Cognitive Function and Anticoagulation Control in Patients With Atrial Fibrillation

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Background—Patients with atrial fibrillation usually are elderly and may have cognitive dysfunction. These patients may receive less effective oral anticoagulation, resulting in more vascular events and bleeding.

Methods and Results—In an analysis of cognitive function associated with the time in therapeutic range (TTR) in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events, 2510 patients (mean age, 71±9.5 years) from 27 countries completed the Mini-Mental State Examination (MMSE). Of these patients, 171 (6.8%) had an MMSE score <24, suggesting dementia, and 194 (7.7%) had intermediate scores of 24 to 25. Low MMSE scores were correlated with a low TTR. Even mild cognitive impairment was associated with a TTR below the median (<65%). Patients with an MMSE score <26 had more vascular events (6.7% versus 3.6% per 100 patient-years; P=0.002) and more bleeding (9.6% versus 7% per 100 patient-years; P=0.04). After controlling for TTR, the MMSE no longer conferred increased risk, suggesting that if improved anticoagulation was provided, vascular events and bleeding would be reduced. Other independent factors associated with a TTR <65% were region of the world, recent initiation of vitamin K antagonist, type of anticoagulant, and concurrent use of amiodarone or insulin. After adjustment for these factors, lower MMSE scores still predicted a reduced TTR.

Conclusions—Cognitive dysfunction is common in elderly patients with atrial fibrillation and is related to less effective anticoagulation and more vascular events. The MMSE identifies patients with atrial fibrillation in whom extra efforts are needed to maintain effective anticoagulation and improve outcomes.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00243178.

Key Words: anticoagulants ■ atrial fibrillation ■ tachycardia

O ral anticoagulation with a vitamin K antagonist reduces stroke in patients with atrial fibrillation (AF), particularly if international normalized ratio (INR) values are maintained between 2.0 and 3.0. INR values >2.0 are associated with an increased risk of stroke,1-4 and INR values >3.0 are associated with an increased risk of bleeding.5-11 Unfortunately, maintaining an INR value between 2.0 and 3.0 is difficult.

The time in therapeutic range (TTR), an estimate of the duration of time spent within a prespecified INR target, is a measure of anticoagulation quality. Low TTR values (<60%) are associated with more strokes, more vascular events, and more bleeding.12-14 In the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W), half the patients had a TTR <65%. In clinical research trials of patients with AF, TTR values as high as 66% to 68% have been reported.15-17 However, in the ordinary practice setting, TTR values are considerably lower, averaging 57%.17 Most patients with AF are elderly and may have an increased risk of cognitive dysfunction.18 Treatment with oral anticoagulants in these patients presents special challenges, considering the periodic changes in dosing based on at least monthly laboratory studies. These patients may not take medications as prescribed and may be unaware of drug or food interactions. The effect of cognitive impairment on TTR is not known. We hypothesized that patients with AF and cognitive dysfunction, as assessed by the Mini-Mental State Examination (MMSE), would have less effective anticoagula-
tion as measured by TTR. As a consequence of less effective anticoagulation, they should have more vascular events and more bleeding. To evaluate the relationship between cognitive function and TTR, we analyzed patients enrolled in the ACTIVE-W who received oral anticoagulation.

WHAT IS KNOWN

- Oral anticoagulation is effective at preventing stroke and systemi emboli in patients with atrial fibrillation if the international normalized ratio is kept between 2.0 and 3.0.

WHAT THE STUDY ADDS

- A low score on the Mini-Mental Status Examination is a powerful predictor of an out-of-range international normalized ratio, and these patients require extra efforts to maintain effective anticoagulation.
- Other factors predicting an out-of-range international normalized ratio are region of the world, recent initiation of oral anticoagulation, oral anticoagulants other than warfarin, and concurrent use of amiodarone or insulin.

Methods

Participants

The results of ACTIVE-W have been published and have shown the superiority of warfarin compared with clopidogrel plus aspirin in stroke prevention in AF. Patients were eligible for ACTIVE-W if they had electrocardiographic evidence of AF and at least one of the following risk factors: (1) on treatment for systemic hypertension; (2) a prior stroke, transient ischemic attack, or non-central nervous system (CNS) embolism; (3) left ventricular dysfunction; (4) peripheral vascular disease; (5) ≥75 years of age; or (6) 55 to 74 years of age with either diabetes mellitus requiring therapy or with a previous myocardial infarction (MI) or documented coronary artery disease. Patients randomized to oral anticoagulation were managed by local practice guidelines either by individual physician offices or by anticoagulation clinics with at least monthly INR testing. For this study, the recommended INR goal was 2.0 to 3.0, consistent with published guidelines. The method of anticoagulation control, either by office practice or anticoagulation center, was determined by each investigator. The trial was performed in 522 centers from 31 countries around the world. The trial was approved by local ethics boards, and all patients provided informed consent for entry.

Procedures

For this analysis, a modification of the TTR was used to estimate the quality of anticoagulation. This method interpolates all available INR values to calculate the percentage of days when the INR is between 2.0 and 3.0. INR values obtained when patients had permanently discontinued oral anticoagulation therapy or had temporarily discontinued it for >1 week (eg, for an invasive procedure) were not included in this analysis.

The modified MMSE used in ACTIVE is a questionnaire comprising 30 questions that assess cognitive function. The questionnaire takes about 10 min to complete and was administered by study personnel at the time of randomization. MMSE data were collected in all English-speaking countries and in countries where a licensed translator in the local language was available. A copy of the MMSE used in ACTIVE is included in the supplemental Appendix (available online at http://circoutcomes.ahajournals.org). Values ≤24 are associated with dementia; values of 24 to 25 are associated with a high likelihood of the development of dementia within 3 years.

Vascular events, including stroke, non-CNS embolism, and MI, were classified based on established guidelines by an events committee blinded to treatment assignment. Major and minor bleeding events were defined in a previous report.

Statistical Analysis

Differences in baseline characteristics by TTR were compared using t test for continuous variables and χ² tests for discrete characteristics. Outcomes by level of MMSE were compared using Cox regression both with and without adjusting for TTR. Models to predict a high (≥65) or low (<65) TTR used a logistic-model treating center as a random effect to adjust for the correlation of TTR by center. A multivariable logistic model was used that included the following variables identified based on known clinical relevance: female sex; MMSE score; persistent AF; systemic hypertension; left ventricular dysfunction; AF duration; heart failure; diabetes mellitus; history of bleeding; systolic blood pressure; heart rate; Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke 2 (CHADS²) score (the commonly used risk stratification scheme that assigns 1 point for congestive heart failure, hypertension, age, and diabetes and 2 points for stroke); baseline use of oral anticoagulation; baseline aspirin use; baseline angiotensin-converting enzyme inhibitor use; baseline use of calcium channel blockers; baseline amiiodarone use; baseline insulin use; type of vitamin K antagonist used during the trial; creatinine clearance <30 mL/h; ethnicity; and income level. A backwards variable selection was used to select among these clinically relevant factors, where the model begins with all factors included and then eliminates the least significant one and repeats until the final model. Backwards selection was used to error on the side of being inclusive in the model. No prior analyses of this type have been done previously, and little a priori knowledge was available about the predictors to include in these models. The significance criteria P to remove was 0.05.

Results

The ACTIVE-W study included 3371 patients with AF who received oral anticoagulation from 522 centers from 31 countries. A total of 2510 (74.5%) ACTIVE patients with complete baseline measurements, including the MMSE, form the basis of this report. The MMSE was not performed in 861 (25.5%) patients because either the entire site did not participate (n=526, 15.6%) or the individual patient did not participate (n=335, 9.6%). Reasons for the patient nonparticipation were due to either patient refusal (n=45) or lack of a translated version or logistical issues (n=285). The reason for lack of patient participation was unknown in 5 patients. Because the reasons for nonparticipation largely were related to site decision or language issues, all missing data were treated as missing completely at random, and the data from the nonparticipating patients were omitted from this analysis.

The mean age of patients in this report was 71±10 years; 34.5% were women; and the mean CHADS² score was 2.0±1.1. During a mean follow-up of 1.3 years, the median TTR was 65% (25th percentile, 47%; 75th percentile, 80%).

Relationship of Cognitive Impairment and TTR

A low score on the baseline MMSE correlated with a low TTR. For every 1-point decline in the MMSE score between 30 and 25, there was a 1-point reduction in TTR. MMSE scores ≤24 were associated with even larger reductions in TTR (Figure 1). The mean TTR for patients with an MMSE score ≤24 was 58.3±1.7. There were 171 (6.8%) patients with an MMSE score ≤24, suggesting dementia, and 194
(7.7%) with a score of 24 to 25, indicating a high likelihood of future dementia.

Other Predictors of TTR
After establishing that the baseline MMSE score was correlated with TTR, other factors affecting TTR were analyzed. Demographic and other baseline variables were compared between patients with a TTR $\geq 65\%$ (median) and patients with a TTR $<65\%$ (Table 1).

Multivariable Analysis
A multivariable analysis was performed to identify independent predictors of TTR (Figure 2). MMSE was an independent predictor of TTR. Region of the world was a strong predictor of TTR. Prior use of oral anticoagulants, the type of vitamin K antagonist, and baseline use of insulin or amiodarone predicted the TTR. After adjusting for these independent variables, MMSE score remained a powerful predictor of TTR.

Relationship of Cognitive Impairment and Vascular Events and Bleeding
Reduced MMSE scores were associated with an increased risk of vascular events and bleeding. Because MMSE scores $<26$ predicted current or future dementia, the risk of clinical events and bleeding was compared between patients with MMSE scores $<26$ and patients with MMSE scores $\geq 26$ (Table 2). For patients treated with oral anticoagulation, the composite of a stroke or non-CNS systemic embolism, vascular death, or MI occurred in 95 of 2145 patients with an MMSE score $\geq 26$ compared to 29 of 365 patients with an MMSE score $<26$ (hazard ratio [HR], 0.64; 95% CI, 0.44 to 0.93; $P=0.02$). Major or minor bleeding occurred in 187 of 2127 patients with an MMSE score $\geq 26$ compared to 43 of 356 patients with an MMSE score $<26$ (HR, 0.84; 95% CI, 0.46 to 1.51; $P=0.55$).

Discussion
There are 4 major findings in the present study. In patients with AF who received vitamin K antagonists, (1) cognitive dysfunction was common in a clinical trial requiring informed consent; (2) the score of the MMSE performed at baseline correlated with poorer anticoagulation control during the 1.3 years of follow-up, with even mild cognitive dysfunction associated with a below-median TTR; (3) the relationship between MMSE and TTR was evident even after controlling for other independent predictors of anticoagulation control; and (4) patients with low MMSE scores had an increased risk of vascular events and bleeding. In patients assigned to oral anticoagulation, the MMSE score no longer conferred increased risk when controlling for TTR, suggesting that in patients with cognitive dysfunction, excess events could be reduced by improved anticoagulation. However, a low MMSE also conferred increased risk for patients assigned to clopidogrel plus aspirin for reasons that still are not clarified.

The idea that impaired cognitive function should be associated with less effective anticoagulation is clinically intuitive but not well documented in practice. Oral anticoagulants are complex medications. Effective use requires daily compliance, periodic adjustment of dose, and a knowledge of drug and food interactions. These variables may be difficult to comprehend for elderly patients with cognitive dysfunction. Hence, a low MMSE score may result in a low TTR. However, although our data establish a relationship between MMSE and TTR, cause and effect
Table 1. Baseline Parameters Comparing Patients With Below-Median and Above-Median TTR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall n</th>
<th>Value</th>
<th>TTR ≥65% n</th>
<th>Value</th>
<th>TTR &lt;65% n</th>
<th>Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>2510</td>
<td>70.9±9.5</td>
<td>1287</td>
<td>71.2±9.1</td>
<td>1223</td>
<td>70.7±9.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Female</td>
<td>1644</td>
<td>34.5%</td>
<td>875</td>
<td>32.0%</td>
<td>769</td>
<td>37.1%</td>
<td>0.007</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2056</td>
<td>81.9%</td>
<td>1106</td>
<td>85.9%</td>
<td>950</td>
<td>77.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black</td>
<td>29</td>
<td>1.2%</td>
<td>8</td>
<td>0.9%</td>
<td>21</td>
<td>1.7%</td>
<td>0.01</td>
</tr>
<tr>
<td>Asian</td>
<td>23</td>
<td>0.9%</td>
<td>12</td>
<td>0.9%</td>
<td>11</td>
<td>0.9%</td>
<td>0.93</td>
</tr>
<tr>
<td>Other</td>
<td>402</td>
<td>16%</td>
<td>161</td>
<td>12.5%</td>
<td>241</td>
<td>19.7%</td>
<td>&lt;0.0001</td>
</tr>
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<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>None</td>
<td>51</td>
<td>2.0%</td>
<td>23</td>
<td>1.8%</td>
<td>28</td>
<td>2.3%</td>
<td>0.37</td>
</tr>
<tr>
<td>Elementary</td>
<td>772</td>
<td>30.8%</td>
<td>380</td>
<td>29.5%</td>
<td>392</td>
<td>32.1%</td>
<td>0.17</td>
</tr>
<tr>
<td>High school</td>
<td>799</td>
<td>31.8%</td>
<td>412</td>
<td>32.0%</td>
<td>387</td>
<td>31.6%</td>
<td>0.84</td>
</tr>
<tr>
<td>Trade school</td>
<td>290</td>
<td>11.6%</td>
<td>158</td>
<td>12.3%</td>
<td>132</td>
<td>10.8%</td>
<td>0.25</td>
</tr>
<tr>
<td>Community college</td>
<td>198</td>
<td>7.9%</td>
<td>104</td>
<td>8.1%</td>
<td>94</td>
<td>7.7%</td>
<td>0.71</td>
</tr>
<tr>
<td>University</td>
<td>391</td>
<td>15.6%</td>
<td>206</td>
<td>16.0%</td>
<td>185</td>
<td>15.1%</td>
<td>0.54</td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 1</td>
<td>565</td>
<td>22.5%</td>
<td>274</td>
<td>21.3%</td>
<td>291</td>
<td>23.8%</td>
<td>0.13</td>
</tr>
<tr>
<td>Range 2</td>
<td>420</td>
<td>16.7%</td>
<td>200</td>
<td>15.5%</td>
<td>220</td>
<td>18.0%</td>
<td>0.10</td>
</tr>
<tr>
<td>Range 3</td>
<td>323</td>
<td>12.9%</td>
<td>169</td>
<td>13.1%</td>
<td>154</td>
<td>12.6%</td>
<td>0.69</td>
</tr>
<tr>
<td>Range 4</td>
<td>183</td>
<td>7.3%</td>
<td>99</td>
<td>7.7%</td>
<td>84</td>
<td>6.9%</td>
<td>0.43</td>
</tr>
<tr>
<td>Range 5</td>
<td>158</td>
<td>6.3%</td>
<td>87</td>
<td>6.8%</td>
<td>71</td>
<td>5.8%</td>
<td>0.33</td>
</tr>
<tr>
<td>Region randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>1014</td>
<td>...</td>
<td>532</td>
<td>52.5%</td>
<td>482</td>
<td>47.5%</td>
<td>...</td>
</tr>
<tr>
<td>South America or Mexico</td>
<td>253</td>
<td>...</td>
<td>97</td>
<td>38.3%</td>
<td>156</td>
<td>61.7%</td>
<td>...</td>
</tr>
<tr>
<td>Western Europe</td>
<td>965</td>
<td>...</td>
<td>560</td>
<td>58.0%</td>
<td>405</td>
<td>42.0%</td>
<td>...</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>226</td>
<td>...</td>
<td>85</td>
<td>37.6%</td>
<td>141</td>
<td>62.4%</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>52</td>
<td>...</td>
<td>13</td>
<td>25%</td>
<td>39</td>
<td>75%</td>
<td>...</td>
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<tr>
<td>Systemic hypertension</td>
<td>2040</td>
<td>81.3%</td>
<td>1023</td>
<td>79.5%</td>
<td>1017</td>
<td>83.2%</td>
<td>0.019</td>
</tr>
<tr>
<td>Stroke/TIA, non-CNS event</td>
<td>353</td>
<td>14.1%</td>
<td>168</td>
<td>13.1%</td>
<td>185</td>
<td>15.1%</td>
<td>0.14</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>414</td>
<td>16.5%</td>
<td>190</td>
<td>14.8%</td>
<td>224</td>
<td>18.3%</td>
<td>0.017</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>443</td>
<td>17.6%</td>
<td>220</td>
<td>17.1%</td>
<td>223</td>
<td>18.2%</td>
<td>0.45</td>
</tr>
<tr>
<td>Heart failure</td>
<td>694</td>
<td>27.6%</td>
<td>328</td>
<td>25.5%</td>
<td>366</td>
<td>29.9%</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>512</td>
<td>20.4%</td>
<td>246</td>
<td>19.1%</td>
<td>266</td>
<td>21.7%</td>
<td>0.10</td>
</tr>
<tr>
<td>CHADS2 risk score</td>
<td>2510</td>
<td>2.0±1.1</td>
<td>1287</td>
<td>1.9±1.1</td>
<td>1223</td>
<td>2.0±1.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 drink/d</td>
<td>2155</td>
<td>85.9%</td>
<td>1098</td>
<td>85.3%</td>
<td>1057</td>
<td>86.4%</td>
<td>0.42</td>
</tr>
<tr>
<td>1–2 drinks/d</td>
<td>236</td>
<td>9.4%</td>
<td>125</td>
<td>9.7%</td>
<td>111</td>
<td>9.1%</td>
<td>0.59</td>
</tr>
<tr>
<td>2–3 drinks/d</td>
<td>71</td>
<td>2.8%</td>
<td>40</td>
<td>3.1%</td>
<td>31</td>
<td>2.5%</td>
<td>0.39</td>
</tr>
<tr>
<td>&gt;3 drinks/d</td>
<td>47</td>
<td>1.9%</td>
<td>23</td>
<td>1.8%</td>
<td>24</td>
<td>2.0%</td>
<td>0.75</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1017</td>
<td>40.5%</td>
<td>521</td>
<td>40.5%</td>
<td>496</td>
<td>40.6%</td>
<td>0.97</td>
</tr>
<tr>
<td>Former</td>
<td>1293</td>
<td>51.5%</td>
<td>675</td>
<td>52.4%</td>
<td>618</td>
<td>50.5%</td>
<td>0.34</td>
</tr>
<tr>
<td>Current</td>
<td>200</td>
<td>8.0%</td>
<td>91</td>
<td>7.1%</td>
<td>109</td>
<td>8.9%</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous bleeding</td>
<td>335</td>
<td>13.3%</td>
<td>186</td>
<td>14.5%</td>
<td>149</td>
<td>12.2%</td>
<td>0.09</td>
</tr>
<tr>
<td>History of cancer</td>
<td>298</td>
<td>11.9%</td>
<td>151</td>
<td>11.7%</td>
<td>147</td>
<td>12.0%</td>
<td>0.82</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>2507</td>
<td>85.05±19</td>
<td>1287</td>
<td>85.4±18.7</td>
<td>1220</td>
<td>84.7±19.3</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or %.
cannot be inferred. An alternative explanation is that patients with a low TTR are those who take medications improperly, resulting in a high rate of MI or stroke that results in cognitive dysfunction. Patients with a low TTR may forget to take prescribed proton pump inhibitors or may take nonsteroidal antiinflammatory agents, which lead to excess bleeding, against recommendation.

To identify patients with cognitive dysfunction, we used the MMSE, which has been in use since 1975\(^{18}\) and has gained international acceptance as a simple method for evaluating memory loss and cognitive function. Scores \(<24\) are suggestive of dementia, and scores of 24 or 25 are associated with an increased risk of developing dementia within 3 years.\(^ {21}\) One previously reported single-center study of 152 patients receiving acenocoumarol for AF reported a relationship between MMSE scores and suboptimal anticoagulation control (defined as an INR of 2.0 to 3.4 \(\leq 70\% \) of the treatment time). Patients with an MMSE score \(<23\) had in-range INRs in 68% of the 1 year before administration of the MMSE. Patients with an MMSE \(\geq 23\) had in-range INRs during 76% of the treatment time.\(^ {22}\) The current study is in agreement with these findings. In addition, this study dem-

### Table 2. Vascular Events and Bleeding Related to the MMSE

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients Assigned to Oral Anticoagulation</th>
<th>Patients Assigned to Clopidogrel Plus Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMSE &lt;26, Rate/100 Person-Years</td>
<td>MMSE (\geq 26), Rate/100 Person-Years</td>
</tr>
<tr>
<td>No. patients</td>
<td>365</td>
<td>2145</td>
</tr>
<tr>
<td>Stroke, vascular death, MI, non-CNS embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular death</td>
<td>23</td>
<td>5.3</td>
</tr>
<tr>
<td>MI</td>
<td>65</td>
<td>1.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>1.1</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>32</td>
<td>7.4</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>11</td>
<td>2.5</td>
</tr>
<tr>
<td>Total bleeding</td>
<td>42</td>
<td>9.6</td>
</tr>
</tbody>
</table>

RR indicates relative risk.

*After adjustment for TTR, there were no significant associations between the MMSE and vascular events and bleeding. See text for details.
onstrates that even mild cognitive dysfunction is associated with lower TTR. A strong correlation exists between the degree of cognitive dysfunction and the level of TTR; thus, MMSE score is a predictor of TTR independent of other factors.

The number of patients potentially affected by these findings is substantial. The prevalence of AF rises with age and exceeds 5% in patients >70 years. Approximately 10% of patients ≥85 years have AF. Cognitive dysfunction also is more prevalent in the elderly population. A large population-based study has shown that the median MMSE score is 27 for subjects 70 to 74 years of age. For subjects ≥85 years, the median MMSE score is 25. Twenty-five percent of patients 70 to 74 years of age have an MMSE score <24, and the percentage in the lower quartile increases with age. In the current analysis, the average age of patients was 71 years, and the average MMSE score was 27.9; only 6.8% of patients had an MMSE score <24, which is a lower percentage than that in the population-based study. This result likely is due to exclusion of patients with obvious dementia or other factors that affect participation in a clinical trial. In clinical practice, the number of patients with AF and cognitive dysfunction likely is considerably greater. The impact of cognitive impairment on drug adherence, especially in elderly patients, is a major public health challenge and is accentuated with drugs such as oral anticoagulants that require care in taking the medication as prescribed, having regular monitoring, and being aware of potential interactions with other drugs.

AF itself is independently associated with cognitive dysfunction. The explanation for this association is uncertain. Silent cerebral infarction is common in patients with AF, and neuroimaging studies have shown asymptomatic brain infarction to be common in the elderly general population. Patients with asymptomatic brain infarction are at increased risk of stroke and cognitive decline. Regardless of the cause, a patient with AF and cognitive dysfunction appears to have a high risk of vascular events and a high risk of bleeding.

This study has a few limitations. The MMSE is an acceptable screening tool for cognitive dysfunction but is oriented to memory function. Low MMSE scores may be related to age, sex, and underlying depression and not necessarily to cognitive dysfunction. There may be educational or cultural biases that affect the MMSE. The tool was the only test for cognitive dysfunction, but multiple tests may better identify patients at risk for dementia. The MMSE was administered only once and only at baseline and did not account for variability in test results of a single cognitive task administered on one occasion. Finally, patients with clinically recognized cognitive dysfunction generally are not recruited into clinical trials like ACTIVE-W; however, the proportion of patients with cognitive impairment or dementia is likely to be higher in clinical practice and, therefore, our study may have underestimated the magnitude of the problem of underanticoagulation due to poor cognitive function.

Our study has several strengths. To our knowledge, it is by far the largest study of cognitive impairment in patients with AF. Its size, the involvement of multiple countries, and the collection of prospective data of the levels of anticoagulation and events make it both unique and applicable to the AF population in general.

In summary, the MMSE, a screening questionnaire to detect cognitive dysfunction, identified a substantial number of ACTIVE-W patients with cognitive impairment. These patients receive less effective anticoagulation, and there was a strong correlation between the level of cognitive impairment and the level of effective anticoagulation. Even patients with mild cognitive impairment received below-average anticoagulation. Patients with cognitive impairment had more vascular events and more bleeding, which may be reduced by high-quality anticoagulation. Other factors associated with poor INR control included region of the world, lack of prior use of anticoagulation, type of anticoagulant, and baseline use of amiodarone or insulin. After adjusting for these factors, the MMSE remained an independent predictor of ineffective anticoagulation. The MMSE is an effective screening tool for the identification of patients with AF who may need additional efforts to maintain high-quality anticoagulation.

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References
8. DiMarco JP, Flaker G, Waldo AL, Corley SD, Greene HL, Safford RE, Rosenfeld LE, Mitriani G, Nemeth M; The AFFIRM Investigators. Factors...


Cognitive Function and Anticoagulation Control in Patients With Atrial Fibrillation
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for the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) Investigators

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Supplementary Material
**Appendix: ACTIVE Mini-Mental Score Examination**

<table>
<thead>
<tr>
<th>PATIENT ID:</th>
<th>Centre No.</th>
<th>Patient No.</th>
<th>PATIENT INITIALS:</th>
<th>M</th>
<th>L</th>
<th>COUNTRY CODE:</th>
<th>840 USA</th>
</tr>
</thead>
</table>

**Baseline Visit date:**

- [ ] year
- [ ] month
- [ ] day

**ORIENTATION TO TIME**

1. What is the year?
2. What is the season?
3. What is the month of the year?
4. What is the day of the week?
5. What is the date?

**ORIENTATION TO PLACE**

6. Where are we now? What is the state [province]?
7. What is the county [or city/town]?
8. What is the city/town [or part of city/neighborhood]?
9. What is the building [name or type]?
10. What is the floor of the building [room number or address]?

**REGISTRATION**

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are...APPLE [pause], PENNY [pause], TABLE [pause]. Now repeat those words back to me. [Repeat up to 5 times, but score only the first trial.]

11. APPLE
12. PENNY
13. TABLE

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

**ATTENTION AND CALCULATION** [Serial 7s]*

Now I’d like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

14. What is 100 take away 7? [93]
15. If needed, say: Keep going. [86]
16. If needed, say: Keep going. [79]
17. If needed, say: Keep going. [72]
18. If needed, say: Keep going. [65]

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task.

Spell WORLD forward, then backward. Correct forward spelling if misspelled, but score only backward spelling.

Mark [X] for each correct letter:

- [ ] D
- [ ] L
- [ ] R
- [ ] O
- [ ] W
RECALL
What were those three words I asked you to remember? [Do not offer any hints.]
19. APPLE  
20. PENNY  
21. TABLE

NAMING*
22. What is this? [Point to a pencil or pen.]
23. What is this? [Point to a watch.]
*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted.

REPETITION
24. Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [Repeat up to 5 times, but score only the first trial.]

COMPREHENSION
Listen carefully because I am going to ask you to do something. Take this paper in your right hand [pause], fold it in half [pause], and put it on the floor (or table).
25. TAKE IN RIGHT HAND
26. FOLD IN HALF
27. PUT ON FLOOR (or TABLE)

READING
Please read this and do what it says. [Show patient the words on the MMSE Worksheet]
28. CLOSE YOUR EYES

WRITING
29. Please write a sentence. [If patient does not respond, say: Write about the weather.]
Place the MMSE Worksheet in front of the patient and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING
30. Please copy this design. [Display the intersecting pentagons on the MMSE Worksheet.]
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Signature of study personnel completing MMSE CRFs: ___________________________  Date: _____/_____/______
Question 28

Instruction: CLOSE YOUR EYES

Question 29

Write a Sentence

Question 30

Copy this design

[Diagram of overlapping pentagons]