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. 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. 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, 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 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.

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.”7 Consistent with the recommendations of the 2003 Working Group was the recent NHLBI 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. 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, and there is evidence that its protection may be limited to mild or moderate injury. In contrast, a study by Manintveld at al. 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. Specifically, the mitochondrial permeability transition pore has emerged as having an important role in cell death during reperfusion and may be inhibited by preconditioning and postconditioning mimetics, although details of the structure and function of the pore are not fully understood. The pore may also participate in apoptotic cell death and may play a physiological role in autophagy.

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. Recent clinical studies have shown no-reflow to be an independent risk factor for poor prognosis for any infarct size. The mechanism of this

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### Table 1. Clinical Trials of Infarct Size Reduction Since 2003

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

MI indicates myocardial infarction.

### Table 2. Proposed Mechanisms and Promising Agents*

| Preconditioning and postconditioning mimetics (block reperfusion injury) |
|-----------------------------|--------------------------|--------------------------|
| Receptor agonists           |                          |                          |
| Adenosine A2B 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<sub>ATP</sub> 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-3β 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.
phenomenon and its potential long-term impact represent a key knowledge gap.

Understanding the Molecular Mechanisms Involved in Conditioning Strategies
The effectiveness of preconditioning, postconditioning, remote preconditioning, and perconditioning (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 and have provided targets for pharmacological interventions and therapeutic strategies. 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. There may also be gender differences in mechanisms of cardioprotection. 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 (e.g., 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 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 re inflations and deflations after placement of an intracoronary stent, pharmacological postconditioning with cyclosporine, and remote perconditioning with brachial cuff inflations and deflations begun in the ambulance. 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 medications 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. Myocardial perfusion imaging with technetium-99m sestamibi has been well validated as a technique for measurement of infarct size. 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. 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. When the classic wavefront theory describing the progression from subendocardial to transmural infarction is considered, 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.

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. However, there may be some unresolved technical issues with this approach, 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. T2-weighted MRI has been validated in humans and compared well with SPECT and invasive angiographic measures of area at risk. T2-weighted MRI has been used successfully in a clinical trial for detecting myocardial salvage with hypothermia protection, 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, 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, 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 peptide66). 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 countries67,68 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.

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