Perioperative N-acetylcysteine to Prevent Renal Dysfunction in High-Risk Patients Undergoing CABG Surgery: A Randomized Controlled Trial

Karen E. A. Burns, MD, MSc, FRCPC
Michael W. A. Chu, MD, MEd
Richard J. Novick, MD, MSc, FRCSC
Stephanie A. Fox, BA, RRT
Kerri Gallo, RN
Claudio M. Martin, MD, MSc, FRCPC
Larry W. Stitt, MSc
A. Paul Heidenheim, MA
M. Lee Myers, MD, FRCSC
Louise Moist, MD, MSc, FRCPC

Context Renal dysfunction is a complication of coronary artery bypass graft (CABG) surgery performed with cardiopulmonary bypass (CPB) that is associated with increased morbidity and mortality. N-acetylcysteine, an antioxidant and vasodilator, counteracts renal ischemia and hypoxia.

Objective To determine whether perioperative intravenous (IV) N-acetylcysteine preserves renal function in high-risk patients undergoing CABG surgery with CPB compared with placebo.

Design, Setting, and Patients Randomized, quadruple blind, placebo-controlled trial (October 2003-September 2004) in operating rooms and general intensive care units (ICUs) of 2 Ontario tertiary care centers. The 295 patients required elective or urgent CABG and had at least 1 of the following: preexisting renal dysfunction, at least 70 years old, diabetes mellitus, impaired left ventricular function, or undergoing concomitant valve or redo surgery.

Interventions Patients received 4 (2 intraoperative and 2 postoperative) doses of IV N-acetylcysteine (600 mg) (n=148) or placebo (n=147) over 24 hours.

Main Outcome Measures The primary outcome was the proportion of patients developing postoperative renal dysfunction, defined by an increase in serum creatinine level greater than 0.5 mg/dL (44 µmol/L) or a 25% increase from baseline within the first 5 postoperative days. Secondary outcomes included postoperative interventions and complications, the requirement for renal replacement therapy (RRT), adverse events, hospital mortality, and ICU and hospital length of stay.

Results There was no difference in the proportion of patients with postoperative renal dysfunction (29.7% vs 29.0%, P=.89; relative risk [RR], 1.03 [95% confidence interval {CI}, 0.72-1.46]) in the N-acetylcysteine and placebo groups, respectively. We noted nonsignificant differences in postoperative interventions and complications, the need for RRT (0.7% vs 2.1%; P=.37), total (6.1% vs 9.6%; P=.26) and serious adverse events, hospital mortality (3.4% vs 2.7%; P>.99), and ICU and hospital length of stay between the N-acetylcysteine and placebo groups. A post hoc subgroup analysis of patients (baseline creatinine level ≥1.4 mg/dL [120 µmol/L]) showed a nonsignificant trend toward fewer patients experiencing postoperative renal dysfunction in the N-acetylcysteine group compared with the placebo group (25.0% vs 37.1%; P=.29).

Conclusions N-acetylcysteine did not prevent postoperative renal dysfunction, interventions, complications, or mortality in high-risk patients undergoing CABG surgery with CPB. Further research is required to identify CABG patients at risk for postoperative renal events, valid markers of renal dysfunction, and to establish renal thresholds associated with important clinical outcomes.

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Box. Inclusion and Exclusion Criteria

Inclusion Criteria
All adult patients admitted for elective or urgent coronary artery bypass graft (CABG) surgery necessitating exposure to cardiopulmonary bypass and deemed high risk for postoperative renal dysfunction

High-risk patients were defined by the presence of 1 or more of the following criteria at the time of preoperative assessment:
- Preexisting renal impairment (baseline serum creatinine level >1.4 mg/dL [120 µmol/L])
- Ejection fraction <35% or grade 3 or 4 left ventricular function
- Age ≥70 years
- Diabetes mellitus treated with insulin or oral hypoglycemic agents
- Concomitant valve or redo surgery

Exclusion Criteria
Emergent CABG, cardiac transplantation, or insertion of left ventricular assist device

Known allergy or hypersensitivity to N-acetylcysteine

Acute renal failure (>1.1 mg/dL [100 µmol/L] increase in serum creatinine level from preadmission to operation)

Enrolled in conflicting research study

Prior renal transplantation

Serum creatinine level >4.5 mg/dL (400 µmol/L)

N-acetylcysteine within 5 days of planned operation

Planned off-pump CABG surgery

The renal dysfunction that occurs after cardiac surgery is multifactorial. Potential causes of renal dysfunction include cardiovascular compromise, prolonged CPB exposure, increased catecholamine level, nonpulsatile flow, hypothermia, renal hypoperfusion, and the induction of inflammatory mediators. These factors may collectively contribute to renal hypoxia and ischemia. Hypoxic-ischemic insults result in direct toxic effects within renal tubular epithelial cells with depletion of local antioxidants and the formation of reactive oxygen species. In addition, hypoxia induces perturbations in renal hemodynamics resulting in enhanced sensitivity to vasoconstrictive stimuli and attenuated responsiveness to nitric oxide–dependent vasodilation. N-acetylcysteine has been shown to attenuate ischemic renal failure through nitric oxide–independent arteriolar vasodilation while functioning as an antioxidant. Several meta-analyses and randomized controlled trials (RCTs) have demonstrated that N-acetylcysteine attenuates contrast-associated declines in renal function. The total dose of N-acetylcysteine received was variable in the RCTs with N-acetylcysteine first administered approximately 24 hours orally and over 30 minutes intravenously immediately before contrast exposure in some beneficial studies.

While inexpensive and infrequently associated with toxicity, N-acetylcysteine is a medication with which many clinicians have considerable clinical experience. If N-acetylcysteine was demonstrated to be beneficial in reducing morbidity in CABG patients exposed to CPB, it may represent a cost-saving preventive strategy.

Because CPB in CABG patients is associated with renal dysfunction, we conducted an RCT to test the hypothesis that perioperative administration of intravenous N-acetylcysteine would preserve renal function in high-risk patients undergoing on-pump CABG surgery compared with placebo.

METHODS

Patients
Between October 2003 and September 2004, we enrolled high-risk patients (BOX) scheduled for elective or urgent CABG surgery at 2 sites of the London Health Sciences Centre in a quadruple-blind (patients, clinicians, data collectors, and the data analyst), placebo-controlled RCT. We identified elective and urgent patients at the time of surgical consultation in preadmission clinics and hospital wards, respectively. The flow of patients through the study and reasons for exclusion are detailed in the FIGURE. This study was approved by the Research Ethics Board at the University of Western Ontario. Approval to use N-acetylcysteine for this indication and in the CABG population was obtained from the Therapeutics Product Directorate of Health Canada. We obtained written informed consent for study participation from all patients or their legal representatives.
N-ACETYLCYSTEINE IN CORONARY ARTERY BYPASS GRAFT PATIENTS

Figure. Patient Flow Through the Study

<table>
<thead>
<tr>
<th>Patients Assessed for Eligibility</th>
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<tr>
<td>471</td>
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</table>

- 176 Excluded
  - 41 Patients Refused Participation
  - 8 Clinicians Refused Participation
  - 82 Met Exclusion Criteria
  - 37 Patients Missed
  - 8 No Consent

- 295 Randomized
  - 148 Assigned to Receive N-acetylcysteine
    - 1 Did Not Receive N-acetylcysteine (Patient Missed)
  - 147 Assigned to Receive Placebo
    - 3 Did Not Receive Placebo
      - 1 Preoperative Death
      - 2 Patients Missed

- 148 Included in Primary Analyses
  - 147 Received N-acetylcysteine as Assigned
    - 1 Did Not Receive N-acetylcysteine
  - 143 Included in Per-Protocol Analyses
    - 142 Had Postoperative Creatinine Level
    - 143 Had Postoperative Creatinine Level

- 147 Included in Primary Analyses
  - 145 Had Postoperative Creatinine Level
  - 143 Included in Per-Protocol Analyses
    - 142 Had Postoperative Creatinine Level

*One patient who did not receive N-acetylcysteine also underwent off-pump surgery. See Footnote to Table 3.

Interventions

At each site, patients underwent delayed randomization on the morning of the scheduled surgery to receive either 4 doses of intravenous N-acetylcysteine (n=148) or placebo (n=147) over a 24-hour period. Randomization was performed by a pharmacy trials coordinator using a permuted block strategy with alternating blocks of 4 and 6. Allocation was concealed using central randomization with drugs prepared by the pharmacy. Patients, health care clinicians, and individuals participating in the data collection and data analysis were blinded to treatment assignment.

Four premixed, prepackaged bags containing either liquid N-acetylcysteine or a color- and consistency-matched placebo were prepared and dispensed by a site pharmacist. Each of the 4 bags contained either N-acetylcysteine (600 mg) or placebo (5% dextrose in water). The first 2 doses of N-acetylcysteine or placebo were administered in the operating room immediately following induction of anesthesia and on successful weaning from CPB. The third and fourth doses were administered in the ICU, 12 and 24 hours after administration of the first dose. Patients requiring reoperation within the first 24 hours remained in the same group to which they were originally randomized and received the 2 postoperative doses at 12 and 24 hours after the initial dose.

Outcome Measures

The primary end point was the proportion of patients developing postoperative renal dysfunction defined as an absolute increase in serum creatinine level of greater than 0.5 mg/dL (44 µmol/L) or a 25% increase from baseline at any time within the first 5 postoperative days. Secondary end points included the requirement for postoperative interventions (vasoactive medications, intraaortic balloon pump insertion, renal dose dopamine, mechanical ventilation for at least 48 hours, or reintubation and reoperation within 24 hours) and postoperative complications (myocardial infarction, stroke, mediastinitis, and bloodstream infections). We recorded the requirement for RRT during hospitalization, hospital mortality, and ICU and hospital length of stay. In addition, we collected information on total and serious drug-related adverse events and their impact on study medication discontinuation. A data and safety monitoring committee comprising an independent nephrologist, cardiologist, and intensivist conducted a blinded interim analysis at 50% of targeted enrollment for safety and efficacy end points.

Operative Management

All patients underwent general anesthesia with a single lumen endotracheal tube. Patients were monitored using a central venous catheter, Swan-Ganz catheter, radial arterial line, Foley catheter, electrocardiography, transesophageal echocardiography, and nasopharyngeal and rectal temperature probes. A median sternotomy incision was performed in all patients. Patients received heparin with an initial dose of 300 to 400 U per kg of body weight, and maintenance doses were administered to maintain the activated clotting time of more than 480 seconds. The ascending aorta and right atrium were cannulated in all patients. The CPB circuit consisted of a roller pump (Jostra HL-20, Jostra AG Maquet Cardiopulmonary, Hirrlingen, Germany), a nonheparin-coated polyvinylchloride circuit (Terumo Cardiovascular Systems Inc, Ashland, Maine), a membrane oxygenator (Capiox SX 18, Terumo Cardiovascular Systems Inc, Elkton, Md), a micron arterial filter (Medtronic 38, Medtronic, Minneapolis, Minn), and an open venous reservoir system. The pump prime solution (1 L lactated Ringer's solution, 500 mL pentastarch, and 1 ampule sodium bicarbonate) and antifibrinolytic agents were administered according to site-specific protocols and surgeon preference, respectively. A low-volume prime, miniaturized, centrifugal pump circuit (Medtronic Resting Heart Bypass Circuit, Medtronic) was used in 3 patients. Flow rates were ti-
trated to maintain perfusion pressures between 60 and 80 mm Hg and a cardiac index of at least 2.4 L/min/m². Intermittent boluses or infusions of phenylephrine, norepinephrine, and vasopressin were administered to treat low intraoperative perfusion pressures at the discretion of the surgical team. The most common myocardial protection strategy used was an antegrade, intermittent, cold blood cardioplegia technique using a cardioplegia delivery system (Medtronic MYOTherm XP, Medtronic). After successfully weaning from CPB, protamine sulfate and vasopressin were administered to reverse systemic heparinization and optimize systemic perfusion pressures and cardiac output, respectively. Patients were transferred to the ICU, intubated, and sedated.

**Study Definitions**

A myocardial infarction was defined by a new 40-ms Q wave in at least 2 contiguous leads on an electrocardiogram, the development of a new dominant R wave in lead V1, or a new left bundle-branch block or the presence of a total creatine kinase (CK) level exceeding 1500 U/L (or CK-MB level >5% of the total) at any time postoperatively. We defined a stroke by the presence of new focal neurological deficit persisting for at least 24 hours or by a new defect on a computed tomogram or magnetic resonance imaging. Mediastinitis was defined by the requirement for reoperation for deep sternal wound infection, while the presence of a postoperative fever in association with 2 positive blood cultures defined bloodstream infection. We defined serious drug-related adverse events to include bronchospasm, hypotension, and anaphylaxis. Additionally, we documented the occurrence of other adverse events including nausea, vomiting, stomatitis, cutaneous rash, urticaria, and facial edema.

**Data Collection**

We collected baseline data including patient weight and serum creatinine level (defined as the serum creatinine level at the time of enrollment in the preoperative clinic [elective cases] or in hospital [urgent cases]). We noted the presence of comorbidities including the following: (1) congestive heart failure (CHF) (defined by an episode within the 30 days of acceptance for surgery); (2) peripheral vascular disease (history of intermittent claudication, decreased pedal pulses, or previous vascular surgery); (3) cerebrovascular disease (history of a stroke or transient ischemic attack); (4) myocardial infarction (within 30 days of acceptance of surgery); (5) diabetes (managed by diet, oral hypoglycemic agents, or insulin); (6) chronic obstructive lung disease (requiring inhaled corticosteroids or bronchodilators or spirometry demonstrating obstructive physiology); and (7) hypertension (active treatment for elevated blood pressure). We documented preoperative use of (1) angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, (2) platelet antiaggregation therapies, and (3) nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitors. In addition, we collected intraoperative data on the procedure performed, number of vessels bypassed, conversions to OPCAB, and the total cross-clamp and CPB time.

**Statistical Analyses**

We used the χ² test (or alternatively, the Fisher exact test when the expected value was <5) for comparing 2 proportions. We compared differences in log-transformed ICU and hospital length of stay in survivors using the unpaired t test and compared ICU and hospital length of stay between groups using time-to-event analysis with censoring of deaths and application of the log-rank test. Intention-to-treat and per-protocol analyses for all primary and secondary outcomes were conducted. In addition, we performed adjusted analyses for clinically important baseline imbalances (CHF and procedure performed [CABG vs other]) using logistic regression and proportional hazards regression for dichotomous and continuous outcomes, respectively. Posthoc we conducted a subgroup analysis to assess for treatment effect in patients with a baseline serum creatinine level greater than 1.4 mg/dL (120 µmol/L). Continuous data are expressed as mean (SD) or median (minimum, maximum). We did not impute missing data. All analyses were conducted using SAS 8.2 (SAS Institute Inc, Cary, NC). We considered P values ≤.05 to be statistically significant.

We used the formula for 2 independent proportions for dichotomous outcomes to estimate the sample size required for the primary outcome: attenuation of postoperative increase in serum creatinine level of greater than 0.5 mg/dL (44 µmol/L) or a 25% increase from baseline within the first 5 postoperative days. Anticipating a 50% reduction in the primary outcome and assuming a baseline event rate of 30%, with a 2-sided α of .05, 1:1 allocation, and assuming a 10% loss to follow-up, a total of 296 patients would result in 80% power to detect a 50% reduction in the proportion of patients with the primary end point.

**RESULTS**

**Participants**

We randomized 295 patients to receive N-acetylcysteine (n = 148) or placebo (n = 147). At the discretion of the attending surgeon, 4 patients randomized to receive N-acetylcysteine underwent OPCAB surgery and 2 patients (1 in the N-acetylcysteine group and 1 in the placebo group) underwent valve surgery only. One N-acetylcysteine patient who underwent OPCAB and 3 placebo patients did not receive any study medication. Whereas all participants were included in the intention-to-treat analyses, only patients undergoing CABG with CPB and receiving at least 1 dose of study medication were included in the per-protocol analyses. Two placebo patients, including 1 patient who died preoperatively prior to receiving study medication, and 1 patient who died postoperatively had no postoperative creatinine measurement. The Figure depicts patient flow through the study.

We present the baseline characteristics and intraoperative data for the study...
participants in Table 1 and Table 2, respectively. The groups were similar with regard to age, sex, weight, baseline serum creatinine level, proportion with renal dysfunction at baseline, ventricular grade, ejection fraction less than 35% or grade 3 or 4 left ventricular function, at least 70 years old, and diabetes mellitus. By chance, compared with the N-acetylcysteine group, more patients in the placebo group had a history of CHF and underwent concomitant valve surgery. Correspondingly, we observed increased pump time in the placebo group compared with the N-acetylcysteine group. Conversely, more patients in the N-acetyl cysteine group were treated at the time of initial assessment with NSAIDs or COX-2 inhibitors. While the former imbalances would be expected to bias against placebo, the latter imbalance would be expected to bias against N-acetylcysteine.

**Primary Outcome**
We observed nonsignificant differences in the proportion of patients developing postoperative renal dysfunction (44/148 [29.7%] vs 42/145 [29.0%]; relative risk [RR], 1.03 [95% confidence interval {CI}, 0.72-1.46]); unadjusted \( P = .89 \); adjusted \( P = .99 \) in the N-acetylcysteine and placebo groups, respectively. Adjusted and per-protocol (43/143 [30.1%] vs 40/142 [28.2%]) analyses confirmed that this result was robust.

**Secondary Outcomes**

**Postoperative Interventions.** We found nonsignificant differences between N-acetylcysteine and placebo patients with regard to the requirement for vasoactive medications, intra-aortic balloon pump insertion, renal dose dopamine, mechanical ventilation of at least 48 hours, or reintubation and reoperation (Table 3).

**Postoperative Complications.** We noted nonsignificant differences in the proportion of patients in the N-acetylcysteine and placebo groups experiencing myocardial infarction, stroke, mediastinitis, or bloodstream infections (Table 3).

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N-acetylcysteine Group (n = 148)</th>
<th>Placebo Group (n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>68.9 (8.9)</td>
<td>69.2 (9.7)</td>
</tr>
<tr>
<td>Men</td>
<td>116.0 (78.4)</td>
<td>117.0 (79.6)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>87.5 (16.6)</td>
<td>84.8 (19.0)</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td>1.1 (0.3)</td>
<td>1.2 (0.4)</td>
</tr>
</tbody>
</table>

**Inclusion criteria**

- Renal dysfunction (creatinine \( > 1.4 \) mg/dL) 32 (21.6) 36 (24.5)
- EF <35% or grade 3-4 LV 34 (23.0) 29 (19.7)
- Age \( \geq 70 \) y 92 (62.2) 88 (59.9)
- Diabetes 66 (44.6) 63 (42.9)
- Planned concomitant valve 15 (10.1) 29 (19.7)
- Redo CABG surgery 2 (1.4) 10 (6.8)

**Ventricle grade**

- I 71 (48.0) 73 (49.7)
- II 43 (29.1) 44 (29.9)
- III 29 (19.6) 25 (17.0)
- IV 5 (3.4) 5 (3.4)

**Comorbidities**

- Hypertension 112 (75.7) 106 (72.1)
- Recent myocardial infarction 36 (24.3) 31 (21.1)
- COPD 32 (21.6) 27 (18.4)
- Peripheral vascular disease 24 (16.2) 26 (17.7)
- Cerebrovascular accident 20 (13.5) 23 (15.7)
- Congestive heart failure 13 (8.8) 30 (20.4)

**Preoperative medications**

- Platelet inhibitors 84 (56.8) 80 (54.4)
- ACE inhibitors or angiotensin blockers 70 (47.3) 66 (44.9)
- NSAIDs or COX-2 inhibitors 16 (10.8) 7 (4.8)

**Table 2. Intraoperative Data**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N-acetylcysteine Group (n = 148)</th>
<th>Placebo Group (n = 147)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>133 (89.9)</td>
<td>117 (80.1)</td>
</tr>
<tr>
<td>CABG + valve</td>
<td>14 (9.5)</td>
<td>28 (19.2)</td>
</tr>
<tr>
<td>Other (valve only)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

**No. of vessels bypassed**

| 0     | 1 (0.7) | 1 (0.7) |
| 1     | 11 (7.4) | 16 (11.0) |
| 2     | 32 (21.6) | 26 (17.8) |
| 3     | 62 (41.9) | 66 (45.2) |
| 4     | 39 (26.4) | 29 (19.9) |
| 5     | 2 (1.4) | 7 (4.8) |
| 6     | 1 (0.7) | 1 (0.7) |

**Pump time, mean (SD), min†**

- N-acetylcysteine 90.4 (28.6)
- Placebo 101.1 (35.6)

**Cross-clamp time, mean (SD), min‡**

- N-acetylcysteine 59.2 (23.9)
- Placebo 65.3 (28.0)

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Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase 2; EF, ejection fraction; LV, left ventricle; NSAIDs, nonsteroidal anti-inflammatory drugs.

SI conversion: To convert serum creatinine to µmol/L, multiply by 88.4.

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Abbreviation: CABG, coronary artery bypass graft surgery.

*Does not include data from 1 placebo patient who died preoperatively.
†Total pump time in 144 N-acetylcysteine and 146 placebo patients.
‡Aortic cross-clamp time available for 142 N-acetylcysteine and 144 placebo patients.
Hospital Outcomes and Length of Stay. The requirement for RRT during hospitalization (0.7% vs 2.1%; \(P = .37\)) was infrequent and did not differ significantly between the N-acetylcysteine and placebo groups, respectively. We found nonsignificant differences in hospital mortality (3.4% vs 2.7%; \(P > .99\)) between patients treated with N-acetylcysteine and placebo, respectively (Table 3). We noted similar median ICU (2.0 days [1, 42] vs 2.0 days [2, 53]; \(P = .57\)) and hospital length of stay (7.0 days [5, 64] vs 8.0 days [5, 372]; \(P = .31\)) between N-acetylcysteine and placebo survivors. Time-to-event analysis confirmed nonsignificant differences in ICU (2.0 days vs 2.0 days; \(P = .82\)) and hospital (7.0 days vs 8.0 days; \(P = .52\)) length of stay in the N-acetylcysteine and placebo groups, respectively. Per-protocol and adjusted analyses remained nonsignificant for all secondary outcomes.

Adverse Events. Nonsignificant differences were also noted between patients treated with N-acetylcysteine and placebo with respect to the incidence of total (6.1% vs 9.6%; \(P = .26\)) and serious (0.7% vs 0%; \(P > .99\)) adverse events (Table 4). The single serious adverse event, an episode of intraoperative hypotension treated with epinephrine and norepinephrine, was possibly related to N-acetylcysteine but other potential causes were present and subsequent doses of N-acetylcysteine were tolerated. No patient discontinued medication as a consequence of an adverse event.

Protocol Compliance. Four N-acetylcysteine (2.7%) and 8 placebo (5.5%) (\(P = .23\)) patients did not receive all 4 doses of medication.

Subgroup Analysis. A post hoc subgroup analysis of patients with a baseline creatinine level greater than 1.4 mg/dL (120 µmol/L) demonstrated a nonsignificant trend toward fewer patients experiencing postoperative renal dysfunction in the N-acetylcysteine group compared with the placebo group (25.0% vs 37.1%; \(P = .29\)).

COMMENT

We conducted an RCT to investigate whether perioperative intravenous N-acetylcysteine or placebo could attenuate postoperative declines in renal function in high-risk CABG surgery patients exposed to CPB. We found nonsignificant between-group difference in the proportion of patients experiencing an increase in serum creatinine level of greater than 0.5 mg/dL (+44 µmol/L) or a 25% increase from baseline within the first 5 postoperative days. We also found nonsignificant between-group differences in the requirement for postoperative interventions, postoperative complications, RRT, total and serious adverse events, hospital deaths, and in ICU and hospital length of stay.

Our study has several strengths. First, to our knowledge, this is the largest RCT investigating a prophylactic intervention in a high-risk population undergoing CABG surgery. During study implementation, we enrolled 62.6% (295/471) of patients assessed for eligibility. Our results are therefore generalizable to a frequently encountered subset of patients undergoing a commonly performed surgery. Second, it is the first RCT to investigate the effect of prophylactic N-acetylcysteine administration on postoperative renal function in elective and urgent CABG patients exposed to CPB. Third, the internal validity of our trial was strengthened by use of central randomization, allocation concealment, and multilevel blinding (patients, physicians, data collectors, and data analysts). Fourth, we used a strategy of delayed randomization to minimize the potential for patients to be exposed to study medication in the event of cancelled, altered, or postponed surgery. Fifth, we admin-

<table>
<thead>
<tr>
<th>Table 3. Postoperative Outcomes*</th>
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<tbody>
<tr>
<td>No. (%)</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
</tr>
<tr>
<td>Increase in serum creatinine level†</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td>Vasoactive drugs</td>
</tr>
<tr>
<td>Renal dose dopamine</td>
</tr>
<tr>
<td>MV &gt;48 h</td>
</tr>
<tr>
<td>IABP insertion</td>
</tr>
<tr>
<td>Reoperation within 24 h</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Bloodstream infection</td>
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<tr>
<td>Mediastinitis</td>
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<tr>
<td><strong>Hospital outcomes</strong></td>
</tr>
<tr>
<td>RRT during hospital stay</td>
</tr>
<tr>
<td>Hospital deaths</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
</tr>
<tr>
<td>Serious adverse events</td>
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<tr>
<td>All adverse events</td>
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</table>

*Abbreviations: IABP, intra-aortic balloon pump; MV, mechanical ventilation; RRT, renal replacement therapy.
*While 148 and 147 patients in the N-acetylcysteine and placebo groups, respectively, were eligible for the intention-to-treat analysis of the primary outcome, serum creatinine measurements were not available for 2 placebo patients who died perioperatively (1 preoperative and 1 postoperative death; comparison, 148 N-acetylcysteine vs 145 placebo). While the number of patients meeting the per-protocol definition for the primary outcome was 143 and 143 in the N-acetylcysteine and placebo groups, respectively, the numbers with serum creatinine measurements available were 143 and 142, respectively. The per-protocol analysis of the primary outcome does not include measurements for 4 off-pump coronary artery bypass graft surgery patients (including 1 patient who did not receive medication) and 1 valve surgery patient in the N-acetylcysteine group. Similarly, it does not include data for 1 patient who underwent valve surgery, 3 patients who did not receive medication (including 1 preoperative death), and 1 postoperative death in the placebo group. Secondary outcomes were not available for 1 patient who died prior to surgery in the placebo group.
†An absolute increase in serum creatinine level greater than 0.5 mg/dL (44 µmol/L) or a 25% increase from baseline at any time within the first 5 postoperative days.
‡Fisher exact \(P\) value.
N-acetylcysteine did not prevent postoperative renal dysfunction. Compared with placebo, RCTs investigating single-dose, preoperative α₁-adrenergic agonists, twelfth infusions of intraoperative nifedipine or prostaglandin E₁ and intraoperative and postoperative fenoldopam or diltiazem in usual-risk patients undergoing CABG surgery with CPB demonstrated that the experimental interventions prevented deterioration in postoperative renal function, and intraoperative and postoperative interventions in high-risk patients undergoing on-pump CABG surgery produced variable results. In a multicenter, prospective cohort study, Ranucci and colleagues evaluated fenoldopam in 216 patients with serum creatinine levels of at least 1.8 mg/dL (160 µmol/L) and an additional entry criterion (age, diabetes, decreased ejection fraction). The authors found significant reductions in the incidence of acute renal failure and death and attenuation of postoperative decrements in creatinine clearance. Investigators also compared the prophylactic administration of pentoxifylline and enoximone (a phosphodiesterase III inhibitor) with placebo in separate studies each involving 40 elderly elective CABG patients. These trials demonstrated reductions in bypass-induced inflammatory mediators and significantly smaller increases in α₁-microglobulin in the intervention groups compared with controls, with no demonstrable effect on serum creatinine level. Conversely, an RCT investigating low- and high-dose diltiazem infusions in 24 elective cardiac surgery patients with elevated preoperative serum creatinine levels found no differences in serum creatinine level and glomerular filtration rate, measured by iothalamate, in the first 5 postoperative days, but a higher glomerular filtration rate 3 weeks after surgery in the diltiazem group compared with the placebo group. A further RCT compared enoximone with placebo in 42 patients older than 65 years and demonstrated significantly decreased creatinine clearance in patients treated with placebo on the first postoperative day. Important differences in the populations studied, interventions applied, and outcomes measured may have resulted in discordant findings between studies investigating usual- and high-risk patients and among studies involving high-risk patients.

While 29% of participants in both groups developed laboratory evidence of renal dysfunction in our study, few patients experienced clinically important morbidity or mortality. It is conceivable that a treatment effect may have been missed as a result of the population studied or the primary outcome selected. Preoperative renal dysfunction and age are important baseline determinants of postoperative renal function and outcomes. Two RCTs investigating high-risk CABG candidates made baseline renal dysfunction (serum creatinine >1.8 mg/dL [160 µmol/L] or between 1.4 mg/dL and 3.4 mg/dL [120 and 300 µmol/L]) a compulsory inclusion criterion. Similar to other studies, we included renal dysfunction (serum creatinine >1.4 mg/dL [120 µmol/L]) as one of several inclusion criteria. As a result, we observed a mean pooled baseline creatinine level of 1.2 mg/dL (103.7 µmol/L), which was lower than studies including elevated baseline creatinine as a compulsory criterion (2.4 mg/dL [216 µmol/L] and 1.8 mg/dL [155 µmol/L]) but higher than studies including it as one of many criteria (1.2 mg/dL [102 µmol/L], 0.9 mg/dL [79.6 µmol/L] and approximately 0.7 mg/dL [60 µmol/L]). Consequently, only 23.0% of our participants had a baseline serum creatinine level greater than 1.4 mg/dL (120 µmol/L). A post hoc subgroup analysis of patients with baseline creatinine level greater than 1.4 mg/dL (120 µmol/L) demonstrated a nonsignificant trend toward fewer patients experiencing renal dysfunction in the N-acetylcysteine group compared with the placebo group.
placebo group. While of interest, this post hoc analysis is underpowered, exploratory in nature, and potentially confounded by other factors influencing postoperative renal function. Similarly, while age of at least 70 years was one of our inclusion criteria, 3 RCTs investigating high-risk patients limited enrollment to patients older than 80 years, 33,35 or older than 65 years. 36 The pooled age in our study was 69.0 years, with 61.1% of our participants at least 70 years old. Therefore, while similar, our cohort was younger than those investigated by the other authors (69.5 years, 32 83.5 years, 33 81.5 years, 34 72.5 years, 35 and 70.5 years16). In summary, compared with other high-risk studies, we identified a slightly younger population with mild to moderate renal dysfunction. Consequently, our population, while at risk for experiencing postoperative renal dysfunction, may not have been at appreciable risk for developing clinically important morbidity or mortality.

The definition and selection of the primary outcome warrant consideration in interpreting our results. We selected a surrogate outcome, commonly used in studies of contrast-induced nephropathy, as the primary outcome. Since the serum creatinine level typically peaks after CABG surgery with CPB on the second postoperative day and returns to baseline by the fourth and fifth postoperative days, 37 we expected to capture postoperative renal dysfunction with our definition. Notwithstanding, while we identified laboratory evidence of renal dysfunction at the thresholds adopted, few patients experienced important clinical events, suggesting that the threshold may be too low for this population. Two observational studies examining renal dysfunction following CABG surgery and demonstrating effects on clinical outcomes used higher thresholds (>0.7 mg/dL [62 µmol/L] increase from baseline or a serum creatinine level >2.0 mg/dL [177 µmol/L] and >0.9 mg/dL [80 µmol/L] increase with a serum creatinine level >2.1 mg/dL [185 µmol/L]). 8,11 A higher threshold may aid in identifying a subset of patients at risk for important sequelae and in differentiating responses to interventions. Conversely, a lower threshold may have captured unimportant events associated with the effects of volume shifts and pressure changes on the kidney. Finally, compared with cystatin C, some authors have recently suggested that serum creatinine may not be a valid marker of postoperative renal dysfunction. 38,39

Regardless of the entry criteria or outcome measure selected, there are several possible reasons why we did not observe a treatment effect. First, N-acetylcysteine may be ineffective in preventing postoperative renal dysfunction following CPB exposure. Second, the dose, while being well studied for prevention of contrast-induced nephropathy, may be inadequate to counteract the hypoxic-ischemic insults to the renal tubular epithelial cells induced by CPB. Third, the timing of administration of the initial dose may be important. We administered the initial dose of N-acetylcysteine at induction of anesthesia leaving marginal time for N-acetylcysteine to interfere with expression of adhesion molecules, N-acetylcysteine activate nuclear factor-kappa B in mesangial cells, and exert its vasodilatory effect. Fourth, the activity of N-acetylcysteine may be overwhelmed by the formation of reactive oxygen species with concurrent depletion of antioxidants during and after CPB. 40-42 Fifth, the multifactorial renal dysfunction observed following CABG surgery may not be amenable to the antioxidant and vasodilatory effects of N-acetylcysteine. Alternatively, postoperative renal insults may be additive, and N-acetylcysteine may only counteract CPB-induced hypoxemic-ischemic insults.

CONCLUSION

In this study, perioperative, intravenous intermittent-dose N-acetylcysteine did not prevent postoperative renal dysfunction, interventions, or complications compared with placebo in high-risk patients undergoing on-pump CABG surgery. Before additional prophylaxis trials are initiated to investigate alternative N-acetylcysteine dosing regimens, further research is required to identify CABG patients at risk for postoperative renal events, valid markers of renal dysfunction, and to establish renal thresholds associated with important clinical outcomes.

Author Affiliations: Divisions of Critical Care Medicine (Drs Burns and Martin), Nephrology (Dr Moist, Ms Gallo, Mr Heidenheim), Cardiac Surgery (Drs Chu, Novick, and Myers and Ms Fox) and the Department of Biostatistics (Mr Stitt) at the University of Western Ontario, London, Ontario.

Author Contributions: Drs Burns and Moist had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Burns, Chu, Novick, Martin, Stitt, Moist.

Acquisition of data: Burns, Chu, Novick, Fox, Gallo, Heidenheim, Myers, Moist.

Analysis and interpretation of data: Burns, Chu, Fox, Gallo, Martin, Stitt, Heidenheim, Moist.

Drafting of the manuscript: Burns, Moist.

Critical revision of the manuscript for important intellectual content: Burns, Chu, Novick, Fox, Gallo, Martin, Stitt, Heidenheim, Myers, Moist.

Statistical analysis: Stitt, Heidenheim.

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N-Acetylcysteine in Coronary Artery Bypass Graft Patients


