

## ANESTHESIOLOGY

# Intravenous Lidocaine Does Not Improve Neurologic Outcomes after Cardiac Surgery

## A Randomized Controlled Trial

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ANESTHESIOLOGY 2019; 130:958–70

Neurocognitive impairment occurs frequently in the increasingly elderly patient population undergoing cardiac surgery. At the time of hospital discharge, up to 50% of cardiac surgical patients may experience postoperative cognitive dysfunction.<sup>1</sup> Despite a general improvement in the initial months after surgery, cognitive dysfunction may persist up to 5 yr postoperatively,<sup>1</sup> resulting in significant loss of functional independence and reduced quality of life.<sup>2</sup>

The mechanisms underlying postoperative cognitive dysfunction after cardiac surgery are not yet fully understood, and despite the investigation of several possibilities,<sup>3–9</sup> a potential preventative or therapeutic agent remains elusive. Previous clinical research has reported a beneficial effect of the drug lidocaine on postoperative cognitive dysfunction after both cardiac and noncardiac surgery.<sup>10–12</sup> Lidocaine is a class 1B antiarrhythmic and local anesthetic that crosses the blood–brain barrier. Potential mechanisms for a neuroprotective effect of lidocaine have been postulated to include reduced cerebral metabolism,<sup>13</sup> deceleration of ischemic ion fluxes,<sup>14,15</sup> preservation of cerebral blood flow,<sup>16</sup> and modulation of

## ABSTRACT

**Background:** Cognitive decline after cardiac surgery occurs frequently and persists in a significant proportion of patients. Preclinical studies and human trials suggest that intravenous lidocaine may confer protection in the setting of neurologic injury. It was hypothesized that lidocaine administration would reduce cognitive decline after cardiac surgery compared to placebo.

**Methods:** After institutional review board approval, 478 patients undergoing cardiac surgery were enrolled into this multicenter, prospective, randomized, double-blinded, placebo-controlled, parallel group trial. Subjects were randomized to lidocaine 1 mg/kg bolus after the induction of anesthesia followed by a continuous infusion (48  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for the first hour, 24  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for the second hour, and 10  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for the next 46 h) or saline with identical volume and rate changes to preserve blinding. Cognitive function was assessed preoperatively and at 6 weeks and 1 yr postoperatively using a standard neurocognitive test battery. The primary outcome was change in cognitive function between baseline and 6 weeks postoperatively, adjusting for age, years of education, baseline cognition, race, and procedure type.

**Results:** Among the 420 allocated subjects who returned for 6-week follow-up (lidocaine: N = 211; placebo: N = 209), there was no difference in the continuous cognitive score change (adjusted mean difference [95% CI], 0.02 [–0.05, 0.08];  $P = 0.626$ ). Cognitive deficit (greater than 1 SD decline in at least one cognitive domain) at 6 weeks occurred in 41% (87 of 211) in the lidocaine group versus 40% (83 of 209) in the placebo group (adjusted odds ratio [95% CI], 0.94 [0.63, 1.41];  $P = 0.766$ ). There were no differences in any quality of life outcomes between treatment groups. At the 1-yr follow-up, there continued to be no difference in cognitive score change, cognitive deficit, or quality of life.

**Conclusions:** Intravenous lidocaine administered during and after cardiac surgery did not reduce postoperative cognitive decline at 6 weeks.

(ANESTHESIOLOGY 2019; 130:958–70)

## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Preclinical and clinical studies suggest that lidocaine might be neuroprotective, which could benefit surgical patients at risk of neurologic compromise

### What This Article Tells Us That Is New

- This multicenter trial of intravenous lidocaine administered during and after cardiac surgery did not show an effect on cognition at 6 weeks postoperatively

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site ([www.anesthesiology.org](http://www.anesthesiology.org)). This article has an audio podcast. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented at the Society for Cardiovascular Anesthesiologists Annual Meeting, 2015.

Submitted for publication August 20, 2018. Accepted for publication February 1, 2019. From the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina (R.Y.K., M.C., T.B., N.T., M.B., M.V.P., M.S.-S., J.P.M.); and the Department of Anesthesiology, University of Kentucky School of Medicine, Lexington, Kentucky (M.F.N.).

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inflammatory mediators.<sup>17–21</sup> Based on these potential mechanisms, lidocaine would appear to be an ideal drug for preventing the biphasic pattern of neurologic injury by both (1) maintaining cerebral blood flow and preventing adverse ion flux during ischemia and (2) ameliorating the secondary inflammatory changes associated with reperfusion. Data published by our group further suggested that intravenous lidocaine administered intraoperatively and for 48 h might have a protective effect against postoperative cognitive dysfunction in nondiabetic cardiac surgical patients.<sup>22</sup> Notably, in this previous study, diabetic subjects receiving lidocaine were more likely to suffer cognitive decline, possibly because of higher lidocaine doses and altered lidocaine metabolism.<sup>22</sup>

Based on these preclinical and clinical data, we hypothesized that the administration of intravenous lidocaine intraoperatively and postoperatively for a total of 48 h would reduce the incidence of postoperative cognitive dysfunction in nondiabetic patients at 6 weeks after cardiac surgery with cardiopulmonary bypass compared to placebo (*i.e.*, superiority). We secondarily assessed neurocognitive outcomes at 1 yr postoperatively, along with quality of life measures at both postoperative time points.

## Materials and Methods

### Study Population

Subsequent to approval by respective institutional review boards (Duke University Medical Center, Durham, North Carolina; and University of Kentucky School of Medicine, Lexington, Kentucky) and informed consent, 478 adults of at least 50 yr of age and scheduled to undergo coronary artery bypass grafting (CABG), valve surgery, or CABG plus valve surgery with cardiopulmonary bypass (CPB) were enrolled into this multicenter, prospective, randomized, double-blinded, placebo-controlled, parallel group clinical trial between July 2009 and June 2016. Subjects were enrolled at Duke University Health System (Durham, North Carolina; N = 448), Cornell Weil Medical Center (New York, New York; N = 2), and Sentara Norfolk General Hospital (Norfolk, Virginia; N = 28). Prospective patients were approached by study staff. Patients were excluded if the procedure included planned circulatory arrest or if patients had a history of diabetes mellitus (documented history, elevated fasting blood glucose, or hemoglobin A1c of 6.5% or higher), symptomatic cerebrovascular disease (*e.g.*, prior stroke) with residual deficit, higher alcohol consumption (more than 2 drinks per day), drug abuse (any illicit drug use in the past 3 months), psychiatric illness (any clinical diagnosis requiring therapy), renal failure (serum creatinine more than 2 mg/dl), hepatic insufficiency (liver function tests more than 1.5 times the upper limit of normal), severe pulmonary insufficiency (requiring home oxygen therapy), left ventricular ejection fraction of less than 20%, preoperative intraaortic balloon pump requirement, liver/heart/lung transplant, current pregnancy, and those who were unable to read and thus

complete the cognitive testing or who scored less than 24 on the baseline Mini Mental State examination or at least 27 on the baseline Center for Epidemiologic Studies–Depression Scale. Informed consent was obtained by study staff.

Subjects were randomized to two treatment groups: (1) the lidocaine group, with a bolus of 1 mg/kg of lidocaine administered after induction of anesthesia and followed immediately by a continuous infusion at  $48 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for the first h,  $24 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for the second hour, and  $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for the next 46 h or (2) the placebo group, with normal saline administered as a bolus and an infusion for 48 h with identical volume and rate changes as the treatment group such that blinding of both the patient and study/clinical team was preserved. This weight-based lidocaine infusion regimen is based on previous pharmacokinetics work by our group to determine the optimal infusion strategy to maintain therapeutic lidocaine levels while avoiding potentially toxic levels (more than  $5 \mu\text{g}/\text{ml}$ ) in patients undergoing CPB.<sup>23</sup> A group assignment schedule was prepared for each site using Nquery software version 7 (SAS, USA) by the study statistician and stored in consecutively numbered sealed envelopes until allocation by study staff.

### Patient Management

Anesthesia was induced with midazolam, fentanyl, and propofol, and isoflurane was used for maintenance. All patients underwent nonpulsatile, hypothermic (30 to 32°C) CPB with a membrane oxygenator (Prim-O<sub>2</sub>X, Sorin Group Inc., USA; Synthesis, Sorin Group Inc., USA; or Terumo FX15 or FX25, Terumo Inc., USA) and arterial line filter by a centrifugal pump (revolution pump head and S5 machine, Sorin Group Inc.) primed with crystalloid and using bio-active tubing (SMART-X, Sorin Group Inc.). Serial hematocrit levels were maintained at 0.21 or greater. Before initiating CPB, heparinization (300 to 400 units/kg) was performed to a target activated coagulation time of more than 480 s. Perfusion was maintained at flow rates of 2 to  $2.4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  throughout CPB to maintain a mean arterial pressure of 50 to 80 mmHg. Arterial blood gases were measured every 15 to 30 min to maintain the  $\text{PACO}_2$  at 35 to 40 mmHg unadjusted for temperature and the  $\text{PAO}_2$  at 150 to 250 mmHg. Cell salvage (BRAT, Cobe CV Inc., USA; or Elite, Haemonetics Inc., USA) was utilized for the majority of cases.

Plasma lidocaine levels were sampled at baseline (before bolus), at end of CPB, and at 24 and 48 h after bolus; analysis was performed by the Duke University Clinical Laboratories. The results were made available by fax only to a study team member to monitor for lidocaine toxicity; plasma levels more than  $5 \mu\text{g}/\text{ml}$  required discontinuation of the study drug. Blinding of the patient, medical care teams, and neurocognitive testers was preserved at all times. If the study drug was discontinued because of high lidocaine levels, the patient and the medical care team were no longer blinded (n = 1).

## Neurocognitive Testing

Neurocognitive testing was performed at baseline (preoperatively), 6 weeks, and 1 yr after surgery by experienced psychometricians blinded to treatment group. In accordance with the consensus statement on assessment of neurobehavioral outcomes after cardiac surgery,<sup>24</sup> the following tests were included in the assessment battery: (1) Hopkins Verbal Learning Test,<sup>25</sup> (2) Randt Short Story Memory Test,<sup>26</sup> (3) Modified Visual Reproduction Test from the Wechsler Memory Scale,<sup>27</sup> (4) Digit Span, Digit Symbol, and Vocabulary subtests from the Wechsler Adult Intelligence Scale–Revised,<sup>27</sup> and (5) Trail Making Test, Parts A and B.<sup>28</sup>

## Quality of Life and Neurologic Outcomes

To assess health-related quality of life outcomes, the following battery was administered at baseline, 6 weeks, and 1 yr postoperatively: (1) Duke Activity Status Index, a measure of functional status derived for use in cardiovascular populations; (2) Center for Epidemiologic Studies–Depression Scale; (3) the State Trait Anxiety Inventory; (4) the Hopkins Symptom Checklist (SCL-90); (5) the Short Form 36; (6) Symptom Limitations Scale; (7) Duke Older American Resources and Services Procedures–Instrumental Activities of Daily Living; (8) Cognitive Difficulties Scale; (9) Perceived Social Support Scale; and (10) Social Anxiety Scale. The change in neurologic outcomes was assessed using the National Institutes of Health Stroke Scale and the Western Perioperative Neurologic Scale and comparing baseline values to 6-week and 1-yr postoperative follow-up values.

## Statistical Analyses

To characterize cognitive function over time while minimizing potential redundancy in the cognitive measures, a factor analysis with oblique rotation (a linear transformation of the data, which allows for correlated factors) was performed on the 14 cognitive test scores from baseline. Scoring coefficients (weights) of each test on each factor were determined using the rotated factor solution from the factor analysis conducted on 452 study patients with completely observed cognitive test scores at the baseline time point. Factors of each patient at all time points were computed using the same scoring coefficients, so that the cognitive domain structure remained consistent and comparable over time. The number of factors was determined based on cumulative variance explained of at least 80%, examination of scree plot for elbow location, and previous experience with this cognitive battery. Factor analysis suggested a five-factor solution, which accounted for 80% of the variability in the original test scores and represents five cognitive domains: (1) structured verbal memory (*i.e.*, the ability to recall from a list); (2) unstructured verbal memory (*i.e.*, the ability to remember from a narrative); (3)

visual memory; (4) executive function; and (5) attention and concentration. Two outcome measures were calculated to represent postoperative cognitive function: (1) continuous outcome: the change in cognitive score calculated by subtracting the baseline cognitive index (the five-domain mean) from the follow-up cognitive index (a change score of 0 indicates no change from baseline, whereas a negative score indicates cognitive decline and a positive score indicates cognitive improvement); and (2) binary outcome (cognitive deficit): defined as a decline of more than 1 SD in at least one domain from before to after surgery.

Categorical and continuous demographic characteristics were compared between treatment groups with two-sided Pearson chi-square tests, Fisher exact tests, independent *t* tests, and Wilcoxon rank sum tests. Normality was assessed *via* Shapiro–Wilks tests, and if evidence of nonnormality was present nonparametric analysis was performed. The effect of lidocaine treatment on the cognitive change score was tested using an *a priori* defined multivariable linear regression modeling accounting for known risk factors of age, years of education, baseline cognition, and procedure type. The following potentially influential covariates were examined for balance between the treatment groups: sex, race, duration of surgery and bypass time, depression, and anxiety. If any clinically important group differences on covariates were identified, we added those factors to the multivariable model to reduce potential confounding of treatment effect estimates. Interactions between treatment group and each of the covariates were also examined. Similarly, the effect of lidocaine on cognitive deficit was tested using multivariable logistic regression accounting age, years of education, baseline cognition, and procedure type, as well as any factor found to be out of balance despite randomization. All analyses were performed with SAS version 9.4 (SAS, USA);  $P < 0.05$  was considered significant.

The primary outcome was change in cognitive function—as both continuous cognitive change score and the binary outcome of cognitive deficit—between baseline and 6 weeks postoperatively as assessed by multivariable linear regression adjusted for *a priori* defined covariates representing known risk factors for cognitive decline. Secondary outcomes included change in cognitive function at 1 yr postoperatively and 6-week and 1-yr changes in quality of life and neurologic outcomes compared between treatment groups. We also investigated adverse event rates and length-of-stay differences between the treatment groups.

For patients returning at follow-up time points but missing test scores required for determination of primary or secondary endpoints, we pursued multiple imputation based on all collected patient and surgical factors as well as observed cognitive, quality of life, and neurologic test scores (imputation performed in SRCWare V 0.2).<sup>29</sup> We created 10 imputation data sets and used standard methods to pool across imputed sets.<sup>30</sup> The primary analyses were conducted

according to the intention-to-treat principle. We conducted four types of sensitivity analyses to assess the impact of analysis strategies on our conclusions as follows: (1) on per-protocol cases to assess impact of protocol deviations (inadvertent bolus lidocaine given on induction of anesthesia [ $n = 8$ ], unblinding and administration of lidocaine for arrhythmia treatment [ $n = 5$ ], termination of study drug for elevated serum lidocaine level [ $n = 1$ ], physician request to terminate study drug [ $n = 2$ ], and error in study drug administration, *e.g.*, interruption in infusion during transfer from intensive care unit to step-down unit [ $n = 12$ ]); (2) on complete cases; (3) on the full set of eligible randomized patients to assess impact of imputation strategy and dropout; and (4) by assigning the worst cognitive performance scores to patients who had suffered an early postoperative stroke and thus lacked 6-week neurocognitive testing to assess impact of unobserved outcomes for patients with expected cognitive impairment. For sensitivity analysis 3, we created a new set of multiple imputation data sets including all randomized and treated patients who met inclusion criteria using the same methods and inputs as we did for the primary analysis.

In our previous work, the lidocaine treatment group showed a change in cognitive index of 0.16 compared to a placebo group change of 0.09, with a common SD of 0.25. Based on these data, we estimated that a sample size of 202 patients in each group would have 80% power to detect a difference in means at  $\alpha = 0.05$ , with a two-sided significance level. Assuming a loss to follow-up of 15%, we planned to enroll 476 patients to achieve an analysis sample of 404.

This trial was conducted in accordance with the original trial protocol as registered on [clinicaltrials.gov](http://clinicaltrials.gov) (NCT00938964). No changes to the outcome definitions were made during or after completion of the trial; however, the registration of the trial outcomes on [clinicaltrials.gov](http://clinicaltrials.gov) was revised on several occasions in response to changes in reporting requirements.

## Results

From July 6, 2009, to June 2, 2016, a total of 550 patients were consented to participate in the study, and 478 met all inclusion criteria and were randomized (fig. 1), with 237 allocated to placebo and 241 allocated to lidocaine treatment. Fifty-eight patients met exclusion criteria or were lost to follow-up after randomization, leaving 209 placebo patients and 211 lidocaine patients for evaluation at 6 weeks postoperatively. A further 43 patients were lost to follow-up between 6 weeks and 1 yr postoperatively, leaving 192 placebo and 185 lidocaine patients for evaluation at 1 yr postoperatively.

Demographic and clinical characteristics of the randomized subjects are listed in table 1. Despite randomization, the lidocaine group had a statistically higher proportion of Caucasian patients, a lower ejection fraction, and lower

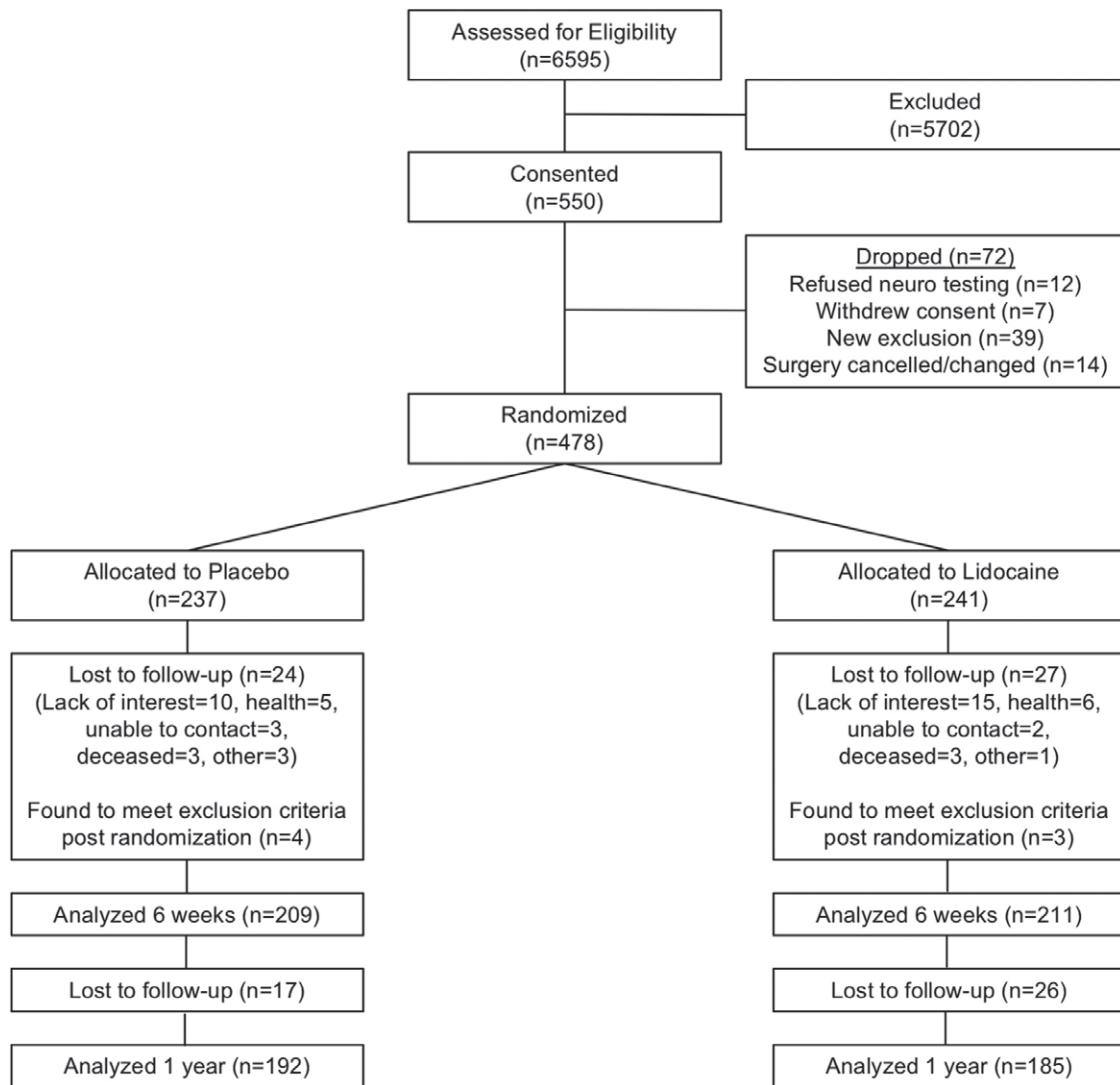
years of education compared to placebo patients; all other characteristics were similar between treatment groups. Supplemental Digital Content 1 (<http://links.lww.com/ALN/B904>) and Supplemental Digital Content 2 (<http://links.lww.com/ALN/B905>) describe the demographic characteristics of patients lost to follow-up at the 6-week and 1-yr time points, respectively.

## 6-week Change in Cognition (Primary Outcome)

Among the 420 subjects who returned for follow-up testing, the continuous cognitive change score was not significantly different between the treatment groups [mean  $\pm$  SD – lidocaine,  $0.074 \pm 0.32$  *vs.* placebo,  $0.072 \pm 0.37$ ;  $P = 0.957$ ]. Cognitive deficit at 6 weeks after surgery was present in 41% (87 of 211) of subjects randomized to lidocaine and in 40% (83 of 209) of subjects randomized to placebo ( $P = 0.700$ ). Multivariable analysis accounting for the covariable effects of age, years of education, baseline cognition, Caucasian race, and procedure type found similar results (adjusted mean difference [95% CI] between groups,  $0.02 [-0.05, 0.08]$ ;  $P = 0.626$ ; table 2). Similarly, logistic regression analysis of the binary postoperative cognitive dysfunction outcome indicated no treatment difference (adjusted odds ratio [95% CI],  $0.94 [0.63, 1.410]$ ;  $P = 0.766$ ; table 2). There was no evidence of any significant interaction effects between treatment and covariates on either cognitive index change or binary postoperative cognitive dysfunction outcomes. As expected, lidocaine levels were significantly higher in the lidocaine group and without achieving toxic levels (fig. 2) at all postbolus measurement points (mean [95% CI] serum lidocaine levels, end-bypass, placebo  $0.02 \mu\text{g/ml}$  [0 to 0.03] *vs.* lidocaine  $1.82 \mu\text{g/ml}$  [1.75 to 1.89]; 24h post-bypass, placebo  $0.03 \mu\text{g/ml}$  [0 to 0.06] *vs.* lidocaine  $2.18 \mu\text{g/ml}$  [2.08 to 2.28]; 48h post-bypass, placebo  $0.01 \mu\text{g/ml}$  [0 to 0.01] *vs.* lidocaine  $2.86 \mu\text{g/ml}$  [2.71 to 3.01]).

## 1-yr Change in Cognition

At 1 yr after surgery, 377 subjects underwent cognitive testing. The continuous cognitive change score was not significantly different between the treatment groups (mean  $\pm$  SD – lidocaine,  $0.09 \pm 0.34$  *vs.* placebo,  $0.07 \pm 0.34$ ;  $P = 0.471$ ). Although we observed a lower rate of cognitive deficit in lidocaine subjects compared to placebo subjects, the difference failed to reach statistical significance (48.1% *vs.* 56.8%;  $P = 0.092$ ). Multivariable linear regression adjusting for age, years of education, baseline cognition, Caucasian race, and procedure type revealed no difference in outcome between treatment groups (adjusted mean difference [95% CI] between groups,  $0.04 [-0.03, 0.10]$ ;  $P = 0.255$ ; table 3). Logistic regression analyses of the binary outcome also indicated a nonsignificant reduction in risk (adjusted odds ratio [95% CI],  $0.69 [0.45, 1.04]$ ;  $P = 0.077$ ). Again, there was no evidence of any significant



**Fig. 1.** CONSORT diagram showing flow of study participants.

interaction effects between treatment and covariates on cognitive index change or binary postoperative cognitive dysfunction outcomes. The trajectory of postoperative cognition over time did not differ between treatment groups (fig. 3). Domain-specific cognitive scores for 6 weeks and 1 yr are provided in Supplemental Digital Content 3 (<http://links.lww.com/ALN/B906>).

### Rate of Adverse Events

Adverse events were not significantly different between treatment groups; among the randomized patients, serious adverse events were recorded in 43.6% of lidocaine and 43.5% of placebo subjects ( $P = 0.981$ ). Nearly all of the adverse events occurred during the index surgical

hospitalization: in-hospital adverse events occurred in 41.9% of lidocaine patients and 41.8% of placebo patients compared to posthospital adverse events, which occurred in 4.6% each of lidocaine and placebo patients. Stroke occurred before discharge in two patients in the lidocaine group and six patients in the placebo group ( $P = 0.173$ ): six were embolic/ischemic, one was hemorrhagic, and one was a transient ischemic attack. The rate of atrial fibrillation was 31.1% in the lidocaine group compared to 31.7% in the placebo group ( $P = 0.902$ ). Among randomized patients, the length of hospital stay was 6 days (interquartile ratio: 5, 7) in the lidocaine group and 6 days (interquartile ratio: 5, 8) in the placebo group ( $P = 0.737$ ). In-hospital and 1-yr mortality rates were not different between the lidocaine and placebo groups (1.2% vs. 0.0%,  $P = 0.249$ ; and 2.5% vs.

**Table 1.** Cohort Summary and Randomization Group Comparison of Patients Returning at 6 weeks

|  | Lidocaine (n = 211) | Placebo (n = 209) |
|--|---------------------|-------------------|
| Age, yr                                    | 67 ± 9.1            | 67 ± 9.5          |
| Sex, n (% female)                          | 60 (28.4)           | 49 (23.4)         |
| Race, n (% Caucasian)                      | 200 (94.8)          | 186 (89.0)        |
| Weight, kg                                 | 83.8 ± 16.5         | 82.8 ± 17.4       |
| History of hypertension, n (%)             | 124 (59.0)          | 128 (61.2)        |
| Previous myocardial infarction, n (%)      | 31 (14.7)           | 38 (18.2)         |
| History of atrial fibrillation, n (%)      | 56 (26.5)           | 50 (23.9)         |
| History of neurologic incident             | 23 (10.9)           | 19 (9.1)          |
| Ejection fraction (Q1, Q3)                 | 55 (50, 55)         | 55 (55, 60)       |
| Ejection fraction < 30%, n (%)             | 2 (0.9)             | 5 (2.4)           |
| Years of education (Q1, Q3)                | 15 (12, 16)         | 16 (13, 17)       |
| Preoperative statin use, n (%)             | 121 (57.3)          | 131 (62.7)        |
| Preoperative platelet inhibitor use, n (%) | 149 (70.6)          | 150 (71.8)        |
| Preoperative cognitive index*              | 0.02 ± 0.7          | 0.01 ± 0.7        |
| Lidocaine level at baseline, µg/ml†        | 0.09 ± 0.3          | 0.06 ± 0.2        |
| Baseline CES-D*                            | 9.0 ± 6.7           | 8.4 ± 6.8         |
| Baseline STAI*                             | 36.7 ± 11.4         | 36.2 ± 10.7       |
| Surgical Procedure, n (%)                  |                     |                   |
| CABG                                       | 61 (28.9)           | 62 (29.7)         |
| CABG + valve                               | 21 (10.0)           | 23 (11.0)         |
| Valve                                      | 129 (61.1)          | 124 (59.3)        |
| Previous CABG/Valve Surgery, n (%)         | 24 (11.4)           | 24 (11.5)         |
| CPB time, min (Q1, Q3)                     | 157 (127, 198)      | 166 (124, 214)    |
| Cross-clamp time, min (Q1, Q3)             | 100 (74, 120)       | 101 (67, 121)     |
| Number of bypass vessels (Q1, Q3)‡         | 3 (2, 4)            | 3 (2, 4)          |

The data are reported as means ± SD or median (Q1, Q3) as appropriate.

\*Missing data imputed using SRCWARE and combined statistics presented here were generated using SAS proc MIANALYZE (SAS, USA). †Baseline values are nonzero numbers because the analytical measurement range of the lidocaine assay is 0.6 to 8.0 µg/ml; thus values below this linear range (including 0 values) may be reported as less than 0.6 µg/ml. ‡Among those that received grafts.

CABG, coronary artery bypass grafting; CES-D, Center for Epidemiologic Studies–Depression Scale; CPB, cardiopulmonary bypass; Q1, quartile 1; Q3, quartile 3; STAI, State Trait Anxiety Inventory.

**Table 2.** Multivariable Linear and Logistic Regression Predicting Cognitive Change and Cognitive Deficit, Respectively, at 6 weeks Postoperatively

| Variable                     | Cognitive Change Index      |         | Cognitive Deficit   |         |
|------------------------------|-----------------------------|---------|---------------------|---------|
|                              | Parameter Estimate (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Age (per yr)                 | −0.01 (−0.02, −0.01)        | < 0.001 | 1.05 (1.02–1.08)    | 0.001   |
| Years of education (per yr)  | 0.01 (−0.003, 0.02)         | 0.127   | 0.88 (0.82–0.96)    | 0.002   |
| Preoperative cognitive index | −0.17 (−0.22, −0.11)        | < 0.001 | 1.45 (0.98–2.13)    | 0.063   |
| Caucasian race               | −0.05 (−0.17, 0.07)         | 0.419   | 1.70 (0.73–3.99)    | 0.222   |
| Valve vs. CABG               | −0.07 (−0.14, 0.001)        | 0.054   | 1.39 (0.87–2.20)    | 0.168   |
| CABG + valve vs. CABG        | −0.09 (−0.20, 0.02)         | 0.122   | 1.74 (0.84–3.58)    | 0.134   |
| Lidocaine treatment          | 0.02 (−0.05, 0.08)          | 0.626   | 0.94 (0.63, 1.41)   | 0.766   |

CABG, coronary artery bypass grafting.

3.0%, *P* = 0.755, respectively). All serious adverse events are outlined in Supplemental Digital Content 4 (<http://links.lww.com/ALN/B907>).

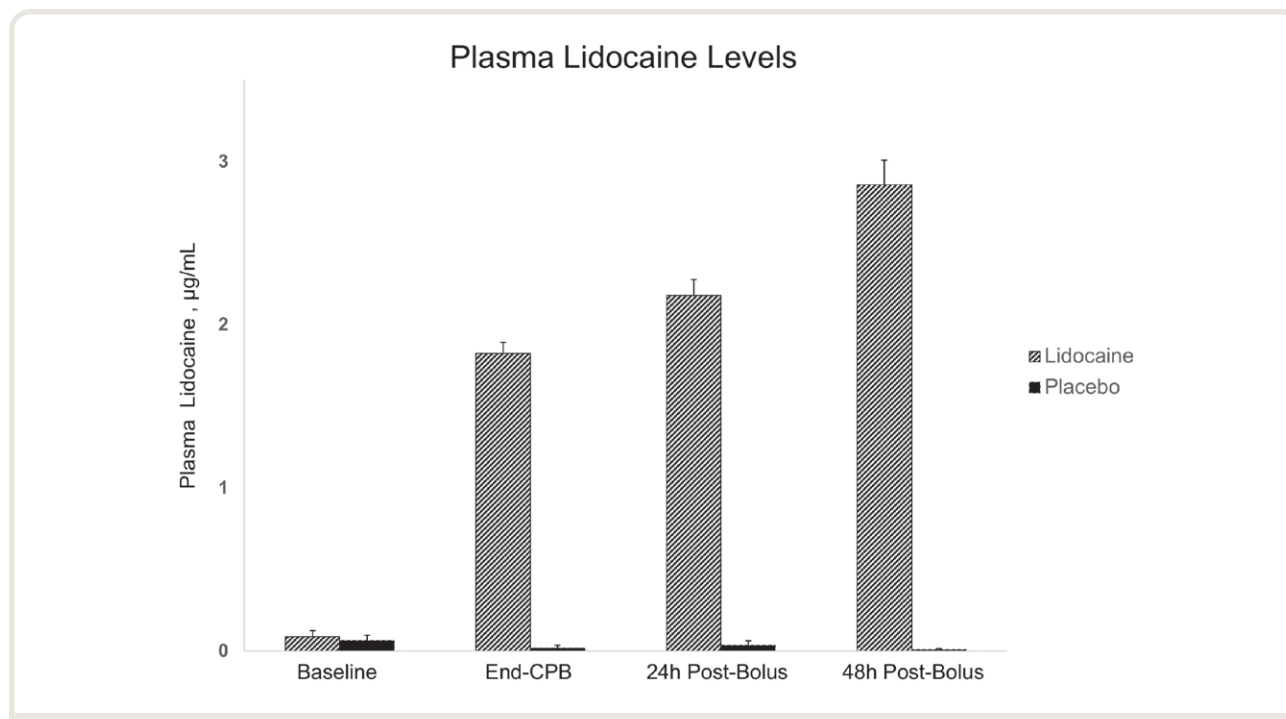
### Quality of Life and Neurologic Outcomes

Comparisons of the various quality of life and neurologic outcomes are summarized for the 6-week (table 4) and

1-yr (table 5) postoperative time points. There were no differences in any of the outcomes between patients who received lidocaine and patients who received placebo.

### Sensitivity Results

Sensitivity analyses were performed for the primary outcome of cognitive index score change at 6 weeks postoperatively



**Fig. 2.** Serum concentration of lidocaine (mean, 95% CI) at the four measurement time points. CPB, cardiopulmonary bypass.

**Table 3.** Multivariable Linear and Logistic Regression Predicting Cognitive Change and Cognitive Deficit, respectively, at 1 yr Postoperatively

| Variable                     | Cognitive Change Index      |         | Cognitive Deficit   |         |
|------------------------------|-----------------------------|---------|---------------------|---------|
|                              | Parameter Estimate (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Age (per yr)                 | -0.01 (-0.02, -0.01)        | < 0.001 | 1.03 (1.00, 1.06)   | 0.023   |
| Years of education (per yr)  | 0.02 (0.01, 0.03)           | < 0.001 | 0.95 (0.88, 1.02)   | 0.190   |
| Preoperative cognitive index | -0.20 (-0.26, -0.14)        | < 0.001 | 1.13 (0.76, 1.68)   | 0.553   |
| Caucasian race               | 0.02 (-0.11, 0.15)          | 0.725   | 0.70 (0.30, 1.63)   | 0.410   |
| Valve vs. CABG               | -0.07 (-0.14, 0.004)        | 0.065   | 0.93 (0.58, 1.49)   | 0.775   |
| CABG + valve vs. CABG        | -0.04 (-0.16, 0.08)         | 0.471   | 0.95 (0.44, 2.05)   | 0.893   |
| Lidocaine treatment          | 0.04 (-0.03, 0.10)          | 0.255   | 0.69 (0.45, 1.04)   | 0.077   |

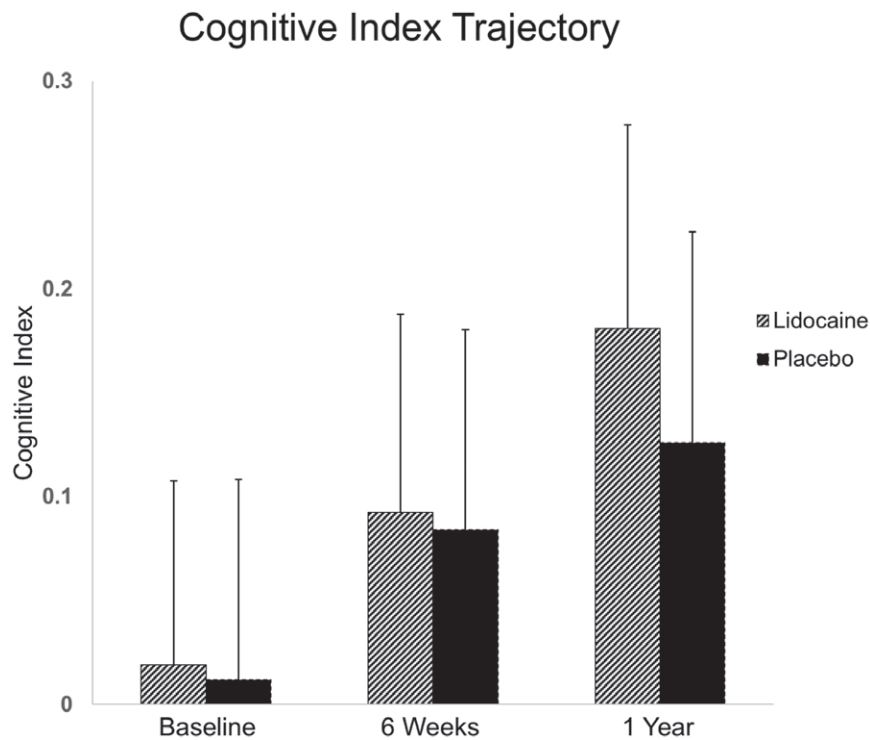
CABG, coronary artery bypass grafting.

for the following: (1) per protocol cases, (2) complete cases, (3) all eligible and randomized cases, and (4) assignment of worst cognitive performance scores to patients who had suffered an early postoperative stroke and thus lacked 6-week neurocognitive testing data. None of these sensitivity analyses identified significant differences in cognitive index score change or binary outcome of cognitive deficit between treatment groups (table 6). Of note, when all eligible and randomized patients were included (n = 471) and all missing values were imputed, we found that the 1-yr rate of postoperative cognitive dysfunction was 49.2% in the lidocaine group compared to 58.4% in the placebo group (P = 0.045).

However, this difference was no longer significant after multivariable adjustment for age, level of education, procedure type, Caucasian race, and baseline cognition (odds ratio [95% CI], 0.76 [0.50, 1.15]; P = 0.197).

### Discussion

In this prospective, placebo-controlled, parallel group, randomized study of the administration of intravenous lidocaine for 48 h during and after cardiac surgery with CPB, we found that lidocaine did not reduce the incidence (binary outcome) or magnitude of cognitive decline (continuous cognitive change score) at 6 weeks postoperatively.



**Fig. 3.** Cognitive index trajectory (mean, 95% CI) from baseline to 6 weeks and 1 yr postoperatively.

**Table 4.** Summary of 6-Week Change Scores in Quality of Life and Neurologic Outcomes Measures

| Variable                      | Lidocaine (mean ± SD) | Placebo (mean ± SD) | P Value* |
|-------------------------------|-----------------------|---------------------|----------|
| <b>Quality of life</b>        |                       |                     |          |
| CES-D (-)                     | 0.57 ± 7.5            | 0.16 ± 8.3          | > 0.999  |
| DASI (+)                      | -10.98 ± 15.4         | -11.67 ± 16.8       | > 0.999  |
| STAI (-)                      | -7.12 ± 12.1          | -6.31 ± 11.4        | > 0.999  |
| Symptoms limitation (-)       | -0.67 ± 4.0           | -0.80 ± 3.9         | > 0.999  |
| OARS-IADL (-)                 | 2.46 ± 4.2            | 2.10 ± 3.9          | > 0.999  |
| Cognitive difficulties (-)    | -3.00 ± 14.6          | -3.21 ± 15.9        | > 0.999  |
| Social activities (-)         | 0.95 ± 3.4            | 1.59 ± 3.2          | 0.084    |
| Social support (+)            | 1.23 ± 14             | -0.49 ± 13.9        | 0.814    |
| Work activities (-)           | 2.71 ± 4.9            | 3.00 ± 4.3          | > 0.999  |
| General health perception (-) | -0.004 ± 1.3          | -0.03 ± 1.2         | > 0.999  |
| <b>Neurologic outcomes</b>    |                       |                     |          |
| NIHSS (-)                     | 0.05 ± 0.5            | 0.04 ± 0.5          | > 0.999  |
| WPNS (+)                      | 0.04 ± 1.1            | -0.01 ± 1.3         | > 0.999  |

A minus sign (-) indicates that a lower score is better; a plus sign (+) indicates that a higher score is better.

\*Adjusted for multiple comparisons.

CES-D, Center for Epidemiologic Studies–Depression Scale; DASI, Duke Activity Status Index; NIHSS, National Institutes of Health Stroke Scale; OARS-IADL, Duke Older American Resources Services Procedures–Instrumental Activities of Daily Living; STAI, State Trait Anxiety Inventory; WPNS, Western Perioperative Neurologic Scale.

Additionally, intravenous lidocaine had no effect on 1-yr cognitive outcomes or on additional measures of neurologic outcomes and quality of life.

Since the early 1980s, preclinical evidence has suggested a neuroprotective effect of lidocaine. Evans *et al.*<sup>31,32</sup> were

the first to demonstrate a protective effect of lidocaine against ischemia from cerebral arterial gas embolism in an animal model. This was followed by multiple preclinical studies corroborating a protective effect of conventional doses of intravenous lidocaine, given both before



**Table 5.** Summary of 1-yr Change Scores in Quality of Life and Neurologic Outcomes Measures

| Variable                      | Lidocaine (mean ± SD) | Placebo (mean ± SD) | P Value* |
|-------------------------------|-----------------------|---------------------|----------|
| Quality of life               |                       |                     |          |
| CES-D (-)                     | -1.27 ± 7.7           | -0.89 ± 7.9         | > 0.999  |
| DASI (+)                      | 6.3 ± 18.3            | 6.96 ± 16.9         | > 0.999  |
| STAI (-)                      | -6.7 ± 12.7           | -6.39 ± 10.3        | > 0.999  |
| Symptoms limitation (-)       | -1.39 ± 3.8           | -1.48 ± 3.8         | > 0.999  |
| OARS-IADL (-)                 | -0.15 ± 2.1           | -0.31 ± 2.6         | > 0.999  |
| Cognitive difficulties (-)    | -0.46 ± 16.1          | -1.02 ± 17          | > 0.999  |
| Social activities (-)         | -0.2 ± 3.2            | 0.03 ± 3.4          | > 0.999  |
| Social support (+)            | 0.71 ± 13.4           | -1.16 ± 12.9        | 0.696    |
| Work activities (-)           | -1.37 ± 4.3           | -1.42 ± 4.1         | > 0.999  |
| General health perception (-) | -0.28 ± 1.2           | -0.43 ± 1.1         | > 0.999  |
| Neurologic outcomes           |                       |                     |          |
| NIHSS (-)                     | 0.05 ± 0.7            | 0.07 ± 0.6          | > 0.999  |
| WPNS (+)                      | 0.02 ± 1.1            | -0.02 ± 1.2         | > 0.999  |

A minus sign (-) indicates that a lower score is better; a plus sign (+) indicates that a higher score is better.

\*Adjusted for multiple comparisons.

CES-D, Center for Epidemiologic Studies–Depression Scale; DASI, Duke Activity Status Index; NIHSS, National Institutes of Health Stroke Scale; OARS-IADL, Duke Older American Resources Services Procedures–Instrumental Activities of Daily Living; STAI, State Trait Anxiety Inventory; WPNS, Western Perioperative Neurologic Scale.

**Table 6.** Sensitivity Analyses

| Sensitivity analysis                                | Cognitive Change Index            |         | Cognitive Deficit            |         |
|---|-----------------------------------|---------|------------------------------|---------|
|   | Adjusted Mean Difference (95% CI) | P Value | Adjusted Odds Ratio (95% CI) | P Value |
| Per-protocol cases (N = 406)                        | 0.02 (-0.05, 0.08)                | 0.638   | 0.90 (0.60, 1.37)            | 0.632   |
| Complete cases (N = 393)                            | 0.02 (-0.05, 0.08)                | 0.621   | 0.88 (0.58, 1.35)            | 0.563   |
| All eligible and randomized cases (N = 470)*        | 0.01 (-0.05, 0.08)                | 0.642   | 0.97 (0.66, 1.45)            | 0.896   |
| Assignment of worst cognitive performance (N = 423) | 0.05 (-0.03, 0.13)                | 0.19    | 0.92 (0.61, 1.38)            | 0.676   |

\*One patient was missing level of education.

and after injury and in multiple models of neurologic insult (reviewed elsewhere<sup>33</sup>).

Among the potential mechanisms for a neuroprotective effect of lidocaine, the most obvious are its sodium channel-blocking effects. Cerebral ischemia produces a depletion of neuronal energy stores with a subsequent loss of ionic hemostasis and consequent depolarization, leading to downstream excitotoxicity and the initiation of apoptosis caused by calcium influx. In an animal model of neuronal ischemia, Astrup *et al.*<sup>13</sup> demonstrated that large doses of lidocaine (100 to 160 mg/kg) reduced the cerebral metabolic rate by 15 to 20% beyond that achieved by barbiturates, thus preserving cellular energy stores. They attributed their findings to lidocaine’s ability to block anoxic sodium influx/potassium efflux that leads to cellular edema and loss of function. Similarly, in rat hippocampal slices exposed to varying concentrations of lidocaine within the therapeutic range, anoxic depolarization was less frequent and delayed when it did occur.<sup>14,34</sup> With conventional dosing of lidocaine (0.2 mg · kg<sup>-1</sup> · min<sup>-1</sup>) in rabbits undergoing cerebral ischemia, anoxic depolarization was delayed.<sup>15</sup> As a

consequence of reduced anoxic depolarization in response to lidocaine, secondary neurotoxic events, such as intracellular edema,<sup>35</sup> cytosolic calcium accumulation,<sup>36</sup> and glutamate<sup>37</sup> and aspartate<sup>38</sup> release, can be attenuated.

Others have purported a neuroprotective effect from lidocaine caused by its antiinflammatory properties, which ties in with studies that have suggested that the magnitude of the inflammatory response to surgery may be a risk factor for postoperative cognitive dysfunction.<sup>39,40</sup> In models of tissue injury, lidocaine has been shown to prevent leukocyte accumulation and endothelial adherence along with consequent microvascular thrombus when applied preventatively and to restore microvascular blood flow by disadhering leukocytes from the endothelium when applied postinjury.<sup>41,42</sup> As part of this study and reported elsewhere,<sup>43</sup> paired jugular venous and arterial samples were drawn on the first 202 randomized patients to measure transcerebral gradients of activated platelets and platelet–leukocyte conjugates. In that cohort, we observed a significant reduction in the transcerebral activation of platelet–monocyte conjugates after aortic cross-clamp release in patients who received lidocaine, which

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we hypothesized might reflect reduced cerebral inflammation during CPB. Despite these results, the data reported here do not show a protective effect of lidocaine on cognition. Analysis of the 202 patients with platelet–leukocyte data showed no difference in cognitive outcomes between lidocaine and placebo groups, suggesting that any drug-related changes in circulating inflammatory cell markers do not impact cognitive outcomes; however, this predefined substudy was not powered to study cognitive outcomes. Cerebrospinal inflammatory markers were also not measured and may better correlate with cognitive outcomes.

Despite the promise demonstrated in preclinical studies, human trials have been conflicting. The first study of intravenous lidocaine for neuroprotection in cardiac surgery was published by Mitchell *et al.*<sup>44</sup> Sixty-five patients undergoing open heart valve surgery were randomized to 48 h of intravenous lidocaine *versus* placebo, and cognition was compared at three postoperative follow-up time points with baseline measures. At the 10-day and 10-week follow-up points, the number of patients with a 1-SD decrement in one cognitive test was significantly lower in the lidocaine group. Wang *et al.*<sup>12</sup> published a similar study in patients undergoing CABG, demonstrating that significantly fewer patients who received lidocaine compared to placebo manifested cognitive deficit at 9 days postoperatively. A large randomized trial of lidocaine *versus* placebo in cardiac surgical patients performed by Mathew *et al.*<sup>22</sup> was unable to demonstrate a protective effect of lidocaine on cognition in the global study cohort. However, diabetes and high lidocaine dose were found to be detrimental to cognition, and secondary analyses pointed to a potentially protective effect of pharmacokinetically driven dosing of lidocaine in nondiabetic cardiac surgical patients. Finally, a follow-up study by Mitchell *et al.*<sup>10</sup> contradicted the results of their original trial, showing no benefit of a 12-h lidocaine infusion on cognition in 158 patients at 10 and 25 weeks after cardiac surgery.

Some have postulated that the variability seen in human trials may reflect differences in procedure types, with the benefit seen primarily in those studies involving open-chamber procedures with higher risk of gas emboli to the brain. This appears plausible given the benefit seen in preclinical models of cerebral injury induced by gas embolism and human data demonstrating enhanced neurologic recovery with intravenous lidocaine in divers suffering decompression sickness.<sup>45–47</sup> Our patient population underwent both open- and closed-chamber procedures, with a preponderance of valve and valve + CABG surgeries in both treatment groups (71% in lidocaine *vs.* 70% in placebo). However, multivariable regression failed to demonstrate an interaction between procedure type and treatment group. In the per-protocol analysis, there was a signal for worse cognition with valve surgery compared to CABG (cognitive index change difference valve *vs.* CABG [95% CI],  $-0.07$  [ $-0.15, 0$ ];  $P = 0.041$ ); however, there was no treatment effect.

The results of this study are in line with the general consensus in the literature that postoperative cerebral injury is a complex phenomenon that is not easily ameliorated. Available evidence suggests a wide range of risk factors and potential mechanisms underlying cognitive decline after general and cardiac surgery, including preoperative cognitive impairment, genetic predisposition, cerebral microembolism or hypoperfusion during CPB, central nervous and systemic inflammatory responses, hemodilution, hyperglycemia, hyperthermia, unmasking of Alzheimer disease, and acceleration of amyloid deposition associated with inhalational anesthetics (reviewed elsewhere).<sup>48</sup> Not surprisingly, individual drugs investigated for neuroprotection during cardiac surgery have thus far produced disappointing results, including several drugs targeting similar physiologic pathways as lidocaine.<sup>49</sup>

Postoperative cognitive dysfunction studies often suffer from the lack of controls and inconsistent measurement and definitions of cognitive decline. Our large, multicenter study was placebo-controlled and involved rigorous neurocognitive testing. We examined cognitive function as both a dichotomous outcome and as a continuous measure; we failed to find an impact of lidocaine on cognitive change by either measure. Loss to follow-up was a limitation of the current study, although the rate was not different between groups. We attempted to adjust for loss to follow-up caused by stroke (*i.e.*, poorest neurologic outcome) by assignment of poor cognitive scores to stroke patients in secondary analyses without a change in the results. There were several other important demographic differences in patients that dropped out before the 6-week or 1-yr evaluation time points (described in Supplemental Digital Content 1, <http://links.lww.com/ALN/B904>; and Supplemental Digital Content 2, <http://links.lww.com/ALN/B905>, respectively). Globally, patients lost to follow-up were more likely to be female, have a lower preoperative ejection fraction, have a lower preoperative cognitive index score, and have had CABG surgery; however, these characteristics were evenly distributed across patients lost to follow-up in both treatment groups.

Additional limitations include the methodology of defining cognitive dysfunction. As yet, there is no standard definition or criteria for diagnosing postoperative cognitive dysfunction, although the International Perioperative Neurotoxicity Group is currently working toward a consensus definition of postoperative cognitive dysfunction. We utilized a standard battery of neuropsychological tests, as outlined by a consensus statement on the assessment of neurobehavioral outcomes after cardiac surgery.<sup>24</sup> The binary outcome of postoperative cognitive dysfunction was defined as a decline of more than 1 SD in at least one domain; both more than 1 SD and more than 2 SD declines are commonly used in the postoperative cognitive dysfunction literature. Furthermore, we reported the continuous cognitive change score from baseline to highlight the magnitude of cognitive change in addition the incidence of the binary cognitive deficit outcome.

Finally, our study was limited by sensitivity for detection of cognitive deficit at the 1-yr follow-up point. Although there appears to be a potential divergence in the cognitive trajectory between lidocaine-treated and placebo patients at the 1-yr time point (fig. 3), we were underpowered for this outcome. To detect a difference between the observed postoperative cognitive dysfunction rate between lidocaine and placebo (48.1% and 56.8%, respectively), a future study would require 517 patients/treatment group (two-sided chi-square test at  $\alpha = 0.05$ ).

In summary, intravenous administration of lidocaine intraoperatively and for a total of 48 h in patients undergoing both open and closed chamber cardiac surgery with CPB did not protect against postoperative cognitive dysfunction or improve cognitive scores at 6-weeks or 1-yr postoperatively. Lidocaine also failed to improve additional measures of postoperative neurologic outcomes or quality of life indices.

### Research Support

Supported by National Institutes of Health grant Nos. HL096978, HL108280, HL109971, and HL130443 (Bethesda, Maryland; to Dr. Mathew).

### Competing Interests

The authors declare no competing interests.

### Reproducible Science

Full protocol available at: [klings004@mc.duke.edu](mailto:klings004@mc.duke.edu). Raw data available at: [klings004@mc.duke.edu](mailto:klings004@mc.duke.edu).

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