Temporal Relationship and Prognostic Significance of Atrial Fibrillation in Heart Failure Patients With Preserved Ejection Fraction
A Community-Based Study
Rosita Zakeri, MBChB; Alanna M. Chamberlain, PhD, MPH; Véronique L. Roger, MD, MPH; Margaret M. Redfield, MD

Background—In patients with heart failure and preserved ejection fraction (HFpEF), atrial fibrillation (AF) may predate, concur with, or develop after HFpEF diagnosis. We sought to define the temporal relationship between AF and HFpEF, to identify factors associated with AF, and to determine the prognostic impact of prevalent and incident AF in HFpEF.

Method and Results—From 1983 to 2010, 939 Olmsted County, Minnesota, residents (age, 77±12 years; 61% female) newly diagnosed with HFpEF (EF ≥0.50) were evaluated. Baseline rhythm classification included prior AF (>3 months before HFpEF diagnosis), concurrent AF (±3 months), or sinus rhythm. Incident AF (>3 months after HFpEF diagnosis) and all-cause mortality were ascertained through February 2012. Prior AF (29%) and concurrent AF (23%) were associated with older age, higher brain-type natriuretic peptide, and larger left atrial volume index at HFpEF diagnosis compared with sinus rhythm. Of HFpEF patients in sinus rhythm at diagnosis, 32% developed AF over a median follow-up of 3.7 years (interquartile range, 1.5–6.7 years; 69 events per 1000 person-years). Age and diastolic dysfunction were positively and statin use was inversely associated with incident AF. With no AF used as the referent, prior or concurrent AF (combined hazard ratio, 1.3; 95% confidence interval, 1.0–1.6; P=0.03) and incident AF, modeled as a time-dependent covariate (hazard ratio, 2.1; 95% confidence interval, 1.4–3.0; P<0.001), were independently associated with death after adjustment for pertinent covariates.

Conclusions—AF occurs in two thirds of HFpEF patients at some point in the natural history and confers a poor prognosis. Further study is required to determine whether intervention for AF may improve outcomes or if statin use can prevent AF in HFpEF. (Circulation. 2013;128:1085-1093.)

Key Words: atrial fibrillation | heart failure, diastolic | population | prognosis

There is an apparent collusion of 3 major trends: aging of the population, a virtual epidemic of atrial fibrillation (AF), and the emergence of heart failure (HF) with preserved ejection fraction (HFpEF) as the dominant form of HF, almost unique to the elderly.1–3 Development of effective therapy for HFpEF has proved challenging, in part because of the heterogeneous and incompletely understood pathophysiological mechanisms that occur in the setting of multiple comorbidities.

Clinical Perspective on p 1093

AF is a common comorbidity in HFpEF, reported in 25% to 39% of HFpEF patients, consistent across trial,4,5 community,6,7 registry,8 and hospitalized9,10 cohorts. AF may occur in patients destined to develop HFpEF as a result of similar risk factors such as aging and hypertension and may precipitate HF in persons with milder impairment in cardiovascular function as a result of effects on heart rate or atrioventricular synchrony. Alternatively, HFpEF may predispose to AF as a result of chronic left atrial hypertension and atrial remodeling. Thus, AF may represent a consequence of HFpEF progression as occurs in HF with reduced ejection fraction (HFrEF),11 in which AF is observed in patients with more severe functional impairment and systolic dysfunction.12

Although previous studies have focused on AF present at the time of recruitment or first HFpEF hospitalization,3,13–16 we examined a large community-based cohort of patients with incident HFpEF who had previous and subsequent ascertainment of AF and vital status. Thus, this cohort provided the unique ability to describe timing of AF occurrence in relation to HFpEF diagnosis. The objective of this study was to

Received January 22, 2013; accepted July 19, 2013.
From the Cardiorenal Research Laboratory (R.Z., M.M.R.) and Department of Health Sciences Research (A.M.C., V.L.R.), and Division of Cardiovascular Diseases (V.L.R., M.M.R.), Mayo Clinic, Rochester, MN.
Guest Editor for this article was Gregg C. Fonarow, MD.
The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.001475/-/DC1.
Correspondence to Rosita Zakeri, MBChB, Cardiorenal Research Laboratory, Guggenheim 9, Mayo Clinic, 200 First St, Rochester, MN 55905. E-mail zakeri_rosita@mayo.edu
© 2013 American Heart Association, Inc.
Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.113.001475
determine whether the association of AF with cardiac dysfunction, HF severity, or prognosis differed according to the temporal relationship of AF to HFpEF onset. We hypothesized that regardless of temporal association, the presence of AF is associated with worse cardiac dysfunction, HF severity, and prognosis in HFpEF.

Methods

Study Setting

This population-based cohort study was conducted within Olmsted County, Minnesota, using resources of the Rochester Epidemiology Project as previously described.6,17

Identification of the HFpEF Cohort

Olmsted County residents with a first diagnosis of HF between January 1, 1983, and December 31, 2010 (n=2852), were identified and HF was validated as part of an ongoing Olmsted County HF surveillance study.6,18 Patients who underwent echocardiography within 2 months of HF diagnosis with an EF ≥0.5 were determined to have HFpEF and formed the final study cohort. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review boards. Informed consent for examination of medical records (or waiver before 1997) was obtained as appropriate.

AF Ascertainment

Prevalent AF was identified by documented AF on a clinically indicated ECG or International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code pertaining to AF (427.31), AF/flutter (427.3), or atrial flutter alone (427.3).19 Prevalent AF was further subdefined as AF occurring prior to (>3 months) or concurrent with (±3 months) HFpEF diagnosis. Patients in sinus rhythm (SR) at HF diagnosis at the time of HFpEF diagnosis formed the referent population for baseline comparisons and ascertainment of incident AF during follow-up. Incident AF diagnosis was defined by date of first documentation of AF or atrial flutter on ECG or relevant ECG code in the medical record >3 months after HFpEF diagnosis, during any hospitalization, or during any outpatient visit. AF-related diagnostic codes were included because 12-lead ECG documentation alone has previously been reported to miss up to 10% of incident AF during follow-up.19 A random sample of 183 positively coded records were reviewed, and ECG or other documentation (rhythm strip or Holter monitor) of AF confirmed AF in all cases.

Data Collection

Patient demographics, clinical diagnoses, laboratory results, and CHADS2, and CHA2DS2-VASc scores were electronically abstracted from medical records (see Methods in the online-only Data Supplement). Echocardiographic data, including EF, left ventricular dimensions, diastolic function, pulmonary artery pressure, left atrial volume index (LAVI), and valvular disease within 2 months of HFpEF diagnosis, were obtained from the Mayo Clinic echocardiographic database.

Ascertainment of Vital Status

Vital status was determined through February 29, 2012, via Rochester Epidemiology Project procedures as previously described.6

Statistical Analysis

Group data are presented as frequencies, mean±SD, or median and interquartile range as appropriate. Because estimated glomerular filtration rate, brain-type natriuretic peptide, and thyroid-stimulating hormone distributions were skewed, values were log-transformed for analysis. Across-group comparisons were made with the Pearson χ² test for categorical variables and 1-way ANOVA or Kruskal-Wallis test for continuous variables. Pairwise comparisons across groups were subject to Bonferroni correction for multiple comparisons. Cox proportional hazards regression was used to identify patient characteristics associated with incident AF. Unadjusted and age- and sex-adjusted Cox models were explored, with additional multivariable models adjusting for pertinent clinical baseline variables. Significant correlations and interactions (P<0.05) were assessed and accounted for.

Overall survival was estimated with the Kaplan-Meier method. Between-group survival was compared by the log-rank test. Cox proportional hazards regression was used to examine the association between all-cause death and AF status, controlling for pertinent covariates. Incident AF was modeled as a time-dependent covariate. All P values were 2 tailed; values of P<0.05 were considered the threshold for statistical significance. Analyses were performed with JMP version 9.0 (SAS Institute, Cary, NC) and R version 2.14.1 (The R Foundation for Statistical Computing).

Results

Population Characteristics

Over the study period, 2852 Olmsted County residents had a new HF diagnosis. In 872 patients, echocardiographic confirmation of EF was unavailable. These patients were older and had more chronic obstructive pulmonary disease but were otherwise comparable to patients with confirmed EFs (Table I in the online-only Data Supplement). From the remaining 1980 patients, 939 (47.4%) had an EF ≥0.50 at HF diagnosis. Among these, 541 of 939 HFpEF patients (57.6%) were captured during a hospitalization; 398 of 939 (42.4%) were outpatients. Of the inpatient cohort, 23.8% were in New York Heart Association class III or IV compared with 12.5% of the outpatient cohort.

Prevalent AF and HFpEF

At HFpEF diagnosis, 270 patients (28.8%) had prior AF, 219 (23.3%) had concurrent AF, and 450 (47.9%) were in SR (Table I and Figure 1). Among patients with prior AF, the median duration of AF was 5.1 years (interquartile range, 2.4–10.0 years). Prevalent AF was defined as prior and concurrent combined and varied but did not appreciably increase over the study duration (1983–1990, 56%; 1991–2000, 45%; 2001–2010, 56%).

Compared with patients in SR, HFpEF patients with prior or concurrent AF were older, had higher brain-type natriuretic peptide and LAVI, had shorter deceleration times, and tended to have higher E/e′ (Table 1). Patients with concurrent AF had higher heart rates than patients with prior AF or SR, lower blood pressure and diabetes mellitus prevalence than HFpEF patients in SR, and lower LAVI and statin use than patients with prior AF. Patients with prior AF had more cerebrovascular disease than patients in SR or with concurrent AF. Importantly, standard HF medications, EF, left ventricular size, and pulmonary pressures were similar regardless of AF status.

Incidence and Risk Factors for AF in HFpEF

Over a median follow-up of 3.7 years, 142 patients (31.6%) in SR at HFpEF diagnosis were subsequently diagnosed with AF, giving an unadjusted incidence of 69 AF events per 1000 person-years. The median time to AF development was 3.1 years (interquartile range, 1.2–5.0 years; Figure 2). No significant secular trend in AF incidence was observed over the study duration (time period: unadjusted P=0.28; age- and sex-adjusted P=0.18).
HFpEF patients who developed AF had less severe symptoms and lower rates of statin use at HF diagnosis than patients who did not; otherwise, they were similar with respect to baseline clinical and echocardiographic characteristics (Table 2). Univariable associations with incident AF included older age, hypertension, lower estimated glomerular filtration rate, larger LAVI, and higher filling pressures (estimated by E/e’; Table 3). LAVI and E/e’ were moderately correlated with each other (Spearman p=0.3; P=0.0005). In multivariable models, higher E/e’ remained associated with...
incident AF after adjustment for age, sex, hypertension, estimated glomerular filtration rate, and statin use (hazard ratio, 1.47; 95% confidence interval, 1.00–2.12; P=0.05; Table II in the online-only Data Supplement). Statin use was associated with a lower incidence of AF before and after adjustment for age and sex (Table 3).20 Pertinent clinical variables (hazard ratio, 0.60; 95% confidence interval, 0.38–0.92; P=0.02; Table II in the online-only Data Supplement), and low-density lipoprotein levels within 1 year of HFpEF diagnosis (hazard ratio, 0.54; 95% confidence interval, 0.32–0.89; P=0.02; Table III in the online-only Data Supplement). The CHADS2 and CHA2DS2-VASc scores were also associated with incident AF (Table 3).20

Impact of AF on Survival in HFpEF
Survival data were available for all patients in this study. The median follow-up was 4.3 years (interquartile range, 1.9–7.2 years) or 3998 person-years after HFpEF diagnosis. There were 684 deaths overall (72.8% of the study population). Survival at 2 years was lower in subjects with prevalent AF compared with SR at HFpEF diagnosis (73.2 versus 79.8%; P=0.02; Figure 3). Compared with HFpEF patients without prevalent or incident AF, prevalent AF was associated with reduced survival even after adjustment for age, sex, and pertinent clinical variables (Table 4). When stratified by AF group, prior AF was associated with reduced age- and sex-adjusted survival (hazard ratio for mortality, 1.40; 95% confidence interval, 1.16–1.70; P<0.0006), while concurrent AF demonstrated a trend toward reduced age- and sex-adjusted survival (hazard ratio, 1.18; 95% confidence interval, 0.96–1.45; P=0.11) compared with patients with no AF. The independent relationship between prior AF and mortality persisted after adjustment for pertinent covariates (Table IV in the online-only Data Supplement). Compared with HFpEF patients without prevalent or incident AF, incident AF was also independently associated with reduced survival after adjustment for pertinent covariates (Table IV). No sex-based differences were observed in AF incidence or HFpEF survival in this study.

Discussion
In this large, population-based cohort study, more than two thirds of HFpEF patients had AF prior to, concurrent with, or subsequent to HFpEF diagnosis, underscoring the interplay of these 2 conditions. At HFpEF diagnosis, patients with prevalent (prior or concurrent) AF were older and had larger atria, worse diastolic dysfunction, and higher brain-type natriuretic peptide levels than those in SR, consistent with more advanced HF. Development of incident AF was associated with older age, hypertension, renal dysfunction, left atrial dilatation, and diastolic dysfunction at HF diagnosis, but fewer patients treated with statins at HF diagnosis developed AF over time. Scores predictive of thromboembolic risk in AF were also associated with incident AF in HFpEF patients. Importantly, both prevalent AF and incident AF were associated with worse survival in HFpEF even after adjustment for potential confounders. These data suggest that AF may be a marker and potentially a mediator of increased mortality in HFpEF independent of other known risk factors.

Prevalence of AF in HFpEF
AF was present in >50% of our community-based HFpEF patients at HF diagnosis, which greatly exceeds previous reported estimates from hospitalized or clinical trial cohorts even with lower EF cutoffs and previous population-based studies. Because there was no increase in AF prevalence over the study period, these data suggest that AF may be more prevalent among HFpEF patients than previously appreciated. Diagnosis of AF can incorporate a number of subtypes, including paroxysmal AF, and a persistent or chronic form. Our inclusion of any prior diagnosis of AF, specifically to include rigorous paroxysmal AF ascertainment from medical records, may account for a higher prevalence compared with other studies determining AF status in HFpEF. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity in Patients With Preserved Left-Ventricular Ejection Fraction (CHARM-Preserved) trial, patients with an ECG demonstrating SR but with a history of AF were nonetheless categorized as no AF. However, progression of paroxysmal AF to persistent and then chronic AF is well recognized, and the clinical associations and adverse
prognostic implications of prevalent AF as classified here support its clinical relevance.

AF and HFrEF share a number of common risk factors. In this study, patients with prevalent AF were older with more cerebrovascular disease (prior AF group) but otherwise had a clinical profile similar to that of HFrEF patients without AF at HF diagnosis. Brain-type natriuretic peptide was higher among patients with prevalent AF, although symptom severity (New York Heart Association class) at presentation was similar between groups. The graded association between LAVI and duration of AF, that is, larger in patients with prior than concurrent AF and smallest in HFrEF patients with no AF, supports a link between left atrial remodeling in HFrEF and AF development. Several clinical studies have reported that diastolic dysfunction is a risk factor for incident AF in the general population.24,25 Among markers of diastolic function,
we also found that a shorter E-wave deceleration time was associated with prevalent AF in HFpEF.

**Incidence of AF in HFpEF**

The incidence rate of AF in this study was 69 cases per 1000 person-years. By comparison, AF incidence rates reported in the general population range from 3 to 6 cases per 1000 person-years\(^{26,27}\) to 28.3 per 1000 person-years\(^{28}\) in US Medicare beneficiaries \(\geq 65\) years of age.\(^{28}\) In keeping with the notion that structural heart disease may promote atrial remodeling and maintenance of AF, a higher observed incidence among HFpEF patients is expected here. Interestingly, however, the incidence rate also exceeds that reported among Framingham HFrEF patients (54 cases per 1000 person-years; mean age, 73±11 years)\(^{29}\) and after myocardial infarction in Olmsted County subjects (42 cases per 1000 person-years; mean age, 68±15 years)\(^{30}\) despite a mean age comparable to that of HFpEF patients presenting in SR. This is noteworthy from a public health perspective because recent studies in clinical trial cohorts have suggested that prevalent AF imparts a greater relative risk of cardiovascular death or hospitalization for worsening HF in HFpEF patients compared to those with HFrEF.\(^{1,22}\)

An incidence rate for AF in HFpEF patients in the community has not been reported previously. In the CHARM-Preserved trial, only 4.9% of the HFpEF (EF \(\geq 0.40\)) cohort in SR at recruitment developed AF by the end of the study (median follow-up, 37.7 months) compared with a crude incidence of 31.6% over 44 months in the present cohort. The CHARM cohort was younger at baseline (mean age, 66.4±11.1 years) and healthy enough to enter a clinical trial. However, CHARM patients had prevalent rather than incident HFpEF and were required to have had a previous cardiovascular hospitalization for inclusion in the trial.\(^{22}\) It is likely that our examination of the broader spectrum of HFpEF patients presenting in SR is noteworthy from a public health perspective because recent studies in clinical trial cohorts have suggested that prevalent AF imparts a greater relative risk of cardiovascular death or hospitalization for worsening HF in HFpEF patients compared to those with HFrEF.\(^{1,22}\)

An incidence rate for AF in HFpEF patients in the community has not been reported previously. In the CHARM-Preserved trial, only 4.9% of the HFpEF (EF \(\geq 0.40\)) cohort in SR at recruitment developed AF by the end of the study (median follow-up, 37.7 months) compared with a crude incidence of 31.6% over 44 months in the present cohort. The CHARM cohort was younger at baseline (mean age, 66.4±11.1 years) and healthy enough to enter a clinical trial. However, CHARM patients had prevalent rather than incident HFpEF and were required to have had a previous cardiovascular hospitalization for inclusion in the trial.\(^{22}\) It is likely that our examination of the broader spectrum of HFpEF patients in the community setting accounts for the differences in AF incidence, further underscoring the difference between clinical trial and community cohorts.

Not unexpectedly, we found that increasing age and degree of diastolic dysfunction (E/e'\(^{\prime}\)) predicted incident AF in HFpEF patients presenting in SR, as has been observed in other clinical contexts.\(^{24,27}\) Our data confirm that these
Association Between AF and Survival in HFpEF

Table 4. AF and Risk of Death in HFpEF: Hazard Ratios (95% Confidence Intervals)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No AF (Referent)</th>
<th>Prevalent AF</th>
<th>Incident AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.51 (1.27–1.78)*</td>
<td>2.75 (2.17–3.49)*</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.00</td>
<td>1.30 (1.09–1.54)†</td>
<td>2.45 (1.93–3.11)*</td>
</tr>
<tr>
<td>Model 1‡</td>
<td>1.00</td>
<td>1.24 (1.04–1.47)†</td>
<td>2.20 (1.72–2.81)*</td>
</tr>
<tr>
<td>Model 2§</td>
<td>1.00</td>
<td>1.27 (1.06–1.51)†</td>
<td>2.22 (1.73–2.84)*</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and HFpEF, heart failure with preserved ejection fraction.

Limitations

Rhythm classification depended on clinical detection and documentation of AF in the medical record. Patients with asymptomatic AF may therefore be underrepresented in AF groups, although any resulting survival bias would more likely underestimate AF incidence and AF-related risk. A portion of patients for whom echocardiographic EF data were unavailable may have been more likely to have HFpEF and AF. As a group, patients without EF assessment were older and had a higher prevalence of chronic obstructive pulmonary disease (Table I in the online-only Data Supplement). Thus, the impact of AF on outcomes in HFpEF may have been underestimated as a result of the exclusion of this particularly high-risk subgroup. Observed associations with incident AF will generalize to HFpEF cases surviving beyond 3 months, as per the definition used. Detailed data on treatment regimens, adequacy of rate control and anticoagulation for AF patients, and cause of death were not ascertained. Similarly, in mortality analyses, information on covariates besides rhythm was unavailable to update over time, including subsequent antiarrhythmic use, and may confound the risk of death observed. The population of Olmsted County is mainly white. Because the prevalence and incidence of AF are higher...
among whites compared with blacks, these data may not be
generalizable to nonwhite populations.

Conclusions
In this large population-based cohort of incident HFpEF, 66%
of patients had AF prior to, concurrent with, or subsequent
to HFpEF diagnosis. Moreover, prevalent AF and incident
AF were independently associated with increased mortality.
In the absence of proven treatment strategies for HFpEF, fur-
ther studies are required to determine whether AF represents
a marker of HFpEF progression and/or a therapeutic target.

Acknowledgments
We sincerely thank Susan A. Weston, MS, and Ruoxiang Jiang for
their assistance in data retrieval and study design.

Sources of Funding
This study was supported by grants from the National Institutes of
Health (R01 HL72435) and the National Institute on Aging (R01
AG034676). Dr Zakeri is a Heart Failure Clinical Research Skills
Development Core Fellow (U10 HL110262) and is supported by the
Mayo Clinic Center for Translational Science Activities (grant
TR000137 from the National Center for Advancing Translational
Science). The contents of this manuscript are solely the responsibility
of the authors and do not necessarily represent the official views of
TR000137 from the National Center for Advancing Translational
Science.

Disclosures
None.

References
1. Braunwald E. Shattuck Lecture: cardiovascular medicine at the turn of
1997;337:1360–1369.
2. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment
Redfield MM. Congestive heart failure in the community: a study of
A, Staiger C, Donovan MJ, Massie BM. Heart failure with preserved
ejection fraction: clinical characteristics of 4133 patients enrolled in the
5. Linnser GC, Rienstra M, Jaarsma T, Voors AA, van Gelder IC, Hillege
HL, van Veldhuisen DJ. Clinical and prognostic effects of atrial fibrillation in
heart failure patients with reduced and preserved left ventricular ejec-
6. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nikomo VT,
Meverden RA, Roger VL. Systolic and diastolic heart failure in the community.
JAMA. 2006;296:2209–2216.
7. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive
heart failure in subjects with normal versus reduced left ventricular
ejunction fraction: prevalence and mortality in a population-based
8. Piccini JP, Hernandez AF, Zhao X, Patel MR, Lewis WR, Peterson ED,
Fonarow GC. Get With The Guidelines Steering Committee and Hospitals.
Quality of care for atrial fibrillation among patients hospitalized for heart
F, Swedberg K, Cleland J, Komajda M. Differences between patients with
a preserved and a depressed left ventricular function: a report from the
Krumholz HM. Gender, age, and heart failure with preserved left vent-
JW. Atrial fibrillation is associated with an increased risk for mortality
and heart failure progression in patients with asymptomatic and symptom-
atic left ventricular systolic dysfunction: a retrospective analysis of the
12. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epide-
micity, pathophysiology, and rationale for therapy. Am J Cardiol.
2003;91:2D–SD.
fibrillation on mortality and readmission in older adults hospitalized with
14. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB,
Maggioli AP, Michelson EL, McMurray JJ, Olsson L, Rouleau JL, Young
JB, Olsson B, Pau M, Yusuf S; CHARM Investigators. Prevention of
atrial fibrillation in patients with symptomatic chronic heart fail-
ure by candesartan in the Candesartan in Heart Failure: Assessment of
Reduction in Mortality and Morbidity (CHARM) program. Am Heart J.
2006;152:86–92.
15. Rossinari D, Leborgne L, Pelletier M, Tribouilloy C. Effect of atrial fibril-
lation on long-term survival in patients hospitalised for heart failure with
L, Komajda M, Pollath F, Swedberg K, Cleland JG. New-onset atrial
fibrillation is an independent predictor of in-hospital mortality in hospitalized
heart failure patients: results of the EuroHeart Failure Survey. Eur Heart
18. Roger VL, Weston SA, Redfield MM, Helliger-Homan JP, Killian J,
Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in
fibrillation and mortality in heart failure: a community study. Circ Heart
MJ. Validation of clinical classification schemes for predicting stroke:
results from the National Registry of Atrial Fibrillation. JAMA.
Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh JB, Aurigemma
GP, Mannolio TA. Outcome of congestive heart failure in elderly persons:
fluence of left ventricular systolic function: the Cardiovascular Health
22. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL,
McMurray JJ, Pau M, Yusuf S, Pfeffer MA; CHARM Investigators. Atrial
fibrillation and risk of clinical events in chronic heart failure with and
without left ventricular systolic dysfunction: results from the Candesartan
in Heart Failure—Assessment of Reduction in Mortality and Morbidity
23. Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M,
Boone J, Sheldon R, Dorian P, Newman D. Progression to atrial fibrillation
after the initial diagnosis of paroxysmal atrial fibrillation: results from the
Canadian Registry of Atrial Fibrillation. Am Heart J.
2005;149:489–496.
JK, Leibson C, Montgomery SC, Seward JB. Left ventricular diastolic dys-
fuction as a predictor of the first diagnosed nonvalvular atrial fibrillation in
fibrillation and congestive heart failure in patients >565 years of age with
abnormal left ventricular diastolic relaxation. Am J Cardiol.
2004;93:54–58.
Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in
Olmsted County, Minnesota, 1980 to 2000, and implications on the pro-
27. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D’Agostino
SR, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel
WB, Wang Tj, Ellison PT, Wolf PA, Vasan RS, Benjamin EJ. Development
of a risk score for atrial fibrillation (Framingham Heart Study): a commu-
28. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert
SB, Benjamin EJ. Incidence and prevalence of atrial fibrillation and associated
RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial
Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) are burgeoning and commonly coexistent cardiovascular epidemics of an aging population. Although previous studies have focused on the association between prevalent AF and outcomes in HFpEF patients, the predictors and clinical impact of incident AF remain unclear. We examined cardiovascular epidemics of an aging population. Although previous studies have focused on the association between prevalence of AF and heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE). Circ Heart Fail. 2011;4:27–35.


Temporal Relationship and Prognostic Significance of Atrial Fibrillation in Heart Failure Patients With Preserved Ejection Fraction: A Community-Based Study
Rosita Zakeri, Alanna M. Chamberlain, Véronique L. Roger and Margaret M. Redfield

Circulation. 2013;128:1085-1093; originally published online August 1, 2013; doi: 10.1161/CIRCULATIONAHA.113.001475
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/10/1085

An erratum has been published regarding this article. Please see the attached page for:
/content/128/24/e465.full.pdf

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2013/08/01/CIRCULATIONAHA.113.001475.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
In the article by Zakeri et al, “Temporal Relationship and Prognostic Significance of Atrial Fibrillation in Heart Failure Patients with Preserved Ejection Fraction: A Community-Based Study,” which published in the September 3, 2013 issue of the journal (Circulation. 2013;128:1085–1093.), the authors omitted a grant number. The Sources of Funding section should read as follows:

“This study was supported by grants from the National Institutes of Health (R01 HL72435) and the National Institute on Aging (R01 AG034676). Dr Zakeri is a Heart Failure Clinical Research Skills Development Core Fellow (U10 HL110262) and is supported by the Mayo Clinic Center for Translational Science Activities (grant TL1 TR00137 from the National Center for Advancing Translational Science). The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.”

The current online version of the manuscript has been corrected. The authors regret the error.
SUPPLEMENTAL MATERIAL
Supplemental methods:

Identification of HF cohort and definition of HFpEF:

All Olmsted County residents with a first diagnosis of HF (incident HF) between January 1, 1983 and December 31, 2010 were identified by medical record documentation of code 428 (heart failure), from the international Classification of Diseases – Ninth Revision – Clinical Modification (ICD-9-CM), as part of our on-going Olmsted County HF community study. The medical records of a random sample of individuals with ICD-9-CM code 428 were reviewed by nurse abstractors and HF diagnosis validated against the modified Framingham criteria\(^1,2,3\). Patients who had underwent echocardiography within 2 months of HF diagnosis, with a left ventricular ejection fraction (LVEF) \(\geq 0.5\) (\(n=939\)), were determined to have HFpEF and formed the final study cohort.

Data collection:

Height (m), weight (kg, prior and closest to HF diagnosis), body mass index (BMI) and body surface area (BSA) were collected. Heart rate, systolic (SBP), and diastolic blood pressure (DBP) readings (average of 3 on usual medications) were taken from a visit closest in time to HF diagnosis. Hypertension was defined by: \(\geq 2\) ambulatory BP recordings (SBP\(\geq 140\)mmHg and/or DBP\(\geq 90\)mmHg) preceding HF diagnosis, a physician diagnosis, or prescribed antihypertensive medication. Diabetes was determined based on American Diabetes Association (ADA) criteria\(^4\); previous myocardial infarction, thyroid disease, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease (previous stroke or transient ischemic attack) from physician diagnoses. Medication at HF diagnosis, prior to HF treatment, was abstracted electronically.
Serum creatinine, plasma brain natriuretic peptide (BNP) and thyroid stimulating hormone (TSH) within 2 months of HF diagnosis were obtained from the Mayo Laboratory Information System. Glomerular filtration rate was estimated using the Modified Diet in Renal Disease Study equation (eGFR)\textsuperscript{5}. Plasma BNP was assessed by an automated 2-site immunoenzymatic sandwich assay (Beckman Coulter DXI 800, Chaska, MN; normal range <200pg/mL).

EF, reported by either transthoracic or transesophageal echo, was based on validated M-mode, quantitative or semi-quantitative (2D) methods. Where multiple values were available, the closest in time to HF diagnosis was selected. Where a range of EF was reported the lower limit was taken as a conservative estimate. LV end-diastolic and end-systolic dimensions were measured by standardized 2D techniques\textsuperscript{6}. Diastolic function assessment included: a) early diastolic mitral inflow E wave deceleration time (pulsed wave, PW, Doppler), b) estimated pulmonary artery systolic pressure (PASP, from peak tricuspid regurgitation velocity), and c) the ratio of early diastolic mitral inflow velocity on PW Doppler to early diastolic (medial) mitral annular velocity on tissue Doppler imaging (E/e’), assessed as continuous variables. Left atrial volume was calculated using the area-length method or ellipsoid formula as directed by the sonographer, and indexed to body surface area (left atrial volume index; LAVI). Valvular disease was defined as the presence of any valve prosthesis or more than moderate valvular stenosis or regurgitation.
**Supplemental Table 1.** Baseline characteristics for patients with and without echocardiographic EF assessment at baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EF unavailable (n=872)</th>
<th>EF&lt;0.5 (n=1041)</th>
<th>EF ≥ 0.5 (n=939)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>78.7±11.6†</td>
<td>72.7±14.1</td>
<td>76.5±12.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>531 (60.9)</td>
<td>451 (43.3)</td>
<td>573 (61.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>28.6±6.8†</td>
<td>28.7 ±7.0</td>
<td>29.7±7.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>172 (19.8)†</td>
<td>276 (26.6)</td>
<td>131 (14.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>540 (62.4)†</td>
<td>628 (60.7)</td>
<td>627 (67.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>199 (22.8)</td>
<td>266 (25.6)</td>
<td>237 (25.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>190 (22.4)</td>
<td>163 (15.9)</td>
<td>176 (19.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>196 (23.2)</td>
<td>219 (21.6)</td>
<td>194 (21.0)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Mean (SD)

†p<0.05 vs. confirmed HFpEF cohort (EF≥0.5)

EF, ejection fraction; BMI, body mass index; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease.
**Supplemental Table 2.** Multivariable Cox proportional hazards regression for prediction of incident atrial fibrillation in HFpEF.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
<th>Model 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (per 10y)</td>
<td>1.28 (1.12-1.48)</td>
<td>0.0003</td>
<td>1.26 (1.09-1.47)</td>
<td>0.001</td>
<td>1.24 (0.95-1.68)</td>
<td>0.11</td>
<td>1.22 (0.96-1.61)</td>
<td>0.11</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.79 (0.56-1.12)</td>
<td>0.18</td>
<td>0.75 (0.53-1.07)</td>
<td>0.12</td>
<td>1.16 (0.54-2.59)</td>
<td>0.71</td>
<td>1.14 (0.46-1.75)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.41 (1.00-2.02)</td>
<td>0.050</td>
<td>1.36 (0.95-1.96)</td>
<td>0.097</td>
<td>3.64 (1.06-22.88)</td>
<td>0.038</td>
<td>1.12 (0.54-2.48)</td>
<td>0.77</td>
</tr>
<tr>
<td>Statin</td>
<td>0.61 (0.38-0.93)</td>
<td>0.021</td>
<td>0.60 (0.38-0.92)</td>
<td>0.019</td>
<td>0.71 (0.35-1.43)</td>
<td>0.35</td>
<td>0.61 (0.32-1.13)</td>
<td>0.11</td>
</tr>
<tr>
<td>eGFR (per 10 ml/min/1.73 m^2)</td>
<td>0.91 (0.83-0.99)</td>
<td>0.032</td>
<td>0.89 (0.75-1.05)</td>
<td>0.18</td>
<td>0.96 (0.82-1.11)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAVI (per 10 ml/m^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/e’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.28 (0.96-1.69)</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.47 (1.00-2.12)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

LAVI and E/e’ were moderately correlated with one another (Spearman’s ρ 0.3, p=0.0005), therefore not included in the same model.

E/e’, ratio of early diastolic mitral inflow velocity (pulsed wave Doppler) to early diastolic (medial) mitral annular velocity (tissue Doppler); eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index.
### Supplemental Table 3. Cox proportional hazards regression for prediction of incident atrial fibrillation in HFpEF (Statin models).

<table>
<thead>
<tr>
<th>Statin model</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>450</td>
<td>0.59 (0.37-0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>450</td>
<td>0.63 (0.39-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for age and LDL*</td>
<td>233</td>
<td>0.54 (0.32-0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for age and diagnosis of hyperlipidemia</td>
<td>447</td>
<td>0.59 (0.36-0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* LDL±1 year HFpEF diagnosis

HR, hazard ratio; LDL, low density lipoprotein.
**Supplemental Table 4.** Atrial fibrillation (by category) and risk of death in HFpEF.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No AF (Referent)</th>
<th>Prior AF</th>
<th>Concurrent AF</th>
<th>Incident AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.62 (1.34-1.97)**</td>
<td>1.38 (1.12-1.69)*</td>
<td>2.75 (2.17-3.49)**</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.00</td>
<td>1.40 (1.16-1.70)**</td>
<td>1.18 (0.96-1.45)</td>
<td>2.45 (1.93-3.11)**</td>
</tr>
<tr>
<td>Model 1†</td>
<td>1.00</td>
<td>1.33 (1.09-1.62)*</td>
<td>1.14 (0.92-1.41)</td>
<td>2.20 (1.72-2.81)**</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>1.00</td>
<td>1.36 (1.12-1.66)*</td>
<td>1.17 (0.95-1.45)</td>
<td>2.22 (1.73-2.84)**</td>
</tr>
</tbody>
</table>

Data are reported as HR (95%CI)

**p<0.001 *p<0.05

†Model 1 covariates include: age, sex, BMI, estimated GFR, hypertension, COPD, ACEI or ARB use, BB use, statin.

‡Model 2 covariates include: Model 1 covariates and AAD use.
Supplemental Material References


