombin production. When a thrombus causes complete occlusion of the coronary artery and interruption of coronary blood flow, myocardial ischemia occurs and may lead to necrosis of myocardial tissues (i.e. myocardial infarction or MI). Most ACS cases involve only one ruptured atherosclerotic plaque in a major coronary artery; however, multiple ruptured plaques can occur and may affect more than one coronary artery. ACS patients with multiple coronary artery involvement usually have a worse prognosis.

Types of ACS

The spectrum of ACS encompasses all clinical syndromes related to acute myocardial ischemia as a result of an imbalance between the oxygen supply and demand in the myocardium.[1] As mentioned before, the disruption of oxygen balance is primarily due to diminished myocardial blood flow secondary to one or more occlusive or partially occlusive coronary artery thrombi. The types of ACS are ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). They are classified according to the electrocardiogram (ECG) and cardiac chemical biomarkers. In STEMI, the coronary artery thrombus is completely occlusive and the ST segment on the ECG is elevated. In both NSTEMI and UA, the coronary artery thrombus is partially occlusive and the ST segment on the ECG is depressed or the T wave is inverted. In order to differentiate between NSTEMI from UA, the level of cardiac biomarkers of myocardial necrosis such as troponin I or T, or creatine kinase myocardial band (CK-MB) are obtained from a blood test. NSTEMI differs from UA in that the extent of ischemia is

usually severe enough to cause myocardial necrosis, resulting in the subsequent release of biomarkers from the damaged tissues into the bloodstream. Therefore, elevated level of cardiac biomarkers is often seen in NSTEMI but not in UA.

Diagnosis & Clinical Presentations

Patients typically present to the emergency department with chest pain greater than 20 minutes that radiates to shoulder, left arm, back, or jaw.[1] Atypical symptoms that can also be seen in patients include nausea and vomiting, diaphoresis, and shortness of breath. These atypical symptoms are more common in women, diabetics, and the elderly. A 12-lead ECG should be obtained and interpreted within 10 minutes of presentation to the emergency department with ischemic symptoms. Upon reviewing the findings on the ECG, patients are either classified as having STEMI or NSTEMI/UA, or their complaint may be due to a non-cardiac issue. Since myocardial ischemia in some parts of the heart may not be detected on the surface by the ECG, it is important to review the ECG along with the cardiac biomarkers. Following the onset of myocardial ischemia, an increase in troponin and CK-MB level in the blood can be detected. One set of cardiac biomarkers obtained in the emergency department is often not long enough to detect any changes in the level of the cardiac biomarkers. Therefore, three sets of cardiac biomarkers are usually obtained 6 to 8 hours apart to avoid a false negative result. Further workup and individual patient risk assessment should be included in the definitive diagnosis of ACS.

ACS Treatment

Because time is crucial in stopping the expansion of infarction and tissue death in ACS patients, early treatment goals involves timely restoration of blood supply to the occluded artery in both STEMI and NSTEMI patients, and in the case of UA, prevention of complete occlusion and MI.[1] Other short-term goals include symptom relief and prevention of other MI complications, recurrent MI, and death.

General treatment approaches for all STEMI and intermediate to high risk NSTEMI or UA patients include hospital admission, continuous ECG and vital signs monitoring, glycemic control, pain relief, and bed rest.[1] Upon emergency department arrival, MONA therapy (see below), and beta-blocker therapy if not contraindicated, should be initiated immediately for all ACS patients. Patients should be triaged by ACS type as determined from ECG and laboratory findings, after which subsequent treatment plan is chosen based on individual patient's signs and symptoms and past medical history.

Initial treatment (MONA therapy plus Beta-blocker)

Initial treatment of ACS patients involves the MONA therapy, which stands for Morphine, Oxygen, Nitroglycerin, and Aspirin. Beta-blockers should also be given to patients if not contraindicated with one or more of the following: 1) signs of heart failure, 2) evidence of low cardiac output, 3) increased risk of cardiogenic shock, 4) second or third degree heart block, or 5) active asthma or reactive airway disease.[2,3] Intravenous morphine is administered as an analgesic to patients who continue to have pain refractory to nitroglycerin and also acts as a vasodilator to reduce preload. Oxygen is administered by nasal cannula to patients with oxygen saturation less than 90% for no more than 6 hours. For patients who do not appear at risk of hypoxemia or respiratory distress, excessive use beyond 6 hours can lead to systemic vasoconstriction, and high flow rates can be harmful to patients with chronic obstructive airway disease.[2,3] Nitroglycerin is administered as continuous IV infusion if patients have continued chest pain, and should be titrated to pain relief. However, there are contraindications to the use of nitrates in patients presenting to emergency department with hypotension, marked bradycardia or tachycardia, MI in the right side of the heart, documented use of a phosphodiesterase type 5 inhibitor such as sildenafil or vardenafil within 24 hours or tadalafil within 48 hours. Enteric-coated aspirin must be chewed and swallowed immediately to break the enteric coating to achieve rapid platelet inhibition. Non-enteric coated formulations may be used for more rapid buccal absorption.[2,3] Beta-blockers should be administered orally early in hospitalization and continue indefinitely to help reduce heart rate, blood pressure, and myocardial contractility. The use of beta-blocker can reduce the risk of recurrent ischemia, infarct size, and ventricular arrhythmias following MI. Cardioselective beta-blockers, such as metoprolol and atenolol, are commonly used, but are not required. IV beta-blockers are no longer recommended routinely due to a high risk of cardiogenic shock.[2,3]

Pharmacologic agents for in-hospital management of ACS

Once the patients have been stabilized with MONA therapy, proper treatment for their specific ACS condition needs to be initiated. Drugs used in this process include anticoagulants, antiplatelets, and fibrinolytics. We will outline the mechanism of action and monitoring parameters of these agents prior to discussing each agent's place in therapy.

Anticoagulant Agents

Anticoagulants essentially inactivate clotting factors to prevent thrombus formation and extension.[2,3] The anticoagulant agents that are commonly used in the treatment of ACS include unfractionated heparin (UFH), enoxaparin, fondaparinux, bivalirudin, and warfarin.

UFH inhibits both factor IIa (thrombin) and factor Xa with equal selectivity.[2,3] The dose is adjusted according to activated clotting time (ACT) or activated partial thromboplastin time (aPTT), but initial dose adjustment for renal or hepatic dysfunction is not required. Some contraindications to therapy include active bleeding, a history of heparin-induced thrombocytopenia (HIT), risk of severe bleeding, and recent stroke. The major side effect is bleeding. When the patient is on UFH, the monitoring parameters are bedside monitoring of ACT or aPTT, platelet count, and signs and symptoms of active bleeding.[2,3]

Enoxaparin (Lovenox) is a low molecular weight heparin (LMWH) that inhibits factor Xa more strongly than factor IIa.[3] Dose reduction is required ifcreatinine clearance (CrCl) < 30 mL/min, and it is to be avoided completely if CrCl < 15 mL/min. Some contraindications include active bleeding, history of HIT, risk of severe bleeding, and recent stroke. The major side effects are bleeding and bruising. Monitoring parameters for enoxaparin include serum creatinine, platelet count, and signs and symptoms of bleeding. An advantage of using enoxaparin over UFH is that it can be administered subcutaneously.

Fondaparinux (Arixtra) is a synthetic

pentasaccharide that selectively inhibits factor Xa.[3] Dose adjustment is not required for renal or hepatic impairment, but the use of fondaparinux is contraindicated if CrCl < 30 mL/min. Other contraindications are active bleeding and risk of severe bleeding. Furthermore, it has an increased risk of catheter thrombosis if used as monotherapy. When the patient is on fondaparinux, the monitoring parameters include serum creatinine and bleeding.

Bivalirudin (Angiomax) is a direct thrombin inhibitor that specifically targets thrombin.[3] Dose reduction is required for severe renal impairment, and contraindications are active bleeding and risk of severe bleeding. Also, it has an increased risk of stent thrombosis. Monitoring parameters include serum creatinine and signs and symptoms of bleeding. Bivalirudin monotherapy has a lower risk of bleeding than the combination therapy of UFH or enoxaparin with GP IIb/IIIa inhibitors. However, the combination of bivalirudin with GP IIb/IIIa inhibitors has a higher risk of bleeding without a corresponding increase in efficacy, and therefore is not recommended to use the combination of bivalirudin and GP IIb/IIIa inhibitors.

Warfarin, a vitamin K antagonist, reduces thrombus formation by inhibiting the activation of vitamin K-dependent clotting factors.[1] The dose is adjusted to maintain a target international normalized ratio (INR) of 2 to 3. Some contraindications include active bleeding, risk of severe bleeding, pregnancy (except in pregnant women with mechanical heart valves)and uncontrolled hypertension. The major side effect is bleeding. When the patient is on warfarin, the monitoring parameters are INR and signs and symptoms of bleeding. Warfarin is not commonly used as monotherapy in ACS and should be prescribed for patients with certain indications for warfarin, such as atrial fibrillation, left ventricular thrombus, and mechanical prosthetic heart valves.

Antiplatelet Agents

Aspirin (ASA)

ASA irreversibly inhibits cyclooxygenase-1 (COX-1) and COX-2 enzymes which prevents the formation of prostaglandin derivative, thromboxane-A, thereby inhibiting platelet aggregation.[1] Dose adjustment is not required for renal or hepatic impairment, but avoid using ASA if CrCl < 10 mL/min or in patient with severe liver disease. Some contraindications are active bleeding, hemophilia, severe untreated hypertension, an active peptic ulcer, or another serious source of gastrointestinal or genitourinary bleeding. The major side effect is gastrointestinal bleeding. It is the preferred antiplatelet agent in all ACS scenarios. It should be administered to patients within 24 hours of hospital admission. The patients will be on ASA therapy indefinitely regardless of the type of ACS.

Glycoprotein IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors bind to the GP IIb/IIIa receptors on the platelet preventing platelet aggregation and thrombus formation.[3] The GP IIb/IIIa inhibitors that are used in the treatment of ACS include abciximab, eptifibitide, and tirofiban.[2,3]

Abciximab (ReoPro) does not require dose adjustment for renal or hepatic impairment.[2,3] Some contraindications include active bleeding, thrombocytopenia, prior stroke and severe uncontrolled hypertension. Abciximab, being a monoclonal antibody, has a risk of immune-mediated thrombocytopenia, which can be treated with platelet transfusions as needed for control of bleeding. The major side effect of abciximab is bleeding, so the main monitoring parameters include signs and symptoms of bleeding and platelet counts.

Eptifibitide (Integrillin) requires dose reduction by 50% in patients with CrCl < 50mL/min.[2,3] Some contraindications include active bleeding, thrombocytopenia, prior stroke, renal dialysis and severe uncontrolled hypertension. Patients can be treated with platelet transfusions as needed to control bleeding due to a risk of thrombocytopenia. The major side effect with eptifibatide is bleeding. Monitoring parameters for this drug include signs and symptoms of bleeding, serum creatinine, and platelet counts.

Tirofiban (Aggrastat) requires dose to be reduced by 50% in patients with CrCl < 30mL/min.[2,3] Some contraindications are active bleeding, thrombocytopenia, prior stroke and severe uncontrolled hypertension. Patients can be treated with platelet transfusions as needed to control bleeding due to risk of thrombocytopenia. The major side effect is bleeding. Monitoring parameters for this drug include signs and symptoms of bleeding, serum creatinine, and platelet counts.

$P2Y_{12}$ receptor antagonists

$P2Y_{12}$ receptor antagonists block the $P2Y_{12}$ receptors on platelets which prevents activation of the GP IIb/IIIa receptor complex, thereby reducing platelet aggregation.[3] The $P2Y_{12}$ receptor antagonists that are used in the treatment of ACS include clopidogrel, prasugrel, and ticagrelor.[2,4]

Clopidogrel (Plavix) is the most frequently prescribed $P2Y_{12}$ receptor antagonist. An advantage of clopidogrel is that it does not require dose adjustment for renal or hepatic impairment.[2,3] It has a Black Box Warning against its use in patients who are poor CYP2C19 metabolizers. This is because clopidogrel is a prodrug that requires a two-step conversion to an active metabolite, and the effectiveness of the drug is dependent on its activation to an active metabolite by CYP2C19. Poor CYP2C19 metabolism results in a smaller antiplatelet effect and an increased risk of cardiovascular events. Some contraindications are hypersensitivity to clopidogrel, active bleeding, and risk of severe bleeding. The major side effect is bleeding.

Prasugrel (Effient) also does not require dose adjustment for renal or hepatic impairment.[2,4] It is also a prodrug, but it requires only a one-step conversion to active metabolite. Some contraindications with prasugrel include history of transient ischemic attack (TIA), stroke, and active bleeding. It has a FDA-labeled warning against its use in patients greater than 75 years old or with a weight less than 60kg due to concerns of an increased risk of fatal and intracranial bleeding. Prasugrel is most beneficial when used in STEMI and diabetic patients.

Ticagrelor (Brilinta) is the most recently approved $P2Y_{12}$ receptor antagonist. It must be administered with a low ASA maintenance dose (less than 100mg daily). Some contraindications include hypersensitivity to ticagrelor, active bleeding, and history of intracranial hemorrhage. Caution should be taken in patients when taking ticagrelor with CYP3A4 inducers or inhibitors. The major side effects of this drug include bleeding and dyspnea.

Fibrinolytic Agents

Fibrinolytics work by degrading existing

fibrin clots to open up the blockage in the arteries in order to increase blood flow.[1] In NSTEMI/UA patients, fibrinolytic therapy is not recommended as clinical trials showed no significant benefit and an increased risk of MI and death.[3] Fibrinolytic therapy is recommended in STEMI patients who do not have timely access to a cardiac catheterization laboratory.[2] Available fibrinolytics differ based on their fibrin-specificity; streptokinase is non-specific, whereas tenectaplase, reteplase and alteplase have a higher fibrin-specificity.[1]

Streptokinase non-selectively binds to either free-flowing or fibrin-bound plasminogen and converts it to plasmin.[5] Plasmin is a proteolytic enzyme that dissolves the fibrin in the blood clot. Dose adjustment is not required for renal or hepatic impairment.[2] Absolute contraindications to fibrinolysis include history of hemorrhagic stroke, ischemic stroke within 3 months, known malignant intracranial neoplasm or arteriovenous malformation, active internal bleeding, suspected aortic dissection, or significant facial or closed head trauma in the last 3 months. Relative contraindications to fibrinolysis include history of prior ischemic stroke more than 3 months ago, significant hypertension with blood pressure over 180/110 mmHg, recent trauma, major surgery within 3 weeks, internal bleeding within 2 to 4 weeks, oral anticoagulant therapy, active peptic ulcer or pregnancy. The major side effect is bleeding. When the patient is on streptokinase, the monitoring parameters include performing a complete blood count (CBC), aPTT, and watching for signs and symptoms of bleeding. Streptokinase has a higher risk of systemic bleeding than the fibrin-specific fibrinolytics.

Tenecteplase, reteplase, and alteplase all selectively bind to plasminogens that are bound to fibrin and convert them to plasmin.[5] Dose adjustment is not required for renal or hepatic impairment. The major side effect for these drugs as with all fibrinolytics is bleeding.[2] Contraindications and monitoring parameters are the same as non-fibrin-specific fibrinolytics. These fibrin-specific fibrinolytics have higher risk of ICH than streptokinase.

STEMI Treatment

STEMI patients are at the highest risk of death according to the Global Registry of Acute Coronary Events (GRACE) report, so initial therapy should be started immediately for these patients, regardless of cardiac biomarkers levels.[1] All STEMI patients should be evaluated for reperfusion therapy immediately upon arrival at the emergency department. Fibrinolytic therapy or primary percutaneous coronary intervention (PCI) is considered first line treatment for restoring coronary artery blood flow in STEMI patients. Primary PCI is generally deemed superior to fibrinolytics due to lower stroke and bleeding risk, lower mortality rate, and higher success rate in opening up an occluded coronary artery than the latter. Timing of treatment is also crucial to patient survival and reducing the extent of damages to the infarcted myocardium. For STEMI patients presenting to a hospital with a cardiac catheterization laboratory, PCI should be performed within 90 minutes of initial presentation.[2] If the hospital is not equipped to perform primary PCI, the next treatment choice should be selected based on individual patient risks such as the time from onset of symptoms, risk of STEMI complications, risk of bleeding with fibrinolysis, presence of shock or severe heart failure, and the time required for transfer to a PCI-capable hospital. Ideally, all patients should be transferred to a PCI-capable hospital immediately if the procedure can be performed within 120 minutes of first medical contact. If the anticipated time for inter-hospital transfer exceeds the target goal, fibrinolytic therapy should be chosen as the primary reperfusion therapy in the absence of contraindications. If appropriate, fibrinolytic agents should be administered within 30 minutes of hospital arrival.

Primary PCI

PCI is a minimally invasive revascularization procedure that is performed by skilled interventional cardiologists in hospitals equipped with a cardiac catheterization laboratory.[6] The procedure can be for diagnostic or interventional purposes, depending on whether revascularization is performed. The initial procedure involves cardiac catheterization whereby access to coronary arteries is commonly obtained through the femoral or radial artery up the aorta to the suspected occlusion site. After inserting the diagnostic catheter, coronary angiography is performed by injecting contrast dye into the blood to visualize the coronary arteries and determine narrowing and blockages of vessels. If, upon examination, an occlusion site is identified and revascularization is indicated, balloon angioplasty can be performed with the help of a guidewire. Balloon angioplasty works by dilating the occluded artery with an inflatable balloon, thereby compressing the atherosclerotic plaque into the vessel wall in order to restore coronary perfusion. Most often, a coronary stent is deployed and left in place to prevent acute closure of the artery. Common types of stents include bare metal stents (BMS) or drug-eluting stents (DES), which are coated with an antiproliferative agent such as sirolimus or paclitaxel. The most common complication of angioplasty is restenosis (i.e. a renarrowing of a previously dilated coronary stenosis). It occurs most frequently in patients with angioplasty without stent placement, less frequently with BMS, and least frequently with DES. DES implantation decreases restenosis rates and the need for subsequent target vessel revascularization owning to the anti-proliferative effect of the coated drugs that helps to retard and minimize cell growth. Despite the advantage of DES over BMS, it is also associated with a higher risk of stent thrombosis, so patients must be adherent to dual antiplatelet therapy for one year following the procedure. If patients are unable to commit to the dual antiplatelet regimen due to factors such as a high risk of bleeding, patient incompliance, or anticipated invasive or surgical procedures in the next year, BMS should be considered as an alternative.[2] Because PCI is an invasive procedure, all patients should receive antithrombotic therapy to prevent thrombotic complications. The regimen should include antiplatelet agents such as ASA, a $P2Y_{12}$ receptor antagonist, and a GP IIb/IIIa inhibitor. In addition, adequate anticoagulation should be achieved throughout the duration of the procedure to prevent thrombosis of the catheter, guidewire, and other thrombotic complications.

ASA should be administered early to all patients without contraindications, most often included in the MONA therapy upon emergency room arrival and within 24 hours of hospital admission, and continued indefinitely after the procedure.[2] High-dose ASA is preferred for patients

undergoing primary PCI in order to achieve a rapid antiplatelet inhibition. If a stent is implanted, patients should continue high-dose ASA for a definite period of time based on the type of stent selected and switch to low-dose ASA thereafter. Low-dose ASA is generally recommended for maintenance due to the lack of clinical efficacy and risk of major bleeding, particularly gastrointestinal bleeding, that is associated with high dose ASA.

Since ASA only inhibits platelet aggregation through one pathway, it does not provide sufficient antiplatelet effect when used alone. Therefore, concomitant administration of a $P2Y_{12}$ receptor antagonist, such as clopidogrel, prasugrel, or ticagrelor, is recommended.[2] In order to achieve faster platelet inhibition effects, a loading dose should be provided to STEMI patients as early as possible or at the time of primary PCI. Following PCI, $P2Y_{12}$ receptor inhibitor therapy should be continued on a maintenance dose for at least 14 days for patients without a stent and up to 1 year for patients with either a BMS or DES implanted in the absence of bleeding complications. In general, selection of a $P2Y_{12}$ receptor antagonist should be based on patient's bleeding risk, genetic predisposition, comorbidities, and additional contraindications for individual agent. Among the $P2Y_{12}$ inhibitors, clopidogrel has the longest history of use for treatment of ACS. Nonetheless, due to the pharmacokinetics of clopidogrel, patients who carry a certain allele of the CYP450 enzyme may have reduced capabilities to metabolize the drug, leading to significant lower levels of active metabolites and diminished platelet inhibition. Consequently, clopidogrel may be undesirable for these patients. Newer agents such as prasugrel and ticagrelor had demonstrated greater efficacy in platelet inhibition and improved patient outcome comparing to clopidogrel in their corresponding landmark trials, namely TRITON-TIMI 38 and PLATO respectively.[7,8]

GP IIb/IIIa inhibitors work on the final common pathway of platelet aggregation and provide additional platelet inhibition when used in combination with other antiplatelet agents. The adjunctive use of GP IIb/IIIa inhibitors in STEMI patients at the time of PCI should be considered on an individual basis and should depend on factors such as choice of anticoagulant, presence of large thrombus, or inadequate $P2Y_{12}$ receptor inhibitor loading.[2] While GP IIb/IIIa inhibitors may be used together with either UFH or enoxaparin, co-administration with bivalirudin should be avoided if possible due to increased risk of major bleeding. If abciximab or tirofiban is chosen, a bolus dose should be administered prior to continuous IV infusion. For eptifibatide, two boluses should be given 10 minutes apart prior to continuous IV infusion. Dosing adjustment is required for eptifibatide and tirofiban in patients with renal dysfunction. For patients presenting with severe renal or hepatic impairment, abciximab may be a better alternative since no dose adjustment is necessary. Following PCI, abciximab can be continued for up to 12 hours, eptifibatide for 12 to 18 hours, and tirofiban for up to 18 hours at the discretion of the physician.[9]

Anticoagulants that are recommended for STEMI patients undergoing primary PCI include UFH and bivalirudin.[2] UFH has a long standing history of use in STEMI and is the most common anticoagulant used in cardiac catheterization laboratory.[1] One advantage of UFH over other anticoagulants is the availability of an antidote (i.e. protamine), which is very useful if a reversal of anticoagulation is necessary. Intensity of anticoagulation, which can be easily monitored at the bedside with ACT, is often dependent on whether a GP IIb/IIIa inhibitor has been administered. Additional boluses may be given as needed to maintain therapeutic ACT levels. Due to bleeding concerns, frequent monitoring is required and is often deemed a limitation for its use. For patients with a contraindication for UFH or are at high risk of bleeding, bivalirudin may be a reasonable alternative to UFH. Bivalirudin has been shown to have a lower bleeding risk than combination of UFH and a GP IIb/IIIa inhibitor, making it the preferred agent for STEMI patients at high risk of bleeding.[2] However, bivalirudin has also been associated with increased risk of acute stent thrombosis.[10] Since the majority of patients receiving PCI have stent placement, bivalirudin should be reserved for those with HIT, higher risk of bleeding, or when the use of GP IIb/IIIa inhibitors is undesirable.[2] Other anticoagulants such as enoxaparin and fondaparinux may be used in primary PCI in certain ACS settings although they are not specifically recommended as first line anticoagulants in primary PCI. Enoxaparin may be continued uninterrupted during rescue PCI in patients who received enoxaparin with prior fibrinolytic therapy.[2] A supplemental IV dose of enoxaparin should be administered if the last dose was administered between 8 and 12 hours earlier. After 12 hours, patients should either receive a full dose of enoxaparin or switch to UFH or bivalirudin for anticoagulation. Fondaparinux should not be used alone because it does not provide adequate anticoagulation for PCI and is associated with higher risk of catheter thrombosis.[2] Therefore, a second anticoagulant like UFH or bivalirudin should be administered together if fondaparinux is to be selected for specific reasons. Regardless of choice of anticoagulant, anticoagulant therapy should be discontinued immediately after PCI to avoid bleeding complications.

Fibrinolysis

Fibrinolytic therapy is recommended for STEMI patients who are ineligible for PCI and present to hospital within 12 hours of the onset of chest discomfort.[2] This time frame has been shown to be most beneficial in decreasing the incidence of mortality. For STEMI patients presenting to the hospital within 12 to 24 hours of symptom onset, fibrinolytic agent may be administered if they experience ongoing ischemia. Because fibrinolytic agents work by dissolving existing clots, patients at high risk of bleeding should be assessed for absolute and relative contraindications (as described previously) prior to administration.[1] While patients presenting with any absolute contraindication are precluded from receiving fibrinolytic therapy, patients presenting with a relative contraindication may still receive treatment if the risk of death from MI outweighs the risk of major bleeding. Special consideration should be taken in patients over 75 years of age. Although the use of fibrinolytics in this age group is not recognized as a contraindication, this patient population has a higher MI mortality rate associated with fibrinolytic use compared to a younger patient population. Therefore, careful dosing efforts should be made to prevent bleeding when administering fibrinolytic and anticoagulation therapies to these patients. In terms of selection of

a fibrinolytic agent, fibrin-specific agents such as tenecteplase, reteplase, or alteplase are preferred over non-fibrin-specific agent like streptokinase. All fibrinolytic agents may potentially cause major bleeding including intracranial hemorrhage (ICH).

Regardless of the choice of a fibrinolytic agent, adjunctive antithrombotic therapy, such as anticoagulant and/or antiplatelet therapies, should be initiated for STEMI patients receiving fibrinolytic therapy.[2] Antiplatelet therapy with fibrinolysis includes both ASA and clopidogrel, which should be administered before or with the fibrinolytic agent. ASA should be continued indefinitely following fibrinolytic therapy. Clopidogrel should be continued for at least 14 days and up to 1 year based on individual patient's risk of reinfarction. Currently, prasugrel and ticagrelor are not recommended to be administered with fibrinolytics because these agents have not been studied with fibrinolytic therapy. GP IIb/IIIa inhibitors are also not recommended for use with fibrinolytics. Furthermore, patients should receive an anticoagulant in addition to their fibrinolytic regimen in order to minimize vessel obstruction and prevent re-occlusion. Enoxaparin is the preferred agent for anticoagulation with fibrinolytic therapy. However, other anticoagulants such as UFH and fondaparinux are also good alternatives. The selected anticoagulant should be continued for a minimum of 48 hours, up to 8 days or until revascularization is performed.

In the event of re-occlusion or failed reperfusion after fibrinolytic therapy, patients may show ongoing ischemic symptoms, or worst, develop cardiogenic shock or acute severe heart failure.[2] These patients are at high risk of mortality, and are good candidates for a rescue PCI and should be transferred to a PCI-capable hospital immediately. If these patients have not received a previous loading dose of clopidogrel with fibrinolytic therapy, a supplemental loading dose should be given before or at the time of PCI.

Coronary Artery Bypass Graft Surgery (CABG)

CABG is a surgical alternative to PCI or medical management for severe coronary artery disease.[2] The indications for CABG are based on severity of ischemia, coronary anatomy, and left ventricular function. In the setting of STEMI, major indications for CABG include patients with multi-vessel (> 3) disease, significant left anterior descending artery stenosis, cardiogenic shock, or failed primary PCI.[11] A number of clinical trials have found CABG to be superior to aggressive medical management or PCI in the long term survival of high risk patients.[12,13] The surgery is performed by cardiothoracic surgeons rather than cardiologists. During the surgical procedure, an artery (internal mammary or radial) or vein (usually the saphenous) harvested from another part of the body is used to form a connection between the aorta and the section of the coronary artery distal to the occlusion site, and consequently, bypassing the occluded area and restoring coronary blood flow.[14] Although this type of surgery most often requires a cardiopulmonary bypass machine, it may be performed "off-pump" by skilled cardiac surgeons and can significantly reduce serious bleeding and thrombotic complications (stroke, MI) after the procedure.[11]

Since CABG is an invasive procedure and puts the patients at high risk of bleeding, all antiplatelet agents, except for ASA, should be withheld before the procedure.[11] Preoperative ASA use has been shown to reduce operative morbidity and mortality rates in CABG patients. In contrast, use of $P2Y_{12}$ receptor antagonists is associated with increased rates of major bleeding which necessitates blood transfusions in post-CABG patients. Therefore, patients undergoing urgent CABG should discontinue clopidogrel and ticagrelor for at least 24 hours prior to surgery. Often, CABG may be an elective surgery for certain patients with high risk of severe MI. In these patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days and prasugrel for at least 7 days to decrease major bleeding complications. Other IV antiplatelet agents such as eptifibatide and tirofiban should be withheld for at least 2 to 4 hours and abciximab for at least 12 hours before surgery to limit blood loss and transfusions. During the surgery, adequate anticoagulation should be maintained with UFH per institutional practice.[3] In the absence of contraindications, beta-blockers should be given 24 hours before CABG to decrease the incidence of postoperative atrial fibrillation. Because the CABG procedure puts the patient at increased risk of developing wound or systemic infections, prophylactic antibiotics (a first or second generation cephalosporin with or without MRSA coverage) should be given to all patients. In addition, tight postoperative glycemic control and lipid management are necessary to ensure the best possible outcome for all patients.

NSTEMI/UA Treatment

Invasive vs. Conservative Strategy

Initial treatment of NSTEMI/UA involves the use of the Thrombolysis In Myocardial Infarction (TIMI) scoring system.[1] This system calculates the risk of composite endpoint of death, MI, or urgent need for revascularization within 14 days. One point (1) is assigned if the patient has each of the following: age greater than 65, three or more cardiac risk factors (HTN, DM, hyperlipidemia, smoking, family history), known history of CAD (greater than 50% stenosis seen on angiogram), two or more episodes of chest discomfort in the last 24 hours, ASA use within the last 7 days, elevated cardiac biomarkers, and ST-segment deviation on an ECG. These criteria are serious risk factors for developing either an MI, death, or urgent revascularization within the next 14 days. Patients presenting with multiple criteria should be treated urgently with an invasive strategy. ASA should be initially given to NSTEMI/UA patients, with a loading dose of clopidogrel, prasugrel, or ticagrelor being as a substitute if ASA is intolerant to the patient.[4]

Initial Invasive Strategy

An initial invasive strategy involves cardiac catheterization, usually within 4 to 24 hours following hospital admission, followed by either revascularization with PCI or CABG.[3] This strategy is recommended for patients with a moderate to high risk of an event according to their TIMI score and other high risk features such as patients who have refractory angina, hemodynamic or electrical instability, or initially stabilized NSTEMI/UA with an elevated risk for clinical events.[4] Patients with definite NSTEMI/UA who are at moderate to high risk should be given dual antiplatelet therapy upon presentation, with ASA being one of the agents.[3] The choice for the second antiplatelet agent can be either clopidogrel, prasugrel, ticagrelor, and a GP IIb/IIIa inhibitor (tirofiban and eptifibatide being the preferred agents).[4] These agents are to be given either before PCI or at

the time of PCI. This is to reduce the risk of ischemic events that may occur during PCI, as trauma frequently occurs during these types of procedures. This results in platelet activation, aggregation, and subsequently a coronary thrombosis. Anticoagulants are needed in invasive strategies because they limit thrombotic complications of ischemic events, especially during angioplasty. They also help prevent thrombosis of catheters and guidewires used during these procedures. Depending on the results of the diagnostic angiography, there are three possible post-angiography management strategies one can initiate, depending on the findings of the angiography: CABG, PCI, or medical therapy.[3]

CABG

CABG surgery is strongly recommended in NSTEMI/UA patients with significant left main coronary artery disease (CAD), 3-vessel disease, 2-vessel disease, or when PCI is not optimal or possible.[11] If CABG is selected, continue ASA therapy; discontinue clopidogrel for least 5 days, prasugrel for at least 7 days, and ticagrelor for at least 5 days prior to CABG procedure.[4] ASA is used to provide antiplatelet therapy during the procedure, while the other antiplatelets are discontinued as they incur a serious risk of bleeding.[3] Prasugrel has an earlier discontinuation time than clopidogrel and ticagrelor because it has a much higher risk of bleeding than those two agents. Intravenous GP IIb/IIIa inhibitors (eptifibatide and tirofiban) must also be discontinued 2 – 4 hours prior to CABG procedure. UFH is to be continued, while enoxaparin must be discontinued 12 to 14 hours, fondaparinux 24 hours, and bivalirudin 3 hours prior to CABG.

PCI

PCI is recommended for NSTEMI/UA patients with 1- or 2- vessel CAD and multi-vessel coronary disease with suitable coronary anatomy.[3] If PCI is selected, ASA is to be continued. A loading dose of clopidogrel, prasugrel, or ticagrelor, and/or GP IIb/IIIa should be given if not given prior to angiography.[4] GP IIb/IIIa inhibitors are highly recommended in addition to ASA and $P2Y_{12}$ inhibitors in PCI patients to reduce morbidity and mortality based on several randomized control trials. A study involving abxicimab or placebo given to patients showed that the patient group receiving abxicimab in addition to clopidogrel showed a significant reduction in the primary end points of death, nonfatal reinfarction, or urgent target-vessel vascularization within 30 days.[15] Once PCI is completed, anticoagulant therapy can be discontinued.[3]

Medical Therapy

Medical therapy is recommended for post-angiographic NSTEMI/UA patients with no signs of significant obstructive CAD on angiography.[4] Antiplatelet and anticoagulant therapy is used in these patients at a physician's discretion. If CAD is detected on angiography, ASA should be continued.[3] A loading dose of clopidogrel or ticagrelor should be given to provide a rapid antiplatelet effect if not given prior to angiogram, as maintenance doses require a few days to achieve full effect. Prasugrel is not recommended because it has only proven benefit in patients undergoing PCI. IV GP IIb/IIIa inhibitors should be discontinued after at least 12 hours if it was started before the angiogram. IV UFH should be continued for at least 48 hours or enoxaparin or fondaparinux for the duration of hospitalization, up to 8 days. Bivalirudin can be continued at a dose of 0.25 mg/kg/hr for up to 72 hours at a physician's discretion if it was given prior to diagnostic angiography.

Initial Conservative Strategy

An initial conservative treatment strategy is recommended for NSTEMI/UA patients with a low stratified TIMI risk score.[4] This treatment strategy involves initial medical management, followed by catheterization and revascularization if an ischemic event occurs despite active drug treatment. Patients presenting with a low risk of death, MI (either initial or recurrent), or refractory angina are usually evaluated in the emergency department. Serum biomarkers are obtained from the patient, and if they are negative for these biomarkers, the patient may be directed to a general medical area to undergo ECG monitoring for any ischemic events or arrhythmias. In addition, a stress test, such as an exercise stress test, can be performed. If there are positive findings in the stress test, diagnostic angiography should be performed.

For these low risk patients, ASA should be initially given, along with either clopidogrel or ticagrelor (loading dose followed by daily maintenance doses) as soon as possible after admission.[4] ASA is to be continued indefinitely while clopidogrel or ticagrelor should be continued for one month and up to 12 months. If the patient is stable and their symptoms are controlled, they can be discharged with recommended antiplatelet therapy such as clopidogrel or ticagrelor for a duration ranging from one month to one year.

If an ischemic event does occur while the patient is on drug therapy, an angiography should be performed, and invasive strategies (CABG, PCI, or medical therapy for CAD) are initiated.[4] Prior to angiography, either an IV GP IIa/IIIb inhibitor (tirofiban or eptifibatide) or a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor, loading dose followed by daily maintenance doses) should be added to ASA and anticoagulant therapy.

Discharge Medications and Secondary Prevention

Once a patient has received appropriate treatment for ACS and is recovering, it is imperative that they be put on appropriate medications for secondary prevention of ischemic events prior to discharge.[1] ACS patients should be on ASA indefinitely, in addition to a beta-blocker and statin therapy. ASA has been shown in a large number of clinical trials to decrease the risk of death, recurrent MI, and stroke following an MI.[3] If the patient is unable to take ASA due to contraindications, clopidogrel is recommended. All patients should be given sublingual nitroglycerin (SL NTG) tablets or a lingual nitroglycerin spray in the event if they experience recurrent chest pain and discomfort. Beta-blockers are recommended indefinitely because they have been shown to decrease the incidence of recurrent MI. However, they are contraindicated in HF patients with acute decompensation. ACE inhibitors are indicated in patients who are not at blood pressure goals on beta-blocker therapy, as well as patients with a reduced ejection fraction or diabetic patients. Angiotensin II receptor blockers can be given if the patient suffers from ACE inhibitor induced angioedema. According to ACC/AHA guidelines, the goal blood pressure for HTN patients with ACS is 130/80 mmHg. In addition, it is imperative that ACS patients receive lipid-lowering agents such as statins, as they are

used to prevent total mortality and stroke. Furthermore, all ACS patients should be provided appropriate pharmacological and non-pharmacological therapy to achieve a goal LDL level of less than 100 mg/dL.

Other modifiable risk factors such as diabetes mellitus and smoking are also important in secondary prevention of ACS. According to ADA guidelines, the goal HgB A1c level for ACS patients with diabetes is < 7%. Smoking cessation is correlated with a significant reduction in all-cause mortality in all ACS patients, and can be achieved by various products such as varenicline or nicotine patches/gums. Proper diet and exercise is also important, as maintaining an ideal weight is essential in preventing the reoccurrence of ACS events.

In certain patients with atrial fibrillation with a $CHADS_2$ score of greater than or equal to 2, mechanical heart valves, venous thromboembolism, or a hypercoagulable disorder, warfarin may be indicated.[2] Co-administration of warfarin and dual antiplatelet therapy may put patients at high risk of severe bleeding. Therefore, the duration of use should be limited to the extent of anticoagulation deemed necessary. A lower INR goal (2.0 – 2.5) should also be considered.

Conclusions

Acute coronary syndromes contribute to a significant number of cardiovascular related deaths in the US.[1] Pharmacists have an important role in managing the disease state for the patient from the beginning in the emergency room to discharging the patients from the hospital. Pharmacists need to be vigilant in selecting the most appropriate therapy for their patients based on the type of ACS and patient specific factors in order to help reduce the risk of developing side effects and complications, re-infarction, and most importantly, death. Pharmacists are an integral part of the health care team that can provide dosing and monitoring recommendations for medications, as well as provide education to patients to prevent recurrent cardiac events.

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Score	Composite endpoint of MI, death, or urgent revascularization	Risk
0 - 1	4.7%	Low
2	8.3%	
3	13.2%	Moderate
4	19.9%	
5	26.2%	High
6 - 7	40.9%	

Source: Adapted from information found in reference **1**

	Agents	Goals of Therapy
Blood Pressure	Beta-blocker (BB) Non-DHP CCB (if intolerant to BB) ACE inhibitors (ACEi) Aldosterone Antagonists (AA)	< 130/80 mmHg ACEi and AA if LVEF < 40%
Lipid Management	Statins	LDL < 100 mg/dL
Diabetes	Various	HgB A_{1c} < 7% (ADA Guidelines)
Smoking Cessation	Various	No smoking
BMI	Exercise 5-7 times/week	18.5 – 24.9 kg/m^2

Source: Adapted from information found in reference **1,3**

Table for Continuing Education Article - Acute Coronary Syndromes: Current Treatment Guidelines and Updates

Source: Adapted from information found in references 1,2,11,16.

DDI indicates drug-drug interaction; ICH, intracranial hemorrhage; CBC, complete blood count; aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; ACT, activated clotting time; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; PCI, percutaneous coronary intervention; LMWH, low molecular weight heparin; SCr, serum creatinine; CrCl, creatinine clearance; SC, subcutaneous; CABG, coronary artery bypass graft; BBW, black box warning; PO, per os (by mouth); BMS, bare metal stent; DES, drug eluting stent.

Full article, including charts, is available for download on the AzPA website in the Journal archives.

ST-elevation myocardial infarction (STEMI)

	Drug	Procedure[ACC/AHA Guideline Recommendations]	Dose Adjustment	Warnings / DDI/ Contraindications*	Monitoring	Dose and Duration of Therapy
Fibrinolytics	Alteplase (tPA) {*Activase®*}	Fibrinolytic therapy ≤ 30 min of hospital arrival [IB]	No	▪ Prior ICH* ▪ Known structural cerebrovascular lesions, such as arterial venous malformation* ▪ Known intracranial malignant neoplasm* ▪ Ischemic stroke ≤ 3 months* ▪ Active bleeding* (excluding menses) ▪ Significant closed head or facial trauma ≤ 3 months*	▪ CBC ▪ aPTT ▪ Bleeding	▪ 15 mg IV bolus, followed by 0.75 mg/kg IV (max 50 mg) over 30 min, then 0.5 mg/kg (max 35 mg) over 60 min (max dose = 100 mg)
	Reteplase (rPA) {*Retavase®*}	Fibrinolytic therapy ≤ 30 min of hospital arrival [IB]				▪ 10 unit IV x 2, 30 min apart
	Tenecteplase (TNK-tPA) {*Tnkase®*}	Fibrinolytic therapy ≤ 30 min of hospital arrival [IB]				▪ < 60 kg: 30 mg IV bolus 60 – 69 kg: 35 mg IV bolus 70 – 79 kg: 40 mg IV bolus 80 – 89 kg: 45 mg IV bolus > 90 kg: 50 mg IV bolus
	Streptokinase {*Streptase®*}	Fibrinolytic therapy ≤ 30 min of hospital arrival [IB]				▪ 1.5 MU (million units) IV over 60 min
Anticoagulants	Unfractionated Heparin (UFH)	Fibrinolytic therapy [IC]	No	▪ Active bleeding* ▪ History of HIT* ▪ Risk of severe bleeding ▪ Recent stroke	▪ aPTT: 50 – 70 sec ▪ ACT: 200-300 sec (with GPI); 250-350 sec (no GPI) ▪ HIT ▪ Bleeding	▪ 60 units/kg IV bolus, then 12 units/kg/hr IV infusion ▪ Continue for 48 hours
		PCI [IC]				▪ With GPI: 50-70 units/kg IV bolus No GPI: 70-100 units/kg IV bolus ▪ Discontinue at the end of PCI
	Enoxaparin (LMWH) {*Lovenox®*}	Fibrinolytic therapy [IA]	Reduce if CrCl < 30 mL/min	▪ Active bleeding* ▪ History of HIT ▪ Risk of severe bleeding ▪ Recent stroke ▪ Avoid if CrCl < 15 mL/min ▪ Avoid if CABG surgery	▪ SCr ▪ HIT ▪ Bleeding	▪ < 75 y.o.: 30 mg IV bolus, then 1mg/kg SC every 12 hr > 75 y.o.: 0.75 mg/kg SC every 12 hr ▪ Continue for the duration of hospitalization (up to 8 days)
		PCI after fibrinolytic therapy [IB]				▪ 1 mg/kg SC every 12 hours (if last dose > 8 hours prior to PCI, administer 0.3 mg/kg IV bolus) ▪ Discontinue at the end of PCI
	Fondaparinux {*Arixtra®*}	Fibrinolytic therapy [IB]	No	▪ Active bleeding* ▪ Risk of severe bleeding ▪ Avoid if CrCl < 30 mL/min ▪ Increase risk of catheter thrombosis if used as monotherapy	▪ SCr ▪ Bleeding	▪ 2.5 mg IV, then 2.5 mg SC daily ▪ Continue for the duration of hospitalization (up to 8 days)
		PCI [III, B] *not as monotherapy*				▪ 2.5 mg IV, then 2.5 mg SC daily (**MUST** administer UFH 50-60 units/kg IV bolus prior) ▪ Discontinue at the end of PCI
	Bivalirudin {*Angiomax®*}	PCI [IB] *can be used in place of UFH + GPI if high risk of bleeding [IIa, B]*	Severe renal function	▪ Active bleeding* ▪ Risk of severe bleeding ▪ Increase risk of stent thrombosis	▪ SCr ▪ Bleeding	▪ 0.75 mg /kg IV bolus, then 1.75 mg/kg/hr IV ▪ Discontinue at the end of PCI
Antiplatelets	Aspirin (ASA)	Initial treatment after hospital admission [IB]	No	▪ Hypersensitivity ▪ Active bleeding ▪ Risk of severe bleeding	▪ Bleeding	▪ 162-325 mg before PCI, then 81 mg maintenance dose daily indefinitely ▪ If a stent is placed after PCI, continue 162-325 mg daily - for a minimum of 30 days (bare metal stent) - for 3 months (sirolimus-eluting stent) - for 6 months (paclitaxel-eluting stent) - then continue 75-162 mg daily indefinitely
	Abciximab {*Reopro®*}	PCI [IIa, A]	No	▪ Active bleeding* ▪ Thombocytopenia* ▪ Prior stroke ≤ 2 years*	▪ SCr ▪ Platelet count ▪ Bleeding	▪ 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion ▪ Continue for up to 12 hr
	Eptifibatide {*Integrilin®*}	PCI [IIa, B]	CrCl <50 mL/min: reduce infusion 50%	▪ Active bleeding* ▪ Prior stroke ≤ 30 days* ▪ Renal dialysis* ▪ Thombocytopenia	▪ SCr ▪ Platelet count ▪ Bleeding	▪ 180 mcg/kg IV bolus x 2, then 2 mcg/kg/min IV infusion ▪ Continue for 12 – 18 hr after PCI
	Tirofiban {*Aggrastat®*}	PCI [IIa, B]	CrCl <30 mL/min: reduce infusion 50%	▪ Active bleeding* ▪ Thombocytopenia* ▪ Prior hemorrhagic stroke*	▪ SCr ▪ Platelet count ▪ Bleeding	▪ 25 mcg/kg IV bolus, then 0.15 mcg/kg/min IV infusion ▪ Continue for 18 hr after PCI
	Clopidogrel {*Plavix®*}	Fibrinolytic [IA]	No	▪ Hypersensitivity ▪ Active bleeding* ▪ Risk of severe bleeding ▪ Reduced 2C19 function (BBW) ▪ Caution with 2C19 inhibitors ▪ Hold 5 days prior to CABG surgery	▪ SCr ▪ Bleeding	▪ < 75 y.o.: 300 mg PO loading dose, then 75 mg daily maintenance dose > 75 y.o.: 75 mg daily ▪ Continue for 14 days to 1 year in absence of bleeding
		PCI [IB]				▪ 300 mg (PCI ≤ 24 hr) or 600 mg (PCI > 24 hr) PO loading dose, then 75 mg PO daily maintenance dose ▪ Continue for 14 days if no stent is placed or 1 year if either a BMS or DES is placed
	Prasugrel {*Effient®*}	PCI [IB]	No	▪ Active bleeding* ▪ History of TIA or stroke (BBW) ▪ Age > 75 y.o.(BBW) ▪ Weight < 60 kg (BBW) ▪ Hold 7 days prior to CABG surgery	▪ SCr ▪ Bleeding	▪ 60 mg PO loading dose, then 10 mg PO daily maintenance dose ▪ Continue for 14 days if no stent is placed or 1 year if either a BMS or DES is placed
	Ticagrelor {*Brilinta®*}	PCI [IB]	No	▪ Hypersensitivity ▪ Active bleeding* ▪ History of ICH (BBW) ▪ Must use with low dose aspirin (BBW) ▪ Caution with 3A4 inducers/ inhibitors ▪ Hold 5 days prior to CABG surgery	▪ SCr ▪ Bleeding	▪ 180 mg PO loading dose, then 90 mg PO twice a day maintenance dose ▪ Continue for 14 days if no stent is placed or 1 year if either a BMS or DES is placed

Table for Continuing Education Article - Acute Coronary Syndromes: Current Treatment Guidelines and Updates

Source: Adapted from information found in references 1,3,4,11.

DDI indicates drug-drug interaction; ICH, intracranial hemorrhage; aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; ACT, activated clotting time; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; PCI, percutaneous coronary intervention; LMWH, low molecular weight heparin; SCr, serum creatinine; CrCl, creatinine clearance; SC, subcutaneous; CABG, coronary artery bypass graft; BBW, black box warning; PO, per os (by mouth).

Non-ST elevation myocardial infarction (NSTEMI) / Unstable angina (UA)

	Drug	Procedure[ACC/AHA Guideline Recommendations]	Dose Adjustment	Warnings / DDI/ Contraindications*	Monitoring	Dose and Duration of Therapy
Anticoagulants	Unfractionated Heparin (UFH)	Invasive strategy: ▪ Before PCI [IA] ▪ PCI [IA]	No	▪ Active bleeding* ▪ History of HIT* ▪ Risk of severe bleeding ▪ Recent stroke	▪ aPTT: 50 – 70 sec ▪ ACT: 200-300 sec (with GPI); 250-350 sec (no GPI) ▪ HIT ▪ Bleeding	▪ 60 units/kg IV bolus, then 12 units/kg/hr IV infusion ▪ Continue for 48 hr or discontinue at the end of PCI
		Conservative strategy [IA]				▪ 60 units/kg IV bolus, then 12 units/kg/hr IV infusion ▪ Continue for 48 hr or until discharge
	Enoxaparin (LMWH) {*Lovenox®*}	Invasive strategy: ▪ Before PCI [IA] ▪ PCI [IA]	Reduce if CrCl < 30 mL/min	▪ Active bleeding* ▪ History of HIT ▪ Risk of severe bleeding ▪ Recent stroke ▪ Avoid if CrCl < 15 mL/min ▪ Avoid if CABG surgery (discontinue 12-24 hrs prior)	▪ SCr ▪ HIT ▪ Bleeding	▪ 1 mg/kg SC every 12 hours (if last dose > 8 hours prior to PCI, administer 0.3 mg/kg IV bolus) ▪ Discontinue at the end of PCI
		Conservative strategy [IA]				▪ 1 mg/kg SC every 12 hours ▪ Continue for the duration of hospitalization (up to 8 days)
	Fondaparinux {*Arixtra®*}	Invasive strategy: ▪ Before PCI [IB] ▪ PCI [III,C] *not as monotherapy*	No	▪ Active bleeding* ▪ Risk of severe bleeding ▪ Avoid if CrCl < 30 mL/min ▪ Avoid if CABG surgery (discontinue 24 hrs prior) ▪ Increase risk of catheter thrombosis if used as monotherapy	▪ SCr ▪ Bleeding	▪ 2.5 mg SC daily (**MUST** administer UFH 50-60 units/kg IV bolus prior) ▪ Discontinue at the end of PCI
		Conservative strategy [IB]				▪ 2.5 mg SC daily ▪ Continue for the duration of hospitalization (up to 8 days)
	Bivalirudin {*Angiomax®*}	Invasive strategy: ▪ Before PCI [IB] ▪ PCI [IB] *can be used if high risk of bleeding*	Severe renal function	▪ Active bleeding* ▪ Risk of severe bleeding ▪ Avoid if CABG surgery (discontinue 3 hrs prior) ▪ Increase risk of stent thrombosis	▪ SCr ▪ Bleeding	▪ Before PCI, 0.1 mg/kg IV bolus, then 0.25 mg/kg/hr IV infusion ▪ If given before PCI, 0.5 mg/kg IV bolus, then 1.75 mg/kg/hr IV infusion ▪ If not given before PCI, 0.75 mg/kg IV bolus, then 1.75 mg/kg/hr IV infusion ▪ Discontinue at the end of PCI
		Conservative strategy: ▪ Angiography [IB]				▪ Before angiography, 0.1 mg/kg IV bolus, then 0.25 mg/kg/hr IV infusion ▪ Discontinue at the end of angiography or continue at 0.25 mg/kg/hr for up to 72 hr if prolonged anticoagulation necessary
Antiplatelets	Aspirin (ASA)	Initial treatment after hospital admission [IA]	No	▪ Hypersensitivity ▪ Active bleeding ▪ Risk of severe bleeding	▪ Bleeding	▪ 162-325 mg before procedure, then 81 mg maintenance dose daily indefinitely ▪ If a stent is placed after PCI, continue 162-325 mg daily - for at least 30 days (bare metal stent) - for 3 months (sirolimus-eluting stent) - for 6 months (paclitaxel-eluting stent) - then continue 75-162 mg daily indefinitely
	Abciximab {*Reopro®*}	Invasive strategy: ▪ PCI [IA]	No	▪ Active bleeding* ▪ Thombocytopenia* ▪ Prior stroke ≤ 2 years*	▪ SCr ▪ Platelet count ▪ Bleeding	▪ 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion ▪ Continue for up to 12 hr after PCI
	Eptifibatide {*Integrilin®*}	Invasive strategy: ▪ Before PCI [1B] ▪ PCI [IA]	CrCl <50 mL/min: reduce infusion 50%	▪ Active bleeding* ▪ Prior stroke ≤ 30 days* ▪ Renal dialysis* ▪ Thombocytopenia	▪ SCr ▪ Platelet count ▪ Bleeding	▪ 180 mcg/kg IV bolus x 2 (10 min apart), then 2 mcg/kg/min IV infusion ▪ Continue for 12 – 18 hr after PCI
		Conservative strategy: ▪ Before angiography [IIb, B] ▪ Angiography [IA]				▪ 180 mcg/kg IV bolus, then 2 mcg/kg/min IV infusion ▪ If no angiography, discontinue ▪ If angiography, continue for up to 72 hr
	Tirofiban {*Aggrastat®*}	Invasive strategy: ▪ Before PCI [1B] ▪ PCI [IA]	CrCl <30 mL/min: reduce infusion 50%	▪ Active bleeding* ▪ Thombocytopenia* ▪ Prior stroke ≤ 2 years*	▪ SCr ▪ Platelet count ▪ Bleeding	▪ 25 mcg/kg IV bolus, then 0.15 mcg/kg/min IV infusion ▪ Continue for up to 18 hr after PCI
		Conservative strategy: ▪ Before angiography [IIb, B] ▪ Angiography [IA]				▪ 50 mcg/mL administered at a rate of 0.4 mcg/kg/min over 30 min, then 0.1 mcg/kg/min IV infusion ▪ If no angiography, discontinue ▪ If angiography, continue for up to 72 hr
	Clopidogrel {*Plavix®*}	Invasive strategy: ▪ Before PCI [1B] ▪ PCI [IA]	No	▪ Hypersensitivity ▪ Active bleeding* ▪ Risk of severe bleeding ▪ Reduced 2C19 function (BBW) ▪ Caution with 2C19 inhibitors ▪ Hold 5 days prior to CABG surgery	▪ SCr ▪ Bleeding	▪ 300 – 600 mg PO loading dose, then 75 mg PO daily maintenance dose ▪ If PCI, continue for at least 12 months. ▪ If no PCI, continue for up to 12 months
		Conservative strategy: ▪ Before angiography [IB] ▪ Angiography [IB]				
	Prasugrel {*Effient®*}	Invasive strategy: ▪ PCI [IB]	No	▪ Active bleeding* ▪ History of TIA or stroke (BBW) ▪ Age > 75 y.o.(BBW) ▪ Weight < 60 kg (BBW) ▪ Hold 7 days prior to CABG surgery	▪ SCr ▪ Bleeding	▪ 60 mg PO loading dose, then 10 mg PO daily maintenance dose ▪ Continue for up to 12 months
	Ticagrelor {*Brilinta®*}	Invasive: ▪ Before PCI [1B] ▪ PCI [IB]	No	▪ Hypersensitivity ▪ Active bleeding* ▪ History of ICH (BBW) ▪ Must use with low dose aspirin (BBW) ▪ Caution: 3A4 inducers/ inhibitors ▪ Hold 5 days prior to CABG surgery	▪ SCr ▪ Bleeding	▪ 180 mg PO loading dose, then 90 mg PO daily maintenance dose ▪ If PCI, continue for at least 12 months ▪ If no PCI, continue for up to 12 months
		Conservative strategy: ▪ No angiography [IB] ▪ Angiography [IB]				

Continuing Education Quiz Questions

Acute Coronary Syndromes: Current Treatment Guidelines and Updates ACPE UAN#0100-0000-13-056-H01-P

1. A 72-year old female presents to the hospital for chest pain that started about 11 hours ago, but has been getting worse in the last 30 minutes. Her EKG reveals ST-segment depression and T- wave inversions. Her first two set of cardiac biomarkers reveals elevated CK-MB and troponins. Which of the following is the most likely diagnosis?
a. NSTEMI
b. STEMI
c. Unstable angina
d. Non-cardiac cause of chest pain
e. Cannot determine based on the information given

2. A 68-year old female patient presents to the hospital with crushing chest pain that started 30 minutes ago. She has received 3 doses of sublingual nitroglycerin, but has been getting worse in the last 15 minutes. According to her past medical history, she has asthma and heart failure (left ventricular ejection fraction 10-15%). Her vital: BP 156/92, HR 72, O2 saturation on room air 79%. Which of the following is the BEST recommendation for this patient?
a. Chew aspirin 325 mg, titrate oxygen to 100% O2 saturation, nitroglycerin 0.4 mg SL, metoprolol 25 mg IV
b. Chew aspirin 325 mg, titrate oxygen to 100% O2 saturation, nitroglycerin 0.4 mg SL, metoprolol 25 mg PO
c. Chew aspirin 325 mg, morphine 2 mg IV, and titrate oxygen to 100% O2 saturation
d. Chew aspirin 325 mg. morphine 2 mg IV, titrate oxygen to 100% O2 saturation, metoprolol 25 mg IV
e. Chew aspirin 325 mg. morphine 2 mg IV, titrate oxygen to 100% O2 saturation, metoprolol 25 mg PO

3. TG is a 60 year old female that was presented to the emergency room with complaints of throbbing chest pain. She was initially given 3 SL tablets of NTG in the last 15 minutes, however she is still having chest pain. Her O2 sats are at 86%. Her LVEF is at 30% according to TTE. What medications and or therapy should this patient being receiving next?
a. Initial invasive strategy with preference for PCI
b. IV morphine + ASA
c. IV morphine + oxygen administered via nasal cannula + ASA
d. Patient does not need anything, as this not an ACS case

4. BN is an 80 year old male who develops crushing chest pain that started 30 minutes ago. The EKG in the ambulance reveals that the patient is having a STEMI. The nearest hospital with a cardiac catheterization laboratory is three hours away. What is the most appropriate initial treatment strategy for this patient?
a. Transfer directly to hospital with catheterization laboratory for PCI
b. Admit to nearest hospital for fibrinolytic therapy
c. Admit to nearest hospital for diagnostic stress test
d. Admit to nearest hospital for CABG

5. JT is a 75 year old male who presents to the emergency department with complaints of chest pain. He states that he has 3 episodes of chest pain in the past 24 hours. In addition, he has a history of coronary artery disease, as well at hypertension and diabetes. A preliminary ECG shows sinus tachycardia. What is his risk assessment based on his TIMI score?
a. Low risk
b. Moderate risk
c. High risk
d. No risk

6. YU has been diagnosed with having NSTEMI because on his ECG readings and cardiac biomarkers. Based on his TIMI score and risk assessment, he is stratified as being moderate risk. What initial strategy should YU undergo for treatment of his NSTEMI?
a. Invasive strategy
b. Conservative strategy
c. No further therapy is needed
d. More information is needed

7. Which of the following laboratory values should be monitored for a patient treated with abciximab?
a. Serum creatinine
b. Liver function tests
c. Platelets
d. Troponin

8. Which of the following describes an advantage of UFH over other anticoagulants used in ACS patients?
a. Lower incidence of heparin-induced thrombocytopenia
b. Can be monitored in catheterization lab with ACT
c. Administration routes include subcutaneously or intravenously
d. Lower incidence of bleeding compared to bivalirudin

ANSWER SHEET AND EVALUATION FOR THIS HOME-STUDY ACTIVITY ARE ON PAGE 50.

9. Which of the following is an absolute contraindication to fibrinolytic therapy?
a. Ischemic stroke within the last 3 months
b. Blood pressure greater than 180/110 mmHg
c. Chronic warfarin therapy
d. Pregnancy

10. A 45 year old male patient weighing 120 kg was admitted to the hospital and diagnosed with having STEMI. He has a history of recent gastrointestinal bleeding and is currently taking omeprazole for it. Which antiplatelet medication would be best given to initially treat this patient for his STEMI?
a. ASA
b. ASA + clopidogrel
c. ASA + prasugrel
d. ASA + ticagrelor
e. None of the above

11. LK is an 80 year old male with a history of COPD. He is afraid taking medications that may exacerbate his COPD. He was admitted to the hospital and was diagnosed with having STEMI. A PCI was performed and a sirolimus stent was implanted in his coronary artery. What medication regimen is appropriate for this patient upon discharge for maintenance of his ACS?
a. ASA 325mg daily for 1 months + clopidogrel 75mg daily for 2 months
b. ASA 325 mg daily for 3 months + ticagrelor 90mg BID for 12 months
c. ASA 325 mg daily for 3 months + prasugrel 10 mg daily for 12 months
d. ASA 325 mg daily for 3 months + clopidogrel 300mg daily for 12 months
e. ASA 325 mg daily for 3 months + prasugrel 10 mg daily for 3 months

12. A 57 year old male patient who is currently on eptifibatide, prasugrel, and unfractionated heparin is about to undergo elective CABG for his NSTEMI. Which of the following changes in his drug are appropriate to make prior to his upcoming procedure?
a. Hold the UFH for at least 2 days
b. Hold the prasugrel for at least 5 days
c. Hold the prasugrel for at least 7 days
d. Hold the eptifibatide for at least 2 hours
e. c and d

13. HT is a 50 year old male patient that was recently treated at the hospital for his STEMI and is ready to be discharged. His past medical history includes hypertension and type 2 diabetes. What medications should HT be placed on prior to him being discharged for secondary prevention of ACS?
a. Atorvastatin
b. Aspirin
c. Metoprolol
d. b and c
e. All of the above