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

Vanessa Roldán, MD, PhD; Juan Antonio Vílchez, Pharm, PhD; Sergio Manzano-Fernández, MD, PhD; Eva Jover, BSc; Josefa Gálvez; Carmen M. Puche, Pharm; Mariano Valdés, MD, PhD; Vicente Vicente, MD, PhD; Gregory Y.H. Lip, MD*; Francisco Marín, MD, PhD*

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.1 Oral anticoagulation (OAC) is highly effective in reducing the risk of stroke and mortality compared with placebo/control.2 To aid decision making for thromboprophylaxis, several risk stratification schemes have been developed using clinical characteristics. A popular risk stratification scheme has been the CHADS2–VASC score (Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke [Doubled]–Vascular disease and Sex category [female]).3 More recently, the value of the CHADS2 scheme has been debated, given its noninclusion of many stroke risk factors and other limitations.4 Thus, the CHADS2 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.5 The CHA2DS2–VASc score has been proposed by the European Society of Cardiology to be used in decision making for OAC,6 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.7,8
are limited data on the prognostic role of biomarkers in anticoagulated 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.10,11 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.12 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,13 and are even predictive for AF.14 The aim of our study was to assess prognostic value to NT-proBNP against warfarin, how several biomarkers (like troponins or NT-proBNP) are predictive for adverse events.10,11 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.12 Indeed, biomarkers may potentially be used to refine stroke and bleeding risk stratification in AF.

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## 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 prostatic heart valves, acute coronary syndrome, stroke (ischemic or embolic), 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–VASC stroke risk score was recorded 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–VASC 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 cardioembolic 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 cardioembolic 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 mean±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–VASC 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–VASC. 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–VASC score was 4 (3–5), and 94% had a CHA₂DS₂–VASC 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 (≥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 (≥282 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 (≥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).

**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.

B-type natriuretic peptides have also been used to predict the risk of AF. In this setting, BNP was reported as an

### 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>Endpoint</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</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>
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<tbody>
<tr>
<td>Stroke/systemic embolism</td>
<td></td>
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<tr>
<td>CHA2DS2–VASc</td>
<td>1.32 (1.17–1.57); 0.001</td>
<td>1.30 (1.09–1.55); 0.004</td>
<td></td>
<td>0.62 (0.59–0.65)</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>
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<tr>
<td>High NT-proBNP (≥822 pg/mL)</td>
<td>2.92 (1.67–5.13); &lt;0.001</td>
<td>2.71 (1.54–4.75); 0.001</td>
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<td>0.68 (0.56–0.71)</td>
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<td>Composite of adverse cardiovascular events</td>
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<tr>
<td>CHA2DS2–VASc score</td>
<td>1.37 (1.23–1.52); &lt;0.001</td>
<td>1.35 (1.21–1.51); &lt;0.001</td>
<td></td>
<td>0.64 (0.61–0.67)</td>
<td>0.540</td>
<td>1.4</td>
<td>&lt;0.001</td>
<td>9.9%</td>
<td>&lt;0.001</td>
<td>15.4</td>
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<tr>
<td>High NT-proBNP (≥304 pg/mL)</td>
<td>2.05 (1.25–3.37); 0.005</td>
<td>1.85 (1.12–3.04); 0.016</td>
<td></td>
<td>0.65 (0.62–0.68)</td>
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<tr>
<td>Mortality</td>
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<tr>
<td>CHA2DS2–VASc score</td>
<td>1.41 (1.27–1.56); &lt;0.001</td>
<td>1.39 (1.26–1.55); &lt;0.001</td>
<td></td>
<td>0.66 (0.64–0.69)</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>
<tr>
<td>High NT-proBNP (≥519 pg/mL)</td>
<td>1.85 (1.29–2.64); 0.001</td>
<td>1.66 (1.16–2.37); 0.006</td>
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<td>0.68 (0.65–0.71)</td>
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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, and elevated NT-proBNP levels predict an increased risk of development of AF independent of other risk factors including echocardiographic parameters. In addition, it has also been reported that B-type natriuretic peptides, in combination with other biomarkers, could better identify cardioembolic stroke, even detecting new AF onset in patients admitted with acute stroke. 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. 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.

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. 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 CHA2DS2-VASc 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, which, in turn, could be a mechanism of atrial embolization. Much of the AF-associated morbidity and mortality is secondary to a 5-fold to 6-fold increased risk of stroke. 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. We recently demonstrated how CHA2DS2-VASc score predicted adverse cardiovascular events beyond thromboembolic risk in patients with AF taking OAC, 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. 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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Disclosures
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References


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抗凝固脳投与中の心房細動脈中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

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表

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<tr>
<th>KEYWORDS</th>
<th>抗凝固薬, 心房細動脈, B 型ナトリウム利尿ペプチド, 脳卒中</th>
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</table>

心房細動脈 (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1。経口凝固薬療法は、ブラスピノールが効果的とされているが、脳卒中および死亡のリスク低下にきわめて有効であると報告されている1。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が複数開発されている。なかでも CHADS2 スコア123は、脳卒中再発のリスクを多段階評価した23。しかし、近年、CHADS2 スコアの有用性が議論されており、多くの脳卒中予防のための治療が考慮されている2。CHADS2 スコアの限界が指摘されている2。こうした議論を受け、CHADS2 スコアは、脳卒中予防に基づく評価を重視する。

CHADS2-VASc スコアは、CHADS2 スコアの一部を追加（年齢、糖尿病、腎不全）したリスク評価法であり、CHADS2-VASc スコアは、CHADS2 スコアに増加したリスクを考慮する。CHADS2-VASc スコアは、リスクを増加させるための治療が考慮されている。

Stroke 2014; 45: 696-701
抗凝固療法投与中の心筋細動病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

患者

当院の経済抗凝固療法外来クリニックから、永続性または発作性AFで経済抗凝固療法を服用中の患者を登録した。被験者を均質化するため、国際標準化比（INR）が6ヶ月以上安定しているコントロール状態が良好[INR 2.0～3.0、治療域内時間（TTR） ≥ 70%]、かつ抗凝固薬としてアセトクロマールを使用している患者を対象とした。人工心臓弁、急性心不全、脳卒中（虚血性または塞塞性）、弁膜症性AF、不安定性胸痛の疑い、血行動態不安定のいずれかを該当する患者、ならびに6ヶ月以内に入院または外科的介入の既往がある患者は研究から除外した。前回の脳卒中の発症から本研究の登録日まで6ヶ月以上間隔をあけている患者は適格とした。本試験への登録は、被験者の詳細な病歴を記録した。

試験開始時における脳卒中リスクの評価として、CHADS2-VAScスコアを記録した4)。CHADS2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、CHADS2-VAScリスクスコアは、うつ血性心不全、高血圧、糖尿病、血管疾患、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、脳/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/過剰摂取（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5)。本試験登録時の中選択基準に基づき、INRコントロール不良については、いずれの患者も0点であり（つまり、全例でINRのコントロールは良好であった）、腎機能障害の有無は患者の病歴から判断した。

追跡調査中の情報は、抗凝固療法外来への受診、また病院の電子カルテシステムから取得し、入手できない場合は電話で聞き取りを行った。主要評価項目は、心塞栓症およびアテローム血栓性脳卒中を通じた脳卒中/一過性脳虚血発作および全身性塞栓症とした。肺次評価項目は、術中心血管イベントであり、心塞栓症およびアテローム血栓性脳卒中を通じた脳卒中/一過性脳虚血発作および全身性塞栓症、急性冠塞症候群、急性心不全、心臓死とした。また、大出血［国際血栓血小板学会（ISTH）の基準による］およびあらゆる原因による死亡（全死亡）も、肺次評価項目として記録した。

血液検査および臨床検査分析

血液検査は非侵襲的に採取し、静置せず、クエン酸三ナトリウム（0.101 mol/L）入りシリンジを使用した。乏血小板血漿分画は4℃、2200 gで20分間遠心分離して採取した。パッチ分析のため分注検体を-80℃で保存した。NT-proBNP値は、自動分析装置（Cobas e 601, Roche Diagnostica, マンハイム, ドイツ）を用い、電気化学発光法で測定した同時測定再現性係数（intra-assay variation coefficient）は5.6%であった。NT-proBNP値の同時測定再現性係数は221 pg/mLで1.5, 4250 pg/mLで3.1%であった。

統計解析

連続変数はKolmogorov-Smirnov検定を用いて正規分布について検定した。連続変数は必要に応じ平均値±SDまたは中央値（四分位範囲）で示し、カテゴリ変数はパーセンテージで示した。本研究対象集団において、NT-proBNP値の最適なカットオフポイントを探索した。追跡調査中の有害イベントとの関連性を特定するため、受信者動作特性（ROC）解析により、予測の判断に役立つカットオフポイントを検討し、最も感度および特異度が高いカットオフポイントを選択した。予後に対するNT-proBNP値の独立した影響についてはCox比例ハザード回帰モデルで評価し、主要評価項目、複合心血管イベントおよび死亡に関する多変量モデルにはCHA2DS2-VAScスコアを取り入れた。また、大出出血イベントについては、HAS-BLEDスコアによる調整を行った。多変量解析では、腎機能障害の追加による影響も肺次的に検討した。
表1 試験開始時におけるAF患者の臨床的特徴：AF患者ホモート全体および主要評価項目の該当者/非該当者間の比較

<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></td>
<td>N = 1172</td>
<td>N = 110</td>
<td>N = 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 (QQR)</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>心不全</td>
<td>359 (30%)</td>
<td>14 (28%)</td>
<td>345 (31%)</td>
</tr>
<tr>
<td>腦卒中にまたはTIaの既往</td>
<td>219 (19%)</td>
<td>22 (43%)</td>
<td>197 (18%)</td>
</tr>
<tr>
<td>冠動脈疾患</td>
<td>226 (19%)</td>
<td>6 (12%)</td>
<td>220 (20%)</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>過去の出血エピソード</td>
<td>91 (8%)</td>
<td>7 (14%)</td>
<td>84 (8%)</td>
</tr>
<tr>
<td>腎機能障害</td>
<td>119 (10%)</td>
<td>3 (6%)</td>
<td>116 (10%)</td>
</tr>
<tr>
<td>併用薬</td>
<td>210 (18%)</td>
<td>9 (18%)</td>
<td>201 (18%)</td>
</tr>
<tr>
<td>ACE阻害薬</td>
<td>387 (33%)</td>
<td>16 (31%)</td>
<td>371 (33%)</td>
</tr>
<tr>
<td>アンジオテンシン-レニンブロッカー</td>
<td>387 (33%)</td>
<td>14 (28%)</td>
<td>373 (33%)</td>
</tr>
<tr>
<td>カルシウム拮抗薬</td>
<td>363 (31%)</td>
<td>19 (37%)</td>
<td>344 (31%)</td>
</tr>
<tr>
<td>グリプロック</td>
<td>504 (43%)</td>
<td>23 (45%)</td>
<td>481 (43%)</td>
</tr>
<tr>
<td>スタチン</td>
<td>352 (30%)</td>
<td>10 (20%)</td>
<td>342 (31%)</td>
</tr>
<tr>
<td>ジゴキシン</td>
<td>293 (25%)</td>
<td>16 (31%)</td>
<td>277 (25%)</td>
</tr>
<tr>
<td>利尿薬</td>
<td>645 (55%)</td>
<td>30 (59%)</td>
<td>615 (54%)</td>
</tr>
<tr>
<td>CHADS2-VASc</td>
<td>4 (3 - 5)</td>
<td>5 (4 - 6)</td>
<td>4 (3 - 5)</td>
</tr>
<tr>
<td>CHADS2-VASc≥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≥2, n(%)</td>
<td>406 (35%)</td>
<td>27 (53%)</td>
<td>379 (34%)</td>
</tr>
<tr>
<td>NT-proBNP, 中央値 (QQR), pg/mL</td>
<td>610 (318 - 1037)</td>
<td>956 (474 - 1460)</td>
<td>601 (312 - 1008)</td>
</tr>
</tbody>
</table>

ACE:アングiotensin変換酵素, AF:心房細動, CHADS2-VASc:うっ血性心不全, 高血圧, 糖尿病, 血管疾患, 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点を付与する評価スコア, HAS-BLED: 高血圧, 腎/肝機能障害（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）, 併用薬/過剰飲酒（各1点）に1点を付与し算出するスコア, IQQR: 四分位範囲, NT-proBNP: N末端プロB型ナトリウム利尿ペプチド, TIA: 一過性脳虚血发作, INR: 国際標準比。

では、CHADS2-VAScスコアのHRは1.39(1.26 - 1.55, p < 0.001), NT-proBNP高値(≥519 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障害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（HR: 1.59, 95%CI: 1.03 - 2.45），主要評価項目（脳
<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>脳卒中と全身性塞栓症</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc スコア</td>
</tr>
<tr>
<td>NT-proBNP 高値 (≥ 822 pg / mL)</td>
</tr>
<tr>
<td>複合心血管有害イベント</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc スコア</td>
</tr>
<tr>
<td>NT-proBNP 高値 (≥ 304 pg / mL)</td>
</tr>
<tr>
<td>死亡</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc スコア</td>
</tr>
<tr>
<td>NT-proBNP 高値 (≥ 519 pg / mL)</td>
</tr>
<tr>
<td>大出血</td>
</tr>
<tr>
<td>HAS-BLED スコア</td>
</tr>
<tr>
<td>NT-proBNP</td>
</tr>
</tbody>
</table>

N 条件における B 型ナトリウム利尿薬 (NT-proBNP) 値による脳卒中および全身性塞栓症、複合心血管有害イベント、死亡の予測では、CHA₂DS₂-VASc スコアを適応した。また、大出血については HAS-BLED スコアを適応した。CHA₂DS₂-VASc がう血性心不全、高血压、糖尿病、脳血管疾患、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点を付与して算出するスコア。CHA₂DS₂-VASc スコアを基に、HAS-BLED/高血压、脳卒中、中等度認知症 (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)、併用薬/過剰投与 (各1点) に1点を付与して算出するスコア。HR: ハザード比、INR: 国際凝固時間。

*有意差が全くないことを示す。

考察

本研究により、血漿 NT-proBNP の上昇 (心血管疾患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 患者の予後不良という点で関連するのが明らかになった。重要な点として、NT-proBNP 値を追加して考慮することで、CHA₂DS₂-VASc (リスク昇髄化スコア) のみの場合よりも、評価項目の予測能は改善した。特に、NRI で解析した場合、NT-proBNP 価により、主要評価項目 (脳卒中) における患者の予測能は 17% 改善した。

B 型ナトリウム利尿薬 (BNP) は 32 アミノ酸ポ

<table>
<thead>
<tr>
<th>表3 CHA₂DS₂-VASc と NT-proBNP の併用による脳卒中、心血管イベント、全死亡の予測能の改善: C 統計量、IDI、NRI を指標として評価</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>脳卒中 / 全身性塞栓症</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc + NT-proBNP 高値 (≥ 822 pg / mL)</td>
</tr>
<tr>
<td>複合心血管イベント</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc + NT-proBNP 高値 (≥ 304 pg / mL)</td>
</tr>
<tr>
<td>死亡</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc + NT-proBNP 高値 (≥ 519 pg / mL)</td>
</tr>
</tbody>
</table>

CHA₂DS₂-VASc: う血性心不全、高血压、糖尿病、脳血管疾患、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点を付与して算出するスコア。 CI: 統計量、IDI: 統計的変数、NRI: 統計的変数、NT-proBNP: N 系統プロ B 型ナトリウム利尿薬ベブチド。
リベプチドであり、主に容量または圧力過負荷などで壁
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。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 18。

BNPはAFリスクの予測にも利用できた。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
19。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、心原性脳塞栓症が
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。抗凝固薬投与中の 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
ることも示されてい

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計数値による判別力もそれほど高いたた
ため、血栓塞栓性イベントの予測能は低いことが示されて
ている25。これを受けて、近年、種々の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
の予測能が高いに有意に改善するかを、C計数値、IDI、
NRIの観点から示した。指標すべき点として、多くの臨
床試験では被験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、併存疾患
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

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
房塞栓の発生機序となることが報告されている26,27。
AFに関連する疾患の罹患数をTop10に多
くの5 ～ 6倍の上昇によるものである28。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きわ
めて有効であるが、投薬量は調整された経口抗凝固薬を
使用するAF患者における脳卒中発症率は1.2 ～
2.0％と報告されている29。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
有害イベントがいかに予測されるかを明らかにした。
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、新薬を
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、明らかな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
動態に起因するか否かは検討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。追跡観察期間中に、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、左心房
容積、心房弁疾患など、NT-proBNPに影響しうる他の
パラメータは評価されていない。

結論として、実際の診療現場の大规模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生
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を併用することで、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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