B-Type Natriuretic Peptides Help in Cardioembolic Stroke Diagnosis
Pooled Data Meta-Analysis

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Background and Purpose—Determining the underlying cause of a stroke is important to optimize secondary prevention treatment. Increased blood levels of natriuretic peptides (B-type natriuretic peptide/N-terminal pro-BNP [BNP/NT-proBNP]) have been repeatedly associated with cardioembolic stroke. Here, we evaluate their clinical value as pathogenic biomarkers for stroke through a literature systematic review and individual participants’ data meta-analysis.

Methods—We searched publications in PubMed database until November 2013 that compared BNP and NT-proBNP circulating levels among stroke causes. Standardized individual participants’ data were collected to estimate predictive values of BNP/NT-proBNP for cardioembolic stroke. Dichotomized BNP/NT-proBNP levels were included in logistic regression models together with clinical variables to assess the sensitivity and specificity to identify cardioembolic strokes and the additional value of biomarkers using area under the curve and integrated discrimination improvement index.

Results—From 23 selected articles, we collected information of 2834 patients with a defined cause. BNP/NT-proBNP levels were significantly elevated in cardioembolic stroke until 72 hours from symptoms onset. Predictive models showed a sensitivity >90% and specificity >80% when BNP/NT-proBNP were added considering the lowest and the highest quartile, respectively. Both peptides also increased significantly the area under the curve and integrated discrimination improvement index compared with clinical models. Sensitivity, specificity, and precision of the models were validated in 197 patients with initially undetermined stroke with final pathogenic diagnosis after ancillary follow-up.

Conclusions—Natriuretic peptides are strongly increased in cardioembolic strokes. Future multicentre prospective studies comparing BNP and NT-proBNP might aid in finding the optimal biomarker, the best time point, and the optimal cutoff points for cardioembolic stroke identification. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.008311.)

Key Words: biomarker ■ etiology

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Ischemic stroke is one of the most important neurological disorders. An accurate pathogenetic classification of ischemic stroke is essential to prescribe the most suitable secondary treatment to prevent recurrences. Patients with cardioembolic stroke are treated with anticoagulant drugs, whereas antiplatelet agents are the treatment of choice for patients with large artery atherosclerosis (LAA) stroke and small vessel disease (SVD). Cardioembolic strokes are generally more severe and more prone to recurrence than LAA or SVD and account for approximately one fifth of ischemic strokes.

However, in spite of the importance of an accurate etiopathogenetic classification, the cause of ≥35% of patients remains undetermined, even after complete evaluation. This group of patients presents a rate of recurrence of ≥30% during the first year after the event, partly explained by an inappropriate secondary prevention treatment. Stroke of undetermined cause is an heterogeneous group that includes patients with ≥2 or more potential causes of stroke, patients with <50% of symptoms and patients with a negative diagnostic workup. From the latter, a negative diagnostic might be caused by a transitory or reversible condition which is difficult to detect, such as atrial fibrillation (AF). AF is a frequent cardiac-rhythm disorder which detection is essential for cardioembolic stroke diagnosis. However, AF can be paroxysmal and thus challenging to detect by standard cardiac monitoring. Recently, a new clinical construct has been described called embolic stroke of undetermined cause (ESUC). Stroke of undetermined cause is an intermittent condition difficult to detect with conventional clinical-radiological evaluations. These evaluations include ECG, transesophageal echocardiography, and transcranial Doppler sonography complemented with chest radiography. Twenty-four-hour Holter monitoring was conducted in 3 out of 5 cohorts of patients with undetermined stroke, the first months after stroke, and any of these patients did not demonstrate the stroke cause at admission that would ultimately be determined after delayed evaluations. These evaluations included ECG, transesophageal echocardiography, and transcranial Doppler sonography complemented with chest radiography. Twenty-four-hour Holter monitoring was conducted in 3 out of 5 cohorts of patients with undetermined stroke, the first months after stroke, and any of these patients did not demonstrate the stroke cause at admission that would ultimately be determined after delayed evaluations. These evaluations included ECG, transesophageal echocardiography, and transcranial Doppler sonography.

Data Collection
Three reviewers independently checked the quality of the selected studies using a 15-point quality questionnaire. Corresponding authors of all selected studies were contacted by e-mail and were asked to share their data for IPD analysis. A template form was fulfilled with IPD, including BNP/NT-proBNP levels (pg/mL), a methodology for BNP/NT-proBNP measurement, time of sample collection since stroke symptoms onset, age, sex, pathogenesis classification system used, diagnosed cause of stroke, type of stroke (established or transient ischemic attack), and presence of risk factors, such as hypertension, diabetes mellitus, dyslipidemia, AF, ischemic cardiomyopathy, other embolic cardiopathy, or tobacco and alcohol consumption. Baseline neurological severity was collected as National Institutes of Health Stroke Scale (NIHSS) score. When Scandinavian Stroke Scale was used, we corrected it to NIHSS score by NIHSS=25.68−0.43×Scandinavian Stroke Scale. BNP and NT-proBNP blood levels among different subtypes in patients with established ischemic stroke or transient ischemic attack were included in the search on PubMed database till November 12, 2013, 4 independent reviewers performed the selection of articles. The terms used for searching were (b-type natriuretic peptide OR brain natriuretic peptide OR BNP) AND stroke AND (Cardioembolic OR atherothrombotic OR lacunar OR subtype OR etiology). Duplicates were only considered once. References from selected studies and published reviews were manually screened to find other relevant studies.

Methods
Methods are registered and available at PROSPERO database (CRD42013005924).

Inclusion Criteria and Search Strategy
All included studies were original articles that determined BNP or NT-proBNP blood levels among different subtypes in patients with established ischemic stroke or transient ischemic attack. After the search on PubMed database till November 12, 2013, 4 independent reviewers performed the selection of articles. The terms used for searching were (b-type natriuretic peptide OR brain natriuretic peptide OR BNP) AND stroke AND (Cardioembolic OR atherothrombotic OR lacunar OR subtype OR etiology). Duplicates were only considered once. References from selected studies and published reviews were manually screened to find other relevant studies.

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the clinical variables considered in these models were obtained at admission. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were given.

All included cohorts identified stroke cause independently of biomarker levels.

**IPD Analysis**

SPSS statistical package 15.0 (SPSS Inc, Chicago, IL) was used, unless contrary is stated.

BNP and NT-proBNP were non-normally distributed (assessed by Kolmogorov–Smirnov test) and Mann–Whitney U or Kruskal–Wallis test was used. Median and interquartile range are reported. Because of heterogeneity on BNP/NT-proBNP levels among different cohorts, we standardized BNP/NT-proBNP levels calculating the \( Z \) score value of BNP or NT-proBNP in each subject as previously reported.\(^{27}\) We compared standardized levels of BNP/NT-proBNP among cardioembolic, LAA, and SVD, and \( P \) values were adjusted by Bonferroni correction. In the univariate analysis, differences between cardioembolic and noncardioembolic patients were assessed by Pearson \( \chi^2 \) test for categorical variables. Correlations were checked through Spearman test for continuous variables.

The highest and the lowest quartiles for BNP/NT-proBNP levels were established as cutoff points to build the predictive models. Because standardized values were used, we were not able to identify cutoff points expressed in units of concentration (ie, pg/mL). Sensitivity, specificity, PPV, and NPV were determined for each cutoff used.

A clinical predictive model was built using basic variables. We forced age, sex, and NIHSS score at admission in a logistic regression analysis using Enter method, and odds ratio, 95% confidence interval, and \( P \) value are given. A second clinical predictive model was built by adding AF to the previous model. Afterward, we added BNP or NT-proBNP to each model, dichotomized by the cutoff points described above, and the corresponding probabilities were obtained.

We performed bootstrap calculation for odds ratio and 95% confidence interval, using a modified version of Car R-package.\(^{28}\) The added value of each biomarker to each clinical model was assessed using receiving operating characteristic curves and compared the area under the curve among models by DeLong’s Method using MedCalc v.12.3 (Mariakerke, Belgium). For that same purpose, we used R software v.2.15.0 (R Development Core Team 2012; Vienna, Austria; Hmisc and PredictABEL packages)\(^{29}\) for Integrated Discrimination Improvement (IDI) index calculation.

**Results**

A total of 651 articles fitted the search criteria. After bibliography checking, 27 articles were included. Because of unavailability of the requested data or lack of response from authors, we finally selected 23 articles (Figure 1).\(^{16–23,30–44}\) The median quality score was 9 (minimum=5 and maximum=11; data not shown). These 23 included articles corresponded to 18 different cohorts of patients, 16 of which had data from patients with a defined cause (cardioembolic, LAA, or SVD) and 2 cohorts containing data of undetermined patients only. These 16 cohorts were included in the IPD (Table I in the online-only Data Supplement) excluding patients with undetermined cause at this step. All patients from 16 cohorts underwent ECG (12-lead ECG, 24-hour ECG, or long-term ECG) to determine cardioembolic cause of cerebral infarction and 11 cohorts underwent specific cardiac monitoring. Echocardiography was performed in 12 cohorts.

In total, we compiled individual data from 2834 patients with defined stroke cause. We found significantly increased levels of NT-proBNP compared with BNP, as previously reported,\(^{25}\) and consequently we considered both markers

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**Figure 1.** Flow chart diagram. BNP indicates B-type natriuretic peptide; and IPD, individual participants’ data.
separately. BNP was analyzed in a cohort of 1570 patients and NT-proBNP in a cohort of 1264 patients.

We found higher BNP/NT-proBNP values in patients with cardioembolic stroke than in patients with LAA ($P<0.0001$) and SVD ($P<0.0001$; Figure 2A and 2B). For BNP, these differences were significant until 72 hours after symptoms onset, whereas NT-proBNP levels remained significantly higher in cardioembolic strokes during 1 week (Figure 2C and 2D). After univariate analysis, patients with cardioembolic stroke were remarkably older, mostly women had more severe stroke. They also showed more cardiac disorders than noncardioembolic patients (Table 1).

Taking the highest quartile for BNP as cutoff point, we were able to distinguish cardioembolic stroke from other causes with 42.3% sensitivity, 90.7% specificity, a PPV of 80%, and a NPV of 37%. Similarly, NT-proBNP highest quartile showed 40% sensitivity, 90.1% specificity for cardioembolic stroke, with a PPV of 59.3% and a NPV of 88%. When the lowest quartile was considered as cutoff point, we obtained 93.68% sensitivity, 41.94% specificity, a PPV of 80%, and a NPV of 40% for BNP; and 86.3% sensitivity, 36.2% specificity, a PPV of 57.3%, and a NPV of 72.8% for NT-proBNP.

In the multivariate logistic regression analysis, we considered the previous cutoff points aiming to obtain a highly specific and a highly sensitive model for each biomarker. In all the predictive models obtained, BNP and NT-proBNP remained as the main predictors of cardioembolic stroke cause after adjusting by age, sex, and NIHSS score at admission (Table 2). Even when AF was added to each model, BNP and NT-proBNP remained as independent predictors with barely altered predictive values (Table II in the online-only Data Supplement). The discrimination of patients with cardioembolic stroke measured by the area under the curves and IDI index was significantly greater when we added BNP or NT-proBNP to clinical data (Table 2). Similar results were obtained when the predictive models were developed considering the presence of AF as the end point, instead of cardioembolic subtype. Unfortunately, we only disposed of enough data of the diagnosis of cardioembolic stroke in the undetermined cohort to attempt the validation of the predictive models; thus, we were not able to validate predictive models of AF (Table III in the online-only Data Supplement).

We attempted to verify the usefulness of the generated predictive models in patients with undetermined cause at baseline (n=83 for BNP; n=114 for NT-proBNP), but with a defined cause after complete diagnostic workup. The predictive models that included NT-proBNP showed greater sensitivity and specificity for cardioembolic stroke cause than those that included BNP. About accuracy, higher area under the curves were also found with NT-proBNP included in the predictive model (Figure 3; Table 3).

Figure 2. B-type natriuretic peptide/N-terminal pro-BNP (BNP/NT-proBNP) levels among ischemic stroke causes. A and B, Standardized values of BNP and NT-proBNP among patients with cardioembolic stroke, atherothrombotic stroke, and small vessel disease. C and D, BNP/NT-proBNP levels depending on sample collection time. *$P<0.05$, **$P<0.0001$, #$P<1\times10^{-10}$, and ##$P<1\times10^{-20}$.
Discussion

Currently, the use of biomarkers in the stroke field is only recommended for research purposes, with the exception of phospholipase A2 in the prediction of stroke risk. However, stroke biomarkers might aid in different scenarios such as stroke diagnosis, screening high-risk subjects, predicting outcome, or detecting the cause of stroke.

Pro-BNP is released from the myocyte because of stretch. Interestingly, despite being produced equimolarly, NT-proBNP has a longer half-life than BNP and fewer fluctuations on its

<table>
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<tr>
<th>Table 1. Univariate Analysis</th>
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<tr>
<td><strong>Non-CE</strong></td>
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<tr>
<td><strong>Age, y</strong></td>
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<tr>
<td><strong>Sex, female</strong></td>
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<tr>
<td><strong>Admission NIHSS</strong></td>
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<tr>
<td><strong>Arterial hypertension</strong></td>
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<tr>
<td><strong>Diabetes mellitus</strong></td>
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<tr>
<td><strong>Smoker</strong></td>
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<td><strong>Ischemic cardiomyopathy</strong></td>
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For categorical variables n (%) is given and for continuous variables median and interquartile range are indicated, in each group. P < 0.05 was considered significant. BNP indicates B-type natriuretic peptide; CE, cardioembolic; NIHSS, National Institutes of Health Stroke Scale; and NT-proBNP, N-terminal pro-BNP.

<table>
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<th>Table 2. Comparison Between Clinical Predictive Models and Predictive Models Adding BNP or NT-proBNP for Cardioembolic Stroke</th>
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<tr>
<td><strong>Clinical Model in BNP Cohort</strong></td>
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<tr>
<td>Highest Quartile</td>
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<tr>
<td><strong>Logistic regression (OR with 95% CI and P value)</strong></td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Sex, female</td>
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<tr>
<td>Admission NIHSS</td>
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<tr>
<td><strong>BNP/NT-proBNP</strong></td>
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<tr>
<td><strong>IDI statistics</strong></td>
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<td><strong>IDIFor cardioembolic</strong></td>
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<td><strong>IDIFornoncardioembolic</strong></td>
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<tr>
<td><strong>Total IDI</strong></td>
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<tr>
<td><strong>Pvalue</strong></td>
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<td><strong>ROC curve</strong></td>
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<td><strong>AUC (95% CI)</strong></td>
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BNP and NT-proBNP were included in the models as standardized values dichotomized by the highest or the lowest quartile cutoff point. OR is indicated in the logistic regression with 95% CI and P value. Bootstrapping gives 95% CI for OR of BNP highest quartile cutoff (3.26–6.45) and BNP lowest quartile cutoff (4.08–7.94); and for OR of NT-proBNP highest quartile cutoff (4.42–9.22) and NT-proBNP lowest quartile (2.44–4.55). AUC indicates area under the curve; BNP, B-type natriuretic peptide; CI, confidence interval; IDI, integrated discrimination improvement index; NIHSS, National Institutes of Health Stroke Scale score; NT-proBNP, N-terminal pro-BNP; OR, odds ratio; and ROC, receiver operating characteristic.
circulating levels.\textsuperscript{46} This phenomenon might explain the fact that higher amounts of NT-proBNP are found in blood compared with BNP.\textsuperscript{25} For this reason, our IPD analysis was performed separately on each of these markers.

Literature-based meta-analyses are considered basic for the elaboration of guidelines and recommendations for disease management.\textsuperscript{47} However, they represent some limitations in front of IPD meta-analyses. IPD meta-analyses allow the analysis of multiple individual factors and their combination, the generation of predictive models and the development of sub-analysis different from those previously reported in the literature.\textsuperscript{24} During the development of this study, a literature-based meta-analysis showed the association of BNP/NT-proBNP with cardioembolic origin of stroke.\textsuperscript{49} Our results strongly support these associations, and following the IPD strategy, we were able to perform further subanalysis to study the predictive value of BNP/NT-proBNP in depth. We could evaluate differences in BNP/NT-proBNP among causes at different time points, develop 2 different predictive models, and validate their usefulness in a cohort of undetermined patients. We found increased levels of BNP/NT-proBNP in patients with cardioembolic stroke than in noncardioembolic and these differences were significant until 72 hours after symptoms onset. Although, there is no clear evidence of the optimal time point to initiate anticoagulation,\textsuperscript{50} an early identification of patients with cardioembolic stroke through BNP/NT-proBNP testing might aid in speeding up the decision-making process.

On clinical daily practice, patients diagnosed with ischemic stroke are evaluated, when indicated, with cardiac ancillary tests, such as ECG, echocardiography, or Holter monitoring to identify possible cardiac sources of embolism. However, some causes of ischemic stroke are transitory (ie, paroxysmal AF) and, as a consequence, might not be detected during diagnostic workup. In these cases, prolonged cardiac monitoring is necessary to increase the percentage of detection of arrhythmias,\textsuperscript{51} challenging the diagnosis of cardioembolic stroke.

<table>
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<tr>
<th>Predictive Model</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables+BNP highest quartile</td>
<td>74.58%</td>
<td>56.52%</td>
<td>81.48%</td>
<td>46.43%</td>
<td>0.758 (0.644–0.873)</td>
</tr>
<tr>
<td>Clinical variables+NT-proBNP highest quartile</td>
<td>78.79%</td>
<td>95.83%</td>
<td>96.3%</td>
<td>76.67%</td>
<td>0.879 (0.810–0.947)</td>
</tr>
<tr>
<td>Clinical variables+BNP lowest quartile</td>
<td>91.53%</td>
<td>39.13%</td>
<td>79.41%</td>
<td>64.29%</td>
<td>0.674 (0.536–0.811)</td>
</tr>
<tr>
<td>Clinical variables+NT-proBNP lowest quartile</td>
<td>93.94%</td>
<td>79.17%</td>
<td>86.11%</td>
<td>90.48%</td>
<td>0.896 (0.832–0.959)</td>
</tr>
</tbody>
</table>

Clinical variables include age, sex, and National Institutes of Health Stroke Scale score at admission. AUC indicates area under curve; BNP, B-type natriuretic peptide; CI, confidence interval; and NT-proBNP, N-terminal pro-BNP.

![Figure 3](http://stroke.ahajournals.org/)

Figure 3. Probabilities of cardioembolic stroke. Patients with undetermined cause reclassified as cardioembolic or noncardioembolic after follow-up. A, Probabilities of being cardioembolic corresponding to the predictive model conformed by age, sex, National Institutes of Health Stroke Scale (NIHSS) at admission, and B-type natriuretic peptide/N-terminal pro-BNP (BNP/NT-proBNP) dichotomized by the highest quartile. B, Probabilities of being cardioembolic corresponding to the predictive model conformed by age, sex, NIHSS at admission and BNP/NT-proBNP dichotomized by the lowest quartile. Leader line indicates 60% of probabilities of being cardioembolic.
this study, both BNP and NT-proBNP were found to predict cardioembolic stroke independently of age, sex, and NIHSS score at admission. We created a high sensitive model for cardioembolic stroke that might ease the selection of suitable subjects for prolonged monitoring aiming to identify cardiac disorders undetected in earlier ancillary tests. Additionally, we built up a predictive model with an elevated specificity for cardioembolic stroke subtype that allows the identification of patients who would benefit from receiving anticoagulation as secondary prevention therapy. Even when AF (one of the strongest predictors of cardioembolic stroke) was included in these predictive models, they showed similar levels of precision than those without AF, maintaining BNP and NT-proBNP significant independent predictors of cardioembolic stroke. This supports that a basic clinical predictive model conforming by easily determinable variables, such as age, NIHSS, and sex, and complemented with circulating BNP/NT-proBNP levels, might be suitable to diagnose cardioembolic stroke, mainly in those cases in which AF detection is difficult, such as the recently described embolic strokes of undetermined cause. In addition, IDI results indicate that both peptides aid to better discriminate cardioembolic from noncardioembolic strokes. It is also important to notice that, although they were not determined in the same patients, NT-proBNP showed a higher predictive value and IDI index than BNP for the specific model, suggesting that NT-proBNP is a more valuable biomarker for cardioembolic cause discrimination. In contrast, BNP showed higher odds ratio and IDI index for cardioembolism when considered in the more sensitive models.

The rate of recurrence in patients with undetermined stroke has been reported to be 14% to 20% during the first 2 years after stroke, mainly attributable to an inappropriate secondary prevention. They also present poorer functional outcome after 3 months and a higher cumulative death rate after 3-year follow-up. The use of biomarkers has been considered as a good approach to reclassify the cause of patients with undetermined stroke. A combined assessment of proatrial natriuretic peptide, creatine kinase-MB, and NT-proBNP has been previously reported to reclassify 41% of undetermined patients as likely CE. NT-proBNP has also shown its usefulness to identify patients with undetermined stroke having risk of developing AF. We followed a similar approach in this study to correctly identify patients likely to be cardioembolic and found higher sensitivity and specificity when NT-proBNP was measured compared with BNP.

Our analysis has been conducted in a wide spectrum of individuals with a defined cause (gold standard) and enabling the assessment of appropriate tests of diagnosis accuracy. Hence, according to evidence classification scheme for a diagnostic measure, as BNP/NT-proBNP showed high sensitivity/specificity for cardioembolic stroke cause, they could be considered to diagnose cardioembolic stroke with a high level of evidence (Class II).

Our study has some limitations. First, although the included studies share the same end point, it is important to notice that the mechanism identification and pathogenic workup of the included articles have been performed in different centers from many countries and during the past 9 years; thus, the reliability of pathogenic subtyping might be uncertain and could be considered as a source of bias. Second, because of BNP/NT-proBNP values standardization, we were not able to provide a cutoff point to differentiate cardioembolic strokes expressed in units of concentration (ie, pg/mL). Third, although the predictive models are based on a considerable number of participants, the subsets of patients with cryptogenic stroke used in the application of these models are sparse. Consequently, the results of this application of the model should be interpreted with caution. In addition, time of follow-up of these undetermined patients was unavailable. In the fourth place, apart from AF, we were not able to include other cardiac disorders, such as embolic cardiopathies, ischemic cardiomyopathy, or previous heart failure in the predictive models because of a drastic reduction in sample size that compromised the statistical power. Finally, we could not establish a direct comparison between BNP and NT-proBNP because we could not avoid interindividual variability.

Next steps to study in depth the applicability of BNP/NT-proBNP in clinical daily practice for cardioembolic stroke identification should include a simultaneous analysis of BNP and NT-proBNP in the same patients in a multicentre prospective study with a validated measurement device that would allow a direct comparison between both peptides. This might aid in finding the optimal biomarker and the best time point to determine its blood levels, as well as the optimal cutoff points for cardioembolic stroke identification. The evaluation and addition of other cardiac disorders in the predictive models would probably aid in increasing sensitivity/specificity of predictive models of future studies. Finally, a clinical trial might clarify whether BNP/NT-proBNP-directed anticoagulation is clinically significant. Taken together, this would increase the level of evidence to definitely implement the clinical use of NT-proBNP or BNP.

In conclusion, our IPD support the role of natriuretic peptides for the identification of cardioembolic origin of ischemic stroke. Their implementation on clinical daily practice might serve as a better trigger for anticoagulation than performing invasive transesophageal echocardiography or waiting weeks to months to detect an episode of AF. Simultaneously, the use of natriuretic peptides may also be useful to effectively rule out the possibility of underlying cardioembolism and therefore obviate the need for transesophageal echocardiography or intensive heart-rhythm monitoring.

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Disclosures

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References


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B-type natriuretic peptides help in cardioembolic stroke diagnosis: a pooled data meta-analysis

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12- Department of Clinical Neuroscience and Therapeutics Hiroshima University Graduate School of Biomedical & Health Sciences, Hiroshima, Japan.
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15- Department of Neurology, University of Ulm, Ulm, Germany.
16- Stroke Unit and Department of Neurology, Hospital Vall d’Hebron, Barcelona, Spain
17- Cardiology Department, AHEPA University Hospital, Thessaloniki, Greece.
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Supplemental table I: Main demographic characteristics of the cohorts included in the Individual Participants’ Data analysis

<table>
<thead>
<tr>
<th>Cohort No, (ref)</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>NIHSS adm</th>
<th>Gender (female) (%n)</th>
<th>Smokers (%n)</th>
<th>AHT (%n)</th>
<th>DM (%n)</th>
<th>DL (%n)</th>
<th>AF (%n)</th>
<th>IC (%n)</th>
<th>EC (%n)</th>
<th>Alcohol (%n)</th>
<th>CE (%n)</th>
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AF, atrial fibrillation; AHT, arterial hypertension; CE, Cardioembolic; DL, dyslipidemia, DM, diabetes mellitus; EC, embolic cardiopathy; IS, ischemic cardiomyopathy; NIHSS, National Institute of Health Stroke Scale score, at admission.
Supplemental table II: Comparison between clinical predictive models and predictive models adding BNP or NT-proBNP for cardioembolic stroke, when AF was considered.

<table>
<thead>
<tr>
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<th>Clinical model in BNP cohort</th>
<th>Clinical model + BNP</th>
<th>Clinical model in NT-proBNP cohort</th>
<th>Clinical model + NT-proBNP</th>
<th>Logistic Regression (OR with 95% CI and p-value)</th>
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<tbody>
<tr>
<td></td>
<td>Highest quartile</td>
<td>Lowest quartile</td>
<td>Highest quartile</td>
<td>Lowest quartile</td>
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<tr>
<td>Age, years</td>
<td>0.988 (0.973-1.003), p=0.103</td>
<td>0.976 (0.960-0.991), p=0.003</td>
<td>0.979 (0.968-0.991), p=0.001</td>
<td>0.975 (0.964-0.987), p&lt;0.0001</td>
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<tr>
<td>Gender, (female)</td>
<td>2.086 (1.449-3.004), p&lt;0.0001</td>
<td>2.012 (1.376-2.942), p&lt;0.0001</td>
<td>1.522 (1.123-2.064), p=0.007</td>
<td>1.431 (1.049-1.952), p=0.024</td>
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</tr>
<tr>
<td>NIHSS score at admission</td>
<td>1.110 (1.080-1.141), p&lt;0.0001</td>
<td>1.101 (1.070-1.133), p&lt;0.0001</td>
<td>1.046 (1.023-1.069), p&lt;0.0001</td>
<td>1.043 (1.019-1.067), p&lt;0.0001</td>
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<td>Atrial Fibrillation</td>
<td>39.537 (25.767-60.666), p&lt;0.0001</td>
<td>33.940 (21.859-52.696), p&lt;0.0001</td>
<td>18.294 (11.352-29.481), p&lt;0.0001</td>
<td>16.242 (10.040-26.277), p&lt;0.0001</td>
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<td>BNP/NT-proBNP</td>
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<td>4.283 (2.667-6.878), p&lt;0.0001</td>
<td>-</td>
<td>4.920 (3.241-7.464), p&lt;0.0001</td>
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**IDI statistics**

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<th>Total IDI</th>
<th>p-value</th>
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<td>0.056</td>
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**ROC curve**

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<th>AUC (95%CI)</th>
<th>p-value</th>
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<tr>
<td></td>
<td>0.908 (0.889-0.928)</td>
<td>0.0076</td>
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<tr>
<td></td>
<td>0.913 (0.894-0.930)</td>
<td>0.001</td>
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</table>

BNP and NT-proBNP were included as standardized values dichotomized by the highest and the lowest quartile cut-off point. Bootstrapping gives 95% CI for OR of BNP highest quartile cut-off (1.87-5.42) and BNP lowest quartile cut-off (2.51-5.96); and for OR of NT-proBNP highest quartile cut-off (3.38-7.62) and NO-proBNP lowest quartile (1.78-3.8).

AUC: area under curve; IDI: integrated discrimination improvement index; NIHSS: National Institutes of Health Stroke Scale
### Supplemental table III: Comparison between clinical predictive models and predictive models adding BNP or NT-proBNP for atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Clinical model in BNP cohort</th>
<th>Clinical model + BNP</th>
<th>Clinical model in NT-proBNP cohort</th>
<th>Clinical model + NT-proBNP</th>
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<tbody>
<tr>
<td></td>
<td>Highest quartile</td>
<td>Lowest quartile</td>
<td>Highest quartile</td>
<td>Lowest quartile</td>
</tr>
<tr>
<td><strong>Logistic Regression (OR with 95% CI and p-value)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>1.061 (1.047-1.076), p&lt;0.001</td>
<td>1.055 (1.041-1.070), p&lt;0.001</td>
<td>1.048 (1.033-1.063), p&lt;0.001</td>
<td>1.060 (1.044-1.076), p&lt;0.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.948 (0.715-1.256), p=0.709</td>
<td>0.913 (0.684-1.219), p=0.538</td>
<td>0.921 (0.688-1.234), p=0.582</td>
<td>1.265 (0.920-1.739), p=0.148</td>
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<tr>
<td>NIHSS score at admission</td>
<td>1.071 (1.051-1.092), p&lt;0.001</td>
<td>1.066 (1.045-1.087), p&lt;0.001</td>
<td>1.065 (1.044-1.86), p&lt;0.001</td>
<td>1.050 (1.027-1.073), p&lt;0.001</td>
</tr>
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<td>BNP/NT-proBNP</td>
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<td>2.922 (2.099-4.070), p&lt;0.001</td>
<td>5.865 (3.821-9.002), p&lt;0.001</td>
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<td><strong>ROC curve</strong></td>
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<tr>
<td>AUC (95%CI)</td>
<td>0.725 (0.693-0.756)</td>
<td>0.755 (0.725-0.784)</td>
<td>0.772 (0.743-0.8)</td>
<td>0.722 (0.687-0.758)</td>
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<td>ref</td>
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</table>
BNP and NT-proBNP were included as standardized values dichotomized by the highest and the lowest quartile cut-off point. Bootstrapping gives 95% CI for OR of BNP highest quartile cut-off (2.077-4.238) and BNP lowest quartile cut-off (3.877-9.574); and for OR of NT-proBNP highest quartile cut-off (2.68-5.419) and NO-proBNP lowest quartile (2.639-7.486). AUC: area under curve; IDI: integrated discrimination improvement index; NIHSS: National Institutes of Health Stroke Scale
Supplemental References


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Pooled Data Meta-Analysis

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José Castillo, MD, PhD; Manuel Rodriguez-Yáñez, MD, PhD; Ana Catarina Fonseca, MD, PhD;
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虚血性脳卒中は最も重要な脳神経障害の1つである。再発予防のための最も適切な二次治療を処方するには、虚血性脳卒中を正確な原因分類が不可欠である。心原性脳塞栓症の患者には抗凝固薬を投与することが、大血管アテローム硬化（LAA）による脳卒中および小血管疾患（SVD）の患者には抗血小板薬を選択される。心原性脳塞栓症は一般的にLAAやSVDに比べて重症化および再発やすく、虚血性脳卒中のおおよそ1/5を占める。

正確な病因分析が重要であるものの、約35％の患者ではあらゆる評価を行っても原因を特定できない。この患者群における発症後1年間の再発率は約30％であり、不適切な二次治療がその一因となっている。原因不明の脳卒中患者は不均等な集団であり、脳卒中の原因が2つ以上のある患者、狭索率50％未満の患者、診断検査結果が陰性の患者が含まれる。後者の陰性診断は、心房細動（AF）など検出が難しい一時的または可逆性の病態が原因である場合がある。AFは、心原性脳塞栓症の診断において検出が不可欠で、頻度の高い心調律障害である。しかし、AFは発作性のことがある、その場合標準的な心臓モニタリングで検出することは難しい。近年、近位動脈狭窄または高リスクの心原性塞栓源がない非ラクナ梗塞（脳神経画像検査に基づく）として定義される。原因不明の塞栓性脳卒中という新しい臨床概念が提唱されている。これらの患者では、血液うっ滞による血栓形成を促進する発作性AFおよびその他の調律障害による左心房由来の血栓性塞栓症、原因不明の塞栓性脳卒中の重要な寄与因子であると考えられる。

最新のガイドラインによると、AFの除外には24時間以上ECGモニタリングが必要である。最近の臨床試験では、AF検出率は連続的モニタリングの期間が長いほど（30日間〜12ヶ月間）上昇することが実証された12,13。特に、通常の経過観察で検出されにくい長期的病態が脳卒中の原因であるような難しい状況下では、血液バイオマーカーが脳卒中の基礎原因の診断において補完的な役割を果たし、貴重な時間や資源の節約にもつながる可能性がある。

B型ナトリウム利尿ペプチド（BNP）は、心臓の線維形成を阻害する心臓ホルモンであり、前駆体pro-BNPの切断により多量の不活性型N末端ペプチド（NT-proBNP）が放出された後、生成される14。Pro-BNPは、壁張力の増加および容量／圧の過负荷に反応して伸張刺激を受け、心筋から放出される。また血行力学的負荷がかかる段階でも放出される15。このpro-BNPと心房振張の関係から、BNP/NT-proBNP値の上昇とAFおよび心原性脳塞栓症との明らかな関連性が示唆される。これらのナトリウム利尿ペプチドと心原性脳塞栓症との関連を示した研究は複数あるが、全般に規模が小さく16-23。心原性脳塞栓症とそれ以外の脳卒中を鑑別するカットオフポイントを示さずでおり、発症からの経過時間も異なる。BNP/NT-proBNPと心原性脳塞栓症との関連は明確にはなっていが、特に難しい症例（発作性AF）における心原性脳塞栓症の診断が速やか化され、補完的な情報を得られるとともに、原因不明の脳卒中の割合を減らす可能性がある。

本研究の目的は、系統的なレビューおよび被験者個別データ（IPD）のメタアナリシスを通じて、心原性脳塞栓症とBNP/NT-proBNPの循環血中濃度の関係について検証を高めること。また、心原性脳塞栓症を特定するための補完的な臨床情報としての有用性を評価すること。そして、原因不明の患者サブセットにおいて心原性脳塞栓症の予測モデルの有効性を検証することである。

### 方法

本研究の方法はPROSPEROデータベース（CRDO213005924）に登録済みであり、閲覧可能である。

### 選択基準および検索方法

検討対象とした研究はすべて、虚血性脳卒中または一過性脳虚血発作の確定患者のさまざまなサブタイプにおいてBNPまたはNT-proBNP血中濃度を測定した原論文であった。2013年11月12日までのPubMedデータベースを検索し、独立したレビュアー4名が論文を選択した。検索に使用した用語は「[b-type natriuretic peptides（B型ナトリウム利尿ペプチド）OR brain natriuretic peptide（脳性ナトリウム利尿ペプチド）OR BNP] AND stroke（脳卒中）AND [cardioembolic（心塞栓性）OR atherothrombotic（アテローム塞栓性）OR lacunar（ラクナ）OR subtype（サブタイプ）OR etiology（病因）]」とした。重複する論文は1回だけ考慮した。選択した研究および公表済みレビューの参考文献を手作業でスクリーニングし、その他の関連研究を特定した。

### データの収集

レビュアー3名が15点評価の品質調査票を用い、選択した研究の質を個別に確認した。選択した全研究の責任著者にEメールで連絡を取り、IPD解析のためにデータの共有を依頼した。テンプレートフォームにIPDが記入された。IPDの内容はBNP/NT-proBNP値（pg/
B型ナトリウムリウムペプチドは心原性脳塞栓症の診断に役立つ

Smirnov 検定による評価）を示したため、Mann–Whitney U 検定または Kruskal–Wallis 検定を使用した。中央値および四分位範囲を報告する。各コホート間で BN/P-NT-proBNP 値は不均一であるため、BN/P-NT-proBNP 値を標準化し、既報のように各被験者について BNP または NT-proBNP の Z スコアを算出した 23。心原性脳塞栓症、LAA、SVD 間で標準化した BN/P-NT-proBNP 値を比較し、Bonferroni 補正により P 値を調整した。

IPD 解析

特に記載しない限り、SPSS 統計パッケージ 15.0 (SPSS Inc. イリノイ州シカゴ) を使用した。

BNP および NT-proBNP は非正規分布（Kolmogorov–
図1 フローチート。BNP：B型ナトリウム利尿ペプチド、IPD：被験者個別データ。

図2 虚血性脳卒中の原因別にみたB型ナトリウム利尿ペプチド／N末端プロBNP（BNP／NT-proBNP）値。AおよびB：心原性脳塞栓症、アテローム血栓形成型中、小血管疾患患者における標準化したBNPおよびNT-proBNP値。CおよびD：検体採用時別によってみたBNP／NT-proBNP値。*P < 0.05、**P < 0.0001、#P < 1 × 10⁻¹⁰、##P < 1 × 10⁻²⁰。

因不明の患者を除外し、16コホートをIPDに含めた（オンラインデータ補遺表1）。16コホートの全患者に対して、脳梗塞の心原性脳塞栓症の原因を評価するためのECG（12誘導ECG、24時間ECG、または長期ECG）が実施され、11コホートには特定の心臓イベントマッピングが実施された。

合計すると、脳卒中の原因が確定した患者2,834例の個別データが蓄積された。既報のとおり25、BNP値に比べNT-proBNP値の有意な上昇が認められたため、これらの2つのマーカーは別々に検討することとした。BNPは1,570例のコホートで、NT-proBNPは1,264例のコホートで解析した。

心原性脳塞栓症患者のBNP/NT-proBNP値は、LAA患者（P < 0.0001）およびSVD患者（P < 0.0001）よりも高かった（図2Aおよび2B）。BNPでは発症後72時間まで有意差が認められたが、NT-proBNPは1週間を経た心原性脳塞栓症患者で有意に高かった（図2Cおよび2D）。単変量解析の結果、心原性脳塞栓症の millisecondsを明らかに高齢であり、女性が多かった。また、心原性脳塞栓症以外の患者と比べ心臓疾患が多かった（表1）。

BNPの最上位四分位値をカットオフポイントにした場合、頸度42.3%、特異度90.7%、PPV 80%、NPV 37%で他の原因と心原性脳塞栓症を鑑別できた。同様にNT-proBNPの最上位四分位値では、心原性脳塞栓症に関して頸度40%、特異度90.1%を示し、PPVは59.3%、
NPVは88%であった。最下位4区分をカットオフポイントにした場合、BNPでは感度93.68％、特異度41.94％、PPV80％、NPV40％、NT-proBNPでは感度86.3％、特異度36.2％、PPV57.3％、NPV72.8％であった。

多変量ロジスティック回帰分析では、各バイオマークについて特異度および感度の高いモデルを得ため、前述のカットオフポイントを検討した。得られたすべての予測モデルにおいて、年齢、性別、入院時のNIHSSスコアで調整後、BNPとNT-proBNPは心原性脳塞栓症の原因に関する主要な予測因子であり（表2）。各モデルにAFを加えた場合も、依然としてBNPとNT-proBNPは独立した予測因子であり、適中率はほとんどうまま変わらなかった（オンラインデータ補遺表II）。BNPまたはNT-proBNPを臨床データに加えると、曲線下面積およびIDI指数による評価において、心原性脳塞栓症患者の鑑別能は有意に上昇した（表2）。心原性脳塞栓症のサブタイプではなく、AFの存在をエンドポイントとして予測モデルを作成した場合も、同様の結果が得られた。残念なことに、予測モデルの検証において、原因不明コホートの心原性脳塞栓症の診断に関する十分なデータのみを処理したため、AFの予測モデルを検証することはできなかった（オンラインデータ補遺表III）。

ベースラインで原因不明であり（BNP 83例、NT-proBNP 114例）、詳細な診断検査の完了後に原因が判明した患者において、作成した予測モデルの有用性を検証した。NT-proBNPを加えた予測モデルは、BNPを加えたモデルとの比較において、心原性脳塞栓症の原因に関する感度および特異度がより高かった。精度についても、NT-proBNPを加えた予測モデルの曲線下面積の方が大きかった（図3、表3）。

### 考察

現在のところ、例外として脳卒中リスクの予測に用いられるホスピターゼA2があるものの、脳卒中分野でのバイオマークの使用は研究目的でのみ推奨されているが45。しかし、脳卒中のバイオマークは、脳卒中の診断、高リスク患者のスクリーニング、転帰の予測、脳卒中原因の特定など、さまざまな場面で役立つ可能性がある13。

Pro-BNPは伸展により筋細胞から放出される。興味深いことに、等モルで産生されても、NT-proBNPの半減期はBNPより長く、循環血中濃度の変動もより少ない46。血中NT-proBNPがBNPよりも多く認められるのは、この現象による可能性がある25。このような理由から、本研究のIPD解析はこれらのバイオマークについて別々に実施した。

文献に基づくメタアナリシスは、ガイドラインや疾患管理の推奨事項を作成するうえで、基本と考えられていている47。しかし、IPDのメタアナリシスに比べるといくつかの限界がある。IPDのメタアナリシスにより、複数の個別因子およびその組み合わせの解析、予測モデルの作成、既報とは異なるサブ解析の実施が可能となる48。本研究の進行中には、文献に基づくメタアナリシスにより、BNP/NT-proBNPと心原性脳塞栓に起因する脳卒中との関連性が報告されている49。今回の研究結果はこの関連性を強く裏付けるものであり、さらにIPDを用い、BNP/NT-proBNPの適中率に関するサブ解析を考える。
表2 心原性脳塞栓症に関する臨床予測モデルとBNPまたはNT-proBNPを追加した予測モデルの比較

<table>
<thead>
<tr>
<th></th>
<th>非BNP測定</th>
<th>コホート</th>
<th>临床モデル+BNP</th>
<th>非NT-proBNP測定</th>
<th>コホート</th>
<th>临床モデル+NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>基準</td>
<td>基準</td>
<td>基準</td>
<td>基準</td>
<td>基準</td>
<td>基準</td>
</tr>
<tr>
<td>年齢、歳</td>
<td>1.03 (1.02～1.04)</td>
<td>P &lt; 0.0001</td>
<td>1.02 (1.01～1.03)</td>
<td>1.01 (1～1.03)</td>
<td>P = 0.0017</td>
<td>1.01 (1～1.02)</td>
</tr>
<tr>
<td>性別、女性</td>
<td>1.4 (1.1～1.7)</td>
<td>P = 0.006</td>
<td>1.36 (1.06～1.74)</td>
<td>1.33 (1.03～1.71)</td>
<td>P = 0.027</td>
<td>1.42 (1.1～1.8)</td>
</tr>
<tr>
<td>入院時NIHSS</td>
<td>1.09 (1.07～1.11)</td>
<td>P &lt; 0.0001</td>
<td>1.08 (1.06～1.1)</td>
<td>1.08 (1.06～1.1)</td>
<td>P &lt; 0.0001</td>
<td>1.06 (1.04～1.08)</td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td>…</td>
<td>P &lt; 0.0001</td>
<td>4.49 (3.26～6.2)</td>
<td>7.10 (4.98～10.12)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>IDI 統計</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>心原性脳塞栓症のIDI</td>
<td>…</td>
<td>0.026</td>
<td>0.042</td>
<td>…</td>
<td>0.067</td>
<td>0.049</td>
</tr>
<tr>
<td>心原性脳塞栓症以外のIDI</td>
<td>…</td>
<td>0.038</td>
<td>0.053</td>
<td>…</td>
<td>0.073</td>
<td>-0.011</td>
</tr>
<tr>
<td>IDI 合計</td>
<td>…</td>
<td>0.064</td>
<td>0.095</td>
<td>…</td>
<td>0.140</td>
<td>0.038</td>
</tr>
<tr>
<td>P 値</td>
<td>P &lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

ROC 曲線

AUC (95% CI) 0.71 (0.68～0.74) 0.75 (0.73～0.78) 0.77 (0.75～0.8) 0.63 (0.6～0.66) 0.71 (0.68～0.74) 0.7 (0.67～0.73)

<table>
<thead>
<tr>
<th>基準</th>
<th>基準</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

BNPとNT-proBNPは、基準を上位または下位20％のカットオフポイントにより二分した基準化値としてモデルに含めた。ロジスティック回帰分析におけるOR、95％CI、P値を示す。BNPの基準化後位分のカットオフ（0.136～0.645）およびBNPの基準化後位分のカットオフ（0.08～0.94）に対するOR、NT-proBNPの基準化後位分のカットオフ（4.42～9.22）およびNT-proBNPの基準化後位分のカットオフ（2.44～4.55）に関するORについて、プートストラップ法により、95％CIを算出した。

AUC は、曲線下積分、B型ナトリウム尿症ペプチド、IDH、統合判別分析指数、NIHSS：米国国立衛生研究所脳卒中スコア（National Institutes of Health Stroke Scale) スコア、NT-proBNP：N末端プロBNP、OR：オッズ比。ROC 曲線：受信者操作特性曲線（Receiver operating characteristic curve）。

実施することができた。本研究では、異なる時期においてさまざまな脳卒中の原因の中でBNP/NT-proBNPの差を評価し、2種類の予測モデルを作成し、原因不明の患者をコホートでその有用性を検証した。心原性脳塞栓症患者では、心原性脳塞栓症を原因としない患者に比べ、BNP/NT-proBNP値が高かった。これは発症後72時間まで有意であった。抗凝固療法の最適な開始時間を含む臨床データを示しているが4)。BNP/NT-proBNP検査により心原性脳塞栓症患者を早期に特定すれば、治療開始の意思決定プロセスの迅速化に役立つ可能性がある。

日々の臨床診療では、虚血性脳卒中と診断された患者に対し、適応があれば、ECG、心エコー検査、ホルター心電図などの補助的検査が行われ、可能性のある心原性脳塞栓症の可能性が特定される。しかし、虚血性脳卒中下の一部の原因は一過性であり（発作性AF）、診断検査の際には検出されない可能性がある。これらの症例では、不整脈の検出率を高めるため心電検査の期間を延長することが必要で、心原性脳塞栓症の診断を困難にしている4)。本研究では、BNPとNT-proBNPの両者を、心原性、虚血性、入院時のNIHSSスコアに関係なく心原性脳塞栓症を予測できることが明らかになった。今回作成した心原性脳塞栓症の高感度モデルを用いれば、初期の補助的検査は検出できなかった心疾患の特定のために、長期モニタリングが必要な患者を選択しやすくなる可能性がある。また、本研究では、心原性脳塞栓症に関する特異度が高く、二次予防のための抗凝固療法が有用と考えられる患者を特定できる予測モデルを作成した。

これらの予測モデルはAF（心原性脳塞栓症の最も強い予測因子の1つ）を含めた場合でも、AFを加えないモデルと同等の精度を示し、BNPとNT-proBNPは依然として心原性脳塞栓症の有意な独立した予測因子であった。すなわち、年齢、NIHSS、性別などの判定が容易で変数に基づくとともに、循環血中BNP/NT-proBNP濃度を補完的に用いた基本的な臨床予測モデルは、最近提唱されたembolic strokes of undetermined source（ESUS）といったAFの検出が困難な症例における心原性脳塞栓症の診断に適している可能性がある。また、IDH指数の結果から、両ペプチドが心原性脳塞栓症とそれ以外の脳卒中とをよりよく識別するうえで役立つことが示唆されている。さらに、重要なことに、同一患者の評価でないが、特定のモデルではBNPに比べてNT-proBNPの方が適中率およびIDH指数が高く、心原性脳塞栓症の原因を判別するパフォーマーとしてNT-proBNPの方が優れていることが示唆された。これとは対照的に、BNPは、
表3 当初は原因不明であり、詳細な診断検査の完了後に原因が判明した患者における予測モデルの適用

<table>
<thead>
<tr>
<th>予測モデル</th>
<th>感度</th>
<th>特異度</th>
<th>險性中位率</th>
<th>險性中位率</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>既往変数 + BNP 最上位4分位</td>
<td>74.58%</td>
<td>56.52%</td>
<td>81.48%</td>
<td>46.43%</td>
<td>0.758 (0.644～0.873)</td>
</tr>
<tr>
<td>既往変数 + NT-proBNP 最上位4分位</td>
<td>78.79%</td>
<td>95.83%</td>
<td>96.3%</td>
<td>76.67%</td>
<td>0.879 (0.810～0.947)</td>
</tr>
<tr>
<td>既往変数 + BNP 最下位4分位</td>
<td>91.53%</td>
<td>39.13%</td>
<td>79.41%</td>
<td>64.29%</td>
<td>0.674 (0.536～0.811)</td>
</tr>
<tr>
<td>既往変数 + NT-proBNP 最下位4分位</td>
<td>93.94%</td>
<td>79.17%</td>
<td>86.11%</td>
<td>90.48%</td>
<td>0.896 (0.832～0.959)</td>
</tr>
</tbody>
</table>

臨床変数には年齢、性別、入院時のNIHSSが含まれる。AUC：曲線下面積、BNP：B型ナトリウム利尿ペプチド、CI：信頼区間、NT-proBNP：N末端プロBNP。

より感度の高いモデルで検討した場合に、心原性脳腔症に関するオッズ比およびIDI指数が高かった。

原因不明の脳卒中を発症した患者では、その後2年間の再発率は14～20％と報告されているが3,22。これは主に不適切な二次予防に起因する。これらの患者は3ヶ月後の機能的転帰も不良であり、3年間の追跡調査における累積死亡率が高い33。バイオマーカーの使用は、原因不明の脳卒中患者において原因を再分類するための優れた方法と考えられてきた。プロトロフィ（protrial）ナトリウム利尿ペプチド、クレアチニンキナーゼ MB、NT-proBNPを併用した評価により、原因不明患者の41％が心原性脳腔症（CE）の可能性が高い症例に再分類されることが報告されている34。NT-proBNPも、AF発症リスクのある原因不明の脳卒中患者の特定に有用であることが示されている35。今回の研究でも、心原性脳腔症の可能性が高い患者を正確に特定するために同様のアプローチに従った結果、NT-proBNPはBNPに比較して感度および特異度が高いことが明らかになった。

今回の解析は原因が確定した（ゴールドスタンダード）、広範囲の患者を対象としており、それぞれの検査法の診断精度を評価できた。すなわち、診断法に関するエピデンスの分類体系に従えば、BNP/NT-proBNPは心原性脳腔症に関して高い感度/特異度を示しており、心原性脳腔症の診断に関して高いエピデンスレベル（クラスII）を有すると考えられる47。

本研究にはいくつかの限界がある。第1に、検討した研究の評価項目は共通しているが、考慮すべき重要な点として、各論文における発症機序の特定および原因の精密検査は、多数の国々さまざまな施設において9年間にわたって行われている。したがって、原因のサブタイプ分類の信頼性は不明確であり、バイアス源になる可能性がある。第2に、BNP/NT-proBNP値を観察値として、心原性脳腔症の診断を基にカットオフポイントを基準値にすることが必要である。第3に、予測モデルは多数の被験者に基づいて作成したが、これらのモデルの検証に用いた原因不明の脳卒中患者のサブセットは少なかった。したがって、このモデルを適用した結果は慎重に解釈しなければならない。また、これらの原因不明の患者では追跡調査期間のデータが得られなかった。第4に、症例数の効果の減少と統計的検出力の低下を理由に、脳腔性心臓症、虚血性心筋症、心不全の既往など、AF以外の他の心疾患を予測モデルに含めることが限定的でなかった。最後に、個人差による変動を回避できなかったため、BNPとNT-proBNPを直接比較することができなかった。

次回の研究段階では、心原性脳腔症の特定を目的とした日常臨床診療におけるBNP/NT-proBNPの適用可能性を詳しく検討することになるが、その際には大量の在院前の試験を行い、妥当性検証済みの設定値を用い、同一患者でBNPとNT-proBNPを同時に解析して両ペプチドを直接比較すべきである。これにより、
心原性脳塞栓症の特定において、最適なカットオフポイントのほか、最適なバイオマーカーおよび血中濃度の最適測定時点を明示しやすくなると考えられる。予測モデルにおける他の心疾患の評価および追加は、今後の研究における予測モデルの感度／特異度の改善に役立つであろう。最終的に、臨床試験がBNP/NT-proBNPを指標とした抗凝固療法の臨床的有用性を明らかにするかもしれない。総合的に考えると、こうした臨床試験が、NT-proBNPまたはBNPの臨床使用を確実に実現するためのエビデンスレベルを高めていくだろう。

結論として、本研究のIPDにより、虚血性脳卒中患者の心原性脳塞栓症の特定においてナトリウム利尿ペプチドの役割が裏付けられた。侵襲的な経食道心エコー検査やAF発作検査までの数週間から数ヶ月間に及ぶ経過観察により、日常臨床診療におけるナトリウム利尿ペプチド検査の方が、抗凝固療法を開始するきっかけとして優れている可能性がある。これと同時に、ナトリウム利尿ペプチドの利用により、根底にある心原性塞栓の可能性を効率的に除外でき、経食道心エコー検査や徹底した心拍モニタリングの必要性がなくなる可能性がある。

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References


The Nutrition Intervention Trials in Linxian, China, conducted in 3318 adults with esophageal dysplasia suggested a nonsignificant lower risk of cerebrovascular disease in multivitamin treatment group (HR, 0.62; 95% CI, 0.37–1.06).20 The Physicians’ Health Study II randomized controlled trial with a total sample of 14,641 men and a mean follow-up of 11.2 years found no benefits of multivitamin for the prevention of stroke (HR, 1.08; 95% CI, 0.76–1.53) or other cardiovascular events.21 It is possible that people with lower intake of fruits and vegetables, which consisted of nearly half of the diet, have a lower risk of stroke mortality. In our subgroup analysis, multivitamin use, particularly frequent use, was associated with a significant lower risk of total and subgroup analysis, multivitamin use, particularly frequent use, was associated with a significant lower risk of total and ischemic stroke mortality among people with lower intake of fruits and vegetables, the United States Preventive Services Task Force reviewed the evidence and concluded that the current evidence is insufficient to assess the balance of benefits or harms of the use of supplements may be necessary for risk reduction.6 In our study, we observed an inverse association of borderline statistical significance between multivitamin use and ischemic stroke mortality among people with lower intake of fruits and vegetables, that consisted of nearly half of the diet.8

Table 3. Multivariable Hazard Ratios* (95% Confidence Interval) of Mortality From Total Stroke According to Multivitamin Use Stratified by Participant Characteristics

<table>
<thead>
<tr>
<th>Age ≤65 y</th>
<th>Nonusers</th>
<th>All Users</th>
<th>Casual Users</th>
<th>Regular Users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
<td>0.91 (0.73–1.14)</td>
<td>0.91 (0.71–1.17)</td>
<td>1.03 (0.70–1.53)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>1.00</td>
<td>0.85 (0.70–1.02)</td>
<td>0.88 (0.70–1.10)</td>
<td>0.85 (0.62–1.15)</td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>0.88 (0.72–1.06)</td>
<td>0.92 (0.73–1.15)</td>
<td>0.82 (0.59–1.16)</td>
</tr>
<tr>
<td>Women</td>
<td>1.00</td>
<td>0.88 (0.71–1.08)</td>
<td>0.90 (0.70–1.17)</td>
<td>0.86 (0.61–1.22)</td>
</tr>
<tr>
<td>Age at completed education &lt;16 y</td>
<td>1.00</td>
<td>0.84 (0.67–1.06)</td>
<td>0.83 (0.63–1.10)</td>
<td>0.91 (0.62–1.32)</td>
</tr>
<tr>
<td>≥16 y</td>
<td>1.00</td>
<td>0.88 (0.71–1.07)</td>
<td>0.96 (0.76–1.22)</td>
<td>0.73 (0.51–1.05)</td>
</tr>
<tr>
<td>Fruit and vegetable intake &lt;3 times/d</td>
<td>1.00</td>
<td>0.80 (0.65–0.98)</td>
<td>0.86 (0.68–1.10)</td>
<td>0.67 (0.45–0.99)</td>
</tr>
<tr>
<td>≥3 times/d</td>
<td>1.00</td>
<td>0.94 (0.76–1.14)</td>
<td>0.94 (0.74–1.21)</td>
<td>0.97 (0.70–1.34)</td>
</tr>
</tbody>
</table>

*Adjusted for age, study area, sex, body mass index, education level, history of hypertension, history of diabetes mellitus, family history of stroke, alcohol use, smoking, sports, walking, mental stress, use of vitamin C or vitamin E supplementation, dietary intakes of fish, red meat, fruits, vegetables, and total energy.
Natriuretic peptides are highly sensitive models for each biomarker. In all the predictive models; thus, we were not able to validate predictive models of undetermined cohort to attempt the validation of the predictive model (Figure 3; Table 3).