N-Acetylcysteine and Contrast-Induced Nephropathy in Primary Angioplasty

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ABSTRACT

BACKGROUND
Patients with acute myocardial infarction undergoing primary angioplasty are at high risk for contrast-medium–induced nephropathy because of hemodynamic instability, the need for a high volume of contrast medium, and the lack of effective prophylaxis. We investigated the antioxidant N-acetylcysteine for the prevention of contrast-medium–induced nephropathy in patients undergoing primary angioplasty.

METHODS
We randomly assigned 354 consecutive patients undergoing primary angioplasty to one of three groups: 116 patients were assigned to a standard dose of N-acetylcysteine (a 600-mg intravenous bolus before primary angioplasty and 600 mg orally twice daily for the 48 hours after angioplasty), 119 patients to a double dose of N-acetylcysteine (a 1200-mg intravenous bolus and 1200 mg orally twice daily for the 48 hours after intervention), and 119 patients to placebo.

RESULTS
The serum creatinine concentration increased 25 percent or more from baseline after primary angioplasty in 39 of the control patients (33 percent), 17 of the patients receiving standard-dose N-acetylcysteine (15 percent), and 10 patients receiving high-dose N-acetylcysteine (8 percent, P<0.001). Overall in-hospital mortality was higher in patients with contrast-medium–induced nephropathy than in those without such nephropathy (26 percent vs. 1 percent, P<0.001). Thirteen patients (11 percent) in the control group died, as did five (4 percent) in the standard-dose N-acetylcysteine group and three (3 percent) in the high-dose N-acetylcysteine group (P=0.02). The rate for the composite end point of death, acute renal failure requiring temporary renal-replacement therapy, or the need for mechanical ventilation was 21 (18 percent), 8 (7 percent), and 6 (5 percent) in the three groups, respectively (P=0.002).

CONCLUSIONS
Intravenous and oral N-acetylcysteine may prevent contrast-medium–induced nephropathy with a dose-dependent effect in patients treated with primary angioplasty and may improve hospital outcome. (ClinicalTrials.gov number, NCT00237614.)
CONTRAST-MEDIUM–INDUCED NEPHROPATHY is a recognized complication in coronary diagnostic and interventional procedures and is associated with prolonged hospitalization and adverse clinical outcomes. Patients with acute myocardial infarction treated with primary angioplasty are at higher risk of contrast-medium–induced nephropathy than are those undergoing elective interventions. In patients with acute myocardial infarction, several conditions may contribute to the development of renal dysfunction. Impaired systemic perfusion due to left ventricular dysfunction, a large volume of contrast medium, and the impossibility of starting renal prophylactic therapies before exposure to contrast medium are among the major factors that seem to be involved. Indeed, more complicated clinical courses and significantly higher inhospital mortality have been reported when contrast-medium–induced nephropathy occurs after primary angioplasty, even in patients who present with normal renal function. Thus, there is a pressing need to find effective strategies for the prevention of contrast-medium–induced nephropathy in this clinical setting in order to improve the outcome of patients treated with primary angioplasty.

Tepel et al. reported that the potent antioxidant N-acetylcysteine may prevent acute renal dysfunction in patients with chronic kidney disease who are undergoing procedures requiring the use of a radiocontrast medium. The ability of scavenging a variety of oxygen-derived free radicals and the improvement of endothelium-dependent vasodilation are properties of N-acetylcysteine that may confer protection against contrast-medium–induced renal dysfunction. Several studies on the prophylactic effect of N-acetylcysteine have been published, with contradictory results.

However, N-acetylcysteine has not been evaluated for the prevention of contrast-medium–induced nephropathy in patients undergoing primary angioplasty. N-acetylcysteine has several features that may play a favorable role in such patients. Notably, it can be administered as an intravenous bolus or rapid infusion immediately before intervention, unlike other measures such as saline hydration or newer preventive treatments that need to be started many hours before exposure to a contrast medium. Moreover, N-acetylcysteine has shown specific cardiac effects. Its administration in patients with acute myocardial infarction has been associated with less oxidative stress, a trend toward more rapid coronary reperfusion, a reduction in infarct size, and the preservation of left ventricular function. Finally, recent studies support the hypothesis of a dose-dependent effect of N-acetylcysteine, suggesting that a higher dose is needed when a greater amount of contrast medium is required. To evaluate the effect of N-acetylcysteine, both at standard and high doses, on the prevention of contrast-medium–induced nephropathy, we performed a prospective, randomized clinical study in patients with acute myocardial infarction who were undergoing primary angioplasty.

METHODOLOGY

STUDY POPULATION
Between February 20, 2003, and May 1, 2005, we screened all consecutive patients admitted to the coronary care unit at our institution, Centro Cardiologico Monzino in Milan, for ST-segment elevation acute myocardial infarction who underwent primary angioplasty. Patients were asked to be in the study if they presented within 12 hours (18 hours in cases of cardiogenic shock) after the onset of symptoms. Exclusion criteria were long-term dialysis and known allergy to N-acetylcysteine. The study was approved by the ethics committee of our institute, and written informed consent was obtained from all patients.

STUDY PROTOCOL
Eligible patients were randomly assigned in a 1:1:1 ratio to receive N-acetylcysteine at a standard dose (standard-dose group), N-acetylcysteine at a double dose (high-dose group), or placebo (control group). Computer-generated random numbers determined randomization. Patients in the standard-dose group received an intravenous bolus of 600 mg of N-acetylcysteine (Flumucil, Zambon Group) before primary angioplasty and a 600-mg tablet orally twice daily for the 48 hours after intervention (total dose of N-acetylcysteine, 3000 mg). Patients in the high-dose group received an intravenous bolus of 1200 mg of N-acetylcysteine before intervention and 1200 mg orally twice daily for the 48 hours after intervention (total dose of N-acetylcysteine, 6000 mg). After intervention, all treated patients and control patients underwent hydration with in-
travenous isotonic saline (0.9 percent) at a rate of 1 ml per kilogram of body weight per hour (or 0.5 ml per kilogram per hour in cases of overt heart failure) for 12 hours.

The decision to use an intraaortic balloon pump, inotropic drugs, abciximab, beta-blockers, angiotensin-converting–enzyme inhibitors, and diuretics was left to the discretion of interventional and coronary care unit cardiologists, as directed by international guidelines. Left ventricular function was evaluated by echocardiography in all patients within 24 hours after admission. Investigators involved in the procedures and those reading echocardiograms were blinded to the treatment randomization.

The primary end point of the study was the occurrence of contrast-medium–induced nephropathy, defined as an increase in the serum creatinine concentration of 25 percent or more from the baseline value within the 72-hour period after primary angioplasty. Creatinine concentration was measured at admission, every day for the next three days, and at hospital discharge. Creatinine clearance was calculated by applying the Cockcroft–Gault formula to the serum creatinine value. The major in-hospital clinical events, including death, were recorded.

Primary Angioplasty
Primary angioplasty was performed according to standard clinical practice. Patients in the coronary care unit received a bolus of 5000 U of heparin, followed by additional intraprocedural boluses to maintain the activated clotting time of 300 seconds or more (or 200 to 250 seconds when abciximab was used). A nonionic, low-osmolality contrast agent, iohexol (350 mg of iodine per milliliter; Omnipaque, Amersham Health), was used in all patients. Bare-metal stents were implanted in all patients according to standard techniques. Poststenting antithrombotic treatment consisted of aspirin and either clopidogrel or ticlopidine at standard dosages. N-acetylcysteine (Fluimucil, Zambon Group) was purchased by our institute.

Statistical Analysis
We calculated the sample size on the basis of a power analysis that assumed a reduction in the average rate of the primary end point of 50 percent in patients treated with N-acetylcysteine as compared with the control group (from 30 to 15 percent). The inclusion of 100 patients in each group allowed for a statistical power of 80 percent, with a type I error of 0.05. Continuous data are reported as means ±SD or medians and interquartile ranges where appropriate. Categorical data are presented as absolute values and percentages. The clinical characteristics of the three groups were compared with the use of the analysis of variance for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. The analysis of covariance was used to compare the time course of creatinine values among the three groups. Incidence of complications was compared among the three groups by the Wald chi-square test with two degrees of freedom and by the Mantel–Haenszel chi-square test for trend. A multivariable logistic-regression model, which included all the potential confounding factors (i.e., age, sex, baseline serum creatinine concentration, volume of contrast medium, and left ventricular ejection fraction), was applied. A P value of less than 0.05 was considered to indicate statistical significance. All calculations were computed with the aid of SAS software (version 8.02).

Results
A total of 354 patients (mean age, 62±12 years; 286 men) were initially enrolled. Of these patients, 119 were randomly assigned to receive placebo, 116 to receive a standard dose of N-acetylcysteine, and 119 to receive a high dose of N-acetylcysteine. Two patients were excluded after randomization, one from the standard-dose group because of death during angioplasty and one from the high-dose group because of emergency coronary bypass surgery due to critical left main stenosis.

Table 1 shows demographic, clinical, and angiographic characteristics of the three groups. There were no significant differences in baseline renal function or the size of myocardial infarction (estimated by creatine kinase MB peak value and left ventricular ejection fraction). At hospital admission, the baseline creatinine concentration was elevated (≥1.5 mg per deciliter [≥133 μmol per liter]) in 20 patients (5.7 percent). However, reduced renal function (creatinine clearance rate, ≤60 ml per minute) was present in 35 patients in the control group (29 percent), 33 in the standard-dose group (29 percent), and 26 in the high-dose group (22 percent) (P=0.36). The volume of contrast medi-
Received was also similar among groups, as were other risk factors for contrast-medium–induced nephropathy (e.g., age >75 years, anterior infarction, intraaortic counterpulsation, more than six hours from the onset of symptoms to reperfusion, and a volume of contrast medium of ≥300 ml).

Overall, contrast-medium–induced nephropathy occurred in 66 (19 percent) of the 352 patients. Its incidence was independently related to the presence of reduced renal function (creatinine clearance, ≤60 ml per minute) at baseline and depressed cardiac function (left ventricular ejection fraction, ≤40 percent) (Fig. 1) at baseline.

Table 2 shows in-hospital complications and deaths in the three groups. One patient in the standard-dose N-acetylcysteine group had a transient systemic rash, probably a side effect of N-acetylcysteine. The rate of contrast-medium–induced nephropathy was 33 percent in the control group, 15 percent in the standard-dose N-acetylcysteine group, and 8 percent in the high-dose N-acetylcysteine group (P<0.001). The frequency of contrast-medium–induced nephropathy was 18 percent, 6 percent, and 3 percent, respectively, when an absolute rise in creatinine (≥0.5 mg per deciliter [≥44 μmol per liter]) was used as the case definition (P<0.001). The multivariate analysis, adjusting for age, sex, baseline serum creatinine, volume of contrast medium, and left ventricular function, resulted in an odds ratio of contrast-medium–induced nephropathy in the control group as com-

### Table 1. Baseline Characteristics of the Patients. *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (N=119)</th>
<th>Standard-Dose N-Acetylcysteine Group (N=115)</th>
<th>High-Dose N-Acetylcysteine Group (N=118)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>62.6±12</td>
<td>62.5±13</td>
<td>62.2±11</td>
<td>0.96</td>
</tr>
<tr>
<td>Age &gt;75 yr — no. (%)</td>
<td>22 (18)</td>
<td>17 (15)</td>
<td>16 (14)</td>
<td>0.55</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>97 (82)</td>
<td>87 (76)</td>
<td>100 (85)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes — no. (%)</td>
<td>18 (15)</td>
<td>16 (14)</td>
<td>20 (17)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypertension — no. (%)</td>
<td>49 (41)</td>
<td>51 (44)</td>
<td>58 (49)</td>
<td>0.46</td>
</tr>
<tr>
<td>Dyslipidemia — no. (%)</td>
<td>37 (31)</td>
<td>35 (30)</td>
<td>51 (43)</td>
<td>0.07</td>
</tr>
<tr>
<td>Smoker — no. (%)</td>
<td>60 (50)</td>
<td>57 (50)</td>
<td>77 (65)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous myocardial infarction — no. (%)</td>
<td>28 (24)</td>
<td>17 (15)</td>
<td>19 (16)</td>
<td>0.17</td>
</tr>
<tr>
<td>Previous CAGB — no. (%)</td>
<td>5 (4)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>0.70†</td>
</tr>
<tr>
<td>LVEF — %</td>
<td>49±10</td>
<td>51±10</td>
<td>50±10</td>
<td>0.30</td>
</tr>
<tr>
<td>LVEF &lt;40% — no. (%)</td>
<td>24 (20)</td>
<td>22 (19)</td>
<td>23 (19)</td>
<td>0.98</td>
</tr>
<tr>
<td>Anterior infarction — no. (%)</td>
<td>58 (49)</td>
<td>56 (49)</td>
<td>49 (42)</td>
<td>0.44</td>
</tr>
<tr>
<td>Time to reperfusion — hr</td>
<td>3.5±2.2</td>
<td>3.4±2.4</td>
<td>3.4±2.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Time to reperfusion &gt;6 hr — no. (%)</td>
<td>15 (13)</td>
<td>16 (14)</td>
<td>15 (13)</td>
<td>0.94</td>
</tr>
<tr>
<td>Serum creatinine — mg/dl‡</td>
<td>1.06</td>
<td>1.01</td>
<td>1.02</td>
<td>0.40‡</td>
</tr>
<tr>
<td>Creatinine clearance — ml/min</td>
<td>75±21</td>
<td>79±29</td>
<td>79±25</td>
<td>0.80</td>
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<tr>
<td>Peak creatine kinase MB — ng/ml</td>
<td>224±213</td>
<td>229±286</td>
<td>262±252</td>
<td>0.45</td>
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<tr>
<td>Abciximab — no. (%)</td>
<td>52 (44)</td>
<td>50 (43)</td>
<td>56 (47)</td>
<td>0.78</td>
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<td>Intraaortic balloon pump — no. (%)</td>
<td>7 (6)</td>
<td>6 (5)</td>
<td>8 (7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Volume of contrast medium — ml</td>
<td>274±113</td>
<td>264±146</td>
<td>253±108</td>
<td>0.45</td>
</tr>
<tr>
<td>Volume of contrast medium ≥300 ml — no. (%)</td>
<td>35 (29)</td>
<td>34 (30)</td>
<td>32 (27)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, and LVEF left ventricular ejection fraction.
† The P value was calculated by Fisher’s exact test.
‡ To convert the values for serum creatinine to micromoles per liter, multiply by 88.4.
§ The P value was calculated by the nonparametric Wilcoxon rank-sum test.
pared with the standard-dose group of 2.60 (95 percent confidence interval, 1.30 to 5.18; P=0.007) and in the control group as compared with the high-dose group of 5.78 (95 percent confidence interval, 2.56 to 13.16; P<0.001).

Overall, in-hospital mortality was 5.9 percent and, as previously reported,7 was significantly higher in patients with contrast-medium–induced nephropathy than in those without (26 percent vs. 1.4 percent, P<0.001). In-hospital mortality was significantly reduced by N-acetylcysteine. The odds ratio of in-hospital death in the control group, as compared with the standard-dose and high-dose groups, was 1.85 (95 percent confidence interval, 0.54 to 6.37; P=0.32) and 5.43 (95 percent confidence interval, 1.24 to 23.81; P=0.05), respectively.

When the combined end point of death, acute renal failure requiring temporary renal replacement therapy, or the need for mechanical ventilation during the acute phase of myocardial infarction was considered, the rate was 18 percent in the control group, 7 percent in the standard-dose group, and 5 percent in the high-dose group (P=0.002). Multivariate analysis resulted in an odds ratio of the composite end point in the control group, as compared with the standard-dose and high-dose N-acetylcysteine groups, of 2.39 (95 percent confidence interval, 0.89 to 6.45; P=0.09) and 4.93 (95 percent confidence interval, 1.61 to 15.15; P=0.006), respectively.

A greater increase in the creatinine concentration was observed in the control patients than in patients treated with N-acetylcysteine (Fig. 2). Notably, N-acetylcysteine seemed to help prevent contrast-medium–induced nephropathy in patients with normal renal function and in those with reduced renal function, as well as in those with mildly or severely reduced left ventricular function (Fig. 3). No significant interactions were found between treatment and creatinine clearance (P=0.25) or left ventricular ejection fraction (P=0.71).

**Discussion**

The major finding of this study is that, among patients with acute myocardial infarction who are undergoing primary angioplasty, prophylactic treatment with an intravenous bolus of N-acetylcysteine followed by oral treatment for 48 hours and saline hydration for 12 hours seems to reduce the rate of contrast-medium–induced nephropathy as compared with a post-procedure 12-hour protocol of saline hydration alone. Moreover, in terms of the prevention of contrast-medium–induced nephropathy, high doses of N-acetylcysteine seem more beneficial than standard doses, suggesting a dose-dependent effect.

The negative effect of contrast-medium–induced nephropathy on the clinical outcome of patients undergoing diagnostic and interventional procedures is well known.4,5 In-hospital and long-term morbidity and mortality are particularly affected by contrast-medium–induced nephropathy in patients with preexisting renal failure and are noticeably increased in patients in whom acute renal failure requiring hemodialysis develops.3,31 Patients undergoing primary angioplasty have been shown to be at high risk for contrast-medium–induced nephropathy. In a previous study, we reported a 19 percent incidence of this serious complication in such patients and a close association with increased in-hospital morbidity and mortality.7

The risk of contrast-medium–induced nephropathy after primary angioplasty extends not only to patients with preexisting renal failure but also to those with normal baseline function. Therefore, in an era in which primary angioplasty is the preferred reperfusion treatment, prophylactic interventions against contrast-medium–induced ne-
Propathcy are warranted. The objective is to further reduce morbidity and mortality in this clinical setting.

Recent attention has been focused on N-acetylcysteine as a drug to attenuate contrast-medium–induced toxicity, owing to its ability to scavenge oxygen free radicals, thereby preventing direct oxidative tissue damage, and to its ability to counteract dye-induced renal vasoconstriction. Recent studies support the hypothesis that a greater dose of N-acetylcysteine may be needed.
when a large volume of contrast medium is used. In the Rapid Protocol for the Prevention of Contrast-Induced Renal Dysfunction (RAPPID) trial, patients with mild-to-moderate chronic renal failure undergoing elective coronary interventions received intravenous N-acetylcysteine at a dose of 150 mg per kilogram before exposure to the contrast medium (volume of contrast medium, >200 ml) and a dose of 50 mg per kilogram over the following four-hour period. In a patient weighing 70 kg, this corresponds to a cumulative dose of 14,000 mg, which is significantly higher than that used in the study by Tepel et al. (2400 mg). The RAPPID trial showed a significantly lower incidence of contrast-medium–induced nephropathy in treated patients as compared with controls (5 percent vs. 21 percent, P=0.04).

In another study involving patients with chronic renal failure, the results of standard (600-mg) or high (1200-mg) doses of N-acetylcysteine orally twice daily were compared before and after administration of the contrast medium. The rate of contrast-medium–induced nephropathy was lower in patients receiving the high dose (4 percent vs. 11 percent, P=0.03). The benefit of high-dose N-acetylcysteine was greater in patients receiving a larger volume of contrast medium (i.e., ≥140 ml). In agreement with these observations, our findings support a dose-dependent protective effect of N-acetylcysteine. In our study, the incidence of contrast-medium–induced nephropathy was significantly lower in patients receiving a cumulative dose of 6000 mg than in those treated with a cumulative dose of 3000 mg. The rate of contrast-medium–induced nephropathy was independently related to the presence of both renal-function impairment at baseline and more depressed left ventricular function. This suggests that renal and cardiac impairment may substantially amplify the risk of contrast-medium–induced nephropathy in such patients and that the observed acute worsening in renal function may be the result of the joint effects of the toxicity of the contrast medium and acute ischemic injury. The preventive and dose-dependent effect of N-acetylcysteine was observed in patients with normal and in those with impaired renal function at baseline, as well as in those with mildly and those with severely impaired ventricular function. This suggests that N-acetylcysteine not only prevents direct contrast-medium–induced nephrotoxicity but also exerts a broader kidney-protective effect.

Given the strong association between contrast-medium–induced nephropathy and in-hospital morbidity and mortality in patients with acute myocardial infarction treated with primary angioplasty, a critical question is whether the prevention of contrast-medium–induced nephropathy has any effect on the clinical outcome. A major limitation of previous studies that used N-acetylcysteine for the prevention of contrast-medium–induced nephropathy is that no conclusive data on morbidity and mortality were reported.

Our study was primarily designed to evaluate the incidence of contrast-medium–induced nephropathy and, hence, was not aimed or powered to assess differences in morbidity and mortality. Despite this limitation, it is noteworthy that in parallel with a reduced rate of contrast-medium–induced nephropathy, the rate of in-hospital death was significantly lower among patients treated with N-acetylcysteine. The mortality rate in our control group was in the upper range of mortality rates reported in registries that reflect real-world clinical practice. Thus, it is possible that some of the observed difference in mortality between the control group and the groups treated with N-acetylcysteine is due to statistical chance. Alternatively, the difference may reflect a beneficial effect of N-acetylcysteine on renal function that in turn resulted in reduced mortality.

Similarly, the beneficial effect of N-acetylcysteine on the combined end point of death and two major clinical complications — acute renal failure requiring temporary renal-replacement ther-

Figure 2. Median and Interquartile Range of Serum Creatinine Concentration before Primary Angioplasty (Baseline), at Days 1, 2, and 3, and at Discharge.
P for trend=0.004. The filled squares, triangles, and circles represent medians, and the I bars represent the interquartile range for each data point.
apy and acute pulmonary edema requiring mechanical ventilation — may have been related to acute impairment of kidney function. It would be premature to draw inferences about the efficacy of N-acetylcysteine on the basis of these clinically meaningful end points. Although our findings are promising, further data are needed before any conclusions can be made. Future studies should also investigate whether the extrarenal effects of N-acetylcysteine play some beneficial role. Indeed, in both clinical and experimental studies of acute myocardial infarction, intravenous infusion of N-acetylcysteine has been associated with decreased infarct size and improvement in left ventricular function, possibly because of the antioxidant properties of this drug and its scavenging of free radicals. These cardiac effects may be enhanced in patients treated with thrombolysis or percutaneous coronary interventions — a clinical setting in which oxidative stress and reperfusion injury have been shown to occur. These deleterious phenomena may be more pronounced after primary angioplasty, owing to increased rates of coronary patency with more rapid and complete flow restoration. Moreover, N-acetylcysteine also inhibits platelet aggregation. Unfortunately, we could not assess how much of the difference in outcome between patients treated with N-acetylcysteine and control patients was due to the expression of a specific renal protective effect of this drug or indirectly to its cardioprotective properties, resulting in greater recovery of left ventricular function and, therefore, amelioration of systemic and renal hemodynamics.

In conclusion, we found that N-acetylcysteine reduced the severity of contrast-medium–induced nephropathy in patients with acute myocardial infarction treated with primary angioplasty. The effect appears to be dose-dependent and is accompanied by a significantly improved in-hospital outcome. The mechanisms underlying the improvement in the in-hospital clinical outcome have not been completely elucidated, and studies of potential extrarenal effects of N-acetylcysteine are warranted.

Supported by Centro Cardiologico Monzino and by a grant (CCS16-RC2003) from the Italian Ministry of Health.

No potential conflict of interest relevant to this article was reported.

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Figure 3. Incidence of Contrast-Medium–Induced Nephropathy in the Three Study Groups Stratified According to the Creatinine Clearance Rate and Left Ventricular Ejection Fraction (LVEF).

Panel A shows normal and reduced creatinine clearance rates (>60 ml per minute and ≤60 ml per minute, respectively), and Panel B LVEF of more than 40 percent and 40 percent or less. P values refer to comparisons among the placebo group, the group receiving a standard dose of N-acetylcysteine, and the group receiving a double dose of N-acetylcysteine (calculated with the use of chi-square for trend). No significant interactions were found between groups and creatinine clearance (P = 0.25) or between groups and LVEF (P = 0.71).
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