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Arterial hypertension and diastolic blood pressure associate with aortic stenosis

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ABSTRACT

Objectives. Due to age-related differences in aortic valve structure, it is likely that the pathophysiology of aortic stenosis (AS) and associated risk factors differ between age groups. Here we prospectively studied the influence of traditional cardiovascular risk factors on AS development requiring surgery among patients without concomitant coronary artery disease (CAD) and stratified for age. **Design.** This study included 322 patients, who had prior to surgery for AS participated in population-based surveys, and 131 of them had no visible CAD upon preoperative coronary angiogram. For each case, we selected four referents matched for age, gender, and geographic area. To identify predictors for surgery, we used multivariable conditional logistic regression with a model including arterial hypertension (or measured blood pressure and antihypertensive medication), cholesterol levels, diabetes, body mass index (BMI), and smoking. **Results.** In patients without CAD, future surgery for AS was associated with arterial hypertension and elevated levels of diastolic blood pressure in patients younger than 60 years at surgery (odds ratio [95% confidence interval]), (3.40 [1.45–7.93] and 1.60 [1.09–2.37], respectively), and with only impaired fasting glucose tolerance in patients 60 years or older at surgery (3.22 [1.19–8.76]). **Conclusion.** Arterial hypertension and elevated diastolic blood pressure are associated with a risk for AS requiring surgery in subjects below 60 years of age. Strict blood pressure control in this group is strongly advocated to avoid other cardiovascular diseases correlated to hypertension. If hypertension and elevated diastolic blood pressure are risk factors for developing AS requiring surgery need further investigations. Notably, elevated fasting glucose levels were related to AS requiring surgery in older adults without concomitant CAD.

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hypertension; diabetes;
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Background



In western countries, aortic valve replacement is the second most common cardiothoracic procedure, following coronary artery by-pass surgery [1]. Among patients with aortic stenosis over 60 years old, tricuspid valves are most prevalent, comorbidity with coronary atherosclerosis is common [2], and traditional cardiovascular risk factors play an important role [3]. However, in patients under 60 years old, bicuspid aortic valve (BAV) is the most common underlying valve pathology, and little information is available regarding the influence of traditional cardiovascular risk factors on aortic stenosis development in this population. Studies of clinical factors related to aortic stenosis development are usually retrospective or cross-sectional, and commonly utilize data obtained near the time of surgery, *i.e.* in patients with severely affected valves. Several possible risk factors, such as hypercholesterolemia, have emerged in this context. However, treatment targeting these risk factors has not been shown to modify the course of disease progression [4–6].

The prevalence of BAV varies with age in aortic valve disease, and can occur with or without concomitant coronary artery disease (CAD); thus, we hypothesised that the influence of traditional cardiovascular risk factors would vary among these groups. In our present study, we prospectively studied the presence of traditional cardiovascular risk factors prior to surgery for aortic stenosis among patients without CAD and stratified for age (<60 years and ≥60 years old).

Methods

Study population

A total of 6691 patients underwent surgery for valvular heart disease and/or disease of the ascending aorta at the Department of Cardiothoracic Surgery, Umeå University Hospital, Umeå, Sweden, between March 1988 and December 2014. Prior to their first surgery, 799 of these patients had participated in one of three population-based

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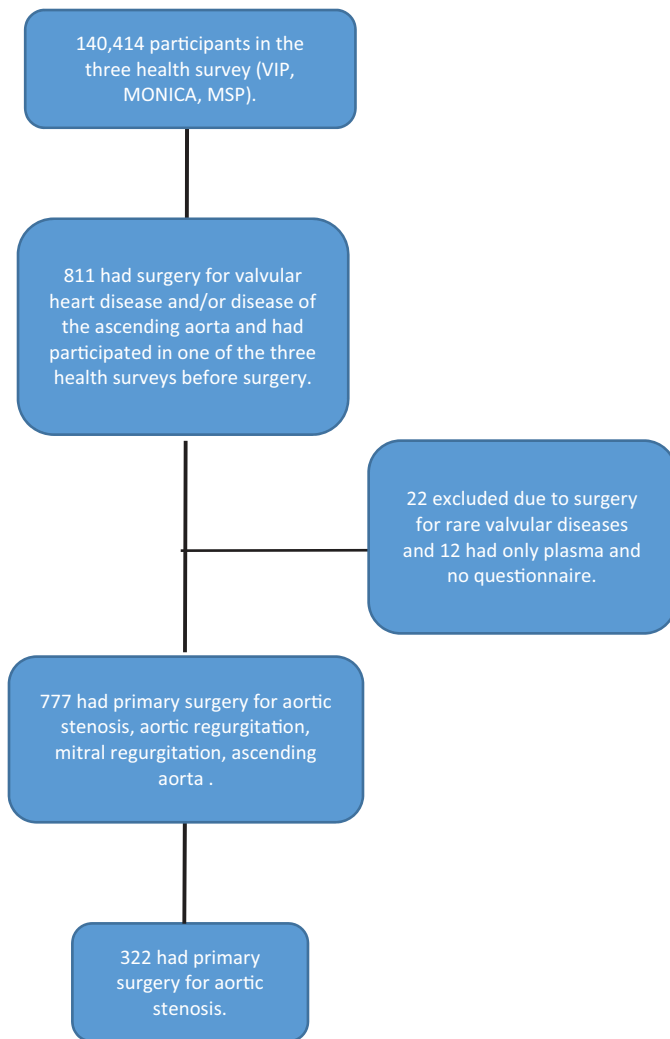


Figure 1. Flow chart illustrating the study base (VIP, MONICA and MSP) and the selection of cases.

health studies in Northern Sweden: 619 patients in the Västerbotten Intervention Program (VIP), 101 patients in the Northern Sweden MONItoring Of trends and Determinants in CARdiovascular Disease (MONICA) survey, and 79 patients in the Mammary Screening Program (MSP). Among these study participants, 322 had undergone surgery for the primary indication of aortic stenosis.

The VIP is an ongoing community intervention program targeting cardiovascular disease and diabetes prevention. At the ages of 30, 40, 50, and 60 years, subjects are asked to participate in a health survey at their primary health centre. MONICA enrolment involves inviting randomly selected individuals to participate in a health survey. Participants are 25–74 years of age, and from the counties of Västerbotten and Norrbotten [7]. The MSP cohort comprises women who attended a routine mammography screening. Altogether, these three surveys included 140,414 participants up to December 2014, with participation rates of 65–75%. The study base and the selection of cases are further illustrated in Figure 1.

For each case, we randomly selected four referents who were matched for sex, age (± 2 years), type of survey (MONICA, VIP, or MSP), date of health survey (± 4

months), and geographical area. We did not exclude participants with a history of cancer or myocardial infarction. Altogether, 2.8% of cases and 5.6% of referents had cancer within 5 years prior to surgery (or the corresponding date for referents). Similarly, 4.3% of cases and 2.0% of referents reported prior myocardial infarction.

The study protocol was approved by the Regional Ethical Review Board in Umeå (07–174M) and complies with the Declaration of Helsinki. All participants gave written informed consent for future use of the data.

Perioperative characteristics

From hospital files, we obtained data from preoperative assessments, including medical history, current medication, anthropometry, blood pressure, electrocardiogram, coronary angiogram, and echocardiography when available. According to established practise, all cases underwent coronary angiogram, and the findings were used to categorize CAD. Any sign of arteriosclerosis or atheromatosis was considered to indicate CAD (found in 59.3% of all cases).

Baseline clinical examinations and biochemical analysis

At the initial health survey, VIP and MONICA participants were asked to complete a health questionnaire regarding their living conditions and cardiovascular risk factors, and anthropometry and blood pressure measurements were taken. Participant weight was measured in light indoor clothing without shoes, and recorded to the nearest 0.2 kg. Height was measured without shoes to the nearest centimetre. Body mass index (BMI) was calculated as weight divided by height squared. Subjects were categorized as daily smokers, ex-smokers, or never-smokers.

An oral glucose tolerance test, including measurements of fasting and post-load glucose levels, was routinely performed in the VIP, was performed in 60% of MONICA participants, and was not performed in the MSP. Diabetes presence was determined based on self-reported usage of anti-diabetic medication, fasting plasma glucose levels ≥ 7.0 mmol/L, and/or post-load plasma glucose levels ≥ 11.1 mmol/L (≥ 12.2 mmol/L based on capillary plasma in the VIP). Impaired fasting glucose was defined as a fasting glucose level of ≥ 6.1 and < 7.0 mmol/L. Impaired glucose tolerance was defined as a post-load glucose level of ≥ 7.8 and < 11.1 (≥ 8.9 and < 12.2 in the VIP) combined with a non-diabetic fasting glucose level.

In all surveys, blood pressure was measured after 5 minutes of rest, using a mercury sphygmomanometer prior to 2004, and using semi-automatic devices since 2004 (Omron M7, Omron Corp., Kyoto, Japan). Patients were seated for blood pressure measurement throughout the MONICA and MSP surveys, whereas in the VIP survey, blood pressure was measured with participants in the recumbent position until September 2009 and thereafter in the sitting position. Measurements obtained with participants in the recumbent position were adjusted using a sex- and age-specific formula [8]. Hypertension was defined as

Table 1. Characteristics of the study population at the time of survey.

	Without CAD			With CAD		
	Cases	Referents	<i>p</i>	Cases	Referents	<i>p</i>
<60 years						
<i>n</i>	49	192		21	84	
Female sex, %	47 (32–61)	48 (41–55)	.75	29 (8–50)	29 (19–38)	1.00
Age at survey, years	44.2 (42.1–46.3)	44.3 (43.3–45.3)	.63	46.5 (44.3–48.8)	46.8 (45.8–47.8)	.95
Age at surgery, years	53.3 (51.9–54.8)			55.4 (54.3–56.6)		
BMI, kg/m ²	25.7 (24.4–27.1)	25.8 (25.2–26.4)	.91	25.8 (23.9–27.8)	25.4 (24.7–26.1)	.64
Fasting glucose, mmol/L	5.1 (5.0–5.3)	5.3 (5.2–5.4)	.37	5.3 (5.0–5.6)	5.4 (5.2–5.6)	.57
Post-load glucose, mmol/L	6.2 (5.8–6.7)	6.2 (6–6.4)	.96	6.3 (5.5–7.1)	6.2 (5.8–6.7)	.87
Diabetes, %	–	1 (0–3)		–	4 (0–8)	–
Total cholesterol, mmol/L	5.6 (5.3–5.9)	5.8 (5.7–6.0)	.74	6.4 (5.9–7.0)	5.9 (5.6–6.2)	.36
Smoking, %			.28			.86
Never smoker	31 (17–44)	42 (35–49)		33 (11–55)	29 (19–38)	
Current smoker	31 (17–44)	26 (20–32)		29 (8–50)	33 (23–44)	
Ex-smoker	29 (15–42)	23 (17–29)		33 (11–55)	32 (22–42)	
Hypertension, %	38 (23–53)	21 (14–27)	.02	62 (39–85)	30 (20–40)	.02
SBP, mmHg	126 (121–132)	125 (123–127)	.39	135 (129–141)	129 (126–132)	.14
DBP, mmHg	83 (80–86)	80 (79–81)	.03	85 (81–88)	83 (81–85)	.58
≥60 years						
<i>n</i>	82	323		170	677	
Female sex, %	59 (48–69)	59 (54–64)	1.00	43 (35–50)	42 (39–46)	.92
Age at survey, years	59.6 (58.2–61.1)	59.5 (58.8–60.2)	.9	59.8 (58.8–60.8)	59.6 (59.2–60.1)	.78
Age at surgery, years	70.5 (69.2–71.8)			71.7 (70.8–72.5)		
BMI, kg/m ²	27.1 (26.1–28)	26.0 (25.6–26.4)	.03	27.1 (26.5–27.6)	26.2 (25.9–26.5)	.02
Fasting glucose, mmol/L	5.7 (5.4–6.0)	5.4 (5.3–5.5)	.06	5.8 (5.5–6.1)	5.4 (5.3–5.5)	.02
Post-load glucose, mmol/L	6.4 (6.0–6.8)	6.6 (6.4–6.9)	.43	7.0 (6.6–7.4)	6.7 (6.5–6.9)	.22
Diabetes, %	8 (0–16)	8 (4–12)	.99	15 (9–21)	6 (4–9)	.01
Total cholesterol, mmol/L	6.4 (6.0–6.7)	6.3 (6.1–6.4)	.55	6.6 (6.4–6.8)	6.4 (6.3–6.5)	.01
Smoking, %			.99			.08
Never smoker	28 (18–38)	31 (26–36)		31 (24–38)	38 (34–42)	
Current smoker	11 (4–18)	11 (8–15)		16 (10–21)	18 (15–21)	
Ex-smoker	24 (15–34)	26 (21–30)		34 (27–41)	27 (23–30)	
Hypertension, %	52 (38–65)	49 (43–56)	.74	70 (62–77)	56 (52–60)	.001
SBP, mmHg	138 (133–143)	136 (134–139)	.49	144 (140–146)	138 (136–139)	.001
DBP, mmHg	85 (84–88)	83 (82–85)	.25	87 (86–88)	85 (84–86)	.03

Values shown are numbers, means and proportions with (95% confidence intervals), and *p* values for cases and referents at survey, stratified for age and coronary artery disease (CAD).

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index.

systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, and/or use of anti-hypertensive medication. The usage of antihypertensive medication was self-reported.

Total serum cholesterol was measured at the time of the health survey using a bench-top analyser (ReflotronR, Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany) in the VIP until September 2009, or at a central laboratory using an enzymatic method (Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany) in MONICA and the VIP after September 2009. Cholesterol values obtained using the bench-top method were adjusted to the results measured at the central laboratory.

Statistical analysis

Missing values for categorical variables were treated as a separate category and are not included in the tables. Data are presented as mean and 95% confidence interval (CI). Student's *t*-tests were used to analyse differences in the means between cases and referents. Continuous variables were categorized into quartiles based on the distribution of the referent values, separately for men and women. In addition, systolic and diastolic blood pressure were analysed as *z*-scores based on the distribution among referents, and

were calculated separately for men and women. As a conservative approach, missing values were replaced with the median value obtained among the referents. Since cases and referents had the same follow-up time within strata in this nested and matched case-referent study, logistic regression analysis (rather than Cox regression) using the conditional maximum likelihood routine designed for matched analysis was used to estimate odds ratios (ORs) and 95% CIs, and the influence of studied variables on surgery for aortic stenosis was tested in univariate and multivariable models. The analyses were stratified for age at surgery (less than 60 years or 60 years and more), presence of any visible CAD on the preoperative angiogram, and time-interval between health survey and valvular surgery (more than 5 years or less). For multivariable analyses, we used a model including established cardiovascular risk factors, *i.e.* arterial hypertension, total cholesterol, BMI, glucose tolerance, and smoking. All calculations were performed using the statistical program SPSS version 24 (IBM, Armonk, NY, USA).

Results

Of the 322 patients operated for the primary indication of aortic stenosis, 70 underwent surgery before 60 years of age and 252 after 60 years of age. Table 1 presents the

Table 2. Predictors of aortic stenosis requiring surgery at the age less than 60 years.

	<60 years							
	Without CAD				With CAD			
	Ref/Case	Trend	Univariate	Multivariable	Ref/Case	Trend	Univariate	Multivariable
Hypertension								
No	136/26	0.02	1.00	1.00	58/8	0.007	1.00	1.00
Yes	35/16		2.82 (1.30–6.13)	3.40 (1.45–7.93)	25/13		3.73 (1.35–10.32)	5.88 (1.46–23.72)
SBP								
Q1	73/16	0.39	1.00		21/4	0.03	1.00	
Q2	50/11		1.02 (0.41–2.51)		31/3		0.56 (0.11–2.81)	
Q3	32/12		1.75 (0.73–4.20)		22/8		2.44 (0.56–10.64)	
Q4	16/4		1.32 (0.36–4.86)		9/6		3.55 (0.82–15.36)	
Z-score			1.15 (0.75–1.77)				1.73 (0.97–3.09)	
DBP								
Q1	77/13	0.13	1.00		26/5	0.2	1.00	
Q2	40/14		2.50 (0.96–6.51)		22/4		1.01 (0.23–4.39)	
Q3	31/5		1.18 (0.36–3.88)		21/6		1.51 (0.38–6.06)	
Q4	23/10		3.36 (1.19–9.53)		14/6		2.15 (0.57–8.09)	
Z-score			1.47 (1.04–2.08)				1.26 (0.76–2.07)	
Glucose tolerance								
NGT	129/35	0.24	1.00	1.00	67/17	0.39	1.00	1.00
IFG	12/2		0.58 (0.11–3.16)	0.51 (0.07–3.94)	10/3		1.15 (0.30–4.44)	1.71 (0.36–8.06)
IGT	8/1		0.48 (0.06–4.02)	0.75 (0.07–8.26)	2/0		–	–
DM	2/0		–	–	3/0		–	–
BMI								
Q1	62/15	0.97	1.00	1.00	22/5	0.49	1.00	1.00
Q2	40/13		1.37 (0.60–3.14)	1.78 (0.71–4.49)	26/4		0.68 (0.15–3.07)	0.50 (0.09–2.79)
Q3	49/9		0.75 (0.29–1.96)	0.80 (0.28–2.31)	22/7		1.40 (0.37–5.26)	1.75 (0.37–8.27)
Q4	41/12		1.20 (0.49–2.94)	1.14 (0.41–3.14)	17/5		1.39 (0.35–5.42)	1.57 (0.34–7.30)
Cholesterol								
Q1	65/16	0.88	1.00	1.00	27/3	0.16	1.00	1.00
Q2	44/11		1.02 (0.44–2.35)	1.01 (0.41–2.50)	23/6		2.73 (0.57–13.16)	1.95 (0.31–12.31)
Q3	38/10		1.10 (0.45–2.68)	1.25 (0.46–3.40)	14/6		4.37 (0.92–20.72)	3.22 (0.54–19.21)
Q4	23/6		1.03 (0.37–2.85)	0.86 (0.29–2.55)	20/6		3.83 (0.64–23.00)	2.00 (0.20–20.09)
Smoking								
Never smoker	81/15	0.21	1.00	1.00	24/7	0.62	1.00	1.00
Ex-smoker	44/14		1.68 (0.73–3.88)	1.24 (0.49–3.18)	27/7		0.88 (0.27–2.83)	1.45 (0.35–6.12)
Current smoker	50/15		1.64 (0.70–3.81)	1.57 (0.65–3.80)	28/6		0.73 (0.22–2.43)	1.00 (0.25–3.96)

Values shown are numbers (referents, cases), *p* for trend and odds ratios (95% confidence intervals), stratified for age and coronary artery disease (CAD).

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus; CAD: coronary artery disease.

Cut-offs for quartiles (Q1 to Q4) were stratified for sex as follows: SBT men, 122.6, 131.1, and 142.6; SBT women, 117.8, 130.8, and 144.4; DBT men, 78.9, 83.6, and 91.3; DBT women, 78.8, 81.7, and 88.7; BMI men, 23.9, 25.9, and 28.1; BMI women, 22.8, 25.1, and 28.2; cholesterol men, 5.3, 6.1, and 6.8; cholesterol women, 5.5, 6.2, and 6.8. Z-scores for SBT and DBT were based on the distribution amongst referents and separately for men and women (mean [SD]): 135 [16.5], 134 [20.2], 85 [9.0], and 82 [9.3], respectively.

characteristics of the study population at the baseline health survey, stratified for age at surgery and presence of CAD. All patients underwent open-chest surgery for aortic valvular replacement and no one had a transcatheter aortic valve implantation (TAVI) procedure. Two patients reported previous surgery for coarctation and had surgery for AS at the age of 55 and 57 years, respectively.

The presence of arterial hypertension predicted independently of other risk markers future aortic valve surgery in patients <60 years of age at surgery, irrespective of coexisting CAD (Table 2). After exclusion of those with valvular surgery within 5 years after survey, the point estimates for increased risk remained although not significant for those with CAD (odds ratio [95% confidence interval]) (6.70 [2.06–21.76] and 6.64 [0.96–45.92] for those without CAD and with CAD respectively). In contrast, a high systolic blood pressure did not independently predict valvular surgery irrespective of coexisting CAD (data not shown). However, a high diastolic blood pressure (z-score) independently predicted valvular surgery in those without CAD

(1.60 [1.09–2.37]), but not in those with CAD (1.22 [0.64–2.31]). These associations were attenuated after further adjustment for self-reported antihypertensive medication (1.47 [0.97–2.23] and 1.09 [0.54–2.21], respectively).

After exclusion of those with valvular surgery within 5 years after survey, diastolic blood pressure (z-score) remained independently associated with surgery in those without CAD (1.98 [1.22–3.21], and 1.73 [1.03–2.91] after further adjustment for antihypertensive medication).

Among patients who underwent surgery at ≥60 years of age and who had concomitant CAD, the risk of future aortic valve surgery was increased by arterial hypertension, diabetes, high cholesterol levels, and active smoking (Table 3). In this group of elderly patients with CAD, a high systolic and diastolic blood pressure (z-scores) also predicted valvular surgery tested in separate models, (1.43 [1.17–1.74] and 1.25 [1.01–1.54], respectively), and remained associated with surgery after exclusion of those with surgery within 5 years, (1.42 [1.13–1.78] and 1.28 [1.02–1.62], respectively). The association between systolic blood pressure (z-score) and

Table 3. Predictors of aortic stenosis requiring surgery at the age of 60 years or higher.

	≥60 years							
	Without CAD				With CAD			
	Ref/Case	Trend	Univariate	Multivariable	Ref/Case	Trend	Univariate	Multivariable
Hypertension								
No	115/27	0.74	1.00	1.00	252/44	0.002	1.00	1.00
Yes	112/29		1.15 (0.64–2.06)	0.93 (0.48–1.81)	318/10		1.94 (1.29–2.92)	2.00 (1.29–3.11)
SBP								
Q1	54/11	0.92	1.00	1.00	106/14	0.001	1.00	1.00
Q2	43/14		1.63 (0.67–3.95)	1.17 (0.50–2.78)	146/26		1.39 (0.68–2.87)	
Q3	60/14		1.17 (0.50–2.78)	1.26/43	126/43		2.67 (1.37–5.23)	
Q4	70/17		1.25 (0.53–2.93)	192/63	192/63		2.73 (1.40–5.32)	
Z-score			1.09 (0.81–1.46)				1.43 (1.18–1.73)	
DBP								
Q1	79/15	0.34	1.00	1.00	131/24	0.01	1.00	1.00
Q2	44/11		1.38 (0.56–3.41)	1.25/26	125/26		1.13 (0.61–2.08)	
Q3	53/17		1.76 (0.80–3.85)	176/48	176/48		1.50 (0.87–2.59)	
Q4	51/13		1.46 (0.62–3.40)	138/48	138/48		1.98 (1.13–3.46)	
Z-score			1.22 (0.92–1.62)				1.26 (1.04–1.53)	
Glucose tolerance								
NGT	151/32	0.58	1.00	1.00	373/89	0.01	1.00	1.00
IFG	15/11		3.74 (1.51–9.30)	3.22 (1.19–8.76)	49/10		0.86 (0.41–1.84)	0.79 (0.36–1.75)
IGT	12/2		0.94 (0.19–4.74)	1.09 (0.20–5.94)	41/9		0.93 (0.43–2.00)	0.87 (0.39–1.94)
DM	16/4		1.36 (0.42–4.43)	1.15 (0.31–4.20)	32/19		2.57 (1.33–4.96)	2.44 (1.23–4.82)
BMI								
Q1	76/14	0.08	1.00	1.00	166/28	0.04	1.00	1.00
Q2	82/20		1.28 (0.61–2.70)	1.21 (0.54–2.72)	156/40		1.51 (0.88–2.57)	1.46 (0.84–2.54)
Q3	89/20		1.20 (0.58–2.51)	1.23 (0.56–2.73)	151/43		1.68 (1.00–2.84)	1.31 (0.76–2.26)
Q4	70/26		2.10 (1.00–4.40)	1.66 (0.72–3.86)	189/55		1.68 (1.02–2.76)	1.32 (0.78–2.23)
Cholesterol								
Q1	49/11	0.59	1.00	1.00	121/21	0.02	1.00	1.00
Q2	55/16		1.25 (0.52–3.03)	1.42 (0.55–3.67)	98/22		1.32 (0.69–2.55)	1.40 (0.70–2.81)
Q3	59/8		0.59 (0.22–1.59)	0.58 (0.20–1.73)	167/43		1.52 (0.85–2.74)	1.52 (0.82–2.81)
Q4	56/19		1.47 (0.62–3.48)	1.19 (0.46–3.10)	182/58		1.93 (1.09–3.42)	2.03 (1.10–3.74)
Smoking								
Never smoker	100/23	0.88	1.00	1.00	256/52	0.42	1.00	1.00
Ex-smoker	83/20		1.04 (0.52–2.09)	0.98 (0.44–2.17)	180/58		1.67 (1.07–2.60)	1.78 (1.12–2.84)
Current smoker	37/9		1.11 (0.45–2.77)	0.99 (0.35–2.80)	121/27		1.15 (0.69–1.95)	1.40 (0.81–2.43)

Values shown are numbers (referents, cases), *p* for trend and odds ratios (95% confidence intervals), stratified for age and coronary artery disease (CAD).

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus; CAD: coronary artery disease.

Cut-offs for quartiles (Q1 to Q4) were stratified for sex as follows: SBT men, 122.6, 131.1, and 142.6; SBT women, 117.8, 130.8, and 144.4; DBT men, 78.9, 83.6, and 91.3; DBT women, 78.8, 81.7, and 88.7; BMI men, 23.9, 25.9, and 28.1; BMI women, 22.8, 25.1, and 28.2; cholesterol men, 5.3, 6.1, and 6.8; cholesterol women, 5.5, 6.2, and 6.8. Z-scores for SBT and DBT were based on the distribution amongst referents and separately for men and women (mean[SD]): 135 [16.5], 134 [20.2], 85 [9.0], and 82 [9.3], respectively.

surgery remained after further adjustment for antihypertensive medication (1.39 [1.14–1.70]).

However, among patients in the older group who did not have CAD, future valvular surgery was predicted only by increased fasting glucose levels expressed as impaired fasting glucose, and this association remained only in those with valvular surgery more than 5 years after the health survey (4.34 [1.36–13.83]). Arterial hypertension, systolic or diastolic blood pressure did not predict surgery in this elderly group without CAD (data not shown).

Multivariable analyses using quartiles of systolic or diastolic blood pressure did not add any extra information (data not shown).

Discussion

Our present results demonstrated that arterial hypertension was associated with future surgery for aortic stenosis among younger patients (<60 years old) who are expected to show a high frequency of bicuspid valves. On the other hand, numerous classical cardiovascular risk factors predicted

surgery among older adults (≥60 years old) with CAD. Notably, impaired fasting glucose was strongly associated with aortic stenosis requiring surgery among older adults without CAD.

Earlier cross-sectional studies have reported that aortic stenosis is associated with hypertension and elevated cholesterol [3,9]. Several randomized clinical trials have examined whether cholesterol level reduction can slow the stenosis progression rate [6,10,11]. However, none of these interventional trials have been effective, likely due to late treatment initiation during an already ongoing and advanced process.

Bicuspid valves occur in about 2% of the population, and a substantial proportion of these patients will require replacement surgery [12]. In our present study, arterial hypertension was more common among the younger patients, which also may increase the life-time risk for other cardiovascular diseases [13]. We suggest that hypertension may be part of the vascular syndrome that includes bicuspid aortic valve, coarctation of the aorta, and ascending aorta dilatation. Correspondingly, arterial hypertension is

common in patients with coarctation of the aorta, even after reconstructive surgery [14,15].

Elevated systolic blood pressure, but not hypertension, is reportedly related to faster aortic valve calcification—notably, with a differential effect on aortic valvular calcium vs. coronary artery calcium [16]. This may be caused by increased mechanical strain that induces mineralization in the aortic valvular interstitial cells [17]. In relation to anti-hypertensive treatment, it is also possible that drugs affecting the renin-angiotensin system could modulate aortic stenosis progression [18].

To our knowledge, a high diastolic blood pressure has not been associated with the development of aortic stenosis requiring surgery. In this study, elevated diastolic blood pressure, but not elevated systolic blood pressure, predicted valvular surgery in younger patients without visible CAD. Diastolic hypertension is a risk factor for cardiovascular disease in younger individuals, and is associated with increased peripheral vascular resistance [19]. In our younger patients with assumingly high frequency of bicuspid valves, alteration in the vascular system as a part of the bicuspid valve vascular syndrome might explain the increase of elevated diastolic pressure.

We used a composite definition of arterial hypertension based on antihypertensive medication or measured high levels of systolic or diastolic blood pressure. This definition has been frequently used in previous trials and case-referent studies and should better mirror lifelong exposure for elevated blood pressure than measured levels at the health survey [13,20,21]. Furthermore, the antihypertensive treatment and the blood pressure effect of the progressing aortic stenosis could also explain why a high systolic blood pressure did not predict valvular surgery in our study. However, the effect of arterial hypertension and elevated diastolic blood pressure on future risk for valvular surgery remained after exclusion of those with surgery within five years from the survey. This indicates that the progressive valvular disease did not explain the results, and that the negative effect of high blood pressure on the aortic valve takes years to develop.

In the older group with concomitant CAD, the high systolic and diastolic blood pressure is probably one of several risk factors involved in the arteriosclerotic process comprising both the coronary arteries and the aortic valve. In fact, the diastolic blood pressure acts on the closed aortic valve and may hypothetically be more important than the systolic pressure that opens the valve.

Reduced glucose tolerance is reportedly associated with CAD, and impaired fasting glucose has been identified as an independent predictor of all-cause mortality and cardiovascular mortality [22–25]. In our present study, we revealed an association between impaired fasting glucose and aortic stenosis requiring surgery in older adults without CAD. These findings have not previously been described and is in line with the theory that impaired fasting glucose is a risk factor for cardiovascular disease.

Limitations

The inclusion criteria for the VIP survey may have affected the age distribution of the patient population, *i.e.* persons

were included only if they had a health survey performed at 30, 40, 50, or 60 years of age. This may have led to underrepresentation of younger patients with bicuspid valves in our study. In this study, we do not have complete data on the underlying valve morphology. However, in patients younger than 60 years of age bicuspid valves are by far the most common valve morphology. Finally, the present study included only patients requiring surgery and, thus, the results cannot necessarily be generalised to patients with less severe disease.

Conclusions

Our results indicate that a diagnosis of arterial hypertension and elevated diastolic blood pressure are more common among patients who require surgery for aortic stenosis before the age of 60 years, regardless of concomitant CAD. On the other hand, a diagnosis of hypertension was not a risk marker for patients who need surgery for aortic stenosis after the age of 60 years and who do not have CAD. Within this patient group, impaired fasting glucose was a risk marker for development of aortic stenosis requiring surgery.

Authors' contributions

SS, BJ and JL designed the study, acquired and analysed data. JL, BJ and SS have drafted the manuscript and all authors have revised the manuscript critically for important intellectual content. All authors approved the final version and are accountable for all aspects of the manuscript.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability

The datasets generated and/or analysed during the current study are not publicly available as the data set contains identifiable patient data but are available from the corresponding author on reasonable request.

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