

Economic Costs Associated with Atrial Fibrillation

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Abstract: As the population ages, the incidence and prevalence of atrial fibrillation (AF) is expected to increase, resulting in significant societal and economic impact. By 2050, AF is projected to affect 15.9 million individuals in the United States. Atrial fibrillation results in a variety of adverse outcomes, including a fivefold increased risk of stroke, impaired quality of life, decreased work productivity, and increased rates of hospitalization. In 2005, there were 470,000 U.S. hospitalizations secondary to AF. In 2004, over 9 million working days were lost because of AF. Costs of AF and its associated complications are enormous. In 2006, costs attributable to AF-associated stroke equaled \$12 billion. In addition, \$41,000 to \$105,000 per patient was spent on aggregate and individual AF care. Because of its increasing prevalence, numerous complications, and large costs, AF presents a significant challenge for patients, clinicians, and health care policymakers. Finding strategies to best care for these patients will become increasingly important.

Keywords: AF hospitalizations; AF cost; Incidence of AF; Prevalence of AF; Stroke.

The number of people affected by atrial fibrillation (AF) is large and growing, both in the United States and internationally. Approximately 2.2 million Americans, or 0.9% of the population, now suffer from AF, with an incidence rate of 75,000 new cases per year.¹⁻³ Both the prevalence and incidence rates of the condition increase with age (Figure 1). Among Framingham Heart Study participants, less than 0.1% of patients under the age of 40 were affected. However, AF incidence rates double with each increasing decade of life, independent of other cardiac conditions.⁴ In those older than 85 years, the annual rate of AF exceeded 10%.² The AF incidence rates also differ by gender. Men were 1.5 times more likely to have AF than women in the Framingham cohort.³ International cohorts illustrate similar findings. In the Renfrew/Paisley cohort, a survey of U.K. subjects conducted in 2000, AF affected 1% of the population. In addition, men were 1.8 times more likely to be affected than women.^{4,5}

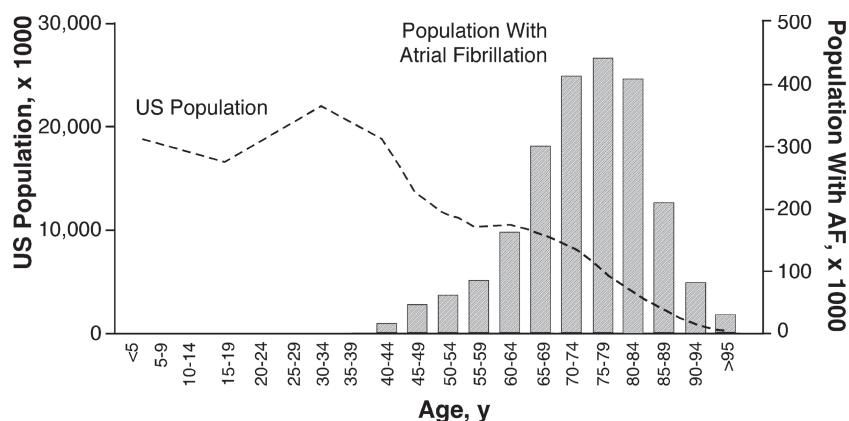


Figure 1 Prevalence of atrial fibrillation (AF) by age. y years. (From ref. 2.)

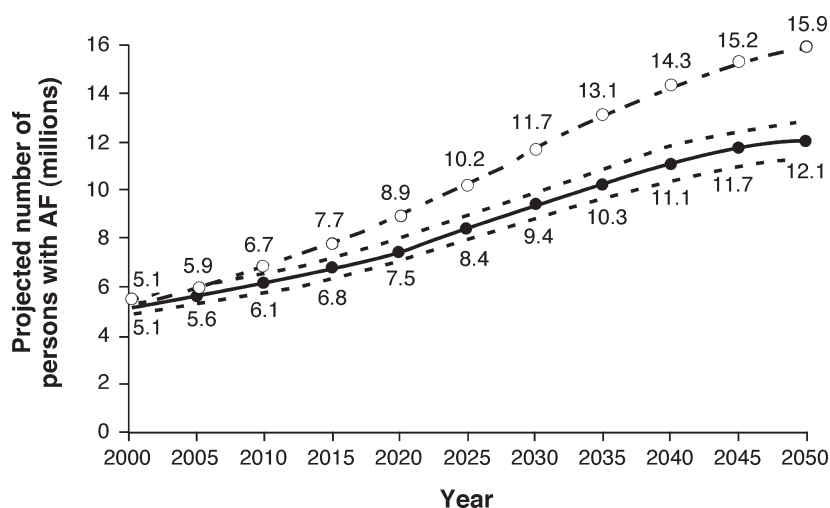


Figure 2 Projected number of persons with atrial fibrillation (AF) in the United States between 2000 and 2050 assuming no further increase in age-adjusted AF incidence (dark circles) and assuming a continued increase in incidence rate as evident in 1980 to 2000 (light circles). (From ref. 79.)

As the population ages and survival from other cardiac conditions improves, the AF burden will increase (Figure 2). For example, U.S. hospitalizations for AF in 2001 increased 34% from 1996 hospitalizations.¹ In the United Kingdom, AF rates among elderly men increased from 1.8 cases/1000 person-years in 1986 to 4.2 cases/1000 person-years in 1995. Similarly,⁵ rates among elderly women increased from 1.8 cases/1000 person-years in 1986 to 3.7 cases/1000 person-years in 1995.

Economic Considerations

Given its large and growing prevalence, AF has substantial economic impact. Proper economic analysis of medical conditions such as AF requires explicit definitions of perspective, costs, and outcomes.

Perspective is the vantage point from which costs and outcomes are assessed. For example, costs can be quantified from the perspective of the patient. In this case, potential costs include AF symptoms, discomfort from therapy, and time lost from work. In contrast, potential costs from the perspective of a payor, such as a health insurance company, include covered services for hospitalization or other treatments and administrative costs in processing claims. Ultimately, a societal perspective, in which all costs and outcomes are assessed regardless of who pays the costs or experiences the outcomes, provides the most complete insight into the economic impact of AF.⁶

In cost accounting, costs should be clearly distinguished from the charges assessed by physicians, hospitals, and other health care providers and should reflect the actual financial resources required to provide care. Costs can be divided into direct and indirect costs. *Direct costs* are those incurred directly from medical care and include inpatient costs (hospital fees, physician fees, procedure and therapy costs) and follow-up costs (physician visits, outpatient testing, medications, home health care providers, long-term care, and future hospitalizations). *Indirect costs* quantify the remaining nonmedical impact of AF, such as missed days of work and lost productivity.⁶ If possible, costs are usually presented in terms of dollar (or other currency) expenditure. When assessment of monetary costs is difficult, such as for mortality or decreased quality of life, proxy values such as lost years of work or lost productivity are used.

In this chapter, we focus primarily on the economic impact of AF and its treatment from a societal perspective. We present those costs associated with AF and its sequelae as well as its evaluation and treatment. Understanding these costs provides important information for both practitioners and policymakers.

Atrial Fibrillation Condition Costs

Atrial fibrillation increases the risk of a variety of adverse outcomes, most notably stroke. It also has an impact on mortality, impairs quality of life, decreases productivity, and increases hospitalization rates. All of these adverse outcomes have substantial costs (Table 1).

Table 1 Assorted atrial fibrillation and cerebrovascular accident costs.

Aggregate and individual CVA costs	
2006 (projected) U.S. CVA costs	\$57.9 billion ¹
2006 (projected) U.S. CVA costs attributable to AF	\$12 billion ¹
2004 U.K. CVA costs	£4.7 billion (\$8.6 billion) ¹⁵
2006 (projected) U.S. acute care CVA costs	\$13,000-20,000/patient ¹
Aggregate and individual AF care and management costs	
2000 U.K. direct medical care costs	£459 million (\$761.5 million) ¹⁸
2000 U.K. nursing home costs	£110.7 million (\$183.7 million) ¹⁵
2004 indirect care costs (e.g., cost of caretakers)	£1.7 billion (\$3.1 billion) ¹⁵
2006 (projected) lifetime medical costs	\$41,000 to \$105,000/patient ¹
Aggregate lost productivity costs associated with AF	
2004 lost working years caused by AF mortality	44,000 ¹⁵
2004 lost working days caused by AF morbidity	9.0 million ¹⁵

All costs and exchange rates valued in the respective study year; see exchanges rates calculator at <http://eh.net/hmit/>.
AF atrial fibrillation, CVA cerebrovascular accident.

Stroke

Stroke is the most debilitating complication of AF. With its associated hypercoagulable state, structural abnormalities in the fibrillating atria, and relative blood stasis, AF fulfills Virchow's triad for the development of thrombi and their subsequent embolization to the cerebral vasculature.^{7,8} As a result, stroke is five times more likely to occur in AF patients than in age-matched controls.¹ Among the Framingham cohort, strokes were four to five times more likely to occur among AF patients than those without AF.⁹ In the Renfrew/Paisley cohort, strokes were 2.5 to 3.2 times more likely in AF patients over a 25-year follow-up compared to those without AF.⁵ Not only does AF predispose to strokes, but also these strokes are more often fatal, debilitating, and recurrent than those not associated with AF.^{4,10–14} In aggregate, AF-related strokes account for 15% to 20% of all strokes annually in the United States.¹

The economic consequences of stroke are massive. In the United States, total costs attributed to strokes in 2007 were projected at \$62.7 billion.¹ Assuming 20% of these strokes are AF related, total costs attributable to AF are approximately \$12 billion. In the United Kingdom, a 2004 survey calculated stroke costs of £4.7 billion (\$8.62 billion). Approximately 44,000 working years were lost to mortality, and 9 million workdays were lost to morbidity. Indirect care costs (time and opportunity costs of nonpaid caregivers for cerebrovascular accident [CVA] patients) exceeded £1.7 billion (\$3.12 billion).¹⁵ For an individual patient, the mean estimated lifetime cost of a stroke, including inpatient care, rehabilitation, and follow-up care for lasting deficits, is \$140,000.¹

Acute care costs, such as hospitalization, diagnostic testing, initial therapy, and rehabilitation, are substantial. The average estimated cost for the first 30 days of stroke care is \$13,000/patient for mild strokes and \$20,000/patient for severe strokes.¹ In addition, inpatient costs can account for 70% of the overall cost of the first year after stroke.¹ Wolf and colleagues illustrated costs of acute care in the first year after stroke using 1991 Medicare data. Among men aged 65 to 74, Medicare spent \$21,231 per patient, 95% of which was spent on acute care needs.⁹

Chronic long-term CVA costs are another major source of expense. One study evaluated lifetime costs of AF patients who suffered strokes. Costs varied from \$41,257 (Australia) to \$104,629 (United Kingdom) per patient.¹⁶ In addition, these costs are increasing, possibly because of the increasing age of the population and a higher prevalence of comorbidities. For instance, the U.S. National Hospital Discharge Survey indicated that increasing numbers of patients are discharged from hospitalization to long-term nursing facilities.¹⁷ In the United Kingdom,¹⁸ nursing home costs associated with AF more than doubled from £46.4 million (\$73.3 million) in 1995 to £110.7 million (\$167.8 million) in 2000.

Mortality

Multiple national and international cohorts describe an independent association between AF and mortality. The mechanism by which AF confers this independent mortality risk is poorly understood. Nonetheless, the Framingham Heart Study illustrated an age-adjusted 1.5 to 1.9 hazard ratio for mortality among patients with AF compared with those without AF.⁴ The U.K. Renfrew/Paisley cohort revealed a 1.5 increased hazard of time to death among patients with

AF.⁵ A study of Canadian men with AF demonstrated a 1.3 to 1.4 increased hazard in time to all-cause and cardiovascular death.¹⁴ A 4-year follow-up survey of the Marshfield Epidemiologic Study Area in the United States described a 2.4 increased hazard in time to all-cause death among AF patients.¹⁹ The Valsartan in Acute Myocardial Infarction (VALIANT) study investigated the effects of valsartan, captopril, or both on patients with acute myocardial infarction (MI) complicated by heart failure or left ventricular (LV) systolic dysfunction. It showed an increased likelihood of mortality or major cardiovascular events (congestive heart failure, MI, resuscitated cardiac arrest, or stroke) among those patients who developed AF compared to those who did not.^{20,21}

Mortality costs are difficult to compute and are generally unavailable. Regardless, the burden of AF, its associated mortality, and its effect on lost earnings and productivity imply substantial societal costs.

Postoperative Atrial Fibrillation

Atrial fibrillation is common in the postoperative recovery period. Between 20% and 50% of U.S. cardiac surgery patients develop AF postoperatively, resulting in prolonged hospital stays and increased treatment costs.^{22–29} One survey revealed that patients with postoperative AF incurred \$6,356 more in hospitalization charges than their AF-free counterparts.²² Another survey demonstrated an adjusted increase in mean length of hospitalization for AF patients of 4.9 days, corresponding to increased costs of at least \$10,005 per patient.²⁹ Yet another investigation concluded that the occurrence of AF after cardiac surgery independently increased the median length of hospitalization by 3.2 days.³⁰

Many strategies have been tested to reduce the incidence and associated costs of postoperative AF.^{31–33} Therapies such as metoprolol, amiodarone, sotalol, procainamide, and atrial pacing have all successfully reduced the incidence of postoperative AF.³³ A meta-analysis examining these various therapies found a 50% reduction in AF incidence and a decrease in length of hospitalization of 1.0 days. However, these clinical improvements did not correspond to a meaningful reduction in costs, possibly because of the expenses associated with the preventive therapies.³³ Only one small study demonstrated significant decreases in both length of hospitalization and costs of care.³⁴ Despite this lack of a clear cost reduction in postoperative AF prevention, prophylaxis may still be warranted to lessen lengths of hospitalization and to mitigate symptoms, especially among those patients who may not tolerate the arrhythmia well.³³

Quality of Life

Atrial fibrillation adversely affects patients' quality of life. Patients with AF and poor rate control have palpitations, fatigue, shortness of breath, or lightheadedness, especially if they have underlying cardiac or pulmonary disease.³⁵ However, even asymptomatic AF patients experience lower perceived health and life satisfaction compared to patients without AF, possibly because of the burden of the diagnosis and its attendant needs for medical care and therapies.³⁶

This reduction in quality of life has a direct impact on costs. Although quantification of quality of life in monetary terms is difficult, symptoms and poor functional status can lead to lost productivity, both professionally and personally. Fortunately, several randomized controlled trials have demonstrated quality

of life improvements with AF therapies.³⁷ Rate and rhythm control strategies were equally efficacious in providing quality-of-life benefits.¹⁹

Productivity

Atrial fibrillation results in significant indirect nonmedical costs, such as lost work and productivity. For example, a French survey of AF patients found that costs caused by missed work accounted for 6% of total AF costs.³⁸ In addition to the workers affected by this condition, employers face increased costs, not only from decreased productivity, but also from increased insurance premiums to cover affected employees. A U.S. study of 16 employers, conducted from 1999 to 2002, found large cost differences between employees with AF and those without. Annually, excess direct medical costs for AF patients were \$12,349 per patient, and excess indirect medical costs were \$2,524 per patient, as compared to patients without AF.³⁹ Although they account for a relatively small portion of overall AF costs, these indirect medical costs play a meaningful role in the overall economic impact of the condition.

Atrial Fibrillation Evaluation and Treatment

Acute Management

Patients with new-onset AF, or an exacerbation of previously diagnosed AF, often require extensive evaluation and treatment. Management approaches for AF vary dependent on patients' hemodynamic stability, symptoms and comorbidities, and the duration of the AF episode. A new diagnosis of AF, either in isolation or in association with another medical condition such as congestive heart failure, initiates an investigation into its cause. These investigations, which can include laboratory testing, monitoring, cardiac imaging, and hospitalization, play a significant role in the economic impact of AF.

One study analyzed costs between AF patients who were hospitalized and those discharged from an emergency department. Admitted patients incurred mean costs of \$2,012 in their care compared to \$1,878 among discharged patients.⁴⁰ A French survey of AF patients found that consultations and investigations for AF patients drove 9% and 8%, respectively, of their overall costs of AF care.³⁸

Several interventions have been proposed to reduce these costs. Dell'Orfano and colleagues developed clinical practice guidelines to mitigate acute AF management costs.⁴¹ Guidelines ensuring appropriate use of direct current cardioversion (DCCV), rate-controlling drugs, and expedited referrals to AF outpatient clinics resulted in decreased hospitalizations, reductions in health care costs of \$1,400 per patient, and no increases in return visits or hospitalizations.⁴²

Hospitalizations for AF management occur frequently. In 2005, AF resulted in 470,000 hospitalizations in the United States.¹ Similar data are seen internationally. Over a 25-year follow-up period in the Multifactor Primary Prevention Cohort in Sweden, 10.1% of male subjects in the cohort were hospitalized with a primary diagnosis of AF.⁴³ Over a 20-year follow-up period among the Renfrew/Paisley cohort in the United Kingdom, 3.6% of men and 3.4% of women were hospitalized with a diagnosis of AF.⁵ In addition, AF hospitalizations, both nationally and internationally, have been

increasing. One study²² found a doubling of U.S. AF hospitalizations between 1982 and 1993. From 1996 to 2001, the number of U.S. hospitalizations with AF as the primary diagnosis increased by 34%.¹ In Scotland,⁴⁴ AF admissions among elderly patients (>65 years) increased from 1.7/1000 person-years in 1985 to 5.5/1000 person-years in 1996, and among younger patients (age 46–65 years) they increased from 0.7/1000 person-years in 1985 to 1.7/1000 person-years in 1996.

These hospitalizations account for a significant portion of the costs associated with AF. A review of U.S. patients admitted for a principal diagnosis of AF demonstrated a mean length of stay of 3.9 days, with average costs of \$6,692 per patient.⁴⁵ In a French survey of 671 AF patients, hospitalization costs accounted for 52% of the expenditures per patient.³⁸ A 1995 U.K. survey revealed that 50% (£122 million, or \$192.6 million) of total annual AF costs were because of hospitalizations.¹⁸ Wolf and colleagues⁹ found that 1-year Medicare hospitalization payments among men aged 65 to 74 years with AF were \$12,654, and 3-year hospitalization costs were \$18,365.

For AF episodes lasting 48 hours or less, cardioversion (either electrical or chemical) may be performed without prohibitive risk of thromboembolism.⁴⁶ Costs of the procedure include anesthesia, monitoring, or further treatments or hospitalization for those who fail to convert to sinus rhythm. In one study at a single center, the total cardioversion cost was \$508 per patient.⁴¹ Variations in the timing and method of cardioversion also affect costs. A single-center trial of AF cardioversion strategies found that patients randomized to a traditional care (hospitalization) pathway incurred median costs of \$1,112 per patient, while those patients who received early DCCV in combination with low molecular weight heparin in the emergency department incurred median costs of \$984 per patient.⁴⁷

Pharmacological cardioversion is another treatment option for patients with recent-onset AF. Although these medicines cost less than DCCV, their cost advantage is attenuated by their inferior efficacy (average cardioversion success rates are reported from 21% to 71%).^{48–50} One review found that, assuming a 45% efficacy rate with ibutilide use and DCCV use in those patients who failed two ibutilide doses, the average cost per patient undergoing chemical cardioversion was \$506, equivalent to the cost of immediate DCCV.⁴¹ Combining antiarrhythmics and DCCV offers another treatment strategy with favorable cost implications. One randomized trial illustrated improved success rates of DCCV with concomitant antiarrhythmic therapy (primarily quinidine) over DCCV alone.⁵¹ The success of this combination approach reduced costs compared to DCCV alone (\$1,240 vs. \$1,917).⁵¹

Approximately 50% of initial episodes of AF convert spontaneously to sinus rhythm within 48 hours, with the majority occurring in the first 24 hours.^{45,52} Accordingly, monitoring AF patients prior to DCCV, to allow for spontaneous conversion, is reasonable. In one center, 24 hours of monitoring cost \$237 per patient. For those patients who failed to spontaneously convert and require DCCV, costs of care increased to \$683 per patient. However, since 50% of patients spontaneously converted, the average cost per patient using the observational strategy was \$460, which compared favorably to early DCCV management strategies.⁴¹

For AF patients presenting with episodes longer than 48 hours, cardioversion should not be attempted because of the excessive risk of thromboembolism.⁵³

In these patients, 3 to 4 weeks of anticoagulation followed by cardioversion is the generally accepted practice. Alternatively, transesophageal echocardiography (TEE) can be performed to exclude intracardiac thrombi, followed by immediate cardioversion and 4 weeks of anticoagulation.⁵⁴ A comparison of these two strategies found similar costs for both (\$6,508 for anticoagulation followed by cardioversion vs \$6,235 for TEE followed by cardioversion).⁵⁵ The greater upfront costs of the TEE strategy were offset by the costs of bleeding complications in the anticoagulation-only strategy.

Chronic Management

After the initial evaluation and treatment of an acute AF episode, focus turns to arrhythmia control and anticoagulation. Arrhythmia control involves antiarrhythmic or atrioventricular (AV) nodal blocking medications. Rhythm control of AF with antiarrhythmic medications can reduce symptoms, improve functional capacity, and lower both stroke and mortality risk.⁵⁶ These benefits must be weighed against the potentially dangerous side effects associated with antiarrhythmic medications. An alternative method of AF management is rate control strategies with AV nodal blocking agents.

Five studies (Paroxysmal Atrial Fibrillation 2 study [PAF2],⁵⁷ Strategies of Treatment of Atrial Fibrillation [STAF],⁵⁸ Pharmacological Intervention in Atrial Fibrillation [PIAF],⁵⁹ Rate Control versus Electrical Cardioversion study [RACE],⁶⁰ and Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM]⁶¹) have examined the efficacy of rate vs rhythm control strategies.⁵⁶ In general, no differences in outcomes were detected between the two treatments. Both strategies appeared equivalent in mortality, stroke risk, functional capacity, and quality of life.^{37,56} Costs, on the other hand, were less with a rate control strategy. Both RACE and AFFIRM demonstrated cost savings in the rate control arm, even after sensitivity analyses. In the 2000 RACE study, mean costs of rate control were 7,386 (\$7,017), while mean costs of rhythm control were 8,284 (\$7,870).⁵⁶ In the AFFIRM trial, the incremental cost of rhythm control over rate control was nearly \$1,500 per patient per year.

Several interventional procedures are an alternative to medication-based antiarrhythmic strategies for AF management. Catheter-based AV node modification or ablation can be used to treat highly symptomatic patients or patients who cannot tolerate rate-controlling agents. The procedure can improve symptoms, functional capacity, and LV function.⁶² In a 1997 report,⁶² costs of AV node modification were \$19,389, and costs of the AV node ablation were \$28,485. Over time, with technical advances, these costs will likely decline, as evidenced by 2003 costs of \$17,173 for AV nodal ablation.⁶³ Emerging technologies in AF ablation, such as maze procedures and pulmonary vein isolation, will also have significant cost implications.

Anticoagulation

Another crucial consideration in long-term AF management is anticoagulation. Among AF patients, warfarin reduced rates of stroke by 60% compared with placebo.^{64–67} Despite this impressive efficacy, anticoagulation comes with a risk of hemorrhage. Warfarin use requires careful and frequent monitoring to ensure therapeutic levels of anticoagulation and to

avoid bleeding complications. Frequent laboratory testing is necessary to maintain a normalized prothrombin clotting time ratio (INR, international normalized ratio) of 2 to 3.

Not surprisingly, anticoagulation medication and its attendant monitoring drives a large portion of AF costs.¹⁸ In a 1995 U.K. survey, drug therapy accounted for 20% (£56 million, or \$88.4 million) of overall AF costs.¹⁸ Similarly, a French survey of 671 AF patients found that 23% of overall AF costs were attributable to drug therapy.³⁸ Although these costs include all medications used in AF therapy, they point to the significant cost impact of anticoagulation.

Anticoagulation complications also affect costs. The risk of bleeding complications increases with higher anticoagulation intensity, older patients, patients with a history of hemorrhage, and patients with serious comorbid conditions.^{68,69} Overall, the reported annual incidence of warfarin-associated bleeding events ranges from 1% to 5%, with 0.5% to 1.0% incidence of fatal hemorrhage.^{70–73} These bleeding events in turn increase costs. The average hospitalization cost for these bleeding events has been estimated at \$15,988 per patient.⁷⁴

Nonadherence to warfarin therapy is another large and costly problem in AF management. The fraction of eligible patients who actually receive anticoagulation is only 22% to 79%.^{75,76} Even among those patients who receive anticoagulation, up to 60% of patients do not achieve therapeutic warfarin levels.⁷⁵ Taken together, these patients represent missed opportunities for stroke prevention and risk the significant costs and adverse outcomes of stroke morbidity and mortality.^{77,78}

Future Directions

Although the current burden of AF, both in the United States and abroad, is already large, forecasts predict major increases over the coming decades. As the population ages and survival from other cardiac conditions that predispose to AF increases, the prevalence of AF will likely rise. Projections for the number of adults in the United States with AF in 2050 range between 5.6 and 15.9 million, as compared to 2.2 million in 2006 (Figure 2).^{1,79} Approximately 50% of this projected population will be over the age of 85 years.¹

As the numbers of AF patients increase, AF care costs will also increase. In the 2004 U.K. survey of AF patients, costs rose from 0.62% (£244 million, or \$418 million) of the National Health Service (NHS) budget in 1995 to 0.97% (£459 million, or \$788 million) of the 2000 NHS budget.¹⁸

Future developments in AF care, such as new anticoagulants and procedures, could have a significant impact on costs. For example, direct anti-thrombin agents or new antiplatelet combinations may show efficacy in AF-related stroke prevention. Since these new therapies do not require the intensive monitoring required by warfarin, substantial cost savings could be realized. Similarly, innovations or improvements in interventional procedures, both in efficacy and safety, could also affect costs.

Atrial fibrillation presents significant challenges to both individual practitioners and policymakers. With its substantial costs in diagnosis, treatment, and outcomes, it will become increasingly important to determine the best strategies in caring for these patients.

References

1. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007; 115(5):e69–171.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med.* 1995;155:469–473.
3. Centers for Disease Control and Prevention. Atrial Fibrillation fact sheet. In: *Fact Sheets and At-a-Glance Reports*. Atlanta: CDC; 2006.
4. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol.* 1998;82:2N–9N.
5. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med.* 2002;113:359–364.
6. Weintraub W, Krumholz H. Cost-effective strategies in cardiology. In: Fuster V, Alexander RW, O'Rourke RA, Roberts R, King SB, Nash IS, Prystowsky EN, eds. *Hurst's: the heart*. 11th ed. New York: McGraw-Hill; 2004.
7. Lip GY. The prothrombotic state in atrial fibrillation: new insights, more questions, and clear answers needed. *Am Heart J.* 2000;140:348–350.
8. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol.* 1999;33:1424–1426.
9. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med.* 1998;158:229–234.
10. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Results from the Perth Community Stroke Study. *Stroke.* 1994;25:1935–1944.
11. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke.* 1996;27:1760–1764.
12. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke.* 1991;22:312–318.
13. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology.* 2003;22:118–123.
14. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med.* 1995;98:476–484.
15. Luengo-Fernandez R, Leal J, Gray A, Petersen S, Rayner M. The cost of cardiovascular disease in the UK. *Heart.* 2006 [Epub ahead of print].
16. Palmer AJ, Valentine WJ, Roze S, Lammert M, Spiesser J, Gabriel S. Overview of costs of stroke from published, incidence-based studies spanning 16 industrialized countries. *Curr Med Res Opin.* 2005;21:19–26.
17. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. *Circulation.* 2003;108:711–716.
18. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart.* 2004;90:286–292.
19. Vidaillet H, Granada JF, Chyou PH, Maassen K, Ortiz M, Pulido JN, Sharma P, Smith PN, Hayes J. A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med.* 2002;113:365–370.
20. Kober L, Swedberg K, McMurray JJ, Pfeffer MA, Velazquez EJ, Diaz R, Maggioni AP, Mareev V, Opolski G, Van de Werf F, Zannad F, Ertl G, Solomon SD,

- Zelenkofske S, Rouleau JL, Leimberger JD, Califf RM. Previously known and newly diagnosed atrial fibrillation: a major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. *Eur J Heart Fail*. 2006 [Epub ahead of print].
21. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893–1906.
 22. Hravnak M, Hoffman LA, Saul MI, Zullo TG, Whitman GR. Resource utilization related to atrial fibrillation after coronary artery bypass grafting. *Am J Crit Care*. 2002;11:228–238.
 23. Caretta Q, Mercanti CA, De Nardo D, Chiarotti F, Scibilia G, Reale A, Marino B. Ventricular conduction defects and atrial fibrillation after coronary artery bypass grafting. Multivariate analysis of preoperative, intraoperative and postoperative variables. *Eur Heart J*. 1991;12:1107–1111.
 24. Cox JL. A perspective of postoperative atrial fibrillation in cardiac operations. *Ann Thorac Surg*. 1993;56:405–409.
 25. Rubin DA, Nieminski KE, Reed GE, Herman MV. Predictors, prevention, and long-term prognosis of atrial fibrillation after coronary artery bypass graft operations. *J Thorac Cardiovasc Surg*. 1987;94:331–335.
 26. Hashimoto K, Ilstrup DM, Schaff HV. Influence of clinical and hemodynamic variables on risk of supraventricular tachycardia after coronary artery bypass. *J Thorac Cardiovasc Surg*. 1991;101:56–65.
 27. Frost L, Molgaard H, Christiansen EH, Hjortholm K, Paulsen PK, Thomsen PE. Atrial fibrillation and flutter after coronary artery bypass surgery: epidemiology, risk factors and preventive trials. *Int J Cardiol*. 1992;36:253–261.
 28. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, Browner WS. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. *JAMA*. 1996;276:300–306.
 29. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, Collins JJ Jr, Cohn LH, Burstin HR. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. *Circulation*. 1996;94:390–397.
 30. Tamis JE, Steinberg JS. Atrial fibrillation independently prolongs hospital stay after coronary artery bypass surgery. *Clin Cardiol*. 2000;23:155–159.
 31. Cooklin M, Gold MR. Implications and treatment of atrial fibrillation after cardiotoracic surgery. *Curr Opin Cardiol*. 1998;13:20–27.
 32. Solomon AJ. Treatment of postoperative atrial fibrillation: a nonsurgical perspective. *Semin Thorac Cardiovasc Surg*. 1999;11:320–324.
 33. Zimmer J, Pezzullo J, Choucair W, Southard J, Kokkinos P, Karasik P, Greenberg MD, Singh SN. Meta-analysis of antiarrhythmic therapy in the prevention of postoperative atrial fibrillation and the effect on hospital length of stay, costs, cerebrovascular accidents, and mortality in patients undergoing cardiac surgery. *Am J Cardiol*. 2003;91:1137–1140.
 34. Daoud EG, Strickberger SA, Man KC, Goyal R, Deeb GM, Bolling SF, Pagani FD, Bitar C, Meissner MD, Morady F. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Engl J Med*. 1997;337:1785–1791.
 35. Jenkins LS, Bubien RS. Quality of life in patients with atrial fibrillation. *Cardiol Clin*. 1996;14:597–606.
 36. Savelieva I, Paquette M, Dorian P, Luderitz B, Camm AJ. Quality of life in patients with silent atrial fibrillation. *Heart*. 2001;85:216–217.
 37. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119:448, e1–e19.

38. Le Heuzey JY, Pazioud O, Piot O, Said MA, Copie X, Lavergne T, Guize L. Cost of care distribution in atrial fibrillation patients: the COCAF study. *Am Heart J*. 2004;147:121–126.
39. Wu EQ, Birnbaum HG, Mareva M, Tuttle E, Castor AR, Jackman W, Ruskin J. Economic burden and co-morbidities of atrial fibrillation in a privately insured population. *Curr Med Res Opin*. 2005;21:1693–1699.
40. Kim MH, Conlon B, Ebinger M, Bruckman D, Kronick S, Lowell M, Morady F, Armstrong WF, Eagle KA. Clinical outcomes and costs associated with a first episode of uncomplicated atrial fibrillation presenting to the emergency room. *Am J Cardiol*. 2001;88:A7, 74–76.
41. Dell'Orfano JT, Kramer RK, Naccarelli GV. Cost-effective strategies in the acute management of atrial fibrillation. *Curr Opin Cardiol*. 2000;15:23–28.
42. Zimetbaum P, Reynolds MR, Ho KK, Gaziano T, McDonald MJ, McClennen S, Berezin R, Josephson ME, Cohen DJ. Impact of a practice guideline for patients with atrial fibrillation on medical resource utilization and costs. *Am J Cardiol*. 2003;92:677–681.
43. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. *J Intern Med*. 2001;250:382–389.
44. Stewart S, MacIntyre K, MacLeod MM, Bailey AE, Capewell S, McMurray JJ. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986–1996. *Eur Heart J*. 2001;22:693–701.
45. Dell'Orfano JT, Patel H, Wolbrette DL, Luck JC, Naccarelli GV. Acute treatment of atrial fibrillation: spontaneous conversion rates and cost of care. *Am J Cardiol*. 1999;83:788–790, A10.
46. Weigner MJ, Caulfield TA, Danias PG, Silverman DI, Manning WJ. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. *Ann Intern Med*. 1997;126:615–620.
47. Kim MH, Morady F, Conlon B, Kronick S, Lowell M, Bruckman D, Armstrong WF, Eagle KA. A prospective, randomized, controlled trial of an emergency department-based atrial fibrillation treatment strategy with low-molecular-weight heparin. *Ann Emerg Med*. 2002;40:187–192.
48. Naccarelli GV, Lee KS, Gibson JK, Vanderlugt J. Electrophysiology and pharmacology of ibutilide. *Am J Cardiol*. 1996;78:12–16.
49. Volgman AS, Carberry PA, Stambler B, Lewis WR, Dunn GH, Perry KT, Vanderlugt JT, Kowey PR. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. *J Am Coll Cardiol*. 1998;31:1414–1419.
50. Capucci A, Boriani G, Rubino I, Della Casa S, Sanguinetti M, Magnani B. A controlled study on oral propafenone vs digoxin plus quinidine in converting recent onset atrial fibrillation to sinus rhythm. *Int J Cardiol*. 1994;43:305–313.
51. de Paola AA, Figueiredo E, Sesso R, Veloso HH, Nascimento LO. Effectiveness and costs of chemical vs electrical cardioversion of atrial fibrillation. *Int J Cardiol*. 2003;88:157–166.
52. Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. *J Am Coll Cardiol*. 1998;31:588–592.
53. Prystowsky EN, Benson DW Jr, Fuster V, Hart RG, Kay GN, Myerburg RJ, Naccarelli GV, Wyse DG. Management of patients with atrial fibrillation. A statement for healthcare professionals. From the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. *Circulation*. 1996;93:1262–1277.
54. Klein AL, Grimm RA, Black IW, Leung DY, Chung MK, Vaughn SE, Murray RD, Miller DP, Arheart KL. Cardioversion guided by transesophageal echocardiography: the ACUTE Pilot Study. A randomized, controlled trial. Assessment

- of cardioversion using transesophageal echocardiography. *Ann Intern Med.* 1997;126:200–209.
55. Klein AL, Murray RD, Becker ER, Culler SD, Weintraub WS, Jasper SE, Lieber EA, Apperson-Hansen C, Heerey AM, Grimm RA. Economic analysis of a transesophageal echocardiography-guided approach to cardioversion of patients with atrial fibrillation: the ACUTE economic data at eight weeks. *J Am Coll Cardiol.* 2004;43:1217–1224.
 56. Vidaillet H, Greenlee RT. Rate control vs rhythm control. *Curr Opin Cardiol.* 2005;20:15–20.
 57. Brignole M, Menozzi C, Gasparini M, Bongiorni MG, Botto GL, Ometto R, Alboni P, Bruna C, Vincenti A, Verlato R. An evaluation of the strategy of maintenance of sinus rhythm by antiarrhythmic drug therapy after ablation and pacing therapy in patients with paroxysmal atrial fibrillation. *Eur Heart J.* 2002;23:892–900.
 58. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U. Randomized trial of rate-control vs rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol.* 2003;41:1690–1696.
 59. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet.* 2000;356:1789–1794.
 60. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JJ, Timmermans AJ, Tijssen JG, Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med.* 2002;347:1834–1840.
 61. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825–1833.
 62. Knight BP, Weiss R, Bahu M, Souza J, Zivin A, Goyal R, Daoud E, Man KC, Strickberger SA, Morady F. Cost comparison of radiofrequency modification and ablation of the atrioventricular junction in patients with chronic atrial fibrillation. *Circulation.* 1997;96:1532–1536.
 63. Goldberg A, Menen M, Mickelsen S, MacIndoe C, Binder M, Nawman R, West G, Kusumoto FM. Atrial fibrillation ablation leads to long-term improvement of quality of life and reduced utilization of healthcare resources. *J Interv Card Electrophysiol.* 2003;8:59–64.
 64. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999;131:492–501.
 65. Warfarin vs aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet.* 1994;343:687–691.
 66. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from three randomized trials. The Atrial Fibrillation Investigators. *Arch Intern Med.* 1997;157:1237–1240.
 67. Go AS. Efficacy of anticoagulation for stroke prevention and risk stratification in atrial fibrillation: translating trials into clinical practice. *Am J Manag Care.* 2004;10:S58–S65.
 68. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest.* 2001;119:108S–121S.
 69. Oden A, Fahlen M. Oral anticoagulation and risk of death: a medical record linkage study. *BMJ.* 2002;325:1073–1075.
 70. Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE. Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. *Arch Intern Med.* 2000;160:1612–1617.

71. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019–1026.
72. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med*. 1994;120:897–902.
73. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. *Am J Med*. 1993;95:315–328.
74. Fanikos J, Grasso-Correnti N, Shah R, Kucher N, Goldhaber SZ. Major bleeding complications in a specialized anticoagulation service. *Am J Cardiol*. 2005;96:595–598.
75. Bushnell CD, Matchar DB. Pharmacoeconomics of atrial fibrillation and stroke prevention. *Am J Manag Care*. 2004;10:S66–S71.
76. Buckingham TA, Hatala R. Anticoagulants for atrial fibrillation: why is the treatment rate so low? *Clin Cardiol*. 2002;25:447–454.
77. Evans A, Davis S, Kilpatrick C, Gerraty R, Campbell D, Greenberg P. The morbidity related to atrial fibrillation at a tertiary centre in 1 year: 9.0% of all strokes are potentially preventable. *J Clin Neurosci*. 2002;9:268–272.
78. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol*. 2002;55:358–363.
79. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.

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