Pathophysiologic Bases for Adjunctive Therapies in the Treatment and Secondary Prevention of Acute Myocardial Infarction

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Summary: Postmyocardial infarction (MI) survival has been steadily improving. This improvement has been due, in part, to the actions of the adjunctive medical therapies for the treatment of MI. Aspirin, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering agents have been shown to improve survival in the treatment and secondary prevention of MI. Nitrates have beneficial effects as well. These medications complement the reperfusion strategies through different mechanisms. Other adjunctive medical therapies, namely magnesium, antiarrhythmic agents, and calcium-channel blockers, have not been shown to improve mortality with routine post-MI use despite their theoretical benefits.

Key words: myocardial infarction, adjunctive medical therapy, treatment, secondary prevention, pathophysiology

Introduction

The past two decades have witnessed a significant improvement in postmyocardial infarction (MI) survival in the United States.^{1–3} Significant decreases in mortality have been noted in several other countries as well.^{4–8} The progressive improvement in survival after MI began prior to the introduction of thrombolytic therapy and appears to be related to a variety of improvements in the care of cardiac patients.

Most recently, these advances in patient care have included improvements in post-MI medical therapy, revascularization techniques, and risk reduction. The decrease in mortality noted in a Swedish medical center by Dellborg *et al.* corresponded to the introduction of several medical therapies for acute MI (Fig. 1). This study calculated that the most substantial impact on mortality was achieved by the introduction of combination therapy with thrombolysis and aspirin (ASA). However, improvements in mortality were also calculated for treatment with both nitrates and beta blockers combined with ASA, and for ASA alone.⁶

This review will concentrate on the mechanisms by which these and other medical therapies improve outcome when administered as an adjunct to thrombolysis after an acute MI. A summary of these adjunctive therapies and their effects is presented in Table I.

Improvements in the Pathophysiology of Acute Myocardial Infarction with Adjunctive Therapies

Several processes contribute to the development of morbidity and mortality in the post-MI setting. These processes include remodeling, reinfarction (or infarct extension), and arrhythmic sudden death. The adjunctive medical therapies are intended to complement the benefits of thrombolysis by ameliorating those processes which contribute to much of the morbidity and mortality after an acute infarct.

The action of thrombolysis during acute MI is to salvage ischemic myocardium directly by establishing reperfusion via lysis of clot in the infarct-related artery. The efficacy of thrombolysis decreases dramatically if administered after the first few hours of an MI, since the amount of live myocardium supplied by the infarct-related artery decreases substantially in this period.^{9, 10} Still, limited benefit may be obtained by lytic reperfusion of the infarct-related territory more than 6 h after the initial event.¹¹

Like thrombolytics, the adjunctive therapies are tailored to limit extension of the infarct, a major source of morbidity and mortality.¹² Aspirin acts to prevent thrombotic reocclusion of the infarct-related artery and, thus, reinfarction. The benefit of ASA is additive to that of thrombolysis.⁹ Beta blockers reduce

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FIG. 1 In-hospital mortality after myocardial infarction (MI) at Ostra Hospital, Sweden, from 1979 to 1990.⁶ The decline in post-MI mortality corresponds to the introduction of various medical therapies, as indicated in the figure. IV = intravenous. Reprinted from Ref. No. 6 with permission.

ischemia and reinfarction by reducing metabolic demand and wall stress in the ischemic or infarcted territory.¹³ By reducing wall stress, beta blockers also reduce the incidence of fatal cardiac rupture in the first day after an infarct.¹⁴ Nitrates, like the beta blockers, reduce metabolic demand and wall stress on the myocardium. By reducing left ventricular end-diastolic pressure and as a coronary vasodilator, nitrates improve perfusion to ischemic myocardium¹⁵ and reduce anginal pain. Thus, through differing mechanisms, ASA, beta blockers, and nitrates are useful in the first hours after MI to prevent infarct extension and to salvage functional myocardium.

Aspirin and beta blockers have proven effective at reducing recurrent infarction and improving survival chronically after an MI.¹⁶⁻¹⁸ Another important chronic therapy after MI is cholesterol-reducing therapy. Lipid lowering is protective against recurrent cardiac events in hypercholesterolemic patients, as well as in those with only borderline elevations in to-

tal cholesterol and low-density lipoproteins (LDL).^{19,20} Lipid lowering probably plays an important role in atheroma stabilization, preventing plaque rupture and recurrent MI.^{21,22}

Another important process responsible for morbid changes after MI is remodeling. In this process, the ventricle progressively enlarges over the course of several months after infarction.²³ Remodeling starts in the first few hours after MI in a process termed infarct expansion, or the progressive thinning and bulging outward of the infarct zone.²⁴ The adjunctive therapies work synergistically with reperfusion strategies to prevent infarct expansion and remodeling in the acute and chronic periods after MI. Both thrombolysis and mechanical reperfusion reduce remodeling and preserve left ventricular function after MI.^{25,26} Mechanical reperfusion may improve left ventricular function by salvaging hibernating myocardium up to several weeks following an infarct.²⁵ Of the adjunctive therapies, angiotension-converting enzyme (ACE) inhibitors have proven most effective in reducing left ventricular remodeling and reducing the progression to heart failure in post-MI patients.^{23,27-30} Nitrates may also play a role in reducing remodeling after MI.³¹ In addition, beta blockers reduce wall stress and help prevent the progression of infarct expansion to frank rupture.¹⁴

Arrhythmic sudden death is also a major contributor to post-MI mortality. However, routine antiarrhythmic therapy does not appear to improve survival in post-MI patients.³²⁻³⁴ Beta blockers, on the other hand, have been found to reduce the occurrence of malignant ventricular arrhythmias after acute MI and improve outcome.^{18,35} Antiarrhythmic therapy, therefore, is limited presently to beta blockers pending further research into the effectiveness and safety of prophylactic amiodarone in the post-MI setting. The major actions of the adjunctive medical therapies on the pathophysiology of acute MI are summarized in Figure 2.

TABLE I Summary of effects of adjunctive therapies in the treatment and secondary prevention of acute myocardial infarction

Adjunctive therapy	Effects	Acute MI	Secondary prevention
Aspirin	↓Reocclusion, reinfarction	+++	+++
Anticoagulation	↓Reocclusion, reinfarction	++	^a
Beta blockers	↓Ischemia, reinfarction cardiac rupture, sudden death	+++	++
ACE-inhibitors	↓Remodeling; plaque-stabilizing effect may reduce reinfarction	++	++
Lipid-lowering agents	Improved plaque stability	—	++
Nitrates	↓Ischemic pain via coronary vasodilator	+ With lytic +++ Without lytic	—
Magnesium	Vasodilator; ↓reperfusion injury; antiplatelet and antiarrhythmic properties	? With lytic + Without lytic	—
Antiarrhythmics	↓Complex ventricular ectopy	—	—
Calcium-channel blockers	Anti-ischemic properties	—	—

^a Anticoagulants have proven no more effective than aspirin alone or in combination with aspirin.

+++ = strongly indicated, ++ = indicated with stratification, + = reasonable, ? = of questionable value, — = no role for routine use.

Abbreviations: MI = myocardial infarction, lytic = thrombolytic therapy, ACE = angiotension-converting enzyme.

FIG. 2 Pathophysiologic sequelae of acute myocardial infarction and major sites of action of several adjunctive medical therapies. ACE = angiotensin-converting enzyme.

Aspirin

Aspirin has proven extremely useful in the setting of acute MI and for secondary prevention after MI. The mechanism of action of ASA is related to its irreversible inhibition of cyclooxygenase. By inhibiting cyclooxygenase, ASA prevents the conversion of arachidonic acid to prostaglandin H_2 . Platelets utilize prostaglandin H_2 to produce thromboxane A_2 , a potent stimulator of platelet aggregation and thrombosis.³⁶ Aspirin is effective at reducing the occurrence of thrombotic reocclusion of the coronary arteries, thus decreasing the rate of both early and late reinfarction after acute MI.⁹

Aspirin emerged as an effective therapy in acute MI with the ISIS-2 trial. ISIS-2 demonstrated that when ASA and streptokinase were combined in the treatment of acute MI, their effects were additive. Combination therapy proved significantly better than the use of either agent alone (Fig. 3).⁹ Antiplatelet therapy is associated with the secondary prevention of recurrent MI, as well as with improved survival after acute MI. The Antiplatelet Trialists' collaboration found significant reductions in the incidence of vascular events (nonfatal MI, nonfatal stroke, or vascular death) with antiplatelet therapy in the first month after MI, and with chronic therapy in those patients with a past history of MI.^{16, 36} As a result of the data supporting the use of ASA during and after MI, its use in the treatment and secondary prevention of MI is strongly indicated and widely accepted.^{37, 38}

Other antiplatelet agents currently in use include the glycoprotein IIb/IIIa blockers. The role of antibodies directed against glycoprotein IIb/IIIa, the final common pathway for platelet aggregation, is currently being evaluated in the setting of acute MI.

Anticoagulation after Myocardial Infarction

Given the thrombogenic milieu at the site of infarction and the high rate of early reinfarction, much attention has been directed toward developing a safe and effective strategy for preventing thrombosis in the setting of an acute MI.¹² After thrombolysis, altered flow characteristics and the thrombo-

FIG. 3 Cumulative vascular mortality in Days 0-35 after acute myocardial infarction (MI) in the ISIS-2 trial.⁹ Both aspirin and streptokinase significantly improve post-MI mortality. In combination, the effects of aspirin and streptokinase are additive. Reprinted from Ref. No. 9 with permission.

genicity of the residual thrombus contribute to rethrombosis.³⁹ These factors may be amenable to systemic anticoagulation with heparin. Heparin acts as an anticoagulant primarily by inactivating thrombin and other clotting factors through an interaction with antithrombin III and, at higher doses, via heparin cofactor II.⁴⁰ Given the frequency of rethrombosis after thrombolysis and its related morbidity and mortality,¹² multiple trials have investigated the optimal anticoagulant strategy for administration with thrombolytic therapy.

The International Study Group, GISSI-2, and ISIS-3 all failed to demonstrate a significant survival benefit when subcutaneous heparin was administered after thrombolysis in comparison with thrombolysis alone.⁴¹⁻⁴³ However, GUSTO-I reported a significant reduction in post-MI mortality when alteplase combined with intravenous heparin was compared with streptokinase (or alteplase plus streptokinase) combined with intravenous or subcutaneous heparin.⁴⁴

Long-term anticoagulation after acute MI has proven effective at improving survival and reducing infarction.^{45, 46} However, long-term anticoagulation with warfarin or a combination of low fixed doses of warfarin and ASA does not appear to be more effective than ASA alone.^{47, 48} Given the excess bleeding sequelae and complicated dosing of warfarin, ASA appears preferable.⁴⁹

Anticoagulation is clearly indicated both acutely and long-term after MI in those at risk for systemic emboli (patients with atrial fibrillation, left ventricular thrombus, or a large MI). Anticoagulation is also indicated for 48 h after thrombol-

ysis with alteplase.³⁷ However, the routine use of heparin in many patients with uncomplicated acute MI without a contraindication to ASA remains controversial.^{38, 37} More recently, newer anticoagulants, such as hirudin and low molecular-weight heparin have shown promise in comparison with unfractionated heparin for the treatment of acute coronary syndromes.⁵⁰⁻⁵³

Beta Blockade after Acute Myocardial Infarction

Beta blockers reduce cardiovascular mortality after MI through a variety of mechanisms. Perhaps the most significant mechanism of action of beta blockade is via a reduction of left ventricular wall stress, which, in turn, reduces the incidence of cardiac rupture after MI.^{13, 14} Beta blockers also reduce the incidence of arrhythmia and thereby decrease the incidence of post-MI sudden death.¹⁸ In addition, beta blockade reduces ischemia and possibly infarct size by decreasing heart rate and blood pressure, thereby decreasing myocardial oxygen demand.^{13, 18} Beta blockade may also limit the extent of infarction by prolonging diastole, thereby increasing the amount of blood flow to ischemic myocardium.³⁷ Despite these theoretic advantages of beta blockade in the setting of acute MI, no overall survival benefit was apparent until the results of ISIS-1 became available in 1986.⁵⁴

The most striking finding in ISIS-1, which parallels data from other trials,^{55, 56} was that the major mortality reduction with beta blockade comes on the first day after MI. Retrospective analysis revealed that a reduction in the incidence of cardiac rupture accounted for a large proportion of the mortality benefit observed in the atenolol group.¹⁴ In the setting of thrombolysis, TIMI-II revealed significant reductions in non-fatal MI and recurrent ischemia for the group immediately treated with metoprolol.⁵⁷ Beta blockers are also useful in the secondary prevention of MI and in the reduction of sudden death after acute MI.^{17, 18, 35}

Based on the available data, beta adrenergic blockade is indicated as soon as possible in all patients presenting with acute MI, excluding those in heart failure or with other major contraindications.^{37, 58} Beta blockers should be continued indefinitely in post-MI patients, especially in those with large infarcts, ischemia, and ventricular ectopy.³⁷

Angiotensin-Converting Enzyme Inhibitors Post Myocardial Infarction

Angiotensin-converting enzyme inhibitors have been shown to attenuate the progression of severe congestive heart failure and to improve the survival of heart failure patients.⁵⁹ After acute MI as well, ACE inhibitors have been found to slow the progression of heart failure and to reduce the incidence of severe left ventricular dysfunction and the need for hospitalization for heart failure.²⁷⁻³⁰ Much of this effect may result from the action of ACE inhibitors to reduce left ventricular remodeling, the process of left ventricular enlargement after MI.²³ The ACE inhibitors appear to have other salutary effects in the post-MI setting, which may help account for the

improvement in survival and decreased reinfarction rates in post-MI patients treated with ACE inhibitors. In addition to neuroendocrine modulation, the ACE inhibitors may have plaque-stabilizing activity through inhibition of macrophage activity.^{60, 61}

Several trials which randomized patients within a few days of MI showed that ACE inhibitors afforded significant reductions in mortality, reinfarction, the development of severe congestive heart failure, and the need for revascularization procedures.^{27, 29, 62, 63} Earlier intravenous ACE inhibitor administration after MI was studied in the second Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II). This study revealed a trend toward increased mortality in the enalapril-treated group. The increased mortality in the treated group may have been related to the excess early hypotension noted in patients treated with enalapril compared with the placebo group.⁶⁴

Subsequent studies have established a survival benefit with early ACE inhibitor treatment of acute MI when administered orally.^{28, 30, 65, 66} Major trials including GISSI-3 and ISIS-4, which randomized patients regardless of ventricular function, confirmed the safety and efficacy of early ACE inhibitor therapy for acute MI. ISIS-4 appeared to reveal a much greater benefit for higher-risk patients, such as those with anterior MI, heart failure, or a history of prior infarction.⁶⁶

Angiotensin-converting enzyme inhibition is indicated for all survivors of MI, particularly those with heart failure, an anterior MI, or left ventricular ejection fraction < 40%.³⁷ While benefit exists for all patients randomized to ACE inhibitors after MI, improvement in survival is most dramatic for patients with moderately or severely reduced ventricular function. Whether post-MI patients with normal or only mildly reduced left ventricular function derive long-term benefit from ACE inhibition remains to be seen.

Lipid-Lowering Therapy

Lipid-lowering therapy has emerged as a powerful tool in the secondary prevention of MI. Epidemiologic data have identified elevated total cholesterol and particularly elevated LDL cholesterol as independent risk factors for coronary artery disease.⁶⁷ Cholesterol-lowering therapies have succeeded in reducing the risk of developing coronary artery disease⁶⁸ and of recurrent cardiac events in patients with known coronary disease.¹⁹

Angiographic trials of cholesterol-lowering therapies have revealed decreased rates of progression or modest regression of atheromatous disease with treatment;⁶⁹ however, improvements in the incidence of recurrent cardiac events were far more impressive than the angiographic data. Thus, it appears that the effects of cholesterol-lowering therapies are not limited to simply modulating the rate of progression of atheromatous disease; in fact, lipid modification improves vascular endothelial function and plaque stability.⁷⁰ As a result of the data favoring lipid lowering in patients with coronary disease, all post-MI patients should have an accurate determination of their serum lipid profile. Aggressive management of abnormal

lipid levels is now an important aspect of the secondary prevention of MI.

Nitrates for Acute Myocardial Infarction

Nitrates have been used to treat angina pectoris for over 100 years.¹⁵ Nitrates are effective as well in reducing ischemic pain during infarction via their vasodilatory effect on coronary arteries, especially at sites of plaque disruption.³⁷ Their mechanism of action derives from activation of guanylate cyclase, which in turn increases intracellular concentrations of cyclic guanosine monophosphate (GMP). Cyclic GMP promotes smooth muscle relaxation, resulting in vasodilatation. Intermediates in the metabolism of nitrates also may have an antiplatelet effect.¹⁵ Clinical and laboratory studies have indicated that nitrates may reduce remodeling, limit infarct size, and improve left ventricular function.⁶⁶ An overview of several small randomized trials of intravenous nitroglycerin and nitroprusside in acute MI indicated a mortality reduction in nonthrombolysed patients treated with nitrates.⁷¹ Two larger randomized trials, GISSI-3 and ISIS-4, failed to demonstrate significant mortality reductions with nitrate therapy in thrombolysed patients after acute MI.^{30, 66, 72}

Available data suggest that nitrates are effective in reducing mortality in nonthrombolysed post-MI patients. In patients with MI who have received thrombolysis, however, survival benefits are marginal. Nonetheless, nitrates are safe in acute MI (in the absence of hypotension) and are effective in reducing ischemic pain. In addition, nitrates may reduce remodeling in patients with large transmural infarcts³¹ and thus should be considered in that setting.

Magnesium

Several important cardiovascular effects of magnesium have been reported from clinical and laboratory studies. These include coronary vasodilatation, decreased afterload, limitation of reperfusion injury, and antiplatelet and antiarrhythmic effects.⁷³⁻⁷⁶ Magnesium, by modulating calcium flux within the cell, appears to have a vasorelaxant effect on smooth muscle. This vasorelaxant effect is helpful in preventing coronary vasospasm and lowering the systemic vascular resistance.⁷⁶ The calcium-blocking effect of magnesium may also play a role in decreasing reperfusion injury by preventing calcium overload during reperfusion.^{73, 77} In addition, a number of clinical trials have suggested that intravenous magnesium may reduce the incidence of ventricular arrhythmias during acute coronary syndrome.⁷⁶

Despite encouraging data from smaller trials of magnesium,^{17, 74, 75, 78, 79} ISIS-4 demonstrated a nonsignificant mortality increase in comparison with controls.⁶⁶ However, magnesium was administered later in the course of MI in ISIS-4 than in the previous trials. Thus, the possibility remains that magnesium may be clinically useful if administered early after the onset of symptoms.

At present, magnesium is not indicated in the routine treatment of acute MI. Recent data suggest, however, that intra-

venous magnesium may have a role in the treatment of infarction in patients who do not receive thrombolysis.⁸⁰ Whether magnesium may be more effective prior to thrombolysis is an unsettled question.

Antiarrhythmic Agents

Several trials have tested the hypothesis that prophylactic antiarrhythmic therapy after MI, or therapy designed to suppress post-MI premature ventricular contractions, may improve mortality. However, trials involving post-MI antiarrhythmic therapy with lidocaine and other type I antiarrhythmic agents indicated that treatment with these agents was associated with increased mortality.³²⁻³⁴ More recently, prophylactic administration of sotalol to post-MI patients with left ventricular dysfunction was associated with increased mortality when compared with placebo.⁸¹

Unlike the previously mentioned antiarrhythmics, amiodarone does not worsen ventricular function.⁸² Unfortunately, amiodarone has not proven effective in reducing mortality in post-MI patients. While smaller studies supported the use of prophylactic amiodarone for post-MI patients, two larger randomized trials failed to demonstrate a significant improvement in total mortality among amiodarone-treated patients, despite reductions in arrhythmic death.⁸³⁻⁸⁵

Routine use of class I antiarrhythmic agents, as well as sotalol, in the post-MI setting should certainly be avoided. While preliminary data regarding prophylactic amiodarone after an infarction are encouraging, no significant survival benefit has been shown in large trials. Thus, we cannot recommend prophylactic amiodarone therapy after MI at the present time. It appears that the only prophylactic adjunctive medical therapy for the prevention of sudden death after MI remains the beta blockers.

Calcium-Channel Blockers

Despite the theoretical benefits of the calcium-channel blockers, data from several trials evaluating their use after acute MI have not been encouraging. Calcium-channel blockers possess anti-ischemic properties as well as antiplatelet and antiatherosclerotic effects.⁸⁶ However, several trials demonstrated no survival benefit with routine administration of calcium-channel blockers after acute MI.⁸⁷⁻⁸⁹

Limited data have emerged through subgroup analysis of randomized trials supporting the use of certain calcium-channel blockers after MI in patients without congestive heart failure or abnormal left ventricular function.^{90, 91} Nonetheless, the routine use of calcium-channel blockers in post-MI patients is not recommended and should be avoided.³⁷

Conclusion

Survival after acute MI has improved substantially over the last two decades. This improvement is due not in any small part to medical therapy as an adjunct to both lytic or

mechanical reperfusion and risk factor modification after MI. Aspirin, beta blockers, and ACE inhibitors benefit post-MI patients via mechanisms which compliment the reperfusion strategies. Aspirin decreases the risk of rethrombosis, thereby reducing reinfarction and improving survival with an efficacy which is additive to thrombolytic therapy. Beta blockers relieve left ventricular wall stress and decrease the incidence of cardiac rupture in post-MI patients; they have also been shown to decrease arrhythmia and reinfarction. Angiotensin-converting enzyme inhibitors prevent the remodeling process and protect against the development of heart failure after MI. Because of their clinical effectiveness, ASA, beta blockers, and the ACE inhibitors have assumed a prominent role in the routine therapy and secondary prevention of acute MI. Lipid-lowering medications, which lower LDL cholesterol and improve atherosclerotic plaque stability, are also highly effective in the secondary prevention of acute MI.

Nitrates, which lower left ventricular end-diastolic pressure and function as a coronary vasodilator, have proven useful in the treatment of ischemic pain during MI. In addition, nitrates afford a survival benefit to nonthrombolysed patients in the setting of MI. Other adjunctive therapies, such as magnesium, antiarrhythmic agents, and the calcium-channel blockers, have not proven efficacious for routine post-MI use despite their theoretical benefits.

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