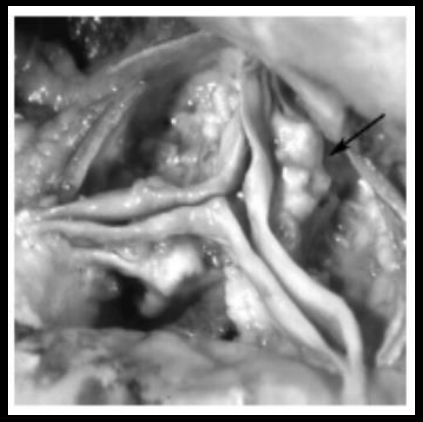
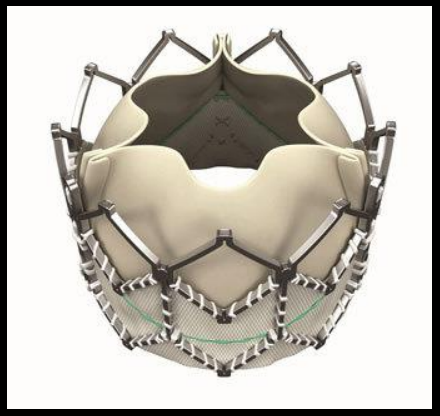
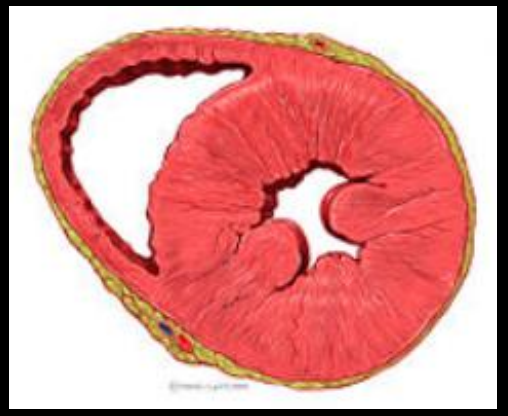
Assessing LV Health in the Management and Treatment of Aortic Stenosis

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ACC – Evolving Valve Management Strategies Roundtable
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Disclosures

- Grant funding
  - American Heart Association
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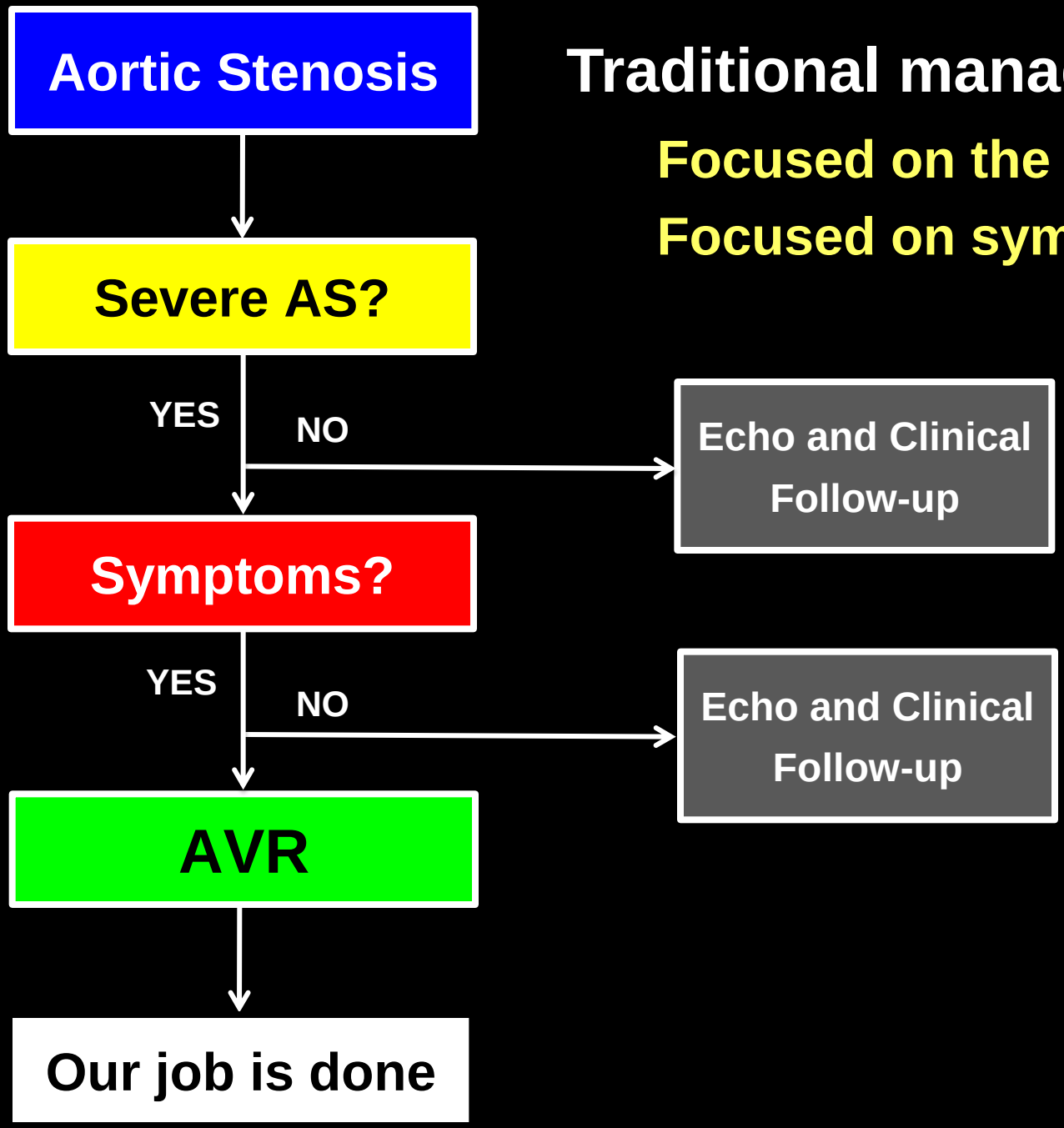
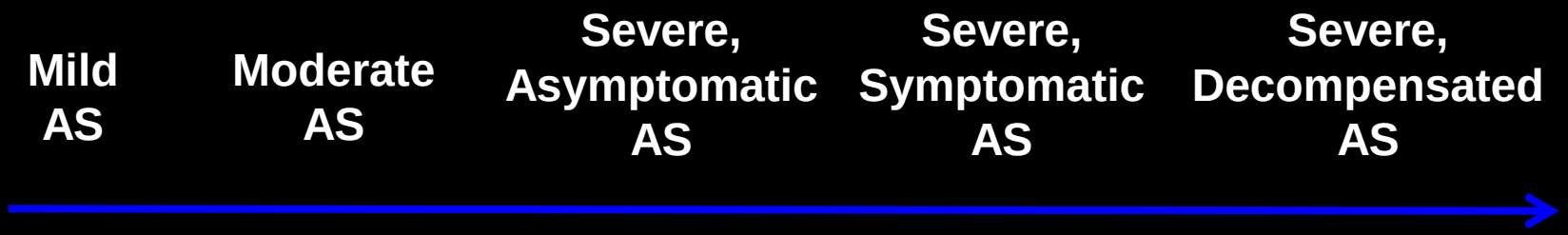
  - Barnes-Jewish Hospital Foundation
- Industry
  - Assay support: Roche and BG-Medicine
  - Scientific Advisory Board: Roche
- Off-label use
  - I will discuss off-label uses for PDE5 inhibitors (sildenafil and tadalafil) and investigational biomarkers

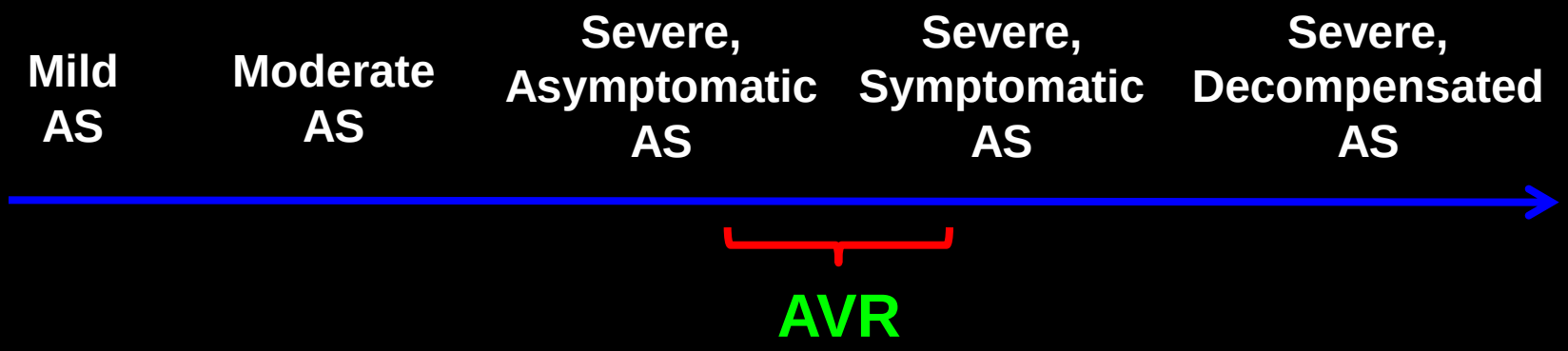


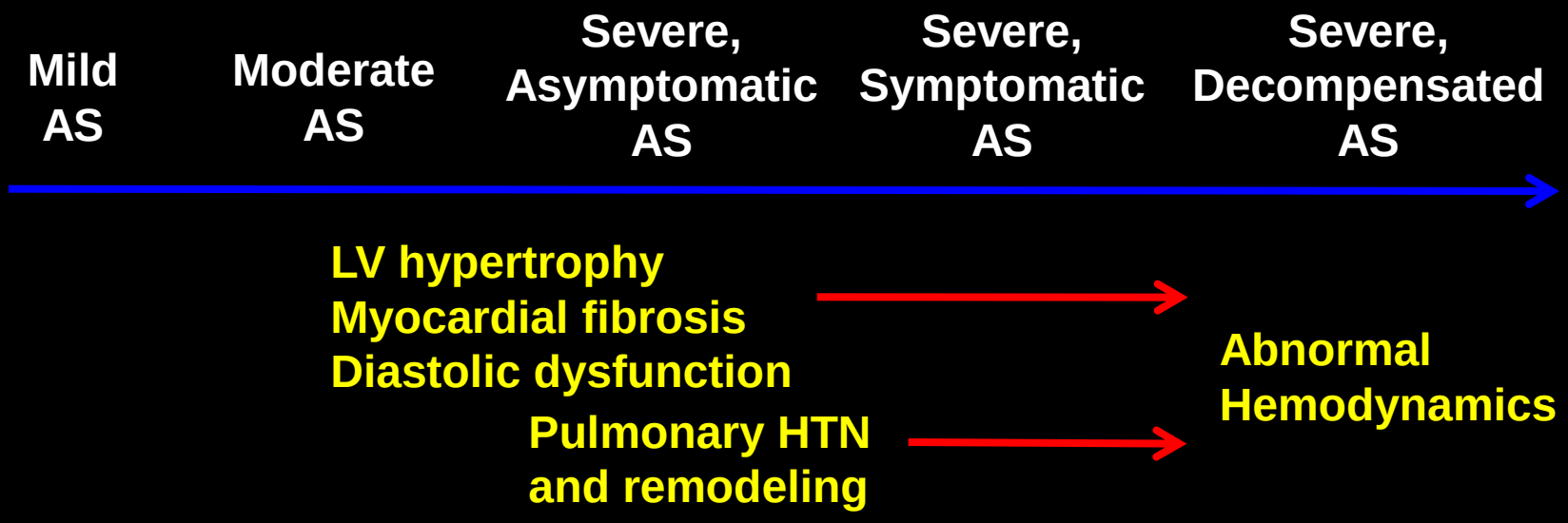
Traditional management of AS

Focused on the valve

Focused on symptoms


Mild AS
Moderate AS
Severe, Asymptomatic AS
Severe, Symptomatic AS
Severe, Decompensated AS


Mild AS
Moderate AS
Severe, Asymptomatic AS
Severe, Symptomatic AS
Severe, Decompensated AS
AVR


Mild AS
Moderate AS
Severe, Asymptomatic AS
Severe, Symptomatic AS
Severe, Decompensated AS
LV hypertrophy
Myocardial fibrosis
Diastolic dysfunction
Pulmonary HTN and remodeling
Abnormal Hemodynamics

Goals of Therapy in AS

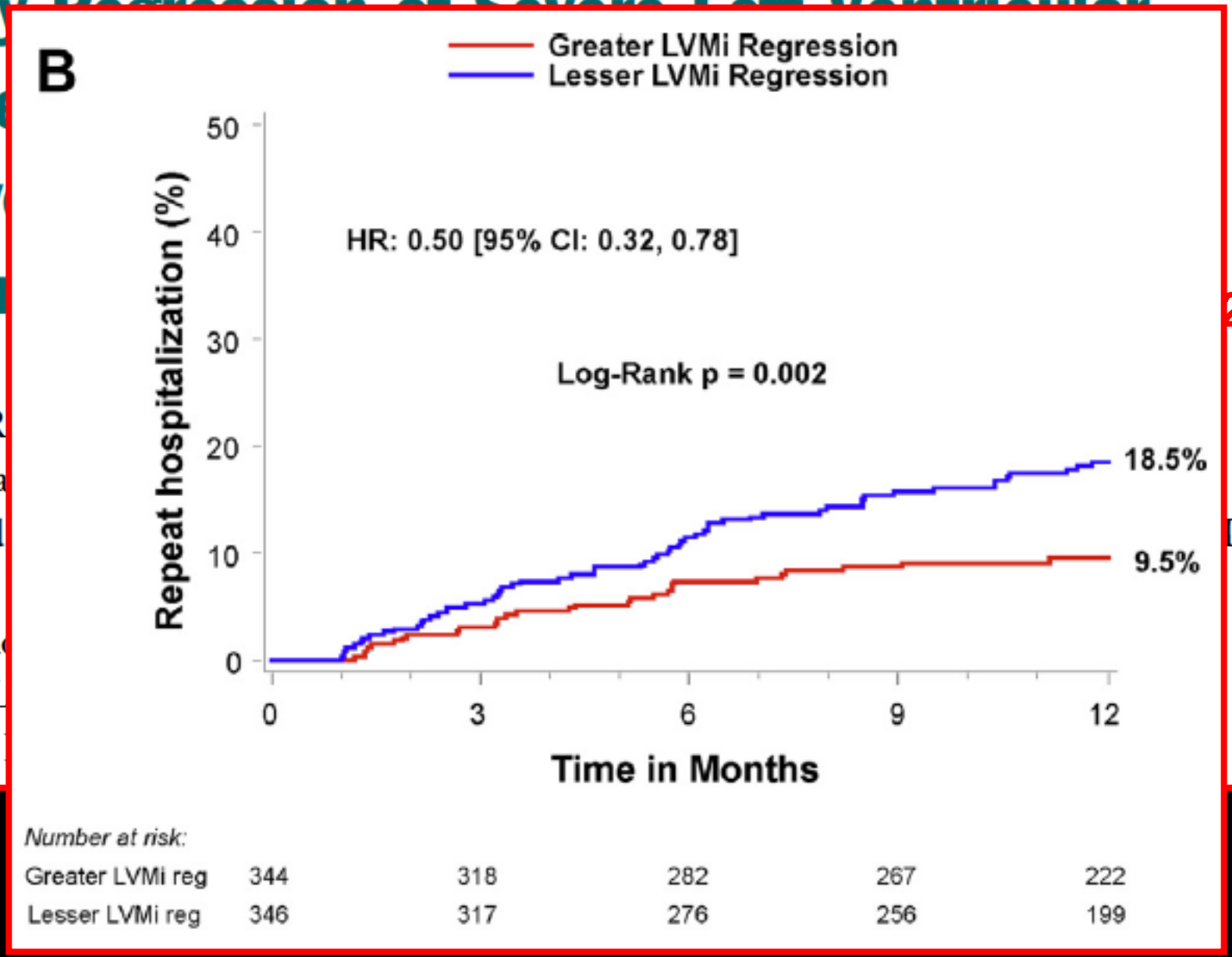
- Optimize survival
- Improve symptoms
- Optimize quality of life and functional capacity
- Avoid / limit hospitalizations

Much depends on LV Health

Early Regression of Severe Left Ventricular Hypertrophy Valve Decr

2014

Brian R PhD,‡
Rebecca
Richard D,††
Wilson
Stamati
Kevin L
Martin



Impact of Myocardial Fibrosis in Patients With Symptomatic Severe Aortic Stenosis

Frank Weidemann, MD*; Sebastian Herrmann*; Stefan Störk, MD; Markus Niemann, MD; Stefan Frantz, MD; Volkmar Lange, MD; Meinrad Beer, MD; Stefan Gattenlöhner, MD; Wolfram Voelker, MD; Georg Ertl, MD; Jörg M. Strotmann, MD

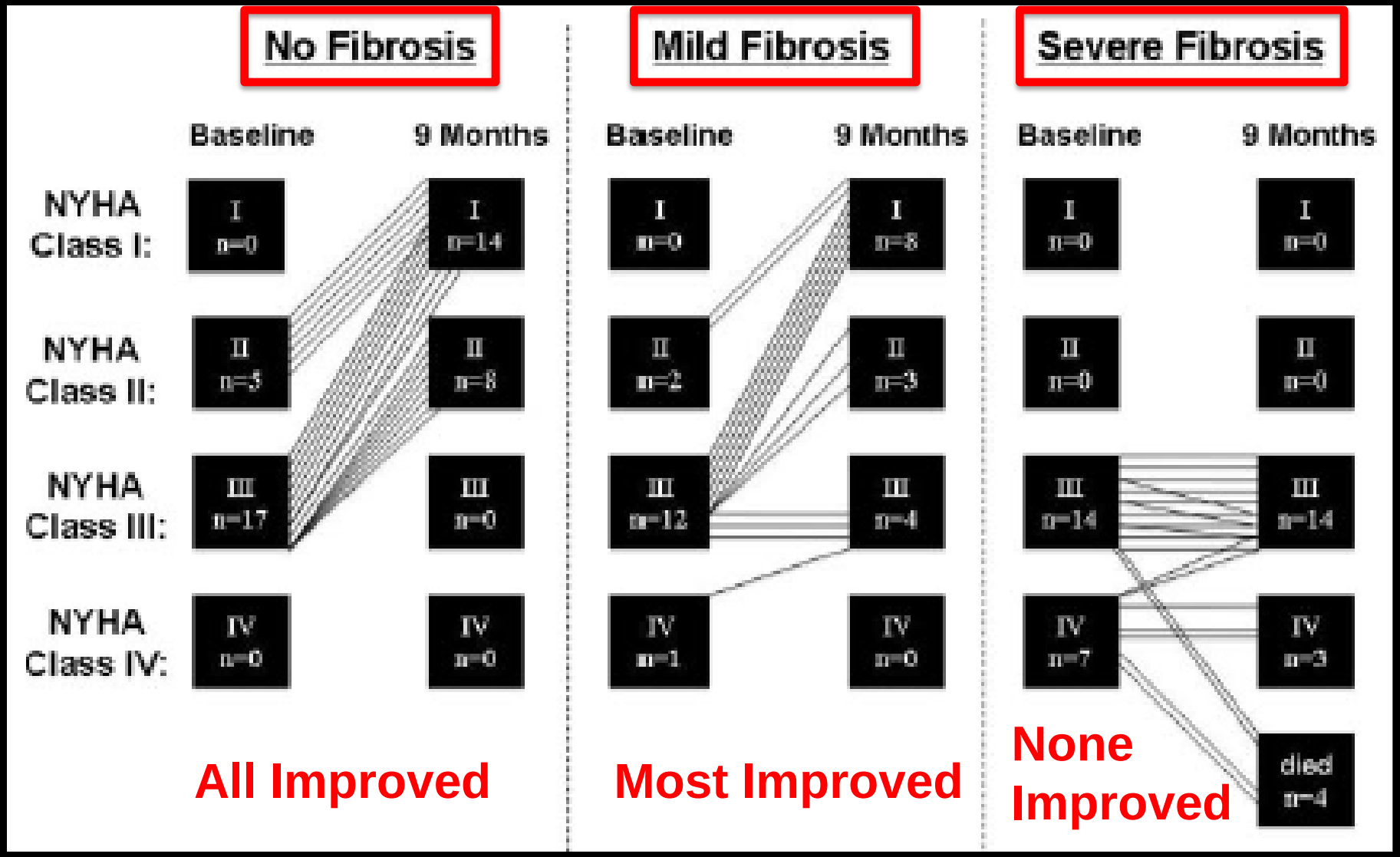
Circulation 2009

Background—In this prospective follow-up study, the effect of myocardial fibrosis on myocardial performance in symptomatic severe aortic stenosis was investigated, and the impact of fibrosis on clinical outcome after aortic valve replacement (AVR) was estimated.

Methods and Results—Fifty-eight consecutive patients with isolated symptomatic severe aortic stenosis underwent extensive baseline characterization before AVR. Standard and tissue Doppler echocardiography and cardiac magnetic resonance imaging (late-enhancement imaging for replacement fibrosis) were performed at baseline and 9 months after AVR. Endomyocardial biopsies were obtained intraoperatively to determine the degree of myocardial fibrosis. Patients were analyzed according to the severity of interstitial fibrosis in cardiac biopsies (severe, n=21; mild, n=15; none, n=22). The extent of histologically determined cardiac fibrosis at baseline correlated closely with New York Heart Association functional class and markers of longitudinal systolic function (all $P<0.001$) but not global ejection fraction or aortic valve area. Nine months after AVR, the degree of late enhancement remained unchanged, implying that AVR failed to reduce the degree of replacement fibrosis. Patients with no fibrosis experienced a marked improvement in New York Heart Association class from 2.8 ± 0.4 to 1.4 ± 0.5 ($P<0.001$). Only parameters of longitudinal systolic function predicted this functional improvement. Four patients with severe fibrosis died during follow-up, but no patient from the other groups died.

Conclusions—Myocardial fibrosis is an important morphological substrate of postoperative clinical outcome in patients with severe aortic stenosis and was not reversible after AVR over the 9 months of follow-up examined in this study. Because markers of longitudinal systolic function appear to indicate sensitively both the severity of myocardial fibrosis and the clinical outcome, they may prove valuable for preoperative risk assessment in patients with aortic stenosis. (***Circulation***. **2009;120:577-584.**)

NYHA Class – Change after AVR



Weidemann et al. Circulation 2009.

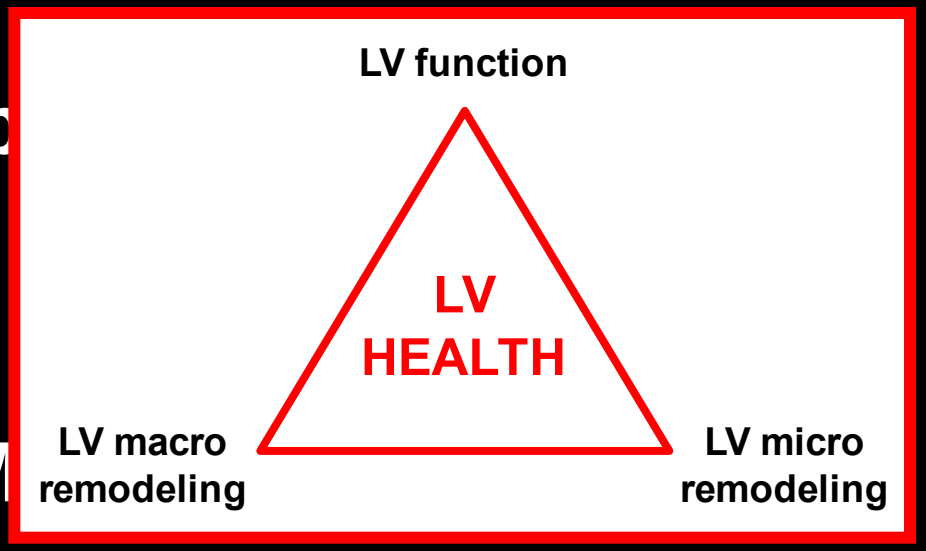
Indicators

Hyp

Flow

Systolic function

M



LV Health

Influencers

Aging

AS severity

Diabetes

Blood pressure

Metabolic

Sex

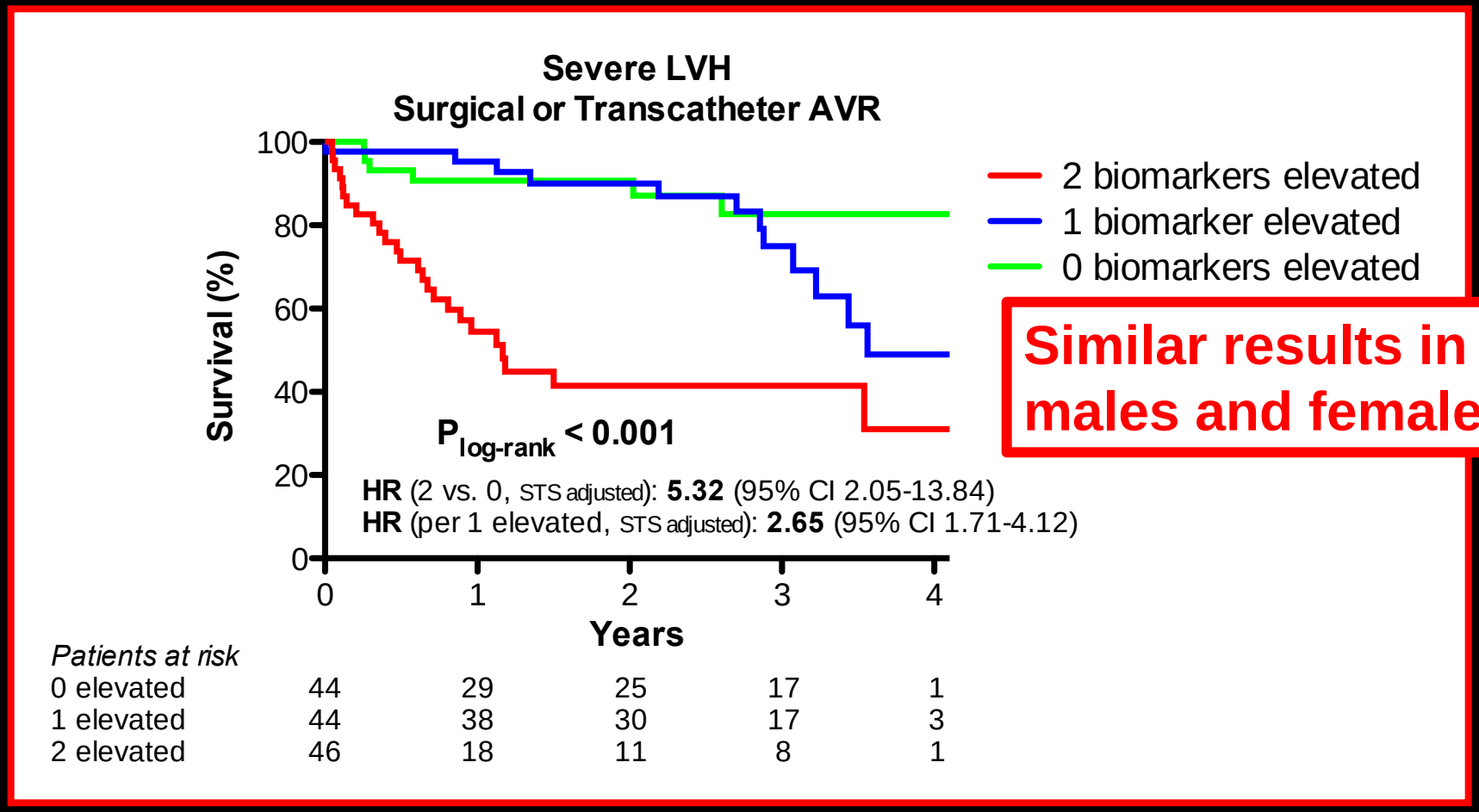
Vascular stiffness

Medications

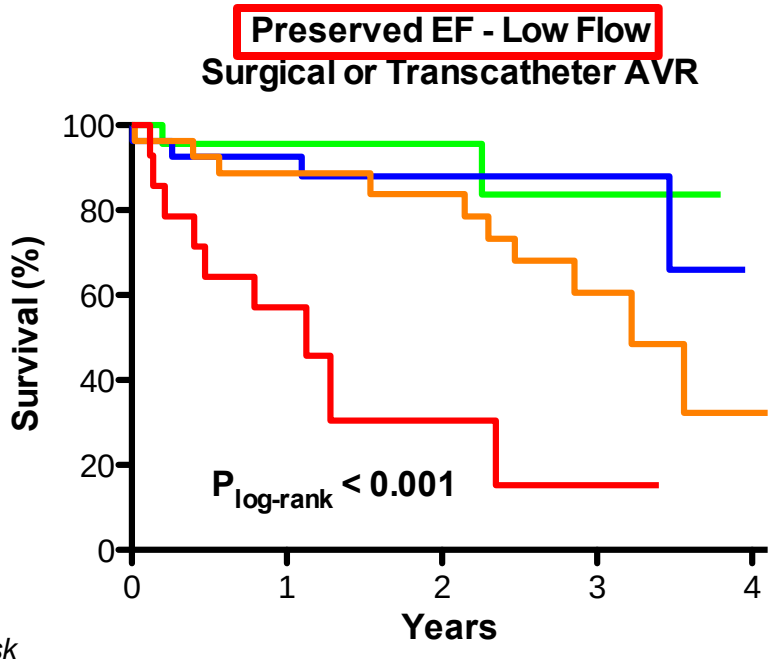
Assessment of LV Health

- **Imaging**
  - Echocardiography
    - LV strain – longitudinal, circumferential, radial, 3D
  - MRI
    - Fibrosis
- **Biomarkers**
  - Natriuretic peptides
  - Others
  - Multimarker approaches

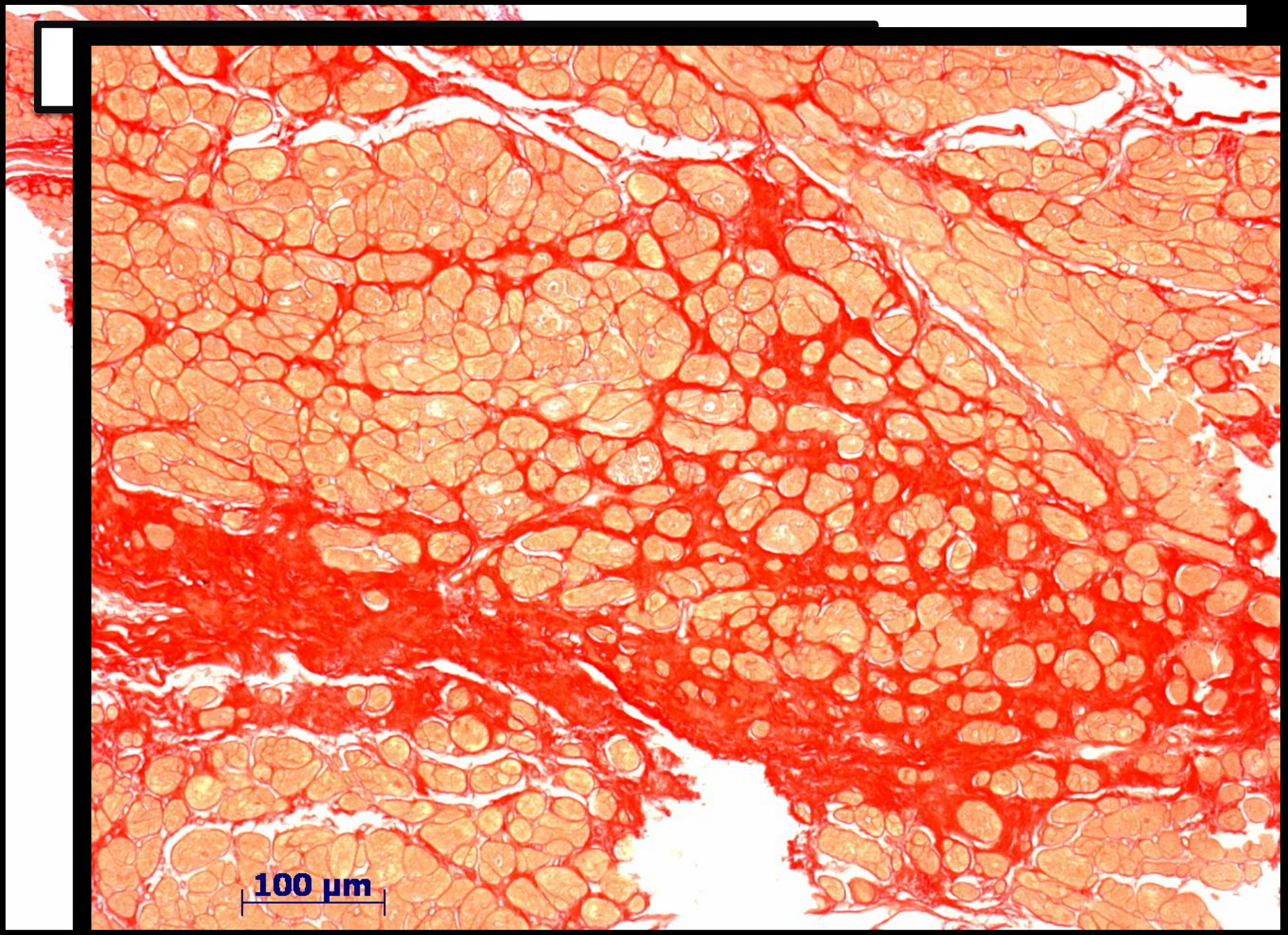
Severe LVH
Mortality by # Biomarkers Elevated



Preserved EF
Mortality by # Biomarkers Elevated



Patients at risk					
0 elevated	23	16	9	5	0
1 elevated	27	20	12	6	0
2 elevated	27	21	16	8	1
3 elevated	14	6	2	1	0

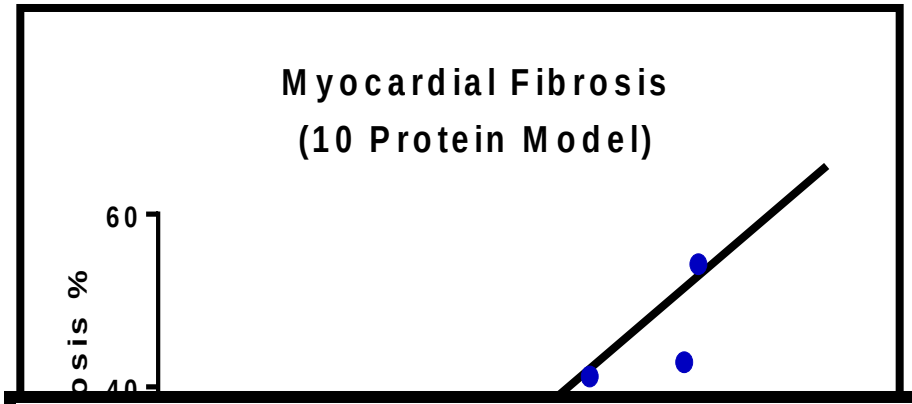

100 µm

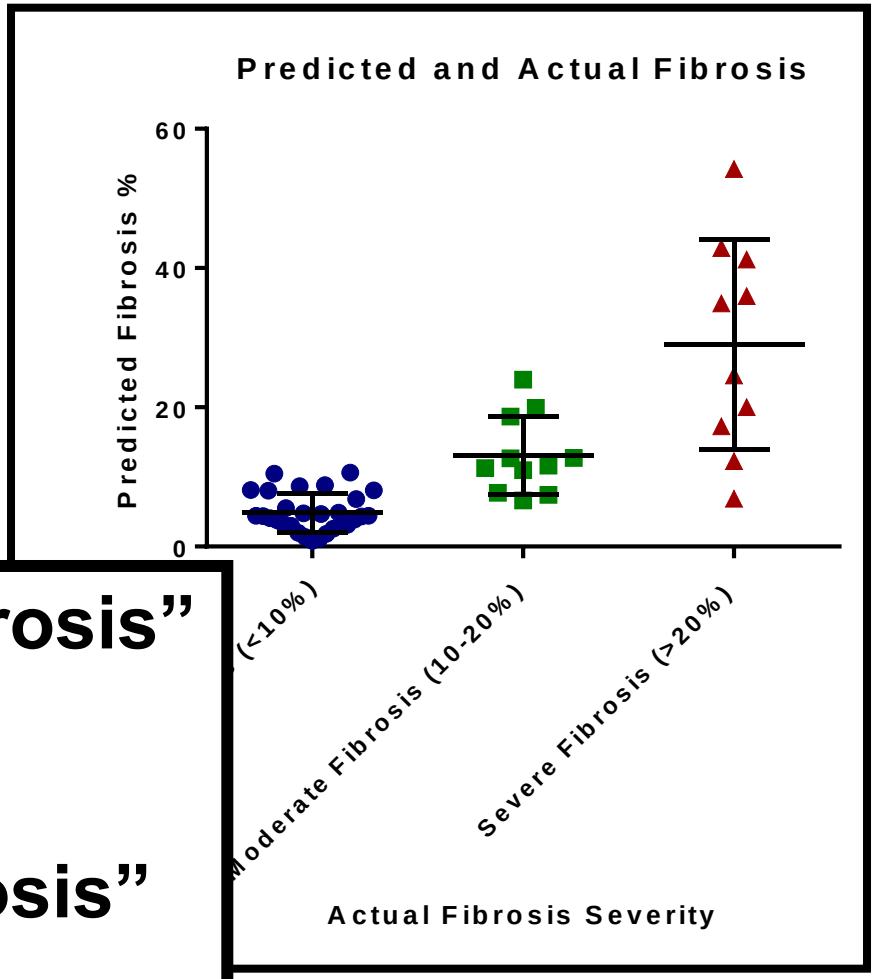
Myocardial Fibrosis

	Fibrosis Tertile 1 (n=16)	Fibrosis Tertile 2 (n=17)	Fibrosis Tertile 3 (n=17)	p-value
GDF15	1394 (1255, 1761)	1065 (738, 2104)	1789 (1122, 2242)	0.47
sST2	24 (18, 31)	27 (19, 43)	28 (24, 40)	0.17
Gal3	16 (12, 20)	17 (14, 19)	18 (13, 20)	0.56
MPO	258 (73, 513)	98 (52, 253)	73 (62, 297)	0.22
hs-cTnT	17 (14, 24)	22 (14, 24)	30 (20, 45)	0.017
NT-proBNP	467 (334, 1332)	500 (227, 749)	936 (403, 4634)	0.11
hsCRP	3.9 (1.2, 9.8)	1.7 (1.5, 3.7)	3.8 (1.9, 12.0)	0.44
MCP-1	185 (161, 232)	181 (166, 250)	213 (208, 235)	0.34

Lindman et al. Heart 2015.

Proteomics Approach





Prediction of "minimal fibrosis"

- **PPV 0.87**
- **NPV 0.89**

Prediction of "severe fibrosis"

- **PPV 0.875**
- **NPV 0.929**

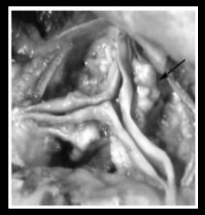
Model R^2 = 0.82 ($P < 0.0001$)

Cross-validated Q^2 = 0.72

		Predicted		
Actual Severity	Total Subjects	Minimal	Moderate	Severe
Minimal	29	27	2	0
Moderate	11	3	7	1
Severe	10	1	2	7

Optimizing LV Health – Improving Patient Outcomes

Pressure Overload from AS

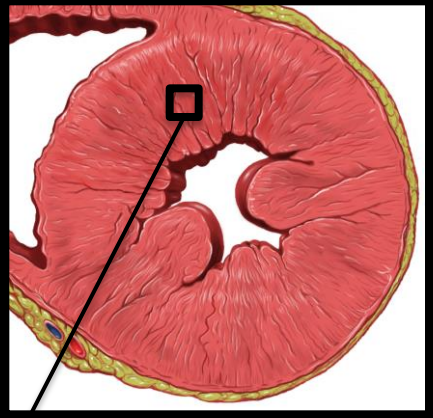


Unhealthy LV

Hypertrophic Remodeling
Cardiac Fibrosis
LV Dysfunction

Influencers

Modifiers



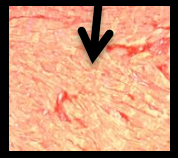
Survival

QoL

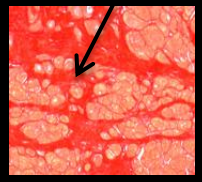
Freedom from heart failure

Avoid hospitalization

Optimal functional capacity



No/minimal fibrosis



Severe fibrosis

Medical therapy to optimize LV health?

Medical therapy to optimize LV health?

Optimizing LV Health Improving Patient Outcomes

- Sensitive surveillance
  - Imaging (Echo, MRI)
  - Biomarkers
- Integrate function and remodeling
- Earlier valve replacement in select patients to optimize long-term LV performance
- Adjunctive medical therapy
  - Prevent “LV unhealth” pre-AVR and/or
  - Help restore LV health after AVR

Thank You