

TRACS Study and Cardiac Cases

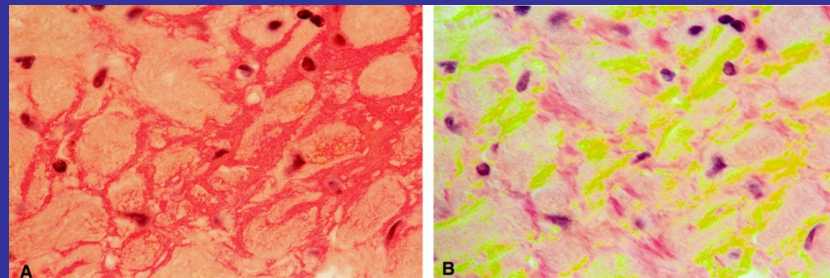
**Morbidity and Mortality of
Transthyretin (TTR) Amyloid Cardiomyopathy:
*TR*ansthyretin Amyloidosis Cardiac Study
(TRACS)
A Prospective Evaluation**

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Background

- Cardiac amyloidosis is a devastating disease that results from protein deposition in the cardiac interstitium producing symptoms of congestive heart failure, dysrhythmias, and death
 - Primary (AL) amyloidosis – immunoglobulin light chain
 - Familial amyloidosis – mutant transthyretin (TTR)
 - Age-related amyloidosis – wild-type transthyretin (TTR)

Characteristic Congo Red Staining in TTR Cardiac Amyloidosis



Congo red

Polarized light

Background

- TTR is a liver-produced protein that transports thyroid hormone, dissociates from tetrameric form to precipitate as amyloid
- TTR amyloidosis can cause cardiomyopathy (ATTR-CM) and/or polyneuropathy with ethnic predilections
 - Val30Met – Portuguese descent
 - Thr60Ala – Northern Irish descent
 - Val122Ile – African descent
 - Allele frequency 4% US African American population (Jacobson, *NEJM* 1997)
 - Contribution of Ile122 heterozygosity to heart failure and death among African Americans is unknown, possibly 10% over age 60 years with advanced heart failure (Buxbaum, *JACC* 2006)
 - Age-related TTR amyloid cardiomyopathy prevalence rate by autopsy of >16% in patients >80 years old (Cornwall, *Am J Med* 1985)

Background

- Overall prognosis of age-related and ATTR-CM better than AL (Ng, *Arch Int Med* 2005; Dubrey, *Heart* 1997)
- Definitive treatment for ATTR-CM is heart and/or liver transplantation
 - Novel small molecule strategies for TTR-stabilization to halt progression of disease
- Rate of disease progression of untreated ATTR-CM is unknown, varies with specific mutation
 - Essential to establish efficacy of treatments and perform comparisons

TRACS Study Design

❑ **Objective:** To examine the natural history and disease progression in patients with ATTR-CM

❑ **Design:**

- Longitudinal, observational, two year study
- Target Enrollment: 25 to 35 patients with ATTR-CM:
 - Familial: Positive TTR genotype for V122I mutation and biopsy positive for amyloid, *or*
 - Age-Related: Normal TTR genotype, biopsy positive for amyloid and for TTR
 - Primary (AL) amyloid excluded
- Assessments (performed at baseline and every 6 months):
 - 6 min walk test (6MWT)
 - NYHA, KCCQ QOL, patient global assessment
 - ECG
 - Cardiac markers NT-Pro-BNP, Troponin,
 - Echo, Cardiac MRI (central interpretation)

Preliminary Results

- 29 patients enrolled across 5 US sites (Johns Hopkins, Columbia, Boston University, Mayo, U of Chicago)
 - Enrollment April 2006 – April 2008
 - On-going data analysis
 - Average study participation duration: 492 days (range 31-865 days)
- Preliminary baseline and month 12 results to be presented
 - Data to be presented by survival status and mutation status

Demographics & Baseline Characteristics

		Total N=29	Age Related N=18	V122I N=11	P Value*
Age (SD)	Mean	73.8 (5.7)	75.8 (5.6)	71.1 (4.9)	<0.05
Race	Caucasian	62%	18 (100%)	0	<0.001
	Black	38%	0	11 (100%)	
Gender	Male	27 (93%)	18 (100%)	9 (82%)	ns
	Female	2 (7%)	0	2 (18%)	
Time from symptom onset (months) (SD)		32.1 (29.4)	36.9 (34.1)	24.2 (18.4)	ns
Time from diagnosis (months) (SD)		11.1 (12.6)	10.4 (7.6)	12.2 (18.5)	ns
Avg. follow-up (days) (SD)		492 (239)	495 (229)	487 (266)	ns

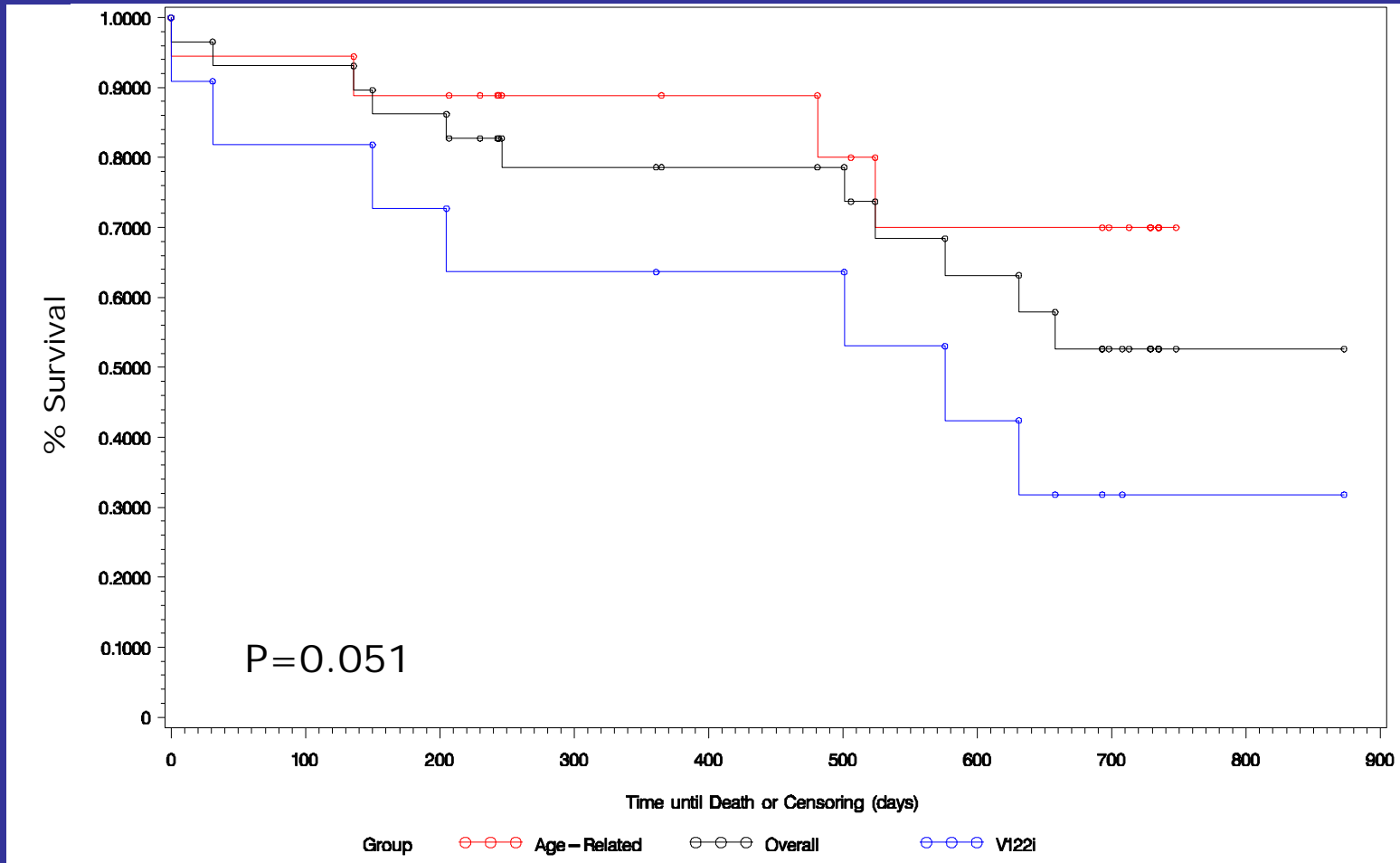
Morbidity & Mortality

	Total N=29	Age Related N=18	V122I N=11	P Value
Death*	11 (38%)	4 (22%)	7 (64%)	<0.05
Cardiovascular Hosp.	10 (35%)	3 (17%)	7 (64%)	<0.01
Death* or CV hosp	16 (55%)	6 (33%)	10 (91%)	0.025

Average Follow-up time 492 days

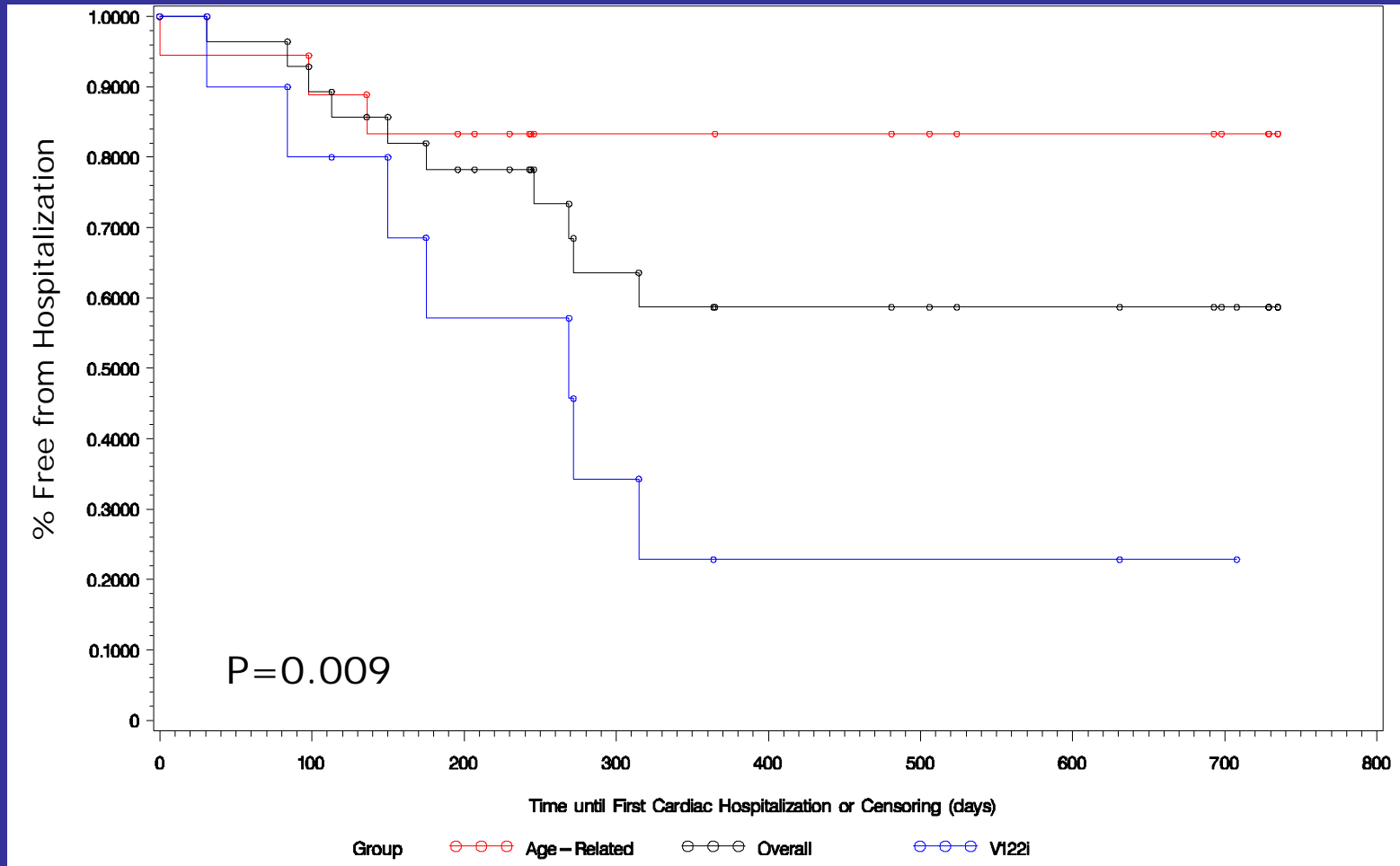
* Includes one patient who underwent cardiac transplant

Time to Death from Enrollment*

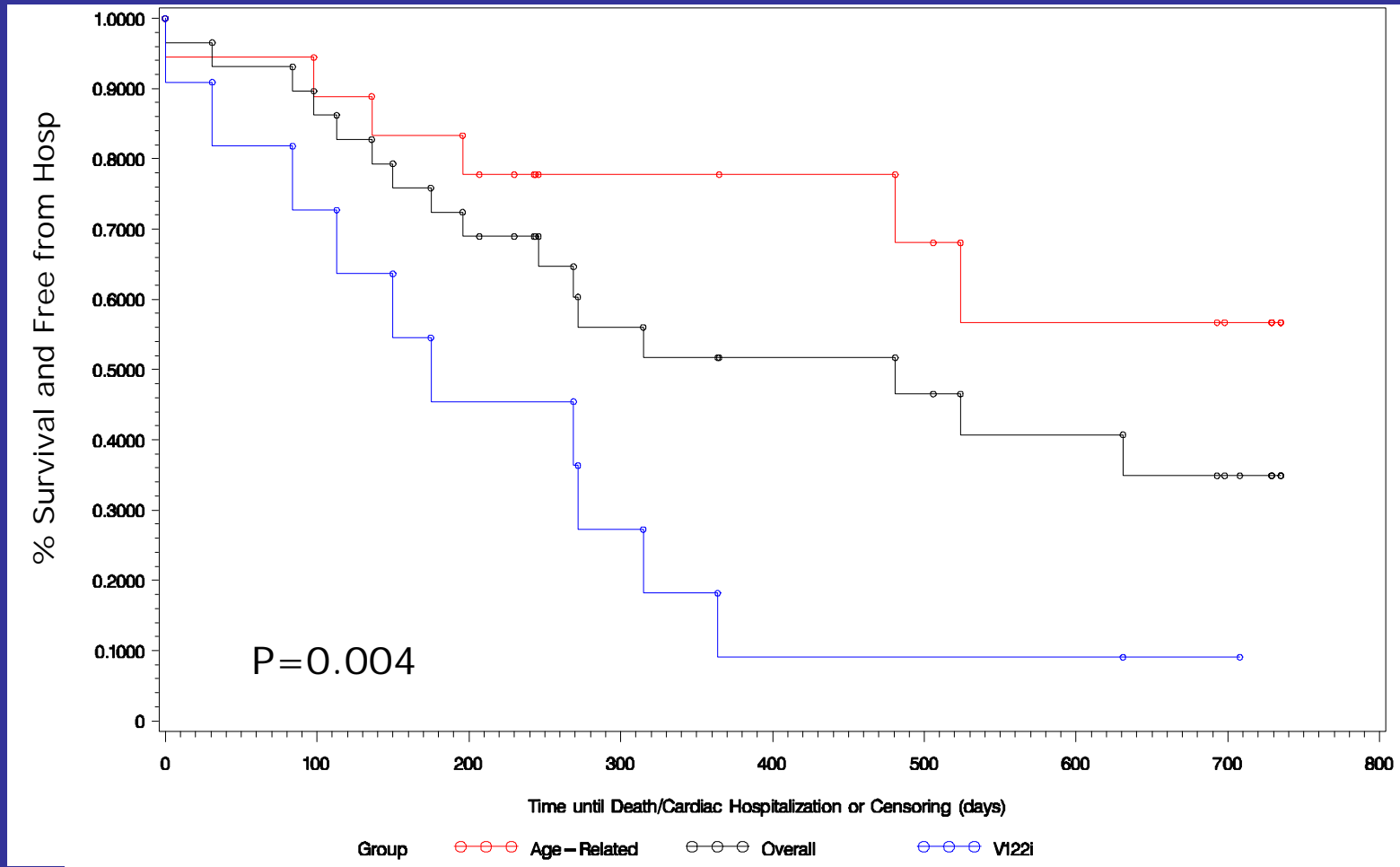


* Includes one patient who underwent cardiac transplant

Time to CV Hospitalization



Time to Death or CV Hospitalization*



* Includes one patient who underwent cardiac transplant

Predictors of Survival

Variable (mean, SD)	Survivor	Non-Survivor	P Value
Black Race	4/18 (22%)	7/11 (64%)	0.026
Distance 6MWT (m)	384 (145)	263 (146)	0.052
Troponin I (ng/ml)	0.08 (0.05)	0.19 (0.10)	0.02
Echo Parameters			
LV Ejection Fraction (%)	60% (11%)	47% (12%)	0.014
Cardiac MRI			
LV Cardiac Output (L/min)	7.0 (0.6)	4.6 (1.1)	0.001
LV Stroke Volume (ml)	99 (23)	62 (19)	0.009
LV Ejection Fraction (%)	59% (10%)	45% (13%)	0.054
RV Ejection Fraction (%)	43% (11%)	30% (5%)	0.02
RV Mass (g)	46 (13)	71 (18)	0.023

Conclusions

- The mortality of ATTR-CM is much greater than previously appreciated
 - Significantly worse outcomes for Ile 122 vs. age related disease
- Measured parameters reflect the predicted decline in cardiac function and worsening of heart failure symptoms
 - Echo, cardiac MRI, functional capacity
- Determinants of survival suggested by baseline measurements
 - Ventricular systolic function, troponin I

Case Presentation

47 year old woman with no significant medical problems was in her USOH until five months prior to presenting to her MD when she began to develop exertional dyspnea and chest pain. She has no cardiac risk factors.

Case Presentation

- First noticed increased shortness of breath with her routine exercises
- Developed intermittent chest pain
 - Substernal, radiated across chest
 - Occurred with exertion and at rest
 - No exacerbating or alleviating factors
 - No history of chest pain

Case Presentation

- Presented to her PMD
 - Abnormal ECG, continued chest pain
 - Referred to an outside hospital

Case Presentation

- Outside Hospital Workup:
 - Troponin elevation to 2.5 ng/ml
 - Echo:
 - Mildly increased wall thickness
 - Normal LV systolic function
 - Moderate diastolic dysfunction
 - Mildly dilated left atrium
 - Left Heart Cath:
 - normal LV function, no MR
 - 10% stenosis of the mid LAD
 - Elevated LVEDP of 20 mm Hg

Case Presentation

- Impression was coronary vasospasm and she was started on a calcium channel blocker
- Felt worse on the medication, self d/c
- Returned to PMD
 - GI workup: barium esophogram revealed GERD
 - PFTs: Unremarkable
 - Holter: Unremarkable

Case Presentation

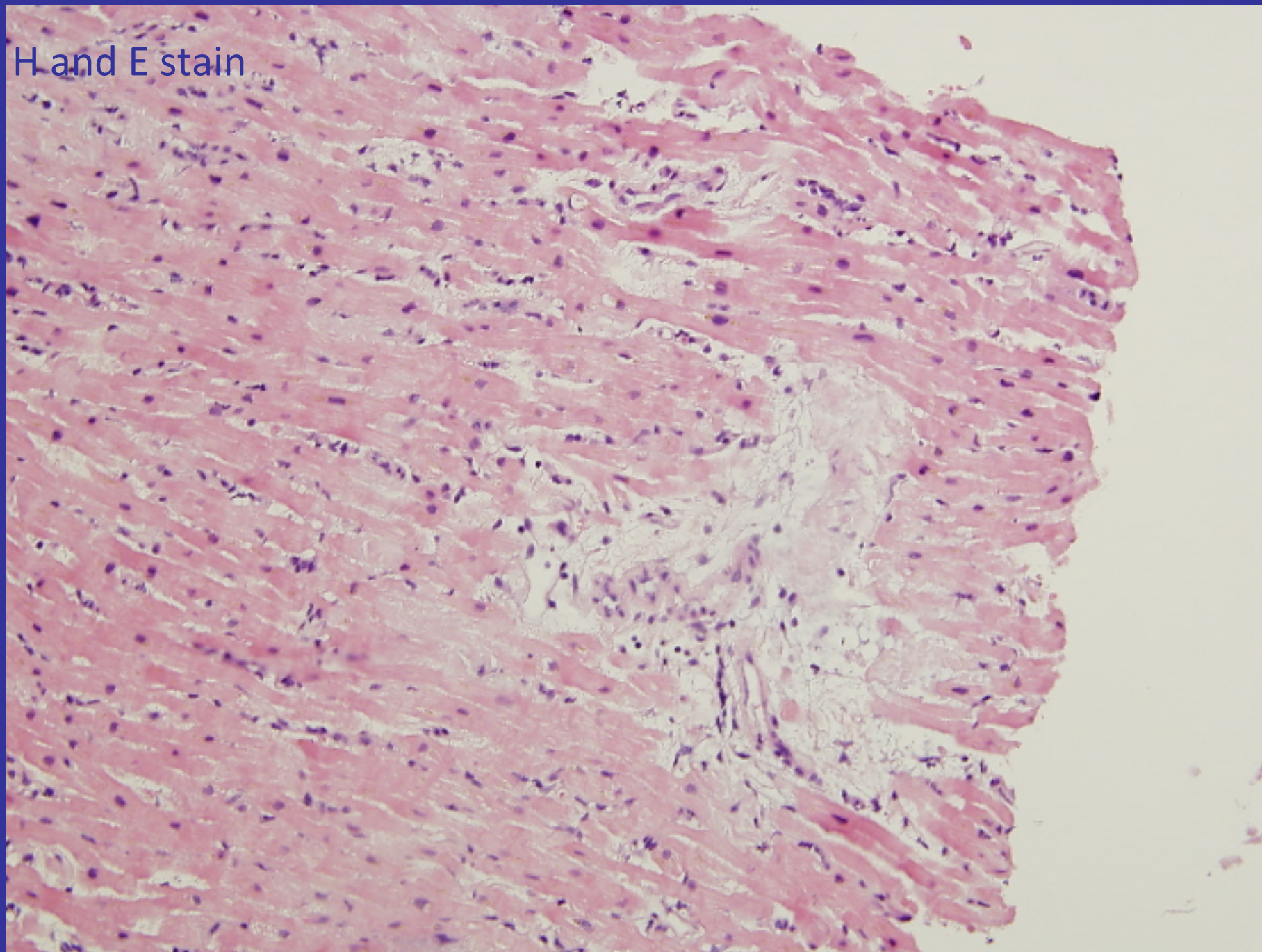
Three months later, the patient continues to be

- Exhausted all of the time
- Occasional Palpitations
- Six months of right sided abdominal pain
 - Described a “poking in her side”
- Denied syncope, PND, orthopnea, cough, nausea, vomiting, fevers, chills, weight loss
- More blood work done:
 - CBC, BMP, LFTs, TFTs, ANA, CRP and ESR: normal
 - BNP: 575 pg/ml

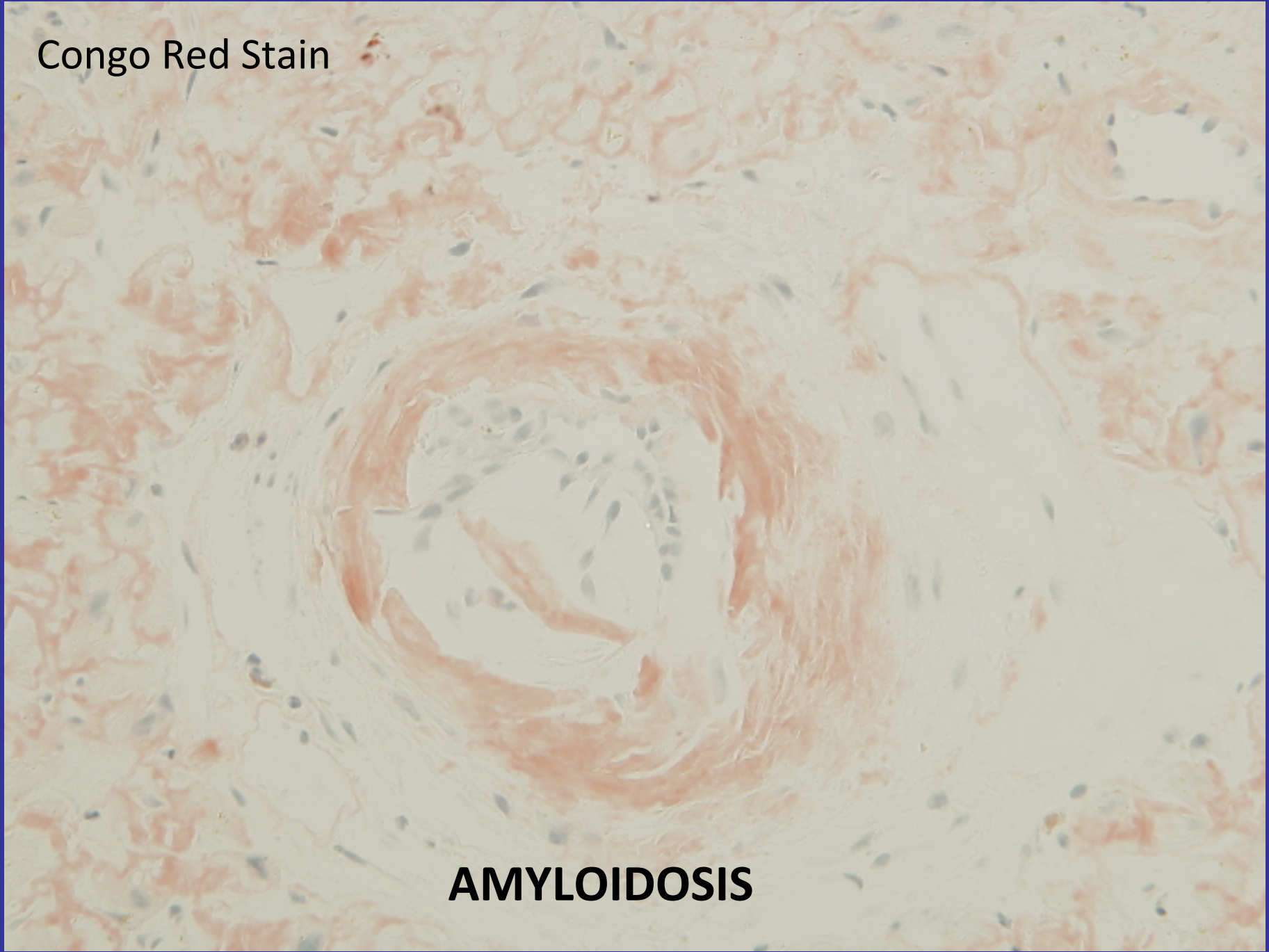
Treatment Plan

- Treatment:
 - ACE inhibitor
 - Furosemide
- The patient did not feel better with treatment
- Plan for right heart catheterization with endomyocardial biopsy

H and E stain

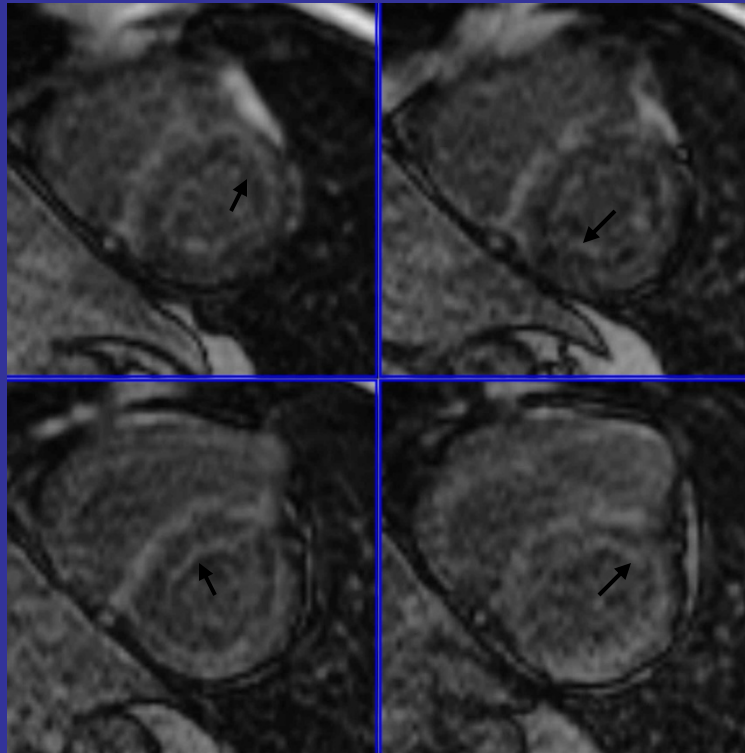


Congo Red Stain



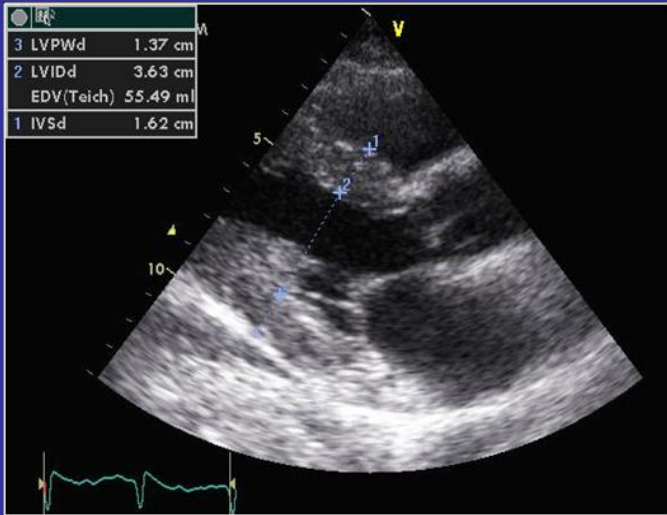
AMYLOIDOSIS

Cardiovascular Magnetic Resonance in Cardiac Amyloidosis

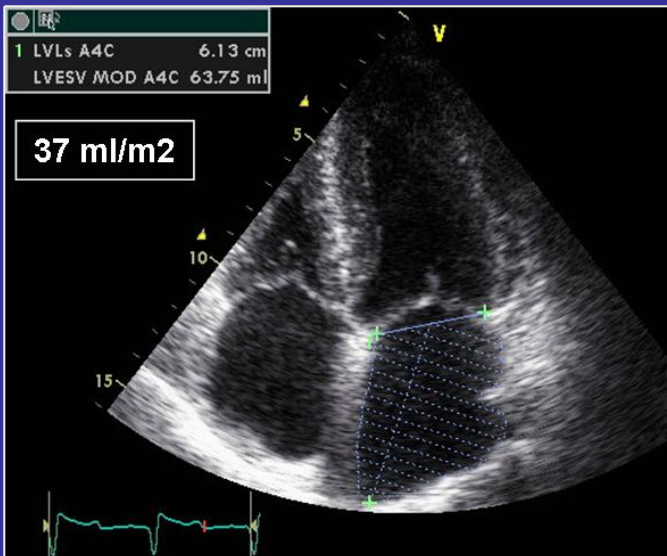


Late gadolinium diffuse global subendocardial enhancement

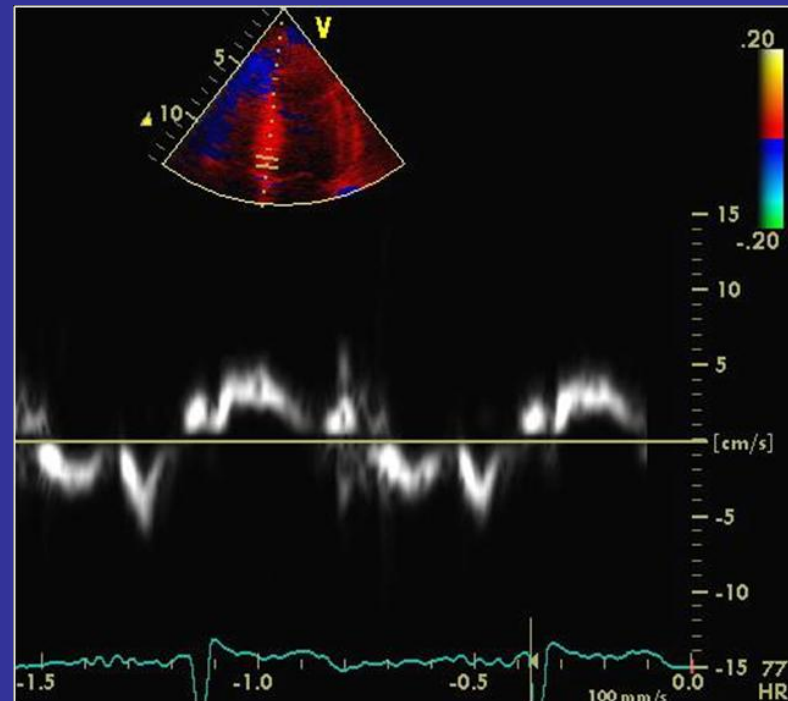
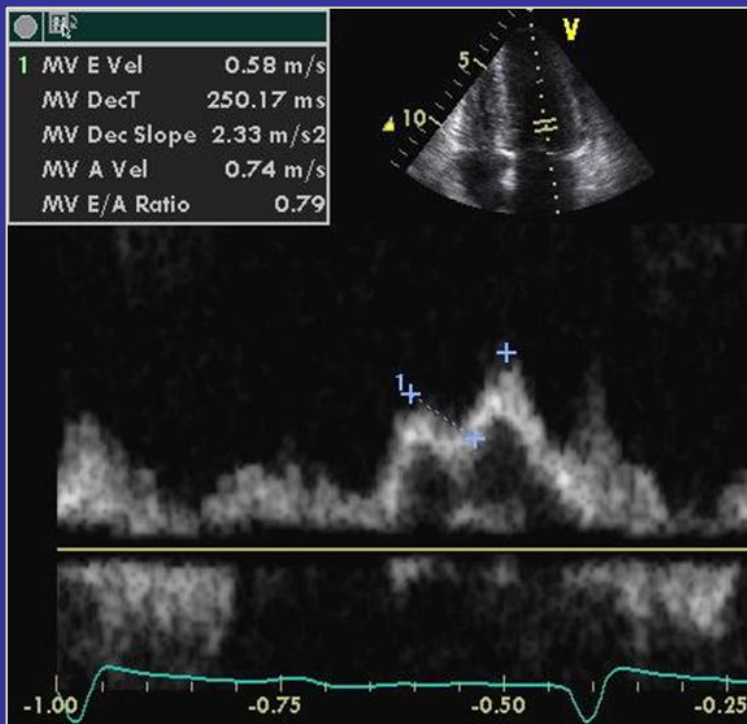
Echocardiographic Findings in Cardiac Amyloidosis



- Increased LV wall thicknesses
- Myocardial sparkling granular texture
- Dilated Atria
- Normal or mildly reduced LV systolic function



Echocardiographic Findings in Cardiac Amyloidosis



Diastolic Dysfunction (continuum from abnormal LV relaxation to restrictive LV filling pattern)