ORIGINAL RESEARCH

Use and Outcomes Associated With Perioperative Amiodarone in Cardiac Surgery

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***Background*—**In randomized controlled trials, perioperative administration of amiodarone has been shown to reduce the incidence of postoperative atrial arrhythmias and length of stay (LOS) among patients undergoing coronary bypass surgery. However, little is known about the use or effectiveness of perioperative amiodarone in routine clinical practice.

***Methods and Results*—**We studied patients ≥18 years old without a previous history of atrial or ventricular arrhythmias who underwent elective coronary bypass surgery between 2013 and 2014 within a network of 235 US hospitals. Perioperative amiodarone was defined as receipt of amiodarone either on the day of or the day preceding surgery. We used covariate-adjusted modeling and instrumental variable methods to examine the association between receipt of amiodarone and the development of atrial arrhythmias, in-hospital mortality, readmission, LOS, and cost. Of 12 758 patients, 2195 (17.2%) received perioperative amiodarone, 3330 (26.1%) developed atrial arrhythmias postoperatively, and the average LOS was 6.4 days (±2.6 days). Instrumental variable analysis showed that receipt of perioperative amiodarone was associated with lower risk of atrial arrhythmias (risk difference −11 percentage points, 95% CI −19 to −4 percentage points; *P*=0.002) and a shorter LOS (−0.7 day, 95% CI −1.39 to −0.01 days; *P*=0.048). There was no association between receipt of perioperative amiodarone and in-hospital mortality, cost, or readmission.

***Conclusions*—**Among patients undergoing coronary bypass surgery without previous arrhythmias, perioperative amiodarone is associated with a lower risk of atrial arrhythmias and shorter LOS. These findings are consistent with previous randomized trials and lend support to current guideline recommendations. **(*J Am Heart Assoc*. 2019;8:e009892. DOI: 10.1161/JAHA.118.009892.)**

Key Words: amiodarone • atrial fibrillation arrhythmia • coronary artery bypass graft surgery • heart valve surgery • postoperative complication arrhythmia

Postoperative atrial fibrillation and atrial flutter are the most common arrhythmic complications following cardiac surgery, affecting 25% to 50% of patients in the postoperative period.[1-3] Atrial arrhythmias typically develop on the second or third postoperative day, and regardless of treatment, they generally resolve within 6 to 8 weeks of surgery.[2] In addition to discomfort, anxiety, and hemodynamic instability, the development of postoperative atrial arrhythmias has been associated with longer length of stay (LOS) and higher hospital costs.[4-6] Observational studies conducted in the 1990s suggested that atrial arrhythmias were associated with a 3- to 5-day longer LOS,[5,7-9] but more recent analyses have found that this association is weaker or even absent, possibly a reflection of changing postoperative management of atrial arrhythmias and discharge practices.[10,11]

Strategies to prevent postoperative atrial arrhythmias include both pharmacological agents and nonpharmacological interventions.[2,11-13] The 2011 American College of Cardiology/American Heart Association/Heart Rhythm Society atrial fibrillation management guidelines recommend β-blockers for all patients without contraindications (class I, level A) and amiodarone in patients at high risk for atrial arrhythmias (class IIa, level A).[2] The basis of the recommendation for amiodarone use is largely derived from reduction of atrial arrhythmias noted in randomized controlled trials (both preoperative and postoperative amiodarone use), the largest and the most recent of which was PAPABEAR (Prophylactic

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009892

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Clinical Perspective

What Is New?

- Previous small randomized controlled studies have established the benefit of perioperative amiodarone in reducing atrial arrhythmias and length of stay (LOS) following cardiac surgery.
- This is the first large observational study to examine the association between amiodarone treatment and outcomes in routine clinical practice.

What Are the Clinical Implications?

- Our analyses suggest that perioperative amiodarone was both safe and effective at reducing the occurrence of postoperative atrial arrhythmias, and receipt was associated with a shorter LOS.
- At the same time, use of perioperative amiodarone remains limited in clinical practice. Future efforts should focus on consistent implementation of perioperative amiodarone protocols, with appropriate patient selection in order to achieve optimal surgical outcomes.

Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair trial).[14] In this study consisting of 601 patients, a perioperative course of oral amiodarone demonstrated a significant reduction in the incidence of postoperative atrial tachyarrhythmia (13.4% absolute risk reduction). A meta-analysis of 19 randomized controlled trials, including 3396 patients, showed that amiodarone reduces atrial arrhythmias (pooled odds ratio 0.50, 95% CI 0.43-0.59).[15] This study also showed a modest reduction in hospital LOS in the amiodarone group (pooled difference of 0.6 days in the amiodarone group, 95% CI 0.4-0.8).

Although amiodarone is recommended in guidelines, little is known about the use of amiodarone among patients undergoing cardiac surgery in the United States or if the benefits reported in randomized controlled trials have been achieved in routine clinical practice. We therefore investigated the application of perioperative amiodarone use among patients admitted for elective cardiac surgery in a large network of US hospitals and compared the outcomes of those receiving perioperative amiodarone to those who did not. We hypothesized that perioperative amiodarone would be associated with a lower incidence of atrial arrhythmias but not with healthcare utilization outcomes such as LOS, cost, or readmission.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files. Based on our data use agreement with the Premier Analytic Database, we are unable to share the primary data set; however, we can make the data analyses from our statistical programs available on specific request (Peter.Lindenauer@baystatehealth.org).

Setting and Subjects

We conducted a retrospective cohort study of patients admitted between January 1, 2013 and December 31, 2014 to a geographically and structurally diverse set of hospitals participating in Premier Incorporated's Perspective (Premier Healthcare Informatics, Charlotte, NC), a voluntary, fee-supported database developed for measuring quality and healthcare utilization. In addition to the information available in the standard hospital discharge file, the Perspective database contains date-stamped logs of all billed items, including medications, laboratory, diagnostic, and therapeutic services at the individual patient level. Diagnostic and procedural information was assessed using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).

Patients were included in our analysis if they were 18 years or older and underwent elective coronary artery bypass surgery (CABG; *ICD-9* procedure codes 36.1x, x=0,1,2,3,4,5,6,7,9) alone or CABG with concomitant heart valve surgery (*ICD-9* procedure codes 35.1x, x=0,1,2,3,4 or 35.2x, x=0,1,2,3,4,5,6,7,8) on the first or second day of their hospitalization. To address the clinical question of whether prophylactic use of amiodarone is effective at preventing arrhythmia, we excluded patients with a previous history of atrial or ventricular arrhythmias (including atrial fibrillation, atrial flutter [427.31, 427.32], ventricular tachycardia/fibrillation [427.1, 427.4x, x=1,2]) or anyone with these codes present on admission. We also excluded those who had received treatment with class I and class III antiarrhythmic drugs (disopyramide, lidocaine, dofetilide, dronedarone, digoxin, sotalol, flecainide, propafenone, mexiletine, ibutilide, procainamide) during an earlier admission or before surgery during the index admission. On similar grounds we excluded patients who had received amiodarone during a previous admission. Patients with chronic obstructive pulmonary disease severe enough to require hospitalization in the past year and those with hypotension or bradycardia at admission were also excluded from the cohort, as these conditions may have represented contraindications to amiodarone treatment. Individuals with a pacemaker were excluded from the cohort because we wished to study pacemaker implantation as an outcome. Last, since our secondary goal was to make inferences about interactions between amiodarone and β-blocker use, we excluded β-blockers that may have been used for other purposes (eg, intraoperative blood pressure control, glaucoma prevention) and included only patients receiving

metoprolol, carvedilol, bisoprolol, atenolol, labetolol, and propranolol.

Permission to conduct the study was obtained by the Institutional Review Board at Baystate Medical Center, where the study was conducted, and the need for written informed consent was waived (IRB# 777703-1).

Patient and Hospital Information

In addition to patient age, sex, race/ethnicity, and insurance status, we recorded the presence of up to 29 unique comorbidities using software provided by the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality (Rockville, MD) based on methods described by Elixhauser et al.[16] Comorbidity burden was summarized as a score using methods described by Gagne et al.[17] For each hospital that participated in the study, we recorded bed size, teaching status, geographic region, and whether it served an urban or rural population.

Use of Amiodarone and Other Treatments

We considered a patient to have received perioperative amiodarone if there was a pharmacy charge for treatment with amiodarone either on the day of or day before surgery. Patients whose first exposure to amiodarone began on or after postoperative day 1 were classified as not having received perioperative amiodarone because this may have represented treatment for new-onset atrial arrhythmias or another arrhythmia rather than for prophylaxis. To control for differences in severity of illness not accounted for by age and comorbidity, as well as the effects of other therapies, we assessed the use of a wide range of diagnostic tests, monitoring devices, and pharmacologic treatments administered before surgery, including loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, nonsteroidal anti-inflammatory drugs, β-blockers, and number of vessels bypassed during CABG.

Outcomes

The primary outcome was the occurrence of postoperative atrial arrhythmia during the index admission, which was defined based on an *ICD-9* discharge diagnosis code of atrial fibrillation or flutter that was not present on admission. Secondary outcomes included in-hospital mortality, all-cause readmission within 1 month (among survivors), LOS, and hospital costs. In addition, we also examined a set of cardiovascular outcomes that might be influenced by amiodarone, including ventricular arrhythmias, stroke, myocardial infarction, hypotension, bradycardia, heart block, pacemaker implantation, cardiogenic shock, and cardiac arrest (not present on admission). These outcomes were assessed using *ICD-9* diagnosis codes (Table S1).

Statistical Analyses

Patient and hospital characteristics were summarized as frequencies: percentages for categorical variables and means with standard deviations or medians with interquartile ranges for continuous variables. Because of the large sample size, we compared the characteristics of patients treated with perioperative amiodarone and patients who did not receive perioperative amiodarone (or received it after postoperative day 1) via absolute standardized differences.[18] A difference greater than 10% was considered to represent significant imbalance between the groups.

To analyze the association between perioperative amiodarone and the study outcomes, we developed multivariable adjusted generalized estimating equation models accounting for patient clustering within hospitals. Logit link models were used for binary outcome models, and identity link models used for continuous outcomes. Our primary outcome, atrial arrhythmia, was frequent in the cohort (>20%); therefore, we assessed this outcome using Poisson models with log link function to estimate a risk ratio. LOS and costs were skewed, so we winsorized these outcomes at their 95th percentile value. A propensity score analysis was also completed but was not presented because it failed to balance important confounder differences.[19,20]

Instrumental Variable Analyses

To address concerns regarding the possibility of residual confounding by unmeasured factors (in which patients receiving amiodarone would be at higher risk of arrhythmias), we performed an instrumental variable analysis using hospital preference for amiodarone as our instrument. To obtain stable estimates of hospital amiodarone prescribing, we first restricted the cohort to hospitals with at least 25 surgical admissions. We then divided hospitals into quintiles, based on the frequency of perioperative amiodarone use among patients undergoing cardiac surgery. Hospital use of perioperative amiodarone defined our instrument, with patients treated at hospitals in the upper 2 quintiles having a high likelihood of perioperative amiodarone and patients at hospitals in the bottom 3 quintiles having a low likelihood of perioperative amiodarone. We performed 2-stage least-squares regression to estimate the risk difference, the absolute difference in risk of outcome among patients at high- versus low-use hospitals. In the first stage, receipt of perioperative amiodarone was modeled as a function of the instrument and confounders, and in the second stage, the outcome was modeled as a function of predicted treatment

from the first-stage model as well as the confounders. The strength of the instrument was measured using the partial F statistic and partial R^2 from stage 1 of the models. Improvement in balance of patient characteristics in the instrumental variable subcohort was assessed via absolute standardized differences. Because the instrument was defined based on hospital use of perioperative amiodarone, to address the possibility of association of the instrument with outcomes, we adjusted all models for hospital characteristics along with patient factors that had a standardized difference of greater than 10% in the instrumental variable cohort. We performed the Durbin-Wu-Hausman test to confirm whether receipt of perioperative amiodarone was correlated with other variables in the model to confirm the value of instrumental variable methods.[21,22]

All analyses were performed using the Statistical Analysis System (version 9.3, SAS Institute, Inc, Cary, NC) and STATA 13 (StataCorp, LLC, College Station, TX).

Results

Of 12 758 patients who met our enrollment criteria (Figure 1), 10 409 (81.6%) at 235 hospitals were admitted for elective CABG alone, while the remaining underwent combined CABG+heart valve surgery. The mean age was 66 years, 75% were male, 73% were white, and Medicare was the most common form of health insurance (Table 1). Hypertension, diabetes mellitus, obesity, heart failure, and peripheral vascular disease were the most frequently recorded comorbidities. Overall, 58% of patients were cared for at nonteaching facilities; 91% of hospitals were urban, and over 90% of the hospitals operated more than 200 beds. The average LOS was 6.4 days, average costs were $33 821, and 3 out of 10 patients were hospitalized for 7 days or longer. A total of 3330 patients (26.2%) developed an atrial arrhythmia during the index admission, 167 (1.3%) died during the hospitalization, and 1653 (13.1%) were readmitted within 1 month of discharge (Table 1). Receipt of warfarin before discharge was higher among patients who had developed atrial arrhythmias than among those who had not (32.9% versus 6.4%).

Use of Amiodarone and Other Treatments

In all, 2195 (17.2%) patients received perioperative amiodarone on either the day of or day before cardiac surgery. The mean duration of amiodarone received was 5.2 days, and mean dose received during the hospitalization was 3.8 g of amiodarone. When compared with those who did not receive perioperative amiodarone, treated patients were slightly younger, more likely

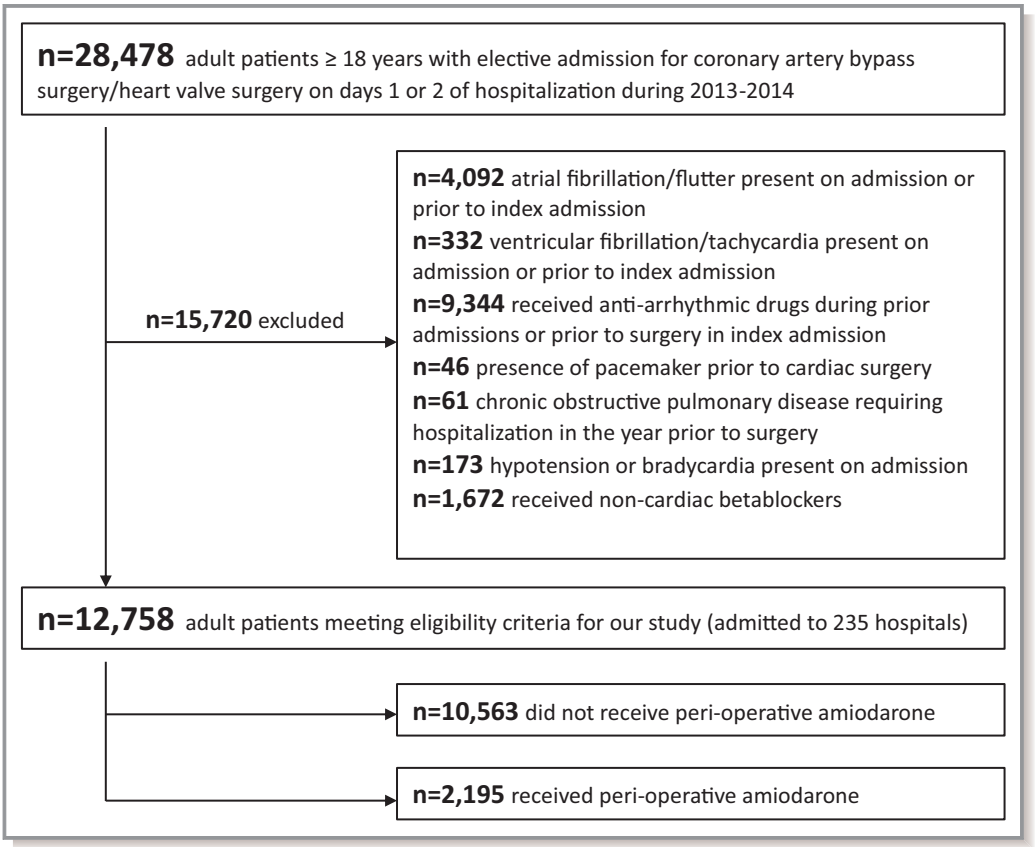


Figure 1. Patient selection flow diagram.

Table 1. Patient Demographics, Treatments, Hospital Characteristics, and Outcomes in the Full Cohort

	Total, n (%)	No Perioperative Amiodarone, n (%)	Perioperative Amiodarone*, n (%)	Absolute Standardized Difference (%)†
	12 758 (100)	10 563 (82.8)	2195 (17.2)	
Patient characteristics				
Age, mean (SD), y	66.0 (10.1)	66.1 (10.1)	65.3 (10.0)	7.5
Sex				
Female	3154 (24.7)	2580 (24.4)	574 (26.2)	4
Race/ethnicity				
White	9285 (72.8)	7466 (70.7)	1819 (82.9)	32.4
Black	700 (5.5)	586 (5.5)	114 (5.2)	
Hispanic	628 (4.9)	551 (5.2)	77 (3.5)	
Other	2145 (16.8)	1960 (18.6)	185 (8.4)	
Insurance payer				
Medicare	7288 (57.1)	6036 (57.1)	1252 (57.0)	14.4
Medicaid	759 (5.9)	642 (6.1)	117 (5.3)	
Managed care	3262 (25.6)	2764 (26.2)	498 (22.7)	
Other	1449 (11.4)	1121 (10.6)	328 (14.9)	
Type of procedure				
CABG	10 409 (81.6)	8620 (81.6)	1789 (81.5)	0.3
CABG+Valve	2349 (18.4)	1943 (18.4)	406 (18.5)	
Gagne combined score, mean (SD)	1.6 (2.2)	1.7 (2.2)	1.6 (2.3)	2.5
Comorbidities				
Hypertension	10 939 (85.7)	9088 (86)	1851 (84.3)	4.8
Tobacco abuse	6174 (48.4)	5013 (47.5)	1161 (52.9)	10.9
Diabetes mellitus	5722 (44.9)	4755 (45)	967 (44.1)	1.9
Obesity	3136 (24.6)	2563 (24.3)	573 (26.1)	4.2
Chronic pulmonary disease	2641 (20.7)	2067 (19.6)	574 (26.2)	15.7
Congestive heart failure	2225 (17.4)	1821 (17.2)	404 (18.4)	3.1
Peripheral vascular disease	2033 (15.9)	1687 (16)	346 (15.8)	0.6
Renal failure	1784 (14)	1499 (14.2)	285 (13)	3.5
Obstructive sleep apnea	1648 (12.9)	1322 (12.5)	326 (14.9)	6.8
Hypothyroidism	1353 (10.6)	1103 (10.4)	250 (11.4)	3
Depression	1035 (8.1)	833 (7.9)	202 (9.2)	4.7
Early therapies and tests‡				
β-Blockers on or before surgery	5729 (44.9)	4445 (42.1)	1284 (58.5)	33.3
Statins	3459 (27.1)	2484 (23.5)	975 (44.4)	45.3
Loop diuretics	2025 (15.9)	1584 (15)	441 (20.1)	13.4
Cardiac catheterization before surgery	1603 (12.6)	1289 (12.2)	314 (14.3)	6.2
CABG: number of vessels bypassed				
4 Arteries	1317 (10.3)	1074 (10.2)	243 (11.1)	11.2
3 Arteries	3193 (25)	2624 (24.8)	569 (25.9)	
2 Arteries	4377 (34.3)	3591 (34)	786 (35.8)	
1 Artery	2946 (23.1)	2463 (23.3)	483 (22)	
Not specified	925 (7.3)	811 (7.7)	114 (5.2)	

Continued

Table 1. Continued

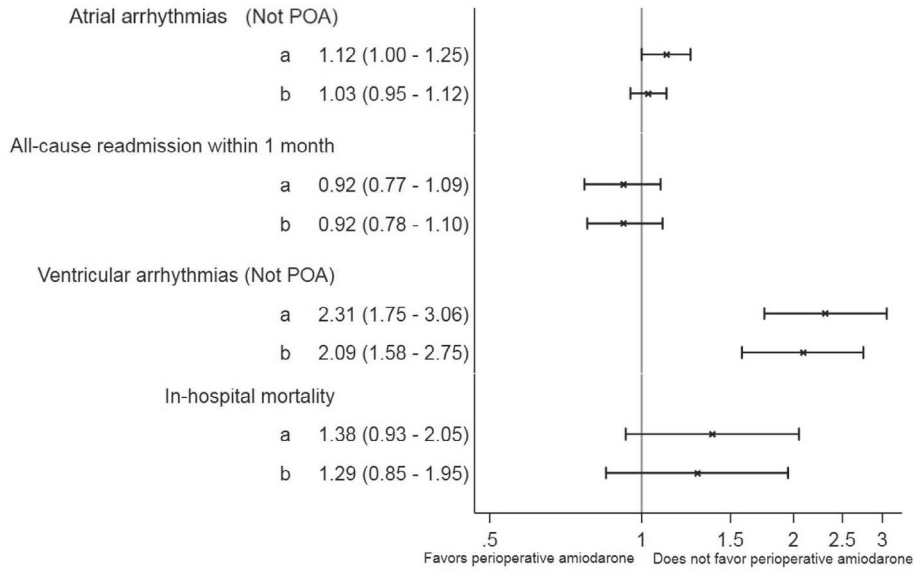
	Total, n (%)	No Perioperative Amiodarone, n (%)	Perioperative Amiodarone*, n (%)	Absolute Standardized Difference (%)†
	12 758 (100)	10 563 (82.8)	2195 (17.2)	
Hospital characteristics				
Number of beds				
≤200 beds	942 (7.4)	790 (7.5)	152 (6.9)	39.3
201 to 400 beds	3900 (30.6)	2896 (27.4)	1004 (45.7)	
≥401 beds	7916 (62.0)	6877 (65.1)	1039 (47.3)	
Population served				
Urban	11 620 (91.1)	9554 (90.4)	2066 (94.1)	13.8
Rural	1138 (8.9)	1009 (9.5)	129 (5.9)	
Hospital region				
Northeast	2795 (21.9)	2492 (23.6)	303 (13.8)	43.1
Midwest	2791 (21.9)	2501 (23.7)	290 (13.2)	
West	1741 (13.6)	1326 (12.5)	415 (18.9)	
South	5431 (42.6)	4244 (40.2)	1187 (54.1)	
Teaching status				
Nonteaching	5316 (41.7)	4164 (39.4)	1152 (52.5)	26.4
Teaching	7442 (58.3)	6399 (60.6)	1043 (47.5)	
Outcomes in full cohort (adjusted)				*P* Value‖
Atrial arrhythmias§	3330 (26.2)	2818 (26.7)	512 (23.4)	<0.001
Ventricular arrhythmias	394 (3.1)	299 (2.8)	95 (4.3)	<0.001
Readmission (all cause) within 1 mo	1653 (13.1)	1383 (13.3)	270 (12.5)	0.34
In-hospital mortality	167 (1.3)	132 (1.2)	35 (1.6)	0.2
LOS, mean (SD), days, winsorized at 95th percentile	6.36 (2.64)	6.36 (2.63)	6.37 (2.71)	0.44
Cost, mean (SD), USD, winsorized at 95th percentile	33 821 (13 216)	33 515 (13 107)	35 295 (13 636)	<0.001

CABG indicates coronary artery bypass surgery; LOS, length of stay.
*Perioperative amiodarone is defined as amiodarone administered on same day or day preceding surgery.
†For continuous variables, absolute standardized difference $= 100 \times (\bar{x}_{treatment} - \bar{x}_{control})/\text{sqrt}([s^2_{treatment} + s^2_{control}]/2)$ where $\bar{x}$ is sample mean in respective groups and s^2 is sample variance in respective groups. For binary variables: $100 \times (p_{treatment} - p_{control})/\text{sqrt}([p_{treatment} \times (1 - p_{treatment})] + [p_{control} \times (1 - p_{control})]/2)$ where p is the prevalence of binary variable in treatment and control groups, respectively. For categorical variables, multivariate Mahalanobis distance is computed.
‡Early therapies and tests are defined as treatment/test on same day or day preceding surgery.
§Atrial arrhythmias are defined as postoperative atrial fibrillation or flutter (not present on admission).
‖*P*-value assessed via chi-squared test for binary outcomes and Kruskal-Wallis test for continuous outcomes.

to be white, and less likely to have private insurance (Table 1). The 2 groups were comparable in terms of comorbidities; however, patients treated with perioperative amiodarone were more likely to receive β-blockers, angiotensin-converting enzyme inhibitors, and statins in the first 2 hospital days. There were no significant differences in terms of the number of vessels bypassed during CABG. Treatment with perioperative amiodarone was more common at urban, nonteaching hospitals and at hospitals in the West.

Unadjusted and Multivariable Adjusted Outcomes

Outcomes from the unadjusted and covariate adjusted analysis are presented in Figure 2. In the adjusted model, atrial arrhythmias occurred in 23.4% of patients treated with perioperative amiodarone as compared with 26.7% of patients not receiving perioperative amiodarone ($P<0.001$). There were no differences in the percentage of patients readmitted within 1 month of discharge (12.5% versus 13.3%, $P=0.3$) or in inpatient mortality (1.6% versus 1.2%, $P=0.2$) between the patients receiving perioperative amiodarone and those not receiving perioperative amiodarone. However, patients receiving perioperative amiodarone were more likely to experience ventricular arrhythmias (4.3% versus 2.8%, $P<0.001$). Although we did not observe clinically meaningful differences in the hospital LOS between the 2 groups, total costs associated with the group treated with perioperative amiodarone were, on average, about $1866



a	Unadjusted outcomes (generalized estimating equation/ GEE model accounting for patient clustering within hospital)
b	Covariate adjusted- generalized estimating equation model (GEE model accounting for patient clustering within hospital)

Figure 2. Forest plot of outcomes from various models. a indicates unadjusted outcomes GEE model/GEE model accounting for patient clustering within hospital; b, covariate-adjusted GEE model/GEE model accounting for patient clustering within hospital; GEE, generalized estimating equation; POA, present on admission.

(95% CI $1250-$2483) higher than those for the group that did not receive perioperative amiodarone ($P<0.001$).

Instrumental Variable Analyses

For the instrumental variable analysis, our cohort was restricted to hospitals with at least 25 surgical admissions. We identified 11 786 patients who underwent cardiac surgery in 129 hospitals of whom 17.0% had received perioperative amiodarone. Of these, 52 hospitals had high perioperative amiodarone use (upper 2 quintiles of amiodarone use), where 4083 patients received treatment. Hospitals in the upper 2 quintiles treated 44.2% of their patients with perioperative amiodarone compared with 2.6% in the hospitals with low amiodarone use (lowest 3 quintiles). Hospitals with higher use were more likely to be small or medium sized, nonteaching, and from the South (Table 2). Results of the instrumental variable analysis (Table 3) suggested that among marginal patients (those whose treatment status can be affected by their choice of hospital: low use of amiodarone versus hospitals with high amiodarone use), receipt of perioperative amiodarone was associated with a lower incidence of atrial arrhythmias (risk difference −11 percentage points, 95% CI −19 to −4.0 percentage points; $P=0.002$) and with shorter LOS (risk difference −0.7 days, 95% CI −1.39 to −0.01 days; $P=0.048$). In contrast to the covariate-adjusted model, the instrumental variable analysis did not find a higher risk of ventricular arrhythmias associated with receipt of perioperative amiodarone in the overall instrumental variable cohort. However, differences were noted in hospitals with low amiodarone use and high amiodarone use. Ventricular arrhythmias were more common at hospitals with low amiodarone use than high use (3.6% versus 2.3%, $P=0.02$) (Table 2) and statistical testing for homogeneity indicated differences in the 2 groups (odds ratio=4.5, 95% CI 3.0-6.9 versus odds ratio=2.3, 95% CI 1.5-3.6; $P=0.024$ for Breslow-Day test for homogeneity).

There were no associations detected between the hospital group where treatment was received (low-use of amiodarone versus high-use hospital) and the risk of in-hospital mortality, 1-month readmission, hospital cost, or any of the other cardiovascular outcomes, including cardiogenic shock and cardiac arrest.

Table 2. Patient Demographics, Treatments, and Hospital Characteristics in Instrumental Variable Analysis Cohort

Patient Characteristics	Hospitals in Lowest 3 Quintiles of Perioperative Amiodarone use (77 hospitals; 59.7%)	Hospitals in Highest 2 Quintiles of Perioperative Amiodarone Use (52 hospitals; 40.3%)	Absolute Standardized Difference (%)*
Number of patients	7703 (65.4)	4083 (34.6)	
Perioperative amiodarone† use	201 (2.6)	1806 (44.2)	
Age, mean (SD), y	66.4 (10.0)	65.3 (10.1)	11.6
Sex			
Female	1883 (24.4)	1030 (25.2)	1.8
Race/ethnicity			
White	5468 (71)	3185 (78)	18.5
Black	410 (5.3)	226 (5.5)	
Hispanic	397 (5.2)	126 (3.1)	
Other	1428 (18.5)	546 (13.4)	
Insurance payer			
Medicare	4478 (58.1)	2276 (55.7)	13
Medicaid	424 (5.5)	277 (6.8)	
Managed care	2016 (26.2)	964 (23.6)	
Other	785 (10.2)	566 (13.9)	
Type of procedure			
CABG	6103 (79.2)	3463 (84.8)	14.6
CABG+Valve	1600 (20.8)	620 (15.2)	
Gagne combined score, mean (SD)	1.7 (2.2)	1.5 (2.2)	9.2
Comorbidities			
Hypertension	6572 (85.3)	3529 (86.4)	3.2
Tobacco abuse	3528 (45.8)	2184 (53.5)	15.4
Diabetes mellitus	3421 (44.4)	1833 (44.9)	1
Obesity	1858 (24.1)	1044 (25.6)	3.4
Chronic pulmonary disease	1441 (18.7)	996 (24.4)	13.9
Congestive heart failure	1362 (17.7)	673 (16.5)	3.2
Peripheral vascular disease	1231 (16)	646 (15.8)	0.4
Renal failure	1086 (14.1)	555 (13.6)	1.5
Obstructive sleep apnea	967 (12.6)	571 (14)	4.2
Hypothyroidism	833 (10.8)	430 (10.5)	0.9
Depression	594 (7.7)	367 (9)	4.6
Early therapies and tests‡			
β-Blockers on or before surgery	3165 (41.1)	2106 (51.6)	21.2
Loop diuretics	1049 (13.6)	844 (20.7)	18.8
Statins	1816 (23.6)	1345 (32.9)	20.9
Cardiac catheterization before surgery	946 (12.3)	511 (12.5)	0.7
CABG: number of vessels bypassed			
4 arteries	827 (10.7)	381 (9.3)	6.6
3 arteries	1902 (24.7)	1028 (25.2)	
2 arteries	2602 (33.8)	1453 (35.6)	
1 artery	1827 (23.7)	909 (22.3)	
Not specified	545 (7.1)	312 (7.6)	

Continued

Table 2. Continued

Patient Characteristics	Hospitals in Lowest 3 Quintiles of Perioperative Amiodarone use (77 hospitals; 59.7%)	Hospitals in Highest 2 Quintiles of Perioperative Amiodarone Use (52 hospitals; 40.3%)	Absolute Standardized Difference (%)*
Hospital characteristics			
Number of beds			
≤200 beds	503 (6.5)	353 (8.6)	45.4
201 to 400 beds	1752 (22.7)	1713 (41.9)	
≥401 beds	5448 (70.7)	2017 (49.4)	
Population served			
Urban	7036 (91.3)	3693 (90.4)	3.1
Rural	667 (8.7)	390 (9.5)	
Hospital region			
Northeast	2143 (27.8)	535 (13.1)	65.3
Midwest	2072 (26.9)	511 (12.5)	
West	607 (7.9)	852 (20.9)	
South	2881 (37.4)	2185 (53.5)	
Teaching status			
Nonteaching	2643 (34.3)	2084 (51.0)	34.3
Teaching	5060 (65.7)	1999 (49.0)	
Outcomes			*P* Value§
Atrial arrhythmias	2210 (28.7)	884 (21.7)	<0.001
Ventricular arrhythmias	275 (3.6)	93 (2.3)	0.02
Readmission (all cause) within 1 mo	971 (12.8)	544 (13.5)	0.57
In-hospital mortality	106 (1.4)	51 (1.2)	0.62
LOS, mean (SD), days, winsorized at 95th percentile	6.4 (2.5)	6.0 (2.5)	0.01
Cost, mean (SD), USD, winsorized at 95th percentile	33 380 (13 140)	34 116 (13 011)	0.60

CABG indicates coronary artery bypass surgery; LOS, length of stay.

*For continuous variables: absolute standardized difference $= 100 \times (\bar{x}_{treatment} - \bar{x}_{control})/\text{sqrt}([s^2_{treatment} + s^2_{control}]/2)$ where $\bar{x}$ is sample mean in respective groups and s^2 is sample variance in respective groups. For binary variables: $100 \times (p_{treatment} - p_{control})/\text{sqrt}([p_{treatment} \times (1 - p_{treatment})] + [p_{control} \times (1 - p_{control})]/2)$ where p is the prevalence of a binary variable in treatment and control groups, respectively. For categorical variables, multivariate Mahalanobis distance is computed.

†Perioperative amiodarone is defined as amiodarone administered on same day or day preceding surgery.

‡Early therapies and tests are defined as treatment/test on the same day or day preceding surgery.

§*P*-value from 2-stage least squares (unadjusted for patient characteristics).

Discussion

In this large national cohort of more than 12 000 patients undergoing cardiac surgery, receipt of perioperative amiodarone was associated with lower risk of atrial arrhythmias and shorter hospital LOS. We found no association with inpatient mortality, readmission, or hospital cost in our primary analysis. These results were confirmed in an instrumental variable analysis (based on hospital preference for amiodarone therapy). Our results are generally consistent with previous meta-analyses and randomized clinical trials.[15,23] Because patients enrolled in randomized studies are highly selected, and trial participants receive protocolized care, it is critical to demonstrate the generalizability of these findings in routine clinical settings. It is not uncommon to find differences in the magnitude and occasionally the direction of effects between randomized clinical trials and large observational studies.[24] In this largest observational study to date of perioperative amiodarone use, we observed benefits of amiodarone treatment that are consistent with the findings of previous randomized studies and that lend support to current guideline recommendations.

Atrial Arrhythmias Following Cardiac Surgery

A number of small randomized controlled studies have shown reduction of atrial arrhythmias with the use of perioperative amiodarone. Of note, earlier randomized controlled studies differed substantially in the amiodarone protocols utilized. There have been 9 studies that initiated amiodarone

Table 3. Results of Instrumental Variable Analysis

Outcomes*	Marginal Patient	
	Risk Difference (95% CI)	*P* Value
Atrial arrhythmias	−0.11 (−0.19, −0.04)	0.002
Ventricular arrhythmias	−0.02 (−0.04, 0.003)	0.09
Readmission (all cause) within 1 mo	0.03 (−0.03, 0.10)	0.31
In-hospital mortality	−0.003 (−0.016, 0.011)	0.67
LOS, mean (SD), days, winsorized at 95th percentile	−0.70 (−1.39, −0.007)	0.048
Cost, mean (SD), US dollars, winsorized at 95th percentile	3650 (−2374, 9675)	0.23

LOS indicates length of stay.
*Adjusted for age, race, insurance payer, type of procedure, chronic lung disease, weight loss, tobacco abuse disorder, loop diuretic on or before surgery day, statins on or before surgery day, β-blockers on or before surgery day, hospital size, region, teaching status.

preoperatively (ranging from 1 to 14 days preoperatively) and 10 studies that initiated amiodarone either intraoperatively or exclusively in the postoperative phase (maximum of 28 days postoperatively).[15] Apart from the PAPABEAR trial (n=601), all these studies were small, enrolling between 70 and 315 patients. As a result, findings from meta-analyses are heavily weighted by the PAPABEAR trial, which utilized a preoperative amiodarone regimen (10 mg/kg daily beginning 6 days before and continuing for 6 days after surgery)[14]. Irrespective of the amiodarone regimen, all studies noted some degree of decrease in the incidence of atrial arrhythmias (absolute risk reductions ranging from 2% to 28%), but secondary outcomes of interest such as mortality, LOS, and readmissions varied (possibly due to low power for secondary outcomes).[15] In comparison, our observational study of a large, contemporary cohort, including 2195 patients who received perioperative amiodarone found an 11% risk reduction in atrial arrhythmias, which is comparable to the 13.4% absolute risk reduction noted in the PAPABEAR trial.[14]

Healthcare Utilization Outcomes Following Cardiac Surgery

Although amiodarone therapy was associated with lower incidence of atrial arrhythmias and modestly shorter hospital LOS, this did not translate into lower readmission rate or reduced hospital costs. At first glance this may seem surprising, but previous studies have found similar results. Historically, there have been conflicting data about the association of atrial arrhythmias with LOS.[10] Additionally, interventions (amiodarone, sotalol, procainamide, overdrive pacing) intended to reduce atrial arrhythmias have had inconsistent effects on LOS,[25] and a Cochrane review of 58 trials of varying interventions did not find a significant effect of these treatments on LOS.[11] Even when the focus is on amiodarone as the prophylactic strategy, the meta-analysis by Bagshaw et al[15] showed the mean hospital LOS to be only modestly improved (9.3±3.3 versus 9.9±3.5 days for the amiodarone and control groups, respectively) with a pooled difference in hospital LOS of 0.6 days (95% CI 0.4-0.8, $P<0.0001$), which is consistent with the −0.7-day difference we observed in our instrumental variable analysis. This −0.7-day difference will be of interest to cardiac surgical programs interested in safely reducing LOS.

Ventricular Arrhythmias Following Cardiac Surgery

In randomized control trials amiodarone use has been shown to reduce rates of ventricular arrhythmias, and the pooled odds ratio in the Bagshaw et al meta-analysis was 0.39 (95% CI 0.26-0.58, $P<0.0001$).[15] We observed a higher rate of ventricular arrhythmias associated with amiodarone use in the covariate-adjusted analysis (4.3% versus 2.8%, $P<0.001$) but no association in the instrumental variable analysis. We also noted greater odds of ventricular arrhythmia among those treated at hospitals with low perioperative amiodarone use as compared with hospitals with high perioperative amiodarone use. It is possible that administration of amiodarone at these low-use perioperative hospitals reflects the treatment of arrhythmias rather than prophylaxis for atrial arrhythmias. It is also worth highlighting that in the PAPABEAR trial, the overall rate of ventricular arrhythmias was only 1.5% (9/601) compared with 3.1% (394/12 758) in our cohort.[14] This may be the result of differences in the underlying risk profile of patients selected for clinical trials compared with those who receive treatment in routine care. Although we went to great lengths to exclude patients with an earlier history of atrial and ventricular arrhythmias from the study (using earlier diagnoses and medication therapy), and our results reflect adjustment for numerous potential confounders, it is also possible that the higher risk of arrhythmia we observed in the conventional multivariable models was the result of residual selection bias in which physicians preferentially prescribed amiodarone to patients who were at higher risk of ventricular arrhythmias. The fact that we did not observe an association between amiodarone and ventricular arrhythmias in the instrumental variable analysis, which was performed to address concern about residual confounding by unmeasured factors, is therefore reassuring.

Limitations

Although our study included a large number of patients from hundreds of US hospitals and used state-of-the-art causal inference methods to estimate the association between amiodarone use and outcomes, our results should be viewed in light of several limitations. First, because treatment assignment was not random, there is a risk of residual

selection bias that could be responsible for the association between receipt of perioperative amiodarone and the outcomes we studied. We undertook several strategies to minimize these threats and to test the robustness of our effect estimates. We employed careful inclusion and exclusion criteria to replicate those used on earlier clinical trials. In addition, we adjusted for numerous potential confounders, including patient demographics, other medical therapies such as β-blockers and statins, and important hospital characteristics. To address concerns about residual unmeasured confounding, we performed an instrumental variable analysis, a common econometric technique used in comparative effectiveness research.[26,27] Second, because we used a database based on hospital claims, we were unable to assess the use of amiodarone before hospital admission with regard to either dose or number of days of use before hospitalization. Third, this study is based on highly detailed billing data using *ICD-9* codes, not chart review. We did not have information about the circumstances or factors that led physicians to prescribe amiodarone, and it is possible that some of the patients received treatment with amiodarone for new arrhythmias rather than for prevention. Although we excluded patients with conditions that could provide an indication for chronic amiodarone other than with the intent of preventing atrial arrhythmias in the postoperative period, we had limited information about medication dosing or specific amiodarone protocols. Thus, we are unable to comment on the relative benefits and risks associated with the timing of amiodarone initiation. Fourth, we chose hospitals with high rates of perioperative amiodarone as our instrument for the instrumental variable analysis. However, it is important to note that even among these hospitals, only half of the patients actually received amiodarone. A final limitation is that we did not have access to long-term outcomes.

Conclusions

In patients undergoing elective cardiac surgery with no previous history or treatment of atrial or ventricular arrhythmias, perioperative amiodarone use was associated with a lower risk of atrial arrhythmias and shorter LOS. It was not associated with significant differences in mortality, hospital cost, or readmission. These findings are consistent with earlier randomized clinical trials and lend support to current guideline recommendations.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 diagnosis codes.

	ICD-9 codes	ICD-9 description
Hypotension	458.29	Other iatrogenic hypotension
		Post-operative hypotension
	458.9	Hypotension, unspecified
		Hypotension (arterial) NOS
Bradycardia	427.81	Sinoatrial node dysfunction
		Sinus bradycardia:
		persistent
		severe
		Syndrome:
		sick sinus
		tachycardia-bradycardia
		Excludes:
		sinus bradycardia NOS (427.89)
Heart block	426.0	Atrioventricular block, complete
		Third degree atrioventricular block
	426.1	Atrioventricular block, other and unspecified
	426.10	Atrioventricular block, unspecified
		Atrioventricular [AV] block (incomplete) (partial)
	426.11	First degree atrioventricular block
		Incomplete atrioventricular block, first degree
		Prolonged P-R interval NOS
	426.12	Mobitz (type) II atrioventricular block
		Incomplete atrioventricular block:
		Mobitz (type) II
		second degree, Mobitz (type) II
	426.13	Other second-degree atrioventricular block
		Incomplete atrioventricular block:
		Mobitz (type) I [Wenckebach's]
		second degree:
		NOS
		Mobitz (type) I
		with 2:1 atrioventricular response [block]
		Wenckebach's phenomenon
	426.2	Left bundle branch hemiblock
		Block:
		left anterior fascicular
		left posterior fascicular
	426.3	Other left bundle branch block
		Left bundle branch block:
		NOS
		anterior fascicular with posterior fascicular
		complete

		main stem
	426.4	Right bundle branch block
	426.5	Bundle branch block, other and unspecified
	426.6	Other heart block
		Intraventricular block:
		NOS
		diffuse
		myofibrillar
		Sinoatrial block
		Sinoauricular block
Supraventricular tachycardias	427.0	Paroxysmal supraventricular tachycardia
		Paroxysmal tachycardia:
		atrial [PAT]
		atrioventricular [AV]
		junctional
		nodal
Post-operative stroke	997.02	
Myocardial infarction	410.X1	initial episode of care
Stroke	433.01	OCL BSLR ART W INFRCT
	433.10	OCL CRTD ART WO INFRCT
	433.11	OCL CRTD ART W INFRCT
	433.21	OCL VRTB ART W INFRCT
	433.31	OCL MLT BI ART W INFRCT
	433.81	OCL SPCF ART W INFRCT
	433.91	OCL ART NOS W INFRCT
	434.00	CRBL THRMBS WO INFRCT
	434.01	CRBL THRMBS W INFRCT
	434.11	CRBL EMBLSM W INFRCT
	434.91	CRBL ART OCL NOS W INFRC
	436	CVA
	430	SUBARACHNOID HEMORRHAGE
	431	INTRACEREBRAL HEMORRHAGE
Ventricular arrhythmias		
	427.1	Paroxysmal ventricular tachycardia
		Ventricular tachycardia (paroxysmal)
	427.4	Ventricular fibrillation and flutter
	427.41	Ventricular fibrillation
	427.42	Ventricular flutter
Cardiogenic shock	785.50	Shock, unspecified
	785.51	Cardiogenic shock
Cardiac arrest	427.5	Cardiac arrest

	V12.53	Sudden cardiac arrest
	99.60	Cardiopulmonary resuscitation, not otherwise specified
	99.63	Closed chest cardiac massage
Pacemaker	37.70	Initial insertion of lead [electrode], not otherwise specified
	37.71	Initial insertion of transvenous lead [electrode] into ventricle
	37.72	Initial insertion of transvenous leads [electrodes] into atrium and ventricle
	37.73	Initial insertion of transvenous lead [electrode] into atrium
	37.78	Insertion of temporary transvenous pacemaker system
	37.80	Insertion of permanent pacemaker, initial or replacement, type of device not specified
	37.81	Initial insertion of single-chamber device, not specified as rate responsive
	37.82	Initial insertion of single-chamber device, rate responsive
	37.83	Initial insertion of dual-chamber device
	37.85	Replacement of any type pacemaker device with single-chamber device, not specified as rate responsive
	37.86	Replacement of any type of pacemaker device with single-chamber device, rate responsive
	37.87	Replacement of any type pacemaker device with dual-chamber device