Management of moderate secondary mitral regurgitation at the time of aortic valve surgery†

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Abstract

OBJECTIVES: To define the impact of surgical strategy [concomitant mitral valve surgery or isolated aortic valve replacement (AVR)] in patients with moderate secondary mitral regurgitation (MR) at the time of AVR.

METHODS: From January 1999 to December 2009, 3339 patients underwent AVR of whom 255 had secondary MR >2+ and constituted the study population. Patients were stratified into two groups, with (Group A, n = 94, 36.8%) and without concomitant mitral valve surgery (Group B, n = 161, 63.2%). Follow-up up to 12 years (1076 patient-years) was analysed for survival, valve-related events and persistent MR. Predictors of late mortality and persistent MR were further analysed. A case-match analysis [age, gender, New York Heart Association (NYHA) and left ventricular ejection fraction] was performed, excluding patients with coronary artery disease (CAD).

RESULTS: The mean age of the population was 67.0 ± 11.7 years, 63.5% male and 64.7% in NYHA III–IV. Group B patients were significantly older and had higher incidence of coronary disease, hypertension and mitral calcification. They also had a higher ejection fraction and transaortic gradients, and lower MR grade (mean MR: 2.8 vs 3.2) and pulmonary artery pressure. Mitral surgery consisted mainly of annuloplasty procedures (96%). Only 2 patients from the entire cohort were reoperated on/for the mitral valve. Thirty-day mortality rate was 0.3%. There was no difference in long-term survival and valve-related complications, even after case-matched analysis. CAD, history of cerebrovascular accident, permanent atrial fibrillation, renal failure and persistence of MR emerged as independent predictors of late mortality (P < 0.05). MR improved in 67.4% of patients from Group B against 82.3% from Group A (P = 0.011). Atrial fibrillation (AF) and higher MR grade at discharge were the only independent predictors for persistent MR (P < 0.05). Patients with persistent MR early after AVR had decreased late survival (hazard ratio: 4.9, P = 0.001).

CONCLUSIONS: Secondary MR improves after AVR even without mitral surgery. Concomitant mitral surgery was significantly associated with greater improvement of postoperative MR, but had no significant impact on survival. However, patients who did not improve immediately after AVR had compromised survival. Patients in AF should have mitral valve repair at the time of surgery.

Keywords: Secondary mitral regurgitation • Aortic valve replacement • Survival • Valve-related events • Persistent mitral regurgitation

INTRODUCTION

Aortic valve replacement (AVR) is the most frequently performed valve surgery in the western world. In the presence of associated mitral regurgitation (MR), the question is often raised whether additional mitral valve surgery is required. Secondary (previously termed functional) MR of varying degrees has been reported in up to two-thirds of patients undergoing AVR [1, 2]. While severe secondary MR obviously requires intervention, non-severe MR is often left unaddressed at the time of AVR. The rationale for this strategy is that, after AVR, there will be a decrease in pressure and/or volume overload which, coupled with the reverse left ventricular remodelling, may have a positive impact on the mitral valve mechanics and, consequently, on the MR [3].

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Moreover, a double valve operation is thought to carry higher postoperative mortality (5–12%) [4].

Relatively few studies, to date, have examined the clinical impact of secondary MR in patients undergoing AVR [5–8], and the majority of prior reports have involved small sample sizes and are confounded by the inclusion of patients with organic or ischaemic mitral valve disease [9–12]. Furthermore, an even smaller number have evaluated the persistence of MR in the long term and its impact on survival. Because of these scattered data and the lack of randomized control trials, a clear recommendation regarding the optimal management of these situations has never been made. The recent 2012 European Guidelines for Valvular Heart Disease (VHD) still do not address this subject, remitting the management of multiple valve disease, other than ischaemic mitral disease, to the recommendation of the predominant VHD [13].
We, therefore, sought to examine: 1—the prevalence of secondary MR in our population; 2—the surgical options (to intervene or not on the mitral valve) and their impact on survival, adverse valve-related events and clinical status; and 3—the evolution of MR over time and possible predictors of persistence.

To the best of our knowledge, this is the first study to make a direct comparison between patients who had concomitant mitral valve surgery and those without, in the context of AVR and secondary MR >2+

**MATERIALS AND METHODS**

**Patient population**

This retrospective study involved 3339 patients who underwent AVR for severe aortic stenosis, insufficiency or mixed lesion, from January 1999 to December 2009. Of these, 255 were considered to have secondary MR >2+. Patients were stratified into two groups, those with concomitant mitral valve surgery (Group A, n = 94, 36.8%) and those without (Group B, n = 161, 63.2%).

Secondary MR was defined, in accordance with the recent guidelines, as dysfunction without structural abnormalities of the mitral apparatus, such as valve prolapse, significant calcification of leaflets or annulus, ruptured chordae and concomitant mitral stenosis. We excluded patients with prior mitral valve intervention from this study, but patients with concomitant procedures besides AVR and mitral valve surgery, such as coronary artery bypass surgery (CABG), tricuspid repair, ascending aorta replacement and aortic root enlargement (ARE), were included.

The patient characteristics, including preoperative echocardiographic findings, are summarized in Table 1. The majority of patients (71.7%) had important aortic valve stenosis, either isolated or as mixed lesions.

Patients in Group A were significantly younger and had higher prevalence of atrial fibrillation, lower ejection fraction and trans-aortic gradients, higher MR severity (mean MR: 3.2 vs 2.8) and higher pulmonary artery pressure. Additionally, left chamber dimensions were statistically greater in this group [left ventricle (LV) (diastolic/systolic) = 67.3 ± 9.6/48.6 ± 9.8 vs 58.8 ± 8.8/40.5 ± 9.9 mm; left atrium (LA) = 50.6 ± 7.8 vs 47.0 ± 7.7 mm].

Group B patients were predominantly female and had higher incidence of coronary disease and hypertension (P < 0.05).

**Echocardiographic analysis**

All patients had a preoperative transthoracic echocardiogram (TTE) before AVR and 86% had an intraoperative two-dimensional transoesophageal echocardiogram (TEE).

The standard TTE included M-mode, two-dimensional, spectral and colour Doppler, obtaining the usual planes (long and short parasternal axes, apical 3-, 4- and 5-chamber views). Anatomical and Doppler measurements were performed according to the recommendations of the American Society of Echocardiography [14, 15], to analyse the parameters associated with the aortic valve (maximum and mean gradients, and valve area estimated from the continuity equation, as well as the presence or absence of aortic regurgitation). The morphology and function of the mitral valve and the presence and degree of left ventricular hypertrophy, systolic function and pulmonary systolic pressure, when they could be estimated, were also analysed. Although quantitative assessment of the degree of MR has recently become part of our clinical practice, over the course of the entire study period MR grading was determined semiquantitatively. Hence, to be consistent with follow-up echocardiography reports, the severity of MR was graded as none (0), trivial (1+), mild (2+), moderate (3+) and severe (4+).

For the purpose of this work, MR grading derived from the TTE was taken as the baseline, in order to standardize the preoperative quantification of MR and to avoid the influence of variable loading conditions produced by mechanical ventilation and anaesthesia, which might have had resulted in the underestimation of MR with pre-bypass TEE. However, there were few discrepancies regarding the MR grade between the two exams and, in several patients, the decision to intervene or not on the mitral valve was made intraoperatively after the TEE.

Postoperative echocardiographic assessment was undertaken in two distinct periods: early phase, during the first month after surgery (mostly discharge echocardiograms) and long term (at least 9 months after AVR). We evaluated 326 postoperative echocardiograms, and 69% of the patients who were alive at the closure of the study had a late follow-up echocardiogram. The mean follow-up echocardiogram time was 4.12 ± 2.7 years (range, 0.75–10.4 years).

A patient was considered to have persistent MR (at discharge or late follow-up) when the severity of MR was unchanged or worsened after surgery.
Operative technique and data

The operative technique was standard for all patients and included cardiopulmonary bypass with mild hypothermia (28–30°C) and intermittent antegrade cold crystalloid cardioplegia, either in the aortic root or directly in the coronary ostia. A ‘hockey-stick’ incision in the ascending aorta was done for AVR, and a left atriotomy, posterior to the interatrial groove, was performed for mitral valve surgery. For replacement of the ascending aorta, the patients were cooled to 24–26°C, and a brief period (5–8 min) of hypothermic circulatory arrest was admitted to perform an open distal anastomosis.

A particular effort was made to insert a large valve prosthesis (minimum size, 21 mm; mean size, 23 ± 1.6 mm), by aortic transannular enlargement, to avoid patient–prosthesis mismatch, particularly in patients with a small aortic annulus. A septal myectomy was performed whenever faced with a bulged asymmetrical hypertrophic septum. The technique of ARE and the modified DeVega have been described in previous reports [16, 17].

Aortic valve bioprostheses were more frequently implanted in Group B (59 vs 41.5%), as might have been expected given the age distribution (Table 2). There were no significant differences between groups regarding associated procedures, except for transannular root enlargement, which was more frequent in Group B (P = 0.013).

Mitrail valve surgery consisted of mitral repair in the majority of patients (96%). Posterior suture annuloplasty (modified Burr/ Paneth) was done in three-quarters of the patients (77.6%). In the remainder, a complete rigid ring (Carpentier-Edwards Physio) was implanted. Additional procedures were done on the mitral valve in 6 patients.

Data collection, follow-up and outcome events

All preoperative data, including clinical and echocardiographic findings, operative reports and postoperative records, including intensive care unit information and complications, were recorded prospectively in a dedicated database by the surgeon performing the procedure and reviewed by two observers (G.C. and P.C.).

Follow-up information was collected during a 3-month period. This was done through a mailed questionnaire or by a telephone interview with surviving patients, family members or the patient’s personal physician, and included information about the level of activity, current symptoms, and occurrence of late cardiac and non-cardiac events.

Echocardiographic follow-up was obtained by querying the institutional echocardiographic database (Cardiology Department), patient records and correspondence from referring cardiologists. The total duration of follow-up for the entire cohort was 1076 patient-years (range, 0–11.4 years), with a mean follow period of 4.48 ± 2.93 years, and was complete for 95% of the patients.

Mortality and morbidity are reported according to the ’Guidelines for reporting mortality and morbidity after cardiac valve interventions’ [18]. Early mortality was defined as death in hospital or within 30 days, and late mortality was defined as death occurring beyond this period.

Freedom from reoperation, major bleeding, endocarditis, thromboembolism and congestive heart failure (CHF) symptoms were assessed. A composite outcome (major adverse valve-related events–MAVEs) composed of valve-related mortality (sudden, unexplained death included), all valve-related morbidity and the need for new permanent pacemaker or defibrillator within 14 days after the valve intervention was considered.

In the interest of most precisely assessing the impact of AVR on secondary MR, survival and event-free survival were further analysed in a subgroup from which we excluded patients with significant coronary artery disease (CAD; if ≥50% narrowing of ≥1 coronary artery was present) who underwent CAGB and with previous myocardial infarction. This subset of patients was case-matched for age (±5 years), sex (exact match) and LV function (±10%) and was constituted of 62 patients in each group (with or without mitral valve surgery).

Statistical analysis

Continuous variables were reported as mean ± standard deviation and compared by Student’s t-test. The values obtained from pre- and postoperative data were compared by the paired t-test. Categorical variables were reported as percentages and were compared using the χ² test. Actuarial survival and event-free survival were plotted using the Kaplan–Meier method, and the two groups were compared using log-rank analysis. Multivariate analysis to identify the risk factors for survival was performed using Cox regression models. Univariate and multivariate predictors for persistent MR were identified using logistic regression models. Criteria for entry and retention into multivariable models were set at the 0.1 and 0.05 confidence level, respectively. Logistic regression models were subjected to 1000

Table 2: Perioperative outcomes

<table>
<thead>
<tr>
<th>OPerative data</th>
<th>Group A (%)</th>
<th>Group B (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB time (min)</td>
<td>87.5 ± 20.7</td>
<td>69.9 ± 18.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>59.7 ± 13.9</td>
<td>42.7 ± 11.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Concomitant procedures</td>
<td></td>
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</tr>
<tr>
<td>CABG</td>
<td>10 (10.6%)</td>
<td>25 (15.5%)</td>
<td>0.274</td>
</tr>
<tr>
<td>Tricuspid modified DeVega</td>
<td>9 (9.6%)</td>
<td>7 (4.3%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Ascending aorta replacement</td>
<td>6 (6.4%)</td>
<td>11 (6.8%)</td>
<td>0.890</td>
</tr>
<tr>
<td>Tailoring aortoplasty</td>
<td>2 (2.1%)</td>
<td>7 (4.3%)</td>
<td>0.354</td>
</tr>
<tr>
<td>Root enlargement</td>
<td>3 (3.2%)</td>
<td>20 (12.4%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Septal myectomy</td>
<td>16 (17.4%)</td>
<td>87 (54.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior annuloplasty</td>
<td>71 (75.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete annuloplasty</td>
<td>19 (20.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve replacement</td>
<td>2 (2.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stented bioprostheses</td>
<td>39 (43.3%)</td>
<td>95 (60.5%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mechanical valves</td>
<td>51 (56.7%)</td>
<td>62 (39.5%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4.2%)</td>
<td>4 (4.2%)</td>
<td>0.500</td>
</tr>
<tr>
<td>Morbidity and mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>0.190</td>
</tr>
<tr>
<td>Reoperation for bleeding</td>
<td>3 (3.2%)</td>
<td>1 (0.6%)</td>
<td>0.111</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>18 (19.1%)</td>
<td>30 (18.6%)</td>
<td>0.919</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>26 (27.7%)</td>
<td>60 (37.3%)</td>
<td>0.117</td>
</tr>
<tr>
<td>New pacemaker implantation</td>
<td>5 (5.3%)</td>
<td>6 (3.7%)</td>
<td>0.546</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>2 (2.1%)</td>
<td>7 (4.3%)</td>
<td>0.354</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (2.1%)</td>
<td>4 (2.5%)</td>
<td>0.856</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>18 (19.1%)</td>
<td>18 (11.2%)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting.
bootstrap replications; 95% confidence intervals (CIs) and P-values were derived from the 1000 replications.

The Hosmer–Lemeshow goodness-of-fit \( \chi^2 \) for this model was 8.0 (\( P = 0.873 \)).

Statistical significance was defined as a two-tailed probability value of \( P < 0.05 \).

The data were analysed using the statistical package program SPSS (version 19, SPSS, Inc., Chicago, IL, USA).

RESULTS

Cardiopulmonary bypass and cross-clamp times were appreciably longer in Group A (87.5 ± 20.7 vs 69.9 ± 18.6 min and 59.7 ± 13.9 vs 42.7 ± 11.5 min, respectively, \( P < 0.001 \)). Nevertheless, it did not have an impact on early mortality (\( P = 0.19 \)). Only 1 patient died (Group A, 1.1%), from severe respiratory failure. There was also no difference in hospital morbidity and the length of hospital stay between groups (\( P = 0.61 \)).

Survival and event-free survival

Overall survival at 1, 5 and 10 years was 93.0 ± 2.8, 84.2 ± 4.2 and 76.7 ± 5.7%, respectively, for Group A, and 98.7 ± 0.9, 79.6 ± 4.2 and 66.6 ± 8.9%, respectively, for Group B. Figure 1 depicts both survival curves; there was no significant statistical difference (\( P = 0.44 \)). Yet, it is possible to see some divergence between groups 5 years after surgery.

Univariate predictors of late mortality included increased age, CAD, chronic renal failure (CRF—defined as a preoperative creatinine level >2.0 mg/dl), previous history of cerebrovascular accidents [cerebrovascular accident (CVA) and transient ischaemic attack], permanent atrial fibrillation (AF), low output syndrome after surgery (inotropic support >24 h, mechanical circulatory support), pacemaker implantation during hospitalization, anticoagulant medication on discharge and early MR persistence. Patients with predominant aortic valve stenosis were somewhat benefited, with regard to late survival, on univariate analysis; nevertheless, this was not confirmed by multivariate analysis.

Only CAD, history of CVA, permanent AF, CRF and MR persistence emerged as independent predictors for overall mortality (Table 3). Patients who showed persistent MR early after surgery had severely compromised long-term survival (Fig. 2). This was the most powerful independent predictor for late mortality [hazard ratio (HR): 4.9; \( P = 0.001 \)].

Freedom from valve-related events (Fig. 3) was also comparable between groups (\( P = 0.91 \)). However, 24 (18.2%) patients from Group B had important congestive heart failure symptoms [New York Heart Association (NYHA) III–IV] against 7 (11.1%) patients from the mitral valve surgery group. Eight patients were reoperated during the study period, though only 2 underwent mitral valve surgery and both were from Group A (early mitro-aortic endocarditis and late mitral repair failure 9 years after surgery).

It is important to stress that the option not to intervene on the mitral valve did not come out as a risk factor for overall survival and event-free survival, in both uni- and multivariable analyses. Even after adjusting both groups for age, LV function, NYHA and gender, we could not find differences in late mortality or valve adverse events, but early MR persistence was an important risk factor for survival.

Postoperative mitral regurgitation (early and late mitral regurgitation persistence analyses)

The prevalence of secondary MR >2+ in the context of AVR in our population was 7.6%.

Immediate improvement of MR severity was, as expected, more noticeable in patients who had mitral valve surgery (Group A). Nevertheless, the early echocardiogram revealed improvement of the MR grade in nearly 82% of patients from Group B (vs 99% from Group A). Eighteen (18%) patients had persistent MR at discharge. Over time, there was an increase in the severity of MR, with 32 (32.6%) patients from Group B showing persistent MR during late follow-up against 8 patients from Group A (17.7%; \( P = 0.045 \)).

Figure 1: Overall survival of patients with secondary MR >2+ submitted to AVR, with (Group A) or without (Group B) concomitant mitral valve surgery. (A) represents the overall survival in the study population and (B) describes the overall survival in a subgroup analysis, case-matched for age, gender, LVEF and NYHA excluding patients with significant CAD. There was no difference in the overall survival in both analyses (\( P > 0.05 \)).
Table 4 shows the independent predictors of persistent MR at early and medium-to-long-term follow-up. Univariate predictors for persistent MR early after surgery included preoperative AF, aortic stenosis, higher preoperative aortic gradients, absence of mitral valve surgery, ARE and postoperative usage of inotropes. By multivariate analysis, only the absence of mitral surgery, ARE and postoperative inotrope support remained significant. Preoperative AF almost reached statistical significance ($P = 0.056$).

Predictors of persistent MR at the time of late follow-up by univariate analysis included AF at discharge, acute renal failure during hospitalization, larger left atrial size and higher MR grade at discharge. In multivariate analysis, however, only the latter and AF emerged as independent risk factors for persistent MR. The left atrial size came close to reaching statistical significance ($P = 0.053$).

### Cardiac remodelling

Both groups experienced significant reverse cardiac remodelling, but this effect was more evident in the group that had mitral surgery (Table 5). Regarding left ventricular remodelling, patients from this group had a mean decrease in LV dimensions (diastole/systole) of $11.1 \pm 9.1$ and $7.1 \pm 9.4$ mm, respectively ($P < 0.001$). The decrease was also significant, but less important in Group B ($5.4 \pm 9.1$ and $2.4 \pm 9.1$ mm, $P = 0.020$). The mean reduction of the left atrial size was $3.4 \pm 8.8$ (P < 0.001) and $2.1 \pm 8.4$ mm ($P = 0.022$) for Groups A and B, respectively.

Group B showed a greater decrease in LV hypertrophy, but this was not significant. Group A patients demonstrated a steep decline of the pulmonary artery pressure late after surgery with a mean reduction of $16.3 \pm 17.9$ (vs $7.6 \pm 16.9$ mmHg; $P < 0.001$). Both groups exhibited recovery of LV function (improvement in the mean ejection fraction), although this was not statistically significant.

### DISCUSSION

Moderate MR in patients with aortic valve disease is often not corrected at the time of AVR because concomitant MR, particularly secondary or ischaemic MR, is expected to decrease after AVR. Ventricular hypertrophy and/or dilatation commonly exist in patients with aortic stenosis or regurgitation and may result in MR. Secondary MR of varying degrees has been reported in up

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>2.97</td>
<td>1.32–6.70</td>
<td>0.009</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>3.25</td>
<td>1.04–10.10</td>
<td>0.041</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>2.74</td>
<td>1.24–6.06</td>
<td>0.013</td>
</tr>
<tr>
<td>CRF</td>
<td>3.01</td>
<td>1.22–7.40</td>
<td>0.016</td>
</tr>
<tr>
<td>MR persistence</td>
<td>4.90</td>
<td>1.92–12.60</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; TIA: transient ischaemic attack; AF: atrial fibrillation; CRF: chronic renal failure; MR: mitral regurgitation; HR: hazard ratio; CI: confidence interval.
to 75% of patients undergoing AVR [2]. In our series, the incidence of secondary MR >2+ in the context of AVR was 7.6%.

To our knowledge, our study is the first to analyse the outcomes of ‘pure’ secondary MR, excluding ischaemic and dilated myocardopathy MR, in the context of severe aortic valve disease, comparing patients with or without concomitant mitral valve surgery. There is only one recent report (from Pai and Varadarajan [19]) that made this type of comparison, but only in patients with aortic regurgitation and including MR other than secondary aetiology. We tried to evaluate whether the decision to intervene or not on the mitral valve significantly influenced long-term outcomes and to determine which patients would benefit the most from a conservative approach or from double valve surgery.

There are several important findings from this study that deserve discussion. First, patients who were submitted to mitral valve surgery were younger, more symptomatic and had altered cardiac parameters suggestive of a more chronic disease, such as pulmonary hypertension, LV dysfunction and left atrial and ventricular dilatation.

Secondly, the majority of patients (96%) who needed concomitant mitral valve surgery for secondary MR had mitral valve repair with clearly demonstrated benefit [20]. Only 1 patient had significant persistent MR at discharge and another required reoperation for mitral repair failure 9 years after surgery. Double valve surgery did not result in an increased operative risk—only 1 patient died during hospitalization (1.1%)—or in perioperative complications, compared with isolated AVR.

Some groups identified the severity of preoperative MR as a risk factor for the 30-day mortality following AVR [21]; however, this was disputed by others [5–7, 12]. In a very recent meta-analysis, Harling et al. [22] revealed a statistically significant increase in the 30-day mortality in patients with moderate preoperative MR when compared with nil–mild preoperative MR, as well as significantly worse 3- and 5-year survival rates in those patients with moderate–severe MR. Additionally, a current report evaluated the outcomes of patients with moderate to severe MR undergoing transcatheter aortic valve implantation (TAVI) these patients showing a higher early, but not late, mortality rate [23]. In our study, the presence of MR did not have an impact on early mortality, and standard AVR without mitral surgery carried a very low surgical risk.

Thirdly, intervention on the mitral valve did not influence the overall survival and the event-free survival, even after adjusting for important variables. Others reported similar results, with no difference in survival in a case–matched comparison of patients with mild vs moderate MR at the time of AVR [5, 7]. However, one should be cautious when analysing our long-term results, because the number of patients at risk at late follow-up (8–10 years) was relatively low. Yet, the survival curves from the two groups diverged after 5 years following AVR, with 10-year survival rates of 77 and 67% for Groups A and B, respectively. But in the aforementioned recent review, the authors found that the 10-year mortality was not significantly affected by preoperative MR severity when only secondary MR was considered.

On the other hand, Barreiro et al. [21] found moderate MR to be an independent predictor of late mortality in elderly patients undergoing AVR, though patients with organic or ischaemic mitral disease constituted almost half of their study population. Interestingly, in the study of Ruel et al. [6], secondary MR >2+ per se had no independent adverse effect on late mortality in patients with either aortic stenosis or insufficiency. Nevertheless, the presence of secondary MR >2+ resulted in a higher risk of a composite CHF outcome (CHF symptoms, CHF death or mitral valve repair/replacement), if it was associated with certain factors, such as left atrial size >5 cm, preoperative peak and mean aortic gradient <60 and <40 mmHg, respectively, or chronic AF. In our study, patients from Group B were more symptomatic and in a higher NYHA class than patients who had mitral valve surgery (18.2 vs 11.1%).

We identified several independent risk factors for mortality common to other studies [5, 6, 21], such as CAD, history of CVA, permanent AF and CRF, but what was a novelty in our work was

### Table 4: Independent predictors for persistent MR at early and late follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At early FU (discharge)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root enlargement</td>
<td>1.53</td>
<td>0.13–3.11</td>
<td>0.006</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>1.34</td>
<td>0.20–2.83</td>
<td>0.012</td>
</tr>
<tr>
<td>No mitral surgery</td>
<td>2.81</td>
<td>1.16–20.30</td>
<td>0.009</td>
</tr>
<tr>
<td>At medium–long-term FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.65</td>
<td>1.02–6.88</td>
<td>0.044</td>
</tr>
<tr>
<td>MR degree at discharge</td>
<td>1.92</td>
<td>1.19–3.09</td>
<td>0.007</td>
</tr>
</tbody>
</table>

FU: follow-up; OR: odds ratio; CI: confidence interval.

### Table 5: Preoperative vs postoperative echocardiographic changes (long term)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MD</td>
<td>95% CI</td>
<td>P-value</td>
<td>MD</td>
<td>95% CI</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>LA (mm)</td>
<td></td>
<td>3.42</td>
<td>0.49–5.33</td>
<td>&lt;0.001</td>
<td>2.16</td>
<td>0.31–4.01</td>
<td>0.022</td>
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<tr>
<td>LVED (mm)</td>
<td></td>
<td>11.06</td>
<td>8.23–13.9</td>
<td>&lt;0.001</td>
<td>5.44</td>
<td>3.55–7.32</td>
<td>&lt;0.001</td>
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<tr>
<td>LVES (mm)</td>
<td></td>
<td>7.11</td>
<td>3.99–10.24</td>
<td>&lt;0.001</td>
<td>2.40</td>
<td>0.38–4.42</td>
<td>&lt;0.001</td>
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<tr>
<td>IVS (mm)</td>
<td></td>
<td>0.02</td>
<td>–1.18–1.24</td>
<td>0.962</td>
<td>0.57</td>
<td>–0.23–1.37</td>
<td>0.161</td>
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<td>Aortic gradient</td>
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<td>48.70</td>
<td>37.43–59.96</td>
<td>&lt;0.001</td>
<td>56.3</td>
<td>48.57–64.09</td>
<td>&lt;0.001</td>
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<td>LVEF (%)</td>
<td></td>
<td>–2.81</td>
<td>–13.41–8.42</td>
<td>0.625</td>
<td>–7.09</td>
<td>–15.69–0.03</td>
<td>0.096</td>
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<tr>
<td>PAP</td>
<td></td>
<td>16.25</td>
<td>8.66–23.82</td>
<td>&lt;0.001</td>
<td>7.6</td>
<td>3.11–12.09</td>
<td>0.001</td>
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</table>

MD: mean difference; CI: confidence interval; LA: left atrium; LVED: left ventricular end-diastolic diameter; LVES: left ventricular end-systolic diameter; IVS: interventricular septum; LVEF: left ventricular ejection fraction; PAP: pulmonary artery pressure.
the striking impact of the early persistence of MR on the overall mortality. Patients who showed persistent MR early after AVR had their survival significantly reduced (HR = 4.9, P = 0.001). For this reason, these patients ought to be followed closely and if MR persists over time, they should probably be sent for earlier rather than late mitral surgery.

The majority of patients from Group B (82.2%) exhibited improvement in the MR grade early after surgery as well as in the long term (67.3%). This finding was consistent with other studies [22] and reveals a relatively benign course regarding the evolution of secondary MR when a conservative approach is chosen. Apparently, the prognosis is worse with aetiologies other than secondary MR. Eyden et al. [9] found the aetiology of MR to be a significant prognostic factor for the improvement in MR and described little improvement in patients with rheumatic and myxomatous valves, suggesting that concomitant mitral valve surgery should be strongly considered in those cases.

In our population, the persistence of MR at discharge was influenced by the surgical strategy (no mitral intervention), associated procedures (ARE) and inotropic support, which means that the involution of MR may take some time. Late persistence of MR was heavily influenced by the degree of MR soon after AVR and AF. The latter, in addition to being an independent predictor of long-term persistent MR (odds ratio: 2.6; P = 0.044), and almost reaching statistical significance for persistent MR also at discharge (P = 0.056), was also associated with poor survival (HR: 2.7; P = 0.013). Recently, Matsumura and Glinov also found that the presence of long-term AF and that of a mitral valve tenting area were independent predictors of postoperative MR severity. This underscores the importance of and a growing trend towards aggressive treatment of this pathology [24].

Finally, AVR was associated with significant reverse cardiac remodelling regardless of mitral valve surgery being performed. Nevertheless, the degree of improvement was greater in those who had mitral surgery, most likely as a consequence of the larger preoperative atria and ventricles of patients in Group A, which together with the decrease of volume overload caused by the reduction in the MR would imply a more significant reduction of the left cavities. Cardiac remodelling and improvement of MR after surgery go hand in hand. Unger et al. [25] documented that the decrease in MR observed in most patients after AVR was associated with the magnitude of acute left ventricular reverse remodelling.

**STUDY LIMITATIONS**

In the absence of precise guidelines, during the study period, the decision to operate on the mitral valve was randomly made, mostly depending on the surgeon’s ‘feeling’. The lack of homogeneity between groups could account for differences in outcomes. We tried to reduce those discrepancies by performing a case-match analysis. As an observational study, it is subject to selection and treatment bias and, despite the use of a priori specified end points and covariates, it is possible that unidentified confounders may have influenced the results.

Another limitation of our study is the incomplete echocardiographic follow-up (69%), even though it is consistent with the reported medium to long-term echocardiographic follow-up in the literature (42–100%). Patients who underwent echocardiography were demographically similar to those who did not; however, there is always the possibility of a sampling bias.

Since this was a long study period and quantitative methods for MR quantification have been applied only recently, this precluded its use in order to standardize the preoperative with the postoperative MR grade evaluation.

Despite these weaknesses, this is a relatively large study with an echocardiographic follow-up in more than two-thirds of patients, which provided valid information regarding survival and persistent MR over time.

**CONCLUSIONS**

Secondary MR in the context of AVR can be treated with a high rate of mitral repair and with low mortality and morbidity. Annuloplasty techniques seem to be adequate, with equivalent good results in the long term. Patients who had concomitant mitral valve surgery had similar survival rates compared with those without, even after a case-match comparison, but the latter were more symptomatic and had a lesser degree of overall cardiac remodelling.

The great majority of patients with secondary MR can expect to improve their degree of MR early after isolated AVR and approximately 67% maintain their improvement in the medium to long term. Patients who do not improve or have an important degree of MR by the first month after AVR are at risk of having significant persistent MR in the future and have severely compromised survival, and hence should be closely followed and referred to mitral valve surgery early.

Patients in AF are also at risk for decreased survival and of persistent MR over time; therefore they should have their mitral valve repaired simultaneously during the AVR procedure and have AF ablation, if indicated.

In conclusion, the question of whether moderate secondary MR should be addressed at the time of AVR is yet to be fully answered and, almost certainly, only a randomized controlled trial could, finally, give a definitive answer.

**Conflict of interest:** none declared.

**REFERENCES**


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Do you have any clue as to why you repaired fewer mitral valves in female patients? Is there any bias involved there because the atria are smaller and the intervention is probably more difficult, and as the longer cross-clamp times with mitral valve repair do not induce higher postop mortality? As you nicely stated during your conclusions, patients who do not improve or have an important degree of MR by the first month, should be closely followed or referred for mitral valve surgery, which is going to be extremely awkward. I think we are allowed to be more aggressive.

My third question is what to do in the case of TAVI, because we know that in TAVI we haven’t got a clue whether mitral regurgitation is going to get better, yes or no.

Dr Coutinho: Regarding the first question of repairing fewer female patients, I think you cannot put it in that way, because female patients preominated in the group without mitral surgery, but they were older patients and probably the component of MR was less important. Concerning the longer clamping times for the procedure, they did not take so long. I think it was a mean cross-clamping time of 65 min. So it was not so long for performing an aortic valve replacement and the mitral valve repair. Furthermore, it did not have an impact on the surgical mortality, because only one patient died.

Regarding the third question, the persistence of MR at discharge, I think you pointed it out very well, because those patients had severely compromised survival. It means that probably we didn’t treat those patients well. Probably those patients should have their mitral valve repaired during the first operation, because the hazard ratio was 4.9, and an important number of those patients died soon after. Therefore we should be more aggressive towards the target of not having an important degree of persistent MR at discharge.

Regarding TAVI, an important study was published this year that showed that in the case of TAVI, MR severity was related to a dismal prognosis. Consequently those patients should have their mitral valve repaired because they could die after the procedure. But in the long term, they acknowledged that MR had no impact on survival, so it’s difficult to answer that question. But I think it’s a very important issue, because TAVI procedures are increasing and we know that surgical patients are getting older, degenerative mitral disease obviously will increase, the functional mitral valve disease in this case will also increase, so I think we have to answer that question.

Dr F. Casselman (Aalst, Belgium): A suggestion. Maybe there is a place for a surgical MitraClip through the aortic valve.

Dr Coutinho: Yes. Probably. I agree completely with you.

Dr K. Sarkar (Calcutta, India): I have just one comment. I think your 5-year survival curves were different. I don’t know what your parameters were, but the survival curves in Group A and B at 5 years did look different.

Dr Coutinho: They were different. From five years after surgery, we could see some divergence of the curves. The 10-year survival in the overall population was 76% for Group A, namely patients who had mitral surgery done, and 67% for patients without mitral surgery. However, we couldn’t find statistical significance.

Dr E. Mostafa (Cairo, Egypt): Ours is probably a similar population to that in Portugal. I have a comment and a question. Briefly, the most important part of the results are those relating to the combined obstructive lesions, the aortic stenosis and mitral stenosis. My question is, how does the aortic annulus or the aorto-ventricular continuity affect your results? I mean, does the small aortic valve annulus really affect the outcome of this mild or moderate mitral regurg?

Dr Coutinho: Well, I don’t have a clear response to that. But when we performed aortic root enlargement, it was associated with persistent MR at discharge. But at late follow-up we couldn’t find that effect. So probably there will be an involvement of MR during the time period. I don’t know.

Dr Casselman: Given your results that the persistence of MR in the postoperative period has some negative influence, did you change your practice or is your attitude still the same towards it?

Dr Coutinho: I think we should be more aggressive in case of atrial fibrillation. Patients with previous atrial fibrillation will probably have mitral persistence over time and at discharge (almost reach statistical significance). So we should be more aggressive.

One message that we tried to communicate with this study was if you have a patient with aortic stenosis, moderate MR and in atrial fibrillation, we should operate on the mitral valve because we probably will get persistent consolidation as it doesn’t give the right lesson as to whether we should do something at the time of surgery, particularly because you showed the evidence that some patients will have a hard time just to survive in the immediate postop period with their residual MR. At least you taught us to prepare in the event of atrial fibrillation, which is very important in case of pulmonary hypertension.
MR during follow-up. As the survival curve showed, patients with atrial fibrillation also have a dismal prognosis. So we should be aggressive probably towards mitral repair and probably atrial fibrillation if indicated.

**Dr S. Livesey** (Southampton, UK): We’re talking about secondary mitral regurgitation here. Now, when we’re dealing with the ischaemic population, we understand quite clearly now that the severity of MR that we see in degenerative is not the same as the severity of MR we see in ischaemic patients, and a much smaller degree of MR has a much greater significance. Do you think this group of patients follow that type of secondary MR, or do you think we can use the same criteria for judging MR that we use in degenerative valve disease?

**Dr Coutinho**: I think the problem is different. There is an important study that showed that if you have degenerative disease or rheumatic disease and you have a problem on the aortic valve, the question is completely different, and you should operate on the mitral valve because that mitral valve would not recover its function after the surgery. Regarding ischaemic MR, we don’t have an answer on that, because we excluded patients with coronary artery disease from this study.

### Secondary mitral regurgitation in patients undergoing aortic valve replacement

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Mitral regurgitation (MR) is frequently found in patients scheduled for aortic valve replacement (AVR). The aetiology of concomitant MR can be organic or functional. Organic MR is the result of rheumatic or myxomatous degeneration or, particularly in the elderly, calcification of the mitral apparatus. Functional MR, on the other hand, is secondary to increased left ventricular (LV) afterload and/or variable degree of LV remodelling and is the most common form of mitral insufficiency in patients requiring AVR. The evidence is clear to not surgically intervene if associated functional MR is only mild. Similarly, there is a general agreement that mitral valve (MV) surgery, possibly repair, should be performed when severe functional MR exists. On the other hand, the question is often raised of whether additional MV surgery is required in patients submitted to AVR who do have concomitant less than severe functional MR [1–3]. Indeed, no randomized trials have been conducted in this setting and the scattered information available is the result of observational studies with small sample sizes, retrospective analyses, heterogeneous populations and different aetiologies of MR. In addition, the presence of concomitant procedures like myocardial revascularization and the use of different echocardiographic parameters in grading preoperative MR further limits direct comparison between studies. In this scenario, not surprisingly, even the last 2012 European Guidelines on the management of Valvular Heart Disease [4] do not specifically address this issue and simply suggest that, as long as there are no significant organic abnormalities of the mitral apparatus, surgical intervention on the MV is generally not necessary at the time of AVR because non-severe secondary MR usually improves after the aortic valve is treated.

The prognostic significance of ‘less than severe’ functional MR in patients undergoing isolated AVR is still debated. Some studies have shown no difference in survival in patients with moderate or moderate-to-severe functional MR vs no (or mild MR) after isolated AVR [2, 5]. Other reports, on the other hand, have demonstrated significantly poorer survival in patients with at least moderate MR submitted to isolated AVR. Organic MV disease and severe degree of MR, however, were usually included in this second group of studies [6, 7]. Those controversial findings explain why some authors have recommended an aggressive approach in operating on the MV [7, 8], whereas others continue to support a more conservative strategy, believing that functional non-severe MR is likely to decrease after the surgical correction of aortic valve disease [2]. Most of the data available demonstrate a general trend towards an improvement of the grade of less-than-severe functional MR after isolated AVR. This is usually due to the postoperative reduction in LV systolic pressure (aortic stenosis) or to the decrease in LV dimensions (aortic regurgitation). Only in about one-third of the patients, preoperative functional MR remains unchanged and in a minority of them it further deteriorates [7]. Whether persistence or worsening in MR severity following AVR directly correlates with mortality remains unclear. The study by Coutinho et al. [9] provides some more light in this controversial field showing that, in the great majority of patients, secondary MR decreases early after isolated AVR and, in ~67% of them, this improvement persists in the medium to long term. This finding confirms a relatively benign evolution of secondary MR in patients submitted to isolated AVR. The second important message emerging from this series is that functional MR, in the