Comparative Effectiveness of Wide Antral Versus Ostial Pulmonary Vein Isolation: A Systematic Review and Meta-Analysis

Running title: Proietti et al.; Wide antral vs ostial PVI

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Abstract:

Background - Over the last decade, electrical pulmonary vein isolation (PVI) has become a procedure implemented worldwide for the treatment of atrial fibrillation (AF). Currently two main approaches are utilized for PVI: ostial isolation of the PVs, and wide antral PVI. The aims of this systematic review are to evaluate the relative merits of each technique with a pooled comparative analysis of efficacy and complications.

Methods and Results - Studies were identified by searching electronic databases for studies on ostial vs. antral PVI. Information was extracted from each included trial. Odds ratio (OR) was the primary measure of treatment effect or side effects. The proportion of patients with recurrences of AF or other atrial tachyarrhythmias was evaluated at the end of the follow-up periods in twelve trials, including 1183 patients. The recurrence rate of total supraventricular arrhythmias was significantly lower in wide antral than in segmental PVI group (OR 0.42 95% CI 0.32 to 0.56, p<0.0001). AF recurrence was significantly lower in the wide antral group (OR 0.33 95% CI 0.24 to 0.46, p<0.0001). A trend towards a higher incidence of left atrial tachycardia occurrence in the waca ablation group was detected, which did not reach statistical significance (OR 1.53 95% CI 0.88 to 2.69; p=0.13).

Conclusions - Our primary finding is that PVI performed with a wide antral approach is more effective than ostial PVI in achieving freedom from total atrial tachyarrhythmia recurrence at long term follow-up.

Key words: atrial fibrillation, wide antral, pulmonary vein isolation, atrial fibrillation ablation
Introduction

Atrial fibrillation (AF) can be triggered by electrical activity of myocardial sleeves around the pulmonary veins (PV), and PV isolation (PVI) with radiofrequency catheter ablation has been consistently shown to confer freedom from AF recurrence in a substantial proportion of patients\(^1\). Over the last decade, PVI has become a procedure implemented worldwide for the treatment of AF\(^2-4\).

Currently two main approaches are utilized for PVI: ostial isolation which is a selective ablation of PV potentials at the ostium of the PVs\(^1\), and wide antral PVI which involves isolation of a wider area that encompasses part of the left atrial posterior wall\(^5\). Thus far, the relative merits of one technique over the other have not been systematically investigated. The aims of this systematic review are: 1) to critically review all studies that compared ostial vs. wide antral pulmonary vein isolation in AF ablation; and 2) to evaluate the relative merits of each technique with a pooled comparative analysis of efficacy and complications.

Methods

Study selection

Randomized controlled studies or cohort studies were included if they met all three of the following criteria: i) inclusion of patients with AF (either paroxysmal or persistent); ii) comparison between ostial versus wide antral PVI. The definition of wide antral circumferential ablation (WACA) was defined as a circumferential isolation performed at least 1.5 cm away from the pulmonary vein ostium as identified by angiography or 3D electroanatomical reconstruction.

Search strategy

Studies were identified by searching electronic databases (PubMed from 1948 to the present and Embase from 1974 to the present). We searched also Cochrane and DARE databases for
additional records. The search strategy adopted was the same for all databases and was developed using as key words 'atrial fibrillation', 'ostial pulmonary vein isolation', 'antral pulmonary vein isolation', 'circumferential pulmonary vein isolation' and 'wide area circumferential ablation'. The last search was run on January 28, 2013. The literature search was conducted by two investigators (RP and WY).

**Data extraction**

Information was extracted from each included trial concerning:

1) Baseline characteristics of trial participants and country where the study was performed;

2) Outcomes:

   a) Efficacy

      i) *Primary outcome:* cumulative recurrence rate of any atrial tachyarrhythmia at the end of the study follow-up

      ii) *Secondary outcomes:*

         1- AF recurrence only,

         2- left atrial tachyarrhythmia recurrence at the end of the follow-

         3- atrial tachyarrhythmia recurrence after first procedure.

         4- procedural data including total procedure duration, fluoroscopy time and radiofrequency application time.

   b) Safety: procedural-related complications

Two authors (RP and WY) independently extracted data from studies and entered in the data extraction form. Disagreements were resolved by discussion with a third author (PS).

**Quality assessment**

We based our assessment on the risk of bias tool from the Cochrane Collaboration\(^6\). Specifically,
the risk of bias was assessed in the following domains: study design, allocation, blinding of outcomes assessment, control of known confounding factors at baseline, attrition, selective reporting of the data.

Every domain could be classified as “high” or “low” risk of bias. If the information reported in the paper was insufficient, the domain was defined as “unclear”.

Summary measures

Odds ratio (OR) was the primary measure of treatment effect or side effects; 95% confidence intervals (CIs) for OR were calculated. Mean difference and its 95% CIs were used for continuous outcomes. We combined the studies using the random-effects model described by DerSimonian and Laird. For the meta-analysis of peri-procedural complications, we used fixed-effect Peto OR, given the low incidence of the outcome. Heterogeneity was assessed by the Q (Chi-squared) and the I-squared statistics (I²). The I² statistic indicates the percentage variability due to between-study (or inter-study) variability. An I² value greater than 50% was classified as substantial presence of heterogeneity. All analyses were performed with the RevMan software.

Results

Study selection

Our literature search identified 347 references. Exclusion of duplicates and irrelevant references left 81 records. Twenty-nine of these citations were considered potentially eligible for inclusion and their full texts were analysed in more detail. We then excluded seventeen of these studies, nine because they did not have a control group, three because different outcomes were considered, two because they did not assess electrical isolation in circumferential ablation, two because they assessed a different ablation strategy, and one because they used different catheter technologies. Finally, a total of twelve studies were included in the analysis.
Study characteristics

The final twelve studies selected were all published prospective intervention trials. The main features of the twelve trials are summarized in supplemental table 1. Overall, 1183 participants were included, with the number of participants in each trial ranging from 66 to 187. Clinical follow-up length in the trials varied from 6 to 48 months. Follow-up intensity (e.g. frequency of clinical visits and/or monitoring for arrhythmia) varied among studies.

Risk of bias evaluation is reported in Supplemental figure 2. Many items were judged at high risk of bias by both investigators.

Total supraventricular arrhythmia recurrence rate (primary outcome)

The proportion of patients with recurrences of AF or other atrial tachyarrhythmias was evaluated at the end of the follow-up periods in the twelve trials that included 1183 patients. The recurrence rate of total supraventricular arrhythmias was significantly lower in the wide antral than in the segmental PVI group (OR 0.42 95% CI 0.32 to 0.56, p<0.00001) (Figure 1).

An analysis on the primary outcome including only studies reporting data at 1 year follow-up (12±3 months) showed a similar lower incidence of arrhythmia recurrence in the waca group versus the segmental group (OR 0.42, 95% CI 0.32 to 0.57).

The same analysis was repeated for patients with only paroxysmal AF (which included 5 studies that were included only paroxysmal AF patients and 2 studies that included both paroxysmal and persistent, but provided separate results for paroxysmal AF patients. A significant effect of wide antral versus ostial PVI was present in paroxysmal AF patients OR 0.58 [0.39, 0.85] (p=0.006). Results for patients with persistent AF are not reported because only two papers reported data on persistent AF.
Because some studies performed an additional lesion on top of PVI, we replicated the analysis on the primary outcome including only the six studies which did not performed additional line of ablation. A significant effect of WACA versus ostial PVI was present (OR 0.37 [0.26, 0.53] p<0.00001).

**Atrial tachyarrhythmia recurrence after first ablation, AF recurrence only and left atrial tachyarrhythmia recurrence at the end of the follow-up (secondary outcome)**

After the first procedure, wide antral ablation also resulted in a statistically significant lower recurrence of tachyarrhythmias (OR 0.59 95% CI 0.45 to 0.78, p=0.00002) (fig. 2). Eight studies24-26, 28, 30, 31, 34 distinguished AF recurrence from other atrial tachyarrhythmia recurrences at long term follow-up. AF recurrence was significantly lower in the wide antral group OR 0.33 95% CI 0.24 to 0.46, p<0.00001(fig. 3). Seven studies24, 25, 28, 31, 33, 34 assessed atrial tachycardia recurrence as a separate outcome. A trend towards a higher incidence of left atrial tachycardia occurrence in the WACA ablation group was detected, which did not reach statistical significance (OR 1.53 95% CI 0.88 to 2.69; p=0.13) (Figure 4).

**Procedural Data**

Data regarding total procedure duration and fluoroscopy time were reported in 824, 25, 27, 28, 30, 32, 33, 35 and 1024-28, 30, 31, 33-35 studies respectively. Overall, the total procedure duration was significantly longer in the waca group than in the segmental PVI group (Mean Difference 17.22 minutes, 95% CI 11.09 to 23.34, p<0.00001), while the total fluoroscopy time was significantly reduced (Mean Difference -9.25 minutes, 95% CI -10.50 to -8.01). A substantial heterogeneity was found for both outcomes (I² 78% and 98% respectively). Radiofrequency application time was reported in 924-28, 30, 31, 34, 35 studies. The WACA group had longer times (Mean Difference 11.87 minutes, 95% CI 10.45 to 13.30 minutes).
Complications

Ten studies reported data on procedure complications, assessed in 1240 participants\textsuperscript{24-29, 31-35}. Major complications, including deaths, pulmonary vein stenosis, embolic events, and/or pericardial tamponade, occurred in 22 of 491 patients in the ostial PVI group (4.4%) and in 17 of 538 (3.1 %) in the wide antral PVI group. The difference between the two groups was not statistically significant (Peto OR 0.72 [0.37, 1.38] p=0.32 , I\textsuperscript{2}= 11\%) (Figure 5). None of the included studies reported PV stenosis requiring intervention or medical therapy in any of the groups.

Discussion

Our primary finding is that PVI performed with a wide antral approach is more effective than ostial PVI in achieving freedom from total atrial tachyarrhythmia recurrence at long term follow-up, which is driven by a striking reduction of AF recurrences. The efficacy of a more extensive ablation approach is also evident when the outcome is assessed after the first ablation.

Few studies have assessed occurrence of left atrial tachycardia as a separate outcome, not revealing any significant difference in patients undergoing wide antral ablation versus segmental PVI. However, these results are based on the analysis of few events reported in only a subgroup of the included studies, and cannot be viewed as definite.

Analysis of procedural data shows a reduced fluoroscopy time with the WACA approach, but with a longer total procedural time. With regards to the incidence of major complications, no difference was detected among the two ablation strategies.

In nine studies\textsuperscript{24-28, 30, 31, 33, 35}, PVI was obtained by ipsilateral pulmonary vein encirclement, while three studies\textsuperscript{29, 32, 34} performed antral ablation about 1.5 cm more proximally than ostial ablation guided by electroanatomical mapping.
Wide antral versus ostial PVI

Current AF catheter ablation techniques have evolved after the description of rapidly firing activity of myocardial sleeves located inside or close to the PV, responsible for initiating and maintaining AF\(^1\). Trans-catheter PV ostial isolation shortly became a landmark therapy for AF\(^2\)-\(^4\). Marrouche et al firstly described PVI with antral ablation\(^5\). The rationale underlying this technique, namely, wide antral PV isolation, was to target a larger area with pro-arrhythmogenic potential while minimizing the risk of complications such as PV stenosis. Later Ouyang et al\(^1\) described achievement of PVI through large ispilateral pulmonary veins encirclement guided by a 3D mapping system and lasso technique.

Our study is the first one to compare the two techniques through a systematic analysis of all the available literature, and shows that wide antral PV isolation is superior to ostial isolation.

Studies carried out in animal heart have shown that microreentry localized at the PV-LA junction plays a critical role in maintaining AF\(^36\)-\(^38\). Changing of myocardial fiber orientation and ionic differences in the channel distribution around pulmonary veins, are responsible respectively for non-uniform anisotropy and shorter action potential duration which favor reentry and may help to explain the preferential anchoring of venous waves at PV-LA junction that are capable of maintaining the atrial fibrillation\(^38\)-\(^40\). Previously Jaïs et al. demonstrated in humans decremental conduction properties of pulmonary veins\(^41\). More recently Kumagai et al, using a 64-pole basket catheter showed exit and entry of the activation front at the PV-LA junction, supporting further evidence for a re-entrant mechanism of atrial fibrillation\(^42\). Atienza et al showed an acceleration of activation frequency at PV-LA junction after adenosine infusion, pointing toward re-entry as the mechanism for AF maintenance\(^43\).

Wide antral PV isolation, through the inclusion of a larger area of PV-LA junction, has
the potential to remove the heterogeneous electrophysiological milieu capable of sustaining re-entry in humans.

Conflicting evidence about automaticity of animal isolated PV myocytes exists, and most studies on PV preparations indicate that the PVs are not spontaneously active under normal conditions but spontaneous and triggered activity can be induced by sympathomimetic activity. Thus the critical role of PV in AF seems to be more attributable to the heterogeneous electrical properties of the PV-LA junction than to the trigger activity of cells within the PVs. Moreover, antrum ablation may include structures as the posterior wall of left atrium, which seems to play a critical role in AF maintenance.

Several findings support this hypothesis: i) the same embryologic origin of PVs and posterior wall, ii) AF termination during ablation prior to complete electrical isolation of the vein, iii) interruption of AF after ablation of short cycle length activity in the posterior left atrium.

In addition, pilot studies have documented successful ablation of ganglionic plexi by PV antrum isolation, which are located at the border of the PVs. Verma et al. documented successful ablation of ganglionic plexi using extended PV antrum isolation.

Therefore several factors may explain the potential advantage of wide antral PVI: i) elimination of re-entry wavelets localized around the PV antrum, ii) autonomic denervation iii) pulmonary vein isolation; iv) extensive debulking of left atrium and v) ablation of non-PV foci localized in the posterior left atrium wall.

A study performed by Tamborero et al which assessed the benefit of a box lesion in the LA posterior wall in patients undergoing trans-catheter radiofrequency AF ablation, did not detect a better outcome of WACA PVI plus posterior box versus WACA PVI alone. These
results suggest that antral ablation already targets the critical points of the LA posterior wall capable of triggering and sustaining arrhythmias and thus no further lesion lines are required. However permanent isolation of the posterior wall was not proven in the study by Tamboero et al. Infact, all patients undergoing repeat procedures showed absence of posterior wall isolation and gaps along the box lesions.

**Limitations**

Systematic reviews and meta-analyses of atrial fibrillation ablation outcomes face a number of challenges. The reasons for this are the overall heterogeneity of extended follow-up time and the methods of assessment of arrhythmia recurrence. Accordingly, a great limitation of our work is the varying follow-up duration of the studies included in the meta-analysis. Since OR is a function of the cumulative incidence over time, the different duration of follow-up can influence the results of our analysis. However most of the trials had a follow-up duration of 12±3 months and all the trials extended the follow-up period for at least longer than the blanking period of 3 months, which for the issue of AF ablation, is particularly relevant. Additionally, a sub-analysis carried out on eight studies that had an average of 1-year follow-up, confirmed that our quantitative results appeared statistically robust and consistent. There were significant heterogeneities between the studies. Most of the studies included in the analysis considered patients with paroxysmal and persistent atrial fibrillation. A sub-analysis was performed for patients with paroxysmal AF, but not persistent AF since only two trials included persistent AF and provided this data separately. Finally, most of the trials included an additional lesion line over PVI during their ablation strategy. However, regarding the main outcome (total atrial tachyarrhythmia recurrence) a sub-analysis including only studies performing PVI only confirmed the superiority of WACA over the segmental approach.
Conclusions

The results of this meta-analysis show that wide antral PVI is superior to ostial PVI for the long-term maintenance of sinus rhythm in patients undergoing catheter ablation of AF. The main advantage of wide antral ablation includes a significant reduction in overall atrial arrhythmia recurrence. According to our analysis, the incidence of left atrial tachycardia is not significantly greater when a wide antral ablation strategy.

Conflict of Interest Disclosures: None.

References:


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Ross DL, Thomas SP. Single-ring posterior left atrial (box) isolation results in a different mode of recurrence compared with wide antral pulmonary vein isolation on long-term follow-up: Longer atrial fibrillation-free survival time but similar survival time free of any atrial arrhythmia. Circ Arrhythm Electrophysiol. 2012;5:968-977.


31. Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:243-248.


Figure Legends:

Figure 1. Antral vs osital: Total supraventricular arrhythmias recurrence.

Figure 2. Antral versus ostial; outcome: atrial tachyarrhythmias recurrence after first procedure.

Figure 3. Antral versus Ostial; outcome: recurrence AF only.

Figure 4. Antral versus Ostial; outcome: left atrial tachycardia recurrence.

Figure 5. Antral versus Ostial; outcome: complications.
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Total events: 118
Heterogeneity: $\chi^2 = 9.54$, df = 12 (P = 0.66); $I^2 = 0$
Test for overall effect: $Z = 6.03$ (P < 0.00001)

Yamane T et al are reported separately for paroxysmal atrial fibrillation* and persistent atrial fibrillation**
Yamane T et al are reported separately for paroxysmal atrial fibrillation* and persistent atrial fibrillation**
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Total events 81 160

Heterogeneity: Chi² = 4.66, df = 8 (P = 0.79); I² = 0%
Test for overall effect: Z = 6.64 (P < 0.00001)

Yamane T et al  are reported separately for paroxysmal atrial fibrillation* and persistent atrial fibrillation**
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Total events 34 22

Heterogeneity: Chi² = 8.69, df = 6 (P = 0.19); I² = 31%

Test for overall effect: Z = 1.50 (P = 0.13)
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<td>Yamane T</td>
<td>0</td>
<td>117</td>
<td>3</td>
<td>70</td>
<td>7.7%</td>
<td>0.07 [0.01, 0.70]</td>
</tr>
</tbody>
</table>

Total (95% CI)      | 538                    | 491   | 100.0%            | 0.72  | [0.37, 1.38] |

Total events       | 17                     | 22    |

Heterogeneity: Chi² = 6.73, df = 6 (P = 0.35); I² = 11%
Test for overall effect: Z = 1.00 (P = 0.32)
Supplemental Material

Supplemental Figure 1. Literature flow

Records identified through database searching (n = 347)

Records after non pertinent papers and duplicates removed (n = 81)

Full-text articles assessed for eligibility (n = 29)

Full-text articles excluded (n = 17)
- 9 no control group
- 3 different outcomes
- 2 did not assess electrical isolation
- 2 considered different ablation strategy
- 1 utilized different catheter technologies

Studies included in quantitative synthesis (meta-analysis) (n = 12)
- 12 Intervention prospective trials
### Supplemental Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of Patients</th>
<th>Mean age (years)</th>
<th>Male</th>
<th>Paroxysmal AF %</th>
<th>Additional Line</th>
<th>Repeated procedure</th>
<th>Follow-up length (month)</th>
<th>Mode of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arentz T</td>
<td>2007</td>
<td>Germany</td>
<td>Prospective Intervention Trial</td>
<td>110</td>
<td>55±10</td>
<td>83</td>
<td>60%</td>
<td>None</td>
<td>19</td>
<td>15</td>
<td>Clinical Visit and Holter monitoring</td>
</tr>
<tr>
<td>Fiala M</td>
<td>2008</td>
<td>Czech Republic</td>
<td>Prospective Intervention Trial</td>
<td>110</td>
<td>52±10</td>
<td>86</td>
<td>100%</td>
<td>None</td>
<td>37</td>
<td>48</td>
<td>Clinical Visit and Holter monitoring</td>
</tr>
<tr>
<td>Hwang HJ</td>
<td>2008</td>
<td>South Korea</td>
<td>Prospective Intervention Trial</td>
<td>81</td>
<td>51±11</td>
<td>70</td>
<td>83%</td>
<td>TI</td>
<td>None</td>
<td>9</td>
<td>Clinical Visit and Holter monitoring</td>
</tr>
<tr>
<td>Lo LW</td>
<td>2007</td>
<td>Taiwan</td>
<td>Prospective Intervention trial</td>
<td>73</td>
<td>53±11</td>
<td>59</td>
<td>79%</td>
<td>Roof, TI, MI</td>
<td>73</td>
<td>15</td>
<td>Clinical Visit and Holter monitoring</td>
</tr>
<tr>
<td>Liu X</td>
<td>2006</td>
<td>China</td>
<td>Prospective Intervention Trial</td>
<td>110</td>
<td>58±9</td>
<td>72</td>
<td>100%</td>
<td>Roof, TI, MI</td>
<td>12</td>
<td>9</td>
<td>Clinical Visit and Holter monitoring</td>
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<tr>
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<td>US</td>
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<td>68</td>
<td>85%</td>
<td>MI</td>
<td>10</td>
<td>21</td>
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</tr>
<tr>
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<td>Denmark</td>
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<td>71</td>
<td>51%</td>
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<td>74</td>
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<td>Clinical Visit and Holter monitoring</td>
</tr>
<tr>
<td>Oral H</td>
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<td>Prospective Intervention Trial</td>
<td>80</td>
<td>53±10</td>
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<td>6</td>
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<td>48</td>
<td>100%</td>
<td>Roof, MI, TI</td>
<td>29</td>
<td>24</td>
<td>Clinical Visit and Holter monitoring</td>
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<tr>
<td>Tan HB</td>
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<td>54</td>
<td>71%</td>
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<td>4</td>
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<tr>
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<td>Japan</td>
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<td>101</td>
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<td>100%</td>
<td>None</td>
<td>None</td>
<td>12</td>
<td>Clinical Visit</td>
</tr>
<tr>
<td>Yamane T</td>
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<td>Japan</td>
<td>Prospective Intervention Trial</td>
<td>187</td>
<td>53±10</td>
<td>144</td>
<td>65%</td>
<td>None</td>
<td>70</td>
<td>12</td>
<td>Clinical Visit</td>
</tr>
</tbody>
</table>

Legend: TI=tricuspidal istmus, MI=mitral istmus
Supplemental Figure 2. Risk of bias table

Legend: Red (-)=high risk of bias; Green (+)= low risk of bias