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Clinical Outcome in Aortic Regurgitation with
Cardiovascular Magnetic Resonance

Running title: Myerson et al.; Aortic Regurgitation: Outcome with CMR

Saul G. Myerson, MBChB, MD, MRCP, FESC1; Joanna d’Arcy, MBChB, MRCP1;
Raad Mohiaddin, PhD, FRCR, FRCP, FESC2; John P. Greenwood, MBChB, PhD3; Theodoros D.
Karamitsos, MD, PhD1; Jane M. Francis, DCR(R), DNM1; Adrian P. Banning, MBBS, MD,
FRCP, FESC1; Jonathan P. Christiansen, MBChB, MD, FRACP, FACC, FCSANZ4;
Stefan Neubauer, MD, FRCP, FACC, FMedSci1

1Depts. of Cardiology & Cardiovascular Medicine; University of Oxford Centre for Clinical
Magnetic Resonance Research, John Radcliffe Hospital, Oxford, 2CMR Unit, Royal Brompton
Hospital and the National Heart and Lung Institute, London; 3Multidisciplinary Cardiovascular
Research Centre (MCRC) & Leeds Institute of Genetics, Health and Therapeutics, University of
Leeds, Leeds, United Kingdom; 4North Shore Hospital, Auckland, New Zealand

Address for Correspondence:
Dr. Saul Myerson
Dept. of Cardiovascular Medicine
John Radcliffe Hospital
Headley Way
Oxford OX3 9DU, United Kingdom
Tel: +44 1865 222770
Fax: +44 1865 740449
E-mail: saul.myerson@cardiov.ox.ac.uk

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Abstract:

Background - Current indications for surgery in patients with significant aortic regurgitation (AR) focus on symptoms and left ventricular (LV) dilation/dysfunction. However, prognosis is already reduced by this stage and earlier identification of patients for surgery could be beneficial. Quantifying the regurgitation may help, but there is limited data on its link with outcome. Cardiovascular magnetic resonance (CMR) can accurately quantify AR, and we examined whether this was associated with the future need for surgery.

Methods and Results - 113 patients with echocardiographic moderate or severe AR were monitored for up to 9 years (mean 2.6±2.1 years) following a CMR scan, and the progression to symptoms or other indications for surgery was monitored. AR quantification identified outcome with high accuracy. 85% of the 39 subjects with regurgitant fraction >33% progressed to surgery (mostly within 3 years) compared to 8% of 74 subjects with regurgitant fraction ≤33% (p<0.0001); area under the curve on receiver operating characteristic analysis 0.93 (p<0.0001). This ability remained strong on time-dependent Kaplan-Meier survival curves. CMR-derived end-diastolic volume (LVEDV) >246ml had good, though lower, discriminatory ability (AUC 0.88) but the combination of this with regurgitant fraction provided the best discriminatory power.

Conclusions - High degrees of CMR-quantified AR were associated with the development of symptoms or other indications for surgery. Quantifying AR showed slightly better discriminatory ability than ‘Gold-standard’ CMR ventricular volume assessment. This could provide a new paradigm for the timing of surgical intervention but requires confirmation in a clinical trial.

Key words: aortic regurgitation; aortic valve replacement; cardiovascular magnetic resonance imaging; outcome; prognosis
Background

Aortic regurgitation (AR) remains an important cardiac condition, although substantial chronic regurgitation can be tolerated for many years, with patients remaining asymptomatic. Aortic valve replacement is usually reserved for when symptoms or significant left ventricular (LV) dilation or dysfunction occur, but prognosis is already reduced by this stage. Earlier surgery has been advocated, but it is also important to avoid the increased risks associated with premature surgery. Optimising the timing of surgery in these patients can therefore be difficult. Quantifying the AR could be valuable for guiding management, especially in asymptomatic patients with significant regurgitation, and might be used for the early identification of patients requiring aortic valve surgery.

Cardiovascular magnetic resonance (CMR) is able to directly quantify aortic regurgitation with high accuracy and reproducibility, using the technique of phase contrast velocity mapping. As CMR also provides highly accurate measurements of left ventricular (LV) mass, volumes and function (and is considered the ‘Gold-standard’ for measuring these), it would appear to be an ideal technique for the assessment of aortic regurgitation, but the utility of CMR to guide clinical management has not been evaluated. We sought to examine whether CMR quantitation of aortic regurgitation and LV indices could identify which asymptomatic patients with significant aortic regurgitation were likely to progress to symptoms or other established indications for surgery in the near future. We also aimed to compare the CMR quantitation of aortic regurgitation and LV volume/function indices for their relative predictive ability.

Methods

Subjects and follow up
Patients at least 18 years of age were recruited from four high-volume CMR centres in Oxford, London, Leeds (UK) and Auckland (New Zealand). All asymptomatic patients with moderate or severe chronic aortic regurgitation on echocardiography by standard (semi-quantitative) assessment\textsuperscript{16} were eligible for inclusion and had a baseline CMR scan. Exclusion criteria included the presence of other significant valve disease or clinical and/or angiographic evidence for coronary disease.

Patients had a baseline CMR scan and were followed for up to 9 years. Those who remained asymptomatic and under conservative management were designated the ‘conservative’ group, while those that developed symptoms or other established indications for surgery\textsuperscript{3} were designated the ‘crossover’ group, with the decision for surgery taken as the point of censoring. All clinical decisions were taken by the treating physician. In Oxford, patients participated in a research study, with annual CMR scans, and clinical decisions were made without knowledge of the CMR data. In the other three centres, study patients were identified from the clinical CMR databases (though were initially diagnosed with echocardiography) and clinicians had access to the CMR data. Events were only counted however if the reason for aortic valve surgery was for established indications (primarily symptoms, excess LV dilation or LV dysfunction). Patients undergoing aortic valve replacement for indications outside the established criteria\textsuperscript{3} (which do not include CMR assessment), or when surgery was primarily for other surgery (e.g. aortic root replacement) were considered to be in the conservative group but censored at the time of surgery.

In addition, a minimum period of two months was required between the CMR scan and the decision for surgery, to avoid the potential bias of patients having a CMR scan ‘en-route’ to surgery that had already been planned.

A third group was also included to compare CMR parameters with both the conservative
and crossover groups. This group included patients already due for aortic valve replacement (the ‘surgical’ group), having developed established indications for surgery.

The research study was approved by the Oxfordshire Central Research Ethics Committee (Project code C02.020) and the Waitemata District Health Board “Knowledge Centre” in New Zealand (Project number RM0980711302); all research subjects gave written informed consent.

**CMR scanning**

All scans were performed on 1.5 Tesla scanners (either Siemens Avanto [Siemens Medical Solutions, Erlangen, Germany] or Philips Achieva scanners [Philips Healthcare, Best, The Netherlands]) and analysed in each centre using the manufacturers’ software (Siemens Argus and Philips ViewForum respectively) for both volumes and flow. All images were electrocardiogram (ECG)-gated and most were obtained during an 8-16 second breath-hold to remove cardiac motion due to the respiratory cycle. Subjects underwent a left ventricular function study as previously described,\(^\text{14}\) consisting of a stack of contiguous short axis cine images from base to apex, from which left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV respectively) and mass were measured. Each value was also indexed to body surface area. Cine image sequences were steady-state free precession (Siemens ‘TrueFISP’ or Philips ‘balanced fast field echo’); temporal resolution 45msec; echo time 1.40-1.54msec; repetition time 2.80-3.08msec; field of view 380x380mm; flip angle 50-60°).

Forward and regurgitant aortic flow were quantified using through-plane phase-contrast velocity-mapping. This involves placing an image slice perpendicular to the direction of flow in the aortic root, and measuring the velocity of flow through the image plane within each voxel. From the resulting images, a region of interest identifying the aortic root is defined, and flow is integrated for the whole cardiac cycle to provide forward and regurgitant flow through the aortic
valve per cardiac cycle. The image plane was placed ~0.5cm above the aortic valve at end-diastole, but maintaining a position in the aortic root throughout the cardiac cycle (Figure 1). Imaging closer to the valve reduces the underestimation of regurgitation that can occur, and although increased turbulent flow can occur close to the valve, we have not found this to be a problem in practice. If significant turbulence or aliasing was seen in the velocity image, the acquisition was repeated a few millimetres further from the valve, and/or with a higher velocity window. The original flow sequences acquire data over many cardiac cycles, taking approximately two minutes with patients breathing freely, while newer magnetic resonance sequences can acquire flow data within a single breath-hold (12-16 heart beats). Others have suggested that the older free-breathing techniques may be more accurate for flow quantification, as the newer sequences may be more prone to background flow offset errors from the faster switching of magnetic field gradients (which can potentially cause significant errors in flow quantification), but this has not been systematically examined. Free-breathing flow sequences were used in Oxford and Leeds, while breath-hold flow sequences were used in the other two centres. In all centres, the potential for background flow offset errors was reduced by i) ensuring all flow sequences were acquired with the region of interest in the image slice located at the isocentre of the magnet to minimise any inhomogeneities in the magnetic field, and ii) using retrospective ECG-gating for all flow sequences, which also helps to ensure coverage of the entire cardiac cycle. Image parameters: temporal resolution 25-55msec; echo time 2.6-3.2msec; repetition time 4.3-7.8msec; field of view 320x320mm; velocity window 2.5-4.0m/sec; signal averages: 1 for breath-hold sequences, 3 for free-breathing sequences; typical acquisition time 12-16 seconds for breath-hold sequences, 2-3 minutes for free-breathing sequences. From these images, forward and regurgitant aortic flow were measured by integrating the flow in each
frame over one cardiac cycle as previously described.\textsuperscript{9,11} Regurgitant fraction (regurgitant volume/forward volume x 100\%) was also calculated.

**Echocardiography**

Clinical echocardiograms were acquired a mean of 22.9 ±81.5 days from the baseline CMR scan, according to standard protocols.\textsuperscript{21} Assessment of the grade of AR on echocardiography was based on multiple semi-quantitative and qualitative two-dimensional imaging parameters, as suggested in the American Society of Echocardiography guidelines,\textsuperscript{16} with senior advice sought in difficult cases. The echocardiograms were not performed specifically for the research study however, and did not include the quantification of LV volumes or aortic regurgitation as current guidelines recommend. Because of this limitation, LV end-diastolic and end-systolic diameters and the semi-quantitative echocardiographic grading were not included in the predictive analysis for comparison with CMR parameters.

**Data assessment and statistical analysis**

Receiver operating characteristic (ROC) analysis was used to determine the ability of the various parameters to discriminate patients who would develop symptoms or other indications for surgery during follow up, from those that remained asymptomatic. Differences in ROC area were compared using the method of DeLong et al.\textsuperscript{22} Cox proportional hazards and multiple logistic regression analyses were applied to any parameters with reasonable discriminatory ability (area under the curve (AUC) on ROC analysis >0.70) to determine if any of these were independent predictors. Cox proportional hazard analysis was performed in a binary fashion, comparing groups above & below the optimal threshold identified on ROC analysis. Multiple logistic regression analysis was performed using continuous variables, with subsequent binary analysis for independent variables, again based on the thresholds identified from ROC analysis. Kaplan-
Meier survival curves are better for time-dependent events, and these were generated for any independent parameters to illustrate their association with the progression to symptoms/surgery. For group comparisons of CMR parameters, including the surgical group, one-way analysis of variance (ANOVA) was used, with Bonferroni post-hoc analysis, after confirming normal distributions of the variables using the Kolmogorov-Smirnov test. All analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, USA) with the exception of the ROC and Cox regression analyses which were performed with MedCalc version 9.3.1 (MedCalc Software, Mariakerke, Belgium). Values shown are means ± standard deviation and a p-value of <0.05 was considered the threshold for statistical significance.

Results

118 asymptomatic patients were considered for inclusion in the study, who had at least moderate AR on echocardiography. Five were excluded because aortic valve surgery occurred within two months of the CMR scan, leaving 113 patients, who were followed for up to 9 years (mean 2.6 ± 2.1 years). Thirty nine patients (35%) underwent aortic valve replacement during the follow-up period, having developed symptoms (n=19) or other established echocardiographic indications for surgery (excessive LV dilation [EDD >7.5cm or ESD >5.5cm], n=17); or reduced LV function [echocardiographic ejection fraction <50%], n=3). These were designated the ‘crossover’ group. The mean time from CMR scan to the decision on surgery in this group was 21 months (median: 11 months), with 90% of events occurring within three years. Eight patients underwent surgery primarily for aortic dilation and remained in the ‘conservative’ group but censored at the time of surgery; mean regurgitant fraction in this group was 19% (range 5-30%). One patient underwent aortic valve replacement surgery without conventional established
indications\textsuperscript{3} and was also retained in the conservative group. This patient was asymptomatic and had surgery for LV ‘dilation’, but the echocardiographic end-diastolic diameter was 6.5cm; his regurgitant fraction on CMR was 19%, and EDV 222ml.

Association with events

The ability of CMR parameters to identify patients at baseline who would develop indications for surgery is shown in table 1 (ROC analyses). Quantitative measures of AR showed excellent discriminatory power, with aortic regurgitant volume having an area under the curve (AUC) of 0.96 (p<0.0001), and regurgitant fraction an AUC of 0.93 (p<0.0001), with no statistical difference between the two. CMR LV volumetric indices also showed good discriminatory ability, though slightly lower than regurgitation quantification, with an AUC of 0.88 for LVEDV and AUC 0.78 for LVESV (both p≤0.01 vs. regurgitant volume). On multivariate analyses (table 2), only regurgitant fraction, regurgitant volume and LVEDV remained as independent predictors. Binary analyses (comparing groups above/below the threshold identified on ROC analysis) showed higher hazard ratios for regurgitant volume and fraction than LVEDV. The differences in AUC and hazard ratios were small however, with some overlap of the confidence limits, the latter likely due to the binary nature of the analyses and moderate sample size. In general, regurgitant volume and fraction showed very similar discriminatory power; regurgitant fraction has the modest advantage of being a body size-independent variable.

Regurgitant fraction >33% had high sensitivity (85%) and specificity (92%) for identifying patients who progressed to symptoms and surgery (Figure 2). A single threshold value may not provide all information however, and the data showed further useful thresholds: all patients with a regurgitant fraction >51% (n=8) progressed to surgery (100% positive predictive value), while all but two patients with a regurgitant fraction >43% (n=20) progressed
to surgery (90% positive predictive value). At the other end of the scale, no patients with a regurgitant fraction <26% (n=45) progressed to surgery (100% negative predictive value). Survival curves are however better for assessing the effect of time on events (to account for the fact that some events require adequate follow up to occur). There was significant separation of the groups over time, with survival without surgery at the median time point (2.0 years) of 95% for patients with regurgitant fraction ≤33% compared to 33% for patients with regurgitant fraction >33% (p<0.0001 by logrank test). The data were also analysed using the highest regurgitant fraction during follow up (there were 20 patients with serial CMR scans). This may allow for increasing values over time and may also be closer to clinical practice (waiting until a threshold is reached). Using the highest regurgitant fraction showed similar discriminatory power on ROC analysis (AUC 0.93), and similar separation of survival curves at the median time point of 1.9 years; surgery-free survival was 93% and 34% for regurgitant fractions ≤33% and >33% respectively (Figure 3). In patients with highest regurgitant fraction ≤33%, longer term surgery-free survival at 8 years showed a slight increase compared to analysis using the first recorded regurgitant fraction (91% and 83% respectively), indicating the few patients that developed higher degrees of regurgitation over time and were moved to the crossover group. All patients with a regurgitant fraction >33% eventually had surgery over 8-9 years of follow up, but subject numbers were small in the later years. The average time to surgery when using the highest regurgitant fraction was slightly reduced, as would be expected (mean: 2.4 years, median: 1.9 years).

The association of aortic regurgitant fraction with outcome remained robust in sub-group analyses. There was no significant difference between Oxford and the other participating centres; table 3, p=0.59 by logrank test on Kaplan-Meier survival analysis (Figure 3c). Comparing
centres using free-breathing CMR flow sequences (Oxford and Leeds) with the other two centres using breath-hold sequences also showed no difference in the association of regurgitant fraction with outcome (p=0.84 by logrank test on Kaplan-Meier survival analysis). Restricting the analyses to only those patients that developed LV dilation or dysfunction as an indication for surgery (excluding patients for whom symptoms developed) again showed a similar association with outcome to the whole group. The area under the curve on ROC analysis was 0.91, and survival without surgery to 2.0 years (the median time point) was 97% for those with regurgitant fractions ≤33%, and 39% for those with regurgitant fraction >33% (p<0.0001 by logrank test).

The association of LVEDV with outcome appeared slightly lower than regurgitation quantification, though the differences were slight and confidence limits overlap. Combining LV end-diastolic volume with regurgitant fraction provided further improvement on either parameter alone however (Figure 3d). The combination may thus provide the most robust discrimination, especially given that both parameters are measured in one CMR examination. LV ejection fraction was not able to predict events (AUC 0.55; p=0.43). CMR LV mass showed some predictive power (AUC 0.74; p<0.0001), but this parameter is closely related to LVEDV, and the similar mass:volume ratios in all groups (table 4) suggests that LVEDV is likely to be a significant confounding factor.

Comparison with the surgical group

Data from the surgical group are shown in table 4. This showed similar mean aortic regurgitation and LV volumetric indices to the crossover group and both were significantly larger than in the conservative group. Ejection fraction was lower in the surgical group (mean 57.1% versus 62.9% and 63.6% for the crossover and conservative groups respectively; p<0.01 for both comparisons), perhaps reflecting a more advanced stage of the disease. The higher proportion of bicuspid
valves in the crossover group (0.55, compared to 0.29 in the conservative group, p=0.003 by Chi-squared analysis), might be explained by the slightly higher mean regurgitant fraction (mean 33.4% vs. 25.8% for tricuspid valves; p=0.004).

Discussion

The association of aortic regurgitation quantitation with outcome

Our data demonstrate the potential value of quantifying aortic regurgitation with CMR, which showed a significant association with the future need for surgery, including patients who developed asymptomatic LV dilation or dysfunction. Patients already destined for surgery (the ‘surgical’ group) also had measures of aortic regurgitation that were not significantly different from the ‘crossover’ group, suggesting that a similar threshold of regurgitation had been reached in the surgical group before symptoms occurred. These CMR parameters might thus be predictors of future events, but this requires testing in a future prospective study.

Comparison with LV volumetric indices

Quantifying the regurgitation showed a slightly better association with events than CMR-derived LV indices, despite highly accurate measurements of LV volumes and function by CMR. LVEDV still had good discriminatory power however, and was an independent predictor on multivariate analyses. The combination of LVEDV with regurgitant fraction provided a slight enhancement over aortic regurgitation alone, and LV volumes and function are important in the overall assessment of the patient. Given these factors, and that both are readily available from a standard CMR scan, the combination of CMR quantification of aortic regurgitation and LV volumes could be a valuable component of the work-up in patients with aortic regurgitation. The slightly stronger association of outcome with aortic regurgitation indices compared to LV
volumes, and the ability of regurgitant fraction to identify patients who would develop excess LV dilation or dysfunction as indications for surgery, suggests that increases in regurgitation may occur before LV dilation. This would be logical given that regurgitation is the physiological stimulus for LV dilation in this patient group, though is not conclusively proven with our data.

LV mass showed reasonable discriminatory ability in identifying patients likely to progress to surgery (AUC 0.74). It is however closely related to LV volume, and was not an independent predictor on multivariate analysis. Other studies have not shown any predictive power of wall thickness and the LV mass to volume ratios were similar for all three subject groups in our study, suggesting that there is no excess increase in mass over that required for the chamber volume increase, and that the apparent association of LV mass with outcome is likely to be confounded by its close link to LV volume.

Comparison with echocardiography and other CMR studies

Echocardiographic techniques for quantifying aortic regurgitation also exist, although there are potential inaccuracies from the calculations and assumptions involved. Quantitative AR assessment by echocardiography is primarily used to aid the grading of regurgitation severity, and may have improved grading from the semi-quantitative assessment used to identify patients in our study. It has also shown an association with the need for surgery, though in that paper 43% of patients with moderate AR on echocardiography progressed to surgery, suggesting a lower ability of quantitative echocardiographic AR grading to identify patients at risk of events. Previous studies comparing CMR with echocardiographic grading suggest only a moderate correlation, with significant overlap of CMR-quantified AR values across the echocardiographic grades, particularly between moderate and severe grades. It is of interest that in the Gabriel paper the AR groups defined as ‘truly severe’ had regurgitant volumes & fractions
predominantly above the thresholds we identified in our study. Other CMR studies of AR quantitation\textsuperscript{11,28,29} also showed significant overlap between quantitative values and AR grades by other techniques, but none have examined the potential value of AR quantitation in clinical management.

**Comparison with previous studies of outcome in aortic regurgitation**

Bonow et al’s 1991 study\textsuperscript{23} had similar methodology to our own, in a similar sized group of patients, and examined the prediction of clinical events in initially asymptomatic patients who underwent echocardiography. Both this and the 1995 Tornos study\textsuperscript{4} showed a predictive ability for end-diastolic diameter (>7.0cm) and end-systolic diameter (>4.0cm but especially >5.0cm). These findings are in keeping with our data which showed an association with outcome for end-diastolic and end-systolic volumes, though the addition of CMR measurements of LV volume and quantification of AR adds to these existing studies with more modern imaging techniques. Other studies have examined the prediction of outcome post-surgery in patients with aortic regurgitation,\textsuperscript{5,6,30} or in a mixed asymptomatic and pre-surgical group of patents,\textsuperscript{31} and confirmed that symptoms, reduced ejection fraction and excess LV dilation are associated with worse long term outcome. These studies helped inform the current guidelines for surgery in aortic regurgitation,\textsuperscript{3} but also highlight the value in identifying patients prior to symptoms or significant LV dilation or dysfunction, as this study aims to do.

**Clinical utility**

The ability to identify patients prior to symptoms or excess LV dilation/dysfunction would be clinically important. These patients might be considered for early surgery, and at the very least could be followed more closely. Our sample size was modest however, and to support a change in clinical practice, particularly where cardiac surgery is concerned, requires better
demonstration of patient benefit in a randomised trial comparing early surgery with surgery based on conventional indications. Quantitative CMR indices may provide the appropriate tool for identifying suitable patients for such a trial. Conversely, patients with lower quantities of aortic regurgitation and LV end-diastolic volume might be reassured of the good medium term prognosis, and may require less frequent follow-up, aiding the efficient use of healthcare resources.

Limitations

The moderate sample size and relatively small number of events limit the strength of our conclusions, though follow up was for a reasonable period of time (mean 2.6 years, and up to 9 years).

The lack of blinding to the CMR data in three of the centres may also have biased results. There are however no current CMR criteria/thresholds for recommending surgery, and we attempted to minimise any bias where possible, and confirmed that there were no significant differences in the association with the progression to surgery between centres. It is possible however that some bias remains, particularly given the subjective nature of symptom assessment. The CMR sequence for flow measurement also differed between centres, as did the analysis software, but the associations with outcome were no different between sub-groups, which suggests the results may be generalizable for both types of sequence and different vendor software.

There remain a limited number of contra-indications to MRI, including most pacemakers and other implanted metallic devices, and a few patients are unsuitable for CMR. Prosthetic heart valves are not a contra-indication, however.
Conclusions

Quantification of aortic regurgitation with CMR showed significant associations with outcome, particularly when combined with CMR-derived LV volume. The study was of moderate size however and not all clinicians were blinded to the CMR results. These CMR parameters might prove useful for identifying suitable patients for early aortic valve replacement, but a clinical trial is recommended to confirm this and determine clinical benefit.

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Conflict of Interest Disclosures: None.

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Table 1. Receiver operating characteristic (ROC) data. Comparison of the ability of each CMR parameter to identify the initially asymptomatic patients who would develop indications for surgery, using receiver operating characteristic (ROC) analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>Threshold</th>
<th>p</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitant fraction (%)</td>
<td>0.93 (0.87-0.97)</td>
<td>&gt; 33</td>
<td>&lt;0.0001</td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td>0.96 (0.90-0.99)</td>
<td>&gt; 42</td>
<td>&lt;0.0001</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>Regurgitant volume index (ml/m²)</td>
<td>0.95 (0.89-0.98)</td>
<td>&gt; 23</td>
<td>&lt;0.0001</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>0.88 (0.80-0.93)</td>
<td>&gt; 246</td>
<td>&lt;0.0001</td>
<td>87</td>
<td>77</td>
</tr>
<tr>
<td>LVEDV index (ml/m²)</td>
<td>0.86 (0.79-0.92)</td>
<td>&gt; 129</td>
<td>&lt;0.0001</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>0.78 (0.70-0.86)</td>
<td>&gt; 88</td>
<td>&lt;0.0001</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>LVESV index (ml/m²)</td>
<td>0.77 (0.68-0.84)</td>
<td>&gt; 45</td>
<td>&lt;0.0001</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.55 (0.45-0.65)</td>
<td>&lt; 59</td>
<td>0.43</td>
<td>38</td>
<td>77</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>0.74 (0.64-0.81)</td>
<td>&gt; 187</td>
<td>&lt;0.0001</td>
<td>72</td>
<td>68</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>0.73 (0.63-0.81)</td>
<td>&gt; 90</td>
<td>&lt;0.0001</td>
<td>74</td>
<td>64</td>
</tr>
</tbody>
</table>

AUC = area under the curve; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; p = p value for ROC curve; Sens = sensitivity; Spec = specificity; threshold = value for each parameter which best identified the ‘crossover’ group.
Table 2. Cox proportional hazard regression and multiple logistic regression analyses for the variables with significant discriminatory ability on ROC analysis (AUC>0.70).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cox proportional hazard regression (binary analysis)</th>
<th>Multiple logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (B-exponent)</td>
<td>p-value</td>
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<tr>
<td>Regurgitant fraction (%)</td>
<td>16.0 (6.7-38.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Regurgitant volume (ml)</td>
<td>13.2 (3.8-45.8)</td>
<td>&lt;0.0001</td>
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<tr>
<td>LVEDV (ml)</td>
<td>16.3 (5.8-45.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>7.0 (3.2-15.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>3.2 (1.6-6.5)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Analysis was binary for the Cox regression (comparing groups above/below the optimal threshold identified from ROC analysis); and continuous for multiple logistic regression (per unit increase), with subsequent binary analysis. Only absolute rather than indexed values were used, as these showed marginally better discriminatory power on ROC analysis and including both would result in significant confounding of the closely related variables. On multivariate analysis, values are shown for the variables with significant independent predictive value. 95% confidence limits are shown in brackets for all results.
Table 3. Proportion of asymptomatic patients developing indications for surgery over time, according to CMR regurgitant fraction, and stratified by CMR centre.

<table>
<thead>
<tr>
<th>CMR Centre</th>
<th>n</th>
<th>Proportion developing indications for surgery</th>
<th>Kaplan-Meier p-value for difference by logrank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Highest CMR regurgitant fraction ≤33%</td>
<td>Highest CMR regurgitant fraction &gt;33%</td>
</tr>
<tr>
<td>Oxford</td>
<td>39</td>
<td>0.04 (n=24)</td>
<td>0.80 (n=15)</td>
</tr>
<tr>
<td>Other centers</td>
<td>74</td>
<td>0.08 (n=48)</td>
<td>0.81 (n=26)</td>
</tr>
</tbody>
</table>

Table 4. CMR parameters by group. Comparison of CMR parameters between the three groups of patients with aortic regurgitation.

<table>
<thead>
<tr>
<th>Number in group</th>
<th>Conservative</th>
<th>Crossover</th>
<th>Surgical</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.8 ±16.8</td>
<td>45.7 ±18.7</td>
<td>55.6 ±16.5*</td>
<td>0.04</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.4 ±10.0</td>
<td>176.6 ±9.0</td>
<td>173.8 ±8.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Proportion of male subjects</td>
<td>0.69</td>
<td>0.92†</td>
<td>0.91†</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.1 ±16.4</td>
<td>83.0 ±13.0</td>
<td>83.2 ±18.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.94 ±0.22</td>
<td>2.00 ±0.18</td>
<td>1.98 ±0.25</td>
<td>0.31</td>
</tr>
<tr>
<td>Bicuspid valve frequency</td>
<td>0.29</td>
<td>0.55†</td>
<td>0.24</td>
<td>0.006</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132.9 ±19.3</td>
<td>134.2 ±16.0</td>
<td>135.1 ±21.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>68.8 ±15.0</td>
<td>59.4 ±13.5</td>
<td>63.5 ±16.3</td>
<td>0.17</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td>27.5 ±15.5</td>
<td>74.7 ±28.5††</td>
<td>80.5 ±38.7††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regurgitant volume index (ml/m²)</td>
<td>14.1 ±7.6</td>
<td>37.4 ±14.5††</td>
<td>41.4 ±21.0††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>21.8 ±9.8</td>
<td>42.0 ±9.5††</td>
<td>45.6 ±11.0††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>209.5 ±54.7</td>
<td>301.1 ±61.6††</td>
<td>315.8 ±91.1††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDV index (ml/m²)</td>
<td>108.0 ±25.3</td>
<td>151.6 ±31.6††</td>
<td>160.6 ±48.6††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>78.7 ±35.5</td>
<td>113.0 ±33.0††</td>
<td>138.4 ±59.4††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESV index (ml/m²)</td>
<td>40.5 ±17.8</td>
<td>57.1 ±17.3††</td>
<td>70.3 ±31.8††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV Ejection fraction (%)</td>
<td>63.6 ±8.7</td>
<td>62.9 ±6.4</td>
<td>57.1 ±10.9††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echo LVEDD (cm)</td>
<td>5.9 ±0.6</td>
<td>6.6 ±0.7††</td>
<td>6.6 ±0.8††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echo LVESD (cm)</td>
<td>3.7 ±0.6</td>
<td>4.1 ±0.6††</td>
<td>4.4 ±0.8††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>173.2 ±73.1</td>
<td>232.2 ±80.1††</td>
<td>277.4 ±77.8††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>88.5 ±34.8</td>
<td>117.1 ±40.0††</td>
<td>143.7 ±41.1††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass/LVEDV ratio (g/ml)</td>
<td>0.83 ±0.26</td>
<td>0.78 ±0.25</td>
<td>0.91 ±0.24</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Abbreviations same as for table 1. Values are means ±standard deviation; p-values shown for one-way ANOVA with the exception of bicuspid valve frequency and proportion of male subjects which were by chi-squared analysis; bold figures indicate p<0.05. Individual group comparisons using Bonferroni correction are also shown: †p<0.01, ††p<0.001 and †††p<0.0001 vs. the conservative group; *p<0.05 surgical vs. crossover groups.
Figure Legends:

Figure 1. CMR flow measurement in aortic regurgitation. Top: still frame from steady-state free precession cine showing left ventricular outflow tract view in diastole with the aortic regurgitation jet (arrowed) and the slice location for through-plane flow measurement (parallel lines). Middle: example through-plane flow images; left – anatomical (magnitude) image in systole, middle – flow (phase) image in systole showing forward flow in white, right – flow (phase) image in diastole showing regurgitant flow in black. Bottom: resulting flow-time curve showing volume of regurgitation. LV = left ventricle, LA = left atrium, Ao = aorta.

Figure 2. Discriminatory ability of aortic regurgitant fraction. Top: receiver operating characteristic (ROC) curve for the ability of aortic regurgitant fraction to identify asymptomatic patients who would develop symptoms or other indications for surgery. Bottom: dot plot showing regurgitant fraction in the conservative and crossover groups, with the optimal threshold of 33% shown.

Figure 3. Surgery-free survival by aortic regurgitant fraction. Kaplan-Meier graphs for survival without surgery in 113 asymptomatic subjects with at least moderate aortic regurgitation initially treated conservatively and followed for up to 9 years. a) Stratified by the highest aortic regurgitant fraction measured by CMR during follow up ≤33% (n=74) and >33% (n=39), with the time of the scan with highest regurgitant fraction used as the baseline. b) Similar graph stratified by CMR-derived LV end-diastolic volume ≤246ml (n=60) and >246ml (n=53). c) Same graph as in a), stratified by both highest CMR regurgitant fraction and CMR centre. d) Similar graph stratified by both highest CMR regurgitant fraction and LV end-diastolic volume.