

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Conduction recovery following catheter ablation in patients with recurrent atrial fibrillation and heart failure

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1627652> since 2019-06-01T16:50:27Z

Published version:

DOI:10.1016/j.ijcard.2017.02.067

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in INTERNATIONAL JOURNAL OF CARDIOLOGY, 240:240-245., 2017, 10.1016/j.ijcard.2017.02.067.

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

- (1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.
- (2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.
- (3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>), 10.1016/j.ijcard.2017.02.067

The publisher's version is available at:

<http://linkinghub.elsevier.com/retrieve/pii/S0167527316333381>

When citing, please refer to the published version.

Link to this full text:

<http://hdl.handle.net/2318/1627652>

1 **Conduction recovery following catheter ablation in patients with recurrent atrial fibrillation**
2 **and heart failure**

3

4 Matteo Anselmino, MD PhD*, Mario Matta, MD*, T. Jared Bunch, MD PhD, Martin Fiala, MD
5 PhD, Marco Scaglione, MD, Georg Nölker, MD, Pierre Qian, MD**, Thomas Neumann,
6 MD, Federico Ferraris, MD*, Fiorenzo Gaita, MD Prof*.

7 *Cardiology Division, Department of Medical Sciences, University of Turin, Turin, Italy.

8 Intermountain Heart Institute, Intermountain Medical Center, Murray, UT, USA.

9 § Department of Cardiology, Heart Centre, Hospital Podlesí, Tinec, Czech Republic.

10 ¶ Division of Cardiology, Cardinal Massaia Hospital, Asti, Italy.

11 ¶ Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University
12 Bochum, Bad Oeynhausen, Germany.

13 **Department of Cardiology, Westmead Hospital, University of Sydney, Australia

14 ¶¶ Department of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany.

15

16 **Word count:** 3,152 words, 4 Tables, 3 Figures, 29 references

17 **Key words:** atrial fibrillation, transcatheter ablation, heart failure, pulmonary veins, linear lesions

18 **Running title:** PVs and lines reconnection in HF patients

19

20 **Corresponding Author:**

21 Fiorenzo Gaita, MD Professor

22 Cardiology Division, Department of Medical Sciences,

23 Città della Salute e della Scienza University of Turin

24 Corso Bramante 88, 10126 Turin, Italy

25 Phone: +39-0116335570 Fax: +39-0116966015

26 Email: fiorenzo.gaita@unito.it

1 **Abstract**

2 **Background.** Atrial fibrillation (AF) catheter ablation is increasingly proposed for patients
3 suffering from AF and concomitant heart failure (HF). However, the optimal ablation strategy
4 remains controversial. We performed this study to assess the prevalence of pulmonary vein (PV) or
5 linear lesion reconnection in HF patients undergoing repeated procedures.

6 **Methods and Results.** At seven high-volume centres, 165 patients with HF underwent a repeat
7 procedure after a first AF ablation including PV isolation alone (47 patients, group A) or PV
8 isolation plus left atrial lines (118 patients, group B). Group A patients presented more often
9 paroxysmal AF ($p<0.001$), less enlarged left atrium ($p<0.001$) and less left ventricular systolic
10 dysfunction ($p=0.031$) compared to Group B, that more commonly had atypical atrial flutter
11 ($p<0.001$). Forty-one (87%) patients in Group A and 69 (58%) in Group B presented at least one
12 reconnected PV ($p<0.001$). Sixty-one (52%) patients in Group B presented at least one reconnected
13 atrial line (left isthmus or roof). Patients without any reconnected PV ($n=54$, 33%) more frequently
14 experienced persistent AF ($p<0.001$), had longer AF duration ($p=0.047$) and larger left atrial
15 volume ($p<0.001$). Twenty-five patients (15%) with no PV and/or line reconnection did not
16 significantly differ, concerning baseline characteristics, compared to those with at least one
17 reconnected ablation site.

18 **Conclusion.** As in the general AF population undergoing catheter ablation, PV reconnection is
19 frequent in patients with HF and symptomatic recurrence. However, one third of patients presented
20 arrhythmic recurrences even in the absence of PV reconnection, highlighting the importance of the
21 underlying atrial substrate.

22

23 Abstract word count: 250

1. Introduction

Atrial fibrillation (AF) catheter ablation is a proven safe and effective therapeutic option for patients suffering from AF and concomitant heart failure (HF) [1-2]. Recent randomized trials [3-5] and a large meta-analysis [6] consistently reported an improvement in systolic HF symptoms and left ventricular ejection function (LVEF) after AF ablation. However, freedom from AF after a single procedure is limited, and when long-term outcomes of 5 years or greater are examined, recurrences occur in the majority of patients [7]. As a consequence, many patients with systolic HF (about one third) require at least two procedures to effectively maintain long-term sinus rhythm (SR) [7].

The optimal first line non pharmacological strategy to address AF in these patients remains controversial: previous studies supported, due to the complexity of the atrial substrate, left atrial linear ablation on top of pulmonary vein isolation (PVI) [8-10]. However, recent studies of AF ablation in general and surgical populations have failed to support the additive benefit of ablation beyond PVI [11-12]. In fact, aiming to investigate the singular role of PVI in AF ablation, a recent study reported, among a general population of patients undergoing repeated procedures for AF recurrence, a high prevalence of PV conduction recovery following the index PVI [13]. In this study, PV re-isolation alone was effective in subsequent SR maintenance, indirectly suggesting a durable role of PV triggers.

AF ablation patients that have concurrent systolic HF may have arrhythmia driven not only by PV triggers, but pathological atrial substrate; the latter reflecting chronic exposure of the atrium to the underlying diastolic and systolic dysfunction [14-15]. Nonetheless, there are no data available concerning sites of recovery or reconnection following a first transcatheter ablation procedure. We therefore conducted the present study aiming to determine the incidence of PV reconnection or failure of other linear lesions in a population of patients with HF undergoing repeated procedures for recurrent atrial arrhythmia following a first, failed, AF ablation procedure.

2. Methods

The present multicentre study involved seven high-volume electrophysiological laboratories routinely performing AF transcatheter ablation in patients with a LVEF lower than 50%. All included patients had a history of drug-refractory, symptomatic, paroxysmal or persistent AF and a concomitant structural cardiomyopathy characterized by a LVEF < 50%, received a prior AF ablation procedure at the same Center (including PV isolation and when appropriate additional left or right atrial lesions), and were referred for at least one additional AF catheter ablation procedure, due to the occurrence of documented AF, atypical atrial flutter or atrial tachycardia symptomatic recurrences. Arrhythmic recurrences were defined as any episode of AF, atypical atrial flutter or atrial tachycardia lasting at least 2 minutes and documented through 12-leads ECG, Holter monitoring or implantable loop recorder. Referral for redo ablation was considered in patients experiencing arrhythmia-related symptoms, left ventricular function and/or functional class impairment related to the arrhythmic recurrences. Patients in whom procedural details concerning the index or the repeated procedure (e.g. PVI, linear lines, etc.) were not complete or validated were excluded. All patients provided written informed consent to the catheter ablation procedures.

2.1. Recovery or reconnection assessment

The number and sites of PV conduction recovery were recorded. Additionally, in case left atrial (LA) linear lesions (roof line, mitral isthmus line, posterior line) had been performed at the first procedure, the persistence of block lines tested by pacing manoeuvres, activation and voltage mapping were registered.

The repeated procedures were then performed, according to each Center's preference or protocols, using 4-mm tip irrigated radiofrequency catheters or cryoballoon. Based on single patients'

1 characteristics and atrial substrate, additional lesions such as PV isolation, LA linear lines, or
2 complex fractionated atrial electrograms (CFAE) were performed [16].

3

4 **2.2. Statistical analysis**

5 Continuous variables were reported as mean (standard deviation, SD) or median (range), and
6 categorical variables as number (%). Continuous data were compared by one-way ANOVA test
7 after normal distribution was confirmed, and, in a selection of cases, additionally analyzed as
8 tertiles. Categorical variables were compared in cross-tabulation tables by Pearson's chi-square test.
9 Due to the potential bias resulting from the inclusion of atypical flutter/tachycardia recurrences, that
10 may rely on different pathophysiological mechanisms than those driving AF, data was also analysed
11 considering only AF recurrences. Aiming to test the independent correlation of the recorded
12 parameters, variables reporting a significant correlation at univariate analysis (p value <0.05) were
13 included in a multiple logistic regression analyses. The best subset models were run applying odds
14 ratio (OR) likelihood scores. All tests of significance were two-tailed, and a p value <0.05 was
15 considered statistical significant. All analyses were performed using SPSS 21.0.

16

17

18

19

20

21

22

3. Results

At seven high-volume centres, out of 719 patients, over a mean period of 3 years (2012-2015), the 165 AF patients with concomitant HF undergoing a repeated transcatheter AF ablation were included (age 55 ± 17 years; 83% males). Baseline characteristics are listed in Table 1. Sixty-four (39%) patients suffered from paroxysmal AF, with a mean AF history duration of 74 ± 84 months. Echocardiographic parameters included a mean LA volume of 121 ± 68 ml, and a mean LVEF $41\pm 8\%$. At the time of the index procedure, 47 (28%, Group A) patients underwent PVI alone, while 118 (72%, Group B) underwent additional LA linear lesions or CFAE ablation; in particular, in 104 patients a roof line and mitral isthmus line were performed, and 44 underwent CFAE ablation. Patients in Group A presented higher prevalence of paroxysmal AF ($p<0.001$), less severely enlarged LA volume ($p<0.001$), less LVEF dysfunction ($p=0.031$), shorter time to AF recurrence ($p<0.001$), and a higher prevalence of prior antiarrhythmic Ic class drugs treatment ($p=0.019$). In comparison, patients in Group B reported a higher prevalence of atypical atrial flutter recurrences, compared to Group A ($p<0.001$).

Details concerning the second procedures are reported in Table 1. Briefly, 61 (37%) patients underwent repeated PVI alone, 61 (37%) underwent PVI and additional LA lesions while 43 (26%) underwent linear lesions or CFAE ablation; complication rate was 3.0%, without difference between Groups A and B ($p=0.391$). Forty-one (87%) patients in Group A and 69 (58%) in Group B presented at least one reconnected PV ($p<0.001$); no significant differences were detected among the prevalence of each of the four PVs recurrence rate (Figure 1 and 2). Among patients in Group B, 61 (52%) and 55 (47%) presented, respectively, left isthmus and roof line reconnection across the line, and these patients underwent repeated linear ablation to achieve conduction block.

Among the two groups, 54 (33%) patients presented without evidence of reconnected PVs (Table 2); these patients were more often affected by persistent AF ($p<0.001$), had a longer AF duration ($p=0.047$), presented with more severely enlarged LA volumes ($p<0.001$), more often were treated

1 with extensive LA ablation at the initial procedure ($p < 0.001$) including lines and CFAE, and were
2 more commonly affected by atypical flutter ($p < 0.001$). The complication rates did not differ
3 between the two groups ($p = 0.688$).

4 Aiming to limit potential bias deriving from the inclusion of atypical flutter/tachycardia
5 recurrences, that may rely on different pathophysiological mechanisms than those driving AF, an
6 additional analysis was run stratifying by AF ($n = 100$) or organized tachycardia ($n = 65$) relapses. The
7 presence of persistent vs. paroxysmal AF ($p < 0.001$), of a larger LA volume ($p = 0.001$), a lower
8 LVEF ($p = 0.027$), an ablation scheme including linear lesions ($p = 0.001$) and CFAE ablation
9 ($p = 0.002$) related to arrhythmic recurrence despite the absence of documented PVs reconnection,
10 also when considering AF recurrences only (Table 3 and Figure 3).

11 At multiple logistic regression analyses, performed to assess the independent significance of each of
12 the above mentioned parameters in relation to AF recurrences despite absence of PV reconnection,
13 LA volume emerged as the only independently related parameter, as the III tertile of LA volume,
14 above 120 ml, presented an OR of 5.09 (95% CI 1.19-26.19; $p = 0.048$) (Table 4). On the other side,
15 conduction recovery over atrial ablation lines was slightly more common within patients relapsing
16 with an atrial tachycardia/atypical flutter: more in details, while the incidence of roof line
17 reconnection did not differ (31 vs. 23%, $p = 0.267$), the left isthmus line, recovered in 17% vs. 64%
18 ($p = 0.013$), in patients suffering AF or organized arrhythmias, respectively.

19 Of note, 25 (15%) patients presented no PV and/or atrial line recovery at the time of the repeated
20 procedure, despite the documented arrhythmia recurrences. Baseline characteristics of these patients
21 were not significantly different, except for a trend towards longer AF duration ($p = 0.078$) and lower
22 LVEF ($p = 0.082$) compared to the remaining population; patients without any reconnection site
23 more frequently underwent CFAE ablation at the initial procedure ($p = 0.044$) and presented with
24 atypical flutter ($p = 0.003$) compared to AF in the alternative group (Supplemental Table A).

1 Fifty (30%) of the 165 patients enrolled underwent a third procedure (Supplemental Table B and C).
2 Among them, 18 (37%) experienced AF, while the majority, 32 (63%), suffered atypical atrial
3 flutter ($p=0.028$). Fifteen of them had previously been approached by PVI alone, while 35 by
4 extensive LA ablation. In the first group, 6 (40%) patients reported no reconnected PVs, while this
5 percentage was higher (24, 70%) in the second; furthermore, in the latter the prevalence of left
6 isthmus and roof line conduction recovery was 67% and 54%, respectively (supplemental Figure A
7 and B).

8

9

10

11

12

13

14

15

16

17

18

19

20

21

1 **4. Discussion**

2 The present work is the first multicentre study aiming to assess the durability of PVI and atrial
3 linear ablation in a population of patients with systolic HF. In light of the latest European guidelines
4 [2] recommending AF ablation in patients with HF (class IIa) to improve functional class and LVEF
5 by breaking the vicious circle between AF and HF, knowledge on conduction recovery patterns is of
6 extreme clinical relevance. Despite the heterogeneity of the population and of the ablation tools and
7 protocols, given that the optimal approach for AF ablation in these patients is controversial, and the
8 lack of clear published data on this population, the present findings are, in our opinion, significant
9 and thought-provoking. In this population, and consistent with other studied populations, the rate of
10 conduction recovery of at least one PV was high in patients that present for a repeated ablation:
11 globally more than half of the previously isolated PVs were found to be reconnected at redo
12 procedure. However, one third of patients undergoing repeated procedures for atrial arrhythmic
13 recurrence had absence of PV reconnection, suggesting the importance of non-PV mechanisms in
14 the AF pathogenesis, in particular within patients with a larger LA volume, lower LVEF that
15 suffered persistent, long-history AF. These parameters, on top of all LA volume, should therefore
16 candidate to identify patients at higher risk of AF recurrences, despite the persistence of PV
17 isolation. In patients with HF, therefore, the PV's role in AF genesis and maintenance seems less
18 pivotal, highlighting the need to further treat external PV antral and the underlying atrial substrate.

20 ***4.1. Reconnection sites and arrhythmic recurrences***

21 Concerning the first procedural approach, less than one third of patients underwent PVI alone, while
22 the majority underwent a more extensive LA ablation. Baseline characteristics of the two groups
23 were different: patients with persistent AF, longer AF history, lower LVEF and larger LA volume
24 underwent more frequently an extensive LA ablation. This is in accordance with previous studies

1 suggesting, in these conditions, a more aggressive substrate modification strategy may be required
2 in addition to PVI to provide long-term arrhythmia free benefit [9,17-18].

3 Index procedure approach predicted arrhythmia outcomes in this cohort of systolic HF patients. In
4 those with PVI alone, AF recurrence alone was more common. In contrast, in patients that had
5 extensive substrate modification recurrent atypical flutter rates were higher. Of note, almost half of
6 the latter patients had recovered conduction along one or more of the previously performed lines,
7 confirming the challenge of achieving a durable line of block [19] and the consequent
8 proarrhythmic role of incomplete lesions [11].

9 One third of all patients presented with no PV conduction recovery, suggesting, in patients with AF
10 and concomitant HF, a relevant role for non-PV mechanisms that trigger and sustain arrhythmic
11 recurrences, not only in case of organized atrial arrhythmias but also of AF recurrences. This
12 prevalence is higher compared to a prior report that examined post-ablation recurrence rates in the
13 general population [13], likely due to the more complex atrial substrate in patients with reduced
14 LVEF. Persistent AF, larger LA volume and more depressed LVEF reflect more advanced atrial
15 disease, in which AF can occur even in the absence or independently of PV triggers.

16 The latter hypothesis is also supported by the larger prevalence of PV reconnection among the PVI
17 alone group compared to PVI + lines group. The PVI alone group likely represents patients
18 with less extensive atrial disease, in whom PV triggers still play a major role. The PVI + lines
19 group includes, instead, patients with more advanced atrial disease, in whom PV triggers are less
20 pivotal compared to the role exerted from reconnection of previous ablation lines or progression of
21 the underlying atrial (extra-PV) disease. In fact, previous literature has already reported high PV
22 reconnection rates even in patients free from arrhythmic recurrences [20].

23 Given the lack of clinical trials clearly testing the active role of PV reconnection in AF recurrences,
24 and/or data deriving from positive controls, especially in the setting of patients with underlying
25 structural disease and reduced LVEF, current practice should be based on the only available

1 observations. Based on the present findings, a severely dilated LA volume is, in our opinion, the
2 strongest predictor of arrhythmia recurrences despite persistent PV isolation, suggesting that
3 patients with severe LA enlargement (i.e. above 120-150 ml) should be treated by an alternative
4 ablation approach at their index ablation procedure. Although among the general population,
5 indirect support to this thesis derives from the recent GAP-AF trial [21]. This study demonstrated
6 that complete is superior to incomplete circumferential PV isolation concerning 3-months AF
7 ablation efficacy; however, this was not due to higher rates of persistent PV isolation. This finding
8 surely suggests that more ablation is more effective than less ablation, but also highlights that the
9 mechanisms of AF recurrences are not strictly linked to PV reconnection and that there, indeed, is a
10 potential relevant role of non-PV mechanisms in AF recurrences also in the general population.

11 Additionally, a recent report suggested that the altered substrate in HF patients may provide a role
12 for non-PV mechanisms even in patients with paroxysmal AF [22]. This finding is consistent with
13 the lower incidence of reconnected PVs among patients treated with PVI + lines compared to those
14 treated with PVI alone: the first group, characterized by more advanced disease, most likely
15 presents a higher burden of atrial fibrosis, that limits the role of PV triggers in supporting
16 arrhythmic recurrences, and may, even more, result in a sort of fibrosis-induced "ablation" of the
17 PVs trigger due to the progressive reduction of muscular sleeves.

18 In further support of non-PV mechanisms in systolic HF patients, those who underwent a third
19 ablation procedure, PV reconnection rates were even lower (44%) compared to that reported in the
20 general population [13]. This subgroup was selected by failure of two prior ablations that targeted
21 the PVs, and is likely a population with a more advanced atrial disease [23], in which PV ectopies
22 are not pivotal, while the atrial substrate plays a dominant role in causing AF recurrence. However,
23 44% of patients still experienced PV reconnection, which also highlights the challenges of obtaining
24 durable PVI even with repeated attempts.

25

1 **4.2. *Absence of reconnection sites and arrhythmic recurrences***

2 About 15% of the patients referred for repeated procedures suffered arrhythmic recurrences without
3 any reconnected PV and/or line. Unfortunately, none of the baseline characteristics permitted
4 differentiation between these “non-responder” patients and the others, though there was a trend
5 towards longer AF duration and lower LVEF. During the repeated procedure, these patients and
6 those with passive residual PV reconnections were, in case of recurrent AF, frequently approached
7 with additional CFAE ablation, felt to be involved in areas of micro-reentry and focal triggers
8 resulting in atrial arrhythmia relapses [24-25]. Following AF conversion into atypical flutter or in
9 case of primary recurrent atrial tachycardia, these extra-PV mechanisms or localized sources could
10 be directly identified to underlie the recurrent arrhythmia mechanism and ablated with more
11 selective approach. Indeed, this subgroup of patients (arrhythmia relapses despite isolated PVs and
12 validated atrial linear blocks) may receive the greatest benefit from an atrial substrate modification
13 approach, failed among unselected general populations [26-29].

14 Indeed, in our opinion, by widening available knowledge, the present findings further support the
15 usefulness of an extensive substrate modification for patients with advanced atrial disease, a
16 frequent feature among patients with HF and severely reduced LVEF.

5. Limitations

First, the retrospective non-randomized design does not permit to perform a standardized evaluation of the parameters analysed. Second, the inclusion of patients from different centres, along with different procedural tools and protocols, although being representative of the real-life picture of current clinical practice, may increase heterogeneity among the population studied. Third, the high prevalence of atypical flutter/tachycardia recurrences suggest that many patients suffered arrhythmic recurrences mainly due to the difficulties in achieving durable conduction block across ablation lines. However, even after considering AF recurrences alone, severe LA enlargement emerged as an independent predictor of AF recurrences despite durable PV isolation, identifying therefore a subgroup of HF patients that warrants extensive substrate modification for rhythm control already at index procedure. Indeed, the active role of PVs in arrhythmic recurrences cannot be confirmed, as the recording of focal activity from PV was not reported. Furthermore, studies that examine the role of durable PVI isolation on arrhythmia recurrence remain significantly limited by the finding that durable PVI is often not achieved. As such, until PVI are completely eliminated through durable electrical isolation, their role in arrhythmia genesis and maintenance cannot be excluded. Last, the relatively limited sample of patients included in the study may limit the statistical relevance.

1 **6. Conclusion**

2 Based on the present findings, atrial substrate in HF patients appears more important than in the
3 general AF population, and substrate modification may be required to reduce atrial arrhythmia
4 recurrences. Severe LA enlargement, severely reduced LVEF and persistent/long standing AF are
5 associated with reduced success of AF control with PVI alone.

6 In this scenario, an alternative LA ablation approach is most probably needed to achieve effective
7 rhythm control, especially among patients with severely enlarged LA. However, if additional
8 ablation is incomplete or allows substrate for re-entry, then such ablation may be proarrhythmic.

9 Nonetheless, the evidence of arrhythmic recurrences in absence of evident reconnection sites in this
10 study, strongly highlights, at least within patients with AF and HF, the importance of substrate
11 modification. In case future research will succeed in increasing knowledge concerning the role of
12 alternative non-PV mechanisms and the interpretation of atrial substrate (e.g. drivers and/or rotors),
13 this will surely improve the outcome of AF catheter ablation in patients at an advanced stage of the
14 disease, as those with HF who most probably require a distinct, targeted ablation approach.

15
16
17 **Conflicts of interest**

18 None.

19 **Fundings**

20 This research did not receive any specific grant from funding agencies in the public, commercial, or
21 not-for-profit sectors.

1 **Reference**

- 2 [1]. Lip GY, Heinkel FR, Gaita F et al. European Heart Rhythm Association/Heart Failure
3 Association joint consensus document on arrhythmias in heart failure, endorsed by the Heart
4 Rhythm Society and the Asia Pacific Heart Rhythm Society. *Eur J Heart Fail.* 2015;17(9):848-74.
5
- 6 [2]. Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial
7 fibrillation, developed in collaboration with EACTS. *Eur Heart J* 2016;37(38):2893-962.
8
- 9 [3]. Jones DG, Haldar SK, Hussain W et al. A randomized trial to assess catheter ablation versus
10 rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol*
11 2013;61:1894-903.
12
- 13 [4]. Khan MN, Jaïs P, Cummings J et al; PABA-CHF Investigators. Pulmonary-vein isolation for
14 atrial fibrillation in patients with heart failure. *N Engl J Med.* 2008; 359:1778-85.
15
- 16 [5]. Hunter RJ, Berriman TJ, Diab I et al. A randomized controlled trial of catheter ablation versus
17 medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm*
18 *Electrophysiol* 2014;7(1):31-8.
19
- 20 [6]. Anselmino M, Matta M, D'Ascenzo F et al. Catheter ablation of atrial fibrillation in patients
21 with left ventricular systolic dysfunction: a systematic review and meta-analysis. *Circ Arrhythm*
22 *Electrophysiol.* 2014;7(6):1011-8.
23
- 24 [7]. Bunch TJ, May HT, Bair TL et al. Five-year outcomes of catheter ablation in patients with
25 atrial fibrillation and left ventricular systolic dysfunction. *J Cardiovasc Electrophysiol.*
26 2015;26(4):363-70.

- 1
- 2 [8]. Gaita F, Riccardi R, Caponi D et al. Linear cryoablation of the left atrium versus pulmonary
3 vein cryoisolation in patients with permanent atrial fibrillation and valvular heart disease:
4 correlation of electroanatomic mapping and long-term clinical results. *Circulation*.
5 2005;111(2):136-42.
- 6
- 7 [9]. Gaita F, Caponi D, Scaglione M et al. Long-term clinical results of 2 different ablation
8 strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm*
9 *Electrophysiol*. 2008;1(4):269-75.
- 10
- 11 [10]. Di Donna P, Olivotto I, Delcrè SD et al. Efficacy of catheter ablation for atrial fibrillation in
12 hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. *Europace*.
13 2010;12(3):347-55.
- 14
- 15 [11]. Verma A, Jiang CY, Betts TR et al.; STAR AF II Investigators. Approaches to catheter
16 ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372(19):1812-22.
- 17
- 18 [12]. Gillinov AM, Gelijs AC, Parides MK et al.; CTSN Investigators. Surgical ablation of atrial
19 fibrillation during mitral-valve surgery. *N Engl J Med*. 2015;372(15):1399-409.
- 20
- 21 [13]. Lin D, Santangeli P, Zado ES et al. Electrophysiologic findings and long-term outcomes in
22 patients undergoing third or more catheter ablation procedures for atrial fibrillation. *J Cardiovasc*
23 *Electrophysiol*. 2015;26(4):371-7.
- 24
- 25 [14]. Anselmino M, Matta M, Gaita F. Catheter ablation of atrial fibrillation in patients with heart
26 failure: can we break the vicious circle? *Eur J Heart Fail*. 2015;17(10):1003-5.

- 1
- 2 [15]. Anselmino M, Matta M, Castagno D, Giustetto C, Gaita F. Catheter ablation of atrial
3 fibrillation in chronic heart failure: state of the art. *Europace* 2016;18(5):638-47.
- 4
- 5 [16]. Anselmino M, Grossi S, Scaglione M et al. Long-term results of transcatheter atrial fibrillation
6 ablation in patients with impaired left ventricular systolic function. *J Cardiovasc Electrophysiol.*
7 2013;24(1):24-32.
- 8
- 9 [17]. Raviele A, Natale A, Calkins H et al.; Venice Chart. Venice Chart international consensus
10 document on atrial fibrillation ablation: 2011 update. *J Cardiovasc Electrophysiol.* 2012;23(8):890-
11 923.
- 12
- 13 [18]. Knecht S, Hocini M, Wright M et al. Left atrial linear lesions are required for successful
14 treatment of persistent atrial fibrillation. *Eur Heart J.* 2008;29(19):2359-66.
- 15
- 16 [19]. Rostock T, O'Neill MD, Sanders P et al. Characterization of conduction recovery across left
17 atrial linear lesions in patients with paroxysmal and persistent atrial fibrillation. *J Cardiovasc*
18 *Electrophysiol.* 2006;17(10):1106-11.
- 19
- 20 [20]. Jiang RH, Po SS, Tung R et al. Incidence of pulmonary vein conduction recovery in patients
21 without clinical recurrence after ablation of paroxysmal atrial fibrillation: mechanistic implications.
22 *Heart Rhythm.* 2014;11(6):969-76.
- 23
- 24 [21]. Kuck KH, Hoffmann BA, Ernst S et al. Impact of Complete Versus Incomplete
25 Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial
26 Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence

1 Network 1 Trial. *Circ Arrhythm Electrophysiol.* 2016 Jan;9(1):e003337. doi:
2 10.1161/CIRCEP.115.003337.
3
4 [22]. Zhao Y, Di Biase L, Trivedi C et al. Importance of non-pulmonary vein triggers ablation to
5 achieve long-term freedom from paroxysmal atrial fibrillation in patients with low ejection fraction.
6 *Heart Rhythm.* 2016;13(1):141-9.
7
8 [23]. Jones DG, Haldar SK, Jarman JW et al. Impact of stepwise ablation on the biatrial substrate in
9 patients with persistent atrial fibrillation and heart failure. *Circ Arrhythm Electrophysiol.*
10 2013;6(4):761-8.
11
12 [24]. Nademanee K, Schwab MC, Kosar EM et al. Clinical outcomes of catheter substrate ablation
13 for high-risk patients with atrial fibrillation. *J Am Coll Cardiol.* 2008;51(8):843-9.
14
15 [25]. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of
16 Atrial Fibrillation by the Ablation of Localized Sources. CONFIRM (Conventional Ablation for
17 Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial. *J Am Coll Cardiol.*
18 2012;60(7):628-36.
19
20 [26]. Verma A, Mantovan R, Macle L et al. Substrate and Trigger Ablation for Reduction of Atrial
21 Fibrillation (STAR AF): a randomized, multicentre, international trial. *Eur Heart J.*
22 2010;31(11):1344-56.
23
24 [27]. Atienza F, Almendral J, Ormaetxe JM et al.; RADAR-AF Investigators. Comparison of
25 radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial

1 fibrillation: a noninferiority randomized multicenter RADAR-AF trial. J Am Coll Cardiol.
2 2014;64(23):2455-67.
3
4 [28]. Dixit S, Marchlinski FE, Lin D et al. Randomized ablation strategies for the treatment of
5 persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol. 2012;5(2):287-94.
6
7 [29]. Bertaglia E, Fassini , Anselmino M et al. Comparison of ThermoCool® SF Catheter versus
8 ThermoCool®Catheter in Achieving Persistent Electrical Isolation of Pulmonary Veins: a Pilot
9 Study. J Cardiovasc Electrophysiol 2013; 24(3):269-73.
10

1 **Table 1.** Baseline characteristics of the study population according to index procedure.

	Overall (n=165)	Group A: PVI alone (n=47)	Group B: PVI + lines (n=118)	p-value
Age, years (SD)	55 (17)	53 (22)	56 (15)	0.401
Male sex, n (%)	137 (83%)	38 (81%)	99 (84%)	0.137
Paroxysmal AF, n (%)	64 (39%)	33 (70%)	32 (27%)	<0.001
Persistent AF, n (%)	43 (26%)	9 (19%)	33 (28%)	
Long-standing persistent AF, n (%)	59 (36%)	5 (10%)	53 (45%)	
AF duration, months (SD)	74 (84)	69 (68)	76 (91)	0.679
Hypertension, n (%)	106 (64%)	33 (70%)	72 (61%)	0.343
Diabetes mellitus, n (%)	26 (16%)	8 (18%)	16 (14%)	0.730
Previous stroke/TIA, n (%)	18 (11%)	5 (11%)	13 (11%)	0.782
CAD, n (%)	20 (12%)	6 (13%)	14 (12%)	0.989
Hyperthyroidism, n (%)	12 (7%)	2 (4%)	11 (9%)	0.093
Amiodarone use, n (%)	56 (34%)	14 (30%)	41 (35%)	0.499
Ic class drug use, n (%)	35 (21%)	16 (34%)	20 (17%)	0.019
Beta-blockers, n (%)	104 (63%)	33 (70%)	72 (61%)	0.296

OAC, n (%)	145 (88%)	38 (81%)	106 (90%)	<0.001
LVEF, % (SD)	41 (8)	44 (7)	41 (8)	0.031
LA volume, ml (SD)	121 (68)	56 (28)	152 (57)	<0.001
PVI alone, n (%)	47 (28%)	47 (100%)	0	-
PVI + lines, n (%)	118 (72%)	0	118 (100%)	-
Left isthmus line, n (%)	104 (62%)	0	104 (88%)	-
Roof line, n (%)	104 (62%)	0	104 (88%)	-
Posterior line, n (%)	21 (13%)	0	21 (18%)	-
CFAE, n (%)	44 (26%)	0	44 (42%)	-
Right isthmus ablation, n (%)	97 (58)	9 (19%)	88 (76%)	<0.001
Complications, n (%)	3 (2%)	1 (2%)	2 (3%)	0.541
Time to recurrence, months (SD)	12 (14)	8 (14)	9 (8)	<0.001
Paroxysmal AF recurrence, n (%)	44 (27%)	30 (63%)	14 (12%)	<0.001
Persistent AF recurrence, n (%)	56 (34%)	14 (30%)	42 (36%)	
Atypical flutter recurrence, n (%)	65 (39%)	3 (7%)	62 (52%)	
Number of reconnected PVs, n (SD)	1.9 (1.6)	3.1 (1.2)	1.5 (1.5)	<0.001

Reconnected PVs				<0.001
- 0	54 (32)	4 (8)	49 (42)	
- 1	16 (9)	1 (2)	15 (13)	
- 2	30 (18)	6 (13)	19 (16)	
- 3	24 (14)	11 (23)	13 (11)	
-4	46 (27)	25 (54)	21 (18)	
<i>Repeated procedure characteristics</i>				
PVI alone, n (%)	61 (37%)	31 (65%)	43 (36%)	<0.001
PVI + lines, n (%)	61 (37%)	14 (30%)	27 (23%)	
Lines/CAFE alone, n (%)	43 (26%)	2 (5%)	48 (41%)	
Left isthmus line, n (%)	74 (44%)	7 (15%)	67 (56%)	<0.001
De novo left isthmus line, n (%)	7 (4%)	7 (15%)	-	-
Roof line, n (%)	70 (42%)	14 (30%)	56 (47%)	0.042
De novo roof line, n (%)	14 (8%)	14 (30%)	-	-
Posterior line, n (%)	23 (14%)	2 (4%)	21 (18%)	0.042
CFAE ablation, n (%)	33 (20%)	7 (15%)	26 (22%)	0.333
Right isthmus ablation, n (%)	42 (25%)	4 (9%)	38 (32%)	0.002
Complications, n (%)	5 (3.0%)	1 (2.1%)	4 (3.4%)	0.391

1

2 PVI: pulmonary vein isolation; AF: atrial fibrillation; TIA: transient ischaemic attack; CAD:
3 coronary artery disease; OAC: oral anticoagulant; LVEF: left ventricular ejection fraction; LA: left
4 atrium. CFAE: complex fractionated atrial electrograms.

5

6

7

1 **Table 2.** Baseline population and procedural characteristics stratified according to the presence or
 2 absence of at least one PV conduction recovery detected at repeated procedure

	PVs reconnection (n=111)	Absence of PVs reconnection (n=54)	p-value
Age, years (SD)	54.9 (18)	55.8 (16)	0.767
Male sex, n (%)	93 (84%)	44 (82%)	0.457
Paroxysmal AF, n (%)	55 (50%)	8 (15%)	<0.001
Persistent AF, n (%)	28 (25%)	15 (28%)	
Long-standing persistent AF, n (%)	28 (25%)	32 (59%)	
AF duration, months (SD)	62 (59)	95 (114)	0.047
Hypertension, n (%)	62 (56%)	37 (69%)	0.357
Diabetes mellitus, n (%)	16 (14%)	9 (17%)	0.960
Previous stroke/TIA, n (%)	12 (11%)	6 (11%)	0.686
CAD, n (%)	13 (12%)	7 (13%)	0.879
Amiodarone use, n (%)	38 (34%)	18 (33%)	0.968
Ic class drug use, n (%)	31 (28%)	4 (7%)	0.004
Beta-blockers, n (%)	69 (62%)	35 (65%)	0.837
OAC, n (%)	82 (74%)	52 (96%)	0.001
LVEF, % (SD)	42.8 (8)	39.8 (7)	0.052
LA volume, ml (SD)	95 (62)	159 (58)	<0.001
PVI alone, n (%)	41 (37%)	6 (11%)	<0.001
PVI + lines, n (%)	70 (63%)	48 (89%)	
Left isthmus line, n (%)	65 (59%)	39 (72%)	0.079

Roof line, n (%)	65 (59%)	40 (74%)	0.036
Posterior line, n (%)	14 (13%)	20 (37%)	0.003
CFAE ablation, n (%)	20 (18%)	32 (59%)	<0.001
Right isthmus ablation, n (%)	57 (51%)	41 (76%)	0.002
Complications, n (%)	2 (1.8%)	1 (1.8%)	0.688
Time to recurrence, months (SD)	13 (14)	10 (14)	0.218
Paroxysmal AF recurrence, n (%)	40 (36%)	4 (7%)	<0.001
Persistent AF recurrence, n (%)	40 (36%)	16 (30%)	
Atypical flutter recurrence, n (%)	31 (28%)	34 (63%)	

1

2 PVI: pulmonary vein isolation; AF: atrial fibrillation; TIA: transient ischaemic attack; CAD:
3 coronary artery disease; OAC: oral anticoagulant; LVEF: left ventricular ejection fraction; LA: left
4 atrium. CFAE: complex fractionated atrial electrograms.

5

6

7

8

1 **Table 3.** Characteristics of patients experiencing paroxysmal/persistent AF recurrences stratified
 2 according to the presence or absence of at least one PV conduction recovery detected at repeated
 3 procedure.

	Overall AF recurrences (n=100)	PVs reconnection (n=80)	Absence of PVs reconnection (n=20)	p-value
Paroxysmal AF, n (%)	52 (52)	51 (64%)	1 (5%)	<0.001
Persistent AF, n (%)	18 (18)	9 (11%)	9 (45%)	
Long-standing persistent AF, n (%)	30 (30)	20 (25%)	10 (50%)	
AF duration, months (SD)	79 (85)	72 (63)	103 (134)	0.228
LVEF, % (SD)	43.0 (8)	43.6 (8.1)	41.0 (6.4)	0.049
LA volume, ml (SD)	93 (66)	75 (57)	146 (65)	0.001
PVI alone, n (%)	49 (49)	47 (59%)	2 (10%)	0.001
PVI + lines, n (%)	51 (51)	33 (41%)	18 (90%)	
Right isthmus ablation, n (%)	38 (38)	26 (32%)	12 (60%)	0.065
Complications, n (%)	1 (1)	1 (1.3%)	0 (0%)	0.657
Time to recurrence, months (SD)	13 (15)	16 (15)	9 (10)	0.016

4

5 PV: pulmonary veins; PVI: pulmonary vein isolation; AF: atrial fibrillation; LVEF: left ventricular
 6 ejection fraction; LA: left atrium. CFAE: complex fractionated atrial electrograms.

7

8

9

10

1 **Table 4.** Multivariate analysis on patients relapsing with AF only (n=100) assessing the
2 independent correlation to recurrences despite absence of PV reconnection of those parameters
3 significant at univariate analysis (p<0.05).

4

	OR	95% CI	p-value
AF type, paroxysmal vs. persistent	0.772	0.171-3.494	0.737
LA volume, III tertile	5.090	1.192-26.188	0.048
LVEF, III tertile	1.078	0.351-3.307	0.896
PVI alone vs. lines/CFAE	8.127	0.119-35,212	0.499

5

6 OR: odds ratio. CI: confidence interval. PV: pulmonary veins; PVI: pulmonary vein isolation; AF:
7 atrial fibrillation; LVEF: left ventricular ejection fraction; LA: left atrium. CFAE: complex
8 fractioned atrial electrograms.

9

10

1 **Figure legends**

2 **Figure 1.** Pattern of PVs conduction recovery detected at repeated procedure (n=165 patients),
3 stratified according to first ablation protocol. PV: pulmonary vein. LSPV: left superior pulmonary
4 vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior
5 pulmonary vein.

6

7 **Figure 2.** Number of reconnected pulmonary veins or incomplete linear lesions documented at
8 repeated procedure, according to index procedure. PVI: pulmonary vein isolation. CFAE: complex
9 fractioned atrial electrograms.

10

11 **Figure 3.** Different patterns of LVEF, stratified by tertiles (A), LA volume, stratified by tertiles (B),
12 atrial fibrillation subtype (C) and catheter ablation protocol performed at index procedure (D)
13 among patients respectively experiencing PVs reconnection or without PVs reconnection at redo
14 procedure. LVEF: left ventricular ejectionfraction. LA: left atrial. AF: atrial fibrillation.

15

16

17

18

19

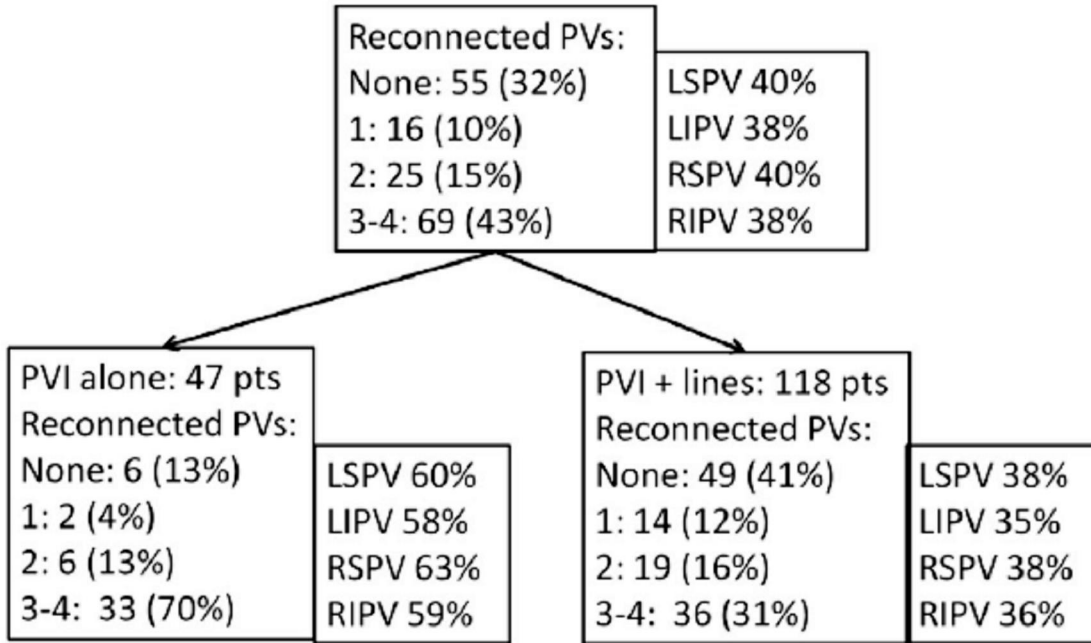
20

21

22

1 **Figure 1.**

2



3

4

5

6

7

8

9

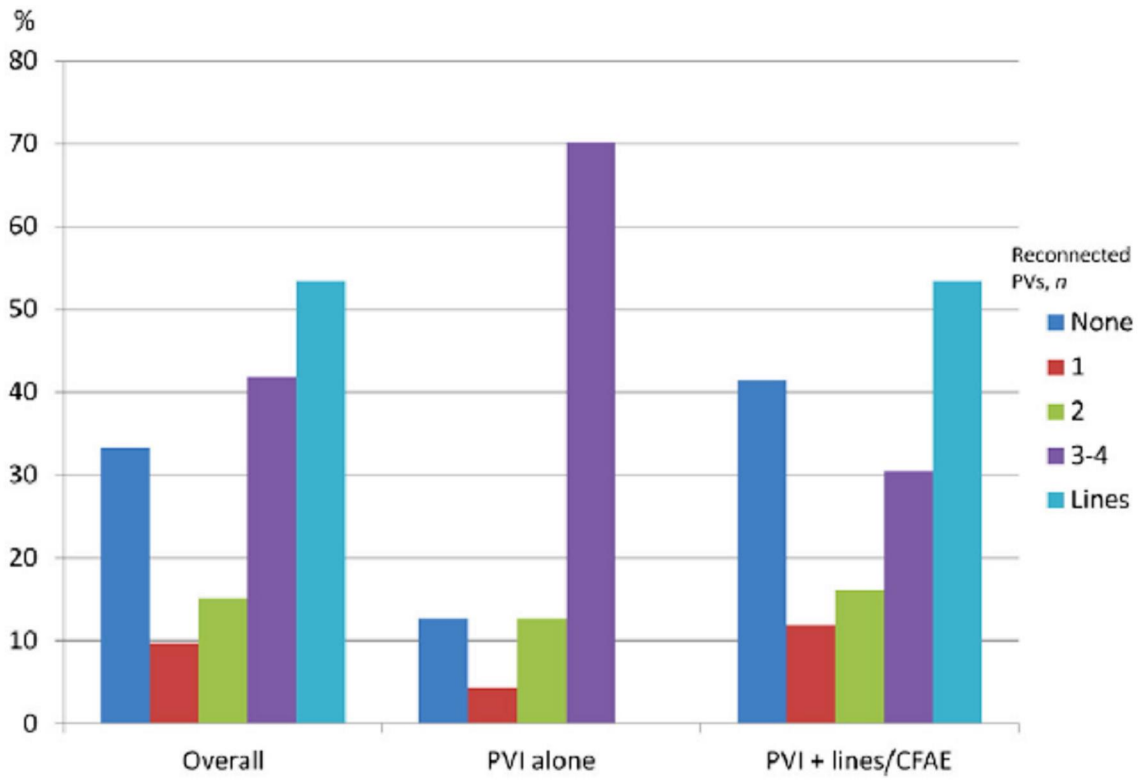
10

11

12

13

1 **Figure 2**



2

3

4

5

6

7

8

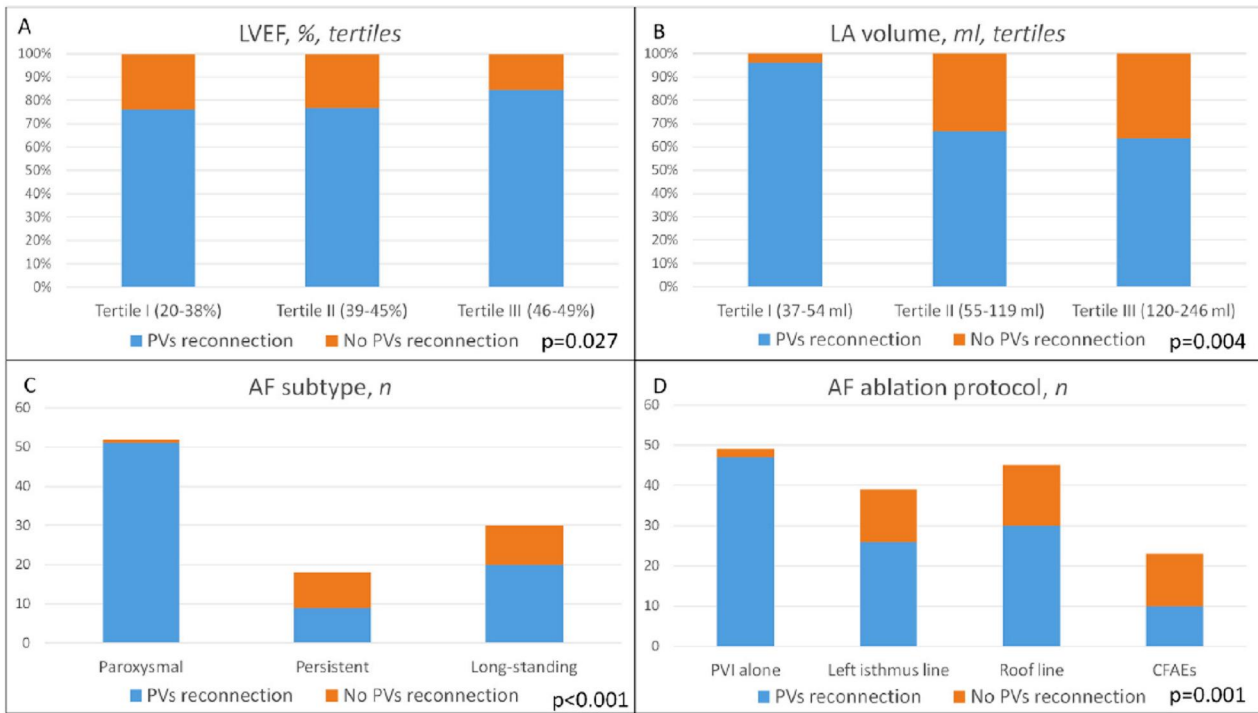
9

10

11

12

1 **Figure 3.**



2

3

4

5

6

7

8