Usefulness of N-Terminal Pro–B-Type Natriuretic Peptide Levels for Stroke Risk Prediction in Anticoagulated Patients With Atrial Fibrillation

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Background and Purpose—Oral anticoagulation is highly effective in reducing stroke and mortality in atrial fibrillation (AF). Several risk stratification schemes have been developed using clinical characteristics. Elevated levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP) are important markers of increased mortality and morbidity in congestive heart failure and general community population. The aim of our study was to assess the predictive value of NT-proBNP levels in an unselected real-world cohort of anticoagulated patients with AF.

Methods—We studied 1172 patients (49% male; median age, 76 years) with permanent AF who were well stabilized on oral anticoagulation (international normalized ratio, 2.0–3.0). Plasma NT-proBNP levels were quantified at baseline. We recorded thrombotic and vascular events, mortality, and major bleeding. The best cutoff points were assessed by receiver-operating characteristic curves.

Results—Median levels (interquartile range) of NT-proBNP were 610 (318–1037) pg/mL. Median follow-up was 1007 (806–1279) days. On multivariate analysis, high NT-proBNP was significantly associated with the risk of stroke (hazards ratio, 2.71; P=0.001) and composite vascular events (acute coronary syndrome or acute heart failure; hazards ratio, 1.85; P=0.016), as well as a significant association with mortality (adjusted hazards ratio, 1.66; P=0.006). No association with bleeding was found (P=0.637). The integrated discrimination improvement (IDI) analysis demonstrated that NT-proBNP improved the Congestive heart failure, Hypertension, Age≥75 (doubled), Diabetes mellitus, Stroke (doubled)–Vascular disease and Sex category (female); CHA2DS2–VASc score for predicting embolic events (relative IDI, 2.8%; P=0.001) and all-cause death (relative IDI, 1.8%; P=0.001).

Conclusions—In real-world cohort of anticoagulated patients with AF, NT-proBNP provided complementary prognostic information to an established clinical risk score (CHA2DS2–VASc) for the prediction of stroke/systemic embolism. NT-proBNP was also predictive of all-cause mortality, suggesting that this biomarker may potentially be used to refine clinical risk stratification in anticoagulated patients with AF. (Stroke. 2014;45:696-701.)

Key Words: anticoagulants ■ atrial fibrillation ■ B-type natriuretic peptide ■ stroke

Atrial fibrillation (AF) is associated with high morbidity and mortality, with an increased risk of stroke and thromboembolism. Oral anticoagulation (OAC) is highly effective in reducing the risk of stroke and mortality compared with placebo/control. To aid decision making for thromboprophylaxis, several risk stratification schemes have been developed using clinical characteristics. A popular risk stratification scheme has been the CHADS, (Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke [Doubled]) score. More recently, the value of the CHADS, scheme has been debated, given its noninclusion of many stroke risk factors and other limitations. Thus, the CHADS, score has been refined with the CHA2DS2–VASc (Congestive heart failure, Hypertension, Age≥75 [doubled], Diabetes mellitus, Stroke [doubled]–Vascular disease and Sex category [female]), emphasizing a risk factor–based approach. The CHA2DS2–VASc score has been proposed by the European Society of Cardiology to be used in decision making for OAC, reflecting a risk factor–based approach to thromboprophylaxis.

The CHA2DS2–VASc score has been validated in multiple independent cohorts, and it has also demonstrated its predictive value for vascular events and mortality.
are limited data on the prognostic role of biomarkers in anti-coagulated patients with AF in relation to adverse events (including thromboembolism), mortality, and major bleeding. However, recent studies of biomarkers in AF have shown that they could substantially improve risk stratification. Indeed, it has been described in 2 large trials of patients with AF, which compared the efficacy and safety of new oral anticoagulants against warfarin, how several biomarkers (like troponins or N-terminal pro–B-type natriuretic peptide [NT-proBNP]) are predictive for adverse events. We recently reported in a large real-world cohort of anticoagulated patients with AF that von Willebrand factor levels (an established biomarker of endothelial damage/dysfunction) were independent predictors for thrombotic, bleeding events and death during a 2-year follow-up period. Indeed, biomarkers may potentially be used to refine stroke and bleeding risk stratification in AF.

Elevated levels of NT-proBNP are important markers of increased mortality and morbidity in congestive heart failure and ischemic heart disease, and are even predictive for AF. The aim of our study was to assess prognostic value to NT-proBNP levels in an unselected real-world cohort of anticoagulated patients with AF seen in everyday clinical practice.

Methods

Patients

We recruited consecutive patients with permanent or paroxysmal AF who were taking OAC from our outpatient anticoagulation clinic. To homogenize the study sample, all patients had good anticoagulation control with stable international normalized ratio (INR) values for 26 months (INRs, 2.0–3.0, time in therapeutic range >70%), and were anticoagulated with acenocoumarol. Patients with prosthetic heart valves, acute coronary syndrome, stroke (ischemic or embolic), valvular AF, potentially unstable chest pain, or any hemodynamic instability as well as patients who had hospital admission or surgical intervention in the preceding 6 months were excluded from the study. Patients with previous stroke occurring >6 months from the inclusion date were eligible. At study entry, a complete medical history was recorded. The CHA2DS2–V ASc risk score was calculated as baseline measures of stroke risk. CHADS2 is based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack, and 1 point is assigned for age ≥75 years, hypertension, diabetes mellitus, or congestive cardiac failure. The CHA2DS2–V ASc risk score assigns 1 point to congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and sex category (female) and 2 points to age ≥75 years and stroke. The 1 point to hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (265 years of age), and concomitant drug/alcohol use (1 point each; HAS–BLED) risk score was calculated as a measure of baseline bleeding risk as a result of adding 1 point to hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (age ≥65 years), and concomitant drug/alcohol use in excess (1 point for each). Based on our inclusion criteria at study entry, labile INR was scored as 0 in every patient (ie, all patients had good INR control), and renal impairment was recorded from medical history of the patients.

Follow-up information was obtained from visits through the anticoagulation clinic, the hospital electronic medical records system or, when unavailable, by telephone interview. The primary end point was stroke/transient ischemic accident, which included both cardio-embolic and atherothrombotic strokes, as well as systemic embolism. The secondary end point was the composite of cardiovascular events defined as stroke/transient ischemic accident, including both cardio-embolic and atherothrombotic strokes, as well as systemic embolism, acute coronary syndrome, acute heart failure and cardiac death.

We also recorded as secondary end points the occurrence of major bleeding (defined by the International Society of Thrombosis and Haemostasis criteria) and all-cause deaths.

Blood Samples and Laboratory Analysis

Blood samples were drawn atraumatically and without stasis into syringes preloaded with trisodium citrate (0.011 mol/L). Platelet-poor plasma fractions were obtained by centrifugation at 4°C for 20 minutes at 2200 g. Aliquots were stored at −80°C to allow batch analysis. NT-proBNP levels were assessed by electrochemiluminescence in an automated analyser (Cobas e 601; Roche Diagnostica; Mannheim, Germany). The intra-assay variation coefficient was 5.6%. The intra-assay coefficient of variation for NT-proBNP was 1.8% for 221 pg/mL and 3.1% for 4250 pg/mL.

Statistical Analysis

Continuous variables were tested for normal distribution by Kolmogorov–Smirnov test. Continuous variables are presented as a means ±SD or median (interquartile range), as appropriate, and categorical variables as a percentage. We explored the best cutoff points for NT-proBNP in our study population, and receiver-operating characteristic curves analyses were generated to test the predictive discrimination cutoff to identify association with adverse events during follow-up. The cut point with the best sensitivity and specificity was chosen. The independent effect of NT-proBNP on prognosis was assessed using a Cox proportional hazards regression model, incorporating the CHA2DS2–V ASc score into the multivariate model for the primary end point, as well as the composite of cardiovascular events and death; and for major bleeding events, adjustment was by HAS–BLED score. The impact of adding renal dysfunction was also explored in a secondary multivariate analysis.

Model performance was evaluated by calculating C-statistics, and the improvement in predictive accuracy was evaluated by calculating the net reclassification improvement (NRI) and integrated discrimination improvement (IDI), as described by Pencina et al, in which the categories of probability for events are defined based on prognostication scheme of the CHADS2 or CHA2DS2–V ASc. A P value <0.05 was accepted as statistically significant. Statistical analysis was performed using SPSS 15.0 for Windows (SPSS, Inc; Chicago, IL).

Results

We studied 1172 patients (49% male; median age 76 years) whose clinical characteristics are shown in Table 1. The median CHA2DS2–V ASc score was 4 (3–5), and 94% had a CHA2DS2–V ASc score ≥2. Median follow-up was 1007 (806–1279) days and, during this period, 51 patients presented with the primary end point stroke (1.6% per year), whereas 143 patients (4.51% per year) died, and 128 patients had an adverse cardiovascular event (4.04% per year).

Median levels (interquartile range) of NT-proBNP were 610 (318–1037) pg/mL. For each end point, we constructed receiver-operating characteristic curves that gave a cutoff point of 822 pg/mL for the primary end point of stroke/embolism (area under the curve, 0.63; 95% confidence interval, 0.60–0.66; sensitivity, 61%; specificity, 66%; positive predictive value, 8%; and negative predictive value, 97%). Second, we identified a cutoff point of 519 pg/mL for mortality (area under the curve, 0.59; 95% confidence interval, 0.56–0.62; sensitivity, 70%; specificity, 45%; positive predictive value, 15%; and negative predictive value, 92%). Third, we identified a cutoff point of 304 pg/mL for adverse cardiovascular events (area under the curve, 0.57; 95% confidence interval, 0.54–0.59; sensitivity, 87%; specificity, 25%; positive predictive value, 12%; and negative predictive value, 94%).
bleeding events, we were not able to find a potential cutoff point (area under the curve, 0.525).

Univariate predictors of stroke/embolism, adverse cardiovascular events, major bleeds, and mortality are shown in Table 2.

On multivariate analysis, high NT-proBNP levels remained significantly associated with prognosis even after adjusting for CHA2DS2–VASc score. The CHA2DS2–VASc score had a hazards ratio (HR) of 1.30 (1.09–1.55), \( P = 0.004 \), and high NT-proBNP (\( \geq 822 \) pg/mL) had an HR of 2.71 (1.54–4.75), \( P = 0.001 \), for stroke. The influence of CHA2DS2–VASc score for the composite of cardiovascular events was 1.35 (1.21–1.51; \( P < 0.001 \)) and for high NT-proBNP (\( \geq 304 \) pg/mL), 1.85 (1.12–3.04; \( P = 0.016 \)). For all-cause mortality, the CHA2DS2–VASc score had an HR of 1.39 (1.26–1.55; \( P < 0.001 \)), and high NT-proBNP (\( \geq 519 \) pg/mL) had an HR of 1.66 (1.16–2.37; \( P = 0.006 \)). Only the HAS–BLED score was predictive for bleeding.

When renal dysfunction was added into the multivariate analysis, the presence of renal impairment only had a significant impact on death (HR, 1.59; 95% confidence interval, 1.03–2.45) and not the primary end point (stroke) nor the composite of cardiovascular events. Of note, the CHA2DS2–VASc score and NT-proBNP remained significant predictors of stroke, the composite of cardiovascular events, and death (full data not shown).

The IDI analysis demonstrated NT-proBNP-improved CHA2DS2–VASc score for predicting embolic events (relative IDI, 2.8%; \( P = 0.001 \)) and all-cause death (relative IDI, 1.8%; \( P = 0.001 \)). Similarly, the NRI showed significantly improved reclassification when NT-proBNP was added to the CHA2DS2–VASc score for stroke (\( P = 0.047 \)), composite cardiovascular events (\( P < 0.001 \)), and death (\( P = 0.006 \); Table 3).

**Table 1. Baseline Clinical Characteristics of Patients With AF in the Global Cohort and Those Who Developed the Primary End Point and Not**

<table>
<thead>
<tr>
<th></th>
<th>Total N=1172</th>
<th>Primary End Point n=51</th>
<th>No Primary End Point n=1121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>575 (49%)</td>
<td>22 (43%)</td>
<td>553 (51%)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>76 (71–81)</td>
<td>80 (75–83)</td>
<td>76 (70–81)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>963 (82%)</td>
<td>42 (82%)</td>
<td>921 (82%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>308 (26%)</td>
<td>13 (26%)</td>
<td>295 (26%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>359 (30%)</td>
<td>14 (28%)</td>
<td>345 (31%)</td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>219 (19%)</td>
<td>22 (43%)</td>
<td>197 (18%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>226 (19%)</td>
<td>6 (12%)</td>
<td>220 (20%)</td>
</tr>
<tr>
<td>Current smoking habit</td>
<td>191 (16%)</td>
<td>8 (16%)</td>
<td>183 (16%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>389 (33%)</td>
<td>14 (28%)</td>
<td>375 (33%)</td>
</tr>
<tr>
<td>Previous bleeding episode</td>
<td>91 (8%)</td>
<td>7 (14%)</td>
<td>84 (8%)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>119 (10%)</td>
<td>3 (6%)</td>
<td>116 (19%)</td>
</tr>
<tr>
<td>Concomitant treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>210 (18%)</td>
<td>9 (18%)</td>
<td>201 (18%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>387 (33%)</td>
<td>16 (31%)</td>
<td>371 (33%)</td>
</tr>
<tr>
<td>Angiotensin–renin blockers</td>
<td>387 (33%)</td>
<td>14 (28%)</td>
<td>373 (33%)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>363 (31%)</td>
<td>19 (37%)</td>
<td>344 (31%)</td>
</tr>
<tr>
<td>( \beta )-blockers</td>
<td>504 (43%)</td>
<td>23 (45%)</td>
<td>481 (43%)</td>
</tr>
<tr>
<td>Statins</td>
<td>352 (30%)</td>
<td>10 (20%)</td>
<td>342 (31%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>293 (25%)</td>
<td>16 (31%)</td>
<td>277 (25%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>645 (55%)</td>
<td>30 (59%)</td>
<td>615 (54%)</td>
</tr>
<tr>
<td>CHA2DS2–VASc</td>
<td>4 (3–5)</td>
<td>5 (4–6)</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>CHA2DS2–VASc ( \geq 2 ), n (%)</td>
<td>1103 (94%)</td>
<td>50 (98%)</td>
<td>1053 (94%)</td>
</tr>
<tr>
<td>HAS–BLED</td>
<td>2 (2–3)</td>
<td>3 (2–3)</td>
<td>2 (2–3)</td>
</tr>
<tr>
<td>HAS–BLED ( \geq 3 ), n (%)</td>
<td>406 (35%)</td>
<td>27 (53%)</td>
<td>379 (34%)</td>
</tr>
<tr>
<td>NT-proBNP, median (IQR) pg/mL</td>
<td>610 (318–1037)</td>
<td>956 (474–1460)</td>
<td>601 (312–1008)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; CHA2DS2–VASc, 1 point to congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 years, and sex category (female) and 2 points to age \( \geq 75 \) years and stroke; HAS–BLED, 1 point to hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile international normalized ratio, elderly (\( \geq 65 \)), and drugs/alcohol concomitantly (1 point each); IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and TIA, transient ischemic accident.

**Discussion**

Our study shows how increased plasma NT-proBNP, an established cardiovascular morbid-mortality marker, is associated with adverse prognosis in patients with AF concerning cardiovascular events, stroke, and systemic embolism and mortality.
Importantly, the addition of NT-proBNP resulted in an improved prediction performance for end points, beyond the CHA2DS2–VASc risk stratification scores. Specifically, NT-proBNP improved the prediction of those patients who had the primary end point (stroke) by 17%, assessed by the NRI analysis.

B-type natriuretic peptide is a 32–amino acid polypeptide secreted by ventricular myocytes mainly in response to increased wall tension such as volume or pressure overload. B-type natriuretic peptide is cleaved into the active hormone (B-type natriuretic peptide) and the inactive NT-proBNP. Circulating levels of NT-proBNP have been reported as markers of increased mortality and morbidity in congestive heart failure, ischemic heart disease, and even in community-based healthy subjects.

Table 3. Evaluating Increased Predictive Ability of NT-proBNP Adding CHA2DS2–VASc for Detection of Stroke, Cardiovascular Events, and All-Cause Death Using C-Statistics IDI and NRI Indexes

<table>
<thead>
<tr>
<th>End Point</th>
<th>C-Statistics (95% CI)</th>
<th>P Value</th>
<th>Relative IDI, %</th>
<th>P Value</th>
<th>NRI</th>
<th>P Value</th>
<th>Percentage of No Events Correctly Reclassified</th>
<th>Percentage of Events Correctly Classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/systemic embolism</td>
<td>CHA2DS2–VASc score</td>
<td>0.62</td>
<td>(0.59–0.65)</td>
<td>0.001</td>
<td>17.4</td>
<td>0.047</td>
<td>−0.3</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td>High NT-proBNP (≥822 pg/mL)</td>
<td>0.68</td>
<td>0.069</td>
<td>2.8</td>
<td>0.001</td>
<td>17.4</td>
<td>0.047</td>
<td>−0.3</td>
</tr>
<tr>
<td>Composite of cardiovascular events</td>
<td>CHA2DS2–VASc score</td>
<td>0.64</td>
<td>(0.61–0.67)</td>
<td>0.001</td>
<td>9.9%</td>
<td>&lt;0.001</td>
<td>15.4</td>
<td>−5.5</td>
</tr>
<tr>
<td></td>
<td>High NT-proBNP (≥304 pg/mL)</td>
<td>0.65</td>
<td>0.540</td>
<td>1.4</td>
<td>&lt;0.001</td>
<td>13.5%</td>
<td>0.006</td>
<td>12.6</td>
</tr>
<tr>
<td>All-cause death</td>
<td>CHA2DS2–VASc score</td>
<td>0.66</td>
<td>(0.64–0.69)</td>
<td>0.001</td>
<td>13.5</td>
<td>0.006</td>
<td>12.6</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>High NT-proBNP (≥519 pg/mL)</td>
<td>0.68</td>
<td>0.178</td>
<td>1.8</td>
<td>&lt;0.001</td>
<td>13.5%</td>
<td>0.006</td>
<td>12.6</td>
</tr>
</tbody>
</table>

CHA2DS2–VASc indicates 1 point to congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 years, and sex category (female) and 2 points to age ≥75 years and stroke; CI, confidence intervals; IDI, integrated discrimination improvement; NRI, net reclassification improvement, and NT-proBNP, N-terminal pro–B-type natriuretic peptide.
independent predictor of new-onset AF in patients with ST elevation myocardial infarction,\textsuperscript{19} and elevated NT-proBNP levels predict an increased risk of development of AF independent of other risk factors including echocardiographic parameters.\textsuperscript{20} In addition, it has also been reported that B-type natriuretic peptides, in combination with other biomarkers, could better identify cardioembolic stroke,\textsuperscript{21,22} even detecting new AF onset in patients admitted with acute stroke.\textsuperscript{23} However, the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy) was the first, which draws on the use of NT-proBNP as event predictor in anticoagulated patients with AF for stroke and mortality.\textsuperscript{10} These results were corroborated by the ARISTOTLE trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation), which also showed an improved risk stratification value with this biomarker.\textsuperscript{11}

Currently used clinical risk scores have shown limited capability in predicting thromboembolic events, with low values for area under the curve, and also modest discriminating value for C-statistics.\textsuperscript{7} Hence, it seems the fact that different recent studies have highlighted the incorporation of biomarkers to improve the prediction power of these scores, enhancing the risk stratification. We showed how NT-proBNP significantly improves the prediction ability of the CHA\textsubscript2DS\textsubscript2-VASe score in terms of C-statistics, IDI, and NRI. It is valuable to state that in the context of clinical trials, patients are often carefully selected, whereas patients with AF in real-life clinical practice tend to be older, with associated comorbidities and polypharmacy, factors that may make accurate estimation of stroke and bleeding risk more difficult.

There is a close relationship between AF-stroke and NT-proBNP. It has been reported that the origin of BNP in AF comes from myocyte stress secondary to atrial dysfunction,\textsuperscript{24,25} which, in turn, could be a mechanism of atrial embolization.\textsuperscript{26,27} Much of the AF-associated morbidity and mortality is secondary to a 5-fold to 6-fold increased risk of stroke.\textsuperscript{28} Although oral anticoagulation is highly effective in reducing the risk for stroke and thromboembolism, the incidence of stroke in patients with AF with adjusted oral anticoagulation ranged from 1.2\% to 2.0\% per year.\textsuperscript{29} We recently demonstrated how CHA\textsubscript2DS\textsubscript2-VASe score predicted adverse cardiovascular events beyond thromboembolic risk in patients with AF taking OAC\textsuperscript{10}; NT-proBNP could better identify patients at risk of stroke and other cardiovascular events, leading to better oral anticoagulant management or use of the new oral anticoagulants.

**Limitations**

A selection bias could be evident because we only recruited patients on stable OAC. Therefore, those unstable patients who are more prone to have adverse events were excluded, and we could discharge that high NT-proBNP levels would be secondary to any hemodynamic instability. Also, we have only determined a unique value of NT-proBNP; changes in this biomarker may occur during follow-up; and these modifications could give additional information. Importantly, BNP levels not only increase during states of hemodynamic stress, but also with age or renal dysfunction.\textsuperscript{30} Unfortunately, we did not have detailed echocardiographic assessments in this real-world study to be able to assess other parameters potentially influencing NT-proBNP, including left atrial volume, valvular heart disease, etc.

In conclusion, in a real-world large cohort of patients with AF, we corroborated the prognostic and independent value of NT-proBNP in predicting new stroke events as well as mortality despite use of oral anticoagulation. This biomarker also permits us to refine stroke risk assessment using the current stroke stratification schemes based on clinical criteria.

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**References**


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Full Article

抗凝固薬投与中の心房細動患者の脳卒中リスク予測における N 末端プロ B 型ナトリウム利尿ペプチド値の有用性

Usefulness of N-Terminal Pro-B-Type Natriuretic Peptide Levels for Stroke Risk Prediction in Anticoagulated Patients With Atrial Fibrillation

KEYWORDS 抗凝固薬、心房細動、B 型ナトリウム利尿ペプチド、脳卒中

心房細動 (AF) は脳卒中および血栓塞栓症のリスクを上昇させ、罹患率や死亡率の上昇に関連する。経口抗凝固療法は、プラセボ（対照）群に比べ、脳卒中および死亡のリスク低下にきわめて有効であることが報告されている。血栓予防に関する判断の材料として、患者の臨床的特徴に基づくリスクを層別化する方法は複数開発されている。なかでも CHADS2 スコア [うっ血性心不全、高血压、年齢、糖尿病、脳卒中 (2 点)] に基づくリスクの評価が多く使用されてきた。しかし、近年、CHADS2 スコアの有用性が議論されており、多くの脳卒中の脳卒中が考慮されていないなど、CHADS2 スコアの限界が指摘されている。こうした議論を受け、CHADS2 スコアは、脳卒中に基づく評価を重要とする CHADS2–VASC [うっ血性心不全、高血压、年齢 75 歳以上 (2 点)、糖尿病、脳卒中 (2 点)、血管疾患、性別 (女性) 基づくリスク] の標準に改良されている。CHADS2–VASC スコアは欧州心臓病学会 (ESC) により提案されたもので、脳卒中に基づく血栓予防を念頭に、経口抗凝固療法の判断材料としての活用を目的とする。CHADS2–VASC スコアは多数の独立したコホートで検証されており、血管イベントや死亡の予測に有用であることが示されています。抗凝固療法中の AF 患者に発生する有害イベント（血栓塞栓症を含む）、死亡、大出血について、予後の予測における生体指標の有用性に関するデータは限られている。しかし、AF における生体指標を検討した最近の研究では、生体指標の活用によ
抗凝固原投与中の心房細動患者の脳卒中リスク予測におけるN末端プロB型抗凝固薬利尿ペプチド値の有用性

方法

患者

当院の経口抗凝固療法外来クリニック、永続性または非発作性AFで経口抗凝固薬を服用中の患者を登録した。

試験開始時における脳卒中リスクの評価として、CHA₂DS₂-VASc スコアを記録した。CHA₂DS₂-VASc スコアは加点方法を採用しており、脳卒中または一過性脳虚血発作の既往に2点、75歳以上、高血圧、糖尿病、うつ血性心不全に1点を付与する。一方、CHA₂DS₂-VAScリスクスコアは、うつ血性心不全、高血液圧、糖尿病、血管疾患、年齢65〜74歳、性別（男性）に1点、年齢75歳以上および脳卒中に2点を付与する。試験開始時における出血リスクの評価として、高血圧、腎/肝機能異常（各1点）、脳卒中、出血の既往または傾向、INRコントロール不良、高齢（65歳以上）、薬物の併用/過剰飲酒（各1点）にそれぞれ1点を付与するリスクスコア（HAS-BLED）を算出した。本試験登録時における患者のジェネティクス倫理委員会の承認を得た。
表1 試験開始時におけるAF患者の臨床的特徴：AF患者コホート全体および主要評価項目の該当者/非該当者別に示す

<table>
<thead>
<tr>
<th></th>
<th>全体</th>
<th>主要評価項目の該当者</th>
<th>主要評価項目の非該当者</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1172</td>
<td>1172</td>
<td>1172</td>
</tr>
<tr>
<td>男性</td>
<td>575 (49%)</td>
<td>22 (43%)</td>
<td>553 (51%)</td>
</tr>
<tr>
<td>年齢（中央値）（IQR）</td>
<td>76 (71~81)</td>
<td>80 (75~83)</td>
<td>76 (70~81)</td>
</tr>
<tr>
<td>高血圧</td>
<td>963 (82%)</td>
<td>42 (82%)</td>
<td>921 (82%)</td>
</tr>
<tr>
<td>糖尿病</td>
<td>308 (26%)</td>
<td>13 (26%)</td>
<td>295 (26%)</td>
</tr>
<tr>
<td>脳卒中またはTIの既往</td>
<td>359 (30%)</td>
<td>14 (28%)</td>
<td>345 (31%)</td>
</tr>
<tr>
<td>冠動脈疾患</td>
<td>219 (19%)</td>
<td>22 (43%)</td>
<td>197 (18%)</td>
</tr>
<tr>
<td>現在の喫煙習慣</td>
<td>191 (16%)</td>
<td>8 (16%)</td>
<td>183 (16%)</td>
</tr>
<tr>
<td>高コレステロール血症</td>
<td>389 (33%)</td>
<td>14 (28%)</td>
<td>375 (33%)</td>
</tr>
<tr>
<td>過去の出血イベント</td>
<td>91 (8%)</td>
<td>7 (14%)</td>
<td>84 (8%)</td>
</tr>
<tr>
<td>臨床機能障害</td>
<td>119 (10%)</td>
<td>3 (6%)</td>
<td>116 (10%)</td>
</tr>
<tr>
<td>併用薬</td>
<td>抗血小板薬</td>
<td>210 (18%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td></td>
<td>アシテーション・レニンブロッカー</td>
<td>387 (33%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td></td>
<td>カルシウム拮抗薬</td>
<td>304 (26%)</td>
<td>11 (23%)</td>
</tr>
<tr>
<td></td>
<td>カプサランプ</td>
<td>615 (54%)</td>
<td>52 (10%)</td>
</tr>
<tr>
<td></td>
<td>CHADS2-VASc</td>
<td>3 (3~5)</td>
<td>4 (3~5)</td>
</tr>
<tr>
<td></td>
<td>CHADS2-VASc ≥ 2, n (%)</td>
<td>1103 (94%)</td>
<td>50 (98%)</td>
</tr>
<tr>
<td></td>
<td>HAS-BLED</td>
<td>2 (2~3)</td>
<td>3 (2~3)</td>
</tr>
<tr>
<td></td>
<td>HAS-BLED ≥ 3, n (%)</td>
<td>406 (35%)</td>
<td>27 (53%)</td>
</tr>
</tbody>
</table>

ACE：アシテーション・レニンブロッカー
Af：心房細動
CHADS2-VASc：うっ血性心不全，高血圧，糖尿病，血栓疾患，年齢65〜74歳，性別（女性）に1点，
 年齢75歳以上および脳卒中に2点を付与して算出されるスコア
 HAS-BLED：高血圧，腎/肝機能異常（各1点），脳卒中，出血の既往または傾向，INRコントロール不全，
 高齢（65歳以上）, 併用薬/過剰飲酒（各1点）に1点を付与して算出すスコア
 IQR：四分位範囲
 NT-proBNP：N末端プロブロビリナミド利尿ペプチド
 TI：一過性脳虚血发作
 INR：国際基準比

では，CHADS2-VASc スコアのHRは1.39 (1.26 ~ 1.55, p < 0.001), NT-proBNP 高値（≥ 259 pg/mL）のHR
 は1.66 (1.16 ~ 2.37, p = 0.006) であった。出血が予
 測できたのはHAS-BLED スコアのみであった。

多変量解析で腎機能不全を追加して考慮した場合，腎機能障害の存在は死亡のみに対して有意な影響を与えた
（HR: 1.59, 95%CI: 1.03 ~ 2.45）, 主要評価項目 (脳

C統計量の算出によりモデルの性能を評価した。予
 測精度の向上については，純再分類改善度（Net
 Reclassification Improvement; NRI）と統合判別改善度
（Integrated Discrimination Improvement; IDI）を算出して
評価した。これはPencinaら17が報告した方法であり,
イベント発生率に関するカテゴリをCHADS2または
CHADS2-VAScの予後分類に基づき判定する。p < 0.05
の場合，統計学的に有意と判断した。統計解析にはSPSS
15.0 for Windows（SPSS inc, イリノイ州シカゴ）を用いた。
表2 脳卒中/全身性塞栓症、複合心血管有害イベント、出血イベント、死亡から成る評価項目の Cox 回帰分析

<table>
<thead>
<tr>
<th>説明</th>
<th>多変量解析 (95% CI)</th>
<th>p 値</th>
<th>単変量解析 (95% CI)</th>
<th>p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc スコア</td>
<td>1.32 (1.17 ~ 1.57)</td>
<td>0.001</td>
<td>1.30 (1.09 ~ 1.55)</td>
<td>0.004</td>
</tr>
<tr>
<td>NT-proBNP 高値 (≥ 822 pg/mL)</td>
<td>2.92 (1.67 ~ 5.13)</td>
<td>&lt; 0.001</td>
<td>2.71 (1.54 ~ 4.75)</td>
<td>0.001</td>
</tr>
<tr>
<td>複合心血管有害イベント</td>
<td>1.37 (1.23 ~ 1.52)</td>
<td>&lt; 0.001</td>
<td>1.35 (1.21 ~ 1.51)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CHA2DS2-VASc スコア</td>
<td>1.37 (1.23 ~ 1.52)</td>
<td>&lt; 0.001</td>
<td>1.35 (1.21 ~ 1.51)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NT-proBNP 高値 (≥ 304 pg/mL)</td>
<td>2.05 (1.25 ~ 3.37)</td>
<td>0.005</td>
<td>1.85 (1.12 ~ 3.04)</td>
<td>0.016</td>
</tr>
<tr>
<td>死亡</td>
<td>1.41 (1.27 ~ 1.56)</td>
<td>&lt; 0.001</td>
<td>1.39 (1.26 ~ 1.55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NT-proBNP 高値 (≥ 519 pg/mL)</td>
<td>1.58 (1.29 ~ 2.64)</td>
<td>0.001</td>
<td>1.66 (1.16 ~ 2.37)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

N末端プロブ型ナトリウム利尿ペプチド（NT-proBNP）は、脳卒中および複合心血管イベントの予測に有用であると示唆されている。NT-proBNPは、心房機能不全、高血圧、糖尿病、心不全、年齢75歳以上、複合心血管イベント、死亡のリスクを反映する。NT-proBNPは、脳卒中および脳血栓症のリスクを高めると考えられている。

表3 CHA2DS2-VASc と NT-proBNP の併用による脳卒中、心血管イベント、全死亡の予測改善：C統計量、IDI、NRIを指標として評価

<table>
<thead>
<tr>
<th>説明</th>
<th>C統計量 (95% CI)</th>
<th>p 値</th>
<th>相対IDI %</th>
<th>p 値</th>
<th>NRI</th>
<th>p 値</th>
<th>正しく再分類されたイベントなしの割合</th>
<th>正しく分類されたイベントの割合</th>
</tr>
</thead>
<tbody>
<tr>
<td>脳卒中/全身性塞栓症</td>
<td>0.62 (0.59~0.65)</td>
<td>0.069  2.8  0.001  17.4  0.047  -0.3  17.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc + NT-proBNP 高値 (≥ 822 pg/mL)</td>
<td>0.68 (0.56~0.71)</td>
<td>0.540  1.4  &lt; 0.001  9.9%  &lt; 0.001  15.4  -5.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>複合心血管イベント</td>
<td>0.63 (0.61~0.67)</td>
<td>0.68 (0.62~0.68)</td>
<td>1.8  &lt; 0.001  13.5%  0.006  12.6  0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

本研究により、血漿NT-proBNPの上昇（心房機能不全の罹患および心血管死の確立されたマーカー）が、心血管イベント、脳卒中、全身性塞栓症、死亡に関し、AF患者の予後改善の改善があることが明らかになった。

B型ナトリウム利尿ペプチド（BNP）は32アミノ酸ポリペプチドで、心不全の診断、監視、治療方針の決定に用いられる。
リベプラチドであり、主に容量または容量過負荷などで壁張力が上昇したときに心室筋細胞から分泌される。BNPは、活性ホルモン（BNP）と不活性のNT-proBNPに切断される11。NT-proBNPの循環血中濃度は、うっ血性心不全および虚血性心疾患の罹患率および死亡率上昇を示すマーカーとして報告されており、健康な地域住民を対象とする研究でも同様の知見が認められている16。

BNPはAFリスクの予測にも利用されてきた。これについては、BNPがST上昇型心筋梗塞患者のAF新規発症に関する独立した予測因子として報告されている17。また、NT-proBNP値の上昇により、心エコー検査所見を含む他の危険因子とは独立して、AF発症リスクの上昇が予測されることが示されている20。さらに、BNPと他の生体指標を併用すると、心元行心収縮機能が発見しやすくなり21,22。急性脳卒中による入院患者のAF新規発症の検出も改善することが報告されている23。抗凝固療法投与中のAF患者において、脳卒中および死亡イベントの予測因子としてNT-proBNPを最初に利用したのは、RE-LY研究（Randomized Evaluation of Long-Term Anticoagulation Therapy）である24。これらの研究結果はARISTOTLE試験（Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation）によって裏付けられ、この生体指標によりリスク層別化が改善することも示されており25。

現在使用されている臨床リスクスコアは、AUCの値が小さくC統計量による判別力をそれほど高くないため、血栓塞栓性イベントの予測性能は低いことが示されている26。これを受け、近年、様々な研究が生体指標の活用に注目し、これらの臨床リスクスコアの予測性能を改善することで、リスク層別化の強化を試みてきた。本研究では、NT-proBNP値によりCHA2DS2-VAScスコアの予測性能が高いに有意に改善するかを、C統計量、IDI、NRIの観点から示した。指摘すべき点として、多くの臨床試験では被検者が慎重に選択されるものの、実際の診療現場ではAF患者はより高齢の傾向にあり、併発疾患や多剤投与などの要因により、脳卒中および出血リスクの正確な推定が困難となりうる。

AFおよび脳卒中は、NT-proBNPと密接に関連する。AF患者におけるBNPは、心房機能障害に統発する心筋細胞のストレスにより産生され24,25，これは結局、心房構造の発生機序となりうることが報告されている26,27。AFに関連する疾患の罹患や死亡の多くは、脳卒中リスクの5～6倍の上昇によるものである30。経口抗凝固薬は脳卒中および血栓塞栓症のリスクを抑制するうえで有効であるが、投与量が調節された経口抗凝固薬を使用するAF患者における脳卒中の年間発症率は1.2～2.0%と報告されている28。最近、本研究の著者らは、経口抗凝固薬服用中のAF患者において、CHA2DS2-VAScスコアにより、血栓塞栓症のリスクだけでなく心血管有病イベントがいかに予測されるかを明らかにした31。NT-proBNP値の活用により、脳卒中および他の心血管イベントのリスクが高い患者を特定しやすくなり、薬を含む経口抗凝固薬による治療を改善できると考えられる。

本研究の限界

本研究は、経口抗凝固薬療法で安定状態にある患者のみを登録しており、明らかに選択バイアスを伴う。すなわち、有害イベントが生じやすいと考えられる不安定な患者は除外されており、NT-proBNP高値が不安定な血行動態に起因するか検証できなかったと考えられる。また、本研究では、単一のNT-proBNP測定値を検討している。追跡調査期間中、NT-proBNPは変化した可能性があり、こうした変化から新たな情報が得られることも考えられる。重要なことは、BNP値は、血行動態に負荷がかかった状態だけでなく、加齢や腎機能障害でも上昇する30。残念ながら、実際の診療現場を対象とした本研究では、詳細な心エコー検査を行っておらず、左心室容積、心臓弁疾患など、NT-proBNPに影響しうる他のパラメーターは評価していない。

結論として、実際の診療現場の大規模AF患者コホートにおいて、NT-proBNPは予後の予測について独立した価値を有し、経口抗凝固薬の使用にもかかわらず発症する、新規脳卒中イベントおよび死亡を予測できることが実証された。NT-proBNPという生体指標は、臨床基準に基づいた現行の層別化法と併用することで、脳卒中のリスク評価の改善にも貢献すると考えられる。

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References