Clinical decision making in elderly with aortic stenosis
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Chapter 7

Determinants of progression of aortic stenosis in the elderly.

Abstract

Whether a patient with an indication for coronary bypass grafting who also has a mild to moderate aortic stenosis should have a concomitant aortic valve replacement is subject of a heated debate. Numerous studies have been published on the progression of aortic stenosis, and several variables have been identified as associated with progression. Their consistency and applicability however, to clinical practice have never been established. We carried out the current study to evaluate the prognostic value of these risk factors.

First, we identified all consecutive patients in our hospital with the initial diagnosis of aortic stenosis, and who underwent at least 2 echocardiograms (minimum interval 6 months). We determined the annual progression in our patient population and determined whether clinical and echocardiographic variables have an association with progression. Second, we searched PubMed for publications on the progression of aortic stenosis. We determined the reported annual progression, and we identified the variables found to be associated with the progression of aortic stenosis. The association of a specific variable with progression of aortic stenosis was considered to be consistent, if a significant multivariate association was found in 2 or more different studies, including our own, and that the number of patients in the positive studies exceeded that of the negative studies. If the latter condition could not be fulfilled, we considered the association as possible.

The cohort in our hospital consisted of 121 patients. The median annual decrease of aortic valve area (AVA) was 0.10 cm² (sd 0.23) per year. The annual progression of systolic gradient was 4.7 mmHg (sd 6.8) per year. With multivariate analysis, initial AVA and serum creatinin were found to be associated with the reduction of AVA. In the literature we found 18 articles on the progression of aortic stenosis. The annual reduction of AVA varied from 0.04 cm² to 0.19 cm². The annual change in maximum pressure gradient varied from 3.9 mmHg to 15 mmHg. Twenty-five different variables (14 clinical - and 11 echocardiographic variables) were reported to have a significant statistical association with the progression of aortic stenosis. A consistent association with the progression of
aortic stenosis was found for initial AVA, use of statins, and renal failure. Current smoking was found to have a possible association.

We concluded that the reported annual progression of aortic stenosis varies widely among and within studies. Of 25 previously reported associations with progression of aortic stenosis, only initial aortic valve area, use of statins, renal failure were consistently found to be associated. Current smoking is probably associated with progression of aortic valve stenosis.

Introduction

Aortic valve stenosis is common in the elderly patient(1). The disease has a progressive nature, and it is postulated that it is a manifestation of atherosclerosis(2). Knowledge about the progression rate of the stenosis severity and its determinants is important in clinical decision making. Should a patient referred for coronary bypass grafting with a mild to moderate aortic stenosis, also have a concomitant aortic valve surgery? The expected progression of the aortic valve stenosis is one of the deciding factors(3,4).

Clinical decision making can be supported by accurate information about the progression rate of aortic stenosis. Knowledge about clinical and echocardiographic factors associated with rapid progression enables further stratification to support or withheld concomitant valve replacement. Numerous studies have been published on the progression rate of aortic stenosis. Many clinical and echocardiographic variables have been identified as associated with progression. In recent years much attention has been paid to the effects of statins on the rate of progression(5-7). Also new echocardiographic variables have been developed, such as the severity index(8) and the rate of change of the aortic valve area during ejection(9), to identify patients with a rapid and a slow progression of the aortic valve stenosis, but the consistency of the findings and applicability of the progression rates to clinical practice have never been established.
Aim of the present study was to assess the progression of the aortic stenosis in our own patient population and to evaluate possible association of clinical and echocardiographic variables for their association with progression. Second, we reviewed the literature for the progression rates of aortic stenosis determined with echocardiography, and identified associations with progression. We determined the consistency of the identified associations of the clinical and echocardiographic variables with the progression of aortic stenosis.

**Methods**

**Patient study**

From the database of our echocardiographic laboratory, we retrospectively identified all patients above 60 years who had (1) an aortic stenosis at baseline, defined as a peak systolic gradient ≥ 2 m/s due to aortic valve thickening, and (2) at least one other echocardiographic examination during follow up with a minimum interval of 6 months.

Clinical and laboratory data at time of the initial echocardiographic diagnosis was collected from medical records. Data about co-morbidity was scored according to Greenfield(10). All initial echocardiograms, which were stored on a super-VHS tape, were independently reviewed by BB and RB. The severity index was scored as described by Bahler et al.(8). M-mode measurements were performed according to the American Society of Echocardiography standards. The Doppler echocardiographic evaluation, as aortic valve area, was performed according to standard methods(11,12).

**Statistical analysis**

We calculated the decrease of aortic valve area per year per patient with linear regression. The average decrease was weighted to the square root of the number of echocardiographic examinations to account for the differences in number of
repeated measurements. We used univariate and multivariate linear regression to identify clinical and echocardiographic variables associated with the annual decrease in aortic valve area in our cohort. Again, the number of observations was used as weight factor. We standardized the continuous variables for sake of comparability. Missing data was analyzed using multiple imputations (Proc MI and MIANALYZE) in SAS (version 8.2, Cary, N.C.)

Review of the literature

We searched Pubmed and the references of all retrieved articles for publications on the progression of aortic stenosis with echocardiography. We used the keywords 'progression', 'aortic stenosis' and 'echocardiography'. Our own study was used as one (published) study. Next, we selected all articles that described the progression of aortic stenosis meeting the following criteria: (1) at least two echocardiographic examinations, (2) minimal peak systolic gradient ≥ 2 m/s due to thickened valve leaflets with diminished opening, (3) adult patients. We excluded those articles: (1) which investigated the association between clinical and laboratory variables and the presence of aortic valve stenosis, (2) which described the progression of aortic valve sclerosis (peak systolic gradient < 2.0 m/s) to aortic stenosis and (3) which presented only the clinical outcome after the diagnosis aortic valve stenosis.

From the selected articles, we noted the annual decrease in aortic valve area and the annual progression of the peak systolic gradient and we recorded which variables were found to be associated with the progression of aortic stenosis in time with both univariate and multivariate analysis.

A pooled and weighed annual decrease of aortic valve area and annual increase of maximum gradient was calculated for all studies which reported the mean annual change, the standard deviation, and the number of patients.

Associations of variables with progression

For each specific clinical and echocardiographic variable we counted the number of studies that identified a specific variable to have no, only a univariate, or a
multivariate association with the progression of aortic stenosis. An association was considered consistent if at least 2 separate studies had identified an association in a multivariate fashion and the number of patients of all positive studies exceeded those in the negative studies. If the latter condition could not be fulfilled, we considered the association as "probably associated". In the event of multiple publications, we only counted the publication with the largest number of patients.

Results

Baseline characteristics of the patient study
A total of 121 consecutive patients with the diagnosis of aortic stenosis at the initial echocardiogram, were identified from our data base. The median age was 76 year (range 60-91). Eighty patients (58%) were female. At the initial echo, the median aortic valve area was 1.2 cm$^2$ (range 0.5-2.6 cm$^2$, 50% range 1.0 cm$^2$ - 1.5 cm$^2$). In four patients the initial aortic valve area exceeded 2.0 cm$^2$. The median of the peak gradient was 32 mmHg (50% range 25 - 42 mmHg). The median of the mean gradient was 18 mmHg (50% range 15 - 26 mmHg). A normal left ventricular function was present in 92 (76%) of the patients.

Follow up of patient study
During follow up 83 patients had three echocardiograms, 36 had 4 echocardiograms, 14 had 5 echocardiograms, 4 had 6 echocardiograms, and 1 had 7 echocardiograms. The median time span between the first and the last echo was 35 months (50% range 19 - 49 months). At the last echocardiographic examination the median aortic valve area was 1.0 cm$^2$ (50% range 0.8 - 1.2 cm$^2$).

The follow up was 1.8 year for patients with an initial aortic valve area of 1.0 cm$^2$ or less, the follow up was 2.7 years in patients with an aortic valve area between 1.0 and 1.5 cm$^2$, 3.2 years in patients with an aortic valve area of 1.5 cm$^2$ or more. During follow up 33 (24%) patients underwent aortic valve replacement. Fifty-seven (41%) patients had died, of whom 5 had undergone an aortic valve replacement.
Table 1. Discrete clinical and echocardiographic characteristics and the rate of progression in the present patient study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>AVA cm$^2$/yr</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>121</td>
<td>-0.10</td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>55</td>
<td>-0.12</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>65</td>
<td>-0.94</td>
<td>0.57</td>
</tr>
<tr>
<td>renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>88</td>
<td>-0.08</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>33</td>
<td>-0.16</td>
<td>0.03</td>
</tr>
<tr>
<td>dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>118</td>
<td>-0.09</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>3</td>
<td>-0.56</td>
<td>0.00</td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>69</td>
<td>-0.08</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>52</td>
<td>-0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>current smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>98</td>
<td>-0.10</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>23</td>
<td>-0.12</td>
<td>0.57</td>
</tr>
<tr>
<td>diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>102</td>
<td>-0.10</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>19</td>
<td>-0.12</td>
<td>0.67</td>
</tr>
<tr>
<td>known cad</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>99</td>
<td>-0.11</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>22</td>
<td>-0.10</td>
<td>0.91</td>
</tr>
<tr>
<td>LV function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>92</td>
<td>-0.10</td>
<td></td>
</tr>
<tr>
<td>reduced</td>
<td>29</td>
<td>-0.11</td>
<td>0.92</td>
</tr>
<tr>
<td>severity index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-7</td>
<td>75</td>
<td>-0.12</td>
<td></td>
</tr>
<tr>
<td>8-10</td>
<td>27</td>
<td>-0.08</td>
<td>0.45</td>
</tr>
</tbody>
</table>

AVA = aortic valve area, LV = left ventricular

The median decrease in aortic valve area was -0.08 cm$^2$ per year (50% range -0.02 to -0.16 cm$^2$/year). The mean reduction in aortic valve area was -
0.10 cm\(^2\) (standard deviation (sd) 0.23). The average increase of peak systolic gradient was 4.6 mmHg per year (sd 6.8 mmHg). The median increase of peak systolic gradient was 4.3 mmHg per year (50% range 1.0 - 7.7 mmHg/year). There was hardly any difference in the rate of progression between patients with a short and long follow up.

*Variables associated with progression in the patient study*

Twenty-one previously reported clinical and echocardiographic variables associated with the decrease in aortic valve area were evaluated in our cohort. Univariate analysis showed that age, renal failure/dialysis/serum creatinin, initial aortic valve area and velocity in the left ventricular outflow tract (LVOT) had univariately a significant association with the annual reduction in aortic valve area (Table 1 and 2). With multivariate analysis serum creatinin and initial aortic valve area were found to to have a significant association with the annual reduction of aortic valve area.

*Review of the literature*

The literature search revealed 18 articles(5-9,12-24) which met our criteria, including three papers describing the same patient cohort. Table 3 the main characteristics of the 18 studies are presented. All studies together comprised 2257 patients. Most studies included patients who had at least 2 echocardiographic exams with a minimum of 6 months between the first and last echocardiographic examination. The study of Roger(22) included only patients with at least three exams, the study of Thoreau(23) included only patients with at least four exams.

The mean age of the patients varied from 58 to 76 years. The average systolic peak gradient at baseline varied from 25 to 64 mmHg, and the average aortic valve area from 0.75 to 1.55 cm\(^2\) (table 3). The annual reduction of aortic valve area varied from varied from 0.04(8) cm\(^2\) to 0.19(20) cm\(^2\).
**Table 2.** Continuous clinical and echocardiographic characteristics and the rate of progression in the present patient study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>25 / 75 quartile</th>
<th>25 / 75 median</th>
<th>AVA β coefficient standardized</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>121</td>
<td>71 / 81</td>
<td>71</td>
<td>-0.00</td>
<td>0.81</td>
</tr>
<tr>
<td>bmi</td>
<td>94</td>
<td>24 / 28</td>
<td>26</td>
<td>0.00</td>
<td>0.97</td>
</tr>
<tr>
<td>cholesterol</td>
<td>89</td>
<td>5.4 / 7.1</td>
<td>6.4</td>
<td>0.00</td>
<td>0.96</td>
</tr>
<tr>
<td>Creatinin</td>
<td>118</td>
<td>72 / 109</td>
<td>84</td>
<td>-0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>Calcium</td>
<td>39</td>
<td>2.3 / 2.4</td>
<td>2.3</td>
<td>-0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>initial AVA</td>
<td>121</td>
<td>1.0 / 1.5</td>
<td>1.3</td>
<td>0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>peak gradient</td>
<td>121</td>
<td>25 / 42</td>
<td>32</td>
<td>0.02</td>
<td>0.33</td>
</tr>
<tr>
<td>mean gradient</td>
<td>105</td>
<td>15 / 27</td>
<td>20</td>
<td>-0.01</td>
<td>0.44</td>
</tr>
<tr>
<td>Ivot velocity</td>
<td>121</td>
<td>0.9 / 1.2</td>
<td>1.0</td>
<td>-0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Lved</td>
<td>79</td>
<td>46 / 57</td>
<td>52</td>
<td>-0.02</td>
<td>0.34</td>
</tr>
<tr>
<td>Lves</td>
<td>74</td>
<td>25 / 39</td>
<td>30</td>
<td>-0.01</td>
<td>0.44</td>
</tr>
<tr>
<td>Iv mass index</td>
<td>71</td>
<td>223 / 358</td>
<td>289</td>
<td>-0.04</td>
<td>0.06</td>
</tr>
</tbody>
</table>

bmi = body mass index, AVA = aortic valve area, Ivot = left ventricular outflow tract velocity, Lves = left ventricular end systolic diameter, Iv mass = left ventricular mass.

β coefficient = beta coefficient.
The latter was in a group of patients who underwent dialysis for end stage renal failure. The standard deviations were larger than the mean. The pooled annual progression was -0.10 cm$^2$ (SD 0.0057) calculated from 7 studies (including our own patient study) concerning 882 patients. The annual change in peak systolic gradient varied from 3.9 mmHg(20) to 15 mmHg(14) (table 3). The pooled annual progression was 6.5 mmHg (SD 0.48) calculated from 4 studies (including our own) concerning 319 patients.

Variables associated with progression

All 18 studies except one(12) presented data on the association of clinical variables and the rate of progression of the aortic stenosis (Table 4). Seven studies performed linear regression analysis to identify univariate and multivariate significant associations with the increase of systolic pressure gradient or decrease of aortic valve area(7,12-15,22,23). Five divided their patient group in slow and rapid progressors. The cut-off values chosen to define rapid progressors were a progression of at least 0.1 cm$^2$ per year(8), 0.2 cm$^2$ per year(9), 0.25 cm$^2$ per year(24), ≥ 5 mmHg per year(17), ≥ 10 mmHg per year(21). Two studies(19,20) did both. The cut-off value used by Palta(19) was an annual reduction in aortic valve area of 7% or more. The study of Perkovic(20) used the 95% upper limit from their (not dialysis) control group. This was not further specified. Two studies divided their cohort into use of statins or not(5,6). Twenty-five variables were identified as having an association with the progression of aortic stenosis.

Clinical variables associated with progression

The majority of the studies (total 18 studies, including 3 sub-studies from one centre) tested age (15 studies), sex (14), hypertension (10), diabetes (9), cholesterol (9), current smoking (8), and presence of coronary artery disease (7). Use of statins (3 out of 4), and renal failure or dialysis (2 out of 5) were conditionally associated with the rate of progression (Table 4.). The study of Wonpraparut(24) was negative, but contained only 58 patients, of whom 11 used
a statin. A lack of power can be the reason that an association was not found. Current smoking was identified as conditionally associated with rate of progression in 3 out of 7 studies, but the number of patients in the positive studies was less than the number of patients in the negative studies. The other clinical variables, such as sex, hypertension, diabetes, total cholesterol and presence of coronary artery disease, were not found to be conditionally associated with the rate of progression of aortic stenosis in more than a single study (Table 4). The number of patients in the positive studies was also far below the number of patients in the negative studies.

**Echocardiographic variables associated with progression**

The majority of studies tested initial aortic valve area (9 studies), initial peak gradient (5) and left ventricular function (6) (Table 4). Other echocardiographic parameters were tested only in a limited number of studies. The only echocardiographic variable that was associated with progression of aortic stenosis in more than one study was the initial aortic valve area.

**Discussion**

**Annual progression of aortic valve stenosis**

In our patient study of 121 unselected patients with aortic stenosis we found a mean decrease of aortic valve area of 0.1 cm$^2$ per year. The review of the literature yielded an average annual decrease of 0.1 cm$^2$ per year, but the annual decrease varied from 0.04 to 0.16 cm$^2$ per year among the studies. The different selections of patients might contribute to this finding. The large standard deviations also indicate a large variation within studies. The variables chosen to test an association with the progression of aortic stenosis differed widely among studies. A prediction of the progression of an individual patient cannot be made on the basis of these data alone.
**Table 3.** Review of the literature: clinical characteristics and rate of progression.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Age in years</th>
<th>Initial Aortic Stenosis</th>
<th>Specific Inclusion Criteria</th>
<th>Mean Follow Up in Months (sd)</th>
<th>Mean Initial Pressure Gradient mmHg</th>
<th>Observed Annual Change mmHg/yr Mean</th>
<th>Mean Initial AVA cm²</th>
<th>Observed Annual Change cm²/yr Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahler(8)</td>
<td>91</td>
<td>68±13</td>
<td>≤ 2.0 cm²</td>
<td>No statin use</td>
<td>22 (11)</td>
<td>27.6</td>
<td>-</td>
<td>1.2</td>
<td>-0.04</td>
</tr>
<tr>
<td>Bellamy(5)</td>
<td>118</td>
<td>78±12</td>
<td>≤ 2.0 cm²</td>
<td>No statin use</td>
<td>44</td>
<td>36</td>
<td>-</td>
<td>1.2</td>
<td>-0.09</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>73±11</td>
<td>≤ 2.0 cm²</td>
<td>Use of statin</td>
<td>44</td>
<td>31</td>
<td>-</td>
<td>1.3</td>
<td>-0.04</td>
</tr>
<tr>
<td>Brener(13)</td>
<td>394</td>
<td>65±12</td>
<td>≥ 2.5 m/s; ≥ 0.9cm²</td>
<td>Asymptomatic</td>
<td>34 (16)</td>
<td>-</td>
<td>-</td>
<td>-0.14</td>
<td>0.15</td>
</tr>
<tr>
<td>Faggiano(14)</td>
<td>45</td>
<td>72±10</td>
<td>≥ 2.5 m/s</td>
<td>Age ≥ 60; correlating risk factors and statin</td>
<td>33 (12)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lester(9)</td>
<td>84</td>
<td>63±15</td>
<td>≥ 2.5 m/s; ≥ 0.9cm²</td>
<td>Age ≥ 60; data on coronary risk factors; AVA measured</td>
<td>28 (21)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>180</td>
<td>82±5</td>
<td>10-25 mmHg</td>
<td>Age ≥ 60; data on coronary risk factors; AVA measured</td>
<td>28 (21)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aronow(7)</td>
<td>102</td>
<td>76±9</td>
<td>Age ≥ 60</td>
<td>Age ≥ 60; data on coronary risk factors; AVA measured</td>
<td>28 (21)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>290</td>
<td>76±9</td>
<td>Age ≥ 60</td>
<td>Age ≥ 60; data on coronary risk factors; AVA measured</td>
<td>28 (21)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Van Ngo(17)</td>
<td>87</td>
<td>71±10</td>
<td>≥ 2 m/s</td>
<td>No use of statin; ef ≥ 50%; ≤ 2+ AI; use of statin; ef ≥ 50%; ≤ 2+ AI</td>
<td>21 (7)</td>
<td>28</td>
<td>-</td>
<td>1.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Novaro(6)</td>
<td>117</td>
<td>67±13</td>
<td>1.0-1.8 cm²</td>
<td>No use of statin; ef ≥ 50%; ≤ 2+ AI; use of statin; ef ≥ 50%; ≤ 2+ AI</td>
<td>21 (7)</td>
<td>28</td>
<td>-</td>
<td>1.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Otto(18)</td>
<td>114</td>
<td>63±16</td>
<td>≥ 2.5 m/s</td>
<td>Asymptomatic</td>
<td>2.5 (1.4)</td>
<td>3.6*</td>
<td>0.32*</td>
<td>0.34</td>
<td>1.3</td>
</tr>
<tr>
<td>Otto(12)</td>
<td>42</td>
<td>66</td>
<td>≥ 2.6 m/s</td>
<td>Asymptomatic</td>
<td>20</td>
<td>3.7*</td>
<td>0.36*</td>
<td>-</td>
<td>-0.10</td>
</tr>
<tr>
<td>Palta(19)</td>
<td>170</td>
<td>71±9</td>
<td>≥ 2.6 m/s</td>
<td>Asymptomatic</td>
<td>23 (11)</td>
<td>2.7*</td>
<td>-</td>
<td>-</td>
<td>-0.10</td>
</tr>
<tr>
<td>Perkovic(20)</td>
<td>28</td>
<td>70</td>
<td>&gt; 2 m/s</td>
<td>Dialysis</td>
<td>19</td>
<td>25</td>
<td>6.5</td>
<td>1.55</td>
<td>-0.19</td>
</tr>
<tr>
<td>Perkovic(20)</td>
<td>56</td>
<td>70</td>
<td>&gt; 2 m/s</td>
<td>Control group</td>
<td>31</td>
<td>29</td>
<td>3.9</td>
<td>1.3</td>
<td>-0.07</td>
</tr>
<tr>
<td>Peter(21)</td>
<td>49</td>
<td>58±16</td>
<td>&gt; 2 m/s</td>
<td>Control group</td>
<td>32 (16)</td>
<td>38</td>
<td>10.6</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Roger(22)</td>
<td>112</td>
<td>69±11</td>
<td>≥ 2 m/s</td>
<td>3 ≥ echo's</td>
<td>25</td>
<td>35</td>
<td>0.23*</td>
<td>0.37</td>
<td>-</td>
</tr>
<tr>
<td>Thoreau(23)</td>
<td>25</td>
<td>63</td>
<td>4 ≥ echo's</td>
<td>-</td>
<td>57</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wongpra(24)</td>
<td>58</td>
<td>75±11</td>
<td>4 ≥ echo's</td>
<td>-</td>
<td>42</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

* m/sec, ** if reported, ^ averaged from all subgroups
Table 4. Reported associations of clinical and echocardiographic characteristics and progression of aortic stenosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>number of studies</th>
<th>Studies reporting no significant Association</th>
<th>Studies reporting a significant association with univariate analysis</th>
<th>Studies reporting a significant association with multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>total patients</td>
<td>References</td>
<td>total patients</td>
<td>Total patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>references</td>
<td>references</td>
</tr>
<tr>
<td>Sex</td>
<td>15</td>
<td>1111</td>
<td>91</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
<td>15</td>
<td>1247</td>
<td>307</td>
<td>6,20,21</td>
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<tr>
<td>body mass index/obese</td>
<td>3</td>
<td>301</td>
<td>-</td>
<td>-</td>
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<tr>
<td>renal failure</td>
<td>5</td>
<td>171</td>
<td>162</td>
<td>8,24</td>
</tr>
<tr>
<td>hypertension</td>
<td>10</td>
<td>868</td>
<td>102</td>
<td>15*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
<td>868</td>
<td>102</td>
<td>15*</td>
</tr>
<tr>
<td>calcium supplements</td>
<td>1</td>
<td>-</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>use of statins</td>
<td>3</td>
<td>58</td>
<td>-</td>
<td>-</td>
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<tr>
<td>coronary artery disease</td>
<td>7</td>
<td>587</td>
<td>-</td>
<td>-</td>
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<tr>
<td>current smoking</td>
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<td>504</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Calcium</td>
<td>4</td>
<td>58</td>
<td>121</td>
<td>x</td>
</tr>
<tr>
<td>cholesterol</td>
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<td>170</td>
<td>19</td>
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<tr>
<td>HDL</td>
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<td>-</td>
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<td>LDL</td>
<td>2</td>
<td>118</td>
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<td>initial AVA</td>
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<td>5,9,13,14</td>
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<td>LVOT velocity</td>
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<td>19,x</td>
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<td>LV end systolic diameter</td>
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<td>91</td>
<td>8</td>
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<tr>
<td>LV end diastolic diameter</td>
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<td>261</td>
<td>170</td>
<td>19</td>
</tr>
<tr>
<td>LV mass</td>
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<td>91</td>
<td>8</td>
</tr>
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<td>left ventricular function</td>
<td>6</td>
<td>578</td>
<td>45</td>
<td>14</td>
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<tr>
<td>Severity index</td>
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<td>121</td>
<td>-</td>
<td>-</td>
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<tr>
<td>rate of change of AVA</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>mitral annulus calcification</td>
<td>2</td>
<td>58</td>
<td>290</td>
<td>16</td>
</tr>
</tbody>
</table>

Bellamy(5), Novaro(6), Aronow(7), Bahler(8), Lester(9), Otto II(12), Brener(13), Faggiano(14), Nassimiha I (15), Nassimiha II(16), van Ngo(17), Otto I(18), Palta(19), Perkovic(20), Peter(21), Roger(22), Thoreau(23), Wongpraparat(24). x current patient study * (sub) studies, all from the single centre
Clinical variables associated with progression

The use of statins and renal failure were the only clinical variables for which a consistent association with the progression of aortic stenosis was found. Current smoking was found to have a probable association, but although three studies independently found an association with the rate of progression, the number of patients in the negative studies exceeded the number of patients in the two positive studies. This limits the conclusions about these findings. In all other 12 clinical variables, as described in Table 4, an association with the progression of aortic stenosis on a multivariate level could not be established.

We found three studies (5-7) which reported a significant association between the use of statins and a reduced progression (table 4). How statins may reduce progression is unclear (5) as cholesterol was not associated with progression. The associated (pleiotropic) effects of statins might play a role, such as their anti-inflammatory effects (25), and their extra-osseous calcifications (26). Future randomized trials might demonstrate the exact benefit of statins in the reduction of progression of aortic stenosis and could be helpful to provide insight in the mechanisms.

Impairment of renal failure was consistently associated with progression. The abnormalities in calcium and phosphate homeostasis lead to hyperphosphataemia, hypocalciemia, and hyperparathyreoidism and subsequently to increased metastatic calcification involving several organs, including in the cardiovascular system (27).

Although some studies found an association between the classical risk factors for coronary artery disease and the presence of aortic stenosis, no consistent or possible association with progression was found (Table 4). Other clinical variables, such as sex, body mass index, calcium, use of calcium supplements, HDL, and LDL, were evaluated in a limited number of studies. These studies were mainly negative. This indicates that the parallel of calcification of the aortic valve with atherosclerosis might not be so obvious (2).
Echocardiographic variables associated with progression

Initial aortic valve area at the index echo was the only echocardiographic parameter which was consistently found to be associated with progression of aortic stenosis on a multivariate level. Patients with a large aortic valve area showed a faster progression than patients with a small aortic valve area. Slow progressors in the group of patients with a small aortic valve area might be over-represented in studies on progression because the patients with a rapid progression are already operated upon before a second echo can be performed. Regression to mean might be another explanation.

Strikingly, although only echocardiographic studies were included, there was an huge variety among studies with respect to echocardiographic variables that were tested as predictors for the progression of aortic stenosis. In the 18 studies 11 different echocardiographic parameters were evaluated. Of these, 6 parameters were explored in three or less studies. Only aortic valve area, peak systolic gradient and left ventricular function were analyzed in most studies.

Methodological differences in the analysis of association of variables with progression

Almost all studies on progression rate of aortic stenosis tried to identify associations of clinical and echocardiographic variables (Table 4). However, a drawback is the large variation in methodology. Seven studies evaluated the association of clinical and echocardiographic variables with progression by comparing these characteristics in patients with rapid and slow progression. The criteria to define rapid and slow progression differed among all studies. The variations in cut-off value illustrate the uncertainty about what might be clinical relevant value. Secondly, it can be questioned whether an arbitrary dichotomization makes optimal use of the data. These arbitrary dichotomizations might explain the variations in findings of the different studies.

Limitations

Research concerning the rate and determinants of progression of aortic stenosis demands a long observation period. Our study was a retrospective analysis of

progression of aortic stenosis
data extracted from the database of our echo laboratory. The data on progression are reliable, because they were collected and stored on the day of the echocardiographic examination. Furthermore, two independent reviewers re-analyzed all videotapes. However, in a retrospective study it is more difficult to determine associations of clinical characteristics, such as use of statins, serum calcium, and so on, with the rate of progression as these data are often not systematically collected at the index event.

We were not able to investigate the association of the rate of change of aortic valve area during the cardiac cycle(9,28) as the measurements were not digitalized. Several laboratory tests, such as pro Brain natriuretic peptide en cardiotrophin-1(29), and lipoproteine(a) (30), have not been investigated, although these factors might also be associated with progression of aortic stenosis.

Not all studies report clearly which variables are investigated. Therefore, a misjudgement about the validity of certain parameters remains possible. Also, a low prevalence of a certain variables could lead to a lack of power, necessary to enter a multivariate model.

Conclusion
The average annual decrease of aortic valve area is 0.1 cm² per year, but varies widely among and within studies. The only clinical and echocardiographic variables which demonstrate a consistent association with progression are: use of statins, renal failure or dialysis and initial aortic valve area. Current smoking probably has an association with progression rate of aortic stenosis. The variables chosen to test an association with the progression of aortic stenosis differ widely among studies. The use of several different strategies of analysis hampers a straightforward comparison. A pooled analysis with individual patient data might allow predictions for individual patients.
References


