Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis

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Abstract

Context Transcatheter ablation of atrial fibrillation (AF) has undergone important development, with acceptable midterm results in terms of the safety and recurrence. A meta-analysis was performed to identify the periprocedural complications, midterm success rates and predictors of recurrence after AF ablation.

Methods and results 4357 patients with paroxysmal AF, 1083 with persistent AF and 1777 with long standing AF were included. The pooled analysis showed that there was an in-hospital complication rate of tamponade requiring drainage of 0.99% (0.44–1.54; CI 99%), stroke with neurological persistent impairment of 0.22% (0.04–0.47; CI 99%), and stroke without of 0.36% (0.03–0.70; CI 99%) After a follow up of 22 (13–28) months and 1.23 (1.19–1.5; CI 99%) procedures per patient, the AF recurrence rate was 31.20% (24.87–34.81; CI 99%). The persistent AF patients exhibited a greater risk of recurrence after the first ablation (OR 1.78 [1.14, 2.77] CI 99%), but a trend towards non significance was present in the patients with more than one procedure (OR 1.69 [0.95, 3.00] CI 99%). The most powerful predictors of an AF ablation failure in the overall population were a recurrence within 30-days (OR 4.30; 2.00–10.80), valvular AF (OR 5.20; 2.22–9.50) and a left atrium diameter of more than 50 mm (OR 5.10 2.00–12.90; all CI 95%).

Conclusions Persistent AF remains burdened from higher recurrence rates, however not so following redo-procedures. Three predictors, valvular AF, a left atrium diameter longer than 50 mm and recurrence within 30 days, could be appraised to drive selection of patients and therapeutic strategy.

1.Introduction

Transcatheter atrial fibrillation (AF) ablation (TCAFA) is usually undertaken in patients with symptomatic episodes of AF resistant to at least one anti-arrhythmic drug. Multiple single center randomized studies and multicenter prospective registries comparing anti-arrhythmic drug therapy with TCAFA have shown significantly higher rates of patients in sinus rhythm after an invasive strategy at one year of follow up [1], [2], [3], [4], [5] and [6].

Many observational studies have reported predictors identified by multivariate analyses including the time spent in persistent AF, structural heart disease, left ventricular impairment, and, perhaps most consistently, the left atrial diameter [7]; in the case in which they were confirmed in larger datasets these clinical features could be very useful for cardiologists and general clinicians both for a correct selection of patients deferred to an invasive strategy and to accurately manage the following procedure. However, to the best of our knowledge, no meta-analyses have been performed to appraise the results of real life observational studies of AF ablation, and their complication rates and the most powerful predictors of recurrence.

2.Methods

The present research was elaborated according to current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, and recommendations from the Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [8], [9], [10] and [11].

2.1. Search strategy and study selection

Medline, the Cochrane Library and Biomed Central were searched for related articles, according to the established methods [12], with terms related to catheter ablation of AF and predictors of recurrence obtained through multivariate analyses. All corresponding authors of the studies were directly emailed for further data and suggestions for additional research [13].

All citations at the abstract level were first appraised by independent reviewers (G.B.-Z, F.DA.) with divergences resolved by consensus. If potentially pertinent, they were then evaluated as complete reports according to the following explicit selection criteria. The inclusion criteria were (all had to be met for inclusion): (i) studies investigating patients undergoing catheter ablation of AF, (ii) reporting predictors of recurrence obtained through multivariate analyses, and (iii) reporting at least 50 patients with recurrence following TCAFA. Exclusion criteria were (any one alone was enough for exclusion): (i) a non-human setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients was included) or (iii) selected patients undergoing AF ablation or ablation techniques reported in only one study.

2.2. Data extraction

Two unblinded independent reviewers (G.B.-Z, F.DA.) extracted the following data on pre-specified forms: authors, journal, year of publication, location of the study group, baseline features, recurrence rates, percentage of complications, and multivariate predictors (point summary estimate of risk, with 99% confidence interval). The end-points of interest were the incidence of in-hospital AF complications, long-term recurrence, multivariate risk for recurrence according to the AF type, and adjusted predictors for recurrence.

2.3. Internal validity and quality appraisal

Unblinded independent reviewers (G.B.-Z, F.DA.) evaluated the quality of the studies included on pre-specified forms. We modified the MOOSE items to take into account the specific features of the studies included [10], and separately extracted and appraised the study design, setting, data source, and statistical methods for the multivariable analyses, as well as the risk of analytical,

selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to the inability to ascertain the underlying risk of bias).

2.4. Data analysis and synthesis

Continuous variables are reported as the mean (standard deviation) or median (range). Categorical variables are expressed as n/N (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). Small study bias was appraised by graphical inspection of the funnel plots. Standard hypothesis testing was set at a two-tailed 0.05 level. The Null hypothesis of statistical homogeneity was refused for a $p < 0.10$ in the Cochran Q test, with I [2] values of around 25%, 50%, and 75% representing, respectively, mild, moderate, and extensive statistical inconsistency.

3. Results

From the 3475 citations first screened, 27 complete reports were evaluated for inclusion in the present research and finally 19 studies were included in the review [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32] and [33] (Fig. 1). One study was excluded because it included patients with hypertrophic cardiomyopathy [35], one because it appraised robotic navigation [34], 4 for duplicate reporting [36], [37], [38] and [39], and one because it included only female patients [40]. The research ended on the 4th of October, 2011.

4357 patients with paroxysmal AF, 1083 with persistent AF and 1777 with long standing AF were included. They were 77% male, (72–81; CI 95%), with an age of 57 years (56–66; CI 95%) and a time from the first AF recording of 60 (48–72; CI 95%) months; the left atrium area and volume were 22 cm2 (22–23; CI 95%) and 90 cm3 (78–116; CI 95%), respectively (Table 1). Concerning the interventional features, additional linear lesions (LLS) were performed in 27% (24–51; CI 95%) and ablation of complex fractionated atrial electrograms (CFAEs) in 15% (14–21; CI 95%) (Table 2). In 6 studies the patients underwent only one ablation procedure; additional linear lesions were performed in 22% (0–44; CI 95%) and a CFAE ablation in 10% (6.5%–14%; CI 95%). In the 12 studies in which more than one procedure was undertaken, LLS were performed in 41% (36–47; CI 95%) and a CFAE ablation in 42% (22–42; CI 95%). The pooled analysis showed that there was an in-hospital complication rate of tamponade requiring drainage of 0.99% (0.44–1.54; CI 99%), stroke with neurological persistent impairment of 0.22% (0.04–0.47; CI 99%), and stroke without of 0.36% (0.03–0.70; CI 99%) (Fig. 2). After a follow up of 22 (13–28) months and 1.23 (1.19–1.5; CI 99%) procedures per patient, the AF recurrence rate was 31.20% (24.87–34.81; CI 99%). After including only the studies with a follow up longer than 30 months [18], [26], [30] and [31] (39; 30–48; CI 99%) the rate of recurrence was of 33.97% (32.11, 37.83; CI 99%). The persistent AF patients exhibited a greater risk of recurrence after the first ablation (OR 1.78 [1.14, 2.77] CI 99%), but not so in the patients with more than one procedure (OR 1.69 [0.95, 3.00] CI 99%) (Fig. 3 and Fig. 4). As demonstrated in Table 3 and Fig. 5, the most powerful predictors of an AF ablation failure in the overall population were a recurrence within 30-days (OR 4.30; 2.00–10.80; CC 95%), valvular AF (OR 5.20; 2.22–9.50; CI 95%) and a left atrium diameter of more than 50 mm (OR 5.10 2.00–12.90; CI 95%). The main methodological features of the studies included are reported in Table A (Appendix, web only). Most of the reports were retrospective, and performed in one center; 8697 patients with AF, 4857 patients with paroxysmal AF, 1183 with persistent AF and 2257 with long standing AF were included. Cox proportional hazard models were the most frequent multivariable

approach used, with a substantially low risk of an assessment bias. Definitions of recurrence, of blanking period, of antiarrhythmics and of anticoagulation management showed low heterogeneity (Table C, Appendix, web only): in most of the studies recurrence was defined as AF or atrial tachycardia lasting more than 30 s, while antiarrhythmic drugs were more frequently maintained for 3 months and then discontinued if sinus rhythm was obtained. Anticoagulation strategy was usually tailored according to risk factors for cerebral ischemic events.

4. Discussion

The main results of the present work were: a) AF ablation procedures remain burdened with in-hospital complications, although infrequent in experienced centers, b) TCAFA ablation obtains satisfactory midterm success rates, c) the success following redo procedures did not differ between paroxysmal and persistent AF, and d) valvular AF, a left atrium diameter of more than 50 mm and recurrence within 30 days, could help to better tailor the clinical and interventional strategies.

The overall symptomatic complication rate of radiofrequency AF ablation in our meta-analysis was lower than that reported in the recent surveys. In a recent world survey by Cappato et al. [8] a major complication occurred in 4.5% of the study subjects: there were 0.15% procedure-related deaths and 0.04% atrium-esophageal fistulae. These data were reported from 8 studies with 3011 patients, and this difference is most probably explained by the level of experience of the high volume centers included. Moreover catheter ablation of AF has been a rapidly evolving technique, and data collected between 2003 and 2006 may have been out of date by 2011. We described the incidence of complications affecting the in-hospital management, in order to clearly discriminate between cardiac tamponade needing and not needing drainage, and strokes without and with neurological impairment, the latter being the most feared but really uncommon complication of TCAFA.

By the mid-term follow up, AF ablation offered freedom from arrhythmias in more than two thirds of the patients. Persistent AF type represented a predictor of redo after a single procedure, while a trend was present towards no significance after redo procedures. Both in the registry of Cappato et al. [8] and the meta-analysis of Balk et al. [41], significant differences according to the AF type were reported, probably because of a lack of a separate appraisal for the results after a single and after redo procedures. This represents an important finding: actually more aggressive interventional strategies [42] and [43] used in patients with persistent AF may reduce the unfavorable outcomes related to the atrial pattern or the patients' baseline features.

The two most challenging aspects of AF management are to obtain a correct timing of the TCAFA and an accurate management of the anticoagulant drugs after the procedures. In the overall population, early recurrence, the presence of more than a mild valvular defect and the left atrium diameter dimension were proven to be the most powerful predictors. The latter are simple and easy to assess prognostic factors, thus allowing an accurate management of these patients.

Our study demonstrates the prognostic negative impact of early recurrence on AF results. The latter was traditionally seen as a “benign” process [44], not affecting long term results. In most of the studies included (Table C) early recurrences were not appraised, because of a blanking period ranging from 4 to 12 weeks. 2 studies, on the contrary, reported that early AT (atrial tachycardia)/AF recurrences represent a risk factor for long term success. The pathophysiological process relates to the proinflammatory effect leading to cellular dysfunction, which is a potential pro-arrhythmogenic trigger [44]. The long term negative impact probably derives from the counterbalance between the reduced vagal activity due to AF ablation and the phenomenon of scar consolidation [[45] and [46]]. Early recurrences should however been evaluated in the management of patients after AF ablation, to correctly manage the risk-benefit or a second procedure.

The present work had several limitations. First, the data about the prevalence were limited to a small subset of patients because of our strategy to include studies that used multivariate analyses to define the predictors; on the other hand a full representation of the results of the AF ablation in centers with high volumes was offered. Prospective studies would give a different perspective as they would use pre-defined parameters, yet the present approach projects a wider perspective across the existing literature, with an overall good quality of included ones (Table A, Appendix). Second, no pooling was made of the predictors; as the most frequent predictors are not necessarily the most powerful ones, a bias would have been created in selecting the ones that were most often reported [47]. The funnel plot (Fig. A, Appendix) is skewed toward showing only the more precise larger studies. Another limitation was that the patient-level data were not used, but again we would have lost many studies if we included that, and thus would have limited the accuracy of the present work. Moreover we appraised a random effect even if the inconsistency was 0%.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Dr. D'Ascenzo conceived the project, and performed the literature search with Dr. Corleto and the analysis with Dr. Biondi-Zoccai. Prof. Gaita, Dr. Anselmino, Dr. Ferraris, Dr. di Biase, Dr. A. Natale, Dr. Hunter, Dr. Schilling, Dr. Miyazaki, Dr. Tada, Dr. Aonuma, Dr. Yenn-Jiang, Dr. Tao, Dr. Ma, Dr. Packer and Dr. Hammill participated in acquisition of data, analysis, interpretation, and manuscript drafting, revising it critically for key intellectual content.

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Figures

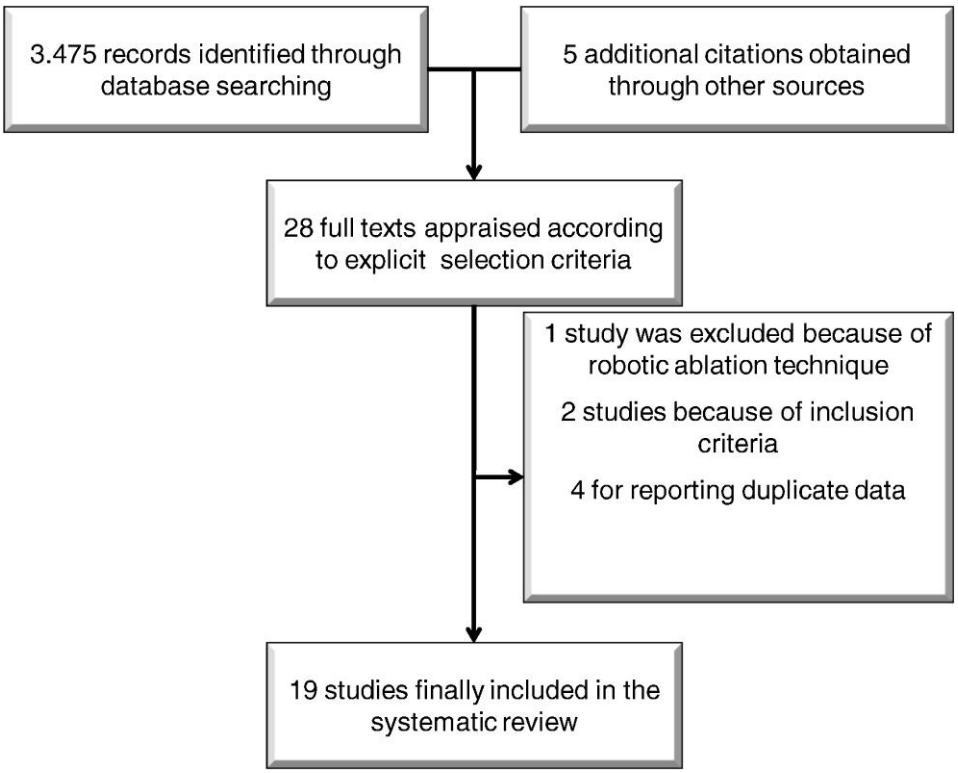


Fig. 1. Review profile

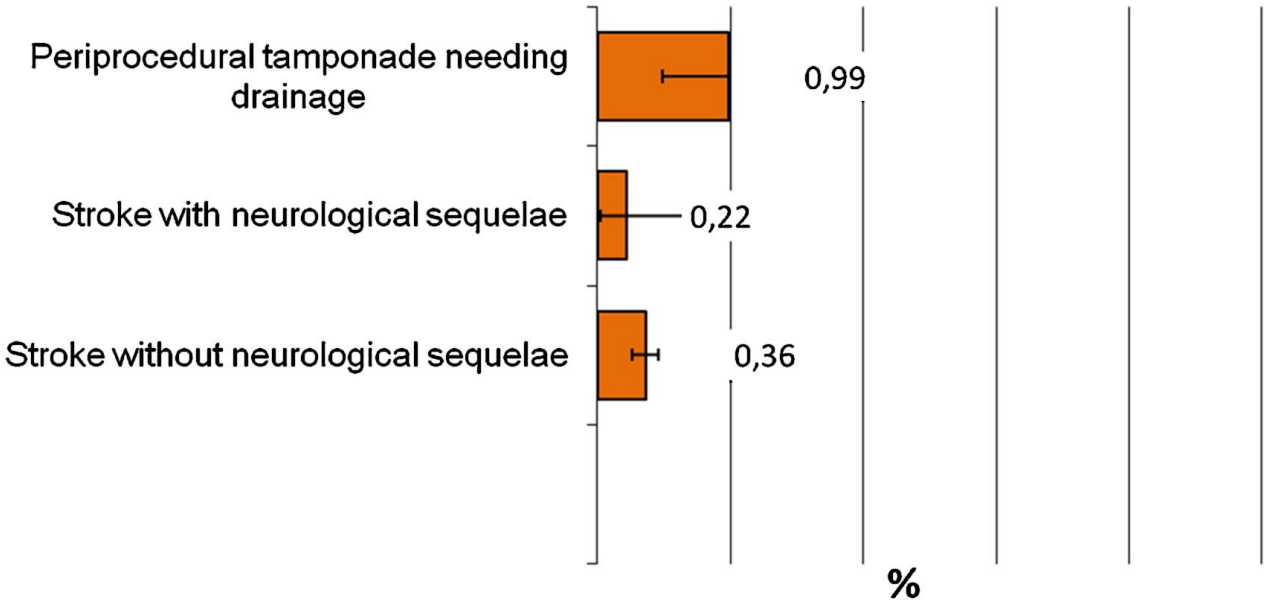
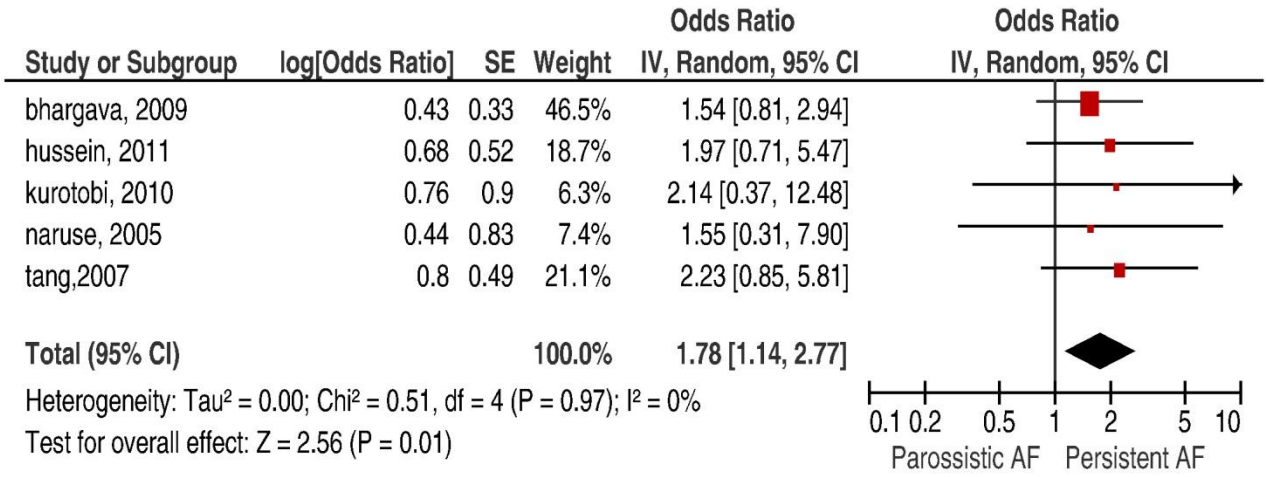


Fig. 2. Pooled analysis of in-hospital complications.



AF= atrial fibrillation; CI= confidence interval; SE= standard error.

Fig. 3. Multivariate Odds ratio of AF recurrence in persistent versus paroxysmal AF in patients undergoing one ablation procedure.

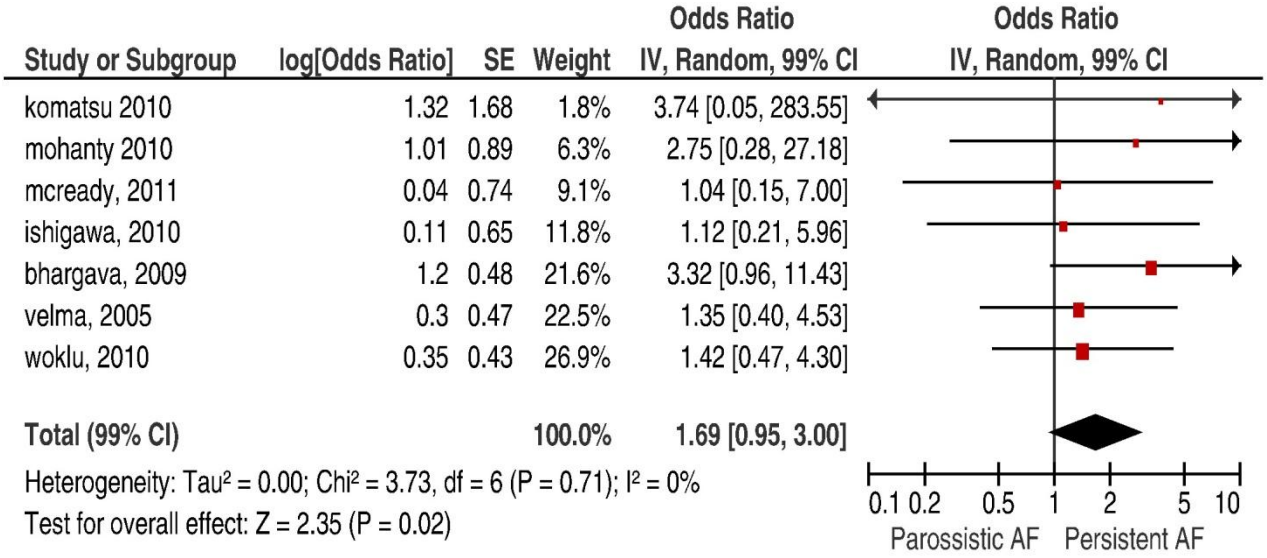


Fig. 4. Multivariate OR (Odds ratio) of AF recurrence in persistent versus paroxysmal AF in patients undergoing more than one ablation procedure.

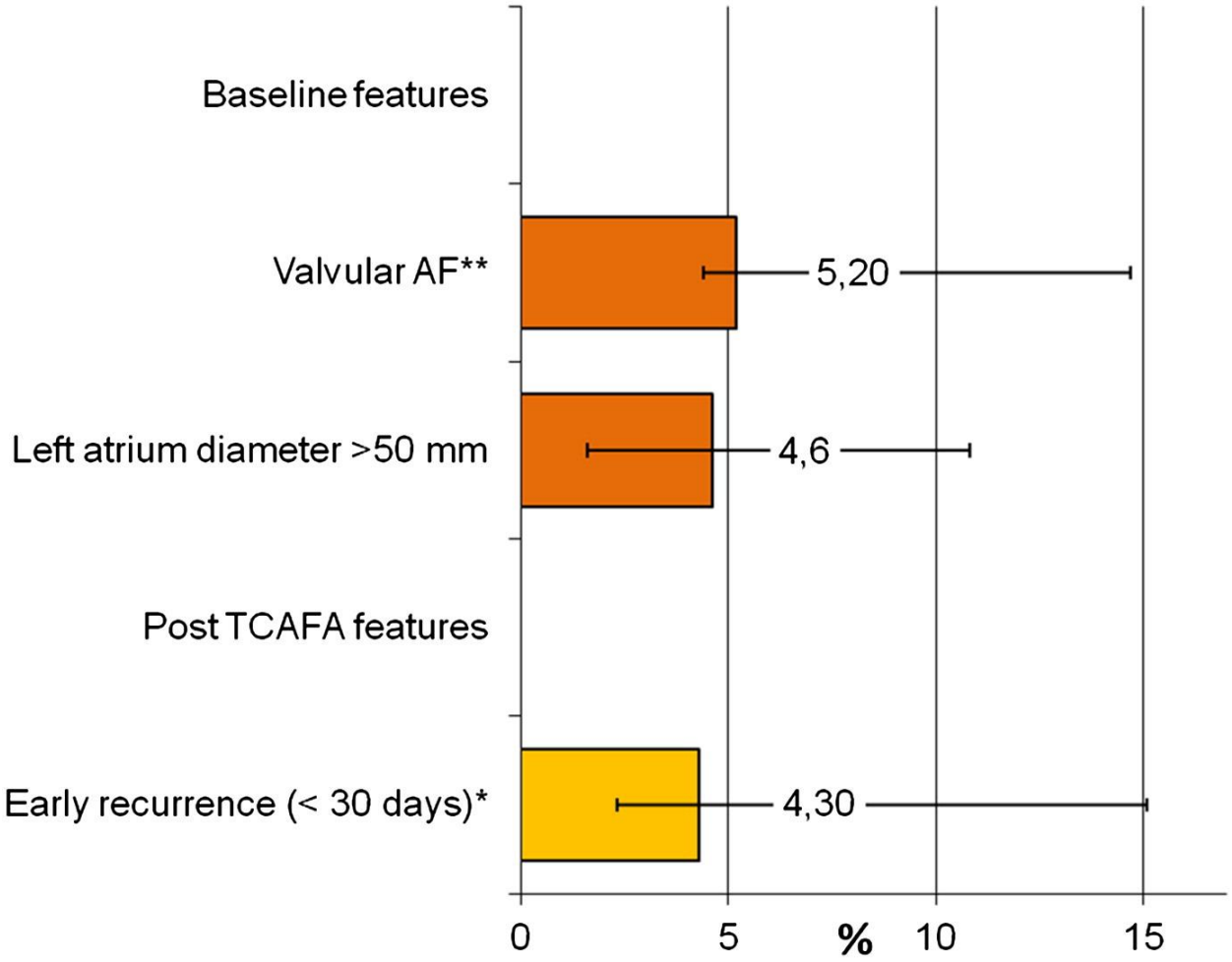


Fig. 5. Most powerful predictors of recurrence after AF ablation (those with an OR of more than 3.5, reported in at least two studies).

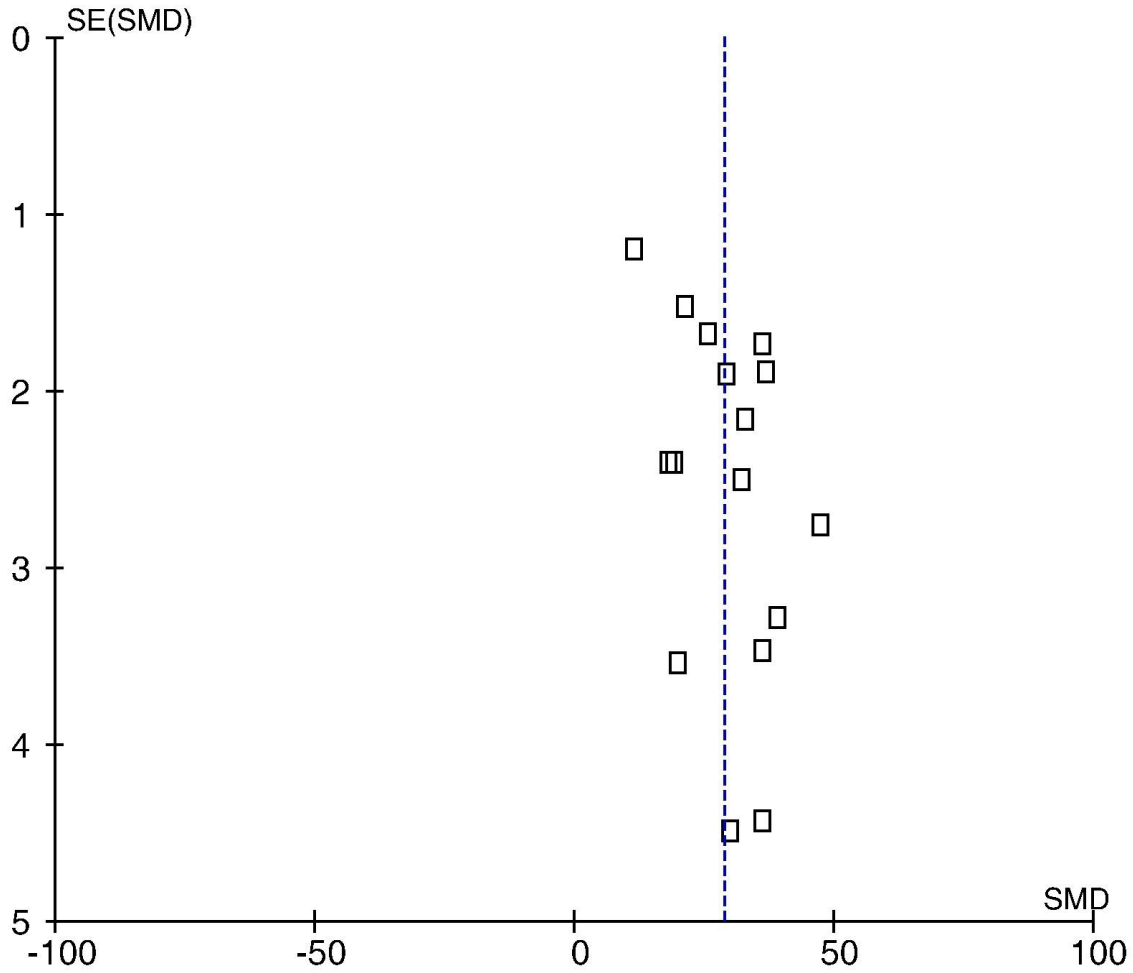


Fig. A. Funnel plot.

Table 1. Key patients' clinical characteristics.[a]

	N = 19
Studies	
Patients with paroxysmal AF	4357
Patients with persistent AF	1083
Patients with long standing persistent AF	1777
Follow-up (months)	22 (13–28)
Baseline features	
Age (years)	57 (56–67)
Male gender (%)	77% (72–82)
Diabetes (%)	8% (4–10)
Hypertension (%)	44% (38–49)
History of ischemic heart disease (%)	10% (8.5–13)
History of heart failure (%)	5% (2.9–6.7)
Time from first AF record (months)	60 (48–72)
Echocardiographical features	
Left ventricular ejection fraction (%)	60% (058–62)
Left atrium area (cm^2)	22 (22, 23)
Left atrium volume (cm^3)	90 (78–116)
Anterior–posterior diameter (cm)	42 (38–45)
Interventional features	
Pulmonary vein typical branching pattern (%)	55.7% (48–64)
Pulmonary vein isolation (%)	100%
Linear lesion (%)	27% (24–51)
CFAEs ablation (%)	15 (14–21)
Number of procedures (n)	1.23 (1.19–1.5)

AF = atrial fibrillation; CFAEs = complex fractionated atrial electrograms.

[a] Reported as n (%) or median (1st–3rd quartile).

Table 2. Clinical and procedural features according to the number of procedures.

	Number of studies	**Number of patients**	**Patients with paroxysmal AF (%)**	**Patients with persistent AF (%)**	**Patients with long standing persistent AF (%)**	**PVI (%; CI 95)**	**Linear lesions (%; CI 95)**	**CFAEs (%; CI 95)**
One TCAF procedure	7[a]	2450	81	–	19	100	24 (0–44)	10 (6.5–13)
More than one TCAF procedure	13[a]	4767	46	19	32	100	42 (36–45)	42 (22–45)

Table 3. Most common predictors of AF recurrence after ablation.

Studies	**N = 19 (%)**
Left atrium (LA) enlargement	9 (47%)
LA diameter as a continuous variable	2 (11%)
LA diameter more than 40 mm	1 (5%)
LA diameter more than 45 mm	1 (5%)
LA diameter more than 50 mm	2 (11%)
LA area as a continuous variable	1 (5%)
LA volume as a continuous variable	2 (11%)
Persistent AF	8 (42)
Non paroxysmal AF	5 (26%)
AF episodes either last longer than 7 days or require termination by cardioversion either with drugs or by direct current cardioversion (DCC)[a]	2 (11%)
Recurrent episodes of AF lasting more than 3 months	1 (5%)
Valvular AF	2 (11)
Diabetes	2 (11)
Early recurrence (in 30 days)	2 (11)
Hypertension	3 (15)
High level of brain natriuretic peptide (500 pg/ml)	2 (11)
Plasma C-reactive protein level (> 2.9 mg/l)	2 (11)

The following predictors were reported only in one study; beta-blockers, BMI (body mass index), coronary artery disease, chronic kidney disease, defibrillation threshold, atrial anterior–posterior diameter > 45 mm, early recurrence, high BNP; metabolic syndrome, non-ischemic dilated cardiomyopathy, presence of a low-voltage zone (voltage < 0.5 mV) in the left atrium, scar, valvular AF, pulmonary vein anatomy; chronic heart failure.

[a]Esc guidelines definition. The abbreviations are the same as in the previous tables.