Title: Increased risk of ischemic stroke in systemic sclerosis: a national cohort study of US veterans

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Abstract

Objective: Previously thought to involve primarily the microvasculature, systemic sclerosis (SSc) has been increasingly linked to macrovascular disease. Cardiovascular and cerebrovascular disease are responsible for 20-30% of mortality in SSc, but few studies have shown an independent association between SSc and stroke. In this study, we assessed whether SSc was an independent risk factor for ischemic stroke.

Methods: We conducted a retrospective cohort study using the national Veterans Affairs administrative database containing records from 1999 to 2014. We obtained data for all patients with a diagnosis of SSc as well as two controls per SSc patient matched on sex, race, smoking status, and VA site. All patients were followed until development of ischemic stroke, death, or last encounter. We used a Cox proportional hazard regression model with adjustments for cardiovascular comorbidities (hypertension, diabetes, atrial fibrillation, non-cerebrovascular atherosclerotic disease, hyperlipidemia), baseline medication use (aspirin, NSAIDs) and Medicare enrollment to estimate risk of ischemic stroke.

Results: Among 4,545 individuals with SSc (83% male, mean age 60.9 years), the incidence rate of ischemic stroke was 15.3 per 1000 person-years (versus 12.2 in the control cohort), with an unadjusted HR 1.28 (95% CI 1.11, 1.47). The adjusted HR was 1.21 (95% CI 1.05, 1.40) after adjusting for baseline cardiovascular risk factors, medications and Medicare enrollment.

Conclusions: SSc is independently associated with a higher risk of ischemic stroke among U.S. veterans. Patients with SSc represent a population likely to benefit from targeted stroke screening or prevention therapies.

Introduction

Systemic sclerosis (SSc) or scleroderma is a rare multisystem autoimmune disease characterized by collagen deposition in the skin and internal organs as well as endothelial damage leading to vasculopathy. Vascular manifestations, including Raynaud's phenomenon, digital ischemia, pulmonary arterial hypertension, and scleroderma renal crisis, are the consequence of endothelial injury and obliteration of the microvascular lumen(1,2). Although previously thought to be primarily a disease of microvasculature, SSc has been increasingly linked to macrovascular disease in the form of coronary and cerebrovascular disease(3,4). Due to improvement in the treatment of many end-organ manifestations of SSc such as scleroderma renal crisis and pulmonary hypertension, atherosclerotic diseases are now responsible for 20-30% of mortality in SSc(3).

Several recent studies have associated SSc with increased risk of atherosclerotic disease as evidenced by both physiologic measurements of atherosclerosis such as carotid intima-medial thickness (5,6) and population-based studies outside of the U.S.(7–12). Three matched cohort studies have demonstrated an increased risk of ischemic stroke in SSc(7,8,11), but the studies were relatively small (<100 ischemic strokes among SSc patients). It is unclear whether any association between SSc and atherosclerotic disease would persist in a U.S. population enriched for traditional atherosclerotic risk factors including male gender.

As the largest healthcare system in the U.S. providing care to over 5 million veterans nationwide, the Veterans Affairs (VA) Health System provides a unique opportunity to evaluate the prevalence and risk factors associated with developing cerebrovascular disease in individuals with SSc. We examined the risk of developing ischemic stroke in individuals with SSc among a large cohort of U.S. veterans.

Patients and Methods

This study was approved by the San Francisco VA Medical Center and University of California San Francisco internal review boards (#16-21058); waiver of informed consent was granted due to the nature of the study.

Data source

The VA Corporate Data Warehouse (CDW) contains data elements extracted from the national VA electronic medical record such as outpatient and inpatient utilization with associated diagnostic and procedure codes, laboratory results and pharmacy data. Data was accessed through the VA Informatics and Computing Infrastructure (VINCI) platform(13). We conducted a retrospective cohort study to determine whether SSc disease status (exposure) is associated with ischemic stroke (outcome). Our study included all patient data from October 1, 1999 to September 30, 2014.

Inclusion and exclusion criteria

We included patients with both prevalent and incident SSc. Cases were required to have at least one encounter with an associated ICD-9 diagnosis code of 710.1. Although there are currently no widely-accepted administrative case definitions of SSc, diagnostic codes from administrative data have been previously demonstrated to have a specificity of 94.9% for SSc, when compared to chart review(14).

Patients were excluded before matching if they were less than 18 years of age at the time of their first encounter, or had an ICD-9 diagnosis code for morphea (701.0), eosinophilic fasciitis (728.89) or nephrogenic systemic fibrosis (710.8), which are known clinical mimics of

scleroderma and likely indicate misdiagnosis of SSc and/or inaccurate coding(15) (1602 cases). Cases with a diagnosis of ischemic stroke or TIA prior to their reference date (327 cases) and those with only one encounter (141 cases) were excluded prior to matching.

Matching

Two controls were matched to each case using a nearest neighbor matching algorithm without replacement, using a Mahalanobis distance metric for date of birth and duration of VA enrollment, defined as the time interval between first and last encounter. Exact matching was performed for categorical variables (sex, race, baseline smoking status, VA site). If patients received care at multiple VA sites, the site with the plurality of encounters was chosen.

The reference date for cases was defined as the earliest encounter with a SSc diagnosis code. The reference date for controls was determined after they were matched to a case, by computing the time interval between the first encounter and reference date for the respective case, and adding that interval to the date of first encounter of the control. The goal of this procedure was to match cases and controls on the amount of time they had to accumulate comorbid conditions after they started receiving care through the VA (**Figure 1**).

To reduce bias from potentially matching patients receiving care at vastly different points in time, we divided the 15-year study period into 5-year periods, and controls were required to have at least one encounter during the 5-year period of their respective cases' reference date. This approach was adapted from a previously published matched cohort study(16).

Both cases and controls for any matched set in which any control had an invalid reference date (prior stroke diagnosis or before enrollment date) were excluded after matching (153 cases), due to the calculation of control reference date after matching. Two cycles of matching were

performed to reduce the number of controls with invalid reference dates. The subject selection process is shown in **Figure 2**.

Definition of ischemic stroke

We identified the first encounter for each patient associated with an ICD-9 code that corresponded to cerebrovascular ischemia (433.x1, 434.x1, 435.x, 436, 437.1), including codes for transient ischemic accident (TIA). Identifying strokes using algorithms involving ICD-9 codes has been previously performed using VA data(17). Positive predictive values for the selected stroke ICD-9 codes were generally found to be >75% in a meta-analysis(18). Patients were followed from date of SSc diagnosis (cases) or matched reference date (controls) until the first diagnosis of ischemic stroke, death, or last encounter, whichever came first.

Assessment of covariates

Baseline traditional cardiovascular risk factors (atrial fibrillation, hypertension, diabetes mellitus, non-cerebrovascular atherosclerotic disease, hyperlipidemia) were assessed during the period between the first encounter and the reference date based on the presence of relevant diagnostic codes. Any previous statin use was also incorporated into the definition of hyperlipidemia. Smoking status at baseline (yes, no, unknown) was assessed using Health Factors data collected by providers in the VA electronic medical record using automated clinical reminders, a method that has been validated in comparison to patient questionnaire(19). Baseline medication use (aspirin, oral non-steroidal anti-inflammatory drugs) was defined as a filled prescription and/or recorded non-VA medication in the 12 months prior to the start of follow-up.

In order to account for potential differences between cases and controls due to differential patterns of health care utilization, we also measured Medicare enrollment as a proxy for non-VA

care. More than half of all veterans report enrollment in Medicare, and these patients likely receive care through both VA and non-VA sources(20). Yearly Medicare enrollment records were extracted from Centers for Medicare and Medicaid Services (CMS) data provided to the VA, and patients were considered enrolled in Medicare if they were enrolled for at least one year during their follow-up. Patients with unavailable Medicare enrollment data were considered to have not been enrolled (N=6).

Statistical analyses

We compared cases and controls on the basis of non-matched characteristics, using chi-squared tests for categorical variables and *t*-tests for continuous variables. The number of cases and controls with ischemic stroke during follow-up and total person-years of follow-up were used to estimate incidence rates. To generate hazard ratios, we employed a Cox proportional hazard regression model stratified by matched sets of patients. Tests of collinearity and evaluation of the proportional hazards assumption were performed. Multivariable analyses were adjusted for baseline traditional cardiovascular risk factors (atrial fibrillation, hypertension, diabetes mellitus, non-cerebrovascular atherosclerotic disease, hyperlipidemia), baseline medication use (aspirin, non-steroidal anti-inflammatory drugs, statins), and Medicare enrollment during follow-up. Extraction of data was performed using Microsoft SQL Server 2014 (Microsoft Corp., Redmond, WA). Statistical analysis was performed with STATA/MP 15.1 (StataCorp, College Station, TX).

Sensitivity analyses

We performed five sensitivity analyses: first, a separate analysis using only cases who were given an SSc diagnosis code during an outpatient rheumatology encounter. We hypothesized that these cases would be more likely to have accurate diagnoses of SSc, based on

a chart review of all SSc cases diagnosed at the San Francisco VA which showed this criteria to the most accurate in distinguishing true diagnoses of SSc. Second, we restricted the SSc cohort to those with at least two SSc diagnosis codes separated by at least 30 days. Third, we excluded patients from both cohorts with any diagnoses of rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), as both diseases increase risk of stroke (21) and may be misdiagnosed as SSc. Finally, the last two sensitivity analyses were performed using Medicare enrollment data to ensure that missing diagnoses from non-VA care were not significantly impacting our results. We analyzed a subset of patients first with additional censoring at the time of the first year of Medicare enrollment, and separately by excluding all patients enrolled in Medicare during follow-up. These two analyses were necessarily unstratified due to the removal of patients who became censored or excluded before their reference date.

Results

We included 4,545 cases and 9,090 matched controls in our primary analysis. Baseline patient characteristics are shown in **Table 1**. Both cases and controls were predominantly male (83%), and white (60%) with an average age of 61 at reference date. SSc patients generally had higher baseline rates of cardiovascular risk factors, higher rates of baseline aspirin and NSAID use and were more likely to be enrolled in Medicare during follow-up ($p<0.001$). The mean reference date was in calendar year 2006, and the mean interval between first VA encounter and reference date was 3.7 years for both groups.

The mean follow-up duration was 5.1 years for SSc patients and 5.2 years for controls. New diagnoses of ischemic stroke or TIA occurred in 353 SSc patients over 23,078 person-years of follow-up (15.3/1000 person-years), and 574 controls over 47,175 person-years of follow-up

(12.2/1000 person-years) (**Table 2**). There was a significantly higher incidence of ischemic events among SSc patients (p = 0.0004), diverging early in the follow-up period (**Figure 3**).

The unadjusted hazard ratio (HR) for cerebrovascular ischemic events in SSc patients was 1.28 (95% CI 1.11, 1.47; **Table 2**). After adjusting for baseline cardiovascular risk factors, medication use, and Medicare enrollment during follow-up, the HR was 1.21 (95% CI 1.05, 1.40). HRs remained consistent for all sensitivity analyses. Limiting cases to the 1,538 SSc patients diagnosed during an outpatient rheumatology encounter resulted in an unadjusted HR of 1.49 (95% CI 1.14, 1.95) and adjusted HR of 1.48 (95% CI 1.10, 1.99). Requiring two SSc diagnosis codes resulted in an unadjusted HR of 1.33 (95% CI 1.09, 1.62) and adjusted HR of 1.33 (95% CI 1.07, 1.64) among 2,201 cases and 4,402 controls. After excluding patients with diagnoses of RA or SLE, there were 3,471 cases and 6,942 controls, with an unadjusted HR of 1.18 (95% CI 1.00, 1.39) and adjusted HR of 1.14 (95% CI 0.96, 1.36). Censoring at time of Medicare enrollment resulted in an unadjusted HR of 1.51 (95% CI 1.22, 1.87) and adjusted HR of 1.31 (95% CI 1.05, 1.62) among 2,020 cases and 4,601 controls. Excluding all patients enrolled in Medicare during follow-up resulted in an unadjusted HR of 1.64 (95% CI 1.26, 2.11) and adjusted HR of 1.37 (95% CI 1.05, 1.78) among 1,142 cases and 2,942 controls.

Discussion

In this cohort of U.S. veterans, the risk of incident stroke or TIA was 20-30% higher in individuals with SSc compared to matched controls. While this effect was somewhat attenuated after adjustment for known stroke risk factors and baseline medication use, it remained statistically significant. As the first study of SSc in a predominantly male U.S. veteran population, this provides evidence that SSc is associated with additional risk of developing

ischemic stroke in U.S. veterans, a population with a significant burden of traditional stroke risk factors. The current study contains the largest cohort of SSc patients to date in which macrovascular disease has been assessed. Our cohort size is within an order of magnitude of the estimated prevalence of SSc in the VA health care system (1,400 – 2,900), based on previously published estimates of scleroderma prevalence in the U.S.(22,23) and number of veterans receiving VA care(24), although it must be noted that the veteran population differs in many ways from the general population, including with various occupational and military exposures during military service that may increase the risk of autoimmune conditions(25).

There are several possible mechanisms for macrovascular disease in SSc. Endothelial dysfunction is a hallmark of SSc, and leads to a characteristic vasculopathy consisting of both proliferative obliterative and destructive features(26). Production of reactive oxygen species can be caused by endothelial dysfunction and vascular inflammation, which leads to oxidation of low density lipoprotein (LDL) and eventually formation of atherosclerotic plaques(27). Cerebral vasospasm as evidenced by angiography is another posited mechanism of cerebrovascular disease in SSc(28).

Prior studies have found an increased prevalence of subclinical cerebrovascular atherosclerotic disease in SSc via measures such as carotid intimal medial thickness on ultrasound, intracerebral calcifications on CT and white-matter hyperintensities on MRI(5). Previous cohort studies have found increased risk of clinical coronary artery disease(7,9,10) and stroke(7,8) in SSc patients compared to controls, in agreement with our findings. Chiang et al. reported an approximately 40% increased risk of ischemic stroke or TIA in a Taiwanese SSc cohort(8), and both Man et al. and Aviña-Zubieta et al. found a two- to threefold increased risk of ischemic stroke (not including TIA) in British and Canadian SSc cohorts, respectively(7,11).

Compared to these previous studies, our study population was older, predominantly male, and had higher rates of cardiovascular risk factors such as hypertension, diabetes and atrial fibrillation, as would be expected in a veteran population, making comparisons to other cohort studies difficult. As the first study to investigate the risk of stroke in SSc in both a U.S. population and a predominantly male cohort, we found lower hazard ratios compared to previous cohort studies, but this may be explained by the higher burden of atherosclerotic risk factors in our cohort that may blunt the additive risk of SSc.

The prevalence of traditional cardiovascular risk factors in our study was significantly higher in the cases than controls, in contrast to data from a matched retrospective cohort study that showed similar baseline rates of hypertension, diabetes, hyperlipidemia and atrial fibrillation between SSc patients and controls(7). This finding may suggest that scleroderma in males and/or veterans is more closely associated with cardiovascular risk factors than in the general scleroderma population, or it may reflect a higher degree of diagnostic delay of SSc as several of these cardiovascular comorbidities are potential complications of scleroderma or its treatment. Males in a European SSc cohort were found to have higher rates of pulmonary hypertension, heart failure, and all-cause mortality compared to females(29), although macrovascular disease was not specifically studied. This might also be an artifact arising from our use of administrative data, since patients diagnosed with a serious and complex condition such as SSc may be more likely to receive comorbid diagnoses around the time of diagnosis due to increased contacts with the healthcare system(22). We attempted to account for this using an algorithm that matched on comorbidity accumulation time, although it is possible that there some residual confounding remained.

The strengths of our study include the use of nationwide administrative database to follow a large number of patients with a rare disease over a sufficiently long timespan to detect cerebrovascular events. As the first study of SSc in U.S. veterans, we have demonstrated the value of studying a female-predominant disease in a male-predominant veteran population. We have also described a novel matching process to generate reference dates in controls while also matching for comorbidity accumulation time.

Limitations of our study include uncertainty about diagnostic accuracy, as with all studies using administrative data. Classification of ischemic stroke as well as atrial fibrillation, diabetes and hypertension by ICD-9 codes were shown to have an 85-90% positive predictive value when compared to chart review(30). To minimize the effect of potential misclassification of SSc, we excluded all patients who had a diagnosis of one or more scleroderma mimics, in addition to performing a sensitivity analysis using only SSc patients diagnosed during a rheumatology outpatient encounter. Based on our chart review, this more specific definition of SSc is more likely to capture correct diagnoses of SSc, at the expense of excluding patients with poor access to specialty care. Our sensitivity analysis excluding patients with RA and SLE diagnoses resulted in a non-significant HR after adjustment, but this analysis likely excluded valid SSc cases who received an alternate diagnosis of RA or SLE near the time of their initial SSc diagnosis during a period of diagnostic uncertainty, or truly had an overlap syndrome.

With many patients in our cohort being enrolled in Medicare and thus likely receiving non-VA care, there is also the risk of missing stroke diagnoses that occurred outside of the VA. However the overall effect of this missing data should generally bias our results towards the null, as more cases than controls were enrolled in Medicare. We did not have access to data such as SSc subtype, organ involvement or disease severity, nor stroke severity. We attempted to analyze

30-day mortality after stroke events but were limited by small sample sizes. Medication data for aspirin and NSAIDs use may be underascertained due to frequent over-the-counter purchase of these medications(31), which is not always captured by provider-entered non-VA medication fields(32); however, we would not expect this underascertainment to be differential among cases and controls. Although we collected data on baseline oral glucocorticoid use, we did not incorporate this variable into our model due to concern that baseline glucocorticoid use reflected a subset of SSc patients with manifestations such as arthritis that preceded a formal diagnosis of SSc.

In conclusion, our study provides evidence that SSc is associated with an increased risk of cerebrovascular disease in the U.S. veteran population, independent of traditional cardiovascular risk factors. Future work should focus on identifying mechanisms and risk factors for cerebrovascular disease in SSc, such as disease subtype or disease manifestations such as vasculopathy, hypercoagulability and vasospasm. Furthermore, our findings suggest that SSc patients in the U.S. veteran population may benefit from targeted stroke screening or prevention strategies.

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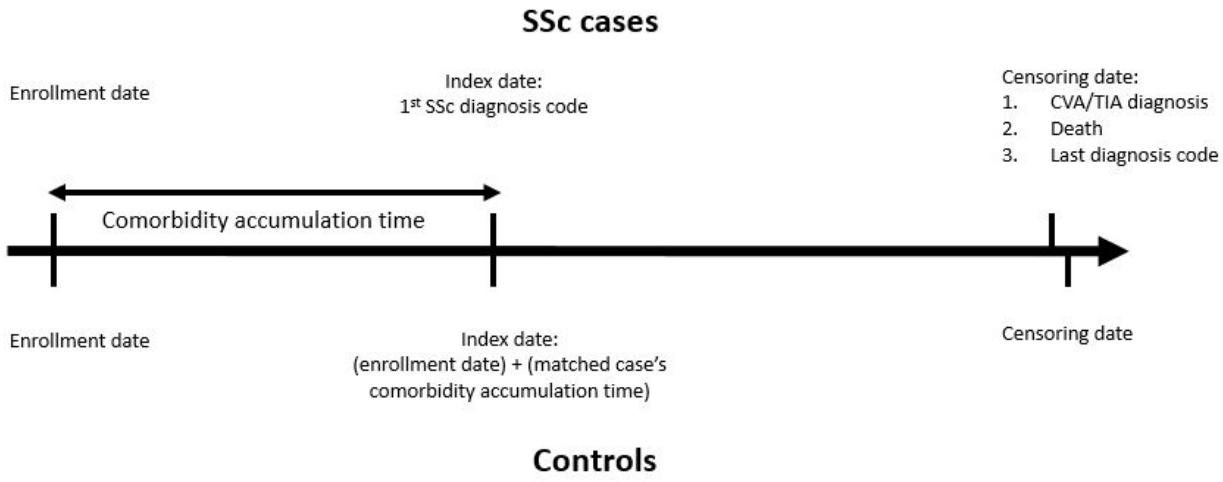
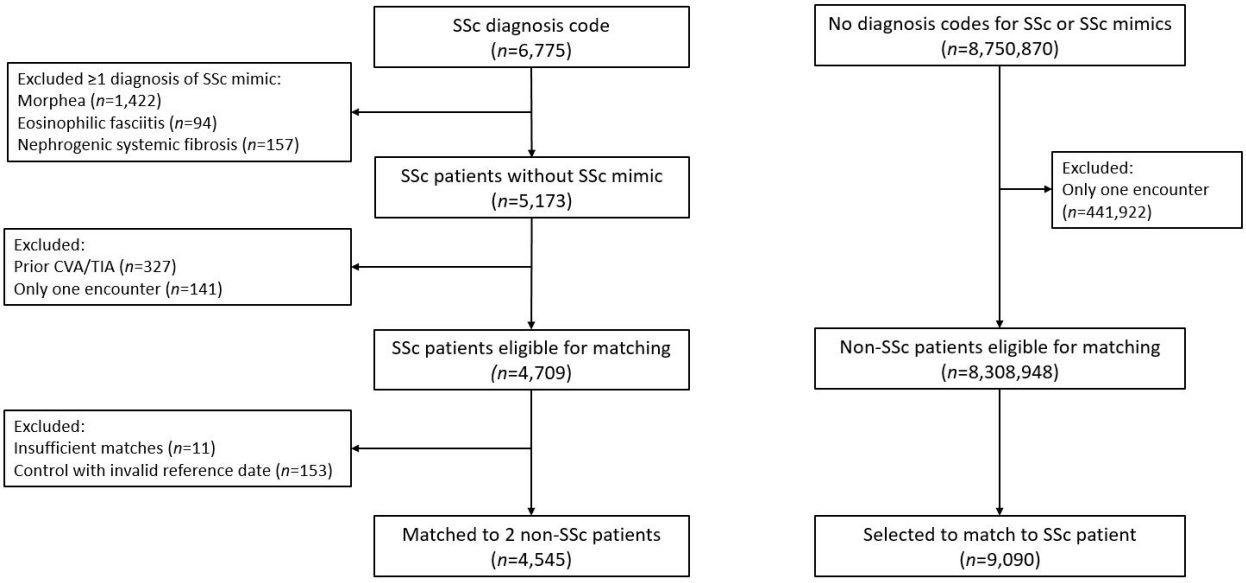
Figure 1: Data timeline schematic for SSc cases and controls.



The enrollment date for cases and controls was defined as the date of the first diagnosis code of any kind. For cases, the reference date was defined as the date of the first encounter associated with a diagnosis code for SSc. For the controls, the reference date was calculated as the enrollment date plus the comorbidity accumulation time of the matched case, defined as the interval between enrollment date and reference date. The censoring date was the date of first CVA/TIA diagnosis, date of death, or date of most recent diagnosis of any kind, whichever came first.

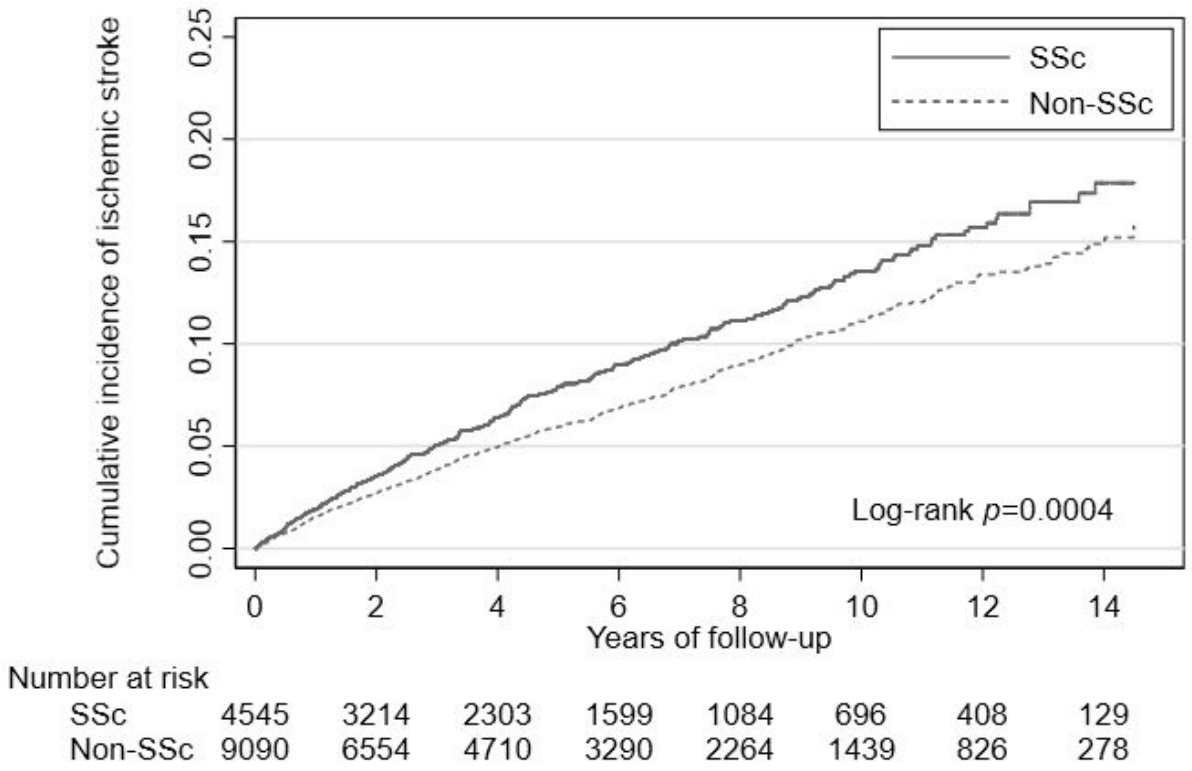
CVA: cerebrovascular accident; SSc: systemic sclerosis; TIA: transient ischemic attack

Figure 2: Flow diagram of subject selection process in case and controls



CVA: cerebrovascular accident; SSc: systemic sclerosis; TIA: transient ischemic attack

Figure 3: Kaplan-Meier estimates of cumulative incidence of cerebrovascular ischemic events



Cumulative incidence of ischemic stroke or transient ischemic attack in 4545 individuals with systemic sclerosis (SSc) as compared with 9090 age-, sex-, race-, VA facility- and smoking status-matched non-SSc individuals.

Table 1: Baseline characteristics of systemic sclerosis (SSc) and matched controls (non-SSc)*

Variables	SSc (n=4545)	Non-SSc (n=9090)	*P*
Age, mean ± SD years	60.9 ± 12.9	61.0 ± 13.1	0.49
Female	789 (17)	1578 (17)	1.00
Race			1.00
White	2725 (60)	5450 (60)	
Black	780 (17)	1560 (17)	
Native Hawaiian/Pacific Islander	29 (0.6)	58 (0.6)	
American Indian/Alaskan Native	27 (0.6)	54 (0.6)	
Asian	26 (0.6)	52 (0.6)	
More than one race	958 (21)	1916 (21)	
Smoking status			1.00
Never	1287 (28)	2574 (28)	
Ever	2247 (49)	4494 (49)	
Unknown	1011 (22)	2022 (22)	
Comorbidity accumulation time, mean ± SD years†	3.7 ± 3.9	3.7 ± 3.9	1.00
Atrial fibrillation	342 (7.5)	425 (4.7)	<0.001
Hypertension	2726 (60)	4807 (52)	<0.001
Diabetes mellitus	1164 (26)	1940 (21)	<0.001
Non-cerebrovascular atherosclerotic disease	1479 (33)	2118 (23)	<0.001
Hyperlipidemia or statin use	2124 (47)	4423 (49)	0.034
Aspirin use‡	784 (17)	1134 (12)	<0.001
Nonsteroidal anti-inflammatory drug use‡	1364 (30)	2008 (22)	<0.001
Medicare enrollment§	3403 (75)	6148 (68)	<0.001

*Except where indicated otherwise, values are the number (percentage)

†Time interval between first VA encounter and reference date

‡Filled prescription and/or recorded non-VA medication in 12 months prior to start of follow-up

§Enrollment in Medicare for at least 1 year during follow-up period

Table 2: Hazard ratios (HR) of incident stroke or TIA according to systemic sclerosis (SSc) status

	SSc N=4545	Non-SSc N=9090
Incident strokes or TIA	353	574
Follow-up duration (mean ± SD years)	5.1 ± 4.1	5.2 ± 4.1
Incidence rate/1000 PY	15.3	12.2
Unadjusted HR (95% CI)	1.28 (1.11 to 1.47)	Ref
+ Medicare enrollment adjusted HR (95% CI)	1.32 (1.15 to 1.52)	Ref
+ Cardiovascular risk factors adjusted HR (95% CI)	1.24 (1.07 to 1.43)	Ref
+ NSAID & aspirin use adjusted HR (95% CI)	1.21 (1.05 to 1.40)	Ref

NSAID: nonsteroidal anti-inflammatory drug; PY: person-years; Ref: reference category