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#### ORIGINAL ARTICLE

CARDIAC SURGERY WILEY

# Mid-term outcomes of concomitant Cox-Maze IV: Results from a multicenter prospective registry

Marc Gerdisch  $MD^1$  | Eric Lehr MD,  $PhD^2$  | Gansevoort Dunnington  $MD^3$  | John Johnkoski  $MD^4$  | Andrew Barksdale  $MD^1$  | Manesh Parikshak  $MD^1$  | Patrick Ryan  $MD^2$  | Samuel Youssef  $MD^2$  | Robert Fletcher  $MA^2$  | Glenn Barnhart  $MD^2$ 

<sup>1</sup>Franciscan Health Indianapolis, Indianapolis, Indiana, USA

<sup>2</sup>Swedish Medical Center, Seattle, Washington, USA

<sup>3</sup>Saint Helena Hospital, St Helena, California, USA

<sup>4</sup>Aspirus Wausau Hospital, Wausau, Wisconsin, USA

#### Correspondence

Marc Gerdisch, MD, Department of Cardiothoracic Surgery, Franciscan Health Indianapolis, 8051 South Emerson Ave, Suite 365, Indianapolis, IN 46237, USA. Email: mgerdisch@openheart.net

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#### Abstract

**Background:** Benefits of concomitant atrial fibrillation (AF) surgical treatment are well established. Cardiac societies support treating AF during cardiac surgery with a class I recommendation. Despite these guidelines, adoption has been inconsistent. We report results of routine performance of concomitant Cox-Maze IV (CMIV) from participating centers using a standardized, prospective registry.

**Methods:** Nine surgeons at four cardiac surgery programs enrolled 807 patients undergoing concomitant CMIV surgery over 12 years. Lesions were created using bipolar radiofrequency clamps and cryoablation probes. Follow-up occurred at 3- and 6-months, then annually for 3 years. Freedom from AF was defined as no episode >30 s of atrial arrhythmia.

**Results:** Sixty-four percent of patients were male, mean age 69 years, mean left atrial size 4.6 cm, mean preoperative AF duration 4.0 years, mean EuroSCORE 6.4, and mean CHADS<sub>2</sub> score 3.1. Thirty-day postoperative mortality and neurologic event rates were 3.3% and 1.3%, respectively. New pacemaker implant rate was 6.3%. Freedom from AF rates at 1- and 3-years stratified by preoperative AF type were: paroxysmal 94.6% and 87.5%, persistent 82.1% and 81.9%, and longstanding persistent 84.1% and 78.1%. At 3-year follow up, 84% of patients were off antiarrhythmic drugs and 74% of sinus rhythm patients were off oral anticoagulants. **Conclusions:** Routine CMIV is safe and effective. Acceptable outcomes can be achieved across multiple centers and multiple operators even in a moderate risk patient population undergoing more complex procedures. Surgeons and institutions should be encouraged by all cardiac societies to adopt the CMIV procedure to maximize patient benefit.

#### KEYWORDS

cardiovascular research, clinical review

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#### 1 | INTRODUCTION

Atrial Fibrillation (AF) remains a growing health care concern both in the United States and globally.<sup>1</sup> Estimated lifetime risk of developing AF for individuals 40–55 years of age is 22%–26%<sup>2,3</sup> and increases to as high as 48% for those with risk factors.<sup>4</sup> Several studies have documented increasing incidence, and by 2050 there will be an estimated 6–12 million cases in the United States.<sup>5</sup> In addition to posing an ongoing individual health risk, it will increase financial burden on an ever-struggling health care system.<sup>6,7</sup>

Multiple unfavorable consequences are associated with AF patients who undergo cardiac surgery including increased incidence of postoperative delirium, stroke, low cardiac output, and mortality.<sup>8</sup> Furthermore, patients who undergo a successful concomitant surgical ablation (SA) at the time of their cardiac surgery will have improved outcomes and left ventricular function with a decrease in perioperative morbidity and mortality.9-11 Ad et al.12 examined outcomes of concomitant surgical AF ablation and demonstrated a decreased incidence of perioperative morbidity (Class II, Level A), a decrease in long-term stroke and transient ischemic attack (TIA), an improvement in short term (Class I, Level A) and long-term survival (Class IIa, Level A), and improved quality of life (Class IIa, Level B). The Society of Thoracic Surgeons and the American Association of Thoracic Surgeons both consider concomitant SA a Class I, Level A indication when performing mitral valve surgery (MVrepair/replace), and a Class I level B indication when performing coronary artery bypass surgery (CABG), aortic valve surgery (AVR), and combined CABG/AVR.<sup>13</sup> The American Heart Association and American College of Cardiology,<sup>14</sup> Heart Rhythm Cardiac Arrythmia Society, Asia Pacific Heart Rhythm Society and SOLAECE Latin American Society of Electrophysiology, and Cardiac Stimulation have all recommended performing SA as a Level I recommendation. The Cox Maze (CM) lesion set has always provided the most reliable means of treating concomitant AF. Damiano et al. developed the Cox-Maze IV (CMIV) to meet the requirements of a complete transmural CM lesion set in a standardized and repeatable procedure.<sup>15</sup> When the bipolar clamp used to perform most of the CMIV received FDA clearance specifically for the treatment of concomitant persistent AF,<sup>16</sup> the CMIV became the most taught and therefore applied method of performing the CM.<sup>17-21</sup> Early concerns regarding the possibility of an increase in operative morbidity or mortality with the addition of the CMIV have been answered by multiple studies.<sup>13</sup>

Even with these societal endorsements and strong evidence, McCarthy et al.<sup>22</sup> found utilization of concomitant SA of any type remains low. Of 79,134 Medicare patients undergoing cardiac surgery, 28% had a prior AF diagnosis, but only 22% of AF patients received a concomitant ablation. Key study findings included that MV patients have a threefold higher treatment rate than other cardiac surgery procedures. Women and patients with diabetes were less likely to receive concomitant treatment than matched patients with similar procedures and comorbidities. Thus, it appears there is significant variability in concomitant treatment; perhaps due to perceived risks associated with some primary cardiac operations and patient subgroups.

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The authors hypothesize that concomitant CMIV can be performed safely and effectively in patients with AF in a real world, nonacademic setting. To address concerns of increased operative morbidity and mortality that continue to influence decision-making and to evaluate sustained efficacy of concomitant CMIV over an intermediate follow-up period, the results of a prospective registry at four centers were analyzed.

#### 2 | MATERIALS AND METHODS

#### 2.1 | Study design

Eight hundred and seven patients were enrolled in the registry from 2006 to 2019 at four centers by nine surgeons. Only patients who received ablation are enrolled in the registry, and only patients who received CMIV were identified for this analysis.

#### 2.2 | Data collection

A standardized data collection form was utilized to capture pre-, peri- and postoperative data for entry into a secure, online database. All patients had documented preoperative AF by electrocardiogram or pacemaker.

#### 2.3 | Follow-up

Follow-up was performed at 3–6 months, then annually for up to 3 years. Monitoring type was individualized by center and included electrocardiogram, event monitors, implantable loop recorders (ILRs), and permanent pacemakers. Freedom from AF, atrial flutter, or atrial tachycardia was defined as <30 s on all monitoring types except for ILRs, which were set at their 2 min minimum detection threshold. Only available data at each visit was used for assessment of AF recurrence. Missing rhythm assessment data were not interpolated. Antiarrhythmia and anticoagulation management was performed by each center's protocols.

#### 2.4 | Surgical technique

All surgeons performed the standard CMIV procedure as previously described using a complete bi-atrial lesion set.<sup>15</sup> Left sided lesion sequence varied depending upon surgeon and procedure. Right atrial lesions were performed before, during, or after the aortic cross clamp depending upon surgeon preference or primary operation type. The only significant variation by some surgeons from the original CMIV was to move the 10 o'clock tricuspid annular lesion to the free wall of the right atrial appendage near the atrioventricular (AV) groove.<sup>23</sup> Lesions were created with bipolar radiofrequency and a cryoablation probe depending upon the lesion's location. Pulmonary vein (PV) entrance and exit block testing were performed by some surgeons but not all. All surgeons performed repeat, overlapping clamp

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ablations for all radiofrequency lesions. At least six repeat ablations were performed by each surgeon on each PV cuff to ensure complete bilateral PV isolation. Cryothermal lesions consisted of at least 2 min freeze applications at each site.

#### 2.5 | Statistics

Rate comparisons were done using  $\chi^2$  tests. Mean values were compared using analysis of variance tests. Significant trends in rates were determined by Mantel–Haenszel  $\chi^2$  test. Confidence level of all tests were performed at the 95% level. Statistical analysis system software was used for descriptive statistics and test *p* values.

#### 3 | RESULTS

#### 3.1 | Baseline patient characteristics

A total of 807 patients were enrolled in the registry. Preoperative patient characteristics are summarized in Supporting Information: Table 1. Numerous variables were statistically significant between different AF types, likely reflecting the degree of illness of each AF type cohort and AF duration. Mean age of the patients was 69 years (range 27–92), and 64% were male. Preoperative AF types were 33% paroxysmal, 32% persistent, and 35% long-standing persistent. Mean left atrial size was 4.6 cm and mean preoperative AF duration was 4.0 years. Mean CHADS<sub>2</sub> score was 3.1 and mean EuroSCORE was 6.4. Seventy-one (8.8%) patients had permanent pacemakers preoperatively.

#### 3.2 | Patient selection

Patient selection was surgeon specific, therefore not all patients with AF needing cardiac surgery received a concomitant CMIV. In general, at all participating centers there was a presumption that patients with AF undergoing cardiac surgery were considered candidates for a concomitant CMIV unless contraindicated. Absolute contraindications included left atrial size >8 cm and calcified left atrium. Relative contraindications might be exceptional frailty and acuity.

#### 3.3 | Surgical technique

All patients in this series received a bi-atrial lesion set. Additionally, most patients had a coronary sinus lesion placed with the use of a Cryoprobe.

#### 3.4 | Procedural outcomes

Primary cardiac procedures included CABG in 118 patients (15%), AVR in 75 patients (9%), MVrepair/replace in 175 patients (22%), CABG/valve/multivalve in 333 patients (42%), and other procedures (primarily atrial septal defect closures, atrial mass, and thrombus removals) in 98 patients (12%).

There were eight hospital deaths (Table 1). No patient died from a technicalerror due to addition of CMIV. Of the 799 patients surviving to hospital discharge, 30-day mortality (including hospital deaths) was 3.3% (26 patients). Thirty-day neurologic event rate was 1.3% (10 patients): 4 strokes and 6 TIAs. New permanent pacemaker implant rate was 6.3% (50 patients). Postoperative AF occurred in 36% (288 patients).

Left atrial appendage (LAA) closure was performed in 778 patients including 639 AtriClip devices, 46 cut-and-oversew procedures, 9 external oversew procedures, 15 stapler closures, and 69 endocardial oversew procedures. Eight patients previously had LAA closure. Data on LAA closure was not available in the registry for 13 patients. For the study period, through entire follow-up for all patients (mean follow-up:  $683 \pm 434$  days), the neurologic event rate was 5.3% (37/703). Fifteen patients had a stroke (2.1%) and 22 (3.1%) had TIA documented in the registry.

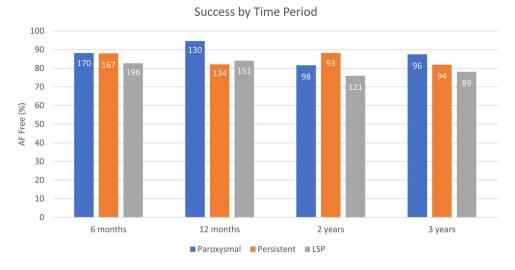
#### 3.5 | Efficacy

There were 2113 patient visits with a mean time to last follow-up visit of  $714 \pm 421$  days for patients who had follow-up after a 90-day blanking period. Overall freedom from AF was 88.3% at 1 year and 84.7% at 3 years. Freedom from AF at 1 and 3 years by preoperative AF type was as follows: paroxysmal 94.6% and 87.5%, persistent 82.1% and 81.9%, and longstanding persistent 84.1% and 78.1% (Figure 1).

TABLE 1 Causes of in-hospital deaths

Patient #	Operation performed	Cause of death
#1	MVR/AVR/Maze	Profound vasoplegia and cardiogenic shock
#2	CABG/Maze	Cardiogenic shock
#3	MVR/TVR/Maze	Multisystem failure 3 weeks postop
#4	MVR/TVR/Maze	Cardiogenic shock on ECMO
#5	MVR/AVR/ TVR/Maze	Right heart failure, hemorrhagic shock
#6	CABG/TV/Maze	Severe preop LV dysfunction; died 1 day postop on IABP
#7	CABG/AVR/Maze	Severe preop LV dysfunction; died PEA arrest postop day 10.
#8	ARR/TVR/Maze	Multisystem failure

Abbreviations: ARR, aortic root replacement; AVR, aortic valve surgery; CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricular; MVR: mitral valve repair; PEA, pulseless electrical activity; TVR, tricuspid valve repair.



**FIGURE 1** Freedom from atrial fibrillation (AF) stratified by preoperative AF type following concomitant Cox-Maze IV surgical ablation. Number of patients is indicated on each bar. LSP, longstanding persistent.

Rhythm monitoring type varied by institution but tended toward longer term methods. Eighteen percent of assessments used electrocardiogram, 50% used 2- to 30-day wearable devices including Holter monitoring and wearable patch, and 32% used continuous recording with ILRs or permanent pacemakers.

When analyzed by monitoring type, freedom from AF ranged between 80% and 90% and was sustained throughout the study period with the only exception being patients with pacemakers, for whom freedom from AF was moderately lower (70%–80%) but not statistically significant (Figure 2).

Cumulative freedom from AF is shown in Figure 3. At 3-year follow-up, 84% of the patients were off anticoagulants. Averaged across all time periods studied, 74% of patients were off antiar-rhythmic drugs (AADs). At last follow-up with available rhythm assessment (mean follow-up  $682 \pm 421$  days), 81% of patients with follow-up post-blanking period were free from AF, and 73% were free from AF and off Class I/III AADs.

#### 4 | DISCUSSION

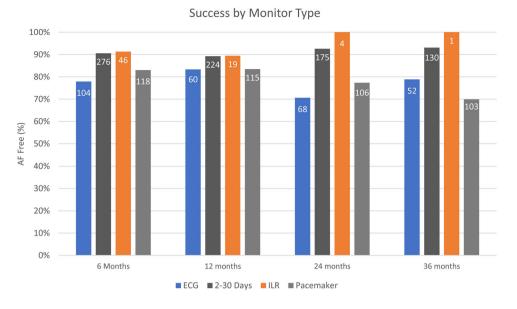
Many surgeons remain apprehensive about routine performance of CMIV despite compelling contemporary literature and society guidelines. Reasons center around perceived lack of durable efficacy and added complexity of the operation prolonging cross-clamp and cardiopulmonary bypass times. An international surgeon survey on concomitant treatment practices and perceptions reported 94% of surgeons surveyed believed patients might benefit from the procedure, but only 53% felt that treated patients would be AF free after 1 year.<sup>24</sup> The respondents thought concomitant treatment added an additional 16% risk of major complications.

The purpose of our study was to evaluate routine CMIV performed in several nonacademic centers by multiple surgeons in a moderately complex set of patients.

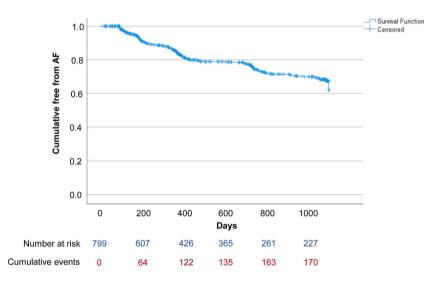
We demonstrated that addition of CMIV is safe; the 30-day operative mortality rate was 3.3% in this patient group with a mean EuroScore of 6.4%. EuroScore was used for risk comparison since STS PROM did not have a field for multi-valve procedures, and AF type was factored into STS PROM well after registry enrollment began. Most patients had more complex procedures, including 73% with at least one valve operation. Our results are consistent with STS/AATS guidelines statement that operative mortality is not increased for patients undergoing MVrepair/replace, CABG, AVR, and AVR/CABG<sup>12,13</sup> and, in fact, perioperative mortality may be decreased for patients undergoing MVrepair/replace with the addition of CMIV.<sup>12</sup>

The 30-day neurologic event rate of 1.3% was low for this complex group of patients; only 4 of 799 (0.5%) patients had a perioperative stroke. Perioperative stroke following cardiac surgery has been reported to be to be 2.03% based on meta-analysis.<sup>25</sup> The stroke rate in intermediate-risk patients undergoing surgical AVR was 6.5%.<sup>26</sup> The low incidence of neurologic events in our study is at least, in part, due to the routine LAA closure; only 13 patients did not have LAA closure documented in the registry. It is well-demonstrated that ischemic stroke is extremely rare in patients undergoing CMIV compared to other cardiac procedures.<sup>27</sup> There is still no randomized data on stopping anticoagulation after CMIV.

Pacemaker insertion rates following CMIV have been reported to be two- to three-fold higher compared to patients with similar operations not undergoing CMIV. Gammie et al.<sup>28</sup> reported a higher incidence of new pacemaker insertion following surgery that included SA. In Gammie's study, patients underwent surgery from 1989 to 2004; a time that was early in surgical atrial ablation experience. Furthermore, it is unclear what ablative lesions were performed. A more recent randomized study by Gillinov et al.<sup>29</sup> compared patients undergoing MV surgery with or without what was labeled CMIV, and the incidence of new pacemaker insertion was 21.5 versus 8.1 implantations per 100 patient years (p = .01). None of the procedures



**FIGURE 2** Freedom from atrial fibrillation (AF) stratified by rhythm monitoring method. ECG, electrocardiography; ILR, implantable loop recorder.



**FIGURE 3** Cumulative freedom from atrial fibrillation (AF) by Kaplan–Meier analysis.

performed were the CMIV used in our study. Additionally, the procedures were performed at multiple sites with variable techniques and various energy sources.<sup>30</sup> Unipolar RF, which is vulnerable to nontransmurality was used and an aligned coronary sinus and mitral isthmus cryothermal lesion to prevent left atrial flutter was not included. Our surgical technique was standardized across all four centers, as described above. Patients in our study experienced an inhospital pacemaker insertion rate of 6.3%. This is low considering that 73% of our patients had at least one valve procedure, 42% had combined CABG/valve/multivalve operations, and 67% had nonparoxysmal AF. A strongly positive correlation exists between AF burden and sinus node (SN) dysfunction. Thus, patients with nonparoxysmal AF are more likely to require a pacemaker when AF is eliminated, and SN dysfunction is unmasked.<sup>31</sup>

The incidence of in-hospital pacemaker insertions following cardiac surgery varies widely depending upon patients' preoperative conduction status and procedure types. New pacemaker insertion following an isolated AVR has been reported by Levack et al.<sup>32</sup> to be 2.6%. However, Moskowitz et al.<sup>33</sup> reported 1-year permanent pacemaker implantation rates between 4.5% (MV repair) and 13.3% (double valve). Eighty percent of these patients had their pacemakers placed at the index hospitalization.<sup>33</sup>

Potential reasons for the low pacemaker rate in the present study are diligent attention to avoiding AV conduction tissue when creating the 10 o'clock lesion and when used, ensuring the right atrial appendage (RAA) free-wall lesion was made in close proximity to the AV groove to avoid injury to the sinoatrial complex. Similarly, the superior vena cava lesion was created as far posteriorly as possible to prevent injury to the pacemaker complex. Importantly, the lower pacemaker insertion rate for the participating centers may reflect tolerance for allowing recovery of native pacemaker automaticity. Time was allowed for sinus rhythm to recover, and well tolerated junctional rhythms were considered acceptable for hospital discharge.

Numerous recent studies have documented CMIV efficacy.<sup>16,34,35</sup> In our study, freedom from AF at 3 years remained high for the entire cohort at 84.7%. Efficacy was maintained for all AF types throughout the study duration. It is encouraging to see durable results in this large series, considering the operations were performed in multiple centers with multiple operators in patients with significant comorbidities. The small differences in success across AF types suggest that all types of AF need to be considered for CMIV.

Inaccuracy in the nomenclature of SA procedures and lack of precise description has resulted in confusion about procedural efficacy. Unfortunately, use of the term "Maze" has become a generic reference to describe a confounding mix of SA lesion sets and energy sources, resulting in a lack of confidence in reported results. Herein, all surgeons performed the CMIV as originally described by Dr. Damiano using the same lesion set and energy sources, with the exception of some surgeons shifting from the 10 o'clock lesion to the free-wall RAA lesion with the assent of Dr. Cox.

Attention to the technical details equates directly to the success of the procedure. First, CMIV always consists of a complete bi-atrial lesion set. Second, transmurality is an inherent quality of any CM and must be achieved for CMIV. A recent pivotal laboratory study demonstrated the importance of a standardized technique for optimize lesion creation.<sup>36</sup> Khiabani et al. demonstrated the completion of two complete energy cycles without opening the clamp jaws achieved 100% transmurality on human cardiac tissue. The technique is consistent with and formalized the method employed by several investigators and may have contributed to our outcomes. Third, strict attention to alignment of the mitral isthmus and coronary sinus cryothermal lines is necessary to prevent left atrial flutter. Last, every transmural lesion must cross another transmural lesion or anchor into nonconductive tissue such as an annulus. The lesion set used by the surgeons in this study was the lesion set as detailed by Damiano<sup>15</sup> and diagrammed in the 2017 guidelines paper.<sup>13</sup> This lesion set was also consistent with AtriCure's IDE study which led to the FDA approval of the AtriCure system for treatment of nonparoxysmal AF.<sup>16</sup>

All cardiac societies endorse concomitant surgical AF ablation, and CMIV's safety and efficacy are well established, yet cardiac surgeons overall have not embraced it. Poor adoption is likely multifactorial including a lack of training and/or experience, lack of familiarity with the positive safety and efficacy literature, and an ever-older patient population with increased comorbidities. For some surgeons, progress may also be hindered by an institutional focus on hospital length-of-stay and procedural costs. Whereas rhythm assessment might lengthen hospitalization, costs related to CMIV become neutral within 2 years of treatment due to overall lower health care costs.<sup>37</sup>

Any of these factors may influence surgeons to not include concomitant CMIV, but as demonstrated here and myriad other studies, a well performed CMIV has durable benefit, while adding no discernable risk.

#### 4.1 | Limitations

Data are from a prospective registry that was analyzed retrospectively. While most of the preoperative data points were complete, as with any retrospective review there were an increasing number of data points and patients lost to follow-up as the study years progressed. Immediate postoperative safety and efficacy data was nearly complete, but freedom from AF follow-up analysis was impacted by the retrospective study design. The ILR has a threshold of 2 min thus some episodes lasting under 2 min may have been missed. The study was not constructed to include the demographic data for different ethnicity; this is unfortunate because AF is not adequately treated in black patients.<sup>22</sup> All surgeons used the concomitant CMIV lesion set but exact numbers of radiofrequency applications and cryothermal times at each position were not recorded; information that may have assisted in identifying reasons for failure. Cardiopulmonary bypass and aortic cross clamp times were not captured in the registry, which may have been helpful quantifying time added by the CMIV. Although, a comparison group without CMIV would be needed

#### 5 | CONCLUSION

Concomitant CMIV is safe and effective. Our study adds to the substantial and growing literature supporting inclusion of concomitant CMIV for all cardiac surgery patients with preoperative AF, unless there are sound preoperative findings risk will be increased. Exclusion due to risk assessment may largely dissipate with diligent training and experience. SA should always be considered for AF patients undergoing cardiac surgery, rather than looking for "ideal" patients. The current study provides real world evidence that literature-reported safety and efficacy can be replicated in multiple centers by multiple surgeons.

Cardiac societies should consider measures to encourage surgeon compliance with the Class I guidelines for AF treatment, so more AF patients benefit. Given the preponderant evidence, perhaps concomitant AF ablation should become a quality metric for cardiac surgery.

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#### CONFLICTS OF INTEREST

M. G.: research grants and consultant fees from AtriCure, Zimmer-Biomet, CryoLife, and CorMatrix. A. B.: proctor for AtriCure, Inc. G. B.: consultant for AtriCure, Inc. and Cryolife, Inc.; Chief Medical Officer for Egnite Healthcare. G. D.: consultant, speaker, and proctor for AtriCure, Inc. J. J.: proctor and speaker for AtriCure, Inc. M. P.: Zoll Medical. The remaining authors declare no conflict of interest.

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#### ETHICS STATEMENT

The registry protocol was approved by the participating centers' respective Institutional Review Boards (IRB) as follows: Aspirus Wausau IRB #17.08.494E (initial approval October 25, 2013, latest approval May 25, 2021); St. Helena IRB (initial approval February 20, 2015; latest approval July 7, 2021); Franciscan Health IRB #1427359-6 (initial approval August 21, 2013, latest approval August 3, 2021); Swedish Medical Center IRB #20130693 (study 1138887) (initial approval October 24, 2013, latest approval April 25, 2022). Some data were retrospectively entered from a prospectively-collected institutional registry. All patients underwent informed consent to participate in the trial.

#### ORCID

Marc Gerdisch 🕩 http://orcid.org/0000-0001-9489-038X

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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