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OUTCOMES OF LONG-STANDING PERSISTENT ATRIAL FIBRILLATION ABLATION: A SYSTEMATIC REVIEW

Brooks et al. *Long-standing persistent AF ablation*

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ABSTRACT

Background: Ablation of long-standing persistent atrial fibrillation (AF) is highly variable with differing techniques and outcomes.

***Objective*:** To undertake a systematic review of the literature with regards to the impact of ablation technique on the outcomes of long-standing persistent AF ablation.

Methods: A systematic search (Database: PubMed) of the contemporary English scientific literature (1st Jan 1990 to 1st June 2009) was performed and identified 32 studies on persistent/long-standing persistent or long-standing persistent AF ablation (including four randomized controlled trials). Single procedure-drug free, multiple procedure and pharmaceutically assisted success at longest follow-up were collated.

Results: Four studies performed pulmonary vein isolation alone (PVI; 21-22% success). Four studies performed PV antrum ablation with (PVAI; n=2; 38-40% success) or without confirmed isolation (PVA; n=2; 37-56% success). Ten studies performed linear ablation (LIN) in addition to PVA (n=5; 11-74% success) or PVAI (n=5; 38-57% success). Three studies performed posterior wall box isolation (n=3; 44-50% success). Five studies performed complex fractionated atrial electrogram (CFAE) ablation (n=5; 24-63% success). Six studies performed CFAE ablation as an adjunct to PVA (n=2; 50-51% success), PVAI (n=3; 36-61% success) or PVAI and linear (n=1; 68% success) ablation. Five studies performed the stepwise ablation approach (38-62% success).

Conclusion: The variation in success, within and between techniques, suggests that the optimal ablation technique for long-standing persistent AF is unclear. Nevertheless, long-standing persistent AF can be effectively treated with a composite of extensive index catheter ablation, repeat procedures and/or pharmaceuticals.

Keywords: atrial fibrillation, ablation, systematic, review, permanent, long-standing persistent, persistent

Abbreviations:

AF=atrial fibrillation

PVI=Pulmonary vein isolation

PVA=Pulmonary vein antrum

PVAI=Pulmonary vein antrum isolation

LIN=Linear ablation

CFAE=Complex fractionated atrial electrogram

INTRODUCTION

The success of catheter ablation in paroxysmal AF patients is now well established[1]. However, when the same approaches are applied to persistent or long-standing persistent AF patients, the clinical success has been limited[2, 3] and has led to the search for the ideal ablation strategy. The vast contrast in success suggests that the mechanisms underlying the maintenance of persistent AF are different to their paroxysmal counterparts. These alternative mechanisms are perhaps partly related to the significant remodeling that the arrhythmia instills on the atria in terms of its structural and electrophysiological properties. Linear lesions and/or electrogram-guided atrial substrate modification, targeted at interrupting self-sustaining macro- or micro-reentrant wavefronts, or focal sources have been variably incorporated into the ablation treatment for persistent/long-standing persistent AF in an attempt to improve outcomes. In order to collate the efficacy and complications of current approaches utilized for long-standing persistent AF ablation we performed a systematic literature review.

METHODOLOGY FOR REVIEWING THE LITERATURE

The English scientific literature was searched in Pubmed using: "atrial AND fibrillation AND ablation AND (persistent OR long-standing persistent OR chronic OR long-term OR long-standing)" in any region of the Pubmed record up until the 1st of June 2009. Circulation: Arrhythmia and Electrophysiology Journal was manually searched due to its limited indexation in Pubmed. The resultant 1286 abstracts were reviewed to ensure that a 1) long-standing persistent or 2) a mixed persistent/long-standing persistent AF cohort undergoing radiofrequency catheter ablation for the treatment of their arrhythmia were included. Manuscripts reporting on a pure persistent, mixed paroxysmal/persistent or pure paroxysmal cohort were excluded. 138 relevant full-text references were examined for a description of baseline characteristics, procedural details, follow-up, complications, and success rates for the group or sub-group of interest. Figure 1 shows the number and reason for the exclusion of studies from the original retrieved articles. Randomized controlled trials (n=4) were reviewed separately, but data were also included in the case-series review to improve estimate of success for each ablation strategy. ***Thirty-two manuscripts met the inclusion criteria and a summary of their results are presented in Table 1.***

This review summarizes outcome data from reports on persistent/long-standing persistent ablation outcomes. There is potential for sample redundancy; however, we have assumed all data are independent in the case series review. Single procedure, drug-free success rate was used as the gold standard comparison criterion. However, multiple procedure and pharmaceutically assisted clinical outcomes are also reported. The following definitions were used:

1) Pulmonary vein isolation (PVI): Ostial ablation of all pulmonary veins with confirmation of electrical block.
2) Pulmonary vein antral (PVA) ablation: Predominately antral anatomical ablation around the pulmonary veins, with an endpoint of on-line voltage abatement and a circumferential lesion set.
3) PVA isolation (PVAI): PVA with electrical disconnection of the encircled veins within the ablated margins.

EVIDENCE FROM RANDOMISED CONTROLLED TRIALS

Four randomised controlled trials (Level II evidence) examining various ablation approaches for long-standing persistent AF have been conducted recently[4-7]. Unfortunately, there is little overlap in the ablation approaches assessed by each study so their data cannot be combined (Figure 2). With respect to the clinical endpoint of single procedure drug free success, these studies showed for long-standing persistent:

1) PVAI is a superior approach compared to PVA ablation alone[7].
2) CFAE ablation alone is an inferior strategy compared to PVA+linear ablation at the roof and mitral isthmus.
3) There is no incremental benefit of additional right atrial CFAE ablation[5] when AF persisted after left atrial CFAE ablation.
4) CFAE ablation may[7] or may not[4] provide incremental benefit when added to PVAI.

PVAI

A five-centre randomised study, with appropriate web-based permuted block randomisation protocol reported that PVAI is an essential component of long-standing persistent AF ablation[7] (Figure 2), which is consistent with recommendations in the most recent ablation guidelines[8].

CFAE Ablation alone

An appropriately randomised (sealed envelopes with treatment assignment) single centre study compared left atrial CFAE ablation to conventional pulmonary vein and linear ablation[6]. Three to five left atrial CFAE sites were ablated along the roof, septum, anterior wall, mitral isthmus and atrial aspect of the mitral annulus with voltage abatement as an endpoint. In the other arm, PVA was performed with lines across the posterior (or roof) and mitral isthmus but without confirmation of block or isolation. The empirical approach was associated with improved outcomes (Figure 2); however, the 24% increase in radiofrequency energy delivery time prevented delineation of technique or debulking as the mediator of success.

CFAE as an adjunct to PVAI

Two randomised controlled trials have assessed whether the addition of CFAE ablation to PVAI improves clinical results, with conflicting results[4,7] (Figure 2). The 5 centre study of Elayi et al.[7] reported a 61% drug free clinical success in their bi-atrial CFAE+PVAI arm, compared to 40% in their PVAI in patients with >1 year of continuous long-standing persistent AF. In CFAE+PVAI arm, a much greater proportion of patients terminated to SR or atrial tachycardia during PVAI *after* CFAE ablation (74%) compared to those who received PVAI alone (44%), even though only 2% of these patients actually terminated during CFAE ablation. In contrast, a single centre study of Oral and colleagues[4] selected their long-standing persistent cohort as those patients with episodes >6 months, but only randomised patients who were non-responsive to PVAI (still inducible or remaining in AF) to either no other ablation and/or CFAE ablation of the left atrium and coronary sinus. Even though the latter group received a 38% increase in ablation due to targeting of CFAE and acute termination occurred in 18% (9/50) of patients during CFAE ablation, the clinical success at a mean follow-up of 9±4 months was the same as those who received no additional ablation. The primary differences between these two conflicting studies include 1) patient characteristics (>1 year vs. >6 months), 2) patient selection (unselected versus resistant to PVAI), 3) bi-atrial vs. left atrial CFAE ablation and 4) the order in which PVAI/CFAE targeting was performed. It is possible that some of these differences may have resulted in the contrasting comparison. The benefits of CFAE ablation as an adjunctive therapy for long-standing persistent AF therefore remain unclear.

EVIDENCE FOR EACH STRATEGY

Randomised controlled trials have answered some of the questions regarding ablation of long-standing persistent AF; however, the critical question of technique over debulking still persists. We reviewed the case series (Level IV evidence) to further investigate the outcomes associated with the different AF ablation strategies not assessed in randomised comparisons.

PULMONARY VEIN ABLATION

Pulmonary vein isolation

In one of the initial descriptions of persistent AF ablation [9], Haissaguerre and colleagues described a 40% single procedure drug free success at 11 months after ablation in a highly selected group of patients in whom high frequency triggers observed following cardioversion of AF were targeted by PVI; however, this sample was not representative of a clinical long-standing persistent cohort and the data are therefore excluded from summary.

Four studies have reported clinical success of PVI in ‘unselected’ persistent or long-standing persistent disease[10-13]. The single procedure, drug-free success rates of between 21 and 22% for three of these studies are consistent with contemporary theory and randomized controlled trials[2, 3] demonstrating that targeting triggers in chronically diseased and remodeled atria has little clinical effect. The outlying efficacy data of Razavi et al.[11] (54% success at 30 months) should be interpreted with caution as the term ‘symptomatically free’ was used to define their success rate, indicating that asymptomatic episodes were not included. Hence, the spuriously high success reported by Razavi et al.[11] has been excluded from further summary.

PVI is associated with a single procedure, drug-free success ranging from 21-22% at almost two years (Table 2). The integration of repeat procedures (mean 1.6/patient) increases *the drug-free success to 37-43%. A combination of drug administration and repeat procedures further increased the success rates to ~54% (Table 1).*

PVA ablation with and without isolation

In the four studies that performed antral encirclement, the majority confirmed PV disconnection[4, 7, 14]. These studies reported superior, but variant (37-56%) single procedure success rates compared to PVI alone (Table 1 and Figure 3). The large variation in success could be due to fact that Pappone and colleagues[15] defined long-standing persistent AF as that >3 months compared to Cheema et al.[14], who enrolled patients with >6 months of continuous AF. The mean LA dimension of 58±11 mm in the latter study was also consistent with a more severely diseased cohort, and hence, the lowest clinical success.

Wide vein encirclement is associated with a single procedure, drug free success ranging from 37-56% at ~1 year (Table 3). The integration of repeat procedures (mean 1.3/patient) increases the drug free success to 59%. The combination of drugs and multiple procedures yielded a success rate of ~77% (Table 1 and Figure 3).

LINEAR ABLATION

Linear ablation eliminates more atrial substrate and partially compartmentalizes the atria aimed at preventing the formation of macro-reentrant circuits that have been postulated to maintain AF. Such linear ablation is anchored to electrically inert structures and has included the roofline, mitral isthmus, anterior line and isolation of the entire posterior left atrium.

Linear substrate ablation as an adjunct to pulmonary vein ablation

PVA/PVAI plus linear ablation, in the form of roof, mitral isthmus and tricuspid isthmus lines is the most common ablation approach in this review. It is important to note that a complete set of linear lesions may not be performed in all patients, with procedures often tailored to the patient's response to ablation.

Ten studies have reported on the clinical success of linear substrate ablation in addition to PVA ablation with and without PVI[7, 16-23]. Gaita et al.[18] reported one of the poorest single procedure, drug free success rates of only 15% in their long-standing persistent sub-group; however, all patients suffered from hypertrophic cardiomyopathy and their results were therefore excluded from summary statistics. Similarly, the data of Siedl et al.[20] have also been excluded as their technique utilized two paired but chronologically-separate procedures of linear ablation that is not consistent with contemporary ablation approaches.

Table 4 demonstrates the chronological transition from PVA encirclement to PVAI being used in conjunction with conventional linear lesions. Four studies using PVA in conjunction with linear substrate modification[6, 7, 19, 21] reported a wide range of success from 11-74% in comparison to 48-57% for studies utilizing PVAI + linear ablation[17, 23]. The highly variable success rate demonstrates that this approach can produce significantly different outcomes in the hands of different operators, perhaps contributed to by differing procedural endpoints or the criteria for linear lesion contiguity.

PVA (or PVAI) with linear substrate modification is associated with a single procedure, drug-free clinical success ranging from 11-74% at ~1.5 years (Table 4). The integration of repeat procedures (mean 1.5/patient) improved success rates to 17-74% (Table 1 and Figure 3). The addition of anti-arrhythmics further increased success to 28-87%.

Posterior wall isolation

Posterior wall isolation incorporates PVI together with the remaining posterior wall tissue. This has been described enbloc or by performing circumferential PVI followed by superior and inferior linear ablation to join left and right encirclement.

Three studies have assessed the efficacy of posterior wall isolation in 27[24], 10[25], and 24 long-standing persistent AF [26] patients with >0.5-1 year of continuous AF. Sanders et al.[24] reported a 44% single procedure, drug free success at 23±3 months for posterior wall isolation in patients with >6 months of continuous AF. Chen et al.[25] described the effectiveness of complete posterior wall isolation by combining roofline and inferior left atrial linear lesions to pulmonary vein isolation lesion sets. Isolation was confirmed by an inability to capture the atrium with posterior wall pacing. The baseline characteristics were reported for the group as a whole (n=42; 18 paroxysmal/24 long-standing persistent) and thus cannot be reported here. The success rate reported was 50% for single procedure and 60% for a mean of 1.5 procedures at an overall follow-up of 20±4 months (Table 5). Kumagai et al[26] reported similar results to those of the initial description of the ablation approach[24] by isolating the posterior wall guided by the Ensite non-contact mapping system.

Posterior wall isolation is associated with a single procedure, drug free success ranging from 42-50% at almost two years (Table 5). The integration of repeat procedures (mean 1.4/patient) increases the drug free success to 60-63% (Table 1 and Figure 3). The incremental efficacy gain with drug administration was increased to 88% in one small sample.

ELECTROGRAM BASED ABLATION

The clinical outcomes associated with the above procedures suggest that regions other than the PVs, PVA and posterior wall may play a role in the maintenance of long-standing persistent AF. In contrast to linear ablation, where a pre-determined linear lesion is created empirically without detailed consideration of the underlying atrial substrate, electrogram-guided substrate modification selectively targets atrial tissue dependent upon the electrogram characteristics at the site. Electrograms can be targeted in a subjective (physician interpretation) or objective (online CFAE detection algorithms) manner.

CFAE ablation alone

Four studies have utilized CFAE ablation alone in persistent/long-standing persistent AF in a total of 270 patients[4, 6, 27, 28]. It is important to note that signals were not objectively characterized using 3D mapping and signal detection algorithms, but instead subjectively assessed by the respective operators. Nademanee et al.[28] were the first to purport the success of pure CFAE ablation but their results have not been reproduced[4, 6, 27]. Reasons for this may include: operator experience, total ablation time differences, the subjectivity of what represented an ‘important’ electrogram and finally, the severity of disease in the cohort. The cohort defined as chronic in Nademanee’s study[28] consisted of a 40/60 split of persistent (AF not terminating in 7 days) and long-standing persistent patients. In addition, left atrial dimensions and other baseline characteristics were not detailed. Nevertheless, they reported a single procedure, drug free success of 63% at 12 months, which improved to 77% with repeat procedures in 19 of the 64 patients (Table 1). A 71% multiple-procedure success rate in 235 long-standing persistent AF patients was also reported recently by these investigators[29]; however, this study was excluded from the review due to insufficient information about the long-standing persistent AF sub-group.

Oral and colleagues have attempted CFAE ablation in three separate long-standing persistent AF cohorts (AF ≥6 months); twice in the setting of a randomized ablation trial[4, 6] and once in a 100 patient series[27]. The single procedure drug free clinical success ranged from

24-33% for these studies with a mean follow-up of 1 to 1.4 years. The only patients that performed well in Oral's randomized controlled trial were the 22% that terminated with left atrial CFAE ablation who had an overall single procedure success of 74%[4]; a finding that is consistent across most ablation techniques. In a 100 patient series[27], a mean 1.5 procedures per patient was associated with a final clinical success of 57% (Table 1). Even in the context of shorter ablation times (35-44 minutes), the success rate of CFAE ablation alone therefore seems inferior to other empirical techniques, which is supported by the single centre randomized controlled trial of Oral et al. [6].

CFAE ablation alone is associated with a single procedure, drug free success ranging from 24-63% at ~1 year (Table 6). The integration of repeat procedures (mean 1.4/patient) increases the drug free success to 52-77% (Table 1 and Figure 3). The incremental efficacy gain with drug administration and multiple procedures was not reported.

CFAE as an adjunct to conventional approaches

Recently, CFAE ablation has been performed as an adjunct to pulmonary vein isolation[30, 31], PVAI[4, 7, 32] or PVAI, roof and mitral isthmus ablation[33]. Schmitt et al.[30] reported the outcomes of a 5.5 hour procedure beginning with subjectively-assessed CFAE ablation at various regions of the left and right atrium and coronary sinus ostium, followed by conventional pulmonary vein isolation. Unfortunately, the authors failed to report the follow-up frequency, or what was defined as failure or success; however, they reported a 50% success rate (intention-to-treat analysis) at 12±3 months follow-up. It is unclear as to whether there is cohort redundancy, but the same investigators reported a similar clinical result for 35 persistent/long-standing persistent AF patients with a follow-up including objective 7 day Holter monitoring [31].

The highest efficacy reported by Porter and colleagues[33] was associated with one of the first attempts to objectively quantify (CARTO; Biosense Webster) and target CFAE in addition to conventional ablation. The algorithms yielded primary CFAE sites in an average 24% of the atrium, which were accordingly ablated. In addition to primary CFAE ablation, PVAI, roof and mitral isthmus lines were deployed. In their follow-up of all long-standing persistent (median AF duration 13 months) patients >1 yr, with Holter monitoring and one month of trans-telephonic monitoring at 6 months, they reported a 68% (17/25) single procedure, drug free clinical success. Although the objective characterization of CFAE could be a contributing factor to the success, equally, this study was the only one to perform roof and mitral isthmus linear lesions in addition to PVAI and CFAE.

Oral and colleagues[4], whose group have had little clinical success with CFAE ablation alone, reported that the addition of CFAE to PVAI resulted in an equally poor success rate compared to PVAI alone and contributed the lowest single procedure, drug free success rate in this category (36%). On the other hand, Elayi and colleagues[7], who compared the same two techniques, found that PVAI and CFAE resulted in a clinical success rate similar (61%) to the other case series in this ablation category and that this approach was superior to PVAI alone.

Pulmonary vein isolation and CFAE ablation is associated with a single procedure, drug-free clinical success of 36-68% at one year (Table 7). Multiple procedures increased the success to between 60-80% at the same follow-up. Objective targeting of CFAEs via automated algorithms in addition to PVAI and linear ablation may improve clinical outcomes but this is yet to be tested in a randomized comparison.

STEPWISE ABLATION APPROACH

The stepwise ablation approach is an integration of most of the aforementioned techniques in a bid to additively improve the success of persistent/long-standing persistent AF ablation. The stepwise approach requires several key ablation techniques, namely: PVI, linear ablation at the roof and mitral isthmus, electrogram-targeted ablation and discretionary right atrial ablation (SVC, intercaval or CTI lines). Each region is targeted in sequence with the effect of ablation assessed by measurement of the AF cycle length. Another important feature of the stepwise approach is that the procedure endpoint is dictated by the termination of AF to sinus rhythm or intermediate atrial tachycardias; thus minimizing ablation for maximal impact. Patients in AF after all key anatomical regions are ablated may be cardioverted at the end of the procedure.

Five studies have reported the clinical success associated with the stepwise ablation approach for persistent/long-standing persistent AF[34-38]. Haissiguerre and colleagues described the stepwise ablation approach in 60 persistent/long-standing persistent AF patients with regards to critical structures for acute AF slowing or termination and long term clinical outcome[38]. These patients had AF for a mean of 17 months, ranging from one month to fourteen years, with 11% being uncardiovertable. The single procedure, drug free success of this strategy was 62% at 11±6 months. Allowing for repeated procedures in almost 50% of patients the success rate increased to 88% (Table 1 and Figure 3).

The outcomes of the stepwise ablation approach have also been reported in three additional patient series from the same group[34, 35, 37]. Sacher et al.[37] enrolled 43 persistent/long-standing persistent AF patients (AF mean 11 months, ranging from 1 month to 6 years) who underwent the same extensive ablation procedure. They reported a longer mean follow-up of 18±5 months and a mean of 1.4 procedures yielded a drug free clinical success of 70% (Table 1). Takahashi et al.[34] characterized the electrograms associated with procedural termination of chronic AF and in doing so reported the clinical success (mean follow-up of 14±3 months) of 40 consecutive patients undergoing the Stepwise ablation technique. The single procedure, drug free success in this cohort was 55% (Table 8). The integration of repeat procedures for atrial tachycardia (mean 1.4 procedures) yielded an 83% success rate (Table 1). The largest and most recent case series of 153 patients[35] demonstrated that the stepwise ablation approach was associated with a single procedure clinical success of 48%, with anti-arrhythmic medication and multiple procedures increasing this to 89%. Taken together, these studies demonstrate a variance of 48 to 62% with a single procedure from a single centre with a well established ablation protocol and potential sample redundancy.

Rostock et al.[36] is the only group outside of Bordeaux to report on the stepwise procedure in 88 consecutive persistent/long-standing persistent AF patients (AF duration range 3-264 months). In this series, the stepwise approach was associated with lower single procedure drug free success rate of 38% at 20 months which improved to 81% with the integration of repeat procedures. These results may have been due to a more severely diseased cohort represented by a higher proportion of structural heart disease (64%), significantly enlarged left atria compared to the other studies in this category and the lower rate of AF termination during the procedure.

The stepwise ablation approach is associated with single procedure, drug-free clinical success ranging from 38-62 % at ~18 months (Table 8). The integration of repeat procedures, mostly for focal atrial tachycardia and flutter, increases the drug free clinical success to 70-88% and finally, the allowance of previously ineffective anti-arrhythmic drug treatment in the patient cohort can further improve clinical success to 84-90% (Table 1 and Figure 3).

SAFETY ASSOCIATED WITH LONG-STANDING PERSISTENT AF ABLATION

Assessment of complications was not a primary aim of this review; hence, case reports were not included. This may lead to potential underestimation of very rare complications such as atrio-esophageal fistula. Twenty-eight of the 32 studies reported peri-procedural complications; however, six of these reported complications from their mixed AF type cohort and are not summarized here. Complications are reported as a percentage of the total 1690 patients (n=22 studies) included in the safety review. A total of 75 complications were reported (4.4%) which included (in descending prevalence): 23 pericardial tamponades/effusions (1.4%), 13 vascular complications (0.80%), 12 symptomatic pulmonary vein stenoses (0.71%), 11 cerebrovascular events (0.65%), 7 delayed left atrial appendage (LAA) emptying or temporary electrical disconnection of atria or LAA (0.41%), 5 phrenic nerve injuries (0.3%) and single cases of atrioesophageal fistula (0.06% each), AV block, pulmonary edema, ST segment elevation and severe back pain and no procedurally related death.

The complication data were too limited and variable to infer any relationship between ablation approach and risk of procedure.

LIMITATIONS

Only two studies[7, 26] in this review clearly stated that *all* of their patients had continuous AF >12 months, which is the most recent classification of long-standing persistent AF[8]. All studies referring to their patient cohorts as chronic, persistent/long-standing persistent, or long-lasting persistent, but with enrollment criteria deviating from the contemporary definition, were included. While the inclusion of these studies allowed for a more stable estimate of the efficacy of various substrate ablation approaches, which was the primary aim of this article, it may have an impact on the efficacy estimates provided in this review.

The most recent guidelines for AF ablation[8] recommend a minimum objective follow-up for at least 12 months in all patients. Only two studies in this review objectively reported this statistic[19, 33]. Another four other studies[7, 13, 24, 28] have presumably followed all of their patients for at least 12 months given their mean and standard deviation; albeit none of these objectively stated this fact. The impact of including studies which have shorter and variable follow-up periods may ultimately overestimate the clinical success for periods greater than 12 months post index ablation procedure.

CONCLUSION

This systematic review collates the success associated with long-standing persistent AF ablation, with a review of randomized controlled trials and an indirect comparison of case-series with different baseline characteristics, treated using a variety of methodologies and followed up with different intensities. The variation in ablation methodology reported in this review demonstrates that the optimal technique for long-standing persistent AF ablation is still the subject of robust debate and clinician preference.

The role of CFAE targeted ablation in long-standing persistent AF is a topic of hot debate and has been addressed by several randomized controlled trials. Randomized controlled comparisons suggest that CFAE ablation alone is an inferior strategy for the treatment of long-standing persistent AF compared to empirical approaches [6] and that confirmed electrical isolation of PVs (PVAI) is a pivotal component of the latter technique to maximize clinical success[7]. The role of CFAE targeted ablation as an effective adjunct to PVAI remains undecided with two randomized controlled trials reporting opposing results [4, 7].

Single procedure, drug free clinical success associated with case series data suggests that, with the exception of PVI alone (mean 21%) and CFAE ablation alone (mean 37%), all contemporary substrate ablation techniques for persistent/long-standing persistent AF provide comparable clinical results (mean 47% success; Table 1 and Figure 3).

Comparisons between contemporary ablation approaches for multiple procedure and anti-arrhythmic drug assisted are restricted because of the confounder of how many patients received an additional ablation or drugs to maintain sinus rhythm and when these interventions occurred during follow-up. However, it is clear that the clinical outcomes of contemporary ablation approaches overall, are significantly improved with repeat procedures (1.4 procedures; mean 65% success) and/or previously ineffective pharmaceuticals (mean 79% success) compared to the mean single procedure drug free clinical success (47%). Repeat procedures and previously ineffective anti-arrhythmic drugs are therefore a critical component of current ablation strategies long-standing persistent AF.

As we continue to understand more about the persistent fibrillatory process, the evolution of more specific ablation techniques will hopefully improve efficacy and safety, and render additional drugs and procedures unnecessary for the effective cure of hitherto long-standing persistent AF.

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Table 1: Single, multiple and AAD-assisted clinical success and complication rates for persistent/long-standing persistent AF.

Reference	N	Technique	Success			Comp (%)
			Single	Multi	AAD	
Kanagaratnam	71	PVI	0.21	.	0.62	5.6
Lim	51	PVI	0.22	0.37 (1.7)	0.45	3.9
Yamada	14	PVI	0.21	0.43 (1.5)	.	.
Pappone	72	PVA	0.56	.	0.68	TG
Cheema	41	PVAI	0.37	0.54 (1.2)	.	9.8
Elayi[RCT2]	48	PVAI	0.40	0.56 (1.3)	0.85	0.0
Oral[RCT3]	50	PVAI	0.38	0.68 (1.4)		TG
Oral[RCT1]	40	PVA + LIN	0.48	.	.	0.0
Vasamreddy	27	PVA + LIN	0.52	.	0.70	TG
Oral	77	PVA + LIN	0.74	.	.	0.0
Elayi[RCT2]	47	PVA + LIN	0.11	0.17 (1.3)	0.28	0.0
Earley	42	PVA/PVAI + LIN	0.36	0.74 (1.6)		11.9
Seow	56	PVAI + LIN	0.48	0.54 (1.5)	0.86	7.1
Miyazaki	25	PVAI + LIN	0.40	.	0.60*	0.0
Fiala	100	PVAI + LIN	0.38	0.66 (1.5)	0.87	.
Sanders	27	BOX	0.44	0.63 (1.4)	.	7.4
Chen	10	BOX	0.50	0.60 (1.5)	.	.
Kumagai	24	BOX	0.42	.	0.88	TG
Nademanee	64	CFAE	0.63	0.77 (1.2)	.	TG
Oral[RCT1]	40	CFAE	0.33	.	.	0.0
Oral	100	CFAE	0.33	0.57 (1.5)	.	3.0
Oral[RCT4]	33	CFAE†	0.24	0.52 (1.4)	.	3.0
Oral[RCT4]	33	CFAE‡	0.30	0.58 (1.2)	.	0.0
Schmitt	30	PVI + CFAE	0.50	.	.	TG
Estner	35	PVI + CFAE	0.51	0.74	.	0.0
Li	92	PVAI + CFAE	0.58	.	.	5.4
Porter	25	PVAI + LIN+ CFAE	0.68	.	.	4.0
Elayi[RCT2]	49	PVAI + CFAE	0.61	0.80 (1.2)	0.94	6.1
Oral[RCT3]	50	PVAI + CFAE	0.36	0.60 (1.4)		0.0
Haissaguerre	60	STEPWISE	0.62	0.88 (1.5)	.	5.0
Sacher	43	STEPWISE	.	0.70 (1.4)	0.84	.
Takahashi	40	STEPWISE	0.55	0.83 (1.4)	0.90	2.5
Rostock	88	STEPWISE	0.38	0.81 (1.8)	.	3.2
O'Neill	153	STEPWISE	0.48	0.74 (1.5)	0.89	3.9

PVI=pulmonary vein isolation; PVA=pulmonary vein antrum ablation; PVAI=pulmonary vein antrum isolation; LIN=conventional linear ablation; BOX=posterior wall isolation; CFAE=complex fractionated electrogram ablation; STEPWISE=Stepwise ablation technique; RF=radiofrequency; Single=single procedure, drug-free; Multi=repeat procedures included, drug-free - the mean number of procedures per patient in parentheses; AAD=multiple procedures and AAD; *single procedure with AAD; †=left atrial CFAE only; ‡=bi-atrial CFAE; §Presumably measured in the long-axis; TG=complications were reported from the total group and therefore cannot be applied to long-standing persistent cohort.

Table 2: Efficacy of PVI for persistent/long-standing persistent AF.

First Author	Year	N	Age	Disease type	LA size	RF time	Procedure time (min)	Recurrence	F/U	Primary success
Kanagaratnam	2001	71	57±12	**LSP** Non-CV Confirmed 4 d Holter	42±8	.	365	Ob	29±8	0.21
Lim	2006	51	59±10	**P/LSP** P AF > 7 d LSP AF - resistant to CV	45±6	.	.	Sub	17±9	0.22
Razavi	2006	28	58	**LSP** > 6 mo Non-CV	.	.	.	Sub	30±11	0.54*
Yamada	2007	14	56±9	**LSP** Non-CV	39±4	.	.	Ob	.	0.21

LSP=Long-standing persistent; P/LSP=mixed persistent/long-standing persistent; RF time=duration of radiofrequency ablation; Ob=Objective; Sub=Subjective; F/U=follow-up; Objective monitoring includes Holter, Loop recorder or trans-telephonic recordings at defined intervals; Subjective monitoring includes clinical review, clinic ECG, symptom-driven investigation or methods not specified; * excluded from summary; † Objective statement reporting that all patients completed a minimum 12 month follow-up.

Table 3: Efficacy of PVA ablation (with$^{\beta}$ and without$^{\alpha}$ PVI) for long-standing persistent AF

Name	Year	N	Age	Disease type	LA size	RF time	Procedure time (min)	Recurrence	F/U	Primary success
Pappone$^{\alpha}$	2001	72	.	**LSP** > 3 mo Non-CV	.	54	148	Ob	10±5	0.56
Cheema$^{\beta}$	2007	41	58±11	**LSP** > 6 mo Non-CV	51±6	.	229	Sub	11±2	0.37
Elayi$^{\beta\ RCT_2}$	2008	48	58±10	**LSP** > 12 mo Non-CV	45±7		183	Ob	16±1	0.40
Oral$^{\beta\ RCT_3}$	2009	50	58±10	**LSP** Not specified 'AF had been persistent for 5±5 yrs'	47±6	54±19	254	Ob	10±3	0.38

LSP=Long-standing persistent; P/LSP=mixed persistent/long-standing persistent; RF time=duration of radiofrequency ablation; Ob=Objective; Sub=Subjective; F/U=follow-up; Objective monitoring includes Holter, Loop recorder or trans-telephonic recordings at defined intervals; Subjective monitoring includes clinical review, clinic ECG, symptomatic driven investigation or methods not specified; $^{\alpha}$ without PV isolation; $^{\beta}$ PV isolation confirmed with circular catheter; † Objective statement reporting that all patients completed a minimum 12 month follow-up.

Table 4: Efficacy of PVA ablation (with[β] and without[α] PVI) + linear substrate modification for persistent/long-standing persistent AF.

Name	Year	N	Age	Disease type Enrollment criteria	LA size	RF time	Procedure time (min)	Recurrence	F/U	Primary success
Seidl[α]	2003	19	58±9	**LSP** Criteria not specified	45±5	.	822	Sub	12±3	.[€]
Oral[α RCT1]	2005	40	52±8	**LSP** > 6 mo AF recurrence < 4 wk post CV	47±4	46	134	Sub	10±3	0.48
Vasamreddy[α]	2005	27	.	**LSP** Criteria not specified	.	.	.	Sub	.	0.52
Oral[α]	2006	77	55±9	**LSP** > 6 mo AF recurrence < 1 wk post CV	45±6	37	96	Ob	12[†]	0.74
Elayi[α RCT2]	2008	47	60±11	**LSP** > 12 mo Non-CV	45±7	.	131	Ob	17±2	0.11
Earley[α, β]	2006	42	51±9	**LSP** AF present for 'some time' AF recurrence < 1 d post CV	46±7	.	314	Ob	8 (2-29)	0.38
Gaita[β]	2007	13	57±8	**LSP** Hypertrophic CM Recurrent stable AF post CV	53±6	.	100	Ob	18±12	0.15[*]
Seow[β]	2007	56	56±9	**P/LSP** >7 d Non-CV	.	.	.	Sub	22±9	0.48
Miyazaki[β]	2008	25	59±10	**LSP** > 6 mo	44±5	.	.	Sub	6	0.40
Fiala[β]	2008	100	55±10	**LSP** > 6 mo Non-CV AF recurrence < 1 wk post CV	47±6	97	291	Sub	26±14	0.57

LSP=Long-standing persistent; P/LSP=mixed persistent/long-standing persistent; RF time=duration of radiofrequency ablation; Ob=Objective; Sub=Subjective; F/U=follow-up; Objective monitoring includes Holter, Loop recorder or trans-telephonic recordings at defined intervals; Subjective monitoring includes clinical review, clinic ECG, symptomatic driven investigation or methods not specified; [α] without PV isolation; [β] PV isolation confirmed with circular catheter; [*] excluded from summary; [†] Objective statement reporting that all patients completed a minimum 12 month follow-up.

Table 5: Efficacy of posterior wall box isolation for long-standing persistent AF

Name	Year	N	Age	Disease type	LA size	RF time	Procedure time (min)	Recurrence	F/U	Primary success
Sanders	2007	27	57±8	**LSP** > 6 mo	43±6	70	199	Ob	23±3	0.44
Chen	2008	10	.	**LSP** > 6 mo Unable to maintain SR post CV	.	.	261[TG]	Sub	.	0.50
Kumagai	2009	24	.	**LSP** > 12 mo	.	50	152[TG]	Ob	9±4	0.42

LSP=Long-standing persistent; P/LSP=mixed persistent/long-standing persistent; RF time=duration of radiofrequency ablation; Ob=Objective; Sub=Subjective; F/U=follow-up; Objective monitoring includes Holter, Loop recorder or trans-telephonic recordings at defined intervals; Subjective monitoring includes clinical review, clinic ECG, symptomatic driven investigation or methods not specified; [TG] Extracted from mixed paroxysmal/long-standing persistent cohort; [†] Objective statement reporting that all patients completed a minimum 12 month follow-up.

Table 6: Efficacy of CFAE ablation for persistent/long-standing persistent AF

Name	Year	N	Age	Disease type	LA size	RF time	Procedure time (min)	Recurrence	F/U	Primary success
Nademanee**	2004	64	.	**P/LSP** > 7 d Non-CV or not attempted	.	.	186	Ob	12	0.63
Oral* RCT1	2005	40	55±10	**LSP** > 6 months AF recurrence < 1 mo post CV	49±6	35	149	Sub	10±3	0.33
Oral*	2007	100	57±11	**LSP** > 6 months	46±6	36	206	Ob	17±7	0.33
Oral RCT4*	2008	33	58±10	**LSP** Not specified 'Persistent for 4±3 yrs (range: 0.5-10yrs) before presentation	47±6	44±9	198	Ob	17±6	0.24
Oral RCT4‡	2008	33	60±10	**LSP** Not specified 'Persistent for 4±3 yrs (range: 0.5-10yrs) before presentation	46±7	43±14	223	Ob	17±6	0.30

LSP=Long-standing persistent; P/LSP=mixed persistent/long-standing persistent; RF time=duration of radiofrequency ablation; Ob=Objective; Sub=Subjective; F/U=follow-up; Objective monitoring includes Holter, Loop recorder or trans-telephonic recordings at defined intervals; Subjective monitoring includes clinical review, clinic ECG, symptomatic driven investigation or methods not specified; *Left atrial CFAE ablation (incl. CS); ‡Left and right CFAE ablation; †Objective statement reporting that all patients completed a minimum 12 month follow-up.

Table 7: Efficacy of CFAE ablation as an adjunct to pulmonary vein ostial isolation (PVI$^{\alpha}$) or PVAI$^{\beta}$ or PVAI and linear ablation$^{\gamma}$ for persistent/long-standing persistent AF

Name	**Year**	**N**	**Age**	**Disease type**	**LA size**	**RF time**	**Procedure time (min)**	**Recurrence**	**F/U**	**Primary success**
Schmitt$^{\alpha}$	2007	30	.	**P/LSP** 25/30 pts > 12 mo	.	66	326	Sub	12±3	0.50
Estner$^{\alpha}$	2008	35	57±9	**P/LSP** > 1 mo	49±6	.	367	Ob	19±12	0.51
Li$^{\beta}$	2008	92	59±6	**LSP** > 6 mo	42±5	.	.	Ob	12±11	0.58
Porter$^{\gamma}$	2008	25	56±10	**LSP** Median duration 13 mo (3-60)	.	64	225	Ob	> 1 yr†	0.68
Elayi$^{\beta}$ RCT2	2008	49	59±12	**LSP** > 12 mo Non-CV	46±6	.	239	Ob	16±1	0.61
Oral$^{\beta}$ RCT3	2009	50	62±8	**LSP** Not specified 'AF had been persistent for 5±5 yrs'	46±6	87±21	329	Ob	10±3	0.36

LSP=Long-standing persistent; P/LSP=mixed persistent/long-standing persistent; RF time=duration of radiofrequency; Ob=Objective; Sub=Subjective; F/U=follow-up; Objective monitoring includes Holter, Loop recorder or trans-telephonic recordings at defined intervals; Subjective monitoring includes clinical review, clinic ECG, symptomatic driven investigation or methods not specified; † Objective statement reporting that all patients completed a minimum 12 month follow-up.

Table 8: Efficacy of the Stepwise ablation technique for persistent/long-standing persistent AF

Name	Year	N	Age	Disease type	LA size	RF time	Proced-ure time (min)	Recur-rence	F/U	Prim-ary success
Haissaguerre	2005	60	54±11	**P/LSP** Median 12 mo (range: 1-168)	45±7	80	264	Ob	11±6	0.62
Sacher	2007	43	53±12	**P/LSP** Median 11 mo (range: 1-72) 4 pts non-CV	.	98	266	Ob	18±5	.
Takahashi	2008	40	59±10	**P/LSP** Median 12 mo (range: 1-84) 17 pts non-CV or recurrent AF in < 1 wk	45±6	82	227	Ob	14±3	0.55
Rostock	2008	88	61±10	**P/LSP** > 3 mo; median 12 mo (range: 3-264)	50±7	.	293	Ob	20±4	0.38
O'Neill	2009	153	56±10	**P/LSP** Median 12 mo (range: 1-240)	45±7	88±27	255	Ob	34 (28-40)[†]	0.48*

LSP=Long-standing persistent; P/LSP=mixed persistent/long-standing persistent; RF time=duration of radiofrequency ablation; Ob=Objective; Sub=Subjective; F/U=follow-up; Objective monitoring includes Holter, Loop recorder or trans-telephonic recordings at defined intervals; Subjective monitoring includes clinical review, clinic ECG, symptomatic driven investigation or methods not specified; [†] Objective statement reporting that all patients completed a minimum 12 month follow-up; $^{\alpha}$ long axis view; *assuming that every patient who failed underwent a redo procedure.

FIGURE LEGENDS

Figure 1: The search criteria and a flow diagram of the literature excluded from the original retrieved abstracts and full-text articles.

Figure 2: Single procedure, drug free clinical success associated with ablation approaches for persistent/long-standing persistent AF assessed in four randomized controlled trials. PVA=pulmonary vein antrum ablation; PVAI=pulmonary vein antrum isolation; LIN=conventional linear ablation; CFAE=complex fractionated electrogram ablation.

Figure 3: Clinical success of various ablation techniques for persistent/long-standing persistent AF. The success rate is presented for a single procedure and drug-free success (white), multiple procedure (diagonal cross hatch) and AAD-assisted success rates (dark double hatch). Error bars represent ± 1 SD; bars are absent when estimate is based on one study. PVI=pulmonary vein isolation; PVA=pulmonary vein antrum ablation; PVAI=pulmonary vein antrum isolation; LIN=conventional linear ablation; BOX=posterior wall isolation; CFAE=complex fractionated electrogram ablation; STEPWISE=Stepwise ablation technique.

Figure 1:

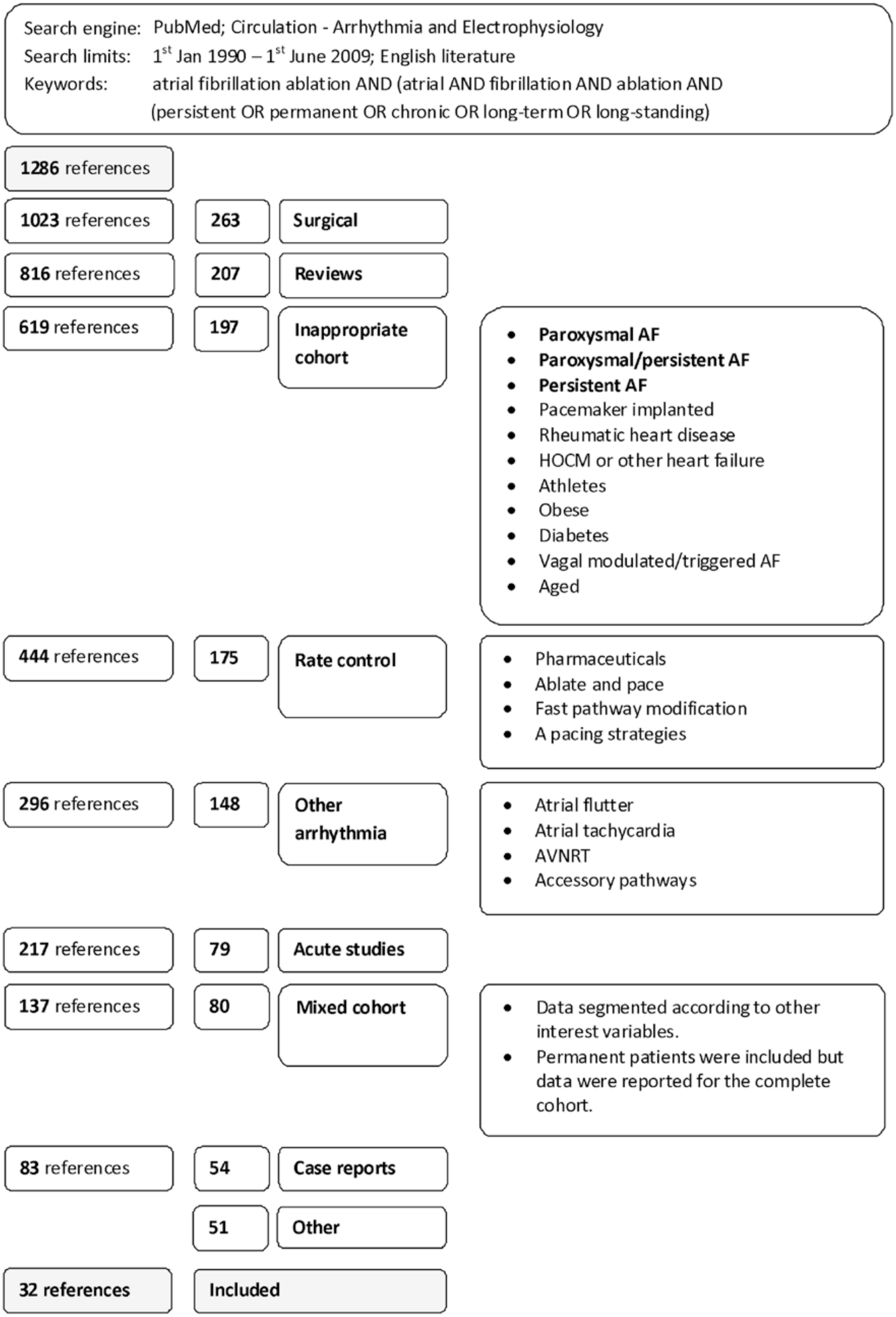

Search engine: PubMed; Circulation - Arrhythmia and Electrophysiology
Search limits: 1st Jan 1990 – 1st June 2009; English literature
Keywords: atrial fibrillation ablation AND (atrial AND fibrillation AND ablation AND (persistent OR permanent OR chronic OR long-term OR long-standing)
1286 references
1023 references
263
Surgical
816 references
207
Reviews
619 references
197
Inappropriate cohort
Paroxysmal AF
Paroxysmal/persistent AF
Persistent AF
Pacemaker implanted
Rheumatic heart disease
HOCM or other heart failure
Athletes
Obese
Diabetes
Vagal modulated/triggered AF
Aged
444 references
175
Rate control
Pharmaceuticals
Ablate and pace
Fast pathway modification
A pacing strategies
296 references
148
Other arrhythmia
Atrial flutter
Atrial tachycardia
AVNRT
Accessory pathways
217 references
79
Acute studies
137 references
80
Mixed cohort
Data segmented according to other interest variables.
Permanent patients were included but data were reported for the complete cohort.
83 references
54
Case reports
51
Other
32 references
Included

Figure 2:

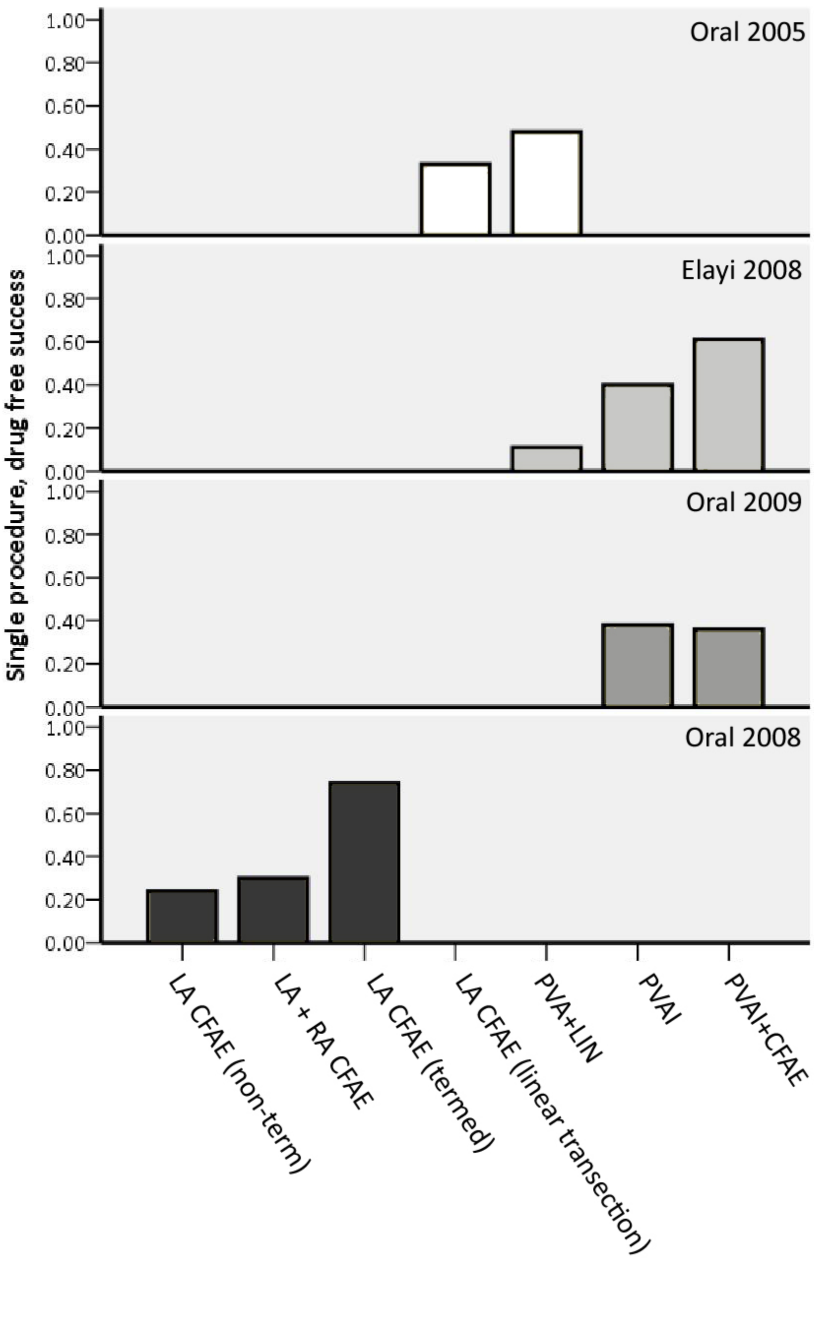
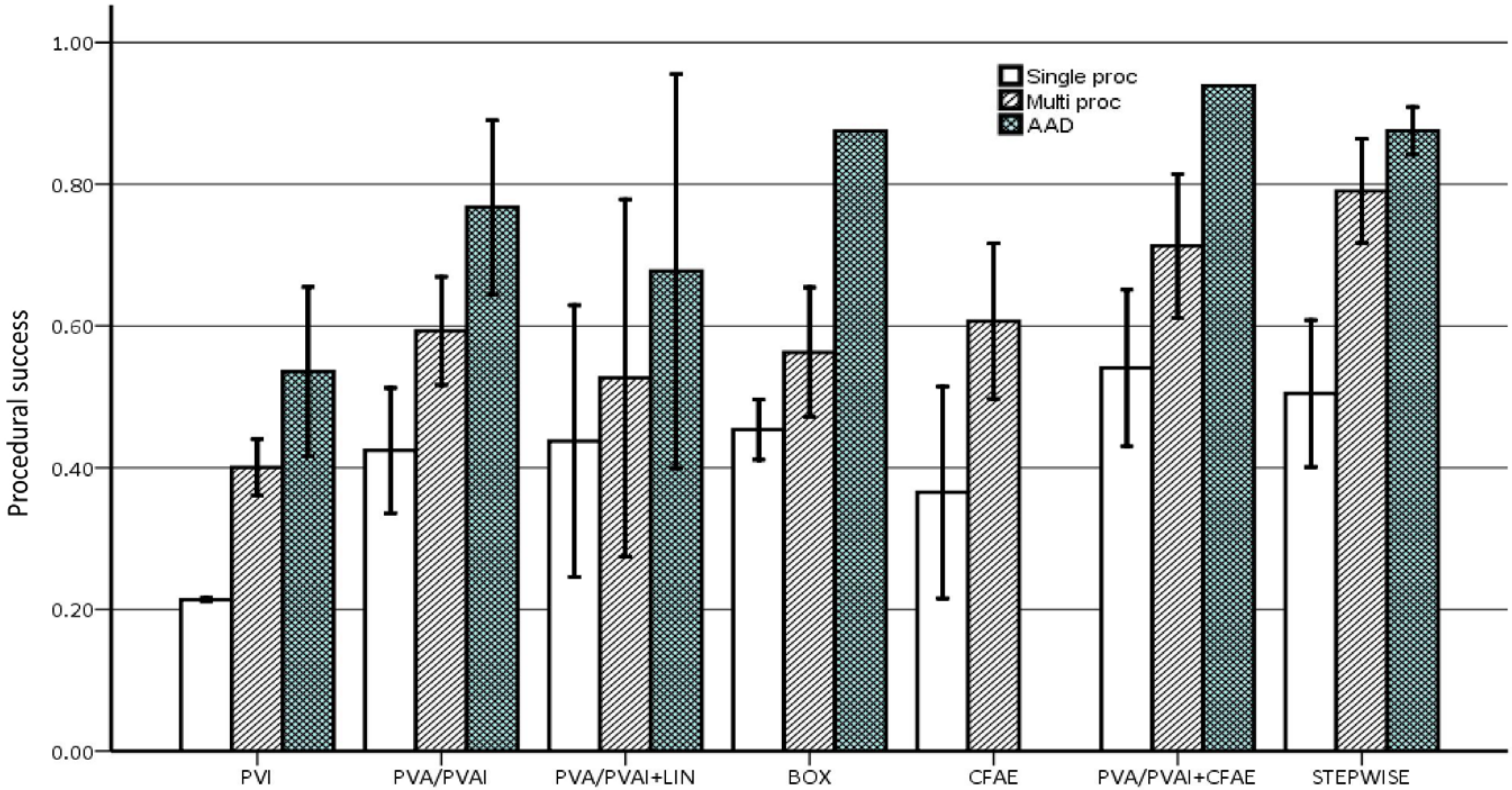

Single procedure, drug free success
Oral 2005
Elayi 2008
Oral 2009
Oral 2008
1.00
0.80
0.60
0.40
0.20
0.00
LA CFAE (non-term)
LA + RA CFAE
LA CFAE (termed)
LA CFAE (linear transection)
PVA+LIN
PVAI
PVAI+CFAE

Figure 3:


1.00
0.80
0.60
0.40
0.20
0.00
Procedural success
Single proc
Multi proc
AAD
PVI
PVA/PVAI
PVA/PVAI+LIN
BOX
CFAE
PVA/PVAI+CFAE
STEPWISE