Pharmacological Intervention for Prevention of Left Ventricular Remodeling and Improving Prognosis in Myocardial Infarction

Hideki Ishii, MD, PhD; Tetsuya Amano, MD, PhD; Tatsuaki Matsubara, MD, PhD; Toyoaki Murohara, MD, PhD

Early reperfusion of totally occluded coronary arteries with thrombolysis and/or percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) reduces infarct size, cardiac mortality, and in-hospital events.1,2 Prompt reperfusion of epicardial blood flow reduces infarct size and mortality rates, in-hospital events, and reinfarction. Furthermore, successful reperfusion greatly affects the reduction in infarct size and left ventricular (LV) function. The reduction in infarct size and the improvement in LV ejection fraction may decrease mechanical stress on the noninfarcted myocardium, preventing LV remodeling, including changes in LV size and shape.3 Preventing LV remodeling is of key importance after AMI because it may be related to a reduction in adverse cardiac events, including exacerbation of congestive heart failure and cardiac mortality rates.4–7 Although reperfusion therapy relieves and reduces ischemia and necrosis, the process of restoring coronary blood flow causes ischemia-reperfusion injury in the ischemic myocardium, which limits the beneficial effects of reperfusion and may contribute to mortality despite successful reperfusion therapy.8,9

Reperfusion injury is triggered by cellular and mitochondrial calcium overload, oxidant stress, endothelial dysfunction, reduction in nitric oxide production, and other factors. Because reperfusion injury limits the efficacy of reperfusion therapy alone, combined use with pharmacological intervention may moderate microcirculatory impairment and clinical outcomes. Such treatments may eventually reduce infarct size and prevent ischemic LV remodeling after AMI. Furthermore, medication in the chronic phase may affect LV remodeling and clinical prognoses. We undertook a systematic review of the literature based on pharmacological reductions in infarct size and prevention of LV remodeling, both of which may be associated with improved clinical outcomes, in cases of MI. In this review, searches through MEDLINE, LILACS, and SCIELO were the sources of information. Articles were selected by their content related to the theme.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Ischemic Preconditioning and Postconditioning in AMI

Transient episodes of angina preceding AMI protect the myocardium from ischemic damage. This phenomenon is known as the preconditioning effect. Murry et al10 first reported the ischemic preconditioning phenomenon in an experimental model; it has been supported by numerous experimental cases11,12 and has been found in humans with ischemic heart disease13–19 (Table 1). Some studies showed that brief episodes of ischemia in patients with repetitive balloon inflation during PCI13,14 relieve angiina attack and ST elevation in an ECG. In cases of AMI, patients with prodromal angina seem to have reduced infarct size and better prognoses.15–19 In addition, LV remodeling is prevented after the onset of MI.18,19 Thus, preconditioning effects are now used in pharmacological adjuncts to reperfusion therapy.

Two forms of ischemic preconditioning are recognized: an early or classic preconditioning, which develops immediately after the ischemic stress and lasts for 1 to 2 hours, and delayed preconditioning or the second window, which reappears 12 to 24 hours later and lasts for 3 to 4 days.20 Although many are still unclear, various mechanisms have been identified through experimentally established signal transduction of such ischemic preconditioning effects. As the cellular pathways to preconditioning, the activation of protein kinase C is triggered by the adenosine A1 and A3 receptors, 5’-nucleotidase activity, and so on.23–27 Beyond the activation of protein kinase C, the mitochondrial and sarcocemmal adenosine triphosphate (ATP)–sensitive K channels play a key role, particularly in early preconditioning.28–32 Mitogen-activated protein kinase families, including p42/p44 mitogen-activated protein kinases, p38 kinase, and the stress-activated c-jun N-terminal kinase, are thought to be important signaling components for both forms of preconditioning.20,33 Nitric oxide induces a late preconditioning against myocardial stunning through a protein kinase C–dependent pathway.34 Early preconditioning is mediated mainly by the opening of the K-ATP channels. In the ischemic myocardium, the sarcocemmal K-ATP channels are activated by intracellular...
K-ATP channel openers help this action. Recent studies have cardioprotective effects on the ischemic heart, and inhibition and reduction of calcium inflow to myocytes may be associated with a reduction in action potential duration, which is linked to preconditioning and inhibits neutrophil adhesion to endothelium and migration into the myocardium.53

In the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial, 236 thrombolytic-treated patients were randomized to receive intravenous 3-hour adenosine infusion (70 μg · kg⁻¹ · min⁻¹) or placebo. Adenosine treatment resulted in a significant 33% relative reduction in infarct size as determined by technetium-99m sestamibi single-photon emission computed tomography imaging compared with control.42 This effect was especially marked in patients with anterior AMI. In a larger trial of intravenous infusion of adenosine as adjunctive reperfusion therapy with fibrinolysis or PCI consisting of a total of 2118 patients, intravenous 3-hour adenosine infusion at 70 μg · kg⁻¹ · min⁻¹, but not at the lower 50-μg · kg⁻¹ · min⁻¹ dose, reduced infarct size in patients with anterior AMI.43 Although reduced infarct size was reported with the intravenous infusion of adenosine, these trials were underpowered to detect efficacy in preventing major adverse cardiac events, and LV functions were not end points.

On the other hand, Marzilli et al44 found that in AMI patients treated with PCI, intracoronary administration of 4 mg adenosine in 2 mL saline into the distal bed of a totally occluded vessel prevented the no-reflow phenomenon, improved LV function a week after PCI, and improved the clinical course.

**Pharmacological Therapy Combined With Reperfusion**

The ability of pharmacological treatment to trigger preconditioning and postconditioning effects has important therapeutic implications. The translation of these effects into the clinical setting has been attempted (Table 2).42–52

How does the pharmacological preconditioning effect occur after the vessel is occluded? There are facets to this question. It is true that the coronary artery is already occluded at the time of hospital admission in patients with AMI. However, even after a sustained episode of myocardial ischemia, some parts of the cardiac myocytes are stunning or viable, ie, reversible ischemic myocardium. Therefore, preconditioning-like actions before myocardial reperfusion may be meaningful and reduce reperfusion injury. Oral or intravenous drugs can be delivered to risk areas through collateral circulation before reperfusion, and intracoronary drugs selectively injected distal to the occlusion site can be delivered directly.

In previously reported studies,21,22 the protocol of the ischemic postconditioning in AMI patients undergoing PCI was invasive. Pharmacological activation of the postconditioning pathway may be effective and safer.

**Adenosine**

Stimulating adenosine A1 and A3 receptors is known to result in ischemic preconditioning.23–25 Like other mechanisms for salutary actions, adenosine has antiinflammatory effects linked to preconditioning and inhibits neutrophil adhesion to endothelium and migration into the myocardium.53

ATP depletion and outflow of potassium increased. This is associated with a reduction in action potential duration, which is believed to reduce calcium inflow to myocytes.26 The inhibition and reduction of calcium inflow to myocytes may have cardioprotective effects on the ischemic heart, and K-ATP channel openers help this action.27 Recent studies appear to indicate that mitochondrial K-ATP channels are involved in preconditioning as an end factor of many signal transduction systems.28,29 As for the second window, it has been reported that nitric oxide plays a major role.33

On the other hand, the postconditioning effect, short-lived episodes achieved by repetitive occlusion and reperfusion in the early minutes after revascularization of AMI, reduces the size of the MI. Zhao et al34 first reported the ischemic preconditioning phenomenon in a dog model and showed that cardioprotection provided by postconditioning is as effective as that provided by preconditioning in reducing infarct size and preserving endothelial function. Recently, in the clinical setting, the beneficial effects of postconditioning have been reported to decrease infarct size and to improve wall motion score index, which is associated with better LV function, but they have been tested with relatively small sample sizes21,22 (Table 1).

Ischemic postconditioning reduces oxidant stress, reduces neutrophil activation and adhesion to coronary endothelium, decreases calcium overload, and attenuates apoptotic cardiomyocyte death, among other benefits. Some mechanisms can be explained, although they are not fully understood. Importantly, postconditioning activates the reperfusion injury salvage kinase pathway, which refers to a group of protein kinases, and inhibits mitochondrial permeability transition pore opening, as does preconditioning.37–40 Furthermore, postconditioning may decrease extracellular levels of protons and lactate and may delay washout of adenosine.41

### Table 1. Ischemic Preconditioning and Postconditioning in Patients With AMI in the Clinical Setting

<table>
<thead>
<tr>
<th>Preconditioning</th>
<th>Postconditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakagawa et al15</td>
<td>84</td>
</tr>
<tr>
<td>Ishihara et al16</td>
<td>350</td>
</tr>
<tr>
<td>Kloner et al17</td>
<td>3002</td>
</tr>
<tr>
<td>Solomon et al18</td>
<td>283</td>
</tr>
<tr>
<td>Colonna et al19</td>
<td>51</td>
</tr>
<tr>
<td>Staat et al20</td>
<td>30</td>
</tr>
<tr>
<td>Ma et al22</td>
<td>94</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombosis in Myocardial Infarction.
Nicorandil

Nicorandil is a K-ATP channel opener and, unlike other K-ATP channels openers such as diazoxide, a nitric oxide donor. Nicorandil exerts beneficial cardioprotective effects by activating the ectosolic 5'-nucleotide, mimicking ischemic preconditioning, and increasing coronary blood flow.26,54,55 Although the opening of the K-ATP channels is related to classic or first-window preconditioning, it has also been reported that nicorandil treatment upregulates the expression of cyclooxygenase-2 and Bcl-2 in MI, resulting in delayed cardioprotection similar to that afforded by the late phase of ischemic preconditioning.56

Reports indicate that intravenous nicorandil treatment ameliorates early functional and clinical problems in patients with AMI. Ito et al45 investigated whether intravenous nicorandil (6 mg for 24 hours after a 4-mg bolus injection) followed by oral administration of nicorandil would exert beneficial effects on microvascular function and clinical outcomes in a prospective, single-center study including 81 patients with a first anterior AMI who received successful PCI within 12 hours after symptom onset. Nicorandil treatment improved regional LV function, wall motion score, and regional wall motion, particularly in patients undergoing PCI <6 hours after symptom onset. However, in the Japan Working Group Studies on Acute Myocardial Infarction for the Reduction of Necrotic Damage by Nicorandil (J-WIND-KATP), a prospective, placebo-controlled, randomized, large multicenter study consisting of 545 AMI patients treated with reperfusion therapy, nicorandil administered intravenously under a protocol similar to that of the Ito et al45 study failed to reduce infarct size or reperfusion injury and had no effect on LV functions and the prevention of cardiac events in the chronic phase.46

We recently reported that an intravenous 12-mg dose of nicorandil before PCI, a dose some 3-fold higher than in the studies mentioned previously,45,46 decreased the incidence of cardiovascular events, including cardiovascular death and rehospitalization for congestive heart failure, for a long period of time (mean, 2.4 years) in 368 patients with ST-elevation AMI.47 In that study, acceleration of ST-segment resolution and
improvement in epicardial coronary flow, resulting in the prevention of reperfusion injury, were also noted. Intravenous nicorandil could prevent LV remodeling and improve chronic LV function after MI. Superior global LV functions and prevention of LV remodeling were seen in the nicorandil group than in the placebo group in the follow-up period, resulting in lower major adverse cardiac events in the late phase. In patients with diabetes or stress hyperglycemia, activation of mitochondrial K-ATP channels is impaired. Therefore, preconditioning effects are abolished in the models with hyperglycemia. A subanalysis of the previous study showed that pretreatment with intravenous nicorandil before PCI reduced major complications in both the early and late phases with much better outcomes in AMI patients with stress hyperglycemia.

Nicorandil may have dose-dependent effects on coronary artery diameters, blood flow, and other physiological parameters, as reported previously. Because the results from the studies of nicorandil mentioned above are mixed in terms of clinical outcomes, further study is needed to determine the optimal methods of administration and doses.

Nitric Oxide
Although many experimental studies showed the effectiveness of nitric oxide such as delayed preconditioning-like action, there are limited data in humans with MI. Before the PCI era, it was reported that nitroglycerin prevented LV remodeling in AMI patients.

A recent double-blind clinical trial showed that the intracoronary administration of nitroprusside (60 μg) selectively injected into the infarct-related artery distal to the occlusion improved clinical outcomes at the 6-month follow-up in AMI patients treated with primary PCI but did not improve myocardial tissue reperfusion. Further study is needed to assess the effects of nitric oxide donors in the prevention of reperfusion injury and LV remodeling and improved clinical outcomes.

Atrial Natriuretic Peptide and Brain Natriuretic Peptide
Atrial natriuretic peptide (ANP), a member of natriuretic peptide family, exerts various biological effects by acting on the receptor-guanylyl cyclase and the elevation of intracellular cGMP. ANP was first identified as a diuretic/natriuretic and vasodilating hormone, but subsequent studies revealed that ANP has various cardioprotective effects such as antiapoptosis, antifibrosis, and antihypertrophy not only as circulating hormones but also as local autocrine and/or paracrine factors. ANP has been reported to accelerate nitric oxide generation, which mediates late preconditioning. Furthermore, ANP activates the reperfusion injury salvage kinase, which acts like ischemic preconditioning and postconditioning. Therefore, ANP may be a pharmaceutical mimetic agent. ANP also suppresses plasma levels of aldosterone, angiotensin II, and endothelin-1, which are associated with LV remodeling. In several studies with a reperfusion model in vivo, ANP showed inhibition of the occurrence of reperfusion arrhythmia, preservation of ATP content in the ischemic myocardium, and inhibition of the neutrophil-induced endothelial cytotoxicity.

Hayashi et al found that ANP infusion prevented LV remodeling better than nitroglycerin in a prospective randomized study including 60 patients. Patients receiving reperfusion therapy with PCI for a first AMI were randomized to a 62-hour infusion of ANP (0.025 μg · kg⁻¹ · min⁻¹) or a 64-hour infusion of nitroglycerin (0.4 μg · kg⁻¹ · min⁻¹). In the ANP group, LV dilation was prevented and LV ejection fraction was improved 1 month after onset. Kasama et al reported the effects of ANP on LV remodeling and cardiac sympathetic nerve activity in patients with AMI. Fifty patients within 6 hours of a first anterior AMI were randomly assigned to receive ANP (0.025 μg · kg⁻¹ · min⁻¹) or isosorbide dinitrate (0.67 μg · kg⁻¹ · min⁻¹). ANP treatment significantly reduced the incidence of reperfusion injury (ST-segment re-elevation, reperfusion arrhythmia) compared with isosorbide dinitrate treatment. The total defect scores, determined by ²⁰¹Tl scintigraphy, were significantly lower in the ANP group than in the isosorbide dinitrate group, indicating that ANP increased the amount of salvaged myocardium after PCI and inhibited the expansion of infarct area. ANP also inhibited LV remodeling and improved LV function 2 weeks after PCI.

A larger multicenter study consisting of 569 AMI patients, the Japan Working Group Studies on Acute Myocardial Infarction for the Reduction of Necrotic Damage by ANP (J-WIND-ANP), was performed to confirm the effects of ANP. In the trial, treatment with ANP together with primary PCI reduced infarct size by 15% and improved LV ejection fraction by 5% compared with placebo. ANP also statistically reduced myocardial reperfusion and the composite end points of cardiac death and cardiac failure.

Brain natriuretic peptide is also a predominant natriuretic peptide in myocardium and has cardioprotective effects and vasodilatory effects. In the rat model, brain natriuretic peptide limits infarct size by opening the K-ATP channels. To date, there have been limited large-scale clinical trials to show the efficacy of treatment with brain natriuretic peptide in patients with AMI.

HMG-CoA Reductase Inhibitor: Statins
Recently, Bell and Yellon showed that atorvastatin administered at the onset of reperfusion attenuated lethal reperfusion injury in mouse hearts by activating the reperfusion injury salvage kinase pathway. In humans, oral pravastatin before reperfusion with PCI has been reported to reduce infarction size and to ameliorate LV function in patients with AMI.

Preoperative treatment with a statin before elective PCI is associated with lower levels of periprocedural creatine kinase elevation. In AMI cases, Iwakura et al reported that patients receiving chronic statin treatment before AMI exhibited lower incidence of the no-reflow phenomenon when assessed by intracoronary myocardial contrast echocardiography. We showed that chronic statin therapy before the onset of AMI is associated with improved epicardial perfusion and...
Pharmacological Therapy in the Chronic Phase After AMI

As is well known, the process of LV remodeling after AMI is influenced by 3 factors: modification of infarct size, infarct healing, and ventricular wall stress. In particular, ventricular stress, ie, mechanical force, is affected by both arterial blood pressure and LV end-diastolic pressure. In response to increased ventricular stress and loss of contractile elements, dilatation and hypertrophy of the noninfarcted zone continue for months or years. In these actions, activation of the renin-angiotensin system and increased norepinephrine release greatly affect LV remodeling. In addition, high blood levels of the inflammatory cytokines, which play an important role in LV remodeling, are seen after AMI. Thus, pharmacological therapy targeting these mechanisms may help to prevent LV remodeling.

Angiotensin-Converting Enzyme Inhibitors

Treatment with angiotensin-converting enzyme (ACE) inhibitors reduces both arterial pressure and LV end-diastolic pressure, ultimately resulting in reduced LV wall stress and the ensuing progressive LV enlargement. In another mechanism with beneficial effects, ACE inhibitors accumulate bradykinin, improving LV diastolic function by suppressing collagen accumulation and augmenting endothelial nitric oxide release. Numerous experimental and clinical studies have shown that ACE inhibitors favorably alter loading conditions for LV, reduce progressive LV remodeling, and improve clinical outcomes. The Survival and Ventricular Enlargement (SAVE) trial, in which approximately half of the patients enrolled did not undergo reperfusion therapy, demonstrated that the long-term administration of captopril improved survival and reduced the incidence of cardiovascular events in AMI patients with LV dysfunction (radionuclide ejection fraction ≤40%). In that study, LV function assessed by 2-dimensional transthoracic echocardiograms was significantly better in the captopril group than in the placebo group; ie, LV remodeling was prevented with long-term treatment with captopril. Many other large-scale clinical trials since the SAVE trial have demonstrated the benefits of ACE inhibitors with respect to improved LV function and clinical outcomes after AMI.

Angiotensin II Receptor Blockers

Angiotensin II receptor blockers (ARBs) block the effects of angiotensin II, particularly at the receptor subtype 1 level, which mediates vasoconstriction, sodium and water retention, cardiac hypertrophy, and cardiac fibrosis. ARBs may block angiotensin II receptors more completely than ACE inhibitors. Although ARBs improve LV function and clinical outcomes after AMI, large randomized trials have failed to demonstrate the superiority of ARBs over ACE inhibitors despite the theoretical advantage of angiotensin II antagonism in patients with AMI.

It has recently been reported that an ACE inhibitor, but not an ARB, inhibited matrix metalloproteinase-9, which induces LV remodeling after AMI. This result may affect clinical prognosis after AMI. Further study is needed.

Spironolactone

High aldosterone levels, which may induce LV remodeling, are often seen in patients with AMI. Aldosterone and mineralocorticoid receptors are believed to play major roles in the progression of LV remodeling after AMI. Hayashi et al showed that transcardiac extraction of plasma aldosterone in the acute phase had a significant correlation with plasma procollagen type III aminoterminal peptide in relation to ventricular fibrosis and had an independent and significant positive relationship with a large LV end-diastolic volume index 1 month after the onset of AMI.

Hayashi et al also demonstrated that spironolactone, a mineralocorticoid receptor antagonist, combined with ACE inhibitors ameliorated LV ejection fraction and prevented LV remodeling 1 month after the onset better than ACE inhibitors alone in a prospective randomized study including 134 anterior AMI patients. Their study also showed that spironolactone administration significantly suppressed transcardiac extraction of aldosterone and plasma levels of procollagen type III aminoterminal peptide, a biological marker of cardiac fibrosis.

Renin Inhibitors

Renin controls the first rate-limiting step of the renin-angiotensin-aldosterone system. Therefore, inhibition of renin may have salutary effects on blood pressure control and may preserve cardiac and renal functions. Renin inhibitors decreased LV end-diastolic pressure and systolic afterload in experimental models with LV failure after MI. In spontaneously hypertensive rats, renin inhibitors caused a similar decrease in LV mass compared with an ACE inhibitor or an ARB. Thus, renin inhibitors may improve LV function and clinical outcome after AMI. However, clinical data in patients with AMI are limited.

Noricandil

As mentioned, noricandil is a hybrid compound of an ATP-sensitive potassium channel opener and a nitric oxide donor. Kasama et al reported that 6 months of long-term oral noricandil therapy after PCI in patients with AMI produced results for cardiac function and LV volumes superior to those found with placebo. The J-WIND-KATP trial provided evidence for the beneficial effects of chronic administration of oral noricandil on LV function. Oral noricandil increased changes in LV ejection fraction between follow-up at 6 to 12 months and the acute phases. However, this was a posthoc analyses; therefore, prospective, larger trials are needed to confirm this finding.
**β-Blockers**

The effects of β-blocker therapy in patients with MI are well demonstrated. In the postthrombolytic era, the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study demonstrated that adding carvedilol to standard modern management for AMI patients with LV dysfunction, including ACE inhibitors, reduces the frequency of all-cause and cardiovascular mortality and recurrent nonfatal MI, although the data on preventing LV remodeling prevention are limited.109

Although the benefits of β-blocker therapy for secondary prevention are well established, attention should be paid when β-blocker therapy is attempted in Japanese patients because in the early post-MI phase, they exhibit a 3-fold greater incidence of vasospastic response to intracoronary acetylcholine in non–infarct-related arteries and infarct-related arteries than white patients. In other words, Japanese generally tend to have coronary vasospastic angina.110

**HMG-CoA Reductase Inhibitor: Statins**

In experimental models, statins may improve LV function after MI through downregulation of angiotensin II type 1 receptor and attenuation of increased matrix metalloproteinase-2 activity because these are potential mechanisms of preventing LV remodeling.111,112

Nakaya et al113 investigated whether pravastatin would exert beneficial effects on LV function in a clinical study including 34 AMI patients with successful reperfusion. Pravastatin treatment reduced serum matrix metalloproteinase-2 levels and changes in LV end-diastolic volume index between follow-up at 6 months and the acute phases. MUSASHI-AMI (Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction) and HJC (The Heart Institute of Japan-Department of Cardiology) investigators found that early administration of standard doses of HMG-CoA reductase inhibitor (HMG-CoA) in patients with acute myocardial infarction (MI) and neurohumoral factors involved offers the promise of new cardioprotective strategies confer benefits to patients with AMI beyond that provided by myocardial reperfusion therapy alone.

Because the LV remodeling process continues for months or years, pharmacological treatment in the chronic phase is also important. Identifying and understanding the mechanical and neurohumoral factors involved offers the promise of new treatments. Strategies for improving clinical outcomes after AMI are now progressing slowly but steadily.

**Disclosures**

None.

**References**


73. Bell RM, Yellon DM. Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway. *J Am Coll Cardiol*. 2003;41:508–515.


Ishii et al Pharmacological Improvement of LV Function in VF AMI 2717


Pharmacological Intervention for Prevention of Left Ventricular Remodeling and Improving Prognosis in Myocardial Infarction
Hideki Ishii, Tetsuya Amano, Tatsuaki Matsubara and Toyoaki Murohara

Circulation. 2008;118:2710-2718
doi: 10.1161/CIRCULATIONAHA.107.748772

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/25/2710

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/