Published in final edited form as:
Circulation. 2011 September 6; 124(10): 1172–1179. doi:10.1161/CIRCULATIONAHA.111.032698.

New Horizons in Cardioprotection Recommendations From the 2010 National Heart, Lung, and Blood Institute Workshop

Lisa Schwartz Longacre, PhD[*], **Robert A. Kloner, MD, PhD**[*,†], **Andrew E. Arai, MD**, **Christopher P. Baines, PhD**, **Roberto Bolli, MD**, **Eugene Braunwald, MD**, **James Downey, PhD**, **Raymond J. Gibbons, MD**, **Roberta A. Gottlieb, MD**, **Gerd Heusch, MD, PhD**, **Robert B. Jennings, MD**, **David J. Lefer, PhD**, **Robert M. Mentzer, MD**, **Elizabeth Murphy, PhD**, **Michel Ovize, MD, PhD**, **Peipei Ping, PhD**, **Karin Przyklenk, PhD**, **Michael N. Sack, MD, PhD**, **Richard S. Vander Heide, MD, PhD**, **Jakob Vinten-Johansen, PhD**, and **Derek M. Yellon, DSc, PhD**

National Heart, Lung, and Blood Institute, Division of Cardiovascular Sciences (L.S.L.) and Division of Intramural Research (A.E.A., E.M., M.N.S.), Bethesda, MD; Good Samaritan Hospital, Los Angeles, CA (R.A.K.); Keck School of Medicine, University of Southern California, Los Angeles (R.A.K.); University of Missouri, Columbia (C.P.B.); University of Louisville, Louisville, KY (R.B.); Harvard University, Boston, MA (E.B.); University of South Alabama, Mobile (J.D.); Mayo Clinic, Rochester, MN (R.J.G.); San Diego State University, San Diego, CA (R.A.G., R.M.M.); University of Essen Medical School, Essen, Germany (G.H.); Duke University, Durham, NC (R.B.J.); Emory University, Atlanta, GA (D.J.L., J.V.-J.); Wayne State University, Detroit, MI (R.M.M., K.P.); University and Hospices Civils of Lyon, Lyon, France (M.O.); University of California, Los Angeles (P.P.); Louisiana State University, New Orleans (R.S.V.H.); and University College London, London, UK (D.M.Y.).

Keywords

cardioprotection; heart; ischemia; myocardial infarction; reperfusion injury

Coronary heart disease is the largest major killer of American men and women and accounted for 1 of every 6 deaths in the United States in 2007.[1] The annual incidence of myocardial infarction in the United States is estimated to be 935 000, with 610 000 new cases and 325 000 recurrent attacks. Survivors have a much higher chance of suffering from congestive heart failure, arrhythmias, and sudden cardiac death.

Prognosis after an acute myocardial ischemic injury is primarily dependent on the amount of myocardium that undergoes irreversible injury.[2–4] Large transmural infarcts yield a higher probability of cardiogenic shock, arrhythmias, adverse remodeling, and development of late chronic heart failure. Although it has been known since the early 1970s that the size of a myocardial infarction can be modified by various therapeutic interventions,[5] early coronary artery reperfusion by fibrinolysis or percutaneous coronary intervention, including balloon angioplasty with or without stenting, remains the only established intervention capable of consistently reducing infarct size in humans. Although reperfusion has led to significant advances in patient care and reduction in hospital mortality, delays in seeking medical

Correspondence to Lisa Schwartz Longacre, PhD, Heart Failure and Arrhythmia Branch, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, 6701 Rockledge Dr, Rockledge Centre II, MSC 7956, Room 8166, Bethesda, MD 20892-7956. schwartzlongal@nhlbi.nih.gov.

[*]Drs Schwartz Longacre and Kloner contributed equally to this work.

[†]Dr Kloner served as Chair of the Workshop.

attention and inherent limitations in initiating fibrinolysis or percutaneous coronary intervention dictate that additional substantive improvements in morbidity and mortality can be achieved only with the development of new adjunctive therapies coupled with reperfusion. In addition, reperfusion therapy itself may induce reperfusion injury, a phenomenon that may encompass stunned myocardium, no-reflow phenomenon, and lethal myocardial cell death. If this injury could be prevented or minimized by administration of adjunctive therapy, then the net benefit of reperfusion could be enhanced.

The problem of acute ischemic injury and myocardial infarction is not limited to patients with acute coronary artery syndrome. It remains a major problem in cardiac surgery as well. It is well documented that the incidence of myocardial necrosis after surgery, as determined by creatine kinase MB enzyme release and troponin levels, ranges somewhere between 40% and 60%, and, depending on its clinical definition, the incidence of myocardial infarction after coronary artery bypass graft surgery may be as high as 19%. The intermediate and long-term implications are considerable. In a recent retrospective analysis of 18 908 patients who underwent coronary artery bypass graft surgery and in whom long-term follow-up was available, it was shown that myocardial enzyme elevation within the first 24 hours of surgery was associated with increasing mortality over the course of months to years. This study confirms earlier reports that even small enzyme elevations after surgery are associated with worse long-term outcomes.[4]

Goals of the Workshop

To expedite progress in cardioprotection against ischemia/reperfusion injury and facilitate translation of promising therapies from preclinical to clinical use, the National Heart, Lung, and Blood Institute (NHLBI) within the National Institutes of Health convened an invitational workshop of leading national and international experts in fundamental, translational, and clinical science on September 20 to 21, 2010, in Rockville, MD. The objectives of the workshop were to (1) identify the highest-priority knowledge gaps and barriers that have prevented the implementation of effective clinical studies on promising cardioprotective technologies; (2) consider approaches that capitalize on current scientific opportunities; (3) focus on areas that require unique NHLBI leadership to promote progress toward translation; and (4) develop recommendations that would provide a strategy to facilitate the translation of experimentally successful cardioprotective therapies developed in basic science studies to patients at risk for acute ischemic myocardial damage. The recommendations generated would be used to guide informed decisions on research priorities and directions in the field of myocardial protection against ischemia/reperfusion injury. Detailed summaries of individual presentations will be published in a focused issue of the Journal of Cardiovascular Pharmacology and Therapeutics. The present article focuses on the gaps in knowledge identified at the workshop and presents the recommendations for clinical and basic studies provided by the workshop participants.

Progress Since the 2003 National Heart, Lung, and Blood Institute Working Group

The workshop was focused on progress made since the 2003 NHLBI Working Group convened on this topic entitled, “Translation of Therapies for Protecting the Heart From Ischemia.”[6] Consistent with the recommendations of the 2003 Working Group was the recent NHBLI support of a multicenter Consortium for Preclinical Assessment of Cardioprotective Therapies (CAESAR) to perform systematic preclinical testing of cardioprotective therapies with the use of standardized and randomized protocols in multiple species, performed by blinded investigators, and analyzed by blinded data analysis cores and a single statistical core, as is done for randomized, multicenter clinical trials. Furthermore,

the consortium offers unique opportunities for productive collaborations with industrial partners who, along with investigators in academia, will have the opportunity to propose therapies for testing in the consortium. The workshop participants expressed enthusiasm for the potential of this consortium as a means to move the field of cardioprotection forward and identify therapies that are truly efficacious in more than 1 animal model of human disease and more than 1 laboratory.

Another key recommendation from the 2003 Working Group was a need for further studies to test the clinical benefit of adenosine. Since 2003, the final results of the Acute Myocardial Infarction Study of Adenosine (AMISTAD) 2 have been reported.[7] In this study, >2100 ST-segment elevation myocardial infarction patients receiving reperfusion therapy were randomized to a 3-hour infusion of either intravenous adenosine (50 or 70 μg/kg per minute) or placebo. There was no difference in the primary end point (congestive heart failure or death within 6 months) between placebo and adenosine. In a prospective substudy, the median infarct size assessed by single photon emission computed tomography (SPECT) was 27% of the left ventricle for the placebo group; it was 11% in the 70-μg/kg per minute adenosine group (P=0.023) and 23% in the 50-μg/kg per minute (P=NS) group. The reduction of infarct size at the higher dose of adenosine confirmed the previous AMISTAD 1 study.[8] The authors of AMISTAD 2 stated that “a likely explanation for failure for the trial to demonstrate a clinical benefit was that it was underpowered, since sample size calculation was based on a reduction of events in the pooled adenosine group by 25%. The reduction observed was only 11%.”[7] In a subsequent analysis of patients reperfused in a timely fashion, adenosine therapy was associated with lower rates of death compared with placebo.[9]

The participants acknowledged promising small clinical trials that suggested the benefit of certain agents and mechanical interventions, sometimes within specific subpopulations, including postconditioning,[10] cyclosporine,[11] remote conditioning,[12] hypothermia,[13] hyperoxemia,[14] and others. The present workshop participants strongly supported clinical trials of new and potentially selective adenosine receptor agonists in addition to adenosine.

The workshop focused on prevention of injury associated with acute myocardial infarction and reperfusion and did not address regeneration of the myocardium. Thus, the use of stem cells even as combination adjunctive therapies with other agents was considered to be beyond the purview of the discussions, although the participants suggested that this could be a future consideration.

Current State of Knowledge

Although a host of adjunctive therapies have failed, recently published clinical trials utilizing conditioning techniques have shown progress with positive benefit on myocardial salvage.[10–12] In addition, basic science studies of cardioprotection have provided important knowledge that has improved our understanding of the physiology, pathology, and molecular biology of myocardial ischemia/reperfusion injury and furthered our understanding of the mechanisms of action of cardioprotective agents. Table 1 lists several of the major trials testing cardioprotective strategies published since the 2003 NHLBI Working Group convened on this topic.[7,10,15–24] Although several of these studies have been negative, others have shown evidence that adjunctive therapy can salvage ischemic myocardium in the clinical setting. There have been significant advances in understanding the biochemical and molecular mechanisms involved in conditioning that have been derived from basic science studies, as summarized in Table 2. From these investigations, new pharmacological agents may be developed that mimic the benefits of conditioning without needing to induce the brief ischemic episodes of conditioning.

Identification of High-Priority Knowledge Gaps

The workshop participants reviewed the current state of knowledge about the mechanisms that provide protection against myocardial ischemia/reperfusion injury and noted key areas for future development. Their aim was to provide basic science understanding as well as to facilitate or enhance translation of cardioprotective strategies to the bedside.

How and When Myocytes Die During Ischemia and Reperfusion

Myocardium exposed to a shorter period of ischemia is still viable but is reversibly injured and can be salvaged by reperfusion alone. With a sufficiently sustained period of severe ischemia, myocardium has the potential to become irreversibly injured and cannot be salvaged by restoration of flow alone. On reperfusion, some of this tissue rapidly undergoes contraction band necrosis and is subsequently replaced by fibrous tissue. The changes that lead to the development of the state of irreversible injury are not fully understood. In 2003, Zhao et al[25] were the first to recognize that treatment of hearts with intermittent periods of ischemia, an intervention called postconditioning, is capable of salvaging myocardium previously made ischemic; these findings supported the concept of a reperfusion-induced component of lethal tissue injury. Postconditioning has been shown to be effective only when applied within the first minute of reperfusion,[26] and there is evidence that its protection may be limited to mild or moderate injury.[27] In contrast, a study by Manintveld at al[28] suggests that postconditioning is deleterious when the duration of ischemia is short and that higher benefit is expected when occlusion is prolonged.

Mitochondria have been identified as a common end effector of conditioning.[29] Specifically, the mitochondrial permeability transition pore has emerged as having an important role in cell death during reperfusion and may be inhibited by preconditioning[30] and postconditioning,[31] although details of the structure and function of the pore are not fully understood.[32] The pore may also participate in apoptotic cell death and may play a physiological role in autophagy.[33]

Uncertainty that exists regarding the magnitude, time course, and nature of lethal reperfusion injury and how it can be modulated represents an important gap of knowledge that may hinder the appropriate design of clinical trials.

No-Reflow Phenomenon: Maintaining Vascular Integrity as a Therapeutic Target

Capillary endothelium swells markedly in the center of an ischemic focus and may impede reflow to the area when reperfusion therapy is applied. In this situation, the phenomenon of no-reflow occurs, and the tissue remains permanently ischemic. Large areas of no-reflow may result in more infarct expansion and adverse left ventricular remodeling in both experimental and clinical studies.[34] Recent clinical studies have shown no-reflow to be an independent risk factor for poor prognosis for any infarct size.[35] The mechanism of this phenomenon and its potential long-term impact represent a key knowledge gap.

Understanding the Molecular Mechanisms Involved in Conditioning Strategies

The effectiveness of preconditioning,[36] postconditioning,[25] remote preconditioning,[37] and perconditioning[38] (the conditioning protocol of brief episodes of ischemia/reperfusion in a remote organ concurrent with the prolonged ischemic event in the target organ) to salvage additional myocardium when combined with reperfusion has been demonstrated in a variety of animal models of ischemia/reperfusion injury. Many molecular and biochemical pathways responsible for the actions of preconditioning have been elucidated[39–42] and have provided targets for pharmacological interventions and therapeutic strategies.[29] The molecular and subcellular mechanisms responsible for postconditioning, remote

conditioning, and perconditioning are less well defined. Optimization of all conditioning strategies could benefit from integration of genomic, metabolomic, and proteomic information together with data denoting phenotypic function to elevate this understanding to the level of systems medicine. There is also a need to determine whether the protective mechanism triggered by remote conditioning is humoral, neural, or both. If it is humoral, then the substance or substances responsible for the benefit need to be defined so that therapies can be developed on the basis of the mechanism. Elucidation of these mechanisms would not only provide additional therapeutic targets but may enable optimization of therapeutic benefit through combined therapies.

Comorbidities and Other Factors That May Influence the Ability to Protect Ischemic/Reperfused Myocardium

Age, obesity, and diabetes mellitus may attenuate the beneficial effects of cardioprotective strategies such as ischemic or pharmacological preconditioning.[43–46] There may also be gender differences in mechanisms of cardioprotection.[47] The impact of concurrent medications on therapeutic strategies can also confound interpretation of the results of clinical trials. The mechanisms by which comorbidities and other factors (eg, medications, gender) can interfere with cardioprotective strategies, as well as development of maneuvers to overcome this interference, remain important knowledge gaps.

Preclinical Studies

There is a wealth of preclinical data supporting a large number of drugs and interventions that have been reported to limit infarct size in animals. Some have been tested only in isolated hearts or cells, whereas others have been studied extensively in an in vivo model with supporting dose and schedule information. The workshop participants identified key criteria that define the minimum requirements for progression from preclinical studies to testing for therapeutic benefit in clinical studies. These include safety, availability of pharmaceutical-grade agent or technique, efficacy as verified in multiple species from multiple laboratories and confirmed in vivo and in large-animal models, and robustness of response. Preclinical studies should be conducted in a randomized, blinded fashion when possible, data should be obtained in acceptable models and reproduced from one laboratory to another and across species, and the effectiveness of treatments should be verified in models of comorbidities.

Clinical Trials

Preconditioning[36] is a powerful maneuver to reduce infarct size in experimental models, but its clinical application is limited to situations in which therapy is administered in advance of a scheduled ischemic event, such as cardiac surgery, planned angioplasty, and organ preservation protocols. Preconditioning is not really practical for treating acute myocardial infarction in patients, an event that is not predictable. However, recent small clinical trials have suggested that other types of conditioning may limit myocardial infarct size in humans, including postconditioning by brief angioplasty balloon reinflations and deflations after placement of an intracoronary stent,[10] pharmacological postconditioning with cyclosporine,[11] and remote perconditioning with brachial cuff inflations and deflations begun in the ambulance.[12] There is a need to develop additional pharmacological strategies that mimic, synergize, or augment the protection exerted by conditioning protocols in conjunction with reperfusion. Moreover, the encouraging results of these recent clinical conditioning trials should be tempered by the fact that in general they were small and should be confirmed in larger trials.

Assessment of the effect of potentially confounding factors, such as diabetes mellitus, age, and concomitant medicine (such as the oral antidiabetic agents that block the protective

K_{ATP} channels), might help to optimize the efficiency of protective interventions in subpopulations of poor responders or nonresponders and aid in the design of future studies that seek to examine protective interventions against lethal reperfusion injury. Clinical situations in which cardioprotective strategies can be effective, including understanding the role of gender, age, comorbidities, and comedications on infarct size, remain a critical knowledge gap.

Tools to Assess Clinical Efficacy of Cardioprotective Strategies

Demonstration of an incremental treatment benefit with reperfusion therapy in acute myocardial infarction is a challenge that requires superior imaging resolution to assess both the infarct and the risk region. Infarct size in patients is highly variable and reflects known variability in confounding factors including myocardium at risk, time to reperfusion, and amount of residual flow to the infarct zone through collaterals or intermittent antegrade flow. Whenever possible, the size of the ischemic zone should be measured and used to stratify the risk in these patients. Sophistication in the measurement of risk zone over the past 10 years has markedly increased, but questions remain concerning the timing and how best to measure myocardial area at risk in patients with myocardial ischemia, whether by coronary angiography, ventriculography, technetium-99m sestamibi SPECT myocardial perfusion imaging, or magnetic resonance imaging (MRI).

MRI offers a new and intriguing alternative to SPECT with regard to imaging myocardial infarct size, area at risk, and myocardial salvage. Infarct size is often assessed by cardiac enzyme release or imaging modalities, such as MRI and SPECT.[48–52] Myocardial perfusion imaging with technetium-99m sestamibi has been well validated as a technique for measurement of infarct size.[49,50] There is a close association between infarct size determined by SPECT sestamibi and left ventricular function, fibrosis in human hearts, subsequent patient mortality, and response of abnormal segments to revascularization.[53,54] Multiple single-center studies have employed paired imaging to measure both the myocardium at risk for infarction and infarct size. Limitations of SPECT include the intrinsic resolution of SPECT images, the logistical difficulty of performing paired imaging to measure myocardium at risk, the small absolute benefit from ancillary therapy in patients receiving successful reperfusion therapy with either fibrinolytic therapy or percutaneous coronary intervention, the potential confounding effect of late myocardial recovery, and the inability to distinguish poor blood flow from fibrosis. Infarct imaging by MRI, with the use of delayed contrast-enhanced imaging with a paramagnetic contrast agent such as gadolinium, has been validated in both animal and clinical studies. The higher-resolution images obtained with the use of cardiac MRI make MRI the first clinically available tool able to resolve the transmural extent of infarction.[48,51] When the classic wavefront theory describing the progression from subendocardial to transmural infarction is considered,[55,56] gadolinium-enhanced MRI is an excellent tool for determining the transmural extent of infarction. A multicenter, multivendor study showed that gadolinium-enhanced MRI is feasible, sensitive, specific, and accurate for detecting acute and chronic myocardial infarction.[57]

More recent developments in T2-weighted MRI and other methods suggest that MRI can detect the area at risk on the basis of regional myocardial edema.[58] However, there may be some unresolved technical issues with this approach,[59] and there is a theoretical concern that some cardioprotective therapies might limit reperfusion-induced edema, resulting in a falsely attenuated risk zone that could lead to an underestimation of myocardial salvage. MRI has the convenience that area at risk and infarct size can be measured in a single examination ≈2 to 7 days after acute myocardial infarction.[58,60] T2-weighted MRI has been validated in humans and compared well with SPECT and invasive angiographic measures of area at risk.[60–62] T2-weighted MRI has been used successfully in a clinical trial for detecting

myocardial salvage with hypothermia protection,[63] but there are relatively few such studies to date.

Summary of Recommendations to the Institute

The participants recommended 4 basic science priorities and 1 comprehensive clinical science strategy that address these knowledge gaps and were identified as key to establishing progress toward improved fundamental understanding of ischemia/reperfusion injury and clinical implementation of cardioprotective therapies. Formal recommendations from this workshop for use in planning and prioritization in concert with the NHLBI mission are summarized as follows (order of presentation does not imply relative priority or recommended sequence):

Basic Science Priorities

- Define effective cardioprotective interventions and the appropriate timing of their administration.
    1. Define interventions that are efficacious at different time windows of the ischemia/reperfusion injury sequence. Clarify the biology and time course of reperfusion injury, especially in large-animal models, and establish how the determinants of ischemic injury, including the duration and severity of the ischemic episode, affect reperfusion injury.
    2. Determine whether microvascular and capillary structure and function can be preserved to prevent or reduce the no-reflow phenomenon, and, if so, identify the long-term effects.
    3. Identify the mechanisms of anti-ischemia/reperfusion injury therapies, including remote preconditioning, preconditioning, perconditioning, postconditioning, and hypothermia.
    4. Evaluate the effectiveness of combination therapies compared with single therapies and determine the optimal timing of administration of the components of combination therapy.
- Establish the identity, physiological function, and regulatory mechanism of the mitochondrial permeability transition pore, implicated as a central mediator of cell death during reperfusion, and define its overall relationship between mitochondrial integrity and ischemia/reperfusion injury.
- Identify molecular markers and/or biomarkers that indicate the presence of a cardioprotected state, indicate responsiveness to a protective agent, or indicate susceptibility to either injury or therapy. Identification of a predictive marker of success may include assessment of tissue by genomics, proteomics, metabolomics, or molecular imaging.
- Evaluate the impact and mechanisms of impact of comorbidities (ie, age, gender, diabetes mellitus, hypertension, dyslipidemia, atherosclerosis) and comedications (ie, statins, angiotensin-converting enzyme inhibitors, aspirin, clopidogrel) on cardioprotection. Develop therapeutic strategies to overcome or supersede the adverse effects of these comorbidities and comedications on enhancing protection.

Clinical Science Strategy

Establish a cardioprotective clinical trial network concurrent with the existing and complementary preclinical network (CAESAR) to test promising cardioprotective agents and strategies in patients in the setting of both acute myocardial infarction and cardiac

surgery. This would both enhance the likelihood of a successful clinical trial and validate the use of animal models for therapy development with the aim of improving outcomes for cardiovascular patients. Advantages of a clinical research network include the opportunity to conduct in a multicenter format important proof-of-concept studies not likely to be pursued by industry, the opportunity to foster and maintain collaboration between member laboratories, an accelerated pace of protocol development through an established infrastructure, reduced operational costs, streamlined training of personnel, and broad recruitment and consideration of protocols through an independent steering committee.

- Because large areas of ischemia are more likely to show beneficial or deleterious effects, utilize well-defined patient populations that include large infarcts (eg, anterior infarcts), successfully reperfused in a timely manner, without complicating features such as previous Q-wave myocardial infarctions.
- Initially conduct Phase II trials with end points of infarct size reduction assessed by nuclear SPECT imaging or MRI as well as enzymatic measures, potentially including Phase III trials as appropriate.
- Include a surgical arm that provides the advantage of pretreatment and determination of the optimal timing of administration of agents (before, during, or after the procedure). The current existence of the Cardiothoracic Surgical Trials Network, supported by the NHLBI, could facilitate this arm of a cardioprotection network through collaboration and shared or consolidated resources.
- Incorporate comparison of MRI and SPECT imaging at centers with these capabilities.
- Include a data coordinating center component and core laboratories to validate study sites for accuracy of imaging.
- Include a preclinical component to characterize biomarkers, delineate mechanisms, and optimize therapeutic agents and protocols. The concurrent and complementary NHLBI consortium CAESAR could be a useful resource for this optimization.
- Candidates for clinical trials might include those who have already been shown to have efficacy in multiple preclinical laboratories, especially in large-animal models, or in smaller clinical trials (ie, cyclosporine, remote conditioning, postconditioning, perconditioning, preconditioning, hypothermia, new sodium-hydrogen exchange inhibitors, and possibly adenosine or adenosine agonists) and combinational therapies (cocktails). The concept of starting with multiple interventions simultaneously might be considered as a best first step to show that reducing infarct size is feasible, with subsequent studies to isolate which portion or portions of the cocktail are active. Workshop participants also expressed interest in newer agents that could be candidates for further testing (eg, ivabradine,[64] chloramphenicol,[65] and glucagon-like peptide[66]). To select therapies that are reproducibly effective at the preclinical level, the clinical trial network could consider interventions recommended by CAESAR.

International Cooperation

The participants appreciate that there is substantial work in the field of cardioprotection in other countries[67,68] and recognize the value of joint efforts in this area. They suggest that there be continued dialogue with groups outside the United States and consideration of future collaborative trials.

Acknowledgments

Additional NHLBI staff participants included Dr Jerome Fleg, Dr Isabella Liang, and Lynn Rundhaugen. We thank Karen Schwartz, Christy Ezell, Kathleen Smith, and Ashley Lewis for their assistance in organizing the meeting.

Sources of Funding This study was supported by the Division of Cardiovascular Sciences, NHLBI, National Institutes of Health.

Disclosures Dr Schwartz Longacre is an employee of National Institutes of Health; Dr Kloner receives research support (>$10K) and honoraria (>$10K) from Gilead (formerly CV Therapeutics), receives research support from Stealth (>$10K), and consulted with Gilead and Stealth; Dr Arai is an employee of National Institutes of Health and receives research support through a US government Cooperative Research and Development Agreement with Siemens (>$10K); Dr Baines receives research support from National Institutes of Health (>$10K) and the American Heart Association (>$10K); Dr Bolli receives National Institutes of Health research support for CAESAR (U24 HL094373), which is a consortium to study cardioprotective therapies (>$10K); Dr Braunwald reports no disclosures; Dr Downey receives research support from National Institutes of Health (>$10K; R01 HL020648); Dr Gibbons receives research support from Ikaria (>$10K); Dr Gottlieb receives research support from National Institutes of Health (R01 HL060590, R01 HL092136, R01 AG033283, and P01 HL085577) (>$10K), receives honoraria for various academic visiting professorships (<$10K), and is a cofounder of Radical Therapeutix, Inc (> $10K invested); Dr Heusch receives research support from the German Research Foundation (>$10K) and honoraria for educational lectures (<$10K) and speakers bureau payments (<$10K) for Servier; Dr Jennings reports no disclosures; Dr Lefer receives research support from National Institutes of Health on nitrate-mediated cardioprotection and H_2Smediated cardioprotection (>$10K); Dr Mentzer receives research support from National Institutes of Health for studies on autophagy, adenosine, and pyruvate protection during heart surgery (>$10K) and is a scientific advisor to the Board of Radical Therapeutix; Dr Murphy is an employee of National Institutes of Health, and a family member receives research support from National Institutes of Health (>$10K) and serves on the ACADESINE advisory board (<$10K); Dr Ovize is conducting the CIRCUS study supported by a program hospitalier de recherche cinique with study treatment (iCsA) provided by NeuroVive (<$10K); Dr Ping has no disclosures; Dr Przyklenk received honoraria for invited lectures on preconditioning and remote preconditioning (> $10K); Dr Sack is an employee of National Institutes of Health; Dr Vander Heide receives research support from National Institutes of Health (>$10K; R01 HL084405 and R21 HL098786); Dr Vinten-Johansen holds 2 patents on postconditioning (<$10K) and is a consultant for Reperfusion Therapeutics, Inc (<$10K); Dr Yellon receives research support from the British Heart Foundation Program (>$10K), British Heart Foundation Project on mitochondria (>$10K), British Heart Foundation Project on Akt Signaling (>$10K), British Heart Foundation Project on Preconditioning (>$10K), and National Institute for Health Research Clinical Trial (>$10K), drugs and research support from Fibrogen (>$10K), drugs and research support from Merck Sharp & Dohme (>$10K), payments for speakers bureau appointments to Pfizer, Bristol-Myers Squibb, and Glaxo (<$10K), honoraria from Roche (<$10K), and consultations for Roche (<$10K).

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011; 123:e18–e209. [PubMed: 21160056]
2. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation. 1990; 81:1161–1172. [PubMed: 2138525]
3. Miller TD, Christian TF, Hopfenspirger MR, Hodge DO, Gersh BJ, Gibbons RJ. Infarct size after acute myocardial infarction measured by quantitative tomographic 99m Tc sestamibi imaging predicts subsequent mortality. Circulation. 1995; 92:334–341. [PubMed: 7634446]
4. Domanski MJ, Mahaffey K, Hasselblad V, Brener SJ, Smith PK, Hillis G, Engoren M, Alexander JH, Levy JH, Chaitman BR, Broderick S, Mack MJ, Pieper KS, Farkouh ME. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA. 2011; 305:585–591. [PubMed: 21304084]
5. Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J Jr, Braunwald E. Factors influencing infarct size following experimental coronary artery occlusions. Circulation. 1971; 43:67–82. [PubMed: 5540853]

6. Bolli R, Becker L, Gross G, Mentzer R Jr, Balshaw D, Lathrop DA. Myocardial protection at a crossroads: the need for translation into clinical therapy. Circ Res. 2004; 95:125–134. [PubMed: 15271864]
7. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol. 2005; 45:1775–1780. [PubMed: 15936605]
8. Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, Eisenberg PR, Bolli R, Casas AC, Molina-Viamonte V, Orlandi C, Blevins R, Gibbons RJ, Califf RM, Granger CB. 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; 34:1711–1720. [PubMed: 10577561]
9. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. Eur Heart J. 2006; 27:2400–2405. [PubMed: 16782719]
10. Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, Aupetit JF, Bonnefoy E, Finet G, Andre-Fouet X, Ovize M. Postconditioning the human heart. Circulation. 2005; 112:2143–2148. [PubMed: 16186417]
11. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, Andre-Fouet X, Revel D, Kirkorian G, Monassier JP, Derumeaux G, Ovize M. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med. 2008; 359:473–481. [PubMed: 18669426]
12. Botker HE, Kharbanda R, Schmidt MR, Bottcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sorensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. Lancet. 2010; 375:727–734. [PubMed: 20189026]
13. Hale SL, Kloner RA. Mild hypothermia as a cardioprotective approach for acute myocardial infarction: laboratory to clinical application. J Cardiovasc Pharmacol Ther. 2011; 16:131–139. [PubMed: 21149829]
14. Stone GW, Martin JL, de Boer MJ, Margheri M, Bramucci E, Blankenship JC, Metzger DC, Gibbons RJ, Lindsay BS, Weiner BH, Lansky AJ, Krucoff MW, Fahy M, Boscardin WJ. Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. Circ Cardiovasc Interv. 2009; 2:366–375. [PubMed: 20031745]
15. Fokkema ML, Vlaar PJ, Vogelzang M, Gu YL, Kampinga MA, de Smet BJ, Jessurun GA, Anthonio RL, van den Heuvel AF, Tan ES, Zijlstra F. Effect of high-dose intracoronary adenosine administration during primary percutaneous coronary intervention in acute myocardial infarction: a randomized controlled trial. Circ Cardiovasc Interv. 2009; 2:323–329. [PubMed: 20031735]
16. Kitakaze M, Asakura M, Kim J, Shintani Y, Asanuma H, Hamasaki T, Seguchi O, Myoishi M, Minamino T, Ohara T, Nagai Y, Nanto S, Watanabe K, Fukuzawa S, Hirayama A, Nakamura N, Kimura K, Fujii K, Ishihara M, Saito Y, Tomoike H, Kitamura S. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. Lancet. 2007; 370:1483–1493. [PubMed: 17964349]
17. Jang IK, Weissman NJ, Picard MH, Zile MR, Pettigrew V, Shen S, Tatsuno J, Hibberd MG, Tzivoni D, Wackers FJ. A randomized, double-blind, placebo-controlled study of the safety and efficacy of intravenous MCC-135 as an adjunct to primary percutaneous coronary intervention in patients with acute myocardial infarction: evaluation of MCC-135 for left ventricular salvage in acute myocardial infarction (EVOLVE). Am Heart J. 2008; 155(113):e111–e118.
18. Bar FW, Tzivoni D, Dirksen MT, Fernandez-Ortiz A, Heyndrickx GR, Brachmann J, Reiber JH, Avasthy N, Tatsuno J, Davies M, Hibberd MG, Krucoff MW. Results of the first clinical study of adjunctive CAldaret (MCC-135) in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: the randomized multicentre CASTEMI study. Eur Heart J. 2006; 27:2516–2523. [PubMed: 17030521]

19. Laskey WK, Yoon S, Calzada N, Ricciardi MJ. Concordant improvements in coronary flow reserve and ST-segment resolution during percutaneous coronary intervention for acute myocardial infarction: a benefit of postconditioning. Catheter Cardiovasc Interv. 2008; 72:212–220. [PubMed: 18546233]
20. Ma X, Zhang X, Li C, Luo M. Effect of postconditioning on coronary blood flow velocity and endothelial function and LV recovery after myocardial infarction. J Interv Cardiol. 2006; 19:367–375. [PubMed: 17020559]
21. Lonborg J, Holmvang L, Kelbaek H, Vejlstrup N, Jorgensen E, Helqvist S, Saunamaki K, Clemmensen P, Treiman M, Jensen JS, Engstrom T. ST-segment resolution and clinical outcome with ischemic postconditioning and comparison to magnetic resonance. Am Heart J. 2010; 160:1085–1091. [PubMed: 21146662]
22. Lincoff, AM. Protection-AMI Trial. Paper presented at: American College of Cardiology 2011 Scientific Sessions. New Orleans, LA: Apr. 2011
23. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, Jenkins JS, Baim DS, Gibbons RJ, Kuntz RE, Popma JJ, Nguyen TT, O'Neill WW. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol. 2002; 40:1928–1934. [PubMed: 12475451]
24. O'Neill, WW.; on behalf of the COOL-MI Investigators. A prospective randomized trial of mild hypothermia during PCI treatment of ST elevation MI. Paper presented at: Transcatheter Cardiovascular Therapeutics 2003. Washington, DC: Sep. 2003
25. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol. 2003; 285:H579–H588.
26. Kin H, Zhao ZQ, Sun HY, Wang NP, Corvera JS, Halkos ME, Kerendi F, Guyton RA, Vinten-Johansen J. Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. Cardiovasc Res. 2004; 62:74–85. [PubMed: 15023554]
27. Tang XL, Sato H, Tiwari S, Dawn B, Bi Q, Li Q, Shirk G, Bolli R. Cardioprotection by postconditioning in conscious rats is limited to coronary occlusions <45 min. Am J Physiol. 2006; 291:H2308–H2317.
28. Manintveld OC, Te Lintel Hekkert M, van den Bos EJ, Suurenbroek GM, Dekkers DH, Verdouw PD, Lamers JM, Duncker DJ. Cardiac effects of postconditioning depend critically on the duration of index ischemia. Am J Physiol. 2007; 292:H1551–H1560.
29. Weiss JN, Korge P, Honda HM, Ping P. Role of the mitochondrial permeability transition in myocardial disease. Circ Res. 2003; 93:292–301. [PubMed: 12933700]
30. Hausenloy DJ, Maddock HL, Baxter GF, Yellon DM. Inhibiting mitochondrial permeability transition pore opening: a new paradigm for myocardial preconditioning? Cardiovasc Res. 2002; 55:534–543. [PubMed: 12160950]
31. Argaud L, Gateau-Roesch O, Raisky O, Loufouat J, Robert D, Ovize M. Postconditioning inhibits mitochondrial permeability transition. Circulation. 2005; 111:194–197. [PubMed: 15642769]
32. Heusch G, Boengler K, Schulz R. Inhibition of mitochondrial permeability transition pore opening: the holy grail of cardioprotection. Basic Res Cardiol. 2010; 105:151–154. [PubMed: 20066536]
33. Gottlieb RA, Mentzer RM. Autophagy during cardiac stress: joys and frustrations of autophagy. Annu Rev Physiol. 2010; 72:45–59. [PubMed: 20148666]
34. Reffelmann T, Kloner RA. The no-reflow phenomenon: a basic mechanism of myocardial ischemia and reperfusion. Basic Res Cardiol. 2006; 101:359–372. [PubMed: 16915531]
35. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, Pache J, Alger P, Mehilli J, Schomig A, Kastrati A. 5-Year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol. 2010; 55:2383–2389. [PubMed: 20488311]
36. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation. 1986; 74:1124–1136. [PubMed: 3769170]
37. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation. 1993; 87:893–899. [PubMed: 7680290]

38. Schmidt MR, Smerup M, Konstantinov IE, Shimizu M, Li J, Cheung M, White PA, Kristiansen SB, Sorensen K, Dzavik V, Redington AN, Kharbanda RK. Intermittent peripheral tissue ischemia during coronary ischemia reduces myocardial infarction through a K_{ATP}-dependent mechanism: first demonstration of remote ischemic perconditioning. Am J Physiol. 2007; 292:H1883–H1890.
39. Yang X, Cohen MV, Downey JM. Mechanism of cardioprotection by early ischemic preconditioning. Cardiovasc Drugs Ther. 2010; 24:225–234. [PubMed: 20505987]
40. Heusch G, Boengler K, Schulz R. Cardioprotection: nitric oxide, protein kinases, and mitochondria. Circulation. 2008; 118:1915–1919. [PubMed: 18981312]
41. Huang C, Yitzhaki S, Perry CN, Liu W, Giricz Z, Mentzer RM Jr, Gottlieb RA. Autophagy induced by ischemic preconditioning is essential for cardioprotection. J Cardiovasc Transl Res. 2010; 3:365–373. [PubMed: 20559777]
42. Hausenloy DJ, Tsang A, Mocanu MM, Yellon DM. Ischemic preconditioning protects by activating prosurvival kinases at reperfusion. Am J Physiol. 2005; 288:H971–H976.
43. Boengler K, Schulz R, Heusch G. Loss of cardioprotection with ageing. Cardiovasc Res. 2009; 83:247–261. [PubMed: 19176601]
44. Ferdinandy P, Schulz R, Baxter GF. Interaction of cardiovascular risk factors with myocardial ischemia/reperfusion injury, preconditioning, and postconditioning. Pharmacol Rev. 2007; 59:418–458. [PubMed: 18048761]
45. Przyklenk K, Maynard M, Darling CE, Whittaker P. Aging mouse hearts are refractory to infarct size reduction with post-conditioning. J Am Coll Cardiol. 2008; 51:1393–1398. [PubMed: 18387442]
46. Przyklenk K, Maynard M, Greiner DL, Whittaker P. Cardioprotection with postconditioning: loss of efficacy in murine models of type-2 and type-1 diabetes. Antioxid Redox Signal. 2011; 14:781–790. [PubMed: 20578962]
47. Murphy E, Steenbergen C. Gender-based differences in mechanisms of protection in myocardial ischemia-reperfusion injury. Cardiovasc Res. 2007; 75:478–486. [PubMed: 17466956]
48. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000; 343:1445–1453. [PubMed: 11078769]
49. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol. 2004; 44:1533–1542. [PubMed: 15489082]
50. Miller TD, Sciagra R, Gibbons RJ. Application of technetium-99m sestamibi single photon emission computed tomography in acute myocardial infarction: measuring the efficacy of therapy. Q J Nucl Med Mol Imaging. 2010; 54:213–229. [PubMed: 20588215]
51. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999; 100:1992–2002. [PubMed: 10556226]
52. Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, Neubauer S. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. Circulation. 2004; 110:1535–1541. [PubMed: 15353496]
53. Udelson JE, Coleman PS, Metherall J, Pandian NG, Gomez AR, Griffith JL, Shea NL, Oates E, Konstam MA. Predicting recovery of severe regional ventricular dysfunction: comparison of resting scintigraphy with 201 Tl and 99m Tc-sestamibi. Circulation. 1994; 89:2552–2561. [PubMed: 8205664]
54. Maes AF, Borgers M, Flameng W, Nuyts JL, van de Werf F, Ausma JJ, Sergeant P, Mortelmans LA. Assessment of myocardial viability in chronic coronary artery disease using technetium-99m sestamibi SPECT: correlation with histologic and positron emission tomographic studies and functional follow-up. J Am Coll Cardiol. 1997; 29:62–68. [PubMed: 8996296]
55. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death, 1: myocardial infarct size vs duration of coronary occlusion in dogs. Circulation. 1977; 56:786–794. [PubMed: 912839]

56. Hillenbrand HB, Kim RJ, Parker MA, Fieno DS, Judd RM. Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. Circulation. 2000; 102:1678–1683. [PubMed: 11015347]
57. Kim RJ, Albert TS, Wible JH, Elliott MD, Allen JC, Lee JC, Parker M, Napoli A, Judd RM. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. Circulation. 2008; 117:629–637. [PubMed: 18212288]
58. Aletras AH, Tilak GS, Natanzon A, Hsu LY, Gonzalez FM, Hoyt RF Jr, Arai AE. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. Circulation. 2006; 113:1865–1870. [PubMed: 16606793]
59. Wince WB, Kim RJ. Molecular imaging: T2-weighted CMR of the area at risk: a risky business? Nat Rev Cardiol. 2010; 7:547–549. [PubMed: 20865026]
60. Carlsson M, Ubachs JF, Hedstrom E, Heiberg E, Jovinge S, Arheden H. Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography. J Am Coll Cardiol Cardiovasc Imaging. 2009; 2:569–576.
61. Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. J Am Coll Cardiol. 2008; 51:1581–1587. [PubMed: 18420102]
62. Berry C, Kellman P, Mancini C, Chen MY, Bandettini WP, Lowrey T, Hsu LY, Aletras AH, Arai AE. Magnetic resonance imaging delineates the ischemic area at risk and myocardial salvage in patients with acute myocardial infarction. Circ Cardiovasc Imaging. 2010; 3:527–535. [PubMed: 20631034]
63. Gotberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, van der Pals J, Algotsson L, Arheden H, Erlinge D. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. Circ Cardiovasc Interv. 2010; 3:400–407. [PubMed: 20736446]
64. Heusch G, Skyschally A, Gres P, van Caster P, Schilawa D, Schulz R. Improvement of regional myocardial blood flow and function and reduction of infarct size with ivabradine: protection beyond heart rate reduction. Eur Heart J. 2008; 29:2265–2275. [PubMed: 18621770]
65. Sala-Mercado JA, Wider J, Undyala VV, Jahania S, Yoo W, Mentzer RM Jr, Gottlieb RA, Przyklenk K. Profound cardioprotection with chloramphenicol succinate in the swine model of myocardial ischemia-reperfusion injury. Circulation. 2010; 122:S179–S184. [PubMed: 20837911]
66. Fields AV, Patterson B, Karnik AA, Shannon RP. Glucagon-like peptide-1 and myocardial protection: more than glycemic control. Clin Cardiol. 2009; 32:236–243. [PubMed: 19452489]
67. Ovize M, Baxter GF, Di Lisa F, Ferdinandy P, Garcia-Dorado D, Hausenloy DJ, Heusch G, Vinten-Johansen J, Yellon DM, Schulz R. Postconditioning and protection from reperfusion injury: where do we stand? Position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology. Cardiovasc Res. 2010; 87:406–423. [PubMed: 20448097]
68. Hausenloy DJ, Baxter G, Bell R, Botker HE, Davidson SM, Downey J, Heusch G, Kitakaze M, Lecour S, Mentzer R, Mocanu MM, Ovize M, Schulz R, Shannon R, Walker M, Walkinshaw G, Yellon DM. Translating novel strategies for cardioprotection: the Hatter Workshop Recommendations. Basic Res Cardiol. 2010; 105:677–686. [PubMed: 20865418]

Table 1

Clinical Trials of Infarct Size Reduction Since 2003

Agent	Effect on Infarct Size	References
Adenosine		
Infusion	Decrease (high dose)	7
Bolus	No change	15
Atrial natriuretic peptide	Decrease	16
Caldaret (intracellular calcium modulator)	No change	17, 18
Conditioning		
Postconditioning	Decrease	10, 19–21
Cyclosporine (postconditioning mimetic)	Decrease	11
Remote conditioning	Increase in salvage index	12
Delcasertib (protein kinase C-δ inhibitor)	No change	22
Hyperoxemia	Decrease	14
Hypothermia	No change (decrease in subgroup of anterior wall MIs cooled to <35°C)	23, 24
Nicorandil	No change	16

MI indicates myocardial infarction.

Table 2

Proposed Mechanisms and Promising Agents*

Preconditioning and postconditioning mimetics (block reperfusion injury)
Receptor agonists
Adenosine A_{2B} agonists: AMP579, BAY 60-6583
δ-Opioid agonists
Sphingosine
Bradykinin
Epidermal growth factor
Tumor necrosis factor
Protein kinase G activators
Phosphodiesterase type 5 inhibitors
Natriuretic peptides
Guanylyl cyclase activators: BAY 58-2667
Mitochondrial K_{ATP} channel openers: diazoxide
Protein kinase C activators
Menadione
Protein kinase C-ϵ–activating peptide
Nitric oxide donors
S-Nitroso-*N*-acetylpenicillamine
Mitochondria-targeted *S*-nitrosothiol
Nitrates
Mitochondrial permeability transition pore inhibitors
Cyclosporine A
Glycogen synthase kinase-3*β* inhibitors
Poorly understood pathway activators
Desferoxamine
Statins
Mineralocorticoid inhibitors
Interventions that block ischemic injury (can be added to the above)
Mild hypothermia
Sodium-hydrogen exchange blockers
Protein phosphatase 2A inhibitors
Other (mechanism uncertain)
Adenosine infusion
Autophagy promoters such as chloramphenicol succinate
Ivabradine
Ranolazine
AMP kinase activators

* Table 2 contributed by Dr James Downey.