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Original Article

Transesophageal echocardiographic thromboembolic risk is associated with smoking status in patients with atrial fibrillation

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ABSTRACT

Background: Smoking is a risk factor for cardiovascular diseases, but it is unclear whether smoking status, including environmental tobacco smoke, increases stroke risk in patients with atrial fibrillation (AF). Abnormalities of the left atrium (LA) and aortic atherosclerosis, as detected by transesophageal echocardiography (TEE), are risk factors for stroke and thromboembolism in AF patients. We investigated the impact of smoking status on thromboembolic risk by TEE in patients with nonvalvular AF.

Methods: In 122 patients with AF (mean age, 63 years; chronic AF 50%) who underwent TEE before catheter ablation of AF or for detection of the potential cardioembolic source, urinary concentrations of cotinine and clinical variables including smoking status and the CHA_2DS_2-VASc score were determined.

Results: Severe aortic atherosclerosis and increased aortic wall thickness were more frequently detected by TEE in current smokers than in non-smokers ($p < 0.05$), though these findings did not significantly differ between non-smokers and environmental smokers. Patients in AF rhythm during TEE, who were environmental smokers and at relatively low risk, as stratified by their CHA_2DS_2-VASc score (≤ 2), showed lower LA appendage flow velocity than those without environmental smoking (47 ± 22 vs. 34 ± 13 cm/sec, $p < 0.05$).

Conclusions: TEE findings indicated that smoking status could be associated with thromboembolic risk in patients with AF.

1. Introductions

Atrial fibrillation (AF) is associated with an increased risk of ischemic stroke and cardiovascular events [1]. Aging, history of stroke, hypertension, diabetes mellitus, and heart failure are significant risk factors for stroke and thromboembolism in patients with AF [2,3]. Cigarette smoking is a well-known risk factor for cardiovascular diseases including ischemic and hemorrhagic stroke [4–7]. Smoking status is associated with atherosclerosis [8], vascular damage (e.g., endothelial dysfunction) [9,10], and incident AF [11,12]. We have previously shown a close relationship between cigarette smoking and adverse cardiovascular events in patients with AF [13], but the effects of exposure to environmental tobacco smoke, in particular, on cardiovascular risk remain to be determined. Despite the careful risk assessment and management that is required for patients with cardiovascular risk factors, the impact of smoking status on stroke risk remains unclear in AF patients. Abnormalities of the left atrium (LA) and aortic atherosclerosis, as detected by transesophageal echocardiography (TEE), are established risk factors for stroke and thromboembolism in AF patients [14]. TEE findings, such as dense LA echo contrast (LASEC), low LA appendage (LAA) flow velocity, LA thrombi, and aortic atherosclerosis, were used as risk markers for thromboembolism in AF [15]. Therefore, in the present study, we determined the impact of smoking status on TEE-detected risk factors in patients with nonvalvular AF.

2. Material and methods

2.1. Study population

This cross-sectional study included 122 consecutive patients with nonvalvular AF who underwent TEE at our University Hospital before catheter ablation of AF or for detection of the potential cardioembolic source. Patients in the acute phase of infection or cardiovascular diseases, as well as those receiving a kidney

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transplant or hemodialysis, were excluded. Chronic AF was defined as AF that was documented electrocardiographically on at least 2 separate occasions (4 weeks apart).

2.2. Study methods

Baseline characteristics including the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age $\geq$75 years [2 points], Diabetes mellitus, Stroke [2 points], Vascular disease, Age 65 to 74 years, Sex category [female]) [1] for each patient were obtained from medical records. Smoking status was categorized as non-smoker, environmental smoker, or current smoker based on self-reporting and urinary cotinine levels [16], as follows: a current smoker was defined as a patient that answered "yes" to the question "Do you currently smoke?" at the time of TEE [13]. Since non-smokers included environmental smokers, non-smokers were considered to be environmental smokers if their urinary cotinine levels were greater than 1.3 ng/mg creatinine (limit of detection). The study was approved by our institutional ethics committee, and informed consent was obtained from each patient.

2.2.1. Urine cotinine levels

The spot urine sample was collected in a 10-mL sterile specimen tube at the time of TEE examination for each patient and was immediately frozen at −20 °C for later analyses. Cotinine direct ELISA kits (Cosmic Co., Japan) were used to measure each patient's urine cotinine concentration [17]. Urine creatinine levels were also measured using enzymatic methods. We used creatinine-adjusted urine cotinine levels in the following analysis.

2.2.1.1. Echocardiography. All patients underwent transthoracic echocardiography and TEE studies. Transthoracic echocardiography was performed with a broadband 3.5-MHz phased-array transducer connected to an ultrasound system (Vivid E9; GE Healthcare, Buckinghamshire, England). LA dimension (LAD), left ventricular end-diastolic dimension (LVDd), and left ventricular ejection fraction (LVEF) were determined from M-mode images.

TEE was performed using a 5-MHz multiplane transducer as previously reported [18]. Briefly, patients were examined in a fasting state with topical anesthesia of the pharynx. LAA flow velocity, LASEC, presence of LA thrombi, and aortic plaque were determined. Subsequently, the severities of LASEC and LAA peak flow velocity were determined. LASEC was diagnosed in the presence of dynamic smoke-like echoes within the LA or LAA with a characteristic swirling motion that was distinct from the white noise artifact. The severity of LASEC was defined using the criteria established by Fatkin et al. [14]; 0=none (absence of echogenicity); 1+=mild (minimal echogenicity detectable only transiently during the cardiac cycle with optimal gain settings); 2+=mild to moderate (transient spontaneous echocardiographic contrast without increased gain settings and a more dense pattern than 1+); 3+=moderate (dense swirling pattern during the entire cardiac cycle); and 4+=severe (intense echo density and very slow swirling patterns in the LAA, usually with a similar density in the main left atrial cavity). Peak LAA flow velocity was determined by pulse-wave Doppler echocardiographic interrogation at the orifice of the appendage.

Intima-media thickness of the thoracic aorta was measured on the B-mode image after freezing the optimal image on the R-wave of the ECG. In addition, the severity of aortic atherosclerosis was evaluated using the grading system of Montgomery et al. [19]: grade I=no disease or intimal thickening; grade II=intimal thickening; grade III=atheroma $<$ 5 mm; grade IV=atheroma $\geq$ 5 mm; and grade V=any mobile atheroma. Two independent observers determined the severity of LASEC and aortic atherosclerosis. Any difference in the determination was resolved by a third independent observer. LA abnormality was defined as thrombi in the LA/LAA, dense LASEC (grade 3 or 4), or peak LAA flow velocity $<$20 cm/s. Severe aortic atherosclerosis with complex aortic plaque was defined as mobile, ulcerated, pedunculated, or wall thickness $\geq$ 5 mm [19].

2.3. Statistical analyses

Data are expressed as the mean $\pm$ SD. All analyses were performed using JMP® 10 (SAS Institute Inc., Cary, NC, USA). Comparison of continuous variables was performed with a one-way analysis of variance, followed by Newman-Keuls multiple comparisons. The proportions of categorical variables, including smoking status and TEE findings, were compared using a chi-square test. Multiple logistic regression analysis was used to determine the independent predictors of the TEE findings. Explanatory variables were selected from clinical variables that had a p value $<$0.1 on univariate analysis, and included the presence of chronic AF, smoking status, and components of the CHA_2DS_2-VASc score. A p value $<$0.05 was considered to be significant.

3. Results

3.1. Baseline characteristics

Table 1 summarizes the baseline characteristics and transthoracic echocardiographic variables according to smoking status. The mean age of the study patients was 63.3 $\pm$ 9.7 years, and 101 patients (82.7%) were men.

Based on urinary cotinine levels, 23 of 88 non-smokers were classified as environmental smokers. Current smokers and environmental smokers tended to be male and about half of each group of patients had paroxysmal AF. Hypertension was the most common comorbidity, followed by paroxysmal AF and heart failure. The frequency of warfarin use was higher in non-smokers than in current smokers and environmental smokers, while the mean prothrombin time-international normalized ratio (PT-INR) level of non-smokers receiving warfarin was comparable to that of the other 2 groups. The frequency of direct oral anticoagulant administration and the mean CHA_2DS_2-VASc scores did not differ significantly among the 3 groups. None of the patients had a CHA_2DS_2-VASc score of more than 8 in this study. In terms of LAD, LVDd normalized by body surface area, and LVEF, there were no significant differences among the 3 groups, whereas the BMI of the environmental smokers was incidentally the highest among the 3 groups.

3.2. Smoking status and aortic wall thickness

Fig. 1 shows the relationship between smoking status and the wall thickness of the thoracic aorta. As expected, the aortic wall thickness was increased to a greater extent in current smokers than in non-smokers. This was also true for environmental smokers versus current smokers ($p < 0.05$). However, the wall thickness did not differ between non-smokers and environmental smokers. Additionally, there was no significant difference in the wall thickness according to paroxysmal and chronic AF in all study patients (2.6 $\pm$ 1.4 mm vs. 2.5 $\pm$ 1.4 mm), while current smokers who had paroxysmal AF had increased aortic wall thickness compared with non-smokers (3.5 $\pm$ 2.0 mm vs. 2.1 $\pm$ 1.0 mm, $p < 0.05$). Severe aortic atherosclerosis with mobile plaque was more frequently observed in current smokers than in environmental and non-smokers (current smokers; 26%, environmental smokers; 17%, non-smokers; 9%, $p < 0.05$).

Table 1
Clinical characteristics of all patients stratified by smoking status.

	Non-smoker $n=65$	Environmental smoker $n=23$	Current smoker $n=34$	P value
Age (years)	64.1 ± 9.5	62.8 ± 11.3	62.3 ± 9.0	0.65
Men	49 (75)	21 (91)	31 (91)	0.07
paroxysmal AF	34 (52)	10 (43)	17 (50)	0.76
Heart failure	16 (25)	2 (9)	5 (15)	0.19
Hypertension	33 (51)	14 (61)	19 (56)	0.68
Hypercholesterolemia	26 (40)	8 (35)	6 (18)	0.07
Age ≥ 65 years	31 (48)	12 (52)	12 (35)	0.38
Age ≥ 75 years	8 (12)	1 (4)	2 (6)	0.39
Diabetes mellitus	8 (12)	3 (13)	4 (12)	0.99
Prior stroke / TIA	10 (15)	2 (9)	4 (12)	0.69
Vascular disease	11 (17)	3 (13)	8 (24)	0.57
CHA2DS2-Vasc score	2.2 ± 1.7	1.8 ± 1.3	1.8 ± 1.3	0.37
Antiplatelet drugs	7 (11)	0 (0)	2 (6)	0.22
DOAC	36 (55)	18 (78)	22 (65)	0.15
Warfarin	27 (42)	3 (13)	9 (26)	0.03
PT-INR	1.97 ± 0.40	2.32 ± 0.92	1.71 ± 0.43	0.13
U-Cotinine (ng/mg creatinine)	0 ± 0	18.8 ± 61.2	4085.3 ± 5252.3	< 0.001
BMI (kg/m^2)	23.5 ± 2.9	25.4 ± 4.0	23.1 ± 3.8	0.01
D-dimer (μg/mL)	0.66 ± 0.47	0.60 ± 0.15	0.68 ± 0.35	0.75
hsCRP (mg/dL)	0.17 ± 0.37	0.10 ± 0.1	0.19 ± 0.43	0.61
LAD (mm)	44.1 ± 5.8	44.8 ± 6.9	43.4 ± 7.3	0.74
LVDd/BSA (mm/m^2)	28.7 ± 3.4	28.6 ± 4.1	27.3 ± 3.1	0.14
LVEF (%)	60.9 ± 11.5	63.3 ± 12.0	61.9 ± 12.5	0.69

Values are mean ± SD or number (%) of patients.
AF, atrial fibrillation; TIA, transient ischemic attack; DOAC, direct oral anticoagulants; PT-INR, prothrombin time-international normalized ratio (measured in patients receiving warfarin); U-Cotinine, urinary cotinine levels (cotinine concentration in urine corrected by creatinine concentration in the urine); BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; LAD left atrial dimension; LVDd, left ventricular end-diastolic diameter; BSA, body surface area; LVEF, left ventricular ejection fraction.

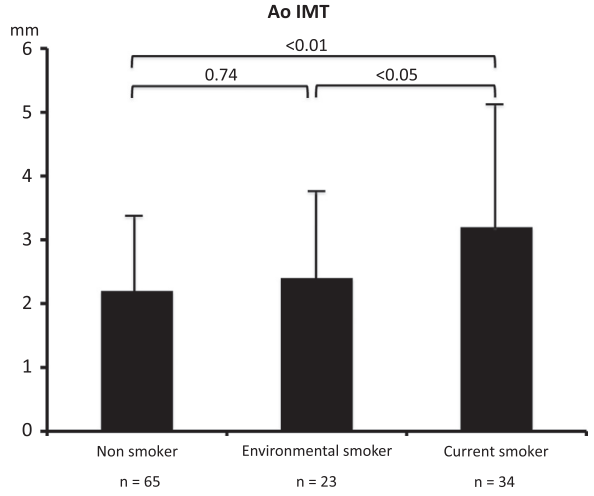

Fig. 1. The relationship between smoking status and aortic intima-media thickness (Ao-IMT). Ao-IMT was greater in current smokers than in both non-smokers and environmental smokers.

3.3. Smoking status and TEE findings in all patients

There were no intergroup differences in LAA flow velocity (non-smokers; 48.1 ± 25.1 cm/sec, environmental smokers; 46.0 ± 28.0 cm/sec, current smokers; 44.6 ± 27.3 cm/sec), since patients with sinus rhythm at the time of TEE were included in each group. Moreover, there was no significant difference in the LASEC grade among groups (non-smokers: 1.8 ± 1.2; environmental smokers: 1.9 ± 1.2; current smokers: 2.0 ± 1.2).

In Table 2, clinical characteristics are compared between patients with and without stroke risk based on TEE findings. Patients with LA abnormalities were older and had a higher frequency of vascular disease and chronic AF than those without LA abnormalities, while older age and vascular disease were observed more frequently in the patients with severe aortic atherosclerosis than in those without. As shown in Table 3, LA abnormality and severe aortic atherosclerosis tended to be related to smoking status. On multiple logistic regression analysis, age ≥ 65 years, vascular disease, and current smoking were independent predictors of both LA abnormality and severe aortic atherosclerosis (Table 4).

Table 2
Clinical characteristics and TEE findings of all patients.

	LA abnormality (-) $n=64$	LA abnormality (+) $n=58$	*P* value
Age (years)	60.2 ± 9.9	66.7 ± 8.3	< 0.001
Men	52 (81)	49 (84)	0.63
Hypertension	35 (55)	31 (53)	0.89
Diabetes mellitus	6 (9)	9 (16)	0.30
Prior stroke / TIA	5 (8)	11 (19)	0.07
Heart failure	10 (16)	13 (22)	0.34
Vascular disease	3 (5)	19 (33)	< 0.001
Age ≥ 65 years	22 (34)	33 (57)	< 0.05
Chronic AF	23 (36)	38 (66)	< 0.01
	Severe aortic atherosclerosis (-) $n=103$	Severe aortic atherosclerosis (+) n = 19	*P* value
Age (years)	62.1 ± 9.6	70.1 ± 7.4	0.01
Men	83 (81)	18 (95)	0.13
Hypertension	55 (53)	11 (58)	0.72
Diabetes mellitus	13 (13)	2 (11)	0.79
Prior stroke / TIA	13 (13)	3 (16)	0.71
Heart failure	20 (19)	3 (16)	0.71
Vascular disease	9 (2)	13 (68)	< 0.001
Age ≥ 65 years	42 (41)	41 (68)	0.03
Chronic AF	52 (50)	9 (47)	0.80

Values are mean ± SD or number (%) of patients.
LA, left atrium; TEE, transesophageal echocardiography; AF, atrial fibrillation. TIA, transient ischemic attack. LA abnormality was defined as positive when. at least one of the following 3 conditions was met: LAA flow velocity < 20 cm/s. presence of thrombus, and dense LASEC (severity grade 3 or 4). Severe aortic. atherosclerosis was defined as mobile or protruding aortic plaque (grade V).

3.4. Subanalysis of thromboembolic risk in environmental smokers

Of 84 patients with a relatively low risk of stroke (CHA_2DS_2-VASc score of $\leq$ 2), 55 had AF rhythm at the time of TEE. LASEC and LAA blood flow velocity according to smoking status are shown in Fig. 2. The severity of LASEC was lower in non-smokers than in current smokers and the peak flow velocity of LAA was higher in non-smokers than in current and environmental smokers, indicating that LAA function was well maintained in patients with AF who were not smoking. No significant differences in the peak LAA flow velocity were observed between the environmental and current smokers.

Table 3
TEE findings and smoking status of all patients.

	Smoking status			
TEE findings	Nonsmoker $n=65$	Environmental smoker $n=23$	Current smoker n=34	*P* value
LA abnormality	25 (38)	10 (43)	23 (68)	$p=0.02$
Severe aortic atherosclerosis	6 (9)	4 (17)	9 (26)	$p=0.07$

Values are number (%) of patients. See Tables 1 and 2 for other abbreviations.

Table 4
Multivariate analysis for predictors of TEE abnormality.

	OR	95% CI	*p* value
LA abnormality			
Age $\geq$ 65 years	3.48	1.42-9.14	<0.01
Vascular disease	8.03	2.29-38.6	<0.001
Chronic AF	4.43	1.83-11.4	<0.001
Prior ischemic stroke / TIA	1.78	0.47-7.38	0.4
Current smoker	4.32	1.60-12.6	<0.01
Severe aortic atherosclerosis			
Age $\geq$ 65 years	4.27	1.09-16.78	0.04
Vascular disease	23.36	6.45-84.59	<0.001
Current smoker	4.46	1.15-17.29	0.03

CI, confidence interval; OR, odds ratio. See Tables 1 and 2 for other abbreviations.

4. Discussion

The major findings of the present study were as follows. First, the severity of aortic atherosclerosis in patients with AF was significantly higher in current smokers than in both non-smokers and environmental smokers. Second, environmental smokers at relatively low risk of stroke, as stratified by their CHA_2DS_2-VASc score (≤ 2), showed significantly lower LAA flow velocity than non-smokers.

4.1. Smoking and aortic atherosclerosis

Smoking is the most important risk factor for cardiovascular disease. Cigarette smoking induced endothelial dysfunction and released inflammatory and proatherogenic cytokines, leading to the activation of macrophages and the uptake of oxidized lipids within the aortic wall [10,20]. Clinical data have shown that aortic atherosclerosis is more common in the descending than in the ascending or transverse arch portions of the thoracic aorta [19,21]. Atherosclerotic disease of the thoracic aorta can be identified noninvasively by TEE. Severe atherosclerosis of the thoracic aorta detected by TEE was an important risk factor for ischemic stroke in patients with AF [18,21]. In the present study, advanced atherosclerotic lesions of the thoracic aorta were observed more frequently in current smokers than in non-smokers and environmental smokers. In addition, autopsy studies showed that the extent and severity of atherosclerotic changes in the thoracic aorta were parallel to those in the aortic arch and carotid arteries [22,23]. Thus, patients with AF who had severe aortic atherosclerosis may be susceptible to cerebral embolism arising from atheromatous lesions in the aorta and carotid arteries. If an ischemic stroke occurs in a current smoker with nonvalvular AF who has a proximal aortic atheroma, the AF may not be the cause of the embolic event. The precise mechanisms of cerebral infarction in AF patients with aortic atherosclerosis should be determined in future studies.

4.2. Smoking status and thromboembolic risk in AF

Although previous reports have linked smoking habits to cardiovascular events, including stroke and death, in the general population [5–7], fewer data are available from studies investigating

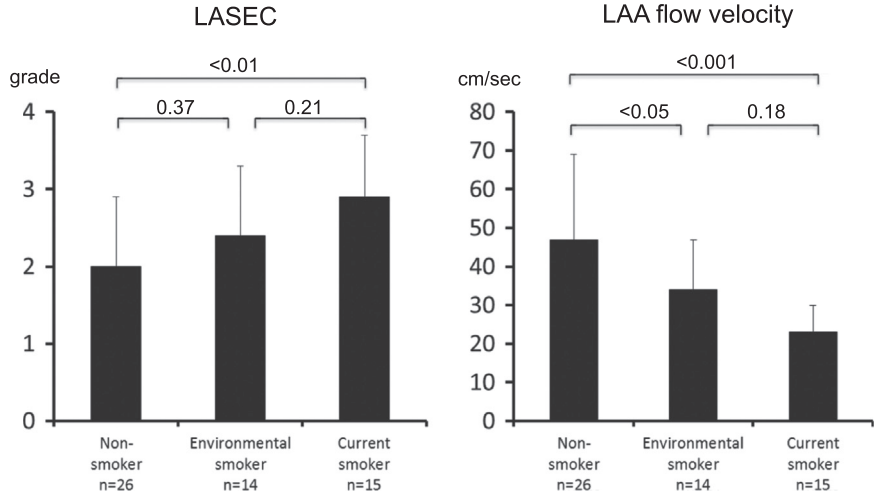

Fig. 2. Left panel. The relationship between smoking status and left atrial spontaneous echo contrast (LASEC) in relatively low-risk patients. LASEC was higher in current smokers than in non-smokers ($p < 0.01$). Right panel. The relationship between smoking status and left atrial appendage (LAA) flow velocity in relatively low-risk patients. LAA flow velocity was lower in current smokers and environmental smokers than in non-smokers.

patients with AF. In particular, the influence of environmental smoking on cardiovascular risks in patients with AF has not been previously reported in large-scale clinical trials. Cotinine, the major metabolite of nicotine, is a reliable biomarker for environmental smoking [17]. Smoking, whether current or environmental, has been shown to stimulate the coagulation cascade and reduce fibrinolysis [20]. In addition, the present result indicates that environmental smoking could increase thromboembolic risk detected by TEE in patients with AF, particularly in those at relatively low risk of thromboembolism, as classified using their CHA_2DS_2-VASc score. Thus, risk stratification by additional information on smoking status in AF patients may be useful for predicting subsequent thromboembolic events [13].

4.3. Smoking and TEE risk

LA abnormality and severe aortic atherosclerosis detected by TEE are well-known risk factors for thromboembolism in patients with AF. Previous studies have demonstrated that dense LASEC and reduced LAA flow velocity are associated with cardiovascular events including thromboembolism [14,18]. Current smokers in the present study showed reduced LAA flow velocity and dense LASEC, indicating the impact of smoking on thromboembolic risk in patients with AF. Goette et al. demonstrated that, in cigarette smokers, chronic nicotine consumption was associated with atrial fibrosis in human tissue samples of atrial appendages [24,25]. The in vitro analysis showed nicotine base induced atrial collagenIIImRNA expression in a concentration-dependent manner [24]. These structural changes could affect LAA function, resulting in reduced LAA flow velocity in smokers. In addition, smoking in AF patients can increase rouleaux formation of erythrocytes, platelet aggregation, and blood coagulability, and may play an important role in the genesis of LASEC. Although the pathophysiologic mechanisms of LAA abnormalities caused by smoking remain unclear, LA endothelial damage via nicotine-induced inflammation, oxidative stress, or impaired nitric oxide bioavailability [20], may be related to LA abnormalities in current smokers [26].

Similarly, environmental smoking has been associated with increased levels of inflammatory biomarkers, the development of cardiovascular disease, and prevalent AF. Taken together with these plausible mechanisms, tobacco smoke exposure may increase thromboembolic risk in patients with AF who are considered at relatively low risk otherwise.

4.4. Limitations

Several limitations of the present study should be addressed. First, this study was performed in a single institution, and the majority of participants were men, although data from a large Danish study suggested that the association between smoking and thromboembolism was stronger in women than in men [27]. Moreover, in patients with low thromboembolic risk as identified by their CHA_2DS_2-VASc scores, the positive association became apparent after statistically controlling for known risk factors. Thus, well-controlled multicenter studies with a large cohort of AF patients are needed to validate the effects of smoking status on the thromboembolic risks detected by TEE. Second, we did not thoroughly quantify the number of cigarettes or the duration of the smoking habit of the smokers in the present study. In addition, past smokers were not considered, because a half-life of 30 hours may limit the usefulness of urinary cotinine in the detection of a previous smoking habit. However, the measurement of urinary cotinine is an objective evaluation that may be more reliable and valid than the use of questionnaires [17]. Third, the present study did not analyze subsequent cardiovascular events. Therefore, the present results could not determine whether current and environmental smokers with AF at low thromboembolic risk should receive antithrombotic therapy for the prevention of stroke.

5. Conclusions

The present study indicates that current smoking, including environmental exposure to smoke, may be associated with potential thromboembolic risks in patients with nonvalvular AF. Further studies are necessary to determine whether smoking status provides useful information for the stratification of thromboembolic risk in patients with AF.

Conflicts of interest

All authors declare no conflict of interest related to this study.

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