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Efficacy of ganglionated plexi ablation in addition to pulmonary vein isolation for paroxysmal versus persistent atrial fibrillation: a meta-analysis of randomized controlled clinical trials

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Abstract

Purpose Adjunctive ganglionated plexi (GP) ablation may improve success rates for treatment of atrial fibrillation (AF) when combined with pulmonary vein (PV) isolation. Existing meta-analyses on GP ablation have included observational studies and have not incorporated more recent randomized clinical trial data. Moreover, the impact of AF subtype (paroxysmal vs. persistent) on outcomes of GP ablation has not been well established.

Methods We performed a meta-analysis of randomized controlled trials (RCTs) comparing GP ablation + pulmonary vein (PV) isolation versus PV isolation alone according to the subtype of AF. The primary endpoint was freedom from sustained AF or atrial tachyarrhythmia (AT) after a single procedure.

Results Across four RCTs, 718 patients (358 and 360 that underwent GP ablation + PV isolation [intervention] vs. PV isolation alone [control], respectively) were included in the study. Mean left atrial size and left ventricular ejection fraction were 45.7 mm and 54.8%, respectively. Among paroxysmal AF patients, GP ablation was linked to significantly higher freedom from AT/AF (75.8 vs. 60.0% for the intervention vs. control arms respectively; OR [95% CI]: 2.22 [1.36–3.61], $P = 0.001$). Among persistent AF patients, GP ablation was associated with a non-significant trend towards higher rates of freedom from AT/AF (54.7 vs. 43.3% for the intervention vs. control arms respectively; OR [95% CI]: 1.55 [0.96–2.52], $P = 0.08$). In all cases, heterogeneity was found to be low (I^2 of 32% or lower).

Conclusions Compared to PV isolation alone, GP ablation + PV isolation is associated with better outcomes in patients with paroxysmal AF and without significant structural heart disease.

Keywords Atrial fibrillation · Ganglionated plexi · Catheter ablation · Pulmonary vein isolation

1 Introduction

Ganglionated plexi (GP) are interconnected clusters of autonomic ganglia that form the intrinsic cardiac autonomic nervous system and innervate the myocardial sleeves of pulmonary veins (PVs) with sympathetic and parasympathetic nervous fibers [1, 2]. Experimental studies have shown that GP hyperactivity can lead to increased firing from PVs, which is associated with initiation and maintenance of atrial fibrillation (AF) [3, 4]. Targeted ablation of the GP has been proposed as either a primary approach or adjunctive approach to treating AF. Initial experimental [5, 6] and clinical studies [7–9] have shown promising results and meta-analyses of clinical studies have reported reduced rates of AF recurrence after combined GP ablation and PV isolation [10, 11]. However, existing meta-analyses have been limited by the use of observational studies and a low number of randomized controlled trials (RCT). The recently published Atrial Fibrillation Ablation and Autonomic

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Modulation via Thoracoscopic Surgery (AFACT) study, a randomized controlled trial showed no additional benefit from thoracoscopic GP ablation in addition to PV isolation [12]. Moreover, the significance of AF type (paroxysmal versus persistent) in influencing outcomes of GP ablation on patients has not been well established. We therefore sought to perform a meta-analysis of RCTs comparing the effect of combined GP ablation and PV isolation versus PV isolation alone on ablation outcomes and to assess for any difference on GP ablation outcomes based on type of AF.

2 Methods

2.1 Search strategy and eligibility criteria

The study protocol was prospectively registered in PROSPERO (PROSPERO 2017:CRD42017056605) and is available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017056605. Medline (PubMed), Embase, and the Cochrane Library databases were searched for primary research papers, published in any language from their dates for inception until January 3rd 2017. The search was performed by two independent reviewers (EO, DC) using the following search algorithm: (“autonomic denervation” OR “ganglion” OR “ganglionic” OR “ganglionated”) AND (“ablation” OR “block”) AND “atrial fibrillation”. Reference lists of all studies previously identified as having met the inclusion criteria were also manually reviewed for additional relevant publications. Disagreements were resolved by consensus with the addition of a third reviewer (JC).

The following studies were excluded: (i) non-randomized controlled trials, (ii) secondary research papers (e.g., reviews, meta-analysis), (iii) experimental studies in animals or basic science studies, (iv) case reports and case series, (v) studies including duplicate populations.

2.2 Data extraction and quality assessment

All data were extracted by two independent researchers (EO, DC) and consensus was reached after the involvement of a third investigator (JC). The primary endpoint was freedom from AF or sustained atrial tachyarrhythmia (AT) after a *single* procedure. Pertinent clinical data were also extracted. The quality of all eligible studies was critically appraised and rated by two reviewers. Studies were assessed by the Cochrane Collaboration’s tool for assessing risk of bias [13].

2.3 Statistical analysis

Categorical variables were reported as proportions, whereas continuous variables were reported as median and range, unless stated otherwise. For each study, the number of events in the control and treatment groups was used to calculate a study-specific odds ratio (OR) for the outcome of interest. In addition, where events in more than two timepoints were reported, we used the outcome date for the latest timepoint. Next, pooled ORs and corresponding 95% confidence intervals (CI) were calculated with the random-effects model estimated by the Mantel-Haenszel method. Statistical heterogeneity between studies was assessed with a χ^2 test and the I^2 statistic; $P < .10$ for the χ^2 test or I^2 greater than 50% indicated significant heterogeneity. Where the exact number of events in our subgroup analysis could not be accurately calculated due to loss of study participants at follow-up, we assumed that participants were lost at equal rates from both groups. The meta-analysis was performed using Review Manager (RevMan), version 5.3 software (Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

3 Results

3.1 Study and clinical characteristics

A total of 475 articles were identified (after duplicates were removed) and 450 studies were excluded based on their title and abstract. Next, screening of the full texts of the remaining 25 articles, identified four studies that met all eligibility criteria, as summarized in the PRISMA chart (Fig. 1). Eligible studies were all randomized, controlled trials comparing the efficacy of GP ablation in addition to PV isolation (intervention group) against PV isolation alone (control group) (n = 4 studies) (Table 1) [7, 12, 14, 15]. Three studies used a catheter-based ablation procedure, whereas thoracoscopic ablation was performed in the AFACT study. GPs were localized using anatomic landmarks and/or high-frequency stimulation according to previously described techniques [16, 17]. Two of the studies recruited patients with paroxysmal AF, one with persistent AF, while the AFACT study included both groups (41% with paroxysmal and 59% with persistent AF). In patients with persistent AF, additional linear lesions [15] or a Dallas lesion set [12] were performed in both groups.

A total of 366 and 365 individuals were included in the intervention and control arms, respectively. Weighted mean age for the total population included in our analysis was 56.6 years (74.3% males). Weighted means for left atrial (LA) size and left ventricular ejection fraction

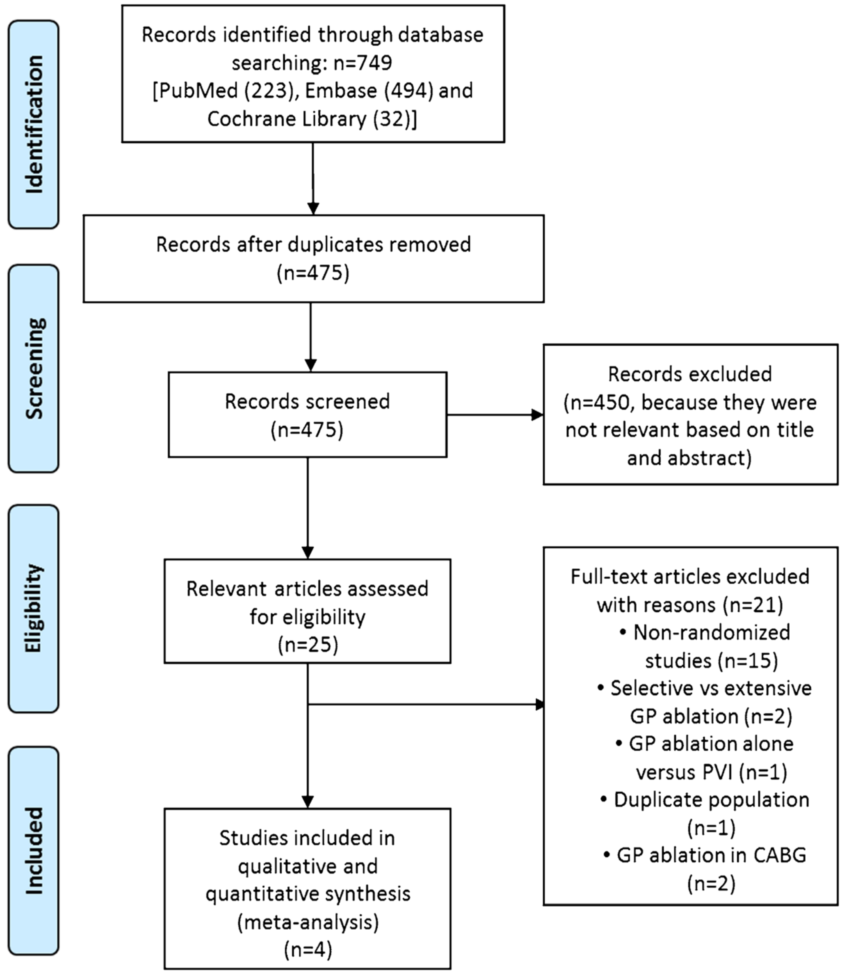

Fig. 1 PRISMA flowchart outlining trial selection process

(LVEF) were 45.7 mm and 54.8%, respectively. Baseline demographics were not significantly different in any of the included studies and are summarized in Table 2. Follow-up was performed at least 1 year after the procedure and up to a maximum of 3 years. All studies used a 3-month blanking period and evaluated the primary endpoint using regular visits, ambulatory ECG-monitoring, and/or implantable monitoring devices.

4 Recurrence of AF

The primary endpoint was assessed in a total of 718 study participants (358 in the intervention arm and 360 controls) across four studies. There was loss to follow-up of 13 participants in the AFACT study; seven in the intervention and six in the control arm. At the end of follow-up, 64.0% of the study participants that underwent GP ablation in addition to PV isolation were free of AT/AF versus 51.1% in the control arm. Performance of adjunctive GP ablation in addition to PV isolation was associated with a significantly lower risk of recurrent AT/AF regardless of the type of AF (OR [95% CI]: 1.81 [1.22–2.67], Fig. 2a). While the AFACT study did not reveal a significant benefit for GP ablation (OR [95% CI]: 1.13 [0.64–1.99]), the result was largely driven by the other three studies, all of which included patients undergoing catheter-based ablation procedures.

Next, we performed a subgroup analysis of patients with paroxysmal versus persistent AF. The primary endpoint was assessed in 321 individuals with paroxysmal AF (157 undergoing GP ablation versus 164 controls) across three studies, whereas two studies reported data on 397 patients with persistent AF (201 undergoing GP ablation versus 196 controls). Among paroxysmal AF patients, GP ablation was linked to a significantly higher freedom from AT/AF (75.8 vs. 60.0% for the intervention vs. control arms, respectively; OR [95% CI]: 2.22 [1.36–3.61], $P = 0.001$, Fig. 2b). Among persistent AF patients, GP ablation was associated with a non-significant trend

Table 1 Summary of studies included in meta-analysis

Study and year	Ablation type	Single- or multi-center	Paroxysmal or persistent AF	Intervention	Control	Mode of GP localization	Primary endpoint	Follow-up	Assessment of endpoint
Katritsis et al. [7]	Catheter-based	2 centers	100% paroxysmal AF	PVI + GP ablation	PVI	Anatomic	Freedom from AT/AF after single procedure	2-year follow-up	Monthly visits, ambulatory ECG-monitoring, implantable loop recorders
Katritsis et al. [14]	Catheter-based	Single-center	100% paroxysmal AF	PVI + GP ablation	PVI	Anatomic	Freedom from AT/AF after one or two procedures (off-antiarrhythmics)	1-year follow-up	Monthly visit, ambulatory ECG-monitoring every 3 months
Pokushalov et al. [15]	Catheter-based	Single-center	100% persistent AF	PVI + GP ablation	PVI + linear lesions	HFS	Freedom from AT/AF	At least 3 years	Implanted monitoring device
Driessen et al. [12]	Thoracoscopic	Single-center	41% paroxysmal, 59% persistent AF	PVI + GP ablation (+ Dallas lesion if persistent AF)	PVI (+Dallas lesion set if persistent AF)	HFS	Freedom from AT/AF	1 year	Clinical visits, ambulatory ECG-monitoring every 3 months

Table 2 Basic demographics of included study populations

Study and year	Arm	*n*	Age (years)	Male gender (%)	HTN (%)	DM (%)	LVEF (%)	LA size (mm)	Duration of AF (years)	Paroxysmal/persistent AF (%)
Katritsis et al. [7]	PVI	78	56 ± 7.6	68	81	1	63 ± 6.8	48 ± 7	–	100/0
	PVI+GPA	82	56 ± 8.5	70	71	4	62 ± 8.1	48 ± 6	–	100/0
Katritsis et al. [14]	PVI	33	53.2 ± 11.3	78.8	60.6	–	56.1 ± 5.3	41.1 ± 3.3	–	100/0
	PVI+GPA	34	55.2 ± 11.6	73.5	47.1	–	56.2 ± 7.7	41.5 ± 5.4	–	100/0
Pokushalov et al. [15]	PVI+LL	132	54 ± 7	79.5	35	11	54.2 ± 6.3	48 ± 7	5.4 ± 3.6	0/100
	PVI+GPA	132	55 ± 6	76.5	33	9	55.1 ± 4.8	49 ± 7	5.9 ± 3.9	0/100
Driessen et al. [12]	PVI	123	60.2 ± 8.2	74	44	7	51.2 ± 9.1	42.3 ± 5.5	5 [2–10]	45/55
	PVI+GPA	117	59.5 ± 8.2	72	41	7	47.9 ± 18	42.1 ± 5.6	4 [2–6]	37/63

Data presented as mean ± standard deviation or mean [interquartile range]

DM diabetes mellitus, *GPA* ganglion plexus ablation, *HTN* hypertension, *LA* left atrium, *LVEF* left ventricular ejection fraction, *PVI* pulmonary vein isolation

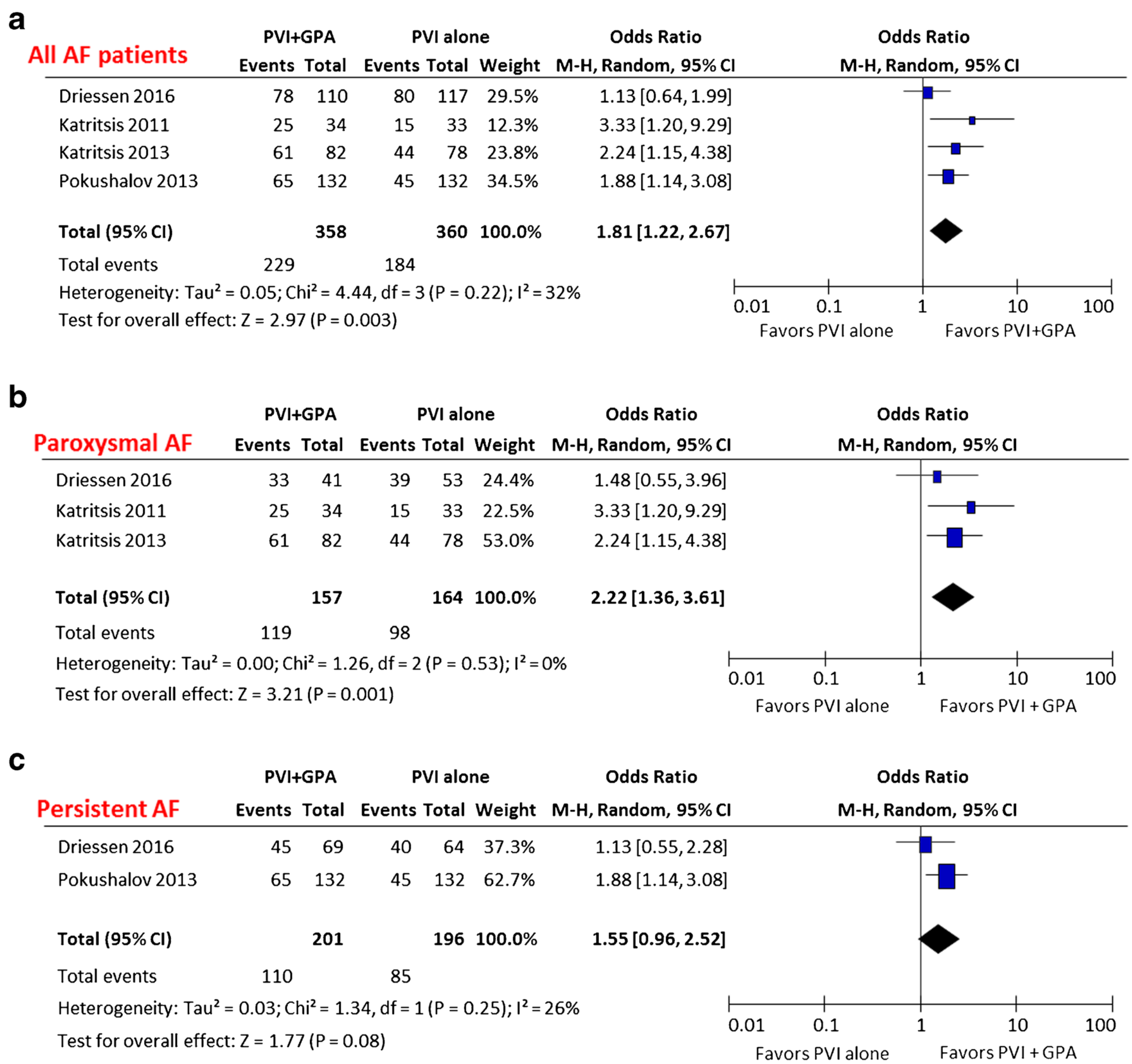

Fig. 2 Comparison of single procedure success rates between PV isolation+ adjunctive GP ablation versus PV isolation alone. A. All AF patients. B. Subgroup of paroxysmal AF patients. C. Subgroup of persistent AF patients. AF = atrial fibrillation; GPA = ganglionated plexi ablation; PVI = pulmonary vein isolation

towards higher rates of freedom from AT/AF (54.7 vs. 43.3% for the intervention vs. control arms, respectively; OR [95% CI]: 1.55 [0.96–2.52], $P = 0.08$, Fig. 2c). In all cases, heterogeneity was found to be low (I^2 of 32% or lower).

5 Other endpoints

Average procedure duration, fluoroscopy time and radiofrequency delivery time (in the catheter-based ablation procedures) were all significantly longer in the GP ablation arm compared to control in all studies that reported this information. GP ablation was found to be safe, with no procedure-related deaths reported in any of the included studies. In the AFACT study, all four deaths in the GP ablation arm were attributed to non-procedure-related events (sarcoidosis, esophageal and pancreatic cancer, and sudden death 316 days after the procedure). Procedural data and outcomes for the included studies are summarized in Table 3.

6 Risk of bias assessment

All studies included in our systematic review and meta-analysis were found to be of low risk of bias with regards to incomplete outcome data and selective reporting, while most of them were also at low risk for the following domains: random sequence generation, allocation concealment, and blinding of outcome assessment. On the other hand, all studies were found to be at high risk of bias for the domain of participant/personnel blinding given the nature of the intervention (Table 4).

Table 3 Procedural data and outcomes

Study and year	Arm	n	Procedure time (minutes)	Fluoroscopy time (minutes)	Freedom from atrial tachyarrhythmia after single procedure	Post-ablation atrial flutter	RF delivery (min.)	Death	MI	TIA/stroke	Tamponade	Major bleeding	SN dysfunction
Katritsis et al. [7]	PVI	78	–	16 ± 3	44 (56%)	4 (5.1%)	41 ± 10	0	0	0	1	–	–
	PVI+ G-PA	82	–	23 ± 5	61 (74%)	5 (6.1%)	67 ± 18	0	0	0	0	–	–
Katritsis et al. [14]	PVI	33	105.2 ± 22.3	15.8 ± 3.3	15 (45.5%)	–	–	0	0	0	0	–	–
	PVI+ G-PA	34	126.0 ± 26.7	22.3 ± 6.8	25 (73.5%)	–	–	0	0	0	1	–	–
Pokushalov et al. [15]	PVI+ LL	132	153 ± 37	29 ± 15	45 (34%)	24 (18%)	58 ± 11	0	–	2	1	–	–
	PVI+ G-PA	132	192 ± 21	34 ± 11	65 (49%)	8 (6%)	69 ± 4	0	–	2	2	–	–
Driessen et al. [12]	PVI	117[a]	168 ± 54	–	80 (68.4%) -paroxysmal: 39/53 (74.5%) -persistent: 40/64 (62.9%)	–	–	0	–	–	–	0	4
	PVI+ G-PA	110[a]	185 ± 54	–	78 (70.9%) -paroxysmal: 33/41 (80.0%) -persistent: 45/69 (65.7%)	–	–	4	–	–	–	9	12

Data presented as *n* (%), unless stated otherwise

GPA ganglion plexus ablation, *MI* myocardial infarction, *PVI* pulmonary vein isolation, *RF* radiofrequency, *SN* sinus node, *TIA* transient ischemic attack

[a] Follow-up was performed in 117 out of 123 individuals in the PVI arm and 110 out of 117 participants in the PVI+GPA arm

7 Discussion

This systematic meta-analysis of randomized controlled clinical trials comparing adjunctive GP ablation plus PV isolation with PV isolation alone demonstrated that additional GP ablation is associated with increased rates of freedom from AT/AF among patients with paroxysmal AF. In contrast, among patients with persistent AF, adjunctive GP ablation resulted only in a non-significant trend towards increased freedom from AT/AF when compared to PV isolation alone.

Prior meta-analyses on this subject have shown the benefit of adding GP ablation to PV isolation [10, 11]. However, these studies included observational studies which may have introduced significant bias. The risk of bias assessment of the included studies was not performed in these previously published meta-analyses. To our knowledge, our study is the first meta-analysis to include only RCTs in the assessment of the efficacy of adjunctive GP ablation. We included the recent AFACT study, which failed to show a benefit of additional GP ablation [12].

The current basis of AF ablation procedures lies on the concept of targeting rapid firing from the myocardial sleeves of PVs and other non-PV sites as well as possibly modifying abnormal left atrial substrate that maintains AF [18, 19]. Current success rates from AF ablation, in particular for patients with persistent AF, remain sub-optimal. While PV isolation has been recognized as a fundamental part of the AF ablation approach, the role for adjunctive ablation remains to be elucidated [20]. Enthusiasm for adjunctive ablation approaches that have incorporated targeting of complex fractionated atrial electrograms and application of linear ablation have been tempered by studies such as the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II (STAR AF II) [21]. While initial studies on the use of focal impulse and rotor mapping-guided ablation for the reduction of recurrent AF were promising [22, 23], more recent studies have yielded conflicting results [24, 25].

Therefore, ganglionated plexi ablation represents a potential remaining target as part of an AF ablation strategy. Ganglionated plexi hyperactivity has been linked to initiation of rapid firing from the myocardial sleeves of PVs [3, 16], suggesting that cardiac autonomic nervous system deregulation may represent an upstream event in the cascade of AF initiation. Autonomic nerve stimulation of isolated PVs by acetylcholine plus norepinephrine induces short bursts of triggering from PVs similar to that recorded in patients with paroxysmal AF [26, 27]. Other experimental studies have reported that early atrial remodeling in the first few hours after rapid atrial pacing correlates with an increase in GP activity that can be reversed after GP ablation [28, 29]. Aside from affecting triggers of AF, GP activity may also be related to some forms of electrical rotors that are associated with long-term maintenance of AF [30]. However, further data are required in support of this hypothesis.

Table 4 Risk of Bias assessment

	Katritsis et al. [7]	Katritsis et al. [14]	Pokushalov et al. [15]	Driessen et al. [12]
Random sequence generation	Low	Unknown	Low	Low
Allocation concealment	Low	Unknown	Low	Low
Blinding of participants and personnel	High	High	High	High
Blinding of outcome assessment	Low	High	Low	Low
Incomplete outcome data	Low	Low	Low	Low
Selective reporting	Low	Low	Low	Low

These studies which demonstrate a link between GP and the cardiac autonomic nervous system with the early pathogenesis of AF and PV triggers [31] would support the findings of our meta-analysis which demonstrated improved outcomes among patients with paroxysmal AF with GP ablation but less significant results among patients with persistent AF. Among patients with persistent atrial fibrillation, AF may be driven more by factors arising outside the PVs, such as atrial fibrosis and non-PV triggers which would not be targeted with GP ablation. Furthermore, since cardiac GP are mostly located around the PVs, GP ablation may be improving outcomes in paroxysmal AF ablation patients by allowing more durable PV as opposed to affecting cardiac autonomic physiology in a significant manner. It should be noted that the majority of the patients in the studies included in this meta-analysis were free from significant structural heart disease (Table 2).

Although there was no statistical heterogeneity present in this meta-analysis (I^2 = 32% for the overall population and 0%, 26% for paroxysmal and persistent AF, respectively), there were procedural differences between the studies used. Two of the four studies used an anatomic approach to localizing and targeting the GP while the other two used high-frequency stimulation to confirm GP location. Importantly, in the AFACT trial, a thoracoscopic surgical approach was used instead of a catheter-based approach [12]. Despite the difference in approaches between the AFACT trial and the other three endocardial catheter-based studies included in our analysis, the AFACT trial has important strengths that argue for its inclusion in any meta-analysis examining the utility of GP ablation for treatment of AF. First, the AFACT trial was a large, randomized trial that utilized both anatomic and rigorous electrophysiologic endpoints to confirm GP location as well as durable isolation of the PVCs and bidirectional line of block across linear lesions. Second, given that the GP fat pads are located epicardially, it can be argued that epicardial surgical ablation would be more effective than endocardial catheter ablation for complete denervation of the PVs. Consequently, the AFACT study may reflect a truer examination of the incremental value of complete GP denervation on top of durably isolated PVs for the treatment. Therefore, the findings of the AFACT study, albeit negative, clearly merited inclusion in our study.

Overall, the major limitations of the current meta-analysis are the limited number of patients, high bias risk across all included studies regarding blinding of participants and personnel, and the absence of fully standardized approach to identification and ablation of GP, including a thoracoscopic surgical approach used in one of the studies.

8 Conclusion

Although the role of GP ablation in addition to pulmonary vein isolation for the treatment of AF remains controversial, the results of this meta-analysis support its use in selected patients, namely those with paroxysmal AF and without significant structural heart disease. The role for adjunctive GP ablation for patients with persistent AF is less clear. Larger RCTs are needed to better define the subset of AF patients who would benefit most from adjunctive GP ablation in addition to conventional PV isolation.

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Compliance with ethical standards

Conflict of interest The other authors declare that they have no conflicts of interest.

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