University of Szeged
Albert Szent-Györgyi Medical School
Doctoral School of Clinical Medicine

Atrial Fibrillation Catheter Ablation Treatment with Novel Mapping Systems

PhD Thesis

Zsuzsanna Kis MD

Supervisor:
Tamás Szili-Török MD, PhD, Habil.

Szeged,
2024

LIST OF PAPERS RELATED TO THE SUBJECT OF THE THESIS

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

Kis Z, Muka T, Franco OH, Bramer WM, De Vries LJ, Kardos A, Szili-Torok T.

Curr. Cardiol Rev. 2017;13(3):199-208.

Doi: 10.2174/1573403X13666170117125124. Review.

Q2

II. Type and rate of atrial fibrillation termination due to rotational activity ablation combined with pulmonary vein isolation.

Kis Z, Theuns DA, Bhagwandien R, Wijchers S, Yap SC, Szili-Torok T.

J Cardiovasc Electrophysiol. 2017 Aug;28(8):862-869. Epub, 2017 Jun 21.

Doi: 10.1111/jce.13240.

IF: 2,875 **Q1**

LIST OF PAPERS NOT RELATED TO THE SUBJECT OF THE THESIS

1.Long-Term Efficacy and Safety of Left Atrial Appendage Closure Procedures
Zadori A, **Kis Z,** Toth T, Szigeti M, Temesvari A, Fontos G, Nyolczas N, Andreka P.
Int Heart J. 2023 Mar 31;64(2):188-195. doi: 10.1536/ihj.22-639. Epub 2023 Mar 15. PMID: 36927928.

IF:1,5 Q3

2. Evaluation of Isolation Area, Myocardial Injury and Left Atrial Function Following High-Power Short-Duration Radiofrequency or Second-Generation Cryoballoon Ablation for Atrial Fibrillation
Kassa K.I.,Nagy Z, Simkovits D, **Kis Z**, Ferenczi T, Som Z, Foldesi Cs, Kardos A
J Dev Dis, 2022 Sep 28;9(10):327.,doi: 10.3390/jcdd9100327.,

IF:2,4, Q1

3. Functional Electrographic Flow Patterns in Patients with Persistent Atrial Fibrillation Predict Outcome of Catheter Ablation
Szili-Torok T, **Kis Z**, Bhagwandien R., Wijchers S., Yap S., Hoogendijk M, Dumas N., Haeusser P, Geczy T., Kong M., Ruppersberg P
J Cardiovasc Electrophysiol. 2021 Aug;32(8):2148-2158. doi: 10.1111/jce.15115. Epub 2021 Jun 7.PMID: 34041824 ,

IF: 2,94 Q1

4. Prospective evaluation of iatrogenic atrial septal defect after cryoballoon or radiofrequency catheter ablation of atrial fibrillation-"EVITA" study.
Nagy Z, **Kis Z**, Géczy T, Temesvari A, Som Z, Borbas S, Breuer T, Molnar D, Foldesi C, Kardos A.
J Interv Card Electrophysiol. 2019 Aug 9. doi: 10.1007/s10840-019-00598-9.

IF: 1,27 Q3

5.Left-sided phrenic nerve injury during redo pulmonary vein isolation long after a previous contralateral self-limiting phrenic nerve palsy.
Kis Z, Noten AME, Wijchers S, Bhagwandien R, Szili-Torok T.
Clin Case Rep. 2019 Jun 11;7(7):1391-1394. doi: 10.1002/ccr3.2199. eCollection 2019 Jul.

Q4

6. Robotic navigation shows superior improvement in efficiency for atrial fibrillation ablation.
Elisabeth Noten AM, **Kis Z**, Akca F, Bhagwandien R, Wijchers S, Yap SC, Szili-Torok T.
J Atr Fibrillation. 2019 Feb 28;11(5):2108. doi: 10.4022/jafib.2108. eCollection 2019 Feb-Mar.

Q3

7. Transapical approach to optimize left ventricular resynchronization in patients with dilated cardiomyopathy.
Kassai I, Pozzoli A, Friedrich O, **Kis Z**, Szili-Torok T, Lapenna E, Benussi S, Alfieri O
Multimed Man Cardiothorac Surg. 2017 Apr 26;2017. doi: 10.1510/mmcts.2017.005

8. Comparison of long-term outcome between patients aged < 65 years vs. ≥ 65 years after atrial fibrillation ablation.
Kis Z, Noten AM, Martirosyan M, Hendriks AA, Bhagwandien R, Szili-Torok T.
J Geriatr Cardiol. 2017 Sep;14(9):569-574. doi: 10.11909/j.issn.1671-5411.2017.09.004.

IF:1,58 Q2

9. Long-term cerebral thromboembolic complications of transapical endocardial resynchronization therapy.
Kis Z, Arany A, Gyori G, Mihalcz A, Kardos A, Foldesi C, Kassai I, Szili-Torok T.
J Interv Card Electrophysiol. 2017 Mar;48(2):113-120. doi: 10.1007/s10840-016-0206-6. Epub 2016 Nov 12.

IF: 1,52 Q2

10. Disappearance of Idiopathic Outflow Tract Premature Ventricular Contractions After Catheter Ablation of Overt Accessory Pathways.
Szili Torok T, DE Vries LJ, Özcan EE, Hasdemir C, **Kis Z,** Kardos A, Géczy T, Kovacs I, Benedek I, Oosterwerff E, Hendriks AA, Khan M, Yap SC.
J Cardiovasc Electrophysiol. 2017 Jan;28(1):78-84. doi: 10.1111/jce.13098. Epub 2016 Oct 6

IF: 2,87 Q1

11. Left atrial appendage thrombus formation during atrial fibrillation ablation under sufficient heparinization.
Kis Z, Bhagwandien R, Nieman K, Wijchers S, Szili-Torok T.
Europace. 2016 Dec;18(12):1800. doi: 10.1093/europace/euw148. Epub 2016 Jun 21.

12. The Role of Atrial Fibrosis Detected by Delayed – Enhancement MRI in Atrial Fibrillation Ablation
Tamas Szili-Torok*, **Kis Z,** Astrid A. Hendriks, Taulant Muka, Wichor M. Bramer, Istvan Kovacs
Current Medical Imaging, DOI : 10.2174/1573405614666180806130327

IF:0,85 Q4

13. Two-Year Follow-Up after Contact Force Sensing Radiofrequency Catheter and Second-Generation Cryoballoon Ablation for Paroxysmal Atrial Fibrillation: A Comparative Single Centre Study.

Kardos A, **Kis Z,** Som Z, Nagy Z, Foldesi C.
Biomed Res Int. 2016;2016:6495753. doi: 10.1155/2016/6495753. Epub 2016 May 22.

IF:2,47 Q1

14. Catheter ablation for paroxysmal atrial fibrillation: new generation cryoballoon or contact force sensing radiofrequency ablation?].
Nagy Z, **Kis Z**, Som Z, Földesi C, Kardos A.
Orv Hetil. 2016 May 29;157(22):849-54. doi: 10.1556/650.2016.30408. Hungarian.

IF:0,35 Q4

15. Aortic Valve Rupture Due to Radiofrequency Ablation of Left Ventricular Outflow Tract Extrasystole.
Kis Z, Pal M, Szabo Z, Kardos A.
J Cardiovasc Electrophysiol. 2016 Aug;27(8):992. doi: 10.1111/jce.12959. Epub 2016 Apr 5.

IF:3,06 Q1

16. Sudden Cardiac Death and Idiopathic Ventricular Arrhythmias
L.Vries, **Kis Z,** SC Yap
Journal of Cardiovascular Emergencies 2015;1(2):65-67, DOI: 10.1515/jce-2015-0009

17. Percutaneous left atrial appendage closure after resolution of left atrial appendage thrombi with dabigatran].
Kis Z, Földesi C, Pál M, Som Z, Csillik A, Abrahám P, Temesvári A, Fontos G, Szatmári A, Andréka P, Kardos A.
Orv Hetil. 2013 Feb 17;154(7):262-5. doi: 10.1556/OH.2013.29550. Hungarian

Q3

18. Surgical technique and the mechanism of atrial tachycardia late after open heart surgery.
Pap R, Kohári M, Makai A, Bencsik G, Traykov VB, Gallardo R, Klausz G, **Kis Z**, Forster T, Sághy L.
J Interv Card Electrophysiol. 2012 Nov;35(2):127-35. doi: 10.1007/s10840-012-9705-2. Epub 2012 Jul 27.

IF:1,38 Q1

Contents

List of abbreviations

AAD - Anti-arrhythmic drug
ACT - Activation clotting time
AF - Atrial fibrillation
AT - Atrial tachycardia
BMI - Body mass index
CBA - Cryoballoon ablation
CHA2DSVaSC score - Calculates stroke risk
COPD - Chronic obstructive pulmonary disease
CTI - Cavo-tricuspid isthmus
CS - Coronary sinus
ECV - Electric cardioversion
FIRM - Focal impulse and rotor modulation
FU - Follow-up
ICE - Intracardiac echocardiography
LA - Left atrium
PAF - Paroxysmal atrial fibrillation
PV - Pulmonary vein
PVI - Pulmonary vein isolation
RA - Right atria
RAP - Rotational activity profile
RCT - Randomized controlled trial
RFCA - Radiofrequency catheter ablation
RoAc - Rotational activity
SD - Standard deviation
SR - Sinus rhythm
TIA - Transient ischemic attack
3D - Three-dimensional

1. Introduction

Atrial fibrillation (AF) is the most common supraventricular tachycardia resulting in reduction of quality of life, functional clinical status and overall survival. [1-3] Atrial fibrillation prevalence as well as its associated comorbidities are progressively increasing with the growing population of elderly patients. Therefore, AF has become an important public health issue. [4-5] The management of AF involves rhythm and rate control therapy. Moreover, treatment of AF focuses on the prevention of AF- associated complications such as stroke, transient ischemic events, and deterioration of heart failure. Catheter ablation of AF with pulmonary vein isolation (PVI) is an increasingly sophisticated, widely applicable non - pharmacological method as rhythm control in AF management. Multiple fundamental and clinical trials have established PVI as the gold standard catheter ablation method of AF and have shown that this is superior to pharmacological treatment, but its long-term success rate remains suboptimal in patients with persistent AF. [6-9] The variable long-term arrythmia free survival data after a technically successful PVI may be related to the technology and to incomplete understanding of the mechanisms of AF. [6] Although, several basic and clinical studies demonstrated that pulmonary vein isolation (PVI) is superior to medical therapy in AF management, the underlying mechanism of PVI efficacy is still not completely clear. [10-13] Haïssaguerre et al. detected that pulmonary veins (PVs) have role in triggering of AF. However, our knowledge about AF drivers responsible for AF maintenance is still far from being complete. [14]

There is substantial evidence that apart from the pulmonary veins other parts of the atria may contribute to triggering and maintaining AF through various mechanisms. [15] Notably, many patients have reconnected pulmonary veins following a successful ablation, while patients with recurrent AF often have isolated pulmonary veins. [1,16] It is still debated what mechanism should be targeted during AF ablation, and it is still not completely clear how it works when it is successful. [17,18] If we agree that elimination of AF sources should result in termination of AF comparable to observations in other arrythmias, then if we could individually define the AF source(s) we should be able to reach more promising results with catheter ablation even in persistent AF patients.[19-22] Pulmonary vein isolation provides a generic anatomical approach to eliminate AF triggers and also the susceptive driver(s) in PVs as well. One can assume if a driver of AF is eliminated then it should result in termination and/or non-inducibility of the arrhythmia.

Pulmonary vein isolation can be successfully achieved with different energy sources. Radiofrequency and cryoballoon catheter ablation of AF are the most frequently used technologies**.** [1]

Recently, the focal impulse and rotor modulation (FIRM) mapping became available, which aims to identify areas of the atria functioning as patient-specific AF driver(s). [16-18] Targeting these atrial substrates ensures a patient-tailored ablation strategy for AF elimination.[23] Despite this, the clinical outcome data of AF termination after FIRM-guided ablation is still controversial. [24-26]

2. Objectives

2.1 Firstly, we aimed to systematically review and perform a meta-analysis by compiling the results of all relevant studies that have evaluated the short-, mid-, and long-term outcome of PVI as a sole treatment strategy (from the same group of investigators) for a homogenous paroxysmal AF patient population.

2.2 Secondly, we evaluated the timing and rate of AF termination using ablation of rotational activity detected by focal impulse and rotor modulation mapping in combination with conventional PVI in persistent AF patients.

3. Materials and methods

3.1 Systematic review and meta-analysis

3.1.1 Data sources and search strategy

This review was conducted in accordance with the PRISMA and MOOSE guidelines (Appendix 1, 2). We aimed to identify all published articles discussing the short-, mid- and long-term follow-up data of percutaneous, manually guided PVI-only procedures with radiofrequency or cryoballoon ablation (CBA) for PAF, which derived from the same group of investigators. We searched Embase.com, Ovid Medline, Web-of-science and the Cochrane Central registry of trials from inception until the 14th of December 2015. Additional references were obtained from PubMed, the subset as supplied by publisher, containing recent references, and the first relevant results from Google scholar. The search strategy was created with the assistance of a medical librarian (WB). The search strategy combined terms for PAF with terms for interventions such as RFCA, CBA and PVI, and searched for cohort, follow-up, and longitudinal studies. The search results were limited to English language articles, but no restriction was used on publication dates. The detailed search methodology for all databases is provided in Appendix 3.

3.1.2 Study selection and eligibility criteria

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

3.1.3 Data extraction process

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

3.1.4 Risk of bias assessments for the included clinical studies

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

3.1.5 Statistical Analysis

The inverse variance weighted method was used to combine success rates to produce a pooled success rate using random-effects models to allow for between study heterogeneity. [27] Additionally, we reported the results using fixed effect models. Fixed-effects models were also used to pool rates of the same study. Heterogeneity was assessed using the Cochrane $\chi 2$ statistic and the I^2 statistic and was distinguished as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $< 75\%$) or high ($I^2 \geq 75\%$) (Higgins et al. 2003).

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

3.2 Prospective study conducting FIRM- guided ablation with PVI for atrial fibrillation

3.2.1 Study population

This single-center, prospective study enrolled thirty-eight consecutive patients with symptomatic persistent AF despite pharmacologic therapy and/or prior ablation undergoing a combined conventional PVI and FIRM-guided ablation between March 2015 and April 2016. "Persistent AF was defined as continuous AF that is sustained beyond seven days. Episodes of AF in which a decision was made to electrically or pharmacologically cardiovert the patient after ≥48 hours of AF, but prior to 7 days, were also be classified as persistent AF episodes."[1] Written informed consent was obtained from all patients. Data collection for this study was approved by the institutional review board and the ethical committee. We did not include patients with paroxysmal AF, and those with presence of intracavital thrombus. Patients with pacemaker or with implantable cardiac defibrillator were not scheduled for the procedure. None of the patients suffered from long-standing AF.

3.2.2 Electrophysiologic Study

The electrophysiologic study was performed without interrupting the anti-arrhythmic drug (AAD) therapy. Of note, this was our AAD policy for persistent and long-standing persistent AF ablation procedures. Decapolar catheters were advanced via femoral venous access to the coronary sinus. If spontaneous AF was not observed, AF was induced by burst pacing starting at 500 ms cycle length and reduced with 50 ms steps to 300 ms then reduced with 10 ms till initiation of AF. Sustained AF after > 10 minutes of duration was mapped. Intravenous heparin was administered to reach ACT > 300 seconds before introduction of the basket catheter. A 64-pole basket catheter spaced along 8 splines (FIRMap, Abbott, Chicago, IL, USA) was passed through an 8,5 Fr SL1 sheath to identify RoAc firstly in the right atrium. Sizing and positioning of the basket catheter such as the confirmation of good atrial contact was ensured by fluoroscopy and/or intracardiac echocardiography (ICE). After identification and elimination of all right-sided RoAcs we placed the basket catheter through ICE-guided transseptal puncture to the left atrium. If all identifiable RoAcs were eliminated we continued the procedure with PVI. If AF termination could not be reached during RoAc ablation then PVI was performed in AF. At the end of the procedure in case of unsuccessful ECV we rechecked the PV reconnections as well.

3.2.3 FIRM mapping and AF sources

Atrial fibrillation was recorded using wide field of view basket catheters. Unipolar and bipolar intracardiac signals from the basket catheter were filtered at 0.05 - 500 Hz and recorded at 1-kHz sampling frequency for export from the electrophysiology recording system to the computational FIRM-mapping system (RhythmView, Topera, San Diego, CA). This system first preprocessed the electrograms to remove the QRS signals to improve the signal-to-noise ratio. [25,28][12, 14]The system then analyzed the AF cycles at each electrode over successive timepoints. The resulting computational phase map depicts the putative propagation of electrical activity of AF. [25] The AF propagation maps are then projected onto a two-dimensional grid. The two-dimensional grid portrays the right atrium opened through the tricuspid annulus vertically, while representing the left atrium opened horizontally through the mitral valve. [25] The location of the rotors and focal sources could be identified by their electrode coordinates based on three-dimensional (3D) electroanatomic map. [28] In the present study NavX (St. Jude Medical, St Paul, MN, USA) 3D electroanatomic mapping system was used. Rotational activity was defined as sustained clockwise or counterclockwise activation around a core, or a centrifugal activation from an origin, which were located on the basis of their electrode coordinates. [29-31] The basket coverage was confirmed in all cases by fluoroscopy and/or ICE, electrograms quality checking and basket visualization on the 3D mapping system. If poor signal quality was achieved, then repositioning of the basket catheter was executed until adequate raw signals could be recorded. The assessment of the RoAc based on the results of rotational activity profile (RAP) software tool of the Topera system. It could be overruled if the quality of raw signals appeared to be inadequate or if RoAc was not clearly identifiable. All effort was done to determine whether each RoAc was reproducible over several 4-sec epochs. The stability of RoAc ensures a rational target for limited ablation. The RAP tool provides easier detection of areas that have more RoAc. Areas of higher RoAc for selected time segments are highlighted superimposed on the relevant grid locations.

3.2.4 Ablation procedure

In all included patients FIRM-mapping and rotational activity (RoAc) ablation was performed prior pulmonary vein isolation (PVI). If FIRM-mapping revealed RoAc, then a FIRM-guided ablation was executed first in the right then in the left atrium. Subsequently, conventional PVI-only was performed.

Only RoAc(s) identified by the RAP feature with a repetitive, spatially stable rotational pattern from the default 4-second time segment were targeted for ablation, except if considered to be a false positive upon a visual assessment of the operator. Using 3,5 mm irrigated-tip catheters radiofrequency energy was applied to the basket grid coordinates, referenced to electrode positions on electroanatomic shells. The power setting was < 25 W for the posterior atrial wall and 40 W for the rest of atria, the temperature limit was set to 43 C^o. In FIRM-guided ablation the RF applications were applied directly to centre of the RoAc bounded by ≈ 2 electrodes distance in each axis for around 300 s in each sides. [16] Whenever, AF terminated rigorous attempts were used in all patients to re-induce AF using pacing manoeuvres protocol for AF initiation. The definition of re-inducibility was to be > 30 sec duration of sustained AF. If AF was re-induced, then a novel FIRM-mapping was indicated. Each additional RoAc sites were similarly ablated until all identifiable RoAc were eliminated based on repeated FIRM-maps. Verification of the pulmonary vein isolation was implemented in all patients using a circular mapping catheter (Lasso, Biosense Webster) after conventional PVI. If AF organized into atrial flutter or tachycardia, then these were treated with application of the appropriate line(s). Additional substrate ablation (roof or mitral isthmus line, non-PV sources) was not routinely accomplished. Electric cardioversion (ECV) was performed only in the absence of conversion to sinus rhythm (SR) after completion of the ablation protocol.

3.2.5 Follow-up

Patients were seen at the outpatient clinic following a 3-month blanking period at post-ablation 3, 6, and 12-months. During these visits, 12-lead ECGs were obtained. In addition, long-term monitoring was obtained by trans-telephonic ECG monitoring between 3 and 4, and between 6 and 7- months post-ablation. At 6 and 12- months follow-up, 7-day Holter-recordings were obtained. Between the 6 and 12-months of follow-up symptom-driven event monitoring was ensured if required. Arrhythmia recurrence was defined as any episode of documented AF/AT > 30 seconds.

3.2.6 Study endpoints

The pre-specified primary efficacy endpoint was the rate and timing of AF elimination during the combined RoAc and PVI ablation procedure. Secondary endpoint was safety, defined as incidence of peri-procedural complication(s).

3.2.7 Statistical Analysis

Normality of distribution was assessed using with the Shapiro-Wilks test. Continuous variables are presented as mean ± standard deviation (SD), if normally distributed, otherwise by median and corresponding 25^{th} and 75^{th} percentile. Data were compared by the ANOVA or Mann-Whitney U test, as appropriate. Categorical variables are expressed as number and percentage (%) and compared with Fisher's exact test. Logistic regression analysis was performed to study the relation between clinical covariates and the type of termination of AF during rotor ablation. The following covariates were considered as presumable predictors of AF termination: AF duration, AF type, rhythm before ablation, location of the rotors. Statistical analysis was performed using SPSS version 21 (IBM Corp., Somers, NY). Statistical significance was defined as $P < 0.05$ (two-tailed).

4. Results

4.1 Systematic review and meta-analysis

4.1.1 Identification of relevant studies

The search strategy identified 2398 citations, out of which, following initial screening based on titles and abstracts, full-texts of 262 articles were evaluated further. Of these, 13 articles (with a total of 1774 patients) were included in the final analysis (Figure 1). A total of 13 studies discussing the short-, mid-and long-term (with mean/median follow-up (FU) >24-month) success rate of PVI in patients with PAF (cryoballoon or conventional radiofrequency), derived from the same group of investigators were included. [32-44]

4.1.2 General characteristics of the included studies

Table 1 and 2 summarize the key characteristics of the included studies. In aggregate, in all included studies, 1774 patients with PAF were included in this review. However, not all studies provided relevant data that could be meta-analysed. Out of 13 included studies, 7 were prospective studies, 6 were retrospective studies. One randomized controlled trial (RCT) and twelve observational studies were included. Out of 13 studies ten single-center, two double-center and one triple-center studies were analysed. The intensity of the follow-up methodology within 1 year after the index procedure was similar in the included studies (Table 1. and 2). Eleven studies reporting the outcome data of PVI ablation conducted a clinical visit and Holter-monitoring at least 4 times per year, furthermore transtelephonic ECGs were obtained in 4 out of 10 studies within 1-year follow-up. In a majority of the studies (5 out of 7) using CBA patients were scheduled for clinical visit, ECG and 24-hour Holter-monitoring quarterly, furthermore in one study a 5-day Holter-monitoring at 3 or at 6 months was assessed.[25] Magnetic resonance scan examination was performed in two studies to assess PV diameters and to exclude PV stenosis. The studies regarding the long-term outcome of PVI beyond 1-year continued the clinical visits and Holter-monitoring 6 monthly or at least annually. Nevertheless, additional visits were scheduled if required on the basis of patient's symptoms. The single-procedure outcome data pertaining to the efficacy of PVI catheter ablation was clearly available in eight studies. Most studies defined single-procedure success rate as the percentage of patients who remained free of atrial fibrillation and/or atrial flutter or atrial tachycardia with or without anti-arrhythmic drug (AAD) therapy following a 3-months blanking period or those not requiring redo procedures. All studies observed a gradual decrease in arrhythmia-free survival

rate over time. Among the observational studies, no studies were judged to be at low risk of bias, six studies were at medium risk of bias, and six studies were evaluated to be at high risk of bias. The quality assessment of the involved studies is reported in Supplement 1 and 2. The only one RCT included in this review demonstrated a medium risk of bias within one or more areas of study quality using Cochrane Collaboration's tool (Supplement 3).

Figure 1.: Flowchart of Studies for outcome of pulmonary vein isolation for paroxysmal atrial fibrillation

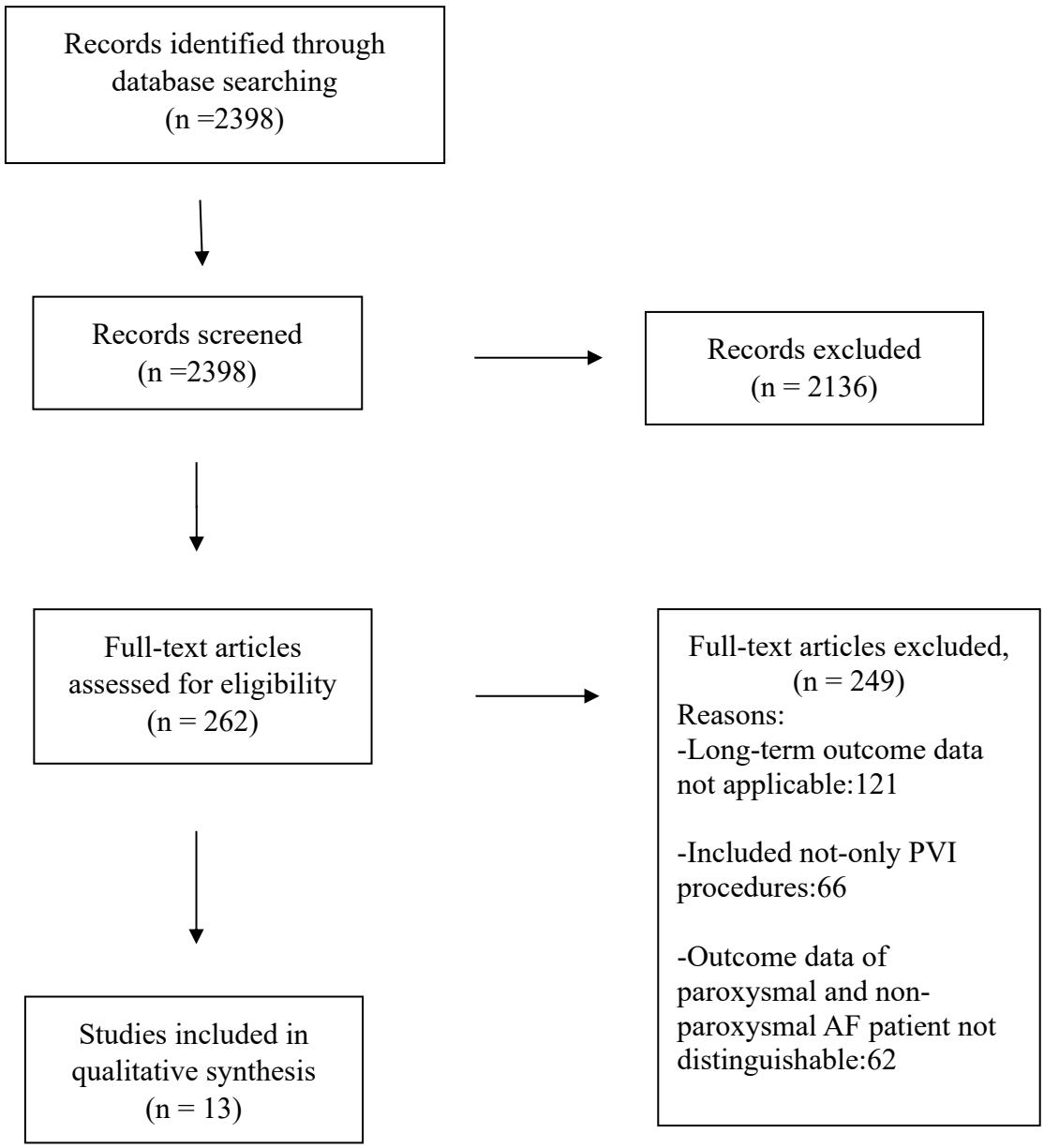
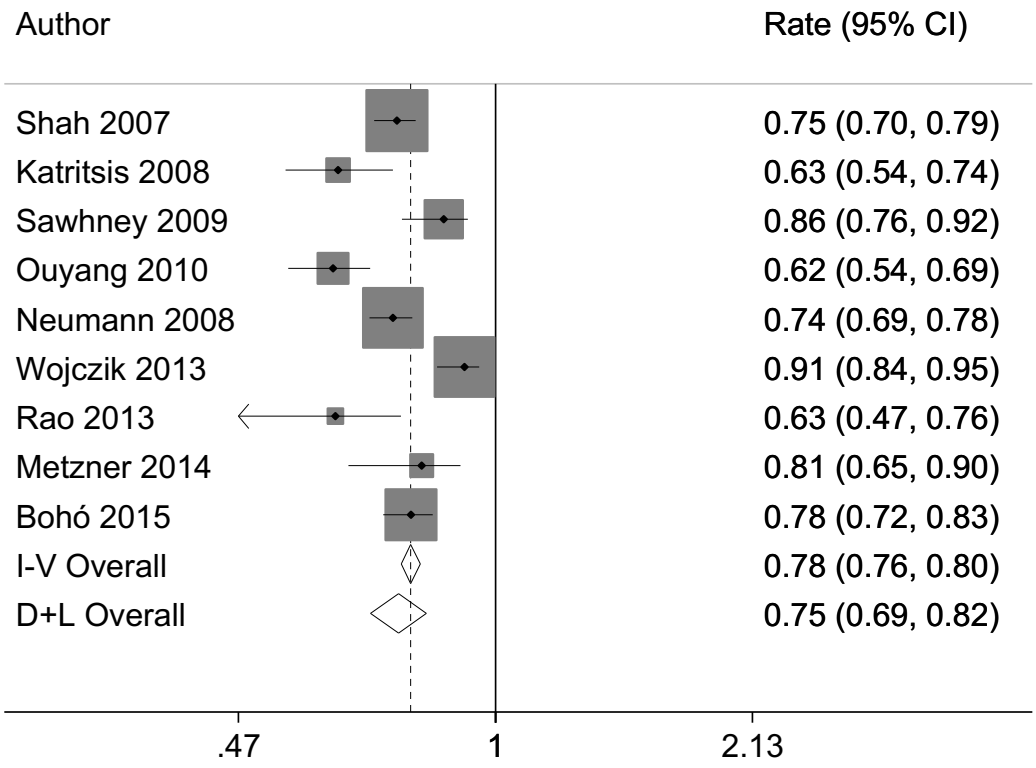
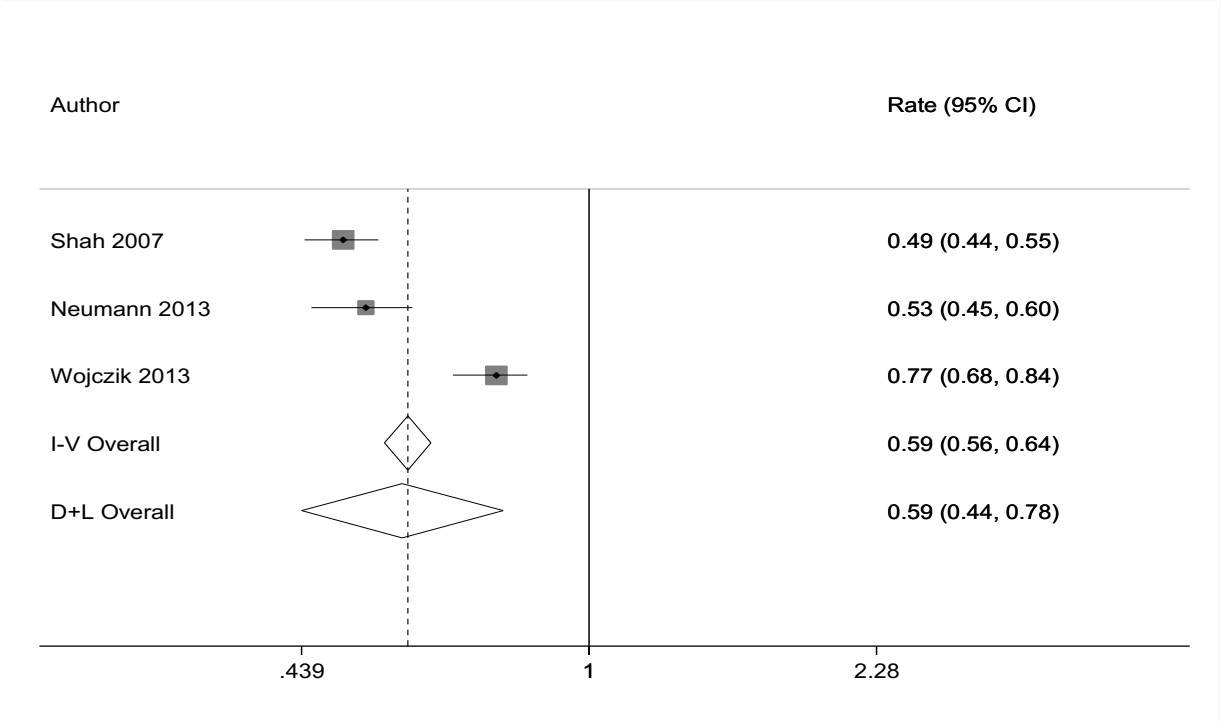


Figure 2.: 12-month success rate of pulmonary vein isolation



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

Figure 3.: 62-month success rate of pulmonary vein isolation



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

Table 1A	**Data from included publication concerning the radiofrequency ablation success rate**								
Publication	Study design	Ablation type	Catheter type	Acute success	Fluoroscopy time (min)	Procedure time (min)	Patient number (n)	Follow-up	Single proc. free of AF
Shah A.N. et al. (2007, USA)	single center, prospective	PVI	RFCA, Biosense Webster	nd	nd	nd	350	1-year 2-year 3-year 4-year 5-year	75% 69,2% 66,2% 62% 49,5%
Fiala M. et al. (2008, Cz)	single center, prospective, randomized	segmental PVI	RFCA, Biosense Webster	nd	46±13,4	255±55	54	6-month 9-month 12-month 48±8-month	68% 62,6% 57,3% 57%
Fiala M. et al. (2008, Cz)	single center, prospective, randomized	circumferential PVI	RFCA, Biosense Webster	nd	45,5±14,9	279±42	56	6-month 9-month 12-month 48±8-month	68% 62,6% 57,3% 57%
Katritsis D. et al. (2008, IT)	double center, prospective	ostial-antral PVI circumferential PVI	RFCA, Biosense Webster	nd	56,3±7,9 28,2±6,1	208,8±26,9 180,1±18,4	41 49	1-year 1-year	61% # 67,4%
Katritsis D. et al. (2008, IT)	double center, prospective	segmental ostial PVI antral PVI	RFCA, Cordis-Webster	nd	nd	nd	35 4	42,2±6-month	21,4%
Sawhney N. et al. (2009, USA)	single center, prospective	segmental ostial PVI	RFCA, Blazer	nd	nd	nd	71	1-year 2-year 5-year	86% 79% 56%
Ouyang F. et al (2010, GER)	single center, prospective	continuous circular PVI	RFCA	100%	29,1±11,9	228±58	161	1 month 3 months 6 months 12 months 24 months 36 months 48 months 4,8 years Over 60 month	78% 73% 69% 62% 53% 52% 49% 46,6% 46%

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

Table 1B	Data from included publication concerning the radiofrequency ablation success rate				
Publication	**Multiple proc. free of AF**	**Complication**	**Follow-up within 1-year FU**	**Follow-up after 1-year FU**	**Quality score**
Shah A.N. et al. (2007, USA)	nd	nd	Clinic visit at 1, 3, 6, 9, 12 months transtelephonic ECG postproc. 3 months Holter-monitor at 3 months	clinical visit annually	8
Fiala M. et al. (2008, Cz)	80%*	PV stenosis (n=1) Hemianopsia (n=1)	Clinic visit and Holter-monitor at 6 week, 3, 6, 8, 12 months transtelephonic ECG when required	clinic visit and Holter-monitor at least twice a year (6-monthly)	
Fiala M. et al. (2008, Cz)	80%*	Femoral pseudoaneurysm (n=1)	Clinic visit and Holter-monitor at 6 week, 3, 6, 8, 12 months transtelephonic ECG when required	clinic visit and Holter-monitor at least twice a year (6-monthly)	
Katritsis D. et al. (2008, IT)	nd	Pericardial tamponade (n=2)	Clinic visit and Holter-monitor at 1, 3, 6, 8, 12 months transtelephonic ECG when required	clinic visit and ECG 3-monthly	8
Katritsis D. et al. (2008, IT)	66,7%*	nd	Clinical visit and ECG monthly transtelephonic ECG when required	Clinical visit and ECG 3 monthly	6
Sawhney N. et al. (2009, USA)	84%*	Femoral hematoma (n=2) Femoral pseudoaneurysm (n=1)	Clinic visit and Holter-monitor at 1, 3, 6, 8, 12 months transtelephonic ECG when required	clinic visit and Holter-monitor at least twice a year (6-monthly)	8
Ouyang F. et al (2010, GER)	79,5%*	Pericardial effusion (n=2) Aspiration pneumonia (n=1)	Clinic visit, surface ECG, transtelephonic ECG	Clinic visit, surface ECG, Holter-monitoring 6-monthly	6

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

Table 2A	Data from included publications concerning the cryoballoon ablation success rate								
Publication	**Study design**	**Ablation type**	**Catheter type**	**Acute success**	**Fluoroscopy time (min)**	**Procedure time (min)**	**Patient number (n)**	**Follow-up**	**Single proc. free of AF**
Neumann T. et al (2008, GER)	single center, prospective	antral or ostial PVI	CB, AF	nd	40	170	346	1-year	74%#
Neumann T. et al (2013, GER)	single center, prospective	antral or ostial PVI	CB, AF	98,9%	50,2	222	163	5-year	53%
Wojczik M. et al (2013, GER,POL)	3-center, prospective	PVI	CB, AF	100%	33	210	103	6-month 1-year 5-year	94% 91% 77%
Rao J.Y. et al (2013, Belgium)	single center, retrospective	PVI	CB, AF	100%	49±12	151±30	40	3-month 6-month 12-month 24-month 36,6-month	72,5% 67% 62% 60% 58%
Metzner A.et al (2014, GER)	single center, retrospective	PVI	CB, AFA	99%	25±8	140±28	36	1-year	81%#
Metzner A.et al (2015, GER)	single center, retrospective	PVI	CB, AFA	99,60%	24±8	138±29	60	2-year	73%#
Bohó A. et al. (2015, SK)	single center, retrospective	PVI	CB, AF	92,70%	23±8,5	187±34,9	205	6-month 12-month 24-month 36-month	93% 78% 53% 34%

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

Table 2B	Data from included publications concerning the cryoballoon ablation success rate				
Publication	**Freedom of AF after multiple proc.**	**Compilcations**	**Follow-up withing 1 year**	**Follow-up after 1 year**	**Quality score**
Neumann T. et al (2008, GER)	nd	pericardial tamponade: n=2	clinical visit, ECG, 7-day Holter 1, 3, 6, 12 mo	clinical visit, ECG, 7-day Holter annually	8
Neumann T. et al (20013, GER)	nd	pericardial effusion: n=3 femoral pseudoaneurysm: n=2 femoral arterio-venous fistula: n=1 transient PNP: 11% TIA: n=1 transient air embolism: n=2 groin hematoma: n=5	clinical visit, ECG, 7-day Holter 1, 3, 6, 12 mo	clinical visit, ECG, 7-day Holter annually	8
Wojczik M. et al (2013, GER,POL)	nd	pericardial tamponade: n=1 transient PNP: n=5 pericardial effusion: n=1	clinical visit, ECG, 7-day Holter 1, 3, 6, 12 mo	clinical visit, ECG, 7-day Holter annually	6
Rao J.Y. et al (2013, Belgium)	nd	pericardial tamponade: n=1 PNP: n=3	Clinical visit, ECG, Holter-monitor 1, 3, 6, 12 mo Five day Holter-monitor at 3 or 5 mo	clinical visit, ECG 6 monthly	6
Metzner A. et al (2014, GER)	nd	transient PNP: n=1 (2%)	clinical visit, Holter-monitor 3, 6, 12 mo		6
Metzner A. et al (2015, GER)	88%*	transient PNP: n=2/60 (3,3%)	clinical visit, Holter-monitor 3, 6, 12, 24 mo		6
Bohó A. et al. (2015,SV)	nd	transient PNP: n=7 persistent PVP: n=7 embolic complication: n=3 TIA: n=2 vascular complication: n=9 pericardial tamponade: n=2	clinical visit, Holter-monitor 3, 6, 9, 12 mo	clinical visit, Holter-monitor 6 monthly	8

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

4.1.3 Overall efficacy of catheter ablation

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

Stratified analysis by type of ablation procedure (radiofrequency ablation or cryoballoon ablation) did not reveal any significant difference (Supplemental Figure 1, 2).

Further three studies could not be assessed to pool outcome data. In the prospective, randomized study by Fiala et al. fifty-four patients had segmental (group1) and fifty-six (group2) patients had circumferential PVI. The 12-month arrhythmia free survival was 58% and 57.3%, while the freedom from AF at the 48±8 month follow-up was 56% and 57% in group1 and group2. [33] The study by Katritsis et al. reported 21.4% success rate after RFCA in 39 patients with 42 months follow-up. [35] The 2-year success rate after CBA in the study by Metzner et al was 73%. [43]

4.1.4 Impact of multiple procedures

Five studies reported outcome data taking into consideration the impact of multiple procedures on PVI ablation success rate. In all these studies additional linear lesions were performed during the repeat ablation procedures. In the study by Fiala et al. fifty-four patients underwent segmental PVI (group 1) while fifty-six patients had circumferential PVI ablation. Following a single procedure, at 48.8-months follow-up a 56% and 57% success rate could be achieved, while after repeat ablation (second ablation: 18 pts in group 1, 19 pts in group 2, third ablation: 5 pts in group 1 and 5 pts in group 2) 80% of the patients were free of arrhythmia in each group.[33] The long-term success rate was 21.4% for patients subjected to a single procedure, 52.6% for patients subjected to a second ablation and 66.7% for patients who underwent a third ablation in the study by Katritsis et al. [35]

This article showed a trend of lower long-term success rates among patients who received the same ablation technique at repeated ablations compared to those in whom the second and the third ablations differed from the initial procedure. [35] The same tendency could be appreciated in the study by Sawhney et al., in which the 5-year single procedure success rate compared to the multi-procedure success rate was 56% vs. 84%.[36] In the study by Ouyang et al. the single and the multiple-procedure success rate after 4.8-year follow-up was 46.6% vs.79.5%.[37]Only one study with cryoballoon ablation reported data after multiple procedures: the 2-year single procedure success rate was 73% for PAF and 71% for persistent AF patients, while the overall success rate reached 88% including repeat procedures in the study by Metzner et al.[43] The higher success rate after multiple-procedures might be attributed to the additional linear lines performed during the redo procedures.

4.1.5 Predictor of arrhythmia recurrence

Four individual studies reported about predictors of AF recurrence after PVI ablation. Sawhney et al. detected that patients with hypertension at the time of index procedure had a significantly higher risk of AF recurrence compared to normotensive patients. [36] Hypertension and hyperlipidaemia as an independent predictor of late AF recurrence were identified by Shah et al. [32] The size of the left atrium was the most consistent predictor of late AF recurrence in the study by Neumann et al. [39] In the study by Bohó et al. the only independent predictor of arrhythmia recurrence was the type of AF. Patients with persistent AF had almost two-fold increased risk for AF recurrence. [44]

4.1.6 Time to atrial fibrillation recurrence

This systematic review demonstrates that many patients develop AF recurrence years after an initially successful AF ablation procedure. In a majority of the studies we analysed, the rate of decline in freedom from arrhythmia was the highest during the first 12 months. [33,37,39,41] However, over time a constant decrease in arrhythmia free survival could be detected in the included studies, with a surprisingly high rate of late AF recurrences. In the study by Sawhney et al. sixteen patients (22.5%) had AF recurrence after 24 months following the ablation. It represented a 7.6% per year recurrence rate of AF between 24 to 48 months. Furthermore, they observed a 17% per year recurrence rate after 48 months following the index procedure.[36] Karitris et al. showed that 56% of the recurrences occurred more than 12 months after the initial procedure, while Ouyang et al. reported a recurrence rate of 14.9% after the same follow-up period. [35,37] Shah et al. found a significant late recurrence rate of 8.7% at 34±16 months, and a 25.5% recurrence rate of patients with 5-year follow-up after an initially successful ablation.[32] It was consistent with the results of Bohó et al. who reported a relatively large number of late recurrences. The 1-year success rate was 78% compared to the 34% success rate of 5-years follow up.[44]

4.1.7 Publication Bias

Visual examination of Begg's funnel plots for the analysis on the 12-month successful rate was moderately symmetrical, therefore providing evidence for publication bias (Fig.2). This was further supported by the results of Egger's test which was significant (Supplemental Fig 3). No evidence of publication bias was observed for the analysis on 24-month success rate (Supplemental Fig 3).

4.2 Prospective study conducting FIRM- guided ablation with PVI for atrial fibrillation

4.2.1 Patient characteristics

Baseline clinical and demographic data is summarized in Table 3. The majority of the patients were male (63%) and had undergone a prior PVI (53%). The mean AF time since the diagnosis before the combined AF ablation procedure was 4,5 ± 3,2 years. The CHA_2DS_2-VaSc score was 1,8 ± 1,2 and the mean left atrial size was 46 ± 7 mm in diameter. All patients had persistent AF. There were 14 pts (37 % of the cohort) who arrived in SR for the ablation due to ECV prior to procedure despite classified as persistent AF pts previously. None of the patients in this patient cohort had long-standing AF. AAD medication was continued during the ablation procedures. Based on the Singh-Vaughan Williams classification, 7 pts were on class I medication, class II drugs were administered in 16 pts, while 19 pts were on class III drugs and 5 pts were treated with digoxin. Following the 3-month blanking period the class III drugs were discontinued in 11 pts, while the class II drugs and/or digoxin were stopped in further 4 pts. At the 6-month follow-up class III drugs in 7 pts and class II drugs in further 5 pts were withdrawn.

4.2.2 Procedural characteristics

Procedural data are summarized in Table 3. Sinus rhythm was presented in 37% of patients (n=14) at the beginning of the procedure, requiring induction of AF. Preparation time for left atrial access took 3-15 minutes after RA RoAc ablation and generally 3-10 minutes between LA RoAC ablation and PVI. Electrical RoAc were seen in 30/38 (79%) patients, with a mean of 0,7±0,8 in the left atrium and a mean of 1,4±1,7 in the right atrium per patient. Left atrial RoAc were identified in 18 patients (47%) while in 27 patients (71%) right sided RoAc were detected. PVI was not performed in 1 of 20 patients who previously underwent AF ablation because PVs were still completely isolated. Pulmonary vein reconnections were revealed in majority of patients (93%) who had undergone prior AF ablation with a mean of 2.4 reconnected PVs, all of these were re-isolated. Cavo-tricuspidal isthmus ablation was performed in 5 (13%) patients. The average procedure duration was 282±62 min with an average of 34±11 min fluoroscopy time, and 2189±1188 seconds of radiofrequency application duration. The size of the basket was selected based on the LA diameter measured by preprocedural TEE and/or ICE. In 21pts (55,3%) the 50 mm, while in 17 pts (44,7%) the 60 mm basket size was used.

The 70 mm basket size was not utilized in this patient cohort. In the right atrium the basket coverage was generally complete, implied by identical spline spacing and balanced basket deployment visualized with fluoroscopy. A segmental mapping and ablation if required was implemented to adjust incomplete basket coverage.

4.2.3 Timing of AF termination

Two distinctive types of the AF termination were defined. The "abrupt termination" of AF presented during PVI RF delivery. It was tended to be more present among patients without RoAc (P = 0.051) (Fig.4) The "late-onset termination" of AF occurring between 3 minutes and 24 hours following RoAc activity ablation was significantly more prevalent in patients with right-sided RoAc. (P = 0.049). (Fig.5) The mean time of "late-onset termination" (excluding the one with 24 hours termination) was 13.8 ± 4 minutes after RoAc ablation.

4.2.4 Rate of AF termination

The overall termination of AF after combined RoAc ablation with PVI was observed in 22 out of 38 patients (58%). (Fig.6) Atrial fibrillation terminated abruptly during PVI RF delivery in 10 out of 38 pts (26%). Late-onset termination was observed in 12 (32%) patients after RoAc ablation (ranging between 3 minutes and 24 hours).

AF organization to atrial tachycardia during ablation was observed in further 4 patients (10%), in whom SR was achieved with additional linear line ablation and ECV. These patients were counted in the "none-terminating group" of patients. Electric cardioversion was attempted in 16 patients (42%) at the end of the ablation procedure. Fourteen of them were electrically converted to SR, while 2 patients remained unconvertible. One patient out of them converted to SR within 24 hours after ablation. Elimination of all RoAcs and isolation of all PVs was reached in 37 of 38 patients (95%). In one patient the RoAc was not ablated due to its proximity to the compact AV-node. Based on the statistical analysis no difference was observed in termination rate among patients who had had prior PVI compared to those who underwent the first PVI procedure combined with FIRM-mapping. Also, no differences were observed in termination rate if AF was induced at the beginning of the procedure or if the patient arrived to the lab in AF.

4.2.5 Complication

Procedural complication occurred in 3 cases (9%) presenting with groin hematoma, in another patient (3%) left atrial appendage thrombus formation was revealed by transoesophageal echocardiography performed right after the ablation for guiding the planned appendage closure procedure.[45]

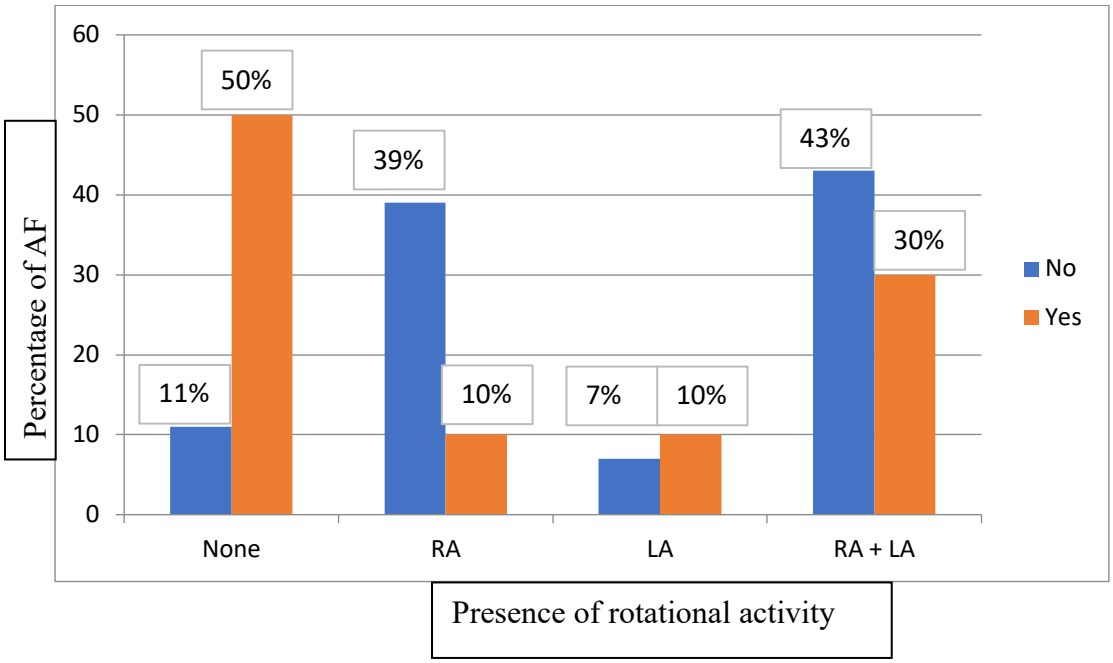
4.2.6 Predictor of AF termination

In univariate analysis, no association between covariates including AF duration, AF type, rhythm before ablation, location of the rotors was found with the type of AF termination.

4.2.7 Follow-up

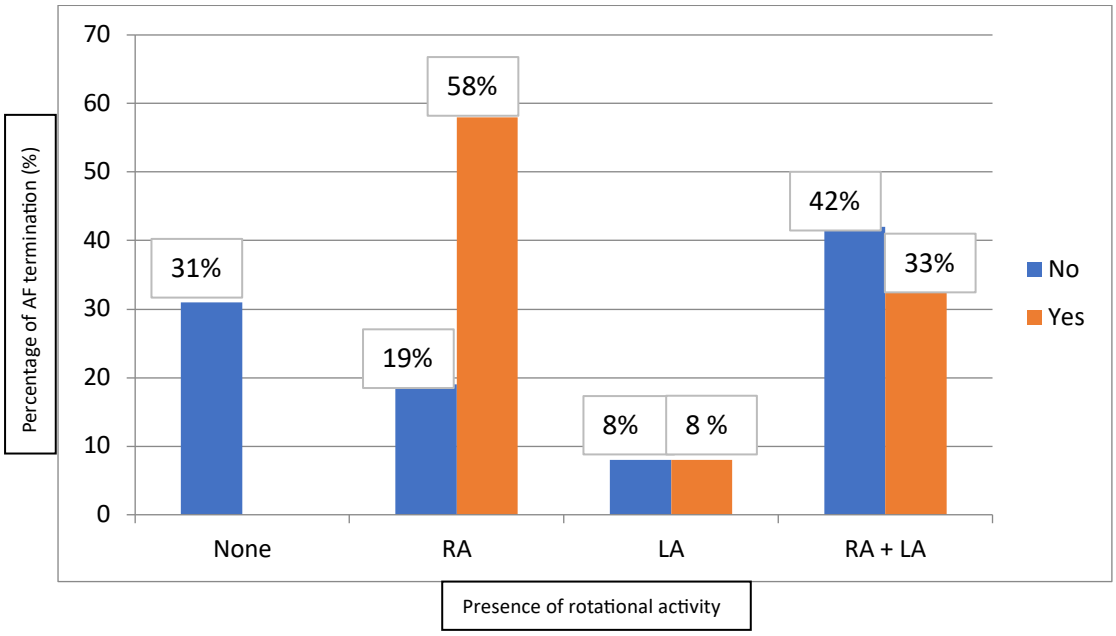
Follow-up data with 3-month blanking period was available for all studied patients. At 3 months of follow-up 26.3% (10/38) of the patients presented with early arrhythmia recurrence. At 6-month follow-up 63.88% (23/36), while at 12-month follow-up 76.1% (16/21) of patients remained free form AF/AT. The 1-year outcome data includes 3 patients with ECV and 3 patients who underwent re-ablation (1 with CTI, 2 with re-do PVI+FIRM-guided ablation) between the 6-12-month FU visits, with 5 patients remaining on at least a reduced dose of a previously ineffective antiarrhythmic medication. The one-year single-procedure success rate was 69,1% (13/21). Figure 7 demonstrates the outcome flowchart at each time interval. At 1-year follow-up freedom form AF/AT was detected in 4 out of 10 patients (25%) within the “abruptly” terminated group, while in 7/12 (58.3%) patients in the “late-onset terminated” group and in 5/16 (31.25%) patients in the “none terminating” group. Neither termination of AF to SR itself nor the termination type predicted the arrhythmia free survival at 1-year follow-up.

Figure 4.: Abrupt termination of atrial fibrillation tended to be more present in patients without identifiable rotational activity n=10 (p=0, 051)



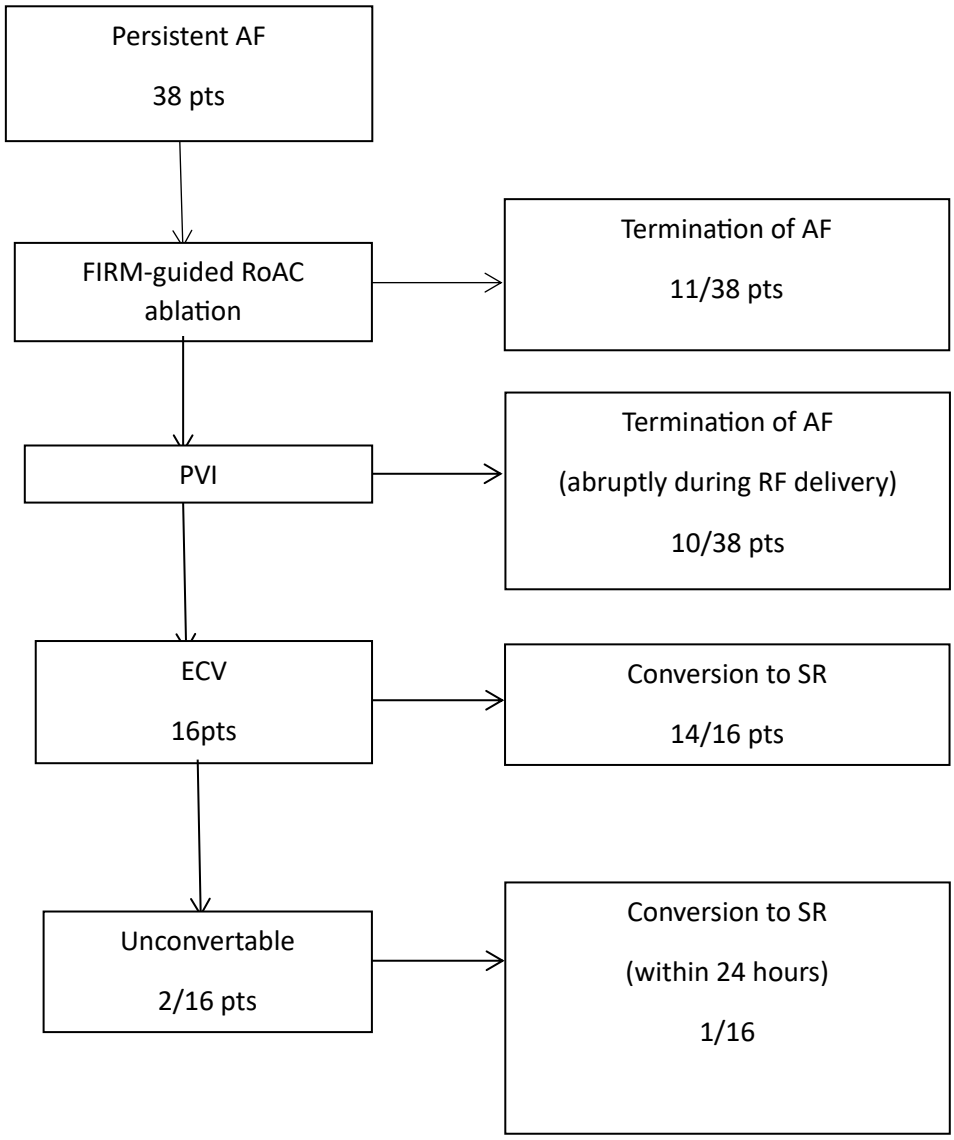
* RA: right atrium, + LA: left atrium, ‡RA+LA: right + left atrium, # None: pts without rotational activity

Figure 5.: Late-onset termination of atrial fibrillation was more prevalent in patients with right-sided rotational activity n=12 (P= 0,049)



*RA: right atrium, + LA: left atrium, ‡RA+LA: right + left atrium, # None: pts without rotational activity

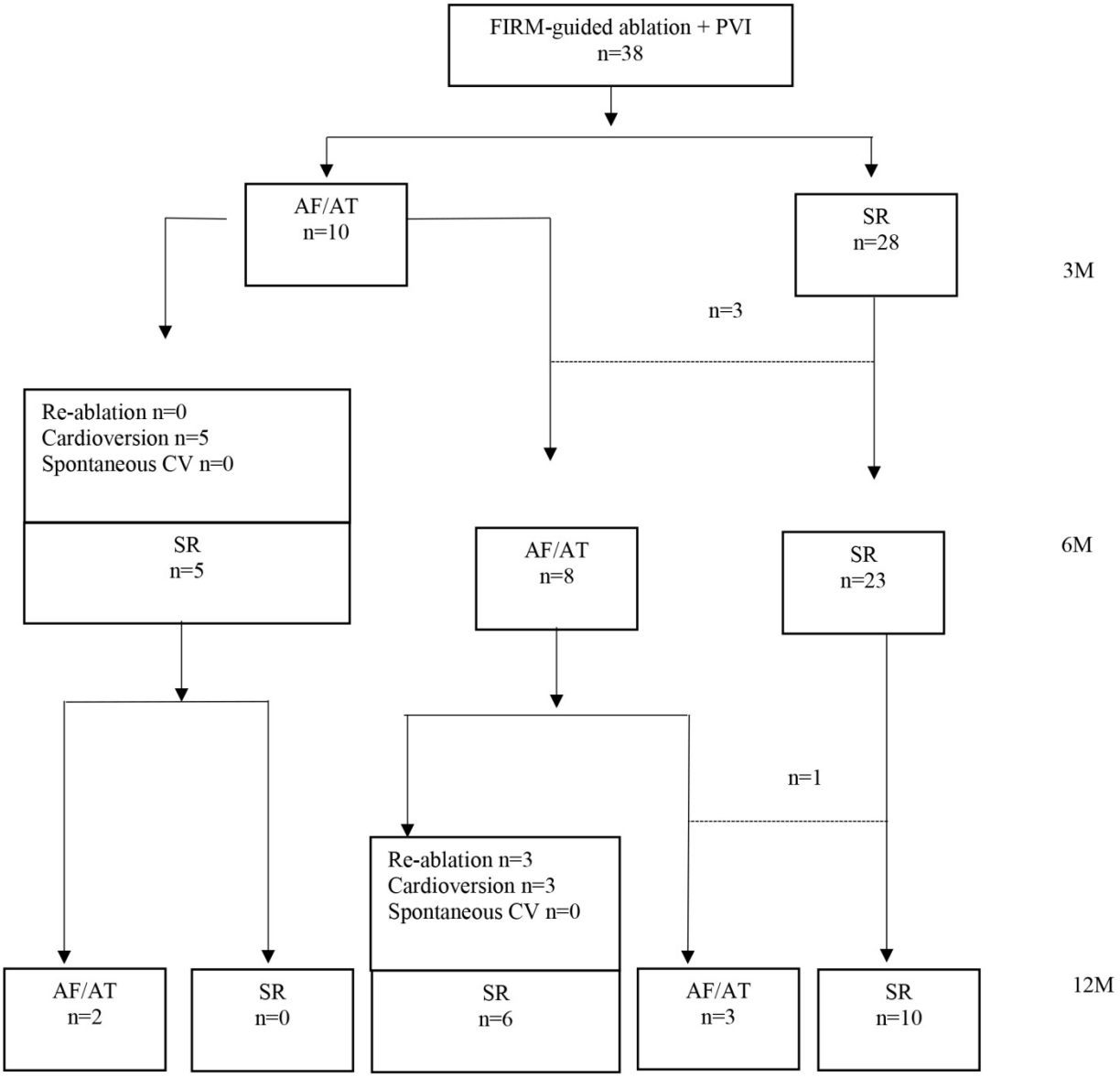
Figure 6: Rate and timing of AF termination during FIRM-guided ablation combined with PVI



* AF: atrial fibrillation, + FIRM: focal impulse and rotor modulation, ‡ RoAc: rotational activity, §PVI: pulmonary vein isolation, II ECV: electrical cardioversion, # SR: sinus rhythm

Figure 7.: Arrhythmia outcome flowchart showing arrhythmia-free survival at 3, 6, 12-month time interval.

PVI=pulmonary vein isolation, SR=sinus rhythm, AF=atrial fibrillation, AT=atrial tachycardia, FU=follow-up, CV=cardioversion



3M: 3-month arrhythmia free survival FU – 73.68% (28/38)

6M: 6-month arrhythmia free survival FU – 63.88% (23/36)

12M: 12-motnh arrhythmia free survival FU – 76.1% (16/21)

Table 3: Demographic, clinical and procedural data of the patient cohort

Age (years)	63±11
Sex (M)	24/38 (63%)
AF duration (years)	4,5±3,2
Prior pulmonary vein isolation	20/38 (53%)
Hypertension	21/38 (55%)
Hyperlipidemia	8/38 (21%)
Diabetes mellitus	6/38 (16%)
Sleep apnea	3/38 (8%)
COPD	2/38 (5.2%)
Pulmonary hypertension	0/38
Left atrial appendage size (mm)	46±7
CHA_2DS_2VASC-score	1,8±1,2
Ischemic heart disease	6/38 (16%)
Dilated cardiomyopathy	4/38 (11%)
Body mass index	28,4±3,8
Type of AF (non-paroxysmal)	38/38 (100%)
AF initiation required at the beginning of the procedure	14/38 (37%)
Rotational activity found	30/38 (79%)
Number of left sided RoAc per patient	0,7±0,8
Number of right sided RoAc per patient	1,4±1,7
Patients with left sided RoAc	18/38 (47%)
Patients with right sided RoAc	27/38 (71%)
Abrupt termination of AF during PVI RF delivery	10/38 (26%)
Late-onset termination of AF	12/38 (32%)
Restoration to sinus rhythm due to ablation	22/38 (58%)
ECV required at the end of the procedure	16/38 (42%)

Fluoroscopy time (min)	34±11
Procedure time (min)	282±62
Radiofrequency application duration (sec)	2189±1188
Cavotricuspidal isthmus ablation	5/38 (13%)
Organization to AT	4/38 (10%)
Reconnected PVs after prior PVI (n)	2.4
Complications	4/38 (11%)
Groin hematoma	3/38 (8%)
Left atrial appendage thrombus formation	1/38 (3%)

*AF: atrial fibrillation, + CHA_2DS_2VASC-score: risk stratification for stroke of AF patients, ++ AT: atrial tachycardia, ‡ ECV: electric cardioversion, § SR: sinus rhythm, II PVI: pulmonary vein isolation, #: RoAc: rotational activity, **COPD: chronic obstructive pulmonary disease

5. Discussion

5.1 Systematic review and meta-analysis

Despite significant technological advances in atrial fibrillation ablation, while superior to medical therapy, the success rate remains lower than for other arrhythmias.[1,46,47] Notably, many patients have reconnected PVs after successful ablation and patients with recurrent AF often have isolated PVs.[1,48] It is still debated what mechanism should be targeted during AF ablation and how ablation works when it is successful.[47,49] There is substantial evidence that apart from the PVs, other parts of the atria such as the PV-left atrial junction, the posterior left atrial wall, the Marshall-vein etc. may contribute to triggering and maintaining AF through various mechanisms. [34]

5.1.1 Comparison to previous systematic reviews

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

In the present systematic review five overlapping studies, enrolling 661 patients can be found compared with the meta-analysis by Ganesan et al. [50] We included further eight unique citations with 1139 patients who underwent PVI-only ablation procedure for paroxysmal atrial fibrillation. We found a low long-term success rate. Moreover, a decline between the short- and long-term follow-up data was observed. Additionally, in this review only patients with PAF, who underwent an exclusive PVI-only ablations were included.

5.1.2 Mechanism of late AF recurrences

The mechanism of AF recurrences in the reviewed studies was thought to be correlated to PV reconnections. However, permanent isolation of PVs is not always necessary for the successful outcome of a PVI procedure.[43,51-53] In the series of Metzner et al. a total of 10 out of 16 patients suffering from atrial tachyarrhythmia recurrence underwent a repeat RF-based redo procedure, which revealed that in 2 out of 10 patients all PVs were completely isolated.[43] Our current analysis may suggest, that the very late recurrence of AF should be related to several other mechanisms, different from the ectopic activity of the PV sleeves. However, ablation may still be effective through mechanisms other than isolation of PVI foci.[35] These possible factors related to late AF recurrences might be: the presence of non-PVI triggers (focal sources or stable rotors may contribute to trigger and maintain AF) and/or a variety of factors leading to structural and electrical remodelling resulting in electrical instability of the atria and/or the failure to target all PVs during initial PVI.

5.1.3 Strengths and Limitations

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

Our searching methodology ensured that we included the most relevant articles in our review enrolling more than 1700 participants. However, there are a number of limitations of this study. Despite all efforts made to undertake a comprehensive search of the published literature, we cannot exclude the possibility of publication bias stemming from under-reporting of negative findings. Also, inclusion of data from potentially poorly conducted studies is undoubtedly a limitation of the current review. Moreover, it is important that the assessment of the effect of different methodologies (segmental, circumferential etc.) of PVI due to the considerable heterogeneity from the original studies made it impossible for us to establish a relation between the method of PVI and the clinical outcome.

Furthermore, high-quality RCTs with adequate sample sizes and standardized long-term follow-up are needed to assess the mid- and long-term outcome of PVI-only ablation for paroxysmal atrial fibrillation. Nevertheless, it would be of a great interest to follow the effect of the ablation therapy for atrial fibrillation over the life course rather than using short time horizon. Last, since the number of available studies in each analysis was generally small, it precluded our ability to investigate the sources of the observed heterogeneity by subgroup analyses involving various study-level characteristics.

5.1.4 Clinical implications

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

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

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

5.2 Prospective study conducting FIRM- guided ablation with PVI for atrial fibrillation

The major finding of our study is a moderate rate (58%) of persistent AF termination with two distinctive timing pattern following FIRM-guided ablation combined with PVI. The "late-onset termination" of AF is significantly more prevalent in patients during right-sided RoAc ablation. The "abrupt termination" of AF is tended to be more present among patients during PVI. Termination does not depend on whether AF is induced or ongoing at the beginning of the procedure.

5.2.1 Drivers of atrial fibrillation

If we agree that elimination of AF drivers should result in termination of AF such as in other arrhythmias, then if we could individually define the AF substrate(s) we should be able to reach more promising long-term results even in persistent AF patients with catheter ablation.

Nowadays, identification of RoAc susceptive of sustaining human AF represents a novel option for catheter ablation approach. Elimination of FIRM-detected RoAcs provides a patient-specific ablation method, however a great debate is going on why AF does not acutely terminate after RoAcs ablation. Schricker et al. reported different possible hypothesis on this topic. Firstly, due to the limitation of the current FIRM- mapping system certain RoAc may remain hidden in the unmapped area of the atria. Secondly, the time period while fibrillatory conduction can sustain AF without driver is still questionable. It may last from seconds to hours. [30] It is still unclear how localized ablation effects on RoAc and what mechanisms lead to the termination of AF. The recent optical mapping studies by Fedorov et al. on human ex vivo heart demonstrated that intramural microanatomic reentry circuits stabilized by micro-anatomic substrates can maintain AF. Endocardial catheter ablation of these microanatomic re-entries stopped AF, suggesting the human 3D atrial architecture may have a key role in the AF 40 maintenance. [54] Further studies are necessary to address these mechanistic questions.

Our results suggest that the two distinctive timing pattern of AF elimination is derived from individual location and mechanism of AF driver(s). The "late-onset termination" of AF occurring between 3 minutes and 24 hours following RoAc activity ablation was significantly more prevalent in patients with right-sided RoAc. Those who had abrupt AF termination during PVI delivery was tended to be more present among patients without RoAc. Our results emphasize that the PVs have role not only in triggering but also in driving AF.

5.2.2 Termination of atrial fibrillation

All in all, only 79% (30/38) of patients had identifiable RoAc in this study, with a lower number of RoAc per patients but with a higher right-sided prevalence compared to previous FIRM-guided AF ablation studies. [25,26,29] The slightly high number of patients without identifiable RoAc (21%) might derive from the technical limitation of the mapping system. The higher percentage of right atrial RoAc(s) in this study is in line with the findings published by Fedorov et al. [55] They demonstrated first in ex vivo human atria with optical mapping experiments that a near 3-fold greater right atria (RA)-to-left atria (LA) adenosine A1 receptor protein expression (specially in supero-lateral RA region) leads to significantly greater RA vs LA repolazation sensitivity in response to adenosine. Sustained adenosine-induced AF was maintained by localized re-entrant drivers in the superior/middle lateral RA, where the shortest action potential duration and the highest A1 receptor expression were observed. [55]

The AF termination rate to SR in our study (58%) is comparable with the results of CONFIRM-trial, in which 56 % (20/36 cases) AF termination rate was reported. [29] Narayan et al. reported that procedural success was more prevalent in those patients who required AF initiation at the beginning of the procedure. [29] In our study the investigated covariates including the rhythm prior ablation was not associated with the type of AF termination. In the first multicenter, non-randomized study the acute endpoint of AF termination was achieved in 67% (8/14 cases). [25] Tilz et al. reported on twelve (48%) patients either with AF termination (24%= 6/25) or with conversion to another rhythm, or cycle length (CL) prolongation ≥10% after rotor ablation.[56] In contrary, lower spontaneous procedural termination rate was observed in 8,6% of patients (5/58) reported by Spitzer et al. and only in 1 out of 20 pts terminated to SR during ablation in the study by Sommer et.al. [57,58]

5.2.3 Clinical outcome

In the present study 38 pts with non-paroxysmal AF after FIRM-guided RoAc ablation combined with PVI demonstrates 76.1% (16/21) freedom from AF/AT with 12-months follow-up with 5 pts on AAD therapy, while our one-year single-procedure success rate was 69.1% (13/21). This is consistent with several previously reported clinical outcome data. [26,56-59] Miller et al. reported 80,5% 1-year freedom for AF in a 10-center independent registry. [26] In addition, Spitzer et al. published a similar 73.1% arrhythmia free survival after a single FIRM-guided procedure with 12-month follow-up, while Tilz et al. reported on 52% single procedure success rate with 13 ± 1 months follow-up. [56,57]

In the study published by Sommer et al. a single-procedure freedom from AF was 80% after a follow-up of 6-months with 1 patient on dronedarone and with all remaining patients being on beta-blocker. Our results are more promising than the 38% arrhythmia free survival reported by Buch et al., which might be explained by different factors: their difficulties in basket placing, application of the precommercial version of the Rhythm View software, challenging patient cohort. [60]

Some studies demonstrated that the lower spontaneous procedural termination was not predictive of long-term outcomes, on the contrary rotor elimination was associated with favourable long-term clinical outcome. [57,58] Present study is in line with these findings as 5 out of 16 patients (31%) within the "none terminating" group presented with SR at 1-year follow-up. The observation that the success rate of FIRM-guided ablation might increase over time, may derive from the reverse remodelling. The FIRM-guided rotor ablation change not only substrate but also may render the substrate to be less vulnerable to AF triggers.

5.2.4 Study limitation

This study has several limitations. Firstly, present study includes the relatively small sample size and lack of control group who underwent exclusively PVI-only ablation alone. The ongoing REAFFIRM study will help us to compare the outcome data of persistent AF patients after conventional PVI versus conventional + FIRM- guided ablation. The small sample size prohibits the identification for predictors of AF termination. Secondly, we cannot exclude that previous procedures might have had impact on RoAcs. Additionally, there may be technical limitations derived from computational approaches for rotor mapping. Further improvements in the design and the resolution of FIRM-mapping system are required to provide better outcome with FIRM-guided ablation. Present study was not powered to assess the potential effect of AAD medication on the outcome of the ablation procedure.

5.2.5 Clinical implication

FIRM-mapping offers a novel and feasible technique for identification of RoAc sustaining human AF. Furthermore, this technique provides a patient-tailored, mechanistically focused method for catheter ablation of AF. Further prospective, randomized controlled studies are needed to define the precise mechanism of AF termination during FIRM-guided ablation combined with PVI.

6. Summary of new findings

6.1 Systematic review and meta-analysis

1) We reviewed 13 articles (including 1774 patients), which assessed the short-mid and long-term outcome of PVI as sole treatment strategy for a homogenous paroxysmal AF patient population. We performed a meta-analysis by compiling the results of these studies.

2) Pooled analysis showed that 12-and 62-month success rates with a single catheter ablation was 78% (95% CI 0.76% to 0.88%) and 59% (95% CI 0.56% to 0.64%) respectively.

3) The results did not differ by the type of ablation method.

4) A progressive and significant decline in freedom from AF between 1,3 and 5-years after a successful pulmonary vein isolation was detected.

5) While AF recurrence was most frequent within the first 12-months after catheter ablation, a surprisingly high rate of late AF recurrence was observed, which seems unlikely to be correlated to pulmonary vein reconnections.

6.2 Prospective study conducting FIRM- guided ablation with PVI for atrial fibrillation

1) FIRM-mapping offers a novel and feasible technique for identification of RoAc sustaining human AF.

2) Furthermore, this technique provides a patient-tailored, mechanistically focused method for catheter ablation of AF.

3) The major finding of our study is a moderate rate (58%) of persistent AF termination with two distinctive timing pattern following FIRM-guided ablation combined with PVI.

4) The “late-onset termination” of AF is significantly more prevalent in patients during right-sided RoAc ablation.

5) The “abrupt termination” of AF is tended to be more present among patients during PVI. Termination does not depend on whether AF is induced or ongoing at the beginning of the procedure.

7. Acknowledgements

I dedicate this thesis to my beloved Palko who stood by me and strengthened me throughout this adventure.

Many years ago, my scientific interest was triggered by my secondary school biology teacher. The exceptional personality and curiosity of Adrien Lengyel guided me how to think critically and how to be passionate about science. Later, as a medical student at the University of Szeged I had the opportunity to work together with Dr. László Sághy, Dr. Róbert Papp, and Dr. Mária Kohári. It was a wonderful and successful journey, especially when as medical students we won a competition organized for young medical investigators, which was a very determinant moment of my life. The award was handed over by Tamás Szili-Török and I did not dare to dream that this would later lead to an amazing scientific cooperation.

I would like to express my gratitude to Dr. Csaba Földesi, who was my supervisor during my first clinical years. I was always astonished by his sharp mind and excellent memory. I am thankful to Dr. Attila Kardos, it was great to work closely with him. I was amazed by his enthusiasm for science, his “flow” grabbed me, and I loved so much waving with him. I learned from him how crucial it is to base ourselves on original ideas in the scientific clinical field. My gratitude goes to Dr. Andrea Csillik, whose decency, empathy and critical mindset has set me an example to follow. I also would like to express my gratitude to Dr. Zoltán Som whose energy, limitless workload and never-ending support meant me so much. Dr. Péter Ofner deserves my deep gratitude, who supported me to extend my scientific interest and to accept a fellowship program in Rotterdam. I must confess that the books I got from him healed my soul when I felt homesick, and I learnt so much about humanity, science, and friendship from these masterpieces. I would like to express my appreciation to all my colleagues who taught and guided me during my internal medicine and cardiology trainings: Dr. Sarolta Borbás, Dr. Éva Sitkei, Dr. Sándor Kancz, Dr. Attila Mohácsi, Dr. Zsolt Piróth, Dr. Sándor Szőke, Dr. József Ványi, Dr. Mátyás Pál, Dr.Kristóf Zupán, Dr. Gábor Uzonyi, Dr. András Temesvari you all formed my personality and my attitude towards patients and clinical work. My deep gratitude goes to Dr. Péter Andréka for his open-minded feedback and reflections on my professional endeavor and for supporting me on my professional journey abroad.

I would like to express my deepest gratitude to my direct supervisor Dr. Tamás Szili-Török, to whom without a doubt I will always be the most indebted. It was a great honour and life-changing experience to work with him. His support was critical in every aspect of my life in Rotterdam. He was not only an excellent coach in the clinical and scientific work, but also a stable and reliable support in my private life. It is almost impossible to describe the ways in which he has influenced me. He had such a fantastic sense how to motivate me, to balance my weak points and strengthen my positive attribute. He always couraged me to leave my comfort zone and beyond that find the gladness of amendment. He teached me to believe in myself, in our innovative ideas and in our scientific results and teached me how to present them properly. I am deeply grateful for experiencing his excellence, his professionalism, his enthusiasm, his endurance, and his visionary leadership which created an amazing, international, highly outstanding, innovative atmosphere at the Electrophysiology Department in Erasmus MC.

I would like to thank the members of the committees for sacrificing their precious time to evaluate this thesis and to attend in the defence.

My deep gratitude goes to Eszter Martinovits and Renáta Bódi for their active help in organizing all official requirements related to the preparation of this defense. I am very grateful for my international fellow colleagues for the great time we spent together. Astrid A. Hendricks you were the sunshine in the cloudy weekdays. Anne-Marie Noten your endurance in meticulous work, your positive attitude to life was very uplifting for me. Lennart de Vries your tricky questions and good jokes made the challenging periods easier. Mihran Martirosyan my Armenian friend you were such a big gift of this route. Tamás Géczy I owe you a lot! You were my strong support and hold me when needed. It was a short but intensive period we worked together with Rita Gagyi, what an amazing companion you were.

My gratitude goes to all colleagues in the EFO-department: Sing Chien-Yap, Rohit Bhagwandien, Sip Wiljchers you showed me the practice of excellent clinical work. Thank you for your kind support. I would like to express my deep gratitude for Alja Lambers, Peter Ruppersberg introducing me innovative mapping techniques. Their excellent knowledge, their close support and their patience were crucial to complete original research in clinical cardiac electrophysiology. I am deeply grateful for Dominic Theuns, Wichor Bramer, Oscar Franco, Taulant Muka, Melissa Kong whose experience and guidance were essential to conduct our studies properly.

I am so lucky to have had the chance to get to know Rita Szili-Torok. Seeing her everyday life, I understood the meaning of: “Behind every great man (and successful child) there stands a wonderful woman”. It was always so heartwarming when invited me for her Michelin star quality dinner. I am very grateful for Éva Vetró, her friendship was the land under my feet in my adulthood.

It is very difficult to express my feelings in words towards my family. I am desperately grateful for my mum. Despite all obstacles she had to fight, she never stopped supporting my dreams. I will never forget how many books she bought for me to get closer to the knowledge I wanted to own, and afore everyone she believed in me. I am grateful for my father who always supported and at the same time always challenged me. I hope this book will make him proud. I am grateful for my sister just being the one who always completely understood me and also questioned me. I am happy for my brother and thank for his support. I am grateful for my whole family standing next to me and supporting me during this amazing self-discovery journey. My sweethearts, Palkó and Bandi you are All for me. I hope one day you will browse this book proudly.

8. References

[1] January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e151. doi: 10.1161/CIR.0000000000000665. Epub 2019 Jan 28. Erratum in: Circulation. 2019 Aug 6;140(6):e285. PMID: 30686041.

[2] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498. doi: 10.1093/eurheartj/ehaa612. Erratum in: Eur Heart J. 2021 Feb 1;42(5):507. Erratum in: Eur Heart J. 2021 Feb 1;42(5):546-547. Erratum in: Eur Heart J. 2021 Oct 21;42(40):4194. PMID: 32860505.

[3] Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Cosedis Nielsen J, Curtis AB, Davies DW, Day JD, d'Avila A, Natasja de Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T; Document Reviewers:. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018 Jan 1;20(1):e1-e160. doi: 10.1093/europace/eux274. PMID: 29016840; PMCID: PMC5834122.

[4] Murphy NF, Stewart S, Hart CL, MacIntyre K, Hole D, McMurray JJ. A population study of the long-term consequences of Rose angina: 20-year follow-up of the Renfrew-Paisley study. Heart. 2006 Dec;92(12):1739-46. doi: 10.1136/hrt.2006.090118. Epub 2006 Jun 28. PMID: 16807274; PMCID: PMC1861298.

[5] Moser JM, Willems S, Andresen D, Brachmann J, Eckardt L, Hoffmann E, Kuck KH, Lewalter T, Schumacher B, Spitzer SG, Hochadel M, Senges J, Hoffmann BA. Complication Rates of Catheter Ablation of Atrial Fibrillation in Patients Aged ≥75 Years versus <75 Years-Results from the German Ablation Registry. J Cardiovasc Electrophysiol. 2017 Mar;28(3):258-265. doi: 10.1111/jce.13142. Epub 2017 Jan 14. PMID: 27925337.

[6] Kis Z, Muka T, Franco OH, Bramer WM, De Vries LJ, Kardos A, Szili-Torok T.The Short and Long-Term Efficacy of Pulmonary Vein Isolation as a Sole Treatment Strategy for Paroxysmal Atrial Fibrillation: A Systematic Review and Meta-Analysis, Current Cardiology Reviews, 2017, 13, 1-11, doi:10.2174/1573403X13666170117125124.

[7] Kardos A, Kis Z, Som Z, Nagy Z, Foldesi C. Two-Year Follow-Up after Contact Force Sensing Radiofrequency Catheter and Second-Generation Cryoballoon Ablation for Paroxysmal Atrial Fibrillation: A Comparative Single Centre Study. Biomed Res Int. 2016;2016:6495753. doi: 10.1155/2016/6495753. Epub 2016 May 22. PMID: 27314032; PMCID: PMC4893449.

[8] Kis Z, Hendriks AA, Muka T, Bramer WM, Kovacs I, Szili-Torok T. The Role of Atrial Fibrosis Detected by Delayed - Enhancement MRI in Atrial Fibrillation Ablation. Curr Med Imaging Rev. 2020;16(2):135-144. doi: 10.2174/1573405614666180806130327. PMID: 32003313.

[9] Kis Z, Noten AM, Martirosyan M, Hendriks AA, Bhagwandien R, Szili-Torok T. Comparison of long-term outcome between patients aged < 65 years vs. ≥ 65 years after atrial fibrillation ablation. J Geriatr Cardiol. 2017 Sep;14(9):569-574. doi: 10.11909/j.issn.1671-5411.2017.09.004. PMID: 29056955; PMCID: PMC5641644

[10] Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ: Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace 2015; 17:370-378.

[11] Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A, Investigators R-: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. Jama 2014; 311:692-700.

[12] Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. Jama 2005; 293:2634-2640.

[13] Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA, ThermoCool AFTI: Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. Jama 2010; 303:333-340.

[14] Haissaguerre M, Jaïs P, Shah DC: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. … England Journal of … 1998.

[15] Katritsis D, Ellenbogen KA, Giazitzoglou E, Sougiannis D, Paxinos G, Fragakis N, Camm AJ. Clinical outcome of left atrial ablation for paroxysmal atrial fibrillation is related to the extent of radiofrequency ablation. J Interv Card Electrophysiol. 2008 Jun;22(1):31-7. doi: 10.1007/s10840-008-9247-9. Epub 2008 Mar 25. PMID: 18363086.

[16] Jiang RH, Po SS, Tung R, Liu Q, Sheng X, Zhang ZW, Sun YX, Yu L, Zhang P, Fu GS, Jiang CY. Incidence of pulmonary vein conduction recovery in patients without clinical recurrence after ablation of paroxysmal atrial fibrillation: mechanistic implications. Heart Rhythm. 2014 Jun;11(6):969-76. doi: 10.1016/j.hrthm.2014.03.015. Epub 2014 Mar 12. PMID: 24632180.

[17] Zaman JA, Narayan SM. Ablating Atrial Fibrillation: Customizing Lesion Sets Guided by Rotor Mapping. Methodist Debakey Cardiovasc J. 2015 Apr-Jun;11(2):76-81. doi: 10.14797/mdcj-11-2-76. PMID: 26306123; PMCID: PMC4547681.

[18] Dimmer C, Szili-Torok T, Tavernier R, Verstraten T, Jordaens LJ. Initiating mechanisms of paroxysmal atrial fibrillation. Europace. 2003 Jan;5(1):1-9. doi: 10.1053/eupc.2002.0273. PMID: 12504634.

[19] Kis Z, Theuns DA, Bhagwandien R, Wijchers S, Yap SC, Szili-Torok T. Type and rate of atrial fibrillation termination due to rotational activity ablation combined with pulmonary vein isolation. J Cardiovasc Electrophysiol. 2017 Aug;28(8):862-869. doi: 10.1111/jce.13240. Epub 2017 Jun 21. PMID: 28471019.

[20] Elisabeth Noten AM, Kis Z, Akca F, Bhagwandien R, Wijchers S, Yap SC, Szili-Torok T. Robotic navigation shows superior improvement in efficiency for atrial fibrillation ablation. J Atr Fibrillation. 2019 Feb 28;11(5):2108. doi: 10.4022/jafib.2108. PMID: 31139295; PMCID: PMC6533826.

[21] Kis Z, Noten AME, Wijchers S, Bhagwandien R, Szili-Torok T. Left-sided phrenic nerve injury during redo pulmonary vein isolation long after a previous contralateral self-limiting phrenic nerve palsy. Clin Case Rep. 2019 Jun 11;7(7):1391-1394. doi: 10.1002/ccr3.2199. PMID: 31360495; PMCID: PMC6637336.

[22] Szili-Torok T, Kis Z, Bhagwandien R, Wijchers S, Yap SC, Hoogendijk M, Dumas N, Haeusser P, Geczy T, Kong MH, Ruppersberg P. Functional electrographic flow patterns in patients with persistent atrial fibrillation predict outcome of catheter ablation. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2148-2158. doi: 10.1111/jce.15115. Epub 2021 Jun 7. PMID: 34041824; PMCID: PMC8453922.

[23] Benharash P, Buch E, Frank P, Share M, Tung R, Shivkumar K, Mandapati R: Quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation. Circ Arrhythm Electrophysiol 2015; 8:554-561.

[24] Narayan SM, Baykaner T, Clopton P, Schricker A, Lalani GG, Krummen DE, Shivkumar K, Miller JM: Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). J Am Coll Cardiol 2014; 63:1761-1768.

[25] Shivkumar K, Ellenbogen KA, Hummel JD, Miller JM, Steinberg JS: Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: First multicenter experience of focal impulse and rotor modulation (FIRM) ablation. J Cardiovasc Electrophysiol 2012; 23:1277-1285.

[26] Miller JM, Kowal RC, Swarup V, Daubert JP, Daoud EG, Day JD, Ellenbogen KA, Hummel JD, Baykaner T, Krummen DE, Narayan SM, Reddy VY, Shivkumar K, Steinberg JS, Wheelan KR: Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: Multicenter FIRM registry. J Cardiovasc Electrophysiol 2014; 25:921-929.

[27] Hartung J, Knapp G, Sinha BK. Statistical meta-analysis with applications: John Wiley Sons 2011.

[28] Narayan SM, Krummen DE, Rappel WJ: Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol 2012; 23:447-454.
[29] Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM: Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012; 60:628-636.
[30] Schricker AA, Zaman J: Role of Rotors in the Ablative Therapy of Persistent Atrial Fibrillation. Arrhythm Electrophysiol Rev 2015; 4:47-52.
[31] Walters TE, Kalman JM: Human persistent atrial fibrillation is maintained by rotors: the jury is still out. Circ Arrhythm Electrophysiol 2015; 8:517-519.
[32] Shah AN, Mittal S, Sichrovsky TC, Cotiga D, Arshad A, Maleki K, et al. Long-term outcome following successful pulmonary vein isolation: Pattern and prediction of very late recurrence. J Cardiovasc Electrophysiol 2008; 19: 661-667.
[33] Fiala M, Chovančík J, Nevřalová R, Neuwirth R, Jiravský O, Nykl I, et al. Pulmonary vein isolation using segmental versus electroanatomical circumferential ablation for paroxysmal atrial fibrillation: Over 3-year results of a prospective randomized study. J Intervent Card Electrophysiol 2008; 22: 13-21.
[34] Katritsis D, Ellenbogen KA, Giazitzoglou E, Sougiannis D, Paxinos G, Fragakis N, et al. Clinical outcome of left atrial ablation for paroxysmal atrial fibrillation is related to the extent of radiofrequency ablation. J Intervent Card Electrophysiol 2008; 22: 31-37.
[35] Katritsis D, Wood MA, Giazitzoglou E, Shepard RK, Kourlaba G, Ellenbogen KA. Long-term follow-up after radiofrequency catheter ablation for atrial fibrillation. Europace 2008; 10: 419-424.
[36] Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK. Five-Year Outcomes After Segmental Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation. Am J Cardiol 2009; 104: 366-372.
[37] Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: Lessons from a 5-year follow-up. Circulation 2010; 122: 2368-2377.
[38] Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol 2008; 52: 273-278.
[39] Neumann T, Wójcik M, Berkowitsch A, Erkapic D, Zaltsberg S, Greiss H, et al. Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success. Europace 2013; 15: 1143-1149.
[40] Wojcik M, Berkowitsch A, Zaltsberg S, Hamm CW, Pitschner HF, Neumann T, et al. Cryoballoon ablation in young patients with lone paroxysmal atrial fibrillation. Rev Esp Cardiol (Engl) 2014; 67: 558-563.
[41] Rao JY, Chierchia GB, De Asmundis C, Casado-Arroyo R, Overeinder I, Sarkozy A, et al. Cryoballoon ablation as index procedure for paroxysmal atrial fibrillation: Long-term results from a single center early experience. J Cardiovasc Med 2014; 15: 194-198.
[42] Metzner A, Reissmann B, Rausch P, Mathew S, Wohlmuth P, Tilz R, et al. One-year clinical outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon. Circ Arrhythmia Electrophysiol 2014; 7: 288-292.
[43] Metzner A, Heeger CH, Wohlmuth P, Reissmann B, Rillig A, Tilz RR, et al. Two-year outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon: lessons from the bonus freeze protocol. Clin Res Cardiol 2015.

[44] Bohó A, Mišíková S, Spurný P, Komanová E, Kerekanič M, Hudák M, et al. A long-term evaluation of cryoballoon ablation in 205 atrial fibrillation patients: a single center experience. Wien Klin Wochenschr 2015; 127: 779-785.
[45] Kis Z, Bhagwandien R, Nieman K, Wijchers S, Szili-Torok T: Left atrial appendage thrombus formation during atrial fibrillation ablation under sufficient heparinization. Europace 2016.
[46] Wellens HJ. Forty years of invasive clinical electrophysiology: 1967-2007. Circ Arrhythm Electrophysiol 2008; 1: 49-53.
[47] Zaman JA, Narayan SM. Ablating Atrial Fibrillation: Customizing Lesion Sets Guided by Rotor Mapping. Methodist Debakey Cardiovasc J 2015; 11: 76-81.
[48] Jiang RH, Po SS, Tung R, Liu Q, Sheng X, Zhang ZW, et al. Incidence of pulmonary vein conduction recovery in patients without clinical recurrence after ablation of paroxysmal atrial fibrillation: Mechanistic implications. Heart Rhythm 2014; 11: 969-976.
[49] Dimmer C, Szili-Torok T, Tavernier R, Verstraten T, Jordaens LJ. Initiating mechanisms of paroxysmal atrial fibrillation. Europace 2003; 5: 1-9.
[50] Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, et al. Long-term outcomes of catheter ablation of atrial fibrillation: A systematic review and meta-analysis. J Am Heart Assoc 2013; 2.
[51] Katritsis D, Ellenbogen KA, Camm AJ. Recurrence of left atrium-pulmonary vein conduction following successful disconnection in asymptomatic patients. Europace 2004; 6: 425-432.
[52] Lemola K, Hall B, Cheung P, Good E, Han J, Tamirisa K, et al. Mechanisms of recurrent atrial fibrillation after pulmonary vein isolation by segmental ostial ablation. Heart Rhythm 2004; 1: 197-202.
[53] Lemola K, Oral H, Chugh A, Hall B, Cheung P, Han J, et al. Pulmonary vein isolation as an end point for left atrial circumferential ablation of atrial fibrillation. J Am Coll Cardiol 2005; 46: 1060-1066.
[54] Hansen BJ, Zhao J, Csepe TA, Moore BT, Li N, Jayne LA, Kalyanasundaram A, Lim P, Bratasz A, Powell KA, Simonetti OP, Higgins RS, Kilic A, Mohler PJ, Janssen PM, Weiss R, Hummel JD, Fedorov VV: Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. Eur Heart J 2015; 36:2390-2401.
[55] Li N, Csepe TA, Hansen BJ, Sul LV, Kalyanasundaram A, Zakharkin SO, Zhao J, Guha A, Van Wagoner DR, Kilic A, Mohler PJ, Janssen PM, Biesiadecki BJ, Hummel JD, Weiss R, Fedorov VV: Adenosine-Induced Atrial Fibrillation: Localized Reentrant Drivers in Lateral Right Atria due to Heterogeneous Expression of Adenosine A1 Receptors and GIRK4 Subunits in the Human Heart. Circulation 2016; 134:486-498.
[56] Tilz RR, Lin T, Rillig A, Heeger CH, Scholz L, Wohlmuth P, Bucur T, Metzner A, Mathew S, Wissner E, Ouyang F, Kuck KH: Focal Impulse and Rotor Modulation for the Treatment of Atrial Fibrillation: Locations and 1 Year Outcomes of Human Rotors Identified Using a 64-Electrode Basket Catheter. J Cardiovasc Electrophysiol 2016.
[57] Spitzer SG, Karolyi L, Rammler C, Scharfe F, Weinmann T, Zieschank M, Langbein A: Treatment of Recurrent Nonparoxysmal Atrial Fibrillation Using Focal Impulse and Rotor Mapping (FIRM)-Guided Rotor Ablation: Early Recurrence and Long-Term Outcomes. J Cardiovasc Electrophysiol 2017; 28:31-38.
[58] Sommer P, Kircher S, Rolf S, John S, Arya A, Dinov B, Richter S, Bollmann A, Hindricks G: Successful Repeat Catheter Ablation of Recurrent Longstanding Persistent Atrial Fibrillation With Rotor Elimination as the Procedural Endpoint: A Case Series. J Cardiovasc Electrophysiol 2016; 27:274-280.

[59] Narayan SM, Krummen DE: Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and …: Am Coll Cardio Found, 2012,
[60] Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K: Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience. Heart Rhythm 2015.

9. Suppplements

Supplement 1: Quality of Included Studies Assessed by using Newcastle-Ottawa Quality Scale for Cohort Studies

Author, Year (Reference)	**Selection**				**Comparability of Cohorts**	**Outcome**		
	Representativeness of Exposed Cohort	Representativeness of the Non-exposed Cohort	Ascertainment of Exposure	Outcome not Present at the Beginning of Study		Assessment of Outcome	Was follow-up long enough?	Adequacy of Follow-up
Shah, 2007 (16)	*	NA	*	*	**	*	*	*
Katritris, 2008 (18)	*	NA	*	*	**	*	*	*
Katritris, 2008 (19)	*	NA	*	*	0	*	*	*
Sawhney, 2009 (20)	*	NA	*	*	**	*	*	*
Ouyang, 2010 (21)	*	NA	*	*	0	*	*	*
Neumann, 2008 (22)	*	NA	*	*	**	*	*	*
Neumann, 2013 (23)	*	NA	*	*	**	*	*	*
Wojczik, 2013 (24)	*	NA	*	*	0	*	*	*
Rao, 2013 (25)	*	NA	*	*	0	*	*	*
Metzner, 2014 (26)	*	NA	*	*	0	*	*	*

Metzner, 2015 (27)	*	NA	*	*	0	*	*	*
Bohó, 2015 (28)	*	NA	*	*	**	*	*	*

NA=not applicable, A study can recieve a maximum of 1 star for each numbered item within the selection and outcome categories, A maximum of 2 star can be given for comparability, O:no star can be given

Supplement 2: Quality of Included Studies Assessed by using the Newcastle-Ottawa Quality Scale for Cohort Studies

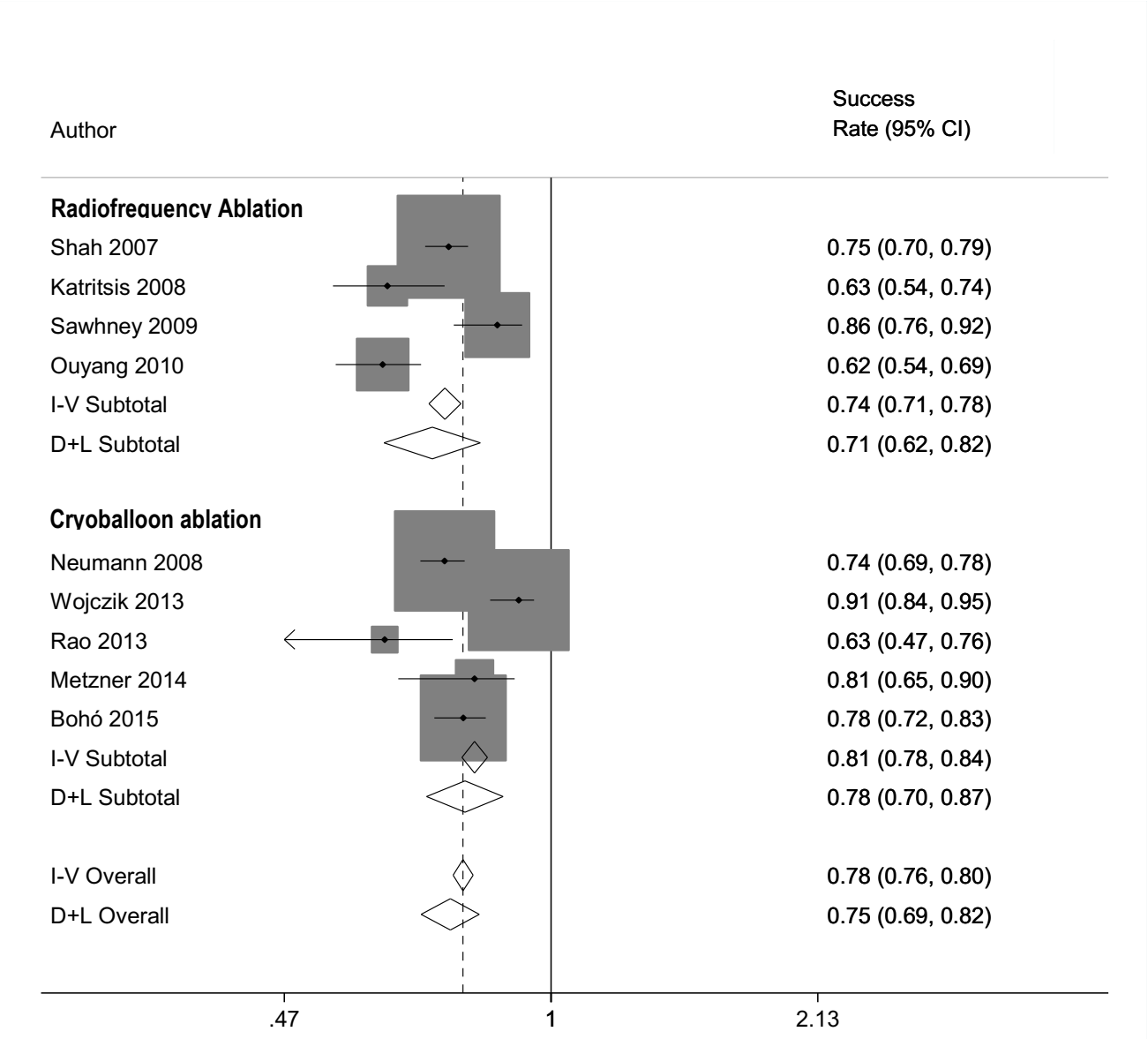
	Stars (n)		
Author, Year (Reference)	Selection	Comparability	Exposure
Shah, 2007 (16)	3	2	3
Katritris, 2008 (18)	3	2	3
Katritris, 2008 (19)	3	0	3
Sawhney, 2009 (20)	3	2	3
Ouyang, 2010 (21)	3	0	3
Neumann, 2008 (22)	3	2	3
Neumann, 2013 (23)	3	2	3
Wojczik, 2013 (24)	3	0	3
Rao, 2013 (25)	3	0	3
Metzner, 2014 (26)	3	0	3
Metzner, 2015 (27)	3	0	3
Bohó, 2015 (28)	3	2	3

n=number

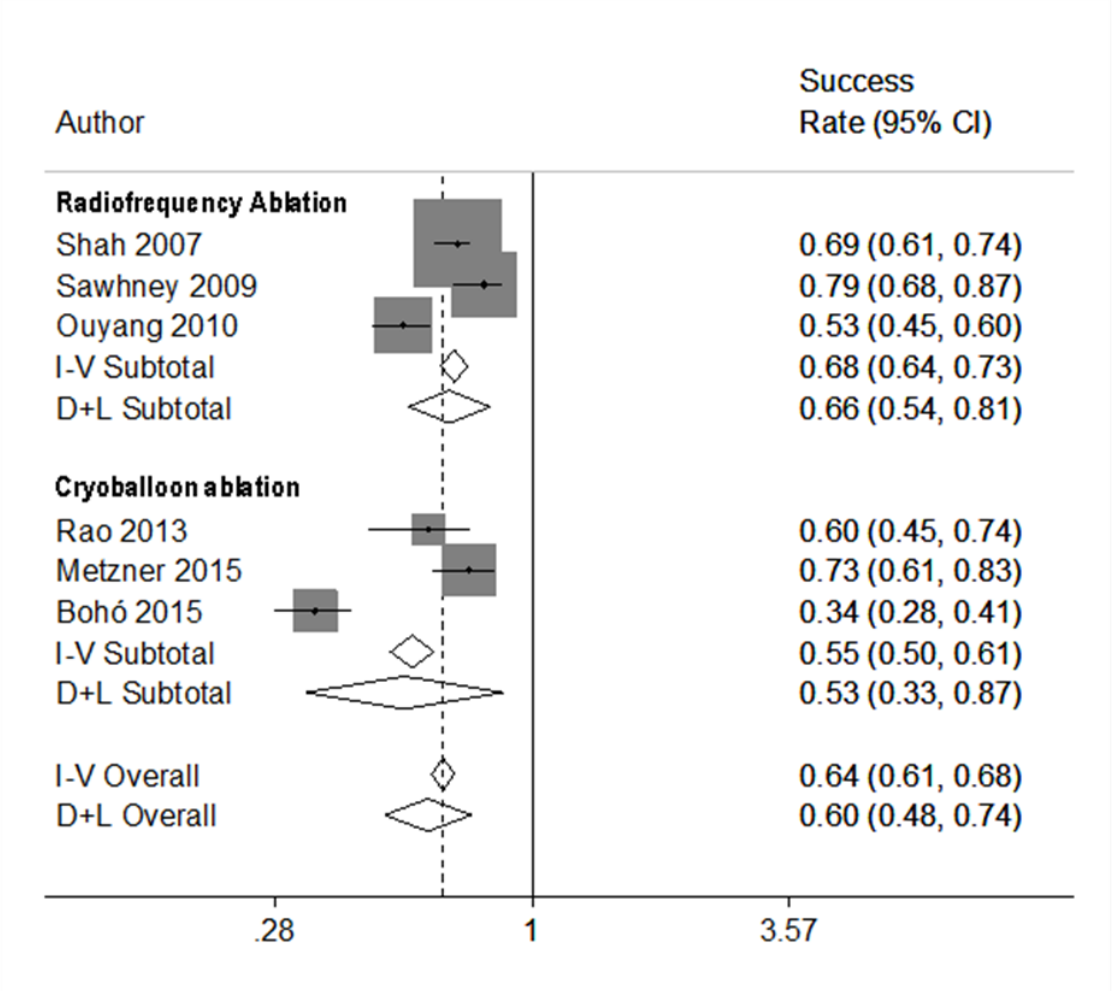
Supplement 3: Quality assessment of the included randomized controlled study using the Cochrane Collaboration's tool

Author, Year (Reference)	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessments**	**Incomplete outcome data**	**Selective reporting**	**Other bias**
Fiala, 2008 (17)	Low	Unclear	Low	Unclear	Low	Low	Unclear

Supplemental Figure 1 S1.: 12-month success rate by type of ablation

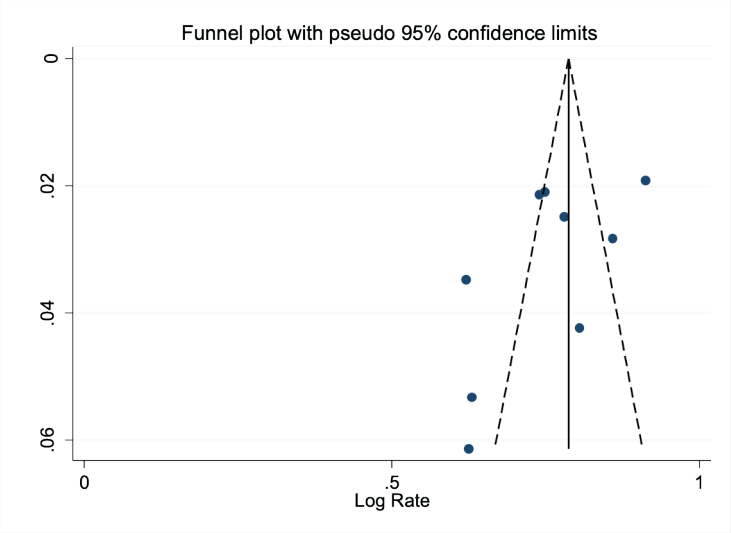


Supplement Figure 2 S2: 62-months success rate by type of ablation

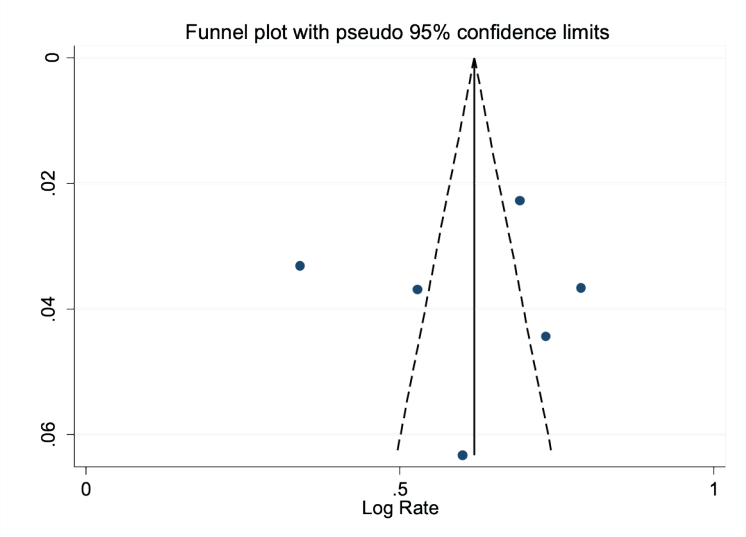


Supplemental Figure 3 S3.: FOREST PLOT

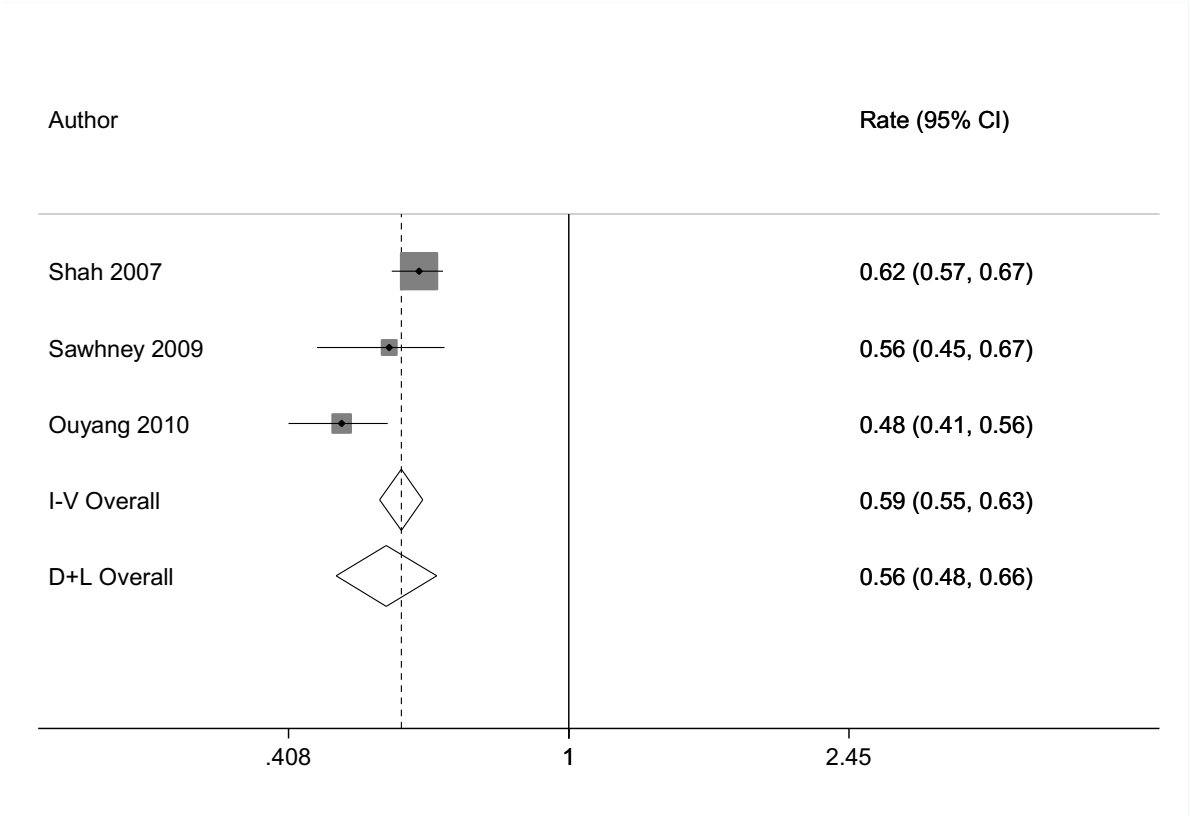
12- month success rate (Egger's P=0.036) P=0.86)



24 -month success rate (Egger's P=0.86)



Supplemental Fig 4 S4.: 48-month success rate of pulmonary vein isolation



Assessment of heterogeneity, X2=7.5, I2=73.3%; P =0.024.

10. Appendix

Appendix 1. PRISMA checklist

Section/topic	#		Reported on page #
TITLE			
Title	1	Identify the report as a systematic review and a meta-analysis	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 and Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review)	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Appendix 4, Suppl. 1, 2,3

Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6,7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Suppl. Fig. 1,2
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1,2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl.1-3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11, Suppl. Fig 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl1, 2,3

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Suppl. Fig. 1, 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-14 Fig. 2, 3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Appendix 2.: MOOSE checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Pulmonary vein isolation(PVI) for paroxysmal atrial fibrillation (PAF) is a worldwide method of catheter ablation treatment. However, little work has been done to systematically review the current literature on the long-term outcome of paroxysmal atrial fibrillation patients after only-pulmonary vein isolation procedure.
√	Hypothesis statement	The exclusive usage of pulmonary vein isolation ablation methodology provides a low long-term rate of freedom from atrial fibrillation.
√	Description of study outcomes	We included studies that estimated the short, mid-, and long-term outcome data of paroxysmal atrial fibrillation patients who underwent pulmonary vein isolation as a sole ablation strategy.
√	Type of exposure or intervention used	Two type of catheter ablation techniques were assessed: cryoballoon and radiofrequency ablation.
√	Type of study designs used	Eligible study designs included randomized controlled trials (RCTs), cohort, case-control studies.
√	Study population	Only studies carried out in adults (>18 years old) were included.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the investigators are indicated in the authors list.
√	Search strategy, including time period included in the synthesis and keywords	Search strategy and time periods are detailed in page 4 of the manuscript and in Figure 1 and the full search strategy is available in Appendix 1.
√	Databases and registries searched	Medline, Embase and Google Scholar, Web-of-Science, Cochrane Central, PubMed
√	Search software used, name and version, including special features	We did not employ a search software. Endnote was used to merge retrieved citations and eliminate duplications.

√	Use of hand searching	We hand-searched bibliographies of retrieved systematic reviews and meta-analysis for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. Citations for the included studies are included in the text and table 1. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed restrictions to English language.
√	Method of handling abstracts and unpublished studies	Systematic reviews were used to identify further references.
√	Description of any contact with authors	Authors of included studies were contacted to retrieve missing full texts and to identify any missing studies.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	A predesigned data collection form was prepared to extract the relevant information from the included full texts, including study design, type of atrial fibrillation, type of catheter ablation, exclusive pulmonary vein isolation methodology
√	Assessment of confounding	We performed qualitative analyses to evaluate differences between studies.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case-control and cohort studies included in this review. The Cochrane Collaboration`s tool was used for randomized controlled studies.
√	Assessment of heterogeneity	We were able to pool the data visually and statistically.
√	Description of statistical methods in sufficient detail to be replicated	We conducted qualitative analysis of the data. Due to large heterogeneity between studies we solely performed qualitative analyses of the data.

√	Provision of appropriate tables and graphics	We included 1 main figure, 4 main tables, and 4 appendices, 2 supplements
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2, 3
√	Table giving descriptive information for each study included	Tables 1 and 2
√	Results of sensitivity testing	Supplemental Fig. 1, 2
√	Indication of statistical uncertainty of findings	95% confidence intervals or SD's were presented if available
Reporting of discussion should include		
√	Quantitative assessment of bias	Not applicable
√	Justification for exclusion	We excluded studies that had no or unclear definition of outcome, or data extraction was not feasible.
√	Assessment of quality of included studies	We used the Newcastle- Ottawa Scale (NOS) to evaluate the quality of cross-sectional, case-control and cohort studies included in this review.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Due to the lack of standardisation of follow-up, it is difficult to provide unifying statements within a larger number of manuscripts hampered by large levels of heterogeneity.
√	Generalization of the conclusions	The generalizability of our findings has been enhanced by the involvement of data, including region of the Americas, Europe. However, there is a clear lack of evidence from West Pacific Region, and the African and Asian, Australian Region.

√	Guidelines for future research	Further work is necessary to standardize the follow-up of paroxysmal atrial fibrillation patients who underwent pulmonary vein isolation.
√	Disclosure of funding source	Nothing to disclose.

Appendix 3.: Data searching setting.

Embase.com 1700

('paroxysmal atrial fibrillation'/exp OR (((paroxysmal*) AND (atrial OR atrium OR auricular) NEAR/3 fibrillation)):ab,ti) AND ('ablation therapy'/de OR 'catheter ablation'/de OR 'cryoablation'/de OR 'radiofrequency ablation'/de OR 'pulmonary vein isolation'/de OR 'radiofrequency'/de OR (ablation* OR radiofrequenc* OR cryoablation* OR cryoblation* OR cryoballoon* OR (cryo NEXT/1 balloon*) OR (pulmonar* NEAR/3 isolat*)):ab,ti) AND ('follow up'/exp OR 'longitudinal study'/de OR 'cohort analysis'/de OR 'long term survival'/de OR 'retrospective study'/de OR 'prospective study'/de OR ((follow* NEXT/1 up*) OR followup* OR longitudinal* OR cohort* OR (long* NEXT/1 term*) OR retrospectiv* OR prospectiv*):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

Medline (ovid) 1313

(("atrial fibrillation"/ AND "Tachycardia, Paroxysmal"/) OR (((paroxysmal*) AND (atrial OR atrium OR auricular) ADJ3 fibrillation)).ab,ti.) AND ("Ablation Techniques"/ OR "Catheter Ablation"/ OR (ablation* OR radiofrequenc* OR cryoablation* OR cryoblation* OR cryoballoon* OR (cryo ADJ balloon*) OR (pulmonar* ADJ3 isolat*)).ab,ti.) AND (exp "Cohort Studies"/ OR ((follow* ADJ up*) OR followup* OR longitudinal* OR cohort* OR (long* ADJ term*) OR retrospectiv* OR prospectiv*).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

Cochrane 286

((((paroxysmal*) AND (atrial OR atrium OR auricular) NEAR/3 fibrillation)):ab,ti) AND ((ablation* OR radiofrequenc* OR cryoablation* OR cryoblation* OR cryoballoon* OR (cryo NEXT/1 balloon*) OR (pulmonar* NEAR/3 isolat*)):ab,ti) AND (((follow* NEXT/1 up*) OR followup* OR longitudinal* OR cohort* OR (long* NEXT/1 term*) OR retrospectiv* OR prospectiv*):ab,ti)

Web-of-science 1520

TS=(((((paroxysmal*) AND (atrial OR atrium OR auricular) NEAR/2 fibrillation))) AND ((ablation* OR radiofrequenc* OR cryoablation* OR cryoblation* OR cryoballoon* OR (cryo NEAR/1 balloon*) OR (pulmonar* NEAR/2 isolat*))) AND (((follow* NEAR/1 (up OR ups)) OR followup* OR longitudinal* OR cohort* OR (long* NEAR/1 term*) OR retrospectiv* OR prospectiv*))) AND DT=(article)

PubMed publisher 62

(("atrial fibrillation"[mh] AND "Tachycardia, Paroxysmal"[mh]) OR (((paroxysmal*[tiab]) AND (atrial OR atrium OR auricular) AND fibrillation))) AND ("Ablation Techniques"[mh] OR "Catheter Ablation"[mh] OR (ablation*[tiab] OR radiofrequenc*[tiab] OR cryoablation*[tiab] OR cryoblation*[tiab] OR cryoballoon*[tiab] OR (cryo balloon*[tiab]) OR (pulmonar*[tiab] AND isolat*[tiab]))) AND ("Cohort Studies"[mh] OR ((follow up*[tiab]) OR followup*[tiab] OR longitudinal*[tiab] OR cohort*[tiab] OR (long

Appendix 4.: Newcastle- Ottawa Quality Assessment Scale

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is definition of NCDs adequate?
   a) Yes, according to a clear and widely used definition *****
   b) Yes, e.g. record linkage or based on self-reports
   c) No description
2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases *****
   b) Excluded cases are random *****
   c) No description of the excluded cases or potential for selection biases or not stated
3) Comparison with a reference group
   a) The results are compared with a reference from community or with the status of the cases prior to the disease *****
   b) The results are compared with the results from other patients
   c) No description/no comparison available
4) Definition of reference
   a) Individuals with no NCD or sample from general population or the same individuals before NCD suffering*****
   b) Non community comparator is described
   c) No description of source

Comparability

1) Comparability of the results on the basis of the design or analysis
   a) The results are described in age and sex sub groups (sex is not applicable for female diseases) *****
   b) The results are additionally adjusted for/described in different socioeconomic factors or disease related confounders*****

Exposure (costs, productivity, households)

1) Ascertainment of exposure
   a) Secure record (e.g. surgical records, hospital records, and administrative records, national…) *****
   b) Structured interview where blind to case/control status *****
   c) Interview not blinded to case/control status
   d) Written self-report or medical record only
   e) No description
2) Same method of ascertainment for NCDs and comparators
   a) Yes *****
   b) No
   c) No comparator group exist
2) Non-Response rate
   a) All participants included or same rate for both groups or respondents and non-respondents have the same characteristics*****
   b) Non respondents described
   c) Rate different and no designation
   d) Response rate not descriptive