Adverse Outcomes and Predictors of Underuse of Antithrombotic Therapy in Medicare Beneficiaries With Chronic Atrial Fibrillation

Brian F. Gage, MD, MSc; Michael Boechler, PhD; Amy L. Doggette, MA; Gary Fortune, DO, MPH; Greg C. Flaker, MD; Michael W. Rich, MD; Martha J. Radford, MD

Background and Purpose—Antithrombotic therapy can prevent strokes and transient ischemic attacks (TIAs) in carefully selected patients who have chronic nonvalvular atrial fibrillation (NVAF). Our objectives were 3-fold: to document the use of warfarin and aspirin therapy in Missouri Medicare beneficiaries with chronic NVAF; to identify factors associated with warfarin and aspirin underuse; and to determine the association between prescription of warfarin and aspirin at hospital discharge and adverse outcomes in this elderly, frail population.

Methods—We linked chart reviews from all Missouri hospitals to Medicare claims data from 1993 to 1996. From chart reviews, we documented Medicare beneficiaries’ demographic factors, comorbid conditions, and antithrombotic therapy prescribed at the time of hospital discharge. From Medicare claims, we determined the date of outcomes—death from any cause or hospitalization for an ischemic event (a stroke, a TIA, or a myocardial infarction).

Results—Only 328 (55%) of the 597 Medicare beneficiaries were prescribed antithrombotic therapy at hospital discharge: 34% received warfarin and 21% received aspirin. Advanced age, female gender, and rural residency predicted underuse of antithrombotic therapy. After controlling for these factors, as well as stroke risk factors and contraindications to anticoagulation, the prescription of warfarin was associated with a 24% relative risk reduction (RRR) in adverse outcomes ($P=0.003$). Prescription of aspirin was associated with a nonsignificant 5% RRR in these events ($P=0.56$).

Conclusions—The underuse of antithrombotic therapy in Medicare beneficiaries who have NVAF is associated with measurable adverse outcomes. The benefit of warfarin therapy may extend to frail, elderly patients, a group that was excluded from randomized controlled trials. The role of antiplatelet therapy in this population deserves further study because many of these patients have relative contraindications to warfarin. (Stroke. 2000;31:822-827.)

Key Words: aged ■ aspirin ■ atrial fibrillation ■ stroke prevention ■ warfarin

Stroke prophylaxis with antithrombotic therapy is a proven, cost-effective therapy for patients aged 65 to 75 years who have chronic nonvalvular atrial fibrillation (NVAF). The Atrial Fibrillation Investigators found that warfarin-sodium therapy reduced the rate of ischemic stroke by 68% and reduced the rate of the combined end point of death, stroke, or systemic embolism by 48%. Similarly, they found that aspirin therapy reduced the rate of stroke by approximately 25% and the combined end point of death, stroke, or systemic embolism by approximately 28%.

Despite these impressive results, antithrombotic therapy is prescribed inconsistently in the NVAF population. At least one fourth of the atrial fibrillation population receives no antithrombotic therapy. The reasons for this underuse are still emerging, but they include physician concern that the benefits of prescribing antithrombotic therapy in clinical trials may not translate into everyday practice. This concern may arise because the randomized trials excluded most of the potential participants, with some trials excluding >90% of screened patients. The most common reasons for trial exclusion were advanced age and relative contraindications to anticoagulation. Thus, these trials demonstrated the efficacy of warfarin under ideal circumstances, for patients with an average age of 69 or 70 years. Whether the results of these studies can be generalized to an older, sicker population remains controversial, and many physicians are ambivalent about prescribing warfarin to this population.

In North America, atrial fibrillation causes nearly 75 000 strokes or transient ischemic attacks (TIAs) each year. Because the risk of these adverse events increases with advancing age and with comorbid conditions, most of...
them occur in patients who are older or frail than trial participants. Thus, documenting the use and effectiveness of antithrombotic therapy in older, sicker populations may help to save lives and prevent ischemic events.

Our study had 3 goals. First, we documented the use of antithrombotic therapy at the time of hospital discharge in Missouri Medicare beneficiaries who had chronic NVAF. Second, we determined factors associated with its underuse. Third, we determined the association between prescription of antithrombotic therapy at hospital discharge and adverse outcomes in clinical practice. To accomplish these goals, the Missouri Patient Care Review Foundation (MPCRF) abstracted the hospital charts of a random sample of Medicare beneficiaries with chronic atrial fibrillation and then linked these abstractions with national Medicare administrative databases to determine the rate of death and other adverse outcomes.

Subjects and Methods

Case Selection
We reviewed Medicare Part A claims for all Missouri hospitals from October 1, 1993, through December 31, 1994. We identified 21,071 cases in which atrial fibrillation was a principal or secondary diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 427.31). We excluded patients who: died during the hospital admission, were aged <65 years, had an ICD-9-CM code of rheumatic heart disease (393–398), had a recent history of a cardiothoracic procedure, left against medical advice, or were transferred to another acute-care facility. After these exclusions, we selected a random sample (with slight oversampling of smaller hospitals) of 1,147 patients.

Of the 1,147 cases with a Medicare claim that included a diagnosis of atrial fibrillation, we excluded 203 cases because the atrial fibrillation was new onset, intermittent, or associated with valvular disease. We excluded 347 cases because no ECG or rhythm strip was recorded during the index hospitalization or because that recording did not document atrial fibrillation. Thus, the remaining 597 cases, which constitute our study sample, had chronic NVAF documented during their index admission. These patients had a median age of 80 years.

For the outcomes analysis, we excluded an additional 134 patients. We excluded 133 patients because they underwent surgery during the index hospitalization or were within 30 days of a surgery or traumatic accident. We excluded these patients from the outcomes analysis because many of these patients might have had their antithrombotic therapy changed once they recovered from their acute illness. We excluded 1 additional case because outcome information was not available. Thus, for our outcomes analysis we had a sample size of 463 patients. The median age in this sample was also 80 years.

Baseline Data Collection
Trained nurses at the Missouri Patient Care Review Foundation abstracted the 1,147 charts. They noted whether any of the following antithrombotic drugs were prescribed at hospital discharge: warfarin, aspirin, persantine, ticlopidine, or heparin. The average interrater agreement was excellent (kappa statistic = 92%). To simplify interrater agreement was excellent (kappa statistic = 0.7). Variables whose probability values were ≤0.10 were entered sequentially into the logistic regression model. For all analyses, we considered a 2-tailed P < 0.05 to be statistically significant. We used JMP 3.2 and SAS 6.12, both by the SAS Institute Inc, to perform the statistical analyses.

We used time-dependent analyses to determine the effect of antithrombotic therapy on adverse outcomes (death from any cause or hospitalization for an ischemic event). We included adverse outcomes that occurred within 500 days of the index hospitalization. Using Kaplan-Meier curves, we examined the effect of the 3 treatment options, warfarin, aspirin, or no therapy. For that graph, we classified the 9 patients who were discharged on both warfarin and aspirin in the warfarin group. We compared the survival curves using the log-rank statistic.

We used a Cox proportional hazards model to quantify the association between prescription of warfarin or aspirin and adverse outcomes. First, we used an unadjusted Cox model and then added the following covariates progressively: age, sex, stroke risk factors, and contraindications to antithrombotic therapy. From the final Cox model, with all of these variables included, we calculated the relative risk reduction (RRR) as 1 minus the hazard rate. Also from the final model, we estimated the 1-year absolute risk reduction of warfarin and aspirin by multiplying the RRRs by the 1-year probability of adverse outcomes observed in the no-therapy group. In a secondary analysis, we used the final model to determine the independent association between the antithrombotic therapy prescribed and a composite outcome of stroke or TIA. In this secondary analysis we censored deaths, except deaths that occurred at the time of a stroke or TIA.

Results

Predictors of Antithrombotic Therapy Use
Overall, 34% of patients were prescribed warfarin, 21% were prescribed aspirin, and 45% were not prescribed any anti-
thrombotic therapy (Table 1). In univariate analyses, patient age and gender were significantly related to antithrombotic therapy prescription, as was location of the facility at which treatment occurred: Patients aged ≥76 years were less likely to receive antithrombotic therapy than were younger patients (P < 0.001), females were less likely than males to receive antithrombotic therapy (P = 0.02), and patients treated in rural facilities were prescribed antithrombotic therapy less frequently than patients in metropolitan facilities (P = 0.02).

Of the relative contraindications to antithrombotic therapy, history of hemorrhage (P < 0.001), recent surgery or trauma (P = 0.001), blood dyscrasia (P < 0.001), and renal or hepatic disease (P = 0.04) were significantly associated with lower use of antithrombotic therapy. Of the specific stroke risk factors, only a history of prior embolic event was associated with significantly higher antithrombotic use (P = 0.003).

Multivariate analysis corroborated the results of the univariate analyses: We found underuse of antithrombotic therapy in NVAF populations that were elderly, female, or rural. Compared with younger patients, the odds (95% CI) of receiving antithrombotic therapy were 1.7 (1.2 to 2.5) times lower in patients aged >75 years (P < 0.01). Likewise, the odds (95% CI) of receiving antithrombotic therapy were 1.5 (1.0 to 2.1) times lower in female rather than male patients (P = 0.05) and 1.7 (1.2 to 2.5) times lower in patients discharged from a rural rather than an urban hospital (P < 0.05).

Among 195 ideal anticoagulation candidates, defined as patients with no contraindication to anticoagulation and at least 1 stroke risk factor (in addition to their NVAF), 46% were prescribed warfarin, 23% were prescribed aspirin, and 31% received no antithrombotic therapy. Among 111 ideal anticoagulation candidates aged ≥75 years, only 41% were prescribed warfarin and 22% were prescribed aspirin.

**Outcomes of Antithrombotic Therapy Use**

The Kaplan-Meier curves (Figure) demonstrated that patients who were prescribed antithrombotic therapy were significantly less likely to have an adverse outcome (death or hospitalization for an ischemic event; P = 0.0001). In a Cox proportional hazards model unadjusted for potential confounders, warfarin was associated with a 31% RRR in the rate of an adverse outcome (P = 0.001) while aspirin was associated with a nonsignificant 11% RRR (P = 0.19). When we adjusted for potential confounders in the Cox proportional hazards model (Table 2), warfarin therapy was associated with a 24% RRR in the rate of an adverse outcome (P = 0.003) while aspirin was associated with a nonsignificant 5% RRR (P = 0.56).

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**TABLE 1. Univariate Analyses of Comorbid Conditions and Demographic Factors and Their Effect on Antithrombotic Therapy Prescribed**

<table>
<thead>
<tr>
<th>Antithrombotic Therapy Prescribed at Discharge</th>
<th>Patients, n</th>
<th>Warfarin, %</th>
<th>Aspirin, %</th>
<th>Neither, %</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>597</td>
<td>34</td>
<td>21</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–75</td>
<td>197</td>
<td>42</td>
<td>23</td>
<td>36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;75</td>
<td>400</td>
<td>29</td>
<td>21</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>269</td>
<td>38</td>
<td>22</td>
<td>42</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>328</td>
<td>29</td>
<td>21</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Hospital location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>158</td>
<td>30</td>
<td>17</td>
<td>54</td>
<td>0.02</td>
</tr>
<tr>
<td>Urban</td>
<td>439</td>
<td>36</td>
<td>23</td>
<td>42</td>
<td></td>
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<tr>
<td>Prior history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Embolic event</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>151</td>
<td>41</td>
<td>23</td>
<td>38</td>
<td>0.005</td>
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<tr>
<td>No</td>
<td>446</td>
<td>30</td>
<td>21</td>
<td>51</td>
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<td>Hemorrhage</td>
<td></td>
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<tr>
<td>Yes</td>
<td>82</td>
<td>21</td>
<td>20</td>
<td>63</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>515</td>
<td>36</td>
<td>24</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Blood dyscrasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>117</td>
<td>24</td>
<td>16</td>
<td>60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>480</td>
<td>35</td>
<td>23</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Renal or hepatic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>75</td>
<td>21</td>
<td>20</td>
<td>62</td>
<td>0.04</td>
</tr>
<tr>
<td>No</td>
<td>522</td>
<td>35</td>
<td>21</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

*In calculating P values, the proportion of patients receiving warfarin, aspirin, or both was compared with the proportion receiving neither. Percentages in rows add to slightly over 100% because some patients were prescribed both warfarin and aspirin.*
By multiplying these RRRs by the 1-year probability of adverse outcomes in untreated patients, we estimated the absolute risk reductions associated with prescribing antithrombotic therapy. In the first year after their index hospitalization, patients who were not prescribed antithrombotic therapy had a 37% probability of suffering an adverse outcome. The annual absolute risk reduction for an adverse outcome was 8.9% with warfarin therapy and 1.9% with aspirin therapy. Thus, approximately 1 death or hospitalization for an ischemic event was averted for each 11 patient-years of warfarin therapy and for each 54 patient-years of aspirin therapy.

In a secondary analysis we examined the association of antithrombotic therapy with hospitalization for stroke or TIA. Among the 463 patients included in this analysis, 33 suffered strokes or TIAs: 9 of these occurred in the 163 patients who were prescribed warfarin, 8 occurred in the 96 patients who were prescribed aspirin, and 16 occurred in the 204 patients who were prescribed neither therapy. In the Cox model that focused on stroke and TIA, warfarin was associated with a nonsignificant 30% RRR \((P=0.4)\) in strokes or TIAs while aspirin was associated with no reduction in these events \((\text{RRR}=−5\%, \ P=0.9)\).

In light of the overwhelming evidence\(^2-5,20-22,37\) that stroke can be prevented by antithrombotic therapy, the low use of warfarin and aspirin in Medicare beneficiaries is disappointing and concerning. Of 597 Missouri Medicare beneficiaries with chronic NVAF, only 328 (55%) were prescribed antithrombotic therapy at hospital discharge: 201 (34%) received warfarin and 127 (21%) received aspirin therapy. The use of antithrombotic therapy was especially low in elderly, female, and rural populations.

The low use of warfarin that we observed corroborates the findings in other populations with atrial fibrillation.\(^9-16\) For example, Stafford and Singer\(^11\) found that the use of antithrombotic therapy was 32% among outpatients with atrial fibrillation who saw a physician in 1992 or 1993. Gurwitz and colleagues\(^12\) found a similar use of antithrombotic therapy among residents living in a long-term care facility between 1993 and 1995. Albers and colleagues\(^12\) noted that at discharge from a university hospital, 44% of ideal anticoagulation candidates were prescribed warfarin—a finding almost identical to the 46% use that we found in the ideal candidates discharged from Missouri hospitals.

There appear to be 2 main reasons for the low use of antithrombotic therapy: inconvenience\(^38\) and physicians’ fear of hemorrhage.\(^16,18,19,28\) Compared with urban patients, rural patients often travel farther to have their INRs monitored, and this greater inconvenience may contribute to their lower use of warfarin.\(^9\) Physicians’ fear of hemorrhage likely arises because the risk of hemorrhage doubles in patients prescribed anticoagulants outside of experimental trials\(^39,40\) and because physicians attach a greater negative value to hemorrhagic strokes than to ischemic ones, even when the health outcomes are the same.\(^41\) The emphasis on avoiding hemorrhagic strokes and other iatrogenic events may cause physicians and patients to choose therapy that minimizes side effects rather than therapy that maximizes benefit.\(^42,43\)

Physicians’ aversion to causing a hemorrhagic stroke\(^16,18,19,27,28\) also may account for the underuse of antithrombotic therapy in the very elderly. Even when we controlled for their higher prevalence of comorbid conditions, Medicare beneficiaries aged \(>75\) years were 1.7 times less likely to receive antithrombotic therapy than younger beneficiaries. Ironically, because of their higher risk of stroke, the net benefit of antithrombotic therapy may be greater in octogenarians than in younger patients.\(^1,2\) The tendency of

**TABLE 2. Association of Antithrombotic Therapy at Discharge and Adverse Outcomes (500-Day Death or Hospitalization for Ischemic Event.)**

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.69 (0.57–0.82)*</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>0.79 (0.66–0.95)*</td>
</tr>
<tr>
<td>Adjusted for age, sex, and stroke risk factors</td>
<td>0.74 (0.61–0.89)*</td>
</tr>
<tr>
<td>Adjusted for age, sex, stroke risk factors, and contraindications to antithrombotic therapy</td>
<td>0.76 (0.62–0.91)*</td>
</tr>
</tbody>
</table>

\(N=463.\)

\(*P<0.01.\)
physicians to use subtherapeutic INRs when they prescribe warfarin in the very elderly\textsuperscript{1,2,10,27} further supports the hypothesis that selection of therapy is based more on avoiding iatrogenic complications than on maximizing expected benefit.

Like the very elderly, the female atrial fibrillation population may be undertreated, but the explanation for their undertreatment is less clear.\textsuperscript{36} Antithrombotic therapy is no less effective in women than in men,\textsuperscript{2} and rates of major hemorrhage are similar in both sexes.\textsuperscript{39}

Inherent to any observational study, our analysis has several limitations. First, we obtained baseline information about the patients and their therapy from chart review. Although the interrater reliability of chart abstraction was excellent, factors relevant to the choice of antithrombotic therapy, such as patients’ preferences,\textsuperscript{44,45} may not have been recorded in the hospital charts. A second limitation is that our analyses relied on charts of beneficiaries hospitalized on or before December 1994, and use of antithrombotic therapy in the NVAF population may be more prevalent today.\textsuperscript{11,31} Third, although we documented the therapy prescribed at the time of hospital discharge, we could not assess the use of antithrombotic therapy during the follow-up interval. Thus, we performed intent-to-treat analyses of the outcomes, rather than on-treatment analyses. Fourth, although we controlled for stroke risk factors and for contraindications to antithrombotic therapy in our outcomes analyses, potential for residual confounding effects remained. Finally, we used administrative data, rather than chart reviews, to assess outcomes.

There are several possible explanations for why the RRRs we observed were lower than the RRRs reported in the clinical trials. First, compliance with antithrombotic therapy, especially with warfarin, is likely to be lower in practice than in the clinical trials.\textsuperscript{46} Second, physicians tend to use suboptimal INRs when treating elderly patients.\textsuperscript{77} Third, our RRRs—24\% for warfarin and 5\% for aspirin—were based on a composite end point of death from any cause and hospitalization for an ischemic event (stroke, TIA, or myocardial infarction). We used a composite outcome as our primary end point because of its clinical relevance and its ability to capture fatal ischemic events that did not result in a hospitalization in Missouri. Finally, the true benefit of antithrombotic therapy in this elderly, frail population may be less than the benefit reported from the clinical trials.

Despite the modest RRRs observed in this population, the absolute risk reductions were substantial. Approximately 1 death or nonfatal ischemic event was averted for each 54 patient-years of aspirin therapy and for each 11 patient-years of warfarin therapy. By applying the latter figure to the 20 000 Missouri Medicare beneficiaries who are hospitalized with NVAF annually, we estimate that increasing the appropriate use of warfarin therapy by 5\% could avert 91 deaths or hospitalizations in the subsequent year.

Our study demonstrates that antithrombotic therapy has been underused in Medicare beneficiaries who have NVAF and that this underuse has led to measurable adverse outcomes. The benefits of warfarin therapy appear to extend to frail, elderly patients, a group that was excluded from randomized controlled trials. Because many of these patients had contraindications to warfarin therapy, further study of antiplatelet therapy in this population is warranted.

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**References**


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