Reports of Original Investigations

N-acetylcysteine for preventing acute kidney injury in cardiac surgery patients with pre-existing moderate renal insufficiency

[Recours à la N-acétylcystéine pour prévenir une atteinte rénale aiguë chez les patients de chirurgie cardiaque souffrant d'une insuffisance rénale modérée préexistante]

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Purpose: N-acetylcysteine may prevent acute kidney injury after cardiac surgery. To determine if N-acetylcysteine warrants definitive evaluation in a large multicentre trial, we evaluated its effects on a surrogate outcome, estimated glomerular filtration rate (eGFR), in a randomized trial.

Methods: One-hundred-seventy-seven cardiac surgery patients with moderate pre-existing renal insufficiency (eGFR ≤ 60 $mL \cdot min^{-1}$) were recruited in a blinded (patients, clinicians, data-collectors) placebo-controlled randomized trial. Eighty-nine were randomized to N-acetylcysteine (100 $mg \cdot kg^{-1}$ *iv* bolus, 20 $mg \cdot kg^{-1} \cdot hr^{-1}$ infusion until four hours after cardiopulmonary bypass), and 88 to placebo. The primary outcome was the percent change in eGFR during the first 72 postoperative hours. Secondary outcomes included renal replacement therapy, mortality, atrial fibrillation, vasoactive medications, and adverse effects. A future multicentre trial was deemed to be warranted if N-acetylcysteine was associated with a percent change in eGFR that was 3.8 better (small benefit), and with an upper 95% confidence interval including 9.5 (moderate benefit).

Results: The median percent change in eGFR was 5.2% better (absolute difference) in the N-acetylcysteine arm (95% confidence interval 2.4% worse to 12.1% better; $P = 0.22$). With regard to secondary outcomes, all-cause mortality was lower in the N-acetylcysteine arm (0% *vs* 8%; $P = 0.007$).

Conclusion: N-acetylcysteine did not cause a statistically significant improvement in postoperative eGFR in this single-centre study. Nonetheless, its treatment effect was consistent with a plausible small-to-moderate benefit. Given this finding, N-acetylcysteine should be definitively evaluated in a large randomized trial.

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Objectif *: La N-acétylcystéine pourrait empêcher une atteinte rénale aiguë après une chirurgie cardiaque. Afin de déterminer si la N-acétylcystéine mérite une évaluation définitive menée par une étude multi-centrique étendue, nous avons évalué ses effets sur un pronostic de remplacement, le taux de filtration glomérulaire estimé (eGFR), dans une étude randomisée.*

Méthode *: Cent soixante-dix-sept patients de chirurgie cardiaque souffrant d'insuffisance rénale modérée préexistante (eGFR ≤ 60 $mL \cdot min^{-1}$) ont été recrutés dans le cadre d'une étude en aveugle (patients, cliniciens, collecteurs de données), randomisée et contrôlée par placebo. Quatre-vingt-neuf patients ont été randomisés à recevoir de la N-acétylcystéine (bolus 100 $mg \cdot kg^{-1}$ iv, perfusion 20 $mg \cdot kg^{-1} \cdot h^{-1}$ jusqu'à quatre heures après la circulation extracor-*

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porelle), et 88 ont reçu un placebo. Le changement en pourcentage du eGFR durant les premières 72 h postopératoires a constitué le résultat primaire. Les résultats secondaires comptaient la dialyse, la mortalité, la fibrillation atriale, les médicaments vasomoteurs administrés, ainsi que les effets secondaires. Une étude multi-centrique ultérieure a été considérée nécessaire si la N-acétylcystéine était associée à une modification en pourcentage du eGFR qui était meilleure de 3,8 (bénéfice modeste), avec un intervalle de confiance de 95 % supérieur comprenant 9,5 (bénéfice modéré).

***Résultats** : Le changement en pourcentage moyen du eGFR était meilleur de 5,2 % (différence absolue) dans le groupe N-acétylcystéine (intervalle de confiance 95 % 2,4 % moins bon à 12,1 % meilleur ; P = 0,22). En ce qui concerne les résultats secondaires, la mortalité – toutes causes – était plus basse dans le groupe N-acétylcystéine (0 % vs 8 % ; P = 0,007).*

***Conclusion** : La N-acétylcystéine n'a pas causé d'amélioration statistiquement significative dans l'eGFR postopératoire dans cette étude uni-centrique. Néanmoins, son effet thérapeutique pouvait correspondre à un bénéfice plausible modeste à modéré. Au vu de cette découverte, la N-acétylcystéine devrait être évaluée de manière définitive dans une étude randomisée étendue.*

ACUTE kidney injury after cardiac surgery is associated with mortality and morbidity.[1,2] The rate of clinically important acute kidney injury is approximately 1.5% to 16%.[2,3] This rate is likely to increase further, as patients undergoing cardiac surgery are increasingly older and have more co-morbidity.[4,5] Strategies that prevent acute kidney injury should, therefore, confer important benefits.

Despite the prognostic implications of acute kidney injury, there are few proven therapies. Diuretics, low-dose dopamine, and mannitol have minimal benefits.[6–9] Other therapies (e.g., clonidine, fenoldopam, diltiazem) have only been evaluated in small clinical trials that had mixed results.[10–13] N-acetylcysteine is an alternative therapy that might prevent perioperative kidney injury. Due to its anti-inflammatory and anti-oxidant properties, N-acetylcysteine attenuates several mechanisms of kidney injury during cardiac surgery: the systemic inflammatory response, free-radical injury, and ischemia.[14] In clinical studies, N-acetylcysteine reduced free-radical activation and systemic inflammation during cardiopulmonary bypass (CPB).[15,16] It also preserved renal function in animal models of ischemic kidney-injury.[17,18]

N-acetylcysteine has already been studied extensively for preventing contrast-induced nephropathy. Despite initial promise, its efficacy in this setting has not been proven definitively.[19,20] An important reason for this persistent uncertainty has been a strategy of repeated evaluation in small randomized trials, as opposed to a single definitive multicentre trial.[20] Despite collectively recruiting 2,284 participants, the 18 published trials of N-acetylcysteine in contrast-induced nephropathy have not proven its efficacy. In contrast, one multicentre trial of 1,800 participants would have definitively established if N-acetylcysteine had important effects on clinically relevant outcomes, such as renal-replacement-therapy (RRT).[20]

In light of the theoretical benefits of N-acetylcysteine, a randomized trial of N-acetylcysteine for perioperative renal protection is needed. Given the experience in the contrast-induced nephropathy literature, definitive evidence for perioperative N-acetylcysteine should entail a large, and potentially expensive, multicentre trial with statistical power to detect effects on clinically relevant outcomes.[20] We therefore performed a preliminary trial that measured a surrogate outcome, estimated glomerular filtration rate (eGFR), to determine if this large future study was worth pursuing.

Methods

Sample

Potential participants were recruited at the preoperative assessment clinic of the Toronto General Hospital (Toronto, Ontario, Canada). Inclusion criteria were: 1) age ≥ 18 yr; 2) pre-existing *moderate* renal insufficiency; and 3) elective coronary-artery-bypass-graft (CABG) and/or valve surgery with CPB. Moderate renal insufficiency was defined by an eGFR (Cockcroft-Gault equation) less than 60 $mL \cdot min^{-1}$.[21–24] Exclusion criteria were: 1) *severe* pre-existing renal insufficiency (creatinine concentration ≥ 300 $\mu mol \cdot L^{-1}$ or dependence on RRT); 2) preoperative hemodynamic instability (intra-aortic balloon pump support or vasoactive medications); 3) N-acetylcysteine or angiographic contrast within 24 hr before surgery; 4) planned off-pump surgery; 5) planned deep-hypothermic-circulatory-arrest; or 6) prior adverse reaction to N-acetylcysteine. Eligible patients who provided informed consent were enrolled in a blinded (patients, clinicians, data-collectors) randomized placebo-controlled trial. Health Canada and the institutional Research Ethics Board approved this study.

Interventions

Participants were randomized on the morning of surgery itself. The institutional pharmacy performed centralized randomization using a computer-generated random number table with random permuted blocks of size four. Allocation was concealed by centralized randomization and preparation of study drugs by an independent pharmacist.

The dose of N-acetylcysteine used for contrast-induced nephropathy (2400 mg) might be inadequate for perioperative use because of higher oxidative stress states during cardiac surgery, and altered pharmacokinetics caused by fluid shifts during CPB.[19] We therefore used a higher dose that caused measurable reductions in oxidative response during cardiac surgery.[25] The treatment arm received N-acetylcysteine 100 $mg \cdot kg^{-1}$ *iv* over 30 min after induction of anesthesia. This loading dose was followed by a 20-$mg \cdot kg^{-1} \cdot hr^{-1}$ infusion until four hours after CPB. N-acetylcysteine was prepared as a 0.4 $mg \cdot kg^{-1} \cdot mL^{-1}$ solution in 5% dextrose in water. The placebo arm received identically packaged 5% dextrose in water.

Operative management

With regard to routine management of preoperative medications, non-steroidal anti-inflammatory drugs were discontinued seven days before surgery; angiotensin-converting-enzyme inhibitors and angiotensin receptor antagonists were withheld on the day of surgery. All participants received modified 'fast-track' cardiac anesthesia with midazolam, fentanyl, pancuronium, isoflurane, and propofol.[26] All participants were monitored with pulmonary artery catheters. Transesophageal echocardiography was reserved for valve procedures and selected high-risk bypass procedures. Tranexamic acid (50–100 $mg \cdot kg^{-1}$ bolus) was used routinely for antifibrinolysis, except for patients deemed to be at very high risk for blood loss. The latter instead received aprotinin (2×10^6 U before sternotomy, 2×10^6 U during CPB, 2×10^6 U infused over four hours after CPB). Anticoagulation was achieved with heparin to target a Kaolin activated-clotting-time greater than 480 sec. The CPB circuit was primed with 1.8 L Ringer's lactate and 50 mL 20% mannitol. Management of CPB included systemic temperature drift to 34°C, alpha-stat pH management, mean perfusion pressure of 50–70 mmHg, and non-pulsatile pump flow rates of 2.0–2.4 $L \cdot min^{-1} \cdot m^{-2}$. Myocardial protection was achieved with intermittent antegrade, and occasionally, retrograde cold blood cardioplegia. After separation from CPB, heparin was neutralized with protamine sulphate to achieve an activated-clotting-time within 10% of baseline. After surgery, patients were transferred to the intensive care unit, intubated and ventilated. Other aspects of care were left to the discretion of responsible clinicians.

Data collection and outcomes

At the time of enrolment, we documented preoperative information on sex, weight, serum creatinine concentration, co-morbidities, and medications. Documented co-morbidities were congestive heart failure, hypertension, left ventricular ejection fraction, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease. We also documented intraoperative data on the surgical procedure, *unplanned* off-pump surgery, *unplanned* deep hypothermic circulatory arrest, cross-clamp time, CPB time, anti-fibrinolytic use, hematocrit, and blood glucose concentration. Hematocrit and blood glucose concentration were measured every 15 min during CPB.

The primary outcome was the percent change in eGFR (Cockcroft-Gault equation) in the first 72 hr after surgery.[21] This mathematical transformation of changes in creatinine concentration results in a less skewed distribution that is more amenable for sample size estimation.[27] Postoperative eGFR does not necessarily approximate directly measured GFR because creatinine concentration would not be in steady state. Nonetheless, percent change in eGFR is a convenient surrogate outcome that is closely associated with mortality, RRT, and prolonged hospitalization.[27] For comparison against similar studies, we also documented the secondary outcome of postoperative acute kidney injury, defined as a 72-hr increase in creatinine concentration greater than 44 $\mu mol \cdot L^{-1}$ or 25%.[28] Serum creatinine concentration was measured at the time of study recruitment (within four weeks before surgery), and then daily for 72 hr after surgery.

Other secondary outcomes included interventions (vasoactive medications, intra-aortic balloon pump, red blood cell transfusion, RRT), complications (mortality, atrial fibrillation, stroke), and adverse effects (bronchospasm, urticaria, facial edema, nausea/vomiting). Nephrologists, who were blinded to treatment assignment, made decisions on implementing RRT. Postoperative atrial fibrillation was defined as any new atrial fibrillation detected by continuous telemetry or 12-lead electrocardiograms. Neurologists, who were also blinded to treatment assignment, diagnosed strokes based on new persistent (≥ 24 hr) neurological deficits.

We collected outcome information for the duration of participants' hospital-stay; patients who were discharged were contacted at 90 days after surgery to determine vital status.

Analyses

We performed all analyses on an intention-to-treat basis, using R 2.3.1.[A] Statistical significance was defined by a two-tailed *P*-value ≤ 0.05. We used the two-sample *t* test to compare continuous outcomes

A *The R Development Core Team*. R. A language and environment for statistical computing (URL http://www.R-project.org). Vienna, Austria: R Foundation for Statistical Computing; 2007.

with normal distributions, and calculated the difference between means with 95% confidence intervals (CI). If the distribution was skewed, we compared medians using the permutation test, and calculated non-parametric 95% bootstrap CI for the difference between medians.[29] Dichotomous outcomes were compared using the χ^2 test or Fisher exact test, as appropriate. Treatment effects were expressed as odds ratios with exact 95% CIs.[30] We calculated a sample size of 176, using assumptions of a 5% decrease in eGFR in the control arm, and 5% increase in eGFR in the N-acetylcysteine arm (SD 19, two-sided alpha 0.05, 90% power, 10% drop-out rate).[27]

Our study aimed to determine if N-acetylcysteine warrants evaluation in a future multicentre trial. For diseases with multifactorial etiologies, efficacious therapies attenuate only some of the underlying mechanisms; hence, these therapies should be expected to have small-to-moderate benefits, as suggested by Yusuf *et al.*[31] Since perioperative kidney injury has a multifactorial etiology, we expected that N-acetylcysteine would also have, at best, a small-to-moderate benefit.[14] Based on a SD of 19 and Cohen's standards for effect sizes, small (0.2 SD) and moderate (0.5 SD) treatment effects on the percent change in eGFR were estimated at 3.8 and 9.5, respectively.[27,33] This preliminary study, therefore, had sufficient statistical power to precisely detect a moderate treatment effect.[32] We also considered that a future multicentre trial was still worth pursuing provided that the 95% CI of the treatment effect was consistent with a plausible small-to-moderate treatment effect.[32] *Minimum* criteria for pursuing a future trial were, therefore, a percent change in eGFR that was 3.8 better in the N-acetylcysteine arm, and an upper 95% CI that included 9.5.

Results

Between September 2003 and October 2005, 177 patients were randomized to N-acetylcysteine (n = 89) or placebo (n = 88) (Figure). Two were excluded because they met exclusion criteria before randomization: severe renal insufficiency (creatinine concentration of 513 $\mu mol \cdot L^{-1}$ in N-acetylcysteine arm), and N-acetylcysteine within 24 hr before surgery (placebo arm).[33] Statistical analyses therefore included 175 participants. At the discretion of the attending surgeon, three patients underwent unplanned off-pump surgery (all in placebo arm), and eight underwent unplanned circulatory-arrest (four in each arm). One patient (N-acetylcysteine arm) received open-label drug intraoperatively. This individual received the bolus dose but not the infusion of the study drug. All patients completed their creatinine measurements.

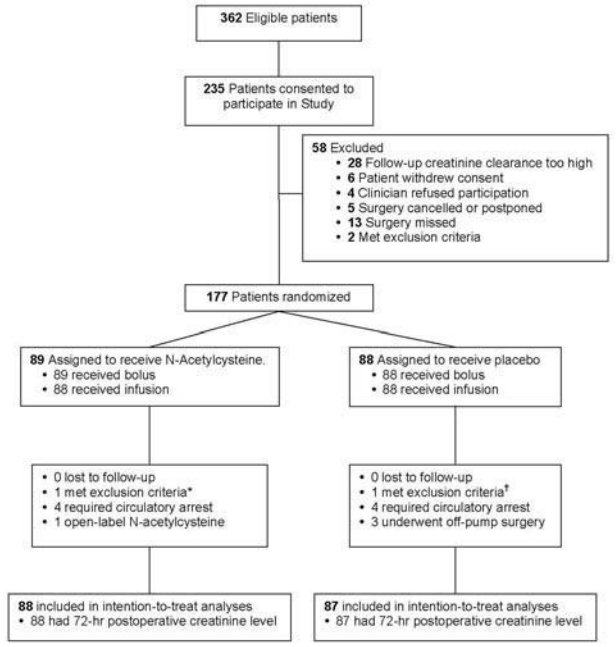

FIGURE Patient flow through study. One patient was excluded from the N-acetylcysteine arm* (preoperative creatinine concentration 513 $\mu mol \cdot L^{-1}$), and one was excluded from the placebo arm† (open-label N-acetylcysteine administered within 24 hr before surgery) after randomization.

Patients were well balanced with regard to most perioperative characteristics (Tables I and II). However, patients in the N-acetylcysteine arm had poorer preoperative renal function and higher glucose concentrations during CPB. They also had a higher prevalence of hypertension and aprotinin use. In contrast, more patients in the placebo arm had left ventricular ejection fractions ≤ 40% and cerebrovascular disease. By chance, the placebo arm had a significantly higher prevalence of procedures other than isolated CABG (P = 0.05). Despite these imbalances, the two groups had similar EuroSCORE risk profiles and CPB times.[34]

Postoperative eGFR decreased in both the N-acetylcysteine (median, 8.4% decrease; interquartile range, 21.9% decrease to 3.1% increase) and placebo (median, 13.6% decrease; interquartile range, 24.3% decrease to 1.7% increase) arms. The between-groups difference was not statistically significant (P = 0.22). The median percent change in eGFR was 5.2% better (absolute difference) in the N-acetylcysteine arm (95% CI 2.4% worse to 12.1% better) (Table III). To estimate the probability of a benefit exceeding a

TABLE I Baseline characteristics of participants*

	N-acetylcysteine (n = 88)	*Placebo (n = 87)*
Demographics		
Age, mean (SD), yr	74 (8)	73 (9)
Female sex	35 (40%)	36 (41%)
Weight, mean (SD), kg	71 (11)	71 (12)
Preoperative renal function		
Creatinine concentration, mean (SD), $\mu mol \cdot L^{-1}$	131 (40)	123 (38)
eGFR, mean (SD), $mL \cdot min^{-1}$	42 (11)	45 (11)
60 $mL \cdot min^{-1} \leq$ eGFR < 30 $mL \cdot min^{-1}$	75 (85%)	77 (89%)
eGFR ≤ 30 $mL \cdot min^{-1}$	13 (15%)	10 (11%)
Preoperative cardiac status		
Congestive heart failure	17 (19%)	16 (18%)
Left ventricular ejection fraction ≤ 40%	13 (15%)	21 (24%)
Co-morbid disease		
Hypertension	72 (82%)	64 (74%)
Diabetes mellitus requiring medication	31 (35%)	26 (30%)
Peripheral vascular disease	15 (17%)	15 (17%)
Cerebrovascular disease	12 (14%)	20 (23%)
Chronic obstructive pulmonary disease	8 (9%)	13 (15%)
Preoperative medications		
β-blocker	61 (69%)	57 (66%)
Calcium channel blocker	35 (40%)	29 (33%)
ACE inhibitor or angiotensin receptor blocker	57 (65%)	49 (56%)
NSAID or COX-2 inhibitor	7 (8%)	6 (7%)
Aspirin	67 (76%)	62 (71%)

eGFR = estimated glomerular filtration rate (Cockcroft-Gault equation);[21] ACE = angiotensin-converting enzyme; NSAID = non-steroidal anti-inflammatory drug; COX = cyclo-oxygenase. *Values are expressed as number (percentage) unless otherwise indicated.

TABLE II Intraoperative characteristics of participants*

	N-acetylcysteine (n = 88)	*Placebo (n = 87)*
Previous cardiac surgery	9 (10%)	7 (8%)
Anti-fibrinolytic use		
Tranexamic acid	78 (89%)	81 (93%)
Aprotinin	11 (13%)	4 (5%)
Procedure type		
Isolated coronary artery bypass graft	53 (60%)	40 (46%)
Isolated valve repair/replacement only	17 (19%)	17 (20%)
Combined procedures	18 (21%)	30 (34%)
CPB time, mean (SD), min	105 (35)	105 (39)
Cross-clamp time, mean (SD), min	79 (31)	81 (29)
Lowest hematocrit during CPB, mean (SD)	0.22 (0.03)	0.22 (0.03)
Highest glucose during CPB, mean (SD), $mmol \cdot L^{-1}$	11.3 (2.8)	10.5 (2.6)
Composite operative risk estimate		
Additive EuroSCORE, mean (SD), points[35]	6.4 (2.5)	6.8 (2.8)
EuroSCORE predicted mortality rate[35]	7.7%	9.4%

CPB = cardiopulmonary bypass. *Values are expressed as number (percentage) unless otherwise indicated.

small treatment effect, we calculated the proportion of bootstrap estimates greater than the criterion of 3.8 better. Sixty-four percent of estimates were better than a small treatment effect. The effect on the secondary outcome of postoperative kidney injury, as defined in a recent similar study, was also statistically non-significant (odds ratio 0.84; 95% CI 0.56–2.05; $P = 0.59$) (Table III).[28] Rates of RRT were not significantly different between study arms (Table III).

Intraoperatively, N-acetylcysteine was not associated with reduced use of inotropes ($P = 0.15$) (Table IV). Postoperatively, N-acetylcysteine was associated with significantly reduced mortality ($P = 0.007$), and trends towards reduced atrial fibrillation ($P = 0.21$).

TABLE III Postoperative renal outcomes

	N-acetylcysteine (n = 88)	*Placebo (n = 87)*			
Primary outcome			*Difference**	*95% CI*	*P*
72-hr % change in eGFR, median (interquartile range)	-8.4 (-21.9 to 3.1)	-13.6 (-24.3 to 1.7)	5.2	-2.4 to 12.1	0.22
Secondary outcomes			*OR†*	*95% CI*	*P*
72-hr increase in creatinine concentration ≥ 44 μmol·L^{-1} or 25%, *n* (%)	25 (28%)	28 (32%)	0.84	0.42 – 1.68	0.59
RRT, *n* (%)	1 (1%)	3 (4%)	0.32	0.007 – 4.12	0.37

eGFR = estimated glomerular filtration rate (Cockcroft-Gault equation);[21] CI = confidence interval; OR = odds ratio; RRT = renal replacement therapy. *Difference in medians between N-acetylcysteine *vs* placebo (95% bootstrap non-parametric CI).[30] †Odds ratio with exact 95% CI.[31]

TABLE IV Non-renal postoperative outcomes

	N-acetylcysteine (n = 88)	*Placebo (n = 87)*			
Dichotomous outcomes, *n* (%)			OR*	95% CI	*P*
Intraoperative medications					
Low-dose dopamine	44 (50%)	55 (63%)	0.58	0.30 – 1.11	0.33
Inotropes†	17 (19%)	25 (29%)	0.60	0.27 – 1.27	0.15
Vasoconstrictors‡	56 (64%)	63 (72%)	0.67	0.33 – 1.33	0.21
Postoperative (24-hr) medications					
Low-dose dopamine	54 (61%)	52 (60%)	1.07	0.56 – 2.05	0.83
Inotropes†	14 (16%)	19 (22%)	0.68	0.29 – 1.55	0.31
Vasoconstrictors‡	62 (70%)	60 (69%)	1.07	0.54 – 2.15	0.83
Mortality§	0 (0%)	7 (8%)	0	0 – 0.66	0.007
Stroke	4 (5%)	4 (5%)	1	0.18 – 5.49	1
Atrial fibrillation	50 (57%)	58 (67%)	0.66	0.34 – 1.27	0.21
Intra-aortic balloon pump support	3 (3%)	4 (5%)	0.73	0.10 – 4.48	0.72
Red cell transfusion	77 (88%)	80 (92%)	0.61	0.19 – 1.84	0.33
Drug-related adverse effects					
Bronchospasm	4 (5%)	2 (2%)	2.01	0.28 – 22.8	0.68
Urticaria	2 (2%)	0 (0%)	∞	0.19 - ∞	0.50
Nausea and/or vomiting	26 (30%)	17 (20%)	1.74	0.82 – 3.78	0.12
Continuous outcomes			*Difference*‖	*95% CI*	*P*
Intensive-care-unit length-of-stay, median (interquartile range), days	1.9 (1 – 4)	1.7 (1 – 3.8)	0.2	-0.7 to 1	0.42
Hospital length-of-stay, median (interquartile range), days	8 (6 – 12)	8 (6 – 12)	0	-2 to 1	0.58

OR = odds ratio; CI = confidence interval; * Odds ratio with exact 95% CI;[31] † Epinephrine or milrinone; ‡ Norepinephrine or vasopressin; § Six deaths were cardiac in cause (one of which required renal replacement therapy). The remaining death was caused by sepsis with multi-organ failure requiring renal replacement therapy. || Difference in medians between N-acetylcysteine *vs* placebo (95% bootstrap non-parametric CI).[30]

There were no significant differences in length-of-stay in hospital or the intensive-care-unit (Table IV).

With regard to drug-related adverse effects, N-acetylcysteine was not associated with significant increases in bronchospasm, facial edema or nausea/vomiting ($P = 0.12$) (Table IV).

Discussion

In this blinded (patients, clinicians, data-collectors) placebo-controlled randomized trial in cardiac surgery patients with moderate pre-existing renal insufficiency, N-acetylcysteine did not cause a statistically significant effect on percent 72-hr change in eGFR. Nonetheless, the point estimate and upper 95% CI are consistent with a biologically plausible small-to-moderate treatment effect. Post-hoc analyses suggest a reasonable likelihood (64%) that the benefit was greater than a small treatment effect. With regard to secondary outcomes, N-acetylcysteine was associated with a reduction in mortality. This hypothesis-generating result mirrors recent data suggesting that N-acetylcysteine reduces mortality after primary angioplasty.[35] N-acet-

ylcysteine also had a generally good safety profile. The combination of potential improvements in renal function, favourable associations with secondary outcomes, and reasonable safety profile justify a definitive large randomized trial of perioperative N-acetylcysteine.

This study warrants comparison with two recent randomized trials that specifically assessed the renal-protective effects of N-acetylcysteine in cardiac surgery.[28,36] Burns *et al.*[28] evaluated the effect of a reduced dose (2400 mg) on postoperative kidney injury, defined as increase in creatinine concentration greater than 44 μmol·L^{-1} or 25%. Participants in Burns *et al.* were generally low-risk; their mean creatinine concentration was 104 μmol·L^{-1}. In contrast, the mean creatinine concentration in our study sample was 127 μmol·L^{-1}. Although Burns *et al.*[28] found no overall effect of N-acetylcysteine on kidney injury (29.7% *vs* 29.0%), closer evaluation suggests similarity with our study. In a subgroup analysis of participants with pre-existing renal insufficiency, N-acetylcysteine was associated with trends towards reduced kidney injury (25.0% *vs* 37.1%).

Ristikankare *et al.*[36] evaluated the effects of a higher dose (300 mg·kg^{-1}) in cardiac surgery patients with pre-existing renal insufficiency. They found no effect on the primary outcome, an increase in urine N-acetyl-β-D-glucosaminidase/creatinine ratio greater than 30%. The clinical significance of this primary outcome is not clear.[37] Of note, N-acetylcysteine was also associated with a non-significantly lower risk of a 44 μmol·L^{-1} or 25% increase in creatinine concentration (42.1% *vs* 48.7%).

The present study has several strengths. First, it upheld high quality standards. Patients, clinicians and data-collectors were blinded. Allocation was concealed. Follow-up was complete. Second, the study targeted an appropriately high-risk population: the mortality rate in the control arm was 8%. This rate was consistent with participants' risk-profiles, as estimated by the EuroSCORE. Finally, we chose a surrogate primary outcome, percent change in eGFR, that was closely associated with patient-relevant outcomes such as mortality and RRT.[27]

Our overall finding, with regard to the effect of N-acetylcysteine on postoperative eGFR, was statistically non-significant. We cannot, therefore, conclude that N-acetylcysteine prevents perioperative kidney injury. Nonetheless, interpretation of feasibility studies, such as our study, should not focus on *P*-values alone. As previously stated, any single therapy will cause, at best, a small-to-moderate effect in a multifactorial disease such as perioperative kidney injury. Consequently, large sample sizes are required to detect plausible treatment effects, even with the use of surrogate continuous outcomes. To illustrate this, the sample size required to detect a small effect-size (0.2 SD) is 788 (two-sided alpha 0.05, 80% power).[32] By comparison, Burns *et al.*[28] included 295 participants in one of the largest randomized trials of perioperative renal-protection. One should, therefore, also evaluate CIs around estimated treatment effects when determining if a renal-protective therapy warrants definitive evaluation in a multicentre trial. In our present study, the 95% CI for the treatment effect was consistent with a plausible small-to-moderate treatment effect. In addition, our estimated treatment effect on the secondary outcome of kidney injury (increase in creatinine concentration greater than 44 μmol·L^{-1} or 25%) was consistent with recent trials of N-acetylcysteine in cardiac surgery patients with pre-existing renal insufficiency. Indeed, if one performs a random-effects meta-analysis using perioperative studies of patients with pre-existing renal insufficiency (Burns *et al.*,[28] Ristikankare *et al.*,[36] and our present study), N-acetylcysteine is associated with a moderate reduction in renal dysfunction that approaches statistical significance (relative risk 0.79; 95% CI 0.59–1.06; $P = 0.12$).

Perioperative N-acetylcysteine should therefore be evaluated in a large randomized trial, for several reasons. N-acetylcysteine is an inexpensive and relatively safe drug with the potential for widespread use. Preliminary single-centre studies, including our study, also suggest that N-acetylcysteine *may* improve perioperative outcomes. These findings must be confirmed by a large trial powered to measure clinically important outcomes. Finally, perioperative researchers should heed the lessons learnt in the contrast-induced nephropathy literature.[20] Instead of proceeding with more small-scale trials, they should form the collaborative networks needed for a definitive large trial.

The results of our present study also help to delineate the design of this future definitive trial. First, this trial should target cardiac surgery patients with pre-existing renal insufficiency. Our results validate an eGFR ≤ 60 mL·min^{-1} as a good criterion for identifying at-risk participants.[23] Second, similar-sized centres (1,500–2,000 cases/year) in a future multicentre trial should expect to recruit approximately 80–90 participants per year. Third, the future trial should be designed with sufficient statistical power to detect a *small-to-moderate* reduction (e.g., 20% relative risk reduction) in clinically important renal outcome.[31] The small-to-moderate size of the treatment effect has specific implications for the design of the future trial. It will likely not be feasible to design the future study to detect a moderate reduction in RRT. Despite

recruiting a high-risk sample, the RRT rate in the control arm of our present study was only 4%; consequently, approximately 17,520 participants would be required to precisely measure a 20% relative risk reduction in RRT (alpha of 0.05, and power of 0.8). An alternative primary outcome that is feasible, but still clinically important, is the consensus-based RIFLE definition for acute kidney injury.[38] Based on an estimated 19% rate of postoperative acute kidney injury (RIFLE criteria) in the control arm, approximately 3,186 participants will be required to precisely measure a 20% relative risk reduction (alpha of 0.05, and power of 0.8).[39] Finally, randomization in the future study should be stratified by important determinants of acute kidney injury, such as preoperative renal function and surgical procedure.[23,40]

Several design-related issues pertinent to this future trial remain unclear. They include the appropriate dose of N-acetylcysteine, and the influence of baseline characteristics (e.g., preoperative medications) on its renal-protective effects. An individual-patient meta-analysis based on randomized trials of perioperative N-acetylcysteine might help clarify these issues. The meta-analysis will also help to better delineate the treatment effect that should be expected in the future definitive trial.

Limitations

This study should be interpreted cautiously. First, eGFR is a surrogate outcome that does not accurately represent the true GFR in the non-steady state of acute kidney injury.[41] Alternative options are, however, limited. Timed measurements of creatinine clearance become inaccurate with falling GFR.[41] Other direct measurements of GFR using clearance of inulin or radiolabeled compounds are not feasible in clinical trials. An alternative is serum cystatin C. A potential advantage of cystatin C is that N-acetylcysteine may decrease serum creatinine concentration, but not cystatin C concentration, independent of changes in renal function.[42] This observation is, however, contradicted by recent data that demonstrate that, when GFR is measured directly using ^{51}Cr-EDTA clearance, N-acetylcysteine improves both GFR and creatinine concentration after ischemic kidney injury.[43]

Second, the observed treatment effect may have been influenced by differences in baseline characteristics that have prognostic significance. Specifically, patients in the N-acetylcysteine arm had poorer preoperative renal function, higher intraoperative glucose concentrations, and a higher prevalence of aprotinin use.[23,44,45] In contrast, more patients in the placebo arm had left ventricular ejection fractions ≤ 40% and underwent complex surgical procedures.[23] Despite the use of concealed randomization, these baseline differences are not surprising. Indeed, under the null hypothesis of no difference between study arms, one would expect at least 5% of the comparisons in Tables I and II to be significant at the 5% level.[46] Importantly, there were no differences in important multi-factorial risk factors, such as CPB duration or EuroSCORE.[34,40] A future individual-patient meta-analysis, with its added statistical power, should explore the potential influence of these baseline characteristics on the efficacy of N-acetylcysteine.

In conclusion, this blinded placebo-controlled randomized trial found that N-acetylcysteine did not cause a statistically significant effect on the percent 72-hr change in eGFR. Nonetheless, the point estimate and upper 95% CI were consistent with a small-to-moderate treatment effect. Given the potential for a biologically plausible treatment effect, as well as reasonable safety profile, N-acetylcysteine should now be evaluated definitively by a large randomized trial. This multicentre trial should focus on cardiac surgery patients with pre-existing renal insufficiency.

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