Clinical Management and Long-Term Prognosis of Combined Left-Sided Valvular Heart Disease

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Summary

In studies on left-sided valve disease, patients with combined lesions are generally excluded. We aimed to describe the clinical management and prognosis of patients with combined left-sided valve disease.

From a single, tertiary care center, a total of 122 patients with combined left-sided valve disease of at least moderate severity were identified and compared with 143 controls with single-lesion valve disease (1VaD) of at least moderate severity. Endpoints were all-cause mortality and the combination of valve intervention and mortality.

Overall survival for patients with two-lesion valve disease was significantly lower than that for patients with 1VaD (estimated 3-year survival: 52% versus 73%, $P < 0.001$). Compared with 1VaD, the combination of aortic stenosis and aortic regurgitation (AS/AR) was associated with a similar overall survival (hazard ratio (HR) (95% confidence interval (CI)): 0.83 (0.47-1.48), $P = 0.53$), the combination of AR and mitral regurgitation (AR/MR) with an intermediate survival (HR (95% CI): 1.76 (1.03-3.00), $P = 0.039$) and the combination of AS and MR (AS/MR) with the poorest survival (HR (95% CI): 3.28 (2.16-4.98), $P < 0.001$). At 2.2 years of follow-up, the majority of patients in all three groups were either dead or had received valve intervention (AS/AR: 72%, AR/MR: 64%, and AS/MR: 80%).

Combined valve disease was relatively rare but was associated with a decreased overall survival. Survival depended on the specific combination of valve lesions, with AS/MR carrying the worst prognosis. The majority of patients in all groups were either dead or had valve intervention performed within 2.2 years.

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Key words: Combined valve disease, Left-sided valve disease, Prognosis

Valvular heart disease is a frequent, progressive disease that often requires intervention. Although most patients have single-lesion valve disease (1VaD), combined valve disease (CVaD) is not uncommon, with combined valve procedures covering 12% of all valve operations.¹⁾ In the Euro Heart Survey, CVaD was seen in 20.2% of patients with valvular heart disease and in 16.8% of patients undergoing first-time valve intervention.²⁾ Combined valve surgery is associated with a doubling or more of the perioperative risk^{3,4)} and accounts for a third of all operative deaths after valve surgery.¹⁾ The available literature on valve disease focuses almost exclusively on 1VaD, and there are very limited data on CVaD. Consequently, no specific recommendations have been developed, and the ESC and ACC/AHA guidelines simply state that each case must be considered individually.^{5,6)} Also, there is a lack of data examining the clinical management and prognostic implications of the different combinations of CVaD. Differences in causes, hemodynamic consequences, and patient comorbidity may influence the prognosis in patients with different combinations of left-

sided valve disease, and knowledge on these could possibly influence the management of this patient population.

Hence, using a large single-center clinical database, we aimed to describe the clinical management, i.e., “watchful waiting” or intervention, and prognosis of patients with CVaD according to the specific combinations of each valve lesion including aortic stenosis (AS), aortic regurgitation (AR), and mitral regurgitation (MR).

Methods

Study population: We retrospectively identified patients with CVaD in the echocardiographic database at Gentofte University Hospital - a tertiary care center where >6,400 echocardiographic examinations are performed annually. CVaD was defined as any combination of at least moderate AS, AR, and/or MR. As mitral stenosis only occurred rarely in this population, we did not include mitral stenosis in the analyses. Patients with CVaD were grouped according to number and combination of valve lesions, with two-lesion valve disease (2VaD) representing any combi-

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Figure 1. Patients with AS/MR, AR/MR, and AS/MR. Grey, dead without intervention; dark blue, dead with intervention; blue, alive with intervention; light blue, alive without intervention.

nation of AS, AR, and MR (including combined regurgitant/stenotic disease of the aortic valve), except for cases with three-lesion valve disease (3VaD) that were considered separately. The study included consecutive patients examined from September 22, 2005, to March 11, 2013.

Control groups: For comparison, we identified control groups of patients with 1VaD of at least moderate severity. For this purpose, a random sample from the same echocardiographic database of 50 patients with at least moderate AS, 50 patients with at least moderate MR, and 43 patients with at least moderate AR were identified and included in the study resulting in a total of 143 control patients with 1VaD.

Echocardiography: Echocardiography was performed by skilled echo technicians, cardiology fellows, or cardiologists. Valve lesion severities were graded at the discretion of the interpreting cardiologist. All echocardiographic examinations and valve lesion gradings were reviewed by cardiologists with subspecialty in echocardiography. Lesions graded as borderline mild to moderate were classified as mild, whereas lesions graded as borderline moderate to severe were classified as moderate. Echocardiographic parameters were obtained from the examination report and included valve lesion etiology, left and right ventricular dimensions, and left ventricular ejection fraction. If the etiology of valve lesions was not defined in the report, it was registered as not available (NA). Chamber quantification was done in accordance with the recommendations of the European Association of Echocardiography and the American Society of Echocardiography.⁷⁾

Medical history and follow-up: Medical history and follow-up data were obtained either from medical records from the hospitals in the Capital Region of Denmark or from the Electronic Health Record that covers medical records from all Danish hospitals since it was implemented in 2009. We recorded history of diabetes (diagnosis and/or diabetes treatment with insulin or oral antidiabetic agents), hypertension, chronic obstructive pulmonary disease, ischemic heart disease (history of percutaneous coronary intervention, coronary artery bypass grafting, or coronary artery disease assessed by coronary angiography), aortic disease, peripheral artery disease, and history of stroke.

Date and decision from the most recent multidisciplinary heart team meetings at the tertiary center, at which

indication for valve intervention was discussed for each patient, were registered.

Follow-up data included information on valve interventions and mortality. The endpoints were time to occurrence of event of interest, defined as death and death or valve operation. Valve intervention was registered as open surgery (repair or replacement) or transcatheter intervention.

Statistics: Statistical analyses were performed using SPSS version 22. Categorical variables are summarized as number and percentage and continuous variables as mean $\pm$ SD. Groups were compared using Student's *t*-test and one-way analysis of variance in case of normal distribution and Mann-Whitney *U* test and Kruskal-Wallis tests in case of non-normal distribution. Categorical variables were compared using chi-squared tests.

Time to death or operation is presented by means of Kaplan-Meier survival curves. Log-rank tests were used to compare groups. Estimated 3-year survival was obtained from the Kaplan-Meier analysis. To determine the independent predictors of survival, risk factors were analyzed using univariate and multivariate cox regression analyses and reported as hazard ratio (HR) and 95% confidence intervals. Results were considered statistically significant when $P < 0.05$. In Figure 1, the follow-up time was limited to the first censored patient, i.e., 2.2 years after diagnosis, to illustrate the patients' status with and without intervention (proportion dead and alive).

Ethics: The study was approved by the Danish Data Protection Agency and the Danish Health Authority.

Results

There were 34,296 patients in the database. Of these, 3,493 (9.8%) had any valve disease of at least moderate severity and 122 of these (3.5%) had CVaD, composed of 117 (3.4%) patients with 2VaD and only 5 patients (0.1%) with 3VaD. As survival for 1VaD did not significantly differ between the lesions ($P = 0.34$) the groups were pooled for comparison with CVaD.

Baseline patient characteristics for 1VaD and 2VaD are summarized in Table I. Compared with patients with 1 VaD, patients with AS/MR were older whereas patients with AR/MR and AS/AR were younger; patients with AS/MR and AR/MR were more often female whereas patients

Table I. Baseline Characteristics

	Single valve disease	Two valve disease, combined	P-value	Two valve disease, each combination			P-value
	All	All		AS + AR	AS + MR	AR + MR	
<i>n</i>	143	117		39	50	28	
Age; years, mean (SD)	72.8 (13.7)	75.6 (13.4)	0.06	70.2 (11.8)	83.3 (8.9)	70.2 (15.7)	<0.001
Sex; female, <i>n</i> (%)	52 (36)	48 (41)	0.44	9 (23)	26 (52)	13 (46)	0.03
Comorbidities, <i>n</i> (%)							
Hypertension	74 (52)	48 (41)	0.09	14 (36)	23 (46)	11 (39)	0.27
COPD	19 (13)	14 (12)	0.75	6 (15)	5 (10)	3 (11)	0.87
Diabetes	19 (13)	12 (10)	0.45	5 (13)	6 (12)	1 (4)	0.54
IHD	60 (42)	35 (30)	0.045	9 (23)	17 (34)	9 (32)	0.16
Stroke	16 (11)	15 (13)	0.69	5 (13)	6 (12)	4 (14)	0.97
PAD	2 (1)	8 (7)	0.023	3 (8)	5 (10)	0 (0)	0.018
Aortic disease	10 (7)	9 (8)	0.83	3 (8)	2 (4)	4 (14)	0.42
Symptoms, <i>n</i> (%)							
NYHA I	37 (26)	18 (15)		10 (26)	3 (6)	5 (18)	
NYHA II	40 (28)	25 (21)		13 (33)	10 (20)	2 (7)	
NYHA III	18 (13)	19 (16)		4 (10)	8 (16)	7 (25)	
NYHA IV	1 (0)	3 (3)		0 (0)	1 (2)	2 (7)	
NYHA: N/A	47 (33)	52 (45)		12 (31)	28 (56)	12 (43)	
CCS 0	64 (45)	30 (26)		11 (28)	10 (20)	9 (32)	
CCS I	3 (2)	4 (3)		2 (5)	2 (4)	0 (0)	
CCS II	4 (3)	7 (6)		3 (8)	3 (6)	1 (4)	
CCS III	1 (1)	1 (1)		0 (0)	1 (2)	0 (0)	
CCS: N/A	71 (49)	75 (64)		23 (59)	34 (68)	18 (64)	
Echocardiography							
LVEF, %	44 (14)	39 (15)	0.005	41 (15)	37 (13)	41 (17)	0.36
IVSd, cm	1.1 (0.3)	1.2 (0.2)	0.013	1.3 (0.2)	1.1 (0.2)	1.1 (0.2)	0.014
LVIDd, cm	5.3 (1.1)	5.2 (0.8)	0.21	5.1 (0.8)	5.1 (0.8)	5.5 (0.7)	0.22
LVPWd, cm	1.0 (0.2)	1.1 (0.2)	0.001	1.2 (0.2)	1.1 (0.2)	1.1 (0.1)	0.040
LVM, g	194 (70)	215 (72)	0.033	239 (78)	200 (71)	203 (39)	0.08
RVIDd, cm	3.2 (0.6)	3.0 (0.6)	0.22	3.1 (0.7)	2.9 (0.5)	3.0 (0.7)	0.71
Valve lesion severity, <i>n</i> (%)							
AS: M, M-S	33 (66)	47 (53)		24 (62)	23 (46)	-	
AS: S	17 (34)	42 (47)		15 (38)	27 (54)	-	
MR: M, M-S	31 (62)	64 (82)		-	45 (90)	19 (68)	
MR: S	19 (38)	14 (18)		-	5 (10)	9 (32)	
AR: M, M-S	38 (88)	61 (91)		38 (97)	-	23 (82)	
AR: S	5 (12)	6 (9)		1 (3)	-	5 (18)	

AR indicates aortic regurgitation; AS, aortic stenosis; CCS, Canadian Cardiovascular Society Angina Classification; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; IVSd, interventricular septum end-diastolic thickness; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal end-diastolic diameter; LVM, left ventricular mass; LVPWd, left ventricular posterior wall end-diastolic diameter; M, moderate; M-S, moderate-to-severe; MR, mitral regurgitation; N/A, not available; NYHA, New York Heart Association Functional Classification; PAD, peripheral arterial disease; RVIDd, right ventricular internal end-diastolic diameter; and S, severe.

with AS/AR were more often male. Patients with 2VaD had more peripheral arterial disease and less ischemic heart disease than patients with 1VaD. We found no difference in the presence of hypertension, chronic obstructive pulmonary disease, diabetes, stroke, and aortic disease between the two groups.

Echocardiographic parameters, at time of diagnosis, are also shown in Table I. Patients with 2VaD had a larger left ventricular mass than patients with 1VaD. Mean ejection fraction was reduced in all groups but was found to be significantly lower in 2VaD compared to 1VaD. Etiology of single-valve disease was for AS degenerative (54%), bicuspid (2%), and NA (44%); for MR degenerative (42%), rheumatic (2%), and NA (56%); and for AR bicuspid (14%), secondary to aortic dilatation (12%), and

NA (74%). The etiology of two-valve disease was for AS in AS/MR degenerative (52%), rheumatic (2%), and NA (46%) and for AS in AS/AR degenerative (51%), bicuspid (10%), rheumatic (5%), and NA (34%); for MR in AS/MR degenerative (26%), infectious (6%), rheumatic (2%), and NA (66%) and for MR in AR/MR degenerative (25%), infectious (18%), rheumatic (4%), and NA (53%); for AR in AS/AR degenerative (46%), bicuspid (10%), and NA (44%) and for AR in AR/MR infectious (18%), degenerative (11%), bicuspid (7%), and NA (64%).

Long-term survival: Median follow-up time was 3.4 years (IQR 1.2-5.2 years, range 0-13.6 years). Follow-up was complete. A total of 54 patients with 1VaD and 71 patients with 2VaD died during follow-up. 1VaD had a total mortality during follow-up of 38% compared with 61%

Figure 2. Overall survival of single-lesion valve disease (AS, AR, and MR pooled) and two-lesion valve disease (AS/AR, AS/MR, and AR/MR shown separately).

for 2VaD ($P = 0.001$), whereof AS/AR had a mortality of 39%, AR/MR of 64%, and AS/MR of 76%, $P < 0.001$.

Overall survival for patients with 2VaD was significantly lower than for those with 1VaD with estimated 3-year survival of 52% for 2VaD, compared with 73% for 1VaD, $P < 0.001$. See Figure 2 for Kaplan-Meier survival curves. AR/AS had the best outcome of 2VaD with an estimated 3-year survival of 76.8%, which was not different from that of 1VaD ($P = 0.37$). AR/MR had an intermediate estimated 3-year survival of 61.0%. The combination of AS/MR was associated with the worst outcome compared with other 2VaD ($P < 0.001$) and 1VaD ($P < 0.001$), with an estimated 3-year survival of only 27.7%. Unadjusted and adjusted HRs are listed in Table II.

Event-free survival: Time to death or intervention is illustrated in Figure 3. Event-free survival was significantly higher for 1VaD than for 2VaD ($P < 0.001$), with a median estimated event-free survival time of 1.8 years for 1VaD and 0.4 years for 2VaD. Within 0.5 years, 56% of patients with AS/AR and 50% of patients with AR/MR and AS/MR, compared with 32% of patients with 1VaD, were either dead or had undergone valve intervention.

Intervention: A total of 97 patients underwent valve intervention during follow-up: 51 (35.7%) patients with 1VaD and 46 (39.3%) patients with 2VaD underwent intervention. One patient with 1VaD MR underwent heart transplantation (which was not considered a valve intervention for the purpose of this analysis). Four patients with AS and two patients with AS/AR underwent transcatheter aortic valve implantation; all other interventions were open valve surgery. Concomitant coronary artery bypass grafting was done in 18 (35%) and 10 (22%) patients with 1VaD and 2VaD, respectively.

In 1VaD patients, 23 (46%) patients with AS and 10

(23%) patients with AR underwent aortic valve intervention, whereas 18 (36%) patients with MR underwent isolated mitral valve surgery. In 2VaD patients with AS/AR, 23 (59%) had isolated aortic valve intervention and 1 (3%) had double valve surgery due to concurrent mild-moderate MR. In 2VaD patients with AR/MR, 2 (7%) had isolated aortic valve intervention, 2 (4%) had isolated mitral valve surgery, and 6 (21%) had double valve surgery. In 2VaD patients with AS/MR, 5 (10%) had isolated aortic valve intervention, 2 (2%) had isolated mitral valve surgery and 5 (10%) had double valve surgery.

Overall survival after intervention did not differ between 1VaD and 2VaD ($P = 0.67$); the estimated 3-year survival for patients after intervention were 90% for 1VaD and 83% for 2VaD. AS/MR was associated with the lowest estimated 3-year survival (58%), but the difference between the three types of 2VaD was not statistically significant. Survival time after intervention is illustrated in Figure 4.

Univariate and multivariate analyses of overall survival and survival after intervention are listed in Table II. Multivariate analyses, adjusting for age, sex, ejection fraction, ischemic heart disease, and diabetes, showed that AS/AR was associated with a similar risk, AR/MR with an approx. 1.7-fold increased risk ($P = 0.06$), and AS/MR with a more than 2-fold increased risk ($P < 0.001$) of overall mortality compared to 1VaD. A similar pattern was observed for survival after intervention, but the differences were not significant.

Two-lesion valve disease intervention and survival: Figure 1 shows the distribution of patients alive and dead, with respect to intervention, as a function of time. At 2.2 years of follow-up, the majority of patients in all three groups were either dead or had received valve intervention

Table II. Overall Survival and Survival after Intervention

	Overall survival				Survival after intervention			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Valvular disease								
1VaD (ref)	1		1		1		1	
2VaD: AS/AR	0.83 (0.47-1.48)	0.53	1.03 (0.57-1.87)	0.92	0.63 (0.16-2.46)	0.51	0.67 (0.16-2.76)	0.58
2VaD: AR/MR	1.76 (1.03-3.00)	0.039	1.69 (0.98-2.94)	0.06	1.16 (0.24-5.47)	0.86	1.54 (0.29-8.38)	0.62
2VaD: AS/MR	3.28 (2.16-4.98)	< 0.001	2.37 (1.50-3.74)	< 0.001	2.92 (0.93-9.21)	0.07	3.09 (0.88-10.89)	0.08
Age	1.06 (1.04-1.08)	< 0.001	1.05 (1.03-1.08)	< 0.001	1.03 (0.99-1.08)	0.15	1.03 (0.98-1.08)	0.21
Sex								
Female (ref)	1		1		1		1	
Male	0.68 (0.48-0.98)	0.036	1.05 (0.71-1.53)	0.82	0.88 (0.31-2.47)	0.80	1.13 (0.37-3.44)	0.83
EF								
> 50% (ref)	1		1		1		1	
31%-50%	2.41 (1.44-4.04)	0.001	1.48 (0.87-2.52)	0.15	1.83 (0.56-6.02)	0.32	1.15 (0.32-4.12)	0.83
< 30%	4.09 (2.44-6.84)	< 0.001	3.18 (1.85-5.47)	< 0.001	2.56 (0.68-9.62)	0.16	2.40 (0.61-9.45)	0.21
DM								
No DM (ref)	1		1		1		1	
DM	0.72 (0.41-1.28)	0.26	0.71 (0.40-1.27)	0.25	0.72 (0.21-2.48)	0.60	0.73 (0.20-2.63)	0.63
IHD								
No IHD (ref)	1		1		1		1	
IHD	1.65 (1.16-2.34)	0.006	1.27 (0.87-1.85)	0.22	1.76 (0.69-4.50)	0.24	1.61 (0.58-4.44)	0.36

HR indicates hazard ratio; CI, confidence interval; AR, aortic regurgitation; AS, aortic stenosis; VaD, valve disease. Multivariate analysis: adjusted for age, sex, ejection fraction (EF), diabetes (DM), and ischemic heart disease (IHD) /valvular disease.

Figure 3. Time without intervention or death for single-lesion valve disease and each component of two-lesion valve disease.

(AS/AR: 72%, AR/MR: 64%, and AS/MR: 80%). The group of patients with AS/AR had the highest fraction of patients with intervention within 2.2 years of diagnosis, as 54% had intervention, compared with 36% and 24% of patients with AR/MR and AS/MR, respectively. The group of patients with AS/MR had the highest fraction of death without intervention 2.2 years after diagnosis, followed by AR/MR and AS/AR, with fractions of 56%, 29%, and

18%, respectively. Patients with AS/MR also had the highest fraction of death despite having had valve intervention, as 33% of patients operated were dead 2.2 years after diagnosis, compared with 20% and 5% for AR/MR and AS/AR, respectively.

Three-lesion valve disease: The five patients diagnosed with 3VaD had a survival time of 0.5-4.2 years, and all died during follow-up. Two patients underwent valve in-

Figure 4. Survival time after operation.

intervention and survived 1.7 and 4.2 years after intervention, compared with 0.5, 0.9, and 1.8 years for the three non-operated patients. Concomitant CABG was done in one of two patients who underwent valve intervention.

Discussion

This study of 122 patients represents the largest specific study of left-sided CVaD with long follow-up to date. Though there was a significantly lower overall survival of patients with 2VaD than those with 1VaD, the outcome was comparable after intervention. This, however, depended on the specific combination of the valve diseases: In patients with AS/AR the overall prognosis was similar to 1VaD, and the prognosis after intervention was good. The combination of AR/MR had a slightly worse overall prognosis, but survival after intervention was similar to 1VaD. The combination of AS/MR was associated with the worst outcome as only 25% of the patients received intervention, and even though mortality remained high after intervention, it was even higher without intervention.

In addition, for all combinations, the majority of patients were either dead or had undergone intervention after 2.2 years of follow-up, challenging a “watchful waiting” strategy in the management of these patients - in particular in patients with combinations involving MR.

Prevalence of CVaD: Studies on the combinations of lesions in CVaD are limited,⁸⁾ but all report a higher prevalence than the 3.5% of any valve disease observed in this study. The Euro Heart Survey included 3,532 patients from 25 countries with moderate to severe native valve disease and found that multiple valve disease was present in 20.2%. In this cohort, however, inclusion criteria were less strict including patients with less severe lesions and,

in addition, 51.4% had rheumatic valve disease, which was thus the most common etiology of CVaD in this cohort.²⁾ Also, Unger et al. reported all degrees of MR to be present in 61%-90% and of at least moderate severity in 13%-74% of patients undergoing aortic valve replacement,^{3,4)} and Honda et al. reported concomitant AR of at least moderate severity in 27% of patients with severe AS, in whom non-surgical treatment was initially planned.⁹⁾ Finally, Pai et al. found concomitant MR of grade 3 or higher in 25% of patients with severe AR.¹⁰⁾ The low prevalence of CVaD in our study is probably mainly caused by our strict inclusion and classification criteria. We only included patients with valve lesions that were considered of at least moderate severity, and in order to include only hemodynamically relevant lesions, we excluded lesions deemed borderline mild to moderate. Also, contributing to the lower prevalence, we did not include right-sided valve disease and excluded mitral stenosis. Both mitral stenosis and CVaD in general occur more frequently in other geographical areas with a higher incidence of rheumatic heart disease.

Survival of patients with combined valve disease: Our findings showed that patients with 2VaD were at a higher risk than patients with 1VaD, which is in agreement with previous findings, though only a few studies have reported the overall survival in CVaD. In the Euro Heart Survey, overall 1-year survival was 92.2% in multiple valve disease ($n = 712$), but compared with this study included patients with milder degrees of valve diseases. For patients with symptomatic severe disease, overall 1-year survival was 89.5% compared with 93.7% in patients with asymptomatic severe disease.¹¹⁾ Regarding AS/AR, Honda et al. found that among patients not admitted for surgery, this combination was associated with a worse survival than 1 VaD AS and found that concomitant AR was an independ-

ent predictor of adverse events.⁹⁾ Regarding AR/MR, Pai et al. found that patients with severe AR had an overall 5-year survival rate of 42% in case of concomitant MR grade 3 or higher and found that concomitant MR was an independent predictor of lower survival.¹⁰⁾ Finally, in AS/MR, several studies have found that severe AS with concomitant MR is associated with an increased mortality.¹²⁻¹⁶⁾

Intervention: In our study, we found that intervention was limited to 24%-54% of patients with CVaD. Previous studies on patients with CVaD undergoing intervention are heterogeneous. The Euro Heart Survey reported valve intervention in 48.2% of patients with severe multiple valve disease with a 1-year survival for symptomatic severe multiple valve disease of 92.8% after intervention.¹¹⁾ Lee et al. found that multiple valve surgery was performed in 10.9% of 623,039 patients undergoing cardiac valve surgery, and they reported multiple valve interventions to be associated with the worst outcome and, hence, suggested earlier referral to surgery.¹⁷⁾

Consistent with our findings, Zilberszac et al. followed 71 patients with asymptomatic moderate AS/AR with preserved ejection fraction and found a high intervention rate of 38% within 2 years without any postoperative cardiac deaths.¹⁸⁾

Regarding AR/MR, we observed a low rate of intervention and a decreased survival after intervention. This is somewhat discordant with Pai et al., who found that patients with severe AR and MR grade 3 or higher only had a 5-year survival rate of 36% with non-surgical treatment but 70% after aortic valve replacement (60% also underwent concomitant mitral valve surgery).

For patients with AS and moderate MR, Schubert et al. reported a 5-year survival of 71.7% after aortic valve replacement and concluded that a more aggressive approach to these patients should be considered.¹⁹⁾ Similar results were found by Harling et al.¹³⁾ These observed survival rates after intervention are inconsistent with our results, as we found a 3-year survival of only 58%. Though there was a relatively high mortality rate at 3 years after intervention in this group, deferring from intervention was associated with an even worse outcome. Though the low number of interventions might be explained by a high burden of comorbidities, 50% of the patients with AS/MR were either dead or operated within half a year after diagnosis. Thus, these findings suggest that a greater proportion of these patients might benefit from intervention.

Implications for clinical management: Our data indicate that patients with combined disease of the aortic valve, i. e., AS/AR, underwent timely intervention and with a good prognosis after intervention, supporting the current management of AS/AR. Conversely, our data indicate a poor prognosis of patients with combinations including MR. Mortality was very high without intervention and remained relatively high after intervention, suggesting that a larger proportion of these patients may require earlier intervention - particularly for patients with the combination of AS/MR. Improving survival of patients with combined aortic valve disease and MR might be achieved by lowering the threshold for intervention, e.g., when both valve diseases are of moderate severity and the patient is symptomatic, preceded by a close follow-up for early detection

of disease progression. As the clinical manifestations of multiple valve disease reflect the interaction of present valve lesions⁴⁾ - one lesion might conceal or enhance the severity of the other lesion⁸⁾ - improved diagnostic tools or techniques have been proposed in the assessment of multiple valve disease, e.g., echocardiography with 2D speckle tracking strain analysis as a supplement.¹²⁾

Significant CVaD is a relatively rare disease, and as it covers a heterogeneous group with numerous combinations, studies are limited and each case must be considered individually. This study highlights that patients with combined aortic valve disease and MR have a poor prognosis with a significant potential for improvement and underlines that further studies are needed to improve the management of CVaD.

Limitations: The study was retrospective, and information on clinical status was registered as noted in the patient records. Standardized information on symptom status was therefore not available. Although diabetes was registered if noted in the patient record and/or if medication included antidiabetic medicine, some cases of diabetes might have been missed. Moreover, although the etiology of valve disease, when not defined, was most likely degenerative for AS, it is more uncertain for MR. Echocardiographic parameters were obtained from the original examination report with potential interobserver variability. As many patients with CVaD, in general, had single-valve disease initially, a considerable fraction of CVaD cases in this study might reflect advanced stages of single-valve disease. An important limitation is that patients were from a single referral center. Some patients were diagnosed or followed at other institutions and referred specifically to evaluate if intervention was required; the patients were therefore more likely to have symptomatic and hemodynamically advanced disease at the time of inclusion in our cohort. Overall, the relatively small number of patients studied is a limitation - particularly concerning outcome after intervention.

Conclusions

We found that significant CVaD was relatively rare. Although combined stenotic and regurgitant disease of the aortic valve had outcome similar to single-valve disease, the combination of significant AS or AR with significant MR was associated with reduced survival. The combination of AS and MR carried an especially poor prognosis, and many patients did not receive valve intervention. Our data indicate that a proportion of patients with CVaD may benefit from earlier intervention.

Disclosure

Conflicts of interest: The authors have no conflicts of interest to declare.

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