Additive Role of Plasma von Willebrand Factor Levels to Clinical Factors for Risk Stratification of Patients With Atrial Fibrillation

Gregory Y.H. Lip, MD; Deirdre Lane, PhD; Carl Van Walraven, MD; Robert G. Hart, MD

Background and Purpose—To aid decisions for thromboprophylaxis in atrial fibrillation (AF), several risk stratification schemes that predict stroke risk according to clinical and echocardiographic features have been published. von Willebrand factor (vWF) is a plasma marker of endothelial damage/dysfunction and is associated with the risk of stroke and vascular events in AF patients. This study determined the additive role of plasma vWF levels to clinical factors for risk stratification in patients with AF.

Methods—We classified 994 AF patients who were enrolled in the SPAF III trial as being at low, moderate, or high risk of stroke and thromboembolism according to the Birmingham and CHADS2 risk stratification schemes. vWF levels were classified as elevated when ≥158 IU/dL. Rates of ischemic stroke and vascular events within each clinical risk stratum with and without plasma vWF levels were compared.

Results—The accuracy of both clinical risk stratification schemes was similar for predicting event rates (Birmingham: ischemic strokes, 0.642; vascular events, 0.670; CHADS2: ischemic strokes, 0.672; vascular events, 0.672). Subsequent addition of categorized vWF levels to both clinical risk stratification schemes further refined risk stratification for stroke and vascular events. When added to the Birmingham and CHADS2 clinical risk stratification, high vWF levels were independently associated with a risk of vascular events (hazard ratio, 2.05; 95% confidence interval, 1.30 to 3.22 and 2.01, 1.27 to 3.18 with Birmingham and CHADS2, respectively) but not ischemic stroke.

Conclusions—When added to clinical risk stratification schemes (Birmingham; CHADS2), plasma vWF levels refined clinical risk stratification for stroke and vascular events among AF patients. vWF levels may aid decisions about thromboprophylaxis, particularly among AF patients at moderate risk. (Stroke. 2006;37:2294-2300.)

Key Words: atrial fibrillation ▪ cerebrovascular accident ▪ prophylaxis ▪ risk assessment ▪ stroke

A though AF is associated with stroke and thromboembolism, the risk is not homogeneous. Various clinical factors and echocardiographic features have been identified as contributing to a risk of stroke and thromboembolism in AF.1,2 Data from clinical trials and prospective cohort studies have prompted the development of several risk stratification models that are used to help clinicians decide which thromboprophylaxis regimen is required for particular AF patients. These models reliably identify high-risk patients, who are usually treated with anticoagulation therapy, and low risk patients, who are usually treated with aspirin.1-6

In 1994, the Atrial Fibrillation Investigators (AFI) performed a multivariate analysis of pooled data from 1593 untreated AF participants in 5 randomized, clinical trials.4 Participants with prior cerebral ischemia (either stroke or transient ischemic attack [TIA]), hypertension, or diabetes mellitus were at high risk of stroke; patients aged 65 years and older without these risk factors were at moderate risk of stroke; and those aged <65 years with no risk factors were at low risk.4 A subsequent multivariate analysis reported that the presence of moderate to severe left ventricular systolic dysfunction on 2-dimensional transthoracic echocardiography was an independent predictor of stroke and thromboembolism.5 In 2001, an amalgamation of the AFI and additional stroke risk data from the Stroke Prevention in AF (SPAF) trials led to the development of the CHADS2 scheme.2 The CHADS2 acronym is derived from the individual stroke risk factors: Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, and prior Stroke or TIA. One point was assigned for each of the risk factors, except for prior stroke or TIA, which was assigned 2 points (hence, the subscripted 2). In a recent analysis, CHADS2 successfully identified primary prevention patients who were at high risk of stroke (5.3 strokes per 100 patient-years); in contrast, patients identified as high risk by other schemes (the original AFI, SPAF, Framingham, and ACCP risk stratification schemes) had 3.0 to 4.2 strokes per 100 patient-years.3 Low-risk patients identified by all schemes had

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risk stratification in AF in this same cohort of patients. A refined clinical risk stratification criteria would adequately identify low- and high-risk subjects with AF at risk of stroke and vascular events, in a comparable manner to the CHADS2 schema. Irrespective of clinical risk stratification scheme used, most AF patients are classified as moderate risk. The CHADS2 scheme also successfully stratified a large outpatient cohort of AF patients who were not receiving anticoagulants.

In the United Kingdom, the original AFI risk stratification was refined for a Birmingham primary care population by the AF Clinical Effectiveness Topic Group on behalf of the Birmingham Effectiveness Group, commissioned by the Birmingham Health Authority. In 1997, this was implemented in the Clinical Management in General Practice Guidelines and as a pan-Birmingham audit project in primary care by the Birmingham Health Authority. Various refinements have been published over the years, with the current one (2005) being used by the UK National Institute for Health and Clinical Excellence (NICE) national guidelines for AF management (www.nice.org.uk) (Figure). For the present analysis, our first hypothesis was that the Birmingham risk stratification criteria would adequately identify low- and high-risk subjects with AF at risk of stroke and vascular events, in a comparable manner to the CHADS2 schema.

Irrespective of clinical risk stratification scheme used, most AF patients are classified as moderate risk. Because annual stroke rates for these patients are only moderately increased in the range of 1.0% to 3.2%, optimal thromboprophylactic care for these people remains unclear. Additional methods to stratify the risk of stroke and other cardiovascular events in moderate-risk AF patients would help clinicians and patients decide whether oral anticoagulation and or antiplatelet therapy would be preferable. Plasma markers of coagulation, endothelial damage/dysfunction, and platelet activation could fill this role. Abnormal levels of these markers have been well described in AF. We recently reported that raised baseline levels of von Willebrand factor (vWF, an index of endothelial damage or dysfunction) were predictive of stroke and vascular events. Because the incidence of thromboembolic events in patients with thyrotoxicosis appears similar to that of other etiologies of AF, anti-thrombotic therapies should be chosen on the basis of the presence of validated stroke risk factors. Owing to a lack of sufficient clear-cut evidence, risk assessment may be decided on an individual basis, and the physician must balance the risks and benefits of warfarin versus aspirin; because stroke risk factors are cumulative, warfarin may (for example) be used in the presence of 2 or more risk factors. Referral and echocardiography may help in cases of uncertainty. CVA indicates cerebrovascular accident.

We tested these hypotheses in 994 participants receiving aspirin 325 mg/d (alone or combined with fixed inefficacious doses of warfarin) in the Stroke Prevention in Atrial Fibrillation (SPAF) III study and related clinical risk criteria, with and without plasma vWF levels, to the risk of subsequent stroke and vascular events. Our objective was to determine whether the use of plasma vWF could be of clinical value in predicting stroke and vascular events when added to clinical risk stratification.

**Methods**

The design and main results of the SPAF III study, which was sponsored by the National Institute of Neurological Disorders and Stroke, have been reported previously. In brief, patients with nonvalvular AF were stratified as low, moderate, or high risk for stroke on the basis of clinical and echocardiographic features predictive of thromboembolic risk in the earlier SPAF I and II studies. Those with any of the 4 high-risk criteria (women >75 years of age, systolic hypertension >160 mm Hg, impaired left ventricular function, and previous thromboembolism) were randomized to receive either adjusted-dose warfarin (target international normalized ratio [INR] 2 to 3) or fixed, low-dose warfarin (target INR, 1.2 to 1.5) plus aspirin 325 mg/d (termed combination therapy). Participants without any of the 4 specific risk factors were classified as moderate or low risk, depending on the presence or absence of a history of hypertension, and received aspirin 325 mg/d alone.

Blood samples were primarily collected at baseline (or after 3 months of enrollment if not available/collected at baseline) from all participants except those enrolled and followed up at outlying clinics, where specimens could not be adequately processed; thus, 69% (1339/1936) of SPAF III participants had ≥1 sample collected at baseline or at 3 months. Those with a sample available for this study were comparable to participants in the main trial. To remove the potentially confounding effect of ischemic stroke reduction by subsequent randomization to adjusted-dose warfarin (compared with aspirin alone or to aspirin combined with fixed inefficacious doses of warfarin [combination therapy]), we excluded those participants randomized to receive adjusted-dose warfarin therapy (INR of 2 to 3) and limited our analysis to those participants receiving aspirin 325 mg/d (alone or as combination therapy). It should be noted that some of the vWF levels among these 994 patients were obtained during prior warfarin anticoagulation at the time the baseline sample was
collected at entry into SPAF III, but previous data do not suggest that warfarin influences vWF levels.\textsuperscript{12,13}

Blood collection materials were prepared at the Laboratory for Clinical Biochemistry Research, Department of Pathology, University of Vermont. Blood for vWF assay was drawn into 3.8% sodium citrate tubes (Becton Dickinson), immediately mixed by gentle inversion, stored on melting ice, and centrifuged at 4°C for 30,000 g-minutes with 1 hour of phlebotomy; plasma was separated for vWF assays. Measurements of vWF were performed with an ELISA with reagents from R&D Systems (Abingdon, UK). The unit for vWF is IU/dL, and was standardized by reference vWF from the National Institute for Biological Standards and Controls, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, UK. Intra-assay coefficients of variation for all ELISAs were $<5\%$, and interassay variances were $<10\%$. The incidence of stroke, myocardial infarction, vascular events, and all-cause mortality during the trial was documented.

### Analysis

Patients were risk-stratified according to the Birmingham (Figure) and CHADS\textsubscript{2} risk stratification criteria. The CHADS\textsubscript{2} scores were stratified into 3 groups\textsuperscript{3} to allow comparison with Birmingham criteria, where a score of zero was low risk, 1 to 2 was moderate risk; and $\geq$3 was high risk. Based on our previous data,\textsuperscript{10} a high plasma vWF level was defined as the top tertile ($\geq$158 IU/dL) of vWF levels in the study cohort. Low plasma vWF levels were defined as $<158$ IU/dL. The relation between clinical risk scores and/or plasma vWF levels and several end points, including ischemic stroke and vascular events, during 2 years of follow-up was assessed. A vascular event was defined as the first incident of ischemic stroke, myocardial infarction, or vascular death.

We used Cox models to determine the association of vWF levels with time to ischemic stroke and vascular event independent of the clinical risk scores. These models included each clinical risk score with vWF levels to determine whether the association of vWF levels with time to ischemic stroke or vascular event was independent of the clinical risk score. We also used multivariate logistic regression to calculate changes in the $c$-statistic in models that added vWF to clinical risk scores. The $c$-statistic (concordance statistic) is the proportion of possible combinations of cases and noncases in the sample for which the logistic model assigns a higher probability of an event occurring to the case. The $c$-statistic is analogous to the area under the receiver operating characteristic (ROC) curve and measures the discriminating ability of the model. We calculated 95\% confidence intervals (CIs) according to the bootstrap method with 1000 random samples with replacement. To directly compare the $c$-statistics of 2 models, we determined whether the 83\% CIs of the 2 models overlapped. Point estimates whose 83\% CIs do not overlap differ significantly with an $\alpha$ error $<0.05$.\textsuperscript{14}

To determine the clinical relevance of vWF levels for risk stratification, we also calculated annualized event rates with 95\% CIs for ischemic stroke and vascular events for each level of the clinical risk score and without vWF values. All tests were 2 tailed, with probability values $\leq0.05$ considered statistically significant. Statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).

### Results

The clinical characteristics of our study cohort are summarized in Table 1, and the proportion of patients with each of the clinical end points at follow-up are also listed in Table 1. Based on the Birmingham risk stratification scheme, 110 (11.0\%) patients were low risk, 551 (55.4\%) were moderate risk, and 333 (33.5\%) patients were high risk. The analogous figures based on the CHADS\textsubscript{2} criteria were 260 (26.1\%), 553 (55.6\%), and 181 (18.2\%), respectively. The differences in classification according to the 2 schemes were statistically significant ($\chi^2=105.7$, $df=2$; $P<0.001$).

The mean follow-up and annualized mortality, ischemic stroke, and vascular event rates in the whole cohort were 1.6 years, 2.32\% , 2.70\%, and 4.88\%, respectively. End points at follow-up among patients with AF stratified by clinical criteria from the Birmingham and CHADS\textsubscript{2} risk stratification schemes are shown in Table 2. Stroke was sustained by 3.4\% (95\% CI, 2.1 to 5.3) of patients at moderate risk and by 7.2\% (95\% CI, 4.7 to 10.5) at high risk, based on the Birmingham risk stratification criteria. The analogous figures based on the CHADS\textsubscript{2} criteria were 4.5\% (95\% CI, 3.0 to 6.6) and 8.3\% (95\% CI, 4.7 to 13.3), respectively. Similarly, 4.9\% (95\% CI, 3.2 to 7.0) of patients at moderate risk and 14.4\% (95\% CI, 10.8 to 18.6) of those at high risk sustained a vascular event, based on the Birmingham criteria; the corresponding figures based on the CHADS\textsubscript{2} criteria were 8.3\% (95\% CI, 6.2 to 10.1) and 13.8\% (95\% CI, 9.1 to 19.7), respectively. Event distribution differed significantly between the Birmingham and CHADS\textsubscript{2} risk schemes for vascular events ($P=0.008$, myocardial infarction ($P=0.0186$), death ($P=0.0093$), and all events ($P=0.0004$) but not stroke ($P=0.0525$) (Table 2). For the Birmingham risk scheme, the area under the ROC curve for ischemic strokes and vascular events was 0.640 (95\% CI, 0.563 to 0.713; 83\% CI, 0.587 to 0.693) and 0.670 (95\% CI, 0.603 to 0.726; 83\% CI, 0.627 to 0.711), respectively. For the CHADS\textsubscript{2} risk scheme, the area under the ROC curve for ischemic strokes and vascular events was 0.673 (95\% CI, 0.582 to 0.754; 83\% CI, 0.611 to 0.731) and 0.672 (95\% CI, 0.605 to 0.737; 83\% CI, 0.627 to 0.715), respectively.

#### TABLE 1. Baseline Characteristics of Patients Receiving Aspirin or Combination Therapy (n=994) and End Points in the SPAF III Trial

<table>
<thead>
<tr>
<th>End Points during SPAF III trial, n (%)</th>
<th>685 (68.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>43 (4.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>17 (1.7)</td>
</tr>
<tr>
<td>Vascular events*</td>
<td>77 (7.7)</td>
</tr>
<tr>
<td>Death</td>
<td>38 (3.8)</td>
</tr>
<tr>
<td>All events</td>
<td>90 (9.1)</td>
</tr>
</tbody>
</table>

*includes ischemic stroke, myocardial infarction, or vascular death.
TABLE 2. End Points at Follow-Up Among Patients With AF, Stratified by the Birmingham and CHADS2 Risk Stratification Schemes

<table>
<thead>
<tr>
<th>End point</th>
<th>Low Risk, n=110</th>
<th>Moderate Risk, n=551</th>
<th>High Risk, n=333</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Birmingham, n=110</td>
<td>CHADS2, n=260</td>
<td>Birmingham, n=551</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0 (1.2%; 0%–3.3%)</td>
<td>3 (1.2%; 0%–3.3%)</td>
<td>24 (7.2%; 4.7%–10.5%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (1.8%; 0.2%–6.4%)</td>
<td>3 (1.2%; 0%–3.3%)</td>
<td>12 (3.6%; 1.9%–6.2%)</td>
</tr>
<tr>
<td>Vascular events*</td>
<td>2 (1.8%; 0.2%–6.4%)</td>
<td>6 (2.3%; 0.8%–5.0%)</td>
<td>48 (14.4%; 10.8%–18.6%)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.4%; 0%–2.1%)</td>
<td>11 (2.0%; 1.0%–3.5%)</td>
<td>27 (8.1%; 5.4%–12.6%)</td>
</tr>
<tr>
<td>All events</td>
<td>2 (1.8%; 0.2%–6.4%)</td>
<td>7 (2.7%; 1.1%–5.5%)</td>
<td>31 (17.1%; 11.9%–23.4%)</td>
</tr>
</tbody>
</table>

For the Birmingham risk score, the area under the ROC curve for ischemic strokes and vascular events was 0.642 and 0.670, respectively. For the CHADS2 risk score, the area under the ROC curve for ischemic strokes and vascular events was 0.673 and 0.714, respectively. For the CHADS2 risk score, the area under the ROC curve for ischemic strokes and vascular events was 0.673 and 0.714, respectively.

End points during the SPAF III trial, by both risk stratification schemes, with the addition of vWF levels are summarized in Table 3. For the Birmingham risk scheme plus vWF levels, the areas under the ROC curve for ischemic strokes and vascular events were 0.673 and 0.672, respectively. Event distribution differed significantly between the Birmingham and CHADS2 risk score for vascular events ($\chi^2=14.2, P=0.008$), myocardial infarction ($\chi^2=7.96, P=0.0186$), death ($\chi^2=9.35, P=0.0093$), and all events ($\chi^2=15.728, P=0.0004$) but not stroke ($\chi^2=5.89, P=0.0525$).

*Includes ischemic stroke, myocardial infarction, or vascular death.

TABLE 3. End Points at Follow-Up Among Patients With AF, Stratified by the Birmingham and CHADS2 Risk Stratification Schemes, With the Addition of plasma vWF Levels as Risk Strata

<table>
<thead>
<tr>
<th>End point, n (95% CI)</th>
<th>Low vWF, n=201</th>
<th>High vWF, n=59</th>
<th>Low vWF, n=362</th>
<th>High vWF, n=191</th>
<th>Low vWF, n=97</th>
<th>High vWF, n=84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke* (n=43)</td>
<td>2 (1.0%; 0.1%–3.6%)</td>
<td>1 (1.7%; 0%–9.1%)</td>
<td>14 (3.9%; 2.1%–6.4%)</td>
<td>11 (5.8%; 2.9%–10.1%)</td>
<td>6 (6.2%; 2.3%–12.8%)</td>
<td>9 (10.7%; 5.0%–19.4%)</td>
</tr>
<tr>
<td>Myocardial infarction (n=17)</td>
<td>2 (1.0%; 0.1%–3.6%)</td>
<td>1 (1.7%; 0%–9.1%)</td>
<td>6 (1.7%; 0.6%–3.6%)</td>
<td>4 (2.1%; 0.6%–5.3%)</td>
<td>0 (0.0%)</td>
<td>4 (4.8%; 1.3%–11.8%)</td>
</tr>
<tr>
<td>Vascular events* (n=77)</td>
<td>4 (2.0%; 0.5%–5.0%)</td>
<td>2 (3.4%; 0.4%–11.7%)</td>
<td>25 (6.9%; 4.5%–10.0%)</td>
<td>21 (11.0%; 6.9%–16.3%)</td>
<td>7 (7.2%; 3.0%–14.3%)</td>
<td>18 (21.4%; 13.2%–31.7%)</td>
</tr>
<tr>
<td>Death (n=38)</td>
<td>1 (0.5%; 0%–2.7%)</td>
<td>0 (0.0%)</td>
<td>13 (3.6%; 1.9%–6.1%)</td>
<td>10 (5.2%; 2.5%–9.4%)</td>
<td>5 (5.2%; 1.7%–11.6%)</td>
<td>9 (10.7%; 5.0%–19.4%)</td>
</tr>
<tr>
<td>All events (n=90)</td>
<td>5 (2.5%; 0.8%–5.7%)</td>
<td>2 (3.4%; 0.4%–11.7%)</td>
<td>29 (8.0%; 5.4%–11.3%)</td>
<td>23 (12.0%; 7.8%–17.5%)</td>
<td>10 (10.3%; 5.1%–18.1%)</td>
<td>21 (25.0%; 16.2%–35.6%)</td>
</tr>
</tbody>
</table>

Low vWF was defined as <158 IU/dL; high vWF was defined as vWF ≥158 IU/dL. For the Birmingham risk score and vWF level, the area under the ROC curve for ischemic strokes and vascular events was 0.673 and 0.714, respectively. For the CHADS2 risk score, the area under the ROC curve for ischemic strokes and vascular events was 0.673 and 0.714, respectively.

*One patient who experienced a stroke did not have vWF levels available.
TABLE 4. Annualized Event Rates for Birmingham (Birm) and CHADS2 Risk Scores by vWF Level

<table>
<thead>
<tr>
<th>Risk Score Level</th>
<th>Annualized Rate (95% CI)</th>
<th>vWF Level</th>
<th>Annualized Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birm, low</td>
<td>0 (0–0)</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1.95 (1.17–2.92)</td>
<td>Low</td>
<td>1.44 (0.69–2.48)</td>
</tr>
<tr>
<td></td>
<td>5.75 (3.68–8.28)</td>
<td>High</td>
<td>3.18 (1.44–5.59)</td>
</tr>
<tr>
<td></td>
<td>0.65 (0.12–1.60)</td>
<td>Low</td>
<td>0.54 (0.05–1.56)</td>
</tr>
<tr>
<td></td>
<td>2.72 (1.76–3.89)</td>
<td>High</td>
<td>1.09 (0.00–4.27)</td>
</tr>
<tr>
<td></td>
<td>7.03 (3.92–11.0)</td>
<td>Low</td>
<td>5.68 (2.04–11.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>8.37 (3.79–14.7)</td>
</tr>
<tr>
<td><strong>Vascular events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birm, low</td>
<td>1.00 (0.09–2.88)</td>
<td>Low</td>
<td>1.25 (0.12–3.58)</td>
</tr>
<tr>
<td></td>
<td>2.78 (1.83–3.93)</td>
<td>Low</td>
<td>1.88 (1.00–3.04)</td>
</tr>
<tr>
<td></td>
<td>11.8 (8.68–15.3)</td>
<td>High</td>
<td>5.02 (2.74–8.00)</td>
</tr>
<tr>
<td></td>
<td>1.31 (0.47–2.57)</td>
<td>Low</td>
<td>1.09 (0.28–2.42)</td>
</tr>
<tr>
<td></td>
<td>5.04 (3.69–6.60)</td>
<td>Low</td>
<td>4.02 (2.60–5.74)</td>
</tr>
<tr>
<td></td>
<td>12.0 (7.78–17.2)</td>
<td>High</td>
<td>7.23 (4.47–10.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.6 (10.4–26.7)</td>
</tr>
</tbody>
</table>

Annualized event rates for Birmingham and CHADS2 risk scores by vWF level are shown in Table 4. The highest risk strata were those with high risk clinical criteria plus high vWF levels. Those with moderate risk clinical criteria plus low vWF levels were at lower risk of an event, but not as low as those identified as low risk, but there was clear separation of the annualized event rates (and 95% CIs) for moderate risk clinical criteria plus low vWF levels versus high risk clinical criteria plus low vWF levels according to the Birmingham risk score.

When added to the Cox model containing the Birmingham risk score, high vWF was independently associated with the risk of vascular events (hazard ratio [HR], 2.05; 95% CI, 1.30 to 3.22) but not ischemic stroke (HR, 1.72; 95% CI, 0.94 to 3.14). When added to the Cox model containing the CHADS2 risk score, high vWF was independently associated with risk of vascular events (HR, 2.01; 95% CI, 1.27 to 3.18) but not ischemic stroke (HR, 1.61; 95% CI, 0.87 to 2.96).

Discussion

In the present study, we applied the Birmingham and CHADS2 clinical risk stratification criteria to a cohort prospectively followed up for stroke and vascular events and found that both schemes were similar for predicting event rates. Furthermore, we have shown for the first time that the addition of plasma vWF levels as another biomarker risk factor would help to refine these clinical risk stratification schemes for stroke and vascular events. When added to both clinical risk stratification schema, high vWF was independently associated with risk of a vascular event (which is defined as the first incident of ischemic stroke, myocardial infarction, or vascular death).

Deciding whether to anticoagulate patients denoted as moderate risk is a dilemma for clinicians, as most guidelines are less clear on their recommendation for either aspirin or warfarin for this group of patients. More than half of the patients in this cohort were classified as moderate risk based on the CHADS2 (55.9%) and Birmingham (55.4%) risk stratification schemes, in keeping with previous reports. Apart from the CHADS2 (and now, the Birmingham scheme), few risk stratification criteria have emphasized the cumulative nature of risk factors, wherein a combination of diseases, such as hypertension and diabetes, would confer a greater risk than either alone. Additional measures to further refine risk stratification in the moderate-risk group would therefore be useful, especially because current treatment guidelines regarding anticoagulation are ambiguous and recommend that either warfarin or aspirin may be used. Our present analysis suggests that measurement of plasma vWF levels may be a means.

Abnormal vWF levels have long been recognized in AF and have been related to abnormal thrombogenesis and intracardiac thrombus. We have recently shown that diabetes mellitus contributes to increasing vWF levels in patients with AF, with further increases apparent in individuals who also had heart failure, in keeping with the observed cumulative nature of stroke risk with increasing numbers of risk factors. When vWF levels were analyzed according to the SPAF III risk stratification criteria, a statistically significant stepwise difference in levels was found.

Nonetheless, high plasma vWF levels have been shown to be prognostically important, eg, in heart failure and acute coronary syndromes. The question therefore arises whether vWF levels bring a new, different physiological factor into stroke prediction in AF patients or simply a measure of severity of previously identified clinical predictors. Plasma vWF levels were associated with age, prior thromboembolism, heart failure, and diabetes, but the $R^2$ was <10%, suggesting a limited influence of these clinical parameters. In our longitudinal study of a cohort of 994 participants with AF, baseline plasma levels of vWF were univariately predictive of subsequent stroke and vascular events; however, after adjusting for age, elevated systolic blood pressure, and prior cerebral ischemia, statistical significance was lost in the relation between tertile of vWF and stroke, but the relation to vascular events remained significant. Broadly similar prognostic data have been described for fibrin D-dimer, an index of thrombogenesis. In previous reports, other prothrombotic markers (soluble P-selectin, fibrinogen, $\beta$-thromboglobulin, prothrombin fragment F1.2, and factor V Leiden) failed to predict outcome in AF. The measurement of plasma vWF levels may therefore be useful, in addition to clinical risk...
factors, in aiding the decision whether to initiate warfarin therapy, particularly among patients considered at moderate risk. However, the question that remains unanswered is whether anticoagulation in patients with high vWF and AF will reduce the number of ischemic strokes; indeed, more potent antithrombotic agents or a combination of agents with different antithrombotic mechanisms of action may be more effective than warfarin in these patients.

Risk stratification schemes are designed to aid decisions on thromboprophylaxis. The differences between various criteria may result in some confusion among the clinical community, but it is important that these schemas are used as a guide to aid management. Indeed, such management decisions should also be made in the context of assessing individual risk factors for bleeding and hemorrhage while on anti-thrombotic therapy. Also, some patients will still decline treatment with warfarin for a wide variety of patient-related reasons, despite discussion of the risks and benefits of antithrombotic therapy (“informed dissent”); the inconvenience of dosing adjustments and regular blood tests to monitor INR levels; dietary restrictions; the risk of minor and major bleeding; underappreciation or lack of knowledge regarding the risk of stroke; or poor adherence to the treatment regimen.22 Also, many patients with AF possess very limited knowledge of AF as well as its consequences and therapy,23 and only a minority felt that their physician had given them “enough information” about their warfarin therapy.24

This study is limited by being an analysis of a trial cohort of patients, which may not necessarily reflect (nor be generalizable to) the AF subjects in the general population. Furthermore, we have only applied the CHADS2 (which is probably the most widely validated3) and the Birmingham fits.25 Conversely, the known (small) beneficial effect of statistical power, but these end points do have a thrombosis, or vascular death), possibly because of sample size and event “informed dissent”21; the inconvenience of dosing adjustments and regular blood tests to monitor INR levels; dietary restrictions; the risk of minor and major bleeding; underappreciation or lack of knowledge regarding the risk of stroke; or poor adherence to the treatment regimen.22 Also, many patients with AF possess very limited knowledge of AF as well as its consequences and therapy,23 and only a minority felt that their physician had given them “enough information” about their warfarin therapy.24

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In conclusion, we have applied a refined clinical risk stratification scheme to a cohort of 994 subjects with AF and shown for the first time that the addition of plasma vWF levels as another biomarker risk factor could help refine clinical risk stratification for stroke and vascular events. Additional prospective studies on larger cohorts of AF patients, perhaps with additional or combinations of plasma prothrombotic indices, may further refine clinical risk stratification in these patients.

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Disclosures

G.Y.H.L. is clinical advisor to the Guideline Development Group writing the UK National NICE Guidelines on atrial fibrillation management (www.nice.org.uk). The other authors have nothing to disclose.

References

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Gregory Y.H. Lip, Deirdre Lane, Carl Van Walraven and Robert G. Hart

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