Effect of Age on Stroke Prevention Therapy in Patients With Atrial Fibrillation

The Atrial Fibrillation Investigators

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Background and Purpose—Stroke risk increases with age in patients who have nonvalvular atrial fibrillation. It is uncertain whether the efficacy of stroke prevention therapies in atrial fibrillation changes as patients age. The objective of this study was to determine the effect of age on the relative efficacy of oral anticoagulants (OAC) and antiplatelet (AP) therapy (including acetylsalicylic acid and triflusal) on ischemic stroke, serious bleeding, and vascular events in patients with atrial fibrillation.

Methods—This is an analysis of the Atrial Fibrillation Investigators database, which contains patient level-data from randomized trials of stroke prevention in atrial fibrillation. We used Cox regression models with age as a continuous variable that controlled for sex, year of randomization, and history of cerebrovascular disease, diabetes, hypertension, and congestive heart failure. Outcomes included ischemic stroke, serious bleeding (intracranial hemorrhage or systemic bleeding requiring hospitalization, transfusion, or surgery), and cardiovascular events (ischemic stroke, myocardial infarction, systemic embolism, or vascular death).

Results—The analysis included 8932 patients and 17 685 years of observation from 12 trials. Patient age increased risk of ischemic stroke (adjusted hazard ratio per decade increase 1.45; 95% CI, 1.26 to 1.66), serious bleeding (1.61; 1.47 to 1.77), and cardiovascular events (1.43; 1.33 to 1.53). Compared with placebo, OAC and AP significantly reduced the risk of ischemic stroke (OAC, 0.36; 0.29 to 0.45; AP, 0.81; 0.72 to 0.90) and cardiovascular outcomes (OAC, 0.59; 0.52 to 0.66; AP, 0.81; 0.75 to 0.88), whereas OAC increased risk of serious bleeding (1.56; 1.03 to 2.37). The relative benefit of OAC versus placebo or AP did not vary by patient age for any outcome. Compared with placebo, the relative benefit of AP for preventing ischemic stroke decreased significantly as patients aged ($P=0.01$).

Conclusions—As patients with atrial fibrillation age, the relative efficacy of AP to prevent ischemic stroke appears to decrease, whereas it does not change for OAC. Because stroke risk increases with age, the absolute benefit of OAC increases as patients get older. (Stroke. 2009;40:1410-1416.)

Key Words: acute stroke ■ analysis ■ anticoagulation ■ antiplatelet drugs ■ aspirin ■ atrial fibrillation ■ biostatistics ■ cardiac emboli ■ cardiac embolism ■ cerebral infarct ■ clinical trials ■ database ■ epidemiology ■ outcomes ■ randomized controlled trials ■ warfarin

Age is an important factor in the management of patients with atrial fibrillation (AF). The prevalence of AF increases with patient age.1 Because AF independently increases stroke risk 5-fold2 and overall stroke risk increases with age,3 the influence of AF on health increases with age.

Age influences stroke prevention therapy in AF. Compared with antiplatelet (AP) therapy or no treatment, oral anticoagulants (OACs) significantly decrease the risk of ischemic stroke and cardiovascular events.4,5 However, elderly people with AF are less likely to receive OACs.6 This may reflect
concern about a higher risk of OAC-associated hemorrhage with increased age. In addition, physicians may be skeptical of OAC benefits in the elderly because they, before the Birmingham Atrial Fibrillation Treatment of the Aged Study trial (BAFTA), were underrepresented in randomized trials.

This is a secondary analysis of patient-level randomized trial data of patients with AF that determined if patient age significantly influenced the effect of OACs and APs on the risk of ischemic stroke, serious bleeding, or cardiovascular events.

**Methods**

**Included Studies: Design and Treatment**

This is a secondary analysis of the Atrial Fibrillation Investigators database. The Atrial Fibrillation Investigators database contains patient-level data from almost all published clinical trials in which patients with nonvalvular AF were randomized to at least 2 of the following treatments: full-dose OAC, APs, or either placebo or control. These trials included the Atrial Fibrillation, Aspirin, and Anticoagulation Study 1 (AFASAK-1), AFASAK-2, the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), the Canadian Atrial Fibrillation Anticoagulation (CAFA), the European Atrial Fibrillation Trial (EAFT), Primary Prevention of Arterial Thromboembolism in Atrial Fibrillation (PAATAF), the Stroke Prevention in Atrial Fibrillation 1 (SPAF-1) study, SPAF-2, SPAF-3 (high risk), and Stroke Prevention in Non-rheumatic Atrial Fibrillation (SPINAF). Patients in SPAF-1 who were eligible for anticoagulation and were randomized to either OAC or APs were reported in the SPAF-2 results. Observation time and events of all other SPAF-1 patients were attributed to SPAF-1.

All patients were adults with nonvalvular AF. Therefore, patients in NASPEAF with mitral stenosis were excluded. The exclusion criteria varied only slightly among the studies (supplemental Table I, available online at http://stroke.ahajournals.org/). In general, patients were excluded if they had clinical indications for, or contraindications to, any of the active therapies.

Patients were randomly assigned to full-dose OAC, APs, or placebo. Each study had at least 2 of the 3 therapies. Patients randomized to OAC were treated with coumarin derivatives, including warfarin sodium and 4-hydroxycoumarin. The target international normalized ratio (INR) varied slightly in each trial (Table 1). Patients randomized to AP were primarily treated with acetylsalicylic acid (ASA) at doses between 75 mg and 325 mg with one study using triflusal (Table 1). Patients receiving ASA were treated with or without low-dose oral anticoagulants. We combined patients treated with AP alone with AP plus low-dose warfarin patients provided the median INR of the latter group was <1.5. We did this because outcomes for patients randomized to combined therapy in which an INR <1.5 did not differ from outcomes of AP alone.

**Baseline Factors**

Patient clinical features were collected by research coordinators and physicians before therapy was started. These included previous stroke or transient ischemic attack (TIA), history of hypertension or systolic blood pressure of ≥160 mm Hg, and presence of Type 1 or Type 2 diabetes. All studies classified patients as hypertensive if they were taking medications given to lower blood pressure. In the NASPEAF and AFASAK studies, patients were considered to have congestive heart failure if it was graded as moderate or severe.

**Outcomes**

We compared the effect of OAC, AP, or no therapy on 3 outcomes, including ischemic stroke, serious bleeding (including intracranial and systemic hemorrhages), and cardiovascular events (including ischemic stroke, myocardial infarction, systemic embolism, or vascular death). Intracranial hemorrhages included intraparenchymal, subarachnoid, and subdural bleeds. Systemic hemorrhages most commonly required hospital admission, surgery, blood transfusion, or a significant drop in hemoglobin. Vascular deaths were due to

<table>
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<th>Trial Group</th>
<th>Total N</th>
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<th>OAC N</th>
<th>INR target</th>
<th>AP N</th>
<th>Control N</th>
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</table>

*Approximated from parathyroid ratio.
1 indicates OAC-eligible; 2, OAC-ineligible; 3, midrisk; 4, high risk.
stroke, myocardial infarction, congestive heart failure, pulmonary embolism, systemic embolism, or sudden death. Supplemental Table II provides the outcome criteria used in each trial.

Patients were followed for a mean of 2.0 (SD, 1.2) years (Table 1). Patients were evaluated at 3- to 6-month intervals or when an outcome event was suspected. With the exception of patients in AFASAK-1, a central events committee blinded to therapeutic assignment reviewed all events.

**Analysis**

The analysis determined if the association of treatment with outcomes varied with patient age after controlling for potential confounders while accounting for clustering of patients within studies. For all analyses, we accounted for clustering of patients within randomization groups within studies using a robust sandwich variance estimator proposed by Lin and Wei.20 We used Cox proportional hazards modeling to determine the independent association of patient age with time to each outcome. In these models, patient age was analyzed as a continuous variable because fractional polynomial function analysis21–23 found this form provided the best fit to the data. Pertinent patient factors were included in the model to control for confounding. We also included randomization year to account for any possible temporal trends in outcome risk.

The models were fit using PROC PHREG (SAS 9.1.3, SAS Institute, Cary NC).24 We accounted for individual study factors that could influence outcomes by including an indicator variable for each study in the model. Interaction terms between age and treatment were used to identify significant changes in relative therapeutic efficacy by age. In all analyses, a 2-sided probability value threshold of 0.05 defined statistical significance.

**Sensitivity Analysis**

Our modeling strategy maximized statistical power for identifying interactions between patient age and treatment efficacy but resulted in direct comparison of patients from different randomization units. We therefore conducted 2 sensitivity analyses to help determine if this analytic method adequately controlled for all confounding. First, we created a stratified Cox model based on randomized treatment comparisons (OAC versus placebo, AP versus placebo, OAC versus AP). These models controlled for all other covariates in the previous models. Second, we repeated our baseline analysis after sequentially excluding each study. We determined if our conclusions were sensitive to the exclusion of any particular study using the DerSimonian and Laird Q-statistic.25

**Results**

The analysis included 8932 patients within 16 randomization groups from 12 studies (Table 1). A total of 3430 patients were randomized to full-dose OACs with the lower target INR ranging between 1.5 and 2.8 and the upper target INR ranging from 2.7 to 4.2. A total of 3430 patients were randomized to AP therapy with all but 235 patients being treated with ASA at a dose ranging from 75 mg to 325 mg daily. The remaining 1971 patients were randomized to no therapy.

Patient details are given in supplemental Table III. Patient age was similar among all studies with the exception of BAFTA (mean age, 81.5 [SD, 4.2] years versus 70.9 [SD, 9.4] years in all other studies). A total of 19.6% of patients were ≥80 years of age. The proportion of patients that were male varied extensively among studies (range, 36.5% to 100%; overall 63%). Prior stroke or TIA also varied among studies (range, 0% to 100%; overall 22%). The presence of diabetes and hypertension was relatively consistent across studies (15% and 50%, respectively). Overall, 20% of patients had congestive heart failure. Patients were essentially identical within randomization groups, indicating adequate randomization in each study.

Patients had a mean follow-up of 2.0 years (SD, 1.2; range, 1.1 to 3.8 years; total 17 685 years). Supplemental Table IV describes outcomes within each study and treatment group. Overall, there were 623 ischemic strokes, 289 serious bleeds, and 1210 cardiovascular events. The proportion of patients having an ischemic stroke varied substantially across studies (range, 1.0% to 22.2%) as did annual stroke rate (range, 1.0% to 11.2%/year). Within each study, patients taking OAC had the lowest ischemic stroke rate followed by patients taking AP. Serious bleeding rates were more consistent across studies (range, 0.2%/year to 3.9%/year). Patients taking OAC tended to have the highest bleeding rates, although the difference with AP and placebo groups was not as large as that for ischemic stroke. Annual rates for cardiovascular events ranged from 2% to 19.7% per year. With the exception of AFASAK-2, patients taking OAC had the lowest cardiovascular event rate.

**Influence of Patient Age and Other Factors on Outcome Risk**

Figure 1 presents the crude annual outcome rates by treatment and age categories. Overall ischemic stroke rates were lowest in the OAC group followed by the AP group (Figure 1A). Stroke rates increased with age in the OAC and AP groups but appeared to plateau in the placebo group after age 70. Compared with stroke, rates of serious hemorrhages were smaller and appeared to be more homogenous among treatment groups (Figure 1B). Cardiovascular event rates changed the most across treatment groups and by patient age (Figure 1C).

Patient age was associated with an increased likelihood of previous stroke or TIA (OR per increased decade, 1.21; 95% CI, 1.11 to 1.32), hypertension (1.07; 1.02 to 1.12), and congestive heart failure (1.25; 1.17 to 1.33). We found that patient age was best expressed as a linear term in the multivariate Cox models for all outcomes.23 After adjusting for treatment and significant covariates, patient age was independently associated with the risk of each outcome, including ischemic stroke (hazard ratio, 1.45 per decade increase in age; 95% CI, 1.26 to 1.66), serious hemorrhage (hazard ratio, 1.61; 95% CI, 1.47 to 1.77), and cardiovascular event (1.43; 95% CI, 1.33 to 1.53; Table 2).

The independent influence of the other covariates on each outcome is also presented in Table 2. Both OAC and AP independently decreased risk of stroke and cardiovascular events. The risk of these events was independently increased by a history of previous cerebrovascular events, diabetes, and hypertension. Patient sex appeared to have opposite effects on outcomes with males being less likely to experience stroke but more likely to experience cardiovascular events. Finally, hemorrhagic risk increased with OAC, history of congestive heart failure, and increased study year.

**Interaction of Patient Age and Stroke Prevention Treatment on Outcome Risk**

There was a trend toward decreased relative benefit of OAC for preventing ischemic stroke as age increased (interaction
3.2, \( P = 0.07 \). Figure 2A presents the adjusted hazard ratio of OAC versus placebo for stroke risk by patient age. This shows that OAC remained significantly protective against stroke regardless of patient age but that protection decreased slightly (ie, its hazard ratio moved toward 1.0) as patients aged. This decrease, however, did not reach statistical significance. Model-based, age-specific hazard ratios ranged from 0.22 (95% CI, 0.11 to 0.41) for 50 year olds to 0.53 (0.35 to 0.81) for 90 year olds. There was no significant interaction between patient age and the relative benefit of OAC versus AP in preventing stroke (Figure 2C).

In contrast, the relative benefit of AP for preventing stroke decreased significantly with age (interaction term \( \chi^2 = 3.2, P = 0.07 \)). Figure 2B shows a notable increase in the hazard ratio of ischemic stroke for patients treated with AP as they age. Although AP treatment significantly decreased the risk of ischemic stroke in younger patients (hazard ratio, 0.40; 95% CI, 0.22 to 0.72 at age 50), this benefit decreased significantly as patients got older. At age 77, the hazard ratio of AP treatment no longer excluded unity. At age 82, the hazard ratio of AP treatment exceeded 1.

Neither OAC nor AP treatment interacted significantly with patient age for either serious hemorrhage (Figure 2D–F) or cardiovascular events (Figure 2G–I).
Sensitivity Analyses

The stratified analysis of AP versus placebo for ischemic stroke was limited to 4 randomization groups containing 2717 patients and 287 events. This analysis did not show a significant interaction of patient age on the association of AP with ischemic stroke (interaction term $\chi^2=0.6; P=0.46$). However, the parameter estimate for the interaction term (0.01093) was similar to that in the base model (0.02901; 95% CI, 0.0067 to 0.0513). The graphical representation of the stratified model (supplemental Figure I, available online at http://stroke.ahajournals.org) shows a change in AP effect on stroke that is similar to the base model (Figure 2B) in shape and direction but with much wider CIs. None of the other interaction terms were significant in the stratified analysis.

The influence of patient age on the effect of antithrombotic therapy in ischemic stroke prevention appeared consistent across studies (supplemental Figure II). Serial exclusion of individual studies did not significantly alter the parameter estimate for the interaction between patient age and antithrombotic efficacy with a probability value for the DerSimonian and Laird Q-test of 0.999. This parameter remained statistically significant after serially excluding half of all the studies.

Discussion

Clinicians are frequently reluctant to prescribe anticoagulants to elderly patients with AF. We believe that the current study is the most in-depth analysis of the impact that age has on this anticoagulation decision. Using patient-level data from nearly all relevant randomized trials, we found that the relative benefit of OACs for preventing ischemic stroke or cardiovascular outcomes did not change significantly with patient age when compared with either placebo or AP agents. In contrast, we found that the benefit of AP for preventing ischemic stroke decreased significantly as patients aged with AP appearing ineffective after patients entered their eighth decade. Neither OAC nor AP interacted with patient age for serious bleeding or cardiovascular events. The preservation of
OAC’s relative risk reduction in the oldest patients, who face a particularly elevated absolute risk of ischemic stroke, translates into a larger absolute therapeutic benefit.

Our results suggest that patient age itself should not be a contraindication for using OAC as preventive therapy in patients with nonvalvular AF. Although we saw a slight decrease in the relative efficacy of OAC for preventing ischemic strokes as patients aged (Figure 2A), OAC remained overwhelmingly beneficial for preventing stroke and cardiovascular outcomes compared with either AP or no treatment. In addition, our data show that AP therapy—the primary alternative to OAC for patients with AF—became significantly less beneficial for stroke prevention as patients aged (Figure 2B). The absence of a significant interaction between OAC versus AP (Figure 2C) is likely due to the slight tapering in efficacy of OAC with increased patient age. Furthermore, the increased risk of serious hemorrhage due to OAC was far smaller than the beneficial reduction in risk of stroke and other adverse vascular outcomes (Figure 1). Although physicians and patients with AF must continue to weigh all factors when deciding whether OAC should be used, the results of this analysis argue strongly against viewing advanced age alone as a contraindication to OAC.

Although the etiology of most ischemic strokes in patients with AF are cardioembolic from embolism of left atrial appendage thrombi, as much as 25% are due to coexisting intracerebrovascular diseases.26 Such patients frequently have coexistent coronary artery disease, hypertension, and diabetes. Warfarin is far superior to aspirin for preventing cardioembolic strokes, whereas aspirin has its major effect on noncardioembolic events.26 Advanced age is associated with an increased likelihood that AF-associated stroke is cardioembolic.27 This may be due to patients with atherosclerotic cerebrovascular disease succumbing to associated diseases, including coronary artery disease, diabetes, and hypertension. These observations could explain our findings of decreased effectiveness of aspirin for stroke prevention in patients with AF with increased age.

The risk of systemic or intracranial hemorrhage was significantly less than the risk of cardiovascular outcomes for all treatments and all age groups (Figure 1). This observation, plus the note that cardiovascular outcomes frequently have graver implications for patient health, should put the increased risk of hemorrhage seen with OAC (Table 2) in proper context. Although the risk of OAC-associated hemorrhage increased slightly with increased patient age (Figure 1), the benefit of OAC to older patients with regard to decreased stroke and cardiovascular outcome risk should make OAC the preventive treatment of choice for patients with AF.

This analysis complements previous studies of the effect patient age has on the relative efficacy of prophylactic therapy in AF. A previous analysis of our group suggested that the relative benefit of OAC versus AP may decrease as patients age.9 Our present analysis shows that the relative benefit of OAC versus AP does not change with patient age (Figure 2B). The discrepancy between these 2 analyses likely stems from additional data (the present analysis added 5 additional studies28–33 containing an additional 154 ischemic strokes and 1359 patients >75 years) and different statistical methodology (the present analysis modeled patient age as a continuous variable rather than arbitrarily cutting patient age at 75 years). Several studies have shown that analytic results can change when continuous variables are categorized.28–33

Our study has notable strengths. Within each trial, antithrombotic therapy was randomly assigned independent of patient age. This excludes the possibility that confounding influenced our analyses of therapeutic impact by age. Because the data came from randomized trials, all patients were followed prospectively with very little observation loss. All trials used explicit criteria when assessing potential outcomes with all but one trial using a blinded events committee to ensure objective outcomes assignment. Our analyses considered important potential confounders and accounted for the clustering of patients within individual studies. Finally, and most importantly, our study had the statistical power to reliably identify or refute clinically important interactions of treatment effect with patient age.

The primary limitation of our study stems from its comparison of patients across randomization groups. This was required because most randomized trials did not include all 3 treatment arms. Our model accounted for clustering of patients within randomization groups and controlled for important patient and study factors that could confound the results. In addition, the results of sensitivity analyses that we conducted, including an analysis limited to randomized comparisons, did not threaten the conclusions made in our base analysis. We believe that the present analysis was required to provide the statistical power required for this analysis. Undoubtedly, a study in which patients are randomized to all 3 treatment arms would provide more accurate results regarding the interaction of patient age and treatment efficacy. However, such a study would require a prohibitively large sample size and would be ethically impossible today given the placebo arm.

Other potential study limitations are also due to the trial source of its data. All participating patients, including the elderly, had to be considered reasonably safe anticoagulation candidates. Bleeding risk may be higher than we observed if patient selection criteria are relaxed in usual clinical care. Patients outside of randomized trials are usually sicker, possibly less compliant, and—for people taking OAC—have worse anticoagulation control.34 If the interaction of patient age with the relative benefit from OAC and AP therapy varies significantly because of one or more of these factors, our results may not generalize to the general community. We believe that this is highly unlikely. Finally, our analysis does not include data from some notable studies of stroke prevention in patients with AF.35,36

Our results support the position that patient age alone is not a contraindication to the use of OAC in AF. The relative risk reduction by OAC for ischemic stroke persists in the oldest patients with AF. This confers an increased absolute reduction in risk of stroke. The significant reduction in the efficacy of AP treatment with increased patient age makes OAC an even more attractive treatment choice for stroke reduction in the elderly with AF.
Acknowledgments

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Disclosures

None.

References


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