History of Atrial Fibrillation as a Risk Factor in Patients With Heart Failure and Preserved Ejection Fraction

Oluleye et al: Atrial Fibrillation in I-PRESERVE

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DOI: 10.1161/CIRCHEARTFAILURE.114.001523

Journal Subject Code: Heart Failure [11] Other heart failure
Abstract

Background—Atrial fibrillation (AFib) is common in heart failure (HF) with preserved ejection fraction (HFP EF). Current AFib stroke risk prediction models include the presence of HF but do not specifically include HFP EF as a risk factor. Whether a history of AFib should be used to identify patients with HFP EF who are at risk has not been established.

Methods and Results—Baseline characteristics and outcomes of patients with HFP EF in the I-PRESERVE Trial were analyzed in relation to AFib. At baseline, 1,209 (29.3%) had a history of AFib. Of these 557 (13.5%) had history of AFib alone, whereas 670 (16.2%) had both a history and AFib on ECG; 2,901 (70.3%) had neither. There were no significant differences in the risk of stroke between the two groups with a history of AFib who did or did not have AFib present on baseline ECG. During a median follow-up of 33 months, a fatal or non-fatal stroke occurred in 6.5% (79/1,209) patients with history of AFib compared to 3.9% (114/2,901) with no AFib. Having a history of AFib was independently associated with higher risk of stroke (hazard ratio 2.2; 95% CI 1.6-3.2; p<0.0001) compared to those with no history of AFib.

Conclusions—In patients with HFP EF, a history of AFib was common and independently associated with increased risk of stroke, regardless of whether AFib was present on ECG. Patients with HFP EF and a history of AFib should be considered at risk. Further studies are needed to determine whether this risk can be safely reduced.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT000095238.

Key Words: heart failure, preserved ejection fraction, atrial fibrillation, prognosis
Atrial fibrillation (AFib) is the most common arrhythmia and is responsible for significant morbidity and mortality in patients with heart failure (HF) with reduced (HFrEF) or preserved ejection fraction (HFpEF).\textsuperscript{1,2} There is a reciprocal relationship between HF and AFib in which HF predisposes to AFib and AFib worsens HF.\textsuperscript{3-5} Much is known about the role of AFib in HFrEF but studies of AFib in HFpEF are more limited. Some recent clinical trial and observational studies have shown that AFib is present in up to 43\% of patients with HFpEF and is perhaps more prevalent than in HFrEF.\textsuperscript{2,3,5-8}

Studies of patients with HFpEF have shown that the presence of AFib on an ECG is independently associated with a higher incidence of cardiovascular morbidity.\textsuperscript{2,7} Recent studies have indicated that periodic ECG’s may miss a number of patients who are at risk from AFib.\textsuperscript{9,10} A history of AFib may help identify some of these at-risk patients. The primary objective of this post-hoc analysis of data from the Irbesartan in Heart Failure with Preserved Ejection Fraction Trial (I-PRESERVE) was to determine whether a history of AFib is an independent risk factor for stroke in patients with HFpEF.

**Methods**

*Study design and patient selection*

I-PRESERVE was a randomized, placebo-controlled, double blind, multi-center trial that enrolled subjects with symptomatic HFpEF to evaluate the efficacy of the angiotensin receptor blocker irbesartan.\textsuperscript{11} Briefly, 4,128 patients, 60 years or older with symptomatic (NYHA class II to IV) HF with a left ventricular ejection fraction > 45\%, and at least one hospitalization for HF during the previous 6 months were eligible to be enrolled. Patients who had not been hospitalized were required to have ongoing class III or IV symptoms with corroborative evidence of HF, or a likely
substrate for HFP EF, such as electrocardiographic or echocardiographic evidence of moderate or severe left ventricular hypertrophy or left atrial enlargement in the absence of atrial fibrillation. The primary end point of the study was the composite of all-cause mortality and protocol specified cardiovascular hospitalizations. There were several secondary endpoints including all-cause mortality, cardiovascular death or HF-hospitalization, HF death or HF-hospitalization (HF composite endpoint). Deaths and hospitalizations were adjudicated by a blinded independent endpoint committee, using pre-specified criteria. Eligible patients were randomized to receive irbesartan or placebo in a 1:1 ratio stratified by site and use of an angiotensin converting enzyme (ACE) inhibitor at baseline. The study was approved by the Institutional Review Board at each center, and all subjects provided a written informed consent.

This analysis focused on patients classified as at risk based on the history of AFib in the case report forms with or without AFib documented on the required baseline ECG. The following study outcomes were analyzed in these groups and compared to the group that had neither a history or ECG indicating AFib: fatal or non-fatal stroke, cardiovascular death or HF-hospitalization, heart failure death or HF-hospitalization and all-cause mortality.

Statistical Analysis

The baseline characteristics of subjects with a history of AFib with or without AFib at baseline on their ECG, and those without any indication of AFib were compared to each other using analysis of variance for continuous variables or cross tabulation for categorical variables with a Bonferroni correction for multiple pairwise comparisons when the overall p-value was significant. Distributions of the natriuretic peptide levels were positively skewed and were transformed using logarithms for analysis. Unadjusted Kaplan-Meier curves are shown to describe the study
outcomes in each group. Because the investigational medication, irbesartan did not have a significant effect on any of the study endpoints, all enrolled subjects were included in this analysis.

Cox regression analyses were employed to estimate hazard ratios for each of the study outcomes for the two distinct groups with a history of AFib, those with or without AFib also present on their baseline ECG, as well as both of these groups combined compared to the group with no history or ECG record of having AFib. The two groups with a history of AFib were compared to each other by simply changing the reference group for the AFib group indicator variable in the Cox regression analyses. Because all but 18 (2.7%) of the 670 subjects that had AFib on their baseline ECG also had a history of AFib, we included these 18 patients whose history was most likely misclassified in the group with both a history of AFib and AFib on ECG. The results were not substantially different when these 18 subjects were excluded from all groups (not reported). Adjusted hazard ratios were estimated by multivariable Cox regression including age at baseline, sex, race, history of ischemic heart disease, chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia, stroke, renal artery disease, diabetes mellitus, hospitalization for HF in previous 6 months, heart block, and other arrhythmias, chronic kidney disease, anemia, systolic blood pressure, left ventricular hypertrophy on ECG, albumin, platelet count, and treatment with irbesartan, antiarrhythmic, antiplatelet agent, antithrombotic agent, calcium channel blocker, beta-blocker, angiotensin converting enzyme inhibitor, digoxin, diuretic, spironolactone, nitrate, lipid lowering drugs, and an ICD/pacemaker. Several clinical variables that could be affected by the presence of ongoing AFib at baseline including pulmonary congestion on x-ray, rales, jugular venous distention, liver enlargement, New York Heart Association class, heart rate and natriuretic peptide weren’t included in these multivariable regression analyses to avoid over adjustment for potential mediators of the effects of AFib on study outcomes. The
proportional hazards assumption for each variable and outcome was examined using Schoenfeld residuals. Stata software version 12.1 was used for all analyses.

Results

Baseline Characteristics in Relation to Atrial Fibrillation Indicators

A history of AFib was present in 29% (1,209/4,128) of the patients, and in approximately half of these (670/1,209) AFib was documented on baseline ECG. There was no history or ECG documentation of AFib in 2,901 out of the 4,128 patients.

Baseline characteristics of the three groups defined by AFib indicators are summarized in Table 1. The groups with or without AFib on their baseline ECG were similar except for several signs and symptoms of decompensated HF, cardiac rhythm disturbances, ischemic heart disease and medications. Both groups with indicators of AFib differed from those without AFib on a number of variables.

Association between Indicators of Atrial Fibrillation and Outcomes

During a median follow-up of 53 months (IQR: 41 to 60 months), fatal or non-fatal stroke occurred in 5.7% (38/670) patients with history and AFib on ECG compared to 7.4% (41/557) with history of AFib alone and in 3.9% (114/2901) with no AFib (Figure 1a), cardiovascular death or heart failure hospitalization occurred in 45% (302/670) patients with history and AFib on ECG compared to 54% (298/557) with history of AFib alone and in 35% (1021/2901) with no AFib (Figure 1b); the HF-death or HF-hospitalization composite endpoint occurred in 29% (196/670) patients with history and AFib on ECG compared to 26% (146/557) with history of AFib alone, and in 13% (367/2901) with no AFib (Figure 1c); 30% (203/670) patients with history and ECG
evidence of AFib died from any cause compared to 28% (156/557) with history of AFib alone and 18% (515/2901) with no AFib (Figure 1d).

Table 2 shows the unadjusted and adjusted comparisons of study outcomes in AFib indicator groups. Except for a higher risk of HF hospitalizations or death in the group with AFib on baseline ECG, there were no significant differences in the outcomes between the two AFib groups defined by ECG. As shown in Table 1, the group with AFib on baseline ECG had more signs and symptoms of heart failure as expected and these variables weren’t included in the adjustment model (see statistical section). The increased risk of stroke was significant and similar in the groups with or without AFib on the baseline ECG. Combining these two groups, the adjusted estimate of the increase in the risk of fatal or nonfatal stroke associated with a history of AFib was HR 2.2 (95% confidence interval 1.6 to 3.2) compared to the group with no indication of AFib. A history of AFib was significantly associated with cardiovascular death or HF-hospitalization, 1.2 (1.0 to 1.4) and HF-death or HF-hospitalization 1.3 (1.1 to 1.6) but not with all-cause mortality.

Discussion

In this analysis of I-PRESERVE we found that although 29% patients had a history of AFib at baseline, AFib was confirmed on ECG in only half (54%) of them (16% of total cohort), and the remaining patients (14% of the cohort) had a history of AFib alone. The presence of AFib on the baseline ECG did not increase the significant risk of stroke associated with a history of AFib. To the best of our knowledge this is the first report to highlight this finding in patients with HFpEF. Although the risk associated with AFib on ECG in patients with HFpEF has been examined previously,2, 7, 12-15 this analysis indicates that a history of AFib is also associated with an increased risk of cardiovascular morbidity and mortality including stroke. These results, therefore, suggest
that a history of AFib should be taken into consideration when assessing the risks of AFib in patients with HFpEF regardless of whether AFib is present on ECG.

Although it is well known that AFib increases the risk of ischemic stroke in patients with HFrEF, only a few recent studies have reported that the risk of stroke is also increased in patients with HFpEF patients. Studies have compared the risk of stroke in patients with AFib and HFrEF or HFpEF. A subgroup analysis of the Atrial Fibrillation Follow up Investigation of Rhythm Management (AFFIRM) trial found that although the history of stroke was more prevalent in patients with HFpEF compared to HFrEF at baseline (16% vs 11%), the subsequent incidence of stroke during the study was no different between the groups. The CHARM study also did not find a difference in the incidence of stroke in AFib patients with either HFrEF or HFpEF. In patients with pre-existing AFib, McManus et al reported a 91% higher risk of ischemic stroke in HFpEF and only 7% higher risk in HFrEF compared to those without AFib. The most recent data comes from the post-hoc analyses of the new oral anticoagulant trials such as ARISTOTLE, ROCET 13 and RE-LY. These studies show that although the risk of stroke or systemic embolism was significantly higher in patients with a diagnosis of HF compared with those with no HF, the risk of stroke or systemic embolism was no different in patients with HF with preserved or reduced EF. These data suggest that the risk of stroke in patients with AFib and HFpEF is at least as high as those in patients with AFib and HFrEF and that the guidelines should specifically emphasize the inclusion of all patients with HF in the CHADS2 and CHA2DS2-VASc scoring system, irrespective of the EF. Furthermore, our data suggest that the same guidelines should also apply to patients with HFpEF even when they only have a history of AFib that is not confirmed on ECG.
The original CHADS2 score (Congestive heart failure, Hypertension, Age, Diabetes mellitus and prior stroke or transient ischemic attack) designed to help estimate the risk of stroke and need of anticoagulation in patients with non-valvular AFib was based on studies in patients with HF with LV dysfunction.\textsuperscript{18} Accordingly, the 2006 and 2011 ACC/AHA/HRS AFib clinical practice guidelines recommended use of CHADS2 score as a guide to anticoagulation of patients with AFib and HF with impaired left ventricular systolic function but did not mention HFpEF.\textsuperscript{19,20} The most recent ESC AFib 2012 guidelines recommend the use of CHA\textsubscript{2}DS\textsubscript{2}-VASc instead of the CHADS\textsubscript{2} score and define HF as “documented moderate-to-severe systolic dysfunction or patients with recent decompensated heart failure requiring hospitalization, irrespective of ejection fraction” but do not include stable patients with HFpEF.\textsuperscript{21} The two most recent HF guidelines also do not specifically mention HFpEF. The 2012 ESC HF guideline endorses thromboembolic prophylaxis in patients with HF and AFib based on the CHA\textsubscript{2}DS\textsubscript{2}-VASc score, defining HF as congestive heart failure or LVEF <40\%,\textsuperscript{22} and the most recent, 2013 ACCF/AHA HF guideline recommends the use of anticoagulant in “patients with chronic heart failure with permanent, persistent, or paroxysmal AF and an additional risk for cardio-embolic stroke”.\textsuperscript{1} Hence, although the intent of the guidelines might have been to include all HF patients irrespective of LVEF, the written document may be ambiguous and clinicians may not be entirely clear on this issue.

\textit{Strengths and Limitations}

This analysis is based on the largest randomized clinical trial of well characterized patients with HFpEF where all outcomes were adjudicated. In addition, we were able to examine AFib separately by history alone and AFib confirmed by ECG along with a number of established prognostic variables including co-morbidities, clinical exam and laboratory data, and medication
use. However, this is a secondary analysis of data from a randomized controlled trial and some of
the findings may be spurious although the results are consistent with previous studies. The results
may not be widely applicable. For example, I-PRESERVE subjects with HFpEF were
predominantly white and the results may not be generalizable to other racial groups. The presence
of atrial fibrillation was assessed at baseline by a single ECG. However, this limitation is unlikely
to change our conclusions since the outcomes were similar in those with history of AFib not
confirmed on ECG. Indeed, a history of AFib seemed to be sufficient to increase the risk and
captured nearly all of the patients with AFib on ECG. Since we did not have data on patients with
HFrEF including sets of covariates, comparisons of the different types of heart failure could not be
made as some previous studies have done.

In conclusion, in this sample of patients with HFpEF a history of AFib was common and
independently associated with increased risk of fatal or non-fatal stroke. Presence of AFib on ECG
did not significantly heighten the risk. Patients with HFpEF and a history of AFib should be
considered at risk of stroke, and HFpEF should be included as a risk factor in stroke prediction
models for patients with AFib. Future studies are needed to determine whether this risk can be
safely reduced.

Sources of Funding
Bristol-Myers Squibb sponsored the I-PRESERVE Trial. T.R. was supported by resources and
facilities of the Minneapolis VA Health Care System. The views expressed herein do not
necessarily represent the views of the Department of Veterans Affairs or the U.S. Government.
Disclosures

OWO, TSR, and SW do not report any conflict of interest. All the remaining authors were consultant to Bristol-Myers Squibb.

References


cardiology/american heart association task force on practice guidelines and the european
society of cardiology committee for practice guidelines (writing committee to revise the
2001 guidelines for the management of patients with atrial fibrillation) developed in
 colaboration with the european heart rhythm association and the heart rhythm society.

*Europace.* 2006;8:651-745.

20. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay
accf/aha/hrf focused updates incorporated into the acc/aha/esc 2006 guidelines for the
management of patients with atrial fibrillation: A report of the american college of
cardiology foundation/american heart association task force on practice guidelines
developed in partnership with the european society of cardiology and in collaboration with
the european heart rhythm association and the heart rhythm society. *J Am Coll Cardiol.*
2011;57:e101-198.

guidelines for the management of atrial fibrillation: An update of the 2010 esc guidelines
for the management of atrial fibrillation--developed with the special contribution of the

22. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V,
Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni
AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J,
ESCCfP. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure
2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of
the european society of cardiology. Developed in collaboration with the heart failure
Table 1. Baseline Characteristics in Groups with and without Indicators of Atrial Fibrillation.

<table>
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<tr>
<th></th>
<th>None</th>
<th>History Only</th>
<th>History &amp; ECG</th>
<th>P-Value</th>
<th>Overall</th>
<th>AFib groups†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>2901 (70%)</td>
<td>557 (14%)</td>
<td>670 (16%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71 (6.8)</td>
<td>73 (6.6)</td>
<td>74 (7.1)</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>1091 (38)</td>
<td>238 (43)</td>
<td>308 (46)</td>
<td></td>
<td>&lt; 0.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Non-White (%)</td>
<td>92</td>
<td>97</td>
<td>97</td>
<td></td>
<td>&lt; 0.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>2609 (90)</td>
<td>480 (86)</td>
<td>561 (84)</td>
<td></td>
<td>&lt; 0.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>785 (27)</td>
<td>159 (29)</td>
<td>182 (28)</td>
<td></td>
<td>0.73 ND</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia, No (%)</td>
<td>1328 (46)</td>
<td>255 (46)</td>
<td>227 (34)</td>
<td></td>
<td>&lt;0.0001 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease, No (%)</td>
<td>1565 (54)</td>
<td>274 (50)</td>
<td>257 (39)</td>
<td></td>
<td>&lt;0.0001 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA, No (%)</td>
<td>243 (8.4)</td>
<td>75 (14)</td>
<td>81 (12)</td>
<td></td>
<td>&lt; 0.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Renal artery disease (%)</td>
<td>10.2</td>
<td>3.0</td>
<td>2.4</td>
<td></td>
<td>0.002 NS</td>
<td></td>
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<tr>
<td>COPD/asthma, No (%)</td>
<td>237 (8.2)</td>
<td>87 (16)</td>
<td>67 (10)</td>
<td></td>
<td>&lt; 0.0001 0.009</td>
<td></td>
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<tr>
<td>Valve disease, No (%)</td>
<td>216 (7.5)</td>
<td>109 (20)</td>
<td>126 (19)</td>
<td></td>
<td>&lt; 0.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Other arrhythmia, No (%)</td>
<td>337 (12)</td>
<td>99 (18)</td>
<td>57 (8.5)</td>
<td></td>
<td>&lt;0.0001 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Heart block, No (%)</td>
<td>54 (1.9)</td>
<td>30 (5.4)</td>
<td>16 (2.4)</td>
<td></td>
<td>&lt; 0.0001 0.02</td>
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<tr>
<td>Pacemaker/ICD Implanted, No (%)</td>
<td>102 (3.5)</td>
<td>91 (16)</td>
<td>71 (11)</td>
<td></td>
<td>&lt; 0.0001 0.04</td>
<td></td>
</tr>
<tr>
<td>HF admission in last 6 months for HF, No (%)</td>
<td>1073 (37)</td>
<td>332 (60)</td>
<td>411 (62)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>Hypertensive HF etiology, No (%)</td>
<td>1933 (66.6)</td>
<td>320 (58)</td>
<td>359 (55)</td>
<td></td>
<td>&lt; 0.0001 NS</td>
<td></td>
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<tr>
<td>Ischemic HF etiology, No (%)</td>
<td>771 (27)</td>
<td>135 (24)</td>
<td>130 (19)</td>
<td></td>
<td>0.001 NS</td>
<td></td>
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<tr>
<td>Diastolic blood pressure, mean (SD), mmHg</td>
<td>79 (8.9)</td>
<td>77 (9.5)</td>
<td>79(9.4)</td>
<td>0.0003 NS</td>
<td></td>
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<tr>
<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>137 (14)</td>
<td>136 (17)</td>
<td>134 (15)</td>
<td>&lt; 0.0001 NS</td>
<td></td>
<td></td>
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<tr>
<td>Heart Rate, mean (SD)</td>
<td>71 (9.8)</td>
<td>70 (11)</td>
<td>76 (12)</td>
<td></td>
<td>&lt; 0.0001 &lt;0.0001</td>
<td></td>
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<tr>
<td>JVD, No. (%)</td>
<td>204 (7.0)</td>
<td>39 (7.0)</td>
<td>103 (16)</td>
<td></td>
<td>&lt; 0.0001 &lt;0.0001</td>
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<tr>
<td>Liver enlargement, No. (%)</td>
<td>533 (18)</td>
<td>81 (14)</td>
<td>139 (21)</td>
<td></td>
<td>0.014 0.015</td>
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<tr>
<td>Rales, No. (%)</td>
<td>790 (27)</td>
<td>142 (25)</td>
<td>226 (34)</td>
<td></td>
<td>0.002 0.006</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy, No. (%)</td>
<td>938 (32)</td>
<td>163 (29)</td>
<td>159 (24)</td>
<td></td>
<td>&lt; 0.0001 NS</td>
<td></td>
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<tr>
<td>Left Bundle Branch Block, No. (%)</td>
<td>244 (8.4)</td>
<td>48 (8.6)</td>
<td>44 (6.6)</td>
<td>0.28</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>History Only</td>
<td>History &amp; ECG</td>
<td>Overall</td>
<td>AFib groups†</td>
<td></td>
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<tr>
<td>Pulmonary Congestion on CXR, No. (%)</td>
<td>999 (36)</td>
<td>244 (45)</td>
<td>347 (54)</td>
<td>&lt; 0.0001</td>
<td>0.006</td>
<td></td>
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<tr>
<td>Left ventricle EF %, mean (SD)</td>
<td>60 (9.1)</td>
<td>59 (8.9)</td>
<td>58 (9.3)</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td></td>
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<tr>
<td>Left Atrial area, cm² mean (SD)¶</td>
<td>21.3 (5.0)</td>
<td>25.3 (6.6)</td>
<td>29.7 (6.3)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td></td>
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<tr>
<td>eGFR, mean (SD), ml/min</td>
<td>74 (22)</td>
<td>69 (23)</td>
<td>69 (21)</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CKD, No (%)</td>
<td>795 (27.7)</td>
<td>219 (40.0)</td>
<td>229 (35.7)</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td></td>
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<tr>
<td>NT-proBNP median (IQR), pg/ml</td>
<td>230 (104-538)</td>
<td>534 (232-1118)</td>
<td>1319 (776-2062)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
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<td>Irbesartan, No. (%)</td>
<td>1,455 (50)</td>
<td>267 (48)</td>
<td>345 (51)</td>
<td>0.37</td>
<td>ND</td>
<td></td>
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<td>ACE inhibitor, No. (%)</td>
<td>696 (24)</td>
<td>154 (28)</td>
<td>183 (27)</td>
<td>0.08</td>
<td>ND</td>
<td></td>
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<td>Antiplatelet, No. (%)</td>
<td>1893 (65)</td>
<td>294 (53)</td>
<td>229 (34)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Antiarhythmic, No. (%)</td>
<td>99 (3.4)</td>
<td>178 (32)</td>
<td>82 (12)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Anticoagulant, No (%)</td>
<td>128 (4.4)</td>
<td>230 (41)</td>
<td>432 (64)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker, No. (%)</td>
<td>1714 (59)</td>
<td>321 (58)</td>
<td>392 (58)</td>
<td>0.80</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker, No. (%)</td>
<td>1221 (42)</td>
<td>194 (35)</td>
<td>222 (33)</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Diuretic, No. (%)</td>
<td>2307 (80)</td>
<td>485 (87)</td>
<td>626 (93)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Lipid lowering, No. (%)</td>
<td>936 (32)</td>
<td>174 (31)</td>
<td>169 (25)</td>
<td>0.002</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Digoxin, No. (%)</td>
<td>131 (4.5)</td>
<td>108 (19)</td>
<td>322 (48)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Nitrate, No. (%)</td>
<td>828 (29)</td>
<td>134 (24)</td>
<td>146 (22)</td>
<td>0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Spironolactone, No. (%)</td>
<td>358 (12)</td>
<td>110 (20)</td>
<td>165 (25)</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

† comparing the two groups that did or didn’t have AFib on baseline ECG if overall ANOVA p-value was < 0.01. ND – not done because overall not significant. NS – not significant with Bonferroni correction for possible 3 pairwise comparisons.

ACE, Angiotensin converting enzyme; AFib, Atrial fibrillation; CABG, Coronary Artery Bypass Surgery; CXR, Chest X-ray; COPD, Chronic obstructive pulmonary disease; CKD, Chronic Kidney disease; CVA, Cerebrovascular disease; ECG, Electrocardiogram; eGFR, estimated glomerular filtration rate; EF, Ejection fraction; Hosp, Hospitalization; ICD, Implantable cardioverter defibrillator; JVD, Jugular venous distension; NT-proBNP, N terminal pro B natriuretic peptide; NYHA, New York Heart Association; PCI, Percutaneous Angioplasty; TIA, Transient ischemic attack.

¶Left atrial area was measured in 696 subjects only.
Table 2. Comparison of Outcomes in Atrial Fibrillation Indicator Groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fatal or Non-fatal Stroke</th>
<th>CV death/HF-hospitalization</th>
<th>HF death/HF-hospitalization</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UnadjustedHR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>UnadjustedHR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>(n=4,128)</td>
<td>(n=3,942)</td>
<td>(n=4,128)</td>
<td>(n=3,942)</td>
</tr>
<tr>
<td>History of AFib without AFib on ECG</td>
<td>1.00 (reference group)</td>
<td>1.00 (reference group)</td>
<td>1.00 (reference group)</td>
<td>1.00 (reference group)</td>
</tr>
<tr>
<td>History of AFib with AFib on ECG</td>
<td>0.94 (0.62-1.44)</td>
<td>1.16 (0.72-1.86)</td>
<td>1.81 (0.99-1.52)</td>
<td>1.28 (1.01-1.64)*</td>
</tr>
<tr>
<td>No AFib on history or baseline ECG</td>
<td>1.00 (reference group)</td>
<td>1.00 (reference group)</td>
<td>1.00 (reference group)</td>
<td>1.00 (reference group)</td>
</tr>
<tr>
<td>History of AFib without AFib on ECG</td>
<td>1.97 (1.38-2.81)</td>
<td>2.12 (1.40-3.21)**</td>
<td>1.85 (1.31-2.61)</td>
<td>2.45 (1.54-3.92)**</td>
</tr>
<tr>
<td>History of AFib with AFib on ECG</td>
<td>1.90 (1.44-2.52)**</td>
<td>2.24 (1.55-3.24)**</td>
<td>1.90 (1.44-2.52)**</td>
<td>2.24 (1.55-3.24)**</td>
</tr>
<tr>
<td>Combined Groups with History of AFib</td>
<td>1.90 (1.44-2.52)**</td>
<td>2.24 (1.55-3.24)**</td>
<td>1.90 (1.44-2.52)**</td>
<td>2.24 (1.55-3.24)**</td>
</tr>
</tbody>
</table>

‡ adjusted for age, sex, race, history of ischemic heart disease, renal artery disease, COPD, hypertension, hyperlipidemia, stroke, diabetes mellitus, HF hospitalization in last 6 months, heart block, other arrhythmias, chronic kidney disease, anemia, systolic blood pressure, left ventricular hypertrophy (ECG), albumin, platelets, treatment with irbesartan, antiarrhythmic, antiplatelet, antithrombotic, calcium channel blocker, beta-blocker, angiotensin converting enzyme inhibitor, digoxin, diuretic, spironolactone, nitrate, lipid lowering, ICD and pacemaker.

* p < 0.01, ** p < 0.001
Figure Legend

Figure 1. Kaplan-Meier curves for time to fatal or non-fatal stroke (panel a), cardiovascular death or HF hospitalization (panel b), HF death or HF hospitalization (panel c), and all-cause mortality (panel d) in groups defined by a history of AFib, a history of AFib confirmed by electrocardiogram or no indication of AFib.
Figure 1a: Fatal or Non-Fatal Stroke

- no AFib
- History of AFib without AFib on ECG
- History of AFib with AFib on ECG

Figure 1b: Cardiovascular Death or HF Hospitalization

- no AFib
- History of AFib without AFib on ECG
- History of AFib with AFib on ECG

Figure 1c: Heart Failure Death or Hospitalization

- no AFib
- History of AFib without AFib on ECG
- History of AFib with AFib on ECG

Figure 1d: All-Cause Mortality

- no AFib
- History of AFib without AFib on ECG
- History of AFib with AFib on ECG

p < 0.0001
History of Atrial Fibrillation as a Risk Factor in Patients With Heart Failure and Preserved Ejection Fraction
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Circ Heart Fail. published online September 15, 2014;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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