Association between degenerative aortic valve disease and long-term exposure to cardiovascular risk factors: results of the longitudinal population-based KORA/MONICA survey

Jan Stritzke¹, Patrick Linsel-Nitschke¹, Marcello Ricardo Paulista Markus¹,², Björn Mayer¹, Wolfgang Lieb¹,⁷, Andreas Luchner³, Angela Döring⁴, Wolfgang Koenig⁵, Ulrich Keil⁶, Hans-Werner Hense⁶, and Heribert Schunkert¹†*, for the MONICA/KORA Investigators

¹Department of Internal Medicine II, University of Lübeck, Lübeck, Germany; ²Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; ³Department of Internal Medicine II, University of Regensburg, Regensburg, Germany; ⁴Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; ⁵Department of Internal Medicine II, University of Ulm, Ulm, Germany; ⁶Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany; and ⁷Institute of Human Genetics, University of Lübeck, Lübeck, Germany

Received 11 February 2009; revised 18 May 2009; accepted 22 June 2009; online publish-ahead-of-print 16 July 2009

See page 1940 for the editorial comment on this article (doi:10.1093/eurheartj/ehp175)

Aims
Degenerative aortic valve disease (DAVD), a common finding in the elderly, is associated with an increased risk of death due to cardiovascular causes. Taking advantage of its longitudinal design, this study evaluates the prevalence of DAVD and its temporal associations with long-term exposure to cardiovascular risk factors in the general population.

Methods and results
We studied 953 subjects (aged 25–74 years) from a random sample of German residents. Risk factors had been determined at a baseline investigation in 1994/95. At a follow-up investigation, 10 years later, standardized echocardiography determined aortic valve morphology and aortic valve area (AVA) as well as left ventricular geometry and function. At the follow-up study, the overall prevalence of DAVD was 28%. In logistic regression models adjusting for traditional cardiovascular risk factors at baseline age (OR 2.0 [1.7–2.3] per 10 years, \( P < 0.001 \)), active smoking (OR 1.7 [1.1–2.4], \( P = 0.009 \)) and elevated total cholesterol levels (OR 1.2 [1.1–1.3] per increase of 20 mg/dL, \( P < 0.001 \)) were significantly related to DAVD at follow-up. Furthermore, age, baseline status of smoking, and total cholesterol level were significant predictors of a smaller AVA at follow-up study. In contrast, hypertension and obesity had no detectable relationship with long-term changes of aortic valve structure.

Conclusions
In the general population we observed a high prevalence of DAVD that is associated with long-term exposure to elevated cholesterol levels and active smoking. These findings strengthen the notion that smoking cessation and cholesterol lowering are promising treatment targets for prevention of DAVD.

Keywords
Epidemiology • Degenerative aortic valve disease • Risk factor • Cholesterol • Smoking

Introduction
Degenerative aortic valve disease (DAVD) is a common finding especially in older adults. In populations above 65 years of age, the prevalence of aortic valve sclerosis, calcification, or thickening is reported to be 21–31%.¹–³ Degenerative aortic valve disease is often complicated by progressive obstruction of the left ventricular outflow that may result in pressure overload of the left ventricle,
congestive heart failure, syncope, and sudden death.\textsuperscript{4,5} Moreover, in ageing populations there is a high prevalence (2–9%) of end-stage DAVD with high-grade aortic stenosis or regurgitation often necessitating valvular replacement.\textsuperscript{3,5} But even in the absence of relevant aortic valve disease, there is an increased risk of death due to cardiovascular causes in individuals with DAVD.\textsuperscript{1}

Traditional pro-atherosclerotic risk factors have been associated with aortic stenosis particularly in older populations.\textsuperscript{6–16} However, in vivo models suggest that even at a younger age hypercholesterolaemia starts a dynamic process that leads to sclerosis and consecutive calcification of the aortic valve.\textsuperscript{17,18} Recent findings also demonstrate a relationship between high total cholesterol levels and calcific aortic valve stenosis in genetic mouse models of ageing.\textsuperscript{19} Taken together, DAVD is a progressive disease starting early with sclerotic degenerations of the valve caused by dynamic changes of the valvular tissue.

Taking advantage of the longitudinal design our study aimed to evaluate the aforementioned association between DAVD and long-term exposure to cardiovascular risk factors in the general population. In addition, we analysed the association of DAVD with left ventricular geometry and function.

**Methods**

**Study population**

Between October 1994 and June 1995, baseline data were derived from the third survey (S3) of the population-based MONICA (Monitoring of Trends and Determinations in Cardiovascular Disease)—Augsburg/KORA (Cooperative Research in the Region of Augsburg) study. Only participants who displayed echocardiographic M-mode tracings with sufficient quality for quantitative measurements at baseline were also eligible for an echocardiographic investigation at follow-up (F3), which was conducted between March 2004 and May 2005. The MONICA Augsburg project was part of the international collaborative WHO MONICA project\textsuperscript{20} and investigated the cardiovascular risk factor profile of randomly selected subjects of the resident population in cross-sectional surveys.\textsuperscript{21,22} The study design, sampling frame, and data collection have been described in detail before.\textsuperscript{20,22}

A number of S3 baseline participants were not eligible for the F3 follow-up for the following conditions: (i) death (58 subjects), (ii) interdiction of contact (63 subjects), (iii) migration (41 subjects), and (iv) heavy illness (7 subjects). From 1248 eligible individuals, 1005 participated in the follow-up study (net response 80.5%).

On both occasions, all participants underwent an interview related to personal and family medical history, life style and nutrition, health behaviour, and psychosocial factors. Body height and weight were measured in light clothing. Body mass index (BMI) was calculated as weight divided by height squared (kg/m\textsuperscript{2}). Obesity was defined according to the National Institutes of Health Consensus Development Panel criteria\textsuperscript{23} as a BMI of 27.8 kg/m\textsuperscript{2} in women and >34 kg/m\textsuperscript{2} for men.\textsuperscript{28} Concentric remodelling was defined as an RWT >0.43.\textsuperscript{28} Left ventricular end-diastolic and end-systolic volumes (LVEDV, LVESV) were determined using the Teichholz equations:\textsuperscript{30,31} LVEDV (mL) = \left[7/(2.4 + LVedd)\right] \times LVedd\textsuperscript{2} and LVESV (mL) = \left[7/(2.4 + LVedd)\right] \times LVedd\textsuperscript{2}. The ejection fraction was calculated as EF = (LVEDV – LVESV)/LVEDV.

**Two-dimensional measurements**

The diameter of left ventricular outflow tract (LVOT) was evaluated in zoomed apical five-chamber view. Aortic valves were scanned from the parasternal short-axis and the apical five-chamber view. Degenerative aortic valve disease was characterized by an abnormal irregular thickening or a focal or diffuse increase of the echogenicity of the leaflets with or without reduced systolic opening.

**Doppler measurements**

All Doppler echocardiographic recordings were registered with 100 mm/s and performed in expiration. Velocity time integrals of flow from LVOT and from aortic valve were evaluated using pulsed-continuous wave Doppler. Using the continuity equation,\textsuperscript{22,23} aortic valve area (AVA) was calculated as AVA (cm\textsuperscript{2}) = \left(VTILVOT/VTIAV\right) \times (0.5 \times LVOT\textsuperscript{2})\times\phi. Aortic valve area was indexed to Body surface area (BSA).

Examinations of mitral inflow were performed by pulsed-wave Doppler with the sample volume at the tips of the mitral valve in the apical four-chamber view. Early (e) and late (a) diastolic velocities and ratio of early and late velocities (e/a) were determined as previously described.\textsuperscript{24} Doppler tissue imaging of the mitral annulus was obtained from the apical four-chamber view, using a 1–2 mm sample volume placed in the septal mitral valve annulus. Early (em) and late (am) myocardial relaxation velocity and the ratio of e/em were determined according to Naghsh et al.\textsuperscript{23}

**Echocardiography**

Echocardiograms were performed using commercially available echocardiographs (in 1994/5: Sonos 1500 with 2.5 or 3.5 MHz transducer; in 2004/5: Sonos 4500 with 2.0–4.0 MHz transducer; Philips Electronics, Eindhoven, Netherlands). Two-dimensionally guided M-mode echocardiograms were performed on each subject by one of two expert sonographers, and M-mode tracings were recorded on strip chart paper in the baseline study. In the follow-up study, all echocardiographic investigations including M-mode and Doppler tracings, as well as two-dimensional loops, were digitally stored. To reduce observer variability, all tracings were analysed by a single cardiologist in each study. Echocardiographic M-mode measurements were corrected for observer- and device-related differences between the two examinations (see Statistical methods section).

**M-mode measurements**

All M-mode tracings were obtained at 50 mm/s. Measurements of left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) and septal wall thickness (SWT) and posterior wall thickness (PWT) as well as left atrial (LA) diameter were performed according to the guidelines of the American Society of Echocardiography.\textsuperscript{24} Relative wall thickness (RWT) was calculated as the ratio of (SWT + PWT) and LVEDD. Left ventricular mass (LVM) was calculated according to the formula LVM (g) = 0.8 x \left[10.04 \times [(LVESD + SWT + PWT)\textsuperscript{2} – LVEDD\textsuperscript{2}]\right] + 0.6 g as described by Devereux and Reichek.\textsuperscript{25,26} Left ventricular mass was indexed (LVMi) for body height in metres, normalized to the allometric power of 2.7, which linearizes the relations between LVM and height and identifies the impact of obesity.\textsuperscript{27} Left ventricular hypertrophy was defined as an LVMi >44 g/m\textsuperscript{2.7} for women and >48 g/m\textsuperscript{2.7} for men.\textsuperscript{28} Concentric remodelling was defined as an RWT >0.43.\textsuperscript{28} Left ventricular end-diastolic and end-systolic volumes (LVEDV, LVESV) were determined using the Teichholz equations:\textsuperscript{30,31} LVEDV (mL) = \left[7/(2.4 + LVedd)\right] \times LVedd\textsuperscript{2} and LVESV (mL) = \left[7/(2.4 + LVedd)\right] \times LVedd\textsuperscript{2}. The ejection fraction was calculated as EF = (LVEDV – LVESV)/LVEDV.

**Echocardiography**

Echocardiograms were performed using commercially available echocardiographs (in 1994/5: Sonos 1500 with 2.5 or 3.5 MHz transducer; in 2004/5: Sonos 4500 with 2.0–4.0 MHz transducer; Philips Electronics, Eindhoven, Netherlands). Two-dimensionally guided M-mode echocardiograms were performed on each subject by one of two expert sonographers, and M-mode tracings were recorded on strip chart paper in the baseline study. In the follow-up study, all echocardiographic investigations including M-mode and Doppler tracings, as well as two-dimensional loops, were digitally stored. To reduce observer variability, all tracings were analysed by a single cardiologist in each study. Echocardiographic M-mode measurements were corrected for observer- and device-related differences between the two examinations (see Statistical methods section).
Observer and reader certification

All echocardiographic investigations and reading procedures were performed strictly following a standardized protocol. To ensure high-quality standard of the echocardiographic investigations and of the reading procedure, observer and reader certifications were obtained at the Institute of Epidemiology and Social Medicine, University of Greifswald, as described previously. Variability within and between the observers and readers was measured by mean differences (% mean bias) as obtained from the Bland–Altman plot. Furthermore, reproducibility within the study sample was analysed. Results of certification procedure are shown in Table 1.

Table 1 Results of certification procedure and quality management

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Results of certification procedure and quality management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observer variability (certification procedure)</strong></td>
<td><strong>Interobserver-reader</strong></td>
</tr>
<tr>
<td>LVM</td>
<td>1.2</td>
</tr>
<tr>
<td>e/a</td>
<td>3.9</td>
</tr>
<tr>
<td>Reader variability (certification procedure)</td>
<td><strong>LVM</strong></td>
</tr>
<tr>
<td>Reader variability (quality management)</td>
<td><strong>LVOT</strong></td>
</tr>
<tr>
<td></td>
<td><strong>VTILVOT</strong></td>
</tr>
<tr>
<td></td>
<td><strong>VTIAV</strong></td>
</tr>
<tr>
<td></td>
<td><strong>AVA</strong></td>
</tr>
</tbody>
</table>

For intraobserver variability, results of six duplicate measurements were marked in a Bland–Altman plot. Subsequently, values for mean bias and 2SD were obtained. For intraobserver variability, results of 25 duplicate measurements were evaluated. Interobserver-reader variability was determined by comparison of 12 respective measurements with an experienced observer of the Institute of Epidemiology and Social Medicine, University of Greifswald. Intrareader variability within the study was determined by comparison of the first and second measurement. 2SD indicates duplicated standard deviation; LVM, left ventricular mass; e/a, ratio of the early (e) and late (a) diastolic transmitral inflow; VTILVOT, velocity–time integral as obtained within the left ventricular outflow tract (LVOT) respective the aortic valve (AVA); AVA, aortic valve area.

Statistical methods

Echocardiographic investigations were carried out with different methods in MONICA baseline survey and in KORA follow-up study. The observers had changed after 10 years as did the devices reflecting technological progress or lack of appropriate maintenance options, for example the strip paper echocardiograph. Systematic differences between surveys likely to occur due to different measurement methods were assessed by using data from all 1005 individuals examined on both occasions using a mixed regression model that estimated the effect of the measurement methods while adjusting for the confounding factors age, sex, BMI, and antihypertensive medication. An interaction term between sex and study was also included. We specified a linear model with a common correlation among the two measurements from a single participant, with correlation being the same for all individuals, by introducing individual random intercepts. Survey-specific differences estimated from these models were used to derive correction values for echocardiographic measurements, separately, for men and women.

There were 457 men and 496 women with a complete set of data for echocardiography, anthropometric measurements, and the other variables. Continuous variables have been checked for normal distribution. Subjects were then compared with regard to their baseline characteristics using frequencies, mean values, and standard deviations. Statistical significances were tested with unpaired t-tests for continuous and χ² tests for categorical variables. We considered the absolute differences between the two groups at baseline and at follow-up as well as the relative change, for each group, from baseline, i.e. (follow-up − baseline)/baseline, expressed in percent. Adjusted mean values in the cross-sectional analysis of baseline clinical and laboratory measurements were calculated with a linear regression model that included age and gender, body height and weight, and systolic blood pressure. For the analyses of the relative changes over the 10-year period, the model included age, gender, height, the baseline value of the respective variable under study plus the baseline values of body weight, and systolic blood pressure as well as their relative changes over the 10-year period. Prevalence odds ratios (POR) for DAVD were calculated in a logistic regression model employing baseline variables on arterial hypertension, obesity, diabetes mellitus, total cholesterol level, and active smoking, as the predictors of interest simultaneously adjusting for age and gender. To estimate the relative impact of predictors on DAVD, we calculated the population-attributable risk percent. Population-attributable risk percent expresses the proportion of DAVD in the study population that is attributable to the exposure of predisposing factors and, theoretically, could be eliminated if the exposure was eliminated. It was calculated using the formula

\[
\text{PAR} = \frac{P_a \times (\text{POR} - 1)}{(P_a \times (\text{POR} - 1) + 1)} \times 100
\]

where \(P_a\) indicates population-attributable risk percent, \(P\) represents the proportion of the population exposed to the risk factor, and POR indicates adjusted POR. To control for influence of haemodynamic relevant aortic valvular stenosis, calculations were also performed excluding individuals presenting with indexed AVA \(<\ 0.6\ \text{cm}^2/\text{m}^2\). All analyses were performed using SPSS version 14.0.0 for Windows.

Results

Prevalence of degenerative aortic valve disease

Baseline characteristics and medication are presented in Table 2. At the follow-up investigation, the prevalence of DAVD was 28%. Comparing individuals with or without changes in aortic valve structure, individuals with DAVD were significantly older. As a result, prevalence of arterial hypertension, obesity, diabetes, hypercholesterolaemia, and cardiovascular diseases (CVDs) was also higher in this group. Figure 1 displays the increasing prevalence of DAVD by the decades of this population sample. Additionally, the impact of age and gender on the prevalence of DAVD was assessed in logistic regression models (Figure 2). While age was significantly related to DAVD (OR 2.0, 95% CI [1.7–2.3], additional risk per decade, \(P < 0.001\)), there were no significant differences between men and women (OR 1.2 [0.9–1.7], risk for males vs. females, \(P = 0.215\) detectable.
Risk factors for aortic valve sclerosis

Table 2  Baseline characteristics and medication (S3)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Without DAVD (n = 682)</th>
<th>DAVID (n = 271, 28%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.8 ± 11.9</td>
<td>55.0 ± 11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Males (%)</td>
<td>46.5</td>
<td>51.7</td>
<td>0.149</td>
</tr>
<tr>
<td>Aortic valve stenosis (%)</td>
<td>—</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>31.5</td>
<td>49.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>31.4</td>
<td>45.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1.3</td>
<td>3.7</td>
<td>0.017</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>13.3</td>
<td>30.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>25.1</td>
<td>25.8</td>
<td>0.820</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>0.7</td>
<td>2.2</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Medication

| Statins (%)                              | 0.7                    | 4.4                  | <0.001  |
| ACE inhibitors (%)                       | 1.8                    | 5.5                  | 0.002   |
| Beta-blockers (%)                        | 5.3                    | 10.7                 | 0.003   |
| Platelet inhibitors (%)                  | 2.1                    | 6.3                  | 0.001   |

Values are mean ± standard deviation for continuous variables. P-values are calculated with t-test for continuous and with χ² test for categorical variables. DAVD, degenerative aortic valve disease; CVD, cardiovascular disease (myocardial infarction and/or stroke). Bold values indicate whether differences for total cholesterol levels were found only for total cholesterol levels, LDL, and LDL/HDL ratio.

Beyond age and gender, the effects of known cardiovascular risk factors on valvular degeneration were also assessed in logistic regression models (Figure 2). There were no significant associations of obesity and arterial hypertension with valvular degeneration, while active smoking (OR 1.7 [1.1–2.4], yes vs. no, P = 0.009) and elevated total cholesterol levels (OR 1.2 [1.1–1.3], additional risk per increase of 20 mg/dL, P < 0.001) at the baseline study were significantly related to DAVD at follow-up. Interestingly, only individuals within the highest quintile of baseline total cholesterol levels (> 268 mg/dL) carried a significantly increased risk (OR 2.6 [1.5–4.4], P = 0.001, vs. lowest (< 197 mg/dL) quintile) for presenting with DAVD after 10 years of follow-up (Figure 3). As estimated by the population-attributable risk, total cholesterol levels higher than 268 mg/dL at baseline accounted for 22.4% (active smoking: 14.4%) of DAVD detected in the entire population after 10 years of follow-up.

To study these relations in further detail, we evaluated total cholesterol levels (Figure 4) and the proportion of active smokers (Figure 5) within different age groups. Comparing individuals presenting with or without DAVD at follow-up, significant differences for total cholesterol levels were found in individuals who were 45–74 years of age at follow-up. A significant relation of active smoking to subsequent presentation with DAVD was only detectable in subjects who were 45–55 years of age at follow-up.

Additionally, relations between degenerations of the mitral and aortic valve have been investigated. In the total study sample, the prevalence of degenerations of the mitral valve was 24.6%. Interestingly, 43.5% of individuals with DAVD also presented with mitral valve sclerosis. In comparison, the prevalence in individuals with smooth aortic valves was significantly lower (17.1%, P < 0.001). This relation was also detectable in adjusted regression models. The POR for mitral valve degenerations in individuals with DAVD was 3.1 (P < 0.001) when compared with individuals with smooth aortic valves.

Left ventricular geometry and function in individuals with degenerative aortic valve disease

The relation of DAVD with structural and functional parameters was assessed by echocardiographic investigations (Table 4). Lower AVA and concomitantly a higher peak transvalvular flow (V max) were found in subjects presenting with DAVD when compared with those with smooth aortic valve leaflets. Furthermore, left ventricular geometry in the DAVD group showed a pattern of concentric remodelling as evident by higher wall thickness (WT) and lower LVEDD. There were also a significantly elevated RWT and a higher LVM index (LVMi) detectable. Additionally, when assessing the temporal changes in terms of relative changes from baseline, the DAVD group displayed significantly more pronounced relative changes of absolute and of relative wall thickness (Table 5). Beyond age, hypertension, and body weight, DAVD was an independent predictor for concentric left ventricular hypertrophy (OR 1.6, P = 0.046). In contrast, there

Risk factors related to aortic valve degeneration

Age- and gender-adjusted clinical, anthropometric, and blood chemistry variables of study participants at baseline investigation are shown in Table 3. Significant differences between individuals presenting with or without DAVD at follow-up investigation

Figure 1  Prevalence of degenerative aortic valve disease by age groups.

Figure 2  Prevalence of degenerative aortic valve disease by age groups.

Figure 3  Prevalence of degenerative aortic valve disease by age groups.

Figure 4  Prevalence of degenerative aortic valve disease by age groups.

Figure 5  Prevalence of degenerative aortic valve disease by age groups.
was no relation to eccentric hypertrophy detectable (OR 0.9, \(P = 0.686\)). Additionally, even after exclusion of individuals presenting with an indexed AVA < 0.6 cm²/m², the prevalence of concentric remodelling/concentric hypertrophy within the DAVD group was significantly higher when compared with individuals without changes of aortic valve structure (Figure 6). While systolic function...
was equal in both groups, measures of diastolic function were impaired in the DAVD group as demonstrated by significantly elevated e/em ratios in affected individuals.

Aortic valve area and cardiovascular risk factors

In order to assess a quantitative parameter for DAVD, we fit a linear regression model with AVA as dependent variable (Table 6). In this model the influence of total cholesterol level was of borderline significance, while active smoking, age, gender, body height, and weight were significantly related to AVA. Model 2 included only individuals without DAVD. In this model, smoking status, total cholesterol levels, and age were no longer significantly related to AVA.

Discussion

In the present study, we defined DAVD by the presence of either valvular sclerosis, calcification, or thickening on echocardiographic examination. As described in the literature, such degeneration of the aortic valve is a common finding especially in the elderly population.1–3 In addition to the already well-established effect of age on DAVD, our data demonstrate that active smoking and elevated total cholesterol levels are major risk factors for DAVD in the general population. Interestingly, DAVD is often accompanied by degenerations of the mitral valves, suggesting common pathogenetic mechanisms. Furthermore, it appears that even in the absence of significant stenosis DAVD impairs the valvular area and, as a consequence, enhances left ventricular afterload resulting in concentric remodelling of the heart. Taken together these findings argue against the notion that DAVD can be considered to be a benign adaptation but rather mount to the increasing evidence that DAVD is associated with an augmented risk of cardiovascular morbidity and mortality.1 Indeed, DAVD appears to be complicated by progressive obstruction of left ventricular outflow that may promote the development of left ventricular hypertrophy, congestive heart failure and increase the risk of cardiac syncope and sudden death.4
Active smoking and elevated total cholesterol levels are risk factors for degenerative aortic valve disease

The present study is remarkable for the associations between risk factors at a baseline study and presence of DAVD 10 years later. In this prospective study design, smoking and hypercholesterolaemia were strong predictors for DAVD. In order to assess the implications of risk factors associated with early stages of DAVD, the present study may thus be helpful for identification of modifiable factors to prevent the development and progression of this condition. Most of the studies published so far have fallen short of this matter because they included only elderly individuals and were therefore unable to detect early or dynamic alterations leading to DAVD. Moreover, previous studies assessed aortic valve morphology and risk factors simultaneously such that sequence of effects could not be estimated. There has been only one systematic evaluation in the general population using a longitudinal design so far. Therefore, the present finding of association...
of smoking and hypercholesterolaemia with DAVD at least 10 years after the baseline study may help to define future strategies of early risk reduction for this progressive disease.

Consistent with prior clinical and autopsy studies, we found an increasing prevalence of DAVD with ageing. In fact, the present findings confirmed that ageing is the most prominent of all risk factors for DAVD. Associations found with traditional cardiovascular risk factors in older populations were inconsistent in previous investigations. Aronow et al. reported a significant relation with hypertension, diabetes, hypercholesterolaemia, and low HDL cholesterol levels. In contrast, the Helsinki Aging Study and others found only some of these parameters as well as age, low BMI, and current smoking status to be significantly related to DAVD. However, none of these studies evaluated long-term exposure to these risk factors that might have decreased the power to detect any dynamic alterations.

There was no significant association of cholesterol levels and active smoking with DAVD in the youngest age group detectable. Thus, some degenerative changes occurring during ageing may be a prerequisite before elevated cholesterol and smoking enhance the progression of DAVD.

### Degenerative aortic valve disease is related to elevated afterload which is translated to left ventricular concentric remodelling

In patients with aortic valve stenosis, the elevation of afterload causes changes in left ventricular geometry resulting in concentric hypertrophy. It was so far not clear whether early stages of DAVD like sclerosis or valve thickening are also associated with changes of LV geometry. Studying a population-based sample that includes mostly clinically healthy individuals, we demonstrate that even mild aortic valve degeneration is associated with a functionally detectable decrease in AVA and a consecutive increase of the transvalvular pressure gradient. As expected this increase in afterload was translated to concentric remodelling of left ventricular geometry. These results offer a potential mechanism by which risk factors for DAVD (smoking, elevated cholesterol) may relate to changes of left ventricular geometry in later life.

### Active smoking and elevated cholesterol levels resulted in decrease of aortic valve area

It must be pointed out that a definition of aortic valve degeneration (e.g., sclerosis, thickening) is relatively arbitrary. High variance between different investigators seems to be mainly influenced by observer’s experience. We therefore investigated association of risk factors with AVA. This parameter can be assessed in a highly standardized fashion and can therefore be considered to be an objective echocardiographic measurement of changes of the aortic valve. To our knowledge this is the first long-term investigation of AVA and associated risk factors in the general population. In adjusted regression models, active smoking and elevated cholesterol levels were again significantly related with decrease of AVA confirming the notion that early DAVD is mainly related to these risk factors.

However, results in this field are contradictory. In line with observations presented within the current article, the RAAVE study showed a correlation between hypercholesterolaemia and a more rapid haemodynamic progression in aortic stenosis. In contrast, other investigators did not find such correlation.

### Limitations

Some limitations of the present study need to be considered. As mentioned above the diagnosis of DAVD is strongly influenced by investigator’s experience. However, the single echocardiographer who performed the present measurements was especially trained for epidemiological studies. Moreover, this investigator was blinded for smoking status and cholesterol levels. Some cases of DAVD might also be related to bicuspid aortic valves. However, the prevalence of this condition in general population is low and ranges between 0.5 and 2.0%. Within this sample, only 2 of 953 individuals were clearly identified as having bicuspid aortic valves. Exclusion of these two subjects had no measurable effect on the data, such that the results should not be affected by this anatomical variation.

Second, in this study, definition of diabetes was insufficient (e.g., there was no fasting glucose level available) and the number of diabetics was relatively small. As a result, the relation of diabetes and DAVD still remains unclear and needs further investigations. Moreover, we had to rely on a single measurement to represent a period of 10 years. Thus, fluctuations of blood pressure, cholesterol levels or other risk factors, or the effects of intermittent medications were not included in our analyses. Nevertheless, with respect to the associations between smoking and cholesterol with DAVD, it is even more remarkable that a single measurement relates to significant alterations after 10 years of follow-up. Owing to the design of the current study, the effects of statins or other medications could not be demonstrated.

Unfortunately, there was no baseline information about valvular morphology available. Our analyses were therefore restricted to prevalent cases of DAVD at follow-up. Nevertheless, the
associations reported were consistent and robust against multiple adjustments in a variety of models. Of note, similar results were also found excluding individuals presenting with moderate or severe aortic valve stenosis.

Degenerative aortic valve disease is known to be associated with an increased risk of death from cardiovascular causes. However, applying adjusted regression models, there was no significant relation between DAVD and CVD detectable within our study. This may be caused by the low threshold for the diagnosis of DAVD, on the one hand, and a limited sensitivity for the detection of CVD in an epidemiological survey, on the other hand.

Conclusions

We report that in the general population DAVD has a very high prevalence and is associated with long-term exposure to high cholesterol levels and active smoking. After adjustment for age, the previously implicated risk factors such as hypertension and obesity had no detectable effects on aortic valve structure in the present analysis. Interestingly, even in the absence of relevant aortic valve stenosis, DAVD was associated with concentric remodelling of the left ventricle as demonstrated by a higher RWT.

Clinical trials for slowing the progression of aortic valve disease have largely been negative, suggesting that this disease is not amenable to therapy.

However, these studies focused on patients with advanced degeneration of the valve. Recently, Antonini-Canterin et al. reported that in a large series of patients with long-term follow-up, statins were effective in slowing the progression of DAVD only in aortic sclerosis and mild stenosis, but not in moderate stenosis. Taken together, the clinical implications of hypercholesterolaemia and smoking for the initiation of DAVD still need further evaluation.

Funding

This work was supported by the Kompetenznetz Herzinsuffizienz (German Heart Failure Network) funded by the Federal Ministry of Education and Research (BMBF), FKZ 01GI0205, and by grant of the Deutsche Forschungsgemeinschaft (DFG Schu 672/1-1, Schu 672/10-1, and Schu 672/12-1) and the Bundesministerium für Forschung und Technologie (H.W.H., H.S., and A.D.) the Medical Faculty, University of Lübeck (J.S., A39-2005), and the EU sponsored project Cardiogenics (LSH-2005-037592). The KORA research platform (KORA: Cooperative Research in the Region of Augsburg) and the MONICA Augsburg studies (MONICA: Monitoring trends and determinants on cardiovascular diseases) were initiated and financed by the GSF-National Research Centre for Environment and Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria.

Conflict of interest: none declared.

References


27. de Simone G, Devereux RB, Kimball TR, Mureddu GF, Roman MJ, Contaldo F, Daniels SR. Interaction between body size and cardiac workload: influence on left ventricular mass during body growth and adulthood. *Hypertension* 1998; **31**:1077–1082.

28. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shewster JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**:1440–1463.


