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Laser balloon ablation for AF: A systematic review and meta-analysis

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Abstract

Introduction: The HeartLight laser balloon ablation system was US Food and Drug Administration approved in 2016 for the treatment of paroxysmal atrial fibrillation (AF), but there have been numerous single-center and multicenter studies published reporting its outcomes, in addition to a few randomized trials. We aimed to systematically review and synthesize currently published outcome data on AF ablation using the laser balloon ablation system.

Methods and Results: We performed a systematic review and meta-analysis of published studies of AF ablation performed using the laser balloon ablation system. Human studies reporting acute procedural results with a minimum of 6 months follow-up were included. Outcomes of interest included acute and 12-month procedural efficacy, safety, and procedure duration. Aggregated data were analyzed with random effects models, using a Bayesian hierarchical approach.

We identified 17 published manuscripts comprising a sample of 1188 patients (mean age 61 years, 80% paroxysmal). At procedure end, 98.8% of targeted pulmonary veins were successfully isolated. The pooled estimate for 12-month freedom from atrial arrhythmia without use of antiarrhythmic drugs for patients with paroxysmal AF was 74.3% (95% confidence interval [CI], 59.9% to 86.4%), and for all AF types combined was 72.9% (65.3% to 79.9%). The most commonly reported procedural complication was phrenic nerve injury (pooled incidence 2.6%; 95% CI, 1.4% to 3.9%), which resolved during follow-up in most cases.

Conclusion: Laser balloon ablation is highly effective at achieving pulmonary vein isolation. Although comparisons are mainly indirect, safety and 12-month efficacy compare favorably with those observed using other currently used AF ablation technologies.

KEYWORDS

atrial fibrillation, CardioFocus, catheter ablation, laser balloon, meta-analysis

1 | INTRODUCTION

Pulmonary vein isolation (PVI) remains the cornerstone of ablative strategies for treating atrial fibrillation (AF), particularly in its paroxysmal form.[1] Despite improvements in three-dimensional (3D) mapping systems and the design of radiofrequency (RF) ablation catheters, including the incorporation of force sensing,[2,3] the achievement of durable PVI with a single procedure continues to be challenging. Failure to achieve permanent PVI has been linked with AF recurrence, contributing to repeat procedures.[4] These and other factors have led to a search for alternatives to traditional RF ablation for the treatment of AF.

The HeartLight Endoscopic Ablation System (CardioFocus, Inc, Marlborough, MA) is designed to achieve PVI with a catheter that includes several unique features including a compliant balloon and a small endoscope, used to aim an adjustable arc of laser energy. The HeartLight system was approved by the US Food and Drug Administration in 2016 for the treatment of paroxysmal AF, primarily on the basis of a 366 patient randomized noninferiority trial comparing outcomes with laser balloon ablation to those with ablation using a previously approved irrigated RF catheter with 3D electroanatomical guidance.[5,6]

Worldwide experience with laser balloon ablation is growing. Although few controlled studies have been completed directly comparing laser balloon ablation to alternative ablation strategies, a larger number of single-center and multicenter studies have now been published reporting on the safety and efficacy of the system for treating AF. To better understand the potential role of laser balloon ablation in clinical practice and quantify expected outcomes with use of this system, we conducted a systematic review and meta-analysis to derive summary estimates of safety, acute procedural success, and medium-term efficacy.

2 | METHODS

2.1 | Literature search

This meta-analysis was conducted in accordance with recommendations from the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) group.[7] As our study used only data from previously published studies and did not involve the collection or analysis of data on any patients from the authors' local institutions, approval of the research by an institutional review board was not sought. A literature search was conducted in PubMed and the Web of Science to identify candidate studies for review. The following search terms were used: AF AND ablation AND ("visually guided" OR endoscopic OR laser OR "laser balloon"). A secondary review was performed by reviewing reference lists from initially selected studies as well as pertinent review articles in the field.

Studies to be included in the meta-analysis were required to meet the following criteria: (a) human study, (b) published in the peer-reviewed medical literature, (c) no restrictions on language provided that non-English publications could be translated sufficiently for data abstraction, (d) reports included patients with AF treated with PVI using the laser balloon ablation system, (e) acute procedural results included, and (f) a minimum of 6 months of clinical follow-up were included. Studies were excluded under the following circumstances: (a) animal study, (b) case-report or limited case series including less than 10 patients, (c) surgical (epicardial) ablation performed.

The abstracts of initially screened papers were reviewed by at least two board certified or board eligible cardiac electrophysiologists. The full-text manuscripts of studies potentially meeting inclusion criteria were obtained for secondary review for inclusion. If any studies were found to report results from redundant or overlapping patient populations, the most recent published report was included.

2.2 | Endpoints and data abstraction

The following outcomes of interest were abstracted from each study publication, when available: proportion of pulmonary veins isolated with first encirclement, and at procedure end using the laser balloon; 12 months freedom from symptomatic atrial arrhythmia (including AF, atrial flutter, and atrial tachycardia) in the absence of antiarrhythmic drug therapy; procedure duration; and fluoroscopy time. Freedom from atrial arrhythmia was examined, where possible, for only patients with paroxysmal AF, and additionally, for all reported patients regardless of AF pattern. Endpoint definitions and rates of specific procedural complications were also abstracted, including phrenic nerve injury (overall and persistent), cardiac perforation/tamponade, stroke, and death. In addition, when reported, the impact of learning curve effects on procedure duration and fluoroscopy time were recorded.

2.3 | Statistical analysis

To accommodate the anticipated heterogeneity across studies, we used random effects meta-analysis to synthesize results. We used a Bayesian hierarchical approach to estimate the random effects model. We assumed a Student's *t*-distribution with 4 degrees of freedom for random effects. The freely available, open-source program OpenBUGS (Bayesian inference using the Gibbs Sampling) was used to fit the models.[8] Noninformative priors (normal distribution with mean = 0, SD = 1000) for the overall mean hazard ratio (HR) and inverse-gamma (0.00001 and 0.00001) for the between study variance were used. Convergence of the markov chain monte carlo (MCMC) sampler was assessed using the Brooks-Gelman-Rubin method.[9] Specifically, we used four chains; convergence of the sampler was established if the ratio of within-chain and between-chain variability for the four chains starting at different initial values was close to 1.

Heterogeneity across studies was assessed using the Cochran *Q* test. Posterior inferences (HR and 95% credible intervals) were calculated by sampling from the posterior distribution of the parameters. Sensitivity analyses were conducted to investigate the robustness of our results. First, we repeated our analysis omitting one study at a time to assess whether any of the included studies had a large influence on the results. Second, we also performed a secondary analysis restricting the data to cohorts of patients treated only for paroxysmal AF.

3 | RESULTS

Our initial literature search (performed 26 January 2018) yielded 428 titles and abstracts (Figure 1). Of these, 45 full-length manuscripts were selected for secondary review, 17 of which met criteria for inclusion in the meta-analysis. The most common reasons for excluding studies

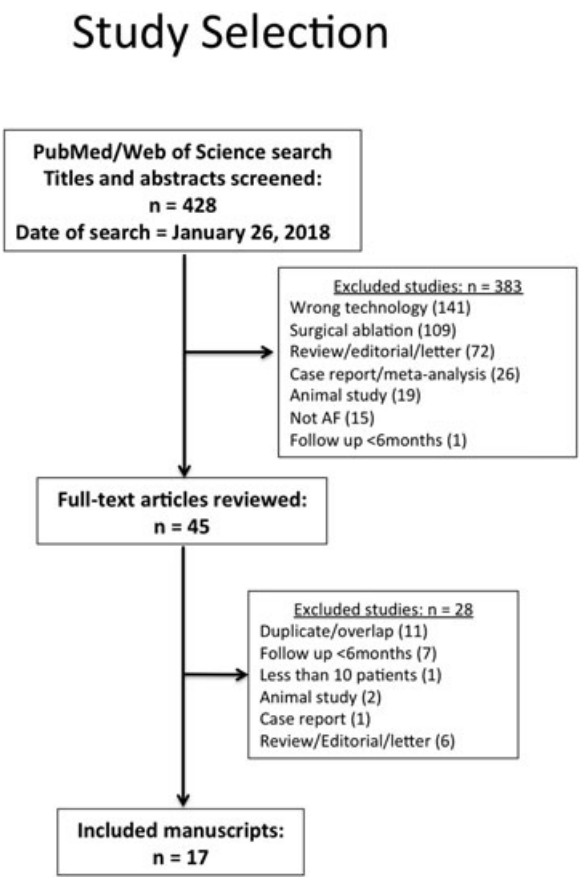

FIGURE 1 Study selection. Algorithm is shown for study search, selection of 17 manuscripts and reasons for excluding other studies

were that studies involved surgical/epicardial ablation and/or some other ablation technology, as shown in Figure 1. Characteristics of the included studies are shown in Table 1. Complete references for the publications are included in the Supporting Information Appendix.

The 17 selected studies included 1188 patients (range 20 to 194) from approximately 40 centers in eight countries. All but one of the studies was performed using the initial commercially available laser balloon ablation system, as changes were made to the original prototype design after publication of the first human series.[10] The mean age of study subjects (weighted average across studies) was 60.6 years, and 67.5% of study participants were male. Of the 17 studies, seven included only subjects with paroxysmal AF, three included only subjects with persistent AF, and seven included both paroxysmal and persistent AF. Overall, 80% of the patients had paroxysmal AF.

3.1 | Acute and 12-month efficacy

The proportion of pulmonary veins (PVs) successfully isolated with the laser balloon by procedure end was reported in all 17 studies (Figure 2), with a pooled rate of 98.8% (95% confidence interval [CI], 97.5% to 99.6%). Although statistical assessment indicated a moderate degree of heterogeneity ($I^2 = 75.2\%$), only two studies reported a rate of isolation below 95%. The frequency (per vein) of PVI with first encirclement by the laser balloon was reported in 11 studies, with a summary estimate of 89.3% (Supporting Information Figure 1).

Efficacy at 12 months for patients with only paroxysmal AF could be abstracted from eight studies (Figure 3), while 13 manuscripts reported 12-month success for either paroxysmal, persistent or mixed paroxysmal/persistent AF groups off of antiarrhythmic drugs (Figure 4). Most of the studies included a standard 3-month blanking period for assessment of efficacy, after which antiarrhythmic drugs were discontinued. In the remaining four studies, 12-month efficacy results free of antiarrhythmic drugs could not be determined. In random effects models, the pooled estimate for 12-month success among groups with only paroxysmal AF was 74.3% (95% CI, 59.9% to 86.4%), and for all AF types combined was 72.9% (65.3% to 79.9%). Substantial heterogeneity was present across studies for estimates of 12-month success. Of the studies included in our meta-analysis, three exclusively enrolled patients with persistent AF; 12-month success was reported in two of the three. In most of the other studies that enrolled a combination of paroxysmal and persistent AF, 12-month success rates were not reported separately by AF type. We therefore elected not to calculate 12-month success for patients with persistent AF.

3.2 | Safety

The most commonly reported procedural complication following AF ablation with the laser balloon was phrenic nerve injury (Figure 5), which was observed in 32 of 1162 procedures across 16 studies (pooled incidence 2.6%; 95% CI, 1.4% to 3.9%). However, there were only six reported cases where phrenic nerve injury persisted through the end of study follow-up. Cardiac perforation or tamponade (Supporting Information Figure 2) had a pooled estimate of 1.1% (95% CI, 0.3% to 2.3%). Among the studies reviewed, there were five reported strokes (frequency ~0.3%) and two transient ischemic attacks. No procedure-related deaths or atrioesophageal fistulae were reported.

3.3 | Procedure duration and learning curve effects

The pooled estimate for procedure duration (Supporting Information Figure 3) across 13 studies was 183 minutes (95% CI, 154 to 212 minutes) with average fluoroscopy times of 28 minutes (Supporting Information Figure 4). In five studies, learning curve effects on procedure duration were reported, by partitioning study samples (by quartiles, tertiles, or sequential groups of 15 to 20 patients) and reporting mean procedure duration for the earliest compared with the most recent subgroups (Figure 6). On average, centers observed a greater than 60-minute decline in procedure duration from their earliest to their most recent groups of patients. After excluding the first human series with the prototype laser balloon ablation system, the mean procedure duration for the most recently completed procedures (where reported) was 154 minutes. Most of these studies included a 30-minute waiting period to assess

TABLE 1 Overview of published manuscripts included in meta-analysis

References	Design	Country	Centers	Patient population	Sample size[a]
Reddy et al[9]	Multicenter pilot/first-in-man	United States, Czech Republic	3	Paroxysmal	30
Metzner (2013)	Multicenter observational	Germany	3	Paroxysmal	72
Sediva et al[19]	Single-center observational	Czech Republic	1	Paroxysmal (92%) or persistent	194
Casella (2014)	Single-center comparative (biomarkers: RF, cryo, laser)	Italy	1	Paroxysmal	20
Wissner (2014)	Single-center comparative (individual vs wide area PVI)	Germany	1	Paroxysmal (76%) or "short-standing" persistent	38
Perrotta et al[18]	Single-center comparative (learning curve)	Germany	1	Paroxysmal (74%) or "short-standing" persistent	150
Dukkipati et al[5]	Multicenter randomized controlled trial (vs irrigated RF)	United States	19	Paroxysmal	167
Dukkipati et al[6]	Multicenter observational	United States	10	Paroxysmal	86
Kumar (2015)	Single-center observational	Netherlands	1	Paroxysmal (90%) or persistent	20
Gal (2015)	Single-center observational	Netherlands	1	Paroxysmal (81%) or persistent	58
Ucer (2015)	Single-center observational	Germany	1	Paroxysmal	26
Stockigt (2016)	Single-center comparative (cryo, laser)	Germany	1	Persistent (29%), long-standing persistent	35
Osca et al[17]	Single-center observational	Spain	1	Paroxysmal (80%) or persistent	71
Bordignon (2016)	Single-center comparative (laser, RF)	Germany	1	Persistent	40
Reissmann (2017)	Single-center observational	Germany	1	Paroxysmal	90
Perrotta et al[15]	Single-center comparative (laser, cryoballoon)	Germany	1	Paroxysmal (70%) or "short-lasting" persistent	20
Schmidt et al[10]	Multicenter randomized controlled trial (vs irrigated RF)	Germany, Czech Republic, Spain	6	Persistent	75

See Supporting Information Appendix for full citations of all included studies.
Abbreviations: cryo, cryoballoon ablation; PVI, pulmonary vein isolation; RF, radiofrequency.
[a]Sample sized indicate number of patients treated with laser balloon ablation.

for acute recovery of PV conduction. In the most recent randomized study comparing laser balloon with RF ablation for persistent AF, procedure times were similar.[11]

4 | DISCUSSION

In this systematic review and meta-analysis of over nearly 1200 patients we found that ablation using the laser balloon system was acutely successful at isolating approximately 98% of targeted PVs, and that this was associated with 12-month freedom from atrial arrhythmias—usually reported after withdrawal of antiarrhythmic drugs—in 70% to 75% of patients. Reported adverse events included phrenic nerve injury in ~2.6% of procedures, which usually resolved during follow-up, pericardial effusion/tamponade in ~1% of procedures, and rare neurologic events. Vascular access complications common to all catheter ablation procedures were also reported, but not systematically analyzed. Experienced users reported procedure times of 2 to 2.5 hours. These data indicate that the laser balloon system is an effective option for achieving PVI.

Although direct comparative data are limited, 12-month clinical success rates appear to be similar to those achieved with alternative ablation systems.[2,3,12–14] This conclusion is supported by the findings from two randomized studies, which reported similar efficacy for laser balloon ablation compared with ablation using irrigated RF catheters in patients with paroxysmal[5,6] and persistent[11] AF. Similar success rates have also been reported in a few small cohort studies comparing laser balloon and cryoballoon ablation.[15,16]

We observed moderate to high amounts of heterogeneity in both acute and 12-month success rates. This could be due to a number of factors, including patient selection, degree of operator or center experience with the laser balloon system, intensity of electrocardiographic monitoring after ablation, or other factors. We did not

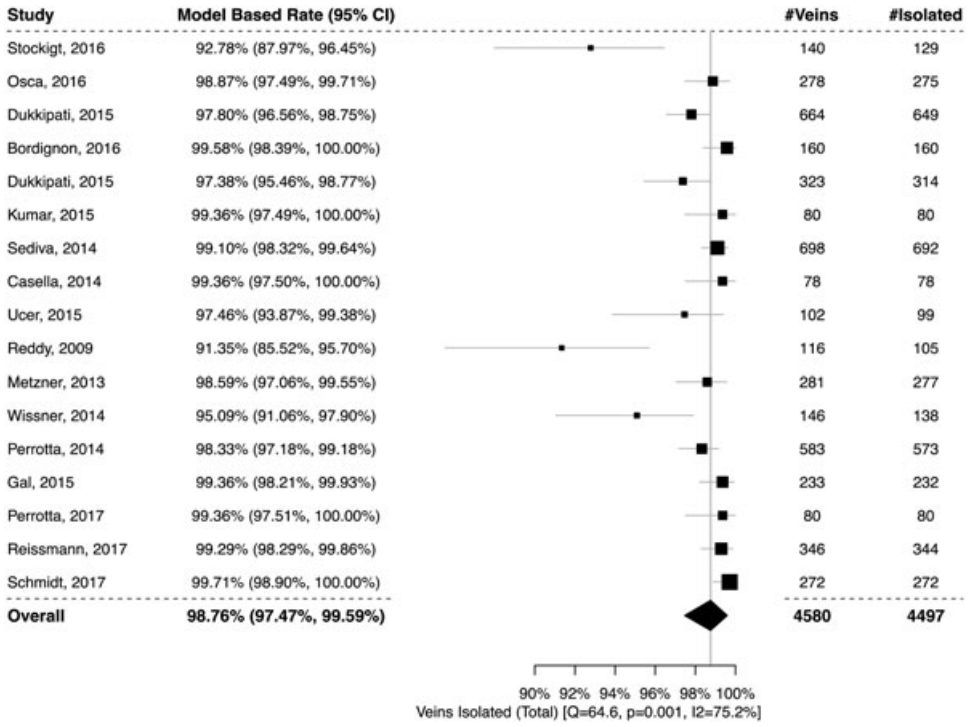

FIGURE 2 Acute success. Forest plot showing proportion of pulmonary veins isolated at procedure end. *Q* = statistic from Cochran's *Q* test (*P*-value is associated with this test). I^2 = Higgins inconsistency measure. Subsequent forest plots use the same reporting scheme. CI, confidence interval

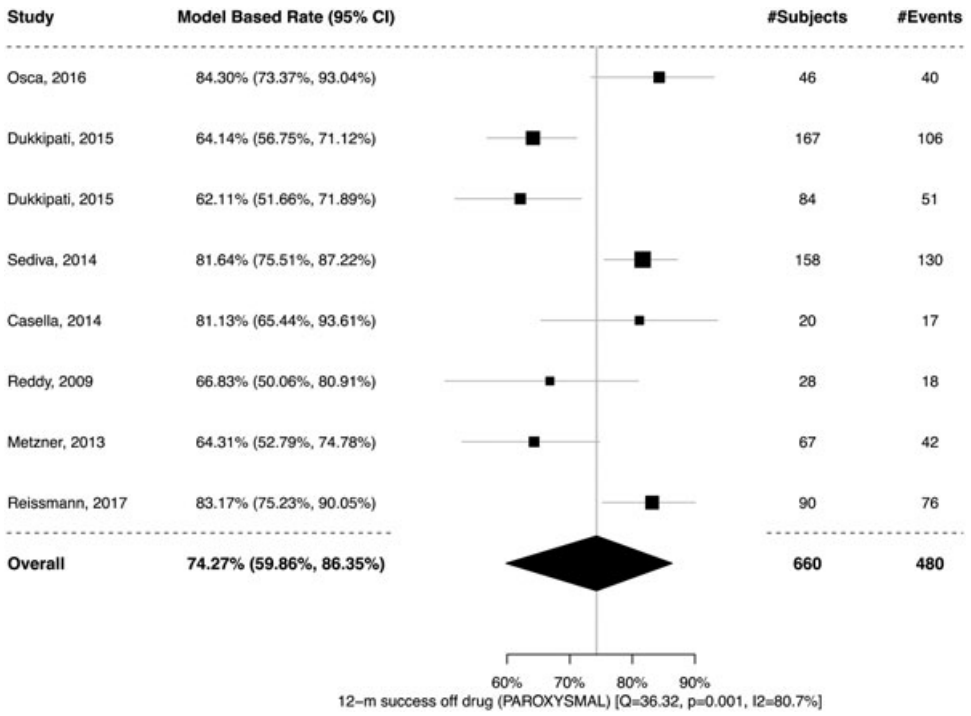

FIGURE 3 Twelve-month success, paroxysmal only. Forest plot showing 12-month freedom from atrial arrhythmia (manuscripts with exclusively paroxysmal atrial fibrillation patients included). CI, confidence interval

observe a clear difference in success between paroxysmal and persistent (or mixed) populations. This may be related to careful selection of persistent AF patients (patients with long-standing persistent AF were generally excluded) and appears consistent with studies suggesting that adjunctive ablation beyond PVI may not improve outcomes in persistent AF patients.[17]

Adverse events observed during ablation with the laser balloon system also appear to be similar in nature and frequency to those

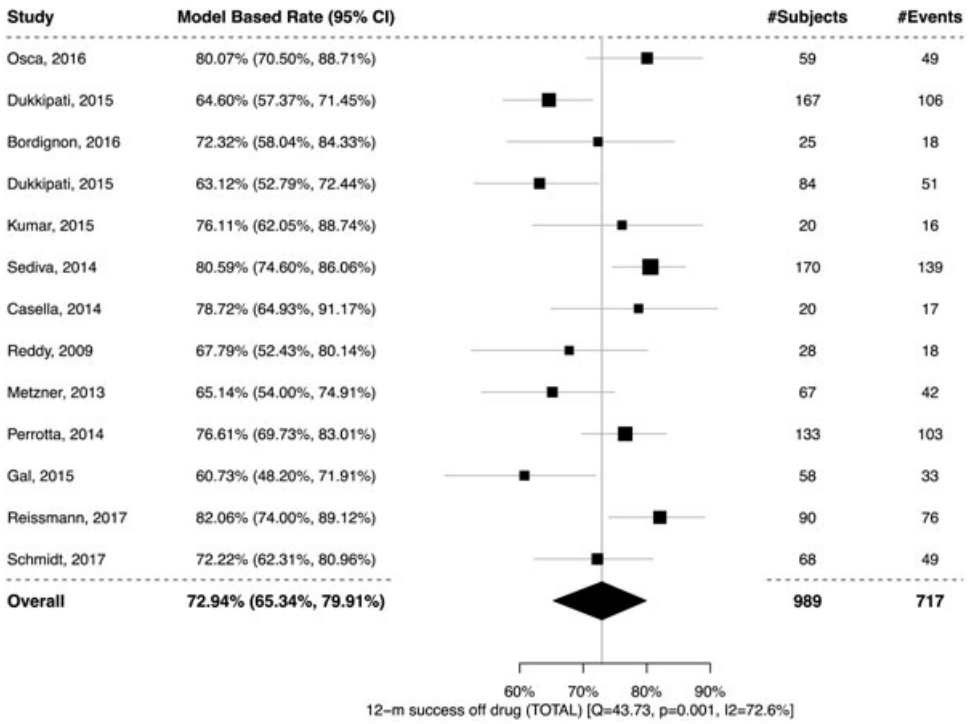

FIGURE 4 Twelve-month success (both). Forest plot showing 12-month freedom from atrial arrhythmia (manuscripts with all atrial fibrillation types included). CI, confidence interval

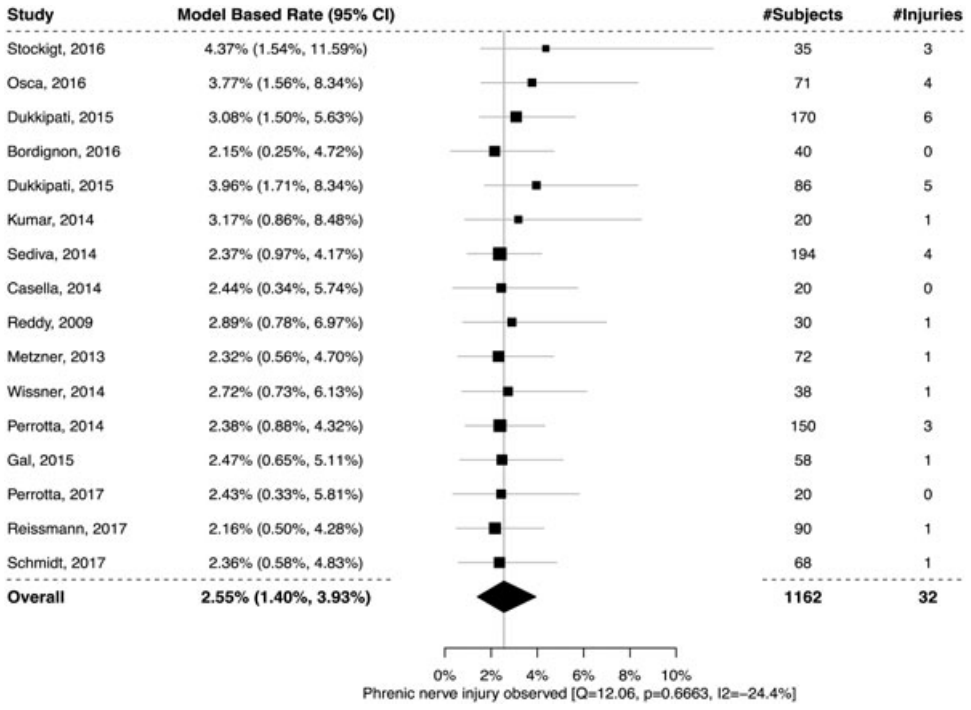

FIGURE 5 Phrenic nerve injury. Forest plot showing rate of phrenic nerve injury from all studies in which it was reported. CI, confidence interval

observed with other AF ablation systems. We observed a 2.5% rate of phrenic nerve injury in meta-analysis, and authors noted that it was rare for this to persist for 12 months or more. As with cryoballoon ablation, phrenic nerve injury, which occurs during ablation around the right-sided PVs, appears to be more common with laser balloon ablation than with RF ablation.[5,12,13] To mitigate the risk of this complication, phrenic nerve pacing should be performed during ablation around the right-sided PVs.

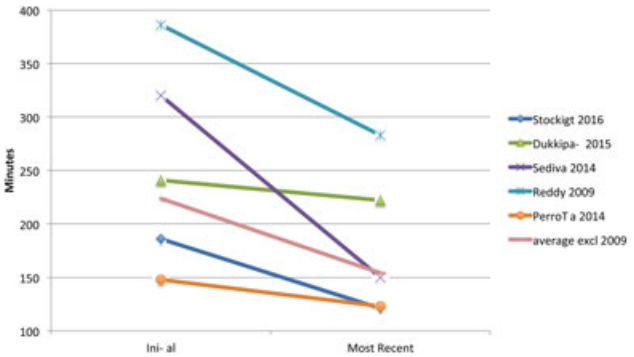

FIGURE 6 Learning curve. Impact of operator experience on average procedure duration is shown from five studies that compared results from their earliest experience to their most recent experience (in quartiles, tertiles, etc). These results were then pooled after excluding the first-in-man study from Reddy et al[10]

In the pivotal US study, no cases of PV stenosis (>50% change in PV diameter from baseline postablation) were found following ablation with the laser balloon system, compared with a rate of 2.9% with RF ablation.[5] No other study in our meta-analysis reported systematic screening for PV stenosis, which has become a rare complication with all current approaches to AF ablation.

Many of the studies included in our meta-analysis involved operators' initial experience with the laser balloon system, and learning curve effects were mentioned in a number of studies.[5,15,18–20] Most often authors reported substantial reductions in procedure duration from their earliest to their most recent experience, along with trends toward lower fluoroscopy time. One group also reported a decrease in adverse events with increased experience.[19] However, likely because of high rates of successful PVI even with limited user experience, a learning curve effect on 12-month efficacy has not been observed.[5,19]

It is worth noting that no major design changes were made to the laser balloon system since soon after the first published human series.[10] Iterative improvements to the system including a new ultra-compliant balloon were incorporated in a second-generation system (Excalibur Balloon, CardioFocus, Inc, Marlborough, MA) recently approved for use in both Europe and the United States. Additional changes to the ablation system, including the use of shorter, high power ablation lesions, are under investigation.

Although the published reports we reviewed have not reported on procedural costs, it is possible that the laser balloon system may offer potential savings relative to alternative systems. Laser balloon ablation does not require 3D mapping. Hence, the cost of certain equipment needed for 3D mapping (eg, reference patches) could potentially be avoided. Further, the very high rate of successful PVI using the laser balloon system should minimize the need for adjunctive use of RF catheters, when a PVI-only ablation strategy is planned.

Our study is subject to limitations. The accuracy and validity of any meta-analysis is always constrained by the quality of its underlying source literature. The rigor of assessing for adverse events and the completeness of follow-up may not have been the same for all of the studies that we included. Most importantly, in our view, few studies—only two randomized—have directly compared the laser balloon system with other approaches to AF ablation. Inferences about how laser balloon ablation compares with other strategies are therefore indirect. A randomized trial comparing laser balloon ablation with contact force-sensing RF among experienced users of both technologies was recently initiated (clinicaltrials.gov identifier NCT03056222).

5 | CONCLUSIONS

In this systematic review and meta-analysis, a growing body of literature showed that the visually guided laser balloon ablation system is highly efficacious at achieving PVI, with a low rate of major adverse events and reported freedom from recurrent arrhythmia in the 70% to 75% range at 12 months. Although mainly indirect, these results compare favorably with those observed with other currently used AF ablation technologies.

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SUPPORTING INFORMATION

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

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