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Short Report

High B-type natriuretic peptide levels predict a hypercoagulable state in otherwise low-risk patients with atrial fibrillation

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ABSTRACT

The D-dimer and B-type natriuretic peptide (BNP) levels in relation to CHADS₂ and CHA₂DS₂-VASC scores in 59 patients with atrial fibrillation who were not receiving anticoagulant therapy were analyzed. Among 19 patients with CHADS₂ scores of 0–1, 3 of the 7 patients with elevated BNP levels also had elevated D-dimer levels. Among 8 patients with CHA₂DS₂-VASC scores of 1, 2 of the 3 patients with elevated BNP levels also had elevated D-dimer levels. Therefore, D-dimer levels can be elevated in low-risk patients when BNP levels are high, and anticoagulation therapy should be considered for these patients.

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1. Introduction

Congestive heart failure (CHF) is known as an established risk factor for stroke in patients with atrial fibrillation (AF) [1]. However, diagnosing CHF is occasionally difficult because of the symptoms that are similar to those of AF, such as dyspnea and palpitations. The adjusted annual stroke rates in AF patients with a CHADS₂ (CHF, hypertension, age \geq 75 years, diabetes, stroke [doubled]) scores of 0 and 1 were reported to be 1.9% and 2.8%, respectively, but these patients were not necessarily considered to have a low-risk for stroke [2]. It can be speculated that latent CHF might have been undiagnosed in patients with low CHADS₂ scores. B-type natriuretic peptide (BNP) can be used as a marker for the differential diagnosis of CHF and could serve as a risk marker in addition to clinical assessment. D-dimer can be used as a coagulation marker in patients with AF [3–5]. We reported that the D-dimer levels predicted subsequent thromboembolic events in AF patients and that BNP levels could be a useful marker for predicting thromboembolic events [6,7]. Recently, the European Society of Cardiology guideline [8] recommended that CHA₂DS₂-VASC (CHF/left ventricular dysfunction, hypertension, age \geq 75 years [doubled], diabetes, stroke [doubled], vascular disease, age of 65–74 years, and sex category [female]) score [9] instead of CHADS₂ score should be used for risk stratification. In the present

study, we analyzed D-dimer levels in relation to CHADS₂ and CHA₂DS₂-VASC scores to evaluate the usefulness of measuring BNP levels in AF patients before initiating anticoagulant therapy.

2. Methods

In our present study, we performed a post hoc analysis of the results of our previous study [10]. Briefly, 59 patients for whom BNP and D-dimer levels were determined on the same day and who had not started warfarin therapy were included.

The study protocol was approved by the institutional ethics committee, and informed written consent was obtained from all of the patients included in this study.

Data were presented as mean \pm SD, median (interquartile range), or percentage values, as appropriate. Comparisons between the 2 groups of data were made with the unpaired Student *t* test or Mann–Whitney test, as appropriate. Event frequencies were compared using the chi-square test. A *p* < 0.05 was considered statistically significant. The statistical software package JMP (version 9, SAS Institute, Cary, NC, USA) was used for the analyses. The cutoff values for D-dimer and BNP levels were set at 0.5 μ g/mL and 100 pg/mL, respectively, according to previous reports [6,10].

3. Results

The clinical characteristics of the patients are presented in Table 1. The mean CHADS₂ score was 2.0 ± 1.1 . There were 6, 13,

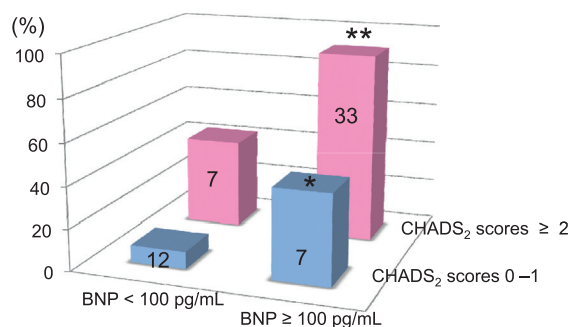
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Table 1
Clinical characteristics of the patients.

	Total	CHADS ₂ score 0–1 (n=19)			CHADS ₂ score ≥ 2 (n=40)		
		BNP < 100 pg/mL	BNP ≥ 100 pg/mL	p value	BNP < 100 pg/mL	BNP ≥ 100 pg/mL	p value
n	59	12	7		7	33	
Age (y/0)	76 ± 10	70 ± 11	68 ± 7	0.70	69 ± 9	81 ± 7	< 0.01
Age ≥ 75 y/o	n (%) 32 (54)	4 (33)	0 (0)	0.086	2 (29)	26 (79)	< 0.01
Female	n (%) 28 (48)	5 (42)	1 (14)	0.22	4 (57)	18 (55)	0.90
Chronic AF	n (%) 21 (36)	2 (17)	4 (57)	0.067	2 (29)	13 (39)	0.59
CHF	n (%) 25 (42)	0 (0)	0 (0)	1 (14)	24 (73)	< 0.01	
Hypertension	n (%) 34 (58)	4 (33)	3 (43)	0.68	6 (86)	21 (64)	0.30
Diabetes mellitus	n (%) 15 (25)	0 (0)	2 (28)	0.050	4 (57)	9 (28)	0.13
History of stroke	n (%) 6 (10)	0 (0)	0 (0)	1 (14)	5 (15)	0.95	
BNP levels (pg/mL)	85 (56–351)	36 (15–60)	182 (133–220)	< 0.01	31 (24–56)	255 (209–432)	< 0.01
BNP ≥ 100 pg/mL	n (%) 40 (68)	0 (0)	7 (100)	< 0.01	0 (0)	33 (100)	< 0.01
BNP ≥ 200 pg/mL	n (%) 29 (48)	0 (0)	3 (43)	0.014	0 (0)	26 (79)	< 0.01
D-dimer levels (μg/mL)	0.91 (0.36–2.1)	0.30 (0.0–0.42)	0.44 (0.35–0.70)	0.10	0.47 (0.0–0.91)	1.52 (0.91–4.3)	< 0.01
D-dimer ≥ 0.5 μg/mL	n (%) 37 (63)	1 (8.3)	3 (43)	0.075	3 (43)	30 (91)	< 0.01
Structural heart disease	n (%) 27 (46)	4 (33)	0 (0)	0.086	3 (43)	20 (61)	0.39
Hypertensive heart disease	n (%) 19 (32)	3 (25)	0 (0)	0.15	3 (43)	13 (39)	0.87
Valvular heart disease	n (%) 7 (12)	0 (0)	0 (0)		0 (0)	7 (21)	0.18
Coronary artery disease	n (%) 6 (10)	0 (0)	0 (0)		1 (14)	5 (15)	0.95
Medications							
Aspirin (100 mg/day)	n (%) 13 (22)	1 (8.3)	0 (0)	0.62	3 (43)	9 (27)	0.41
ACEI/ARB	n (%) 39 (66)	5 (42)	5 (71)	0.21	4 (57)	25 (76)	0.32
β blockers	n (%) 14 (24)	4 (33)	0 (0)	0.086	2 (29)	8 (24)	0.81
Diuretics	n (%) 21 (36)	1 (8.3)	0 (0)	0.62	1 (14)	19 (58)	0.038

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin type II receptor blocker; BNP: B-type natriuretic peptide; CHF: congestive heart failure; p value: BNP < 100 pg/mL vs. BNP ≥ 100 pg/mL in the same category.



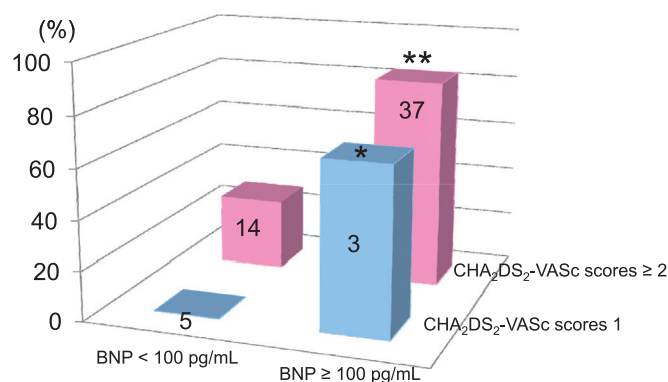
* $p = 0.075$, BNP ≥ 100 vs. BNP < 100 pg/mL
 ** $p < 0.01$, BNP ≥ 100 vs. BNP < 100 pg/mL, CHADS₂ scores ≥ 2 vs. scores 0–1

Fig. 1. Percentage of the patients with high D-dimer levels (≥ 0.5 μg/mL) in relation to the CHADS₂ scores and BNP levels. The numbers shown in the bar denote the number of patients in each category.

and 40 patients with CHADS₂ scores of 0, 1, and ≥ 2, respectively. The D-dimer levels were significantly higher in the patients with CHADS₂ scores ≥ 2 than in those with CHADS₂ scores of 0–1 (median D-dimer level, 1.16 μg/mL [0.72–3.23 μg/mL] vs. 0.36 μg/mL [0.0–0.44 μg/mL], $p < 0.01$).

In the patients with clinically diagnosed CHF (NYHA class ≥ II symptoms and/or congestive signs requiring loop diuretics), the median BNP level was 371 pg/mL (236–450 pg/mL), and BNP levels were elevated (≥ 100 pg/mL) in 24 (96%) of the 25 patients. In the 34 patients without CHF, the median BNP level was 77 pg/mL (26–175 pg/mL), and BNP levels were elevated in 16 patients (47%).

Fig. 1 shows the percentage of patients with high D-dimer levels (≥ 0.5 μg/mL) in relation to the CHADS₂ scores and BNP levels. The D-dimer levels were elevated in 33 (83%) of the 40 patients with CHADS₂ scores ≥ 2. None of the patients with CHADS₂ scores of 1 had CHF. Among the 19 patients with CHADS₂



* $p = 0.035$, BNP ≥ 100 vs. BNP < 100 pg/mL
 ** $p < 0.01$, BNP ≥ 100 vs. BNP < 100 pg/mL

Fig. 2. Percentage of patients with high D-dimer levels in relation to the CHA₂DS₂-VASc scores and BNP levels.

scores of 0 or 1, the D-dimer levels were elevated in 3 (43%) of the 7 patients with elevated BNP levels and in only 1 (8.3%) of the 12 patients whose BNP levels were not elevated ($p = 0.075$). Furthermore, in 6 patients with CHADS₂ scores of 0, the D-dimer levels were elevated in 1 of the 2 patients with elevated BNP levels but not in the remaining 4 patients whose BNP levels were not elevated.

Fig. 2 shows the percentage of patients with high D-dimer levels in relation to the CHA₂DS₂-VASc scores and BNP levels. None of the patients had a CHA₂DS₂-VASc score of 0. The BNP levels were elevated in 3 (38%) of the 8 patients with CHA₂DS₂-VASc scores of 1, and the D-dimer levels were elevated in 2 of these 3 patients. Among the patients with CHA₂DS₂-VASc scores of 1, none of the 5 patients whose BNP levels were not elevated had elevated D-dimer levels.

4. Discussion

BNP levels have been shown to be elevated in patients with AF [11,12], even in those who have preserved left ventricular systolic function. As shown in Figs. 1 and 2, the D-dimer levels were elevated in some patients with low CHADS₂ or CHA₂DS₂-VASc scores who did not have CHF but had elevated BNP levels. Using the RE-LY database, Hijazi et al. [13] recently reported that the annual rate of composite thromboembolic events was even higher in AF patients with high (top-quartile) NT-proBNP levels and CHADS₂ scores of 0 or 1 than in patients with CHADS₂ scores ≥ 3 and low (lowest-quartile) NT-proBNP levels. Although this study used D-dimer levels as a surrogate marker for thromboembolisms, our results were consistent with those of Hijazi et al. [13]. It can be speculated that latent CHF with a possible hypercoagulable state was undiagnosed in patients with few clinical risk factors, although some other factors that might cause a hypercoagulable state other than CHF might coexist.

5. Limitations

First, although high D-dimer levels ≥ 0.5 $\mu\text{g/mL}$ could predict thromboembolic events in patients with AF during anticoagulation therapy [6], it is not known whether these levels could be applied to patients who are not undergoing anticoagulant therapy. Second, we performed a post hoc analysis with a small number of patients; thus, there might have been selection biases. Therefore, drawing definite conclusions was not possible.

6. Conclusions

Therefore, D-dimer levels can be elevated in AF patients with few clinical risk factors when BNP levels are high, and anticoagulation treatment should be considered for these patients.

Conflict of interest

None.

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