UNIVERSITY OF LEEDS

This is a repository copy of *Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification*.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/100181/

Version: Accepted Version

Article:
Myerson, SG, D'Arcy, J, Christiansen, JP et al. (7 more authors) (2016) Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification. Circulation, 133 (23). pp. 2287-2296. ISSN 0009-7322

https://doi.org/10.1161/CIRCULATIONAHA.115.017888

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

White Rose university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

DOI: 10.1161/CIRCULATIONAHA.115.017888

Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantitation

Running title: *Myerson et al.; Mitral regurgitation: outcome with CMR*

Saul G. Myerson, MB, ChB, MD, FRCP, FESC[1]; Joanna d'Arcy, MB, ChB, MRCP, DAvMed[1]; Jonathan P. Christiansen MB, ChB, MD, FRACP, FACC, FCSANZ[2]; Laura E. Dobson, MBChB, MRCP[3]; Raad Mohiaddin, PhD, FRCR, FRCP, FESC[4]; Jane M. Francis, DCR(R), DNM[1]; Bernard Prendergast, DM, FRCP, FESC[1]; John P. Greenwood, MB ChB, PhD, FRCP[3]; Theodoros D. Karamitsos, MD, PhD[1]; Stefan Neubauer, MD, FRCP, FACC, FMedSci[1]

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

Address for Correspondence:
Saul Myerson, MB, ChB, MD, FRCP, FESC
Department of Cardiovascular Medicine
John Radcliffe Hospital
Headley Way
Oxford OX3 9DU, United Kingdom
Tel: +44 1865 234597
Fax: +44 1865 740449
E-mail: saul.myerson@cardiov.ox.ac.uk

Journal Subject Terms: Magnetic Resonance Imaging (MRI); Valvular Heart Disease

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

Abstract

Background—Surgery for severe mitral regurgitation (MR) is indicated if symptoms or LV dilation/ dysfunction occur. However, prognosis is already reduced by this stage and earlier surgery on asymptomatic patients has been advocated if valve repair is likely, but identifying suitable patients for early surgery is difficult. Quantifying the regurgitation may help, but evidence for its link with outcome is limited. Cardiovascular magnetic resonance (CMR) can accurately quantify MR, and we examined whether this was associated with the future need for surgery.

Methods and Results—109 asymptomatic patients with echocardiographic moderate or severe MR had baseline CMR scans and were followed for up to 8 years (mean 2.5±1.9 years). CMR quantification accurately identified patients who progressed to symptoms or other indications for surgery: 91% of subjects with regurgitant volume ≤55ml survived to 5 years without surgery compared to only 21% with regurgitant volume >55ml ($p<0.0001$); similar separation was observed for regurgitant fraction below and above 40%. CMR-derived end-diastolic volume index showed a weaker association with outcome (proportions surviving without surgery at 5 years: 90% for LVEDVi <100ml/m^2 versus 48% for ≥100ml/m^2) and added little to the discriminatory power of regurgitant fraction/volume alone.

Conclusions—CMR quantification of mitral regurgitation was associated with the development of symptoms or other indications for surgery, and showed better discriminatory ability than 'reference-standard' CMR-derived ventricular volumes. CMR may be able to identify appropriate patients for early surgery, with the potential to change clinical practice, though the clinical benefits of early surgery require confirmation in a clinical trial.

Key words: mitral regurgitation; prognosis; outcome; cardiovascular magnetic resonance imaging; mitral valve

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

Background

Mitral regurgitation (MR) is usually well tolerated, and even those with severe asymptomatic regurgitation can survive many years, though around a third develop indications for surgery by 5 years.[1] Mitral valve repair or replacement is indicated once symptoms or adverse cardiac features develop[2] (e.g. left ventricular dysfunction/excess dilation), as prognosis is significantly reduced without treatment.[3-5] However, even with surgery prognosis may be reduced at this stage, and early surgery for severe regurgitation has been advocated.[6, 7] The latest guidelines now consider this to be 'reasonable' (class 2a indication) if severe MR is present, the chance of mitral repair is high (>95%), and the surgery is carried out in a centre of excellence with a very low mortality, or other conditions exist (pulmonary hypertension or new onset atrial fibrillation).[2] This 'aggressive' approach has to be balanced against the favourable natural history of untreated mitral regurgitation without symptoms or other adverse features, and the risks of early surgery, particularly in an elderly population in whom the risks of surgery are higher. There is therefore considerable debate between those who advocate a 'watchful waiting' strategy[1] versus those who favour early surgery.[8, 9] Determining the correct clinical approach is hindered by the lack of any controlled trial of early surgery, and the difficulty in identifying which patients should be offered this while asymptomatic. Advance identification of those patients likely to progress to symptoms or other indications for surgery in the near future could highlight the group most likely to benefit, and facilitate early surgery before prognosis was reduced.

Quantifying the MR in those with significant regurgitation (rather than qualitative grading) might be one method to identify such patients. This can be achieved with echocardiography (Echo),[10] though Echo quantitation is primarily used to aid grading into mild, moderate and severe regurgitation,[10] rather than identifying patients for surgery. One important

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

study has shown an association of quantitative Echo MR grading with mortality in medically-treated patients,[11] but this did not address the identification of patients for surgery.

Cardiovascular magnetic resonance (CMR) is able to quantify mitral regurgitation with high accuracy and reproducibility, using a combination of left ventricular (LV) volumetric measurement and aortic flow quantification with phase contrast velocity mapping.[12] Given that left ventricular (LV) volumes and function are also important for MR assessment, and that CMR is considered the 'reference-standard' method for measuring these,[13] it would appear to be an optimal technique for the assessment of mitral regurgitation. We previously used this technique in patients with aortic regurgitation, and demonstrated a strong association of the quantification of regurgitation with outcome.[14] We therefore sought to examine whether a similar approach using CMR quantitation of mitral regurgitation and LV indices might be able to predict which asymptomatic patients with significant (moderate or severe) MR were likely to progress to symptoms or other established indications for surgery. We also aimed to compare the CMR quantitation of mitral 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, Leeds, London (UK) and Auckland (New Zealand). All asymptomatic patients with moderate or severe chronic organic mitral regurgitation on echocardiography were eligible for inclusion and underwent baseline CMR scanning. Exclusion criteria included the presence of 'functional' mitral regurgitation (secondary to annular dilation or LV dysfunction), other significant valve

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

disease and clinical and/or angiographic evidence of coronary disease.

Subjects were followed for up to 8 years. Those who remained asymptomatic and under conservative management were designated the 'conservative' group, while those who developed symptoms or other established indications for surgery[2] were designated the 'crossover' group, with the decision for surgery taken as the point of censoring. Subjects were only included in the crossover group if the surgery was indicated on established criteria,[2] which do not include CMR assessment. Any subjects undergoing mitral valve replacement/repair for indications outside these criteria (including mitral repair performed for asymptomatic severe MR without other indications of adverse prognosis) remained in the conservative group but were censored at the time of surgery. In addition, a minimum period of one month was required between the CMR scan and the decision for surgery, to avoid the potential bias of patients having a predesignated CMR scan 'en-route' to surgery. All clinical decisions were taken by the treating physician. In Oxford, patients participated in a research study, 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 (having been initially diagnosed with Echo) and clinicians had access to the CMR data, although as indicated above, there are no CMR-based criteria for surgery.

A third group was also included to compare CMR parameters with both the conservative and crossover groups. This group included patients who had already developed established indications for surgery[2] and were scheduled for mitral valve repair/replacement (the 'surgical' group). They underwent identical CMR scans to the other groups.

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.

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

CMR scanning

All scans were performed on clinical 1.5 Tesla scanners (Siemens Avanto [Siemens Medical Solutions, Erlangen, Germany] or Philips Intera [Philips Healthcare, Best, Netherlands] and analysed in each centre using dedicated software (Argus [Siemens], CMR42 [Circle Cardiovascular Imaging, Calgary, Canada] or CMRtools [Cardiovascular Imaging Solutions, London, UK]) for both volumes and flow, according to standard acquisition guidelines.[12] 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, 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, and LV stroke volume (LVSV) was derived from: LVEDV-LVESV. Each value was also indexed to body surface area. Cine image sequences were steady-state free precession; temporal resolution 35-45msec; echo time 1.40-1.54msec; repetition time 2.80-3.08msec; field of view 380x380mm; flip angle 50-60^{o}).

Aortic forward flow was quantified using through-plane phase-contrast velocity-mapping as previously described,[15, 16] with the image plane placed either just above the aortic valve at end-diastole or at the sinotubular junction (Figure 1). 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. Free-breathing flow sequences were used in Oxford, while breath-hold flow sequences were used in the other three centres. Our previous work has shown that the choice of pulse sequence (free-breathing versus breath-hold) does not significantly affect the quantitative results.[14] In all centres, the potential for background flow offset errors was reduced[17] by ensuring flow sequences were acquired with the region of interest located at the

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

isocentre of the magnet to minimise any inhomogeneities in the magnetic field. Image parameters: temporal resolution 25-55msec; echo time 2.6-3.2msec; repetition time 4.3-7.8msec; field of view 320x320mm; velocity window 2.0-2.5m/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.

Standard CMR quantification of MR involves the deduction of aortic flow from LV stroke volume (LVSV – aortic forward flow). In the absence of inter-ventricular shunting, this equates to the volume of mitral regurgitation. This technique is robust in the presence of changing degrees of MR during systole, in addition to eccentric and/or mobile mitral regurgitant jets. Regurgitant fraction was also determined (regurgitant volume/LV stroke volume x 100%).

Echocardiography

Transthoracic echocardiograms were acquired for clinical management a mean of 47.1 ±71.6 days from the baseline CMR scan, according to standard protocols.[18] The images for the prospectively followed subjects (conservative and crossover groups) were re-assessed by the researchers, blinded to CMR and outcome data, and determination of the grade of MR on echocardiography was made. This was based on multiple two-dimensional imaging parameters, as described in the American Society of Echocardiography guidelines.[10] These were both qualitative and semi-quantitative, and quantitative assessments were used wherever feasible (including assessment of effective regurgitant orifice area (EROA) by the proximal isovolumetric surface area method[19]) if accurate measurements could be obtained.

Data assessment and statistical analysis

Receiver operating characteristic (ROC) analysis was used as the initial test to identify the imaging parameters with a reasonable ability (area under the curve [AUC] >0.75) to identify

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

patients who would develop symptoms or other indications for surgery during follow up. The optimal threshold for sensitivity and specificity was determined using the Youden index. Step-wise Cox proportional-hazards regression analysis was also performed on these parameters to determine which were independent predictors.

Kaplan-Meier survival curves are more appropriate for assessing the occurrence of events over time, and these were generated for parameters with an ROC AUC >0.70 to identify the strongest predictors. There are however no existing CMR thresholds for regurgitation severity to determine the sub-groups for comparing progression over time. In addition, it is likely that there is an increasing (continuous) risk with increasing regurgitation/ventricular size, and a single threshold may not necessarily be appropriate. To determine the best cut-off thresholds for separating groups, Cox proportional hazards was used, with each parameter investigated separately in a univariate Cox model. The factors were dichotomised at different cut-off levels, and discrimination was assessed by Harrell's C and Somers' D statistics. The cut-off thresholds with the highest Harrell's C and Somers' D statistics were used to separate groups in the survival analyses.

All analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, USA) with the exception of the ROC analyses which were performed with MedCalc version 9.3.1 (MedCalc Software, Mariakerke, Belgium), and the Cox proportional hazards assessment of different cut-off thresholds, which was performed in 'R' version 3.2.3. Values shown are means ±standard deviation and a p-value of <0.05 was considered the threshold for statistical significance.

Results

109 asymptomatic patients with at least moderate MR on echocardiography were included in the

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

study and followed for up to 8 years (mean 2.5 ± SD 1.9 years; median 1.6 years; 25th percentile 0.8 years; 75th percentile 3.5 years). Twenty five patients (23%) underwent mitral valve repair/replacement during the follow-up period (the 'crossover' group), having developed symptoms (n=19) or other established echocardiographic indications for surgery (excessive LV dilation [ESD >4.0cm], n=4; or pulmonary hypertension [>50mmHg] with a repairable valve, n=2). The mean time from CMR scan to the decision on surgery in this group was 1.9 years (median: 1.1 years; 25th and 75th percentiles 0.4 and 3.0 years respectively), with 85% of events occurring within four years. Seven patients underwent mitral surgery but did not have conventional indications, and remained in the 'conservative' group, though censored at the time of surgery. The surgery in these seven subjects was mainly mitral repair for severe MR but without clear indications of adverse prognosis; the mean regurgitant fraction was 36% (range 26-56%).

Association with the need for surgery

The ROC analyses identified several baseline CMR parameters associated with the development of indications for surgery (table 1). Quantitative measures of MR (mitral regurgitant volume and fraction) both had a high area under the curve (AUC), with good sensitivity and specificity. CMR LV volumetric indices also showed good discriminatory ability. LV mass showed some predictive power, but this parameter is closely related to LVEDV, and the similar mass:volume ratios in all groups (table 2) suggests that LVEDV is likely to be the main determinant of LV mass. Cox regression analysis showed independent associations for regurgitant volume (b exponent 1.03 [95% CI 1.01-1.05] per ml increase, p=0.01), and for regurgitant fraction (b exponent 1.05 [95% CI 1.01-1.09] per % increase, p=0.01) if assessed separately from regurgitant volume – this was otherwise too closely related. Assessment of the best dichotomous

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

cut-off threshold for discrimination of the need for surgery was performed for regurgitant volume, regurgitant fraction and LVEDVindex. For regurgitant volume, cut-off levels between 30 and 65 ml were analysed using Cox proportional hazards, and the highest values of the Harrell's C and Somers' D statistics were associated with a cut-off threshold of 55 ml. For regurgitant fraction, cut-off levels between 20 and 50% were investigated, and the optimum cut off level was 40%. For LVEDVindex, cut-off levels between 80 and 130 ml/m^2 were investigated, and the optimum cut off level was 100 ml/m^2. These thresholds were then used to separate sub-groups in the survival analyses.

CMR measures of regurgitation demonstrated substantial separation of groups over time. Subjects with a regurgitant volume ≤55ml had a very high chance of remaining free of symptoms or surgery: 95% at the median time (1.6 years) and 91% at 5 years. This contrasted with 54% at 1.6 years and 21% at 5 years for patients with regurgitant volume >55ml ($p<0.0001$ by logrank, Figure 2a). Similar differences in survival without surgery were seen for regurgitant *fraction* above and below 40%. Inclusion of an additional threshold at a regurgitant fraction of 50% however (dividing the cohort into 3 sub-groups of ≤40%, 41-50% and >50%) revealed a further separation in survival without surgery, and we have illustrated this incremental risk of surgery with increasing regurgitant fraction in figure 2b. There were no significant differences in survival curves amongst the participating centres ($p=0.80$ by logrank test).

LVEDV also showed a reasonable association with outcome over time, though slightly weaker than for measures of regurgitation (proportions surviving without surgery at the median of 1.6 years: 96% for LVEDVi <100ml/m^2 versus 71% for ≥100ml/m^2; $p=0.0001$), Figure 2c. However, stratifying groups by LVEDV in addition to regurgitant volume in the survival analysis did not provide any further separation of the curves than those for regurgitant volume

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

alone, which was a better predictor (Figure 3a). There were only 2 subjects with high regurgitant volumes (>55ml) but lower LVEDVi (<100ml/m^2), suggesting that in almost all cases, once a high volume of MR was present, LVEDV was increased (as might be expected).

Echocardiographic grading of MR performed less well in predicting subjects who progressed to surgery, despite the use of quantitative assessment to guide grading where feasible (n=53, 49% of the total). Many of those identified as severe MR on Echo had MR volumes on CMR <55ml, and remained asymptomatic (n=28). There was much less of a tendency to underestimate the MR with Echo (compared to CMR), with only 5 subjects with moderate MR on Echo and regurgitant volume >55ml by CMR. Overall, if the CMR threshold of a regurgitant volume >55ml is used to define severe MR, 33 subjects (30% of the total) were reclassified by CMR compared to echocardiographic grading. The prediction of events using only quantitative Echo thresholds for severity (effective regurgitant orifice area above and below 0.40cm^2) showed only modest separation of survival curves (figure 2d), though numbers in this sub-group were smaller (n=53), and the difference in outcome was not statistically significant. Using Echo-derived regurgitant volume >60ml as the threshold provided very similar results (data not shown). Furthermore, in both moderate and severe echocardiographic MR sub-groups, there was similar separation of survival curves by CMR quantitation (Figure 3b). 65 subjects had follow-up echocardiograms during the study period and these were also analysed in the same blinded fashion as the initial studies. Nearly all had similar findings to the first scan, with only one subject who progressed to surgery showing a change in the grade of MR by Echo (from moderate to severe), but this may not be surprising given the tendency for the initial Echo to overestimate the severity of MR, highlighted above.

Comparison with the surgical group

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

Descriptive data from all groups, including the surgical cohort, are shown in table 2. Statistical comparisons were not made between groups however, as the time-dependent (i.e. incomplete) nature of the separation into conservative and crossover groups would make this statistically inappropriate. The surgical cohort showed similar mean mitral regurgitation and LV volumetric indices to the crossover group, and both parameters were larger than in the conservative group. There were no significant differences in ejection fraction, or RV parameters. Systolic blood pressure was lower in the surgical group compared to the conservative one.

Discussion

The association of mitral regurgitation quantitation with outcome

Quantifying mitral regurgitation with CMR showed a strong association with the future need for surgery over the subsequent 5 years, demonstrating the potential value of this approach. Patients already destined for surgery (the 'surgical' group) also had measures of mitral regurgitation that were similar to 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 useful clinical predictors of the need for surgery. In addition to the potential for high quantitative indices of regurgitation to identify candidates for early surgery, subjects with lower amounts of MR (regurgitant volume ≤55ml or fraction ≤40%) had a very low chance of requiring surgery over the subsequent few years and could be followed up less frequently, with a favourable impact on healthcare resources. We identified the best single thresholds to predict the groups with different outcomes, but it is likely that there is an increasing risk with increasing values of the parameters, as the separation of the three groups for mitral regurgitant fraction illustrate (figure 2b). The thresholds identified in this study should be treated with caution

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

however, as there are some important limitations to the study. The cohort was only a moderate size, and the lack of a separate validation cohort resulted in the optimal cut-off thresholds being derived from and applied to the same dataset. The degree of separation between groups is therefore likely to be optimistic and may not be as strong in other studies/cohorts. For similar reasons, the value of the cut-off threshold should also be treated with caution, and a validation cohort would be required to confirm these thresholds.

The separation of the Kaplan-Meier event curves was slightly less pronounced than in our previous work in aortic regurgitation,[14] and this may be due to a number of factors. Mitral regurgitation is dependent on other factors (e.g. fluid balance, filling pressures, LV function), and the quantity of MR may vary more widely over a period of time than for aortic regurgitation. Thus, a single measurement may show a weaker link with outcome. Secondly, the CMR technique for quantification is indirect and relies on both LV stroke volume measurement and aortic forward flow quantification, introducing more potential for error, which could also weaken the association with outcome. The threshold of regurgitant fraction that best differentiated the groups likely to progress to surgery was also higher for mitral regurgitation (40%, versus 33% for aortic regurgitation), which may reflect a greater ability of the left ventricle to cope with mitral regurgitation before the development of symptoms, particularly as the additional volume load is ejected into the low pressure left atrium rather than the high pressure aorta. Our findings also suggest that the thresholds for identifying severe mitral and aortic regurgitation should differ. There are currently no CMR-specific thresholds, but the AHA-ACC echocardiographic thresholds indicating severe regurgitant volume (60ml) and fraction (50%) are the same for both valve lesions.[2] Interestingly, these values are close to the thresholds for the best identification of future symptoms in the present study, both for mitral regurgitant volume (55ml) and for fraction,

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

especially with the higher rate of progression to symptoms with a regurgitant fraction >50% (Figure 2b). For aortic regurgitation however, the AHA-ACC thresholds are somewhat higher than the optimal thresholds identified in our previous study (regurgitant fraction 33% or volume 42ml), which may suggest that different thresholds for each valve lesion and/or CMR-specific thresholds should be considered.

Comparison with LV and RV volumetric indices

The highly accurate measurements of LVEDV by CMR showed a reasonable association with survival without surgery over time, but regurgitation quantification showed a better separation of survival curves. Further, combining LVEDV and regurgitant volume sub-groups did not improve survival curves over regurgitant volume alone, and subjects with low regurgitant volumes (figure 3a) had similarly low rates of surgery irrespective of the LVEDVi. This suggests that LVEDV may partly be a function of the quantity of regurgitation (supported by the strong association of LVEDV with mitral regurgitant volume).[20] 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, and the several subjects with higher LVEDVi but low regurgitant volume (figure 3a) suggests there are other factors influencing LVEDV. Despite its longstanding use in previous guidelines, LVESV did not have a particularly strong association with outcome. However, LV volumes and function are important in overall assessment and readily available from a standard CMR scan. LV mass showed an apparent association with progression to surgery but this parameter is closely related to LV volume and it was not an independent predictor. Other studies have not shown any predictive power of wall thickness[21] and LV mass:volume ratios were similar for all three 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

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

outcome is likely to be confounded by its close relation to LV volume. The lack of any notable association of RV parameters (including volumes and ejection fraction) with outcome, together with the similar (normal) values in all three groups, suggests that RV dilation or dysfunction may be a late and uncommon occurrence, and may only occur secondary to LV dysfunction and the resulting pulmonary hypertension.

Systemic blood pressure

Systemic blood pressure was lower in the crossover and surgical groups, which may reflect the larger mitral regurgitant volumes (and reduced aortic forward flow) in these groups. It is possible the lower blood pressure was a confounding factor that might have increased the chance of developing indications for surgery, although no previous study has suggested a causal link between blood pressure and the need for surgery in mitral regurgitation. Further, systolic blood pressure was not a good discriminator on the initial receiver operating characteristic analysis (area under the curve − 0.64).

Comparison between echocardiography and CMR

In our study, transthoracic echocardiographic grading showed a more modest ability to discriminate between subjects progressing to surgery and those remaining asymptomatic, with significant spread of the Echo grades across the conservative and crossover groups, and a tendency for Echo to overestimate the degree of regurgitation when compared to CMR. We were however only able to apply quantitative Echo grading in ~50% of subjects, and had this been possible in all subjects, it may have improved the results for Echo. Previous studies also suggest only moderate agreement between CMR and Echo,[22-24] and limited reproducibility for quantitative Echo grading.[25, 26] This may be in part due to assumptions in the PISA technique (the commonest Echo quantitative method). The peak PISA measurement assumes a static

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

degree of regurgitation throughout systole, and this may not hold true for some subjects, particularly those with mitral prolapse - this could result in over-estimation of the degree of regurgitation.[27] Other aspects may also reduce the accuracy of PISA Echo quantitation, including irregular regurgitant jets (eccentrically-directed, fan-shaped/crescentic, or multiple), non-hemispheric geometry of the PISA shell and difficulty in identifying the regurgitant orifice.[26-28] Although it is acknowledged there is no ideal gold standard for comparison, CMR quantitation of regurgitation has shown better intra- and inter-observer variability,[29] and good agreement with *in-vitro* models[23] and post-surgical LV remodelling.[24]

Previous studies of outcome in mitral regurgitation

Earlier studies examined outcomes after mitral valve surgery, demonstrating poorer 10 year survival following the development of symptoms[3] or LV impairment,[4] and poorer post-operative LV function once pre-operative end-systolic dimension exceeded 5.0cm (an indicator of both dilation and reduced function).[30] These studies informed the current guideline indications for surgery in mitral regurgitation[2] and, like the present study, highlight the value of identifying patients prior to symptoms or significant LV dilation/dysfunction. Chronic mitral regurgitation also increases left atrial size and can raise pulmonary pressure, resulting in RV dysfunction. Both increased atrial size[21, 31] and reduced RV or biventricular function[32] have been shown to predict medium and long term survival following mitral surgery. Reduced RV function on exercise has also shown some association with symptoms and outcome.[33, 34] The lack of an association of RV function with future progression to surgery in our study might indicate that this is a late sign in decompensated mitral regurgitation, which is usually absent in an asymptomatic population such as ours – several of the previous studies involved patients with symptoms. We also did not assess RV function during exercise, and it is unclear whether this might explain some of the difference.

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

Few studies have predicted outcome (mostly progression to surgery) in an initially asymptomatic group of patients. The Mayo Clinic study[11] showed a significant association of quantitative echocardiographic grading with prognosis (both mortality and cardiac events), although this study did not specifically assess the progression to cardiac surgery, which was not included as a cardiac event. Subjects with moderate MR also had a significant cardiac event rate (40%, versus 62% for severe MR), which suggests a weaker ability of quantitative Echo to identify patients at risk of events, and highlights the difficulty in separating moderate and severe mitral regurgitation in some patients - the very group examined in our study.

Clinical utility

Accurate assessment of the severity of mitral regurgitation and LV volumes/function is crucial in clinical decision making[7] and CMR would already seem well suited for this. The additional ability to predict the onset of symptoms or other indications for surgery just prior to their occurrence would be clinically important, and might identify a suitable cohort for careful surveillance and early surgery. Conversely, patients with less severe mitral regurgitation might be reassured of the good medium term prognosis, and require less frequent follow-up, thereby improving the efficient use of healthcare resources.

Observational studies have shown better outcomes in patients undergoing early surgery for mitral regurgitation,[6, 35] but their limitations are well recognised. A randomised trial comparing early surgery with surgery based on conventional indications is required to demonstrate patient benefit, and our study may provide the basis for such a trial, with quantitative CMR indices providing the appropriate tool for identifying suitable patients.

Limitations

The moderate sample size and relatively small number of events limit the strength of our

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

conclusions, though follow up was for a reasonable period of time (mean 2.5 years, maximum 8 years). Although the study suggests that CMR may be used to identify candidates for early mitral surgery, there is no evidence that operating earlier achieves a clinical benefit. This would require a clinical trial, which we strongly encourage. In addition, our thresholds for separating groups were derived from a single cohort, without a separate validation cohort to confirm the cut-points or the degree of separation. It is likely therefore that the degree of separation between sub-groups may be lower than in this study, and/or the thresholds for separating groups may vary. A validation cohort would be required to confirm these thresholds. In addition, the use of single cut-points to separate groups may underestimate the degree to which there is an incremental risk with increasing values of the parameters. Although we only identified further separation with multiple thresholds for mitral regurgitant fraction, larger sample sizes and different cohorts may reveal an incremental risk for other parameters.

The lack of blinding to the CMR data in three of the investigating centres may also have biased outcome. However, there are no current CMR criteria/thresholds for recommending surgery, and we attempted to minimise bias where possible and confirmed that there were no significant differences in the association with the progression to surgery between centres. Nevertheless, remaining bias is possible, particularly given the subjective nature of symptom assessment.

The echocardiographic studies were acquired for clinical purposes, and it is possible that these were not as comprehensive as those performed specifically for a research study might be. Every effort was made however to ensure the best quality assessment, including blinded re-analysis by the researchers.

This study relies on events over time and it is possible that some subjects assigned to the

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

'conservative' group were censored before they had developed symptoms. These subjects would be likely however to have higher degrees of mitral regurgitation, which would have likely resulted in a greater separation between groups if more time had occurred, rather than a reduction in the discriminatory ability observed in the study.

We did not include data on subjects' medication, and it is possible that outcome may have been influenced by this. However, no previous studies have shown a significant effect of any drug on outcome in mitral regurgitation.

Conclusions

Quantification of mitral regurgitation with CMR showed a significant association with the future need for mitral valve surgery, and was superior to CMR-derived LV volume and echocardiographic grading of regurgitation. These CMR parameters might prove useful for identifying suitable patients for early mitral valve repair/replacement, and a randomised controlled trial is recommended to confirm these findings and determine clinical benefit. The same parameters may also be used to identify patients at low risk of future events, potentially facilitating reduced frequency of follow up and efficient use of healthcare resources.

Funding Sources: The research study was funded by a project grant from the Garfield-Weston Trust, London, UK (PMS/MMS – 02/03-620). The work was also supported by the Oxford National Institute for Health Research (NIHR) Biomedical Research Centre programme, and the NIHR Cardiovascular Biomedical Research Unit of the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London. SN acknowledges support from the Oxford British Heart Foundation Centre of Research Excellence.

Conflict of Interest Disclosures: None.

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

References:

1. Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, Schemper M, Maurer G, Baumgartner H. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238-2244.

2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD. 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. *Circulation*. 2014;129:e521-643.

3. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, Orszulak TA, Bailey KR, Tajik AJ, Frye RL. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: Rationale for optimizing surgical indications. *Circulation*. 1999;99:400-405.

4. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation*. 1994;90:830-837.

5. Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL, Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation: Determinants and long-term outcome. *J Am Coll Cardiol*. 2002;40:84-92.

6. Samad Z, Kaul P, Shaw LK, Glower DD, Velazquez EJ, Douglas PS, Jollis JG. Impact of early surgery on survival of patients with severe mitral regurgitation. *Heart*. 2011;97:221-224.

7. Nishimura RA, Otto C. 2014 acc/aha valve guidelines: Earlier intervention for chronic mitral regurgitation. *Heart*. 2014;100:905-907.

8. Enriquez-Sarano M. Timing of mitral valve surgery. *Heart*. 2002;87:79-85.

9. Schlant RC. Timing of surgery for patients with nonischemic severe mitral regurgitation. *Circulation*. 1999;99:338-339.

10. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777-802.

11. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005;352:875-883.

12. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (cmr) protocols, society for cardiovascular magnetic resonance:

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

Board of trustees task force on standardized protocols. *J Cardiovasc Magn Reson*. 2008;10:35.

13. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, Pennell DJ. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J*. 2000;21:1387-1396.

14. Myerson SG, d'Arcy J, Mohiaddin R, Greenwood JP, Karamitsos TD, Francis JM, Banning AP, Christiansen JP, Neubauer S. Aortic regurgitation quantification using cardiovascular magnetic resonance: Association with clinical outcome. *Circulation*. 2012;126:1452-1460.

15. Dulce MC, Mostbeck GH, O'Sullivan M, Cheitlin M, Caputo GR, Higgins CB. Severity of aortic regurgitation: Interstudy reproducibility of measurements with velocity-encoded cine mr imaging. *Radiology*. 1992;185:235-240.

16. Sondergaard L, Lindvig K, Hildebrandt P, Thomsen C, Stahlberg F, Joen T, Henriksen O. Quantification of aortic regurgitation by magnetic resonance velocity mapping. *Am Heart J*. 1993;125:1081-1090.

17. Kilner PJ, Gatehouse PD, Firmin DN. Flow measurement by magnetic resonance: A unique asset worth optimising. *J Cardiovasc Magn Reson*. 2007;9:723-728.

18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: A report from the american society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-1463.

19. Enriquez-Sarano M, Bailey KR, Seward JB, Tajik AJ, Krohn MJ, Mays JM. Quantitative doppler assessment of valvular regurgitation. *Circulation*. 1993;87:841-848.

20. Uretsky S, Supariwala A, Nidadovolu P, Khokhar SS, Comeau C, Shubayev O, Campanile F, Wolff SD. Quantification of left ventricular remodeling in response to isolated aortic or mitral regurgitation. *J Cardiovasc Magn Reson*. 2010;12:32.

21. Reed D, Abbott RD, Smucker ML, Kaul S. Prediction of outcome after mitral valve replacement in patients with symptomatic chronic mitral regurgitation. The importance of left atrial size. *Circulation*. 1991;84:23-34.

22. Van De Heyning CM, Magne J, Pierard LA, Bruyere PJ, Davin L, De Maeyer C, Paelinck BP, Vrints CJ, Lancellotti P. Assessment of left ventricular volumes and primary mitral regurgitation severity by 2d echocardiography and cardiovascular magnetic resonance. *Cardiovasc Ultrasound*. 2013;11:46.

23. Brugger N, Wustmann K, Hurzeler M, Wahl A, de Marchi SF, Steck H, Zurcher F, Seiler C.

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

Comparison of three-dimensional proximal isovelocity surface area to cardiac magnetic resonance imaging for quantifying mitral regurgitation. *Am J Cardiol*. 2015;115:1130-1136.

24. Uretsky S, Gillam L, Lang R, Chaudhry FA, Argulian E, Supariwala A, Gurram S, Jain K, Subero M, Jang JJ, Cohen R, Wolff SD. Discordance between echocardiography and mri in the assessment of mitral regurgitation severity: A prospective multicenter trial. *J Am Coll Cardiol*. 2015;65:1078-1088.

25. Biner S, Rafique A, Rafii F, Tolstrup K, Noorani O, Shiota T, Gurudevan S, Siegel RJ. Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. *JACC Cardiovasc Imaging*. 2010;3:235-243.

26. Gottdiener JS, Panza JA, St John Sutton M, Bannon P, Kushner H, Weissman NJ. Testing the test: The reliability of echocardiography in the sequential assessment of valvular regurgitation. *Am Heart J*. 2002;144:115-121.

27. Topilsky Y, Michelena H, Bichara V, Maalouf J, Mahoney DW, Enriquez-Sarano M. Mitral valve prolapse with mid-late systolic mitral regurgitation: Pitfalls of evaluation and clinical outcome compared with holosystolic regurgitation. *Circulation*. 2012;125:1643-1651.

28. Enriquez-Sarano M, Miller FA, Jr., Hayes SN, Bailey KR, Tajik AJ, Seward JB. Effective mitral regurgitant orifice area: Clinical use and pitfalls of the proximal isovelocity surface area method. *J Am Coll Cardiol*. 1995;25:703-709.

29. Cawley PJ, Hamilton-Craig C, Owens DS, Krieger EV, Strugnell WE, Mitsumori L, D'Jang CL, Schwaegler RG, Nguyen KQ, Nguyen B, Maki JH, Otto CM. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. *Circ Cardiovasc Imaging*. 2013;6:48-57.

30. Wisenbaugh T, Skudicky D, Sareli P. Prediction of outcome after valve replacement for rheumatic mitral regurgitation in the era of chordal preservation. *Circulation*. 1994;89:191-197.

31. Le Tourneau T, Messika-Zeitoun D, Russo A, Detaint D, Topilsky Y, Mahoney DW, Suri R, Enriquez-Sarano M. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. *J Am Coll Cardiol*. 2010;56:570-578.

32. Le Tourneau T, Deswarte G, Lamblin N, Foucher-Hossein C, Fayad G, Richardson M, Polge AS, Vannesson C, Topilsky Y, Juthier F, Trochu JN, Enriquez-Sarano M, Bauters C. Right ventricular systolic function in organic mitral regurgitation: Impact of biventricular impairment. *Circulation*. 2013;127:1597-1608.

33. Hochreiter C, Niles N, Devereux RB, Kligfield P, Borer JS. Mitral regurgitation: Relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients. *Circulation*. 1986;73:900-912.

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

34. Rosen SE, Borer JS, Hochreiter C, Supino P, Roman MJ, Devereux RB, Kligfield P, Bucek J. Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. *Am J Cardiol*. 1994;74:374-380.

35. Kang DH, Kim JH, Rim JH, Kim MJ, Yun SC, Song JM, Song H, Choi KJ, Song JK, Lee JW. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation*. 2009;119:797-804.

American Heart Association.
Circulation

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

Clinical Perspective

Early surgery has been advocated for asymptomatic patients with severe mitral regurgitation if valve repair is likely, but identifying suitable patients is difficult as many would remain asymptomatic for years without surgery. A greater ability to identify those that might benefit from early surgery would be highly advantageous. We assessed the ability of cardiovascular magnetic resonance (CMR) quantification of mitral regurgitation to predict the development of symptoms or other conventional indications for surgery in the near future, as these patients might represent a suitable group for early surgery. 109 asymptomatic patients with echocardiographic moderate or severe MR had baseline CMR scans and were followed for up to 8 years. CMR quantification showed a strong ability to predict patients who progressed to require surgery: 91% of subjects with regurgitant volume ≤55ml survived to 5 years without surgery compared to only 21% with regurgitant volume >55ml ($p<0.0001$); and similar separation was observed for regurgitant fraction below and above 40%. CMR-derived end-diastolic volumes or function did not add to the discriminatory power of regurgitant fraction/volume alone but are important for overall patient assessment. CMR may thus be able to identify patients likely to develop symptoms or other conventional indications for surgery in the near future, who would be an appropriate target group for early surgery, to avoid the potential reduced prognosis by the time symptoms occur. The clinical benefits of early surgery require confirmation in a clinical trial however.

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

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.

	AUC	Threshold	p	Sens (%)	Spec (%)
Regurgitant volume (ml)	0.81 (0.72-0.88)	> 55	<0.0001	72	87
Regurgitant volume index (ml/m^2)	0.79 (0.70-0.87)	> 29	<0.0001	78	82
Regurgitant fraction (%)	0.79 (0.70-0.86)	> 40	<0.0001	76	74
LVEDV index (ml/m^2)	0.75 (0.65-0.83)	≥ 95	<0.0001	91	56
LV mass (g)	0.77 (0.67-0.85)	> 171	<0.0001	74	73
LVESV index (ml/m^2)	0.71 (0.61-0.79)	> 36	0.0008	74	68
LV ejection fraction (%)	0.71 (0.61-0.79)	< 65	0.0006	60	76
RV ejection fraction (%)	0.62 (0.51-0.72)	<59	0.08	58	54

AUC = area under the curve; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; RV = right ventricular; p = p value for ROC curve; Sens = sensitivity; Spec = specificity; threshold = value for each parameter which best identified the 'crossover' group using the Youden index for optimal sensitivity and specificity.

American Heart Association.
Circulation

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

Table 2. CMR parameters by group. Comparison of CMR parameters between the three groups of patients with mitral regurgitation.

	Conservative	Crossover	Surgical
Number in group	84	25	43
Age (years)	65.1 ±14.9	63.8 ±12.6	66.3 ±7.5
Proportion of male subjects	0.65	0.76	0.60
Proportion in atrial fibrillation	0.19	0.32	0.24
Height (cm)	172.8 ±10.1	174.2 ±10.4	171.3 ±9.7
Weight (kg)	74.8 ±12.0	75.8 ±10.6	75.2 ±14.1
Body surface area (m^2)	1.88 ±0.18	1.89 ±0.24	1.91 ±0.17
Heart rate (beats/min)	68.5 ±13.9	67.3 ±10.3	73.0 ±13.8
Systolic BP (mmHg)	143.9 ±23.1	132.1 ±20.1	120.9 ±13.2
Diastolic BP (mmHg)	77.8 ±10.8	77.4 ±8.8	73.9 ±11.3
Regurgitant volume (ml)	39.4 ±20.0	65.9 ±23.7	70.1 ±29.5
Regurgitant fraction (%)	32.1 ±12.4	45.7 ±11.7	46.7 ±14.0
LVEDV (ml)	182.7 ±50.3	224.3 ±47.8	229.1 ±49.4
LVEDV index (ml/m^2)	97.9 ±25.1	117.5 ±23.0	122.1 ±23.8
LVESV (ml)	62.1 ±26.1	81.8 ±29.0	82.7 ±36.7
LVESV index (ml/m^2)	33.5 ±13.8	42.5 ±13.3	44.2 ±18.3
LV Ejection fraction (%)	66.9 ±7.6	63.9 ±7.4	64.9 ±9.3
LV mass (g)	144.5 ±49.9	192.9 ±46.4	192.9 ±61.6
LV mass index (g/m^2)	76.2 ±24.6	102.7 ±23.9	103.4 ±25.6
LV mass/LVEDV ratio (g/ml)	0.83 ±0.27	0.89 ±0.17	0.87 ±0.23
Echo LVEDD (cm)	5.4 ±0.8	6.2 ±0.5	6.1 ±0.8
Echo LVESD (cm)	3.3 ±0.7	3.6 ±0.6	3.8 ±0.9
Echo ERO (cm^2) ‡	0.58 ±0.75	0.57 ±0.28	
Echo regurgitant volume (ml) ‡	74.3 ±73.9	89.3 ±35.8	
RVEDV (ml)	149.1 ±45.1	147.2 ±36.3	154.8 ±40.7
RVESV (ml)	66.8 ±25.7	68.0 ±26.8	71.4 ±27.4
RV ejection fraction (%)	56.0 ±8.5	54.1 ±9.9	52.4 ±11.3

Values are means ±standard deviation. Note statistical comparisons are not made between groups, as the time-dependent nature of the allocation to conservative and crossover groups would make this inappropriate.
Abbreviations same as for table 1 except ERO = effective regurgitant orifice area. ‡ n=53 for these two parameters

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

DOI: 10.1161/CIRCULATIONAHA.115.017888

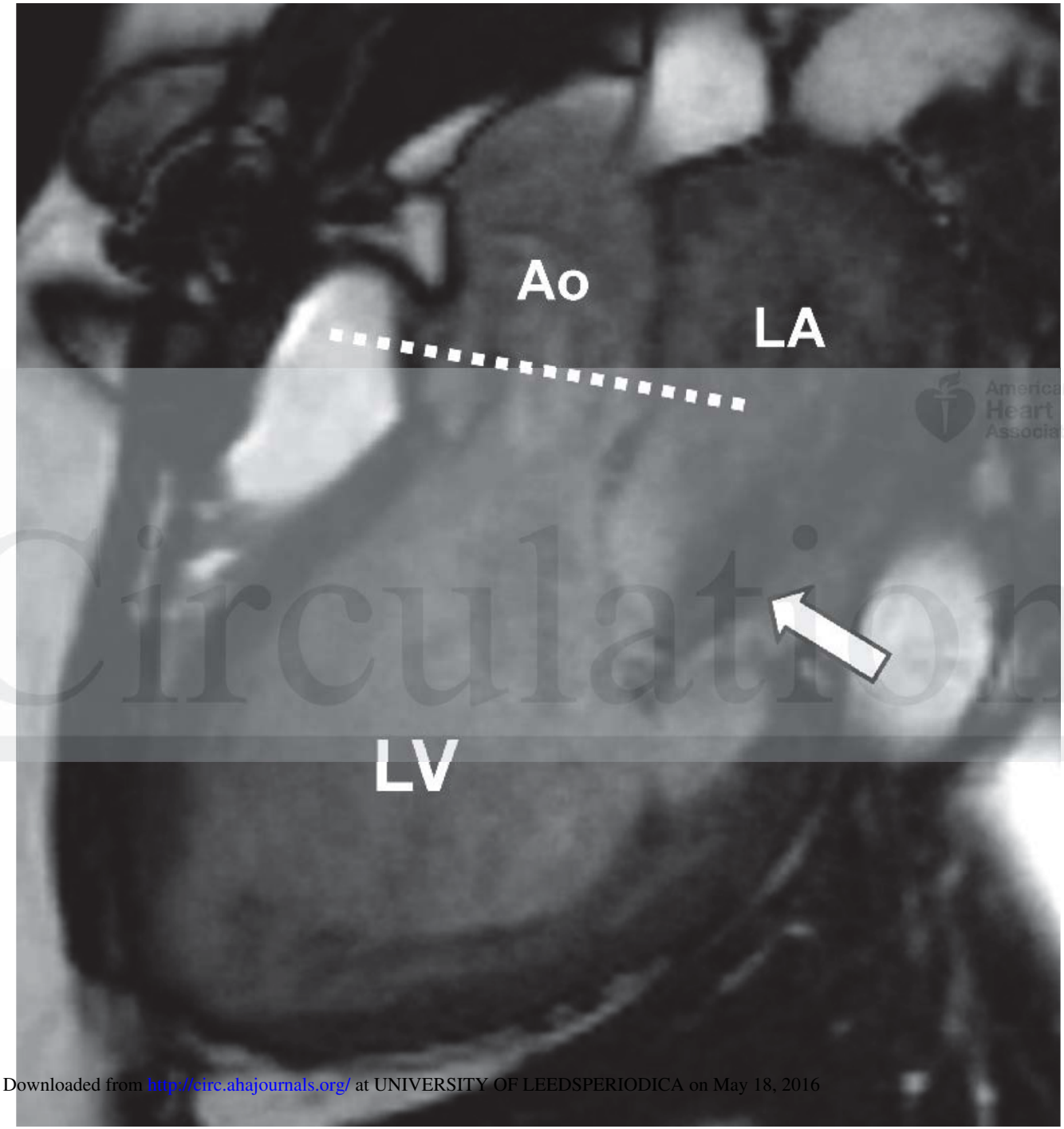
Figure Legends:

Figure 1. CMR flow measurement in mitral regurgitation. Still frame from steady-state free precession cine showing left ventricular outflow tract view in systole with the mitral regurgitation jet (arrowed) and the slice location for aortic through-plane flow measurement (dashed line). LV = left ventricle, LA = left atrium, Ao = aorta. Mitral regurgitant volume is calculated as: LV stroke volume – aortic forward flow.

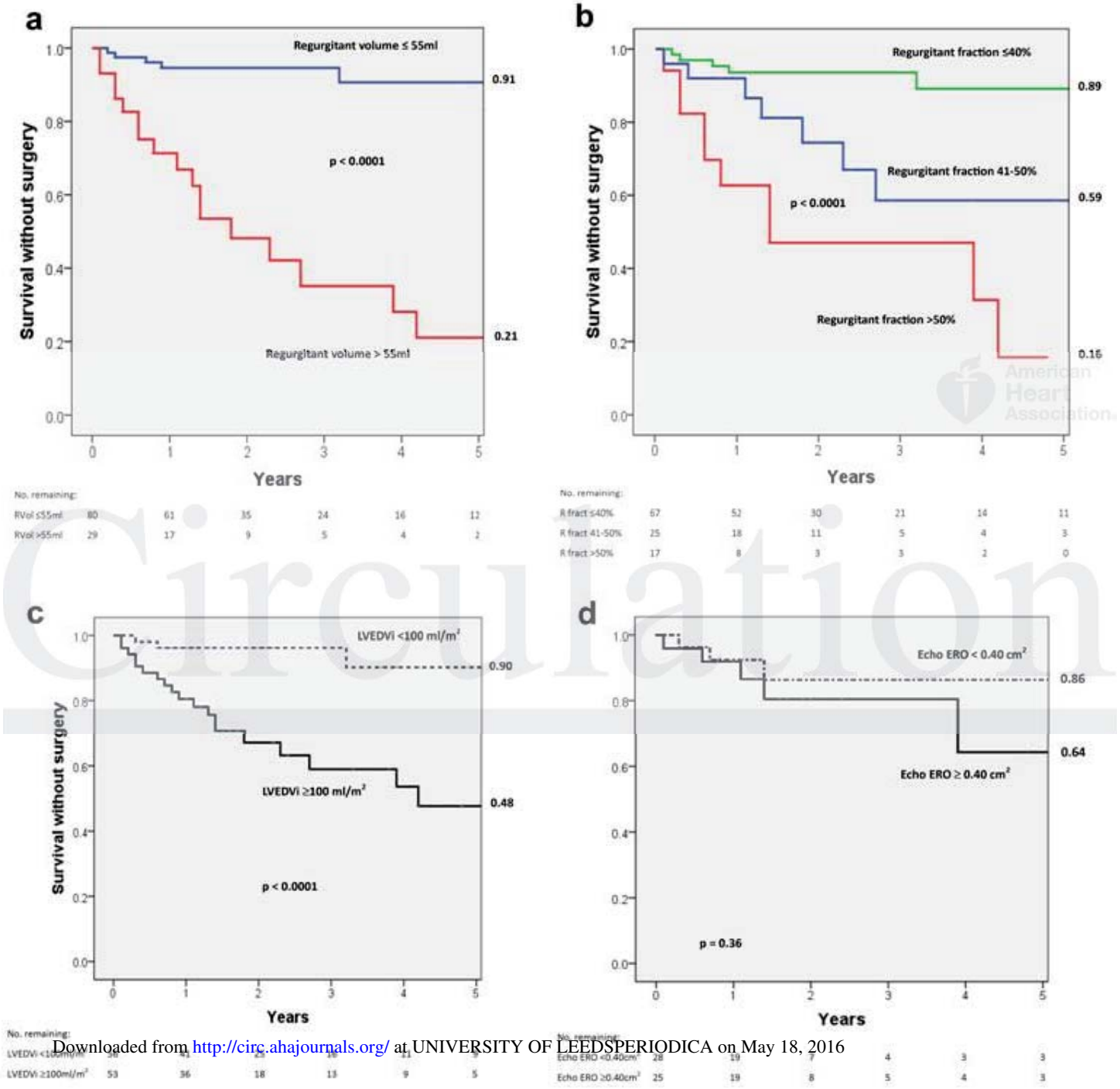
Figure 2. Surgery-free survival according to mitral regurgitant volume/fraction and LVEDVi. Kaplan-Meier graphs for survival without surgery in 109 asymptomatic subjects with at least moderate mitral regurgitation initially treated conservatively and followed for up to 8 years, stratified by CMR-derived a) mitral regurgitant volume; b) mitral regurgitant fraction; c) LV end-diastolic volume index (LVEDVi); and d) echocardiographic effective regurgitant orifice area (Echo ERO) $<0.40cm^2$ and $\geq 0.40cm^2$ (n=53 for this group).

Figure 3. a) Surgery-free survival, stratified by both CMR regurgitant volume and LVEDVi (NB there were too few subjects [n=2] with CMR regurgitant volume ≤55ml and LVEDVi $\geq 100ml/m^2$ and this group was excluded); b) CMR regurgitant volume and echocardiographic MR grade. Note: the group with CMR regurgitant volume >55ml and moderate MR on echo contains only 5 subjects.

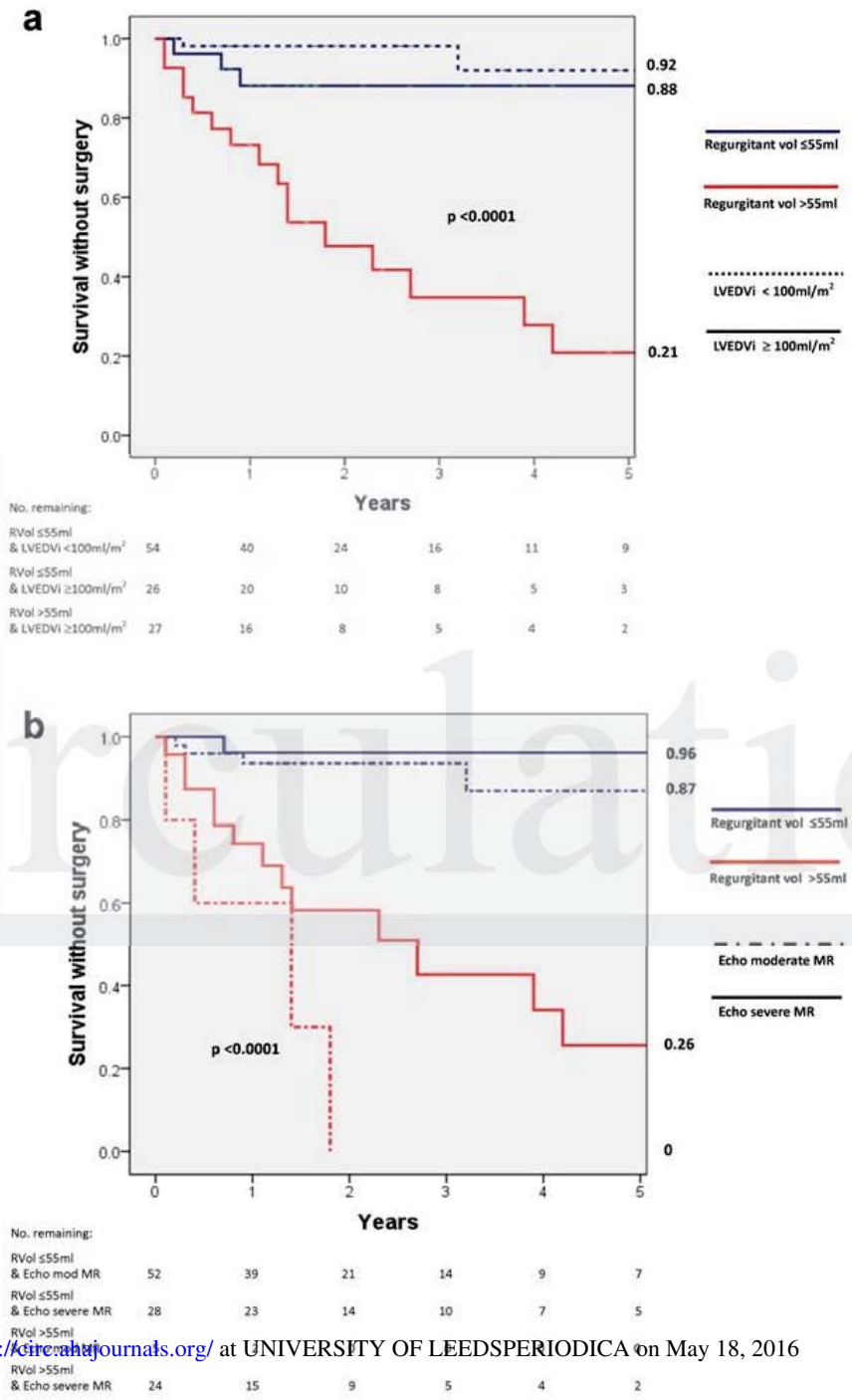
Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016



Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016



Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016



Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantitation

Saul G. Myerson, Joanna d'Arcy, Jonathan P. Christiansen, Laura E. Dobson, Raad Mohiaddin, Jane M. Francis, Bernard Prendergast, John P. Greenwood, Theodoros D. Karamitsos and Stefan Neubauer

Circulation. published online May 17, 2016;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2016/05/13/CIRCULATIONAHA.115.017888

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/

Downloaded from http://circ.ahajournals.org/ at UNIVERSITY OF LEEDSPERIODICA on May 18, 2016