

The Evolving Face of Myocardial Reperfusion in Acute Coronary Syndromes: A Primer for the Internist



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Abstract

Acute coronary syndromes (ACSs) account for a large proportion of disease burden in the United States and worldwide, and our understanding of ACS management continues to evolve. In this review we take a practical approach to evaluating and treating a patient with ACS, focusing on the optimal timing and methods of coronary reperfusion. Beginning with initial assessment and risk stratification, a provider managing the patient with ACS must be able to expeditiously decide on and implement the correct guideline-directed pathway to optimize outcomes. With an ever-growing body and weight of knowledge in this field, the clinician is tasked with several challenges. First, there are a variety of pathways of care to be considered; second, adjunctive medical therapies are expanding; and third, when coupled with the multiple combinations of adjunctive supportive therapies for revascularization, the variety of potential therapeutic options can be overwhelming and confusing. Herein, we carefully review all the relevant guidelines and the contributing literature, taking a 4-step approach: (1) review the importance of risk stratification before engaging in a particular strategy of care, (2) define the reperfusion strategies available, (3) review the specific agents (antiplatelet and anticoagulant) that support reperfusion strategies, and (4) apply the strategies of care in the context of the clinical presentation.

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The treatment of acute ischemic heart disease has evolved, leading to dramatically better outcomes during the past 40 years. Although acute myocardial infarction (MI) was once treated with weeks of bed rest, the reperfusion era has heralded a therapeutic revolution using critical systems of rapid recognition and initiation of reperfusion strategies coupled with adjunctive medical therapies that support reperfusion. These critical pathways minimize myocardial injury and decrease morbidity and mortality. These advances have come at the cost of an ever-increasing complexity of therapeutic strategies; there are numerous combinations of therapeutic options available to treat patients with acute coronary syndromes (ACSs), creating challenges in decision making at the bedside. The therapeutic options are, however, well defined, but a major challenge is the dissemination of appropriate and prompt therapy into the community at large.

We searched PubMed and MEDLINE from January 1, 1980, through September 1, 2017, using the terms *acute coronary syndrome*,

guidelines, *thrombolysis*, *anticoagulation*, *STEMI*, *NSTEMI*, *NSTE-ACS*, *fibrinolysis*, and *PCI*, incorporating larger groundbreaking studies—both observational and randomized in nature—that have affected international guidelines. This review also carefully reviews all major societal guidelines for ACS and synthesizes and focuses on the initial recognition, risk stratification, and medical stabilization of patients with ACS. By outlining broad reperfusion strategies, punctuated with details of specific caveats related to adjunctive supportive medical therapies, we provide the reader with the tools to select and execute the optimal treatment approach for patients with ACS.

RISK STRATIFICATION IN PATIENTS WITH ACS

Appropriately identifying patients at higher risk for morbidity and mortality is imperative in the evaluation of ACS because in high-income countries, patients with non-ST-elevation ACS (NSTEMI-ACS) are surpassing those presenting with ST-elevation MI (STEMI) and with



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ARTICLE HIGHLIGHTS

- Diagnosis, risk stratification, and determining the etiology of acute coronary syndrome (ACS) are key aspects leading to efficient and proper reperfusion strategies.
- A distinction between ST-elevation myocardial infarction (STEMI) and non-ST-elevation ACS (NSTEMI) should be made to appropriately initiate the correct treatment pathways.
- Percutaneous coronary intervention (PCI) for STEMI is pursued if the patient is at a PCI-capable facility or if he or she can be transferred to a PCI-capable facility with a first medical contact to device time of less than 120 minutes.
- Fibrinolysis is reserved for patients with STEMI unable to be invasively revascularized within 120 minutes and should include loading with full-strength aspirin (325 mg), clopidogrel (300 mg if age ≤ 75 years; 75 mg if age > 75 years), and full unfractionated heparin dosing.
- Patients with NSTEMI who are at higher risk or show a deteriorating clinical status should be managed with invasive reperfusion within a 24-hour window. These patients should be loaded with dual antiplatelet therapy and unfractionated heparin before catheterization with the intent toward PCI.
- Coronary artery bypass graft surgery is an alternative revascularization strategy in patients with NSTEMI with multivessel disease or who would require high-risk PCI and in patients with STEMI with angiographic findings not amenable to PCI.

increasing levels of morbidity and mortality.¹ Components of the initial evaluation should include a careful history and physical examination with attention to pretest probability (ie, known coronary disease), intravascular volume status, and adequacy of systemic perfusion (Figure 1). Rapidly available diagnostic testing should include electrocardiography (ECG) (within 5 minutes of arrival if suspected ACS), chest radiography (with attention to cardiac size and pulmonary congestion as well as aortic size and configuration), and laboratory testing, including biomarkers of myocardial injury (specifically, cardiac troponins).^{2,3} Consideration should also be given to the use of bedside echocardiography and repeated ECG—potentially in right-sided or posterior leads—particularly in patients in whom the clinical diagnosis is uncertain.

A clear discrepancy between STEMI, which implies a completely occluded coronary

artery, and NSTEMI-ACS should be made early in the assessment because treatment pathways and outcomes depend on this distinction. Beyond the immediate evaluation with ECG and the distinction between STEMI and NSTEMI-ACS, serial biomarkers are important for prognosis and for distinguishing cardiac from noncardiac chest pain.^{2,3} Multiple risk scores include troponin elevations and ECG changes in their equation (Figure 1). These risk scores include TIMI (Thrombolysis in Myocardial Infarction),⁴ HEART (History, ECG, Age, Risk factors, and Troponin),⁵ PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy),⁶ and GRACE (Global Registry of Acute Coronary Events) scores.⁷ The TIMI risk score^{8,9} uses 7 key risk factors to estimate morbidity and mortality at 14 days from NSTEMI-ACS. The sum total of the respective points for each of these factors renders the percentage risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization at 14 days (from 4.7% for 0-1 points to 40.9% for 6-7 points).

The GRACE score is more complicated and requires the use of a calculator.⁷ It integrates age, heart rate, systolic blood pressure, Killip classification of acute heart failure, renal function, ST-segment deviation, presence of cardiac arrest at presentation, and elevated cardiac biomarkers. The GRACE score predicts the risk of mortality and repeated ACS during hospitalization and at 6 months and can be used to guide therapeutic decisions. A GRACE score greater than 140 indicates greater than 3% in-hospital mortality, and a score greater than 120 indicates 6-month mortality of more than 8%. Moreover, in the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial,¹⁰ allocating patients with high-risk NSTEMI-ACS (GRACE score > 140) to an early invasive strategy improved outcomes. Risk stratification informs further treatment decisions. As a patient's clinical risk increases, so too does the urgency and benefit of early invasive therapies.

REPERFUSION STRATEGIES

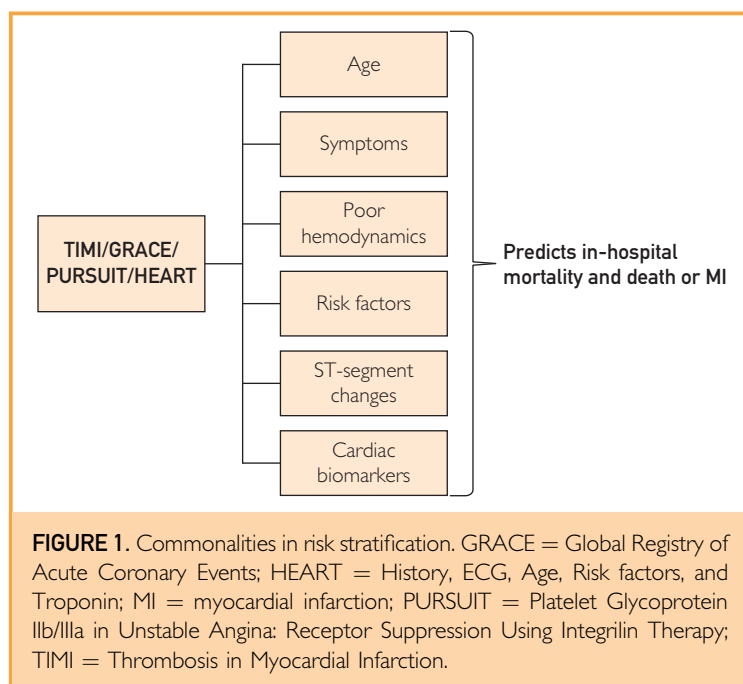
The cornerstone of the management of ACS is coronary revascularization in candidates with suitable anatomy. In patients with STEMI,

immediate revascularization should be sought with either a percutaneous approach (preferable if logistically feasible) or fibrinolysis. Antiplatelet and anticoagulant therapies support reperfusion where intracoronary plaque rupture or erosion and thrombosis are the underlying mechanisms. These strategies are used in synergy with fibrinolysis therapy in the case of STEMI or with revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) across the full spectrum of ACS, from unstable angina and NSTEMI to STEMI.¹¹

Medical Reperfusion: Fibrinolysis

When delivered early to selected patients with STEMI, fibrinolytic therapy can be one of the simplest and most cost-effective reperfusion strategies. Over time, acute thrombus matures and becomes more firm, with increased fibrin cross-linking. All fibrinolytic agents work to increase plasmin, which breaks down fibrin, thus removing the fibrin cross-links in the thrombus and allowing dissolution. The primary fibrinolytic agents in use include streptokinase (no longer available in the United States), alteplase (tissue plasminogen activator), tenecteplase (the primary agent used in the United States), and reteplase.

Fibrinolytic agents are most effective when administered within 120 minutes of the onset of ischemia, when the thrombus is softer, with less fibrin cross-linking.¹² Fibrinolytic therapy (the pharmacoinvasive strategy) is currently indicated for patients presenting with STEMI to a hospital without primary PCI capability if transfer for primary PCI will result in more than 120 minutes from first medical contact (FMC) to device time.¹¹ The door-to-needle time should be less than 30 minutes after arrival. Fibrinolysis is particularly effective in patients with anterior STEMI if administered within 60 minutes of onset. Overall, there is a 1.5% risk of major bleeding with the use of fibrinolysis. For patients with STEMI, fibrinolytic therapy should be simultaneously accompanied by antithrombotic (eg, heparin) and antiplatelet (aspirin plus clopidogrel) therapies. Given the importance of time considerations in patients with STEMI, it is important for each treatment center to develop a plan that integrates their role within a larger STEMI network to ensure an efficient and effective track to appropriate therapy. Also note that



the establishment of a well-organized, cohesive, and efficient STEMI network is a class I indication as directed by the American Heart Association American/College of Cardiology (AHA/ACC) guidelines.¹¹

Urgent angiography with a view toward “rescue PCI” should be pursued if there is less than 50% resolution of ST-segment elevation 90 minutes after administration.¹¹ Resolution of chest pain and the presence or absence of reperfusion arrhythmias are also useful markers of successful reperfusion. Importantly, patients should be given a full 90 minutes after fibrinolytic therapy before being taken to the catheterization laboratory because percutaneous intervention immediately after fibrinolysis (ie, so-called facilitated PCI) has been shown to worsen outcomes. Moreover, patients who receive fibrinolytics should be routinely transferred to a PCI-capable hospital for planned angiography (3-16 hours after receiving fibrinolytics) regardless of clinical status as part of the delayed-invasive strategy of care (class IIa recommendation).¹¹

Compared with percutaneous reperfusion strategies in patients with NSTEMI-ACS, outcomes such as death, nonfatal MI, and recurrent ischemia are worse with fibrinolysis with the added risk of increased fatal and nonfatal bleeding.¹³ Thus, there is no role for fibrinolytic

TABLE 1. Absolute and Relative Contraindications to Fibrinolysis

Absolute contraindications	Relative contraindications
Any previous intracranial bleeding	Hypertension (>180/110 mm Hg)
Known structural cerebral vascular lesion (eg, AVM)	Ischemic stroke >3 mo earlier
Recent ischemic stroke within the past 3 mo	Recent internal bleeding
Active bleeding (excluding menses)	Previous allergic reaction
Suspected aortic dissection	Pregnancy
Non—ST-elevation acute coronary syndromes	

AVM = arteriovenous malformation.

therapy in the treatment of NSTEMI-ACS. Furthermore, fibrinolysis should not be administered to patients receiving oral anticoagulation because the risk of bleeding while taking warfarin is unacceptably high, and there are no data on fibrinolysis and novel oral anticoagulant agents. The same can be said for patients receiving intravenous glycoprotein (GP) IIb/IIIa inhibitors as the risk of bleeding surpasses the potential benefit. Absolute and relative contraindications to fibrinolysis are provided in Table 1, with specific agents and characteristics listed separately (Supplemental Table, available online at <http://www.mayoclinicproceedings.org>).

Adjunctive Anticoagulation and Antiplatelet Therapies to Support Fibrinolysis

All fibrinolytic agents function by generating plasmin, which breaks down fibrin cross-links and yields fibrin degradation products. These degradation products can, themselves, be thrombogenic, so patients given fibrinolytics should also be given antithrombotic therapy with unfractionated heparin (UFH), enoxaparin, or bivalirudin (in patients with previous documented heparin-induced thrombocytopenia).¹⁴ Unfractionated heparin is used with an initial infusion of 4000 to 5000 IU (or up to 80 IU/kg) and then is titrated with an infusion to reach an activated partial thromboplastin time 1.5 to 2 times normative values (usually 75-80 seconds). Treatment with UFH should be continued for at least 48 hours, until subsequent PCI, or through the duration of the hospitalization (maximum of 8 days). Similarly, bivalirudin can be used at standard doses if there is a patient contraindication to heparin.¹¹

In addition to anticoagulation, patients with STEMI treated with fibrinolysis should receive dual antiplatelet therapy (DAPT) with

aspirin plus clopidogrel. Dual antiplatelet therapy should be completed with the initiation of a 300-mg loading dose of clopidogrel for patients 75 years and younger (75-mg starting dose for patients older than 75 years), and continued at a dose of 75 mg/d thereafter. Data on the safety of the newer DAPT agents, such as ticagrelor, prasugrel, or cangrelor, with fibrinolysis are not currently available,¹¹ and their increased risk of bleeding compared with clopidogrel should preclude their routine use with fibrinolysis.

Mechanical Reperfusion: PCI

Percutaneous coronary intervention is the most common reperfusion strategy for ACS in North America, Europe, and Asian countries such as Japan and Korea, using percutaneous transluminal coronary angioplasty with balloons to dilate critical stenosis of the culprit lesion, followed by stent deployment to increase long-term patency by reducing elastic recoil and restenosis. Drug-eluting stents are most frequently used today¹⁵ and reduce target vessel revascularization by impeding smooth muscle growth (neointimal proliferation) in the stent and subsequent in-stent restenosis. The benefit of drug-eluting stents is greatest with longer stents and in patients with diabetes.¹⁶

Aspiration thrombectomy in patients with STEMI was initially shown to improve myocardial blush grade and was previously supported by the AHA/ACC guidelines. It was believed that thrombus removal decreased microvascular obstruction and may reduce infarct size. Unfortunately, subsequent studies have not supported the net benefit, and the recommendation is currently to avoid the routine use of aspiration thrombectomy. It may still have a role in selected patients and circumstances, with careful attention to minimizing the risk of thrombus translation (moving to another vessel, eg, from the left anterior descending artery to the circumflex artery) and embolization (eg, stroke).¹⁶ Emerging data are promoting "complete" revascularization during the index ACS hospitalization.^{17,18} Although traditionally taught as a class III recommendation,¹¹ practice is now evolving to revascularize all physiologically significant lesions in patients who present with ACS (class IIb recommendation), although not necessarily during the initial intervention in the acute setting. More data with larger trials

that analyze staged vs simultaneous revascularization are needed to demonstrate a potential effect on repeated ACS and cardiovascular disease (CVD)—related death—not just repeated revascularization—before this is considered a class I indication.¹⁹

In anticipation of PCI, the preferred method of revascularization in STEMI, patients should receive usual guideline-driven antithrombotic and antiplatelet therapy, including a 1-time loading dose of aspirin, 325 mg, to be continued at 81 mg/d indefinitely, plus a P2Y₁₂ inhibitor. Antithrombotic therapy does not need to be interrupted before angiography or PCI.²⁰

Although femoral arterial access was historically used in PCI, transradial PCI is becoming the new standard in the acute setting because of improved outcomes and reduced bleeding complications. Multiple prospective randomized studies have demonstrated a survival benefit to the use of radial access compared with femoral arterial access in patients with STEMI; however, the explanation as to the mechanism of benefit remains speculative^{21,22} but might be related to a decrease in major bleeding, which has a significant influence on short- and long-term survival. In addition to reduced repeated events and mortality, radial access increases ambulation after the procedure and reduces bleeding complications.²³

Mechanical Reperfusion: CABG

In patients with multivessel disease presenting with NTE-ACS, left main coronary artery disease (CAD), or high-risk 2-vessel disease, CABG remains a valuable revascularization strategy.¹¹ The decision between surgical and percutaneous revascularization in ACS should be individualized and use a heart team approach. Lesion anatomy, ventricular function, patient medication adherence, patient preferences, and comorbidities should all be considered. There are limited randomized data regarding revascularization strategy in patients with ACS; however, emerging data point toward the benefit of complete revascularization and particularly surgical revascularization in diabetic patients with multivessel disease involving the left anterior descending artery and left ventricular dysfunction.

In patients with planned surgical revascularization, it is optimal to continue aspirin (81 mg) through surgery; however, their P2Y₁₂ antagonist should be held before surgery.

Clopidogrel or ticagrelor should be held 5 days before surgery, and prasugrel, with its class III indication for use before angiography, should be held for 7 days. However, unstable patients should proceed with surgery without delay.¹¹

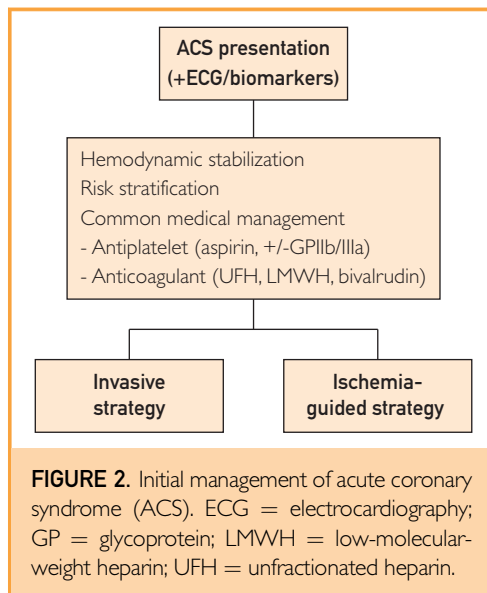
Unfractionated heparin can be continued until the time of surgery, whereas enoxaparin should be discontinued 12 to 24 hours before the surgery. Bivalirudin should be discontinued at least 3 hours before surgery. For patients in whom the GPIIb/IIIa inhibitors tirofiban and eptifibatide have been used, they should be held 2 to 4 hours before surgery. Abciximab should be held for 12 hours before surgery (class Ib¹¹). If there is an emergency clinical need, it is reasonable to proceed to the operating room at any time, irrespective of antiplatelet/anticoagulant treatment, at the discretion of the surgeon (class IIb).¹¹

APPROACH TO REPERFUSION STRATIFIED BY TYPE OF ACS

NSTE-ACS/Unstable Angina

Although the overall rate of CVD events is declining in the United States, the proportion of those events that are NSTEMI continues to increase.²⁴ Elderly patients are more likely to have complications from NSTEMI, such as bleeding, heart failure, and readmission with 4-fold higher in-hospital mortality. Another underrepresented population in NSTEMI data is women, despite CVD being the leading cause of morbidity and mortality in women throughout the world. Women have higher rates of NSTEMI and are more likely to have occult symptoms or complications from such an episode.

Invasive Treatment. An invasive strategy implies the decision to pursue angiography with the intent to treat a lesion(s) with a mechanical reperfusion strategy (PCI or CABG). The optimal timing of angiography in patients with ACS was tested in the ABOARD (Angioplasty to Blunt the rise Of troponin in Acute coronary syndromes Randomized for an immediate or Delayed intervention), TIMACS, and ISAR-COOL (Intracoronary Stenting With Antithrombotic Regimen Cooling Off) trials, and the cumulative evidence was analyzed by Katritsis and Ioannidis²⁵ in a meta-analysis. The



meta-analysis showed that patients with higher-risk profiles, eg, a GRACE score greater than 140 as in the TIMACS trial, had benefit from earlier intervention. Furthermore, there was no benefit to “cooling off,” there is no early hazard with an invasive approach, and with the earlier invasive patients there was less recurrent ischemia and shorter length of stay. Overall, with the increased availability and improved safety of cardiac catheterization laboratories, an early invasive approach, not necessarily immediate as in STEMI, has become the best strategy for patients with definite or likely ACS and markers of increased risk, such as ischemic ECG changes or rising troponin levels (Figure 2).

For patients with positive biomarkers and ECG changes with a high TIMI or GRACE score, this should lead one to use an invasive strategy (Figure 3). The timing of intervention is usually based on the clinical scenario. One should risk stratify to determine whether immediate (2-4 hours) revascularization should be pursued or if an early invasive approach will suffice (within 24 hours). Most cases proceed now within 24 hours per the TIMACS trial.¹⁰ Formerly, a delayed invasive strategy (24-72 hours) was thought to be best to medically optimize the patient and allow inflammatory mediators to abate; however, this strategy has repeatedly been found to have no benefit and a potential to harm.

Once the decision is made to proceed to PCI, antiplatelet therapy should continue with aspirin and P2Y₁₂ inhibitor (clopidogrel and ticagrelor can be administered upstream of angiography; prasugrel should not be commenced until coronary anatomy has been delineated), and anticoagulation can continue until near the beginning of the procedure, usually with UFH. Bivalirudin can also be used in this situation but should be continued beyond the procedure (unlike UFH) to avoid early in-stent thrombosis. Glycoprotein IIb/IIIa inhibition can be initiated for ongoing ischemia, complex PCI, concerns over inadequate P2Y₁₂ loading, and should really be used only with UFH.²

If clinical circumstances necessitate, mechanical circulatory support including intra-aortic balloon pump may be considered if there is a need to reduce afterload and improve coronary artery perfusion. This can actually be done after PCI or even if no PCI is performed, and the patient's anatomy is more suited for CABG. In fact, CABG is not an uncommon therapeutic option for patients presenting with NSTEMI-ACS because some databases report an 11% to 13%^{26,27} incidence of CABG in the same hospitalization as the index event, with much lower morbidity and mortality rates than would be predicted by their presenting GRACE scores.²⁸

Initial Ischemia-Guided Treatment Strategy. An initial ischemia-guided strategy involves optimal medical treatment (OMT) followed by an ischemia evaluation and is contrasted with an early invasive strategy in which patients are taken for angiography after OMT (Figure 2). An initial ischemia-guided strategy is recommended when ACS is less likely, if the patient has extensive comorbidities making an early invasive strategy prohibitive, or when the patient is exceedingly low risk (particularly low-risk women). After the initial hemodynamic assessment and management, the goal of an ischemia-guided strategy remains to reduce the oxygen supply/demand mismatch and reduce thrombus formation in the coronary arteries. Patients should be treated with antiplatelet and antithrombotic therapies in addition to OMT per ACS guideline recommendations (Figure 3).^{2,3} Notably, patients can cross over

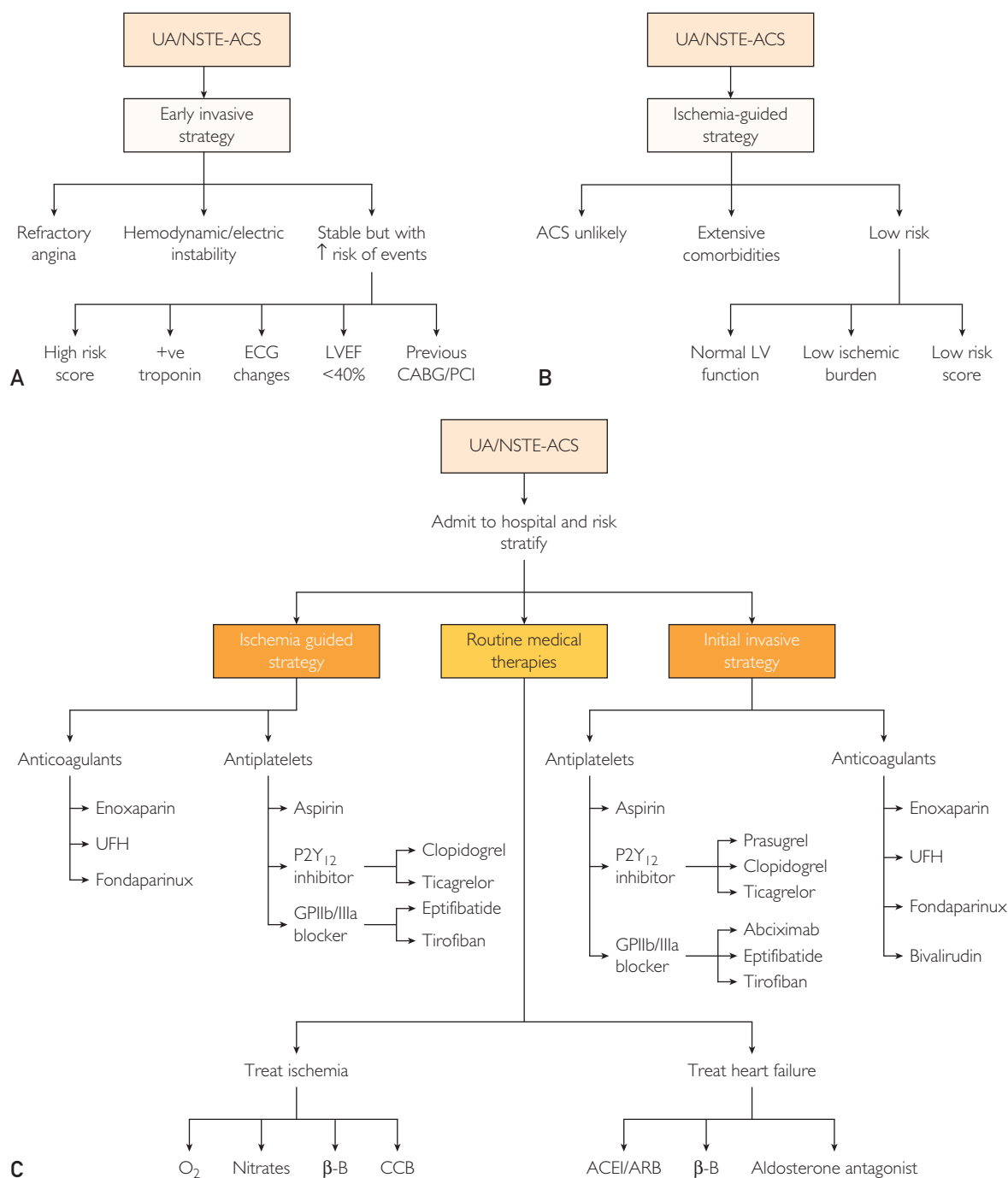
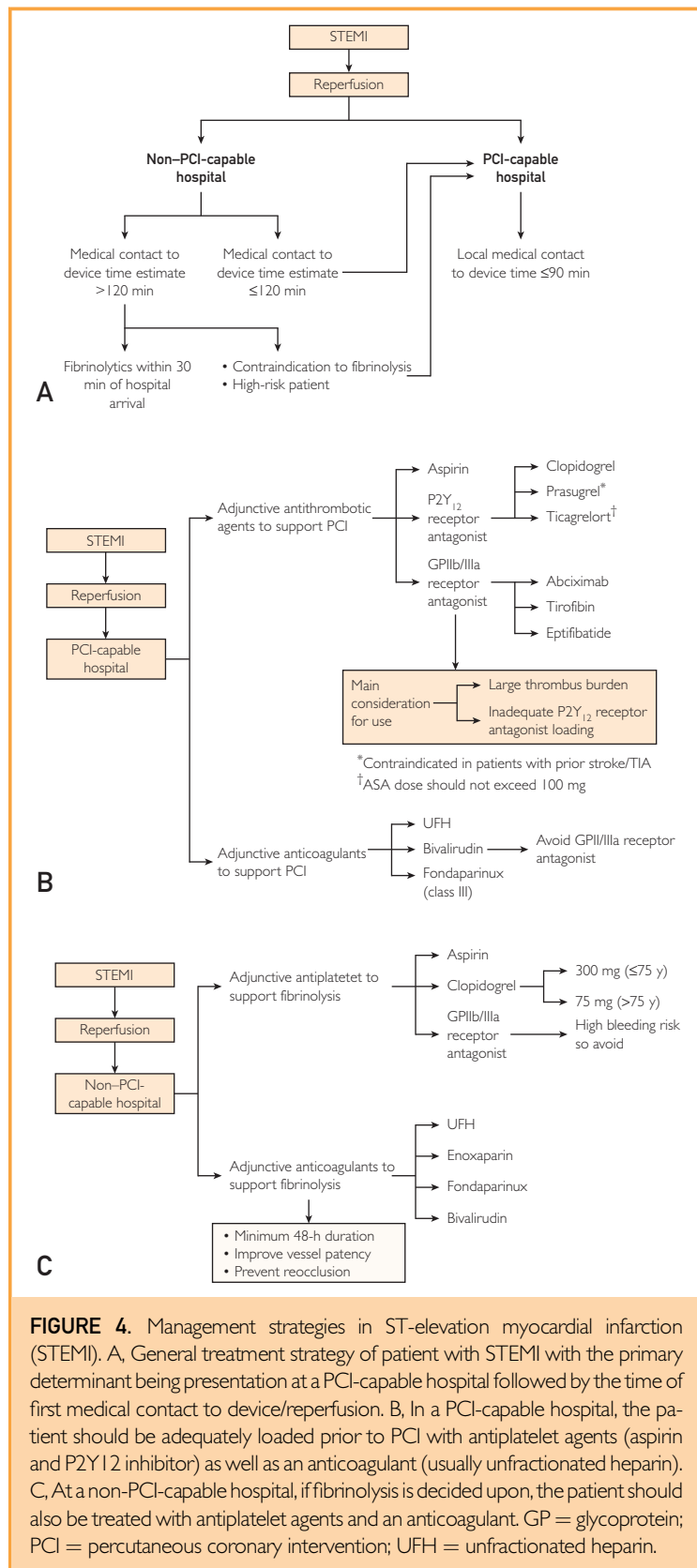


FIGURE 3. Initial invasive (A), ischemia-guided (B), and medical management (C) strategies for non-ST-elevation acute coronary syndrome (NSTE-ACS). ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; β-B = Beta blocker; CABG = coronary artery bypass graft surgery; CCB = calcium channel blocker; ECG = electrocardiography; GP = glycoprotein; LMWH = low-molecular-weight heparin; LV = left ventricular; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; UA = unstable angina; UFH = unfractionated heparin.



between the different treatment strategies at any point based on the clinical situation. The care team should engage in a process of evaluating and reevaluating the patient to craft the best care plan while remaining vigilant to indications and contraindications of medications and certain therapies.

ST-Elevation MI

ST-elevation MI remains diagnosed based on the presence of ST elevation on the surface ECG in a compatible clinical context and represents acute coronary vessel closure. Once the diagnosis of STEMI has been made, one must expeditiously decide whether an invasive or noninvasive approach is best (Figure 4). Reperfusion therapy should be offered to all patients with STEMI with a symptom onset less than 12 hours¹¹ or in the presence of ongoing pain even after 12 hours because it is sometimes difficult to pinpoint the precise onset of MI. Just as in NSTEMI-ACS, concomitant therapies to alleviate patient symptoms, optimize hemodynamics, and stabilize arrhythmias should constantly be revisited. Supportive therapy alone is also a consideration in the patient in whom serious comorbidities may increase the risk of any procedure beyond the purported benefit or if the wishes of the patient align with a less aggressive approach.

Pharmacologic Reperfusion in STEMI. The pharmacoinvasive reperfusion strategy with initial fibrinolysis should not be considered a definitive reperfusion strategy but rather a bridge to definitive mechanical reperfusion, be it percutaneous or surgical revascularization. The consideration for a pharmacoinvasive strategy with lytic therapy is based on the availability of a catheterization laboratory at the site of presentation, the duration of symptoms, and the time required to transfer a patient to a facility with a catheterization laboratory. Time to reperfusion in STEMI is the critical determinant of myocardial salvage; therefore, geography plays a large role in the initial reperfusion strategy with STEMI. If a patient is diagnosed at a PCI-capable facility within 12 hours of symptoms, primary PCI to the culprit artery should be performed with an FMC to device time of less than 90 minutes.¹¹ For patients diagnosed at a non-PCI-capable facility, if the patient can be

safely transferred to a PCI-capable facility and receive interventional reperfusion (ie, device) within 120 minutes of FMC, then this should be the strategy of care.¹¹ The door in–door out time is becoming an increasingly important metric for transferring facilities and should be less than 30 minutes. However, if the FMC-to-device time will be more than 120 minutes it is reasonable to provide fibrinolysis and then transfer to a PCI-capable center for further evaluation and medical management. Fibrinolysis in the setting of very short duration of symptoms (ie, within 60 minutes of symptom onset) may provide the advantage of the potential to abort the infarction completely (particularly in the setting of anterior infarction). This is an acceptable initial strategy, with the caveat that transfer to a PCI-capable facility is still recommended for diagnostic angiography and mechanical reperfusion.

Primary PCI. The preferred strategy for treatment of STEMI is primary PCI with a target door-to-balloon time of 90 minutes. Despite increasing efforts to reduce this time variable, the industry finds itself reaching a point of limited returns as door-to-balloon times have been reduced toward 60 minutes with diminishing improvements in outcomes.¹⁶

The remainder of the post-STEMI care is similar to that of NSTEMI-ACS discussed previously herein. Concomitant medical management should be continued, including aspirin, 81 mg orally indefinitely. Dual antiplatelet therapy should be in place for at least 1 year, with reconsideration of risks/benefits of continuation undertaken at that time.^{2,3}

CABG for STEMI. Just as with NSTEMI-ACS, CABG is a viable and sometimes necessary reperfusion strategy in STEMI after coronary anatomy has been defined and risk stratification has revealed this to be the most beneficial strategy, for example, in patients with STEMI involving adjacent critical left main coronary artery stenosis or multivessel disease.¹¹ Unlike NSTEMI-ACS, these high-risk procedures tend to have worse outcomes; however, revascularization options for the patient are usually limited at that point. Parameters for anticoagulation are not as strict as the situation is more urgent. Antiplatelet therapy can continue, but no further P2Y₁₂ inhibition

should be provided. Unfractionated heparin use should continue into surgery, but all other antithrombotics should be halted, as should GPIIb/IIIa inhibitors presuming that the patient will go to surgery within a few hours. Postoperative care is just as in CABG for NSTEMI-ACS or post-STEMI care.

Supportive Therapy for Mechanical Reperfusion: Antiplatelet Therapies. Antiplatelet therapy with a combination of aspirin plus a P2Y₁₂ inhibitor is essential as platelet activation and adhesion occurs during thrombus formation in STEMI and NSTEMI-ACS. With plaque rupture or erosion, exposed endothelium activates platelets via von Willebrand factor, collagen, and tissue factor. In addition to continued aggregation, platelets undergo shape and conformational changes in a feed-forward mechanism to solidify the platelet plug with thrombin and fibrin cross-linking. The activated platelet shape change releases thromboxane A₂, adenosine diphosphate (ADP), and thrombin. Both thromboxane A₂ and ADP are directly affected by antiplatelet therapy, with thrombin thought to be indirectly inhibited through antiplatelet therapies.¹⁴

Acetylsalicylic Acid. Acetylsalicylic acid (aspirin) irreversibly acetylates and inhibits cyclooxygenase (COX)—preferentially COX-1 over COX-2. Cyclooxygenase is responsible for the production of thromboxane A₂ and prostacyclin. Thus, aspirin has an important role in inhibiting continued platelet aggregation. In addition, COX inhibition permits continued production of vasodilatory and anti-aggregation prostaglandins. Once bound, aspirin is effective for the life of the platelet (7–10 days). The initial dose of aspirin (325 mg) should be administered in the emergency department if not en route to the hospital. Aspirin administration should be continued at a dose of 81 to 162 mg/d thereafter, indefinitely, regardless of STEMI or NSTEMI-ACS. An ongoing government-funded clinical trial, ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness), is asking the question regarding the optimal daily dose of aspirin in patients with stable CAD, with results expected soon.²⁹ WILLOW-ACS (Will Lower Dose Aspirin be More Effective

TABLE 2. P2Y₁₂ Inhibition for Acute Coronary Syndrome

Characteristic	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analog
Administration	Oral	Oral	Oral	Intravenous
Loading dose	600 mg orally	60 mg orally	180 mg orally	30 µg/kg bolus and 4 µg/kg/min infusion
Daily dose	75 mg orally	10 mg orally	90 mg orally twice daily	NA
Reversibility?	No	No	Yes	Yes
Activation	Prodrug, variable hepatic metabolism	Prodrug, stable hepatic metabolism	Active drug with active metabolites	Active drug
Onset of action	2-6 h	30 min	30 min	2 min
Duration of effect	3-10 d	7-10 d	3-5 d	1-2 h
Withdrawal before surgery	5 d	7 d	5 d	1 h
Plasma half-life	30-60 min	30-60 min	6-12 h	5-10 min

ATP = adenosine triphosphate; NA, not applicable.

Following ACS?) will also evaluate aspirin dose with the DAPT combination of ticagrelor. Should the patient have surgical CAD, based on angiographic findings, aspirin can be continued through the perioperative period.^{2,3,11}

P2Y₁₂ Antagonists. P2Y₁₂ inhibitors disrupt the ADP P2Y₁₂ interaction on the activated platelet, thus limiting further platelet aggregation, decreasing thrombosis, and reducing the overall procoagulant milieu during ACS. These powerful antiplatelet drugs improve morbidity and mortality and also have a class I indication in ACS (Table 2).^{2,3,11}

P2Y₁₂ inhibition is recommended in the hospital course for ACS or at the time of angiography in STEMI and NSTEMI-ACS. Patients are provided loading doses to expedite the therapeutic effect. Timing of the initiation of the P2Y₁₂ antagonist portion of DAPT inhibition, however, remains controversial. The AHA/ACC guidelines state that DAPT should be initiated before PCI but give no timetable for this therapy. Furthermore, early loading with DAPT could potentially delay CABG if the surgeon is uncomfortable with operating with the patient on DAPT. The ACCOAST (A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention [PCI] or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) registry³⁰ and a large British meta-analysis³¹ demonstrate no direct benefit in terms of outcomes to early initiation and

loading of P2Y₁₂ inhibition. Although PCI-CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) showed a benefit on major adverse cardiac events at 30 days and long-term in patients pretreated with clopidogrel, the median pretreatment time was 6 to 10 days, and not necessarily within the 4 to 24 hours of the currently used early invasive strategy.³² As a counterpoint, however, early oral DAPT initiation may reduce GPIIb/IIIa use, which will reduce bleeding complications in the catheterization laboratory. Bleeding has been demonstrated to be a poor short- and long-term prognostic indicator. Furthermore, newer meta-analytic data point to a reduction in 30-day events with clopidogrel pretreatment.³³ The decision on timing of adding a P2Y₁₂ inhibitor to aspirin should be carefully balanced in each patient, weighing the risks of inadequate antiplatelet coverage during PCI vs the potential delay in patients requiring CABG.

It is recommended to treat patients with ACS with DAPT for 1 year based on the CURE trial,³⁴ irrespective of the strategy of reperfusion. In addition, the AHA/ACC guidelines were updated in 2016 to recommend using P2Y₁₂ inhibition for 1 year (class I) in patients after CABG after ACS.²⁰ Emerging data suggest that an extended period of DAPT (up to 30 months) could be beneficial toward a reduction in stent thrombosis and repeated CVD events in patients who tolerate the first 12 months of DAPT. That being said, for 1000 patients continued on DAPT therapy, 3 will avoid stent thrombosis

and 6 MI at the cost of 5 major bleeds with an increase in noncardiac mortality.³⁵ At this point, the optimal duration of DAPT after ACS remains controversial and is an evolving area with specific trials designed to answer this question. Ultimately, the length of DAPT can be individualized based on risk factors and other comorbidities using the DAPT calculator,³⁶ with ongoing trials examining various lengths and permutations.

Clopidogrel. Clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Pharmaceuticals) is a second-generation thienopyridine converted from prodrug to its active form via CYP3A4 and 2C19 isoenzymes in the liver and intestines. In its active form, clopidogrel irreversibly inhibits the binding of ADP to P2Y₁₂. The recommended loading dose of clopidogrel in ACS is 600 mg orally to expedite its onset of action, achieving maximal platelet inhibition at 2 hours. Subsequent dosing should be 75 mg/d taken orally. Because clopidogrel is a prodrug requiring metabolic activation by CYP2C19, any genetic abnormality of that particular allele can increase or decrease the active amount of the drug circulation in the body. Rapid in-stent thrombosis in patients compliant with their clopidogrel regimen should prompt an evaluation for CYP2C19 allelic variants to investigate whether a medication change to another P2Y₁₂ inhibitory agent should be pursued. Currently, there are no recommendations to support investigating genetic variants upstream of clopidogrel use³⁷; however, there are ongoing studies investigating this notion.³⁸ Furthermore, large trials have shown no benefit to improving CVD outcomes using platelet activity testing concurrently with P2Y₁₂ inhibition therapy.³⁹

Prasugrel. Prasugrel (Effient; Eli Lilly & Co), a newer-generation thienopyridine, is also a hepatically transformed prodrug that irreversibly and noncompetitively inhibits P2Y₁₂ binding to ADP. Prasugrel should be loaded with 60 mg by mouth once, then continued at 10 mg by mouth daily for at least 1 year. Prasugrel has a faster onset of action and should be administered only after the diagnostic angiogram is completed and a decision to pursue percutaneous intervention is confirmed. Prasugrel is substantially more potent than clopidogrel and demonstrated a greater than 50% relative reduction in in-stent

thrombosis at a cost of increased bleeding compared with those treated with clopidogrel.⁴⁰ Owing to the increased bleeding risk, guideline therapy does not recommend administering prasugrel to patients who are older than 75 years or to those with low body weight (<60 kg); and prasugrel is contraindicated in those with a history of stroke or transient ischemic attack.² Furthermore, it should be noted that there are no data supporting the use of long-term use of prasugrel in patients with ACS who do not undergo PCI.⁴¹ Similar to clopidogrel, major adverse effects are bleeding and thrombocytopenia.

Ticagrelor. Ticagrelor (Brilinta; AstraZeneca), unlike clopidogrel and prasugrel, is not a prodrug; therefore, its onset is faster than that of other P2Y₁₂ inhibitors. This oral reversible noncompetitive inhibitor of the P2Y₁₂ receptor has a 12-hour half-life; therefore, it is administered as a 180-mg oral loading dose and 90-mg oral doses twice daily.¹⁴ Higher doses of aspirin (ie, >100 mg) should be avoided if given concomitantly with ticagrelor.⁴² Notable adverse effects with ticagrelor include dyspnea (related to increased adenosine bioavailability), bradycardia, bleeding, and rare atrioventricular block. Similar to clopidogrel, there are data supporting the use of ticagrelor in patients with ACS who do not undergo PCI via the invasive treatment strategy for up to 1 year.⁴³

Cangrelor. Cangrelor (Kengreal; Chiesi USA Inc) is an intravenous short-acting potent competitive inhibitor of P2Y₁₂. Platelet inhibition occurs within 20 minutes and returns with cessation of the intravenous infusion. Large randomized controlled trials have demonstrated its efficacy over and above that of clopidogrel, with no increase in cardiac surgical bleeding.⁴⁴ Although seemingly an ideal fit for patients with NSTEMI-ACS suspected of having multivessel CAD best suited to surgical revascularization, drug availability and cost have limited the real-world experience in the United States. Nevertheless, cangrelor could be an attractive option for immediate P2Y₁₂ inhibition in patients admitted to the hospital with high-risk ACS or STEMI in whom the coronary anatomy is unknown until the optimal revascularization strategy can be determined.

Vorapaxar. Vorapaxar (Zontivity; Aralez Pharmaceuticals US Inc) is a potent, oral, highly selective, competitive protease-activated receptor-1 antagonist shown to reduce CVD events in patients with a history of MI through the direct inhibition of thrombin-mediated platelet activation. This agent has yet to be widely used secondary to cost and increased bleeding risk, including intracranial hemorrhage in the setting of incremental clinical benefit,^{45,46} but should be considered in high-risk patients with repeated ACS.

Oral Antiplatelet Therapies, Special Situations: Atrial Fibrillation. With the standard practice of DAPT for up to 12 months after PCI, special consideration must be made when the patient has concomitant atrial fibrillation requiring anticoagulation with warfarin or a novel oral anticoagulant. Emerging data have shown no increase in adverse outcomes regarding stroke or stent thrombosis using a short duration (up to 1 month) of aspirin, 1 year of clopidogrel, and lifelong anticoagulation with warfarin⁴⁷ or rivaroxaban.⁴⁸ An ongoing group of trials will soon report results on various P2Y₁₂ inhibitors and novel oral anticoagulants on patients percutaneously revascularized traditionally requiring “triple therapy”—aspirin, P2Y₁₂ inhibitor, and oral anticoagulation. The emerging theme throughout these trials will likely be the increased risk in bleeding without a clinical benefit with the longer duration of use of aspirin in addition to the P2Y₁₂ inhibitor and anticoagulant. Furthermore, until other studies can show the safety and efficacy of other P2Y₁₂ inhibitors, such as ticagrelor or prasugrel, in patients who require anticoagulation, clopidogrel should be the long-term default second antiplatelet agent. Certainly, if clinically indicated secondary to the immediate need of an ACS presentation, one could presumably load with ticagrelor and then reload with clopidogrel at a later date because that strategy would seem to have a reduced bleeding risk as opposed to initiating a GPIIb/IIIa agent during urgent PCI. The preferred strategy for patients after 1 year of clopidogrel and anticoagulant (warfarin or rivaroxaban) is also undetermined and should be reevaluated for each patient based on his or her risk of events vs bleeding.

GPIIb/IIIa Inhibitors. Glycoprotein inhibitors are intravenously administered agents that directly block platelet adhesion and activation by binding at receptor integrin α IIb β 3 (a second target of ADP) and are categorized as small molecule (eg, tirofiban and eptifibatide) or monoclonal antibody (ie, abciximab). Their use has diminished in contemporary practice secondary to the success of potent DAPT regimens. Currently, GP inhibitor use is reserved for the catheterization laboratory when faced with a large thrombus burden or inadequate oral P2Y₁₂ inhibition most commonly in STEMI (Table 3). Although there remains a class IIa guideline recommendation to add either GPIIb/IIIa inhibitors eptifibatide or tirofiban to maximal medical therapy in patients with ongoing ischemia and symptoms, this is only for patients who are going for percutaneous revascularization.² Should the patient be referred for surgical revascularization after diagnostic angiography, then GPIIb/IIIa inhibition should be discontinued 4 hours before surgery. The primary adverse effect, aside from bleeding, is the increased risk of thrombocytopenia (0.3%-6%) seen 5 to 11 days after administration, which is more than doubled with abciximab.

Supportive Therapies for Mechanical Reperfusion: Anticoagulant Therapies. Anticoagulation therapy is recommended (class I) for all patients with ACS regardless of the decision to use an invasive or an ischemia-guided approach and can be accomplished with UFH, enoxaparin, fondaparinux, or bivalirudin. Anticoagulation is continued for at least 48 hours, up to 8 days, or the duration of the hospitalization in medically managed patients. It is discontinued after PCI if the patient goes on to an invasive strategy (Table 4).¹⁴

Unfractionated heparin remains a mainstay in the treatment of ACS because it potentiates the action of antithrombin III to inactivate thrombin and prevents conversion of fibrinogen to fibrin. In patients who have a known history of heparin-induced thrombocytopenia, heparin should be avoided. Alternatives include bivalirudin or fondaparinux for antithrombotic treatment.

Enoxaparin is a low-molecular-weight (4500 Da vs 16,000 Da for UFH) component of heparin that works to inhibit predominantly factor Xa and has a longer half-life (2-4 times

TABLE 3. Antiplatelet Agents in Acute Coronary Syndrome^{a,b}

Agent	Loading dose	Maintenance dose	Duration	Adverse effects	Contraindications	Comments
COX inhibitors						
Aspirin	324 mg	81 mg	Indefinitely	Bleeding, thrombocytopenia	Allergic reaction	
P2Y ₁₂ inhibitors						
Clopidogrel	300-600 mg	75 mg	1 mo bare metal stent 12-30 mo drug-eluting stent	Bleeding, thrombocytopenia		300 mg load for fibrinolysis or if PCI
Prasugrel	60 mg	10 mg BID	12 mo	Bleeding, thrombocytopenia	Previous stroke; age ≤75 y or weight <60 kg	
Ticagrelor	180 mg	90 mg BID	12 mo	Dyspnea, bleeding, bradycardia		
Cangrelor	30 µg/kg IV bolus infused over 1 min	4 µg/kg/min	2 h or duration of PCI	Bleeding, thrombocytopenia		
GP1Ib/IIla inhibitors						
Abciximab	0.25 mg/kg up to 1 h before PCI	0.125 µg/min for up to 24 h	12 h	Thrombocytopenia (2.4%)		Monoclonal antibody
Tirofiban	25 µg/kg over 5 min	0.15 µg/kg/min	Up to 18 h	Bleeding, thrombocytopenia		Target ACT >250 s Dose is 50% for CrCl <60mL/min/1.73 m ²
Eptifibatide	180 µg/kg 0.5 µg/kg/min for PCI	2 µg/kg/min (72 h) 0.5 µg/kg/min for PCI	24-72 h 24 h	Bleeding, thrombocytopenia		UFH bolus 5000 IU and 1000 IU/h infusion (APTT at 50-70 s)
Protease-activated receptor-1 antagonist						
Vorapaxar	NA	2.08 mg/d oral	Indefinite	Bleeding, retinopathy	High bleeding risk	Taken with aspirin and P2Y ₁₂ inhibitor

^aACT = activated clotting time; APTT = activated partial thromboplastin time; BID = twice daily; CrCl = creatinine clearance; GP = glycoprotein; IV = intravenous; NA = not available; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

^bSI conversion factor: To convert CrCl to mL/s/m², multiply by 0.0167.

TABLE 4. Antithrombotic Strategies for Acute Coronary Syndrome

Agent	Mechanism of action	Dose	Duration	Adverse effects	Contraindications	Comments
Unfractionated heparin	Antithrombin activation and binding of thrombin-antithrombin complex	Load: 60 U/kg Maintenance: 12 U/kg/h	Up to time of PCI or 2-8 d	Bleeding, HIT	Previous HIT, active bleeding	APPT of 1.5-2.0 times normal (60-80 s)
Enoxaparin	Activation of antithrombin directly	Load: 1 mg/kg every 12 h Maintenance: 1 mg/kg every 12 h	2-8 d	Bleeding, HIT	Previous HIT, active bleeding	Largely reserved for ischemia-guided strategy
Fondaparinux	Specific factor Xa inhibitor	<50 kg: 5 mg SC once daily 50-100 kg: 7.5 mg SC once daily >100 kg: 10 mg SC once daily	2-8 d	Bleeding, HIT	Upcoming invasive angiography Previous HIT, active bleeding	Should not be used for patients going to the catheter laboratory
Bivalirudin	Direct thrombin (factor IIa) inhibitor, halting thrombin-induced conversion of fibrinogen to fibrin	Load: 0.75 mg/kg Maintenance: 1.75 mg/h	Through time of PCI (or up to 8 h after PCI)			Alternative in patients with previous HIT

APTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; PCI = percutaneous coronary intervention; SC = subcutaneous.

longer) than UFH. Enoxaparin's effect is more consistent than that of UFH, and monitoring is not usually necessary. Although several trials have shown improved outcomes and less bleeding overall with the use of enoxaparin compared with UFH, analysis from the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial⁸ showed increased bleeding when switching between UFH and enoxaparin. Enoxaparin should be discontinued 12 to 14 hours before surgery.

Fondaparinux (Arixtra; GlaxoSmithKline) is a specific factor Xa inhibitor with once-daily dosing and a favorable bleeding profile. Unfortunately, there is an increase in the incidence of cardiac catheterization thrombus formation with fondaparinux,⁴⁹ so it is best reserved for patients who are not going to the cardiac catheterization laboratory. For patients undergoing angiography, additional anticoagulation is necessary.

Bivalirudin (Angiomax; The Medicines Company) is an intravenous direct thrombin (factor IIa) inhibitor that has consistently shown similar results to UFH in terms of efficacy in reducing ischemia with reduced bleeding events. Bivalirudin works by inhibiting the coagulation cascade further downstream, at the thrombin-induced conversion of fibrinogen to fibrin. The ACUTY (Acute Catheterization and Urgent Intervention Triage strategy) trial supports bivalirudin use as an alternative to UFH plus GPIIb/IIIa therapy in patients experiencing NSTEMI-ACS and undergoing planned or urgent PCI.⁵⁰ Bivalirudin use was associated with less bleeding than UFH plus GPIIb/IIIa use at a cost of increased stent thrombosis. Although the cumulative evidence from bivalirudin trials seems to suggest a net benefit over UFH, these combined outcomes incorporate both bleeding events and major cardiovascular events.⁵¹ The addition of the GPIIb/IIIa agent to UFH likely contributed to the increased bleeding rates; likewise, the use of radial access likely reduced bleeding rates in both arms.⁵² Bivalirudin may be best characterized as a pharmacologic component of a bleeding avoidance strategy; however, the recent trials would seem to show no difference in bleeding between the two,⁵² with potentially reduced postprocedural events with heparin.⁵³

MI With Nonobstructive CAD. One percent to 14% of patients with an acute chest pain syndrome will have positive biomarkers or ECG changes, or both, without clear coronary stenosis at the time of angiography, and some registry data suggest that these could be as frequent as 25% to 65%.⁵⁴ Nonetheless, there is an increasingly recognized subset of patients with NSTEMI-ACS in which the underlying pathologic mechanism is not clearly related to myocardial supply/demand mismatch. Some have myocarditis or pericarditis, and other possible etiologies in MI with nonobstructive CAD (MINOCAD) include microvascular dysfunction, missed complete and occult coronary artery occlusions, stress-induced cardiomyopathy (also known as Takotsubo cardiomyopathy), spontaneous coronary artery dissection (SCAD), or, rarely, vasospasm.

In patients with MINOCAD it is important to pursue additional imaging, for example, cardiac magnetic resonance imaging, to ascertain the mechanism of the event because it may alter management. Myocarditis/pericarditis will be treated differently than stress-induced cardiomyopathy, vasospasm, SCAD, or microvascular disease. Importantly, for patients with SCAD, recent case series data place an importance on aspirin monotherapy, hemodynamic stabilization with β -blockade to reduce heart rate, and the cessation of statin therapy (in the absence of traditional risk factors necessitating their administration) because there is a signal for worse outcomes in those who continue/initiate HMG-CoA reductase inhibitors. Percutaneous intervention in SCAD has also been associated with a high complication rate.⁵⁵

FUTURE DIRECTIONS AND CONTROVERSIES

Despite the voluminous body of literature spanning decades there remain unanswered and emerging questions regarding reperfusion in ACS. Ongoing and upcoming trials will hopefully shed light on these contentious issues in ACS.

There is a move to reevaluate the notion of door to balloon time and reframe the prerevascularization timing paradigm,⁵⁶ noting the diminishing mortality returns despite improved door to balloon times.⁵⁷ Moreover,

door to balloon time is not the only metric being evaluated to most appropriately treat patients with ACS; recent feasibility data from the RAPID STEMI (A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction) trial has demonstrated feasibility of point of care genotyping for the CYP2C19*2 allele potentially providing more individualized antithrombotic therapy.⁵⁸ As self-monitoring and communicative technology continue to improve, these innovative means to personalize ACS care could provide the largest gains in expeditiously treating patients with ACS.

In addition, the radial access is a class 1 recommendation according to European Society of Cardiology guidelines, whereas the AHA/ACC guidelines do not give an explicit recommendation.⁵⁹ Radial access will continue to surpass femoral access, and its mortality benefit has been repeatedly shown. In the setting of unstable STEMI/ACS necessitating temporary pacing and/or large-bore access for hemodynamic support, it is unclear whether there is still superiority with radial access. Furthermore, the soon-to-be-published ARISE (AngioSeal versus the Radial approach In acute coronary SyndromE) trial⁶⁰ will also provide data comparing vascular closure devices using a femoral approach and radial access in NSTEMI-ACS. Could radial access become the default in all patients with ACS? Despite the increased expertise of operators and the wealth of data supporting its use, there might still be a need for future trials to sway guideline statements.

Finally, debate regarding the duration of “triple therapy” (DAPT and warfarin) remains one of if not the most unsettling in ACS therapeutics. The burgeoning number of patients necessitating anticoagulation as part of their medical regimen presents immense challenges in terms of balancing the risk of thrombosis secondary to ischemic heart disease on the one hand vs bleeding secondary to aggressive antithrombotic therapies on the other. Fortunately, recent studies such as PIONEER-AF (Prevention of bleeding in patients with atrial fibrillation undergoing PCI)⁴⁸ and ReDUAL-PCI Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients

with Nonvalvular Atrial Fibrillation Undergoing PCI⁶¹ are providing some insight into acceptable anticoagulant + antiplatelet regimens for this growing group of patients, with newer trials such as TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention)⁶² potentially providing data to support less-intensive approaches. Clearly, this is an unsettled realm of ACS reperfusion, and one most ripe for future thought and discussion.

CONCLUSION

Thus, careful evaluation and risk stratification are early initial tools in the management of patients presenting with ACS. These myriad options in treating this highly variable and potentially mortal entity can be navigated successfully by following appropriate algorithms detailing antiplatelet, anticoagulant, and reperfusion strategies.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: ACS = acute coronary syndrome; ACT = activated clotting time; ADP = adenosine diphosphate; AHA/ACC = American Heart Association American College of Cardiology; APTT = activated partial thromboplastin time; AVM = arteriovenous malformation; BID = twice daily; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; COX = cyclooxygenase; CrCl = creatinine clearance; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; ECG = electrocardiography; FMC = first medical contact; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; IV = intravenous; LMWH = low-molecular-weight heparin; MI = myocardial infarction; MINOCAD = myocardial infarction with nonobstructive coronary artery disease; NSTE-ACS = non-ST-elevation acute coronary syndrome; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SC = subcutaneous; SCAD = spontaneous coronary artery dissection; STEMI = ST-elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin

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