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ORIGINAL PAPER

Short-course of ranolazine prevents postoperative atrial fibrillation following coronary artery bypass grafting and valve surgeries

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Abstract
Background Postoperative atrial fibrillation (POAF) is a common complication arising after coronary artery bypass grafting (CABG) and valve replacement or repair surgeries. POAF has been associated with increased mortality, morbidity and cost.
Methods The study was conducted to evaluate the incidence of POAF following CABG, valve or combination surgeries when perioperative ranolazine (1,000 mg preoperatively, then 1,000 mg twice daily for 7 days or until discharge) was or was not added to standard therapy.
Results A total of 205 patients were evaluated for POAF after CABG, valve or combination surgeries. POAF occurred less frequently in the ranolazine group compared with the non-ranolazine group in unmatched analysis (10.1 vs. 41.9 %, $p < 0.0001$). After adjusting for potential sources of bias through propensity-score matched-pair analysis and conditional logistic regression, ranolazine was an independent predictor of preventing POAF ($p < 0.0001$). There were no differences in bradycardia, new renal failure or neurological events between the two groups. Early, symptomatic hypotension occurred more frequently in the ranolazine group ($p = 0.0004$) although this difference did not persist after 72 h. No significant difference was found in the length of stay in the intensive care unit following cardiac surgery. While a significant difference was found in the hospital readmission rate for a cardiac cause within 30 days in the unmatched analysis ($p = 0.046$), this difference was nonexistent after matching ($p = 0.39$). No difference was found in 30-day cardiovascular mortality.
Conclusion Adding ranolazine to standard therapy was independently associated with a significant decrease in POAF development after CABG, valve or combination surgeries.

Keywords Ranolazine · Postoperative atrial fibrillation · Coronary artery bypass grafting · Heart valve surgery

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Introduction

Atrial fibrillation (AF) is a common adverse event after cardiac surgeries, particularly coronary artery bypass

grafting (CABG) and valve replacement or repair [1–11]. The incidence varies depending on the type of surgery in addition to preoperative, intraoperative and postoperative variables. When pharmacologic prophylactic agents are not utilized, postoperative atrial fibrillation (POAF) occurs in 16–70 % of cardiac surgeries [12–15]. Beta-blockers are recommended preferentially to other pharmacologic agents for the prevention of POAF [16]. Preoperative and postoperative amiodarone has demonstrated reduced rates for POAF; however, only preoperative amiodarone is recommended in patients at high risk of developing POAF [1, 6–10, 16, 17]. Other agents, such as ranolazine, have been evaluated for prevention of this complication, but there is no formal recommendation of its use in recent guidelines [11, 16–19].

Ranolazine is FDA approved for chronic angina and also possesses antiarrhythmic properties [11, 20–39, add other new trials here and maybe clean up a little bit]. Ranolazine suppresses arrhythmogenesis through early and delayed afterdepolarization suppression by selectively inhibiting atrial inward late I_{Na} currents and outward I_{Kr} currents to decrease AF development [20]. Ranolazine also prevents the propagation of atrial fibrillation through inhibition of outward I_{Kr} currents that induce significant post-repolarization refractoriness selectively in atrial tissues. In theory, ranolazine helps to prevent the atria from developing and sustaining AF [20]. These effects are more pronounced in failing hearts, where ranolazine significantly prolonged atrial post-repolarization refractoriness and depressed sodium channel current-dependent parameters. Ranolazine did not promote ventricular arrhythmias or significantly alter conduction parameters in the ventricles [31, 32]. Among patients who had recently experienced a non-ST elevation acute coronary syndrome and could be at risk for developing POAF, ranolazine reduced the incidence of paroxysmal AF and overall AF burden [23, 33]. Ranolazine may reduce AF recurrence following electrical cardioversion [34]. Ranolazine's lack of proarrhythmia occurrences and suppression of ventricular arrhythmias suggest its safety in these patient populations compared to other classes of antiarrhythmic agents [40]. The purpose of this study was to evaluate the incidence of POAF following CABG, valve or combination surgeries when perioperative ranolazine was or was not added to standard therapy.

Materials and methods

A single-center, IRB-approved, retrospective cohort study of all patients admitted to an academic medical center from February 1, 2012 to May 7, 2014 for a CABG and/or valve surgery were considered for inclusion in the study. February 1, 2012 was chosen because a new electronic health record was instituted then. Patients were excluded if they were in atrial fibrillation at the time of cardiac surgery, were taking an antiarrhythmic medication other than a beta-blocker, had a QT_C interval >500 ms before cardiac surgery, expired during surgery or underwent a separate cardiac surgery. One of three board-certified cardiothoracic surgeons performed standard, open-heart surgeries via midline sternotomy using the same intraoperative techniques, including cardiopulmonary bypass, during the entire study period. Cold blood cardioplegia solution was administered antegrade and retrograde for myocardial protection. Surgical techniques were unchanged during the study period.

Evaluated patients could have received beta-blocker therapy as part of the standard perioperative care for their cardiothoracic surgery. Patients were then stratified on whether they received perioperative ranolazine. The medical center began using perioperative ranolazine on July 1, 2013, and all patients received the therapy unless contraindications to therapy existed. Patients in the ranolazine group received a preoperative dose of 1,000 mg on the morning of surgery and continued therapy of 1,000 mg every 12 h starting the evening after surgery. Therapy was continued for a total of 7 days after surgery, until hospital discharge or ranolazine was discontinued for any reason. Patients in the ranolazine group had to receive at least two doses of ranolazine for study enrollment.

The primary end point was the difference in rates of POAF within 7 days following CABG, valve or combination surgery. Each patient was attached to continuous electrocardiographic monitoring throughout the hospital stay. POAF was defined as any apparent AF that was documented in the patient's electronic medical record by a member of the healthcare team. Secondary end points included the incidence of other adverse events, intensive care unit (ICU) length of stay (LOS) following cardiac surgery, 30-day readmission for a cardiac cause and 30-day mortality from a cardiac cause. ICU LOS following cardiac surgery was defined as the number of days from the day of cardiac surgery to discharge from the cardiovascular ICU.

Medical and laboratory data were extracted from electronic medical records. Data collected included baseline clinical and demographic characteristics, including age, gender, ethnicity, comorbidities and preoperative medications. The operative procedure and postoperative clinical course were also evaluated, including postoperative medications, adverse events, ICU LOS following surgery, 30-day readmission for a cardiac cause and 30-day mortality from a cardiac cause. Cardiac causes included chest pain, arrhythmia and redo or emergent cardiac surgery. Other safety parameters evaluated included bradycardia, new renal failure, stroke/transient ischemic attack and

symptomatic hypotension. Symptomatic hypotension was defined as a patient requiring vasopressor therapy following cardiac surgery that was documented in the electronic medical record.

In the full sample, comparisons for demographic, baseline characteristics, times to POAF development and LOS between the two groups were assessed using the nonparametric Wilcoxon Rank-Sum test for continuous data. Categorical data, including the incidence of POAF, were analyzed using the Fisher's exact tests. The overall comparison of POAF rates adjusted for the surgery type (CABG, valve and combination) was assessed using the Cochran–Mantel–Haenszel test for stratified data. A p value <0.05 was considered significant. An a priori sample size calculation estimated that 196 patients would be needed to achieve statistical power of 80 % based on estimates of a 35 % rate of POAF in the non-ranolazine group and 17.5 % in the ranolazine group [1–11, 18]. Kaplan–Meier curves were used to display the cumulative probability of an individual remaining free of POAF at any time within the first 7 days in the two groups. Patients who did not develop POAF in the first 7 days were censored at day 7. The nonparametric log-rank test was used to investigate if there were differences in POAF-free survival time between the ranolazine and non-ranolazine groups. A coinvestigator separately extracted and reviewed 10 % of the data collected for interrater reliability, which resulted in 100 % agreement.

Because the use of ranolazine was not randomly assigned due to the retrospective nature of the study, these two groups were subject to potential bias. Propensity scores were estimated to control for this potential bias and balance observed covariates between the two groups. Using a logistic regression model, the predicted probability of receiving ranolazine (i.e., the propensity score) was estimated for each individual in the data set [41]. Variables entered into the logistic regression model were age, ethnicity, insurance, gender, admission medications (beta-blocker, ACE inhibitor, aspirin, statin), past medical history (atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, previous myocardial infarction and previous cardiac surgery) and surgery type. Patients in the ranolazine group were matched to those in the non-ranolazine group who had comparable propensity scores. The matching process was completed using a SAS® macro that uses a greedy matching algorithm based on 5–1 digit matching [41, 42]. Once a match was made, the individuals were not resampled. For the matched analysis, differences between matched pairs were assessed using the nonparametric signed-rank test for continuous data and the McNemar test for binary data or the Bowker's test of symmetry for categorical data with more than two levels.

Conditional logistic regression analysis was used on the matched data to determine whether the development of POAF was associated with the treatment, adjusting for baseline variables such as type of cardiac surgery, preoperative medications (ACE inhibitor, aspirin, beta-blocker and statin) and past medical history (atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, previous myocardial infarction and previous cardiac surgery). Variable selection was used to determine the best predictive model among the baseline predictors. This approach uses the likelihood score statistic and fits all one through six-variable models. Although variables may be correlated, reviewing the best models in this manner allowed for determination of multicollinearity. All statistical analyses were performed using the SAS®, version 9.3 (SAS, Cary, North Carolina).

Results

Of the 305 patients screened for inclusion, a total of 205 patients who received a CABG, valve or combination surgery were included in the analysis of all efficacy and safety endpoints. Figure 1 lists the reasons for exclusion. Baseline demographic and patient characteristics were similar between groups [Table 1]. The majority of patients in each group underwent a CABG surgery; although, greater than 30 % in each group received a valve or combination surgery.

In the unmatched comparison, the majority of patients in the ranolazine and non-ranolazine groups received preoperative beta-blocker therapy (69.6 vs. 78.7 %, $p = 0.17$), respectively. However, the use of postoperative beta-blockers increased significantly in the ranolazine group compared to the non-ranolazine group (24.6 vs. 5.9 %, $p < 0.0002$). The average number of ranolazine doses patients received was 10 (interquartile range 8–13). Thirteen percent of patients in the ranolazine group did not receive the 1,000 mg preoperative dose of ranolazine, and more patients in the ranolazine group were discharged on a statin.

Patients in the ranolazine group were less likely to develop POAF within 7 days of cardiac surgery (10.1 vs. 41.9 %, odds ratio [OR] 0.157, 95 % confidence interval [CI] 0.067–0.367, $p < 0.0001$). Overall, 57 pairs (82.6 % of ranolazine group) of patients were matched on propensity scores that were estimated using age, gender, ethnicity, comorbidities, surgery type, urgency of surgery, preoperative medications and type of insurance. After matching, no significant differences were noted between the two groups with respect to the baseline covariates used to calculate the propensity scores. Baseline characteristics for the propensity-score matched pairs are shown in Table 1. In

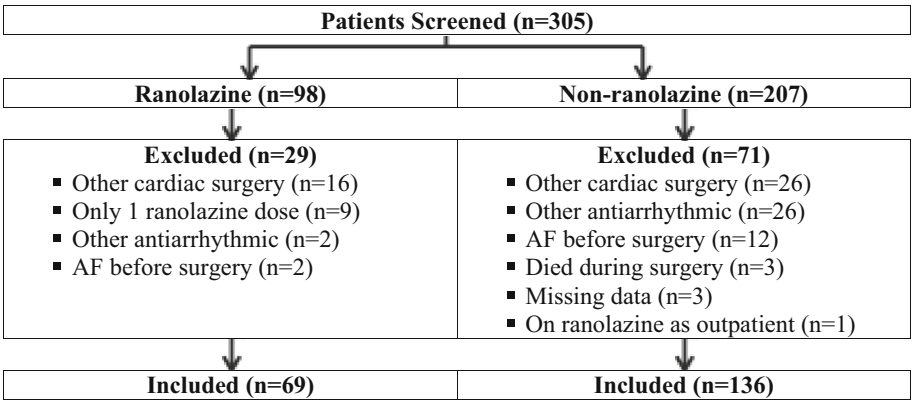

Fig. 1 In total, 305 patients were screened for inclusion. After 100 patients were excluded, 205 patients were included in the unmatched analysis. Study design

Table 1 Demographic and patient characteristics

Characteristic	Unmatched data			Matched-pair analysis		
	Ranolazine ($n = 69$)	Non-ranolazine ($n = 136$)	*P* value	Ranolazine ($n = 57$)	Non-ranolazine ($n = 57$)	*P* value
Age (years)[f]	59.7 ± 10.8	62.2 ± 11.8	0.078[a]	60.3 ± 11.1	59.6 ± 11.5	0.711[c]
Male gender	47 (68.1)	77 (56.6)	0.131[b]	38 (66.7)	38 (66.7)	1[d]
Race/ethnicity			0.129[b]			0.689[e]
African						
American	27 (39.1)	31 (22.8)		19 (33.3)	24 (42.1)	
Asian	1 (1.4)	2 (1.5)		0	1 (1.8)	
Caucasian	37 (53.6)	95 (69.9)		35 (61.4)	27 (47.4)	
Hispanic	3 (4.3)	5 (3.7)		2 (3.5)	4 (7)	
Other	1 (1.4)	3 (2.2)		1 (1.8)	1 (1.8)	
Past medical history						
AF	1 (1.4)	4 (2.9)	0.665[b]	1 (1.8)	1 (1.8)	1[d]
COPD	8 (11.6)	20 (14.7)	0.668[b]	7 (12.3)	8 (14)	1[d]
DM	26 (37.7)	56 (41.2)	0.653[b]	20 (35.1)	20 (35.1)	1[d]
HF	26 (37.7)	41 (30.1)	0.345[b]	18 (31.6)	19 (33.3)	1[d]
HTN	54 (78.3)	113 (83.1)	0.448[b]	45 (78.9)	48 (84.2)	0.629[d]
MI	22 (31.9)	56 (41.2)	0.225[b]	18 (31.6)	19 (33.3)	1[d]
Previous cardiac surgery	12 (17.4)	45 (33.1)	0.021[b]	12 (21.1)	15 (26.3)	0.607[d]
Surgery type			0.525[b]			0.723[e]
CABG	43 (62.3)	90 (66.2)		36 (63.2)	34 (59.6)	
Valve	22 (31.9)	34 (25)		18 (31.6)	17 (29.8)	
Combo	4 (5.8)	12 (8.8)		3 (5.3)	6 (10.5)	
Preoperative						
ACEI	28 (40.6)	67 (49.3)	0.300[b]	26 (45.6)	28 (49.1)	0.851[d]
ASA	59 (85.5)	113 (83.1)	0.694[b]	49 (86)	48 (84.2)	1[d]
BB	48 (69.6)	107 (78.7)	0.170[b]	41 (71.9)	42 (73.7)	1[d]
Statin	49 (71)	107 (78.7)	0.230[b]	42 (73.7)	42 (73.7)	1[d]
Postoperative						
ACEI	42 (60.9)	77 (56.6)	0.66[b]	35 (61.4)	30 (52.6)	0.405 [d]
ASA	67 (97.1)	128 (94.1)	0.50[b]	55 (96.5)	55 (96.5)	1[d]
BB	65 (94.2)	115 (84.6)	0.07[b]	53 (93)	48 (84.2)	0.227 [d]
Statin	66 (95.7)	116 (85.3)	0.03[b]	54 (94.7)	47 (82.5)	0.065[d]

Data are number (%), unless otherwise indicated

ACEI angiotensin II-converting enzyme inhibitor, *statin* HMG-CoA reductase inhibitor, *AF* atrial fibrillation, *COPD* chronic obstructive pulmonary disease, *CABG* coronary artery bypass grafting

[a] Wilcoxon rank-sum test

[b] Fisher's exact test

[c] Signed rank test

[d] McNemar's test

[e] Bowker's test of symmetry

[f] mean ± standard deviation

this analysis, the incidence of POAF was significantly higher in patients who did not receive ranolazine (10.5 vs. 45.6 %, OR 0.09, 95 % CI 0.021–0.387, $p < 0.0001$). The incidence of POAF for each type of surgery was determined for ranolazine and non-ranolazine groups respectively: CABG (14 vs. 36.7 %), valve (4.5 vs. 47.1 %) and combination (0 vs. 66.7 %). The probability of remaining POAF free at day 7 was 90 % (95 % CI, 80–95 %) in the ranolazine group and 58 % (95 % CI, 49–66 %) in the non-ranolazine group ($p < 0.0001$) [Fig. 2].

Additional baseline variables were assessed for the matched-pair analysis, including past medical history (AF, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, previous myocardial infarction and previous cardiac surgery), age, gender, ethnicity, nature of surgery (elective, urgent or emergent) and ranolazine use. The omission of perioperative prophylaxis with ranolazine was determined to be an independent predictor of POAF in the matched-pair sample. Using best subset selection, the "best" model selected was the model including only ranolazine use ($p < 0.0001$) as a significant predictor.

There were no differences in bradycardia, new renal failure or stroke/transient ischemic attack between the two groups. Symptomatic hypotension within the first 72 h occurred more frequently in the ranolazine group (52.2 vs. 35.3 %, $p = 0.0004$). However, this difference did not persist during the 72 h to 7-day time frame (15.9 vs. 12.5 %, $p = 0.38$). Ranolazine was discontinued in 1 patient for symptomatic hypotension. No other patients discontinued ranolazine for any potential adverse effect.

There was no difference in the ICU LOS following cardiac surgery between groups in unmatched or matched analysis (6 vs. 6 days). While significantly fewer patients in the ranolazine group were readmitted to the hospital for a cardiac cause within 30 days (10.2 vs. 23.5 %, $p = 0.046$) in the unmatched analysis, this difference was not seen in the matched analysis (10.4 vs. 25.5 %, $p = 0.39$). There was no difference in 30-day cardiovascular mortality in the unmatched or matched analysis.

Discussion

This is the first study to evaluate the role of ranolazine in patients who underwent CABG, valve or combination surgeries. In this study, greater than 30 % of patients in unmatched and matched analyses underwent valve or combination CABG and valve surgeries. In matched analysis, a short-course of ranolazine was associated with a 35.1 % absolute reduction in POAF following CABG and valve surgeries.

Lack of perioperative ranolazine therapy was found to be an independent predictor for the development of POAF. Propensity-score matching adjusted for baseline characteristics to control for potentially confounding variables. The odd's ratios for the unmatched (OR 0.157, 95 % CI 0.067–0.367) and matched analyses (OR 0.09, 95 % CI 0.021–0.387) were similar, which confirmed the finding that ranolazine therapy was associated with a decreased incidence of POAF.

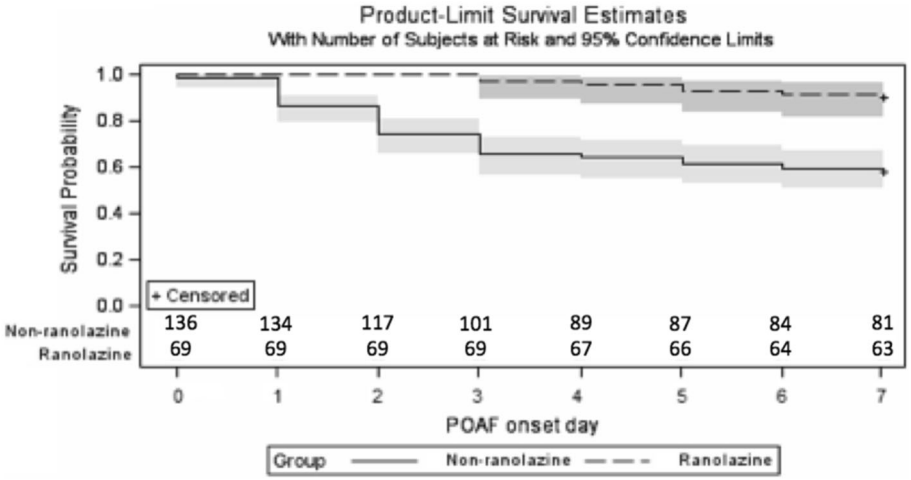

Fig. 2 Kaplan–Meier survival curves of POAF-free survival in relation to use of perioperative ranolazine, with follow-up duration of 7 days after CABG, valve and combination surgeries (total $n = 205$). Censored values (*plus*) indicate the patients who were POAF free at postoperative day 7, but were still hospitalized. The *dashed line* represented patients who received perioperative ranolazine, while the *solid line* represents patients in the non-ranolazine group. Perioperative ranolazine use was associated with a significant POAF-free survival difference. The *p* value was determined using a log-rank test. POAF-free survival

Numerous triggers have been described that may affect the incidence and degree of POAF, including increased sympathetic outflow, myocardial damage, hypoxia, electrolyte abnormalities, inflammation and oxidative stress [43, 44]. Through a variety of proposed mechanisms, ranolazine helps to reduce early after depolarizations that develop when the Na^+/Ca^{2+} exchanger is affected. This inhibition of the late phase of inward sodium current and the resultant decrease in intracellular calcium leads to a prolonged action potential duration, which makes developing an atrial arrhythmia more difficult [20–23, 32, 35, 36]. The effects of ranolazine are more pronounced in atrial tissues, which led to its study in treatment and suppression of atrial fibrillation following cardiac surgeries [21–23, 32, 35, 36].

Ranolazine has been shown to reduce the incidence of POAF following CABG surgeries. Tagarakis and colleagues demonstrated that patients who received ranolazine (375 mg twice daily for 3 days prior to CABG through discharge) had a decreased incidence of POAF (8.8 vs. 30.8 %, $p < 0.001$) [18]. In addition, Miles and colleagues compared patients receiving perioperative ranolazine (1,500 mg preoperatively followed by 1,000 mg twice daily for 10–14 days) with those receiving amiodarone (400 mg preoperatively followed by 200 mg twice daily for 10–14 days). Patients who received ranolazine had a lower incidence of POAF when compared to patients who received amiodarone (17 vs. 26.5 %, $p = 0.035$) [11]. In comparison to the ranolazine regimen duration in the previous trials, patients in this study received up to 7 days of ranolazine, which mirrors the timeframe for potentially developing POAF [11–13, 18]. Only one patient (in the non-ranolazine group) was identified during post hoc analysis to have developed AF after postoperative day 7; therefore, a 7-day duration of therapy may be more appropriate than the previously studied 10- to 14-day duration.

Surgeries with a valvular intervention have a greater incidence of POAF development compared to non-valvular surgeries [13, 14]. This study included patients who underwent valve replacement or repair surgeries and combination CABG and valve surgeries. In the ranolazine group, 4.5 % patients undergoing a valve surgery developed POAF versus 47.1 % in the non-ranolazine group. Similarly, no patients in the combination CABG and valve surgery group developed POAF versus 66.7 % in the non-ranolazine group. In total, greater than 30 % of the enrolled patients underwent valve replacement or repair surgeries and combination CABG and valve surgeries.

Both groups experienced minimal adverse effects. Symptomatic hypotension in the first 72 h occurred more frequently in the ranolazine group. Due to the production of oxygen-free radicals and intracellular calcium overload during coronary artery reperfusion, the myocardium may be stunned and recovering following cardiac surgery [45]. However, ranolazine's mechanisms of action do not suggest it should greatly enhance these effects [21–23, 30]. When used as an anti-anginal, ranolazine has minimal effects on blood pressure and heart rate, with incidence being $\leq$4 % in patients [30]. Because an appreciable rate of symptomatic hypotension has not been reported in this patient population previously, further studies assessing the incidence of early, symptomatic hypotension should be conducted. Because all patients received ranolazine after July 1, 2013, strategies for maintaining optimal hemodynamic parameters after cardiac surgery may have changed compared to the first portion of the study time frame. There was a significant increase in beta-blocker therapy from before to after the surgeries in the ranolazine group compared to the control group. In addition, a higher percentage of patients were on an ACE inhibitor in the postoperative period compared to the preoperative period. The greater use of hemodynamically active medications may have increased the incidence of hypotension in the ranolazine group. There was no difference in late hypotension (>72 h after surgery) between the two groups.

During this study, no episodes of ventricular arrhythmias were recorded in either group. Although early after depolarizations have been reported to lead to torsades de pointes with other agents such as sotalol, ranolazine has not been associated with this proarrhythmic effect [32, 35]. Conversely, ranolazine may possess antiarrhythmic effects in ventricular arrhythmias [37, 38]. Ranolazine reduced ventricular tachycardia burden and implantable cardiac defibrillator shocks in patients who were otherwise refractory to medical management with amiodarone or sotalol plus mexiletine or lidocaine [37]. Ranolazine reduced premature ventricular complex burden and eliminated ventricular tachycardia in a case series of eight patients with persistent symptoms from ventricular dysfunction [38].

Ranolazine was not combined with other classes of antiarrhythmic medications beside beta-blockers in this trial. However, in another trial ranolazine alongside amiodarone did show a trend toward increasing the rate of successful conversion within 24 h of recent-onset AF versus amiodarone alone (88 vs. 65 %, $p = 0.056$) [20]. There were no proarrhythmic events in either group. In a separate trial, ranolazine in combination with dronedarone reduced AF burden in patients with paroxysmal AF. The potential synergistic mechanisms of lower dosed dronedarone and ranolazine blocking active and inactive sodium channels may have provided this benefit [39].

This study does have limitations. Accurate documentation of data collected retrospectively and in a nonblinded manner from the electronic medical record was assumed.

Propensity-score matching balanced baseline covariates effectively to match patients; however, unobserved and unaccounted for covariates could have confounded the data despite matching. In particular, intraoperative variables were not evaluated. These unobserved and unaccounted for variables potentially could affect the likelihood of a patient developing POAF [13, 14]. In addition, the time of medication initiation and titration schemes following cardiac surgery were not evaluated. It is common practice to initiate hemodynamically active medications as soon as parameters allow; nevertheless, consideration for potentially different uses of these medications between the two groups cannot be excluded. Although patients in each group may have been stable enough to receive care in a progressive care unit rather than the ICU after initial recovery from the surgery, our patients routinely remained in the cardiovascular ICU until hospital discharge. Because there was not a reliable method for determining retrospectively when each patient progressed from needing an ICU level of care, this may have artificially increased the ICU LOS in both groups.

In conclusion, the present study suggests a decrease in POAF development following CABG, valve replacement and repair, and combination surgeries with the addition of perioperative ranolazine to standard therapy. These data need to be confirmed in prospective, randomized controlled trials. At this time, a short-course of ranolazine may be considered in addition to standard perioperative care in patients undergoing cardiac surgery, including CABG, valve or combination surgeries.

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Conflict of interest None.

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