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ORIGINAL ARTICLE

# Pivotal Study of a Novel Motor-Driven Endoscopic Ablation System

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**BACKGROUND:** The HeartLight endoscopic ablation system has proven similar efficacy as radiofrequency guided pulmonary vein (PV) isolation in prospective randomized studies though longer procedure times were reported. Recently, the option of a new ablation mode (RAPID) was added, during which the laser arc generator is swept around the PV antrum by an integrated motor drive at a predefined speed for continuous ablation. We sought to determine the performance of the new endoscopic ablation system (X3).

**METHODS:** The study was prospective, 2-center, and historically controlled (comparison to pivotal HeartLight study). The primary end point was ablation time (time from insertion of the X3 catheter to the end of the last 30-minute wait period). Transtelephonic monitoring was performed from 90 days to 12 months after ablation.

**RESULTS:** A total of 60 patients were enrolled at 2 centers. Except one, all PVs were treated with RAPID mode. Acute PV isolation was achieved in 225/228 of these PVs (98.7%). The ablation time was significantly shorter with X3 than in the HeartLight study (77.3±25.8 versus 173.8±46.6 min; $P<0.0001$). Procedure time and fluoroscopy time were also significantly shorter (103.7±32.3 versus 236.0±52.8 min; $P<0.0001$; 6.9±3.5 versus 35.6±18.2; $P<0.0001$). PV isolation after the first circular lesion was achieved in 91.6% of PVs (206/225). Two strokes and one late pericardial effusion were noted in the treatment group that were not deemed device related. The 6-month and 12-month atrial fibrillation–free rates for X3 compare favorably with the rates reported for HeartLight, 89.5% versus 75.0% and 71.9% versus 61.1%, respectively.

**CONCLUSIONS:** The novel X3 generation endoscopic ablation system allows for rapid PV isolation by continuous lesion deployment. This was associated with a significant reduction in ablation and procedure times while maintaining the safety and chronic effectiveness in comparison to historical controls.

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**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** atrial fibrillation ■ catheter ■ laser ■ pulmonary vein



Balloon catheters are increasingly used to perform pulmonary vein (PV) isolation (PVI) in patients with symptomatic paroxysmal atrial fibrillation. Both the cryo-balloon (Arctic Front Advance, Medtronic, MI) as well as the endoscopic ablation system (EAS; HeartLight, CardioFocus; Marlborough, MA) have proven similar efficacy as irrigated radiofrequency current wide area circumferential PVI in prospective randomized studies.[1–3] While the first is designed as a single-shot device, the EAS allows for visually controlled point-by point ablation with precise overlap of individual lesions to ensure transmurality and contiguity. In comparison to radiofrequency current ablation, this resulted in significantly longer ablation and procedure times.

Since the initial EAS approval changes have been made to the balloon to further increase its compliance resulting in improved tissue exposure (Excalibur).[4] Most recently, the option of a new ablation mode (RAPID) was added, during which the laser arc generator is swept around the PV antrum by an integrated motor drive at a predefined speed of 2.25 degrees per second to allow for continuous (drag-and burn like) ablation (X3).

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## WHAT IS KNOWN?

- The HeartLight endoscopic ablation system demonstrated similar efficacy as irrigated radiofrequency current ablation for atrial fibrillation ablation.
- Point-by-point laser ablation, however, led to longer procedure times.

## WHAT THE STUDY ADDS?

- The novel X3 generation endoscopic ablation system allows for rapid pulmonary vein isolation by continuous lesion deployment.
- This was associated with a significant reduction in ablation and procedure times.
- Safety and chronic effectiveness in comparison to historical controls were maintained with a trend towards higher efficacy at the 12-month follow-up.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AE** | adverse events |
| **AF** | atrial fibrillation |
| **EAS** | endoscopic ablation system |
| **PV** | pulmonary vein |
| **PVI** | PV isolation |

Extensive preclinical work was performed to guarantee similar efficacy and safety of lesion generation with the continuous ablation mode using the same 980 nm diode laser. At first, a multi-physics simulation model that closely followed regulatory guidance for modeling medical device performance was computed to simulate lesion contiguity and depth as well as tissue temperature during continuous ablation. The model predicted that 13 and 15 W continuous ablation resulted in comparable lesion depth and tissue temperatures as 8.5 and 12 W manual spot ablation, respectively. Remarkably, the estimated tissue temperature was well below 100°C to minimize the risk for steam pop. Subsequently, the new ablation mode was validated for lesion equivalence in a turkey thigh model as well as in an in vivo pig model confirming lesion contiguity and transmurality.

To assess the acute safety and performance as well as chronic efficacy of the X3 EAS (X3), a prospective, historically controlled, single-arm pivotal multi-center study was initiated. Procedural as well as 12 months follow-up data were compared with a historical control group from the HeartLight US IDE (Investigational Device Exemption) pivotal study.[2]

# METHODS

The authors declare that all supporting data are available within the article and in the Data Supplement. The study protocol was approved by the local ethics committees. The study was registered. All patients enrolled in the study provided written informed consent.

At each study site, patients with drug-refractory paroxysmal atrial fibrillation, defined as failure or intolerance to at least one class I to III antiarrhythmic drug, aged 18 to 75 years, were enrolled.

Exclusion criteria included >4 cardioversions in the year before enrollment, documented left atrial thrombus, a left ventricular ejection fraction <30%, prior left atrial ablation for atrial fibrillation (AF) or atrial flutter, New York Heart Association class III or IV symptoms, myocardial infarction within the prior 60 days, unstable angina, any cardiac surgery in the prior 3 months, coronary artery bypass graft procedure in the prior 6 months, thromboembolic event in the prior 3 months, uncontrolled bleeding, active infection, atrial myxoma, severe pulmonary disease or gastrointestinal bleeding, a prior valvular cardiac surgical procedure, presence of an implanted 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

The study was prospective, multi-center, and historically controlled. It was conducted at 2 study sites with ablation procedures performed by a total of 4 primary operators (2 at each site). A maximum of 70 participants were to be enrolled in this study with the goal of treating up to 60 participants. This sample size allowed up to a 15% drop-out rate after enrollment and before treatment.

The study was powered for the primary study hypothesis, which was to test whether ablation time with HeartLight X3 was less than ablation time with the currently available HeartLight System. A sample size of 60 treated participants yielded >80% power to demonstrate the ablation time for HeartLight X3 was less than the ablation time in the historical control assuming a 20 minutes reduction in ablation time with equal variance using a SD of 46.6. For the secondary acute end point of procedure time, 60 treated participants yielded >80% power to demonstrate the procedure time for HeartLight X3 was decreased over the procedure time in the historical control study assuming a 23 minutes reduction in procedure time with equal variance (SD=52.8). For the secondary acute efficacy end point, 60 participants (conservatively estimated to yield 210 treated PVs) also had well above 80% power to demonstrate the percent of PVs isolated was not different than the rate of PVs isolated in the historical control study (97.7%) with a noninferiority margin of 10%. For the secondary acute safety end point, 60 treated participants yielded >80% power to demonstrate the rate of primary adverse events (AE) was not different than the rate of primary AE in the historical control study (5.3%) with a noninferiority margin of 10%.

The study protocol design was near identical to the HeartLight IDE pivotal study with similar inclusion and exclusion criteria, end point definitions and follow-up schedules.

Following informed consent, participants underwent baseline evaluation and testing. Required assessments were medical history, physical exam, pregnancy test for females of childbearing potential, a 12-lead echocardiogram and a transthoracic echocardiogram. The study was monitored by an independent contract research organization, and safety was reviewed by an independent Medical Monitor (experienced electrophysiologist).

## Investigational Device

The X3 catheter is an update of the existing Excalibur system. The primary difference is the integration of a motor into the catheter handle to enable controlled, continuous energy delivery in addition to the conventional point-by-point ablation mode. The balloon has a variable-diameter, compliant balloon delivered to the left atrium through a 12F deflectable sheath. Within the central shaft of the balloon catheter is a 2F endoscope that permits real-time visualization of the target tissue. Due to the eccentric position of the endoscope riding on the central catheter shaft, the endoscopic view to the PV ostium is limited to ≈300°.

The central shaft also contains lumens for circulating the balloon-filling media ($D_2O$) which cools the balloon, and 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 advanced, retracted, and rotated to any location along the surface of the balloon to allow aiming and then ablation using diode laser energy (980 nm). The catheter tip is equipped with a flexible tip segment to minimize the risk of catheter-induced trauma. The shaft of the catheter contains a radiopaque marker that can be visualized on fluoroscopy to align the endoscopic image with the fluoroscopic position of the balloon.

During the course of the clinical study, a prototype version of the X3 was used that had a reusable motor cable assembly and a motor control box external to the console.

In addition to the conventional, manually controlled point-by point ablation mode with preset power (5.5–12 W) and lesion duration (20–30 seconds), the X3 offers a novel RAPID mode. During RAPID mode, the lesion generator is continuously moved around the PV ostium (either clockwise or counterclockwise) at a preset speed (2.25° per second) by an integrated motor. In this study, ablation power could be titrated to 13, 15, or 18 W.

## Ablation Procedure

All ablations were performed under intravenous sedation using propofol, midazolam, and sufentanyl. After femoral venous access, transseptal puncture was performed using a 8F sheath and a Brockenbrough needle with fluoroscopy guidance. Intravenous heparin was administered as boluses and as a continuous infusion to maintain an activated clotting time ≥300 seconds. The transseptal sheath was then exchanged for the 12F deflectable sheath. Preablation electrical mapping of PV potentials was performed using a circular mapping catheter. The use of intracardiac ultrasound was optional. Esophageal temperature monitoring was mandatory using a commercial temperature probe (Circa S-Cath, Circa Scientific or SensiTherm, Abbott). Ablation was stopped if the esophageal temperature exceeded 38.5 °C.

Using the deflectable sheath, the X3 catheter was positioned at the ostium of the target PV, and the balloon was inflated. Ablation was performed under visual guidance. Ablation consisted of ablative energy delivery segments of either RAPID mode or manual mode energy delivery or a combination of both. If at least one segment of RAPID mode energy was delivered into a PV, that PV was considered treated in RAPID mode. After placement of the initial anatomically guided encircling lesion set, the circular mapping catheter was used to assess for electrical isolation of the PV. If the PV was not isolated, X3 was again used to deliver lesions to the area of electrical breakthrough or alternatively another lesion set completely encircling the PV was delivered. During ablation of the right-sided PVs, phrenic nerve pacing was always performed from the superior vena cava to minimize the risk of phrenic nerve injury by monitoring for diaphragmatic movement.

After 30 minutes postablation, PVs were reassessed for electrical isolation. A circular mapping catheter was used to identify entrance block. At the discretion of the investigators, ancillary right-sided atrial flutter ablation was allowed for participants with a history of atrial flutter as well as for individuals who experienced atrial flutter during the ablation procedure.

## Follow-Up

At discharge, appropriate anticoagulation therapy was initiated. A follow-up visit occurred at 1 month and included a 12-lead ECG, physical exam and assessment of AE.

Follow-up visits at 3 and 12 months were required during the chronic phase of the study to assess for safety, evidence of AF recurrence, and additional interventions. Participants were given transtelephonic monitors before they completed the 90-day postablation blanking period. Transtelephonic monitoring (Physiomem PM 100; Medical Data Transfer, Brno, Czech Republic) was performed starting at 90 days and continued through 12 months, as was done in the control study. Participants were required to transmit all symptomatic cardiac episodes. They were also required to provide additional scheduled transmissions irrespective of symptoms weekly starting at 90 days through study month 12. One 24-hour Holter monitor (Faros Holter; MDT, Brno, Czech Republic) was required at 12 months for all participants. All data was source checked by the clinical research organization, and all safety data were reviewed and re-evaluated by the independent Medical Monitor.

## Study End Points

The primary end point was ablation time defined as the time from insertion of the X3 catheter into the participant to the end of the last 30-minute wait period. Ablation time was calculated independent of delivery mode (RAPID mode, manual HeartLight mode, or a combination of the 2 modes).

Prespecified additional comparisons between the 2 groups included the following secondary end points:

- Procedure time, defined as the time from venous access to the end of the last 30-minute wait period.
- Acute efficacy was calculated by taking the number of PVs successfully isolated by RAPID mode divided by the number of PVs attempted to be treated using RAPID mode.
- Safety; 30-day primary AE rate defined as follows: transient ischemic attack (within 1 month of treatment), cerebrovascular accident including stroke caused by air embolism (within 1 month of treatment), major bleeding that requires transfusion (life-threatening bleeding requiring ≥2 units packed red blood cells or resulting in an absolute decrease in hematocrit ≥10% within 1 week of treatment), cardiac perforation, tamponade, or clinically significant pericardial effusion (within 1 month of treatment), myocardial infarction (Q-wave only—within 1 week of treatment), diaphragmatic paralysis, atrio-esophageal fistula, death (during the evaluation period and cause possibly related to device or procedure or if unknown).

- Chronic effectiveness—6- and 12-month AF-free rates defined as the absence of symptomatic AF lasting 1 minute or more as documented on event monitor, ECG or Holter monitor beyond the 90-day blanking period and during the 12-month evaluation period. Ablation-induced left atrial flutter or atrial tachycardia (atypical atrial flutter or atrial tachycardia) occurring after the 90-day blanking period was considered a treatment failure. Treatment failure was also defined as any participant that did not have all clinically relevant PVs isolated. Any class I, II, III antiarrhythmic drug prescribed for AF during the 9 to 12 months postablation index procedure was also considered a treatment failure. Any participant who had cardiac surgery, left heart ablation, or an implantable implantable cardioverter defibrillator for AF during follow-up before the 12-month visit was considered a treatment failure.
- Safety through 12-month follow-up confirmed by careful recording of all AE. All AEs were reviewed and adjudicated by the Medical Monitor.

## Statistical Analysis

The statistical design was prospective and historically controlled. The statistical analysis of the primary end point was a test of superiority using a 2-sample *t* test. Raw data from the HeartLight study (25-3002) was used for the control arm in all end point analyses and comparisons. Additionally, an ANOVA was performed to adjust for differences in baseline characteristics between groups, specifically age, gender, and duration of AF.

The 3 secondary end points were tested in a prespecified order to address alpha adjustment for multiple testing. Procedure time was evaluated first using a 2-sample *t* test for superiority. Acute efficacy was evaluated next. The Farrington-Manning method was used to test the one-sided hypotheses of noninferiority in differences between the 2 groups with an absolute noninferiority margin of 10%. The last secondary end point evaluated was the 30-day primary adverse event rate. The Farrington-Manning method was used to test the one-sided hypothesis of noninferiority in the differences between groups with a noninferiority margin of 10%. For this end point, the rate in the historical control was adjusted based on the elimination of 2 events. PV stenosis was eliminated because there were no reports of PV stenosis in the HeartLight study, and cardioversion was eliminated as it is no longer typically considered a complication of AF ablation.

Descriptive statistics were used to summarize all data relevant to the study. Continuous variables are presented as means and SDs with 95% CIs, as well as medians and ranges. For categorical variables, relative frequencies are provided and include 95% CIs for study end points. Statistical comparisons were performed using 2-sided significance tests and 95% CIs for the differences between groups. Statistical comparisons were performed using 2-sided significance tests. The analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

# RESULTS

Between February and November 2018, a total of 60 patients were enrolled at 2 centers and were evaluable for the primary end point. Data was compared with 170 patients from the pivotal HeartLight study.

Demographic details are given in Table 1. In brief, more female patients were enrolled (n=31; 51.7%), and mean age was 63.6±8.0 years, thus significantly older than in the HeartLight study. The median history of AF-related symptoms was 1 year (range, 0.1–33 years), and 43% and 17% of patients had used class I or class III antiarrhythmic drugs, respectively. Electrical cardioversions had been performed in 31/60 patients. Co-morbidities were prevalent in most patients without any significant differences compared with the control population. Echocardiography showed a mean left ventricular ejection fraction of 62±8%.

## End Points

Except one PV treated only with manual mode, PVs were treated with some (76/229, 33.2%) or all (152/229, 66.4%) RAPID mode (Table 2; Movie I in the Data Supplement). Acute PVI using RAPID mode was achieved in 225/228 of these PVs treated with RAPID mode (98.7%; Figure 1). The primary end point, ablation time, was significantly shorter with X3 than in the HeartLight study (77.3±25.8 versus 173.8±46.6 min; $P<0.0001$; Figure 2). Results were similar after adjusting for baseline characteristics ($P<0.0001$).

Similarly, total procedure time was significantly shorter (103.7±32.3 versus 236.0±52.8 min; $P<0.0001$). This was accompanied by a significantly shorter fluoroscopy time (6.9±3.5 versus 35.6±18.2; $P<0.0001$). At the same time, the absolute ablation energy deployed was significantly lower (13.3±4.2 versus 27.6±7.6 kJ; $P<0.0001$).

Of note, compared with the irrigated RF ablation control arm in the HeartLight IDE study, procedure (193.0±63.7 mins), ablation (151.2±56.2 mins), and fluoroscopy (29.7±21 mins) times were also significantly shorter ($P<0.0001$; Figure 2).

PVI after the first circular lesion was achieved in 91.6% of PVs isolated (206/225). First pass isolation was achieved in 65/74 PVs (88%) and 141/151 PVs (93%) after partial and exclusive RAPID mode use, respectively. In 9/60 (15%) cases, a second EAS ablation catheter had to be used because of pinhole in the balloon (n=8) or lesion generator malfunction (n=1). Additional ablation was performed in 1 patient to treat right-sided typical atrial flutter.

In total, 11 procedure-related serious AE within the first 30 days were reported (Table 3). This included arrhythmia recurrence (n=4), stroke (n=2), vascular access-related complications (n=2), thermal esophageal lesions (n=2), and pericardial tamponade (n=1). None of the events was deemed definitely or probably device related by the investigators or the independent Medical Monitor.

In one patient, ischemic stroke occurred 7 days postablation and immediately postcardioversion despite an INR of 4.1. A computed tomography and magnetic

**Table 1. Demographic Data**

| Demographics | | | |
|---|---|---|---|
| | X3 | HL | |
| | N=60 | N=170 | *P* value |
| Age, y | 63.6±8.0 (60) | 59.7±10.4 (170) | 0.009 |
| Gender | | | 0.005 |
| Male | 48.3% (29/60) | 69.4% (118/170) | |
| Female | 51.7% (31/60) | 30.6% (52/170) | |
| Race* | | | 0.660 |
| White | 100.0% (35/35) | 96.5% (164/170) | |
| Black | 0% (0/35) | 2.9% (5/170) | |
| Asian | 0% (0/35) | 0.6% (1/170) | |
| Duration of AF, y | 1 (0.08–33) | 2 (0.08–40) | 0.043 |
| Hypertension | 70.0% (42/60) | 59.4% (101/170) | 0.252 |
| Coronary artery disease | 10.0% (6/60) | 21.2% (36/170) | 0.244 |
| Myocardial infarction | 1.7% (1/60) | 4.1% (7/170) | 1.000 |
| CABG | 1.7% (1/60) | 2.9% (5/170) | 0.591 |
| CHF | 5.0% (3/60) | 5.3% (9/170) | 1.000 |
| Diabetes | 21.7% (13/60) | 15.3% (26/170) | 0.085 |
| Neurological deficit | 8.3% (5/60) | 6.5% (11/170) | 0.294 |
| Atrial flutter history | 15.0% (9/60) | 24.7% (42/170) | 0.389 |
| Atrial flutter ablation | 3.3% (2/60) | 8.8% (15/170) | 0.317 |
| Ejection fraction, % | 62.0±8.1 (60) | 60.6±7.4 (170) | 0.224 |
| Failed antiarrhythmic medications† | | | |
| Class I | 43.3% (26/60) | 49.4% (84/170) | |
| Class II | 83.3% (50/60) | 50.6% (86/170) | |
| Class III | 16.7% (10/60) | 57.6% (98/170) | |

AF indicates atrial fibrillation; CABG, coronary artery bypass graft; CHF, congestive heart failure; and HL, HeartLight.

*Race not reported for 25 participants. Percentages calculated based on reported data only.

†Participants may fail >1 antiarrhythmic drug.

resonance imaging of the brain was performed showing a small ischemic lesion. After the patient had been switched from warfarin to dabigatran, symptoms (leg weakness) completely resolved.

The second 72-year-old female patient with a history of hypertension, carotid atherosclerosis, and prior hemiparesis stroke developed hemiparesis ≈5 hours after an uneventful procedure and imaging revealed a lacunar stroke. After neurological rehabilitation, symptoms regressed to a minimal degree (weakness of left leg).

The above-mentioned pericardial tamponade developed 8 days after the ablation procedure, and 380 mL of serous fluid were removed from the pericardial space after subxiphoid puncture. Subsequently, pericarditis was diagnosed, and the patient recovered completely.

One patient underwent surgery and vascular repair for a large left groin hematoma, the other was treated by thrombin injection for a pseudoaneurysm. It is important to note that the HeartLight sheath and catheter had been introduced into the right groin.

## Chronic Effectiveness

Of 60 patients undergoing X3 ablation 57 were evaluable for the primary chronic effectiveness end point. The remaining 3 patients withdrew consent before completion of the 6-month follow-up. In the control group, 170 patients were analyzable. At the 6-month and 12-month follow-up, 51/57 (89.5%) and 41/57 (71.9%) patients were free of AF in the X3 study group, respectively. This compared favorably with the rates reported for HeartLight (75.0% at 6 months and 61.1% at 12 months; Figure 3). Of note, chronic effectiveness was 61.7% in the irrigated RF group of the HeartLight IDE study.

In the X3 study group, 4/60 (6.7%) patients underwent a repeat procedure as opposed to 25/170 (14.7%) in the HeartLight historic control and 22/172 (12.8%) in the RF arm of the HeartLight IDE study.

Of the 12 patients who were deemed effectiveness failures for the primary end point, 3 did not have all PVs acutely isolated, 7 patients had symptomatic AF recurrences, 1 patient had symptomatic atrial tachycardia recurrence, 1 patient had a repeat ablation, and 4 patients were still on antiarrhythmic drug treatment.

# DISCUSSION

The study reports the first in human pivotal study of the novel X3 EAS for rapid PVI. The main findings were that (1) RAPID mode can be applied to almost all PVs, (2) X3 leads to acute PVI in almost all PVs, (3) this is accompanied by a drastic decrease in ablation and procedural time compared with the conventional HeartLight system, and (4) the chronic effectiveness is favorable leading to freedom from symptomatic AF off antiarrhythmic drug in 72% of patients during a 12-month follow-up period.

Previous studies on EAS have already demonstrated a similar chronic efficacy for the treatment of patients with drug-refractory paroxysmal as well as persistent AF.[2,3] However, the system had the drawback of prolonged ablation and procedure times. The X3 system now offers a RAPID ablation mode that clinically and statistically reduces ablation and procedure times. Notably, the procedure times were not only significantly shorter than in the historical EAS control group but also shorter than in the irrigated radiofrequency ablation group in the IDE pivotal study.[2] In the historical control study, irrigated RF procedure and ablation times were 193.0±63.6 and 151.2±56.2 minutes, respectively. These times are statistically significantly longer than with X3. The X3 pivotal study showed that RAPID mode was applicable in virtually all PVs, leading to a high rate of first pass PVI. Given this promising change, EAS has evolved from a point-by-point balloon towards a single-shot device approach.

The HeartLight balloon demonstrated a high rate of durable PVI in remapping studies.[5] The fact that the amount of ablation energy that was deployed using X3

**Table 2. Procedural Data**

| Primary end point population | | | |
|---|---|---|---|
| | X3 | HL | Difference |
| | N=60 | N=170 | X3–HL (95% CI) |
| Duration of overall procedure, mins* | | | |
| Mean±SD, N | 103.7±32.3 (60) | 236.0±52.8 (168) | −132.3 (−146.7 to −118.0) |
| Median, min–max | 98.5 (60.0–199.0) | 233.0 (90.0–458.0) | |
| Procedure left atrial time, mins† | | | |
| Mean±SD, N | 90.8±26.1 (60) | 204.2±49.5 (168) | −113.4 (−126.7 to −100.2) |
| Median, min–max | 85.0 (57.0 to 183.0) | 195.5 (72.0 to 423.0) | |
| Duration of ablation, mins‡ | | | |
| Mean±SD, N | 77.3±25.8 (60) | 173.8±46.6 (168) | −96.53 (−109.0 to −84.04) |
| Median, min–max | 72.5 (45.0 to 169.0) | 164.5 (60.0 to 389.0) | |
| Overall fluoroscopy time, mins | | | |
| Mean±SD, N | 6.9±3.5 (60) | 35.6±18.2 (167) | −28.66 (−33.32 to −24.00) |
| Median, min–max | 6.3 (0.8 to 18.1) | 35.0 (3.8 to 123.6) | |
| No. of catheters used | | | |
| 1 | 85.0% (51/60) | 84.1% (143/170) | 0.9% (−9.7% to 11.5%) |
| 2 | 15.0% (9/60) | 15.3% (26/170) | −0.3% (−10.8% to 10.2%) |
| 3 | 0.0% (0/60) | 0.6% (1/170) | −0.6% (−1.7% to 0.6%) |
| No. of veins attempted | | | |
| Mean±SD, N | 3.8±0.4 (60) | 3.9±0.4 (170) | −0.09 (−0.22 to 0.04) |
| Median, min–max | 4.0 (3.0 to 5.0) | 4.0 (1.0 to 5.0) | |
| No. of veins attempted | | | |
| 1 | 0.0% (0/60) | 0.6% (1/170) | −0.6% (−1.7% to 0.6%) |
| 2 | 0.0% (0/60) | 0.6% (1/170) | −0.6% (−1.7% to 0.6%) |
| 3 | 20.0% (12/60) | 8.8% (15/170) | 11.2% (0.2% to 22.2%) |
| 4 | 78.3% (47/60) | 87.6% (149/170) | −9.3% (−20.9% to 2.2%) |
| 5 | 1.7% (1/60) | 2.4% (4/170) | −0.7% (−4.6% to 3.3%) |
| No. of joules | | | |
| Mean±SD, N | 13 286±4198.7 (60) | 27 558±7552.7 (163) | −14 273 (−16 302 to −12 243) |
| Median, min–max | 12 136 (7836.0 to 27 160) | 26 802 (6713.0 to 59 508) | |
| Energy delivery mode per vein | | | |
| RAPID only | 66.4% (152/229) | | |
| RAPID and manual | 33.2% (76/229) | | |
| Manual only | 0.4% (1/229) | | |
| No. of mappings to final block per vein (for veins where block was achieved) | | | |
| 1 | 91.6% (207/226) | 89.8% (583/649) | 1.8% (−2.5% to 6.1%) |
| 2 | 4.9% (11/226) | 6.9% (45/649) | −2.1% (−5.5% to 1.4%) |
| 3 | 3.1% (7/226) | 2.3% (15/649) | 0.8% (−1.8% to 3.3%) |
| >3 | 0.4% (1/226) | 0.9% (6/649) | −0.5% (−1.6% to 0.7%) |
| Ancillary procedures performed during index procedure | 1.7% (1/60) | 13.5% (23/170) | −11.9% (−17.9% to −5.8%) |
| Type of ancillary procedures performed | | | |
| Right-sided flutter ablation | 1.7% (1/60) | 12.4% (21/170) | −10.7% (−16.6% to −4.8%) |
| Other left-sided procedures | 0.0% (0/60) | 0.6% (1/170) | −0.6% (−1.7% to 0.6%) |
| Other | | 1.2% (2/170) | |
| Ablation completed with nonstudy catheter§ | 0.0% (0/60) | 2.4% (4/170) | −2.4% (−4.6% to −0.1%) |
| No. of days in hospital | | | |
| Mean±SD, N | 3.0±0.9 (60) | 2.3±1.2 (170) | 0.68 (0.34 to 1.02) |
| Median, min–max | 3.0 (2.0 to 7.0) | 2.0 (2.0 to 10.0) | |

HL indicates HeartLight.
*Defined as the time from venous access to the time at conclusion of the last 30 min wait period.
†Defined as the time from transseptal puncture to the time at conclusion of the last 30 min wait period.
‡Defined as the time from the insertion of the ablation catheter to the time at conclusion of the last 30 min wait period.
§Isolation of all veins not achieved with the ablation catheter, procedure completed with a nonstudy catheter.

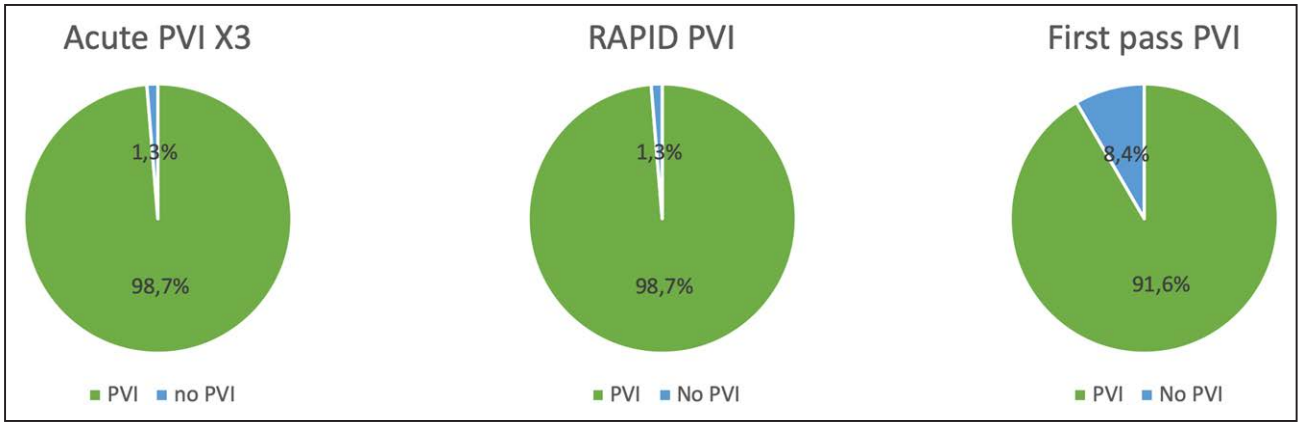


**Figure 1. Fraction of pulmonary vein (PVs) acutely isolated using X3.**
**A**, Acute PV isolation (PVI) in total. **B**, Acute PVI using RAPID mode. **C**, Acute PCI after the first lesion set using X3.

was significantly less may raise the concern that lesion durability may be compromised. While, remapping data was not collected, the favorable chronic effectiveness data is, however, reassuring.

During the study, 18 W rapid was rarely used, and so this power setting has been eliminated from the commercial version of the X3 System.

## Comparison to Single-Shot Devices

The cryo-balloon offers the ability to record on-line intracardiac electrograms via a circular mapping catheter that is placed distally to the balloon via the central lumen of the catheter shaft. In experienced centers, single-shot PVI rates with on-line electrogram recordings may be achieved in up to 85% of PVs.[6] Comparably, the first pass PVI rates after a single circular lesion set were close to 92% per PV. However, the proof of electrical PVI requires catheter exchange maneuvers to place a separate circular mapping catheter. It would be desirable, that future versions of the EAS are equipped with a circular mapping catheter or distal electrodes.

Alternatively, given the high first pass isolation rate with X3, one could consider abandoning PV remapping as suggested by most recent studies. In the AVATAR study (Ablation Versus Anti-Arrhythmic Therapy for Reducing All Hospital Episodes From Recurrent Atrial Fibrillation), using the cryo-balloon, a standard PVI with proven electrical PVI did not show differences in effectiveness compared with a streamlined ablation protocol with two 120 seconds applications without electrogram recordings (AVATAR study).

## Safety

All safety events that were observed in the X3 feasibility study were expected and have been reported in earlier studies using EAS.[7,8] Of note, no phrenic nerve palsy was observed, which is a typical balloon-associated complication occurring at a rate of 1% to 2.5% using EAS.[9,10] This may be the consequence of a more antral lesion set

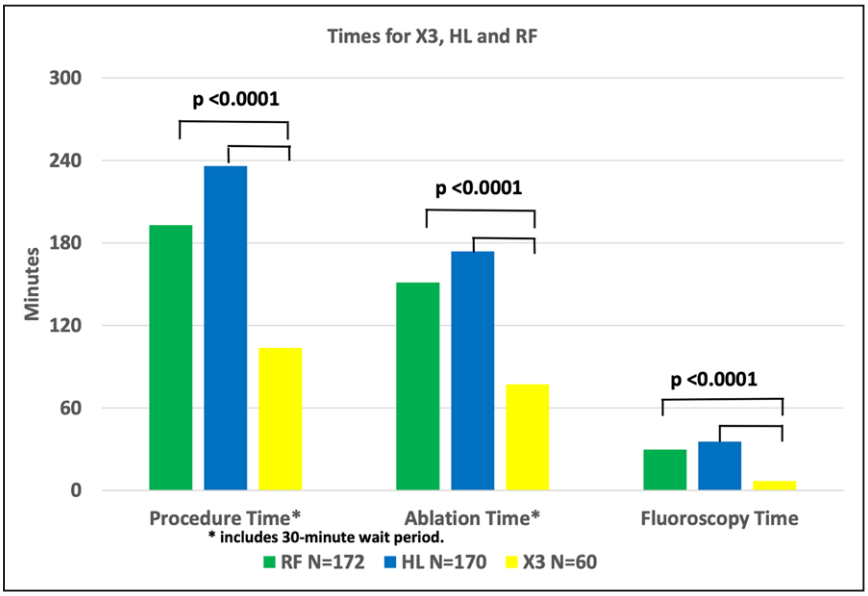


**Figure 2. Procedural characteristics in comparison to the HL IDE study (HeartLight Investigational Device Exemption)**
Green bars–Control group using irrigated radiofrequency current ablation. Blue bars–HeartLight group in the HL IDE study. Yellow bars–X3 group.

**Table 3. Serious Adverse Events**

| Safety population | | | |
|---|---|---|---|
| | X3 definition (3) | HL definition (4) | |
| | X3 (n=60) | X3 (n=60) | HL (n=170) |
| Serious adverse event name* | | | |
| Arrhythmia | 5.0% (3/60) | 0.0% (0/60) | 0.0% (0/170) |
| Atrial fibrillation | 1.7% (1/60) | 0.0% (0/60) | 0.0% (0/170) |
| SVT; AVNRT | 1.7% (1/60) | 0.0% (0/60) | 0.0% (0/170) |
| Tachyarrhythmia absoluta | 1.7% (1/60) | 0.0% (0/60) | 0.0% (0/170) |
| Cardiac tamponade | 0.0% (0/60) | 0.0% (0/60) | 1.2% (2/170) |
| Cerebrovascular event stroke | 3.3% (2/60) | 3.3% (2/60) | 0.6% (1/170) |
| Chest pain/discomfort | 1.7% (1/60) | 0.0% (0/60) | 0.6% (1/170) |
| Diaphragmatic paralysis | 0.0% (0/60) | 0.0% (0/60) | 0.6% (1/170) |
| Hematoma/ecchymosis | 1.7% (1/60) | 1.7% (1/60) | 0.0% (0/170) |
| Phrenic nerve injury leading to diaphragmatic paralysis | 0.0% (0/60) | 0.0% (0/60) | 2.4% (4/170) |
| Pseudoaneurysm | 1.7% (1/60) | 0.0% (0/60) | 0.6% (1/170) |
| Other | 3.3% (2/60) | 1.7% (1/60) | 0.6% (1/170) |
| Dyspepsic difficulties | 1.7% (1/60) | 0.0% (0/60) | 0.0% (0/170) |
| Esophageal erosion | 1.7% (1/60) | 0.0% (0/60) | 0.0% (0/170) |
| Moderate drop in hemoglobin | 0.0% (0/60) | 0.0% (0/60) | 0.6% (1/170) |
| Pericardial/pleural effusion clinically significant | 1.7% (1/60) | 1.7% (1/60) | 0.0% (0/170) |

AVNRT indicates atrioventricular-nodal reentry tachycardia; HL, HeartLight; and SVT, supraventricular tachycardia.

A participant is counted only once within each serious adverse event name category, however, could be counted multiple times across different serious adverse event name categories and, therefore, the percentage might not add up to 100%. Two participants experienced 3 other serious adverse events.

*Adverse event terms specified by the protocol are presented.

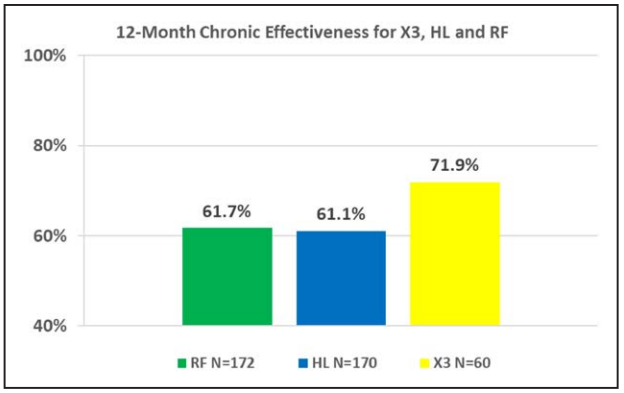


**Figure 3. Chronic effectiveness data 12 mo after index ablation.**
Green bars–Control group using irrigated radiofrequency current ablation. Blue bars–HeartLight (HL) group in the HL IDE (Investigational Device Exemption) study. Yellow bars–X3 group.

using the more compliant balloon. Future studies including more patients will have to show the optimal strategy to avoid phrenic nerve palsy. Similarly, the rate of thermal esophageal injury is in line with previous reports and temperature monitoring or esophageal deviation seem to be appropriate measures for risk reduction.[11]

The stroke rate of 3.3% must be put into clinical context. One stroke occurred 7 days after the ablation at an INR of 4.1 and within 24 hours of a cardioversion, a potential risk factor for stroke.[12] The second stroke occurred in a patient with a preprocedure CHADSVASC score of 5 in whom heparin was administered immediately after transseptal puncture and multiple catheter exchanges had been performed for a defect balloon and for PV mapping. No acute signs of air embolism (eg, ST changes) were observed.

Placing ablation lesions in the close vicinity to blood, particularly when high ablation power is used, may increase the risk for balloon pinholes. In the current study, this was observed at a rate of 12% and is well in line with previous reports on the second-generation balloon.[4] The ablation system provides various options to the operator to mitigate the risk such as placing manual lesions with reduced power and optimizing balloon to tissue contact by varying the balloon size. Users can avoid pinholes by only delivering energy into moving blood at the lowest energy setting of 5.5 W. On the contrary, the device could benefit from 2 innovative features: (1) a warning system to detect excessive balloon heating or (2) a more durable balloon material.

## Limitations

The present study compared X3 procedural data to a historical control cohort of the HeartLight IDE study. While the results reflect the technological progress, one should not underestimate the influence of operator experience. A considerable number of operators in the HeartLight IDE study were novice EAS users, whereas all operators in the X3 study had several years of EAS experience. On the contrary, the X3 procedural results were favorable when compared with the experienced user group in the HeartLight IDE study.

Ultimately, prospective randomized comparisons are warranted to compare X3 to contemporary single-shot ablation devices in terms of procedural speed, effectiveness, and safety.

## Conclusions

The novel generation EAS allows for rapid PVI using an integrated motor drive for continuous lesion deployment. This was associated with a drastic reduction in ablation and procedure times while maintaining the safety and chronic effectiveness compared with the previous EAS generation.

## ARTICLE INFORMATION

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