Risks and Benefits of Oral Anticoagulation Compared With Clopidogrel Plus Aspirin in Patients With Atrial Fibrillation According to Stroke Risk

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W)

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Background and Purpose—In ACTIVE-W, oral anticoagulation (OAC) was more efficacious than combined clopidogrel plus aspirin (C+A) in preventing vascular events in patients with atrial fibrillation. However, because OAC carries important bleeding complications, risk stratification schemes have been devised to identify patients for whom the absolute benefits of OAC exceed its risks.

Methods—Participants were risk-stratified with the widely-used CHADS2 scheme. Treatment-specific rates of stroke and major bleeding were calculated for patients with a CHADS2 = 1 and compared to those with a CHADS2 > 1.

Results—Observed stroke rates for those with a CHADS2 = 1 were 1.25% per year on C+A and 0.43% per year on OAC (RR = 2.96, 95% CI: 1.26 to 6.98, P = 0.01). Among patients with a CHADS2 > 1, the stroke rates were 3.15% per year on C+A and 2.01% per year on OAC (RR = 1.58, 95% CI: 1.11 to 2.24, P = 0.01) (P for interaction between stroke risk category and efficacy of OAC = 0.19). The risk of major bleeding during OAC was significantly lower among patients with CHADS2 = 1 (1.36% per year) compared to those with CHADS2 > 1 (2.75% per year) (RR = 0.49, 95% CI 0.30 to 0.79, P = 0.003).

Conclusions—In this clinical trial, patients with a CHADS2 = 1 had a low risk of stroke, yet still derived a modest (<1% per year) but statistically significant absolute reduction in stroke with OAC and had low rates of major hemorrhage on OAC. (Stroke. 2008;39:1482-1486.)

Key Words: atrial fibrillation □ stroke □ risk stratification □ anticoagulation

Atrial fibrillation (AF) is a major cause of disabling ischemic stroke.1-3 A prior history of stroke or transient ischemic attack is the most potent clinical risk factor for stroke among patients with AF4-6; however, the presence of hypertension, heart failure, diabetes, coronary artery disease, female sex, and advancing age have also been reported to convey an increased risk.4-6 Several risk stratification schemes have been developed to more precisely quantify the risk of stroke in individual patients with AF.5,8 The CHADS2 is a simple well-validated scheme,5 which assigns 1 point for a history of congestive heart failure, hypertension, age > 75, or diabetes and 2 points for a history of stroke or TIA. Patients with 2 or more points using this scheme are predicted to have an annual stroke risk of over 4%, whereas those with no points have a predicted annual risk of less than 1 to 2%.5 Randomized trials in patients with AF have conclusively demonstrated that compared to placebo, oral anticoagulation (OAC) with adjusted-dose warfarin reduces the incidence of stroke by approximately 60%.8 However, in addition to the need for frequent blood testing, difficulties maintaining a therapeutic anticoagulation intensity, and the risk of drug interactions, warfarin is associated with an annual incidence of serious bleeding of approximately 1% to 3%.9-11 Up to 10% to 15% of serious bleeds are fatal.11,12

In an effort to balance benefit with risk for individual patients, stroke risk stratification schemes (such as CHADS2) have been used to identify atrial fibrillation patients at low-risk of stroke (≤1% to 2% per year),4,5 for whom the risks and inconvenience of OAC outweigh its potential benefits.13,14 In patients identified as having an intermediate risk of stroke (2 to 4% per year), available evidence from clinical trials is inconclusive, and the present AHA/ACC/ESC guidelines for the management of atrial fibrillation15 indicate

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that the choice between OAC and aspirin in these patients is discretionary, depending on each patient’s risk of bleeding and personal preferences.\(^4,6,17\)

In the design of the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W), it was hypothesized that combination antiplatelet therapy might provide similar protection against stroke as OAC with fewer bleeding complications. However, ACTIVE-W demonstrated that OAC was superior to the combination clopidogrel plus aspirin (C+A) for the prevention of vascular events, including stroke, in patients with atrial fibrillation with one or more risk factors for stroke.\(^9\) This large, recent clinical trial provides an opportunity to reevaluate existing stroke risk stratification schemes in the setting of contemporary antihypertensive and cardiovascular therapy, and to determine whether patients with an intermediate risk of stroke (CHADS\(_2\)=1) derive an advantage from OAC therapy compared with combination antiplatelet therapy.

Methods

The design and results of the ACTIVE-W trial have previously been reported in detail.\(^12,18\) Briefly, 6706 patients with a documented history of permanent, persistent, or at least 2 episodes of paroxysmal atrial fibrillation and at least 1 additional risk factor for stroke were randomized to receive OAC or to the combination of C+A.\(^7\)

Stroke events were adjudicated by an events committee without knowledge of antithrombotic therapy and included all strokes, ischemic and hemorrhagic, that were associated with focal neurological symptoms lasting more than 24 hours. Stroke severity was assessed using the modified Rankin scale at the time of hospital discharge or at 7 days after the stroke, whichever was later. The primary outcome for all analyses in this exploratory study is stroke alone, with secondary analyses examining a composite including stroke, noncentral nervous system (CNS) systemic embolism, myocardial infarction, and cardiovascular death. The influence of CHADS\(_2\) category on treatment effect (C+A versus OAC) was assessed using a formal statistical test for interaction or trend, where appropriate.

The ACTIVE-W included 178 patients with a CHADS\(_2\) score of 0, but who were over the age of 55 years and who had evidence of coronary or peripheral vascular disease (eligible according to the ACTIVE protocol). These conditions have been independent risk factors for stroke in some, but not all earlier studies, owing in part to differences in the way these conditions were defined.\(^19\) However, at least 1 set of clinical practice guidelines suggests that these conditions warrant the use of oral anticoagulation.\(^19\) For the purpose of this analysis, these patients are categorized together with patients having a CHADS\(_2\) score of 1; however, event rates for patients with a CHADS\(_2\) score of 0 are also presented separately. The rate of major bleeding (defined as bleeding associated with any of the following: death, drop in hemoglobin of at least 2 g/dL, significant hypotension with the need for inotropic agents, bleeding requiring surgical intervention [other than vascular site repair], symptomatic intracranial hemorrhage, intraocular hemorrhage causing loss of vision, or the requirement for a transfusion of at least 2 U of blood), was reported for all groups. Patients were defined as OAC-naïve if they were not receiving warfarin at the time of study entry.

Among patients assigned to C+A, the independent effects of age, gender, prior history of stroke or TIA, diabetes, coronary artery disease, heart failure, hypertension, systolic and diastolic blood pressure (as time-dependent covariates) on the risk of subsequent stroke were determined using Cox proportional hazard modeling. All variables with a probability value of <0.10 were kept in the final multivariate model.

The main goals of this analysis were to determine the absolute rates of stroke and major bleeding among patients with a CHADS\(_2\)=1 treated with warfarin compared with C+A, and to compare the relative efficacy of warfarin in this group to those with CHADS\(_2\)>1.

Results

For the 6706 ACTIVE-W participants, the mean age was 70 years and 66% were men. During an average follow-up of 1.28 years, 159 strokes were observed (87% ischemic and 13% hemorrhagic).

Independent Predictors of Stroke in Patients Assigned Dual Antiplatelet Therapy

In the 3335 patients on C+A, stroke occurred in 100 individuals (2.4% per year). Prior histories of TIA (HR=3.24, 95% CI: 2.02 to 5.21, \(P<0.0001\)) or stroke (HR=2.49, 95% CI: 1.53 to 4.07, \(P=0.0003\)) were the strongest independent predictors of stroke risk in these patients. Age (HR=1.03 per year, 95% CI: 1.01 to 1.05, \(P=0.01\)) and a history of diabetes (HR=2.06, 95% CI: 1.37 to 3.10, \(P=0.0006\)) were also significant independent predictors of stroke. Neither a history of hypertension nor diastolic blood pressure (as a time-dependent covariate; using the most recent follow-up blood pressure at the time of a clinical event) predicted stroke (Table 1); however systolic blood pressure (as a time-dependent covariate) did (HR=1.01 per 1 mm Hg, 95% CI: 1.00 to 1.02, \(P=0.037\)). Female sex, history of heart failure, and history of coronary artery disease did not independently predict stroke (Table 1).

CHADS\(_2\)-Specific Rates of Stroke and Effect of Treatment Allocation

Eighty-seven percent of patients in ACTIVE-W had a CHADS\(_2\) score of 1, 2, or 3 (Table 2). All subgroups derived a greater benefit from OAC compared to C+A, regardless of their baseline CHADS\(_2\) score (\(P\) for trend=0.27; Table 2).

For patients with CHADS\(_2\)=1, stroke rates were: 1.25% per year for patients receiving C+A and 0.43% per year for patients receiving OAC (RR=2.96, 95% CI: 1.26 to 6.98, \(P=0.01\)). For patients with a CHADS\(_2\)>1, stroke rates were 3.15% per year and 2.01% per year, respectively (RR=1.58, 95% CI: 1.11 to 2.24, \(P=0.01\)). The benefits of OAC were not significantly different between these 2 groups, based on CHADS\(_2\) score (\(P\) for interaction=0.19), although there was a somewhat greater absolute reduction in stroke among patients with CHADS\(_2\)>1 than in patients with CHADS\(_2\)=1 (1.14% per year versus 0.82% per year). The proportion of mild strokes (Modified Rankin 0 to 2) to severe strokes (Modified Rankin 3 to 6) was similar in patients with CHADS\(_2\)=1 and >1 (Table 3).

Patients with prior stroke or TIA (secondary prevention cohort) had a stroke rate of 6.22% per year when assigned to C+A, compared to 2.99% per year when assigned to OAC (RR=2.13, 95% CI: 1.23 to 3.69, \(P=0.007\)). Patients with no prior stroke or TIA had stroke rates of 1.77% per year on C+A and 1.12% per year on OAC, and although they derived a similar relative benefit (RR=1.60, 95% CI: 1.08 to 2.39, \(P=0.02\)), their absolute reduction in stroke with OAC was much lower (0.65% per year versus 3.23% per year).

Among patients with a CHADS\(_2\) score of 1, 76% had hypertension, 12% were over age 75 years, 8% had heart
failure, and 3% had diabetes as their sole risk factor for stroke. There were only 5 strokes among 573 patients with only diabetes, heart failure, or age >75 as their only risk factor for stroke; too few events to conclusively evaluate the relative effect of C/A to OAC. There were 20 strokes among 1863 patients with hypertension as their only risk factor, with a stroke rate of 1.5% per year in patients assigned to C/A and 0.2% per year among patients assigned to OAC (RR = 8.79, 95% CI: 2.04 to 37.9, P = 0.004).

**Effect of Treatment on Vascular Events**
The ACTIVE primary outcome (stroke, noncentral nervous system systemic embolism, all-cause mortality, and myocardial infarction) occurred more frequently in patients on C/A, both with CHADS2 = 1 (3.28% per year versus 1.92% per year, RR = 1.72, P = 0.01) and with CHADS2 > 1 (7.14% per year versus 5.18% per year, RR = 1.40, P = 0.0035). CHADS2 status did not significantly affect the relative benefit of OAC for this outcome (P for interaction = 0.41).

**Bleeding Complications**
CHADS2-specific major bleeding rates were determined for both treatment groups (Table 4). For patients with CHADS2 = 1, the rate of major bleeding was 2.09% per year on C/A, which was higher than the rate of 1.36% per year on OAC (RR = 1.55, 95% CI: 0.91 to 2.64, P = 0.11). For patients with CHADS2 > 1, major bleeding occurred at a rate of 2.63% per year on C/A and 2.75% per year on OAC (RR = 0.97, 95% CI: 0.69 to 1.35, P = 0.84). The relative risk of major bleeding with C/A, compared to OAC, was not significantly different between patients with high and low CHADS2 scores (P for interaction = 0.15); however, the absolute risk of major bleeding on OAC was significantly lower among patients with CHADS2 = 1 compared to CHADS2 > 1 (RR = 0.49, 95% CI 0.30 to 0.79, P = 0.0003). Among OAC-naïve patients, the rate of major bleeding with OAC was 1.81% per year for patients with CHADS2 = 1 and 3.76% per year for patient with CHADS2 > 1. Among OAC-experienced patients, the rates were 1.33% per year for CHADS2 = 1 and 2.47 for CHADS2 > 1.

**Table 1. Risk Factors for Stroke: Baseline Prevalence and Predictive Value in Multivariate Analysis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Baseline Prevalence</th>
<th>Multivariate HR for Stroke</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent predictors included in final model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>509 (15.3%)</td>
<td>2.49</td>
<td>1.53 to 4.07</td>
<td>0.0003</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>3.24</td>
<td>2.02 to 5.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIA</td>
<td></td>
<td>2.06</td>
<td>1.37 to 3.10</td>
<td>0.0006</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>712 (21.3%)</td>
<td>1.03</td>
<td>1.01 to 1.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, y</td>
<td>70.2 ± 9.4</td>
<td>1.01</td>
<td>1.00 to 1.02</td>
<td>0.037</td>
</tr>
<tr>
<td>Systolic BP, per 1 mm Hg</td>
<td>133 ± 19.1*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables not included in final model*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>573 (17.0%)</td>
<td>1.10</td>
<td>0.70 to 1.74</td>
<td>0.67</td>
</tr>
<tr>
<td>Diastolic BP, per 1 mm Hg</td>
<td>79.3 ± 11.7*</td>
<td>1.00</td>
<td>0.97 to 1.02</td>
<td>0.65</td>
</tr>
<tr>
<td>Female</td>
<td>1116 (33.5%)</td>
<td>1.18</td>
<td>0.78 to 1.79</td>
<td>0.43</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>991 (29.7%)</td>
<td>1.00</td>
<td>0.63 to 1.58</td>
<td>0.99</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>2755 (82.6%)</td>
<td>1.53</td>
<td>0.83 to 2.82</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Baseline values. Blood pressure analyzed as a time-dependent covariate.

**Table 2. CHADS2-Specific Stroke Rates for Patients Treated With Clopidogrel Plus Aspirin vs Oral Anticoagulation (OAC)**

<table>
<thead>
<tr>
<th>CHADS Score</th>
<th>Stroke Rate With ASA (/100 pt-yr)*</th>
<th>No. of Patients in ACTIVE-W</th>
<th>Stroke Rate C+A (/100 pt-yr)</th>
<th>Stroke Rate OAC (/100 pt-yr)</th>
<th>Relative Risk (C+A vs OAC)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.8</td>
<td>178 (3%)</td>
<td>1.90</td>
<td>0.80</td>
<td>3.02</td>
</tr>
<tr>
<td>1</td>
<td>2.2</td>
<td>2436 (36%)</td>
<td>1.21</td>
<td>0.40</td>
<td>3.11</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>2286 (34%)</td>
<td>1.93</td>
<td>1.86</td>
<td>1.04</td>
</tr>
<tr>
<td>3</td>
<td>8.6</td>
<td>1107 (17%)</td>
<td>2.79</td>
<td>1.72</td>
<td>1.62</td>
</tr>
<tr>
<td>4</td>
<td>10.9</td>
<td>490 (7%)</td>
<td>6.73</td>
<td>3.16</td>
<td>2.07</td>
</tr>
<tr>
<td>5</td>
<td>12.3</td>
<td>183 (3%)</td>
<td>11.65</td>
<td>2.69</td>
<td>7.01</td>
</tr>
<tr>
<td>6</td>
<td>13.7</td>
<td>26 (0.4%)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Annual rate of stroke among 2580 aspirin-treated patients with atrial fibrillation.†
†Influence of baseline CHADS score on RR (P trend = 0.29).
¶Patients had to have evidence of peripheral vascular disease or coronary artery disease and be older than 55 years.
Net Risk

The net risk (vascular events plus major bleeding) was significantly higher in patients receiving C+A, both with CHADS$_2$=1 (5.25% per year versus 2.97% per year, RR=1.79, $P=0.001$) and with CHADS$_2$=1 (9.10% per year versus 7.00% per year, RR=1.32, $P=0.005$). The absolute reduction in this outcome with OAC was similar in patients with CHADS$_2$=1 (2.28% per year) as in those with a CHADS-2 score of >1 (2.10% per year) ($P=0.18$).

Effect of Blood Pressure on Treatment Effect

Patients with a baseline systolic blood pressure above the median value (133 mm Hg) experienced a much higher risk of stroke when treated with C+A (3.25% per year) compared to OAC (1.30% per year; RR=2.53, 95% CI: 1.60 to 3.99, $P<0.0001$), whereas patients with a baseline systolic blood pressure below the median value had a low rate of stroke, irrespective of treatment allocation: C+A (1.65% per year) versus OAC (1.50% per year) (RR=1.12, 95% CI: 0.70 to 1.80, $P=0.63$). The baseline systolic blood pressure had a statistically significant influence on the benefit observed with OAC ($P$ for interaction=0.01).

Discussion

This analysis has 4 major findings. Among ACTIVE-W patients with CHADS$_2$=1, regardless of treatment assignment, the risk of stroke was low. However, they experienced a small but statistically significant reduction in stroke with OAC compared to C+A. Patients with a CHADS$_2$=1 had a low rate of major bleeding on OAC, significantly lower than that of patients with CHADS$_2$=1. Finally, study data reinforce the importance of treating hypertension as an additional means of stroke prevention among patients with atrial fibrillation.

In the ACTIVE-W study, patients with CHADS$_2$=1 treated with C+A had a very low rate of stroke (1.2% per year). The rates of stroke in patients with CHADS$_2$=2 (1.9% per year) and 3 (2.8% per year) were also lower than those observed in a prior study of aspirin-treated patients (Table 2).

Table 3. Total Number of Strokes (and Annual Rate), According to Severity, and CHADS$_2$ Score

<table>
<thead>
<tr>
<th>Stroke Severity</th>
<th>CHADS=1</th>
<th>CHADS=1</th>
<th>RR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rankin 0 to 2</td>
<td>2 (0.12%)</td>
<td>15 (0.58%)</td>
<td>0.21 (0.05 to 0.92)</td>
<td>0.04</td>
</tr>
<tr>
<td>Rankin 3 to 6</td>
<td>5 (0.31%)</td>
<td>35 (1.35%)</td>
<td>0.23 (0.09 to 0.58)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Patients with a CHADS$_2$ score of 2 or 3, these low rates were in part attributable to the enrollment of fewer patients with a history of stroke or TIA. However, the lower event rates observed in ACTIVE-W may also reflect a benefit of combination antiplatelet therapy, or improvements in the management of treatable risk factors such as heart failure and hypertension.

This analysis indicates that combination antiplatelet therapy with C+A is not an equivalent alternative to OAC for patients with CHADS$_2$=1. In these patients OAC reduces the risk of stroke and is also associated with a lower risk of major bleeding. Earlier studies have shown that aspirin alone is associated with less bleeding than OAC (9 fewer major bleeds per 1000 patient-years), which makes it a potentially attractive alternative to OAC in patients whose baseline risk of stroke is low (ie, CHADS$_2$=1). However, ACTIVE-W suggests that patients’ risk of bleeding on OAC is also influenced by their CHADS$_2$ score and that patients with CHADS$_2$=1, who were treated with OAC had a very low rate of major bleeding (1.4% per year), that is similar to the bleeding risk of patients treated with aspirin alone in earlier trials (1.3% per year). Thus, although patients with CHADS$_2$=1 derive only a small absolute reduction in stroke with OAC, the low bleeding rates with OAC in this subgroup make OAC potentially attractive.

The 2006 AHA/ACC/ESC guidelines for the management of atrial fibrillation recommend that either aspirin or OAC are appropriate for stroke prevention in patients with CHADS$_2$=1. However, the present analysis suggests that there is a small but significant advantage of OAC in this group of patients. This is in part attributable to a lower rate of major bleeding with OAC than was seen in earlier studies, partially explained by the high proportion of ACTIVE-W participants who were treated with OAC before study entry, who had a lower rate of major bleeding with OAC than OAC-naïve subjects. Thus, there appears to be a small, but clear advantage for patients with CHADS$_2$=1 to remain on OAC (particularly if no history of bleeding complications and good INR control); however, the benefit of initiating OAC among corresponding OAC-naïve patients is less clear. Given the low annual risk of stroke in all patients with CHADS$_2$=1, the selection of appropriate stroke-prevention strategies for an individual patient must be individualized and should incorporate patient preference, convenience, and baseline risk of bleeding.

Among ACTIVE-W patients treated with C+A, a history of hypertension (but not actual blood pressure levels) was not an independent predictor of stroke. Although it is possible that the prognostic value of hypertension is different for patients treated with C+A, rather than aspirin alone, it is also possible that the true influence of hypertension may have changed over the past 10 years. During this interval, clinical guidelines have suggested more aggressive diagnosis and management of systolic hypertension, which is reflected in the substantially lower mean baseline systolic blood pressure in both the ACTIVE-W (133 mm Hg) and SPORTIF-V (130 mm Hg) trials, compared to the earlier SPAF-III trial (140 mm Hg).

In ACTIVE-W, a lower systolic blood pressure during follow-up was associated with a lower risk of stroke. Among
patients with a systolic blood pressure less than the median value (133 mm Hg), the rate of stroke was low (approximately 1.5% per year), regardless of treatment allocation (OAC versus C+A), and concomitant risk factors for stroke. Although these data might suggest that, even in the presence of multiple risk factors, a low systolic blood pressure obviates the need for OAC, the posthoc nature of this and multiple other analyses precludes such a conclusion. However, the treatment of hypertension, according to present guidelines, has been conclusively shown to prevent stroke in the broader population of patients with hypertension.21 Thus it is reasonable to stress the importance of appropriate blood pressure control in patients with hypertension and atrial fibrillation.22 Among hypertensive patients with atrial fibrillation, who are unable to tolerate OAC, the treatment of hypertension is of particular importance as it may be the only feasible and proven method to reduce stroke risk, beyond treatment with aspirin.

Further research is needed to determine whether more aggressive blood pressure lowering results in a further reduction in stroke among patients with atrial fibrillation,18 although some early work suggests that this may be the case.23–25 A posthoc analysis from the PROGRESS study,23 of 476 patients who had atrial fibrillation at study entry, demonstrated a 38% reduction in vascular events among patients treated with perindopril (with or without a diuretic) after a recent stroke. This effect was statistically homogeneous among patients regardless of the use of warfarin and the presence of hypertension (baseline blood pressure greater than 160/90 mm Hg).24 This hypothesis will now be prospectively tested in the ACTIVE-I trial, which will determine whether empirical therapy with irbesartan reduces vascular events in over 9000 patients with atrial fibrillation and a systolic blood pressure of at least 110 mm Hg.

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Disclosures

None.

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