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ORIGINAL INVESTIGATIONS

Influence of Cardiac Remodeling on Clinical Outcomes in Patients With Aortic Regurgitation

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ABSTRACT

BACKGROUND Quantitative cardiac magnetic resonance (CMR) outcome studies in aortic regurgitation (AR) are few. It is unclear if volume measurements are beneficial over diameters.

OBJECTIVES This study sought to evaluate the association of CMR quantitative thresholds and outcomes in AR patients.

METHODS In a multicenter study, asymptomatic patients with moderate or severe AR on CMR with preserved left ventricular ejection fraction (LVEF) were evaluated. Primary outcome was development of symptoms or decrease in LVEF to <50%, development of guideline indications for surgery based on LV dimensions, or death under medical management. Secondary outcome was the same as the primary outcome, excluding surgery for remodeling indications. We excluded patients who underwent surgery within 30 days of CMR. Receiver-operating characteristic analyses for the association with outcomes were performed.

RESULTS We studied 458 patients (median age: 60 years; IQR: 46-70 years). During a median follow-up of 2.4 years (IQR: 0.9-5.3 years), 133 events occurred. Optimal thresholds were regurgitant volume of 47 mL and regurgitant fraction of 43%, indexed LV end-systolic (iLVES) volume of 43 mL/m^2, indexed LV end-diastolic volume of 109 mL/m^2, and iLVES diameter of 2 cm/m^2. In multivariable regression analysis, iLVES volume of ≥43 mL/m^2 (HR: 2.53; 95% CI: 1.75-3.66; $P < 0.001$) and indexed LV end-diastolic volume of ≥109 mL/m^2 were independently associated with the outcomes and provided additional discrimination improvement over iLVES diameter, whereas iLVES diameter was independently associated with the primary outcome but not the secondary outcome.

CONCLUSIONS In asymptomatic AR patients with preserved LVEF, CMR findings can be used to guide management. CMR-based LVES volume assessment performed favorably compared to LV diameters.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

aHR = adjusted HR

AR = aortic regurgitation

AUC = area under the curve

AVR = aortic valve replacement or repair

CMR = cardiac magnetic resonance

ECV = extracellular volume fraction

EuroSCORE II = European System for Cardiac Operative Risk Evaluation

LV = left ventricular

LVED = left ventricular end-diastolic

LVEF = left ventricular ejection fraction

LVES = left ventricular end-systolic

SCMR = Society for Cardiovascular Magnetic Resonance

Cardiac magnetic resonance (CMR) is a reproducible noninvasive method to quantify the severity of aortic regurgitation (AR)[1-7] and is also the current reference standard for assessment of left ventricular (LV) volume, ejection fraction, and mass, which are the principal parameters for evaluating the effects of the combined pressure and volume overload of chronic AR.[8,9] Current management of patients with AR relies primarily on symptom assessment, LV ejection fraction (LVEF), and linear LV end-systolic (LVES) diameter, the last of which can vary with measuring technique and the pattern of LV dilation and remodeling.[10,11] There is recent evidence that outcomes of AR patients could be improved with earlier surgery[12-14] before clinical decompensation, but the identification of clinical, laboratory, and imaging markers to prevent irreversible decompensation remains an area of research.

The American College of Cardiology/American Heart Association guidelines endorse the use of CMR in AR, particularly in cases of uncertain echocardiographic assessment, but they highlight an evidence gap regarding the relationship between LV volumes and outcomes in AR.[8] Data on the prognostic value of CMR assessment has thus far come from small cohorts or included symptomatic patients.[6,7,15] Furthermore, whether CMR LVES volume assessment is advantageous over linear LVES diameters is uncertain. In this multicenter study of 4 prospective registries, we aimed to address these knowledge gaps by evaluating CMR-based outcomes in asymptomatic AR patients with preserved LV systolic function.

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METHODS

PATIENT SELECTION. Across 4 U.S. prospective institutional registries, we included consecutive and unique patients with moderate or severe AR, defined as a regurgitant volume of ≥30 mL or regurgitant fraction of ≥30% measured by CMR phase contrast imaging. We excluded patients with: 1) greater than mild concomitant valvular disease (other than secondary tricuspid regurgitation); 2) prior valve intervention or surgery; 3) New York Heart Association functional class II-IV; 4) LVEF of <50% or a primary cardiomyopathy unrelated to AR (eg, hypertrophic cardiomyopathy, amyloidosis, sarcoidosis); 5) congenital heart disease except bicuspid aortic valve; and 6) end-stage systemic disease with competing mortality risk such as metastatic cancer; 7) additionally, patients who underwent aortic valve replacement or repair (AVR) within 30 days of CMR were excluded to avoid the potential bias of patients having a predesignated CMR scan "en route" to surgery or those who underwent AVR because of the CMR findings themselves. No patients with acute AR (eg, caused by aortic dissection) were included in the study. The patient enrollment process is summarized in Figure 1. Institutional Review Board approval for use of the data encompassed in this study was obtained at each participatory site.

MULTICENTER DATA AGGREGATION AND ANALYSIS. The study was performed through the Society for Cardiovascular Magnetic Resonance (SCMR) registry, which is a growing international collaborative registry, currently with 19 participating sites. Four centers participated in this study, and Houston Methodist Hospital was the data coordinating center.

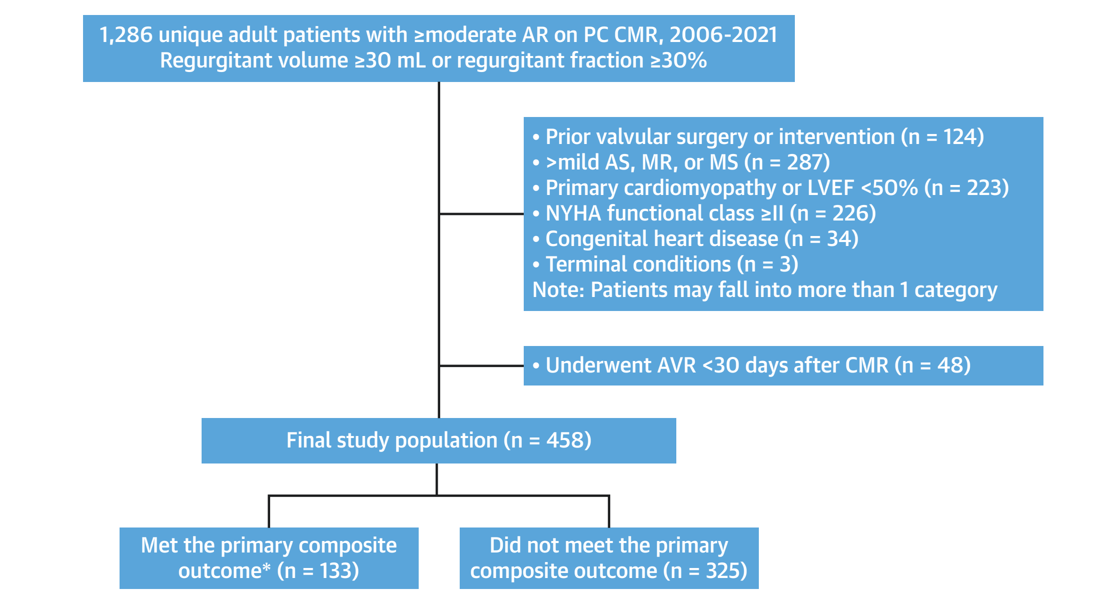
At each institution, patients underwent a baseline interview and review of medical records by local personnel at the time of CMR. The collected clinical data included demographic characteristics, cardiovascular risk factors, comorbidities, and New York Heart Association functional class. Echocardiographic findings on AR severity were recorded. Each of the 4 participating centers used the same software for onsite clinical CMR image interpretation and reporting, as well as for cloud-based data aggregation (Precession, Heart Imaging Technologies). At each site, the structured data from the finalized clinical CMR reports were stored in an internal relational database. The structured clinical report data and associated images from each of the centers were automatically deidentified and transmitted to the cloud. The deidentified patient imaging data sets were made accessible to the coordinating center at Houston Methodist Hospital for imaging analysis.

CMR STUDY PROTOCOL. CMR studies were acquired using either 1.5-T or 3.0-T clinical scanners (Siemens) with a phased-array coil system. A typical aortic valve assessment by CMR has been previously described[16] and is detailed in the Supplemental Appendix.

CMR ANALYSIS. LV and right ventricular end-diastolic volume, end-systolic volume, and ejection fraction as well as LV mass were measured, consistent with the guidelines.[17] LV end-diastolic (LVED) and LVES diameters were measured from the 3-chamber view on CMR at the mitral leaflet tips.[18-20] LV volumes and diameters were indexed to body surface area.

The regurgitant volume was calculated using the direct method from phase contrast imaging at the

FIGURE 1 Patient Enrollment



A total of 115 of 458 (25.1%) of patients had their last known alive date censored before the end of study date, March 2022. The loss of follow-up was usually caused by patients being referred from outside institutions or cities. *Primary composite outcome: development of symptoms, decrease in LVEF to ≤50%, referral for AVR based on guideline recommended thresholds of left ventricular dilation (left ventricular end-systolic diameter >5 cm, indexed left ventricular end-systolic diameter ≥2.5 cm/m^2, or left ventricular end-diastolic diameter >6.5 cm), or death during medical management. AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement or repair; CMR = cardiac magnetic resonance; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MS = mitral stenosis; NYHA = New York Heart Association; PC = phase contrast.

level of the sinotubular junction, 0.5 cm above the aortic valve, as is recommend by current guidelines.[21] The regurgitant fraction was calculated as: (reverse volume/forward volume × 100%). Phase contrast imaging in the ascending aorta and the difference between aortic and net pulmonic forward stroke volume were used as secondary checks for the regurgitant volume quantitation. All analyses were done on the same software (Precession, Heart Imaging Technologies). All studies were analyzed, at the time of imaging, by a similarly trained group of individuals who were blinded to clinical outcomes. We did not remeasure LV volumes or LV diameters to reflect their real-world use and because the interpreting physicians were blinded to the patients' outcomes.

CLINICAL FINDINGS AND OUTCOME ASSESSMENT. Each of the institutions updated patient mortality by comparing local patient identifiers to the U.S. Social Security Death Index, and any changes in vital status were automatically transmitted to the cloud. Mortality events were also collected through electronic health record review and/or telephone calls with patients' relatives and then updated in the cloud. Participating investigators at each site collected ancillary findings, comorbid conditions, outcomes with AVR/aortic valve repair vs medical management, and European System for Cardiac Operative Risk Evaluation (EuroSCORE II). Clinical follow-up was initiated prospectively from the time of CMR imaging.

The primary outcome was a composite of adverse events during longitudinal follow-up, whichever occurred first, including the development of symptoms related to AR as determined by cardiology or cardiac surgery evaluations, decrease in LVEF to <50%, referral for AVR based on guideline-recommended thresholds of LV dilation (LVES diameter of >5 cm, indexed LVES diameter of ≥2.5 cm/m^2, or LVED diameter of >6.5 cm), or death during medical management. The secondary composite outcome was defined as development of symptoms as described, decrease in LVEF of <50%, or death during medical management. Patients who underwent AVR as a combined procedure with aortic aneurysm repair without meeting guideline-specific thresholds or indications for AR were not considered to have met the

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TABLE 1 Baseline Patient Characteristics

	Total (N = 458)	No Primary Composite Event (n = 325)	Met the Primary Composite Event (n = 133)	*P* Value
Clinical findings				
Age, y	60.0 (46.0-70.0)	59.0 (47.0-71.0)	61.0 (45.0-70.0)	0.98
Sex				0.75
Female	82 (17.9)	57 (17.5)	25 (18.8)	
Male	376 (82.1)	268 (82.5)	108 (81.2)	
White	337 (73.6)	244 (75.1)	93 (69.9)	0.26
Heart rate, beats/min	67.0 (60.0-74.0)	67.0 (60.0-74.0)	68.0 (59.5-75.0)	0.91
SBP, mm Hg	135.0 (124.0-148.0)	135.0 (125.0-149.0)	135.0 (120.0- 147.0)	0.17
DBP, mm Hg	68.0 (62.0-76.0)	70.0 (64.0-78.0)	65.0 (60.0-71.0)	<0.001
Sinus rhythm during CMR	439 (95.9)	312 (96.0)	127 (95.5)	0.80
Body surface area, m^2	2.0 (1.9-2.2)	2.0 (1.9-2.2)	2.0 (1.9-2.1)	0.053
Body mass index, kg/m^2	26.8 (24.4-30.7)	27.0 (24.4-31.1)	26.3 (24.4-30.1)	0.33
Coronary artery disease	50 (10.9)	35 (10.8)	15 (11.3)	0.87
Diabetes	30 (6.6)	18 (5.5)	12 (9.0)	0.17
Hyperlipidemia	198 (43.2)	133 (40.9)	65 (48.9)	0.12
Hypertension	273 (59.6)	194 (59.7)	79 (59.4)	0.95
Current or previous smoking	123 (26.9)	85 (26.2)	38 (28.6)	0.60
Atrial fibrillation	64 (14.0)	45 (13.8)	19 (14.3)	0.90
EuroSCORE II	0.8 (0.5-1.4)	0.7 (0.5-1.2)	1.0 (0.6-1.6)	<0.001
Medications				
RAAS inhibitor	200 (43.7)	151 (46.5)	49 (36.8)	0.06
Anticoagulation	54 (11.8)	43 (13.2)	11 (8.3)	0.14
Antiplatelet	163 (35.5)	112 (35.0)	51 (39.2)	0.40
Beta-blocker	169 (36.9)	126 (38.8)	43 (32.3)	0.19
Nitrates	12 (2.6)	10 (3.1)	2 (1.5)	0.34
Diuretic	89 (19.4)	64 (19.7)	25 (18.8)	0.83
Statin	164 (35.8)	115 (35.4)	49 (36.8)	0.77

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primary or secondary composite outcome and were censored at the time of surgery. The event status (censor date) for patients was checked until March 2022. Patients were treated before the latest valvular heart disease guideline update,[8] and thus, the LVEF threshold of 50% was used.

STATISTICAL ANALYSIS. Descriptive data are reported as median (IQR) for continuous variables and as frequencies and proportions for categorical variables. Differences between groups were compared using the chi-square or Fisher exact tests for categorical variables and Kruskal-Wallis test for continuous variables. Differences between groups were compared using the log-rank test. Receiver-operating characteristic curve analysis with the Youden index[22] was used to identify the optimal thresholds of indexed LVES volume, indexed LVED volume, LVES diameter, indexed LVES diameter, regurgitant fraction, and regurgitant volume in discriminating the primary and secondary composite outcomes. Cubic spline plots were used to present the relationship of CMR parameters and the unadjusted HR for the primary and secondary composite outcomes. Cox proportional hazards modeling was used to determine the contribution of potential prognostic variables to the patient outcomes. The selection of covariates for the multivariable models was based on both the clinical importance and the least absolute shrinkage and selection operator method with the cross-validation selection option. The least absolute shrinkage and selection operator program suggested good models that included the variables with a high probability of being a risk factor. The likelihood ratio test was used to further reduce model subsets. To avoid overfitting, some variables that were significant in the univariate analysis but insignificant in multivariable modeling were not selected in the final model if their exclusion did not affect the diagnostic performance of the final model. Proportional hazards assumption of covariates included in the Cox models was tested as part of the modeling process based on Schoenfeld residuals. Those variables with HRs not being proportional over time were processed as time-varying in the models. We also performed the multivariable Cox regression modeling both binary analysis with

TABLE 1 Continued

	Total (N = 458)	No Primary Composite Event (n = 325)	Met the Primary Composite Event (n = 133)	*P* Value
CMR findings				
LVEF, %	62.4 (58.0-67.0)	62.4 (58.1-66.7)	62.4 (57.4-67.5)	0.59
RVEF, %	54.0 (50.0-59.0)	54.0 (50.0-59.0)	54.0 (48.5-58.9)	0.38
Indexed LVEDV, mL/m^2	105.7 (86.8-124.9)	99.9 (84.7-117.8)	118.6 (99.6-135.4)	<0.001
Indexed LVEDV ≥109 mL/m^2	210 (45.9)	123 (37.8)	87 (65.4)	<0.001
Indexed LVESV, mL	39.6 (30.5-48.6)	37.6 (29.4-45.1)	44.1 (35.2-54.2)	<0.001
Indexed LVESV ≥43 mL/m^2	176 (38.4)	102 (31.4)	74 (55.6)	<0.001
Indexed RVEDV, mL/m^2	79.5 (65.2-92.6)	79.5 (64.0-93.1)	79.5 (68.0-92.1)	0.74
Indexed RVESV, mL/m^2	36.3 (29.2-44.6)	35.3 (28.8-44.7)	37.0 (30.3-43.3)	0.63
LVEDD, cm	5.7 (5.2-6.2)	5.6 (5.1-6.1)	6.0 (5.4-6.6)	<0.001
LVEDD >6.5 cm	62 (13.5)	22 (6.8)	40 (30.1)	<0.001
LVESD, cm	3.8 (3.3-4.2)	3.7 (3.2-4.1)	4.0 (3.4-4.5)	<0.001
LVESD ≥4 cm	175 (38.4)	108 (33.4)	67 (50.4)	<0.001
Indexed LVESD, cm/m^2	1.9 (1.6-2.1)	1.8 (1.6-2.1)	2.0 (1.8-2.2)	<0.001
Indexed LVESD ≥2 cm/m^2	159 (34.9)	93 (28.9)	66 (49.6)	<0.001
Indexed LVESV and indexed LVESD group				<0.001
Indexed LVESV <43 mL/m^2 and indexed LVESD <2 cm/m^2	231 (50.8)	183 (56.8)	48 (36.1)	
Indexed LVESV <43 mL/m^2 and indexed LVESD ≥2 cm/m^2	48 (10.5)	37 (11.5)	11 (8.3)	
Indexed LVESV ≥43 mL/m^2 and indexed LVESD <2 cm/m^2	65 (14.3)	46 (14.3)	19 (14.3)	
Indexed LVESV ≥43 mL/m^2 and indexed LVESD ≥2 cm/m^2	111 (24.4)	56 (17.4)	55 (41.4)	
Indexed LV mass, g	82.9 (69.4-100.0)	80.9 (69.3-96.2)	89.6 (71.8-105.5)	0.004
Indexed LA volume, mL	42.6 (33.7-53.4)	42.1 (33.0-53.1)	44.0 (36.6-54.9)	0.20
Aortic regurgitant volume, mL	41.0 (32.0-59.0)	39.0 (31.0-53.0)	52.0 (35.0-73.0)	<0.001
Aortic regurgitant volume ≥47 mL	190 (41.5)	108 (33.2)	82 (61.7)	<0.001
Aortic regurgitant fraction, %	37.0 (31.0-44.0)	35.0 (30.0-42.0)	42.0 (33.0-50.8)	<0.001
Aortic regurgitant fraction >43%	138 (30.1)	73 (22.5)	65 (48.9)	<0.001
Tricuspid regurgitant volume, mL	18.0 (12.0-25.0)	17.0 (11.0-25.0)	21.5 (13.0-30.0)	0.12
Tricuspid regurgitant fraction, %	20.0 (15.0-28.0)	19.5 (14.0-27.5)	23.0 (20.0-29.0)	0.17
Tricuspid regurgitant fraction ≥30%	22 (21.0)	17 (20.2)	5 (23.8)	0.72
Aortic leaflet morphology				0.81
Trileaflet	289 (63.1)	205 (63.1)	84 (63.2)	
Bicuspid	168 (36.7)	119 (36.6)	49 (36.8)	
Quadricuspid	1 (0.2)	1 (0.3)	0 (0.0)	
AR severity on CMR				<0.001
Moderate	250 (54.6)	205 (63.1)	45 (33.8)	
Moderate-severe	89 (19.4)	60 (18.5)	29 (21.8)	
Severe	119 (26.0)	60 (18.5)	59 (44.4)	
Echocardiogram within 6 months of CMR (n = 265)				
AR severity				<0.001
Mild	25 (9.4)	20 (10.9)	5 (6.2)	
Moderate	130 (49.1)	98 (53.3)	32 (39.5)	
Moderate-severe	50 (18.9)	38 (20.7)	12 (14.8)	
Severe	60 (22.6)	28 (15.2)	32 (39.5)	

Values are median (IQR) or n (%). No corrections for multiple testing were applied.

AR = aortic regurgitation; CMR = cardiac magnetic resonance; DBP = diastolic blood pressure; EuroSCORE II = European System for Cardiac Operative Risk Evaluation; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; RAAS = renin-angiotensin-aldosterone; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; SBP = systolic blood pressure.

the optimal thresholds and continuous CMR covariates. Because the study has a single composite primary outcome and because of the study's exploratory nature, the adjustment for multiplicity was not needed.[23] Sensitivity analysis for the optimal CMR thresholds was done in patients with echocardiographic studies done within 6 months of CMR. A sensitivity analysis was also done in the group with LVEF of ≥55%. All analyses were performed on Stata version 17.0 (StataCorp LLC). A *P* value of <0.05 was considered statistically significant.

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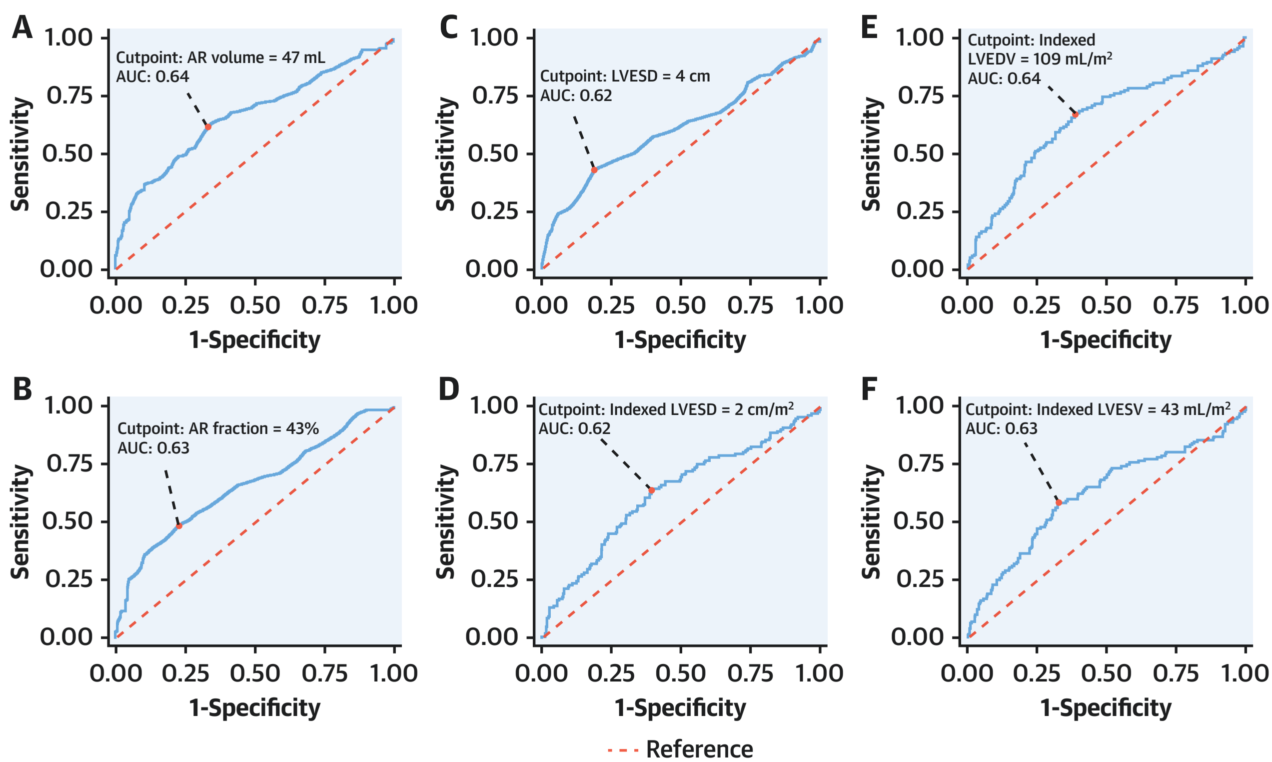
FIGURE 2 Optimal Thresholds Associated With the Primary Composite Outcome



Receiver-operating curve analysis arranged by **(A)** regurgitant volume, **(B)** regurgitant fraction, **(C)** LVESD, **(D)** indexed LVESD, **(E)** indexed LVEDV, and **(F)** indexed LVESV. No corrections for multiple testing were applied. AUC = area under the curve; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; other abbreviations as in Figure 1.

RESULTS

STUDY POPULATION. Baseline characteristics are displayed in Table 1. There were 458 asymptomatic patients; the median age was 60 years (IQR: 46-70 years), 82.1% were male, 26.4% were non-White, and 36.7% had a bicuspid aortic valve. The median regurgitant volume was 41.0 mL (IQR: 32.0-59.0 mL), and the median regurgitant fraction was 37% (IQR: 31%-44%). The median EuroSCORE II was 0.8% (IQR: 0.5%-1.4%). Coronary artery disease was present in 11% of patients, and diabetes mellitus was present in 6.6% of patients.

TABLE 2 Optimal Thresholds Associated With the Primary Composite Outcome

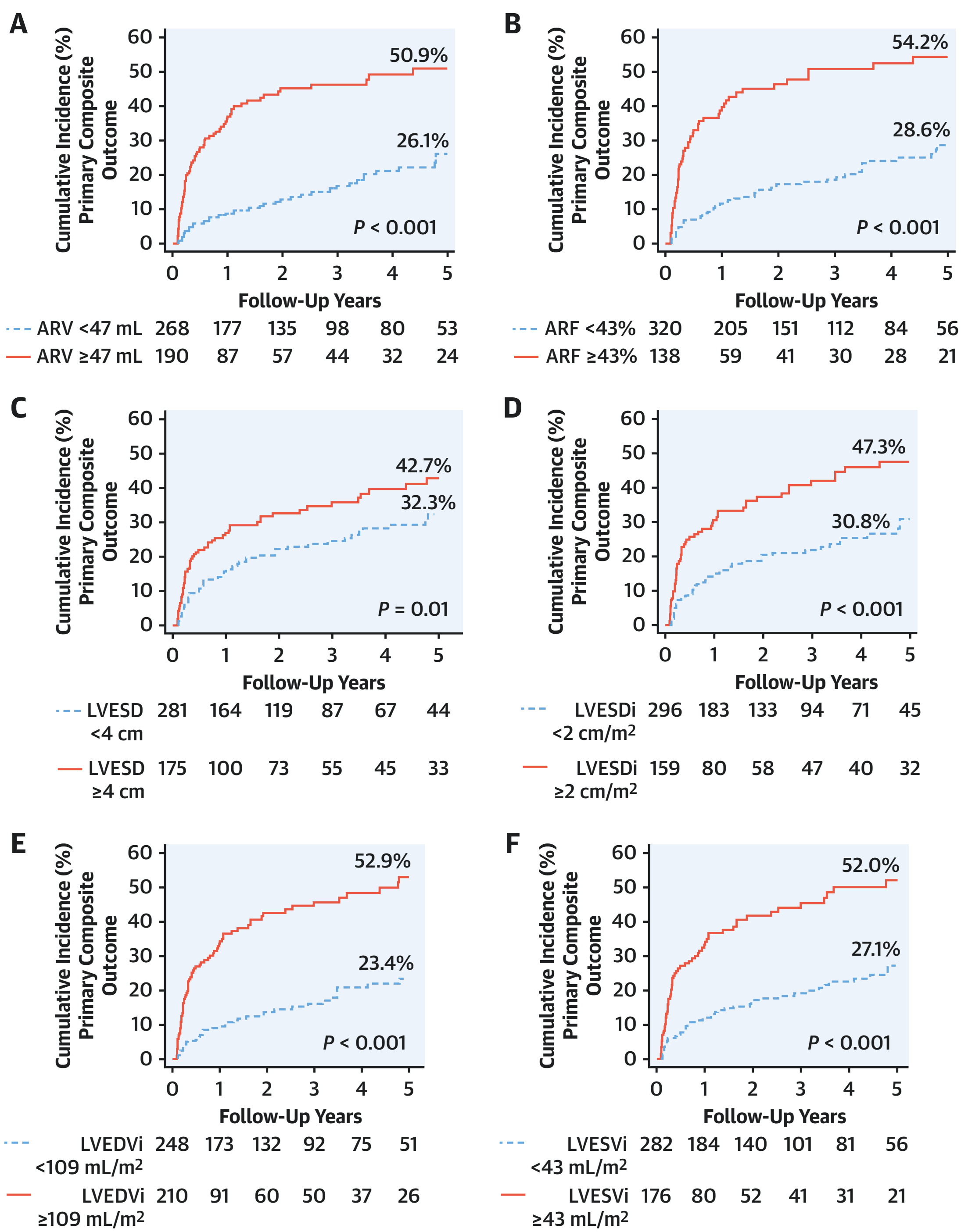
Classification Variable	ARV, mL	ARF, %	LVESD, cm	LVESDi, cm/m^2	LVEDVi, mL/m^2	LVESV, %
Empirical optimal cutpoint	47	43	4	2	109	43
Youden index (J)	0.28	0.26	0.24	0.25	0.29	0.26
SE (J)	0.05	0.05	0.05	0.05	0.05	0.05
Sensitivity at cutpoint	0.62	0.49	0.43	0.64	0.67	0.59
Specificity at cutpoint	0.67	0.77	0.81	0.61	0.62	0.67
Area under ROC curve	0.64	0.63	0.62	0.62	0.64	0.63

Optimal thresholds associated with the primary composite outcome (development of symptoms, decrease in LVEF to <50%, referral for AVR based on guideline-recommended thresholds of LV dilation, or death during medical management). Method: Youden. Reference variable: Primary composite event.

ARF = aortic regurgitant fraction; ARV = aortic regurgitant volume; LVEDVi = indexed left ventricular end-diastolic volume; LVESDi = indexed left ventricular end-systolic diameter; ROC = receiver-operating characteristic; SE = standard error; other abbreviations as in Table 1.

OUTCOME ANALYSIS. After a median follow-up of 2.4 years (IQR: 0.9-5.3 years), 133 patients met the primary composite outcome. Of the 133 patients with adverse events, 67 developed symptoms and 4 developed a decline in LVEF without symptoms; all these patients underwent AVR on follow-up. In addition, 34 patients met guideline indications for surgery based on LVES diameter or LVED diameter, and 28 patients died under medical management. There were 16 patients who underwent AVR as a combined procedure with aortic aneurysm repair without meeting AR guideline-specific thresholds, and they were not included with the primary or

FIGURE 3 Kaplan-Meier Curves of the Primary Composite Outcome



Kaplan-Meier curves stratified by **(A)** ARV, **(B)** ARF, **(C)** LVESD, **(D)** indexed LVESD, **(E)** indexed LVEDV, and **(F)** indexed LVESV. ARF = aortic regurgitant fraction; ARV = aortic regurgitant volume; LVESD = left ventricular end-systolic diameter; LVESDi = indexed left ventricular end-systolic diameter; LVEDVi = indexed left ventricular end-diastolic volume; LVESVi = indexed left ventricular end-systolic volume.

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TABLE 3 Univariable Cox Regression for the Primary Composite Outcome

	Univariable	
	HR (95% CI)	*P* Value
Clinical findings		
Age, y	1.00 (0.99-1.01)	0.88
Sex		
Female	(Reference)	
Male	0.95 (0.62-1.47)	0.83
White	0.92 (0.63-1.34)	0.66
Heart rate, beats/min	1.00 (0.99-1.02)	0.80
SBP, mm Hg	1.00 (0.99-1.01)	0.42
DBP, mm Hg	0.97 (0.95-0.98)	<0.001
Sinus rhythm during CMR	0.98 (0.43-2.23)	0.96
Body surface area, m^2	0.67 (0.33-1.35)	0.26
Body mass index, kg/m^2	0.99 (0.96-1.02)	0.47
Coronary artery disease	0.79 (0.46-1.36)	0.39
Diabetes	1.78 (0.98-3.23)	0.06
Hyperlipidemia	1.35 (0.96-1.89)	0.09
Hypertension	0.94 (0.67-1.33)	0.74
Current or previous smoking	1.24 (0.85-1.82)	0.26
Atrial fibrillation	0.90 (0.55-1.46)	0.66
EuroSCORE II	1.23 (1.14-1.33)	<0.001
Medications		
RAAS inhibitor	0.65 (0.46-0.93)	0.02
Anticoagulation	0.71 (0.38-1.32)	0.28
Antiplatelet	1.02 (0.72-1.45)	0.92
Beta-blocker	0.93 (0.64-1.34)	0.69
Nitrates	0.40 (0.10-1.63)	0.20
Diuretic	0.89 (0.57-1.37)	0.58
Statin	1.04 (0.73-1.48)	0.82

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secondary outcome groups and were censored at the time of surgery.

In total, there were 121 patients who underwent AVR >30 days after CMR. The AVR group had a higher regurgitant volume (59.0 mL [IQR: 46.0-77.3 mL] vs 37.0 mL [IQR: 31.0-51.0 mL]; $P < 0.001$) and a higher regurgitant fraction (44.0% [IQR: 34.0%-51.0%] vs 35.0% [IQR: 30.0%-41.0%]; $P < 0.001$). The annualized mortality was 1.2% per year in the surgery arm and 2.9% per year in the medical management arm.

AR SEVERITY ANALYSIS. The optimal AR severity thresholds associated with the primary composite outcome were regurgitant volume of 47 mL and regurgitant fraction of 43% (area under the curve [AUC] of 0.64 and 0.63, respectively, at these thresholds) (**Figure 2, Table 2**). The optimal thresholds associated with the secondary composite outcome were aortic regurgitant volume of 55 mL and regurgitant fraction of 43% (Supplemental Table 1, Supplemental Figure 1). Supplemental Figures 2 and 3 show the HR cubic spline plots for the primary and secondary outcomes, respectively, in their association with aortic regurgitant volume and fraction.

LV REMODELING ANALYSIS. Optimal LV remodeling thresholds associated with the primary composite outcome were indexed LVED volume of 109 mL/m^2 and indexed LVES volume of 43 mL/m^2. Linear LV diameter thresholds were LVES diameter of 4.0 cm and indexed LVES diameter of 2.0 cm/m^2 (AUC ranged from 0.62 to 0.64 for all measures) (**Table 2**). The optimal CMR thresholds associated with the secondary composite outcome were, overall, consistent with the primary results and are shown in Supplemental Figure 1 and listed in Supplemental Table 1. Supplemental Figures 4 and 5 show the cubic spline plots for LV volumes in their association with outcomes.

Kaplan-Meier curves for the cumulative hazard of the primary and secondary composite outcomes using quantitative CMR parameters are shown in **Figure 3** and Supplemental Figure 6, respectively. The association of LVEF with the primary and secondary composite outcomes had lower AUCs of 0.52 and 0.55, respectively (Supplemental Table 2, Supplemental Figure 7) (patients with LVEF of <50% excluded). The primary composite outcome was not significantly different between men and women ($P = 0.80$) or in patients with tricuspid vs bicuspid valves ($P = 0.27$).

The agreement between echocardiography and CMR on AR severity was overall fair (median time difference between studies: 21 days; agreement: 48.7%; $\kappa = 0.21$; $P < 0.001$) (Supplemental Figure 8). The optimal thresholds in patients with echocardiograms done within 6 months of CMR showing ≥moderate AR were overall consistent with the primary findings in the overall cohort (Supplemental Table 3), with similar thresholds for CMR regurgitant fraction (43%) and a higher threshold of CMR regurgitant volume (66 mL for the primary composite outcome). The optimal thresholds of LV volumes and diameters by CMR were consistent with findings from the overall study cohort.

Factors associated with developing the primary composite outcome (**Table 3**) were greater LV remodeling and hypertrophy, as well as greater aortic regurgitant volume and regurgitant fraction. We stratified patients based on categories of indexed LVES volume and indexed LVES diameter above or below the optimal thresholds. Both LVES volume and diameter were concordant (both below and above the optimal thresholds) in 341 of 456 (75%) of cases. However, in 25% of cases, the indexed LVES diameter and indexed LVES volume were “discordant.”

Patients with indexed LVES volume of ≥43 mL/m² but indexed LVES diameter of <2 cm/m² had an increased hazard for the primary outcome (HR: 1.88; 95% CI: 1.10-3.21; P = 0.02), whereas patients with indexed LVES diameter of >2 cm/m² but indexed LVES volume of <43 mL/m² had a similar outcome to those with normal values of both variables (P = 0.62) (**Central Illustration**). Consistent findings were noted in evaluating the secondary composite outcome (Supplemental Figures 9 and 10).

In multivariable Cox regression analysis adjusting for diastolic blood pressure, EuroSCORE II, and regurgitant fraction (**Table 4**), indexed LVES volume (adjusted HR [aHR]: 1.03; 95% CI: 1.01-1.04; P < 0.001), indexed LVED volume (aHR: 1.01; 95% CI: 1.01-1.02; P < 0.001), and indexed LVES diameter (aHR: 1.82; 95% CI: 1.13-2.93; P < 0.001) were independently associated with the primary composite outcome. The C-statistic for the model with indexed LV volume was higher (0.75) than the model with indexed LVES diameter (C-statistic: 0.73; discrimination improvement for continuous variables: −0.02; 95% CI: −0.04 to −0.003; P = 0.02). Other models did not show a statistically significant discrimination improvement. The multivariable Cox regression analyses in the subgroup of patients with echocardiography data were overall consistent, with indexed LVES volume being independently associated with the primary and secondary composite outcomes but not indexed LVES diameter (Supplemental Tables 4 and 5).

In the secondary composite outcome analysis (development of symptoms, decrease in LVEF, or death), the indexed LVES diameter was not independently associated with the secondary outcome (P = 0.43), whereas the indexed LVES volume was (aHR: 1.01; 95% CI: 1.00-1.03; P = 0.04) (**Table 5**).

In a sensitivity analysis excluding patients with LVEF of <55%, results were largely consistent with the primary findings for the primary composite outcome (Supplemental Table 6).

TABLE 3 Continued

	Univariable	
	HR (95% CI)	***P* Value**
CMR findings		
LVEF, %	0.98 (0.96-1.01)	0.19
RVEF, %	1.00 (0.98-1.02)	0.82
Indexed LVEDV, mL/m²	1.02 (1.01-1.02)	<0.001
Indexed LVEDV ≥109 mL/m²	3.06 (2.14-4.39)	<0.001
Indexed LVESV, mL/m²	1.03 (1.02-1.04)	<0.001
Indexed LVESV ≥43 mL/m²	2.73 (1.93-3.86)	<0.001
Indexed RVEDV, mL/m²	1.00 (0.99-1.01)	0.70
Indexed RVESV, mL/m²	1.00 (0.99-1.02)	0.78
LVEDD, cm	1.86 (1.46-2.36)	<0.001
LVEDD >6.5 cm	3.75 (2.58-5.45)	<0.001
LVESD, cm	1.65 (1.27-2.14)	<0.001
LVESD ≥4 cm	1.56 (1.11-2.20)	0.01
Indexed LVESD, cm/m²	2.60 (1.66-4.09)	<0.001
Indexed LVESD ≥2 cm/m²	1.86 (1.32-2.62)	<0.001
Indexed LVESV and indexed LVESD group		
Indexed LVESV <43 mL/m² and indexed LVESD <2 cm/m²	(Reference)	
Indexed LVESV <43 mL/m² and indexed LVESD ≥2 cm/m²	0.85 (0.44-1.64)	0.62
Indexed LVESV ≥43 mL/m² and indexed LVESD <2 cm/m²	1.88 (1.10-3.21)	0.02
Indexed LVESV ≥43 mL/m² and indexed LVESD ≥2 cm/m²	3.02 (2.05-4.46)	<0.001
Indexed LV mass, g/m²	1.01 (1.00-1.01)	0.001
Indexed LA volume, mL/m²	1.01 (1.00-1.02)	0.03
Aortic regurgitant volume, mL	1.03 (1.02-1.04)	<0.001
Aortic regurgitant volume ≥47 mL	2.83 (1.99-4.02)	<0.001
Aortic regurgitant fraction, %	1.05 (1.03-1.07)	<0.001
Aortic regurgitant fraction >43%	2.59 (1.84-3.66)	<0.001
Tricuspid regurgitant volume, mL	0.99 (0.97-1.01)	0.45
Tricuspid regurgitant fraction, %	0.99 (0.96-1.02)	0.57
Tricuspid regurgitant fraction ≥30%	0.62 (0.22-1.77)	0.37
Aortic leaflet morphology		
Trileaflet	(Reference)	
Bicuspid	1.08 (0.76-1.53)	0.68
Quadricuspid	–	–
AR severity on CMR		
Moderate	(Reference)	
Moderate-severe	1.80 (1.13-2.88)	0.01
Severe	3.52 (2.38-5.20)	<0.001
AR severity on echocardiography (n = 265)		
Mild	(Reference)	
Moderate	1.22 (0.47-3.18)	0.68
Moderate-severe	1.26 (0.44-3.63)	0.67
Severe	3.79 (1.45-9.93)	0.01

Univariable Cox regression for the primary composite outcome (development of symptoms, decrease in LVEF to <50%, referral for AVR based on guideline-recommended thresholds of LV dilation, or death during medical management). No corrections for multiple testing were applied.
Abbreviations as in **Table 1**.

DISCUSSION

In this multicenter study of asymptomatic patients with chronic AR and preserved LV systolic function, we identified quantitative CMR measures of regurgitation severity and LV remodeling that were associated with outcomes and could be useful in guiding patient management. Our study supports the use of LV volumes over LV diameters in patients with moderate or severe AR. The threshold of indexed LVES diameter identified by CMR is 2 cm/m², which is lower than current guideline recommendations (in keeping with recent echocardiographic data),[12-14] and the threshold of indexed LVES volume is 43 mL/m². This is consistent with LVES volume index thresholds reported by Yang et al[24] using echocardiography and Hashimoto

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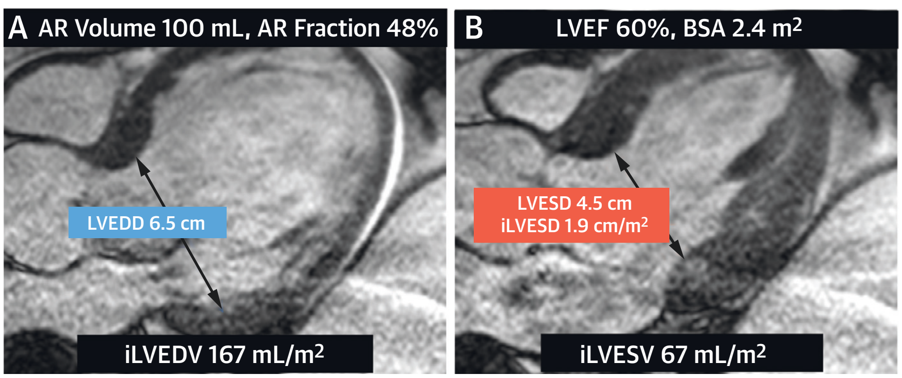
CENTRAL ILLUSTRATION **Parameters Associated With Adverse Events in Asymptomatic Aortic Regurgitation Patients**

Asymptomatic Chronic AR Patients With Preserved LV Function

Quantitative CMR Findings to Predict Development of Symptoms, Decrease in Ejection Fraction, Surgery for Established LV Remodeling Thresholds, or Death Under Medical Management

Regurgitant Volume ≥47 mL Regurgitant Fraction ≥43%	Indexed LVESV ≥43 mL/m^2	Indexed LVEDV ≥109 mL/m^2	LVESD ≥4 cm Indexed LVESD ≥2 cm/m^2



Use of LVESV Threshold Performed Favorably Compared to Diameter Measures, Which Can Introduce Higher Variability

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A patient example is shown, highlighting the potential advantages of using LV volumes. A 52-year-old man with a BSA of 2.4 m^2 and severe aortic regurgitation (regurgitant volume: 100 mL; regurgitant fraction: 48%). The left ventricle is severely dilated (LVEDV: 401 mL; indexed LVEDV: 167 mL/m^2) with an LVEF of 60%. **(A)** Variations in LVEDD assessment of a severely enlarged spherical ventricle. The LVEDD at the mitral annulus tips is 6.5 cm, and the largest LVEDD at midcavity is 9 cm. **(B)** The LVESD is 4.5 cm at the mitral annulus tips (the indexed LVESD is 1.9 cm/m^2), and the LVESD at the largest diameter is 6.5 cm (indexed LVESD: 2.7 cm/m^2). AR = aortic regurgitation; AVR = aortic valve replacement or repair; BSA = body surface area; CMR = cardiac magnetic resonance; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume.

et al[15] using CMR. Despite the known underestimation of LV volumes by echocardiography compared to CMR, this issue may be less pronounced with end-systolic volume relative to end-diastolic volume, although this has not been demonstrated in all studies.[11] Nonetheless, the consistency of this finding across modalities will further support its implementation in decision making.

Our data also support previous observations[15,24,25] that a significant proportion of patients (25% in our series) meet the threshold of LVES volume while not meeting the threshold of LVES diameter, and these patients were at a significantly increased hazard for AVR/death compared with those who met the diameter threshold but not the volume threshold, independent of regurgitant fraction. The optimal regurgitant fraction threshold for the association with adverse outcomes was slightly different in our study compared to prior studies of CMR in AR. Possible explanations include variations in the populations studied and the outcomes chosen.

Prior and emerging data suggest that women with AR have a different extent and pattern of LV remodeling compared to men and that women with AR may have a worse prognosis, potentially because of delayed referral to AVR.[26-28] We found no significant association of sex with the primary or secondary outcomes. However, we note that the number of women was relatively low in this study, consistent with the epidemiology of aortic regurgitation, and further study is needed to evaluate outcomes and optimal thresholds for intervention in men and women. Similarly, we found no significant

TABLE 4 Multivariable Cox Regression for the Primary Composite Outcome

	Multivariable, Model 1 (n = 421)		Multivariable, Model 2 (n = 421)		Multivariable, Model 3 (n = 419)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Models using binary CMR variables						
DBP, mm Hg	0.98 (0.96 to 0.99)	0.01	0.98 (0.96 to 1.00)	0.02	0.98 (0.96 to 0.99)	0.01
EuroSCORE II	1.23 (1.15 to 1.33)	<0.001	1.20 (1.12 to 1.29)	<0.001	1.21 (1.13 to 1.31)	<0.001
Aortic regurgitant fraction >43%	2.69 (1.75 to 4.16)	<0.001	2.49 (1.59 to 3.87)	<0.001	2.86 (1.85 to 4.42)	<0.001
Indexed LVESV ≥43 mL/m^2	2.53 (1.75 to 3.66)	<0.001	–	–	–	–
Indexed LVEDV ≥109 mL/m^2	–	–	2.43 (1.65 to 3.59)	<0.001	–	–
Indexed LVESD ≥2 cm/m^2	–	–	–	–	1.51 (1.04 to 2.19)	0.03
C-statistic (95% CI)	0.75 (0.71 to 0.80)		0.75 (0.70 to 0.79)		0.73 (0.68 to 0.78)	
Compared with model 1						
Discrimination improvement (95% CI)	–		−0.01 (−0.03 to 0.01) *P* = 0.56		−0.03 (−0.05 to 0.001) *P* = 0.06	
Models using continuous CMR variables						
DBP, mm Hg	0.98 (0.96 to 1.00)	0.02	0.98 (0.97 to 1.00)	0.053	0.98 (0.96 to 1.00)	0.02
EuroSCORE II	1.21 (1.13 to 1.30)	<0.001	1.19 (1.11 to 1.28)	<0.001	1.19 (1.11 to 1.28)	<0.001
Aortic regurgitant fraction, %	1.05 (1.03 to 1.08)	<0.001	1.05 (1.03 to 1.07)	<0.001	1.06 (1.04 to 1.08)	<0.001
Indexed LVESV, mL/m^2	1.03 (1.01 to 1.04)	<0.001	–	–	–	–
Indexed LVEDV, mL/m^2	–	–	1.01 (1.01 to 1.02)	<0.001	–	–
Indexed LVESD, cm/m^2	–	–	–	–	1.82 (1.13 to 2.93)	0.01
C-statistic (95% CI)	0.75 (0.70 to 0.79)		0.75 (0.70 to 0.79)		0.73 (0.68 to 0.77)	
Compared with model 1						
Discrimination improvement (95% CI)	–		−0.0004 (−0.01 to 0.01) *P* = 0.94		−0.02 (−0.04 to −0.003) *P* = 0.02	

Multivariable Cox regression for the primary composite outcome. Primary composite outcome is defined as having development of symptoms, decrease in LVEF to <50%, referral for AVR based on guideline-recommended thresholds of LV dilation, or death during medical management. No corrections for multiple testing were applied

Abbreviations as in Table 1.

association of age with outcomes in our study, which may be attributable to development of symptoms being the major contributor to the outcome chosen in our study.

Our findings highlight that the regurgitant volume and fraction thresholds that define prognostically significant AR are different from traditional thresholds derived from echocardiography.[7,15,21] Furthermore, an advantage to CMR over echocardiography is the reduced interobserver variability of LVES volume assessment. Although recent studies have shown improved variability of echocardiographic assessment,[24,25,29] the reduced variability of LV volume assessment by CMR may be advantageous for AR patients, particularly if echocardiographic studies are performed without contrast or 3-dimensional implementation or have reduced endocardial border visualization. Once patients are identified as having moderate or severe AR, an abbreviated noncontrast 15-minute CMR scan—where available—can be used to follow LV function and volumes longitudinally to guide management in identifying the optimal timing of AVR.

STUDY LIMITATIONS. This is a select group of patients referred for advanced imaging studies beyond echocardiography, and selection biases may apply to this cohort beyond the general AR population. Because management decisions were made at the discretion of the treating physician, who was not blinded to CMR results, it is possible that CMR findings influenced the ultimate decision to intervene during the follow-up period. However, we note that thresholds for intervention based on CMR findings were not well established during the time course of the study, so thresholds of LV volumes are less likely to have influenced decision making. We attempted to reduce this bias by excluding patients who underwent surgery within 30 days of CMR. We did not evaluate the association of other markers such as extracellular volume fraction (ECV) and indexed ECV because the focus of this study was on severity of AR and LV remodeling. Prior work has shown the potential incremental value of adding ECV analyses to LVES volume.[30] The determination of symptom development and its attribution to AR were ascertained by the treating cardiologist or cardiac surgeon

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TABLE 5 Multivariable Cox Regression for the Secondary Composite Outcome

	Multivariable, Model 1 (n = 421)		Multivariable, Model 2 (n = 421)		Multivariable, Model 3 (n = 419)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Models using binary CMR variables						
DBP, mm Hg	0.98 (0.96 to 1.00)	0.04	0.98 (0.96 to 1.00)	0.06	0.98 (0.96 to 1.00)	0.046
EuroSCORE II	1.26 (1.16 to 1.36)	<0.001	1.24 (1.15 to 1.33)	<0.001	1.25 (1.15 to 1.35)	<0.001
Aortic regurgitant fraction >43%	2.45 (1.48 to 4.07)	0.001	2.33 (1.39 to 3.90)	0.001	2.51 (1.51 to 4.18)	<0.001
Indexed LVESV ≥43 mL/m^2	1.77 (1.15 to 2.71)	0.01	–	–	–	–
Indexed LVEDV ≥107 mL/m^2	–	–	1.72 (1.11 to 2.67)	0.02	–	–
Indexed LVESD ≥2 cm/m^2	–	–	–	–	1.33 (0.86 to 2.06)	0.20
C-statistic (95% CI)	0.72 (0.66 to 0.77)		0.71 (0.65 to 0.77)		0.71 (0.64 to 0.77)	
Compared with model 1						
Discrimination improvement (95% CI)	–		−0.003 (−0.02 to 0.02) *P* = 0.79		−0.01 (−0.04 to 0.01) *P* = 0.43	
Models using continuous CMR variables						
DBP, mm Hg	0.98 (0.96 to 1.00)	0.04	0.98 (0.96 to 1.00)	0.06	0.98 (0.96 to 1.00)	0.04
EuroSCORE II	1.24 (1.14 to 1.34)	<0.001	1.23 (1.14 to 1.33)	<0.001	1.23 (1.13 to 1.33)	<0.001
Aortic regurgitant fraction, %	1.04 (1.02 to 1.07)	0.001	1.04 (1.02 to 1.07)	0.002	1.05 (1.02 to 1.07)	<0.001
Indexed LVESV, mL/m^2	1.01 (1.00 to 1.03)	0.04	–	–	–	–
Indexed LVEDV, mL/m^2	–	–	1.01 (1.00 to 1.01)	0.07	–	–
Indexed LVESD, cm/m^2	–	–	–	–	1.26 (0.72 to 2.21)	0.43
C-statistic (95% CI)	0.71 (0.65 to 0.77)		0.70 (0.64 to 0.77)		0.69 (0.63 to 0.75)	
Compared with model 1						
Discrimination improvement (95% CI)	–		−0.001 (−0.01 to 0.01) *P* = 0.80		−0.01 (−0.03 to 0.01) *P* = 0.18	

Multivariable Cox regression for the secondary composite outcome. Secondary composite outcome is defined as development of symptoms, decrease in LVEF to <50%, or death during medical management. No corrections for multiple testing were applied.

Abbreviations as in Table 1.

and can have an element of subjectivity. We did not collect or systemically perform exercise testing in our patient cohort to objectively demonstrate the development of symptoms. Although this is reflective of real-world practice, this is a limitation of our current investigation. In addition, patients also did not undergo systematic coronary angiography to exclude coronary artery disease. Not all patients underwent echocardiography and CMR within a reasonable period of time, and agreement in AR severity assessment was only fair. However, in the group with available echocardiographic findings, results were consistent with the overall cohort. The SCMR registry participation agreement does not encompass sharing of echocardiographic DICOM (Digital Imaging and Communications in Medicine) data sets, and systematic evaluation of echo volumes and AR severity could not be done for this study.

CONCLUSIONS

In this multicenter study of asymptomatic AR patients with preserved LV systolic function, we identified quantitative CMR parameters associated with clinical outcomes that can guide clinical management decisions. These results support the incorporation of LV volumes rather than LV diameters in the evaluation and management of patients with moderate or severe AR.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with asymptomatic aortic regurgitation, measurements of regurgitant volume, regurgitant fraction, left ventricular systolic and diastolic volumes and diameters derived from CMR imaging are associated with clinical outcomes.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine how best to integrate data with clinical and echocardiographic parameters to guide clinical management.

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KEY WORDS **aortic regurgitation, aortic valve surgery, cardiac magnetic resonance, cardiac remodeling**

APPENDIX **For supplemental figures, tables, and methods, please see the online version of this paper.**

SUPPLEMENTAL APPENDIX

Methods

CMR studies were acquired using either 1.5- or 3.0-T clinical scanners (Siemens, Erlangen, Germany) with a phased-array coil system. A CMR examination for aortic valve assessment began with cine-CMR for anatomic and functional assessment in a short-axis stack, and standard 2-, 3-, and 4-chamber views using a steady-state free-precession (SSFP) sequence with typical flip angle of 65° to 85°; repetition time of 3.0 ms; echo time of 1.3 ms; in-plane spatial resolution of 1.7 to 2.0 mm × 1.4 to 1.6 mm; slice thickness of 6 mm, with 4 mm interslice gap; and temporal resolution of 35 to 40 ms.

Anatomic assessment of the aortic valve was performed with the use of cine SSFP sequences. The 3-chamber view and coronal left ventricular outflow views were used to prescribe a parallel series of at least 3 thin (4-5 mm) slices in short axis to provide assessment of the aortic valve's morphology.

Phase contrast CMR was performed at the level of the sinotubular junction, left ventricular outflow tract, ascending aorta, and the pulmonary artery. The typical parameters were flip angle of 25-30°, repetition time of ~5 ms, echo time of 2.4 ms, reconstructed in-plane spatial resolution of ~2.0 x 2.4 mm, slice thickness of 6 mm, and temporal resolution of ~40-50 ms

<u>CMR analysis</u>

LV and right ventricular (RV) end diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (LVEF and RVEF), and LV mass were measured according to guidelines (1). The regurgitation volume was calculated using the direct method from phase contrast imaging at the level of the sinotubular junction. The difference between the left ventricular outflow tract and pulmonary artery forward stroke volume was used as a secondary assessment for regurgitant volume calculation. The regurgitant fraction was calculated as (reverse volume/forward volume * 100%) (2). All analysis was done on the same software (Precession, Heart Imaging Technologies).

Supplemental Table 1. Optimal cut point estimation in predicting having the secondary composite outcome.

Method: Youden; Reference variable: Secondary composite event						
Classification variable	**ARV (mL)**	**ARF (%)**	**LVESD (cm)**	**LVESDi (cm/m2)**	**LVEDVi (mL/m2)**	**LVESVi (mL/m2**
Empirical optimal cut point	55	43	4	2	107	43
Youden index (J)	0.17	0.18	0.11	0.16	0.16	0.12
SE(J):	0.06	0.06	0.05	0.06	0.06	0.06
Sensitivity at cut point	0.43	0.44	0.34	0.54	0.61	0.49
Specificity at cut point	0.73	0.74	0.76	0.62	0.55	0.62
Area under ROC curve	0.58	0.59	0.55	0.58	0.58	0.56

LVESDi: indexed left ventricular end-systolic diameter, LVEDVi: indexed left ventricular end-diastolic volume, LVESVi: indexed left ventricular end-systolic volume; Secondary composite outcome is defined as development of symptoms, decrease in LVEF to < 50%, or death during medical management

Supplemental Table 2: Optimal LVEF thresholds associated with the primary and secondary composite outcomes

Method: Youden		
Reference variable:	**Primary composite event**	**Secondary composite event**
Classification variable	LVEF (%)	LVEF (%)
Empirical optimal cut point	68	68
Youden index (J)	0.05	0.11
SE(J):	0.04	0.05
Sensitivity at cut point	0.23	0.28
Specificity at cut point	0.82	0.82
Area under ROC curve	0.52	0.55

LVEF: left ventricular ejection fraction; Primary composite outcome is defined as having development of symptoms, decrease in LVEF to<50%, referral for AVR based on guideline recommended thresholds of LV dilation, or death during medical management; Secondary composite outcome is defined as development of symptoms, drop in EF on follow up, or death

Supplemental Table 3. Optimal cut point estimation in predicting having the primary and secondary composite outcome in patients having ≥moderate AR on echocardiography, done within 6 months of CMR (N = 240)

A. Primary composite outcome							
Classification variable	**ARV (mL)**	**ARF (%)**	**LVESD (cm)**	**LVESDi (cm/m2**	**LVEDVi (mL/m2**	**LVESVi (mL/m2)**	**LVEF (%)**
Empirical optimal cut point	66	43	4	2	107	49	71
Youden index (J)	0.33	0.28	0.24	0.22	0.29	0.24	0.05
SE(J)	0.06	0.07	0.06	0.07	0.06	0.06	0.05
Sensitivity at cut point	0.45	0.54	0.41	0.64	0.72	0.43	0.14
Specificity at cut point	0.88	0.74	0.83	0.58	0.56	0.80	0.91
Area under ROC curve	0.67	0.64	0.62	0.61	0.64	0.62	0.53
B. Secondary composite outcome							
Classification variable	**ARV (mL)**	**ARF (%)**	**LVESD (cm)**	**LVESDi (cm/m2**	**LVEDVi (mL/m2**	**LVESVi (mL/m2)**	**LVEF (%)**
Empirical optimal cut point	58	41	4	2	107	37	71
Youden index (J)	0.20	0.20	0.17	0.14	0.19	0.15	0.06
SE(J)	0.07	0.07	0.07	0.07	0.07	0.07	0.05
Sensitivity at cut point	0.47	0.56	0.37	0.59	0.66	0.75	0.15
Specificity at cut point	0.73	0.64	0.80	0.54	0.52	0.40	0.91
Area under ROC curve	0.60	0.60	0.58	0.57	0.59	0.57	0.53

LVESDi: indexed left ventricular end-systolic diameter, LVEDVi: indexed left ventricular end-diastolic volume, LVESVi: indexed left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; Primary composite outcome is defined as having development of symptoms, decrease in LVEF to<50%, referral for AVR based on guideline recommended thresholds of LV dilation, or death during medical management; Secondary composite outcome is defined as development of symptoms, drop in EF on follow up, or death

Supplemental Table 4: Multivariable Cox regression for the primary composite outcome in patients with ≥moderate AR on echocardiography, done within 6 months of CMR (N=240)

	Multivariable, model 1 (*n*=212)		Multivariable, model 2 (*n*=212)		Multivariable, model 3 (*n*=212)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
A. Models using binary CMR variables						
DBP (mm Hg)	0.97 (0.95, 0.99)	0.02	0.97 (0.95, 1.00)	0.04	0.97 (0.95, 1.00)	0.03
EuroSCORE II	1.23 (1.12, 1.35)	<0.001	1.18 (1.08, 1.28)	<0.001	1.20 (1.09, 1.31)	<0.001
Aortic regurgitant fraction >43(%)	2.10 (1.19, 3.68)	0.01	1.87 (1.05, 3.32)	0.03	2.15 (1.20, 3.86)	0.01
Indexed LVESV ≥ 43 (mL/m2)	2.38 (1.45, 3.90)	0.001	--	--	--	--
Indexed LVEDV ≥109 (mL/m2)	--	--	2.61 (1.53, 4.45)	<0.001	--	--
Indexed LVESD ≥2 (cm/m2)	--	--	--	--	1.32 (0.79, 2.21)	0.29
C-statistic (95% CI)	0.73 (0.67, 0.79)		0.74 (0.68, 0.80)		0.71 (0.65, 0.78)	
Compared with model 1 Discrimination improvement (95% CI); p-value	--		0.01 (-0.02, 0.04); p=0.55		-0.01 (-0.05, 0.03); p=0.51	
B. Models using continuous CMR variables						
DBP (mm Hg)	0.98 (0.95, 1.00)	0.049	0.98 (0.96, 1.00)	0.10	0.98 (0.96, 1.00)	0.06
EuroSCORE II	1.22 (1.11, 1.33)	<0.001	1.18 (1.08, 1.29)	<0.001	1.19 (1.08, 1.30)	<0.001
Aortic regurgitant fraction (%)	1.03 (1.00, 1.06)	0.06	1.03 (1.00, 1.06)	0.06	1.04 (1.01, 1.07)	0.01
Indexed LVESV (mL/m2)	1.03 (1.02, 1.05)	<0.001	--	--	--	--
Indexed LVEDV (mL/m2)	--	--	1.02 (1.01, 1.02)	<0.001	--	--
Indexed LVESD (cm/m2)	--	--	--	--	1.68 (0.91, 3.12)	0.10
C-statistic (95% CI)	0.74 (0.67, 0.80)		0.73 (0.67, 0.79)		0.71 (0.65, 0.77)	
Compared with model 1 Discrimination improvement (95% CI)	--		-0.01 (-0.03, 0.01); p=0.53		-0.02 (-0.06, 0.01); p=0.17	

DBP, diastolic blood pressure; LVESD: left ventricular end-systolic diameter, LVESV: left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; n, number of patients having complete data for all covariates of the multivariable models; Primary composite outcome is define as having development of symptoms, decrease in LVEF to <50%, referral for AVR based on guideline recommended thresholds of LV dilation, or death during medical management; No corrections for multiple testing were applied

Supplemental Table 5: Multivariable Cox regression for the secondary composite outcome in patients with ≥moderate AR on echocardiography, done within 6 months of CMR (N=240)

	Multivariable, model 1 (*n*=212)		Multivariable, model 2 (*n*=212)		Multivariable, model 3 (*n*=212)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
A. Models using binary CMR variables						
DBP (mm Hg)	0.99 (0.96, 1.01)	0.30	0.99 (0.96, 1.02)	0.40	0.99 (0.96, 1.01)	0.34
EuroSCORE	1.25 (1.14, 1.38)	<0.001	1.21 (1.11, 1.33)	<0.001	1.24 (1.12, 1.36)	<0.001
Aortic regurgitant fraction >43(%)	2.17 (1.13, 4.19)	0.02	2.02 (1.04, 3.94)	0.04	2.17 (1.10, 4.27)	0.03
Indexed LVESV ≥ 43 (mL/m2)	1.93 (1.10, 3.39)	0.02	--	--	--	--
Indexed LVEDV ≥107 (mL/m2)	--	--	2.07 (1.15, 3.72)	0.02	--	--
Indexed LVESD ≥2 (cm/m2)	--	--	--	--	1.32 (0.73, 2.40)	0.36
C-statistic (95% CI)	0.71 (0.64, 0.78)		0.72 (0.65, 0.79)		0.70 (0.63, 0.78)	
Compared with model 1 Discrimination improvement (95% CI)	--		0.01 (-0.03, 0.05); p=0.63		0.01 (-0.05, 0.03); p=0.60	
B. Models using continuous CMR variables						
DBP (mm Hg)	0.99 (0.96, 1.01)	0.29	0.99 (0.96, 1.01)	0.37	0.99 (0.96, 1.01)	0.30
EuroSCORE	1.25 (1.13, 1.37)	<0.001	1.22 (1.11, 1.34)	<0.001	1.23 (1.11, 1.35)	<0.001
Aortic regurgitant fraction (%)	1.02 (0.98, 1.05)	0.29	1.02 (0.99, 1.05)	0.26	1.02 (0.99, 1.06)	0.15
Indexed LVESV (mL/m2)	1.02 (1.00, 1.04)	0.02	--	--	--	--
Indexed LVEDV (mL/m2)	--	--	1.01 (1.00, 1.02)	0.07	--	--
Indexed LVESD (cm/m2)	--	--	--	--	1.43 (0.69, 2.97)	0.33
C-statistic (95% CI)	0.70 (0.62, 0.78)		0.70 (0.62, 0.77)		0.69 (0.61, 0.77)	
Compared with model 1 Discrimination improvement (95% CI)	--		-0.002 (-0.03, 0.03); p=0.88		-0.01 (-0.05, 0.03); p=0.67	

DBP, diastolic blood pressure; LVESD: left ventricular end-systolic diameter, LVESV: left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; n, number of patients having complete data for all covariates of the multivariable models; Secondary composite outcome is defined as having development of symptoms, decrease in LVEF to < 50%, or death during medical management; No corrections for multiple testing were applied.

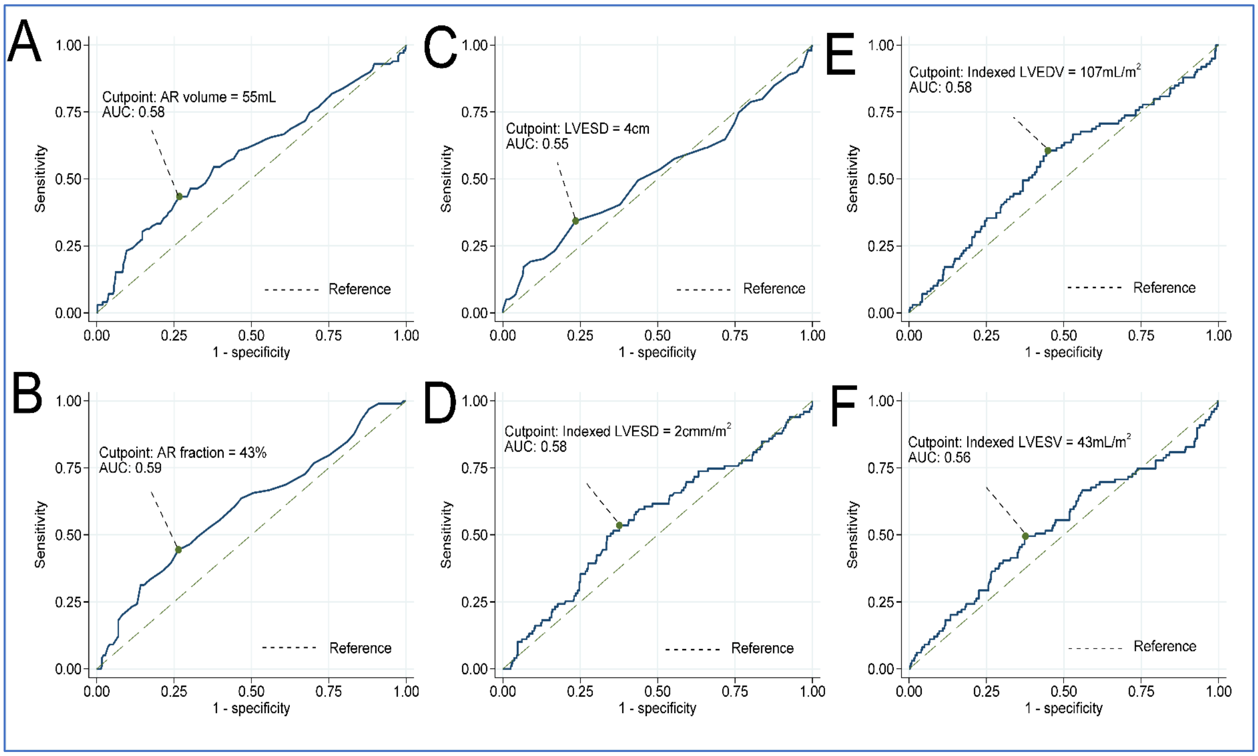
Supplemental Table 6: Multivariable Cox regression for the primary composite outcome in patients with LVEF≥55%

	Multivariable, model 1 (*n*=372)		Multivariable, model 2 (*n*=372)		Multivariable, model 3 (*n*=370)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
A. Models using binary CMR variables						
DBP (mm Hg)	0.97 (0.96, 0.99)	0.01	0.98 (0.96, 1.00)	0.01	0.97 (0.95, 0.99)	0.004
EuroSCORE	1.23 (1.14, 1.33)	<0.001	1.20 (1.12, 1.30)	<0.001	1.21 (1.12, 1.31)	<0.001
Aortic regurgitant fraction >43(%)	2.78 (1.73, 4.48)	<0.001	2.56 (1.58, 4.17)	<0.001	3.04 (1.89, 4.89)	<0.001
Indexed LVESV ≥ 43 (mL/m2)	2.16 (1.45, 3.23)	<0.001	--	--	--	--
Indexed LVEDV ≥109 (mL/m2)	--	--	2.32 (1.52, 3.53)	<0.001	--	--
Indexed LVESD ≥2 (cm/m2)	--	--	--	--	1.25 (0.83, 1.90)	0.28
C-statistic (95% CI)	0.75 (0.70, 0.80)		0.75 (0.70, 0.80)		0.73 (0.67, 0.78)	
Compared with model 1 Discrimination improvement (95% CI); p-value	--		-0.0003 (-0.02, 0.02); p=0.98		-0.02 (-0.05, 0.01); p=0.12	
B. Models using continuous CMR variables						
DBP (mm Hg)	0.98 (0.96, 1.00)	0.02	0.98 (0.96, 1.00)	0.03	0.98 (0.96, 0.99)	0.01
EuroSCORE	1.21 (1.12, 1.31)	<0.001	1.20 (1.11, 1.29)	<0.001	1.19 (1.10, 1.29)	<0.001
Aortic regurgitant fraction >43(%)	1.06 (1.04, 1.08)	<0.001	1.06 (1.03, 1.08)	<0.001	1.06 (1.04, 1.09)	<0.001
Indexed LVESV ≥ 43 (mL/m2)	1.02 (1.01, 1.04)	0.001	--	--	--	--
Indexed LVEDV ≥109 (mL/m2)	--	--	1.01 (1.01, 1.02)	<0.001	--	--
Indexed LVESD ≥2 (cm/m2)	--	--	--	--	1.53 (0.89, 2.61)	0.12
C-statistic (95% CI)	0.74 (0.69, 0.80)		0.74 (0.69, 0.80)		0.73 (0.67, 0.78)	
Compared with model 1 Discrimination improvement (95% CI); p-value	--		0.003 (-0.01, 0.01); p=0.48		-0.01 (-0.03, 0.003); p=0.13	

DBP, diastolic blood pressure; LVESD: left ventricular end-systolic diameter, LVESV: left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; Primary composite outcome is defined as having development of symptoms, decrease in LVEF to <50%, referral for AVR based on guideline recommended thresholds of LV dilation, or death during medical management; No corrections for multiple testing were applied

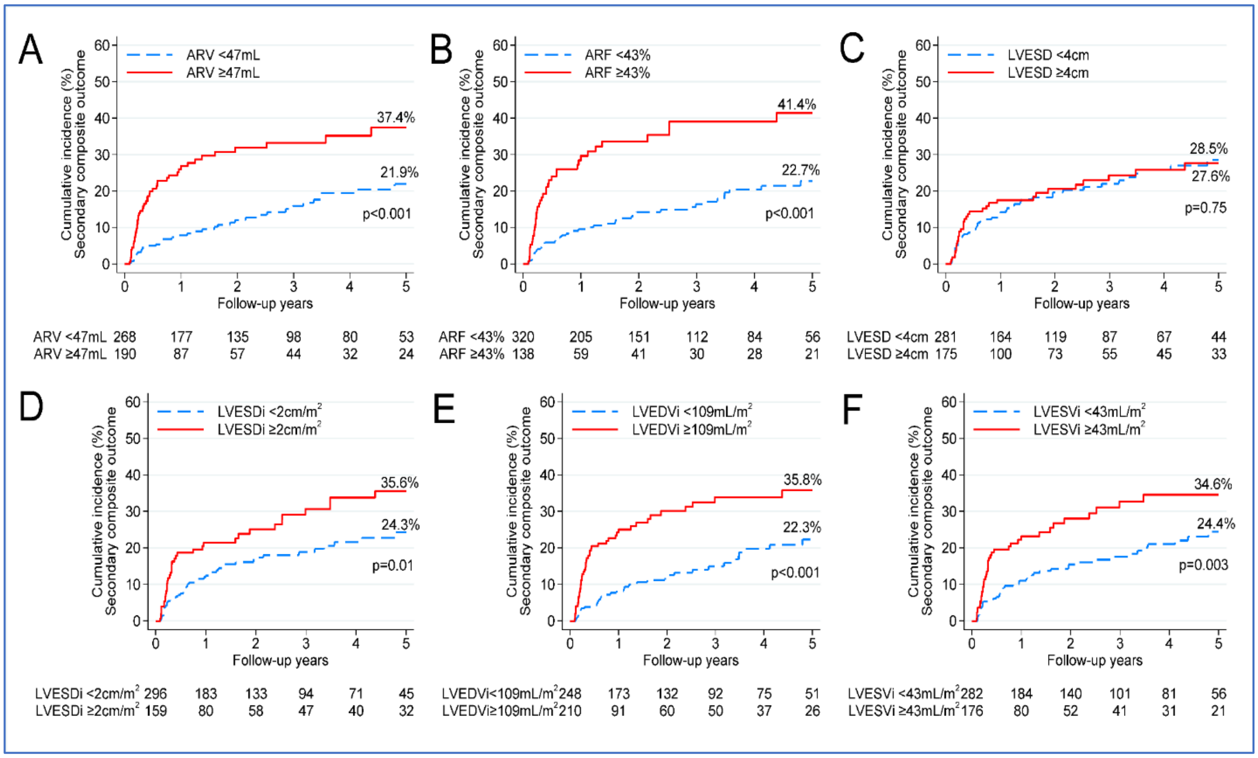
Supplemental Figure 1: Receiver operating curve figures displaying the optimal thresholds for the predication of the secondary composite outcome

Receiver operating curve figures displaying the optimal thresholds for the predication of the secondary composite outcome, evaluated by regurgitant volume (A), regurgitant fraction (B), LVES diameter (C), indexed LVES diameter (D), indexed LVED volume (E), and indexed LVES volume (F)



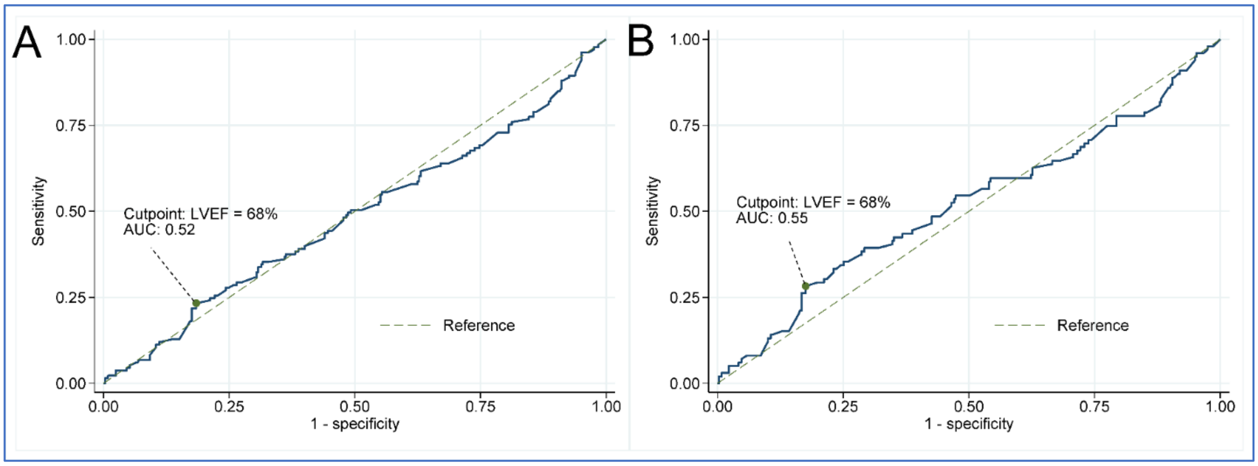
AVR: aortic valve replacement or repair, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVESD: left ventricular end-systolic diameter. AR: aortic regurgitation

Supplemental Figure 6: Kaplan Meier Curves of the secondary composite event
Kaplan Meier curves stratified by stratified by ARV (A), ARF (B), LVESD (C), indexed LVESD (D), indexed LVEDV (E), and indexed LVESV (F)



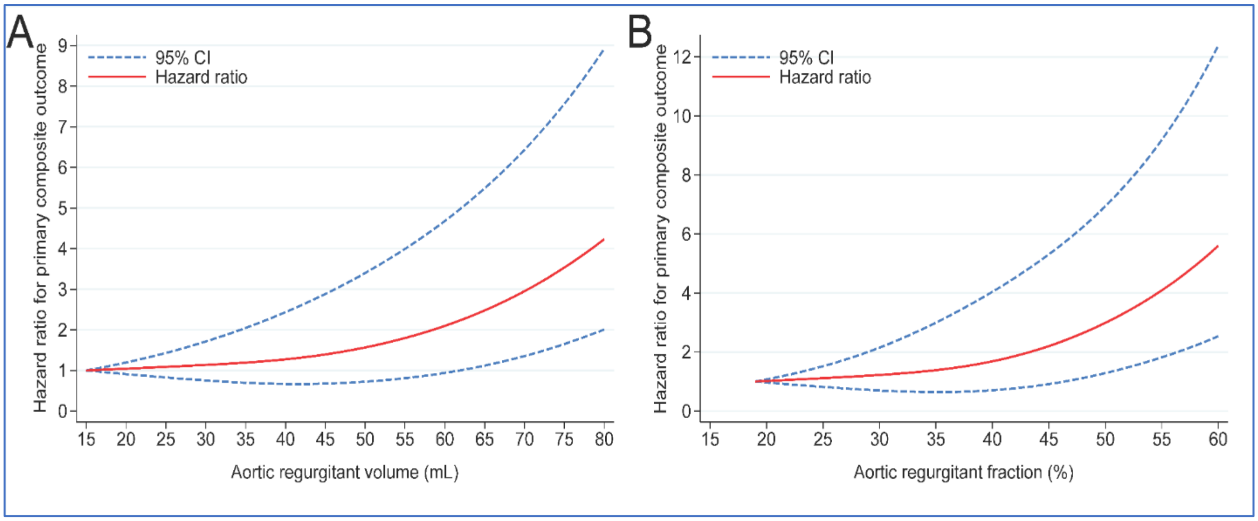
ARV: aortic regurgitant volume, ARF: aortic regurgitant fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVESD: left ventricular end-systolic diameter. AR: aortic regurgitation

Supplemental Figure 7: Receiver operating curve figures displaying the optimal cut points for the association of the primary (A) and secondary (B) composite outcomes, evaluated by LVEF

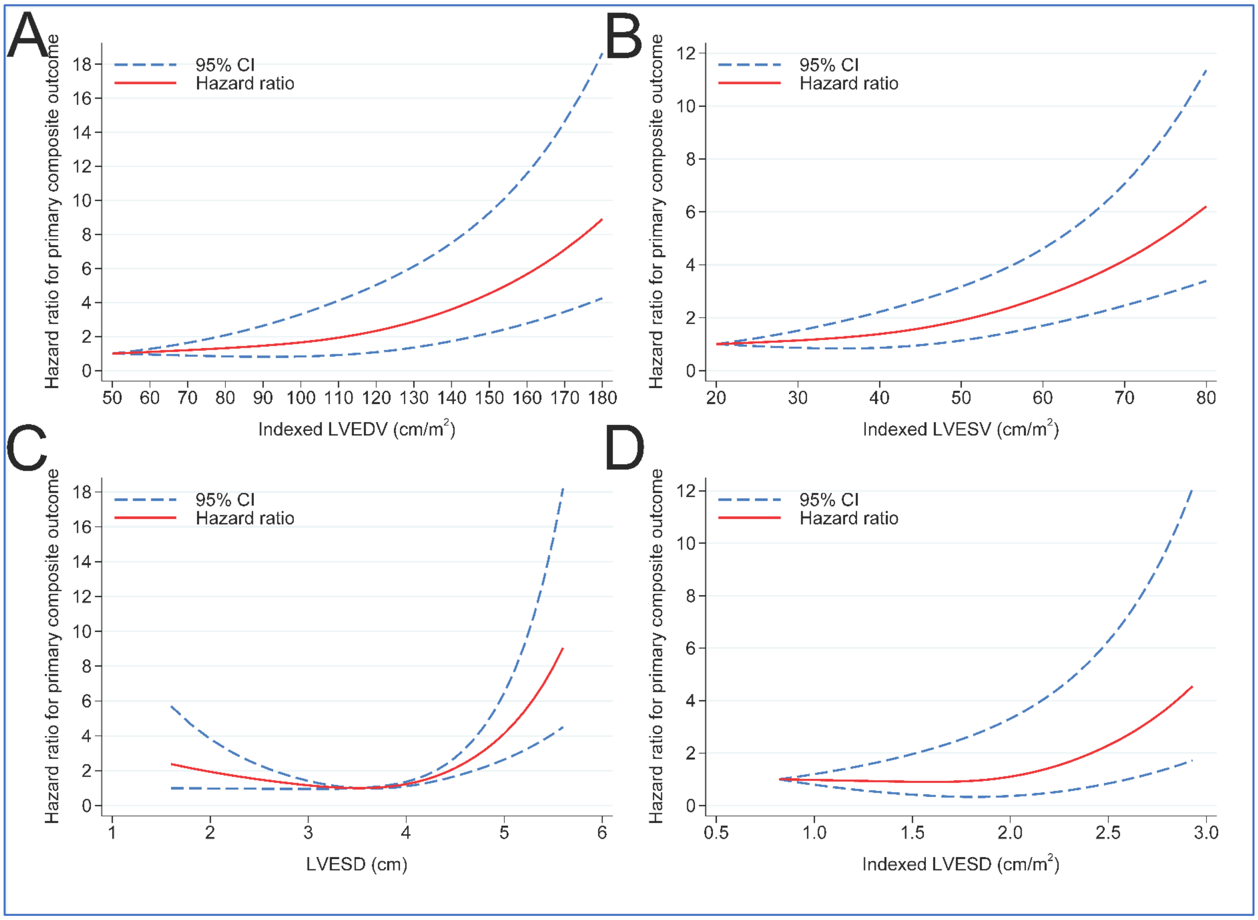


LVEF, left ventricular ejection fraction

Supplemental Figure 2: Cubic spline plots of the hazard ratio for the primary composite outcome, evaluated by regurgitant volume (A) and regurgitant fraction (B).

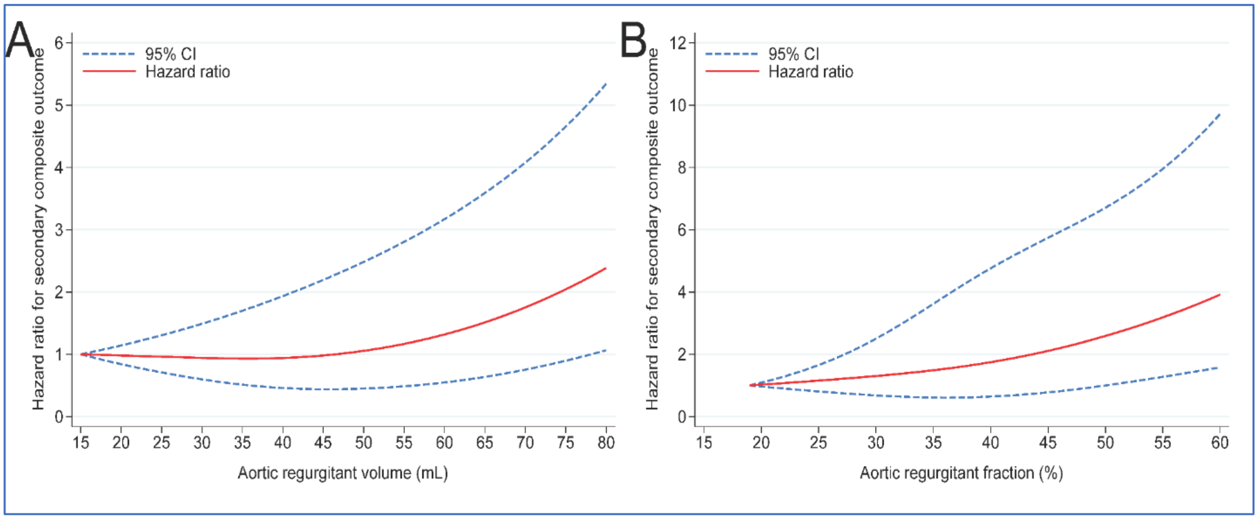


Supplemental Figure 4: Cubic spline plots of the hazard ratio for the primary composite outcome, evaluated by indexed LVEDV (A), indexed LVESV (B), LVESD (C), and indexed LVESD (D).

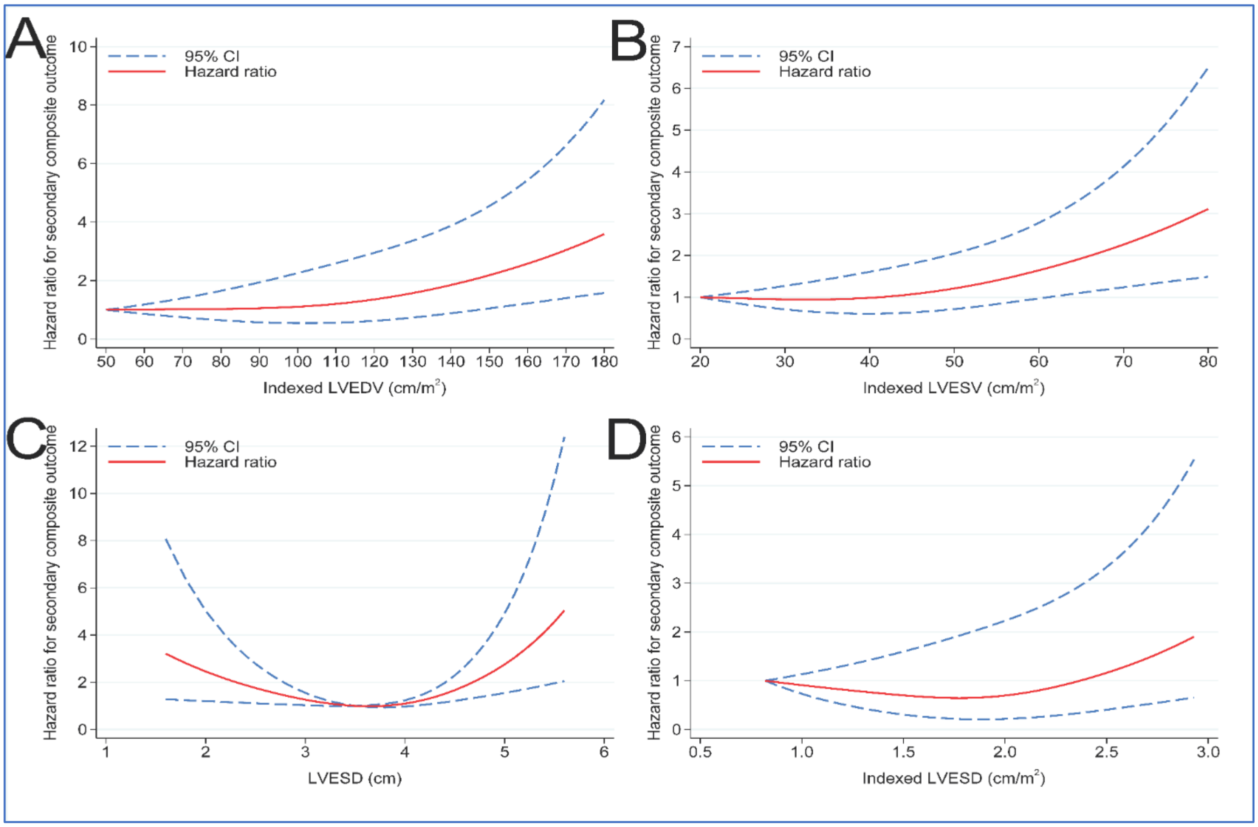


LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVESD: left ventricular end-systolic diameter

Supplemental Figure 3: Cubic spline plots of the hazard ratio for the secondary composite outcome, evaluated by regurgitant volume (A) and regurgitant fraction (B).



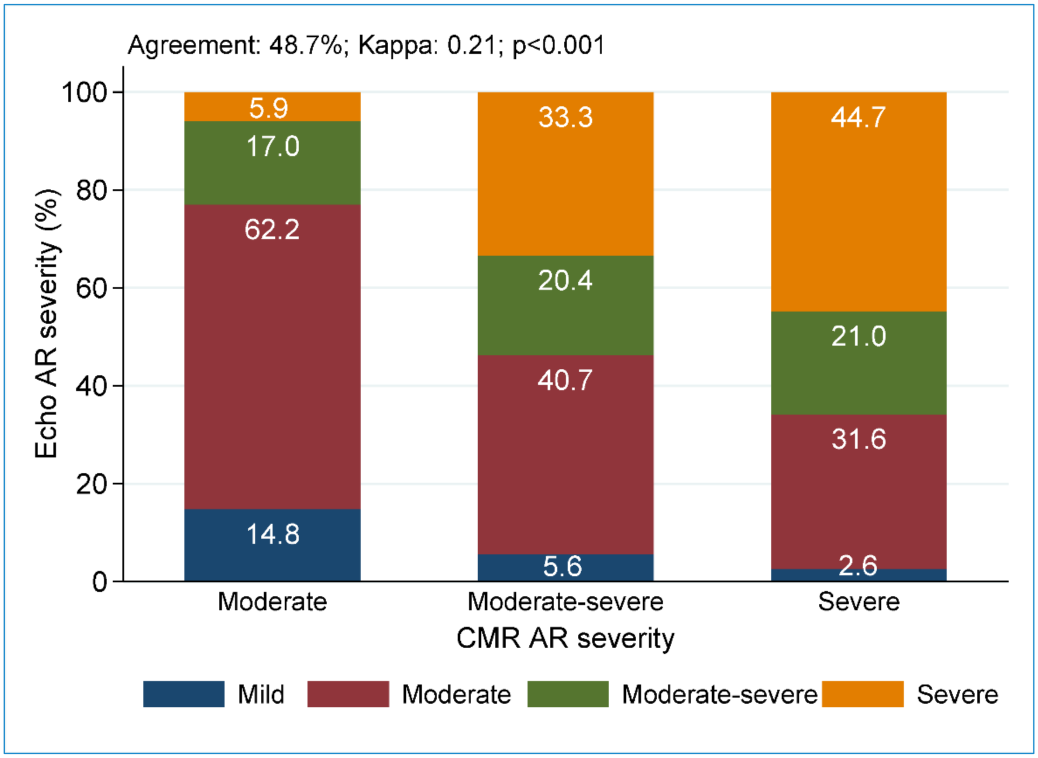
Supplemental Figure 5: Cubic spline plots of the hazard ratio for the secondary composite outcome, evaluated by indexed LVEDV (A), indexed LVESV (B), LVESD (C), and indexed LVESD (D).



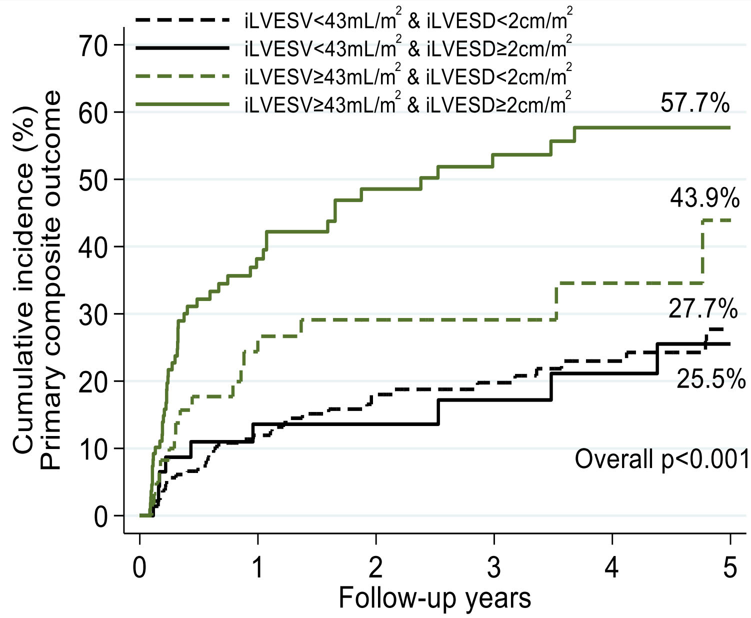
AVR: aortic valve replacement or repair, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVESD: left ventricular end-systolic diameter.

Supplemental Figure 8. Agreement between echo and CMR in classifying AR severity

Agreement between echocardiography and CMR in classifying AR severity, in patients who had echo within 6 months of CMR (N=265)

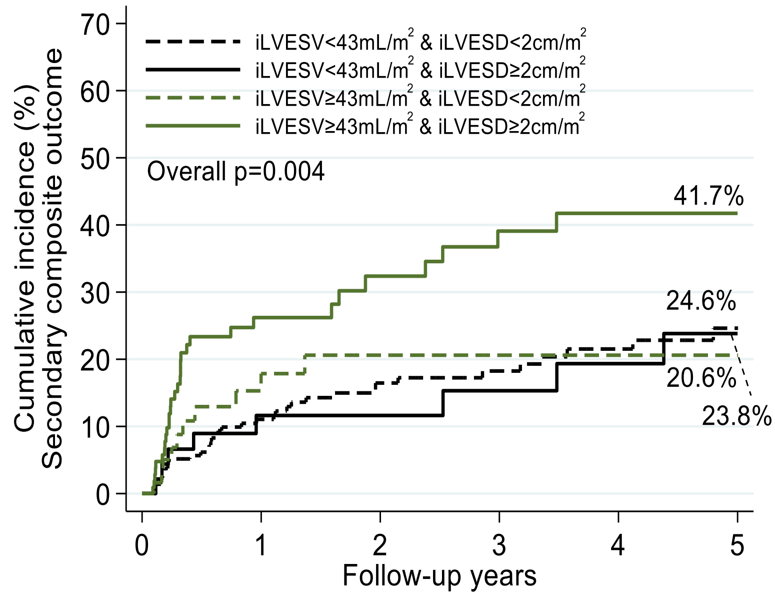


Supplemental Figure 9. Cumulative incidence of primary composite outcome, by index LVESV & index LVESD (index LVESD cutoff of 2)



iLVESV<43 & iLVESD<2	231	151	112	79	61	41
iLVESV<43 & iLVESD≥2	48	32	27	21	19	15
iLVESV≥43 & iLVESD<2	65	32	21	15	10	4
iLVESV≥43 & iLVESD≥2	111	48	31	26	21	17

Supplemental Figure 10. Cumulative incidence of secondary composite outcome, by indexed LVESV & indexed LVESD subgroups



iLVESV<43 & iLVESD<2	231	151	112	79	61	41
iLVESV<43 & iLVESD≥2	48	32	27	21	19	15
iLVESV≥43 & iLVESD<2	65	32	21	15	10	4
iLVESV≥43 & iLVESD≥2	111	48	31	26	21	17

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