Underutilization of Anticoagulation Therapy in Chronic Atrial Fibrillation

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SUMMARY

Atrial fibrillation, the most common chronic arrhythmia, results in an increased risk of stroke. Anticoagulation therapy can reduce this risk, but appears to be underused. The objective of this study was to examine the use of warfarin and prevalence of stroke in patients with rheumatic, nonrheumatic valvular and nonvalvular atrial fibrillation.

Between January 1993 and December 1998, 457 chronic atrial fibrillation patients with continuous follow-up in our hospital were identified as having rheumatic heart disease (n = 114); nonrheumatic valvular disease (n = 65); or nonvalvular disease (n = 278). Warfarin was used less often in patients with nonrheumatic valvular (16.7%) and nonvalvular diseases (20.1%) than in those with rheumatic heart disease (81.6%, p < 0.001). In contrast, the prevalence of stroke among patients with nonvalvular disease was 40.3% which was similar to the 33.3% found in patients with rheumatic heart disease but significantly higher than the 24.6% found in patients with nonrheumatic valvular disease (p < 0.05). A history of stroke did not alter the trend of use of warfarin among the three groups of patients. Only 20.6% of patients on warfarin received monthly monitoring of prothrombin time.

In conclusion, the anticoagulation therapy in our patients with chronic atrial fibrillation, regardless of their associated valvular diseases, is significantly underutilized. This underuse could account for a high prevalence of stroke. This risk of stroke, however, is less in patients with nonrheumatic valvular disease than in those with nonvalvular atrial fibrillation. (Jpn Heart J 2001; 42: 55-65)

Key words: Anticoagulation, Nonvalvular atrial fibrillation, Valvular atrial fibrillation

BASED on the results of several clinical trials, the American Heart Association in 1996 recommended that anticoagulation be used in all atrial fibrillation patients at high risk for stroke. They further recommended that patients who cannot safely receive anticoagulation or who are at low risk for stroke be given aspirin. Despite these clear recommendations, several studies mainly in patients with nonvalvular atrial fibrillation have demonstrated a significant underuse of antico-
The use of anticoagulation therapy in atrial fibrillation patients with valvular diseases, however, has not been reported. These patients deserve attention as they are generally considered to have a high risk for stroke even though no randomized trials have been conducted in this patient population. The purpose of this study was to examine the use of anticoagulation therapy and prevalence of stroke in patients with rheumatic, nonrheumatic valvular and non-valvular atrial fibrillations.

**METHODS**

Between January 1993 and December 1998, a list of about 2500 patients discharged with an International Classification of Diseases, 9th Revision, code of 427.31 (atrial fibrillation) was obtained from the Medical Record Department of our hospital. These charts were then reviewed. Patients with transient or paroxysmal atrial fibrillation or with implanted prosthetic valves were excluded. Four hundred and fifty-seven patients with documented chronic atrial fibrillation who remained under continuous follow-up in our hospital clinics till July 1999 were included in this study. The age, sex, duration of atrial fibrillation, coexisting medical conditions, and echocardiographic data including left atrial size and ejection fraction, were studied by reviewing the entire medical record of each patient (Table I). We also researched for and reviewed any history of stroke, factors suggesting risk of anticoagulation, use of anticoagulation with warfarin, mon-

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<th>Table I. Clinical Characteristics of Study Patients</th>
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<td>Age (y)</td>
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<td>RHD (n = 114)</td>
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<td>VD (n = 65)</td>
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<td>NV (n = 278)</td>
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*p < 0.001, RHD versus VD; #, p < 0.001, RHD versus NV; †, p < 0.0001, RHD versus NV. AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; EF = ejection fraction; LA = left atrial; LV EF = left ventricle ejection fraction; NV = nonvalvular atrial fibrillation; RHD = rheumatic atrial fibrillation; VD = nonrheumatic valvular atrial fibrillation.
monitoring of prothrombin time and antiplatelet therapy throughout the follow-up period.

Based on echocardiographic studies, patients were considered to have rheumatic heart diseases if they had mitral or aortic stenosis and calcification in addition to any other valvular diseases. Patients with moderate to severe aortic, mitral, or tricuspid regurgitation but without clear evidence of mitral or aortic calcification or stenosis were considered to have nonrheumatic valvular disease. Patients were considered to have nonvalvular diseases if they had no significant valvular stenosis or regurgitation.

**Data analysis:** The data from these three groups of patients are expressed as the mean ± standard deviation. The analyses of variance with pairwise comparisons using Tukey’s test were used to compare mean values among groups. Chi-square test and Fischer’s exact test were used to determine differences of categorical data among groups. Multiple logistic regression analysis was used to determine the risk factor of stroke. A probability value of less than 0.05 was considered to be statistically significant.

**RESULTS**

**Clinical characteristics of study patients:** The clinical characteristics of study patients with chronic atrial fibrillation are shown in Table I. There were 114 patients with rheumatic heart disease, 65 patients with nonrheumatic valvular disease and 278 patients with nonvalvular disease. Of the patients with nonrheumatic valvular disease, 14 had moderate to severe aortic regurgitation, 43 had moderate to severe mitral regurgitation, 5 had concomitant moderate mitral and aortic regurgitations, and 3 had concomitant mitral and tricuspid regurgitations. The patients with rheumatic heart disease were significantly younger ($p < 0.001$) but had a longer duration ($p < 0.001$) of atrial fibrillation than the patients in the other two groups. In contrast, the proportion of hypertension was higher among patients with nonrheumatic valvular ($p < 0.001$) and nonvalvular diseases ($p < 0.0001$) than in patients with rheumatic heart disease.

**Prevalence of stroke in patients with atrial fibrillation:** The prevalence of stroke was similar in patients with nonvalvular disease (40.3%) and those with rheumatic heart disease (33.3%, $p = 0.18$) (Figure 1), despite the fact that the patients with rheumatic heart disease had a longer average duration of atrial fibrillation. In contrast, the prevalence of stroke in patients with nonrheumatic valvular disease (24.6%) was significantly less than in patients with nonvalvular disease ($p < 0.05$). This prevalence did not differ from that in patients with rheumatic heart disease ($p = 0.19$). When clinical vari-
ables that may be important for the occurrence of stroke were considered, a multiple logistic analysis identified only age and hypertension as significant risk factors associated with stroke ($p < 0.01$).

**Antithrombotic therapy in atrial fibrillation:** Twenty-four patients with a history of hemorrhagic stroke, intracranial bleeding or gastrointestinal ulcers with bleeding were considered ineligible for warfarin therapy. Therefore, the use of warfarin versus antiplatelets including aspirin, ticlopidine, and dipyridamole was studied in our patients considered eligible for some kind of antithrombotic therapy. Warfarin was used significantly more frequently in patients with rheumatic heart disease (81.6%) than in patients with nonrheumatic valvular (16.7%, $p < 0.001$) or nonvalvular (20.1%, $p < 0.0001$) diseases (Figure 2). Antiplatelets, however, were used more often in patients with nonrheumatic valvular (58.3%) and nonvalvular (53.3%) diseases than in patients with rheumatic heart disease (13.1%, $p < 0.0001$). A similar percentage of patients with nonrheumatic valvular and nonvalvular diseases had received warfarin, antiplatelets or no antithrombotic treatment. There was a higher percentage of patients with nonrheumatic valvular (25.0%) and nonvalvular diseases (26.6%) not receiving any antithrombotic agents than patients with rheumatic heart disease (5.3%, $p < 0.0001$). Among all three groups, a history of stroke did not generally

![Figure 1. Prevalence of stroke in patients with atrial fibrillation. NV, nonvalvular atrial fibrillation; RHD, rheumatic atrial fibrillation; VD, nonrheumatic valvular atrial fibrillation.](image-url)
determine whether warfarin or antiplatelets were used although the patients with nonvalvular disease were significantly less likely to receive treatment (17.9%) compared with the patients with rheumatic heart disease (2.6%, $p < 0.05$) (Figure 3). Similar to the patients with rheumatic heart disease, only 6.3% of patients with nonrheumatic valvular disease did not receive antithrombotic treatment ($p = 0.53$).

**Recurrence of stroke:** The use of antithrombotic therapy in the prevention of recurrent stroke was also examined (Figure 4). Patients receiving warfarin therapy had significantly fewer recurrent strokes (9.3%) than patients receiving antiplatelets (30%, $p < 0.01$). They also tended to have fewer recurrent strokes than patients given no antithrombotic therapy at all (22.7%, $p = 0.12$).

**Complications and monitoring of warfarin therapy:** Few complications occurred in our 155 patients on warfarin therapy. Two patients had cerebral hemorrhage, 2 had ecchymosis and 4 had mild gastrointestinal bleeding, none of whom died of these complications.

Only 20.6% (32 / 155) of patients receiving warfarin underwent monthly monitoring of prothrombin time. Most patients received infrequent (7.1%) or sporadic (72.3%) monitoring of prothrombin time. It is worth noting that four of the five patients with recurrent stroke while on
Figure 3. Antithrombotic therapy in patients with a history of stroke. Abbreviations as in Figure 1.

Figure 4. Recurrence of stroke in atrial fibrillation patients treated with warfarin, antiplatelet, or no antithrombotic agents.
warfarin did not undergo monthly monitoring of prothrombin time.  

Preference of anticoagulation therapy among specialties: Cardiologists and neurologists commonly see patients with atrial fibrillation or stroke. Therefore, we examined the pattern of warfarin use in patients with chronic atrial fibrillation in these two specialties versus other specialties, including general internal medicine, family practice and all others (Table II). The patients with rheumatic heart disease seen by cardiologists were more likely to undergo warfarin therapy than the same patients seen by physicians with other specialties. The patients with nonvalvular disease received warfarin most frequently from cardiologists followed by neurologists and physicians with other specialties. In the patients with nonrheumatic valvular disease, there was no statistically significant difference in the use of warfarin among the various specialties.

**DISCUSSION**

The results of the present study indicate that warfarin was used less often in patients with nonrheumatic valvular (16.7%) and nonvalvular atrial fibrillation (20.1%) than in those with rheumatic atrial fibrillation (81.6%) (Figure 2). A history of stroke did not generally alter the trend of use of warfarin among these three groups of patients (Figure 3). As compared with the reported 34 - 98% of patients with nonvalvular atrial fibrillation treated with anticoagulant, anticoagulation therapy was grossly underutilized in our patients. Although patients with rheumatic atrial fibrillation should greatly benefit from anticoagulation therapy, not all of our patients with rheumatic heart disease had received it. The prevalence of stroke in our patients with chronic atrial fibrillation, however, is high and ranged from 24.6% to 40.3% over 5 years of follow-up,
depending on whether they had valvular diseases or not. Our data indicate that the underutilization of anticoagulation therapy could account for the high prevalence of stroke in these patients.

The present study was not intended to evaluate the efficacy of anticoagulation in preventing ischemic stroke in our Chinese patients with chronic atrial fibrillation. We expected that atrial fibrillation patients with rheumatic heart disease should have a higher prevalence of stroke than those with nonvalvular disease, but our data showed no statistical difference ($p = 0.18$) in the prevalence of stroke in these two groups of patients. This similarity can be explained by the fact that patients in the former group received warfarin more frequently than those in the latter group did (Figure 2). Furthermore, among the patients with a history of stroke, warfarin significantly reduced the incidence of recurrent stroke as compared with those using antiplatelets (Figure 4). Warfarin also had appreciably better efficacy than no treatment in preventing recurrent stroke, although not statistically significant (9.3% vs 22.7%, $p = 0.12$). These insignificant statistics probably result from a type 2 error due to the small number of patients in our study. It should be noted that four of the five patients with recurrent stroke while on warfarin did not receive adequate monitoring of anticoagulation. Thus, even though recommendations of anticoagulation therapy were based on clinical trials predominately involving Caucasians,1-8) our data strongly support a universal applicability of anticoagulation therapy in preventing stroke in chronic atrial fibrillation patients at risk of stroke, regardless of ethnic origin.

In our study, chronic atrial fibrillation patients with nonrheumatic valvular diseases had fewer strokes than patients with nonvalvular atrial fibrillation despite similar proportions of patients taking warfarin in these two groups, however, the mechanism behind this finding is not clear. It is interesting to note that in patients with rheumatic atrial fibrillation, valvular regurgitations are not predictors of ensuing embolization.15) Since 51 out of 65 (78%) patients with nonrheumatic valvular atrial fibrillation in our study had moderate to severe mitral regurgitation, we speculate that the left atria in this group of patients had good reverse blood flow during the systolic phase, thereby minimizing the thrombus formation and incidence of stroke. Nevertheless, the 24.6% prevalence of stroke in this group of patients warrants anticoagulation therapy.

Many clinical variables, such as congestive heart failure, hypertension, age, diabetes mellitus, previous arterial thromboembolism, coronary artery disease, cardiomyopathy, artificial pacemakers, treated ventricular arrhythmia, left bundle block and congenital heart disease, have been
implicated as risk factors for stroke in patients with nonvalvular atrial fibrillation.\textsuperscript{1,2,5,16} Pooled data analysis and a case control study, however, have only identified a history of stroke, diabetes mellitus, hypertension and age as independent risk factors for stroke in nonvalvular atrial fibrillation.\textsuperscript{17,18} The echocardiographic features, such as left atrial morphology, left atrial thrombus, contrast echo, and aortic plaque in high-risk patients with atrial fibrillation may confer an additional risk of stroke.\textsuperscript{19,20} In our patients, we also identified age and hypertension as risk factors for stroke. The failure to identify other clinical features such as diabetes mellitus or coronary artery disease as risk factors of stroke in our patients may be due to the fact this is a nonrandomized and nonprospective study involving a small number of patients.

The monitoring of the anticoagulation was extremely infrequent during the follow-up in our patients. Only 20.6\% of our patients received a monthly check of prothrombin time and adjustment of warfarin dose. This probably was due to both the physician’s attitude and patient’s reluctance to have regular blood drawn at each clinical visit. Probably for the same reasons, warfarin was often not used in our patients with chronic atrial fibrillation. Another study has also indicated that the physicians’ attitudes affected the use of anticoagulant.\textsuperscript{11} Despite the inadequate monitoring in our patients, serious complications from the use of warfarin occurred rarely with only 2 out of 155 suffering intracerebral hemorrhage.

McCrory, \textit{et al.}\textsuperscript{11} reported no consistent trend favoring the use of anticoagulation therapy among clinical specialties. Stafford and Singer,\textsuperscript{12} on the other hand, reported that cardiologists and general internists were more likely to prescribe warfarin to patients with atrial fibrillation than physicians with other specialties. Among the specialties in our study (Table II), cardiologists and neurologists were more likely to use warfarin in patients with nonvalvular atrial fibrillation and only cardiologists often treated patients with rheumatic atrial fibrillation with warfarin. Despite the fact that these two kinds of specialists frequently encounter patients with atrial fibrillation or stroke, all clinicians who see patients with chronic atrial fibrillation should be aware of and follow the clinical guidelines suggested by the clinical trials\textsuperscript{1-9} to reduce the incidence of stroke.

There were several limitations in our study. First, we relied on data from a retrospective analysis restricted to patients who had continuous clinical follow-ups in one hospital. The precise incidence of stroke in patients with chronic atrial fibrillation or of complications from warfarin cannot be certain. Secondly, the relatively small number of patients eligible for analysis in this study may render it difficult to generalize the
results and apply them to other patient populations. However, our atrial fibrillation patients with nonrheumatic valvular and nonvalvular diseases certainly received anticoagulants less often than their counterparts in western countries where 34 - 98% of patients with nonvalvular atrial fibrillation underwent anticoagulation therapy. A recent report by Chiang, et al. indicated that only 60% of atrial fibrillation patients with mitral stenosis in northern Taiwan received anticoagulants. In contrast, only about 10-20% of patients with atrial fibrillation in mainland China received anticoagulants. Our results, coupled with the above data, suggest that anticoagulation therapy be generally underutilized in East Asian countries. Thirdly, the classification of rheumatic or nonrheumatic valvular heart diseases was based purely on the echocardiographic findings. We do not have clinical evidence to exclude the possibility that some of the patients with nonrheumatic valvular heart diseases may have rheumatic etiology. Even with this limitation, the conclusion of this study would not be altered because warfarin was found to be underutilized across the three groups of patients.

In conclusion, anticoagulation therapy is generally underutilized in our patients with chronic atrial fibrillation regardless of their associated valvular diseases. This underutilization could contribute to a remarkable prevalence of stroke in these patients. Our results raise the issue of implementation of the guidelines regarding the use of warfarin in patients with atrial fibrillation. Research for an effective and convenient alternative treatment is warranted.

REFERENCES


