Aortic valve surgery in patients with Takayasu's arteritis: a nationwide analysis of 1,197 patients during a 9-year period

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Abstract

Objective

Takayasu's arteritis (TAK) is associated with an elevated risk of valvular heart disease, especially in the aortic valve. This study aimed to evaluate the rate and risk factors of aortic valve surgery (AVS) in patients with TAK.

Methods

The clinical data of 1,197 patients were identified in the Korean National Health Insurance Claims database between 2010 and 2018. Case ascertainment was done by using the ICD-10 code of TAK and inclusion in the Rare Intractable Diseases registry. The incidence rate/1,000 person-years was calculated to compare the age- and sex- adjusted incidence rate ratio (IRR) of AVS according to the time period between TAK diagnosis and AVS: <1 year, 1–2 years, 2–3 years, and 3 years. Evaluation of factors associated with AVS was performed using a time-dependent Cox regression analysis.

Results

Forty-five patients (3.8%) underwent AVS during the follow-up. The mean follow-up duration of patients with AVS was 1.2 years, and two-thirds of the patients (66.7%) underwent AVS within 1 year. The adjusted IRR was significantly higher among patients who underwent AVS <1 year after the diagnosis of TA than among those who underwent AVS ≥3 years after diagnosis (adjusted IRR: 10.31; 95% confidence interval [CI]: 4.29–24.81). A history of hypertension before the diagnosis of TAK was an independent risk factor for AVS (adjusted hazard ratio: 2.18; 95% CI: 1.12–4.24).

Conclusion

Approximately 4% of patients with TAK undergo AVS, usually within the first year of TAK diagnosis. Previous history of hypertension is a risk factor for AVS.

Key words

Takayasu's arteritis, aortic valve surgery, aortic regurgitation, hypertension, risk factor

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Introduction

Takayasu's arteritis (TAK) is an idiopathic chronic autoimmune disease that usually affects young females and is common in Asian countries. Vascular involvement, especially in the aorta and its major branches, is a cardinal feature of TAK (1). In the early disease stages of TAK, inflammation begins in the adventitia and advances to the intima. The dysregulation of cellular immunity is thought to play a critical role in the amplification and maintenance of autoimmunity in TAK (2, 3). As a result, long-standing intravascular inflammation leads to progressive vessel damage, which is associated with the occurrence of stenosis and ultimately occlusion in the affected vessels in addition to vascular aneurysms and dilatation (4, 5). Accordingly, it has been reported that the risks of cardiac manifestations such as limb claudication, blood pressure discrepancies in the upper extremities, coronary heart disease, cardiac valvular disease, cardiomyopathy, and cerebrovascular accidents are increased in patients with TAK (6).

Valvular heart disease, especially involving the aortic valve, has been reported as relatively common in patients with TAK. A previous study reported that 41% of patients with TAK who underwent echocardiography had aortic regurgitation (AR) (7). Another study reported that 47.9% of patients with TA were found to have AR (8), and valvular regurgitation was reported in 34.9% of patients with TAK, of which AR accounted for nearly 70% of the cases (9). Furthermore, a single-centre study reported that more than 60% of patients with TAK had cardiac valvular involvement and that aortic valve involvement was the most common type (10). Although recent advances in the management of TAK have improved clinical outcomes, aortic insufficiency continues to be one of the most deteriorating complications of TAK (11), and surgical treatment is required when severe aortic insufficiency is present. Nevertheless, the rate of aortic valve surgery (AVS) in patients with TAK has not been well described, which may be attributed to the rarity and difficulty in diagnosing TAK. Therefore, this study assessed the rate and risk factors of AVS in patients with TAK.

Materials and methods

Case ascertainment from the Korean National Health Insurance Claims database

All patient data were obtained through a search of the Korean National Health Insurance Claims database from January 2008 to December 2018. In brief, the Korean National Health Insurance Claims database is a nationwide data repository that records healthcare service usage (hospital care and prescriptions) covered by the national health insurance for the majority of residents (more than 50 million) in South Korea. In this database, data regarding patients' age, sex, insurance type, and area of residence are available, as well as the principal diagnosis and comorbid conditions in the form of International Classification of Diseases (ICD)-10 codes.

We identified incident cases of TAK by applying a 2-year washout period and selecting patients who were diagnosed with TAK (ICD-10 code: M31.4) in a secondary or tertiary care hospital and also registered in the Rare Intractable Diseases (RID) programme of South Korea. In South Korea, patients that are included in the RID programme have 90% of their medical expenses associated with the corresponding diagnosis subsidised by the South Korean government. Accordingly, the RID program promotes regular medical care and optimal disease management. The index date of the diagnosis of TAK was defined as the first date of the ICD-10 code M31.4 in the Health Insurance and Review Agency database. Patients who received AVS after a diagnosis of TA were identified by the procedural codes for AVS (M6532, O1783, O1793, O1796, and O1799) available in the healthcare big data hub provided by the Health Insurance Review & Assessment service.

This study was approved by the Institutional Review Board of Severance Hospital (IRB approval no.: 4-2020-0826), and all research procedures were performed in accordance with the principles of the Declaration of Helsinki. The

requirement of informed consent was waived by the review board due to the retrospective nature of this study.

Collection of demographic data, comorbid conditions, medications and outcomes

Data regarding patient age, sex, type of AVS, follow-up duration, type of insurance, and area of residence were collected from the database. The follow-up duration was defined as the time between the first appearance of the ICD-10 code for TAK to the date of AVS for patients who underwent AVS, or to the date of the last follow-up for patients who did not undergo AVS. Data regarding the following comorbidities within 1 year of the date of the diagnosis of TAK were extracted from the database: hypertension (HTN) (ICD-10 code: I10-15), diabetes mellitus (DM) (E10-14), dyslipidaemia (E78), and chronic kidney disease (CKD) (N18). The use of immunosuppressive agents (glucocorticoids, methotrexate, and azathioprine/mizobribine), antiplatelet drugs, and statins during the follow-up period of the patients were recorded. Glucocorticoids included prescriptions for prednisone, prednisolone, methylprednisolone, triamcinolone, deflazacort, dexamethasone, hydrocortisone, budesonide, and betamethasone. The clinical outcome of immediate in-hospital mortality after AVS was also investigated.

Collection of data of patients without TAK who underwent aortic valve replacement

To compare whether there are differences in the clinical characteristics of age, sex, and in-hospital mortality after AVS or aortic valve replacement (AVR), data from 119 patients who underwent AVR at our hospital without a diagnosis of TAK between January 2010 to December 2010 were retrospectively obtained.

Statistical analyses

Continuous variables are presented as means standard deviations and categorical variables are presented as frequencies (percentages). The t-test and chi-square or Fisher's exact tests were used to compare continuous and categorical variables, as appropriate. The incidence rate/1,000 person-years was calculated to compare the adjusted incidence rate ratio (IRR) of AVS in patients with TA according to the time period between diagnosis and AVS (divided as: time to AVS <1 year, time to AVS=1–2 years, time to AVS=2–3 years, and time to AVS ≥3 years). The age- and sex-adjusted IRRs and 95% confidence intervals (CIs) were calculated using Poisson regression. Evaluation of factors associated with AVS was performed using a time-dependent Cox regression analysis with medication usage as a time-dependent variable. Statistical analyses were performed with SAS version 9.4 Enterprise Guide (SAS Institute Inc., Cary, North Carolina), and statistical significance was set at $p<0.05$.

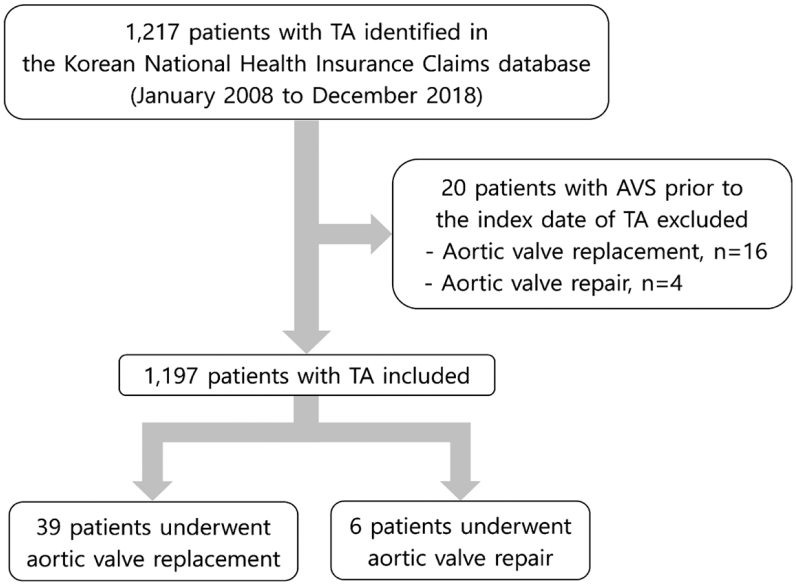

Fig. 1. Flowchart of patients.
TAK: Takayasu's arteritis; AVS: aortic valve surgery.

Results

Comparison of clinical characteristics of patients who underwent AVS and those who did not

Of the 1,217 patients with TAK that were identified, 20 were excluded due to a history of AVS before the diagnosis of TAK; the final analysis included 1,197 patients. A total of 45 patients (3.8%) underwent AVS (Fig. 1). The mean follow-up duration was significantly longer in patients who did not undergo AVS (patients who underwent AVS: 1.2 years; patients who did not undergo AVS: 4.4 years; $p<0.001$). Furthermore, patients who did not undergo AVS were more often administered glucocorticoids ($p=0.020$), aspirin and clopidogrel ($p<0.001$ and $p=0.028$), and statins ($p<0.001$). There were no significant differences in age, sex, or in-hospital mortality between the groups (Table I).

Comparison of AVS rates according to the time period and characteristics of patients who underwent redo AVS

Two-thirds (66.7%) of the patients with TAK underwent AVS within 1 year of being diagnosed with TAK. The incidence rate/1,000 person-years was highest among patients who underwent AVS within 1 year of TAK diagnosis (26.91; 95% CI 18.39–37.72), and the age- and sex- adjusted IRR was significantly higher among these patients than among patients who underwent AVS ≥3 years after diagnosis (adjusted IRR: 10.31; 95% CI: 4.29–24.81) (Table II). Among the 45 patients with TAK who underwent AVS, three were required to undergo a second AVS. These patients were 30–40 years of age, and all underwent AVR. Glucocorticoid and aspirin were commonly used in these patients, and the time between the first AVS and second AVS ranged from 0.90 to 7.37 years (Table III).

Comparison of patients with TAK who underwent AVS and patients without TAK who underwent AVR

Patients with TAK who underwent AVS were significantly younger than patients without TAK who underwent AVR (p<0.001). In addition, the number of female patients was significantly higher among patients with TA who underwent AVS than among patients without TAK who underwent AVR (p<0.001). None of the patients with TAK who underwent AVS died in the hospital after the AVS procedure. The in-hospital mortality rate was not significantly different between the two groups (p=0.562) (Table IV).

Risk factors of AVS in patients with TAK

The administration of glucocorticoids and aspirin were associated with AVS in an unadjusted analysis. However, after adjustment, a history of HTN before a diagnosis of TAK was the only predictive factor of AVS (adjusted hazard ratio [HR]: 2.18; 95% CI: 1.12–4.24; p=0.022). In contrast, the administration of glucocorticoids (adjusted HR: 2.10; 95% CI: 0.96–4.59; p=0.064) and aspirin (adjusted HR: 0.53; 95% CI: 0.27–1.05; p=0.068) were not predictive of AVS in an adjusted model (Table V).

Table I. Patient baseline data.

	Total, (n=1,197)	Patients with AVS (n=45)	Patients without AVS (n=1,152)	p-value
Demographic data				
Age (years)	48.0±15.2	45.9±11.4	48.1±15.3	0.224
Sex, n (%)				
Female	973 (81.3)	39 (86.7)	934 (81.1)	0.454
Male	224 (18.7)	6 (13.3)	218 (18.9)	
AVS type				n/a
Aortic valve replacement	-	39 (86.7)	n/a	
Aortic valve repair	-	6 (13.3)	n/a	
Follow-up duration (years)	4.3 ± 2.6	1.2 ± 1.7	4.4 ± 2.6	<0.001
Insurance type, n (%)				
National Health Insurance	1153 (96.3)	44 (97.8)	1109 (96.3)	0.320
Medical aid	44 (3.7)	1 (2.2)	43 (3.7)	
Residence area, n (%)				
Seoul	645 (53.9)	23 (51.1)	622 (54.0)	0.820
Outside Seoul	552 (46.1)	22 (48.9)	530 (46.0)	
Comorbid conditions, n (%)				
Hypertension				
Yes	591 (49.4)	25 (55.6)	566 (49.1)	0.488
No	606 (50.6)	20 (44.4)	586 (50.9)	
Diabetes mellitus				
Yes	254 (21.2)	5 (11.1)	249 (21.6)	0.132
No	943 (78.8)	40 (88.9)	903 (78.4)	
Dyslipidaemia				
Yes	624 (52.1)	19 (42.2)	605 (52.5)	0.229
No	573 (47.9)	26 (57.8)	547 (47.5)	
Chronic kidney disease				
Yes	32 (2.7)	0 (0.0)	32 (2.8)	0.289
No	1165 (97.3)	45 (100.0)	1120 (97.2)	
Medication usage during follow-up, n (%)				
Immunosuppressive agents				
Glucocorticoid	1051 (87.8)	34 (75.6)	1017 (88.3)	0.020
Methotrexate	403 (33.7)	15 (33.3)	388 (33.7)	1.000
Azathioprine/mizoribine	220 (18.4)	7 (15.6)	213 (18.5)	0.762
Antiplatelet drugs				
Aspirin	791 (66.1)	17 (37.8)	774 (67.2)	<0.001
Clopidogrel	408 (34.1)	8 (17.8)	400 (34.7)	0.028
Statins	741 (61.9)	15 (33.3)	726 (63.0)	<0.001
Outcome, n (%)				
In-hospital mortality	66 (5.5)	5 (11.1)	61 (5.3)	0.097

Continuous variables are shown as means ± standard deviations and categorical variables are shown as frequencies (percentages).
AVS: aortic valve surgery; n/a: not applicable.

Table II. Comparison of AVS rates according to the time period after TAK diagnosis.

Time period after TAK diagnosis	Event numbers	PY	IR/1,000 PY (95% CI)	Adjusted IRR (95% CI)¶
AVS <1 year	30	1,114.78	26.91 (18.39-37.72)	10.31 (4.29-24.81)
1 year ≤ AVS <2 years	3	9,72.98	3.08 (0.77-7.99)	1.18 (0.29-4.71)
2 years ≤ AVS <3 years	6	829.56	7.23 (2.87-14.65)	2.74 (0.88-8.50)
AVS ≥3 years	6	2,246.96	2.67 (1.06-5.41)	1.00 (ref)

AVS: aortic valve surgery; TAK: Takayasu's arteritis; PY: person-years; IR: incidence rate; CI: confidence interval; IRR: incidence rate ratio.
¶Adjusted for age and sex.

Discussion

The International Chapel Hill Consensus Conference defines TAK as a representative large vessel vasculitis that predominately affects large vessels, including the aorta and the brachiocephalic, common carotid, and subclavian arteries (12). Abnormalities of the aortic valve, particularly aortic valve regurgitation, are commonly reported in patients with TAK as a result of aortitis and aneurysmal changes within the ascending aorta (6). This study found that nearly 4% of patients with TAK underwent AVS during the observation period, which is consistent with a previous retrospective study from China that reported 5.3% of patients with TAK underwent AVR (13). We also found that AVS was typically performed within the first year after a diagnosis of TAK. Furthermore, it was observed that patients with TAK who underwent AVS were younger and more often female than patients without TAK who underwent AVR, showing a different clinical characteristic. Additionally, the presence of HTN before the diagnosis of TAK was independently associated with AVS.

Most of the patients in this study un-

Table III. Characteristics of patients who underwent redo AVS.

Patient number	Age	Sex	Baseline comorbid conditions	First AVS	Second AVS	Medication usage from initial diagnosis to first AVS	Medication usage after first AVS to second AVS	Time interval of first AVS to second AVS (years)
#1	46	Female	None	Aortic valve replacement	Aortic valve replacement	Glucocorticoid, MTX, Aspirin	Glucocorticoid, MTX	0.90
#2	37	Female	None	Aortic valve replacement	Aortic valve replacement	Glucocorticoid, Aspirin, Statins	Glucocorticoid, Aspirin, Statins	4.38
#3	43	Female	Hypertension	Aortic valve replacement	Aortic valve replacement	Glucocorticoid, Aspirin, Statins	Glucocorticoid, Aspirin, Statins	7.37

AVS: aortic valve surgery; MTX: methotrexate.

Table IV. Comparison of clinical characteristics between patients with TAK who underwent AVS and patients without TAK who underwent AVR.

	Patients with TAK who underwent AVS (n=45)	Patients without TAK who underwent AVR (n=119)	*p*-value
Age (years)	47.1 ± 11.9	61.5 ± 13.5	<0.001
Sex, n (%)			
Female	39 (86.7)	53 (44.5)	<0.001
Male	6 (13.3)	66 (55.5)	
In-hospital mortality after AVS or AVR	0 (0.0)	3 (2.5)	0.562

Continuous variables are shown as means ± standard deviations and categorical variables are shown as frequencies (percentages).
TAK: Takayasu's arteritis; AVS: aortic valve surgery; AVR: aortic valve replacement.

derwent AVS within 1 year of receiving a diagnosis of TAK. In line with this finding, several studies have suggested that aortic valve abnormalities may be asymptomatic (even when severe) and could be present on initial diagnosis of TAK (14-16). Moreover, compared to patients without TAK who underwent AVR, patients with TAK who underwent AVS were younger and more often female, which may be influenced by the underlying disease. There is novelty in this study that this is the first to

Table V. Factors associated with AVS in patients with TAK.

	Crude hazard ratio			Adjusted hazard ratio		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Demographic data						
Age	0.99	(0.98-1.01)	0.514	1.00	(0.98-1.02)	0.981
Sex						
Female	1.00 (ref)			1.00 (ref)		
Male	0.69	(0.29-1.62)	0.388	0.61	(0.26-1.46)	0.268
Insurance type						
National Health Insurance	1.00 (ref)			1.00 (ref)		
Medical aid	0.59	(0.08-4.31)	0.606	0.63	(0.09-4.61)	0.648
Residence area						
Outside Seoul	1.00 (ref)			1.00 (ref)		
Seoul	1.10	(0.62-1.98)	0.742	1.11	(0.61-2.02)	0.729
Comorbid conditions						
Hypertension	1.32	(0.73-2.38)	0.355	2.18	(1.12-4.24)	0.022
Diabetes mellitus	0.48	(0.19-1.23)	0.127	0.45	(0.17-1.19)	0.108
Dyslipidaemia	0.71	(0.39-1.29)	0.258	0.71	(0.37-1.40)	0.326
Chronic kidney disease*	-			-		
Medication usage¶						
Immunosuppressive agents						
Glucocorticoid	2.18	(1.05-4.51)	0.036	2.10	(0.96-4.59)	0.064
Methotrexate	1.85	(0.97-3.53)	0.063	1.43	(0.72-2.83)	0.311
Azathioprine/mizoribine	1.52	(0.67-3.45)	0.321	1.31	(0.56-3.06)	0.534
Antiplatelet drugs						
Aspirin	0.50	(0.27-0.94)	0.030	0.53	(0.27-1.05)	0.068
Clopidogrel	0.67	(0.31-1.45)	0.310	0.82	(0.35-1.90)	0.644
Statins	0.65	(0.34-1.22)	0.178	0.87	(0.42-1.81)	0.709

*Not included as none of the patients with chronic kidney disease underwent AVS.
¶Included as a time-dependent variable.
AVS: aortic valve surgery; TAK: Takayasu's arteritis; HR: hazard ratio; CI: confidence interval.

assess the incidence of AVS in Korean patients with TAK using a nationwide population-based data. Our results emphasise that patients with TAK should be carefully and regularly monitored for signs of aortic valve insufficiency via physical examination and echocardiography, even in the absence of signs and symptoms. Finally, based on the fact that other valvular abnormalities in the mitral and tricuspid valve are also prevalent in patients with TAK (9), a full echocardiographic evaluation is essential in patients with TAK at baseline to evaluate the presence of valvular heart diseases.

In our study, glucocorticoid usage was associated with increased risk of AVS in an unadjusted Cox regression analysis, indicating that patients with TAK who underwent AVS were more likely to have higher disease activity. This result is consistent with the previous study that reported patients with higher disease activity are more likely to have frequent cardiovascular complications (17). As sustained inflammation is believed to be necessary for the development of complications in TAK, optimal disease treatment is necessary to prevent the development of cardiovascular manifestations (18, 19). However, none of the immunosuppressive agents were found to be protective against AVS following adjustment. In addition, aspirin, which is most often used for the primary prevention of cardiovascular events (20), was seemingly beneficial in AVS; however, its impact on the incidence of AVS was not statistically significant, and the effects of drugs on the need for AVS in patients with TAK remain unclear. Well-designed prospective studies with a large patient population are required to further investigate the effects of medications on AVS.

There are two main indications of AVS in patients with TAK: AR and aortic stenosis (AS). In general, the risk of AVR has been associated with patient age, HTN, and the presence of medical conditions that directly involve the heart and cardiac valves (21, 22). In contrast, AS has been associated with HTN, DM, dyslipidaemia, and CKD (23). In this study, no differences in comorbidities were found between patients with TAK who underwent AVS and those who did not at baseline. However, in a Cox regression analysis, the history of HTN before the diagnosis of TAK, which is a shared risk factor for both AR and AS, was exclusively predictive of AVS in patients with TAK (24, 25). Therefore, careful monitoring and implementation of measures to detect aortic valve dysfunction during the follow-up period are required in patients with TA and a history of HTN.

This study is not without limitations. First, echocardiography and clinical data (*i.e.* disease severity and its extent) of the patients undergoing AVS were not available in the Korean National Health Insurance Claims database. Thus, the information of previous and current abnormalities in the cardiac valves and the heart was not accessible, and the indication for AVS could be not be determined precisely. Second, the number of patients requiring AVS may have been underestimated as some patients who required AVS may not have been surgical candidates owing to poor general condition or may have refused surgery. Third, the presence of comorbid conditions was evaluated using ICD-10 codes; this may have resulted in an overestimation of the comorbidities. Fourth, the use of the ICD-10 code and RID to identify patients with TAK may have influenced in the study results. This definition requires verification as there is currently no gold standard for the identification of TAK in epidemiologic studies. Finally, due to the short follow-up of patients who underwent AVS, interpretation of the results of risk factor analysis seems to be limited.

In conclusion, approximately 4% of patients with TAK undergo AVS, and the majority of these patients undergo AVS within 1 year of being diagnosed with TAK. Patients with TAK who required AVS were younger and more likely to be female than patients without TAK undergoing AVR. In addition, a history of HTN before the diagnosis of TAK was identified as a risk factor for AVS. These results should be taken into consideration in order to provide optimal patient care in TAK.

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