Prevalence and Associated Findings

Thomas M. Maddox, MD, SM; Kimberly J. Reid, MS; John A. Spertus, MD, MPH; Murray Mittleman, MD, PhD; Harlan M. Krumholz, MD, SM; Susmita Parashar, MD, MPH; P. Michael Ho, MD, PhD; John S. Rumsfeld, MD, PhD

**Background:** Eradication of angina is a primary goal of care after myocardial infarction (MI). However, the prevalence of angina 1 year after MI and factors associated with it are unknown.

**Methods:** From January 1, 2003, through June 28, 2004, 2498 patients with acute MI were recruited from 19 hospitals in the United States. Among this multicenter cohort of patients, angina was measured by the Seattle Angina Questionnaire 1 year after hospitalization for MI. Multivariate regression modeling identified the sociodemographic factors, clinical history, MI presentation, inpatient treatments, and outpatient treatments associated with 1-year angina, adjusted for site.

**Results:** Of 1957 patients in the cohort, 389 (19.9%) reported angina 1 year after MI. After multivariate analysis, patients with 1-year angina were more likely to be younger (relative risk [RR] per 10-year decrease, 1.19; 95% confidence interval [CI], 1.09-1.30), to be nonwhite males (RR, 1.50; 95% CI, 1.16-1.96), to have had prior angina (RR, 1.78; 95% CI, 1.54-2.06), to have undergone prior coronary artery bypass graft surgery (RR, 1.92; 95% CI, 1.51-2.44), and to experience recurrent rest angina during their hospitalization (RR, 1.54; 95% CI, 1.22-1.93). Among the outpatient variables, patients with 1-year angina were more likely to continue smoking (RR, 1.23; 95% CI, 1.02-1.48), to undergo revascularization after index hospitalization (percutaneous coronary intervention or coronary artery bypass graft) (RR, 1.37; 95% CI, 1.09-1.73), and to have significant new (RR, 1.96; 95% CI, 1.34-2.87), persistent (RR, 1.88; 95% CI, 1.29-2.75), or transient (RR, 1.77; 95% CI, 1.49-2.11) depressive symptoms.

**Conclusions:** Angina occurs in nearly 1 of 5 patients 1 year after MI. It is associated with several modifiable factors, including persistent smoking and depressive symptoms.

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**METHODS**

**PATIENT SAMPLE**

From January 1, 2003, through June 28, 2004, 2498 patients with acute MI were recruited into the PREMIER study from 19 hospitals in the United States. The methods of the PREMIER study have previously been described. Institutional research board approval was obtained at each participating institution, and patients signed informed consent for baseline and follow-up interviews.

**DATA COLLECTION**

As described previously, comprehensive inpatient and outpatient data from medical record abstractions and patient interviews were col-
Disorders
sive disorder in the Questionnaire (PHQ-9). The PHQ-9 is a depression symptom scale that is based on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision). The PHQ-9 is valid, reproducible, and sensitive to changes in depressive symptoms. Higher PHQ-9 scores indicate greater depressive symptom severity. In addition, PHQ-9 scores of 10 or higher are 88% sensitive and specific for a diagnosis of major depression.10-12

OUTCOMES ASSESSMENT

The primary outcome of this study was the presence of angina 1 year after hospitalization for MI. We measured angina using the Seattle Angina Questionnaire (SAQ), which assesses anginal symptoms that occur during the previous 4 weeks. We dichotomized the SAQ-AF score between the presence (SAQ-AF score, <100) and absence (SAQ-AF score, 100) of angina, given the distribution of scores with a significant proportion of patients having no angina at 1 year. For additional descriptive purposes, scores were also presented in categories: daily angina (SAQ-AF score, 0-30), weekly angina (SAQ-AF score, 31-60), angina less than once per week (SAQ-AF score, 61-99), and no angina (SAQ-AF score, 100).7

Because the presence of anginal symptoms is partially dependent on a patient's level of activity, sedentary patients may have significant cardiac disease but may not report anginal symptoms because of their lack of activity. To understand the impact of this potential source of misclassification, we examined patients' activity level as assessed by the SAQ. For various types of activities, patients reported that they experienced angina, did not experience angina, or did not perform the activity for reasons other than anginal symptoms. For each activity assessed, the proportion of patients who reported not performing the activity for reasons other than anginal symptoms (eg, sedentary patients) did not differ between those with and those without 1-year angina (data not shown). Because the proportion of sedentary patients was evenly distributed between patients with and without anginal symptoms, they would not be expected to influence our results.

POTENTIAL FACTORS ASSOCIATED WITH ANGINA

Potential factors associated with 1-year angina were chosen a priori based on prior research.13-19 Candidate factors were grouped into categories: sociodemographic (age, sex, race, educational level, and health insurance), coronary artery disease (CAD) risk factors (history of diabetes mellitus, hypertension, or hyperlipidemia), presence of CAD (previous MI, previous percutaneous coronary intervention [PCI], or previous coronary artery bypass grafting [CABG] surgery), MI presentation and inpatient treatment characteristics (baseline angina [SAQ-AF score], Q waves on presenting electrocardiogram, multivessel CAD, inpatient revascularization [either PCI or CABG], recurrent angina during hospitalization, MI type [ST-segment elevation MI vs non-ST-segment elevation MI]), and outpatient factors (participation in cardiac rehabilitation; early [within 1 month of discharge] follow-up physician visit; smoking cessation; revascularization after index hospitalization; medication adherence to aspirin, β-blocker, and statin medications; and outpatient depressive symptoms [as measured by the PHQ-9]).

Because several of the outpatient factors were measured serially during outpatient follow-up, categories were created based on their clinical relevance to the 1-year angina outcome. Smoking cessation categories were constructed by using smoking assessments at the index hospitalization (“had smoked within the 30 days before admission”) and smoking assessments at the 1-year interview (“had smoked within the 30 days before the interview”). Three categories were created from these data: nonsmokers (‘no’ response at both assessments), quitters (‘yes’ response at hospitalization and “no” response at 1 year), and persistent smokers (‘yes’ response at 1 year). Few patients were nonsmokers at hospitalization and smokers at 1 year (n=47), so these patients were grouped with the persistent smokers in our model.

Depression categories were constructed using the standard cutoff score of 10 or higher for the PHQ-9. To assess the trajectory of depressive symptoms after hospitalization, we used baseline and 6-month PHQ-9 data. Four categories were created: never depressed (PHQ-9 score <10 at both assessments), transiently depressed (PHQ-9 score ≥10 at hospitalization and PHQ-9 score <10 at 6 months), persistently depressed (PHQ-9 score ≥10 at both assessments), and newly depressed (PHQ-9 score <10 at hospitalization and PHQ-9 ≥10 at 6 months).

To assess medication persistence, medications that are indicated for all patients who have had an MI, barring contraindication, were evaluated. These included aspirin, β-blockers, and statins. Patients discharged with these medications and receiving them at 1 year (irrespective of dose) were considered to be persistent in taking their medications.

Finally, several first-order interaction terms were entered into the model to explore potential effect modification of related variables, based on prior research.17,20 These terms included age and sex, sex and race, race and revascularization after index hospitalization, race and depression, depression and smoking, cardiac rehabilitation and smoking, and depression and medication adherence.

STATISTICAL ANALYSIS

After classifying patients by the presence or absence of angina at 1 year, candidate factors, as described herein, were compared by patient group. Categorical variables were compared with x² or Fisher exact tests, and continuous variables were compared with t tests.

Then, to examine those factors that are associated with 1-year angina, a multivariate modified Poisson regression model, using the candidate factors described herein, was developed. We entered sociodemographic, clinical history, MI presentation and treatment, and outpatient factors in sequential groups into our multivariate model to assess when various factors no longer demonstrated significant relationships with 1-year angina and to explore for potential colinearity and changes in variable estimates. A site variable was entered into the model as a random effect to account for patient clustering by hospital. A modified Poisson regression model was used because the outcome of interest, angina, was not rare, which can result in overestimation of effect using the odds ratios generated from logistic regression models. In comparison, the modified Poisson regression model directly estimates relative risks.21

We also performed a secondary analysis to identify factors associated with more frequent angina (daily or weekly angina, as defined by an SAQ-AF score ≤60) at 1 year, using the same modeling methods of the primary analysis. In addition, we ex-
Table. Patient Characteristics by Presence or Absence of 1-Year Angina* (cont)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes (n=389)</th>
<th>No (n=1568)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and complications (cont)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure (as a complication of the MI)</td>
<td>22 (5.7)</td>
<td>116 (7.4)</td>
<td>.23</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>25 (6.4)</td>
<td>146 (9.3)</td>
<td>.07</td>
</tr>
<tr>
<td>β-Blocker prescribed at discharge</td>
<td>338 (86.9)</td>
<td>1399 (89.2)</td>
<td>.19</td>
</tr>
<tr>
<td>Aspirin prescribed at discharge</td>
<td>358 (92.0)</td>
<td>1450 (92.5)</td>
<td>.79</td>
</tr>
<tr>
<td>Any oral antiplatelets (aspirin or clopidogrel bisulfate) at discharge</td>
<td>369 (94.9)</td>
<td>1483 (94.6)</td>
<td>.83</td>
</tr>
<tr>
<td>ACEI or ARB prescribed at discharge</td>
<td>285 (73.3)</td>
<td>1148 (73.2)</td>
<td>.98</td>
</tr>
<tr>
<td>Lipid-lowering agents prescribed at discharge</td>
<td>328 (84.3)</td>
<td>1313 (83.7)</td>
<td>.78</td>
</tr>
<tr>
<td>Calcium channel blocker prescribed at discharge</td>
<td>58 (14.9)</td>
<td>189 (12.1)</td>
<td>.13</td>
</tr>
<tr>
<td>Acute MI quality indicators received, mean (SD), %</td>
<td>87.7 (16.2)</td>
<td>88.4 (16.9)</td>
<td>.47</td>
</tr>
<tr>
<td>Referral for cardiac rehabilitation provided</td>
<td>179 (46.0)</td>
<td>854 (54.4)</td>
<td>.003</td>
</tr>
<tr>
<td>Smoking cessation counseling provided to current smokers</td>
<td>121 (72.5)</td>
<td>328 (75.0)</td>
<td>.51</td>
</tr>
<tr>
<td>Outpatient treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participation in cardiac rehabilitation within 1 y after discharge</td>
<td>133 (34.2)</td>
<td>692 (44.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of follow-up physician visits within 1 y after discharge, mean (SD)</td>
<td>3.4 (1.6)</td>
<td>3.3 (1.6)</td>
<td>.07</td>
</tr>
<tr>
<td>Any follow-up visit with a cardiologist after discharge</td>
<td>328 (84.3)</td>
<td>1336 (85.2)</td>
<td>.66</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked (referent)</td>
<td>204 (56.5)</td>
<td>1028 (68.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Persistent smoker (smoking at 12 mo)</td>
<td>97 (26.9)</td>
<td>242 (16.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Quit smoking (smoking at baseline and quit at 12 mo)</td>
<td>60 (16.6)</td>
<td>223 (14.9)</td>
<td></td>
</tr>
<tr>
<td>Revascularization procedure as an outpatient (PCI or CABG)</td>
<td>50 (12.9)</td>
<td>112 (7.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

(continued)

(continued)
RESULTS

Overall, of the 1957 patients, 389 (19.9%) reported angina 1 year after their index MI hospitalization. Twenty-four patients (1.2%) reported daily angina, 59 patients (3.0%) reported weekly angina, and 306 patients (15.6%) reported angina less than once a week.

In unadjusted analysis, patients with angina 1 year after MI were more likely to be younger, a race other than white, less educated, and less insured (Table). In addition, they were more likely to have prior cardiac disease, more likely to have had angina before their MI, and had more cardiac risk factors (hypertension and hypercholesterolemia), more depressive symptoms, and higher rates of smoking. However, MI presentation and treatment characteristics were similar between groups. After hospital discharge, patients with angina at 1 year were less likely to participate in cardiac rehabilitation, more likely to smoke, and more likely to have transient, persistent, or new depressive symptoms.

In multivariate analysis (Figure), patients with 1-year angina were more likely to be younger, to be nonwhite males (vs white males), to have had angina before MI hospitalization, to have undergone CABG surgery before MI hospitalization, and to experience recurrent rest angina during their hospitalization. Among the outpatient variables, patients with 1-year angina were more likely to continue smoking, to undergo revascularization after the index hospitalization (PCI or CABG), and to have new, persistent, or transient depressive symptoms. Among the interaction terms tested, the only effect modification noted was between race and sex, with nonwhite males more likely to experience 1-year angina than white males; no effect modification was found for females.

Our secondary analysis of patients with more frequent 1-year angina yielded similar results to the primary multivariate model. We also examined antianginal medication class use at 1 year in patients with and without 1-year angina to assess whether lower rates of medication use might account for the higher prevalence of angina (Table). At 1 year, patients with angina were as likely as those without angina to be taking calcium channel blockers (12.1% vs 11.4%; \( P = .71 \)) and β-blockers (69.2% vs 70.0%; \( P = .78 \)) and more likely to be taking nitrates (51.4% vs 32.4%; \( P < .001 \)). We also examined the proportion of patients with angina who were not taking medications from all possible antianginal medication classes. At 1 year, 87.9% of patients with angina were not taking calcium channel blockers, 30.8% were not taking β-blockers, and 48.6% were not taking nitrates (Table).

### Table 1. Patient Characteristics by Presence or Absence of 1-Year Angina (cont)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes (n=389)</th>
<th>No (n=1568)</th>
<th>( P )</th>
<th>( \text{Value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication adherence at 1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>295 (78.5)</td>
<td>1173 (77.9)</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>269 (75.1)</td>
<td>1097 (74.3)</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>269 (76.0)</td>
<td>1082 (76.7)</td>
<td>.78</td>
<td></td>
</tr>
<tr>
<td>Antianginal medication use at 1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>47 (12.1)</td>
<td>179 (11.4)</td>
<td>.71</td>
<td></td>
</tr>
<tr>
<td>β-Blockerb</td>
<td>269 (69.2)</td>
<td>1097 (70.0)</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>200 (51.4)</td>
<td>508 (32.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None at baseline or 12 mo (referent)</td>
<td>185 (55.7)</td>
<td>1161 (81.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent (PHQ-9 score &gt;10 at baseline and 12 mo)</td>
<td>34 (10.2)</td>
<td>42 (2.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Transient (PHQ-9 score &gt;10 at baseline and 12 mo)</td>
<td>81 (24.4)</td>
<td>182 (12.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New as output 9 (PHQ-9 score &lt;10 at baseline and &gt;10 at 12 mo)</td>
<td>32 (9.6)</td>
<td>39 (2.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery bypass grafting; CABG, coronary artery bypass grafting; MI, myocardial infarction; NSTEMI, non–ST-segment elevation MI; PCI, percutaneous coronary intervention; PHQ-9, 9-item Patient Health Questionnaire; SAQ, Seattle Angina Questionnaire; STEMI, ST-segment elevation MI.

a Percentages are calculated using available data for each variable.

b Data are given as number (percentage) unless otherwise indicated.

c Percentages of β-blockers are different between medication adherence and use because the denominator of medication adherence is those patients prescribed β-blockers at hospital discharge and the denominator of antianginal medication use is all patients.

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To our knowledge, few prior studies have evaluated 1-year angina outcomes in clinical practice. Because a primary goal of cardiac care after MI is the identification and treatment of anginal symptoms, it is critical to understand the prevalence of post-MI angina and factors associated with it. In addition, angina has been associated with a variety of adverse cardiac outcomes, including poor functional status, diminished health-related quality of life, recurrent MI, and mortality. Accordingly, identification of those factors associated with persistent angina can allow clinicians to remain vigilant for the condition and the adverse outcomes that accompany it.

Several clinical trials have evaluated the prevalence of angina among patients 1 year after an ACS. The Randomized Intervention Trial of Unstable Angina 3 compared early invasive with conservative management strategies for patients with non–ST-segment elevation MI. One year after their MI, 37% of patients undergoing early invasive management and 40% of patients undergoing conservative management had residual angina, as assessed by the Canadian Cardiovascular Society angina classification. More recently, the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes trial also compared invasive with conservative strategies for patients with non–ST-segment elevation MI. At 1 year, 14% of patients who received invasive therapies experienced angina compared with 13% of patients who received conservative therapies, as assessed by the Canadian Cardiovascular Society classification. Our study expands on these previous findings by providing a unique, real-world insight into angina rates in contemporary clinical practice, outside the controlled clinical trial environment.

In addition to providing insights into angina prevalence, the PREMIER study evaluated a broad, comprehensive list of both inpatient and outpatient factors during an entire year after MI hospitalization. In particular, the results of this study provide new insights by examining the critical outpatient period between hospital discharge and 1-year follow-up, in contrast to most prior studies in which follow-up ended at hospital discharge. Accordingly, we were able to examine the association between 1-year angina and outpatient cardiac rehabilitation, early follow-up physician visits, medication persistence, revascularization after index hospitalization, and outpatient depressive symptoms.

One of the strongest associations with 1-year post-MI angina was the presence of depressive symptoms either during or after MI hospitalization. This association remained significant even after adjustment for a wide range of demographic, prior history, and treatment variables. The recognition that depressive symptoms, especially those that manifest after hospital discharge, were associated with anginal symptoms is critical in providing optimal outpatient care for patients after MI. Patients with depressive symptoms are at an elevated risk for a wide variety of adverse cardiac outcomes, including cardiac death and subsequent hospitalization. Ideal care after MI for these patients may require routine screening for depressive symptoms to identify those at higher risk for angina and other adverse outcomes after an MI. Once depression is identified, effective therapies are available and safe among cardiac patients, although their specific efficacy with regard to reducing angina and improving other cardiac-specific outcomes remains uncertain and is an important area of future research.

Persistent smoking after MI hospitalization was also associated with 1-year angina. Previous studies have established smoking as a risk factor for incident CAD and for adverse outcomes among patients with CAD, including elevated risk of MI, cardiac mortality, and all-cause mortality. In addition, smoking cessation among patients with CAD leads to reduced mortality rates and recurrent MI. To our knowledge, the association between smoking and angina outcomes has not been well characterized. Although 2 prior studies have noted decreased angina rates among patients who have undergone CABG and who stopped smoking after surgery, no investigations have characterized smoking behavior and angina among patients after MI. Our study, which demonstrates that smoking is associated with 1-year angina, reinforces the importance of post-MI smoking cessation and suggests that targeting smoking cessation after dis-
charge from the hospital after MI may lead to less angina and to other improved outcomes.

Some of the other factors associated with 1-year angina, such as age, nonwhite male, prior CABG surgery, prior angina, and recurrent rest angina during hospitalization may identify specific patient subgroups that warrant increased surveillance for the development of angina in the year after MI. In addition, prior CABG surgery, a history of angina before MI hospitalization, and recurrent rest angina during MI hospitalization may indicate patients with more extensive myocardial ischemia and may warrant more intensive evaluation and treatment of their coronary disease. Future studies are needed to confirm this finding and to evaluate whether interventions targeted to these patients (eg, more aggressive antianginal therapies, disease management programs, and surveillance for recurrent or persistent ischemia to guide the need for revascularization) can improve outcomes. For example, our analysis demonstrated similar rates of use of antianginal medication classes between symptomatic and asymptomatic patients at 1 year. However, our analysis also revealed that many patients with angina were not receiving 1 or more antianginal therapies, suggesting an opportunity for more aggressive antianginal therapies in these patients.

Finally, higher rates of revascularization after the index hospitalization were noted among patients with 1-year angina. This association likely represents reverse causation and is a marker, rather than a cause, of increased angina rates, because symptomatic patients may be offered and may undergo more revascularization procedures in an attempt to relieve their angina.

Our process of sequentially entering groups of clinical and treatment factors into our multivariate model allowed for insight into the correlations between these groups and the presence of 1-year anginal symptoms. For example, lack of health insurance and less than a high school education demonstrated significant associations with 1-year angina in univariate analysis. However, when all sociodemographic variables were entered into the multivariate model, the relationship between lack of health insurance and 1-year angina was no longer significant, implying that other factors, such as age, provided greater explanatory power for anginal symptoms at 1 year. An examination of these relationships can generate exploratory hypotheses for future research between the various clinical and treatment aspects of patients with MI and their subsequent angina outcomes.

Our study has several potential limitations. First, some patients died or had missing data, including 1-year angina assessments. Accordingly, survivor bias and/or missing data could have led to incorrect assessments of the true prevalence of angina and its associated factors. However, imputation methods and propensity models did not suggest a bias in our findings. Second, outpatient factors were collected by patient self-report, which theoretically could lead to bias in the data collection through incomplete or inaccurate patient recall. However, our use of trained interviewers administering standardized interviews and of validated, reproducible questionnaires for symptom assessment minimizes the impact of this potential bias. Third, although we were able to demonstrate that use of agents from various antianginal medication classes was similar between patients with and without angina at 1 year, we did not have specific dosing information for the medications. Thus, we cannot determine if maximal doses of antianginal medications were being used in individual patients with angina. Finally, as with all observational studies, unmeasured confounding could account for some of the observed relationships between patient and treatment factors and 1-year angina. However, our broad collection of clinical and treatment data, combined with our statistical modeling of candidate factors, was designed to minimize this. Observational studies are the best method by which real-world assessments of cardiac disease, treatment, and outcomes can occur, and the results should inform hypotheses to be tested in subsequent efficacy studies (eg, targeting the factors found in this study for post-MI interventions).

In summary, this study found that angina is present in approximately 1 in 5 patients 1 year after MI hospitalization. Multiple factors were associated with 1-year angina, including demographic, clinical, inpatient, and outpatient characteristics. Recognition of these relationships will be important in monitoring at-risk patients after acute MI. In addition, future investigation into modifiable factors, such as depression and smoking cessation, will be important in the quest to alleviate angina and improve subsequent cardiac outcomes among patients after MI.

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Correspondence: Thomas M. Maddox, MD, SM, Cardiology Section (111B), Denver Veterans Affairs Medical Center, 1055 Clermont St, Denver, CO 80209 (thomas.maddox@va.gov).

Author Contributions: Study concept and design: Maddox, Reid, Spertus, Krumholz, and Rumsfeld. Acquisition of data: Maddox, Reid, and Spertus. Analysis and interpretation of data: Maddox, Reid, Spertus, Mittleman, Parashar, Ho, and Rumsfeld. Drafting of the manuscript: Maddox and Reid. Critical revision of the manuscript for important intellectual content: Maddox, Spertus, Mittleman, Krumholz, Parashar, Ho, and Rumsfeld. Statistical analysis: Reid and Mittleman. Obtained funding: Spertus. Administrative, technical, and material support: Spertus. Study supervision: Mittleman and Rumsfeld.
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REFERENCES


