# Title: Characteristics of Takayasu Arteritis Patients with Severe Ischemic Events

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## Abstract

**Objective:** Takayasu arteritis (TAK) is a rare large vessel vasculitis with a high risk of developing severe ischemic events (SIE). Outcomes for TAK patients with SIE are poorly understood. We aim to describe the characteristics of TAK patients experiencing SIE.

**Methods:** All TAK patients with at least one follow-up visit seen between 1988 and 2015 were included from 3 academic centres in Ontario, Canada. Diagnosis was based on American College of Rheumatology (ACR) criteria, physician opinion and vascular imaging. SIE were defined as cerebrovascular accident (CVA), acute coronary syndrome (ACS), ischemic cardiomyopathy, ischemic blindness and/or ischemic bowel or limb requiring surgery.

**Results:** Of the 52 TAK patients included in the study, 51 (98%) were female and 22 (42%) were of European descent. The mean age was 31 (standard deviation [SD] 12) at the time of diagnosis and the follow-up time was 6 (SD 5) years. Fifteen (29%) experienced a SIE: 5 CVA, 5 ACS, 1 ischemic cardiomyopathy and 4 limb ischemia. 13/15 (87%) SIE occurred at or before diagnosis. Patients with SIE were more likely than those without SIE to be started on corticosteroids combined with immunosuppressants (p=0.03) and anti-platelet agents (p=0.0003). Outcomes including disease activity and damage scores were similar between patients with and without SIE.

**Conclusion:** SIE are common in patients with TAK and occur early in the disease. With aggressive treatment, patients with SIE had a favourable prognosis.

**Ischemic Events in TAK**

Takayasu arteritis (TAK) is a rare form of granulomatous vasculitis, characterized by inflammation of the aorta and its major branches, and is found most commonly in young Asian females (1,2). Diagnosis remains challenging due to several factors, including its rarity, lack of disease awareness, heterogenous disease presentations, and early non-specific symptoms (2,3). A major consequence of delayed TAK diagnosis is stenosis and occlusion of vessels leading to end-organ ischemia (2,3).

A recent meta-analysis demonstrated that TAK patients have high rates of developing severe ischemic events (SIE) (4). The most commonly reported forms of SIE are strokes, transient ischemic attacks (TIA) (4,5) and acute coronary syndromes (ACS) (4,6). Other manifestations of SIE, including ischemic induced blindness (7), ischemic limb requiring surgical intervention (8) and ischemic gut (9), are not as consistently reported in the literature (4). In addition, there is a lack of studies describing characteristics, treatment and outcomes of patients with SIE over time.

In this study, we investigated TAK patients from a Canadian cohort with long follow-up to describe the clinical characteristics of those patients with SIE and their management.

**Methods**

The patients included in this study were seen at three Canadian academic centers: St. Joseph's Health Care in London; Mount Sinai Hospital in Toronto; and St. Joseph's Healthcare in Hamilton (all in Ontario) (10). All TAK patients seen at these centers between 1988 and 2015 were included in the study if they had available and complete data at diagnosis, at least one follow-up visit and if written informed consent was obtained. Diagnosis was based on American College of Rheumatology (ACR) classification criteria (11) and/or physician opinion based on

clinical presentation and vascular imaging. The study was approved by the research ethics boards of each sites: REB1000012364, 102078, and 15-034.

Patient data were collected at diagnosis, and when available at 6 months, 12 months, every relapse and last follow-up using standardized forms. Information collected consisted of demographics, medical history and co-morbidities (including traditional cardiovascular risk factors: diabetes, hypertension, dyslipidemia and obesity), clinical manifestations laboratory and imaging investigations, current treatments or interventions and the following composite measure the Indian Takayasu Activity Score (ITAS2010) (12). ITAS was completed retrospectively. To confirm diagnosis all patients underwent vascular imaging by computed tomography angiography (CTA), magnetic resonance angiography (MRA), and/or conventional digital-subtraction angiography. For follow-up, the usual practice at our centers is to perform vascular imaging for a suspected TAK flare that cannot be confirmed by clinical examination or to identify complications (aneurysm or critical ischemia). PET and MRA is not readily available at our centres; CTA for follow-up is avoided to reduce radiation exposure.

SIE were defined as CVA (stroke or TIA), ACS (ST elevation MI (STEMI) or non-ST elevation (NSTEMI) MI) , ischemic cardiomyopathy, ischemia-induced blindness, limb or bowel ischemia requiring surgical intervention. Stroke was defined by a neurologist as an ischemic or hemorrhagic event causing acute focal neurologic signs and/or symptoms and confirmed by MRI imaging. TIA was defined as a temporary neurologic ischemic event with reversible focal neurological signs and/or symptoms.. ACS and ischemic cardiomyopathy were diagnosed by a cardiologist based on clinical symptoms and confirmed by electrocardiography, echocardiography, laboratory investigations and/or coronary angiography. Limb ischemia was

determined based on clinical findings of reduced vascular flow (i.e. decreased pulses, cyanosis cutaneous ulcers, gangrene) that required surgery (including amputation, vascular bypass, arthroplasty and stent placement). Ischemia-induced blindness was defined by an ophthalmologist on examination of the retina and bowel ischemia requiring surgical intervention by pathology of the surgical specimen. The following ischemic manifestations were not considered severe and were excluded: Raynaud's phenomenon, ischemic neuropathy, syncope due to decreased cerebral blood flow, renal ischemia not requiring dialysis, cutaneous ulcerations, digital cyanosis/periungal infarcts, claudication symptoms, or bowel ischemia not requiring surgical intervention.

Active TAK was defined by the treating physician as new or worsening symptoms attributable to TAK or ongoing symptoms with elevations in acute phase reactants and/or evidence of disease activity by imaging. Remission was the absence of symptoms, elevations in acute phase reactants (APR) or imaging findings of active TAK disease. Relapse was defined by the recurrence of TAK symptoms, new symptoms or progression of vascular lesions on imaging, with or without an elevation in APR, and leading to a change in treatment in patients previously in remission. Imaging findings that were deemed indicative of active or relapsing disease were new or persistent vessel wall thickening plus enhancement, worsening stenosis or aneurysm..

Descriptive statistical analysis was performed using GraphPad Prism 6.0. Patients with SIE were compared to those without SIE using Fisher's exact test for categorical variables and unpaired T-test for continuous variables; p-values of $<0.05$ were considered statistically significant.

## Results

### *Patient demographics and frequency of SIE*

This cohort included 52 patients, 50 meeting the ACR criteria for TAK, and 2 were based on physician opinion. Two patients were diagnosed with TAK based on physician opinion: a 22-year-old female presenting with MI, elevated inflammatory markers and aortic wall thickening on MRA and a 47-year-old female with carotidynia, weight loss, elevated ESR with subclavian stenosis and aortic wall thickening on imaging. Most were female, 51/52 (98%) and 42% were of European descent. The mean age at diagnosis was 31 (SD 12) years and the mean follow-up time was 6 (SD 5) years. On vascular imaging, the most commonly affected arteries were the aorta, carotid and subclavian arteries at diagnosis (Supplementary Table 1). Of the 52 patients included in the study, 17 had follow-up imaging. New lesions were more frequently detected in the first 6 months of follow-up and after 6 months imaging was mostly stable. There were no significant differences in new imaging findings at follow-up between patients with and without SIE (Supplementary Table 2).

Within this population, 15/52 (29%) had a single event over the course of the study.. Most SIE (87%) occurred at or before diagnosis. Of the patients with SIE: 5/15 (33%) patients had CVA (2 presented with ischemic stroke and 2 presented with TIA at or before diagnosis, 1 presented with TIA at 6 months), 6/15 (40%) had cardiovascular SIE (2 with STEMI, 2 with NSTEMI and 1 with ischemic cardiomyopathy at or before diagnosis, 1 with STEMI at 6 months) and 4/15 (27%) presented at or before diagnosis with severe limb ischemia. No patients had ischemia-induced blindness or severe ischemic bowel.

### *Characteristics of patients with and without SIE*

Demographics and presenting features of the study population are summarized in Table 1 and Supplementary Table 1. The median diagnostic delay for patients with SIE was 5 (range: 0-182) months and for those without SIE, 13 (range: 1-446) months; p=0.0313. Patients with SIE presented more often with symptoms related to their specific type of SIE. For example, patients with cardiovascular SIE (ACS or ischemic cardiomyopathy) were more likely to have classic MI symptoms on presentation, such as angina and dyspnea; patients with severe limb ischemia were more likely to present with cutaneous manifestations, including livedo reticularis and digital ulcerations. Traditional CVD risk factors, including diabetes, hypertension, dyslipidemia (precise lipid levels were not available), smoking, obesity (BMI >30) and family history of CVD were infrequent at baseline. The study was not powered to determine if traditional CVD risk were associated with SIE.. Hypertension was present at baseline in 3 SIE patients and an additional 3 patients developed hypertension over the follow-up period. Data on other CVD risk factors at follow-up was not collected.

### *Medical Treatments and Vascular Interventions*

At diagnosis, 13/15 (87%) of SIE patients and 30/37 (81%) of non-SIE patients were started on prednisone, mean doses of 51.5 (SD 9.9) mg/day and 53.3 (17.0) mg/day, respectively (p>0.05, Table 2). For patients diagnosed after 2008, the starting dose of prednisone was higher than those diagnosed before then: 47.3 (SD 25.3) vs. 33.81 (20.8) mg/day, p=0.038. Patients with SIE were more likely than those without SIE to be started on combination therapy (corticosteroids (CS) plus an immunosuppressants): 8/15 (53%) vs. 9/37 (25%) respectively (p=0.003)

(Supplementary Table 3). SIE patients were also more likely to be started on anti-platelet therapy: 4/15 (93%) vs. 19/37 (51%); p=0.004.

The prednisone dosage decreased over time for both groups. Non-SIE patients were more likely to remain on prednisone treatment, 19/35 (59%), than SIE patients, 3/13 (17%); p=0.01 (Table 2). At last follow-up, SIE and non-SIE patients diagnosed after 2008 were more likely to be prescribed immunosuppressants combined with CS than those diagnosed before then: 11/20 (55%) vs. 5/15 (33%), p=0.014. ; There were no significant differences between SIE and non-SIE patients in the use of immunosuppressants, biologics, or anti-hypertensives drugs at the follow-up visits (Table 2 and Supplementary Table 3). As per usual care at our centres and because of drug reimbursement practices, biologic therapies were utilized after failure of multiple conventional immunosuppressants combined with CS. Before 2008, only 1/15 (7%) patient was treated with biologic drugs, compared to 5/20 (25%) after 2008; p>0.05).

Eleven revascularization procedures were performed on 8 patients with SIE and 2 without SIE, p=0.00007. The procedures were 3 coronary artery stents, 2 coronary artery bypass surgeries, 2 embolectomies in limb vessels, 1 subclavian artery angioplasty, 1 right subclavian artery, 1 renal and 1 aortic stent.

***Patient Outcomes and Disease Activity***

Table 3 summarizes the outcomes of SIE compared to non-SIE patients. There were no significant differences in relapses over the course of the study: 6/15 (40%) SIE patients relapsed, with one of them relapsing twice, vs. 8/37 (21%) in the non-SIE patients, with two of them relapsing twice (p=0.190). None of the patients died during the study period. There was no difference in the mean ITAS for SIE vs. non-SIE patients at diagnosis:11.4 (SD 5.8) vs. 9.19 (SD 3.9).

Despite patients diagnosed after 2008 being treated more aggressively, the outcomes were not different when compared to those diagnosed before 2008.

**Discussion**

In this cohort of Canadian patients with TAK and long follow-up, SIE were common and occurred mostly at or before diagnosis. The most frequent SIE were ACS and CVA, occurring in 12% and 10%, respectively.

The proportion of patients experiencing SIE in this cohort is consistent with prior studies of TAK that estimated the prevalence of stroke orTIA to be 8-15% (4,13) and of myocardial infarction, 3-22% (4,6,14). Conversely, the observed rate of new SIE at follow-up was lower than reported in a recent meta-analysis which estimated 9.2% and 7.4% of patients had a stroke and MI respectively at follow-up (4). In our study with a mean follow-up of 6 years, only 2 patients (1.3%) experienced a new SIE (1 TIA and 1 MI), occurring within the first 6 months after diagnosis. There are several possible explanations for this difference: our population included more patients of European descent, a demographic reported to have less severe disease (15), and all of the SIE patients in our study received anti-platelet therapy at diagnosis, which has been shown to reduce ischemic events in an observational study of TAK patient (16). The patients in our study were also started on aggressive treatment with corticosteroids combined with immunosuppressants at diagnosis.

Over the course of follow-up, SIE patients had similar disease activity based on ITAS compared to non-SIE patients. Despite SIE patients having numerically more relapses, they were more likely to be off corticosteroids. The reason for this finding is unclear, but it is possible that physicians aimed to avoid corticosteroid exposure in SIE patients because it is known to increase

the risk of atherosclerotic events. The use of other immunosuppressants was similar for SIE and non-SIE patients.

Although detailed information on the management of all cardiovascular risk factors in this cohort were incomplete, the proportion of patients with traditional cardiovascular risk factors was low, as expected from a study population consisting predominantly of young women. Hence, mechanisms other than atherosclerosis are likely contributing to SIE in TAK. For example, direct vascular inflammation from TAK leading to stenosis, thrombosis or embolism can directly cause ACS and CVA. Unfortunately, the imaging modalities employed in this study (conventional angiogram, CTA and 1.5T MRA) are limited in their ability to differentiate vascular inflammation from atherosclerosis (17). Higher resolution MRA, cardiac MRI and PET scan was not readily available at our centres.

The study has some limitations, including its small sample size; thus, it was not possible to identify independent risk factors for SIE. We included all TAK patients seen at three large centers in Ontario, the most populous province of Canada, and the study sample reflects the rarity of TAK in Canada. Data collection was retrospective, but patients lost to follow-up and missing data were minimal. In this “real-world” study some important variables that are not routinely collected in usual care were not available, such as functional scores and quality of life indicators.

In conclusion, SIE were common in this cohort of patients with TAK. Given that most SIE occurred at or before diagnosis, methods to diagnose TAK and initiate treatments earlier may help prevent or minimize some of these complications.

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**Table 1.** ***Demographics and presentation of TAK patients with and without SIE at diagnosis.***

| Features | With SIE<br>n=15 | Without SIE<br>n=37 |
|---|---|---|
| **Mean Age±SD**, years | 31±12 | 32±11 |
| **Mean Diagnostic Delay±SD**, months | 27±58 | 46±92 |
| **Gender** | | |
| Female | 15 (100) | 36 (97) |
| **Ethnicity** | | |
| Asian | 1 (7) | 4 (11) |
| Black | 0 | 3 (8) |
| European descent | 8 (53) | 14 (38) |
| East Indian | 4 (27) | 6 (16) |
| Hispanic | 0 | 3 (8) |
| Other | 2 (13) | 7 (19) |
| **CVD risk factors** | | |
| Diabetes | 0 | 0 |
| Hypertension | 2 (13) | 2 (5) |
| Dyslipidemia | 1 (7) | 0 |
| Prior or Current Smoking | 4 (27) | 5 (14) |
| Obesity | 0 | 0 |
| Family History | 1 (7) | 4 (11) |
| **Presenting Symptoms*** | | |
| Systemic | 10 (67) | 32 (87) |
| Rheumatic | 6 (40) | 17 (46) |
| Ocular | 3 (20) | 5 (14) |
| Neurologic | 5 (33) | 12 (32) |
| Cardiovascular | 15 (100) | 37 (100) |
| Cutaneous | 7 (47) | 4 (11) |
| Gastrointestinal | 1 (7) | 1 (3) |
| Genitourinary | 0 | 1 (3) |
| Respiratory | 5 (33) | 4 (11) |
| **Lab results, Mean±SD** | | |
| Hemoglobin, g/L | 113.21±14.73 | 122.08±19.76 |
| ESR, mm/hr | 41.73±23.12 | 42.26±21.33 |
| CRP, mg/L | 31.62±32.39 | 33.28±28.00 |
| Creatinine, µmol/L | 66.46±13.01 | 63.42±18.20 |

Data are presented as numbers (%) unless otherwise indicated.

*Details of presenting symptoms provided in Supplementary Table 1.

**Table 2.** ***Treatments in SIE and non-SIE patients***

| **Medications started at diagnosis** | **With SIE n = 15** | **Without SIE n = 37** | **p-value** |
|---|---|---|---|
| Prednisone | 13 (87) | 30 (81) | 0.63 |
| Mean prednisone dosage in mg/day ±SD | 51.5±9.9 | 53.3±17.0 | 0.363 |
| Corticosteroid + immunosuppressants | 8 (53) | 9 (25) | **0.04** |
| Anti-platelet | 14 (93) | 19 (51) | **0.004** |
| Anti-coagulant | 2 (13) | 3 (8) | 0.56 |
| Anti-hypertensive | 2 (13) | 6 (16) | 0.79 |
| **Medications at 6-month visit** | **With SIE n = 15** | **Without SIE n = 36** | **p-value** |
| Prednisone | 13 (87) | 31 (86) | 0.88 |
| Mean prednisone dosage in mg/day ±SD | 23.2±17.2 | 23.1±15.3 | 0.49 |
| Corticosteroid + Immunosuppressants | 10 (67) | 21 (58) | 0.56 |
| Corticosteroid + biologics | 0 | 2 (6) | 0.34 |
| Any change in hypertensive medication | 2 (13) | 3 (8) | 0.57 |
| **Medications at 12-month visit** | **With SIE n = 13** | **Without SIE n = 35** | **p-value** |
| Prednisone | 12 (92) | 28 (80) | 0.23 |
| Mean prednisone dosage mg/day ±SD | 8.6±4.8 | 13.8±14.4 | 0.11 |
| Corticosteroid + Immunosuppressants | 12 (92) | 25 (71) | 0.09 |
| Corticosteroid + biologics | 0 | 3 (9) | 0.21 |
| Any change in hypertensive medication | 2 (15) | 2 (6) | 0.21 |
| **Medications at last follow-up** [a] | **With SIE n = 13** | **Without SIE n = 35** | **p-value** |
| Prednisone | 3 (17) | 19 (54) | **0.01** |
| Mean prednisone dosage in mg/day ±SD | 1.5±3.1 | 5.0±8.2 | 0.07 |
| Corticosteroid + Immunosuppressants | 8 (61) | 15 (43) | 0.07 |
| Corticosteroid + biologics | 1 (0.07) | 5 (14) | 0.13 |
| Any change in hypertensive medication | 2 (15) | 2 (6) | 0.06 |

[a] Includes patients with last follow-up at >12 months from baseline
Data is presented as numbers (%) unless otherwise indicated
SIE=severe ischemic event

**Table 3.** ***Outcomes and disease activity scores in SIE and non-SIE patients***

| **Outcomes at diagnosis** | **With SIE n = 15** | **Without SIE n = 37** | **p-value** |
|---|---|---|---|
| Active, n (%) | 15 (100) | 37 (100) | 1.00 |
| ITAS, mean (SD) | 11.4 (5.8) | 9.19 (3.9) | 0.06 |
| **Outcomes at 6-month visit** | **With SIE n = 15** | **Without SIE n = 36** | **p-value** |
| Total remission/improving, n (%) | 10 (67) | 30 (83) | 0.18 |
| Active, n (%) | 1 (6) | 2 (6) | 0.84 |
| Relapse, n (%) | 4 (27) | 4 (11) | 0.16 |
| ITAS, mean (SD) | 1.27 (1.7) | 0.83 (1.4) | 0.17 |
| **Outcomes at 12-month visit** | **With SIE n = 13** | **Without SIE n = 35** | **p-value** |
| Total remission/improving, n (%) | 12 (92) | 28 (80) | 0.23 |
| Active, n (%) | 0 | 2 (6) | 0.284 |
| Relapse, n (%) | 1 (8) | 5 (14) | 0.40 |
| ITAS, mean (SD) | 0.46 (0.9) | 0.71 (1.6) | 0.30 |
| **Outcomes at last follow-up[a]** | **With SIE n = 13** | **Without SIE n = 35** | **p-value** |
| Total remission/improving, n (%) | 11 (85) | 34 (97) | **0.04** |
| Active, n (%) | 0 | 0 | N/A |
| Relapse, n (%) | 2 (18) | 1 (3) | **0.04** |
| ITAS, mean (SD) | 0.08 (0.28) | 0.54 (2.0) | 0.19 |

[a] Includes patients with last follow-up at >12months from baseline
SIE=severe ischemic event; ITAS=Indian Takayasu Activity Score