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Heart Rhythm Disorders

Are Transthoracic Echocardiographic Parameters Associated With Atrial Fibrillation Recurrence or Stroke?

Results From the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study

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OBJECTIVES The purpose of this study was to evaluate the associations of transthoracic echocardiographic parameters with recurrent atrial fibrillation (AF) and/or stroke.

BACKGROUND The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, an evaluation of elderly patients with AF at risk for stroke, provided an opportunity to evaluate the implications of echocardiographic parameters in patients with AF.

METHODS Transthoracic echocardiographic measures of mitral regurgitation (MR), left atrial (LA) diameter, and left ventricular (LV) function were evaluated in the AFFIRM rate- and rhythm-control patients who had sinus rhythm resume and had these data available. Risk for recurrent AF or stroke was evaluated with respect to transthoracic echocardiographic measures.

RESULTS Of 2,474 patients studied, 457 had $\geq 2^{+}/4^{+}$ MR, and 726 had a LA diameter >4.5 cm. The LV ejection fraction was abnormal in 543 patients. The cumulative probabilities of at least one AF recurrence/stroke were 46%/1% after 1 year and 84%/5% by the end of the trial (> 5 years), respectively. Multivariate analysis showed that randomization to the rhythm-control arm (hazard ratio [HR] = 0.64; $p < 0.0001$) and a qualifying episode of AF being the first known episode (HR = 0.70; $p < 0.0001$) were associated with decreased risk. Duration of qualifying AF episode >48 h (HR = 1.55; $p < 0.0001$) and LA diameter ($p = 0.008$) were associated with an increased risk of recurrent AF. Recurrent AF was more likely with larger LA diameters (HR = 1.21, 1.16, and 1.32 for mild, moderate, and severe enlargement, respectively). No transthoracic echocardiographic measures were associated with risk of stroke.

CONCLUSIONS In the AFFIRM study, large transthoracic echocardiographic LA diameters were associated with recurrent AF, but no measured echocardiographic parameter was associated with stroke. (J Am Coll Cardiol 2005;45:2026–33) © 2005 by the American College of Cardiology Foundation

Atrial fibrillation (AF) occurs most frequently in elderly patients (1), who are at risk for recurrent AF if an episode resolves or is cardioverted. Transthoracic echocardiographic parameters, including left atrial (LA) diameter, left ventricular (LV) ejection fraction, and mitral regurgitation (MR), may be associated with recurrent AF, stroke, or death (2–7).

The management of AF includes the prevention of thromboembolic events, slowing the ventricular response rate, and the establishment, followed by maintenance, of sinus rhythm. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study, a large, multicenter, randomized trial sponsored by the National Heart, Lung, and Blood Institute, compared rate- and rhythm-control approaches for AF patients at high risk for stroke or death. The primary end point was all-cause mortality (8–10).

The rate-control strategy included treatment designed to prevent thromboembolic events and to control the ventricular response rate, but not to establish or maintain sinus rhythm. The rhythm-control strategy included therapy designed to maintain sinus rhythm and to prevent thromboembolic events. The AFFIRM study offered the opportunity to evaluate echocardiographic LA diameter, LV ejection fraction, and/or MR measures as predictors of AF recurrence or stroke in patients with AF at high risk for stroke or death.

METHODS

The AFFIRM study design, detailed elsewhere (8), was approved by the AFFIRM Steering Committee, by the

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
AF	= atrial fibrillation
AFFIRM	= Atrial Fibrillation Follow-Up Investigation of Rhythm Management
CAD	= coronary artery disease
CHF	= congestive heart failure
ECG	= electrocardiogram
LA	= left atrial/atrium
LV	= left ventricular/ventricle
MR	= mitral regurgitation

Institutional Review Board of the University of Washington (for the Clinical Trial Center), by the Data and Safety Monitoring Board, and by each participating site's local institutional review board. All patients gave informed, written consent to participate in the trial. The AFFIRM study indicated that the rhythm-control strategy offered no survival benefit (10).

This substudy considered all AFFIRM study patients in the rate- and rhythm-control arms in whom: 1) restoration of sinus rhythm was documented within two months of randomization, either spontaneously or with electrical and/or chemical cardioversion, and 2) a transthoracic echocardiogram was reported. We evaluated the association of specific echocardiographic parameters with AF recurrence and stroke (7,9,10).

Recurrent AF was identified on an electrocardiogram (ECG) or rhythm strip after the qualifying episode of AF had stopped spontaneously or was converted electrically and/or pharmacologically to sinus rhythm. Twelve-lead ECGs were obtained at 4 and 12 months after randomization, and a rhythm strip was obtained at each 4-month visit. The ECGs or rhythm strips were also recorded at any time that symptoms suggested AF recurrence. The time between restoration of sinus rhythm and AF recurrence was analyzed.

Stroke was defined as a focal neurologic deficit of any severity lasting >24 h. All strokes were adjudicated by a Stroke Events Committee composed of neurologists blinded to the treatment assignment.

Treatment during follow-up. Patients assigned to the rhythm-control strategy in the AFFIRM study were prescribed antiarrhythmic drugs commonly used to establish and/or maintain sinus rhythm. Patients assigned to the rate-control strategy received digoxin, non-dihydropyridine calcium antagonists, and/or beta-blockers (10). The treating physician prescribed rhythm- and rate-control drugs based on prespecified guidelines (7,9–11). Adequacy of rhythm- and rate-control was determined by history, physical examination, and an ECG rhythm strip performed at least at each four-month visit. Rate- and rhythm-control drugs were adjusted as necessary. Cardioversion was performed as needed in the rhythm-control group. If adequate rhythm or rate control could not be achieved with at least two medications given separately, the treating physician could proceed with an innovative therapy (7).

Echocardiographic procedures. Patients were included in this study if they had a transthoracic two-dimensional and M-mode echocardiogram (with Doppler measurements to assess MR). The test was performed with various types and models of equipment and by various cardiac sonographers at 213 clinical sites, according to local practice. Echocardiograms performed within 12 months of qualifying AF episodes were reported and interpreted locally. The echocardiogram was performed within 30 days in 1,557 (63%) patients, between 31 and 59 days in 267 (11%) patients, between 60 and 89 days in 170 (7%) patients, and at >90 days in 479 (19%) patients. Measurements collected were LA diameter, LV ejection fraction, and qualitative assessment of MR. Transesophageal echocardiography data were not recorded for purposes of this trial.

Data collection. Baseline clinical data were tabulated. Follow-up data related to AF recurrence and stroke was collected at two months and at four-month intervals thereafter.

Statistics. The LA size was analyzed both as a dichotomous variable (≤4.5 cm vs. >4.5 cm) and as a categorical variable (<4.1 cm, 4.1 to 4.5 cm, 4.6 to 5.5 cm, or >5.5 cm). Mitral regurgitation was analyzed as a dichotomous variable ($\geq 2^+/4^+$ vs. $<2^+$). The LV ejection fraction, analyzed as a categorical variable, was divided into normal (≥50%), mild dysfunction (40% to 49%), moderate dysfunction (30% to 39%) and severe dysfunction (<30%).

Means and standard deviations were calculated for continuous variables. Frequencies and percentages were calculated for categorical variables. Continuous variables were analyzed using *t* tests. Categorical variables were analyzed using chi-square tests for homogeneity.

Cumulative survival probabilities were calculated by the Kaplan-Meier method. Survival distributions were compared using log-rank statistics.

Cox proportional hazards models were used for multivariate analyses of time to recurrent AF and time to stroke. An initial stepwise analysis was used to select significant demographic variables (age, gender, qualifying episode as first AF episode, duration of qualifying episode >48 h, history of: coronary artery disease [CAD], congestive heart failure [CHF], hypertension, diabetes, smoking, stroke, and myocardial infarction, and New York Heart Association functional class at baseline). A full model containing the demographic variables that were selected in the stepwise analysis, plus treatment arm and the echocardiographic variables (LA size, MR $\geq 2^+$ and LV ejection fraction) was run. A second stepwise model was used to select the significant echocardiographic variables after controlling for significant demographic variables and treatment arm. Those variables found significant in this stepwise model were included in the final, reduced model. Significance was indicated by a p value <0.05.