Atrial Fibrillation and Stroke in the General Medicare Population

A 10-Year Perspective (1992 to 2002)

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Background and Purpose—Clinical trials have illustrated warfarin’s protective effect on stroke risk in patients with atrial fibrillation (AF). The current study investigated temporal trends in AF prevalence, warfarin use, and its relation to stroke risk in Medicare patients with AF from 1992 to 2002.

Methods—The Medicare 5% sample for 1992 to 2002 was used to create 1-year cohorts of patients with Medicare as primary payer throughout the year. International Classification of Diseases, Ninth Revision, Clinical Modification codes were used to identify AF, ischemic and hemorrhagic stroke, and comorbid conditions. A previously validated surrogate measure, prothrombin/international normalized ratio claims, was used to identify warfarin use. Cox proportional hazards regression was used to examine time to stroke with warfarin use as a time-dependent variable.

Results—Among Medicare patients aged ≥65 years, AF prevalence increased from 3.2% in 1992 to 6.0% in 2002 with higher prevalence in older subsets of the study population. Among patients with AF, warfarin use increased significantly (P<0.001) for each year examined, from 24.5% in 1992 to 56.3% in 2002. Stroke rates per 1000 patient-years declined from 46.7 in 1992 to 19.5 in 2002 for ischemic stroke but remained fairly steady for hemorrhagic stroke (range, 1.6 to 2.9). Time-to-event modeling confirmed a protective association of warfarin against ischemic stroke among Medicare patients with AF.

Conclusions—This analysis represents an observational validation of stroke prevention in AF trials. The significant increase in warfarin use among patients with AF illustrates diffusion of trial evidence into clinical practice. (Stroke. 2006;37:1969-1974.)

Key Words: atrial fibrillation ■ Medicare ■ warfarin

Atrial fibrillation (AF), an important independent risk factor for stroke, is estimated to result in a possible fivefold increase in ischemic stroke risk1 and to account for up to one fourth of all strokes in elderly patients.1,2 Current prevalence of AF in the United States is estimated at 2.3 million cases, projected to increase 2.5-fold over the next 50 years.3 Randomized clinical trials have demonstrated that the relative risk of stroke in patients with chronic nonvalvular AF (CNVAF) can be reduced by 68%.4 The American College of Chest Physicians (ACCP) guidelines support the use of anticoagulation with warfarin to reduce cardioembolic stroke risk in most patients with CNVAF, including those aged 75 years or older and patients with high-risk features such as diabetes, congestive heart failure, prior stroke, and history of hypertension.5 Well-managed warfarin therapy in clinical trials nearly nullifies the increased risk of CNVAF-associated stroke.6 Reports regarding translation of these study results into community practice are mixed. Some studies suggest a significant evidence–practice gap.7,8 Others indicate increased incidence of bleeding complications from warfarin use in the community.9,10 Recent studies using managed care system data indicate that real-world effectiveness in clinical practice results in relative risk reduction of only approximately 20%.10 An integrated delivery system with 80% of patients managed by a coagulation service achieved a 50% relative risk reduction.11

Motivated by interest in temporal trends in patient care and diffusion of trial evidence into clinical practice over time, we present trends in AF prevalence and warfarin use in patients with AF in the general Medicare population. Our data span 1992 to 2002, a period during which results from well-designed stroke prevention trials in patients with AF reported in the early 1990s12–14 should have diffused into clinical practice.
practice. A corollary is the extent to which results promised by the trials are achieved in real life. We examined the impact of warfarin use on stroke risk in the general Medicare population of patients aged 65 years or older, a population ideal for examining warfarin risks and benefits, both of which increase with age.15,16

Methods

Study Population
The Medicare 5% sample is a rolling replacement cohort provided annually by the Centers for Medicare & Medicaid Services that ensures a representative sample of the Medicare population. Once included, a Medicare beneficiary is followed until death. Each year, beneficiaries who meet the selection criteria are added. We used the sample from 1992 to 2002 to identify 1-year cohorts of general Medicare beneficiaries aged 65 years and older who were alive and had Medicare as the primary payer throughout the year.

Identification of AF, Warfarin Use, Stroke Events, and Comorbid Conditions
Patients were classified with AF if they had at least one Medicare Part A institutional/inpatient claim or two outpatient or Part B physician/supplier claims with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for AF and atrial flutter (427.3x). Prevalence of AF was identified during each calendar year. Prevalent AF cases were additionally classified as incident only if they were not identified as prevalent from the preceding year. Patients identified as having cardiac valvular diseases were excluded.

Because Medicare claims data lack direct information on warfarin use, we used a surrogate measure to identify it. Patients with AF were considered to be receiving warfarin if they had at least three prothrombin test (protime/international normalized ratio [INR]) claims during a 1-year period after AF diagnosis. This surrogate measure of warfarin therapy (89% sensitivity, 92% specificity) was previously validated (unpublished data) using the Medicare Current Beneficiary Survey, which contains prescription drug and claims data. When patients with AF met the three-surrogate-claim criteria, we considered that warfarin was in use at the time of the third INR claim.

Hospitalizations for acute ischemic and hemorrhagic strokes were identified from inpatient Medicare claims identifying stroke as the principal diagnosis using the following ICD-9-CM codes, which have high specificity and sensitivity for stroke identification17: ischemic strokes, 434, 436, hemorrhagic strokes, 430 to 431. Risk factors for ischemic stroke18 were identified in each cohort year using one Part A institutional/inpatient claim or two outpatient or Part B physician/supplier claims as markers for the presence of the condition. The following ICD-9-CM codes were used: diabetes mellitus, 250.x, 357.2, 362.0, 366.41; hypertension, 362.11, 401 to 405, 437.2; congestive heart failure, 398.91, 402.x1, 404.x3, 425, 428. Transient ischemic attacks, code 435.x, were not counted among stroke outcomes but were used for stroke risk stratification.

Risk factors for bleeding or falls were identified for the 2002 cohort year using one Part A institutional/inpatient claim or two outpatient or Part B physician/supplier claims as markers for the presence of the condition. The following ICD-9-CM codes were used: gastrointestinal hemorrhage, 535.1, 569.85, 578.x.

Statistical Analysis
We examined AF trends among general Medicare enrollees and warfarin-use trends among prevalent patients with AF for each cohort year from 1992 to 2002. We analyzed the effect of stroke risk stratification on warfarin use using CHADS2, for risk stratification. CHADS2 has been validated for predicting stroke risk18; we have demonstrated its reliability using Medicare claims data.19 CHADS2 calculates risk levels for patients with AF by assigning 1 risk point to age 75 years or older, diabetes mellitus, hypertension, and recent congestive heart failure and 2 points to ischemic stroke/transient ischemic attack (Figure 1). Ischemic strokes before AF diagnosis date were used in risk stratification. A CHADS2 score of 0 is considered low risk (<2 strokes per 100 patient-years), scores of 1 or 2, moderate risk (2 to 4 strokes per 100 patient-years), and scores greater than 2, high risk (>4 strokes per 100 patient-years). We examined warfarin use for each risk category. We explored the role of bleeding and fall-risk factors on warfarin use rates for the 2002 cohort year.

We calculated the rates of ischemic and hemorrhagic strokes among patients with AF for each cohort year. Finally, we examined the effect of warfarin on stroke outcomes using a survival-analysis framework, illustrated in Figure 1, to model time to a stroke event. Each cohort year was modeled separately. The AF diagnosis date started the “patient clock” for each patient in each cohort year, after which stroke events and INR claims were examined for 1 year. Time to stroke was analyzed using Cox proportional hazards regression, adjusted for demographic variables and CHADS2, comorbid conditions, with warfarin use as a time-dependent variable. Patients with three INR claims before a stroke were assumed to be under warfarin treatment as of their third claim. The CHADS2 score was not included as an adjuster because the model includes all of its elements.

Because patients in the Medicare 5% sample are carried over from 1 cohort year into subsequent years unless they die or withdraw from Medicare, use of the survival-analysis framework across multiple cohort years can lead to bias in the assignment of outcome events. A patient diagnosed with AF in 1 cohort year can potentially be followed into the next calendar year. For example, a stroke event occurring at time X as shown in Figure 1 could be counted toward the year when X occurred and toward the previous year, depending on the patient’s AF claims dates, leading to double-counting of stroke events. To avoid this problem, the time-to-stroke analysis was done for every other year from 1992 to 2000. The models were applied separately to ischemic, hemorrhagic, or any stroke as outcomes. All analyses were done with SAS 8.2 software (SAS Institute).

Sponsor’s Role
Before submission of the paper for peer review, the manuscript was reviewed by the sponsor (AstraZeneca). Comments were sent to the authors, who were solely responsible for the final version.

Results
Temporal trends of AF incidence and prevalence (Figure 2A) suggest a steady incidence and rising prevalence ($P<0.0001$)
across the cohort years. The age-specific prevalence (Figure 2B) also shows a rising trend across the cohort years, with prevalence doubling in each age category. As expected, the highest proportion of AF cases was in the oldest age group (age ≥85 years). Mean age of patients with AF increased from 77.8 (standard deviation [SD] 0.04) years in 1992 to 78.5 (SD 0.03) years in 2002. A comparison of the demographic and comorbid profiles of patients with AF in 1992 and 2002 is shown in the supplemental Table I, available online at http://stroke.ahajournals.org.

Figure 3 and Table 1 describe trends in warfarin use and overall acute ischemic and hemorrhagic strokes among prevalent patients with AF. Warfarin use rates among patients with AF increased significantly (P < 0.001) across the cohort years, ranging from 24.5% in 1992 to 56.3% in 2002. Trends indicate the rate of warfarin use increasing as the rate of ischemic strokes decreased, with hemorrhagic stroke rates remaining fairly steady. Paralleling the decline in ischemic stroke rates, the overall stroke rate shows a downward trend (Table 1). Analysis of warfarin use by CHADS2 risk categories is shown in the supplemental Figure I, available online at http://stroke.ahajournals.org.

Discussion

The AF prevalence in the general Medicare population examined in our study is consistent with estimates reported by other studies.1,20 As expected, we found AF prevalence increasing with increasing age and rising AF prevalence in patients aged 65 years and older. Incidence has remained flat; rising prevalence likely reflects improved survival of patients with AF. This increasing trend in AF prevalence adds to the burden of cardiovascular morbidity in this population and represents a considerable public health problem because of the risk of AF-related stroke and subsequent disability.

The trend toward increased rates of warfarin use across the cohort years (25% in 1992% to 56% in 2002) is encouraging and illustrates diffusion of clinical trial evidence into community practice. However, treatment rates appear to have flattened in recent years (Figure 3). We found rates of warfarin use in Medicare patients with AF comparable to those reported by Jencks et al.21 Their rates of 55% to 57% for 1998 to 2001 are

<table>
<thead>
<tr>
<th>Year</th>
<th>All Patients With AF, n</th>
<th>Warfarin Use, n (%)</th>
<th>Ischemic Hemorrhagic Any Stroke Rates Per 1000 Patient-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>39 329</td>
<td>9652 (24.5)</td>
<td>46.7 2.9 49.7</td>
</tr>
<tr>
<td>1993</td>
<td>42 052</td>
<td>13 027 (31.0)</td>
<td>43.1 2.4 45.5</td>
</tr>
<tr>
<td>1994</td>
<td>46 025</td>
<td>16 299 (35.4)</td>
<td>38.3 2.6 40.8</td>
</tr>
<tr>
<td>1995</td>
<td>48 922</td>
<td>19 280 (39.4)</td>
<td>36.7 2.6 39.3</td>
</tr>
<tr>
<td>1996</td>
<td>52 979</td>
<td>23 169 (43.7)</td>
<td>31.3 2.1 33.4</td>
</tr>
<tr>
<td>1997</td>
<td>56 020</td>
<td>26 363 (47.1)</td>
<td>29.4 2.5 31.9</td>
</tr>
<tr>
<td>1998</td>
<td>57 946</td>
<td>28 625 (49.4)</td>
<td>25.7 2.7 28.4</td>
</tr>
<tr>
<td>1999</td>
<td>59 803</td>
<td>30 584 (51.1)</td>
<td>25.4 1.6 27.1</td>
</tr>
<tr>
<td>2000</td>
<td>62 515</td>
<td>33 357 (53.4)</td>
<td>23.7 2.4 26.1</td>
</tr>
<tr>
<td>2001</td>
<td>65 944</td>
<td>36 064 (54.7)</td>
<td>22.1 2.1 24.1</td>
</tr>
<tr>
<td>2002</td>
<td>67 341</td>
<td>37 940 (56.3)</td>
<td>19.5 1.7 21.2</td>
</tr>
</tbody>
</table>

Figure 4 shows the influence of bleeding and fall-risk factors on warfarin use in the 2002 cohort. Warfarin use rates differed significantly different between patients with AF with and without these contraindications (49.2% versus 59.9%, P = 0.001). Among 43 291 patients without identified contraindications, 36% were not anticoagulated and had moderate or high CHADS2 risk scores.

Table 2 illustrates the Cox model hazards for ischemic, hemorrhagic, and any stroke for patients on warfarin. The estimates are adjusted for CHADS2 comorbidities, age, race, and sex. The risk of ischemic stroke in patients with AF on warfarin is significantly (P < 0.05) lower across all cohort years. The risk of hemorrhagic stroke for patients on warfarin is higher but does not approach statistical significance. The hazard for any stroke is decreased significantly (P < 0.05) for warfarin users compared with nonusers for each cohort year and appears to closely parallel the ischemic stroke hazards. The adjusted hazard ratio for any stroke varied from 0.74 to 0.83 across cohort years.
slightly higher than our rates for the same time period (Table 1). A Danish study\textsuperscript{22} reports an increasing trend in warfarin use between 1995 and 2002 and a doubled rate from 13\% to 26\% in patients aged 80 to 99 years. Interestingly, this study shows plateauing or slight decline in warfarin use rates among men and older women after 2000.

The plateaued warfarin use rates in recent years (Figure 3) could indicate an evidence–practice gap or a ceiling effect reflecting the subgroup of patients with AF who may not need anticoagulation or have contraindications to it. Not all patients with AF, even those in the Medicare 65-years-and-older group, require warfarin; some low-risk patients in the 65- to 74-year-old age range may be reasonably managed on aspirin.\textsuperscript{12} However, analysis of warfarin use by risk stratification (supplemental Figure I) does not show differential use among the various risk groups. We found that 36\% of patients with no identified contraindications were not anticoagulated despite moderate or high CHADS\textsubscript{2} risk scores. In Bungard et al.'s\textsuperscript{7} review, anticoagulation treatment rates ranged from 15\% to 79\% among patients without contraindications. The Cardiovascular Health Study\textsuperscript{23} reports no significant difference in anticoagulation rates among those with and without contraindications. Although our data show a significant increase in warfarin use among patients with AF across the cohort years, warfarin remains underused.

The decrease in ischemic stroke rates (Figure 3, Table 1) among patients with AF mirrors the increase in warfarin use. The association of warfarin with reduced risk of ischemic stroke suggested by the findings shown in Figure 3 is confirmed by our time-to-stroke modeling (Table 2).

Hemorrhagic stroke rates appear to hold steady despite increasing warfarin use. Figure 3 and Table 1 show numbers representing AF patient stroke rates for each cohort year regardless of warfarin use by individual patients. Hence, one could infer an absence of significant increases in intracerebral hemorrhage rates in the Medicare AF population despite increased warfarin use in the population as a whole. Results of the

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Year & Ischemic Stroke & Hemorrhagic Stroke & Any Stroke \\
\hline
1992 & 0.81 (0.68–0.97) & 1.23 (0.72–2.10) & 0.83 (0.70–0.98) \\
1994 & 0.84 (0.72–0.97) & 1.08 (0.67–1.74) & 0.86 (0.75–0.99) \\
1996 & 0.73 (0.64–0.84) & 1.43 (0.94–2.18) & 0.76 (0.67–0.87) \\
1998 & 0.68 (0.59–0.78) & 1.28 (0.86–1.93) & 0.67 (0.63–0.82) \\
2000 & 0.74 (0.64–0.85) & 1.10 (0.74–1.63) & 0.74 (0.67–0.87) \\
\hline
\end{tabular}
\caption{Adjusted Hazard Ratios (AHR)\textsuperscript{*} With 95\% CI of Time-Dependent Warfarin-Use Variable on Time to Stroke After AF Diagnosis}
\end{table}
time-to-event modeling of the hemorrhagic stroke hazard among warfarin users suggest a greater risk, although it does not approach statistical significance for any cohort year. Hazard values for time to any stroke are dominated by ischemic stroke hazards because of much larger ischemic stroke event rates compared with hemorrhagic stroke. The hazard values suggest that the overall effect of warfarin on stroke risk is protective; however, because this article relies on observational data and is not a randomized clinical trial, causality cannot be established. Our analysis aimed not to establish warfarin’s beneficial effect on stroke risk in patients with AF, because this has already been shown in well-planned clinical trials. Rather, we validated that clinical trial results can be achieved in community practice even in large elderly groups of patients such as our Medicare cohorts.

An obvious epidemiologic question is the extent to which the notable decline in ischemic stroke rates across the cohort years (Figure 3) is the result of increased warfarin use or other factors such as increased recognition and management of hypertension. Our administrative data prevent us from answering this question directly. Unlike clinical trials, patients are not assigned to warfarin or nonwarfarin groups, but may transition between treatment groups; we cannot observe, for example, stroke trends in aspirin users across the cohort years. However, our results and other published data suggest that a combination of factors (increased warfarin use and improved management of risk factors) influence the observed stroke trends. The hazard ratios in the time-to-event models (Table 2) indicate that warfarin use is associated with reduced risk of ischemic stroke across the cohort years. The rising trend in warfarin use across these years would thus reasonably translate into a declining trend in ischemic stroke rates. PROGRESS trial data suggest that blood pressure reduction is protective against major vascular events even among anticoagulated patients with AF. NHANES data show nationwide improvement in rates of hypertension treatment and control through the 1990s. A community-based AF study reported declining ischemic stroke risk, rising antithrombotic use, and improved systolic blood pressures from 1980 to 2000. Despite rising warfarin use as shown in our data, hemorrhagic stroke rates remain stable. Plausibly, improved hypertension management influences observed stroke trends by helping reduce ischemic stroke rates and hemorrhagic stroke risk. In summary, AF prevalence in the general Medicare population is increasing. Warfarin use among patients with AF in this population shows an upward trend that seems to be plateauing, illustrating the continuing challenge of diffusion of trial evidence into clinical practice. The downward trend in ischemic stroke rates in the AF population, mirroring the rise in warfarin use, is encouraging. The hemorrhagic stroke rate appears to be fairly stable over time. Our work suggests that warfarin is still considerably underused in patients with CNVAF.

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Disclosures
None.

References
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