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; Josefina 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 multivariable 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 (Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke [Doubled]) score.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 CHA2DS2–VASc (Congestive heart failure, Hypertension, Age≥75 [doubled], Diabetes mellitus, Stroke [doubled]–Vascular disease and Sex category [female]) emphasizes 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 There

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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 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 (INR, 2.0–3.0, time in therapeutic range >70%), and were anticoagulated with acenocoumarol. Patients with prothrombin time values, acute coronary syndrome, stroke (ischemic or embolic), congestive heart failure, 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)15 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 analyses. 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 (≥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 (≥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>
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<th>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</th>
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<tr>
<td><strong>C-Statistics</strong></td>
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<tr>
<td>Stroke/systemic embolism</td>
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<td>CHA2DS2–VASc</td>
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<td>CHA2DS2–VASc+high NT-proBNP (≥822 pg/mL)</td>
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<td>Composite of cardiovascular events</td>
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<td>CHA2DS2–VASc</td>
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<td>CHA2DS2–VASc+high NT-proBNP (≥304 pg/mL)</td>
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<td>All-cause death</td>
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<td>CHA2DS2–VASc+high NT-proBNP (≥519 pg/mL)</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.

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
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 secondarily driven by new emboli, which, in turn, could be a mechanism of atrial embolization.24,25 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 OACs; 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**

There are no disclosures in relation to this article for all authors.

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**References**


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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

Stroke 2014; 45: 696-701
抗凝固酰投与中の心房細動患者の脳卒中リスク予測におけるNT-proBNP型抗凝固酰の有用性

方 法

患者

当院の軽症抗凝固酰治療外来クリニックから、永続性または発作性AFで軽症抗凝固酰薬を服用中の患者を登録した。検査を均質化するため、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（TTTR）70%]、かつ抗凝固酰薬としてアセノクラモールを使用している患者を対象とした。人工心臓弁、急性冠症候群、脳卒中（虚血性または塞栓性）、弁膜症性AF、不安定性心疾患の疑い、血液動態不安定のいずれかに該当する患者、ならびに6か月以内に入院または外科的介入の既往がある患者は本研究から除かった。前回の脳卒中発症から本研究の登録日まで6か月以上隔閡が生じている患者は適格とした。本試験への登録時、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、CHA2DS2-VAScスコアを記録した16。CHA2DS2-VAScスコアの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、高血压、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、高血压、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、高血压、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17。本試験登録時の選択基準に基づき、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、抗凝固酰療法外来への受診、または病院の電子カルテシステムから取得し、入院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、心塞栓性およびアテローム血栓性脳卒中を含む脳卒中/一過性脳虚血発作および全身性塞栓症とした。次評価評価項目は複合心血管イベントであり、心塞栓性およびアテローム血栓性脳卒中を含む脳卒中/一過性脳虚血発作、および、全身性塞栓症、急性冠症候群、急性心不全、心臓死とした。また、大出血[国際血栓止血学会（ISTH）の基準による]およびあらゆる原因による死亡（全死亡）を、次評価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）入りシリコンを使用した。乏血小板血漿分離は4℃、2,200 gで20分間遠心分離して採取した。パッチ分析のため分光検体を-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の同時測定再現性係数は221 pg/mLで1.5%、4,250 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（四分割値）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、信頼性動作特性（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次評価的に検討した。
表1 試験開始時におけるAF患者の臨床的特徴：AF患者コホート全般および主要評価項目の該当者／非該当者に示す

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<th>主要評価項目の該当者</th>
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<td></td>
<td>N＝1172</td>
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<td>男性</td>
<td>575 (49%)</td>
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<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>脳卒中またはTI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>近過去の血栓症</td>
<td>91 (8%)</td>
<td>7 (14%)</td>
<td>84 (8%)</td>
</tr>
<tr>
<td>脳機能障害</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>ACI治療薬</td>
<td>387 (33%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td></td>
<td>アンジオテンシンⅡ阻害薬</td>
<td>387 (33%)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td></td>
<td>カルシウム拮抗薬</td>
<td>363 (31%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td></td>
<td>βブロッカー</td>
<td>504 (43%)</td>
<td>23 (45%)</td>
</tr>
<tr>
<td></td>
<td>スタチン</td>
<td>352 (30%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td></td>
<td>ジゴキシン</td>
<td>293 (25%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td></td>
<td>利尿薬</td>
<td>645 (55%)</td>
<td>30 (59%)</td>
</tr>
<tr>
<td></td>
<td>CHADS2-VASc</td>
<td>4 (3-5)</td>
<td>5 (4-6)</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>
<tr>
<td>NT-proBNP, 中央値 (IQR), 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2点を付与して算出するスコア, HAS-BLED：高血圧, 脳/胎機能異常（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）, 併用薬/過剰薬物（各1点）1点を付与して算出するスコア, IQR：四分位範囲, NT-proBNP：N末端プロボルバトリン, HAS-BLED：一部性脳梗塞発作, 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。

多変量解析で脳機能不全を追加して考慮した場合、脳機能障害の存在が死亡の危険因子であることを示唆する結果であった。
表2 腦卒中 / 全身性塞栓症、複合心血管有害イベント、出血イベント、死亡からなる評価項目の Cox 回帰分析

<table>
<thead>
<tr>
<th></th>
<th>単変量解析（HR, 95% CI）</th>
<th>多変量解析（HR, 95% CI）</th>
</tr>
</thead>
<tbody>
<tr>
<td>腦卒中と全身性塞栓症</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc スコア</td>
<td>1.32 (1.17～1.57); 0.001</td>
<td>1.30 (1.09～1.55); 0.004</td>
</tr>
<tr>
<td>NT-proBNP 高値（ ≥ 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>
</tr>
<tr>
<td>複合心血管有害イベント</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc スコア</td>
<td>1.37 (1.23～1.52); &lt; 0.001</td>
<td>1.35 (1.21～1.51); &lt; 0.001</td>
</tr>
<tr>
<td>NT-proBNP 高値（ ≥ 304 pg/mL）</td>
<td>2.05 (1.25～3.37); 0.005</td>
<td>1.85 (1.12～3.04); 0.016</td>
</tr>
<tr>
<td>死亡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc スコア</td>
<td>1.41 (1.27～1.56); &lt; 0.001</td>
<td>1.39 (1.26～1.55); &lt; 0.001</td>
</tr>
<tr>
<td>NT-proBNP 高値（ ≥ 519 pg/mL）</td>
<td>1.85 (1.29～2.64); 0.001</td>
<td>1.66 (1.16～2.37); 0.006</td>
</tr>
<tr>
<td>大出血</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED スコア</td>
<td>1.91 (1.61～2.26); &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>1.00 (1.00～1.00)*; 0.421</td>
<td></td>
</tr>
</tbody>
</table>

N末端プロB型ナトリウム利尿ペプチド (NT-proBNP) 高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 スコアで調整した。また、大出血については HAS-BLED スコアで調整した。CHA2DS2-VASc が + 被験者全、高血圧、糖尿病、心臓疾患、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 点を付与して算出するスコア。CI：信頼区間。NT-proBNP：N末端プロB型ナトリウム利尿ペプチド。

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

<table>
<thead>
<tr>
<th></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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>0.62 (0.59～0.66)</td>
<td>0.19</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>0.069</td>
<td>2.8</td>
<td>0.001</td>
<td>17.4</td>
<td>0.047</td>
<td>-0.3</td>
<td>17.7</td>
</tr>
<tr>
<td>複合心血管イベント</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>0.64 (0.61～0.67)</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc + NT-proBNP 高値（ ≥ 304 pg/mL）</td>
<td>0.65 (0.62～0.68)</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>
<td>-5.5</td>
</tr>
<tr>
<td>全死亡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>0.66 (0.64～0.69)</td>
<td>0.062</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc + NT-proBNP 高値（ ≥ 519 pg/mL）</td>
<td>0.68 (0.65～0.71)</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>
<td>0.9</td>
</tr>
</tbody>
</table>

NT-proBNP：N末端プロB型ナトリウム利尿ペプチド。
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）と不活性なNT-proBNPに切断される。NT-proBNPの循環血中濃度は、うつ血性
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。

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。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。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急速、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。抗凝固療法中の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。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
ることも示唆されている。

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もそれほど高くなっ
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いる。これを受け、近年、種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、リスク層別化的強化を試みてきた。本研
究では、NT-proBNP値によりCHADS-VAScスコアの
予測能が改善し有意に改善するかを、C統計量、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、心房機能障害に続く心
房細胞のストレスにより産生され、これは結局、心
房塞栓の発生機序となりうることが報告されている。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。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生率は2.0〜

本研究の限界

本研究は、経口抗凝固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
者を除外されており、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。重要なこととは、BNP値は、血行動態に
負荷がかかる状態だけでなく、加齢や腎機能障害でも
上昇する。残念ながら、実際の臨床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、心房弁疾患など、NT-proBNPに影響しうる他の
パラメーターが評価されていない。

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
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
準に基づいた現在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


