The Value of Myocardial Perfusion Single-Photon Emission Computed Tomography in Screening Asymptomatic Patients With Atrial Fibrillation for Coronary Artery Disease

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Objectives
We sought to determine if screening for coronary artery disease (CAD) with stress single-photon emission computed tomography (SPECT) is of value in patients with atrial fibrillation (AF) who do not have symptoms of chest pain or dyspnea.

Background
Although noninvasive stress testing is often done to screen for CAD in asymptomatic patients with AF and is considered to be appropriate in selected patients, its potential utility has not been demonstrated.

Methods
A retrospective study was conducted of 374 asymptomatic patients with AF referred for the detection of CAD. Mean follow-up was 5.7 ± 3.8 years. The study group was compared with a control group of 374 asymptomatic age and gender-matched patients without AF.

Results
The mean summed stress score (SSS) was not significantly different between AF patients and control subjects (3.6 ± 5.3 vs. 3.5 ± 5.9; p = 0.35). Compared with controls, asymptomatic AF patients had similar rates of abnormal SPECT studies (51.6% vs. 48.4%; p = 0.38) and high-risk studies (14.4% vs. 14.4%; p = 1.0). The SSS was a significant predictor of outcome in both AF patients and control subjects. However, total mortality was significantly greater in AF patients (5-year overall mortality 27% vs. 18%, 10-year overall mortality 47% vs. 40%; p < 0.001), and this difference persisted (p = 0.01) after adjusting for multiple clinical variables and the SSS.

Conclusions
Screening for CAD using stress SPECT in asymptomatic AF patients has a yield similar to age- and gender-matched control patients without AF. Although SSS predicts mortality in patients with and without AF, patients with AF have increased total mortality independent of the findings on stress SPECT. These results suggest that factors other than obstructive CAD are responsible for the increased mortality in AF. (J Am Coll Cardiol 2007; 50:1080–5) © 2007 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is an independent predictor of mortality (1); however, the relationship between ischemic heart disease and AF has been variable. Atrial fibrillation patients (most with symptoms), have been reported to have more abnormal myocardial perfusion single-photon emission computed tomographic (SPECT) studies and a higher risk of cardiac death compared with patients without AF (2).

Given these reported associations between AF and coronary artery disease (CAD), there is increased interest in screening selected patients with AF for CAD, in an effort to improve their prognosis. Recent appropriateness criteria for myocardial perfusion SPECT have been published (3). These criteria reported that it was appropriate to screen asymptomatic patients with new-onset AF who were at high clinical risk for CAD; in contrast, in patients at low clinical risk, screening was judged to be of uncertain appropriateness. Although AF may be associated with CAD, current practice guidelines (4) do not recommend routine stress imaging and only recommend exercise testing before treatment of selected patients with a type IC antiarrhythmic drug. The aim of the present study was to determine if screening for CAD with stress SPECT is of value in patients with AF who do not have symptoms of chest pain or dyspnea or a history of CAD.
Methods

Patient population. The study was approved by the Mayo Clinic Institutional Review Board. Patients referred for stress SPECT between January 1986 and December 2003 were identified using the nuclear cardiology database. Exclusion criteria included: chest pain, dyspnea, history of CAD, valvular heart disease, left bundle branch block, and paced rhythm. Patients with AF by electrocardiogram at the time of the stress study were then identified. The final study population consisted of 374 asymptomatic patients (i.e., no chest pain or dyspnea) referred for stress SPECT for the purpose of CAD screening. Using identical exclusion criteria, 374 age- and gender-matched controls without AF referred for stress SPECT for the purpose of CAD screening during that same time period were identified for comparison purposes. As previously described (5), clinical characteristics were recorded prospectively.

Clinical risk score. A simple 10-point score was used to estimate clinical risk. The clinical score is determined by assessing 5 variables (age, gender, prior myocardial infarction [MI], angina, and diabetes) each of which has an independent association with angiographically determined severe CAD (6). For the purpose of this study, only 3 of the 5 variables contributed to the overall score, because patients with angina or a history of MI were excluded. Patients were subdivided into groups of low clinical risk (score ≤4), intermediate clinical risk (score = 5), and high clinical risk (score ≥6). These groupings have been shown to effectively stratify levels of risk for overall mortality, cardiac death, and cardiac death/MI (7).

Stress testing, radionuclide imaging protocol, and image interpretation. These methods have been described previously (5). Patients referred for exercise (n = 193 [51.6% of the AF group] and n = 195 [52.1% of the non-AF group]) underwent a symptom-limited treadmill test (Bruce, modified Bruce, or Naughton protocol). Adenosine was the pharmacologic stress agent in 151 (40.4%) of the 374 AF patients and 126 (33.7%) of the 374 non-AF patients, with less frequent use of dipyridamole (6.4% and 9.4%, respectively) and dobutamine (1.6% and 4.8%, respectively). Patients receiving 201Tl (n = 128 [34.2% of the AF patients] and n = 165 [44.1% of the non-AF patients]) underwent a 1-day protocol. Patients receiving 99mTc sestamibi (n = 246 [65.8% of the AF patients] and n = 209 [55.9% of the non-AF patients]) underwent either a 1-day or 2-day protocol. The summed rest score (SRS), summed stress score (SSS), and summed difference score (SDS) were determined. Using previously published criteria, SSS results were divided into 3 groups: 0 to 3 (low risk), 4 to 8 (intermediate risk), and ≥9 (high risk) (8). Cardiac enlargement was determined by a qualitative visual assessment.

Survival analysis. Total mortality was determined using the Social Security Death Index and Mayo Clinic records. Survival was estimated using the Kaplan-Meier method. Mean duration of follow-up was 5.7 ± 3.8 years.

Statistical analysis. Categoric factors were compared between groups using the chi-square test for independence. The Wilcoxon rank sum test was used to compare continuous variables. Potential risk factors for mortality were evaluated using Cox proportional hazards models. Differences between survival curves were compared between groups using the log rank test.

Results

Baseline characteristics. The clinical characteristics of each group are shown in Table 1. Whereas patients with AF were more likely to be on rate-controlling agents (beta-blockers and calcium-channel blockers), only about a third of AF patients were taking these medications. A small number of AF patients (7.8%) were on antiarrhythmic medications. The clinical risk scores did not differ between AF and non-AF patients.

Stress test results. The stress test characteristics and results are shown in Table 2. Overall, the results of SPECT imaging were very similar between patients with and without AF. Approximately half of the patients in the AF and non-AF groups had normal images (48.4% vs. 51.6%,
There were no significant differences between the AF and non-AF groups in the mean SSS, the mean SDS, or the percentages of patients in the SSS categories (Fig. 1). The SRS in both AF and non-AF groups was low; however, the area of fixed perfusion abnormality was higher in the AF group. This may reflect prior “silent MI” or fibrosis related to nonischemic cardiomyopathy. Cardiac enlargement was more common in patients with AF.

### Association between clinical risk score and SSS

There was no correlation between the clinical risk score and SSS in patients with AF ($p = 0.97$). There was a statistically significant but weak correlation between the clinical risk score and SSS in patients without AF ($r = 0.17; p < 0.001$). The test for formal interaction between AF, the clinical risk score, and SSS was significant ($p < 0.01$), implying that the relationship between the clinical risk score and SSS is different depending on the presence or absence of AF. In AF patients, the clinical risk score was not helpful for predicting a high-risk SSS, because 14.5% of AF patients at low clinical risk (clinical risk score of $5$) had a high-risk SSS, compared with 12.3% of AF patients at high clinical risk (clinical risk score of $>5$; $p = 0.03$) (Fig. 2A). For non-AF patients, the prevalence of high-risk perfusion scans (SSS $\geq 9$) increased from 11.7% of patients at low clinical risk to 21.6% of patients at high clinical risk (Fig. 2B); however, this difference was not significant ($p = 0.13$).

### Outcome

The SSS was a significant predictor of mortality in both AF patients ($p < 0.001$) (Fig. 3A) and non-AF patients ($p < 0.001$) (Fig. 3B). However, survival was significantly worse in the AF patients ($p < 0.001$) than in the non-AF patients despite their similar SSS results (Fig. 4). The 5- and 10-year survival rates were 73% and 53%, respectively, in the AF patients compared with 82% and 60%, respectively, in the non-AF group ($p < 0.001$). Using a multivariate model, AF was independently associated with mortality ($p = 0.01$) after adjusting for clinical variables and the results of SPECT imaging (Table 3). The SSS was also an independent predictor of mortality ($p = 0.04$). The interaction term between AF and SSS was significant ($p = 0.03$) in this model, implying that the relationship between SSS and mortality is different depending on the presence of AF (Fig. 5).

### Discussion

There were no significant differences in abnormal SPECT images or SSS categories between asymptomatic patients...
with and without AF. Thus, AF patients did not have an excess amount of occult CAD compared with patients without AF. Despite the similarity in both overall SSS and the prevalence of high-risk SSS between the AF and non-AF groups, patients with AF had significantly higher total mortality rates. The increase in total mortality in asymptomatic patients with AF remained significant after adjusting for clinical variables and the stress myocardial perfusion imaging results, suggesting that it was not due to obstructive CAD.

**ACCF/ASNC appropriateness criteria.** The American College of Cardiology Foundation (ACCF)/American Society of Nuclear Cardiology (ASNC) appropriateness criteria include recommendations for CAD screening in asymptomatic patients with new-onset AF according to the Framingham risk score (3). Intermediate-risk patients were not specifically addressed by these criteria. Low-risk patients were assigned to the uncertain category, indicating that the test may be appropriate but further research is needed in order to help further define this category (3). Screening for CAD in asymptomatic AF patients and a high-risk Framingham risk score was considered appropriate (3). In the present study we did not apply the Framingham scoring system, because this technique requires measured lipid values to calculate risk. Instead, we used a different clinical risk scoring system based only on clinical variables that has been validated in prior studies (6,7,9). When tested as a continuous variable, the clinical risk score was associated with a higher SSS in the non-AF group but not in the AF group. Although the reasons for this are uncertain, AF patients who underwent an exercise stress SPECT study had a reduced functional aerobic capacity compared with the control group. Thus, the potential for underestimating the extent and severity of ischemia exists. However, this only applies to approximately one-half of the AF patients; 48.4% underwent pharmacologic stress testing. Earlier studies. The only earlier study evaluating the outcome of AF patients undergoing stress SPECT was published by Abidov et al. (2). Their study included higher-risk AF patients, with more than one-half being symptomatic (38% with angina and 16% with dyspnea) and/or having known CAD (23% with prior MI, 17% with prior coronary

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Multivariate Predictors of Total Mortality</th>
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<tr>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (1.06–1.10)</td>
</tr>
<tr>
<td>Gender</td>
<td>1.06 (0.74–1.54)</td>
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<tr>
<td>Smoking</td>
<td>1.38 (1.13–1.69)</td>
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<tr>
<td>Family history</td>
<td>0.91 (0.64–1.29)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>0.64 (0.48–0.85)</td>
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<tr>
<td>Diabetes</td>
<td>1.39 (1.14–1.68)</td>
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<tr>
<td>Hypertension</td>
<td>1.60 (1.18–2.16)</td>
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<tr>
<td>Antiarrhythmics</td>
<td>0.83 (0.44–1.59)</td>
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<tr>
<td>Beta-blockers</td>
<td>0.77 (0.56–1.05)</td>
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<tr>
<td>Calcium-channel blockers</td>
<td>1.08 (0.81–1.44)</td>
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<tr>
<td>Digoxin</td>
<td>0.93 (0.68–1.29)</td>
</tr>
<tr>
<td>Summed stress score</td>
<td>1.04 (1.00–1.07)</td>
</tr>
<tr>
<td>Summed rest score</td>
<td>1.02 (0.97–1.07)</td>
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<tr>
<td>Cardiac enlargement</td>
<td>1.20 (0.86–1.68)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.51 (1.10–2.07)</td>
</tr>
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CI = confidence interval.
The principal finding in their study included a significant increase in both noncardiac and cardiac death in patients with AF. Patients were classified into subsets on the basis of SPECT results (normal, mildly abnormal, and moderately to severely abnormal). In all subsets, patients with AF had higher rates of cardiac death than those without AF. In the present study also, overall mortality was higher in AF patients, and this difference persisted after adjustment for the SSS. In both studies, resting images were worse in AF versus non-AF patients; however, the SRS of AF patients in our study was less than half that reported by Abidov et al. (2). Owing primarily to a higher SRS, the mean SSS of AF patients reported by Abidov et al. (2) was significantly higher than that of patients without AF; in contrast, the mean SSS between AF and non-AF patients in the present study was not significantly different. These differences in the SRS and SSS between the 2 studies likely reflect the underlying differences in each patient population as we excluded AF patients who were symptomatic or had known CAD.

**Cost-effective screening.** Identifying patients who may benefit from CAD screening in a cost-effective manner is challenging. In an earlier study, we found that 18% of asymptomatic diabetic patients without known CAD undergoing screening stress SPECT had a high-risk scan (5). More than 25% of certain subgroups (patients with an abnormal resting electrocardiogram and those with peripheral arterial disease) had a high-risk SSS. An accompanying editorial (10) suggested that the >25% prevalence of a high-risk SSS in these subgroups was an excellent yield but that the lower yield of screening all asymptomatic diabetic patients needed to be augmented to be clinically- and cost-effective. Only 14.4% of patients in the present study had a high-risk SSS, well below the recommended 25% threshold. Application of the clinical risk score did not increase the yield of high-risk SSS results in AF patients.

**Study limitations.** The study population reflects patients referred to a single tertiary center. Our results may not be applicable to a broader community-based population. The determination of whether a patient had AF depended on its presence at the time of the stress study; patients with paroxysmal AF who were in sinus rhythm at the time of the stress study were not included. Conversely, the possibility exists that some patients in the control group had paroxysmal AF that was unknown. Baseline clinical characteristics were similar between the 2 groups; however, the percentage of patients with hypertension was modestly higher in the AF group, whereas a history of cigarette smoking and hyperlipidemia were more common in the non-AF group. The ACCF/ASNC appropriateness criteria used the Framingham risk score to categorize AF patients as high risk or low risk for CAD; we used a different clinical risk scoring system, because concurrent cholesterol measurements were not available in all patients or were confounded by the use of statins during the study period. Total mortality was the only outcome variable measured; thus, the type of death or the impact of cerebrovascular accidents, MIs, or major bleeds on the observed increased mortality rates in AF patients could not be studied.

**Conclusions**

The findings of the present study indicate that routine screening for CAD using stress SPECT in asymptomatic AF patients is no different than in age- and gender-matched patients without AF, and that the low yield does not support routine screening. The increased total mortality in AF patients does not appear to be due to obstructive CAD. Whether certain subgroups (i.e., patients being considered for type IC antiarrhythmic medications) would benefit more from stress SPECT is uncertain.

**References**


