

REVIEW ARTICLE

The Short and Long-Term Efficacy of Pulmonary Vein Isolation as a Sole Treatment Strategy for Paroxysmal Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Abstract: Background: Pulmonary vein isolation (PVI) is an accepted treatment strategy for catheter ablation (CA) of paroxysmal atrial fibrillation (PAF). In this study, we aimed to assess the short, mid- and long-term outcome of PVI as a sole treatment strategy for PAF.

Methods: Six bibliographic electronic databases were searched to identify all published relevant studies until December 14, 2015. Search of the scientific literature was performed for studies describing outcomes with mean follow-up > 24 months after PAF ablation. Only articles with 1, 3 or 5-year follow up were included, from the same group of investigators.

Results: Of the 2398 references reviewed for eligibility, 13 articles (enrolling a total of 1774 patients) were included in the final analysis. Pooled analysis showed that the 12- and 62 -month success rate of a single CA procedure was 78% (95% CI 0.76% to 0.855) and 59% (95% CI 0.56% to 0.64%), respectively. The results did not differ by type of CA performed. Major complications mentioned in the enrolled studies were cerebrovascular event, pericardial tamponade and PV stenosis.

Conclusion: There is a progressive and significant decline in freedom from AF between 1, 3 and 5-year after successful PVI in patients with PAF. Our analysis suggests that a high short-time success rate after PVI does not necessarily result in high chronic success rate.

Keywords: Paroxysmal atrial fibrillation, pulmonary vein isolation, catheter ablation, efficacy of ablation, cerebrovascular event, transient ischemic attack.

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1. INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular tachycardia and it is associated with reduction in quality of life, functional clinical status and overall survival [1-3]. Multiple randomized clinical trials have established that catheter ablation of atrial fibrillation is a superior therapeutic method compared to pharmacological treatment [4-6]. Pulmonary vein isolation (PVI) is the cornerstone of the current catheter ablation techniques and it has been established as a standard therapeutic option for symptomatic paroxysmal atrial fibrillation (PAF) with class I recommendations according to the current guidelines [7, 8]. To achieve PVI,

multiple approaches with different mapping systems have been developed [9-13]. Despite significant improvements in catheter ablation technology, pulmonary vein (PV) reconnection is thought to be a major contributor to postablation arrhythmia recurrence [14]. The contradictory data concerning the long-term arrhythmia free-survival after successful PVI may be related to the technology and/or to the incomplete understanding of the AF mechanism.

The aim of this study was to systematically review the available evidence on the short, mid- and long-term outcome of PVI for PAF.

2. METHODS

2.1. Data Sources and Search Strategy

This review was conducted in accordance with the PRISMA and MOOSE guidelines (Appendix 1, 2). We

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aimed to identify all published articles discussing the short-, mid- and long-term follow-up data of percutaneous, manually guided PVI-only procedures with radiofrequency or cryoballoon ablation (CBA) for PAF, which derived from the same group of investigators. We searched Embase.com, Ovid Medline, Web-of-science and the Cochrane Central registry of trials from inception until the 14th of December, 2015. Additional references were obtained from PubMed, the subset as supplied by publisher, containing recent references, and the first relevant results from Google scholar. The search strategy was created with the assistance of a medical librarian (WB). The search strategy combined terms for PAF with terms for interventions such as RFCA, CBA and PVI, and searched for cohort, follow-up and longitudinal studies. The search results were limited to English language articles, but no restriction was used on publication dates. The detailed search methodology for all databases is provided in Appendix 3.

2.2. Study Selection and Eligibility Criteria

We included studies that reported outcome data of patients after PAF PVI, with both a short and at least a median/mean follow-up period of >24 months. If success rate outcome data with either on- and off-drug therapy was available, the off-drug data was used. Studies involving surgical AF ablation or AV-nodal ablation, or those using adjunctive, stepwise linear ablation methodology after PVI were also excluded. The articles focusing on the AF ablation outcome of patients with structural heart disease were excluded as well. Individual case reports, editorials, review articles and meeting abstracts were not included.

2.3. Data Extraction Process

Firstly, two authors (ZK, TST) independently reviewed the included articles and analysed the following data: catheter ablation type, catheter type, procedural and fluoroscopy time, follow-up time, ablation success rate and procedural complications. Secondly, the authors cross-checked their findings to ensure accuracy. Finally, if there was no complete agreement, the authors discussed the results and a consensus decision was made.

2.4. Risk of Bias Assessments for the Included Clinical Studies

Study quality was assessed by two independent reviewers (ZK, TM) based on the nine-star Newcastle–Ottawa Scale (NOS) using three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Studies that received a score of nine stars were judged to be of at low risk of bias; studies that scored seven or eight stars were considered at medium risk; those that scored six or less were considered at high risk of bias. (Appendix 4) The Cochrane Collaboration's tool was used for assessing the risk of bias for randomized controlled studies.

2.5. Statistical Analysis

The inverse variance weighted method was used to combine success rates to produce a pooled success rate using random-effects models to allow for between study heterogeneity [15]. Additionally, we reported the results using fixed effect models. Fixed-effects models were also used to pool rates of the same study. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic, and was distinguished as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $< 75\%$) or high ($I^2 \geq 75\%$) (Higgins *et al.* 2003).

For the analysis that included 5 or more studies, publication bias was evaluated through a funnel plot and Egger's test (Egger *et al.* 1997). All tests were two-tailed and p-values of 0.05 or less were considered significant. STATA release 12 (Stata Corp, College Station, Texas) was used for all statistical analyses.

3. RESULTS

3.1. Identification of Relevant Studies

The search strategy identified 2398 citations, out of which, following initial screening based on titles and abstracts, full-texts of 262 articles were evaluated further. Of these, 13 articles (with a total of 1774 patients) were included in the final analysis (Fig. 1). A total of 13 studies discussing the short-, mid-and long-term (with mean/median follow-up (FU) >24-month) success rate of PVI in patients with PAF (cryoballoon or conventional radiofrequency), derived from the same group of investigators were included [16-28].

3.2. General Characteristics of the Included Studies

Tables 1 and 2 summarize the key characteristics of the included studies. In aggregate, in all included studies, 1774 patients with PAF were included in this review. However, not all studies provided relevant data that could be meta-analysed. Out of 13 included studies, 7 were prospective studies, 6 were retrospective studies. One randomized controlled trial (RCT) and twelve observational studies were included. Out of 13 studies ten single-center, two double-center and one triple-center studies were analysed. The intensity of the follow-up methodology within 1 year after the index procedure was similar in the included studies (Tables 1 and 2). Eleven studies reporting the outcome data of PVI ablation conducted a clinical visit and Holter-monitoring at least 4 times per year, furthermore transtelephonic ECGs were obtained in 4 out of 10 studies within 1-year follow-up. In a majority of the studies (5 out of 7) using CBA patients were scheduled for clinical visit, ECG and 24-hour Holter-monitoring quarterly, furthermore in one study a 5-day Holter-monitoring at 3 or at 6 months was assessed [25]. Magnetic resonance scan examination was performed in two studies to assess PV diameters and to exclude PV stenosis. The studies regarding the long-term outcome of PVI beyond 1-year continued the clinical visits and Holter-monitoring 6 monthly or at least annually. Nevertheless, additional visits were scheduled if required on the basis of patient's symptoms. The single-procedure outcome data pertaining to the efficacy of PVI catheter ablation was clearly available in eight studies. Most studies defined single-procedure success

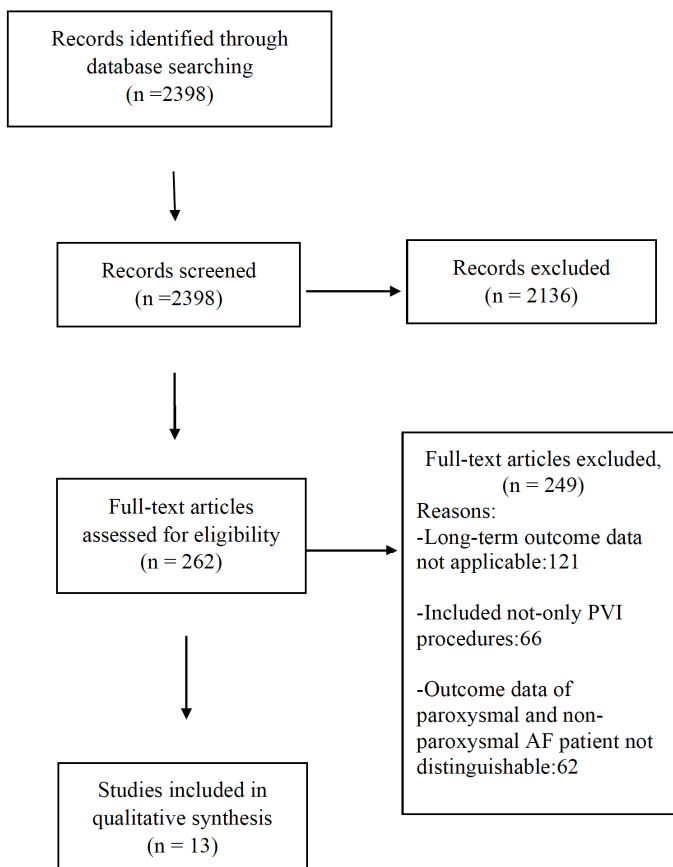


Fig. (1). Flowchart of Studies for outcome of pulmonary vein isolation for paroxysmal atrial fibrillation.

Table 1A. Data from included publication concerning the radiofrequency ablation success rate.

Publication	Study design	Ablation type	Catheter type	Acute success	Fluoroscopy time (min)	Procedure time (min)	Patient number (n)	Follow-up	Single proc. free of AF
Shah A.N. <i>et al.</i> (2007, USA)	Single center Prospective	PVI	RFCA, Biosense Webster	nd	nd	nd	350	1-year 2-year 3-year 4-year 5-year	75% # 69.2% 66.2% 62% 49.5%
Fiala M. <i>et al.</i> (2008, Cz)	Singel center Propective Randomized	Segmental PVI	RFCA, Biosense Webster	nd	46 ± 13.4	255 ± 55	54	6-month 9-month 12-month 48 ± 8 month	69% 63.5% 58% 56%
Fiala M. <i>et al.</i> (2008, Cz)	Single center Prospective Randomized	Circumferential PVI	RFCA, Biosense Webster	nd	45.5 ± 14.9	279 ± 42	56	6-month 9-month 12-month 48 ± 8 month	68% 62.6% 57.3% 57%
Katritris D. <i>et al.</i> (2008, IT)	Double center, Prospective	Ostial – antral PVI Circumferential PVI	RFCA, Biosense Webster	nd	56.3 ± 7.9 28.2 ± 6.1	208.8 ± 26.9 180 ± 18.4	41 49	1-year 1-year	61% # 67.4%

(Table 1A) Contd...

Publication	Study design	Ablation type	Catheter type	Acute success	Fluoroscopy time (min)	Procedure time (min)	Patient number (n)	Follow-up	Single proc. free of AF
Katritris D. <i>et al.</i> (2008, IT)	Double center, Prospective	Segmental ostial PVI Antral PVI	RFCA, Cordis-Webster	nd	nd	nd	35 4	42.2 ± 6 month	21.4%
Sawhney N. <i>et al.</i> (2009, USA)	Singer center, Retrospective	Segmental ostial PVI	RFCA, Blazer	nd	nd	nd	71	1-year 2-year 5-year	86% 79% 56%
Ouyang F. <i>et al.</i> (2010, GER)	Single center, Retrospective	Continuous circular PVI	RFCA	100%	29.1 ± 11.9	228 ± 58	161	1-month 3-month 6-month 12-month 24-month 36-month 48-month 4,8-year over 60 month	78% 73% 69% 62% 53% 52% 49% 46.6% 46%

AF=atrial fibrillation, nd=no data, PVI=pulmonary vein isolation, RFCA= radiofrequency catheter ablation, # = effect of multiple procedures not available.

Table 1B. Data from included publication concerning the radiofrequency ablation success rate.

Publication	Freedom of AF after multiple proc.	Complication	Follow-up within 1-year FU	Follow-up after 1-year FU	Quality score
Shah A.N. <i>et al.</i> (2007, USA)	nd	nd	Clinical visit at 1,3,6,9,12 month Transtelephonic ECG for postproc.3 month Holter-monitor at 3-month	Clinical visit annually	8
Fiala M. <i>et al.</i> (2008, Cz)	80% *	PV stenosis (n=1) Hemianopsia (n=1)	Clinical visit and Holter-monitor at 6-week,3,6,9-,12 month Transtelephonic ECG when required	Clinical visit and Holter-monitor at least twice a year (6-monthly)	
Fiala M. <i>et al.</i> (2008, Cz)	80% *	Femoral pseudoaneurysm (n=1)	Clinical visit and Holter-monitor at 6-week,3,6,9-,12 month Transtelephonic ECG when required	Clinical visit and Holter-monitor at least twice a year (6-monthly)	
Katritris D. <i>et al.</i> (2008, IT)	nd	Pericardial tamponade (n=2)	Clinical visit and Holter-monitor at 1,3,6,9,12 month Transtelephonic ECG when required	Clinical visit and ECG 3 monthly	8
Katritris D. <i>et al.</i> (2008, IT)	66.7% *	nd	Clinical visit and ECG monthly Transtelephonic ECG when required	Clinical visit and ECG 3 monthly	6
Sawhney N. <i>et al.</i> (2009, USA)	84% *	Femoral hematoma (n=2) Femoral pseudoaneurysm (n=1)	Clinical visit and Holter-monitor at 1,3,6,9,12 month	Clinical visit and Holter-monitor at least twice a year (6-monthly)	8
Ouyang F. <i>et al.</i> (2010, GER)	79.5% *	Pericardial effusion (n=2) Aspiration pneumonia (n=1)	Clinical visit, surface ECG, transtelephonic ECG, Holter-monitor at 1,3,6,12 month	Clinical visit, surface ECG, Holter-monitor 6 monthly	6

ECG=electrocardiogram, n=number, nd=no data, PV=pulmonary vein, PVI=pulmonary vein isolation, *=success rate after not-only PVI ablation.

Table 2A. Data from included publication concerning the cryoballoon ablation success rate.

Publication	Study design	Ablation type	Catheter type	Acute success	Fluoroscopy time (min)	Procedure time (min)	Patient number (n)	Follow-up	Single proc. free of AF
Neumann T. <i>et al.</i> (2008, GER)	Single center, Prospective	Antral or Ostial PVI	CB, AF	nd	40	170	346	1-year	74%#
Neumann T. <i>et al.</i> (2013, GER)	Single center, Prospective	Antral or Ostial PVI	CB, AF	98.9%	50.2	222	163	5-year	53%
Wojcik M. <i>et al.</i> (2013, POL, GER)	3-center, Prospective	PVI	CB, AF	100%	33	210	103	6-month 1-year 5-year	94% 91% 77%
Rao J.Y. <i>et al.</i> (2013, Belgium)	Single center, Retrospective	PVI	CB, AF	100%	49 ± 12	151 ± 30	40	3-month 6-month 12-month 24-month 36,6-month	72.5% 67% 62% 60% 58%
Metzner A. <i>et al.</i> (2014, GER)	Single center, Retrospective	PVI	CB, AFA	99%	25 ± 8	140 ± 28	36	1-year	81%#
Metzner A. <i>et al.</i> (2015, GER)	Single center, Retrospective	PVI	CB, AFA	99.6%	24 ± 8	138 ± 29	60	2-year	73%#
Bohó A. <i>et al.</i> (2015, UK)	Single center, Retrospective	PVI	CB, AF	92.7%	23 ± 8.5	187 ± 34.9	205	6-month 12-month 24-month 36-month	93% 78% 53% 34%

AF= atrial fibrillation, AF=Artic Front, AFA= Artic Front Advanced, CB=cryoballoon, n=number, PVI=pulmonary vein isolation, #=effect of multiple procedures not available.

Table 2B. Data from included publication concerning the cryoballoon ablation success rate.

Publication	Freedom of AF after multiple proc.	Complication	Follow-up within 1-year FU	Follow-up after 1-year FU	Quality score
Neumann T. <i>et al.</i> (2008, GER)	nd	Pericardial tamponade (n=2)	Clinical visit, ECG, 7-day Holter-monitor at 1,3,6,12 month	Clinical visit, ECG, 7-day Holter-monitor annually	8
Neumann T. <i>et al.</i> (2013, GER)	nd	Pericardial effusion (n=3), Femoral pseudoaneurysm (n=2) Femoral arterio-venous fistula (n=1) Transient PNP (11%) TIA (n=1) Transient air embolism (n=2) Groin hematoma (n=5)	Clinical visit, ECG, 7-day Holter-monitor at 1,3,6,12 month	Clinical visit, ECG, 7-day Holter-monitor annually	8
Wojczik M. <i>et al.</i> (2013, POL, GER)	nd	Pericardial tamponade (n=1) Transient PNP (n=5) Pericardial effusion (n=1)	Clinical visit, ECG, 7-day Holter-monitor at 1,3,6,12 month	Clinical visit, ECG, 7-day Holter-monitor annually	6
Rao J.Y. <i>et al.</i> (2013, BEL)	nd	Pericardial tamponade (n=1) PNP (n=3)	Clinical visit, ECG, Holter-monitor at 1,3,6,12 month Five-day Holter-monitor at 3 or 5 month	Clinical visit, ECG 6 monthly	6

(Table 2B) Contd...

Publication	Freedom of AF after multiple proc.	Complication	Follow-up within 1-year FU	Follow-up after 1-year FU	Quality score
Metzner A. <i>et al.</i> (2014, GER)	nd	Transient PNP (n=1)	Clinical visit, Holter-monitor at 3, 6, 12 month	-	6
Metzner A. <i>et al.</i> (2015, GER)	88% *	Transient PNP (n=2)	Clinical visit, Holter-monitor at 3, 6, 12, 24 month	-	6
Bohó A. <i>et al.</i> (2015, SV)	nd	Transient PNP (n=7) Persistent PNP (n=7) Embolic complication (n=3) TIA (n= 2) Vascular complication (n=9) Pericardial tamponade (n=2)	Clinical visit, Holter-monitor at 3,6,9,12 month	Clinical visit, Holter-monitor 6 monthly	8

ECG=electrocardiogram, n=number, nd=no data, PNP= phrenic nerve palsy, TIA= transient ischaemic attack, *=freedom from AF after not-only PVI.

rate as the percentage of patients who remained free of atrial fibrillation and/or atrial flutter or atrial tachycardia with or without anti-arrhythmic drug (AAD) therapy following a 3-months blanking period or those not requiring redo procedures. All studies observed a gradual decrease in arrhythmia-free survival rate over time. Among the observational studies, no studies were judged to be at low risk of bias, six studies were at medium risk of bias, and six studies were evaluated to be at high risk of bias. The quality assessment of the involved studies is reported in Supplement Tables S1 and S2. The only one RCT included in this review demonstrated a medium risk of bias within one or more areas of study quality using Cochrane Collaboration's tool (Supplement Table S3).

3.3. Overall Efficacy of Catheter Ablation

Outcome data concerning the freedom from AF after PVI for PAF were available in all studies. The pooled 12-month and 62-month success rate for 9 observational studies reporting outcome for PAF PVI-only procedure was 78% (95% CI 0.76% to 0.855, Fig. 2) and 59% (95% CI 0.56% to 0.64%, Fig. 3) respectively. There was evidence of between-study heterogeneity across these analyses ($I^2=86%$, $P<0.001$ for 12-month success rate and $I^2=94.5%$, $P<0.001$ for 62 month-success rate).

Stratified analysis by type of ablation procedure (radiofrequency ablation or cryoballoon ablation) did not reveal any significant difference (Supplemental Figs. S1, S2).

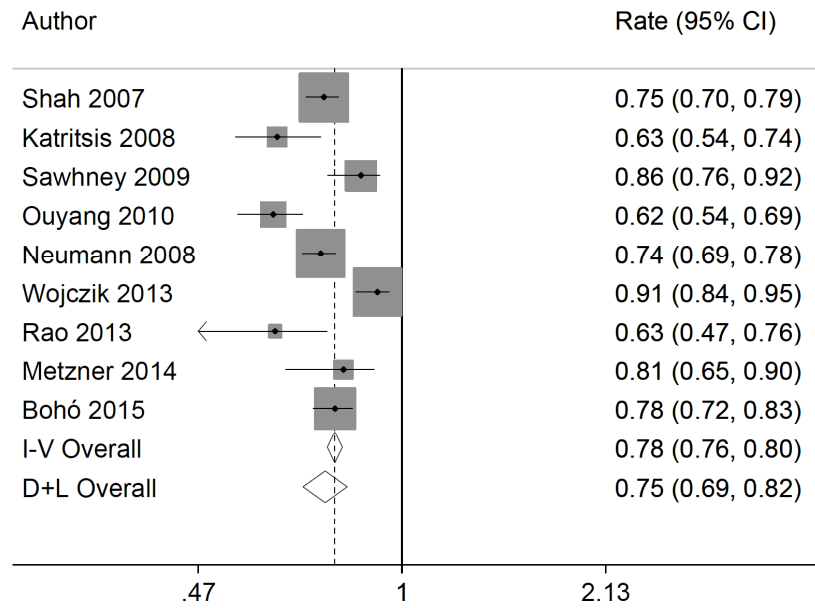
Further three studies could not be assessed to pool outcome data. In the prospective, randomized study by Fiala *et al.* fifty-four patients had segmental (group1) and fifty-six (group2) patients had circumferential PVI. The 12-month arrhythmia free survival was 58% and 57. 3%, while the freedom from AF at the 48 ± 8 month follow-up was 56% and 57% in group1 and group2 [17]. The study by Katritsis *et al.* reported 21.4% success rate after RFCA in 39 patients with 42 months follow-up [19]. The 2-year success rate after CBA in the study by Metzner *et al.* was 73% [27].

3.4. Impact of Multiple Procedures

Five studies reported outcome data taking into consideration the impact of multiple procedures on PVI ablation success rate. In all these studies additional linear lesions were performed during the repeat ablation procedures. In the study by Fiala *et al.* fifty-four patients underwent segmental PVI (group 1) while fifty-six patients had circumferential PVI ablation. Following a single procedure, at 48.8-months follow-up a 56% and 57% success rate could be achieved, while after repeat ablation (second ablation: 18 pts in group 1, 19 pts in group 2, third ablation: 5 pts in group 1 and 5 pts in group 2) 80% of the patients were free of arrhythmia in each group [17]. The long-term success rate was 21.4% for patients subjected to a single procedure, 52.6% for patients subjected to a second ablation and 66.7% for patients who underwent a third ablation in the study by Katritsis *et al.* [19]. This article showed a trend of lower long-term success rates among patients who received the same ablation technique at repeated ablations compared to those in whom the second and the third ablations differed from the initial procedure [19]. The same tendency could be appreciated in the study by Sawhney *et al.*, in which the 5-year single procedure success rate compared to the multi-procedure success rate was 56% vs. 84% [20]. In the study by Ouyang *et al.* the single and the multiple-procedure success rate after 4.8-year follow-up was 46.6% vs.79.5% [21]. Only one study with cryoballoon ablation reported data after multiple procedures: the 2-year single procedure success rate was 73% for PAF and 71% for persistent AF patients, while the overall success rate reached 88% including repeat procedures in the study by Metzner *et al.* [27]. The higher success rate after multiple-procedures might be attributed to the additional linear lines performed during the redo procedures.

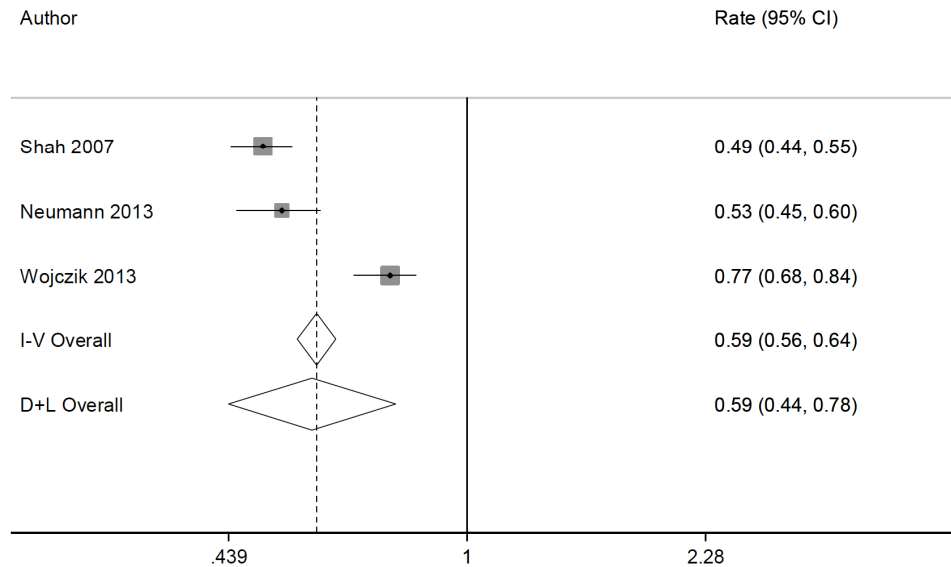
3.5. Predictor of Arrhythmia Recurrence

Four individual studies reported about predictors of AF recurrence after PVI ablation. Sawhney *et al.* detected that patients with hypertension at the time of index procedure had a significantly higher risk of AF recurrence compared to normotensive patients [20]. Hypertension and hyperlipidaemia as an independent predictor of late AF recurrence were



Assessment of heterogeneity, $X^2=57.3$, $I^2=86.0\%$; $P < 0.001$.

Fig. (2). 12-month success rate of pulmonary vein isolation.



Assessment of heterogeneity, $X^2=36.1$, $I^2=94.5\%$; $P < 0.001$.

Fig. (3). 62-month success rate of pulmonary vein isolation.

identified by Shah *et al.* [16]. The size of the left atrium was the most consistent predictor of late AF recurrence in the study by Neumann *et al.* [23]. In the study by Bohó *et al.* the only independent predictor of arrhythmia recurrence was the type of AF. Patients with persistent AF had almost two-fold increased risk for AF recurrence [28].

3.6. Time to Atrial Fibrillation Recurrence

This systematic review demonstrates that many patients develop AF recurrence years after an initially successful AF ablation procedure. In a majority of the studies we analysed, the rate of decline in freedom from arrhythmia was the high-

est during the first 12 months [17, 21, 23, 25]. However, over time a constant decrease in arrhythmia free survival could be detected in the included studies, with a surprisingly high rate of late AF recurrences. In the study by Sawhney *et al.* sixteen patients (22.5%) had AF recurrence after 24 months following the ablation. It represented a 7.6% per year recurrence rate of AF between 24 to 48 months. Furthermore, they observed a 17% per year recurrence rate after 48 months following the index procedure [20]. Karitris *et al.* showed that 56% of the recurrences occurred more than 12 months after the initial procedure, while Ouyang *et al.* reported a recurrence rate of 14.9% after the same follow-up

period [19, 21]. Shah *et al.* found a significant late recurrence rate of 8.7% at 34 ± 16 months, and a 25.5% recurrence rate of patients with 5-year follow-up after an initially successful ablation [16]. It was consistent with the results of Bohó *et al.* who reported a relatively large number of late recurrences. The 1-year success rate was 78% compared to the 34% success rate of 5-years follow up [28].

3.7. Publication Bias

Visual examination of Begg's funnel plots for the analysis on the 12-month successful rate was moderately symmetrical, therefore providing evidence for publication bias (Fig. 2). This was further supported by the results of Egger's test which was significant (Supplemental Fig. S3). No evidence of publication bias was observed for the analysis on 24-month success rate (Supplemental Fig. S3).

4. DISCUSSION

Despite significant technological advances in atrial fibrillation ablation, while superior to medical therapy, the success rate remains lower than for other arrhythmias [1, 29, 30]. Notably, many patients have reconnected PVs after successful ablation and patients with recurrent AF often have isolated PVs [1, 31]. It is still debated what mechanism should be targeted during AF ablation and how ablation works when it is successful [30, 32]. There is substantial evidence that apart from the PVs, other parts of the atria such as the PV-left atrial junction, the posterior left atrial wall, the Marshall-vein etc. may contribute to triggering and maintaining AF through various mechanisms [18].

5. COMPARISON TO PREVIOUS SYSTEMATIC REVIEWS

This is the first paper comparing the short-, mid- and long-term follow-up data of PVI-only ablation procedures. The unique feature of this review is that we attempt to study a homogenous patient population purely with PAF and without structural heart disease. The systematic review and meta-analysis published by Ganesan *et al.* evaluating the long-term single and multi-procedure efficacy of PVI ablation included a significant heterogeneity in the type of AF and the methodology of AF ablation (PVI-trigger, non-PVI-trigger, adjunctive stepwise ablation) [33]. They included nineteen studies enrolling 6167 patients with paroxysmal and persistent atrial fibrillation. The exclusive use of pulmonary vein isolation ablation strategy was performed only in seven of their included studies with wide heterogeneity of atrial fibrillation type. They found that a single catheter ablation procedure may be sufficient to achieve freedom from AF in ~50% of patients with a median follow-up of >3 years. However, with multiple-procedures freedom of AF was achieved in around 80% of patients [33].

In the present systematic review five overlapping studies, enrolling 661 patients can be found compared with the meta-analysis by Ganesan *et al.* [33]. We included further eight unique citations with 1139 patients who underwent PVI-only ablation procedure for paroxysmal atrial fibrillation. We found a low long-term success rate. Moreover, a decline between the short- and long-term follow-up data

was observed. Additionally, in this review only patients with PAF, who underwent an exclusive PVI-only ablations were included.

6. MECHANISM OF LATE AF RECURRENCES

The mechanism of AF recurrences in the reviewed studies was thought to be correlated to PV reconnections. However, permanent isolation of PVs is not always necessary for the successful outcome of a PVI procedure [27, 34-36]. In the series of Metzner *et al.* a total of 10 out of 16 patients suffering from atrial tachyarrhythmia recurrence underwent a repeat RF-based redo procedure, which revealed that in 2 out of 10 patients all PVs were completely isolated [27]. Our current analysis may suggest, that the very late recurrence of AF should be related to several other mechanisms, different from the ectopic activity of the PV sleeves. However, ablation may still be effective through mechanisms other than isolation of PVI foci [19]. These possible factors related to late AF recurrences might be: the presence of non-PVI triggers (focal sources or stable rotors may contribute to trigger and maintain AF) and/or a variety of factors leading to structural and electrical remodelling resulting in electrical instability of the atria and/or the failure to target all PVs during initial PVI.

7. STRENGTHS AND LIMITATIONS

To the best of our knowledge, this is the first systematic review attempted to pull together the different existing studies that evaluated the short-, mid- and long-term outcome of pulmonary vein isolation as a sole treatment strategy for paroxysmal atrial fibrillation which arose from the same group of investigators. One of the reasons for this is that the available literature fulfilling our inclusion criteria is limited and novel, with almost half of included studies published in the past two years. Previous systematic-reviews focused on the short- and long term outcome of a mixed population with paroxysmal and non-paroxysmal atrial fibrillation, not distinguishing the different ablation methodologies (PVI-only, non-PVI trigger, linear line ablation).

Our searching methodology ensured that we included the most relevant articles in our review enrolling more than 1700 participants. However, there are a number of limitations of this study. Despite all efforts made to undertake a comprehensive search of the published literature, we cannot exclude the possibility of publication bias stemming from under-reporting of negative findings. Also, inclusion of data from potentially poorly conducted studies is undoubtedly a limitation of the current review. Moreover, it is important that the assessment of the effect of different methodologies (segmental, circumferential *etc.*) of PVI due to the considerable heterogeneity from the original studies made it impossible for us to establish a relation between the method of PVI and the clinical outcome. Furthermore, high-quality RCTs with adequate sample sizes and standardized long-term follow-up are needed to assess the mid- and long-term outcome of PVI-only ablation for paroxysmal atrial fibrillation. Nevertheless, it would be of a great interest to follow the effect of the ablation therapy for atrial fibrillation over the life course rather than using short time horizon. Last, since the number of available studies in each analysis was generally small, it pre-

cluded our ability to investigate the sources of the observed heterogeneity by subgroup analyses involving various study-level characteristics.

8. CLINICAL IMPLICATIONS

The PVI-only ablation methodology is not enough to ensure long-term arrhythmia free survival in majority of patients. After primary successful atrial fibrillation ablation, the arrhythmia recurrence occurs most frequently within the first 12 months. Nevertheless, a decline in arrhythmia free survival can be observed between the short- and long-term follow-up period, which seems unlikely to be correlated to PV reconnections.

Data from published studies confirm that a high success rate at 12-month follow-up does not necessarily mean a high chronic success rate. Further attempts should be made to establish a certain classification method for identifying those, in whom PVI-only ablation is not enough to maintain long-term AF-free survival. We should also emphasize that the late recurrence of atrial fibrillation after primary successful ablation remains an important clinical phenomenon. It has a serious impact on medical treatment after ablation especially in preventing cerebrovascular thromboembolism. The high rate of recurrences after PVI may support the concept that PVI is a “palliative” rather than a “curative” treatment option for atrial fibrillation. However, the optimal adjunctive ablation methodology still remains unknown.

CONCLUSION

In conclusion, the contradicting data concerning the efficacy of pulmonary vein isolation for paroxysmal atrial fibrillation with short-, mid- and long-term follow-up requires further investigation for a better understanding of the mechanism and location of atrial fibrillation.

LIST OF ABBREVIATIONS

AF	=	Atrial fibrillation
CBA	=	Cryoballoon ablation
FU	=	Follow-up
PAF	=	Paroxysmal atrial fibrillation
PV	=	Pulmonary vein
PVI	=	Pulmonary vein isolation
RCT	=	Randomized controlled trial
RFCA	=	Radiofrequency catheter ablation
SR	=	Sinus rhythm
TIA	=	Transient ischemic attack

ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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