

# **Pharmacotherapy in the Management of Acute Myocardial Infarction; Rationale & Guidelines**

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This review is based largely on guidelines published in 1999 & 2000 by task forces from the American College of Cardiology and the American Heart Association. (Circulation 1999; 100:1016; J Am Coll Cardiol 2000: 36:970). The emphasis is on the rationale behind the use of various drugs for the treatment of acute myocardial infarction.

## **I. Introduction**

The management of acute myocardial infarction (AMI) has come a long way since the concept of coronary care was introduced several decades ago. Defibrillation, percutaneous coronary angioplasty, thrombolysis, other new drugs, have all been all life-saving advances in medicine. Numerous large multi-centered trials have been completed adding invaluable information to our understanding of this life-threatening condition with regard to both treatment and prognosis.

## **II. Initial Approach to the Management of Acute Coronary Syndrome**

When a patient presents with chest pain and acute coronary syndrome is suspected, the initial approach should consist of the following (J Am Coll Cardiol 2000: 36:970):

- 1) Determine the likelihood of acute ischemia caused by CAD;
- 2) Early risk stratification focuses on anginal symptoms, physical exam, ECG, and biomarkers of cardiac injury;
- 3) A 12-lead ECG should be obtained immediately (within 10 minutes) in patients with ongoing chest discomfort ; and
- 4) a. Biomarkers of cardiac injury should be measured in all patients who present with chest discomfort consistent with ACS;  
b. Cardiac troponin is the preferred marker; c. CK-MB is also acceptable.  
In patients with negative cardiac markers within 6 hours of the onset of pain, another sample should be drawn in the 6- to 12-hr time frame.

## **III. Pharmacotherapy in the Management of AMI - Rationale & Guidelines**

Once the diagnosis of AMI has been made, there is a long list of medications that will need to be considered for administration. The following is a brief summary of the major drugs for the treatment of AMI.

### **1. *Aspirin***

That aspirin reduces mortality in AMI has been shown by multiple studies. The important meta-analysis of the placebo-controlled trials with aspirin by the Antiplatelet Trialists Collaboration showed a >25% reduction in the risk of infarction, stroke, or vascular death among 70,000 high risk patients. (BMJ 1994; 308:81) Additional benefit was documented by the addition of heparin to aspirin in patients with unstable angina/non-ST elevation MI (UA/NSTEMI). The combination reduces the risk of death and MI by 48% compared with aspirin alone. (N Engl J Med 1988; 319: 1105; Lancet 1990 336: 827.) Aspirin 160-320 mg should be given to all patients on day 1 of AMI unless there are contraindications and continued indefinitely on a daily basis.

### **2. *Nitroglycerin***

No definite mortality benefits have been shown with nitrate therapy. (JACC 1996; 27:337) Sublingual nitroglycerin should be given when the patient first presented and acute coronary syndrome is considered. Once the diagnosis of AMI has been made, prophylactic nitrates have never shown to be useful, although IV nitroglycerin may be given during the first 24 to 48 hours in patients with AMI and CHF, large anterior infarction, persistent ischemia, or hypertension.. It should not be used in patients with systolic blood pressure less than 90 mm Hg or severe bradycardia (less than 50 bpm). (Circulation 1999; 100:1016). After the first 24-48 hours of IV therapy, oral or transdermal patches may be used. A nitrate free interval of 8-12 hours should be given to prevent nitrate tolerance. It may be given for post-infarction angina.

### **3. *B-blocker Therapy***

The administration of B-blockers post-MI have been shown by multiple studies to reduce mortality, including all cause mortality, cardiac death, resuscitated cardiac arrest and arrhythmic death. (Am J Cardiol 1994; 74:674; JAMA 1993; 270: 1589; Circulation 1999; 99:2268) When given with thrombolytic therapy. it lowers the risk of intracerebral hemorrhage. B-blockers are generally under-prescribed in the management of AMI and is indicated in 1) patients without a contraindication to B-blocker therapy who can be treated within 12 hours of onset of infarction, irrespective of administration of concomitant thrombolytic therapy or performance of primary angioplasty; 2) patients with continuing or recurrent ischemic pain; 3) patients with tachyarrhythmias, such as AF with a rapid ventricular response. It is contraindicated in patients with severe LV failure.

### **4. *Magnesium Sulfate***

Magnesium sulfate is indicated in: 1) patients with documented magnesium (and/or potassium) deficits, especially in pts receiving diuretics before onset of infarction; 2) episodes of torsade de pointes–type VT associated with a prolonged QT interval. It may be considered in high-risk patients such as the elderly and/or those for whom reperfusion therapy is not suitable. (Circulation 1999; 100:1016)

### **5. *ACE Inhibitors***

In post-MI patients, ACE inhibitors have been shown by large trials to reduce mortality (Lancet 95; 345:669; Lancet 94: 343: 1115). . In patients with impaired LV function, ACE inhibitors improve LV function, decrease both short and long term mortality, decrease the risk of CHF, and may have an indirect antiarrhythmic effect. It should be considered in patients within the first 24 hrs of suspected AMI with ST-segment elevation in 2 precordial leads or with clinical CHF in the absence of hypotension (systolic BP <100 mm Hg) or known contraindications to use of ACE inhibitors. Patients with AMI and EF<40% or patients with clinical CHF should also receive ACEI. (Circulation 1999; 100:1016).

#### **6. Calcium Channel Blockers**

No calcium channel blocker has been shown to decrease mortality after AMI. In particular, short acting dihydropyridines such as nifedipine are contraindicated in AMI. On the other hand, both verapamil or diltiazem may be given to patients in whom  $\beta$ -blockers are ineffective or contraindicated for relief of ongoing ischemia or control of a rapid HR with AF after AMI in the absence of CHF, LV dysfunction, or AV block. Patients with CHF should generally not receive calcium channel blockers. (Circulation 1999; 100:1016).

#### **7. Thrombolysis**

Patients with acute ST elevation MI (STEMI) should receive thrombolytic therapy in the absence of contraindications. In contrast, those with acute non-ST elevation (NSTEMI) should not receive thrombolytic therapy. (Circulation 1999; 100:1016; J Am Coll Cardiol 2000; 36:970). The earlier the STEMI patient receives therapy, the higher the likelihood of achieving patency of the infarct-related artery. The earlier the treatment, the higher the number of lives saved and the better the prognosis. Therefore, once the diagnosis of STEMI is made, immediate steps should be taken to transfer the patient to a center where a thrombolytic agent can be administered. The choice of thrombolytic agent depends on cost and balancing patency rates with stroke rates. rTPA is more effective than streptokinase in achieving artery patency but is associated with a higher incidence of stroke complication than streptokinase. rTPA is also more expensive than streptokinase. If rTPA is preferred, then the front loaded regimen should be used. In the GUSTO-1 Trial, rTPA is associated with a 1% absolute reduction (6.3% versus 7.3%) in mortality compared with streptokinase. (N Engl J Med 1993; 329:673)

#### **8. Heparin**

Heparin is given with rTPA for 24-48 hours; it is unclear if patency rates are enhanced by giving heparin for more than 24 to 48 hours. Currently there are no data to support routine heparin in patients receiving non-fibrin-specific thrombolytic agents (streptokinase, anistreplase, or urokinase), as long as aspirin is given; possible exceptions include patients with a large anterior or apical MI, in whom heparin may reduce risk of mural thrombosis and systemic embolization. (Circulation 1999; 100:1016) In patients who have not received thrombolytic therapy, heparin may be of value. Low molecular weight heparins have become more popular in recent years as a result of placebo controlled trials showing similar or slightly better protection than unfractionated heparin. Advantages Of LMWH include a more favorable pharmacokinetic profile with twice daily injection but without frequent laboratory monitoring .(Lancet 2000; 355:1936)

### **9. *Glycoprotein IIb/IIIa inhibitor***

These are products of modern biotechnology. Trials with abciximab with tirofiban and eptifibatide have shown a benefit and reduction in the rates of death and MI in patients with unstable angina or NSTEMI. Benefits are also seen with interventional procedures. (Lancet 1998; 352:87; Lancet 1997; 349: 1429; N Engl J Med 1998; 338:1488). However, the oral inhibitors have been disappointing. Primarily it is used in patients experiencing NSTEMI who have some high-risk features and/or refractory ischemia, provided they do not have a major contraindication due to a bleeding risk.

### **10. *Antiarrhythmic Therapy***

Patients with VT/VT should be defibrillated or cardioverted promptly and this is one of the main reasons why coronary care units have been successful in saving lives. There is no indication for treatment of isolated ventricular premature beats, couplets, runs of accelerated idioventricular rhythm, and nonsustained VT. There is no indication for prophylactic administration of antiarrhythmic therapy when using thrombolytic agents. (Circulation 1999; 100:1016)

## **IV. Cardiac Catheterisation**

### **1. Primary PTCA versus Thrombolysis for STEMI**

There are contraindications to IV thrombolytic therapy which include recent major surgery, uncontrolled hypertension, trauma or active bleeding etc. The incidence of stroke in elderly patients receiving thrombolytic therapy is also high. Primary PTCA offers an attractive alternative in view of life-threatening complication rates of 1-3 % with an artery patency rate of only 50-80% achievable with thrombolytic agents. Primary PTCA decreases incidence of death and reinfarction. (JACC 1999; 33:640) In comparing primary PTCA with noninvasive therapy, a pooled analysis of 10 randomised trials with 2606 patients showed mortality benefits with primary PTCA over that of thrombolysis. (JAMA 1997; 278: 2093) Glycoprotein IIb/IIIa inhibitors have also made it safer to perform interventional procedures soon after AMI.

Primary PTCA should be considered as an alternative to thrombolytic therapy. (Circulation 1999; 100:1016) In patients with AMI who can undergo angioplasty of the infarct-related artery within 12 hours of the onset of symptoms or beyond 12 hours if ischemic symptoms persist. It may also be considered in patients with cardiogenic shock, are <75 yr old and in whom revascularisation can be performed within 18 hours of the onset of shock. It can be used to achieve reperfusion when contraindications to thrombolytic therapy are present. It should be emphasized that primary PTCA should be performed only in centers experienced in this procedure.

### **2. Angiography +/-PTCA following Thrombolysis**

Patients with spontaneous post-infarction angina and/or demonstrable ischemia provoked by noninvasive testing should be considered for angiography with a view to performing PTCA or CABG as needed. (Circulation 1997; 96: 748; Circulation 1998; 98:1860; Circulation 1999; 100:1464) An in-depth review is beyond the scope of today's lecture.

## **V. Post-MI Lipid Management**

Multiple secondary prevention trials have demonstrated the benefit of lipid lowering in patients with coronary disease. (Lancet 1994; 344:1383; N Eng J Med 1996; 335: 1001) This benefit has been demonstrated in post-MI patients with marked hypercholesterolemia as well as those with high normal or only mildly elevated lipid levels. The possibility that statins have anti-inflammatory properties as well as favorable effects on endothelial function are especially intriguing. The *Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study* (73rd AHA Scientific Session, November 2000) suggested that early initiation of statin therapy may have mortality benefits. Other studies also support a role for statin therapy after AMI. (Circulation 1998; 98(suppl 1): 1-45; N Engl J Med 1998; 339:1349)

### ***Guidelines to Lipid Management***

The patient should go on a diet similar to the AHA Step II diet, which is low in saturated fat and cholesterol (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol). Patients with LDL cholesterol levels greater than 125 mg/dL despite the AHA Step II diet should be placed on drug therapy with the goal of reducing LDL to less than 100 mg/dL. Patients with normal plasma cholesterol levels who have a high-density lipoprotein (HDL) cholesterol level less than 35 mg/dL should receive nonpharmacological therapy (eg, exercise) designed to raise it. Drug therapy using either niacin or gemfibrozil can be added regardless of the LDL and HDL levels, when the triglyceride level is > 200 mg%. Statin produces the greatest reduction in LDL cholesterol. Niacin is less effective in reducing LDL although it is more effective in raising HDL. Resins are rarely sufficiently effective alone but they can be used to supplement niacin or statins. For lipid lowering, statin therapy is generally preferred. The statin dosage should be titrated every four to six weeks to achieve an LDL-cholesterol level of 90 to 100 mg/dL (2.3 to 2.6 mmol/L). Patients on statins should have their LFT's and CPK at regular intervals. The timing for the initiation of statin therapy has yet to be determined but data suggest that it may need to be started early in the course of AMI.

## **VI. Predischarge Noninvasive Testing for the Identification of High-Risk Patients**

Echocardiography, 24 Holter monitoring, treadmill exercise stress testing, myocardial scintigraphy, signal averaging, heart rate variability are all noninvasive tools that provide prognostic information. A detailed review is beyond the scope of today's lecture.