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## Cardiovascular disease burden in thoracic aortopathy

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## Chapter 3

# A comparative evaluation of coronary disease burden: bicuspid valve disease is not athero-protective

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## **Abstract**

### *Objective*

Bicuspid aortic valve (BAV) has been associated with less atherosclerosis as compared to tricuspid aortic valve (TAV) patients. It however remains unclear whether this reflects the older age of TAV patients and/or accumulation of atherosclerotic risk factors or that the BAV phenotype is athero-protective. Therefore, we compared the atherosclerotic disease burden of BAV and TAV patients, with that of the general (age-matched) population.

### *Methods*

The prevalence of coronary artery disease (CAD) and CAD risk factors in BAV and TAV patients who underwent aortic valve surgery were compared with the Dutch general practitioner's registry-data. BAV (n=454) and TAV (n=1101) patients were divided into four groups: BAV with aortic valve stenosis (BAV-AoS), BAV with aortic valve regurgitation (BAV-AR), TAV with AoS (TAV-AoS) and TAV with AR (TAV-AR). The atherosclerotic disease burden of each group was compared with that of the corresponding age cohort for the general population.

### *Results*

CAD risk factors hypertension and hypercholesterolemia were more prevalent in the surgery groups than the age-matched general population (all  $p < 0.001$ ). All BAVs (BAV-AoS and BAV-AR) and TAV-AR had a similar incidence of CAD history as compared to the age-matched general populations ( $p = 0.689$ ,  $p = 0.325$  and  $p = 0.617$  respectively), whereas TAV-AoS had a higher incidence (21.6% versus 14.9% in the age-matched general population,  $p < 0.001$ ).

### *Conclusions*

Stenotic TAV disease is part of the atherosclerotic disease spectrum, while regurgitant TAV and all BAVs are not. Although the prevalence of cardiovascular risk factors is higher in all BAV patients, the prevalence of CAD is similar to the general population.

## **Introduction**

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly, and associates with an increased risk for aortic valve abnormalities (i.e. stenosis and regurgitation) and ascending aortic dilatation [1]. The etiology underlying thoracic aortic wall pathology in BAV has not been elucidated yet. Most studies indicate a mechanism that is distinct from the aneurysm formation in tricuspid valve (TAV) disease, which does not, or to a lesser extent involve aspects of the atherosclerotic process [2, 3]. Indeed, a comparison of the coronary artery atherosclerosis burden (coronary calcium scores) of BAV patients requiring aortic valve replacement with that of patients with a TAV showed a significantly lower coronary artery calcium burden in BAV patients. An observation which is consistent with less atherosclerosis in BAV patients. A critical question is whether these conclusions reflect the general older age of TAV patients and/or an accumulation of atherosclerotic risk factors in TAV patients requiring aortic valve replacement/repair [4] or, non-exclusively, that the BAV phenotype is athero-protective [3, 5, 6, 7, 8]. To address these aspects, we considered a comparison of the atherosclerotic disease burden of BAV and TAV patients, with that of the general (age-matched) population relevant.

## **Methods**

### *Study population*

The prevalence of CAD and CAD risk factors in BAV and TAV patients were compared with the general population (Dutch general practitioners) registry data [9]. Hospital patients were divided into four groups, namely: BAV with an aortic valve stenosis (BAV-AoS), BAV with an aortic valve regurgitation (BAV-AR), TAV with AoS (TAV-AoS) and TAV with AR (TAV-AR). Patients with a combined aortic valve vitium were included in either the stenotic or regurgitant group based on the most severe aortic valve pathology. All included hospital patients were surgically treated between 2006 and 2019 and were obtained from a retrospective study conducted at the Leiden University Medical Center (LUMC) in the Netherlands [3]. Approval for that study was granted by the medical ethics committee of the Leiden University Medical Center (METC LDD, case number G19.113) and patient consent was waived. Subsequently, the atherosclerotic disease burden of each group was compared with that of the corresponding (matched) age cohort for the general population.

### *Definitions*

Preoperative coronary angiographies were scored for all hospital patients [3], but could not be used to compare CAD with the general population since angiographies were not available for this group. Therefore, it was chosen to define CAD in the general population as a previous myocardial infarction or instable angina pectoris.

Deduplication was performed for the hospital patients that had a history of both a myocardial infarction and instable angina pectoris [3].

Cardiovascular risk factors included hypertension, diabetes mellitus (type 1 and 2) and hypercholesterolemia. Current guidelines define hypertension as a blood pressure of  $\geq 140/90$  mmHg. In the NIVEL primary care database however hypertension is till date defined as a blood pressure  $\geq 160/95$  mmHg. Therefore hypertension was defined as a diastolic pressure of  $\geq 95$  mmHg, a systolic pressure of  $\geq 160$  mmHg on two separate occasions, or as the usage of antihypertensive drugs to be able to compare the study groups [9]. Hypercholesterolemia was scored if the patient had a total cholesterol level of  $\geq 6,5$  mmol/L or used lipid-lowering medications [9]. Diabetes was defined as either a blood glucose level of  $\geq 7,0$  mmol/l on two separate (fasted) occasions, a glucose level of  $\geq 11,1$  mmol/l plus symptoms of hyperglycemia, or use of anti-diabetic medication.

### *Data sources*

Data from general practitioners participating in the NIVEL Primary Care Database (NPCD, 2019) were used. The NPCD is a longitudinal database in which data from Dutch general practitioners is collected for study purposes. The database provides a representative sample of the Dutch population [9]. Included diagnoses were coded by the primary care physicians using the International Classification of Primary Care (ICPC) [9]. Data regarding the BAV and TAV hospital patients were from a single center cohort of 1555 (454 BAV, 1101 TAV) patients who underwent aortic valve repair or replacement [3]. The medical history of these patients were all re-evaluated for the prevalence of CAD and risk factors.

### *Patient and public involvement*

Patients were not involved.

### *Statistical analysis*

Continuous data are presented as mean and standard deviation, categorical data as frequencies and percentages. The Fischer's exact test was used for analyzing categorical data. All variables with a  $p < 0.2$  in the univariate analyses were included in a multivariate model in order to correct the differences between the groups (e.g. age, sex and date of surgery). A  $p$ -value of  $< 0.05$  was considered to be significant. All statistical analyses were conducted using IBM SPSS for Windows version 25.0.

## Results

### *Cardiovascular burden: BAV vs TAV patients*

Baseline and CAD-related factors of the hospital population are summarized in table 1. Cardiovascular risk factors were more common in TAV patients (AoS and AR) than in BAV patients (AoS and AR) (all  $p < 0.001$ ). Similarly, TAV patients were more likely to have a history of CAD (odds ratio (OR): 3.07 (95%CI 2.10-4.48);  $p < 0.001$ ). This difference remained after correction for age, sex and date of surgery (corrected OR<sub>(age, sex, intervention date)</sub>: 2.73 (95%CI 1.83-4.09);  $p < 0.001$ ). Comparison of echocardiographic characteristics were already made in a previous study, which showed higher aortic valve gradients in BAV patients (peak gradient of 73 vs 62 mmHg,  $p < 0.001$ ) [3].

Sub-analysis showed a higher prevalence of risk factors hypercholesterolemia and diabetes mellitus in TAV-AoS vs TAV-AR (both  $p < 0.001$ ), as well as with a higher prevalence of previous CAD (corrected OR<sub>(age and sex)</sub> for TAV-AR vs TAV-AoS: 1.08 (95%CI 1.06-1.10);  $p = 0.001$ ). Comparison of BAV-AoS patients with BAV-AR patients only showed a higher prevalence of diabetes mellitus in BAV-AoS patients ( $p < 0.001$ ).

### *Cardiovascular burden: BAV and TAV patients vs general population*

The prevalence of cardiovascular risk factors and CAD in the patients and the respective reference (age-matched) general populations are summarized in figure 1.

With the exception of hypercholesterolemia in the TAV-AR group, hypertension and hypercholesterolemia were more prevalent in the surgery groups than in the age-matched general population (all  $p < 0.001$ ).

Compared to the general population, a diagnosis of diabetes mellitus was more common in the TAV-AoS group ( $p \leq 0.001$ ), less common in the TAV-AR and BAV-AR groups (9% versus 16.9%,  $p < 0.001$  resp. 2.2% versus 6.6%,  $p \leq 0.001$ ) and similar in the BAV-AoS group.

The prevalence of a history of CAD was similar in BAV patients (both BAV-AoS and BAV-AR), TAV-AR patients, and the age-matched general populations ( $p = 0.689$ ,  $p = 0.325$  and  $p = 0.617$  respectively). In contrast, TAV-AoS associated with a higher incidence of a history of CAD (21.6% versus 14.9% in the age-matched general population,  $p < 0.001$ ).

Table 1: Characteristics and prevalence of CAD and CAD risk factors of the hospital population

Characteristic	<u>Aortic valve morphology</u>			
	<u>Bicuspid aortic valve</u>		<u>Tricuspid aortic valve</u>	
	AoS	AR	AoS	AR
	n = 365	n = 89	n = 931	n = 170
Male sex	248 (67.9)	75 (84.3)	575 (61.8)	118 (69.4)
Age at surgery (years ± SD)	63 ± 9.9	53.8 ± 10.6	71.9 ± 8.3	64.7 ± 11.4
Body Mass Index (kg/m <sup>2</sup> )	26.3 (24-29.1)	25.9 ± 4.3	26.8 (24.5-30.1)	26.2 (23.2-28.4)
Smoking status	361/365*	84/89*	884/931*	161/170*
Never	161 (44.1)	44 (49.4)	422 (45.3)	79 (46.5)
Former	119 (32.6)	16 (18)	331 (35.6)	44 (25.9)
Current	81 (22.2)	24 (27)	131 (14.1)	38 (22.4)
	346/365*	83/89*	866/931*	152/170*
Family history of CAD	48 (13.2)	11 (12.4)	136 (14.6)	20 (11.8)
Diabetes	52 (14.2)	2 (2.2)	253 (27.2)	16 (9.4)
Hypertension	179 (49)	51 (57.3)	619 (66.5)	113 (66.5)
Hypercholesterolemia	105 (28.8)	19 (21.3)	415 (44.6)	43 (25.3)
History of CAD	32 (8.8)	2 (2.2)	201 (21.6)	18 (10.6)

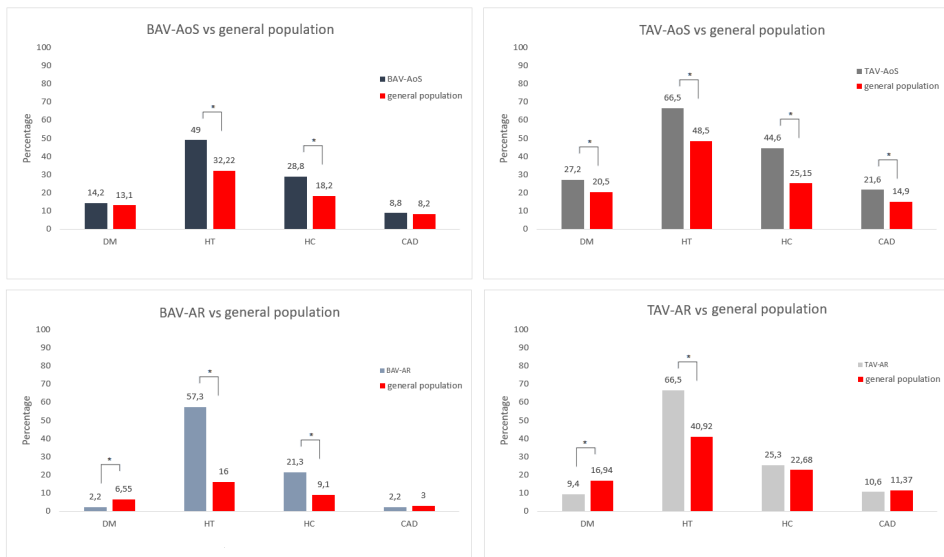
AR= Aortic regurgitation, AoS = Aortic valve stenosis, BAV = Bicuspid aortic valve, CAD = Coronary artery disease, TAV = Tricuspid aortic valve. Hypertension is defined as a systolic blood pressure >160 mm Hg. Hypercholesterolemia: total cholesterol level of ≥6,5 mmol/L or use of lipid-lowering medication. Diabetes: as a blood glucose level of ≥ 7,0 mmol/l on two separate (fasted) occasions, a glucose level of ≥ 11,1 mmol/l plus symptoms of hyperglycemia or usage of anti-diabetic medication.

\* Denominator represents variables with incomplete data

## Discussion

The findings of this study characterize stenotic TAV disease as a part of the atherosclerotic disease spectrum (based on cardiovascular risk factors and more prevalent CAD compared to the general population), while TAV-AR and BAV (both AR and AoS) do not. Although the prevalence of cardiovascular risk factors was higher in the BAV groups, the prevalence of CAD was similar to the general population.

Figure 1: Comparison of CAD and CAD risk factors in BAV and TAV groups vs the age and sex-matched general population.



AR= Aortic regurgitation, AoS = Aortic valve stenosis, BAV = Bicuspid aortic valve, CAD = Coronary artery disease, DM = Diabetes mellitus, HT = Hypertension, HC = Hypercholesterolemia, TAV = Tricuspid aortic valve  
 \* =  $p \leq 0.001$

The relationship of CAD and the aortic valve morphology and a possible athero-protective effect of BAV is a topic of ongoing debate [5, 6, 7, 8]. Previous studies have shown a significantly larger aortic valve calcium volume in BAV patients than TAV patients [5], but strikingly also a lower prevalence of cardiovascular risk factors, coronary calcification, CAD, and coronary revascularization [3, 6, 7, 8]. These observations imply that the aortic valve calcifications in BAV disease merely reflect local degenerative changes rather than systemic atherosclerotic changes [3,6]. Our previous report focusing on an in-hospital population implied a protective relationship between BAV and atherosclerosis [3]. The similar prevalence of CAD in BAV patients and the general population, and the increased prevalence of CAD in TAV-AoS patients observed in this study suggests that the conclusions with regard to a possible athero-protective phenotype of BAV are interfered by the strong association of atherosclerosis and TAV-AoS disease. Nevertheless, BAV patients present with a more unfavorable cardiovascular risk profile than the general population. This observation could support an athero-protective phenotype in BAV disease, yet it cannot be excluded that the higher prevalence of risk factors reflects a referral phenomenon with



increased awareness on the assessment and treatment of cardiovascular risk factors in the clinical setting.

### *Limitations*

Due to incomplete data of the general population not all cardiovascular risk factors such as laboratory findings, tobacco usage or family history of CAD could be included in this study. Available data of the general population might be biased by aspects such as under-reporting, a more systematic screening for risk factor in the hospital population and a reliance on coding (NPCD). Nevertheless, it is important to point out that the coding of general practitioners have improved significantly in the last few years [9]. Comparisons of CAD were made based solely on chart review, as coronary angiographies were not available for the general population. Finally, the definition of hypertension (>160 mmHg) used in this study was dictated by NIVEL Primary Care Database. This definition is higher than the consensus threshold, and may consequently lead to under-reporting of hypertension in the general population. We consider it unlikely that this higher threshold influences the conclusions with regard to the hospital population, since these diagnoses were all based on antihypertensive drugs usage and not on actual blood pressure.

### **Conclusion**

BAV patients and TAV-AR present with a worse cardiovascular risk profile than, but similar prevalence of CAD as the general population. These conclusions do not characterize BAV as athero-protective. On the other hand, the higher prevalence of cardiovascular risk factors and CAD in TAV-AoS patients characterizes TAV-AoS as a part of the atherosclerotic spectrum of diseases.

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