National Trends in Antiarrhythmic and Antithrombotic Medication Use in Atrial Fibrillation

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Background: Atrial fibrillation is the most common cardiac arrhythmia associated with significant medical complications. We examined trends in the medical therapy of atrial fibrillation in the United States from 1991 through 2000.

Methods: Data from 1355 visits among patients with atrial fibrillation were obtained from the National Ambulatory Medical Care Survey, a nationally representative assessment of office-based practice. We assessed trends in medication use for ventricular rate control (digoxin, β-blockers, and calcium channel blockers), sinus rhythm maintenance (class IA, IC, and III antiarrhythmics), and thromboembolism prevention (oral anticoagulants and aspirin).

Results: Overall rate control medication use decreased from 72% of visits in 1991-1992 to 56% in 1999-2000 (P=.01 for trend) due to declining digoxin use (64% to 37%, P<.001 for trend). β-Blocker and calcium channel blocker use remained unchanged. Although there was no change in overall sinus rhythm medication use over time, amiodarone hydrochloride use increased from 0.2% to 6.4% (P<.001 for trend), while quinidine use decreased from 5.0% to 0.0% (P=.01 for trend). Oral anticoagulant use increased (28% to 41%, P=.01 for trend), with the greatest increase in patients aged 80 years and older (14% to 48%, P<.001 for trend). Despite this, only 46.5% of patients at high risk for stroke were taking anticoagulants in 1999-2000.

Conclusions: Digoxin use in atrial fibrillation decreased over time, without concomitant increases in β-blocker or calcium channel blocker use. Amiodarone replaced quinidine as the dominant sinus rhythm medication. Although oral anticoagulant use increased over time, particularly in the oldest patients, fewer than half of the patients at high risk for stroke were anticoagulated.

Arch Intern Med. 2004;164:55-60

Atrial Fibrillation (AF) is the most common significant cardiac arrhythmia, affecting an estimated 2.3 million adults in the United States. Its prevalence is increasing, particularly in older persons, and roughly 10% of persons aged 80 years or older are affected.1,2 Pharmacologic management traditionally had been directed toward 3 goals: control of rapid ventricular rate, restoration and maintenance of sinus rhythm, and prevention of thromboembolic complications.3 Medical therapy has been shown to ameliorate several of the complications associated with AF, particularly with regard to reducing stroke risk.4 Atrial fibrillation has increasingly been the focus of clinical trials and practice guidelines, but it is unclear whether recent clinical practice has changed in accord with published recommendations. We analyzed National Ambulatory Medical Care Survey (NAMCS) data from 1991 through 2000 to assess trends in the prescribing behavior of US office-based physicians in the management of AF. We hypothesized that digoxin use would decline, being replaced by increasing use of β-blockers and calcium channel blockers. We also expected a growing interest in the use of medications for sinus rhythm maintenance, in particular, newer agents such as amiodarone hydrochloride and sotalol hydrochloride. Finally, we expected anticoagulant use to increase over time, especially in patients at the highest risk for stroke.
tient visits within physician practices. During a randomly selected 1-week period, surveyed physicians record information on visit characteristics, medical diagnoses, and medications prescribed for each patient visit. Participating physicians are not eligible to be surveyed again for at least 3 years. The participation rate of physician practices declined somewhat over time, from 72% in 1991 to 68% in 2000. We restricted our study to 1991 through 2000 because individual physician codes were available during this period and could be used to account for potential clustering effects at the individual physician level.

A maximum of 3 diagnoses per patient visit coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) can be listed in the NAMCS. We searched the NAMCS database for ICD-9-CM code 427.31, corresponding to a diagnosis of AF. Atrial flutter (code 427.32) was not included in our search. There were 1486 visits with a code for AF from 1991 through 2000. Because management of AF falls primarily within the fields of internal medicine and cardiology, we excluded 131 visits to providers not in internal medicine, general practice, family practice, cardiology, or cardiac electrophysiology. Excluded visits were to physicians in a wide range of other specialties, the most common being general surgery (32 visits) and pulmonary disease (23 visits). The 1355 patient visits meeting our inclusion criteria occurred in the following years: 112 in 1991, 131 in 1992, 94 in 1993, 149 in 1994, 162 in 1995, 139 in 1996, 145 in 1997, 138 in 1998, 107 in 1999, and 178 in 2000.

The NAMCS instructed physicians to record all new or continued medications ordered, supplied, or administered at each visit. A maximum of 5 medication codes could be recorded for each year from 1991 to 1994 and 6 medications for 1995 to 2000. We assessed use of medications for ventricular rate control and maintenance of sinus rhythm, up to the maximum number of possible medication codes available for each year. All drugs were searched using generic and proprietary name codes. For ventricular rate control, these drugs included digoxin, 15 different β-blockers (a complete list is available from M.C.F.), and 2 calcium channel blockers (verapamil hydrochloride and diltiazem hydrochloride). For restoration and maintenance of sinus rhythm, we searched for Vaughan Williams class IA antiarrhythmics (quinidine, procainamide hydrochloride, and disopyramide phosphate), class IC antiarrhythmics (flecainide acetate, encainide hydrochloride, and propafenone hydrochloride), and 2 newer antiarrhythmics with class III properties (amiodarone hydrochloride and sotalol hydrochloride). Most rate control and sinus rhythm maintenance medications were coded as 1 of the first 3 available codes (82% and 81%, respectively).

When assessing use of antithrombotic therapy, we excluded 20 patient visits with diagnoses that may contraindicate anticoagulation, although this list was incomplete and overly inclusive. These contraindications included dementia, gait abnormalities, epilepsy, intracranial hemorrhages, gastritis or duodenitis, gastrointestinal ulcer disease, gastrointestinal hemorrhages, chronic liver disease, alcoholism, purpura, hematuria, and neoplasms of the central nervous system and gastrointestinal or genitourinary systems. Within the remaining 1335 visits, we assessed the use of oral anticoagulants (warfarin sodium, dicumarol, anisindione, and phenprocoumon) and aspirin. We also examined antithrombotic medication use in patients who had diagnoses associated with a high stroke risk in AF: age older than 75 years, prior transient ischemic attack or stroke (excluding intracranial hemorrhages), valvular heart disease, hypertension, and congestive heart failure. Most oral anticoagulants and aspirin were coded as 1 of the first 3 available codes (79% and 63%, respectively).

We then examined several visit characteristics collected through the NAMCS for association with antiarrhythmic and antithrombotic medication use. Age was divided into younger than 65 years, 65 to 79, and 80 or older. The NAMCS categorized geographic location into 4 US Census regions (Northeast, Midwest, South, and West). Because most subjects reported Medicare coverage, insurance status was divided into Medicare and “other,” which included Medicaid, self-pay, private insurance, no charge, and workers’ compensation. Physician specialty was divided into cardiologists and noncardiologists.

National estimates and 95% confidence intervals (CIs) were calculated using weights provided by the National Center for Health Statistics. The center provides weights for each visit-level record that account for the probability of sampling based on the physician’s practice, specialty, and geographic region. These weights allow extrapolation to national estimates. Calculations were weighted using the National Center for Health Statistics visit sampling weight in the method described by Potthoff and colleagues. We assessed trends in medication use over time by calculating the odds ratio (OR) of medication use by 2-year intervals; P values for trend were calculated using generalized estimating equations to account for clustering at the individual physician level. Two-year intervals were used to provide more reliable estimates, and we report data from 1991-1992 and 1999-2000 as points of comparison. SAS statistical software was used for these analyses.

We then developed a multivariate model to assess independent predictors of medication use among patients with AF in recent years (1997-2000). Logistic regression was used to assess the bivariate OR between medication use and visit characteristics. Covariates significant at P=.30 on bivariate analysis were put into a multivariate logistic regression model to obtain adjusted ORs and 95% CIs. Age and sex were considered clinically significant covariates and were included in each model. Confounders were added back to the model. In these analyses, SUDAAN statistical software was used to account for the complex sampling design of the NAMCS.

The estimated number of annual visits for AF in the United States increased from 2.9 million in 1991 (95% CI, 2.0-3.8 million) to 4.5 million in 2000 (95% CI, 3.1-5.9 million). The overall prevalence of an AF diagnosis in adults in the NAMCS data set was 0.57%. Of all visits among patients with AF, the prevalence of lone AF (defined as age <65 years and with no significant stroke risk factors) was 11.8% and did not change significantly over time. Patient age, sex, race, geographic region, and proportion with reported Medicare coverage also did not change significantly over time in patients with AF (Table 1). The prevalence of cardiologist visits increased over time (28% in 1991-1992 to 37% in 1999-2000, P=.02 for trend). The number of medications reported in NAMCS AF visits (median, 5.0) did not change significantly during this time.

### MEDICATIONS FOR VENTRICULAR RATE CONTROL

The proportion of visits with reported use of rate controlling medications decreased over the last decade, from 72% in 1991-1992 to 56% in 1999-2000 (P=.01 for trend) (Table 2). This was primarily due to a significant decline in digoxin use, from 64% to 37% (P<.001 for trend). β-Blocker use increased, but the change was not significant (16% to 22%, P=.09 for trend). Calcium channel blocker use did not change significantly over time (16%...
vs 14%, P = .13 for trend) (Figure 1). The proportion of visits with reported use of 2 or more classes of medications for rate control decreased over time (P = .01 for trend), reflecting the decline in digoxin use. Concomitant use of a β-blocker and calcium channel blocker was unusual (0.33% vs 1.02%, P = .61 for trend).

MEDICATIONS FOR SINUS RHYTHM MAINTENANCE

The overall proportion of visits with reported use of drugs to maintain sinus rhythm did not change significantly over the last decade (10% in 1991-1992 to 12% in 1999-2000, P = .88 for trend) (Table 2). However, significant shifts occurred in the use of individual medications (Figure 2). Class IA drug use fell from 9.2% to 2.2% (P = .003 for trend), largely because of the declining use of quinidine (5.0% to 0.0%, P = .01 for trend). Class IC drug use increased modestly from 0.5% to 2.9% (P < .001 for trend). By 1998, amiodarone replaced quinidine as the most frequently reported medication used for the maintenance of sinus rhythm, increasing from 0.2% of visits in 1991-1992 to 6.4% in 1999-2000 (P < .001 for trend). Sotalol use did not change significantly (0.0% vs 0.8%, P = .35 for trend).

ANTITHROMBOTIC MEDICATIONS

The proportion of patient visits with reported use of antithrombotic therapy increased over time, from 36% in 1991-1992 to 46% in 1999-2000 (P = .05 for trend) (Table 2). This effect was primarily due to the increase in oral anticoagulant use, from 28% to 41% (P = .01 for trend). The increase in anticoagulant use was similar when we excluded the 185 visits among patients with lone AF (P = .001 for trend). When stratified by age, the most significant increase in anticoagulant use was observed in persons aged 80 years or older (14% to 48%, P < .001 for trend). Overall use of aspirin did not change significantly over time (8.9% vs 7.6%, P = .40 for trend), nor did aspirin use in persons not taking anticoagulants (P = .99 for trend). Concomitant use of aspirin and an anticoagulant was uncommon (0.8% vs 1.8%, P = .49 for trend).

We assessed predictors of medication use using data from the 568 surveys among patients with an AF diagnosis in 1997 through 2000. Potential predictors included age, gender, region, presence of congestive heart failure, hypertension, and whether the patient had a prior cardiac visit. We found that female patients, those with congestive heart failure, and those who had a prior cardiac visit were more likely to use anticoagulant therapy (Table 1). The proportion of patient visits with reported use of anticoagulant therapy increased from 25% in 1991-1992 to 46.5% in 1999-2000 (P = .002 for trend), and aspirin use remained unchanged (8.2% vs 7.1%, P = .67 for trend).

Because the maximum number of medications that could be listed on the survey form differed depending on the visit year, we repeated the analyses using only the first 5 medications listed for each visit. Restricting the number of medications used in the analyses did not significantly change our results.

Table 1. Comparison of Baseline Visit Characteristics Over Time (N = 1355)*

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age, mean, y</td>
<td>72.6 (71.2-74.0)</td>
<td>71.5 (70.8-73.9)</td>
<td>.90</td>
</tr>
<tr>
<td>Female</td>
<td>45.5 (36.8-54.3)</td>
<td>45.7 (37.7-53.8)</td>
<td>.65</td>
</tr>
<tr>
<td>White</td>
<td>96.4 (91.7-98.9)</td>
<td>96.6 (92.4-98.8)</td>
<td>.90</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td>.67 for trend</td>
</tr>
<tr>
<td>Northeast</td>
<td>29.4 (21.8-37.9)</td>
<td>31.2 (24.1-39.1)</td>
<td>.10</td>
</tr>
<tr>
<td>Midwest</td>
<td>18.8 (12.6-26.6)</td>
<td>22.1 (15.9-29.4)</td>
<td>.10</td>
</tr>
<tr>
<td>South</td>
<td>21.7 (15.0-29.6)</td>
<td>27.5 (20.7-35.2)</td>
<td>.10</td>
</tr>
<tr>
<td>West</td>
<td>30.2 (22.5-38.7)</td>
<td>19.1 (13.3-26.2)</td>
<td>.10</td>
</tr>
<tr>
<td>Medicare</td>
<td>70.6 (62.1-78.2)</td>
<td>62.6 (54.6-70.2)</td>
<td>.20</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11.2 (6.4-17.8)</td>
<td>19.5 (13.6-26.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>16.3 (10.5-23.7)</td>
<td>15.1 (9.9-21.6)</td>
<td>.43</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11.7 (6.8-18.4)</td>
<td>16.2 (10.8-22.9)</td>
<td>.12</td>
</tr>
<tr>
<td>Cardiologist visit</td>
<td>28.0 (20.5-36.4)</td>
<td>36.9 (29.3-44.9)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Data are given as percentage (95% confidence interval) unless otherwise indicated.

Table 2. Comparison of the Use of Rate and Rhythm Modifying Agents Over Time (N = 1355)*

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Agents for ventricular rate control</td>
<td>71.6 (63.1-79.0)</td>
<td>56.2 (48.1-64.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Digoxin</td>
<td>64.4 (55.6-72.5)</td>
<td>36.7 (29.1-44.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>16.3 (10.5-23.7)</td>
<td>22.2 (16.0-29.5)</td>
<td>.09</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>15.8 (10.0-23.1)</td>
<td>13.5 (8.6-19.9)</td>
<td>.13</td>
</tr>
<tr>
<td>Digoxin plus β-blocker</td>
<td>12.6 (7.5-19.5)</td>
<td>9.4 (5.3-15.0)</td>
<td>.46</td>
</tr>
<tr>
<td>Digoxin plus calcium channel blocker</td>
<td>11.0 (6.2-17.6)</td>
<td>4.9 (2.1-9.5)</td>
<td>.001</td>
</tr>
<tr>
<td>β-Blocker plus calcium channel blocker</td>
<td>0.3 (0.0-3.4)</td>
<td>1.0 (0.1-4.1)</td>
<td>.61</td>
</tr>
<tr>
<td>Agents for sinus rhythm maintenance</td>
<td></td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>Class IA</td>
<td>9.2 (4.9-16.4)</td>
<td>2.2 (0.5-5.9)</td>
<td>.003</td>
</tr>
<tr>
<td>Quinidine</td>
<td>5.0 (2.0-10.2)</td>
<td>0.0 (0.0-2.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Class IC</td>
<td>0.5 (0.0-3.6)</td>
<td>2.9 (0.9-6.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Amiodarone hydrochloride</td>
<td>0.2 (0.0-3.0)</td>
<td>6.4 (3.1-11.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sotalol hydrochloride</td>
<td>0.0 (0.0-2.7)</td>
<td>0.8 (0.0-3.8)</td>
<td>.35</td>
</tr>
<tr>
<td>On both a rate control and sinus rhythm medication</td>
<td>6.6 (3.0-12.3)</td>
<td>6.8 (3.4-11.9)</td>
<td>.77</td>
</tr>
<tr>
<td>On neither a rate control nor sinus rhythm medication</td>
<td>25.3 (18.2-33.6)</td>
<td>38.4 (30.7-48.4)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Data are given as percentage (95% confidence interval).
sex, race, geographic region, Medicare status, visit to a cardiologist, and diagnoses of congestive heart failure, hypertension, and ischemic heart disease. When assessing antithrombotic therapy use, we also included increased stroke risk (defined as having ≥1 stroke risk factor) as a potential predictor.

We found no significant predictors of rate control medication use on bivariate or multivariate analysis. Use of sinus rhythm medication was associated on bivariate analysis with male sex (OR, 2.3; 95% CI, 1.2-4.6) and visits to cardiologists (OR, 3.0; 95% CI, 1.2-7.4). Persons aged 80 years and older were less likely to be taking sinus rhythm medications (OR, 0.18; 95% CI, 0.07-0.42). In the multivariate model, the significant independent predictors were male sex (OR, 2.0; 95% CI, 1.1-3.7). Persons aged 80 years and older remained less likely to be taking medications for sinus rhythm (OR, 0.21; 95% CI, 0.09-0.48).

Oral anticoagulant use was associated on bivariate analysis with the presence of 1 or more stroke risk factors (OR, 1.6; 95% CI, 1.1-2.6) and was less likely in persons younger than 65 years (OR, 0.55; 95% CI, 0.34-0.90). On multivariate analysis, persons younger than 65 years continued to have less anticoagulant use (OR, 0.57; 95% CI, 0.33-0.95), but stroke risk no longer was significant (OR, 1.5; 95% CI, 0.98-2.40). We assessed aspirin use by restricting the analysis to those not taking anticoagulants, as concomitant therapy was rarely reported. In bivariate and multivariate analysis, the only significant predictor for aspirin use was visit to a cardiologist (OR, 7.0; 95% CI, 2.7-18.5).

**COMMENT**

Atrial fibrillation is an increasingly common medical problem, and numerous clinical trials and guidelines have focused on determining its optimal medical management. To facilitate the translation of randomized trial data into effective clinical care, it is important to monitor physician practice patterns. The NAMCS provides unique insight into the actual clinical management of AF in the United States over time. Our study demonstrates that agents used for ventricular rate control remain the most commonly reported medications used for AF, but shows that digoxin use significantly declined. Digoxin use was reported in 76% of patients with AF in 1980-1981, but was reported in only 37% of patient visits by 1999-2000 in our study. This change may reflect reports that digoxin is less effective than β-blockers or calcium channel blockers in controlling effort-related tachycardia.
Although guidelines have recommended that digoxin be used as second-line therapy for rate control,
we were surprised that the decline in digoxin use was not more offset by increases in the use of other medications for rate control. It is unlikely that significant numbers of patients were taking sinus rhythm medications for rate control purposes, as only 10.7% of patients not taking a medication for rate control were taking a medication for sinus rhythm. It is also unlikely that a significant proportion of patients had procedures such as radiofrequency ablation, although we were unable to determine this using NAMCS data. Further investigation may be helpful to assess whether our results indicate an underuse of β-blockers and calcium channel blockers among patients with AF. Suboptimal rate control may impair patients’ physical functioning, adversely affect hemodynamics, and raise concern about tachycardia-induced cardiomyopathy.

The recently completed AFFIRM, RACE, and PIAF trials will likely reduce enthusiasm for a strategy favoring sinus rhythm restoration over rate control.
Even before publication of these studies, guidelines were not specific regarding choice of antiarrhythmic medication. Despite this, there have been significant changes in the use of medications for sinus rhythm maintenance in the last decade, most notably seen in the rapid rise in the use of amiodarone and the diminishing use of quinidine. Although quinidine use has been associated with an increased risk of cardiovascular mortality, a 1993 survey of US internists and cardiologists found it to be the preferred medication for the maintenance of sinus rhythm.
Our study shows that by 1998 amiodarone replaced quinidine as the dominant antiarrhythmic used for sinus rhythm maintenance. Indeed, quinidine was used in no AF patients in the 1999–2000 surveys. Amiodarone has relatively little cardiac toxicity compared with other antiarrhythmics, and its initiation requires less intensive initial electrocardiographic monitoring, characteristics that may have contributed to its increasing popularity. We anticipate that the results of recent trials comparing rate to rhythm control will slow this sharp rise in amiodarone use and therefore contribute to an overall reduction in the use of sinus rhythm medications. As greater emphasis is placed on rate control, we expect to see increases in β-blocker and calcium channel blocker use in future years, as well as a continued emphasis on appropriate antithrombotic therapy.

It has been well documented that oral anticoagulants dramatically reduce stroke risk in AF. These studies suggest that the oldest patients may derive the most benefit from anticoagulation, although few subjects older than 80 years participated in the clinical trials. Despite strong recommendations advocating the use of anticoagulants for most patients with AF, previous studies have shown suboptimal rates of warfarin use in the oldest patients. Our analyses demonstrate a marked increase in anticoagulant use in persons aged 80 years and older. The finding that nearly half of these individuals were prescribed anticoagulants is substantially higher than a fairly contemporaneous assessment in a health maintenance organization, which reported only a 35% use in persons with AF aged 85 years or older. Additional surveys are needed to assess the consistency and generalizability of our results, as our estimate has a moderately wide CI. The increase in anticoagulant use in those aged 65 to 80 years was less dramatic and may indicate an area for continued quality improvement. Although overall anticoagulant use has increased among patients with AF, aspirin use has not changed significantly, and fewer than half of the people at the highest stroke risk were taking anticoagulants (Table 3).

Medication use was not uniform in all patient groups. In the multivariate analysis, use of agents for sinus rhythm maintenance was associated with visits to cardiologists, which may reflect their greater familiarity with use of these medications. Men were more likely to be taking these agents as well, although the CI for this difference was wide. Not surprisingly, oral anticoagulation was less likely in persons younger than 65 years, reflecting current recommendations. However, an increased stroke risk did not predict anticoagulant use on multivariate analysis, and it is probable that other factors influenced physicians’ decision making with regard to anticoagulation. Aspirin use was more frequently associated with visits to cardiologists. Reasons for this cannot be determined using the NAMCS, but it remains possible that cardiologists may be more likely to report aspirin use on the survey form.

Limitations in the NAMCS should be acknowledged. The NAMCS does not capture the longitudinal experience of individual patients, and because the unit of measurement is by patient visit, frequent users of care may be overrepresented. The limited number of diagnoses that could be reported on the survey form may have prevented us from capturing all visits among patients with AF or all contraindications to anticoagulant use. In particular, AF patients with multiple comorbidities may not have been listed. Similarly, underreporting of medications may have occurred, leading to artificially lower estimates of medication use, in particular, aspirin. Another limitation in the NAMCS is that it does not distinguish between different types of AF, such as paroxysmal vs persistent, nor does it specify the duration of disease. Important clinical data such as hemodynamic and echocardiographic data were not available, and we were unable to determine specific reasons that patients were not taking medications, such as adverse drug reactions or patient preference. Because of these factors, determining the appropriateness of care was difficult.
Nevertheless, the NAMCS provides distinctive information on trends in the medical management of AF. Our study documents substantial changes in the treatment of AF in the United States over the last decade. Notably, digoxin use continues to decrease, without a concomitant increase in the use of other agents for rate control. Amiodarone has become the most commonly reported medication for sinus rhythm maintenance, while quinidine use is now rare. Although oral anticoagulant use increased, it remains concerning that many patients at high stroke risk are not anticoagulated. As new evidence becomes available on the optimal management of AF, continued monitoring of trends in clinical practice is crucial to help identify areas for quality assessment and practice improvement.

Accepted for publication February 20, 2003.

This study was supported by National Research Service Award 5T32PE11001-13 from the National Institutes of Health, Bethesda, Md (Dr Fang), and by the Donald W. Reynolds Cardiovascular Clinical Research Center, Stanford University, Palo Alto, Calif (Dr Stafford).

This study was presented in part at the Society of General Internal Medicine Northeast Regional Meeting; March 8, 2002; Boston, Mass; and at the Society of General Internal Medicine National Meeting; May 3, 2002; Atlanta, Ga.

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