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Atrial Fibrillation and Managed Care: Current Approaches and Future Directions for Long-Term Therapy

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FACULTY

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A frequent national lecturer, Dr. Sanoski speaks on numerous topics in cardiovascular disease management, including cardiac arrhythmias, acute coronary syndrome, and acute decompensated heart failure. She has published in a number of peer-reviewed journals, including *Archives of Internal Medicine*, *Formulary*, *Pharmacotherapy*, *Chest*, *Journal of Pharmacy Practice*, and *The Journal of Applied Research*. She has also written several book chapters on the management of acute and chronic arrhythmias and medication-induced cardiovascular adverse effects. Dr. Sanoski is a reviewer for several journals, including *Pharmacotherapy*, *Clinical Therapeutics*, *Journal of Pharmacy Practice*, *Current Medical Research and Opinion*, and *American Journal of Managed Care*. She also serves on the editorial boards of the *Journal of Pharmacy Practice* and *Current Medical Research and Opinion*. She is also board-certified as a pharmacotherapy specialist.

Dr. Sanoski is an active member of the American Association of Colleges of Pharmacy, American College of Clinical Pharmacy (ACCP), and American Society of Health-System Pharmacists, and in all of these organizations she has been a member of program and publication committees. Within ACCP, she has served on the Publications Committee, Residency Task Force, Credentials Committee, and several Spring Forum and Annual Meeting Program committees. She also has served as Chair and Secretary of the ACCP Cardiology Practice and Research Network (PRN) and Secretary-Treasurer of the Education and Training PRN. While at the University of the Sciences in Philadelphia, she was awarded the university's Faculty Special Recognition Award. In 2007, Dr. Sanoski was elected as a Fellow of ACCP.

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In his research, Dr. Kalus focuses on atrial fibrillation (AF), including the pathophysiology of AF occurring after cardiac surgery and novel strategies for the treatment and prevention of AF. He has written several textbook chapters and many articles published in peer-reviewed journals, including the *American Journal of Health-System Pharmacy*, *Annals of Pharmacotherapy*, *Annals of Thoracic Surgery*, *Circulation*, *Journal of Electrocardiology*, *Pharmacoeconomics*, and *Pharmacotherapy*. He also serves on the editorial board of *The Annals of Pharmacotherapy*, Cardiology Panel.

Complementing the practice and research interests of Dr. Kalus is his involvement in professional associations. A member of the American Society of Health-System Pharmacists (ASHP), he regularly speaks at educational sessions at the ASHP Midyear Clinical Meeting. As a member of the 2007 Research Affairs Committee of the American College of Clinical Pharmacy, he co-authored the report "Recommended Education for Pharmacists as Competitive Clinical Scientists," published in the March 2009 issue of *Pharmacotherapy*. The Southeastern Michigan Society of Health-System Pharmacists honored him with the 2008 Preceptor of the Year Award and the 2006 Innovative Practice Award. He also has received the Drug Therapy Research Award from the ASHP Research and Education Foundation.

Samuel G. Johnson, PharmD, BCPS (AQ-Cardiology), CACP, is Clinical Pharmacy Specialist in Cardiology, Kaiser Permanente Colorado, Denver, Colorado. Dr. Johnson's roles and responsibilities include screening patients for enrollment into the Amiodarone Monitoring Service (AMS) and the Endothelin Receptor Antagonist (ERA) Service and providing pharmacotherapy consultations regarding heart failure, resistant hypertension, and pulmonary hypertension. He also provides cardiovascular pharmacotherapy education for nurses and physicians. Before assuming this position in 2006, he was Clinical Pharmacy Specialist in Anticoagulation Management, also at Kaiser Permanente Colorado in Denver.

Dr. Johnson is involved in teaching pharmacy students and residents. He serves as Preceptor for the postgraduate year 2 ambulatory care specialty residency program at Kaiser, and he is Clinical Instructor in the nontraditional doctor of pharmacy program at the University of Colorado (UC) Denver School of Pharmacy. In addition, he precepts students on externship rotations in the doctor of pharmacy degree programs at UC-Denver, Creighton University in Omaha, Nebraska, and Ohio Northern University in Ada, Ohio.

Dr. Johnson earned his bachelor of science degree in biology from Truman State University in Kirksville, Missouri. After completing his doctor of pharmacy degree at the University of Missouri in Kansas City, he completed a cardiology specialty residency at Kaiser Permanente Colorado. He is board-certified as a pharmacotherapy specialist with added qualifications in cardiology and is a certified anticoagulation care provider (CACP).

Dr. Johnson's research focuses on the risks associated with combination antithrombotic therapy in managed care populations and the evaluation of clinical pharmacy services at Kaiser, including anticoagulation management services and amiodarone surveillance. His work has been published in peer-reviewed journals, including *Chest*, *Journal of Thrombosis and Thrombolysis*, and *Thrombosis Research*. He is a member of the American Heart Association, American College of Clinical Pharmacy, and Colorado Pharmacists Society.

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Target Audience

The target audience for this knowledge-based activity is pharmacists who practice in a managed care setting.

Learning Objectives

Upon completion of this knowledge-based activity, participants will be able to

1. Describe trends in the prevalence, incidence, and economic burden of atrial fibrillation (AF) in the United States; discuss the etiology of and morbidity and mortality from AF; and identify risk factors for AF
2. Predict the risk for AF in an individual and the risk for stroke in a patient with AF based on patient characteristics.
3. List the 3 primary goals of pharmacotherapy in patients with AF and compare and contrast the efficacy and safety of currently available and emerging drug therapies for AF
4. Recommend an antiarrhythmic drug regimen for an individual with AF based on patient-specific factors.
5. Identify pharmacoeconomic considerations in managing AF.
6. Describe mechanisms through which managed care pharmacists can help improve the cost-effectiveness of and outcomes from drug therapy for AF

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Pharmacist Continuing Education Credit

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. A total of 0.2 CEUs (2.0 contact hours) will be awarded for successful completion of this continuing pharmacy education activity (program no. 204-000-09-406-H01P).

There is no fee for this continuing pharmacy education (CPE) activity. To complete this continuing pharmacy education activity, go to either www.amcp.org (CE/CME Center) or the ASHP Learning Center (<http://ce.ashp.org>) to access the posttest and evaluation. A passing grade of 70% is required to receive CPE credit for this activity. Upon successful completion of the online CE test, participants may print their official CPE statement.

Faculty Disclosures

Cynthia A. Sanoski, PharmD, FCCP, BCPS, reports no conflicts of interest related to the subject of this educational activity including consulting or speaking fees other than receipt of an honorarium for writing this manuscript.

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Disclosure of Off-Label Use

In this educational activity, Kalus discusses the off-label (unapproved) use of disopyramide and amiodarone for the treatment of atrial fibrillation, and Johnson discusses the off-label use of amiodarone for the treatment of atrial fibrillation. Dronedarone was recently approved by the FDA for use in patients with atrial fibrillation who do not have severe heart failure.

All articles published represent the opinions of the authors and do not reflect the official policy of the Academy of Managed Care Pharmacy, the authors' institutions, sanofi-aventis U.S., ASHP, or ASHP Advantage unless so specified.

Introduction

Cynthia A. Sanoski, PharmD, FCCP, BCPS

Atrial fibrillation (AF), a common age-related arrhythmia, is a major public health problem in the United States. Roughly two-thirds of emergency room visits for AF result in hospital admission, and AF accounts for one-third of arrhythmia-related admissions.¹ Currently, approximately 2.2 million Americans have AF, and the prevalence is expected to increase to between 5.6 and 15.9 million by the year 2050.¹⁻³ More than half of the patients with AF will be more than 80 years old in 2050. The costs of AF are high and could increase dramatically in the coming decades.^{2,4}

The treatment of AF continues to be challenging because of difficulties selecting appropriate antiarrhythmic and antithrombotic therapies and monitoring these therapies. Currently available antiarrhythmic and antithrombotic agents are problematic because of the potential for toxicity and the need for intensive monitoring to prevent patient harm. The shortcomings of currently available agents represent opportunities for pharmacists to become involved in the management of patients with AF, especially in the managed care setting. Managed care pharmacists are uniquely qualified to intervene to improve the cost-effectiveness of and outcomes from drug therapy.

Now, for the first time in nearly a decade, a new antiarrhythmic drug, dronedarone, has been approved for the treatment of AF. Several other promising antiarrhythmic agents and a few antithrombotic therapies may become therapeutic options for AF in the future. Pharmacists will play an important role in evaluating these new therapies in the context of currently available agents. Pharmacists will continue to make a vital contribution to the management of drug therapy in patients with AF.

The first article in this supplement describes trends in the prevalence and incidence of AF in the United States and the etiology of, risk factors for, complications of, and economic burden of AF. Information is provided for use in predicting a patient's risk for developing AF and AF-related stroke.

The second article in this supplement describes the 3 primary goals of pharmacotherapy in patients with AF and compares and contrasts the efficacy and safety of established and investigational drug therapies for AF. Information is provided to enable the reader to recommend a drug regimen for an individual with AF based on patient-specific factors.

In the third article, key pharmacoeconomic considerations

in managing AF are discussed. Ways in which managed care pharmacists can improve the cost-effectiveness of and outcomes from drug therapy in patients with AF are described in detail.

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Susan R. Dombrowski, MS, RPh, provided assistance with the medical writing, and Catherine N. Klein, RPh, provided editorial assistance.

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Clinical, Economic, and Quality of Life Impact of Atrial Fibrillation

Cynthia A. Sanoski, PharmD, FCCP, BCPS

ABSTRACT

BACKGROUND: Atrial fibrillation (AF) is a common, age-related arrhythmia that disproportionately affects men, adversely affects quality of life, and causes considerable morbidity and mortality.

OBJECTIVES: To describe trends in the prevalence and incidence of AF in the United States; discuss the etiologies and complications of AF; characterize the economic burden of AF; and predict an individual's risk for developing AF and AF-related stroke.

SUMMARY: The prevalence and incidence of AF in the United States are expected to increase in the coming decades because of the aging of the population; improved survival rates associated with coronary heart disease, heart failure, and hypertension; and increased rate of performance of surgical procedures. The economic burden of AF is substantial because of high rates of hospitalization and other health resource utilization. Hypertension, coronary heart disease, and systolic heart failure are the most important risk factors for AF. Ischemic stroke is the most devastating complication of AF. Risk factors for stroke in patients with AF include recent congestive heart failure, hypertension, advanced age, diabetes mellitus, and a history of stroke or transient ischemic attack. Risk scoring systems have been developed to predict an individual's risk for developing AF and the risk for stroke in a patient with AF. The estimated lifetime risk for AF in men and women aged 40 years of age or older is 1 in 4, which is higher than the risk for other diseases that are a common cause for concern among elderly patients.

CONCLUSIONS: The clinical and economic burden of AF in the United States is large and will continue to increase in the future. The use of scoring systems to predict the risk of AF and AF-related stroke affords clinicians the opportunity to intervene to minimize these risks and improve patient outcomes.

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Susan R. Dombrowski, MS, RPh, provided assistance with the medical writing, and Catherine N. Klein, RPh, provided editorial assistance.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately 2.2 million Americans.¹ The prevalence of AF increases with age, with 70% of cases occurring in patients between the ages of 65 years and 85 years (Figure 1).² Atrial fibrillation is also more common in men than in women at all ages. For example, a cohort of 2,090 men and 2,641 women who participated in the Framingham Heart Study and did not have AF at the time of enrollment were followed for 38 years.³ After adjusting for age and other AF risk factors, the men were 50% more likely to develop AF than were the women. The higher risk of AF in men persisted in each decade between 55 and 94 years of age (Figure 2).

Etiology

Underlying cardiovascular diseases, including hypertension (HTN), coronary heart disease (CHD), and left ventricular systolic dysfunction are the most common risk factors for AF (Table 1). Other cardiovascular conditions, including left ventricular hypertrophy and valvular heart disease (especially mitral valve disease), are also associated with an increased risk for AF. In general, all of these cardiovascular diseases predispose to AF primarily by causing atrial dilation, which subsequently promotes electrical instability.

Other causes of AF include pulmonary diseases, such as chronic obstructive pulmonary disease and pulmonary embolism, which also can lead to atrial dilation. Atrial fibrillation may also be the result of excessive sympathetic stimulation in patients with hyperthyroidism or alcohol intoxication (i.e., sometimes referred to as "holiday heart" which results from brief binges of alcohol consumption). Surgery, especially cardiothoracic surgery, is a major risk factor for AF because of the excessive sympathetic stimulation that occurs in this setting. Electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia) are also risk factors for arrhythmias in general, including AF. Lone AF occurs in the absence of structural heart disease in patients less than 60 years of age. This form of AF is uncommon, occurring in less than 12% of all patients with the arrhythmia.⁴

Hemodynamic Consequences

Atrial fibrillation is often accompanied by a rapid, irregular ventricular rate (i.e., tachycardia), which may manifest as palpitations, hypotension (due to a tachycardia-induced reduction in cardiac output), fatigue, shortness of breath, and reduced exercise tolerance (i.e., a progressive increase in symptoms with increasing amounts of exercise). Patients with underlying ischemic heart disease who develop AF may experience angina because the tachycardia causes an increase in myocardial oxygen demand. Syncope also may occur if the ventricular rate becomes significantly elevated leading to a reduction in cardiac output.

If AF with a rapid ventricular rate goes untreated for an extended period of time, a tachycardia-induced cardiomyopathy

FIGURE 1 Relationship Between Prevalence of Atrial Fibrillation and Age

Adapted from Feinberg WM, et al.²
FIGURE 2 Comparative Incidence of Atrial Fibrillation in Men and Women by Age

Adapted from Benjamin EJ, et al.³
TABLE 1 Risk Factors for Atrial Fibrillation

Cardiovascular diseases
hypertension, especially with left ventricular hypertrophy
coronary heart disease
systolic heart failure
valvular heart disease
Pulmonary diseases
chronic obstructive pulmonary disease
pulmonary embolism
Hyperthyroidism
Alcohol intoxication ("holiday heart")
Surgery
Electrolyte abnormalities

The development of AF in patients with left ventricular systolic dysfunction often leads to an exacerbation of HF symptoms (e.g., fatigue, shortness of breath, edema) and can result in hospitalization. The AF-induced tachycardia can lead to a reduction in cardiac output, which can induce a worsening of HF symptoms. Additionally, AF can lead to the loss of the patient's atrial "kick," which may also worsen HF symptoms. Ordinarily, patients with systolic HF rely on the contribution of atrial contraction immediately before ventricular systole (i.e., atrial "kick") to increase ventricular filling and cardiac output during ventricular contraction as a compensatory mechanism. This atrial kick often is lost because of the rapid atrial contraction that occurs when

may develop as a result of disturbances in the structure and function of the left ventricle.⁵ The resulting heart failure (HF) may be reversible once the ventricular rate is controlled; however, there is also a possibility that this myocardial damage may be irreversible.

TABLE 2 CHADS₂ Stroke Risk Scoring System for Patients With AF^a

Characteristic	Points
Recent CHF	1
Hypertension	1
Age ≥ 75 years	1
Diabetes mellitus	1
History of stroke or transient ischemic attacks	2

Adapted from Gage BF, et al.⁸

^aPatients are considered to be at high risk for stroke if the CHADS₂ score is 2 or higher, at intermediate risk if the score is 1, and low risk if the score is 0.⁸

AF=atrial fibrillation; CHF=congestive heart failure.

AF develops in patients with systolic HF, which further compromises cardiac output.

Thromboembolic Consequences

Thromboembolic complications, namely ischemic stroke, are the most devastating potential consequences of AF. At least 15%-20% of all strokes occur in patients with AF.^{1,6} Atrial fibrillation is an independent risk factor for stroke.^{6,7} In fact, the risk of stroke is increased 4- to 5-fold by this arrhythmia.⁶ The risk of stroke in patients with AF increases with age, with the annual attributable risk increasing from 1.5% in patients aged 50-59 years to nearly 24% in those aged 80-89 years.⁷ The annual risk of ischemic stroke in patients with AF who do not receive antithrombotic therapy is approximately 5%.⁶

Various systems for predicting the risk of stroke in patients with AF have been developed. A risk scoring system known as CHADS₂ (Table 2) was validated in a study of more than 1,700 Medicare beneficiaries between 65 and 95 years who had nonvalvular AF and were not receiving warfarin at the time of hospital discharge.⁸ In this study, the CHADS₂ index was compared with 2 other stroke risk prediction schemes and was found to be the most accurate predictor of stroke in these patients. In fact, the stroke rate per 100 patient-years without antithrombotic therapy increased by a factor of 1.5 for each 1-point increase in the CHADS₂ score.⁸

The most recent American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy in AF have adapted the CHADS₂ risk scoring system for stroke risk stratification.⁶ Patients with AF and a prior ischemic stroke, transient ischemic attack, or systemic embolism (e.g., pulmonary embolism, deep vein thrombosis) or 2 or more of the following risk factors: (a) moderately or severely impaired left ventricular systolic function and/or HF, (b) HTN, (c) age > 75 years, and (d) diabetes are considered at high risk for stroke. This high risk category corresponds to a CHADS₂ score of 2 or more. Patients with AF who have only 1 of the above 4 risk factors (moderately or severely impaired left ventricular systolic function and/or HF, HTN, age > 75 years, or diabetes) are at intermediate risk for stroke. Patients with AF who are 75 years

of age or younger and have none of the risk factors in the high or intermediate risk categories are at low risk for stroke. The intermediate and low risk categories correspond to a CHADS₂ score of 1 and 0, respectively. This risk stratification process is ultimately used to determine the most appropriate antithrombotic therapy for patients with AF.

Impact on Mortality

In addition to its impact on morbidity, AF has been associated with an increase in mortality. The mortality trends associated with this arrhythmia were recently evaluated in a community cohort of 4,618 adults who experienced their first documented episode of AF between 1980 and 2000 and were followed until 2004 or their death.⁹ When compared with an age- and gender-matched population that did not have AF, the risk of death was 2-fold higher in patients with AF ($P < 0.001$). When analyzing these results based upon the time from diagnosis, the mortality risk was even higher within the first 4 months of diagnosis (hazard ratio [HR] = 9.62, 95% confidence interval [CI] = 8.93-10.32). However, the increased risk of mortality associated with AF still remained significant beyond the initial 4 months of diagnosis (HR = 1.66, CI = 1.59-1.73).

The increased mortality associated with AF has been attributed to several possible mechanisms. Currently, it is unclear whether AF itself confers a greater risk of mortality or whether the interaction between AF and other comorbid conditions provides a substrate for increased mortality. However, data from several studies have linked the increased mortality in patients with AF with the presence of underlying structural heart disease. The presence of AF has been shown to have a detrimental effect on survival in patients with left ventricular (LV) systolic dysfunction.^{10,11} While the mechanisms for increased mortality in patients with HF are likely multifactorial, 1 potential theory is that AF-induced hemodynamic instability may lead to pump failure and eventual death. The development of AF-related stroke also increases the risk of mortality.⁶ In addition, the potential, paradoxical proarrhythmic effects of antiarrhythmics being used to restore and maintain sinus rhythm in patients with AF may also contribute to the increased mortality associated with this arrhythmia.

Quality of Life

Quality of life is an important consideration for patients with AF. The impact of AF on quality of life has not been extensively evaluated in clinical trials, and only a few of the trials that have been conducted used validated instruments to evaluate quality of life. Most of the studies that have evaluated the impact of treatment strategies on quality of life involved patients who underwent radio frequency ablation procedures. In contrast, relatively few studies have evaluated quality of life at baseline and after initiation of pharmacologic treatment for AF.

In 1 particular study, quality of life was assessed using the 36-item Short Form-36 (SF-36), a generic health scale, in 154

patients with AF and 49 control subjects without AF.¹² Total functional capacity was measured using an activity scale, and global life satisfaction was measured using a visual analogue scale (ranging from 1 for worst to 10 for best possible life). Those with AF included 116 patients who were symptomatic and 38 patients with silent AF (i.e., asymptomatic or with very mild symptoms). Patients with AF had significantly worse quality of life compared with control subjects ($P<0.003$). Furthermore, symptomatic patients with AF had significantly lower scores on the SF-36 than patients with silent AF ($P<0.005$). Total functional capacity and global life satisfaction also were significantly lower in the symptomatic patients than in those with silent AF ($P<0.005$). The results of other studies that have been conducted in patients with AF have been relatively consistent with these findings, showing that AF adversely impacts quality of life and overall well-being.^{13,14}

Health Resource Utilization and Costs

In addition to the adverse impact that AF has on patients, this arrhythmia has imposed a significant burden on the health care system because of significant utilization of health care resources. In particular, hospitalizations due to AF have significantly increased over the years. In a study that involved patients aged at least 35 years whose data were included as part of the National Hospital Discharge Survey, the number of hospitalizations for AF as the primary diagnosis more than doubled between 1985 and 1999.¹⁵ The number of hospitalizations for AF as any of 7 possible diagnoses nearly tripled during this time frame.

In another study of 4,498 patients with a new diagnosis of AF, 2,503 patients (56%) were admitted to the hospital for a cardiovascular cause at least once during a mean follow-up period of 5.5 years.¹⁶ The likelihood of hospitalization was greatest during the first year after diagnosis of AF, with a cumulative incidence of hospitalization of 31%. The cumulative incidence of hospitalization 3 years and 5 years after diagnosis of AF was 48% and 59%, respectively.

As one might expect, the increased utilization of health care resources with AF subsequently leads to increased health care costs. An analysis of 2001 data from 3 federal databases (the Healthcare Cost and Utilization Project database, the National Ambulatory Medical Care Survey database, and the National Hospital Ambulatory Medical Care Survey database) revealed that approximately 350,000 hospitalizations, 5 million office visits, 276,000 emergency room visits, and 234,000 outpatient visits are attributed to AF annually in the United States.¹⁷ Attaching costs to these encounters, the total cost of treating AF in 2005 dollars was estimated at \$6.65 billion, including \$2.93 billion (44%) for hospitalizations with a principal discharge diagnosis of AF, \$1.95 billion (29%) for the incremental inpatient cost of AF as a comorbid diagnosis, \$1.53 billion (23%) for the outpatient treatment of AF, and \$235 million (4%) for prescription drugs (Figure 3). The mean cost per AF-related hospitalization exceeded \$8,000, and the mean length of stay was about 3.5 days.

FIGURE 3 Costs of Treating Atrial Fibrillation

Adapted from Coyne KS, et al.¹⁷

Future Burden

With the aging population, improved survival rates associated with CHD, HF, and HTN, as well as the increased frequency of surgical procedures being performed, it is expected that the prevalence of AF will considerably increase in the near future, thereby potentially transforming this disease into a major public health concern. In fact, it is estimated that the prevalence of AF is anticipated to increase by nearly 3-fold to 12.1-15.9 million by the year 2050.¹⁸

An analysis of more than 8,000 Framingham Heart Study participants who were at least aged 40 years and did not have AF at the start of the study revealed an estimated lifetime risk of developing AF of 26% in men and 23% in women.¹⁹ The lifetime risk did not change appreciably with advancing age. Therefore, the estimated lifetime risk for AF in men and women at least aged 40 years is estimated to be 1 in 4. Even when those patients with a prior or current history of HF or myocardial infarction were excluded from the analysis, the lifetime risk of developing AF remained relatively high (1 in 6) despite the absence of these significant risk factors for AF. By comparison, the lifetime risk for HF is 1 in 5 at the age of 40 or older.¹⁹ The lifetime risk of breast cancer in women is 1 in 8 at the age of 40 and 1 in 14 at the age of 70. The lifetime risk of hip fracture at the age of 50

TABLE 3 Risk Scoring System for Determining 10-Year Risk of AF^a

Age (yr)	Score (women)	Score (men)
45-49	-3	1
50-54	-2	2
55-59	0	3
60-64	1	4
65-69	1	5
70-74	4	6
75-79	6	7
80-84	7	7
≥85	8	8
BMI (kg/m ²)	Score (women and men)	
<30	0	
≥30	1	
Systolic blood pressure (mm Hg)	Score (women and men)	
<160	0	
≥160	1	
Treatment for hypertension		
No	0	
Yes	1	
PR interval on the ECG (msec)	Score (women and men)	
<160	0	
160-99	1	
≥200	2	
Age at diagnosis of clinically significant cardiac murmur (yr)	Score (women and men)	
45-54	5	
55-64	4	
65-74	2	
75-84	1	
≥85	0	
Age at diagnosis of heart failure (yr)	Score (women and men)	
45-54	10	
55-64	6	
65-74	2	
≥75	0	
Total score (women and men)	Predicted risk of AF (%)	
≤0	≤1	
1	2	
2	2	
3	3	
4	4	
5	6	
6	8	
7	12	
8	16	
9	22	
≥10	>30	

Adapted from Schnabel RB, et al.²⁰

^aThis risk scoring system predicts the 10-year risk of AF in an individual aged 45-95 years based on the total score obtained by adding the scores for each of the seven variables in this table.

AF=atrial fibrillation; BMI=body mass index; ECG=electrocardiogram.

is 1 in 6 for white women and 1 in 20 for white men. Thus, the overall lifetime risk of AF is higher than the risk for these other diseases, which further emphasizes the need to develop effective primary prevention strategies to help reduce the prevalence of this arrhythmia in the future.

The substantial morbidity and mortality associated with AF prompted the development of a risk scoring system to predict the risk of developing AF within a 10-year period for individuals aged 45-95 years (Table 3).²⁰ This scoring system is based on data from 4,764 participants in the Framingham Heart Study in this age group who did not have AF at the start of the study and were followed for up to 10 years. Seven risk factors associated with AF were identified (age, sex, body-mass index [BMI], systolic blood pressure, treatment for HTN, PR interval, clinically significant heart murmur, and HF), and a point system was developed for use in calculating a total score that corresponds to the 10-year risk for AF in individuals aged 45-95 years. Although this scoring system still requires validation in an independent cohort, it is the first tool available that provides a specific, numerical assessment of an individual's risk for developing AF in 10 years. Therefore, this risk score could then be used as the basis for initiating or intensifying therapies targeted at modifying risk factors for AF (e.g., BMI, systolic blood pressure).

Conclusions

Atrial fibrillation is a growing public health problem with an economic burden that is expected to increase in the future. The risk for AF and the risk for stroke in patients with AF can be predicted, and strategies can be developed to intervene to reduce these risks, thereby minimizing the impact of AF.

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Pharmacologic Management of Atrial Fibrillation: Established and Emerging Options

James S. Kalus, PharmD, BCPS

ABSTRACT

BACKGROUND: In patients with atrial fibrillation (AF), antiarrhythmic drug therapy currently plays a greater role in maintaining sinus rhythm after cardioversion than it does in converting AF to sinus rhythm. Amiodarone is the most effective antiarrhythmic agent for maintaining sinus rhythm after cardioversion in patients with AF. However, its pharmacokinetics is complex; the drug interacts with many commonly used medications; and long-term use can cause thyroid dysfunction, hepatotoxicity, and other severe extracardiac adverse effects. The use of antiarrhythmic strategies in patients with AF has decreased because of evidence of greater safety and lower costs for hospitalization obtained from the use of rate-control strategies instead. Nevertheless, some patients require a rhythm-control strategy. Warfarin is used to prevent embolic stroke in many patients with AF, but its use is also complex and requires monitoring. Therefore, efforts have been made to develop antiarrhythmic agents with improved tolerability and anticoagulants that are easy to use.

OBJECTIVES: To describe the 3 primary goals of pharmacotherapy in patients with AF, compare and contrast the efficacy and safety of established and investigational pharmacotherapies for AF, and recommend a drug regimen for an individual with AF based on patient-specific factors.

SUMMARY: Currently available antiarrhythmic agents differ in their efficacy for maintaining sinus rhythm after cardioversion in AF patients with tolerability problems, comorbidities (particularly heart failure and renal impairment), and potential drug interactions. Hence, when selecting drug therapy to maintain sinus rhythm after cardioversion, it is important to take into consideration patient characteristics, including age, disease states, renal function, and concurrent drug therapies. Outpatient self-administration of single loading doses of flecainide or propafenone with what is referred to as the pill-in-the-pocket approach may be considered for carefully selected patients with recurrent episodes of symptomatic AF. The recently approved antiarrhythmic agent dronedarone has electrophysiologic properties similar to those of amiodarone, but its lack of iodine may improve upon the pharmacokinetic and tolerability issues associated with amiodarone. Vernakalant is another investigational antiarrhythmic agent that may prove useful for cardioversion and maintenance of sinus rhythm after cardioversion in patients with AF. New oral anticoagulants that do not require close laboratory monitoring and are simpler to use than warfarin have been used investigationally for prevention of venous thromboembolism and are in clinical trials for prevention of embolic stroke in patients with AF.

CONCLUSIONS: Pharmacotherapy for patients with AF should be individualized based on patient-specific factors. New therapeutic options may become available to facilitate treatment of these patients.

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Off-Label Disclosure Statement

In this article, the following off-label use of antiarrhythmic agents is discussed: disopyramide and amiodarone for the treatment of atrial fibrillation. Dronedarone was recently approved by the FDA for use in patients with atrial fibrillation who do not have severe heart failure.

Atrial fibrillation (AF) is associated with substantial morbidity and mortality and negatively impacts quality of life. Pharmacologic agents are used in the management of atrial fibrillation for prevention of embolic stroke, control of ventricular rate, and restoration and maintenance of normal sinus rhythm.¹ Optimization of therapy for the patient with AF requires the pharmacist to consider patient comorbidities, medication efficacy, and medication toxicities when designing a treatment regimen and monitoring plan. While currently available agents used in the management of AF have substantial limitations in terms of both safety and efficacy, new therapeutic options may soon become available.

Antithrombotic Therapy

The decision to use antithrombotic therapy and the type of antithrombotic therapy selected to prevent thromboembolic events in patients with AF are based on the risks and benefits of such therapy and the risk of stroke. The CHADS₂ risk scoring system is used to determine the risk for stroke in patients with AF.² Warfarin is used in patients at high or intermediate risk for stroke, but its use is complicated by a narrow therapeutic index, risk for bleeding, and the continuous need for laboratory monitoring.³ Aspirin is recommended for patients at low or intermediate risk for stroke. Overall, aspirin is less effective than warfarin for the prevention of stroke in patients with AF.³

Rate Versus Rhythm Control

There are 2 phases to ventricular rate control in patients with AF. Acute ventricular rate control is provided to reduce heart rate and control symptoms at the time of initial patient presentation. Chronic ventricular rate control is provided as a long-term maintenance strategy. Acute ventricular rate control usually involves the intravenous use of a nondihydropyridine calcium channel blocker (e.g., diltiazem or verapamil), β -blocker, or digoxin. When a long-term rate control strategy will be used to manage

a patient with AF, the patient is allowed to remain in AF, and the heart rate is maintained at a target of less than 80 beats per minute (at rest) or 100 beats per minute (with exercise) using an oral nondihydropyridine calcium channel blocker, β -blocker, or digoxin.¹ Underlying disease states and blood pressure should be considered when selecting drug therapy for acute and chronic rate control. For example, digoxin could be used as a rate-controlling agent in patients with underlying systolic heart failure. Digoxin could also be a useful option when blood pressure is low.¹

Rhythm control involves restoring and maintaining sinus rhythm through the use of antiarrhythmic drugs, electrical cardioversion, or both. There has been considerable debate about the comparative efficacy and cost of rate-control and rhythm-control strategies. Study results suggest that mortality, quality of life, and health care costs are similar regardless of which strategy is used.^{1,4-6} In 1 of the largest randomized studies that enrolled 4,060 patients with AF and at least 1 risk factor for stroke (Atrial Fibrillation Follow-Up Investigation of Rhythm Management [AFFIRM] trial), there was no significant difference in mortality between the rate-control (25.9%) and rhythm-control (26.7%) groups ($P=0.08$).⁴ The incidence of ischemic stroke, a secondary endpoint, also was similar in the 2 groups (5.5% with rate control vs. 7.1% with rhythm control, $P=0.79$). The incidence of torsades de pointes, which is a ventricular tachyarrhythmia with QT interval prolongation, was significantly lower with rate control (0.2%) than with rhythm control (0.8%, $P=0.007$). Pulmonary and gastrointestinal events, bradycardia, and prolongation of the QT interval on the electrocardiogram (ECG) also were significantly less common in the rate-control group than in the rhythm-control group ($P<0.001$). The incidence of hospitalization during follow-up was significantly lower with rate control compared with rhythm control (73.0% and 80.1%, respectively, $P<0.001$).

Findings of the AFFIRM study and other rate versus rhythm studies suggesting greater safety and lower costs for hospitalization from the use of rate-control strategies compared with rhythm-control strategies has led to a reduction in the use of rhythm-control strategies in patients with AF.^{7,8} However, studies comparing rate- and rhythm-control strategies might be limited by the fact that these studies enrolled a mostly elderly and sedentary patient population. Also, an initial criticism of AFFIRM was that the study included few patients with heart failure, a group commonly afflicted with AF. However, the Atrial Fibrillation and Congestive Heart Failure study also demonstrated similar outcomes between a rate- and rhythm-control strategy, echoing the results of AFFIRM.⁹

Patients presenting with hemodynamic instability require rhythm control and should immediately undergo electrical cardioversion.¹ If a patient is hemodynamically stable, the clinician can take some time deciding on a therapeutic strategy (i.e., rate control vs. rhythm control, and pharmacotherapy vs. electrical cardioversion to achieve rhythm control if that strategy is selected).¹

The use of rhythm-control strategies is limited by the toxicity of many antiarrhythmic drugs and higher rate of hospitalization.^{1,4} Nevertheless, rhythm-control interventions may be required for patients whose heart rate remains elevated (>80 beats per minute) despite the use of rate-control strategies; patients who remain symptomatic despite effective ventricular rate control (<80 beats per minute); and patients who are physically active and have poor exercise tolerance with the use of rate-control strategies.¹

Drug therapy plays a minimal role in acute conversion of AF to sinus rhythm because electrical cardioversion is more effective than pharmacologic cardioversion with success rates of 90% and approximately 40%, respectively.¹⁰ Nevertheless, drug therapy may play a role before and after electrical cardioversion to improve the likelihood of successful conversion to and maintenance of sinus rhythm.¹ The rate of recurrence of AF (i.e., relapse) after conversion to sinus rhythm is high, with only about 15% of patients remaining in sinus rhythm 1 year after electrical cardioversion.^{1,11-13}

Class I and class III antiarrhythmic agents are the primary pharmacologic agents used for achieving rhythm control in patients with AF. Patterns of use of these agents have changed in recent years. The use of class Ia agents, particularly quinidine, decreased between 1991 and 2000.¹³ The oral formulation of the class Ia antiarrhythmic agent procainamide was recently withdrawn from the market because of lack of use. There has also been a small decline in the use of class Ic antiarrhythmic agents (e.g., flecainide and propafenone). By contrast, in the 1990s there was a considerable increase in the use of the class III agents amiodarone and sotalol, which are the most commonly used antiarrhythmic drugs for AF.¹³ Changes in use patterns for the various antiarrhythmic drugs have likely resulted from concerns about drug toxicities and efficacy considerations that will be discussed below.

■ Class Ia and Ic Agents

The class Ia antiarrhythmic agents disopyramide and quinidine and class Ic antiarrhythmic agents flecainide and propafenone are used less often than class III drugs in patients with AF primarily because of their potential adverse effects. Disopyramide is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of AF (quinidine, flecainide, and propafenone are FDA-approved for AF).¹⁴ All of these agents are associated with a risk of proarrhythmia. The tolerability of disopyramide and quinidine is particularly poor. Anticholinergic adverse effects (e.g., urinary retention, dry mouth) are associated with disopyramide, and rash, photosensitivity, and gastrointestinal adverse effects (e.g., diarrhea, abdominal pain, and cramps) can occur with quinidine.^{1,15} Flecainide and propafenone are better tolerated than disopyramide and quinidine, but these class Ic antiarrhythmic agents are not safe to use in patients with structural heart disease (e.g., coronary heart disease, left ventricular hypertrophy, heart failure, valvular dysfunction) because they can increase mortality.¹⁶⁻¹⁸

TABLE 1 Advantages and Disadvantages of Currently Available Antiarrhythmic Agents for Maintaining Sinus Rhythm in Patients With Atrial Fibrillation

Antiarrhythmic Drug Class or Agent	Efficacy Assessment and Advantages	Disadvantages
Class Ia		
Disopyramide ^a	Low efficacy	Proarrhythmia (torsades de pointes) Anticholinergic adverse effects
Quinidine	Low efficacy	Proarrhythmia (torsades de pointes) Gastrointestinal adverse effects
Class Ic		
Flecainide	Modest efficacy	Proarrhythmias Not safe in structural heart disease Drug interactions
Propafenone	Modest efficacy	Proarrhythmia Nonselective β blockade (bradycardia, exacerbation of chronic obstructive pulmonary disease) Not safe in structural heart disease Drug interactions
Class III		
Amiodarone ^a	High efficacy Low risk of proarrhythmia Safe in heart failure	Extracardiac effects Drug interactions
Sotalol	Modest efficacy Not expected to interact with drugs metabolized by CYP enzymes	Nonselective β blockade (bradycardia, exacerbation of chronic obstructive pulmonary disease) Proarrhythmia (torsades de pointes) Eliminated renally Inpatient initiation
Dofetilide	Modest efficacy Safe in heart failure Generally well tolerated (except for torsades de pointes)	Proarrhythmia (torsades de pointes) Eliminated renally Drug interactions Inpatient initiation

^aNot approved by the U.S. Food and Drug Administration for atrial fibrillation.
Sources = references.^{1,13a15-32}

Class III Agents

Amiodarone

Amiodarone is the most commonly used antiarrhythmic drug in patients with AF, largely because it is the most effective agent for maintaining sinus rhythm (an indication not approved by the FDA) and has a low risk of proarrhythmic effects (Table 1).^{1,19,20} Amiodarone does not increase mortality in patients with heart failure; therefore, it is safe to use in this patient population.²¹⁻²⁴

Nevertheless, amiodarone is among the most toxic antiarrhythmic agents; it is associated with a high incidence of potentially severe extracardiac effects.¹ These effects include neuropathy, thyroid dysfunction (a common effect manifesting as either hypothyroidism or hyperthyroidism), pulmonary fibrosis (a rare but potentially serious complication), hepatotoxicity, rash or photosensitivity, blue-grey skin discoloration, and ophthalmic effects (corneal deposits and optic neuritis).¹ These extracardiac effects may not be observed during initial therapy; however, the risk increases after more than 6 months of treatment.¹

The pharmacokinetics of amiodarone are complex. The drug has a long half-life, which complicates loading dosing, adverse effect management, and transition from amiodarone to another antiarrhythmic drug.²⁵ Amiodarone also has a large volume of distribution into a wide variety of tissues, including extracardiac tissues, which accounts for the relatively high incidence of extracardiac adverse effects associated with this drug.

The potential for drug interactions is an important consideration in the use of amiodarone. Many of these interactions are mediated by cytochrome P-450 (CYP) drug-metabolizing enzymes, specifically potent inhibition of the CYP1A2, 2C9, 2D6, and 3A4 enzymes, which are responsible for significant clinical interaction with drugs such as simvastatin and warfarin.²⁶ Another method by which amiodarone can cause interactions is via transporter-based mechanisms; for example, digoxin inhibits the P-glycoprotein membrane transporter, resulting in increased serum drug concentrations and a potential risk of increased toxicity.^{25,26}

Sotalol

Sotalol is a commonly used class III antiarrhythmic agent that is approved by the FDA for the maintenance of normal sinus rhythm in patients with symptomatic AF/atrial flutter who are currently in sinus rhythm.²⁷ Its efficacy in maintaining sinus rhythm is only modest.¹

Because sotalol is eliminated renally, dosage reduction is required for patients with renal impairment. Proarrhythmia is the major side effect from sotalol. The incidence of torsades de pointes associated with the use of sotalol in patients with AF or other supraventricular arrhythmias ranges from 0.3% to 3.2%, depending on dosage.²⁸ The likelihood of proarrhythmia also depends on patient characteristics (e.g., sex, heart failure, renal function). To minimize the risk of proarrhythmia, sotalol therapy should be initiated on an inpatient basis.¹ The adverse

effect profile of sotalol primarily reflects its β -blocking properties (e.g., asthma, bradycardia, exacerbation of chronic obstructive pulmonary disease).¹ Sotalol is neither metabolized by, nor is it an inducer or inhibitor of, the CYP enzyme system.

Dofetilide

Dofetilide, a class III antiarrhythmic agent, has been available for approximately 10 years. It is indicated for the maintenance of normal sinus rhythm in patients with AF/atrial flutter of greater than one week duration who have been converted to normal sinus rhythm. It is modestly effective for conversion and maintenance of sinus rhythm in patients with AF.^{29,30} Like amiodarone, this drug does not increase mortality and is considered safe to use in patients with heart failure.³¹

Dofetilide is generally well tolerated; however, torsades de pointes is the adverse effect of primary concern.³² The incidence of torsades de pointes in dofetilide clinical trials ranged from 0.3% to 4.7%, depending on dosage and patient characteristics (e.g., sex, renal function).¹ As with sotalol, the kidneys play an important role in elimination of dofetilide; therefore, dosage reduction is required for patients with renal impairment. Additionally, initiation of therapy should be performed on an inpatient basis to minimize the risk of proarrhythmia.³⁰

Dofetilide is associated with numerous drug interactions. Its use concomitantly with verapamil, hydrochlorothiazide, ketoconazole, cimetidine, or trimethoprim is contraindicated because of the potential for increased dofetilide plasma concentrations and increased risk of torsades de pointes.³³ The concurrent use of dofetilide and drugs that prolong the QT interval (e.g., phenothiazines) is not recommended due to the risk for additive QT prolongation.

Comparative Efficacy and Safety

In a meta-analysis, all of the class Ia, Ic, and III agents listed in Table 1 reduced the risk of recurrence of AF in patients in whom sinus rhythm had been restored.³⁴ Amiodarone was most effective, and the class Ia agents were least effective.

Many comparative studies use both efficacy for maintaining sinus rhythm and adverse effects as endpoints in patients with AF. In 1 such study of 254 patients, propafenone was more effective than sotalol with fewer adverse effects.³⁵ In another study of 665 patients, amiodarone and sotalol were similarly effective for conversion of atrial fibrillation and amiodarone was more effective than sotalol for maintaining sinus rhythm.³⁶ There was no significant difference between the 2 drugs in major adverse effects. In another study, amiodarone was more effective than propafenone in maintaining sinus rhythm after conversion in 146 patients with recurrent symptomatic AF, but propafenone caused fewer adverse effects.³⁷ The safety advantage of propafenone outweighed the greater efficacy of amiodarone. While few studies directly compare different antiarrhythmic agents, it is clear that consideration of both efficacy and safety is critical when selecting therapy.

Pill-in-the-Pocket Approach

Certain patients with recurrent episodes of symptomatic AF may be candidates for outpatient self-administration of single loading doses of flecainide or propafenone using what is referred to as the "pill-in-the-pocket" approach to terminating AF.¹ The efficacy and safety of this approach were demonstrated in 210 patients with mild or no heart disease who came to the emergency room with recent-onset AF that was hemodynamically well tolerated.³⁸ If flecainide or propafenone was successful in converting the patient from AF in the emergency room, they were eligible for inclusion in the study. Included patients were advised to take a dose of flecainide or propafenone 5 minutes after the onset of palpitations on an outpatient basis. The mean duration of follow-up was 15 months. Treatment was successful in 534 (94%) of 569 episodes. Compared with the year before study enrollment, there were significantly fewer visits to the emergency room each month (4.9 vs. 45.6, $P < 0.001$) and hospitalizations each month (1.6 vs. 15.0, $P < 0.001$) during the follow-up period. These large reductions in emergency room visits and hospitalization occurred even though there was no significant difference in the mean number of symptomatic episodes per month before and after study enrollment (59.8 and 54.5, respectively). The most recent AF treatment guidelines recommend that this pill-in-the-pocket approach be used if the patient has had a safe response to single-dose therapy as an inpatient. However, this strategy should be avoided in patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome (a hereditary arrhythmia), or structural heart disease.¹

Inpatient Initiation

Because antiarrhythmic drugs can be proarrhythmic, 1 strategy to minimize risk with these agents is to initiate the drug in a hospital or other facility where continuous ECG monitoring, creatinine clearance (CrCl) calculation, and cardiac resuscitation are available.^{28,30} Inpatient initiation is required for both dofetilide and sotalol but is often used for other agents as well.^{27,33} For inpatient initiation, patients should be admitted for at least 3 days. Calculation of the CrCl should be performed, and dosage reductions should be made in patients with renal dysfunction. Potassium and magnesium serum concentrations should be monitored, and electrolyte replacement should be provided as needed. The corrected QT (QTc) interval should be measured at baseline to ensure that it is within normal limits (450 msec or less for sotalol and 440 msec or less for dofetilide) before initiating either of these antiarrhythmics.^{27,33} The QTc interval should be checked several hours after each dose because dosage adjustment or discontinuation of drug therapy may be required if the QTc interval is excessively prolonged. If AF persists for more than 3 days, electrical cardioversion should be attempted to restore sinus rhythm.^{27,33}

Emerging Agents

Problems with proarrhythmia, particularly torsades de pointes, and hospitalization because of AF recurrence or extracardiac toxicities have hindered the use of rhythm-control strategies in patients with AF.⁸ Efforts to develop new antiarrhythmic agents with improved safety and tolerability could cause clinicians to re-examine the debate about rate control versus rhythm control.

Dronedaron

Dronedaron is a recently FDA-approved antiarrhythmic agent with electrophysiologic effects that are similar to those of amiodaron, although dronedaron may be less likely to prolong the QT interval.^{39,40} The chemical structure of dronedaron differs from that of amiodaron in its lack of iodine, which could minimize the impact of dronedaron on thyroid function. The lack of iodine also could make dronedaron less lipophilic and limit its distribution and potential for extracardiac toxicities.⁴⁰

Dronedaron has a considerably shorter half-life than amiodaron (1-2 days vs. 30-55 days), which could make dosing more reliable and facilitate the use of loading doses.⁴⁰ Like amiodaron, dronedaron is a CYP3A4 substrate and inhibits CYP2D6; therefore, interactions with drugs metabolized by these isoenzymes could occur.^{41,42}

Dronedaron has been extensively studied in several phase III randomized, double-blind, placebo-controlled studies. All of these studies involved a dosage of 400mg orally twice daily, but the patient inclusion and exclusion criteria varied.

The first reported clinical trial results were from 2 identical trials known as EURIDIS (EUROPEAN trial In atrial fibrillation patients receiving Dronedaron for the maintenance of Sinus rhythm) and ADONIS (American-Australian-African trial with Dronedaron In atrial fibrillation patients for the maintenance of Sinus rhythm) that involved a total of 1,237 patients with paroxysmal or persistent (i.e., lasting less than 12 months) AF or atrial flutter.⁴³ Patients with New York Heart Association (NYHA) class III or IV HF were excluded from both studies. One study (EURIDIS) was conducted in Europe, and the other study (ADONIS) was conducted in the United States and other non-European countries. Patients were randomly assigned in a 2:1 ratio to receive dronedaron 400mg or matching placebo orally twice daily. The mean age was 63 years. Most patients (90%) had AF; 41% had structural heart disease; and NYHA class I or II HF was present in approximately 17% of patients (left ventricular ejection fraction approximately 60%). Thus, the study population was relatively young and free from heart failure, although a substantial number of patients had structural heart disease (type not specified). Patients were followed for 12 months.⁴³ The time to recurrence of AF (primary endpoint) was longer with dronedaron (116 days) than with placebo (53 days, *P* value not reported). The rate of recurrence of AF after 12 months was 64.1% with dronedaron and 75.2% with placebo (*P*<0.001). The rate of hospitalization or death also was significantly lower

in the dronedaron group (22.8%) than in the placebo group (30.9%, *P*=0.01). The only adverse event that was associated with dronedaron was elevation of serum creatinine, which occurred in 2.4% of patients treated with dronedaron and 0.2% of patients treated with placebo (*P*=0.004).

The Antiarrhythmic Trial with Dronedaron in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) study had a planned enrollment of 1,000 patients hospitalized with symptomatic heart failure, moderate or severe left ventricular systolic dysfunction (NYHA class III or IV), and a left ventricular ejection fraction of 35% or less.⁴⁴ The primary endpoint was a composite of death from any cause or hospitalization for heart failure. The study was terminated prematurely after 627 patients had enrolled (median of 2 months) because of a significantly higher rate of all-cause mortality in dronedaron-treated patients (8.1%) compared with placebo-treated patients (3.8%, *P*=0.03). Most of the deaths in the dronedaron group were cardiovascular deaths associated with worsening heart failure. There was no significant difference between dronedaron and placebo in the primary endpoint (53 events [17.1%] with dronedaron and 40 events [12.6%] with placebo, *P*=0.12).

The ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedaron 400mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter) study involved 4,628 patients with paroxysmal or persistent AF who were (a) aged 70 years or older with hypertension managed with at least 2 antihypertensive medications from different classes; diabetes mellitus; previous stroke, transient ischemic attack, or systemic embolism; large left atrial diameter; or left ventricular ejection fraction of 40% or less; or (b) aged 75 years or older without any of these risk factors.⁴⁵ Exclusion criteria included permanent AF, hemodynamic instability (decompensated heart failure within the previous 4 weeks), NYHA class IV heart failure (HF), bradycardia, and heart block. The mean age was 72 years. Structural heart disease was present in 60% of patients; 21% of patients had a history of heart failure (17% with NYHA class II HF and 4% with NYHA class III HF); and 12% of patients had a left ventricular ejection fraction less than 45%.⁴⁵ Thus, the patients in this study were older and more likely to have structural heart disease compared with those in the EURIDIS and ADONIS studies, although heart failure was not common or severe in these 3 studies.

In ATHENA, the primary outcome was first hospitalization for a cardiovascular event or death.⁴⁵ The mean duration of follow-up was 21 months (range 1-2.5 years). Compared with placebo, dronedaron was associated with a significantly lower incidence of the primary outcome (31.9% vs. 39.4% with placebo, *P*<0.001). Most of this difference was attributed to a significantly lower incidence of cardiovascular hospitalization in the dronedaron group compared with placebo (29.3% vs. 36.9%, respectively, *P*<0.001), and this reduced incidence was driven mainly by a reduction in

hospitalizations for AF (14.6% with dronedarone vs. 21.9% with placebo, $P<0.001$) and for acute coronary syndrome (2.7% with dronedarone vs. 3.8% with placebo, $P=0.03$).

Adverse events reported by significantly more dronedarone-treated patients than placebo-treated patients in the ATHENA study included gastrointestinal events (26.2% vs. 22.0%, $P<0.001$), elevation of serum creatinine (4.7% vs. 1.3%, $P<0.001$), bradycardia (3.5% vs. 1.2%, $P<0.001$), rash (3.4% vs. 2.0%, $P=0.006$), and QT-interval prolongation (1.7% vs. 0.6%, $P<0.001$).⁴⁵ One case of torsades de pointes was reported in the dronedarone group. There was no significant difference between the dronedarone group and the placebo group in the incidence of pulmonary fibrosis, liver function test elevation, or thyroid dysfunction. Some of the patients were followed for a period as short as 1 year, and whether this duration was sufficient to detect the true incidence of the most serious adverse events might be questioned.

The efficacy for maintaining sinus rhythm and the safety of dronedarone and amiodarone were compared in the DIONYSOS (Efficacy & Safety of Dronedaron Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation) study, which has yet to be published.⁴⁶ Results presented in this article are only available from the manufacturer's press release. In this double-blind, parallel-group study, 504 patients with persistent AF were randomized to receive dronedarone 400mg orally twice daily or amiodarone 600mg per day orally for 28 days followed by 200mg per day orally. The primary endpoint was AF recurrence or premature study discontinuation for intolerance or lack of efficacy. After a mean follow-up of 7 months, the primary endpoint had been reached by significantly more patients in the dronedarone group (73.9%) than patients in the amiodarone group (55.3%, $P<0.001$). The rate of recurrence of AF was 36.5% with dronedarone and 24.3% with amiodarone (P value not reported). There was no significant difference between treatment groups in the incidence of the predefined main safety endpoint, which included thyroid, hepatic, pulmonary, neurologic, skin, ocular, and gastrointestinal adverse events. Of note, neither pulmonary fibrosis nor liver toxicity was noted to occur in either group in this study, although the follow-up may not have been long enough to observe these adverse effects.⁴⁷ The protocol also called for analysis of safety data excluding the gastrointestinal adverse events (e.g., diarrhea, vomiting, nausea), and the number of non-gastrointestinal adverse events was significantly lower in dronedarone-treated patients (61) than in amiodarone-treated patients (99, $P=0.002$).

The results of dronedarone studies conducted to date suggest that the drug should not be used in patients with moderate or severe heart failure. While the precise language for the explicit label indications for dronedarone were unclear at the time that this article was prepared, dronedarone will have a black-box warning against the use of this drug in patients with severe heart failure. Dronedaron is effective for maintaining sinus rhythm in patients with AF, albeit possibly less so than amiodarone.

However, dronedarone may have some safety advantage over amiodarone, since the occurrence of pulmonary fibrosis, liver dysfunction, and thyroid dysfunction with dronedarone has been shown to be similar to placebo.⁴³

In mid-2009, the role of dronedarone in the care of patients with AF is evolving. Publication of the results of the DIONYSOS study and future clinical trials will provide additional insight into the efficacy and safety of the drug compared with currently available antiarrhythmic agents. Studies with a longer duration than those conducted to date may be needed to provide an accurate assessment of drug tolerability. In March 2009, the FDA Cardiovascular and Renal Drugs Advisory Committee recommended approval of dronedarone in patients with persistent or paroxysmal AF who have an ejection fraction greater than 35%.^{47,48} and the FDA approved dronedarone for use in the United States on July 2, 2009. According to information released by the FDA, the specific label will indicate that dronedarone is "approved to help maintain normal heart rhythms in patients with a history of atrial fibrillation or atrial flutter (heart rhythm disorders). The drug is approved to be used in patients whose hearts have returned to normal rhythm or who will undergo drug or electric-shock treatment to restore a normal heart beat. Dronedaron may cause critical adverse reactions, including death, in patients with recent severe heart failure."⁴⁹ The drug's label will contain a boxed warning, the FDA's strongest warning, cautioning that the drug should not be used in severe heart failure patients.⁴⁹

Vernakalant

Vernakalant is a mixed sodium and potassium channel blocker currently under review by FDA for acute conversion of AF. It is available in both intravenous and oral forms. Phase III studies comparing the intravenous formulation with placebo for acute cardioversion in patients with recent-onset AF have found that the drug significantly improves the likelihood of restoring sinus rhythm (45% vs. 15%, $P<0.001$).⁵⁰ Most patients included in these studies had AF of recent onset (<7 days). Conversion rates in these studies ranged from 45% to 61% with the most commonly used regimen (2mg per kg vernakalant followed by 3mg per kg 30 minutes later if AF continues).⁴⁶ Conversion rate was greater than with placebo, yet much lower (6% to 9%) in studies that included patients with onset of AF within 8 to 45 days.^{50,51}

An oral formulation has been evaluated for the maintenance of sinus rhythm in patients with AF in phase II, placebo-controlled, dose-ranging studies, with promising results achieved with the use of 300mg or 600mg twice daily.⁵⁰ Commonly reported adverse effects during vernakalant treatment include dysgeusia, sneezing, and paresthesia. Proarrhythmia with the use of vernakalant have not been reported to date and will be important in weighing the risks versus the benefits of this agent. The FDA Cardiovascular and Renal Drugs Advisory Committee has recommended approval of intravenous vernakalant.⁵²

Future Directions in Antiarrhythmic Development

Study of both azimilide and tedisamil for treatment of AF has also been undertaken. However, it is unlikely that either of these agents will be approved in the future for use in patients with AF. While azimilide was found to be safe in patients with structural heart disease in the Azimilide Post Infarct Survival Evaluation (ALIVE),⁵³ the drug does not appear to be efficacious for maintenance of sinus rhythm in patients with either paroxysmal or persistent AF.⁵⁴⁻⁵⁶ Tedisamil was submitted to the FDA for approval as a treatment for acute pharmacologic conversion of AF. While this drug demonstrated efficacy similar to other antiarrhythmic medications for acute conversion, safety concerns led the FDA Advisory Panel to recommend against approval of tedisamil.¹³

Other medications under development for treatment of AF are mostly in the earlier stages of development. The pharmacologic targets of most experimental agents for AF are potassium channels other than the rapid delayed inward rectifying potassium channel (I_{Kr}). Most commonly, drugs targeting the ultra-rapid delayed inward rectifying potassium channel (I_{Kur}) are being developed.⁵⁷ Targeting this channel may allow for antiarrhythmic efficacy with fewer proarrhythmic side effects, since these channels are mainly found in atrial tissues.⁵⁶

Nonantiarrhythmic Agents

Activation of the renin-angiotensin-aldosterone system has been proposed as a contributing factor in AF.¹ Re-analysis of data from randomized controlled studies of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) found a significant reduction in the risk of new-onset AF from the use of these drugs compared with placebo or active control (e.g., a β -blocker).⁵⁸⁻⁶² Pooling data from other controlled studies of patients with AF revealed lower rates of AF recurrence after cardioversion associated with the use of ACE inhibitors or ARBs usually in combination with amiodarone compared with placebo or with amiodarone alone (odds ratio = 0.39, $P = 0.005$).^{58,62,63,64,66} Additional research is needed to clarify the role of ACE inhibitors and ARBs in preventing AF and maintaining sinus rhythm after cardioversion in patients with AF. Neither of these uses of ACE inhibitors or ARBs is approved by the FDA.

Oral Anticoagulants

Rivaroxaban, a factor Xa inhibitor, and dabigatran, a direct thrombin inhibitor, are investigational oral anticoagulant agents that have been used successfully to prevent venous thromboembolism (VTE) in patients undergoing orthopedic surgery.⁶⁷ Clinical trials of these agents for the prevention of embolic stroke in patients with AF are also in progress. Rivaroxaban and dabigatran offer several potential advantages over warfarin. Neither of these agents requires the close laboratory monitoring that is required during warfarin therapy. Rivaroxaban and dabigatran also have more predictable pharmacodynamics than warfarin, which should facilitate dosing. In March 2009, the

FDA Cardiovascular and Renal Drugs Advisory Committee recommended approval of rivaroxaban for the prophylaxis of VTE in patients undergoing hip- and knee-replacement surgery.⁶⁸ FDA approval of dabigatran is not anticipated before 2010. While data with these agents are not yet available, studies are ongoing. Therefore, these agents could emerge as an alternative to long-term anticoagulation with warfarin in patients with AF. Pharmacoeconomic considerations will need to be assessed in addition to efficacy and safety issues when these new anticoagulants are evaluated for the management of AF.

Conclusions

Although rate-control strategies are currently favored in patients with AF, rhythm-control strategies are required for some patients. The choice among antiarrhythmic drug therapies is based on patient-specific characteristics. Emerging antiarrhythmic agents with potentially improved safety and anticoagulants that require less frequent monitoring than warfarin may become therapeutic options in the future. The role of these new agents will be clearer in the future as data regarding the relative efficacy, safety, and economic impact of these drugs become available. The preference for rate-control strategies over rhythm-control strategies could change if antiarrhythmic agents with improved tolerability are introduced.

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Improving Cost-Effectiveness of and Outcomes From Drug Therapy in Patients With Atrial Fibrillation in Managed Care: Role of the Pharmacist

Samuel G. Johnson, PharmD, BCPS

ABSTRACT

BACKGROUND: The medical care costs for procedures, medications, and testing associated with atrial fibrillation (AF) in the United States are high and projected to increase markedly in the future as the number of Americans affected grows. The burden on patient quality of life, the health care system, and society are pharmacoeconomic considerations in managing AF.

OBJECTIVES: To identify key pharmacoeconomic considerations in managing AF and describe ways in which managed care pharmacists can improve the cost-effectiveness of and outcomes from drug therapy for AF.

SUMMARY: The high medical care costs of AF are largely the result of the high cost of hospitalization and inpatient procedures. Recurrence of AF dramatically increases costs, especially for hospital care.

Managed care pharmacists have many opportunities to provide cost-effective care to and improve outcomes in patients with AF. Policy and process review, population management, and case management are key strategies for improving outcomes in patients with AF. Pharmacist input into policy and process review, including pharmacy benefits design, formulary management, and the use of information technology, can help ensure that the use of drug therapy for AF is cost-effective. Population management strategies, such as development of clinical pathways and patient registries, seek to improve the quality, consistency, and cost-effectiveness of care and the likelihood that desired therapeutic outcomes are achieved through targeted interventions. Case management strategies focus on longitudinal care for individuals in order to improve quality. Pharmacist-managed anticoagulation services and antiarrhythmic drug monitoring are the 2 most widely known case management strategies for patients with AF. Managed care pharmacists can screen patients with AF for the use of anticoagulation, which is needed to prevent embolic stroke but is under-used, even though recommended by evidence-based guidelines. The clinical efficacy and cost-effectiveness of pharmacist-managed anticoagulation services for patients with AF are well documented. Pharmacist-managed antiarrhythmic drug monitoring is a less well-known case management strategy that facilitates early detection and intervention to minimize toxicity.

CONCLUSIONS: Managed care pharmacists can play an instrumental role in implementing strategies to improve the cost-effectiveness of and outcomes from drug therapy for AF.

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In this article, amiodarone is discussed for the off-label use in atrial fibrillation. While widely used for this indication, amiodarone is not approved for this use in the United States.

Pharmacoeconomics can be defined as the study of economic factors related to the cost of drug therapy, including the impact on health care systems and society.¹ Alternatively, pharmacoeconomics can be defined as the study of cost-benefit ratios of drugs compared with other therapies or similar drugs, where costs include both financial and quality-of-life measures.² The fact that drug therapy is associated with a measurable cost both financially and with respect to patient quality of life is a common theme regardless of which definition is used. One aspect of pharmacoeconomics that, because of the growing number of cases, has attracted considerable attention is the management of atrial fibrillation (AF).³

Pharmacoeconomic considerations include the cost burden of managing AF on the health care system, patients, and society. The types of costs taken into consideration include the costs of procedures, medications, and testing. New technologies, including electronic medical records, as well as internet-based registry tools, have had a profound impact on the costs of managing AF and other diseases, leading to their promotion by the current presidential administration as an example of meaningful health care reform. Arguably, the largest challenge that we as a society face is how to determine which technologies—pharmacologic and nonpharmacologic—provide the greatest value for our health care dollars.

Costs of Atrial Fibrillation

Annual AF-related health care costs in the first few years after diagnosis amount to roughly \$4,700 per patient in the United States.⁴ Although this figure may not seem large, the total annual cost of AF in the United States, obtained by extrapolating this figure to the 2.3 million Americans currently affected, is nearly \$11 billion. Furthermore, projections of the number of Americans with AF by the year 2050 range from more than 5.6 million to nearly 16 million, so the disease's economic impact could become enormous.^{3,5}

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FIGURE 1 Annual Costs of Atrial Fibrillation-Related Medical Care

Adapted from: Reynolds MR et al.⁴

Analysis of medical, drug, and disability claims data from 16 employers and 2 million enrollees in private insurance programs in the United States during the period 1999-2002 revealed that the annual direct costs of AF (i.e., medical service and prescription drug costs), expressed in 2002 dollars, were more than 5-fold higher in 3,944 patients with AF (\$15,553) than in 3,944 persons (matched 1:1 for age, gender, and health plan status) without the disease (\$2,792).⁶ The indirect costs of lost work time (i.e., productivity), calculated using disability claims and data for absenteeism due to medical conditions for 603 employees, were 4-fold higher in patients with AF (\$2,847) compared with persons without the disease (\$713). The average annual medical service costs were \$13,749, with the largest portion (\$8,486; 62%) for inpatient hospital care and a lesser portion (\$4,622; 34%) for outpatient care (e.g., physician office visits). Annual prescription drug costs were comparatively lower—\$1,804 per patient.⁶

Medical care costs associated with recurrence of AF were analyzed using data from the Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle (FRACTAL) registry of 973 patients with AF who were followed beginning at the time of diagnosis for a mean of 24 months.⁴ Patients with permanent AF for whom a rate-control strategy was chosen had the lowest medical care costs; patients for whom rhythm-control strategies are chosen typically require costly hospital admission for initiation of antiarrhythmic drug therapy. Not surprisingly, recurrence of AF dramatically increased annual medical care costs, which include costs for hospital care, outpatient services, and medications (Figure 1).⁴ Hospital costs included costs for direct current cardioversion, AF ablation, and other inpatient procedures (e.g., MAZE [open-heart surgery to create non-conductive scar tissue] procedure). Outpatient services costs included emergency room

TABLE 1 Strategies to Improve Outcomes in Patients with Atrial Fibrillation

Policy and process review
Pharmacy benefits design
Formulary management
Use of information technology
Population management
Clinical pathway development
Creating and maintaining patient registries
Case management
Pharmacist-managed anticoagulation
Pharmacist-managed antiarrhythmic drug monitoring
Medication therapy management services through Medicare Part D

and physician office visits. Medication costs reflected laboratory monitoring costs as well as drug acquisition costs based on average wholesale prices.

Each recurrence of AF increased annual medical care costs by approximately \$1,600, expressed in U.S. 2002 dollars.⁴ The largest component of the cost increase associated with AF recurrence was for hospital charges, with lesser amounts attributed to outpatient services and medications. The costs used in the analysis for some procedures (\$2,300 for AF ablation, \$760 for cardioversion, and \$640 for a single emergency room visit without admission) were considerably higher than the annual costs for some medications (e.g., \$180 for warfarin, \$1,100 for amiodarone).

Pharmacist's Role

Managed care pharmacists have many opportunities to develop, provide, and implement cost-effective strategies to improve outcomes in patients with AF. For example, a variety of approaches may be used to improve outcomes in patients with AF (Table 1). Pharmacist input into policy and process review, including pharmacy benefits design, formulary management, and the use of information technology, can help ensure that the use of drug therapy for AF is cost-effective.

Pharmacists play a vital role in advising clinicians who prescribe the problematic antiarrhythmic drug to monitor renal function. Pharmacists also should counsel patients about the risks associated with drug therapy and the warning signs of problems that warrant prompt medical attention. Talking points should be developed for the pharmacists to use when interacting with prescribers and patients. Programming electronic alerts about the need for renal function monitoring into the computerized prescriber order entry (CPOE) system is an application of information technology that can help meet the goals of improving renal function monitoring and drug safety. Establishing prescribing restrictions through the formulary management process might be considered. Creating a database of all patients receiving the medication to identify adverse effects may be useful for detecting trends and identifying underlying causes.

Policy and Process Review

Pharmacy benefits design, a component of policy and process review, is a logical approach to provide consistent care and make resources available to all patients. In the past, pharmacy benefits were designed using a one-size-fits-all approach, with a single-benefit tier. Under such benefit plans, insurance premiums were prepaid, and out-of-pocket costs for acute care were low for most patients. Recently, 3- and 4-tier pharmacy benefit plans with high deductibles and out-of-pocket costs for medications and acute care have been developed in an attempt to mitigate cost increases associated with the emergence of new technologies and therapies and a need to shift some of these costs to patients, especially patients with chronic diseases.

In today's health care environment, formulary management has assumed a greater role than before. Formulary management involves the timely review of new drugs approved by the U.S. Food and Drug Administration (FDA). Restrictions on which clinicians may prescribe the drug (i.e., prior authorization requirements) and types of patients who may receive the drug can be established based on efficacy, safety, and cost compared with the standard of care. The development of treatment algorithms and protocols to ensure appropriate use of medications to manage diseases also may be part of the formulary management process. The need for and costs of monitoring therapy and the costs of treating adverse effects should be taken into consideration along with drug acquisition costs.

The antiarrhythmic agent dronedarone was approved by the FDA in early July 2009 for use in certain patients with AF, and the anticoagulant rivaroxaban (which is under consideration for approval for prophylaxis of venous thromboembolism following orthopedic surgery) may soon be approved by the FDA.^{7,8} Pharmacists can play an important role in evaluating the available clinical data, identifying knowledge gaps, and making recommendations for use of the drugs in the organization. For example, pharmacists may participate in the development of a cogent clinical pathway that alerts prescribers that dronedarone should not be used in patients with severe heart failure (HF).⁹ Few data currently are available about the comparative efficacy and safety of dronedarone and amiodarone (the standard of care, although the drug is not approved formally by FDA for patients with AF), but one drug may be preferred over the other for some patients. The development and use of treatment algorithms and protocols for patients with AF based on what is known about the efficacy and safety of dronedarone, amiodarone, and other antiarrhythmic agents can facilitate and ensure consistency in the therapeutic decision-making process.

Another example is rivaroxaban, which will probably be approved initially only for the prevention of venous thromboembolism in patients undergoing hip- and knee-replacement surgery, although clinical trials of the drug for preventing embolic stroke in patients with AF are under way.^{8,10} The formulary management process should address the uses of rivaroxaban that will be

permitted within the organization. As new clinical data become available, prescribing restrictions and treatment algorithms and protocols should be updated.

Drug utilization and safety programs are an important part of the formulary management process. Such programs may include algorithm development to guide safe and effective prescribing, prior authorization reviews, and regular drug-use evaluations. These programs should be adapted to accommodate the need for postmarketing surveillance of adverse effects from new drugs for AF and other disease states. Using dronedarone as an example, an appropriate use of clinical pharmacy services would be for proactive development of a clinical prescribing algorithm to be vetted together with cardiologists, hospitalists, and primary care physicians. In essence, this would establish a process of care that maximizes safe and effective use of dronedarone for appropriate patients. Adjunctively, periodic drug-use evaluations by pharmacy staff would provide a snapshot of overall drug use and may afford opportunities for a therapeutic "course correction" if needed.

The expanded use of information technology (e.g., electronic medical records, electronic alerts in CPOE systems) to coordinate and streamline the delivery of health care (e.g., reduce duplicate testing, facilitate evidence-based practice) has the potential to both improve patient outcomes and decrease costs. These goals have gained prominence in recent years, especially in managed care. Examples that apply to patients with AF include electronic prescriber alerts that provide clinicians with monitoring recommendations for amiodarone (or other antiarrhythmic agents) and the ability to quickly extract administrative-level data (including comorbidities, demographic characteristics, and treatment information) to assess overall quality of care provided.

Population Management

Population management strategies are based on an appreciation of the 80/20 rule—the fact that typically the majority (80%) of health care costs are incurred by a minority (20%) of patients.¹¹ Population management strategies seek to improve the quality, consistency, and cost-effectiveness of care and the likelihood that desired therapeutic outcomes are achieved. In patients with AF, these outcomes might include a reduction in hospital readmission rates for AF recurrence.

The development of evidence-based clinical pathways for drug therapy management and patient registries to track safety outcomes from drug therapies are probably the 2 most important managed care population management strategies for patients with AF. These strategies facilitate the consistent delivery of high quality, cost-effective patient care. Managed care pharmacists can seek opportunities to become involved in these strategies, including the development and implementation of evidence-based clinical pathways for the management of patients with AF. Many successful examples of these strategies are available for the management of a variety of disease states, including diabetes (a

risk factor for embolic stroke in patients with AF), asthma, and depression; however, to date, there are no published examples of specific strategies for patients with AF.¹²⁻¹⁵

Registries. Patient registries make a valuable contribution to population management by facilitating prompt and systematic intervention to ensure patient safety. For example, if an alert is issued by the FDA with an urgent drug recall for safety reasons, a registry can expedite the identification of patients receiving the drug, and action can be taken to prevent or minimize harm.

Registries also can be helpful for providing effective case management (i.e., ensuring proper care for individual patients). Potential disadvantages of registries include the cost of implementation and maintenance, difficulty establishing an interface with information technology infrastructure, and challenges associated with ensuring data accuracy.

Data from registries of patients with AF can be used to evaluate the clinical importance of the proarrhythmic effects from class Ic and class III antiarrhythmic drugs and critical drug interactions involving prolongation of the QT interval. Another application of registries is to support clinical initiatives to ensure that patients with AF receive safe and effective antithrombotic therapy to prevent embolic stroke. The registries can also be used to identify patients with AF who are on class Ic antiarrhythmic drugs and develop screening algorithms for coronary artery disease (CAD) because class Ic antiarrhythmic agents are contraindicated in patients with CAD or other important structural heart disease.

Case Management

Case management strategies focus on individuals instead of populations. The 2 most widely known case management strategies for patients with AF are pharmacist-managed anticoagulation and pharmacist-managed antiarrhythmic drug monitoring. Medication therapy management services provided through Medicare Part D are another form of case management. These services are designed to improve outcomes in patient safety and efficacy.

Pharmacist-Managed Anticoagulation. Anticoagulation is under-used in patients with AF, despite the fact that these patients are at increased risk for embolic stroke, and evidence-based guidelines recommend the use of anticoagulation in patients with AF.¹⁶⁻¹⁹ For example, one study examined adherence to these evidence-based guidelines in the 6-month period after diagnosis of AF in members of a large health plan.¹⁶ For the 444 health plan members at high risk for stroke, 48% received warfarin alone, 11% received warfarin plus aspirin, 17% received aspirin alone, and 24% received no antithrombotic therapy.¹⁶ The authors attributed lack of adherence to physicians being less likely to initiate warfarin therapy for single episodes of AF without recurrence, despite the patients' underlying risk for stroke. They speculated that this may have been because the AF had resolved by the time the treatment decision had been made.

Each year 40,000 preventable strokes at a cost of \$600 million

have been attributed to the underuse of warfarin in Americans with AF, largely because of what some people consider an exaggerated fear of adverse effects.²⁰ Major hemorrhage and thromboembolic complications are serious concerns associated with the use of anticoagulation. The need for close monitoring to prevent these complications may serve as a deterrent to the use of anticoagulation. It also provides impetus to develop new anticoagulants that do not require such close monitoring.

The clinical efficacy and cost-effectiveness of pharmacist-managed anticoagulation services are well documented.²⁰⁻²³ These services are readily integrated into most managed care settings because the resources needed to support the services (e.g., clinical laboratory services, information technology) are widely available. For example, outcomes from a centralized clinical pharmacy anticoagulation service, conducted primarily by telephone, were compared with those from conventional anticoagulation management by physicians in a retrospective, observational cohort study of 6,645 ambulatory patients receiving warfarin at a large non-profit, group-model health maintenance organization.²¹ Roughly 40% of patients had AF or atrial flutter. The primary outcome was complications from warfarin therapy (fatal or nonfatal major bleeding or thromboembolic complications). The pharmacy anticoagulation service was associated with a 39% reduction in the primary outcome compared with physician-managed anticoagulation (hazard ratio [HR]=0.61, 95% confidence interval [CI]=0.42-0.88). This reduction was largely due to a 62% reduction in the risk of cerebrovascular accident (CVA), and other thromboembolic complications (HR=0.38, 95% CI=0.21-0.69). The incidence of CVA was significantly lower with pharmacist-managed anticoagulation (0.4%) than with physician-managed anticoagulation (1.4%). The risk of major bleeding was reduced by 7% in the pharmacist-managed group (HR=0.93, CI=0.54-1.59). Nonetheless, major hemorrhage remains a safety concern with the use of anticoagulation.

The development and implementation of pharmacist-managed anticoagulation services can pose challenges, especially in private practice settings. Such services are resource intensive, and the cost is not universally reimbursed by third-party payers. Furthermore, the patient outreach methods employed, including direct patient care visits, point-of-care testing, at-home patient self-testing, telephone management, and online management, differ, which could affect outcomes. In addition, it is possible that these pharmacist-implemented strategies might face resistance from patients and physicians. Nevertheless, several studies reported that both these groups were generally supportive of such initiatives.²⁴

The cost-effectiveness of pharmacist-managed anticoagulation services has been demonstrated despite the need for costly resources.^{20,22} The estimated annual cost savings from such services for patients receiving warfarin for a variety of indications, including AF, ranges from \$1,621 to \$4,072 per patient.^{20,22} Much of the cost savings is derived from a reduction in thromboembolic complications (by nearly 80% at 1 pharmacist-managed

anticoagulation clinic), which leads to fewer emergency room visits and hospitalizations.²⁰

The costs of pharmacist-managed anticoagulation services for ambulatory patients with AF in a group-model health maintenance organization were quantified and analyzed based on the risk for stroke.²⁵ The monthly cost per patient (calculated in terms of U.S. 2000 dollars) for anticoagulant medications and dispensing fee, laboratory testing fees (including international normalized ratio tests), and clinical pharmacist specialist fees was \$19.09 (37% of the total cost), \$18.38 (36%), and \$13.78 (27%), respectively. These costs did not differ significantly based on the level of risk for stroke (i.e., high, intermediate, and low). The cost of the clinical pharmacist represented a relatively small part of the cost of pharmacist-managed anticoagulation services compared with drug costs and laboratory testing fees.

In the future, rivaroxaban, dabigatran, and other new alternatives to warfarin that do not require close laboratory monitoring may become available, possibly increasing the use of anticoagulation in patients with AF who are unable or unwilling to take warfarin or whose physician was disinclined to initiate anticoagulation.^{8,10} The cost of these new medications may be competitive with that of warfarin if the costs of laboratory testing and monitoring by clinicians are taken into consideration. However, the new agents probably will not initially supplant warfarin for certain high-risk patients (e.g., patients with AF and mechanical valve prostheses as well as known thrombophilias) because of the established clinical effectiveness of warfarin in these patients.²⁶

Until new drugs or devices that eliminate the need for warfarin become available, pharmacist-managed anticoagulation services are a cost-effective means for improving clinical outcomes in patients with AF. Because there is evidence of underuse of warfarin in patients with AF, managed care pharmacists can improve outcomes by screening patients for the need for therapy.¹⁶⁻¹⁸

Antiarrhythmic Drug Monitoring. Pharmacist-managed antiarrhythmic drug monitoring services have been developed to prevent or minimize toxicity and drug interactions, although fewer outcomes data are available for these services than for pharmacist-managed anticoagulation services.^{27,28} Antiarrhythmic drug monitoring services often focus on amiodarone, which is associated with long-term extracardiac toxicities (e.g., thyroid dysfunction, pulmonary fibrosis, hepatotoxicity, corneal deposits, optic neuritis) and interactions with numerous commonly used medications.²⁹⁻³¹

A variety of effective approaches have been used in antiarrhythmic drug monitoring programs. An electronic alert about the need for testing to detect toxicity in patients receiving amiodarone was incorporated into the CPOE system at a Veterans Administration health system.²⁷ A template was used to retrieve past test results, detect trends (changes in test results over time suggesting possible adverse reactions), and allow surveillance for toxicities. A retrospective observational study compared the rate

of testing for 341 patients with amiodarone prescriptions written in the 6-month period before implementation of a computerized interactive template with 316 patients with prescriptions written after implementation. The template was used to retrieve the patients' liver, thyroid, and pulmonary function test results as well as the chest x-ray and ophthalmologic slit lamp examination reports from the electronic medical record. The template then offered links to order sets that automated test reordering and was used to track past test results in 172 of the 316 patients. In these 172 patients, there were significant increases in adherence to recommended testing for amiodarone toxicity compared with the period before implementation; increases were observed in the rate of testing of liver function tests (from 64% to 89%), thyroid function tests (from 56% to 85%), and pulmonary function tests (from 21% to 29%); chest X-rays (from 35% to 75%); and eye examinations (from 35% to 69%). However, the rate of testing after implementation of the electronic alert in the 144 patients for whom the template was not used to track past test results did not increase significantly compared with the 6-month period before implementation of the electronic alert. Providing automated decision support to the prescriber probably was cost neutral because the information technology was already established, although the study did not address costs. There was room for improvement in adherence to testing during amiodarone therapy despite the use of the electronic alert and template for monitoring past test results.

A multidisciplinary case management approach was used in an ambulatory clinic to monitor amiodarone therapy in 60 patients with various arrhythmias (ventricular arrhythmias as well as AF) who were receiving amiodarone.²⁸ Patients were referred to the clinic by primary physicians. A multidisciplinary team composed of a cardiovascular pharmacist, nurse, and physician specialists created a database with the patient medical history, current drug therapy, and baseline laboratory values, and various tests (e.g., liver, thyroid, and pulmonary function tests, chest X-rays) were scheduled in accordance with published guidelines. The mean duration of follow-up was 16 months before referral to the clinic and 9 months after referral. The number of patients with guideline-recommended laboratory testing increased from 14 (23%) before referral to 54 (90%) after enrollment in the clinic ($P < 0.001$). Previously unrecognized adverse events (e.g., pulmonary fibrosis, QT interval prolongation, liver enzyme elevation, hypothyroidism, hyperthyroidism, asthma exacerbation) were detected in 21 (35%) patients after referral to the clinic. Amiodarone was discontinued in 6 (10%) patients, including 4 patients with suspected pulmonary toxicity. The amiodarone dosage was adjusted in 29 (48%) patients. Thus, establishing the multidisciplinary clinic facilitated the prompt detection of toxicity from amiodarone and provided the opportunity for early intervention to minimize harm.

In the future, the need for pharmacist-managed

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antiarrhythmic drug monitoring services may be diminished by the introduction of new antiarrhythmic agents with improved safety or the increased use of ablation procedures or other non-pharmacologic interventions for AF. However, the availability of dronedarone is unlikely to eliminate the use of amiodarone based on the current clinical results. If the role of antiarrhythmic agents in AF management decreases, pharmacists might change their focus to primary prevention of AF through improved pharmacologic management of hypertension and other AF risk factors. Certain antihypertensive therapies (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) may play a role in AF prevention.³²

Conclusions

The growing cost of AF in the United States and the problems associated with drug therapies used to manage AF represent both challenges and opportunities for pharmacists in managed care. Managed care pharmacists can play an instrumental role in improving the cost-effectiveness of and outcomes from drug therapy in patients with AF through a variety of strategies.

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Atrial Fibrillation and Managed Care: Current Approaches and Future Directions for Long-Term Therapy

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. A total of 0.2 CEUs (2.0 contact hours) will be awarded for successful completion of this continuing pharmacy education activity (program no. 204-000-09-406-H01P).

There is no fee for this continuing pharmacy education (CPE) activity. To complete this continuing pharmacy education activity, go to either www.amcp.org (CE/CME Center) or the ASHP Learning (<http://ce.ashp.org>) to access the posttest and evaluation. A passing grade of 70% is required to receive CPE credit for this activity. Upon successful completion of the online CE test, participants may print their official CPE statement.

Continuing pharmacy education credit for this activity is available from August 1, 2009, through June 30, 2012.

Posttest Worksheet: Atrial Fibrillation and Managed Care: Current Approaches and Future Directions for Long-Term Therapy

- Which of the following statements about the relationship between sex and the prevalence of atrial fibrillation (AF) is correct?
 - The prevalence is higher in men than in women regardless of age.
 - The prevalence is higher in women than in men regardless of age.
 - The prevalence is similar in men and women until the age of 50 years after which it becomes higher in women than in men.
 - The prevalence is similar in men and women until the age of 65 years after which it becomes higher in women than in men.
- SD is an African American man aged 76 years with diabetes, hypertension, and peripheral vascular disease. Which of the following characteristics increase his risk for AF?
 - African American race, diabetes, hypertension, and peripheral vascular disease
 - Male sex, diabetes, hypertension, and peripheral vascular disease
 - Advanced age, male sex, diabetes, and peripheral vascular disease
 - Advanced age, male sex, diabetes, and hypertension
- Which of the following conditions can lead to the development of AF as a result of excessive sympathetic stimulation?
 - Hyperthyroidism
 - Hypokalemia
 - Hypothyroidism
 - Pulmonary embolism
- Which of the following are hemodynamic consequences of AF?
 - Increased ventricular diastolic filling time and decreased cardiac output
 - Increased ventricular diastolic filling time and increased cardiac output
 - Decreased ventricular diastolic filling time and increased cardiac output
 - Decreased ventricular diastolic filling time and decreased cardiac output
- AF increases the risk of ischemic stroke
 - By 4% to 5%
 - By 15% to 20%
 - 4- to 5-fold
 - 15- to 20-fold

To complete this continuing pharmacy education activity, go to either www.amcp.org (CE/CME Center) or the ASHP Learning Center (<http://ce.ashp.org>) to access the posttest and evaluation.

6. The risk for stroke in a man aged 70 years with AF and diabetes mellitus but no history of hypertension or heart failure using the CHADS₂ index is
 - a. High
 - b. Intermediate
 - c. Low
 - d. Impossible to determine based on the information provided
7. Which of the following statements about the mortality risk over time in patients with newly diagnosed AF is correct?
 - a. The mortality risk is higher in the first 4 days after diagnosis than after this time period.
 - b. The mortality risk is higher in the first 4 months after diagnosis than after this time period.
 - c. The mortality risk is lower in the first 4 days after diagnosis than after this time period.
 - d. The mortality risk is lower in the first 4 months after diagnosis than after this time period.
8. Which of the following future trends in the prevalence and burden of AF is anticipated in the United States?
 - a. The prevalence and burden will decrease because of improvements in AF treatment.
 - b. The prevalence and burden will decrease because of improvements in management of risk factors for AF.
 - c. The prevalence and burden will increase because of the aging of the population.
 - d. The prevalence and burden will increase because patients with heart failure and coronary heart disease are not being treated appropriately.
9. All of the following are among the primary goals of pharmacotherapy in patients with AF EXCEPT
 - a. Ventricular rate control
 - b. Maintenance of renal function
 - c. Maintenance of sinus rhythm
 - d. Prevention of thromboembolic events (primarily stroke)
10. Which of the following antiarrhythmic agents would be safe to use in a woman aged 67 years with AF, heart failure, and normal renal function?
 - a. Amiodarone or dofetilide
 - b. Flecainide or propafenone
 - c. Flecainide or sotalol
 - d. Propafenone or sotalol
11. Which of the following outcomes was achieved with the use of the pill-in-the-pocket approach in terminating AF outside the hospital, using single oral loading doses of flecainide or propafenone?
 - a. Significant cost savings
 - b. Significant reductions in hospitalization and emergency room visits
 - c. Significant reduction in mortality
 - d. Significant improvement in quality of life
12. Which of the following characteristics of dronedarone may confer an advantage over amiodarone?
 - a. Longer half-life and less frequent dosing
 - b. Shorter half-life and less complicated loading dosing
 - c. Lower risk of thyroid dysfunction due to the presence of iodine
 - d. Greater lipophilicity and larger volume of distribution
13. Which of the following conditions in a patient with AF probably precludes the use of dronedarone based on the findings of the ANDROMEDA study?
 - a. Severe heart failure
 - b. Severe hepatic disease
 - c. Severe pulmonary disease
 - d. Severe renal failure
14. Through which of the following mechanisms does the emerging agent vernakalant act in patients with AF?
 - a. Blockade of calcium channels and restoration and maintenance of sinus rhythm
 - b. Blockade of sodium and potassium channels and restoration and maintenance of sinus rhythm
 - c. Factor Xa inhibition and prevention of embolic stroke
 - d. Direct thrombin inhibition and prevention of embolic stroke
15. Through which of the following mechanisms does the emerging agent rivaroxaban act in patients with AF?
 - a. Blockade of calcium channels and conversion and maintenance of sinus rhythm
 - b. Blockade of sodium and potassium channels and conversion and maintenance of sinus rhythm
 - c. Factor Xa inhibition and prevention of embolic stroke
 - d. Direct thrombin inhibition and prevention of embolic stroke
16. The largest component of the cost of AF recurrences is
 - a. Hospital costs
 - b. Outpatient costs
 - c. Drug costs
 - d. Indirect costs

17. Pharmacy benefits design to ensure quality care for patients with AF is considered an example of
 - a. Case management
 - b. Disease management
 - c. Policy and process review
 - d. Population management
18. Which of the following interventions is an example of a population management strategy for patients with AF?
 - a. Clinical pathway development
 - b. Use of electronic alerts in prescription order entry systems
 - c. Pharmacy benefits design
 - d. Use of an antiarrhythmic electronic alert
19. Which of the following statements summarizes the 80/20 rule of population management that might be applied to patients with AF?
 - a. 80% of patients fill their prescriptions, but the other 20% of patients cannot afford their copayments.
 - b. 80% of patients adhere to recommended treatment, but the other 20% of patients are nonadherent.
 - c. 80% of patients experience adverse events but only 20% of these events are reported.
 - d. 80% of health care costs are incurred by 20% of patients.
20. Pharmacist involvement in medication therapy management services for patients with AF under Medicare Part D is an example of
 - a. Case management
 - b. Disease management
 - c. Policy and process review
 - d. Population management
21. Which of the following statements about pharmacist-managed anticoagulation services for patients with AF is correct?
 - a. The clinical effectiveness of services is well documented, but the cost-effectiveness is not well documented.
 - b. Integration of services into managed care settings often presents a challenge because of the limited use of information technology.
 - c. Reductions in emergency department visits and hospitalizations for AF have not yet been demonstrated.
 - d. The need for services is supported by the underprescribing of anticoagulation in patients with AF despite the availability of evidence-based guidelines.
22. Which of the following were achieved after implementation of a multidisciplinary amiodarone clinic with referral-based care, creation of a patient database, scheduling of various tests, and dosage adjustment for selected patients?
 - a. A reduction in duplicate testing
 - b. An increase in patient adherence to prescribed therapy
 - c. An increase in prescribing of dosages in accordance with accepted guidelines
 - d. An increase in the detection of previously unrecognized adverse events

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Supplement Evaluation

1. All the learning objectives were met. ☐ Yes ☐ No
Please list the objectives that were not met. _____
2. My educational needs were met. ☐ Yes ☐ No
Please list the needs that were not met. _____
3. How effective were the faculty or authors? Please rate on a scale of 1-4 with 4 being the highest.
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ N/A ☐ Text box for free response.
Comments: _____
4. How effective were the teaching methods? Please rate on a scale of 1-4 with 4 being the highest.
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ N/A
5. How effective were the instructional materials? Please rate on a scale of 1-4 with 4 being the highest.
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ N/A
6. How effectively were you able to answer the assessment questions based on what you learned from this activity? Please rate on a scale of 1-4 with 4 being the highest. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ N/A
7. Please indicate the extent to which you agree or disagree with the following statement: "Faculty statements and therapeutic recommendations in this activity were based on supported evidence or professional opinion and did not evidence commercial bias."
☐ Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree
If you answered strongly disagree or disagree to question 7, what commercial bias did you perceive in this activity?

8. What did you find to be the most helpful aspect of this activity?

9. What was the least helpful aspect of this activity?

10. How will you change your practice as a result of participating in this activity? (Select all that apply.)
☐ Create or revise protocols, policies, or procedures ☐ Change the management or treatment of my patients
☐ Change my leadership or management practices ☐ This activity validated my current practice
☐ I will not make any changes to my practice ☐ No change anticipated because I am not currently in practice
☐ Other (please provide further details) _____
11. How confident are you that you will be able to apply these changes in your practice?
☐ Very confident ☐ Somewhat confident
☐ Not confident ☐ N/A (not currently in practice)
12. Please indicate any barriers you perceive to implementing these changes. (Select all that apply.)
☐ Cost ☐ Lack of experience
☐ Lack of opportunity (patients) ☐ Lack of opportunity (equipment)
☐ Lack of administrative support ☐ Lack of time to assess or counsel patients
☐ Reimbursement or insurance issues ☐ Patient compliance issues
☐ Lack of consensus or professional guidelines ☐ No barriers
☐ N/A (not currently in practice) ☐ Other (please provide further explanation below)

13. What questions do you still have about this topic? _____
14. What else would you like ASHP to know about this activity? _____

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Supplement