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.

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.\(^5\) 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.\(^6\) Combined valve surgery is associated with a doubling or more of the perioperative risk\(^7,8\) and accounts for a third of all operative deaths after valve surgery.\(^9\) 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.\(^5,10\) 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-
nation of AS, AR, and MR (including combined regurgi-
tant/stenotic disease of the aortic valve), except for cases
with three-lesion valve disease (3VaD) that were consid-
ered 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 sever-
ity. 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 cardiolo-
gists. Valve lesion severities were graded at the discretion
of the interpreting cardiologist. All echocardiographic ex-
aminations and valve lesion gradings were reviewed by
cardiologists with subspecialty in echocardiography. Le-
sions graded as borderline mild to moderate were classi-
ced as mild, whereas lesions graded as borderline moder-
to severe were classified as moderate. Echocardi-
ographic parameters were obtained from the examina-
tion 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).

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 re-
cords 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 multidiscipli-

dary 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 inter-
ventions and mortality. The endpoints were time to occur-
rence of event of interest, defined as death and death or
valve operation. Valve intervention was registered as open
surgery (repair or replacement) or transcatheter interven-
tion.

Statistics: Statistical analyses were performed using SPSS
version 22. Categorical variables are summarized as num-
ber and percentage and continuous variables as mean ±
SD. Groups were compared using Student’s t-test and
one-way analysis of variance in case of normal distribu-
tion and Mann-Whitney U test and Kruskall-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 in-
dependent predictors of survival, risk factors were analyzed
using univariate and multivariate cox regression analyses
and reported as hazard ratio (HR) and 95% confidence in-
tervals. Results were considered statistically significant
when P < 0.05. In Figure 1, the follow-up time was lim-
ited to the first censored patient, i.e., 2.2 years after diag-
nosis, to illustrate the patients’ status with and without in-
tervention (proportion dead and alive).

Ethics: The study was approved by the Danish Data Pro-
tection 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 dif-
fer 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

![Figure 1. Patients with AS/MR, AR/MR, and AS/MR. Grey, dead without intervention; dark blue, dead with intervention; blue, alive with inter-
vention; light blue, alive without intervention.](image-url)
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%.
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.
(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-

### 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      |
| Valvular disease |             |         |             |         |             |         |
| 1VaD (ref) | 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.
tervention 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, 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. 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, 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. Finally, Pai et al. found concomitant MR of grade 3 or higher in 25% of patients with severe AR. 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. 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. 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. Finally, in AS/MR, several studies have found that severe AS with concomitant MR is associated with an increased mortality.

**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. 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.

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.

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 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. Similar results were found by Harling et al. 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 lesions - one lesion might conceal or enhance the severity of the other lesion - 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.

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**

The authors have no conflicts of interest to declare.

**References**

1. Rankin JS, He X, O’Brien SM, et al. The Society of Thoracic Surgeons risk model for operative mortality after multiple valve
surgery. Ann Thorac Surg 2013; 95: 1484-90.
2. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003; 24: 1231-43.
3. Unger P, Dedobbeleer C, Van Camp G, Plein D, Cosyns B, Lancellotti P. Republished review: mitral regurgitation in patients with aortic stenosis undergoing valve replacement. Postgrad Med J 2011; 87: 150-5.
4. Unger P, Rosenhek R, Dedobbeleer C, Berrebi A, Lancellotti P. Management of multiple valve disease. Heart 2011; 97: 272-7.
5. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the Management of Valvular Heart Disease. 2012 version the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012; 42: S1-44.
6. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 2014; 148: e1-132.
7. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233-70.
8. Vahanian A, Himbert D, Brochet E. Multiple valve disease - assessment, strategy and intervention. EuroIntervention 2015; 11: W14-6.
9. Honda S, Kitai T, Okada Y, et al. Impact of aortic regurgitation on the prognosis of severe aortic stenosis. Heart 2012; 98: 1591-4.
10. Pai RG, Varadarajan P. Prognostic implications of mitral regurgitation in patients with severe aortic regurgitation. Circulation 2010; 122: S43-7.
11. Iung B, Baron G, Tornos P, Gohlke-Bärwolf C, Butchart EG, Vahanian A. Valvular heart disease in the community: a European experience. Curr Probl Cardiol 2007; 32: 609-61.
12. Gonçalves A, Solomon SD. Mitral regurgitation in transcatheter aortic valve replacement: the complexity of multivalvular disease. Circulation 2013; 128: 2101-3.
13. Harling L, Saso S, Jarral OA, Kourliouros A, Kidher E, Athanasiou T. Aortic valve replacement for aortic stenosis in patients with concomitant mitral regurgitation: should the mitral valve be dealt with? Eur J Cardiothorac Surg 2011; 40: 1087-96.
14. Nombela-Franco L, Eltchaninoff H, Zahn R, et al. Clinical impact and evolution of mitral regurgitation following transcatheter aortic valve replacement: a meta-analysis. Heart 2015; 101: 1395-405.
15. Chakravarty T, Van Belle E, Jilaihawi H, et al. Meta-analysis of the impact of mitral regurgitation on outcomes after transcatheter aortic valve implantation. Am J Cardiol 2015; 115: 942-9.
16. Ramakrishna H, Kohl BA, Jassar AS, Augoustides JGT. Incidental moderate mitral regurgitation in patients undergoing aortic valve replacement for aortic stenosis: review of guidelines and current evidence. J Cardiothorac Vasc Anesth 2014; 28: 417-22.
17. Lee R, Li S, Rankin JS, et al. Fifteen-year outcome trends for valve surgery in North America. Ann Thorac Surg 2011; 91: 677-84.
18. Ziberszac R, Gabriel H, Schemper M, et al. Outcome of combined stenotic and regurgitant aortic valve disease. J Am Coll Cardiol 2015; 61: 1489-95.
19. Schubert SA, Yarboro LT, Madala S, et al. Natural history of coexistent mitral regurgitation after aortic valve replacement. J Thorac Cardiovasc Surg 2016; 151: 1072-9.