Clinical, functional and prognostic implications of severe atrial dilation in secondary mitral regurgitation

Habib Layoun,1 Amgad Mentias,1 Emmanuel Akintoye,1 Milad Matta,2 Chris Kanaan,2 Remy Daou,3 Jay Ramchand,1 Daniel Burns,1 A Marc Gillinov,1 Sanjeeb Bhattacharya,1 Rishi Puri,1 Patrick Collier,1 Brian Griffin,1 Samir Kapadia,1 Serge C Harb

INTRODUCTION

Mitrval regurgitation (MR) is very common, affecting 22% of people over 65 years with a 2.3% prevalence of significant (moderate/severe) disease.1,2 It is classically categorised as either primary when driven by valvular pathology, or secondary MR (SMR) when due to left ventricle (LV) dysfunction.3–5 The regurgitant MR jet leads to left atrial (LA) volume overload which, over time, can lead to LA remodelling and severe atrial dilation (SAD). SAD has been previously shown to be predictive of adverse outcomes in patients with primary MR.6–8 However, its clinical and prognostic implications, in addition to the mitral apparatus functional/geomtric alterations that occur with SAD, have not been explored in SMR. With the increasing number of mitral transcatheter technologies,9 10 such information may be useful in patient selection, device choice and timing of intervention.

We sought to define and describe the prevalence, clinical and echocardiographic characteristics of patients with SAD in the setting of severe SMR (SADMR) and explore the therapeutic and prognostic implications.

METHODS

Patient population
All adult patients (≥18 years old) who underwent transthoracic echocardiography (TTE)
at the Cleveland Clinic from January 2012 to March 2021 were screened. We included the first TTE showing severe SMR, defined as 3+ to 4+ or 4+MR with a left ventricular ejection fraction (LVEF) of 20% to 50% in the absence of leaflet pathology (flail, endocarditis, prolapse, rheumatic and calcific mitral valve disease). We excluded patients with intracardiac masses (thrombus, vegetation, tumour), hypertrophic, restrictive, constrictive and infiltrative cardiomyopathies, and patients with prior mitral valve repair or replacement.¹¹ Also, a minimum of 1 month of follow-up was required for inclusion. Based on the degree of concomitant LA enlargement, the 2011 remaining patients were divided into two: (1) those with SADMR, defined as SMR with severe LA dilation (ie, indexed LA volume >48 mL/m² according to the American Society of Echocardiography (ASE) guidelines¹²) and (2) those without SADMR, defined by SMR with non-severe LA dilation (ie, LA volume indexed ≤48 mL/m²) (figure 1).

Clinical variables were collected by chart review and included age, sex, body mass index (BMI), New York Heart Association (NYHA) class, medications and comorbidities (hypertension, hyperlipidaemia, coronary artery disease, diabetes and atrial fibrillation/flutter) at time of TTE.

Echocardiography

Standard TTE examinations were performed and interpreted by experienced cardiologists in compliance with the guidelines.¹³ ¹⁴ The severity of MR was graded using a multiparametric approach as advocated by the ASE, including calculating the effective regurgitant orifice area (EROA) using the proximal iso-velocity surface area method. Concomitant tricuspid valve regurgitation (TR) was noted. Cardiac chambers’ size and function were also quantified by standard ASE recommendations.¹²

The systolic pulmonary arterial pressure (SPAP) was estimated based on the TR jet maximum velocity and the estimated right atrial pressure.¹⁵ As for diastology data, tissue Doppler and pulse wave Doppler were obtained according to guidelines,⁶ and the following variables were recorded: E wave, A wave (in patients with sinus rhythm), the average of lateral and medial E/e’ ratios, and the MV deceleration time.

Strain and mitral valve geometrical measurements

LA and LV strains were not routinely reported. Therefore, we performed manual strain analysis on matched samples from both groups. For that purpose, 200 patients with SADMR were randomly chosen, and then 200 patients without SADMR were matched using a propensity score based on age, sex, and BMI with a 1:1 ratio to the nearest neighbour (calibre of 0.1 on a scale of 0–100) (online supplemental table 1). For further adjustments to LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), we employed a second propensity score matching model including age, sex, body surface area (BSA), LVEDV and LVESV (online supplemental table 2).

We performed an offline analysis of speckle tracking echocardiography using Velocity Vector Imaging (2.0; Siemens, Erlangen, Germany) on both groups. To measure the LA longitudinal reservoir strain function, we used the QRS complex (end-diastole) as the zero reference. The LA strain curve’s peak systolic values from the apical four-chamber and two-chamber views were averaged. For the LV global longitudinal strain (LVGLS), the endocardial borders were automatically tracked throughout the cardiac cycle and adjusted manually where required.

Using the same samples of 200 patients each, we also compared the following MV anatomic features measured on an apical three-chamber view: anteroposterior annular diameter, anterior and posterior leaflet angles, leaflet...
length/annular diameter ratio, and tenting height. To adjust for LV volumes, we compared the same variables on a second propensity score matching model based on age, sex, BSA, LVEDV and LVESV.

Follow-up
Patients were followed for the occurrence of mitral valve interventions including surgeries (repair or replacement) or transcutaneous edge-to-edge repair (TEER), and LV assistance device (LVAD) implantation or heart transplantation. We also recorded electrophysiology arrhythmias ablations, pacemaker and intracardiac defibrillator implantations, and LA appendage occlusion procedures.

Endpoints
The primary outcome was defined as all-cause mortality. To control for interfering interventions, patients who underwent mitral valve surgeries or TEER, LVAD or heart transplantation were excluded from the survival analysis. In addition, for those who had TEER, we defined significant residual MR as >2+ on the postprocedural TTE and compared its occurrence between both SMR groups.

Statistical analysis
Categorical variables are presented as percentages, whereas continuous variables are presented as mean with SD in case of a normal distribution and median with the IQR when not normally distributed. Categorical variables are compared using Pearson’s $\chi^2$ test for independence, and continuous variables are compared using the Student’s t-test or Mann-Whitney U test, as appropriate. Time-to-event analysis was performed using the Kaplan-Meier survival method. To test whether SAD was an independent predictor of mortality, we employed a cox proportional-hazard model that included age, sex, and the echocardiographic parameters that significantly predicted mortality on univariable analysis. The LA volume as a continuous variable violated the proportional hazards assumption so it was not explored. All analyses

| Table 1 Baseline patients’ clinical characteristics |
|-----------------------------------------------|
| Variable                                      | Population (n=2011) | SMR without SAD (n=592) | SADMR (n=1419) | P value |
| Age                                          | 69.7±13.9          | 68.2±14.2                | 70.4±13.8      | <0.01   |
| BMI                                          | 28.2±11.5          | 29.3±9.9                 | 27.7±12.1      | 0.01    |
| Female sex                                   | 830 (41%)          | 287 (48%)                | 543 (38%)      | <0.001 |
| Hypertension                                 | 1552 (77%)         | 446 (75%)                | 1106 (78%)     | 0.21    |
| Hyperlipidaemia                              | 1283 (64%)         | 359 (61%)                | 924 (65%)      | 0.06    |
| Coronary artery disease                      | 1327 (66%)         | 392 (66%)                | 935 (66%)      | 0.89    |
| Diabetes                                     | 783 (39%)          | 210 (35%)                | 573 (40%)      | 0.04    |
| Atrial fibrillation                          | 1282 (64%)         | 389 (66%)                | 893 (63%)      | 0.24    |
| Atrial flutter                               | 293 (15%)          | 92 (16%)                 | 201 (14%)      | 0.43    |

Medications

| Aspirin                                      | 1829 (91%)         | 533 (90%)                | 1296 (81%)     | 0.36    |
| Cholesterol lowering agents                 | 1351 (67%)         | 382 (65%)                | 969 (48%)      | 0.1     |
| ACEI/ARB/ARNi                                | 1722 (86%)         | 492 (83%)                | 1230 (87%)     | 0.04    |
| Diuretics                                    | 1919 (95%)         | 555 (94%)                | 1364 (96%)     | 0.02    |
| Betablockers                                 | 1930 (96%)         | 559 (95%)                | 1371 (97%)     | 0.02    |
| CCB                                          | 922 (46%)          | 269 (45%)                | 653 (46%)      | 0.81    |
| Antiarrhythmics                              | 1825 (91%)         | 531 (90%)                | 1294 (92%)     | 0.29    |
| Warfarin                                     | 1021 (51%)         | 311 (53%)                | 710 (50%)      | 0.31    |
| DOAC                                         | 662 (33%)          | 177 (30%)                | 485 (34%)      | 0.06    |

NYHA class

| Class I                                      | 170 (9%)           | 41 (7%)                  | 130 (9%)       | 0.58    |
| Class II                                     | 629 (31%)          | 185 (31%)                | 445 (31%)      |        |
| Class III                                    | 888 (44%)          | 278 (47%)                | 609 (43%)      |        |
| Class IV                                     | 323 (16%)          | 89 (15%)                 | 235 (17%)      |        |

Significant p-values (<0.05) are highlighted in bold.
ACEI, ACE inhibitor; ARB, angiotensine receptor blocker; ARNi, angiotensine receptor-neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blocker; DOAC, direct oral anticoagulant; NYHA, New York Heart Association; SAD, severe atrial dilation; SMR, secondary mitral regurgitation.
were conducted using SPSS V.23.0 (IBM) and R studio V.1.4.1717 (R Foundation for Statistical Computing, Vienna, Austria).

### Patient and public involvement

No participants were involved in the design, conduct, reporting, or dissemination plans of the research question or outcome measures.

### RESULTS

#### Baseline patients’ characteristics

Of the total cohort, 1419 patients (70.6%) had SADMR while the remaining 592 patients (29.4%) did not have concomitant SAD (figure 1). Patients’ clinical characteristics are summarised in table 1. Patients with SADMR were older (70.4 vs 68.2 years, p<0.01), had lower BMI (27.7 vs 29.3, p=0.01), and were less likely females (38% vs 48%, p<0.001). Both groups had similar comorbidities including atrial fibrillation (63% vs 66%, p=0.24). However, diabetes was more frequent in the SADMR group (40% vs 35%, p=0.04). There were no differences in the NYHA classes between both groups.

On TTE, both groups had similar EF (33.1%±9.1 vs 33.5%±9.3, p=0.34), though LV volumes were larger in the SADMR group (191.5 vs 160.4 mL p<0.001 for end-diastolic volumes and 130.4 vs 108.2 mL for end-systolic volumes). However, there were no differences in the NYHA classes between both groups.

#### Table 2 Baseline echocardiographic parameters

| Variable                        | Population (n=2011) | SMR without SAD (n=592) | SADMR (n=1419) | P value |
|---------------------------------|---------------------|-------------------------|----------------|---------|
| LV end-diastolic volume, mL     | 182.9±73.5          | 160.4±60.9              | 191.5±76.1     | <0.001  |
| LV end-systolic volume, mL      | 124.3±59.6          | 108.2±48.2              | 130.4±62.3     | <0.001  |
| LV EF, %                        | 33.2±9.2            | 33.5±9.3                | 33.1±9.1       | 0.34    |
| MV mean gradient, mm Hg         | 3.78±1.5            | 3.97±1.5                | 3.77±1.5       | 0.31    |
| MV peak gradient, mm Hg         | 10.4±3.8            | 12±8.1                  | 11.6±9         | 0.72    |
| MR Vmax, m/sec                  | 4.9±0.8             | 4.9±0.8                 | 4.9±0.8        | 0.59    |
| EROA, mm²                       | 41.7±26.1           | 41.2±29.4               | 41.9±24.7      | 0.63    |
| Mitral annulus calcification    | 600 (30%)           | 164 (28%)               | 436 (31%)      | 0.16    |
| SPAP, mm Hg                     | 50.8±15.1           | 49±15                   | 52±15          | 0.001   |
| Moderate or severe RV dilation, %| 733 (36)            | 170 (29)                | 563 (40)       | <0.001  |
| Moderate or severe RV dysfunction, % | 672 (33)           | 181 (31)                | 491 (35)       | 0.09    |
| Moderate or severe tricuspid regurgitation, % | 1200 (60)          | 300 (51)                | 900 (63)       | <0.001  |

#### Table 3 Strain analysis and mitral valve anatomic features

| Variable                        | Population (n=400) | SMR without SAD (n=200) | SADMR (n=200) | P value |
|---------------------------------|---------------------|-------------------------|----------------|---------|
| LA strain, %                    | 12.35±7.5           | 15.51±8.63              | 9.71±4.97      | <0.001  |
| LVGLS, %                        | −6.57±3.3           | −6.26±3.22              | −6.86±3.43     | 0.14    |
| Mitral annular diameter/BSA, cm/m² | 2.03±0.38           | 1.84±0.37               | 2.18±0.36      | <0.001  |
| Anterior leaflet length/annular diameter | 0.62±0.09          | 0.67±0.91               | 0.58±0.76      | <0.001  |
| Posterior leaflet length/annular diameter | 0.61±0.09          | 0.66±0.87               | 0.58±0.78      | <0.001  |
| Anterior leaflet angle, degrees  | 34.2 (26.8, 42.1)   | 41.19 (36.29, 46.07)    | 28.51 (24.16, 33.48) | <0.001  |
| Posterior leaflet angle, degrees | 35.7±10.2           | 41.54±8.86              | 30.64±8.54     | <0.001  |
| Tenting height, cm              | 1.34 (1.1, 1.6)     | 1.55 (1.33, 1.79)       | 1.14 (0.91, 1.38) | <0.001  |

Significant p-values (<0.05) are highlighted in bold.

EF, ejection fraction; EROA, effective regurgitant orifice area; LV, left ventricle; MR, mitral regurgitation; MV, mitral valve; RV, right ventricle; SAD, severe atrial dilation mitral; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary arterial pressure; Vmax, maximum velocity.

Significant p-values (<0.05) are highlighted in bold.

BSA, body surface area; LV, left atrium; LVGLS, left ventricular global longitudinal strain; SADMR, severe atrial dilation mitral regurgitation.
Valvular heart disease

In terms of MR severity, both groups had similar EROA (41.9±24.7 mm² vs 41.2±29.4 mm², p=0.63). Also, the peak and mean MV gradients and maximum velocity of the MR jet (Vmax) were comparable (Table 2). However, patients with SADMR had higher estimated SPAP (52 vs 49 mm Hg, p=0.001) and more frequent moderate/severe RV dilation and moderate or more TR (40% vs 29% p<0.001% and 63% vs 51% p<0.001, respectively).

In terms of diastology (Table 2), the measured parameters were comparable, except for the peak A wave which was lower in the SADMR group (0.61 vs 0.72 cm/s p<0.001). Also, strain analysis (Table 3) showed significantly lower LA strain in the SADMR group (9.71% vs 15.51%, p<0.001), with similar LVGLS (-6.26 vs -6.86 p=0.14). Geometrically, SADMR had larger mitral valve annulus (2.18 vs 1.84 cm p<0.001), shallower anterior and posterior leaflet angles (28.51° vs 41.19° and 30.64° vs 41.54°, respectively, both p<0.001), smaller anterior and posterior leaflets to annulus ratio (0.58 vs 0.67 and 0.58 vs 0.66, respectively, p<0.001), and lower tenting height (1.14 vs 1.55 cm, p<0.001). Similar results were also found after adjusting for LVEDV and LVESV (online supplemental table 2). On subgroup analysis, patients with or without atrial fibrillation, and with ischaemic versus non-ischaemic cardiomyopathy, had similar mitral valve measurements and LA and LV strain (online supplemental tables 3 and 4). In contrast, patients in the SADMR group with an EF ≥40% had lower tenting height, anterior and posterior angles (online supplemental table 5).

Interventions and outcomes

The median follow-up was 13 months (IQR 2.4–39 months). SAD patients underwent less mitral interventions

| Variable | Population (n=2011) | SMR without SAD (n=592) | SADMR (n=1419) | P value |
|----------|---------------------|------------------------|----------------|---------|
| Mitral valve interventions | 425 (21%) | 139 (23%) | 286 (20%) | 0.04 |
| Surgical repair | 200 (10%) | 71 (12%) | 129 (9%) | |
| Surgical replacement | 182 (9%) | 57 (9%) | 125 (9%) | |
| TEER | 43 (2%) | 11 (2%) | 32 (2%) | |
| LVAD and/or heart transplant | 99 (5%) | 16 (3%) | 83 (6%) | 0.003 |
| AF ablation | 27 (1%) | 6 (1%) | 21 (1%) | 0.53 |
| SVT/VT ablation | 42 (2%) | 8 (1%) | 34 (2%) | 0.09 |
| Pacemaker | 49 (2%) | 18 (3%) | 31 (2%) | 0.17 |
| ICD | 233 (12%) | 62 (10%) | 171 (12%) | 0.18 |
| LAA occlusion | 8 (0.4%) | 1 (0.2%) | 7 (0.5%) | 0.27 |

Significant p-values (<0.05) are highlighted in bold.

AF, atrial fibrillation; ICD, intracardiac defibrillator; LAA, left atrial appendage; LVAD, left ventricular assist device; SAD, severe atrial dilation; SMR, secondary mitral regurgitation; SVT, supraventricular tachycardia; TEER, transcatheter edge to edge repair.

Table 5 All-cause mortality: univariate and multivariable Cox regression analysis

| Variable | Univariate HR (95% CI) | P value | Multivariate HR (95% CI) | P value |
|----------|------------------------|---------|--------------------------|---------|
| Severe atrial dilation | 1.36 (1.11 to 1.67) | 0.003 | 1.26 (1.01 to 1.57) | 0.04 |
| ≥moderate RV dilation | 1.32 (1.11 to 1.58) | 0.002 | 1.15 (0.95 to 1.39) | 0.15 |
| ≥moderate RV dysfunction | 1.13 (0.94 to 1.36) | 0.19 | N/A | N/A |
| TAPSE | 0.93 (0.72 to 1.20) | 0.93 | N/A | N/A |
| ≥2+ TR | 1.48 (1.22 to 1.78) | <0.001 | 0.16 (0.94 to 1.44) | 0.17 |
| SPAP | 1.02 (1.01 to 1.02) | <0.001 | 1.01 (1.00 to 1.02) | 0.002 |
| EROA | 1.00 (0.99 to 1.01) | 0.4 | N/A | N/A |
| LVEF | 1.00 (0.99 to 1.01) | 0.98 | N/A | N/A |
| LV end-diastolic volume | 0.99 (0.99 to 1.00) | 0.31 | N/A | N/A |
| LV end-systolic volume | 0.99 (0.99 to 1.00) | 0.36 | N/A | N/A |
| Age | 1.03 (1.02 to 1.04) | <0.001 | 1.03 (1.02 to 1.04) | <0.001 |
| Female sex | 0.79 (0.67 to 0.95) | 0.01 | 0.85 (0.71 to 1.03) | 0.09 |

Significant p-values (<0.05) are highlighted in bold.

EROA, effective regurgitant orifice area; LV, left ventricle; LVEF, left ventricular ejection fraction; N/A, not available; RV, right ventricle; SPAP, systolic pulmonary arterial pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion; TR, tricuspid regurgitation.

Table 4 Cardiac interventions during follow-up

| Variable | Population (n=2011) | SMR without SAD (n=592) | SADMR (n=1419) | P value |
|----------|---------------------|------------------------|----------------|---------|
| Mitral valve interventions | 425 (21%) | 139 (23%) | 286 (20%) | 0.04 |
| Surgical repair | 200 (10%) | 71 (12%) | 129 (9%) | |
| Surgical replacement | 182 (9%) | 57 (9%) | 125 (9%) | |
| TEER | 43 (2%) | 11 (2%) | 32 (2%) | |
| LVAD and/or heart transplant | 99 (5%) | 16 (3%) | 83 (6%) | 0.003 |
| AF ablation | 27 (1%) | 6 (1%) | 21 (1%) | 0.53 |
| SVT/VT ablation | 42 (2%) | 8 (1%) | 34 (2%) | 0.09 |
| Pacemaker | 49 (2%) | 18 (3%) | 31 (2%) | 0.17 |
| ICD | 233 (12%) | 62 (10%) | 171 (12%) | 0.18 |
| LAA occlusion | 8 (0.4%) | 1 (0.2%) | 7 (0.5%) | 0.27 |

Significant p-values (<0.05) are highlighted in bold.

AF, atrial fibrillation; ICD, intracardiac defibrillator; LAA, left atrial appendage; LVAD, left ventricular assist device; SAD, severe atrial dilation; SMR, secondary mitral regurgitation; SVT, supraventricular tachycardia; TEER, transcatheter edge to edge repair.
(20% vs 23% p=0.04) but more LVAD and/or heart transplantation (6% vs 3% p=0.003). Other interventions were similar between both groups (table 4).

In terms of the primary outcome, there were more deaths in the SADMR group (50% vs 43%, p=0.004). On multivariable Cox regression analysis, SAD and SPAP were the only variables that were independently associated with mortality (HR 1.26 p=0.04 and HR 1.01 p<0.001, respectively) (table 5). On Kaplan-Meier survival analyses, patients with SADMR had significantly worse survival (figure 2). However, on subgroup analysis, patients with SADMR who underwent mitral interventions (surgical or TEER) had improved outcomes (age and gender adjusted log-rank p<0.001) (figure 3).

**Figure 2** Kaplan-Meier curves for the association of SADMR versus SMR without SAD with all-cause mortality. SAD, severe atrial dilation; SMR, secondary mitral regurgitation.

**Figure 3** Kaplan-Meier curves for the association of mitral valve (MV) interventions with all-cause mortality in patients with SADMR. SADMR, severe atrial dilation mitral regurgitation.
Regarding TEER results, of the 43 patients that underwent the procedure, 14% had significant residual MR, which was not associated with the SADMR or the measured geometrical parameters (online supplemental table 6).

**DISCUSSION**

There are multiple key observations from this study. SAD is present in 70.6% of patients with severe SMR and, when present, it is associated with specific mechanistic and geometrical alterations, limited therapeutic options and worse outcomes (figure 4). Previous studies established the negative prognostic value of atrial enlargement in primary MR. Although SAD is frequently present in chronic SMR and could reflect its severity and longer duration, the ensuing mitral geometrical alterations and the clinical, therapeutic and prognostic implications have not been previously explored. Our findings of distinct functional and anatomic alterations along with divergences in the management and outcomes, for the same degree of MR and LV function, suggest that this subgroup of SMR patients may need to be considered separately. Specifically, we found SADMR, compared with SMR without SAD, has distinctive geometrical changes (larger annular size, and shallower leaflets angulations and tenting), and more pronounced LA dysfunction (lower A waves and LA strain). In addition, the management options were more limited, with less referral for mitral interventions, and the outcome was worse.

Mechanistically, patients with SADMR had significantly lower A wave velocity on diastology and lower LA strain (though with similar LVGLS), supporting the hypothesis of significant coexisting LA myopathy superimposed on the LV cardiomyopathy. LA dysfunction in patients with heart failure is associated with a higher risk of developing atrial fibrillation. Interestingly, in our study, there were no significant differences in the prevalence of atrial fibrillation between both groups; However, a time-to-event analysis could be necessary to sense the difference in the onset of new atrial fibrillation. Nevertheless, type 2 diabetes was more common in SADMR and prior studies have shown an association between diabetes and atrial dysfunction.

From a geometrical perspective, the lower tenting height, shallower leaflet angulations, larger annulus and smaller leaflets to annulus ratio in SADMR suggest a dual interaction—both ventricular and atrial. From one side, ventricular dysfunction/enlargement leads to apical tethering of the leaflets with increased tenting, as has been typically described in ventricular SMR. On the other side, the concomitant presence of SAD is associated with outward annular stretching and flattening of the leaflets as has been described with atrial SMR. Our findings support an additive effect whereby the leaflets are tethered by the ventricular component but to a lesser extent due to the atrial component. While annular dilation is a key component of both ASMR and VSMR, our study shows that SADMR is associated with an even greater annular dilation.

From a management standpoint, both groups had high utilisation rates of guideline directed medical therapy (GDMT) with overall relatively low referrals for advanced heart failure therapies, in concordance with recently reported literature. Interestingly, mitral interventions, both surgical and percutaneous, were less frequent in the SADMR group despite the association with improved outcomes. This may be due to the older population and the severity of LA enlargement. However,
our findings suggest that SADMR may still benefit from mitral interventions. This is in concordance with the recent subanalysis of the COAPT trial showing markedly improved survival in patients with SMR and atrial fibrillation undergoing TEER, with similar effect of intervention as patients without atrial fibrillation. Similarly, in our study, significant residual MR was not different between both groups suggesting that the degree of LA enlargement should not deter from intervening.

In terms of prognosis, the SADMR group had worse survival and the concomitant presence of atrial dilation in SMR was found to be an independent predictor of mortality. While this finding is relatively novel for SMR, it is not unexpected given the preponderance of data suggesting that LA enlargement is a marker of worse outcomes across the spectrum of cardiac disorders.

Study limitations
There are multiple limitations to our study. First, this is a retrospective single-centre observational study with all the inherent limitations including lack of causality and external validity. Second, the dynamic nature of SMR is well established with its severity being variable with loading conditions and medical therapy. However, the high rates of GDMT utilisation in our study suggest that this may not have been impactful on our findings. Third, SMR and heart failure are progressive diseases over time, and SADMR patients might have been exposed to a longer duration of the disease which could be impactful on outcomes. Lastly, patients lost to follow-up may affect our study results. We tried to mitigate this risk by excluding patients who came for one visit or did not have a follow-up beyond 1 month from inclusion.

CONCLUSION
For the same degree of MR and severity of LV dysfunction, SAD in the setting of severe SMR is associated with distinct mechanistic and geometrical alterations, fewer referrals for mitral interventions and worse outcomes.

Contributors
HL, AM and SCH conceived and designed the study; HL, EA, AM and SCH collected, analysed, and interpreted the data; HL, EA, AM, MM, CK and SCH drafted and critically reviewed the manuscript; RD, JR, DB, AMG, SB, RP, PC, BG, SK and SCH supervised the study; HL and SCH are responsible for the overall content and serve as guarantors. All authors read and approved the final manuscript.

Funding
The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests
None declared.

Patient consent for publication
Not applicable.

Ethics approval
The institutional review board of Cleveland Clinic approved this study (21-603).

Provenance and peer review
Not commissioned; internally peer reviewed.

Data availability statement
No data are available.

Supplemental material
This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Serge C Harb http://orcid.org/0000-0002-7442-4928

REFERENCES
1 d’Arcy JL, Coffey S, Loudon MA, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxValVE population study. Eur Heart J 2016;37:3515–29.
2 Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart disease: a population-based study. Lancet 2006;368:1005–11.
3 Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015;65:1231–48.
4 Pierard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. Eur Heart J 2010;31:2996–3005.
5 de Marchena E, Badiye A, Robalino G, et al. Respective prevalence of the different carpentier classes of mitral regurgitation: a stopping stone for future therapeutic research and development. J Card Surg 2011;26:385–92.
6 Essayagh B, Antoine C, Benfari G, et al. Prognostic Implications of Left Atrial Enlargement in Degenerative Mitral Regurgitation. J Am Coll Cardiol 2019;74:858–70.
7 Le Tourneau T, Messika-Zeitoun D, Russo A, et al. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. J Am Coll Cardiol 2010;56:570–8.
8 Kar S, Lancellotti P, Tribouilloy C, et al. Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: results from a large international multicenter study. Circ Cardiovasc Imaging 2011;4:473–81.
9 Hensey M, Brown RA, Lal S, et al. Transcatheter mitral valve replacement: an update on current techniques, technologies, and future directions. JACC Cardiovasc Interv 2021;14:489–500.
10 Mack M, Carroll JD, Thourani V, et al. Transcatheter mitral valve therapy in the United States: a report from the STS-ACC TVT registry. J Am Coll Cardiol 2021;78:2326–53.
11 Asch FM, Grayburn PA, Siegel RJ, et al. Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT trial. J Am Coll Cardiol 2019;74:2969–79.
12 Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2015;28:1–39.
13 Zoghi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
14 Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–44.
15 Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of echocardiography endorsed by the European association of echocardiography, a registered branch of the European Society of cardiology, and the Canadian Society of echocardiography. J Am Soc Echocardiogr 2010;23:685–713.
16 Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.
17 Kar S, Mack MJ, Lindner J, et al. Relationship between residual mitral regurgitation and clinical and quality-of-life outcomes after...
Valvular heart disease

transcatheter and medical treatments in heart failure: COAPT trial. Circulation 2021;144:426–37.

18 Park JJ, Park J-H, Hwang I-C, et al. Left atrial strain as a predictor of new-onset atrial fibrillation in patients with heart failure. JACC Cardiovasc Imaging 2020;13:2071–81.

19 Mondillo S, Cameli M, Caputo ML, et al. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. J Am Soc Echocardiogr 2011;24:898–908.

20 Gertz ZM, Hermann HC, Lim DS, et al. Implications of atrial fibrillation on the mechanisms of mitral regurgitation and response to MitraClip in the COAPT trial. Circ Cardiovasc Interv 2021;14:e010300.

21 Agricola E, Oppizzi M, Maisano F, et al. Echocardiographic classification of chronic ischemic mitral regurgitation caused by restricted motion according to tethering pattern. Eur J Echocardiogr 2004;5:326–34.

22 Matta M, Ayoub C, Abou Hassan OK, et al. Anatomic and functional determinants of atrial functional mitral regurgitation. Structural Heart 2021;5:498–507.

23 Kim D-H, Heo R, Handschumacher MD, et al. Mitral valve adaptation to isolated annular dilation: insights into the mechanism of atrial functional mitral regurgitation. JACC Cardiovasc Imaging 2019;12:665–77.

24 Kagiyama N, Hayashida A, Toki M, et al. Insufficient leaflet remodeling in patients with atrial fibrillation: association with the severity of mitral regurgitation. Circ Cardiovasc Imaging 2017;10:e005451.

25 Kaji S, Nasu M, Yamamuro A, et al. Annular geometry in patients with chronic ischemic mitral regurgitation. Circulation 2005;112:i-409–i-414.

26 Chinitz JS, Chen D, Goyal P, et al. Mitral apparatus assessment by delayed enhancement CMR: relative impact of infarct distribution on mitral regurgitation. JACC Cardiovasc Imaging 2013;6:220–34.

27 Goodwin M, Nemeh HW, Borgi J, et al. Resolution of mitral regurgitation with left ventricular assist device support. Ann Thorac Surg 2017;104:811–8.

28 Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014;63:493–505.

29 O’Gara PT, Mack MJ. Secondary mitral regurgitation. N Engl J Med Overseas Ed 2020;383:1458–67.