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Adjunctive medical therapy for acute coronary syndromes

ABSTRACT

Adjunctive therapy is critical in treating acute coronary syndromes. Aspirin, nitrates, beta-blockers, ACE inhibitors, HMG-CoA reductase inhibitors (statins), and intra-aortic balloon pumps all have important roles and should be considered on a case-by-case basis.

KEY POINTS

Give a 325-mg non-enteric coated aspirin to all patients presenting with an acute coronary syndrome unless it is absolutely contraindicated.

Consider nitroglycerin for all patients presenting with acute coronary syndromes, especially those with acute MI associated with congestive heart failure, large anterior infarction, persistent ischemia, or hypertension.

We cannot overstate the benefit of beta-blockers. A common mistake in using beta-blockers is to give subtherapeutic doses, resulting in inadequate hemodynamic control.

There is growing evidence to suggest that statins have effects besides lipid lowering, such as an anti-inflammatory effect.

WITH THE DRAMATIC DECLINE in the cardiac death rate over the last 50 years, a sense of complacency has emerged. Various studies have found that even simple medical interventions, such as aspirin, beta-blockers, and ACE inhibitors are woefully underused, even though they could save thousands of lives annually.

At the same time, the many medical and interventional options now available for treating acute coronary syndromes are expensive. Patients younger than 65 years who present with an acute coronary syndrome incur an average cost of $23,000 per hospital admission.[1]

The challenge for physicians is to use an evidence-based approach to ensure that they make the most correct and complete therapeutic choices for their patients, while at the same time using these new treatment options in a prudent, cost-efficient manner.

There certainly is no reason for complacency. Coronary artery disease remains the single largest killer of Americans, responsible for 26% of all deaths recorded in 1996 (roughly half a million people).[1] An estimated 1.1 million Americans will have a new or recurrent coronary event this year alone.

This article examines the evidence and makes recommendations for using aspirin, nitrates, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, HMG-Co-A reductase inhibitors (statins), and intra-aortic balloon pumps in acute coronary syndromes. (Glycoprotein IIb/IIIa inhibitors were discussed in a previous article in this series.[2])

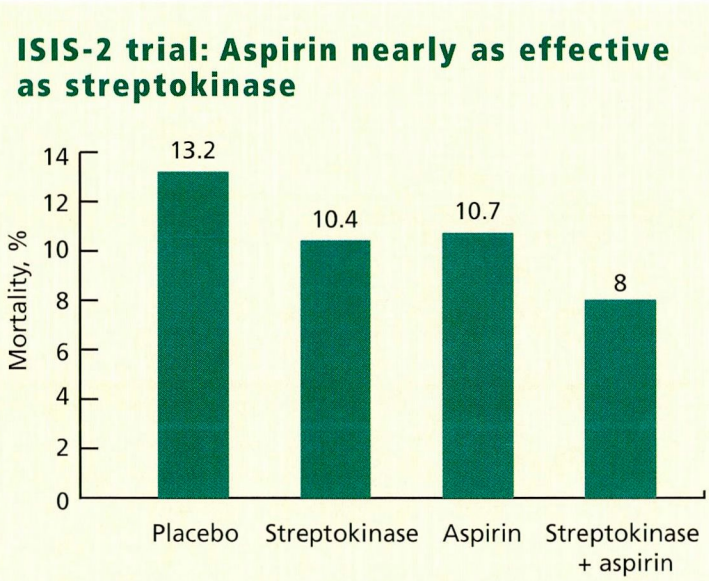

FIGURE 1. In the ISIS-2 trial, patients with acute myocardial infarction who received monotherapy with aspirin or streptokinase had similar reductions in mortality (23% vs 25%, respectively). Combination therapy with both aspirin and streptokinase had an additive effect with a 42% reduction in mortality.

DATA FROM BOISSEL JP. [THE ISIS-2 STUDY (INTERNATIONAL STUDY OF INFARCTION SURVIVAL)]. REV PRAT 1988; 38:1285–1288.

ACUTE CORONARY SYNDROMES SHARE A COMMON PATHOGENESIS

The onset of an acute coronary syndrome is invariably the result of rupture or erosion of a thin-capped, lipid-rich atheromatous plaque with ensuing platelet aggregation and thrombus formation. The degree to which the thrombus occludes the affected vessel, either partially or completely, determines whether the event will be classified as unstable angina, non–ST-elevation myocardial infarction (MI), or ST-elevation MI.

Given that all three types of coronary syndrome share a common pathophysiology, most of the pharmacologic therapies are applicable in all three. However, there are notable exceptions: for example, fibrinolytic agents are indicated only in ST-elevation MI. This review focuses on therapies appropriate in any of the acute coronary syndromes.

ASPIRIN

We cannot overstate the role of aspirin, as it is the most cost-effective therapy available for treating acute coronary syndromes.[3] And as Tan et al[3] noted in an earlier article in this series, aspirin is woefully underused.

Briefly, aspirin acts primarily by inhibiting cyclooxygenase, an enzyme that catalyzes the formation of prostaglandin endoperoxides PGH2 and PGG2. These are precursors to the potent platelet agonist thromboxane A_2.

Studies of aspirin

Aspirin has proved effective in both primary and secondary prevention of MI.

In acute MI, the Second International Study of Infarct Survival (ISIS-2)[4] found that monotherapy with aspirin 160 mg/day reduced the mortality rate by 23%—nearly as much as monotherapy with streptokinase, which reduced the mortality rate by 25%. Combining aspirin and streptokinase had an additive effect, reducing mortality by 42% (FIGURE 1).

In unstable angina, many studies showed that aspirin reduced the mortality rate by 57% to 71%.[3] The doses most commonly used ranged from 160 to 325 mg/day.

Aspirin: Recommendations

Give a 325-mg non-enteric coated aspirin to all patients presenting with an acute coronary syndrome unless it is absolutely contraindicated (eg, because of well-documented anaphylaxis to aspirin or active bleeding).

Of importance: Do not use enteric-coated aspirin in an acute coronary syndrome, because it has a delayed onset of action.

NITRATES

Oral or intravenous nitroglycerin or both are routinely used in treating acute coronary syndromes. Although no data indicate that nitrates reduce mortality, their role in relieving ischemic chest pain is well established.[5,6]

Studies of nitrates

In a study from 1988, Jugdutt et al[7] randomized 310 patients with MI to receive either nitroglycerin or placebo. Patients who received nitroglycerin had significantly small-

er infarcts than did controls, improved significantly in other indices of infarct size (left ventricular asynergy, left ventricular ejection fraction, and Killip class score), and had fewer infarct-related major complications (infarct expansion syndrome, left ventricular thrombus, cardiogenic shock, and infarct extension). Most importantly, fewer patients died who received nitroglycerin, both in the hospital and at 1-year follow-up; however, only those with anterior infarctions experienced this advantage.

Neither the much larger International Infarct and Survival trial (ISIS-4, N = 58,050)[8] nor the *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico* (GISSI-3, N = 19,394)[9] found any significant reduction in mortality with nitrates, but they did note reductions in chest pain, post-infarct ischemia, and cardiogenic shock in the nitrate-treated groups.

Nitrates: Recommendations

Consider nitroglycerin for all patients presenting with acute coronary syndromes, especially those with acute MI associated with congestive heart failure, large anterior infarction, persistent ischemia, or hypertension, as these patients tend to derive the greatest benefit.

We usually start nitroglycerin at 5 to 10 µg/minute intravenously and titrate it to a typical dose of 40 to 80 µg/minute while not allowing the systolic blood pressure to drop below 90 mm Hg or the mean arterial pressure to drop below 70 to 75 mm Hg. Patients with right ventricular infarcts seem to be more susceptible to nitrate-induced hypotension, and nitroglycerin should be used cautiously, if at all, in such patients.

BETA-BLOCKERS

Many studies strongly support the use of beta-blockers in acute coronary syndromes, although most of them predate the era of reperfusion therapy.

Studies of beta-blockers

During an acute MI. ISIS-1,[10] the largest trial (16,027 patients) to investigate the use of beta-blockers in acute MI, reported a decrease in all vascular mortality of 15% at both 7 days and 1 year. It also demonstrated a significant reduction in the combined endpoint of death, cardiac arrest, or reinfarction. The data suggested that by treating 200 MI patients with a beta-blocker, one could prevent one reinfarction, one cardiac arrest, and one death in the first week.

After an MI, nearly all studies showed that beta-blockers increased the survival rate. The Norwegian Multicenter Study[11] reported that timolol reduced mortality by 39% at 33 months if it was started 7 to 21 days after an acute MI. The Beta-Blocker Heart Attack Trial[12] reported that propranolol reduced mortality by 28% if it was started 5 to 21 days after an acute MI.

A retrospective review[13] of New Jersey Medicare patients from 1987 to 1992 identified 5,332 elderly patients who survived at least 30 days after an acute MI, of whom 3,737 were judged to be eligible for beta-blocker therapy. The mortality rate among beta-blocker recipients, controlled for other predictors of survival, was 43% less than among nonrecipients. Effects on mortality were substantial in all age groups. Unfortunately, only 21% of eligible patients received beta-blockers.

A 1994-1995 study[14] analyzed 115,015 patients nationwide aged 65 years or older who survived hospitalization with a confirmed acute MI. Of the 45,308 patients who were candidates for beta-blockers, only 50% received them as a discharge medication. At 1 year, the mortality rate among recipients, after adjustment for potential confounding factors, was 14% lower than among nonrecipients. Fewer patients died who received beta-blockers regardless of age, sex, or left ventricular ejection fraction.

In unstable angina, beta-blockers decreased the incidence of recurrent ischemia and MI in many studies.[15–17]

Beta-blockers: Recommendations

We cannot overstate the benefit of beta-blockers. They should be strongly considered in all patients presenting with an acute coronary syndrome, unless there is an absolute contraindication.

A common mistake is to give subtherapeutic doses, resulting in inadequate hemody-

Consider nitroglycerin especially for MI patients with CHF, larger anterior MIs, persistent ischemia, or hypertension

namic control. Patients with acute coronary syndromes vary widely in their hemodynamic responses to doses of beta-blockers. We commonly use doses ranging from 5 mg to 50 mg of intravenous metoprolol, guided by heart rate, blood pressure, and symptoms. Our goal is a heart rate near 60 beats per minute while maintaining a systolic blood pressure higher than 100 mm Hg.

Oral beta-blockers can be started early, with supplemental intravenous doses given if angina recurs or if chronotropic control is inadequate. As with intravenous metoprolol, the appropriate dose of oral metoprolol varies widely among patients.

Contraindications to beta-blockers include cardiogenic shock, acute pulmonary edema, high-degree AV block, and severe obstructive airway disease.

ACE INHIBITORS

Physicians have been slow to embrace using ACE inhibitors in acute coronary syndromes, even though these drugs have gained wide acceptance in treating left ventricular dysfunction, and in spite of compelling clinical and basic science evidence supporting their efficacy in acute coronary syndromes.

With beta-blockers, the goal is a heart rate near 60 and SBP > 100

ACE inhibition has been postulated to improve endothelial function, inhibit atherogenesis and cell proliferation, modulate sympathetic activity, and prevent ventricular remodeling after MI.[18,19]

Studies of ACE inhibitors

Some concern over the use of ACE inhibitors early in the course of MI may have arisen from the CONSENSUS II trial,[20] in which patients with acute MI and blood pressure higher than 100/60 mm Hg were randomly assigned to receive either enalapril or placebo, in addition to conventional medical therapy. The enalapril group first received an intravenous infusion of enalaprilat in the first 24 hours after the onset of chest pain, followed by oral enalapril. Mortality rates in the two groups at 1 and 6 months were not significantly different, although early hypotension occurred significantly more often in the enalapril group than in the placebo group (12% vs 3%, $P < .001$).

In contrast, GISSI-3[9] and ISIS-4[8] both reported a significant reduction in mortality in patients who received an ACE inhibitor compared with placebo within 24 hours of an MI. (In GISSI-3, patients received lisinopril 2.5 mg to 10 mg by mouth once a day with a follow-up of 42 days; in ISIS-4, patients received captopril 6.25 mg to 50 mg twice a day with a follow-up of 30 days).

Similarly, the SOLVD,[21] SAVED,[22] and AIRE[23] trials all reported significant reductions in mortality in patients randomized to receive an ACE inhibitor vs placebo from 3 to 16 days after an MI. Follow-up for these trials was more than 1 year. Individual results from SOLVD, SAVE, AIRE, GISSI-3, and ISIS-4 suggest that ACE inhibitors reduce morbidity and mortality significantly in patients with ischemic heart disease, MI, and a wide range of ventricular function.[24]

Recent data from the Heart Outcomes Prevention Evaluation (HOPE) trial[25] appear to extend the role of ACE inhibitors to patients with atherosclerotic disease and no evidence of left ventricular dysfunction or clinical heart failure. In this study, patients randomized to receive ramipril had a significant reduction in MI, stroke, and cardiovascular death (FIGURE 2).

ACE inhibitors: Recommendations

Consider an ACE inhibitor for all post-MI patients who do not have significant hypotension or a known contraindication, particularly patients known to derive the greatest benefit: those with Killip class 2 to 3 heart failure, a heart rate greater than 100, or anterior infarctions. Stop the ACE inhibitor if hypotension develops, but consider restarting it after a period of hemodynamic stabilization.[26,27]

We prefer always to start an ACE inhibitor early, within 24 hours, if the patient is hemodynamically stable and at highest risk. We use captopril because it has a short half-life, and start at 6.25 mg by mouth three times a day. The goal is to titrate the dose to 50 mg three times a day as tolerated. As discharge approaches, a longer-acting ACE inhibitor can be substituted to simplify the regimen and improve compliance.

ACE inhibitors vs beta-blockers? Whether to use an ACE inhibitor rather than

a beta-blocker in acute coronary syndromes depends on the individual patient's cardiovascular hemodynamics during presentation and recovery. The following recommendations should serve only as a guide, as each patient and clinical situation will likely mandate a varying strategy.

- ACE inhibitors should be used preferentially (and titrated to goal doses) in patients with large MIs and evidence of left ventricular dysfunction. A beta-blocker is then started once there is no evidence of congestive heart failure, and slowly titrated, as tolerated, over months.
- An ACE inhibitor and a beta-blocker can be started simultaneously and titrated with caution in patients who present with large MIs who are hemodynamically stable and without signs of pulmonary congestion or low cardiac output.
- Beta-blockers probably should be used preferentially in patients with small amounts of myonecrosis and inadequate heart rate control (especially with recurrent ischemia) or with atrial or ventricular arrhythmias. ACE inhibitors can be started to control hypertension and may benefit this subset of patients even in the absence of left ventricular dysfunction.

HMG-CoA REDUCTASE INHIBITORS

The benefit of lipid-lowering therapy, particularly with HMG-CoA reductase inhibitors ("statins"), is well established in patients with chronic coronary atherosclerotic disease. Their role in acute coronary syndromes is not yet well established, but they seem to have benefits beyond lipid-lowering, suggesting they may become an integral part of the regimen irrespective of the presenting cholesterol levels.

Initially, statins were believed to work solely by lowering serum cholesterol levels and reducing the lipid content of plaques, thus helping to stabilize the plaque and possibly allowing it to regress. Recent research, however, suggests that patients begin to benefit even before their lipid levels decline by any significant amount, and long before any significant changes occur in plaque morphology. This would suggest that statins do more than reduce serum lipid levels. In fact, evidence is growing to suggest these agents have an anti-inflammatory effect, as they can alter regulation of DNA transcription, regulate natural-killer cell cytotoxicity, inhibit platelet-derived growth factor, induce DNA synthesis, decrease macrophage production of metalloproteinases, and significantly reduce inflammatory markers such as C-reactive protein.[28–31]

The HOPE trial: Ramipril effective in ischemic heart disease

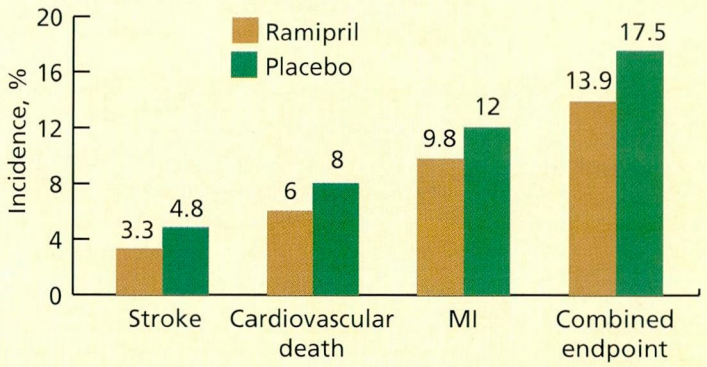

FIGURE 2. In the recent HOPE trial, there was a significant decrease in stroke, myocardial infarction, and cardiovascular death in patients treated with the ACE inhibitor ramipril. These were patients with ischemic heart disease and/or vascular disease with no evidence of LV dysfunction or clinical heart failure.

DATA FROM THE HOPE INVESTIGATORS. EFFECTS OF AN ANGIOTENSIN CONVERTING ENZYME INHIBITOR, RAMIPRIL, ON DEATH FROM CARDIOVASCULAR CAUSES, MYOCARDIAL INFARCTION, AND STROKE IN HIGH RISK PATIENTS. N ENGL J MED. 2000; 342:145–153

Studies of statins

In patients with coronary artery disease, large trials such as the Scandinavian Simvastatin Survival Study (4S)[32] and the Cholesterol and Recurrent Events (CARE) trial[33] demonstrated that treatment with simvastatin and pravastatin, respectively, significantly decreased the incidence of cardiac death, recurrent MI, and need for revascularization.

In patients with hypercholesterolemia but without known heart disease, the West of Scotland Coronary Prevention Study (WOSCOPS)[34] noted similar results. Participants (all men) in this large trial received either pravastatin 40 mg/day or placebo. There was a marked reduction in

ACE inhibitors have most benefit in large anterior MIs, Killip class 2 or 3 heart failure, or heart rate > 100

coronary events, nonfatal infarctions, and cardiovascular death in patients treated with pravastatin.

In acute coronary syndromes, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial will enroll patients with unstable angina or non–Q-wave MI within the previous 4 days, and randomize them to receive either atorvastatin 80 mg/day or placebo. Follow-up will be for 16 weeks, and the primary endpoints include recurrent hospitalization for myocardial ischemia, nonfatal MI, resuscitated cardiac arrest, and death.

Statins: Recommendations

We follow the recommendations of the National Cholesterol Education Program (NCEP)[35] and usually start a statin before hospital discharge if the patient's LDL level is greater than 130 mg/dL and he or she has no contraindications to statins. In fact, we often consider starting a statin even if the LDL level is as low as 100 mg/dL.

MAGNESIUM

We often start a statin with an LDL as low as 100

Magnesium has many potential cardioprotective mechanisms including vasodilation, reduction in platelet aggregation, stabilization of cell membranes, and protection of the myocardial cell from catecholamine-induced necrosis.[36–39]

Studies of magnesium

The use of magnesium in acute coronary syndromes has long been debated, with some small trials and meta-analyses suggesting that giving magnesium early in an acute coronary syndrome may limit infarct size and reperfusion injury, but larger trials showing no survival benefit.

For instance, the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2)[40] enrolled 2,316 patients with suspected acute MI. The mortality rate from ischemic heart disease was 21% lower and the all-cause mortality rate was 16% lower in patients treated with magnesium.

In contrast, the ISIS-4 trial[8] enrolled 58,050 patients with suspected MI. Patients were randomized to receive a 24-hour infusion of magnesium or placebo in addition to standard therapy. Magnesium treatment in this trial proved to be detrimental and was associated with a significant increase in morbidity (heart failure, cardiogenic shock, and bradycardia), while mortality was increased by a statistically insignificant 6%.

A National Institutes of Health-sponsored trial (Magnesium In Cardiac Arrest—MAGIC) should help clarify the role, if any, of magnesium in acute MI.

Magnesium: Recommendations

Until further data are available, magnesium is not recommended as standard therapy for MI except to replenish subtherapeutic levels.[27]

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are widely used in treating cardiovascular disease, but their role in acute coronary syndromes is controversial.

Studies of calcium channel blockers

Recent publications[41–45] cast doubt on the safety and efficacy of this drug class, indicating that they may paradoxically increase the incidence of heart attack and death. Unfortunately, these investigations focused only on the short-acting dihydropyridine calcium channel antagonists, which are known for rapidly reaching high plasma concentrations and having a potential for causing hypotension, coronary "steal," and sympathetic activation. It is not clear if the potential deleterious effects noted with dihydropyridines can be extrapolated to the nondihydropyridine calcium channel blockers (ie, verapamil and diltiazem) or even to the newer dihydropyridines such as amlodipine.

Two smaller studies[46,47] (combined N = 123) noted a reduction in signs and symptoms of myocardial ischemia in patients receiving verapamil or diltiazem vs beta-blockers.

These findings were reinforced in the second Danish Verapamil Infarction Trial (DAVIT II),[48] in which verapamil was associated with a significant reduction in overall mortality and reinfarction at 6 months. Similarly, the Multicenter Diltiazem Postinfarction Research Trial (MDPIT)[49] noted a reduced rate of reinfarction and car-

diac death in those receiving diltiazem vs placebo. In both trials, however, adverse events increased and success decreased in patients with evidence of left ventricular dysfunction.

A recent large meta-analysis[50] comparing calcium channel blockers with beta-blockers found no significant differences in the rates of MI and cardiac death; however, there were fewer episodes of angina and fewer adverse events per week with beta-blockers.

Calcium channel blockers: Recommendations

Calcium channel blockers are appropriate in patients with documented vasospastic angina and in patients with ischemia and noncompensatory tachycardia (eg, atrial fibrillation or supraventricular tachycardia) with no evidence of left ventricular dysfunction, and a contraindication to beta-blockers.[27]

These agents should be avoided in patients with hemodynamic instability, acute pulmonary edema, or high-degree AV block.

There is no conclusive evidence that calcium channel blockers are more beneficial than beta-blockers in the early treatment of acute MI, and they may be associated with increased adverse events. We avoid these agents, and use them in acute coronary syndromes only when there are *absolute* contraindications to beta-blockers such as severe chronic obstructive pulmonary disease.

The role of calcium channel blockers is controversial

INTRA-AORTIC BALLOON PUMP (IABP)

Although not a drug, the intra-aortic balloon pump (IABP) deserves mention, as it often plays a critical role in the management of acute coronary syndromes.

IABPs are generally placed percutaneously through the femoral artery and positioned in the descending aorta with the tip just distal to the left subclavian artery. The balloon is timed to the cardiac cycle, with inflation occurring during diastole and deflation during systole. The diastolic inflation improves coronary perfusion and thus improves myocardial oxygen supply. Deflation decreases afterload, thereby decreasing myocardial work and oxygen consumption.

IABPs have a well-established role in stabilizing acute MI patients with cardiogenic shock.[51,52] They often serve as a temporizing "bridge" to revascularization, placement of a ventricular assist device, or cardiac transplantation. More recently, it has been suggested that IABPs improve vessel patency in acute MI patients treated with fibrinolytics or primary percutaneous transluminal coronary angioplasty.[53–55] Most patients with unstable angina can be adequately treated with medications alone; however, for patients with refractory angina, placement of an IABP has been shown to relieve symptoms effectively.[56]

IABP: Recommendations

Consider an IABP in patients who present with unstable angina refractory to medical therapy or acute MI complicated by cardiogenic shock, assuming there are no contraindications (severe peripheral vascular disease, suprarenal aortic aneurysm, or significant aortic insufficiency).

Given the array of technical issues involved in proper patient selection, balloon insertion and maintenance, potential complications, and appropriate post-IABP management, we recommend that these patients be cared for in a cardiac intensive care unit.

In recent years, we have become more liberal in our use of IABPs, and believe that they are underused.

INFLAMMATION AND ATHEROSCLEROSIS

Inflammation is now recognized as the major component in the initiation and progression of atherosclerosis.[57–59] Elevations in inflammatory markers such as monocytosis, fibrinogen, C-reactive protein, and amyloid A after MI or unstable angina have all been linked to a significant risk of future cardiovascular events.[60–63] As mentioned above, the HMG-CoA reductase inhibitors have been shown to reduce cardiovascular mortality and morbidity, although the reduction in events is not tightly coupled to the reduction of LDL levels to below 125 mg/dL.[64] As we learn more about the diverse actions of this class of drugs, perhaps more specific anti-inflammatory therapy will become available.

We now have considerable evidence to implicate infection and inflammation in the progression of atherosclerosis. Although investigations have targeted cytomegalovirus, *Helicobacter pylori*, and herpes viruses, the evidence is most compelling for *Chlamydia pneumoniae*.[65,66] Early animal studies reported that treatment with a macrolide antibiotic reduced intimal thickening in C *pneumoniae*-infected animals.[67] In a study of 202 patients with unstable angina or non–Q-wave MI, those who received roxithromycin (150 mg twice a day for 30 days) had significantly fewer cardiovascular events at 30 days than did those who received placebo; however, the benefit was not sustained at 6 months.[68] In a larger trial, 302 patients with C *pneumoniae* IgG titers of 1:16 or higher and a documented history of coronary artery disease were randomized to receive azithromycin or placebo. Although global tests for markers of inflammation improved at 6 months in the azithromycin group, there was no difference in antibody titers or clinical events.[69]

In a recent retrospective analysis of the DAVIT II trial,[70] patients who had been taking a nonsteroidal anti-inflammatory drug (NSAID) were found to have a 41% lower mortality rate and a 33% lower rate of major events, but the differences were not statistically significant.

Currently, the literature does not fully support treating acute coronary syndromes with NSAIDs or antibiotics, but the issue is under study. Numerous ongoing studies are focusing on identifying the various causes of inflammation and their role in the progression of atherosclerosis. Investigations of novel therapeutics directed at attenuating this inflammatory response are soon to follow.

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