Reduced Poststroke Mortality in Patients With Stroke and Atrial Fibrillation Treated With Anticoagulants
Results From a Danish Quality-Control Registry of 22 179 Patients With Ischemic Stroke

Klaus Kaae Andersen, MS, PhD; Tom Skyhøj Olsen, MD, PhD

Background and Purpose—The preventive effect of anticoagulation in patients with stroke and atrial fibrillation (AF) is documented only in trials of minor stroke. Although anticoagulation reduced stroke recurrence, those trials did not demonstrate an influence of anticoagulation on survival.

Methods—A nationwide registry that was started in 2001 with the aim of registering all hospitalized stroke patients in Denmark now includes 24 791 patients. We studied the survival of patients with ischemic stroke and AF with respect to anticoagulation treatment. All underwent an evaluation for stroke severity (according to the Scandinavian Stroke Scale), computed tomography scan, and an evaluation for cardiovascular risk factors. Follow-up duration was 4 years (mean, 1.2 years).

Results—Of all patients, 22 179 (89.4%) experienced an ischemic stroke. In total, 3670 (16.5%) had AF, and 1909 had no contraindication to anticoagulation treatment. Anticoagulation treatment was initiated in 1149 of these patients (60.2%) but omitted in 760 (39.8%) despite no contraindication to such treatment. Of the patients so treated, 18.9% died during follow-up versus 45.2% without treatment. Patients who received treatment were younger (76.7±9.5 versus 80.7±9.0 years, P<0.0001) and had less severe strokes (Scandinavian Stroke Scale score, 42.0±15.0 versus 33.6±18.2, P<0.0001). A Cox proportional-hazards model was built to study the effect of anticoagulation on survival in patients without contraindications to treatment while controlling for stroke severity, sex, and cardiovascular risk factors. Patients without anticoagulation treatment were at greater risk of dying (hazard ratio=1.91, 95% CI=1.44 to 2.52) compared with patients who received anticoagulation treatment.

Conclusions—Our data suggest that anticoagulation treatment reduces poststroke mortality in patients with ischemic stroke and AF. (Stroke. 2007;38:259-263.)

Key Words: anticoagulation • atrial fibrillation • prevention • prognosis • stroke

Anticoagulation therapy reduces the risk of recurrent stroke by approximately two thirds in patients with minor ischemic stroke and atrial fibrillation (AF). Most probably, mortality is also reduced, but evidence for this has never been established, as the available 2 randomized, controlled studies on anticoagulation in patients with stroke and AF were not sufficiently powered to demonstrate an effect on survival.1-3

The frequency of AF increases almost exponentially with age and is highest in patients with the most severe strokes.4 Evidence for the effect of anticoagulation in patients with stroke and AF is, however, based on data from patients with minor strokes and those at the younger end of the AF spectrum.1-3 With reference to this evidence, however, it is widely accepted in clinical practice to also use anticoagulation in elderly patients and in patients with moderate to severe strokes associated with AF. There are no secondary prevention studies under way on the effect of anticoagulation in elderly patients and in patients with moderate to severe strokes, and there are no indications that these studies will appear in the near future.

The present study was undertaken to investigate whether anticoagulation in elderly patients and/or in patients with moderate to severe strokes associated with AF affects survival. An ongoing, nationwide Danish stroke registry was established on March 1, 2001, with the aim of registering all patients hospitalized for stroke. By August 1, 2005, the registry included 24 791 patients hospitalized for acute stroke, among whom we identified 3670 patients who had experienced an ischemic stroke and AF. Among these patients, 1909 did not have any contraindication to anticoagulation treatment. On the basis of this sizeable number of
patients included without regard to age or stroke severity, we studied the effect of anticoagulation treatment on survival up to 4 years after stroke in patients without contraindication to anticoagulation treatment, while controlling for age, stroke severity, sex, and relevant cardiovascular risk factors.

**Patients and Methods**

The study is based on data collected during the Danish National Indicator Project (NIP). NIP was established in 2001 as a concerted action among a number of Danish institutions, including the Ministry of Internal Affairs, the Ministry of Health, the National Board of Health, the Centre for Evaluation and Assessment of Medical Technology, the Danish Association of County Councils, the counties of Denmark, the Copenhagen Hospitals Cooperative, the Danish Nursing Association, the Joint Danish Nursing Societies, the Danish Physiotherapists’ Association, the Occupational Therapists’ Association, the Danish Medical Association, and the Danish Medical Society. NIP measures the quality of care provided by Danish hospitals to groups of patients with specific medical conditions, initiated in 1149 of these patients (60.2%) but omitted in 760 patients (39.8%) despite no contraindication to such treatment. We therefore compared rates of survival in these 2 groups of patients. Basic characteristics of the NIP and the Danish Data Protection Agency.

### Statistical Analyses

First, a risk profile with respect to receiving anticoagulation treatment was obtained by a multiple logistic-regression analysis according to a generalized additive model. Age and stroke severity were modeled with a smooth nonlinear function, because the effect of both covariates cannot be assumed to be linear. Significance of sex and cardiovascular risk factors was tested on the basis of a likelihood ratio test.

Second, independent predictors of death were identified with a Cox proportional-hazards model. Age was modeled as a delayed entry, because the patients entered the study at random ages. This implies that survival time was chosen to be the patient’s age at death (by any cause). Any patient entering at a later age than a given event time (death) was not included in the risk set. To assess whether the baseline hazard functions were proportional, log-log plots were performed for each variable, as well as tests and diagnostics based on weighted residuals. In all statistical analyses, a significance level of 5% was adopted.

In identifying the final model, only complete cases were included in the analysis. Approximately 15% of the cases were excluded owing to 1 or more missing covariates. Our analysis led us to believe that the nature of the missing data were not informative. The statistical software R was used for the statistical analyses.

**Results**

Of the 24,791 patients admitted with acute stroke, 22,179 (89.5%) had ischemic stroke, of whom 3670 patients (16.5%) had AF. In 1909 patients (52%), there was no contraindication to anticoagulation treatment. Anticoagulation treatment was initiated in 1149 of these patients (60.2%) but omitted in 760 patients (39.8%) despite no contraindication to such treatment. We therefore compared rates of survival in these 2 groups of patients. Basic characteristics of the 2 groups of patients are shown in the Table. Patients who received anticoagulation treatment were younger (76.7 ± 9.5 versus 80.7 ± 9.0 years, P < 0.0001) and had less severe strokes (SSS score, 42.0 ± 15.0 versus 33.6 ± 18.2, P < 0.0001). Of the patients who received anticoagulation treatment, 18.9% died during follow-up versus 45.2% of those without such treatment (P < 0.0001).

In the multiple-regression model, with the objective of determining which factors were independently associated with initiation of anticoagulation treatment, only age, stroke severity, and intermittent claudication were found significant in the model. The effect of age could not be assumed to be linear. The prevalence of receiving anticoagulation treatment as a function of age is shown in Figure 1. Anticoagulation was initiated in ~75% to 80% of patients <60 years of age but in <65% of patients >80 years of age, with a sharp decrease in the prevalence of receiving treatment in older patients. The prevalence of receiving anticoagulation as a function of stroke severity expressed by the SSS score is shown in Figure 1. Here, prevalence is increasing almost linearly with increasing SSS score, ie, decreasing stroke severity. The slope indicates a linear relation, corresponding to a relative risk of 1.28 per 10–SSS point decrease (CI = 1.18 to 1.39, P < 0.0001). Patients without intermittent claudica-
tion had a 2 times higher probability of receiving anticoagulation treatment (CI=1.12 to 3.63, P=0.019).

Independent predictors of death after stroke in patients without contraindications to anticoagulation treatment were identified by the Cox proportional-hazards model, wherein age was modeled as a delayed entry. The hazard ratios of risk factors are given in the Table. Age and stroke severity score were clearly the strongest predictors of survival. Age was accounted for by delayed entry, and hence, no hazard ratio is given. Similarly, no hazard ratio is given for the influence of SSS score, because this was modeled with a restricted cubic spline because the effect on survival was nonlinear.

Most important, survival was almost doubled in patients treated with anticoagulation compared with patients who did not have this treatment (hazard ratio=1.91, 95% CI=1.44 to 2.52). It should be noted that in our analysis, patients who died in hospital were included. If these patients (8% in total) were excluded from the analyses, the effect of anticoagulation treatment would be slightly smaller (hazard ratio=1.74, 95% CI=1.26 to 2.39). Survival curves stratified by anticoagulation treatment are given in Figure 2. The better survival probability for patients receiving anticoagulation is evident.

Discussion
We found that patients with stroke and AF who had no contraindications to anticoagulation treatment had an almost 50% reduction in their hazard of death when secondary prevention with anticoagulation treatment was instituted. This effect was independent of age, sex, stroke severity, and complicating cardiovascular risk factors.

Weaknesses and Strengths
The study was not randomized, and our conclusions should be considered a supportive supplement to current evidence from available randomized trials.1,2 The patients who received anticoagulation were selected and differed from patients who were not given anticoagulants, despite no contraindications to such treatment, as they were younger and had less severe...
strokes. In our Cox proportional-hazards model, however, we were able to adjust for these 2 important factors as well as for relevant cardiovascular risk factors.

Although the Danish NIP was designed as a nationwide registration of all patients admitted for acute stroke, coverage is not yet complete (presently \( \approx 75\% \)), and because of the large number of persons involved in a nationwide registration, missing data are unavoidable. As we registered whether anticoagulation therapy was instituted, we did not register compliance or adherence to treatment, nor did we register treatment of comorbidities, such as hypertension, hypercholesterolemia, etc. The presence of AF on acute admission does not necessarily imply causality, as AF may develop as a consequence of the acute illness, eg, stroke.\(^{11}\)

Our study’s strength lies in its large sample size, allowing for sufficient statistical power. It is the first nationwide study on secondary prevention of stroke with AF, with the largest number of patients in a study on this issue to date.\(^{12}\) In contrast to the 2 available randomized studies on secondary stroke prevention in patients with AF,\(^{1,2}\) our study included patients without limitations on age or stroke severity. Stroke severity was measured in all patients with a well-validated, neurological scale, and all patients underwent a standardized risk factor evaluation. Furthermore, we had survival data on nearly all patients, with \(< 0.2\%\) lost to follow-up.

We acknowledge the advantages of the randomized, controlled design. However, we consider large observational studies like ours indispensable supplementary information. Although meta-analyses of available randomized, controlled studies demonstrate the effectiveness of anticoagulation in preventing strokes in patients with AF, this evidence relates to relatively young patients with minor strokes and transient ischemic attacks.\(^{3}\) Furthermore, there is still no established evidence for reducing mortality, and it is questionable whether it is at all possible to establish randomized, controlled studies with enough statistical power to provide the evidence for this design.

Survival
Our study suggests that anticoagulation in patients with stroke and AF reduces poststroke mortality, if there are no contraindications to treatment. Evidence for the effect of anticoagulation in patients with stroke and AF originates from randomized studies on patients who had minor strokes and transient ischemic attacks.\(^{1,2}\) Our study provides evidence of a preventive effect of anticoagulation also in patients with severe strokes. The mean age of patients participating in the randomized studies was 71 to 72 years, whereas the mean age of patients receiving anticoagulation in our study population was 76.7 years. Our study thus provides evidence of a preventive effect regardless of age.

Use of Anticoagulation
Only 60.2\% of the patients with stroke and AF had anticoagulation, despite the lack of contraindications. Initiation of treatment was strongly associated with age and stroke severity, whereas the presence of cardiovascular risk factors had no influence. Our results are in line with other studies.\(^{13–16}\) There has been no clear contraindication to warfarin in \( \approx 2 \) to 3 times the number of patients actually receiving it, and most estimates of the underuse of warfarin in patients with AF exceed 40\%. Even in the mildest end of the stroke spectrum, the use of anticoagulation did not exceed 70\% in our study population, whereas in patients with severe strokes, such usage was \(< 50\%\). Anticoagulation was initiated in \( \approx 75\% \) to 80\% of patients below the age of 60 years, but after that age, usage fell; especially after the age of 75 to 80 years, it fell abruptly.

The main reason for omitting anticoagulation treatment in patients with AF is fear of bleeding complications.\(^{17}\) The
advantage of avoiding the risk of bleeding events, however, should be weighed not only against the risk of recurrent stroke but, as indicated is this study, also against a substantial risk of premature death, which is present regardless of age and stroke severity. We are aware of a natural relation between stroke severity, age, and compliance, but we excluded those patients who had contraindications to anticoagulation treatment. Hence, our study indicates an exaggerated caution in regard to the elderly with severe strokes, which seems to be out of balance with the obvious benefit of treatment shown in our study.

Conclusions

Our study suggests that anticoagulation reduces poststroke mortality in patients with ischemic stroke and AF, regardless of age and stroke severity. The risk of serious bleeding complications should be substantial before omission of preventive anticoagulation treatment is decided.

Disclosures

None.

References

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