Iloprost Prevents Contrast-Induced Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention

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Background—The prevention of contrast-induced nephropathy, which accounts for considerable morbidity and mortality, remains a vexing problem. Contrast-induced renal vasoconstriction is believed to play a pivotal role in the pathogenesis of contrast-induced nephropathy. The aim of this study was to examine the efficacy of the prostacyclin analog iloprost in preventing contrast-induced nephropathy in patients with renal dysfunction undergoing a coronary procedure.

Methods and Results—We conducted a randomized, double-blind, placebo-controlled trial of iloprost in 208 patients with a serum creatinine concentration \( \geq 1.4 \) mg/dL who underwent coronary angiography and/or intervention. Iloprost 1 ng \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1}\) or placebo was administered intravenously beginning 30 to 90 minutes before and ending 4 hours after the procedure. Contrast-induced nephropathy was defined by an absolute increase in serum creatinine \( \geq 0.5 \) mg/dL or a relative increase \( \geq 25\% \) measured 2 to 5 days after the procedure. Contrast-induced nephropathy occurred in 23 of the 105 patients (22\%) in the control group and in 8 of the 103 patients (8\%) in the iloprost group (odds ratio, 0.29; 95\% confidence interval, 0.12 to 0.69; \( P = 0.005 \)). In the control group, the estimated glomerular filtration rate declined from 49.7 ± 15.5 to 46.6 ± 16.6 mL \( \cdot \) min\(^{-1} \cdot \) 1.73 m\(^{-2}\) (\( P = 0.01 \)). In the iloprost group, the estimated glomerular filtration rate increased marginally from 47.5 ± 14.5 to 48.6 ± 16.1 mL \( \cdot \) min\(^{-1} \cdot \) 1.73 m\(^{-2}\) (\( P = 0.26 \)). The mean absolute estimated glomerular filtration rate decline in the control group was greater than its change in the iloprost group (difference, 4.2 mL \( \cdot \) min\(^{-1} \cdot \) 1.73 m\(^{-2}\); 95\% confidence interval, 1.1 to 7.3; \( P = 0.008 \)).

Conclusion—Prophylactic administration of iloprost may protect against contrast-induced nephropathy in high-risk patients undergoing a coronary procedure. (Circulation. 2009;120:1793-1799.)

Key Words: angiography, contrast media, iloprost, prostaglandins

The intravascular administration of iodinated contrast agents can result in traceable kidney injury. The acute decline in renal function is generally mild and transient, although some patients may experience a more prolonged decrease and, in rare cases, require temporary or permanent renal replacement therapy. The most commonly used definition of contrast-induced nephropathy (CIN) is an absolute increase in serum creatinine concentration of at least 0.5 mg/dL or a relative increase of at least 25\% from the baseline value.1 The development of this complication is associated with prolonged hospitalization, increased healthcare costs, and substantial morbidity and mortality.2-7 Unfortunately, an effective CIN prevention strategy has proved to be an elusive goal. Except for intravenous hydration, attempts to prevent CIN by the prophylactic use of various agents have generally met with failure.8,9 An increasing number of patients suffer CIN as a consequence of the ever-increasing demand for procedures involving intravascular contrast medium injections, and this continues to fuel research for an effective CIN prevention strategy.

Ischemic kidney injury caused by prolonged renal vasoconstriction instigated by contrast media is thought to have a pivotal role in the mechanism of CIN; adequate medullary blood flow is normally maintained by the interplay of vasodilator and vasoconstrictor influences, mediated by local nitric oxide, prostaglandin, adenosine, and endothelin systems within the medulla.10 Prostaglandins (PGs) E and I\(_2\) of the arachidonic acid cascade are the most important mediators of renal effects.11 Animal experiments have shown that contrast agents increase the release of PGEs but decrease the release of prostacyclin (PGI\(_2\)) from the kidney.12 Iloprost, a stable prostacyclin analog, has been shown to protect animal kidneys against ischemic and toxic insults and to significantly attenuate the effects of contrast media in the renal cortex of rats, as assessed by near-infrared reflection spectroscopy.13,14 Beraprost, a synthetic analog of prostacy-
clin, has also been shown to protect against direct tubular damage and apoptosis induced by contrast media. These findings suggest that attenuation of the renal vasodilatory action of prostacyclin may be a critical factor underlying the development of CIN.

Here, we report the results of a randomized, double-blind, placebo-controlled trial of the prostacyclin analog iloprost for the prevention of CIN in patients with renal dysfunction undergoing an invasive coronary procedure.

Methods

Patients

Consecutive patients undergoing clinically driven coronary angiography or intervention in our institution were eligible for inclusion if their serum creatinine concentration was at least 1.4 mg/dL (124 μmol/L) on their most recent sample drawn within 1 month before the planned procedure. Patients were excluded for any of the following reasons: circulatory shock for any reason, systolic blood pressure <95 mm Hg, acute renal failure or end-stage renal disease requiring dialysis, intravascular administration of contrast medium within the previous 10 days or anticipated readministration of contrast medium within the following 6 days, inability to administer study medication at least 30 minutes before the procedure, and primary intervention for acute ST-elevation infarction. The institutional research ethics committee and the National Drugs Administration approved the study protocol, and all patients gave written, informed consent before inclusion.

Study Protocol

The safety of administering intravenous iloprost in a similar patient population has been investigated in a pilot study. This study used the same methodology as the present study, and 45 patients were assigned in a 1:1:1 fashion to receive intravenous iloprost 1 or 2 ng · kg⁻¹ · min⁻¹ or placebo (saline that was identical in appearance to the study medication). This pilot study showed that the lower dose of 1 ng · kg⁻¹ · min⁻¹ was associated with a good safety profile and was well tolerated for periprocedural administration in patients with renal dysfunction undergoing a coronary procedure. Iloprost 2 ng · kg⁻¹ · min⁻¹ was not well tolerated; one third of the patients given this higher dose developed serious hypotension requiring discontinuation of the study drug. Therefore, we decided to investigate the lower dose of iloprost (1 ng · kg⁻¹ · min⁻¹) in the present study.

A research fellow not involved in the procedure was designated for the random assignment of treatment and for preparation of the study drugs. Randomization was performed locally in blocks of 10 by means of sealed boxes. Study drug infusion (Iliomedine, Bayer AG, Leverkusen, Germany; diluted in normal saline or identical in appearance normal saline) was begun 30 to 90 minutes before the procedure. Infusion of study drug was initiated at half of the target dose and was increased to the final dose in the catheterization laboratory after arterial sheath insertion and invasive blood pressure monitoring for at least 30 minutes before the procedure, and primary intervention for acute ST-elevation infarction. The institutional research ethics committee and the National Drugs Administration approved the study protocol, and all patients gave written, informed consent before inclusion.

Monitoring for adverse events was performed from the start of study drug infusion until the end of the follow-up period. The following adverse safety outcomes were prespecified: severe hypotension events requiring study drug discontinuation (systolic blood pressure <80 mm Hg for any reason), hypotension events requiring study drug nonuptitration or downtitration (systolic blood pressure <90 mm Hg or an absolute drop from baseline of >40 mm Hg), and bleeding complications. A 1-night hospital stay after either coronary angiography or intervention is mandatory in our institution.

Outcomes

The primary end point of CIN was defined as an absolute increase in serum creatinine concentration of at least 0.5 mg/dL or a relative rise of at least 25% from baseline on the follow-up blood sample drawn 2 to 5 days after the procedure. The need for dialysis during the follow-up period was ascertained. Other secondary definitions of CIN (absolute increase of serum creatinine concentration of at least 0.3 or 0.5 mg/dL or a relative rise of at least 25% from baseline) were also explored as separate end points.

Statistical Methods

Sample size was determined by reference to a previous study. If a 21% incidence of the study end point in the control group (as observed in the placebo group of our previous randomized study of ascorbic acid for CIN prevention) were assumed, a sample size of 208 patients would be required (104 per treatment group) to detect a 70% relative reduction in the incidence of the end point by iloprost with 80% power at the conventional, 2-sided significance level of 5%.

Explorative statistical methods were used to compare the study groups. Data were reported as mean±SD for continuous variables and as percentages for discrete variables. Continuous variables were analyzed by the 2-sample independent or paired t test as appropriate and categorical variables by the χ² or Fisher exact test. Logistic regression was performed with the primary end point of CIN as the dependent variable (binary outcome) and the study treatment assignment as the independent variable. Other definitions of CIN were also explored as secondary end points. Secondary analyses included comparison of the absolute changes in eGFR and serum creatinine concentration among the study groups and of the mean baseline and follow-up eGFR and creatinine concentration within each group. The prespecified analysis was performed on an intention-to-treat basis in all randomized patients. A sensitivity analysis was also performed in which patients lost to follow-up were deemed to have a CIN outcome in favor of the placebo and against iloprost treatment. All tests were 2 sided, and a significance level of 5% was used. Statistical analyses were performed with SPSS software (version 11.0.1, SPSS Inc, Chicago, Ill).

Results

Of the 208 patients randomized, 204 (102 each in the iloprost and placebo groups) completed the study (Figure 1). Three patients failed to return for the follow-up serum creatinine measurement (2 randomized to placebo and 1 to iloprost), and 1 patient (randomized to placebo) died owing to cardiac arrest the night before the procedure and before any contrast exposure. None of the patients completing the study developed acute renal failure requiring dialysis during the study follow-up or were rehospitalized during the immediate postprocedural period.

The clinical, biochemical, and procedural characteristics of the study patients are shown in Table 1. The study groups were well balanced; the mean volumes and types of contrast...
agent used and the mean duration and volumes of intravenous hydration were similar. Their predicted risk of CIN development, as assessed by the Mehran et al20 risk score, was also similar. The rates of study drug discontinuation or dose reductions were very low and comparable between study groups. The rare incidences of hypotension potentially related to the study drug administration were promptly reversed through the use of simple supportive measures. The preprocedural and the lowest hematocrit, hemoglobin, and platelet count values obtained after the procedure were similar in the study groups. There were no significant differences between groups in the need for blood transfusions after the procedure. The mean length of hospital stay was 2.7 days in both study groups.

In the control group, the eGFR declined from 49.7 ± 15.5 to 46.6 ± 16.6 mL · min⁻¹ · 1.73 m⁻² (P = 0.01), whereas in the iloprost group, it increased marginally from 47.5 ± 14.5 to 48.6 ± 16.1 mL · min⁻¹ · 1.73 m⁻² (P = 0.26). The mean absolute decline in the eGFR in the control group was significantly greater than its change in the iloprost group (difference, 4.2 mL · min⁻¹ · 1.73 m⁻²; 95% confidence interval [CI], 1.1 to 7.3; P = 0.008). Moreover, the mean serum creatinine concentration increased in the placebo group (1.59 ± 0.49 to 1.73 ± 0.66 mg/dL; P = 0.001) but not in the iloprost group (1.63 ± 0.49 to 1.66 ± 0.72 mg/dL; P = 0.51). The mean absolute increase in serum creatinine concentration was 0.11 mg/dL greater in the control group (95% CI, −0.03 to 0.23; P = 0.11). Despite the observed increases in serum creatinine concentrations, serum urea concentrations decreased significantly in both study arms the day after the procedure (control group: from 65.4 ± 26.9 to 62.3 ± 28.2 mg/dL, P = 0.046; iloprost group: from 72.4 ± 34.2 to 65.8 ± 32 mg/dL, P < 0.001; Table 2). The mean times of follow-up serum creatinine concentration measurement were similar in the study groups: 2.9 ± 1.2 days for the placebo group versus 2.8 ± 1.1 days in the iloprost group (P = 0.52).

The primary end point of CIN, by our definition, occurred in 31 patients (15%); 28 of the 103 patients (24%) in the control group and 8 of the 103 patients (8%) in the iloprost group (odds ratio, 0.29; 95% CI, 0.12 to 0.69; P = 0.005). The secondary end point of CIN, defined as at least a 0.5-mg/dL absolute increase in serum creatinine concentration, occurred in 17 patients (16%) in the control group and in 6 patients (6%) in the iloprost group (odds ratio, 0.31; 95% CI, 0.12 to 0.83; P = 0.018; Table 2 and Figure 2).

In the hypothetical sensitivity analysis including patients lost to follow-up and favoring the placebo treatment, CIN occurred in 23 of the 105 patients (22%) in the control group and 9 of the 103 patients (9%) in the iloprost group (odds ratio, 0.34; 95% CI, 0.15 to 0.77; P = 0.01).
Percutaneous coronary intervention (PCI) was undertaken in 85 stable patients and in 11 patients presenting with troponin-positive acute coronary syndrome. Among the former, the mean maximum postprocedural troponin concentration was 1.37±0.3 mg/dL in 44 control patients and 0.89±0.2 mg/dL in 41 iloprost patients (P=0.42), and sizable myocardial necrosis (troponin levels >5 ng/mL) occurred in 25% of patients in the iloprost arm of this study. Among the patients presenting with troponin-positive acute coronary syndrome, the mean maximum postprocedural troponin concentration was 12.18±22.4 ng/mL in 5 control patients and 7.95±11.2 ng/mL in 6 iloprost patients (P=0.69).

**Discussion**

The key finding of this study is that prophylactic intravenous administration of iloprost, a stable prostacyclin analog, appears to diminish the incidence of CIN by ≈70% in patients with impaired renal function undergoing percutaneous coronary procedures. Therefore, only 7 such high-risk patients would need to be treated to prevent 1 CIN event. In addition, the decrease in eGFR after contrast agent administration was reversed by administration of intravenous iloprost.

The baseline characteristics and risk of CIN development were well balanced between treatment groups. The Mehran et al 20 risk score was ≤10 in both study groups, which corresponds to a CIN incidence of just over 20% in the score development data set of the original study by Mehran et al. Therefore, the observed CIN incidence of 22% in the control group is consistent with the predicted CIN incidence, adding to the validity of this study. The CIN incidence, defined as a 25% relative rise in creatinine in the iloprost arm of this study, was 7% compared with 11% in the Cardiac Angiography in Renally Impaired Patients (CARE) trial, in which all 414 patients received optimal bicarbonate hydration and 41% received N-acetylcysteine. The addition of N-acetylcysteine in that study did not reduce the incidence of CIN. The mean eGFR in CARE was similar to that in our study population (49.8 versus 48.6 mL·min⁻¹·1.73 m⁻²), but the Mehran et al 20 risk score was not reported. The mean contrast volume per patient in our study was ∼120 mL greater than that in CARE, and the incidence of diabetes mellitus was higher (50% versus 41%). Therefore, we submit that our patients were likely at greater risk for development of CIN than those in CARE. However, the CIN incidence in the iloprost arm of our study was still lower than that observed in CARE patients.

The most commonly used definition of CIN in clinical trials is a rise in serum creatinine concentration of 0.5 mg/dL or a 25% increase from the baseline value assessed 48 hours after the procedure. Although arbitrary, this definition has been widely used in previous studies of CIN and has been...
linked to prolonged hospitalization and increased in-hospital and long-term mortality in patients undergoing PCI. The European Society of Urogenital Radiology defines CIN as an increase in serum creatinine of at least 0.5 mg/dL, or at least 25% within 72 hours after intravascular administration of contrast medium, and given that the increase in serum creatinine peaks up to 5 days afterward, we, like researchers in other recent large CIN trials, elected to extend the follow-up period up to 5 days. This approach is also supported by our previous trial of ascorbic acid, which showed a tendency for a higher CIN occurrence among patients who had their serum creatinine concentration measured in days 3 to 5 compared with day 2.

Several potential safety concerns should be considered. Significant hypotension in the process of obtaining arterial access for performing cardiac catheterization is not an unusual event and is usually attributed to vasovagal reactions. However, because hypotension is also the principal, dose-dependent side effect of iloprost, we closely monitored all serious hypotension events in this study. The decision to downtitrate or discontinue iloprost because of potential drug-related side effects in this study was rare, and its incidence was not significantly different between study groups. Three of the 6 instances of study drug downtitration or discontinuation in the iloprost group and 1 of the 3 instances in the control group were due to severe hypotension. All patients who experienced severe hypotension during the study responded within minutes to discontinuation of the study drug and to the intravenous administration of saline. Severe hypotension resulting from iloprost is rapidly reversible because of its very short (12-minute) half-life, and patients normally respond well to the usual remedial measures. As a final point, we should mention that the safety profile of iloprost 1 ng · kg⁻¹ · min⁻¹ was comparable to that of placebo in a pilot study, except for minor side effects (ie, facial flush and nausea).

Another potential area of concern in this trial with regard to safety was the possibility of bleeding at the arterial access site resulting from the platelet-inhibition properties of iloprost. However, iloprost at a dose of 1 ng · kg⁻¹ · min⁻¹ causes minor (<50%) inhibition of ADP-induced platelet aggregation and has no effect on the intrinsic clotting system, plasma coagulation tests, and template bleeding time. The antiplatelet effect of iloprost is short-lived, and iloprost is rapidly eliminated. Indeed, the results of the present study are reassuring in that the mean declines in hemoglobin concentration and hematocrit observed after the procedure were similar between study groups, as was the need for blood transfusions. On the other hand (and in theory), the combination of antiplatelet and vasodilatory effects of iloprost may exert a protective role against myocardial ischemia in patients undergoing PCI. Although this study was not designed to investigate this, we performed an analysis of the observed peak troponin concentrations after PCI procedures and noticed a nonsignificant but consistent reduction in procedure-related myonecrosis in patients randomized to iloprost. This incidental observation may merit further investigation.

The only PG analog investigated previously with regard to CIN prevention in humans was PGE₁ (alprostadil). A small placebo-controlled pilot study evaluated the prevention of CIN by alprostadil 10, 20, or 40 ng · kg⁻¹ · min⁻¹. However, only patients receiving the middle dose of alprostadil (20 ng · kg⁻¹ · min⁻¹) had significantly smaller increases in mean serum creatinine levels than the placebo group.

It is currently believed that disturbances in renal hemodynamics and direct tubular epithelial cell toxicity by contrast media are the primary factors responsible for CIN. Renal vasocostriction has been documented repeatedly and is the basis for the hypothesis that renal ischemia is a major factor in the pathogenesis of CIN. A number of compounds that can improve renal blood flow such as adenosine antagonists, atrial natriuretic peptides, and endothelin antagonists have been clinically tested for the prevention of CIN, but none has proved to be effective. There is controversial evidence from clinical trials that antioxidant agents such as N-acetylcysteine and ascorbic acid might be marginally effective in CIN prevention, suggesting that oxidative stress may play a role in the development of CIN. However, even if antioxidant agents are protective, modulation of renal hemodynamics by means of the nitric oxide system may play a role because they are established protectors of endogenously produced nitric oxide.

Certain observations suggest that suppression of prostacyclin, rather than activation of the renin-angiotensin system, is the principal cause of CIN; administration of contrast media in dogs has been shown to cause an initial brief increase followed by a sustained 20% decrease in renal blood flow and creatinine clearance, no significant changes in angiotensin II and renin levels, and a significant decline in the renal secretory rate of 6-keto-PGF₁α, a PGI₂ metabolite. In particular, contrast media have been shown to increase release of PGEs but to decrease release of PGI₂ from the kidney.

In vitro and in vivo studies in rats have shown that prostaglandins (PGE₁, PGE₂, and PGL₁) protect the kidneys against ischemic and toxic injury by means of a cellular effect. Coadministration of iloprost significantly attenuated the effects of contrast media in the renal cortex of rats, as assessed by near-infrared reflection spectroscopy. Furthermore, iloprost preserves rabbit kidney function against anoxia and attenuates ischemic acute renal failure in rats after clamping of the left renal artery. Indomethacin, a prostanooid inhibitor, has also been shown to reduce renal outer medulla blood flow after contrast medium administration and to elicit radiocontrast toxicity in rats. Although the protective effect of prostacyclin is considered to be primarily a result of its vasodilatory action, a direct protective action on renal epithelial cells has also been shown in an in vitro model of hypoxia/reoxygenation-induced injury in cultured rat proximal renal tubular cells. Recently, beraprost, a synthetic prostacyclin analog, has been shown to attenuate the ioversol-induced decrease in the viability of LLC-PK1 cells (a porcine renal tubular cell line) in a concentration-dependent manner (10 to 1000 nmol/L). Stimulation of prostacyclin receptors enhances the synthesis of cyclic AMP and the protective effect of beraprost was dependent on the elevation of cellular cyclic AMP and subsequent activation of protein
kinase A. The protective effect of beraprost has also been shown in vivo in a mouse model of CIN in which beraprost protected renal tissues against ioversol-induced tubular and interstitial cell injury in a concentration-dependent manner. In addition, prostacyclin has been shown to mitigate the progression rate of renal dysfunction in patients with chronic renal insufficiency. Moreover, low-dose prostacyclin (2 ng·kg⁻¹·min⁻¹) started immediately before cardiac surgery and continued for a maximum of 48 hours has been shown to preserve renal function in high-risk patients with impaired left ventricular fraction undergoing surgical revascularization.

Some limitations of our study should be noted. Although appropriately powered, it included only 208 patients from a single institution. In view of the low incidence of contrast-induced renal failure requiring supportive measures, like most previous studies of CIN prevention, a more liberal definition of CIN was used. Surrogate end points may not always correlate with clinical events, but a study designating renal failure as the primary end point would require a prohibitively large sample size. Although the occurrence of CIN as defined in our study has been linked to prolonged hospitalization, increased healthcare costs, and substantial morbidity and mortality, the exact clinical impact of the study findings remains largely unknown. However, our results on clinical outcomes such as need for blood transfusions, length of hospital stay, and PCI-related myocardial necrosis are at least encouraging relative to the safety of the investigational preventive treatment.

Our results on the eGFR changes should be viewed with caution because the MDRD Study prediction equation is inaccurate, although more accurate than other prediction equations based on serum creatinine concentration, for patients not in a steady state of creatinine balance. However, the MDRD equation overestimates residual renal function in such circumstances and therefore has a built-in conservative aspect that tends to reduce differences between therapies and not to result in spurious differences.

Apparenty, iloprost reduced but did not eliminate CIN in our study. This finding probably indicates that the mechanism of CIN is multifactorial and that prostacyclin replenishment can nullify part of it. A dose-related preventive effect of iloprost cannot be excluded on the basis of the results of our pilot study; however, this preventive effect would be attained at the expense of poorer drug tolerability. Finally, the relative efficacy of iloprost used concomitantly with other potential preventative agents such as N-acetylcysteine, administered in only 9% of our study patients, remains unknown.

In conjunction with the aforementioned experimental and clinical data that suggest a possible nephroprotective role of prostacyclin, our study demonstrates that prophylactic intravenous iloprost, a prostacyclin analog, has a good safety profile, is generally well tolerated, and is effective in preventing CIN in patients with renal dysfunction undergoing a coronary procedure. This benefit was observed despite routine hydration and use of modern isoosmolar or low-osmolar radiographic contrast agents.

Source of Funding
This study was supported by a restricted research grant from Bayer AG, Leverkusen, Germany.

Disclosures
None.

References
Iloprost and Contrast-Induced Nephropathy

Spargias et al

Contrast-induced renal vasocstriction is believed to play a pivotal role in the pathogenesis of contrast-induced nephropathy (CIN). The present study found that prophylactic periprocedural intravenous administration of the prostacyclin analog iloprost at a dose of 1 ng · kg⁻¹ · min⁻¹ in patients with renal dysfunction undergoing a coronary procedure reduced the incidence of CIN by ≈70% (odds ratio, 0.29; 95% confidence interval, 0.12 to 0.69; \( P=0.005 \)). Importantly, the rate of side effects leading to iloprost discontinuation or dose reduction was very low and comparable to that observed in the control group. The important new information provided by this study is the proof of principle that CIN can be prevented by a mechanism distinct from volume expansion or direct antioxidant effects, namely prostacyclin replenishment. Furthermore, the efficacy of iloprost to prevent CIN at the dose studied is noteworthy. The prevention of CIN, which accounts for considerable morbidity and mortality, remains a vexing problem. Although preliminary data, mostly from single studies, have previously suggested that numerous specific pharmaceuticals had a preventive effect, more recent research has failed to confirm their efficacy. With questions lingering, volume expansion remains the only indisputable strategy. In this respect, although the results of this trial appear convincing and support the use of iloprost for efficient prevention of CIN in high-risk patients undergoing a coronary procedure, recommendation for widespread use should await further trial confirmation.
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_Circulation_. 2009;120:1793-1799; originally published online October 19, 2009; doi: 10.1161/CIRCULATIONAHA.109.863159
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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:
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