Journal of Cardiology 65 (2015) 429–433

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Impact of persistent smoking on long-term outcomes in patients with nonvalvular atrial fibrillation

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ARTICLE INFO

Article history:
Received 24 February 2014
Received in revised form 25 June 2014
Accepted 18 July 2014
Available online 13 August 2014

Keywords:
Nonvalvular atrial fibrillation
Smoking
Prognosis

ABSTRACT

Background: Although smoking is a risk factor for cardiovascular diseases, little is known about the impact of smoking on long-term outcomes in patients with atrial fibrillation (AF).
Methods: In 426 consecutive patients with nonvalvular AF (mean age, 66 years; 307 men; mean follow-up, 5.8 ± 3.2 years), clinical variables including smoking status, $CHADS_2$, and CHA_2DS_2-VASc score, incidences of cardiovascular events (stroke, myocardial infarction, or admission for heart failure), bleeding, and mortality were determined.
Results: Incidences of intracranial bleeding (0.7% vs 0.1%/year, $p < 0.01$), all-cause mortality (4.9% vs 2.6%/year, $p < 0.01$), and death from stroke (0.8% vs 0.2%/year, $p < 0.05$) were higher in patients with history of smoking than in those without it. Incidence of intracranial bleeding was significantly higher in persistent smokers than in non-persistent smokers (1.2% vs 0.2%/year, $p < 0.01$). History of smoking predicted all-cause mortality [hazard ratio (HR), 2.7; 95% confidence interval (CI), 1.7–4.5; $p < 0.01$] and death from stroke (HR 4.7; 95% CI 1.0–22.3; $p < 0.05$) independent of age, antithrombotic treatment, $CHADS_2$, and CHA_2DS_2-VASc score. Persistent smoking predicted intracranial bleeding (HR 4.4; 95% CI 1.1–17.6; $p < 0.05$) independent of age and antithrombotic treatment.
Conclusions: Smoking status, independent of age, antithrombotic treatment, and clinical risk factors, predicted long-term adverse outcomes including bleeding events in patients with nonvalvular AF. There might be an obvious impact of persistent smoking on intracranial bleeding.

Introduction

Balancing clinical benefit of thromboprophylaxis by risk of bleeding is the critical issue in anticoagulation treatment for patients with atrial fibrillation (AF) [1–5]. However, considerable risk factors for stroke and thromboembolism in AF (e.g. aging, history of stroke, hypertension, and renal dysfunction) [2–7] are also risk factors for bleeding, and cardiovascular damage or remodeling [8–12]. Cigarette smoking is a well known risk factor for cardiovascular diseases including ischemic and hemorrhagic strokes [13–16]. Smoking status relates to atherosclerosis [17], vascular damage (e.g. endothelial dysfunction) [18,19], and AF incidence [20,21] as well. In a recent study, a close relationship between stroke and bleeding risk was shown [22]. Despite careful risk assessment and management needed in patients with AF and cardiovascular risks, little is known about the impact of smoking on outcomes in AF patients. In the present study, we determined the impact of smoking status on long-term outcomes in patients with nonvalvular AF.

Methods

Study population

From November 1994 to May 2007, 745 patients with AF underwent transesophageal echocardiography at Toyama

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http://dx.doi.org/10.1016/j.jjcc.2014.07.012
0914-5087/

University Hospital. Of these, 526 patients with nonvalvular AF gave written informed consent to participate in the follow-up study. Four hundred and twenty-six patients with nonvalvular AF in whom smoking status could be determined from their medical records and follow-up questionnaires (307 men, mean age 66 ± 11 years) constituted the study group. Patients in the acute phase of infection or cardiovascular diseases including stroke, and those receiving kidney transplant or hemodialysis were excluded. Chronic AF was defined as AF documented electrocardiographically on at least two separate occasions (4 weeks apart). Baseline characteristics including $CHADS_2$ [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke (2 points)] [2], CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age 65–74 years, Sex category (female)] [3] score, or HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio, Elderly, Drugs/alcohol) [9] for each patient were obtained from medical records. Serial prothrombin time-international normalized ratio (PT-INR) or liver function could not be assessed; therefore, we used modified HAS-BLED (mHAS-BLED) score (omitting labile INR and liver function). Smoking status was classified as follows: positive versus negative history of smoking, and persistent versus non-persistent smokers. Persistent smoking was defined if patients answered "yes" to the question "Do you currently smoke?" at the end of follow-up or in the follow-up questionnaires. Non-persistent smokers consisted of former smokers and those who had never smoked. The point of PT levels we used was at the entry of follow-up. The study was approved by the institutional ethics committee at Toyama University Hospital, and informed consent was obtained from each patient as indicated above.

Outcomes

The composite end points of all-cause death, stroke (ischemic and hemorrhagic), cardiac events (myocardial infarction or hospitalization for worsening of heart failure), and bleeding (gastrointestinal and intracranial hemorrhages) were determined in October 2008. Stroke and cardiac events constituted cardiovascular events. Information on the end points was collected from hospital databases and responses to questionnaires by patients themselves or their family members. Ischemic stroke was defined as a neurological deficit of sudden onset, lasting >24 h and confirmed by brain computed tomography or magnetic resonance imaging. Myocardial infarction was defined as typical chest symptoms with electrocardiographic changes and increases in cardiac enzymes.

Statistical analyses

Data are expressed as mean ± SD. All analyses were performed using IBM SPSS Statistics (Version 20, IBM Corp., Chicago, IL, USA). The mean values and proportion of variables were compared with analysis of variance and χ^2 test, respectively. The outcomes were displayed with Kaplan–Meier survival curves and compared with the log-rank test. Cox proportional hazards regression was used to determine independent predictors of the end points. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Table 1 shows clinical characteristics according to smoking status. Patients with a history of smoking were younger, populated with a higher proportion of men and had lower CHA_2DS_2-VASc score compared to those without history of smoking. Proportions of warfarin and antiplatelet administration, or mean value of mHAS-BLED score did not differ significantly between the groups. There were no patients with both warfarin and dual antiplatelet therapy.

Outcomes

During a follow-up period of 5.8 ± 3.2 years, 87 (20%) patients died, 64 (15%) had cardiac events (6 myocardial infarction and 58 hospitalization for worsening of heart failure), 45 (11%) had stroke (37 ischemic and 8 hemorrhagic), and 2 (0.5%) had gastrointestinal bleeding. Table 2 shows causes of death. Long-term survival was significantly lower (71% vs 85%, $p < 0.01$), and there were more deaths from malignancy (9% vs 3%, $p < 0.01$) in patients with history of smoking than in those without it. There were 59 persistent smokers. The incidences of intracranial bleeding, all-cause mortality,

Table 1
Clinical characteristics according to smoking status.

	Overall	History of smoking		*p*-value*
	n = 426	Negative *n* = 255	Positive *n* = 171	
Age (years)	66 ± 11	68 ± 12	65 ± 11	<0.01
Men	307 (72)	143 (56)	164 (96)	<0.001
Chronic AF	204 (48)	118 (46)	86 (50)	0.50
Heart failure	97 (23)	57 (22)	40 (23)	0.80
Hypertension	162 (38)	97 (38)	65 (38)	0.99
Age ≥75 years	101 (24)	67 (26)	34 (20)	0.13
Diabetes mellitus	68 (16)	36 (14)	32 (19)	0.21
Prior stroke/TIA	102 (24)	60 (24)	42 (25)	0.81
$CHADS_2$ score	1.5 ± 1.4	1.5 ± 1.4	1.5 ± 1.3	0.93
≥2	175 (41)	104 (41)	71 (42)	0.88
CHA_2DS_2-VASc score	2.8 ± 1.9	3.0 ± 1.9	2.6 ± 1.8	<0.05
≥2	314 (74)	195 (76)	119 (70)	0.12
mHAS-BLED score	1.3 ± 0.9	1.3 ± 0.9	1.2 ± 1.0	0.24
Antiplatelet drugs	106 (25)	55 (22)	51 (30)	0.10
Dual antiplatelet therapy	8 (2)	4 (2)	4 (2)	0.57
Warfarin	319 (75)	195 (77)	124 (73)	0.33
PT-INR	1.7 ± 1.2	1.8 ± 1.4	1.6 ± 0.8	0.40

Values are mean ± SD or number (%) of patients.
AF, atrial fibrillation; PT-INR, prothrombin time-international normalized ratio (determined in patients receiving warfarin); TIA, transient ischemic attack.
* Negative versus positive history of smoking.