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Impact of High-Dose *N*-Acetylcysteine Versus Placebo on Contrast-Induced Nephropathy and Myocardial Reperfusion Injury in Unselected Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial

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Objectives The aim of this randomized, single-blind, controlled trial was to assess *N*-acetylcysteine effects on contrast-induced nephropathy and reperfusion injury in ST-segment elevation myocardial infarction patients undergoing primary angioplasty with moderate contrast volumes.

Background High-dose *N*-acetylcysteine reduced the incidence of contrast-induced nephropathy in patients with high contrast volumes and reduced reperfusion injury in animal trials.

Methods Patients undergoing primary angioplasty were randomized to either high-dose *N*-acetylcysteine (2 × 1,200 mg/day for 48 h; n = 126) or placebo plus optimal hydration (n = 125). The 2 primary end points were: 1) the occurrence of >25% increase in serum creatinine level <72 h after randomization; and 2) a reduction in reperfusion injury measured as myocardial salvage index by magnetic resonance imaging.

Results The median volume of an iso-osmolar contrast agent during angiography was 180 ml (interquartile range [IQR] 140 to 230 ml) in the *N*-acetylcysteine and 160 ml (IQR 120 to 220 ml) in the placebo group (p = 0.20). The primary end point contrast-induced nephropathy occurred in 14% of the *N*-acetylcysteine group and in 20% of the placebo group (p = 0.28). The myocardial salvage index was also not different between both treatment groups (43.5; IQR 25.4 to 71.9 vs. 51.5; IQR 29.5 to 75.3; p = 0.36). Activated oxygen protein products and oxidized low-density lipoprotein as markers for oxidative stress were reduced by as much as 20% in the *N*-acetylcysteine group (p < 0.05), whereas no change was evident in the placebo group.

Conclusions High-dose intravenous *N*-acetylcysteine reduces oxidative stress. However, it does not provide an additional clinical benefit to placebo with respect to CIN and myocardial reperfusion injury in nonselected patients undergoing angioplasty with moderate doses of contrast medium and optimal hydration. (Myocardial Salvage and Contrast Dye Induced Nephropathy Reduction by N-Acetylcysteine [LIPSIA-N-ACC]; NCT00463749) (J Am Coll Cardiol 2010;55:2201–9) © 2010 by the American College of Cardiology Foundation

Infarct size is a major determinant of mortality in acute myocardial infarction (AMI). Currently, the most effective way to limit infarct size is to reperfuse the infarct-related artery as soon as possible, preferably by percutaneous coronary intervention (PCI) (1–3). Although reperfusion is undoubtedly beneficial, reperfusion itself can induce processes of myocardial reperfusion injury resulting in additional death of cardiomyo-

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Abbreviations and Acronyms

AMI = acute myocardial infarction
AOPP = advanced oxidation protein products
CIN = contrast-induced nephropathy
IQR = interquartile range
MRI = magnetic resonance imaging
MSI = myocardial salvage index
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction

cytes that were viable at the time of reperfusion (4). Oxidative stress is one of the major factors contributing to reperfusion injury (4,5). *N*-acetylcysteine might reduce the infarct size by its antioxidant properties (6,7).

In addition, patients with AMI treated by PCI are at increased risk of contrast-induced nephropathy (CIN), which is associated with prolonged hospitalization and adverse clinical outcome (8–10). Major factors associated with an increased CIN risk are impaired systemic perfusion, large contrast volume, and the inability to perform adequate prophylaxis. In a recent trial, optimal hydration in combination with high-dose *N*-acetylcysteine prevented CIN in patients with relatively high contrast doses (8).

The low cost of *N*-acetylcysteine, its ease of administration, and its limited adverse effects are compelling reasons to further investigate its role in patients with AMI. This randomized, single-blind, placebo-controlled trial was therefore conducted to assess the effects of high-dose *N*-acetylcysteine on reperfusion injury and CIN prevention after moderate contrast doses.

Methods

Study population. This trial was conducted at the University of Leipzig–Heart Center between November 2006 and February 2008 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The study protocol was approved by the local ethics committee and the Bundesinstitut für Arzneimittel und Medizinprodukte, Germany. All patients gave written informed consent.

Patients with AMI undergoing primary PCI were eligible if their symptoms lasted <12 h and if they had ST-segment elevation of ≥0.1 mV in ≥2 extremity leads or ≥0.2 mV in ≥2 pre-cordial leads. Exclusion criteria were previous fibrinolysis <12 h, known *N*-acetylcysteine allergy, chronic dialysis, and pregnancy. Furthermore, patients with contraindications to magnetic resonance imaging (MRI) at study entry were excluded.

Study protocol. Eligible patients were randomly assigned in a 1:1 ratio to receive high-dose *N*-acetylcysteine or matching placebo using computer-generated random numbers. *N*-acetylcysteine (ACC inject; Hexal AG, Holzkirchen, Germany) patients received an intravenous bolus of 1,200 mg before angioplasty and 1,200 mg intravenously twice daily for the 48 h after PCI (total dose 6,000 mg), whereas control patients received matching placebo (10 ml of NaCl 0.9% at each injection). After PCI, all treated and control patients underwent hydration with intravenous NaCl (0.9%) infusion at a rate of 1 ml/kg of body weight per h for 12 h (or 0.5 ml/kg/h in overt heart failure). Patients and investigators assessing the outcomes were unaware of the group assignment.

Primary angioplasty and subsequent treatment. PCI was performed according to standard clinical practice using a nonionic, low-osmolality contrast agent, iopromide (Ultravist 370, Schering, Berlin, Germany). The use of bare metal or drug-eluting stents was left to the interventionalist's discretion. Additional use of thrombectomy was recommended depending on thrombus in the infarct-related artery. All patients received 500 mg of aspirin and heparin (60 U/kg of body weight) intravenously before PCI. Clopidogrel (600 mg orally during PCI, followed by 75 mg/day for at least 12 months) was mandatory. Aspirin was given indefinitely at a dose of 100 mg/day (1).

Outcomes. The 2 primary outcomes were: 1) the occurrence of CIN within 72 h after PCI; and 2) reperfusion injury measured as the myocardial salvage index (MSI) by MRI. The secondary outcome measure for CIN was the need for temporal renal replacement therapy. For reperfusion injury, the secondary outcome parameters were infarct size and microvascular obstruction measured by MRI (11), early ST-segment resolution (11), and infarct size measured as the area under the curve of creatine kinase-MB release derived from measurements every 6 h over 2 days. Oxidative stress occurring before, immediately after, and within 72 h after PCI was measured for further causal explanations; in addition, a clinical composite of major adverse cardiovascular events within 6 months after randomization was assessed.

Definition of nephropathy. CIN was defined as an increase in serum creatinine concentration of ≥25% from baseline within 72 h after PCI. Creatinine concentration was measured at admission and every day in the morning for the next 3 days. Creatinine clearance was estimated using the Modification of Diet in Renal Disease study equation (12).

Definitions of reperfusion injury. Reperfusion injury was determined as MSI derived from MRI at days 2 to 4 after the index event. The area at risk, infarct size, and microvascular obstruction were acquired on a 1.5-T scanner (Philips Intera CV, Best, the Netherlands). Left ventricular function was assessed by a steady-state free precession technique. For area at risk determination, short-axis slices covering the whole ventricle using a T2-weighted turbo spin echo sequence were obtained (13,14). Early and delayed enhancement images covering the whole ventricle were acquired approximately 1 and 15 min after intravenous administration of 0.2 mmol/kg of body weight of gadobutrol (Gadovist, Schering) (11). Total left ventricular myocardial mass, early and late microvascular obstruction, area at risk, and infarct size were assessed manually by fully blinded operators (11,15). The following parameters were calculated as described

previously (11,16): 1) area at risk = volume edema/volume left ventricular mass; 2) % infarct size = volume infarct/volume left ventricular mass; % microvascular obstruction = volume microvascular obstruction/volume left ventricular mass; and 3) myocardial salvage = area at risk − infarct size; 4) MSI = area at risk − infarct size/area at risk. The core laboratory has excellent reproducibility for infarct size measurement, and the bias and limits of agreement for MSI assessment are 0.3 ± 5.0 (15).

ST-segment resolution. The percentage of ST-segment resolution (approximately 90 min after PCI) was calculated as described previously (16).

Infarct size measured by enzyme release. Infarct size was indirectly measured by the area under the curve of creatine kinase-MB release derived from measurements every 6 h over 2 days.

Oxidative stress. For oxidative stress measurements before, directly after PCI, and subsequently for up to 3 days, venous blood samples were collected and plasma was stored at −80°C until used for measurements. Parameters measured by enzyme-linked immunosorbent assay (Immundiagnostik, Bensheim, Germany) as indirect markers for oxidative stress included advanced oxidation protein products (AOPPs) and oxidized low-density lipoprotein.

Clinical end points. Clinical end points were a composite of death, reinfarction, and the occurrence of new congestive heart failure <6 months after randomization. Post-hospital follow-up included one 6-month outpatient visit. The diagnosis of reinfarction was based on previous definitions (11). New heart failure was defined as any congestive heart failure (rales, dyspnea, New York Heart Association functional class III/IV) occurring >24 h after the index event. Outcomes were adjudicated by a clinical events committee unaware of the patient's assigned treatment.

Statistical analysis. The number of patients included in this study was based on a previous trial of *N*-acetylcysteine for CIN prevention (8). Assuming a slightly lower incidence, because of lower contrast volumes, we assumed a reduction in the average nephropathy rate from 25% to 10% in *N*-acetylcysteine–treated patients. The inclusion of 113 patients in each group allowed for a statistical power of 80% with a type I error of 0.05.

For reperfusion injury, we assumed an MSI of 50 ± 15% (17). With a power of 80% and a 2-sided α value of 0.05, we estimated that 100 patients would be required in each group to detect an absolute difference of 6% in MSI. A total of 251 patients were included to allow for the possibility of missing MRI studies and missing creatinine values.

Continuous data are reported as medians and interquartile ranges (IQRs), if not otherwise stated. Categorical data are presented as absolute values and percentages. Differences between treatment groups were assessed by the Fisher exact or the chi-square test for categorical variables and by the Student

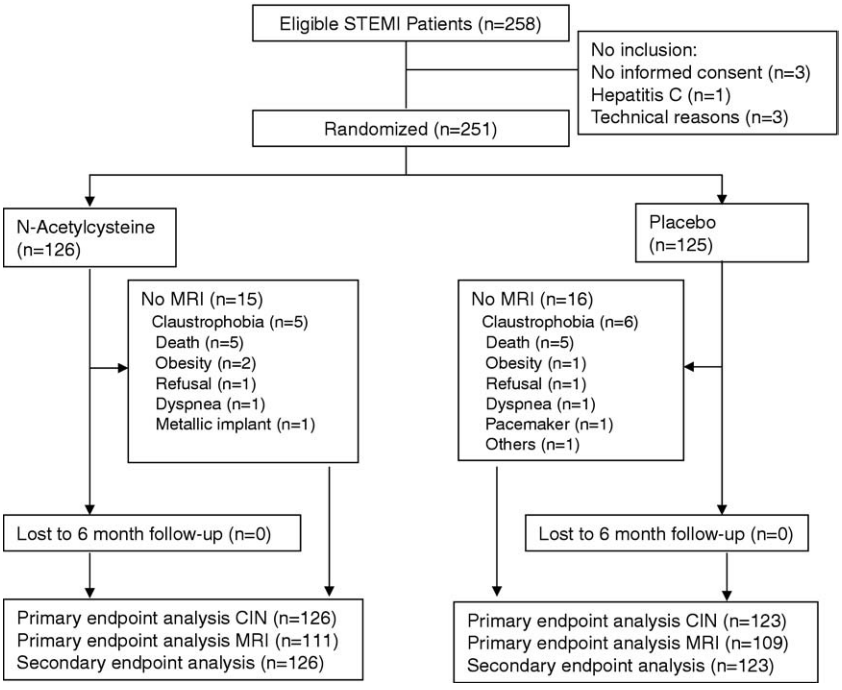

Figure 1 Study Flow and Distribution of Procedures

Study flow, excluded patients, and number of patients for end point analysis in each treatment group.
CIN = contrast-induced nephropathy; MRI = magnetic resonance imaging; STEMI = ST-segment elevation myocardial infarction.

t test for continuous data with normal distribution. Otherwise the nonparametric Mann-Whitney test was used.

Serial creatinine concentrations, creatinine clearance, and oxidative stress parameters were compared within and between groups using repeated-measures analysis of variance. A multivariable logistic regression model including age, sex, diabetes, hypertension, baseline serum creatinine concentration, creatinine clearance, contrast volume, and left ventricular ejection fraction was applied to assess confounders for nephropathy. For reperfusion injury, symptom duration, infarct location, and pre- and post-interventional Thrombolysis In Myocardial Infarction (TIMI) flow were added to a linear multivariable model. All statistical tests were performed with SPSS software, version 15.0 (SPSS, Inc., Chicago, Illinois). A 2-tailed p value <0.05 was considered statistically significant.

Results

Of the 251 patients enrolled, 126 were randomly assigned to *N*-acetylcysteine and 125 to placebo (Fig. 1). Only 7 eligible patients were not included during the study period. All patients received the assigned treatment. The baseline characteristics and medication were similar between groups (Table 1). There were no adverse events during *N*-acetylcysteine administration. Reperfusion times were similar with a median time from symptom onset to PCI of 230 min (IQR 147 to 375 min) and 263 min (IQR 160 to 422 min; p = 0.28), respectively. The door to balloon time was 27 min (IQR 20 to 35 min) versus 26 min (IQR 22 to 35 min; p = 0.66).

In the *N*-acetylcysteine group, 2 patients had apical ballooning syndrome and in the placebo group, 1 had myocarditis; thus, these patients had normal coronary arteries. In all other patients, PCI was performed. In 17% versus 22%, drug-eluting stents were used (p = 0.34). Post-PCI TIMI flow grade 3 was achieved in 91% versus 92% (p = 0.89). In the placebo group, 2 patients died during catheterization with the consequence of no further assessment of creatinine and oxidative stress parameters (Fig. 1).

Table 1 Main Patient Characteristics

Variable	*N*-Acetylcysteine (n = 126)	Placebo (n = 125)	p Value
Age, yrs	68 (57–75)	68 (56–76)	0.33
Male sex	89 (71)	82 (66)	0.47
Cardiovascular risk factors			
Current smoking	40 (32)	54 (43)	0.08
Hypertension	89 (71)	92 (74)	0.70
Hypercholesterolemia	40 (32)	46 (37)	0.48
Diabetes mellitus	32 (25)	41 (33)	0.25
Previous myocardial infarction	13 (10)	16 (13)	0.68
Previous coronary artery bypass grafting	1 (1)	4 (3)	0.36
Anterior myocardial infarction	57 (45)	64 (51)	0.41
Number of diseased vessels			0.95
0	2 (2)	1 (1)	
1	62 (49)	62 (50)	
2	32 (25)	33 (26)	
3	30 (24)	29 (23)	
Killip class on admission			0.78
1	87 (69)	84 (67)	
2	32 (26)	30 (24)	
3	4 (3)	7 (6)	
4	3 (2)	4 (3)	
Intra-aortic balloon pump	7 (6)	7 (6)	0.80
Concomitant medications			
Beta-blockers	124 (98)	122 (98)	0.99
ACE-inhibitors/AT-1-antagonist	124 (98)	122 (98)	0.99
Aspirin	125 (99)	124 (99)	0.62
Clopidogrel	124 (98)	123 (98)	0.00
Statins	125 (99)	123 (98)	0.99
Aldosterone antagonist	5 (4)	5 (4)	0.76
Glycoprotein IIb/IIIa inhibitor	117 (93)	118 (94)	0.81
Serum creatinine, μmol/l	81 (69–97)	78 (67–90)	0.32
Creatinine clearance, ml/min	85 (67–97)	86 (69–99)	0.59
Volume of contrast agent, ml	180 (140–230)	160 (120–220)	0.20
Volume of contrast agent ≥300 ml	19 (15)	17 (14)	0.88

Values are median (interquartile range) or n (%).
ACE = angiotensin-converting enzyme; AT-1 = angiotensin 1.

CIN. There were no significant differences in baseline renal function, the volume of contrast medium, and the number of patients with high contrast volume of ≥300 ml (Table 1). The baseline creatinine concentration was elevated (≥105 μmol/l) in 21 (17%) patients in the *N*-acetylcysteine and 16 (13%) patients in the placebo group (p = 0.53), whereas the creatinine clearance was reduced (≤60 ml/min) in 24 (19%) versus 23 (19%; p = 0.98).

Overall, CIN occurred in 18 (14%) patients in the *N*-acetylcysteine and 25 (20%) patients in the placebo group (p = 0.28) with no significant differences in patients with or without impaired creatinine clearance at baseline (Fig. 2). The change in serum creatinine concentration and creatinine clearance for both treatment groups is shown in Figure 3. Twenty-three percent of patients with high contrast doses had CIN (8 of 35 patients) versus 16% (35 of 213 patients; p = 0.49), and there was no difference in *N*-acetylcysteine versus placebo in patients with high contrast volumes. In total, 5 patients needed dialysis (n = 4 *N*-acetylcysteine vs. n = 1 placebo; p = 0.37).

In a multiple logistic regression model for development of nephropathy, the strongest predictors of CIN were age, female sex, and creatinine clearance (p < 0.05 for all). *N*-acetylcysteine use was not a predictor (p = 0.53).

Reperfusion injury. MRI. Results of MRI were available for 111 (88%) patients in the *N*-acetylcysteine group and for 109 (87%) patients in the placebo group (Fig. 1). Reasons for not undergoing MRI are listed in Figure 1. The median time between randomization and MRI was 3 days (IQR 2 to 4) for both groups (p = 0.38). There was no difference in the primary end point MSI or in any other parameter derived from MRI (Table 2). There was also no effect of *N*-acetylcysteine in different subgroups of AMI (anterior vs. nonanterior infarction, symptom duration <6 h vs. >6 h, TIMI flow grade 3 vs. <3). In a multivariable linear regression model, the strongest predictors of MSI were post-PCI TIMI flow, symptom duration, and anterior infarct location (p < 0.01 for all). *N*-acetylcysteine use had no effect on MSI (p = 0.21).

ENZYMATIC INFARCT SIZE. The enzymatic infarct size assessed by the area under the curve of creatine kinase-MB release was similar between the *N*-acetylcysteine and placebo groups with 338 μmol/l/h (IQR 290 to 383 μmol/l/h) versus 313 μmol/l/h (IQR 260 to 356 μmol/l/h; p = 0.13).

ST-SEGMENT RESOLUTION. In 2 placebo patients, the ST-segment resolution was not interpretable because the patients died during angioplasty. ST-segment resolution was not different between the groups (66.7%; IQR 45.6% to 100.0% vs. 68.1%; IQR 33.3% to 100.0%; p = 0.57).

Oxidative stress. The baseline oxidative stress was similar in both treatment groups (AOPP, 40.4 μmol/l; IQR 27.5 to 54.3 μmol/l vs. 40.9 μmol/l; IQR 29.9 to 58.9 μmol/l; p = 0.30; oxidized low-density lipoprotein, 32.3 ng/ml; IQR 12.7 to 141.8 ng/ml vs. 34.8 ng/ml; IQR 16.4 to 95.1 ng/ml; p = 0.94). However, in the *N*-acetylcysteine group, there was a reduction in AOPP for measurements at days 1 and 2 and oxidized low-density lipoprotein at days 1, 2, and 3 in contrast to the placebo group (Fig. 4).

Clinical outcome. At 6-month follow-up, there were 12 (9.6%) deaths in each group. Nonfatal reinfarctions occurred in 3 (2.4%) after *N*-acetylcysteine and in 4 (3.2%)

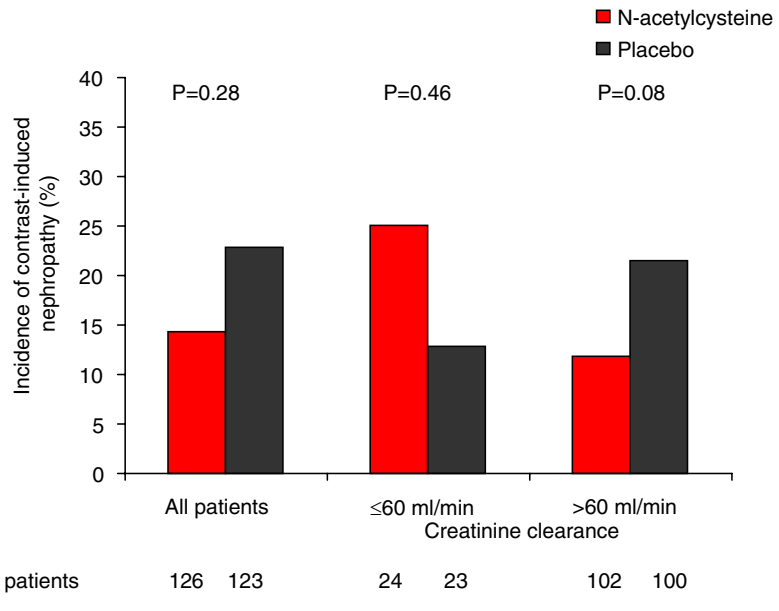

Figure 2 **Incidence of CIN**

Overall incidence of contrast-induced nephropathy (CIN) in patients with creatinine clearance ≤60 ml/min and >60 ml/min and the corresponding p values.

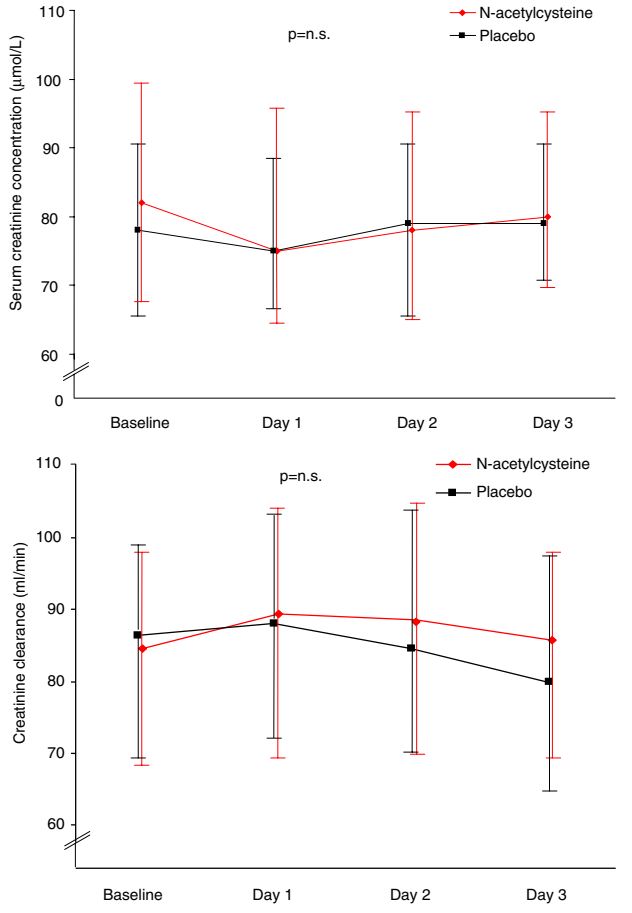

Figure 3 **Change in Serum Creatinine Concentration and Creatinine Clearance**

Median and interquartile range of serum creatinine concentration **(A)** and creatinine clearance **(B)** before primary angioplasty (baseline), at days 1, 2, and 3. There was no significant difference for any of the values between the treatment groups.

after placebo administration. New congestive heart failure occurred in 11 (8.7%) and 7 (5.6%), respectively. Thus, the composite major adverse cardiac event rate at 6-month follow-up was 20.6% after *N*-acetylcysteine and 18.4% after placebo administration (p = 0.77).

Discussion

In this prospective, randomized, single-blind trial, *N*-acetylcysteine significantly reduced oxidative stress. However, it was ineffective in preventing CIN and did not lead to a measurable benefit in reperfusion injury in patients undergoing primary PCI for AMI. This lack of efficacy of *N*-acetylcysteine was independent of typical risk factors for the development of CIN and also for confounders in infarction and MSI.

Because of its ability to scavenge oxygen free radicals and to counteract dye-induced renal vasoconstriction, *N*-acetylcysteine has been used in several previous trials for CIN attenuation. Since the first positive results after administration of 600 mg *N*-acetylcysteine before and after elective contrast medium exposure plus hydration (18), there has been no conclusive evidence of the effectiveness (19–21). Recently published trials in elective contrast administration in patients with chronic renal insufficiency suggested a dose-dependent effect (22,23). This was confirmed in a nonblinded trial in patients with AMI in whom high-dose *N*-acetylcysteine (cumulative dose 6,000 mg vs. 3,000 mg vs. placebo) was more effective in CIN prevention (8). Moreover, the dose-dependent effect was accompanied by improved in-hospital outcome. In the current single-blind trial, the same high-dose was administered; however, overall, there was no benefit. This might be explained in part by the different dose of contrast medium (170 ml vs. 250 to 270 ml). However, in the current trial, there was no preventive effect in high contrast doses of >300 ml. Another potential explanation might be the slightly better renal function at baseline (mean 81 and 85 ml/min vs. 75 to 79 ml/min) (8). Overall, this difference was small, making it unlikely that these differences had influenced the results. It might be argued that *N*-acetylcysteine is only preventive in patients with severely impaired renal function, which, due to the disease's nature, cannot be assessed

Table 2 **Magnetic Resonance Results**

Variable	*N*-Acetylcysteine (n = 111)	Placebo (n = 109)	p Value
Area at risk, %LV	34.4 (28.0–44.8)	34.5 (28.6–41.7)	0.78
Infarct size, %LV	17.4 (9.1–25.9)	14.3 (8.0–26.2)	0.47
Myocardial salvage, %LV	13.2 (8.1–26.5)	15.9 (9.6–24.5)	0.41
Myocardial salvage index	43.5 (25.4–71.9)	51.5 (29.5–75.3)	0.36
Early microvascular obstruction, %LV	2.1 (0.8–4.8)	1.9 (0.4–3.9)	0.38
Late microvascular obstruction, %LV	0.7 (0.2–1.5)	0.6 (0.0–1.2)	0.25
LV ejection fraction, %	52.1 (43.5–59.2)	50.6 (41.6–58.6)	0.23
LV end-diastolic volume, ml	145.0 (118.8–167.8)	136.0 (119.0–159.3)	0.19
LV end-systolic volume, ml	68.4 (50.7–89.6)	70.9 (49.3–89.1)	0.99

Data are presented as median (interquartile range).
LV = left ventricular.

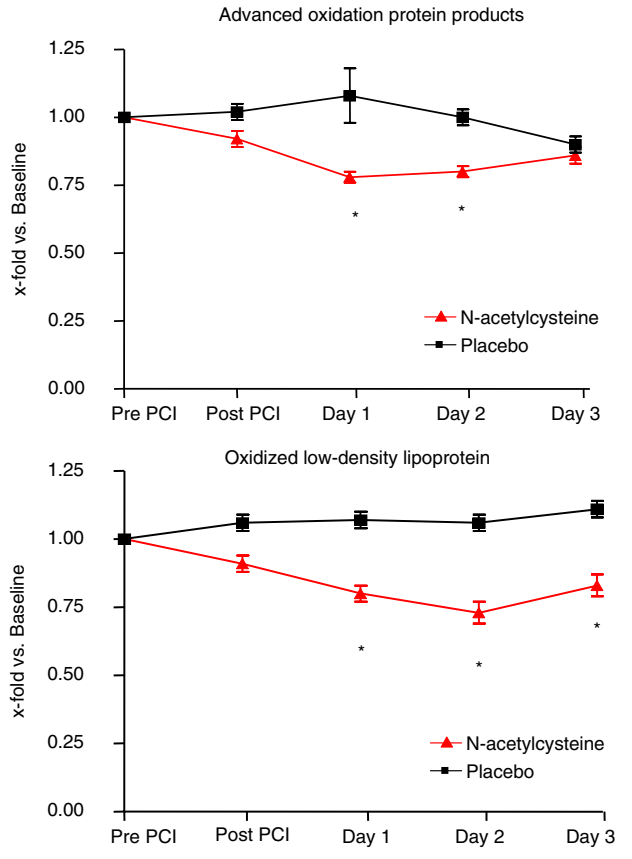

Figure 4 **Oxidative Stress**

Mean ± SEM of the percentage of change in oxidative stress (advanced oxidation protein products **[A]**; oxidized low-density lipoprotein **[B]**) from baseline (pre-angioplasty) to post-angioplasty and days 1, 2, and 3. *$p < 0.05$ for the change in oxidative stress from baseline and in comparison to placebo. PCI = percutaneous coronary intervention.

before primary PCI because of time constraints. In this previous trial, under the specific circumstances of AMI with impaired systemic perfusion, high contrast volume, and without optimal preventive measures, *N*-acetylcysteine prevented CIN in patients irrespective of baseline creatinine clearance (8). In the current trial, there was no effect for patients with and without impaired creatinine clearance, underscoring the lack of effect. Overall, the differences between the 2 trials can hardly explain the observed differences in CIN prevention and reflects the overall heterogeneity across *N*-acetylcysteine studies (21).

Negative study results raise a question of power. Despite performing an a priori sample power calculation based on previous results, which was adapted due to the lower contrast volume, the estimate was still inaccurate (8). Based on the current results with 20% versus 14% CIN occurrence in the placebo and *N*-acetylcysteine groups, respectively, a study would need 647 patients in each group to detect a difference with 80% power. As there were virtually no changes in creatinine and creatinine clearance and also on the clinical requirement for renal replacement therapy, any clinical benefit is highly questionable. Given the current evidence of elective contrast administration with potential sample sizes of 32,200 patients to prevent CIN by *N*-acetylcysteine, it will be even more difficult to show any clinical benefit in AMI (20).

Another limitation of previous randomized trials of CIN in elective and urgent cardiac catheterization is the limited follow-up beyond the first days after contrast exposure and, despite beneficial effects in CIN prevention in some trials, evidence of any improvement in outcome at long-term follow-up is still lacking (8,21,24,25). In the current study, clinical adverse events up to 6 months are reported among all randomized patients. However, there were no statistically significant differences in the combined composite end point between treatment groups.

Reperfusion injury caused by the restoration of coronary blood flow after an ischemic episode has been addressed by numerous trials, and oxidative stress is one of the potential targets (4). In previous trials, *N*-acetylcysteine reduced animal infarct sizes and led to preservation of left ventricular function in a small human trial (6,7,26). However, it also led to a more heterogeneous appearance of the infarcts with increased ventricular arrhythmias (26). In addition, there are several positive effects on platelet and vascular function (27,28). Similar to several previous trials of reperfusion injury reduction, translation of these beneficial effects into the clinical setting has been disappointing (4). In comparison with nuclear techniques, a very sensitive imaging method has been used (29). Therefore, it is unlikely that any difference in MSI or infarct size has been missed. As there was virtually no effect on MSI, it is extremely unlikely that the trial was underpowered to detect differences in MSI. Furthermore, in contrast to previous trials assessing MSI, a 3-dimensional dataset of the area at risk and the infarct size was acquired, leading to a complete coverage of the left ventricle with further accuracy of the imaging method (14). In addition, the observed infarct size and MSI were in the range of those of previously reported trials in primary PCI, reflecting the appropriateness of the imaging method (11,16,30).

Experimental and clinical studies have shown that reperfusion of ischemic myocardium induces oxidative stress, which reduces the bioavailability of nitric oxide, thereby leading to neutrophil accumulation, activation of superoxide radicals, and impairment of coronary blood flow (4,5). *N*-acetylcysteine can reduce oxidative stress in conjunction with fibrinolysis as early as 4 h after reperfusion (31). In general, oxidative stress agents are highly active, short-lived, and almost immediately react with surrounding molecules at the site of formation. However, these species leave a detectable trace of modified oxidative products. Therefore, the measured markers in the

current trial are likely to represent the consequences of oxidative stress. However, similar to previous trials, the change in oxidative stress did not result in a measurable clinical benefit (4).

Study limitations. The primary study end point of CIN and MSI could not be determined in 0.7% and 12.4%, respectively. Because the number of patients in both groups was identical and the baseline characteristics of patients undergoing and those not undergoing end point assessment were similar, this minimizes a potential selection bias. The exclusion of patients from MRI is inherent to this imaging method (11). Moreover, these patients were included in the analysis of clinical adverse events. Although the interventionalists coronary care unit physicians were blinded to all laboratory, electrocardiographic, and MRI measurements, they were aware of the group assignment. However, the single-blind design rules out a potential patient bias. Finally, despite performing a multivariate analysis, it cannot entirely be ruled out that slight imbalances in baseline clinical and procedural risk factors may have led to the diminished effect of *N*-acetylcysteine.

Conclusions

High-dose intravenous *N*-acetylcysteine reduces oxidative stress after reperfusion for AMI. However, it does not provide an additional clinical benefit to placebo with respect to nephropathy and myocardial reperfusion injury in a nonselected patient group undergoing primary PCI with moderate doses of contrast medium and optimal hydration given the powered effect size. Any true difference of intravenous *N*-acetylcysteine administration in addition to hydration is likely to be small and presumably not clinically relevant.

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Key Words: contrast media ■ free radicals ■ infarction ■ magnetic resonance imaging ■ nephropathy ■ reperfusion.