

Supplementary material: Survival of people with valvular heart disease in a large, English community-based cohort study

Supplementary Table 1 Classifications of mitral annular calcification and aortic sclerosis

ECHO report	Classification	Mitral annular calcification	Aortic sclerosis (thickening and/or calcification)
No	None	No involvement	0 - Normal (No involvement)
Mild	Early	Focal calcification with limited circumferential extent	1 - Mild (Minor involvement of one leaflet)
Moderate	Advanced	Marked calcification involving 1/3 to 1/2 of the mitral annular circumference;	2 - Moderate (Minor involvement of two leaflets or extensive involvement of one leaflet)
Severe		Marked calcification involving more than 1/2 of the mitral annular circumference, and/or intrusion into the LV outflow tract.	3 - Severe (Extensive involvement of two leaflets or involvement of all three leaflets)

Aortic sclerosis is defined as aortic valve cusp thickening without the development of a gradient across the aortic valve. The severity of aortic sclerosis on a scale of 0-3 (normal to severe) is quantified by echocardiography for echogenicity, thickening, or calcification of the valve leaflet as follows (Chandra et al., 2004).

Supplementary Table 2: Comparison of baseline clinical and echocardiographic characteristics of OxVALVE study participants according to the availability of long-term mortality data.

Characteristic	ONS linkage		P-value
	Yes	No	
N	3511	498	
Age, Mean (SD)	72.64 (5.9)	75.11 (6.4)	<0.0001
Men, n (%)	1769 (50.4)	279 (56.0)	0.009
Medical history			
Angina, n (%)	261 (7.4)	48 (9.6)	0.07
Angiography, n (%)	282 (8.0)	54 (10.8)	0.03
Ankle Oedema, n (%)	493 (14.0)	91 (18.3)	0.008
Atrial Fibrillation, n (%)	224 (6.4)	32 (6.4)	0.91
Coronary Artery Bypass Graft, n (%)	57 (1.6)	12 (2.4)	0.19
Cerebrovascular Attack/Transient Ischaemic Attack, n (%)	199 (5.7)	45 (9.0)	0.002
Diabetes, n (%)	391 (11.1)	66 (13.3)	0.13
Hyperlipidaemia, n (%)	1305 (37.2)	206 (41.4)	0.13
Hypertension, n (%)	1556 (44.3)	248 (49.8)	0.010
Myocardial Infarction, n (%)	157 (4.5)	33 (6.6)	0.03
NYHA Class, n (%)			0.003
<i>I</i>	2811 (80.1)	372 (74.7)	
<i>II</i>	629 (17.9)	97 (19.5)	
<i>III-IV</i>	71 (2.0)	22 (4.4)	
Percutaneous Coronary Intervention, n (%)	135 (3.9)	18 (3.6)	0.85
Rheumatic Fever, n (%)	73 (2.1)	11 (2.2)	0.82
Smoking Status, n (%)			0.02
Non-Smoker	1883 (53.6)	230 (46.2)	
Ex-Smoker	1396 (39.8)	226 (45.4)	
Smoker	230 (6.6)	35 (7.0)	
Index of multiple deprivation (quintile), n (%)			0.003
1 (least deprived)	1029 (29.3)	111 (22.3)	
2	1228 (35.0)	247 (49.6)	
3	749 (21.3)	75 (15.1)	
4	364 (10.4)	54 (10.8)	
5 (most deprived)	127 (3.6)	4 (0.8)	
Examination			
Height, Mean (SD)	1.67 (0.10)	1.66 (0.09)	0.02
Weight, Mean (SD)	77.8 (15.7)	74.57 (15.0)	<0.0001
Body Mass Index, Mean (SD)	27.7 (4.8)	26.9 (4.7)	0.0004
Systolic Blood Pressure, Mean (SD)	143.7 (20.2)	139.8 (20.2)	<0.0001
Diastolic Blood Pressure, Mean (SD)	80.4 (11.4)	78.7 (11.9)	0.004
Heart rate, Mean (SD)	72.8 (12.1)	73.1 (11.9)	0.62
Echocardiography			
Mitral Regurgitation, n (%)	1009 (28.7)	111 (23.5)	0.012
Mitral Stenosis, n (%)	5 (0.14)	5 (2.2)	0.0004
Aortic Regurgitation, n (%)	579 (16.5)	87 (18.7)	0.40
Aortic Stenosis, n (%)	40 (1.1)	11 (3.4)	0.11
Aortic Sclerosis, n (%)	1653 (47.0)	195 (40.4)	0.0002
Tricuspid Regurgitation, n (%)	1074 (30.6)	144 (30.1)	0.24
Pulmonary Regurgitation, n (%)	18 (0.51)	3 (1.8)	0.78
Bicuspid Aortic, n (%)	8 (0.23)	2 (1.6)	0.46
Mitral Prolapse, n (%)	59 (1.7)	4 (2.0)	0.32
Mitral Annular Calcification, n (%)	463 (13.2)	66 (14.5)	0.06

Supplementary Table 3 Valvular heart disease phenotypes ranked according to frequency (moderate and severe disease are grouped together as advanced (aortic sclerosis or mitral annular calcification) or significant disease (Valvular Heart Disease).

Characteristic	n	(%)
Aortic sclerosis, n (%)		
No	1858	(52.92)
Early	1574	(44.83)
Advanced	79	(2.25)
Tricuspid regurgitation, n (%)		
No	2437	(69.41)
Mild	1009	(28.74)
Significant	65	(1.85)
Mitral regurgitation, n (%)		
No	2502	(71.26)
Mild	941	(26.80)
Significant	68	(1.94)
Aortic regurgitation, n (%)		
No	2932	(83.51)
Mild	524	(14.92)
Significant	55	(1.57)
Mitral annular calcification, n (%)		
No	3048	(86.81)
Early	417	(11.88)
Advanced	46	(1.31)
Mitral valve prolapse, n (%)		
None/trivial	3452	(98.32)
Mild	55	(1.57)
Significant	4	(0.11)
Aortic stenosis, n (%)		
No	3471	(98.86)
Mild	21	(0.60)
Significant	19	(0.54)
Pulmonary regurgitation, n (%)		
No /Mild	3493	(99.49)
Significant	18	(0.51)
Bicuspid aortic valve, n (%)		
None/trivial/Mild	3503	(99.77)
Significant	8	(0.23)
Mitral stenosis, n (%)		
No	3506	(99.86)
Mild	4	(0.11)
Significant	1	(0.03)

Supplementary Table 4 Valvular heart disease phenotypes ranked according to frequency and severity of disease.

VHD Subtype	None/trivial		Mild		Moderate		Moderate-to-Severe		Severe	
	N	%	N	%	N	%	N	%	N	%
Aortic sclerosis	1858	52.9	1574	45.0	73	2.08	0	0	6	0.17
Tricuspid regurgitation	2437	69.4	1009	29.0	49	1.40	5	0.14	11	0.31
Mitral regurgitation	2502	71.3	941	27.0	59	1.68	7	0.20	2	0.06
Aortic regurgitation	2932	83.5	524	15.0	52	1.48	3	0.09	0	0
Mitral annular calcification	3048	86.8	417	12.0	45	1.28	0	0	1	0.03
Mitral prolapse	3452	98.3	55	1.60	4	0.11	0	0	0	0
Aortic stenosis	3471	98.9	21	0.60	14	0.40	1	0.03	4	0.11
Pulmonary regurgitation	3493	99.5	0	0	18	0.51	0	0	0	0
Bicuspid aortic valve	3503	99.8	0	0	8	0.23	0	0	0	0
Mitral stenosis	3506	99.9	4	0.10	0	0	1	0.03	0	0

Supplementary Table 5 Number and causes of death for OxVALVE study participants with significant, mild and no valvular heart disease.

Cause of death	VHD						Any VHD		Overall	
	Significant	%	Mild	%	None	%		%		%
Any	24	100	185	100	152	100	361	100	361	100
Cancer	3	12.5	76	41.8	79	52.0	79	21.9	158	43.8
Cardiovascular disease										
Primary cause of death	8	33.3	44	24.2	34	22.4	52	14.4	86	23.8
Any cause of death	12	50.0	94	51.7	65	42.8	106	29.4	171	47.4
Respiratory disease	5	20.8	19	10.4	14	9.21	24	6.6	38	10.5
Other causes of death	8	33.3	43	23.6	25	16.5	51	14.1	76	21.1

* Causes of death affecting <10 individuals in either of the groups being compared were grouped together.

There were three individuals for whom we could not obtain the cause of death.

Supplementary Table 6 Association of individual valvular heart disease phenotypes with all-cause mortality

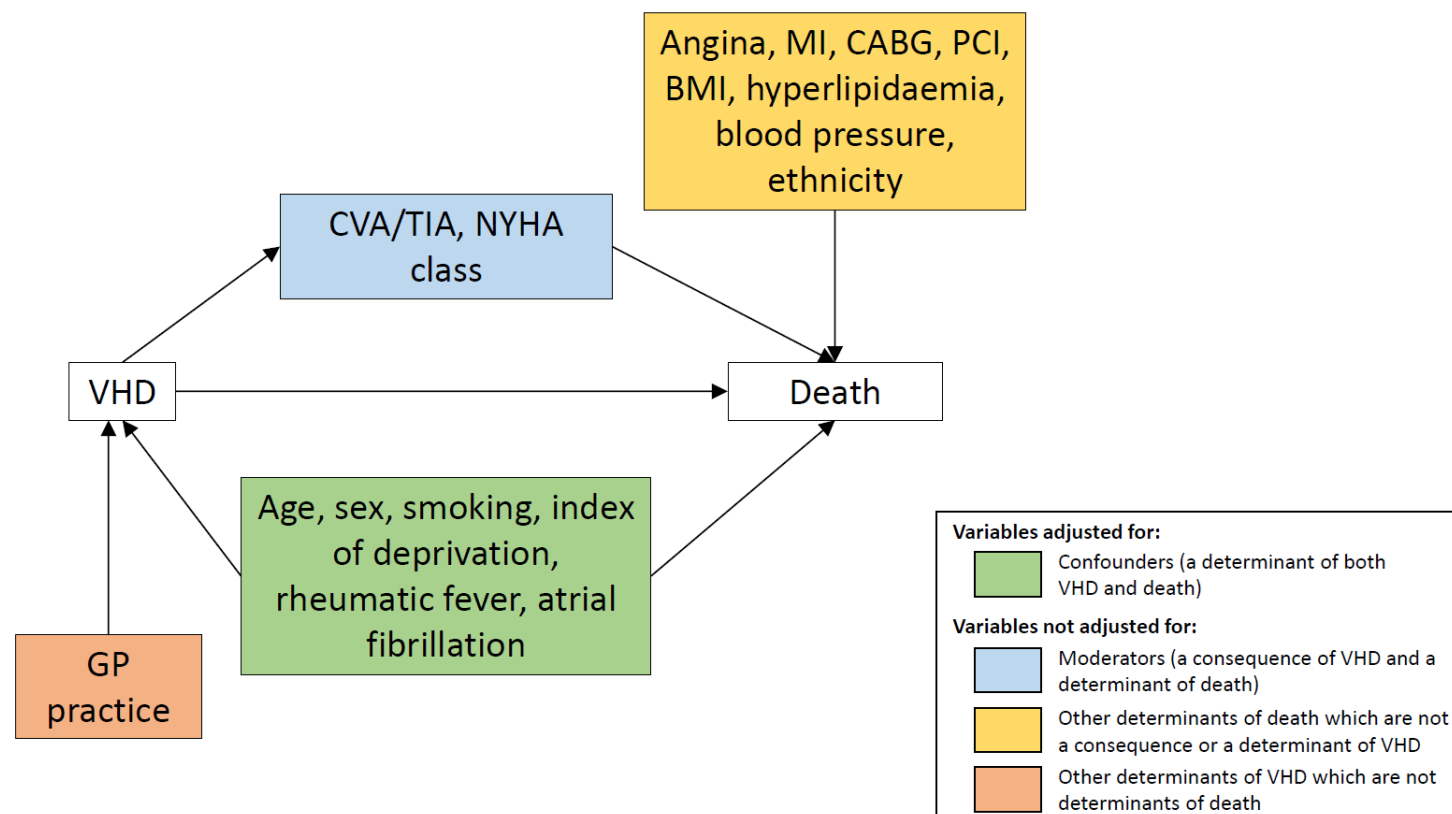
Valve disease subtype	Category	N	n	PYs	MR	Model 1 ^a	Model 2 ^b
Valvular heart disease sub-types							
Tricuspid regurgitation	No	2437	229	15,603	14.7	1.00 Reference	1.00 Reference
	Mild	1009	125	6,169	20.3	1.34 (1.06 to 1.69)	1.13 (0.88 to 1.44)
	Significant	65	7	298	23.5	1.15 (0.48 to 2.73)	0.73 (0.30 to 1.80)
Mitral regurgitation	No	2502	251	16,241	15.5	1.00 Reference	1.00 Reference
	Mild	941	99	5,524	17.9	1.01 (0.79 to 1.3)	0.95 (0.74 to 1.23)
	Significant	68	11	305	36.1	1.93 (0.96 to 3.86)	1.48 (0.73 to 3.03)
Aortic regurgitation	No	2932	282	18,608	15.2	1.00 Reference	1.00 Reference
	Mild	524	74	3,216	23.0	1.37 (1.05 to 1.80)	1.09 (0.83 to 1.44)
	Significant	55	5	245	20.4	1.15 (0.46 to 2.89)	0.87 (0.34 to 2.25)
Other valve abnormalities							
Mitral annular calcification	No	3048	285	19,256	14.8	1.00 Reference	1.00 Reference
	Early	417	63	2,571	24.5	1.55 (1.16 to 2.05)	1.34 (1.01 to 1.78)
	Advanced	46	13	243	53.5	3.36 (1.92 to 5.89)	2.51 (1.41 to 4.49)
Aortic sclerosis	No	1858	1982	12,689	15.1	1.00 Reference	1.00 Reference
	Early	1574	148	8,953	16.5	0.98 (0.78 to 1.24)	0.83 (0.66 to 1.06)
	Advanced	79	21	427	49.1	2.79 (1.74 to 4.46)	2.05 (1.28 to 3.30)

Abbreviations: N: number at risk of death within category; n: number of deaths within category; PYs: person-years; MR: Mortality rate per 1,000 person-years.

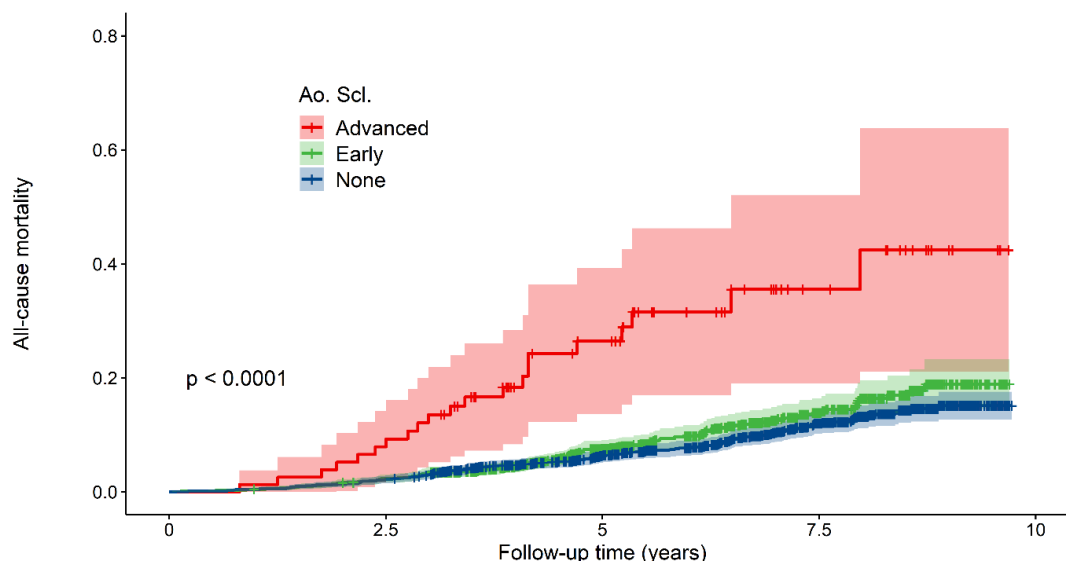
^a Model 1 was adjusted for all other VHD subtypes.

^b Model 2 was adjusted for all other VHD subtypes and sex, age, smoking status, index of multiple deprivation, blood pressure (systolic and diastolic), diabetes, and rheumatic fever.

Supplementary Figure 1 Simplified directed acyclic graph



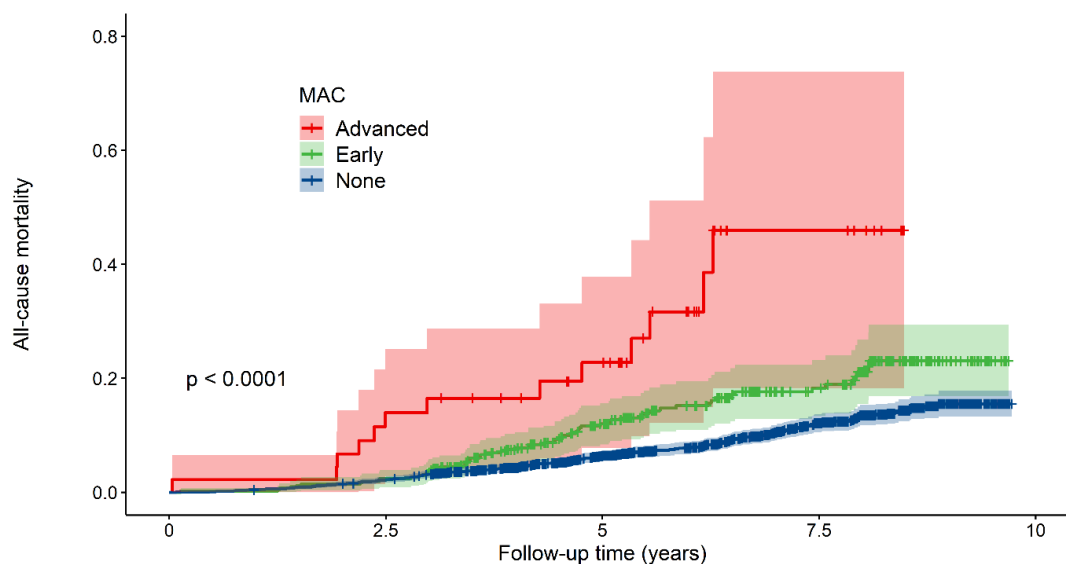
Supplementary Figure 2 Kaplan-Meier curves demonstrating the unadjusted rates of all-cause mortality for people with aortic sclerosis (AoScl) or mitral annular calcification (MAC).



Number at risk (number censored)

	0	2.5	5	7.5	10
Ao. Scl. Advanced	79 (0)	73 (0)	45 (17)	16 (43)	0 (58)
Ao. Scl. Early	1574 (0)	1535 (3)	1012 (460)	317 (1119)	0 (1426)
Ao. Scl. None	1858 (0)	1818 (0)	1502 (247)	848 (834)	0 (1666)

Follow-up time (years)



Number at risk (number censored)

	0	2.5	5	7.5	10
MAC Advanced	46 (0)	40 (0)	30 (7)	8 (25)	0 (33)
MAC Early	417 (0)	407 (0)	291 (83)	153 (207)	0 (354)
MAC None	3048 (0)	2979 (3)	2238 (634)	1020 (1764)	0 (2763)

Follow-up time (years)