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Effect of Active Smoking on Comparative Efficacy of Antithrombotic Therapy in Patients With Atrial Fibrillation

The Loire Valley Atrial Fibrillation Project

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BACKGROUND: Active smoking is associated with elevated thrombotic risk. Smoking status has recently been incorporated into the SAMe-TT_2R_2 (sex female, age < 60 years, medical history [more than two comorbidities], treatment [interacting drugs, eg, amiodarone for rhythm control], tobacco use [doubled], race [doubled]) score that can help predict poor international normalized ratio control in patients with atrial fibrillation (AF) treated with vitamin K antagonists (VKAs). The clinical benefit of antiplatelet therapy (APT) has been seen primarily in smokers. We hypothesized that active smoking may differently influence the risks of stroke and bleeding in patients with AF treated with VKAs or with APT.

METHODS: We examined the clinical course of 7,809 consecutive patients with AF seen between 2000 and 2010. Outcomes in patients who were active smokers were compared with those in other patients.

RESULTS: Among 7,809 patients with AF, 1,034 (13%) were active smokers. APT was prescribed on an individual basis for 2,761 patients (35%) and VKAs for 4,534 (57%). After a follow-up of 929 ± 1,082 days (median = 463 days, interquartile range = 1,564 days), smoking was not independently associated with a higher risk of stroke/thromboembolic event in patients with AF (hazard ratio [HR], 0.95; 95% CI, 0.78-1.22; $P = .66$). On multivariate analysis, smoking was independently associated with a worse prognosis for the risk of severe bleeding (HR, 1.23; 95% CI, 1.01-1.49; $P = .04$) and for the risk of major Bleeding Academic Research Consortium bleeding (HR, 1.40; 95% CI, 1.02-1.90; $P = .03$). Smoking was independently associated with a higher risk of bleeding in patients treated with VKAs (HR, 1.32; 95% CI, 1.04-1.67; $P = .02$), whereas the risk was nonsignificant in patients treated with APT (HR, 1.28; 95% CI, 0.94-1.74; $P = .11$).

CONCLUSIONS: In AF, there was a higher risk of severe bleeding in smokers, mainly in those treated with VKAs.

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ABBREVIATIONS: AF = atrial fibrillation; APT = antiplatelet therapy; BARC = Bleeding Academic Research Consortium; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 years, sex category (female); HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs (antiplatelet drugs or nonsteroidal antiinflammatory drugs)/alcohol excess concomitantly; HR = hazard ratio; INR = international normalized ratio; SAMe-TT_2R_2 = sex female, age < 60 years, medical history (more than two comorbidities), treatment (interacting drugs, eg, amiodarone for rhythm control), tobacco use (doubled), race (doubled); TTR = time in therapeutic range; VKA = vitamin K antagonist

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Atrial fibrillation (AF) confers a fivefold increased risk of stroke, and 15% to 20% of all strokes are caused by AF. Importantly, mortality, morbidity, and economic burden from stroke complicating AF are particularly high. The European Society of Cardiology guidelines recommend the use of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$ 75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 years, and sex category [female]) score to evaluate the individual thromboembolic risk associated with AF and to determine the risk to benefit ratio of antithrombotic therapy.[1,2] Until recently, the latter essentially referred to oral anticoagulants (mainly vitamin K antagonists [VKAs]), or antiplatelet therapy (APT), usually aspirin.[1,3] The main adverse effect of antithrombotic therapy is bleeding and, as recommended by the European Society of Cardiology guidelines, this risk may be assessed using the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [$>$ 65 years], drugs [antiplatelet drugs or nonsteroidal antiinflammatory drugs]/alcohol excess concomitantly) score.[1,4]

Active smoking is a frequent cardiovascular risk factor usually associated with a higher risk of thrombotic events. Smoking independently influences poor international normalized ratio (INR) control and has been incorporated into a simple score (the SAMe-TT_2R_2 [sex female, age $<$ 60 years, medical history (more than two comorbidities), treatment (interacting drugs, eg, amiodarone for rhythm control), tobacco use (doubled), race (doubled)] score) in patients with AF to predict the likelihood of good anticoagulation control in a patient initiated on VKAs.[5] Moreover, the clinical benefit of clopidogrel in reducing myocardial infarction and stroke in randomized clinical trials has been seen primarily in smokers, with little benefit seen among nonsmokers.[6] Smoking status could, therefore, expose patients treated for AF to an excess risk of thromboembolic events linked to "low efficacy of their antithrombotic treatment" and/or an excess risk of bleeding complications associated with a "larger efficacy of their antithrombotic treatment." In the current study, we investigated whether active smoking would differently influence the risks of stroke and bleeding in patients with AF treated with VKAs or with APT.

Materials and Methods

We included all patients with a diagnosis of AF, atrial flutter, or both seen in the cardiology department of the Centre Hospitalier Universitaire Trousseau, Tours, France between January 2000 and December 2010. Patient characteristics were obtained from the records of the institution's computerized codification system for each patient. Extensive information on date of admission, discharge, diagnosis, clinical presentation, comorbidities, medication, and subsequent hospitalization were collected.

For each patient, the thromboembolic risk was estimated using the CHA_2DS_2-VASc score and the hemorrhagic risk using the HAS-BLED bleeding risk score. The SAMe-TT_2R_2 score was used to predict poor INR control in patients with AF treated with VKAs. The SAMe-TT_2R_2 score was calculated as the sum of points after the addition of one point each for female sex, age $<$ 60 years, medical history of more than two comorbidities (from among hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease), treatment (interacting drugs [eg, amiodarone for rhythm control]), and two points each for tobacco use and nonwhite race. Because recording a patient's race is not allowed in any electronic file in France, the last item was actually not included in the addition, but the local population was essentially white. Patients with a SAMe-TT_2R_2 score of 0 to 2 were deemed to have low-moderate risk and those with a score $>$ 2 to have a high risk of poor INR control with a VKA.[5] We also calculated the CHA_2DS_2-VASc score (one point each for a history of heart failure, a history of hypertension, age 65 to 75 years, the presence of diabetes or vascular disease, and sex category [female]; two points for a prior stroke or transient ischemic attack or age $\geq$ 75 years)[2] and the HAS-BLED bleeding risk score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [$>$ 65 years], drugs/alcohol concomitantly) to assess bleeding risk, where a score of $\geq$ 3 indicates high risk.[4]

Information on stroke, thromboembolism, and bleeding events was recorded whenever documented within the institution, which includes a total of four hospitals covering all specialties, and was obtained by searching in the medical computerized database. Severe bleeding was defined as a decrease of $>$ 5.0 g/dL in the blood hemoglobin level (including the period around the coronary interventional procedure), the need for transfusion of one or more units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage, or any combination of these events. We also considered major bleedings, using the Bleeding Academic Research Consortium (BARC) bleeding definitions: intracranial hemorrhage, intraocular compromising vision, overt bleeding plus hemoglobin drop of $>$ 5 g/dL, tamponade, bleeding requiring surgical or percutaneous intervention for control (excluding dental/nose/skin/hemorrhoids) or inotropes (BARC type 3A), any transfusion with overt bleeding, overt bleeding plus hemoglobin drop of 3 to 5 g/dL (BARC type 3B), or fatal bleeding.[7,8] Finally, we considered separately the GI location of bleeding because smoking is a known risk factor for GI bleeding.

The Centre Hospitalier Regional et Universitaire de Tours serves a population of approximately 400,000 and is the only public institution in an area of around 4,000 km^2. Patients were followed up for stroke and thromboembolic and bleeding events. In addition, deaths were identified using an online search tool dedicated to local news, covering an area of 35,000 km^2 (http://nrco.lanouvellerepublique.fr/dossiers/necro/index.php).The outcomes in patients with active smoking were compared with those in other patients.[9]

Statistical Analysis

Patients' characteristics were reported as percentages or means $\pm$ SD. Comparisons between groups were made using χ^2 tests to compare

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