Cardiac Amyloidosis

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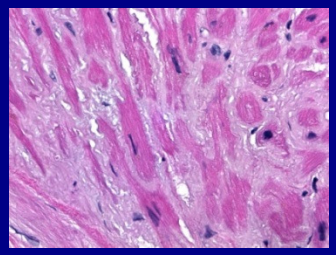
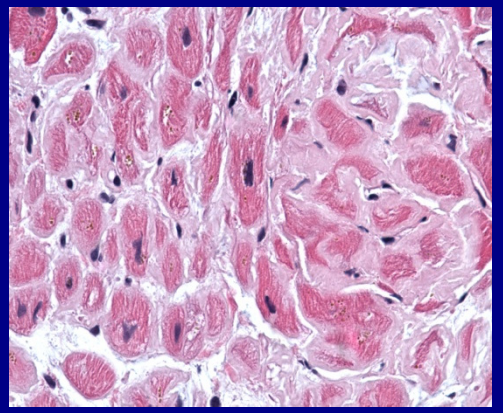
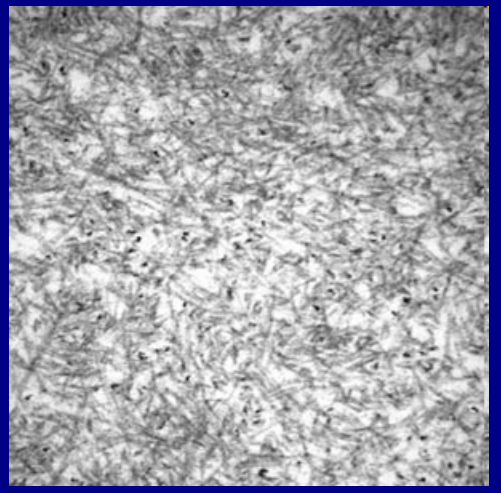


Amyloidosis: What is it?

- *Amylum* – Starch (Latin)

- Generic term for ***many*** diseases:
  - Protein misfolds into β-sheets →
  - Forms into 8-10 nm fibrils →
  - Extracellular deposition into amyloid deposits



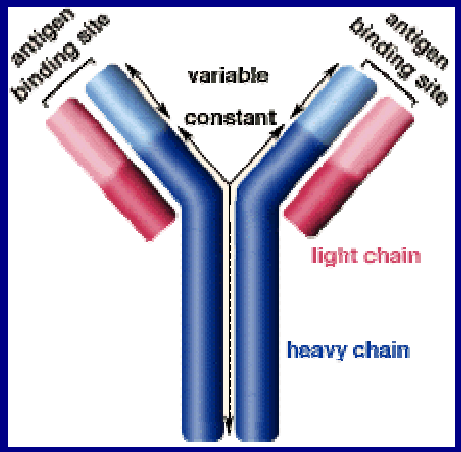


Types of Amyloid – Incomplete List

- **Systemic:**
  - **Light chains (AL)** – "Primary"
  - **Transthyretin (ATTR)** – "Senile" or "Familial" or "FAC" or "FAP"
  - Serum amyloid A (AA) – "Secondary"
- Localized – Not to be memorized!
  - Beta-2 microglobulin (A-β2) – Dialysis (osteoarticular structures)
  - Apolipoprotein A-1 (AApoA-I) – Age-related (aortic intima, cardiac, neuropathic)
  - Apolipoprotein A-2 (AApoA-2) – Hereditary (kidney)
  - Calcitonin (ACal) – Complication of thyroid medullary CA
  - Islet amyloid polypeptide (AIAPP) – Age-related (seen in DM)
  - Atrial natriuretic peptide (AANF) – Age-related (atrial amyloidosis)
  - Prolactin (APro) – Age-related, pituitary tumors
  - Insulin (AIns) – Insulin-pump use (local effects)
  - Amyloid precursor protein (ABeta) – Age-related/hereditary (Alzheimers)
  - Prion protein (APrPsc) – Hereditary/sporadic (spongiform encephalopathies)
  - Cystatin-C (ACys) – Hereditary (cerebral hemorrhage)
  - Fibrinogen alpha chain (AFib) – Hereditary (kidney)
  - Lysozome (ALys) – Hereditary (Diffuse, especially kidney, spares heart)
  - Medin/Lactadherin – Age-related (medial aortic amyloidosis)
  - Gelsolin (AGel) – Hereditary (neuropathic, corneal)
  - Keratin – Cutaneous

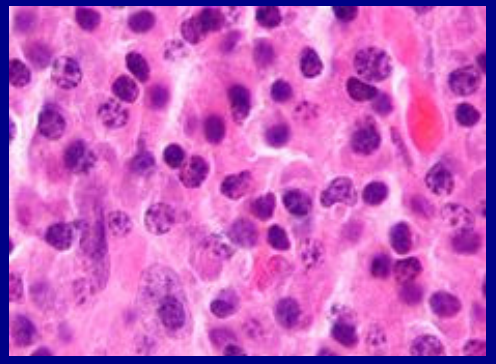
AL: A Brief Dive into Hematology…

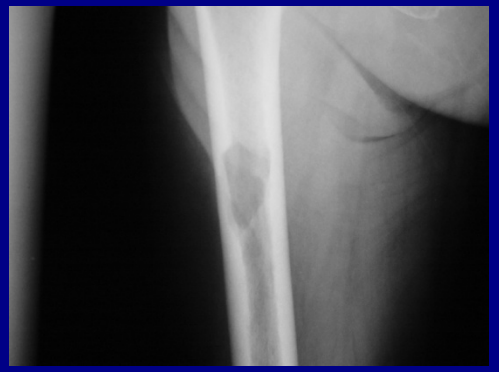
- Plasma cells: Make antibodies
- Antibodies: Made up of light chains & heavy chains
  - Light chain: Two types (κ and λ) – determine part of antibody's specificity
- What happens when someone develops a clonal plasma cell population?

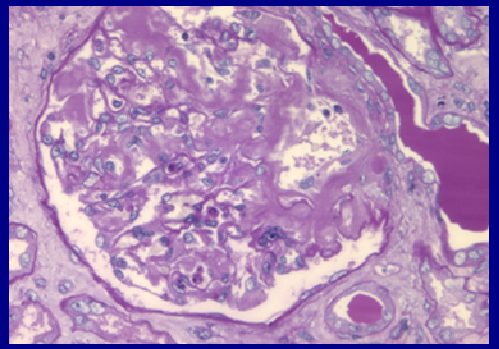


Plasma Cells Gone Wrong

- Three things happen:
  - Plasma cell clones take over % of bone marrow
  - Plasma cells produce a clonal antibody (IgG-λ)
  - Plasma cells produce excess light chain (λ)
- Possible outcome 1:
  - Only small % of marrow taken over, circulating light chains don't deposit → MGUS
- Possible outcome 2:
  - Large % of marrow taken over (and possible consequences thereof) → Myeloma
- Possible outcome 3:
  - Circulating light chains deposit in tissue → AL Amyloidosis
- Note: Possibilities 2 & 3 can coexist – but don't have to

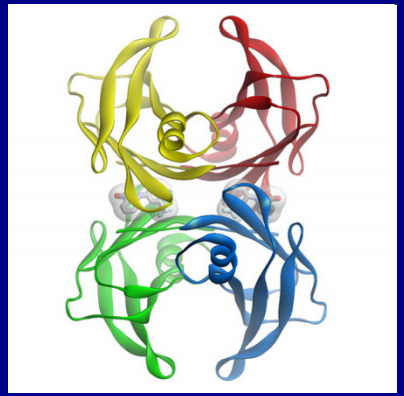






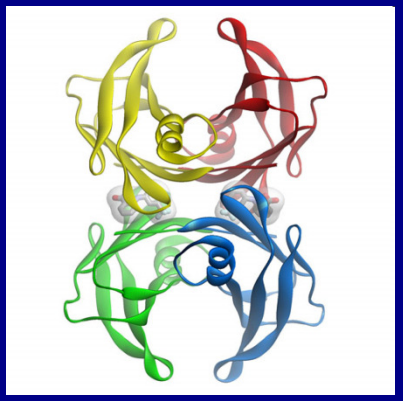
Transthyretin (TTR)

- Transthyretin = "**Trans**ports **thy**roxine and **retin**ol"
  - Prealbumin by any other name…
- Almost completely circulates as a tetramer
  - In steady-state with monomeric form
- Monomeric TTR is inherently 'amyloidogenic'
- Mutations in TTR can make it even more amyloidogenic



Wild-Type "Senile" ATTR Amyloidosis

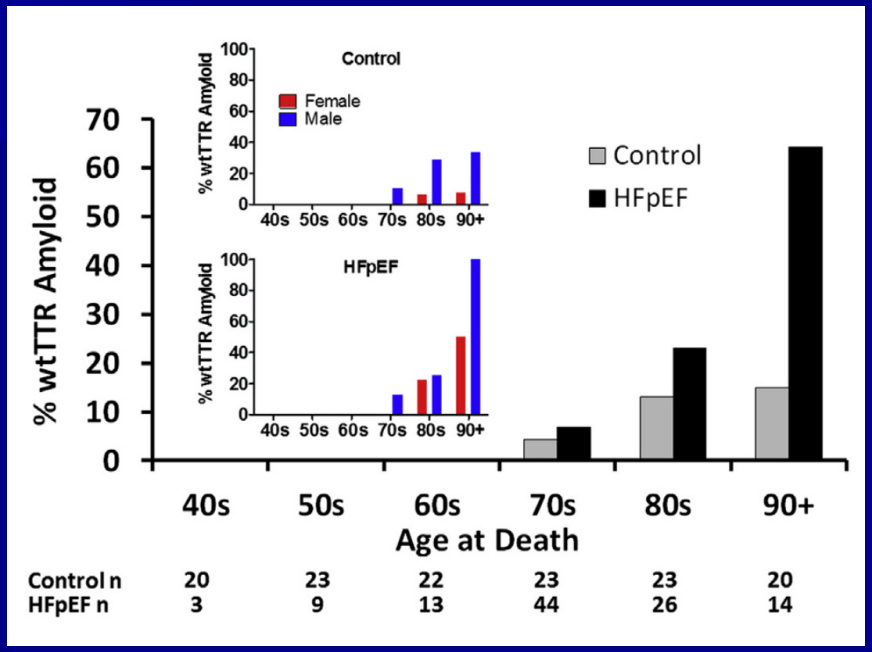
- Normal transthyretin protein



- Almost exclusively deposits in heart
  - Men >>> Women
  - Previously called "benign deposits" in hearts of elderly

Study of wtTTR Amyloid Prevalence

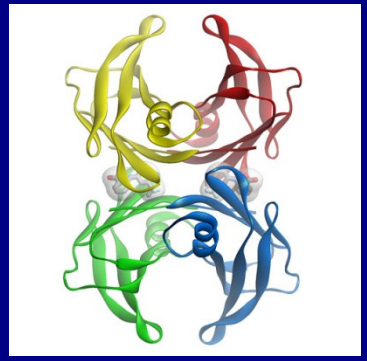
- Study from Mayo Clinic published in April 2014
- Reviewed autopsies from:
  - 109 patients with antemortem diagnosis of HFpEF without any clinical suspicion of amyloidosis
  - Age-matched control patients without antemortem HF diagnosis
- Blinded pathology review



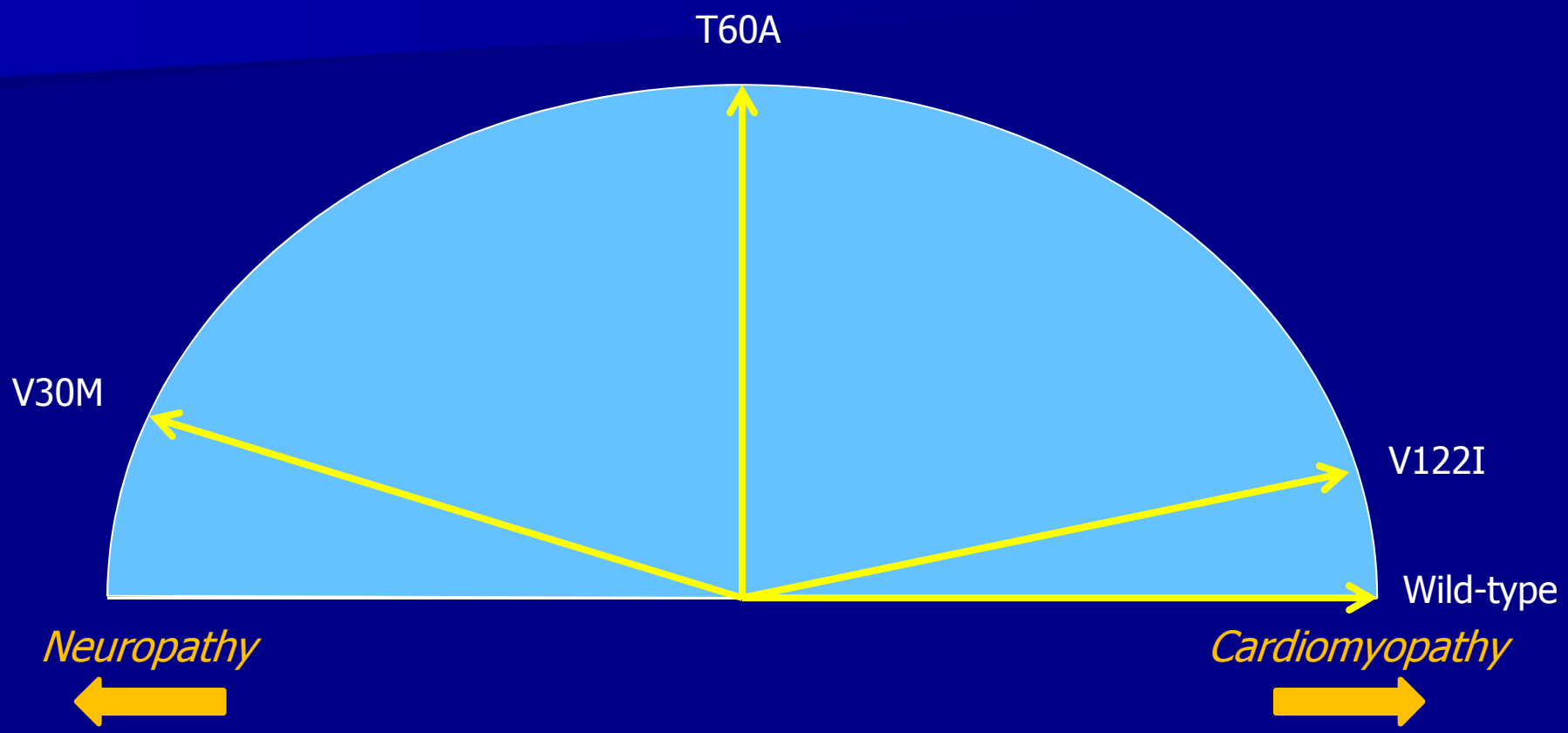
Adapted from Mohammed et al. J Am Coll Cardiol HF. 2014;2:113-22.

Familial ATTR Amyloidosis

- Predominant manifestations:
  - Cardiomyopathy
  - Peripheral neuropathy
- Dozens of mutations described!
  - Type of mutation correlates with severity, age of onset, and clinical manifestations of disease
  - V30M mutation: Most common in Portugal (1/600)
    - Familial amyloid polyneuropathy ("FAP")
  - V122I mutation: Seen in 3-4% of individuals of African descent (!)
    - By far the most common mutation encountered in USA
    - Familial amyloid cardiomyopathy ("FAC")

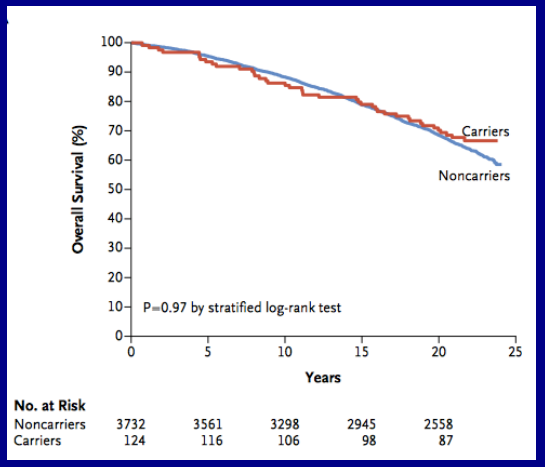


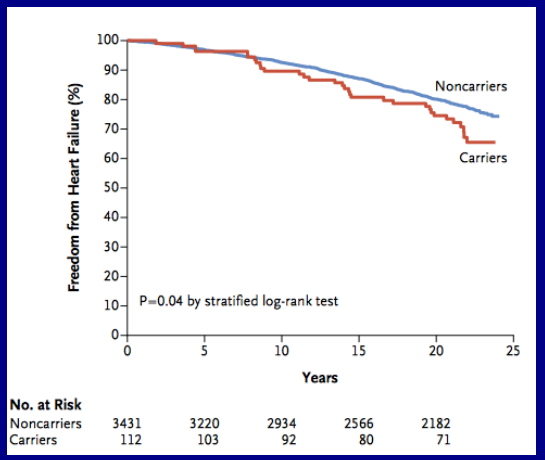
Spectrum of Disease By Mutation



V-122I: How Common, How Important?

- 3856 black participants in Atherosclerosis Risk in Community (ARIC) study recruited from 1987-1989
  - Note: Only 36% male, average age 52 at entry
- Each participant genotyped for TTR gene
- Findings:
  - Mutation in self-reported black population: 124/3732 (3.2%)
  - Mutation in non-black population: 2/10893 (0.02%)
  - More systolic/diastolic dysfunction, higher NT-BNP in V-122I carriers
    - 7% of carriers with overt amyloid CM



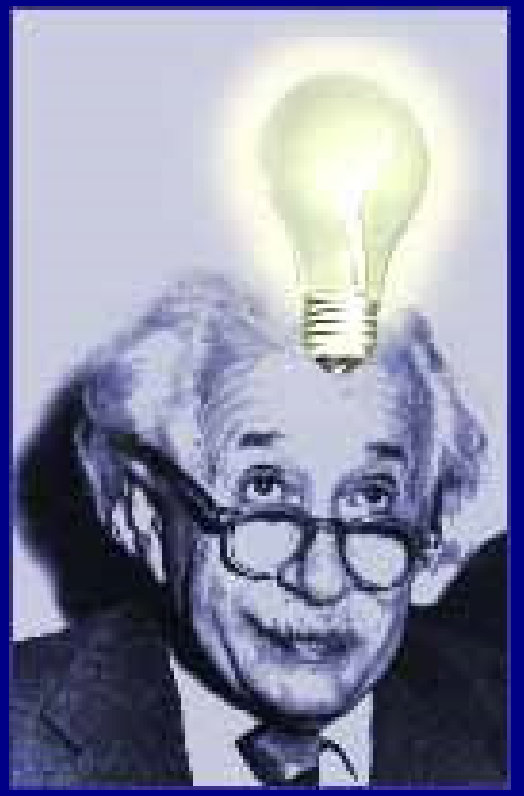


Adapted from Quarta et al. NEJM. 2015. 372:21-9.

Clinical Presentation and Diagnosis

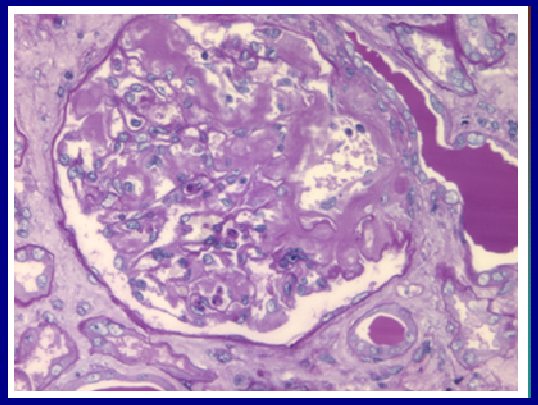
Amyloidosis: Diagnosis

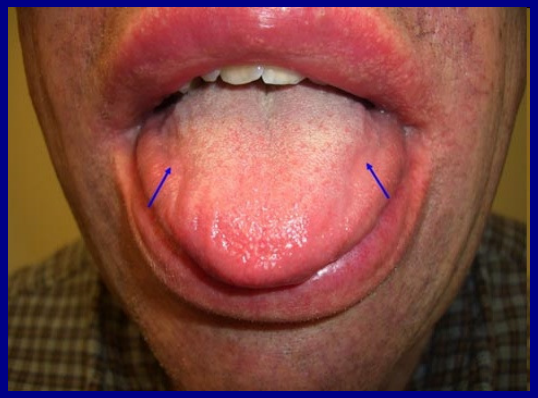
"The only way to diagnose amyloidosis is to consider the diagnosis."

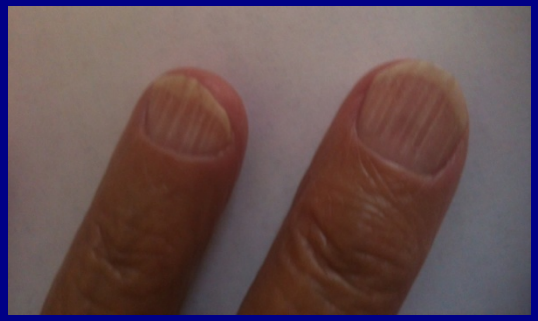


AL Amyloidosis: Clinical Features

- Multiorgan system involvement:
  - Cardiac: Heart failure, arrhythmias, hypotension, imaging abnormalities
  - Renal: Proteinuria, renal failure
  - Neurologic: Peripheral neuropathy, autonomic dysfunction
  - GI: Dysphagia, malabsorption, GI bleeding, constipation, nausea, liver dysfunction (alk phos elevation)
  - Soft tissue/ENT: Macroglossia, carpal tunnel syndrome, voice changes, nail changes

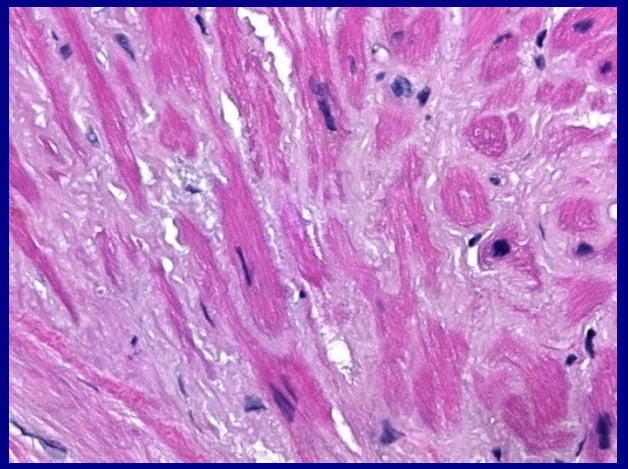






Cardiac Manifestations

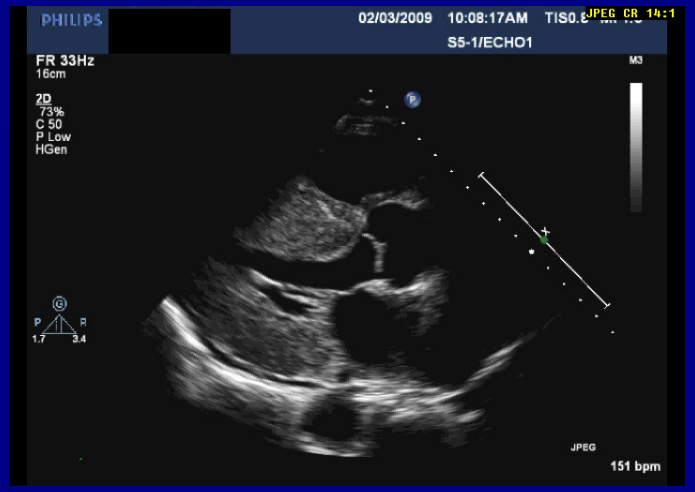
- Heart failure
  - Diastolic dysfunction > Systolic dysfunction
- Electrophysiologic
  - Heart block
  - Tachyarrhythmias
  - Low voltages on EKG (*)
- Imaging/Laboratory
  - Left ventricular “hypertrophy”
  - Elevated troponin

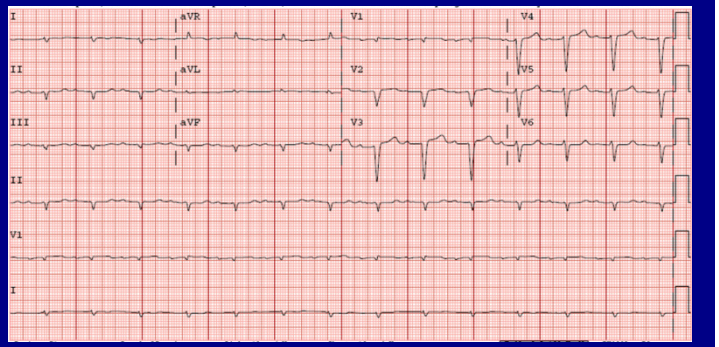


Cardiac Amyloid: Diagnosis by Imaging

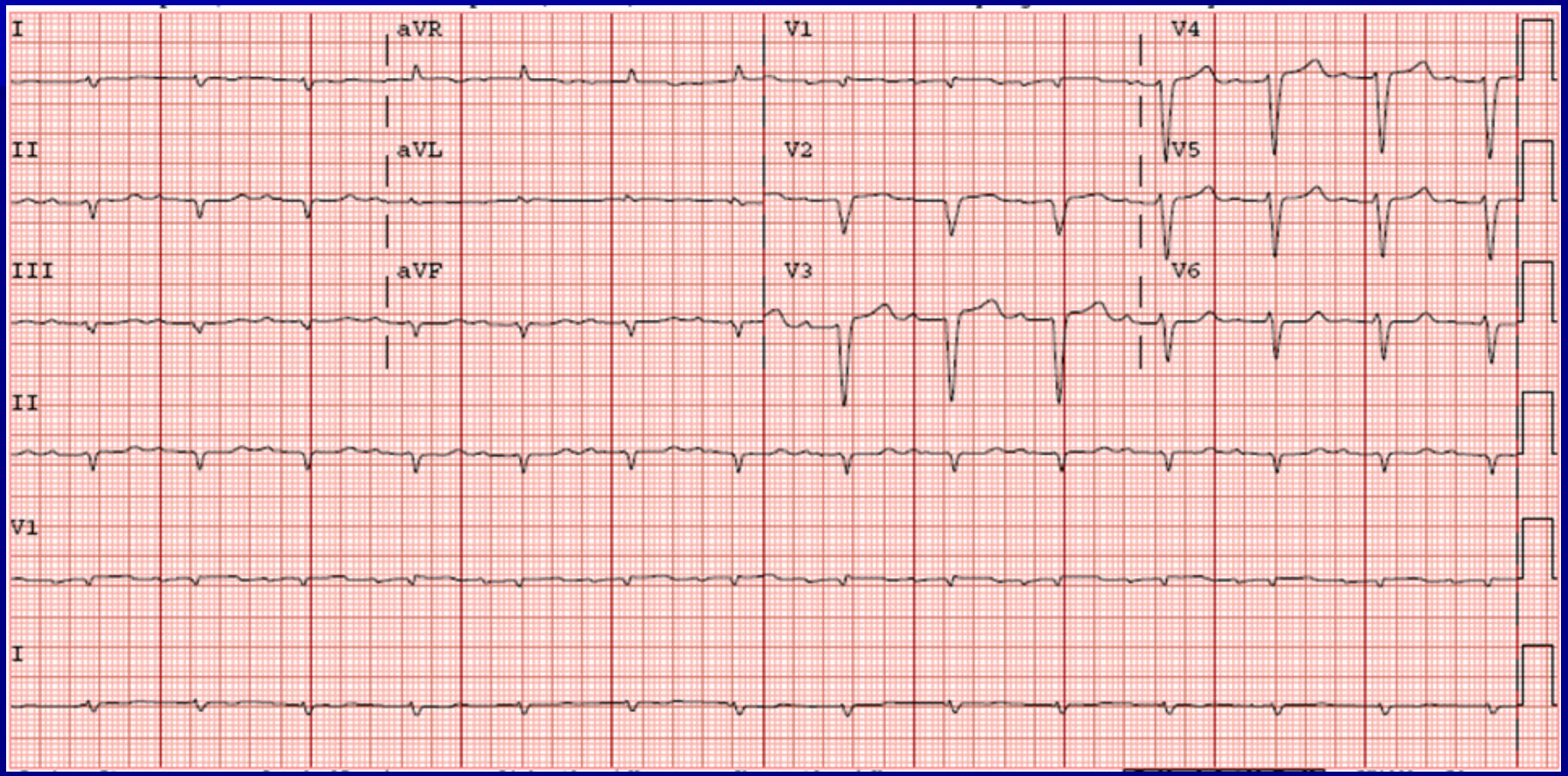
- Increased ventricular thickness
  - RV thickened as well

- Combination of increased ventricular mass & low voltages → quite specific for amyloid.

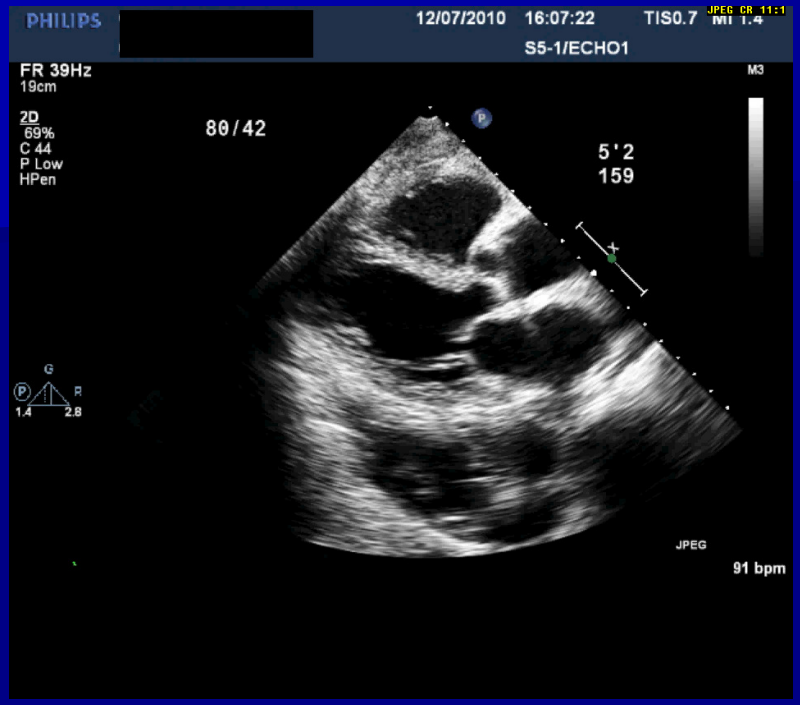


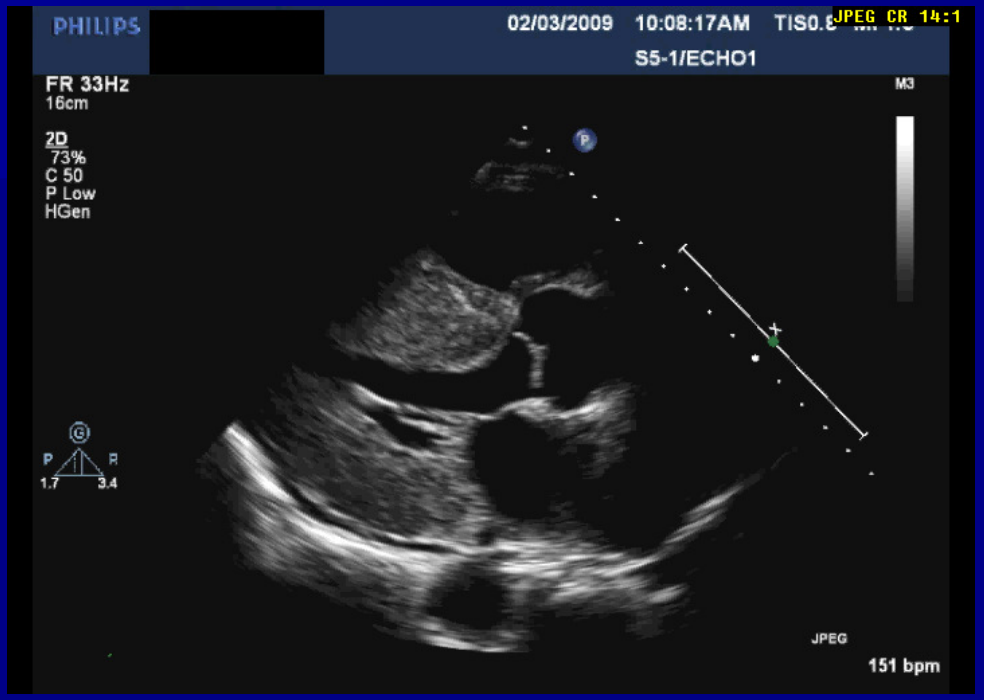


Typical EKG in Cardiac Amyloidosis



Which of These is Amylodiosis?





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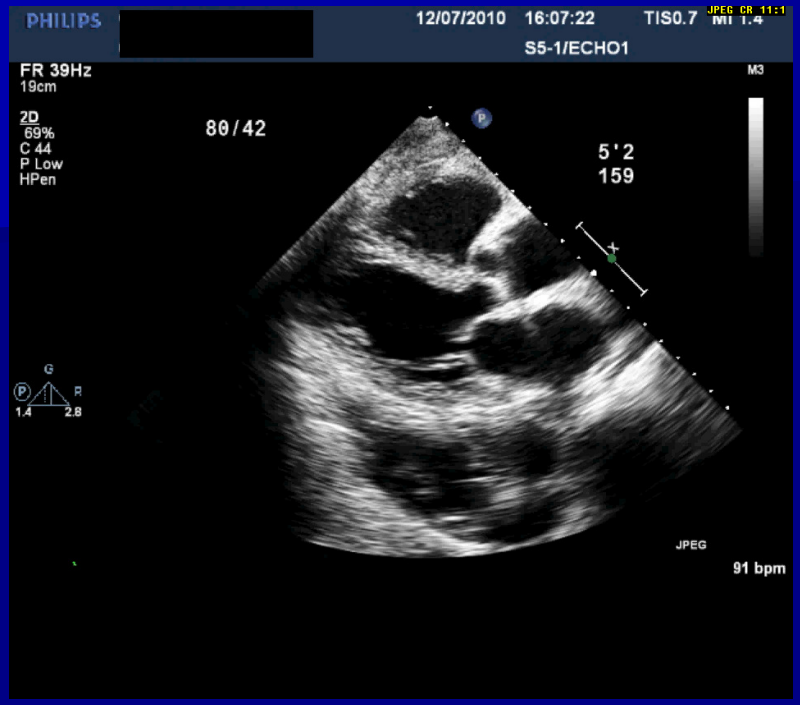
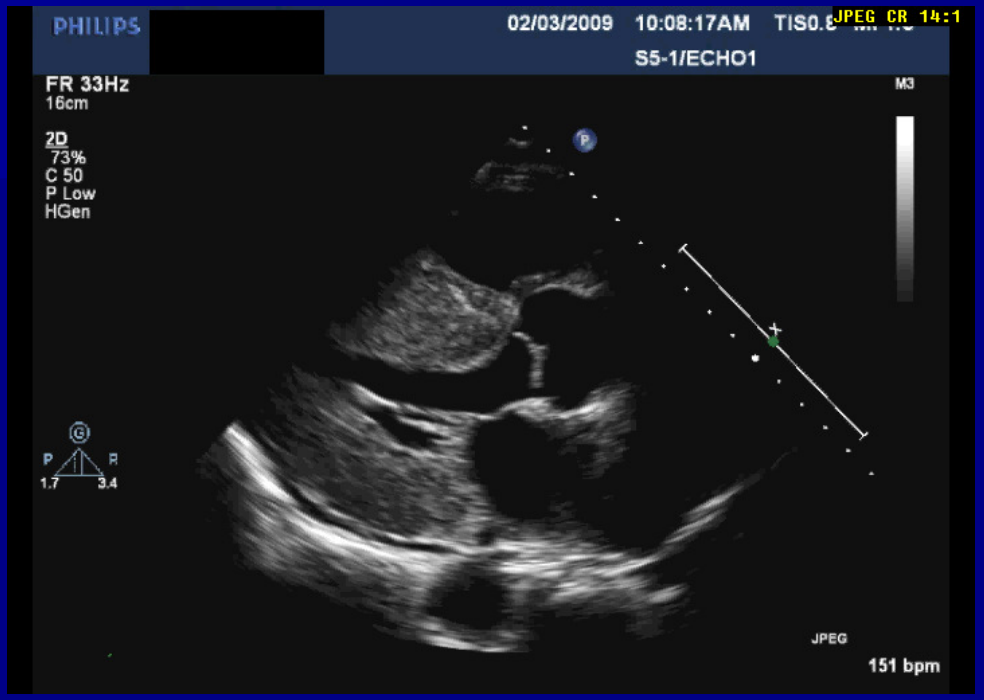


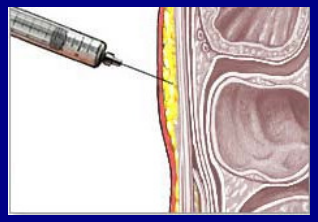


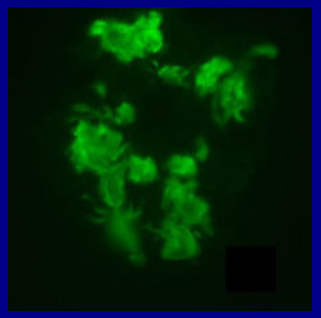
Answer: Both!

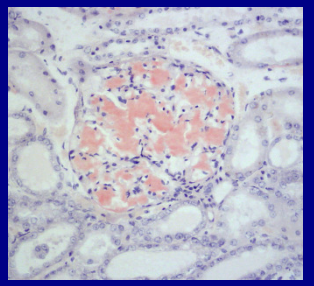
How to Diagnose – Biopsy!

- Cannot r/o with lab assessment
- Technetium-pyrophosphate scans?
- Our general practice:
  - Biopsy of clinically involved organ
- Testing for amyloid subtype – plan ahead!
  - Know thy pathologist
  - Congo Red
  - Immunofluorescence or Mass spectrometry

Organ	**Sensitivity**
Abdominal fat pad	"70%" (?)
Bone marrow	50-56%
Rectal	70-85%
Clinically involved organ	Nearly 100%

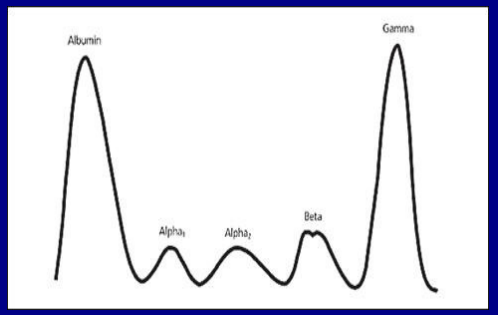






Adjunctive Laboratory Tests

- SPIEP: Looks for monoclonal immunoglobulins in serum
- UPIEP: Looks for monoclonal light chains in urine (enriched in urine)
- Free light chain assay: Measures ratio of κ to λ in serum
  - Normal ratio: Approximately 1:1
  - If significant excess: Implies monoclonal light chain production
  - Main assay to assess hematologic response to Rx
- BNP, Troponin, alkaline phosphatase, urine albumin:Cr ratio
- TTR amyloidosis: Genetic testing



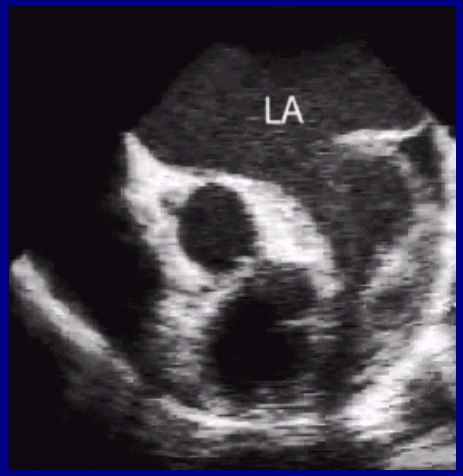
AL Amyloid Treatment Strategy: Parallel Paths

- Treatment of consequences of organ dysfunction

- Treatment of clonal plasma cell disorder
  - Chemotherapy
  - Stem cell transplant

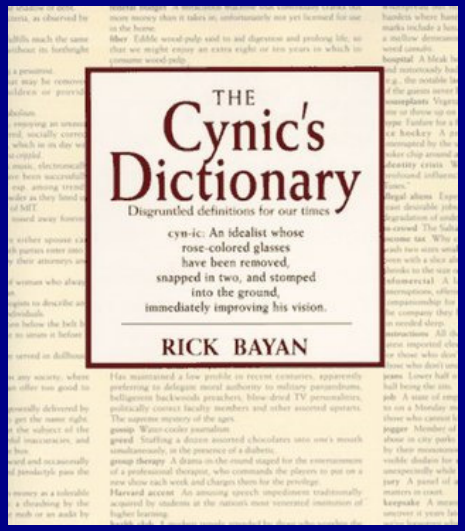
Treatment: Cardiac-Specific

- Diuretics/salt restriction
  - Often have large amounts of peripheral edema/ascites
- To generally be avoided:
  - Digoxin
  - Beta-blockers
  - Calcium-blockers
  - Vasodilators (ACE-I/ARBs)
- Midodrine
  - Can be useful in orthostatic hypotension
- Treatment of atrial & ventricular arrhythmias



Sudden Death in Amyloidosis – The Old Paradigm

- "Most sudden death is due to EMD/hypotension, not arrhythmias. Don't place an ICD!"
- "ICDs don't work in amyloidosis. They usually fail to convert the rhythm!"
- "ICDs don't work in amyloidosis. Even when they do convert the rhythm, the patient is left in PEA!"
- "The prognosis is terrible in amyloidosis – why would you want to convert a peaceful sudden death to a miserable heart-failure-with-gruesome-shocks death?"



ICDs: Mayo Data (2000-2009)

- 53 patients with cardiac amyloidosis underwent ICD placement (41 primary prevention, 12 secondary prevention)
- Appropriate ICD shocks in first year = 32% (!)
- AL more likely to receive appropriate shocks than ATTR
- No clear survival advantage, though…
  - Underpowered to detect difference
  - Many of the patients met 'traditional' ICD indications (probably too late given low LVEF = late finding)
  - Study conducted before development of many of the newer chemotherapy regimens

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Implantable Cardioverter Defibrillators in Patients with Cardiac Amyloidosis

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ICD in Cardiac Amyloidosis. *Background:* Cardiac amyloidosis (CA) is associated with increased risk of sudden cardiac arrest. Although ICD therapy improves survival in patients with cardiomyopathy due to other etiologies, the benefit of ICD therapy in patients with CA is unclear in large part due to limited data on the precise mechanism of sudden cardiac arrest and selection of patients with cardiac amyloidosis for ICD therapy.

Objective: The objective was to determine the benefit of ICD therapy in cardiac amyloidosis.

Methods: We reviewed all ICD implant indications, procedures, and therapies, of CA patients evaluated at Mayo Clinic between 2000 and 2009.

Results: A total of 53 patients with CA (33 AL, 10 senile, 9 familial, and 1 AA) who underwent ICD implantation were included. Indication for ICD implantation was for primary prevention of sudden cardiac arrest in 41 (77%) patients and secondary prevention in 12 (23%) patients. The rate of appropriate ICD shocks was 32% in the first year and was observed almost exclusively in AL amyloidosis patients, occurring in 15 patients (12 AL amyloidosis, 2 senile, 1 AA). Appropriate ICD shocks were more frequent in patients with prior sudden cardiac arrest or sustained ventricular arrhythmias (secondary prevention indication), and less frequent in patients who presented with decreased ejection fraction or syncope.

Conclusions: A high rate of appropriate ICD shocks was observed especially in patients with AL-type amyloidosis. However, appropriate ICD therapy did not translate into overall survival benefit, suggesting that selection of patients with CA who might be candidates for ICD is imprecise. *(J Cardiovasc Electrophysiol, Vol. 24, pp. 793-798, July 2013)*

cardiac amyloidosis, heart failure, sudden death, implantable cardioverter defibrillator, ventricular tachycardia

Introduction

Systemic amyloidosis with cardiac involvement is characterized by progressive concentric myocardial and valvular thickening and restrictive physiology and is associated with a high mortality due either to worsening heart failure or sudden cardiac arrest.[1-4] Despite high cardiovascular mortality associated with cardiac amyloidosis (CA) the potential benefit of ICD therapy in this population is unclear since unlike patients with other forms of cardiomyopathy only limited data relate to outcomes following ICD implantation in patients with CA.[3,5] Therefore, we sought to determine whether ICD therapy in patients with CA impacts mortality and whether specific subgroups of patients most likely to benefit from ICD therapy can be identified.

Methods

Study Population

All patients evaluated at Mayo Clinic between January 1, 2000 and March 30, 2009 who had previously undergone ICD implantation were included. In all cases, systemic amyloidosis was diagnosed by tissue biopsy and cardiac involvement confirmed either by right ventricular biopsy or the presence of typical echocardiographic features of cardiac amyloidosis (left ventricular hypertrophy with wall thickness >12 mm in the absence of other etiologies).[1,2,7]

Comprehensive clinical evaluation including transthoracic echocardiography was performed and cardiac troponin T and N-terminal pro-natriuretic peptide (NT pro-BNP) measured at the time of diagnosis for staging and prognosis of immunoglobulin light chain (AL) amyloidosis (Stage 1 NT pro-BNP < 332 ng/L and troponin T < 0.035 μg/L, Stage 2 NT pro-BNP > 332 ng/L or troponin T > 0.035 μg/L, Stage 3 NT pro-BNP > 332 ng/L and troponin T > 0.035 μg/L).[8,9] Death notification was obtained from the Mayo Clinic medical or administrative records, or the Social Security Death Index database. Surviving patients were followed to their most recent Mayo Clinic evaluation or until June 5, 2009.

Implantable Cardioverter Defibrillator Implantation

All ICDs were implanted via transvenous placement of a right ventricular lead for shocking and pacing using standard techniques. Defibrillation threshold (DFT) testing was performed during which ventricular fibrillation was induced to determine the minimum energy required to restore sinus rhythm. An adequate DFT was defined as DFT ≥10 J below the maximal output of the defibrillator.

No disclosures.

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Manuscript received 4 September 2012; Revised manuscript received 15 January 2013; Accepted for publication 12 February 2013.

doi: 10.1111/jce.12123

Adapted from Lin et al. J Cardiovasc Eltrophys. 2013. 24(7):793-798.

ICDs: Stanford Data (2008-2012)

- 31 consecutive patients with cardiac involvement but without advanced heart failure → ambulatory telemetry monitoring
- 23/31 (74%) patients with NSVT
  - ICDs placed in 19 patients
- 6 patients with ICDs had sustained VT
  - Rhythm successfully broken in 5/6 patients
- Our practice – ICD consideration if life expectancy >1 year and:
  - History of non-postural syncope *or*
  - VT seen on ambulatory telemetry

CREATIVE CONCEPTS

Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis

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Introduction

Cardiac amyloidosis has traditionally been associated with a poor prognosis, with a median survival of less than 1 year once patients present with heart failure.[1] As consensus guidelines recommend against implantable cardioverter-defibrillator (ICD) placement for the primary prevention of sudden cardiac death (SCD) in patients with a life expectancy of less than 1 year, ICDs have typically not been implanted in patients with this disease.[2] Furthermore, SCD has frequently been attributed to electromechanical dissociation (EMD) rather than a primary arrhythmic cause in this patient population.[1,3]

Over the past decade, concomitant with advances in disease-specific therapy for light-chain amyloidosis (AL), the prognosis of patients with cardiac amyloidosis has improved.[4–6] At the same time, there has been an increasingly recognized association between cardiac amyloidosis and ventricular arrhythmias, including several reports of successful defibrillation in patients with ICDs.[7,8] This raises the possibility that ICDs may have a role in the management of patients with this disease, which previously was often not considered when the overall prognosis was more dismal.

The 2 main types of cardiac amyloidosis encountered are AL (owing to amyloid deposits comprised primarily of a pathologic monoclonal light chain) and transthyretin amyloidosis (ATTR; owing to amyloid deposits composed primarily of wild-type or mutant transthyretin, an abundant serum protein). Cardiac involvement in AL is common, and the prevalence of ventricular arrhythmias has been documented as high as 27% of the patients.[1] In case series of patients with cardiac amyloidosis, SCD has been shown to be one of the most common causes of death.[1,2] There has been little data published for patients with ATTR, and so it remains unclear whether they benefit from ICDs.

Whether there is a specific population of patients with cardiac amyloidosis at risk of SCD owing to ventricular arrhythmias (vs EMD) who would benefit from ICD placement has yet to be defined. In this study, we report our experience with ICD implantation in patients with cardiac amyloidosis and present our proposed criteria for selecting appropriate candidates.

Methods

After the approval from the institutional review board, we used the Stanford Amyloid Center's database to identify all patients with AL or ATTR who had ambulatory cardiac monitoring. This included patients who had undergone interrogation of an ICD or pacemaker and those who had ambulatory monitoring in the outpatient setting with either a Holter monitor or Ziopatch (iRhythm technologies, San Francisco, CA). The results of device interrogations and outpatient telemetry monitoring were examined for the presence of nonsustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (VT), and ventricular fibrillation (VF) and whether ICD therapies were delivered. Three patients had SCD suspicious for arrhythmia but did not have any form of telemetry monitoring available and were thus not included in the study. Heart failure symptoms were assessed by New York Heart Association classification at the time of device implantation. Owing to concerns for the risk of EMD after shocks in patients with cardiac amyloidosis, defibrillation testing is not routinely performed at device

KEYWORDS Cardiac amyloidosis; Implantable cardioverter-defibrillator; Ventricular tachycardia; Sudden cardiac death

ABBREVIATIONS **AL** = light-chain amyloidosis; **ATP** = antitachycardia pacing; **ATTR** = transthyretin amyloidosis; **EMD** = electromechanical dissociation; **ICD** = implantable cardioverter-defibrillator; **LVEF** = left ventricular ejection fraction; **NSVT** = nonsustained ventricular tachycardia; **NT-proBNP** = N-terminal pro–brain natriuretic peptide; **SCD** = sudden cardiac death; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia (Heart Rhythm 2014;11:158–162)

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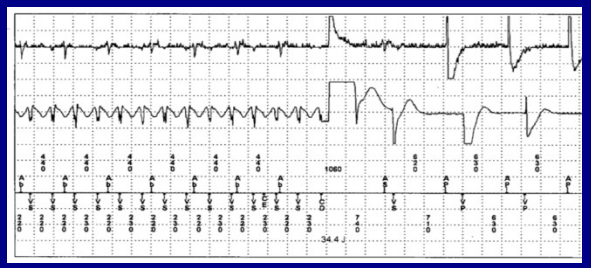
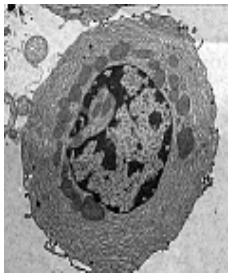
http://dx.doi.org/10.1016/j.hrthm.2013.10.026



Adapted from Varr et al. Heart Rhythm. 2014. 11(1):158-162.

AL Amyloidosis – Prognosis & Chemotherapy Approaches

Immunoglobulin light chain amyloidosis (AL)



Plasma cell clone

Misfolded light chain

Interactions with cells & microenvironment (GAGs, metals, proteases, shear forces) of target organs

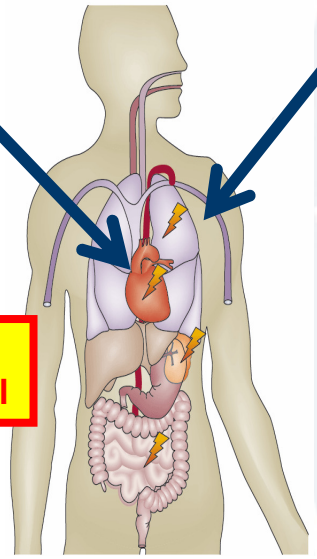
SAP

- **Heart 76%**
  - (NYHA≥II, 47%)
- **Kidney 68%**
  - Nephrotic s. 42%
  - Renal failure 45%
- Liver 15%
- GI 8%
- Soft tissues 17%
- PNS/ANS 12%/10%

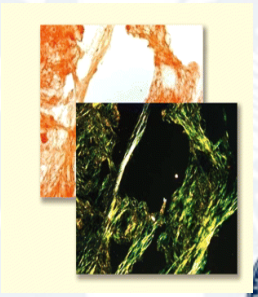
Proteotoxicity

Oligomers

Amyloid fibrils



Organ dysfunction and reduced survival



Adapted from Merlini

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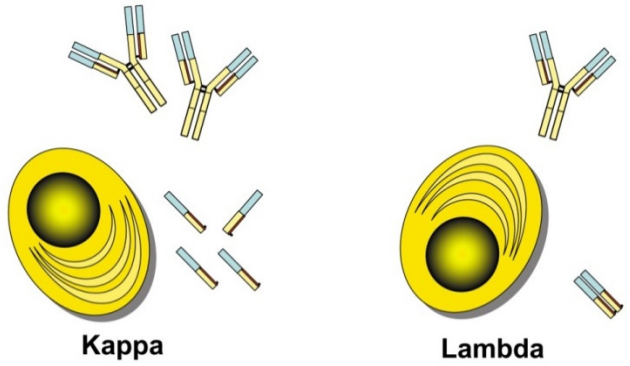
Plasma cells and immunoglobulin light chains?

- Plasma cells produce immunoglobulins
  - Heavy chain IgG, A, M, D, E,
  - Light chain: kappa and light chain
- Serum free light chain levels can now be measured (FreeLite, The Binding Site)
  - Plasma cell production
  - Renal clearance
- Some light chains have amyloidogenic potential



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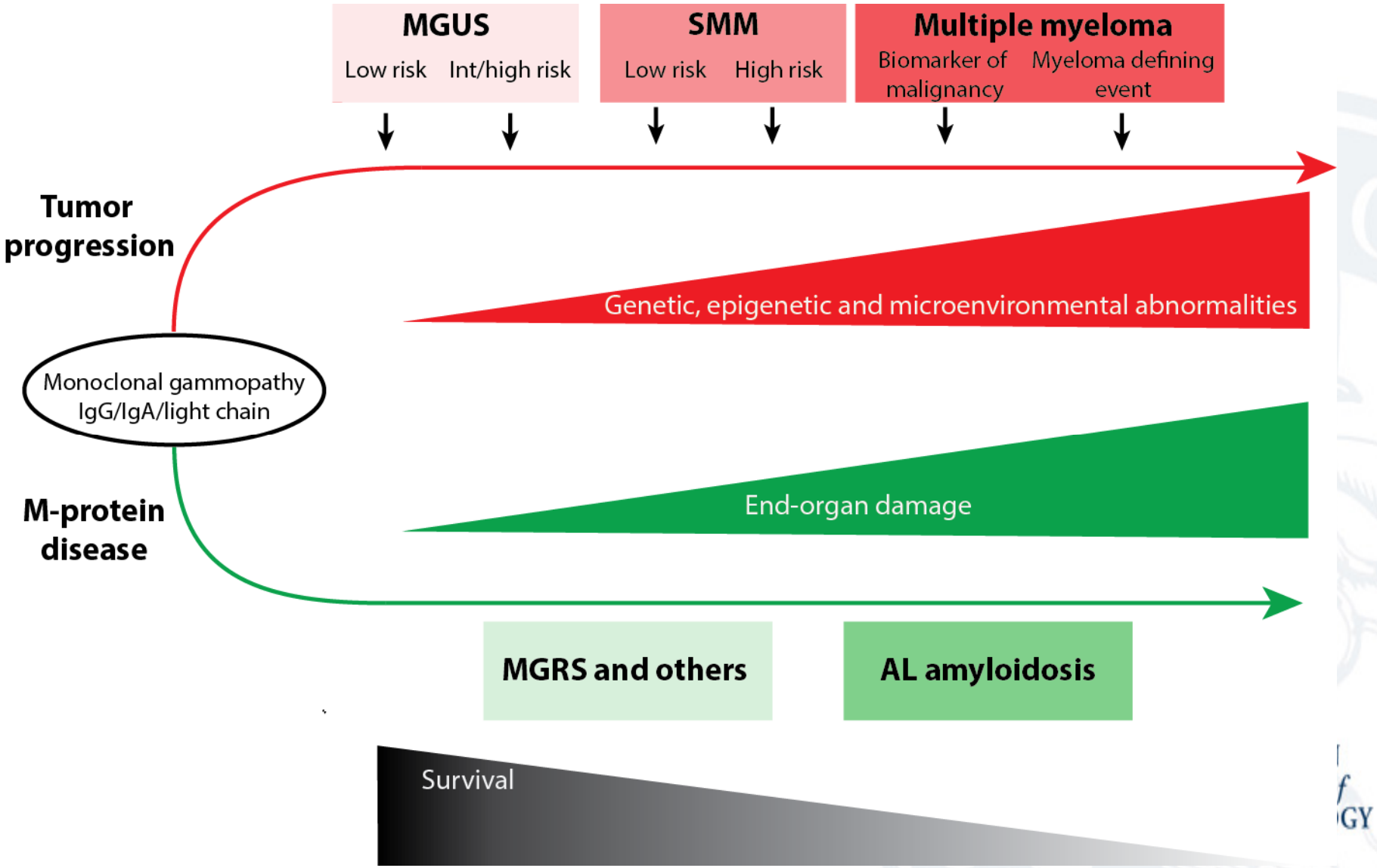
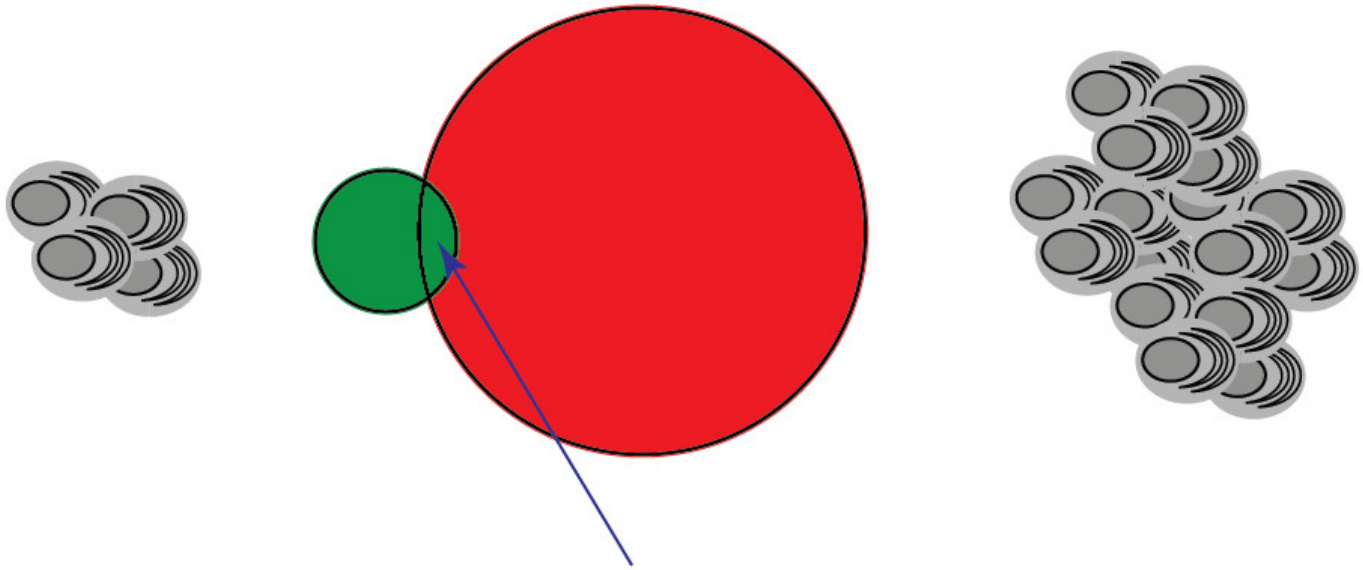
Spectrum of plasma cell disorders



AL amyloidosis is not multiple myeloma

Amyloidosis
Low tumor burden
Protein-mediated organ dysfunction

Multiple myeloma
High tumor burden
Tumor-mediated organ dysfunction



Amyloidosis & multiple myeloma
High tumor burden
Protein- and tumor-mediated organ dysfunction

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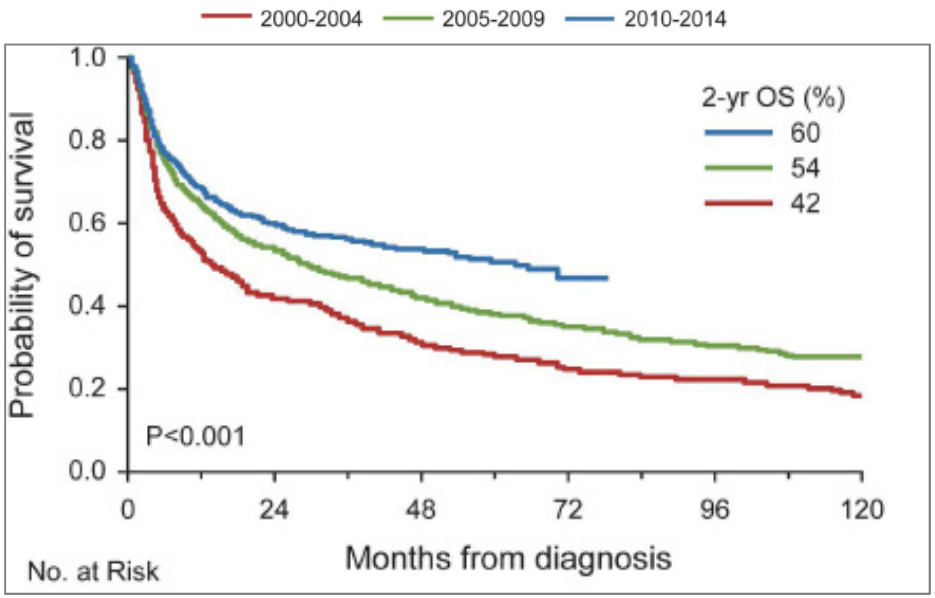
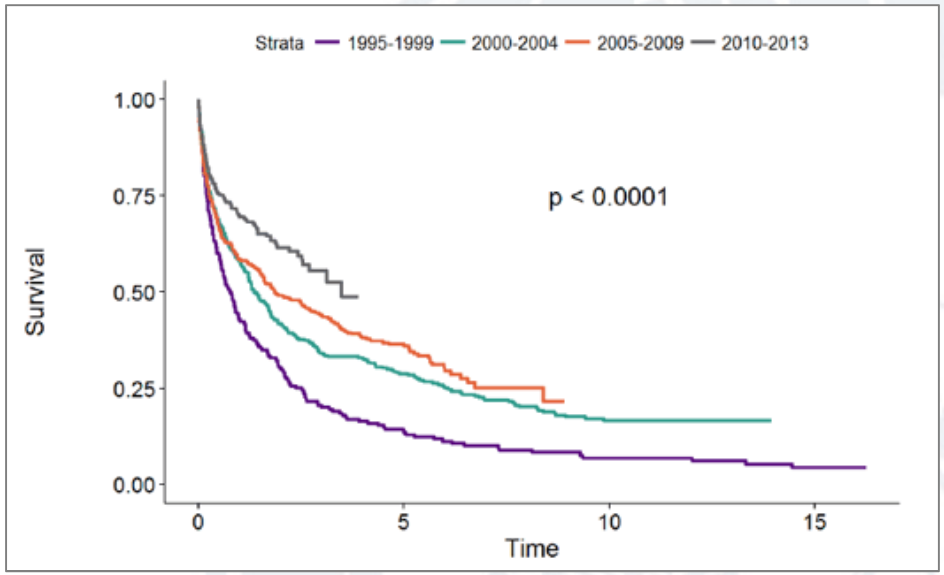
Outcomes in AL amyloidosis

- Overall survival is improving due to novel agents for multiple myeloma
- Early mortality appears to be improving

Mayo Clinic 2000-14



Sweden 1995-2013



Muchtar Blood 2017, Weiss ASH 2016

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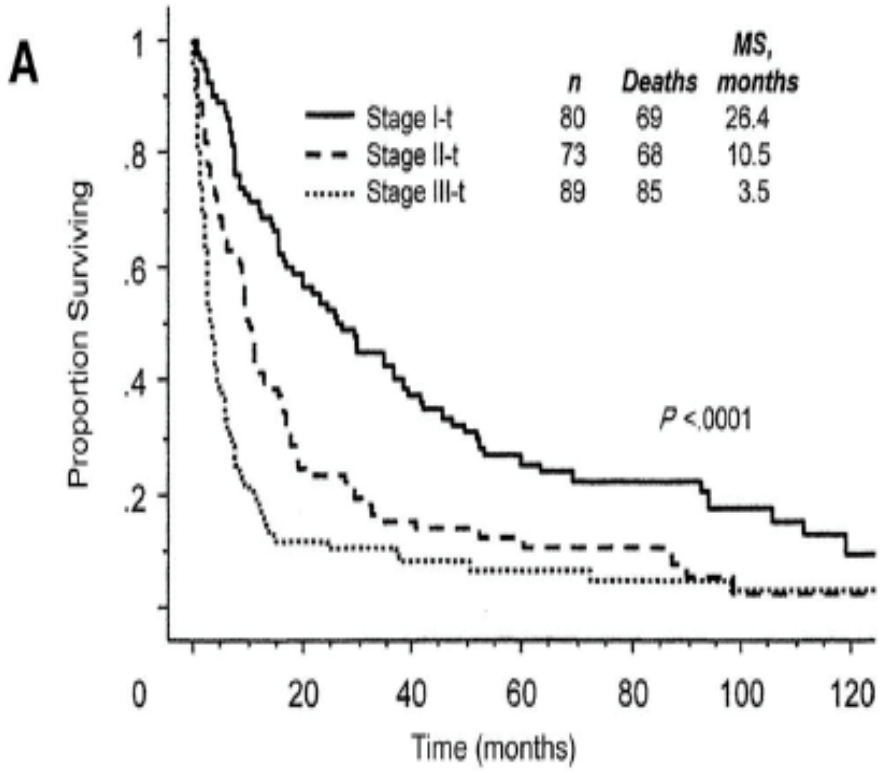
Prognosis in AL – Mayo 2004 staging

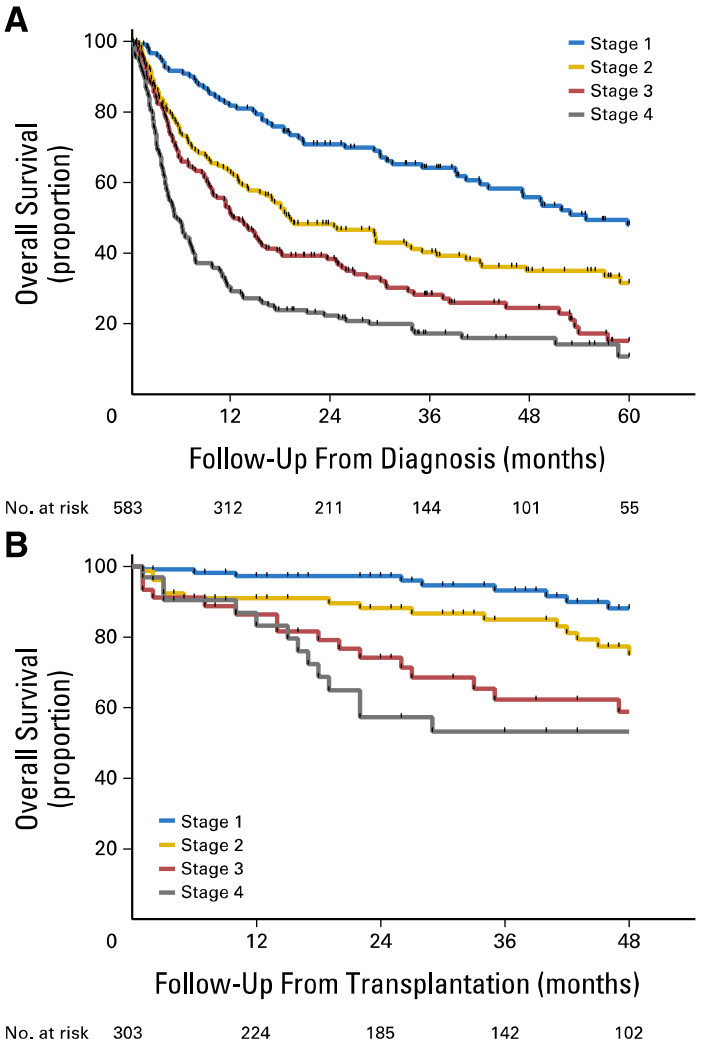
- Extent of cardiac involvement in AL drives outcome
- Mayo Clinic study of 261 AL patients seen between 1979-2000
- Factors
  - cTnT <0.035 ug/L
  - NT-pro-BNP <332 ng/L

Stage	%	Median OS (mos)
I	33	26.4
II	30	10.5
III	37	3.5



Dispenzieri J Clin Oncol 2004

Prognosis in AL – Mayo 2012 staging



- Cardiac involvement + plasma cell clone
- Factors
  - cTnT ≥ 0.025 ng/mL
  - NT-proBNP ≥1,800 pg/mL
  - FLC-diff ≥ 180 mg/L

Stage	%	Median OS (mos)
I	25	94.1
II	27	40.3
III	25	14.0
IV	23	5.8

Kumar S J Clin Oncol 2012

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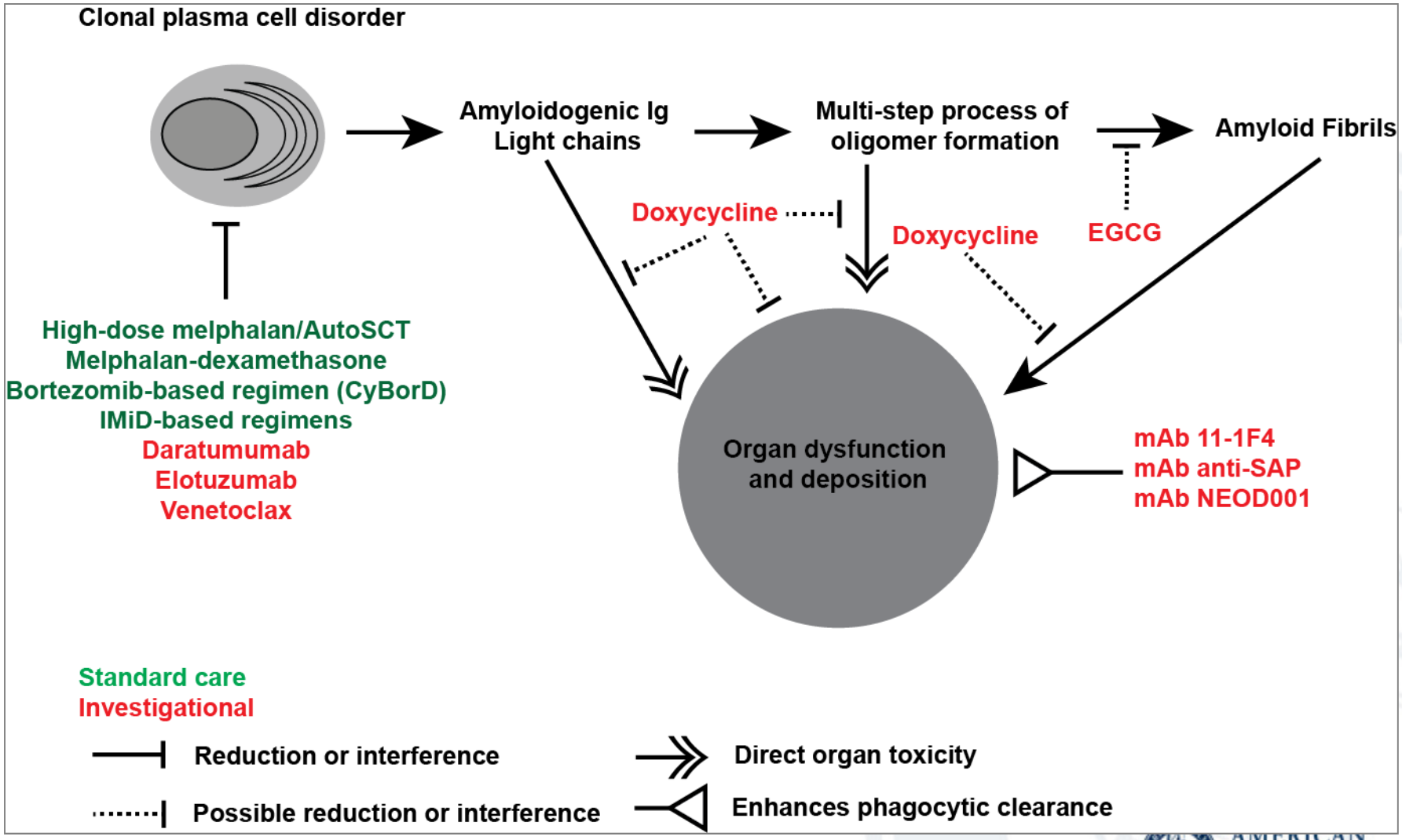
Goals of therapy in AL amyloidosis

- Obtain rapid, deep and sustained clonal remissions
  - Defined by serum free light chain response
  - Hematologic “very good partial remission” = FLC-diff <40 mg/L or better
- Reducing toxic serum free light chains
  - Improves cardiac function
  - Allows for clearance of tissue amyloid by native immune system
- Interfere with amyloid formation?
- Stimulate therapeutic clearance of amyloid from tissues?
- Prolong survival
- Cure?

Therapeutic approaches to AL amyloidosis

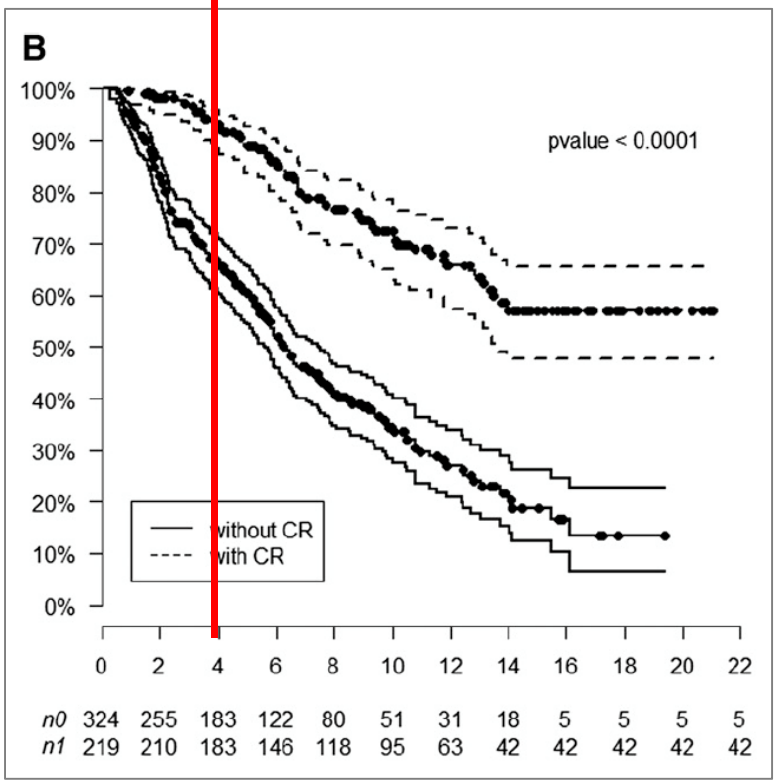


Modified from Weiss Blood 2016

Achieving a deep hematologic remission is the key to prolonged survival – but how to get there?

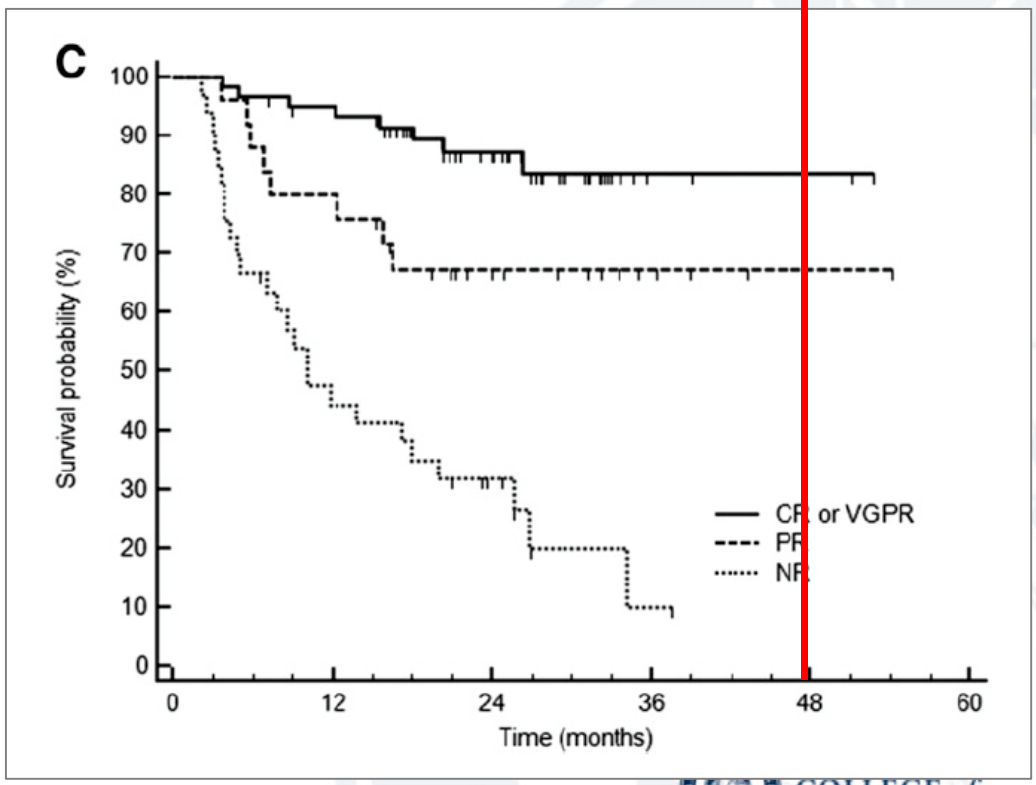
HDM/ASCT
Boston University 1994-2014
n = 629

4 years



Chemotherapy (CyBorD)
UK NAC & Pavia 2006-2013
n = 230

4 years



Sanchorawala Blood 2015, Palladini Blood 2015

HDM/ASCT Pro-Con

Pro

Favor HDM/ASCT

- Deep hematologic responses
- Durable responses - most
- Matched-case control favors HDM/ASCT
- Transplant related mortality now 3-5%

Con

Favor chemotherapy

- RCT favors chemotherapy
- All patients are candidates
- Treatment related morality <2%
- Many agents available to achieve response

An individualized, risk-adapted, multi-disciplinary treatment plan by clinicians experienced in amyloidosis is required for all patients.

Sher Biol Blood Marrow Transplant 2016,
Devine Biol Blood Marrow Transplant 2014

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Who is eligible for HDM/ASCT?

- Only about 25% of all patients are eligible
- Criteria (Mayo)
  - ”Physiologic” age ≤70 years

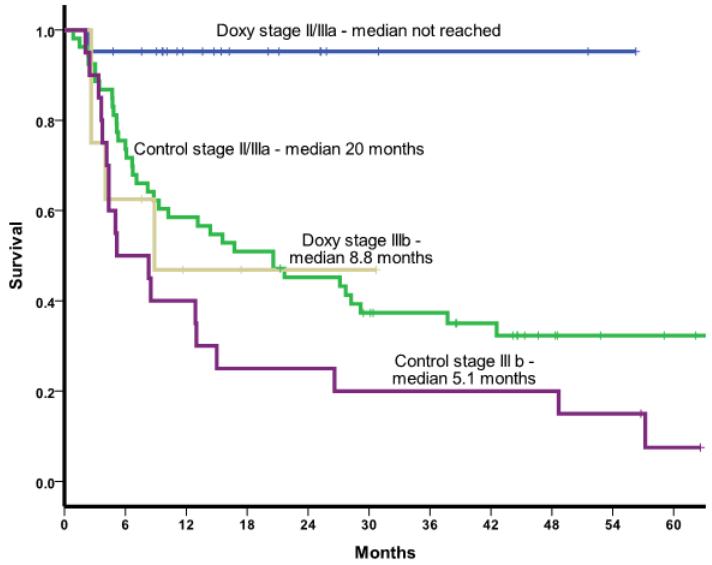
The role of HDM/ASCT is diminishing, in particular for cardiac amyloidosis

  - Troponin T <0.06 ng/mL,
  - CrCl ≥30 mL/min (unless on HD)
  - NYHA I/II
  - No more than 2 organs *significantly* involved (liver, heart, kidney, autonomic nerve)

Doxycycline may reduce early death in cardiac AL

- Doxycyline may be cardioprotective
  - Interfere with amyloid fibril formation
  - May accelerate amyloid clearance
  - Reduces cardiotoxicity of light chains
- Matched case-control study from UK NAC

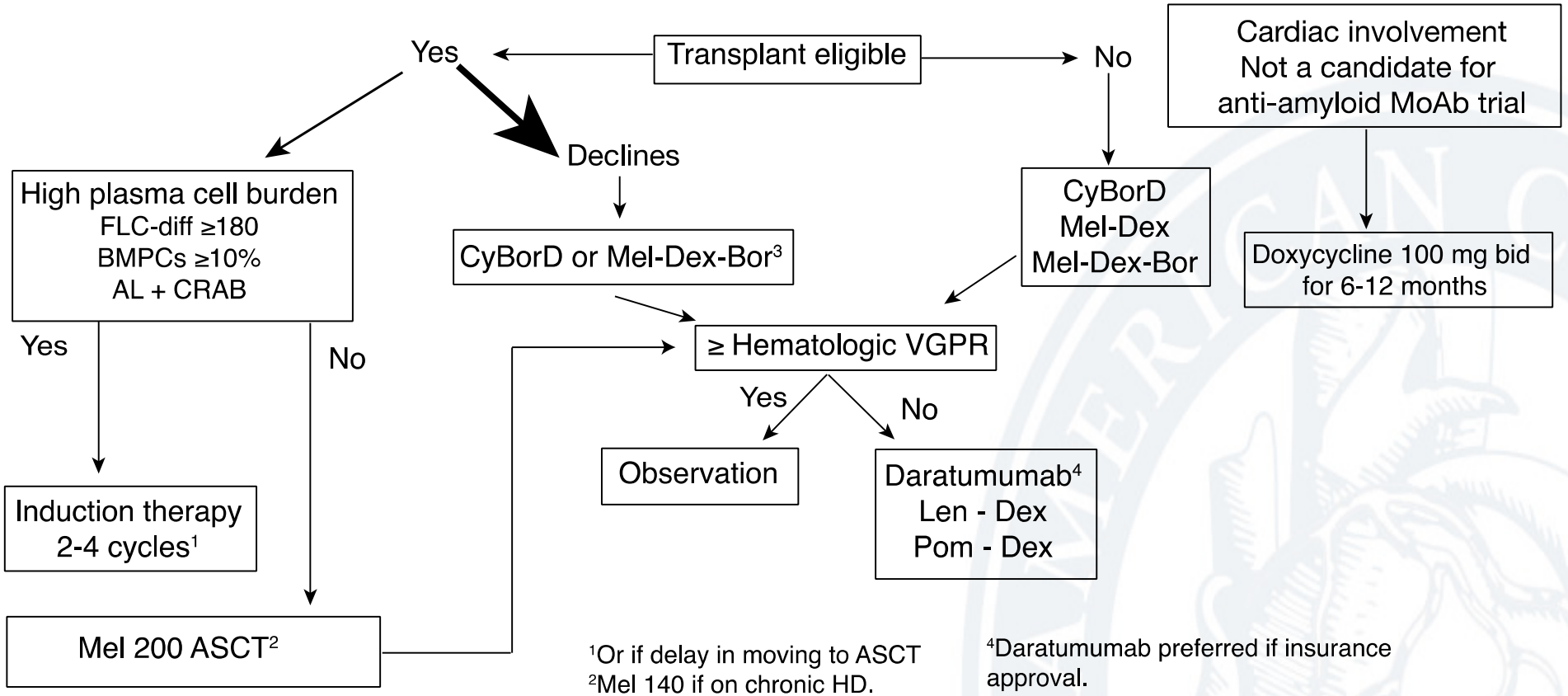
	Doxy	Control	
Patients, n	30	73	
Hematologic CR/VGPR, %	56/10	35/8	
Cardiac response, %	60	18	<0.0001
Median OS, months	NR	13	
12 month survival, %	82	53	<0.001
24 month survival , %	82	40	



Wechelakar ASH 2015

COLLEGE of CARDIOLOGY

An approach to AL amyloidosis for 2017



[1]Or if delay in moving to ASCT
[2]Mel 140 if on chronic HD.
[3]Do not use Mel if candidate for ASCT in second line.

[4]Daratumumab preferred if insurance approval.

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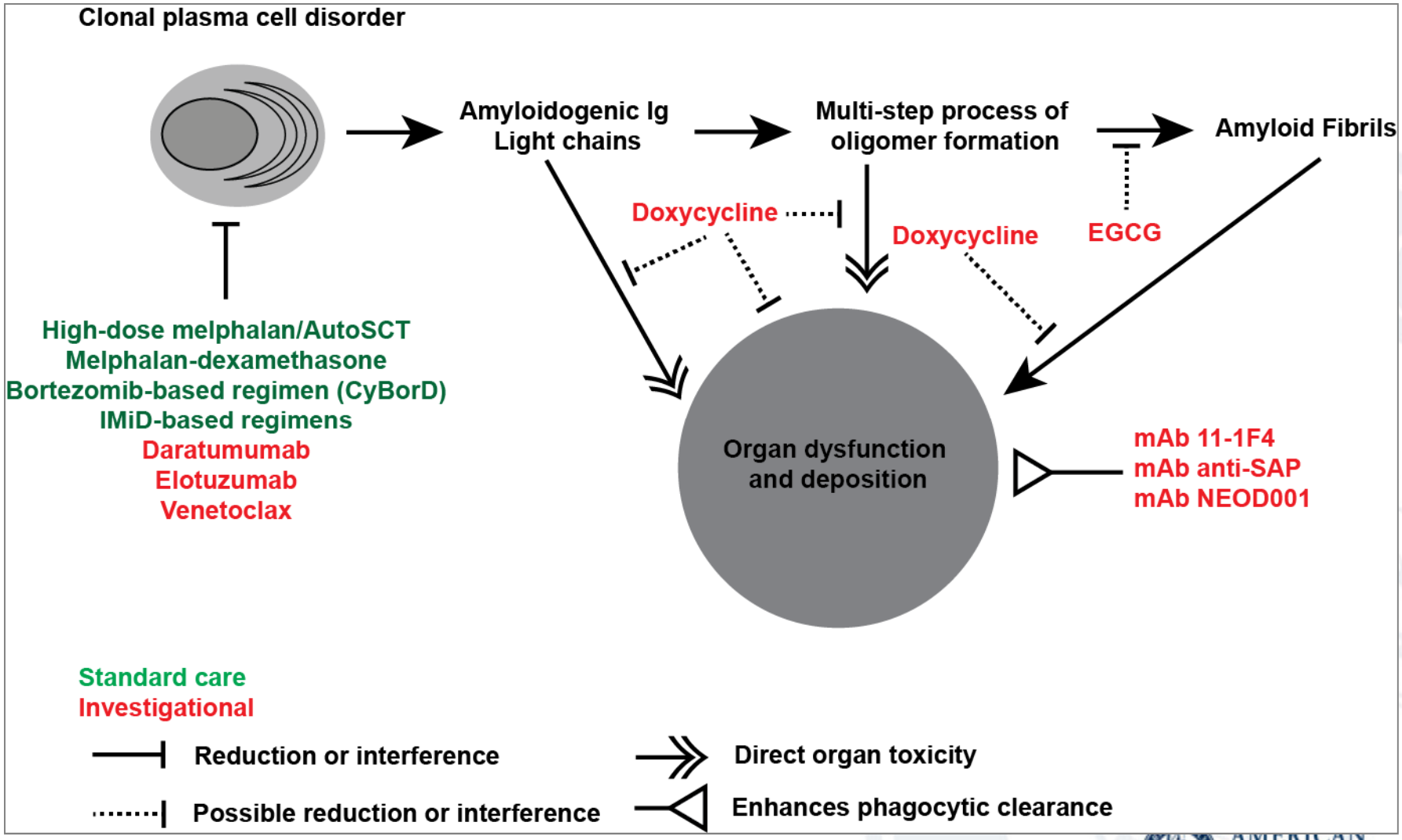
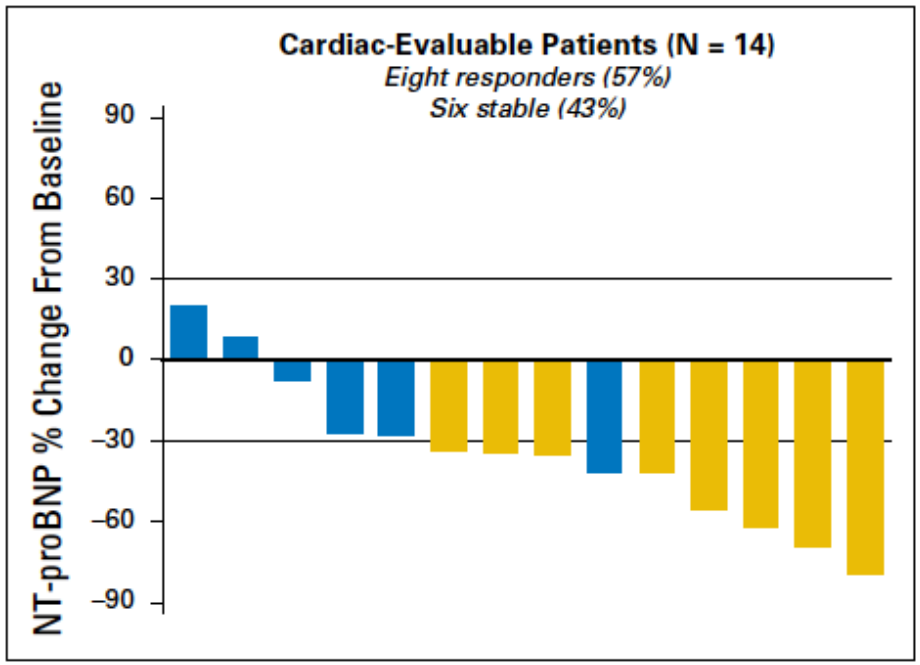
Therapeutic approaches to AL amyloidosis

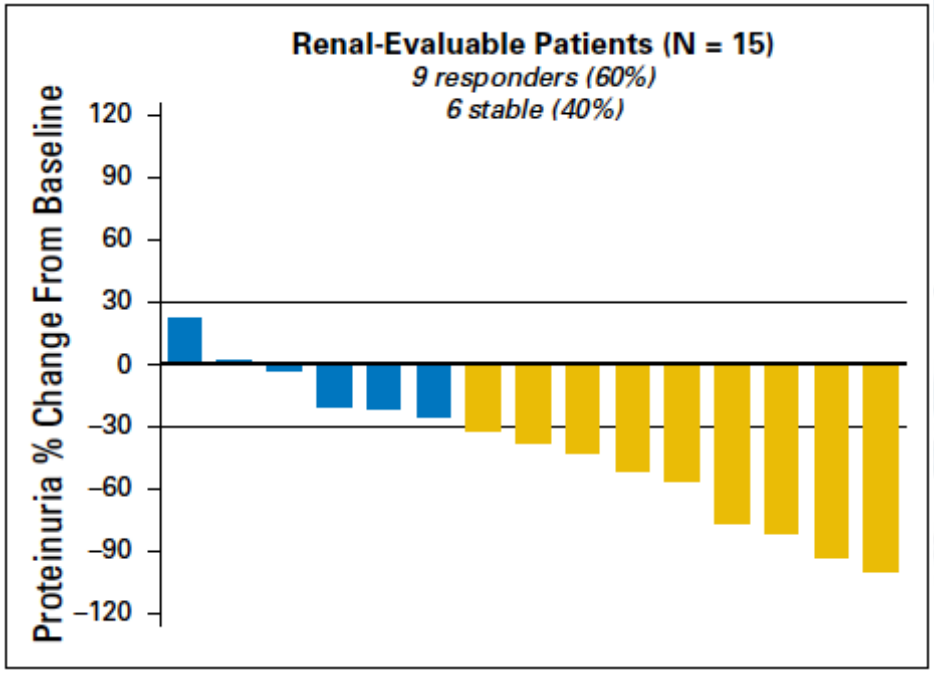


Modified from Weiss Blood 2016

NEOD001 in AL amyloidosis

- NEOD001 is a monoclonal antibody targets epitope on amyloid deposits
- Believed to trigger phagocytic clearance by macrophages
- Phase 1 study of monthly IV infusions in patients with persistent organ dysfunction after chemotherapy
- Safe with encouraging cardiac and renal responses



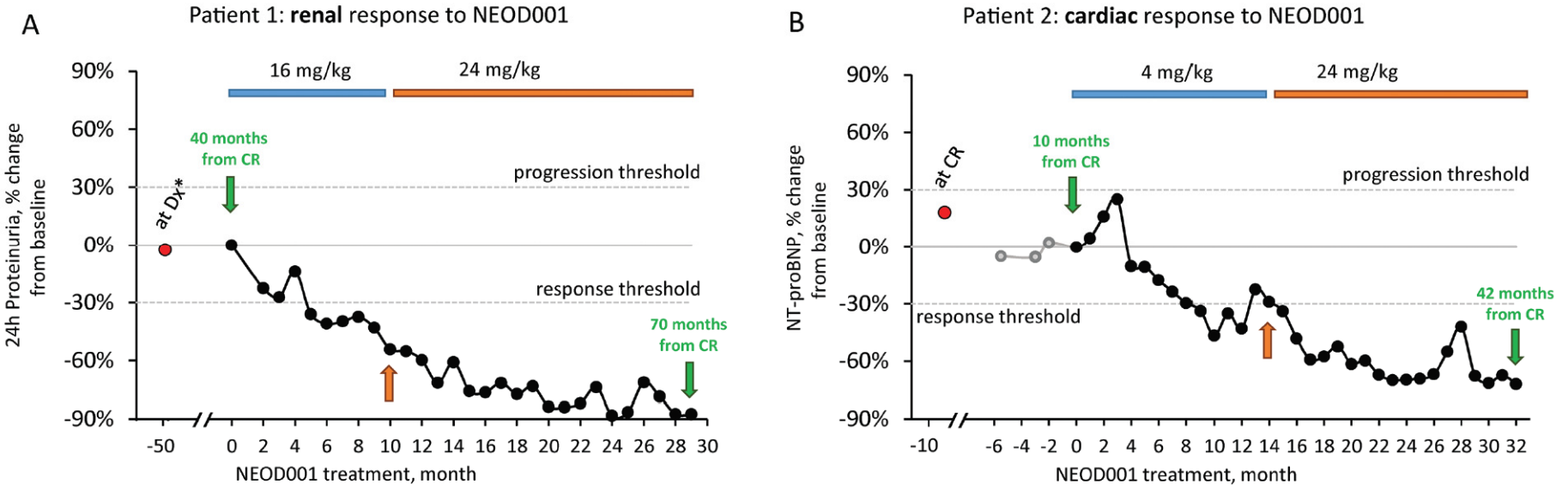


Gertz J Clin Oncol 2016

Gertz *J Clin Oncol* 2016

What about the impact of prior chemotherapy?

- NEOD001 induces organ improvement in patients in long-term hematologic remissions
  - Patient 1: Renal response 40 months after hem CR
  - Patient 2: Cardiac response 10 months after hem CR

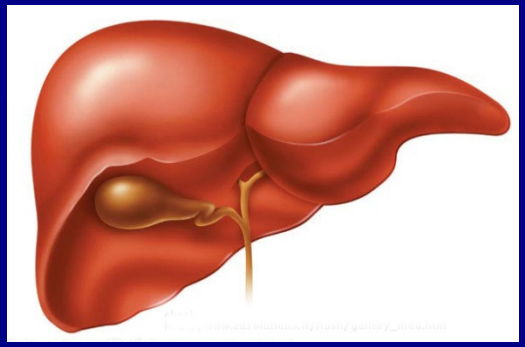


Gertz, Landau, Weiss Am J Hematol 2016

Treatment: ATTR Amyloidosis

ATTR Amyloidosis: Traditional View

- Wild-type ("senile") ATTR:
  - Supportive Rx only

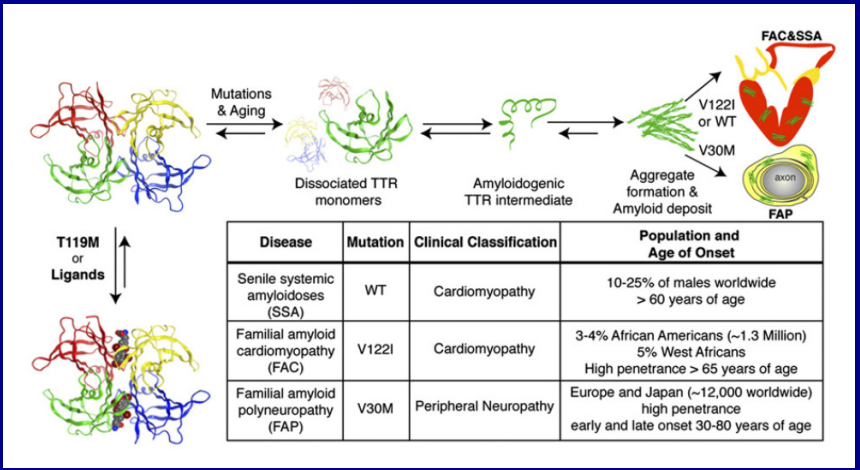


- Familial ATTR: Early liver transplant
  - TTR is almost exclusively produced by the liver
  - If replaced the liver → remove mutated TTR protein → slow or halt disease progression
  - Used primarily for "FAP"
    - Early age of onset
    - Disabling neuropathy

Strategies to Prevent TTR Amyloid Deposition

- Stabilize tetrameric form of TTR by binding to L-thyroxine receptor
  - Tafamidis
  - NSAIDs (diflunisal)
  - Other investigational agents...
    - Tolcapone
    - AG10

- Inhibit production of TTR in all forms
  - RNA inhibition/interference



Disease	Mutation	Clinical Classification	Population and Age of Onset
Senile systemic amyloidoses (SSA)	WT	Cardiomyopathy	10-25% of males worldwide > 60 years of age
Familial amyloid cardiomyopathy (FAC)	V122I	Cardiomyopathy	3-4% African Americans (~1.3 Million) 5% West Africans High penetrance > 65 years of age
Familial amyloid polyneuropathy (FAP)	V30M	Peripheral Neuropathy	Europe and Japan (~12,000 worldwide) high penetrance early and late onset 30-80 years of age

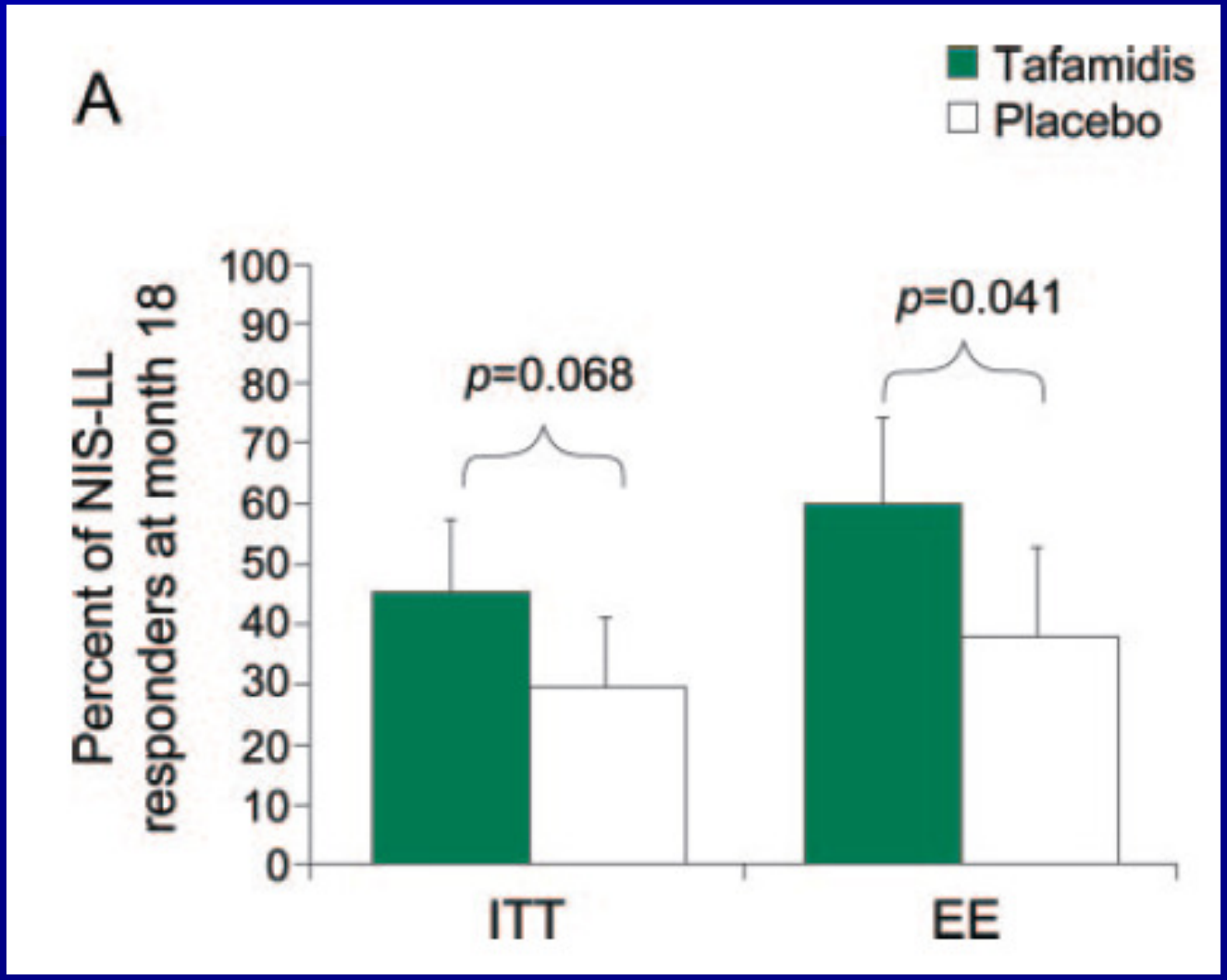
Adapted from Penchala et al. PNAS. 2013;110:9992-9997.

Tafamidis Trial in "FAP"

- Phase 3 trial conducted at 8 sites in Europe & South America

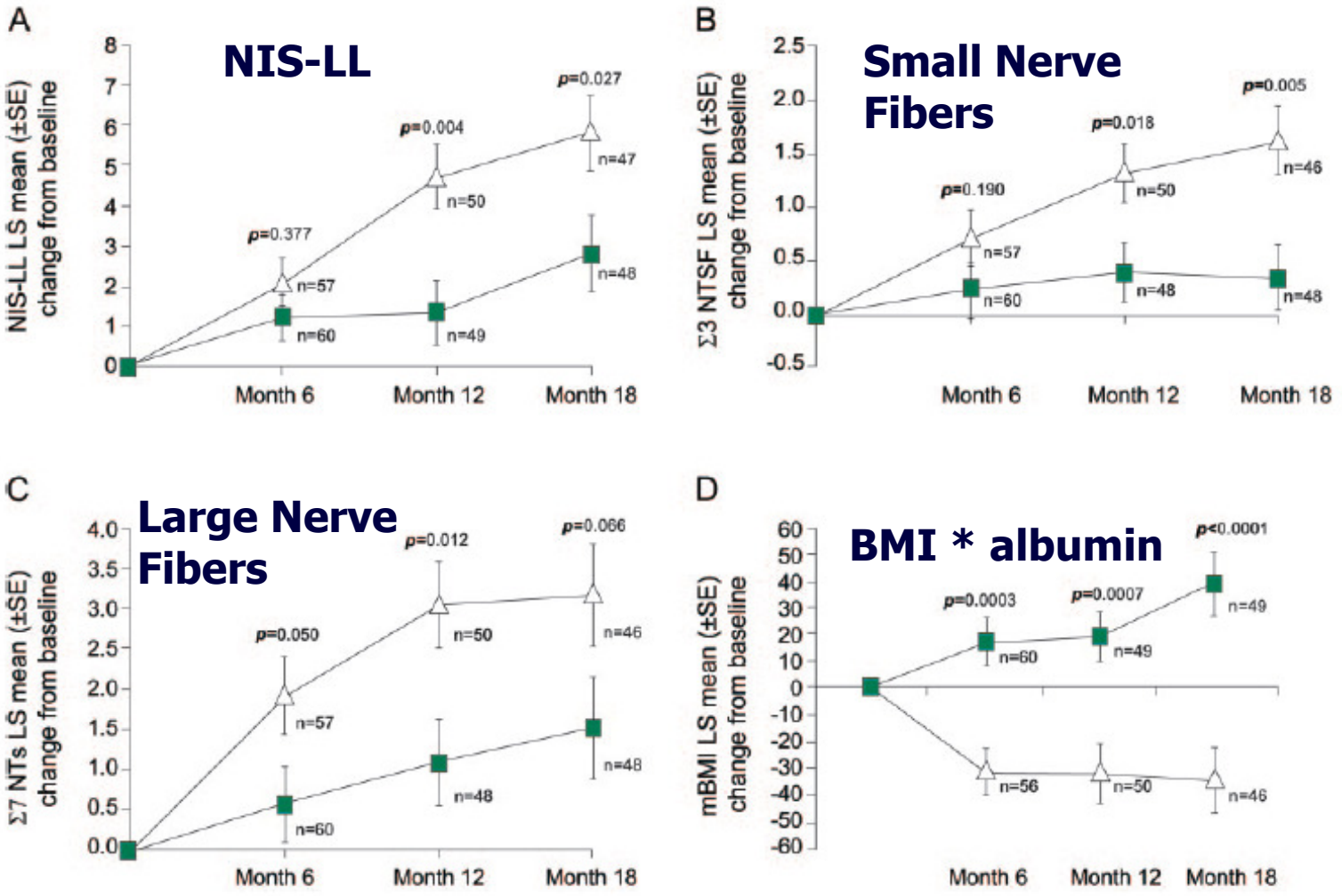
- 128 patients with FAP due to V30M mutation randomized to tafamidis or placebo x 18 months
  - Primary endpoint: "Responder" or "Nonresponder"
  - Occurrence of liver transplant → "Nonresponder"
    - 69% on liver transplant list at start of study (!)
    - 13 patients in each group (21%) transplanted during study

Tafamidis FAP Trial



Adapted from Coelho et al. Neurology. 2012;79:785-792.

Secondary Endpoints



Adapted from Coelho et al. Neurology. 2012;79:785-792.

Tafamidis Approval for FAP

Tafamidis Approval for FAP

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

pmda
JAPAN

FDA

Tafamidis Approval for FAP

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pmda
JAPAN

FDA

Tafamidis Approval for FAP

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pmda
JAPAN

FDA

ATTR-ACT Study – Tafamidis for ATTR Cardiomyopathy

- Phase 3, Randomized, Placebo-Controlled clinical trial of tafamidis for ATTR cardiomyopathy
  - Wild-type or familial
  - 441 patients worldwide x 2.5 years
  - Primay endpoint: Mortality & CV Hospitalization
  - Completed enrollment summer, 2015

NSAIDs/Diflunisal

- NSAIDs – Found on screening to stabilize transthyretin
- Diflunisal: FDA approved for arthritis pain
  - Found to be most effective NSAID at binding to TTR
- Double-blind, placebo-controlled clinical trial for FAP reported in December, 2013

Research

Original Investigation

Repurposing Diflunisal for Familial Amyloid Polyneuropathy
A Randomized Clinical Trial

John L. Berk, MD; Ole B. Suhr, MD, PhD; Laura Obici, MD; Yoshiki Sekijima, MD, PhD; Steven R. Zeldenrust, MD, PhD; Taro Yamashita, MD, PhD; Michael A. Heneghan, MD; Peter D. Gorevic, MD; William J. Litchy, MD; Janice F. Wiesman, MD; Erik Nordh, MD, PhD; Manuel Corato, MD, PhD; Alessandro Lozza, MD; Andrea Cortese, MD; Jessica Robinson-Papp, MD; Theodore Colton, ScD; Denis V. Rybin, MS; Alice B. Bisbee, MPH; Yukio Ando, MD, PhD; Shu-ichi Ikeda, MD, PhD; David C. Seldin, MD, PhD; Giampaolo Merlini, MD; Martha Skinner, MD; Jeffery W. Kelly, PhD; Peter J. Dyck, MD; for the Diflunisal Trial Consortium

IMPORTANCE Familial amyloid polyneuropathy, a lethal genetic disease caused by aggregation of variant transthyretin, induces progressive peripheral nerve deficits and disability. Diflunisal, a nonsteroidal anti-inflammatory agent, stabilizes transthyretin tetramers and prevents amyloid fibril formation in vitro.

OBJECTIVE To determine the effect of diflunisal on polyneuropathy progression in patients with familial amyloid polyneuropathy.

DESIGN, SETTING, AND PARTICIPANTS International randomized, double-blind, placebo-controlled study conducted among 130 patients with familial amyloid polyneuropathy exhibiting clinically detectable peripheral or autonomic neuropathy at amyloid centers in Sweden (Umeå), Italy (Pavia), Japan (Matsumoto and Kumamoto), England (London), and the United States (Boston, Massachusetts; New York, New York; and Rochester, Minnesota) from 2006 through 2012.

INTERVENTION Participants were randomly assigned to receive diflunisal, 250 mg (n=64), or placebo (n=66) twice daily for 2 years.

MAIN OUTCOMES AND MEASURES The primary end point, the difference in polyneuropathy progression between treatments, was measured by the Neuropathy Impairment Score plus 7 nerve tests (NIS+7) which ranges from 0 (no neurological deficits) to 270 points (no detectable peripheral nerve function). Secondary outcomes included a quality-of-life questionnaire (36-Item Short-Form Health Survey [SF-36]) and modified body mass index. Because of attrition, we used likelihood-based modeling and multiple imputation analysis of baseline to 2-year data.

RESULTS By multiple imputation, the NIS+7 score increased by 25.0 (95% CI, 18.4-31.6) points in the placebo group and by 8.7 (95% CI, 3.3-14.1) points in the diflunisal group, a difference of 16.3 points (95% CI, 8.1-24.5 points; $P < .001$). Mean SF-36 physical scores decreased by 4.9 (95% CI, −7.6 to −2.2) points in the placebo group and increased by 1.5 (95% CI, −0.8 to 3.7) points in the diflunisal group ($P < .001$). Mean SF-36 mental scores declined by 1.1 (95% CI, −4.3 to 2.0) points in the placebo group while increasing by 3.7 (95% CI, 1.0-6.4) points in the diflunisal group ($P = .02$). By responder analysis, 29.7% of the diflunisal group and 9.4% of the placebo group exhibited neurological stability at 2 years (<2-point increase in NIS+7 score; $P = .007$).

CONCLUSIONS AND RELEVANCE Among patients with familial amyloid polyneuropathy, the use of diflunisal compared with placebo for 2 years reduced the rate of progression of neurological impairment and preserved quality of life. Although longer-term follow-up studies are needed, these findings suggest benefit of this treatment for familial amyloid polyneuropathy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00294671

JAMA. 2013;310(24):2658-2667. doi:10.1001/jama.2013.283815

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Diflunisal Trial Consortium are listed at the end of this article.

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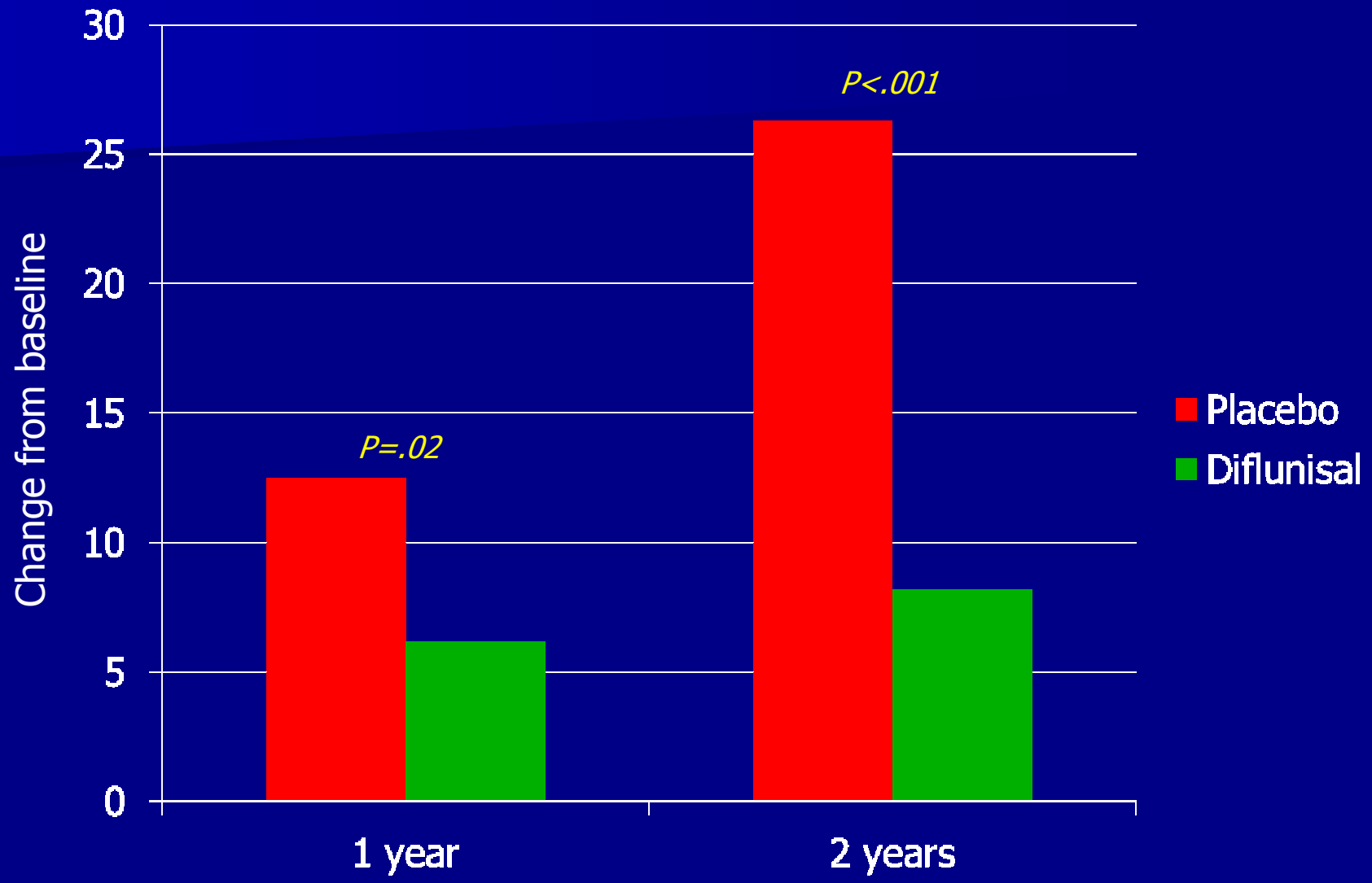
jama.com

Adapted from Berk et al. JAMA. 2013;310:2658-2667.

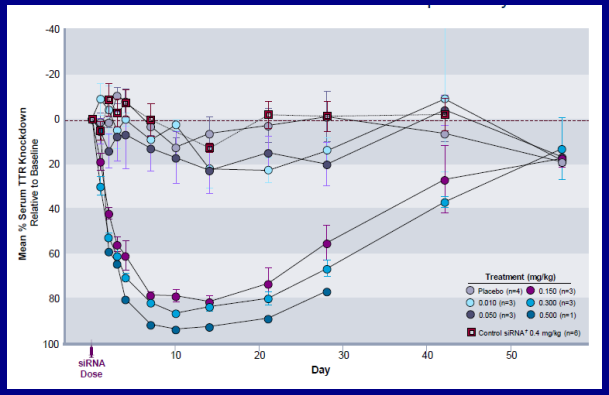
Diflunisal Study: NIS+7 Score



Adapted from Berk et al. JAMA. 2013;310:2658-2667.

RNA Interference & Antisense

- RNA interference (ALN-TTR)
  - Decreases circulating TTR by approximately 85%
  - IV form:
    - Phase 3 study (IV) in FAP – "APOLLO"
      - 225 patients x 18 months
      - Estimated completion: August, 2017
  - Sub-Q form:
    - Phase 3 study in FAC – "ENDEAVOUR":
    - Stopped early due to excess mortality in treatment arm



Adapted from Coelho et al. N Engl J Med. 2013;369:819-29.

- Antisense Technology (IONIS-TTR)
  - Phase 2/3 Study (SQ) in FAP currently ongoing
    - 195 patients x 64 weeks
    - 2016: Concerns raised re: thrombocytopenia
  - Cardiac trial originally planned... Now not.

Summary of Clinical Trials

- Polyneuropathy ("FAP")
  - Tafamidis (oral):
    - Borderline positive results → Approved in Europe/Japan, not USA
  - Diflunisal (oral): Positive trial
  - ALN-TTR (IV): Current phase 3 trial
  - IONIS-TTR (SQ): Current phase 2/3 trial

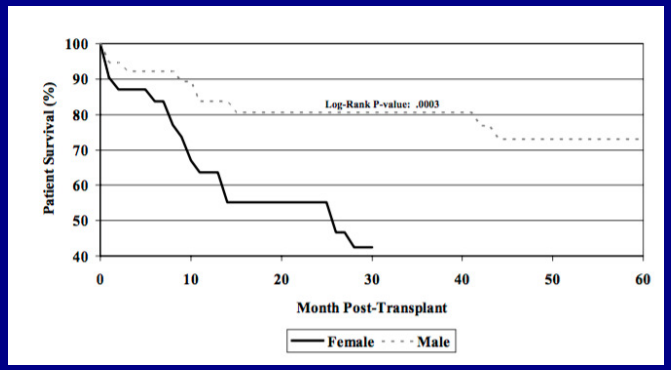
- Cardiomyopathy
  - Tafamidis (oral): Current phase 3 trial (ATTR-ACT) – Wild-type & FAC
    - Enrollment completed
  - ALN-TTR (SQ): Phase 3 trial (ENDEAVOUR) – Stopped early due to harm
  - IONIS-TTR: Planned trial halted before it began

Heart Transplant: Is it Crazy?

- 1980s-1990s: Amyloid outcomes when transplanted → Terrible
  - Mainly AL amyloidosis, mainly late, poor chemotherapy options!
- Patients died from:
  - Multiorgan dysfunction from amyloid infiltration
  - Recurrent amyloid deposition in new graft
- But what if…
  - Patients were selected who had little-no significant extracardiac involvement
  - Patients received effective chemotherapy as part of their treatment

Early 2000s: Still Discouraging…

- 2004: Report on UK transplants for amyloidosis 1982-2002
  - 24 transplants for amyloid (17 AL)
  - Median survival: 29 months
  - AL amyloid: 59% 1-year survival

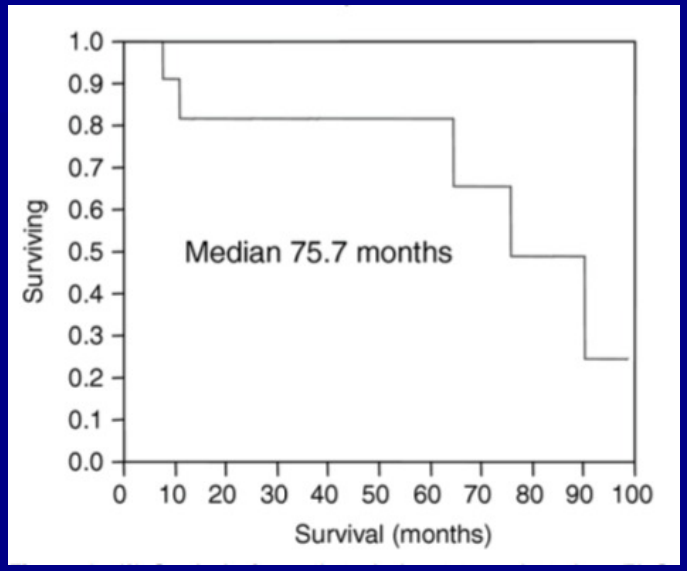


- 2005: Report on all 69 patients transplanted in USA per UNOS 1987-2002
  - 1-year survival: 74.6%
  - 5-year survival: 54.0%
  - Worse than nonamyloid transplant survival (P=0.03)
  - Men survived longer than women
    - ? Surrogate for ATTR vs. AL

Adapted from Dubrey et al. J Heart Lung Transplant. 2004;23:1142-11 and Kpodonu et al. J Heart Lung Transplant. 2005;24:1763-5.

Mayo Experience

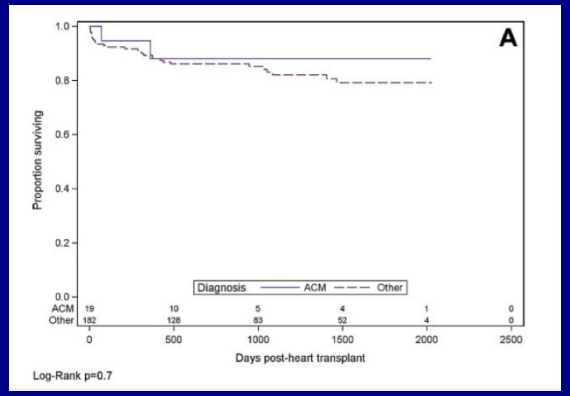
- Reported on 11 patients who underwent heart transplant for AL amyloidosis from 1994-2005
- All were screened for evidence of significant extracardiac organ involvement
- All underwent sequential heart transplant → SCT
- Outcomes:
  - Worse than average heart transplant...
  - But acceptable?



Adapted from Lacy et al. J Heart Lung Transplant. 2008;27:823-829.

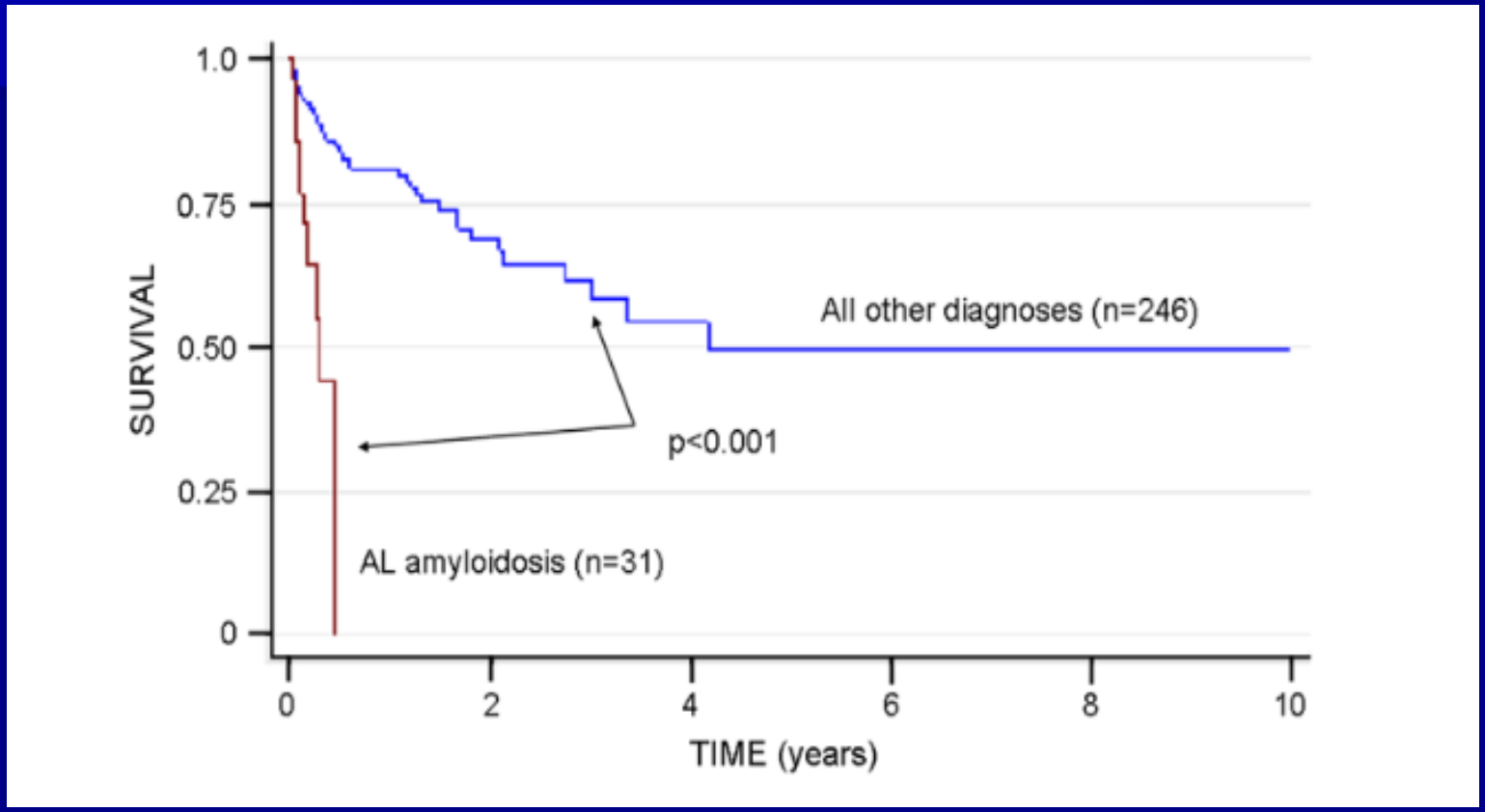
Stanford Experience

- Stanford 2008-2013: 19 transplants for end-stage cardiac amyloidosis – data published in 2015
  - AL: 9 patients
  - ATTR: 10 patients
- Current status: 22/24 (92%) transplanted since 2008 are alive
  - AL: 10/10 patients alive
    - 9 with no deposition up to >8 years out
    - 1 with mild deposition in new graft
    - **Not all automatically slated for SCT**
  - ATTR: 12/14 patients alive
    - 2 deaths (unrelated to amyloid)
    - 12 patients without recurrent amyloid deposition in new graft



Adapted from Davis et al. Am J Transplant. 2015. 15(3):650-658.

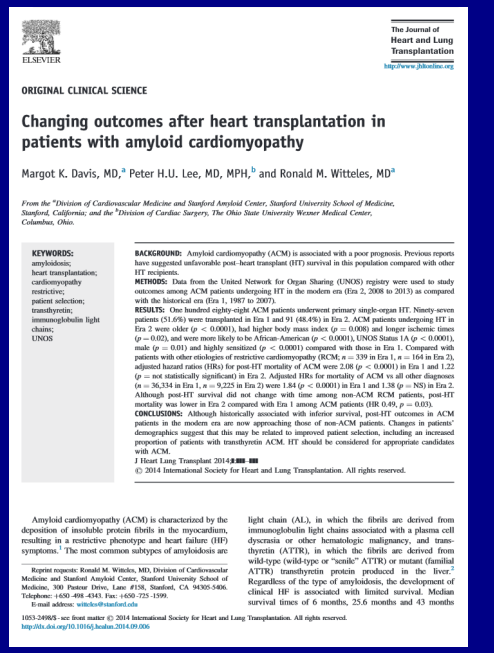
High Wait-List Mortality: MGH Experience 2000-2011 of 31 patients listed for OHT



Adapted from Gilstrap et al. J Heart Lung Transplant. 2014;33:149-156

Heart Transplant: National Data

- UNOS Registry: Amyloid vs. Other RCM vs. All others
- Examined Era 1 (1987-2007) vs. Era 2 (2008-2013)
- Could not differentiate AL from ATTR
- Findings:
  - Era 1: 111 amyloid/36483 total (0.3%)
  - Era 2: 110 amyloid/9383 total (1.2%)
  - Demographics: Era 2 = Older, higher % black, higher % male (compared with Era 1)
  - Survival significantly better in Era 2 vs. Era 1 for amyloid patients (unchanged for other RCM patients)
  - Survival not statistically different from overall cohort or other RCM patients in Era 2 (much worse in Era 1)



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ORIGINAL CLINICAL SCIENCE

Changing outcomes after heart transplantation in patients with amyloid cardiomyopathy

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KEYWORDS: amyloidosis; heart transplantation; cardiomyopathy restrictive; patient selection; transthyretin; immunoglobulin light chains; UNOS

BACKGROUND: Amyloid cardiomyopathy (ACM) is associated with a poor prognosis. Previous reports have suggested unfavorable post–heart transplant (HT) survival in this population compared with other HT recipients.
METHODS: Data from the United Network for Organ Sharing (UNOS) registry were used to study outcomes among ACM patients undergoing HT in the modern era (Era 2, 2008 to 2013) as compared with the historical era (Era 1, 1987 to 2007).
RESULTS: One hundred eighty-eight ACM patients underwent primary single-organ HT. Ninety-seven patients (51.6%) were transplanted in Era 1 and 91 (48.4%) in Era 2. ACM patients undergoing HT in Era 2 were older ($p < 0.0001$), had higher body mass index ($p = 0.008$) and longer ischemic times ($p = 0.02$), and were more likely to be African-American ($p < 0.0001$), UNOS Status 1A ($p < 0.0001$), male ($p = 0.01$) and highly sensitized ($p < 0.0001$) compared with those in Era 1. Compared with patients with other etiologies of restrictive cardiomyopathy (RCM), n = 339 in Era 1, n = 164 in Era 2), adjusted hazard ratios (HRs) for post-HT mortality of ACM were 2.08 ($p < 0.0001$) in Era 1 and 1.22 ($p =$ not statistically significant) in Era 2. Adjusted HRs for mortality of ACM vs all other diagnoses (n = 36,334 in Era 1, n = 9,225 in Era 2) were 1.84 ($p < 0.0001$) in Era 1 and 1.38 ($p =$ NS) in Era 2. Although post-HT survival did not change with time among non-ACM RCM patients, post-HT mortality was lower in Era 2 compared with Era 1 among ACM patients (HR 0.49, $p = 0.03$).
CONCLUSIONS: Although historically associated with inferior survival, post-HT outcomes in ACM patients in the modern era are now approaching those of non-ACM patients. Changes in patients' demographics suggest that this may be related to improved patient selection, including an increased proportion of patients with transthyretin ACM. HT should be considered for appropriate candidates with ACM.
J Heart Lung Transplant 2014;■■■-■■■

Amyloid cardiomyopathy (ACM) is characterized by the deposition of insoluble protein fibrils in the myocardium, resulting in a restrictive phenotype and heart failure (HF) symptoms.[1] The most common subtypes of amyloidosis are light chain (AL), in which the fibrils are derived from immunoglobulin light chains associated with a plasma cell dyscrasia or other hematologic malignancy, and transthyretin (ATTR), in which the fibrils are derived from wild-type (wild-type or "senile" ATTR) or mutant (familial ATTR) transthyretin protein produced in the liver.[2] Regardless of the type of amyloidosis, the development of clinical HF is associated with limited survival. Median survival times of 6 months, 25.6 months and 43 months

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http://dx.doi.org/10.1016/j.healun.2014.09.006

Adapted from Davis et al. J Heart Lung Transplant. 2015;34:658-66.

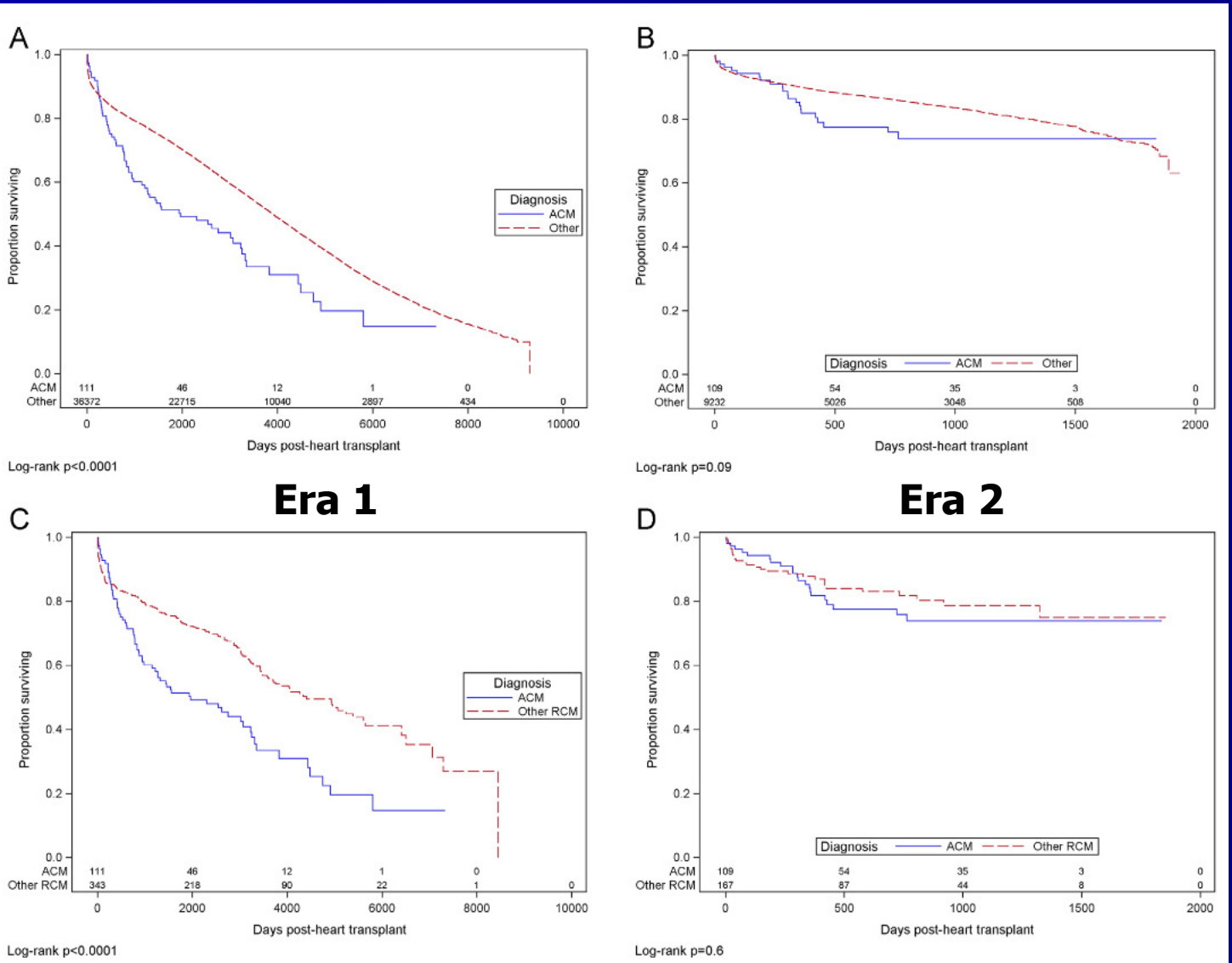
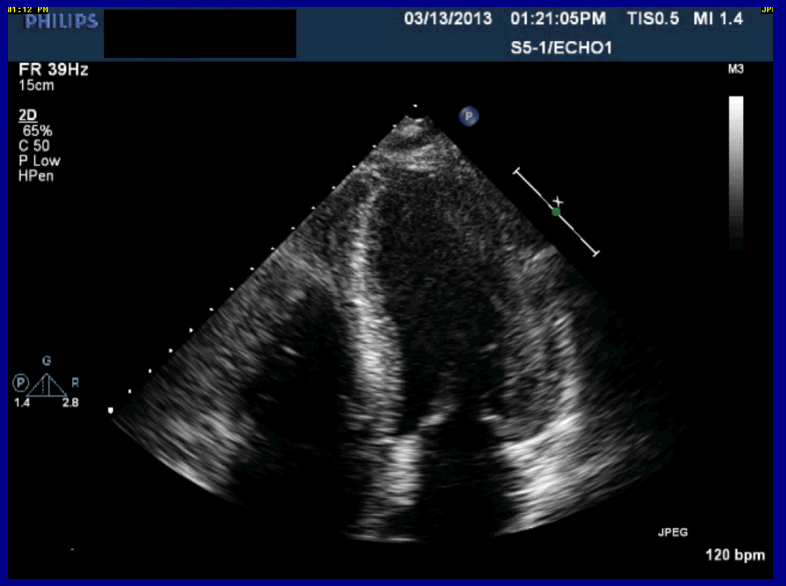


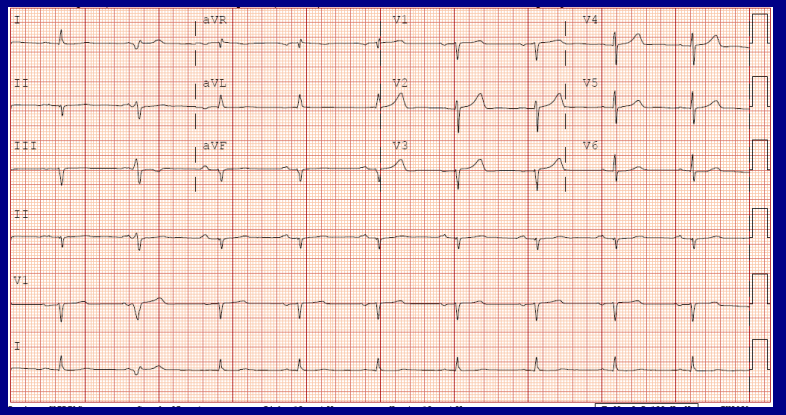
Figure 2 (A) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs all other diagnoses in Era 1 (1987 to 2007). (B) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs all other diagnoses in Era 2 (2008 to 2013). (C) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs other restrictive cardiomyopathies (RCM) undergoing heart or heart–liver transplantation in Era 1 (1987 to 2007). (D) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs other restrictive cardiomyopathies (RCM) undergoing heart or heart–liver transplantation in Era 2 (2008 to 2013).

Adapted from Davis et al. J Heart Lung Transplant. 2015;34:658-66.

Case #1

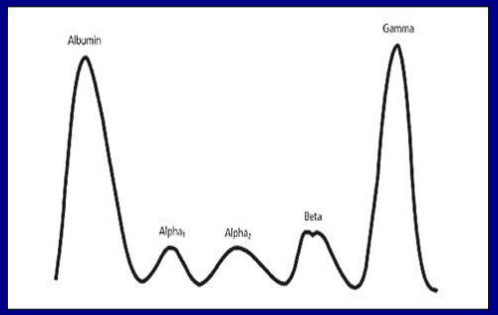
- 70 year-old Caucasian man
- Elevated screening PSA → Prostate CA → Radical prostatectomy
- Following 2 months:
  - LE/scrotal edema
  - TTE → moderate concentric LVH, normal systolic function, severe diastolic dysfunction, RVSP = 52 mmHg.
  - EKG performed





Case Presentation #1

- Laboratory studies:
  - SPIEP: Trace IgM-lambda monoclonal spike
  - Serum free light chain assay:
    - Significantly elevated free lambda light chain



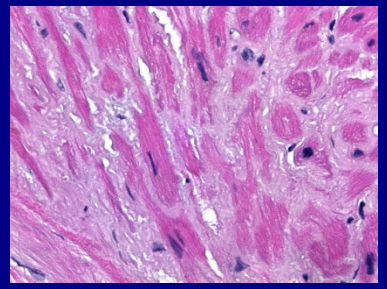
- Bone marrow biopsy
  - Small lambda-restricted plasma cell population
  - + Amyloid deposits in blood vessels

- Referred for consideration of the best chemotherapy options

Which is the Best Option?

- 1) Autologous stem cell transplant (ASCT)
- 2) Proteasome inhibitor-based regimen (e.g. CyBorD)
- 3) Daratumumab
- 4) None of the above – the diagnosis still isn't clear

What Happened...



- Pathology sent for mass spectrometry:
  - Amyloid deposits = TTR (!), wild-type
- Endomyocardial biopsy
  - Diffuse amyloid involvement → stained strongly for TTR
- Clinical course
  - ATTR amyloidosis
    - Symptomatic treatment
    - Enrolled in tafamidis Phase 3 trial
  - MGUS – no chemotherapy indicated
  - Doing well >3 years since diagnosis

Question #2

- Case presentation
- 63 year-old female with
  - Severe fatigue and nausea
  - Multiple episodes of presyncope
  - Pain and tingling in legs and hands
  - Dyspnea on exertion and lower extremity edema
  - 20 pound weight gain
- Exam: BP 70/44 P 117, 4+ edema
- Laboratory data
  - NT-proBNP 10,744, troponin T 0.3
  - 24 hour urine protein 12 grams

A Congo Red stain is positive on an aspirate of abdominal fat. The serum free light chain differential is 250 mg/L and a bone marrow biopsy shows 15% lambda-restricted plasma cells.

Question

What anti-plasma cell therapy is clearly contraindicated in this patient?

A.Cyclophosphamide and prednisone
B.Melphalan and dexamethasone
C.Bortezomib and dexamethasone
D.High-dose melphalan and autologous stem cell transplantation

Answer Question #2

- High dose melphalan and ASCT is contraindicated in this patient due to NT-proBNP >5,000, positive troponin T and systolic blood pressure <90.
- Bortezomib is relatively contraindicated in this patient given the SBP <90. A trial of midodrine and/or fludricortisone can increase the blood pressure to allow for use of bortezomib.
- The other regimens can be given with careful attention to the patient's volume status and would be preferred if attempts to raise the blood pressure were unsuccessful.

Take Home Points

- Think about amyloidosis!
- Importance of determining subtype
- Amyloidosis ≠ death sentence
- AL amyloidosis treatments:
  - We have effective chemotherapy now
  - Hematologic response is key to controlling the disease
  - Emerging therapies to target amyloid deposits
- ATTR: Emerging therapies in clinical trials
  - But some recent hiccups
- Role of ICDs/heart transplant
- Importance of multidisciplinary approach, centers of excellence, clinical trials