



## Risk factor profile of calcific aortic stenosis



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### ABSTRACT

**Background:** Calcific aortic stenosis and coronary artery disease share common risk factors. In some of the previous studies statins have been used to retard the progression of aortic stenosis, but the results were inconsistent.

**Methods:** One hundred and ten patients of CAS above the age of 40 years have undergone clinical, biochemical and echocardiographic evaluation. Coronary angiograms were done in 66% of them.

**Results:** Male to female ratio was 2:1. Patients of CAS with CAD showed higher prevalence of diabetes, hypertension, dyslipidemia, smoking and family history of CAD. Prevalence of obesity and bicuspid aortic valve by echocardiogram was high in those without CAD.

**Conclusions:** On comparison of prevalence of risk factor in those with and without associated CAD, there was higher prevalence of diabetes (65% vs 30%), hypertension (52% vs 43%), dyslipidemia (69% vs 52%), smoking (24% vs 18%) and family history of CAD (34% vs 16%) in those with associated CAD. The incidence of obesity was higher in those without CAD (20% vs 30%). The difference observed in diabetes alone was found to be statistically significant.

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## 1. Introduction

Calcific aortic stenosis (CAS) is the most common valve disorder in the western world<sup>1</sup> and is the most common indication for aortic valve replacement (AVR) in the elderly.<sup>2</sup> In general population, 1–2% of subjects have bicuspid aortic valve (BAV) which predisposes to early development of aortic stenosis (AS).<sup>3</sup> There is growing experimental evidence suggesting that aortic valve (AV) calcifications is an active biological process with some similarities to vascular atherosclerosis.<sup>4–7</sup>

Pomerance<sup>8</sup> described calcification of AV cusps that was preceded by lipid deposition similar to that seen in coronary atherosclerosis. Both atherosclerosis and CAS were found to be associated with familial hypercholesterolemia. Stewart et al.<sup>9</sup> from the Cardiovascular Health Study reported that independent risk factors associated with CAS included elevated LDL cholesterol and LP(a), hypertension, male gender, smoking and these risk factors

were similar to those observed with coronary artery disease (CAD) in the Framingham study. This new information opens up new avenue that can be targeted with statins in the medical management of CAS to prevent or retard the progression of CAS.<sup>10,11</sup> There is no data available regarding risk factor profile in patients with CAS in Indian literature. The aim of the present prospective study was to evaluate the risk factors and compare the risk factor profile in patients of CAS with and without associated CAD.

## 2. Material and methods

This prospective study was carried out at a tertiary hospital at Chennai between January and December 2012. One hundred and ten patients of CAS satisfying the inclusion criteria of age  $\geq 40$  years were included in the study. Informed written consent was obtained from all of them and ethics committee approval was obtained as per mandatory hospital regulation. There were 74 males (67%) and 36 females (33%). Their ages ranged between 40 and 84 years (mean age 56.2 years). The age distribution was shown in Table 1. The majority of patients were above the age of 60 years. Those with rheumatic heart disease, associated mitral valve disease, those with more than mild aortic regurgitation, atrial

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**Table 1**  
Sex distribution in different age groups.

Age group	Male n (%)	Female n (%)	Total (n=110)
40–49 years	8 (7.1%)	1 (0.9%)	9 (8%)
50–59 years	21 (19%)	9 (8%)	30 (27%)
60–69 years	29 (26%)	15 (14%)	44 (40%)
70–79 years	15 (14%)	10 (9%)	25 (23%)
≥80 years	1 (0.9%)	1 (0.9%)	2 (2%)

fibrillation those in clinical heart failure and those with serum creatinine more than 2 mg% were excluded from the study.

Data was recorded by taking detailed history, clinical examination and biochemical tests. The variables collected were pulse rate, blood pressure, BMI and detailed cardiovascular system examination. BMI more than 30 was considered as obese. Biochemical parameters were mainly to evaluate the risk factor profile which included routine hemogram, renal function tests, lipid profile, blood sugar levels, including glycosylated hemoglobin%. ECG, chest X-ray PA view and 2D echocardiograms (Echo) were performed in all of them. Risk factor profiles and their age groups were shown in Table 2.

### 2.1. Echocardiography

Echo evaluation included AV jet velocity, AV area and transaortic mean gradients. Echo evaluation also helped to detect mitral valve disease, severity of aortic regurgitation and associated mitral annular calcification. In addition echo evaluation revealed associated regional wall motion abnormalities and left ventricle ejection fraction (LVEF). Echo parameters were shown in Table 3.

### 2.2. Coronary angiography

It was performed in 73 patients (66%) who were subjected to AVR. When the coronary anatomy revealed more than 50% diameter stenosis they were labeled as significant coronary obstruction. Coronary artery involvement was shown in Table 4. Subgroup comparative analysis of the risk factors was done in those with and without associated CAD (Table 5).

The analysis was carried out using SPSS software version 11.0. All the categorical variables were expressed as percentages. Comparisons between categorical variables were done using Chi square test and Fisher's exact test when the number of observations were small.

## 3. Results

In our study we found high incidence of CAS in males compared to females. Regarding age distribution 65% of our CAS patients

**Table 2**  
Distribution of atherosclerotic risk factors in different age groups.

Risk factors	Age groups (n=110)				
	40–49 years (n=9)	50–59 years (n=30)	60–69 years (n=44)	70–79 years (n=25)	≥80 years (n=2)
Diabetes mellitus	0	14	19	11	1
Systemic hypertension	1	13	22	16	2
Dyslipidemia	3	15	29	13	1
Smoking	3	5	12	4	0
Obesity	2	7	13	5	0
Family history of CAD	0	8	7	3	0
Tobacco chewing	0	0	1	0	0

**Table 3**  
Echocardiographic parameters in our study group.

Parameters	Number of patients (n=110)	Percentage
Ejection fraction		
≥55%	85	77.3%
45–54%	08	7.3%
30–44%	14	12.7%
<30%	03	2.7%
Aortic valve area (cm <sup>2</sup> )		
<1.0	72	65.5%
1–1.5	38	34.5%
AV jet velocity (m/s)		
<3	01	0.9%
3–4	15	13.6%
>4	94	85.5%
Mean gradient (mmHg)		
<25	01	0.9%
25–40	09	8.2%
>40	100	90.9%
Mitral annular calcification	20	18.2%
Bicuspid Aortic valve	24	22%

**Table 4**  
Prevalence of CAD in calcific AS (n=73).

Coronary angiogram	Number	Percentage	RWMA by echo
Normal coronaries	44	60.3%	
Single vessel disease	09	12.3%	
Double vessel disease	10	13.7%	2
Triple vessel disease	10	13.7%	3

RWMA, regional wall motion abnormality.

were above 60 years. Majority of those above the age of 50 years had diabetes mellitus and hypertension. Our observations revealed 61 patients (55%) were dyslipidemic, 54 patients (49%) had hypertension, 45 patients (41%) had diabetes mellitus, 27 patients (25%) were obese (BMI more than 30), 24 patients (22%) were smokers and only 1 patient gave history of tobacco chewing. Family history of CAD was noted in 18 patients (16%) (Table 2). The distribution of atherosclerotic risk factors did not show any particular age preferences except that smoking was more common above the age of 50 years.

### 3.1. Echocardiography (Table 3)

Out of 110 patients, 24 (22%) had BAV. 85 patients (77.5%) had normal LVEF. Eight patients (7.3%) had mild LV dysfunction,

**Table 5**  
Prevalence of risk factors in calcific AS patients with and without CAD.

Risk factor (%)	Calcific AS with CAD n=29 (40%)	Calcific AS without CAD n=44 (60%)	P value
Diabetes n (%)			
Yes	19 (65)	13 (30)	0.00243
No	10 (35)	31 (70)	
Hypertension			
Yes	15 (52)	19 (43)	0.4740
No	14 (48)	25 (57)	
Dyslipidemia			
Yes	20 (69)	23 (52)	0.156
No	9 (31)	21 (48)	
Smoking			
Yes	7 (24)	8 (18)	0.53
No	22 (76)	36 (82)	
Family history of CAD			
Yes	10 (34)	7 (16)	0.06
No	19 (66)	37 (84)	
Obesity			
Yes	6 (20)	13 (30)	0.398
No	23 (80)	31 (70)	

14 patients (12.7%) had moderate LV dysfunction. Only 11 patients (10%) showed regional wall motion abnormality suggestive of associated CAD. In the present study we found 72 patients (65.5%) had AVA  $\leq 1$  cm<sup>2</sup> while 94 patients (85.5%) had aortic jet velocity  $\geq 4$  m/s and 100 patients (90.9%) showed mean gradients of  $\geq 40$  mmHg across AV. Associated mitral annular calcifications were observed in 20 patients (18.2%).

### 3.2. Coronary angiography

Among the 73 patients who have undergone coronary angiography 29 patients (40%) had associated CAD. 9 patients had single vessel disease, 10 patients had two vessel disease and rest 10 patients had triple vessel disease (Table 4).

Subgroup analysis of risk factor in patients of CAS with and without associated CAD revealed diabetes in 19 out of 29 (65%) with CAD, hypertension in 15 patients (52%), dyslipidemia in 20 patients (69%) and smoking in 7 patients (24%). When CAS patients with CAD compared to those without CAD none of the variables were found to be statistically significant except diabetes (*P* value 0.00243).

## 4. Discussion

Several studies have documented strong association of traditional risk factors with CAS as well as with coronary atherosclerosis.<sup>10</sup> The largest prospective population based study<sup>9</sup> the cardiovascular health study included 5621 subjects above the age of 65 years, reported a strong positive association between CAS with atherosclerotic risk factors like age, male gender, smoking, hypertension, elevated levels of LP(a) and LDL cholesterol.

Mean age in our study was 56.2 years. In the Monica/Kora survey<sup>12</sup> the mean age was 55 years while in SEAS study<sup>13</sup> it was 67 years and in SALTIRE<sup>14</sup> group it was 68 years. In the study by Hachicha et al.<sup>15</sup> the mean age was 69 and 73 years in normal flow and low flow groups respectively. It is understandable that in the Hachicha study, low flow patients were elderly as majority of them included had severe LV dysfunction. The age distribution in our (Indian) patients is comparable to most of the previously reported studies mentioned above.

In the present study, males versus females was 67%:33%, showing a male preponderance. In the Monica/Kora study<sup>11</sup> 52% were males, in SALTIRE<sup>14</sup> group 70%, in SEAS study<sup>13</sup> 61.3% were males. In the study reported by Hachicha et al.,<sup>15</sup> revealed 61% males in the normal flow group and 49% in the paradoxical low flow group with an average 56% males. Ortlepp et al.,<sup>16</sup> reported male preponderance (55%) but in RAAVE study<sup>17</sup> males were only 47%. Our study is in agreement with previously reported studies as regards gender preponderance excepting the RAAVE study.

In our study 55% had dyslipidemia which is high compared to other studies. In Kora/Monica study it was 31%, in SALTIRE study 10% in the statin group and only 6% in placebo group. In the study by Ortlepp et al. it was 49% and Hachicha et al. reported

dyslipidemia in more than 50% cases in both normal flow and low flow groups. This makes a point to initiate statin therapy in these patients. However the SEAS study<sup>13</sup> which is the largest randomized study to date failed to show any benefit of Simvastatin and Ezetimibe combination in reducing cardiovascular risk in patients of CAS.

Hypertension was noted in around 50% of cases in the present study. Even in SEAS study and Kora/Monica survey it was around 50% but the percentage of hypertensives was high in other studies, SALTIRE (65%), Ortlepp (59%) and Hachicha et al. (70%). The high percentage in Hachicha's study could be due to inclusion of low flow, low gradient patients in whom associated hypertension can result in double load over the left ventricular ejection. Essential hypertension has been described as a classical risk factor for progression of CAS.<sup>9</sup> Optimal treatment of hypertension becomes a major target for the management of CAS.

The percentage of diabetics (41%) was very high in our study compared to Kora/Monica study (3.7%), SALTIRE study (5%), Hachicha et al. (27%) while Ortlepp et al. reported diabetes in only 20% of their cases. This can be explained due to high prevalence of diabetes in our population and partly could be due to less number of patients in our study.

Twenty five percent were obese (BMI  $\geq 30$ ) in our study, whereas it was 33% in Hachicha study. In Kora/Monica study 45% were obese and the high percentage of obese subjects in this study can be explained on the basis that they used NIH consensus development panel criteria (BMI  $\geq 27.3$  in men and 27.8 in women).

In our study 22% were smokers and more or less similar observations was noted in Kora/Monica study (25.8%), SEAS study (20%) and in Ortlepp study smoking was reported in 41%. Family history of CAD was reported in 28% by Ortlepp et al. while in our study we observed only in 16% of our cases. Our observations of risk factor profile were compared with some of the major studies as shown in Table 6.

Among 73 subjects who underwent coronary angiograms 40% showed significant CAD in our study. In the Ortlepp study it was 53% and in SALTIRE study it was 28%. In Hachicha study 60% had associated CAD, a very high prevalence, which was due to inclusion of low flow low gradient AS patients. In the VA cooperative study on valvular heart disease,<sup>18</sup> 429 (48%) out of 896 of AS patients had  $\geq 50\%$  stenosis of one or more coronary arteries. In our study we did not perform coronary angiogram in those below age of 50 years and also those who were low risk candidates for CAD.

On comparison of prevalence of risk factor in those with and without associated CAD, there was higher prevalence of diabetes (65% vs 30%), hypertension (52% vs 43%), dyslipidemia (69% vs 52%), smoking (24% vs 18%) and family history of CAD (34% vs 16%) in those with associated CAD but the incidence of obesity was higher in those without CAD (20% vs 30%). The difference observed in diabetes alone was found statistically significant (Table 5).

**Table 6**  
Comparison of risk factors of calcific aortic stenosis in different studies.

Study	Kora/Monica <sup>12</sup>	SEAS <sup>11</sup>	SALTIRE <sup>14</sup>	Ortlepp et al. <sup>16</sup>	Hachicha et al. <sup>15</sup>	RAAVE <sup>17</sup>	Present study
Mean age	55	67	68	70	70	73	56.2
Male gender %	52	61.3	70	55	55	47	63
Dyslipidemia %	31	100	Statin 10% Placebo 6%	49	49	50.4	55
Hypertension %	49.8	51	52	59	59	63.6	50
Diabetes %	3.7	–	5	20	27	32.2	41
Smoking %	25.8	55	22	41	–	3.3	22
Obesity %	45	–	–	–	32	–	25

## 5. Strengths and limitations of the study

To our knowledge there was no previously reported studies on CAS in Indian patients. Though this was a prospective study the number of cases were less. Only two thirds of them have undergone coronary angiograms. There was no long term follow up.

## 6. Conclusions

This is the first Indian prospective study where CAS with association of coronary risk factors was studied. Our study revealed high prevalence of male gender, dyslipidemia, hypertension and diabetes. The prevalence of diabetes was high in our study compared to other published studies. It is worthwhile starting statin therapy in them at early stages with a presumption of retarding progression of CAS. Optimal control of co morbid risk factors is also important.

## Conflicts of interest

The authors have none to declare.

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