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CLINICAL RESEARCH
Valvular heart disease

Characteristics, management, and outcomes of patients with multiple native valvular heart disease: a substudy of the EURObservational Research Programme Valvular Heart Disease II Survey

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See the editorial comment for this article 'Transcatheter interventions spark a paradigm change for management of patients with mixed valve disease', by Rebecca T. Hahn *et al.*, https://doi.org/10.1093/eurheartj/ehac229.

Abstract

Aims To assess the characteristics, management, and survival of patients with multiple native valvular heart disease (VHD).

Methods and results Among the 5087 patients with ≥1 severe left-sided native VHD included in the EURObservational VHD II Survey (maximum 3-month recruitment period per centre between January and August 2017 with a 6-month follow-up), 3571 had a single left-sided VHD (Group A, 70.2%), 363 had one severe left-sided VHD with moderate VHD of the other ipsilateral valve (Group B, 7.1%), and 1153 patients (22.7%) had ≥2 severe native VHDs (left-sided and/or tricuspid regurgitation, Group C). Patients with multiple VHD (Groups B and C) were more often women, had greater congestive heart failure (CHF) and comorbidity, higher left atrial volumes and pulmonary pressures, and lower ejection fraction than Group A patients (all $P \leq 0.01$). During the index hospitalization, 36.7% of Group A ($n = 1312$), 26.7% of Group B ($n = 97$), and 32.7% of Group C ($n = 377$) underwent valvular intervention ($P < 0.001$). Six-month survival was better for Group A than for Group B or C (both $P < 0.001$), even after adjustment for age, sex, body mass index, and Charlson index [hazard ratio (HR) 95% confidence interval (CI) 1.62 (1.10–2.38) vs. Group B and HR 95% CI 1.72 (1.32–2.25) vs. Group C]. Groups B and C had more CHF at 6 months than Group A (both $P < 0.001$). Factors associated with mortality in Group C were age, CHF, and comorbidity (all $P < 0.010$).

Conclusion Multiple VHD is common, encountered in nearly 30% of patients with left-sided native VHD, and associated with greater cardiac damage and leads to higher mortality and more heart failure at 6 months than single VHD, yet with lower rates of surgery.

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Structural Graphical Abstract

Key Question

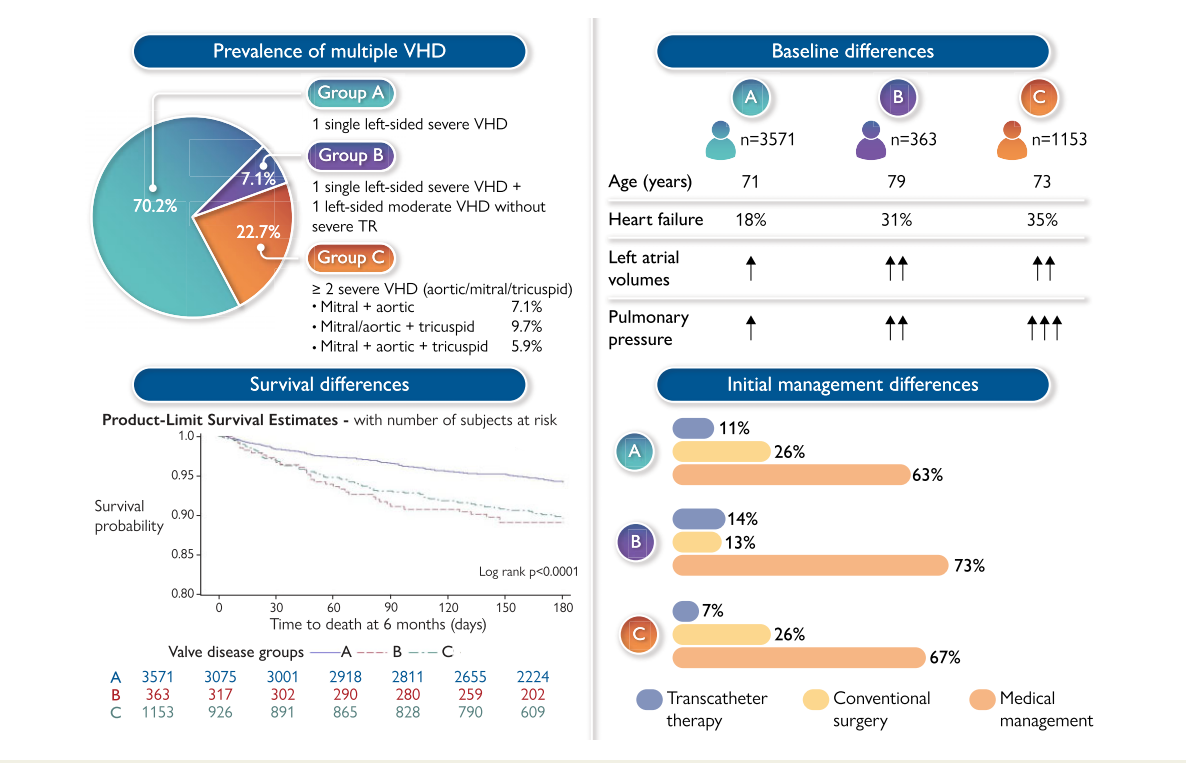
What are the characteristics, management and outcome of patients with multiple valvular heart disease (VHD) in clinical practice in Europe?

Key Finding

Multiple VHD are common and associated with greater cardiac damage, higher mortality, and more heart failure at six months than single VHD, yet they undergo valve intervention less often.

Take Home Message

These results highlight the difficulties in decision-making for patients with multiple VHD for whom current guidelines provide limited recommendations. There is a strong need to improve the management of patients with multiple VHD.



Characteristics, survival and management differences in patients with multiple valvular heart disease.

Keywords Multiple valvular heart disease • Native valvular heart disease • Survival • Management • Cardiac surgery • Valvular Heart Disease II Survey

Introduction

Multiple valvular heart disease (VHD), defined by the presence of a regurgitant and/or stenotic lesions associated with at least two cardiac valves, is a highly prevalent condition.[1–7] In a Swedish nationwide hospital register-based study on the epidemiology of VHD,[1] 10% of patients had multiple VHD. In the first EuroHeart Survey,[2] 16.8% of patients treated by valvular surgery had multiple VHD and, according to the American Society of Thoracic Surgeons Database,[3] 11% of patients undergoing valvular surgery have double-valve procedures.

Yet, despite their prevalence, there is a considerable lack of data in the literature concerning multiple VHD and current knowledge is based on small retrospective studies or expert consensus opinion. Accordingly, current guidelines of the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS)[4] do not allow for evidence-based recommendations to support and guide clinical decision-making in multiple VHD, as most studies on VHD have been focused on single-valve disease.

We addressed these knowledge gaps using data of the EURObservational Research Programme (EORP) VHD II Survey,[5] which was prospectively designed to evaluate current practices for severe valve disease in Europe. An important and unique characteristic of this prospective survey was to include consecutive patients with severe valve disease, whether the VHD was single or multiple.[5] The aims of the study were four-fold: (i) to assess the frequency and distribution of multiple native VHD, (ii) to describe the characteristics of

patients with multiple native VHD, (iii) to evaluate the management, and (iv) to evaluate the survival of patients with multiple native VHD relative to patients with single-native VHD in this large contemporary cohort.

Methods

Study population

The VHD II Survey was conducted between 16 January and 28 August 2017 in 222 centres of 28 European countries. The recruitment period was 3 months for each centre, with no limit to the maximum number of patients enrolled. Therefore, the recruitment period differed across centres but did not exceed 3 months and ended on 28 August 2017, i.e. immediately prior to the publication of the revised ESC/EACTS guidelines on VHD in order to capture an accurate picture of clinical practice before the guideline update. In total, 7247 patients with severe native VHD as defined by echocardiography using an integrative approach according to guidelines[6] or patients with any previous surgical or transcatheter valvular intervention were included, of which, 5219 (72%) had severe native VHD. A more detailed description of the inclusion and data collection has already been published.[5] Written informed consent was given by all participants. The survey was supervised by an executive committee and managed by the EORP department of the ESC, which was in charge of study management, data quality control, and statistical analysis.[5]

Classification of valvular heart disease

Patients were eligible for this study if they had at least one valve affected by severe left-sided native VHD. The study population was then divided into three groups according to the number and severity of valvular lesions.

(1) Group A: single left-sided native VHD, defined as severe VHD (regurgitation, stenosis, or mixed) affecting a single valve without concomitant $\geq$ moderate left-sided VHD on the other ipsilateral valve, without associated severe tricuspid regurgitation (TR).
(2) Group B: severe left-sided native VHD, with a moderate VHD lesion on the other ipsilateral valve (according to echocardiographic criteria), without concomitant severe TR.
(3) Group C: at least two severe native VHD lesions (left-sided and/or TR). This group was divided into three subgroups:
    - C1: severe aortic-valve disease and severe mitral-valve disease, without severe TR.
    - C2: severe aortic-valve disease or severe mitral-valve disease and severe TR.
    - C3: severe aortic-valve disease and severe mitral-valve disease associated with severe TR.

Follow-up and endpoints

Follow-up was planned at 6 months after the date of index patient hospitalization or outpatient visit, either during a patient visit or by contacting the treating physician or the patient. Data collected at 6 months included vital status (and cause of death if applicable), NYHA class, hospitalizations for cardiac reasons, and the performance of a new valvular intervention.[5] The primary endpoint was all-cause mortality and the secondary endpoint was cardiovascular events (cardiovascular death or hospitalization for cardiac reasons).

Statistical analysis

For descriptive analyses, continuous variables are expressed as medians and interquartile ranges and categorical variables as percentages. Comparisons between groups were performed using a χ^2 test for categorical variables and a Kruskal–Wallis test for continuous variables. Six-month survival rates were assessed using the Kaplan–Meier method and compared by the log-rank test. Survival between the groups was compared using multivariable Cox analyses after adjustment for age, sex, body mass index, and comorbidities (assessed by the Charlson index). Factors associated with mortality and cardiovascular events for patients with multiple left-sided VHD (Groups B and C) were identified by Cox multivariable analysis. After inclusion of significant variables in univariate analyses ($P < 0.10$), a backward model selection was performed at level 0.05 to identify variables to include in the multivariate model. The proportional hazards assumption was confirmed with a Schoenfeld residuals test and their graphical validation over time. A two-sided P-value of <0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Among the 5219 patients of the survey with severe native VHD, 5087 fulfilled the inclusion criteria of this study. The distribution of VHD is presented in *Table 1*. Among patients with single left-sided severe native VHD and no severe TR (Group A, $n = 3571$), aortic stenosis (AS) was most frequent (57.2%), followed by mitral regurgitation (MR; 22.4%), aortic regurgitation (AR; 7.3%), mixed aortic VHD (AS + AR, 6.4%), mitral stenosis (MS; 4.9%), and mixed mitral VHD (MR + MS, 1.8%). Among patients with severe left-sided native VHD with a moderate VHD lesion on the other ipsilateral valve without concomitant severe TR (Group B, $n = 363$), the most frequent association was severe AS and moderate MR (54.0%), followed by severe AS and moderate MS (12.4%). Of the 1153 patients with $\geq$2 severe native VHDs (left-sided and/or TR, Group C), 361 had two severe left-sided native VHDs without severe TR (C1, 31.3%), mainly severe AS combined with severe MR (36.0%), 492 had one severe single left-sided native VHD associated with severe TR (C2, 42.7%), mainly severe MR (58.7%), and 300 had two severe left-sided native VHDs and severe TR (C3, 26.0%), with the most common association being severe AS + severe MR + severe TR (24.7%; Supplementary material online, *Table S1*).

Baseline characteristics of the study population are detailed in *Table 1*. Patients with multiple valve diseases (Groups B and C) were more often women, more frequently had congestive heart failure (CHF) and atrial fibrillation at inclusion and lower creatinine clearance, and had been more frequently hospitalized for heart failure in the previous year than patients with single VHD (Group A). They also had more severe comorbidity, with a higher Charlson index and EuroSCORE II than patients with single VHD (Group A), and were more frequently under oral anti-coagulation therapy, diuretics, beta-blockers, and digoxin (*Table 1*). Patients with multiple valve diseases (Groups B and C) had greater left atrial volumes and pulmonary pressures, and a lower left ventricular ejection fraction (LVEF) than patients with single VHD (Group A). Age was comparable between patients in Groups A and C (71 vs. 73 years, $P = 0.90$) but was higher for those of Group B (79 years, $P < 0.001$).

A comparison of the baseline characteristics between subgroups C1, C2, and C3 is presented in Supplementary material online,

Table 1 Baseline characteristics of the study population

Patient characteristics	Group A N = 3571 (70.2%)	Group B N = 363 (7.1%)	Group C N = 1153 (22.7%)	Overall *P*-value	*P*-value (A vs. B)	*P*-value (A vs. C)
Age (years), median (Q1–Q3)	71.0 (62.0–80.0)	79.0 (71.0-84.0)	73.0 (62.0–80.0)	<0.001	<0.001	0.905
Female sex, *n* (%)	1515 (42.4)	209 (57.6)	620 (53.8)	<0.001	<0.001	<0.001
Body mass index (kg/m^2), median (Q1–Q3)	27.2 (24.2–30.5)	27.0 (23.6–30.4)	26.3 (23.4–29.7)	<0.001	0.281	<0.001
Hospitalization for heart failure during the last year, *n* (%)	620/3570 (17.4)	92/363 (25.3)	322/1153 (27.9)	<0.001	<0.001	<0.001
NYHA class, *n* (%)				<0.001	<0.001	<0.001
I	752 (21.1)	42 (11.6)	149 (12.9)			
II	1502 (42.1)	131 (36.1)	366 (31.7)			
III	1187 (33.2)	159 (43.8)	538 (46.7)			
IV	130 (3.6)	31 (8.5)	100 (8.7)			
Congestive heart failure at baseline, *n* (%)	641 (18.0)	114 (31.4)	404 (35.0)	<0.001	<0.001	<0.001
Atrial fibrillation, *n* (%)	641/3567 (18.0)	113/363 (31.1)	442/1152 (38.4)	<0.001	<0.001	<0.001
Creatinine clearance (mL/min), median (Q1–Q3)	69.7 (50.1–92.8)	54.2 (40.9–78.8)	61.5 (43.5–83.4)	<0.001	<0.001	<0.001
Risk factors, *n* (%)						
Hypertension	2482 (69.5)	268 (73.8)	779 (67.6)	0.074	0.087	0.215
Dyslipidaemia	1736 (48.6)	196 (54.0)	525 (45.5)	0.015	0.051	0.069
Diabetes mellitus	795/3570 (22.3)	85/363 (23.4)	271/1153 (23.5)	0.639	0.617	0.383
Comorbidities						
Chronic pulmonary disease, *n* (%)	396/3548 (11.2)	57/361 (15.8)	139/1141 (12.2)	0.029	0.009	0.345
Previous myocardial infarction, *n* (%)	329/3547 (9.3)	44/361 (12.2)	140/1136 (12.3)	0.005	0.073	0.003
Charlson comorbidity index, median (Q1–Q3)	4.0 (2.0–5.0)	5.0 (3.0–7.0)	4.0 (2.0–5.0)	<0.001	<0.001	<0.001
EuroSCORE II (%), median (Q1–Q3)	1.7 (1.0–3.2)	3.1 (1.8–5.9)	2.4 (1.3–4.7)	<0.001	<0.001	<0.001
Type of valve disease, *n* (%)						
Native valve disease aetiology				<0.001	<0.001	<0.001
Degenerative	2455/3477 (70.6)	286/359 (79.7)	669/1125 (59.5)			
Rheumatic	331/3477 (9.5)	37/359 (10.3)	231/1125 (20.5)			
Congenital	262/3477 (7.5)	12/359 (3.3)	28/1125 (2.5)			
Prior endocarditis	22/3477 (0.6)	0/359 (0.0)	6/1125 (0.5)			
Secondary MR	220/3477 (6.3)	10/359 (2.8)	131/1125 (11.6)			
Other	187/3477 (5.4)	14/359 (3.9)	60/1125 (5.3)			
Drug therapy at admission, *n* (%)						
Oral anti-coagulant therapy				<0.001	<0.001	<0.001
VKA	571 (16.0)	91 (25.1)	339 (29.4)			
NOAC	256 (7.2)	43 (11.8)	140 (12.1)			
Diuretics	1764/3503 (50.4)	240/360 (66.7)	768/1118 (68.7)	<0.001	<0.001	<0.001
Beta-blockers	1873/3501 (53.5)	230/360 (63.9)	729/1116 (65.3)	<0.001	<0.001	<0.001
ACE inhibitors/ARBs/MRAs	1839/3500 (52.5)	224/360 (62.2)	608/1116 (54.5)	0.002	<0.001	0.259

Continued

Table 1 *Continued*

Patient characteristics	Group A N = 3571 (70.2%)	Group B N = 363 (7.1%)	Group C N = 1153 (22.7%)	Overall *P*-value	*P*-value (A vs. B)	*P*-value (A vs. C)
Digoxin	168/3503 (4.8)	27/360 (7.5)	135/1117 (12.1)	<0.001	0.026	<0.001
Echocardiography						
LV end-diastolic diameter (mm), median (*Q*1–*Q*3)	52.0 (46.0–58.0)	51.0 (45.0–57.0)	52.0 (47.0–60.0)	0.001	0.050	0.006
LV end-systolic diameter (mm), median (*Q*1–*Q*3)	35.0 (29.0–41.0)	34.0 (29.0–42.0)	36.0 (31.0–44.0)	<0.001	0.644	<0.001
Left atrial volume (mL/m^2), median (*Q*1–*Q*3)	43.0 (32.0–59.0)	51.0 (40.0–68.0)	52.0 (40.0–71.5)	<0.001	<0.001	<0.001
LV ejection fraction <30%, *n* (%)	140/3513 (4.0)	27/362 (7.5)	95/1122 (8.5)	<0.001	0.002	<0.001
Systolic pulmonary arterial pressure groups (mmHg), *n* (%)				<0.001	<0.001	<0.001
<30	1388/3256 (42.6)	63/354 (17.8)	180/1069 (16.8)			
30–55	1488/3256 (45.7)	204/354 (57.6)	559/1069 (52.3)			
>55	380/3256 (11.7)	87/354 (24.6)	330/1069 (30.9)			

Overall *P*-value corresponds to the comparison of all three Groups A–C. *P*-values for pairwise comparisons are displayed in the next column.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LV, left ventricular; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NOAC, non-vitamin K antagonist oral anti-coagulant; NYHA, New York Heart Association; *Q*1–*Q*3, 25th–75th percentile; VKA, vitamin K antagonist.

Table S2. Patients with a single severe left-sided VHD and severe TR (C2) were younger, had more frequent CHF and atrial fibrillation, and received oral anti-coagulation therapies more frequently than C1 and C3 patients. Patients with three severe VHDs (C3) had higher pulmonary pressure than C1 patients (Supplementary material online, *Table S2*).

Management of patients

The cardiac investigations conducted in the study population are summarized in *Table 2*. There were no significant differences between Groups A and B in terms of the cardiac investigations carried out. Trans-oesophageal echocardiography and cardiac catheterization were more often performed for Group C than Group A (both $P < 0.001$) and Group B ($P = 0.025$ and $P < 0.001$, respectively). Among Group C patients, cardiac catheterization was more frequently used for patients with three severe VHDs (C3) than for the two other subgroups (Supplementary material online, *Table S3*).

A valvular intervention was scheduled or performed for 66.5% of patients of Group A ($n = 2375$), 58.4% of Group B ($n = 212$), and 51.6% of Group C ($n = 595$) ($P < 0.001$). During the index hospitalization, 36.7% of patients of Group A ($n = 1312$), 26.7% of Group B ($n = 97$), and 32.7% of Group C ($n = 377$) underwent valvular intervention ($P < 0.001$). Patients in Groups B and C were more frequently in a critical preoperative state than those of Group A (both $P < 0.001$). The type of procedure is reported in *Table 3* and Supplementary material online, *Table S4*. Surgical procedures on both the mitral and aortic valves, tricuspid valve repair, atrial fibrillation (AF) ablation, and left atrial appendage exclusion were more common among patients with severe multiple VHD (*Table 3*). In-hospital mortality of patients who underwent valvular intervention was 2% for Group A, 1.1% for Group B, and 2.2% for Group C ($P = 0.76$): 2.9% for C1, 2.0% for C2, and 1.9% for C3 ($P = 0.82$). Overall, 893 patients of the study population (17.5%) had no indication for an intervention (surgical or trans-catheter) according to the responsible practitioners, and 43.5% of patients who had an intervention scheduled but not performed during the index hospitalization underwent valvular intervention during the 6-month follow-up (45.5% in Group A, 44.2% in Group B, and 31.1% in Group C).

Outcomes

The clinical follow-up at 6 months for the study population is presented in *Table 4* and Supplementary material online, *Table S5*. Among patients who were alive at discharge (or outpatient) and whose vital status was known at 6 months ($n = 4409$), 297 (6.7%) died. Six-month mortality was higher for patients in Groups B and C (multiple valve disease) than for those with single-valve disease (Group A; log-rank $P < 0.001$ and <0.001, respectively; *Figure 1*). After adjustment for age, sex, body mass index, and the Charlson comorbidity index, survival was significantly different for Group B patients [adjusted hazard ratio (HR) 95% confidence interval (CI) 1.62 (1.10–2.38)] and Group C patients [adjusted HR (95% CI) 1.72 (1.32–2.25)] compared with those of Group A (Supplementary material online, *Figure S1*). There was no significant difference in 6-month survival among patients with single severe left-sided valve disease (Group A) according to the type of valve disease (overall log-rank $P = 0.056$), in particular after adjustment for age, sex, body mass index, and Charlson comorbidity index ($P = 0.56$).

There were no differences among groups in terms of cause of death (i.e. cardiac or non-cardiac cause of death). At 6 months, patients in Groups B and C were in a higher NYHA class than those of Group A (both $P < 0.001$) and were more often hospitalized for heart failure (both $P < 0.001$; *Table 4*). After adjustment for

Table 2 Investigations performed in the study population

	Group A N = 3571 (70.2%)	Group B N = 363 (7.1%)	Group C N = 1153 (22.7%)	Overall P-value	P-value (A vs. B)	P-value (A vs. C)
Trans-oesophageal echocardiography	692 (19.4)	71 (19.6)	292 (25.3)	<0.001	0.934	<0.001
Coronary angiography	1980 (55.4)	205 (56.5)	611 (53.0)	0.289	0.707	0.145
Cardiac catheterization	270 (7.6)	23 (6.3)	155 (13.4)	<0.001	0.397	<0.001
Magnetic resonance imaging	66 (1.8)	3 (0.8)	19 (1.6)	0.353	0.158	0.656
Computed tomography scan	689 (19.3)	85 (23.4)	119 (10.3)	<0.001	0.060	<0.001
Stress test	128 (3.6)	8 (2.2)	14 (1.2)	<0.001	0.170	<0.001

Values are presented as *n* (%).

age, sex, body mass index, and the Charlson comorbidity index, there was a significant difference in terms of cardiovascular events (cardiovascular death or hospitalization for cardiac reasons) for Group B patients [adjusted HR (95% CI) 1.28 (1.05–1.56)] but not for Group C patients [adjusted HR (95% CI) 1.07 (0.93–1.23)] compared with those of Group A.

Factors associated with 6-month mortality among Group B patients identified by Cox univariable analysis were age, Charlson index, CHF, LVEF <30%, and systolic pulmonary artery pressure >55 mmHg (all $P < 0.030$). After multivariable Cox analysis, only age [HR (95% CI) 1.05 (1.00–1.09)] and CHF [HR (95% CI) 2.62 (1.34–5.13)] remained independently associated with 6-month mortality (Supplementary material online, *Table S6*). By Cox univariable and multivariable analysis, no variables were significantly associated with the occurrence of cardiovascular events (cardiovascular death or hospitalization for cardiac reasons) in Group B patients.

The three subgroups of patients with multiple VHD (C1, C2, and C3) experienced higher mortality than patients with single-valve disease (log-rank $P < 0.001$) but there were no differences in survival between these subgroups (log-rank $P = 0.51$; Supplementary material online, *Table S5*, *Figure 2*). After adjustment, there was no significant difference in cardiovascular events between C1, C2, and C3 subgroups (all $P > 0.20$). Overall, the NYHA class of patients with multiple VHD improved at 6 months in all three subgroups (Supplementary material online, *Figure S2*). Among patients with severe multiple VHD (Group C), factors associated with 6-month mortality identified by Cox univariable analysis were age, Charlson index, CHF at baseline, LVEF <30% (all $P < 0.001$), and systolic pulmonary artery pressure >55 mmHg ($P = 0.004$). After multivariable Cox analysis, age, Charlson index, and CHF remained independently associated with 6-month mortality (*Table 5*). In Cox univariable analysis, factors associated with cardiovascular events (cardiovascular death or hospitalization for cardiac reasons) among patients with severe multiple VHD (Group C) were age, CHF at baseline, Charlson index, and systolic pulmonary artery pressure >55 mmHg (all $P <$ 0.001). After multivariable Cox analysis, age, body mass index, CHF, and systolic pulmonary artery pressure >55 mmHg were independently associated with the occurrence of cardiovascular events (Supplementary material online, *Table S7*).

In Group A, B and C patients with no indication for an intervention and patients who underwent an intervention during the survey period had better 6-month survival than those in whom there was a theoretical indication but no intervention was performed (Supplementary material online, *Figures S3–S5*).

Discussion

This prospective study, based on a contemporary European survey specifically designed to evaluate the management of patients with VHD in a wide range of centres, is the first large report to assess the characteristics, outcomes, and management of patients with multiple VHD. Our results are of great importance and can be summarized as follows: (i) multiple VHD is common, encountered in nearly 30% of patients with left-sided native VHD, (ii) patients with multiple VHD exhibit higher mortality and more heart failure at 6 months than those with single VHD, (iii) patients with severe left-sided native VHD and a moderate lesion on the other ipsilateral valve are older, with more comorbidities, and are less frequently referred for surgery but more often for trans-catheter therapies than those with single VHD, and (iv) patients with multiple severe VHD are more symptomatic and present with more cardiac repercussions, yet undergo far fewer valvular interventions than single-VHD patients, despite being of comparable age (*Structured Graphical abstract*). The reasons for such differences in management and outcomes are likely manifold and should be investigated.

Challenges in the evaluation and management of multiple valvular heart disease

The evaluation and management of multiple VHD is challenging.[4,7–11] The presence of a stenotic or regurgitant lesion on another valve may influence the haemodynamics of any VHD.[7–10] Indeed, all 'flow-dependent' or 'loading condition-dependent' echocardiographic parameters of quantification are sources of error in the context of multiple VHD.[12] Multi-modality imaging is often required by trans-oesophageal echocardiography, stress echocardiography, cardiac magnetic resonance, cardiac computed tomography, and cardiac catheterization in difficult cases.[8] Accordingly, in our study, patients with severe multiple VHD (Group C) had more cardiac investigations than those with single VHD (Group A).

Table 3 Type of procedure for patients who underwent valve intervention during the survey period

	Group A N = 1312	Group B N = 97	Group C N = 377	Overall P-value	P-value (A vs. B)	P-value (A vs. C)
Critical preoperative state	32 (2.4)	10 (10.3)	24 (6.4)	<0.001	< 0.001	<0.001
Conventional surgery						
Aortic-valve replacement	631 (48.1)	38 (39.2)	148 (39.3)	0.004	0.090	0.002
Mitral-valve replacement	126 (9.6)	15 (15.5)	131 (34.7)	<0.001	0.063	<0.001
Aortic-valve repair	19 (1.4)	0 (0.0)	9 (2.4)	0.191	0.636	0.208
Mitral-valve repair	147 (11.2)	6 (6.2)	86 (22.8)	<0.001	0.125	<0.001
Trans-catheter						
TAVI	345 (26.3)	50 (51.5)	66 (17.5)	<0.001	<0.001	<0.001
Trans-catheter mitral therapy (%)	49 (3.7)	1 (1.0)	13 (3.4)	0.377	0.252	0.794
Conventional surgery: associated valvular procedures						
Aortic-valve replacement + mitral-valve replacement	2/918 (0.2)	8/46 (17.4)	44/298 (14.8)	<0.001	<0.001	<0.001
Aortic-valve replacement + mitral-valve repair	3/918 (0.3)	5/46 (10.9)	26/298 (8.7)	<0.001	<0.001	<0.001
Aortic-valve repair + mitral-valve replacement	0/918 (0.0)	0/46 (0.0)	5/298 (1.7)	0.002	NA	<0.001
Aortic-valve repair + mitral-valve repair	0/918 (0.0)	0/46 (0.0)	1/298 (0.3)	0.273		
Tricuspid valve repair	76/918 (8.3)	7/46 (15.2)	143/298 (48.0)	<0.001	0.106	<0.001
Tricuspid valve replacement	3/918 (0.3)	0/46 (0.0)	5/298 (1.7)	0.066		
Associated procedures						
Percutaneous coronary intervention	51 (3.9)	5 (5.2)	7 (1.9)	0.114	0.585	0.056
CABG	191/918 (20.8)	16/46 (34.8)	61/298 (20.5)	0.072	0.024	0.901
Supra-coronary replacement	41/918 (4.5)	1/46 (2.2)	12/298 (4.0)	0.733	0.716	0.747
Root replacement	29/918 (3.2)	2/46 (4.3)	11/298 (3.7)	0.838	0.656	0.654
AF ablation	47/918 (5.1)	2/46 (4.3)	44/298 (14.8)	<0.001	1.000	<0.001
LAA exclusion	71/918 (7.7)	2/46 (4.3)	64/298 (21.5)	<0.001	0.571	<0.001

Values are presented as *n* (%). Overall *P*-value corresponds to the comparison of all three Groups A, B, and C. *P*-values for pairwise comparisons are displayed in the next column. AF, atrial fibrillation; CABG, coronary artery bypass grafting; LAA, left atrial appendage; TAVI, trans-catheter aortic-valve implantation.

The correction of a single-valve lesion can exacerbate, or, on the contrary, reduce the severity of another through changes in loading conditions and reverse remodelling.[7,8] For example, secondary MR usually decreases after the correction of AS due to the drop in left ventricular (LV) pressure. Hence, several considerations should be addressed by the heart team in determining the optimal management strategy of patients with multiple VHD: the risk of combined surgery,[2,3,13] the type of intervention, the morbidity of valvular prostheses[14] and iterative valvular replacements,[15] the potential reduction in MR after correction of a downstream valve lesion,[16] the patient's wishes, his/her surgical risk and frailty, and the possibility for percutaneous treatment.[9] Therefore, careful quantification of the risk, taking into account potential diagnostic pitfalls,[7] and careful assessment of the consequences of valve lesions are required before considering an intervention and defining the type for patients with multiple VHD. Because of these challenges, the management and follow-up of patients with multiple VHD must be performed by experienced teams in heart valve clinics or centres.[17,18]

Association of severe and moderate left-sided valvular heart disease

The prevalence of severe and moderate left-sided VHD (without severe TR) among patients with VHD is not known, as most studies on this topic did not report VHD severity[1] or focused on the combination of a severe VHD with another 'at least moderate VHD' and did not exclude patients with severe TR.[19–22] For example, the association of severe AS with moderate or severe MR is frequent, reaching up to 20% of patients undergoing aortic-valve replacement [surgical or trans-catheter aortic-valve implantation (TAVI)][19–21] and is associated with poor outcomes.[20,22]

The prevalence, management, and outcomes of combining severe AS with 'only' moderate MR are not well described. Such an

Table 4 Six-month clinical follow-up in the study population

	Group A $N = 3571$ (70.2%)	Group B $N = 363$ (7.1%)	Group C $N = 1153$ (22.7%)	Overall *P*-value	*P*-value (A vs. B)	*P*-value (A vs. C)
Vital status						
Dead	179/3141 (5.7)	31/324 (9.6)	87/944 (9.2)	<0.001	0.005	<0.001
Cause of death				0.639	0.950	0.352
Cardiac	112/179 (62.6)	20/31 (64.5)	48/87 (55.2)			
Non-cardiac	40/179 (22.3)	7/31 (22.6)	20/87 (23.0)			
Unknown	27/179 (15.1)	4/31 (12.9)	19/87 (21.8)			
At 6-month follow-up						
NYHA class				<0.001	<0.001	<0.001
I	1262/2754 (45.8)	85/274 (31.0)	258/810 (31.9)			
II	1163/2754 (42.2)	120/274 (43.8)	379/810 (46.8)			
III	300/2754 (10.9)	68/274 (24.8)	147/810 (18.1)			
IV	29/2754 (1.1)	1/274 (0.4)	26/810 (3.2)			
Hospitalization for cardiac reasons	816/2877 (28.4)	103/290 (35.5)	230/834 (27.6)	0.027	0.011	0.657
Hospitalization for heart failure	148/2876 (5.1)	34/290 (11.7)	100/834 (12.0)	<0.001	<0.001	<0.001

Values are presented as *n* (%). Overall *P*-value corresponds to the comparison of all three Groups A–C. *P*-values for pairwise comparisons are displayed in the next column.
NYHA, New York Heart Association.

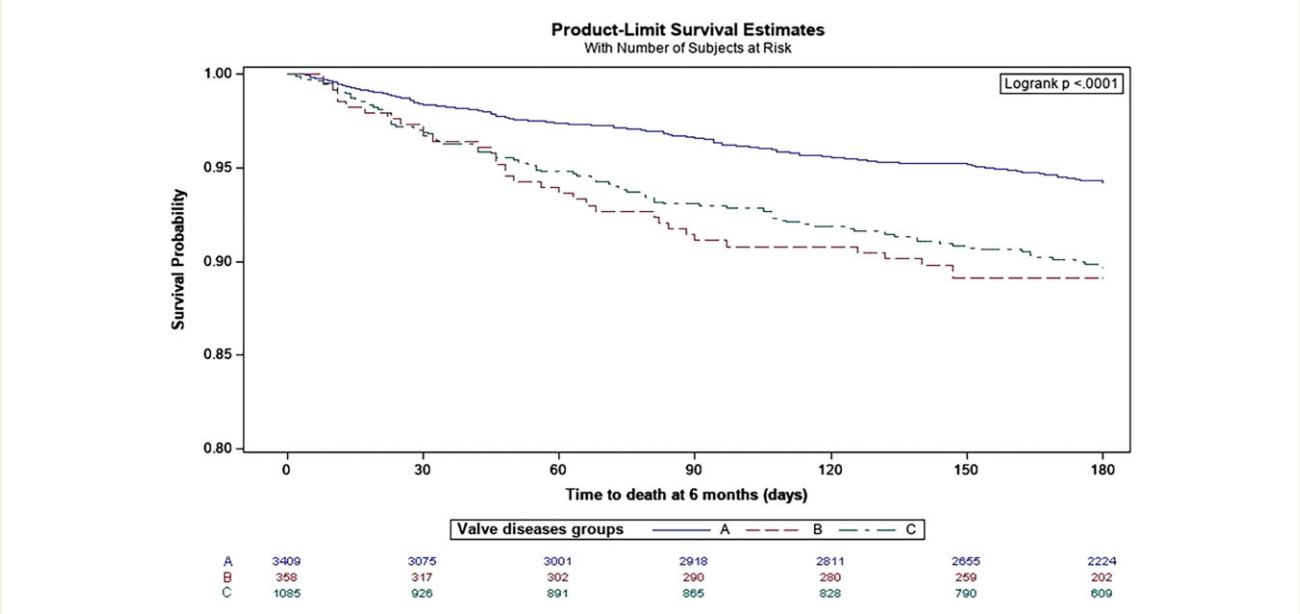


Figure 1 Kaplan–Meier overall survival curves at 6 months between Groups A, B, and C.

association of a severe left-sided VHD and a moderate lesion on the other left-sided valve, without severe TR, found in 7.1% of the study population, consisted mainly of the combination of severe AS and moderate MR (54%) and was essentially of degenerative origin (79.7%). These patients were older, had more comorbidities, were consequently less often referred for surgery but more often for TAVI, and had higher 6-month mortality than those of Group A. They still experienced greater 6-month mortality after adjusting for potential confounders than patients with single-valve disease. The associated management of the moderate lesion in case of surgery on a severe valvular lesion is not well codified, and only a study comparing the two strategies (treatment of the moderate lesion at

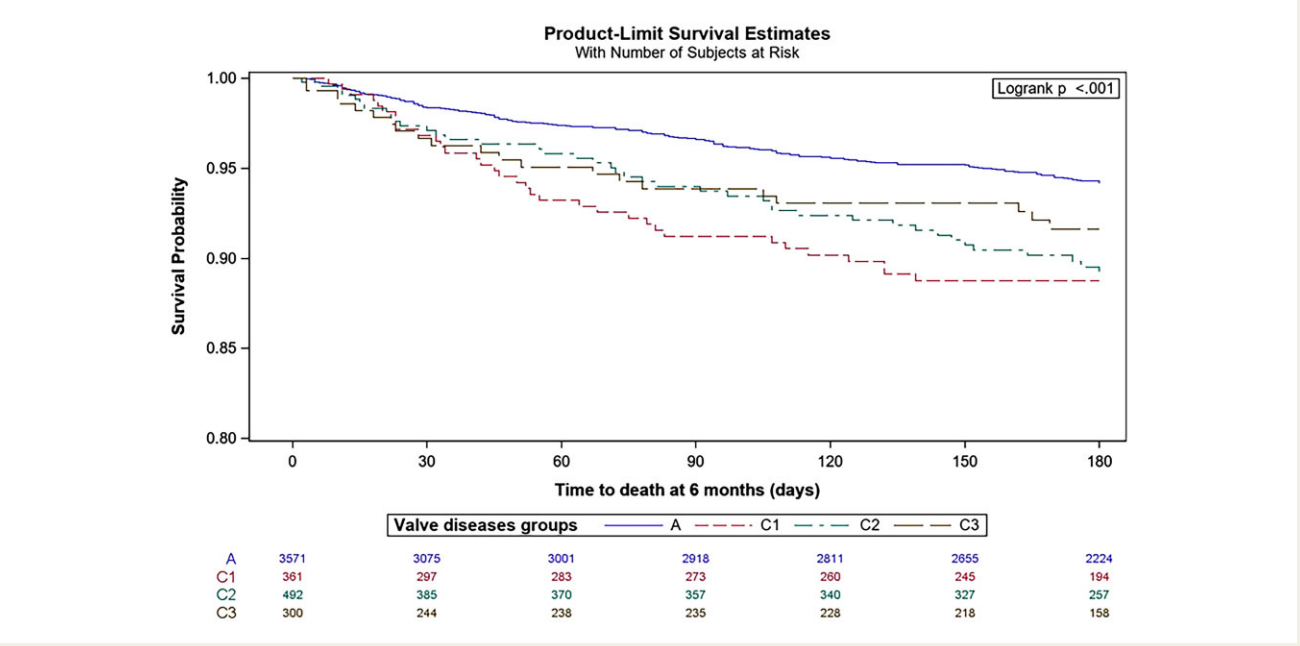


Figure 2 Kaplan–Meier overall survival curves at 6 months between Groups A, C1, C2, and C3.

Table 5 Factors associated with 6-month mortality in multiple severe valvular heart disease (Group C)

Variable	Univariable analysis HR (95% CI)	*P*-value	Multivariable analysis HR (95% CI)	*P*-value
Age (per year)	1.04 (1.02–1.06)	<0.001	1.04 (1.02–1.06)	<0.001
Gender (female vs. male)	0.85 (0.57–1.27)	0.424	—	—
Body mass index (kg/m^2)	0.98 (0.94–1.02)	0.361	—	—
Congestive heart failure at baseline (yes vs. no)	2.63 (1.75–3.94)	<0.001	2.39 (1.58–3.63)	<0.001
Atrial fibrillation/flutter (yes vs. no)	0.85 (0.56–1.29)	0.446	—	—
LVEF (≥30% vs. <30%)	0.38 (0.23–0.63)	<0.001	—	—
Systolic pulmonary artery pressure (mmHg)				
>55 vs. <30	3.06 (1.43–6.54)	0.004	—	—
(30–55) vs. <30	1.80 (0.85–3.82)	0.126	—	—
Charlson index (per unit)	1.08 (1.05–1.11)	<0.001	1.06 (1.02–1.11)	0.008

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

the same time as the severe lesion vs. waiting until the moderate lesion is severe) could answer this interesting question. According to guidelines, surgical aortic-valve replacement should be considered in patients with moderate AS undergoing another valve intervention (Class IIaC) after heart team discussion.[4] In contrast, there are no recommendations regarding the management of moderate AR during mitral surgery or the management of moderate mitral VHD during aortic-valve surgery. Nevertheless, the risk of combined intervention should be weighed by the heart team against the evolution of untreated valve disease and the inherent risk of subsequent intervention.[4] Further studies are required to understand the reasons for such poor survival to improve the management of these high-risk patients.

Combination of multiple severe valvular heart disease

Data on multiple severe VHD are scarce because most studies on VHD were focused on single-valve disease. Furthermore, the heterogeneous nature of multiple VHD due to the various possible combinations, the interactions between valve diseases in terms of echocardiographic quantification, and their evolution after surgical

or trans-catheter correction have hampered the performance of studies on this topic.[7,8] Consequently, even the most recent European[4] and American[11] guidelines on multiple VHD are based either on data from small retrospective studies or expert consensus opinion and are therefore mostly of Grade C level. According to European guidelines, the association of multiple severe VHD can be encountered in rheumatic and congenital heart disease, as well as, less frequently, degenerative valve disease.[4] In the present survey, this association was prevalent, encountered in 22.7% of patients, and consisted mainly of degenerative causes (59.5% vs. 20.5% rheumatic). Despite an age comparable with that of patients with a single VHD, patients in this group were at more advanced stages of their disease, with more heart failure, LV dysfunction, and pulmonary hypertension, and exhibited greater 6-month mortality. These differences can be partially explained by the difficulties of the echocardiographic quantification of multiple valve diseases, with the risk of underestimating the severity of valvular lesions[4,7–11] and therefore of delayed diagnosis. Furthermore, the operative risk of multiple VHD[2,3,23,24] may discourage physicians from considering valvular surgery. Surgery is probably performed too late and insufficiently. Indeed, only 32.7% of patients with severe multiple VHD (Group C) underwent a valvular intervention (surgical or percutaneous) during the index hospitalization and 18.9% had a procedure scheduled later, of which only 31.1% actually benefited during the survey period. Our results do not allow determining whether the poor prognosis of patients with severe multiple VHD is related to the fact that they are undertreated (less frequent intervention or sometimes just partial treatment with correction of only a single VHD), that they are treated too late when the operative risk is too important, or that they present an excess risk of mortality despite appropriate treatment, induced by the sole fact of the valvular prejudice. Nevertheless, patients with multiple severe VHD who underwent valvular intervention during the survey period had better outcomes than those managed conservatively. These findings highlight the particular difficulties in decision-making for patients with multiple VHD, for whom current guidelines provide limited recommendations due to the low level of evidence in the literature.[4,11]

Limitations

The VHD II Survey was a voluntary survey and not a comprehensive population-based epidemiological study. Therefore, it may not be completely representative and we cannot exclude a certain level of selection bias. Nevertheless, the inclusion of 28 countries, with a wide range of healthcare facilities, provides a comprehensive overview of the contemporary presentation and management of VHD in Europe.[5] The fact that patients with moderate concomitant ipsilateral valve disease have a worse prognosis than patients with single-valve disease needs to be confirmed by larger studies, because this group was of relatively modest size and represented only 7.1% of the study population. The absence of valvular intervention in a significant number of patients is probably related to multiple causes such as refusals from patients or a procedural risk considered too important by clinicians (elderly patients with numerous comorbidities). These causes are only hypothetical and the specific reasons for the absence of intervention were not collected in this survey. However, this low rate of intervention underlines that guidelines are not well followed in practice and that there is a need for a better management of patients with multiple VHD in Europe. Further studies are needed in Europe and other continents, as aetiologies can vary considerably between countries, especially in developing countries in which rheumatic aetiology is predominant, with very different patient profiles, management, and prognoses than in Europe. The main challenge in the investigation of multiple VHD resides in the heterogeneity of combinations of valve disease and variability in severity and mechanisms among valvular lesions, leading to a wide range of clinical situations.

Conclusion

This unique contemporary survey enabled the assessment of the frequency, characteristics, management, and prognosis of patients with multiple VHD in various healthcare structures in Europe. Our study shows that multiple VHD is frequent and associated with greater cardiac damage than single VHD, with higher left atrial volumes and pulmonary artery pressure and lower LVEF, even if the second VHD is of only moderate severity. Patients with multiple VHD experience higher mortality and more heart failure at 6 months than those with single VHD and yet undergo valvular surgery less frequently. Further studies are required to more closely investigate the differences between specific associations of VHD in patients with multiple VHD and provide guidance for decision-making in indications for interventions.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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