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The Impact of Associated Diabetic Retinopathy on Stroke and Severe Bleeding Risk in Diabetic Patients With Atrial Fibrillation

The Loire Valley Atrial Fibrillation Project

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BACKGROUND: Diabetes mellitus is recognized as a stroke risk factor in atrial fibrillation (AF). Patients with diabetes with retinopathy have an increased risk for systemic cardiovascular complications, and severe diabetic retinopathy predisposes to ocular bleeding. We hypothesized that patients with diabetes, retinopathy, and AF have increased stroke/thromboembolism (TE) and severe bleeding risks when compared with patients with diabetes and AF who do not have retinopathy or to patients with AF and without diabetes.

METHODS: We tested our hypothesis in a large "real-world" cohort of individuals with AF from the Loire Valley Atrial Fibrillation project.

RESULTS: Of 8,962 patients with AF in our dataset, 1,409 (16%) had documented diabetes mellitus. Of these, 163 (1.8% of the whole cohort) were patients with diabetic retinopathy. After a follow-up of 31 ± 36 months, when compared with patients without diabetes, the risk of stroke/TE in patients with diabetes with no retinopathy increased 1.3-fold (relative risk [RR], 1.30; 95% CI, 1.07-1.59; $P = .01$); in patients with diabetes with retinopathy, the risk of stroke/TE was increased 1.58-fold (RR, 1.58; 95% CI, 1.07-2.32; $P = .02$). There was no significant difference when patients with diabetes with no retinopathy were compared with patients with diabetes with retinopathy (RR, 1.21; 95% CI, 0.80-1.84; $P = .37$). A similar pattern was seen for mortality and severe bleeding. On multivariate analysis, the presence of diabetic retinopathy did not emerge as an independent predictor for stroke/TE or severe bleeding.

CONCLUSIONS: Crude rates of stroke/TE increased in a stepwise fashion when patients without diabetes and with AF were compared with patients with diabetes with no retinopathy and patients with diabetes with retinopathy. However, we have shown for the first time, to our knowledge, that the presence of diabetic retinopathy did not emerge as an independent predictor for stroke/TE or severe bleeding on multivariate analysis. CHEST 2015; 147(4):1103-1110

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ABBREVIATIONS: AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke, or transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 years, and 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); RR = relative risk; TE = thromboembolism

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Atrial fibrillation (AF) confers a fivefold increase in stroke overall, but this risk is not homogeneous and is dependent upon the presence of one or more risk factors in combination with AF.[1] Individual stroke risk factors do not necessarily carry a uniform risk weight, and the presence of more "severe" disease with a particular stroke risk factor may confer added weight to stroke risk. For example, hypertension contributes to stroke risk in patients with AF, and the risk is increased with higher quartiles of BP such that those patients with uncontrolled BP have higher risks for stroke and thromboembolism (TE).[2]

Diabetes mellitus is recognized as a stroke risk factor in AF, scoring one point on the $CHADS_2$ (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, prior stroke, or transient ischemic attack) or 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]) scores.[3] However, diabetes is not a homogeneous entity, and the presence of associated target-organ damage (eg, retinopathy, nephropathy, or neuropathy) indicates more advanced or severe disease.[4,5] Given the association with visual loss, patients with diabetes with significant retinopathy are often managed by ophthalmologists, and, indeed, many such patients have an increased risk for systemic cardiovascular complications.[4,5] Also, diabetic retinopathy predisposes to ocular bleeding, and one concern is the increased risk of severe bleeding among patients with AF, especially GI bleedings, if oral anticoagulation therapy is used.[6]

We hypothesized that patients with diabetes with retinopathy and AF have added stroke/TE and severe bleeding risks in AF, when compared with patients with diabetes and AF but no retinopathy or to patients with AF and without diabetes. We tested the hypothesis in a large "real-world" cohort of individuals with AF from the Loire Valley Atrial Fibrillation project.

Materials and Methods

Study Population

The methods of the Loire Valley Atrial Fibrillation Project, which is based at the Centre Hospitalier Régional et Universitaire in Tours, France, have been previously reported.[7] The institution includes four hospitals covering all medical and surgical specialties and is the only public institution in an area of around 4,000 km^2, serving approximately 400,000 inhabitants. All patients diagnosed with nonvalvular AF or atrial flutter by the Cardiology Department between 2000 and 2010 were identified.[7] Patients with valvular AF were excluded. Treatment at discharge was obtained by screening hospitalization reports, and information on comorbidities was obtained from the computerized coding system. Patients were followed from the first record of nonvalvular AF after January 1, 2000 (ie, index date) up to the latest data collection at the time of study (December 2010).

Diabetes mellitus, with and without retinopathy, was defined from clinical history or medical records. For each patient, the $CHADS_2$[8] and CHA_2DS_2-VASc[9] scores were calculated. The $CHADS_2$ score was the sum of points obtained after adding one point for congestive heart failure, hypertension, age $\geq$ 75 years, and diabetes, and two points for previous stroke or TE.[9] The CHA_2DS_2-VASc score was the sum of points after adding one point for congestive heart failure, hypertension, diabetes, vascular disease (including history of coronary, cerebrovascular or peripheral vascular disease), age 65 to 74 years, and female sex, and two points for previous stroke or TE and age $\geq$ 75 years.[9] According to the two risk scores, patients with a score of 0 on either schema were considered as at low risk, 1 as at intermediate risk, and $\geq$ 2 as at high risk for stroke and TE.

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 is a validated scoring system for bleeding risk stratification in patients with AF.[10] For each patient, the HAS-BLED score was also calculated as the sum of the points obtained after adding one point for the presence of each individual factor. Patients with HAS-BLED score of 0 to 2 were deemed to have low bleeding risk and those with a HAS-BLED score of $\geq$ 3 were classified as at high bleeding risk.

During follow-up, information on outcomes of TE, that is, stroke (ischemic or hemorrhagic), transient ischemic attack, severe bleeding, and mortality, were recorded. Severe bleeding was defined as a decrease in the blood hemoglobin level of > 5.0 g/dL (including the period around the coronary interventional procedure), the need for transfusion of one or more unit of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage, or any combination of these events.

Statistical Analysis

Risk factors were investigated by Cox regression. Baseline characteristics were determined based on the presence of diabetic retinopathy or not, and differences were investigated using the χ^2 test for categorical covariates and Kruskal-Wallis test for continuous covariates.

Event rates of stroke/TE were calculated for all patients. The risk associated with diabetes with or without retinopathy was estimated in Cox proportional-hazard models. Both univariate and multivariate (including all the CHA_2DS_2-VASc risk factors) Cox regression models were applied. A two-sided P value < .05 was considered statistically significant. All analyses were performed with SPSS statistical software, version 18.0 (IBM Corp).

Ethics Approval

The study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) on December 7, 2010, and registered as a clinical audit. Ethical review, therefore, was not required. Patient consent was not sought. Patient data were used only to facilitate the cross referencing of data sources and records were otherwise anonymous. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care.