enroll in such plans can take advantage of lower prices if they choose to do so.

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Low Yield of Myocardial Perfusion Imaging in Asymptomatic Patients With Atrial Fibrillation

Current appropriate use criteria endorse myocardial perfusion imaging (MPI) in asymptomatic patients with atrial fibrillation, especially in patients at high global cardiovascular risk, although the evidence to support this practice is limited.2,3 Our study therefore had 2 aims: (1) Does baseline clinical risk inform the overall yield of MPI to detect inducible ischemia in asymptomatic patients with atrial fibrillation? (2) Do perfusion abnormalities in these patients provide incremental prognostic information beyond clinical risk?

Methods | Our retrospective cohort included 1700 consecutive asymptomatic patients with atrial fibrillation from October 2006 through December 2014 who had rest-stress MPI at our institution. Patients were classified as asymptomatic if they did not have chest pain or dyspnea. Our primary outcome was greater than 5% ischemic myocardium. Risk stratification was possible in 1258 patients, and high global cardiovascular risk was defined as a history of coronary artery disease (CAD) or a greater than 20% 10-year risk according to the pooled cohort equation. All-cause mortality was assessed with the Social Security and Ohio Death Indices through 2012 because the Ohio Death Index is not yet updated for 2013 and 2014. A baseline Cox proportional hazard model was created using the pooled cohort equation and an inability to adequately exercise (pharmacologic test). Additional models were then created by adding imaging variables. The assumptions of the proportionality of hazards were met, and a 2-sided P < .05 was considered statistically significant for all tests. The institutional review board of the Cleveland Clinic approved this study with a waiver for informed consent.

Results | Our patients were elderly (mean [SD] age, 69.9 [10.4] years), mostly male (63.8%), and comorbidities were common (hypertension in 77.9%, hyperlipidemia in 68.3%, obesity in 50.0%). Most patients (70.1%) were taking anticoagulant drugs, and 30.6% were taking antiarrhythmic drugs. Most patients (78.0%) had had a pharmacologic stress test. In patients with lipid values, the 10-year global cardiovascular risk was intermediate to high (median risk, 22.8% [interquartile range, 12.1%-36.4%]). In the entire cohort of 1700 patients, only 78 (4.6%) had greater than 5% ischemic myocardium. Of these patients, 37 had invasive coronary angiography, and obstructive CAD was found in only 16 patients, with subsequent revascularization in 7 patients. Therefore, the yield to detect ischemia that resulted in revascularization was 0.4%.

In patients with high global cardiovascular risk, the yield for detecting ischemia was low and similar to other patients (Figure). Finally, in 841 patients with mortality data, 47 pa-

![Figure. Incidence of Ischemia in Asymptomatic Patients With Atrial Fibrillation, Stratified by Clinical Risk](image-url)
patients died during a mean follow-up of 2.6 (1.8) years. In multivariable analysis, high global cardiovascular risk, pharmacologic test, and ejection fraction of less than 45% were all associated with increased mortality. Conversely, ischemia was not associated with increased mortality (Table).

Discussion | In our single-center study of asymptomatic patients with atrial fibrillation, the yield for detecting ischemia was low and did not significantly increase with increasing clinical risk. Furthermore, after adjusting for baseline clinical risk, inducible ischemia did not provide incremental information to predict overall mortality. Notable limitations of our study include that nonfatal myocardial infarction was not assessed, and mortality data were not available for all patients. Therefore, the strength of our conclusions regarding the lack of prognostic value of ischemia in these patients is limited. However, our data regarding the yield to detect ischemia are more compelling. Recently, the decreasing yield of MPI to detect inducible ischemia has been highlighted with a contemporary incidence of only 5.0%. The yield was similar in our study, suggesting that the presence of atrial fibrillation does not identify asymptomatic patients that are more likely to have occult myocardial ischemia. Instead, stress MPI should likely be reserved for patients with atrial fibrillation who have an intermediate to high likelihood of CAD based on their symptoms.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Model, χ^2, P Value</th>
<th>Model 1, χ^2, P Value</th>
<th>Model 2, χ^2, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High global cardiovascular risk</td>
<td>2.1 (1.1-4.3)</td>
<td>.03</td>
<td>2.0 (1.1-4.2)</td>
</tr>
<tr>
<td>Pharmacologic test</td>
<td>3.1 (1.1-13.0)</td>
<td>.03</td>
<td>3.0 (1.1-12.6)</td>
</tr>
<tr>
<td>EF &lt; 45%</td>
<td>NI</td>
<td>NI</td>
<td>2.6 (1.3-3.9)</td>
</tr>
<tr>
<td>&gt;5% Ischemic myocardium</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>

Abbreviations: EF, ejection fraction; HR, hazard ratio; NI, not included in that specific model.

* Data are given as hazard ratio (95% CI).

Statistical analysis: Cremer, Wazni, Tchou.

Conflict of Interest Disclosures: None reported.

Editor’s Note

Appropriate Use Criteria Require Data

Appropriate use criteria (AUC) have been released by the American College of Cardiology since 2005 to help cardiologists decide on the risks and benefits of various cardiac procedures. The process has evolved greatly since when I was a member of an AUC cardiac imaging writing group in 2006; our instructions were to put ourselves in the position of the practicing physician in deciding what would be reasonable without any review of the literature.

Today, AUC incorporate published evidence to guide clinicians in the labyrinth of clinical choices presented by individual patients. For each scenario, the procedure is rated as appropriate, may be appropriate, or rarely appropriate.

Of course, the benefits of including the published literature in AUC development depends on the availability of useful data. This is well illustrated by an article by Cremer et al2 in this issue. For example, myocardial perfusion imaging (MPI), a commonly used cardiac stress test, is rated as appropriate or may be appropriate for asymptomatic patients with atrial fibrillation to identify silent ischemia. Cremer et al2 analyzed 8 years of experience of performing MPI at the Cleveland Clinic in asymptomatic patients with atrial fibrillation. They found that the yield for detecting cardiac ischemia was low; even in
A Randomized Trial Testing US Food and Drug Administration “Breakthrough” Language

In colloquial terms, “breakthrough” connotes an important, definitive advance. Since the 2012 US Food and Drug Administration (FDA) Safety and Innovation Act became law, however, the FDA can assign the breakthrough designation to a drug that “treats a serious or life-threatening condition” and “may demonstrate a substantial improvement...over available therapies” based only on preliminary evidence (eg, uncontrolled studies, surrogate outcomes). Such drugs often receive “accelerated approval.”

All FDA press releases announcing approval of breakthrough-designated drugs use the term breakdown; about half use promising. Patients can easily find these press releases searching the Internet or hearing about them in the news. Unless patients understand the FDA's usage of breakthrough, they may have unwarranted confidence in the evidence supporting drug claims. In a randomized trial, we test how these terms affect lay judgments (NCT02428556).

**Methods** We recruited an online sample of 597 Americans (mean age, 36 years [range, 19-83 years]; 41% were women; 55% had a college and/or graduate degree) in June 2014 from an online service (Amazon’s Mechanical Turk [MTurk]). Participants received $1 for completing “a 10-minute medical drug survey.”

Participants were randomized to 1 of 5 vignettes—short descriptions of a recently approved drug (Table 1), based on an FDA press release for a metastatic lung cancer breakthrough drug conditionally approved based on the surrogate outcome tumor shrinkage. The facts-only condition described the drug as meeting the breakthrough criteria, but without using the term. The breakthrough and promising conditions added those terms. The tentative explanation used FDA-required language for professional labeling. The definitive explanation changed “may be contingent” to “is contingent.” Participants judged the drug’s benefit, harm, and strength of evidence (Table 2 includes full question text). A Kruskal-Wallis test was performed followed by Mann-Whitney U-tests comparing individual groups. A Bonferroni-correction accounted for multiple comparisons, α = .01 (IBM SPSS Statistics; version 23.0).

**Results** Adding either description (promising or breakdown) increased the percentage of participants rating the drug as “very” or “completely effective” compared with facts-only: 23% and 25% vs 11%; P = .002 and P = .001 (Table 2). It significantly increased the percentage believing that the evidence supporting the drug is “strong” or “extremely strong”:

**Table 1. Distinguishing Text by Vignette**

<table>
<thead>
<tr>
<th>Vignette</th>
<th>Distinguishing Text*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facts-only</td>
<td><strong>New lung cancer drug approved by the FDA</strong>&lt;br&gt;The FDA recently approved a new lung cancer drug named Zykanta. The FDA called the medication a “breakthrough” drug. All groups read the “facts-only” vignette text. The “breakthrough” groups and “promising” group also read additional text detailed in Table 1.</td>
</tr>
<tr>
<td>Breakthrough + facts</td>
<td><strong>New lung cancer drug approved by the FDA</strong>&lt;br&gt;The FDA recently approved a new lung cancer drug named Zykanta. The FDA called the medication a “breakthrough” drug. + Facts</td>
</tr>
<tr>
<td>Breakthrough + tentative explanation</td>
<td><strong>New lung cancer drug approved by the FDA</strong>&lt;br&gt;The FDA pointed out that the drug was approved based on tumor shrinkage but that an improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent on verification and description of clinical trial benefit in confirmatory trials.</td>
</tr>
<tr>
<td>Breakthrough + definitive explanation</td>
<td><strong>New lung cancer drug approved by the FDA</strong>&lt;br&gt;Breakthrough + facts</td>
</tr>
</tbody>
</table>

Abbreviation: FDA, US Food and Drug Administration.
* The text corresponds exactly to what participants saw during the trial. + Facts indicates that participants saw the complete text from the “facts-only” vignette in addition to the unique text in their own vignette group.