Effects of Smoking on Ischemic Stroke, Intracranial Hemorrhage, and Coronary Artery Events in Japanese Patients With Non-Valvular Atrial Fibrillation

Shinkaen Database Analysis

Shinya Suzuki, MD, Takayuki Otsuka, MD, Koichi Sagara, MD, Hiroaki Semba, MD, Hiroto Kano, MD, Shunsuke Matsuno, MD, Hideaki Takai, MD, Yuko Kato, MD, Tokuhisa Uejima, MD, Yuji Oikawa, MD, Kazuyuki Nagashima, MD, Hajime Kirigaya, MD, Junji Yajima, MD, Takashi Kunihara, MD, Hitoshi Sawada, MD, Tadanori Aizawa, MD, and Takeshi Yamashita, MD

SUMMARY

The effects of smoking on the prognosis of non-valvular atrial fibrillation (NVAF) patients are unclear. The Shinken Database 2004-11 (n = 17,517) includes all new patients visiting the Cardiovascular Institute between June 2004 and March 2012. Among these cases, 2,102 NVAF patients were identified. The effects of smoking on ischemic stroke (IS), intracranial hemorrhage (ICH), and coronary artery events including percutaneous coronary intervention (PCI) and acute coronary syndrome (ACS) were analyzed. Smokers were younger and had lower risk profiles compared with non-smokers. A similar tendency was observed between current and former smokers. In contrast, patients with high tobacco consumption were older and had higher risk profiles, including uncontrolled hypertension, compared with those with low tobacco consumption. In 8,159 patient-years, IS, ICH, PCI, and ACS occurred at rates of 7.7, 2.7, 12.4, and 3.0 per 1000 patient-years. In multivariate Cox regression analysis, smoking was not significantly associated with any adverse event. However, different effects of smoking were observed when stratified by age. In patients ≥ 65 years old, current smokers were independently associated with PCI. Moreover, current smokers and smokers with a total tobacco amount ≥ 800 were marginally and independently associated with IS. In patients < 65 years, current smokers were independently associated with ICH.

Age appears to be one of the contributors to differentiation of the effects of smoking on cardiovascular events in our NVAF patients. In elderly patients who still smoke, smoking was associated with the promotion of atherosclerosis or thromboembolism, whereas in young patients it was associated with bleeding. (Int Heart J 2017; 58: 506-515)

Key words: Tobacco consumption, Epidemiology, Risk factors

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in developed countries and is strongly associated with an increase in cardiovascular mortality and morbidity. Ischemic stroke is the most serious complication in AF patients, and the mortality at 1 year after ischemic stroke in AF patients has been reported to be ~50%. To prevent ischemic stroke, anticoagulant administration is considered to be the most effective method, but it increases the risk of intracranial hemorrhage, which is also a life-threatening complication.

Smoking is associated with an increased risk of ischemic stroke. Smoking also increases hypertension, which increases the risk of intracranial hemorrhage under anticoagulant therapy. Moreover, smoking has been reported to be associated with coronary artery events, although the direct mechanism is still a topic of discussion. Thus, smoking may have a significant impact on the prognosis in AF patients.

In the present study, we investigated the association between smoking and the prognosis of AF patients using a single hospital-based cohort in an urban area of Japan (Shinken Database).

METHODS

Study participants: The Shinken Database, which was established...
lished in June 2004, contains data on all new patients who visit the Cardiovascular Institute Hospital in Tokyo (abbreviated in Japanese as ‘Shinken’), excluding foreign travelers and patients with active cancer. The principle aim of establishing this hospital-based database was to monitor the prevalence and prognosis of cardiovascular diseases in urban areas of Japan.17,20 Data on patient health status and the incidences of cardiovascular events and mortality are linked with hospital medical records and data collected through a postal survey repeated approximately once or twice annually.17,20

The data used in this study were derived from the records of 17,517 new patients between June 2004 and March 2012 (Shinken Database 2004–2011). Among these 17,517 patients, 2,102 diagnosed as having non-valvular AF (NVAF) were selected as the study population.

**Data collection at initial visit:** After obtaining an electrocardiogram and chest X-ray, the cardiovascular status of the patients was evaluated using echocardiography, an exercise test, 24-hour Holter recordings, and blood laboratory data from the initial visit. In addition to gender, age, height and weight, we collected data on cardiovascular diseases, including heart failure (New York Heart Association class ≥ 2), valvular heart disease (moderate or severe stenosis or regurgitation using echocardiography), coronary artery disease (diagnosed by angiography or scintigraphy), hypertrophic and dilated cardiomyopathy (diagnosed by echocardiography or magnetic resonance imaging), left ventricular non-compaction (diagnosed by echocardiography or magnetic resonance imaging), and history of a disabling cerebral infarction or transient ischemic attack (diagnosed by computed tomography or magnetic resonance imaging). The presence of cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure of ≥ 90 mmHg on admission), diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin ≥ 6.5%), dyslipidemia (use of a statin or drugs for lowering triglycerides, low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, or triglycerides ≥ 150 mg/dL), chronic kidney disease (estimated glomerular filtration rate < 60 mL/minute/1.73 m²), chronic obstructive pulmonary disease, and use of anticoagulant and antiplatelet medications were determined. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The glomerular filtration rate (GFR) was estimated using the new Japanese coefficient for the modified isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) study equation (GFR = 194 x serum creatinine [SCr]0.018 g/dL x Age-0.203 x 0.739 [if female]).

**Definition of AF:** AF was diagnosed by electrocardiographic recordings, including 12-lead surface electrocardiograms and 24-hour Holter recordings, on the initial visit. It was also diagnosed by any medical history of AF from a referring physician.

**Patient outcome:** The incidences of ischemic stroke, intracranial hemorrhage, percutaneous coronary intervention, and

### Table I. Baseline Characteristics of Patients From the Shinken Database 2004–2011, Tokyo, Japan

| Variable                                      | Non-smokers | Smokers | P (Smokers versus Non-smokers) | Former | Current | P (Current versus Former) |
|-----------------------------------------------|-------------|---------|--------------------------------|--------|---------|--------------------------|
| Age, years                                    | 64.9 ± 13.2 | 61.2 ± 11.9 | < 0.001                              | 62.6 ± 11.5 | 56.9 ± 12.0 | < 0.001 |
| BMI, kg/m²                                     | 23.6 ± 3.5  | 24.3 ± 3.3  | < 0.001                              | 24.2 ± 3.2  | 24.6 ± 3.6  | 0.087    |
| Cigarette-years                                | 579.5 ± 496.3 | 539.4 ± 511.0 | 694.4 ± 432.7                     | 539.4 ± 511.0 | 694.4 ± 432.7 | < 0.001 |
| Age < 30 years                                 | 9 (0.8)     | 5 (0.5)    | < 0.001                              | 2 (0.3)   | 3 (1.2)   | < 0.001 |
| 30-49                                         | 140 (12.3)  | 141 (14.7) | 83 (11.6)                           | 58 (23.8) |
| 50-69                                         | 542 (47.5)  | 583 (60.7) | 429 (59.9)                           | 154 (63.1) |
| ≥ 70                                          | 451 (39.5)  | 231 (24.1) | 202 (28.2)                           | 29 (11.9) |
| Men                                           | 716 (62.7)  | 880 (91.7) | < 0.001                              | 660 (92.2) | 220 (90.2) | 0.348    |
| BMI ≥ 25 kg/m²                                 | 322 (28.2)  | 367 (38.2) | < 0.001                              | 266 (37.2) | 101 (41.4) | 0.253    |
| Hypertension                                  | 514 (45.0)  | 420 (43.8) | 0.567                                | 332 (46.4) | 88 (36.1)  | 0.006    |
| Uncontrolled hypertension                     | 226 (19.8)  | 164 (17.1) | 0.115                                | 132 (18.4) | 32 (13.1)  | 0.061    |
| Diabetes mellitus                             | 152 (13.3)  | 134 (14.0) | 0.702                                | 100 (44.0) | 34 (13.9)  | 1.000    |
| Dyslipidemia                                  | 274 (24.0)  | 228 (23.8) | 0.918                                | 174 (24.3) | 54 (22.1)  | 0.542    |
| Metabolic syndrome (modified)                 | 82 (7.2)    | 105 (10.9) | 0.003                                | 81 (11.3)  | 24 (9.8)   | 0.555    |
| Heart failure                                 | 121 (10.6)  | 62 (6.5)   | < 0.001                              | 42 (5.9)   | 20 (8.2)   | 0.227    |
| Valvular heart disease                        | 105 (9.2)   | 52 (5.4)   | 0.001                                | 38 (5.3)   | 14 (5.7)   | 0.870    |
| Coronary artery disease                       | 96 (8.4)    | 76 (7.9)   | 0.014                                | 61 (8.5)   | 15 (6.1)   | 0.273    |
| Hypertrophic cardiomyopathy                   | 24 (2.1)    | 15 (1.6)   | 0.419                                | 9 (1.3)    | 6 (2.5)    | 0.230    |
| Dilated cardiomyopathy                        | 24 (2.1)    | 24 (2.5)   | 0.561                                | 17 (2.4)   | 7 (2.9)    | 0.640    |
| Cerebral infarction or transient ischemic attack | 63 (5.5) | 56 (5.8) | 0.777                                | 49 (6.8)   | 7 (2.9)    | 0.026    |
| Chronic kidney disease                        | 341 (29.9)  | 205 (21.4) | < 0.001                              | 161 (22.5) | 44 (18.0) | 0.149    |
| Chronic obstructive pulmonary disease         | 4 (0.4)     | 16 (1.7)   | 0.003                                | 11 (1.5)   | 5 (2.0)    | 0.569    |
| Anemia (hemoglobin < 11 g/dL)                 | 48 (4.2)    | 23 (2.4)   | 0.028                                | 18 (2.5)   | 5 (2.0)    | 0.812    |
| Hypothyroidism                                | 15 (1.3)    | 21 (2.2)   | 0.132                                | 14 (2.0)   | 7 (2.9)    | 0.447    |
| Statin use                                    | 155 (13.6)  | 113 (11.8) | 0.237                                | 98 (13.7)  | 15 (6.1)   | 0.001    |
| Renin-angiotensin system inhibitor use        | 351 (30.7)  | 230 (24.0) | < 0.001                              | 184 (25.7) | 46 (18.9) | 0.030    |
| Anticoagulant use                             | 528 (46.2)  | 453 (47.2) | 0.693                                | 347 (48.5) | 106 (43.4) | 0.182    |
| Antiplatelet use                              | 424 (37.1)  | 360 (37.5) | 0.892                                | 268 (37.4) | 92 (37.7) | 0.939    |

Categorical and continuous variables are presented as numbers (%) and mean ± standard deviation, respectively. P for continuous and categorical variables were calculated by unpaired t-test and chi-square test, respectively. The metabolic syndrome (modified) was defined as BMI ≥ 25 kg/m² and 2 or more of following: hypertension, diabetes mellitus, and dyslipidemia.
Statistical analysis: All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL). The level of statistical significance was set at P < 0.05. Patients were divided into non-smokers and smokers, and the smokers were further divided into 2 subcategories: 1) former and current smokers, and 2) total tobacco amount < 800 and ≥ 800 cigarette-years, and unknown. In the patient backgrounds, categorical and consecutive data are presented as number (%) and mean ± standard deviation, respectively. The chi-square test and Fisher’s exact test were used for group comparisons of categorical data and the unpaired t-test or one-way analysis of variance were used for group comparisons of consecutive data, as appropriate. The incidences of 4 types of adverse events (ischemic stroke, intracranial hemorrhage, percutaneous coronary intervention, and acute coronary syndrome) in the total patient population and in each smoking category were calculated by the person-years method with 95% confidence intervals (CI), and the effects of smokers (versus non-smokers), current and former smokers (versus non-smokers), and total tobacco amount of < 800 and ≥ 800 cigarette-years and/or unknown amount (versus non-smokers) on the incidences of the 4 types of adverse events were evaluated by two types of multivariate Cox regression analyses: model 1, adjusted for age and sex; model 2, adjusted for all variables displayed in Table I using the stepwise method. Additionally, considering the strong inverse correlation between age and smoking (smokers were more prevalent in younger patients) in the baseline patient characteristics, we further analyzed in separate categories stratified at age 65 years which was approximately the median age of our study population (64 years).

Ethical issues: The Ethical Committee of the Cardiovascular Institute granted ethical approval for this study and all patients provided written informed consent.

Results

Table II. Baseline Characteristics of Patients with Smoking Habits by Total Tobacco Amount

| Variable                                | < 800 cigarette-years (n = 648) | ≥ 800 cigarette-years (n = 220) | Unknown (n = 92) | P     |
|-----------------------------------------|---------------------------------|---------------------------------|------------------|-------|
| Age, years                              | 59.1 ± 12.1                     | 65.2 ± 9.1                      | 66.6 ± 12.1      | <0.001|
| BMI, kg/m²                              | 24.2 ± 3.3                      | 24.5 ± 3.3                      | 24.3 ± 3.6       | 0.591 |
| Cigarette-years                         | 365.7 ± 218.3                   | 1,214.3 ± 542.0                 | —                | <0.001|
| Former smokers                          | 152 (23.5)                      | 72 (32.7)                       | 20 (21.7)        | 0.017 |
| Current smokers                         | 496 (76.5)                      | 148 (67.3)                      | 72 (78.3)        |       |
| Age < 30 years                          | 5 (0.8)                         | 0 (0.0)                         | 0 (0.0)          | <0.001|
| ≥ 30–49                                 | 128 (19.8)                      | 7 (3.2)                         | 6 (6.5)          |       |
| ≥ 50–69                                 | 386 (59.6)                      | 145 (65.9)                      | 52 (56.5)        |       |
| ≥ 70                                    | 129 (19.9)                      | 68 (30.9)                       | 34 (37.0)        |       |
| Men                                     | 589 (90.9)                      | 212 (96.4)                      | 79 (85.9)        | 0.044 |
| ≥ BMI 25 kg/m²                          | 235 (36.3)                      | 93 (42.3)                       | 39 (42.4)        | 0.196 |
| Hypertension                            | 247 (38.1)                      | 121 (55.0)                      | 52 (56.5)        | <0.001|
| Uncontrolled hypertension               | 86 (13.3)                       | 57 (25.9)                       | 21 (22.8)        | <0.001|
| Diabetes mellitus                       | 75 (11.6)                       | 43 (19.5)                       | 16 (17.4)        | 0.008 |
| Dyslipidemia                            | 140 (21.6)                      | 58 (26.4)                       | 30 (32.6)        | 0.039 |
| Metabolic syndrome (modified)†          | 55 (8.5)                        | 31 (14.1)                       | 19 (20.7)        | <0.001|
| Heart failure                           | 30 (4.6)                        | 21 (9.5)                        | 11 (12.0)        | 0.003 |
| Valvular heart disease                  | 33 (5.1)                        | 14 (6.4)                        | 5 (5.4)          | 0.772 |
| Coronary artery disease                 | 37 (5.7)                        | 28 (12.7)                       | 11 (12.0)        | 0.004 |
| Hypertrophic cardiomyopathy             | 9 (1.4)                         | 5 (2.3)                         | 1 (1.1)          | 0.611 |
| Dilated cardiomyopathy                  | 13 (2.0)                        | 8 (3.6)                         | 3 (3.3)          | 0.362 |
| Cerebral infarction or transient ischemic attack | 26 (4.0)  | 21 (9.5) | 9 (9.8) | 0.002 |
| Chronic kidney disease                  | 126 (19.4)                      | 55 (25.0)                       | 24 (26.1)        | 0.112 |
| Chronic obstructive pulmonary disease   | 3 (0.5)                         | 11 (5.0)                        | 2 (2.2)          | <0.001|
| Anemia (hemoglobin < 11 g/dL)           | 10 (1.5)                        | 8 (3.6)                         | 5 (5.4)          | 0.029 |
| Hyperthyroidism                         | 20 (3.1)                        | 1 (0.5)                         | 0 (0.0)          | 0.022 |
| Statin use                              | 62 (9.6)                        | 33 (15.0)                       | 18 (19.6)        | 0.005 |
| Renin-angiotensin system inhibitor use  | 125 (19.3)                      | 79 (35.9)                       | 26 (28.3)        | <0.001|
| Anticoagulant use                       | 294 (45.4)                      | 111 (50.5)                      | 48 (52.2)        | 0.257 |
| Antiplatelet use                        | 228 (35.2)                      | 97 (44.1)                       | 35 (38.0)        | 0.062 |

Categorical and continuous variables are presented as numbers (%) and mean ± standard deviation, respectively. P for continuous and categorical variables were calculated by unpaired t-test and chi-square test, respectively. † Metabolic syndrome (modified) was defined as BMI ≥ 25 kg/m² and 2 or more of following 3: hypertension, diabetes mellitus, and dyslipidemia.
amount (≥ 800 cigarette-years; n = 220) were older and had higher prevalences of uncontrolled hypertension, diabetes mellitus, coronary artery disease, history of ischemic stroke and transient ischemic attack, and chronic obstructive pulmonary disease (Table II).

**Incidence of ischemic stroke:** The total observation period among the 2,102 patients was 8,159 person-years. Ischemic stroke occurred in 62 during the observation period of 8,000 person-years (7.7 per 1000 person-years, 95%CI; 6.0–9.9, Table III). Unexpectedly, the incidence rate of ischemic stroke was slightly lower in smokers (6.8 per 1000 person-years, 95%CI; 4.5–10.2) than in non-smokers (8.5 per 1000 person-years, 95%CI; 6.2–11.6). However, the incidence was slightly higher in current smokers (8.5 per 1000 person-years, 95%CI; 4.1–17.5) than in former smokers (6.2 per 1000 person-years, 95%CI; 3.8–10.1). Similarly, the incidence was slightly higher in patients with a high total tobacco amount (≥ 800 cigarette-years: 11.1 per 1000 person-years, 95%CI; 5.8–21.0) than in those with a low total tobacco amount (< 800 cigarette-years: 4.8 per 1000 person-years, 95%CI; 2.7–8.6). Patients whose total tobacco amount was unknown had a higher incidence of ischemic stroke (10.2 per 1000 person-years, 95%CI; 3.5–30.1).

In multivariate Cox regression models, no significant association was observed between smoking categories and the incidence of ischemic stroke, although the hazard ratios (HRs) commonly increased in the adjusted models compared with the non-adjusted models (Table IV).

We further analyzed according to age ≥ 65 years and < 65 years. In patients ≥ 65 years old, although the incidence of ischemic stroke was similar between smokers and non-smokers, the incidences in current smokers and smokers with a total tobacco amount ≥ 800 cigarette-years were approximately twice those of former smokers and smokers with a total tobacco amount < 800 cigarette-years, respectively (Table V). In Cox regression analysis, the effects of current smokers (HR; 2.49, 95%CI; 0.85–7.28) and smokers with a total tobacco amount ≥ 800 cigarette-years (HR; 2.43, 95%CI; 0.95–6.27) were marginally significant (Table VII). However, in patients < 65 years old, the incidence of ischemic stroke was mostly similar between smoking categories, with the exception of smokers with an unknown total tobacco amount (Table VI). In multivariate Cox regression analysis, no significant association was observed between smoking category and the incidence of ischemic stroke in patients in this age stratification (Table VIII).

**Incidence of intracranial hemorrhage:** In the total patient population, intracranial hemorrhage occurred in 22 during the

| Variable                        | No. of events | Person-years | Incidence rate (per 1000 person-years) | 95% confidence interval |
|---------------------------------|---------------|--------------|----------------------------------------|-------------------------|
| Ischemic stroke                 |               |              |                                        |                         |
| Total                           | 62            | 8000         | 7.7                                    | 6.0–9.9                 |
| Non-smoker                      | 39            | 4611         | 8.5                                    | 6.2–11.6                |
| Smoker                          | 23            | 3389         | 6.8                                    | 4.5–10.2                |
| Former                          | 16            | 2565         | 6.2                                    | 3.8–10.1                |
| Current                         | 7             | 824          | 8.5                                    | 4.1–17.5                |
| Total tobacco amount < 800      | 11            | 2283         | 4.8                                    | 2.7–8.6                 |
| Total tobacco amount ≥ 800      | 9             | 814          | 11.1                                   | 5.8–21.0                |
| Total tobacco amount unknown    | 3             | 293          | 10.2                                   | 3.5–30.1                |
| Intracranial hemorrhage         |               |              |                                        |                         |
| Total                           | 22            | 8121         | 2.7                                    | 1.8–4.1                 |
| Non-smoker                      | 12            | 4691         | 2.6                                    | 1.5–4.5                 |
| Smoker                          | 10            | 3430         | 2.9                                    | 1.6–5.4                 |
| Former                          | 7             | 2595         | 2.7                                    | 1.3–5.6                 |
| Current                         | 3             | 835          | 3.6                                    | 1.2–10.6                |
| Total tobacco amount < 800      | 7             | 2297         | 3.0                                    | 1.5–6.3                 |
| Total tobacco amount ≥ 800      | 2             | 837          | 2.4                                    | 0.7–8.7                 |
| Total tobacco amount unknown    | 1             | 296          | 3.4                                    | 0.6–19.1                |
| Percutaneous coronary intervention |            |              |                                        |                         |
| Total                           | 97            | 7793         | 12.4                                   | 10.2–15.2               |
| Non-smoker                      | 52            | 4502         | 11.6                                   | 8.8–15.1                |
| Smoker                          | 45            | 3292         | 13.7                                   | 10.2–18.3               |
| Former                          | 34            | 2487         | 13.7                                   | 9.8–19.1                |
| Current                         | 11            | 805          | 13.7                                   | 7.6–24.5                |
| Total tobacco amount < 800      | 23            | 2240         | 10.3                                   | 6.8–15.4                |
| Total tobacco amount ≥ 800      | 19            | 768          | 24.7                                   | 15.8–38.6               |
| Total tobacco amount unknown    | 3             | 284          | 10.6                                   | 3.6–31.1                |
| Acute coronary syndrome         |               |              |                                        |                         |
| Total                           | 24            | 8083         | 3.0                                    | 2.0–4.4                 |
| Non-smoker                      | 19            | 4641         | 4.1                                    | 2.6–6.4                 |
| Smoker                          | 5             | 3442         | 1.5                                    | 0.6–3.4                 |
| Former                          | 3             | 2605         | 1.2                                    | 0.4–3.4                 |
| Current                         | 2             | 837          | 2.4                                    | 0.7–8.7                 |
| Total tobacco amount < 800      | 2             | 2310         | 0.9                                    | 0.2–3.2                 |
| Total tobacco amount ≥ 800      | 2             | 836          | 2.4                                    | 0.7–8.7                 |
| Total tobacco amount unknown    | 1             | 296          | 3.4                                    | 0.6–19.1                |
observation period of 8,121 person-years (2.7 per 1000 person-years, 95%CI: 1.8–4.1, Table III). The incidence of intracranial hemorrhage was similar between the smokers (2.6 per 1000 person-years, 95%CI: 1.5–4.5) and non-smokers (2.9 per 1000 person-years, 95%CI: 1.6–5.4). The incidence was slightly higher in current smokers (3.6 per 1000 person-years, 95%CI: 1.2–10.6) than in former smokers (2.7 per 1000 person-years, 95%CI: 1.3–5.6). However, the incidence was slightly lower in patients with a high total tobacco amount (≥ 800 cigarette-years: 2.4 per 1000 person-years, 95%CI: 0.7–8.7) than in those with a low total tobacco amount (< 800 cigarette-years: 3.0 per 1000 person-years, 95%CI: 1.5–6.3). Patients whose total tobacco amount was unknown had a higher incidence of intracranial hemorrhage (3.4 per 1000 person-years, 95%CI: 0.6–19.1).

In multivariate Cox regression analysis, no significant association was observed between smoking category and the incidence of intracranial hemorrhage. Although the HRs increased from the non-adjusted models to the adjusted models in the former and current smokers, the HRs decreased in patients with a high total tobacco amount (Table IV).

We further analyzed according to age ≥ 65 years and < 65 years. In patients ≥ 65 years old, the incidence of intracranial hemorrhage was similar between all the different smoking categories (Table V), and no significant association was observed between any smoking category and the incidence of intracranial hemorrhage (Table VII). In contrast, in patients < 65 years old, the incidence of intracranial hemorrhage in all categories with smokers was markedly higher than that in non-smokers (Table VI). The risk of current smokers (HR; 15.95, 95%CI: 1.12–227.67) was statistically significant in the full-adjusted model with Cox regression analysis (Table VIII).

Incidence of coronary artery events:

In the total patient population, percutaneous coronary intervention was performed and acute coronary syndrome occurred in 97 and 24 during the observation period of 7,793 and 8,083 person-years (12.4 and 3.0 per 1000 person-years, 95%CI: 10.2–15.2 and 2.0–4.4, Table III), respectively. Different trends were observed in each smoking category between percutaneous coronary intervention and acute coronary syndrome: 1) although the incidence of admission for percutaneous coronary intervention was slightly higher in smokers (13.7 per 1000 person-years, 95%CI: 10.2–18.3) than in non-smokers (11.6 per 1000 person-years, 95%CI: 8.8–15.1), the incidence of acute coronary syndrome was lower in smokers (1.5 per 1000 person-years, 95%CI: 0.6–3.4) than in non-smokers (4.1 per 1000 person-years, 95%CI: 2.6–

---

### Table IV. Multiple Cox Regression Models for Adverse Events

| Variable                        | Non-adjusted Hazard ratio | 95%CI | Age, sex-adjusted Hazard ratio | 95%CI | Full-adjusted Hazard ratio | 95%CI |
|---------------------------------|---------------------------|-------|--------------------------------|-------|---------------------------|-------|
| **Ischemic stroke**             |                           |       |                                |       |                           |       |
| Smokers (versus Non-smokers)    | 0.78                      | 0.46–1.30 | 1.17                      | 0.66–2.07 | 1.09                      | 0.62–1.92 |
| Current and former smokers      |                           |       |                                |       |                           |       |
| Smokers                          | 0.72                      | 0.40–1.28 | 1.02                      | 0.54–1.92 | 0.91                      | 0.48–1.71 |
| Former smokers                  | 0.97                      | 0.43–2.16 | 1.73                      | 0.75–3.99 | 1.85                      | 0.80–4.29 |
| Total tobacco amount (versus Non-smokers) |                   |       |                                |       |                           |       |
| Smokers, total tobacco amount < 800 | 0.55                    | 0.28–1.08 | 0.91                      | 0.45–1.86 | 0.90                      | 0.44–1.83 |
| Smokers, total tobacco amount ≥ 800 | 1.28                   | 0.62–2.64 | 1.82                      | 0.84–3.99 | 1.62                      | 0.74–3.57 |
| Smokers, total tobacco amount unknown | 1.12                | 0.34–3.62 | 1.21                      | 0.57–3.97 | 0.99                      | 0.30–3.24 |
| Intracranial hemorrhage         |                           |       |                                |       |                           |       |
| Smokers (versus Non-smokers)    | 1.20                      | 0.52–2.78 | 1.49                      | 0.60–3.71 | 1.13                      | 0.45–2.82 |
| Current and former smokers      |                           |       |                                |       |                           |       |
| Smokers                          | 1.11                      | 0.43–2.82 | 1.28                      | 0.47–3.46 | 0.89                      | 0.33–2.44 |
| Current smokers                 | 1.49                      | 0.42–5.29 | 2.37                      | 0.64–8.75 | 2.54                      | 0.67–9.56 |
| Total tobacco amount (versus Non-smokers) |                   |       |                                |       |                           |       |
| Smokers, total tobacco amount < 800 | 1.26                | 0.49–3.21 | 1.72                      | 0.64–4.67 | 1.54                      | 0.56–4.26 |
| Smokers, total tobacco amount ≥ 800 | 0.95               | 0.21–4.26 | 1.05                      | 0.22–4.98 | 0.76                      | 0.16–3.66 |
| Smokers, total tobacco amount unknown | 1.47            | 0.19–11.37 | 1.33                      | 0.17–10.38 | 0.62                      | 0.08–4.99 |
| Percutaneous coronary intervention |                       |       |                                |       |                           |       |
| Smokers (versus Non-smokers)    | 1.08                      | 0.73–1.62 | 1.08                      | 0.71–1.65 | 1.29                      | 0.84–1.99 |
| Current and former smokers      |                           |       |                                |       |                           |       |
| Smokers                          | 1.11                      | 0.43–2.82 | 1.28                      | 0.47–3.46 | 0.96                      | 0.35–2.63 |
| Current smokers                 | 1.49                      | 0.42–5.29 | 2.37                      | 0.64–8.75 | 2.62                      | 0.71–9.75 |
| Total tobacco amount (versus Non-smokers) |                   |       |                                |       |                           |       |
| Smokers, total tobacco amount < 800 | 0.78             | 0.47–1.29 | 0.87                      | 0.52–1.46 | 1.10                      | 0.65–1.85 |
| Smokers, total tobacco amount ≥ 800 | 1.99          | 1.17–3.36 | 1.70                      | 0.99–2.93 | 1.56                      | 0.90–2.70 |
| Smokers, total tobacco amount unknown | 1.04        | 0.38–2.88 | 0.82                      | 0.29–2.28 | 0.89                      | 0.32–2.48 |
| Acute coronary syndrome         |                           |       |                                |       |                           |       |
| Smokers (versus Non-smokers)    | 0.33                      | 0.12–0.89 | 0.28                      | 0.10–0.76 | 0.28                      | 0.10–0.77 |
| Current and former smokers      |                           |       |                                |       |                           |       |
| Smokers                          | 0.27                      | 0.08–0.90 | 0.21                      | 0.06–0.71 | 0.21                      | 0.06–0.72 |
| Current smokers                 | 0.54                      | 0.13–2.33 | 0.60                      | 0.14–2.65 | 0.60                      | 0.14–2.66 |
| Total tobacco amount (versus Non-smokers) |                   |       |                                |       |                           |       |
| Smokers, total tobacco amount < 800 | 0.20           | 0.05–0.85 | 0.18                      | 0.04–0.80 | 0.20                      | 0.05–0.89 |
| Smokers, total tobacco amount ≥ 800 | 0.57       | 0.13–2.43 | 0.40                      | 0.09–1.75 | 0.34                      | 0.08–1.50 |
| Smokers, total tobacco amount unknown | 0.72     | 0.10–5.37 | 0.49                      | 0.06–3.65 | 0.47                      | 0.06–3.52 |

CI indicates confidence intervals.
6.4), 2) although the incidence of admission for percutaneous coronary intervention was similar between former smokers (13.7 per 1000 person-years, 95%CI; 9.8–19.1) and current smokers (13.7 per 1000 person-years, 95%CI; 7.6–24.5), the incidence of acute coronary syndrome was slightly higher in current smokers (2.4 per 1000 person-years, 95%CI; 0.7–23.0) than in former smokers (1.2 per 1000 person-years, 95%CI; 0.4–3.4), and 3) the incidences of percutaneous coronary intervention and acute coronary syndrome tended to be higher in patients with a high total tobacco amount than in those with a low amount.

In multivariate Cox regression models, no significant association was observed between smoking category and the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events including coronary artery intervention and acute coronary syndrome in Japanese NVAF patients in a cardiovascular hospital. In the total patient population, no significant difference was observed between the smoking categories for the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events (Tables V-VIII). In multivariate Cox regression models, no significant association was observed between smoking category and the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events including coronary artery intervention and acute coronary syndrome in Japanese NVAF patients in a cardiovascular hospital. In the total patient population, no significant difference was observed between the smoking categories for the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events (Tables V-VIII). In multivariate Cox regression models, no significant association was observed between smoking category and the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events including coronary artery intervention and acute coronary syndrome in Japanese NVAF patients in a cardiovascular hospital. In the total patient population, no significant difference was observed between the smoking categories for the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events (Tables V-VIII). In multivariate Cox regression models, no significant association was observed between smoking category and the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events including coronary artery intervention and acute coronary syndrome in Japanese NVAF patients in a cardiovascular hospital. In the total patient population, no significant difference was observed between the smoking categories for the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events (Tables V-VIII). In multivariate Cox regression models, no significant association was observed between smoking category and the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events including coronary artery intervention and acute coronary syndrome in Japanese NVAF patients in a cardiovascular hospital. In the total patient population, no significant difference was observed between the smoking categories for the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events (Tables V-VIII). In multivariate Cox regression models, no significant association was observed between smoking category and the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events including coronary artery intervention and acute coronary syndrome in Japanese NVAF patients in a cardiovascular hospital. In the total patient population, no significant difference was observed between the smoking categories for the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events (Tables V-VIII). In multivariate Cox regression models, no significant association was observed between smoking category and the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events including coronary artery intervention and acute coronary syndrome in Japanese NVAF patients in a cardiovascular hospital. In the total patient population, no significant difference was observed between the smoking categories for the incidence of ischemic stroke, intracranial hemorrhage, and coronary artery events (Tables V-VIII).
smoking categories and patient outcomes. However, in patients ≥ 65 years old, being a current smoker was significantly associated with the incidence of percutaneous coronary intervention, and marginally significantly associated with the incidence of ischemic stroke: smokers with a total tobacco amount ≥ 800 cigarette-years were marginally significantly associated with the incidence of ischemic stroke. In contrast, in patients < 65 years old, there was a significant association between current smokers and the incidence of intracranial hemorrhage.

Incidence of ischemic stroke: The incidence of ischemic stroke was 7.7 per 1000 person-years in the total patient population, and was slightly lower in smokers (6.8 per 1000 person-years) than in non-smokers (8.5 per 1000 person-years). This result is difficult to understand because previous studies have reported that smoking causes endothelial dysfunction and atherosclerosis, and thus increases ischemic stroke.

Incidence of intracranial hemorrhage: The incidence of intracranial hemorrhage was 2.7 per 1000 person-years in the total patient population, and was similar between smokers (2.6 per 1000 person-years) and non-smokers (2.6 per 1000 person-years). This result is again difficult to understand because several studies have reported that smoking increases the risk of intracranial hemorrhage via an increase in blood pressure. However, it may be understandable when we consider there are several confounders. First, when the smokers were separated into former and current smokers, the incidence was slightly higher in current smokers than in former smokers (3.6 versus 2.7 per 1000 person-years). Second, although their crude HRs were similar, they were inevitably different after adjustment for various cofactors (HRs, 2.54 versus 0.89 in the full-adjusted model), suggesting that differences in patient backgrounds (ie, age) may mask the true risk of smoking on ischemic stroke.

Table VI. Incidences of Adverse Events According to Smoking Status (Age < 65 years)

| Variable | No. of events | Person-years | Incidence rate (per 1000 person-years) | 95% confidence interval |
|----------|---------------|--------------|----------------------------------------|-------------------------|
| Ischemic stroke | | | | |
| Total | 20 | 4242 | 4.7 | 3.1–7.3 |
| Non-smoker | 11 | 2206 | 5.0 | 2.8–8.9 |
| Smoker | 9 | 2036 | 4.4 | 2.3–8.4 |
| Former | 6 | 1447 | 4.1 | 1.9–9.0 |
| Current | 3 | 589 | 5.1 | 1.7–15.0 |
| Total tobacco amount < 800 cigarette-years | 5 | 1507 | 3.3 | 1.4–7.8 |
| Total tobacco amount ≥ 800 cigarette-years | 2 | 398 | 5.0 | 1.4–18.3 |
| Total tobacco amount unknown | 2 | 131 | 15.3 | 4.2–55.7 |
| Intracranial hemorrhage | | | | |
| Total | 4 | 4283 | 0.9 | 0.4–2.4 |
| Non-smoker | 1 | 2231 | 0.4 | 0.1–2.5 |
| Smoker | 3 | 2052 | 1.5 | 0.5–4.3 |
| Former | 1 | 1463 | 0.7 | 0.1–3.9 |
| Current | 2 | 589 | 3.4 | 0.9–12.4 |
| Total tobacco amount < 800 cigarette-years | 2 | 1517 | 1.3 | 0.4–4.8 |
| Total tobacco amount ≥ 800 cigarette-years | 1 | 401 | 2.5 | 0.4–14.1 |
| Total tobacco amount unknown | 0 | 133 | 0.0 | 0.0–28.9 |
| Percutaneous coronary intervention | | | | |
| Total | 21 | 4198 | 5.0 | 3.3–7.6 |
| Non-smoker | 12 | 2177 | 5.5 | 3.2–9.6 |
| Smoker | 9 | 2021 | 4.5 | 2.3–8.5 |
| Former | 7 | 1437 | 4.9 | 2.4–10.1 |
| Current | 2 | 584 | 3.4 | 0.9–12.5 |
| Total tobacco amount < 800 cigarette-years | 4 | 1508 | 2.7 | 1.0–6.8 |
| Total tobacco amount ≥ 800 cigarette-years | 5 | 379 | 13.2 | 5.6–30.9 |
| Total tobacco amount unknown | 0 | 133 | 0.0 | 0.0–28.9 |
| Acute coronary syndrome | | | | |
| Total | 15 | 6533 | 2.3 | 1.4–3.8 |
| Non-smoker | 14 | 3725 | 3.8 | 2.2–6.3 |
| Smoker | 1 | 2808 | 0.4 | 0.1–2.0 |
| Former | 1 | 2072 | 0.5 | 0.1–2.7 |
| Current | 0 | 736 | 0.0 | 0.0–5.2 |
| Total tobacco amount < 800 cigarette-years | 0 | 1966 | 0.0 | 0.0–2.0 |
| Total tobacco amount ≥ 800 cigarette-years | 1 | 616 | 1.6 | 0.3–9.2 |
| Total tobacco amount unknown | 0 | 226 | 0.0 | 0.0–17 |
Incidence of coronary artery events: It is important to reduce the risk. Smoking is associated with intracranial hemorrhage, and quitting smoking is very important. The continuation of smoking increases intracranial hemorrhage, and therefore, we believe that quitting smoking is very important. In young patients, the effect of current smoking on intracranial hemorrhage was enhanced by antiplatelet agents by cigarettes. When we extracted patients ≥ 65 years old, the incidence of percutaneous coronary intervention was 1.5 times higher in current smokers than in former smokers and patients with a total tobacco amount ≥ 800 cigarette-years. Their effects were significant in the full-adjusted models with Cox regression analysis, supporting the concept that the confounding of these confounding factors in young patients may mask the true risk of smoking for promoting coronary atherosclerosis.

### Table VII. Multiple Cox Regression Models for Adverse Events (Age ≥ 65 years)

| Variable                  | Non-adjusted Hazard ratio | 95%CI | Age, sex-adjusted Hazard ratio | 95%CI | Full-adjusted Hazard ratio | 95%CI |
|---------------------------|---------------------------|-------|--------------------------------|-------|----------------------------|-------|
| **Ischemic stroke**       |                           |       |                                |       |                            |       |
| Smokers (versus Non-smokers) | 0.86                      | 0.45–1.64 | 1.36                          | 0.67–2.79 | 1.25                      | 0.61–2.58 |
| Current smokers           | 0.75                      | 0.36–1.54 | 1.15                          | 0.52–2.56 | 1.01                      | 0.46–2.25 |
| Former smokers            | 1.42                      | 0.50–4.05 | 2.25                          | 0.77–6.54 | 2.49                      | 0.85–7.28 |
| Total tobacco amount      |                           |       |                                |       |                            |       |
| Smokers, total tobacco amount < 800 | 0.65                  | 0.27–1.57 | 1.05                          | 0.41–2.69 | 1.07                      | 0.42–2.76 |
| Smokers, total tobacco amount ≥ 800 | 1.43                     | 0.63–3.28 | 2.82                          | 1.11–7.16 | 2.43                      | 0.95–6.27 |
| Smokers, total tobacco amount unknown | 0.48                   | 0.06–3.49 | 0.60                          | 0.08–4.46 | 0.46                      | 0.06–3.47 |
| **Intracranial hemorrhage** |                           |       |                                |       |                            |       |
| Smokers (versus Non-smokers) | 1.15                      | 0.44–2.97 | 1.13                          | 0.41–3.11 | 0.82                      | 0.29–2.28 |
| Current smokers           | 1.20                      | 0.44–3.25 | 1.15                          | 0.40–3.35 | 0.79                      | 0.27–3.21 |
| Former smokers            | 0.92                      | 0.12–7.14 | 0.99                          | 0.12–7.89 | 1.06                      | 0.13–8.57 |
| Total tobacco amount      |                           |       |                                |       |                            |       |
| Smokers, total tobacco amount < 800 | 1.47                    | 0.51–4.22 | 1.41                          | 0.46–4.30 | 1.31                      | 0.42–4.04 |
| Smokers, total tobacco amount ≥ 800 | 0.51                     | 0.07–3.94 | 0.50                          | 0.06–4.05 | 0.34                      | 0.04–2.77 |
| Smokers, total tobacco amount unknown | 1.41                   | 0.18–10.99 | 1.32                          | 0.17–10.42 | 0.53                      | 0.07–4.39 |
| **Percutaneous coronary intervention** |                           |       |                                |       |                            |       |
| Smokers (versus Non-smokers) | 1.52                      | 0.97–2.38 | 1.27                          | 0.79–2.05 | 1.54                      | 0.94–2.52 |
| Current smokers           | 1.38                      | 0.85–2.24 | 1.13                          | 0.67–1.89 | 1.40                      | 0.83–2.36 |
| Former smokers            | 2.19                      | 1.06–4.51 | 2.00                          | 0.95–4.19 | 2.37                      | 1.08–5.22 |
| Total tobacco amount      |                           |       |                                |       |                            |       |
| Smokers, total tobacco amount < 800 | 1.34                    | 0.77–2.34 | 1.13                          | 0.63–2.02 | 1.65                      | 0.90–3.01 |
| Smokers, total tobacco amount ≥ 800 | 1.95                     | 1.06–3.59 | 1.63                          | 0.86–3.09 | 1.67                      | 0.87–3.21 |
| Smokers, total tobacco amount unknown | 1.27                   | 0.45–3.55 | 1.06                          | 0.38–2.99 | 1.04                      | 0.37–2.93 |
| **Acute coronary syndrome** |                           |       |                                |       |                            |       |
| Smokers (versus Non-smokers) | 0.56                      | 0.20–1.54 | 0.38                          | 0.14–1.07 | 0.39                      | 0.14–1.10 |
| Current smokers           | 0.41                      | 0.12–1.40 | 0.27                          | 0.08–0.95 | 0.28                      | 0.08–0.97 |
| Former smokers            | 1.28                      | 0.29–5.60 | 1.01                          | 0.23–4.53 | 1.12                      | 0.24–5.19 |
| Total tobacco amount      |                           |       |                                |       |                            |       |
| Smokers, total tobacco amount < 800 | 0.40                    | 0.09–1.73 | 0.27                          | 0.06–1.20 | 0.31                      | 0.07–1.40 |
| Smokers, total tobacco amount ≥ 800 | 0.74                     | 0.17–3.24 | 0.50                          | 0.11–2.23 | 0.46                      | 0.10–2.05 |
| Smokers, total tobacco amount unknown | 0.85                   | 0.11–6.41 | 0.59                          | 0.08–4.47 | 0.49                      | 0.06–3.75 |

CI indicates confidence intervals.

we extracted patients < 65 years old, the risk of intracranial hemorrhage due to smoking, especially current smoking (continuing to smoke), was inevitably high. In young patients, the effect of current smoking on intracranial hemorrhage was statistically significant irrespective of the small number of events, indicating the strong impact in this age stratification. Meanwhile, although the reason is unclear, the effect of current smoking was not significant in patients ≥ 65 years old. Considering these confounding factors, we believe our results support the concept that the continuation of smoking increases intracranial hemorrhage, and inversely, quitting smoking is very important to reduce the risk.

**Incidence of coronary artery events:** The incidences of admission for percutaneous coronary intervention and acute coronary syndrome were 12.4 and 3.0 per 1000 person-years in the total patient population, respectively. The tendency of the relationship with smoking was opposite between these 2 events: the incidence of percutaneous coronary intervention was slightly higher in smokers than in non-smokers (13.7 versus 11.6 per 1000 person-years), whereas that of acute coronary syndrome was much lower in smokers than in non-smokers (1.5 versus 4.1 per 1000 person-years). Although the reasons for the discrepancy are unclear, such paradoxical evidence regarding acute coronary syndrome has been identified in non-AF subjects in another hospital-based cohort in Japan, suggesting a younger age is a confounding factor and a possible enhanced effect of antiplatelet agents by cigarettes. When we extracted patients ≥ 65 years old, the incidence of percutaneous coronary intervention was 1.5 times higher in current smokers and patients with a total tobacco amount ≥ 800 cigarette-years than in former smokers and patients with a total tobacco amount < 800 cigarette-years, respectively. Their effects were significant in the full-adjusted models with Cox regression analysis, supporting the concept that the confounding of younger patients may mask the true risk of smoking for promoting coronary atherosclerosis. Much evidence has clarified the adverse effects of smoking on atherosclerotic pathogenesis, including causing increases in systemic inflammation and oxidative stress, and consequent endothelial dysfunction and thrombosis formation, and therefore, we believe that the apparent paradoxical inverse association between smoking and acute coronary syndrome in our cohort and others does not have any essential meaning for the prevention of coronary artery diseases. It should be emphasized that smoking is not encouraged by the apparent negative associations in our data in the total population.
Study limitations: The present study failed to identify any statistically significant effects of smoking on the prognosis of NVAF patients using a single center cohort in a cardiovascular hospital. The inconsistency of the risks of smoking on ischemic stroke that were significant in previous reports and insignificant in our data may derive from the difference in age, which was approximately 10 years younger in our cohort than in previous reports. Actually, in patients ≥ 65 years old, a significant risk of smoking on the incidence of ischemic stroke and percutaneous coronary intervention was observed. From another point of view, the relatively small number of events in ischemic stroke, intracranial hemorrhage, and coronary artery events may be another reason for the negative effect of smoking due to a lack of statistical power. Because the information regarding smoking in the present study was based on data obtained at registration, the temporal changes in smoking were not taken into consideration. Patients in a cardiovascular hospital like ours may be educated to quit or reduce smoking, and therefore the true effects of smoking on the prognosis may be underestimated.

Conclusions: Age seemed to be one of the contributors to determine the effects of smoking on cardiovascular events in our NVAF patients. In elderly patients, continuing to smoke was associated with promoting atherosclerosis or thromboembolism, whereas in young patients it was associated with bleeding.

Acknowledgments

We thank Shiro Ueda and Nobuko Ueda of Medical Edge Co., Ltd. for assembling the database using the Clinical Study Supporting System, and Ineko Hayakawa, Hiroaki Arai, and Hirokazu Aoki for the data management and system administration.

Disclosure

Conflict of interests: Dr. Suzuki received research funding and remuneration from Boehringer Ingelheim. Dr. Yamashita received research funding from Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Boehringer Ingelheim, Daiichi-Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Eisai, and Ono Pharmaceutical.
REFERENCES

1. Wolf PA, Mitchell JB, Baker CS, Kannel WB, Agostino RBD. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998; 158: 229-34.

2. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003; 107: 2920-5.

3. Okamura K, Komatsu T, Yamashita T, et al. Time in the therapeutic range during warfarin therapy in Japanese patients with nonvalvular atrial fibrillation. Circ J 2011; 75: 2087-94.

4. Ogawa S, Koretsune Y, Yasaka M, et al. Antithrombotic therapy in atrial fibrillation: evaluation and positioning of new oral anticoagulant agents. Circ J 2011; 75: 1539-47. (Review)

5. Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Ori-gasa H. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation. Circ J 2011; 75: 1328-33.

6. Kabo M, Kiyohara Y, Ninomiya T, et al. Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. Neurology 2006; 66: 1539-44.

7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007; 146: 857-67.

8. Albertsen IE, Overvad TF, Lip GY, Larsen TB. Smoking, atrial fibrillation, and ischemic stroke: a confluence of epidemics. Curr Opin Cardiol 2015; 30: 512-7. (Review)

9. Tsai CF, Anderson N, Thomas B, Sudlow CL. Risk factors for ischemic stroke and its subtypes in Chinese vs. Caucasians: Systematic review and meta-analysis. Int J Stroke 2015; 10: 485-93. (Review)

10. Pandey MR. Tobacco smoking and hypertension. J Indian Med Assoc 1999; 97: 367-9.

11. Halimi JM, Giraudou B, Vol S, Cases E, Nivet H, Tichet J. The risk of hypertension in men: direct and indirect effects of chronic cigarette smoke exposure. Arterioscler Thromb Vasc Biol 2013; 33: 1460-7. (Review)

12. Vedres A, Giannarelli C, Neves MF, Taddei S, Ghidoni L. Cigarette smoking and hypertension. Curr Pharm Des 2010; 16: 2518-25. (Review)

13. Toyoda K, Yasaka M, Uchiyama S, et al. Blood pressure levels and bleeding events during antithrombotic therapy: the Bleeding with Antithrombotic Therapy (BAT) Study. Stroke 2010; 41: 1440-4.

14. Arima H, Anderson C, Omae T, et al. Effects of blood pressure lowering on intracranial and extracranial bleeding in patients on antithrombotic therapy: the PROGRESS trial. Stroke 2012; 43: 1675-7.