


# Incidence, prevalence and risk of stroke in patients with Takayasu arteritis: a nationwide population-based study in South Korea

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## ABSTRACT

**Background** Takayasu arteritis (TAK) is a disease associated with increased risk of cardiovascular complications. We aimed to evaluate the incidence, prevalence and risk of stroke in patients with TAK. **Methods** Data from 1065 patients were obtained from a national database (2010–2018). The annual incidence and prevalence per 100 000 persons were estimated using the registration population in the midst of every year, and the standardised incidence ratio (SIR) of stroke was compared with the general population based on the data from the 2006 national report for cardiovascular and cerebrovascular diseases. Age-adjusted incidence rate ratio (IRR) of stroke based on the time interval after diagnosis was also calculated. A time-dependent Cox regression was conducted to investigate predictive factors of stroke.

**Results** The overall incidence rate of TAK ranged between 0.2 and 0.3/100 000 person-years annually; the prevalence of TAK gradually increased, reaching 3.25/100 000 person-years in 2018. Seventy-three (6.9%) patients experienced stroke during follow-up, and the risk of developing stroke was higher than the general population (overall SIR 7.39, 95% CI 5.79 to 9.29; men: SIR 5.70, 95% CI 2.84 to 10.20; women: SIR 7.06, 95% CI 5.41 to 9.05). Most stroke events (90.9%) were cerebral infarction for men, whereas the proportion of cerebral infarction was lower (62.9%) in women. Over half of stroke events occurred within 6 months after diagnosis, and stroke was more common within 6 months of diagnosis compared with after 3 years in women (IRR 13.46, 95% CI 6.86 to 26.40). In Cox regression analysis, age was the sole predictor of stroke (adjusted HR 1.02, 95% CI 1.00 to 1.04,  $p=0.043$ ).

**Conclusions** The annual incidence of TAK was similar to the previous studies from Asia, and the risk of stroke increased in TAK. Different patterns of subtype and incidence of stroke were found according to sex, although age was the only predictor.

## INTRODUCTION

Takayasu arteritis (TAK) is a rare inflammatory disease of unknown aetiology that typically affects the aorta and its main branches and is categorised as a large vessel vasculitis according to the 2012 International Chapel Hill Consensus Conferences (CHCC)

definition.<sup>1,2</sup> TAK is particularly common in women under the age of 40 years and in Asia, while a variable incidence and prevalence has been reported according to geographical regions.<sup>3</sup> A characteristic pathological feature of TAK is the presence of granulomatous inflammation in the affected vasculatures, leading to intravascular fibrosis, vascular thickening, and the development of occlusive and stenotic lesions in the late disease stage.<sup>4</sup> In patients with TAK, a wide variety of symptoms could be present, including weight loss, mild fever and fatigue, joint pain and carotidynia.<sup>4</sup> In addition, patients may complain of gastrointestinal, respiratory, nervous, ocular and dermatological manifestations.<sup>5</sup> Among the various clinical presentations, it has been increasingly recognised that the occurrence of cardiovascular complications increases in TAK as a consequence of intravascular inflammation.

Existing literature indicates that cardiovascular complications arising in TAK could be largely variable. In particular, hypertension is common in TAK, which may be related to alterations of vascular elasticity. Chronic vascular inflammation may cause narrowing and obstruction of blood vessels, which present as decreased pulse rate and limb claudication, and the formation of aneurysms in the affected vessels may occur.<sup>5</sup> Moreover, the risk of developing cardiovascular diseases such as coronary artery disease, valvular disease and heart failure is heightened.<sup>6</sup> Notably, it has also been reported that patients with TAK are susceptible to stroke, which is a serious life-threatening medical condition that necessitates careful monitoring. Multicentre studies conducted in France have revealed that 6.3% of patients with TAK developed stroke and 7.5% experienced stroke/transient ischaemic attack after disease diagnosis.<sup>7,8</sup> Alternatively, studies in South Korea and China using a

large single-centre database have suggested that 11.1% and 5.4% of patients, respectively, subsequently experienced ischaemic stroke after the onset of TAK.<sup>9,10</sup> Given that TAK involves the major vasculatures supplying blood to the brain and causes vascular obliteration, it could be hypothesised that the risk of stroke is increased in patients with TAK. However, due to the disease rarity, the incidence of stroke in TAK has not been well described in a large number of patients and a better understanding is necessary. Moreover, the risk of developing stroke in patients with TAK compared with that in the general population still remains largely unclear. Thus, the present study aimed to evaluate the incidence, prevalence and risk of stroke in patients with TAK by using a nationwide claims database in South Korea.

## METHODS

### The Korean Health Insurance and Review Agency database and case identification

The Health Insurance and Review Agency (HIRA) database, which is operated by the South Korean government, includes information of nearly all healthcare utilisation of the South Korean population (more than 50 million individuals).<sup>11</sup> This is possible because the usage of every hospital procedure (including medical procedures and drug prescriptions) should be submitted to the Korean National Health Insurance Service by healthcare providers to request financial compensation, which is subsequently stored in the HIRA database. It allows for access to nationwide data generated by medical institutions for epidemiological studies. Besides the use of medical service, other types of information such as clinical information, diagnosis and comorbidities based on International Classification of Disease (ICD)-10 codes are also available in the HIRA database.

We identified the demographic information of patients with TAK, including age, sex and type of insurance, by searching the HIRA database from January 2008 to December 2018. Cases that were granted the ICD-10 code (M31.4) for TAK in a general or tertiary hospital and were also subject to a medical expense reduction for patients with rare and incurable diseases by the Korean National Health Insurance Service were defined to have TAK. The index date of TAK diagnosis was designated as the date when the patient was first enrolled with the ICD-10 code of TAK in the HIRA database. To select incident cases of TAK, a washout period of 2 years was given to exclude cases that were diagnosed as TAK before study inclusion. Prevalent cases of TAK were defined as those who visited a general or tertiary hospital during the study period (2008–2018) with the ICD-10 code for TAK and who were granted a reduction in medical expenditure by the Korean National Health Insurance. The incidence and prevalence of TAK were estimated as the number of cases in the corresponding year per 100 000 persons, using the registration population in the midst of every year.

### Comorbidities, definition of stroke and medications

For the comorbidities assessed, the presence of hypertension (ICD-10 code: I10–I15), diabetes mellitus (E10–E14), dyslipidaemia (E78), and atrial fibrillation and flutter (I48) within 1 year of the index date for TAK was identified. Patients with TAK were defined as having stroke when they were admitted to a hospital and were simultaneously registered with the ICD-10 codes for stroke (I60–I64) after the TAK diagnosis.<sup>12</sup> The follow-up duration for patients with TAK and stroke was determined as the index date of diagnosis to the date of stroke event, while it was set as the last follow-up date in patients who did not experience stroke.

Medication prescriptions, which included immunosuppressants, antiplatelet therapy and statins, given to patients after disease diagnosis before the occurrence of stroke or the last follow-up were also investigated. Glucocorticoid usage was defined as administering methylprednisolone, hydrocortisone, prednisone, prednisolone, triamcinolone, budesonide, betamethasone, dexamethasone or deflazacort.

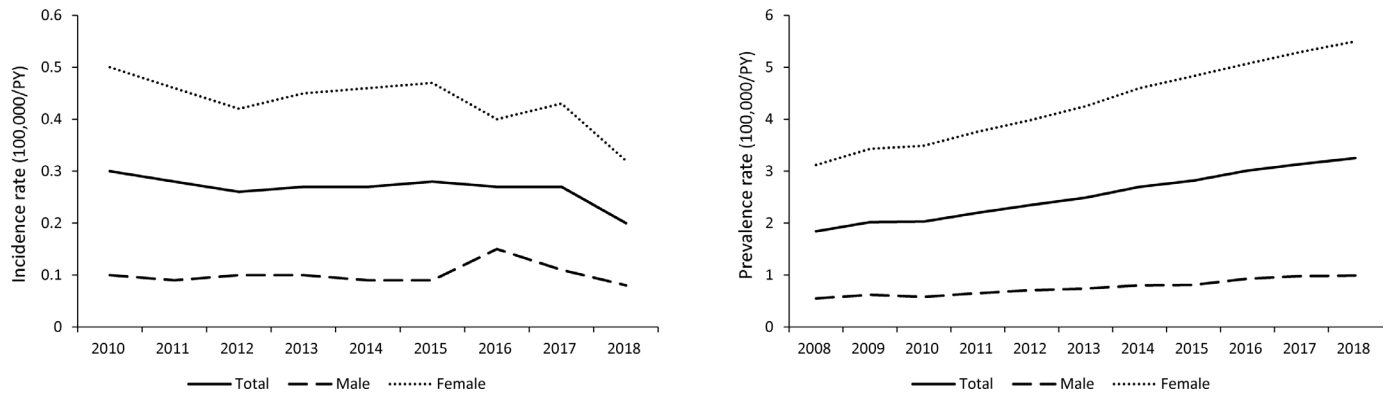
### Statistical analysis

All statistical analyses were performed using SAS V.9.4 Enterprise Guide (SAS Institute). Data were presented as mean±SD for continuous variables and frequencies (percentages) for categorical variables. Student's t-test and the  $\chi^2$  or Fisher's exact tests were used to compare continuous and categorical variables, respectively. Poisson regression was carried out to test whether there was a linear trend in the prevalence of stroke, and the age-adjusted standardised incidence ratio (SIR) of stroke in patients with TAK was estimated by dividing the number of observed cases by expected cases. The number of expected cases was derived by dividing the age of patients into three groups (age ≤54, 55–74 and ≥75 years old), based on the data from the 2006 national report for cardiovascular and cerebrovascular diseases.<sup>13</sup> The incidence rate/1000 person-years was calculated to compare stroke in patients with TAK according to the time interval after diagnosis. A Poisson regression with an offset for person-years was used to obtain the incidence rate ratio (IRR) and 95% CI, adjusted for age by stratifying into five different groups as follows: (1) stroke <6 months, (2) 6 months≤stroke<1 year, (3) 1 year ≤stroke<2 years, (4) 2 years ≤stroke<3 years, and (5) stroke ≥3 years. The cumulative incidence rate of stroke after disease diagnosis was also calculated. Predictive factors of stroke in patients with TAK were investigated using time-dependent Cox regression analysis, including administered medications as the time-dependent variable. In all analyses, a two-tailed p value of <0.05 was considered significant.

## RESULTS

### Incidence and prevalence of TAK and comparison of baseline characteristics of patients with and without stroke

Among the 1217 patients with TAK identified in the HIRA database, 152 cases were excluded because stroke event



**Figure 1** Annual incidence and prevalence of TAK. The annual incidence and prevalence of TAK were calculated by using the population estimates in the midst of every year. PY, person-years; TAK, Takayasu arteritis.

was present prior to disease diagnosis. In the remaining 1065 cases, 867 (81.4%) patients were women and 198 (18.6%) were men (online supplemental figure 1). The overall incidence rate of TAK ranged between 0.2 and 0.3/100 000 person-years annually, and the prevalence of TAK gradually increased during the study period, which reached 3.25/100 000 person-years in 2018. The incidence and prevalence were higher in women than in men, but the prevalence of TAK was found to increase consistently in both women and men over the decade (all  $p < 0.001$ ; figure 1).

During the mean follow-up period of 4.29 years, 73 (6.9%) out of 1065 patients experienced stroke. When comparing the baseline characteristics of patients with and without stroke, the mean follow-up duration was significantly shorter in patients with stroke (1.44 years vs 4.51 years,  $p < 0.001$ ). In addition, patients who had a stroke were less likely to receive immunosuppressive treatments, aspirin and statins compared with those who had no stroke during follow-up. However, no significant difference was found regarding age at diagnosis, sex, type of insurance and the presence of comorbidities (table 1).

#### Increased risk of stroke in patients with TAK compared with that in the general population

The overall risk of developing stroke was significantly higher in patients with TAK than in the general population (SIR 7.39, 95% CI 5.79 to 9.29), even though the risk did not differ significantly in patients who were  $\geq 75$  years old. The increased risk of stroke was similar for both sexes (men: SIR 5.70, 95% CI 2.84 to 10.20; women: SIR 7.06, 95% CI 5.41 to 9.05). In both men and women, the risk of stroke was identified to be highest in those who were  $\leq 54$  years old (men: SIR 8.16, 95% CI 2.22 to 20.90; women: SIR 24.85, 95% CI 17.91 to 33.59) (figure 2).

#### Stroke in patients with TAK according to time interval after diagnosis

Of the 73 patients experiencing stroke, cerebral infarction (67.1%) was the most common subtype of stroke, and both subarachnoid and intracerebral haemorrhage accounted for 13.7% of stroke events. In men, cerebral

infarction (90.9%) consisted of the majority of events, while cerebral infarction occurred in 62.9% of women. More than half of stroke events (56.2%) occurred within 6 months after TAK diagnosis; however, the occurrence of stroke in men within 6 months of TAK diagnosis was present in only 36.4% of patients, which was lower than that shown in women (59.7%; table 2). In a cumulative incidence plot, the overall cumulative rates of stroke were 4.16% at 1 year, 7.01% at 5 years and 9.52% at 9 years. The incidence of stroke showed an abrupt increase in the very early stages of disease diagnosis and consistently increased thereafter, and a similar pattern of stroke incidence was demonstrated in women. In contrast, while a steep increase of stroke events was also found in men in the early period of TAK, a second peak of stroke was observed at the fifth year after disease diagnosis (online supplemental figure 2).

When comparing the risk of stroke by time interval after diagnosis, the incidence rate/1000 person-years was the highest in the stroke  $< 6$  months group in men and women equally (men: 41.74; women: 90.65). In women, the risk of developing stroke within 6 months of TAK diagnosis was significantly higher than that of developing stroke within  $\geq 3$  years of TAK diagnosis in an age-adjusted analysis (adjusted IRR 13.46, 95% CI 6.86 to 26.40), even though this difference was not evident in men (table 3).

#### Predictive factors of stroke in patients with TAK

In a Cox regression analysis to evaluate the predictive factors of stroke in patients with TAK, age at diagnosis was significantly associated with the occurrence of stroke in an unadjusted analysis (HR 1.02, 95% CI 1.00 to 1.03,  $p = 0.049$ ). No other factors were relevant to the development of stroke. Age was the sole predictor of stroke in an adjusted analysis, similar to the unadjusted analysis (HR 1.02, 95% CI 1.00 to 1.04,  $p = 0.043$ ; table 4).

#### DISCUSSION

Although researches on TAK significantly contributed to the increased understanding of this disease, epidemiological studies investigating the incidence of stroke in

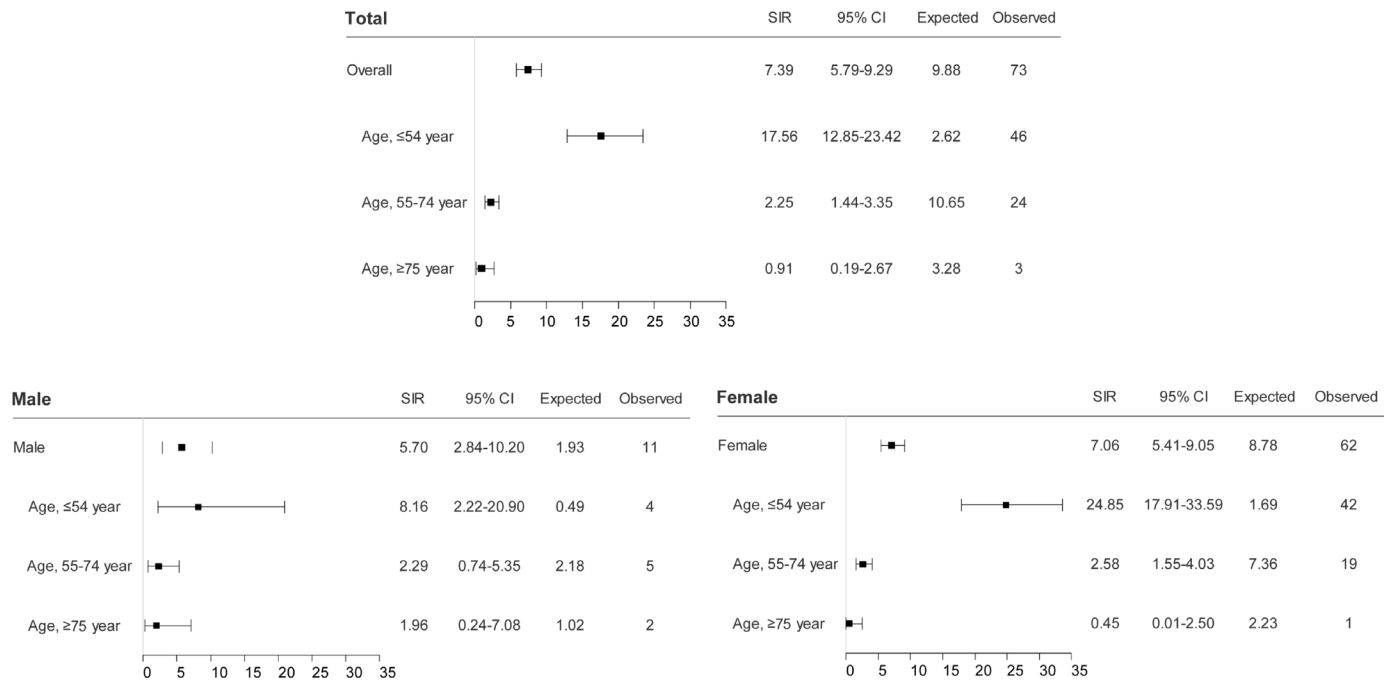
**Table 1** Baseline characteristics of patients with TAK included in the study

|                                    | Total (n=1065) | Patients who had a stroke (n=73) | Patients who had no stroke (n=992) | P value |
|------------------------------------|----------------|----------------------------------|------------------------------------|---------|
| Age at diagnosis (years)           | 46.7±15.0      | 49.5±13.4                        | 46.5±15.2                          | 0.101   |
| <20                                | 51 (4.8)       | 3 (4.1)                          | 48 (4.8)                           | 0.116   |
| 20–29                              | 113 (10.6)     | 1 (1.4)                          | 112 (11.3)                         |         |
| 30–39                              | 146 (13.7)     | 12 (16.4)                        | 134 (13.5)                         |         |
| 40–49                              | 263 (24.7)     | 18 (24.7)                        | 245 (24.7)                         |         |
| 50–59                              | 280 (26.3)     | 26 (35.6)                        | 254 (25.6)                         |         |
| 60–69                              | 152 (14.3)     | 8 (11.0)                         | 144 (14.5)                         |         |
| ≥70                                | 60 (5.6)       | 5 (6.8)                          | 55 (5.6)                           |         |
| Sex, n (%)                         |                |                                  |                                    | 0.518   |
| Female                             | 867 (81.4)     | 62 (84.9)                        | 805 (81.1)                         |         |
| Male                               | 198 (18.6)     | 11 (15.1)                        | 187 (18.9)                         |         |
| Type of insurance, n (%)           |                |                                  |                                    | 0.157   |
| National Health Insurance          | 1034 (97.1)    | 69 (94.5)                        | 965 (97.3)                         |         |
| Medical aid                        | 31 (2.9)       | 4 (5.5)                          | 27 (2.7)                           |         |
| Comorbidities                      |                |                                  |                                    |         |
| Hypertension                       |                |                                  |                                    | 0.904   |
| No                                 | 569 (53.4)     | 40 (54.8)                        | 529 (53.3)                         |         |
| Yes                                | 496 (46.6)     | 33 (45.2)                        | 463 (46.7)                         |         |
| Diabetes mellitus                  |                |                                  |                                    | 0.924   |
| No                                 | 858 (80.6)     | 58 (79.4)                        | 800 (80.6)                         |         |
| Yes                                | 207 (19.4)     | 15 (20.6)                        | 192 (19.4)                         |         |
| Dyslipidaemia                      |                |                                  |                                    | 0.436   |
| No                                 | 544 (51.1)     | 41 (56.2)                        | 503 (50.7)                         |         |
| Yes                                | 521 (48.9)     | 32 (43.8)                        | 489 (49.3)                         |         |
| Atrial fibrillation and flutter    |                |                                  |                                    | 0.303   |
| No                                 | 1029 (96.6)    | 69 (94.5)                        | 960 (96.8)                         |         |
| Yes                                | 36 (3.4)       | 4 (5.5)                          | 32 (3.2)                           |         |
| Administered medication            |                |                                  |                                    |         |
| Immunosuppressive treatments       |                |                                  |                                    |         |
| Glucocorticoid treatment ≥3 months | 538 (50.5)     | 16 (21.9)                        | 522 (52.6)                         | <0.001  |
| Azathioprine                       | 201 (18.9)     | 6 (8.2)                          | 195 (19.7)                         | 0.024   |
| Methotrexate                       | 366 (34.4)     | 11 (15.1)                        | 355 (35.8)                         | <0.001  |
| Antiplatelet therapy               |                |                                  |                                    |         |
| Aspirin                            | 655 (62.4)     | 31 (42.5)                        | 634 (63.9)                         | <0.001  |
| Clopidogrel                        | 299 (28.1)     | 16 (21.9)                        | 283 (28.5)                         | 0.281   |
| Statins                            | 610 (57.3)     | 25 (34.3)                        | 585 (59.0)                         | <0.001  |
| Follow-up duration (years)         | 4.29 (2.66)    | 1.44 (2.06)                      | 4.51 (2.57)                        | <0.001  |

Values are shown as mean (SD) or number (percentages).  
TAK, Takayasu arteritis.

TAK, especially in a large number of patients, are scarce. Our observations revealed that the proportion of patients suffering from stroke (6.9%) after disease diagnosis was consistent with a publication reporting the frequency of stroke and transient ischaemic attack between 3% and 9% in TAK.<sup>14</sup> In addition, a recent retrospective study of

two tertiary referral hospitals in our institution revealed that cerebrovascular events occurred in 7.2% of patients with TAK, which validates the results from the present study.<sup>15</sup> Importantly, it was also demonstrated that the risk of developing stroke in patients with TAK increased compared with the general population, irrespective of



**Figure 2** The SIR of stroke in patients with TAK compared with that in the general population. Patients with TAK more often experienced a stroke compared with the general population. In addition, the risk of stroke was higher in both men and women with TAK in a similar manner. The risk of stroke was the highest in those patients ≤54 years old. SIR, standardised incidence ratio; TAK, Takayasu arteritis.

sex. In particular, in both men and women, the risk of stroke was especially higher in patients who were ≤54 years old. Considering that older age is generally accompanied with a higher risk of stroke in the general population, this inverse tendency emphasises that patients with TAK should be closely monitored for the occurrence of stroke regardless of age.

Although the incidence of TAK in the general population has not been well established, a generally higher incidence of TAK was found in Asia than in Western countries.<sup>16</sup> A nationwide, hospital-based study from Japan showed that the incidence of TAK was identified as 1–2 people per

million/year, and a study from Kuwait reported that the overall incidence of TAK was 2.2 people per million/year. In contrast, it was identified that the incidence of TAK was less than 1 person per million/year in Germany and the UK, which is lower than the incidence in Asia.<sup>3</sup> The incidence of TAK identified through the HIRA database ranged between 0.2 and 0.3/100 000 person-years annually, which is similar to estimates proposed in previous studies in Asia. Notably, our findings revealed that the prevalence of TAK is gradually increasing in South Korea, which could be attributed to increased disease recognition by attending physicians and advancements in patient care.

**Table 2** Stroke events and time interval of occurrence after TAK diagnosis

| Event of stroke                                    | Total (n=73) | Male (n=11) | Female (n=62) | P value |
|--|--------------|-------------|---------------|---------|
| Subarachnoid haemorrhage                           | 10 (13.7)    | 0 (0.0)     | 10 (16.1)     | 0.500   |
| Intracerebral haemorrhage                          | 10 (13.7)    | 1 (9.1)     | 9 (14.5)      |         |
| Other non-traumatic intracranial haemorrhage       | 0 (0.0)      | 0 (0.0)     | 0 (0.0)       |         |
| Cerebral infarction                                | 49 (67.1)    | 10 (90.9)   | 39 (62.9)     |         |
| Stroke, not specified as haemorrhage or infarction | 4 (5.5)      | 0 (0.0)     | 4 (6.5)       |         |
| Time interval of stroke occurrence after diagnosis | Total (n=73) | Male (n=11) | Female (n=62) | P value |
| Stroke <6 months                                   | 41 (56.2)    | 4 (36.4)    | 37 (59.7)     | 0.320   |
| 6 months ≤stroke <1 year                           | 3 (4.1)      | 1 (9.1)     | 2 (3.2)       |         |
| 1 year ≤stroke <2 years                            | 8 (11.0)     | 1 (9.1)     | 7 (11.3)      |         |
| 2 years ≤stroke <3 years                           | 6 (8.2)      | 1 (9.1)     | 5 (8.1)       |         |
| Stroke ≥3 years                                    | 15 (20.5)    | 4 (36.4)    | 11 (17.7)     |         |

Values are shown as number (percentages).  
TAK, Takayasu arteritis.

**Table 3** Incidence rate ratio (IRR) of stroke in patients with TAK stratified by time interval after diagnosis

| After diagnosis         | Male        |        |                        |                      |                        | Female      |         |                         |                       |                        |
|-------------------------|-------------|--------|------------------------|----------------------|------------------------|-------------|---------|-------------------------|-----------------------|------------------------|
|                         | # of events | PY     | IR/1000 PY (95% CI)    | Crude IRR (95% CI)   | Adjusted IRR (95% CI)* | # of events | PY      | IR/1000 PY (95% CI)     | Crude IRR (95% CI)    | Adjusted IRR (95% CI)* |
| Stroke <6 months        | 4           | 95.83  | 41.74 (12.96 to 96.95) | 3.62 (0.91 to 14.48) | 2.94 (0.73 to 11.81)   | 37          | 408.17  | 90.65 (64.49 to 123.07) | 13.61 (6.95 to 26.69) | 13.46 (6.86 to 26.40)  |
| 6 months ≤stroke<1 year | 1           | 90.35  | 11.07 (6.31 to 48.69)  | 0.96 (0.11 to 8.59)  | 0.80 (0.09 to 7.14)    | 2           | 384.13  | 5.21 (0.87 to 16.07)    | 0.78 (0.17 to 3.53)   | 0.77 (0.17 to 3.49)    |
| 1 year ≤stroke<2 years  | 1           | 164.99 | 6.06 (0.35 to 26.66)   | 0.53 (0.06 to 4.70)  | 0.46 (0.05 to 4.10)    | 7           | 694.35  | 10.08 (4.33 to 19.49)   | 1.51 (0.59 to 3.90)   | 1.50 (0.58 to 3.87)    |
| 2 years ≤stroke<3 years | 1           | 135.45 | 7.38 (4.21 to 32.47)   | 0.64 (0.07 to 5.73)  | 0.60 (0.07 to 5.40)    | 5           | 602.48  | 8.3 (2.98 to 17.84)     | 1.25 (0.43 to 3.58)   | 1.24 (0.43 to 3.56)    |
| Stroke ≥3 years         | 4           | 346.95 | 11.53 (3.58 to 26.78)  | 1.00 (ref)           | 1.00 (ref)             | 11          | 1651.45 | 6.66 (3.46 to 11.41)    | 1.00 (ref)            | 1.00 (ref)             |

\*IRR was calculated by adjusting for age.

IR, incidence rate; IRR, incidence rate ratio; PY, person-years; TAK, Takayasu arteritis.

**Table 4** Predictive factors of stroke in patients with TAK during disease course

|  | Crude HR   |              |         | Adjusted HR |              |         |
|--|------------|--------------|---------|-------------|--------------|---------|
|  | HR         | 95% CI       | P value | HR          | 95% CI       | P value |
| Age                                      | 1.02       | 1.00 to 1.03 | 0.049   | 1.02        | 1.00 to 1.04 | 0.043   |
| Sex                                      |            |              |         |             |              |         |
| Female                                   | 1.00 (ref) |              |         | 1.00 (ref)  |              |         |
| Male                                     | 0.78       | 0.41 to 1.49 | 0.455   | 0.83        | 0.44 to 1.58 | 0.573   |
| Type of insurance                        |            |              |         |             |              |         |
| National Health Insurance                | 1.00 (ref) |              |         | 1.00 (ref)  |              |         |
| Medical aid                              | 1.88       | 0.69 to 5.16 | 0.219   | 1.93        | 0.70 to 5.33 | 0.205   |
| Comorbidities                            |            |              |         |             |              |         |
| Hypertension                             | 0.96       | 0.60 to 1.51 | 0.844   | 0.85        | 0.51 to 1.42 | 0.527   |
| Diabetes mellitus                        | 1.13       | 0.64 to 2.00 | 0.666   | 1.13        | 0.62 to 2.09 | 0.688   |
| Dyslipidaemia                            | 0.88       | 0.55 to 1.39 | 0.572   | 0.80        | 0.47 to 1.36 | 0.408   |
| Atrial fibrillation and flutter          | 1.95       | 0.71 to 5.34 | 0.196   | 1.66        | 0.59 to 4.69 | 0.340   |
| Administered medication*                 |            |              |         |             |              |         |
| Immunosuppressive treatments             |            |              |         |             |              |         |
| Glucocorticoid treatment $\geq 3$ months | 0.74       | 0.38 to 1.46 | 0.388   | 0.82        | 0.38 to 1.79 | 0.624   |
| Azathioprine                             | 0.72       | 0.31 to 1.70 | 0.458   | 0.86        | 0.35 to 2.12 | 0.740   |
| Methotrexate                             | 0.72       | 0.37 to 1.39 | 0.322   | 0.85        | 0.41 to 1.77 | 0.660   |
| Antiplatelet therapy                     |            |              |         |             |              |         |
| Aspirin                                  | 0.84       | 0.51 to 1.37 | 0.483   | 0.78        | 0.45 to 1.34 | 0.364   |
| Clopidogrel                              | 1.25       | 0.70 to 2.21 | 0.454   | 1.40        | 0.75 to 2.60 | 0.290   |
| Statins                                  | 0.91       | 0.55 to 1.51 | 0.718   | 0.83        | 0.46 to 1.50 | 0.544   |

\*The administration of medication was included as time-dependent covariates. CI, confidence interval; HR, hazard ratio; TAK, Takayasu arteritis.

In the recent decades, several criteria for the classification of TAK were proposed, including the 1990 American College of Rheumatology (ACR) criteria, Ishikawa's diagnostic criteria and its recent revisions in 1995 by Sharma *et al.*<sup>17–19</sup> The mean age of patients in this study was 46.7 years, and 755 (70.9%) and 294 (46.2%) patients were over 40 and 50 years old, respectively, when the initial TAK diagnosis was established. Although the age of our study population seems to be higher compared with the previous literature,<sup>20</sup> recent publications that were performed in South Korea reported a comparable estimates of age.<sup>15–21</sup> Therefore, it could be suggested that a different epidemiology according to geographical region seems to exist. In particular, the criterion of age  $\leq 40$  years is included in the 1990 ACR criteria and is an obligatory criterion in Ishikawa's criteria, whereas the standard for age is more flexibly reflected in the 2012 CHCC definitions by age  $\leq 50$  years. Given that there is accumulating evidence which suggests TAK could be present even in those aged  $\geq 50$  years,<sup>22</sup> our results clearly indicate that an absolute cut-off age could not be uniformly applied in TAK diagnosis and support the idea that a TAK diagnosis should be considered based on patients' clinical presentation.

In our analysis, the overall incidence of stroke in TAK showed an abrupt increase in the very early stages of disease and continued to consistently increase throughout follow-up. We found that the time interval of stroke occurrence after the diagnosis of TAK was less than 6 months in more than 50% of patients. Consistently, a growing body of literature emphasises that stroke could be an initial manifestation of TAK,<sup>23</sup> implying that a systemic evaluation for TAK should be considered in subjects with stroke in the absence of traditional risk factors or with features suggesting TAK. Furthermore, on analysing the subtype (ie, ischaemic or haemorrhagic) of stroke affecting men and women, cerebral infarction was the predominant type of stroke in men, which seemed higher than that in the general population.<sup>24</sup> In contrast, the incidence of haemorrhagic stroke accounted for more than 30% in women. Additionally, the risk of developing stroke was significantly higher within 6 months of TAK diagnosis compared with after 3 years in women (adjusted IRR 13.46), and according to the cumulative incidence plot, another peak of stroke incidence was found in men at the fifth year after TAK diagnosis. Thus, different clinical attention based on sex should be given in cases of TAK concerning the subtype and incidence of stroke.

The underlying pathogenesis of TAK is characterised by the presence of chronic inflammation in the affected vessels.<sup>5</sup> Recent studies indicate that abnormalities of cellular and humoral immunity are responsible for the initiation and perpetuation of inflammation in TAK, resulting in vascular damage and the development of occlusion and malformation within blood vessels.<sup>25</sup> As these immunological mechanisms of TAK suggest that anti-inflammatory treatment could be beneficial, a time-dependent Cox regression analysis was performed by imputing the administration of medications as a time-dependent covariate. Unfortunately, our data showed that age was exclusively associated with stroke and failed to reveal a protective effect of immunosuppressant administration, along with antiplatelet therapy and statins. Although age is a widely accepted risk factor for stroke,<sup>26</sup> the absence of other predictive factors could be partly explained by the relatively small number of patients with stroke, the large proportion of patients affected by stroke in the early stages after diagnosis or the limited data accessible through the HIRA database. Therefore, further research is essential to identify whether immunosuppressive agents provide therapeutic benefits to prevent stroke in TAK.

The most important result of this study was that we assessed the occurrence of stroke in patients with TAK using a nationwide database, which enabled us to include a large number of patients. However, several issues could be considered limitations of this study. First, since the habitual factors such as smoking, alcohol, obesity and physical activity could not be identified, the effects of these factors in stroke events could not be assessed. Second, symptoms of the patients and the type of vascular involvement patterns in TAK, as proposed in a previous study,<sup>27</sup> could not be identified due to limitations of data available in the HIRA database. Third, the laboratory results of acute phase reactants (ie, erythrocyte sedimentation rate and C reactive protein) and lipid profiles, which may affect the occurrence of stroke, could not be obtained. Fourth, the risk of stroke in TAK compared with the general population was evaluated using the 2006 national report for cardiovascular and cerebrovascular diseases as a reference, and a direct comparison of risk factors in patients with TAK and the general population could not be made. Fifth, the administration and clinical effect of tumour necrosis factor- $\alpha$  inhibitors, including infliximab and etanercept in suppressing stroke, could not be investigated as this agent is not covered by the National Health Insurance System. Finally, it should be verified in the future whether the utilisation of ICD-10 code and medical expense reduction for patients with rare and incurable diseases are appropriate in identifying patients with TAK.

## CONCLUSIONS

This study demonstrated that the annual incidence of TAK in South Korea is similar to that reported in studies

conducted in Asia. In addition, the risk of stroke increased in patients with TAK compared with that in the general population, which was most pronounced in the early stages after TAK diagnosis. Moreover, a different pattern of subtype and incidence of stroke was observed in men and women. The results emphasise that strict surveillance of stroke is necessary in patients with TAK, and a systematic investigation for TAK should be considered in subjects with stroke upon clinical suspicion.

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