Use and Effectiveness of Warfarin in Medicare Beneficiaries With Atrial Fibrillation

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Background and Purpose—More than 2 million Americans have atrial fibrillation, and without antithrombotic therapy, their stroke rate is increased 5-fold. In randomized controlled trials, warfarin prevented 65% of ischemic strokes (hazard ratio [HR], 0.35; 95% CI, 0.26 to 0.48) compared with no antithrombotic therapy. However, the effectiveness of warfarin therapy outside of clinical trials is unknown, especially in black and Hispanic populations. Our goal was to quantify use of warfarin therapy, frequency of International Normalized Ratio monitoring, and effectiveness for stroke prophylaxis in Medicare beneficiaries with atrial fibrillation.

Methods—This was a cohort study of Medicare beneficiaries with atrial fibrillation who were hospitalized between March 1998 and April 1999 in all 50 US states. The primary outcome was incident hospitalizations for ischemic stroke based on validated International Classification of Diseases, 9th Revision, Clinical Modification codes.

Results—Two thirds of ideal anticoagulation candidates were prescribed warfarin on hospital discharge. In unadjusted analyses, the stroke rates per 100 patient years of warfarin therapy were 5.2 in (non-Hispanic) white Medicare beneficiaries, 10.6 in black beneficiaries, and 12.2 in Hispanic beneficiaries. After adjusting for comorbid conditions, warfarin prescription was more frequent and monitoring more regular in white Medicare beneficiaries than in black or Hispanic beneficiaries (P<0.0001). Warfarin use was associated with 35% fewer ischemic strokes (HR, 0.65; 95% CI, 0.55 to 0.76) compared with no antithrombotic therapy but was less effective in black and Hispanic beneficiaries (P for interaction=0.048).

Conclusions—The use, monitoring, and effectiveness of warfarin therapy are suboptimal in Medicare beneficiaries, especially in black and Hispanic beneficiaries. (Stroke. 2006;37:1070-1074.)

Key Words: atrial fibrillation ■ continental population groups ■ stroke ■ warfarin

In randomized trials of participants with atrial fibrillation, warfarin reduced ischemic stroke rate by 65% (hazard ratio [HR], 0.35; 95% CI, 0.26 to 0.48) compared with no antithrombotic therapy.1 Because clinical trials often excluded >90% of patients with atrial fibrillation and monitored warfarin therapy meticulously,2,3 the effectiveness of warfarin therapy is likely to be lower in clinical practice. To date, the effectiveness of warfarin has been quantified only in cohorts that were small4-7 or had access to well-managed anticoagulation clinics.8 Furthermore, even the largest trial of anticoagulants for atrial fibrillation included only 125 black subjects.9 Thus, the effectiveness of warfarin in general practice, and in minority populations in particular, is uncertain.

Indirect evidence suggests that warfarin therapy may be less effective in these minority populations. Compared with white patients, Hispanic and especially black patients are more likely to have strokes associated with diabetes or hypertension,10,11 and warfarin is no more protective for these noncardioembolic strokes than is aspirin.12 In this study, we quantify the use, monitoring, and effectiveness of warfarin therapy in Medicare beneficiaries of all races in all 50 US states and the District of Columbia.

Subjects and Methods

Data Set and Cohort Formation

As detailed previously,13 we created the National Registry of Atrial Fibrillation II data set from 23 657 patient records gathered by quality improvement organizations/peer-review organizations (QIOs/PROs) for the National Stroke Project. The data set includes Medicare part A claims records and chart-abSTRACTed demographic and clinical data for Medicare beneficiaries who were hospitalized with atrial fibrillation. All US states and 3586 hospitals were included in this state-stratified random sample. Using an anonymous

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The conclusions presented are solely those of the authors and do not represent those of the QIOs/PROs, American Heart Association, or CMS. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of commercial products imply endorsement of them by the US Government. The authors assume full responsibility for the accuracy and completeness of the ideas presented.

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Outcomes Assessment and Data Analysis
We used logistic regression to quantify prescription of warfarin based on race, ethnicity, new versus previous atrial fibrillation, atrial fibrillation at discharge, relative contraindications to antithrombotic therapy,14 fall propensity,13 nursing home residency, neuropsychiatric disorders and risk of stroke (CHADS2 score).16,17 We calculated the CHADS2 score by adding 1 point for each of the following conditions: congestive heart failure, hypertension, age >75 years, or diabetes, and 2 points for a previous stroke or transient ischemic attack. We quantified relative contraindications to antithrombotic therapy using the HEMORR2HAGES bleeding score.14 Hepatic or renal disease, Ethanol abuse, Malignancy, Older age (>75 years), Reduced platelet count or function, Rebleeding risk (ie, a previous bleed), Hypertension (uncontrolled), Anemia, Genetic factors (not available), Excessive fall risk (including neuropsychiatric disease), Stroke. We defined loss to follow-up as absence of INR monitoring in the first 90 days after baseline in beneficiaries discharged with warfarin prescription. From the analysis of warfarin effectiveness, we excluded patients who were lost to follow-up or had >90 days between INR monitoring visits.

We identified ischemic strokes by recently validated13 International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (433.x1, 434.x1, 437.1, 437.9) in Medicare part A records. To improve specificity for acute stroke, we omitted ICD-9-CM codes for transient cerebral ischemia (435),19 for late hemorrhage are approximately 0.96 and 0.86 in the Medicare population.13 To assess the effect of warfarin on rate of ischemic stroke, we performed both unstratified and race-stratified analyses using a stepwise Cox proportional hazards model, adjusting for gender, CHADS2 stroke score, nursing home residency, and neuropsychiatric impairments. We censored patients at the earliest of: death, end of follow-up (December 31, 1999), probable changes in antithrombotic therapy, or hospitalization for hemorrhage or myocardial infarction. We identified probable changes in antithrombotic therapy from initiation or discontinuation of INR monitoring. For subjects who died outside of hospital, we censored patients at the time of last hospitalization. In addition, we excluded beneficiaries without discharge charges orders for warfarin but who had >1 INR monitoring visit within 90 days of discharge. We verified the proportional hazards assumption by time-dependent variables and graphically. We used SAS version 9.0 for statistical analyses.

Results

Cohort Characteristics
After exclusions (Appendix) the cohort consisted of 16 007 (92.7%: non-Hispanic) white, 797 (4.6%) black, and 468 (2.7%) Hispanic subjects. Mean age was 79.3 years, and mean CHADS2 stroke score was 2.7. Black patients were the youngest and had highest CHADS2 and HEMORR2HAGES scores. Previous stroke or transient ischemic attack was more common among black than white patients (odds ratio [OR], 1.3; 95% CI, 1.2 to 1.4) and marginally higher among black than Hispanic patients (OR, 1.2; 95% CI, 1.0 to 1.4). White subjects were significantly more likely to have a history of prebaseline atrial fibrillation. The most common reasons for the baseline hospitalization were heart failure (15.7%), atrial fibrillation (13.5%), coronary artery disease (8.8%), and pneumonia (6.6%). Patients averaged 2.2 outpatient visits per month after the baseline hospitalization, regardless of race/ethnicity (Table). For patients who did not experience stroke in the postbaseline period, the mean follow-up time was 11.4 months.

Racial Differences in Warfarin Prescription and Monitoring
Warfarin therapy was prescribed or planned for 49.1% of patients at discharge and aspirin was prescribed or planned for 30.8% (Table). The rate of warfarin prescription was 64.6% among the ideal candidates (CHADS2 stroke score >1 and HEMORR2HAGES bleeding score <2). Compared with (non-Hispanic) white patients, the adjusted ORs (95% CI) for warfarin prescription were 0.69 (0.60 to 0.81) in black and 0.50 (0.41 to 0.62) in Hispanic patients. Of Medicare beneficiaries discharged on warfarin, black and Hispanic patients were more likely to be lost to INR monitoring (21.3% and 16.7%, respectively) than white patients (9.7%) and to have warfarin monitored less than every 90 days (17.9% in black, 13.6% in Hispanic and 7.9% in white patients).

Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>White (n=16 007)</th>
<th>Black (n=797)</th>
<th>Hispanic (n=468)</th>
<th>P (racial difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>79.4 (7.3)</td>
<td>78.3 (7.9)</td>
<td>79.1 (7.4)</td>
</tr>
<tr>
<td>Male gender</td>
<td>43.5%</td>
<td>35.9%</td>
<td>50.9%</td>
</tr>
<tr>
<td>CHADS2 score, mean (SD)</td>
<td>2.6 (1.4)</td>
<td>3.1 (1.4)</td>
<td>2.9 (1.3)</td>
</tr>
<tr>
<td>HEMORR2HAGES score, mean (SD)</td>
<td>2.3 (1.5)</td>
<td>2.4 (1.5)</td>
<td>2.0 (1.4)</td>
</tr>
<tr>
<td>Warfarin at discharge</td>
<td>49.7%</td>
<td>43.2%</td>
<td>40.2%</td>
</tr>
<tr>
<td>Aspirin at discharge</td>
<td>31.1%</td>
<td>29.2%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Nursing home</td>
<td>20.6%</td>
<td>23.8%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Neuropsychiatric impairment</td>
<td>13.8%</td>
<td>18.9%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack history</td>
<td>28.6%</td>
<td>36.2%</td>
<td>30.9%</td>
</tr>
<tr>
<td>No atrial fibrillation before baseline</td>
<td>24.1%</td>
<td>27.4%</td>
<td>37.6%</td>
</tr>
<tr>
<td>Outpatient visits per month, median</td>
<td>2.2</td>
<td>2.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

CHADS2 stroke score and the HEMORR2HAGES bleeding score were calculated as described in the text and elsewhere.14,17
Ischemic Stroke

Overall, the rate (95% CI) of stroke per 100 patient years of warfarin was 5.2 (4.6 to 5.8) for white, 12.2 (8.0 to 18.5) for black, and 10.6 (6.0 to 18.7) for Hispanic Medicare beneficiaries. In a Cox model adjusting for race, CHADS2 score, nursing home residency, and neuropsychiatric impairment, warfarin use was associated with 35% fewer ischemic strokes (HR, 0.65; 95% CI, 0.55 to 0.76) compared with no therapy and 25% fewer ischemic strokes (HR, 0.75; 95% CI, 0.63 to 0.89) compared with aspirin. However, the difference in warfarin effectiveness compared with no antithrombotic therapy varied among the 3 cohorts (P=0.048 for interaction): warfarin appeared protective in (non-Hispanic) white patients (HR, 0.61; 95% CI, 0.52 to 0.72) but not in black (HR, 1.49; 95% CI, 0.78 to 2.85), or Hispanic patients (HR, 0.98; 95% CI, 0.45 to 2.11). Likewise, warfarin was more protective than aspirin in white (HR, 0.70; 95% CI, 0.58 to 0.83) but not in black (HR, 2.04; 95% CI, 0.90 to 4.61), or Hispanic (HR, 1.39; 95% CI, 0.48 to 4.00) beneficiaries. A lower effectiveness of warfarin in minority populations remained after matching black and white subjects on frequency of monitoring, neuropsychiatric impairments, and stroke risk factors. Warfarin effectiveness also was significantly lower for patients with neuropsychiatric impairments than for those without (P=0.01 for interaction). In an adjusted model, patients discharged with a warfarin prescription or plan for warfarin but who were lost to follow-up were more likely to have a stroke than either patients on warfarin therapy who had INR monitoring visits (HR, 2.7; 95% CI, 2.1 to 3.6) or patients who were discharged without warfarin prescription (HR, 1.7; 95% CI, 1.3 to 2.2).

Postbaseline Bleeding

In a Cox model that controlled for HEMORRHAGES score, warfarin and race were significant predictors of subsequent hospitalizations with bleeding. The HR (95% CI) of warfarin being discharged without a warfarin prescription (HR, 1.7; 95% CI, 1.3 to 2.2).

Discussion

We found that warfarin therapy was underutilized in Medicare beneficiaries with atrial fibrillation whose baseline hospitalization was in 1998 to 1999. The rate of warfarin prescription was 64% among beneficiaries with few contraindications to warfarin who were at significant risk for stroke. For comparison, older studies of similar patients8,20 reported slightly lower rates of warfarin use (38% to 61%). Warfarin use was especially low in black and Hispanic beneficiaries. Although black beneficiaries were more likely to have had a previous stroke, they were 31% less likely to be discharged on warfarin, and Hispanic Medicare beneficiaries were 50% less likely to receive warfarin than (non-Hispanic) white beneficiaries. Inadequate INR monitoring was common, especially in black and Hispanic beneficiaries.

The effectiveness of warfarin therapy was also disappointing. In clinical trials, participants randomized to warfarin had 65% fewer strokes than patients randomized to no antithrombotic therapy1 and 52% fewer strokes than patients randomized to aspirin.28 In our study, warfarin was associated with only a 35% reduction (HR, 0.65) compared with no antithrombotic therapy and a 25% (HR, 0.75) reduction compared with aspirin. The results were even more discouraging in black and Hispanic Medicare beneficiaries, for whom there was no evidence that warfarin prevented strokes. Largely because of the disappointing effectiveness of warfarin therapy in black and Hispanic Medicare beneficiaries, they experienced twice the rate of ischemic stroke. Likewise, nonwhite Medicaid patients prescribed warfarin for atrial fibrillation experienced twice the rate of ischemic stroke compared with white Medicaid patients in a recent study.21 How the current study should affect physician prescribing depends on whether the disappointing effectiveness of warfarin in Medicare beneficiaries is caused by biological or psychosocial factors or by confounding.

It is unlikely that the race–warfarin interaction is primarily biological. Although the prevalence of certain cytochrome P450 2C9 polymorphisms vary across races,22 they affect warfarin clearance rather than effectiveness. Although polymorphisms in the vitamin K epoxide reductase gene affect warfarin sensitivity and vary in prevalence in different populations,23 warfarin resistance can be overcome by greater warfarin doses. Furthermore, if warfarin resistance had played a significant role in the greater stroke rate in black patients prescribed warfarin, their hemorrhage rates should have been lower, whereas the opposite was observed. A more likely explanation is that black and Hispanic patients experience noncardioembolic strokes more commonly, the type of ischemic strokes that warfarin is less effective at preventing. These noncardioembolic strokes reflect a greater burden of diabetes and hypertension in these populations.

The suboptimal warfarin monitoring likely contributed to its disappointing effectiveness. Medicare beneficiaries, especially black and Hispanic patients, were followed less consistently than trial participants. We could not determine when poor monitoring was caused by the quality of or access to services versus patient noncompliance. However, after adjusting for frequency of INR monitoring, warfarin still appeared to be less effective in black and Hispanic Medicare beneficiaries, but this secondary analysis could not adjust for patient compliance.

Poor healthcare access, distrust of physicians, low perceptions of warfarin benefits, and inability to comprehend sophisticated educational materials contribute to noncompliance, especially in minority populations.24 Neuropsychiatric disease, which also contributes to noncompliance,25 was associated with lower warfarin effectiveness and was more common in black and Hispanic Medicare beneficiaries. Minority populations also have less access to cardiologists and to anticoagulation clinics, which facilitate warfarin therapy.26 Furthermore, when monitored by an anticoagulation clinic or clinical trial, patients are in their target INR range more commonly and have fewer adverse events.27 In summary, psychosocial factors and fragmentation of health services likely contribute to the suboptimal
effectiveness of warfarin in Medicare beneficiaries, especially in black and Hispanic beneficiaries.

The apparent lack of benefit of warfarin in the minority beneficiaries may have been exaggerated by chance. Although larger than in clinical trials, the black (n=797) and Hispanic (n=468) cohorts were relatively small, resulting in moderate power to quantify the interaction with warfarin effectiveness. Although warfarin had no significant protection from stroke in Hispanic beneficiaries, the 95% CI of the HR was wide (0.48 to 2.14) and included the possibility of up to a 52% stroke reduction. Also, confounding by indication may have exaggerated the apparent lack of protection of warfarin; if patients prescribed warfarin therapy were at greater risk of stroke, even after controlling for key comorbid conditions, then warfarin would appear to be less protective. Because confounding and poor monitoring may be responsible for the apparent poor protection against stroke, especially in minority populations, our findings should not be used to justify withholding warfarin therapy to any population.

Our study has potential limitations. First, it was impossible to determine patient compliance with warfarin therapy; we could only observe dates of INR monitoring. Second, ischemic stroke subtype could not be determined from the administrative data. Likewise, administrative data cannot capture all adverse events, especially if rapidly fatal. Third, some patients who did not have aspirin listed on their discharge medication sheet may have taken it. However, even if many patients not prescribed warfarin eventually began aspirin, the warfarin effectiveness that we observed (35%) is disappointing compared with randomized trials of warfarin versus aspirin.28 Finally, black race or Hispanic ethnicity may be a proxy for lower socioeconomic status, which correlates with greater stroke risk, but was not available in this study.

The limitations of our study are outweighed by its strengths. This is the only national study of the real-life effectiveness of warfarin therapy in elderly Medicare beneficiaries with atrial fibrillation and the first study to quantify the effectiveness of warfarin in minority populations with atrial fibrillation.

Our study has important implications. First, prescribing warfarin should be accompanied by a more consistent commitment for INR monitoring, especially at the time of hospital discharge and in minority populations. Second, anticoagulation clinics and patient self-testing should be encouraged by healthcare systems and payers. Since July 2002, Medicare has reimbursed physicians to monitor patient self-testing of INR but only in patients who have mechanical heart valves. There is no physician reimbursement to monitoring patient self-testing or other INR testing done outside of the physician’s office. Third, given the inconsistent monitoring and suboptimal use of warfarin therapy, there is a great need for anticoagulants that do not require monitoring. Finally, future clinical trials of anticoagulant therapy should enroll more diverse populations and test for a race–warfarin interaction. Ideally, these future studies would also determine whether genetic factors predict response to warfarin therapy.

Appendix

Exclusion Criteria

<table>
<thead>
<tr>
<th>24152 Patient-records</th>
<th>23588 Discharged Alive</th>
<th>23111 Patients</th>
<th>22292 Age 65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>20000 White, Black, or Hispanic</td>
<td>[19847 No Terminal illness]</td>
<td>19604 warfarin discharge orders not missing</td>
<td>17272 At least one Part B claim</td>
</tr>
</tbody>
</table>

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References


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