The extent of ischemic necrosis after a complete proximal coronary artery occlusion is not fixed. Numerous experimental studies have shown that reperfusion therapy and reperfusion therapy coupled with various maneuvers and pharmacological therapies may prevent the wavefront of necrosis that spreads from subendocardium to subepicardium within the ischemic risk zone.1,2 Smaller, treated myocardial infarcts may be less likely to manifest long-term adverse left ventricular (LV) remodeling compared with untreated large, transmural myocardial infarcts3 (Figure). Although in the clinical literature, early and complete reperfusion of the infarct-related occluded coronary artery is the standard of care, debate continues as to the role of adjunctive pharmacological agents administered along with reperfusion for the sole purpose of further reducing myocardial infarct size.4

In a series of recent articles my colleagues and I reviewed clinical trials performed in the 2000s that tested pharmacological and other adjunctive therapies’ ability to limit the size of myocardial infarctions (MIs).4–7 Although many agents seemed promising in experimental studies, they failed to translate to successful clinical translation. Antiplatelet agents are emerging as some of the newest agents that seem to have cardioprotective capabilities. Postconditioning has become a bit more controversial in the clinical literature; remote conditioning, early and rapid cooling, adenosine, and ranolazine are intriguing therapies deserving of larger studies. Certain agents and maneuvers, such as erythropoietin, protein kinase C δ inhibitors, iron chelation, and intra-aortic balloon counterpulsation, perhaps should be retired. The correct adjunctive therapy administered along with reperfusion has the capability of further reducing myocardial injury during ST-segment–elevation myocardial infarction. (Circ Res. 2013;113:451-463.)

Key Words: acute myocardial infarction ■ adenosine ■ adjunctive therapy ■ platelet aggregation inhibitors ■ conditioning ■ infarct size ■ reperfusion injury
of myocardial edema after reperfusion and that this reduction in edema was independent of infarct size. In this same study, postconditioning also reduced myocardial infarct size measured by MRI, as well as creatine kinase (CK) release.10

Lønborg et al11 studied 118 patients assigned to conventional percutaneous coronary intervention (PCI) or PCI plus ischemic postconditioning. There was a trend for better acute resolution of STEMI in the postconditioning group; patients with better STEMI resolution had smaller infarct sizes (by cardiac MRI and peak troponin T levels).11 In another analysis, Lønborg et al12 showed that postconditioning resulted in a 19% reduction of infarct size assessed by 3-month MRIs (51% of the risk area developed infarction in the postconditioning group versus 63% [P<0.01] in the control group). Fewer patients in the postconditioned group developed heart failure (27% versus 46%; P=0.048).

Garcia et al13 reported the results of 43 patients with first STEMI randomized to standard primary percutaneous coronary angioplasty or PCI followed by postconditioning (4 cycles of 30 second reocclusion by inflating an angioplasty balloon followed by 30 seconds of reperfusion). Postconditioning significantly reduced infarct size assessed enzymatically (CK-MB 195 IU/L in the postconditioning group versus 242 IU/L in the control group; P<0.01), and improved early ejection fraction (EF; postconditioning 52% versus control 43%; P=0.05). At 3.4 years there was still a trend toward a better EF in the postconditioning group. Postconditioning was associated with a better myocardial perfusion grade. Sörensson et al14 studied 76 patients with STEMI and randomized them to PCI or PCI plus postconditioning. Infarct size was assessed by MRI and area at risk was determined by measuring abnormally contracting LV segments by angiography. Overall, infarct size as a percentage of the risk zone did not differ between groups; but the slope of the regression line of infarct size to area at risk did differ between groups such that infarct size was significantly smaller in the postconditioned groups among patients with large ischemic risk areas.

Xue et al15 showed that patients (n=43) with MI who were postconditioned developed significantly reduced enzymatically determined infarct size, lower high sensitivity cardiac reactive protein, had more complete resolution of STEMI and had a better EF at 7 days (57% versus 47%; P=0.002). In addition, infarct size also measured by Tc99m sestamibi was reduced by 46% in the postconditioning group (13% versus 24%; P=0.002).

However, not all studies of ischemic postconditioning are positive. Freixa et al16 reported 79 patients undergoing PCI for a first STEMI who were randomized to postconditioning (4 cycles of 1 minute angioplasty balloon inflation followed by 1 minute deflation) or PCI. Cardiac MRI was used to measure infarct size, myocardial salvage, and LVEF. There were no significant differences in either infarct size or LVEF between groups at either 1 or 6 months after infarction, and surprisingly, postconditioning was associated with a lower index of myocardial salvage than controls. The authors concluded that postconditioning does not reduce infarct size or improve postreperfusion LV function and in fact might have a harmful effect. Is it possible that in this study, repetitive balloon inflation and deflation dislodged atherosclerotic or thromboemboli

<table>
<thead>
<tr>
<th>Nonstandard Abbreviations and Acronyms</th>
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<tr>
<td>CHF = congestive heart failure</td>
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<tr>
<td>CK, CK–MB = creatine kinase, creatine</td>
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<td>kinase MB</td>
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<tr>
<td>EF = ejection fraction</td>
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<tr>
<td>GIK = glucose–insulin–potassium</td>
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<tr>
<td>IABC = intra-aortic balloon counterpulsation</td>
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<td>LV = left ventricle</td>
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<td>PCI = percutaneous coronary intervention</td>
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<td>STEMI = ST-segment–elevation myocardial infarction</td>
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<td>TIMI = thrombolysis in myocardial infarction</td>
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Therapies Related to Endogenous Cardioprotection

Postconditioning refers to stuttering or interrupted reperfusion induced by several brief coronary artery reocclusion-reperfusion cycles before full and final reperfusion. Some1 but not all experimental studies showed that postconditioning reduced myocardial infarct size. In our laboratory, the effect of postconditioning has been much more impressive in reducing reperfusion arrhythmias than reducing infarct size.9 A recent study of 50 patients with ST-segment–elevation MI (STEMI) showed that ischemic postconditioning significantly reduced the amount
which then caused downstream damage? Another possibility is that the more common use of dual antiplatelet agents and higher doses of antiplatelet agents may have masked a beneficial effect of postconditioning (see antiplatelet agents section).

The largest study to examine postconditioning was recently presented at the 2012 Transcatheter Cardiovascular Therapeutics conference. This was a study of 700 patients with STEMI undergoing primary PCI with a postconditioning protocol (4 cycles of 1 minute coronary angioplasty balloon occlusion and then 1 minute reflow) versus no postconditioning. The primary end point of >70% resolution of the STEMI on the ECG did not differ between groups (41% in the postconditioning versus 42% in the conventional group P=0.79). There was a nonsignificant trend for thrombolysis in MI (TIMI) grade 3 to be higher with postconditioning (92%) versus without (88%; P=0.08). There was no difference in myocardial blush grade between groups. At 1 month, mortality rate was 4% with postconditioning versus 3% in the conventional treatment group (P=0.53). There was no difference in major adverse cardiovascular events between groups at 1 month. However, since these investigators did not provide data on myocardial infarct size, it is difficult to compare this negative study to other postconditioning studies in which a major end point was myocardial infarct size.

In summary, most postconditioning studies presented in the past few years show a reduction in infarct size or a trend toward a reduction; but 1 recently published trial and 1 large recently presented trial were negative, for reasons that are not entirely clear.

Cyclosporine

The concept of using cyclosporine for cardioprotection ties in closely with the postconditioning concept. One of the mechanisms by which postconditioning works is thought to be by inhibiting the opening of the mitochondrial permeability transition pore at the time of reperfusion. Cyclosporine is known to keep this pore closed and has been likened to chemical postconditioning. In an earlier study by Piot et al, cyclosporine, given at reperfusion in patients with STEMI undergoing PCI, was shown to reduce enzymatic estimate of acute myocardial infarct size. The same group of researchers extended this study by analyzing cardiac MRI at 5 days and 6 months in 28 patients from this study. Mewton et al found that at 6 months, patients who had received cyclosporine showed a persistent reduction in myocardial infarct size compared with controls (29 versus 38 g; P=0.04). At 6 months, LV end-systolic volume (mL) was reduced in patients who received cyclosporine compared with controls (45 versus 50 mL; P=0.01). In addition, LV ejection fraction was also improved in patients who received cyclosporine (54% versus 49%; P=0.06).

In summary, cyclosporine appears to be a promising agent for reducing myocardial infarct size and improving LV function following STEMI. Further studies are needed to determine the optimal timing and duration of cyclosporine administration in order to achieve the maximal benefit.

Figure. Schematic showing how reducing myocardial infarct size early could have benefit on long-term structure of the heart. The left hand drawings show a schematic derived from the wavefront concept of Reimer and Jennings. After proximal coronary occlusion, a portion of the left ventricle (LV) becomes ischemic, defined as the ischemic risk region. When a blue dye is injected into the vasculature the blue dye circulates to areas receiving blood flow and fails to penetrate the ischemic zone. If reperfusion occurs after ~40 minutes of ischemia, irreversible myocardial damage—that is necrosis (pale white area) is confined to the subendocardial myocardium. Viable myocardium within the risk zone is stained red by triphenyl tetrazonium chloride (TTC). If reperfusion is delayed (after 60 minutes) or after 3 to 6 hours, the extent of necrosis expands from subendocardium to subepicardium within the ischemic risk zone. This march of necrosis becomes transmural or nearly transmural if reperfusion is not instituted within ~3 to 6 hours or if reperfusion does not occur. Large transmural infarcts may then go on to result in severe LV remodeling with infarct expansion, LV cavity dilatation, LV aneurysm formation, and eccentric hypertrophy of the noninfarcted tissue. If agents are administered to reduce infarct size or if very early reperfusion is instituted the size of the infarct can be limited (first transverse LV slice shown in right column). During the long term, this smaller infarct will shrink in size with a minimum of subendocardial scar tissue and substantial viable tissue remaining in the midmyocardial wall. LV remodeling will be minimized with less infarct wall thinning, less LV dilation, and less eccentric hypertrophy. In addition LV function will be better preserved.
significantly lower in the cyclosporine group (67 mL) versus the control group (84 mL; \( P=0.05 \)) and there was a nonsignificant trend toward lower LV end diastolic volume in the cyclosporine group as well. These results suggested that the early benefit of cyclosporine on myocardial infarct size persisted at 6 months and had some benefit on LV systolic volumes. The concept of chemical postconditioning with agents, such as cyclosporine, is moving forward with a large European study called the Does Cyclosporine Improve Clinical Outcome in ST Elevation Myocardial Infarction Patients? trial in which the agent cyclosporin A is being tested in patients with MI.

Remote Ischemic Conditioning

Experimental studies have shown that brief episodes of ischemia in 1 region of the heart can protect a remote region from a more prolonged episode of ischemia. In addition, brief episodes of ischemia of a limb can protect the heart from ischemic necrosis. This concept of remote ischemic conditioning has now been the subject of numerous clinical trials. Bottker et al previously showed that ischemic conditioning, induced by brief inflations and deflations of a blood pressure cuff on the arm, started in the ambulance, improved myocardial salvage in patients undergoing PCI for STEMI. The same group recently assessed the effect of remote ischemic conditioning on LV function after MI. A total of 242 patients with STEMI were randomized to remote ischemic conditioning induced by 4 cycles of 5 minutes of upper arm ischemia using a blood pressure cuff, during transfer to the hospital for PCI. Although the overall patient cohort did not show a difference in EF (echocardiography) at days 1 and 30 between groups, patients with large risk zones (nuclear myocardial perfusion imaging) showed benefits of remote conditioning on cardiac function. At 30 days, LVEF was 0.51 in this conditioning subgroup versus 0.46 in the control group; \( P=0.05 \). There was also a benefit of remote conditioning in patients with anterior MIs who had better EF compared with controls on both day 1 (0.51 versus 0.46; \( P=0.03 \)) and day 30 (0.55 versus 0.50; \( P=0.04 \)). Although these patients had similar ischemic risk zones, infarct size was significantly reduced by remote conditioning from 16% in controls to 7% of the LV in the treated group (\( P=0.01 \)).

Hoole et al showed that remote ischemic preconditioning before elective PCI reduced cardiac troponin release and reduced major adverse cardiac events long term, at 6 years (23 versus 36%; \( P=0.039 \)).

Although the focus of this article has been cardioprotection of myocardium in patients with acute STEMI, there is an emerging literature on the concept that remote ischemic preconditioning can protect the heart of patients undergoing cardiac surgery. Not all studies have been positive, but a very recent presentation at the 2012 American Heart Association Scientific Sessions suggested better long-term clinical outcome in patients that received remote conditioning. In this study, 300 patients undergoing elective coronary artery bypass surgery with cardiopulmonary bypass and cardioplegia received either 3 cycles of 5 minutes of arm ischemia and 5 minutes reperfusion after induction of anesthesia or no arm ischemia. Remote conditioning resulted in a 32% reduction in the area under the curve of cardiac troponin I compared with controls. Survival during a mean of 483 days was better in the remote conditioning group (1 death) compared with the control group (6 deaths; \( P=0.03 \)). Hence this study, for the first time, showed a long-term prognostic benefit of conditioning. Remote ischemic conditioning is a fine example of how a phenomenon first observed in the experimental laboratory can be translated to a clinical benefit.

Protein Kinase C Isoforms

The activation and translocation of protein kinase C were one of the earliest suggested mechanisms for explanation of the preconditioning phenomenon. This concept was refined to suggest that specific protein kinase C isoenzymes that were activated and translocated to membranes and organelles were crucial. Although therapy with protein kinase C \( \delta \) inhibitor delacarsib had no beneficial effect on reducing myocardial infarct size or improving clinical outcome.

Adenosine

Adenosine and adenosine agonists have been studied in numerous experimental models and some but not all studies showed cardioprotective effects. A variety of mechanisms of action of a cardioprotective effect for adenosine has been suggested, including its role as a trigger for conditioning (which might include preconditioning, perconditioning, and postconditioning), a vasodilator effect—dilating coronary and systemic arteries, a hemodynamic effect that may reduce oxygen demand—including reduction of heart rate and blood pressure, an antiplatelet effect, and others. Previously, 2 large multicenter studies, Acute Myocardial Infarction Study of Adenosine (AMISTAD) 1 and AMISTAD 2, showed that high-dose 3-hour intravenous infusion of adenosine started near the time of reperfusion significantly reduced anterior wall myocardial infarct size as determined by nuclear imaging. Although adenosine did not significantly reduce death/congestive heart failure (CHF) in the overall population of AMISTAD 2, this study was underpowered to do so. However, a substudy of patients reperfused within the median door to balloon time of 3.2 hours revealed that adenosine infusion was associated with lower death/CHF rates than placebo. A recent study by Desmet et al studied the effects of a high-dose intracoronary bolus of adenosine just before initial angioplasty balloon inflation on MRI infarct size. A total of 112 patients with STEMI were randomized to intracoronary adenosine 4 mg or placebo. There was no benefit of adenosine on myocardial infarct size assessed by MRI at 4 months. Adenosine did not improve TIMI flow grade, TIMI frame count, blush grade, or microvascular obstruction assessed by MRI. Fokkema et al also studied the effect of high-dose intracoronary adenosine boluses on myocardial infarct size and parameters of myocardial reperfusion. Four hundred forty-eight patients with acute STEMI were randomized to placebo or 2 bolus injections of intracoronary adenosine (2x120 \( \mu \)g in 20-mL saline). Atenosine did not improve the incidence of residual STEMI deviation, myocardial blush grade, TIMI
scores, or enzymatic infarct size. However, it is important to remember that the intravascular half-life of adenosine is extremely brief—seconds—thus it is difficult to imagine how a single or double bolus would result in a significant effect. It may be that long intravenous infusions are needed to truly result in a cardioprotective effect. In addition, in both of the negative studies, high-dose clopidogrel (600 mg) was administered. It is possible that the high-dose antiplatelet agent masked a beneficial effect of adenosine.

**Antiplatelet Therapies**

**Abciximab**

Some previous clinical trials suggested that the glycoprotein IIb/IIIa platelet receptor inhibitor abciximab could reduce myocardial infarct size and lead to improved clinical outcomes when administered early to patients with myocardial infarct or when given via an intracoronary route compared with an intravenous route, but not all studies were positive. Some of these studies suggested better coronary perfusion with abciximab, implying that inhibition of platelet aggregation was the mechanism of action. However, recent experimental studies have suggested that some antiplatelet agents may reduce myocardial infarct size in ischemia/reperfusion models that do not primarily involve a thrombus as the cause of the coronary occlusion but that induce ischemia with a mechanical coronary occlusion. Such a finding would imply that some of these antiplatelet agents might work through pleiotropic mechanisms, such as second messenger pathways. In the past 3 years, there have been several clinical trials that have further explored the potential benefit of antiplatelet agents to reduce myocardial infarct size. Most of these studies have involved the use of abciximab, often on top of standard clopidogrel therapy; tirofiban has also been studied.

Eitel et al. studied intracoronary versus intravenous bolus abciximab in patients with STEMI and assessed long-term, 6-month effects on myocardial infarct size and LV function. A total of 154 patients with STEMI undergoing PCI were randomized to intracoronary or intravenous abciximab. Median infarct size, assessed by delayed enhancement MRI after 6 months, was significantly smaller (16.7%) in the intracoronary abciximab group compared with the intravenous group (24.1%; P=0.002). Recovery of LV function was observed with intracoronary but not intravenous abciximab. Intracoronary abciximab group had less LV remodeling and a trend toward fewer major adverse cardiovascular events.

The same investigators studied the effect of intracoronary versus intravenous abciximab on the extent of aborted MI (which they defined as major ≥50% STEMI resolution and a lack of subsequent cardiac enzyme rise ≥2 the upper normal limit). They also assessed aborted MI as a lack of ischemic myocardial necrosis determined by MRI. The results showed that aborted MI was significantly more likely with intracoronary than intravenous abciximab and that aborted MI was a predictor of improved clinical outcome.

It seems that not all glycoprotein IIb/IIIa inhibitors are equal in their ability to reduce myocardial infarct size in the setting of rescue PCI when fibrinolytic therapy has failed. Bajaj et al. compared 2 glycoprotein IIb/IIIa inhibitors: abciximab versus eptifibatide in this clinical setting. This study was a prospective, non-randomized analysis of 241 consecutive patients; 162 received abciximab and 79 received eptifibatide. Patients receiving abciximab had lower peak CK (2484) compared with eptifibatide (2650 U/L, P=0.01), had less STEMI, and had better corrected TIMI frame count and better myocardial blush grade. The authors concluded that abciximab was superior to eptifibatide for improving angiographic and electrocardiographic assessment of coronary perfusion, as well as for reducing myocardial infarct size.

Petronio et al. compared early abciximab with late abciximab in patients needing transportation to another facility for primary PCI. A total of 110 patients were randomized to early (in emergency room) versus late (in the catheterization laboratory) abciximab therapy. Myocardial infarct size assessed by delayed-enhancement MRI and determined at 6 months did not differ between groups. However, early abciximab therapy was associated with better STEMI resolution and a greater reduction in the transmurality of the infarct (−9.2% versus −5.9%; P=0.03). Early abciximab was associated with greater reductions in infarct size when ECG to catheterization laboratory times were delayed by >60 minutes. These findings suggested that early abciximab may be beneficial when there is a delay in the transportation time to a facility for primary PCI of STEMI.

In a recent study by Stone et al., 452 patients presenting within 4 hours of STEMI with proximal or mid left anterior descending coronary artery occlusion and undergoing PCI plus bivalirudin as anticoagulation were randomized to bolus intracoronary abciximab, no abciximab, and to manual aspiration thrombectomy versus no thrombectomy in a 2×2 factorial design. The intracoronary abciximab bolus dose was 0.25 mg/kg. The groups that received intracoronary abciximab bolus had smaller infarct size at 30 days assessed by MRI (median, 15.1% for abciximab versus 17.9% for controls; P=0.03). Absolute infarct mass was also reduced in the abciximab-treated patients (18.7 versus 24.0 g; P=0.03). Randomization to aspiration thrombectomy did not reduce infarct size (17.0%) compared with no thrombectomy (17.3%). Neither therapy significantly affected abnormal wall motion score, although abciximab was associated with a small (median 7 versus 8; P=0.08) nonsignificant favorable trend. Therefore, the authors concluded that in patients with large STEMI undergoing PCI plus bivalirudin that addition of intracoronary abciximab bolus significantly reduced myocardial infarct size. Not all recent clinical trials with abciximab have been positive. Schulz et al. examined the administration of abciximab in addition to 600-mg clopidogrel after 1 year. An earlier study showed that abciximab did not reduce infarct size compared with clopidogrel alone. A total of 800 patients were randomized to either abciximab or placebo. At 1 year, the composite of death, recurrent MI, stroke, or revascularization was similar in the 2 groups (23.0% abciximab versus 25.7% in the placebo group; P=nonsignificant [NS]). However, the need for infarct-related artery revascularization was lower in the abciximab group (16.3%) compared with the placebo group (22.3%; P=0.04). It may be that the recent trend to use the higher loading dose of clopidogrel masked the beneficial effect of abciximab.

Thiele et al. compared intracoronary abciximab bolus during primary PCI with intravenous bolus in patients with
STEMI. This large open-label, multicenter trial randomized >2000 patients to intracoronary versus intravenous bolus (0.25 mg/kg) abciximab followed by a 12-hour intravenous infusion of 0.125 μg/kg per minute. The primary composite end point at 90 days (all-cause mortality, recurrent MI, or new CHF) was similar in the intracoronary group (7.0%) versus the intravenous group (7.6%; \( P=0.58 \)). Whereas the incidence of death and reinfarction did not differ between groups, fewer patients in the intracoronary group developed new CHF (2.4% versus 4.1%; \( P=0.04 \)). The authors concluded that intracoronary abciximab is safe and might be considered to reduce the rates of CHF. However, other secondary end points in this study, including enzymatic myocardial infarct size, were negative.

High-Versus Low-Dose Clopidogrel

Patti et al\(^44\) assessed the effect of a 600 mg versus a 300 mg loading dose of clopidogrel in patients undergoing primary PCI for STEMI. Two hundred one patients were randomized to high- or low-dose clopidogrel before PCI. Infarct size was determined by area under the curve of enzymatic markers. Median CK-MB was 2070 ng/mL at the 600-mg clopidogrel dose versus 3049 ng/mL at the 300-mg dose (\( P=0.0001 \)). Troponin-I was 255 ng/mL at the 600-mg dose versus 380 ng/mL at the 300-mg dose (\( P=0.0001 \)). The 600-mg dose was also associated with better TIMI flow grade and improved LVEF at discharge (52 versus 49%; \( P=0.026 \)). In addition, higher dose clopidogrel was associated with lower rates of major adverse cardiovascular events (5.8% versus 15%; \( P=0.049 \)). The secondary end points of bleeding and complications at the catheter entry sites were not increased by high-dose clopidogrel.

Tirofiban

Tirofiban is another antiplatelet drug of the glycoprotein IIb/IIIa inhibitor class. There are a few recent studies that have investigated the effects of this agent on myocardial infarct size. In a small study, Song et al\(^45\) tested high-dose tirofiban plus PCI versus conventional primary PCI, assessing infarct size by contrast-enhanced MRI at 1 month. Although tirofiban improved TIMI flow grade and myocardial blush grade during the index procedure at 1 month, myocardial infarct size was similar in the tirofiban plus facilitated PCI group versus primary PCI group (22 versus 25%; \( P=\text{NS} \)). There was also no difference in echocardiographically determined LVEF between the 2 groups at 6 months.

In a study by Timmer et al\(^46\) prehospital tirofiban did seem to reduce infarct size in the subgroup of patients with diabetes mellitus undergoing PCI for STEMI. Their study was a subanalysis of the randomized On-Time II trial. Two hundred twenty patients with diabetes mellitus from this trial of patients with STEMI treated with primary PCI received either tirofiban (\( n=119 \)) or placebo (\( n=101 \)) before hospitalization. In these patients with diabetes mellitus, tirofiban reduced enzymatically determined myocardial infarct size (CK=1694 U/L with tirofiban versus 2040 U/L in the placebo group; \( P=0.02 \)). Tirofiban also reduced residual STEMI and resulted in a nonsignificant trend toward lower mortality at 1 year (4.6% versus 11.6%; \( P=0.07 \)). Benefits of tirofiban were more evident in patients with diabetes mellitus than non–diabetes mellitus.

In summary, antiplatelet agents (especially glycoprotein IIb/IIIa inhibitors, such as abciximab) seem to have a myocardial infarct size reducing property. This benefit might be related to reduction in platelet aggregation, thus keeping the infarct-related coronary artery patent. Alternatively, it might be related to less emboli plugging the microvasculature or some pleiotropic effect. The fact that most patients with STEMI are treated with PCI involving stents means that most patients with STEMI are receiving at least dual antiplatelet therapy with aspirin plus some other antiplatelet agent or agents. If these agents truly reduce myocardial infarct size, then it may explain why so many previous trials of other types of infarct size reducing agents have failed in clinical trials, if antiplatelet agents were already on-board and already reducing infarct size above and beyond reperfusion therapy.\(^36\)

Mechanical Cardioprotection

Thrombus Aspiration

At the time of PCI with either dilation of an angioplasty balloon or deployment of a stent, there is concern that disruption of the thrombus within the infarct-related coronary artery could cause distal microemboli that could contribute to microvascular obstruction. Thrombus aspiration has been studied to try to reduce both microvascular obstruction and reduce myocardial infarct size. Studies published during the past few years have shown mixed results with this approach.

Sardella et al\(^47\) assessed a manual thrombectomy device (Export Medtronic) as adjunctive therapy to primary PCI in patients with STEMI. A total of 175 patients with STEMI were randomized to standard PCI versus thrombus aspiration. The primary end points were measures of microvascular obstruction, including myocardial blush grade and STEMI resolution. Myocardial blush grade of ≥2 (suggesting less microvascular obstruction) occurred in 88% of the thrombus aspiration group compared with 60% of the control group (\( P=0.001 \)). STEMI resolution was more frequent with thrombus aspiration (64% versus 39%; \( P=0.001 \)). MRI-determined acute microvascular obstruction was lower in the thrombus aspiration group. From day 3 to 5 to 3 months, myocardial infarct size (MRI) was reduced only in the thrombus aspiration group (14–9%) but not in the control group (13–11%). At 9 months, there was a lower incidence of cardiac death in the thrombus aspiration group (0%) than the control group (4.6%; \( P=0.02 \)).

Ciszewski et al\(^48\) also reported encouraging results with aspiration thrombectomy. A total of 137 patients with first STEMI were randomized to either aspiration thrombectomy followed by PCI, including stenting, or to standard primary PCI without thrombectomy. Microvascular salvage index was determined by Tc99m sestamibi single-photon emission computed tomography imaging. The final infarct size was 23% in the aspiration thrombectomy group versus 29% in the controls; \( P=0.002 \). The myocardial salvage index was significantly greater with aspiration thrombectomy at 25% versus 18.5% in controls (\( P=0.02 \)).

A smaller study by Lipieccki et al\(^49\) was negative. A total of 44 patients with STEMI and documented total coronary occlusions were randomly assigned to aspiration thrombectomy (Medtronic Export Catheter) or PCI alone. At 6 days,
infarct size as a percentage of the LV or as a percentage of the ischemic zone (determined by nuclear study) was similar between groups. In addition, the transmurality score determined by MRI was the same in both groups (2.03 in the thrombus aspiration group; 2.16 in the control group; \( P=\text{NS} \)). There was also no effect of aspiration thrombectomy on LV global or regional function.

As mentioned earlier in this article, a study by Stone et al.\(^4\) comparing intracoronary abciximab and aspiration thrombectomy showed that while abciximab reduced myocardial infarct size, aspiration thrombectomy did not. Thus, aspiration thrombectomy remains a controversial approach to reducing myocardial infarct size and microvascular obstruction.

**IABC Pulsation**

Although early studies in the experimental literature suggested that IABC in the setting of STEMI might limit cardiac damage, there has been little recent clinical literature on the subject. The Counterpulsation to Reduce Infarct Size Pre-PCI Acute MI (CRISP-AMI) trial\(^5\) was a prospective, open-label, multicenter, randomized controlled trial assessing the effect of IABC on myocardial infarct size in patients with anterior STEMI but without cardiogenic shock. Patients received either IABC before PCI and then continued for 12 hours or PCI alone. Myocardial infarct size was determined by MRI at 3 to 5 days after PCI. Mean infarct size was 42.1% in the IABC group versus 37.5% in the PCI alone group (\( P=\text{NS} \)). At 6 months, there was no difference in all-cause mortality between IABC (3 patients) versus PCI alone group (9 patients; \( P=0.12 \)). The authors concluded that IABC plus primary PCI did not reduce myocardial infarct size. Of note, a very recent article showed that IABC did not improve clinical outcomes in patients with cardiogenic shock.\(^5\)

**Rapid Cooling**

In experimental studies in our laboratory,\(^5^2\)-\(^5^5\) as well as in other laboratories,\(^5^6\) moderate hypothermia induced before reperfusion consistently reduces myocardial infarct size. Reductions of myocardial temperature <35°C are usually all that is needed to reduce ischemic necrosis. There have been some pilot studies as described in our previous reviews suggesting that patients with anterior STEMI who are rapidly cooled to <35°C before reperfusion showed reduction of infarct size. The problem has been that the cooling devices used, such as endovascular heat exchange devices, take considerable time to induce reduction in core temperatures. With increased emphasis on short door to balloon times for the treatment of STEMs, interventional cardiologists are not willing to delay revascularization to induce cooling. However, other techniques, including cooling suits that can be applied in the ambulance and endovascular cooling with infusions of cold saline into the vasculature, can induce more rapid cooling without lengthening the door to balloon time.\(^5\) Göteborg,\(^5\) in a small pilot trial, randomized 20 patients to normothermia or hypothermia, induced by intravenous infusion of cold saline before PCI. Both ischemic risk zone and infarct size were determined by MRI at 4 days. Using this technique of infusion of cold saline, core body temperature of <35°C was attained before reperfusion and with a door to balloon time of 43±7 versus 40±6 minutes in the control group (\( P=\text{NS} \)). Myocardial infarct size as a percentage of the ischemic risk zone was 29.8% in the hypothermia group versus 48.0% in the control group (\( P=0.04 \)). Hence, hypothermia reduced myocardial infarct size by 38%. Hypothermia also decreased enzymatic evidence of necrosis in this protocol. The authors concluded that cooling core temperature to <35°C before reperfusion significantly reduced infarct size and could be achieved without delaying door to balloon time. This study is an example of a therapy first developed in the experimental animal laboratory being successfully translated to a pilot clinic trial. Of course larger clinical studies will be needed to confirm Göteborg’s work.

**Other Older and Newer Pharmacological Approaches**

**Erythropoietin**

Although some experimental studies suggested that acute administration of erythropoietin could reduce myocardial infarct size,\(^5^8\) studies in our own laboratory were negative.\(^5^9\) There have been several clinical trials of erythropoietin for myocardial infarct size during the past few years—with mixed results. Two small studies showed positive effects. Taniguchi et al.\(^6^0\) studied the effect of low-dose erythropoietin (6000 IU during PCI for acute MI) on in-stent neointimal volume, myocardial infarct size, and LV function. There was no significant difference in absolute infarct size between groups at 4 days or 6 months. However, myocardial infarct size assessed acutely and then at 6 months by nuclear imaging was decreased by 38.5% (\( P=0.0003 \)) in the erythropoietin group but not the control group. Peak CK values did not differ between groups. There was a significant increase in LVEF in the erythropoietin group and reduction in LV end systolic volume. Erythropoietin did not affect in-stent neointimal volume (determined by intravascular ultrasound).

A second small study by Ferrario et al.\(^6^1\) showed benefits of erythropoietin in the setting of acute MI. This was a single-center study of 30 patients with a first uncomplicated MI undergoing PCI who were randomized to erythropoietin (33×10^3 IU) before PCI, and then 24 and 48 hours after admission versus placebo. Erythropoietin patients had smaller infarct size with a 30% decrease in CK-MB release (\( P=0.025 \)), reduced adverse LV remodeling, and improved mobilization of CD34+ cells. Peripheral blood gene expression shifted to anti-apoptotic, proangiogenic, and anti-inflammatory pathways.

Larger studies of erythropoietin in patients with MI were negative. The Reduction of Infarct Expansion and Ventricular Remodeling with Erythropoietin After Large MI (REVEAL) was a multicenter study of 222 patients with STEMI who underwent PCI and were randomized in this double-blind, placebo-controlled trial to 60 000 U of epoetin alfa (intravenous) or placebo within 4 hours of reperfusion. Infarct size (% LV mass) was measured by cardiac magnetic resonance done early (2–6 days after therapy) and late (12 weeks). Infarct size was similar in the erythropoietin group (15.8% LV mass) and placebo group (15.0%; \( P=\text{NS} \)) during the early assessment of infarct size. At 12 weeks, infarct size was still similar between the 2 groups (10.6% LV mass for erythropoietin versus, 10.4% for placebo; \( P=\text{NS} \)). A surprising finding was that in patients
aged >70 years, mean infarct size was actually larger with erythropoietin than placebo.62,63

Prunier et al64 reported a study of 110 patients with STEMI treated with PCI who received either 1000 U/kg of erythropoietin β immediately after reperfusion or standard care. Myocardial infarct size was determined by contrast-enhanced cardiac MRI at 3 months. Secondary end points were LV volumes and incidence of MRI-determined microvascular obstruction. Median infarct size did not differ between erythropoietin-treated patients (17.5 g) versus controls (16.0 g; P=NS). However, erythropoietin did reduce the incidence of MRI-determined microvascular obstruction (44% versus 65%; P=0.03) and did decrease LV volume, mass, and functional impairment at 5 days. There was no difference in frequency of major adverse cardiac events between groups.

Voors et al65 reported a prospective, multicenter, randomized trial of 529 patients receiving either 60000 IU erythropoietin or standard medical care within 3 hours after PCI for STEMI. The primary end point was LVEF at 6 weeks assessed by radionuclear ventriculography and secondary end points included infarct size measured enzymatically and major adverse cardiac events. There was no difference in LVEF in the erythropoietin group (0.53) versus the control group (0.52; P=NS). Median infarct size determined by CK area under the curve >72 hours was 50 136 for erythropoietin and 53 510 for controls (P=0.058). Erythropoietin was associated with fewer major adverse cardiac events (8 versus 19; P=0.03). The authors concluded that erythropoietin was associated with fewer adverse cardiac events but did not improve LVEF at 6 weeks. It did not significantly reduce infarct size (although there was a modest trend).

Ott et al66 described a randomized, double-blind trial of 138 patients with STEMI who received erythropoietin-β (3.33×10^4 U) or placebo immediately after PCI and at 24 and 48 hours later. Primary end point was LVEF at 6 months, determined by MRI; secondary end point was myocardial infarct size at day 5 and 6 months. At 5 days, myocardial infarct size was 27% in the erythropoietin group and 28% in the control group (P=NS). At 6 months, infarct size decreased in both groups, but there was no difference between groups (17% in the erythropoietin group and 21% in the control group; P=NS). LVEF was 52% in the erythropoietin group and 52% in the placebo group at 6 months. LVEF also did not differ between groups at 5 days (49% in the erythropoietin group; 51% placebo; P=NS). There was no significant difference in the composite incidence of death, recurrent MI, stroke, or target vessel revascularization at 6 months in the erythropoietin group (13%) versus the placebo group (5.7%; P=0.15); however, the authors did note that erythropoietin may increase clinical adverse events.

Suh et al67 reported a smaller negative trial of erythropoietin. A total of 57 patients with STEMI received intravenous bolus of recombinant human erythropoietin (50 U/kg) immediately before PCI or usual therapy. On day 4 after infarction, infarct size was determined by analysis of cardiac enzyme (CK, CK-MB) release and MRI. Myocardial infarct size assessed by enzyme release did not differ between groups. MRI assessment of infarct size was 52.4 cm^3 in the erythropoietin group and 54.8 cm^3 in the control group (P=NS). The authors concluded that while erythropoietin was safe that it did not reduce myocardial infarct size.

Thus, most of the larger recent clinical studies that have examined the effect of erythropoietin on myocardial infarct size have been negative.

**Glucose–Insulin–Potassium**

Of all the agents that have been administered to try to reduce myocardial infarct size or improve acute clinical outcome of STEMI, perhaps none is more controversial than GIK. The debate on GIK has been described in detail in the past and has raged for decades.68 The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial was recently published.69 This large, randomized, placebo-controlled, double-blind, multicenter trial tested the efficacy of administering a 12-hour infusion of GIK started in the out-of-hospital setting by paramedics in patients with high probability of acute coronary syndromes. The primary outcome was the progression of the acute coronary syndrome to MI determined by enzymatic markers and ECG. There was no difference in percentage of patients that progressed to MI in the GIK group (n=200; 48.7%) compared with the placebo group (n=242; 52.6%; P=NS), nor was there a difference in 30-day mortality between the GIK group (4.4%) and placebo group (6.1%; P=NS).69 Patients who presented with STEMI on their ECG were equally likely to progress to MI in the GIK group (85.3%) as in the placebo group (88.7%; P=NS). However, the composite of cardiac arrest or in-hospital mortality was lower at 4.4% of GIK patients compared to 8.7% in the placebo patients (P=0.01). Of note, there was a small subgroup of patients who underwent Tc99m sestamibi imaging at 30 days (n=110) who showed smaller infarct size (2% of LV mass) in the GIK group versus the placebo group (10%; P=0.01). In addition, among participants who presented with STEMI, imaged infarct size at 30 days was also lower in the GIK group (3% of LV) compared with placebo (12%; P=0.05). Thus, although the primary end point of this study was negative (perhaps because many patients presenting with acute coronary syndrome may have already manifested biomarker evidence of MI at the onset), some of the secondary end points, including infarct size, were positive in a small cohort. Thus, once again, the use of GIK for acute MI remains controversial and will require further studies.

**Statins**

High-dose statins have been shown to reduce long-term adverse events in patients with acute coronary syndromes and some experimental studies have suggested that statins can actually reduce myocardial infarct size in nonatherosclerotic models, presumably via some type of pleiotropic effect. There are few clinical trials that have focused on the issue of whether statins can reduce myocardial infarct size in humans. Hahn et al70 randomized 173 patients undergoing PCI for STEMI to high-dose atorvastatin (80 mg before PCI and for 5 days after) or to low dose (10 mg daily after PCI). Patients were included when PCI was performed within 12 hours of symptoms. Myocardial infarct size, measured by technetium 99 m tetrofosmin between days 5 and 14 did not show a difference in myocardial infarct size between the high dose (22.2% of the LV) or the low dose (21.6%; P=NS), nor was there a difference in myocardial blush grade or ST segment resolution.
between groups. Limitation of this study was inclusion of patients late after symptoms onset and the possibility that the 10-mg dose was equally effective; however, having a placebo only control would likely have raised ethical concerns.

Bauer et al71 assessed the effect of prior statin exposure on enzymatic myocardial infarct size, but in patients with non-STEMI. Infarct size estimated from peak CK was 238 U/L in statin users versus 283 U/L in nonstatin users (P=0.0001). There was also a decrease in-hospital mortality with statins. Although encouraging, the authors cautioned that this was an observational study; and again this study did not include patients with STEMI. Because of the wide use of statins in patients with all acute coronary syndromes, it is unlikely that we will see a study in which patients with STEMI are randomized to acute statin versus placebo for infarct size assessment.

Antidiabetic Drugs
There are a few recent studies suggesting that the antidiabetic drugs pioglitazone and exenatide might reduce myocardial infarct size in humans. Kataoka et al72 studied 319 patients with diabetes mellitus with STEMI treated with PCI, who had been receiving pioglitazone versus those that were not. There was a trend, although short of statistically significant, for lower peak CK level (2041, IU/L) in the pioglitazone group than a trend, although short of statistically significant, for lower peak CK level (2041, IU/L) in the pioglitazone group than in controls (3207, IU/L; P=0.04). A regression analysis of infarct size versus 0.62; P=0.032). Patients with collaterals also showed a significant decrease in MRI-determined total late enhancement zone (7.3% versus 15.2%; P=0.04). The authors concluded that FX06 reduces myocardial infarct size at 4 months in patients who had time-to-therapy of <3 hours and in those with collaterals. Again the concept that adjunctive therapy might only work if coupled with early reperfusion was suggested in this study, in the exenatide, and the clinical outcome component of the adenosine study in AMISTAD 2.

Iron Chelation
Chan et al77 randomized 60 patients with STEMI to intravenous deferoxamine before PCI and then for 12 hours versus placebo. Infarct size (MRI) did not differ between groups at either 3 days or 3 months after MI. Enzymatic estimates of infarct size also did not differ between groups. At 3 months, there was no difference in LVEF between groups. Post-PCI serum iron levels and measures of oxidative stress were reduced by deferoxamine, but this was not associated with cardioprotection.

Ranolazine
Ranolazine is a late sodium current inhibitor that is approved as an antianginal agent. Experimental studies have shown that it is capable of reducing ischemic necrosis.76,77 There has yet to be a clinical trial examining ranolazine in patients with STEMI, but there is 1 study that confirms that in humans, ranolazine is capable of reducing necrosis induced by ischemia/reperfusion. Pelliccia et al80 reported 70 patients with stable angina scheduled for elective PCI who were randomized to ranolazine (1000 mg twice a day) or placebo for 7 days before the PCI. Enzymatic measures of cardiac necrosis (CK-MB and troponin-1) were determined at 8 and 24 hours post-PCI. Postprocedural increase of CK-MB ≥3 times upper limit of normal (which was considered periprocedural MI) occurred in 6% of ranolazine-treated patients versus 22% of controls (P=0.04). Peak CK-MB and peak troponin-1 were also significantly lower in the ranolazine group. These clinical findings support the experimental observation that ranolazine reduces ischemic/reperfusion myocardial necrosis. A study of ranolazine in the setting of STEMI is warranted.

Discussion
MI remains a major cause of mortality and morbidity. Although early reperfusion with PCI or thrombolysis has
Mechanical cardioprotection

To further reduce cardiac damage.82,83 I have discussed the basic concept of infarct size reduction, its importance, and attempts to achieve it during the past few decades in a series of recent review articles.4–7 My purpose here was to review very recent clinical trials from the past 3 years. I observed a number of studies in the literature related to the concept of endogenous cardioprotection, antiplatelet therapy, cooling, thrombectomy, and other various pharmacological protectant agents. The results of this search are summarized in the Table.

### Table. Recent Clinical Trials of Cardioprotection for STEMI

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Summary of Outcome</th>
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<tr>
<td>Postconditioning</td>
<td>Several studies suggested a benefit; however 2 recent sizable studies were negative</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>One small study was positive. A larger clinical trial is underway in Europe</td>
</tr>
<tr>
<td>Remote ischemic conditioning</td>
<td>One sizable study suggests benefits on salvage and change in function. Its benefit on protecting myocardium during cardiac surgery has been mixed</td>
</tr>
<tr>
<td>PKC isoforms</td>
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</tr>
<tr>
<td>Adenosine</td>
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</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td>Intracoronary may be superior to intravenous for myocardial salvage; abciximab was superior to eptifibatide; early abciximab reduced transmurality of infarction; in a recent large study abciximab reduced infarct size by MRI vs control, whereas thrombectomy was ineffective. A large study did not show reduced infarct size with intracoronary vs intravenous abciximab but did show less new heart failure</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>600-mg loading dose superior to 300-mg dose for reducing infarct size in patients undergoing primary PCI</td>
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<tr>
<td>Tirofiban</td>
<td>In a small study tirofiban improved TIMI flow and blush grades but not infarct size. In a larger trial prehospital tirofiban did reduce infarct size in diabetic patients compared to placebo</td>
</tr>
<tr>
<td>Mechanical cardioprotection</td>
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<tr>
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</tr>
<tr>
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<td>IV cooling</td>
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</tr>
<tr>
<td>Other older and new pharmacological agents</td>
<td></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Mixed results of smaller studies. Large REVEAL study showed no reduction of infarct size and several other recent trials were negative for infarct size reduction.</td>
</tr>
<tr>
<td>Glucose–insulin–potassium</td>
<td>Recent large IMMEDIATE trial assessed 12 h GIK infusion started out-of-hospital. No decrease in progression to enzymatic evidence of infarction. Composite of cardiac arrest and in-hospital mortality lower in GIK group</td>
</tr>
<tr>
<td>Statins</td>
<td>Acute high dose statin before PCI did not reduce infarct compared to low dose; prior statin exposure in patients with non-STEMI did reduce infarct size</td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
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<td>FX06 (fibrin-derived peptide)</td>
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<td>Iron chelation</td>
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<tr>
<td>Ranolazine</td>
<td>Reduced enzymatic measures of cardiac necrosis associated with elective PCI</td>
</tr>
</tbody>
</table>

AMISTAD indicates Acute Myocardial Infarction Study of Adenosine; GIK, glucose–insulin–potassium; IMMEDIATE, Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care; MI, myocardial infarction; PCI, percutaneous coronary intervention; PKC, protein kinase C; STEMI, ST-segment–elevation MI; TIMI, thrombolysis in myocardial infarction; and REVEAL, Reduction of Infarct Expansion and Ventricular Remodeling with Erythropoietin After Large MI.

Endogenous cardioprotection as first described by Murry et al84 as preconditioning has been a reliable and reproducible technique to reduce myocardial infarct size in a host of animal models. Unfortunately, this approach does not work well as a therapy for patients with acute STEMI because the timing of onset of myocardial infarcts is unpredictable and the preconditioning stimulus would need to be applied before the acute coronary occlusion. However, postconditioning can easily be applied in the catheterization laboratory by reinflating and the deflating a coronary angioplasty balloon after deployment of a stent. However, in our hands postconditioning does not reliably reduce infarct size in several animal models. Yet, some clinical trials that used this approach were positive, as discussed above, while others were negative.

The concept that antiplatelet agents may have cardioprotective effects that are pleiotropic in nature is intriguing.
This observation might account for a host of negative trials, whereby the benefit of antiplatelet therapy masks the benefit of other agents. Certainly, a surprise to this author was the number of very recent articles in the literature suggesting that a number of antiplatelet agents, such as abciximab, reduced myocardial infarct size in patients. Whether these antiplatelet agents reduced infarct size by a true antiplatelet effect (keeping the infarct artery patent, preventing platelet emboli) or by stimulating postconditioning pathways or some other pleiotropic effect, remains to be determined.

Another therapy that has consistently reduced experimental myocardial infarct size in our hands is hypothermia. Cooling the myocardium to 32°C to 34°C reduces infarct size; however, therapy must be initiated during ischemia to work. 

Administration of hypothermia at reperfusion or after reperfusion did not reduce myocardial infarct size, but did reduce no-reflow. The concept of hypothermia has been taken hold in the resuscitation literature, but larger studies are needed in the acute MI realm using newer devices, such as cooling suits that rapidly cool core temperature, and can be applied in the ambulance.

The review of this very recent literature also suggests that certain agents do not reduce myocardial infarct size when subjected to large multicenter studies, and perhaps further pursuit of an effect in these agents should be dropped: protein kinase C δ inhibitor, erythropoietin, IABC, and iron chelation are examples.

Finally, review of this literature suggests that there are some promising novel agents on the horizon: certain antidiabetic drugs, such as exenatide, FX06, and ranolazine, are worthy of further studies.

Conclusions

Just in the past 3 years, there have been a plethora of clinical studies showing that some adjunctive agents are capable of further reducing myocardial infarct size on top of reperfusion. These findings have raised new optimism for the concept of further improving outcomes in patients with MI. Ongoing experimental studies from single and multicenters will help feed the pipeline for hopeful candidate drugs to be used as adjunctive therapy in STEMI.

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References


Current State of Clinical Translation of Cardioprotective Agents for Acute Myocardial Infarction

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