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Potentially Preventable Strokes in High-Risk Patients With Atrial Fibrillation Who Are Not Adequately Anticoagulated

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Background and Purpose—Warfarin is the most effective stroke prevention medication for high-risk individuals with atrial fibrillation, yet it is often underused. This study examined the magnitude of this problem in a large contemporary, prospective stroke registry.

Methods—We analyzed data from the Registry of the Canadian Stroke Network, a prospective database of consecutive patients with stroke admitted to 12 designated stroke centers in Ontario (2003 to 2007). We included patients admitted with an acute ischemic stroke who (1) had a known history of atrial fibrillation; (2) were classified as high risk for systemic emboli according to published guidelines; and (3) had no known contraindications to anticoagulation. Primary end points were the use of prestroke antithrombotic medications and admission international normalized ratio.

Results—Among patients admitted with a first ischemic stroke who had known atrial fibrillation (n=597), strokes were disabling in 60% and fatal in 20%. Preadmission medications were warfarin (40%), antiplatelet therapy (30%), and no antithrombotics (29%). Of those taking warfarin, three fourths had a subtherapeutic international normalized ratio (<2.0) at the time of stroke admission. Overall, only 10% of patients with acute stroke with known atrial fibrillation were therapeutically anticoagulated (international normalized ratio ≥ 2.0) at admission. In stroke patients with a history of atrial fibrillation and a previous transient ischemic attack or ischemic stroke (n=323), only 18% were taking warfarin with therapeutic international normalized ratio at the time of admission for stroke, 39% were taking warfarin with subtherapeutic international normalized ratio, and 15% were on no antithrombotic therapy.

Conclusions—In high-risk patients with atrial fibrillation admitted with a stroke, and who were candidates for anticoagulation, most were either not taking warfarin or were subtherapeutic at the time of ischemic stroke. Many were on no antithrombotic therapy. These findings should encourage greater efforts to prescribe and monitor appropriate antithrombotic therapy to prevent stroke in individuals with atrial fibrillation. (*Stroke*. 2009;40:235-240.)

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

Cardioembolism due to atrial fibrillation accounts for approximately one in 6 ischemic strokes (one in 4 in the elderly) and is a potentially preventable cause of stroke-related disability, dementia, and death.¹ Atrial fibrillation-related strokes are generally severe and 1-year mortality is estimated at 50%.¹ The prevalence of atrial fibrillation is reaching epidemic proportions and the public health implications are enormous.^{2,3} Over 2 million individuals have atrial fibrillation in the United States alone, and this figure is projected to increase to over 5.6 million by the year 2050.^{2,3}

Warfarin is highly effective for stroke prevention in atrial fibrillation, reducing the relative risk of ischemic stroke by 67% and death by approximately 25%, whereas antiplatelet

therapy reduces stroke risk by 22%.⁴ Guidelines have strongly recommended warfarin rather than aspirin for stroke prevention in individuals with atrial fibrillation (paroxysmal or persistent) who are older than age 75 years or who have any one of the following high-risk factors for thromboembolism: previous stroke, transient ischemic attack (TIA), or systemic embolism; history of hypertension; poor left ventricular systolic function; rheumatic mitral valve disease; or prosthetic heart valve.^{5,6} Warfarin is also recommended for patients with more than one of the following moderate-risk factors: age 65 to 75 years, diabetes, or coronary artery disease with preserved left ventricular function.⁶ Either warfarin or aspirin is recommended for patients with only one

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moderate-risk factor, and aspirin is sufficient if there are no high-risk or moderate-risk factors and no clinical or echocardiographic evidence of cardiovascular disease.⁶ Dual antiplatelet therapy with aspirin and clopidogrel is inferior to warfarin for stroke prevention in atrial fibrillation and associated with higher bleeding rates.⁷ The recommended target international normalized ratio (INR) is 2.5 (range, 2.0 to 3.0); stroke risk increases significantly with an INR <2.0.⁸ In addition to protecting against stroke, antithrombotic agents reduce stroke severity; patients taking warfarin at the time of stroke onset have less disabling strokes compared with individuals taking aspirin or no antithrombotic therapy, and stroke severity is negatively correlated with INR at stroke onset.^{8,9}

Despite numerous treatment guidelines based on convincing evidence from 29 high-quality randomized trials of antithrombotic therapy for atrial fibrillation since 1989,⁴ warfarin tends to be underused in patients who would benefit from such therapy.^{10–20} Using a large contemporary provincial registry of patients admitted with stroke, we investigated the type and intensity of antithrombotic use before ischemic stroke for patients with a known history of atrial fibrillation. We restricted our analysis to high-risk patients with atrial fibrillation for whom warfarin would be indicated and for whom there were no known contraindications to anticoagulation.

Methods

Design and Setting

This study is based on data from Phase 3 of the Registry of the Canadian Stroke Network (RCSN), the largest prospective practice audit of stroke care in Canada.²¹ Phase 3 is a nonconsent registry that captures data on all consecutive patients with stroke presenting to designated stroke centers. For the present study, we included data from all 10 of the primary (regional) stroke centers in Ontario, Canada, plus 2 Ontario district stroke centers. Data collection was performed by dedicated research coordinators who prospectively identified eligible patients through reviews of daily emergency department records and hospital admission logs. Chart abstraction was performed by trained coordinators. Standardized data collection forms with carefully defined fields were used to record patient demographics, stroke characteristics, stroke severity, medical history, medications (preadmission, in hospital, and discharge), diagnostic tests, treatments, and discharge disposition. Laboratory results, including INR at hospital admission, were recorded. Data were entered using specialized RCSN software that checks the ranges and internal consistency of data to increase data quality. The diagnosis of atrial fibrillation was obtained from the patient's medical history rather than by electrocardiography. Echocardiography for risk stratification was not performed. The validity and reliability of data from this stroke-specific registry are greater than that from administrative databases.²² Chart validation by repeat abstraction has shown excellent interrater reliability (kappa statistics or intraclass correlation coefficients >0.94) for key data elements in our registry, including history of atrial fibrillation, preadmission medications, and INR. The registry was approved by the research ethics boards at each of the participating institutions. Informed consent was not a requirement because only anonymized data were collected.

Eligibility Criteria

The present analysis included patients presenting to the emergency department with a most responsible diagnosis of acute ischemic stroke between July 2003 and June 2007. Patients with TIA, intracerebral hemorrhage, or an in-hospital stroke were not included.

The main inclusion criterion was a known history of atrial fibrillation before admission as documented in the patient's medical history; patients with newly diagnosed atrial fibrillation in the hospital were not included. We did not include patients with atrial fibrillation with a history of cardiac valve replacement.

Furthermore, we selected only patients whom we considered "ideal" candidates for warfarin. We required that patients meet criteria for high stroke risk as defined by the sixth American College of Chest Physicians (ACCP) guidelines; patients were classified as high risk if they had one high-risk factor or more than one moderate-risk factor.⁶ High-risk factors used in this study were: previous stroke, TIA, or systemic embolism; history of hypertension; history of congestive heart failure or pulmonary edema (as an indicator of probable poor left ventricular systolic function); and age >75 years. Moderate-risk factors were: age 65 to 75 years, diabetes mellitus, and coronary artery disease with preserved left ventricular systolic function (identified in our database as patients with a history of angina, previous myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention/angioplasty without a history of congestive heart failure/pulmonary edema). We did not include moderate-risk or low-risk patients with atrial fibrillation in this study.

We excluded patients with known contraindications to anticoagulation and patients not considered appropriate for warfarin based on the medical history documented in the chart. Exclusions were: history of intracranial hemorrhage, neuroimaging evidence of previous hemorrhage, peptic ulcer disease, previous gastrointestinal bleed, cirrhosis, metastatic cancer, renal failure requiring dialysis, Alzheimer disease, or dementia. Additionally, patients were excluded if they were not independent in activities of daily living in the 3 months before admission or if they were living in a nursing home.

Analysis

The primary end points were the proportion of patients taking preadmission warfarin or antiplatelet medications and the admission INR. The database collected information on the use of all antithrombotic medications, including warfarin, aspirin, clopidogrel, ticlopidine, and dipyridamole; dual antiplatelet therapy was recorded if patients were taking aspirin plus clopidogrel, aspirin plus ticlopidine, aspirin plus dipyridamole, or aspirin/extended-release dipyridamole. Standard descriptive statistics were used. Data analysis was performed in 2 separate cohorts: (1) primary stroke prevention was assessed in patients presenting with a first ischemic stroke (excluding those with a previous history of stroke or TIA); and (2) secondary stroke prevention was assessed using the same criteria but including only patients who had a history of ischemic stroke or TIA before the index stroke admission. A logistic regression analysis using backward selection was performed for the combined cohorts to identify predictors of warfarin use using the variables listed in Table 1. Probability values <0.05 were considered statistically significant.

Results

Of 2135 patients with ischemic stroke and known atrial fibrillation, 597 met our inclusion/exclusion criteria for the primary prevention analysis. Of 891 patients with ischemic stroke, known atrial fibrillation, and a history of stroke or TIA, 323 met our eligibility criteria for the secondary prevention analysis. Patient characteristics are shown in Table 1. As expected, the average patient was elderly and hypertensive, and many had diabetes and coronary artery disease.

For patients with known atrial fibrillation presenting to the hospital with a first-ever acute ischemic stroke (n=597), strokes were disabling (discharge modified Rankin scale score ≥2) in the majority (59.7%) and fatal in one fifth. Only 39.9% were taking warfarin before admission, and 29.0% were not taking any antithrombotic prophylaxis. Of those

Table 1. Patient Characteristics

	Primary Prevention Cohort (n=597)	Secondary Prevention Cohort (n=323)
Female, %	55.9	53.7
Age, years, mean (SD)	77.6 (9.5)	78.1 (8.8)
Age >75 years, %	65.3	67.5
Age 65–75 years, %	25.1	24.8
Hypertension, %	81.7	83.6
Congestive heart failure, %	19.4	21.1
Diabetes, %	21.8	30.0
Angina, %	31.0	35.9
Previous myocardial infarction, %	19.8	27.2
Previous coronary artery bypass grafting or coronary angioplasty, %	11.9	15.2
Smoking, %	27.1	31.0
Previous ischemic stroke,* %	0	67.8
Previous transient ischemic attack,* %	0	47.7

*Some patients had a history of both ischemic stroke and transient ischemic attack.

taking warfarin, 74.2% had a subtherapeutic INR (<2.0) at admission; the median INR was 1.6 (IQR, 1.2 to 2.0; Figure 1).

For patients presenting with acute ischemic stroke who had known atrial fibrillation and a history of ischemic stroke or TIA (n=323), 57.3% were taking warfarin before admission. Of these, 68.3% had a subtherapeutic INR at admission, and the median INR was 1.6 (IQR, 1.2 to 2.2). Neither warfarin nor antiplatelet therapy was used before admission in 15.2% (Figure 2).

The only significant predictor of warfarin use was a history of ischemic stroke (OR, 1.7; 95% CI, 1.2 to 2.3; $P=0.001$) or TIA (OR, 1.6; 95% CI, 1.1 to 2.3; $P=0.007$). Age, sex, and other patient characteristics did not significantly distinguish warfarin users from nonusers.

Interpretation

This study found that most patients admitted with a stroke who had previously recognized atrial fibrillation were subop-

timally anticoagulated before their stroke. Among the cohort of high-risk patients presenting with a first ischemic stroke, only 40% were taking warfarin for primary prevention before admission. Furthermore, the INR was subtherapeutic in three fourths of those who were taking warfarin. Overall, 90% of patients with ischemic stroke with known atrial fibrillation were not appropriately anticoagulated at the time of their first ischemic stroke. Surprisingly, up to one third was not taking any antithrombotic medications at all. Among the cohort of patients with acute stroke who had a history of ischemic stroke or TIA (the highest risk subgroup for stroke in atrial fibrillation), there were slightly more patients who were appropriately anticoagulated for secondary prevention purposes. However, 43% were not taking warfarin, and of those who were taking warfarin, 68% had a subtherapeutic INR at admission (ie, only 18% were therapeutically anticoagulated at the time of stroke recurrence). Moreover, 15% of patients with a previous ischemic stroke or TIA were not taking any antithrombotic therapy.

These findings are particularly troublesome given that all subjects selected for inclusion in this study were considered high risk for stroke according to published criteria,⁶ were living independently, and considered “ideal” candidates for anticoagulation. We purposely excluded patients for whom warfarin might have been contraindicated (eg, history of prior bleeding), and to be conservative, we also excluded patients for whom warfarin may be considered undesirable (eg, certain medical comorbidities, dementia, nursing home residents). Patients deemed to be at low risk for stroke (for whom aspirin is usually sufficient) were not included in this study. Finally, our study reinforces the high morbidity and mortality of stroke associated with atrial fibrillation, which may be reduced if antithrombotic therapy practices could be optimized.^{8,9}

Our findings cannot be used to estimate the proportion of patients with atrial fibrillation who received appropriate antithrombotic therapy, because we studied only those patients admitted with a stroke. However, in many of these patients, there is little doubt that appropriate antithrombotic therapy could have prevented their stroke. These findings are sadly in line with many studies from other countries demonstrating suboptimal rates of appropriate antithrombotic therapy for patients with atrial fibrillation.^{11–17, 20} It is astonishing

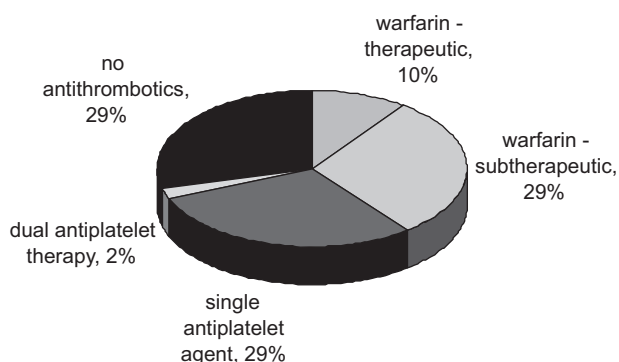


Figure 1. Preadmission medications in patients with known atrial fibrillation who were admitted with acute ischemic stroke (high-risk cohort, n=597).

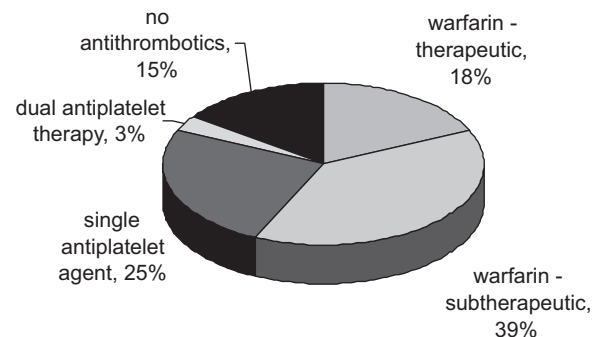


Figure 2. Preadmission medications in patients with known atrial fibrillation and a previous ischemic stroke/TIA who were admitted with acute ischemic stroke (very high-risk cohort, n=323).

that warfarin, which is so inexpensive and has been convincingly proven to be the most effective stroke prevention medication worldwide by a large margin, remains so underused.

Warfarin underuse may relate to patient factors, physician factors, or regional practice variations.^{10,23} Some eligible patients may decline or be denied warfarin therapy because of the perceived inconvenience and responsibility associated with INR monitoring, drug and food interactions, and potential bleeding risks. Unfortunately, physicians tend to overestimate the bleeding risks of warfarin, underestimate its benefits, and overestimate the benefits of antiplatelet therapy for stroke prevention in atrial fibrillation.^{24,25} Overestimating the risks of anticoagulation results in patients not taking effective therapy that could prevent fatal and nonfatal strokes. Major bleeding events associated with warfarin occur with a low annual incidence²⁶ but can profoundly bias physician prescribing behavior. For example, Choudhry et al demonstrated that physicians were less likely to prescribe warfarin if a previous patient had a major warfarin-related hemorrhage in the preceding year; conversely, physicians were not more motivated to prescribe warfarin to subsequent patients if one of their patients with atrial fibrillation experienced a stroke while not anticoagulated.²⁷ The likelihood of warfarin prescribing is also inversely proportional to the age of the patient's family physician.²⁸ The most feared complication is intracerebral hemorrhage, which has a high mortality rate²⁹ but a low annual incidence (0.3% in trials, $\leq 0.8\%$ in practice).^{26,30} Patients prone to falling are often denied warfarin for fear of subdural hematoma, although it has been estimated that one must fall 295 times before the risks of warfarin outweigh its benefits.³¹ The older age of our cohort may explain some of our findings because there is frequently concern about prescribing warfarin to elderly patients.^{19,20,32–34} However, safety of anticoagulation in the elderly has been established,^{24,25,35} and in a recent randomized trial of patients with atrial fibrillation aged ≥ 75 years, warfarin was associated with significantly fewer stroke events than aspirin without an increase in hemorrhage risk.³⁶ In addition to physician factors, individual patient knowledge and preferences have an impact on adherence to anticoagulation. In one study of patients with atrial fibrillation taking warfarin, approximately half did not know that atrial fibrillation was a risk factor for stroke and could not state why they were taking it.³⁷ Drug cost is not an issue that should limit warfarin use; in Ontario, the average monthly cost is approximately \$15 and it is covered by a government drug plan for citizens older than age 65 years.

A limitation of our study is that it does not provide specific reasons for the observed low rates of warfarin use or the high rates of subtherapeutic INRs. Although we took into account known contraindications to anticoagulation, it is possible that we overestimated warfarin eligibility and underreported contraindications.³⁸ For example, we did not have data about previous attempts at warfarin use, intolerance to antiplatelet therapy, duration of prior antithrombotic therapy, other past hemorrhages, falls, patient refusal, or history of nonadherence to therapy. In some cases, warfarin nonuse may have been justified for medical reasons that could not be captured in this

Table 2. Potential Strategies to Reduce Practice Gaps in Anticoagulation Management for Patients With Atrial Fibrillation

System-level strategies
Increasing the number of anticoagulant clinics
Increasing physician reimbursement for anticoagulant monitoring
Inserting a reminder about stroke risks associated with atrial fibrillation and a summary of current treatment guidelines on all electrocardiogram and Holter reports documenting atrial fibrillation
Pharmacist flagging of nonanticoagulated patients with atrial fibrillation
Patient and physician strategies
Online warfarin dosing calculators to assist with warfarin initiation (eg, www.warfarindosing.org)
Patient information about warfarin (eg, Thrombosis Interest Group of Canada [www.tigc.org])
Decision aids (eg, the University of Ottawa Atrial Fibrillation Decision Aid has been evaluated in a randomized trial; ⁴⁸ this tool is available at www.canadianstrokenetwork.ca and can be used for counseling about the benefits and risks of warfarin versus aspirin)
Ongoing patient education to reinforce long-term adherence with therapy
Patient self-monitoring or self-management of anticoagulation with Internet-based warfarin dosing programs for patients ⁴⁹

database, and submaximal warfarin therapy may have been intentionally prescribed for certain patients. We cannot ascertain how many strokes may have occurred after intentional discontinuation of antithrombotics for a diagnostic or surgical procedure; although patients are often advised to temporarily withhold antithrombotics for minor procedures, this practice is associated with increased stroke risk.³⁹ Patients are also vulnerable to unintentional discontinuation of warfarin after hospitalizations for surgery.⁴⁰ Patient preferences likely accounted for some of the warfarin underuse (patient preferences may be influenced by physician preferences), and some patients may not have had a family physician to monitor their anticoagulation. Because this study focused only on patients who had a stroke, we do not know the proportion of all patients with atrial fibrillation who were anticoagulated. We also acknowledge that mechanisms other than cardioembolism could have accounted for some of the ischemic strokes in this study.

Our findings have implications for clinical practice for both primary and secondary stroke prevention. Improved knowledge–translation strategies are needed to facilitate compliance with evidence-based guidelines, some of which are listed in Table 2. It is sobering to realize that patients in the community taking warfarin are outside the therapeutic range approximately half of the time according to a systematic review of 67 studies.⁴¹ In Ontario, it has been estimated that subtherapeutic INR is responsible for 11% of all serious thromboembolic events in patients with atrial fibrillation, ie, approximately one in every 10 thromboembolic events could be avoided if anticoagulation control were optimal.⁴² Studies show that the quality of anticoagulation can be significantly enhanced (and anticoagulant-related complications reduced) by specialized physician- or pharmacist-run anticoagulant clinics^{41,43,44} or by patient self-monitoring or self-management using a home finger-stick INR device.^{41,45} For example, in one randomized trial, anticoagulant clinic

management involving patient education, participation, and self-testing found that the INR was in the therapeutic range almost twice as much as in the usual care group, and the incidence of major bleeding was reduced by half.⁴⁶

In conclusion, this study highlights missed opportunities for stroke prevention in patients with atrial fibrillation. Taken in conjunction with many other studies worldwide, our results should encourage increased efforts to prescribe and monitor warfarin to reduce the risk of a disabling or fatal stroke in high-risk individuals with atrial fibrillation. We hope this study will stimulate similar audits in other regions as well as the development of quality improvement interventions to optimize stroke prevention for individuals with atrial fibrillation. More widespread implementation of anticoagulation clinics and further evaluation of other interventions to increase appropriate warfarin use and anticoagulation control are urgently needed and could substantially reduce the number of strokes per year and their associated direct and indirect costs.^{42,47}

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Disclosures

None.

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