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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

Updates in Anti-anginal and Anti-ischemic Therapies for Acute Coronary Syndromes

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Abstract

Purpose of Review Acute coronary syndrome is a major health problem affecting ~ 1.5 million individuals a year in the USA. We review the contemporary role of anti-anginal and anti-ischemic therapies in the management of an individual presenting with an acute coronary syndrome.

Recent Findings Early diagnosis and appropriate evidence-based therapies significantly improve clinical outcomes in acute coronary syndrome patients. Typically, acute coronary syndrome is associated with rupture of an atherosclerotic plaque and either partial or complete thrombotic occlusion of a coronary artery. Management of an acute coronary syndrome is targeted towards this underlying pathophysiology. The last few years have seen significant advances in anti-anginal and anti-ischemic therapies in the management of patients with acute coronary syndrome.

Summary It is important to have a team effort to target risk reduction measures and to emphasize medication and dietary compliance. Long-term pharmacotherapy should include aspirin, beta-blocker, DAPT (for at least 1 year), statins, and ACE inhibitors and PCSK9 inhibitors if indicated.

Keywords Acute coronary syndrome · Anti-anginal therapies · Anti-ischemic therapies · Anti-platelet therapies · Myocardial infarction · Outcomes

Introduction

Coronary artery disease (CAD) affects 18.2 million individuals ≥ 20 years of age in the USA, with a slight male predominance based on the 2019 Heart Disease and Stroke Statistics update of the American Heart Association [1]. Among patients with CAD, acute coronary syndrome (ACS) is a major health problem. Approximately every 40 s, an American will have a myocardial infarction (MI) with an estimated annual incidence of 605,000 new MI and 200,000 recurrent MI attacks [1].

Patients with CAD may present either as stable angina or with an acute coronary syndrome (ACS). The spectrum of ACS includes unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). UA is characterized by the clinical presentation of angina with or without ischemic electrocardiographic (ECG) changes (ST segment depression or new T wave inversion). NSTEMI is similar to UA, but is characterized by positive cardiac biomarkers in the setting of angina and/or ECG changes. The presence of myonecrosis as evident by positive cardiac markers portends a higher risk than those presenting with just UA. UA and NSTEMI are pathophysiologically and clinically related and may be initially indistinguishable as biomarkers may not be elevated at presentation. STEMI is characterized by complete thrombotic occlusion of a coronary artery with ST segment elevation noted in an electrocardiogram.

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Therapies

After establishing the diagnosis of ACS, focus should be on optimizing management [2]. The goal of treatment is relief of symptoms and very importantly prevention of cardiovascular morbidity and mortality. Management strategies include determining risk of adverse events, use of pharmacological therapies, and myocardial revascularization as indicated. Of note, UA and NSTEMI are distinguishable primarily by elevated troponin in the contemporary era which may not be detectable immediately; the initial management for both syndromes is similar.

General Measures

Oxygen, usually by nasal cannula, is indicated to sustain O_2 saturation ≥ 90% in individuals with hypoxemia and in those with respiratory distress [3••]. Continuous electrocardiographic monitoring or telemetry helps detect and treat arrhythmias. ST segment monitoring may detect ongoing ischemia that may not be otherwise identified early. Use of morphine should ideally be reserved for patients with severe pain since there is evidence that its use is associated with worse outcomes [4]. Figure 1 provides an algorithm for management of patients presenting with an ACS based on American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Table 1 enumerates common anti-ischemic therapies, mode of administration, doses, and side effects.

Anti-ischemic Agents

Nitrates

Nitrates reduce cardiac oxygen demand mostly by decreasing preload, lowering afterload moderately, dilating coronary arteries, and potentially increasing collateral flow to ischemic regions [2]. They thereby decrease myocardial wall stress and oxygen demand reducing supply demand mismatch. In addition, nitroglycerin produces a late preconditioning-mimetic effect that mitigates the ECG manifestations of ischemia during exercise and improves exercise capacity [5]. Sublingual nitroglycerin is administered to patients presenting with ACS-associated chest pain, followed by intravenous nitroglycerin in patients with persistent pain after three sublingual nitroglycerin tablets. If sublingual nitroglycerin is ineffective in ameliorating ischemia, intravenous nitroglycerin may be used while carefully monitoring blood pressure [2]. Intravenous nitroglycerin is typically initiated at a rate of 10 μg/min and dose increased by 10 μg/min every 3 to 5 min until chest pain resolves or blood pressure drop > 30 mmHg is noted [6]. In patients without refractory symptoms, intravenous nitroglycerin should be converted to an oral or transdermal patch form within 24 h, with nitrate-free periods to avoid tolerance. Tolerance to the effects of nitrates is dose and duration dependent and is usually seen after 24 h of continuous therapy. Patients with ACS who require continued intravenous nitroglycerin beyond 24 h may require dose increases to maintain efficacy. Lower dose, shorter acting, and intermittent dosing may mitigate the development of tolerance [6]. The mechanism of tolerance is not fully elucidated, but available data suggests that nitroglycerin-induced reactive oxygen species inhibit the bioactivation of nitroglycerin by thiol oxidation of aldehyde dehydrogenase with the increased oxidative stress and impaired bioactivation of nitroglycerin, responsible for nitroglycerin tolerance and cross-tolerance [7]. Nitrates should be avoided in settings in which hypotension is likely or could result in serious hemodynamic decompensation, such as right ventricular infarction or severe aortic stenosis. Use of phosphodiesterase inhibitors such as sildenafil in the preceding 24-h period is a contra-indication to the use of nitrates as it promotes a prolonged and exaggerated hypotension, which may lead to MI and even death [8].

Beta-blockers

Beta-blockers are recommended for all patients with ACS, unless contraindicated. If there is evidence of ongoing ischemia, they are initially given intravenously followed by oral delivery. However, based upon the results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) trial, intravenous beta-blockers can be deferred in patients who are hemodynamically compromised [9]. This study reported that use of early beta-blocker therapy in acute MI reduces the risks of reinfarction and ventricular fibrillation, but increases the risk of cardiogenic shock, especially during the first day or so after admission. Of note, 93% had ST segment elevation or bundle branch block in this study and the results may be less applicable to ACS population without ST elevation [9]. A meta-analysis of sixteen studies enrolling 73,396 participants including the COMMIT/CCS-2 study reported that intravenous beta-blockers early in the course in those with ongoing ischemia or chest pain appear to be associated with significant reduction in the risk of short-term cardiovascular outcomes, including a reduction in the risk of all-cause mortality [10•].

Beta-blockers decrease myocardial contractility, blood pressure, and heart rate, thereby reducing myocardial oxygen demand and providing relief to the ischemic myocardium. Although there are no proven differences in outcome among agents, beta-1 selective blockers (metoprolol or atenolol) are preferred over non-selective agents and those with intrinsic sympathomimetic activity. For patients with active asthma, those presenting with severe conduction disturbances, congestive heart failure, bradycardia, or hypotension beta-blockers should be avoided initially but may be used once resolved [4].

The 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes states as a class I recommendation that oral beta-blocker therapy should be initiated within the first 24 h in patients who do not have signs of HF, evidence of low-output state, increased risk for cardiogenic shock, or other contraindications to beta-blockade (e.g., PR interval > 0.24 s, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) [3••]. Administration of intravenous beta-blockers is potentially harmful in patients with NSTE-ACS who have risk factors for shock and was designated a Class III recommendation [3••]. The 2015 ESC Guidelines for the management of ACS recommends as Class I early initiation of beta-blocker treatment in ACS patients with ongoing ischemic symptoms and without contraindications and also as Class I intravenous beta-blocker therapy for those with recurrent angina, uncontrolled hypertension, or signs of heart failure [11•].

Calcium Channel Blockers

Calcium channel blockers have not been shown to lower mortality in ACS and should not be used as first-line agents. They may cause vasodilation, decrease myocardial contractility, increase AV block, and slow the heart rate and may be considered in those without failure [12]. These agents are useful in patients with angina due to coronary spasm, in those recurrent ischemia despite nitrates and beta-blockers, intolerance to beta-blockers, or uncontrolled hypertension. Essentially, they are a third-line anti-anginal medication after beta-blockers and nitrates.

Ranolazine

Ranolazine inhibits the late inward sodium current and reduces the harmful effects of intracellular sodium and calcium overload that is seen with myocardial ischemia. Ranolazine is approved for treatment of chronic angina, and the MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes-Thrombosis In Myocardial Infarction) 36 trial did not show benefit in ACS patients [13]. The recommended initial dose of ranolazine is 500 mg twice daily, which can be increased to a maximum of 1000 mg twice daily.

Anti-platelet Therapy

Anti-platelet therapy with an aspirin and a platelet $P2Y_{12}$ receptor blocker is indicated in all patients with an ACS unless there are absolute contraindications to their use.

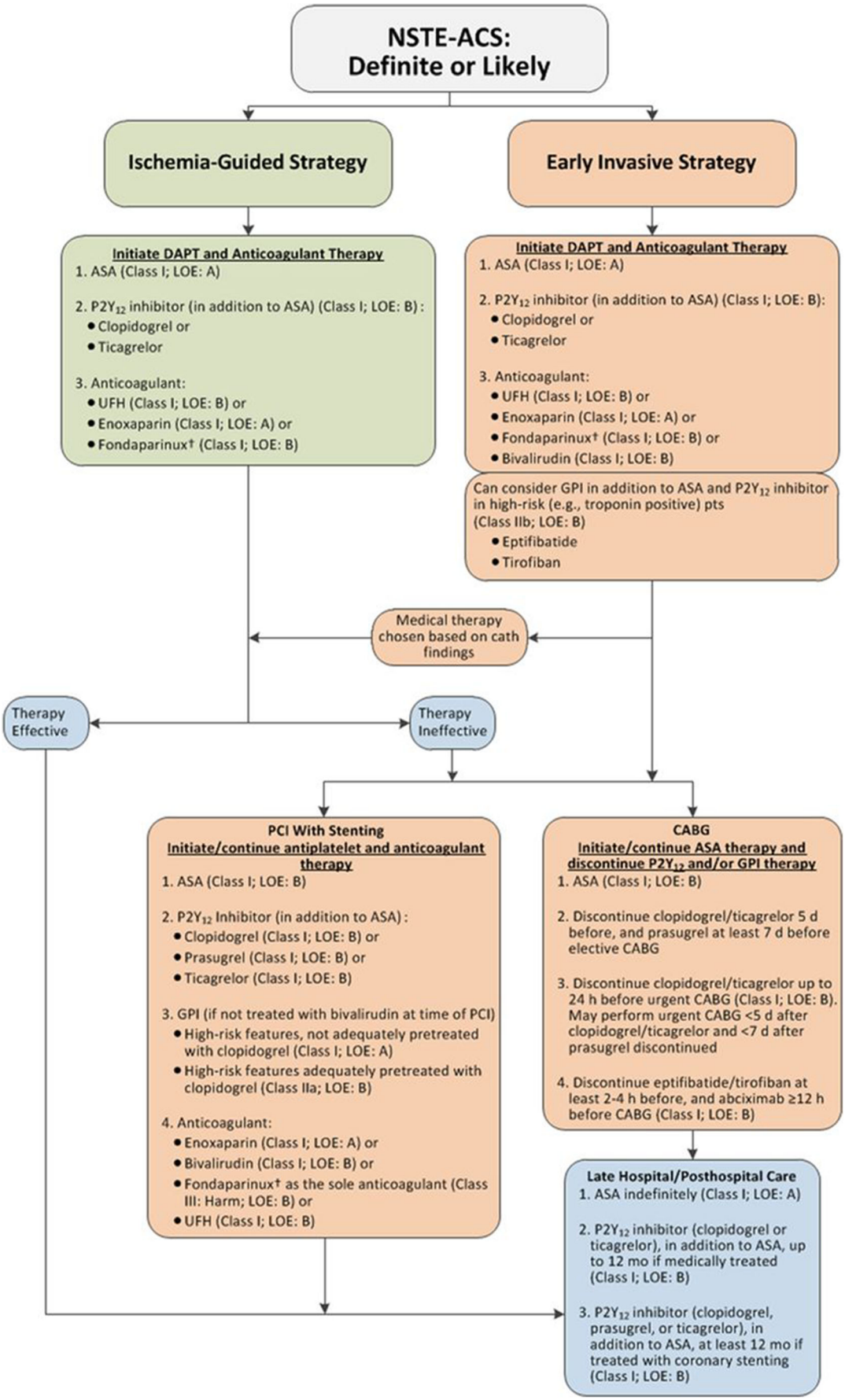
Aspirin Platelet activation and aggregation plays a critical role in the pathophysiology of ACS in the formation of thrombus. Aspirin works primarily by inhibiting thromboxane A_2 pathway, and has additive anti-inflammatory effects. Non-enteric-coated, chewable aspirin (162–325 mg) should be administered to all patients with ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin 81 mg (75 to 150 mg) per day continued indefinitely [3••, 14, 11•].

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, the benefit of ticagrelor over clopidogrel was limited to patients taking 75 to 100 mg of aspirin with the lowest risk of cardiovascular death, myocardial infarction, or stroke with ticagrelor compared with clopidogrel associated with a low maintenance dose of concomitant aspirin [15]. Current guidelines recommend a maintenance dose of aspirin 81 mg (75 to 150 mg) per day continued indefinitely in those treated with dual anti-platelet therapy [14].

$P2Y_{12}$ Receptor Blocker All individuals presenting with an ACS should be treated with a $P2Y_{12}$ inhibitor in addition to aspirin which is alluded to as dual anti-platelet therapy (DAPT). The choice of the $P2Y_{12}$ inhibitor and the timing of its administration depend on the choice of treatment strategy. DAPT is directed at limiting platelet adhesion and aggregation, which prevents additional thrombus formation.

The CURE trial randomly assigned 12,562 patients within 24 h of ACS to aspirin alone (75–325 mg/day) or aspirin with clopidogrel (300-mg loading dose and 75 mg/day maintenance dose) for 3 to 12 months [16]. The majority of patients met high-risk criteria based on either electrocardiogram changes of ST depression ≥ 1 mm or T wave inversion ≥ 2 mm or elevated cardiac biomarkers. Majority of patients, i.e., > 60%, were treated medically. The primary end point of the study was a composite of cardiovascular death, myocardial infarction (MI), or stroke. At 9 months of follow-up, DAPT was associated with a significant reduction in the combined primary end point of cardiovascular death, nonfatal MI, or stroke (9.3 versus 11.4%), which was primarily driven by fewer MIs [16].

For ACS patients managed with an ischemia-guided approach, ticagrelor is preferred to clopidogrel and for ACS patients undergoing percutaneous coronary intervention (PCI) with stenting ticagrelor and prasugrel are preferred to clopidogrel. Of note, ticagrelor should be avoided in patients with symptomatic bradycardia, including those with 2nd or 3rd degree atrioventricular block on the electrocardiogram [17] and prasugrel should not be given prior to coronary angiography. The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 open-label trial directly compared ticagrelor and prasugrel in 4018 ACS patients and reported a lower risk of ischemic events with prasugrel compared with ticagrelor [18]. Given the limitations of the ISAR-REACT 5 trial including open-label design and telephone follow-up in


NSTE-ACS:
Definite or Likely
Ischemia-Guided Strategy
Early Invasive Strategy
Initiate DAPT and Anticoagulant Therapy
1. ASA (Class I; LOE: A)
2. P2Y12 inhibitor (in addition to ASA) (Class I; LOE: B):
Clopidogrel or
Ticagrelor
3. Anticoagulant:
UFH (Class I; LOE: B) or
Enoxaparin (Class I; LOE: A) or
Fondaparinux† (Class I; LOE: B)
Initiate DAPT and Anticoagulant Therapy
1. ASA (Class I; LOE: A)
2. P2Y12 inhibitor (in addition to ASA) (Class I; LOE: B):
Clopidogrel or
Ticagrelor
3. Anticoagulant:
UFH (Class I; LOE: B) or
Enoxaparin (Class I; LOE: A) or
Fondaparinux† (Class I; LOE: B) or
Bivalirudin (Class I; LOE: B)
Can consider GPI in addition to ASA and P2Y12 inhibitor in high-risk (e.g., troponin positive) pts (Class IIb; LOE: B)
Eptifibatide
Tirofiban
Medical therapy chosen based on cath findings
Therapy Effective
Therapy Ineffective
PCI With Stenting
Initiate/continue antiplatelet and anticoagulant therapy
1. ASA (Class I; LOE: B)
2. P2Y12 Inhibitor (in addition to ASA):
Clopidogrel (Class I; LOE: B) or
Prasugrel (Class I; LOE: B) or
Ticagrelor (Class I; LOE: B)
3. GPI (if not treated with bivalirudin at time of PCI)
High-risk features, not adequately pretreated with clopidogrel (Class I; LOE: A)
High-risk features adequately pretreated with clopidogrel (Class IIa; LOE: B)
4. Anticoagulant:
Enoxaparin (Class I; LOE: A) or
Bivalirudin (Class I; LOE: B) or
Fondaparinux† as the sole anticoagulant (Class III: Harm; LOE: B) or
UFH (Class I; LOE: B)
CABG
Initiate/continue ASA therapy and discontinue P2Y12 and/or GPI therapy
1. ASA (Class I; LOE: B)
2. Discontinue clopidogrel/ticagrelor 5 d before, and prasugrel at least 7 d before elective CABG
3. Discontinue clopidogrel/ticagrelor up to 24 h before urgent CABG (Class I; LOE: B). May perform urgent CABG <5 d after clopidogrel/ticagrelor and <7 d after prasugrel discontinued
4. Discontinue eptifibatide/tirofiban at least 2-4 h before, and abciximab ≥12 h before CABG (Class I; LOE: B)
Late Hospital/Posthospital Care
1. ASA indefinitely (Class I; LOE: A)
2. P2Y12 inhibitor (clopidogrel or ticagrelor), in addition to ASA, up to 12 mo if medically treated (Class I; LOE: B)
3. P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), in addition to ASA, at least 12 mo if treated with coronary stenting (Class I; LOE: B)

◀ **Fig. 1** Algorithm for management of patients with an acute coronary syndrome (ACS). †In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anti-coagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. ASA, aspirin; CABG, coronary artery bypass graft; cath, catheter; COR, Class of Recommendation; DAPT, dual anti-platelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; LOE, level of evidence; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; pts., patients; and UFH, unfractionated heparin. (Reprinted with permission. Circulation. 2014;130:2354–94. ©2014 by the American Heart Association) [3••]

more than 90% of patients, until additional studies validate these results, either prasugrel or ticagrelor is a reasonable choice for patients with ACS who undergo diagnostic angiography. Available date suggests that prasugrel is associated with net harm in patients with a history of cerebrovascular events including increased risk of intracranial hemorrhage and no clinical benefit in patients > 75 years of age or those with low body weight (< 60 kg) [19]. Prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke and is generally not recommended in patients > 75 years of age owing to increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (e.g., diabetes or prior MI). A lower prasugrel maintenance dose of 5 mg in patients < 60 kg may be considered to reduce bleeding risk. The results of the Elderly ACS 2 study did not show clinical benefit of prasugrel 5 mg versus clopidogrel in elderly patients with ACS [20]. All ACS patients should ideally receive DAPT for at least 12 months unless there has been a significant bleeding episode or if there is a very high bleeding risk.

Evolving data suggests that short-duration DAPT (3 months) followed by ticagrelor monotherapy for 12 months results in less bleeding compared with longer-duration DAPT (additional 12 months) among ACS patients undergoing PCI with a DES and at high ischemic or bleeding risk with no increase in ischemic rates [21]. Among ACS patients in the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial, the primary outcome of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding at 12 months, for ticagrelor monotherapy vs. aspirin + ticagrelor was 3.6% vs. 7.6% ($p < 0.001$); TIMI major bleeding: 0.5% vs. 1.0% ($p = 0.08$); all-cause mortality, MI, stroke: 4.3% vs. 4.4% ($p = 0.84$); all-cause mortality: 1.0% vs. 1.5% ($p = 0.14$); any MI: 3.1% vs. 3.1% ($p = 0.99$); and stent thrombosis: 0.4% vs. 0.6% ($p = 0.38$) [21]. Similar findings were also reported with clopidogrel in the Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy After DES (SMART-CHOICE) [22] and ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study (STOPDAPT-2) trials [23]. Although all of these studies included ACS patients, none of them was dedicated ACS trials and a definitive prospective ACS trial is indicated to assess effectiveness of shorter DAPT followed by $P2Y_{12}$ monotherapy.

Glycoprotein IIb/IIIa Inhibitors The platelet GP IIb/IIIa receptor plays a pivotal role in platelet aggregation. After platelets are activated, the GP IIb/IIIa receptor undergoes a structural change leading to fibrinogen-mediated linking and aggregation of platelets. GP IIb/IIIa inhibitors impede this penultimate pathway of platelet aggregation, and function clinically as potent inhibitors of platelet aggregation from various stimulants. At this time, with availability of potent $P2Y_{12}$ inhibitors, majority of patients with ACS scheduled for PCI do not require glycoprotein (GP) IIb/IIIa inhibitor therapy. However, a GP IIb/IIIa inhibitor may be considered for high-risk patients such as those with evidence of ongoing ischemia (e.g., persistent chest pain and electrocardiographic evidence of ischemia) or with large thrombus burden seen at the time of angiography or as a bailout for intraprocedural thrombotic complications. GP IIb/IIIa inhibitors are typically not administered to ACS patients treated conservatively or with an ischemia-guided approach.

Anti-coagulants

All ACS patients should receive anti-coagulant therapy as soon as possible after the diagnosis. There is long-term experience with unfractionated heparin (UFH) as anti-coagulant for ACS, and it remains the drug of choice for those undergoing PCIs for ACS. Heparin is linear polysaccharide and a mixture of different chain lengths with variable anti-coagulant activity. UFH binds to anti-thrombin causing a structural change that accelerates its inhibition of thrombin and factor Xa thus preventing thrombus formation and propagation [2]. UFH binds to other plasma proteins blood cells, and endothelial cells affecting its bioavailability and anti-coagulant activity and is a disadvantage. Low molecular weight heparin has several advantages compared with UFH including lower plasma protein binding, greater bioavailability when given subcutaneously thus allowing for less frequent dosing, greater resistance to offset by platelet factor 4, and release of tissue factor pathway inhibitor (TFPI) resulting in a more consistent anti-coagulant effect [2]. Low molecular weight heparin is also associated with a lower incidence of heparin-induced thrombocytopenia. Direct thrombin inhibitors inhibit clot-bound thrombin and are not inhibited by circulating plasma proteins and platelet factor 4 offering an advantage over heparins. Bivalirudin, a reversible direct thrombin inhibitor, binds to the catalytic and anionic exosite of both circulating and clot-bound thrombin resulting in consistent anti-coagulation. Fondaparinux, a synthetic pentasaccharide, is a novel factor Xa inhibitor which works by binding to anti-thrombin and inhibiting factor Xa. The Fifth Organization to

Table 1 Common anti-ischemic therapies, mode of administration, doses, and side effects

Therapies	Route	Dosage	Side effects
Nitrates	Sublingual	0.3 to 0.4 mg every 5 min for up to 3 doses	Headache Hypotension
	Intravenous	10 μg/min and dose increased by 10 μg/min every 3 to 5 min	Hypotension
Beta-blockers			
Metoprolol	Oral	12.5 to 50 mg every 6 to 12 h, transitioning to daily	Bradycardia Heart block Low output state
Carvedilol	Oral	6.25 mg twice daily, titrate up to 25 mg twice daily as tolerated	Bradycardia Heart block Low output state
Anti-platelet			
Aspirin	Oral	160–325 mg (not enteric-coated and 81 mg once/day long-term	Bleeding Gastrointestinal ulcer
Clopidogrel	Oral	600-mg loading dose, then 75 mg daily for 12 months	Bleeding
Prasugrel	Oral	60-mg loading dose, then 10 mg daily	Bleeding Epistaxis
Ticagrelor	Oral	180-mg loading dose, followed by 90 mg daily	Dyspnea, bleeding Ventricular pauses and bradyarrhythmias
Anti-coagulant			
Unfractionated heparin	Intravenous	Loading dose of 60 U per kg (maximum of 4000 U) followed by an infusion of 12 U per kg per hour (maximum of 1000 U per hour)	Bleeding Thrombocytopenia
Enoxaparin	Subcutaneous	1 mg per kg every 12 h (reduce dosage to 1 mg per kg every 24 h in patients with creatinine clearance < 30 mL per minute per 1.73 m^2)	Bleeding Thrombocytopenia
Fondaparinux	Subcutaneous	2.5 mg per day	Bleeding
Bivalirudin	Intravenous	Loading dose of 0.1 mg per kg, followed by 0.25 mg per kg per hour	Bleeding
Lipid-lowering agents			
Statins	Oral	Atorvastatin 40–80 mag daily or rosuvastatin 20–40 mg daily	Myalgia Hepatic dysfunction
Ezetimibe	Oral	10 mg daily	Diarrhea
Evolocumab	Subcutaneous	140 mg every 2 weeks or 420 mg once monthly	Local injection reactions
Alirocumab	Subcutaneous	75 mg subcutaneously once every 2 weeks	Local injection reactions

Assess Strategies in Ischemic Syndromes (OASIS-5) trial reported that the composite of death, myocardial infarction, or refractory ischemia at 9 days occurred in 5.8% of patients on fondaparinux compared with 5.7% patients assigned to enoxaparin (hazard ratio, 1.01; 95% confidence interval, 0.90 to 1.13). Of note, the composite of death, myocardial infarction, refractory ischemia, or major bleeding occurred in 7.3% in the fondaparinux group, as compared with 9.0% of the patients in the enoxaparin group (hazard ratio, 0.81; 95% confidence interval, 0.73 to 0.89; $p < 0.001$) at 9 days driven by significant bleeding reduction [2].

The choice between the different anti-coagulants, i.e., UFH, enoxaparin, bivalirudin, or fondaparinux, is determined by whether the patient is managed with an invasive strategy or a conservative strategy. For patients managed with a conservative approach, either fondaparinux or enoxaparin is preferred. For ACS patients managed invasively, UFH or bivalirudin is usually given at the time of diagnosis. For patients who undergo coronary intervention, and who were started on fondaparinux, switching to heparin or bivalirudin is indicated, as the risk of catheter thrombosis is increased with fondaparinux monotherapy.

Angiotensin-Converting Enzyme (ACE) Inhibitors and Receptor Blockers (ARB)

The inclusion of an ACE inhibitor or ARB to standard medical therapy (including DAPT, beta-blocker, and statin) in patients with recent MI improves cardiovascular outcomes [24, 25]. The benefit of an ACE or an ARB is evident in patients with either ST-elevation or non-ST elevation MI with the magnitude of benefit stronger for patients with clinical heart failure or less than normal left ventricular ejection fraction (LVEF). Current guidelines recommend the addition of an

ACE inhibitor or an ARB to standard medical therapy in patients with ACS who are at high risk (heart failure, LVEF ≤ 40%, diabetes, or chronic kidney disease) of a subsequent cardiovascular event [3••].

Statins

Statin therapy should be started early and continued long term in all ACS patients irrespective of baseline LDL. The benefit of statin therapy is potentially related to plaque stabilization, improvement of endothelial function, reduced thrombogenicity, and diminished inflammation above and beyond that of lowering LDL [26]. Available evidence suggests improved clinical efficacy without major adverse effects with very low LDL levels (even < 40 mg/dL), and all ACS patients should receive high-intensity statin therapy with either atorvastatin 40–80 mg daily or rosuvastatin 20 or 40 mg daily regardless of baseline low-density lipoprotein-cholesterol level.

Ezetimibe

Ezetimibe inhibits absorption of cholesterol at the brush border of the small intestine via the sterol transporter, and may be added to intensive statin therapy for an ACS patient with an LDL-C ≥ 50 mg/dL. The IMProved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE IT) trial [27] reported that ezetimibe with simvastatin combination therapy lowered the average LDL-C to 53 mg/dL from 69 mg/dL with a reduction in the primary composite end point (cardiovascular death, nonfatal MI, unstable angina requiring hospitalization, coronary revascularization more than 29 days after randomization, or nonfatal stroke) in the ezetimibe-simvastatin arm.

PCSK9 Inhibitors

PCSK9 inhibitors significantly lower LDL-C and have been shown to improve outcomes in high-risk subjects such as those with an ACS. It seems reasonable for selected ACS patients to be started on PCSK9 inhibitors in view of their lipid-lowering and additional protective mechanisms in ACS particularly in those with an LDL-C of ≥ 70 mg/dL or individuals who cannot tolerate high-dose statin therapy and do not lower their LDL-C below 70 mg/dL on either low dose or no statins plus ezetimibe.

Coronary Revascularization

Coronary angiography helps define the extent and location of CAD, ventricular function, and presence of any other significant valvular problems. Patients with the following characteristics are at very high risk of adverse events and should be referred for immediate coronary arteriography and possible revascularization.

- Hemodynamic instability or cardiogenic shock
- Severe left ventricular dysfunction or heart failure
- Recurrent or persistent rest angina despite intensive medical therapy
- New or worsening mitral regurgitation or new ventricular septal defect
- Sustained ventricular arrhythmias

Predictive models have been recommended by the guidelines to guide invasive versus conservative strategy [3••]. Patients with intermediate or high-risk TIMI scores (≥ 3) or GRACE risk score (> 140) benefit from early invasive strategy. The choice of revascularization modality after angiography depends upon the location and extent of disease. Among patients with an ACS, PCI is most often performed, but CABG is preferred for the treatment of patients with left main or left main equivalent disease, or three- or two-vessel disease involving the proximal left anterior descending artery with left ventricular dysfunction or treated diabetes mellitus.

Follow-up and Long-term Therapy

After an initial ACS event, ongoing plaque instability and abnormal endothelial function persist for a while (weeks to months). Furthermore, lingering inflammation and a prothrombotic state persists for weeks. Of critical importance is the utilization of aggressive and intensive risk reduction strategies initiated in the hospital in the outpatient as well. These include lifestyle and pharmacological strategies to control BP, lipid reduction with statins (target LDL < 70), smoking cessation, and maintenance of adequate weight [28].

Long-term Therapy

Long-term use of medications such as statins, PCSK9 inhibitors in selected patients, DAPT, ACE/ARB, and beta-blockers is beneficial in patients presenting with ACS. These agents when used in combination have even greater beneficial effects and should be prescribed together to ACS patients unless there is a contraindication to an agent [29••].

Patients with ACS are at high risk for future cardiovascular events, and prevention is particularly compelling and cost-effective. Clinicians can use the index ACS event to aggressively treat the underlying pathophysiological process through therapeutic lifestyle modifications and potent drug therapies. By using management strategies aggressively, clinicians can improve survival and reduce future cardiovascular events in ACS patients.

Conclusions

Acute coronary syndrome is associated with high rates of future cardiovascular events despite available therapies. There is robust data that early diagnosis and optimal evidence–based therapies improve clinical outcomes. Typically, in the USA, most ACS patients undergo angiography and revascularization if indicated. An early invasive strategy is particularly beneficial in high-risk patients; current guidelines endorse such a strategy [2]. The use of DAPT, adjunctive effective anti-thrombotic drugs, and third-generation drug eluting stents continue to improve clinical outcomes in ACS patients undergoing percutaneous revascularization.

A multidisciplinary endeavor to continue the discharge risk reduction initiatives and to emphasis on medication and dietary compliance is imperative. Long-term management should include DAPT (for at least 1 year followed by aspirin lifelong), beta-blocker, statins, ACE inhibitors, and PCSK9 inhibitors if indicated in addition to lifestyle changes. There is evidence that higher-risk patients are less likely to receive optimal guideline-directed therapy [30] despite the fact that these individuals benefit the most from it and there needs to be structured strategies to optimize secondary preventative therapies for all patients with an ACS.

Compliance with Ethical Standards

Conflict of Interest Abhizith Deoker, Angelica Lehker, and Debabrata Mukherjee declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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