Acute coronary syndromes (ACS) constitute a spectrum of clinical presentations ranging from unstable angina and non–ST-segment elevation myocardial infarction to ST-segment myocardial infarction. Myocardial ischemia in this context occurs as a result of an abrupt decrease in coronary blood flow and resultant imbalance in the myocardial oxygen supply–demand relationship. Coronary blood flow is further compromised by other mechanisms that increase coronary vascular resistance or reduce coronary driving pressure. The goals of treatment are to decrease myocardial oxygen demand, increase coronary blood flow and oxygen supply, and limit myocardial injury. Treatments are generally divided into disease-modifying agents or interventions that improve hard clinical outcomes and other strategies that can reduce ischemia. In addition to traditional drugs such as β-blockers and inhibitors of the renin–angiotensin–aldosterone system, newer agents have expanded the number of molecular pathways targeted for treatment of ACS. Ranolazine, trimetazidine, nicorandil, and ivabradine are medications that have been shown to reduce myocardial ischemia through diverse mechanisms and have been tested in limited fashion in patients with ACS. Attenuating the no-reflow phenomenon and reducing the injury compounded by acute reperfusion after a period of coronary occlusion are active areas of research. Additionally, interventions aimed at ischemic pre- and postconditioning may be useful means by which to limit myocardial infarct size. Trials are also underway to examine altered metabolic and oxygen-related pathways in ACS. This review will discuss traditional and newer anti-ischemic therapies for patients with ACS, exclusive of revascularization, antithrombotic agents, and the use of high-intensity statins. (Circ Res. 2014;114:1944-1958.)

Key Words: acute coronary syndrome ■ ischemic preconditioning ■ reperfusion injury
Pathophysiology of Myocardial Ischemia

Myocardial ischemia derives from an imbalance between myocardial oxygen supply and demand. Because myocardial oxygen extraction is near maximal in the resting state, any increase in tissue oxygen delivery in response to increased demand occurs mainly through an increase in coronary blood flow (CBF). In the setting of an acute coronary syndrome (ACS), ischemia is driven in large measure by an abrupt decrease in CBF consequent to the formation of a fully or partially obstructing platelet-fibrin thrombus at the site of rupture or erosion of a vulnerable plaque. CBF can be further compromised by increases in left ventricular (LV) diastolic pressures rise. Most anti-ischemic pharmacological strategies are targeted to modulating ≥1 components of the oxygen supply–demand relationship.

Myocardial Ischemia and Reperfusion

The time course of irreversible ischemic myocardial injury (infarction) depends on the interplay between the forces dictating myocardial oxygen supply and demand. Infarction (myocyte necrosis) typically develops after 20 minutes of complete coronary artery obstruction in the absence of collateral flow. The injury begins in the subendocardial layer and spreads centrifugally as a wavefront to the subepicardium with completion of a nearly complete transmural infarction by 6 hours. Reperfusion injury with release of oxygen-free radicals and other toxic substances can further accelerate myocardial cell death; migration of leukocytes into the area of injury amplifies the process. Later in the time course of evolution, programmed cell death (apoptosis) occurs, adding to the amount of injury but doing so independently of the inflammatory cascade. Autophagy is an additional mechanism leading to cell death in the chronic phase of healing. Attenuation of these several processes may limit the extent of injury and adverse postinfarction remodeling.

After acute reperfusion in the setting of coronary occlusion or relief of a severe ischemic insult, regional myocardial function remains depressed for variable periods of time, a process referred to as stunning and indicative of a downward shift in the tightly coupled relationship between CBF and function. Functional recovery is anticipated in the absence of repeated ischemic insults. Importantly, restoration of epicardial flow after a period of occlusion does not always correlate with tissue perfusion, which may be further compromised by endothelial cell swelling, microembolization, and vasoconstriction. The angiographic demonstration of no-reflow after culprit artery recanalization equates with larger infarcts and higher risks of complications. Mechanical and pharmacological efforts to improve tissue perfusion in this context have thus far met with neutral or at best mixed results.

Attempts to reduce infarct size and shorten the period of regional myocardial dysfunction via pre- or postconditioning
mechanisms may also be of value. Ischemic preconditioning attenuates myocyte necrosis by the production of brief, reversible periods of ischemia (induced either locally or remotely) before coronary artery occlusion. Patients with an antecedent history of angina tend to have smaller infarcts than those who do not have angina leading up to the acute event. Similarly, the magnitude of ST-segment elevation seen during coronary artery occlusion at time of percutaneous coronary intervention (PCI) decreases with each successive balloon inflation. Delayed preconditioning can persist for several days after coronary artery occlusion and may protect the heart from ischemia/reperfusion-mediated stunning. Ischemic preconditioning may reduce the amount of myocardial necrosis by the production of intermittent ischemia or delivery of pharmacological agonists at the time of reperfusion, a strategy that may hold relatively greater promise for clinical application.

Nonatherosclerotic ACS
There are several nonatherosclerotic causes of ACS, including, among others, primary vasospasm (Prinzmetal or variant angina), stress cardiomyopathy (Takotsubo), cocaine ingestion, and spontaneous coronary dissection. The several mechanisms by which these entities result in myocardial ischemia include intense vasoconstriction, platelet activation, endothelial dysfunction, catecholamine toxicity, or luminal obstruction from an intimal flap. In the case of spontaneous or cocaine-induced spasm, vasodilator therapy with nitrates or calcium channel blockers (CCBs) constitutes the initial management strategy. There is no effective therapy for stress cardiomyopathy, a transient phenomenon presumably because of catecholamine excess and regionalized LV stunning.

Overview of Therapy for ACS
The term ACS constitutes a spectrum of clinical disorders, ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation MI (STEMI). Differentiation of these entities is based on ECG interpretation and measurement of elevated cardiac biomarker levels. The clinical manifestations of the syndrome, in turn, relate chiefly to the extent and duration of coronary artery obstruction. Therapies in addition to urgent mechanical reperfusion/revascularization and antithrombotic agents are important adjuncts to any management strategy that seeks to limit the ischemic insult and its downstream consequences. Whereas some interventions may only attenuate the symptoms and signs of acute ischemia, others may indeed be disease-modifying, by virtue of their proven ability to reduce the risk of hard clinical outcomes, including recurrent MI and death. Late events after treatment of ACS can develop as a consequence of the initial injury (arrhythmia, LV remodeling, heart failure [HF], aneurysm formation, functional mitral regurgitation) or because of repeated ischemic insults in the same or remote arterial distributions. Aggressive efforts at secondary prevention, therefore, are critical. In the following sections, we will focus on traditional (Tables 1 and 2) and newer anti-ischemic (Table 3) methods of treatment for ACS, exclusive of revascularization, antithrombotic strategies, and lipid-lowering treatments. Information about the use of such traditional medical therapies is especially relevant in countries with developing economies where 80% of cardiovascular mortality now occurs and PCI is either too costly or not available.

Traditional Pharmacological Approaches
Traditional pharmacological therapies used in the management of ACS include those that reduce oxygen demand or increase myocardial oxygen supply chiefly by augmentation of CBF. Reduction of myocardial oxygen demand may be accomplished by decreasing heart rate, lowering wall stress, or reducing myocardial contractility. Wall stress is lowered by decreases in preload (the radius term in the Laplace relationship) or afterload (the pressure term in the Laplace relationship). Increases in CBF and augmented myocardial oxygen delivery are generally achieved through vasodilation of coronary resistance and conduit vessels.

The outcomes associated with the agents discussed in this section were studied mostly during an era before the use of contemporary methods for coronary reperfusion and revascularization, routine administration of potent antithrombotic

<table>
<thead>
<tr>
<th>Class of Medications</th>
<th>Mechanism of Action</th>
<th>Efficacy for Hard Clinical Outcomes in ACS</th>
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<tbody>
<tr>
<td>β-Blockers</td>
<td>Decrease heart rate, blood pressure, and contractility through antagonism of β1 receptors</td>
<td>Decrease mortality in ACS. Increases in reducing risk of cardiogenic shock. Long-term secondary prevention benefit is less certain in patients without heart failure or reduced left ventricular systolic function</td>
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<tr>
<td>Nitrates</td>
<td>Decrease preload through venodilation; vasodilate coronary arteries</td>
<td>No benefit on mortality</td>
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<tr>
<td>Calcium channel blockers</td>
<td>May vasodilate, reduce heart rate, or decrease contractility depending on specific drug</td>
<td>No clear benefit on mortality or reinfarction in ACS. Increased reinfarction rate when nifedipine is used alone in ACS</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Block conversion of angiotensin I to angiotensin II and decrease systemic vascular resistance</td>
<td>Decrease mortality and heart failure when used in acute myocardial infarction. Long-term secondary prevention benefit in patients with normal ejection fraction is less certain</td>
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<tr>
<td>Angiotensin II receptor blockers</td>
<td>Displace angiotensin II from the angiotensin II type 1 receptor and decrease systemic vascular resistance</td>
<td>Noninferior to ACE-I in reducing mortality and cardiovascular events after ST-segment elevation myocardial infarction</td>
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<tr>
<td>Aldosterone antagonists</td>
<td>Competitively inhibit binding of aldosterone to receptors and prevent detrimental effects of renin–angiotensin–aldosterone system cascade</td>
<td>Reduce mortality and sudden cardiac death in patients with acute MI with reduced ejection fraction and symptoms of heart failure or diabetes mellitus</td>
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</table>
The results of clinical trials studying the use of β-blockers in ACS indicate improved outcomes from both early and chronic use. A cumulative meta-analysis of 28 trials indicated a mortality decrease of 28% at 1 week after MI with most of the benefit occurring in the first 48 hours.18 There was also an overall 18% reduction in the cumulative rate of reinfarction and a 15% reduction in the cumulative rate of cardiac arrest. A meta-analysis of 82 randomized trials of β-blockers in patients with acute or previous MI demonstrated a significant reduction in long-term mortality.19 The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry showed that patients with UA/NSTEMI treated with β-blocker therapy had a 34% risk-adjusted decrease in hospital mortality (P<0.001).20 Conversely, a propensity score–matched analysis of 21,860 patients with either CAD risk factors, known CAD, or prior MI in the Reduction
of Atherothrombosis for Continued Health (REACH) registry did not show any reduction in a composite of cardiovascular death, nonfatal MI, or nonfatal stroke with β-blocker therapy. In addition, the UA/NSTEMI guidelines indicate that it may be harmful (COR III, LOE A) to give intravenous β-blockers to patients with STEMI and no contraindications. It is reasonable to administer (COR IIa, LOE B) intravenous β-blocker therapy >3 years, but this is now a weaker recommendation than in the past guidelines (COR IIa, LOE B), as corroborated by the findings in the REACH registry. The European Society of Cardiology (ESC) guideline recommendations for β-blockers in patients with STEMI and NSTEMI27,28 are generally similar to the ACC/AHA guidelines on secondary prevention26 state that β-blocker therapy after MI should be continued for ≤3 years in the absence of LV dysfunction (COR I, LOE A). It is reasonable to continue β-blocker therapy >3 years, but this is now a weaker recommendation than in the past guidelines (COR IIa, LOE B), as corroborated by the findings in the REACH registry. The European Society of Cardiology (ESC) guideline recommendations for β-blockers in patients with STEMI and NSTEMI27,28 are generally similar to the ACC/AHA guidelines but include a specific COR I (LOE: A for STEMI, B for NSTEMI) recommendation for the use of oral β-blockers in all patients with LV dysfunction without contraindications.

### Nitrate Therapy

Drug therapy with nitrates exerts beneficial effects by decreasing preload and LV end-diastolic volume, thereby reducing myocardial oxygen demand. Nitrates also dilate both normal and diseased coronary arteries, an action that potentially increases both antegrade and collateral CBF. When given in the presence of phosphodiesterase inhibitors, the vasodilation resulting from nitroglycerin is substantially increased and prolonged and results in profound hypotension.29 Thus, its use

<table>
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<th>Table 3. Newer and Experimental Agents in ACS</th>
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<tr>
<td><strong>Therapeutic Agent</strong></td>
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<tr>
<td>Ranolazine</td>
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<td>Trimetazidine</td>
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<td>Nicorandil</td>
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<td>Ivabradine</td>
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<td>Adenosine</td>
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<td>Cyclosporine</td>
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<td>TR040303</td>
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<tr>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Glucose/insulin/potassium</td>
</tr>
<tr>
<td>Metformin</td>
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<tr>
<td>Oxygen</td>
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</table>

ACS incidates acute coronary syndrome.

It is reasonable to administer (COR IIa, LOE B) intravenous β-blockers to patients with STEMI and no contraindications who are hypertensive or have ongoing ischemia. Similar recommendations are made for patients with UA/NSTEMI34,25. In addition, the UA/NSTEMI guidelines indicate that it may be harmful (COR III, LOE A) to give intravenous β-blockers to patients with signs of HF, low-output state, or other risk factors for cardiogenic shock. Notably, the current ACC/AHA guidelines on secondary prevention26 state that β-blocker therapy after MI should be continued for ≤3 years in the absence of LV dysfunction (COR I, LOE A). It is reasonable to continue β-blocker therapy >3 years, but this is now a weaker recommendation than in the past guidelines (COR IIa, LOE B), as corroborated by the findings in the REACH registry. The European Society of Cardiology (ESC) guideline recommendations for β-blockers in patients with STEMI and NSTEMI27,28 are generally similar to the ACC/AHA guidelines but include a specific COR I (LOE: A for STEMI, B for NSTEMI) recommendation for the use of oral β-blockers in all patients with LV dysfunction without contraindications.

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must be avoided when treating patients with UA/NSTEMI or STEMI who have taken sildenafil or tadalafil within the previous 24 to 48 hours, respectively. Nitrates should also be avoided in patients with right ventricular dysfunction who are exquisitely preload-dependent.

Typically, nitrates are used in patients with ACS who have hypertension or HF and in those with continued angina. Although a review of small studies in the era before reperfusion suggested a reduction in mortality for patients with MI receiving nitrates, a major benefit was not confirmed in 2 large RCTs. The Fourth International Study of Infarct Survival (ISIS-4) trial randomized 58,050 patients with acute MI in a 2x2 fashion to various therapies, including oral isosorbide mononitrate versus placebo. There was no difference in 18-month mortality or the combined end point of mortality and severe LV dysfunction.

The ACC/AHA guidelines make no formal recommendations for the use of nitrates in patients with STEMI. Nitrate therapy is recommended for patients with UA/NSTEMI with ongoing ischemic discomfort (COR I, LOE C), for patients with ECG changes indicative of ischemia, and for chest discomfort after cocaine use (COR I, LOE C). The ESC guidelines for STEMI recommend intravenous nitrate use in patients with elevated blood pressure (COR IIa, LOE C), in patients with HF who are intolerant of both angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs; COR IIa, LOE C), and in patients with Killip class III HF without hypotension (COR I, LOE C). Thus, the evidence base for nitrate use in ACS from RCTs is limited, and existing guideline recommendations derive exclusively from expert consensus opinion only (ie, LOE C).

**Calcium Channel Blockers**

CCBs may cause vasodilation, reduce heart rate, or decrease myocardial contractility. Because these effects occur to a variable extent with the various CCBs, there is not a class effect. Dihydropyridine CCBs such as nifedipine and amiodipine predominately produce vasodilation, resulting in a fall in blood pressure and reflex tachycardia. The nondihydropyridine CCBs, diltiazem and verapamil, decrease heart rate, the rate of atrioventricular conduction, blood pressure, and myocardial contractility. Short-acting dihydropyridines such as the nonsustained release form of nifedipine must not be given to patients with ACS in the absence of β-blocker therapy because of the associated deleterious risk of reflex tachycardia. Similarly, verapamil and diltiazem, because of their negative inotropic effects, should be avoided in patients with pulmonary edema or severe HF. The Danish Verapamil Infarction Trial (DAVIT-II) study examined 1775 patients with acute MI who were treated with verapamil or placebo. There was no difference in 18-month mortality with verapamil therapy compared with placebo. However, when analyzing trial patients without HF, verapamil was associated with a reduction in mortality (P=0.02). The Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) studied nifedipine and metoprolol in patients with UA/NSTEMI and was stopped early because of an increased reinfarction rate in the nifedipine group compared with the metoprolol group. In contrast, patients treated with metoprolol benefited from the addition of nifedipine in terms of a reduction in rates of recurrent ischemia or MI <48 hours. A review of 28 RCTs involving 19,000 patients with ACS showed no benefit from CCB therapy on infarct size, rate of reinfarction, or death. Thus, the major benefit from CCB use in ACS is a symptom or augmented hemodynamic control, and they are not recommended as routine, initial therapeutic agents.

The ACC/AHA UA/NSTEMI guidelines recommend that for patients with continuing or frequent ischemia in whom a β-blocker cannot be given, a nondihydropyridine CCB should be administered (COR I, LOE B) in the absence of clinically significant LV dysfunction or other contraindications. It is reasonable to give a nondihydropyridine CCB (COR IIa, LOE C) to patients with recurrent ischemia after β-blockers and nitrates have been fully used. The guidelines emphasize that immediate-release dihydropyridine CCBs should not be administered to patients with UA/NSTEMI in the absence of a β-blocker (COR III, LOE A). The ACC/AHA STEMI guidelines make no formal recommendations about CCB use. The ESC NSTEMI ACS guidelines have a COR I, LOE B recommendation for CCBs (dihydropyridine type) for symptom relief in patients already receiving nitrates and β-blockers, and for patients with contraindications to β-blockade (benzothiazepine or phenylethylamine [nondihydropyridine] type). There is a COR I, LOE C recommendation that CCBs be given to patients with vasospastic angina. The ESC guidelines also state that nifedipine or other dihydropyridines are not recommended unless combined with β-blockers (COR III, LOE B).

**Inhibitors of the Renin–Angiotensin–Aldosterone System**

Activation of the renin–angiotensin–aldosterone system by several factors is known to occur in the setting of ACS, resulting in increased production of angiotensin II with subsequent increases in vascular resistance, myocardial workload, and myocardial oxygen demand. Accordingly, a variety of therapies known to inhibit the activated renin–angiotensin–aldosterone system has been studied in clinical trials to determine their potential efficacy to improve outcomes among patients with ACS. Use of these agents to disrupt renin–angiotensin–aldosterone signaling also inhibits the downstream detrimental pathways of long-term fibrosis and both myocardial and vascular remodeling.

**Angiotensin-Converting Enzyme Inhibitors**

ACE-Is block the conversion of angiotensin I to angiotensin II, thereby reducing the vasoconstrictive and aldosterone-stimulating effects of angiotensin II. ACE-Is have been studied extensively in patients with MI both with and without HF. The Survival and Ventricular Enlargement (SAVE) trial
randomized 2231 patients with LV systolic dysfunction (LV ejection fraction [EF] <0.40) but without overt HF after MI to captopril or placebo. There was a 19% risk reduction in all-cause mortality during an average follow-up of 42 months (P=0.019), as well as significant reductions in severe HF, HF hospitalizations, and recurrent MI. The Acute Infarction Ramipril Efficacy (AIRE) study examined the effects of ramipril versus placebo in 2006 patients with clinical evidence of HF after an acute MI. There was a 27% risk reduction in all-cause mortality (P=0.002). Lastly, the Trandolapril Cardiac Evaluation (TRACE) study compared treatment with trandolapril versus placebo in 1749 patients with LV dysfunction (EF <0.35) followed for 24 to 50 months after MI. The relative risk (RR) of all-cause death in the trandolapril group was 0.78 (95% confidence interval [CI], 0.67–0.89; P=0.001). Trandolapril also reduced the risk of death from cardiovascular causes (RR, 0.75; 95% CI, 0.63–0.89; P=0.001) and sudden death (RR, 0.76; 95% CI, 0.59–0.98; P=0.03). Progression to severe HF was less frequent in the trandolapril group (RR, 0.71; 95% CI, 0.56–0.89; P=0.003).

In addition to these selective trials in post-MI patients with LV dysfunction, 2 large trials looked at the nonselective use of ACE-Is in survivors of MI. The ISIS-4 trial randomized 58050 patients with acute MI in a 2x2 fashion to various therapies, including captopril versus placebo. There was a 7% reduction in 5-week mortality with captopril (P=0.01), and this survival advantage persisted at 12 months. There was more severe hypotension in the captopril group. The GISSI-3 trial studied the effects of lisinopril, transdermal glyceryl trinitrate, and their combination in 19394 unselected patients with acute MI. Lisinopril use was associated with a reduction in 6-week mortality (odds ratio, 0.88; 95% CI, 0.79–0.99), as well as a composite end point of mortality and severe ventricular dysfunction (odds ratio, 0.90; 95% CI, 0.84–0.98). These findings persisted when lisinopril and nitrates were used in combination. Oral ACE-Is have been shown to improve outcomes among patients with STEMI in a manner that is independent of other therapies, including aspirin, fibrinolytics, and β-blockers. Their renal protective effects make their use in patients with diabetes mellitus or chronic kidney disease especially beneficial. The magnitude of their effect on mortality in RCTs has been relatively higher in patients with LV dysfunction after MI. Early administration of ACE-Is to high-risk patients such as those with anterior MI, LVEF <0.40, and HF has consistently been shown to improve acute and long-term outcomes. The long-term secondary prevention benefits of ACE-Is in lower-risk patients with atherosclerotic CAD and normal LVEF who have been revascularized and optimally treated with other secondary prevention therapies such as statins and aspirin are less certain. The ACC/AHA STEMI guidelines state that ACE-Is should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or LVEF ≤0.40, unless contraindicated (COR I, LOE A). ACE-Is are reasonable for other patients with STEMI (COR IIa, LOE A). The ACC/AHA NSTEMI guidelines are similar except that diabetes mellitus is a COR I indication for ACE-I therapy. The ESC recommendations for STEMI similarly state that ACE-Is are indicated starting within the first 24 hours of STEMI in patients with evidence of HF, LV systolic dysfunction, diabetes mellitus, or anterior infarct (COR I, LOE A), and ACE-Is should be considered in all patients in the absence of contraindications (COR IIa, LOE A). The ESC NSTEMI guidelines recommend ACE-Is <24 hours in patients with LVEF ≤0.40 and in patients with HF, diabetes mellitus, hypertension, or chronic kidney disease (COR I, LOE A). Importantly, ACE-Is are recommended for all other patients to prevent recurrence of ischemic events, with preference given to agents and doses of proven efficacy (COR I, LOE B).

Despite the extensive study of ACE-Is, there remains some difference of opinion about their need and efficacy among lower-risk patients with normal LVEF who have been revascularized and are on optimal medical therapy. There are also questions about potential differences among the ACE-Is used in the major trials suggesting that there may not be a class effect. Future trials should be designed to resolve these issues.

**Angiotensin II Receptor Blockers**

An alternative method to therapy with ACE-Is is presented by ARBs, which work by displacing angiotensin II from its angiotensin II type 1 receptor, causing a decrease in systemic vascular resistance without an accompanying change in heart rate or cardiac output. The resulting increase in angiotensin II levels has not been associated with deleterious effects. A major difference between ACE-Is and ARBs is the lack of increase in kinin levels with ARB use. Elevated kinins (eg, bradykinin) may contribute to some of the benefits of ACE-I therapy but also produce the cough that renders ACE-I therapy unacceptable to a sizeable proportion of patients. Similar to ACE-Is, ARBs have renal protection benefits for patients with diabetes mellitus or chronic kidney disease. Treatment of patients with STEMI with ARBs has been compared with ACE-I therapy in 2 major RCTs. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study of 5477 patients with STEMI failed to show superiority or noninferiority when losartan was compared with captopril with respect to all-cause mortality during a mean follow-up of 2.7 years. However, significantly fewer patients discontinued losartan in comparison with captopril (P<0.0001). The Valsartan in Acute Myocardial Ventricular Trial (VALIANT) compared valsartan with captopril or combined therapy in 14703 patients with recent STEMI complicated by clinical HF or LV systolic dysfunction. Valsartan was found to be noninferior to captopril in terms of the primary end point of all-cause mortality, as well as fatal and nonfatal cardiovascular events during a median follow-up of 24.7 months. Discontinuation of therapy was more frequent in the captopril-treated patients because of cough. Combination therapy had the most drug-related adverse events.

The ACC/AHA STEMI guidelines state that ARBs should be given to patients with STEMI who have indications for but are intolerant of ACE-Is (COR I, LOE B). The ACC/AHA UA/NSTEMI guidelines similarly recommend that an ARB should be given to patients intolerant of ACE-Is who have clinical or radiographic signs of HF or an LVEF ≤0.40. The ESC STEMI guidelines state that an ARB, preferably valsartan, is an alternative to ACE-I particularly in patients with HF.
or systolic dysfunction if they are unable to tolerate ACE-I therapy (COR I, LOE B). The ESC NSTEMI guidelines recommend ARB therapy when patients are intolerant of ACE-Is (COR IIa, LOE B).

Aldosterone Antagonists

These agents competitively inhibit the binding of aldosterone to mineralocorticoid receptors. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) evaluated the effect of eplerenone, a selective aldosterone blocker, on morbidity and mortality in 6642 patients with acute MI with LVEF <0.40 and symptoms of HF or diabetes mellitus, already treated with a β-blocker and either an ACE-I or ARB.48 There was a significant reduction in the primary end point of all-cause death in the eplerenone-treated group during a mean follow-up of 16 months (RR, 0.85; 95% CI, 0.75–0.96; P=0.008). The rate of secondary cardiovascular end points, including sudden death from cardiac causes, was also reduced by eplerenone (RR, 0.79; 95% CI, 0.86–0.98; P=0.02). There was, however, an increased rate of severe hyperkalemia in the eplerenone group (P=0.002).

The ACC/AHA guidelines state that an aldosterone antagonist should be given to patients with STEMI (COR I, LOE B) or UA/NSTEMI (COR I, LOE A) and no contraindications who are already receiving a β-blocker and ACE-I and have an EF <0.40 and either symptoms of HF or diabetes mellitus. The ESC STEMI guidelines recommend that aldosterone antagonists are indicated in patients with an EF <0.40 and HF or diabetes mellitus, provided there is no renal failure or hyperkalemia (COR I, LOE B). The ESC NSTEMI guidelines have a similar recommendation using an EF <0.35, stating that the findings in patients with STEMI may be extrapolated to those with NSTEMI.

Newer Pharmacological Agents

Ranolazine

Cardiac ischemia is associated with alterations in intracellular sodium and calcium concentrations, leading to arrhythmias, decreased contractility, and myocyte death.49 Ranolazine is a piperazine derivative approved for use in the United States in 2006 for patients with chronic stable angina. Its anti-ischemic effects are mediated independently of alterations in heart rate and blood pressure. Initially thought to shift myocardial substrate use from fatty acid oxidation to glucose utilization, ranolazine also seems to reduce calcium overload in ischemic myocytes via inhibition of the late inward sodium current.49,50 The subsequent reduction in intracellular sodium alters the influx of calcium into the cell via the sodium–calcium exchanger. Ranolazine preserves intracellular ATP levels, improves myocardial function, and limits the extent of ischemic myocardial necrosis. Its role in patients with ACS is less well-defined than its demonstrated usefulness in some patients with chronic stable angina.51 The Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction (MERLIN-TIMI 36) trial randomized 6560 patients with UA/NSTEMI managed with guideline-directed medical and interventional therapy to ranolazine or placebo and examined a composite primary outcome of cardiovascular death, MI, or recurrent ischemia during a median follow-up of 348 days after presentation.52 There was no significant difference in the composite primary end point, although there was a reduction in the isolated secondary outcome of recurrent ischemia with ranolazine therapy (hazard ratio, 0.87; 95% CI, 0.76–0.99, P=0.03), particularly among patients with a history of chronic angina. Ranolazine did not affect the incidence of symptomatic arrhythmias during the trial, although 7-day Holter monitoring showed decreased cumulative rates of ventricular tachycardia, supraventricular tachycardia, and ventricular pauses.53 Salutary effects on the development of atrial fibrillation have also been reported.54 The potential role of ranolazine to reduce ACS-related arrhythmias may warrant additional investigation. Nonelectrophysiological effects of ranolazine include a reduction in hemoglobin A1c levels.55 The ACC/AHA and ESC guidelines both discuss the results of MERLIN-TIMI 36, but neither makes a formal recommendations for its use.

Trimetazidine

Trimetazidine is also a piperazine derivative that shifts myocardial metabolism from fatty acid oxidation to more oxygen-efficient glucose oxidation pathways, thus reducing ischemia without measurable changes in the heart rate–blood pressure product.56,57 It has been shown to reduce the extent of reperfusion injury in a rat model.58 In small clinical trials, trimetazidine has been shown to reduce ischemic injury when given before PCI59,60 or coronary artery bypass grafting.61,62 The European Myocardial Infarction Project–Free Radicals (EMIP-FR) trial was a prospective, randomized, double-blinded, multicenter trial in which 19725 patients presenting with symptoms of acute STEMI within the previous 24 hours were randomized to a 48-hour infusion of intravenous trimetazidine or placebo.63 Stratification was according to thrombolytic therapy (56%) or no thrombolytic therapy (44%). By intention-to-treat analysis, there was no difference between treatment groups in the primary end point of 35-day all-cause mortality. There was a small but not statistically significant increase in deaths in the trimetazidine group that received thrombolytic therapy. In a per protocol analysis, however, trimetazidine was associated with a reduction in 35-day all-cause mortality among patients who did not receive thrombolyis (13.3% versus 15.1% for placebo; P=0.027). Trimetazidine is approved as a third-line agent for stable angina64 in Europe and other parts of the world.

Nicorandil

Nicorandil is a drug that activates ATP-sensitive K⁺ channels and dilates peripheral and coronary arterioles.65 This K⁺ channel function is also postulated to induce cardiac protection via an ischemic preconditioning-like effect.66 In a small study, nicorandil infusion seemed to be as effective as coronary balloon inflation at inducing ischemic preconditioning and reducing ST segment changes.57 Nicorandil also has a secondary nitrate-like mechanism of action that results in dilatation of the venous system and coronary arteries.65,66 The drug seems to improve multiple cardiac end points in patients with chronic stable angina66,69 and may also be beneficial in variant angina.70,71 In the Clinical European Studies in Angina
and Revascularization (CESAR 2) trial, 188 patients admitted with UA were randomized in a double-blinded fashion to nicorandil or placebo for a minimum of 48 hours.72 Compared with placebo, nicorandil significantly reduced the incidence of any tachycardia (P=0.04) and the cumulative number of episodes of transient myocardial ischemia (mostly silent; P=0.003). The anti-ischemic (and secondary antiarrhythmic) effect was postulated to be because of a preconditioning-like effect. The larger Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage (J-WIND) trial enrolled 1216 patients undergoing reperfusion for acute MI to either an intravenous nicorandil infusion or placebo.73 The primary end points of total infarct size (estimated by creatine kinase) and EF at 12 months were not different among the groups. There was, however, a small improvement in EF in a subset of patients who had been placed on chronic oral nicorandil therapy. Currently, nicorandil is used in Japan and Europe for the treatment of stable angina.

Ivabradine

Ivabradine is an agent that specifically inhibits the inward funny (If) current of the sinoatrial node, which controls heart rate.74 Through inhibition of this current, the slope of the rate of diastolic depolarization decreases, and heart rate is reduced without effects on blood pressure or contractility. It has shown efficacy similar to atenolol at improving exercise tolerance in patients with stable angina.75 In the large, multicenter Morbidity-Mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) trial of 10917 patients with CAD and reduced EF, ivabradine did not reduce the rates of death and admission for HF, but did decrease the rate of admissions for CAD-related events in select patients.76 In the Systolic HF Treatment with If Inhibitor Ivabradine Trial (SHIFT) of 6558 patients with HF with a resting heart rate >70 beats per minute while on usual therapy, ivabradine reduced the composite outcome of cardiovascular death and HF admission (hazard ratio, 0.82; CI, 0.75–0.90; P<0.0001).77 It is yet to be studied, however, in patients with ACS with the exception of early studies designed to evaluate clinical safety.78 Its use in Europe is limited to stable angina or patients with HF with elevated heart rate when β-blockers are not adequate or cannot be tolerated.

Areas for Investigation

No-Reflow and Reperfusion Injury

No-reflow is a phenomenon characterized by poor tissue perfusion in an ischemic region despite relief of a complete coronary artery occlusion.79 It results from the loss of microvascular integrity consequent to ischemic injury of vascular endothelial cells.8,80,81 Such damage causes microluminal occlusion and prevents restoration of normal tissue blood flow even after infarct artery reperfusion. Continued ischemia, in combination with the inflammation and vasoconstriction seen with reperfusion injury, results in subendocardial myocyte death.82 The lack of adequate blood flow to the vulnerable region prevents the tissue delivery of intravenous or intracoronary medications meant to protect and heal the myocardium.

Prompt revascularization is one method to attenuate no-reflow, because a longer period of complete occlusion leads to more microvascular damage. The paradox of reperfusion injury has been described previously.

Prevention of no-reflow with reperfusion injury before they occur is a desirable strategy.80 Mechanical thrombus aspiration during PCI seems to reduce distal embolization, no-reflow, and reperfusion injury; there may be some role for distal embolic protection devices, such as filters, in PCI of saphenous vein grafts but not in native coronary arteries.83,84 Drugs and biologics that target vasoconstriction, free radical formation, and inflammation are some of the agents that have been tested in limited fashion before and during PCI. Intracoronary adenosine and verapamil have shown some promise in preventing no-reflow in small clinical trials.85 In a small study, nitroprusside (a NO donor) did not improve CBF and reperfusion despite its association with improved clinical outcomes.85 Glycoprotein IIb/IIIa inhibitors may have a beneficial effect by preventing distal platelet-fibrin embolization to the already damaged microvasculature.80,86 In a trial of 368 patients with STEMI, a single administration of intravenous nicorandil before PCI compared with placebo improved TIMI flow grade and the long-term clinical end points of HF hospitalizations or cardiovascular death at a mean follow-up of 2.4 years.87 The investigational agent, FX06, is a fibrin-derived peptide that attempts to limit microvascular injury by binding to vascular endothelial-cadherin and preventing leukocyte infiltration and plasma leakage.88 In the Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury (FIRE) trial, 234 patients with STEMI were randomized to an intravenous bolus of FX06 or placebo during reperfusion.89 There was no difference in the primary outcome of infarct size at 5 days as measured by cardiac MRI or in the secondary outcomes of infarct size at 40 days and troponin I levels. There was a significant reduction in the secondary outcome of necrotic core zone size at 5 days with FX06 (P=0.025).

Pexelizumab, a humanized monoclonal antibody to C5 complement, was shown in animal models to inhibit apoptosis and inflammatory damage with a resultant decrease in infarct size.90 An initial clinical trial (Complement Inhibition in Myocardial Infarction Treated with Angioplasty [COMMA]) in 960 patients undergoing PCI for STEMI with pexelizumab infusion compared with placebo revealed no change in infarct size between the groups.91 However, there was a statistically significant decrease in 90-day mortality with the agent (1.8% with pexelizumab versus 5.9% with placebo; P=0.014). This observation led to the design and execution of the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial that randomized 5745 patients undergoing PCI for STEMI to intravenous pexelizumab or placebo.92 There was no difference between groups in the primary end point of 30-day mortality or in the secondary composite end point of death, cardiogenic shock, and HF at 30 to 90 days.

Eniporide is a specific inhibitor of the Na+H+ exchange system that is thought to be activated during reperfusion with consequent calcium overload and myocyte injury.93 In the Evaluation of the Safety and Cardioprotective Effects of Eniporide in Acute Myocardial Infarction (ESCAMI) trial, patients presenting with STEMI received eniporide or...
placebo before reperfusion. There was no difference between the groups in either enzymatic infarct size or clinical outcomes (death, cardiogenic shock, HF, life-threatening arrhythmias).94

Exenatide is a glucagon-like peptide analog used in the treatment of type 2 diabetes mellitus that has been shown to be cardioprotective during reperfusion in animal models of ischemia/reperfusion.85 Its mechanism of action has not been fully elucidated but is postulated to be partially because of the activation of a receptor-mediated survival pathway.96 In a trial of 172 patients with STEMI undergoing PCI, compared with placebo, intravenous exenatide increased the salvage index (P=0.003) and reduced infarct size in relation to myocardial area at risk at 90 days (P=0.003).97

Administration of adenosine has been a mainstay of treatment for no-reflow, although verapamil and nicorandil have also been tested.80,81,86 The Acute Myocardial Infarction Study of Adenosine (AMISTAD-II) trial studied 50 and 70 μg/kg per minute infusions of adenosine compared with placebo in 2118 patients with anterior STEMI undergoing either thrombolysis or angioplasty.98 Compared with placebo, adenosine did not result in any change in the primary end points of new HF, first rehospitalization for HF, or death at 6 months. There was no change in infarct size in the pooled adenosine groups compared with placebo, although there was a smaller final median infarct size with the high-dose (70 μg/kg per minute) adenosine infusion compared with placebo (P=0.023). Given the lack of effective alternatives, however, adenosine is the primary treatment used to treat no-reflow when it occurs after PCI.81,86 Continued research is clearly needed to discover novel agents that can prevent the no-reflow phenomenon and limit reperfusion injury.

**Ischemic Pre- and Postconditioning**

Additional work is also warranted in the field of ischemic pre- and postconditioning. It was shown first in animal studies that exposure of the heart to brief episodes of ischemia (preconditioning) results in improved cardiomyocyte survival during prolonged ischemia.12,13 Subsequent studies in humans have used the induction of remote, transient upper limb ischemia through hypersystolic blood pressure cuff inflation to mimic preconditioning. Cardiac surgeons have used a similar technique, as well as aortic cross-clamping, to induce preconditioning.99 Trials in acute MI have shown some benefit with preconditioning in reducing infarct size and clinical end points.100,101 A recent 4-year follow-up of 333 patients with STEMI randomized to remote ischemic preconditioning before PCI showed a reduction in all-cause mortality (hazard ratio, 0.32; CI, 0.12–0.88; P=0.027).102 Nicorandil, as mentioned previously, has also been shown to induce ischemic preconditioning. Diazoxtide is a drug for the treatment of hypoglycemia and hypertensive emergencies, which in animal studies seems to induce metabolic changes similar to a preconditioning state.103,104 This effect is likely mediated through multiple pathways, including mitochondrial K⁺ channels. It seems currently that the mechanism of ischemic preconditioning may also involve adenosine production, ATP-sensitive K⁺ channels, inducible NO synthase, reactive oxygen species, and apoptotic pathways.8,104 Better understanding of the precise molecular mechanisms may enable development of selective drugs and biologics targeting these pathways without the risk of inducing ischemia.

Ischemic postconditioning is the process of inducing brief cycles of coronary artery reperfusion and occlusion before final complete reperfusion in order to attempt to limit myocardial injury. Although technically more feasible than preconditioning in a clinical context because it can be performed at the same time as rather than before PCI, results with this intervention in both animal and human models have been inconsistent.8,88,105 The Effects of Postconditioning on Myocardial Reperfusion in Patients with STEMI (POST) trial was the largest study to examine the efficacy of postconditioning and randomized 700 patients who had just undergone primary PCI for STEMI to four 1-minute intracoronary angioplasty balloon inflations after initial infarct artery opening or to standard therapy.106 There was no difference between groups in the primary end point of complete ST-segment resolution at 30 minutes after PCI. There was also no change in the rate of major adverse cardiac events at 30 days with postconditioning. Despite this result, there are several ongoing clinical trials to further evaluate the potential benefits of ischemic postconditioning on clinical outcomes and infarct size during primary PCI for STEMI (NCT00992675, NCT01324453, NCT01435408). There is also an active clinical trial to see if remote postconditioning, induced by occluding blood flow to the thigh, can reduce myocardial infarct size during STEMI (NCT02021760).

The mechanism of postconditioning is not fully elucidated but is thought to rely on limiting the magnitude of reperfusion injury and no-reflow during revascularization.88,107 Thus, similar pathological processes are at work, including distal embolization, myocardial cell swelling and death, localized inflammation, vasconstriction, and free radical formation. Postconditioning in part allows brief opportunities for aerobic metabolism to repair the sarcolemma without causing rupture from calcium overload.8 The actions of cyclosporine have shed some light on this mechanism by inducing a postconditioning effect at least partially because of inhibition of the mitochondrial permeability transition pore, a key player in reperfusion injury.88 By preventing pore opening during reperfusion, myocytes are thought to be given time to undergo repair processes and survive. Small studies of cyclosporine in acute MI show a benefit in reducing infarct size.108,109 The larger Cyclosporine and Prognosis in Acute MI Patients (CIRCUS; NCT01502774) trial is ongoing in Europe to further examine the benefit of cyclosporine in acute MI. TRO40303 is a novel small molecule that also reduces opening of the mitochondrial permeability transition pore and, its clinical efficacy will be examined in the European MitoCare study.110,111 The reperfusion injury salvage kinase pathway is thought to play a related role in cardioprotection, partly through downstream inhibition of mitochondrial permeability transition pore opening.112 Atrial natriuretic peptide administration has been shown to activate the reperfusion injury salvage kinase pathway and reduce infarct size.73,113 As is the case with ischemic preconditioning, however, improved understanding of the molecular pathways at play in ischemic postconditioning is needed to enable more effective therapeutic strategies. The Figure summarizes the complex,
overlapping pathways involved in the pathogenesis of reperfusion injury and no-reflow that may be targeted with therapies including pre/postconditioning.

**Other Areas of Investigation**

There have been other intriguing areas of investigation for nonantithrombotic therapies for the management of ACS. The role of inflammation in the lifecycle of the vulnerable plaque is well described, although trials of various anti-inflammatory agents in ACS from corticosteroids to monoclonal antibodies have been mostly disappointing. However, efforts continue to define more precisely the exact inflammatory mechanisms at play in CAD and ACS and thus identify new agents targeting relevant pathways. For example, an inhibitor of p38 mitogen-activated protein kinase has been shown to decrease inflammation and infarct size in animal models, and human studies are underway. Previously, it was thought that deficiencies of electrolytes such as magnesium during MI could result in worse clinical outcomes because of effects on multiple ion gradient and energy production processes. The Magnesium in Coronaries (MAGIC) trial randomized 6213 patients with acute STEMI to a magnesium infusion or placebo. There was no difference between groups in the primary end point of 30-day mortality. Similarly, a glucose/insulin/potassium mixture was postulated to be beneficial in MI by suppressing uptake of free fatty acids, providing glucose as fuel for the heart, and reducing ventricular arrhythmias induced by potassium depletion. However, the Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latinoamerica (CREATE-ECLA) trial composed of 20201 patients with acute STEMI randomized to glucose/insulin/potassium infusion or placebo revealed no difference between groups in the primary outcome of 30-day mortality. There was also no effect on rates of development of cardiac arrest, cardiogenic shock, and reinfarction at 30 days. On a related metabolic front, metformin has been proposed to limit myocardial injury and adverse remodeling after MI possibly through phosphorylation of adenosine monophosphate–activated kinase. The Glycometabolic Intervention as Adjunct to Primary Percutaneous Intervention in STEMI (GIPS-III) trial is currently underway to examine the effects of metformin therapy on EF after STEMI in nondiabetic patients. Others have proposed focusing on pathways induced by hypoxia during ischemia and the role of adenosine receptors in this process. Research on this front remains in an early investigational stage in animal models, although the Detox-AMI trial is underway to determine whether there is any benefit to the standard practice of oxygen supplementation in patients with ACS.

**Conclusions**

The immediate goals of treatment in patients with ACS are to decrease myocardial oxygen demand, increase CBF and oxygen supply, and limit myocardial injury, thereby reducing the short- and longer-term risks of HF, arrhythmia, and death. Traditional pharmacological therapies center around β-blockers and renin–angiotensin system inhibitors, which have the most robust clinical trials evidence base for efficacy. There is some role for nitrates and CCBs in specific clinical circumstances. Other agents such as ranolazine and nicorandil, are primarily used in patients with stable angina although their mechanisms of action suggest possible benefits in patients with ACS, and additional trials are needed. More research is also warranted to further understand the molecular mechanisms of the no-reflow phenomenon, reperfusion injury, and ischemic pre/postconditioning. Knowledge of these pathways is critical to discovering novel therapeutic agents targeted to key components of these processes. Finally, although this review specifically focuses on nonantithrombotic medical therapies, appropriate secondary prevention should be used in all patients with ACS to decrease the risk of late cardiac events. Such a program includes lifestyle modification, intensive risk factor intervention, and guideline-directed medical management with antithrombotic agents and high-intensity statins. Clearly, much work remains to be done to...
optimize the use of available therapies and discover new means to reduce the morbidity and mortality associated with ACS.

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References
ischemia in patients treated with nifedipine or metoprolol or both. Br Heart J. 1986;56:400–413.
2 investigation. Clinical European studies in anina and revascularization.


107. Soukoulis et al Nonantithrombotic Therapies in ACS 1957

108. Soukoulis et al Nonantithrombotic Therapies in ACS 1957


Nonantithrombotic Medical Options in Acute Coronary Syndromes: Old Agents and New Lines on the Horizon

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