Identifying Patients at High Risk for Stroke Despite Anticoagulation

A Comparison of Contemporary Stroke Risk Stratification Schemes in an Anticoagulated Atrial Fibrillation Cohort

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Background and Purpose—The risk of stroke in patients with atrial fibrillation (AF) is not homogeneous, and various clinical risk factors have informed the development of stroke risk stratification schemes (RSS). Among anticoagulated cohorts, the emphasis should be on the identification of patients who remain at high risk for stroke despite anticoagulation.

Methods—We investigated predictors of thromboembolism (TE) risk in an anticoagulated AF clinical trial cohort (n=7329 subjects) and tested the predictive value of contemporary RSS in this cohort: CHADS2, Framingham, NICE 2006, American College of Cardiology/American Heart Association/European Society of Cardiology 2006, the 8th American College of Chest Physicians guidelines and the CHA2DS2-VASc schemes.

Results—On multivariate analysis, significant predictors of TE were stroke/TIA (hazard ratio [HR], 2.24; P<0.001), age 75 years or older (HR, 1.77; P=0.0002), coronary artery disease (HR, 1.52; P=0.0047), and smoking (HR, 2.10; P=0.0005), whereas reported alcohol use (HR, 0.70; P=0.02) was protective. Comparison of contemporary RSS demonstrated variable classification of AF patients into risk strata, although c-statistics for TE were broadly similar among the RSS tested and varied between 0.575 (NICE 2006) and 0.647 (CHA2DS2-VASc). CHA2DS2-VASc classified 94.2% as being at high risk, whereas most other RSS categorized two-thirds as being at high risk. Of the 184 TE events, 181 (98.4%) occurred in patients identified as being at high risk by the CHA2DS2-VASc schema. There was a stepwise increase in TE with increasing CHA2DS2-VASc score (P_trend<0.0001), which had the highest HR (3.75) among the tested schemes. The negative predictive value (ie, the percent categorized as “not high risk” actually being free from TE) for CHA2DS2-VASc was 99.5%.

Conclusion—Coronary artery disease and smoking are additional risk factors for TE in anticoagulated AF patients, whereas alcohol use appears protective. Of the contemporary stroke RSS, the CHA2DS2-VASc scheme correctly identified the greatest proportion of AF patients at high risk, despite the similar predictive ability of most RSS evidenced by the c-statistic. (Stroke. 2010;41:2731-2738.)

Key Words: atrial fibrillation ■ warfarin

Atrial fibrillation (AF) is associated with a substantial risk of stroke and thromboembolism (TE), but this risk is not homogeneous. Various clinical risk factors have formed the basis for stroke risk stratification schemes (RSS) and clinical practice guidelines for stroke prevention in patients with AF.1 Although stroke rates in AF cohorts are declining,2 the relative risk reduction achieved with warfarin over aspirin applies to patients with AF at intermediate or moderate risk as well as to patients at high risk.3 Incorporation of these trends into clinical practice requires contemporary data to assess stroke risk factors and the relative predictive value of RSS. As novel anticoagulants are developed that are safer and more convenient than the vitamin K antagonists,4 stroke RSS must evolve to more accurately identify subjects at “truly low risk,” because a higher proportion of the remainder becomes candidates for anticoagulation. These RSS should also minimize classification of patients into the “intermediate/moderate risk” category because optimum antithrombotic therapy is less clearly defined according to current guidelines.5-7

Many risk factors have been derived from analyses of cohorts of the nonwarfarin arms of clinical trials,8 and others have not been systematically assessed or documented in the trial setting. Inclusion of stroke risk factors into RSS requires validation in multiple populations, although many have been derived and validated largely in trial cohorts. For example,
one of the most commonly used schemes, the CHADS2 (Congestive heart failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score, evolved from the AF Investigators and Stroke Prevention in AF (SPAF) Investigators risk stratification scheme, and was validated in the National Registry of Atrial Fibrillation cohort\(^a\) as well as in a pooled analysis of patients treated with aspirin.\(^{10}\) More recently, the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guideline risk scheme\(^a\) evolved into the CHA\(_2\)DS\(_2\)-VASc score (Cardiac failure or dysfunction, Hypertension, Age \(\geq 75\) [Doubled], Diabetes, Stroke [Doubled], Vascular disease, Age 65–74 and Sex category [Female]) score, which was validated in a European cohort of 1084 subjects who were not anticoagulated at baseline.\(^{11}\)

A recent paradigm shift toward a preference for anticoagulation over antiplatelet therapy for stroke thromboprophylaxis\(^{12}\) highlights the importance of evaluating the ability of stroke RSS to identify patients at moderate or high risk for stroke. In addition, the identification of patients who remain at high risk for stroke despite appropriately managed anticoagulation (adequate time in therapeutic international normalized ratio range) is paramount and data on the ability of current stroke RSS to do this are limited,\(^{13,14}\) with only 1 small study comparing the predictive ability of contemporary stroke RSS.\(^{14}\)

The objective of the present analysis was to identify risk factors for TE in a dataset of 2 large contemporary phase III clinical trials, the Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials, which compared warfarin against the oral direct thrombin inhibitor ximelagatran for prevention of stroke and systemic embolism in patients with AF at moderate–high risk.\(^{15,16}\) We used this cohort to assess the predictive value of contemporary stroke RSS (CHADS\(_2\),\(^{9}\) Framingham,\(^{17}\) NICE 2006,\(^{8}\) ACC/AHA/ESC 2006,\(^{6}\) ACCP\(^8\),\(^{7}\) and CHA\(_2\)DS\(_2\)-VASc\(^{11}\) in identifying patients at high risk for stroke despite anticoagulation as well as providing additional validation of the CHA\(_2\)DS\(_2\)-VASc scheme in an anticoagulated clinical trial cohort.

### Subjects and Methods

#### Study Population

We investigated predictors of TE risk in an anticoagulated clinical trial cohort of 7329 subjects with AF (using warfarin or ximelagatran) participating in the SPORTIF III and V trials and tested the predictive value of several contemporary RSS, specifically the CHADS\(_2\),\(^{9}\) Framingham,\(^{17}\) NICE 2006,\(^{8}\) ACC/AHA/ESC 2006,\(^{6}\) ACCP\(^8\),\(^{7}\) CHA\(_2\)DS\(_2\)-VASc,\(^{11}\) and the modified CHADS\(_2\) scheme by Rietbrock et al.\(^{18}\)

The rationale, design, and results of SPORTIF III and SPORTIF V have been published.\(^{15,16}\) In summary, these randomized, multicenter, parallel group trials compared ximelagatran with warfarin for prevention of stroke and systemic embolism in patients with nonvalvular persistent paroxysmal or permanent AF at moderate–high risk for stroke based on the 2001 guideline recommendations.\(^{19,20}\) Participants were randomized to either fixed-dose ximelagatran, 36 mg twice daily, or dose-adjusted warfarin to maintain the international normalized ratio between 2.0 and 3.0. Treatments were administered as open-label in SPORTIF III and as double-blind in SPORTIF V.

### Ascertainment of Outcomes

After randomization, patients were seen at 1, 4, and 6 weeks, and then at 2, 3, 4, 5, 6, 8, 10, and 12 months, and every 3 months thereafter for detection of stroke or systemic embolism (primary events), TIA, acute MI, or bleeding complications. Periodic administration of a standard stroke symptom questionnaire enhanced event detection; positive responses prompted additional evaluation. A study-affiliated neurologist or stroke specialist, blinded to treatment allocation, evaluated all possible primary events and TIA as quickly as feasible based on clinical findings and results of CT or MRI of the brain. An independent, central, clinical event adjudication committee, also blinded to treatment, reviewed clinical reports of all primary and secondary events.

#### Classification Schemes

The various stroke risk schemes examined in this cohort are summarized in Table 1. The Framingham and CHADS\(_2\) schemes are point-based scores, the Framingham is based on a mathematical formula that assigns point values to age, gender, systolic blood pressure, diabetes, and previous stroke or transient ischemic attack,\(^{17}\) and the CHADS\(_2\) is based on 1 point for congestive heart failure, hypertension, age older than 75 years, and diabetes, and 2 points for previous stroke or TIA.\(^{9}\) We defined the CHADS\(_2\) score in 2 ways: (1) classical, whereby scores of 0=low risk, 1=intermediate risk, and 2=high risk; and (2) revised, whereby scores of 0=low risk, 1=intermediate risk, and 2=high risk. We categorized the Framingham score in a manner similar to that proposed by Fang et al\(^{12}\) as follows: score 0 to 7=low risk, 8 to 15=intermediate risk, and 16 to 31=high risk. The CHA\(_2\)DS\(_2\)-VASc score includes categories of 0=low risk, 1=intermediate risk, and 2=high risk.\(^{11}\) In addition to these (artificial) definitions commonly used in clinical practice, the predictive abilities of the Framingham, CHADS\(_2\), and CHA\(_2\)DS\(_2\)-VASc scores were also evaluated (perhaps more appropriately) as continuous variables.

#### Statistical Analyses

With the combined datasets from SPORTIF III and SPORTIF V, the primary study for this analysis compared the predictive accuracy of the classification schemes for the first occurrence of stroke (ischemic or hemorrhagic) or systemic embolic event. The intention-to-treat analyses included all randomized participants until study closure irrespective of continuation of treatment actually received. Cox regression modeling with TE as the dependent variable was used to estimate the impact of individual risk factors on primary and secondary events. Hazard ratios (HR) were obtained through these models with 95% CI. All potential TE risk factors investigated in the univariate analyses were analyzed in a multivariate Cox regression analysis, in which only variables with \(P<0.05\) in the presence of other selected variables were retained in the final model. For all investigated risk stratification schemes, TE rates per patient-year were estimated after stratification of patients into categories of low, intermediate, and high risk, with HR obtained for each increase in risk cohort from Cox regression modeling. The c-statistic, a measure of the area under the receiver-operator characteristic curve, quantified the predictive validity of the classification schemes using the scoring schemes as continuous variables and tested the hypothesis that these schemes performed significantly better than chance (indicated by a c-statistic \(\geq 0.5\)). The c-statistic quantifies discriminatory ability, whereas the HR quantifies the increased relative risk of stroke across risk strata.

### Results

The univariate and multivariate predictive powers of various stroke risk factors and TE are shown in Table 2. By univariate analysis, previous stroke, TIA, or systemic embolism, age 75 years or older, coronary artery disease, smoking, and female gender predicted an increased risk of TE, whereas reported alcohol use predicted lower risk. Of note, diabetes mellitus, hypertension, and left ventricular systolic dysfunction were
Table 1. Risk Stratification Schemes Used to Predict Thromboembolism in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Risk Scheme</th>
<th>Ref</th>
<th>Low Risk</th>
<th>Intermediate Risk (Heart Failure/LVEF ≤ 40)</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 (2001)—classical</td>
<td>9</td>
<td>Score 0</td>
<td>Score 1–2</td>
<td>Score 3–6</td>
</tr>
<tr>
<td>CHADS2-revised</td>
<td>5</td>
<td>Age ≤ 65y with no moderate/high risk factors</td>
<td>Age ≥ 65y with no high risk factors</td>
<td>Previous stroke/TIA or thromboembolic event Age ≥ 75y with hypertension, diabetes or vascular disease Clinical evidence of valve disease or heart failure, impaired left ventricular function</td>
</tr>
<tr>
<td>Framingham (2003)</td>
<td>15</td>
<td>Score 0–7</td>
<td>Score 8–15</td>
<td>Score 16–31</td>
</tr>
<tr>
<td>NICE guidelines (2006)</td>
<td>6</td>
<td>No risk factors</td>
<td>Age ≥ 75y, or hypertension, or heart failure, or LVEF ≤35%, or diabetes</td>
<td>Previous stroke, TIA or embolism, or ≥2 moderate risk factors of (age ≥75y, hypertension, heart failure, LVEF ≤35%, diabetes)</td>
</tr>
<tr>
<td>ACC/AHA/ESC guidelines (2006)</td>
<td>16</td>
<td>Score 0</td>
<td>Score 1–5</td>
<td>Score 6–14</td>
</tr>
<tr>
<td>8th ACCP guidelines (2008)†</td>
<td>7</td>
<td>No risk factors</td>
<td>Age ≥ 75y, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes</td>
<td>Previous stroke, TIA or embolism, or ≥2 moderate risk factors of (age ≥75y, hypertension, moderately or severely impaired LVEF and/or heart failure, diabetes)</td>
</tr>
<tr>
<td>CHADS2-VASc (2009)</td>
<td>11</td>
<td>No risk factors</td>
<td>One “clinically relevant non-major” risk factor: (heart failure/LVEF ≤40, hypertension, diabetes, vascular disease*, female gender, age 65–74)</td>
<td>One “major” risk factor [Previous stroke, TIA or embolism, or age ≥75y], or ≥2 “clinically relevant non-major” risk factors (heart failure/LVEF ≤40, hypertension, diabetes, vascular disease*, female gender, age 65–74)</td>
</tr>
</tbody>
</table>

*Risk factor: (heart failure/LVEF ≤ 35%, or diabetes)*

†This risk stratification is a modified version of CHADS2 where Age is categorised into the following age groups: 40–64, 65–69, 70–74, 75–79, 80–84, 85–115 with the score assigned to each group increasing with age 1–6 points, respectively; females score 1 point; those with diabetes mellitus score 1 point and those with a history of stroke or TIA score 6 points.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Event Rate (% per Patient-Year)</th>
<th>Univariate Analyses</th>
<th>Multivariate Analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Hazard Ratio† (95% CI)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>3.05</td>
<td>1.28</td>
<td>2.35 (1.74, 3.17)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2.25</td>
<td>1.26</td>
<td>1.78 (1.34, 2.38)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.04</td>
<td>1.31</td>
<td>1.57 (1.17, 2.10)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.68</td>
<td>1.54</td>
<td>1.75 (1.16, 2.63)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.31</td>
<td>1.91</td>
<td>0.69 (0.51, 0.93)</td>
</tr>
<tr>
<td>Systemic embolic event</td>
<td>3.24</td>
<td>1.56</td>
<td>2.08 (1.24, 3.47)</td>
</tr>
<tr>
<td>Female</td>
<td>2.08</td>
<td>1.44</td>
<td>1.44 (1.07, 1.93)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.92</td>
<td>1.55</td>
<td>1.23 (0.89, 1.71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.72</td>
<td>1.38</td>
<td>1.24 (0.86, 1.79)</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>1.67</td>
<td>1.62</td>
<td>1.03 (0.77, 1.39)</td>
</tr>
</tbody>
</table>

*Only factors associated with P<0.05 in the presence of other selected variables were retained in the final model. These results did not appear to be related to major differences in anticoagulation control amongst warfarin-treated patients; for example, amongst the 3665 patients treated with warfarin, the mean of the patients individual mean INR amongst nonsmokers (n=3331) was 2.42, and the mean of the individual patients time in range (INR 2–3) was 66.1%. Corresponding results for smokers (n=334) were 2.44 and 66.7%.

†Hazard ratio resulting from Cox regression model.

TIA, transient ischaemic attack.
The various RSS classified patients differently (Table 3, Figure 1). Because of the SPORTIF inclusion criteria, very few, if any, patients were classified as low risk by the various RSS, with the exception of the Framingham risk schema, which classed 40.1% as low risk using the cut-offs used by Fang et al.\textsuperscript{21} CHA\textsubscript{2}DS\textsubscript{2}-VASc did not categorize any patients as low risk, whereas 2% of patients were classified as “low risk” by the other RSS (Table 3). All RSS with the exception of CHADS\textsubscript{2} (classical) and CHA\textsuperscript{2}DS\textsubscript{2}-VASc categorized approximately two-thirds of the patients at high risk for stroke, whereas CHA\textsuperscript{2}DS\textsubscript{2}-VASc categorized most patients at high risk (94.2%).

One hundred eighty-four TE events occurred during the 11 233 patient-years of follow-up (1.64% per 100 patient-years). The highest TE event rate occurred in patients defined as high risk by the Framingham schema (2.98%), with all other risk schema, with the exception of CHA\textsuperscript{2}DS\textsubscript{2}-VASc, reporting a 2% TE event in those at high risk. Of note, CHA\textsuperscript{2}DS\textsubscript{2}-VASc correctly identified 181 (98.4%) who experienced a TE event as being at high risk.

All RSS had $c$-statistics $>0.50$, demonstrating greater predictive accuracy for TE than chance. The $c$-statistics for TE ranged from 0.575 (NICE 2006) to 0.647 (CHA\textsubscript{2}DS\textsubscript{2}-VASc).

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
 & \multicolumn{3}{c|}{Categorization of TE Risk} & \multicolumn{2}{c|}{Predictive Ability} \\
 & Low & Intermediate & High & $c$ statistic & Hazard Ratio (95\% CI) \\
\hline
CHADS\textsubscript{2} – classical & & & & & \\
% in risk category & 2.0 & 64.0 & 34.0 & 0.637 & 2.26* \\
TE events, N (\%) & 0/238=0.00 & 87/7276=1.20 & 97/3731=2.61 & (0.607, 0.674) & (1.71, 3.00) \\
\hline
CHADS\textsubscript{2} – revised & & & & & \\
% in risk category & 2.0 & 31.1 & 66.9 & 0.637 & 2.50 \\
TE events, N (\%) & 0/238=0.00 & 31/3563=0.87 & 153/7431=2.06 & (0.607, 0.674) & (1.72, 3.63) \\
\hline
Framingham & & & & & \\
% in risk category & 40.1 & 38.2 & 21.7 & 0.621 & 1.81 \\
TE events, N (\%) & 41/4547=0.90 & 72/4299=1.67 & 71/2386=2.98 & (0.589, 0.658) & (1.50, 2.18) \\
\hline
NICE 2006 & & & & & \\
% in risk category & 0.0 & 31.8 & 68.2 & 0.575 & 2.28 \\
TE events, N (\%) & 0/2=0.00 & 32/3651=0.88 & 152/7580=2.01 & (0.547, 0.600) & (1.56, 3.34) \\
\hline
ACC/AHA/ESC 2006 & & & & & \\
% in risk category & 1.8 & 30.3 & 67.9 & 0.587 & 2.58 \\
TE events, N (\%) & 0/212=0.00 & 29/3469=0.84 & 155/7551=2.05 & (0.557, 0.611) & (1.75, 3.79) \\
\hline
Rietbrock et al & & & & & \\
% in risk category & 0.1 & 70.0 & 29.9 & 0.629 & 2.59 \\
TE events, N (\%) & 0/10=0.00 & 89/7964=1.12 & 95/3258=2.92 & (0.587, 0.668) & (1.94, 3.46) \\
\hline
ACCP 2008 & & & & & \\
% in risk category & 1.8 & 30.4 & 67.8 & 0.587 & 2.59 \\
TE events, N (\%) & 0/212=0.00 & 29/3479=0.83 & 155/7541=2.06 & (0.557, 0.612) & (1.76, 3.81) \\
\hline
CHA\textsubscript{2}DS\textsubscript{2}-VASc & & & & & \\
% in risk category & 0.0 & 5.8 & 94.2 & 0.647 & 3.75 \\
TE events, N (\%) & 0/2=0.00 & 3/653=0.46 & 181/10578=1.71 & (0.613, 0.678) & (1.20, 11.73) \\
\hline
\end{tabular}
\caption{Risk Categorization, Incidence of Thromboembolism and Discriminatory Power for Contemporary Risk Stratification Schema}
\end{table}

*A hazard ratio of, eg, 2.26 indicates a 126\% increase in the likelihood of a TE for each increase in risk cohort (low to intermediate or intermediate to high).

†Ischemic stroke, pulmonary embolism or peripheral embolism.

CHADS\textsubscript{2} indicates congestive heart failure, Hypertension, Age $>75$, Diabetes, prior Stroke/TIA; NICE, National Institute for health and Clinical Excellence; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ACCP, American College of Chest Physicians. Risk schemes, as defined in Table 1.

Figure 1. Proportions categorized as low, moderate, and high risk for thromboembolism in relation to stroke risk stratification schema.
Typically, in randomized, controlled trials of antithrombotic therapy for stroke prevention, hypertensive patients must have good pressure control. An earlier analysis of the SPORTIF dataset demonstrated that the mean (SD) blood pressure was 131.8 (13.6)/77.5 (7.9) mm Hg, and that TE event rates were low with well-controlled hypertension and increased with poor blood pressure control. In addition, the importance of heart failure as a predictor of stroke risk in patients with AF has been questioned. In keeping with a link between stroke and atherothrombotic vascular disease in patients with AF, we found that coronary artery disease was an independent predictor of primary events, given the high cardiovascular risk of AF associated with MI and peripheral arterial disease.

Cigarette smoking was associated with an increased risk of stroke, whereas reported alcohol use appeared protective. Smoking or nicotine may influence drug pharmacokinetics, as well as other stroke risk factors. The AF Investigators failed to find that smoking was a significant independent risk factor for stroke, although there was a higher incidence of stroke in smokers compared to nonsmokers. Smoking has been associated with decreased mortality in the Copenhagen Stroke study, although this effect was significantly attenuated by age in multivariate analyses. In contrast, alcohol abuse is commonly regarded as contraindication to anticoagulation and was a reason for exclusion from clinical trials (including SPORTIF). One small, cross-sectional study found diabetes, alcohol, smoking, and left ventricular hypertrophy were risk factors for stroke among 60- to 69-year-old men with AF. Alcohol abuse has been associated with multiple medical complications, including stroke, and although modest alcohol consumption has been associated with reduced rates of cardiovascular events, we are unaware of reports of a stroke-preventive effect in patients with AF.

This work also extends the validation of the CHA2DS2-VASc score in the Euro Heart survey of AF to a large anticoagulated clinical trial cohort. In the Euro Heart analysis, which was confined to nonanticoagulated AF patients at baseline, the CHA2DS2-VASc score performed marginally better than other schemes in that patients classified as “low risk” experienced no TE events during follow-up. In the present analysis, we were unable to confirm the predictive accuracy of this low-risk stratification, because patients without risk factors were excluded by the protocol, although 40% were still classified as “low risk” according to the Framingham score. Furthermore, compared to the CHADS2, which classified >60% into the intermediate/moderate risk category, and the scheme of Rietbrock et al, which classified 70% into the intermediate/moderate risk category, only 15% were assigned to this risk stratum by the CHA2DS2-VASc scheme.

Previous comparisons of stroke RSS have been published, but only the recent analyses by Lip et al and Poli et al have included the contemporary ACC/AHA/ESC 2006, NICE 2006, and ACCP8 schemes. Most validation studies have been based on clinical trial cohorts, and few have applied the published schemes to unselected patients encountered in general clinical practice.
derived from the nonwarfarin arms of clinical trial cohorts, in which the risk factors are often inadequately defined or incompletely recorded; also, the generalizability of trial cohorts have been questioned because only <10% of those screened in the initial trial cohorts were randomized. As examples, peripheral artery disease and MI—well-established risk factors for stroke and mortality—do not factor in most schemes, apart from NICE, CHA2DS2-VASc, and van Walraven et al. Female gender increases the risk of stroke in patients with and without AF; however, women are under-represented in clinical trials of stroke prevention, prompting debate over the biological plausibility of this risk factor. Of note, female gender is a risk factor in the Framingham and the SPAF schemes, and this has not been incorporated into all guideline recommendations.

Two studies compared the ACCP6, ACCP7, SPAF, AFI, Framingham, van Walraven, and CHADS2 schemes in cohorts of anticoagulated AF patients; one is based on patients in an anticoagulation clinic with limited follow-up and another is based on the SPORTIF population. Even the analysis of Gage et al is based on subjects receiving antiplatelet therapy, which may have a small effect on event rates. The analysis we describe extends these by using more contemporary stroke RSS and tries to identify those patients remaining at high risk for stroke or TE despite anticoagulation. Because the availability of a contemporary nonanticoagulation AF cohort is increasingly unlikely, a hypothetical exploration of TE event rates in relation to the CHA2DS2-VASc score if the population were not anticoagulated is shown in Figure 2.

It is worth emphasizing that the c-statistic in one validation study cannot be compared to that derived from another study, given the differences in study population and event rates. Nonetheless, published schemes have not improved their predictive ability (c-statistics still ~0.6) despite the evolution of RSS over the past 15 years. More accurate identification of patients at low risk will be important as better anticoagulant drugs are introduced that offer a wider therapeutic margin than vitamin K antagonists, allowing more effective treatment to a broader segment of the AF population. In the present study, the negative predictive value for CHA2DS2-VASc was high and greater than that of any of the other schema undergoing comparison.

**Limitations**

Stroke rates and risk factors derived from clinical trial populations may differ from those in clinical practice. The inclusion criteria for the SPORTIF trials resulted in under-representation of patients at low risk, preventing definitive conclusions about the value of these indices to identify those at truly low risk, as was evident in our earlier analysis. In addition, this analysis did not identify hypertension, diabetes mellitus, and heart failure as independent predictors of TE, partly because patients were selected for inclusion into the trials on the basis of these risk factors. As mentioned previously, better control of blood pressure reduces the rate of stroke and it is possible that within the clinical trial setting, modifiable risk factors for stroke, such as hypertension, diabetes mellitus, and heart failure, are better-detected and managed, thereby reducing the effect of these risk factors on TE, which may explain the lack of an association demonstrated in the present analyses. Perhaps most important, because this analysis was confined to anticoagulated patients, risk factors most effectively ameliorated by anticoagulation may not be identified. The value of one RSS schema over another needs to be tested in a cohort of patients, either nonanticoagulated or anticoagulated, including patients with a wider range of risk factors, ie, low, moderate, and high, to determine the predictive ability and identify the most appropriate RSS. The use of an anticoagulated cohort with both warfarin and ximelagatran may introduce potential heterogeneity between treatment allocation; however, in the prespecified pooled analysis of the 2 trials, there was no significant difference in TE between the treatments (1.62% per year in those using ximelagatran and 1.65% per year in those using warfarin; \( P=0.941 \)). The results for the impact of individual risk factors between the treatments was also surprisingly consistent when analyzed (data not shown).

Identification of patients who remain at high risk for stroke despite anticoagulation may affect treatment strategies in clinical practice. Outside of the clinical trial setting, maintenance of an adequate time in therapeutic range is more difficult to attain, but this would be of paramount importance in anticoagulated AF patients at high risk to reduce the risk of TE or major hemorrhage. These patients may require more frequent international normalized ratio testing and dose adjustment, or self-management of omeprazole-amoxicillin-clarithromycin therapy to improve time in therapeutic range.

**Figure 2.** Stroke or other thromboembolism per patient-year based on the CHA2DS2-VASc scoring system.
may be an option,37 and such patients might benefit from pharma
geneic dosing.38 In addition, the current practice of withholding omeprazole-amoxicillin-clarithromycin therapy for elective surgical procedures may need to be re
decided in patients at high risk for stroke despite anticoagulation, war
ting a reduction in omeprazole-amoxicillin-clarithromycin or bridging therapy.

**Conclusion**

This analysis identifies coronary artery disease and smoking as additional potential risk factors for TE in patients with AF. Of the available RSS, the CHA2DS2-VASc scheme correctly identified the greatest proportion of AF patients at high risk, despite the similar predictive ability of most RSS evidenced by the c-statistic.

**Acknowledgments**

The SPORTIF III and V investigators are listed in references 15 and 16.

**Disclosure**

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12. Lip GY, Halperin J. Improving stroke risk stratification in atrial fibril-


15. Olsson SB, Executive Steering Committee of the SPORTIF III Investi-


Identifying Patients at High Risk for Stroke Despite Anticoagulation: A Comparison of Contemporary Stroke Risk Stratification Schemes in an Anticoagulated Atrial Fibrillation Cohort

Gregory Y.H. Lip, Lars Frison, Jonathan L. Halperin and Deirdre A. Lane

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항응고 치료에도 불구하고 뇌졸중 발생 위험이 높은 환자의 감별에 관한 연구

항응고 치료를 받는 심방세동 코호트에서 동시대의 뇌졸중 위험 분류 체계의 비교

배경과 목적
심방세동(atrial fibrillation, AF)을 가진 환자의 뇌졸중 위험도는 동일하지 않으므로 다양한 임상 위험인자를 뇌졸중 위험 분류 체계(risk stratification schemes, RSS)의 발달을 제공해 주고 있다. 항응고 치료 코호트 중에서 강조되어야 할 것은 항응고 치료에도 불구하고 여전히 뇌졸중의 고위험에 놓여 있는 환자들을 감별하는 데 있어야 한다는 것이다.

방법
저자들은 항응고 치료를 받은 지 2019년 9월에서 재발전역(THROMBOEMBOLISM, TEAM) 위험의 예측 인자들을 조사하였고, 이 코호트에서 동시대에 사용되고 있는 RSS(CHADS2, Framingham, NICE 2006, 미국심장병학회(American College of Cardiology)/미국심장학회(American Heart Association)/유럽심장학회(European Society of Cardiology) 2006, 제8차 미국심부의학회(American College of Chest Physicians), CHA2DS2-VASc 체계)의 예측치를 결정하였다.

결과
다변량 분석에서 TEAM의 중요한 예측 변수로는 뇌졸중/일관성혈관전(thromboembolism, TE) 위험의 예측 인자로 조사되었다. 이 코호트에서 동시대에 사용되고 있는 RSS는 2006년(CHA2DS2-VASc로 정관화된 뇌졸중 위험)의 예측력(예를 들면 TEAM 위험에 포함되지 않는 경우를 고위험군에 아닌 것으로 구분한 결과)은 99.5%였다.

결론
관상동맥질환과 흡연은 항응고 요법을 받는 AF 환자에서 TE 발생의 추가적인 위험인자였고, 반면 응주는 예방 인자로 조사되었다. 동시에 사용되고 있는 뇌졸중 RSS는 c-statistics에 의해 감증된 예측력이 유사할에도 불구하고, 그 총 CHA2DS2-VASc 체계가 많은 수의 AF 환자를 고위험군으로 정확하게 구분하였다.
### Table 1. Risk Stratification Schemes Used to Predict Thromboembolism in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Risk Scheme</th>
<th>Ref</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS₂ (2001)</td>
<td>9</td>
<td>Score 0</td>
<td>Score 1–2</td>
<td>Score 3–6</td>
</tr>
<tr>
<td>CHADS₂-revised</td>
<td></td>
<td>Score 0</td>
<td>Score 1</td>
<td>Score 2–6</td>
</tr>
<tr>
<td>Framingham (2003)</td>
<td>15</td>
<td>Score 0–7</td>
<td>Score 8–15</td>
<td>Score 16–31</td>
</tr>
<tr>
<td>NICE guidelines (2006)</td>
<td>5</td>
<td>Age &lt;65y with no moderate/high risk factors</td>
<td>Age ≥65y with no high risk factors</td>
<td>Previous stroke/TIA or thromboembolic event Age ≥75y with hypertension, diabetes or vascular disease Clinical evidence of valve disease or heart failure, or impaired left ventricular function</td>
</tr>
<tr>
<td>ACC/AHA/ESC guidelines (2006)</td>
<td>6</td>
<td>No risk factors</td>
<td>Age ≥75y, or hypertension, or heart failure, or LVEF ≤35%, or diabetes</td>
<td>Previous stroke, TIA or embolism, or ≥2 moderate risk factors of (age ≥75y, hypertension, heart failure, LVEF ≤35%, diabetes)</td>
</tr>
<tr>
<td>Rietbrock et al (2008)†</td>
<td>16</td>
<td>Score 0</td>
<td>Score 1–5</td>
<td>Score 6–14</td>
</tr>
<tr>
<td>8th ACCP guidelines (2008)</td>
<td>7</td>
<td>No risk factors</td>
<td>Age &gt;75y, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes</td>
<td>Previous stroke, TIA or embolism, or ≥2 moderate risk factors of (age &gt;75y, hypertension, moderately or severely impaired LVEF and/or heart failure, diabetes)</td>
</tr>
<tr>
<td>CHADS₂-VASc (2009)</td>
<td>11</td>
<td>No risk factors</td>
<td>One “clinically relevant non-major” risk factor: (heart failure/LVEF ≤40, hypertension, diabetes, vascular disease*, female gender, age 65–74)</td>
<td>One “major” risk factor (Previous stroke, TIA or embolism, or age ≥75y), or ≥2 “clinically relevant non-major” risk factors (heart failure/LVEF ≤40, hypertension, diabetes, vascular disease*, female gender, age 65–74)</td>
</tr>
</tbody>
</table>

*Myocardial infarction, peripheral artery disease or aortic plaque.
†This risk stratification is a modified version of CHADS₂ where Age is categorised into the following age groups: 40–64, 65–69, 70–74, 75–79, 80–84, 85–115 with the score assigned to each group increasing with age 1–6 points, respectively; females score 1 point; those with diabetes mellitus score 1 point and those with a history of stroke or TIA score 6 points.

ACC indicates American College of Cardiology; ACCP, American College of Chest Physicians; AHA, American Heart Association; CHADS₂, Congestive heart failure, Hypertension, Age ≥75, Diabetes, prior Stroke/TIA; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; NICE, National Institute for health and Clinical Excellence; TIA, transient ischaemic attack.

---

### Table 4. Stroke or Other Thromboembolism Events per Patient Year Based on the CHADS₂-VASc Scoring System

<table>
<thead>
<tr>
<th>CHADS₂-VASc Score</th>
<th>N</th>
<th>No. of TE Events/PY</th>
<th>TE Rate During 1 Year (95% CI)</th>
<th>TE Rate During 1 Year, Adjusted for Warfarin use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0/2</td>
<td>0.00 (0.00, 0.00)</td>
<td>0.00 (0.00, 0.00)</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>3/653</td>
<td>0.46 (0.10, 1.34)</td>
<td>1.3 (0.4, 3.8)</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>15/1913</td>
<td>0.78 (0.44, 1.29)</td>
<td>2.2 (1.1, 4.1)</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>31/2673</td>
<td>1.16 (0.79, 1.64)</td>
<td>3.2 (2.1, 5.1)</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>36/2665</td>
<td>1.43 (1.01, 1.95)</td>
<td>4.0 (2.6, 6.1)</td>
</tr>
<tr>
<td>5</td>
<td>1599</td>
<td>42/1732</td>
<td>2.42 (1.75, 3.26)</td>
<td>6.7 (4.0, 10.9)</td>
</tr>
<tr>
<td>6</td>
<td>679</td>
<td>36/1016</td>
<td>3.54 (2.49, 4.67)</td>
<td>9.8 (6.4, 14.9)</td>
</tr>
<tr>
<td>7</td>
<td>254</td>
<td>15/436</td>
<td>3.44 (1.94, 5.62)</td>
<td>9.6 (5.6, 16.9)</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>3/125</td>
<td>2.41 (0.53, 8.88)</td>
<td>6.7 (2.5, 15.7)</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>1/18</td>
<td>5.47 (0.91, 27.0)</td>
<td>15.2 (4.4, 52.6)</td>
</tr>
</tbody>
</table>

Total 7329 184/11233 P value for trend P<0.0001

*Theoretical TE rates without therapy: assuming that warfarin provides a 64% reduction in TE risk, based on Hart et al. 34 CI indicates confidence interval.
Original Contributions

Identifying Patients at High Risk for Stroke Despite Anticoagulation
A Comparison of Contemporary Stroke Risk Stratification Schemes in an Anticoagulated Atrial Fibrillation Cohort

Gregory Y.H. Lip, MD; Lars Frison, PhD; Jonathan L. Halperin, MD; Deirdre A. Lane, PhD

Background and Objectives: Atrial fibrillation (AF) patients have multiple clinical risk factors for stroke, and risk stratification schemes (RSS) are used to guide antithrombotic therapy. Anticoagulation reduces stroke risk in AF, but stroke prevention remains a challenge in patients with multiple risk factors.

Methods: This study assessed the stroke risk stratification schemes of CHADS2, CHA2DS2-VASc, and the ACCP guidelines in a cohort of 7329 anticoagulated AF patients.

Results: In a multivariable model, history of stroke/TIA (HR 2.24, P < 0.001), age ≥75 years (HR 1.77, P = 0.0002), and coronary artery disease (HR 1.52, P = 0.0047) were significant predictors of stroke. CHA2DS2-VASc was significantly better at identifying patients with stroke risk than CHADS2 (P < 0.0001). Sensitivity analysis showed that CHA2DS2-VASc was more accurate in identifying patients with high stroke risk.

Conclusion: CHA2DS2-VASc is a superior stroke risk stratification tool for anticoagulated AF patients compared to CHADS2.

Keywords: Atrial fibrillation, stroke risk stratification
较具有更安全更便利的特点[4]，这就需要卒中风险分层方案必须能够更为精准的识别出“真正的卒中低风险”的房颤患者，这样才能使更多的危险人群可以成为接受抗凝治疗的候选者。这些卒中风险分层方案同时应尽可能缩小“中等风险”组的患者数量，因为目前的指南对于何为最优血栓栓塞方案尚无一清晰的定义[5]。


目前对于卒中二级预防药物的选择更趋向于用抗凝药物取代抗血小板药物[12]，这就更强调卒中风险分层方案能够准确识别出处于卒中中重度风险级别的患者。另外，在已经规范应用抗凝治疗的患者中，维持国际标准化比值(INR)在2.0-3.0之间的华法林(维持INR在2.0-3.0之间)、SPORTIF III期临床试验为双盲试验，而SPORTIF V期临床试验为开放性试验，而SPORTIF V期临床试验为双盲试验。

研究对象和方法

研究人群


SPORTIF III期及V期临床试验的基本原理、试验设计以及试验结果已经发表[15,16]。概括来说，这项随机、多中心、平行对照试验根据2001年指南推荐的非瓣膜病的阵发性房颤、持续性房颤及永久性房颤患者中选择出处于卒中中、高危人群，在这部分人群中预防性应用希美加群或华法林，比较这两种药物对脑卒中或全身性栓塞事件的预防效果[19,20]。受试者随机接受固定剂量的希美加群(每日两次，每次36mg)或根据个体情况调整用量的华法林(维持INR在2.0-3.0之间)。SPORTIF III期临床试验为开放性试验，而SPORTIF V期临床试验为双盲试验。

临床终点的判断

在随机分组之后，起初在第1、4、6周随访患者，之后随访时间在2、3、4、5、6、8、10及12个月，之后每3个月随访患者一次，直至监测到发生脑卒中或全身性血栓栓塞(主要事件)、短暂性脑缺血发作(TIA)、急性心肌梗塞或出血性并发症。定期对患者进行标准化卒中症状问卷调查有助于帮助发现卒中事件的发生；对于有阳性结果的患者则需进行进一步评估。由一位研究相关的神经病学家或卒中专家利用临床发现及颅脑CT或MRI的辅助检查结果尽可能迅速的对所有可能的主要事件及TIA做
表 1 卒中风险分层方案在房颤患者中用于预测血栓栓塞事件发生的应用情况

### 风险分层方案

<table>
<thead>
<tr>
<th>风险分层方案</th>
<th>参考文献</th>
<th>低风险</th>
<th>中风险</th>
<th>高风险</th>
</tr>
</thead>
<tbody>
<tr>
<td>经典 CHADS2 评分</td>
<td></td>
<td>积分 0</td>
<td>积分 1-2</td>
<td>积分 3-6</td>
</tr>
<tr>
<td>改良 CHADS2 评分</td>
<td></td>
<td>积分 0</td>
<td>积分 1</td>
<td>积分 2-6</td>
</tr>
<tr>
<td>Framingham 危险评分</td>
<td></td>
<td>积分 0</td>
<td>积分 7</td>
<td>积分 16-31</td>
</tr>
<tr>
<td>NICE 指南 2006</td>
<td></td>
<td>年龄 &lt;65 岁</td>
<td>年龄 ≥65 岁, 无中、高危险因素</td>
<td>既往出现过卒中 /TIA 或血栓栓塞病史</td>
</tr>
<tr>
<td></td>
<td></td>
<td>无中、高危险因素</td>
<td>年龄 &lt;75 岁, 伴有高血压、糖尿病或血管疾病</td>
<td>年龄 ≥75 岁, 伴有高血压、糖尿病或血管疾病</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>临床证据表明存在瓣膜病变, 心衰或左心功能不全</td>
</tr>
<tr>
<td>ACC/AHA/ESC 指南 2006</td>
<td></td>
<td>年龄 ≥75 岁</td>
<td>年龄 ≥75 岁, 合并高血压或 LVEF ≤50%</td>
<td>既往出现过卒中 /TIA 或血栓栓塞病史</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>或 ≥2 项中等危险因素 (年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
<td>(年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rietbrock 等人 2008 改良版†</td>
<td></td>
<td>年龄 &gt;75 岁</td>
<td>年龄 ≥75 岁, 合并高血压或 LVEF ≤50%</td>
<td>既往出现过卒中, TIA 或血栓栓塞病史</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>或 ≥2 项中等危险因素 (年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
<td>(年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ACCP 指南第八版 (2008)</td>
<td></td>
<td>年龄 ≥75 岁</td>
<td>年龄 ≥75 岁, 合并高血压或 LVEF ≤50%</td>
<td>既往出现过卒中, TIA 或血栓栓塞病史</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>或 ≥2 项中等危险因素 (年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
<td>(年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc 评分 (2009)</td>
<td></td>
<td>年龄 ≥75 岁</td>
<td>年龄 ≥75 岁, 合并高血压或 LVEF ≤50%</td>
<td>既往出现过卒中 /TIA 或血栓栓塞病史</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>或 ≥2 项中等危险因素 (年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
<td>(年龄 ≥75 岁, 高血压、心衰或 LVEF ≤50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 心肌梗塞, 周围动脉疾病或大动脉斑块形成。
† 此风险分层方案为 CHADS2 积分的改良版。此方案将年龄分为以下六个年龄组: 40-64, 65-69, 70-74, 75-79, 80-84, 85-115。每个组的积分随年龄而增加, 分别记为 1-6 分; 女性患者记 1 分; 合并糖尿病的患者记 1 分; 既往曾有过脑卒中或 TIA 病史记 6 分。

ACC: 美国心脏病协会; ACCP: 美国胸科医师学会; AHA: 美国心脏协会; CHADS2: 充血性心衰, 高血压, 年龄 >75 岁, 糖尿病, 既往脑卒中 /TIA 病史; ESC: 欧洲心脏病协会; LVEF: 左心室射血分数; NICE: 英国国家卫生与临床研究院; TIA: 短暂性脑缺血发作。

表 2 各危险因素对血栓栓塞事件预测能力的单因素及多因素分析结果

<table>
<thead>
<tr>
<th>危险因素</th>
<th>事件发生率 (每患者 - 年)</th>
<th>是否存在危险因素</th>
<th>风险比 (HR)†</th>
<th>P 值 (95% CI)</th>
<th>多因素分析*</th>
<th>风险比 (HR)†</th>
<th>P 值 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>既往脑卒中 /TIA 病史</td>
<td>3.05 1.28</td>
<td>是</td>
<td>2.35 (1.74, 3.17)</td>
<td>&lt;0.0001</td>
<td>2.24 (1.66, 3.02)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>年龄 ≥75 岁</td>
<td>2.25 1.26</td>
<td>是</td>
<td>1.78 (1.34, 2.38)</td>
<td>&lt;0.0001</td>
<td>1.77 (1.32, 2.38)</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>冠心病</td>
<td>2.04 1.31</td>
<td>是</td>
<td>1.57 (1.17, 2.10)</td>
<td>0.0025</td>
<td>1.52 (1.14, 2.04)</td>
<td>0.0047</td>
<td></td>
</tr>
<tr>
<td>吸烟</td>
<td>2.68 1.54</td>
<td>是</td>
<td>1.75 (1.16, 2.63)</td>
<td>0.0074</td>
<td>2.10 (1.38, 3.18)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>酗酒</td>
<td>1.31 1.91</td>
<td>是</td>
<td>0.69 (0.51, 0.93)</td>
<td>0.014</td>
<td>0.70 (0.52, 0.95)</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>全身性血栓栓塞事件</td>
<td>3.24 1.56</td>
<td>是</td>
<td>2.08 (1.24, 3.47)</td>
<td>0.0052</td>
<td>2.10 (1.38, 3.18)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>女性</td>
<td>2.08 1.44</td>
<td>是</td>
<td>1.44 (1.07, 1.93)</td>
<td>0.016</td>
<td>1.20 (0.89, 1.63)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>糖尿病</td>
<td>1.92 1.55</td>
<td>是</td>
<td>1.23 (0.89, 1.71)</td>
<td>0.21</td>
<td>1.23 (0.89, 1.71)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>高血压</td>
<td>1.72 1.38</td>
<td>是</td>
<td>1.24 (0.86, 1.79)</td>
<td>0.24</td>
<td>1.24 (0.86, 1.79)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>左心室功能不全</td>
<td>1.67 1.62</td>
<td>是</td>
<td>1.03 (0.77, 1.39)</td>
<td>0.84</td>
<td>1.03 (0.77, 1.39)</td>
<td>0.84</td>
<td></td>
</tr>
</tbody>
</table>

* 考察的危险因素中仅 P<0.05 的危险因素保留至最终的回归模型中。在华法林治疗的患者中, 以上危险因素与作为对照应用的抗凝治疗似乎并无很大的相关性, 例如, 在 3665 名接受华法林治疗的患者中, 非吸烟者 (n=3334) 中平均 INR 值为 2.44, INR 控制在 2-3 之间的人群占 66.1%; 而吸烟者 (n=334) 中平均 INR 值为 2.44, INR 控制在 2-3 之间的人群占 65.7%。
† 风险比结果来自于 Cox 回归模型。
TIA 即短暂性脑缺血发作。
风险分层方案

表 1 总结了研究人员在这项队列研究中对危险因素进行评估时采用的各种卒中风险分层方案,其中国 Framingham 危险评分及 CHADS2 评分是基于分数的分层方法。Framingham 危险评分是对患者的年龄、性别、收缩压水平、糖尿病情况、既往出现过卒中或 TIA 事件进行赋值,通过数学公式计算得出[17]; 而 CHADS2 评分则将充血性心衰、高血压、年龄超过 75 岁及糖尿病各记 1 分,既往出现过卒中或 TIA 事件记 2 分叠加后得出[9]。研究人员采用两种不同的方式定义 CHADS2 评分: (1) 经典 CHADS2 评分: 评分分为 0 记为低风险组, 评分 1-2 为中度风险组, 评分 >2 为高风险组; (2) 改良 CHADS2 评分: 评分分为 0 记为低风险组, 评分 1 为中度风险组, 评分 ≥2 为高风险组。研究人员利用 Framingham 危险评分进行的风险分层方案在某种意义上与 Fang 等人[21]提出的方案相类似; 评分在 0-7 之间的为低风险组, 评分在 8-15 之间的为中度风险组, 评分在 16-31 之间的为高风险组。而 CHA2DS2-VASC 评分分层方案则将评分为 0 记为低风险组, 评分为 1 记为中度风险组, 评分为 ≥2 记为高风险组[11]。这些人为的定义方法已普遍应用于临床实践, Framingham 危险评分、CHADS2 评分以及 CHA2DS2-VASC 评分的预测性也应作为连续变量接受评估(似乎更为恰当)。
统计分析

结合SPORTIF III及V期临床试验数据，研究的首要工作即分析风险分层方案对脑卒中（缺血性或出血性）及全身血栓栓塞事件发生的预测准确性。意向治疗分析的研究对象包括所有接受随机分组的受试者直至研究结束，而无论其是否真正从始至终接受了该组的治疗。Cox回归模型将血栓栓塞作为因变量，通过单因素分析评估各个危险因素对因变量（血栓栓塞）的影响。从建立的这些模型中可以获得风险比（Hazard ratios, HR）及其95%可信区间（CI）。将所有潜在致血栓栓塞的危险因素都通过一个多因素Cox回归分析模型进行单因素分析，从这些待选择的变量中筛选出P<0.05的变量纳入最终的多因素Cox回归分析模型。对于所有调查的风险分层方案，在将患者分为低、中、高危组后分别对各组每患者年血栓栓塞事件的发生率进行评估，从Cox回归分析模型中获得各个危险组的HR值。并通过计算c-统计量，一个度量受试者操作特征曲线下面积的统计量，则将每一种危险分层方案的预测效度加以量化，即将分层方案的积分作为一连续变量，建立此风险分层方案的实施对于卒中事件发生的预测是具有统计学意义的假设，对其进行假设检验（当c-统计量≥0.5时假设检验即成立）。C-统计量将各个风险分层方案对于卒中危险因素的识别能力加以量化，而HR则对随着危险分层级别的增高其发生卒中事件增加的相对风险进行了量化。

结果

表2记录了各种危险因素对血栓栓塞事件预测能力的单因素及多因素分析。在单因素分析中，既往脑卒中、TIA及全身性血栓形成病史、年龄≥75岁、冠心病、吸烟及女性患者均预示着会增加血栓栓塞事件发生的危险性，而饮酒则预示着低风险。值得注意的是糖尿病、高血压及左心功能不全在这些患者中未能预测血栓栓塞事件的发生。在多因素分析中对血栓栓塞的发生具有统计学意义的预测值仅有以下四项：既往脑卒中或TIA病史（HR，2.24；95%CI，1.66-3.02；P<0.001），年龄≥75岁（HR，1.77；95%CI，1.32-2.38；P=0.0002），冠心病（HR，1.52；95%CI，1.14-2.04；P=0.0047）以及吸烟（HR，2.10；95%CI，1.38-3.18；P=0.0005），而饮酒似乎成为了血栓栓塞事件发生的保护因素（HR，0.70；95%CI，0.52-0.95；P=0.02）。

不同的风险分层方案对患者的分类不同（表3，图1），因为SPORTIF试验的纳入标准所限，几乎所有风险分层方案均将很少的患者归类于低风险组，而Framingham危险评分是一个特例，以Fang等人的判断标准40.1%的受试者被纳入低风险组[21]。CHA2DS2-VASC评分分层方案没有将任何一名患者纳入低风险组，而其他风险分层方案纳入低风险组的患者占所有受试者的比例大约为2%（表3）。所有风险分层方案除经典CHA2DS2评分和CHA2DS2-VASC评分外，基本上约2/3的患者被纳入卒中高风险组，而采取CHA2DS2-VASC评分的风险分层方案几乎绝大多数的患者均纳入高风险组（94.2%）。

在11 233人年的随访期中共发生184件血栓栓塞事件（发病密度每100患者-年1.64%）。各种风险分层方案所分类的高危组患者中，以Framingham风险分层方案的高危组人群中血栓栓塞事件的发生率最高（2.98%），除CHA2DS2-VASC评分外，其他风险分层方案在高危组中血栓栓塞事件的发生率均在2%以上。值得注意的是，CHA2DS2-VASC评分所评价为卒中高风险组的患者中有高达181名患者日后发生了血栓栓塞事件（占所有发生血栓栓塞事件患者的98.4%）。所有的风险分层方案在预测血栓栓塞事件发生的准确性并非偶然。C-统计量的值从0.575（NICE 2006指南）到0.647（CHA2DS2-VASC）不等。

以CHA2DS2-VASC评分分层方案为例，随着CHA2DS2-VASC评分的增加，血栓栓塞事件发生率

<table>
<thead>
<tr>
<th>CHA2DS2-VASC评分</th>
<th>患者数量</th>
<th>血栓栓塞事件数/患者年</th>
<th>血栓栓塞发生率 (95%CI)</th>
<th>治疗影响</th>
<th>统计值</th>
<th>趋势P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>1/18</td>
<td>5.47 (0.91, 27.0)</td>
<td>15.2</td>
<td>P=0.0001</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1469</td>
<td>36/1016</td>
<td>3.54 (2.49, 4.87)</td>
<td>9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>294</td>
<td>15/436</td>
<td>3.44 (1.94, 5.62)</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>3/125</td>
<td>2.41 (0.53, 6.88)</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>1/18</td>
<td>5.47 (0.91, 27.0)</td>
<td>15.2</td>
<td>P=0.0001</td>
<td></td>
</tr>
<tr>
<td>总和</td>
<td>7329</td>
<td>184/11233</td>
<td>1.64%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
亦在逐步增加（$P_{\text{趋势}}<0.0001$，表 4），此项风险分层方案有著较高的 HR(3.75；95% CI, 1.20-11.73), 预示着随着风险分层等级的增高 (由低风险级别升至中风险级别，或从中风险级别升至高风险级别)，患者日后罹患血栓栓塞性疾病的可能性增加 275%，而其他危险分层方案随着患者所处风险等级的增高，日后血栓栓塞事件发生危险性的增加幅度在 80% (Framingham 危险评分) 到 150% 之间 (表 3)。而 CHA2DS2-VASc 评分的阴性预测值 (即归类于非卒中高危组的患者中在随访期内实际上也没有发生血栓栓塞性事件的比例) 高达 99.5%，超过了其他的风险分层方案 (数据未罗列)。

讨论

这次研究对比了几种卒中风险分层方案在接受抗凝治疗的房颤患者中的应用，证实 CHADS2 评分、Framingham 危险评分及 CHA2DS2-VASc 评分对可能发生的血栓栓塞事件有着相似的预测能力 (分别为 0.64、0.62 及 0.65)，与其他风险分层方案相比，CHA2DS2-VASc 评分分类于高风险组的患者人数最多 (达 94.2%)，而其他绝大多数风险分层方案 (除 Framingham 危险评分之外) 中高风险组的患者一般占总人群的 2/3。尽管以 c-统计量作为卒中危险因素识别能力量化指标的证据显示各个风险分层方案对于卒中事件预警能力相似，但是 CHA2DS2-VASc 评分可以更准确地预测 98.4% 日后发生血栓栓塞事件的高危人群并将其归类于高风险组。另外 CHA2DS2-VASc 评分的风险比最高，预示随风险等级的增高患者日后发生血栓栓塞事件的几率也在明显增加；同时 CHA2DS2-VASc 评分亦有着很高的阴性预测值。

通过多因素分析，在各种可能的危险因素中对血栓栓塞事件具有统计学意义的预测指标包括既往卒中或 TIA 病史、高龄患者 (年龄 ≥75 岁)、冠心病、吸烟以及不饮酒。以上这些研究发现与先前的一些研究分析相一致 [8,22]，而先前经研究证实的另一些危险因素，如高血压、糖尿病、心衰及左心功能不全在此次的临床试验中被认为并非血栓栓塞事件独立的预测因素。

此次研究分析证实缺少高血压与血栓栓塞事件必然相关的证据，这个结果可能可以归因于血压的控制。一般来说，在一个为了考察抗血栓治疗对卒中预防影响的随机临床对照试验中，高血压患者必须将血压控制在一个良好的水平，早期 SPORTIF 临床试验分析显示受试者平均血压为 131.8(13.6)/77.5(7.9) mmHg，血压水平控制理想，血栓栓塞事件发生率低；血压水平控制不理想，血栓栓塞事件发生率高 [23]。另外，心衰作为房颤患者发生卒中风险预测因素的重要性也备受质疑 [8]。卒中事件与房颤患者间的相关性同动脉粥样硬化血栓形成性疾病与后者之间的联系相一致，研究人员发现冠心病是血栓栓塞事件一个独立的预测因素，房颤合并冠心病患者为发生心肌梗塞 [22,24,25] 或外周动脉疾病 [26,27] 等心血管血栓形成事件的高风险人群。

吸烟增加了卒中事件发生的风险，与此同时，饮酒似乎成为了卒中的保护因素。同其他的卒中危险因素，尼古丁可能通过影响药代动力学起作用。先前房颤研究人员未能发现吸烟是卒中事件发生的独立危险因素，尽管吸烟的房颤患者中卒中的发生率较非吸烟的房颤患者增高 [23]。在哥本哈根卒中研究中，吸烟曾被认为与死亡率的降低有关 [29]，但通过多因素分析同时考虑年龄因素的影响后这种相关性即明显减小了。相反，酒精的滥用普遍被认为是抗凝治疗的禁忌，同时也是许多临床试验选择受试者时的排除标准之一 (包括 SPORTIF 临床试
验)。一项小型的横断面研究显示糖尿病、饮酒、吸烟及左心室肥大在60-69岁的房颤男性人群中均为卒中事件发生的危险因素[9]。酗酒与多种医学并发症相关，包括卒中。尽管小量适量的饮酒被认为可以减少卒中风险，但研究未发现饮酒对房颤患者卒中事件起预防作用的相关报道。

继房颤欧洲心脏调查[11]及另一个大型抗凝临床试验队列研究之后，此次研究再次验证了CHA2DS2-VASc评分对卒中的预测价值。房颤欧洲心脏调查分析选择未接受抗凝治疗的房颤患者为研究人群，在随访过程中发现CHA2DS2-VASc评分所分类的低风险组患者卒中事件发生率较其他风险分层方案所定义的低风险组患者卒中事件发生率稍有降低。但在本研究分析中，研究人员无法肯定这种低风险分层对卒中风险预测的准确性，因为不伴有任何危险因素的患者根据试验纳入标准在试验开始前即被排除了。尽管根据Framingham危险评分仍有40%的患者被分类于低风险组。此外，对比将60%的患者纳入中风险组的CHADS2评分分层方案与将70%的患者纳入中风险组的Rietbrock等人改良版风险分层方案[16]，CHA2DS2-VASc评分分层方案仅将15%的患者纳入中风险组。


有两项研究比较了ACCP6、ACCP7、SPAF、AFI、Framingham风险评分、van Walraven改良评分及CHADS2评分分层方案在抗凝治疗的房颤患者中的应用，一个研究是基于在有限随访期内接受抗凝治疗患者的临床研究[14]，而另一个研究是基于SPORTIF临床试验[13]。Gage等人[10]的研究也是基于接受了抗凝治疗的房颤患者队列的可可行性不大可能增加，研究人员推测在未接受抗凝治疗患者其血栓栓塞事件发生率与CHA2DS2-VASc评分的分层关系，见图2。

值得注意的是，从一个验证性试验得出的c-统计量不能同其他研究得到的c-统计量相比拟，他们在研究人群及事件发生率均存在差异。虽然如此，尽管过去的15年抗凝分层方案在不断的演变，已发表的抗凝分层方案并未改进他们的预测能力(c-统计量仍≈0.6)。鉴于目前愈来愈多的好的抗凝药物被研制出来，他们较维生素K拮抗剂有着更广的治疗窗宽，这就需要研究者可以更为准确的识别出处于卒中低风险组的房颤患者以使得更多的房颤人群可以得到更为有效的治疗[15]。根据目前的研究，CHA2DS2-VASc评分较其他的风险分层方案有着更高的正性预测值。

局限性

临床试验人群中得出的卒中发生率及其危险因素与那些从临床实践中得出的数据并不相同。因SPORTIF临床试验纳入标准的限制导致其低风险组的患者并不具有普通代表性，正如我们之前分析的，这显然妨碍了关于风险分层方案对真正低卒中风险患者识别能力的最终判断[11]。除此之外，这项分析不能确定高卒中的危险性，研究者在这些危险因素的基础上选择合适的患者纳入研究。如之前提及的，控制血压在一个良好的水平可以降低卒中事件的发生率，这就可能在进行临床试验的时候，一些可以控制的卒中危险因素，如高血压、糖尿病
及心衰被发现并控制在一个良好的水平，因此影响了这些危险因素对血栓栓塞事件的影响，这或许可以解释为何本研究显示上述危险因素与卒中事件的发生缺乏相关性。也许最重要的一点在于，本研究分析局限在未接受抗凝治疗的患者中，因此很多危险因素对血栓栓塞治疗的影响改善，这造成我们分析时判断上的困难。而一种卒中风险分层方案是否较另一种优越，这需要通过一系列队列研究来证实，不仅针对接受抗凝治疗的患者，也针对未接受抗凝治疗的患者，要求纳入的研究对象具有不同程度的危险因素。如涵盖低、中、高三风险等级，从中确定风险分层方案的预测能力，并发现最为适合的风险分层方案。另外，接受希美加群及华法林抗凝治疗的患者中因治疗方案分配的不同而应存在潜在的异性。然而预分析的荟萃分析显示两个治疗组血栓栓塞发生率并无具有统计学意义的差异存在(希美加群治疗组每年血栓栓塞发生率为1.62%，而华法林治疗组每年血栓栓塞事件的发生率为1.65%，P=0.094)[30]，而对两个治疗组危险因素的分析结果也提示令人惊异的一致性(结果未在此罗列)。

在临床工作中识别出在接受抗凝治疗的同时存在卒中高风险的患者影响着临床治疗策略的选择。在临床试验以外，将患者的治疗时间维持在一个合适的水平非常困难，但这对于接受抗凝治疗的卒中高风险房颤患者将血栓栓塞事件及严重出血事件的发生率是尤为重要的。这些患者需要更为频繁的监测INR值，进行药物剂量调整或自我管理奥美拉唑。阿莫西林-克拉霉素等影响华法林药代动力学药物的使用，以控制抗凝时间在治疗范围内[31]。这部分患者可能从依药理学给药中获益[32]。此外，接受抗凝治疗的卒中高风险房颤患者在准备进行择期外科手术时需要暂停奥美拉唑[33]。也提示令人惊异的一致性(结果未在此罗列)。

## 结论

此项分析研究认为冠心病和吸烟也是房颤患者发生血栓栓塞事件的潜在危险因素之一。而在目前所有可行的风险分层方案之中，尽管利用c-统计量考量其对卒中事件的预警能力时得到的是相近的结果，但CHA2DS2-VASc评分其实可以辨别可能患有血栓栓塞事件的房颤患者并将其归类于高危组的比例最高。
25. Li et al. Stroke Risk Schemes in AF
