Cost Efficiency of Anticoagulation With Warfarin to Prevent Stroke in Medicare Beneficiaries With Nonvalvular Atrial Fibrillation

Catherine J. Mercaldi, MPH; Mike Ciarametaro, MBA; Beth Hahn, PhD; George Chalissery, MS; Matthew W. Reynolds, PhD; Stephen D. Sander, PharmD; Gregory P. Samsa, PhD; David B. Matchar, MD

Background and Purpose—In controlled trials, anticoagulation with warfarin reduces stroke risk by nearly two thirds, but the benefit has been less pronounced in clinical practice. This report describes the extent of warfarin use, its effectiveness, and its impact on medical costs among Medicare patients with nonvalvular atrial fibrillation.

Methods—Using claims from >2 million beneficiaries in the Centers for Medicare and Medicaid Services 5% Sample Standard Analytic Files, we identified patients with nonvalvular atrial fibrillation from 2004 to 2005. Warfarin use was inferred from 3 or more tests of the international normalized ratio within 1 year. Incidence of ischemic/hemorrhagic stroke and major bleeding was evaluated. Adjusted risk was calculated by Cox proportional-hazards regression. Medical costs (reimbursed amounts in 2006 US dollars) were estimated by multivariate linear regression.

Results—Of patients with nonvalvular atrial fibrillation (N=119 764, mean age=79.3 years), 58.5% were categorized as warfarin users based on the study definition. During an average of 2.1 years' follow-up, the rate of ischemic stroke was 3.9 per 100 patient-years. After multivariate adjustment, ischemic stroke incidence was 27% lower in patients taking warfarin than in patients not taking warfarin ($P<0.0001$), with no increase in hemorrhagic stroke and a slightly elevated risk of a major bleed. Use of warfarin was independently associated with lower total medical costs, averaging $9836 per patient per year.

Conclusions—These results indicate that 41.5% of Medicare patients with nonvalvular atrial fibrillation are not anticoagulated with warfarin. The incidence of stroke and overall medical costs were significantly lower in patients treated with warfarin. **(*Stroke*. 2011;42:112-118.)**

Key Words: atrial fibrillation ■ warfarin ■ stroke, ischemic ■ stroke, hemorrhagic ■ hemorrhage

Approximately 2.3 million people in the United States are currently diagnosed with atrial fibrillation (AF), and US Census projections estimate that count will more than double by 2050.[1] Although uncommon before 60 years of age, the prevalence of AF doubles with each decade of life and occurs in ≈10% of the population by 80 years. Nonvalvular AF (NVAF) is associated with a 5-fold increase in risk of ischemic stroke and accounts for 15% to 20% of all strokes.[2] Healthcare utilization associated with AF is substantial due, at least in part, to costs associated with ischemic stroke.[3] Nearly 350 000 hospitalizations and 5 million office visits were attributed to NVAF in the United States in 2001, and the costs related to managing AF were $6.65 billion (in 2005 US dollars).[4] The total direct cost to treat the first year of AF-related strokes was $2.6 billion (2003 US dollars), with well-controlled warfarin therapy projected to save more than $1.1 billion of this amount. Bleeding events resulting from prophylactic warfarin use were estimated to add an expense of $21.4 million.[5]

Anticoagulation with adjusted-dose warfarin reduces the risk of ischemic stroke in patients with NVAF by one half to two thirds in clinical trials.[6–8] For this reason, evidence-based clinical guidelines recommend anticoagulation with warfarin for patients with NVAF at moderate to high risk for stroke, who comprise ≈90% of the NVAF population.[9,10] Despite an increase in warfarin use from 9% in the early 1980s to 30% by the year 2000, according to estimates from the Mayo Clinic, these rates fall short of encompassing all NVAF patients at elevated risk of stroke.[11] The stroke risk reduction in patients anticoagulated in ordinary clinical practice appears

Received June 9, 2010; accepted September 22, 2010.

From United BioSource Corp (C.J.M., M.C., B.H., M.W.R.), Bethesda, Md; hMetrix LLC (G.C.), Bala Cynwyd, Pa; Boehringer Ingelheim Pharmaceuticals, Inc (S.D.S.), Ridgefield, Conn; Center for Clinical Health Policy Research, and Department of Biostatistics and Bioinformatics (G.P.S., D.B.M.), Duke University Medical Center, Durham, NC; and Department of Medicine, Duke University Medical Center, Durham, NC, and Program in Health Services and Systems Research, Duke-NUS Graduate Medical School (D.B.M.), Singapore.

The online-only Data Supplement is available at http://stroke.ahajournals.org/content/full/STROKEAHA.110.592907/DC1.

Correspondence to Catherine Mercaldi, United BioSource Corp, 7101 Wisconsin Ave, Suite 600, Bethesda, MD 20814. E-mail katie.mercaldi@unitedbiosource.com

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.592907**

to be considerably lower, with risk reductions of 22% to 32%.[12,13] The reduced benefit of warfarin on the risk of stroke appears to be due, at least in part, to the low prevalence and quality of anticoagulation in ordinary clinical practices compared with controlled clinical trials. One likely reason for underuse of warfarin in clinical practice is overestimation of the risk of bleeding compared with the risk of stroke, especially in elderly patients. However, evidence from trials in elderly patients demonstrates that in the absence of a clear contraindication to anticoagulation, warfarin is safe and effective for stroke prevention in this population.[8,14]

The objective of this study was to describe the current epidemiology of NVAF and incidence of ischemic stroke, hemorrhagic stroke, and bleeding events in a sample of Medicare patients from 2004 to 2006. Furthermore, we examined treatment with warfarin in this largely elderly population with NVAF and the effects of anticoagulation on the incidence of clinical outcomes described earlier, as well as associated medical costs.

Materials and Methods

Data Source

The study cohort was defined from claims between 2004 and 2005 from the Centers for Medicare and Medicaid Services 5% Sample Standard Analytic Files Limited Data Set. Claims from years 2003 and 2006 were used to establish enrollment eligibility, as well as defining baseline variables and follow-up for study outcomes. These files contain final action claims with all adjustments resolved for a 5% sample of all Medicare beneficiaries in each calendar year. Data in the files include International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9) diagnosis and procedure codes, dates of service, reimbursement amount, and beneficiary demographic information. The timing of each claim is recorded as a calendar quarter based on date of service.

Study Population

All reported codes are from the ICD-9 unless otherwise noted. Patients included in the study had at least 2 outpatient medical claims or 1 inpatient claim for AF between January 1, 2004, and December 31, 2005, with continuous eligibility for at least 4 quarters both before the first AF claim to assess medical history and for 4 quarters after the first AF claim to detect study outcomes, with the exception of patients who died before 4 quarters of follow-up elapsed to avoid excluding event-related deaths. Medicare was the primary provider for all patients. Thus, claims from 2003 were used to evaluate baseline eligibility for AF patients identified in 2004, and similarly, claims from 2006 were used to ensure a minimum follow-up of 1 year for patients identified in 2005.

Patients with reversible causes for AF were excluded from the cohort. These conditions included valvular heart disease or valve replacement, cardiac surgery, pericarditis, myocarditis, and pulmonary embolism within 1 quarter before the onset of AF, as well as concomitant hyperthyroidism (see Appendix for specific ICD-9 and Current Procedural Terminology codes used in the online-only Data Supplement, available at http://stroke.ahajournals.org).

Warfarin Exposure

The Medicare 5% data do not include prescription claims; therefore, patients with NVAF were considered to have taken warfarin therapy if they had claims for at least 3 tests of the international normalized ratio (INR) within a 4-quarter period during the study. The use of INR tests as a reasonable surrogate measure of warfarin therapy was validated from the Medicare Current Beneficiary Survey (unpublished data), with 89% sensitivity and 92% specificity.[13] Patients with NVAF satisfying the 3-claim INR test threshold were considered to be taking warfarin beginning with the quarter with the first test.

Stroke and Bleeding Risk Factors

ICD-9 and Current Procedural Terminology codes used to identify clinical conditions associated with an increased risk of stroke or hemorrhage are given in the Appendix. We used the $CHADS_2$ score to estimate stroke risk for each patient with NVAF.[15] The clinical conditions used to calculate $CHADS_2$ were prior stroke or transient ischemic attack, age $\geq$75 years, diabetes mellitus, hypertension, and congestive heart failure. $HEMORR_2HAGES$ score was used to estimate bleeding risk.[16] Conditions that compose the $HEMORR_2HAGES$ score are prior bleeding, hepatic or renal disease, alcohol abuse, malignancy, age $\geq$75 years, reduced platelet count or function, hypertension, anemia, excessive fall risk or neuropsychiatric disease, and prior ischemic or hemorrhagic stroke.

Determination of Outcomes

Outcomes of interest included ischemic stroke, hemorrhagic stroke, and major bleeds. Major bleeding events included only extracranial hemorrhages. Each outcome was identified using ICD-9 diagnosis codes, with all codes used reported in the Appendix. Previously published work was used to select the codes we used to identify ischemic stroke.[17,18] Only strokes or bleeds resulting in a hospitalization or emergency room visit were counted as events.

Statistical Analysis

We compared patients anticoagulated with warfarin versus those who did not fulfill the study definition for warfarin use. To assess risk of stroke and bleeding outcomes, unadjusted incidence rates were computed for all patients. The effect of warfarin use on outcomes was measured by using incidence rate ratios in unadjusted analyses and Cox proportional-hazards regression in adjusted analyses. Covariates included in the ischemic stroke model were age, sex, prior bleed, prior ischemic stroke or transient ischemic attack, hypertension, diabetes mellitus, coronary heart disease, and congestive heart failure, including left ventricular dysfunction.[15,19] For hemorrhagic stroke and major bleeding event Cox models, covariates examined were variables expected to influence risk of hemorrhagic events from evidence in the literature[13,16] and included age, sex, prior bleed, Parkinson disease, gait abnormality, dizziness, diabetic or alcoholic polyneuropathy, esophageal varices, and dementia. Follow-up time was calculated by the number of quarters from the index date until the patient disenrolled or the study ended.

All costs are the amounts reimbursed by Medicare in 2006 US dollars. Costs were annualized by taking the average annual cost weighted by duration of follow-up.[20] Total and specific healthcare costs are reported descriptively for the entire NVAF population, by warfarin use status, and by whether the patient had an adverse event. Adjusted total annual costs by warfarin use were estimated by using a generalized linear model with log link function,[21] with covariates of age, sex, warfarin use, stroke and bleeding risk factors, and duration of follow-up with time-event interaction terms. To estimate the change in cost after an event over time, we calculated costs per quarter up to 1 year after occurrence of an adverse event among patients who had each type of event during follow-up. We analyzed only the first event for patients with multiple events. We estimated the annualized incremental cost of an outcome by taking the difference in adjusted costs between patients with each outcome and those without outcomes.

Results

The 5% sample of Medicare patients from January 1, 2004, to December 31, 2005, included 2 315 846 individuals, of whom 216 395 (9.3%) had at least 1 inpatient or 2 outpatient claims with a diagnosis of AF. Of patients with AF, 22 512 did not meet enrollment eligibility criteria, 61 727 had evidence of valvular heart disease/valve replacement, and 12 392 had other potentially reversible causes of AF, leaving a cohort of

Table 1. Baseline Characteristics for Patients With NVAF by Patient Population

	All Patients With NVAF	Patients Taking Warfarin	Patients Not Taking Warfarin
No. of patients	119 764	70 057	49 707
Age, y			
Mean (SD)	79.3 (8.6)	78.4 (8.1)	80.6 (9.2)*
Median (min–max)	80 (21–98)	79 (23–98)	81 (21–98)
Age in years, categorized, No. (%)			
<65	4229 (3.5%)	2431 (3.5%)	1798 (3.6%)*
65–74	28 651 (23.9%)	18 545 (26.5%)	10 106 (20.3%)
75–84	53 287 (44.5%)	33 276 (47.5%)	20 011 (40.3%)
85+	33 597 (28.1%)	15 805 (22.6%)	17 792 (35.8%)
Sex, No. (%)			
Male	55 142 (46.0%)	34 145 (48.7%)	20 997 (42.2%)*
Female	64 622 (54.0%)	35 912 (51.3%)	28 710 (57.8%)
US geographic location, No. (%)†			
Midwest	31 959 (26.7%)	19 261 (27.5%)	12 698 (25.6%)*
Northeast	25 056 (20.9%)	15 228 (21.7%)	9828 (19.8%)
South	43 945 (36.7%)	24 951 (35.6%)	18 994 (38.2%)
West	18 371 (15.3%)	10 430 (14.9%)	7941 (16.0%)
Other	433 (0.4%)	187 (0.3%)	246 (0.5%)
$CHADS_2$ score			
Median (min–max)	4 (0–6)	4 (0–6)	3 (0–6)
Mean (SD)	3.6 (1.5)	3.7 (1.5)	3.5 (1.5)*
$HEMORR_2HAGES$ score			
Median (min–max)	5 (0–11)	5 (0–11)	5 (0–11)
Mean (SD)	5.2 (2.0)	5.4 (2.0)	5.0 (2.0)*

Min indicates minimum; max, maximum.

*$P<0.0001$ vs patients receiving warfarin from t tests (means) or χ^2 tests (proportions).

†Geographic regions are as follows. Midwest=Wisconsin, Michigan, Illinois, Indiana, Ohio, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa, and Missouri. Northeast=Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, and New Jersey. South=Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida, Kentucky, Tennessee, Mississippi, Alabama, Oklahoma, Texas, Arkansas, and Louisiana. West=Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona, New Mexico, Alaska, Washington, Oregon, California, and Hawaii. Other=Puerto Rico, Africa, Canada, Central America and the West Indies, Europe, Mexico, Oceania, Philippines, South America, US Possessions, American Samoa, Guam, Saipan, Northern Marianas, or Unknown.

119 764 patients with NVAF after these exclusions. The most common reasons for exclusion were evidence of valvular heart disease or valve replacement (31.8%), cardiac surgery (4.9%), and pulmonary embolism (1.3%). Prevalence of this NVAF cohort increased with age, from 5% among those <75 years old to 8.0% for individuals age 75 to 84 years, and 12.7% for ages ≥85 years. Among all patients in this cohort, 58.5% (n=70 057) were categorized as warfarin users and 41.5% (n=49 707) as nonusers (Table 1). The mean age of the cohort was 79.3±8.6 years. Median $CHADS_2$ scores were higher for warfarin users than nonusers, whereas median $HEMORR_2HAGES$ scores were similar (Table 2).

Patients with NVAF contributed 247 761 person-years of follow-up (Table 2). The crude incidence of ischemic stroke in patients with NVAF was 3.6 events per 100 person-years among patients taking warfarin and 4.6 per 100 person-years for those not taking treatment. After adjusting for age, sex, and risk factors, warfarin use was associated with a 27% relative risk reduction in ischemic stroke compared with patients who did not receive warfarin. There were far fewer hemorrhagic strokes (n=1378) than ischemic strokes (n=9774) in this population of patients with NVAF, occurring at a rate of 0.56 hemorrhagic stroke per 100 person-years (Table 2). The incidence of hemorrhagic stroke was lower in warfarin users than nonusers, an association that did not change appreciably after adjusting for risk factors for hemorrhage. The incidence of major bleeding was 7.6 per 100 person-years for the entire population. After adjusting for risk factors, the rate of major bleeding was slightly but significantly higher among patients treated with warfarin (Table 2).

Patients taking warfarin had an average of 12.9 INR claims (median=12.7, with a range of 0 to 200) per year. Warfarin users averaged significantly more office/outpatient visits (21 vs 13, $P<0.0001$) yet had fewer hospitalizations than nonusers (0.8 vs 1.0, $P<0.0001$). The aver-

Table 2. Risk of Adverse Events and Utilization by Patient Population

	All Patients With NVAF	Patients Taking Warfarin	Patients Not Taking Warfarin
No. of patients	119 764	70 057	49 707
Mean duration of follow-up, y†	2.1	2.3	1.8
Adverse events			
Ischemic stroke			
No. of events	9774	5640	4134
Event rate per 100 person-years	3.94	3.56	4.63
IRR (95% CI)		0.77 (0.74–0.80)	1.0 (Ref)
Adjusted HR (95% CI)		0.73 (0.70–0.76)	1.0 (Ref)
Hemorrhagic stroke			
No. of events	1378	810	568
Event rate per 100 person-years	0.56	0.51	0.64
IRR (95% CI)		0.80 (0.72–0.90)	1.0 (Ref)
Adjusted HR (95% CI)		0.81 (0.72–0.90)	1.0 (Ref)
Major bleeding events			
No. of events	18 779	12 039	6740
Event rate per 100 person-years	7.58	7.60	7.54
IRR (95% CI)		1.01 (0.98–1.04)	1.0 (Ref)
Adjusted HR (95% CI)		1.04 (1.01–1.07)	1.0 (Ref)
Utilization and costs			
Total medical costs			
Cost per year, mean (SD)	$19 888 ($41 734)	$18 621 ($38 249)	$22 135 ($46 048)*
Cost per year, median (min–max)	$10 687 ($0-$2 263 373)	$10,270 ($0–$1 238 556)	$11 509 ($0–$2 263 373)
Inpatient utilization			
Patients with hospitalizations, n (%)	84 604 (70.6%)	47 506 (67.8%)	37 098 (74.6%)*
Hospitalizations per year, mean (SD)	0.9 (1.9)	0.8 (1.8)	1.0 (2.0)*
Cost per year, mean (SD)	$8597 ($27 881)	$7842 ($23 424)	$9936 ($33 087)*
Cost per year, median (min–max)	$3465 ($0–$2 228 421)	$3696 ($0–$1 195 158)	$3024 ($0–$2 228 421)
Outpatient utilization			
Patients with outpatient visits, n (%)	115 391 (96.3%)	69 291 (98.9%)	46 100 (92.7%)*
Outpatient visits per year, mean (SD)	18.0 (17.8)	21.1 (19.1)	12.6 (12.8)*
Cost per year, mean (SD)	$1769 ($6598)	$1844 ($6985)	$1636 ($6006)*
Cost per year, median (min–max)	$643 ($0–$172 959)	$712 (0–$172 959)	$530 ($0–$120 1044)

IRR indicates incidence rate ratio; HR, hazard ratio. Ratios compare patients receiving warfarin vs those not receiving warfarin. Multivariate analysis of ischemic stroke was adjusted for age, sex, prior bleed, prior ischemic stroke or transient ischemic attack, hypertension, diabetes mellitus, coronary heart disease, and congestive heart failure, including left ventricular dysfunction. Hemorrhagic stroke and major bleeding event model covariates included age, sex, prior bleed, Parkinson disease, gait abnormality, dizziness, chronic orthostatic hypertension, diabetic or alcoholic polyneuropathy, esophageal varices, and dementia.

*$P<0.0001$ vs patients receiving warfarin from t tests (means) or χ^2 tests (proportions).

†Mean duration of follow-up was estimated from quarterly data.

age total medical cost of the entire cohort was $19 888/patient per year (Table 2). Inpatient costs were the largest contributor to total cost, averaging $8597 per year. Patients with NVAF and no major events during follow-up had an average annual total healthcare cost of $15 718. Those who had an ischemic stroke, hemorrhagic stroke, or major bleed at any time during the study had an average cost of $43 937, $60 123, and $39 943 per year, respectively (Table 3). For all events, costs were highest in the quarter in which the event occurred and then dropped by nearly half in the next quarter (Table 3). Costs were also highest in the first quarter for patients who had no events, likely because the cohort would have contained a portion of incident NVAF patients whose initial treatment costs would have exceeded prevalent patients. By the fourth quarter after the event, costs had stabilized but remained nearly twice as high as those for patients who never had an event. The incremental cost relative to average annual cost of patients with no events ($15 718) was $34 201 per ischemic stroke, $44 716 per hemorrhagic stroke, and $29 965 per major bleed. After multivariate adjustment, total medical costs per patient per patient year were, on average, $9836 lower in patients taking warfarin than in patients not taking warfarin ($P<0.0001$).

Table 3. Annualized Event-Related Costs (in 2006 US Dollars) for Patients With NVAF

	No Event	Ischemic Stroke	Hemorrhagic Stroke	Major Bleed
No. of patients	87 262	9774	1378	18 779
Total costs				
Mean (SD)	$15 718 ($36 842)	$43 937 ($49 568)*	$60 123 ($61 917)*	$39 943 ($56 278)*
Median	$7429	$30 034	$40 216	$24 992
(Min–max)	($0–$2 092 210)	($0–$901 487)	($1965–$1 035 993)	($0–$2 282 334)
Total cost by quarter after event				
Quarter 1				
Patients evaluated, n (%)	87 262 (100%)	9774 (100%)	1378 (100%)	18 779 (100%)
Mean (SD)	$7967 ($15 444)	$23 334 ($20 213)*	$28 646 ($29 902)*	$20 985 ($24 654)*
Median	$1906	$17 131	$18 315	$13 921
(Min–max)	($0–$523 053)	($0–$326 808)	($491–$288 298)	($0–$570 584)
Quarter 2				
Patients evaluated, n (%)	78 302 (89.7%)	6961 (71.2%)	636 (46.2%)	14 957 (79.6%)
Mean (SD)	$4964 ($12 085)	$12 761 ($18 757)*	$18 131 ($27 574)*	$10 282 ($17 002)*
Median	$930	$5206	$8170	$3428
(Min–max)	($0–$377 499)	($0–$329 952)	($30–$229 097)	($0–$318 237)
Quarter 3				
Patients evaluated, n (%)	70 834 (81.2%)	5662 (57.9%)	505 (36.6%)	12 453 (66.3%)
Mean (SD)	$3635 ($8745)	$7074 ($13 205)*	$7354 ($15 708)*	$7396 ($14 161)*
Median	$734	$1795	$1750	$1928
(Min–max)	($0–$277 758)	($0–$296 066)	($0–$217 077)	($0–$417 462)
Quarter 4				
Patients evaluated, n (%)	62 254 (71.3%)	4697 (48.1%)	410 (29.8%)	10 312 (54.9%)
Mean (SD)	$3454 ($8236)	$6750 ($13 777)*	$6303 ($13 857)*	$7020 ($13 573)*
Median	$719	$1676	$1671	$1660
(Min–max)	($0–$237 864)	($0–$268 050)	($16–$168 520)	($0–$419 941)

Min indicates minimum; max, maximum.
*$P<0.0001$ vs patients with no event from *t* tests.

Discussion

In this population of Medicare enrollees, 58.5% of patients with NVAF were anticoagulated with warfarin under study definitions, a rate slightly higher than estimated in this population by Lakshminarayan and colleagues in 2002.[13] The rate of ischemic stroke (3.9%) was higher than has typically been observed in clinical trials,[6,8] potentially because of the high-risk status of this study population, which had a median $CHADS_2$ score of 4. Of those anticoagulated with warfarin, the incidence of stroke was lower than in patients not taking warfarin, although the benefit was not as marked as in trials. The overall medical costs were lower for patients taking warfarin than for those not taking warfarin. Our results support previous work suggesting that anticoagulation may be indicated in a larger proportion of elderly patients than is currently treated in clinical practice today.

Real-world studies have shown that relative risk reduction for stroke in patients with NVAF is lower than observed in controlled clinical trials with dose-adjusted warfarin.[14,15] In our study, the estimated risk of ischemic stroke was 27% for patients on warfarin, which is similar to the 26% reduction observed by Lakshminarayan and colleagues, who used 2000 data from a similar population of Medicare patients,[13] and to the 25% reduction relative to presumed aspirin use observed in the National Registry of Atrial Fibrillation II, a composite dataset of Medicare part A claims and chart-abstracted data from 23 657 AF patients.[22] If we assume all patients not taking warfarin were given antiplatelet therapy (aspirin or other therapies), this reduction is just over half of the 52% estimated risk reduction from trials.[23] Reasons for this disparity likely include suboptimal anticoagulation control and/or targeting lower levels of anticoagulation than those observed in clinical trials. Go and colleagues[24] demonstrated in a 2003 study that warfarin use in clinical practice can approach stroke risk reductions similar to trials (51%) with close monitoring, as 80% of these patients received warfarin in anticoagulation clinics rather than through routine medical care settings. Thus, it is important to not only ensure that patients who are eligible for warfarin receive therapy but also that the quality of care is high. The significantly lower rate of hemorrhagic stroke in patients on warfarin versus patients not taking warfarin was unexpected and unexplained. It is possible that patients at high risk of hemorrhagic events were channeled into the warfarin nonuser group in such a way that could not be identified or adequately controlled for by using claims data.

The cost-effectiveness of warfarin has been estimated previously in economic modeling studies. On the basis of

information from clinical trials, Gage and colleagues[25] concluded that warfarin use is appropriate for NVAF patients with at least 1 risk factor for stroke, with treatment costing $8000 (in 1995 US dollars) per quality-adjusted life-year saved. A more recent study incorporated data from real-world warfarin use patterns and found that the cost-effectiveness of warfarin was largely dependent on the quality of anticoagulation achieved.[26] Although causation cannot be assumed, our observation suggests that in the Medicare population, costs associated with warfarin use may be offset by the reduction in ischemic stroke. After accounting for differences in patient characteristics and balancing the differential rates of adverse events plus the costs of treatment with warfarin, including monitoring, the total healthcare savings was nearly $10 000/y per patient for patients taking warfarin. Prevention of ischemic stroke without increasing the rate of hemorrhagic events remains clinically and economically important, as each bleeding event added an incremental cost of $30 000 to $45 000 per patient per year above the typical costs of treatment of patients with NVAF.

Limitations

The Medicare 5% sample data do not contain prescription information, so warfarin exposure had to be inferred from claims for INR tests. Although this method was previously validated for determining warfarin use in this dataset,[13] we cannot rule out the possibility that some misclassification of treatment stratification occurred. For example, patients who had INR testing done by home monitoring or in extended long-term care facilities would be classified as nonusers of warfarin. The observed utilization rates of short-term nursing facility and hospice care services were only marginally higher in the group of patients who never received warfarin; therefore, we believe that any underestimate of treatment with warfarin would be slight. It is also possible that patients with hepatic or hematologic disease could have received several INR tests unrelated to warfarin use but would have been considered warfarin users under our study definition. Conversely, patients who received warfarin but had poor follow-up monitoring might not satisfy the definition for warfarin use and be incorrectly categorized as nonusers. An additional limitation of the unavailability of prescription claims was that we could not determine whether patients might have received aspirin or other therapies to prevent stroke or estimate the impact of medications that might interact with warfarin. Another important weakness of this analysis is the lack of any measurement of the quality of anticoagulation. The data do not provide values for the INRs for submitted claims, so we have no way of assessing the quality of anticoagulation with warfarin, a major determinant of efficacy for prevention of stroke in patients with NVAF. Similarly, some hemorrhagic risk factors may have been more accurately measured if laboratory values had been available, such as hepatic/renal disease and reduced platelet count.[16] Finally, only the first outcome of interest that occurred was considered. It is possible that patients with multiple outcomes or those who experienced events not examined in this study may have had an impact on cost estimates that have not been considered.

Summary

Older individuals, such as those in the Medicare population, have the highest prevalence of NVAF and are also at the highest risk for ischemic stroke and bleeding. The results of this analysis suggest that the majority of Americans >65 years old with NVAF are treated with warfarin for stroke prevention. As reported in previous studies, we found that treatment with warfarin reduced the risk of ischemic stroke and was associated with significantly lower total healthcare costs. Substantial medical and economic benefits could be achieved if more patients eligible for anticoagulation were treated with appropriately dosed warfarin. Further studies with access to accurate prescription and INR laboratory data are needed to better assess the quality and extent of anticoagulation with warfarin among the high-risk elderly population.

Sources of Funding

This study was funded by Boehringer Ingelheim Pharmaceuticals, Inc.

Disclosures

Dr Sander is an employee of Boehringer Ingelheim. The other authors have disclosed no conflicts of interest.

References

1. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am.* 2008;92:17–40, ix.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983–988.
3. Luengo-Fernandez R, Gray AM, Rothwell PM. Costs of stroke using patient-level data: a critical review of the literature. *Stroke*. 2009;40: e18–e23.
4. 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;9:348–356.
5. Caro JJ. An economic model of stroke in atrial fibrillation: the cost of suboptimal oral anticoagulation. *Am J Manag Care.* 2004;10:S451–S458; discussion S458–S461.
6. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med.* 1990;323:1505–1511.
7. Stroke prevention in atrial fibrillation study: final results. *Circulation.* 1991;84:527–539.
8. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370:493–503.
9. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GYH, Manning WJ. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:546–592.
10. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: The Framingham Heart Study. *J Am Med Assoc*. 2003;290: 1049–1056.
11. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Seward JB, Bailey KR, Iwasaka T, Tsang TS. Time trends of ischemic stroke incidence and mortality in patients diagnosed with first atrial fibrillation in 1980 to 2000: report of a community-based study. *Stroke*. 2005;36:2362–2366.
12. Darkow T, Vanderplas AM, Lew KH, Kim J, Hauch O. Treatment patterns and real-world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system. *Curr Med Res Opin*. 2005;21: 1583–1594.
13. Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002). *Stroke*. 2006;37:1969–1974.

14. Aronow WS, Ahn C, Kronzon I, Gutstein H. Effect of warfarin versus aspirin on the incidence of new thromboembolic stroke in older persons with chronic atrial fibrillation and abnormal and normal left ventricular ejection fraction. *Am J Cardiol*. 2000;85:1033–1035.
15. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *J Am Med Assoc*. 2001;285:2864–2870.
16. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713–719.
17. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. *Stroke*. 2002;33:2465–2470.
18. Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke*. 1998;29:1602–1604.
19. Walker AM, Bennett D. Epidemiology and outcomes in patients with atrial fibrillation in the United States. *Heart Rhythm*. 2008;5:1365–1372.
20. Diehr P, Yanez D, Ash A, Hornbrook M, Lin DY. Methods for analyzing health care utilization and costs. *Annu Rev Public Health*. 1999;20:125–144.
21. Moran JL, Solomon PJ, Peisach AR, Martin J. New models for old questions: generalized linear models for cost prediction. *J Eval Clin Pract*. 2007;13:381–389.
22. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke*. 2006;37:1070–1074.
23. Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest*. 2005;127:2049–2056.
24. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *J Am Med Assoc*. 2003;290:2685–2692.
25. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *J Am Med Assoc*. 1995;274:1839–1845.
26. Sorensen SV, Dewilde S, Singer DE, Goldhaber SZ, Monz BU, Plumb JM. Cost-effectiveness of warfarin: trial versus 'real-world' stroke prevention in atrial fibrillation. *Am Heart J*. 2009;157:1064–1073.