ANESTHESIOLOGY

Amiodarone with or without *N*-Acetylcysteine for the Prevention of Atrial Fibrillation after Thoracic Surgery: A Double-blind, Randomized Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The American Association for Thoracic Surgery's guidelines for the prevention and management of perioperative atrial fibrillation and flutter provide a class IIa recommendation for administration of amiodarone to prevent postoperative atrial fibrillation in intermediate- and high-risk patients undergoing lung resection and esophagectomy
- However, approximately 15% of patients receiving amiodarone still develop postoperative atrial fibrillation
- *N*-Acetylcysteine has anti-inflammatory properties, but its efficacy in reducing atrial fibrillation in noncardiac thoracic surgical patients has not been well studied

What This Article Tells Us That Is New

- This double-blinded randomized trial of noncardiac thoracic surgery patients was done to test the hypothesis that the addition of *N*-acetylcysteine to concurrent amiodarone administration would reduce the incidence of postoperative atrial fibrillation when compared with placebo being concurrently administered with amiodarone
- The study was halted midway for futility, as there was no difference in postoperative atrial fibrillation in the patients who received *N*-acetylcysteine plus amiodarone *versus* the patients who received placebo plus amiodarone

ABSTRACT

Background: Postoperative atrial fibrillation may identify patients at risk of subsequent atrial fibrillation, with its greater risk of stroke. This study hypothesized that *N*-acetylcysteine mitigates inflammation and oxidative stress to reduce the incidence of postoperative atrial fibrillation.

Methods: In this double-blind, placebo-controlled trial, patients at high risk of postoperative atrial fibrillation scheduled to undergo major thoracic surgery were randomized to *N*-acetylcysteine plus amiodarone or placebo plus amiodarone. On arrival to the postanesthesia care unit, *N*-acetylcysteine or placebo intravenous bolus (50 mg/kg) and then continuous infusion (100 mg/kg over the course of 48 h) was administered plus intravenous amiodarone (bolus of 150 mg and then continuous infusion of 2 g over the course of 48 h). The primary outcome was sustained atrial fibrillation longer than 30 s by telemetry (first 72 h) or symptoms requiring intervention and confirmed by electrocardiography within 7 days of surgery. Systemic markers of inflammation (interleukin-6, interleukin-8, tumor necrosis factor α, C-reactive protein) and oxidative stress (F_2-isoprostane prostaglandin $F_{2\alpha}$; isofuran) were assessed immediately after surgery and on postoperative day 2. Patients were telephoned monthly to assess the occurrence of atrial fibrillation in the first year.

Results: Among 154 patients included, postoperative atrial fibrillation occurred in 15 of 78 who received *N*-acetylcysteine (19%) and 13 of 76 who received placebo (17%; odds ratio, 1.24; 95.1% CI, 0.53 to 2.88; $P = 0.615$). The trial was stopped at the interim analysis because of futility. Of the 28 patients with postoperative atrial fibrillation, 3 (11%) were discharged in atrial fibrillation. Regardless of treatment at 1 yr, 7 of 28 patients with postoperative atrial fibrillation (25%) had recurrent episodes of atrial fibrillation. Inflammatory and oxidative stress markers were similar between groups.

Conclusions: Dual therapy comprising *N*-acetylcysteine plus amiodarone did not reduce the incidence of postoperative atrial fibrillation or markers of inflammation and oxidative stress early after major thoracic surgery, compared with amiodarone alone. Recurrent atrial fibrillation episodes are common among patients with postoperative atrial fibrillation within 1 yr of major thoracic surgery.

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Transient atrial fibrillation after noncardiac thoracic or general surgery has long been thought to be a benign and self-limited disorder; however, new evidence suggests it may be a sentinel event that can be used to identify patients who are at risk of developing subsequent atrial fibrillation and who have a greater risk of short- and long-term stroke.[1–4] Postoperative atrial fibrillation may have hemodynamic consequences and result in treatment-related adverse events, such as bleeding, drug toxicity, and extended hospital stay of 2 to 4 days, with greater average cost of care of more than 30%.[1] As is the case for atrial fibrillation not related to surgery, age

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greater than 60 yr is strongly associated with postoperative atrial fibrillation. Other proven risk factors in observational studies of atrial fibrillation after noncardiac thoracic surgery include history of atrial fibrillation, extent of surgery, and preoperative subclinical higher brain natriuretic peptide level.[5,6] Proposed pathophysiologic changes underlying heightened risk of atrial fibrillation after noncardiac thoracic surgery include oxidative stress, inflammation, autonomic imbalance, and damage to autonomic fibers.[1] The onset of arrhythmia peaks 2 to 3 days after surgery, with approximately 85% of these episodes reverting to sinus rhythm by the use of rate or rhythm control strategies during hospitalization.[1] Amiodarone has received a class IIa recommendation from the American Association for Thoracic Surgery (Beverly, Massachusetts) Taskforce for the prevention of postoperative atrial fibrillation in intermediate- and high-risk patients undergoing lung resection and esophagectomy.[1] More than 15% of patients at high risk will experience atrial fibrillation after thoracic surgery when amiodarone is used for prevention, and amiodarone may be associated with transient bradycardia, hypotension, and, rarely, pulmonary toxicity.[1,7] An effective treatment that specifically targets inflammation and oxidative distress to reduce the incidence of postoperative atrial fibrillation has been elusive.

N-Acetylcysteine is an antioxidant anti-inflammatory agent with a demonstrated effect on proinflammatory cytokines, oxygen-free radicals, and ischemia reperfusion injury. In a limited number of studies, intravenous *N*-acetylcysteine has been shown to reduce the incidence of postoperative atrial fibrillation related to cardiac surgery,[8,9] but it has not been tested in patients undergoing noncardiac thoracic surgery. Oxidative stress in patients undergoing thoracic surgery has been reported, with one-lung ventilation routinely used to facilitate operative conditions.[10] Furthermore, *in vitro* studies have shown that *N*-acetylcysteine reduced inflammation and oxidative stress in response to injury in human airway smooth muscle cells.[11] In patients undergoing major thoracic surgery who were identified to have a greater risk of postoperative atrial fibrillation by use of a novel prediction tool,[5,6] we tested the hypothesis that the addition of *N*-acetylcysteine to amiodarone would reduce the incidence of postoperative atrial fibrillation, compared with amiodarone alone.

Materials and Methods

Study Design and Participants

The current study was an investigator-initiated, randomized, double-blind, placebo-controlled trial comparing intravenous *N*-acetylcysteine plus amiodarone with *N*-acetylcysteine–matched placebo plus amiodarone conducted at two centers (Memorial Sloan Kettering Cancer Center [New York, New York] and Washington University Medical Center [St. Louis, Missouri]; ClinicalTrials.gov identifier, NCT02750319; https://clinicaltrials.gov/ct2/show/NCT02750319; principal investigator, David Amar; date of registration, April 25, 2016; full protocol available on request). Eligible patients were aged 18 yr or older, were scheduled for elective major thoracic surgery (anatomic pulmonary resection [segmentectomy, lobectomy, bilobectomy, or pneumonectomy] or esophagectomy), were in sinus rhythm preoperatively, and had one of the following four risk criteria: (1) female sex and preoperative brain natriuretic peptide of 25 pg/ml or greater; (2) male sex, age less than 75 yr, and preoperative brain natriuretic peptide 25 pg/ml or greater; (3) male sex and age 75 yr or older; and (4) history of atrial fibrillation. As patients undergoing Ivor Lewis esophagectomy consisting of abdominal and right thoracic cavity incisions often experience postoperative atrial fibrillation,[1] these patients were included as well. The risk criteria were derived from our previously published work, which showed a higher incidence of atrial fibrillation in men, those age 75 yr or older, and those with a history of atrial fibrillation; brain natriuretic peptide 25 pg/ml or greater (median for cohort) helped distinguish risk among women and men age less than 75 yr.[5,6] The brain natriuretic peptide measurements were performed using an Alere triage meter (Alere North America, USA) at both institutions. The exclusion criteria were hemodynamic instability, second-degree atrioventricular block, hypersensitivity to amiodarone or *N*-acetylcysteine, current use of class Ic or III antiarrhythmic drugs, hepatic insufficiency (more than 2.0 times the

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upper limit of normal of transaminase levels), renal insufficiency (creatinine 2.0 mg/dl or greater), or pregnancy. To avoid withdrawal symptoms, preoperative β-blockers and calcium channel blockers were continued postoperatively. Potential candidates were screened for eligibility by dedicated research staff who introduced the study to patients, written informed consent was obtained by the attending surgeon from each patient, and the study was approved by the institutional review boards of Memorial Sloan Kettering Cancer Center and Washington University Medical Center.

Randomization

Patients underwent routine preoperative evaluation, including brain natriuretic peptide measurement, and were randomized 1:1 to a study group before the day of surgery. The Memorial Sloan Kettering Cancer Center statisticians responsible for randomization (independent of the study statistician) set up the parameters for the allocation sequence, which occurred in real time once patients were registered as eligible and consented to the trial. Randomization was accomplished by computer algorithm using the method of random permuted blocks (of random sizes of 2, 4, or 6), stratified by procedure type (lung resection or esophagectomy). The randomization schedule was concealed from Memorial Sloan Kettering Cancer Center investigators by use of a centralized randomization module that generated allocations in real time only to Memorial Sloan Kettering Cancer Center hospital pharmacists. The randomization schedule was concealed from Washington University investigators by use of a centralized randomization module housed at Memorial Sloan Kettering Cancer Center, which generated allocations in real time only to Memorial Sloan Kettering Cancer Center statisticians responsible for randomization, a team independent of the study statistician. The sequence of assignments for Memorial Sloan Kettering Cancer Center patients was administered in real time to Memorial Sloan Kettering Cancer Center hospital pharmacists, who dispensed the study drugs. The sequence of assignments for Washington University patients was administered in real time to Memorial Sloan Kettering Cancer Center randomization statisticians, who then securely emailed the assignments only to the Washington University pharmacist who dispensed the study drugs.

Interventions

Anesthesia and surgical techniques followed standard institutional care. Anesthesia was induced with midazolam, propofol, and fentanyl and maintained with volatile anesthetics and a nondepolarizing muscle relaxant. Epidural analgesia was used during and after surgery only for patients who underwent open surgical procedures. Surgical procedures for lung resection included both open thoracotomy and minimally invasive video-assisted thoracoscopic or robotic-assisted approaches and Ivor Lewis esophagectomy consisting of abdominal and right thoracic cavity incisions using either minimally invasive laparoscopy and thoracoscopy or open incisions. No robotic esophagectomies were included. Patients who underwent ineligible surgical procedures (*e.g.*, lung wedge resection or biopsy only) that were protocol-prespecified as ineligible were not treated in the study, taken off the study, and removed from all analyses.

The study drug and placebo were prepared at both sites by the institutional pharmacy, and all investigators, clinical care team members, and patients were blinded to treatment allocation. All patients received amiodarone, as per routine practice, as follows—loading dose: 150 mg of amiodarone intravenously in the postanesthesia care unit over the course of 1 h and then 2 g over the course of 48 h. The patients were randomized to receive either *N*-acetylcysteine loading dose 50 mg/kg intravenously in the postanesthesia care unit over the course of 1 h and then by continuous infusion 100 mg/kg over the course of 48 h or matching saline placebo. The selected dose of *N*-acetylcysteine has been described.[8,9] We chose not to administer *N*-acetylcysteine before surgery to avoid the exclusion of treated patients from the primary analysis who later were found to have undergone ineligible procedures. The patients were monitored with continuous telemetry for a minimum of 72 h or longer if needed. Rhythm strips from the telemetry system and the QT interval in response to drug therapy were monitored in accordance with the standard of care.

All patients who developed acute postoperative atrial fibrillation and did not respond to first-line drugs for rate control, such as diltiazem or metoprolol, were managed by a consulting cardiologist. The CHA_2D_2S-VASc (congestive heart failure, hypertension, age 75 yr or older, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 yr, sex category [female]) score for each patient was recorded. For patients with arrhythmia less than 48 h in duration, anticoagulant therapy was considered after weighing the risk of postoperative bleeding, but ultimately the decision was left to the treating physician. Anticoagulation therapy was considered for patients with a CHA_2D_2S-VASc score of 1 and was recommended for those with a score of 2 or higher. Patients with postoperative atrial fibrillation more than 48 h in duration received anticoagulant therapy unless the risk of postoperative bleeding was judged to be too high.[1]

Outcomes

The primary outcome was new onset of either sustained postoperative atrial fibrillation (greater than 30 s) detected by telemetry (first 72 h) or symptomatic postoperative atrial fibrillation requiring intervention and documented by 12-lead electrocardiography within 7 days of surgery. The primary outcome was verified by a clinical cardiologist and investigators blinded to the treatment assignment. Secondary outcomes were differences between the groups in perioperative systemic markers of inflammation and

oxidative stress and incidence of atrial fibrillation up to 1 yr after discharge regardless of treatment assignment. At the time of hospital discharge, patients who developed postoperative atrial fibrillation in-hospital were equipped with mobile electrocardiography monitors (AliveCor, USA) that adhere to a smart phone or tablet and were instructed to transmit weekly electrocardiogram recordings for up to 1 yr from surgery. Continuous heartbeat data (rhythm strip) were recorded and transmitted wirelessly in real time. All patients, regardless of whether they developed postoperative atrial fibrillation, were contacted by phone at 7, 14, and 30 days and then monthly for the first year after surgery. We reviewed the subsequent follow-up physician visits and electronic medical records of all study patients for any evidence of hospitalization or treatment for new-onset atrial fibrillation. Length of hospital stay and 30- and 90-day mortality were recorded from a regularly maintained hospital database. Additional secondary outcomes were cardiovascular complications (including myocardial infarction, stroke, thromboembolic events, and major bleeding requiring reoperation) and pulmonary complications (including atelectasis, pneumonia, pneumonitis, and acute respiratory failure). Treatment-related adverse events, such as allergic reaction to *N*-acetylcysteine or transient hypotension or bradycardia with amiodarone, were recorded.

Biospecimen Analysis

To assess markers of inflammation and oxidative stress, plasma and urine samples, respectively, were collected at the end of surgery and again on the morning of postoperative day 2 from all patients. Interleukin-6, interleukin-8, and tumor necrosis factor α were measured by enzyme-linked immunosorbent assay (Ella Simple Plex, ProteinSimple, USA). C-reactive protein was measured by means of an immunoturbidometric method using the Abbott Architect analyzer (USA). Urine samples were collected to assess systemic markers of oxidative stress (urinary F_2-isoprostane prostaglandin $F_{2\alpha}$ and isofuran). Measurements of these markers were assessed by the use of specific gas chromatography–mass spectrometry in the Eicosanoid Core Laboratory (Vanderbilt University Medical Center, by G.L.M.), as previously described.[12] Plasma and urine samples were processed similarly at both study sites and stored at –80°C until analysis. Planned analyses of samples from both sites, in duplicate, were to be performed for plasma inflammatory markers at Memorial Sloan Kettering Cancer Center and for urine oxidative markers at Vanderbilt University Medical Center.

Statistical Analysis

Sample-size calculations were based on an anticipated proportion of patients with postoperative atrial fibrillation of 16% in the placebo group and 5% in the *N*-acetylcysteine group (absolute decrease of 11% and relative difference of 69%). The hypothesized rate of 5% postoperative atrial fibrillation is the rate among low-risk patients in the population based on historical data.[5] Furthermore, the hypothesized relative difference of 69% (11 of 16) was based on the approximately 65% response rate reported in published studies using *N*-acetylcysteine.[8,9] A sample size of 244 evaluable patients (122 patients in each group) would therefore achieve 80% power at a two-sided 5% α level. One formal interim analysis was planned halfway through enrollment (122 evaluable patients), using a Lan–DeMets spending function approach with O'Brien–Fleming stopping boundaries for both efficacy and futility. At the interim analysis, if $P \leq 0.002$, enrollment would be discontinued, and we would conclude that amiodarone plus *N*-acetylcysteine significantly decreased the rate of postoperative atrial fibrillation, compared with amiodarone alone (efficacy). If $P \geq 0.719$, enrollment would be stopped for futility. If $0.002 < P < 0.719$, the trial would continue to full enrollment, and we would conclude that *N*-acetylcysteine significantly reduced postoperative atrial fibrillation if $P < 0.049$. The planned interim analysis was conducted by the study statistician without knowledge of the treatment group labels.

On February 5, 2019, an interim analysis was conducted on 122 evaluable patients with primary endpoints, as detailed in the previous paragraph. Comparison of the two groups in the overall cohort indicated that the futility boundary was crossed. However, the chair of the Data Safety Monitoring Board, who reviewed the interim analysis results, recommended that the study continue accruing patients until all members of this committee could review the updated data at the annual meeting. During the Data Safety Monitoring Board meeting on June 20, 2019, the committee reviewed the updated results and recommended that the study be terminated due to futility. The study thus stopped enrolling patients at that point, with 154 evaluable patients. All data reported herein are based on the patients accrued up to that point.

The primary analysis was conducted using the intention-to-treat principle. Evaluable patients were randomized and had the primary endpoint available. Ideally, randomization would have occurred intraoperatively after confirming that the patient's final surgical procedure met the eligibility criteria of either anatomical lung resection or esophagectomy. However, intraoperative randomization was not feasible, given the need to ensure the same randomization time point and accommodate logistic considerations at both study sites. The decision process to withdraw randomized patients intraoperatively because of violation of eligibility criteria was prespecified in the protocol and followed objective protocol-based criteria before initiation of treatment and without knowledge of the assigned group. Exclusion of these patients from the analysis was deemed appropriate and consistent with statistical principles of clinical trials.[13,14] Other postrandomization exclusions included

cancelled surgery and patient withdrawal before surgery, both of which would not provide study endpoints.

Continuous data were summarized as median (25th to 75th percentile) and categorical data as frequency (percentage). The proportions of patients with postoperative atrial fibrillation were summarized and compared between the two groups using the Mantel–Haenszel test of homogeneity of odds ratio across the stratification factor of procedure type (lung resection or esophagectomy). Length of hospital stay was compared between groups using zero-truncated Poisson regression models. Incidences of cardiovascular and pulmonary adverse events and 30- and 90-day mortality were compared between the groups using the chi-square test. With an overall study-wise type I error (α) set to 0.05 (two-sided), the α for the final analysis of the primary endpoint was 0.049, and thus, 95.1% CI values were used in reporting the odds ratios from the primary outcome analysis. For all other analyses, no adjustments were made, and an α level of 0.05 was used, along with corresponding 95% CI when reporting contrasts. All analyses were two-sided and conducted using Stata 15.1 (StataCorp, USA).

Results

Patient Characteristics

Between September 16, 2016, and July 18, 2018, 308 patients were enrolled, and 188 were randomized (95 in the *N*-acetylcysteine group, 93 in the placebo group; fig. 1). In the *N*-acetylcysteine group, 17 patients were excluded; in the placebo group, 17 were excluded (reasons summarized in fig. 1). In total, the population for analysis included 154 evaluable patients (78 in the *N*-acetylcysteine group, 76 in the placebo group). The distribution of patient clinical and surgical characteristics is summarized in table 1. All patients in the analysis set are from Memorial Sloan Kettering Cancer Center. The Washington University Medical Center site randomized one patient, who was later found to be ineligible intraoperatively and was removed from the study before any treatment. All 154 evaluable patients included in the analysis had complete primary and secondary endpoints, except for inflammatory and oxidative stress markers on postoperative day 2 (missing in 16). Demographic and clinical data were complete for all evaluable patients, except for predicted forced expiratory volume in 1 s (FEV_1; missing in 39) and predicted diffusing capacity for carbon monoxide (%; missing in 42; table 1). None of these baseline factors was necessary for stratification or hypothesis testing.

Primary Outcome

Postoperative atrial fibrillation occurred in 28 of the 154 patients (18%), at a median of 2 days after surgery, with a median (25th to 75th percentile) duration of 12 (2 to 49) h. One patient had mixed atrial fibrillation and atrial flutter. The incidence of postoperative atrial fibrillation was not statistically significantly different between the two groups after stratification by procedure type (19% [15 of 78] in the *N*-acetylcysteine group *vs.* 17% [13 of 76] in the placebo group; odds ratio, 1.24; 95.1% CI, 0.53 to 2.88; $P = 0.615$; table 2). The first interim analysis was performed as planned after 122 patients (50% of the maximum sample size) had completed their 30-day follow-up in February 2018. The Data and Safety Monitoring Board met annually, and at their recommendation, the trial was stopped for futility after the interim analysis.

The median (25th to 75th percentile) day of onset of postoperative atrial fibrillation was not statistically significantly different between the *N*-acetylcysteine group (2 [1 to 3] days) and the placebo group (2 [2 to 4] days; $P = 0.106$). One patient developed postoperative atrial fibrillation after discharge on postoperative day 4. In 14 of the 28 patients with postoperative atrial fibrillation (50%; 8 in the *N*-acetylcysteine group and 6 in the placebo group), postoperative atrial fibrillation was symptomatic. None of the patients with postoperative atrial fibrillation required emergency electrical cardioversion. The rate of atrial fibrillation was not significantly different between those who received β-blockers and those who did not (22% *vs.* 16%; $P = 0.504$) or between those who received calcium blockers and those who did not (20% *vs.* 18%; $P = 0.804$).

Secondary Outcomes

Of the 28 patients with postoperative atrial fibrillation, 4 (14%) received oral anticoagulants after surgery and remained on oral anticoagulant therapy at the time of discharge. Of these, 3 remained in atrial fibrillation, and 1 had a history of paroxysmal atrial fibrillation and was discharged in sinus rhythm. At 1 yr of follow-up, 7 of the 28 patients with postoperative atrial fibrillation (25%) had recurrent episodes of atrial fibrillation, and 1 patient had persistent atrial fibrillation. None of these patients developed a stroke, as determined from regular phone follow-ups and review of the medical record during the first year after surgery. Of the 28 patients with postoperative atrial fibrillation, 16 (57%) were compliant with ambulatory monitoring guidelines. Among the 7 patients with recurrent atrial fibrillation, diagnosis was made by ambulatory monitoring in 3 and by phone follow-up and electronic medical record surveillance in 4. Within 1 yr of surgery, no patient without postoperative atrial fibrillation reported being treated for symptomatic atrial fibrillation episodes. Length of hospital stay and mortality were similar between the groups, as were other secondary outcomes (table 2).

Treatment-related Adverse Events

Adverse outcomes were infrequent and were not attributed to the experimental therapy. One patient developed signs and symptoms of a severe allergic reaction near the conclusion of study medication infusion, which the surgical

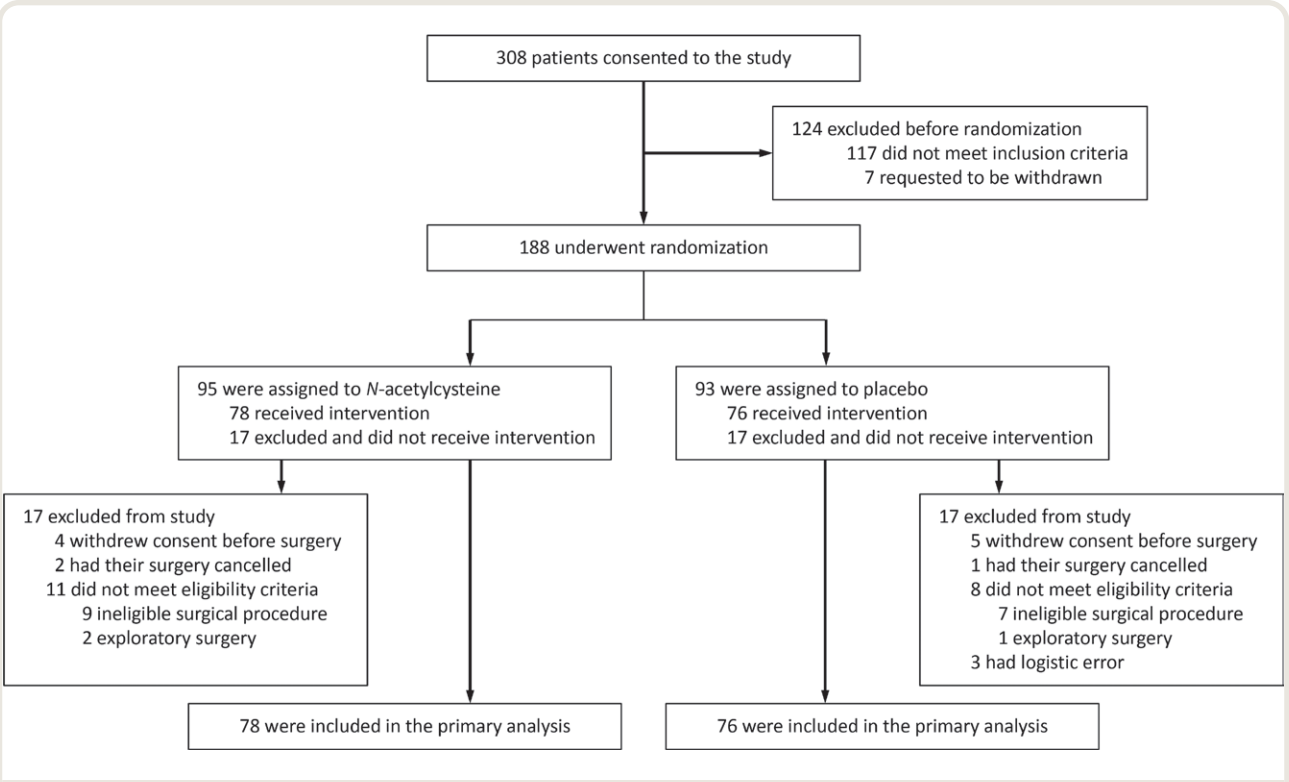

Fig. 1. Consolidated Standards of Reporting Trials diagram of the study population.

team attributed to oxycodone ingestion. The infusion of amiodarone was associated with hypotension and was transiently stopped or terminated in 31 of the 154 patients (20%; 16 in the *N*-acetylcysteine group and 15 in the placebo group). The amiodarone infusion was also transiently stopped because of bradycardia (heart rate less than 50 beats/min) in 3 of the 154 patients (2%; all in the placebo group).

Inflammatory and Oxidative Stress Markers

The levels of C-reactive protein, tumor necrosis factor α, interleukin-6, and interleukin-8 were similar between the groups immediately after surgery and on postoperative day 2 (table 3). Moreover, urinary isoprostane and isofuran levels were not statistically different immediately after surgery or on postoperative day 2 (table 3).

Discussion

To our knowledge, this is the first trial to investigate *N*-acetylcysteine plus amiodarone to prevent postoperative atrial fibrillation in patients undergoing anatomical lung or esophageal resection determined to be at high risk of postoperative atrial fibrillation by use of novel clinical and biomarker criteria. With amiodarone prophylaxis, the overall incidence of postoperative atrial fibrillation was 18% in our study and near the anticipated rate of 16% used for our sample size calculation for the placebo group. The addition of *N*-acetylcysteine to amiodarone did not reduce the incidence of postoperative atrial fibrillation; we therefore terminated the study early for futility after the interim analysis. The compelling rationale for testing *N*-acetylcysteine in patients undergoing noncardiac thoracic surgery is that *N*-acetylcysteine had been demonstrated to robustly reduce postoperative atrial fibrillation related to cardiac surgery when used alone or in addition to other drugs.[8,9] Because cardiac and thoracic surgery share some similar intraoperative surgical stressors that may contribute to postoperative atrial fibrillation, we hypothesized that the addition of the antioxidant *N*-acetylcysteine to the multichannel antiarrhythmic drug amiodarone would provide a synergistic and more effective prevention regimen against postoperative atrial fibrillation than amiodarone alone. We acknowledge that *N*-acetylcysteine administration before surgery could have mitigated inflammatory and oxidative stressors and affected our results; however, we chose to wait to include patients until establishing that their cancer operation could be performed and that they met the study eligibility criteria. Earlier meta-analyses reporting the effects of *N*-acetylcysteine on cardiac surgery–related postoperative atrial fibrillation showed that *N*-acetylcysteine reduced the incidence of atrial fibrillation after heart surgery and all-cause mortality, compared with controls.[15] More recently,

Table 1. Patient Characteristics by Treatment Group

Characteristic	*N*-Acetylcysteine (n = 78; 51%)	Placebo (n = 76; 49%)	Absolute Standardized Mean Difference
Age, yr	71 (67–76)	70 (67–76)	0.061
Male sex	39 (50)	43 (57)	0.131
Body mass index	27.7 (23.8–32.5)	27.3 (24.2–30.1)	0.015
ASA physical status			0.283
II	2 (2.6)	7 (9.2)	
III	76 (97)	69 (91)	
Coronary artery disease	15 (19)	19 (25)	0.138
Hypertension	60 (77)	53 (70)	0.162
Chronic obstructive pulmonary disease	18 (23)	17 (22)	0.017
Diabetes	14 (18)	16 (21)	0.078
Smoking history	64 (82)	62 (82)	0.012
History of atrial fibrillation	5 (6.4)	5 (6.6)	0.007
Preoperative chemotherapy	22 (28)	25 (33)	0.101
Preoperative radiotherapy	12 (15)	16 (21)	0.146
Medications			
β-Blocker	28 (36)	22 (29)	0.148
Angiotensin-converting enzyme/angiotensin II receptor blocker	18 (23)	20 (26)	0.075
Calcium channel blocker	20 (26)	15 (20)	0.140
Statin	41 (53)	44 (58)	0.107
Brain natriuretic peptide, pg/ml	55 (36–88)	52 (33–92)	0.060
FEV_1 predicted (n = 115), %	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.027
Missing	17	22	
Lung diffusion capacity for carbon monoxide predicted (n = 112), %	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.056
Missing	19	23	
CHA_2D_2S-VASc score			0.109
< 2	9 (12)	10 (13)	
2 to 3	48 (62)	49 (64)	
≥ 4	21 (27)	17 (22)	
Procedure			0.106
Lung resection	62 (79)	57 (75)	
Lobectomy	50	50	
Pneumonectomy	0	1	
Segmentectomy	12	6	
Esophagectomy	16 (21)	19 (25)	
Minimally invasive surgery	68 (87)	60 (79)	0.219
Lung resection (n = 119)	62	57	
Open	5 (8)	9 (16)	
Video-assisted thoracic surgery	28 (45)	18 (31)	
Robotic-assisted thoracic surgery	29 (47)	30 (53)	
Esophagectomy (n = 35)	16	19	
Open	5 (31)	7 (37)	
Minimally invasive	11 (69)	12 (63)	

The data are presented as no. (%) or median (25th to 75th percentile). All patients in the analysis set are from Memorial Sloan Kettering Cancer Center. The Washington University Medical Center site randomized one patient, who was later found to be ineligible intraoperatively and was removed from the study before any treatment.

ASA, American Society of Anesthesiologists; CHA_2D_2S-VASc, congestive heart failure, hypertension, age 75 yr or more, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 yr, sex category (female); FEV_1, forced expired volume in 1 s.

a meta-analysis of randomized controlled trials, published shortly after the completion of this randomized controlled study, showed that the addition of *N*-acetylcysteine during cardiac surgery did not meaningfully reduce clinically important outcomes such as arrhythmia, length of hospital stay, or mortality.[16] Larger studies have found conflicting results regarding whether perioperative supplementation with oral n-3 polyunsaturated fatty acids and/or vitamin C or E in patients undergoing cardiac surgery is associated with a meaningful reduction in the incidence of postoperative atrial fibrillation.[17,18]

Among the patients with postoperative atrial fibrillation in our study, 25% had recurrence of atrial fibrillation within 1 yr of surgery. Importantly, no patients with postoperative atrial fibrillation developed a stroke. However, our findings likely underreported the true rate of subsequent atrial fibrillation, as more than 40% of our patients were not compliant with the ambulatory monitoring protocol. In a similar population to ours, Higuchi *et al.*[19] used ambulatory event recorders and demonstrated a rate of atrial fibrillation recurrence of 30% in patients who developed postoperative atrial fibrillation within 1 yr of cancer surgery (65% of these patients

Table 2. Outcomes by Treatment Group

Variable	*N*-Acetylcysteine (n = 78; 51%)	Placebo (n = 76; 49%)	Odds Ratio (95% CI)*	*P*†
Primary endpoint: postoperative atrial fibrillation within 7 days				
All patients	15/78 (19)	13/76 (17)	1.24 (0.53–2.88)‡	0.615
Lung resection (n = 119)	8/62 (13)	8/57 (14)	0.91 (0.272–3.03)	
Esophagectomy (n = 35)	7/16 (44)	5/19 (26)	2.18 (0.42–11.6)	
Secondary endpoints				
Symptomatic postoperative atrial fibrillation	8 (10)	6 (7.9)	1.33 (0.44–4.0)	
Recurrent atrial fibrillation within 1 yr	3/15 (20)	4/13 (31)	—	
Length of hospital stay, days				
All patients	5 (3–8)	6 (4–9)	0.97 (0.78–1.21)	
Lung resection	4 (3–6)	5 (2–7)	—	
Esophagectomy	8 (7–15)	9 (7–10)	—	
Pulmonary complications§	5 (6.4)	6 (7.9)	0.80 (0.233–2.74)	
Reoperation for bleeding	0 (0)	2 (2.6)	—	
Transient ischemic attack	1 (1.3)	0 (0)	—	
Venous thromboembolism	1 (1.3)	3 (3.9)	—	
Overall mortality				
30-day	0 (0)	0 (0)	—	
90-day	1 (1.3)	1 (1.3)	—	

Summary values are presented as no. (%) or median (25th to 75th percentile).

*Estimates for *N*-acetylcysteine *versus* placebo contrasts were extracted from logistic regression models for dichotomous outcomes (odds ratios, for outcomes with at least 10 events) and linear regression models for log-transformed length of stay outcome (coefficient, percentage increase in length of stay). As an adjustment for the interim analysis, 95.1% CI values are presented for the primary endpoint; all others are 95% CI. †*P* value is presented for the primary outcome from the Mantel–Haenszel test of homogeneity of odds ratio across the stratification factor of procedure type. A descriptive summary of exploratory secondary outcomes is shown. Given the potential for type I error due to multiple comparisons and the low event rate, no formal hypothesis testing was conducted for secondary outcomes. ‡Mantel–Haenszel estimate of the odds ratio stratified by procedure type. §Atelectasis, pneumonia, pneumonitis, and respiratory failure.

Table 3. Inflammatory and Oxidative Stress Markers by Treatment Groups

Marker	*N*-Acetylcysteine (n = 78; 51%)	Placebo (n = 76; 49%)	Coefficient (95% CI)*
C-reactive protein, pg/ml			
Immediately after surgery	0.3 (0.1 to 0.6)	0.3 (0.1 to 0.7)	
Postoperative day 2 (n = 139)	14.7 (8.8 to 21.6)	12.3 (9.0 to 18.0)	1.2 (–1.3 to 3.7)
Interleukin-6, pg/ml			
Immediately after surgery	98.0 (57.0 to 160.0)	78.0 (43.5 to 166.0)	
Postoperative day 2 (n = 139)	73.5 (45.0 to 142.1)	83.0 (36.0 to 135.0)	5.9 (–29.7 to 41.4)
Interleukin-8, pg/ml			
Immediately after surgery	21.9 (14.5 to 32.8)	19.8 (14.0 to 36.0)	
Postoperative day 2 (n = 139)	25.8 (16.0 to 42.4)	28.5 (19.6 to 39.8)	–3.5 (–10.6 to 3.6)
Tumor necrosis factor α, pg/ml			
Immediately after surgery	7.0 (5.3 to 8.0)	6.7 (5.0 to 8.0)	
Postoperative day 2 (n = 139)	9.0 (7.0 to 12.0)	9.0 (7.0 to 10.0)	1.4 (–0.7 to 3.4)
F_2-isoprostane prostaglandin $F_{2\alpha}$, ng/mg creatinine†			
Immediately after surgery	1.4 (0.8 to 2.2)	1.4 (1.0 to 1.9)	
Postoperative day 2 (n = 138)	0.9 (0.7 to 1.4)	0.9 (0.6 to 1.3)	0.0 (–0.2 to 0.2)
Isofuran, ng/mg creatinine†			
Immediately after surgery (n = 153)	1.9 (1.4 to 3.0)	2.0 (1.5 to 2.9)	
Postoperative day 2 (n = 138)	1.6 (1.2 to 2.1)	1.6 (1.1 to 2.2)	0.0 (–0.3 to 0.3)

The values are presented as medians (25th to 75th percentile).

*Coefficients and corresponding 95% CI values are extracted from linear regression models with placebo as the reference group and adjustment for immediately after surgery marker values. †According to standard laboratory methods, these values have been adjusted for urine creatinine concentration and reported as ng/mg creatinine before statistical analyses.

had undergone thoracic surgery). In a retrospective study of a defined population of patients who underwent noncardiac surgery, development of subsequent atrial fibrillation was more common among patients who had postoperative atrial fibrillation than among patients who did not have postoperative atrial fibrillation.[4] Several observational studies using large databases have shown a clear link between postoperative atrial fibrillation after noncardiac surgery and subsequent

development of stroke and thromboembolic events within 1 to 5 yr after the index surgery.[2,20,21] Two of these studies also found an association between postoperative atrial fibrillation and higher risk of death and myocardial infarction. Using the Danish nationwide registry, Butt *et al.*[3] matched patients who developed postoperative atrial fibrillation with patients who had nonvalvular atrial fibrillation not related to surgery and found that the long-term risk of thromboembolism was similar between these two populations. The implications of our results and those of the above studies on further management of postoperative atrial fibrillation, such as the need for anticoagulation, require investigation in future randomized trials.

Laboratory and human tissue studies have shown an association between higher levels of inflammation and monoamine oxidase and NADPH oxidase activity and the development of postoperative atrial fibrillation after cardiac surgery.[22,23] In a large study of patients who underwent cardiac surgery, urinary isoprostane and isofuran levels were associated with postoperative atrial fibrillation in the perioperative period, whereas plasma concentrations were not found to be associated with postoperative atrial fibrillation.[24] That the use of *N*-acetylcysteine was not associated with lower markers of inflammation and oxidative stress may help to explain the lack of a reduction in postoperative atrial fibrillation in this study.

Limitations

Our study had several limitations. First, we did not include a third group of patients who received only placebo—that is, no amiodarone—as our standard of care was to include postoperative atrial fibrillation prevention for at-risk patients.[1,5–7] Second, the duration of *N*-acetylcysteine infusion used in our trial could have been longer; however, we sought to administer the drug during the peak time that patients are most likely to develop postoperative atrial fibrillation, which is up to 48 h postoperatively. Third, ambulatory monitors were provided only to patients who developed postoperative atrial fibrillation; therefore, the rate of atrial fibrillation among patients without postoperative atrial fibrillation is not known. We did, however, contact all patients by phone at 7, 14, and 30 days and monthly for the first year after the surgery and reviewed the electronic medical records of all study patients for any evidence of hospitalization or treatment for new-onset atrial fibrillation, and no subsequent atrial fibrillation in patients without postoperative atrial fibrillation was reported. Last, we were not able to accrue enough patients from our second site (Washington University Medical Center), mostly because of administrative delays.

Conclusions

N-Acetylcysteine was not associated with a lower incidence of atrial fibrillation within 7 days after anatomical lung resection or esophagectomy. Recurrent episodes of atrial fibrillation confirmed by either mobile electrocardiography monitoring or symptomatically within 1 yr of noncardiac thoracic surgery were common among patients who developed postoperative atrial fibrillation.

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Competing Interests

Dr. Park has served as a proctor for Intuitive Surgical (Sunnyvale, California) and consultant for COTA (New York, New York). Dr. Isbell is a consultant for Genentech (San Francisco, California), has an equity interest in LumaCyte LLC (Charlottesville, Virginia), and has a financial relationship with Guardant Health (Redwood City, California). Dr. Molena is a consultant for Johnson & Johnson (New Brunswick, New Jersey), Urogen (New York, New York), Intuitive Surgical, and Boston Scientific (Marlborough, Massachusetts). Dr. Fischer is a consultant for Edward Lifesciences (Irvine, California). Dr. Rusch reports grant support (institutional) from Genelux (San Diego, California) and Genentech, travel support from Intuitive Surgical, and travel support and payments from the National Institutes of Health Coordinating Center for Clinical Trials. Dr. Jones serves as a consultant for AstraZeneca (Cambridge, United Kingdom) and is on a clinical trial steering committee for Merck (Kenilworth, New Jersey). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: amard@mskcc.org. Raw data available at: amard@mskcc.org.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Ethereal Breath of the Gods: Always Circulating Aither

Humans breathe air. In contrast, the gods of ancient Greek mythology inspired *aither*, *aether*, or *ether*. Rather than the transparent gas inhaled by mortals, the deities breathed the blue gas found on mountain tops and in the heavens—all that lofty atmosphere above ground but beneath the solid dome of the Sky (*Ouranos*, Latinized as Uranus). Unlike earthly elements, which moved linearly, *Aither* circulated around heavenly bodies in circular orbits within ethereal spheres. In his *Cratylus*, Plato suggests that *aither* derives from *aei thein* ("always running"). Aither also serves as a backdrop for parts of Giulio Romano's c.1533 *trompe l'oeil* frescoed ceiling in the *Chamber of the Giants* (a portion *above*), Palazzo del Te, Mantua, Italy. Volatile and intoxicating, our earthly anodyne, ether, may have seemed a gift from the gods. Alas, the only "blues" ether elicited in 19th-century mortals arose from recreational overindulgence. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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