Rate Control and Sinus Rhythm Maintenance in Atrial Fibrillation

National Trends in Medication Use, 1980-1996

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Background: Little is known about national patterns of pharmacological treatment of atrial fibrillation, in particular, use of medications for ventricular rate control and for restoration and maintenance of sinus rhythm.

Methods: We analyzed 1555 visits by patients with atrial fibrillation to randomly selected office-based US physicians included in National Ambulatory Medical Care surveys conducted in 1980, 1981, 1985, and 1989 through 1996. To determine national trends, we evaluated the proportion of atrial fibrillation visits with reported use of rate control medications (digoxin and antiarrhythmics in classes II and IV) and sinus rhythm medications (classes IA, IC, and III).

Results: The use of rate control agents decreased from 79% of atrial fibrillation visits in 1980-1981 to 62% in 1994-1996. Declining use was noted for both digoxin (76% in 1980-1981 to 53% in 1994-1996) and β-blockers (19%-13%). After their introduction, the use of verapamil hydrochloride and diltiazem hydrochloride increased to 15% of atrial fibrillation visits in 1994-1996. Sinus rhythm agent use decreased from 18% of visits in 1980-1981 to 4% in 1992-1993 and then rose to 13% in 1994-1996. The use of class IA agents declined from 18% in 1980-1981 to 3.5% in 1992-1993 and then increased to 8% in 1994-1996. Quinidine remained the most widely used sinus rhythm medication, despite its declining share of this category. Newly available sotalol hydrochloride and amiodarone hydrochloride were used in 3.6% of visits in 1994-1996.

Conclusions: Despite changes in the treatment of atrial fibrillation, digoxin remains the dominant rate control medication. Medications for sinus rhythm maintenance are not widely used. Quinidine use declined prominently in the 1980s, possibly because of concerns about proarrhythmic effects. The use of sinus rhythm agents, however, is now rising.

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Atrial fibrillation is the most common significant cardiac arrhythmia, occurring in 1% of the US population. The prevalence of atrial fibrillation increases strikingly with older age; 4% of the population older than 60 years and 10% older than 80 years have atrial fibrillation. With the aging of the US population, atrial fibrillation is increasing in prevalence.

Antiarhythmic medication therapy for atrial fibrillation is targeted at 2 goals: (1) controlling the rate of ventricular response to minimize physiologically inefficient tachycardia, and (2) restoring and maintaining normal sinus rhythm. The first goal can frequently be achieved through treatment with commonly used and relatively nontoxic medications. However, rate control is often not optimal; cardiac function continues to be compromised by a lack of coordinated atrial contractions; distressing symptoms of dyspnea, diminished effort tolerance, and palpitations may continue; and an increased risk of stroke persists. Restoring and maintaining sinus rhythm alleviates all these complications of atrial fibrillation. However, the drugs currently used to achieve sinus rhythm are incompletely effective and raise the risk of several toxic effects. The merits of rate vs rhythm control in atrial fibrillation are actively debated and are the focus of a large randomized trial sponsored by the National Heart, Lung, and Blood Institute. Despite current controversy, little is known about the use of antiarrhythmic medications for atrial fibrillation in actual clinical practice. Using a national database on visits to office-based physicians, we report patterns of antiarrhythmic medication use in patients with atrial fibrillation from 1980 through 1996.

RESULTS

Estimated annual office visits by patients with atrial fibrillation in the United States increased from 1.3 million (95% CI, 1.0 mil-
METHODS

Data for this study come from the National Ambulatory Medical Care surveys (NAMCSs) for 1980, 1981, 1985, and 1989-1996. Conducted by the National Center for Health Statistics (NCHS, Rockville, Md), these surveys provide an ongoing assessment of the practices of office-based US physicians. The sampling process made use of American Medical Association (Chicago, Ill) and American Osteopathic Association (Chicago) master lists of all patient care US physicians. A sample of physicians from these lists was selected by random stratified sampling according to geographic area and specialty. Among eligible physicians, annual participation rates varied from 70% (1994) to 78% (1981). For each participating physician in each year, patient visits during a randomly selected week were sampled systematically. The survey includes between 33,998 (1994) and 71,594 (1985) annual outpatient visits to between 1704 (1994) and 2879 (1985) physicians. For some statistical analyses, we grouped the data into the 5 periods of 1980-1981, 1985, 1989-1991, 1992-1993, and 1994-1996 to provide more statistically powerful comparisons across periods.

For each selected patient visit, physicians completed encounter forms detailing the specific clinical services provided during the visit, as well as patient demographics and diagnoses. Continuing and newly ordered over-the-counter and prescribed medications also were listed for each visit. For each visit record, the NCHS provided a visit weight calculated from the physician and visit sampling rates, adjusted for nonresponse. Statistical aggregation using these visit weights allows extrapolation to national patterns of practice. We modified these weights using the method of Potthoff et al to derive effective sample sizes for use in statistical testing. Relative standard error figures of the NCHS surveys include between 33,598 (1994) and 71,594 (1985) annual outpatient visits to between 1704 (1994) and 2879 (1985) physicians. For some statistical analyses, we grouped the data into the 5 periods of 1980-1981, 1985, 1989-1991, 1992-1993, and 1994-1996 to provide more statistically powerful comparisons across periods.

Visits by patients with atrial fibrillation were identified by an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code of 427.31 among any of the 3 diagnoses coded for each visit. Visits by patients with atrial flutter (ICD-9-CM code 427.32) were not included. A total of 1,353 visits by patients with atrial fibrillation were reported: 111 in 1980, 141 in 1981, 175 in 1985, 94 in 1989, 146 in 1990, 120 in 1991, 141 in 1992, 131 in 1993, 164 in 1994, 177 in 1995, and 152 in 1996.

Patients receiving antiarrhythmic medications for ventricular rate control (digoxin and class IV and II agents) or for the restoration and maintenance of sinus rhythm (class I A, IC, and III agents) were identified. Either 8 (1980-1981), 5 (1985-1994), or 6 (1995-1996) possible codes for new or continuing medications were available for each visit. Generic or proprietary names for the following medications were reported: quinidine, procainamide hydrochloride, disopyramide phosphate (class IA), flecaïnide acetate, encainide hydrochloride, propafenone hydrochloride (class IC), 17 different β-blockers (class II), amiodarone hydrochloride, sotalol hydrochloride (class III), verapamil hydrochloride, diltiazem hydrochloride (class IV), and digoxin. We specifically evaluated medication coding practices relative to the number of possible codes available. We found few cases coded with the maximal number of medications and noted that most rate control (84.3% in recent years) and sinus rhythm (88.4%) medications were coded in the first 3 available codes.

A number of patient and physician characteristics reported in the NAMCSs were evaluated to determine their association with medications for ventricular rate control and sinus rhythm maintenance. Geographic area was defined by the 4 US Census regions of West, South, Northeast, and Midwest. Private insurance was defined as the reporting of private insurance coverage, either as primary insurance or as a supplement to Medicare. The specialty of the physician seen by the patient was defined using American Medical Association categories. Congestive heart failure was defined by the ICD-9-CM diagnostic codes 398.91, 402, or 428 among any of the 3 diagnoses coded for each visit.

National patterns in the proportion of patients with atrial fibrillation currently taking antiarrhythmic medications were assessed by cross tabulation of patient visit information weighted by NCHS visit sampling weights. Potential predictors of antiarrhythmic medication use were evaluated statistically using χ² tests for association or for trend by year based on our calculated effective sample sizes.

Independent predictors of antiarrhythmic medication use were determined using multiple logistic regression to estimate the natural logarithm of the odds of sinus rhythm maintenance agent and ventricular rate control agent use in atrial fibrillation. The set of variables included sex, age, physician specialty, and region of the country. Using data from 1994-1996, this cross-sectional logistic regression model gauged the independent effect of these predictors for the most recent practice patterns. Statistical analyses were performed using SAS software, including the LOGIST and FREQ procedures.

Considering the results of the Cardiac Arrhythmia Suppression Trial and other studies documenting the proarrhythmic effects of sinus rhythm agents, we hypothesized that the use of these medications would diminish after the publication of these studies in the late 1980s and early 1990s.
blocks increased from 19.1% in 1980-1981 to 27.4% in 1994-1996 (*P* = .01).

Based on visits by patients with atrial fibrillation in 1994-1996, we assessed the effect of several patient and physician characteristics on the likelihood of rate control agent use. Geographic region had an effect on use, with the Northeast (71.9% of visits) having higher rate control agent use than the West (63.0%), Midwest (57.5%), and South (54.1%, *P* = .001). The use of rate control medications showed a tendency to be more likely in nonwhites (80.9%) than whites (60.6%, *P* = .06). Age did not have a significant effect on rate control agent use (59.9% in patients younger than 65 years, 62.1% in those aged 65-74 years, 62.9% in those aged 75-79 years, and 62.7% in those aged 80 years and older). Use of these agents also did not significantly differ between men and women, physicians of different specialties, or patients with and without private insurance. Logistic regression analysis of 1994-1996 data confirmed greater rate control agent use among visits in the Northeast compared with other regions (odds ratio [OR], 1.89; 95% CI, 1.07-3.32) and suggested that nonwhites tended to more likely to receive these medications (OR, 3.01; 95% CI, 0.97-9.34).

### SINUS RHYTHM MAINTENANCE

The use of agents for restoring and/or maintaining sinus rhythm decreased from 18.1% of atrial fibrillation visits in 1980-1981 to 4.1% in 1992-1993 (*P* < .001 for trend), but then increased to 13.1% by 1994-1996 (OR = .002, Table). The greatest change occurred with class IA agents (quinidine, procainamide, and disopyramide), whose use declined from 18.1% in 1980-1981 to 3.5% in 1992-1993 (*P* < .001) and then increased to 8.2% in 1994-1996 (OR = .05). The use of quinidine declined from 12.9% in 1980-1981 to 2.5% in 1992-1993 (*P* < .001) and then increased nonsignificantly to 3.8% in 1994-1996 (OR = .44). Disopyramide use declined from 3.9% in 1980-1981 to 0.6% in 1992-1993 (OR = .09) and then rose to 2.0% in 1994-1996 (OR = .26). Procainamide use increased modestly from 1.3% in 1980-1981 to 2.4% in 1994-1996 (OR = .57).

The use of class IC agents (flecainide, encaïnide, and propafenone) was rarely reported from 1980 to 1993 (0.1% of visits), but was reported in 1.4% of visits in 1994-1996. By 1994-1996, there was limited adoption of the newly available class III medications (3.6% of visits), including sotalol (1.6%) and amiodarone (2.0%).

The use of more than 1 agent to maintain sinus rhythm was noted in only 0.2% of all visits from 1980-1996. For 1994-1996, the use of rate control medications was equally likely to be reported among patients taking (63.9%) and not taking (61.8%) sinus rhythm medications.

For 1994-1996, the use of sinus rhythm agents was evaluated across a range of patient and physician characteristics. Their use was more likely to be reported by cardiologists (21.5%) than by family and general practitioners (10.6%), internists (9.4%), and other physicians (5.6%, *P* = .04). Physicians in the West (17.0%) and Northeast (16.3%) tended to report the use of sinus rhythm medications more often than those in the South (10.4%) and Midwest (8.1%, *P* = .07). The diagnosis of congestive heart failure increased the likelihood of sinus rhythm agent use (17.2% with congestive heart failure, 12.6% without), although this finding was not statistically significant (OR = .45). There were no significant differences by age group or between whites and nonwhites, males and females, and patients with and without private insurance coverage. When the independent effects of potential predictors were evaluated through logistic regression analysis of 1994-1996 data, cardiologists were more likely than noncardiologists to report the use of sinus rhythm medications (OR, 2.4; 95% CI, 1.2-5.0). No other predictor had a statistically significant impact on sinus rhythm agents use in this regression model.

### COMMENT

In the past decade and a half, there have been substantial changes in the use of antiarrhythmic agents in atrial fibrillation. While medications for ventricular rate control remain the most common form of medical therapy in atrial fibrillation, their use has declined. Increasing use...
of calcium channel blockers (class IV agents) did not make up for the sizable declines in both digoxin and β-blocker use. Because of the considerable evidence suggesting that adequate ventricular rate control improves patient quality of life and reduces the physiological complications of tachycardia, the overall decline in the use of rate control medications was not expected. It also is surprising that only 27% of patients with atrial fibrillation were taking calcium channel blockers or β-blockers in 1994-1996. Given their greater effectiveness compared with digoxin in preventing exercise-induced tachycardia and their lack of required laboratory monitoring, these classes of medications may be inadequately used.

Not all patients were equally likely to receive rate control medications. In particular, nonwhites tended to be more likely than whites to receive these medications. Patients living in the Northeast also were more likely to be taking rate control medications than were those in other regions of the country.

The use of medications aimed at restoring and maintaining sinus rhythm in patients with atrial fibrillation was highest in 1980-1981, when they were reported in 18% of atrial fibrillation visits. The overall use of these agents may be limited by their incomplete effectiveness in restoring and maintaining sinus rhythm and their substantial adverse effects that interfere with long-term use. The modest use of these agents, however, contrasts with recent evidence suggesting a place for the maintenance of sinus rhythm in patients with recurrent episodes of atrial fibrillation.

Between 1980-1981 and 1992-1993, there was a substantial decline in the use of sinus rhythm agents. Much of this decline is attributable to the results of the Cardiac Arrhythmia Suppression Trial, which demonstrated a significant increase in mortality in patients treated with encainide and flecainide. Additional evidence from studies focused on atrial fibrillation management also became available in the late 1980s and early 1990s. This evidence of proarrhythmic effects may have prompted physician reluctance to prescribe sinus rhythm agents.

After 1992-1993, the use of sinus rhythm medications increased significantly, although not to the level noted in 1980-1981. A small portion of this recent increase was attributable to newly available class III medications. The use of amiodarone, released in 1985, and sotalol, released in 1987, was reported in only 3.6% of all atrial fibrillation visits in 1994-1996. Class IA agents accounted for most of the recent increase in the use of sinus rhythm medications. Although quinidine remains the most commonly used sinus rhythm medication, by 1994-1996 the use of disopyramide and procainamide approached that of quinidine. The recent resurgence of sinus rhythm medication use may be related to an increasing belief that maintenance of sinus rhythm reduces the risk of both cardiomyopathy and thromboembolism associated with atrial fibrillation.

Several limitations of the data from the NAMCSs must be acknowledged. Physician reporting of medications may not be complete. The reported use of these medications in the NAMCSs also may differ from a population-based estimate for all patients with atrial fibrillation. Patients enumerated in the NAMCSs may be older, have more comorbidities, or be taking other medications (such as warfarin) that require close monitoring. Although the NAMCSs provide a representative sample of office-based visits in the United States, our extrapolations to national patterns of practice are based on a sample of only 1555 visits. We were unable to assess several important clinical characteristics of patients that might alter decision making for antiarrhythmics in atrial fibrillation and provide us with greater ability to comment on appropriateness. In particular, no information was available on the chronicity of atrial fibrillation, history of electrocardiography or current cardiac rhythm at the time of the office visit. By extension, we also were unable to assess the adequacy of therapy for either ventricular rate control or sinus rhythm maintenance. Physician coding practices may affect the identification of patients with atrial fibrillation. In particular, we may have excluded those patients who were successfully converted from atrial fibrillation to sinus rhythm if their physicians failed to regard them as still having atrial fibrillation. Although these issues may diminish our ability to gauge the appropriateness of antiarrhythmic medication use in any given year, the relative trends we note are much less likely to be affected by these factors. Finally, we have a limited ability to define the specific mechanisms leading to the variations in medication use that we note.

Evidence of proarrhythmic effects may have prompted physician reluctance to prescribe sinus rhythm agents.

Despite these limitations, the NAMCSs provide a unique, national time-series of patterns of antiarrhythmic medication use in patients with atrial fibrillation. Our analysis suggests that newer medications with potential advantages over traditional agents have been adopted only slowly. Our evidence suggests that current practices are dictated more by clinical tradition than by clinical science. This issue is of particular concern for ventricular rate control, for which digoxin remains the dominant medication. The relative decline in sinus rhythm medication use noted between 1980-1981 and 1992-1993 is consistent with heightened concern about these medications following the publication of studies documenting proarrhythmic effects of sinus rhythm agents. The relative magnitude of this change in medication use is particularly large compared with that reported in other studies assessing the impact of clinical trial results on practices, suggesting that physicians respond more quickly to reports of toxic reactions than to those of efficacy.

Finally, we found nonclinical clinical variations in prescribing practices. Physicians in the West and Northeast were more likely to report prescribing antiarrhythmic medications for their patients with atrial fibrillation. Other studies also have noted regional variations in the prescribing of cardiovascular disease medications, including greater use of warfarin in atrial fibrillation in the Northeast.

The results of this study reinforce the need for careful assessment of the appropriateness of antiarrhythmic
therapy for patients with atrial fibrillation. In particular, there may be a need for greater vigilance in controlling the ventricular rate in these patients. Our findings also highlight the need to determine the relative merits of strategies focusing on rate control vs sinus rhythm maintenance, an issue the Atrial Fibrillation Follow-up Investigation of Rhythm Management was designed to address.

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REFERENCES