UNIVERSITÀ DEGLI STUDI DI TORINO

Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis

Matteo Anselmino, MD PhD[1], Mario Matta, MD[1], Fabrizio D'Ascenzo, MD[1], T. Jared Bunch, MD[2], Richard J. Schilling, MD[3], Ross J. Hunter, MD PhD[3], Carlo Pappone, MD PhD[4], Thomas Neumann, MD[5], Georg Noelker, MD[6], Martin Fiala, MD PhD[7], Emanuele Bertaglia, MD[8], Antonio Frontera, MD[9], Edward Duncan, MD[9], Chrishan Nalliah BSc, MBBS[10], Pierre Jais, MD[11], Rukshen Weerasooriya, MD[11,12], Jon M. Kalman, MD PhD[13], Fiorenzo Gaita, MD Prof[1].

[1]Cardiology Division, Department of Medical Sciences, University of Turin, Turin, Italy

[2]Intermountain Heart Institute, Intermountain Medical Center, Murray, UT, USA

[3]Cardiovascular Biomedical Research Unit, St. Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom.

[4]Department of Arrhythmology, Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy.

[5]Department of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany

[6]Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

[7]Department of Cardiology, Heart Centre, Hospital Podlesi as, Třinec, Czech Republic

[8]Department of Cardiological, Thoracic, and Vascular Sciences, University of Padua, Padova, Italy

[9]Department of Cardiology, Bristol Heart Institute, University Hospital Bristol NHS Trust, Bristol, UK

[10]Department of Cardiology, Westmead Hospital & University of Sydney, Sydney, Australia

[11]Department of Cardiac Electrophysiology, Hopital Cardiologique du Haut-Leveque, Bordeaux-Pessac, France.

[12]University of Western Australia, Crawley, Western Australia.

[13]Department of Cardiology, The Royal Melbourne Hospital, Melbourne, Australia.

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Corresponding author:

Fiorenzo Gaita, MD Professor (fiorenzo.gaita@unito.it)
Cardiology Division, Città della Salute e della Scienza,
Department of Medical Sciences,

University of Turin, Turin, Italy

Corso Dogliotti 24, 10126 Turin, Italy
Phone: +39-011-6335570
Fax: +39-011-6966015

Abstract

Background. Catheter ablation of atrial fibrillation (AFCA) is an established therapeutic option for rhythm control in symptomatic patients. Its efficacy and safety among patients with left ventricular systolic dysfunction is based on small populations, and data concerning long-term outcome are limited. We performed this meta-analysis to assess safety and long-term outcome of AFCA in patients with left ventricular systolic dysfunction, to evaluate predictors of recurrence and impact on left ventricular function.

Methods and Results. A systematic review was conducted in MEDLINE/PubMed and Cochrane Library. Randomized controlled trials, clinical trials and observational studies including patients with left ventricular systolic dysfunction undergoing AFCA were included. Twenty-six studies were selected, including 1,838 patients. Mean follow-up was 23 (95% Confidence Interval: 18-40) months. Overall complication rate was 4.2 (3.6-4.8)%. Efficacy in maintaining sinus rhythm at follow-up end was 60 (54-67)%. Meta-regression analysis revealed that time since first AF ($p=0.030$) and heart failure ($p=0.045$) diagnosis related to higher, while absence of known structural heart disease ($p=0.003$) to lower incidence of AF recurrences. Left ventricular ejection fraction improved significantly during follow-up by 13% ($p<0.001$), with a significant reduction of patients presenting an ejection fraction <35% ($p<0.001$). NT-proBNP blood levels decreased by 620 pg/ml ($p<0.001$).

Conclusions. AFCA efficacy in patients with impaired left ventricular systolic function improves when performed early in the natural history of AF and heart failure. AFCA provides long-term benefits on left ventricular function, significantly reducing the number of patients with severely impaired systolic function.

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Introduction

Catheter ablation of atrial fibrillation (AFCA) is a well-established and growing treatment option for patients with symptomatic atrial fibrillation (AF) refractory to antiarrhythmic drugs[1]. In fact, despite a relatively high incidence of late recurrences, the long-term efficacy in maintaining sinus rhythm (SR) remains encouragingly high, especially if compared to pharmacologic approaches[2].

AFCA has shown satisfactory safety and efficacy even in patients with moderate-severe structural heart disease and impaired left ventricular (LV) systolic function, with SR maintenance rates comparable to those of patients with normal LV function, although redo ablation procedures are more commonly required[3,4]. However these outcome data are based on small observational studies and no conclusive indication for AFCA in patients with reduced LV ejection fraction (LVEF) has been agreed.

Therefore, the present systematic review and meta-analysis aims to investigate long-term outcome of AFCA in patients with reduced LVEF, focusing on procedural safety, rhythm control efficacy, predictors of recurrence and their impact on LV function.

Methods

The present study was conducted in accordance 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, as well as recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[5,6].

Search strategy and study selection

MEDLINE/PubMed and Cochrane database were searched for pertinent articles published in English from 2002 until October 2013. Details on search strategy and terms, results selection and

data extraction are provided in the Supplemental Methods. Of note, 13 (50%) studies did not differentiate persistent and long-standing persistent AF.

Statistical analysis

Continuous variables were reported as mean (standard deviation) or median (range), and categorical variables as n (%), weighted for sample size of each study and according to standard error by logarithmic transformation. Funnel plot analysis was used to evaluate potential publication bias, and Cochran Q2 tests and I2 to investigate heterogeneity. Using rates of event as dependent variables, a meta-regression analysis was performed to test whether an interaction between incidence of AF recurrences and time since first AF and heart failure diagnosis, absence of known structural heart disease and AFCA protocol was present. Due to the observational design of most of the included studies, random effect was performed for all analysis. Statistical analyses were performed with Comprehensive Metanalysis (Trial Version) and Review Manager.

Results

Search results are summarized in Figure 1 and described in details in the Supplemental Results.

Fifteen studies[7-21] meeting the pre-specified inclusion criteria, and 11 long-term (at least 2 years) AFCA studies[22-32], for which the corresponding Author was contacted and agreed to participate, were eventually included.

First Author, study design, publication date and main characteristics of each included study are reported in Supplemental Table 1 (Supplemental Material).

Baseline patients characteristics

A total of 1,838 patients were finally included from 26 studies. Baseline characteristics, derived combining confidence intervals from all studies, are shown in Table 1. The mean age from each

study ranged from 51 to 61 years and 38% were women. Paroxysmal AF accounted for 45% of the population. The mean LVEF ranged from 35% to 46% (mean value 40%) while mean left atrial antero-posterior diameter was 59 mm. LV systolic dysfunction was idiopathic in 39% of the patients, while coronary artery disease was the most common aetiology of LV impairment. The majority of patients were symptomatic from heart failure, with only 20% in NYHA class I at baseline. The time since first AF and heart failure diagnosis ranged from 29 to 46 and 20 to 28 months, respectively. Basal pro-BNP levels were heterogeneously elevated ranging from 678 to 1,400 pg/ml.

Catheter ablation protocols and complications

AFCA procedural characteristics are reported in Table 2. All patients underwent pulmonary veins (PV) isolation, while 45% and 54% of the patients were treated with additional linear lesions or focal ablation of complex fractioned atrial electrograms (CFAE) in the left atrium at first or redo procedure, respectively. Major procedural complications rate ranged from 3.6 to 4.8% (mean 4.2%; Figure 2). The most frequent complications were related to the access site and to cerebral thromboembolic events. Redo procedures were performed in 32 (24-36)% of the cases.

Follow-up and recurrences

Mean follow-up was 23 months, ranging from 18 to 40 months. Recurrences were defined, consistently within all the studies, as episodes of AF or atrial tachycardia or atypical atrial flutter lasting at least 30 seconds detected during follow-up (eTable 1), with a blanking period of 3 months after ablation. Overall AFCA long-term efficacy at the end of follow-up period was 60 (54-67)%. Efficacy after a single procedure ranged, instead, from 36% to 44% (mean value 40%; Figure 2).

As shown in Figure 3, mean LVEF improved from 40 to 53% during follow-up, with a significant reduction of patients presenting an LVEF lower than 35% ($p<0.001$). Moreover, NT-proBNP levels decreased from 1,187 pg/ml before ablation to 567 pg/ml at follow-up end ($p<0.001$).

At meta-regression analysis (Figure 4), performed to test whether an interaction between relevant baseline clinical features[2,33] and incidence of AF recurrence was present, time since first AF and heart failure diagnosis related to a higher recurrence rate, while absence of known structural heart disease was associated to a lower recurrence rate of AF. A PV isolation alone approach versus an AFCA with extensive left atrial ablation (additional linear lesions or CFAE) did not relate to higher SR long-term maintenance.

Discussion

The efficacy and safety of AFCA in patients with LV systolic dysfunction is based on small observational studies or meta-analyses that largely comprise a maximum of 500 patients. Through contacting each corresponding author of published long-term AFCA experiences in search of quantitative details on patients with impaired LV function, the present is the first study, to the best of our knowledge, to include a substantial number of patients with LV systolic dysfunction undergoing AFCA. In addition, the outcomes presented are based on long-term retrieved data specific to only those patients impaired LV systolic function.

Based on the present analysis, overall complication rate of AFCA in patients with reduced LVEF was of 4.2 (3.6-4.8)%, a safety profile similar to that reported amongst the general AFCA population[2,34]. Indeed the AFCA in more complex and frail anatomical substrate, secondary to the LV dysfunction and elevated left chambers filling pressure, has been in previous single center studies related to higher complication rates[17]; however, a clear excess of undesirable events has not emerged in the present large multicenter real-world population.

In the present analysis, first procedure efficacy was relatively low (40%), a finding reflective of the complexity of arrhythmia substrate in patients with reduced LVEF. However, with inclusion of repeat procedures the long-term AFCA efficacy improved to 60%, which is comparable to long-

term outcomes reported from general AFCA populations[2,26]. Of note, based on meta-regression analysis, performing AFCA early in the natural history of the disease significantly improves outcome. This finding is consistent with recent data that suggest increasing time from initial ECG diagnosis of AF to ablation significantly increased risk of AF recurrence after AFCA, independently of the AF subtype[35]. We anticipate the delays in rhythm treatment may be augmented in patients with LV dysfunction, as AF and heart failure share many strong pathophysiologic links that mutually influence atrial fibrosis, anatomical and electrical remodeling[36].

The AFCA protocol used for the patients included in the present study was PV isolation alone in 55% and 46% of the cases at first and redo procedure, respectively. In patients with reduced LV systolic function, especially in case of persistent AF, previous literature has shown that, due to complex atrial substrate sustaining multiple reentry circuits, PV isolation ablation protocols may not be optimal[37,38]. As such, an upfront strategy of PV isolation alone in the majority of patients with LV dysfunction may have impacted the long-term success rates and need for redo procedures. However, if ablation approaches evolve to consistently obtain transmural PV isolation during the initial procedure, additional substrate modification or linear ablation may not be requisite[39]. Further, linear lesions and ablation of CFAE deemed beneficial for substrate modification may increase risk of iatrogenic atypical atrial flutters or atrial tachycardias, if they are incomplete or not anchored to electrically inert structures[40]. As such the consequences of these recurrences may counterbalance the benefit derived by more aggressive atrial substrate modification. In fact, based on meta-regression analysis, the AFCA protocol did not significantly relate to long-term outcome.

An interesting finding was that all the studies included in the present analysis consistently reported improvement in LV function during the follow-up period. Other studies have also demonstrated a benefit in LV function after AFCA even in presence of preserved LV function[41]. These findings highlight the role of atrial contraction in preserving normal hemodynamic function. In addition, 39% of the population did not present a known aetiology of their structural heart disease, therefore

LV function improvement could partially be explained by inclusion of patients with LV dysfunction secondary only to uncontrolled ventricular response (tachycardiomyopathy). However, recent randomized data suggest a similar improvement in LV function with definitive restoration of SR by AFCA, with little if any effect by increasing rate control[13,21]. Since AFCA is recommended only in case of rate and pharmacological rhythm control strategies failure, the incidence of real isolated tachycardiomyopathies should, therefore, be limited. Also, removal of long-term antiarrhythmic drug therapy when AFCA is successful, which often has a negative inotropic effect, may also provide pervasive benefit on LV function. Consistent with improvements in cardiac function over time, NT-proBNP levels declined significantly during follow-up after AFCA. NT-proBNP reduction has shown, after effective AFCA, to relate to favorable atrial remodeling and reduction in left atrial wall stress[42]. These findings are also applicable to those patients with severe disease. During the long-term follow-up, the number of patients with an LVEF lower than 35% significantly decreased. Patients with severe LV dysfunction are the most vulnerable to morbidity, mortality, and proarrhythmia from the majority of antiarrhythmic drugs for rhythm control[43]. As such, the pharmacologic options for these patients are often very limited, which translates to a direct need of nonpharmacologic options such as AFCA to improve long-term quality of life, morbidity and mortality associated in patients with coexistent AF and heart failure. Moreover, given current guideline recommendations for invasive treatments such as implantable defibrillators or cardiac resynchronization therapy, an LVEF improvement above 35% has relevant implications in terms of potentially reducing unnecessary device implantations, leading to a more focused patient selection and allocation of resources.

Limitations

This study presents the following limitations. First, AFCA is a relatively recent and developing procedure, with different centers using different protocols and tools. AFCA procedural

characteristics may grow heterogeneity, and influence safety and efficacy outcomes. Second, prevalence of patients with long-standing persistent AF is low; the AFCA outcome reported in this study may therefore be scarcely reflective of this subgroup of patients. Third, although heterogeneity was appraised by random effect, this meta-analysis, in order to include the largest amount of data available from current literature, combines randomized controlled trials with observational studies. The enrolled population may therefore be affected by selection bias of single centers' experience and preference in referring patients to AFCA, excluding patients with heart failure considered unlikely to benefit from the procedure.. Finally, meta-regression analysis does not allow clinicians to drive causative inferences, but only speculative; large prospective multicenter clinical trials are needed to define AFCA safety and efficacy in this group of patients.

Conclusion

. AFCA long-term SR maintenance in patients with impaired LV systolic function is comparable to that reported on the long-term among the general population, especially when AFCA is performed early in the natural history of AF and heart failure. Moreover, LV function consistently improves over the follow-up, significantly reducing the proportion of patients with severely impaired LV systolic function. Large prospective multicenter trials are advised to clearly define the true safety and efficacy of AFCA in this subset population.

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Disclosures

Conflicts of interest: none.

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Table 1. Clinical features of patients included in the selected studies (1,838 patients).

	Mean value (Lower-Upper 95%Confidence Interval)
Age, years	59 (51-61)
Female gender, %	38 (29-43)
BMI, kg/m^2	29 (24-31)
Mean follow-up, months	23 (18-41)
Type of AF - Paroxysmal, % - Persistent, % - Long-standing persistent, %	 45 (41-56) 50 (35-54) 5.0 (2.0-7.0)
Time since first AF diagnosis, months	42 (29-46)
Hypertension, %	63 (57-68)
Diabetes mellitus, %	12 (9.0-15)
Prior stroke/TIA, %	13 (11-19)
Time since first heart failure diagnosis, months	27 (20-28)
Basal 6 minute walking test, meters	534 (250-670)
Basal pro-BNP (pg/ml)	11,187 (678-11,400)
Thyroid disease - Hyperthyroidism, % - Hypothyroidism, %	 7.5 (5.5-8.5) 3.5 (3.0-5.0)
Chronic lung disease, %	5.0 (1.0-10)
Obstructive sleep apnea, %	15 (7.5-19)
NYHA class - I, % - II, % - III or IV, %	 20 (15-25) 45 (35-49) 35 (30-45)
Cardiomiopathy - Ischemic, % - Hypertensive, %	 41 (35-46) 10 (5.0-14)

- Valvular heart disease, %	10 (6.0-15)
- Idiopathic, %	39 (35-45)
QRS duration at ECG, msec	83 (80-120)
Baseline medical therapy	
- Amiodarone, %	33 (25-40)
- Oral anticoagulants, %	56 (45-69)
- Beta-blockers, %	70 (43-82)
LVEF, %	40 (35-46)
Left atrial AP diameter, mm	59 (40-110)

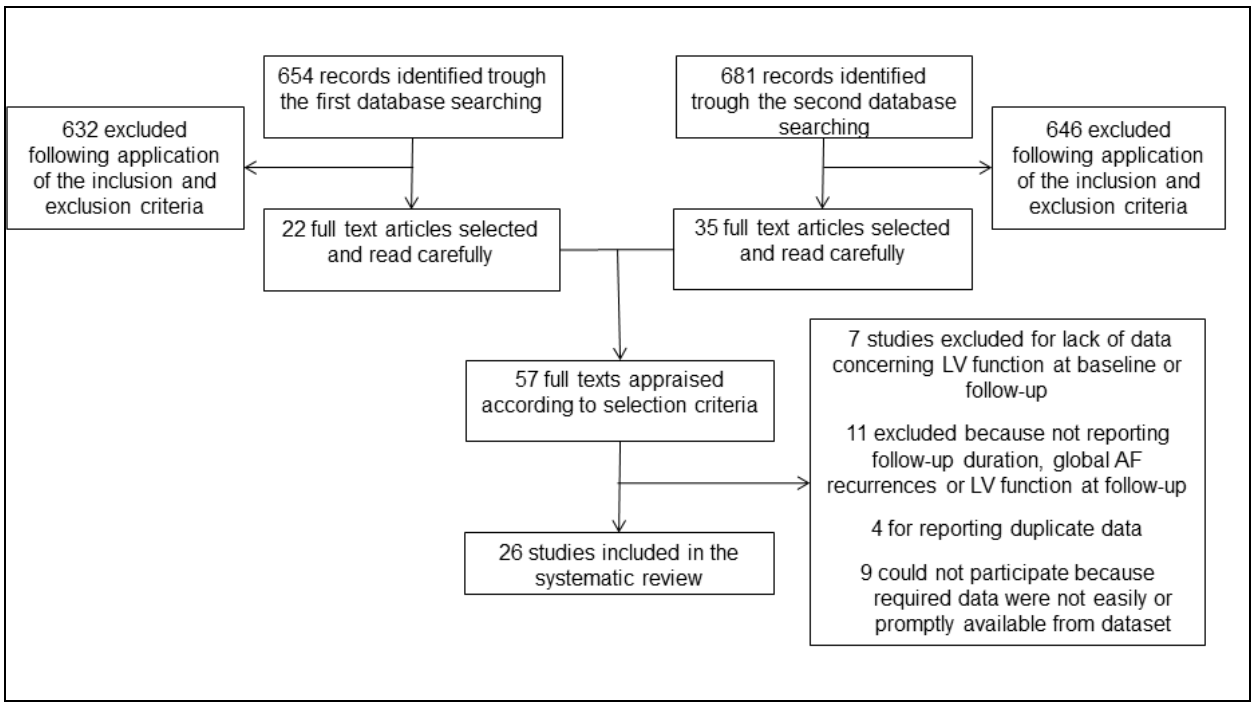
BMI: body mass index; AF: atrial fibrillation. TIA: transient ischemic attack; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; AP: antero-posterior.

Table 2. Procedural features and efficacy rates of atrial fibrillation catheter ablation in the selected studies (1,838 patients).

	Mean value (Lower-Upper 95% Confidence Interval)
First procedure	
PV isolation, %	100 (100-100)
PV isolation alone, %	55 (51-76)
Left isthmus line, %	35 (10-50)
Roof line, %	46 (34-48)
CFAE, %	5.0 (1.0-7.0)
Fluroscopy time, minutes	39 (24-64)
Procedural time, hours	3.1 (2.6-3.8)
Post procedural cardioversion, %	53 (30-65)
Overall complications, %	4.2 (3.6-4.8)
Access site complications, %	2.0 (1.0-2.5)
Stroke/TIA, %	1.0 (0.6-1.5)
Cardiac tamponade, %	1.2 (0.6-1.5)
Others, %	1.2 (0.7-1.6)
Redo procedures, 32 (24-36)% of patients	
Time after first procedure, months	12 (9.0-15)
PV isolation, %	100 (100-100)
PV isolation alone, %	46 (43-56)
Left isthmus line, %	25 (21-29)
Roof line, %	35 (31-34)
CFAE, %	5.0 (1.0-7.0)
First procedure efficacy, %	40 (36-44)
Final efficacy, %	60 (54-67)

PV: pulmonary veins; CFAE: complex fractioned atrial electrograms; TIA: transient ischemic attack.

Figure 1. Search criteria and flow chart of the studies screened and included in the systematic review.



LV: left ventricular. AF: atrial fibrillation.

Figure 2. Funnel plot of the included studies concerning complication rates (A) and efficacy after first procedure (B) or at follow-up end (C).

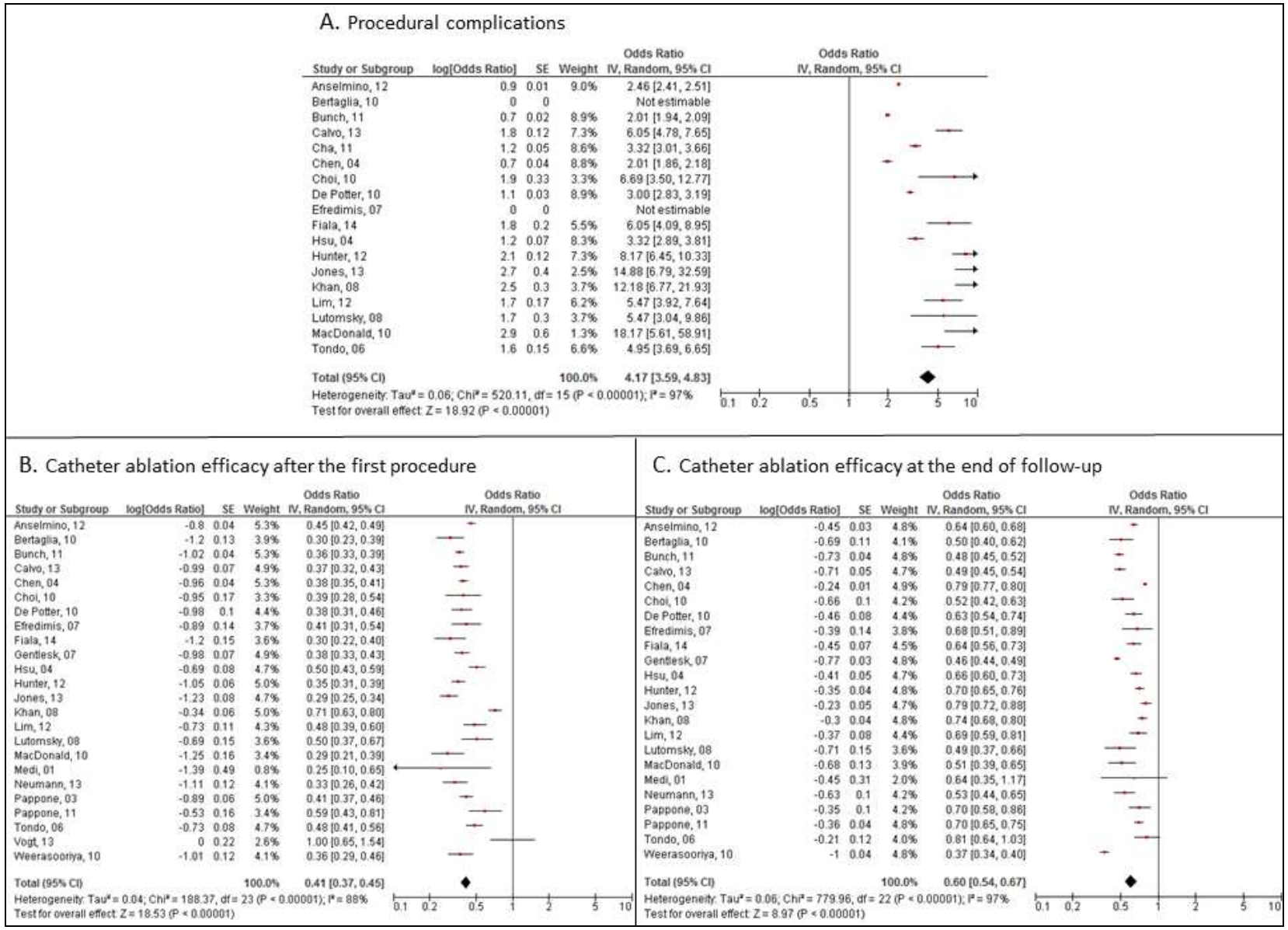
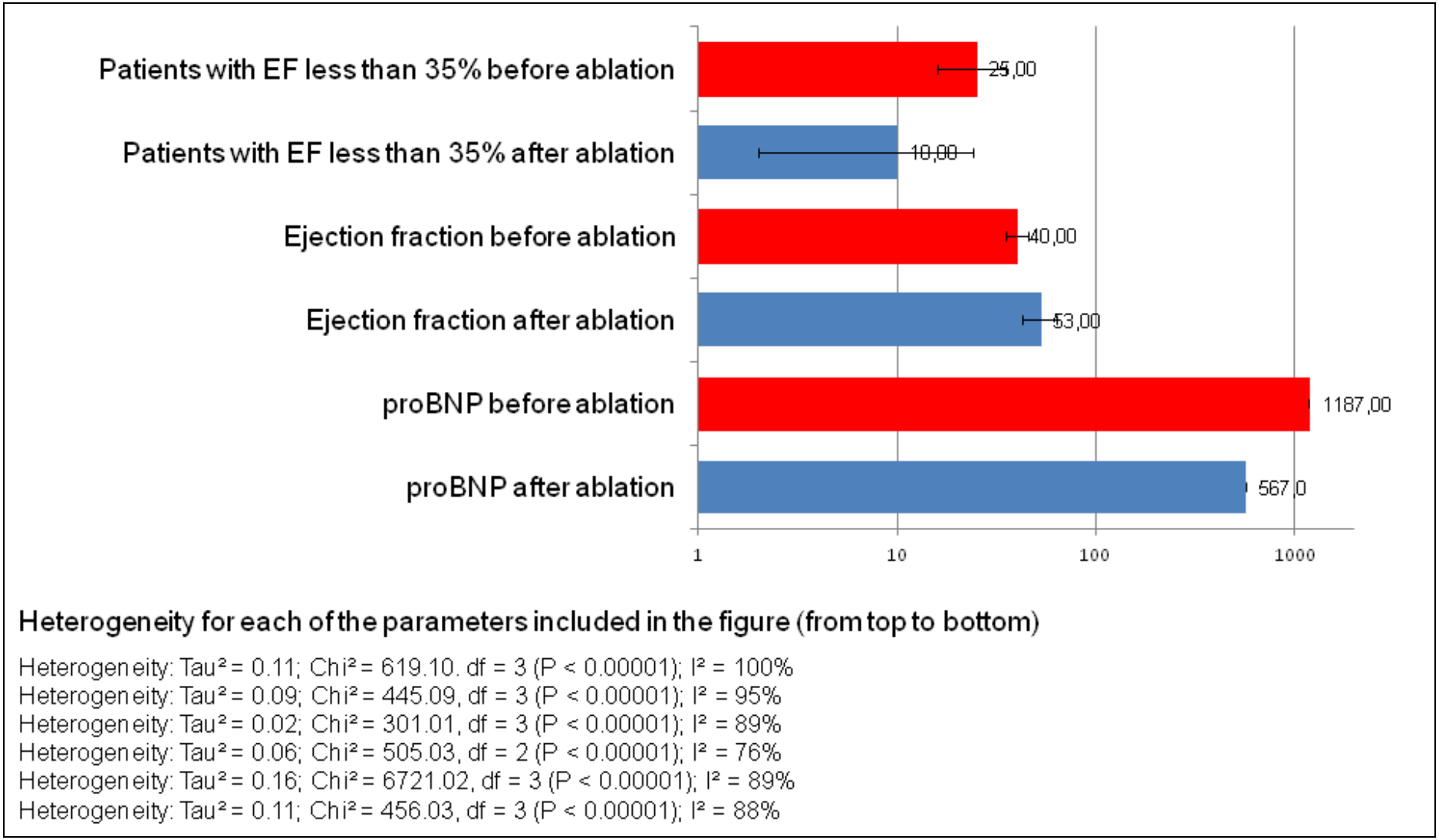
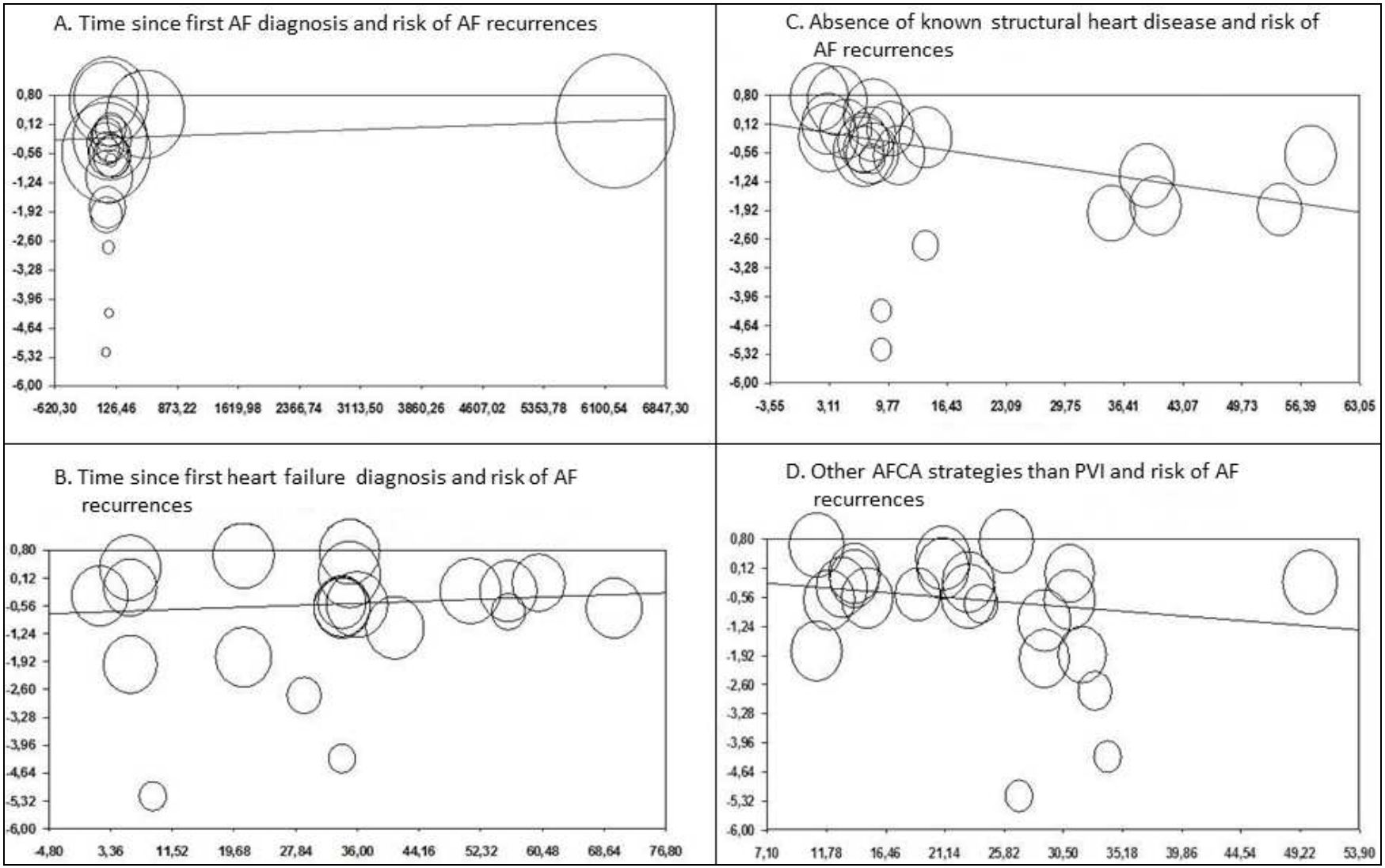


Figure 3. Improvement of instrumental (echocardiographic and laboratory) parameters after atrial fibrillation catheter ablation.



EF: left ventricular ejection fraction.

Figure 4. Meta regression analysis assessing the impact of time since first AF diagnosis (A, Beta 1.1: p=0.030), time since first heart failure diagnosis (B, Beta 0.67: p=0.045), absence of known structural heart disease (C, Beta -0.02: p=0.003), and other AFCA strategies than pulmonary veins isolation (D, Beta -0.023: p=0.340) on long-term incidence of AF recurrences.



AF: atrial fibrillation. AFCA: atrial fibrillation catheter ablation.