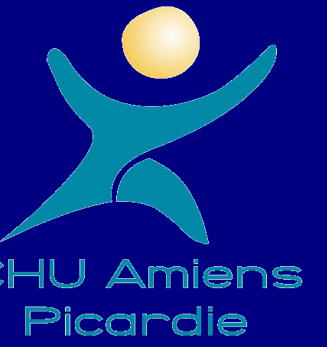




# Risk factors for aortitis among patients with pathological examination after resection of the ascending aorta in Denmark 1997-2009



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## Background

Aortitis is defined as the inflammation of the aortic wall. Numerous medical conditions have been reported associated with aortitis, and they can be categorized as 1. infectious aortitis, 2. aortitis associated with inflammatory condition (mainly Takayasu arteritis, and giant cell arteritis), 3. idiopathic aortitis. Population-based data on prevalence and risk factors for aortitis are scarce. The aim of our study was to assess them in a nationwide population-based cross-sectional study in Denmark.

## Methods

This cross-sectional study was conducted in Denmark, with a population of 5,489,022 as of July 1, 2008 (Statistics Denmark). The Danish National Health Service provides free access to tax-supported health care (primary care and hospital care). A unique civil personal registration number assigned to each Danish citizen at birth, which is included in all health databases, allowed us to link the different databases accurately. We identified all adults (over age 15) with first-time surgery on the thoracic ascending aorta between January 1, 1997 and March 1, 2009 in Denmark. Patients were identified from the Danish National Patient Registry (DNPR), using the Nordic Medico-Statistical Committee classification of surgical procedure codes. Only patients with resection of the aorta during the procedure were included. Presence of aortic inflammation was ascertained through linkage to a nationwide pathology registry. The National Pathology Registry contains data on all pathological examinations performed in Denmark since January 1, 1997, using the systematized nomenclature of medicine codes. For each eligible patient, a complete hospitalization history including major medical diagnoses and comorbidities was available through linkage to the DNPR. Diagnoses included in DNPR were coded by physicians according to the International Classification of Diseases, 8th revision until the end of 1993, and 10th revision afterwards.

We used logistic regression to compute prevalence odds ratios (ORs) for sex, age at surgery, cardiovascular risk factors, cancer, connective tissue disease, and infectious diseases associated with presence of aortitis. In a second logistic regression model we examined predictors for performance of a pathological examination as the outcome variable, in order to assess potential detection biases. The study was approved by the Danish Data Protection Agency.

## Results

Between 1997 and 2009, 1,210 patients underwent resection of the ascending aorta. Of these, 610 had a sample of tissue from the aorta submitted for pathological examination (50.4%). Among patients with pathological examination, 37 were diagnosed with inflammation of the aortic wall (6.1%). Ten of these patients were diagnosed with a condition known to be closely associated with aortitis or aortic aneurysm (5 with previously diagnosed temporal arteritis, 1 with Crohn's disease, 1 with rheumatoid arthritis, 1 with systemic lupus erythematosus, 1 with infectious aortitis, and 1 with Marfan's disease). Thus, 27 patients had idiopathic aortitis. Among the 37 patients with aortitis, granulomatous inflammation or presence of giant cells were reported in 8 patients. Aortitis patients were significantly older than those without this condition: their mean age was 65 [range: 57-70] years vs. 59 [range: 47-67] years for patients without aortitis ( $p = 0.03$ ). Patients diagnosed with aortitis were predominantly men (62%), as were patients without aortitis (68.9%), ( $p = 0.39$ ).

The prevalence of potential risk factors for aortitis is summarized in Table 1 (logistic regression analysis, adjusted ORs). Aortitis patients were older than patients without inflammation. Among comorbidities, a history of connective tissue disease was a strong risk factor for aortitis (OR 4.7, 95% CI 1.6, 13.6). Diabetes was associated with a markedly increased risk for aortitis. Pathologies associated with atherosclerosis were not associated with aortitis. As well, potential triggers in the pathophysiology of aortitis (such as past history of cancer and infection) did not prove to be risk factors for aortitis in our study.

The main recorded indications for surgery are listed in Table 2. As expected, aortic aneurysm and dissection were the most common indications. In logistic regression analyses, valve dysfunction was associated with aortitis.

Factors associated with a pathological examination were the center where the patient underwent surgery (OR 4.5, 95% CI 2.8, 7.3 for examination at the center with most examinations vs. the reference center with least examinations) and aneurysm or dissection as the surgical indication (OR for pathological examination 1.9, 95% CI 1.4, 2.7). A past history of hypertension (OR 0.7, 95% CI 0.6, 0.9) and older age (OR 0.3, 95% CI 0.2, 0.5) were negatively associated with a pathological examination, as was a diagnosis of infection of the valve (OR 0.4, 95% CI 0.2, 0.8).

## Discussion

Our study was restricted to the subgroup of aortitis patients with complications requiring a surgical procedure, and for whom a surgical sample was submitted for pathological examination. Patients with aortitis not requiring surgical intervention or with asymptomatic mild disease thus were not included. These limitations are shared by other studies on this topic. However, restricting our sample to patients with a pathological sample allowed accurate diagnosis and enhanced the study's internal validity.

One of our study's main strengths is its nationwide population-based design. It is the first study to use a nationwide population-based cross-sectional design spanning 13 years and set in a country with more than 5 million residents.

The population-based design allowed us to determine the exact proportion of idiopathic vs. secondary aortitis of the ascending portion of the aorta among patients undergoing surgery, avoiding the potential selection biases that may occur in vasculitis referral centers.

**Table 1: Demographics variables, comorbidities, and cardiovascular risk factors in 1,210 patients with and without pathological examination, and with and without inflammation of the ascending aorta, Denmark, 1997-2009.**

Variable	With pathological examination of aorta			Without pathological examination of aorta, n = 600 (%)
	Without aortitis, n = 573 (%)	With aortitis, n = 37 (%)	OR for aortitis (95% CI)	
Male gender	395 (69)	23 (62)	1.1 (0.5-2.4)	410 (68)
Cancer	37 (6)	2 (5)	0.7 (0.1-3.2)	51 (8)
Stroke	56 (10)	3 (8)	0.8 (0.2-2.8)	95 (16)
Ischemic heart disease	163 (28)	10 (27)	0.8 (0.4-1.9)	227 (38)
Renal failure	36 (6)	1 (3)	0.5 (0.1-4.0)	49 (8)
Connective tissue disease	28 (5)	7 (19)	4.7 (1.6-13.6)	33 (5)
Peripheral vascular disease	47 (8)	3 (8)	0.8 (0.2-2.9)	55 (9)
Infection	83 (14)	3 (8)	0.4 (0.1-1.5)	107 (18)
Hypertension	183 (32)	13 (35)	1.2 (0.5-2.5)	261 (43)
Diabetes	10 (2)	2 (5)	5.2 (0.9-29.7)	19 (3)
Age, years				
15-47	148 (26)	6 (16)	1.0 (ref.)	79 (13)
47-59	147 (26)	8 (21)	1.4 (0.5-4.4)	145 (24)
59-67	143 (25)	9 (24)	1.5 (0.4-4.5)	156 (26)
67-84	135 (2)	14 (38)	2.5 (0.8-7.6)	220 (37)
Surgical center				
1	118 (21)	9 (24)	1.0 (ref.)	238 (40)
2	110 (19)	2 (5)	0.2 (0.1-1.0)	54 (9)
3	114 (20)	5 (14)	0.6 (0.2-2.1)	55 (9)
4	162 (28)	13 (35)	1.1 (0.4-2.9)	219 (36)
5	69 (12)	8 (22)	1.7 (0.6-4.9)	34 (6)

Logistic regression analysis, adjusted ORs for aortitis

**Table 2: Main indication for surgery of the ascending aorta in 1,210 patients with and without pathological examination, and with and without a diagnosis of aortitis, Denmark 1997-2009.**

Variable <sup>a</sup>	With pathological examination of aorta			Without pathological examination of aorta, n = 600 (%)
	Without aortitis, n = 573 (%)	With aortitis, n = 37 (%)	OR for aortitis (95% CI)	
Aneurysm <sup>b</sup>	469 (82)	30 (81.1)	1.3 (0.5-3.3)	423 (81.8)
Pathology of the aortic valve <sup>c</sup>	261 (45.6)	24 (64.9)	2.3 (1.1-4.9)	279 (46.6)
Malformation <sup>d</sup>	21 (3.7)	1 (2.7)	0.7 (0.1-5.2)	19 (3.2)
Infection	8 (1.4)	1 (2.7)	1.7 (0.2-14.9)	30 (5)

Logistic regression analysis, adjusted OR for aortitis

OR: odds ratio; CI: confidence interval  
<sup>a</sup> Several conditions / indications could be present for the same patient.  
<sup>b</sup> With or without dissection.  
<sup>c</sup> Refers to aortic valve functional status, *i.e.* insufficiency, stenosis.  
<sup>d</sup> Refers to anatomic information, *i.e.* bicuspid valve, other congenital malformation.

## Conclusions

During the 1997-2009 period, pathologically confirmed aortitis was present in 6% of patients undergoing resection of the ascending part of the aorta in Denmark. This prevalence underscores the value of systematic pathological examination of removed tissue. The majority of cases were classified as 'idiopathic', with known vasculitides or inflammatory conditions found only in 27% of cases. Idiopathic aortitis thus is a condition deserving further epidemiological and pathophysiological studies, with emphasis on older patients and patients with diabetes. Finally, it must be noted that the surgical procedure does not allow for assessment of the extension of the inflammatory process in the aortic arch. Thus the prognosis of patients with aortitis and the potential evolution of the inflammatory process in the remaining aorta should be assessed in future studies.