Oral Anticoagulants vs Aspirin in Nonvalvular Atrial Fibrillation
An Individual Patient Meta-analysis

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Context Patients with nonvalvular atrial fibrillation (AF) have an increased risk of stroke and other vascular events.

Objective To compare the risk of vascular and bleeding events in patients with nonvalvular AF treated with vitamin K–inhibiting oral anticoagulants or acetylsalicylic acid (aspirin).

Design Pooled analysis of patient-level data from 6 published, randomized clinical trials.

Patients A total of 4052 patients with AF randomly assigned to receive therapeutic doses of oral anticoagulant or aspirin with or without low-dose oral anticoagulants.

Main Outcome Measures Ischemic and hemorrhagic stroke, other cardiovascular events, all-cause death, and major bleeding events. Person-year incidence rates were calculated to provide crude comparisons. Relative efficacy was assessed using proportional hazards modeling stratified by study. The variation of the oral anticoagulant’s relative effect by pertinent patient factors was explored with interaction terms. All analyses were conducted using the intention-to-treat principle.

Results Patients receiving oral anticoagulant and aspirin were balanced for important prognostic factors. There was no significant heterogeneity between trials in the relative efficacy of oral anticoagulant vs aspirin for any outcome. Patients receiving oral anticoagulant were significantly less likely to experience any stroke (2.4 vs 4.5 events per 100 patient-years; hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.43-0.71), ischemic stroke (HR, 0.48; 95% CI, 0.37-0.63), or cardiovascular events (HR, 0.71; 95% CI, 0.59-0.85) but were more likely to experience major bleeding (2.2 vs 1.3 events per 100 patient-years; HR, 1.71; 95% CI, 1.21-2.41). The reduction in ischemic stroke risk was similar in patients with paroxysmal AF (1.5 vs 4.7 events per 100 patient-years; HR, 0.32; 95% CI, 0.16-0.61; P < .001). Treating 1000 patients with AF for 1 year with oral anticoagulant rather than aspirin would prevent 23 ischemic strokes while causing 9 additional major bleeds. Overall all-cause survival did not differ but appeared to improve for oral anticoagulant patients 3 years after therapy was started.

Conclusions Compared with aspirin, oral anticoagulant significantly decreases the risk of all strokes, ischemic strokes, and cardiovascular events for patients with nonvalvular chronic or paroxysmal AF but modestly increases the absolute risk of major bleeding. The balance of benefits and risks varies by patient subgroup.

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among patients on oral anticoagulants
than on aspirin.31 to 33 Considerable un-
certainty about the value of long-term an-
ticoagulation compared to antiplatelet
therapy.40 This uncertainty of the rela-
tive benefit of oral anticoagulant vs as-
pirin in AF might explain the relatively
low use of oral anticoagulant in usual
practice.46

All prior meta-analyses have been
limited to using summary data avail-
able in published trial reports. We ana-
alyzed the pooled individual patient data
from all published randomized trials
comparing oral anticoagulant and as-
pirin for AF. These data are distinct
by permitting true time-to-event
analyses, exploration of subgroup ef-
effects, and comparison of the efficacy of
oral anticoagulant vs aspirin on a num-
ber of important cardiovascular out-
comes in addition to ischemic stroke.

METHODS
Included Studies: Design and Treatment

This study included patient-level data
from every published clinical trial in
which patients with AF were randomly
assigned to full-dose oral anticoagulant
or aspirin. These trials included the Atrial
Fibrillation, Aspirin, Anticoagulation
(AFASAK) Studies 12 and 3. Primary
Prevention of Arterial Thromboembo-
lism in patients with Nonrheumatic
Atrial Fibrillation in Primary Care
(PATAF),4 the European Atrial Fibrilla-
tion Trial (E-AFT),5 and the Stroke Pre-
vention in Atrial Fibrillation (SPAF)
Studies 1, 6 2, 6 and 3. Since SPAF 1 pa-
tients randomized to receive oral anti-
coagulant or aspirin all continued into
SPAF 2, SPAF 1 data are combined with
SPAF 2 as in the original publication.7
To our knowledge, there are no other
published studies in which AF patients
were randomized to receive a full-dose
of oral anticoagulant or aspirin.

All patients were adults with non-
valvular AF. The exclusion criteria var-
ed only slightly between the studies.
In general, patients were excluded if they
had clinical indications for, or contrain-
dications to, oral anticoagulation or aspi-
rin. These contraindications included
pregnancy, alcoholism, renal or hepatic
failure, thrombocytopenia, or bleeding
disorders. With the exception of the
AFASAK studies,5,3 patients were also
excluded if they had a recent acute coro-
nary event or cardiac revascularization.
All studies also excluded patients with
thyrotoxicosis except for AFASAK 1,
which included only 28 such patients.

Patients were randomly assigned to
receive a full-dose of oral anticoagu-
lation or aspirin with or without low-
dose oral anticoagulant. Patients in the
oral anticoagulant group were treated
primarily with coumarin derivatives in-
cluding warfarin sodium and 4-hy-
droxyxcoumarin. The target interna-
tional normalized ratio (INR) varied
slightly in each trial (TABLE 1). The
daily aspirin dose ranged between 75
and 325 mg (TABLE 1).

In our analyses, we combined patients
treated with aspirin alone with patients
treated with aspirin plus low-dose war-
farin because there were no significant
differences in outcomes between such
patients.3 We also reasoned that, if low-
dose warfarin has a previously unmea-
sured effect on cardiovascular out-
comes, including such patients would
likely decrease the differences between
the oral anticoagulant and aspirin groups
for cardiovascular outcomes. The
AFASAK 2 and SPAF 3 trials were the
only ones in which patients receiving
aspirin also received low-dose warfarin
in dosages of 1.25 mg/d and a median of
2.0 mg/d, respectively, and with negli-
gible prolongation of the INR. To
ensure that adding low-dose warfarin to
aspirin did not bias our study, we repeated
the analyses after excluding patients tak-
ing aspirin plus low-dose warfarin.

Baseline Factors
Patient clinical features were collected by
research coordinators and physicians be-
fore the initiation of therapy (see eTable
1 at: http://www.jama.com). These in-
cluded previous stroke or transient is-
chemic attack, hypertension, conges-
tive heart failure, diabetes, and coronary
artery disease. All studies classified pa-
tients as hypertensive if they were tak-
ing medications given to lower blood
pressure. In the AFASAK studies, pa-
tients were considered to have congest-
tive heart failure if it was graded as mod-
erate or severe. We used the Atrial
Fibrillation Investigators risk stratifica-
tion to classify patient stroke risk.18 Us-
ing these data, we labeled the patients
with hypertension, diabetes, or prior ce-
cerebral ischemia as high risk. Patients with-
out these risk factors were considered low
risk if they were younger than 65 years.
All others were considered moderate risk.

Outcomes

We compared the relative efficacy of oral
anticoagulant and aspirin for 6 out-
comes: ischemic or hemorrhagic stroke;
ischemic stroke alone; hemorrhagic
stroke alone (including subarachnoid
and subdural hemorrhage); aggregate
cardiovascular events (including ische-
mic stroke, myocardial infarction, sys-
temic embolism, or cardiovascular
death); major bleeding (including in-
tracranial and systemic bleeding); and
all-cause death. Cardiovascular deaths
included those due to stroke, myocar-
dial infarction, congestive heart fail-
ure, pulmonary embolism, or systemic
embolism. Ischemic stroke and major
bleeds were classified as lethal if death
occurred within 30 days of the event.
(For outcome criteria for each trial, see
eTable 2 at: http://www.jama.com.)

Patients were followed up for a mean of
1.9 years (Table 1). Patients were rou-
tinely seen every 3 to 6 months by study
investigators or when an outcome event
was suspected. With the exception of pa-
tients in AFASAK 1, a central events
committee that was blinded to thera-
peutic group reviewed and confirmed all
events. Of all strokes, 97% were as-
sessed by neuroimaging, almost exclu-
sively by computed tomography.

Analysis

Crude event rates were calculated as
events per 100 person-years of obser-
vation and compared using the nor-
mal approximation of the Poisson dis-
tribution as described by Rothman and
Greenland.17 Kaplan-Meier curves were
generated to compare time to each out-
come, and the log-rank statistic deter-

mined the significance of differences between the curves. We used proportional hazards regression modeling to estimate the relative effect of oral anticoagulant on all 6 outcomes. Each model was stratified by study, thereby allowing different hazard functions to be estimated for each study and then a pooled hazard ratio (HR) across all studies was estimated. Such modeling helps adjust for factors that might be unique to a particular study. We tested the proportional hazards assumption for all Cox models using an interaction term between the predictor variable and time. If the P value for this term was less than .05, we concluded that the assumption of proportional hazards was not met over time.

We assessed heterogeneity between studies for each outcome by visually comparing HRs for each study with the overall estimate and by calculating the DerSimonian and Laird Q statistic for heterogeneity. To measure interactions between treatment group and baseline factors, appropriate interaction terms were included in the model. All analyses were conducted using SAS 8.1 software (Cary, NC).

RESULTS

Table 1 describes the patients according to the study in which the patients were enrolled. Atrial fibrillation was non-paroxysmal in 83% and was present for more than a year in 67% of patients. Sixty-five percent of patients were classified as having high, 27% as having moderate, and 8% as having low risk of stroke. Reflecting different patient selection criteria between studies, the prevalence of patient characteristics varied between trials (Table 1). After pooling patients from all 6 trials, patients receiving oral anticoagulant and aspirin were well matched (Table 2).

Compared with aspirin, oral anticoagulant significantly decreased the rate of all stroke, ischemic stroke, and cardiovascular events (Table 3). The decrease in the rate of all stroke was due to a large decrease in ischemic stroke with only a small absolute increase in hemorrhagic stroke. Of all ischemic strokes, 12.5% were lethal. Oral anticoagulants also decreased the lethal ischemic stroke rate (0.5 vs 0.2 events per 100 patient-years; P = .01). The significant decrease in cardiovascular events seen in the oral anticoagulant group was due primarily to decreased rates of ischemic stroke and myocardial infarction.

The use of oral anticoagulant significantly increased the rate of major bleeding (Table 3), with 15.3% of all major bleeding episodes being lethal. Hemorrhagic stroke accounted for 21.9% of all major bleeding and 52.4% of fatal bleeding events. Patients receiving oral anticoagulant had a nonsignificantly increased rate of lethal hemorrhages. Overall mortality did not differ between patient groups.

Life-table analyses (Figure 1) confirmed the crude-rate comparisons and demonstrated, with the exception of all-cause death, a consistent relative ben-

Table 1. Description of Patients and Studies*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 4052)</th>
<th>AFASAK 1 (n = 671)</th>
<th>EAFIT (n = 455)</th>
<th>PATAF (n = 272)</th>
<th>SPAF 2 (n = 1100)</th>
<th>AFASAK 2 (n = 510)</th>
<th>SPAF 3 (n = 1044)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71.7 (8.8)</td>
<td>72.6 (8.5)</td>
<td>71.1 (7.1)</td>
<td>70.5 (5.2)</td>
<td>70.3 (10.0)</td>
<td>73.5 (7.5)</td>
<td>72.3 (9.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>144.5 (21.0)</td>
<td>152.6 (19.5)</td>
<td>145.8 (20.1)</td>
<td>148.4 (17.1)</td>
<td>137.6 (19.2)</td>
<td>148.8 (19.1)</td>
<td>142.2 (22.8)</td>
</tr>
<tr>
<td>Men</td>
<td>2465 (60.8)</td>
<td>360 (53.7)</td>
<td>270 (59.3)</td>
<td>125 (46)</td>
<td>767 (69.7)</td>
<td>308 (60.4)</td>
<td>635 (60.8)</td>
</tr>
<tr>
<td>Previous TIA or stroke</td>
<td>986 (24.3)</td>
<td>37 (5.5)</td>
<td>455 (100.0)</td>
<td>3 (1.1)</td>
<td>67 (6.1)</td>
<td>44 (8.6)</td>
<td>380 (36.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2042 (50.4)</td>
<td>220 (32.8)</td>
<td>207 (45.5)</td>
<td>99 (36.4)</td>
<td>583 (53)</td>
<td>216 (42.4)</td>
<td>717 (68.7)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>834 (20.6)</td>
<td>27 (4.0)</td>
<td>41 (9)</td>
<td>0 (0)</td>
<td>226 (20.5)</td>
<td>79 (15.5)</td>
<td>461 (44.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>583 (14.4)</td>
<td>51 (7.6)</td>
<td>56 (12.3)</td>
<td>46 (16.9)</td>
<td>174 (15.8)</td>
<td>65 (12.7)</td>
<td>191 (18.3)</td>
</tr>
<tr>
<td>Angina or previous myocardic infarction</td>
<td>875 (21.6)</td>
<td>167 (24.9)</td>
<td>72 (15.8)</td>
<td>50 (18.4)</td>
<td>191 (17.4)</td>
<td>93 (18.2)</td>
<td>302 (28.9)</td>
</tr>
<tr>
<td>Study factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target INR</td>
<td>2.8-4.2</td>
<td>2.5-4.0</td>
<td>2.5-3.5</td>
<td>2.0-4.0</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
<td></td>
</tr>
<tr>
<td>Daily aspirin dose, mg</td>
<td>75</td>
<td>300</td>
<td>150</td>
<td>325</td>
<td>300</td>
<td>325</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of observation, mean (SD)</td>
<td>1.9 (1.3)</td>
<td>1.2 (0.7)</td>
<td>2.2 (1.1)</td>
<td>3.8 (1.4)</td>
<td>2.7 (1.2)</td>
<td>1.6 (0.9)</td>
<td>1.1 (0.7)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>270 (6.7)</td>
<td>25 (3.7)</td>
<td>72 (15.8)</td>
<td>7 (2.6)</td>
<td>75 (6.8)</td>
<td>30 (5.9)</td>
<td>61 (5.8)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>248 (6.1)</td>
<td>24 (3.6)</td>
<td>72 (15.8)</td>
<td>6 (2.2)</td>
<td>64 (5.8)</td>
<td>28 (5.5)</td>
<td>54 (5.2)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>30 (0.7)</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>18 (1.6)</td>
<td>2 (0.4)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>514 (12.0)</td>
<td>50 (7.5)</td>
<td>113 (24.8)</td>
<td>32 (11.8)</td>
<td>143 (13.0)</td>
<td>66 (12.9)</td>
<td>110 (10.5)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>137 (3.4)</td>
<td>3 (0.4)</td>
<td>17 (3.7)</td>
<td>25 (9.2)</td>
<td>56 (5.1)</td>
<td>8 (1.6)</td>
<td>28 (2.7)</td>
</tr>
<tr>
<td>Death</td>
<td>404 (10.0)</td>
<td>44 (6.6)</td>
<td>86 (18.9)</td>
<td>29 (10.7)</td>
<td>128 (11.6)</td>
<td>40 (7.8)</td>
<td>77 (7.4)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) unless otherwise indicated. Target international normalized ratio (INR) represents the objective anticoagulation range for patients randomized to oral anticoagulation. Patients assigned to receive oral anticoagulation were treated with warfarin sodium or 4-hydroxycoumarin. Years of observation lists the observation time with stroke as the outcome. AFASAK indicates Atrial Fibrillation, Aspirin, Anticoagulation study; EAFIT, European Atrial Fibrillation Trial; PATAF, Primary Prevention of Atrial Thromboembolism in patients with Nonrheumatic Atrial Fibrillation in Primary Care; SPAF, Stroke Prevention in Atrial Fibrillation studies; and TIA, transient ischemic attack.
eficial effect of oral anticoagulant over time. All-cause death was the only outcome for which the assumption of proportionality was not satisfied. This is reflected in the survival plots for death showing a difference between treatment groups starting 2½ years into observation (Figure 1).

The outcomes for each trial are presented in Figure 2. The relative effect of oral anticoagulant for each outcome was similar across studies with the exception of major bleeds. For major bleeding, EAFT and SPAF 3 provided particularly high and low HRs, respectively.

However, the DerSimonian and Laird Q statistic for heterogeneity in treatment effect was not significant for any outcome, including major bleeding.

To determine whether our conclusions changed without patients assigned to receive aspirin plus low-dose warfarin, we repeated the analysis after excluding such patients. This analysis excluded SPAF 3 and the combined aspirin-low-dose warfarin group of AFASAK 2, resulting in 2837 patients. We noted similar results for all stroke, 2.4 events among those taking oral anticoagulant vs 3.8 taking aspirin per 100 patient-years (HR, 0.65; 95% CI, 0.49-0.86; P = .003); ischemic stroke, 2.0 vs 3.7 events per 100 patient-years (HR, 0.56; 95% CI, 0.41-0.76; P < .001), cardiovascular events, 5.3 vs 6.9 events per 100 patient-years (HR, 0.76; 95% CI, 0.62-0.93; P = .02); and death, 4.7 vs 5.1 (HR, 0.92; 95% CI, 0.74-1.15; P = .41). There was a slight increase of the difference between the 2 groups in hemorrhagic stroke, 0.5 vs 0.2 events per 100 patient-years (HR, 2.26; 95% CI, 0.93-5.50; P = .06) and major bleeding, 2.2 vs 1.2 events per 100 patient-years (HR, 1.93; 95% CI, 1.30-2.88; P = .001). The HRs excluding those who received combined aspirin-low-dose warfarin are similar to HRs attained with the entire cohort (Table 3). When the patients taking aspirin and low-dose warfarin were excluded, cardiovascular outcome rates did not change extensively in the oral anticoagulant group but were noticeably lower in the aspirin group. This is likely due to the exclusion of high-risk patients enrolled in the SPAF 3 study.

**Effect of Treatment in Patient Subgroups**

We explored the interaction of treatment effect with relevant patient features on ischemic stroke and major bleeding (Figure 3). In almost all patient subgroups, oral anticoagulant was significantly more efficacious than aspirin for reducing the risk of ischemic stroke. Although we noted some variability in the relative benefit of oral anticoagulant between patient subgroups, most of these interactions were not significant with P > .10. There were 2 possible exceptions. The relative benefit of oral anticoagulant vs aspirin in ischemic stroke prevention appeared greater for patients younger than 75 years vs those who were 75 years or older (P for interaction = .08) and for women vs men (P for interaction = .04). The increased risk of major bleeding for patients taking oral anticoagulants appeared consistent in all patient subgroups and none of the interaction terms had a P < .10.

The absolute rate reduction in ischemic stroke by oral anticoagulant vs aspirin varied with stroke risk (Figure 3).

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**Table 2.** Patient Features by Treatment Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oral Anticoagulant (n = 1939)</th>
<th>Aspirin† (n = 2113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of observation, mean (SD)</td>
<td>1.9 (1.3)</td>
<td>1.9 (1.3)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71.5 (8.9)</td>
<td>71.9 (8.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>143.4 (20.8)</td>
<td>145.5 (21.1)</td>
</tr>
<tr>
<td>Men</td>
<td>1150 (59.3)</td>
<td>1315 (62.2)</td>
</tr>
<tr>
<td>Nonparoxysmal AF</td>
<td>1592 (82.1)</td>
<td>1788 (84.6)</td>
</tr>
<tr>
<td>AF &gt; 1 year‡</td>
<td>1259 (66.3)</td>
<td>1376 (66.8)</td>
</tr>
<tr>
<td>Previous TIA or stroke</td>
<td>473 (24.4)</td>
<td>513 (24.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>975 (50.3)</td>
<td>1067 (50.5)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>411 (21.2)</td>
<td>423 (20.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>283 (14.6)</td>
<td>300 (14.2)</td>
</tr>
<tr>
<td>Angina or previous MI</td>
<td>419 (21.6)</td>
<td>456 (21.6)</td>
</tr>
<tr>
<td>High risk of stroke§</td>
<td>1260 (65.0)</td>
<td>1373 (65.0)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) unless otherwise indicated. AF indicates atrial fibrillation; TIA, transient ischemic attack; and MI, myocardial infarction.
†With or without low-dose warfarin.
‡Information was missing for 92 patients (oral anticoagulants, n = 1899; aspirin, n = 2061).
§Based upon Atrial Fibrillation Investigators criteria.

**Table 3.** Comparison of Oral Anticoagulants and Aspirin for Several Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rates (Events per 100 Patient-Years)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Oral Anticoagulant</td>
<td>Aspirin†</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2.4 (4.5)</td>
<td>0.55 (0.43-0.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2.0 (4.3)</td>
<td>0.48 (0.37-0.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.5 (0.3)</td>
<td>1.84 (0.87-3.87)</td>
<td>.19</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>5.5 (7.8)</td>
<td>0.71 (0.59-0.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.7 (1.0)</td>
<td>0.63 (0.39-1.04)</td>
<td>.01</td>
</tr>
<tr>
<td>Systemic emboli</td>
<td>0.2 (0.3)</td>
<td>0.71 (0.29-1.74)</td>
<td>.27</td>
</tr>
<tr>
<td>Vascular death</td>
<td>3.1 (3.2)</td>
<td>0.95 (0.75-1.20)</td>
<td>.18</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.2 (1.3)</td>
<td>1.71 (1.21-2.41)</td>
<td>.02</td>
</tr>
<tr>
<td>Lethal bleeding</td>
<td>0.4 (0.2)</td>
<td>2.15 (0.87-5.41)</td>
<td>.16</td>
</tr>
<tr>
<td>Death</td>
<td>4.9 (5.2)</td>
<td>0.93 (0.76-1.13)</td>
<td>.32</td>
</tr>
</tbody>
</table>

*Hazard ratios below 1 indicate that oral anticoagulants decreased outcome risk. Hazard ratios whose 95% confidence interval (CI) excludes 1 are statistically significant at the 5% level. P values are provided for the crude rate comparison. For death, the assumption of proportionality was not satisfied. Therefore, the presented HR represents an average relative risk over the study period. Vascular death includes death from stroke, myocardial infarction, congestive heart failure, pulmonary or systemic emboli, sudden death, and presumed arrhythmic death.
†With or without low-dose warfarin.
**Figure 1. Outcomes Survival Curves**

In each plot, the horizontal axis represents time in years. The P value is a log-rank statistic. All strokes included ischemic and hemorrhagic events. Cardiovascular events included ischemic strokes, myocardial infarctions, systemic emboli, and vascular death. Major bleeding events included intracranial and major systemic bleeds.

For each study, the relative effect of oral anticoagulants vs aspirin (with or without low-dose warfarin) is presented for all 6 outcomes as a hazard ratio. Hazard ratios below 1 indicate that oral anticoagulant decreases the risk of the event. Hazard ratios whose 95% confidence interval (error bars) excludes 1 are statistically significant at the 5% level. Because hemorrhagic strokes were uncommon events, a hazard ratio could not be estimated for each study individually. The P value for the DerSimonian and Laird Q statistic, as a measure of heterogeneity, is presented for each outcome in the top right-hand corner. AFASAK indicates Atrial Fibrillation, Aspirin, Anticoagulation study; EAFT, European Atrial Fibrillation Trial; PATAF, Primary Prevention of Atrial Thromboembolism in patients with Nonrheumatic Atrial Fibrillation in Primary Care; SPAF, Stroke Prevention in Atrial Fibrillation studies.

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The absolute risk reduction in ischemic stroke achieved with oral anticoagulant was greater in patients at highest baseline risk of stroke. Patients with a previous history of stroke or transient ischemic attack had an absolute risk reduction of 6.0% per year (number needed to treat [NNT], 17) while those patients without previous cerebrovascular disease had an absolute risk reduction of 1.2% per year (NNT, 83). Patients who were classified as being at high risk of ischemic stroke by the AF investigators’ criteria had an absolute risk reduction of 3.3% per year (NNT, 30), whereas those at low risk of ischemic stroke only had an absolute risk reduction of 0.4% per year (NNT not significant). In contrast to ischemic stroke, the absolute risk increase of major bleeding with oral anticoagulant vs aspirin was more consistent between patient subgroups.

**COMMENT**

Compared with aspirin, oral anticoagulant significantly decreased the risk of all strokes, ischemic strokes, and cardiovascular events in patients with nonvalvular paroxysmal or chronic AF. The absolute risk reductions of these events were not substantially offset by small but statistically significant increases in major hemorrhage. In these patients, the overall risk of stroke or cardiovascular events was substantially higher than that of major bleeding.

These results support the use of oral anticoagulant as first-line preventive therapy for high-risk patients with nonvalvular AF. Among trial participants, the absolute rate reduction for all stroke (2.1 events per 100 patient-years), ischemic stroke (2.3 events per 100-patient-years), and cerebrovascular events (2.2 events per 100 patient-years) was considerable. Since the absolute rate increase of major bleeding with oral anticoagulant is 0.9 events per 100 patient-years, treating 1000 AF patients for 1 year with oral anticoagulant rather than aspirin would prevent 23 ischemic strokes while causing 9 additional major bleeding episodes.

We believe that our results both highlight and clarify the trade-off between potential harms and benefits of oral anticoagulant prophylaxis for AF patients. Compared with aspirin, oral anticoagulant decreased the risk of ischemic stroke but increased the risk of major bleeding. We also found that the overall absolute risk of ischemic stroke was approximately twice that for major bleeding. Several studies show that patients with AF perceive stroke as a much more serious outcome than bleeding. Hing et al also found that patients had a strong aversion to strokes and would take warfarin if it reduced the absolute risk of stroke by 1% annually. The AF patients that Gage et al interviewed gave a median utility value of 0.03 for moderate strokes and 0.0 for major stroke, with death having a utility value of 0.52. In a study by Solomon et al, patients equated the utility of severe stroke with that of death. Devereaux et al found that the average patient would take warfarin if it reduced the absolute risk of stroke by at least 0.9 events per year but would only stop the drug if it increased the risk of bleeding by 8.7 events per year. These findings show that patients fear the consequences of having a stroke more than

### Table 3.

The Effect of Patient Baseline Factors on the Efficacy of Oral Anticoagulants or Aspirin on Ischemic Stroke and Major Bleeding

<table>
<thead>
<tr>
<th>Ischemic Stroke</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events per 100 Patient-Years</strong></td>
<td><strong>Events per 100 Patient-Years</strong></td>
</tr>
<tr>
<td>Oral Anticoagulants</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Overall</td>
<td>2.0</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1.3</td>
</tr>
<tr>
<td>&gt;75</td>
<td>3.7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.8</td>
</tr>
<tr>
<td>Men</td>
<td>2.2</td>
</tr>
<tr>
<td>Prior TIA or Stroke</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.0</td>
</tr>
<tr>
<td>No</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.4</td>
</tr>
<tr>
<td>No</td>
<td>1.6</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.2</td>
</tr>
<tr>
<td>No</td>
<td>2.0</td>
</tr>
<tr>
<td>Paroxysmal Atrial Fibrillation</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.5</td>
</tr>
<tr>
<td>No</td>
<td>2.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.5</td>
</tr>
<tr>
<td>No</td>
<td>1.8</td>
</tr>
<tr>
<td>Stroke Risk</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2.6</td>
</tr>
<tr>
<td>Medium</td>
<td>1.2</td>
</tr>
<tr>
<td>Low</td>
<td>0.8</td>
</tr>
</tbody>
</table>

For subgroups in each patient factor (left), outcomes are presented as relative risks with 95% confidence intervals (error bars). Relative hazards that are less than 1 indicate that oral anticoagulants are associated with a decreased risk of the outcome. The event rates for each subgroup, expressed as the number of events per 100 patient-years of observation, are presented to the left of each plot. Patients were classified as being at high risk of stroke if they had hypertension, diabetes, or prior cerebral ischemia. Patients without these risk factors were classified as being at low risk if they were younger than 65 years. All others were classified as being at moderate risk. TIA indicates transient ischemic attack.
they fear the consequences of being prone to severe bleeding, which supports the use of oral anticoagulant treatment for such patients.

However, our results also highlight the importance of determining baseline risk to identify AF patients most likely to benefit from oral anticoagulant. There were some notable variations in the absolute difference of stroke rates (Figure 3). For patients at higher risk of ischemic stroke, such as the elderly or those with previous cerebrovascular disease, the absolute risk reduction in ischemic stroke with oral anticoagulant supercedes the associated bleeding risk. In contrast, patients at low risk of ischemic stroke have only a small absolute risk reduction in ischemic stroke. Therefore, proper risk stratification is essential to identify patients who have the best chance of benefiting from oral anticoagulant. This is especially true for patients without prior cerebrovascular disease for whom the absolute benefit of oral anticoagulant is less (Figure 3). Several risk stratification schemes have been published and further research is required to better refine our estimates of stroke risk in AF patients.

Three meta-analyses have compared oral anticoagulant with antiplatelet therapy for patients with AF. These analyses have summarized reported aggregate rates of trial outcome events. Our analysis used individual patient data, which allows a more complete and accurate comparison of outcome risk between oral anticoagulant and aspirin for patients with AF. Individual patient data permitted full survival analyses of a variety of relevant outcome events, not just ischemic stroke. We were able to provide absolute as well as relative comparisons of person-year rates of outcomes. Finally, analysis of pooled individual patient data allowed the exploration of treatment effects in relevant patient subgroups, such as those with paroxysmal AF. Because we pooled individual patient data, we had the opportunity to study 672 patients with paroxysmal AF. It is noteworthy that these patients had a similar reduction in stroke risk with oral anticoagulant (Figure 3).

Our results differ most from the meta-analysis by Taylor et al., which concluded that "the evidence for current clinical practice in long-term anticoagulation for patients with nonrheumatic atrial fibrillation is not strong." In addition to the methodological differences between the studies, other factors explain why our findings were considerably different. Taylor et al excluded the EAFT study and the high-risk component of the SPAF 3 study, both of which showed considerable advantage of oral anticoagulant over aspirin for all strokes, ischemic strokes, and cardiovascular events (Figure 2). The EAFT study was excluded from the analysis by Taylor et al because data were not presented to allow direct comparison of patients randomized to oral anticoagulant and aspirin. Our access to individual patient data avoided this problem. The SPAF 3 study was excluded because patients taking low-dose warfarin were included with those taking aspirin. We believe that it was preferable to include these patients in our analysis because including patients taking low-dose warfarin in an analysis with those taking aspirin patients would, if anything, decrease differences in cardiovascular events. Excluding these patients from the analysis did not alter our results. The only study that randomized patients to receive aspirin or low-intensity oral anticoagulant with aspirin found no significant differences in outcomes when low-dose warfarin was added to aspirin for patients with AF. Finally, their meta-analysis dichotomized outcomes into exclusive fatal and nonfatal events. This greatly decreases their statistical power to identify differences between treatment groups.

A potential limitation of our analyses stems from their uncertain applicability to AF patients outside of clinical trials. When compared with other patients, those enrolled in clinical trials tend to be healthier and more compliant. In addition, study investigators might more effectively monitor oral anticoagulant therapy than usual clinical caregivers. As a consequence, both bleeding and stroke rates might be higher among patients anticoagulated in general clinical practice. However, a recently published systematic review of anticoagulated AF patients in actual clinical practice found stroke and bleeding rates that were very similar to those found in randomized trials, supporting the external validity of our conclusions.

In summary, oral anticoagulant is more effective than aspirin in decreasing the risk of stroke and other cardiovascular events in patients with nonvalvular AF. Although oral anticoagulant also increases the risk of major bleeding, the frequency of strokes and the gravity of their consequences exceed that of therapy-associated bleeding events in most patients with AF. As a result, oral anticoagulant should be the preferred prophylactic treatment for patients with AF at a significant risk of thromboembolism.

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Author Contributions: Study concept and design: van Walraven, Hart, Singer, Laupacis, Connolly. Acquisition of data: Hart, Singer, Petersen, Koudstaal, Chang, Hellemons. Analysis and interpretation of data: van Walraven, Hart, Singer, Laupacis, Connolly. Drafting of the manuscript: van Walraven, Hart, Connolly, Petersen, Koudstaal.

Critical revision of the manuscript for important intellectual content: van Walraven, Hart, Singer, Laupacis, Connolly, Petersen, Chang, Hellemons. Statistical expertise: van Walraven, Singer, Connolly, Chang. Administrative, technical, or material support: Hart, Petersen. Study supervision: Laupacis, Connolly.

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47. Ebrahim S, Taylor F. Review: anticoagulants may be better than antiplatelet agents for nonfatal stroke but not other vascular or fatal events in nonrheumatic atrial fibrillation. J Fam Pract. 2001;50:135-141.
**Table 1. Definition of Baseline Factors**

<table>
<thead>
<tr>
<th>Disease</th>
<th>AFASAK 1</th>
<th>SPAF 2 and 3</th>
<th>EAFT</th>
<th>PATAF</th>
<th>AFASAK 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or TIA</td>
<td>From patient history and</td>
<td>From patient history</td>
<td>From patient history</td>
<td>From patient history</td>
<td>TIA from an acute onset focal</td>
</tr>
<tr>
<td></td>
<td>medical chart</td>
<td></td>
<td></td>
<td></td>
<td>deficit of presumed vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>genesis lasting &lt;24 h</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Taking or previously took</td>
<td>Blood pressure &gt;160/90 mm Hg on</td>
<td>Excluded if SBP &gt;180 or DBP</td>
<td>Taking or previously took</td>
<td></td>
</tr>
<tr>
<td></td>
<td>antihypertensive medications.</td>
<td>multiple determinations or</td>
<td>&gt;100 mm Hg.</td>
<td>antihypertensive medications.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension documented in chart.</td>
<td>receiving antihypertensive</td>
<td>SBP &gt;160 ± DBP &gt;95 mm Hg.</td>
<td>Medically verified diagnosis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>medications.</td>
<td>Hypertension in the medical</td>
<td>Excluded if SBP &gt;180 or DBP &gt;100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluded if SBP &gt;180 or DBP &gt;100</td>
<td>record.</td>
<td>mm Hg.</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>From patient history</td>
<td>From patient history</td>
<td>From patient history</td>
<td>From patient history</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>From patient history</td>
<td>From patient history</td>
<td>From patient history</td>
<td>From patient history</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>From patient history</td>
<td>Typical chest pain needing rest</td>
<td>From patient history</td>
<td>From patient history</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or nitroglycerin for relief.</td>
<td>From patient history</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical record documenting angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>by symptoms, antianginal drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>therapy, or mechanical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>revascularization.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>From patient history, medical</td>
<td>Consistent serial ECG or CK-MB</td>
<td>From patient history</td>
<td>From patient history or from ECG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>records, and ECG.</td>
<td>levels. Clinical syndrome with Q</td>
<td>From patient history</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or R wave changes or LV wall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>abnormalities. CAD on angiograph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>with ventricular dysrythymy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospitalization for chest pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>with reported MI. Q waves without</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>clinical syndrome (silent MI).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Segmental LV dysfunction.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AFASAK indicates Atrial Fibrillation, Aspirin, Anticoagulation study; EAFT, European Atrial Fibrillation Trial; PATAF, Primary Prevention of Atrial Thromboembolism in patients with Nonrheumatic Atrial Fibrillation in Primary Care; SPAF, Stroke Prevention in Atrial Fibrillation studies; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHF, congestive heart failure; MI, myocardial infarction; ECG, electrocardiogram; CK-MB, creatine kinase MB fraction; LV, left ventricle; and CAD, coronary artery disease.*
### Table 2. Definition of Outcomes*

<table>
<thead>
<tr>
<th>Disease Outcome</th>
<th>AFASAK 1</th>
<th>SPAF 2 and 3</th>
<th>EAFT</th>
<th>PATAF</th>
<th>AFASAK 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>Acute onset of neurologic deficit lasting &gt;24 h with clinical signs</td>
<td>Acute focal neurologic deficit with symptoms or signs lasting &gt;24 h. No hemorrhage on imaging.</td>
<td>Focal neurologic deficit &gt;24 h without primary hemorrhage on CT scan</td>
<td>Acute signs and symptoms of focal cerebral defect lasting &gt;24 h or causing early death with no apparent cause other than vascular</td>
<td>Acute focal neurologic deficit of presumed vascular genesis lasting &gt;24 h. No hemorrhage seen on CT or MRI.</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Neurologic deficits with CT scan result showing blood</td>
<td>Neurologic deficits with CT scan result showing blood</td>
<td>Neurologic deficits with CT scan result showing blood</td>
<td>Neurologic deficits with CT scan result showing blood</td>
<td>Neurologic deficits with CT scan result showing blood</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Consistent history, serial ECGs and enzymes at the time of the event</td>
<td>Included both silent (detected on routine ECG) and symptomatic (severe chest pain, ECG changes, CK-MB &gt;1.5 normal, new segmental abnormality on echo, autopsy evidence of subacute MI)</td>
<td>At least 2 of the following: chest discomfort; CK-MB &gt;twice normal; new Q waves on ECG</td>
<td>ECG and enzyme changes</td>
<td>At least 2 of the following: typical chest pain; typical serial CK-MB; typical ECG changes</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Required hospitalization, transfusion, or was fatal. Included intracranial, respiratory, or abdominal bleeds.</td>
<td>Required hospitalization, transfusion, or surgery. Included intracranial, respiratory, or abdominal bleeds.</td>
<td>Required hospitalization, transfusion, surgery, or shown at autopsy. Included intracranial, respiratory, or abdominal bleeds.</td>
<td>Required hospital admission, transfusion of at least 2 units of blood, or death. Included intracranial, respiratory, or abdominal bleeds.</td>
<td>Required hospitalization, transfusion, or death. Included intracranial, respiratory, or abdominal bleeds.</td>
</tr>
<tr>
<td>Vascular death</td>
<td>Death from stroke, MI, or sudden death</td>
<td>Death from stroke, MI, CHF, pulmonary embolism, arrhythmia, sudden collapse with no other probable cause, or unwitnessed death with known history of CAD</td>
<td>Death from stroke, MI, CHF, systemic embolism, pulmonary embolism, sudden death (with reliably short time between symptoms and death), or noncerebral bleeding</td>
<td>Death from stroke, MI, CHF, systemic embolism, pulmonary embolism, sudden death, or noncerebral bleeding</td>
<td>Death from stroke, MI, CHF, cardiac arrhythmia, sudden unexpected nonsuicidal death, or noncerebral bleeding</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>Embolism to kidneys, spleen, gut, lungs, or extremities documented by angiography, surgery, or autopsy</td>
<td>Embolism to kidney, spleen, gut, extremity documented on angiography (except splenic embolus)</td>
<td>Embolism to the limbs or internal organs with evidence of arterial occlusion in the absence of previous obstructive disease</td>
<td>Acute-onset vascular occlusion resulting in full recovery, permanent sequelae (major or minor), or death</td>
<td>Embolism to kidneys, spleen, gut, lungs, or extremities verified by angiography, surgery, scintigraphy, or autopsy</td>
</tr>
</tbody>
</table>

*AFASAK indicates Atrial Fibrillation, Aspirin, Anticoagulation study; EAFT, European Atrial Fibrillation Trial; PATAF, Primary Prevention of Atrial Thromboembolism in patients with Nonrheumatic Atrial Fibrillation in Primary Care; SPAF, Stroke Prevention in Atrial Fibrillation studies; CT, computed tomography; MRI, magnetic resonance imaging; ECG, electrocardiogram; CK-MB, creatine kinase MB fraction; MI, myocardial infarction; CHF, congestive heart failure; and CAD, coronary artery disease.

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