EUROVALVE

& STRUCTURAL CARDIOMYOPATHIES

NH PALERMO

SAVE
THE DATE
OCTOBER
24&25,2024

Diagnostic and treatment of patients with aortic regurgitation

Follow-up and medical treatment

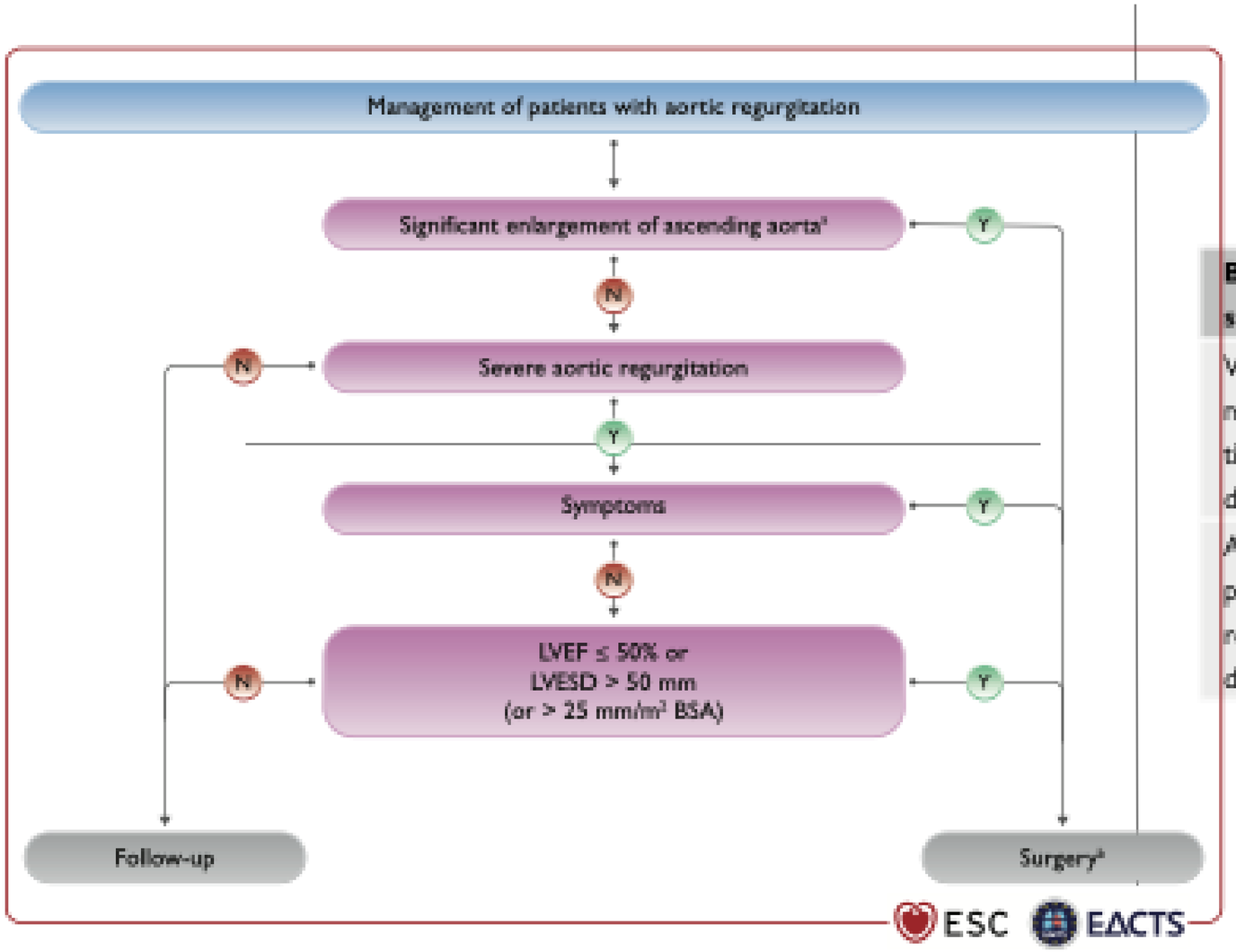
Anna Sannino MD, PhD
Federico II University, Napoli, Italy

COURSE DIRECTORS
Patrizio Lancellotti, Belgium
Khalil Fattouch, Italy
Gilbert Habib, France
José Luis Zamorano, Spain
Philippe Pibarot, Canada
Mani Vannan, USA
Madalina Garbi, United Kingdom
Bernard Cosyns,Belgium

LOCAL HOST
Khalil Fattouch, Italy

What do the Guidelines say?

EU Guidelines



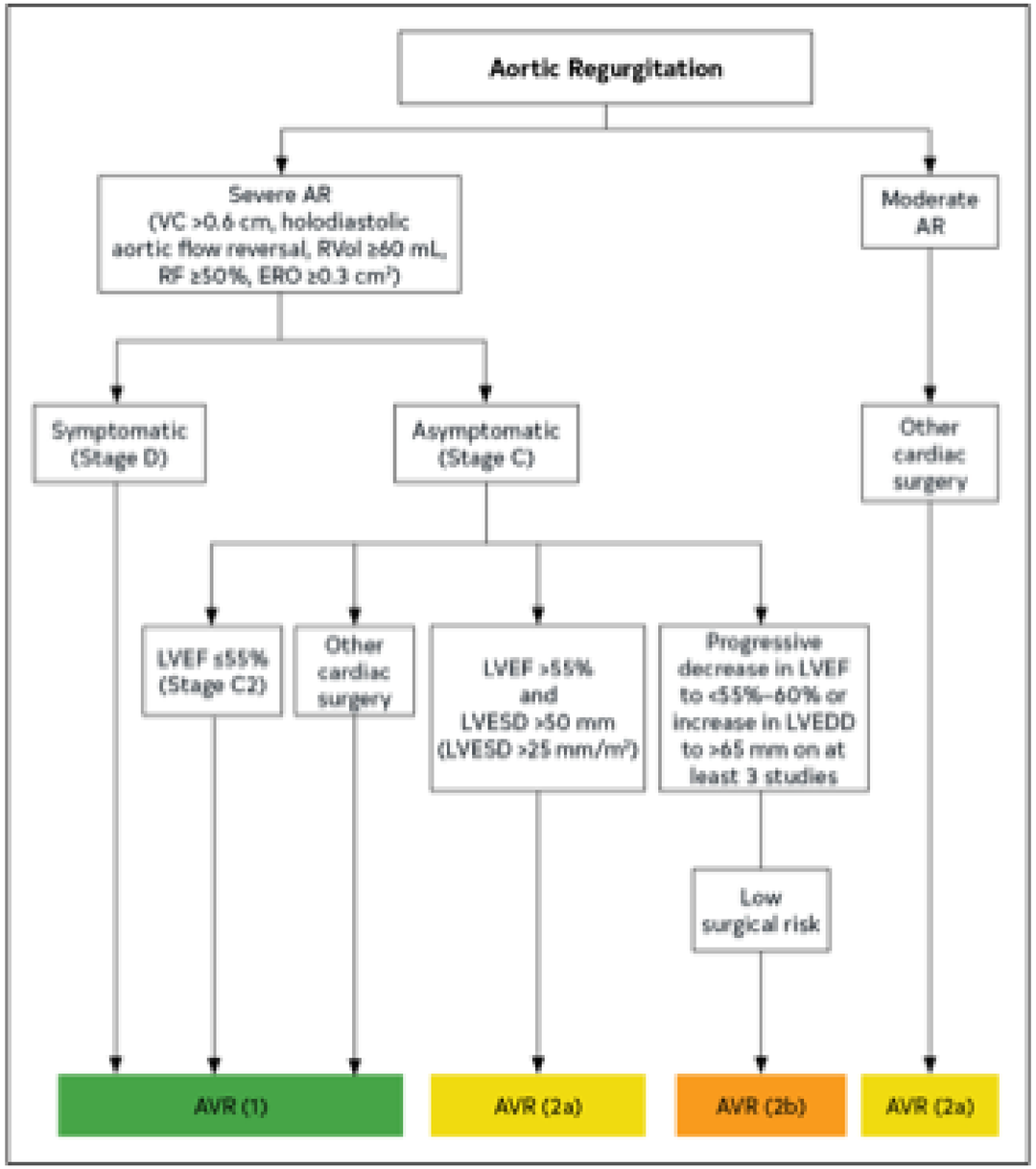
Indications for surgery	Class[a]	Level[b]
A) Severe aortic regurgitation		
Surgery is recommended in symptomatic patients regardless of LV function.[105–109]	I	B
Surgery is recommended in asymptomatic patients with LVESD >50 mm or LVESD >25 mm/m² BSA (in patients with small body size) or resting LVEF ≤50%.[107,108,112,114,115]	I	B
Surgery may be considered in asymptomatic patients with LVESD >20 mm/m² BSA (especially in patients with small body size) or resting LVEF ≤55%, if surgery is at low risk.	IIb	C
Surgery is recommended in symptomatic and asymptomatic patients with severe aortic regurgitation undergoing CABG or surgery of the ascending aorta or of another valve.	I	C
Aortic valve repair may be considered in selected patients at experienced centres when durable results are expected.	IIb	C
TGFBR1 or *TGFBR2* mutation (including Loeys–Dietz syndrome).[e] • ≥50 mm in the presence of a bicuspid valve with additional risk factors[d] or coarctation.		
When surgery is primarily indicated for the aortic valve, replacement of the aortic root or tubular ascending aorta should be considered when ≥45 mm.[f]	IIa	C

Vahanian et al. EHJ 2022

What do the Guidelines say?

US Guidelines

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AR	BAV (or other congenital valve anomaly) Aortic valve sclerosis Diseases of the aortic sinuses or ascending aorta History of rheumatic fever or known rheumatic heart disease IE	AR severity: none or trace	None	None
B	Progressive AR	Mild to moderate calcification of a trileaflet valve BAV (or other congenital valve anomaly) Dilated aortic sinuses Rheumatic valve changes Previous IE	Mild AR: Jet width <25% of LVOT Vena contracta <0.3 cm Regurgitant volume <30 mL/beat Regurgitant fraction <30% ERO <0.10 cm^2 Angiography grade 1 Moderate AR: Jet width 25%–64% of LVOT Vena contracta 0.3–0.6 cm Regurgitant volume 30–59 mL/beat Regurgitant fraction 30% to 49% ERO 0.10–0.29 cm^2 Angiography grade 2	Normal LV systolic function Normal LV volume or mild LV dilation	None
C	Asymptomatic severe AR	Calcific aortic valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes IE with abnormal leaflet closure or perforation	Severe AR: Jet width ≥65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta Regurgitant volume ≥60 mL/beat Regurgitant fraction ≥50% ERO ≥0.3 cm^2 Angiography grade 3 to 4 In addition, diagnosis of chronic severe AR requires evidence of LV dilation	C1: Normal LVEF (>55%) and mild to moderate LV dilation (LVESD <50 mm) C2: Abnormal LV systolic function with depressed LVEF (≤55%) or severe LV dilation (LVESD >50 mm or indexed LVESD >25 mm/m^2)	None; exercise testing is reasonable to confirm symptom status
D	Symptomatic severe AR	Calcific valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes Previous IE with abnormal leaflet closure or perforation	Severe AR: Doppler jet width ≥65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta Regurgitant volume ≥60 mL/beat Regurgitant fraction ≥50% ERO ≥0.3 cm^2 Angiography grade 3 to 4 In addition, diagnosis of chronic severe AR requires evidence of LV dilation	Symptomatic severe AR may occur with normal systolic function (LVEF >55%), mild to moderate LV dysfunction (LVEF 40% to 55%), or severe LV dysfunction (LVEF <40%) Moderate to severe LV dilation is present	Exertional dyspnea or angina or more severe HF symptoms



Otto et al. Circulation 2021

Editorial Comment

Aortic Regurgitation

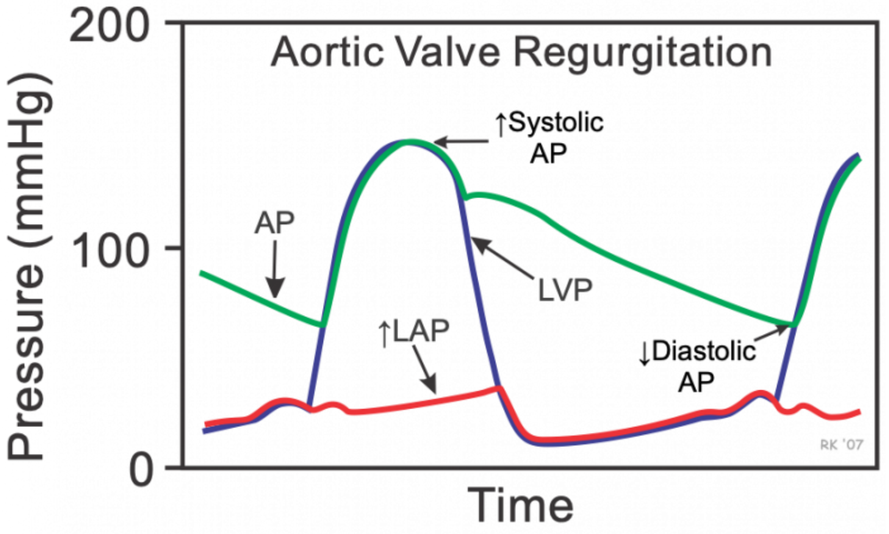
A Lesion With Similarities to Both Aortic Stenosis and Mitral Regurgitation

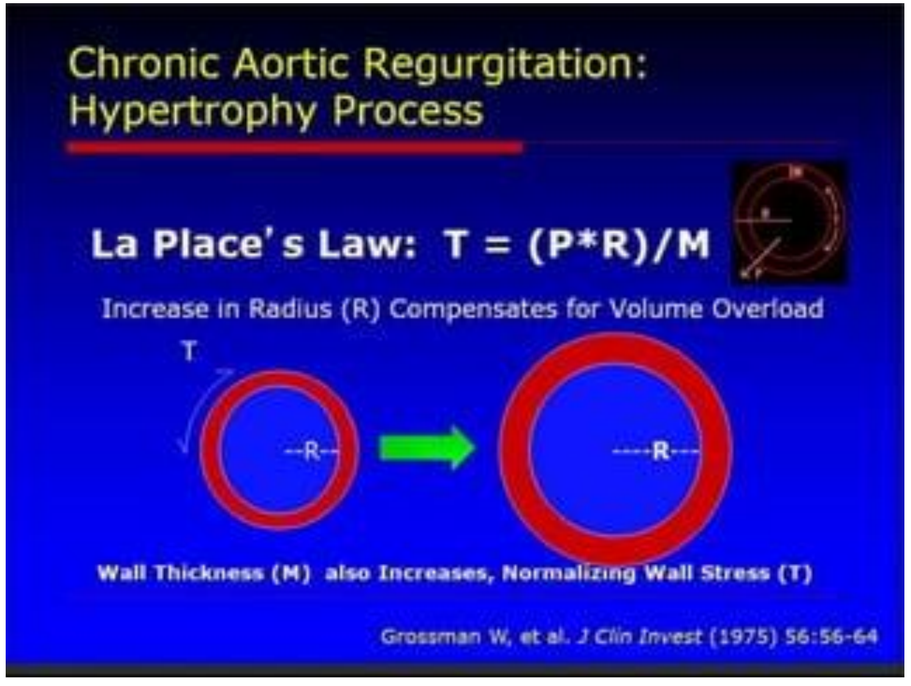
Blase A. Carabello, MD

Hemodynamic overload imposed upon the left ventricle by valvular heart disease was previously classified as pressure overload or volume overload. Aortic stenosis was the prime example of pressure overload and aortic and mitral regurgitation were classified as volume overload lesions. Aortic regurgitation clearly increases the volume-pumping requirements of the left ventricle and thus it does impose a volume overload. However, aortic regurgitation also produces a significant amount of excess left ventricular afterload (systolic wall stress) as well as volume overload.[1,2] In fact, not only is systolic wall stress in patients with aortic regurgitation increased significantly when compared with patients with similar amounts of mitral regurgitation, but it may reach a level similar to that found in aortic stenosis.[3]

or a worsening of ejection performance following surgery.[5–8] Correction of mitral regurgitation removes the low impedance pathway for ejection into the left atrium and acutely increases afterload, thereby reducing ejection performance.[9]

In this issue of *Circulation*, Taniguchi et al[10] add to previous evidence that ejection performance improves after correction of aortic regurgitation if ejection performance was mildly to moderately depressed preoperatively.[5,10–13] Their study demonstrates that reduced afterload after surgery for aortic regurgitation is at least one mechanism by which previously depressed ejection performance improves postoperatively, a finding consistent with a previous report by Bonow et al.[14] Besides demonstrating one mechanism by which ejection performance is

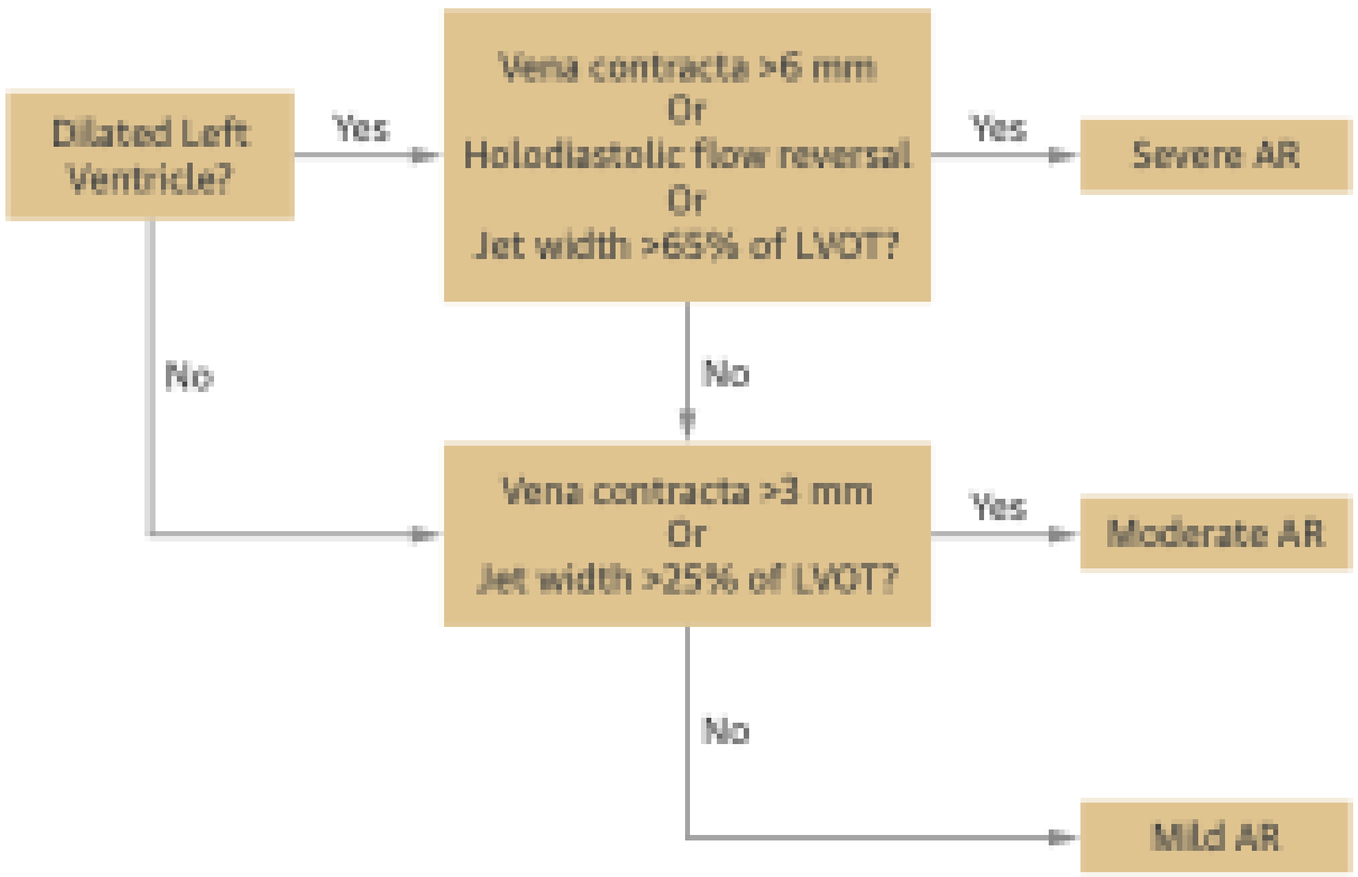




Assess AR Severity

Echocardiography

Qualitative
Valve morphology
Colour flow regurgitant jet
CW signal of regurgitant je
Other
Semiquantitative
Vena contracta width (mm)
Pressure half-time[b] (ms)
Quantitative
EROA (mm^2)
Regurgitant volume (mL/be
Enlargement of cardiac chambers



Recommendations for Diagnostic Testing of Chronic AR
Referenced studies that support the recommendations are
nt 14.

ns
h signs or symptoms of AR, TTE assessment of the cause and urgitation, LV size and systolic nosis, and timing of valve
h a BAV or with known dilation nuses or ascending aorta, TTE is aluate the presence and severity
moderate or severe AR and images or a discrepancy l and TTE findings, TEE, CMR, terization is indicated for the V systolic function, systolic and es, aortic size, and AR severity[20-24]

Popovic et al. JIMG 2018

Vahanian et al. EHJ 2022

Otto et al. Circulation 2021

Aortic Regurgitation

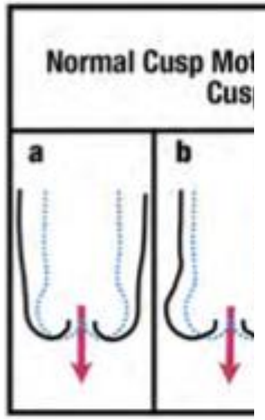


Table 11 Grading the s

Structural parameters
Aortic leaflets
LV size
Qualitative Doppler
Jet width in LVOT, colo
Flow convergence, colo
Jet density, CW
Jet deceleration rate, C
Diastolic flow reversal i aorta, PW
Semiquantitative paramet
VCW (cm)
Jet width/LVOT width,
Jet CSA/LVOT CSA, ce
Quantitative parameters[b]
RVol (mL/beat)
RF (%)
EROA (cm^2)

Chronic Aortic Regurgitation by Doppler Echocardiography

Does AR meet specific criteria of mild or severe AR?

* Yes, mild

Specific Criteria for Mild AR
- VC width < 0.3 cm
- Central Jet, width < 25% of LVOT
- Small or no flow convergence
- Soft or incomplete jet by CW
- PHT > 500 ms
- Normal LV size

≥ 4 criteria
Definitively mild
(quantitation not needed)

2-3 criteria

Intermediate Values:
AR Probably moderate

Perform quantitative methods whenever possible to refine assessment

Yes, severe *

Specific Criteria for Severe AR
- Flail Valve
- VC width > 0.6 cm
- Central Jet, width ≥ 65% of LVOT
- Large flow convergence
- PHT < 200 ms
- Prominent holodiastolic flow reversal in the descending aorta
- Enlarged LV with normal function

2-3 criteria

≥ 4 criteria
Definitively severe
(may still quantitate)

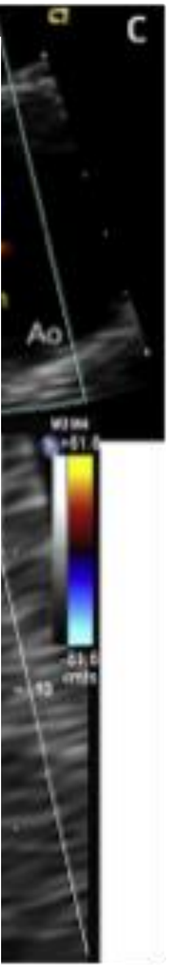
RVol < 30 mL RF < 30% EROA <0.1 cm^2 *AR Grade I*	RVol 30-44 mL RF 30-39% EROA 0.10-0.19 cm^2 *AR Grade II*	RVol 45-59 mL RF 40-49% EROA 0.20-0.29 cm^2 *AR Grade III*	RVol ≥ 60 mL RF ≥ 50% EROA ≥0.3 cm^2 *AR Grade IV*

3 specific criteria for severe AR

Mild AR | **Moderate AR** | **Severe AR**

- Poor TTE quality or low confidence in measured Doppler parameters
- Discordant quantitative and qualitative parameters and/or clinical data

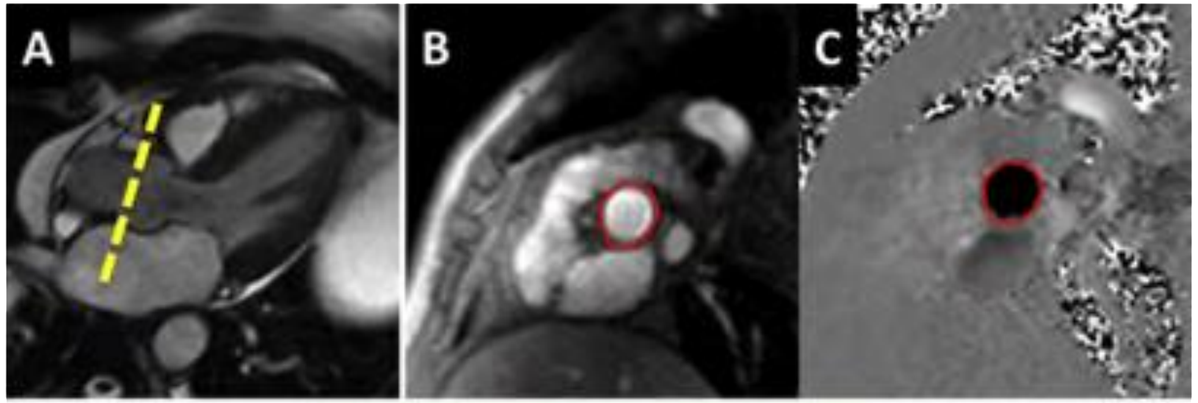
Indeterminate AR
Consider further testing:
TEE or CMR for quantitation

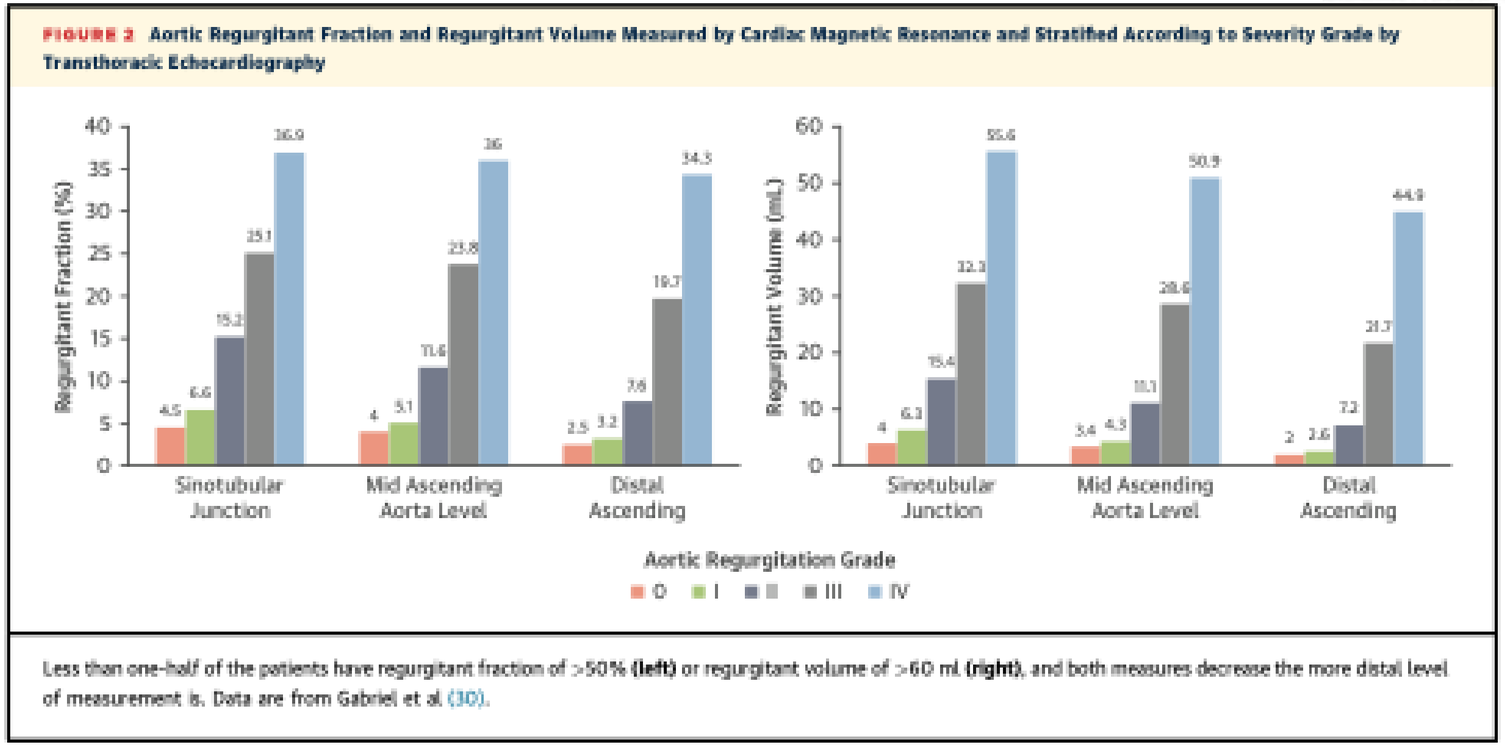


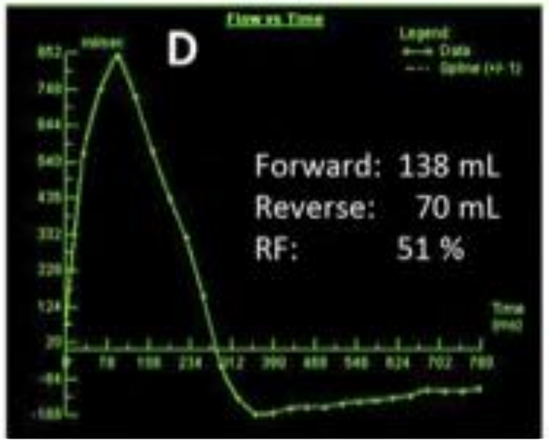
Zoghbi et al. JASE 2017
Yang et al. JACC 2019

Assess AR Severity

CMR





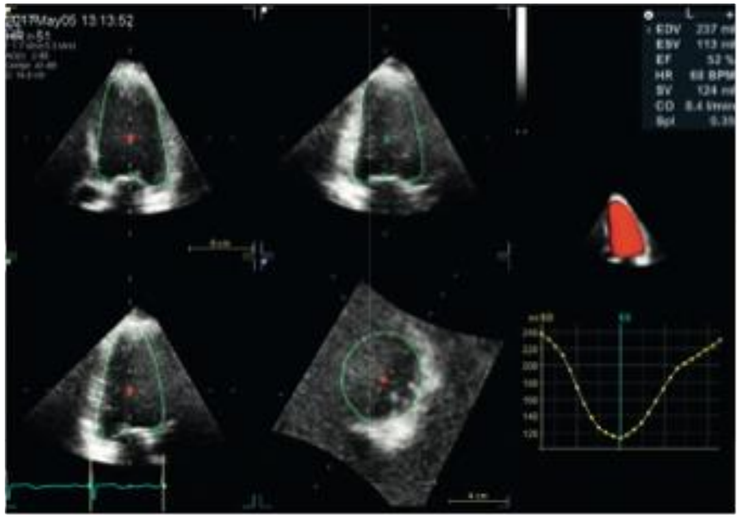


Popovic et al. JIMG 2018

Zoghbi et al. JASE 2017

Assess LV function and dimensions

Echocardiography & CMR



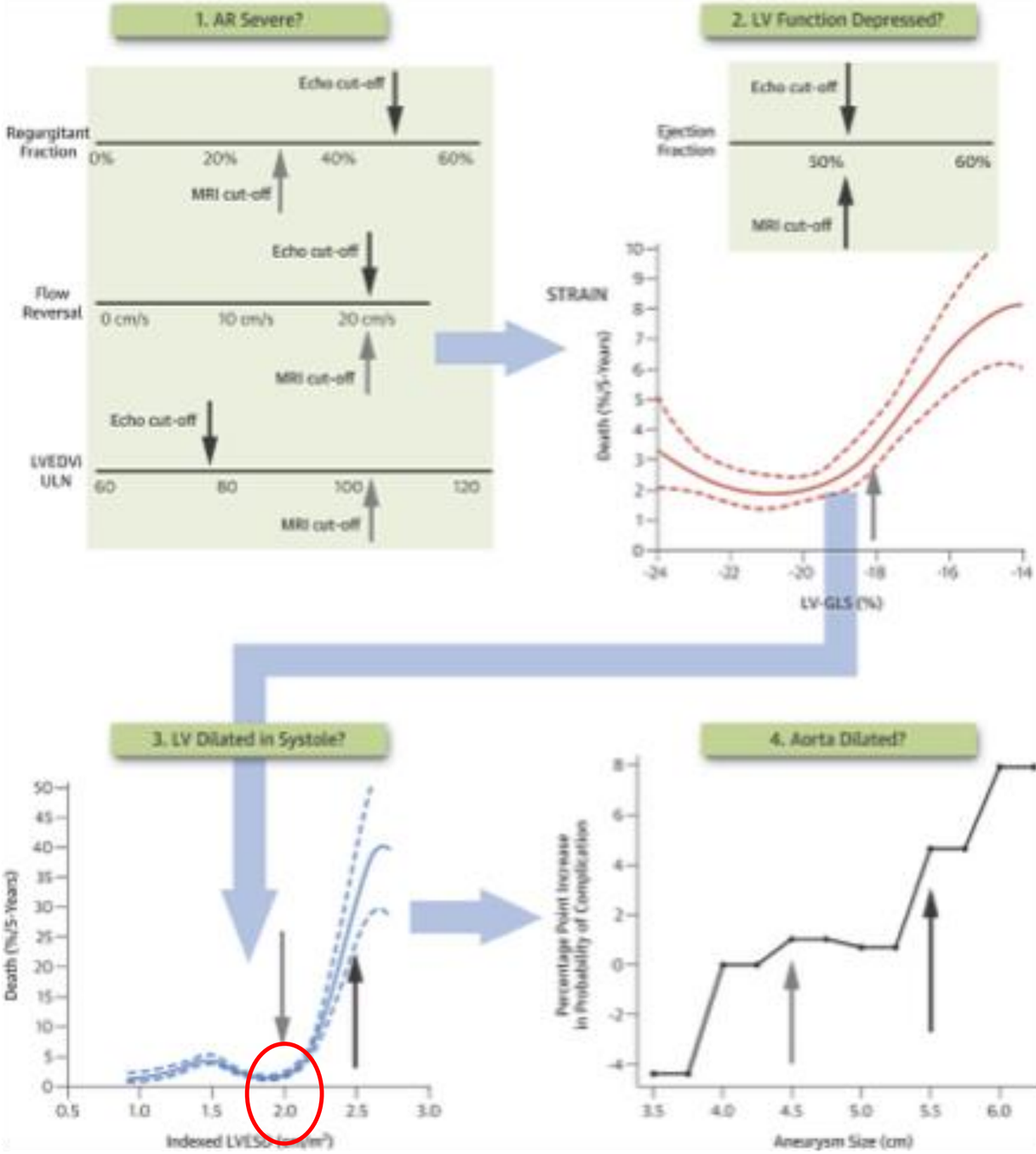


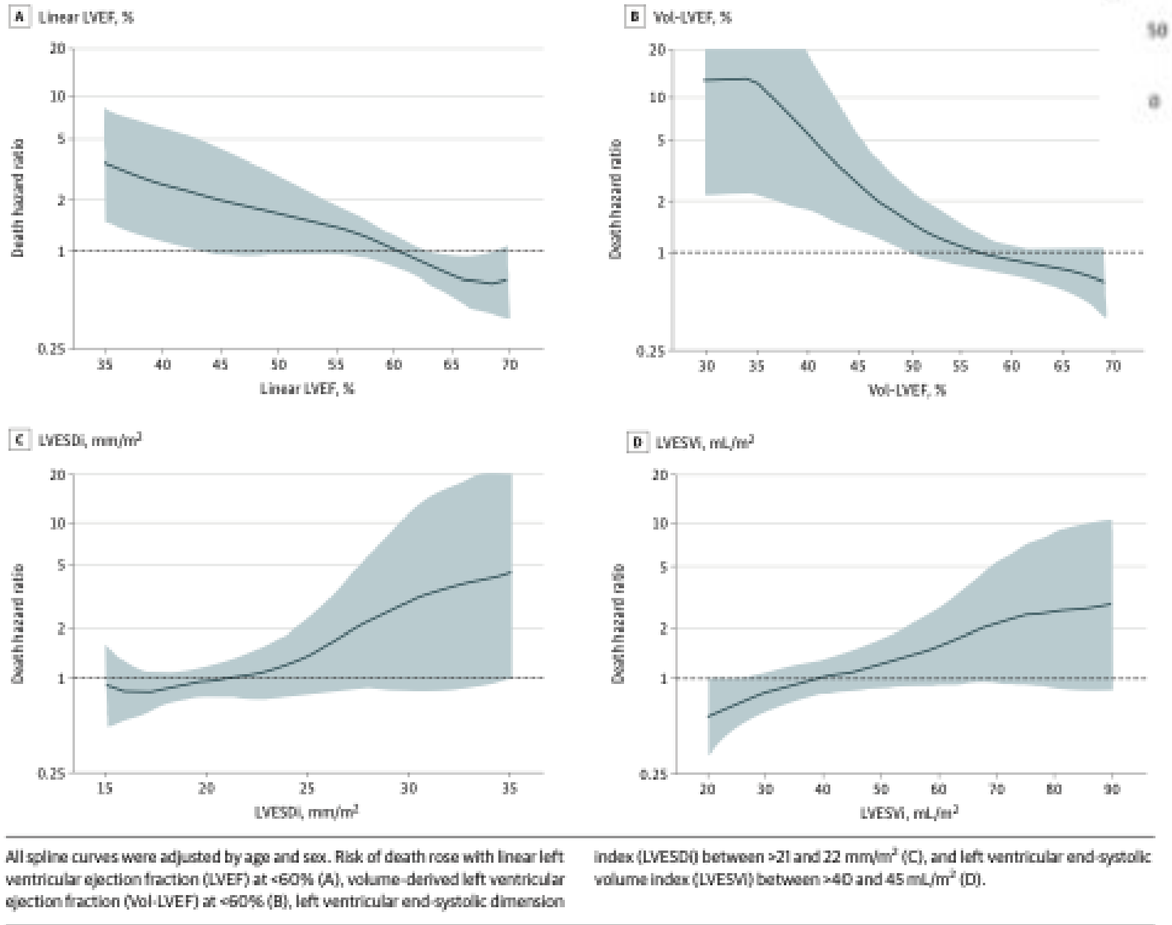
TABLE 2 Studies That Evaluated Cutoff Values of GLS That Can Be Used to Predict Time to AVR or Time to Death

First Author (Ref.#)	Publication Date	n	Follow-Up Period, Months	Software	Hazard Ratio (95% CI)	GLS Cutoff Value (Method of Determination)
Time-to-AVR						
Olsen et al. (47)	2011	64	19 ± 8	EchoPac	Not available	−18% (Youden index)
Kusunose et al. (12)	2014	159	30 ± 21	VVI	1.63 (1.06–2.30)	−18% (median value)
Ewe et al. (24)	2015	49	50 ± 38	EchoPac	1.21 (1.02–1.45)	−17.4% (Youden index)
Time-to-death						
Park et al. (48)	2015	60	64 ± 33	EchoPac	1.313 (1.01–1.71)	−12.5% (Youden index)
Alashi et al. (46)	2018	1,063	82 ± 36	VVI	1.11 (1.04–1.19)	−19% (GLS vs. 5-yr cumulative mortality plot)

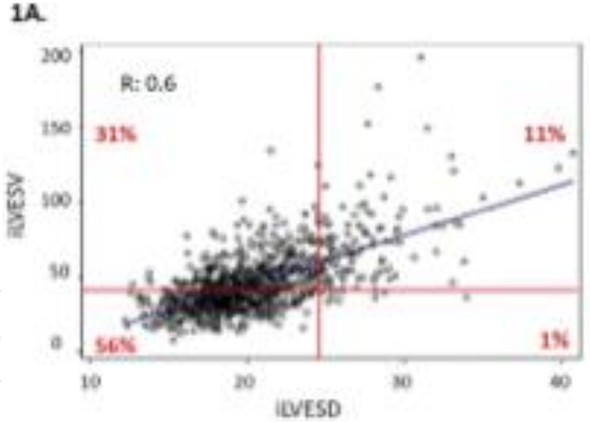
AVR = aortic valve replacement; CI = confidence interval; GLS = global longitudinal strain.

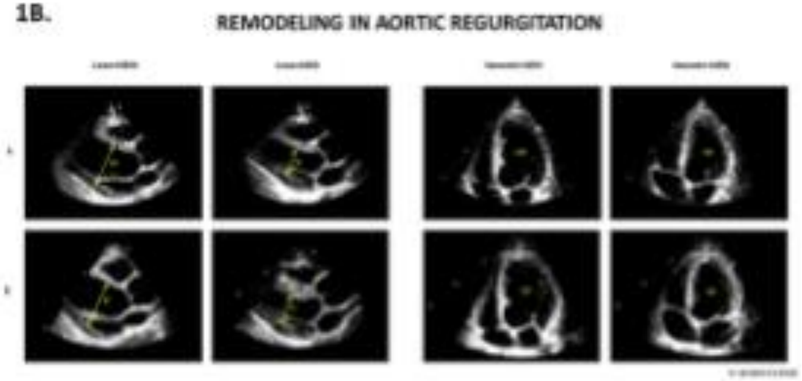
Popović, Z.B. et al. J Am Coll Cardiol Img. 2018;11(10):1499–513.

Role of LV Volumes in risk stratification

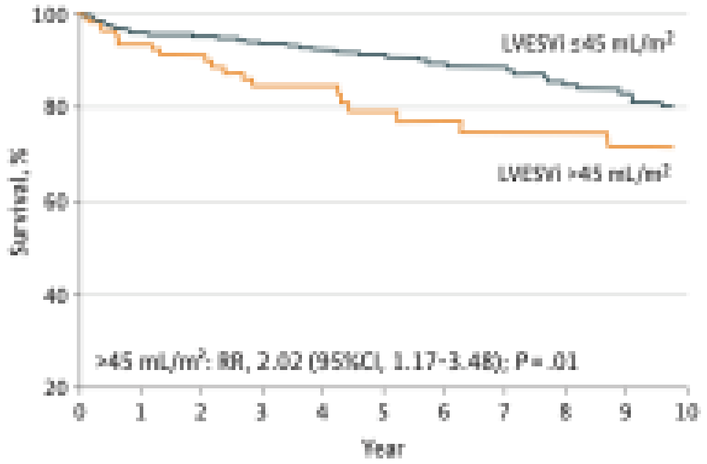


All spline curves were adjusted by age and sex. Risk of death rose with linear left ventricular ejection fraction (LVEF) at <60% (A), volume-derived left ventricular ejection fraction (Vol-LVEF) at <60% (B), left ventricular end-systolic dimension index (LVESDi) between >21 and 22 mm/m² (C), and left ventricular end-systolic volume index (LVESVi) between >40 and 45 mL/m² (D).





Linear LVEF and Vol-LVEF were lower than 60%, LVESDi higher than 21 to 22 mm/m$_2$, and LVESVi higher than 40 to 45 mL/ m$_2$.



No. at risk

LVESVi ≤45mL/m²	328	228	166	118	86	59
LVESVi >45 mL/m²	164	97	63	44	30	23

Anand et al. JASE 2021

Yang et al. JAMA Cardiol 2021

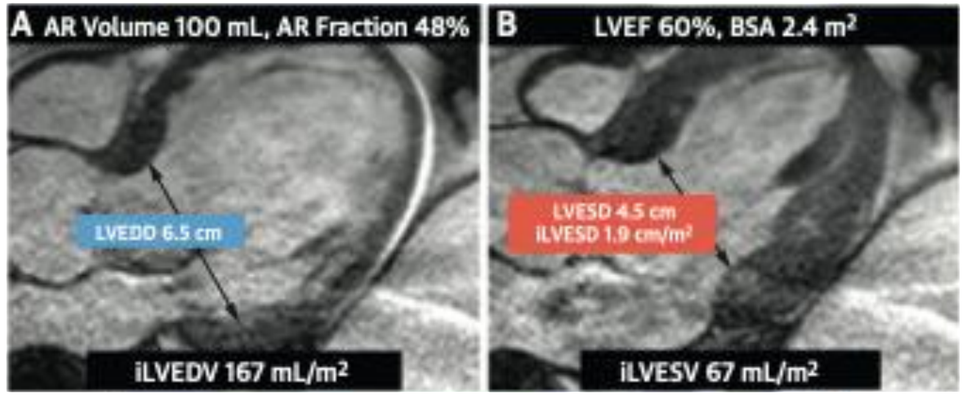
Role of LV Volumes in risk stratification

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

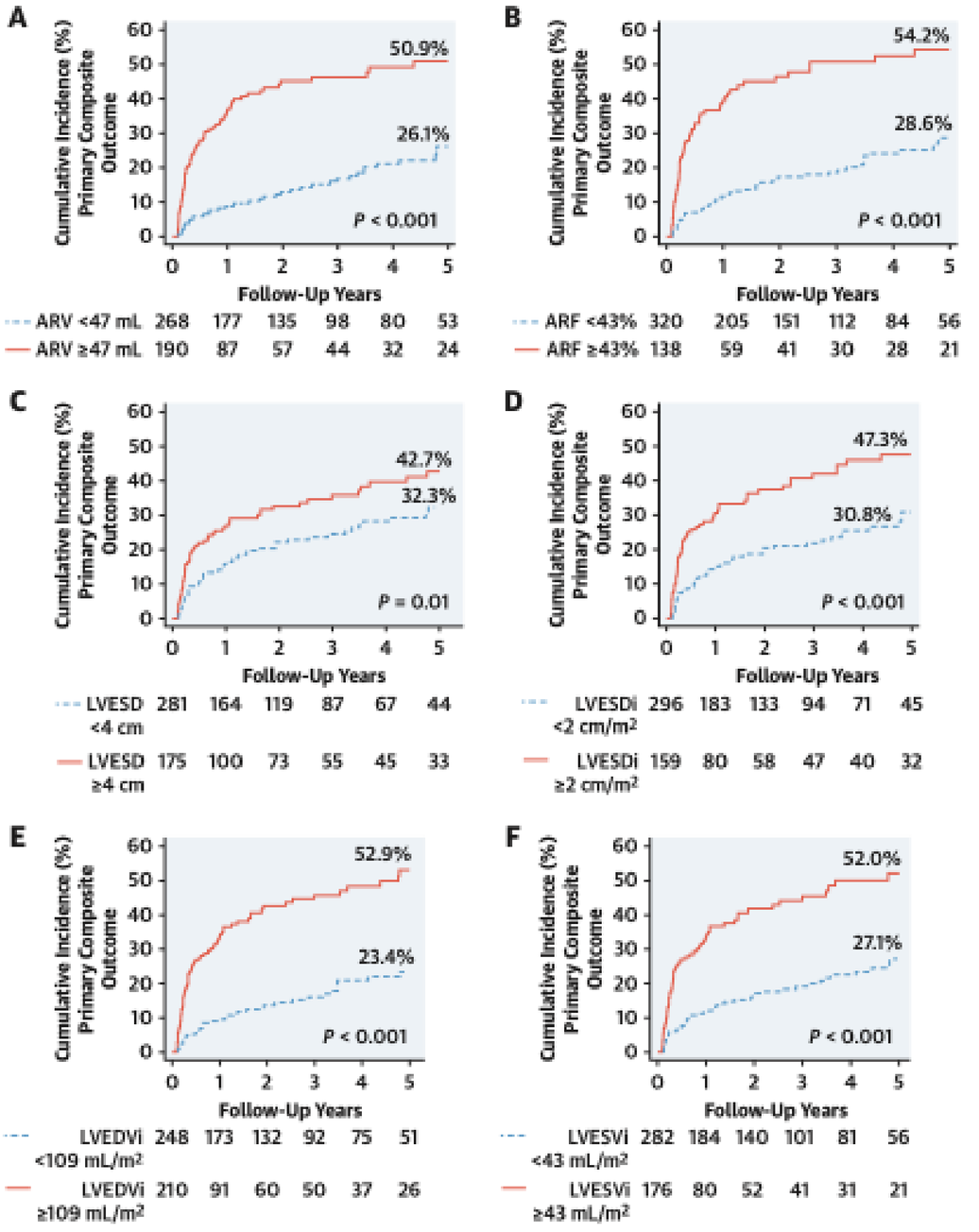
Regurgitant Volume ≥47 mL Regurgitant Fraction ≥43%	Indexed LVESV ≥43 mL/m²	Indexed LVEDV ≥109 mL/m²	LVESD ≥4 cm Indexed LVESD ≥2 cm/m²



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

Malahfji M, et al. J Am Coll Cardiol. 2023;81(19):1885-1898.

Patients with indexed LVES volume of ≥43 mL/m$_2$ but indexed LVES diameter of <2 cm/m$_2$ 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/m$_2$ but indexed LVES volume of <43 mL/m$_2$ had a similar outcome to those with normal values of both variables (P = 0.62)



Malahfji et al JACC 2023

Serial Testing and AR Progression

Table 5. Frequency of Echocardiograms in Asymptomatic

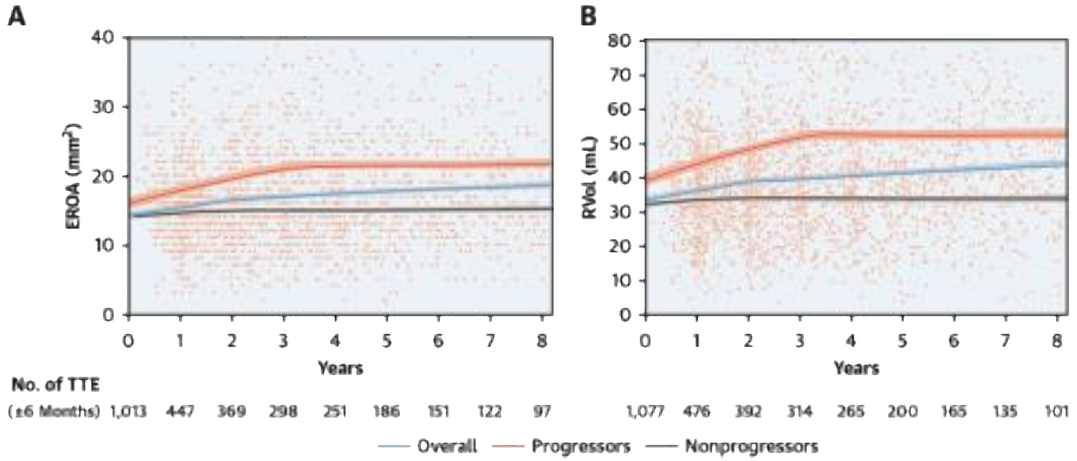
TABLE 2 Predictors for Progres

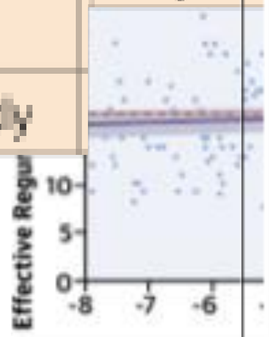
Stage	Aortic Stenosis*
Progressive (Stage B)	Every 3–5 y (mild severity; V_{max} 2.0–2.9 m/s)
	Every 1–2 y moderate severity; V_{max} 3.0–3.9 m/s)
Severe asymptomatic (Stage C1)	Every 6–12 mo (V_{max} ≥4 m/s)

Aortic Regurgitation
Every 3–5 y (mild severity)
Every 1–2 y (moderate severity)
Every 6–12 mo
Dilating LV: More frequently

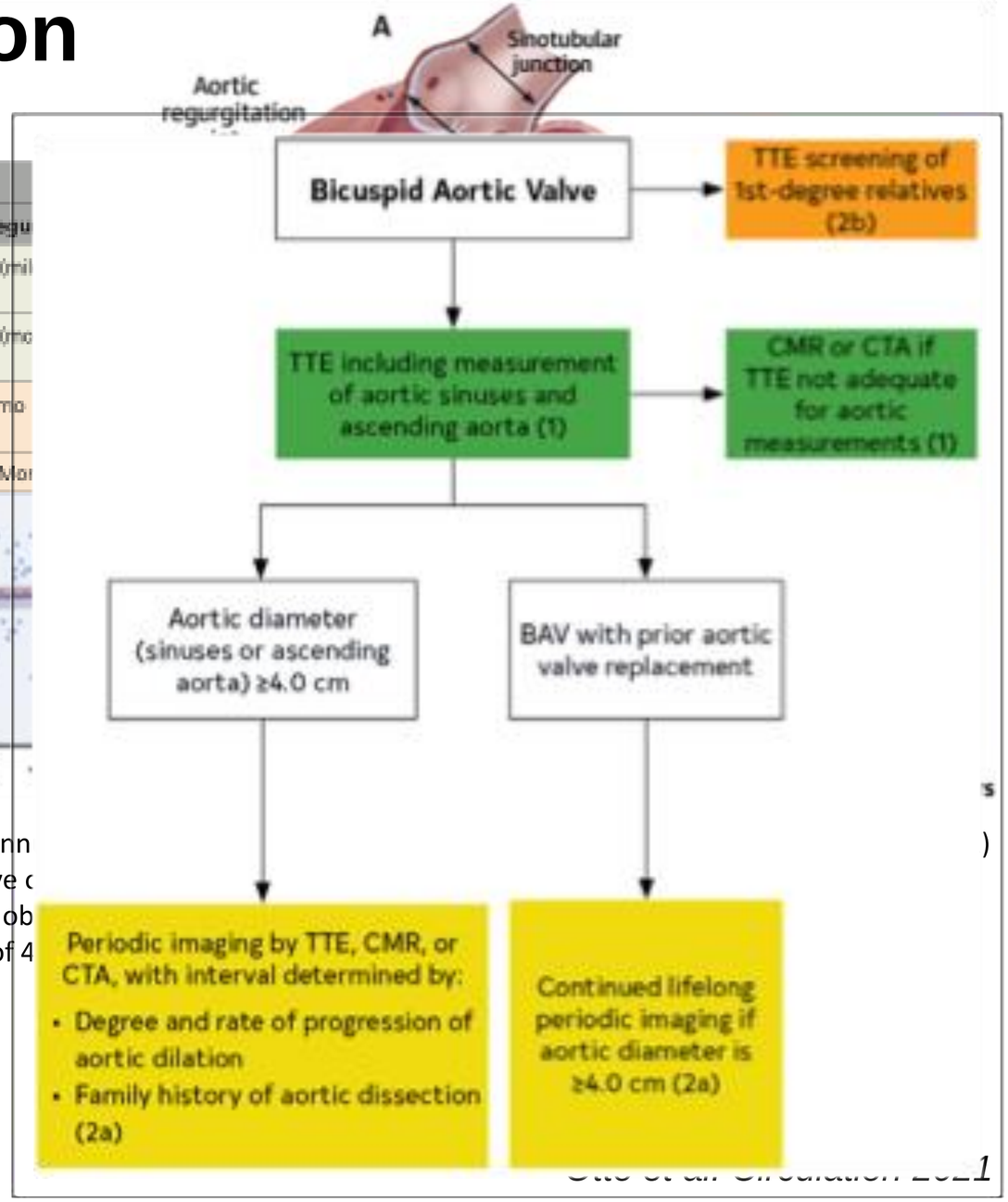
Model 2. AR severity by integrated qualitative assessment†

Age, yrs		
Male		
Bicuspid aortic valve	0.70 (0.45–1.09)	0.12
Annulus/5 mm	1.94 (1.37–2.74)	0.0002
STJ/5 mm	1.30 (1.12–1.51)	0.0004
Mild-to-moderate AR vs. trivial/mild AR	2.25 (1.24–4.08)	0.007
Moderate AR vs. trivial/mild AR	4.71 (2.65–8.37)	<0.0001





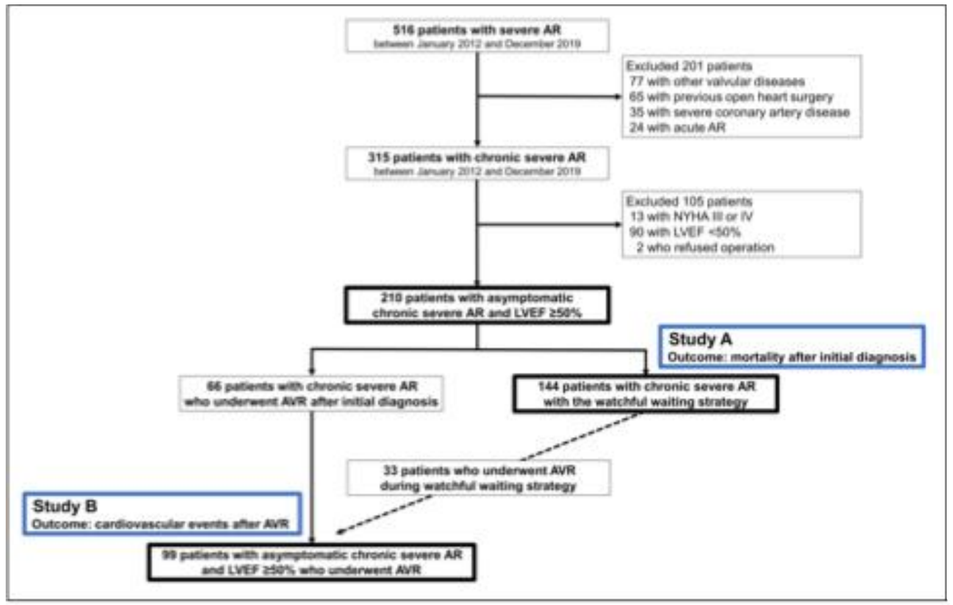
Dilatation of ann)
were predictive
became more ob
and at a rate of 4



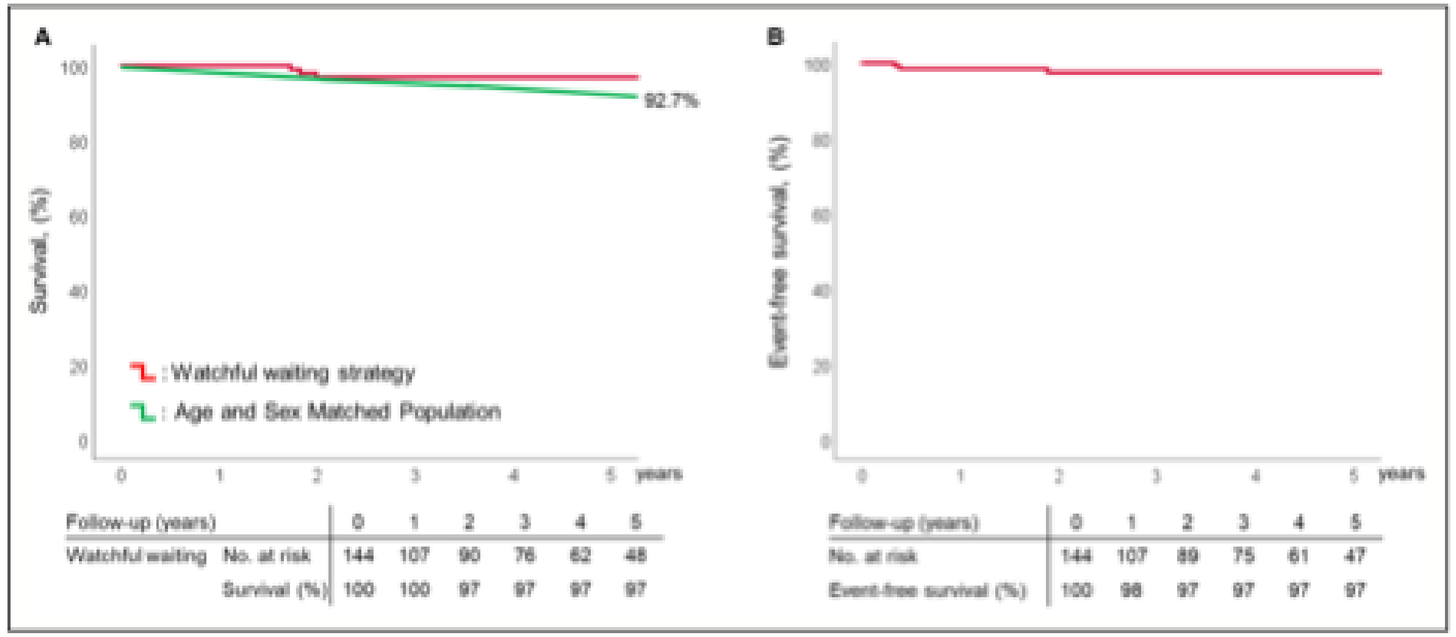
Otto et al. Circulation 2021

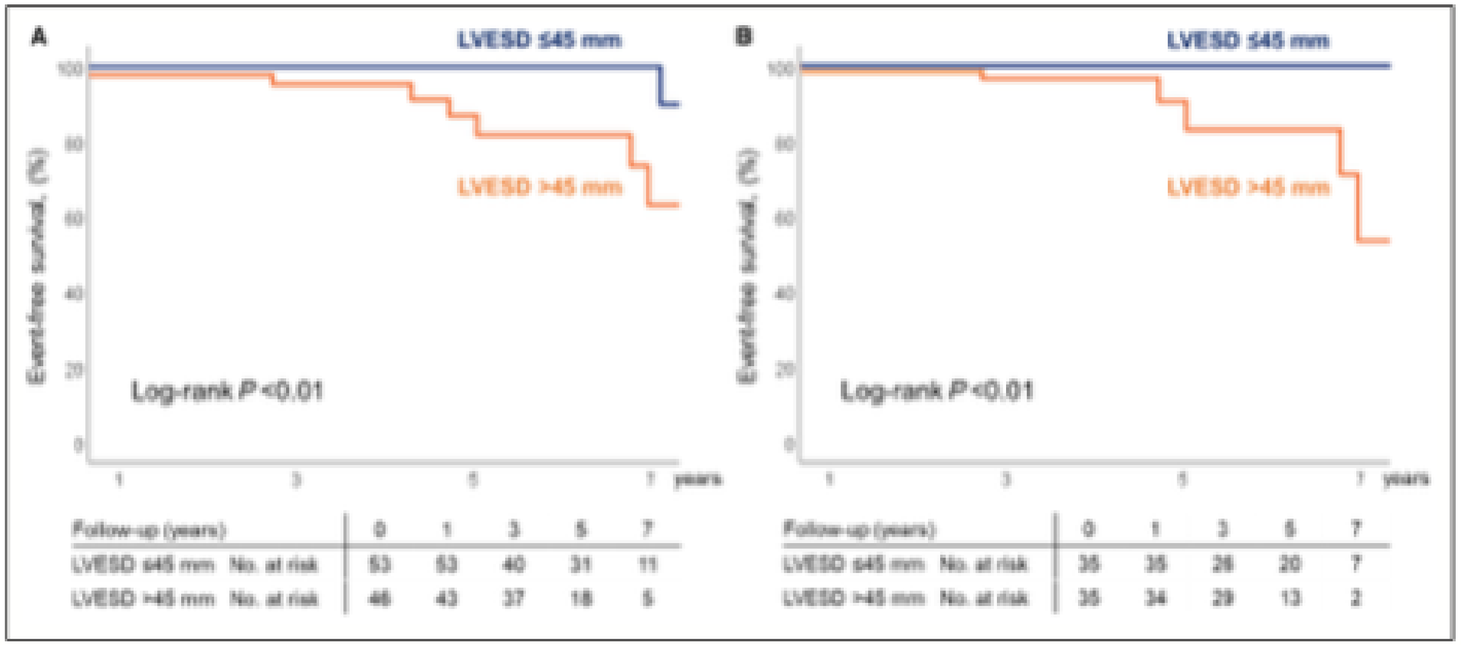
Yang, L.-T. et al. J Am Coll Cardiol. 2019;74(20):2480–92.

Timing of Intervention in Aortic Regurgitation



- The optimal timing for surgery in asymptomatic or equivocally symptomatic patients with chronic severe aortic regurgitation and preserved left ventricular ejection fraction remains controversial.
- In this study, the watchful waiting strategy was achieved safely, showing a prognosis similar to that of an age- and sex-matched general population, and surgery after watchful waiting was not a postoperative cardiovascular event risk; thus, it was a feasible approach for patients with chronic severe aortic regurgitation.
- **LVESD >45mm** could be an optimal cut-off value among a population of small body size for predicting postoperative cardiovascular events.





Suzuki et al. JAHA 2024

4.3.2. Medical Therapy

Recommendations for Medical Therapy of Chronic AR

Referenced studies that support the recommendations are summarized in Online Data Supplement 14.

COR	LOE	Recommendations
1	B-NR	1. In asymptomatic patients with chronic AR (Stages B and C), treatment of hypertension (systolic blood pressure >140 mm Hg) is recommended.[1-3]
1	B-NR	2. In patients with severe AR who have symptoms and/or LV systolic dysfunction (Stages C2 and D) but a prohibitive surgical risk, GDMT for reduced LVEF with ACE inhibitors, ARBs, and/or sacubitril/valsartan is recommended.[4]

Otto et al. Circulation 2021

Take Home Messages

- Assessment of severity of Chronic Aortic Regurgitation by TTE can be challenging. Multimodality imaging is key.
- CMR, TEE and Exercise Echocardiography can and should be used when TTE leads to indeterminate results
- Attempting AR quantification is recommended whenever possible.
- Evaluation of LV dimensions and function is crucial, as, together with symptomatic status, guides intervention.
- New evidences are shifting the cut-offs towards earlier surgical referral.
- Cut-offs for LVESD should be adjusted by body size
- Role of LV Volumes in the prediction of prognosis remain relatively under-investigated
- Sex differences in the progression of the disease are evident, yet no sex-specific recommendation have been implemented