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Association of Left Ventricular Remodeling Assessment by Cardiac Magnetic Resonance With Outcomes in Patients With Chronic Aortic Regurgitation

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IMPORTANCE Chronic aortic regurgitation (AR) causes left ventricular (LV) volume overload, which results in progressive LV remodeling negatively affecting outcomes. Whether cardiac magnetic resonance (CMR) volumetric quantification can provide incremental risk stratification over standard clinical and echocardiographic evaluation in patients with chronic moderate or severe AR is unknown.

OBJECTIVE To compare LV remodeling measurements by CMR and echocardiography between patients with and without heart failure symptoms and to verify the association of remodeling measurements of patients with chronic moderate or severe AR but no or minimal symptoms with clinical outcomes receiving medical management.

DESIGN, SETTING, AND PARTICIPANTS This multicenter retrospective cohort study included consecutive patients with at least moderate chronic native AR evaluated by 2-dimensional transthoracic echocardiography and CMR examination within 90 days from each other between January 2012 and February 2020 at Allina Health System. Data were analyzed from June 2021 to January 2022.

EXPOSURES Clinical evaluation and risk stratification by CMR.

MAIN OUTCOMES AND MEASURES The end point was a composite of death, heart failure hospitalization, or progression of New York Heart Association functional class while receiving medical management, censoring patients at the time of aortic valve replacement (when performed) or at the end of follow-up.

RESULTS Of the 178 included patients, 119 (66.9%) were male, 158 (88.8%) presented with no or minimal symptoms (New York Heart Association class I or II), and the median (IQR) age was 58 (44-69) years. Compared with patients with no or minimal symptoms, symptomatic patients had greater LV end-systolic volume index (LVESVi) by CMR (median [IQR], 66 [46-85] mL/m^2 vs 42 [30-58] mL/m^2; $P < .001$), while there were no significant differences by echocardiography (LVESVi: median [IQR], 38 [30-58] mL/m^2 vs 27 [20-42] mL/m^2; $P = .07$; LV end-systolic diameter index: median [IQR], 21 [17-25] mm/m^2 vs 18 [15-22] mm/m^2; $P = .17$). During the median (IQR) follow-up of 3.3 (1.6-5.8) years, 50 patients with no or minimal symptoms receiving medical management developed the composite end point, which, in multivariate analysis adjusted for age and EuroSCORE II, was independently associated with LVESVi of 45 mL/m^2 or greater and aortic regurgitant fraction of 32% or greater, the latter adding incremental prognostic value to CMR volumetric assessment.

CONCLUSIONS AND RELEVANCE In patients with chronic moderate or severe AR, patients presenting with heart failure symptoms have greater LVESVi by CMR than those with no or minimal symptoms. In patients with no or minimal symptoms, CMR quantification of LVESVi and AR severity may identify those at risk of death or incident heart failure and therefore should be considered in the clinical evaluation and decision-making of these patients.

Viewpoint and Editorial
Multimedia
Supplemental content

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Chronic aortic regurgitation (AR) causes long-standing volume and pressure overload[1] leading to left ventricular (LV) remodeling and eventual dysfunction that may become irreversible[2] and affect outcomes despite successful aortic valve replacement (AVR).[3] Recent American College of Cardiology/American Heart Association Valvular Heart Disease Guidelines emphasized that, in addition to symptoms, it is essential to also consider the presence of LV dysfunction or LV remodeling using prespecified thresholds as indicators for AVR.[4]

Although these recommendations are based on traditional 2-dimensional transthoracic echocardiography (TTE)–derived LV end-systolic dimension and ejection fraction, LV linear dimensions are hindered by a wide range of uncertainty, particularly with increasing LV enlargement.[5] Thus, attempts to quantify LV remodeling by LV volumes have been a long-term goal of cardiac imaging in the evaluation of patients with AR. Recent data suggest that LV volumes assessment by echocardiography in chronic AR is associated with adverse outcomes.[6,7] Detection of LV remodeling is particularly crucial because AR tends to be clinically tolerated without symptoms for many years, while LV remodeling and dysfunction progresses. Hence, the current guideline's linear-dimension thresholds for AVR performance have been questioned, given their associated increased risk, in a move toward earlier intervention.[8,9]

One limitation of detecting LV remodeling by TTE is the general tendency to underestimate it by both linear dimensions and LV volumes,[10] whereas accurate LV assessment requires expertise and time,[11] rarely compatible with routine practice. Conversely, the use of cardiac magnetic resonance (CMR) is widely considered the reference standard for LV assessment because of its accurate and reproducible volumetric quantification.[12-14] However, in the present AR clinical guidelines, CMR remains reserved to situations where Doppler echocardiography is equivocal and/or TTE image quality is suboptimal.[4] Seminal CMR studies focused on CMR in patients with chronic AR[15-20] had either small cohorts,[16] mostly included mild AR,[20] or did not focus on the link between LV remodeling and outcomes.[18] It remains uncertain whether, in addition to guideline-recommended TTE measurements, CMR LV remodeling is associated with the development of symptoms and ultimately clinical outcomes.

We hypothesized that CMR volumetric quantification provides incremental risk stratification and is associated with outcomes over standard clinical and echocardiographic evaluation of LV remodeling in patients with chronic moderate or severe AR identified by echocardiography.

Key Points

Question In patients with chronic moderate or severe aortic regurgitation (AR), can cardiac magnetic resonance (CMR) volumetric quantification of left ventricular (LV) remodeling provide incremental risk stratification beyond clinical and echocardiographic evaluation?

Findings In this cohort study including 178 patients, CMR provided physiologically sound and sensitive quantification of adverse LV remodeling and AR severity, which were associated with progression of heart failure symptoms, heart failure admission, and all-cause mortality.

Meaning CMR quantification of LV remodeling and AR severity add incremental risk stratification to clinical and echocardiographic findings and should be considered in decision-making of patients with chronic AR with no or minimal symptoms receiving medical management.

Methods

Study Population and Design

This is a multicenter, retrospective cohort study of patients 18 years and older diagnosed with moderate or severe chronic AR by TTE and who had CMR performed within 90 days of baseline diagnosis between January 2012 and February 2020 at Allina Health System encompassing 3 hospitals in Minnesota (Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis; United Hospital, St Paul; Mercy Hospital, Coon Rapids). Exclusion criteria were (1) acute aortic regurgitation caused by bacterial endocarditis or aortic dissection; (2) inadequate image quality for TTE or CMR quantification owing to artifacts and/or suboptimal endocardial border visualization; (3) patients with prior surgical or transcatheter AVR; (4) infiltrative cardiomyopathy and hypertrophic cardiomyopathy based on the review of the entire CMR examination and pattern of late gadolinium enhancement, when available; and (5) severe concomitant valvular disease other than AR. Other moderate or less concomitant valvular diseases were not excluded to allow for a real-world scenario of AR assessment and clinical management. The study workflow chart is in eFigure 1 in the Supplement. The study was approved by the Allina Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All patients provided informed consent for the use of medical records for research purposes, in accordance with Minnesota law.

The electronic medical records were extensively reviewed in their entirety for retrieving patients' clinical characteristics, comorbid conditions, vital signs, therapeutic interventions, and clinical outcomes. The details of CMR and TTE imaging acquisition are described in the eMethods in the Supplement.

Quantitative CMR analysis was performed by a trained imaging specialist (G. H.) with 2 years of experience in CMR imaging blinded to clinical outcomes and baseline characteristics. Interrater variability of CMR measurements for LV volumes, aortic regurgitant volume, and aortic regurgitant fraction (ARF) were assessed in 20 randomly chosen patients and evaluated by 2 investigators (G. H. and J. L. C.) blinded to each other's results.

TTE data were obtained from clinical echocardiography reports using the American Society of Echocardiography guidelines recommendations for chamber quantification[21] by trained experienced sonographers and verified by the senior cardiologists. Interrater variability of TTE measurements, including LV internal dimensions and LV volumes, was assessed in

20 randomly chosen patients and compared between the clinical echocardiography reports by trained imaging specialist (G. H.).

Outcomes

The primary composite end point was defined as all-cause death, heart failure (HF) hospitalization, or exacerbation of HF symptoms by a worsening of 1 or more New York Heart Association (NYHA) functional classes while receiving medical management. Therefore, follow-up was censored at the time of AVR in those who underwent AVR or the end of follow-up for those who did not undergo AVR. Death occurrence and date was confirmed by records of the Social Security Death Index. The definition of HF hospitalization was standardized as per societal guidelines after comprehensive examination and review of electronic medical records for clinical events. HF hospitalization was defined as an urgent, unscheduled hospital admission with a primary diagnosis of HF, where the patient exhibited new or worsening of objective signs and symptoms of HF on presentation and received initiation or intensification of specific HF treatment. Exacerbation of HF symptoms was judged based on physician's documentation of their office visit. Patients referred for clinical evaluation prior to surgical AVR were not included in the outcome since they were referred to CMR evaluation for the purpose of surgical AVR and therefore are subject to selection bias. The decision on the indication of AVR was at the discretion of the physician. The outcome data were frozen on September 30, 2020.

Statistical Analysis

Patients' characteristics were summarized for continuous variables as either means with SDs or medians with IQRs, depending on the distribution; categorical variables were reported as counts and percentages. Baseline clinical, demographic, and outcome variables were compared between patient groups (initial NYHA class I or II HF vs NYHA class III or IV HF) using *t* tests or Wilcoxon rank sum tests for continuous variables or χ^2 or Fisher exact tests for categorical variables, as appropriate. Measurements of LV end-diastolic volume (EDV), end-systolic volume (ESV), and LV mass on CMR and TTE were displayed using Bland-Altman plots and compared using paired *t* tests. Intraclass correlation coefficient (ICC) was assessed by measuring LVEDV, LVESV, aortic regurgitant volume, and ARF in 20 random CMR studies. The interrater reliability estimates were high (LVEDV: ICC = 0.998; 95% CI, 0.997-0.999; LVESV: ICC = 0.997; 95% CI, 0.996-0.999; aortic regurgitant volume: ICC = 0.997; 95% CI, 0.996-0.999; ARF: ICC = 0.997; 95% CI, 0.995-0.999). Similarly, for the 2-dimensional TTE measurements in 20 random studies were chosen and remeasured by the imaging expert at the Core Lab of the Minneapolis Heart Institute Foundation. The interrater reliability estimates for the echocardiography-derived LV end-diastolic dimension, LV end-systolic dimension (ESD), LVEDV, and LVESV were also high (LV end-diastolic dimension: ICC = 0.999; 95% CI, 0.999–0.999; LVESD: ICC = 0.999; 95% CI, 0.999-0.999; LVEDV: ICC = 0.998; 95% CI, 0.997-0.999; LVESV: ICC = 0.999; 95% CI, 0.997-0.999). Volumetric 2-dimensional TTE measurements measured by the imaging expert at the Core Lab were in agreement with those from the clinical report (eFigure 2 in the Supplement); the corresponding intraclass correlations coefficients for LV end-diastolic dimension, LVESD, LVEDV, LVESV were 0.995 (95% CI, 0.988-0.998), 0.989 (95% CI, 0.973-0.996), 0.957 (95% CI, 0.898-0.983), and 0.973 (95% CI, 0.934-0.989), respectively.

Outcomes were assessed by the Kaplan-Meier method, and the time to first adverse event was analyzed. Cox proportional hazards models were used to estimate the association between baseline and imaging variables and the risk of composite end point, both in univariate and multivariable analysis.

These models were all adjusted for age and European System for Cardiac Operative Risk Evaluation (EuroSCORE II) score at diagnosis and in selected models by the ARF. Estimated hazard ratios (HRs) are reported with their 95% CIs and *P* values. Receiver operating characteristics curve (ROC) analysis was used to determine the ARF threshold to discriminate asymptomatic from minimally symptomatic patients who develop the composite end point.

Risk thresholds were based on previous publications, ie, LVESV index (LVESVi) of 45 mL/m^2 or greater[7,11] and LVESD index (LVESDi) of 25 mm/m^2 or greater and 20 mm/m^2 or greater by TTE as per guidelines or recent series.[8,9,22] Sensitivity analysis was done excluding patients with moderate or severe mitral regurgitation and moderate or severe aortic stenosis. The relative hazard for the composite primary end point was estimated using a penalized cubic spline. Analyses were performed using SPSS statistics version 25 (IBM) and R version 4.0 (The R Foundation) in the RStudio environment (RStudio).

Results

Of the 178 included patients, 119 (66.9%) were male, 158 (88.8%) presented with no or minimal symptoms (New York Heart Association class I or II), and the median (IQR) age was 58 (44-69) years. The most common indication for CMR was the assessment of AR severity and/or aortic dilatation (127 [71.3%]).

Baseline Characteristics

Baseline clinical characteristics of the cohort are summarized in **Table 1**. A total of 69 patients (38.8%) had bicuspid aortic valve and the median (IQR) EuroSCORE II was 0.9% (0.6%-1.6%), implying a low risk of in-hospital death after cardiac surgery for these patients. Most patients (158 [88.8%]) presented with no or minimal symptoms (NYHA class I or II HF). Cardiac comorbidities were frequent, particularly a history of hypertension, which was present in 125 patients (70.2%). AVR was performed ultimately in 66 of 178 patients (37.1%). Of the 20 more symptomatic patients (NYHA class III or IV HF), 17 of 20 received AVR (85% [SD, 8%] at 1 year from diagnosis), whereas 49 of 158 with NYHA class I or II HF received AVR (20% [SD, 3%] at 1 year from diagnosis).

Table 1. Baseline Clinical Characteristics of Patients With Chronic Moderate or Severe Aortic Regurgitation

Characteristic	No. (%)			*P* value
	Total population (N = 178)	Initial NYHA HF class of I or II (n = 158)	Initial NYHA HF class of III or IV (n = 20)	
Age, median (IQR), y	58 (44-69)	57 (42-68)	64 (59-70)	.02
Sex				
Female	59 (33)	53 (34)	6 (30)	.75
Male	119 (67)	105 (66)	14 (70)	
Body surface area, mean (SD), m^2	2.0 (0.3)	2.0 (0.3)	2.1 (0.2)	.21
Systolic blood pressure, mean (SD), mm Hg	129 (19)	129 (19)	130 (22)	.84
Diastolic blood pressure, median (IQR), mm Hg	68 (62-76)	69 (62-76)	67 (63-81)	.88
BNP, median (IQR), pg/mL (n = 69)[a]	223 (67-677)	198 (50-429)	548 (250-1609)	.006
EuroSCORE II, median (IQR), %	0.9 (0.6-1.6)	0.9 (0.6-1.5)	1.9 (1.0-4.8)	<.001
STS predicted risk of mortality, median (IQR), %	0.8 (0.6-1.4)	0.8 (0.6-1.4)	1.0 (0.7-2.8)	.04
Bicuspid aortic valve	69 (39)	63 (40)	6 (30)	.39
Hypertension	125 (70)	107 (68)	18 (90)	.04
Dyslipidemia	86 (48)	74 (47)	12 (60)	.27
Diabetes	14 (8)	9 (6)	5 (25)	.01
Chronic kidney disease (stage ≥III)	12 (7)	11 (7)	1	.51
Coronary artery disease	27 (15)	22 (14)	5 (25)	.19
Stroke	7 (4)	7 (4)	0	>.99
COPD	12 (7)	10 (6)	2 (10)	.63
Concomitant valvular disease				
Moderate AS	16 (9)	13 (8)	3 (15)	.35
Moderate MR	18 (10)	15 (8)	3 (15)	>.99
Moderate TR	14 (8)	10 (6)	4 (20)	.51
Atrial fibrillation/atrial flutter	40 (22)	34 (22)	6 (30)	.40
Medications				
Aspirin	86 (48)	74 (47)	12 (60)	.27
ACE-I or ARB	96 (54)	84 (53)	12 (60)	.56
β-Blocker	86 (48)	72 (46)	14 (70)	.04
Calcium channel blocker	23 (13)	20 (13)	3 (15)	.77
Diuretic	54 (30)	45 (28)	9 (45)	.13
Aldosterone antagonist	16 (9)	13 (8)	3 (15)	.40

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AS, aortic stenosis; BNP, brain-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; HF, heart failure; MR, mitral regurgitation; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation.

SI conversion factor: To convert BNP to ng/L, multiply by 1.

[a] Data collected for 69 patients, including 56 with NYHA HF class of I or II and 13 with NYHA HF class of III or IV.

To ascertain whether a referral bias could be detected among patients receiving a CMR, we compared these patients with patients with similar AR grading and not referred to CMR within the same study period. This comparison showed that patients referred to CMR had greater remodeling with larger LV, greater predominance of males (119 of 178 [66.9%] vs 763 of 1371 [55.7%]; *P* = .006), less concomitant aortic stenosis (16 of 178 [9.0%] vs 497 of 1371 [36.3%]; *P* < .001), consistent with a more severe and pure AR phenotype (eTable 1 in the Supplement). Therefore, this comparison revealed an appropriate clinical indication of CMR based on AR evaluation without bias.

Imaging Characteristics and LV Remodeling by TTE and CMR

AR severity by TTE was moderate in approximately half of patients (96 of 178 [53.9%%]), and the remainder had moderate to severe or severe AR (82 of 178 [46.1%]) (**Table 2**). In addition, 16 patients (9.0%) had moderate aortic stenosis, 18 (10.1%) had moderate mitral regurgitation, and 14 (7.9%) had moderate tricuspid regurgitation. By TTE, symptomatic patients with NYHA class III to IV HF had greater AR severity, slightly larger linear LV dimensions, and LVESVs than less symptomatic patients. LV mass index was consistent with eccentric hypertrophy when compared with the reference normal TTE values[21] but did not differ between patients with NYHA class I or II HF vs III or IV HF (Table 2). eFigure 3 in the Supplement demonstrates underestimation of LV volumes and overestimation of LV mass by TTE compared with CMR.

Prominent LV remodeling was observed by CMR across the entire cohort and to a greater extent in those with NYHA class III or IV HF, who also had greater ARF (Table 2; eFigure 4 in the Supplement). LV systolic function, forward

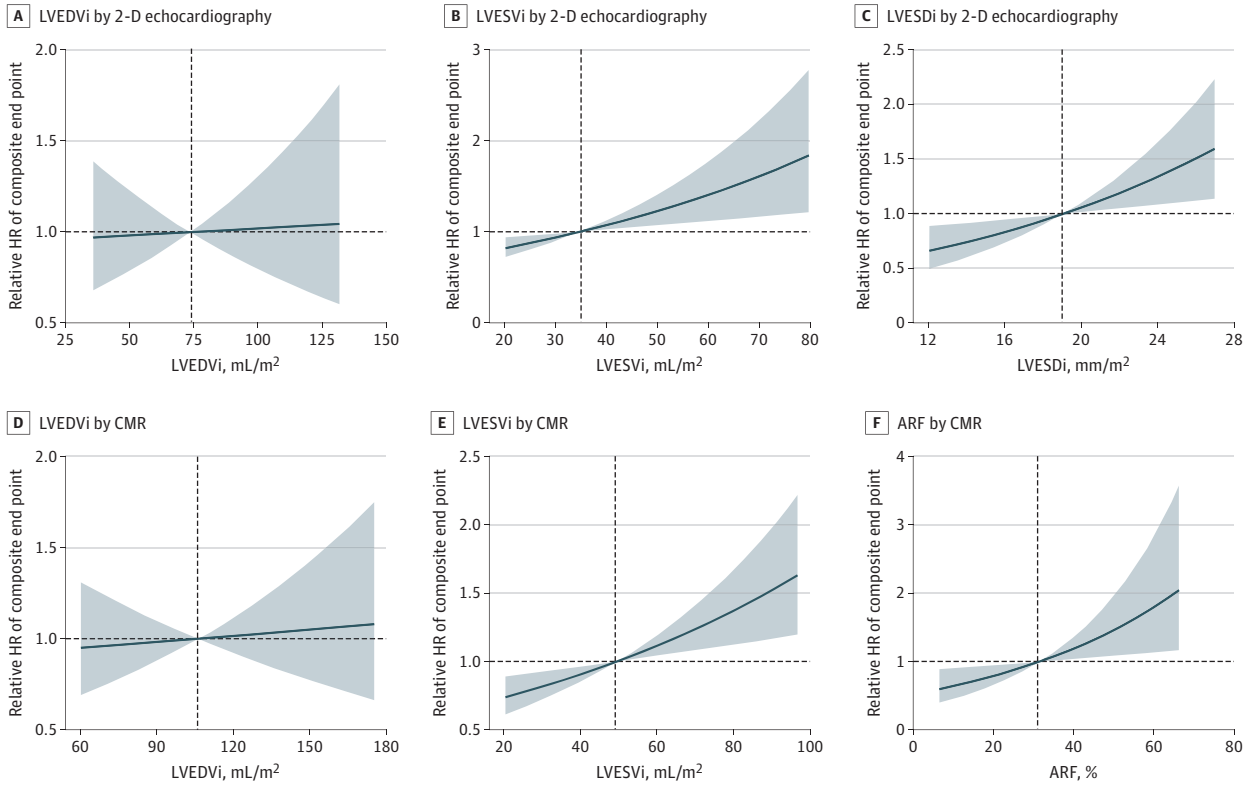
Table 2. Imaging Characteristics According to Echocardiography and Cardiac Magnetic Resonance (CMR)

Characteristic	Median (IQR)			*P* value
	Total population (N = 178)	Initial NYHA HF class of I or II (n = 158)	Initial NYHA HF class of III or IV (n = 20)	
Transthoracic echocardiography parameters				
Heart rate at TTE, beats per minute	66 (59-76)	65 (59-74)	76 (65-90)	.004
AR severity, No. (%)				
Moderate	96 (54)	90 (57)	6 (30)	<.001
Moderate to severe	44 (25)	41 (26)	3 (15)	
Severe	38 (21)	27 (17)	11 (55)	
LVEDD, mm	55 (47-60)	54 (47-59)	58 (51-64)	.06
LVEDD index, mm/m^2	27 (24-30)	27 (24-30)	28 (24-32)	.57
LVESD, mm	37 (31-44)	36 (31-43)	43 (34-50)	.03
LVESD index, mm/m^2	18 (15-22)	18 (15-22)	21 (17-25)	.17
LVEDV, mL	142 (100-181)	139 (98-180)	161 (103-205)	.31
LVEDV index, mL/m^2	68 (54-88)	65 (54-87)	76 (57-93)	.51
LVESV, mL	58 (38-86)	55 (38-82)	79 (64-113)	.04
LVESV index, mL/m^2	29 (20-42)	27 (20-42)	38 (30-58)	.07
LVSV (biplane), mL	72 (55-97)	72 (56-97)	66 (39-93)	.23
LVSV (biplane) index, mL/m^2	38 (27-47)	38 (28-47)	33 (17-46)	.16
LVSV (Doppler), mL	95 (72-119)	95 (73-120)	91 (61-114)	.35
LVSV index (Doppler), mL/m^2	49 (37-61)	49 (38-61)	42 (29-53)	.16
LVEF, %	58 (48-65)	59 (49-66)	52 (39-55)	.01
LV mass, g	256 (205-315)	251 (205-315)	282 (212-326)	.26
LV mass index, g/m^2	129 (106-158)	129 (105-158)	131 (108-156)	.62
CMR parameters				
Heart rate at CMR, beats per minute	64 (58-71)	64 (58-70)	73 (65-80)	.002
LVEDV, mL	204 (160-267)	202 (155-265)	256 (184-338)	.02
LVEDV index, mL/m^2	99 (80-129)	96 (80-123)	133 (83-151)	.02
LVESV, mL	89 (60-129)	83 (57-124)	142 (101-184)	.001
LVESV index, mL/m^2	43 (32-64)	42 (30-58)	66 (46-85)	.001
LVSV, mL	107 (86-137)	108 (88-137)	102 (67-169)	.58
LVSV index, mL/m^2	54 (45-67)	54 (46-66)	54 (31-78)	.60
LVEF, %	57 (49-64)	58 (50-64)	51 (29-56)	.004
LV mass, g	157 (126-195)	149 (123-194)	177 (141-235)	.03
LV mass index, g/m^2	79 (62-94)	77 (62-93)	88 (73-103)	.04
Aortic regurgitant fraction, %	31 (19-45)	30.2 (18.6-43.5)	40.9 (23.8-57.8)	.04
Forward SV index, mean (SD), mL/m^2	42 (13)	43 (13)	36 (14)	.03
Forward CI, mean (SD), mL/min/m^2	2.7 (0.8)	2.7 (0.8)	2.5 (0.9)	.29
Composite echocardiography-CMR measures				
Forward SV index (echocardiography biplane), mL/m^2	24 (13-33)	26 (15-34)	13 (6-24)	.004
Forward CI (echocardiography biplane), mL/min/m^2	1.6 (0.9-2.1)	1.6 (1.1-2.1)	0.9 (0.4-1.4)	.01
Forward SV index (echocardiography Doppler), mL/m^2	34 (24-45)	36 (24-48)	27 (18-33)	.01
Forward CI (echocardiography Doppler), mL/min/m^2	2.3 (1.5-2.9)	2.3 (1.5-3.1)	1.9 (1.4-2.6)	.12

Abbreviations: AR, aortic regurgitation; CI, cardiac index; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association Functional Classification; SV, stroke volume; TTE, transthoracic echocardiography.

stroke volume index, and forward cardiac index were on average preserved (Table 2). Patients with no or minimal symptoms at baseline but who developed a composite event at follow-up vs those who did not develop an event had larger LVESVi (mean [SD], 57 [43] mL/m^2 vs 45 [24] m:/m^2; *P* = .03) and greater ARF (mean [SD], 37% [18%] vs 28% [17%]; *P* = .006). Furthermore, the forward stroke volume index and cardiac index were underestimated by TTE, particularly notable for biplane Simpson method and slightly less for Doppler method (eFigure 5 in the Supplement).

Figure 1. Estimated Relative Hazards of the Composite End Point (Death, Heart Failure, or Worsening Symptoms)



Calculated using a penalized cubic spline, censoring at the time of aortic valve replacement (when performed) or at the end of follow-up time for echocardiographic and cardiac magnetic resonance (CMR) variables. Dashed horizontal line demarcates the threshold above which increased relative hazard for the combined end point occurs. Curve fit and 95% CIs (shaded area) for each of the parameters are displayed. 2-D indicates 2-dimensional; ARF, aortic regurgitant fraction; EDVi, end-diastolic volume index; ESDi, end-systolic diameter index; ESVi, end-systolic volume index; HR, hazard ratio; LV, left ventricular.

Long-term Outcomes in Patients With No or Minimal Symptoms

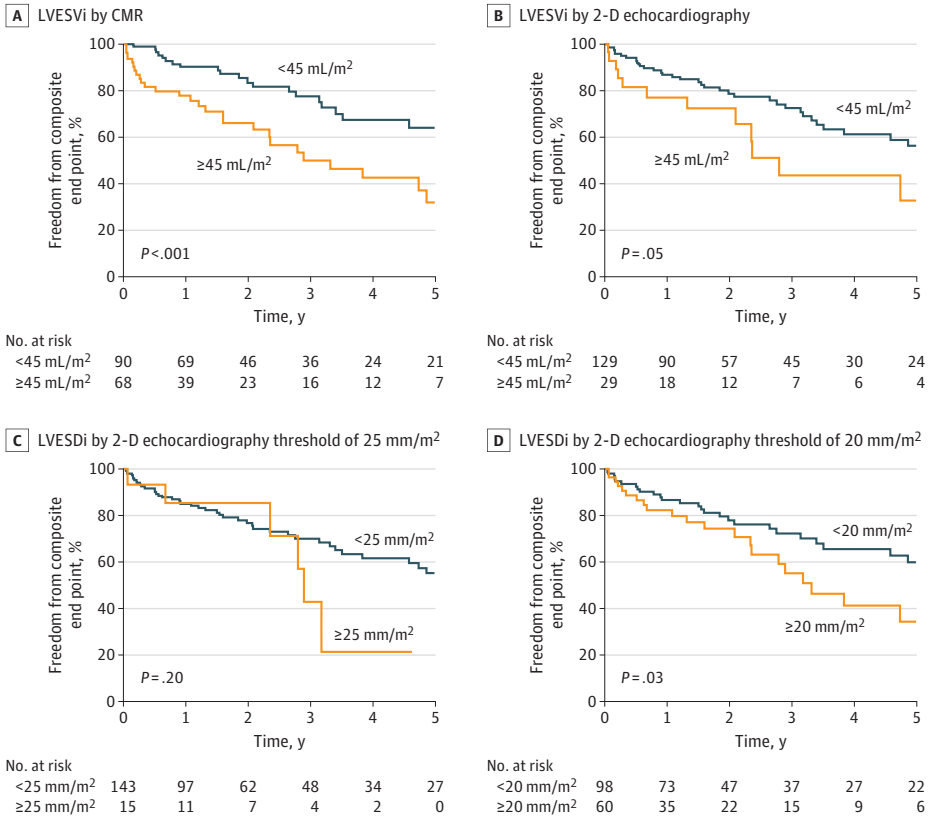
The subset of 158 patients with no or minimal symptoms (NYHA class I or II HF) at baseline, including 123 asymptomatic patients (77.8%), was further evaluated for the outcomes analysis. In these patients, the median (IQR) follow-up period was 3.3 (1.6-5.8) years, during which 49 patients (31.0%) underwent AVR. Clinical events occurred in 50 patients receiving medical management (31.6%). The first index event in these patients included progression of symptoms with worsening NYHA class in 36 patients (22.8%), HF hospitalization in 10 patients (6.3%), and 4 deaths when receiving medical treatment (2.5%). Total events in these 50 patients included 8 deaths, 29 hospitalizations for HF exacerbation, and 39 progressions of symptoms with worsening NYHA class. In univariate analysis, among the CMR variables, larger LVESVi, greater ARF, and lower LVEF were associated with increased risk of the composite end point (eTable 2 in the Supplement).

In the spline curve analysis (**Figure 1**), the observed threshold for excess risk of composite events was LVESVi greater than 49 mL/m^2 by CMR. Given that this threshold is close to the 45 mL/m^2 threshold from the echocardiographic literature,[7,11] we chose this validated cut point for outcomes analysis. By TTE, the best LVESDi threshold was 19 mm/m^2.

By Kaplan-Meier analysis for composite events while receiving medical management, excellent risk discrimination was observed using a CMR LVESVi threshold of 45 mL/m^2 (**Figure 2**A) but not with the guideline-recommended TTE LVESDi threshold of 25 mm/m^2 (Figure 2B), which only captured a small number of patients at risk. A lower TTE LVESDi threshold of 20 mm/m^2 better discriminated the risk for the development of composite events while receiving medical management (Figure 2C).

Multivariate Cox proportional hazards models adjusted for age and EuroSCORE II are presented in **Table 3**. LVESVi by CMR either as a continuous or as a dichotomous variable was associated with increased risk of composite events. For TTE measures, higher LVESDi as a continuous variable was marginally associated with increased risk of adverse events but not when using either the guideline-recommended cutoff of 25 mm/m^2 or the lower threshold of 20 mm/m^2. The ARF cutoff associated with the composite end point by receiver operating characteristics curve analysis was 32% (sensitivity = 73%; specificity = 68%; area under receiver operating characteristic curve = 0.70), which is similar to the previously reported CMR

Figure 2. Kaplan-Meier Estimates of Time to the Composite End Point (Death, Heart Failure, or Worsening Symptoms) in Asymptomatic Patients Receiving Medical Management



A, Stratified by a left ventricular (LV) end-systolic volume index (ESVi) threshold of 45 mL/m^2 measured by cardiac magnetic resonance (CMR). B, Stratified by an LVESVi threshold of 45 mL/m^2 measured by 2-dimensional (2-D) echocardiography. C, Stratified according to guideline linear-dimension LV end-systolic diameter index (ESDi) threshold of 25 mm/m^2 measured by 2-D echocardiography. D, Stratified according to more sensitive linear-dimension LVESDi threshold of 20 mm/m^2 measured by 2-D echocardiography.

threshold.[16] Adding AR quantification by CMR using ARF of 32% or greater to the model with CMR LVESVi of 45 mL/m^2 or greater showed that both variables were associated with the development of the composite end point (Table 3) for these patients receiving medical management. Furthermore, incremental risk discrimination was seen when combining ARF of 32% or greater to LVESVi of 45 mL/m^2 or greater (χ^2 increase from 2.72 to 9.58; P = .002).

Of the 143 patients with LVESDi less than 25 mm/m^2, 115 patients had NYHA class I HF and therefore would not have met the guideline indication threshold for surgical AVR. A total of 43 of 115 (37.4%) had CMR LVESVi of 45 mL/m^2 or greater, which remained associated with adverse outcomes in this subset (eFigure 6 in the Supplement). Sensitivity analysis excluding patients with at least moderate mitral regurgitation or at least moderate AS led to similar results (eTable 3 in the Supplement).

Discussion

In this multicenter cohort analysis of patients with chronic moderate to severe AR, intermodality comparative assessment of LV volumes by CMR and TTE yielded new insights. First, despite good intraobserver and interobserver reliability of both TTE and CMR measurements, LV volumes are greater by CMR than by TEE and are more closely associated with patients with symptoms at the time of presentation. Second, in patients with no or minimal symptoms, CMR LVESVi was independently associated with symptom progression, HF hospitalization, and all-cause mortality. Third, CMR LVESVi was independently associated with the composite end point, whereas TTE LVESVi and the current guideline-recommended TTE linear threshold of LVESDi of 25 mm/m^2 or greater were not. Conversely, a lower LVESDi cutoff of 20 mm/m^2 or greater by TTE discriminated risk better on univariate analysis but not after adjustment. Fourth, CMR quantification of AR severity using ARF was independently associated with outcomes, adding incremental prognostic value to CMR volumetric assessment. Fifth, in 37% of asymptomatic patients who did not meet guideline linear-dimension thresholds for AVR, significant LV remodeling by CMR (ie, LVESVi of 45 mL/m^2 or greater) was already present and, importantly, associated with adverse outcomes, strengthening the message that physiologically sound volumetric assessment by CMR in asymptomatic patients with AR can provide incremental data beyond echocardiographic measurements for risk stratification. Taken together, our findings support CMR as a valuable imaging tool for both the quantification of LV dilation and AR severity. In addition to clinical evaluation, CMR improved risk stratification of patients with chronic AR, which is important for decision-making.

Table 3. Hazards Estimates for the Risk of Composite End Point (Death, Heart Failure, or Worsening Symptoms) in Asymptomatic or Minimally Symptomatic Patients Receiving Medical Management[a]

Characteristic	HR (95% CI)	*P* value
LVESVi by CMR (per 1 mL/m^2)	1.01 (1.00-1.02)	.02
LVESVi ≥45 mL/m^2 by CMR	2.28 (1.30-4.00)	.004
LVESDi by echocardiography (per 1 mm/m^2)	1.05 (1.00-1.09)	.05
LVESDi ≥25 mm/m^2 by echocardiography	1.49 (0.62-3.56)	.37
LVESDi ≥20 mm/m^2 by echocardiography	1.56 (0.89-2.74)	.12
LVEF by CMR (per 1% unit)	0.98 (0.96-0.996)	.02
ARF ≥32% by CMR	3.32 (1.67-6.59)	<.001
ARF ≥32% by CMR adjusted for LVESVi ≥45 mL/m^2	3.18 (1.60-6.34)	<.001
LVESVi ≥45 mL/m^2 by CMR adjusted for ARF ≥32%	1.89 (1.01-3.56)	.04

Abbreviations: ARF, aortic regurgitant fraction; CMR, cardiac magnetic resonance; HR, hazard ratio; EF, ejection fraction; ESDi, end-systolic dimension index; ESVi, end-systolic volume index; LV, left ventricular.

[a] All hazards estimates were adjusted for age and EuroSCORE II.

LV Remodeling Assessment by TTE and CMR

LV remodeling is a determinant of outcomes in many cardiac conditions,[23-25] including AR.[6-9,16,22] Although TTE basal linear LV diameters are useful for the prognostication of patients with chronic AR, they might come at a risk of poorly capturing the true LV remodeling and eccentric LV dilation that commonly occurs.[26] The best LVESDi threshold by TTE was 19 mm/m^2, which is in agreement with 3 recent single-center data[8,9,22] and again lower than the 25 mm/m^2 cutoff recommended by the current American College of Cardiology/American Heart Association and European guidelines.[4,27]

Two-dimensional TTE underestimates LV volumes, particularly if contrast agents are not used, as demonstrated by recent trials and outcome studies.[12,28] This is because of difficulty in 2-dimensional TTE measurement related to the presence of trabeculations, apical foreshortening, or papillary muscle shadowing, which can underestimate the true LV volume. This trend is confirmed in our study whereby LV volumes by TTE were underestimated compared with those by CMR. Greater accuracy of volumetric assessment by CMR is caused by the superior blood pool–endocardial border definition of conventional steady-state free precession cine imaging, leading to greater reproducibility of tracing and avoidance of apical foreshortening.

Together, these factors translate into reduced measurement error with CMR and a better estimate of biological (rather than measurement) variability.[29,30] Conversely, while use of contrast agents may provide better volume measurements with TTE,[10] these measurements remain biplane with extrapolation of the LV contour between these planes. Our findings of physiologically coherent ventricular volumes by CMR are consistent with recent data, including mostly mild AR cases.[31] Building on that, our findings focusing on a sizable, multicenter cohort of mostly asymptomatic and minimally symptomatic patients with moderate or severe AR emphasize the relevance of CMR evaluation for the clinical management in these patients.

In our cohort, CMR LVESVi was found to be the strongest CMR outcome-related parameter, rather than previously reported LVEDVi.[20,31] LVESVi reflects a combination of both LV contractility and LV remodeling, rather than just remodeling. Recent work by Malahfji et al[32] showed that myocardial scar was present in one-third of patients with AR with similar LVEDVi but larger LVESVi and worse LVEF. Although myocardial fibrosis using late-gadolinium enhancement imaging was not consistently evaluated in this cohort, it is possible that presence of myocardial scarring may reflect greater adverse LV remodeling, which is captured by LVESVi.

Clinical Management of Chronic AR

Chronic AR is a slowly progressive entity with ongoing LV volume and pressure overload and causes remodeling and adaptive eccentric hypertrophy with increase in LV volumes and LV mass (both cellular and interstitial), facilitating the development myocardial fibrosis, diastolic dysfunction, and, ultimately, impairment of contractile function.[33] The decision-making for chronic AR management relies on 3 main pillars: presence or absence of symptoms, correctly identifying severe AR, and accurately quantifying LV remodeling. In the current series, CMR assessment of LVESVi was more sensitive than 2-dimensional TTE in separating patients with more severe HF symptoms at initial presentation. This finding is crucial, as attributing symptoms to AR is often complex in older patients and in women[34] but has profound outcome implications,[35] even after surgery.[9] The coherence of symptoms and objective assessment of LV remodeling are key to prompt indications for intervention.[4,27] In patients with no or minimal symptoms, it is critical to quantify severity of LV volume overload, as previous publications have underscored the relatively late nature of current thresholds for intervention in the course of clinically significant AR.[9]

Lacking sufficient evidence, volumetric data have not been established in the current guidelines as an indication for AVR in chronic AR, whether by 2-dimensional or 3-dimensional TTE (with or without contrast) or by CMR. Our study shows that CMR provides volumetric markers that are physiologically sound, reproducible, and independently associated with subsequent outcomes in asymptomatic or minimally symptomatic patients. The LVESVi threshold of 45 mL/m^2 is consistent with previous TTE data by Yang et al[7] that this value identifies patients at risk of clinical events undergoing medical management. Furthermore, our observation that a significant proportion of asymptomatic patients with LVESDi less than 25 mm/m^2 (43 of 115 [37.4%]) already have significant LV remodeling by CMR, which in turn is associated with poor outcomes, underscores the need to reconsider the current guideline recommendations and to use lower linear systolic thresholds.[8,9,22] In view of the scarce evidence in the current literature regarding CMR in the treatment of patients with AR,[16,18,19,31] the current data provide insights into the usefulness of CMR assessment of LVESVi and ARF in risk assessment, which will require properly designed randomized clinical trials to test this hypothesis.

However, current guidelines for management of AR[4,23] suggest the use of CMR only in limited circumstances (ie, signs of

Doppler echocardiographic severity are equivocal and/or the quality of echocardiography images is suboptimal). We believe that the current data provide a foundation for more routine CMR assessment of AR severity and LV remodeling[30] in the clinical management of patients with chronic AR.

Limitations

Our study has to be interpreted in light of its limitations. Requiring CMR performance for study inclusion has an inherent selection bias to the included patients and suitability of CMR examination performance. This observational study is not a consecutive series of patients with moderate or severe AR that were referred for CMR as part of their preoperative testing. In fact, most patients were asymptomatic, reflecting real-world clinical practice and clinical dilemma. As described earlier, despite their predominantly asymptomatic status, potential selection and referral bias were observed with greater LV remodeling seen by 2-dimensional TTE compared with similar contemporary cohort of patients with moderate or severe AR but who did not undergo CMR evaluation at our health system. Generalizing indications to the wider range of all patients with clinically significant AR and/or patients with intracardiac devices will provide future validation of our findings and allow earlier detection of LV remodeling. This cohort includes an important percentage of patients with hypertension. Despite antihypertensive drug treatment, LV remodeling cannot be entirely ascribed to the AR and therefore may be a confounding factor.

Although we included CMR assessment at a single time point, follow-up CMR imaging data could have provided a quantifiable measure of chamber remodeling changes over time and should be investigated, in view of the present results. Our aim is to assess the performance of CMR and compare it with 2-dimensional TTE and not to undermine TTE performance in assessing LV remodeling in patients with clinically significant AR, albeit understanding its potential limitations. While standard 2-dimensional TTE LV volumes were lower and not physiologically sound, ESD index by TTE was associated with outcomes on univariate analysis, but not after adjustments. Although this could be a reflection of a type II error, the higher HR of CMR volumetric measures strengthens their clinical importance, along with AR severity quantification for decision-making.

Additionally, CMR measurements were performed offline by a trained imaging specialist, while TTE measurements were obtained in routine clinical practice. However, for TEE, randomly selected examination reinterpretation by imaging cardiologist demonstrated excellent agreement of the values measured, suggesting that underestimation of LV volumes is intrinsically linked to the standard TTE methodology. In this context, the potential of 3-dimensional TTE and/or systematic use of contrast echocardiography in improving accuracy and coherence of LV remodeling assessment could warrant future comparative studies.

Conclusions

In this study, among patients with chronic moderate or severe AR, patients presenting with HF symptoms had greater LVESVi by CMR than patients with no or minimal symptoms. In patients with no or minimal symptoms and receiving medical management, CMR assessment of both LVESVi and ARF were independently associated with adverse clinical events, including death and incident HF. Hence, these data support CMR as a valuable imaging tool for the clinical evaluation and risk stratification of selected patients with chronic AR.

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