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Original article

Assessment of the frequency of cardiovascular risk factors in patients with Takayasu's arteritis

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Abstract

Objectives. The prevalence of atherosclerotic risk factors and disease in Takayasu's arteritis (TAK) has not been well defined. We aimed to assess the frequency of cardiovascular (CV) risk factors and the incidence of CV events (CVEs) in patients with TAK from two ethnically different populations.

Methods. Patients with TAK followed at Mayo Clinic, Rochester, MN, USA and Marmara University, Istanbul, Turkey were included in this retrospective study. Patients with TAK were compared with age-, sex- and calendar year-matched controls from the same geographical region without TAK. The 2008 Framingham 10-year general CV risk score (FRS) was used for the evaluation of CV risk at the time of TAK incidence/index date.

Results. In total, 191 patients with TAK and 191 non-TAK controls were included. Hypertension and the prevalence of lipid-lowering treatments were significantly more frequent in TAK. Prior to the incidence/index date, occurrence of CVE was significantly higher in TAK. The FRS was significantly higher in TAK compared with non-TAK at incidence/index date. The cumulative incidence of CVE was 15.4% at 10 years in TAK *vs* 5.8% in non-TAK; the risk of CVE was increased among patients with TAK (hazard ratio = 4.36; 95% CI: 1.25, 15.13).

Conclusion. CV risk factors are more common in patients with TAK, particularly hypertension. The FRS is higher in patients with TAK at the time of diagnosis. The cumulative incidence of CVE was also significantly higher during follow-up in TAK. Our results suggest that patients with TAK should undergo careful assessment of CV risk factors, and an aggressive risk modification approach is warranted.

Key words: Takayasu's arteritis, atherosclerotic risk, cardiovascular event

Rheumatology key messages

- Cardiovascular risk factors are more common in patients with Takayasu's arteritis, particularly hypertension.
- The Framingham Risk Score and cumulative incidence of cardiovascular event were significantly higher in Takayasu's arteritis.
- Careful assessment of cardiovascular risk and an aggressive risk modification approach is warranted in Takayasu's arteritis.

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Introduction

Takayasu's arteritis (TAK) is a rare, chronic large-vessel vasculitis (LVV) that predominantly affects the aorta, its major branches and the pulmonary arteries. Chronic vascular inflammation can lead to stenosis, occlusion, dilatation or aneurysm formation during the course of the disease. Among different series, 10-year mortality rates range between 3 and 15% [1]. Disease phenotype and

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severity of disease expression due to ethnicity, differences in medical therapy (e.g. less frequent use of glucocorticoids and cytotoxic agents) and variations in access to surgical therapy may give rise to different mortality rates [2]. In a recent series, Schmidt *et al.* [3] observed overall survival rates of 97% at 10 years and 86% at 15 years in the USA.

Cardiovascular (CV) diseases are the most frequent cause of death in developed countries. The morbidity and mortality from CV diseases are increased in patients with inflammatory rheumatic diseases such as RA, AS and SLE, compared with the general population [4–6]. In a recent study, accelerated atherosclerosis was also described in systemic vasculitides, although the causal factors have not yet been fully elucidated [7]. Diabetes mellitus, hypertension (HTN), dyslipidaemia, abdominal obesity, impaired renal function, persistent proteinuria and increased production of CRP are common in patients with systemic vasculitis [8, 9]. In ANCA-associated vasculitis, an increased mortality as a consequence of CV disease is well documented [7]. Among the large vessel vasculitides, there are conflicting data for GCA [10]. Some epidemiological studies suggest that long-term mortality in this disease is not increased compared with the general population of the same age [11, 12]. However, in a large retrospective cohort study, GCA was found to be associated with an increased risk of CV diseases [13].

There are limited data about the risk of CV disease and atherosclerotic burden in TAK. Seyahi *et al.* [14] first observed that the frequency of atherosclerotic plaques is increased in TAK, similar to SLE, a disease associated with systemic premature atherosclerosis. In a small study evaluating 22 patients, a higher number of CV risk factors was reported; HTN and hypertriglyceridaemia were the most frequent [15]. Da Silva *et al.* [16] also reported a high prevalence of metabolic syndrome in patients with TAK.

In this study, we assessed the frequency of CV risk factors and atherosclerotic vascular events in patients with TAK compared with age- and sex-matched controls without TAK from two ethnically different populations.

Methods

Patients

This retrospective cohort study included subjects fulfilling the ACR criteria for TAK [17] from two referral rheumatology centres (Mayo Clinic, Rochester, MN, USA and Marmara University, Istanbul, Turkey). Patients with TAK were compared with controls from available diagnostic databases at each respective institution and were matched based on age, sex and calendar year, and geographical region. Each comparator subject in the non-TAK cohort was assigned an index date corresponding to the TAK index date of the matched patient in the TAK cohort. Index date was defined as the date of diagnosis of TAK or the date of first presentation at Mayo Clinic or Marmara University, if the diagnosis date was not available. Index date for controls was the date of visit closest to the index date of the matched TAK patient.

Data on CV risk factors at the time of TAK diagnosis and incident CV events (CVEs) during follow-up were abstracted from the available medical records into a research electronic data capture program that is located on a secured server with access available only to study investigators. All subjects were followed longitudinally through all available medical records until their last visit or date of death. The study was approved by the Mayo Clinic Institutional Review Board and Marmara University Ethics Committee. Patient consent was not required.

Data collection

In both cohorts, data were collected around the index date for traditional CV risk factors such as age, sex, chronic kidney disease, obesity, current smoking history, diabetes mellitus and family history of premature onset CVE. Upper extremity systolic and diastolic blood pressure readings closest to the index date were recorded. In cases in which bilateral upper extremities were involved with stenosis/occlusion, lower extremity pressures were obtained. Use of antihypertensive medication in the 12-month period prior to or 3 months post-index date were collected. Laboratory test results, including acute phase reactants, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides, up to 12 months prior to or 3 months post-index date were collected. Data were also collected on the use of statins during this period. BMI was calculated based on height and weight data available up to 12 months prior to the index date and 3 months post-index date. Obesity was defined as BMI $\geqslant 30\,kg/m^2$. Smoking history was collected based on the data entered in the patient charts. Family history of premature CVE was collected based on physician-entered or patient-provided data in the medical record.

Evaluation of CV risk and atherosclerotic vascular events

The 2008 Framingham 10-year general CV risk score (FRS) [18] and Systemic Coronary Risk Evaluation (SCORE) risk calculation system for high risk countries [19] were used for the evaluation of CV risk at the time of TAK incidence/index date for patients aged $\geqslant 30$ years. The European Society of Cardiology advocates the use of the SCORE system for the 10-year risk assessment of fatal myocardial infarction, stroke, aortic aneurysm and other atherosclerotic vascular events. The FRS for general CVD predicted CV risk for non-fatal CVE, as well as peripheral vascular disease and heart failure. For patients without lipid measurements, the office-based FRS, which does not require lipid values (using BMI instead of lipids), was computed according to previously published algorithms [18]. We collected data from available medical records regarding all documented episodes of coronary artery disease [i.e. myocardial infarction, angina, CV death, revascularization procedures (i.e. percutaneous coronary angioplasty, coronary artery bypass grafts)],

congestive heart failure, cerebrovascular events (i.e. stroke, transient ischaemic attack) and atherosclerotic peripheral arterial disease (i.e. abdominal aortic aneurysm, peripheral vascular disease, renal artery stenosis, arterial thrombosis).

Statistical analysis

Descriptive statistics (means, percentages, etc.) were used to summarize the characteristics of each cohort. Comparisons between cohorts were performed using chi-square and rank sum tests. The cumulative incidence of CVE adjusted for the competing risk of death was estimated for each cohort. Patients with a CVE prior to incidence/index date were excluded from this analysis. Cox models were used to compare the rate of CVE events between cohorts adjusting for age, sex and country. Cox models were also used to examine associations between potential predictors and CVE among patients with TAK. A P-value <0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 191 patients with TAK and 191 non-TAK controls were included in the study (115 from Mayo Clinic, 76 from Marmara University for each group). Baseline characteristics of the two cohorts at the index date are shown in Table 1. Mean age was 34.1 (S.D. 10.9) years in TAK group *vs* 34.7 (S.D. 10.8) years in non-TAK group. The majority of patients were female in both cohorts (91% in TAK group *vs* 92% in non-TAK group). There was no difference between the Turkish and American cohorts regarding age and sex ($P = 0.52$ and $P = 0.14$, respectively). Corticosteroid treatment were given to all TAK patients after diagnosis. The majority of the patients (88%) had types V and I disease according the Hata classification [20]. While, the most frequent type was type V (58%) in the US cohort, it was type I (57%) in the Turkish cohort. Among patients aged $\geqslant 30$ years at index date (118 TAK, 122 non-TAK), complete data to calculate FRS were available in 99 TAK and 91 non-TAK subjects.

There was no difference in the mean total cholesterol, LDL and HDL cholesterol, and triglyceride levels between the TAK and control groups. No differences were noted in smoking status, obesity or diabetes mellitus between the two cohorts. However, HTN and use of lipid-lowering medications were significantly more frequent in the TAK group compared with the non-TAK group. Renovascular HTN was present in one-half of the patients having HTN in the TAK group (37/73). Baseline aspirin usage was significantly higher in the TAK group.

Prior to incidence/index date, the occurrence of CVE was significantly higher in the TAK group (23% *vs* 5%; $P < 0.001$). The mean overall FRS was significantly higher in the TAK group compared with non-TAK at incidence/index date [7.6 (S.D. 9.7)% *vs* 4.4 (S.D. 5.4)%; $P = 0.001$; Table 1]. The SCORE was also higher among the TAK than the non-TAK [0.9 (S.D. 2.5)% *vs* 0.3 (S.D. 0.4)%], but this difference did not reach statistical significance ($P = 0.058$).

The American and Turkish cohorts had no differences in the prevalence of CV risk factors such as HTN, diabetes mellitus, smoking, obesity and hyperlipidaemia ($P > 0.05$ for all). Only family history of atherosclerotic vascular events was significantly higher in the Turkish cohort (47% *vs* 28%; $P = 0.012$). Prior to the incidence/index date, the occurrence of CVE was significantly higher in the Turkish cohort, particularly ischaemic coronary artery disease (32% *vs* 18%, $P = 0.025$). However, CV risk scores were similar between the two cohorts with both FRS and SCORE risk calculation system ($P = 0.63$ and $P = 0.95$, respectively).

Follow-up

One hundred and forty-four patients with TAK and 110 patients with non-TAK had follow-up data. The mean follow-up duration was 7.3 years in TAK and 7.4 years in the non-TAK group. After excluding patients with prevalent CVE, new CVE developed in 18 TAK and 3 non-TAK patients during the follow-up period. In the TAK group, 11 cerebrovascular events, 5 coronary arterial events and 3 cases of peripheral arterial disease developed, while in in non-TAK group 2 cerebrovascular events, 1 coronary arterial event and 1 peripheral arterial disease developed. The cumulative incidence of CVE was 15.4 (S.D. 3.9)% at 10 years in TAK group *vs* 5.8 (S.D. 3.5)% in non-TAK group and the risk of CVE was increased among patients with TAK (hazard ratio = 4.36; 95% CI: 1.25, 15.13 adjusted for age, sex and country) (Fig. 1).

We did not identify any baseline predictors (clinical or laboratory characteristics) for the development of CVE during follow-up. Aspirin usage for cardioprotection was associated with a 2-fold increased risk for incident CVE during follow-up (hazard ratio: 2.13; 95% CI: 0.80, 5.66), likely due to confounding by indication, but this association did not reach statistical significance ($P = 0.13$).

Discussion

This large cohort study is the first to assess CV risk factors of patients with TAK in two different ethnic cohorts at the time of TAK diagnosis. We observed that CV risk factors are more common in patients with TAK, particularly HTN. The FRS was higher in patients with TAK at the time of diagnosis compared with non-TAK subjects of similar age and sex. We also found that CVE prior to TAK diagnosis was more prevelant in TAK compared with the non-TAK group. There are very limited data assessing CV risk in this rare disease. De Souza *et al.* reported that CV risk factors were present in 91.7% of the 48 patients with TAK during a follow-up period of 76.5 months after diagnosis. HTN, high levels of LDL and obesity were the most common CV risk factors. Acute ischaemic events were present in 14 (29%) patients. The majority of the events were ischaemic cerebrovascular events and coronary arterial disease. Aspirin use (100–200 mg/day) appeared to have a protective effect in reducing the risk of ischaemic events in TAK [21]. In the

Table 1 Baseline characteristics of TAK and non-TAK cohorts at incidence/index dates

Characteristic	TAK (n = 191)	Non-TAK (n = 191)	P-value
Age, mean (S.D.), years	34.1 (10.9)	34.7 (10.8)	0.56
Sex (female/male)	171/20	174/16	0.49
Smoking status			0.27
Never	102 (55)	113 (60)	
Former	41 (22)	29 (16)	
Current	44 (24)	45 (24)	
Obesity (BMI $\geqslant 30\,kg/m^2$)	33/148 (22)	37/153 (23)	0.84
Systolic blood pressure, mean (S.D.), mmHg	133 (31) (n = 184)	117 (14) (n = 160)	**<0.001**
Diastolic blood pressure, mean (S.D.), mmHg	75 (16) (n = 183)	74 (11) (n = 160)	0.73
Hypertension	73 (38)	27 (14)	**<0.001**
Anti-hypertensive use	79 (42)	26 (14)	**<0.001**
CRP level, median (IQR), mg/l	12 (4–35) (n = 119)	2.9 (2.9–3.9) (n = 11)	**<0.001**
ESR, median (IQR), mm/h	37 (18–72) (n = 167)	10 (5–17) (n = 46)	**<0.001**
Diabetes mellitus	12 (6)	12 (6)	0.99
End stage renal disease	3 (2)	4 (2)	0.71
Any prior cardiovascular event	44 (23)	9 (5)	**<0.001**
Cerebrovascular disease	17 (9)	1 (1)	**<0.001**
Coronary arterial disease	18 (10)	4 (2)	**0.002**
Peripheral vascular disease	8 (4)	5 (3)	0.40
Heart failure	4 (2)	0 (0)	**0.045**
Lipid profile, mean (S.D.)			
Total cholesterol, mg/dl	199 (50) (n = 119)	190 (37) (n = 60)	0.25
Low density lipoprotein, mg/dl	119 (42) (n = 109)	108 (35) (n = 51)	0.12
High density lipoprotein, mg/dl	53 (18) (n = 103)	54 (15) (n = 53)	0.60
Triglycerides, mg/dl	136 (88) (n = 114)	126 (96) (n = 60)	0.12
Lipid lowering treatment	23 (12)	9 (5)	**0.011**
Aspirin usage	91 (48)	9 (5)	**<0.001**
Family history of cardiovascular disease	59/172 (34)	67/181 (37)	0.60
Framingham risk score, median (IQR), %	3.6 (1.2–5) (n = 99)	2.4 (2.0–10) (n = 91)	**0.001**
SCORE for high risk countries, median (IQR), %	0.1 (0–0.5) (n = 75)	0.1 (0–0.3) (n = 33)	0.058

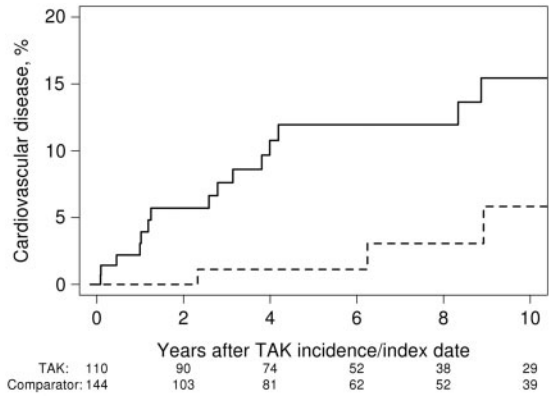
Values in table are n (%) unless otherwise specified. Bold P-values are statistically significant at < 0.05. TAK: Takayasu arteritis.

current study, HTN, cerebrovascular disease, coronary arterial disease and use of lipid lowering agents were significantly higher in TAK. However, diabetes, smoking, obesity and family history of CVEs were similar between the groups at the time of diagnosis. The majority of atherosclerotic vascular events occurring prior to TAK diagnosis and during the follow-up period were ischaemic cerebrovascular events and coronary arterial disease, similar to the study by De Souza *et al*. [20]. However, aspirin usage did not have a significant effect on the risk of CVE development in our study.

In a recent study, Liu *et al.* [22] assessed CV disease, defined as ischaemic coronary arterial disease and stroke, in 262 patients with TAK. CV disease was found in 24.4% of patients after 9.6 years of follow-up from date of diagnosis. Similar to our study, HTN (particularly renovascular in origin) was the most frequent CV risk factor. In multivariate analysis, CV disease independently associated with anaemia, low BMI, hyperlipidaemia and family history for CV disease in this study. In the present study, we did not find any association between these factors and CV disease.

It is well known that atherosclerosis is an inflammatory vascular process [23]. In autopsy studies, an excess of atherosclerotic lesions was previously observed in patients with TAK [24, 25]. We previously detected significantly decreased flow-mediated dilatation of the brachial artery and increased carotid intima media thickness in TAK, suggesting a marked endothelial dysfunction, which is a sign of premature atherosclerosis [26]. Arterial wall abnormalities and atherosclerotic lesions may lead to the increased risk of thrombotic ischaemic events in TAK. Moreover, a hypercoagulable state related to enhanced platelet function and activation of procoagulant factors was also shown in TAK [27, 28]. In a small study, elevated homocysteine levels, which are an independent risk factor for atherosclerotic vascular disease, were found associated with acute arterial ischaemic events in TAK [29]. De Carvalho *et al.* [30] detected a proatherogenic lipid profile, mainly characterized by low HDL during active disease. However, the high prevalence of atherosclerosis in TAK patients does not seem to be explained by only an excess of risk factors for CV disease; it may also be related to chronic endothelial stimulation, chronic inflammation and glucocorticoid use [31]. Therefore, as both arterial vasculitic

Fig. 1 Cumulative incidence of cardiovascular events among patients with Takayasu's arteritis and comparators



The numbers under the figure indicate the number of patients under observation in each group over time. Solid line: Takayasu's arteritis; dashed line: comparators without TAK. TAK: Takayasu's arteritis.

involvement and accelerated atherosclerosis can cause ischaemic CVE in patients with TAK, it is difficult to differentiate the actual cause of CVE in TAK.

The results of these investigations suggest that assessment of actual atherosclerotic risk with the current assessment tools is difficult in TAK. Moreover, prediction of CV risk can differ based on the prediction model utilized. While the FRS was higher in patients with TAK compared with non-TAK comparators in this current study, the SCORE risk assessment did not differ significantly ($P = 0.06$). Although the reason for this discrepancy is not fully known, similar differences between CV scoring assessments have been observed in other populations. Indeed, Selvarajah *et al*. [32] reported in an Asian cohort that the SCORE model was unable to distinguish intermediate and high CV risk among females. Similar findings of lower SCORE modeling performance among females compared with males was also observed in an Australian cohort [33]. Given the majority of patients with TAK are female, the SCORE model may underestimate prediction of CVE in TAK, as observed in the current study. Also, low numeric SCORE values due to the inclusion of only fatal events in the SCORE could be the reason for not achieving statitistical significance between groups in the present study. The differences between currently available models highlight that disease-specific CV risk assessment tools are greatly needed in LVV affecting major arterial systems like atherosclerosis and remain an area requiring further investigation and prospective validation.

The main limitation of our study was its retrospective design, which may limit the applicability of its observations to current patient follow-up. Missing data and lack of follow-up in some patients also may underestimate the CVE incidence in our study group. The small number of events led to limited statistical power to detect associations between potential risk factors and events. In addition, comparators were referral patients presenting to a tertiary facility who therefore may be less healthy than general population comparators, which may lead to underestimation of risk difference between TAK and non-TAK cohorts

In conclusion, we observed a higher frequency of CV risk factors in patients with TAK, particularly HTN. The FRS was higher in patients with TAK at the time of diagnosis compared with non-TAK subjects of similar age and sex. The cumulative incidence of CVE in this study was also higher during follow-up. Therefore we suggest that patients with TAK should undergo careful assessment of CV risk factors and an aggressive risk modification approach is warranted. Current CV risk assessment tools may not reflect the actual risk of CVE in TAK and better disease-specific risk scores for predicting CVE in large-vessel vasculitides are needed.

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