Mortality and cardiovascular morbidity among patients diagnosed with Takayasu's arteritis: a Danish nationwide cohort study

K. Egebjerg[1], B. Baslund[1], N. Obel[2], M. Faurschou[1]

[1]Copenhagen Lupus and Vasculitis Clinic, Centre for Rheumatology and Spine Diseases; [2]Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

Kristian Egebjerg, BMsc
Bo Baslund, MD, PhD
Niels Obel, MD, DMSci
Mikkel Faurschou, MD, PhD

Please address correspondence to:
Kristian Egebjerg,
Copenhagen Lupus and Vasculitis Clinic, Centre for Rheumatology and Spine Diseases,
Copenhagen University Hospital, Rigshospitalet,
9 Blegdamsvej,
DK-2100 Copenhagen, Denmark.
E-mail: kristian.egebjerg@gmail.com

Received on January 3, 2020; accepted in revised form on February 24, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 124): S91-S94.

Key words: vasculitis, Takayasu's arteritis, cardiovascular diseases, mortality

Funding: this work was supported by the Board of Research at the Copenhagen University Hospital, Rigshospitalet, Denmark (MF).

Competing interests: none declared.

ABSTRACT

Objective. *To assess the long-term mortality and risk of cardiovascular events (CVE) among Danish patients with Takayasu's arteritis (TAK).*

Methods. *Administrative registers with nationwide coverage were used to identify patients diagnosed with TAK in Denmark during 1994-2014 and construct an age- and gender-matched cohort of population-controls. CVE were identified by means of hospital discharge diagnoses and categorised as major or minor, based on severity. Cox regression analyses were used to calculate hazard ratios (HRs) for death and first-time hospitalisations for CVE as a measure of relative risk.*

Results. *79 patients with TAK were identified, corresponding to an incidence rate of 0.7 (95% confidence interval (CI): 0.6-0.9)/million/year. Median duration of follow-up in the TAK cohort was 6.4 (IQR: 3.7-11) years. Mortality was significantly higher among the TAK patients than among the population controls during the first 3 years of follow-up* [*HR for death: 8.0 (95% CI: 3.0-21)*], *but not after >3 years* [*HR for death: 0.5 (95% CI: 0.1-3.5)*]. *Risk of CVE was significantly increased among TAK patients after ≤3 years* [*HR for major CVE: 12 (95% CI: 3.8-37), HR for minor CVE: 19 (95% CI: 7.5-50)*] *as well as after >3 years* [*HR for major CVE: 7.6 (95% CI: 2.8-21), HR for minor CVE: 3.0 (95% CI: 1.01-9.0)*].

Conclusion. *Compared to the general population, patients with TAK experience markedly increased mortality during early follow-up periods. The long-term risk of CVE is high among patients affected by the disease.*

Introduction

Takayasu's arteritis (TAK) is a primary large-vessel vasculitis (1, 2). In northern European countries, an incidence of TAK of 0.4-1.5/million/year has been reported (3-6). The disease has a higher incidence among females than among males (7). In a nationwide study from France, the majority of TAK patients were of non-Caucasian descent (8). A comparable observation was made in a Norwegian study (6).

Varied mortality estimates have been reported for TAK patients diagnosed during different calendar-periods and in different countries, probably due to variable diagnostic options and changes in treatment practices over time (9). A study from Japan showed 15-year survival rates of 79.9% and 96.5% among TAK patients diagnosed during 1957-1975 and 1976–1990, respectively (10). A recent French cohort study encompassing patients diagnosed with TAK between 1970 and 2014 showed a 5% mortality rate after a median of 6.1 years of follow-up (8).

Cardiovascular events (CVE) constitute a major cause of morbidity and mortality in TAK (8, 11-13). CVE related to TAK can develop as a consequence of vasculitis activity resulting in arterial wall stenoses and/or aneurisms (14-17). A range of studies have provided data on how the risk of CVE develops over time among patients diagnosed with TAK (8, 18-21). A high incidence of CVE has been observed in several cohorts (7, 18, 20), and Alibaz-Oner *et al.* described a 4.36 times increased risk of CVE among 191 TAK patients compared with 191 controls (17).

We previously reported on mortality and cardiovascular complications in a cohort of 19 patients diagnosed with TAK in Eastern Denmark during 1990-2009 (4). In the present study, we performed a nationwide population-based analysis of patients diagnosed with TAK in the entire country of Denmark between 1994 and 2014. Our aim was to compare the long-term risk of death and

cardiovascular morbidity among Danish TAK patients with that among age- and gender-matched population-controls.

Patients and methods

TAK cohort

Denmark has a tax-financed, public health care system, and TAK is only treated at specialised hospital departments. The Danish National Hospital Register (NHR) has collected information concerning somatic inpatient admissions from 1977 onwards and information regarding inpatient, outpatient, and emergency department contacts from 1995. The registry covers >99% of hospital contacts in the country (22). In the NHR, we identified all patients registered with a first-time diagnosis of TAK during 1994-2014 (International Classification of Diseases (ICD)-8 code: 446.91, ICD-10 code: M31.4). To reduce the risk of studying misclassified cases of TAK, we subsequently selected patients with at least two TAK-related hospital-contacts during this calendar-period. Date of study inclusion was defined as the date of the second hospital-contact for TAK. Patients for whom the time interval between the first and the second TAK-related hospital-contact exceeded 6 months were excluded from further analyses to ensure that all patients enrolled in the TAK cohort had newly diagnosed vasculitis at date of study inclusion.

Comparison cohort

Each patient was matched with 10 age- and gender-matched population-controls. These were identified by means of data from the Danish Civil Registration System (CRS) and the NHR. The CRS was founded in 1968 and contains information on birthdate, gender, and vital status of all citizens of Denmark (23). The controls were required to be alive and living in Denmark at date of study inclusion of the patient to whom they were matched, and they were assigned the same date of study inclusion as their corresponding patient.

Deaths and migrations

Information regarding deaths and migrations was obtained from the CRS (23).

Cardiovascular events

We used the NHR to identify hospitalisations for CVE. Owing to rules for data handling precluding the presentation of data that can be attributed to an individual person, cardiovascular diagnoses were pooled and categorised as either major or minor CVE based on the severity of the recorded event. We included the following cardiovascular diagnoses in the category of major CVE: Myocardial infarction (ICD-10: I21; ICD8: 410), aneurism and dissection (ICD10: I25.4, I71-I72; ICD8: 441-442), arterial embolism and thrombosis (ICD-10: I74; ICD-8: 444), and stroke (ICD10: I60-64; ICD8: 430-431, 433-434, 436.01, 436.90). The following diagnoses were included in the category of minor CVE: angina pectoris (ICD-10: I20; ICD-8: 413), valvular heart disease (ICD-10: I05-I08, I34-I37, I39.0-I39.4; ICD8: 394-397.01, 424.00-424.92), and transitory cerebral ischaemic attacks (ICD-10: G45; ICD8: 435).

Several studies have demonstrated high positive predictive values for cardiovascular diagnoses in the NHR (24, 25).

Statistics

Study outcomes were time to death, time to a first-time minor CVE, and time to a first-time major CVE. In the analysis of mortality, follow-up began at date of study inclusion and continued until date of death, emigration, loss-to-follow-up, or December 31, 2014, whichever came first. In the analyses of risk of CVE after date of study inclusion, follow-up began at date of study inclusion and continued until date of first CVE, death, emigration, loss-to-follow-up, or December 31, 2014, whichever came first. If a first-time hospitalisation for a major CVE as well as a minor CVE had been registered for a person after date of study inclusion, these events were counted once in each of the appropriate categories. Cox regression analyses were used to calculate hazard ratios (HRs) for death, major CVE, and minor CVE as a measure of relative risk. HRs were adjusted for age at date of study inclusion and gender.

A Kaplan-Meier table was computed to determine cumulative survival at 10 years of follow-up. IBM® SPSS Statistics v. 24 was used for the analyses.

Ethics

This study was approved by the Danish Data Protection Agency (jr. no.: 30-0604) and by the Danish National Board of Health.

Results

Baseline characteristics for TAK patients and population-controls

A total of 79 TAK patients were identified by means of our search strategy. Characteristics of patients and population-controls are shown in Table I. For the patients, the median time-interval between first-ever hospitalisation for TAK and date of study inclusion was 20 (interquartile range (IQR): 7–45) days.

Incidence of TAK in Denmark during 1994-2014

Based on the size of the Danish population during 1994–2014, the incidence of TAK in Denmark during the study-period was estimated to be 0.7 (95% confidence interval (CI): 0.6–0.9)/million/year.

Mortality and cardiovascular morbidity

A total of 8 deaths occurred among the TAK patients, and the cumulative survival in the cohort was 89% after 10 years of follow-up. Compared with the population-controls, the HR for death was 8.0 (95% CI: 3.0–21) after ≤3 years of follow-up and 0.5 (95% CI: 0.1–3.5) after >3 years among the TAK patients (Table II).

12 TAK patients were hospitalised for a first-time major CVE during follow-up, while 15 patients were registered with a first-time hospital-contact for a minor CVE after date of study inclusion. The risk of major and minor CVE was substantially increased in the TAK cohort after ≤3 years as well as after >3 years of observation (Table II).

Discussion

The age- and gender-characteristics of Danish TAK patients are comparable to those reported for patients diagnosed with TAK in other countries,

Table I. Characteristics of patients diagnosed with Takayasu's arteritis in Denmark during 1994-2014 and of matched population-controls[1].

	Patients	Controls
Number	79	790
Women, number (%)	70 (88)	700 (88)
Age at date of study inclusion[2], median (IQR), years	43 (33-56)	43 (33-56)
Duration of follow-up, median (IQR), years	6.4 (3.7-11)	6.8 (4.6-11)

IQR: Interquartile range.
[1]Each patient was matched with 10 population controls of similar age and gender.
[2]As defined in text.

Table II. Risk of death and risk of major and minor cardiovascular events in 79 patients diagnosed with Takayasu's arteritis during 1994-2014 compared with 790 population-controls[1], according to the duration of follow-up.

	HR ≤3 years (95% CI)	HR >3 years (95% CI)
Death	8.0 (3.0-21)	0.5 (0.1-3.5)
Major cardiovascular event[2]	12 (3.8-37)	7.6 (2.8-21)
Minor cardiovascular event[2]	19 (7.5-50)	3.0 (1.01-9.0)

HR: hazard ratio, adjusted for age and gender; CI: confidence interval.
[1]Each patient was matched with 10 population-controls of similar age and gender.
[2]As defined in text.

with a high female:male ratio and a median age of the patients of 43 years at time of diagnosis (7). The calculated incidence rate of 0.7/million/year is in agreement with the incidence of TAK observed in neighbouring Northern European countries (3-6).

In the current TAK cohort, the mortality was heavily increased during the first three years of follow-up. After more than 3 years of observation, the risk of death among the TAK patients was not increased compared with that among age- and gender-matched population-controls. The cumulative survival rate after 10 years of follow-up was 89%, which is very similar to the 10-year survival rate of 87.2% reported in a South Korean study (11) but higher than reported from China (58.0% survival after 10 years of follow-up) (26) and lower than reported in a US cohort study (97% survival after 10 years of follow-up) (27).

The current data do not allow us to determine the reasons for the non-increased mortality observed in our TAK cohort after more than 3 years of observation. It could be speculated, however, that patients followed for TAK at specialised hospital departments are likely to be appropriately diagnosed and treated in case of CVE, and that mortality rates decrease after the initial phases of vasculitis therapy due to timely diagnosis and treatment of cardiovascular (and other) complications.

Our analyses demonstrate that TAK patients have a high long-term risk of experiencing CVE. Thus, we observed a markedly increased risk of both early- and late-occurring hospitalisations for CVE, with relative risk estimates of 12 and 7.6 calculated for major CVE occurring ≤3 years and >3 years after date of study inclusion, respectively. In agreement with these observations, a 4.36 times increased risk of CVE was demonstrated among TAK patients compared with non-TAK controls in a US-Turkish long-term follow-up study (mean duration of follow-up in the TAK cohort: 7.3 years) (18). Moreover, the French Takayasu network reported vascular complication rates of 30.1% at 5 years and 46.3% at 10 years among 318 TAK patients (8), while a study on paediatric TAK patients demonstrated CVE-free survival rates of 45.9% at 5 years and 29.1% at 10 years (21).

Our study has methodological strengths and limitations. The register-based approach allowed us to identify all patients diagnosed with TAK in Denmark during 1994–2014, and we studied outcomes (death and CVE), which are registered with high validity in Danish nationwide administrative registers (24, 25). The rarity of TAK makes studying the disease difficult. The present study is based on only 79 patients, and the relatively low number of study subjects restricted the statistical power in our analyses. Our study was also affected by rules for data handling, which preclude publication of data that can be attributed to specific individuals. For this reason, cardiovascular events had to be pooled into two relatively broad categories. To reduce the risk of studying diagnostically misclassified patients, we required a minimum of 2 TAK-related hospital-contacts for patients to be included in our TAK cohort. Since we excluded patients with only 1 TAK-related inpatient or outpatient hospital-contact and those with more than 6 months between first and second TAK-related hospitalisation, we probably underestimated the incidence of TAK in the Danish population slightly.

In summary, the present study demonstrates that Danish TAK patients experience increased mortality during early disease phases compared with the general population. Moreover, the risk of CVE was substantially increased in our TAK cohort during both early and late follow-up periods. These observations underscore the necessity of prolonged monitoring for cardiovascular complications in patients diagnosed with TAK.

References

1. KIM ESH, BECKMAN J: Takayasu arteritis: challenges in diagnosis and management. *Heart* 2018; 104: 558-65.
2. ELEFANTE E, BOND M, MONTI S *et al.*: One year in review 2018: Systemic vasculitis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S12-32.
3. REINHOLD-KELLER E, HERLYN K, WAGNER-BASTMEYER R, GROSS WL: Stable incidence of primary systemic vasculitides over five years: Results from the German vasculitis register. *Arthritis Rheum* 2005; 53: 93-9.
4. DREYER L, FAURSCHOU M, BASLUND B: A population-based study of Takayasu's arteritis in Eastern Denmark. *Clin Exp Rheumatol* 2011; 29 (Suppl. 64): S40-2.
5. MOHAMMAD AJ, MANDL T: Takayasu arteritis in Southern Sweden. *J Rheumatol* 2015; 42: 853-8.
6. GUDBRANDSSON B, MOLBERG Ø, GAREN T, PALM Ø: Prevalence, incidence, and disease characteristics of Takayasu arteritis by ethnic background: data from a large, population-based cohort resident in Southern Norway.

Arthritis Care Res (Hoboken) 2017; 69: 278-85.
7. ONEN F, AKKOC N: Epidemiology of Takayasu arteritis. *Presse Med* 2017; 46: e197-203.
8. COMARMOND C, BIARD L, LAMBERT M *et al*.: Long-term outcomes and prognostic factors of complications in Takayasu arteritis. *Circulation* 2017; 136: 1114-22.
9. PHILLIP R, LUQMANI R: Mortality in systemic vasculitis: a systematic review. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S94-104.
10. ISHIKAWA K, MAETANI S: Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. *Circulation* 1994; 90: 1855-60.
11. PARK MC, LEE SW, PARK YB, CHUNG NS, LEE SK: Clinical characteristics and outcomes of Takayasu's arteritis: analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. *Scand J Rheumatol* 2005; 34: 284-92.
12. OGINO H, MATSUDA H, MINATOYA K *et al*.: Overview of late outcome of medical and surgical treatment for Takayasu arteritis. *Circulation* 2008; 118: 2738-47.
13. WATANABE Y, MIYATA T, TANEMOTO K: Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan. *Circulation* 2015; 132: 1701-9.
14. MASON JC: Takayasu arteritis – advances in diagnosis and management. *Nat Rev Rheumatol* 2010; 6: 406-15.
15. KANG E-J, KIM SM, CHOE YH, LEE GY, LEE K-N, KIM D-K: Takayasu arteritis: assessment of coronary arterial abnormalities with 128-section dual-source CT angiography of the coronary arteries and aorta. *Radiology* 2014; 270: 74-81.
16. LEE GY, JANG SY, KO SM *et al*.: Cardiovascular manifestations of Takayasu arteritis and their relationship to the disease activity: Analysis of 204 Korean patients at a single center. *Int J Cardiol* 2012; 159: 14-20.
17. ZHANG Y, YANG K, MENG X *et al*.: Cardiac valve involvement in Takayasu arteritis is common: a retrospective study of 1,069 patients over 25 years. *Am J Med Sci* 2018; 356: 357-64.
18. ALIBAZ-ONER F, KOSTER MJ, UNAL AU *et al*.: Assessment of the frequency of cardiovascular risk factors in patients with Takayasu's arteritis. *Rheumatology* 2017; 56: 1939-44.
19. COUTURE P, CHAZAL T, ROSSO C *et al*.: Cerebrovascular events in Takayasu arteritis: a multicenter case-controlled study. *J Neurol* 2018; 265: 757-63.
20. DE SOUZA AWS, MACHADO NP, PEREIRA VM *et al*.: Antiplatelet therapy for the prevention of arterial ischemic events in takayasu arteritis. *Circ J* 2010; 74: 1237-41.
21. FAN L, ZHANG H, CAI J *et al*.: Clinical course and prognostic factors of childhood Takayasu's arteritis: over 15-year comprehensive analysis of 101 patients. *Arthritis Res Ther* 2019; 21: 31.
22. ANDERSEN TF, MADSEN M, JØRGENSEN J, MELLEMKJOER L, OLSEN JH: The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; 46: 263-8.
23. PEDERSEN CB, GØTZSCHE H, MØLLER JØ, MORTENSEN PB: The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006; 53: 441-9.
24. THYGESEN SK, CHRISTIANSEN CF, CHRISTENSEN S, LASH TL, SØRENSEN HT: The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011; 11: 83.
25. SUNDBØLL J, ADELBORG K, MUNCH T *et al*.: Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016; 6: e012832.
26. YANG L, ZHANG H, JIANG X *et al*.: Clinical manifestations and longterm outcome for patients with Takayasu arteritis in China. *J Rheumatol* 2014; 41: 2439-46.
27. SCHMIDT J, KERMANI TA, BACANI AK *et al*.: Diagnostic features, treatment, and outcomes of Takayasu arteritis in a US cohort of 126 patients. *Mayo Clin Proc* 2013; 88: 822-30.