Phenotyping Heart Valve Disease: Why?

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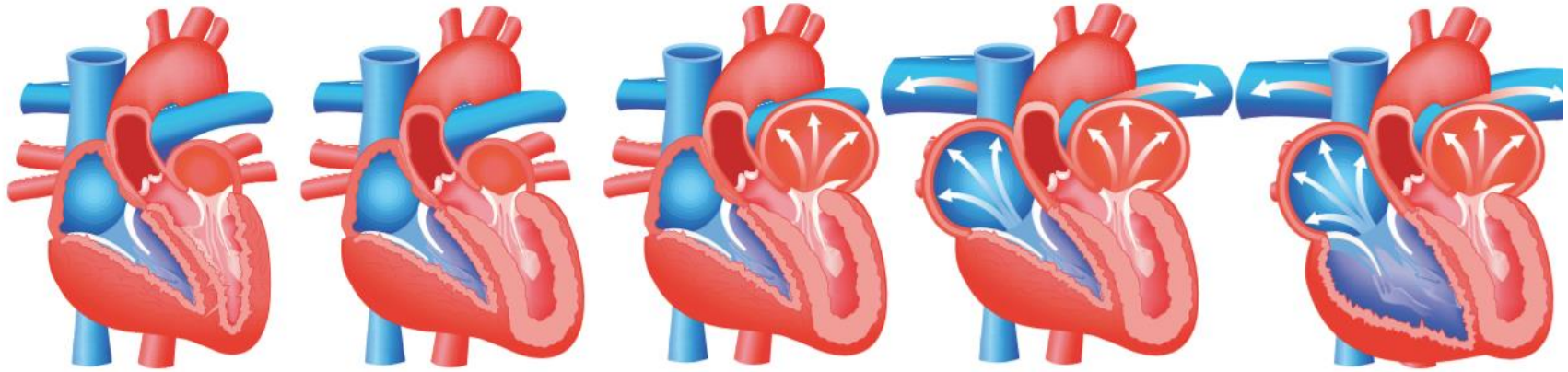
Staging Aortic Stenosis

Incorporating Extra-Valvular Damage



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/m^2 (Male) >95 g/m^2 (Female)	Indexed left atrial volume >34mL/m^2	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		

Genereux P, Pibarot P et al., EHJ 2017;38:3351–3358

Aortic Stenosis

Continuous Risk

CENTRAL ILLUSTRATION: Mortality Associated With Untreated Aortic Stenosis

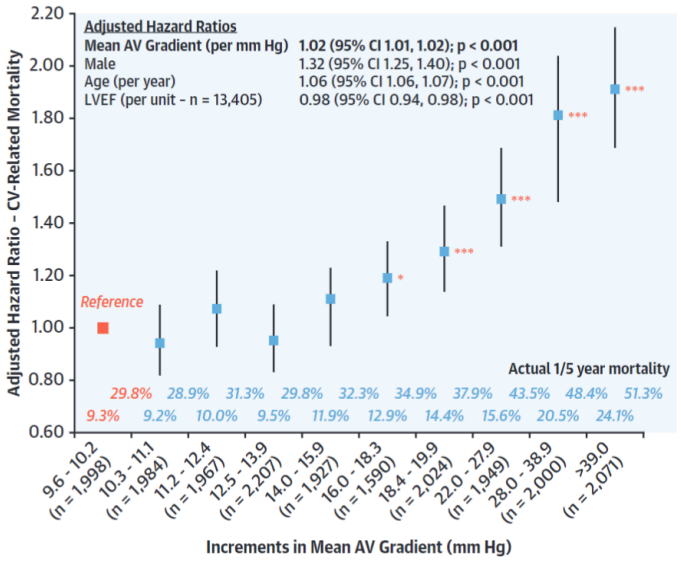
595,120 Patients With AS Assessment

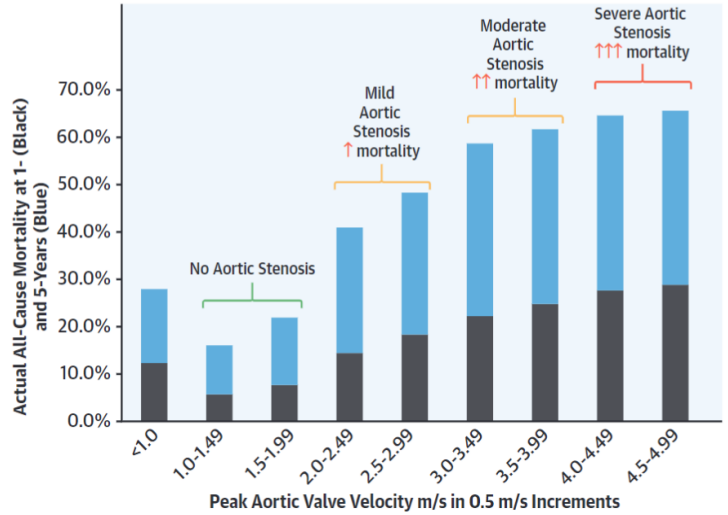
No AS
524,342 (88.1%)

AS Dx
70,778 (11.9%)

AS Severity	ACC/AHA Dx	Intermediate Dx	4-Year Treatment Rates With AVR	4-Year Mortality Without AVR
	61,293 (86.6%)	9,485 (13.4%)		
Mild AS	34,614 (48.9%)		1.0%	25.0%
Mild-to-Moderate AS	5,796 (8.2%)		4.2%	29.7%
Moderate AS	14,550 (20.6%)		11.4%	33.5%
Moderate-to-Severe AS	3,689 (5.2%)		36.7%	45.7%
Severe AS	12,129 (17.1%)		60.7%	44.9%

Généreux P, et al. J Am Coll Cardiol. 2023;82(22):2101-2109.





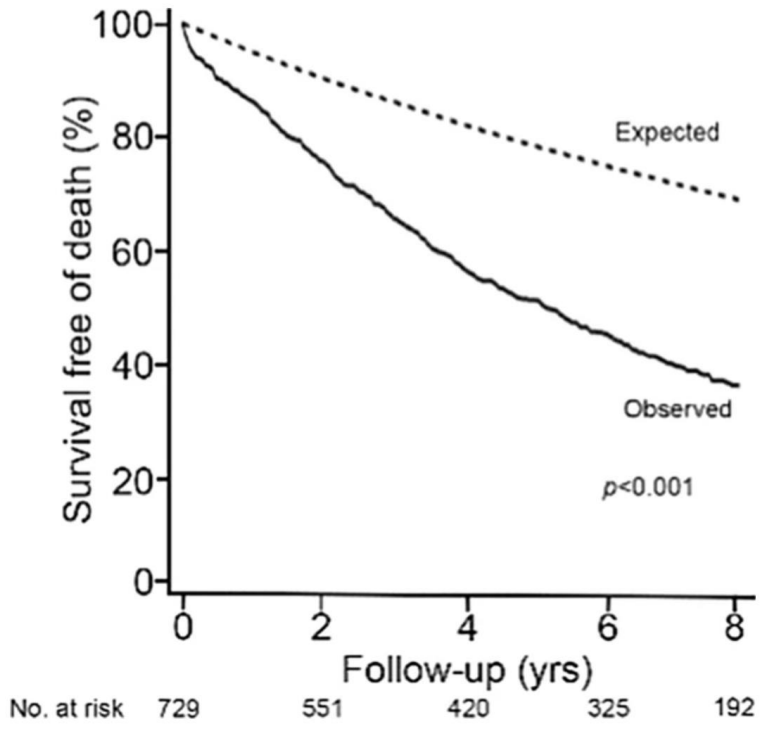
Strange, G. et al. J Am Coll Cardiol. 2019;74(15):1851-63.

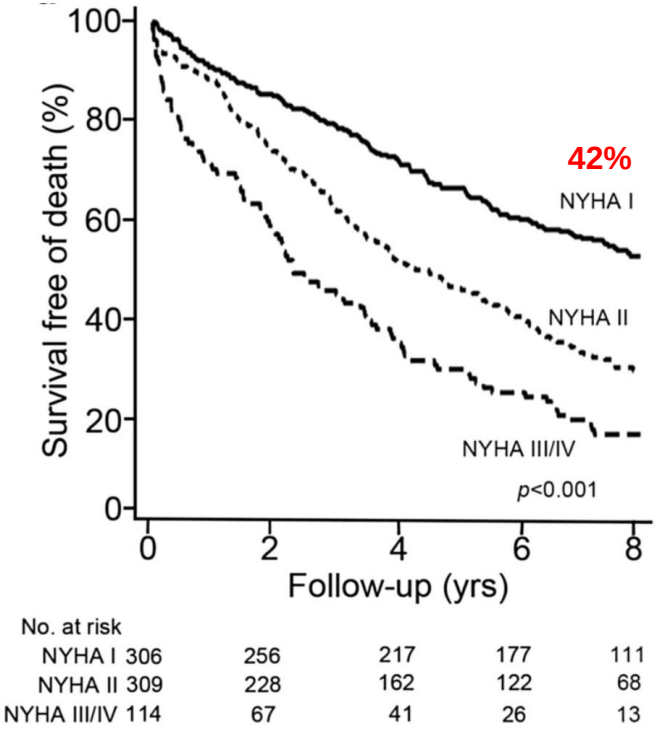
110,197 Patients With AS, 3,315 With Moderate AS AVA 1.4±0.0.4 cm², Mean PG 24.3±6 mm Hg

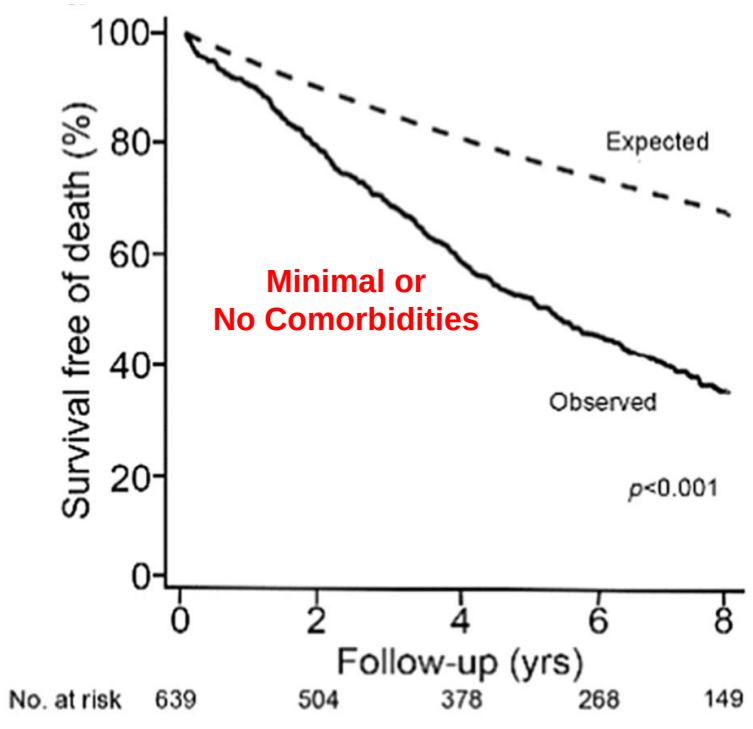
Survival Probability in Moderate AS

Vs. Comparable General Population

729 patients, Moderate AS (median AVA 0.79 cm^2/m^2, median mean PG 9.1 mmHg, median FU 5 years





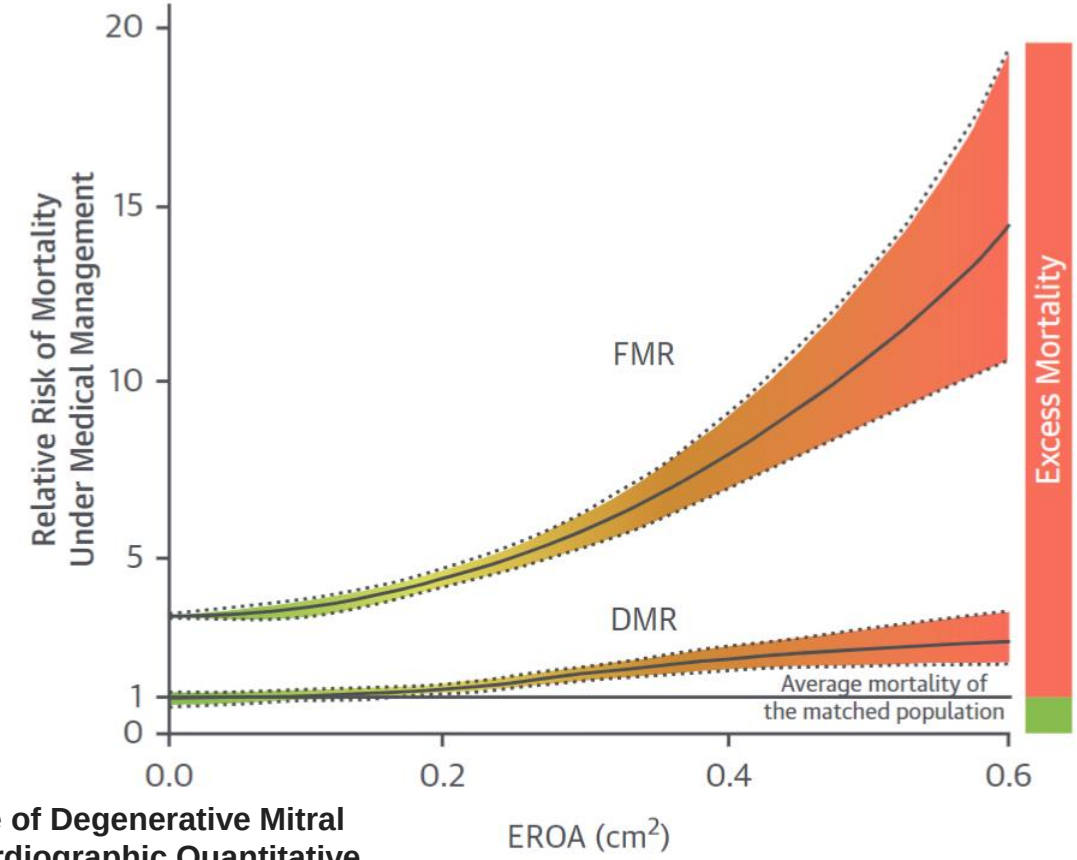


Du, Y., Gössl, M., Garcia, S. *et al.* Natural history observations in moderate aortic stenosis. *BMC Cardiovasc Disord* 21, 108 (2021).

Excess Mortality Risk in FMR

Vs. Comparable Population With No MR

6,381 patients with HFrEF with Any or no MR

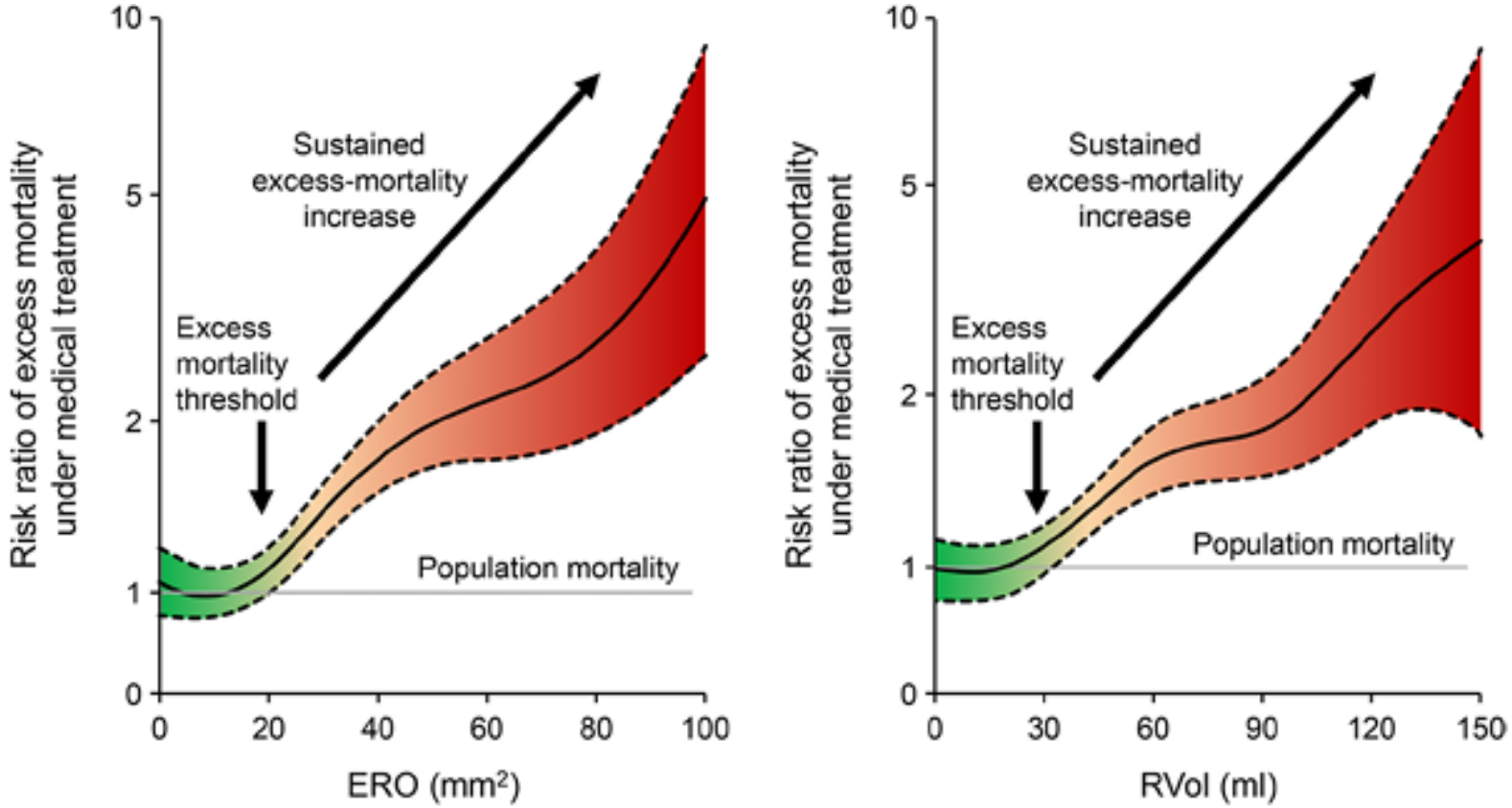


Antoine C, Benfari G, et al. Clinical Outcome of Degenerative Mitral Regurgitation: Critical Importance of Echocardiographic Quantitative Assessment in Routine Practice. Circulation. 2018 ;138:1317-1326.

Excess Mortality: DMR

Vs. General Population

3914 patients, 62±17 yrs., DMR [mean EROA 19 mm^2 (19-40)] EF 63± 8%, Balanced comorbidities, Mean FU 6.7 (4.3-9.3) yrs.

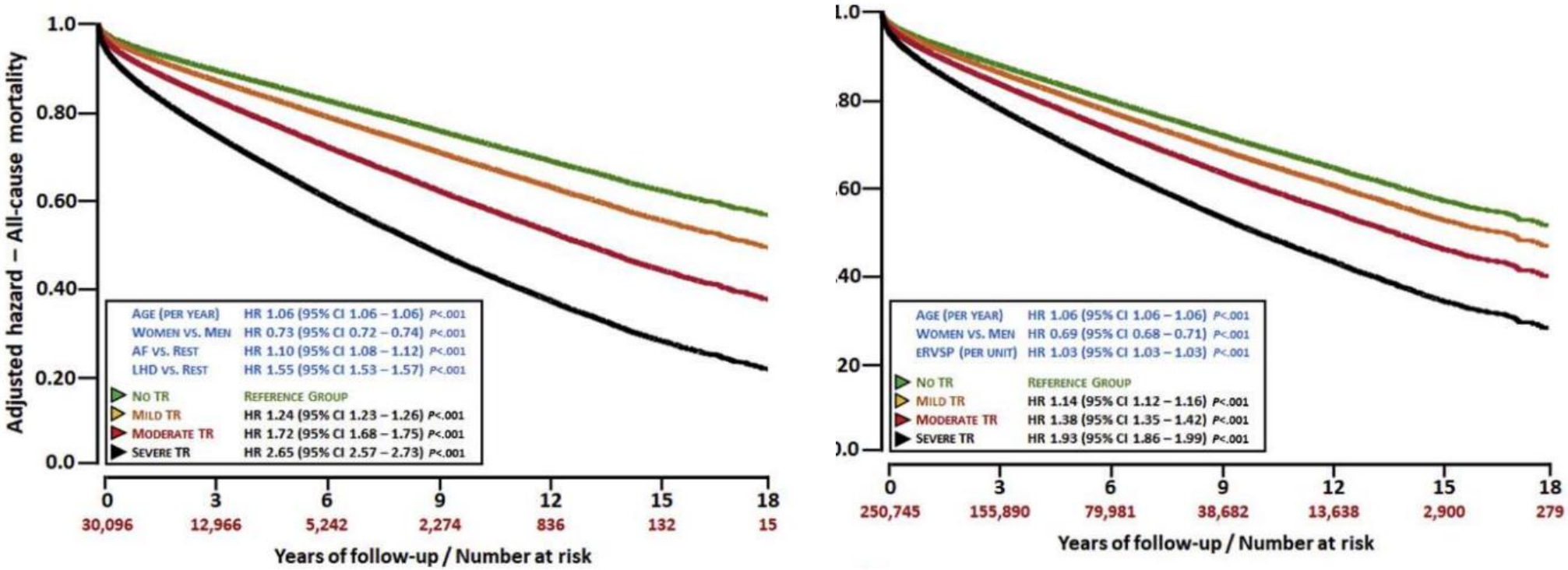


Antoine C, Benfari G, et al. Clinical Outcome of Degenerative Mitral Regurgitation: Critical Importance of Echocardiographic Quantitative Assessment in Routine Practice. Circulation. 2018 ;138:1317-1326.

Mortality Risk in TR

Vs. Comparable Population With No TR

120,228 patients From The NEDA Database

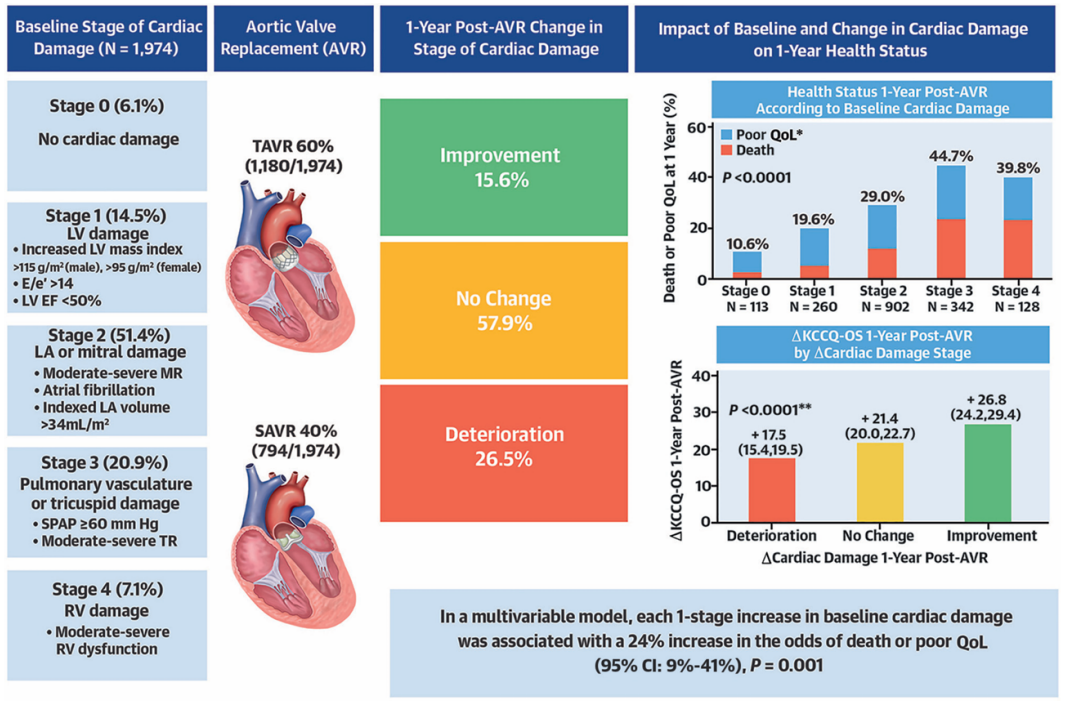


Offen S. et al. JASE. 2022;35:810-817

Staging and QOL After AVR

PARTNER 2 and 3 Trials

CENTRAL ILLUSTRATION Impact of Cardiac Damage on Health Status After Aortic Valve Replacement



Généreux P, et al. J Am Coll Cardiol. 2023;81(8):743-752.

Among 1,974 patients undergoing AVR, 6.1% were in stage 0, 14.5% were in stage 1, 51.4% were in stage 2, 20.9% were in stage 3, and 7.1% in stage 4 of cardiac damage before AVR. At 1 year after AVR, 15.6% improved at least by 1 stage, 57.9% remain unchanged, and 26.5% deteriorated by at least 1 stage. One-year change in stage of cardiac damage was significantly associated with health status outcomes at 1 year after AVR. In a multivariable model, each 1-stage increase in baseline cardiac damage was associated with a 24% increase in the odds of a poor outcome (95% CI: 9%-41%; $P = 0.001$). Change in stage of cardiac damage at 1 year after AVR was associated with the extent of improvement in KCCQ-OS over the same period (mean change in 1-year KCCQ-OS: improvement ≥1 stage +26.8 [95% CI: 24.2-29.4] vs no change +21.4 [95% CI: 20.0-22.7] vs deterioration ≥1 stage +17.5 [95% CI: 15.4-19.5]; $P < 0.0001$). *Poor QoL defined as KCCQ-OS <60 or decline in KCCQ-OS >10. **Adjusted for baseline KCCQ-OS and baseline stage of cardiac damage (ANCOVA); values are ΔKCCQ-OS (95%CI). AVR = aortic valve replacement; EF = ejection fraction; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; QoL = quality of life; RA = right atrial; SPAP = systolic pulmonary pressure.

CONCLUSIONS

The extent of cardiac damage before AVR has an important impact on patient's health status, both cross-sectionally and after AVR. Moreover, regression of cardiac damage within the first year after AVR is associated with greater improvement in health status relative to patients whose cardiac damage stage was unchanged or worsened. These findings emphasize the importance of assessing extravalvular cardiac damage before AVR to provide clinicians and patients with accurate projections of long-term outcomes and should prompt investigation into developing strategies to minimize the development of cardiac damage before AVR and to regress damage after AVR, as both approaches are needed to optimize patient-centered outcomes.

The “Rise” of AI-Based Phenotyping

JACC: CARDIOVASCULAR IMAGING

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

The Need for Comprehensive Risk Phenotyping in Aortic Stenosis

Federico Fortuni, MD,[a,b,c] Paul A. Grayburn, MD[a]

Taking all these together, the clinical focus should not be on whether cardiac abnormalities are caused primarily by AS, comorbidities, or both, but rather on comprehensive risk phenotyping. Accordingly, multiple parameters of AS severity, patient comorbidities, and concomitant cardiac and noncardiac conditions could be combined to identify high risk patients (Figure 1). Applying artificial intelligence to large data sets of high-quality data offers the potential to identify high-risk patients who may need referral to heart teams experienced in diagnosis and treatment of AS. For some patients, further evaluation might reveal severe AS that was misclassified on an initial echocardiogram.

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M-L Phenotyping Vs. Conventional Multivariable Analysis

Global Epidemiology 8 (2024) 100168

Comparing AI/ML approaches and classical regression for predictive modeling using large population health databases: Applications to COVID-19 case prediction

Lise M. Bjerre [a,b,c,*,1], Cayden Peixoto [a], Rawan Alkurd [d], Robert Talarico [c,e], Rami Abielmona [d,f,1]

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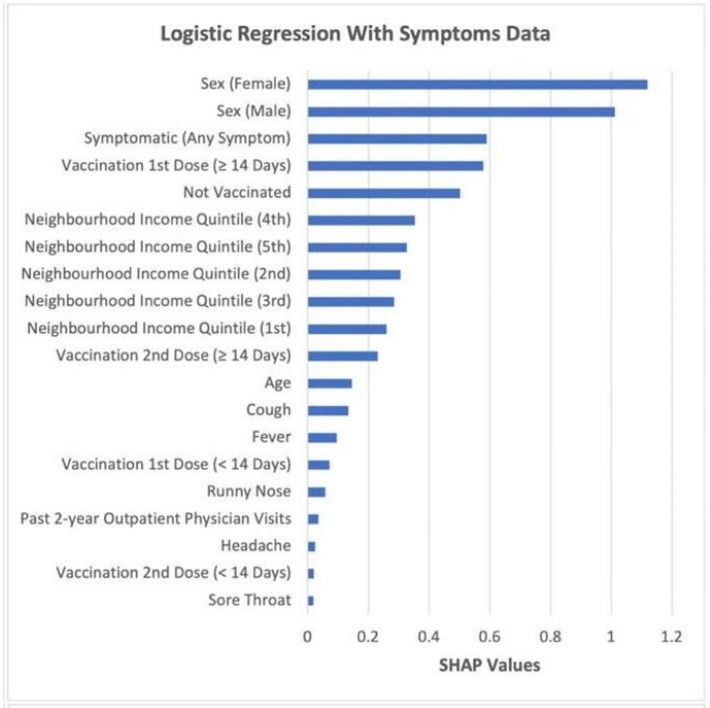

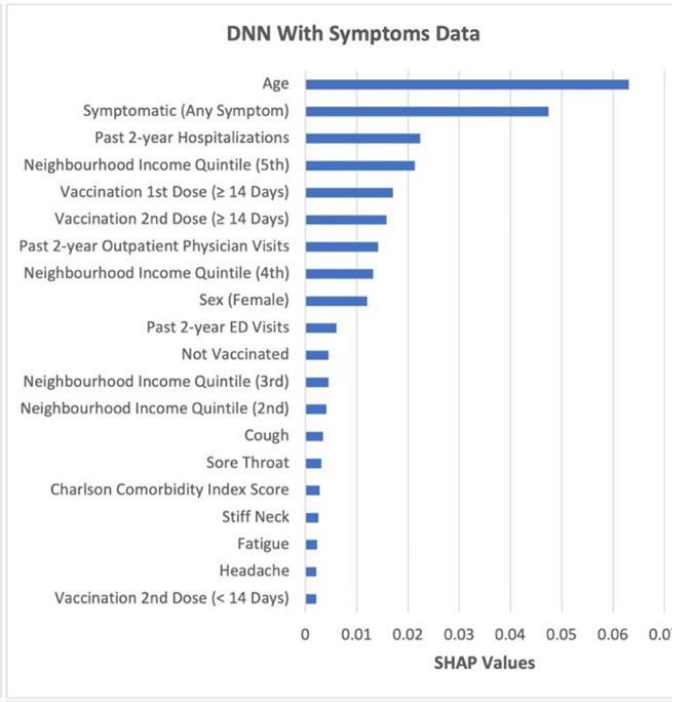

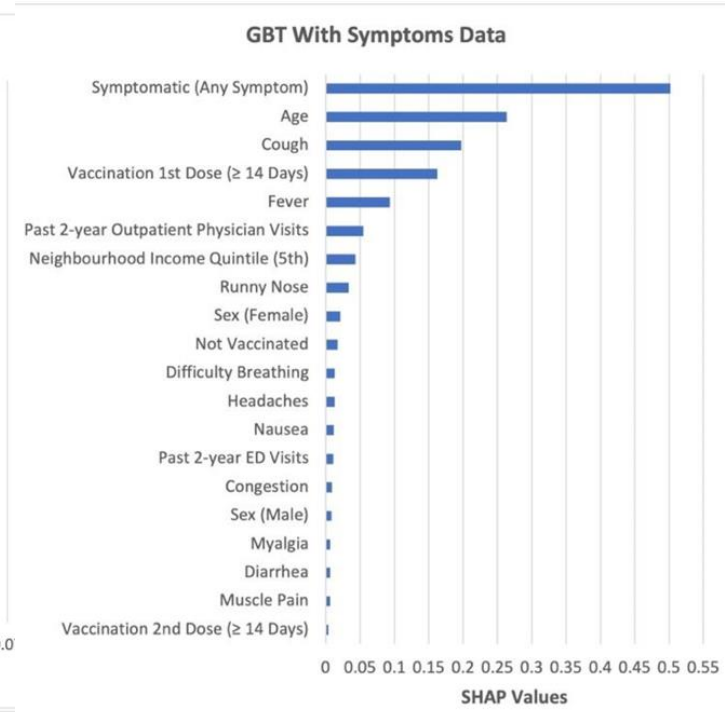

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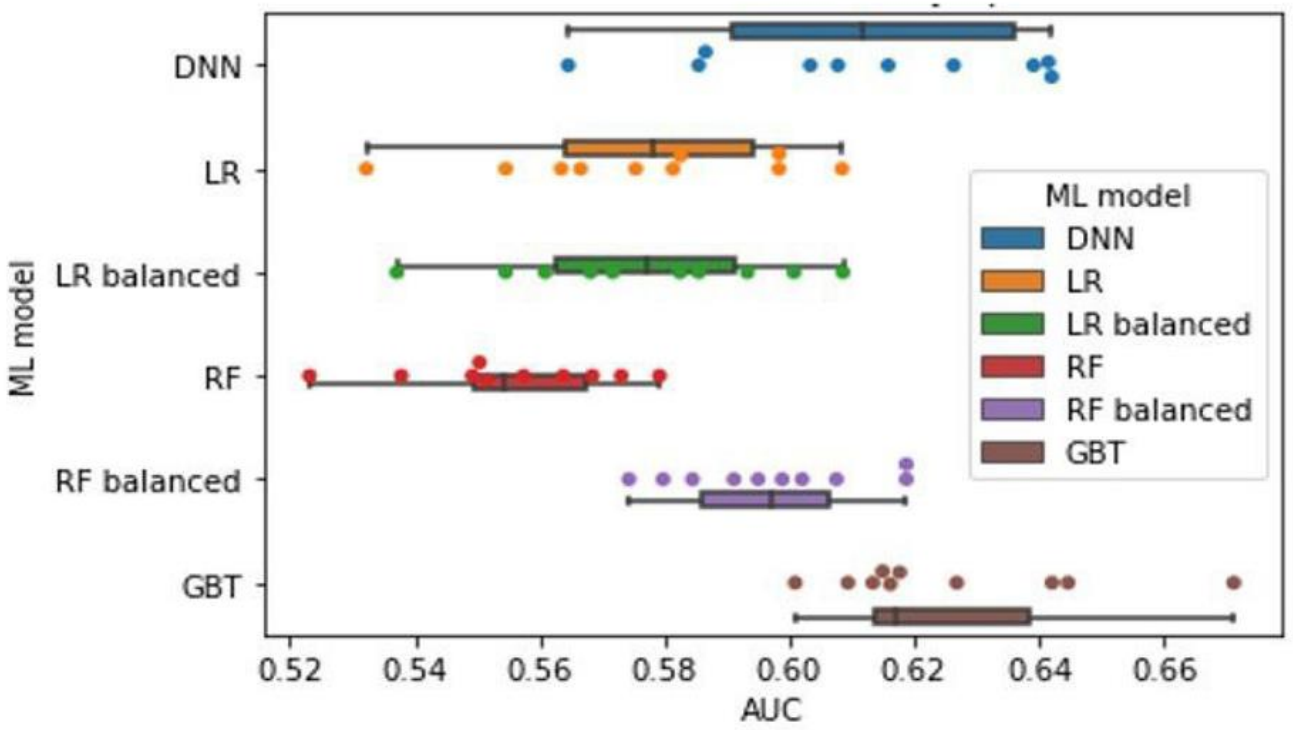
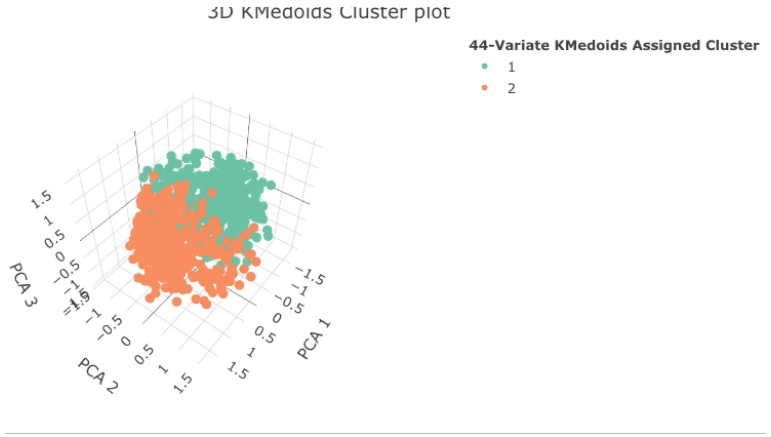
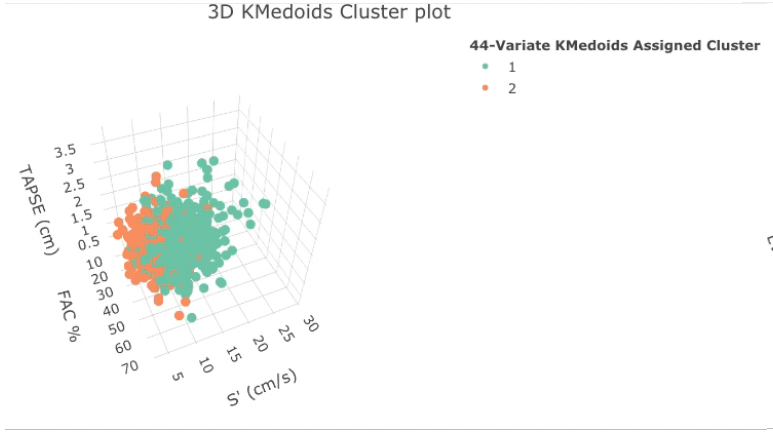
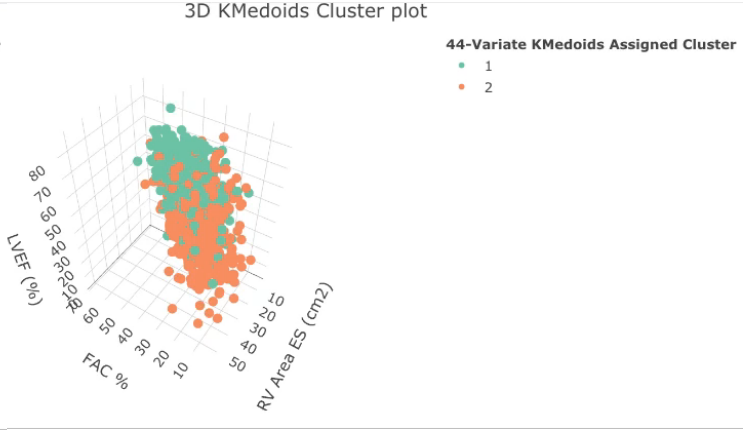


M-L Phenotyping

856 Patients with FTR







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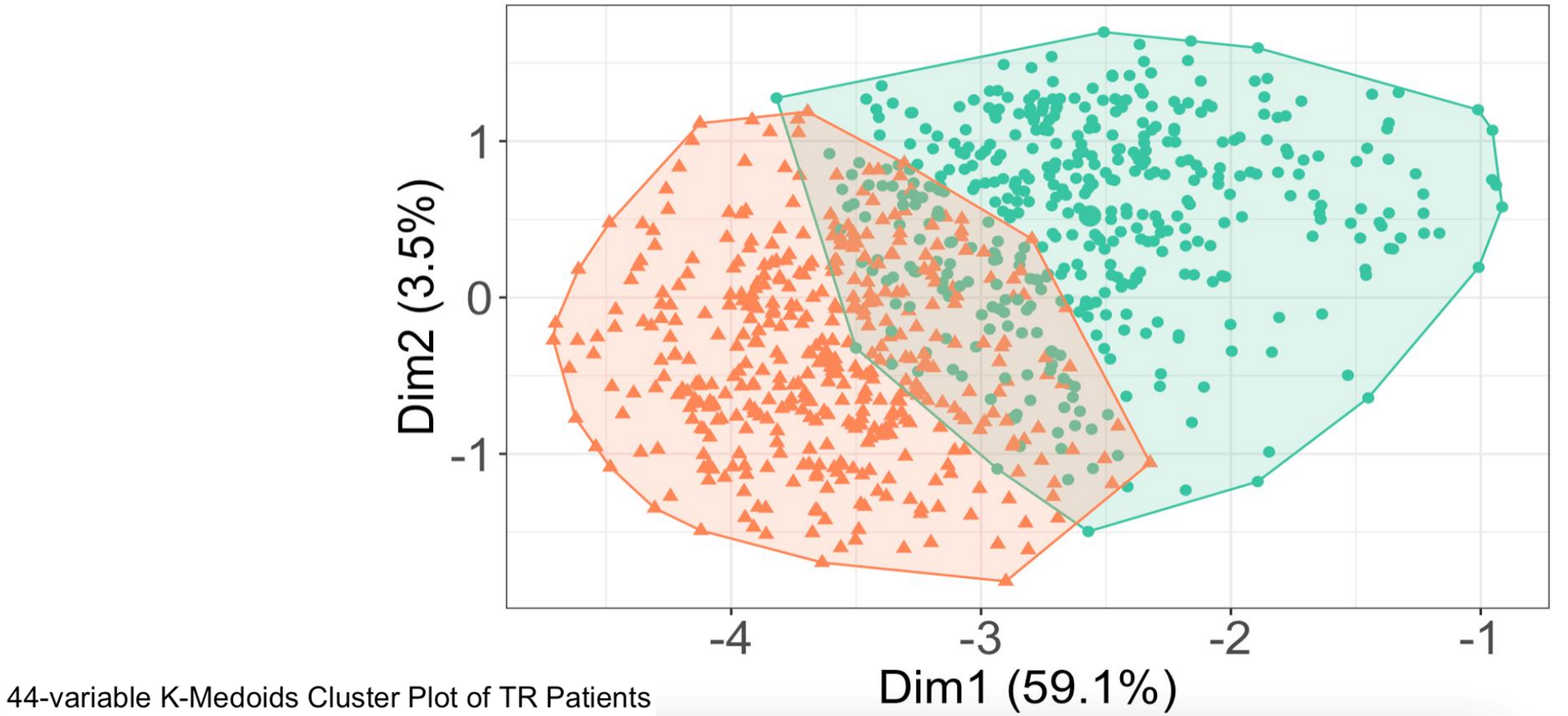
M-L Phenotyping - Clusters

856 Patients with FTR



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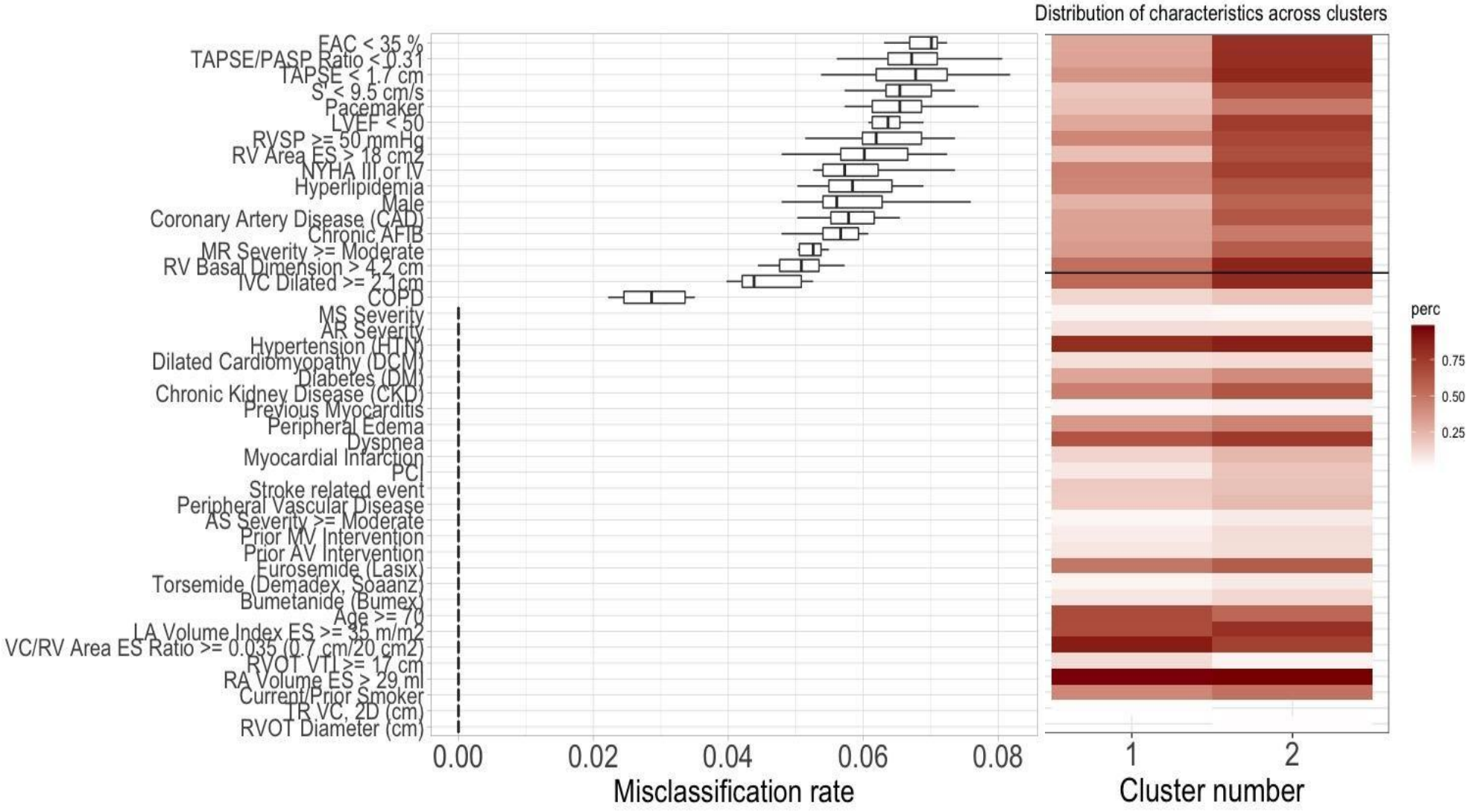
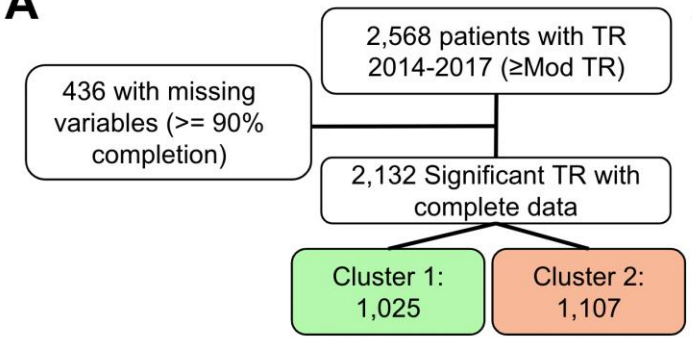
Distribution of Variables in Clusters

856 Patients with FTR



M-L Based Phenotyping TR

A



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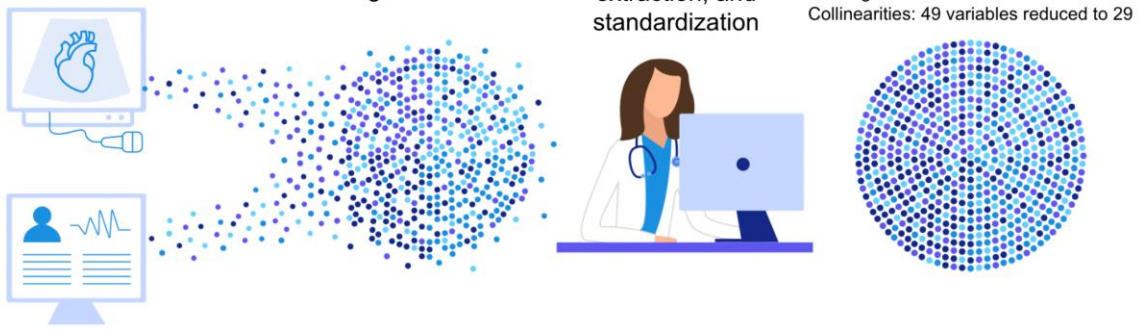

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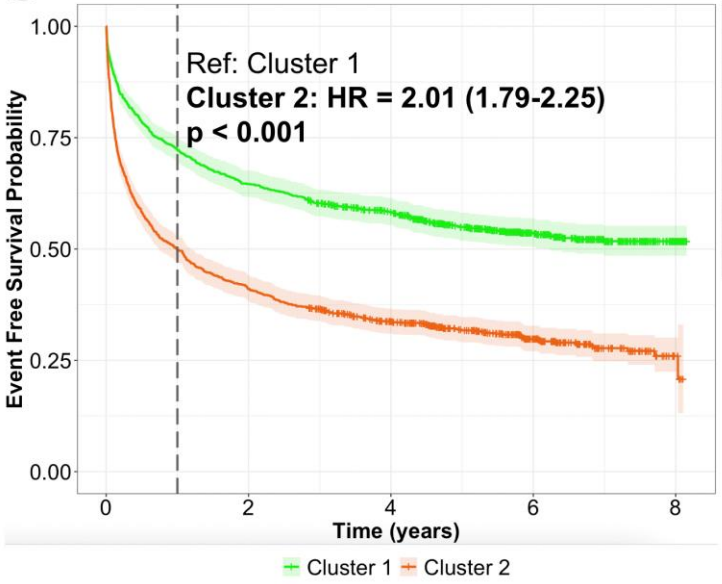


Total N (%)	Cluster 1 1025 (48%)	Cluster 2 1107 (52%)	p
LVEF (%)	56.49 (±11.7)	37.33 (±17.2)	<0.001
TR Peak Gradient (mmHg)	38.96 (±16.0)	39.63 (±14.7)	0.316
TAPSE/PASP Ratio	0.42 (±0.2)	0.32 (±0.2)	<0.001
RV Basal Dimension (cm)	4.16 (±0.9)	4.64 (±0.9)	<0.001
RA Area ES (cm2)	21.99 (±8.1)	25.11 (±7.9)	<0.001
AS Severity ≥ Moderate	45 (4%)	62 (6%)	0.233
MR Severity ≥ Moderate	275 (27%)	549 (50%)	<0.001
AR Severity ≥ Moderate	309 (30%)	272 (25%)	0.004
TR Severity > Moderate	468 (46%)	671 (61%)	<0.001

Echocardiographic variables

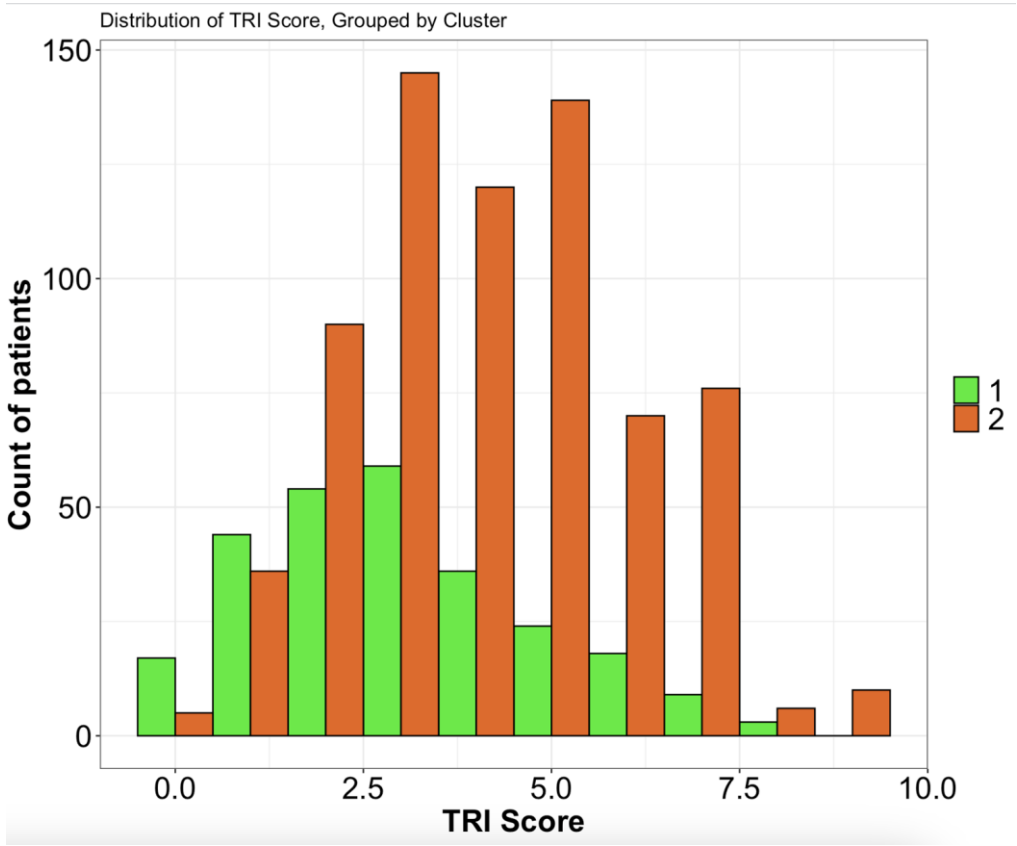
D

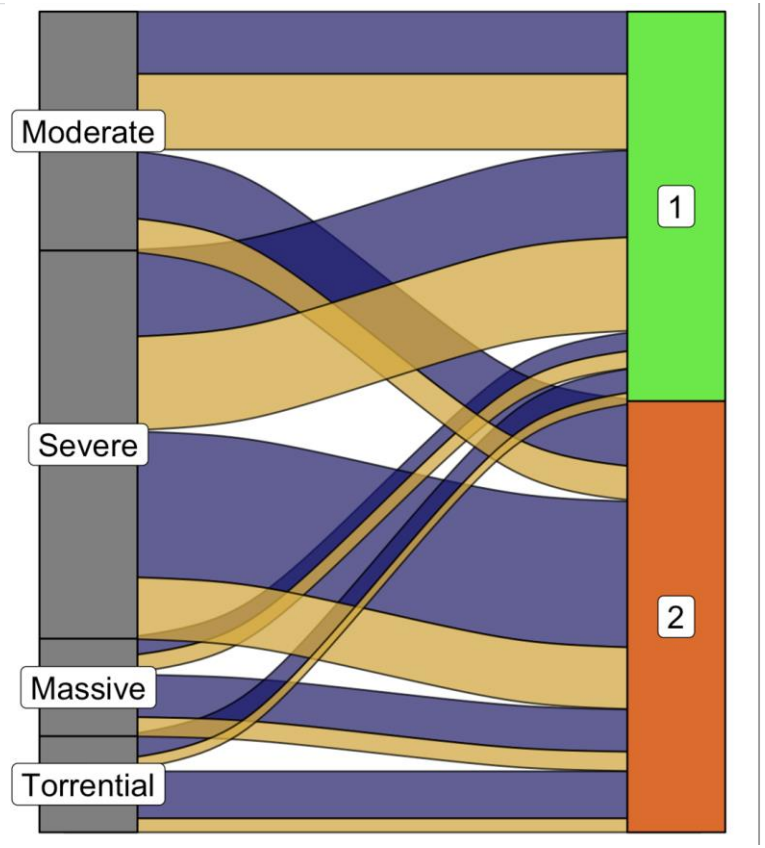
Total N (%)	Cluster 1 1025 (48%)	Cluster 2 1107 (52%)	p
Male	288 (28%)	604 (55%)	<0.001
On Diuretics	339 (33%)	955 (86%)	<0.001
Pacemaker	179 (17%)	464 (42%)	<0.001
Percutaneous Coronary Intervention	39 (4%)	160 (14%)	<0.001
NYHA III or IV	349 (34%)	737 (67%)	<0.001
Dyspnea	600 (59%)	826 (75%)	<0.001
Current/Prior Smoker	381 (37%)	626 (57%)	<0.001
Atrial Fibrillation (AFIB)	482 (47%)	662 (60%)	<0.001
Hypertension (HTN)	794 (77%)	974 (88%)	<0.001
Coronary Artery Disease (CAD)	266 (26%)	738 (67%)	<0.001
Dilated Cardiomyopathy (DCM)	65 (6%)	160 (14%)	<0.001
Previous Myocarditis	6 (1%)	36 (3%)	<0.001
Myocardial Infarction	71 (7%)	293 (26%)	<0.001
Hyperlipidemia	409 (40%)	702 (63%)	<0.001
Diabetes (DM)	236 (23%)	487 (44%)	<0.001
COPD	105 (10%)	235 (21%)	<0.001
Chronic Kidney Disease (CKD)	322 (31%)	629 (57%)	<0.001
Peripheral Edema	312 (30%)	507 (46%)	<0.001
Stroke related event	128 (12%)	232 (21%)	<0.001
Peripheral Vascular Disease	101 (10%)	227 (21%)	<0.001

Gender and comorbidities

Tri-Score and TR Severity Distribution In The Phenotypes

Predicting Event-Free Survival





AS “Phenotypes”

Clinical “Classification”

Circulation

ON MY MIND

New Classification to Describe Clinical Presentation in Aortic Stenosis: Stable, Progressive, and Acute Valve Syndrome

Table. **Proposed clinical presentation classification for aortic stenosis**

Clinical presentation of AS	SVS	PVS	AVS
Description	Presentation with no signs or symptoms	Presentation with mild and progressive signs or symptoms	Presentation with acute, advanced, or severe signs or symptoms
Signs and symptoms	None	Presentation with progressive mild symptoms such as fatigue, dyspnea, NYHA class II symptoms, lightheadedness, angina CCS 2 Increase in BNP or NT-proBNP ≥1.5 and <3 times the above the upper limit of normal adjusted for age	Cardiac arrest or resuscitated sudden death Cardiogenic shock Acute heart failure with pulmonary edema NYHA class III–IV Syncope Angina CCS 3-4 New-onset atrial fibrillation New-onset ventricular fibrillation Increase in BNP or NT-proBNP 3 times above the upper limit of normal adjusted for age. New decrease in left ventricular ejection fraction >10%
Association with death or HFH 2 y after AVR from previous litterature5	Reference	Death: adjusted HR, 1.1 (95% CI, 0.9–1.4) HFH: adjusted HR, 1.5 (95% CI, 1.3–1.8) Death or HFH: adjusted HR, 1.4 (95% CI, 1.2–1.6)	Death: adjusted HR, 2.2 (95% CI, 1.8–2.6) HFH: adjusted HR, 3.3 (95% CI, 2.9–3.8) Death or HFH: adjusted HR, 2.9 (95% CI, 2.6–3.3)
Trigger type (not mutually exclusive)	Type 1 (primary): Mainly due to the valve disease per se or its progression Type 2 (secondary): Due to or associated with another potential causal condition (eg, ischemic coronary artery disease, medical noncompliance, rapid atrial fibrillation, cardiac amyloidosis, bleeding, non–valve-related sepsis or infection, exacerbated COPD) Type 3: Due to valve infection (endocarditis) or thrombosis The degree of causality should be qualified further as probable, possible, or not related.		
Valve type	Native Autograft Homograft Bioprosthesis Mechanical valve		

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The aim of this new classification is to better characterize and classify clinical presentation of patients with AS. Similar to the nomenclature used in coronary artery disease such as acute coronary syndrome, the term AVS captures a group of patients presenting with a specific phenotype of signs and symptoms, having a different prognosis than patients with more stable disease, and most likely requiring different care such as pharmacotherapy or urgent invasive therapy. Compared with patients with no signs or symptoms, patients presenting with AVS clearly have worse outcomes after valve replacement (Table).[5] Identifying and treating patients before they evolve to a severe and decompensated disease state would be ideal. Such classification could be useful to better identify and prioritize patients who would need urgent treatment and for monitoring the proportion of patients treated in each category (stable valve syndrome versus PVS versus AVS) as a quality metric for institutions and national registries. It could also be important for the research community for trial and study design, to better describe and stratify the enrolled population, to serve as an end point for natural history study, to assess pharmacotherapy, or to better capture outcomes beyond the usual end points of death, stroke, and heart failure hospitalization. It would also be interesting to evaluate the incidence of AVS compared with PVS among patient presenting with moderate AS or other types of AS such as low-flow, low-gradient AS and to assess its triggers and determinants. Last, as mentioned, it could easily be expanded to other valve diseases (eg, aortic regurgitation, mitral regurgitation).

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