EuroIntervention 2016;12:1176-1184

Mitral annular calcification is not associated with decreased procedural success, durability of repair, or left ventricular remodelling in percutaneous edge-to-edge repair of mitral regurgitation

Richard Cheng[1], MD; Emily Tat[1], BA; Robert J. Siegel[1], MD; Reza Arsanjani[2], MD; Asma Hussaini[1], PA; Moody Makar[3], MD; Yukiko Mizutani[1], MD; Alfredo Trento[4], MD; Saibal Kar[1]*, MD

1. Division of Cardiology, Cedars-Sinai Heart Institute, Los Angeles, CA, USA; 2. Division of Cardiovascular Diseases, Mayo Clinic, Scottsdale, AZ, USA; 3. Department of Anesthesiology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; 4. Division of Cardiothoracic Surgery, Cedars-Sinai Heart Institute, Los Angeles, CA, USA

R. Cheng and E. Tat contributed equally to the manuscript.

KEYWORDS

- MitraClip therapy
- mitral annulus calcification
- mitral valve insufficiency
- transcatheter mitral valve intervention
- valvular heart disease

Abstract

Aims: Mitral annular calcification (MAC) negatively influences outcomes in surgical mitral valve (MV) repair for mitral regurgitation (MR). However, there are no data on whether MAC impacts on outcomes of MitraClip percutaneous MV edge-to-edge repair. This study sought to investigate whether the presence of MAC impacts on the procedural success and durability of percutaneous transcatheter repair of MR using the MitraClip.

Methods and results: One hundred and seventy-three patients undergoing MitraClip repair for significant MR were studied. Patients with moderate-or-severe MAC (n=28) were compared to those with no-or-mild MAC. Post-procedural MR severity was not different (p=0.642) and MR reduction to moderate-or-less was equally high in patients with moderate-or-severe MAC (100%) and those without (96.7%), p=1.000. At one year, MR severity was not different (p=0.831), and there was no difference in the repair durability when comparing patients with moderate-or-severe MAC (93.8%) to those without (90.6%), p=1.000. All patients with moderate-or-severe MAC assessed at one year were in NYHA functional Class I-II and had haemodynamic improvements with a decrease in pulmonary artery systolic pressure (-6.5±13.1 mmHg), p=0.021, and end-diastolic left ventricular internal diameter (-3.9±6.5 mm), p=0.034, not different to those achieved by patients without MAC (both p>0.100).

Conclusions: Moderate-or-severe MAC scored by echocardiography and confirmed on fluoroscopy was not associated with decreased procedural success or durability of repair. Patients with moderate-or-severe MAC had improvements in clinical symptoms and haemodynamics, as well as decreased left ventricular dimensions.

**Corresponding author: Division of Cardiology, Cedars-Sinai Heart Institute, 8631 W 3rd Street, Suite 415E, Los Angeles, CA 90048, USA. E-mail: karsk@cshs.org*

SUBMITTED ON 04/03/2016 - REVISION RECEIVED ON 02/05/2016 - ACCEPTED ON 09/06/2016

DOI: 10.4244/EIJV12I9A191

EuroIntervention 2016;12:1176-1184

Introduction

Mitral annular calcification (MAC) is a degenerative process affecting the fibrous annulus of the mitral valve (MV) and is often associated with mitral regurgitation (MR)[1]. MAC is commonly found in patients referred for MV surgery and is associated with an increased intraoperative conversion from valve repair to replacement and negatively influences surgical outcomes[2]. In high surgical risk patients with significant MR, percutaneous edge-to-edge repair with the MitraClip® (Abbott Vascular, Santa Clara, CA, USA) has emerged as an alternative corrective therapy which results in significantly reduced MR, improvement of clinical symptoms, haemodynamics[3], and left ventricular function and decreased left ventricular (LV) dimensions[4,5]. However, it is not known whether MAC impacts on procedural success, durability of repair, and clinical and echocardiographic outcomes in percutaneous edge-to-edge repair of MR.

The development and acceleration in the severity of MAC has been hypothesised to be due to increased MV annular stress from increased afterload conditions such as from elevated systemic blood pressure and outflow track obstruction, leading to increased closing pressure and excess annular tension and resulting annulus degeneration[6]. MAC is also associated with coronary artery disease (CAD)[7], significant chronic kidney disease and haemodialysis[8,9], as well as age, female gender, hypertension, and diabetes mellitus[10,11]. MAC is also associated with increased rates of cardiovascular events and excess mortality[12].

MAC is most frequently identified by echocardiography. Multiple studies have utilised echocardiographic scoring systems to classify the severity of MAC[9,12,13]. Grading is carried out based on the degree of involvement of the mitral posterior annulus. MAC has been classified as mild when it involves less than one third of the annulus, moderate when it involves one third to two thirds of the annulus, and severe when it involves more than two thirds of the annulus[9,13,14].

In patients with significant MV disease with concomitant MAC undergoing surgery, the preferred surgical approach is the complete decalcification of MAC and reconstruction of the mitral annulus[15,16]. This process leads to increased operating time, a significant risk of cardiac rupture and injury to the circumflex artery[15,16], and an increased conversion from valve repair to replacement, all of which negatively influences surgical outcomes[2]. If MV replacement is attempted without annular decalcification, there is increased difficulty with securing the prosthetic valve inside a calcified annulus and a greater potential for periprosthetic leak and inadequate prosthetic valve sizing[16]. As surgery for MV disease with significant MAC can be challenging, there remains a clinical need for an alternative approach for this clinical situation.

This study sought to investigate whether the presence of MAC without significant leaflet calcification impacts on the procedural success and durability of percutaneous transcatheter repair using the MitraClip.

Methods

Patients who underwent MitraClip therapy between April 2009 and May 2014 were included in the analysis. Patients were divided into two groups based on having no-or-mild MAC versus moderate-or-severe MAC. The grading of MAC severity was performed on baseline pre-procedure transthoracic echocardiogram by two authors independently, disagreements being scored by consensus. Standard criteria were used to define MAC as mild if annular calcification involved one third or less of the posterior annulus, moderate if it involved one third to two thirds of the posterior annulus, and severe if it involved over two thirds of the posterior annulus[9,13,14]. Subsequently, fluoroscopy was used to confirm the presence of MAC. In cases of significant discrepancy, fluoroscopy was used to relabel patients with mild MAC on echocardiography to moderate-or-severe MAC if significant radiographic MAC was found, and to relabel patients with moderate-or-severe MAC on echocardiography to no-or-mild if no fluoroscopic MAC was found. The number of patients relabelled is reported. The severity and aetiology of MR were assessed by transthoracic and transoesophageal echocardiography by site echo physicians using a multiparametric approach to grade MR as described by the Mitral Valve Academic Research Consortium consensus and by standard American Society of Echocardiography guidelines[17,18].

BASELINE DEMOGRAPHICS AND ECHOCARDIOGRAPHIC PARAMETERS

Baseline demographic parameters compared between patients with no-or-mild MAC versus moderate-or-severe MAC included age, female gender, MR severity, chronic heart failure, CAD, myocardial infarction, atrial fibrillation, hypertension, diabetes, hyperlipidaemia, haemodialysis, creatinine, New York Heart Association (NYHA) functional class, Society of Thoracic Surgeons (STS) score, and left ventricular ejection fraction (LVEF). Additional baseline echocardiographic characteristics included are listed in **Table 1**. Severity of leaflet thickening, restriction, and calcification are graded based on a previously validated scoring system[9,13].

PROCEDURAL SUCCESS AND ECHOCARDIOGRAPHIC AND CLINICAL CHARACTERISTICS AT DISCHARGE AND ONE-YEAR FOLLOW-UP

Procedural success defined as MR reduction to moderate or less, mild-to-moderate or less, and mild or less was reported and compared between patients with and without moderate-or-severe MAC. In addition, pulmonary artery systolic pressure (PASP) at discharge, severity of MR at one year, PASP at one year, NYHA functional class at one year, and subsequent MV surgery were compared between groups.

DURABILITY OF PERCUTANEOUS REPAIR

Durability of repair was defined as successful retention of procedural success on the one-year post-MitraClip repair follow-up transthoracic echocardiogram. In patients who achieved MR reduction to moderate or less (≤2+), persistence of MR reduction of moderate or less at one year was reported and compared between groups. Retention of the same level or better MR reduction for patients who obtained initial MR reduction mild-to-moderate or less, and mild or less is also reported and compared between groups.

Table 1. Baseline echocardiographic characteristics.

	No-or-mild MAC n=145	Moderate-or-severe MAC n=28	*p*-value
LVID, end-diastolic (mm)	54.6±8.8	49.2±6.9	0.001
LVID, end-systolic (mm)	39.7±11.7	33.3±9.1	0.002
Vena contracta (mm)	6.3±2.0	5.9±2.0	0.419
Effective regurgitant orifice area (cm^2)	0.52±0.23	0.47±0.30	0.431
Regurgitant volume (mL)	73.9±29.1	68.0±34.7	0.419
Pulmonary vein flow reversal (%)	103/145 (71.0)	17/28 (60.7)	0.274
Mean mitral gradient, baseline (mmHg)	1.8±0.9	2.2±0.8	0.040
Peak mitral gradient, baseline (mmHg)	6.2±2.8	7.6±3.7	0.055
PASP, baseline (mmHg)	49.2±15.8	51.0±16.2	0.616
Leaflet thickening (%)			
None	40/145 (27.6)	3/28 (10.7)	0.068
Mild	84/145 (57.9)	19/28 (67.9)	
Moderate	19/145 (13.1)	6/28 (21.4)	
Severe	2/145 (13.8)	0/28 (0)	
Posterior mitral leaflet restriction (%)	76/145 (52.4)	9/28 (32.1)	0.063
Anterior mitral leaflet restriction (%)	25/145 (17.2)	3/28 (10.7)	0.576
Mitral valve calcification			
None	47/145 (32.4)	2/28 (7.1)	0.018
Mild	88/145 (60.7)	24/28 (85.7)	
More-than-mild	10/145 (6.9)	2/28 (7.1)	

LVID: left ventricular internal diameter; MAC: mitral annular calcification; PASP: pulmonary artery systolic pressure

CHANGES IN ECHOCARDIOGRAPHIC CHARACTERISTICS AS COMPARED BY PAIRED SAMPLES

End-diastolic left ventricular internal diameter (LVID), end-systolic LVID, ejection fraction, and PASP were compared at the time of baseline transthoracic echocardiogram and at one-year echocardiogram. In addition, PASP was compared at the time of baseline echocardiogram and at post-procedure discharge echocardiogram.

MITRAL ANNULAR CALCIFICATION AND SURVIVAL AFTER PERCUTANEOUS REPAIR

Cox proportional hazards regression for the presence of moderate-or-severe MAC on all-cause mortality is reported. In addition, a multivariate modelling was performed to include pre-specified variables previously reported to be associated with MAC (age, female gender, CAD, hypertension, diabetes, and haemodialysis status), as well as demographic and baseline characteristics that were different between patients with moderate-or-severe MAC and no-or-mild MAC (when p>0.100).

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS, Version 22 (IBM Corp., Armonk, NY, USA). Fisher's exact test was used for two-by-two categorical variables, a two-tailed Student's t-test was used for continuous variables, and a paired samples t-test was used for paired analysis of continuous variables. The Mann-Whitney U test was used for non-parametric variables, and the paired samples Wilcoxon signed-rank test was used for paired analysis of non-parametric variables. The study was approved by our institutional review board.

Results

One hundred and seventy-three patients were included in the analysis and mean clinical follow-up was 29.2±20.4 months; 6/173 (3.5%) patients were followed by their referring physician, and the remaining patients had at least one-year follow-up in the clinic unless the patient was no longer alive. Mean age at percutaneous repair was 77.1±12.5 years and 71/173 (41.0%) were female. MAC was present in 82/173 (47.4%) patients: mild in 54/82 (65.9%) cases, moderate in 18/82 (22.0%) cases, and severe in 10/82 (12.2%) cases. Five patients with mild MAC on echocardiography were found to have significant MAC on fluoroscopy and were relabelled as having moderate-or-severe MAC. Three patients with moderate MAC on echocardiography were found to have no-or-trivial MAC on fluoroscopy and were relabelled as having no-or-mild MAC. No patients with no MAC on echocardiography were found to have significant MAC on fluoroscopy, and no patients with severe MAC on echocardiography were found to have no-or-trivial MAC on fluoroscopy. Examples of patients who were relabelled are illustrated in **Figure 1**. Fluoroscopic examples of mild, moderate, and severe MAC are illustrated in **Figure 2**.

DEMOGRAPHIC, BASELINE, AND ECHOCARDIOGRAPHIC CHARACTERISTICS

Patients with moderate-or-severe MAC were older than patients without (84.2±8.1 vs. 75.7±12.8, p<0.001), more likely to be female (60.7% vs. 37.2%, p=0.034), and with a history of hypertension (100% vs. 76.7%, p=0.002). The distribution of NYHA functional class was more severe in patients with moderate-or-severe MAC (Mann-Whitney p=0.043) as was severity of STS score (13.2±7.3% vs. 10.1±8.0%, p=0.048). However, LVEF was higher (59.9±12.8 vs. 49.4±18.1%, p=0.001). The proportion of degenerative and functional MR was not different between the groups (p>0.010). Myxomatous degeneration or Barlow's disease occurred in 5/173 (2.9%) patients. Demographic and baseline characteristics are summarised in **Table 2**.

Patients with moderate-or-severe MAC had smaller end-diastolic LVID (49.2±6.9 vs. 54.6±8.8 mm, p=0.001) and end-systolic LVID (33.3±9.1 vs. 39.7±11.7 mm, p=0.002), and a marginally higher mean mitral gradient (2.2±0.8 vs. 1.8±0.9 mmHg, p=0.040). Severity of MR by vena contracta, effective regurgitant orifice area, regurgitant volume, and pulmonary vein systolic flow reversal was not different between the groups (all p>0.100). MV calcification was more severe in patients with moderate-or-severe MAC (Mann-Whitney p=0.018) but overall was low in the entire cohort (none-or-mild 93.1%). There was a trend towards

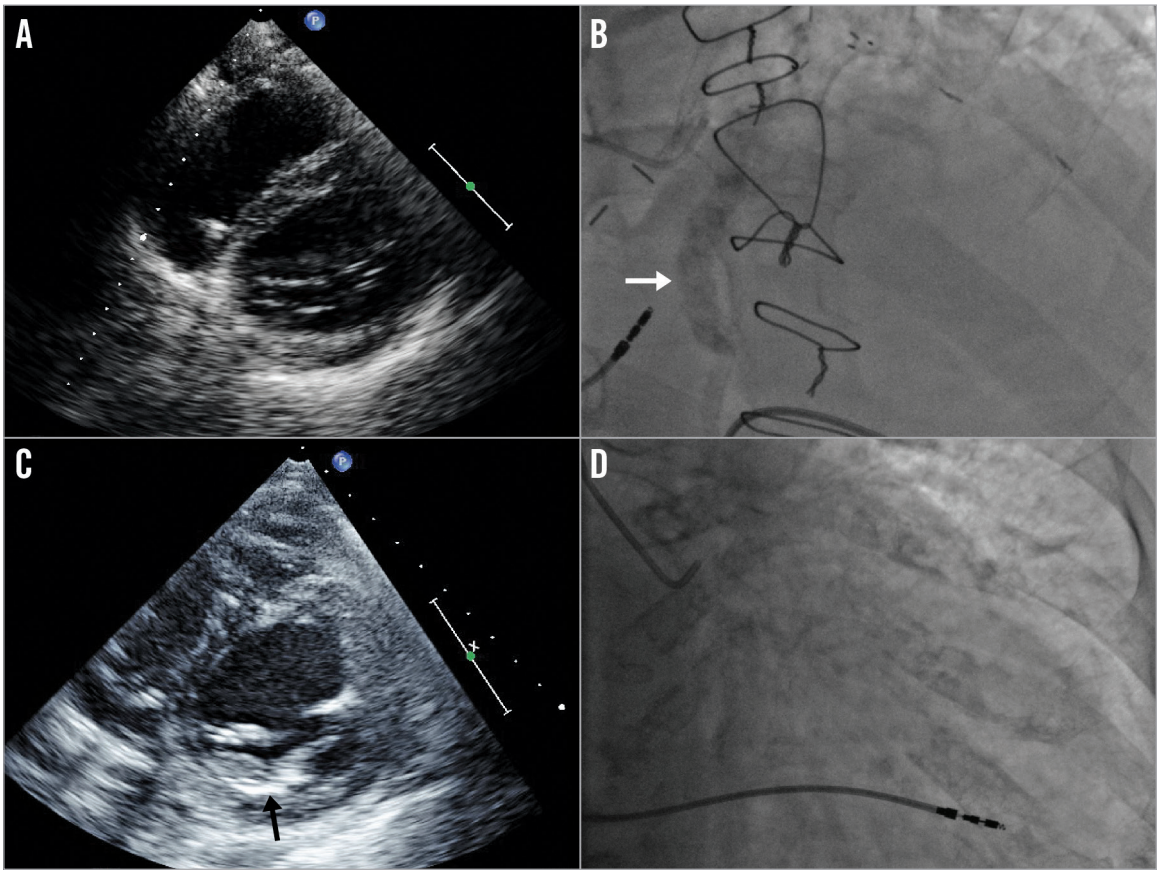

Figure 1. *Transthoracic echocardiographic and fluoroscopic examples of patients relabelled after confirmation fluoroscopy. Case example 1. An 89-year-old male with moderate-to-severe mitral regurgitation and prolapse of the posterior leaflet with no mitral annular calcification (MAC) on parasternal short-axis view at the level of the mitral valve (A) relabelled as having moderate-to-severe MAC when confirmation fluoroscopy (B) showed significant MAC (arrow) in a right anterior oblique cranial view. Case example 2. An 84-year-old female with severe central mitral regurgitation and restriction of the posterior leaflet with moderate MAC (arrow) on parasternal short-axis view at the level of the mitral valve (C) relabelled as having no-to-mild MAC when confirmation fluoroscopy (D) did not show the presence of significant MAC in a right anterior oblique caudal view.*

increased leaflet thickening in patients with moderate-or-severe MAC (Mann-Whitney p=0.068) but overall was low in the entire cohort (none-or-mild 84.4%). Baseline echocardiographic characteristics are summarised in **Table 1**.

PROCEDURAL SUCCESS AND ECHOCARDIOGRAPHIC AND CLINICAL CHARACTERISTICS AT DISCHARGE AND ONE-YEAR FOLLOW-UP

MR reduction to moderate or less occurred in 168/173 patients (97.1%), mild-to-moderate or less in 141/173 patients (81.5%), and mild or less in 112/173 patients (64.7%). Patients with moderate-or-severe MAC were equally likely to have procedural success as compared with patients with no-or-mild MAC with regard to distribution of MR severity (Mann-Whitney p=0.642), MR reduction to moderate or less (100% vs. 96.7%, p=1.000), MR reduction to mild-to-moderate or less (89.3% vs. 80.0% p=0.300), and MR reduction to mild or less (67.9% vs. 64.1% p=0.830).

At one year, MR reduction to moderate or less was present in 114/125 patients (91.2%), mild-to-moderate or less in 90/125 patients (72.0%), and mild or less in 73/125 patients (58.4%). There was no difference in MR severity at one year between patients with moderate-or-severe MAC and patients without (Mann-Whitney p=0.831). PASP at discharge and one year was decreased as compared with pre-procedural PASP (both $p<0.05$), and NYHA functional class at one year, and subsequent MV surgery **(Figure 3)** were not different between the groups. Results of echocardiographic and clinical characteristics at discharge and one-year follow-up are summarised in **Table 3**.

DURABILITY OF PERCUTANEOUS REPAIR

In patients with MR reduction to moderate after the procedure, 111/122 (91.0%) retained a reduction of moderate or less at one year. There was no difference in retention of MR reduction between patients with moderate-or-severe MAC (15/16; 93.8%) as compared with patients with no-or-mild MAC (96/106; 90.6%,

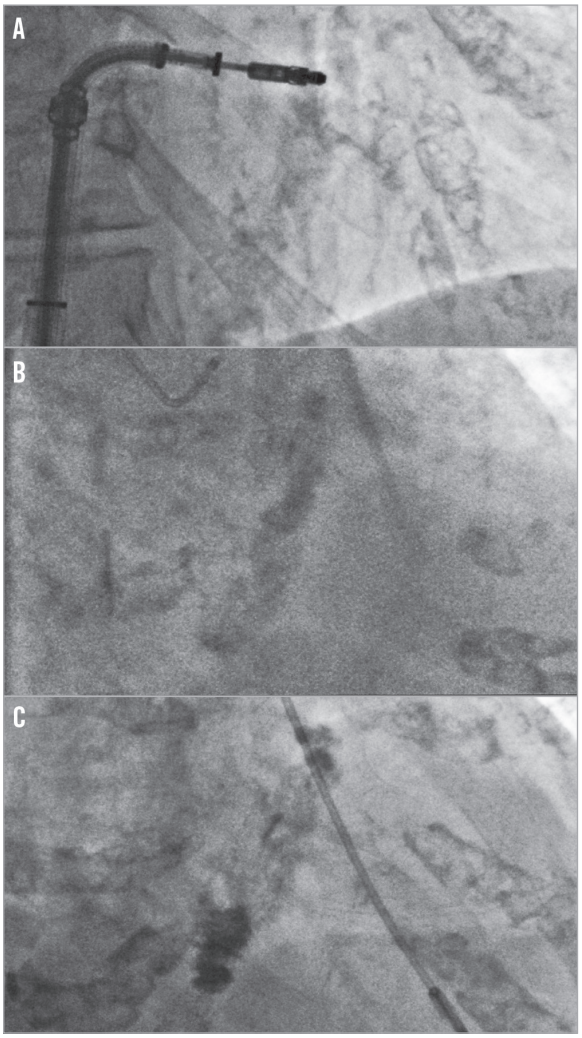

Figure 2. *Fluoroscopic scoring of mitral annular calcification. Fluoroscopic examples of mild (A), moderate (B), and severe (C) mitral annular calcification.*

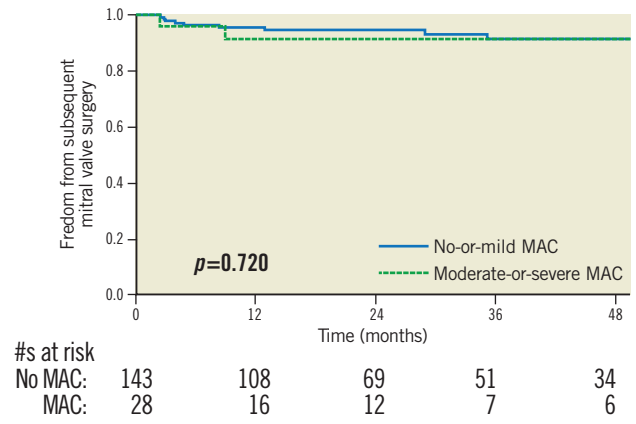

Figure 3. *Freedom from subsequent mitral valve surgery. Overall freedom from subsequent mitral valve surgery at 4 years was 91.2±2.7% and did not differ between patients with or without moderate-or-severe mitral annular calcification (MAC) (p=0.720).*

Table 2. Demographic and baseline characteristics.

	No-or-mild MAC n=145	Moderate-or-severe MAC n=28	*p*-value
Age (yrs)	75.7±12.8	84.2±8.1	<0.001
Female (%)	54/145 (37.2)	17/28 (60.7)	0.034
Mitral regurgitation severity (%)			
Moderate-to-severe	24/145 (16.7)	11/28 (39.3)	0.010
Severe	121/145 (83.4)	17/28 (60.7)	
Chronic heart failure (%)	108/145 (74.5)	20/28 (71.4)	0.814
Coronary artery disease (%)	76/145 (52.4)	18/28 (64.3)	0.302
Myocardial infarction (%)	38/145 (26.2)	6/28 (21.4)	0.813
Atrial fibrillation (%)	97/145 (66.9)	20/28 (71.4)	0.826
Hypertension (%)	111/145 (76.7)	28/28 (100)	0.002
Diabetes (%)	40/145 (27.6)	6/28 (21.4)	0.642
Hyperlipidaemia (%)	90/145 (62.1)	20/28 (71.4)	0.397
Haemodialysis (%)	10/145 (6.9)	0/28 (0)	0.369
Creatinine, baseline (mg/dL)	1.5±1.0	1.3±0.5	0.109
NYHA functional Class, baseline (%)			
I	1/143 (0.7)	0/28 (0)	0.043
II	23/143 (16.1)	1/28 (3.6)	
III	97/143 (67.8)	20/28 (71.4)	
IV	22/143 (15.4)	7/28 (25)	
NYHA functional Class III or IV, baseline (%)	119/143 (83.2)	27/28 (96.4)	0.082
STS score (%)	10.1±8.0	13.2±7.3	0.048
Left ventricular ejection fraction, baseline (%)	49.4±18.1	59.9±12.8	0.001

MAC: mitral annular calcification; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons

p=1.000). In patients with MR reduction to mild-or-moderate or less, 81/104 (77.9%) retained a reduction of mild-or-moderate or less at one year. There was no difference in retention of MR reduction between patients with moderate-or-severe MAC (11/15; 73.3%) as compared with patients with no-or-mild MAC (70/89; 78.7%, p=0.738). In patients with MR reduction to mild or less, 58/86 (67.4%) retained a reduction of mild or less at one year. There was no difference in retention of MR reduction between patients with moderate-or-severe MAC (7/12; 58.3%) as compared with patients with no-or-mild MAC (51/74; 68.9%, p=0.515). The distribution of MR severity in 125 patients who had complete baseline, discharge, and one-year echocardiograms is illustrated in **Figure 4**.

CHANGES IN ECHOCARDIOGRAPHIC CHARACTERISTICS AS COMPARED BY PAIRED SAMPLES

End-diastolic LVID decreased between baseline and one year both in patients with moderate-or-severe MAC (–3.9±6.5 mm, paired samples p=0.034) and in patients with no-or-mild MAC (–1.4±6.7 mm, p=0.039). PASP decreased between baseline and discharge both in patients with moderate-or-severe MAC

Table 3. Echocardiographic and clinical characteristics at discharge and one-year follow-up.

	No-or-mild MAC n=145	Moderate-or-severe MAC n=28	*p*-value
Clips (#)	1.6±0.6	1.4±0.5	0.029
MR severity, discharge			
None-or-mild	93/145 (64.1)	19/28 (67.9)	0.642
Mild-to-moderate	23/145 (15.9)	6/28 (21.4)	
Moderate	24/145 (16.7)	3/28 (10.7)	
Severe	5/145 (3.4)	0/28 (0)	
MR reduction to moderate or less	140/145 (96.7)	28/28 (100)	1.000
MR reduction to mild-to-moderate or less	116/145 (80.0)	25/28 (89.3)	0.300
MR reduction to mild or less	93/145 (64.1)	19/28 (67.9)	0.830
PASP, discharge (mmHg)	43.3±13.2	45.4±13.3	0.475
MR, one year			
None-or-mild	64/109 (58.7)	9/16 (56.3)	0.831
Mild-to-moderate	15/109 (13.8)	2/16 (12.5)	
Moderate	20/109 (18.3)	4/16 (25.0)	
Severe	10/109 (9.2)	1/16 (6.3)	
MR reduction to moderate or less, one year	99/109 (90.8)	15/16 (93.8)	1.000
MR reduction to mild-to-moderate or less, one year	79/109 (72.5)	11/16 (68.8)	0.770
MR reduction to mild or less, one year	64/109 (58.7)	9/16 (56.3)	1.000
PASP, one year (mmHg)	41.4±15.1	47.9±21.0	0.272
NYHA functional Class, one year (%)			
I	53/98 (54.1)	5/15 (33.3)	0.285
II	37/98 (37.8)	10/15 (66.7)	
II	8/98 (8.2)	0/15 (0)	
IV	0/98 (0)	0/15 (0)	
NYHA functional Class II or less, one year (%)	86/94 (91.5)	15/15 (100)	0.596
Subsequent mitral valve surgery	9/145 (6.2)	2/28 (7.1)	0.720*

*Log-rank. MAC: mitral annular calcification; MR: mitral regurgitation; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure

(–6.5±13.1 mmHg, p=0.021) and in patients with no-or-mild MAC (–6.5±15.5 mmHg, p<0.001). End-systolic LVID nominally decreased between baseline and one year in patients with moderate-or-severe MAC (-1.6±7.7 mm) but did not reach significance (p>0.05). The results of paired samples analysis including changes in mean mitral gradient are summarised in **Table 4** and **Figure 5**.

MITRAL ANNULAR CALCIFICATION AND SURVIVAL AFTER PERCUTANEOUS REPAIR

By univariate Cox proportional hazards regression, the presence of moderate-or-severe MAC was not associated with all-cause mortality (hazard ratio [HR] 1.280, 95% CI: 0.688-2.380, p=0.436). In a multivariate model that included pre-specified demographic and baseline characteristics of age, female gender, CAD, hypertension, diabetes, and haemodialysis status, as well as the additional variables of MR severity, baseline NYHA functional class, STS score, and LVEF (as these variables were different between the two groups, p<0.100), the presence of moderate-or-severe MAC remained not associated with all-cause mortality (HR 1.121, 95% CI: 0.552-2.275, p=0.753). In this model, NYHA functional

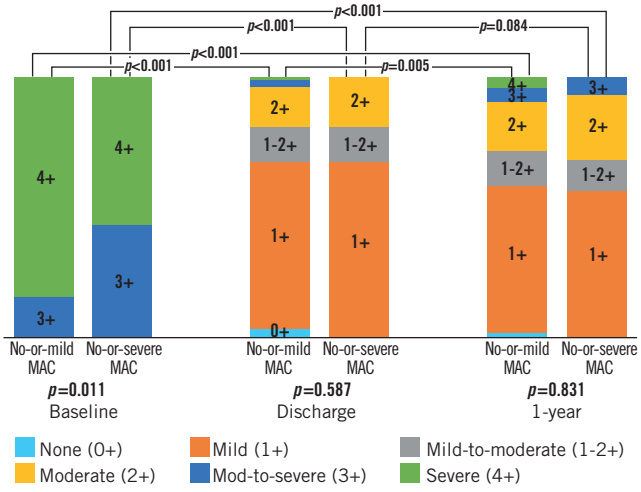

Figure 4. *Distribution of severity of mitral regurgitation at baseline, discharge, and follow-up. Patients are divided by the presence of no-or-mild mitral annular calcification (MAC) and moderate-or-severe MAC at time of baseline echocardiogram with fluoroscopic confirmation. Mann-Whitney U test was used to compare between groups at each time point, and a paired samples Wilcoxon signed-rank test was used to compare within each group across time points.*

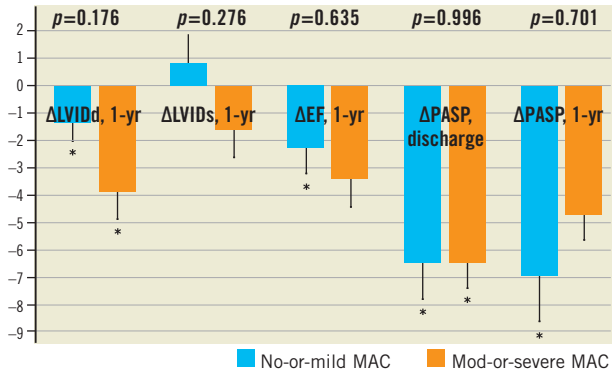

Figure 5. *Changes in end-diastolic left ventricular internal diameter, end-systolic left ventricular internal diameter, ejection fraction, and pulmonary artery systolic pressure. Standard error bars, and p-values of between group comparisons are illustrated. Asterisks (*) indicate that the change was statistically significant as compared by paired samples between the stated time points (p<0.05).*

Table 4. Left ventricular internal diameter, ejection fraction, and pulmonary artery systolic pressure at baseline and follow-up as compared by paired samples.

		Baseline	Discharge	One year	Difference	*p*-value	Inter *p*-value
LVID, end-diastolic (mm)	No-or-mild MAC n=102	53.9±8.3	–	52.5±9.3	–1.4±6.7	0.039	0.176
	Mod-or-severe MAC n=15	48.5±7.8		44.6±10.2	–3.9±6.5	0.034	
LVID, end-systolic (mm)	No-or-mild MAC n=102	37.3±10.9	–	38.1±11.7	0.8±9.5	0.381	0.276
	Mod-or-severe MAC n=15	31.7±7.4		30.0±9.7	–1.6±7.7	0.426	
Ejection fraction (%)	No-or-mild MAC n=108	51.5±17.5	–	49.2±15.6	–2.3±1.0	0.020	0.635
	Mod-or-severe MAC n=16	61.1±12.5		57.7±13.2	–3.4±8.7	0.134	
PASP (mmHg)	No-or-mild MAC n=125	50.4±15.7	43.9±12.9	–	–6.5±15.5	<0.001	0.996
	Mod-or-severe MAC n=25	52.5±15.8	46.0 ±13.1		–6.5±13.1	0.021	
PASP (mmHg)	No-or-mild MAC n=83	48.7±15.2	–	41.7±15.2	–7.0±15.7	<0.001	0.701
	Mod-or-severe MAC n=14	52.1±17.3		47.4±21.7	–4.7±20.6	0.408	
Mean mitral gradient (mmHg)	No-or-mild MAC n=142	1.8±0.9	3.5±1.7	–	1.6±1.6	<0.001	0.170
	Mod-or-severe MAC n=28	2.2±0.8	4.4±2.0		2.2±2.0	<0.001	
Mean mitral gradient (mmHg)	No-or-mild MAC n=90	1.9±0.8	–	3.5±1.8	1.6±1.6	<0.001	0.218
	Mod-or-severe MAC n=15	2.3±0.8		4.5±2.1	2.3±1.8	<0.001	

LVID: left ventricular internal diameter; MAC: mitral annular calcification; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure

Class III or IV was associated with mortality (HR 5.835, 95% CI: 1.287-26.458, p=0.022). Both female gender (HR 0.605, 95% CI: 0.350-1.046, p=0.072) and STS score per 1% (HR 1.037, 95% CI; 0.998-1.077, p=0.063) trended towards an association with all-cause mortality. The hazard ratio for age per one year was 1.017 (95% CI: 0.984-1.052, p=0.311).

Discussion

MAC is commonly found in patients referred for MV surgery for repair of significant MR and is associated with an increased intraoperative conversion from valve repair to replacement and negatively influences surgical outcomes[2,19]. However, our study demonstrates a high procedural success rate and durability of MR reduction in patients who underwent percutaneous MitraClip repair in the presence of MAC without severe leaflet calcification. Excellent surgical results can be obtained in experienced centres for MV surgery even in the presence of MAC; however, in patients with prohibitively high surgical risk from comorbidities and older age, the MitraClip procedure offers an alternative option for repair. Significant MAC as scored by transthoracic echocardiography and confirmed by fluoroscopy was associated with equally high MR reduction and durability of repair which was not affected by the presence or severity of MAC. Moreover, patients with or without significant MAC had decreases in LV dimensions, PASP, and improvements in NYHA functional class.

The overall age of patients included in the study is over a decade older than the typical age reported for patients undergoing MV surgery[2], and represents a high surgical risk cohort. Patients with moderate-or-severe MAC were nearly a decade older than patients with no-or-mild MAC with higher STS scores. While LVEF was lower in patients with no-or-mild MAC, patients with moderate-or-severe MAC were more limited as assessed by NYHA functional class. Echocardiographic measures of MR severity *vis-à-vis* vena contracta width, effective regurgitant orifice area, regurgitant volume, and prevalence of pulmonary vein flow reversal were not different between patients with moderate-or-severe MAC and those without. Interestingly, despite the association of haemodialysis with MAC[8,9], patients on haemodialysis in our cohort had either no MAC (2.9%) or mild MAC (2.9%), which may be due to random chance given the overall low incidence of haemodialysis in the entire cohort (10/173; 5.8%), non-significant p-value=0.369. In these patients, median time on haemodialysis was only five months (IQR 19.5 months), with 7/9 (77.8%) on haemodialysis for a short time (<13 months).

Procedural success and durability of repair were similarly high in patients with or without moderate-or-severe MAC, and moderate-or-less MR was achieved in >95% of patients. Durability of repair at one year as well as NYHA functional Class I-II at one year were achieved in >90% of patients. The need for subsequent MV surgery was uncommon (6.4%, 2.4-year mean follow-up), and occurred equally frequently in patients with moderate-or-severe MAC and in those without (p=0.720). While annular decalcification and reconstruction are needed for optimal surgical repair[16,20,21], favourable LV remodelling occurs in percutaneous repair[4], a phenomenon we observed in patients with significant MAC as well. In paired samples analysis of echocardiographic parameters, both patients with moderate-or-severe MAC and those without had decreases in PASP and LV dimensions. We found no differences

in the success rate, durability, or clinical and echocardiographic outcomes of percutaneous repair of MR for patients with or without significant MAC. These results are in contrast to previous reports of surgical edge-to-edge mitral repair, in which patients with annular calcification had significantly greater reoperation rates (77±22%) than those patients without annular calcification (95±4.6%), p=0.03[20]. The stark differences in results between surgical repair and MitraClip repair may be due to careful case selection in the latter case, with avoidance of patients with severe leaflet calcification.

The results of our study support the feasibility and midterm durability of repair using the MitraClip device for carefully selected MR patients with significant MAC and without severe leaflet calcification. There are alternatives under investigation including the transcatheter implantation of valves originally designed for placement in the aortic position in the native MV anchored by MAC[22], an approach that would be specifically suitable where there is severe extension of calcification onto the leaflets. Moreover, a plethora of percutaneous transcatheter MV replacement devices designed for placement in the native MV is emerging[23]. However, the procedural success and long-term durability data of these novel devices are lacking. In the absence of those data, our study confirms that the MitraClip is a safe and effective option for patients with MR and significant MAC.

Limitations

This was a single-centre retrospective study. The large experience in our single site helped in the uniformity of assessment and care of the patients. However, the number of patients with severe MAC in this series is small. As such, the potential complications with percutaneous repair in patients with MAC have not been fully elucidated by this series. Further studies are warranted to investigate the incidence of complications, such as leaflet rupture, in this patient cohort. Myxomatous degeneration or Barlow's disease with bulky billowing leaflets and multi-segmental prolapse was present only in 2.9% of the cohort and our findings may not be generalisable to these patients due to their small numbers. The grading of MAC was qualitative and not quantitative, as performed by computed tomography Agatston score; nonetheless, our data are clinically applicable to patients undergoing the MitraClip procedure. The echocardiographic data and clinical data were analysed by the local site without confirmation from an independent core lab or adjudication of clinical data by an independent monitor.

Conclusions

Our study demonstrates the safety, feasibility, and midterm durability of the MitraClip in the treatment of MR in patients with significant MAC but without severe leaflet calcification or thickening. Patients with moderate-or-severe MAC had demonstrable improvements in clinical symptoms and decreased left ventricular dimensions.

Impact on daily practice

Mitral annular calcification (MAC) is commonly found in patients referred for surgical repair of mitral regurgitation (MR) but is associated with increased intraoperative conversion from repair to replacement and worse outcomes, in part due to the need for decalcification and reconstruction of the mitral annulus. Data about its impact on pecutaneous MR repair are lacking. This study demonstrates that significant MAC was not associated with decreased procedural success or durability of repair with the MitraClip device. Percutaneous MV repair, therefore, provides a therapeutic option for patients with significant concomitant MAC and MR, with similar and demonstrable improvements in clinical symptoms, haemodynamics, and left ventricular dimensions as those found for patients without significant MAC.

Funding

There were no sources of support for the research.

Conflict of interest statement

R. Siegel has received consulting fees from Abbott and is a member of the speakers bureau for Philips Ultrasound. A. Trento has received lecture fees from Abbott Cardiovascular. S. Kar has received grant support and/or consulting fees from Abbott Vascular, Boston Scientific and St. Jude Medical. The other authors have no conflicts of interest to declare.

References

1. Abramowitz Y, Jilaihawi H, Chakravarty T, Mack MJ, Makkar RR. Mitral Annulus Calcification. *J Am Coll Cardiol.* 2015;66:1934-41.

2. Fusini L, Ghulam Ali S, Tamborini G, Muratori M, Gripari P, Maffessanti F, Celeste F, Guglielmo M, Cefalu C, Alamanni F, Zanobini M, Pepi M. Prevalence of calcification of the mitral valve annulus in patients undergoing surgical repair of mitral valve prolapse. *Am J Cardiol.* 2014;113:1867-73.

3. Siegel RJ, Biner S, Rafique AM, Rinaldi M, Lim S, Fail P, Hermiller J, Smalling R, Whitlow PL, Herrmann HC, Foster E, Feldman T, Glower D, Kar S; EVEREST Investigators. The acute hemodynamic effects of MitraClip therapy. *J Am Coll Cardiol.* 2011;57:1658-65.

4. Glower DD, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, Whitlow PL, Rinaldi MJ, Grayburn P, Mack MJ, Mauri L, McCarthy PM, Feldman T. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol.* 2014;64:172-81.

5. Beigel R, Wunderlich NC, Kar S, Siegel RJ. The evolution of percutaneous mitral valve repair therapy: lessons learned and implications for patient selection. *J Am Coll Cardiol.* 2014;64:2688-700.

6. Silbiger JJ. Anatomy, mechanics, and pathophysiology of the mitral annulus. *Am Heart J.* 2012;164:163-76.

7. Atar S, Jeon DS, Luo H, Siegel RJ. Mitral annular calcification: a marker of severe coronary artery disease in patients under 65 years old. *Heart.* 2003;89:161-4.

8. Asselbergs FW, Mozaffarian D, Katz R, Kestenbaum B, Fried LF, Gottdiener JS, Shlipak MG, Siscovick DS. Association of renal function with cardiac calcifications in older adults: the cardiovascular health study. *Nephrol Dial Transplant.* 2009;24:834-40.

9. Movva R, Murthy K, Romero-Corral A, Seetha Rammohan HR, Fumo P, Pressman GS. Calcification of the mitral valve and annulus: systematic evaluation of effects on valve anatomy and function. *J Am Soc Echocardiogr.* 2013;26:1135-42.

10. Kanjanauthai S, Nasir K, Katz R, Rivera JJ, Takasu J, Blumenthal RS, Eng J, Budoff MJ. Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis.* 2010;213:558-62.

11. Elmariah S, Budoff MJ, Delaney JA, Hamirani Y, Eng J, Fuster V, Kronmal RA, Halperin JL, O'Brien KD. Risk factors associated with the incidence and progression of mitral annulus calcification: the multi-ethnic study of atherosclerosis. *Am Heart J.* 2013;166:904-12.

12. Fox CS, Vasan RS, Parise H, Levy D, O'Donnell CJ, D'Agostino RB, Benjamin EJ; Framingham Heart Study. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation.* 2003;107:1492-6.

13. Pressman GS, Crudu V, Parameswaran-Chandrika A, Romero-Corral A, Purushottam B, Figueredo VM. Can total cardiac calcium predict the coronary calcium score? *Int J Cardiol.* 2011;146:202-6.

14. Kohsaka S, Jin Z, Rundek T, Boden-Albala B, Homma S, Sacco RL, Di Tullio MR. Impact of mitral annular calcification on cardiovascular events in a multiethnic community: the Northern Manhattan Study. *JACC Cardiovasc Imaging.* 2008;1:617-23.

15. Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve anulus: pathology and surgical management. *J Thorac Cardiovasc Surg.* 1996;111:718-29; discussion 729-30.

16. Okada Y. Surgical management of mitral annular calcification. *Gen Thorac Cardiovasc Surg.* 2013;61:619-25.

17. 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; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777-802.

18. Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, Schofer J, Cutlip DE, Krucoff MW, Blackstone EH, Genereux P, Mack MJ, Siegel RJ, Grayburn PA, Enriquez-Sarano M, Lancellotti P, Filippatos G, Kappetein AP; Mitral Valve Academic Research Consortium (MVARC). Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles: A Consensus Document From the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol.* 2015;66:278-307.

19. d'Alessandro C, Vistarini N, Aubert S, Jault F, Acar C, Pavie A, Gandjbakhch I. Mitral annulus calcification: determinants of repair feasibility, early and late surgical outcome. *Eur J Cardiothorac Surg.* 2007;32:596-603.

20. Maisano F, Caldarola A, Blasio A, De Bonis M, La Canna G, Alfieri O. Midterm results of edge-to-edge mitral valve repair without annuloplasty. *J Thorac Cardiovasc Surg.* 2003;126:1987-97.

21. De Bonis M, Lapenna E, Maisano F, Barili F, La Canna G, Buzzatti N, Pappalardo F, Calabrese M, Nisi T, Alfieri O. Long-term results (</=18 years) of the edge-to-edge mitral valve repair without annuloplasty in degenerative mitral regurgitation: implications for the percutaneous approach. *Circulation.* 2014;130:S19-24.

22. ClinicalTrials.gov. Mitral implantation of transcatheter valves in native mitral stenosis. Unique identifier: NCT02370511. https://clinicaltrials.gov/ct2/results?term=NCT02370511&Search=Search

23. De Backer O, Piazza N, Banai S, Lutter G, Maisano F, Herrmann HC, Franzen OW, Sondergaard L. Percutaneous transcatheter mitral valve replacement: an overview of devices in preclinical and early clinical evaluation. *Circ Cardiovasc Interv.* 2014;7:400-9.