Risks and Benefits of Anticoagulation in Atrial Fibrillation
Insights From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry

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Background—Patients with atrial fibrillation (AF) at the highest stroke risk derive the largest benefit from oral anticoagulation (OAC). Those with the highest stroke risk have been paradoxically less likely to receive OAC. This study assessed the association between stroke and bleeding risk on rates of OAC.

Methods and Results—We analyzed OAC use among 10,098 patients with AF from 174 community-based outpatient practices enrolled in 2010–2011 in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). OAC was defined as warfarin or dabigatran use at study enrollment. Stroke and bleeding risk were calculated using congestive heart failure, hypertension, age, diabetes mellitus, prior stroke (CHADS2), and anticoagulation and risk factors in AF (ATRIA) scores, respectively. The mean subject age was 73 years; 58% were men. Overall, 76% of patients received OAC (71% warfarin and 5% dabigatran). The use of OAC increased among those with higher CHADS2 scores, from 53% for CHADS2=0 to 80% for CHADS2≥2 (P<0.001). OAC use fell slightly with increasing ATRIA bleeding risk score, from 81% for ATRIA=3 to 73% for ATRIA≥5 (P<0.001). A significant interaction existed between ATRIA and CHADS2 scores (P=0.021). Among those with low bleeding risk, use of OAC increased significantly with increasing stroke risk. Among those with high bleeding risk, CHADS2 stroke risk had a smaller impact on use of OAC.

Conclusions—In community-based outpatients with AF, use of OAC was high and driven by not only predominantly stroke but also bleeding risk. Stroke risk significantly affects OAC use among those with low bleeding risk, whereas those with high bleeding risk demonstrate consistently lower use of OAC regardless of stroke risk. (Circ Cardiovasc Qual Outcomes. 2013;6:00-00.)

Key Words: anticoagulants • atrial fibrillation • hemorrhage • risk factors • stroke prevention

Atrial fibrillation (AF) is the most common cardiac arrhythmia.1 Guidelines strongly and uniformly recommend anticoagulation in patients with AF and risk factors for cardioembolic events to mitigate the likelihood of stroke or thromboembolism.2–4 The benefits of oral anticoagulant therapy are directly proportional to the underlying stroke risk as measured by the congestive heart failure, hypertension, age, diabetes mellitus, prior stroke (CHADS2) or congestive heart failure or left ventricular systolic dysfunction, hypertension, age, diabetes mellitus, prior stroke, vascular disease, and sex (CHA2DS2-VASc) scores.6 Despite the documented benefits of anticoagulation in high-risk patients, several prior studies have found that those with higher CHADS2 scores are less likely to receive anticoagulation compared with healthier patients at lower risk for thromboembolism. This risk-treatment paradox with AF has been described in patients after acute ischemic stroke or transient ischemic attack,7 in patients hospitalized for heart failure,8 and in patients with acute coronary syndromes.9,10 The reasons for these patterns remain unclear. One hypothesis suggests that providers may withhold anticoagulation from

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WHAT IS KNOWN

- Patients with atrial fibrillation at the highest risk of stroke derive the greatest benefit from anticoagulation with regard to reduction of thromboembolic risk.
- Prior work has demonstrated that patients at higher risk of stroke are paradoxically less likely to receive anticoagulation, but these studies have occurred in acutely ill patients and have not necessarily analyzed this phenomenon according to patients’ bleeding risk.

WHAT THE STUDY ADDS

- This study found that, in a population of stable outpatients with atrial fibrillation enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, rates of oral anticoagulation increased commensurate with patients’ stroke risk.
- Furthermore, although bleeding risk influenced decisions on anticoagulation, stroke risk demonstrated a larger effect on provision of anticoagulation than bleeding risk.
- These findings suggest that the risk–treatment paradox observed in hospitalized patients does not occur and that stroke risk drives decisions on anticoagulation more than bleeding risk in stable, community-based outpatients with atrial fibrillation.

Please note that the text continues with detailed study findings, methods, and statistical analysis, exploring the interaction of stroke and bleeding risk in patients with AF.
risk, high bleeding risk, prior intracranial hemorrhage, comorbid medical conditions such as liver or renal disease, prior bleeding, allergy to OAC, patient refusal, frequent falls, and pregnancy. For this analysis, the definition of prior bleeding included any gastrointestinal bleeding, regardless of whether it occurred in the past 6 months or more remotely. All analyses performed for the initial study cohort were also performed for the sensitivity analysis. Logistic regression tested the interaction between stroke risk (ie, CHADS2 score) and bleeding risk (ie, ATRIA score) on rates of OAC in both the primary and secondary sensitivity analyses. We performed this test for interaction to determine whether bleeding risk changed the association between stroke risk and OAC in both the primary analysis and the secondary sensitivity analysis cohorts. The logistic regression accounted for site variability with generalized estimating equations. We used P<0.05 as our threshold for statistical significance. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

**Results**

**Baseline Characteristics**

In ORBIT-AF, 10098 patients had complete baseline data. No patients were excluded for lack of data on OAC. We excluded 141 patients for moderate or severe mitral stenosis. The final study cohort included 9957 patients.

Of the 9957 study subjects, 7563 subjects (76.0%) received OAC at baseline. Among the patients who received OAC, 7070 (71.0%) received warfarin alone, 486 (4.9%) received dabigatan alone, and 7 (0.1%) received both warfarin and dabigatan. No patients received warfarin and dabigatan concomitantly. Overall, 58% of the study subjects were men, and 89% were white. As Table 1 shows, patients receiving OAC at baseline were older, less likely to have normal left ventricular systolic function, and more likely to have persistent or permanent AF than patients not receiving OAC. Patients receiving OAC were more likely to have a history of anemia, diabetes mellitus, heart failure, chronic kidney disease, hyperlipidemia, hypertension, obstructive sleep apnea, smoking history, previous stroke or transient ischemic attack, or implantable cardioverter-defibrillator (Table 1). Finally, patients receiving OAC were less likely to receive aspirin, clopidogrel, or dual antiplatelet therapy (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=9957)</th>
<th>No OAC (n=2394)</th>
<th>OAC (n=7563)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>75 (67–82)</td>
<td>73 (63–82)</td>
<td>75 (68–82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>58.0</td>
<td>57.6</td>
<td>58.1</td>
<td>0.65</td>
</tr>
<tr>
<td>White race, %</td>
<td>89.3</td>
<td>88.6</td>
<td>89.5</td>
<td>0.34</td>
</tr>
<tr>
<td>Heart rate, bpm, median (IQR)</td>
<td>70 (63–80)</td>
<td>70 (62–79)</td>
<td>70 (64–80)</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, median (IQR)</td>
<td>126 (116–138)</td>
<td>126 (118–138)</td>
<td>125 (116–138)</td>
<td>0.067</td>
</tr>
<tr>
<td>LVEF≥50%, %</td>
<td>70.2</td>
<td>73.4</td>
<td>69.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of atrial fibrillation, %</td>
<td>14.7</td>
<td>14.7</td>
<td>14.7</td>
<td>0.95</td>
</tr>
<tr>
<td>Type of atrial fibrillation</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New onset, %</td>
<td>4.7</td>
<td>7.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal, %</td>
<td>50.7</td>
<td>64.9</td>
<td>46.2</td>
<td></td>
</tr>
<tr>
<td>Persistent or permanent, %</td>
<td>44.5</td>
<td>28.0</td>
<td>49.7</td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia, %</td>
<td>18.1</td>
<td>20.6</td>
<td>17.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>29.4</td>
<td>25.9</td>
<td>30.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>23.7</td>
<td>23.4</td>
<td>23.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Cognitive impairment or dementia, %</td>
<td>3.0</td>
<td>3.8</td>
<td>2.8</td>
<td>0.011</td>
</tr>
<tr>
<td>CHF, %</td>
<td>32.1</td>
<td>26.2</td>
<td>34.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(Continued)
OAC Use According to Stroke and Bleeding Risk
Comparing rates of OAC across levels of stroke and bleeding risk found highest rates of OAC among patients with high CHADS$_2$ and low ATRIA scores (82.1%; 95% CI, 81.1–83.2; Table 2). Conversely, rates of OAC were lowest among patients with low CHADS$_2$ and high ATRIA scores (63.8%; 95% CI, 58.1–69.4; Table 2). Among patients with a low bleeding risk, rates of OAC increased commensurate with stroke risk (Figure 1). Higher bleeding risk tended to decrease rates of OAC among patients with increasing stroke risk (Figure 1). Tests for interaction between low versus high CHADS$_2$ and ATRIA scores found a significant relationship between bleeding and stroke risk on rates of OAC (Table 2; P=0.021). This suggests that differences in rates of OAC between those with low and high CHADS$_2$ scores differ by ATRIA score. In patients with low ATRIA scores, rates of OAC increase more moving from low to high CHADS$_2$ scores than they do in patients with high ATRIA scores.

Sensitivity Analysis
We performed a secondary sensitivity analysis to assess the impact of excluding those with contraindications to OAC. This analysis included all patients in the primary analysis.
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The sensitivity analysis included 8564 subjects. In this group, 7097 subjects (82.9%) received OAC at baseline. Rates of OAC increased across the spectrum of CHADS₂ scores, from 56.9% (95% CI, 52.9–60.9) among subjects with a CHADS₂ score of 0 to 91.4% (95% CI, 88.9–93.9) among those with a CHADS₂ score of 5 to 6 ($P < 0.001$). Rates of OAC increased slightly with increasing ATRIA scores, from 82.3% (95% CI, 81.4–83.3) among those with a low ATRIA score ≤ 3 to 84.6% (95% CI, 83.1–86.2) among those with an ATRIA score ≥ 4 ($P = 0.037$). Tests for interaction between low versus high CHADS₂ and ATRIA scores did not find a significant relationship between bleeding and stroke risk on rates of OAC ($P = 0.090$; Table 4).

### Discussion

In this analysis of outpatients with AF, we found an overall rate of OAC of 76%. Rates of OAC increased with increasing stroke risk in patients with both high and low bleeding risks. This suggests, in this population of stable outpatients, that the risk-treatment paradox does not exist and that stroke risk primarily drives clinical decisions on provision of OAC.

### Overall Rates of OAC

This study found a 76% rate of OAC among all patients and an 83% rate of OAC among those without contraindications to anticoagulation. Previous studies have documented a rate of anticoagulation of 50% to 65% in appropriate patients. Many reasons may account for the higher rates of OAC in the current study. Earlier studies documenting lower rates of anticoagulation enrolled patients in the 1990s, shortly after publication of trials supporting its efficacy and before widespread adoption of anticoagulation into clinical practice. Many of these studies focused on underserved populations, including Medicaid beneficiaries, who may receive less medical care. In contrast, few members of the ORBIT-AF cohort come from traditionally underserved populations. Those studies investigating patients in health maintenance organizations or other managed care settings documented rates of anticoagulation closer to those in the ORBIT-AF cohort.

### Table 2. Rates of Anticoagulation According to Stroke and Bleeding Risk*  

<table>
<thead>
<tr>
<th>ATRIA Score</th>
<th>CHADS₂ Score, n/N (%)</th>
<th>CHADS₂ Score, n/N (%)</th>
<th>Total, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0–3)</td>
<td>1633/2458 (66.4)</td>
<td>4011/4884 (82.1)</td>
<td>5644/7342 (76.9)</td>
</tr>
<tr>
<td>High (≥4)</td>
<td>261/409 (63.8)</td>
<td>1656/2202 (75.2)</td>
<td>1917/2611 (73.4)</td>
</tr>
<tr>
<td>Total</td>
<td>1894/2867 (66.1)</td>
<td>5667/7086 (80.0)</td>
<td>7561/9953 (76.0†)</td>
</tr>
</tbody>
</table>

ATRIA indicates anticoagulation and risk factors in atrial fibrillation; and CHADS₂, congestive heart failure, hypertension, age, diabetes mellitus, prior stroke.  
* $P$ value=0.021 for the interaction between CHADS₂ and ATRIA scores.  
† This calculation excludes 4 subjects without ATRIA or CHADS₂ scores.
group. For example, 73% of all patients received warfarin or aspirin in a population-based study of patients with newly detected AF in a large health plan.

It is also possible that OAC use has improved as a result of quality control measures and publication of American College of Cardiology/American Heart Association performance measures for AF. More recent studies focusing on outpatients with AF have documented higher rates of anticoagulation. For example, a study from the AFFECTS (Atrial Fibrillation: Focus on Effective Clinical Treatment Strategies) Registry, enrolling patients from 2005 to 2007, documented that 64% of eligible patients received warfarin and 83% received warfarin or aspirin.

ORBIT-AF enrolled patients from anticoagulation, cardiology, and electrophysiology clinics. Previous studies have shown lower rates of OAC among patients who do not see cardiologists. It is possible that sites voluntarily participating in ORBIT-AF may reflect providers at those sites who are more aware of guideline recommendations and quality measures. Therefore, some degree of selection bias could explain the higher rates of OAC observed in this study.

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**Figure 2.** Rate of oral anticoagulation (OAC) according to congestive heart failure, hypertension, age, diabetes mellitus, prior stroke (CHADS\textsubscript{2} stroke score (A) and anticoagulation and risk factors in atrial fibrillation bleeding score (B). $^p$ values <0.001 for the relationship of CHADS\textsubscript{2} and ATRIA scores, respectively, to rates of OAC. OAC defined as warfarin or dabigatran use at time of study enrollment.
Anticoagulation in Low-Risk Patients
The higher relative rates of OAC in our study persisted among patients at low risk for stroke. Our study found that 52.5% of patients with a CHADS₂ score of 0 received OAC. These rates of OAC are higher than previously reported in some groups of patients at this stroke risk level.²⁰,²² Other reports, however, have documented rates of OAC exceeding 50% in stable outpatients with AF and a CHADS₂ score of 0.²⁴,²⁵ In our subjects with CHADS₂ scores of 0, rates of OAC increased with additional stroke risk factors (Table 3). This finding suggests that clinicians caring for these patients were incorporating the CHADS₂-VASC score or other risk prediction models into their clinical decision making, thus lowering the threshold at which patients qualify for OAC.⁴ It is also possible that these patients may have been anticoagulated for conditions other than AF, such as valvular heart disease or venous thromboembolic events. However, it is unlikely that these conditions alone would account for the relatively high OAC rates. Finally, clinicians may be anticoagulating these patients simply because they have AF, regardless of their low rate of thrombotic events.³⁸ Regardless, these high rates of OAC in patients at low risk for stroke in this study and other reports²⁴,²⁵ raise the question about the potential for inappropriate anticoagulation in some patients with AF. Future studies are necessary to determine the specific reasons for these trends.

Association of OAC With Stroke and Bleeding Risk
Our data suggest that the overall decision to anticoagulate patients remains driven predominantly by stroke rather than bleeding risk in the population under study. The increase in OAC moving from low to high stroke risk seems greater than the decrease in OAC moving from low to high bleeding risk.

Table 3. Prevalence of Additional Stroke Risk Factors and Rates of Anticoagulation Among Subjects With CHADS₂ Score of 0

<table>
<thead>
<tr>
<th>Number of Additional Risk Factors*</th>
<th>N (%) of Subjects With CHADS₂ Score of 0†</th>
<th>N (%) of Subjects on OAC‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>230 (35.1)</td>
<td>103 (44.8)</td>
</tr>
<tr>
<td>1+</td>
<td>425 (64.9)</td>
<td>241 (56.7)</td>
</tr>
</tbody>
</table>

ATRIA indicates anticoagulation and risk factors in atrial fibrillation; CHADS₂-VASC, congestive heart failure or left ventricular systolic dysfunction, hypertension, age, diabetes mellitus, prior stroke, vascular disease, and sex; and OAC, oral anticoagulation, defined as warfarin or dabigatran use at time of study enrollment.

Additional risk factors were based on components of the CHADS₂-VASC score that were not part of the CHADS₂ score. These included left ventricular dysfunction without heart failure, female sex, 65 to 74 years of age, and vascular disease. Vascular disease was defined as any one of 3 components: coronary artery disease, peripheral vascular disease, and aortic plaque. Data on left ventricular dysfunction were missing in 84 subjects. We considered these patients as those who did not have congestive heart failure or left ventricular dysfunction unless they also had clinical congestive heart failure.

For example, rates of OAC decreased from 76.9% to 73.4% among all subjects with low versus high ATRIA scores, for a marginal difference of 3.5% (Table 2). In contrast, rates of OAC increased from 66.1% to 80.0% among all subjects with low versus high CHADS₂ scores, for a marginal difference of 21.9% (Table 2). Our sensitivity analysis excluding those with contraindications to OAC demonstrated similar marginal differences (Table 4). Furthermore, the test for interaction demonstrated that rates of OAC increase more moving from low to high CHADS₂ scores among patients with low bleeding risk than they do in patients with high bleeding risk (Table 2). The large difference in magnitude of effect and significant interaction between stroke and bleeding risk demonstrates that stroke risk drives decisions on OAC more than bleeding risk in the ORBIT-AF population of stable outpatients with AF.

Despite the importance of stroke risk, bleeding risk still influenced OAC decisions. In the primary analysis, bleeding risk impacted OAC use the most in patients with high stroke risk. In patients with a CHADS₂ score ≤1, rates of OAC were 66.4% in those with low versus 63.8% in those with high ATRIA scores. In contrast, among those with a CHADS₂ score ≥2, rates of OAC dropped from 82.1% in those with low ATRIA scores to 75.2% in those with higher ATRIA scores (Table 2).

It is possible that investigators rationalized a decision not to treat patients with OAC by justifying high bleeding risk as a contraindication to OAC regardless of the potential net benefit of OAC. This underscores the phenomenon that those who benefit the most from OAC are still less likely to receive OAC if their bleeding risk is high. Although withholding OAC in those at high risk for bleeding may seem intuitive, several potential downsides exist to such an approach. First, stroke risk and bleeding risk are highly correlated. Patients at high risk of bleeding are often at the highest risk of stroke. Furthermore, a clear positive correlation exists between stroke risk and the absolute benefit derived from OAC.²⁷,²⁸ Although it would seem logical to withhold OAC from patients with AF at high bleeding risk, current data suggest that most patients with high bleeding or stroke scores derive clinical benefit from OAC through reduced stroke risk.²⁹,³² No prospective studies have ever tested whether withholding OAC in those at high risk of bleeding results in net clinical benefit. Future prospective studies are necessary to determine if a combined bleeding and stroke-score–guided approach to OAC results in improved survival. Future work must also assess the degree to which bleeding risk should impact decisions on OAC. Despite
the limited data available, data from this study suggest that clinicians caring for stable outpatients with AF are withholding OAC from the patients at highest stroke and bleeding risk without prospective data demonstrating a benefit from that approach.

Differences Between Inpatient and Outpatient Populations
Recent studies have clearly documented a negative correlation between stroke risk and provision of OAC.7-10,33 This phenomenon has been observed most prominently in acutely ill inpatients. This study, in contrast, describes a positive correlation between stroke scores and provision of OAC in a large cohort of community outpatients. It is possible that the findings documented in the studies of inpatients occurred because clinicians withheld OAC in the context of concurrent acute illnesses or use of other antithrombotic medications, such as aspirin or clopidogrel. Other data would suggest that the risk-treatment paradox in these studies may be isolated to the inpatient setting. For instance, studies of outpatients have documented a positive correlation between rates of OAC and stroke risk.14,15,20,22 These findings imply a need for prospective studies to assess uptake of OAC among acutely ill inpatients as they transfer to stable outpatient care.

Limitations
Several limitations exist in this analysis. Participation in ORBIT-AF was voluntary, and it is possible that subject enrollment or site participation in ORBIT-AF could alter local clinical practice. The patient population in this study was also a largely white and male population, suggesting that the data may be less applicable to minority or female populations. Selection bias may also have influenced the results, as it is possible that including patients from specialty clinics, such as electrophysiology or thrombophilia practices, may have led to higher rates of OAC than observed in primary care settings. We did not include other available methods of calculating bleeding risk in our analysis. In particular, we did not use the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly score because we do not have baseline data on international normalized ratio lability, one of the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly (ie, HAS-BLED) score components, on patients in ORBIT-AF.2,34 Finally, this study did not assess the impact of stroke and bleeding risk on provision of newer anticoagulants. Although overall rates of OAC remain unchanged, despite rising use of dabigatran, it is possible that provision of OAC may increase as rivaroxaban and apixaban permeate clinical practice.35

Conclusions
In this analysis of outpatients with AF, we found that rates of OAC exceed those reported in previous studies, perhaps reflecting wider adoption of stroke prophylaxis guidelines in contemporary community practice. In contrast to prior studies, we found that use of OAC rose appropriately with increasing stroke risk, as defined by the CHADS2 score. This rise in the use of OAC occurred in patients at both high and low bleeding risks. However, in the highest risk patients, rates of OAC were driven predominantly by stroke risk.

Despite these improvements, quality initiatives remain necessary to improve overall stroke prevention treatment in patients with AF. Prospective studies must test the benefit of a combined bleeding and stroke score approach to anticoagulation.

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