



The Impact of Smoking on Thromboembolism and Mortality in Patients With Incident Atrial Fibrillation

Insights From the Danish Diet, Cancer, and Health Study

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Background: Smoking and atrial fibrillation (AF) are major health problems worldwide and are responsible for substantial health-care costs. Our aim was to investigate whether smoking impacts the risk of stroke and death in patients with AF. To test this hypothesis, we analyzed data from a large Danish cohort: the Diet, Cancer, and Health study.

Methods: This was a cohort study of 57,053 people (27,178 men; 29,876 women) aged 50 to 64 years. The risk of thromboembolism (ischemic stroke/arterial thromboembolism) or death according to smoking habits among 3,161 patients with incident AF (mean age, 66.9 years; 2,032 men, 1,129 women) was assessed using Cox proportional hazard models after a median follow-up of 4.9 years.

Results: Of those with AF, 34% were current smokers and 37% former smokers. After adjustment for vitamin K antagonist treatment, the hazard ratios (HRs) (95% CI) of thromboembolism or death were 3.13 (1.72-6.37) and 2.73 (2.02-3.70) among women and men who currently were heavy smokers (> 25 g/d), respectively. The associations remained after adjustment for well-established risk factors with HRs of 3.64 (1.88-7.07) and 2.17 (1.59-2.95) among women and men, respectively. In a sensitivity analysis, smoking was still strongly associated with thromboembolism or death after censoring people with a cancer diagnosis during follow-up.

Conclusions: Smoking is associated with a higher risk of thromboembolism or death in patients with AF even after adjusting for well-recognized risk factors used in stroke risk stratification schemes. The associations may be modified by sex, as the associations were strongest among women.

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Abbreviations: AF = atrial fibrillation; CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category; DCH = Diet, Cancer, and Health; HR = hazard ratio; ICD = *International Classification of Diseases*; IDI = integrated discrimination improvement; NRI = net reclassification improvement; VKA = vitamin K antagonist

Smoking is a dominant health hazard worldwide and responsible for major health-care costs.¹ Indeed, smoking is associated with a higher incidence of vascular disease mortality² and contributes independently to the risk of stroke.³⁻⁵ Furthermore, smoking has been associated with higher risk of atrial fibrillation (AF).⁶⁻⁹

AF is the most common cardiac arrhythmia, with a lifetime risk for development of one in four.¹⁰ AF is an independent risk factor for stroke, thromboembolism, and death.^{8,11} The risk of thromboembolism and stroke in patients with AF is not homogenous and var-

ies according to the presence of common stroke risk factors.¹²⁻¹⁴

The few prospective studies examining smoking as a risk factor for stroke in patients with AF have been restricted to dichotomous analyses of smoking habits and have revealed inconsistent results.¹⁵⁻¹⁹ Hence, smoking has not been comprehensively assessed as a risk factor for adverse outcomes among patients with AF.

We hypothesized that smoking would be associated with a higher risk of thromboembolism and death among patients with incident AF. To test this hypothesis,

we analyzed data from a large Danish prospective cohort, the Diet, Cancer, and Health (DCH) study, to assess the risk of thromboembolism and/or death among incident AF cases according to smoking status.

MATERIAL AND METHODS

The DCH cohort was established between 1993 and 1997. The study design has been reported in detail elsewhere.²⁰ The primary objective of this prospective study was to investigate the etiologic role of diet and lifestyle in the development of cancer; 27,178 men and 29,876 women were enrolled. The participants were aged 50 to 64 years and were without a cancer diagnosis registered in the Danish Cancer Registry²¹ at baseline. The DCH cohort has detailed information on demographics, existing comorbidities, and individual risk factors, including detailed information on smoking habits.

Case Finding

The DCH study subjects were linked to the National Patient Register²¹ dating back to 1977, using the Danish Personal Identification number. This is a unique and national identification number, which is part of the personal information stored in the Civil Registration System. The study population in this study included participants who developed incident AF during follow-up: April 1995 until December 30, 2009.

Codes from the *International Classification of Diseases* (ICD)-10 were used to extract admissions for AF. AF and atrial flutter have one ICD-10 code (I48). Therefore, some atrial flutter cases have been included in the present study.

Exposure

The exposure variable studied was smoking. Information on tobacco consumption was obtained from a standardized questionnaire at baseline and at 5 years after inclusion. In this study, the information most recent and prior to the AF diagnosis was obtained. Current tobacco consumption in grams per day was calculated by equating a cigarette with 1 g, a cheroot or pipe with 3 g, and a cigar

with 4.5 g of tobacco. Participants were arbitrarily categorized into four groups: nonsmokers, former smokers, moderate current smokers (1-25 g/d), and heavy current smokers (> 25 g/d). The exposure level for current smokers was also investigated as a continuous variable.

Information on relevant baseline characteristics and comorbid variables was found in the National Patient Register using ICD and Anatomical Therapeutic Chemical classification system codes (e-Table 1). In Denmark, ICD-8 was used until 1995, after which ICD-10 was used.

Medical treatment status was obtained by evaluating the prescription pattern obtained from the Danish National Prescription Registry²¹ of medics within the specified Anatomical Therapeutic Chemical classification system group. The treatment period was initiated at time of the first prescription and was considered to proceed if the next prescription was within 1 year or not exceeding the previous period length by a factor 1.5. The treatment period was assumed to continue after the last prescription date according to the number of daily doses in the last package, as estimated from the previous period.

Outcomes

We defined our primary outcome as the composite of thromboembolism or death during follow-up, with thromboembolism comprising ischemic stroke and arterial thromboembolism. Separate analyses were performed for the components of the primary composite end point, namely, thromboembolism and death. Information on emigration or death was available from the National Civil Registration System. Incident cases of ischemic stroke and arterial thromboembolism were found in the National Patient Register.

Statistical Methods

Associations between tobacco exposure and risk of event were reported in terms of incidence and subsequently analyzed by Cox proportional regression analyses using time since AF as the underlying time axis. End of study or emigration was considered as outcome independent censoring. For the secondary outcome event thrombosis, death was considered as a censoring event but also as a competing risk.

All analyses were stratified by sex. Since oral anticoagulation therapy significantly reduces stroke/thromboembolism and death in patients with AF,²² vitamin K antagonist (VKA) treatment was incorporated as a time-varying indicator for being in treatment in all analyses using the counting-process approach.²³ The multivariate analyses were adjusted for well-known risk factors included in established guidelines: congestive heart failure, hypertension, diabetes, prior stroke/thromboembolism, vascular disease, and age.^{12,13} The risk factors were derived at the time of AF diagnosis and assumed constant throughout time at risk. Age was included as a cubic spline with four knots.²⁴ The dose-response for tobacco exposure (dose in g/d) was analyzed by allowing the exposure of the current smokers to be modeled using a natural cubic spline with four knots. The results are presented graphically and reported as hazard ratios (HRs) with 95% CIs.

The associations among the low-risk participants, defined as men with a CHA₂DS₂-VASc (congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category) score of 0 and women with a score of 1, were analyzed by a Cox regression model adjusted for VKA treatment and age. A sensitivity-analysis was undertaken to see if the association between smoking and event was primarily driven by death because of cancer; therefore, all death recordings for patients with a cancer diagnosis during follow-up were treated as a censoring event. A similar

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