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Non-Antithrombotic Medical Options in ACS: Old Agents and New Lines on the Horizon

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Abstract

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 beta-blockers and inhibitors of the reninangiotensin-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 post-conditioning 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, anti-thrombotic agents, and the use of high-intensity statins.

Keywords

Acute coronary syndrome; reperfusion injury; pre-conditioning

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Introduction

Pathophysiology of Myocardial Ischemia

Myocardial ischemia derives from an imbalance between myocardial oxygen supply and demand. As 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).[1,2] 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.[3] CBF can be further compromised by reactive constriction of vascular smooth muscle cells, leading to deleterious increases in coronary vascular resistance (CVR) at the arteriolar level and further narrowing of the larger, epicardial conduit artery. CVR is mediated by a host of factors, including paracrine factors released from activated platelets, adenosine, local availability of nitric oxide (NO), prostacyclin, endothelin, hypoxia, acidosis, adenosine tri-phosphate (ATP)-sensitive K+ channels, neurohumoral agonists, neural tone, and vascular shear stress.[4,5] An intact and functional endothelium serves as the gatekeeper. Atherosclerosis leads to a reduction in NO availability and paradoxical increases in CVR on exposure to substances such as acetylcholine, which would otherwise cause vasodilation and a fall in CVR in normal arterial segments.[6]

Myocardial compressive forces also contribute to CVR. Nutrient supply to the more vulnerable subendocardium can be compromised by increases in left ventricular (LV) diastolic pressure with a resultant decrease in the coronary driving pressure, which is represented by the difference between the aortic and LV diastolic pressures. Isolated reductions in aortic diastolic pressure, as seen in patients with significant aortic regurgitation or in some elderly patients with aggressively treated systolic hypertension, may also decrease coronary driving pressure. Higher LV diastolic pressures in the context of ischemia can further reduce coronary driving pressure. Because the majority of left coronary artery blood flow occurs during diastole, decreases in diastolic filling times at rapid heart rates will also reduce CBF. Myocardial oxygen supply is additionally influenced by the oxygen-carrying capacity of blood, and severe anemia (hemoglobin < 7g/dL) may precipitate ischemia in vulnerable patients.[7] In some patients with chronic coronary artery disease (CAD), the extent and severity of an acute ischemic insult can be attenuated by flow through collateral channels.

The three major drivers of myocardial oxygen demand (consumption) are heart rate, contractility, and wall stress.[1] Increases in heart rate both reduce diastolic filling time and increase oxygen demand. Compensatory increases in contractility of non-ischemic/non-infarcted myocardial segments can also increase demand. Wall stress is approximated by the Laplace relationship and varies directly as a function of chamber pressure and radius and inversely as a function of wall thickness [stress=(pressure × radius)/(2 × wall thickness)]. Thus, wall stress increases as the LV dilates and chamber pressures rise. Most anti-ischemic pharmacological strategies are targeted to modulating one or more 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 “wave front” 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.[8,9] 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.[10] Attenuation of these several processes may limit the extent of injury and adverse post-infarction remodeling.

Following 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.[11] Functional recovery is anticipated in the absence of repeated ischemic insults. Importantly, restoration of epicardial flow following a period of occlusion does not always correlate with tissue perfusion, which may be further compromised by endothelial cell swelling, micro-embolization, and vasoconstriction.[8] The angiographic demonstration of “no-reflow” following 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- and/or post-conditioning mechanisms may also be of value. Ischemic pre-conditioning attenuates myocyte necrosis by the production of brief, reversible periods of ischemia (induced either locally or remotely) prior to coronary artery occlusion.[12,13] 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 PCI decreases with each successive balloon inflation. Delayed pre-conditioning can persist for several days after coronary artery occlusion and may protect the heart from ischemia-reperfusion mediated stunning. Ischemic post-conditioning 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.

Non-Atherosclerotic ACS

There are several non-atherosclerotic 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, and/or luminal obstruction from an intimal

flap.[14-16] In the case of spontaneous or cocaine-induced spasm, vasodilator therapy with nitrates and/or calcium channel blockers constitutes the initial management strategy. There is no effective therapy for stress-cardiomyopathy, a transient phenomenon presumably due to catecholamine excess and regionalized left ventricular stunning. [16,17]

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 anti-thrombotic 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, 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 1-2) and newer “anti-ischemic” (Table 3) methods of treatment for ACS, exclusive of revascularization, anti-thrombotic 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 percutaneous coronary intervention (PCI) is either too costly or not available.

Traditional Pharmacologic Approaches

Traditional pharmacologic therapies used in the management of ACS include those that reduce oxygen demand and/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) and/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 prior to the use of contemporary methods for coronary reperfusion and revascularization, the routine administration of potent anti-thrombotic agents, and the use of high-intensity statin therapy. It is generally held, however, that they are beneficial for ACS patients managed with either an invasive or conservative strategy. Randomized controlled trials (RCTs) remain the gold standard for the development of evidence-based clinical practice guidelines and landmark trials will be cited here as appropriate.

Beta-adrenergic Receptor Blockers

Beta-adrenergic receptor blockers decrease heart rate, blood pressure, and contractility, resulting in a reduction in myocardial oxygen demand. These effects are primarily the result of competitive antagonism of the beta-1 cardiomyocyte receptors. The evidence supporting their clinical benefit is largely derived from earlier studies in patients with acute MI prior to the current era of reperfusion therapy for STEMI. The findings have been extrapolated to include patients with UA and NSTEMI.

The results of clinical trials studying the use of beta-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 beta-blockers in patients with acute or previous MI demonstrated a significant reduction in long term mortality.[19] The CRUSADE Registry (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines) showed that patients with UA/NSTEMI treated with beta-blocker therapy had a 34% risk-adjusted decrease in hospital mortality ($p<0.001$).[20] Conversely, a propensity score-matched analysis of 21860 patients with either CAD risk factors, known CAD, or *prior* MI in the REACH (Reduction of Atherothrombosis for Continued Health) registry did not show any reduction in a composite of cardiovascular death, nonfatal MI, or nonfatal stroke with beta-blocker use over a median follow-up of 44 months.[21]

The use of intravenous therapy with beta-blockers has been evaluated in COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) where early intravenous (IV) metoprolol followed by oral therapy was compared to placebo alone in 45852 patients presenting with ACS, predominantly STEMI.[22] There was no difference in the co-primary outcomes of death from any cause or the composite of death/ reinfarction/cardiac arrest by either hospital discharge or day 28 (whichever came first). Although rates of ventricular fibrillation ($p=0.001$) and recurrent myocardial infarction ($p=0.001$) were lower in the treated group, a significantly higher rate of cardiogenic shock ($p<0.00001$) was seen after IV metoprolol, especially in certain high-risk subgroups that included patients >70 years old, those with systolic BP < 120 mm Hg, and those presenting with heart rate > 110 beats per minute (bpm).

The ACC/AHA guidelines[23] state that oral beta-blockers should be initiated (Class of Recommendation [COR] I, Level of Evidence [LOE] B) in the first 24 hours for patients with STEMI who do not have: signs of heart failure (HF), low output state, increased risk for cardiogenic shock, or contraindications to beta-blocker therapy. Beta-blockers should be continued (COR I, LOE B) during and after hospitalization. Patients with initial contraindications to the use of beta-blockers should be reevaluated (COR I, LOE C) to determine their subsequent eligibility. It is reasonable to administer (COR IIa, LOE B) IV beta-blockers to patients with STEMI and no contraindications who are hypertensive or have ongoing ischemia. Similar recommendations are made for patients with UA/NSTEMI.[24,25]

In addition, the UA/NSTEMI guidelines indicate that it may be harmful (COR III, LOE A) to give IV beta-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 prevention[26] state that beta-blocker therapy after MI should be continued for at least 3 years in the absence of LV dysfunction (COR I, LOE A). It is reasonable to continue beta-blocker therapy beyond 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 ESC guideline recommendations for beta-blockers in patients with STEMI and NSTEMI[27,28] 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 beta-blockers in all patients with LV dysfunction without contraindications.

Nitrates

Therapy with nitrates exerts beneficial effects by decreasing preload and left ventricular 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 coronary blood flow. 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 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 heart failure and in those with continued angina. Although a review of small studies in the era before reperfusion suggested a reduction in mortality for MI patients receiving nitrates[30], a major benefit was not confirmed in two large RCTs. The ISIS-4 (Fourth International Study of Infarct Survival) trial randomized 58050 patients with acute MI in a 2x2 fashion to various therapies including oral isosorbide mononitrate versus placebo.[31] There was no difference in 5-week mortality between the nitrate and placebo groups, but there was an increase in hypotension with nitrate therapy. The GISSI-3 (Gruppo Italiano per lo Studio Della Sopravvivenza nellinfarto Miocardico) trial studied the effects of lisinopril, transdermal glyceryl trinitrate, and their combination in 19394 patients presenting with acute MI.[32] The transdermal nitrate did not result in a reduction in 6-week mortality or the combined endpoint 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 a 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 IV 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 receptor blockers (ARBs) (COR IIa, LOE C), and in patients with Killip Class III heart failure 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 (i.e., LOE C).

Calcium Channel Blockers

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 amlodipine predominately produce vasodilation, resulting in a fall in blood pressure and reflex tachycardia. The non-dihydropyridine CCBs, diltiazem and verapamil, decrease heart rate, the rate of atrio-ventricular (AV) conduction, blood pressure, and myocardial contractility. Short-acting dihydropyridines such as the non-sustained release form of nifedipine must not be given to patients with ACS in the absence of beta-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 heart failure. The DAVIT-II (Danish Verapamil Infarction Trial) study examined 1775 patients with acute MI who were treated with verapamil or placebo.[33] There was no difference in 18-month mortality with verapamil therapy compared to placebo. However, when analyzing trial patients without heart failure, verapamil was associated with a reduction in mortality (p=0.02). The HINT (Holland Interuniversity Nifedipine/metoprolol Trial) trial studied nifedipine and metoprolol in patients with UA/NSTEMI and was stopped early because of an increased re-infarction rate in the nifedipine group compared with the metoprolol group.[34] In contrast, patients treated with metoprolol benefited from the addition of nifedipine in terms of a reduction in rates of recurrent ischemia or MI within 48 hours. A review of 28 RCTs involving 19000 patients with ACS showed no benefit from CCB therapy on infarct size, rate of reinfarction, or death.[35] Thus the major benefit from CCB use in ACS is 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 beta-blocker cannot be given a non-dihydropyridine 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 non-dihydropyridine CCB (COR IIa, LOE C) to patients with recurrent ischemia after beta-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 beta-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 beta-blockers, and for patients with contraindications to beta-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 beta-blockers (COR III, LOE B).

Inhibitors of the Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin-aldosterone system (RAAS) by a number of 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 have 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.[36]

Angiotensin-Converting Enzyme Inhibitors (ACE-Is)—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 heart failure. The SAVE (Survival And Ventricular Enlargement) trial randomized 2231 patients with LV systolic dysfunction (LV ejection fraction (EF)<0.40) but without overt heart failure after MI to captopril or placebo.[37] There was a 19% risk reduction in all-cause mortality over an average follow-up of 42 months (p=0.019), as well as significant reductions in severe heart failure, heart failure hospitalizations, and recurrent MI. The AIRE (Acute Infarction Ramipril Efficacy) study examined the effects of ramipril versus placebo in 2006 patients with clinical evidence of heart failure after an acute MI.[38] There was a 27% risk reduction in all-cause mortality (p=0.002). Lastly, the TRACE (TRAndolapril Cardiac Evaluation) study compared treatment with trandolapril versus placebo in 1749 patients with LV dysfunction (EF < 0.35) followed for 24-50 months after MI.[39] The relative risk (RR) of all-cause death in the trandolapril group was 0.78 (95% CI 0.67-0.91; p=0.001). Trandolapril also reduced the risk of death from cardiovascular causes (RR 0.75; 95% CI 0.63 to 0.89; p=0.001) and sudden death (RR 0.76; 95% CI 0.59 to 0.98; p=0.03). Progression to severe heart failure was less frequent in the trandolapril group (RR 0.71; 95 % CI 0.56 to 0.89; p=0.003). In addition to these *selective* trials in post-MI patients with LV dysfunction, two large trials looked at the *nonselective* use of ACE-s 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.[31] 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.[32] Lisinopril use was associated with a reduction in 6-week mortality (OR 0.88; 95% CI 0.79-0.99), as well as a composite endpoint of mortality and severe ventricular dysfunction (OR 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 beta-blockers. Their renal protective effects make their use in patients with diabetes and/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 heart failure has consistently been shown to improve acute and long-term outcomes.[37,40] 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 is less certain.[41-44]

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 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, 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 within 24 hours in patients with LVEF ≤0.40 and in patients with HF, diabetes, 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 utilized 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 (ARBs)—An alternative method to therapy with ACE-Is is presented by ARBs, which work by displacing angiotensin II from its angiotensin II type 1 (AT-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 (e.g. 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.[45] Similar to ACE-Is, ARBs have renal protection benefits for patients with diabetes and/or chronic kidney disease. Treatment of STEMI patients with ARBs has been compared to ACE-I therapy in two major RCTs. The OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) study of 5477 patients with STEMI failed to show superiority or non-inferiority when losartan was compared to captopril with respect to all-cause mortality during a mean follow-up of 2.7 years.[46] However, significantly fewer patients discontinued losartan in comparison to captopril ($p<0.0001$). The VALIANT (VALsartan In Acute myocardial 10entricula Trial) study compared valsartan with captopril or combined therapy in 14703 patients with recent STEMI complicated by clinical heart failure and/or LV systolic dysfunction.[47] Valsartan was found to be non-inferior to captopril in terms of the primary endpoint 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 due to 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 EPHESUS (Eplerenone Post-acute myocardial infarction Heart failure Efficacy and Survival Study) trial evaluated the effect of eplerenone, a selective aldosterone blocker, on morbidity and mortality in 6642 acute MI patients with LVEF < 0.40 and symptoms of heart failure or diabetes, already treated with a beta-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 over a mean follow-up of 16 months (RR 0.85, 95% CI 0.75-0.96, p=0.008). The rate of secondary cardiovascular endpoints, 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 beta-blocker and ACE-I and have an EF of <0.40 and either symptoms of HF or diabetes. The ESC STEMI guidelines recommend that aldosterone antagonists are indicated in patients with an EF <0.40 and HF or diabetes, provided there is no renal failure or hyperkalemia (COR I, LOE B). The ESC NSTEMI guidelines have a similar recommendation using an EF of <0.35, stating that the findings in STEMI patients may be extrapolated to those with NSTEMI.

Newer Pharmacologic 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 piperazine derivative approved for use in the US in 2006 for patients with chronic stable angina. Its anti-ischemic effects are mediated independently of alterations in heart rate and blood pressure. Initially felt to shift myocardial substrate utilization from fatty acid oxidation to glucose utilization, ranolazine also appears to reduce calcium overload in ischemic myocytes via inhibition of the late inward sodium current (I_{Na}).[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 ACS patients is less well-defined than its demonstrated usefulness in some patients with chronic, stable angina.[51] The MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes)-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 CV death, MI, or recurrent ischemia over a median follow-up of 348 days after presentation.[52] There was no significant difference in the composite primary endpoint, although there was a reduction in the isolated secondary outcome of recurrent ischemia with ranolazine therapy (HR 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, though 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 further investigation. Non-electrophysiologic 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 PCI[59,60] or CABG.[61,62] The EMIP-FR (European Myocardial Infarction Project – Free Radicals) trial was a prospective, randomized, double-blind, multicenter trial in which 19.725 patients presenting with symptoms of acute STEMI within the previous 24 hours were randomized to a 48-hour infusion of IV 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 thrombolysis (13.3% vs 15.1% for placebo; p=0.027). Trimetazidine is approved as a third-line agent for stable angina[64] 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 appeared to be as effective as coronary balloon inflation at inducing ischemic pre-conditioning and reducing ST segment changes.[67] 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 appears to improve multiple cardiac endpoints in patients with chronic stable angina[68,69] and may also be beneficial in variant angina.[70,71] In the CESAR 2 (Clinical European Studies in Angina and Revascularization) trial, 188 patients admitted with unstable angina were randomized in a double blind fashion to nicorandil or placebo for

a minimum of 48 hours.[72] Compared with placebo, nicorandil significantly reduced the incidence of any tachycarrhythmia (p=0.04) and the cumulative number of episodes of transient myocardial ischemia (mostly silent; p=0.003). The anti-ischemic (and secondary anti-arrhythmic) effect was postulated to be due to a pre-conditioning-like effect. The larger J-WIND (Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage) trial enrolled 1216 patients undergoing reperfusion for acute MI to either an IV nicorandil infusion or placebo.[73] The primary endpoints 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 (I_f) 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 BEAUTIFUL (morbidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) trial of 10917 patients with CAD and reduced EF, ivabradine did not reduce the rates of death and admission for heart failure, but did decrease the rate of admissions for CAD-related events in select patients.[76] In the SHIFT (Systolic Heart failure treatment with I_f inhibitor ivabradine Trial) study of 6558 heart failure patients with a resting heart rate greater than 70 bpm while on usual therapy, ivabradine reduced the composite outcome of cardiovascular death and heart failure admission (HR 0.82, CI 0.75-0.90, p<0.0001).[77] It has yet to be studied, however, in ACS patients with the exception of early studies designed to evaluate clinical safety.[78] Its use in Europe is limited to stable angina or heart failure patients with elevated heart rate when beta-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, since 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 appears 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.[80] In one small study, nitroprusside (a NO donor) did not improve coronary blood flow 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 IV nicorandil before PCI compared to placebo improved Thrombolysis in Myocardial Infarction (TIMI) flow grade and the long-term clinical endpoints of heart failure 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 (VE)-cadherin and preventing leukocyte infiltration and plasma leakage.[88] In the FIRE (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial, 234 patients with STEMI were randomized to an IV 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 (COMMA: COMplement inhibition in Myocardial infarction treated with Angioplasty) in 960 patients undergoing PCI for STEMI with pexelizumab infusion compared to 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 vs 5.9% with placebo, $p=0.014$). This observation led to the design and execution of the APEX-AMI (Assessment of PEXelizumab in Acute Myocardial Infarction) trial that randomized 5745 patients undergoing PCI for STEMI to IV pexelizumab or placebo.[92] There was no difference between groups in the primary endpoint of 30-day mortality or in the secondary composite endpoint of death, cardiogenic shock, and heart failure at 30-90 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 ESCAMI (Evaluation of the Safety and Cardioprotective effects of eniporide in Acute Myocardial Infarction) trial, patients presenting with STEMI received eniporide or placebo prior to reperfusion. There was no difference between the groups in either enzymatic infarct size or clinical outcomes (death, cardiogenic shock, heart failure, life-threatening arrhythmias).[94]

Exenatide is a glucagon-like peptide (GLP)-1 analog used in the treatment of type 2 diabetes that has been shown to be cardioprotective during reperfusion in animal models of ischemia-reperfusion.[95] Its mechanism of action has not been fully elucidated but is postulated to be partially due to the activation of a receptor-mediated survival pathway.[96] In a trial of 172 patients with STEMI undergoing PCI, compared with placebo, IV 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 AMISTAD-II (Acute Myocardial Infarction Study of Adenosine) trial studied 50 and 70 mcg/kg/min infusions of adenosine compared to 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 endpoints of new HF, first re-hospitalization for HF, or death at 6 months. There was no change in infarct size in the pooled adenosine groups compared to placebo, although there was a smaller final median infarct size with the high dose (70 mcg/kg/min) adenosine infusion compared to 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 Post-Conditioning

Further work is also warranted in the field of ischemic pre- and post-conditioning. It was shown first in animal studies that exposure of the heart to brief episodes of ischemia (pre-conditioning) results in improved cardiomyocyte survival during prolonged ischemia.[12,13] Subsequent studies in humans have utilized the induction of remote, transient upper limb ischemia through hypersystolic blood pressure cuff inflation to mimic pre-conditioning. Cardiac surgeons have utilized a similar technique, as well as aortic cross-clamping, to induce pre-conditioning.[99] Trials in acute MI have shown some benefit with preconditioning in reducing infarct size and clinical endpoints.[100,101] A recent 4-year follow-up of 333 patients with STEMI randomized to remote ischemic pre-conditioning before PCI showed a reduction in all-cause mortality compared to standard care (HR 0.32, CI 0.12-0.88, p=0.027).[102] Nicorandil, as mentioned previously, has also been shown to induce ischemic pre-conditioning. Diazoxide is a drug for the treatment of hypoglycemia and hypertensive emergencies that in animal studies seems to induce metabolic changes similar to a pre-conditioning state.[8,103] This effect is likely mediated through multiple pathways, including mitochondrial K^+ channels. It appears currently that the mechanism of ischemic preconditioning may also involve adenosine production, ATP-sensitive K^+ channels, inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), 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 post-conditioning is the process of inducing brief cycles of coronary artery reperfusion and occlusion prior to final complete reperfusion in order to attempt to limit

myocardial injury. While technically more feasible than pre-conditioning 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 POST (Effects of POSTconditioning on myocardial reperfusion in patients with STEMI) trial was the largest study to examine the efficacy of post-conditioning 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 endpoint 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 post-conditioning. Despite this result, there are several ongoing clinical trials to further evaluate potential benefits of ischemic post-conditioning on clinical outcomes and infarct size during primary PCI for STEMI (NCT00922675, NCT01324453, NCT01435408). There is also an active clinical trial to see if remote post-conditioning, induced by occluding blood flow to the thigh, can reduce myocardial infarct size during STEMI (NCT02021760).

The mechanism of post-conditioning is not fully elucidated but is believed to rely on limiting the magnitude of reperfusion injury and no-reflow during revascularization.[84,107] Thus, similar pathologic processes are at work, including distal embolization, myocardial cell swelling and death, localized inflammation, vasoconstriction, and free radical formation. Post-conditioning 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 due to inhibition of the mitochondrial permeability transition pore (MPTP), 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 CIRCUS (Cyclosporine and Prognosis in Acute MI Patients; 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 MPTP, and its clinical efficacy will be examined in the European MitoCare study.[110,111] The Reperfusion Injury Salvage Kinase (RISK) pathway is believed to play a related role in cardioprotection, partly through downstream inhibition of MPTP opening.[112] Atrial natriuretic peptide (ANP) administration has been shown to activate the RISK 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. Figure 1 summarizes the complex, overlapping pathways involved in the pathogenesis of reperfusion injury and no-reflow that may be targeted with therapies including pre/post-conditioning.

Other Areas of Investigation

There have been other intriguing areas of investigation for non-antithrombotic therapies for 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.[114] 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.[115] Previously, it was thought that deficiencies of electrolytes such as magnesium during MI could result in worse clinical outcomes due to effects on multiple ion gradient and energy production processes.[116] The MAGIC (MAGnesium In Coronaries) trial randomized 6213 patients with acute STEMI to a magnesium infusion or placebo.[117] There was no difference between groups in the primary endpoint of 30-day mortality. Similarly, a glucose/insulin/potassium (GIK) 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.[118] However, the CREATE-ECLA (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latinoamerica) trial composed of 20201 patients with acute STEMI randomized to GIK infusion or placebo revealed no difference between groups in the primary outcome of 30-day mortality.[119] 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 (AMP) kinase.[120] The GIPS-III (Glycometabolic Intervention as adjunct to Primary percutaneous intervention in STEMI) trial is currently underway to examine the effects of metformin therapy on EF after STEMI in non-diabetic patients.[121] Others have proposed focusing on pathways induced by hypoxia during ischemia and the role of adenosine receptors in this process.[122,123] 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 coronary blood flow and oxygen supply, and limit myocardial injury, thereby reducing the short and longer-term risks of heart failure, arrhythmia, and death. Traditional pharmacological therapies center around beta-blockers and renin-angiotensin system inhibitors, which have the most robust clinical trials evidence base for efficacy. There is some role for nitrates and calcium channel blockers in specific clinical circumstances. Other agents, such as ranolazine and nicorandil, are primarily used in patients with stable angina though 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/post-conditioning. 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 non-antithrombotic medical therapies, appropriate secondary prevention should be utilized in all ACS patients to decrease the risk of late cardiac events. Such a program includes lifestyle modification, intensive risk factor intervention, and guideline-directed medical management with anti-thrombotic 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-Standard Abbreviations

CBF	Coronary blood flow
COR	Class of recommendation
CVR	Coronary vascular resistance
LOE	Level of evidence
MPTP	Mitochondrial permeability transition pore
RCT	Randomized controlled trial

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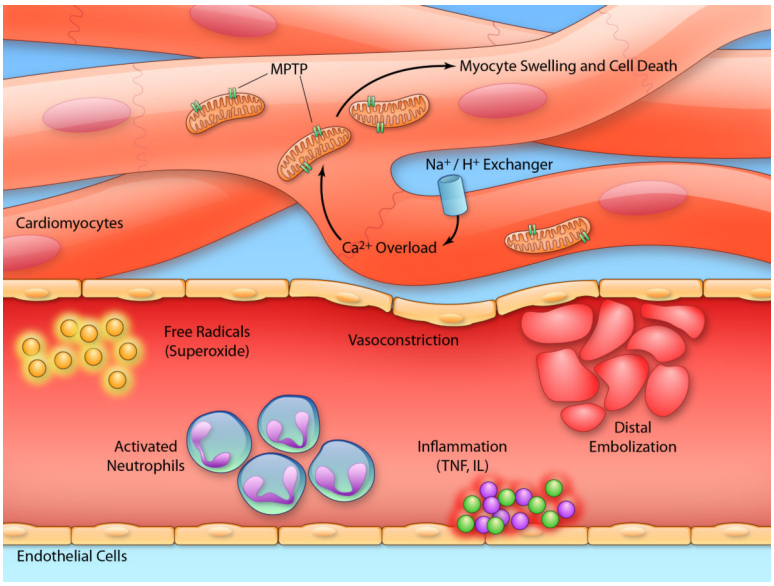

Figure 1.

Mechanisms of reperfusion injury and no-reflow in the coronary vasculature (Illustration Credit: Ben Smith).

Table 1

Traditional Pharmacological Approaches for Acute Coronary Syndrome (ACS)

Class of Medications	Mechanism of Action	Efficacy for Hard Clinical Outcomes in ACS
β-Blockers	Decrease heart rate, blood pressure, and contractility through antagonism of β1 receptors	Decrease mortality in ACS,[18–20] Intravenous use increases risk of cardiogenic shock,[22] Long-term secondary prevention benefit is less certain in patients without heart failure or reduced left ventricularsystolic function[21]
Nitrates	Decrease preload through venodilation; vasodilate coronary arteries	No benefit on mortality[31,32]
Calcium channel blockers	May vasodilate, reduce heart rate, or decrease contractility depending on specific drug	No clear benefit on mortality or reinfarction in ACS,[35] Increased reinfarction rate when nifedipine is used alone in ACS[34]
Angiotensin-converling enzyme inhibitors	Block conversion of angiotensin 1 to angiotensin II and decrease systemic vascular resistance	Decrease mortality and heart failure when used in acute myocardial infarction.[31,32,37,38] Long-term secondary prevention benefit in patients with normal ejection fraction is less certain[41–44]
Angiotensin II receptor blockers	Displace angiotensin II from the angiotensin II type 1 receptor and decrease systemic vascular resistance	Noninferiorto ACE-I in reducing mortality and cardiovascular events after ST-segment elevation myocardial infarction[47]
Aldosterone antagonists	Competitively inhibit binding of aldosterone to receptors and prevent detrimental effects of renin–angiotensin–aldosterone system cascade	Reduce mortality and sudden cardiac death in patients with acute Ml with reduced ejection fraction and symptoms of heart failure or diabetes mellitus[48]

Table 2

Summary of Major Society Guideline Recommendations for ACS Therapies

Class of Medications	ACC/AHA Recommendations	ESC Recommendations
β-Blockers	•(Vblockers should be initiated <24 h of any ACS if no contraindications (1B} • β-blockers should be continued for <3 y after ACS presentation in the absence of LV dysfunction (1 A); indefinite therapy can be considered (lla B)	•β-blockers should be considered in all patients witii STEMI without contraindications (lla B) •β-blockers are indicated in all patients with LV dysfunction(STEMI: 1 A; NSTEMI: 1 B)
N trates	•Nitrates should be administered for ongoing ischemia in UA/NSTEMI (IC) •No recommendation for use in STEM 1	•Nitrates are indicated to relieve angina in NSTEMI (1 C) •Mitrates are recommended in STEMI for Killip class III heart failure (1 C) and for hypertension (lla C)
CCBs	•Nonelihydropyridine CCBs should be given for ongoing schem ain NSTEMI if β-blockers are contraindicated (1B) •Nondihydropyridine CCBs should bp given for recurrentischemia in NSTEMI after β-blockers and nitrates have beenfully used (lla C) •Immediate-release dihydropyridine CCBs should not beadministered in the absence of βblockers (III A} •No recommendat on for use in &TEMI	•CCBs are recommended for symptom relief in NSTEMI inpatients already receiving βblockers and nitrates or with contraindications to β-blockers (1B) •CCBs are recommended in vasospastic angina (1C) •Dihydropyridine CCBs should not be administered in the absence of (β-blockers (III B) •Mo recommendation for use in STEMI
ACE-ls	•ACE-ls should be administered <24 h of STEMI in patients withanterior Ml, HR. or LVEF ≤0.40 (1 A}; reasonable to use in all other patients (lla A) •ACE-ls should be administered <24 h of UA/NSTEMI in patients with pulmonary congestion or LVEF ≤0.40 (1 A); reasonable to use in all other patients (lla B)	•ACE-ls should be administered <24 h of STEMI to patientswith anterior Ml, HP diabetes mellitus, or LVEF ≤0.40 (1 A); reasonable to use in all other patients (lla A} •ACE-ls should be administered within <24 h of NSTEMI to patients with HF, diabetes mellitus. hypertension, renal diseas or LVEF ≤0.40 (1 A); recommended for all other patients (1 B)
ARBs	•ARBs should be given to patients with STEMI who have indications for but are intolerant of ACE-ls (1 B) •ARBs should be given to patients with UA/NSTEMI who are intolerant of ACE-ls with signs of HF or LVEF ≤0.40 (1 A)	•ARBs (especially valsartan) are alternatives to ACE-ls in patien with STEMI or HF or LVEF≤0.40, especially if intolerant to ACE-ls **(1**B) •ARBs are recommended in patients with NSTEMI intolerant of ACE-ls (1B)
Aldosterone antagonists	• Aldosterone antagonists should be given to patients with ACS without contraindications who are already on an ACE-ls and β-blockers and who have an LVEF ≤0.40, symptomatic HF, or diabetes mellitus (STEMI: 1 B; UA/NSTEMI: 1 A)	• Aldosterone antagonists are indicated in patients with STEMI patients with LVE≤0.40, HF, or diabetes mellitus if no renal failure or hyperkalemia (1 B) • Aldosterone antagonists (epl ere none) are indicated in patients with NSTEM with an LVEF ≤0.35 and HF or diabetes me itus no renal failure or hyperkalemia (1 A)

Table 3

Newer and Experimental Agents in ACS

Therapeutic Agent	Mechanism of Action	Clinical Effects in ACS
Ranolazine	Inhibits late inward sodium current	Decreases recurrent ischemia and arrhythmias[52,53]
Trimetazidine	Shifts myocardial metabolism from fatty acid to glucose use	Decreases mortality in subset of patients with ACS not receiving thrombolysis[63]
Nicorandil	Activates ATP-sensitive K^+ channels and dilates arterioles; may have ischemic preconditioning-like effect	Decreases arrhythmias and transient ischemia.[72] No effect on infarct size or EF[73]
Ivabradine	Inhibits inward funny current and decreases heart rate	Not studied yet for efficacy in ACS
FXOG	Binds to vascular endothelial-cadherin and prevents leukocyte infiltration and plasma leakage	Reduces necrotic core size but not infarct size[39]
Pexelizumab	Monoclonal antibody to C5 complement	No effect on mortality or secondary composite cardiovascular end point[32]
Eniporide	Inhibits Na^+/H^+ exchange system involved in reperfusion injury	No effect on infarct size or clinical outcomes[94]
Exenatide	Glucagon-like peptide analog that may activate receptor-mediated survival pathway	Reduces infarct size in relation to area at risk[97]
Adenosine	Multifactorial effects on endothelium including vasodilation, neutrophil inhibition, decreased free radical formation	No effect on clinical outcomes; reduces infarct size at higher doses[98]
Cyclosporine	Inhibitor of the mitochondrial permeability transition pore involved in reperfusion injury	Reduces infarct size in small studies; larger clinical trial in progress
TR040303	Reduces opening of the mitochondrial permeability transition pore	Clinical trial in progress
Atrial natriuretic peptide	Activates reperfusion injury salvage kinase pathway	Reduces infarct size and reperfusion injury[73]
Magnesium	Electrolyte repletion	No effect on mortality[117]
Glucose/insulin/potassiurri	Electrolyte and glucose repletion	No effect on mortality or clinical outcomes[119]
Metformin	Possibly phosphorylates adenosine monophosphate–activated kinase	Clinical trial in progress
Oxvaen	Reduces hvrjoxia	Clinical trial in Droaress