CLINICAL RESEARCH STUDY

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Early Cardiovascular Disease After the Diagnosis of Systemic Sclerosis

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ABSTRACT

PURPOSE: The purpose of this study is to assess risk and time trends of newly recorded myocardial infarction and stroke in cases with systemic sclerosis.

METHODS: We conducted a matched incident cohort study (1996-2010) among patients satisfying at least one of the following: 1) diagnosis of systemic sclerosis on at least 2 visits within a 2-year period by a nonrheumatologist physician; or 2) diagnosis of systemic sclerosis on at least one visit by a rheumatologist or from hospitalization; as well as receiving no prior systemic sclerosis diagnosis between 1990 and 1995. Ten controls were matched by birth year, sex, and calendar year of exposure from the general population for each case. Incident myocardial infarction, stroke, and myocardial infarction or stroke was recorded from hospital or death certificates. We estimated incidence rate ratios and hazard ratios (HRs) after adjusting for confounders.

RESULTS: Among 1239 individuals with systemic sclerosis and no history of myocardial infarction (83% female, 56 years old), the incidence rate for myocardial infarction was 13.0/1000 person-years vs 4.1/1000 person-years in the comparison cohort. The incidence rate for stroke was 8.0/1000 person-years vs 3.7/1000 among controls. The adjusted HRs were 3.49 (95% confidence interval [CI], 2.52-4.83) and 2.35 (95% CI, 1.59-3.48) for myocardial infarction and stroke, respectively. For myocardial infarction and stroke, the risk was highest within the first year following diagnosis (HR 8.95; 95% CI, 5.43-14.74 and HR 5.25; 95% CI, 2.90-9.53, respectively).

CONCLUSION: This large general population-based study indicates an increased risk of myocardial infarction and stroke in patients with systemic sclerosis, especially within the first year of diagnosis.

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KEYWORDS: Acute myocardial infarction; Cardiovascular disease; Risk; Stroke; Systemic sclerosis

Systemic sclerosis is a chronic disease of unknown etiology involving autoimmunity, and is characterized by vasculopathy and fibrosis of the dermis and visceral organs. The microvascular complications of systemic sclerosis, which are primarily a result of obliterative vasculopathy involving intimal proliferation in the small arterioles, manifest as Raynaud's phenomenon, pulmonary hypertension, and scleroderma renal crisis.[1]

Increased risk of macrovascular disease, manifesting as higher rates of stroke and myocardial infarction, has been well established in other rheumatic diseases, such as rheumatoid arthritis[2,3] and systemic lupus erythematosus.[4,5] Many studies have examined subclinical radiographic evidence of atherosclerosis (ie, carotid intima-media thickness,

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Authorship: Drs Avina-Zubieta and Sayre had access to the data and all authors had a role in writing the manuscript.

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brachial artery flow-mediated vasodilation) in systemic sclerosis.[6-8] Although the underlying causes are still unclear, 2 meta-analyses have concluded that patients with systemic sclerosis have more atherosclerosis than controls.[9,10]

Our group was the first to demonstrate that patients with systemic sclerosis have an increased risk of myocardial infarction, stroke, and peripheral vascular disease using The Health Improvement Network (THIN), a primary care database of electronic medical records from the United Kingdom.[11] The increased risk of myocardial infarction also has been confirmed in other populations.[12-14] Additionally, a large study from a catastrophic illness insurance database has shown a significantly increased risk of stroke.[15] However, some biases may limit the validity and generalizability of these results, including the use of prevalent cohorts,[12,16] selected samples,[11] controls not representative of the general population,[12] inclusion of transient cerebral ischemia as stroke,[15] and lack of adjustment for unmeasured confounders or competing risks.[12-15] To address some of the limitations of previous studies and to assess, for the first time, the time-based risks after the diagnosis of systemic sclerosis, we evaluated the risk of myocardial infarction and stroke in an incident cohort of patients with systemic sclerosis compared with controls randomly selected from the general population.

CLINICAL SIGNIFICANCE

- Patients with new onset of systemic sclerosis have an increased risk of myocardial infarction and stroke compared with the general population.
- The highest risk of myocardial infarction and stroke occurred within the first year after the diagnosis, suggesting that inflammation plays a pathogenic role in these complications.
- Our findings support increased vigilance in cardiovascular prevention, surveillance, and risk modification in patients with systemic sclerosis.

PATIENTS AND METHODS

Data Source

Universal health coverage is available for all residents in British Columbia (BC), Canada (population ~ 4.7 million). Population Data BC captures all provincially funded health care services since 1990, including: all outpatient medical visits,[17] hospital admissions and discharges,[18] interventions,[17] investigations,[17] demographic data,[19] cancer registry,[20] and vital statistics.[21] Furthermore, Population Data BC encompasses the comprehensive prescription drug database PharmaNet,[22] which includes all dispensed medications for all BC residents since 1996. Numerous population-based studies have been successfully conducted using these databases.[23,24]

Study Design

Using Population Data BC, we conducted cohort analyses of incident myocardial infarction, stroke, and both outcomes combined among individuals with incident systemic sclerosis as compared with age-, sex-, and entry time-matched individuals without systemic sclerosis from a sample of 400,000 individuals randomly selected from the general population by Population Data BC. We created an incident systemic sclerosis cohort with cases diagnosed for the first time between January 1996 and December 2010 defined as individuals who received one of the following: 1) one International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for systemic sclerosis by a rheumatologist (ICD-9-CM 710.1) or from hospitalization (ICD-9-CM 710.1 or ICD-10-CM M34.0); or 2) diagnosis of systemic sclerosis (>18 years) on at least 2 visits, at least 2 months apart, and within a 2-year period by a nonrheumatologist physician; as well as an absence of a prior systemic sclerosis diagnosis between January 1990 and December 1995 (to ensure incident systemic sclerosis cases). The use of ICD-9 codes to identify systemic sclerosis patients in administrative health databases has been successfully employed in a US study where the incidence rate of systemic sclerosis found was similar to other validated US estimates in the literature.[25] Moreover, a validation study of ICD-9 codes in a Canadian context found the specificity of systemic sclerosis diagnosis from administrative health data was 94.9% (95% confidence interval [CI], 93.0-96.2).[26]

To further improve specificity, we excluded individuals with at least 2 visits ≥2 months apart subsequent to the systemic sclerosis diagnostic visit with a diagnosis of other systemic autoimmune rheumatic diseases (eg, rheumatoid arthritis, systemic lupus erythematosus). For each comparison cohort, we matched up to 10 individuals, randomly selected from the general population, without systemic sclerosis to each systemic sclerosis case based on age, sex, and calendar year of study entry. We excluded systemic sclerosis cases and controls with myocardial infarction or stroke before the index date.

Individuals with systemic sclerosis entered the case cohort after all inclusion and exclusion criteria had been met. Systemic sclerosis cases and controls were followed until they experienced an outcome, died (29% vs 10%, respectively), left the province (8% vs 13%, respectively), or the follow-up period ended (December 31, 2010), whichever occurred first.

Ascertainment of Myocardial Infarction and Stroke

The primary outcomes were the first myocardial infarction or stroke event during follow-up. We identified myocardial infarction (ICD-9 CM 410 or ICD-10 CM I21) and ischemic stroke events (ICD-9 CM 433 and 434 or ICD-10 CM I63-I66) from hospitalization data[18]; and defined death from