

ACUTE MYOCARDIAL INFARCTION

STATE-OF-THE-ART PAPER

Cardiac Protection During Acute Myocardial Infarction: Where Do We Stand in 2004?

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Despite better outcomes with early coronary artery reperfusion for the treatment of acute ST-elevation myocardial infarction (MI), morbidity and mortality from acute myocardial infarction (AMI) remain significant, the incidence of congestive heart failure continues to increase, and there is a need to provide better cardioprotection (therapy that reduces the amount of necrosis that may be coupled with better clinical outcome) in the setting of AMI. Since the introduction of the concept of cardiac protection over a quarter of a century ago, various interventions have been investigated to reduce myocardial infarct size. Intravenous beta-blockers administered in the early hours of infarction were clearly shown to be of benefit. Intravenous adenosine appeared promising for anterior wall AMIs, as did cariporide in some studies. Glucose-insulin-potassium infusion was beneficial in certain subgroups of patients, particularly diabetics. A variety of other medications were studied with negative or marginal results. The best strategy to limit infarct size is early reperfusion with percutaneous coronary stenting or thrombolytic therapy. Stenting is superior and should be adopted whenever there is a qualified laboratory available. Available resources should focus on decreasing time from onset of symptoms to start of reperfusion and maintaining vessel patency. Future studies powered to better assess clinical outcome are needed for adjunctive therapy with adenosine, K_{ATP} channel openers, Na^+/H^+ exchange inhibitors, and hypothermia. (J Am Coll Cardiol 2004;44:276–86) © 2004 by the American College of Cardiology Foundation

HISTORY

Early after the description of acute myocardial infarction (AMI) in the beginning of the 20th century, its treatment was quite limited. The main focus was on complete bed rest and dealing with the complications when they arose. It was not until the late 1960s to early 1970s that a new concept surfaced—the concept that the extent of necrosis could be limited by pharmacologic therapy. This concept of damage control was suggested by Braunwald in 1974 when he wrote, “I believe that we now stand at the threshold of a new era in the treatment of AMI . . . it is now fair to accept the position that just because myocardial tissue lies within the distribution of a recently occluded coronary artery does not mean that it is necessarily condemned to death” (1).

In this review we will focus on which agents actually work to limit necrosis in AMI in the clinical setting. The term “cardioprotection” will be used to indicate that the agent reduces acute myocardial infarct size or prevents perioperative infarction (in the setting of cardiac surgery) and, as a result, reduces the consequences of AMI, including less mortality, less heart failure (HF), and fewer myocardial-infarct-associated ventricular arrhythmias.

EARLY REPERFUSION

The realization that the progression of necrosis could be interrupted by early reperfusion and that occlusive thrombi were present in the coronary arteries of most ST-segment elevation/Q-wave myocardial infarctions (MIs) ushered in the era of reperfusion. Reimer et al. (2) performed mechanical coronary occlusions in the circumflex artery of dogs. The occlusions were transient for different time periods up to 6 h or were permanent without reperfusion. There was a progressive increase in cardiac necrosis, with time beginning in the subendocardial region and marching toward the subepicardial tissue (referred to as the wave-front phenomenon). If reperfusion was instituted before 3 h of coronary artery occlusion, significant salvage within an anatomic risk zone occurred. If reperfusion was instituted beyond 3 to 6 h, little or no salvage occurred compared with a permanent (non-reperfused) coronary occlusion.

Experimentally, early reperfusion has remained the best strategy so far to limit infarct size (3). Another pivotal study paved the way for our modern management of AMI. DeWood et al. (4) studied 322 patients presenting with AMI with a coronary angiogram. The study proved beyond a doubt that a thrombus is the usual cause of Q-wave MI, and it showed that performing coronary angiography during the early hours of AMI is safe. Reperfusion therapy with thrombolytic agents consistently showed a reduction of myocardial infarct size measured in a variety of fashions: electrocardiographic (ECG)—preservation of R waves and reduction in development of Q waves; enzymes—reduction

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
CABG	= coronary artery bypass grafting
CK-MB	= creatine kinase-MB
ECG	= electrocardiogram/electrocardiographic
GIK	= glucose-insulin-potassium
HF	= heart failure
LV	= left ventricle/ventricular
MI	= myocardial infarction
NHE	= sodium-hydrogen exchange
RR	= risk reduction

in blood levels of creatine kinase MB (CK-MB), lactic dehydrogenase, beta-hydroxybutyrate, and others (5–9). Thrombolysis reduced mortality (7–9) and improved cardiac function (10). In addition, compared with thrombolysis, the use of angioplasty and stents for early reperfusion results in better infarct artery patency, left ventricular (LV) function, and lower mortality (11–21). Both thrombolytic therapy and early percutaneous coronary intervention became the standard therapy for patients with MI.

In recent years, studies have attempted to fine-tune the success of early reperfusion with antiplatelet and antithrombin agents that should help keep the infarct artery patent. Unquestionably, aspirin has been shown to be a useful adjunct in this regard and is standard therapy for AMI (22). Agents such as low-molecular-weight heparin, rather than unfractionated heparin, and glycoprotein IIb/IIIa platelet inhibitors have shown promise in some studies (23,24).

CARDIAC PROTECTION DURING EARLY PERCUTANEOUS INTERVENTION

Strategies that proved successful are those that help to make the intervention successful in achieving early Thrombolysis In Myocardial Infarction (TIMI)-III flow. Glycoprotein IIb/IIIa receptor blockade is an important therapy during early coronary stenting. Both eptifibatid and abciximab are being utilized with good success in routine clinical practice. In the Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) study, 300 AMI patients were randomized to abciximab or placebo (25). Abciximab patients had better coronary patency, LV function, and clinical outcomes. Even in patients who had their intervention within 48 h after the onset of symptoms, abciximab was clinically superior to placebo, with better coronary flow and enhanced recovery of contractile function (26). In a controlled trial of 400 patients with AMI undergoing stenting, Antoniucci et al. (27) randomized the patients to abciximab or control. The composite end point of death, reinfarction, and target vessel revascularization was significantly less in the abciximab group. In addition, infarct size as measured by technetium-99m (^{99m}Tc) sestamibi scintigraphy was smaller in the abciximab group (27). These studies as well as others suggest that a IIb/IIIa receptor blocker such as

abciximab should be administered to AMI patients undergoing stenting (28).

One potential mechanism by which glycoprotein IIb/IIIa inhibitors may improve outcomes in the setting of early interventions is by limiting no-reflow, as recently discussed (29,30). Intracoronary injection of verapamil, adenosine, or nitroprusside may also be used to restore blood flow when faced with the no-reflow phenomenon in the setting of intervention (31). Prophylactic intracoronary adenosine administration is effective and is utilized by a significant number of interventional cardiologists, particularly in vein graft intervention. Besides its use in the clinical setting of no-reflow, adenosine may have other benefits in the setting of intervention. Leesar et al. (32) randomized 30 patients to intracoronary infusion of adenosine 2 mg/min over 10 min or placebo before percutaneous coronary angioplasty. The adenosine group had less coronary ischemia and enhanced preconditioning when compared with the control group. Similar protocols with other agents are being utilized in catheterization laboratories (33).

EARLY ADJUNCTIVE PHARMACOLOGIC THERAPY IN MI

Given early and successful coronary artery reperfusion, what else can be done to further help protect the myocardium from various interrelated insults? This is where adjunctive pharmacologic therapy may be important. In this section we will refer to early adjunctive therapies as cardioprotective approaches used for AMI that show benefit other than attaining or maintaining patency of the proximal infarct artery. Thus, agents such as thrombolytic agents, aspirin, glycoprotein IIb/IIIa inhibitors, unfractionated heparin will not be considered adjunctive therapies here. Also, angiotensin converting enzyme inhibitors, known to reduce LV dilation and remodeling when administered over the long term after MI, will not be considered early adjunctive therapy. Statins clearly play an important role in the coronary patient and even in those with acute coronary syndromes. However, primarily this section will focus on pharmacologic agents administered early that are thought to further reduce ST-segment elevation myocardial infarct size or have short-term antiarrhythmic effects on the ischemic/reperfused myocardium, with the assumption that reperfusion therapy has been successful.

Beta blockers. Some (34,35), but not all (36), experimental studies performed in large animal models observed that beta blockade, coupled with reperfusion, reduced myocardial infarct size. Beta blockade in the setting of a permanent coronary artery occlusion failed to reduce infarct size in our models (37). Potential mechanisms for benefits in the reperfusion models included a reduction in heart rate and contractility with a decrease in myocardial oxygen demand that may have slowed the progression of necrosis into the peri-infarct tissue, preservation of mitochondrial structures,

stabilization of the vasculature, stabilization of cell membranes, or other as yet unknown mechanisms (34,38,39).

In the pre-reperfusion era Multicenter Investigation of the Limitation of Infarct Size (MILIS) study (40), propranolol started at an average of 8.5 h after onset of symptoms did not reduce infarct size estimated by measure of serum CK-MB, technetium pyrophosphate myocardial scintigram, or preservation of R-waves. In retrospect, it is unlikely that any agent would reduce infarct size if administered 8 h after coronary artery occlusion.

However, beta-blockers, when administered early, were shown to reduce myocardial infarct size even in some studies done before common use of thrombolytics. Yusuf et al. (41) studied 475 patients suspected of having had an AMI within <12 h before randomization. Patients received intravenous atenolol and then oral atenolol for 10 days or were assigned to a control group. In those patients admitted with ECG changes that were definitive for MI at entry, atenolol reduced cardiac enzyme release by one-third and preserved R-waves. Atenolol also decreased incidence of R-on-T ventricular ectopic beats and reduced the number of episodes of repetitive arrhythmias in the first 24 h. In this study the mean time from chest pain to randomization was 5 h. The earlier time to therapy may have explained why this study was positive in contrast with the MILIS study. Peter et al. (42) in a small pre-thrombolytic study showed that intravenous propranolol administered within 4 h of onset of MI in patients who demonstrated pathologic Q waves resulted in 27% lower CK levels compared with control patients.

The International Collaborative study group (43) assessed 144 patients admitted for AMI within 4 h after onset of chest pain. Intravenous timolol was administered at a mean of 3.4 h after symptom onset and was continued for 24 h, and then orally thereafter for the duration of the hospitalization. Maximal cumulative CK release was reduced by 30%, and there were fewer alterations in QRS vector in patients receiving timolol versus those receiving placebo. Timolol accelerated the reduction of ST-vector, reduced chest pain, and reduced the need for analgesia.

Hjalmarson et al. (44) reported the results of a 1,395 patient study in which metoprolol or placebo was started upon patient arrival with AMI and therapy was continued for 90 days. Initial therapy was intravenous metoprolol followed by oral therapy. In the placebo group, there was a mortality rate of 8.9%, while in the metoprolol group, mortality rate was 5.7% ($p < 0.03$). Infarct size data were not provided.

In the large multicenter Metoprolol in Acute Myocardial Infarction (MIAMI) trial, intravenous metoprolol reduced myocardial infarct size by enzymatic analysis in patients who received therapy within 7 h of symptoms (45). There was a 15% reduction in mortality by one week in patients who were randomized to intravenous atenolol versus placebo in the First International Study of Infarct Survival (ISIS)-1 study (46). Patients received therapy within an average of

5 h of symptoms of suspected AMI. Also of note, treated patients had a lower incidence of death due to ventricular rupture when receiving beta blockade. The mortality benefit of atenolol was maintained for at least the first year of follow-up.

In the TIMI-IIIB study (47), the effect of immediate versus deferred beta-blocker was studied in patients with AMI that were treated with recombinant tissue-type plasminogen activator. Patients received either three intravenous injections of 5 mg of metoprolol and then 50 mg twice a day orally for one day and 100 mg twice a day orally thereafter (immediate therapy), or on day six, 50 mg twice a day orally for one day and then 100 mg twice a day.

While there was no overall difference in mortality between groups, six-week mortality in low-risk patients was 0% and 2.8% in the immediate and deferred beta-blocker therapy groups, respectively ($p = 0.007$). Reinfarction rates were lower at six days and six weeks in the immediate treatment group versus the delayed treatment group. However, there was no difference at one year.

Basu et al. (48) showed that early carvedilol was tolerated in AMI patients and at six months was associated with fewer cardiac events than placebo.

In the Beta-Blocker Heart Attack trial (also from the pre-thrombolytic era), patients receiving long-term propranolol treatment, beginning 5 to 21 days after infarction for 27 months, demonstrated reduced total mortality, cardiovascular mortality, and sudden death (49). It is likely that this was an antiarrhythmic effect. Because the beta-blocker was administered late, this effect could not have involved infarct size reduction. Similar observations were made with long-term timolol treatment starting seven to 28 days after AMI and continuing for 12 to 33 months. Timolol reduced mortality, sudden death, and reinfarction rates when compared with placebo (50).

In summary, when administered very early, beta-blockers have been suggested to reduce infarct size (even in some pre-reperfusion era studies). Beta-blockers also appear to reduce cardiac arrhythmias and mortality. Early beta-blocker therapy is now a standard part of therapy for AMI in those patients who can tolerate beta-blockers. Patients with severe congestive HF, bronchospasm, bradycardia, or atrioventricular block may not be candidates for beta-blocker therapy.

Glucose-insulin-potassium infusion. Experimental studies suggest that glucose-insulin increases glycolytic ATP synthesis during hypoxia (51,52). The concept is that insulin drives glucose into the cells making more glucose available for anaerobic glycolysis while suppressing levels of free fatty acid and reducing myocardial free fatty acid uptake. Glucose-insulin-potassium (GIK) infusion also stimulates potassium re-uptake into cardiac cells, thus decreasing ectopy. Apstein et al. (53,54) have reviewed the rationale for GIK. Some experimental studies suggested that GIK reduced ischemic myocardial damage (55), while others did not (56).

In the pre-thrombolytic era, a number of studies were conducted to investigate the effect of GIK infusion in the first few hours of MI. Most did not have enough statistical power to reach a definitive conclusion. A meta-analysis by Fath-Ordoubadi and Beatt (57) suggested that GIK has a mortality benefit in the setting of acute infarction.

In the thrombolytic era, Diaz et al. (58) randomized 407 patients with suspected AMI to GIK or a comparable placebo. Some of those patients (38%) did not receive a reperfusion strategy. There was a trend toward a mortality benefit in the overall study population who received GIK. In patients who had a reperfusion strategy, there was a statistically significant mortality benefit (risk reduction [RR] = 0.34; 95% confidence interval [CI] 0.5 to 0.78; $p = 0.008$), and these patients showed a non-significant trend toward less severe congestive HF and ventricular fibrillation. The benefit was more marked in patients who started treatment soon after the onset of symptoms, a trend that is consistent in all proven therapies for MI. The incidence of electromechanical dissociation was lower in the GIK group versus controls (1.5% vs. 5.8%; $p = 0.016$). Of note in this study, the mortality rate in the control group was 11.5%, which is more than double the current mortality rate for AMI.

Malmberg et al. (59) randomized 306 AMI patients with diabetes mellitus to glucose-insulin infusion or to conventional therapy. Diabetic patients who received the active therapy had a significant reduction in mortality at one year after the onset of the infarction (18.6% vs. 26.1%; $p = 0.03$). At 3.4 years, the benefit in mortality persisted (33% vs. 44%; $p = 0.01$).

van der Horst et al. (60) randomized 940 AMI patients eligible for percutaneous transluminal coronary angioplasty to continuous GIK infusion versus no infusion beginning 15 to 20 min after hospital admission. The primary end point of the study was 30-day mortality. At 30 days, 23 of 476 patients (4.8%) died in the GIK group versus 27 of 476 (5.8%) in the placebo group ($p = \text{NS}$). In patients ($n = 856$) without HF, GIK significantly reduced mortality (from 4.2% in controls to 1.2% in the GIK group; RR = 0.28; 95% CI 0.1 to 0.75). In contrast, in patients with signs of HF ($n = 84$), 30-day mortality was 36% in the GIK group versus 26.5% in the controls (RR = 1.44; 95% CI 0.65 to 3.22). Infarct size parameters were not reported.

The last word on GIK has yet to be written. There clearly is a suggestion that this therapy may reduce mortality in certain subgroups of patients, but it is not at all clear that this is related to an infarct size-reducing effect. There is a need for a large clinical infarct size study using this agent combined with reperfusion.

Sodium-hydrogen exchange inhibitors. A number of studies with the sodium-hydrogen exchange (NHE) inhibitor agent cariporide were positive in experimental models (61,62). In our studies, 30 min of coronary artery occlusion and 3 h of reperfusion cariporide reduced infarct size by 55% in a rabbit model. The mechanisms by which cariporide and other NHE work involve a decrease in the influx of sodium

into ischemic cells. This ultimately inhibits the exchange of sodium for calcium. Calcium overload of the myocardial cell is thought to lead to major disruption of metabolism and architectural disruption, including the formation of contraction band-type necrosis and precipitation of calcium phosphate granules within the mitochondria.

Rupprecht et al. (63) gave 40 mg cariporide or placebo intravenously over 10 min followed by percutaneous transluminal coronary angioplasty in AMI patients. End-systolic volume increased over three weeks in the placebo group (80 to 97 ml) but decreased in the cariporide group (77 to 69 ml; $p = 0.048$). Ejection fraction was unchanged over three weeks in the placebo group (40% to 40%) but increased in the cariporide group (44% to 50%; $p < 0.05$). There was also improvement in regional wall motion abnormality with cariporide. Cariporide reduced myocardial infarct size, as the area under the curve for CK-MB was lower in the cariporide group versus the placebo group ($p = 0.047$).

Although the Guard During Ischemia Against Necrosis (GUARDIAN) trial (64) was not primarily an acute Q-wave MI trial, it did investigate the effects of different doses of cariporide versus placebo in patients with various ischemic syndromes (unstable angina, non-ST-elevation MI, and high-risk percutaneous or surgical revascularization). The primary end point of all-cause mortality or MI at 36 days did not differ between groups. The highest dose (120 mg) showed a non-significant 10% reduction in the primary outcome. The 20- and 80-mg doses showed no trend. At 120 mg, the benefit was limited to patients undergoing coronary artery bypass grafting (CABG) (RR, 25%; 95% CI, 3.1 to 41.5; $p = 0.03$) and was maintained at six months. Overall, CK-MB scores were similar among the four groups. The ratio of peak CK-MB elevation to the upper limit of normal tended to be lower with increasing doses of cariporide in surgical patients. The rate of Q-wave MI was decreased 32% across all entry diagnoses ($p = 0.005$). The rate of non-Q-wave MI was decreased in CABG patients only. Thus, in patients undergoing CABG, cariporide very effectively reduced the incidence of perioperative Q- and non-Q-wave myocardial infarcts, perhaps underscoring the importance of early therapy in an ischemic event. This will be discussed in more detail in the section of protection during CABG.

Eniporide, another inhibitor of the NHE, was investigated in patients with AMI (65). A total of 1,411 patients were randomized to eniporide or placebo. There was no difference in the infarct size between the groups. Moreover, there was a trend toward excess death and stroke in patients receiving eniporide. Thus, while NHE inhibitors appeared beneficial in some studies, not all were positive, and there were some unpredictable adverse events when administered in a recent cardiac surgical study (see the following text). Clearly additional research on these agents is needed.

Adenosine. Adenosine or adenosine receptor agonists have been shown to reduce AMI in some experimental studies (66,67). Adenosine can induce coronary artery vasodilation,

reverse coronary spasm, and replenish high-energy phosphates. It can reduce afterload and heart rate, thus decreasing myocardial oxygen demand. In addition, it has antiplatelet and anti-neutrophil effects that may help prevent no-reflow in the clinical setting. Adenosine receptor stimulation also is thought to be a key component in ischemic preconditioning (66). As mentioned, when adenosine was administered to patients before angioplasty, there was less chest pain and ST-segment change on the ECG. Preliminary studies with intracoronary adenosine showed some promise during early intervention for MI (68). In a randomized study of 54 AMI patients, adenosine resulted in improved ventricular function and less cardiac enzyme release (69). Adenosine agonist, however, in the AMP579 Delivery for Myocardial Infarction REDuction (ADMIRE) study did not result in a significant effect on infarct size. In the contemporary interventional practice, intracoronary adenosine use is limited to treatment of no-reflow—and at a much smaller dose than the one utilized in the published studies (70).

In a pilot study, Mahaffey et al. (71) examined the effect of 70 $\mu\text{g}/\text{kg}/\text{min}$ adenosine infusion for 3 h in the setting of AMI. A total of 236 patients were randomized to adenosine or placebo in an open-label study. The adenosine group had a significant reduction in the size of MI assessed by technetium-99m sestamibi single photon emission computed tomography. No clear conclusion was reached regarding clinical event rate. Quintana et al. (72) reported that adenosine reduced cardiac complications in patients with acute anterior wall MI. In that study, 680 patients with AMI were randomized to intravenous adenosine infusion or placebo. Although there was no mortality or hemodynamic benefit in the overall cohort, those with anterior AMI had a statistically better survival with adenosine. These studies paved the way for a more definitive study, the Acute Myocardial Infarction Study of Adenosine (AMISTAD) II (73). In this study, 2,084 patients with AMI were randomized to a 3-h infusion of adenosine or placebo within 15 min of reperfusion. Adenosine therapy was associated with smaller infarct sizes and a non-significant trend toward less incidence of congestive HF or death. Median myocardial infarct size measured utilizing technetium-99m sestamibi single photon emission computed tomography imaging at 120 to 216 h after randomization was 27% in the placebo group, 23% in the 50- $\mu\text{g}/\text{kg}/\text{min}$ adenosine group, and 11% ($p < 0.05$ vs. placebo) in the 70- $\mu\text{g}/\text{kg}/\text{min}$ group. Whether adenosine had a direct effect of cardioprotection on the heart muscle cells or had a beneficial effect by its known antiplatelet effect (antiplatelet aggregation), and thus by keeping the infarct artery or the microvasculature open, is not clear. Although adenosine and adenosine agonists are known to have preconditioning-like effects, it is unlikely that such an effect was the mechanism in the AMISTAD studies, because the drug was not administered until after coronary occlusion, usually later in the occlusion phase.

Calcium channel blockers. Since their discovery, calcium channel blockers were investigated in a variety of cardiovascular diseases, including chronic angina, variant angina, hypertensive heart disease, and other conditions, with clear success. One condition, however, in which this group of drugs demonstrated no clear benefit was AMI, despite the fact that calcium channel blockers were shown to limit myocardial infarct size in some experimental models (74). However, even in these experimental models, the calcium channel blockers had to be on board during the period of ischemia (that is, not just reperfusion) to demonstrate a benefit (75). Goldbourt et al. (76) administered nifedipine in a dose up to 60 mg or placebo to 1,006 patients with AMI. There was increased mortality in the nifedipine group and no clinical benefit noted. This may be related to a decrease in perfusion pressure, thus decreasing collateral coronary blood flow among other possibilities. Calcium channel blockers are not routinely recommended in the setting of AMI. Diltiazem and verapamil may be used only if there is another clear clinical indication (such as hypertension or rapid arrhythmia) and in the absence of congestive HF and heart block. Amlodipine, felodipine, and nisoldipine may be safer agents to administer for ongoing hypertension or angina in the setting of HF. They, unlike diltiazem, verapamil, and nifedipine, do not appear to exacerbate HF. Short-acting calcium channel blockers should not be used, as they may induce reflex tachycardia and hypotension.

K_{ATP} channel openers. Many investigators believe that a major mechanism for the beneficial effects of ischemic preconditioning is the opening of K_{ATP} channels (77), either on the cardiac sarcolemmal membrane or mitochondrial membranes. Numerous experimental animal studies have shown that K_{ATP} channel openers such as nicorandil, bemakalin (78), and diazoxide (a mitochondrial K_{ATP} channel opener) have preconditioning mimetic properties, while K_{ATP} channel blockers (glibenclamide) (79) can actually block ischemic preconditioning. There are several presumed mechanisms that have been suggested. Initially, it was hypothesized that by opening K_{ATP} channels, the cell would become bathed in K⁺, resulting in a decrease in action potential duration, hence, a localized cardioplegic effect (77). A newer theory postulates that K_{ATP} channel blockade of the mitochondrial membrane is crucial for preserving mitochondrial respiration and cellular metabolism (80). There is a scarcity of clinical data that have examined the effect of K_{ATP} channels in humans in the midst of an AMI. Nicorandil is a K_{ATP} channel opener that also has some nitrate-like activity. It is approved in some countries for the treatment of angina. The Impact Of Nicorandil in Angina (IONA) trial assessed the potential cardioprotective effects of nicorandil in patients with stable angina (81). Patients ($n = 5,126$ with stable angina) receiving optimal medical therapy were randomized to nicorandil or placebo and followed up for a mean of 1.6 years. Coronary heart disease mortality was 2.3% in the nicorandil group versus 2.9% in

Table 1. No Consistent Benefits as Early Adjunctive Therapy in Clinical Trials

Inhibitors of neutrophil adhesion
Calcium channel blockers
hSOD (superoxide dismutase)
Reothrex (110)
Trimetazidine (antioxidant)
Molsidomine (nitric oxide donor) (111)
Fluosol (112)
Hyaluronidase (pre-thrombolytic study) (113)
Corticosteroids
Beta blockers (given late and without reperfusion)
Complement inhibition (no effect on infarct size; reduced mortality in one study)

the placebo group. The primary combined end point of coronary heart disease mortality, MI, or hospital admission for cardiac chest pain occurred in 13.1% in the nicorandil group versus 15.5% in the placebo group (hazard ratio, 0.83; 95% CI, 0.72 to 0.97; $p = 0.014$). Coronary heart disease mortality or MI occurred in 4.2% versus 5.2% in the nicorandil versus placebo group ($p = 0.068$). The secondary end point of coronary heart disease mortality, MI, or unstable angina was 6.1% in the nicorandil group versus 7.6% in the placebo group ($p = 0.028$). Nonfatal MI occurred in 2.1% in the nicorandil group versus 2.8% in the placebo group. Thus, although nicorandil showed benefits in certain combined end points, at least a portion of this benefit may have been secondary to its antianginal effect. Future studies in which infarct size is measured using K_{ATP} channel openers are indicated, especially given the positive effect reported with such agents in experimental trials.

Negative and controversial modalities. Inhibition of leukocyte adhesion was thought to be beneficial in reducing infarct size. Two separate clinical trials utilizing antibodies to leukocyte adhesion molecules have failed to show any benefit (82,83). Despite promising results in laboratory animals, studies of oxygen radical scavenging drugs such as trimetazidine (84) and superoxide dismutase (85) have been negative in humans. Data on early administration of magnesium in MI have been mixed. In one older study (86) intravenous magnesium administered early reduced 28-day mortality from 10.3% in the placebo group to 7.8% in the magnesium group ($p = 0.04$). Magnesium also reduced clinical left ventricular HF. In a more recent trial, there was no difference in mortality, HF, or incidence of ventricular fibrillation in patients who received magnesium versus control (87). There are a lack of data regarding its effect on myocardial infarct size in man. Two recent reports showed that complement antibodies administered to patients receiving either thrombolytics (88) or angioplasty (89) had no effect on myocardial infarct size. However the anti-C5 complement agent did reduce mortality at 90 days (1.8% vs. 5.9%; $p = 0.014$) in patients treated with primary percutaneous intervention, suggesting a benefit unrelated to infarct size (89). Table 1 lists these and other agents that, in

general, have not shown reductions in myocardial infarct size or other reproducible benefits in humans.

Hypothermia is a useful technique in reducing or delaying necrosis of cells. In laboratory animals, it was shown to reduce myocardial infarct size (90). However, in order to reduce infarct size, hypothermia had to be on board during the phase of ischemia. Hypothermia only at the time of reperfusion was unsuccessful (91). A recent preliminary report by the COOL-MI trial (TCT Meeting, Washington, DC, September 2003) showed no overall reduction in AMI size in patients undergoing cooling via a heat exchange catheter placed into the inferior vena cava before angioplasty. However, in patients with anterior wall MIs, it was observed that patients cooled to temperatures less than 35°C at the time of reperfusion had significantly smaller infarcts (9.3% of the LV) versus controls (18.2%; $p = 0.05$). One problem noted by the investigators was that core temperatures were not cooled quickly enough before angioplasty, while angioplasty was accomplished rather quickly.

In reviewing the literature on reduction of AMI, it is clear that many positive studies in the experimental animal literature have failed to translate to benefit in clinical trials. Why? There are several potential reasons. One is that, in nearly all animal studies, the MI is produced by mechanically occluding an otherwise normal proximal coronary artery. Atherosclerosis is not present, and atherosclerotic debris, thrombus, and emboli that may occur in the setting of early percutaneous intervention are less of an issue. In addition, the non-infarct-related coronary arteries are free of disease in most of these models. Perhaps in humans where platelets and neutrophils are more likely to adhere to damaged endothelial, a multipronged approach is needed. An example might be that antibodies to CD18 adhesion molecules were found to reduce infarct size in some experimental models, but failed to reduce infarct size in humans (82,83). Perhaps if CD18 inhibitors had been coupled with glycoprotein IIb/IIIa inhibitors, preventing neutrophil adhesion as well as platelet aggregates, a benefit might have been observed. Another issue is that clinical trials have often been based on experimental observations from only one or two experimental laboratories. Sometimes the laboratories have a vested interest in the compound. Often drugs are not tested in a randomized or blinded fashion. Sometimes bias, subconscious or otherwise, creeps in. Fellows may fear that a negative result will adversely affect their career or upset the senior investigator, who is convinced the compound works. A consortium of experimental laboratories that use similar techniques and that can test compounds in a multicenter approach (much like most clinical trials are conducted) may successfully be used to screen compounds. We recently had the opportunity to participate with two other laboratories in this multicenter approach. All three laboratories used a rabbit model and similar basic techniques for assessing risk zone and myocardial infarct size. In addition, all three laboratories were blinded to drug therapy, and administration of drug versus placebo was randomized. All three

laboratories found similar results (92). Although the results of our study did not show a positive effect of the compound, we probably saved the company sponsoring the study millions of dollars had they proceeded with a clinical trial based on positive results from only a single laboratory. In the authors' opinion, there is a need for a national or international consortium of basic science laboratories that can reliably test the effect of compounds on myocardial infarct size in an unbiased, randomized, and blinded fashion. These types of translational experimental studies could be carried out in a parallel fashion to the large clinical multicenter studies now so common in the cardiovascular literature.

CARDIAC PROTECTION DURING SURGERY

As early as the 1960s, the perioperative complication of microinfarctions was recognized as a problem that could lead to the syndrome of low cardiac output and even death (93). Perioperative MI is one of the most important adverse events occurring during bypass surgery. The incidence varies widely in various studies because there is no uniform definition and ranges between 3% and 30% (94). In a review of 499 consecutive CABG patients at Brigham and Women's Hospital in 1992 to 1993, 5% of patients were reported to have had perioperative MIs, and 2% had probable perioperative infarctions. The definitions included total peak creatine kinase >700U/l, a CK-MB of more than 30 ng/ml with definite pathologic Q-wave, or new regional wall motion abnormalities. Multivariate analysis showed that emergency surgery, aortic cross-clamp time more than 100 min, recent MI within one week, previous revascularization, and diabetes were associated with increased incidence.

In another review by Mayo Clinic investigators (95), other factors that affected the incidence of perioperative MI included collateral flow, duration of aortic cross-clamping, the extent of coronary artery disease, need for endarterectomy, and adequacy of myocardial protection. In the last few years, off-pump CABG has emerged as a viable alternative to traditional surgery. Even though the surgery is done on a beating heart, perioperative MI in the non-bypassed regions has been reported. Recent comparative studies showed that off-pump cases are associated with fewer short-term complications, yet in long-term follow-up, graft patency was

Table 2. Proven Benefit in Acute Myocardial Infarction

Early reperfusion—attain and maintain coronary patency
Stents > percutaneous transluminal coronary angioplasty > thrombolysis
Agents to help maintain patency:
Aspirin
Low-molecular-weight heparin
Glycoprotein IIb/IIIa inhibitor with percutaneous coronary intervention
Intravenous beta-blocker (given early)

Table 3. Possible Benefit as Early Adjunctive Therapy

Glucose-insulin-potassium or glucose-insulin
Adenosine (anterior wall myocardial infarctions)
Cariporide
Hypothermia (in anterior wall myocardial infarctions with temperature <35°C)

lower. Perioperative myocardial injury is associated with elevated early and late mortality (96).

Perioperative infarction also may be related to the increase in myocardial oxygen demand that occurs during anesthesia induction, during the period of cardiopulmonary bypass itself, or in the early postoperative recovery period (97). The most vulnerable period for development of myocardial necrosis is during the surgery itself. The ischemic injury during cardiopulmonary bypass is not necessarily related solely to the presence or severity of coronary artery disease. Hultgren et al. (98) studied 126 patients undergoing valve replacement in which there was no evidence of coronary artery disease. Significant creatine phosphokinase release occurred in 40% of patients. Despite the current techniques utilized to protect the heart during cardiac surgery, cardiac enzyme release still occurs in over half the patients undergoing CABG (99). Mortality appears to be related to the extent of enzyme release (100). The following discussion reviews some of the new techniques and drugs that have been investigated for myocardial protection during CABG.

Ischemic preconditioning. It is thought that because ischemic preconditioning is protective during various ischemic insults, it may play a role during cardiac surgery (101). Ghosh and Galinanes (102) investigated the effect of preconditioning during cardiopulmonary bypass and in off-pump bypass. In the former, ischemic preconditioning was done by brief aortic cross-clamping for 5 min followed by 5 min of reperfusion before the intervention. There was no benefit noted. In off-pump bypass, the individual coronary artery was clamped for 5 min followed by 5 min of reperfusion before the coronary surgery, and patients were compared with a control group. The ischemic preconditioning group had less troponin T enzyme release 48 h after surgery. Many surgeons performing off-pump bypass now utilize this technique.

Pharmacologic intervention. A variety of medications had been investigated either by direct administration in the cardioplegic solution or by systematic administration just

Table 4. Agents Administered Over the Long Term After Myocardial Infarction That Have Benefit by Decreasing Left Ventricular Remodeling or Improving Outcome by Other Means

Angiotensin converting enzyme inhibitors
Eplerenone (aldosterone receptor antagonist)
Angiotensin receptor blockers
Statins
n-3 polyunsaturated acids
Long-term beta-blockade

before initiation of cardiopulmonary bypass. Some studies with adenosine (103) and esmolol (104) did not have a significant clinical benefit despite the initial enthusiasm that was derived from animal studies (105). One study, however, provided some hope with high-dose adenosine added to cold blood cardioplegia. Mentzer et al. (106) randomized 253 patients into high-dose adenosine, low-dose adenosine, or no adenosine. There was a trend towards a lower incidence of perioperative MI and less need for hemodynamic support in the high-dose adenosine group. A large-scale study utilizing the high dose will settle this issue. A small randomized study utilizing nifedipine cardioplegia in a 24-patient study showed some benefit in decreasing cardiac necrosis and arrhythmias after cardiopulmonary bypass (107). This study was neither confirmed nor had any impact on today's clinical practice.

The most recent emphasis in clinical investigation is the drugs that affect NHE activation during myocardial ischemia and reperfusion. Cardiac ischemia leads to intracellular acidosis. The NHE is activated with an increase in the $\text{Na}^+ - \text{Ca}^{2+}$ exchange with significant intracellular hypercalcemia that may contribute to myocyte necrosis. Cariporide, an NHE inhibitor, may have the potential of interrupting this cycle with a decrease in cardiac necrosis during cardiopulmonary bypass. Boyce et al. (108) reported the effect of a varying dose of cariporide infusion 1 h before surgery at loading doses ranging from 20 to 120 mg. Only the dose of 120 mg had a significant reduction in all-cause mortality and MIs. The clinical benefit was maintained for about six months. A more definitive study randomized 5,761 patients to cariporide (180 mg/h preoperatively followed by 40 mg/h infusion for 24 h and 20 mg/h for an additional 24 h) or placebo (109). Although patients in the cariporide group had significantly fewer perioperative MIs, there was a surprisingly significant increase in mortality, strokes, and renal failure. The increase in ischemic strokes continued to be noted six months after randomization. This study keeps the concept of cardioprotection by inhibiting NHE system alive, yet it raises a real question about the safety of this particular drug or its dose. The quest for cardioprotection during cardiopulmonary bypass, however, should continue, particularly because patients who are having this procedure now are older and a higher risk population who may require longer cross-clamp time.

CONCLUSIONS

Many pharmacologic agents and strategies have been administered for cardiac protection during AMI. Tables 1 to 4 review those agents that failed to show short-term benefit in large clinical trials (110–113), those strategies that have been shown to benefit AMI in the short term, those agents that may possibly benefit AMI in the short term, and those agents that benefit the heart when administered over the long term. It is clear that the best cardioprotection in the setting of AMI is opening the coronary occlusion as early as

possible and a restoration of TIMI-III coronary flow. Early coronary intervention is superior when it can be done in a timely manner by an experienced center. Our resources should be focused on decreasing the period between onset of symptoms and early intervention. Efforts should include better public awareness of the symptoms of infarction and specific hospital initiatives to shorten the time from arriving at the emergency department to initiation of thrombolytic therapy, or inflation of the first coronary balloon, or placement of stent. Regarding active adjunctive therapy, intravenous beta blockers (where tolerated) clearly show benefit.

FUTURE DIRECTIONS

Additional clinical trials are needed to study those classes of pharmacologic agents that show promise as adjunctive therapies. Studies investigating the effect of K_{ATP} channel openers, adenosine, adenosine receptor agonists, GIK, and newer NHE inhibitors are needed. Early hypothermia shows promise if cooling can be achieved more rapidly, that is, before coronary artery reperfusion.

During early coronary intervention, intravenous IIb/IIIa administration and intracoronary verapamil or adenosine infusion provide significant cardiac protection from no-reflow during the procedure. Temporary arterial occlusion provides protection during off-pump CABG. Sodium-hydrogen exchange and various cardioplegic solutions are under active investigation to achieve the best cardioprotection strategy during on-pump bypass surgery.

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REFERENCES

1. Braunwald E. Editorial: reduction of myocardial-infarct size. *N Engl J Med* 1974;291:525–6.
2. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. I. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;56:786–94.
3. Ellis SG, Henschke CI, Sandor T, Wynne J, Braunwald E, Kloner RA. Time course of functional and biochemical recovery of myocardium salvaged by reperfusion. *J Am Coll Cardiol* 1983;1:1047–55.
4. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;303:897–902.
5. Anderson JL, Marshall HW, Bray BE, et al. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med* 1983;308:1312–8.
6. Simoons ML, Serruys PW, van den Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986;7:717–28.
7. The I.S.A.M. Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.): mortality, morbidity, and infarct size at 21 days. *N Engl J Med* 1986;314:1465–71.

8. Stampfer MJ, Goldhaber SZ, Yusuf S, Peto R, Hennekens CH. Effect of intravenous streptokinase on acute myocardial infarction: pooled results from randomized trials. *N Engl J Med* 1982;307:1180-2.
9. Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fritz JK. The western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12-month follow-up report. *N Engl J Med* 1985;312:1073-8.
10. Patel B, Kloner RA. Analysis of reported randomized trials of streptokinase therapy for acute myocardial infarction in the 1980s. *Am J Cardiol* 1987;59:501-4.
11. Schomig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction: Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction study investigators. *N Engl J Med* 2000;343:385-91.
12. Garcia E, Elizaga J, Perez-Castellano N, et al. Primary angioplasty versus systemic thrombolysis in anterior myocardial infarction. *J Am Coll Cardiol* 1999;33:605-11.
13. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;328:680-4.
14. Bauters C, Lablanche JM, Van Belle E, et al. Effects of coronary stenting on restenosis and occlusion after angioplasty of the culprit vessel in patients with recent myocardial infarction. *Circulation* 1997;96:2854-8.
15. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction study group. *N Engl J Med* 1993;328:673-9.
16. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;349:733-42.
17. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction: Stent Primary Angioplasty in Myocardial Infarction study group. *N Engl J Med* 1999;341:1949-56.
18. Loubeyre C, Morice MC, Lefevre T, Piechaud JF, Louvard Y, Dumas P. A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. *J Am Coll Cardiol* 2002;39:15-21.
19. Suryapranata H, Ottervanger JP, Nibbering E, et al. Long term outcome and cost-effectiveness of stenting versus balloon angioplasty for acute myocardial infarction. *Heart* 2001;85:667-71.
20. Cox DA, Stone GW, Grines CL, et al. Outcomes of optimal or "stent-like" balloon angioplasty in acute myocardial infarction: the CADILLAC trial. *J Am Coll Cardiol* 2003;42:971-7.
21. Scheller B, Hennen B, Severin-Kneib S, Ozbek C, Schieffer H, Markwirth T. Long-term follow-up of a randomized study of primary stenting versus angioplasty in acute myocardial infarction. *Am J Med* 2001;110:1-6.
22. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
23. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 trial. *Circulation* 2002;105:1642-9.
24. de Lemos JA, Antman EM, Gibson CM, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction: observations from the TIMI 14 trial. *Circulation* 2000;101:239-43.
25. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;344:1895-903.
26. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;98:2695-701.
27. Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol* 2003;42:1879-85.
28. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. *J Am Coll Cardiol* 2003;42:1886-9.
29. Kunichika H, Ben-Yehuda O, Lafitte S, Kunichika N, Peters B, DeMaria AN. Effects of glycoprotein IIb/IIIa inhibition on microvascular flow after coronary reperfusion: a quantitative myocardial contrast echocardiography study. *J Am Coll Cardiol* 2004;43:276-83.
30. Kloner RA, Dai W. Glycoprotein IIb/IIIa inhibitors and no-reflow. *J Am Coll Cardiol* 2004;2:284-6.
31. Rezkalla SH, Kloner RA. No-reflow phenomenon. *Circulation* 2002;105:656-62.
32. Leesar MA, Stoddard M, Ahmed M, Broadbent J, Bolli R. Preconditioning of human myocardium with adenosine during coronary angioplasty. *Circulation* 1997;95:2500-7.
33. Assali AR, Sdringola S, Ghani M, et al. Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of "no reflow" phenomenon. *Catheter Cardiovasc Intervent* 2000;51:27-32.
34. Maroko PR, Kjekshus JK, Sobel BE, et al. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 1971;43:67-82.
35. Hammerman H, Kloner RA, Briggs L, Braunwald E. Enhancement of salvage of reperfused myocardium by early beta-adrenergic blockade (timolol). *J Am Coll Cardiol* 1984;3:1438-43.
36. Jennings RB, Reimer KA. Effect of beta-adrenergic blockade on acute myocardial ischemic injury. In: Gross F, editor. *Modulation of Sympathetic Tone in the Treatment of Cardiovascular Diseases*. Berne: Hans Huber, 1979:103-14.
37. Lange R, Nieminen M, Kloner RA. Failure of pindolol and metoprolol to reduce the size of non-reperfused infarcts in dogs using area at risk techniques. *Cardiovasc Res* 1984;18:37-43.
38. Rasmussen MM, Reimer KA, Kloner RA, Jennings RB. Infarct size reduction by propranolol before and after coronary ligation in dogs. *Circulation* 1977;56:794-8.
39. Kloner RA, Fishbein MC, Braunwald E, Maroko PR. Effect of propranolol on mitochondrial morphology during acute myocardial ischemia. *Am J Cardiol* 1978;41:880-6.
40. Rude RE, Buja LM, Willerson JT. Propranolol in acute myocardial infarction: the MILLIS experience. *Am J Cardiol* 1986;57:38F-42F.
41. Yusuf S, Sleight P, Rossi P, et al. Reduction in infarct size, arrhythmias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation* 1983;67:132-41.
42. Peter T, Norris RM, Clarke ED, et al. Reduction of enzyme levels by propranolol after acute myocardial infarction. *Circulation* 1978;57:1091-5.
43. The International Collaborative Study Group. Reduction of infarct size with the early use of timolol in acute myocardial infarction. *N Engl J Med* 1984;310:9-15.
44. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. *Lancet* 1981;2:823-7.
45. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI): a randomised placebo-controlled international trial. *Eur Heart J* 1985;6:199-226.
46. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986;2:57-66.
47. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II-B study. *Circulation* 1991;83:422-37.
48. Basu S, Senior R, Raval U, van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction: a placebo-controlled, randomized trial. *Circulation* 1997;96:183-91.
49. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247:1707-14.
50. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801-7.

51. Eberli FR, Weinberg EO, Grice WN, Horowitz GL, Apstein CS. Protective effect of increased glycolytic substrate against systolic and diastolic dysfunction and increased coronary resistance from prolonged global underperfusion and reperfusion in isolated rabbit hearts perfused with erythrocyte suspensions. *Circ Res* 1991;68:466–81.
52. Cave AC, Ingwall JS, Friedrich J, Liao R, Saupe KW, Apstein CS. ATP synthesis during low-flow ischemia: influence of increased glycolytic substrate. *Circulation* 2000;101:2090–6.
53. Apstein CS, Taegtmeier H. Glucose-insulin-potassium in acute myocardial infarction: the time has come for a large, prospective trial. *Circulation* 1997;96:1074–7.
54. Apstein CS. The benefits of glucose-insulin-potassium for acute myocardial infarction (and some concerns). *J Am Coll Cardiol* 2003;42:792–5.
55. Sybers HD, Maroko PR, Ashraf M, Libby P, Braunwald E. The effect of glucose-insulin-potassium on cardiac ultrastructure following acute experimental coronary occlusion. *Am J Pathol* 1973;70:401–20.
56. Bellows SD, Kloner RA. Glucose-insulin-potassium does not reduce myocardial infarct size in an ischemic/reperfusion rabbit model. *J Thromb Thrombolysis* 1998;5:25–7.
57. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation* 1997;96:1152–6.
58. Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction: the ECLA (Estudios Cardiologicos Latino-america) collaborative group. *Circulation* 1998;98:2227–34.
59. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26:57–65.
60. van der Horst IC, Zijlstra F, van't Hof AW, et al. Glucose-insulin-potassium infusion in patients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. *J Am Coll Cardiol* 2003;42:784–91.
61. Hale SL, Kloner RA. Effect of combined K(ATP) channel activation and Na⁺/H⁺ exchange inhibition on infarct size in rabbits. *Am J Physiol Heart Circ Physiol* 2000;279:H2673–7.
62. Reffelmann T, Kloner RA. Is microvascular protection by cariporide and ischemic preconditioning causally linked to myocardial salvage? *Am J Physiol Heart Circ Physiol* 2003;284:H1134–41.
63. Rupprecht HJ, vom Dahl J, Terres W, et al. Cardioprotective effects of the Na⁺/H⁺ exchange inhibitor cariporide in patients with acute anterior myocardial infarction undergoing direct PTCA. *Circulation* 2000;101:2902–8.
64. Theroux P, Chaitman BR, Danchin N, et al. Inhibition of the sodium-hydrogen exchanger with cariporide to prevent myocardial infarction in high-risk ischemic situations: main results of the GUARDIAN trial. Guard during ischemia against necrosis (GUARDIAN) investigators. *Circulation* 2000;102:3032–8.
65. Zeymer U, Suryapranata H, Monassier JP, et al. The Na⁺/H⁺ exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction: results of the evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction (ESCAMI) trial. *J Am Coll Cardiol* 2001;38:1644–50.
66. Downey JM, Liu Y, Ytrehus K. Adenosine and the anti-infarct effects of preconditioning. In: Przyklenk K, Kloner RA, Yellon DM, editors. *Ischemic Preconditioning: The Concepts of Endogenous Cardioprotection*. Boston: Kluwer, 1994:137–52.
67. Hale SL, Bellows SD, Hammerman H, Kloner RA. An adenosine A₁ receptor agonist, R(-)-N-(2-phenylisopropyl)-adenosine (PIA), but not adenosine itself, acts as a therapeutic preconditioning-mimetic agent in rabbits. *Cardiovasc Res* 1993;27:2140–5.
68. Heidland UE, Heintzen MP, Schwartzkopff B, Strauer BE. Preconditioning during percutaneous transluminal coronary angioplasty by endogenous and exogenous adenosine. *Am Heart J* 2000;140:813–20.
69. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000;101:2154–9.
70. Kopecky SL, Aviles RJ, Bell MR, et al. A randomized, double-blinded, placebo-controlled, dose-ranging study measuring the effect of an adenosine agonist on infarct size reduction in patients undergoing primary percutaneous transluminal coronary angioplasty: the ADMIRE (AmP579 Delivery for Myocardial Infarction REduction) study. *Am Heart J* 2003;146:146–52.
71. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of Adenosine (AMISTAD) trial. *J Am Coll Cardiol* 1999;34:1711–20.
72. Quintana M, Hjemdahl P, Sollevi A, et al. Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis, results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 2003;59:1–9.
73. Ross A, Gibbons R, Kloner RA, Marder VJ, Stone GW, Alexander RW. Acute myocardial infarction study of adenosine (AMISTAD II). *J Am Coll Cardiol* 2002;39 Suppl A:338A.
74. Kloner RA, Braunwald E. Effects of calcium channel antagonists on infarcting myocardium. *Am J Cardiol* 1987;59:84B–94B.
75. Lo HM, Kloner RA, Braunwald E. Effect of intracoronary verapamil on infarct size in the ischemic, reperfused canine heart: critical importance of the timing of treatment. *Am J Cardiol* 1985;56:672–7.
76. Goldbourt U, Behar S, Reicher-Reiss H, Zion M, Mandelzweig L, Kaplinsky E. Early administration of nifedipine in suspected acute myocardial infarction: the Secondary Prevention Reinfarction Israel Nifedipine trial 2 study. *Arch Intern Med* 1993;153:345–53.
77. Gross GJ, Yao Z, Auchampach JA. Role of ATP-sensitive potassium channels in ischemic preconditioning. In: Przyklenk K, Kloner RA, Yellon DM, editors. *Ischemic Preconditioning: The Concepts of Endogenous Cardioprotection*. Boston, MA: Kluwer, 1994:125–35.
78. Yao Z, Gross GJ. Effects of the K_{ATP} channel opener bimakalim on coronary blood flow, monophasic action potential duration, and infarct size in dogs. *Circulation* 1994;89:1769–75.
79. Gross GJ, Auchampach JA. Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. *Circ Res* 1992;70:223–33.
80. Sato T, Marban E. The role of mitochondrial K(ATP) channels in cardioprotection. *Basic Res Cardiol* 2000;95:285–9.
81. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact of Nicorandil in Angina (IONA) randomized trial. *Lancet* 2002;359:1269–75.
82. Baran KW, Nguyen M, McKendall GR, et al. Double-blind, randomized trial of an anti-CD18 antibody in conjunction with recombinant tissue plasminogen activator for acute myocardial infarction: limitation of myocardial infarction following thrombolysis in acute myocardial infarction (LIMIT AMI) study. *Circulation* 2001;104:2778–83.
83. Faxon DP, Gibbons RJ, Chronos NA, Gurbel PA, Sheehan F, HALT-MI Investigators. The effect of blockade of the CD11/CD18 integrin receptor on infarct size in patients with acute myocardial infarction treated with direct angioplasty: the results of the HALT-MI study. *J Am Coll Cardiol* 2002;40:1199–204.
84. The EMIP-FR Group. Effect of 48-h intravenous trimetazidine on short- and long-term outcomes of patients with acute myocardial infarction, with and without thrombolytic therapy: a double-blind, placebo-controlled, randomized trial. *European Myocardial Infarction Project—Free Radicals*. *Eur Heart J* 2000;21:1537–46.
85. Flaherty JT, Pitt B, Gruber JW, et al. Recombinant human superoxide dismutase (h-SOD) fails to improve recovery of ventricular function in patients undergoing coronary angioplasty for acute myocardial infarction. *Circulation* 1994;89:1982–91.
86. Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992;339:1553–8.
87. Magnesium in Coronaries (MAGIC) Trial Investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries (MAGIC) trial: a randomised controlled trial. *Lancet* 2002;360:1189–96.
88. Mahaffey KW, Granger CB, Nicolau JC, et al. Effect of pexelizumab, an anti-C5 complement antibody, as adjunctive therapy to fibrinolysis in acute myocardial infarction: the COMPLEMENT inhibition in myocardial infarction treated with thrombolytics (COMPLY) trial. *Circulation* 2003;108:1176–83.
89. Granger CB, Mahaffey KW, Weaver WD, et al. Pexelizumab, an anti-C5 complement antibody, as adjunctive therapy to primary percutaneous coronary intervention in acute myocardial infarction:

- the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial. *Circulation* 2003;108:1184-90.
90. Dave RH, Hale SL, Kloner RA. Hypothermic, closed circuit peri-cardioperfusion: a potential cardioprotective technique in acute regional ischemia. *J Am Coll Cardiol* 1998;31:1667-71.
 91. Hale SL, Dave RH, Kloner RA. Regional hypothermia reduces myocardial necrosis even when instituted after the onset of ischemia. *Basic Res Cardiol* 1997;92:351-7.
 92. Baxter GF, Hale SL, Miki T, et al. Adenosine A₁ agonist at reperfusion trial (AART): results of a three-center, blinded, randomized, controlled experimental infarct study. *Cardiovasc Drugs Ther* 2000;14:607-14.
 93. Taber RE, Morales AR, Fine G. Myocardial necrosis and the postoperative low-cardiac-output syndrome. *Ann Thorac Surg* 1967;4:12-28.
 94. Greaves SC, Rutherford JD, Aranki SF, et al. Current incidence and determinants of perioperative myocardial infarction in coronary artery disease. *Am Heart J* 1996;132:572-88.
 95. McGoon MD, Fuster V, Gersh BJ, Mullany CJ. Coronary revascularization: indications and outcomes. In: Giuliani ER, Gersh BJ, McGoon MD, Hayes DL, Schaff HV, editors. *Mayo Clinic Practice of Cardiology*. St. Louis: Mosby, 1994:1387-97.
 96. Steuer J, Hörte LG, Lindahl B, Stahle E. Impact of perioperative myocardial injury on early and long-term outcome after coronary artery bypass grafting. *Eur Heart J* 2002;23:1219-27.
 97. Lell WA, Walker DR, Blackstone EH, Kouchoukos NT, Allarde R, Roe CR. Evaluation of myocardial damage in patients undergoing coronary-artery bypass procedures with halothane-N₂O anesthesia and adjuvants. *Anesth Analg* 1977;56:556-63.
 98. Hultgren HN, Miyagawa M, Buch W, Angell WW. Ischemic myocardial injury during cardiopulmonary bypass surgery. *Am Heart J* 1973;85:167-76.
 99. Costa MA, Carere RG, Lichtenstein SV, et al. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). *Circulation* 2001;104:2689-93.
 100. Mentzer RM Jr. Does size matter? What is your infarct rate after coronary artery bypass grafting? *J Thorac Cardiovasc Surg* 2003;126:326-8.
 101. Perrault LP, Menasché P. Preconditioning: can nature's shield be raised against surgical ischemic-reperfusion injury? *Ann Thorac Surg* 1999;68:1988-94.
 102. Ghosh S, Galinanes M. Protection of the human heart with ischemic preconditioning during cardiac surgery: role of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2003;126:133-42.
 103. Belhomme D, Peynet J, Florens E, Tibourtine O, Kitakaze M, Menasché P. Is adenosine preconditioning truly cardioprotective in coronary artery bypass surgery? *Ann Thorac Surg* 2000;70:590-4.
 104. Rinne T, Harmoinen A, Kaukinen S. Esmolol cardioplegia in unstable coronary revascularisation patients: a randomised clinical trial. *Acta Anaesthesiol Scand* 2000;44:727-32.
 105. Vinten-Johansen J, Zhao ZQ, Corvera JS, et al. Adenosine in myocardial protection in on-pump and off-pump cardiac surgery. *Ann Thorac Surg* 2003;75:S691-9.
 106. Mentzer RM, Jr., Birjiniuk V, Khuri S, et al. Adenosine myocardial protection: preliminary results of a phase II clinical trial. *Ann Surg* 1999;229:643-9.
 107. Trubel W, Zwoelfer W, Moritz A, Laczkovics A, Haider W. Cardioprotection by nifedipine cardioplegia during coronary artery surgery. *Eur J Anaesthesiol* 1994;11:101-6.
 108. Boyce SW, Bartels C, Bolli R, et al. Impact of sodium-hydrogen exchange inhibition by cariporide on death or myocardial infarction in high-risk CABG surgery patients: results of the CABG surgery cohort of the GUARDIAN study. *J Thorac Cardiovasc Surg* 2003;126:420-7.
 109. Mentzer RM, Jr. EXPEDITION: Sodium-proton exchange inhibition to prevent coronary events in acute cardiac conditions trial. Paper presented at the American Heart Association Scientific Sessions, November 12, 2003; Atlanta, Georgia.
 110. Collaborative Organization for RheothRx Evaluation (CORE). Effects of RheothRx on mortality, morbidity, left ventricular function, and infarct size in patients with acute myocardial infarction. *Circulation* 1997;96:192-201.
 111. European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group. The ESPRIM trial: short-term treatment of acute myocardial infarction with molsidomine. *Lancet* 1994;334:91-7.
 112. Wall TC, Califf RM, Blankenship J, et al. Intravenous Fluosol in the treatment of acute myocardial infarction: results of the Thrombolysis and Angioplasty in Myocardial Infarction 9 trial. TAMI 9 research group. *Circulation* 1994;90:114-20.
 113. MILIS Study Group. Hyaluronidase therapy for acute myocardial infarction: results of a randomized, blinded, multicenter trial. *Am J Cardiol* 1986;57:1236-43.