Ascorbic Acid Prevents Contrast-Mediated Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention

Konstantinos Spargias, Elias Alexopoulos, Stamatis Kyrzopoulos, Panayiotis Iacovis, Darren C. Greenwood, Athanassios Manginas, Vassilis Voudris, Gregory Pavlides, Christopher E. Buller, Dimitrios Kremastinos and Dennis V. Cokkinos

_Circulation_ 2004;110:2837-2842; originally published online Oct 18, 2004;
DOI: 10.1161/01.CIR.0000146396.19081.73

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2004 American Heart Association. 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/cgi/content/full/110/18/2837

An erratum has been published regarding this article. Please see the attached page or:

http://circ.ahajournals.org/cgi/content/full/circulationaha;111/3/379-a

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

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail: journalpermissions@lww.com

Reprints: Information about reprints can be found online at http://www.lww.com/reprints
Ascorbic Acid Prevents Contrast-Mediated Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention

Konstantinos Spargias, MD; Elias Alexopoulos, MD; Stamatis Kyrzopoulos, MD; Panayiotis Iacovis, MD; Darren C. Greenwood, MSc; Athanassios Manginas, MD; Vassilis Voudris, MD; Gregory Pavlides, MD; Christopher E. Buller, MD; Dimitrios Kremastinos, MD; Dennis V. Cokkinos, MD

Abstract—Contrast agents can cause a reduction in renal function that may be due to the generation of reactive oxygen species. Conflicting evidence suggests that administration of the antioxidant acetylcysteine prevents this renal impairment. The action of other antioxidant agents has not been investigated.

Methods and Results—We conducted a randomized, double-blind, placebo-controlled trial of ascorbic acid in 231 patients with a serum creatinine concentration ≥1.2 mg/dl who underwent coronary angiography and/or intervention. Ascorbic acid, 3 g at least 2 hours before the procedure and 2 g in the night and the morning after the procedure, or placebo was administered orally. Contrast-mediated nephropathy was defined by an absolute increase of serum creatinine ≥0.5 mg/dL or a relative increase of ≥25% measured 2 to 5 days after the procedure. Contrast-mediated nephropathy occurred in 11 of the 118 patients (9%) in the ascorbic acid group and in 23 of the 113 patients (20%) in the placebo group (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.17 to 0.85; P=0.02). The mean serum creatinine concentration increased significantly in the placebo group (from 1.36±0.50 to 1.50±0.54 mg/dL, P<0.001) and nonsignificantly in the ascorbic acid group (from 1.46±0.52 to 1.52±0.64 mg/dL, P=0.07). The mean increase in serum creatinine concentration was greater in the placebo group than in the ascorbic acid group (difference of 0.09 mg/dL; 95% CI, 0.00 to 0.17; P=0.049).

Conclusions—Prophylactic oral administration of ascorbic acid may protect against contrast-mediated nephropathy in high-risk patients undergoing a coronary procedure. (Circulation. 2004;110:2837-2842.)

Key Words: contrast media • kidney • angiography • angioplasty • antioxidants

Acute deterioration in renal function caused by radiographic contrast agents is generally mild and transient but can result in lasting renal dysfunction and the need for renal replacement therapy and is the third leading cause of new-onset renal failure in hospitalized patients. Moreover, contrast-mediated nephropathy (CMN) has been associated with increased in-hospital and long-term morbidity, mortality, and extended hospitalization. Commonly used definitions of CMN include (1) an absolute increase in the serum creatinine concentration of at least 0.5 mg/dL and (2) a relative increase of at least 25% from the baseline value. The incidence of CMN in the general patient population undergoing coronary angiography is low and has been estimated to be <2%. However, patients with preexisting renal impairment and diabetes mellitus are at substantially greater risk of developing CMN, in the range of 20% to 80%. Other factors may also contribute to risk, including volume depletion, the volume and osmolality of the contrast agent used, and congestive heart failure.

Although the precise insult underlying CMN is uncertain, it has been speculated that it occurs because of the vulnerability of the renal medullary circulation to stimuli that disrupt the balance between the high metabolic needs of its tubular segments and their hypoxic environment. 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. Infusion of radiographic contrast agents, with the attendant increases in osmotic load and viscosity, increases the hypoxia of the renal medulla and increases renal free-radical production through posts ischemic oxidative stress.

Several interventions for the prevention of CMN have been tested in clinical trials. At present, only hydration and use of iso-osmolar contrast agents have shown consistent benefit. Recent studies have produced conflicting results regarding the efficacy of the antioxidant acetylcysteine.
The antioxidant ascorbic acid has been shown to attenuate renal damage caused by a variety of insults, such as postischemic stress, cisplatin, aminoglycosides, and potassium bromate in animals and has an extensive safety record as a dietary supplement in humans.26–29 We undertook a randomized, placebo-controlled trial of ascorbic acid for prevention of CMN in patients with impaired renal function undergoing an invasive coronary procedure.

Methods

Patients

Patients undergoing clinically driven, nonemergent coronary angiography or intervention in our institution were eligible for inclusion if their serum creatinine concentration was ≥1.2 mg/dL (106 μmol/L) on their most recent sample drawn within 3 months of the planned procedure. Patients were excluded for any of the following reasons: known acute renal failure, end-stage renal disease requiring dialysis, intravascular administration of contrast medium within the previous 6 days, anticipated readministration of contrast medium within the following 6 days, use of vitamin C supplements on a daily basis during the week before the procedure, or inability to administer the study medication at least 2 hours before the procedure. The institutional review board approved the study protocol, and all patients gave written, informed consent before inclusion.

Study Protocol

The patients were randomly assigned to receive either 3 g of ascorbic acid supplied in chewable tablets or placebo the night and the morning after the procedure. Patients were excluded for any of the following reasons: known acute renal failure, end-stage renal disease requiring dialysis, intravascular administration of contrast medium within the previous 6 days, anticipated readministration of contrast medium within the following 6 days, use of vitamin C supplements on a daily basis during the week before the procedure, or inability to administer the study medication at least 2 hours before the procedure. The institutional review board approved the study protocol, and all patients gave written, informed consent before inclusion.

Study Protocol

The patients were randomly assigned to receive either 3 g of ascorbic acid supplied in chewable tablets or placebo the night and the morning after the procedure. Randomization was performed locally in blocks of 10 by means of sealed boxes. A Research Fellow not involved in the procedure was designated for the following: the study drugs and random assignment of treatment. Hydration with 50 to 125 mL/h IV normal saline was started in all patients from randomization until at least 6 hours after the procedure. The variation of the hydration rate allowed for adjustments according to the left ventricular ejection fraction and the presence of clinical heart failure in individual patients. Hospital procedures require accurate hourly recording of all in-hospital volume inputs in patients undergoing percutaneous coronary interventions. All patients were encouraged to drink if they were thirsty. The choice of the type of contrast agent was left to the interventional cardiologist performing the procedure, but use of a nonionic, low- or iso-osmolar contrast agent was encouraged.

Baseline serum creatinine concentration was measured from a blood sample drawn at the time of randomization, and the follow-up serum creatinine concentration was measured 2 to 5 days after the procedure. All measurements were performed in a single, hospital-based laboratory with consistent methodology. Baseline and follow-up creatinine clearances were calculated by applying the Cockcroft-Gault formula, with adjustment for female patients.30 CMN was defined as an absolute rise of serum creatinine concentration measured 2 to 5 days after the procedure of at least 0.5 mg/dL or a relative rise of at least 25% from baseline. No patients lost to follow-up were deemed to have changes in postprocedural renal function that reflected the change seen in the overall study population. All tests were 2-sided, and a significance level of 5% was used. Statistical analyses were performed with SPSS software (version 9.05, SPSS, Inc).

Results

Of the 238 patients randomized, 231 completed the study (Figure 1). None developed acute renal failure requiring dialysis. Of the 7 patients who did not return for the follow-up serum creatinine concentration measurement, none was rehospitalized during the immediate postprocedural period for any reason.

The baseline clinical, biochemical, and procedural characteristics of the 231 patients are shown in Table 1. The mean volumes and types of contrast agent used and the mean volumes of hydration were similar between the study groups. Patients in the ascorbic acid group were somewhat older.

In the control group, the mean serum creatinine concentration increased from 1.36±0.50 to 1.50±0.54 mg/dL (P<0.001). In the ascorbic acid group, the mean serum creatinine concentration increased from 1.46±0.52 to 1.52±0.64 mg/dL (P=0.07). The mean absolute increase in serum creatinine concentration was significantly greater in the control compared with the ascorbic acid group (difference of 0.09 mg/dL; 95% confidence interval [CI], 0.00 to 0.17; P=0.049; Table 2). In a similar manner, the mean creatinine clearance decreased significantly in the control group but not in the ascorbic acid group (Table 2). The mean absolute

![Figure 1. Flow chart of trial progress.](image)
decline in creatinine clearance was significantly greater in the control group compared with the ascorbic acid group (difference of 5.4 mL/min; 95% CI, 3.0 to 7.8; \( P<0.001 \)). Despite the increases in serum creatinine concentrations observed, serum urea concentrations decreased significantly in both study arms the day after the procedure (Table 2).

By our definition of CMN, this condition occurred in 34 patients (15%): 11 of the 118 patients (9%) in the ascorbic acid group and 23 of the 113 patients (20%) in the control group (odds ratio [OR], 3.8; 95% CI, 1.7 to 8.5; \( P=0.02 \)). The results of the logistic regression analysis remained unchanged after adjusting for imbalances in age (OR, 3.6; 95% CI, 1.7 to 7.6; \( P=0.01 \)), systolic blood pressure (OR, 0.59; 95% CI, 0.33 to 1.0; \( P=0.05 \)), diabetes mellitus requiring pharmaceutical treatment (OR, 2.27; 95% CI, 1.18 to 4.38; \( P=0.015 \)), or both (OR, 2.35; 95% CI, 1.17 to 4.7; \( P=0.01 \)).

In the sensitivity analysis including patients lost to follow-up, CMN occurred in 35 patients (15%): 11 of the 121 patients (9%) in the ascorbic acid group and 24 of the 117 patients (21%) in the placebo group (OR, 0.39; 95% CI, 0.18 to 0.83; \( P=0.015 \)).

The mean times of follow-up serum creatinine concentration measurement were similar in the study groups: for the ascorbic acid group, 2.36±0.74 days and for the control group, 2.27±0.70 days (\( P=0.34 \)). A history of diabetes mellitus requiring pharmaceutical treatment was present in 24% of patients either with or without CMN occurrence.

The CMN incidence tended to be higher among patients having their serum creatinine concentration measured on days 3 to 5 compared with day 2 (Figure 2). Table 3 shows the incidence of other commonly used definitions of acute contrast agent–induced reduction in renal function in the study groups.

The mean absolute change in the total antioxidant status after study drug administration was 0.03±0.09 mmol/L in the ascorbic acid group versus −0.9±0.14 mmol/L in the control group (difference of 0.12 mmol/L; 95% CI, 0.02 to 0.22; \( P=0.02 \)). Total antioxidant status decreased significantly in the control group on the morning after the procedure (from 1.46±0.11 to 1.36±0.12 mmol/L, \( P=0.03 \)) but not in the ascorbic acid group (from 1.32±0.09 to 1.30±0.15 mmol/L, \( P=0.61 \)).

**Discussion**

The key finding of this study is that prophylactic oral administration of the antioxidant ascorbic acid appears to diminish the incidence of CMN in patients with impaired renal function undergoing percutaneous coronary procedures. Concordantly, the absolute increase in serum creatinine concentration and the absolute decrease in creatinine clearance after contrast agent administration were reduced by administration of oral ascorbic acid.

Minor imbalances of baseline characteristics observed between treatment groups are typical of small studies. In the present study, both the mean baseline serum creatinine concentration and age tended to be higher and the baseline creatinine clearance lower in the ascorbic acid group. It has been shown that in patients undergoing cardiac catheterization, there is an exponential increase in the risk for CMN above a threshold baseline serum creatinine concentration of 1.2 mg/dL.31 Advancing age has also been associated with an increased incidence of CMN in some studies.5,31 The imbalances that we observed would be expected to increase the incidence of the primary end point in the ascorbic acid group and therefore, tend to strengthen our overall findings.

We defined CMN as at least a 0.5 mg/dL absolute or a 25% relative increase in the baseline serum creatinine concentration measured 2 to 5 days after the procedure. Though arbitrary, these definitions have been widely used in previous studies of CMN and have been linked to prolonged hospitalization and increased in-hospital and long-term mortality in patients undergoing percutaneous coronary interventions.3,7 The incidence rates of CMN are, however, sensitive to the definition used. When the definition of at least a 0.5 mg/dL or at least a 25% relative increase in the baseline serum concentration was used, CMN occurred in 34 patients (15%): 11 of the 118 patients (9%) in the ascorbic acid group and 23 of the 113 patients (20%) in the control group (odds ratio [OR], 3.8; 95% CI, 1.7 to 8.5; \( P=0.02 \)). The results of the logistic regression analysis remained unchanged after adjusting for imbalances in age (OR, 3.6; 95% CI, 1.7 to 7.6; \( P=0.01 \)), systolic blood pressure (OR, 0.59; 95% CI, 0.33 to 1.0; \( P=0.05 \)), diabetes mellitus requiring pharmaceutical treatment (OR, 2.27; 95% CI, 1.18 to 4.38; \( P=0.015 \)), or both (OR, 2.35; 95% CI, 1.17 to 4.7; \( P=0.01 \)).

In the sensitivity analysis including patients lost to follow-up, CMN occurred in 35 patients (15%): 11 of the 121 patients (9%) in the ascorbic acid group and 24 of the 117 patients (21%) in the placebo group (OR, 0.39; 95% CI, 0.18 to 0.83; \( P=0.015 \)).

The mean times of follow-up serum creatinine concentration measurement were similar in the study groups: for the ascorbic acid group, 2.36±0.74 days and for the control group, 2.27±0.70 days (\( P=0.34 \)). A history of diabetes mellitus requiring pharmaceutical treatment was present in 24% of patients either with or without CMN occurrence.

The CMN incidence tended to be higher among patients having their serum creatinine concentration measured on days 3 to 5 compared with day 2 (Figure 2). Table 3 shows the incidence of other commonly used definitions of acute contrast agent–induced reduction in renal function in the study groups.

The mean absolute change in the total antioxidant status after study drug administration was 0.03±0.09 mmol/L in the ascorbic acid group versus −0.9±0.14 mmol/L in the control group (difference of 0.12 mmol/L; 95% CI, 0.02 to 0.22; \( P=0.02 \)). Total antioxidant status decreased significantly in the control group on the morning after the procedure (from 1.46±0.11 to 1.36±0.12 mmol/L, \( P=0.03 \)) but not in the ascorbic acid group (from 1.32±0.09 to 1.30±0.15 mmol/L, \( P=0.61 \)).

**Discussion**

The key finding of this study is that prophylactic oral administration of the antioxidant ascorbic acid appears to diminish the incidence of CMN in patients with impaired renal function undergoing percutaneous coronary procedures. Concordantly, the absolute increase in serum creatinine concentration and the absolute decrease in creatinine clearance after contrast agent administration were reduced by administration of oral ascorbic acid.

Minor imbalances of baseline characteristics observed between treatment groups are typical of small studies. In the present study, both the mean baseline serum creatinine concentration and age tended to be higher and the baseline creatinine clearance lower in the ascorbic acid group. It has been shown that in patients undergoing cardiac catheterization, there is an exponential increase in the risk for CMN above a threshold baseline serum creatinine concentration of 1.2 mg/dL.31 Advancing age has also been associated with an increased incidence of CMN in some studies.5,31 The imbalances that we observed would be expected to increase the incidence of the primary end point in the ascorbic acid group and therefore, tend to strengthen our overall findings.

We defined CMN as at least a 0.5 mg/dL absolute or a 25% relative increase in the baseline serum creatinine concentration measured 2 to 5 days after the procedure. Though arbitrary, these definitions have been widely used in previous studies of CMN and have been linked to prolonged hospitalization and increased in-hospital and long-term mortality in patients undergoing percutaneous coronary interventions.3,7 The incidence rates of CMN are, however, sensitive to the definition used. When the definition of at least a 0.5 mg/dL or at least a 25% relative increase in the baseline serum concentration was used, CMN occurred in 34 patients (15%): 11 of the 118 patients (9%) in the ascorbic acid group and 23 of the 113 patients (20%) in the control group (odds ratio [OR], 3.8; 95% CI, 1.7 to 8.5; \( P=0.02 \)). The results of the logistic regression analysis remained unchanged after adjusting for imbalances in age (OR, 3.6; 95% CI, 1.7 to 7.6; \( P=0.01 \)), systolic blood pressure (OR, 0.59; 95% CI, 0.33 to 1.0; \( P=0.05 \)), diabetes mellitus requiring pharmaceutical treatment (OR, 2.27; 95% CI, 1.18 to 4.38; \( P=0.015 \)), or both (OR, 2.35; 95% CI, 1.17 to 4.7; \( P=0.01 \)).

In the sensitivity analysis including patients lost to follow-up, CMN occurred in 35 patients (15%): 11 of the 121 patients (9%) in the ascorbic acid group and 24 of the 117 patients (21%) in the placebo group (OR, 0.39; 95% CI, 0.18 to 0.83; \( P=0.015 \)).

The mean times of follow-up serum creatinine concentration measurement were similar in the study groups: for the ascorbic acid group, 2.36±0.74 days and for the control group, 2.27±0.70 days (\( P=0.34 \)). A history of diabetes mellitus requiring pharmaceutical treatment was present in 24% of patients either with or without CMN occurrence.
creatinine concentration was applied in previous studies, the incidence of CMN after coronary intervention was found to be 14.5% in unselected patients (mean serum creatinine value of 1.3 ± 0.4 mg/dL) and 37% in patients with a baseline serum creatinine value ≥1.8 mg/dL. When the definition of at least a 0.5 mg/dL absolute serum creatinine increase was applied in previous studies, the incidence of CMN was found to be 2.5% in patients with a baseline serum creatinine value of 1.2 to 1.9 mg/dL and 22.4% in patients with a serum creatinine of 2.0 to 2.9 mg/dL. In another study including elderly patients with a mean serum creatinine level of 1.3 ± 0.7 mg/dL, the incidence of this end point was 11.5%. Therefore, the incidence of CMN is considerably lower when the definition of at least a 0.5 mg/dL absolute increase is used. This fact is confirmed by the findings of our study (Table 3).

Serum creatinine concentration peaks 3 to 5 days after exposure to contrast media. In contradiction to other studies that measured serum creatinine concentration within 48 hours after exposure, we opted to measure it at least 48 hours and as long as 5 days after exposure to increase the sensitivity and capture size of the effect. The tendency for a higher CMN occurrence among our patients having their serum creatinine concentration measured in days 3 to 5 compared with day 2 supports this approach.

Recent studies have demonstrated that isotonic (rather than half-isotonic) hydration and the use of the iso-osmolar, nonionic agent ioxaglate rather than the low-osmolar, nonionic iohexol reduced CMN (defined as a ≥0.3 mg/dL absolute increase and a ≥25% relative increase in the baseline serum creatinine concentration) by an estimated 65% and 88%, respectively. All patients in our study received isotonic hydration commencing at least 2 hours before the procedure and for at least 6 hours afterward. The randomization effect and available data from 41% of study patients ensure that hydration was well balanced between the study groups, and for the given baseline risk of our patients, the mean volume inputs were comparable to those observed in landmark studies, such as the NEPHRIC and CONTRAST trials. The significant decline in mean serum urea concentrations observed in both study groups the day after the procedure alludes to the efficiency of the hydration protocol used. In addition, an iso-osmolar contrast

---

**Table 2.** Baseline and Follow-Up Creatinine Clearance, Serum Urea, and Creatinine Concentrations; Absolute Changes From Baseline After Administration of Contrast Agent; and Incidence of CMN in the Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ascorbic Acid Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance, mL/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61.1±23.9*</td>
<td>68.1±26.8†</td>
<td>0.04</td>
</tr>
<tr>
<td>Follow-up (2 to 5 days after)</td>
<td>60.0±23.7*</td>
<td>61.6±24.7†</td>
<td>0.59</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−1.1±8.6</td>
<td>−6.5±9.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum urea concentration, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>56±29‡</td>
<td>53±26§</td>
<td>0.43</td>
</tr>
<tr>
<td>Follow-up (1 day after)</td>
<td>52±31‡</td>
<td>51±26§</td>
<td>0.79</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−4±11</td>
<td>−2±9</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum creatinine concentration, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qualifying</td>
<td>1.47±0.51</td>
<td>1.43±0.45</td>
<td>0.61</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.46±0.52</td>
<td>1.36±0.50#</td>
<td>0.13</td>
</tr>
<tr>
<td>Follow-up (2 to 5 days after)</td>
<td>1.52±0.64‡</td>
<td>1.50±0.54#</td>
<td>0.81</td>
</tr>
<tr>
<td>Absolute change</td>
<td>0.06±0.35</td>
<td>0.14±0.30</td>
<td>0.049</td>
</tr>
<tr>
<td>Incidence of acute reductions in renal function, n (%)</td>
<td>11 (9.3)</td>
<td>23 (20.4)</td>
<td>0.03**</td>
</tr>
</tbody>
</table>

P values for the paired comparisons: *0.17, †<0.001, ‡<0.001, §0.02, |0.07, and #<0.001.

**Fisher exact test was used for comparison between the groups.**

---

**Figure 2.** Occurrence of CMN in relation to day of follow-up creatinine concentration measurement. Lighter-color stacks represent patients with CMN. Numbers in stacks represent proportions within overall study population. P=0.07 for comparison of CMN incidence between day 2 and days 3 to 5. Abbreviation is as defined in text.
agent was used in the majority of patients overall and in a slightly greater proportion of control patients (66.4% versus 58.5%). These practices would be expected to have resulted in a reduced incidence of CMN in our study group compared with older studies. Importantly, our results indicate that ascorbic acid is effective when added to these previously proven interventions.

Contrast agents reduce the medullary partial pressure of oxygen even though they increase medullary blood flow, probably because of osmotic diuresis and increased workload in medullary tubules. Results of work in both animals and humans have implicated reactive oxygen species in the pathogenesis of contrast-induced nephrotoxicity. Based on these observations, the effect of the thiol-containing antioxidant acetylcysteine in preventing CMN was first tested by Tepel et al in patients undergoing computed tomography scanning. An impressive 90% reduction in the incidence of contrast-induced nephropathy (defined as a ≥0.5 mg/dL absolute serum creatinine increase) was noted. Although several subsequent studies examining the effect of oral or intravenous acetylcysteine in the incidence of CMN in patients undergoing percutaneous coronary procedures showed disparate results, a meta-analysis of 7 randomized, placebo-controlled studies including 805 patients showed that compared with hydration alone, acetylcysteine significantly reduced the risk of CMN in patients with impaired renal function. The lack of consistency in the results of the acetylcysteine trials is reminiscent of the trials of antioxidants for the primary and secondary prevention of vascular disease and cardioprotection. Among the possible explanations suggested of how this can be so are ineffective antioxidants and inappropriate selection of patients and end points.

Ascorbic acid is a potent, water-soluble antioxidant capable of scavenging a wide array of reactive oxygen species that can cause damage to macromolecules such as lipids, DNA, and proteins. In addition, ascorbic acid can regenerate other antioxidants, acting as a coantioxidant. The bioavailability of orally administered ascorbic acid doses of 2 to 3 g is 36% to 44%, and the time of its maximum excretion rate is 2.7 hours. These doses of oral ascorbic acid have been shown to reverse endothelial vasomotor dysfunction within 2 hours after administration in patients with coronary artery disease and are therefore, biologically relevant. The significant differences observed in the changes of the plasma total antioxidant status as early as 2 hours after administration of the study drug in our patients denote the biological effect of ascorbic acid.

Some limitations of our study should be noted. Although appropriately powered, it included only 231 patients from a single institution. In view of the low incidence of contrast-mediated renal failure requiring supportive measures, a more liberal definition of CMN was used. Surrogate endpoints 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 CMN as defined in our study has been linked to prolonged hospitalization and increased in-hospital and long-term mortality in patients undergoing percutaneous coronary interventions, the exact clinical impact of the study findings remains largely unknown.

All patients were discharged from the hospital at least 1 day after the procedure, and those who underwent complex percutaneous coronary interventions were discharged 2 days after the procedure. No further clinical follow-up was required after hospital discharge, but patients demonstrating a significant rise in serum creatinine level were contacted and their clinical status was ascertained. Unlike the majority of previous studies, our study did not exclude patients undergoing elective and ad hoc percutaneous coronary interventions. This resulted in a larger contrast load, which might have placed our patients at higher risk for developing CMN from what their baseline renal function would justify. However, the other way of seeing this is that the increased contrast load may have led to a higher incidence of CMN in the placebo group and therefore, may have increased the power of the study to detect the ascorbic acid effect.

The results of this study show that ascorbic acid, a safe, well-tolerated, inexpensive, and readily available oral antioxidant, appears to prevent the complication of CMN after invasive coronary imaging procedures in patients with pre-existing renal dysfunction. This benefit was observed despite routine hydration and use of modern iso-osmolar or low-osmolar radiographic contrast agents. These findings are consistent with the hypothesis that CMN is caused in whole or in part by oxidative stress.

References


In the article by Huynh et al, “Aspirin, Warfarin, or the Combination for Secondary Prevention of Coronary Events in Patients With Acute Coronary Syndromes and Prior Coronary Artery Bypass Surgery,” which published in the June 26, 2001, issue (Circulation. 2001;103:3069–3074), the authors now realize errors appeared in Tables 3 and 4. The percentages of events and complications were presented on the basis of the number of patients’ visits rather than on the total number of patients.

Overall, the corrected results did not change the implication of the study. There was no benefit of warfarin alone or combined with aspirin in the secondary prevention of ischemic events in this study of patients with previous coronary artery bypass surgery and an acute coronary syndrome; there was a significant excess in minor bleeding compared with the aspirin-alone group.

Corrected versions of Tables 3 and 4 appear below.

### TABLE 3. End-Point Events According to Treatment

<table>
<thead>
<tr>
<th>Events</th>
<th>Warfarin + Placebo (n=45)</th>
<th>Aspirin + Placebo (n=46)</th>
<th>Warfarin + Aspirin (n=44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, n (%)</td>
<td>18 (40.0)</td>
<td>13 (28.3)</td>
<td>11 (25.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>4 (8.9)</td>
<td>1 (2.2)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>UA, n (%)</td>
<td>16 (35.6)</td>
<td>13 (28.3)</td>
<td>10 (22.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>6 (13.3)</td>
<td>1 (2.2)</td>
<td>3 (6.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Repeat CABG, n (%)</td>
<td>2 (4.4)</td>
<td>2 (4.3)</td>
<td>2 (4.5)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

UA indicates unstable angina requiring rehospitalization; PCI, percutaneous coronary intervention; and MI, myocardial infarction. Primary end point is any-cause mortality, MI, or UA requiring hospitalization.

### TABLE 4. Complications and Adherence to Protocol by Patients

<table>
<thead>
<tr>
<th>Complications</th>
<th>Warfarin + Placebo (n=45)</th>
<th>Aspirin + Placebo (n=46)</th>
<th>Warfarin + Aspirin (n=44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding, n (%)</td>
<td>10 (22.2)</td>
<td>2 (4.3)</td>
<td>9 (20.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Blood transfusions, n (%)</td>
<td>2 (4.4)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Compliance, %*</td>
<td>90.1</td>
<td>86.7</td>
<td>86.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Protocol completion, %*</td>
<td>77.6</td>
<td>78.5</td>
<td>69.9</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Compliance and protocol completion were calculated per visit.

DOI: 10.1161/01.CIR.0000155489.11621.70
In the article by Haïssaguerre et al, “Mapping and Ablation of Ventricular Fibrillation Associated With Long-QT and Brugada Syndromes,” which appeared in the August 26, 2003, issue (Circulation. 2003;108:925–928), the authors would like to note the following errors:

1. In the byline, Jerónimo Farré’s name incorrectly appeared as “Gerónimo Farre.”
2. José Angel Cabrera and Jerónimo Farré work at Fundación Jiménez Díaz in Madrid, Spain.
3. The work of Drs Cabrera and Farré was supported by Redes Temáticas de Cooperación, Red Cardiovascular C01/03.

DOI: 10.1161/01.CIR.0000155483.25082.D4

In the article by McRae and Ginsberg, “Initial Treatment of Venous Thromboembolism,” which appeared in the August 31, 2004, supplement sponsored by the Society for Vascular Medicine and Biology (Circulation. 2004;110[suppl I]:I-3–I-9), an error appeared in Table 2. The footnote of the table erroneously states that “For enoxaparin, 100 anti-Xa U/kg corresponds to a dose of 100 mg/kg.” The legend should have read, “For enoxaparin, 100 anti-Xa U/kg corresponds to a dose of 1 mg/kg.”

DOI: 10.1161/01.CIR.0000155484.25082.1A

In the article by Bauer et al, “Acute Improvement in Global and Regional Left Ventricular Systolic Function After Percutaneous Heart Valve Implantation in Patients With Symptomatic Aortic Stenosis,” which appeared in the September 14, 2004, issue (Circulation. 2004;110:1473–1476), two errors of note appeared in the table on page 1474. Under “Endocardiographic data,” the rows for “LV end-systolic volume, mm Hg” and “LV end-diastolic volume, mm Hg” should have appeared as the following:

<table>
<thead>
<tr>
<th>LV end-diastolic volume, mL</th>
<th>102±36 (baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-systolic volume, mL</td>
<td>49±25 (baseline)</td>
</tr>
</tbody>
</table>

DOI: 10.1161/01.CIR.0000155485.32706/1C

Because of a typesetting error, several mathematical symbols appeared incorrectly in the article by Solomon et al, “Effect of Candesartan on Cause-Specific Mortality in Heart Failure Patients: The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Program,” which appeared in the October 12, 2004, issue (Circulation. 2004;110:2180–2183). On page 2180, in the abstract and in the text of the article, there were several instances in which “LVEF=40%” should have appeared as “LVEF≤40%.” In addition, in the last sentence of the first paragraph of the article, please note that “9% borderline risk” should read “9% borderline significant risk.” The corrected version is available online at http://circ.ahajournals.org/cgi/content/full/110/15/2180. (The previous version can be accessed by selecting the “Previous Version of This Article” link.) We regret these errors.

DOI: 10.1161/01.CIR.0000155486.26868.C9

In the AHA Scientific Statement by Drew et al, “Practice Standards for Electrocardiographic Monitoring in Hospital Settings: An American Heart Association Scientific Statement From the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young,” which appeared in the October 26, 2004, issue (Circulation. 2004;110:2721–2746), Figure 4 contained an error. The text in the figure refers to the “Angle of Lewis.” The correct name is “Angle of Louis.” The Association regrets this error.

DOI: 10.1161/01.CIR.00001155490.19245.B0
In the article by Noujaim et al, “From Mouse to Whale: A Universal Scaling Relation for the PR Interval of the Electrocardiogram of Mammals,” which appeared in the November 2, 2004, issue (Circulation. 2004;110:2802–2808), the name of Ary L. Goldberger, MD, was misspelled as “Goldberg” in reference 12. The authors regret this error.

DOI: 10.1161/01.CIR.0000155482.89456.78

In the article by Spargias et al, “Ascorbic Acid Prevents Contrast-Mediated Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention,” which appeared in the November 2, 2004, issue (Circulation. 2004;110:2837–2842), the name of author Panagiotis Iokovis was spelled incorrectly as “Panagiotis Iocovis.” The authors regret this error.

DOI: 10.1161/01.CIR.0000155487.34492.0D


DOI: 10.1161/01.CIR.0000155488.34492.E9