Translating the Results of Randomized Trials into Clinical Practice

The Challenge of Warfarin Candidacy Among Hospitalized Elderly Patients With Atrial Fibrillation

Elaine M. Hylek, MD, MPH; James D’Antonio, MD; Carmella Evans-Molina, MD; Carol Shea, RN; Lori E. Henault, MPH; Susan Regan, PhD

Background and Purpose—Numerous studies have documented under use of warfarin particularly among elderly patients. A better understanding of the discrepancy between trials and clinical practice will help inform stroke prevention strategies in this vulnerable age group. The study objective was to prospectively assess the use of antithrombotic therapy among a contemporary cohort of patients with atrial fibrillation at the time of hospital discharge. In addition to baseline characteristics, we sought to define the physician-cited reason for not prescribing warfarin for each patient.

Methods—Patients with atrial fibrillation were prospectively identified and followed to hospital discharge. Enrolled patients were ≥65 years of age, not taking warfarin on admission, and had their longitudinal care provided at our institution. Predictors of warfarin use were determined and physician-cited contraindications were compared across age groups.

Results—Fifty-one percent (n = 206) of patients were discharged on warfarin: 75% of those 65 to 69 years of age, 59% 70 to 79, 45% 80 to 89, and 24% age ≥90 years. Of the remaining 199 patients, 83% had ≥2 major risk factors for stroke, and 98% were felt to have contraindications including nearly 25% who were unable to tolerate warfarin in the past. Among patients age ≥80, falling was the most often physician-cited reason for not prescribing warfarin (41%) followed by hemorrhage (28%).

Conclusion—Our findings suggest that many elderly patients at high risk for stroke may not be optimal candidates for anticoagulant therapy. There is a pressing need for alternative stroke prevention strategies for this expanding patient population. (Stroke. 2006;37:1075-1080.)

Key Words: atrial fibrillation □ geriatrics □ warfarin

Approximately 25% of strokes in patients age ≥80 years are attributable to atrial fibrillation (AF). AF–related stroke is associated with a 30-day mortality of ≈24%. The prevalence of AF increases with age approaching 10% for individuals age ≥80 years. It is projected that 3.3 million adults in the United States will have AF by the year 2020 largely attributable to the aging of our population.

Warfarin has been shown to be highly effective in preventing stroke in AF. Despite its proven benefit, numerous studies have documented under use of warfarin particularly among elderly patients who would seem to benefit the most from anticoagulant therapy. These findings have raised concerns regarding quality of care, physician adherence to guidelines, and translation of clinical trial results into real-world practice.

An important unanswered question is whether published estimates of warfarin use represent inappropriate under-prescribing or withholding of therapy attributable to questionable patient candidacy for a class of drugs with associated toxicity. Estimates of warfarin use vary depending on study methodology. Existing data, based largely on retrospective studies or secondary analyses, may overestimate the proportion of patients eligible for anticoagulation because of incomplete identification of contraindications. Resolution of this issue is central to the care of aging patients. Published low rates of warfarin use have importantly focused attention on the need to better inform physicians and patients on the benefits and risks of anticoagulant therapy. However, if the low rate of warfarin use represents a growing and problematic group of patients in whom anticoagulant therapy is felt not to be safe, a critical problem in stroke prevention is emerging. Patients at the highest risk of stroke currently have little in the way of an effective alternative. Given the proven benefit...
of anticoagulant therapy, it is important that we understand
the factors that are driving the discrepancy between published
recommendations and actual practice. Direct patient-level
assessment is needed to better inform strategies aimed at
optimizing stroke prevention in this vulnerable age group.

The objective of our study was to prospectively assess the
use of antithrombotic therapy among a contemporary cohort
of patients with AF at the time of hospital discharge. In
addition to baseline characteristics, we also sought to deter-
mine the physician-cited reason for not prescribing warfarin
for each patient.

Methods

Study Participants
Consecutive patients were prospectively identified by daily searches
of electronic admission notes and ECGs of all patients admitted to
the medical service of our hospital from January 2001 to June 2003.
Searches intentionally did not include patients admitted to the
surgical service or stroke unit. To be eligible, patients had to be ≥65
years of age, had to have AF verified by ECG, could not be taking
warfarin on admission or have another indication for long-term
therapy, and had to have their longitudinal care provided by a
physician at our institution. The eligibility criterion related to site of
care minimized referral bias of more complex procedure-oriented
patients and ensured that the anticoagulation decision would not be
defered at the time of discharge to the patient’s outside physician. It
also ensured access to the comprehensive ambulatory and hospital
medical records. In addition, the presence of an on-site anticoagula-
tion clinic helped to minimize any logistical barriers to warfarin
prescription.

Baseline Patient Characteristics
Demographic data and medical diagnoses were extracted from the
medical record. Major risk factors for stroke included age ≥75 years,
diabetes mellitus, heart failure, hypertension, prior stroke, and age ≥65
years with coronary artery disease.24–26 Risk factors for hemorrhage
and potential contraindications to warfarin included history of hemorrhage,
falls, cognitive impairment or dementia, active alcohol abuse, liver
disease, advanced malignancy, and renal dysfunction defined as creat-
inine concentration >133 μmol/L or 1.5 mg/dL.27 To better discern
absolute versus relative contraindication, hemorrhage was further de-
defined as (1) intracranial, (2) recurrent, (3) related to the index hospital-
ization, or (4) warfarin-related. Similarly, prior falls were further
characterized by the presence or absence of associated head trauma or
fracture. Past history of warfarin use and reason for discontinuation were
also recorded.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of Hospitalized Patients With AF, Stratified by Warfarin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, y, mean</td>
</tr>
<tr>
<td>Women, n (%)</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
</tr>
<tr>
<td>AF, n (%)</td>
</tr>
<tr>
<td>First clinical episode</td>
</tr>
<tr>
<td>Recurrent episode</td>
</tr>
<tr>
<td>Persistent</td>
</tr>
<tr>
<td>Risk factors for stroke, n (%)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Prior stroke</td>
</tr>
<tr>
<td>Risk factors for stroke, n (%)</td>
</tr>
<tr>
<td>No major</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>≥3</td>
</tr>
<tr>
<td>Risk factors for hemorrhage, n (%)</td>
</tr>
<tr>
<td>Prior hemorrhage</td>
</tr>
<tr>
<td>Prior fall</td>
</tr>
<tr>
<td>Cognitive impairment/dementia</td>
</tr>
<tr>
<td>Active alcohol abuse</td>
</tr>
<tr>
<td>Advanced malignancy</td>
</tr>
<tr>
<td>Renal dysfunction*</td>
</tr>
<tr>
<td>Liver disease</td>
</tr>
<tr>
<td>Length of hospital stay, d, median</td>
</tr>
</tbody>
</table>

*Creatinine concentration >133 μmol/L or 1.5 mg/dL.
Discharge Antithrombotic Medication and Physician-Cited Reason for Not Prescribing Warfarin

Patients were followed from hospital admission to the day of discharge. Prescription of antithrombotic therapy was ascertained from 2 sources: the discharge summary and the electronic discharge medication list. The reason for not prescribing warfarin was recorded as explicitly stated in the discharge summary or, if ambiguous, as clarified by the treating physician on inquiry by the study nurse.

The study was approved by the institutional review board at Massachusetts General Hospital (Boston, Mass). The nature of the study did not require written informed consent.

Statistical Analysis

Baseline characteristics of patients according to warfarin status were compared using $\chi^2$ test for proportions for categorical variables and Student $t$ test for continuous variables. Independent predictors of warfarin use were determined using multivariate logistic regression. Variables whose probability values were $\leq 0.10$ on univariate analysis were included in the multivariate model. For all analyses, a 2-sided probability value $<0.05$ was considered statistically significant. For the subset of patients who were not discharged on warfarin, we also sought to define the patient features associated with prescription of either low dose aspirin, 81 mg per day, or no antithrombotic therapy compared with those patients discharged on full dose aspirin, 325 mg per day. Five patients with missing data on aspirin dose were excluded from this analysis. Analyses were performed using Stata statistical software, release 8.0 (Stata Corporation).

Results

Patient Clinical Characteristics

During the study period, 426 patients were identified with ECG-verified AF, were $\geq 65$ years of age, were not taking warfarin on admission, and had an established physician at our institution. Twenty-one patients died before discharge. Of the 405 patients, 74% were age $\geq 75$ years (51% 80 years or greater), 74% had hypertension, 47% heart failure, and 12% prior stroke (Table 1). Ninety-seven percent of those 65 to 69 years of age, 75% of those 65 to 69 years of age, 75% of those 70 to 79, 45% 80 to 89, and 24% age $\geq 90$ ($P<0.001$). Seventy-five percent of patients starting warfarin had $\geq 2$ major stroke risk factors versus 83% of those patients not taking warfarin. Patients starting warfarin were younger, more likely to be male, newly presenting with AF, and less likely to have a history of hemorrhage, falls, or cognitive impairment. Twenty-two percent of patients not started on warfarin had at least 1 documented spontaneous fall that resulted in closed head trauma or an orthopedic fracture. Among patients age $\geq 80$ years, falling-related hemorrhage for 33% (n=66), falls for 32% (n=64), and patient refusal or history of nonadherence for 14% (n=27). To better validate hemorrhage, we further characterized the bleeding experienced by those patients with hemorrhage cited as the reason warfarin was not prescribed. Of the 66 patients, 31 had recurrent bleeding, 9 had a prior intracranial hemorrhage, 16 had evidence of bleeding during the index hospitalization, and 7 of the remaining 10 patients had sustained a warfarin-related hemorrhage in the past. Among patients with falls cited as the contraindication, 53% had at least 1 documented spontaneous fall that resulted in closed head trauma or an orthopedic fracture. Among patients age $\geq 80$ years, falling

<table>
<thead>
<tr>
<th>Reason</th>
<th>All, n=199*</th>
<th>&lt;80 Years, n=76</th>
<th>$\geq$80 Years, n=123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage, n (%)</td>
<td>66 (33)</td>
<td>32 (42)</td>
<td>34 (28)</td>
</tr>
<tr>
<td>Recurrent bleeding</td>
<td>31 (16)</td>
<td>17 (22)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Current bleeding</td>
<td>16 (8)</td>
<td>7 (9)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Past intracranial bleeding</td>
<td>9 (4)</td>
<td>3 (4)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Past other bleeding</td>
<td>10 (5)</td>
<td>5 (7)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Falls</td>
<td>64 (32)</td>
<td>14 (18)</td>
<td>50 (41)</td>
</tr>
<tr>
<td>Patient refused or history of nonadherence</td>
<td>27 (14)</td>
<td>13 (17)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>6 (3)</td>
<td>1 (1)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Active alcohol abuse</td>
<td>4 (2)</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Advanced illness, comfort care</td>
<td>16 (8)</td>
<td>4 (5)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Other†</td>
<td>16 (8)</td>
<td>8 (11)</td>
<td>8 (7)</td>
</tr>
</tbody>
</table>

*Includes 46 (23%) patients who had been taken off warfarin in the past. Twenty-seven patients had sustained a warfarin-related hemorrhage (6 intracranial, 21 extracranial), and 19 patients had their warfarin discontinued because of falls (n=9), nonadherence (n=8), and other (n=2).
†Includes 2 patients with an intracranial mass, 2 table hypertension, 2 previous hypersensitivity reaction, 5 anticipated procedures, and major surgery, 4 normal sinus rhythm after cardioversion, 1 pericarditis.
was the most often-cited reason for not prescribing warfarin (41%) followed by hemorrhage (28%).

**Alternative Antithrombotic Therapy**

Overall, 44 patients (11%) were not discharged on any antithrombotic medication. Thirty-eight percent (n=155) of patients were discharged on antiplatelet therapy. We stratified discharge antithrombotic therapy and prescribed dose of aspirin by the physician-cited warfarin contraindication to gain insight into physician choice of alternative medication (Table 4). Among patients prescribed aspirin, 62% were taking 325 mg per day and 38% 81 mg. Hemorrhage was the only independent predictor of receiving either no antithrombotic therapy or low-dose aspirin versus full-dose aspirin at hospital discharge (adjusted odds ratio, 5.4 [95%CI, 2.1 to 13.7]). After controlling for bleeding complications, older patients were not more likely to be prescribed low-dose aspirin or no antithrombotic medication (adjusted odds ratio, 1.1 [95% CI, 0.7 to 1.6]). The breakdown of antithrombotic therapy at hospital discharge by age is shown in the Figure.

**Discussion**

AF is a powerful risk factor for stroke. Stroke is a leading cause of death and disability. Warfarin has been shown to reduce the risk of stroke in AF by 68% compared with placebo, which is far superior to the relative risk reduction of 21% associated with full-dose aspirin. Despite its proven efficacy, numerous studies have documented underutilization of warfarin, most notably in the elderly. In our study among 405 patients identified with AF, 51% (n=206) were discharged on warfarin. Of the remaining 199 patients, 97% had major risk factor for stroke and 83% had 2. All of these patients had been considered for anticoagulant therapy, reflecting an understanding of the stroke risk imparted by AF and current evidence-based guidelines. However, nearly all of these patients were felt to have contraindications that precluded its safe use including nearly 25% of patients who had taken warfarin in the past, but were unable to tolerate it long-term. Hemorrhage, falls, and patient refusal or history of nonadherence to therapy constituted nearly 80% of the physician-cited reasons for not prescribing warfarin. Currently, there is no effective treatment option for these patients. Despite its modest effect, aspirin is widely used in this setting.

Our study is the first prospective assessment of warfarin prescription at the time of the treatment decision among consecutive patients admitted and discharged with AF. In addition to baseline patient characteristics, we directly determined the reason for not prescribing warfarin for each patient. We independently validated the physician-cited contraindications of hemorrhage and falls and qualified their severity. Retrospective studies and studies based on secondary analysis of administrative databases have likely underreported contraindications and have overestimated warfarin eligibility among hospitalized patients of age ≥80 years. Accurate assessment of warfarin candidacy using these methodologies is limited by the extent of documentation and reliance on search strategies using ICD-9-CM codes (International Classification of Diseases, Ninth Edition, Clinical Modification) that would not comprehensively capture patient-specific clinical details. Most notably, recurrent nonhospitalized falls, previous attempts at warfarin use, recurrent bleeding, patient preference, patient nonadherence, excessive alcohol use, and comfort care status would not be systematically ascertained.
Our study illustrates the challenges that physicians and patients face when trying to apply recommendations derived from clinical trials to older patients with AF in real-world practice. Few patients >80 years were enrolled in the early trials of oral anticoagulation versus placebo. Two meta-analyses of these trials report 20% of the study population being ≥75 years of age. This is in contrast to the patients enrolled in our study of which 51% were ≥80 years of age (74% age ≥75 years). Two more recently conducted trials that compared warfarin to ximelagatran enrolled 16% of patients age ≥80 years (38% age ≥75). However, unlike the early AF trials that compared warfarin to placebo, 74% and 84% of patients, respectively, were taking a vitamin K antagonist at entry, thereby selecting populations at already proven lower risk for hemorrhage. Six percent of patients had a prior history of bleeding compared with 24% in this study.28–30

A limitation of our study is that it was conducted at a single center: a large, urban, teaching hospital which may not reflect other practice settings. However, our finding that 51% of patients with AF were discharged on warfarin is consistent with a study funded by the Health Care Financing Administration assessing the quality of care delivered to Medicare beneficiaries during the period 1998 to 1999.20 Using hospital claims data, performance in the median state was 55% and ranged from 42% to 65%. A more recent retrospective study of 21 teaching, 13 community, and 4 Veterans Administration hospitals similarly found that 55% of patients with AF were discharged on warfarin in 2002 (53% among the teaching hospitals).31 Another potential limitation of our study is that physicians who were directly queried may have altered their subsequent prescribing behavior. However, we would expect this bias to have resulted in more warfarin use. In addition, the reason for not prescribing warfarin was explicitly stated in the discharge summary for the majority of patients.

The study institution has several features that overcome limitations of other settings. The existence of an anticoagulation clinic minimized monitoring as a potential barrier to warfarin prescription. In addition, stroke awareness is high among physician staff, many of whom participated in the Boston Area Anticoagulation Trial for Atrial Fibrillation which helped to establish the efficacy of warfarin.32 Enrolled patients had established providers at our institution, which facilitated validation and severity assessment of contraindications in the outpatient and inpatient medical records, and ensured that the warfarin decision was not deferred to an outside provider. Because we did not include referral patients, we believe our study population is similar to that of other large, general, urban hospitals serving a Medicare population.

Our data suggest that among very elderly patients with AF the decision to prescribe warfarin is strongly influenced by contraindications. More research is needed to discern absolute from relative contraindications to help guide physicians and patients in their assessment of the overall risks and benefits of therapy.33–35 Strategies are needed to optimize candidacy among elderly patients, particularly interventions to reduce hemorrhage and falls.36–38 Prospective studies are needed to better define the true hazard of falls in the presence of anticoagulant therapy. In addition, our study underscores the need for continued research on the mechanisms of AF and triggers for thrombus formation, insights which may lead to alternative stroke prevention strategies without the attendant hemorrhagic risk.39–41

Summary

Despite the first published evidence of warfarin’s efficacy 16 years ago, prophylaxis against stroke in AF remains suboptimal particularly among those at highest risk, patients of age ≥80 years. Given the aging of the population, stroke prevention in AF is a pressing health imperative.

Acknowledgments

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