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Acetylcysteine for Prevention of Acute Deterioration of Renal Function Following Elective Coronary Angiography and Intervention

A Randomized Controlled Trial

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CONTRAST NEPHROPATHY IS A recognized complication after coronary angiography and intervention that has been associated with prolonged hospitalization and adverse clinical outcomes.¹⁻³ It is reported that 14.5% of patients develop a 25% increase in serum creatinine levels following cardiac catheterization.² This problem assumes greater and greater importance with increased use of invasive radiological procedures to diagnose and treat coronary artery disease.

Contrast nephropathy is potentially preventable because the administration of radiocontrast agent is predictable and high-risk populations also have been identified.⁴ Patients at greatest risk are those with impaired renal function,⁵ particularly that caused by diabetic nephropathy.⁶ However, other than the use of intravenous hydration² and low-osmolality contrast media,⁷ no previ-

For editorial comment see p 606.

Context The antioxidant acetylcysteine prevents acute contrast nephrotoxicity in patients with impaired renal function who undergo computed tomography scanning. However, its role in coronary angiography is unclear.

Objective To determine whether oral acetylcysteine prevents acute deterioration in renal function in patients with moderate renal insufficiency who undergo elective coronary angiography.

Design and Setting Prospective, randomized, double-blind, placebo-controlled trial conducted from May 2000 to December 2001 at the Grantham Hospital at the University of Hong Kong.

Participants Two hundred Chinese patients aged mean (SD) 68 (6.5) years with stable moderate renal insufficiency (creatinine clearance <60 mL/min [1.00 mL/s]) who were undergoing elective coronary angiography with or without intervention.

Intervention Participants were randomly assigned to receive oral acetylcysteine (600 mg twice per day; n=102) or matching placebo tablets (n=98) on the day before and the day of angiography. All patients received low-osmolality contrast agent.

Main Outcome Measures Occurrence of more than a 25% increase in serum creatinine level within 48 hours after contrast administration; change in creatinine clearance and serum creatinine level.

Results Twelve control patients (12%) and 4 acetylcysteine patients (4%) developed a more than 25% increase in serum creatinine level within 48 hours after contrast administration (relative risk, 0.32; 95% confidence interval [CI], 0.10-0.96; *P*=.03). Serum creatinine was lower in the acetylcysteine group (1.22 mg/dL [107.8 μmol/L]; 95% CI, 1.11-1.33 mg/dL vs 1.38 mg/dL [122.9 μmol/L]; 95% CI, 1.27-1.49 mg/dL; *P*=.006) during the first 48 hours after angiography. Acetylcysteine treatment significantly increased creatinine clearance from 44.8 mL/min (0.75 mL/s) (95% CI, 42.7-47.6 mL/min) to 58.9 mL/min (0.98 mL/s) (95% CI, 55.6-62.3 mL/min) 2 days after the contrast administration (*P*<.001). The increase was not significant in the control group (from 42.1 to 44.1 mL/min [0.70 to 0.74 mL/s]; *P*=.15). The benefit of acetylcysteine was consistent among various patient subgroups and persistent for at least 7 days. There were no major treatment-related adverse events.

Conclusion Acetylcysteine protects patients with moderate chronic renal insufficiency from contrast-induced deterioration in renal function after coronary angiographic procedures, with minimal adverse effects and at a low cost.

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ous strategies have been convincingly shown to prevent contrast nephropathy in high-risk patients. Efficacious and safe prophylactic intervention of contrast nephropathy is expected to decrease morbidity and mortality during hospitalization, including the need for dialysis, and thus reduce health costs.

Acetylcysteine is an antioxidant that has been shown to attenuate ischemic renal failure in animal studies.^{7,8} It prevents acute renal dysfunction in noncardiac patients with chronic renal insufficiency exposed to small doses of contrast agents during computed tomography.⁹ Patients with renal disease also frequently have severe coronary disease and are referred for coronary angiography and intervention.¹⁰ In addition to the use of larger volumes of contrast media, cardiac catheterization involves greater renal vasoconstriction with intra-arterial injections in patients with variable hemodynamic status. A higher incidence of contrast media-induced nephrotoxicity has been demonstrated in patients undergoing cardiac catheterization.¹¹ The low cost of acetylcysteine, its ease of administration, and its limited adverse effects are all compelling reasons to further investigate its role in patients undergoing angiography. We therefore conducted a prospective randomized clinical trial with detailed measurement of renal function to determine the effect of oral acetylcysteine in patients with chronic renal impairment who were at high risk for contrast nephrotoxicity after elective diagnostic and/or interventional coronary angiographic procedures.

METHODS

Study Population

This prospective, randomized double-blind, placebo-controlled trial was conducted at the Grantham Hospital at the University of Hong Kong between May 2000 and December 2001, in accordance with the principles of good clinical practice and the Declaration of Helsinki. The study protocol was approved by the Research and Ethics Committee of Grantham Hospital. All patients gave written informed consent.

Patients scheduled for elective coronary angiography and/or intervention were eligible for the study if they had a serum creatinine concentration above 1.2 mg/dL (106 μ mol/L) or creatinine clearance below 60 mL/min (1.0 mL/s). Creatinine clearance was estimated from serum creatinine concentration using the Cockcroft-Gault formula¹² and subsequently confirmed by collection of urinary creatinine over 24 hours. Eligible patients were adults with known chronic renal impairment and stable serum creatinine concentrations. Dialyzed patients were excluded from participation, as were patients who had acute renal failure, who had a change in use of diuretic or antihypertensive agents, or who had received iodinated contrast media or nephrotoxic agents within the 30 days prior to the study entry. We did not enroll patients with overt congestive heart failure, severe valvular disease, or advanced left ventricular systolic dysfunction defined as left ventricular ejection fraction less than 35%. Patients who had acute chronic obstructive lung disease or asthma exacerbation, or allergy to acetylcysteine, were ineligible.

Study Protocol

All eligible patients (N=200; mean [SD] age, 68 [6.5] years) were randomly allocated to either the acetylcysteine group or the control group based on random numbers generated by computer. Participants, those administering the interventions, and those assessing the outcomes were unaware of the group assignment. Patients were randomized to receive either oral acetylcysteine (Flumucil [Zambon Group SpA, Milan, Italy], 600-mg tablet twice daily) or matching placebo on the day before and on the day of administration of the contrast agent, for a total of 2 days. Three doses were given before and 1 dose after cardiac catheterization. Physiological (0.9%) saline was given intravenously at a rate of 1 mL/kg of body weight per hour for 12 hours before and for 6 hours after the contrast exposure. Liberal intake of oral fluid was encouraged to ensure good hydration status, except for the 4 hours preprocedure or

when clinically contraindicated. Volume status and body weight were monitored closely. Serum creatinine and urea levels were measured at the time of admission, then at 24 hours, 48 hours, and 7 days following the administration of contrast medium. Twenty-four-hour urine creatinine levels were collected at the time of admission, then at 48 hours and 7 days after contrast administration. Bromhexine was used as a mucolytic agent if clinically indicated. Metformin was withheld before cardiac catheterization due to its potential toxic accumulation after acute contrast nephrotoxicity¹³ and reinstated after the completion of study. Oral sulphonylurea or insulin was used to optimize blood sugar levels if necessary.

Standard coronary angiography and/or percutaneous coronary intervention were performed. All patients received a nonionic, low-osmolality contrast agent (iopamidol). Adjunctive drug therapy and the dose of contrast agent were left to the discretion of the attending cardiologist.

Outcomes

The primary outcome was the occurrence of acute contrast-induced reduction in renal function; the second primary outcome was change in creatinine clearance and serum creatinine concentration. Secondary outcomes were acute pulmonary edema, major adverse cardiac events, need for dialysis, and length of hospitalization.

Definitions

Stable serum creatinine concentration was defined as a difference of 0.1 mg/dL (8.8 μ mol/L) or less between serum creatinine levels measured 1 to 2 months before angiography and baseline levels measured 12 to 24 hours before coronary angiography. Acute contrast-induced reduction in renal function was defined as a greater than 25% increase in serum creatinine level^{2,14-16} that occurred within 48 hours after contrast exposure and for which alternative explanations for renal impairment had been excluded. Major adverse cardiac events were defined as cardiac death,

nonfatal myocardial infarction (defined as >3 times upper limit of creatine kinase-MB levels), or revascularization of the target lesion.

Statistical Analysis

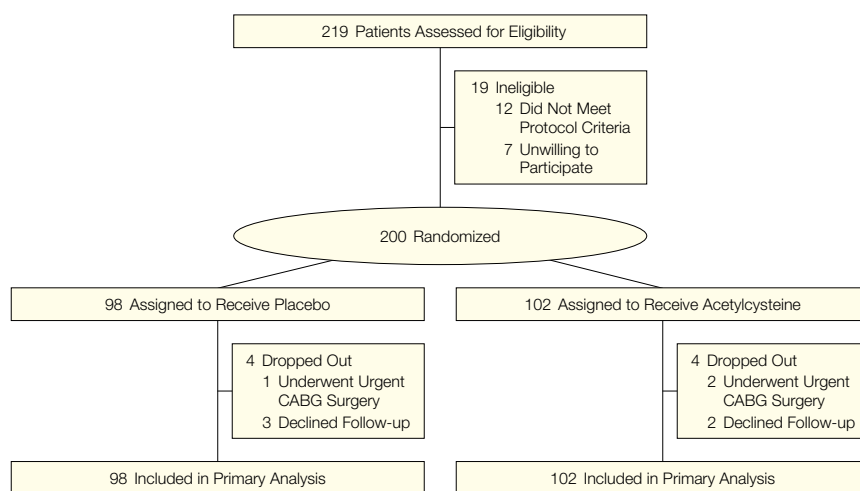
Based on previous findings that the SD of serum creatinine levels in the angiographic population at high risk for contrast nephropathy would be 0.85 mg/dL (75.1 $\mu\text{mol/L}$),¹⁷ a sample size of approximately 80 patients in each treatment group (a 2-tailed significance level of .05 and a statistical power of 0.95) was required to detect a difference in serum creatinine level of 0.5 mg/dL (44.2 $\mu\text{mol/L}$) (a standardized difference of 0.59 or an effect size of 0.29), a difference that is comparable to that detected in previous studies.^{9,17} To account for the possibility of patients lost to follow-up and to ensure a real clinical difference, the planned sample size was 200 patients.

The Kolmogorov-Smirnov test was used to determine if continuous variables were normally distributed. Baseline characteristics of the study groups were compared using the 2-tailed *t* test, or Mann-Whitney test where appropriate, for continuous data and the χ^2 test for categorical data. Modified intention-to-treat analysis was carried out on all randomized patients who received at least 1 dose of the study medication (no patients were excluded because they did not receive a first dose). Difference in incidence of acute contrast-induced reduction in renal function between the 2 treatment groups was tested using a χ^2 test. Serial serum creatinine concentrations and creatinine clearance were compared within and between groups using repeated-measures analysis of variance followed by contrast. While the overall α level was set at .05, the sharpened Bonferroni method¹⁸ was used to adjust for individual α level when multiple tests were performed. Data were analyzed with SPSS v10.0 (SPSS Inc, Chicago, Ill).

RESULTS

The trial profile is shown in FIGURE 1. In terms of baseline characteristics the 8 patients without follow-up data did

Figure 1. Flow of Patients Through the Trial



CABG indicates coronary artery bypass graft.

not differ significantly from the remaining population.

The mean (SD) baseline serum creatinine level and 24-hour creatinine clearance for all patients were 1.36 (0.44) mg/dL (120.2 [38.9] $\mu\text{mol/L}$) and 43.5 (12.3) mL/min (0.7 [0.2] mL/s), respectively. The study groups were similar in their baseline characteristics (TABLE 1). The causes of chronic renal impairment were determined by clinical assessments and were not significantly different between the groups. Most patients were scheduled for cardiac angiography and/or intervention because of symptomatic coronary ischemia. The mean volume of administered contrast medium was 139 (53) mL for all patients. The study groups were similar in terms of left ventricular ejection fraction (LVEF), angiographic diagnoses, and volume of contrast agent administered. No patient had significant hypotension or dysarrhythmias during or after cardiac catheterization that might have altered renal function.

Clinical outcomes are given in TABLE 2. Patients receiving acetylcysteine experienced acute contrast-induced reduction in renal function two thirds less frequently (12% vs 4%, $P=.03$). The average length of hospitalization was also a half-day shorter in the group receiving acetylcysteine ($P=.02$). A trend to-

ward a lower incidence of oliguria and acute increase in serum creatinine levels of at least 50% was noted in patients assigned to acetylcysteine treatment. No patients in this study developed acute nephrotoxicity requiring dialysis as a result of the administration of contrast material. One patient receiving acetylcysteine developed congestive heart failure due to unstable angina. There were no major adverse cardiac events except 1 patient in the control group sustained an uncomplicated non-ST-segment elevation myocardial infarction after coronary intervention.

The changes in the serum creatinine concentrations and creatinine clearance after the administration of contrast material are described in FIGURE 2. The mean serum creatinine concentration and creatinine clearance before radiocontrast administration were similar in the 2 groups. The serum creatinine concentration decreased after angiography in the acetylcysteine group compared with the control group (Figure 2). In the acetylcysteine group, the mean serum creatinine concentration decreased significantly from 1.35 to 1.22 mg/dL (119.3 to 107.8 $\mu\text{mol/L}$, $P<.001$) at day 2 after the administration of the contrast medium. In the control group, the change in mean serum creatinine concentration (1.36 to 1.38 mg/dL

[120.2 to 122 $\mu\text{mol/L}$] was not significant ($P=.13$). The differences in changes (from baseline) between the control and

acetylcysteine groups were significant at day 1 (1.32 vs 1.22 mg/dL [116.7 vs 107.8 $\mu\text{mol/L}$], $P=.02$) and day 2 (1.38

[95% CI, 1.27-1.49] vs 1.22 [95% CI, 1.11-1.33] mg/dL [122 vs 107.8 $\mu\text{mol/L}$], $P=.006$) after administration of contrast medium, but not significant at day 7 (1.38 vs 1.31 mg/dL [122 vs 115.8 $\mu\text{mol/L}$], $P=.23$) (Figure 2).

When 24-hour creatinine clearance was examined (Figure 2), the increase in the control group was only significant vs baseline at day 7 (42.1 to 48.4 mL/min [0.70 to 0.81 mL/s], $P<.001$) after the administration of contrast (at day 2: 42.1 to 44.1 mL/min [0.70 to 0.74 mL/s], $P=.15$). Patients in the acetylcysteine group, on the other hand, had a 30% increase, from 44.8 (0.75 mL/s) (95% CI, 42.7-47.6) to 58.9 (0.98 mL/s) (95% CI, 55.6-62.3) mL/min (0.7 to 1.0 mL/s, $P<.001$) at day 2 after angiography. The change was significantly different between the 2 groups ($P<.001$). A higher creatinine clearance was also evident at day 7 after angiography (55.2 mL/min [0.92 mL/s], $P=.045$).

The consistency of the benefits of acetylcysteine in a number of key subgroups is shown in FIGURE 3. There was a tendency toward a greater benefit among patients who had diabetes mellitus ($P=.001$) and who received a volume of contrast medium greater than 100 mL ($P<.001$).

The changes in weight after angiography were nonsignificant in both groups. The groups also did not differ significantly in the ratio of serum urea levels to serum creatinine levels and in total urinary output after angiography.

One patient assigned to placebo discontinued the study medication because of nausea. No other adverse effects were reported.

COMMENT

This study demonstrates that acetylcysteine prevents contrast nephrotoxicity in patients with moderate chronic renal insufficiency undergoing coronary diagnostic and/or interventional procedures. Its renoprotective effects were similar in various patient subgroups. The similar changes in serum urea and creatinine concentrations suggest that the changes in glomerular fil-

Table 1. Baseline Characteristics

Characteristic	Study Group		P Value
	Control (n = 98)	Acetylcysteine (n = 102)	
Age, median (IQR), y	69 (48-82)	69 (50-81)	.60
Men, No. (%)	62 (63)	61 (60)	.62
Body mass index, mean (SD)	23.7 (3.0)	23.7 (3.2)	.84
Blood pressure, mean (SD), mm Hg			
Systolic	139 (12)	140 (13)	.47
Diastolic	78 (8)	76 (9)	.37
Causes of renal impairment, No. (%)			
Diabetic nephropathy	29 (30)	38 (37)	.34
Hypertensive nephropathy	36 (37)	33 (32)	
Obstructive nephropathy	23 (23)	16 (16)	
Other	2 (2)	1 (1)	
Unknown	8 (8)	14 (14)	
Serum urea, median (IQR), mg/dL*	18.8 (9.2-60.2)	17.4 (7.8-39.2)	.50
Serum creatinine, median (IQR), mg/dL*	1.26 (0.75-3.64)	1.24 (0.77-2.99)	.65
Serum creatinine >2.5 mg/dL, No. (%)	3 (3)	4 (4)	.74
Estimated creatinine clearance, mL/min†	44.8 (16.0-58.6)	46.4 (13.9-57.8)	.46
24-h creatinine clearance, mL/min	45 (12.7-59.8)	47 (14.0-59.4)	.11
Diabetes mellitus, No. (%)‡	35 (36)	40 (39)	.61
Hypertension, No. (%)§	42 (43)	39 (38)	.51
Previous myocardial infarction, No. (%)	37 (38)	37 (36)	.83
Previous CABG surgery, No. (%)	3 (3)	8 (8)	.14
Previous PCI, No. (%)	22 (22)	15 (15)	.16
LVEF 35%-50%, No. (%)	25 (26)	30 (29)	.54
Medications, No. (%)			
ACE inhibitor	39 (40)	40 (39)	.71
Diuretic	20 (20)	21 (21)	.98
Calcium channel blocker	37 (38)	46 (45)	.29
Angiotensin II receptor inhibitor	4 (4)	8 (8)	.26
Cardiac angiographic procedure, No. (%)			
Coronary angiography	65 (66)	61 (60)	.63
Coronary angiography and ad hoc PCI	27 (28)	33 (32)	
PCI	6 (6)	8 (8)	
Left ventriculography, No. (%)	93 (95)	93 (91)	.30
LVEF, median (SD), %	61 (22.0)	58.5 (18.3)	.18
Angiographic diagnosis, No. (%)			
Normal	12 (12)	8 (8)	.73
Nonobstructive disease	16 (16)	16 (16)	
Single-vessel disease	25 (26)	27 (26)	
Double-vessel disease	18 (18)	25 (25)	
Triple-vessel disease	25 (26)	22 (22)	
Graft disease	2 (2)	4 (4)	
Volume of contrast agent, median (IQR), mL	120 (70-380)	130 (75-320)	.29
Volume of contrast agent per body weight, median (IQR), mL/kg	2.1 (1.1-7.6)	2.2 (1.1-5.5)	.74

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; IQR, interquartile range; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

*To convert from mg/dL to $\mu\text{mol/L}$, multiply serum urea values by 0.357; multiply serum creatinine values by 88.4.

†For men, estimated creatinine clearance = $(140 - \text{age}) \times \text{weight} / \text{serum creatinine} \times 72$, with age in years, weight in kg, and serum creatinine in mg/dL. For women, estimated creatinine clearance = $0.85 \times$ value calculated for men. To convert mL/min to mL/s, multiply values by 0.0167.

‡Glycosylated hemoglobin level $\geq 6.2\%$ or concurrent use of insulin or oral hypoglycemic therapy.

§Arterial pressure $\geq 140/90$ mm Hg or current use of antihypertensive therapy.

tration underlie the prophylactic effects of acetylcysteine.

Contrast nephropathy results from direct renal tubular toxicity and renal medullary ischemia.⁶ Administration of contrast medium increases the production of nephrotoxic oxygen free radicals.^{19,20} Besides scavenging oxygen free radicals that mediate cell necrosis after myocardial infarction²¹ and after angioplasty,²² acetylcysteine may act as an antioxidant to inhibit ischemic cell death in the kidney.^{7,8} Previous studies also suggest that acetylcysteine has vasodilatory properties.^{23,24} Therefore, acetylcysteine may prevent contrast nephrotoxicity by inhibiting direct oxidative tissue damage and by improving renal hemodynamics.

We studied patients with moderate chronic renal insufficiency because they represent the majority of patients at high risk of contrast nephropathy who are selected for coronary procedures. Moderate renal insufficiency also doubles the risks of in-hospital major adverse cardiac events.²⁵

A more than 25% increase in serum creatinine level following contrast administration was a marker of poor clinical outcomes in a recent study²⁶ and was the typical definition of an acute contrast-induced reduction in renal function in the preceding studies.^{2,13-16,19} Our incidence (12%) is in agreement with a previous large epidemiologic study.² Such complication may prolong hospitalization because of additional laboratory testing and postponement of further radiographic contrast exposure or surgical intervention.^{1,27} We found a slight but statistically significant decrease in length of hospitalization among the patients receiving acetylcysteine.

One percent of our patients developed a more than 50% increase in creatinine level after contrast exposure and no patient required acute dialysis. This reinforces the previous finding^{5,28,29} that the more severe forms of contrast nephrotoxicity are uncommon. Acute dialysis is uncommon (0.77%) after coronary intervention.² Clinically serious

renal injury is expected to be more common in daily clinical practice because our patients were carefully selected, op-

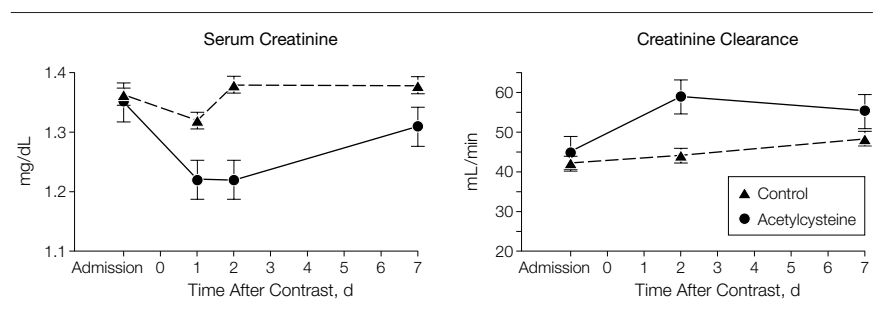
timally hydrated, and free of other factors that may predispose them to contrast nephropathy.

Table 2. Clinical Outcomes in the Control and Acetylcysteine Groups

Outcome	Study Group		RR (95% CI)	P Value
	Control (n = 98)	Acetylcysteine (n = 102)		
Acute contrast-induced reduction in renal function, No. (%) [*]	12 (12)	4 (4)	0.32 (0.10-0.96)	.03
Serum creatinine level increased >50% over baseline, No. (%)	2 (2)	0 (0)		.15
Oliguria [†]	3	1	0.32 (0.03-3.03)	.29
Length of hospitalization, mean (SD), d [‡]	3.9 (2.0)	3.4 (0.9)	0.52 (0.08-0.96) [§]	.02

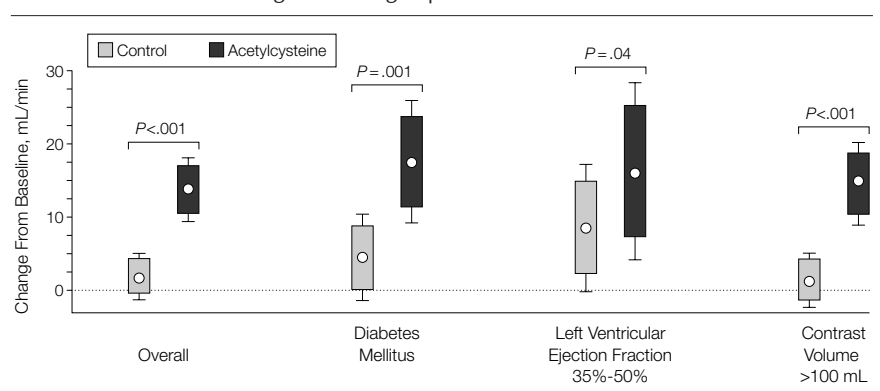
Abbreviations: CI, confidence interval; RR, relative risk.
^{*}Defined as >25% increase in serum creatinine level within 48 hours after exposure to contrast agent.
[†]Hourly urine output <0.5 mL × body weight in kg.
[‡]From admission to discharge.
[§]Values indicate difference between groups (95% CI).

Figure 2. Change in Mean Serum Creatinine Concentration and 24-Hour Creatinine Clearance After Administration of Contrast Agent



Data are presented as mean (SEM). A, Mean serum creatinine concentration at day 1 and day 2 decreased significantly in the acetylcysteine group and changed insignificantly in the control group (for acetylcysteine vs control: $P = .02$ at day 1; $P = .006$ at day 2). For day 7 vs baseline: $P < .001$ (acetylcysteine) and $P = .13$ (control). To convert mg/dL to $\mu\text{mol/L}$, multiply values by 88.4. B, Mean creatinine clearance in the acetylcysteine group was significantly higher at day 2 and remained higher at day 7 (for acetylcysteine vs control: $P < .001$ at day 2 and $P = .045$ at day 7). For day 7 vs baseline: $P < .001$ for both groups.

Figure 3. Change in 24-Hour Creatinine Clearance From Baseline to Day 2 After Administration of Contrast Agents in Subgroups



Creatinine clearance in the acetylcysteine group increased significantly after contrast exposure. The benefit of acetylcysteine is consistent among various patient subgroups. Circles indicate means; boxes, 95% confidence intervals; and error bars, 99% confidence intervals.

Less than 5% of our patients had serum creatinine levels above 2.5 mg/dL (221 μ mol/L). Even low doses of contrast (30-100 mL) have been shown to induce the need for dialysis in patients with severe renal disease.^{6,10} Little is known about the most appropriate treatments of coronary artery disease in patients with advanced renal insufficiency. The clinical outcomes of these patients undergoing a percutaneous coronary intervention are poor. Best et al²⁵ have reported significant higher cumulative 1-year mortality and cardiac events in patients with creatinine clearance <30 mL/min (0.5 mL/s) than those with moderate renal disease (25% vs 10%, $P < .001$).

Acetylcysteine has been used to prevent acute renal damage in a small number of patients with serum creatinine levels above 1.5 mg/dL (132.6 μ mol/L) and undergoing cardiac catheterization.³⁰⁻³² Shyu et al³³ have recently demonstrated the renoprotective effect of acetylcysteine in 121 patients with a mean serum creatinine level of 2.8 mg/dL (247.5 μ mol/L) and undergoing coronary angiography or intervention. Their findings correlate well with our significant treatment difference in the change of serum creatinine levels after coronary procedures. Acute dialysis was uncommon (1.6% of control patients) and not significantly affected by administration of acetylcysteine. Major cardiac events were not reported. Acute nephrotoxicity following contrast administration, defined as an increase in serum creatinine level of at least 0.5 mg/dL (44.2 μ mol/L), occurred in 15 (25%) of 61 control patients. We administered a larger mean dose of radiocontrast agent (140 vs 120 mL). Contrast nephrotoxicity by the same definition, however, occurred less often in our study. This may be related to the smaller body mass index of our patients and lower baseline serum creatinine concentrations of our samples.

We concluded that oral acetylcysteine is a safe, effective, and inexpensive prophylactic treatment against acute renal dysfunction for patients with moderate chronic renal insufficiency undergoing coronary angiographic procedures. Additional larger studies will be re-

quired to determine if acetylcysteine reduces the morbidity (eg, acute dialysis) and mortality of nephrotoxicity following administration of contrast media.

Author Contributions: Dr Kay, as principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. *Study concept and design:* Kay, Chow, Chan, Kwok, Yip, Lee.

Acquisition of data: Kay.

Analysis and interpretation of data: Kay, Chow, Chan, Lo, Kwok, Yip, Fan, Lam.

Drafting of the manuscript: Kay, Lee.

Critical revision of the manuscript for important intellectual content: Kay, Chow, Chan, Lo, Kwok, Yip, Fan, Lam.

Statistical expertise: Kay, Lo.

Obtained funding: Kay.

Administrative, technical, or material support: Kay, Chan, Lee, Lam.

Study supervision: Chow, Kwok, Yip, Fan.

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Role of the Sponsor: Zambon (H.K.) Ltd provided samples of the study drug as well as a research assistant to assist in data entry and analysis for 3 months during the final stage of the study. All statistical analysis was performed by Drs Kay and Lo, outside the employment of the Zambon Company.

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