Cardiac Damage Staging in Moderate or Greater Aortic Regurgitation

A New Framework for Risk Stratification

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Accepted to *Structural Heart*

Disclosure of Relevant Financial Relationships

I, Francisco Alexandrino, DO NOT have any financial relationships to disclose.

How do we assess RISK in AR?

- *Progressive volume and pressure overload* [1]
- *Severe AR + symptoms or LVEF <55% or ventricle enlargement* [2]
- *Asymptomatic moderate AR is associated with adverse outcomes* [3]
- *LV remodeling in moderate and severe AR is similar* [4]

1. Wisenbagh et al. JACC 1984 2. Otto et al. Circulation 2021
3. Généreux et al. JACC Advances 2024 4. Hashimoto JAMA Cardiology 2022

How can we BETTER assess risk?

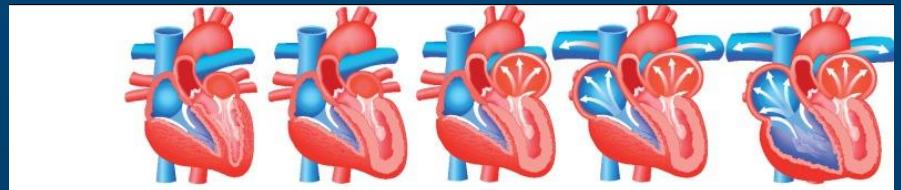
- *AR is not frequently in isolation* [1]
- *Early LV dysfunction increases risk* [2]
- *Ongoing trials in moderate AS and moderate FMR*

Risk is a continuum

1. Yang et al. JACC 2020 2. Anand et al. JACC: Cardiovascular Imaging 2025

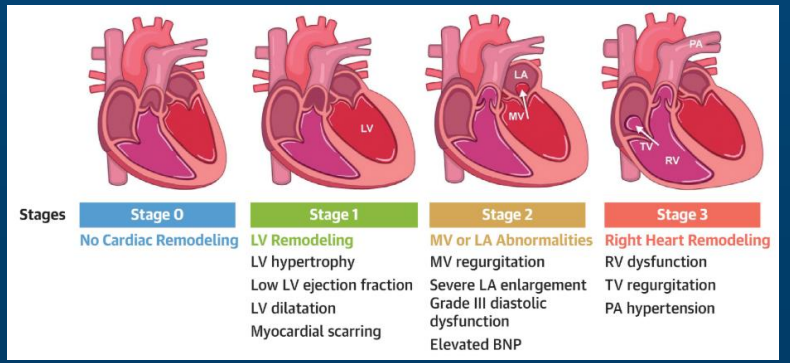
What has been done?

Cardiac damage in severe aortic stenosis [1]



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

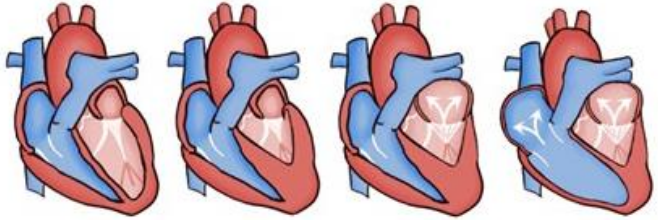
Cardiac damage in moderate to severe aortic regurgitation [2]



**Cardiac MRI*

1. Généreux et al. Eur Heart J 2017 2. Malahfji et al. JACC: Cardiovascular Imaging 2025

Methodology



	Stage 0 (n=28)	Stage 1 (n=101)	Stage 2 (n=210)	Stage 3 (n=93)
	No cardiac damage	LV damage	LA or Mitral valve damage	Pulmonary valve, Tricuspid valve, or RV damage
Echocardiographic staging		GLS > -19.5%	LAVI > 34 mL/m^2	≥ moderate TR
		EF < 55%	Atrial fibrillation	Any RV systolic dysfunction
		iLVESD > 2	≥ moderate MR	RVSP > 60 mmHg

- *AR moderate-severe*
- *2008-2020*
- *Exclusion criteria*
- *n=432*
- *Hierarchical staging*
- *Criteria based on validated thresholds* [1,2,3]

1. Otto et al. Circulation 2021 2. Zhao et al. Front Cardiovascular Med 2022
3. Alashi et al JACC Cardiovascular Imaging 2018

Results – rate of each individual component

	Stage 0 (n=28)	Stage 1 (n=101)	Stage 2 (n=210)	Stage 3 (n=93)
GLS > -19.5%	0 (0%)	94 (93.1%)	164 (78.1%)	82 (88.2%)
iLVESD > 2	0 (0%)	15 (14.9%)	43 (20.5%)	26 (28.0%)
LVEF < 55%	0 (0%)	23 (22.8%)	42 (20%)	40 (43.0%)
LAVI > 34	0 (0%)	0 (0%)	135 (64.3%)	71 (76.3%)
Atrial fibrillation	0 (0%)	0 (0%)	155 (73.8%)	72 (77.4%)
≥ moderate MR	0 (0%)	0 (0%)	37 (17.6%)	29 (31.2%)
RVSP > 60 mmHg	0 (0%)	0 (0%)	0 (0%)	21 (22.6%)
≥ moderate TR	0 (0%)	0 (0%)	0 (0%)	75 (80.6%)
RV systolic dysfunction	0 (0%)	0 (0%)	0 (0%)	36 (38.7%)

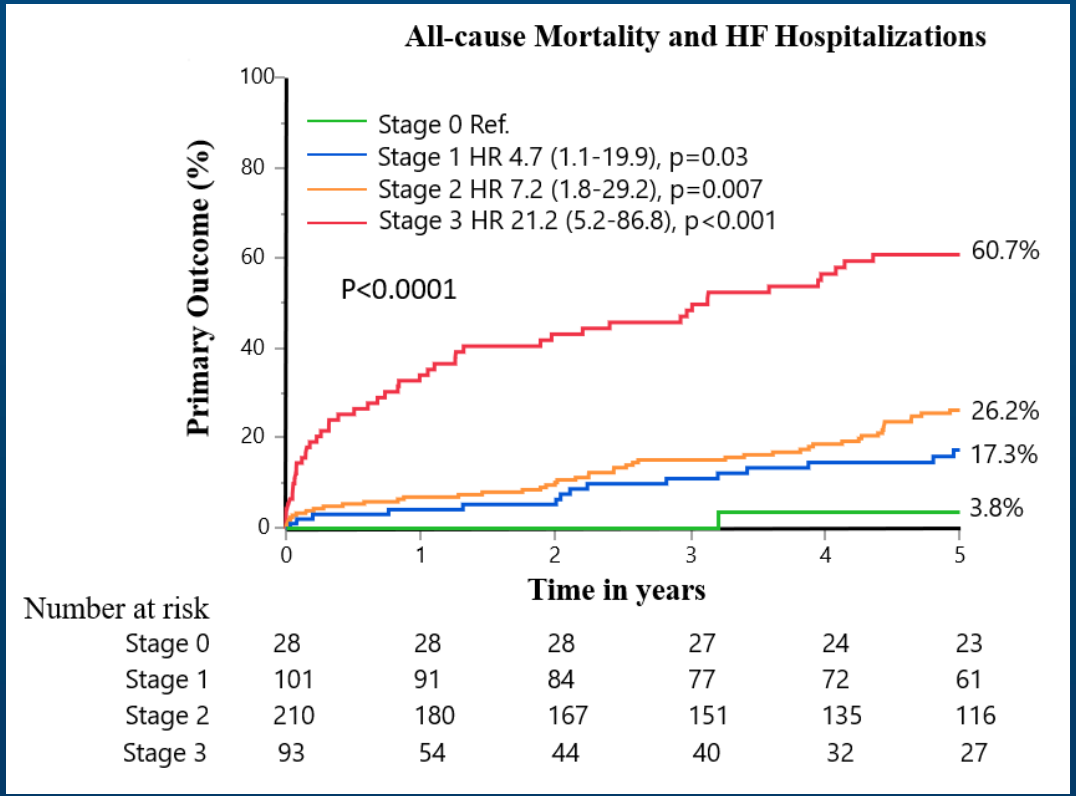
Results – baseline characteristics

	Stage 0 (n=28)	Stage 1 (n=101)	Stage 2 (n=210)	Stage 3 (n=93)	P-value
Female	11 (39.3%)	50 (49.5%)	85 (40.5%)	46 (49.5%)	0.30
Age	56.5 (43-68)	63 (50.5-74.0)	68.0 (58.0-76.0)	74.0 (63.0-82.5)	<0.0001
NT pro BNP	76 ± 11	1,293 ± 3,398	4,852 ± 1,755	8,934 ± 1,682	0.14
Atrial fibrillation	0 (0%)	0 (0%)	55 (26.2%)	21 (22.6%)	<0.0001
Severe AR	11 (39.3%)	36 (35.6%)	81 (38.6%)	50 (53.7%)	0.048
HF	9 (32.1%)	49 (48.5%)	140 (66.7%)	82 (88.2%)	<0.0001
CKD	3 (10.7%)	23 (22.8%)	64 (30.5%)	38 (40.9%)	0.005

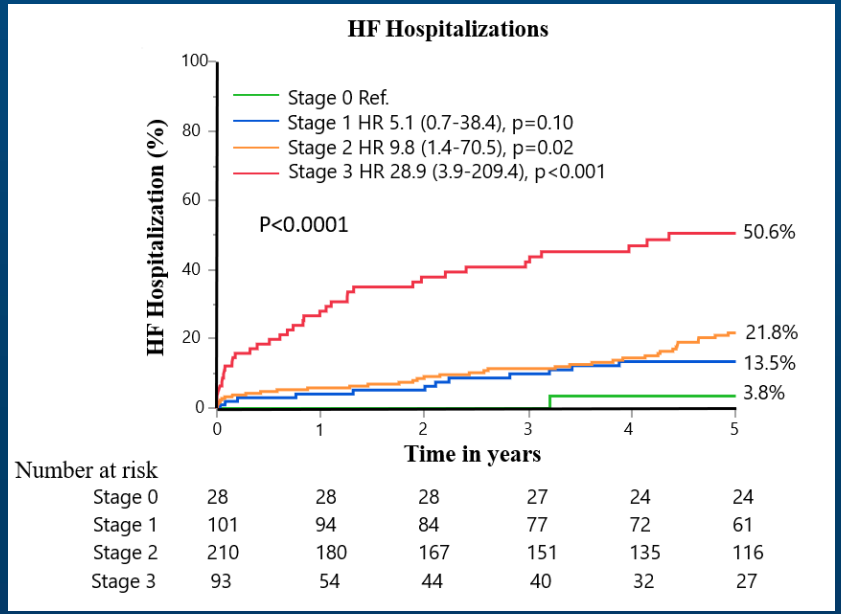
Results – echocardiography

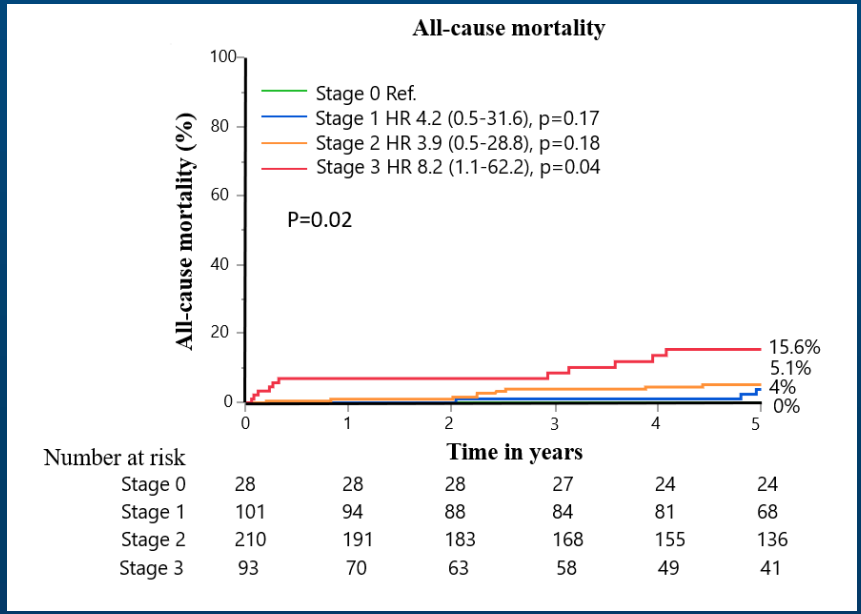
	Stage 0 (n=28)	Stage 1 (n=101)	Stage 2 (n=210)	Stage 3 (n=93)	P-value
LVEF (%)	61.9 (60.0-65.0)	60.0 (55.0-62.5)	59.1 (55.0-62.7)	55.0 (45.0-60.0)	<0.0001
RVSP (mmHg)	26.5 (23.0-30.1)	28.0 (24.0-33.9)	30.3 (27.1-37.7)	45.5 (35.8-56.9)	<0.0001
LAVI (mL/m^2)	24.7 (20.4-30.8)	25.7 (21.1-29.4)	36.7 (29.0-46.9)	46.6 (35.4-58.5)	<0.0001
GLS endocardium (%)	-20.7 (-22.8- -20.1)	-16 (-18.5- -13.7)	-15.7 (-19- -12.8)	-12.2 (-16.7- -8.0)	<0.0001
LVEDD (cm)	4.7 (4.4-5.0)	4.7 (4.2-5.3)	5.0 (4.4-5.5)	4.7 (4.3-5.4)	0.10
LVESD (cm)	2.8 (2.6-3.0)	3.0 (2.6-3.5)	3.2 (2.7-3.7)	3.3 (2.8-4.0)	<0.0001
>=mod MR	0 (0%)	0 (0%)	37 (17.6%)	29 (31.2%)	<0.0001
>=mod TR	0 (0%)	0 (0%)	0 (0%)	75 (80.7%)	<0.0001
MV E/e' septal	9.5 (8.5-12.4)	11.9 (9.0-15.9)	14.6 (11.0-20.6)	16.9 (13.4-36.0)	<0.0001

Results – outcomes

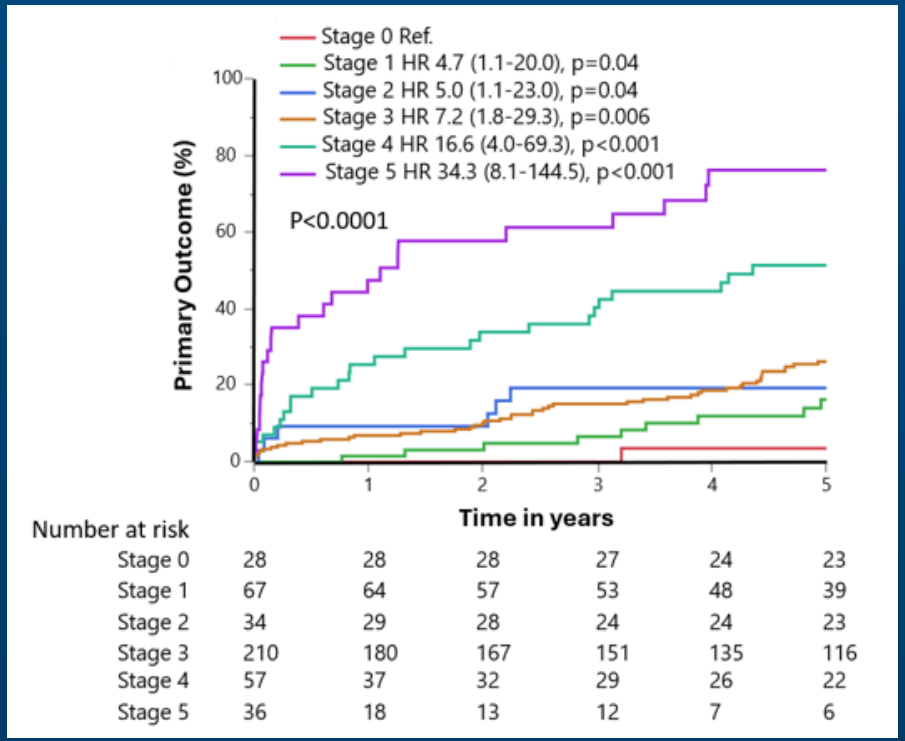


Results – outcomes



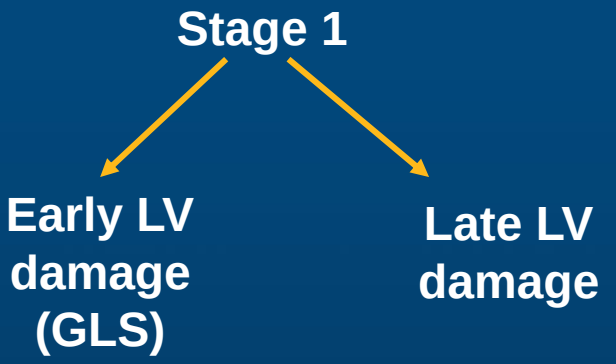


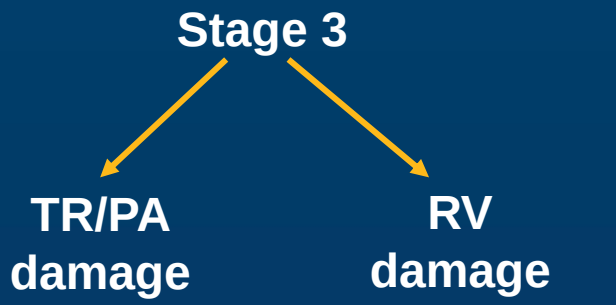
Results – sensitivity analysis



Number at risk

Stage 0	28	28	28	27	24	23
Stage 1	67	64	57	53	48	39
Stage 2	34	29	28	24	24	23
Stage 3	210	180	167	151	135	116
Stage 4	57	37	32	29	26	22
Stage 5	36	18	13	12	7	6





Results – multivariate model

All-cause mortality and HF hospitalizations

	HR (95% CI)	P-value
Stage (per each level increase)	2.1 (1.6-2.6)	<0.01
Age (per each year increase)	1.05 (1.03-1.07)	<0.01
HF	2.0 (1.3-3.1)	<0.01
Prior CABG	1.8 (1.2-2.6)	<0.01
DM	1.9 (1.4-2.7)	<0.01

Cardiac damage staging has the strongest association with the primary outcome

Limitations

- *Single center and retrospective study*
- *Qualitative assessment*
- *GLS is variable among different institutions*
- *Age and comorbidities are highly associated with staging*

Conclusions

- *Novel AR-specific cardiac damage staging system was developed and tested*
- *Staging incorporates GLS, structural and functional echocardiographic markers*
- *Progressive cardiac damage was strongly associated with adverse clinical outcomes*

Future

Cardiac damage captures continuum risk

- More advanced stages benefit from early AVR?
- What's the degree of cardiac damage in mild AR?
- Is there structural recovery after AVR?

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