Catheter Ablation of Atrial Fibrillation in Patients With Left Ventricular Systolic Dysfunction: A Systematic Review and Meta-Analysis

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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 1838 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 atrial fibrillation ($P=0.030$) and heart failure ($P=0.045$) diagnosis related to higher, whereas absence of known structural heart disease ($P=0.003$) to lower incidence of atrial fibrillation 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% ($P<0.001$). N-terminal pro-brain natriuretic peptide 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 atrial fibrillation and heart failure. AFCA provides long-term benefits on left ventricular function, significantly reducing the number of patients with severely impaired systolic function. (Circ Arrhythm Electrophysiol. 2014;7:1011-1018.)

Key Words: atrial fibrillation ■ catheter ablation ■ heart failure ■ meta-analysis

Catheter ablation of atrial fibrillation (AFCA) is a well-established and growing treatment option for patients with symptomatic atrial fibrillation (AF) refractory to anti-arrhythmic drugs.1 Despite a relatively high incidence of late recurrences, the long-term efficacy in maintaining sinus rhythm (SR) remains encouragingly high, especially when compared with pharmacological approaches.2

Clinical Perspective on p 1018

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 with 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 with 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 Each included study was approved by an institutional review committee, and all subjects gave informed consent.

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 Methods in the Data Supplement. 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. Because of the observational design of most of the included studies, random effect was performed for all analysis. Statistical analyses were performed with Comprehensive Meta-analysis (Trial Version) and Review Manager.

Results

Search results are summarized in Figure 1 and described in details in the Results in the Data Supplement. Fifteen studies7–21 meeting the prespecified inclusion criteria, and 11 long-term (≥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 Table 1 in the Data Supplement (Material in the Data Supplement).

Baseline Patients Characteristics

A total of 1838 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%), whereas mean left atrial anteroposterior diameter was 59 mm. LV systolic dysfunction was idiopathic in 39% of the patients, while coronary artery disease was the most common etiology of LV impairment. The majority of patients were symptomatic from heart failure, with only 20% in New York Heart Association 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-brain natriuretic peptide levels were heterogeneously elevated, ranging from 678 to 1400 pg/mL.

Catheter Ablation Protocols and Complications

AFCA procedural characteristics are reported in Table 2. All patients underwent pulmonary vein (PV) isolation, while 45% and 54% of the patients were treated with additional linear lesions or focal ablation of complex fractionated atrial electrograms in the left atrium at first or redo procedure, respectively. Major procedural complication 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 ≥30 seconds detected during follow-up (Table 1 in the Data Supplement), 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
As shown in Figure 3, mean LVEF improved from 40% to 53% during follow-up, with a significant reduction in patients presenting an LVEF<35% (P<0.001). Moreover, N-terminal pro-brain natriuretic peptide levels decreased from 1187 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 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 complex fractionated atrial electrogram) 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 4.2% (3.6%–4.8%), a safety profile similar to that reported among the general AFCA population. Indeed, the AFCA in more complex and
frail anatomic substrate, secondary to the LV dysfunction and elevated left chambers filling pressure, has been in previous single-center studies related to higher complication rates\(^1\); 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 with 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.

Figure 2. Funnel plot of the included studies concerning complication rates (A) and efficacy after first procedure (B) or at follow-up end (C). CI indicates confidence interval.
that suggest increasing time from initial ECG diagnosis of AF to ablation significantly increased the risk of AF recurrence after AFCA, independently of the AF subtype.\textsuperscript{35} We anticipate that the delays in rhythm treatment may be augmented in patients with LV dysfunction because AF and heart failure share many strong pathophysiologic links that mutually influence atrial fibrosis, anatomic and electric remodeling.\textsuperscript{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, because of complex atrial substrate sustaining multiple reentry circuits, PV isolation ablation protocols may not be optimal.\textsuperscript{37,38} As such, an upfront strategy of PV isolation alone in the majority of patients with LV dysfunction may have affected the long-term success rates and the 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.\textsuperscript{39}

Furthermore, linear lesions and ablation of complex fractionated atrial electrogram deemed beneficial for substrate modification may increase the risk of iatrogenic atypical atrial flutters or atrial tachycardias, if they are incomplete or not anchored to electrically inert structures.\textsuperscript{40} As such, the consequences of these recurrences may counterbalance the benefit derived by more aggressive atrial substrate modification. 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.\textsuperscript{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 etiology 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.\textsuperscript{13,21} Because 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 provide pervasive benefit on LV function. Consistent with improvements in cardiac function over time, N-terminal pro-brain natriuretic peptide levels declined significantly during follow-up after AFCA. N-terminal pro-brain natriuretic peptide reduction has shown, after effective AFCA, to relate to favorable atrial remodeling.
and reduction in left atrial wall stress. These findings are also applicable to those patients with severe disease. During the long-term follow-up, the number of patients with an LVEF<35% significantly decreased. Patients with severe LV dysfunction are most vulnerable to morbidity, mortality, and proarrhythmia from the majority of antiarrhythmic drugs for rhythm control. As such, the pharmacological options for these patients are often limited, which translates to a direct need of nonpharmacologic options such as AFCA to improve long-term quality of life, morbidity, and mortality associated with 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 >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, the 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, 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 with 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.

Acknowledgment
We thank all contacted centers for the professionalism demonstrated by promptly collaborating and sharing data with the only aim to improve current medical knowledge.

Disclosures
None.

References
Atrial fibrillation (AF) is common in patients with heart failure and is associated with increased mortality, but antiarrhythmic drug therapy to maintain sinus rhythm has not been shown to be beneficial. Catheter ablation of AF is an established therapeutic option for rhythm control in selected patient populations, with increasing interest in its use in heart failure, although data are limited. This meta-analysis of studies reporting catheter ablation of AF in patients with heart failure supports its safety and suggests a positive effect on outcome, although repeat procedures are commonly needed. Catheter ablation of AF was associated with an improvement in LV function and reduction in N-terminal pro-brain natriuretic peptide. Appropriate patient selection is likely critical; patients with a short clinical history of AF and heart failure may be most likely to benefit. These findings support further study of catheter ablation of AF in patients with heart failure.
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SUPPLEMENTAL MATERIAL

Supplemental Methods

Search strategy and study selection

MEDLINE/PubMed and Cochrane database were searched for pertinent articles published in English from 2002 until October 2013, according to published recommendations. The following terms: “atrial fibrillation” AND “catheter ablation” AND (“heart failure” OR “reduced left ventricular function” OR “left ventricular systolic dysfunction”) were used to identify all the published articles referring to this specific population. A second search was then performed using the following terms: “atrial fibrillation” AND “catheter ablation” AND (“long-term outcome” OR “long-term results”), to retrieve published articles referring to long-term results of this procedure among the general population; among them, all the studies presenting a mean follow-up of at least 2 years were included, and the corresponding Author was contacted for quantitative details on patients with impaired LV function enrolled in their studies, offering coauthorship in this work. Each included study was approved by an institutional review committee and all subjects gave informed consent.

Data extraction

Retrieved citations were first screened independently by 2 unblinded reviewers (authors: M.A. and M.M.) with divergences resolved after consensus. If the citations were deemed potentially pertinent, they were then appraised as complete reports according to the following explicit selection criteria: (i) human studies, (ii) published between 2002 and October 2013, (iii) investigating patients with impaired LV systolic function, defined as LVEF < 50%, undergoing AFCA, or (iv) studies with unselected patients undergoing AFCA with a mean follow-up of at
least 2 years. Exclusion criteria were (one enough for exclusion): (i) non-human setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients was selected), (iii) studies including patients undergoing surgical or hybrid AF ablation, or (iv) studies without comprehensive follow-up description, including duration, clinical and echocardiographic data concerning at least one among New York Heart Association (NYHA) functional class, NT-proBNP levels, LVEF.

**Supplemental Results**

*Search results*

The first search identified 654 abstracts referring to AFCA in patients with LV systolic dysfunction; among this group, 632 were excluded following application of the inclusion and exclusion criteria; 22 of them were selected and full text was read by two Authors; 7 were excluded because of inclusion of patients with normal LV function or because of incomplete baseline or follow-up characteristics.

The second search identified 681 abstracts referring to long-term results of AFCA; among them, 646 were excluded following application of the inclusion and the exclusion criteria. Thirty-five of them were selected and full text was read by two Authors; 11 were excluded because of incomplete baseline or follow-up characteristics and 4 because reporting duplicate data. After this selection, 20 trials were identified, and the corresponding Author contacted, offering co-Authorship in return for data concerning patients with LV systolic dysfunction. Besides 9 Authors which did not agree to participate, most likely due to the fact that the required data were not easily or promptly available from their dataset, 11 provided requested data regarding the heart failure population.
**Supplemental Table.**

**Supplemental Table 1.** First Author, publication date, population and main characteristics of the included studies.

<table>
<thead>
<tr>
<th>First Author, Country, Year of Publication</th>
<th>Study design</th>
<th>N. patients</th>
<th>Follow-up (months)</th>
<th>AF recurrence monitoring</th>
<th>Paroxysmal AF (%)</th>
<th>Age (years)</th>
<th>Mean LVEF (%)</th>
<th>SR following first procedure (%)</th>
<th>SR at follow-up end (%)</th>
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</thead>
<tbody>
<tr>
<td>Chen, USA, 2004 (2)</td>
<td>Retrospective, single center</td>
<td>94</td>
<td>14</td>
<td>ECG and 24-hours Holter ECG at 2, 3, 6, 12 months</td>
<td>51%</td>
<td>57</td>
<td>36%</td>
<td>73%</td>
<td>96%</td>
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<tr>
<td>Hsu, France, 2004 (3)</td>
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<td>58</td>
<td>12</td>
<td>ECG and 48-hours Holter ECG at 1, 3, 6, 9, 12 months</td>
<td>9%</td>
<td>56</td>
<td>35%</td>
<td>50%</td>
<td>78%</td>
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<tr>
<td>Tondo, Italy, 2006 (4)</td>
<td>Prospective, single center</td>
<td>40</td>
<td>14</td>
<td>ECG and 24-hours Holter ECG at 1, 3, 6, 12 months</td>
<td>25%</td>
<td>57</td>
<td>33%</td>
<td>62%</td>
<td>87%</td>
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<td>Study Location</td>
<td>Study Design, Setting</td>
<td>Follow-Up</td>
<td>ECG and Visit Schedule</td>
<td>Follow-Up ECG</td>
<td>Dropout Rate (All Reasons)</td>
<td>Lost to Follow-Up</td>
<td>LTFP Rate</td>
<td>Study Authors and Country</td>
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<td>Gentlesk, USA, 2007 (5)</td>
<td>Prospective, single center</td>
<td>67</td>
<td>20</td>
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<td>70%</td>
<td>54</td>
<td>42%</td>
<td>58%</td>
<td>86%</td>
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<tr>
<td>Efremidis, Greece, 2007 (6)</td>
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<td>13</td>
<td>9</td>
<td>ECG and 24-hours Holter ECG at 1, 3, 6, 9, 12 months</td>
<td>0%</td>
<td>54</td>
<td>36%</td>
<td>62%</td>
<td>62%</td>
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<tr>
<td>Nademanee, USA, 2008 (7)</td>
<td>Prospective, single center</td>
<td>129</td>
<td>27</td>
<td>ECG and visit every 3 months; 24-hours Holter ECG every 12 months</td>
<td>40%</td>
<td>67</td>
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<td>-</td>
<td>79%</td>
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<td>Khan, France-USA-Italy-Australia-Czech Republic-Germany, 2008 (8)</td>
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<td>6</td>
<td>Event monitor from second to sixth month</td>
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<td>60</td>
<td>27%</td>
<td>71%</td>
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<td>ECG/Tele-ECG Method</td>
<td>Follow-up (n)</td>
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<td>Event-Free Survival Rate</td>
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<td>ECG and 24-hours Holter ECG at 3, 6, 12 months</td>
<td>39%</td>
<td>52</td>
<td>41%</td>
<td>50%</td>
<td>63%</td>
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<td>Choi, USA, 2010 (11)</td>
<td>Retrospective, single center</td>
<td>15, 16</td>
<td>ECG and 24-hours Holter ECG at 1, 3, 6, 12 months; tele-ECG for 2 weeks.</td>
<td>67%</td>
<td>56</td>
<td>37%</td>
<td>47%</td>
<td>73%</td>
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<td>62</td>
<td>36%</td>
<td>40%</td>
<td>50%</td>
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<td>ECG and 24-hours Holter ECG at 3, 12 months</td>
<td>28%</td>
<td>55</td>
<td>35%</td>
<td>-</td>
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<td>97</td>
<td>6</td>
<td>ECG and 48-hours Holter ECG at 3, 6 and every 6 months</td>
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<td>52</td>
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<td>12</td>
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<td>0%</td>
<td>64</td>
<td>22%</td>
<td>69%</td>
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<td>137</td>
<td>29</td>
<td>ECG and 24-hours Holter ECG at 1, 3, 6, 12 and every 6 months</td>
<td>69%</td>
<td>65</td>
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<td>72</td>
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<td>59</td>
<td>42%</td>
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<td>Pappone, Italy, 2011</td>
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<td>ECG and 48-hours Holter ECG at 3, 6, 12 months</td>
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<td>61</td>
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<td>5-Year</td>
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<tr>
<td>Medi, Australia, 2011 (20)</td>
<td>Retrospective, single center</td>
<td>40</td>
<td>ECG and 24-hours Holter ECG at 3, 6, 12 and every 6 months</td>
<td>100%</td>
<td>43</td>
<td>40%</td>
<td>25%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Weerasooriya, France, 2001 (21)</td>
<td>Prospective, single center</td>
<td>61</td>
<td>ECG and 24-hours Holter ECG at 1, 3, 6, 12 and every 12 months</td>
<td>25%</td>
<td>62</td>
<td>42%</td>
<td>25%</td>
<td>25%</td>
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</tr>
<tr>
<td>Bunch, USA, 2011 (22)</td>
<td>Retrospective, single center</td>
<td>71</td>
<td>ECG and visit at 3, 6, 12 and every 12 months</td>
<td>35%</td>
<td>67</td>
<td>35%</td>
<td>36%</td>
<td>45%</td>
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</tr>
<tr>
<td>Hunter, UK, 2012 (23)</td>
<td>Retrospective, multi center</td>
<td>43</td>
<td>ECG and 24-hours Holter ECG at 3, 6, 12 and every 12 months</td>
<td>36%</td>
<td>59</td>
<td>35%</td>
<td>35%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Lim, Australia, 2012 (24)</td>
<td>Prospective, single center</td>
<td>56</td>
<td>ECG and at 3, 6, 12 months; 7-days Holter ECG at 6, 12 months</td>
<td>30%</td>
<td>59</td>
<td>44%</td>
<td>48%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>M</td>
<td>Screening Method</td>
<td>Follow-up Schedule</td>
<td>AF Rate</td>
<td>N</td>
<td>LVEF</td>
<td>SR Rate</td>
</tr>
<tr>
<td>--------------------------------------</td>
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</tr>
<tr>
<td>Neumann, Germany, 2013 (25)</td>
<td>Prospective, single center</td>
<td>40</td>
<td>25</td>
<td>ECG and 7-days Holter ECG at 3, 6, 9, 12 and every 12 months</td>
<td></td>
<td>27%</td>
<td>58</td>
<td>43%</td>
<td>40%</td>
</tr>
<tr>
<td>Vogt, Germany, 2013 (26)</td>
<td>Prospective, single center</td>
<td>40</td>
<td>25</td>
<td>ECG and 7-days Holter ECG at 3, 6, 9, 12 months; ECG every 6 months later</td>
<td></td>
<td>97%</td>
<td>59</td>
<td>46%</td>
<td>37%</td>
</tr>
<tr>
<td>Fiala, Czech Republic, 2014 (27)</td>
<td>Prospective, single center</td>
<td>34</td>
<td>41</td>
<td>ECG and 24-hours Holter ECG at 3, 6, 12 and every 6 months; tele-ECG for 3 weeks</td>
<td></td>
<td>0%</td>
<td>59</td>
<td>38%</td>
<td>30%</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; LVEF: left ventricular ejection fraction; SR: sinus rhythm.
Supplemental Reference


