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Pulmonary Vein Isolation Using the Visually Guided Laser Balloon

A Prospective, Multicenter, and Randomized Comparison to Standard Radiofrequency Ablation

Srinivas R. Dukkipati, MD,* Frank Cuoco, MD,† Ilana Kutinsky, DO,‡ Arash Aryana, MD,§ Tristram D. Bahnson, MD,‖ Dhanunjaya Lakkireddy, MD,¶ Ian Woollett, MD,# Ziad F. Issa, MD,** Andrea Natale, MD,†† Vivek Y. Reddy, MD,* for the HeartLight Study Investigators

ABSTRACT

BACKGROUND Balloon catheters have been designed to facilitate pulmonary vein (PV) isolation in patients with paroxysmal atrial fibrillation (AF). The visually guided laser balloon (VGLB) employs laser energy to ablate tissue under direct visual guidance.

OBJECTIVES This study compared the efficacy and safety of VGLB ablation with standard irrigated radiofrequency ablation (RFA) during catheter ablation of AF.

METHODS Patients with drug-refractory paroxysmal AF were enrolled in a multicenter, randomized controlled study of PV isolation using either the VGLB or RFA (control). The primary efficacy endpoint was freedom from protocol-defined treatment failure at 12 months, including symptomatic AF occurring after the 90-day blanking period. The primary efficacy and safety endpoints were powered for noninferiority.

RESULTS A total of 353 patients (178 VGLB, 175 control) were randomized at 19 clinical sites. The mean procedure, ablation, and fluoroscopy times were longer with VGLB compared with controls. The primary efficacy endpoint was met in 61.1% in the VGLB group versus 61.7% in controls (absolute difference −0.6%; lower limit of 95% confidence interval [CI]: −9.3%; $p = 0.003$ for noninferiority). The primary adverse event rate was 11.8% in the VGLB group versus 14.5% in controls (absolute difference −2.8%; upper limit of 95% CI: 3.5; $p = 0.002$ for noninferiority), and was mainly driven by cardioversions. Diaphragmatic paralysis was higher (3.5% vs. 0.6%; $p = 0.05$), but PV stenosis was lower (0.0% vs. 2.9%; $p = 0.03$) with VGLB.

CONCLUSIONS Despite minimal prior experience, the safety and efficacy of VGLB ablation proved noninferior to RFA for the treatment of paroxysmal AF. (Pivotal Clinical Study of the CardioFocus Endoscopic Ablation System-Adaptive Contact [EAS-AC] [HeartLight] in Patients With Paroxysmal Atrial Fibrillation [PAF] [HeartLight]; NCT01456000) (J Am Coll Cardiol 2015;66:1350-60) © 2015 by the American College of Cardiology Foundation.

From the *Icahn School of Medicine at Mount Sinai, New York, New York; †Medical University of South Carolina, Charleston, South Carolina; ‡William Beaumont Hospital, Royal Oak, Michigan; §Regional Cardiology Associates, Sacramento, California; ‖Duke Center for Atrial Fibrillation and the Clinical Cardiac Electrophysiology Section, Duke University Medical Center, Durham, North Carolina; ¶Mid-America Cardiology, Kansas City, Kansas; #Sentara Cardiovascular Research Institute, Norfolk, Virginia; **Prairie Heart Institute, Springfield, Illinois; and the ††Texas Cardiac Arrhythmia Institute, Austin, Texas. The study was funded by CardioFocus, Inc. Dr. Dukkipati has received honoraria from CardioFocus; and research funding from Biosense Webster. Drs. Aryana and Cuoco are consultants to Biosense Webster. Dr. Bahnson has received grant support from Biosense Webster, St. Jude Medical, Medtronic, Biotronic, Boston Scientific, and CardioFocus; speakers fees from Janssen Pharmaceuticals; and is a consultant and clinical events committee member for Laguna Pharmaceuticals. Dr. Lakkireddy has received speakers honoraria from St. Jude Medical, Janssen Pharmaceuticals, Boehringer Ingelheim, and Pfizer; and is an advisory board member of SentreHEART. Dr. Natale has received honoraria from CardioFocus; is a consultant to St. Jude Medical, Biosense Webster, Boston Scientific, Janssen Pharmaceuticals, and Medtronic; and has received research funding from Biosense Webster. Dr. Reddy has received research funding from and is a consultant to CardioFocus and Biosense Webster. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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The mainstay of catheter-based therapy for patients with paroxysmal atrial fibrillation (AF) is pulmonary vein (PV) isolation (1). Despite high rates of acute electrical isolation, long-term efficacy is mainly limited by PV reconnections (2,3). This may be attributable to the technical difficulty in achieving a transmural and contiguous ring of necrosis around the PVs with point-by-point ablation. To facilitate this process, balloon catheters

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using a variety of energy sources, including radiofrequency, laser, and cryoenergy, have been introduced (4–6). Although many of these balloon catheters share similar features, the visually guided laser balloon (VGLB) is unique in that it uses: 1) a compliant, variable diameter balloon, thus allowing a single balloon catheter to accommodate multiple PV sizes/shapes; 2) a 2-F endoscope to provide real-time direct visualization of the target tissue; and 3) a maneuverable (~30°) aiming arc that allows the operator to easily target the location of the PV ostium/antrum and titrate the amount of laser energy delivered.

Clinical experience with the VGLB has been limited to several single and multicenter nonrandomized experiences that have demonstrated reasonable safety and efficacy (6–10). Although the VGLB is routinely used clinically in Europe, no multicenter, randomized studies have compared it with other technologies. Here, we report the first prospective, multicenter, randomized study comparing the safety and efficacy of the VGLB with standard irrigated radiofrequency ablation (RFA) in patients with paroxysmal AF.

METHODS

The study protocol was approved by the institutional review boards at each of the 21 sites in the United States. Of these sites, 19 entered the study's randomized phase (Online Appendix). Two sites enrolled subjects into the training phase of the study but did not randomize any patients. The study design stipulated that only randomized patients would be included in the primary analyses. All patients enrolled in the study provided written informed consent.

Patients with drug-refractory paroxysmal AF were enrolled in the study. Inclusion criteria included: ≥2 symptomatic AF episodes (≥1 min) within the previous 6 months; 1 documented AF episode within the previous 12 months; and refractory or intolerance to an antiarrhythmic drug (AAD) (class I, II, or III). The exclusion criteria included: PV size >35 mm; left atrial (LA) thrombus; LA diameter >50 mm; left ventricular ejection fraction <30%; previous LA ablation for AF or atrial flutter (AFL); New York Heart Association class III or IV symptoms; myocardial infarction within the previous 60 days; unstable angina; cardiac surgery within the previous 3 months; coronary artery bypass grafting within the previous 6 months; any history of cardiac valve surgery; a thromboembolic event within the previous 3 months; uncontrolled bleeding; active infection; atrial myxoma; severe pulmonary disease or gastrointestinal bleeding; a previous valvular cardiac surgical procedure; presence of an implantable cardioverter-defibrillator; women of childbearing potential who were pregnant, lactating, or not using adequate birth control; and inability to be removed from antiarrhythmic drug therapy.

STUDY PROTOCOL. Patients were randomized in a 1:1 manner to VGLB ablation or RFA (control). After randomization, patients underwent ablation according to their assignment. Following hospital discharge, telephone follow-up was performed at 1 week. Follow-up visits occurred at 1, 3, 6, and 12 months and included 12-lead electrocardiogram, physical examination, and assessment of adverse events. Continued use of oral anticoagulation therapy was recommended for 12 months. Use of any U.S. Food and Drug Administration-approved anticoagulation drug, including warfarin, dabigatran, or rivaroxaban, was permitted (apixaban and edoxaban were not approved as of this study's initiation). Patients were permitted to be discharged on the same AAD regimen for AF that was used pre-procedure until the end of the 90-day blanking period, at which time it was discontinued.

All patients were given transtelephonic monitors before the end of the blanking period, and monitoring was performed starting at 3 months and continuing through 12 months. Patients were required to transmit for all symptoms and also weekly irrespective of symptoms. Holter monitoring was performed at 6 and 12 months. Either a computed tomography (CT) scan or cardiac magnetic resonance imaging (CMR) was required within 6 months before enrollment and at 3 months after the procedure. Patients who had stenosis of 1 or more PVs (defined as >50% reduction in greatest diameter) were also required to have CT or CMR at 12 months. The National Institutes of Health Stroke Scale (NIHSS) was administered to participants before randomization, pre-discharge, and at the 12-month visit. A safety monitoring committee reviewed all serious adverse events throughout the conduct of the study.

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AF = atrial fibrillation
AFL = atrial flutter
AT = atrial tachycardia
CI = confidence interval
CMR = cardiac magnetic resonance imaging
CT = computed tomography
LA = left atrial
PAE = primary adverse event(s)
PV = pulmonary vein
RFA = radiofrequency ablation
VGLB = visually guided laser balloon

ABLATION GROUPS. Anesthesia during cases was determined by the individual sites, with most using general anesthesia for all cases. Following transseptal puncture, a 12-F deflectable sheath was positioned at the LA. In most cases, a second transseptal was performed with an 8-F sheath and was used for a circular mapping catheter. Intravenous heparin was administered to maintain an activated clotting time ≥300 s. The use of intracardiac echocardiography and esophageal temperature monitoring was mandated by the protocol.

Ablation was performed with the VGLB system (HeartLight, CardioFocus, Marlborough, Massachusetts). The VGLB catheter is a variable-diameter, compliant balloon with a flexible tip that is delivered through a 12-F deflectable sheath. Within the central shaft of the balloon catheter is a 2-F endoscope that permits real-time visualization of the target tissue. The central shaft contains lumens for circulating deuterium oxide (D_2O) to cool the balloon, a maneuverable optical fiber that generates a ~30° arc/spot of both nonablative visible light and near-infrared ablative light energy. This arc of light can be maneuvered to any location along the surface of the balloon to allow aiming and then ablation using diode laser energy (980 nm). The shaft of the catheter contains a radiopaque marker that can be visualized on fluoroscopy and allows correlation orientation between endoscopic and fluoroscopic images.

Using the deflectable sheath, the VGLB catheter was inflated at the ostium of the target PV. Under visual guidance, ablation lesions were delivered in a circumferential, contiguous, and overlapping manner around the PV. After placement of the initial anatomically guided encircling lesion set, the circular mapping catheter was used to assess electrical PV isolation. If the PV was not isolated, the VGLB catheter was again used to deliver lesions to the area of anatomic breakthrough. All PVs were targeted in a similar manner. During ablation of the right superior PV, phrenic nerve pacing was performed from the superior vena cava to monitor for phrenic nerve injury. Ablation was terminated with loss of capture of the phrenic nerve or at any time when the esophageal temperature exceeded 38.5°C. After 30 min post-ablation, PVs were reassessed for electrical isolation with a circular mapping catheter. Use of isoproterenol was not required by the protocol.

The typical dose of laser energy used was 8.5 W × 20 s and less commonly, 7, 10, or 12 W per lesion. To minimize thrombus formation risk, a 5.5 W × 30 s dose was used when ablation was required in regions of overlapping moving blood along the periphery of the endoscopic view. Stagnant blood at the center of the endoscopic image represents blood from the target PV that is completely occluded by the balloon. Ablation is avoided in this region due to risk of thrombus formation at any laser energy dose. Lesion overlap during ablation was recommended as 50% for the 5.5 W × 30 s dose and approximately 30% for other doses. Cavotricuspid isthmus ablation using RFA could be performed for participants with a history of typical AFL or where typical AFL was observed during the procedure. Other ablation lesion sets were not allowed by protocol.

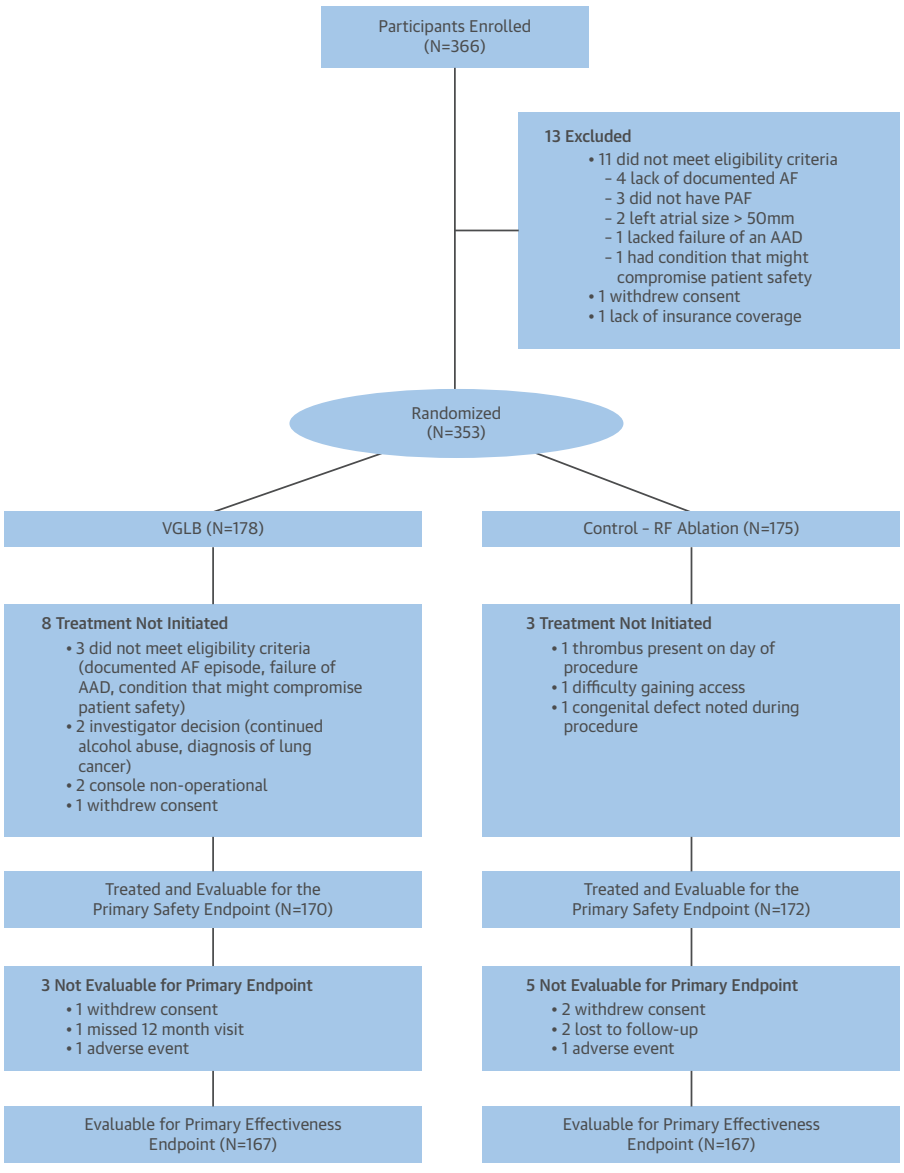
Patients randomized to the control arm underwent ablation using an irrigated RFA catheter (ThermoCool Navistar, Biosense Webster, Diamond Bar, California) and CARTO electroanatomic mapping system (Biosense Webster) guidance. Circumferential ablation was performed to achieve PV isolation. Unique to the control arm, additional ablation was allowed at investigator discretion. These could include linear lesions, ablation of electrogram fractionation, and cavotricuspid isthmus ablation. Esophageal temperature monitoring was required. After 30 min post-ablation, PV isolation was reassessed with a circular mapping catheter. Only entrance block was required, and verification of exit block was optional. Also unique to the control arm, patients were allowed a repeat ablation procedure within 80 days if they had a documented, symptomatic episode of AF.

EFFICACY AND SAFETY ENDPOINTS. There was a 90-day blanking period for the primary efficacy endpoint. The primary efficacy endpoint was freedom from protocol-defined treatment failure, which included: 1) documented symptomatic AF (≥1 min); 2) ablation-induced LA flutter or atrial tachycardia (atypical AFL or AT) or AFL/AT of unknown origin; 3) failure to acutely isolate all PVs; 4) use of any AAD (class I, II, or III); or 5) left heart ablation/surgery or implantable cardioverter-defibrillator placement for AF.

All adverse events experienced by patients were recorded beginning with the ablation procedure through 12 months of follow-up. Primary adverse events (PAEs) were defined as: transient ischemic attack (within 1 month of treatment) or stroke; cardiac perforation; tamponade; significant effusion; PV stenosis; diaphragmatic paralysis (persisting beyond blanking period); atrio-esophageal fistula; death; major bleeding requiring transfusion; myocardial infarction (Q-wave only—within 1 week of treatment); and AF/AFL requiring cardioversion.

Additional comparisons between the study groups included the following pre-specified secondary endpoints: 1) percentage of patients with all PVs acutely

FIGURE 1 Study Flow



Patients with paroxysmal atrial fibrillation (PAF) were randomized to ablation using either the VGLB or a standard irrigated radiofrequency ablation catheter (control). Primary efficacy was assessed over 12 months of follow-up. AAD = antiarrhythmic drug; RF = radiofrequency; VGLB = visually guided laser balloon.

isolated; 2) percentage of PVs that remained isolated acutely without reconnection during procedure; 3) rate of chronic/durable PV isolation in patients undergoing second catheter ablation (redo) procedures during follow-up; and 4) frequency of PV narrowing and stenosis.

STATISTICAL METHODS. The protocol-defined primary statistical analysis of the primary endpoints was noninferiority for both safety and efficacy. Continuous variables are presented as the mean ± SD with 95% confidence intervals (CIs) for the differences in means, as well as medians and ranges. For categorical variables, relative frequencies are provided with 95% CIs for the difference in proportions. Survival analysis utilized the Kaplan-Meier method. All tests of significance were 2-sided, with $p \leq 0.05$

TABLE 1 Patient Demographics

	VGLB (n = 170)	Control (n = 172)	p Value
Age, yrs	59.7 ± 10.4	60.1 ± 8.9	0.69
Sex			
Male	118 (69.4)	109 (63.4)	0.24
Female	52 (30.6)	63 (36.6)	
Race			0.51
White	164 (96.5)	168 (97.7)	
Black	5 (2.9)	0 (0)	
Asian	1 (0.6)	2 (1.2)	
Other	0 (0)	2 (1.2)	
Duration of AF, yrs	2 (IQR 6.25)	3 (IQR 5.67)	0.33
Hypertension	101 (59.4)	100 (58.1)	0.81
Coronary artery disease	36 (21.2)	35 (20.3)	0.85
Myocardial infarction	7 (4.1)	7 (4.1)	0.98
CABG	5 (2.9)	7 (4.1)	0.57
CHF	9 (5.3)	4 (2.3)	0.15
Diabetes mellitus	26 (15.3)	17 (9.9)	0.13
Stroke or TIA	11 (6.5)	13 (7.6)	0.69
Atrial flutter	42 (24.7)	41 (23.8)	0.85
Atrial flutter ablation	15 (8.8)	15 (8.7)	0.97
Ejection fraction, %	60.6 ± 7.4	60.2 ± 7.4	0.60
Left atrial diameter, cm	4.0 ± 0.56	4.0 ± 0.55	0.61
Antiarrhythmic medications			–
Class I	84 (49.4)	101 (58.7)	
Class II	86 (50.6)	81 (47.1)	
Class III	98 (57.6)	99 (57.6)	

Values are mean ± SD, n (%), or median (IQR).
AF = atrial fibrillation; CABG = coronary artery bypass grafting; CHF = congestive heart failure; IQR = interquartile range; TIA = transient ischemic attack; VGLB = visually guided laser balloon.

considered statistically significant. The analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

The primary safety endpoint was pre-specified as a comparison of the rate of patients with 1 or more PAEs between the 2 groups. The null hypothesis was the PAE rate for the VGLB was inferior to the PAE rate for the control device, assuming a non-inferiority delta of 8.0%. The primary efficacy endpoint was pre-specified as a comparison of the treatment success rates between the groups. For the primary efficacy endpoint, the null hypothesis was pre-specified that the rate of treatment success for the VGLB was inferior to the success rate of the control device, assuming a noninferiority delta of 15.0%.

RESULTS

In this study, a total of 342 patients (170 VGLB, 172 controls) underwent ablation, and 334 patients (167 each group) were evaluable for the primary efficacy endpoint after 12 months of follow-up (Figure 1).

PATIENT AND PROCEDURAL CHARACTERISTICS. Of the 342 patients who underwent ablation, there were no significant differences between the groups with respect to age, sex, AF duration, LA size, and left ventricular ejection fraction (Table 1). Patients who qualified for the study by failing only a class II AAD (beta-blocker) represented 11.8% (20 of 170) and 9.3% (16 of 172) of the enrollments in the VGLB and control arms, respectively (p = 0.46).

As shown in Table 2, acute PV isolation was achieved in 649 of 664 (97.7%) targeted PVs using the VGLB and in 658 of 664 (99.1%) using the RFA catheter (p = 0.05). In the VGLB arm, using visual guidance alone, 583 of 664 (87.8%) PVs were electrically isolated after first encirclement. In controls, for whom ablation was commonly guided by real-time PV electrogram feedback with a circular mapping catheter, 553 of 664 (83.3%) PVs were isolated after first encirclement (p = 0.02). Patients who did not have all PVs isolated acutely using the randomized device represented 5.9% (10 of 170) and 4.1% (7 of 172) of the patients in the VGLB and control arms, respectively (p = 0.44). The mean number of ablation lesions delivered per PV was 40.1 ± 19.8 for VGLB, and the mean RF time per PV was 13.0 ± 8.4 min for RFA. The percentage of PVs that reconnected by the end of the 30-min waiting period was 2.7% (18 of 664) for VGLB and 5.7% (38 of 664) for RFA (p = 0.006).

Fluoroscopy, ablation, and procedure times were all shorter in the control arm. Additional ablation lesion sets beyond PV isolation were delivered more frequently in controls compared with the VGLB group (33.7% vs. 13.5%; p < 0.0001). In the control group, the protocol permitted redo procedures (within 80 days of the index procedure) were performed in 2.3% (4 of 172) of patients.

CLINICAL OUTCOMES. At 12 months, the primary efficacy endpoint was met in 61.1% in the VGLB group versus 61.7% in controls (absolute difference: −0.6%; lower limit of 95% CI: −9.3%; p = 0.003 for non-inferiority). Figures 2 and 3 show Kaplan-Meier survival curves and reasons for primary efficacy failure in each arm, respectively. Overall, 12-month drug-free rate of freedom from symptomatic AF or atypical AFL/AT was 63.5% (106 of 167 patients) and 63.9% (106 of 166) in the VGLB and control arms, respectively (p = 0.94). In patients who underwent repeat ablation, the rate of durable PV isolation was 52.7% (49 of 93 PVs) for those who initially underwent VGLB ablation and 46.4% (32 of 69 PVs) in controls (p = 0.43).

The PAE rate was 11.8% in the VGLB group versus 14.5% in controls (absolute difference: −2.8%; upper limit of 95% CI: 3.5%; p = 0.002 for noninferiority) (Table 3). The PAE rate reflects the number of patients experiencing at least 1 PAE rather than the total number of PAEs. There were a total of 24 PAEs (14.1%) in the VGLB group and 27 (15.7%) among controls (p = NS). Diaphragmatic paralysis persisting beyond the blanking period occurred in 6 (3.5%) and 1 (0.6%) in the VGLB and control groups, respectively (p = 0.05). Of these, 3 (1.8%) persisted at 12 months in the VGLB group, with 1 resolving after 12 months. The single diaphragmatic paralysis in the control arm was persistent at 12 months. There were no instances in which diaphragmatic paralysis occurred but resolved before procedure conclusion or before the blanking period ended. At 3 months, CT or CMR demonstrated a significantly higher rate of significant PV stenosis (>50% diameter decrease) in controls (2.9% vs. 0.0%; p = 0.03). The rate of PV narrowing (>20% but ≤50% diameter decrease, evaluated on a per-vein basis) was 21.9% in those who underwent VGLB ablation compared with 24.7% in controls. There were 2 strokes in the VGLB arm (1 before discharge, 1 a week after discharge) and 1 in the control group (p = 0.56). The VGLB patient who experienced a stroke after discharge was not anticoagulated before ablation but received dabigatran beginning the day of ablation. All 3 strokes completely resolved. There were no atrio-esophageal fistulas. There was 1 death in follow-up in the VGLB arm that was not classified as a PAE. This was a patient with severe pulmonary hypertension who died approximately 7 months after the index procedure and approximately 3 months after an additional ablation for typical AFL. There were no unanticipated adverse device effects. The NIHSS was administered pre-treatment, pre-discharge, and at study exit, and demonstrated no differences between the groups, with no VGLB patient having a worsening >1, considered a moderate change using this assessment tool.

EFFECT OF OPERATOR EXPERIENCE. Because all 30 operators had extensive experience with standard RFA and limited experience with VGLB, the learning curve effects were assessed in the latter group (Figure 4). By study's end, only 15 of the operators had performed more than 3 VGLB cases in this study. The 5 operators with ≥15 lifetime cases of experience with VGLB (VGLB-High; 40 cases) were compared with the 25 operators with <15 lifetime cases of experience (VGLB-Low; 130 cases). An experience threshold of 15 cases was selected because it has been previously used to determine the VGLB learning curve (6). There was a nonsignificant increase in the primary efficacy endpoint from 59.4% (VGLB-Low) to 65.0% (VGLB-High) with increased experience (p = 0.56). There was also a trend toward more improved safety with more experience. The PAE rate was 13.8% in VGLB-Low versus 5.0% in the VGLB-High groups (p = 0.08). Case times (241.0 ± 55.0 min vs. 222.0 ± 42.0 min; p = 0.06) and fluoroscopy times (38.4 ± 18.6 min vs. 27.3 ± 13.4 min; p = 0.0003) improved significantly with more VGLB experience. When comparing the VGLB-High group to controls, the primary efficacy endpoint was nonsignificantly higher in the VGLB-High group (65.0% vs. 61.7%; p = 0.70), and the PAE rate was lower (5.0% vs. 14.5%; p = 0.10). The overall procedure time was still lower in controls (222.0 ± 42.0 min vs. 193 ± 63.6 min; p = 0.006), but fluoroscopy time was lower (27.3 ± 13.4 min vs. 29.7 ± 21.0 min; p = 0.038) in the VGLB-High group.

TABLE 2 Procedural Data

	VGLB (n = 170)	Control (n = 172)	p Value
Procedure time, min*	236.0 ± 52.8	193.0 ± 63.6	<0.0001
Ablation time, min†	173.8 ± 46.6	151.2 ± 56.2	<0.0001
Fluoroscopy time, min	35.6 ± 18.2	29.7 ± 21.0	0.006
Number of PVs attempted	3.9 ± 0.4	3.9 ± 0.5	0.34
PVs isolated	649/664 (97.7)	658/664 (99.1)	0.05
PVs isolated on first attempt	583/664 (87.8)	553/664 (83.3)	0.02
Attempts per PV to achieve isolation			0.0001
1	583 (89.8)	553 (84.0)	
2	45 (6.9)	91 (13.8)	
3	15 (2.3)	6 (0.9)	
≥4	6 (0.9)	8 (1.2)	
Number of ablation catheters used	1.2 ± 0.4	1.0 ± 0.2	<0.0001
1	143 (84.1)	167 (97.1)	<0.0001
2	26 (15.3)	5 (2.9)	
3	1 (0.6)	0 (0.0)	
Additional ablation lesions	23 (13.5)	58 (33.7)	<0.0001
CTI ablation	21 (12.4)	25 (14.5)	
LA roof line	0 (0.0)	20 (11.6)	
Mitral isthmus line	1 (0.6)	3 (1.7)	
LA septal line	0 (0.0)	5 (2.9)	
RA intercaval line	1 (0.6)	1 (0.6)	
Other	1 (0.6)	21 (12.2)	

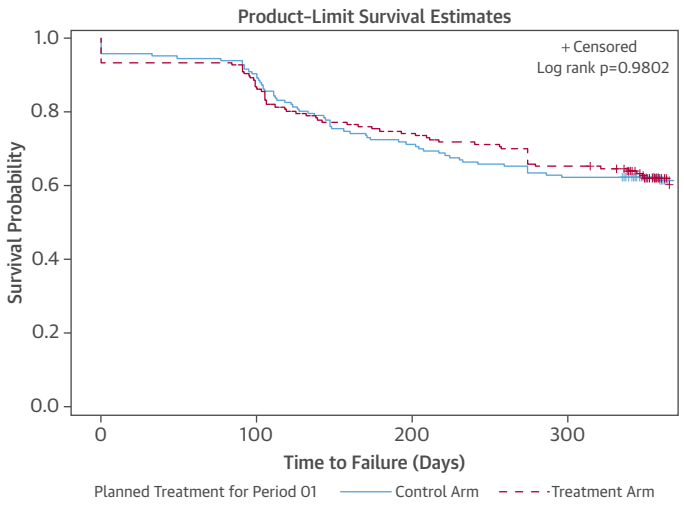
Values are mean ± SD, n/N (%), or n (%). *Defined as time from venous access to end of last 30-min wait period. †Defined as time from insertion of catheter to end of last 30-min wait period.

CTI = cavotricuspid isthmus; LA = left atrium; PV = pulmonary vein; RA = right atrium; VGLB = visually guided laser balloon.

DISCUSSION

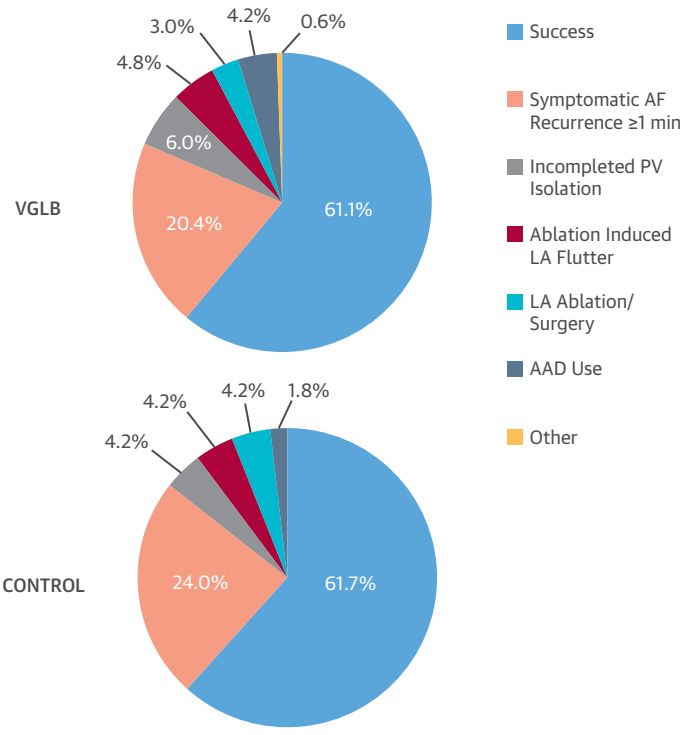
This is the first multicenter, randomized, controlled study comparing VGLB ablation versus RFA (control). The major finding is that VGLB ablation

FIGURE 2 Primary Efficacy Endpoint



Per the Kaplan-Meier curves, the primary efficacy endpoint was similar for the VGLB **(red)** and control **(blue)** groups. The abrupt change in both curves at 90 days reflects treatment failure following the end of the blanking period. VGLB = visually guided laser balloon.

FIGURE 3 Causes for Primary Efficacy Endpoint Failure



The pie charts show treatment success and reasons for failure for the VGLB and control groups. LA = left atrial; PV = pulmonary vein; other abbreviations as in Figure 1.

proved to be equivalent to RFA with respect to the primary efficacy (61.1% vs. 61.7%; p = 0.003 for noninferiority) and safety (11.8% vs. 14.5%; p = 0.002 for noninferiority) endpoints in patients with paroxysmal AF. These findings are noteworthy particularly given the minimal experience of operators with the VGLB, and the fact that unlike in the VGLB arm, ancillary ablation beyond PV isolation and ablation of typical AFL was allowed in controls as were redo procedures during the blanking period. There seems to be a learning curve effect with the VGLB because there was a trend toward improvement in the primary efficacy and adverse event endpoints with increased VGLB experience (≥15 cases) relative to those operators with less experience (<15 cases) or controls. However, these differences did not meet statistical significance, likely due to the sample size for these comparisons. Although there was no difference in the overall PAE rate between the VGLB and controls, diaphragmatic paralysis was more frequent with VGLB ablation compared with RFA (3.5% vs. 0.6%; p = 0.05), as seen with other balloon technologies. However, PV stenosis was more frequent with RFA compared with the VGLB (0.0% vs. 2.9%; p = 0.03), a finding that is atypical for balloon-based ablation.

EFFICACY OF VGLB ABLATION. A component of the primary efficacy endpoint was freedom from symptomatic AF or atypical AFL/AT off AADs, which occurred in 63.5% and 63.9% at 12 months in the VGLB and control arms, respectively (p = 0.94). These outcomes with the VGLB are impressive, given the aforementioned inexperience of the operators and a study protocol that favored controls because of the ability to perform ancillary ablation and redo procedures during the blanking period. However, it should be noted that the RFA catheter used in this study did not incorporate contact force information, which has been shown to improve AF ablation efficacy, particularly when contact force is optimized (11).

This early experience with the VGLB compares favorably with that seen with the early cryoballoon experience in the STOP AF (Sustained Treatment of Paroxysmal Atrial Fibrillation) study (4) (**Central Illustration**). The drug-free single-procedure rate of freedom from symptomatic AF or atypical AFL/AT at 12 months was 57.7% in that study versus 63.5% with VGLB in this study. Furthermore, only 83% were able to achieve isolation with the cryoballoon alone; additional "spot" ablation was required in the remaining patients. In the present study, 94.1% of patients were able to achieve electrical isolation of all PVs with the

VGLB alone. Although the mean procedure (236 vs. 193 min) and fluoroscopy (36 vs. 30 min) times were significantly greater with the VGLB compared with conventional RFA, these, too, were much shorter when compared with the STOP AF experience, which reported mean procedure and fluoroscopy times of 371 min and 63 min with the cryoballoon, respectively. It should be noted that the STOP AF trial was performed with the first-generation cryoballoon. Subsequent studies with increased operator experience with this first-generation balloon, as well as a newer second-generation balloon, demonstrate improved procedure/fluoroscopy times, ability to isolate PVs, and efficacy compared with the initial STOP AF experience (12–14).

SAFETY OF VGLB ABLATION. The PAE rates were lower with the VGLB compared with controls, which fulfilled the pre-specified criteria to for noninferiority (11.8% vs. 14.5%; p = 0.002 for noninferiority). These event rates were primarily driven by an 8.2% and a 9.3% rate of cardioversions in the VGLB and control arms, respectively. Stroke rates were 1.2% for the VGLB group and 0.6% in controls (p = 0.56).

Phrenic nerve palsy occurred in 3.5% and 0.6% of patients for the VGLB and control groups, respectively. These rates are consistent with other experiences with the VGLB (6,10). Although most studies reported complete resolution of the phrenic nerve palsy during follow-up, in this study, the rate of persistent diaphragmatic paralysis at 1 year was 1.8%. However, these rates are less than reported in STOP AF for cryoballoon ablation: 13.5% and 2.5% for reversible and persistent phrenic nerve paralysis (4).

Significant PV stenosis with the VGLB did not occur in this study and, indeed, has never been reported with the VGLB. By contrast, the rate of significant PV stenosis with RFA in this study was 2.9% and was reported to be 3.1% for the cryoballoon in STOP AF. Of note, the rates of these complications are consistent with those reported for RFA (15,16).

OPERATOR LEARNING CURVE. As expected with the adoption of any new technology, learning curve effects

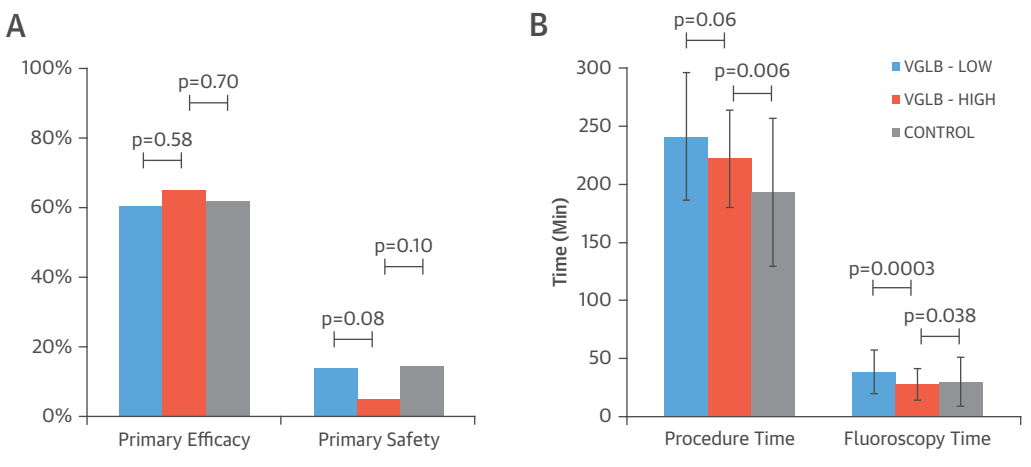
TABLE 3 Primary Adverse Events

	VGLB (n = 170)	Control (n = 172)	p Value
Stroke	2 (1.2)	1 (0.6)	0.56
TIA	0 (0.0)	0 (0.0)	–
Cardiac tamponade, perforation, or significant effusion	2 (1.2)	3 (1.7)	0.66
Diaphragmatic paralysis	6 (3.5)	1 (0.6)	0.05
Atrio-esophageal fistula	0 (0.0)	0 (0.0)	–
PV stenosis >50%	0 (0.0)	5 (2.9)	0.03
Cardioversion for atrial arrhythmias	14 (8.2)	16 (9.3)	0.73
Major bleeding requiring transfusion	0 (0.0)	1 (0.6)	0.32
Myocardial infarction	0 (0.0)	0 (0.0)	–
Death	0 (0.0)	0 (0.0)	–
Total PAEs	24 (14.1)	27 (15.7)	NS
Total PAE rate*	20 (11.8)	25 (14.5)	

Values are n (%). *The total PAE rate reflects the number of patients experiencing a PAE rather than the total of the number of PAEs.

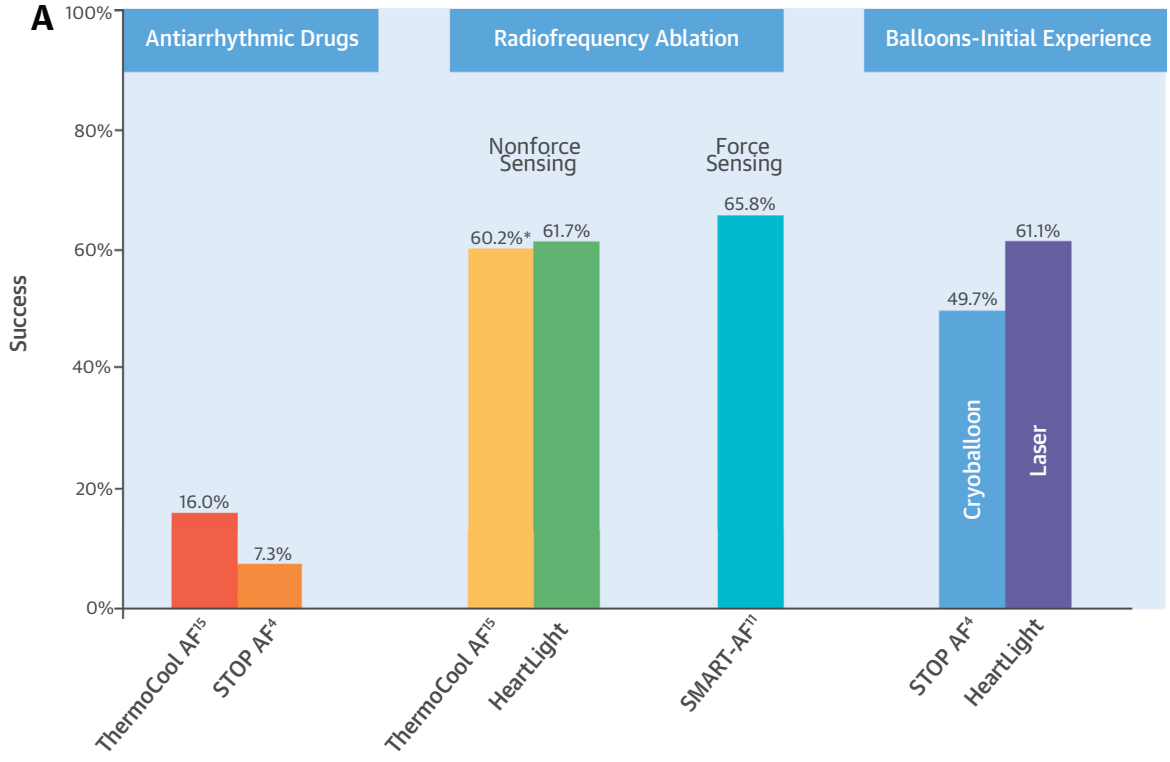
PAE = primary adverse event(s); other abbreviations as in Tables 1 and 2.

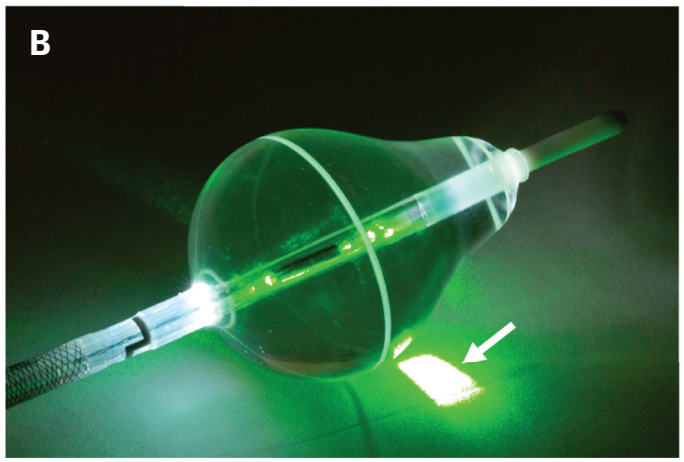
FIGURE 4 VGLB Operator Learning Curve

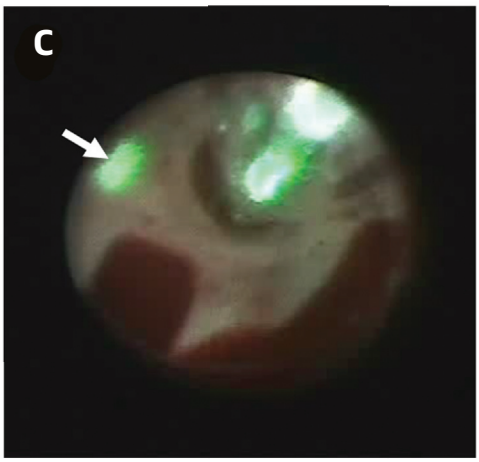


(A) When comparing those with high (≥15 cases) and low (<15 cases) VGLB experience, there was a nonsignificant improvement in both primary efficacy and safety with increased experience. **(B)** Procedure and fluoroscopy times also improved with increased VGLB experience. VGLB = visually guided laser balloon.

CENTRAL ILLUSTRATION **Maintenance of Sinus Rhythm in Paroxysmal AF**







Dukkipati, S.R. et al. J Am Coll Cardiol. 2015; 66(12):1350–60.

(A) Freedom from atrial fibrillation (AF) and atrial tachycardia/flutter at 1 year with antiarrhythmic drugs, radiofrequency ablation, and balloon catheters are shown. The success rates shown are the drug-free single procedure success rates, with the exception of the radiofrequency ablation arm of ThermoCool AF **(asterisk),** which included redo procedures during the blanking period. **(B)** The visually guided laser balloon is shown with the aiming and ablation spot of light **(arrow)**. **(C)** An endoscopic view is shown with the balloon positioned in the left superior pulmonary vein. The maneuverable aiming and ablation spot is shown, and the left inferior pulmonary vein and left atrial appendage are seen.

are expected, as demonstrated with the cryoballoon experience (12). Similarly, learning curve effects were evident with the VGLB. Although the favorable trends in procedure times, complications, and efficacy did not reach statistical significance (likely due to sample size), another study with similar findings did demonstrate statistically significant improvement in some of these parameters with >15-case previous experience (6). Furthermore, a single-center study with a few very experienced operators performing 150 VGLB ablations demonstrated continued improvement in the ability to acutely isolate PVs as well as in fluoroscopy and procedure times when the patients' data were divided into tertiles (17).

Although none of the previous VGLB studies demonstrated an improvement in freedom from AF with increased operator experience, there is evidence that ablation at higher doses of laser energy may improve success (18). Bordignon et al. (18) demonstrated that freedom from AF at 12 months was 60.0% with a low (5.5 to 8.5 W) laser energy ablation strategy versus 83.0% with a high-dose (>8.5 W) strategy ($p = 0.04$). In the present study, laser energy dosing was at operator discretion, with only very general energy delivery guidelines. Therefore, the effects of high- versus low-energy dosing cannot be elucidated further in this study. Given this, and the relative inexperience with VGLB ablation (versus RFA) of even the most experienced operators in this study, it is reasonable to expect further improved procedure times, safety, and efficacy with more VGLB experience and a higher laser energy dosing strategy.

CLINICAL PERSPECTIVE: COMPARISON OF BALLOON ISOLATION TECHNOLOGIES. As compared with cryoballoon-based PV isolation, the VGLB catheter has the potential advantage of providing the operator greater flexibility with power titration. For example, during ablation along the anterior aspects of the PVs, where the tissue tends to be thicker, one can apply more energy, whereas less energy can be delivered along the posterior LA. This may be important because excessive energy deposition along the posterior LA may damage the esophagus, leading to gastric dysmotility and rarely, but devastatingly, atrio-esophageal fistula. Furthermore, during right superior PV isolation, one has the capability of varying the location of ablation with the VGLB catheter so as to avoid damaging the phrenic nerve. Conversely, with the cryoballoon catheter, if the phrenic nerve starts to become affected, there is little one can do other than ceasing cryoablation and switching to ablation using a separate point-by-point ablation catheter.

Of course, these are theoretical advantages; the true relative safety and efficacy of the cryoballoon and VGLB catheters can only be determined by a prospective randomized trial, ideally conducted by operators experienced with both technologies. Although no such multicenter randomized comparative studies exist, there is 1 single-center randomized study that compared these 2 technologies (10). This study revealed: 1) similarly high rates of acute PV isolation and procedure times between groups; 2) phrenic nerve palsy was nonsignificantly higher with the cryoballoon (5.7% vs. 4.2%); and 3) freedom from AF at 12 months was nonsignificantly higher with the VGLB (73.0% vs. 63.0%; $p = 0.18$).

STUDY LIMITATIONS. The duration of AF necessary to be considered a treatment failure in this study was 60 s rather than the standard 30-s duration. This may have overestimated the success rates of VGLB ablation. However, because this was a randomized comparison between the VGLB and RFA, both treatment groups are likely to be similarly affected and the findings of the study are unlikely to differ. The CT and CMR studies used to ascertain PV stenosis were interpreted at individual centers rather than a core laboratory, and this may have implications on reported PV stenosis rates. However, it should be noted that no significant PV stenosis has ever been reported with the VGLB.

CONCLUSIONS

In this multicenter randomized controlled study, VGLB ablation was noninferior to standard irrigated RFA in terms of the primary efficacy and safety endpoints. There was a 3.5% rate of phrenic nerve injury, but no PV stenosis; both complications are frequently reported with other balloon technologies. Evaluation of operator learning-curve effects demonstrated that with increased operator experience, there was a significant improvement in fluoroscopy time and nonsignificant trends to improvement in procedure time, efficacy, and safety. The findings of this study are encouraging, given the relative lack of operator experience with the VGLB and a study protocol that tended to favor RFA due to the ability to perform ancillary ablation in the index procedure and redo procedures during the blanking period, which were not permitted in the VGLB arm.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Vivek Y. Reddy, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, New York 10029. E-mail: vivek.reddy@mountsinai.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Catheter ablation of AF is generally more effective than AAD therapy in maintaining sinus rhythm.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The laser balloon delivers adjustable laser energy at operator-determined sites guided by endoscopic visualization with results equivalent to RFA in maintaining sinus rhythm in patients with AF.

TRANSLATIONAL OUTLOOK: Prospective comparative studies are needed to identify the characteristics of patients with AF that predict better responses to ablation performed with one type of energy versus another.

REFERENCES

1. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2012;9:632–96.e21.

2. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation 2010;122:2368–77.

3. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol 2011;57:160–6.

4. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol 2013;61:1713–23.

5. Sohara H, Takeda H, Ueno H, Oda T, Satake S. Feasibility of the radiofrequency hot balloon catheter for isolation of the posterior left atrium and pulmonary veins for the treatment of atrial fibrillation. Circ Arrhythm Electrophysiol 2009;2:225–32.

6. Dukkipati SR, Kuck KH, Neuzil P, et al. Pulmonary vein isolation using a visually guided laser balloon catheter: the first 200-patient multicenter clinical experience. Circ Arrhythm Electrophysiol 2013;6:467–72.

7. Metzner A, Wissner E, Schmidt B, et al. Acute and long-term clinical outcome after endoscopic pulmonary vein isolation: results from the first prospective, multicenter study. J Cardiovasc Electrophysiol 2013;24:7–13.

8. Dukkipati SR, Neuzil P, Kautzner J, et al. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. Heart Rhythm 2012;9:919–25.

9. Sediva L, Petru J, Skoda J, et al. Visually guided laser ablation: a single-centre long-term experience. Europace 2014;16:1746–51.

10. Bordignon S, Chun KR, Gunawardene M, et al. Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. J Cardiovasc Electrophysiol 2013;24:987–94.

11. Natale A, Reddy VY, Monir G, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. J Am Coll Cardiol 2014;64:647–56.

12. Andrade JG, Khairy P, Guerra PG, et al. Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies. Heart Rhythm 2011;8:1444–51.

13. Aytemir K, Gurses KM, Yalcin MU, et al. Safety and efficacy outcomes in patients undergoing pulmonary vein isolation with second-generation cryoballoon. Europace 2014;17:379–87.

14. Martins RP, Hamon D, Cesari O, et al. Safety and efficacy of a second-generation cryoballoon in the ablation of paroxysmal atrial fibrillation. Heart Rhythm 2014;11:386–93.

15. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010;303:333–40.

16. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:32–8.

17. Perrotta L, Bordignon S, Dugo D, Furnkranz A, Chun KJ, Schmidt B. How to learn pulmonary vein isolation with a novel ablation device: learning curve effects using the endoscopic ablation system. J Cardiovasc Electrophysiol 2014;25:1293–8.

18. Bordignon S, Chun KR, Gunawardene M, et al. Energy titration strategies with the endoscopic ablation system: lessons from the high-dose vs. low-dose laser ablation study. Europace 2013;15:685–9.

KEY WORDS antiarrhythmic drug, atrial fibrillation, catheter ablation, paroxysmal

APPENDIX For an expanded list of the HeartLight study investigators and the study centers, please see the online version of this article.