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R E V I E W

Costs and clinical consequences of suboptimal atrial fibrillation management

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Abstract: Atrial fibrillation (AF) places a considerable burden on the US health care system, society, and individual patients due to its associated morbidity, mortality, and reduced health-related quality of life. AF increases the risk of stroke, which often results in lengthy hospital stays, increased disability, and long-term care, all of which impact medical costs. An expected increase in the prevalence of AF and incidence of AF-related stroke underscores the need for optimal management of this disorder. Although AF treatment strategies have been proven effective in clinical trials, data show that patients still receive suboptimal treatment. Adherence to AF treatment guidelines will help to optimize treatment and reduce costs due to AF-associated events; new treatments for AF show promise for future reductions in disease and cost burden due to improved tolerability profiles. Additional research is necessary to compare treatment costs and outcomes of new versus existing agents; an immediate effort to optimize treatment based on existing evidence and guidelines is critical to reducing the burden of AF.

Keywords: atrial fibrillation, pharmacoeconomics, stroke, health-related quality of life

Introduction

Atrial fibrillation (AF), the ineffective and uncoordinated contraction of the atria, is the most common sustained heart rhythm disturbance seen in clinical practice.[1,2] An estimated 3.03 million Americans had AF in 2005, and the prevalence is expected to rise to 7.56 million by 2050.[3] Between 1985 and 1999, the number of hospitalizations with AF as a principal diagnosis increased by 144% according to the National Hospital Discharge Survey.[4] These numbers are probably even greater, since arrhythmias represented 10.6% of patients with a principal diagnosis related to the circulatory system.[5] Research demonstrates a potential link between AF and atherosclerotic vascular disease, hypertension, chronic inflammation, and metabolic syndrome.[6] AF is also associated with substantial morbidity (stroke, heart failure), mortality, and poor health-related quality of life.[7–14] Based on these issues, AF imposes a considerable cost burden on the patient, the health care system, and society.[15–17]

AF treatment is complex. Comprehensive management of the patient with AF requires a multifaceted approach directed at first identifying any underlying, reversible, treatable causes,[18] and then controlling symptoms and protecting the patient from central and peripheral embolism.[19,20] The American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society (ACCF/AHA/HRS) task force recommend that AF management involve three nonmutually exclusive objectives: rate control, prevention of thromboembolism, and correction of the rhythm disturbance (Figure 1).[19] The initial management decision is either a rate-control or rhythm-control strategy.

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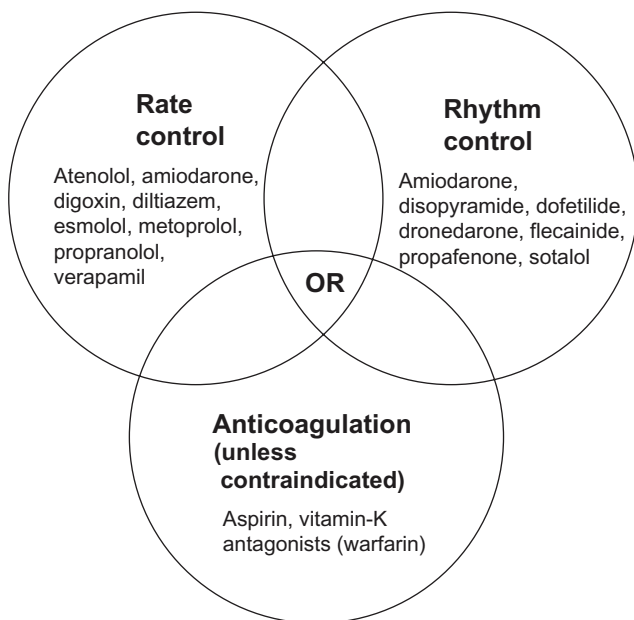Tel +1 202 745 8115
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Figure 1 AF treatment. Drugs are listed alphabetically.[19]
Abbreviation: AF, atrial fibrillation.

Table 1 CHADS$_2$ index stroke risk in patients with nonvalvular AF not treated with anticoagulation and recommended antithrombotic therapy by risk factors[a]

CHADS$_2$ risk criteria	Score
Prior stroke or TIA	2
Age > 75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1
Risk category[b]	**Recommended therapy**
No risk factors	Aspirin, 81 to 325 mg daily
1 moderate risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high risk factor or >1 moderate risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)

Notes: [a]Guideline-based therapy recommendations include consideration of CHADS$_2$ and other risk factors; [b]moderate risk factors: all CHADS$_2$ risk factors with a score of 1 as well as left ventricular ejection fraction $\leq$ 35%; high risk factors: prior stroke, TIA, or embolism; mitral stenosis; prosthetic heart valve (if mechanical valve, target INR > 2.5).
Copyright© 2011, Elsevier. Adapted with permission from Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol.* 2011;57(11):e101–e198.[19]
Abbreviations: TIA, transient ischemic attack; INR, international normalized ratio.

Using the rate-control strategy, the ventricular rate is controlled with no commitment to restore or maintain sinus rhythm, unlike the rhythm-control strategy, which attempts restoration and maintenance of sinus rhythm.[19]

Anticoagulation therapy is to be considered regardless of which rate or rhythm control therapy is prescribed, because current agents used for rate and rhythm control do not reduce stroke risk and cannot be substituted for antithrombotic treatment.[21,22] The CHADS$_2$ scoring system, which utilizes age and comorbid conditions to stratify a patient's stroke risk, is recommended to aid in the decision to use antithrombotic therapy (Table 1).[19,23] Despite the guidelines, AF may be managed suboptimally due to the complexity of treatment. It has been shown that compliance with some antiarrhythmic agents is poor and patients who discontinue treatment are unlikely to restart therapy.[24] Suboptimal management of AF could result in a delay in reverting the patient to normal sinus rhythm, which in turn could promote atrial remodeling, making future sinus rhythm maintenance difficult.[25] This article discusses the clinical consequences and associated costs of suboptimal management of AF in the United States (US), as well as treatment strategies that may reduce the burden of AF and improve patient outcomes.

Overall economic burden of AF in the US

Although there are numerous cost-comparison studies of different AF treatments, there are few US-based direct cost assessments of AF treatments. A recent national survey estimated that direct medical costs were 73% higher in patients with AF compared with matched control subjects, representing a net incremental cost of $8705 per patient per year and a national incremental cost between $6.0 and $26.0 billion (2008 US dollars [USD]).[26] A 2001 study found that approximately 234,000 hospital outpatient department visits, 276,000 emergency room visits, 350,000 hospitalizations, and 5 million office visits were attributable annually to AF.[15] It has been shown that in the year following index hospitalization, 12.5% of chronic AF patients and 10.1% of newly diagnosed AF patients are readmitted for AF.[27] The total annual medical cost for the treatment of AF in the inpatient, emergency department, and hospital outpatient settings was estimated at $6.65 billion (2005 USD; inflation-adjusted to 7.71 billion 2011 USD) (Figure 2), and is likely an underestimate as costs for long-term anticoagulation, stroke prevention, inpatient drugs, and hospital-based physician services were not included.[15] This assessment included billed hospital charges and costs of procedures for which AF was the principal discharge diagnosis ($2.93 billion), incremental inpatient costs due to AF as a comorbid diagnosis ($1.95 billion), and physician fees, drugs, procedures, and facility costs for ambulatory/outpatient treatment of AF ($1.76 billion).[15]
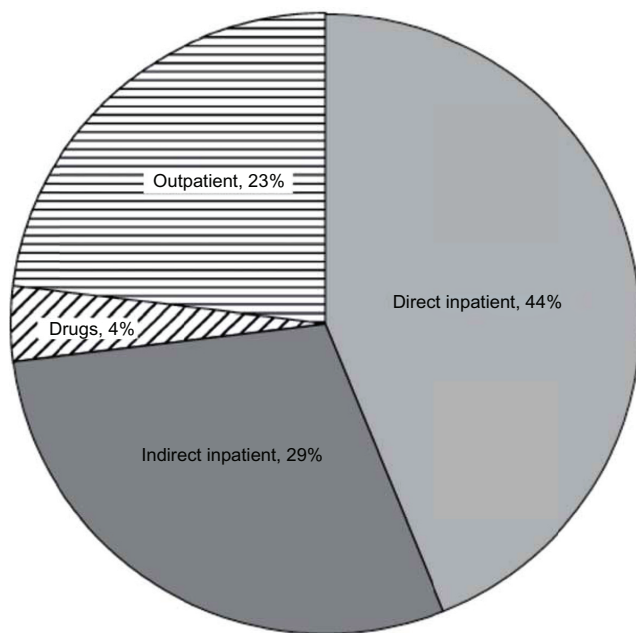
Figure 2 Distribution of total medical costs for treating AF in the United States (2005).
Copyright© 2006, John Wiley and Sons. Reprinted with permission from Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health.* 2006;9(5):348–356.[15]
Abbreviation: AF, atrial fibrillation.

One study estimated the direct and indirect costs of AF (2002 USD) in a privately insured US population aged <65 years. The direct annual cost of AF was $15,553 per patient compared with $3204 for enrollees without AF. These costs were adjusted to $19,575 and $4809 in 2011 USD.[16] Indirect costs (ie, disability claims and absenteeism) were $2134 higher annually for AF patients compared with enrollees without AF ($2847 [$3583 2011 USD] vs $713 [$897 2011 USD], respectively). Regarding patients aged >65 years, a Medicare database study found that the adjusted mean incremental treatment cost of AF was $14,199 (2004 USD; $17,019 2011 USD) in patients diagnosed with AF and followed for 1 year.[17] Some of this cost

was attributable to the incidence of stroke and heart failure 1 year after diagnosis.[17] In another study, inpatient costs were $11,307 (2006 USD; $12,699 2011 USD) and outpatient costs were $2827 ($3175 2011 USD) for primary AF hospitalization; for hospitalized patients with secondary AF, AF-related inpatient costs were $5181 ($5819 2011 USD) and outpatient costs were $1376 ($1545 2011 USD).[28] Table 2 contains recently published data on direct health care costs attributable to an AF diagnosis, including cost adjustments to 2011 USD (differing costs may reflect variations in study designs and data sets).[28–30]

Inpatient drug initiation and costs of adverse events and adverse-event monitoring significantly add to the overall economic burden of AF treatment. A recent analysis examined the costs associated with initiating sotalol and dofetilide in the inpatient setting.[31] Treatment guidelines recommend inpatient initiation of dofetilide, while the initiation of sotalol is mandated by the US Food and Drug Administration (FDA), with a recommended minimum hospital stay of 3 days to assess for ventricular proarrhythmia.[19,32,33] Mean total inpatient costs per patient were $3278 in the sotalol group and $3610 in the dofetilide group (2007 USD; $3580 and $3942 2011 USD, respectively). The greatest costs were for room and board followed by cardiology/electrocardiograms.[31] The incidence and cost of suspected adverse events and adverse-event monitoring during AF rhythm control and/or rate-control therapy was also high.[34] Overall, 50.1% of treated patients had a suspected adverse event and/or function test for adverse-event monitoring (45.5% with rate control, 53.5% with rhythm control, and 61.2% with combined rhythm/rate control). The mean cost of adverse events and adverse-event monitoring among treated patients was $3089 per patient (2006 USD; $3469 2011 USD).[34]

Cost of stroke in patients with AF
Stroke is a leading cause of death in the world and a leading cause of morbidity in adults aged >60 years.[35]

Table 2 Recently published AF health care costs

Study (USD)	Diagnosis	Patient population	Inpatient costs[a]	Outpatient costs[a]	Total AF-related costs[a]
Patel[29] (2006 USD)	Nontransient AF/AFL	32,905 patients in US claims database (mean age 74 years, 56% male, 1/04–12/07)	$22,582 ($25,362)	$15,688 ($17,620)	$38,270 ($42,982)
Kim[28] (2006 USD)	Primary AF	35,255 patients in US claims database (mean age 64 years, 65% male, 1/05–12/06)	$11,307 ($12,699)	$2827 ($3175)	$14,134 ($15,874)
	Secondary AF		$5181 ($5819)	$1376 ($1545)	$6557 ($7364)
Kim[30] (2007 USD)	AF	3605 patients in US claims database (mean age 63 years, 69% male, 4/01–3/07)	$3872 ($4228)	$2293 ($2504)	$6165 ($6732)

Note: [a]Costs inflation-adjusted to 2011 USD using the Bureau of Labor Statistics CPI inflation calculator.
Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; USD, United States dollars.

AF independently increases the risk of ischemic stroke by four- to fivefold.[36] In the absence of antithrombotic therapy, the annual risk of stroke in patients with AF (with risk factors including history of hypertension, diabetes, and history of prior stroke/transient ischemic attack [TIA]) is 4.9% in patients aged <65 years and 8.1% in patients aged >75 years.[37] Because the prevalence of AF increases with age and older age confers an increased risk of stroke, the proportion of strokes attributable to AF increases with age.[37]

Stroke is associated with substantial inpatient and long-term costs.[38] A review of published data on AF prevalence found that survivors of AF-related stroke were more likely to have longer hospital stays, disability, and need for long-term care, all of which increase health care costs.[39] A review of 14 studies found that patients with AF-related stroke had worse outcomes than patients with non-AF-related stroke, including higher mortality, severity, recurrence, functional impairment, and dependency.[40] A retrospective chart review showed that patients with AF-associated ischemic stroke were 2.23 times more likely to be bedridden than patients who had strokes from other causes.[41] Importantly, previously diagnosed AF patients in this chart review were not receiving therapeutic anticoagulation at the time of their stroke.[41]

A recent retrospective observational cohort study utilized medical and pharmacy claims from a managed care organization to identify continuously benefit-eligible AF patients without prior valvular disease or warfarin use between 2000 and 2002 (costs adjusted to 2004 USD).[42] All patients were followed for at least 6 months, until plan termination or the end of study follow-up. Stroke risk was assessed using the $CHADS_2$ index. Inpatient and outpatient cost benchmarks were utilized to estimate total direct health care costs (pre- and post-AF index claim). Total direct health care costs were also assessed for patients with TIA, ischemic stroke (IS), and major bleed (MB). Pre- versus post-AF diagnosis total direct health care costs were $412 and $1235 per member per month (pmpm), respectively ($494 and $1480 2011 USD, respectively). Of the 448 (12%) patients with a TIA, IS, or MB, pmpm costs post-AF diagnosis ranged from $2235 to $3135 ($2679–$3758 2011 USD) correlating with $CHADS_2$ stroke-risk status and exposure to warfarin. Total cohort pmpm costs pre- and post-event increased 24% from $3447 to $4262 ($4132–$5109 2011 USD).[42]

Cost benefits of optimal anticoagulation

In the US, increasing rates of AF-related stroke due to the aging population will come at a high cost to society given the overlap between AF-attributable stroke and the age of Medicare eligibility. The need for optimal anticoagulation was demonstrated in a pooled analysis of five large, randomized, controlled AF antithrombotic trials, which showed that warfarin reduced the frequency of all strokes by 68% (95% confidence interval [CI]: 50%–79%); the efficacy of aspirin was less consistent.[37] A conservative economic model estimated a Medicare saving of $1.14 billion annually (2003 USD; $1.4 billion 2011 USD) through maintaining patients eligible for anticoagulation on therapeutic doses of warfarin.[43] Depending on the study population, anticoagulant therapy has been shown to decrease the risk of stroke by 42% to 86%.[44]

Although several randomized clinical trials have documented the benefits of warfarin in preventing AF-related stroke, a growing body of evidence indicates that anticoagulants are routinely underutilized for stroke prevention in patients with AF.[45,46] It has been estimated that half of the patients receiving warfarin do not receive the appropriate anticoagulant therapy.[44] Anticoagulant therapy with warfarin has a narrow therapeutic index requiring coagulation monitoring by a physician or, in some cases, pharmacists and nurses;[47,48] this requirement, along with the inherent properties of warfarin related to its bleeding risk, may contribute to its low levels of utilization.[45] A comparative study between usual medical care and a clinical pharmacist-run anticoagulation clinic showed that pharmacist supervision improved anticoagulation control, reduced bleeding and thromboembolic event rates, and saved $162,058 per 100 patients annually (1998 USD; $225,112 2011 USD) in reduced hospitalizations and emergency department visits.[49] Figure 3 presents a disease model showing the effects of suboptimal versus optimal oral anticoagulation on stroke rates. The economic model considers a stable population of patients with AF, such as that which might be found in a managed care organization or a state's Medicare group; it allows for movement of individuals with AF in and out of the population during the course of a year. Scenarios are created (eg, "if half of all those who currently do not receive anticoagulation were to receive well-controlled warfarin") to represent the current situation in the population of interest compared with other potential scenarios of care. According to this model, stroke rates and associated costs could decrease dramatically if 50% of warfarin-eligible patients were optimally coagulated. Approximately 1.265 million patients currently not receiving prophylaxis suffer over 58,000 strokes annually. If half of those not receiving warfarin were optimally anticoagulated, approximately 19,000 strokes would be prevented.[43]
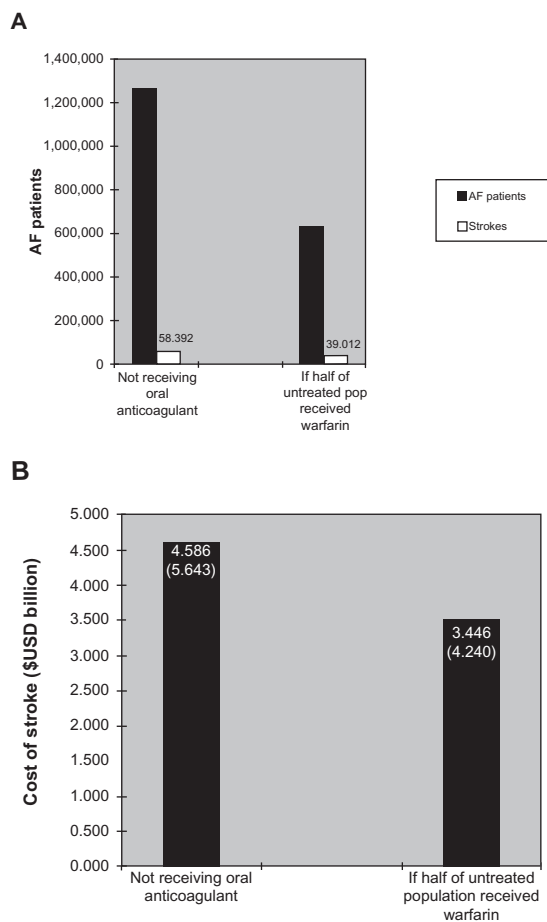
A

B

Figure 3 Model results: (**A**) reductions in AF-related stroke based upon half of untreated patients receiving warfarin and (**B**) cost of stroke.[43] The economic model considers a stable population of patients with AF, such as that which might be found in a managed care organization or a state's Medicare group.
Notes: Cost estimates were based on published epidemiologic data and 2003 Medicare cost data. Values in parentheses are inflation-adjusted costs to 2011 US dollars using the Bureau of Labor Statistics CPI inflation calculator.
Abbreviation: AF, atrial fibrillation.

Warfarin therapy is monitored to ensure that patients remain within the target international normalized ratio (INR) range of 2.0 to 3.0. Studies of the quality of anticoagulation management in patients with AF found that up to 60% of patients receiving warfarin have INR outside the recommended therapeutic target range.[50–52] It is likely that these studies can be generalized to the US population as they included AF patients in a range of settings (emergency department, long-term care, and community); one can therefore conclude that the majority of patients with an AF diagnosis in the US are not optimally treated with anticoagulant therapies. Such suboptimal therapy places patients at risk for complications and further management expenditures.[53]

One real-world study estimated the cost effectiveness of different warfarin treatment scenarios.[53] A semi-Markov transition model (11 primary health states with four additional

states representing temporary discontinuation of therapy) was designed due to the chronic nature of AF and its treatment and the varying but continuous risk of stroke and hemorrhage. The scenarios included in the model were: (1) perfect warfarin control (100% of patients within target INR and following guideline recommendations[19,54] for ideal treatment goal); (2) trial-like warfarin control (clinical trial conditions; INRs within target 68% of the time as reported in the Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation [SPORTIF] V trial);[55] (3) "real-world" warfarin control (routine clinical practice conditions; INRs within target 48% of the time based on data from a retrospective study of US outpatient physician practices);[56] and (4) real-world prescription (and control) of warfarin, aspirin, or neither for warfarin-eligible patients at moderate-to-high risk of stroke (routine clinical practice conditions, in which a proportion of warfarin-eligible patients were prescribed either aspirin [12%] or neither warfarin nor aspirin [23%]).[56] The total number of primary and recurrent ischemic strokes in a cohort of 1000 patients (age 70 years) was assessed, and the model showed increased numbers of strokes as real-world conditions increased and trial-like management declined. Both clinical and cost outcomes were found to be dependent on the quality of anticoagulation (Table 3).

In another cost-effectiveness semi-Markov decision analysis model of patients with AF, the lifetime cost per patient for anticoagulation using a monitoring service was found to be $8661 versus $10,746 for usual care (2004 USD; $10,381 vs $12,880 2011 USD).[57] The model predicted that anticoagulation services improved the effectiveness (measured in quality-adjusted life-years [QALYs]) and reduced costs (estimated at $2100; $2517 2011 USD), and was therefore superior to usual care.

In terms of the cost of MB events with warfarin use, a recent database study of warfarin-treated patients with AF found that MB events associated with warfarin therapy, although nearly twice as costly compared with patients without MB events, were relatively rare; among 47,437 total patients, only 194 (0.4%) had intracranial MB events and 919 (1.9%) experienced gastrointestinal MB events.[58]

In addition to warfarin and other anticoagulants (eg, unfractionated heparin and low-molecular-weight heparin), direct thrombin inhibitors represent a newer class of anticoagulants.[59] Newer antithrombotic agents include rivaroxaban, apixaban, and dabigatran, which are selective for specific coagulation factors such as factor Xa and thrombin.[60–62] Advantages shared by these newer anticoagulants over existing antithrombotic agents consist of selective

Table 3 Results of a cost-effectiveness model predicting clinical trial versus "real-world" warfarin usage for AF-related stroke prevention[53]

	Base case[a]: total medical costs/patient (2006 USD/2011 USD[b])	Base case: total # primary and recurrent IS	Model[c]: total # primary and recurrent IS
Scenario 1: perfect warfarin control	$68,039/$76,416	626	503
Scenario 2: clinical trial-like warfarin control	$77,764/$87,338	832	737
Scenario 3: real-world warfarin control	$84,518/$94,924	984	909
Scenario 4: real-world warfarin, aspirin, or neither	$87,248/$97,990	1171	1120

Notes: [a]Base case: N = 1000, age 70, moderate-to-high risk of stroke, followed for remaining lifetime; [b]costs inflation-adjusted to 2011 USD using the Bureau of Labor Statistics CPI inflation calculator; [c]perfect warfarin adherence.
Abbreviations: IS, ischemic stroke; USD, United States dollars.

targeting for a single coagulation factor, rapid onset of action, fewer drug interactions, and no required dosage adjustment according to patient age, gender, body weight, or mild renal impairment.[62] Clinical trials with these new anticoagulants in patients with AF include ROCKET-AF (rivaroxaban vs warfarin), ARISTOTLE (apixaban vs warfarin) and AVER-ROES (apixaban vs aspirin in patients unsuitable for warfarin). The ROCKET-AF trial showed that rivaroxaban was noninferior to warfarin with regard to stroke or systemic embolism in patients with nonvalvular AF.[63] Rivaroxaban is approved by the FDA for the prevention of stroke in patients with nonvalvular AF.[64] In the AVERROES study, apixaban reduced the risk of stroke or systemic embolism without significantly increasing major bleeding or intracranial hemorrhage,[65] while the ARISTOTLE study demonstrated that apixaban was superior to warfarin in preventing stroke or systemic embolism.[66] An important limitation to the use of these agents is the lack of readily available reversal agents or antidotes.

Dabigatran is a novel oral direct thrombin inhibitor that is approved in the US (October 2010) to reduce the risk of stroke and systemic embolism in patients with AF.[67] In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, two fixed doses of dabigatran (110 and 150 mg, administered in a blinded fashion) were compared with open-label use of warfarin in patients with AF and an increased risk for stroke.[68,69] After a follow-up of 2 years, the primary endpoint of stroke or systemic embolism occurred in 182 patients in the dabigatran 110 mg group (1.53%/year), 134 patients in the dabigatran 150 mg group (1.11%/year), and 199 patients in the warfarin group (1.69%/year). Both dabigatran doses were found to be noninferior to warfarin ($P < 0.001$), and the dabigatran 150-mg dose was found to be superior to warfarin ($P < 0.001$). Hemorrhagic stroke rates were 0.38% per year in the warfarin group versus 0.12% per year in the dabigatran 110 mg group and 0.10% per year in the dabigatran 150 mg group ($P < 0.001$, both comparisons). This decrease in the number of strokes with dabigatran may decrease the costs and economic burden associated with stroke. The 2011 ACCF/AHA/HRS guidelines recommend dabigatran as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients who have paroxysmal to permanent AF and risk factors for stroke/systemic embolization and who do not have a prosthetic heart valve, hemodynamically significant valve disease, severe renal failure, or advanced liver disease.[70]

Cost effectiveness of treatment strategies for AF

The Fibrillation Registry Assessing Costs, Therapies, Adverse Events, and Lifestyle (FRACTAL) study showed that patients with AF who are managed with cardioversion and pharmacotherapy incur AF- and cardiovascular-related health care costs of $4000 to $5000 per year (2002 USD; $5034–$6293 2011 USD).[71] AF-related health care costs averaged $4700 ($5915 2011 USD) per patient per year during the first few years following diagnosis,[71] but subsequent annual costs varied greatly according to the AF clinical course, with hospital care contributing the largest and most variable component of total cost. Among patients with recurrent AF, the frequency of recurrence was strongly associated with higher resource utilization, with each recurrence increasing annual costs by an average of $1600 (2002 USD; $2014 2011 USD).[71] Several recent studies comparing rate and rhythm control strategies have found no meaningful differences in terms of mortality from cardiovascular causes and stroke.[8,21,72–75] Additionally, drivers of cost in patients with AF are not fully elucidated.

A post-hoc cost-effectiveness analysis from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study was published shortly after the FRACTAL study and demonstrated that patients randomized to pharmacologic rate control had less resource utilization and lower costs than patients randomized to rhythm control

(cost savings range, $2189–$5481 per patient, 2002 USD; $2755–$6898 2011 USD).[76] Another post-hoc analysis of AFFIRM clinical treatment data suggested that the benefits of rhythm control may have been offset by the adverse effects of antiarrhythmic therapy, specifically amiodarone, which was used for rhythm control in the study.[77] Whether these AFFIRM cost data would be affected if different antiarrhythmic agents (with better adverse-effect profiles than amiodarone) were analyzed in the model is unknown; however, as the adverse effects had considerable influence over the cost model, cost data can be expected to be affected.[77]

Newer anticoagulants and antiarrhythmic agents may present cost savings compared with older treatments. In an analysis including patients aged $\geq$65 years with AF who were at increased risk of stroke, dabigatran was shown to be a cost-effective alternative to warfarin.[78] The analysis estimated a cost of $45,372 per QALY (2008 USD; $47,715 2011 USD) gained with high-dose dabigatran (150 mg twice daily) compared with warfarin.[78] Another study compared the cost-effectiveness of dabigatran 150 mg twice daily with warfarin, employing a Markov decision-analysis model in a hypothetical cohort of 70-year-old patients with AF and a cost-effectiveness threshold of $50,000/QALY.[79] The analysis found dabigatran to be cost-effective in AF populations at high risk of hemorrhage or stroke (CHADS$_2$ score $\geq$ 3) and warfarin to be cost-effective in moderate-risk AF populations (CHADS$_2$ score 1 or 2). Dabigatran was cost-effective for patients with a CHADS$_2$ score of 2 only if they were at a high risk of major hemorrhage or had poor INR control with warfarin.[79] In a separate cost-effectiveness analysis employing a Markov decision-analysis model in a hypothetical cohort of 70-year-old patients with AF and a history of stroke or transient ischemic attack, dabigatran provided 0.36 additional QALYs versus warfarin at a cost of $9000 (2010 USD; $9314 2011 USD), yielding an incremental cost-effectiveness ratio of $25,000 ($25,873 2011 USD). However, dabigatran was not cost-effective if its relative risk of stroke compared with warfarin exceeded 0.92.[80] Lastly, in a cost-effectiveness analysis in the United Kingdom of simulated patients at moderate-to-high risk of stroke with a mean baseline CHADS$_2$ score of 2, dabigatran 150 mg twice daily was associated with positive incremental net benefits versus warfarin, but was unlikely to be cost-effective in clinics able to achieve good INR control with warfarin.[81]

Given the 24% relative reduction in hospitalizations demonstrated with dronedarone use in the A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) trial,[82] this agent has the potential to reduce costs in patients with AF. One retrospective study analyzed the incidence and direct costs of ATHENA-type outcomes in 15,552 patients with AF who were covered by Medicare supplemental insurance from 2004 to 2007.[83] Mean hospitalization cost per patient was $11,085 (2006 USD; $12,450 2011 USD). Mean costs per patient varied from $7476 (mean cost per hospitalization for AF/supraventricular rhythm disorder [primary diagnosis, nonfatal]) to $37,067 (mean hospitalization cost per death, cardiovascular transcutaneous intervention procedure, or cardiovascular surgical intervention) ($8396 to $41,631, respectively, 2011 USD).[83] Novel antiarrhythmic therapies such as dronedarone, with the potential to reduce cardiovascular hospitalizations and mortality in similar patients, could decrease health care costs.

New antiarrhythmic agents for the treatment of AF

Data demonstrate limited efficacy and partially deleterious adverse-effect profiles for conventional antiarrhythmic agents for AF.[84] Antiarrhythmic agents that have atrial-selective actions and target multiple ion channels may be more tolerable and free of proarrhythmic effects.[85] New agents (ie, dronedarone and vernakalant) offer promise in optimizing the management of AF by potentially reducing AF burden and costs through more favorable tolerability profiles.

Dronedarone

Dronedarone, a noniodinated benzofuran derivative, is a recently (2009) approved multichannel antiarrhythmic agent. Dronedarone is indicated in the US to reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF.[86] According to the 2011 ACCF/AHA/HRS guidelines, dronedarone is recommended as first-line therapy in patients with AF who have no or minimal heart disease, hypertension without left ventricular hypertrophy, or coronary heart disease (class IIa recommendation).[70] In the ATHENA trial, dronedarone demonstrated a significant risk reduction (24%, $P < 0.001$) in hospitalizations due to cardiovascular events or deaths from any cause compared with placebo in patients with paroxysmal or persistent AF/AFL.[82] In an analysis of stroke in the ATHENA trial, dronedarone reduced the risk of

stroke from 1.8% per year to 1.2% per year ($P = 0.027$).[87] In the Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During Atrial Fibrillation (ERATO) study, dronedarone was found to control ventricular rate in patients diagnosed with permanent AF already treated with standard therapies.[88]

Dronedarone was demonstrated to be effective in maintaining sinus rhythm in The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) study and the American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) study.[89] The most common adverse events seen with dronedarone include gastrointestinal problems including diarrhea, nausea, and abdominal pain.[82,88–91] Dronedarone is contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or New York Heart Association (NYHA) class IV heart failure and in patients with AF who will not or cannot be cardioverted into normal sinus rhythm.[86]

The PALLAS study, a trial assessing potential cardiovascular outcomes in patients with permanent AF, was prematurely terminated due to increased adverse cardiovascular events in the dronedarone arm.[92] There were 25 deaths in the dronedarone group (21 from cardiovascular causes) and 13 in the placebo group (10 from cardiovascular causes) ($P = 0.046$). The coprimary outcome, a composite of stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes, occurred in 43 patients receiving dronedarone and 19 patients receiving placebo ($P = 0.002$). These data indicate that dronedarone should not be used in patients with permanent AF who are at risk for major vascular events.[92]

There have been several postmarketing reports of hepatocellular liver injury and hepatic failure in patients receiving dronedarone, including two reports of acute hepatic failure that required transplantation and new-onset or worsening heart failure.[93,94] Obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment with dronedarone, is recommended.[86] Postmarketing cases of increased INR with or without bleeding events have also been reported in patients on warfarin initiated on dronedarone.[86,95] Postmarketing cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have also been reported.[86] Exposure to dabigatran is also higher when it is administered with dronedarone than when it is administered alone.[86]

The US FDA recently completed a safety review of dronedarone based on data from the PALLAS and ATHENA trials.

This review showed that dronedarone increased the risk of serious cardiovascular events, including death, when used by patients with permanent AF.[96] The prescribing information for dronedarone has been revised to include recommendations from the FDA regarding the use of dronedarone to manage the potential serious cardiovascular risks with the drug.[86,96] These recommendations include: dronedarone should not be used in patients with AF who cannot or will not be converted into normal sinus rhythm (permanent AF); heart rate should be monitored by electrocardiogram at least once every 3 months, and if the patient is in AF, dronedarone should be stopped or, if clinically indicated, the patient should be cardioverted; dronedarone is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of nonpermanent AF (known as paroxysmal or persistent AF); and patients taking dronedarone should receive appropriate antithrombotic therapy.[86,96]

Vernakalant

Intravenous vernakalant, a sodium and potassium channel blocker with atrial-selective action, is approved in the European Union, Iceland, and Norway for the rapid conversion of recent-onset AF to sinus rhythm in adult nonsurgery patients with AF of ≤7 days duration and for adult post-cardiac surgery patients with AF of ≤3 days duration.[97] In the AVRO study, intravenous vernakalant was more effective than amiodarone for acute conversion of recent-onset AF.[98] For the oral formulation, early phase II studies demonstrated that oral vernakalant successfully maintained sinus rhythm compared with placebo, and no proarrhythmias relating to vernakalant have been reported to date.[99] There were also no serious adverse events related to vernakalant in phase II trials.[100] Vernakalant was found to be an effective agent for conversion to normal sinus rhythm in patients with recent-onset AF.[99] In a review of six early-phase clinical trials, vernakalant rapidly and effectively terminated recent-onset AF and was found to be well tolerated and efficacious at AF conversion in patients with postoperative AF.[99] Further studies are warranted to better define the role of vernakalant in the management of AF in order to determine whether its benefits translate into a decreased cost burden.

Catheter ablation

For AF patients whose symptoms are not well controlled with pharmacologic therapy, catheter ablation is an increasingly used treatment option. According to the 2011ACCF/AHA/HRS guideline update, catheter ablation may be useful to maintain sinus rhythm in selected patients

with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic agent and have normal or mildly dilated left atria, normal or mildly reduced left ventricular function, and no severe pulmonary disease (class I recommendation upgraded from class IIa, but remaining a class IIa recommendation in both Europe and Canada); to treat symptomatic persistent AF (class IIa recommendation); and to treat symptomatic paroxysmal AF in patients with significant left atrial dilatation or with significant left ventricular dysfunction (class IIb recommendation).[70] Recent studies have reported that catheter ablation successfully treats paroxysmal AF in >80% of cases and persistent AF in >70% of cases.[101] However, catheter ablation is associated with major complications (reported in about 6% of procedures) such as pulmonary vein stenosis, thromboembolism, atrioesophageal fistula, and left atrial flutter.[19,102]

The cost-effectiveness of catheter ablation is difficult to determine due to a number of factors, including differences in the experience levels of centers, use of technology, and rates of reimbursement, which affect cost calculations.[101] Studies evaluating the cost-effectiveness of AF ablation compared with rhythm control or antiarrhythmic agents have shown that ablation treatment results in improved quality-adjusted life expectancy, but at a higher cost.[103–105]

Conclusion

Recent data present a compelling picture of the burden of AF on the US health care system and society. As the US population ages and the prevalence of AF increases, it is clear that AF management strategies need to be optimal. Suboptimal management of AF places patients at risk for AF-associated stroke, the most costly AF-associated event. Numerous studies demonstrate the efficacy of anticoagulation in reducing the risk of AF-related embolic events and preventing hospitalizations, but efficacy is compromised by inadequate and suboptimal treatment patterns. Therapeutic strategies such as rate control, rhythm control, and anticoagulation provide cost-effective means to optimally manage the patient with AF, as do treatment options such as new antiarrhythmic agents or catheter ablation. Given that nearly 75% of the total costs associated with AF are attributed to direct and indirect hospitalization costs,[15] clinical strategies that can reduce AF-related hospitalizations may optimize care by improving clinical outcomes and reducing costs. Further research is necessary to compare new antiarrhythmic agents with existing therapies to assess clinical and economic differences in real-world settings.

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