About OMICS Group

OMICS Group is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

About OMICS International Conferences

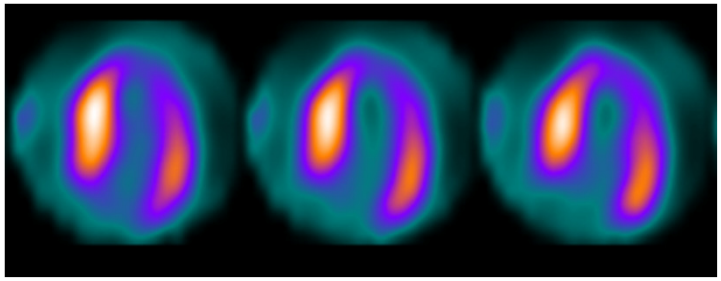
OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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5th International Conference on
Clinical & Experimental Cardiology
April 27-29, 2015 Philadelphia, USA

Cardiac Amyloidosis - A changing landscape?



Dr Ashutosh Wechalekar

National Amyloidosis Centre

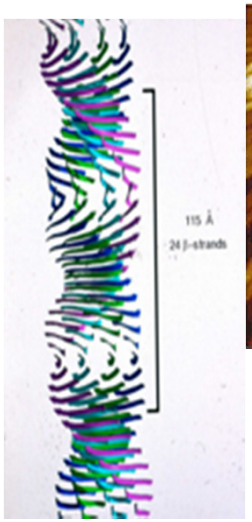
University College London

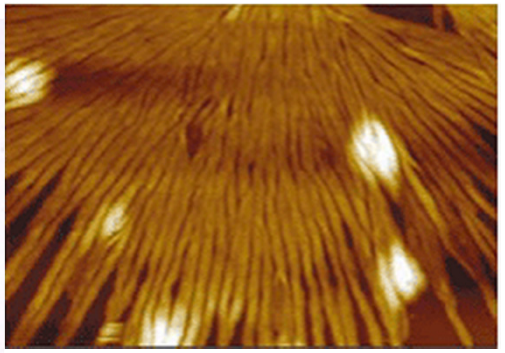
UK

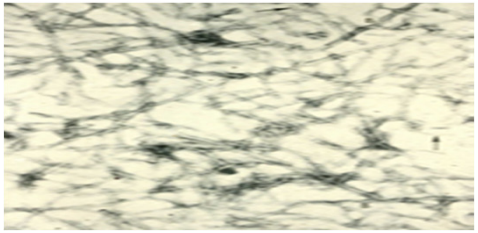
Amyloidosis and amyloid fibrils

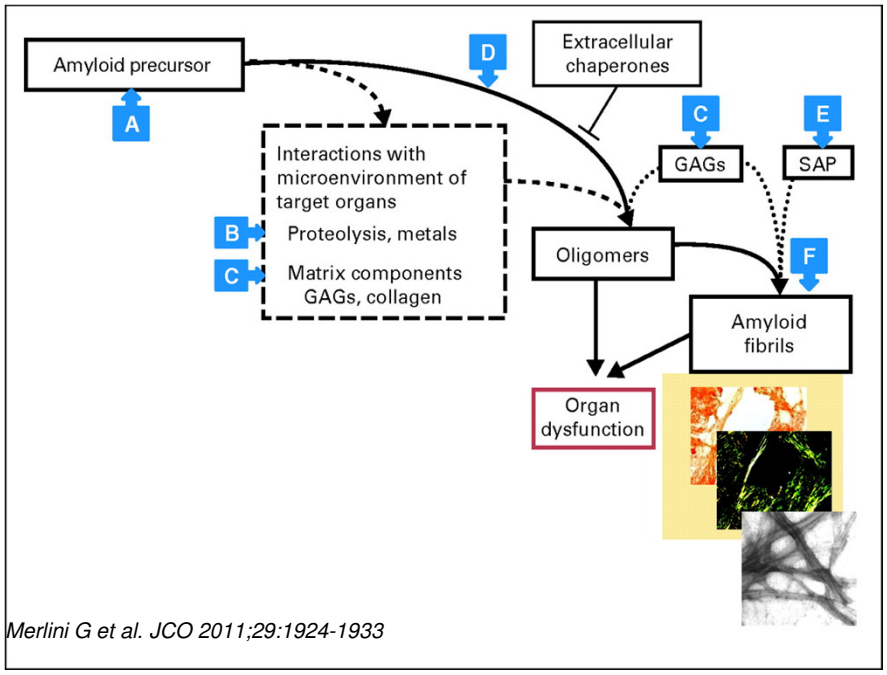
Disorder of protein folding

Structurally diverse precursors adopt an abnormal common fibrillar conformation

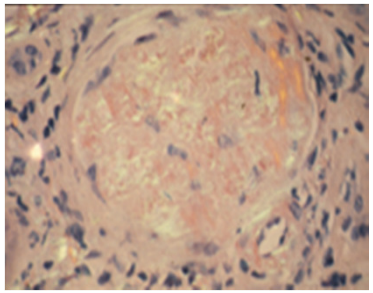


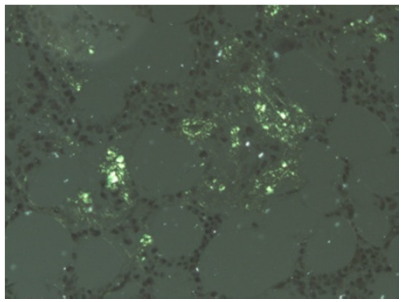






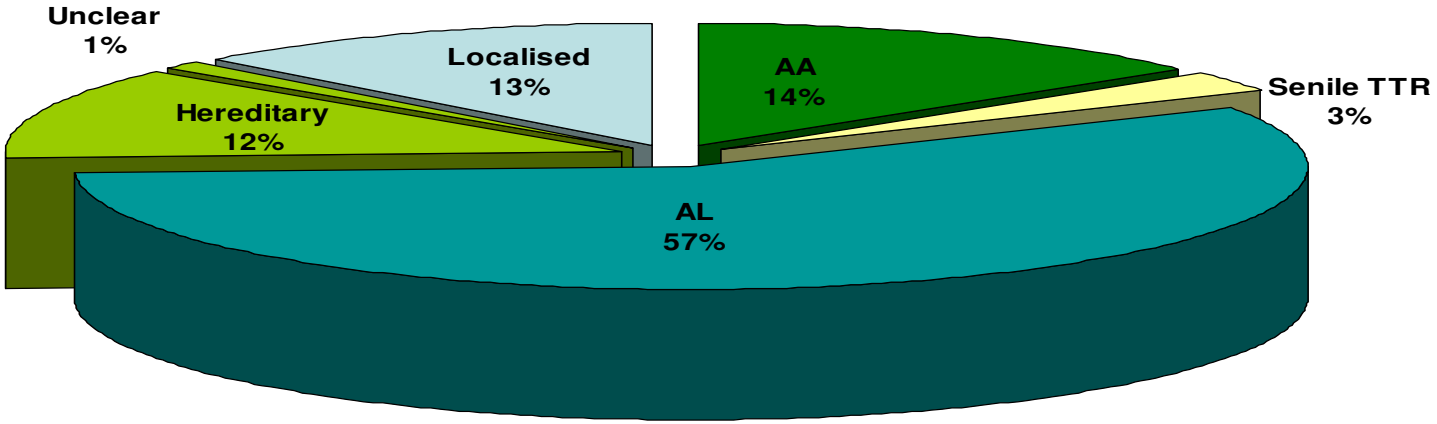
Merlini G et al. JCO 2011;29:1924-1933





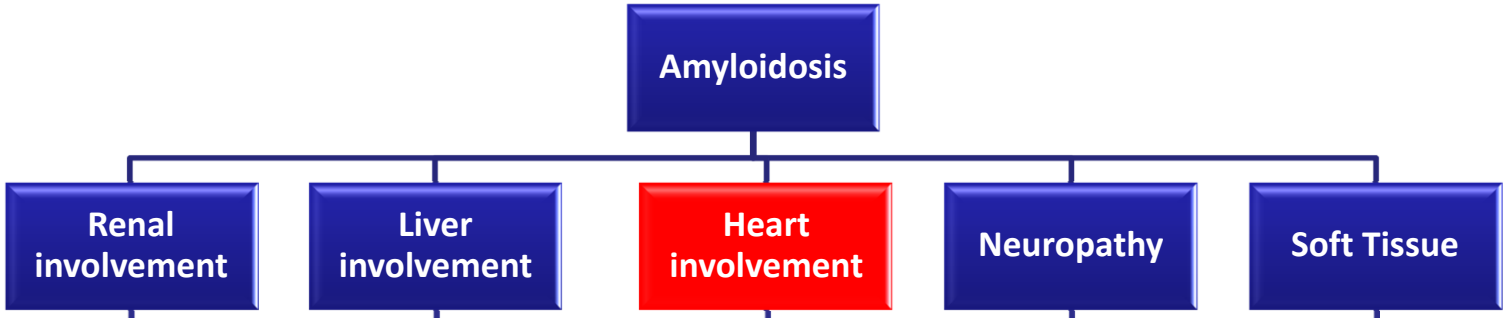
Types of amyloidosis

Amyloid Type	Number of patients (%)
AL	3468 (56%)
Localised AL	599 (12%)
AA	633 (12%)
ATTR	507 (10%)
Hereditary ATTR	339 (6.6%)
Wild type (senile) ATTR	168(3.2%)

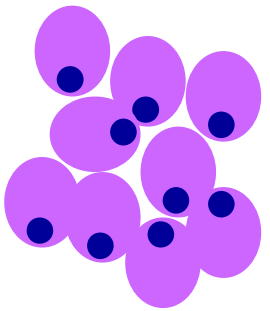


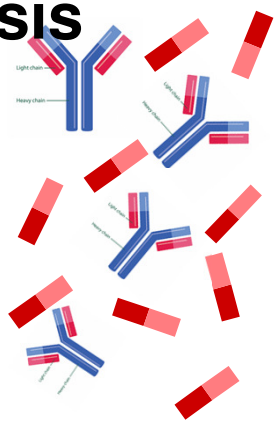
UK data - unpublished

Organ involvement and amyloid type

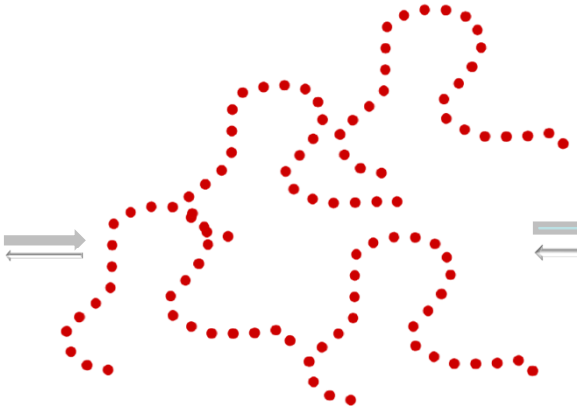


AL Amyloidosis

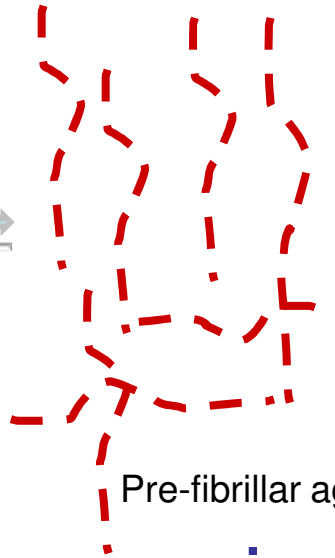




Excess production of unstable FLC



Misfolded light chains allowing exposure of hidden epitopes which allow aggregation



Pre-fibrillar aggregates



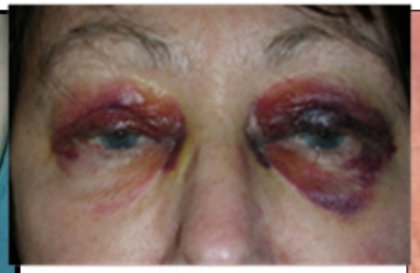
Amyloid fibrils formation in an ordered β-pleated sheet structure in tissues

Organ damage due to fibril deposition

Direct tissue toxicity (mainly affecting the heart)



Renal



Periorbital purpura



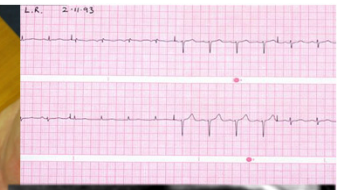
Macroglossia

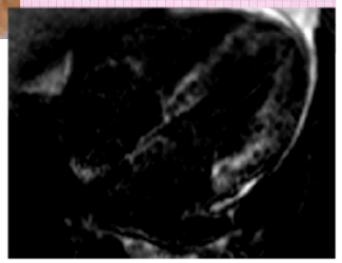


Nail dystrophy



Soft tissue

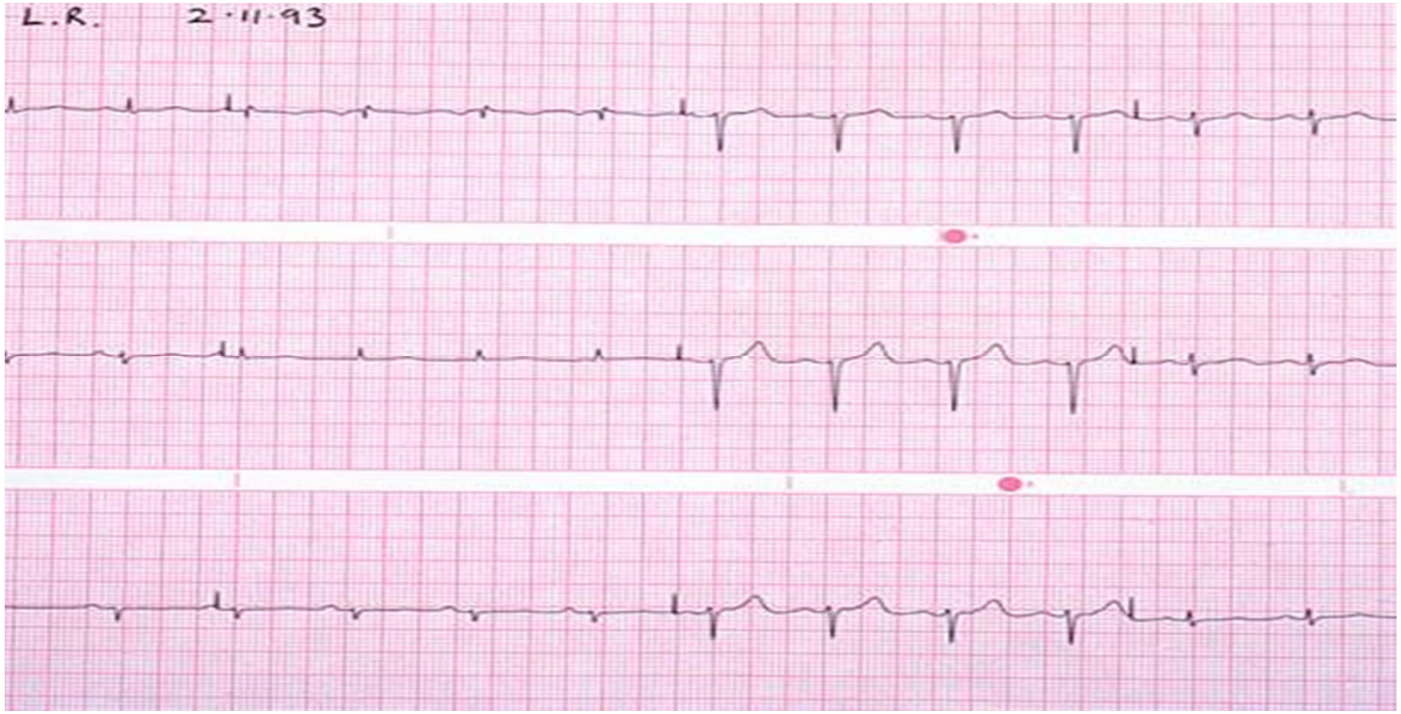




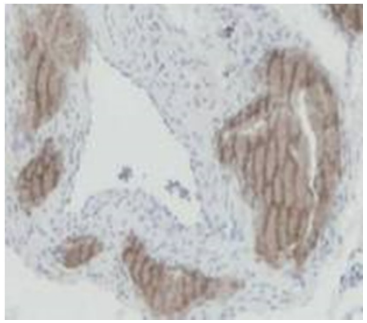
Heart

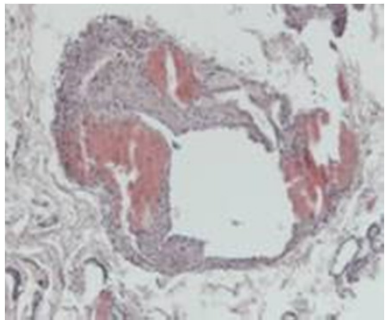
Cardiac presentation – 70%

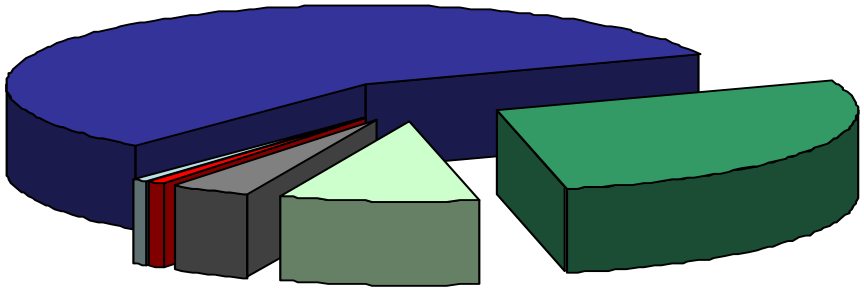
- Thick walled heart with normal or low voltage ECG
- Diastolic dysfunction
- ECG - low voltage, pseudo infarct
- Systolic failure near end stage



Hereditary Amyloidosis

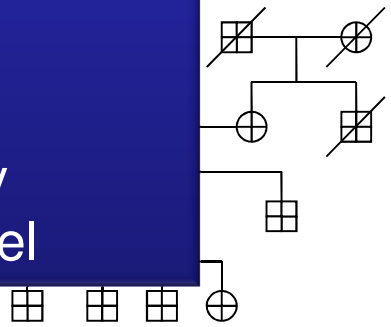






- ~ 12% of all patients
  - Transthyretin
    - Familial a
    - Familial a
  - Fibrinogen A
  - ApoA1
  - Lysozyme
  - Gelsolin
  - ApoA2
  - Cystatin C

Problems in diagnosis:
No Family history in ~ 50%
Variable phenotype
Incidental MGUS in 20%+
Difficult immunohistochemistry
Multiple mutations – often novel

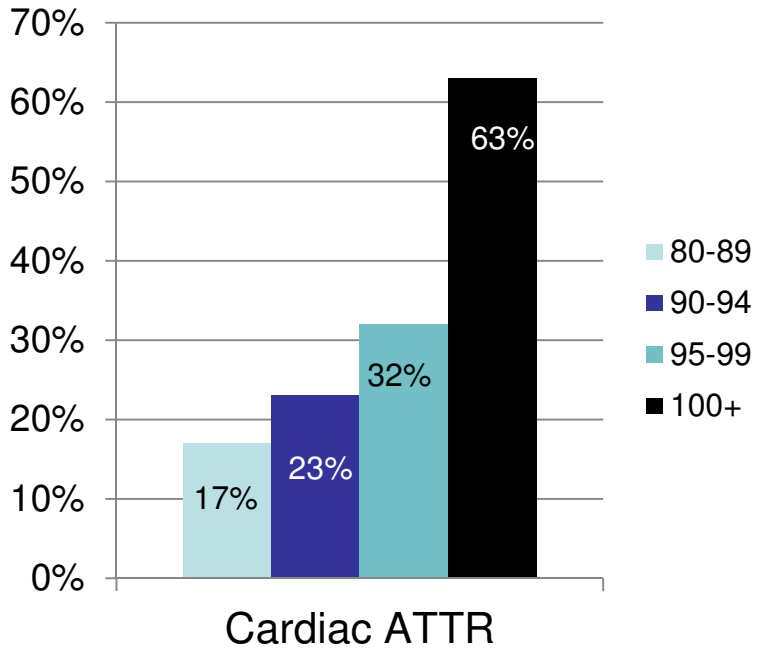


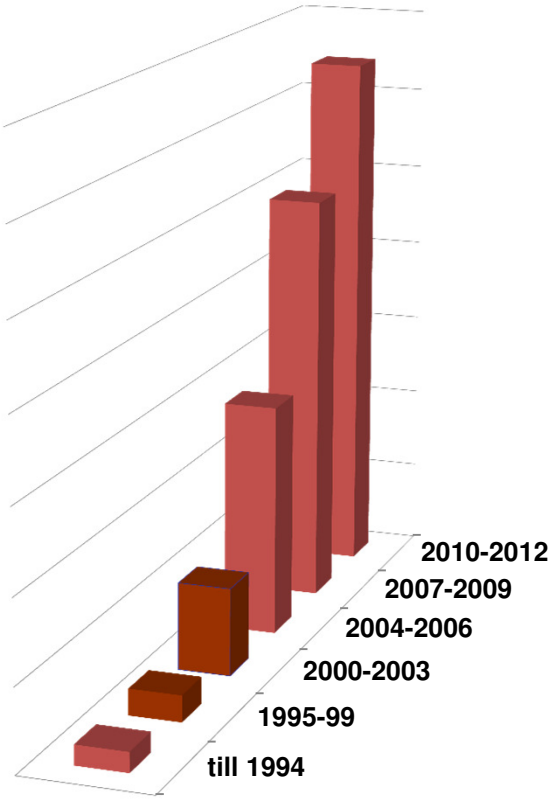
Lachmann et al NEJM 2002

Cardiac ATTR amyloid
A 'silent' public health problem?

Autopsy study (age ≥ 80 yrs)

ATTR-wild type detected in the heart in 25%



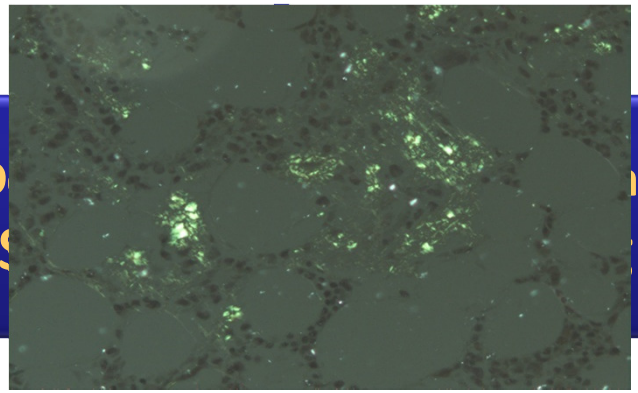


Tanksenan et al, Annals of Med. 2008;232-9

What proportion of older pts with heart failure and preserved ejection fraction have ATTR amyloidosis?

Approach to a patient with suspected amyloidosis

Confirm diagnosis of amyloidosis – A biopsy

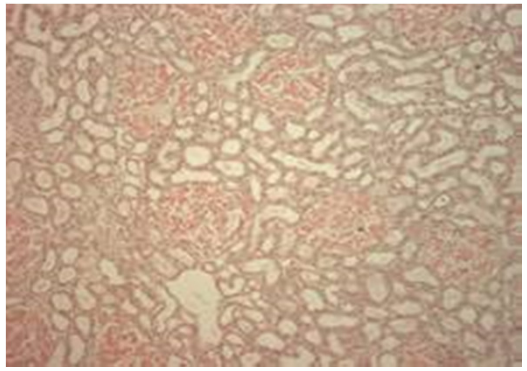


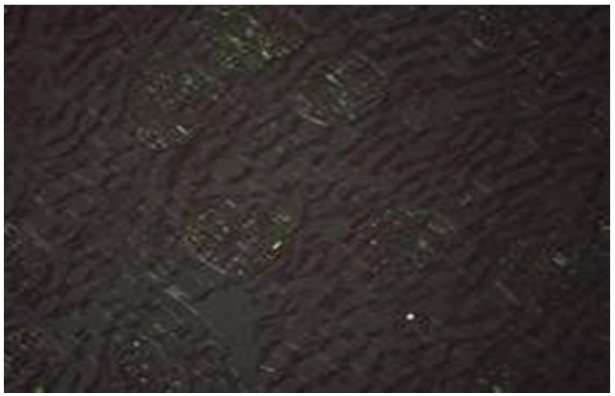
Management plan –
Definitive
Supportive

Confirm the diagnosis – A biopsy

- Congo Red positivity is the only gold standard
  - apple green birefringence under high-intensity cross-polarised light
  - thick (6 micron) sections reduce false negatives
- What it can and can't tell us
  - amyloid is there and where

    …. BUT its absence does not rule it out, esp if biopsy inadequate
  - amyloid type ≠ LM appearance

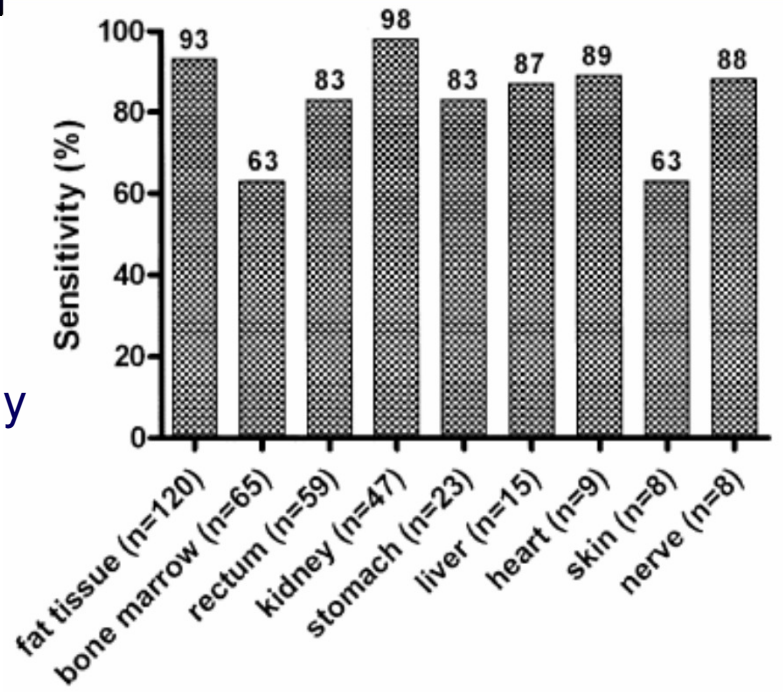


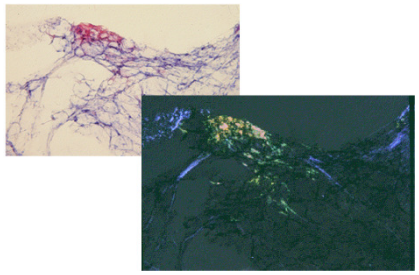


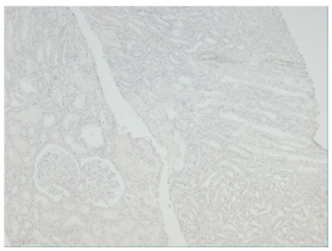
UCL

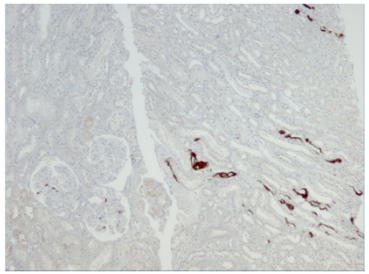
Looking for amyloid –where?

- **Biopsy of affected organ**
- Screening biopsy
  - Abdominal fat FNA
    - highly variable sensitivity
  - Rectal
    - more invasive, also not highly sensitive









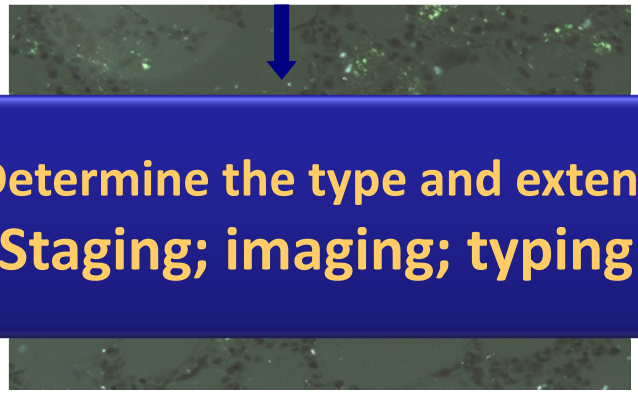
- 2007 – 2010 @ NAC
- Among biopsies received for review
- 101 false positive
- 102 false negative

Van Gameren, Arth&Rheum 2006;54:2015

Ansari-Lari, Diagn Cytopathol 2004;30:178

Approach to a patient with suspected amyloidosis

Confirm diagnosis of amyloidosis – A biopsy



Determine the type and extent

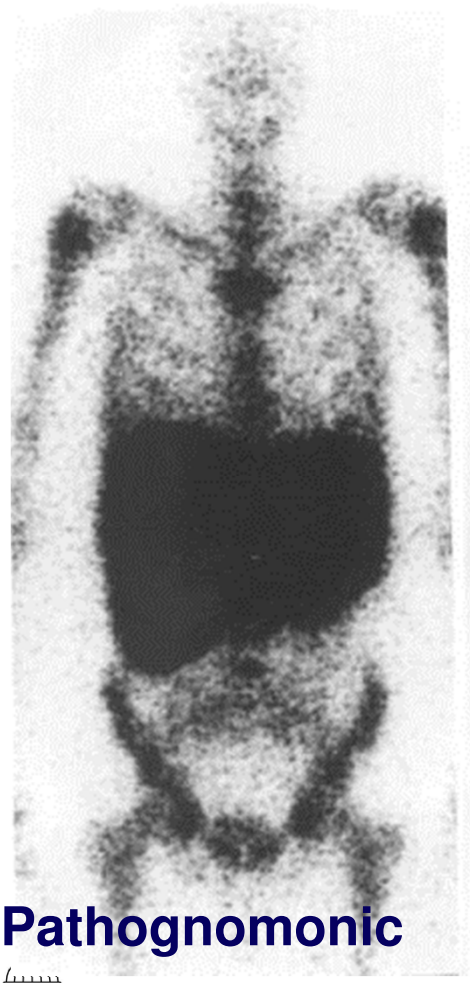
Staging; imaging; typing

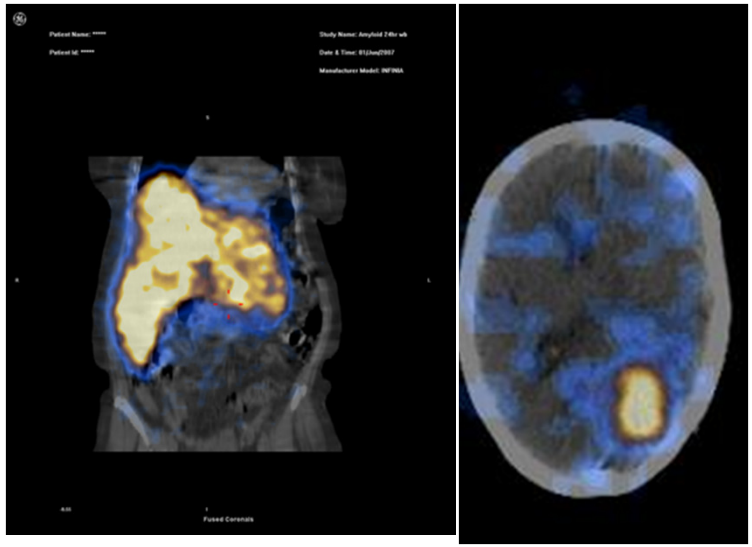
Management plan –

Definitive

Supportive

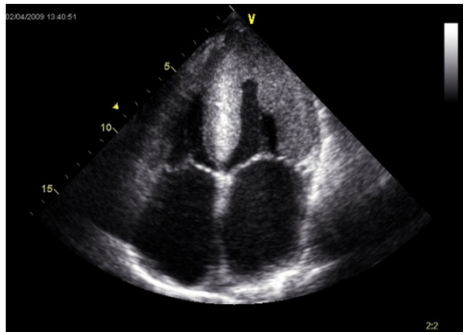
I^{123} labelled SAP scintigraphy



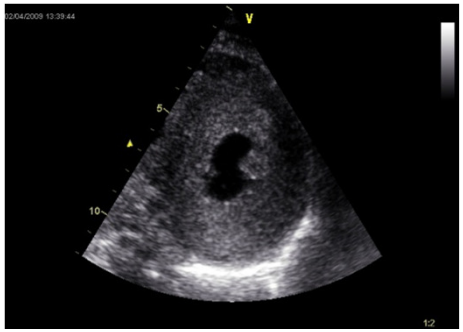


Pathognomonic of AL amyloidosis

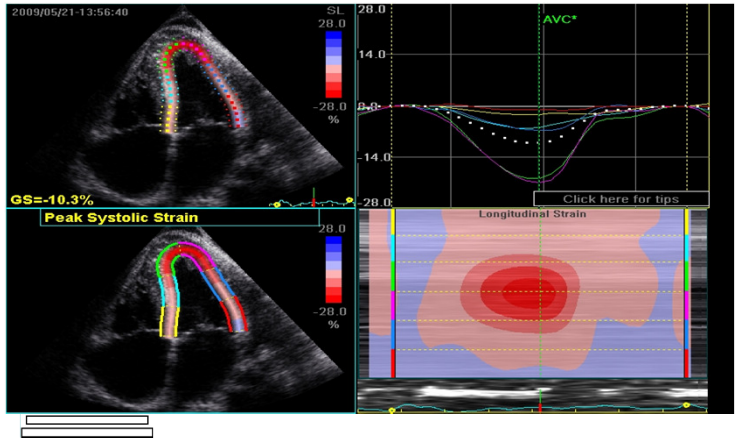
Echocardiography



A thick walled heart. Amyloid? And how much?



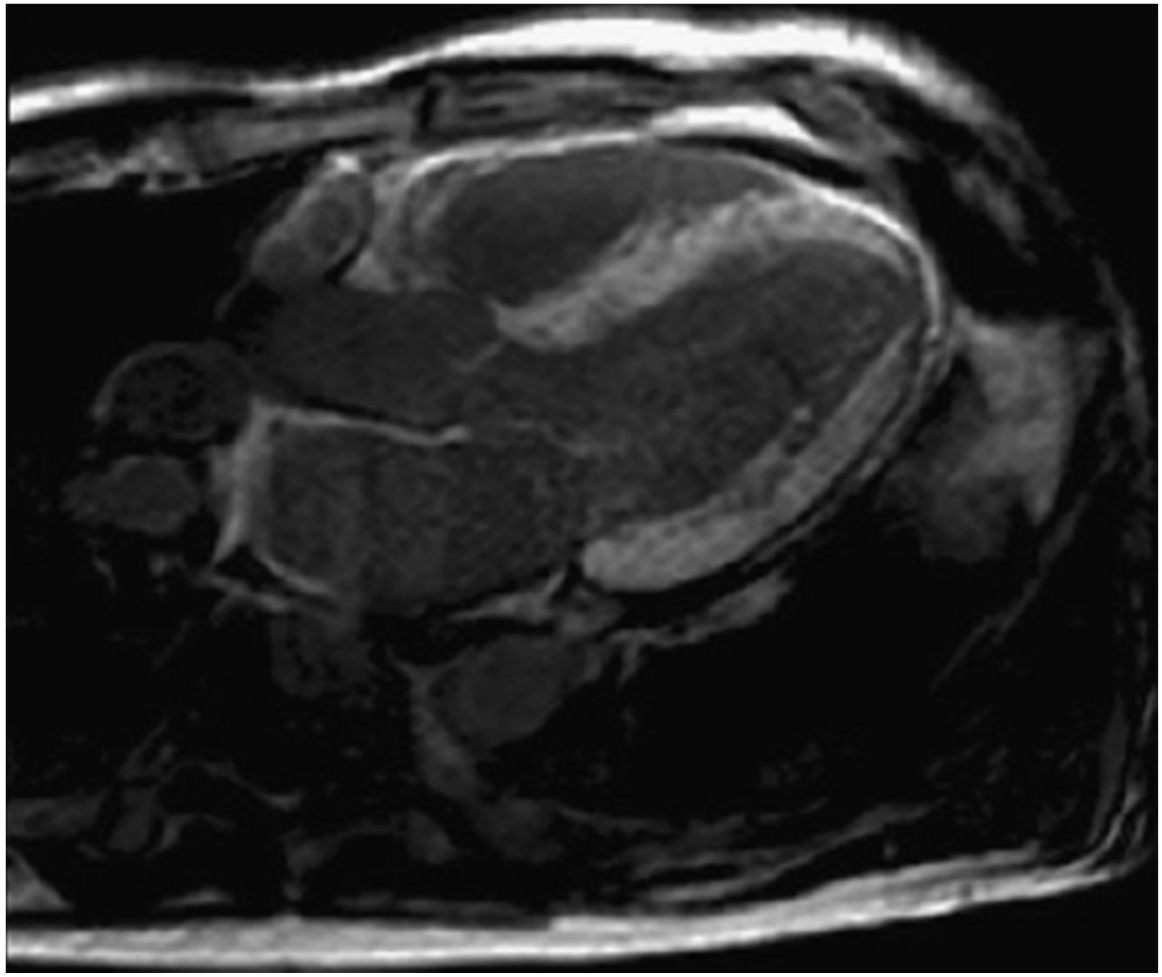
2 D strain
is very useful



		CA	HCM	Controls
RS [%]	Basal			
	Mid			
	Apical			
CS [%]	Basal			-CS
	Mid			
	Apical			
LS [%]	Basal			-LS
	Mid			
	Apical			

Baccouche H et al. Echocardiography. 2012 Jul;29(6):668-77

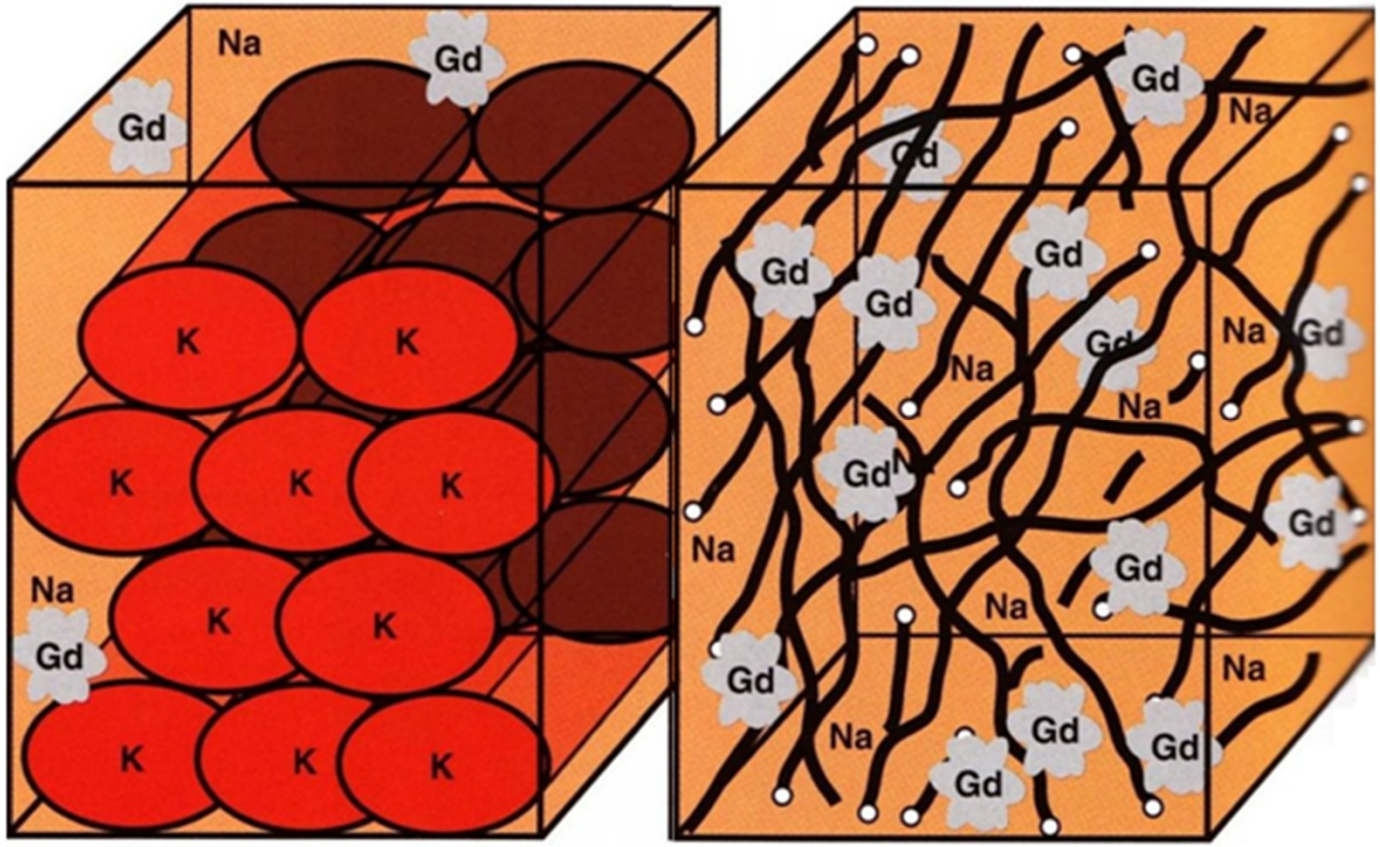
Cardiac MRI: Diffuse Late Gadolinium Enhancement in a patient with senile cardiac (ATTR) amyloidosis



Gadolinium DTPA

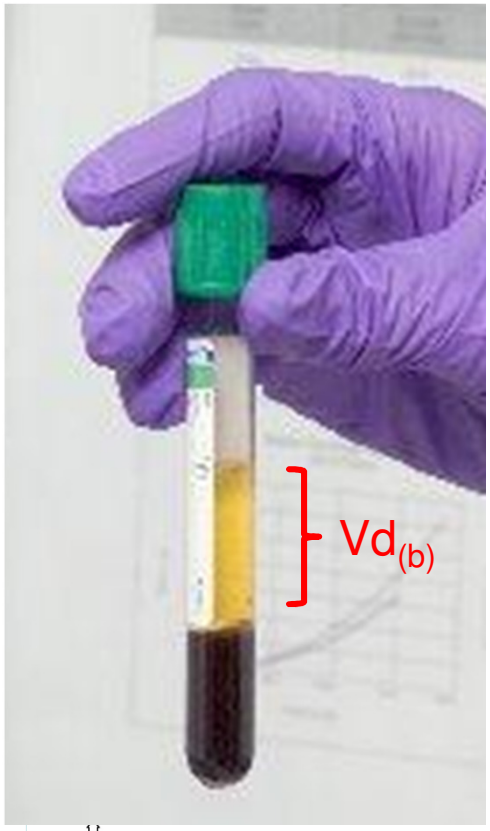
Normal myocardium

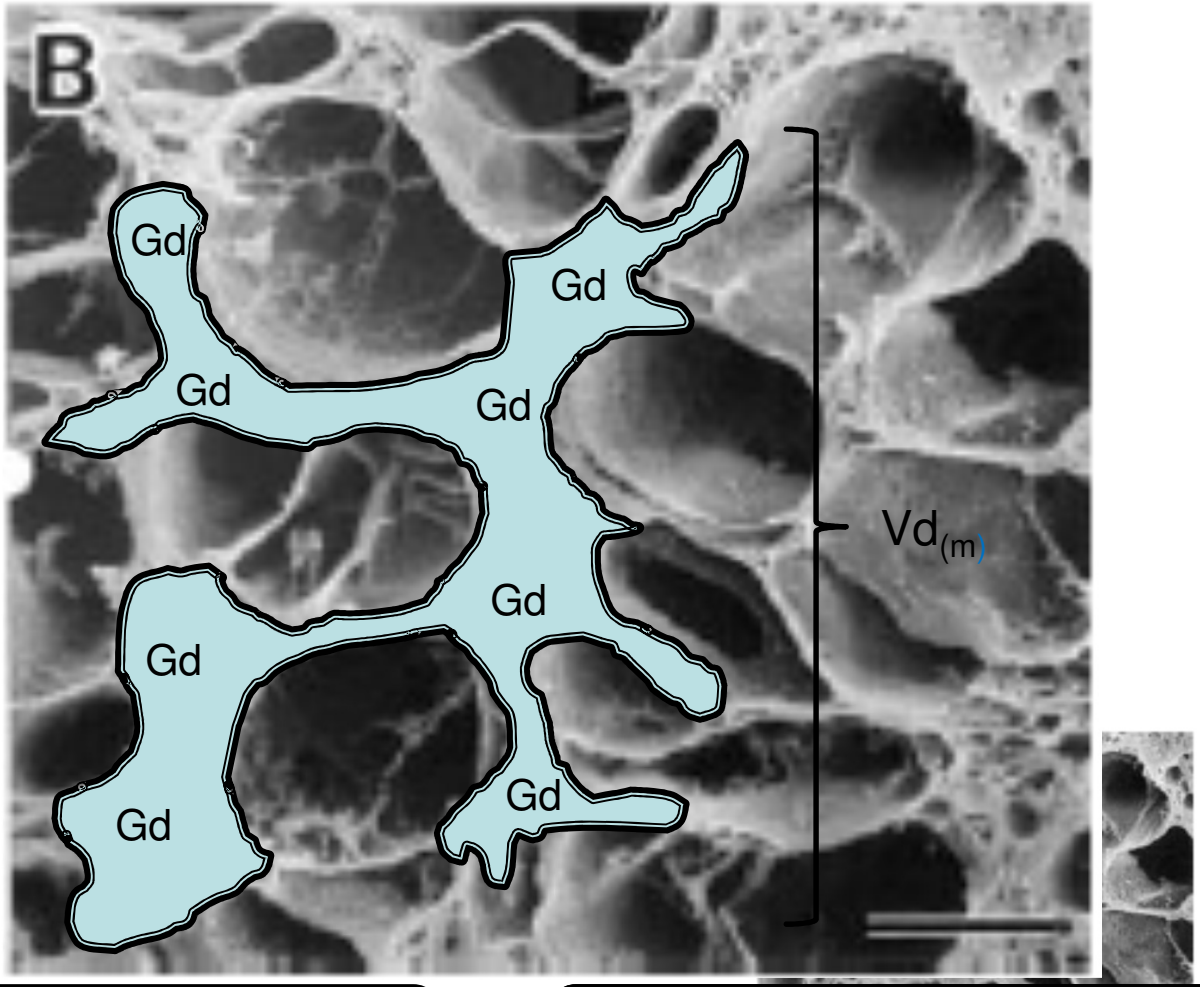
Scar/Amyloid



Mahrholdt et al. Eur Heart J 2002, 23:602-619

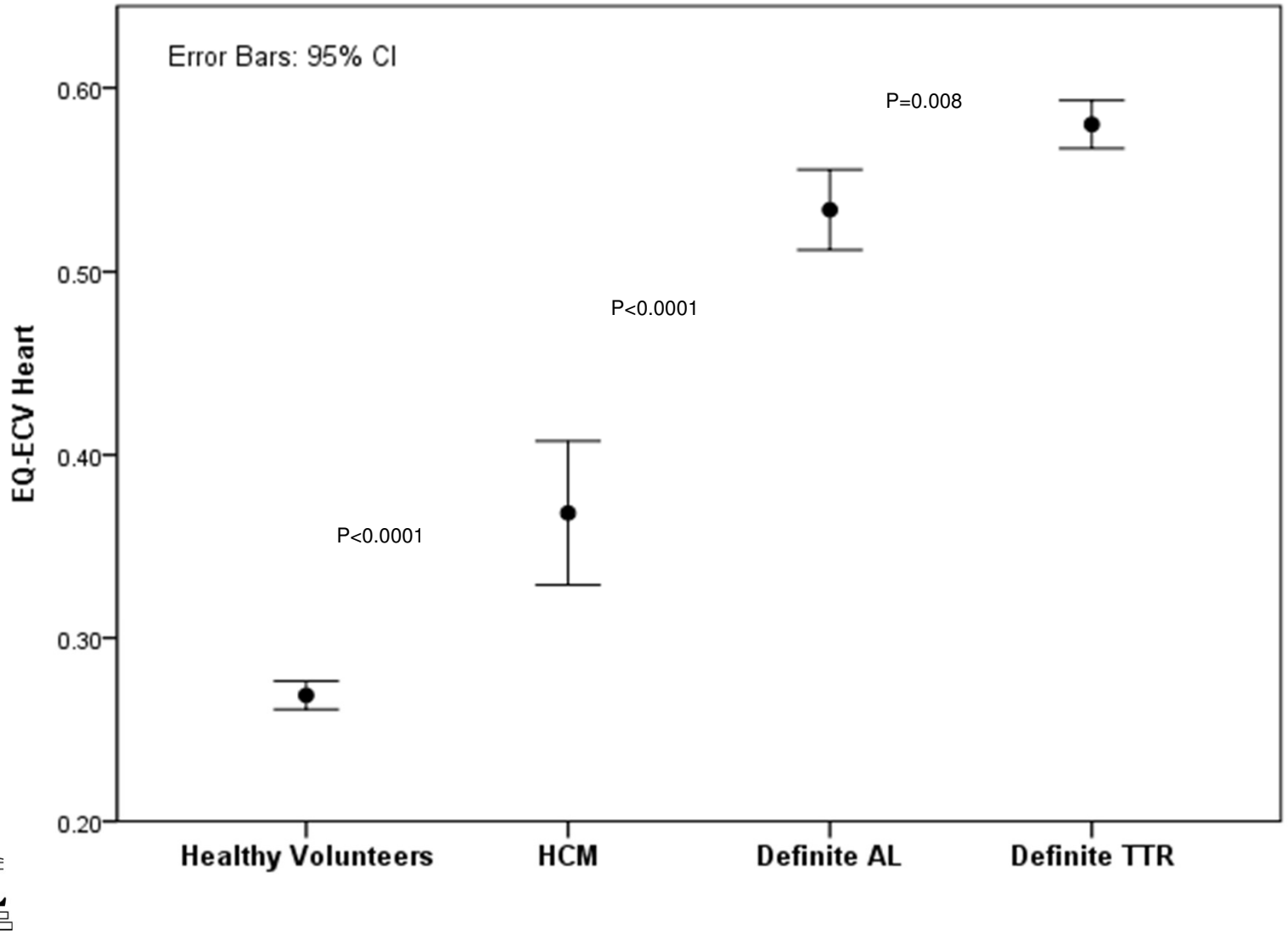
Measuring the Extracellular volume
A Quantitative MRI test for amyloid

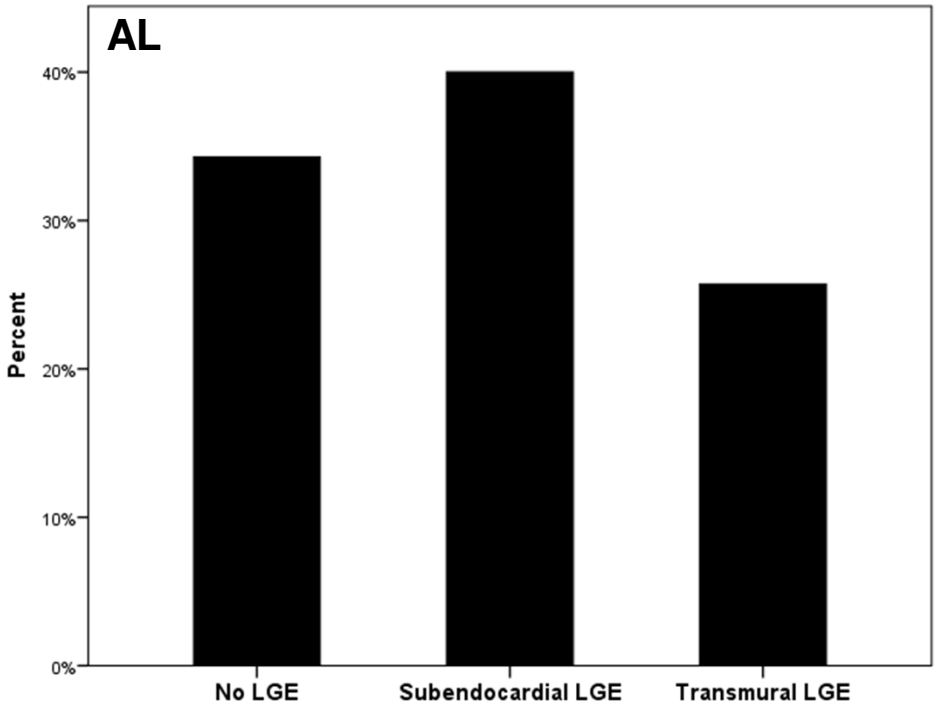


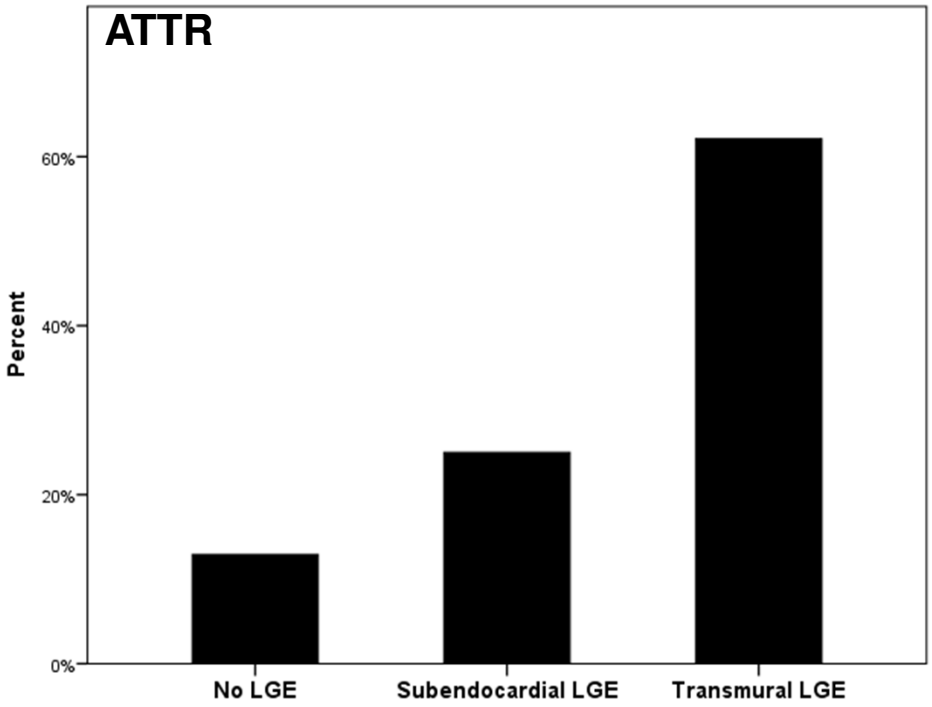


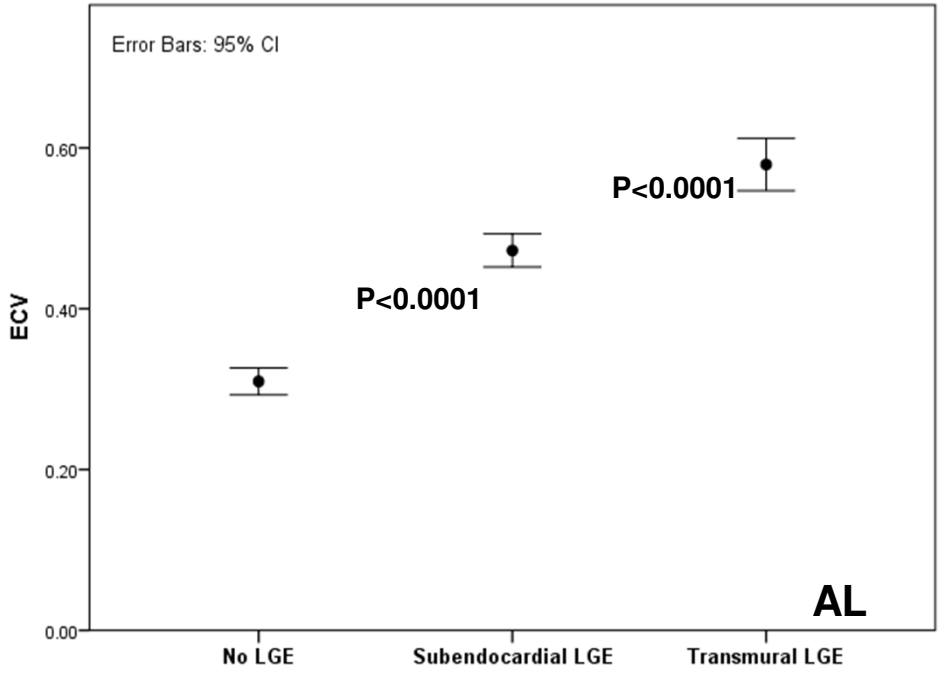
Steady State → $[Gd]_{Bl}=[Gd]_{Myo}$ → $\Delta R1_{myo} \div \Delta R1_{bl}=Vd_{myo} \div (1\text{-}hct)$

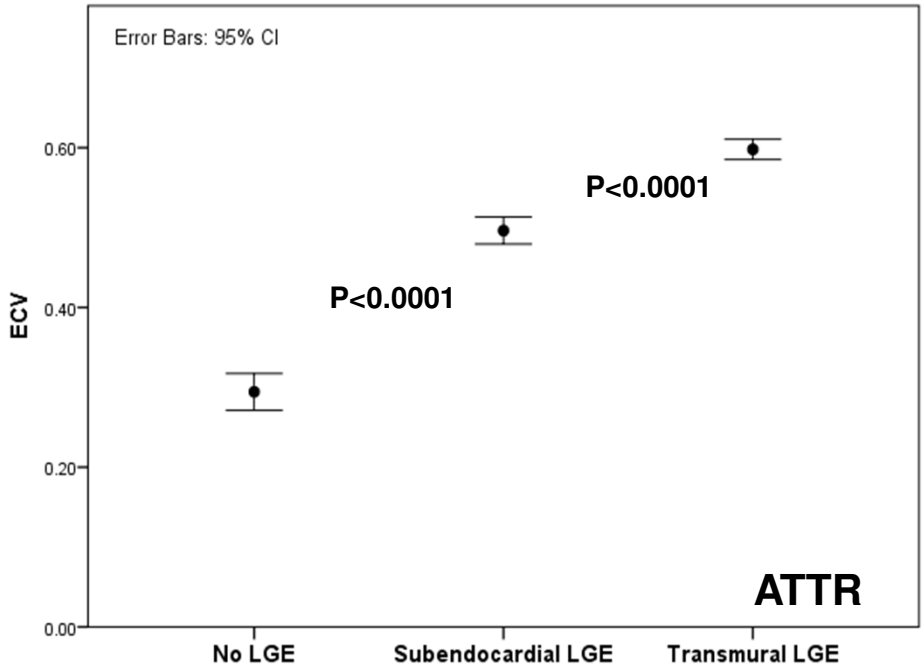
Measuring the Extracellular volume
A Quantitative MRI test for amyloid




AL
40%
30%
20%
10%
0%
Percent
No LGE
Subendocardial LGE
Transmural LGE


ATTR
60%
40%
20%
0%
Percent
No LGE
Subendocardial LGE
Transmural LGE


Error Bars: 95% CI
0.60
0.40
0.20
0.00
ECV
P<0.0001
P<0.0001
AL
No LGE
Subendocardial LGE
Transmural LGE


Error Bars: 95% CI
0.60
0.40
0.20
0.00
ECV
P<0.0001
P<0.0001
ATTR
No LGE
Subendocardial LGE
Transmural LGE

T1 mapping – a useful non-contrast technique

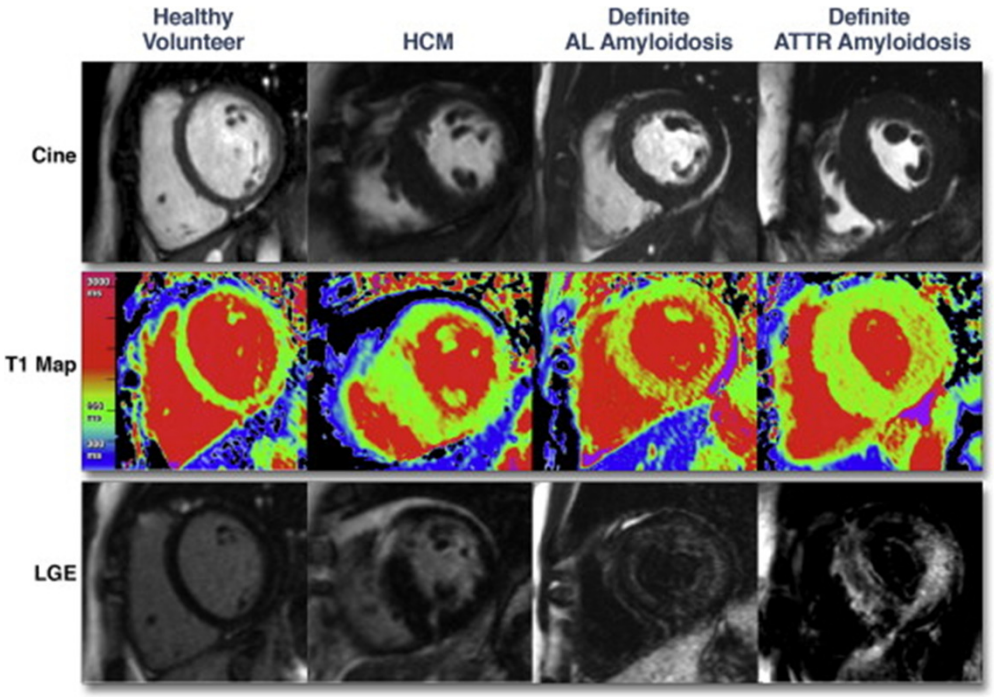


Figure 2 Characteristic Examples From CMR Scans CMR end-diastolic cine still (top) , shortened modified look-locker inversion recovery native T1 map (middle), and late gadolinium enhancement (LGE) images (bottom) in (left to right) healthy volunteer...

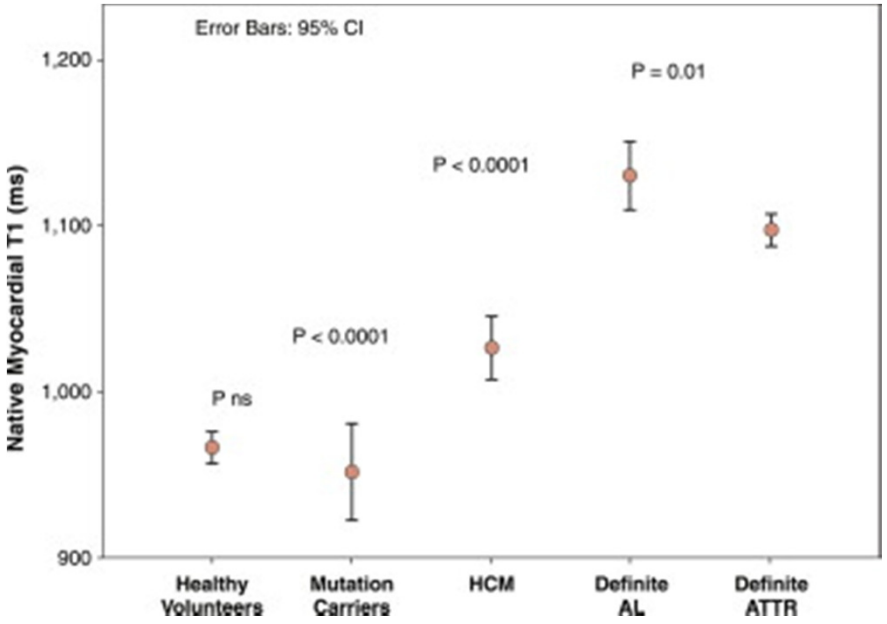
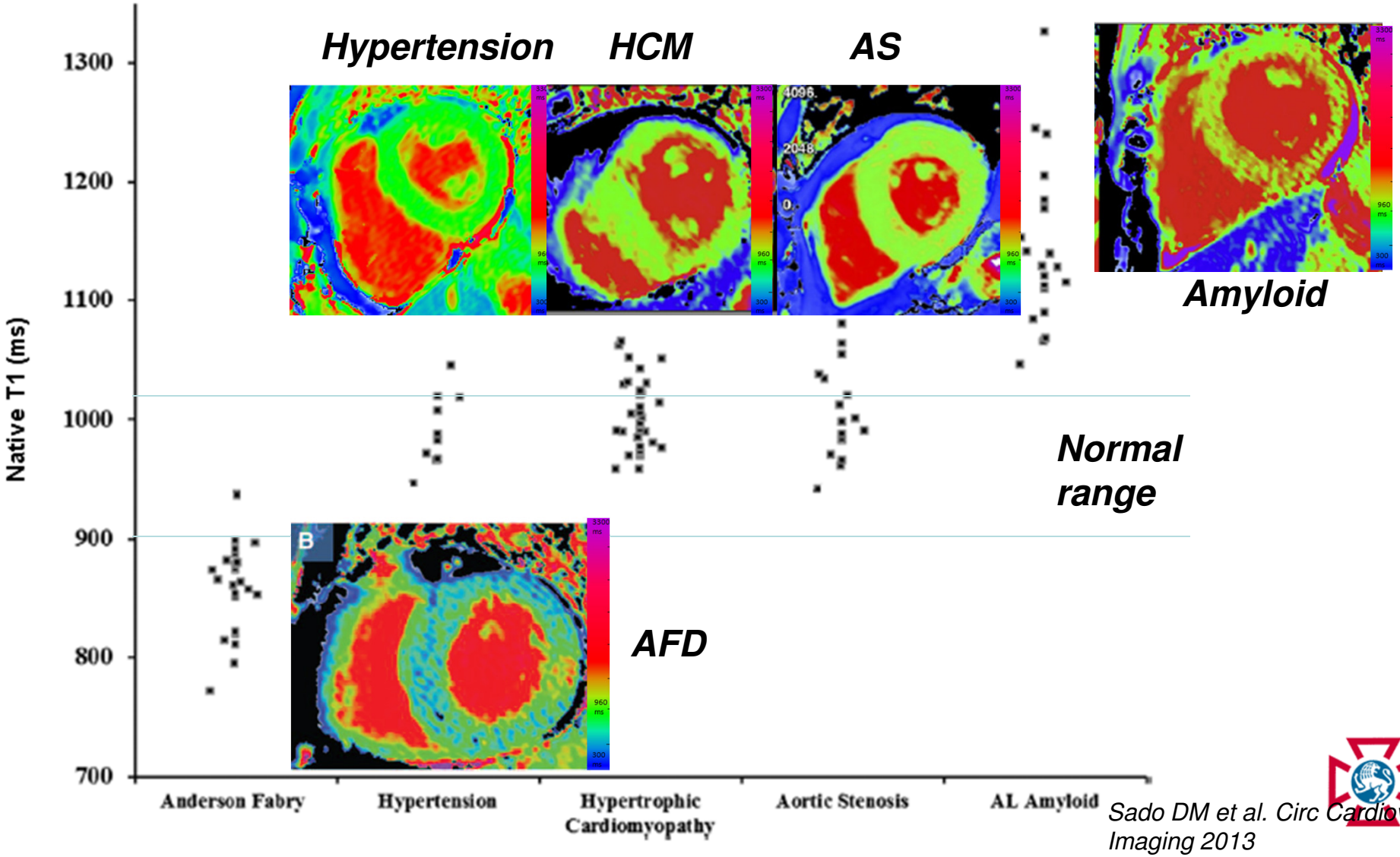


Figure 3 Native T1 in Healthy Volunteers, Mutation Carriers, HCM, Definite AL, and Definite ATTR Mean native myocardial T1 ± 2 SE in healthy control subjects, gene carriers, patients with definite AL cardiac amyloidosis, and patients with definite ATTR ca.

Fontana M et al; JACC: Cardiovascular Imaging, Volume 7, Issue 2, 2014, 157 - 165

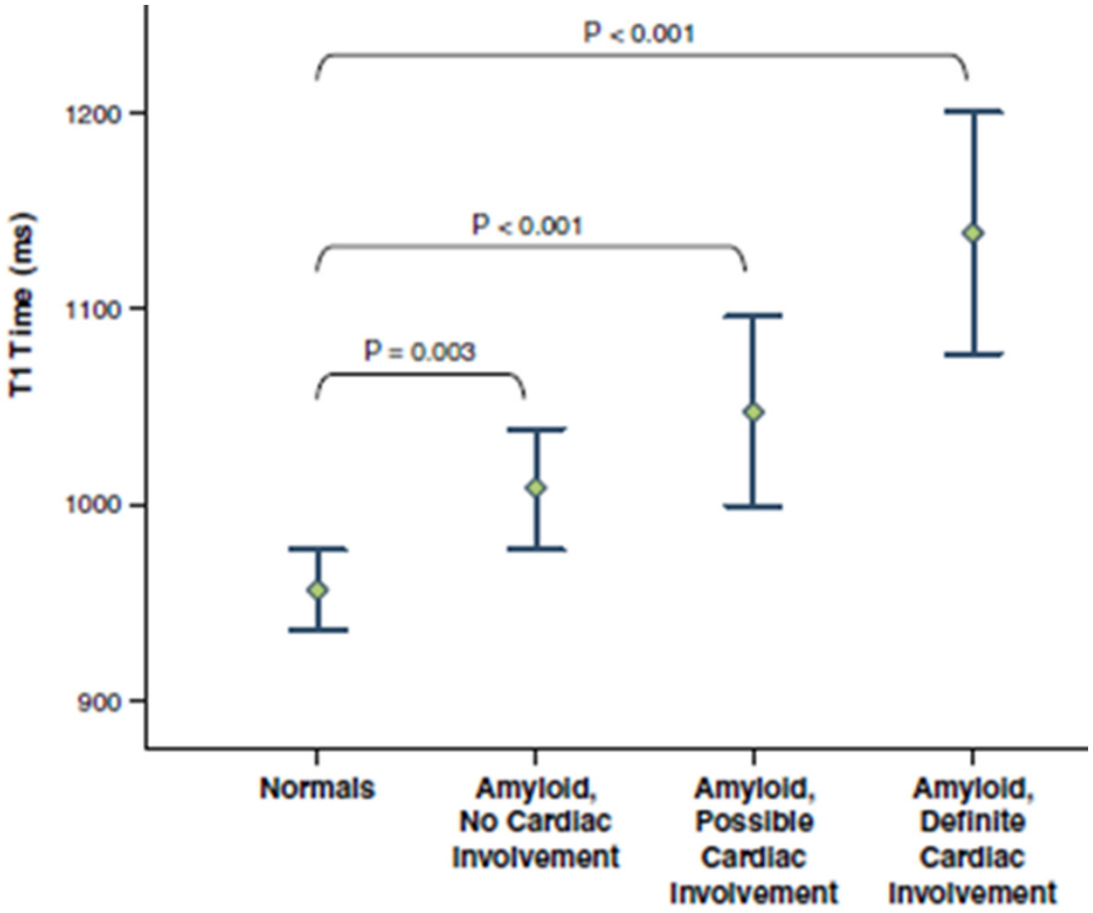
UCL

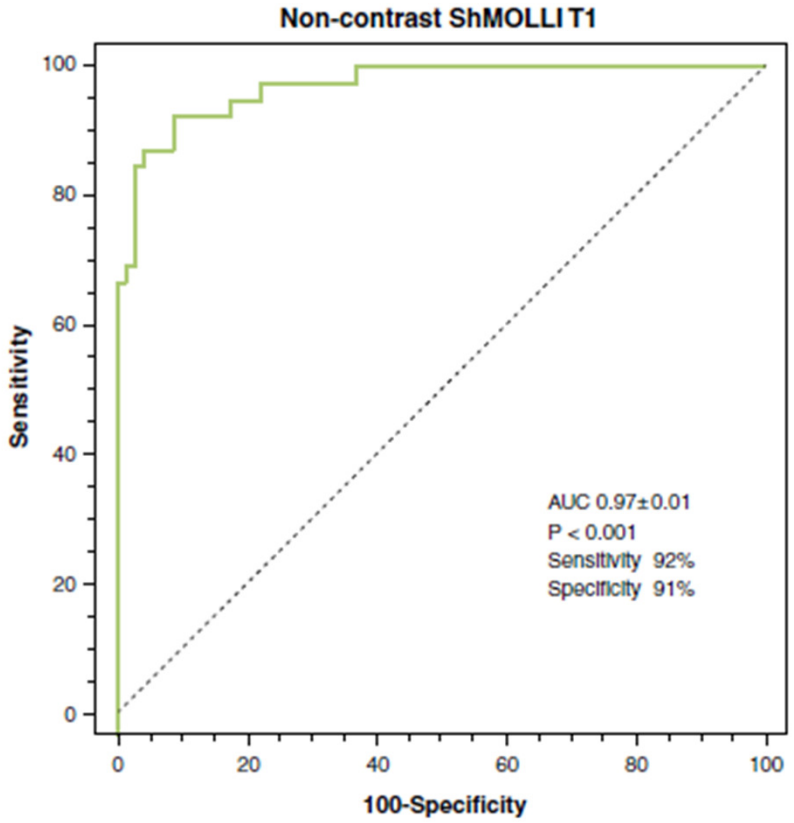
Native T1 in the hypertrophic phenotype



Sado DM et al. Circ Cardiovasc Imaging 2013

Native T1 in amyloidosis diagnostic accuracy





Karamitsos TD et al. JACC Cardiovasc Imaging 2012

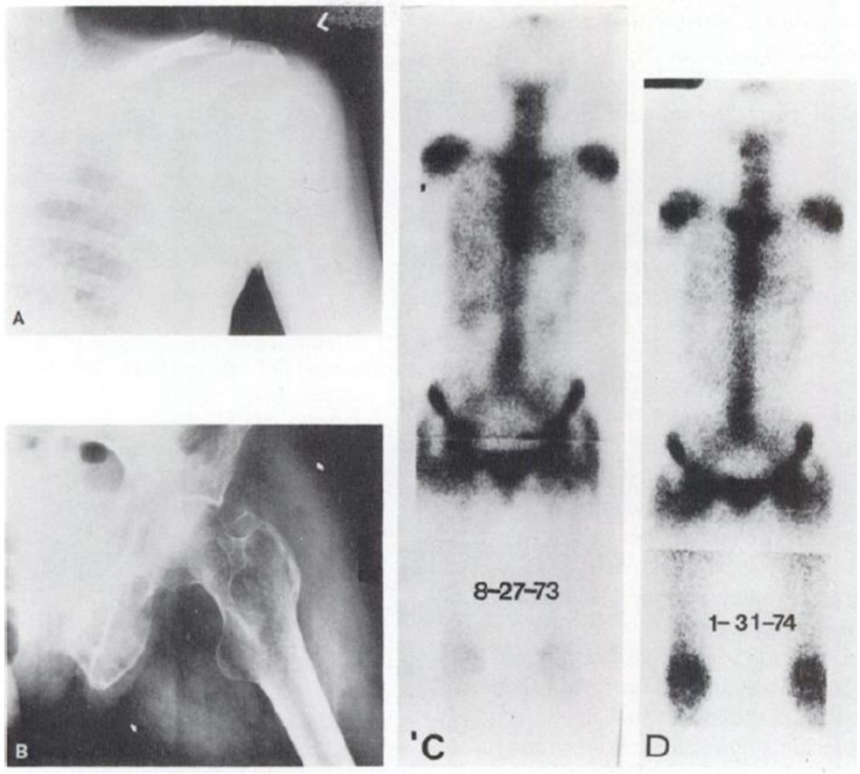
Imaging cardiac amyloid with diphosphonate bone agents

jnm/CASE REPORT

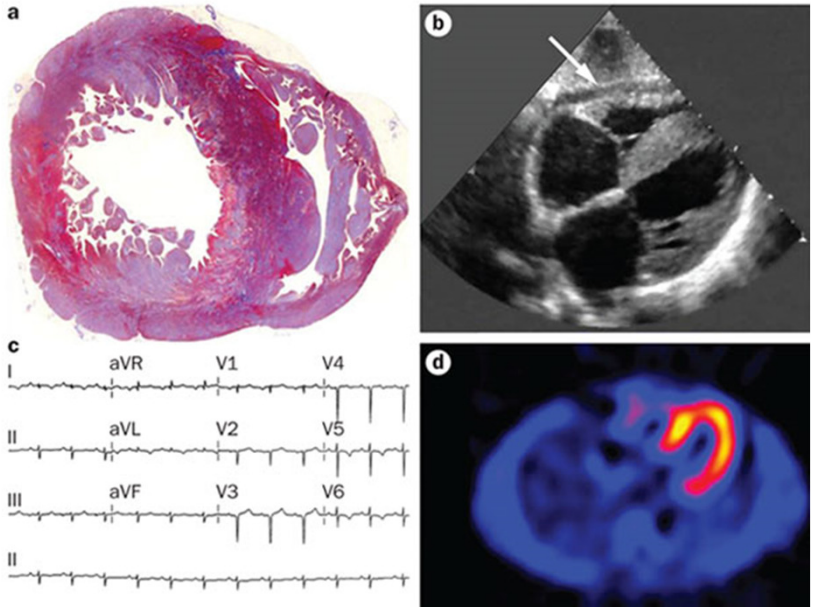
Received June 10, 1974; revision accepted Oct. 20, 1974.
For reprints contact: J. D. VanAntwerp, Div. of Nuclear Medicine, Arizona Medical Center, Tucson, Ariz. 85724.

TECHNETIUM-99m-DIPHOSPHONATE ACCUMULATION IN AMYLOID

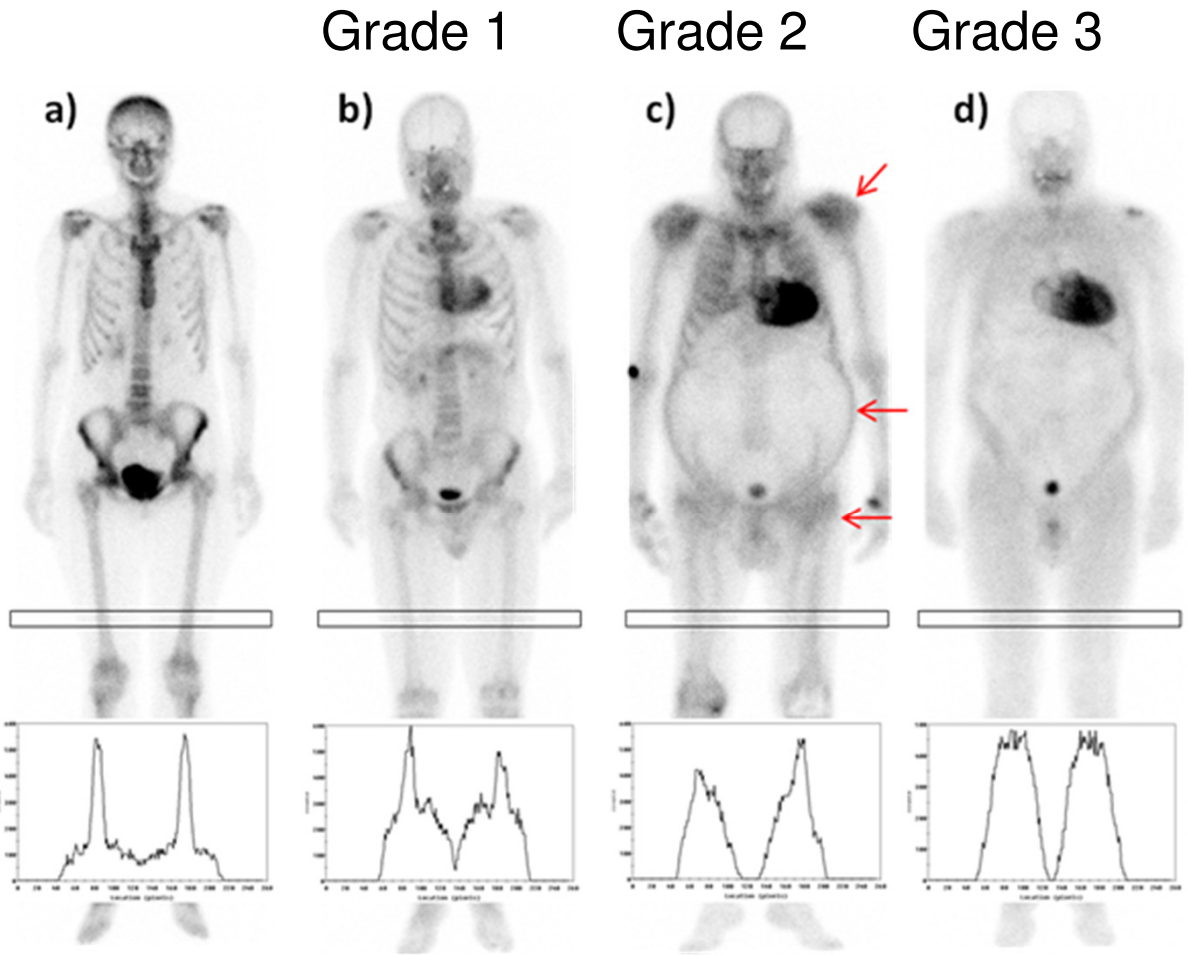
J. D. VanAntwerp, R. E. O'Mara, M. J. Pitt, and S. Walsh
University of Arizona Medical Center, Tucson, Arizona

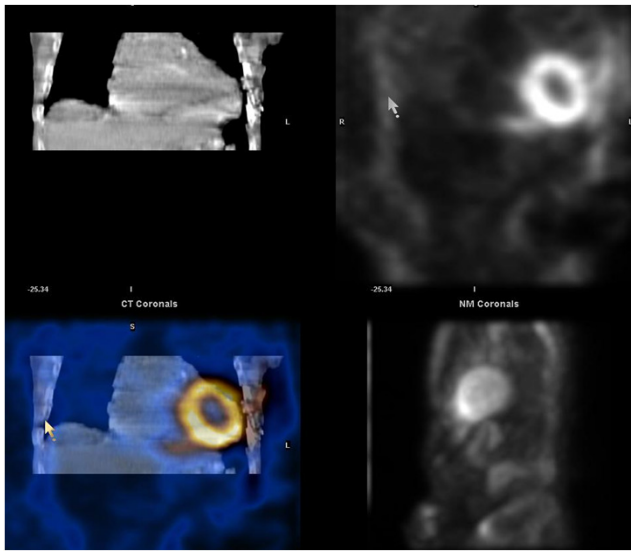


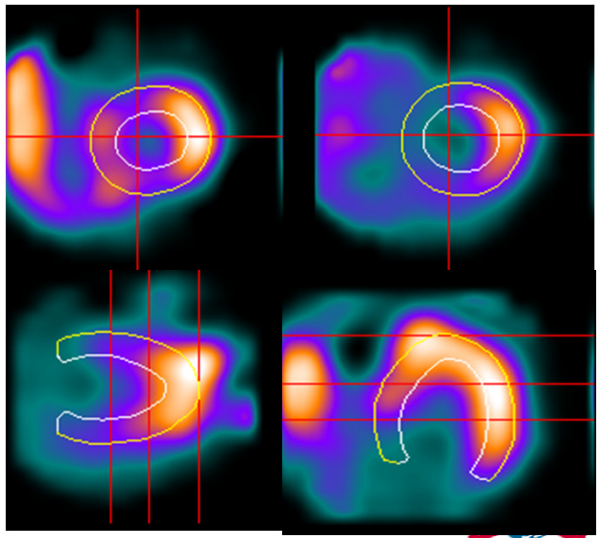
Group from Bologna reported uptake of ^{99m}Tc-DPD in cardiac amyloidosis



Grading ^{99m}Tc-DPD uptake in the heart





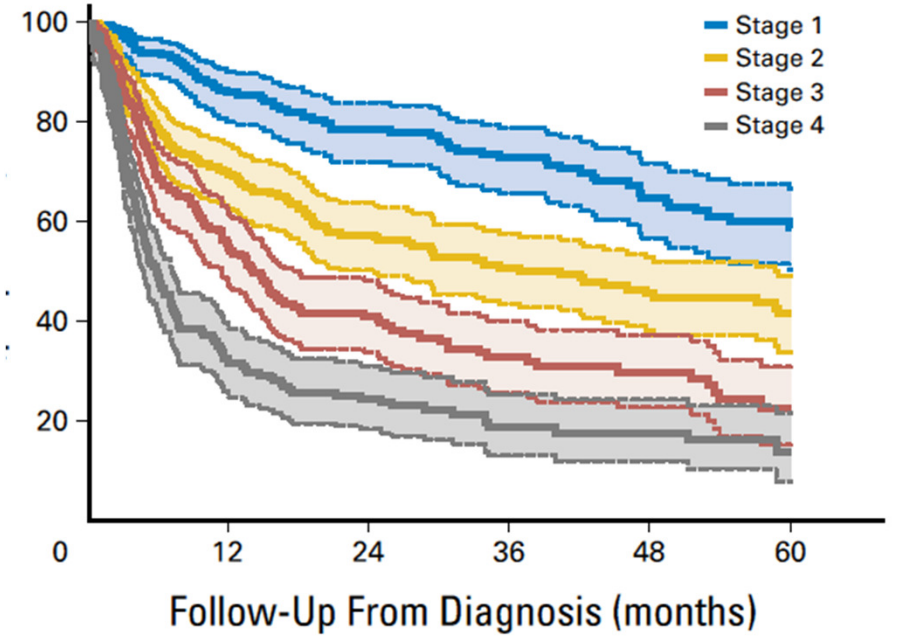


Bone

Cardiac

Cardiac biomarkers determine stage
Mayo staging system

NT-ProBNP	**≥ 1800 pg/ml**
cTroponin-T	**≥ 0.025 ng/ml**
dFLC	**≥ 18mg/dl**

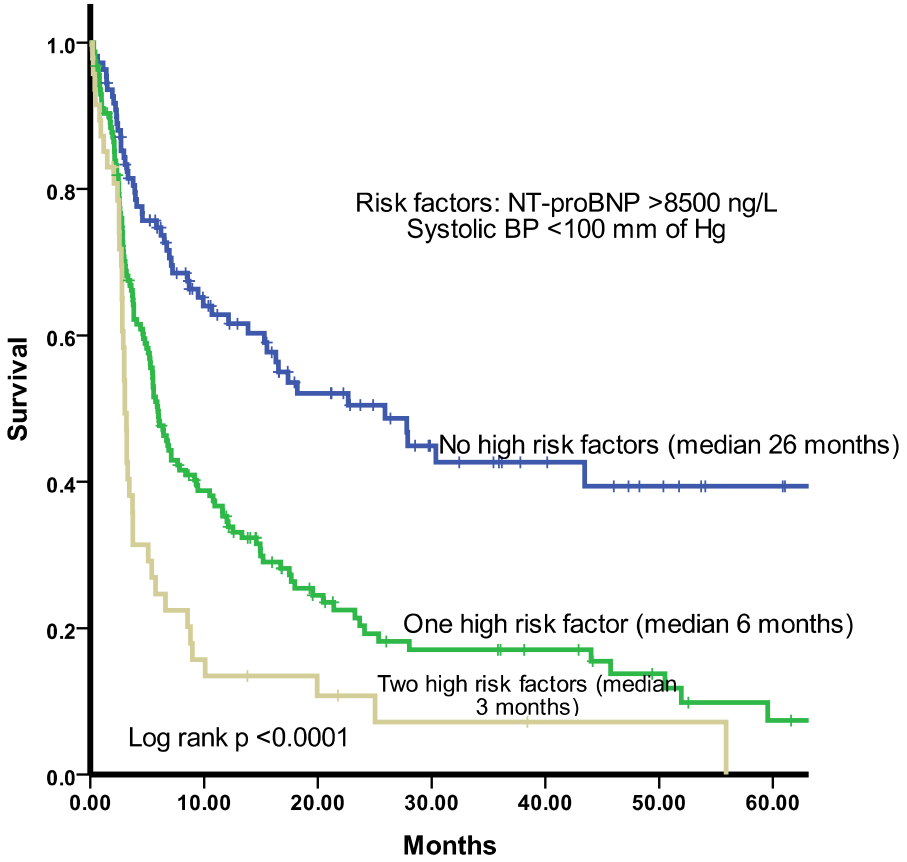


Stage	N	Median survival
Stage I	189	94 months
Stage II	206	40 months
Stage III	186	14 months
Stage IV	177	5.8 months

Kumar et al, JCO; 2012;10.1200/JCO.2011.38.5724

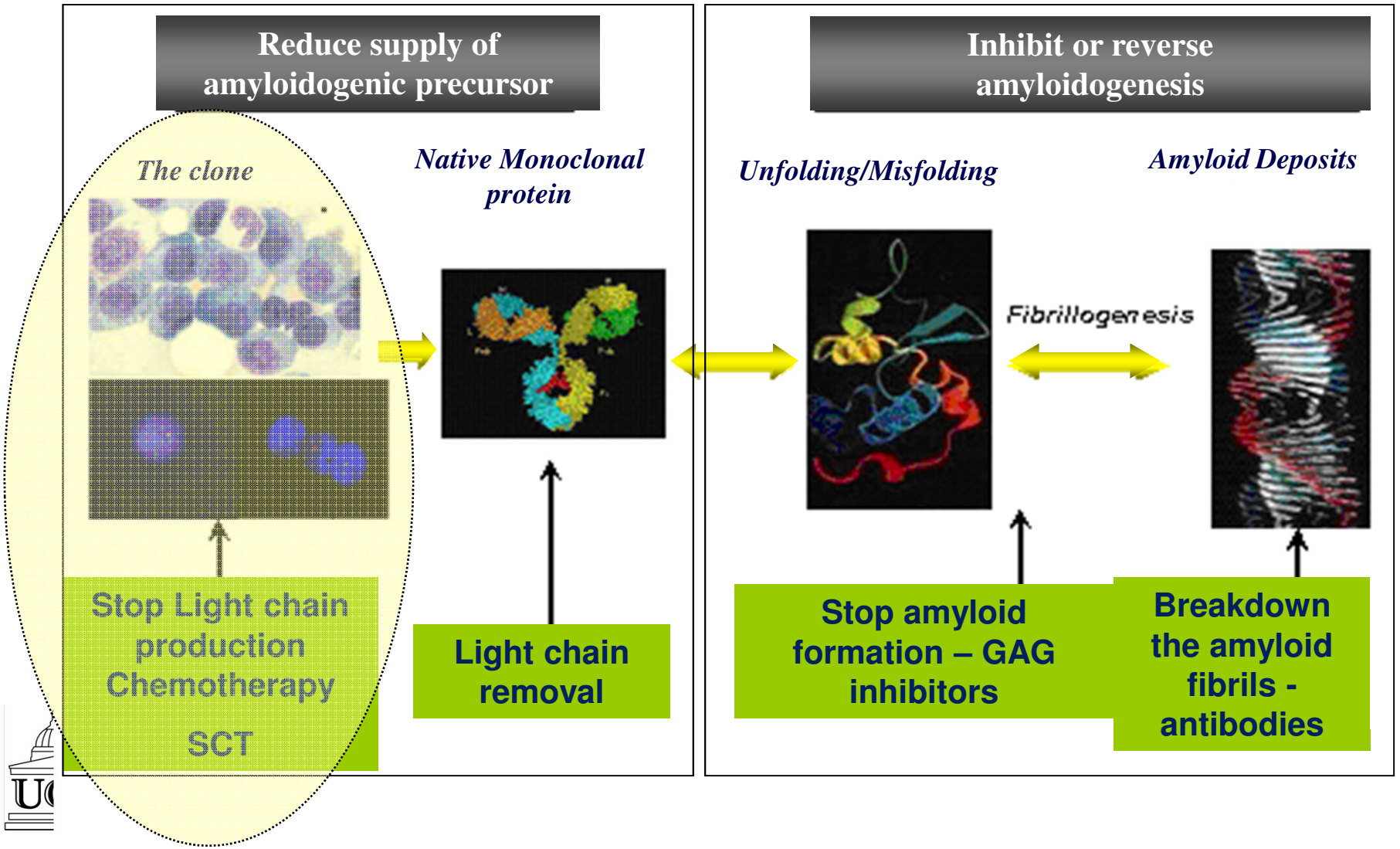
Advances stage disease – further stratification

- **Two risk factors**
  - NT-proBNP >1003 pMol/L
  - Systolic BP <100mm of Hg
- **Hazard ratios:**
  - One risk factor HR 2.1
  - Two risk factors HR 3.7

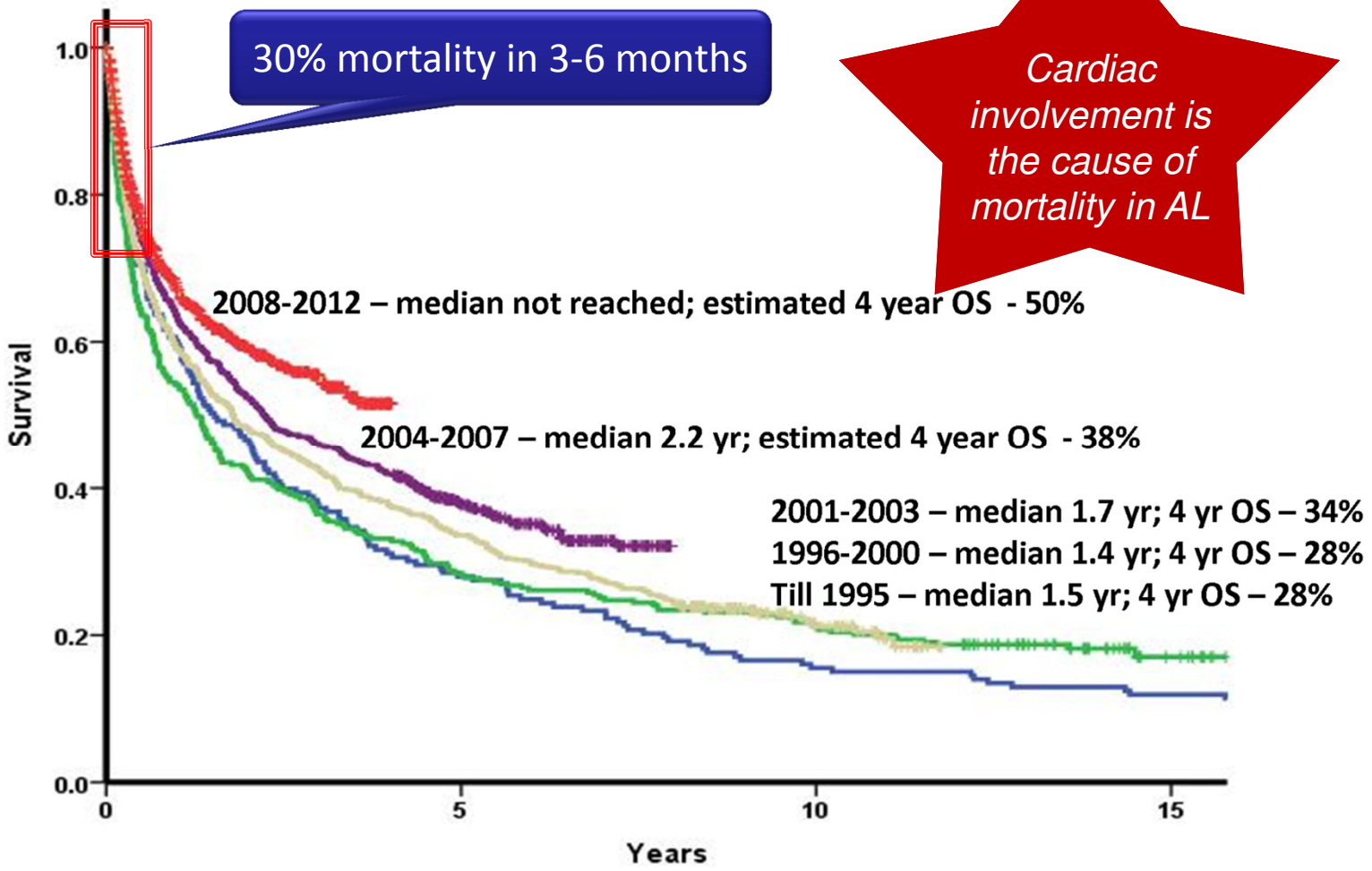


Wechalekar A et al, Blood Dec 2013

Plan management



Outcomes are improving in AL



Wechalekar et al Lancet 2015 accepted for publication

Managing symptoms

Nephrotic Syndrome

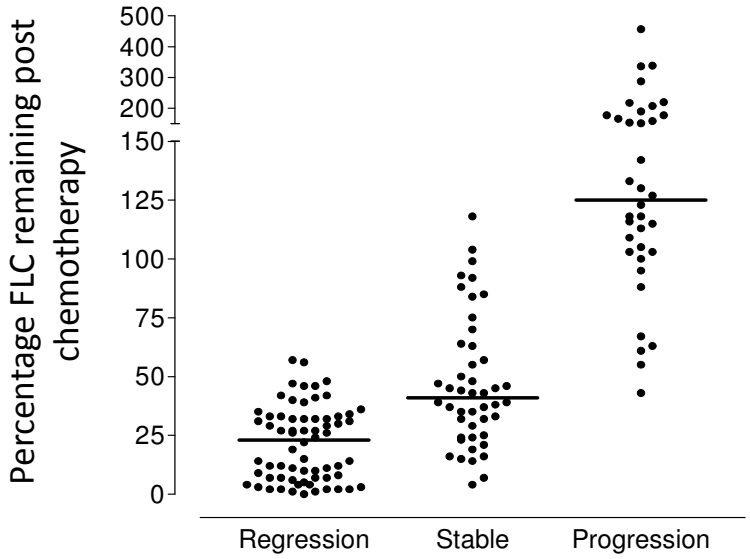
- **Proteinuria** —
  - Aim for a blood pressure of <120/80 mmHg – ACEI + ARB
- **Oedema** —
  - dietary sodium restriction + Fluid restriction
  - Pressure stockings
  - Combination of Fursemide/Bumetanide + Spironolactone
    - This needs to be done gently –to avoid low blood fluid levels and low blood pressure.
  - Injections of albumin may be required in severe cases
- **Hypercholesterolaemia** —
  - Statins but beware of interactions
- **Thrombotic risk** —
  - High if albumin <25g/L – Consider anticoagulation but balance again increase bleeding risk

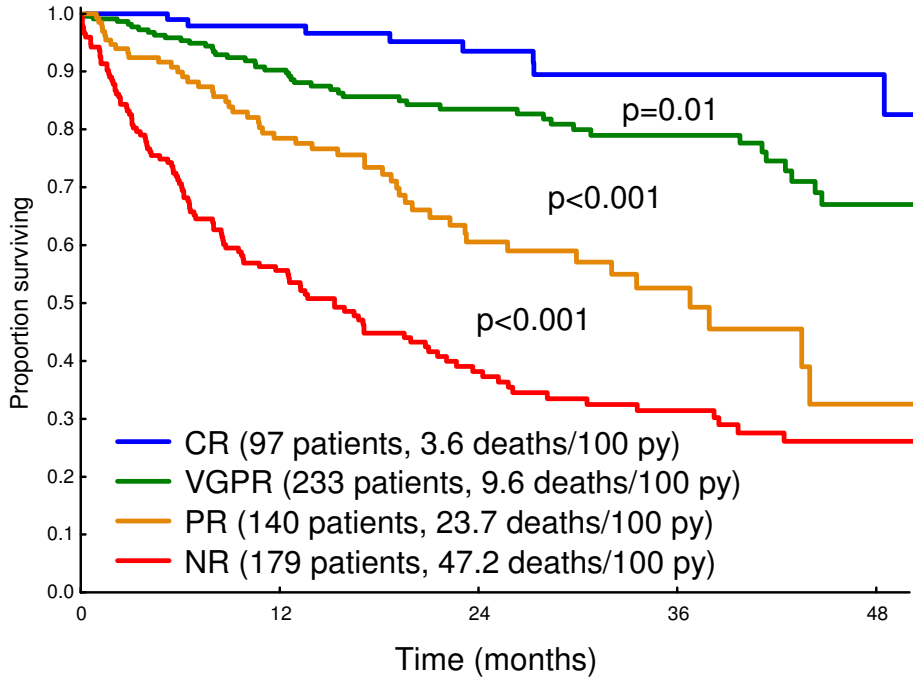
Cardiac

- **Diuretics** — mainstay
- **ACE inhibitors – Oedema** —
  - Poorly tolerated
  - Little evidence of efficacy
  - Limit duiretic dose
- **Betablockers** —
  - May abruptly worsen symptoms
- **Fluid restriction**
- **Daily weights**
- **Diuretic self adjustment**
- **Involvement of a heart failure nurse**

UCL

Reducing amyloidogenic light chains directly improves survival in AL





Palladini et al. Validation of Response Criteria in AL Amyloidosis . JCO 2012

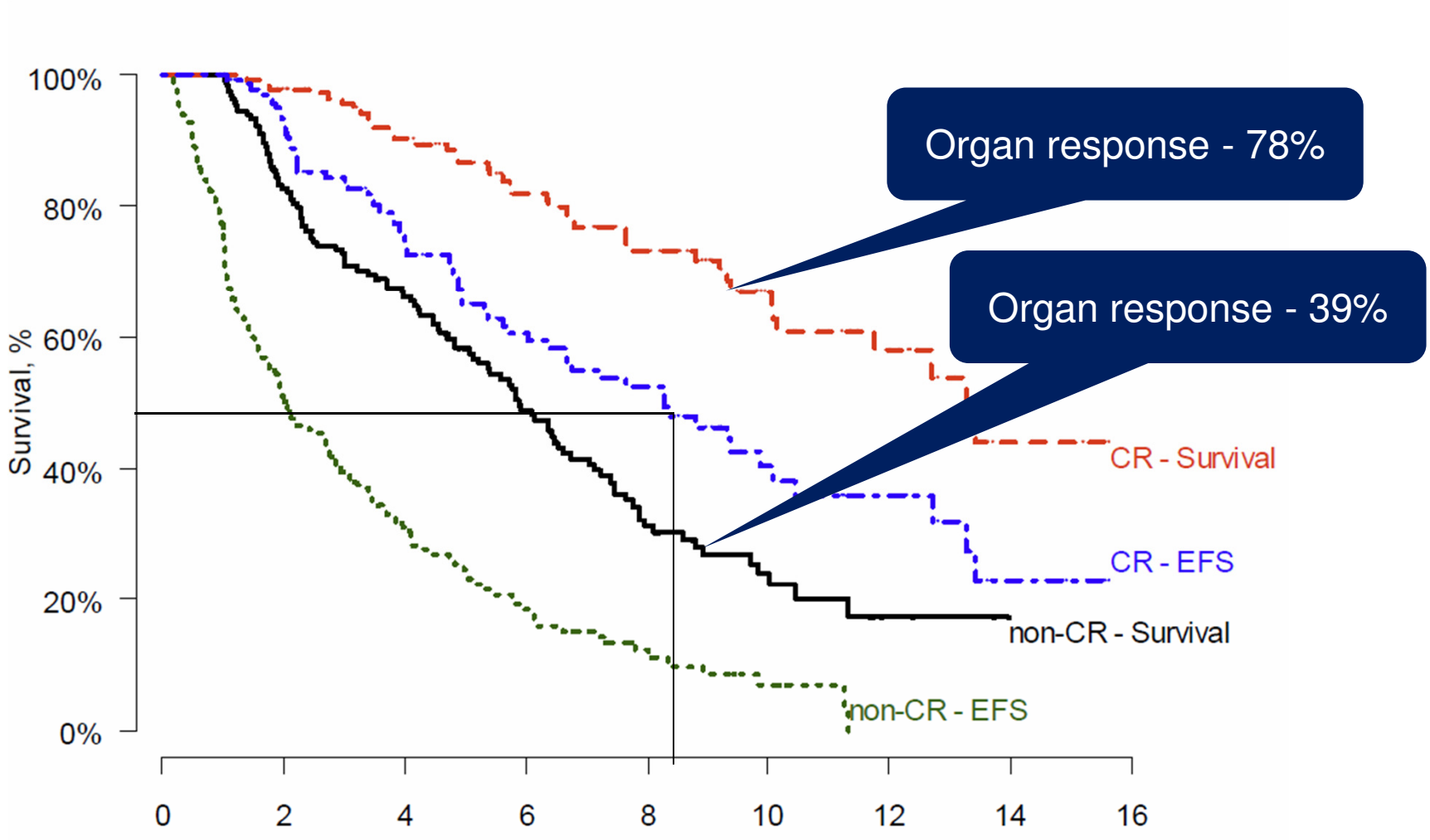
Risk stratified treatment is critical

AL with Low risk disease (15-20%)

- Stage 1/Early stage 2
- Young
- Good performance status
- NT-proBNP <500 pMol/L
- Good renal function

HDM-ASCT
Full dose chemo

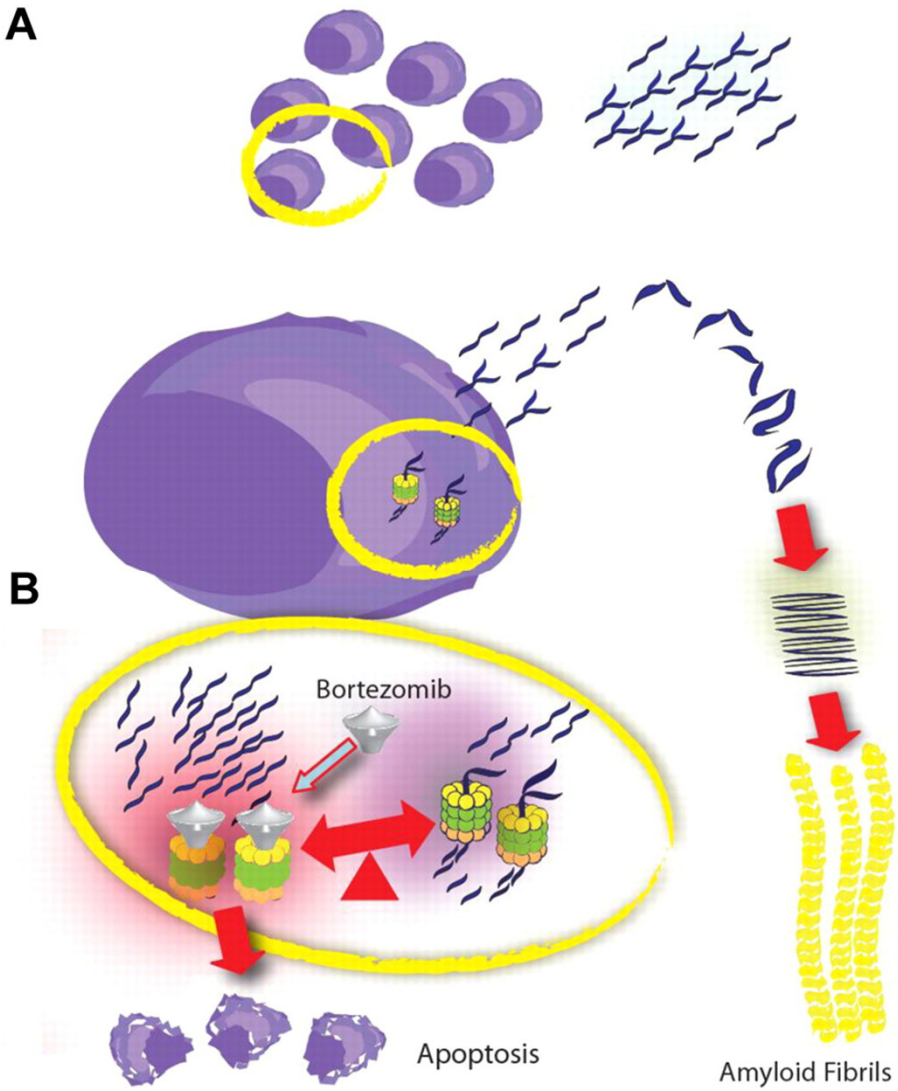
Long term outcomes after ASCT



Cibeira et al. Blood; 2011; 118 (16);4646-52

Proteosome inhibitors in AL

Increased proteasomal workload (**caused by misfolded light chains**) - higher apoptotic sensitivity of plasma cells to proteasome inhibitor



©2011 by American Society of Hematology

Dimopoulos M A , Kastritis E Blood 2011;118:827-828

Bortezomib-combinations in AL amyloidosis

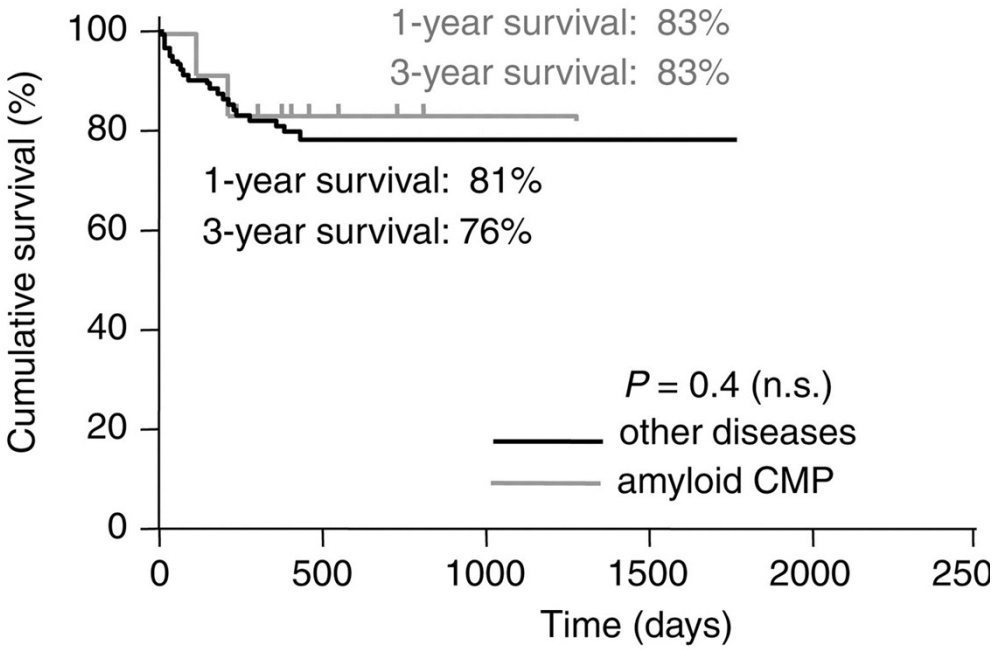
	Zonder et al	*Mikhael et al*	*Venner et al*	*Palladini et al*
Patients	33	10 (upfront)	20 (upfront)	50 (upfront)
Regime	**V-MDex**	**C-V-D**	**C-V-D**	**V-Mdex – 33 C-V-D - 17**
Hematologic response	94%	93%	95%	Stage I/II – 67% Stage III – 40%
CR	63%	60%	65%	Stage I/II – 27% Stage III – 5%
Organ response	62%	40%	46%	NA

Zonder et al. Blood (ASH Annual Meeting Abstracts) 2010
Mikhael et al. Blood 2012 119:4391-4394
Venner et al. Blood 2012 119:4387-4390
Pallidini et al. Blood (ASH Annual Meeting Abstracts) 2011

Addressing mortality in advanced cardiac AL

- Prognosis of advanced cardiac AL poor
  - One year OS – 40%
  - 4 year OS - <15%
- Treatment can result in mortality
- Role of ICD
  - still controvertial
  - But useful in selected cases
- Role of LVAD
  - Interesting
  - Some reports of utility
  - Needs exploring

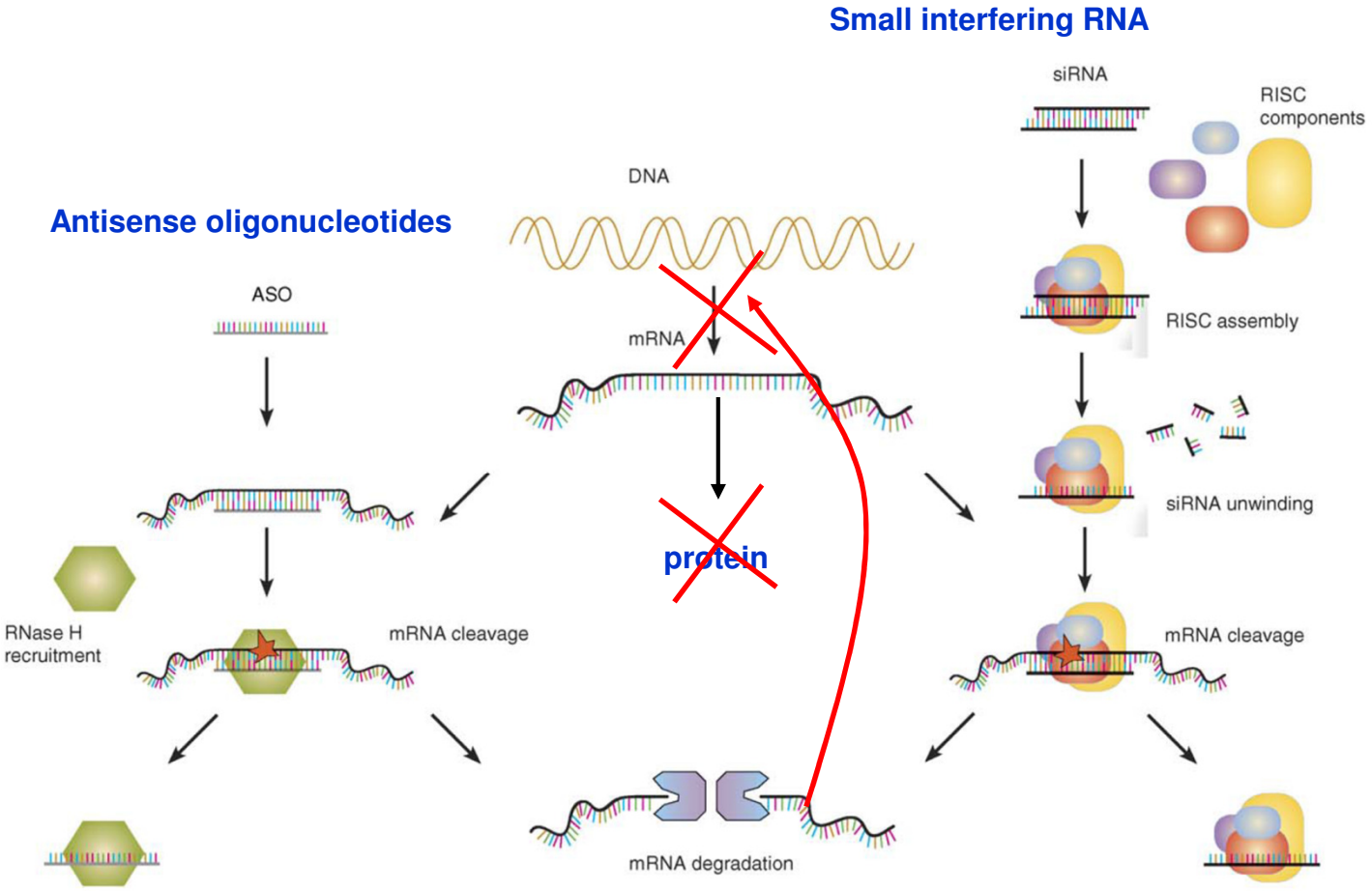
- Selected patients with single organ involvement and suitable for ASCT post cardiac Tx



amyloid	*n* = 12	*n* = 4
others	*n* = 102	*n* = 75

Kristen A V et al. Eur J Heart Fail 2009;11:1014-1020

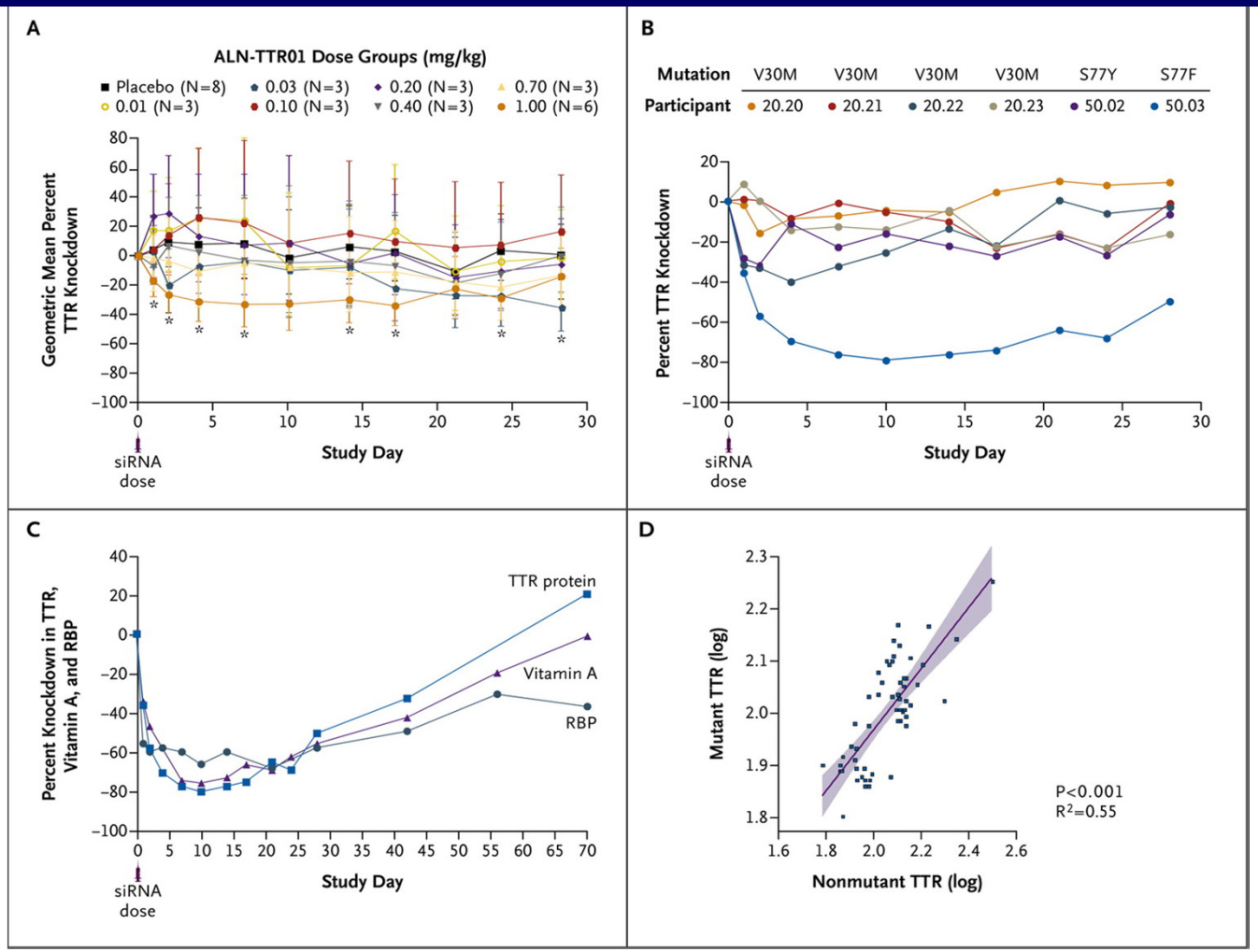
siRNA and ASO in the treatment of amyloidoses



Basic principle of the mechanism of action of conventional ASO and siRNA. Both antisense molecules pair with their complementary target RNA and inhibit synthesis of target proteins on the transcript level.(RISC:RNA induced silencing complex)

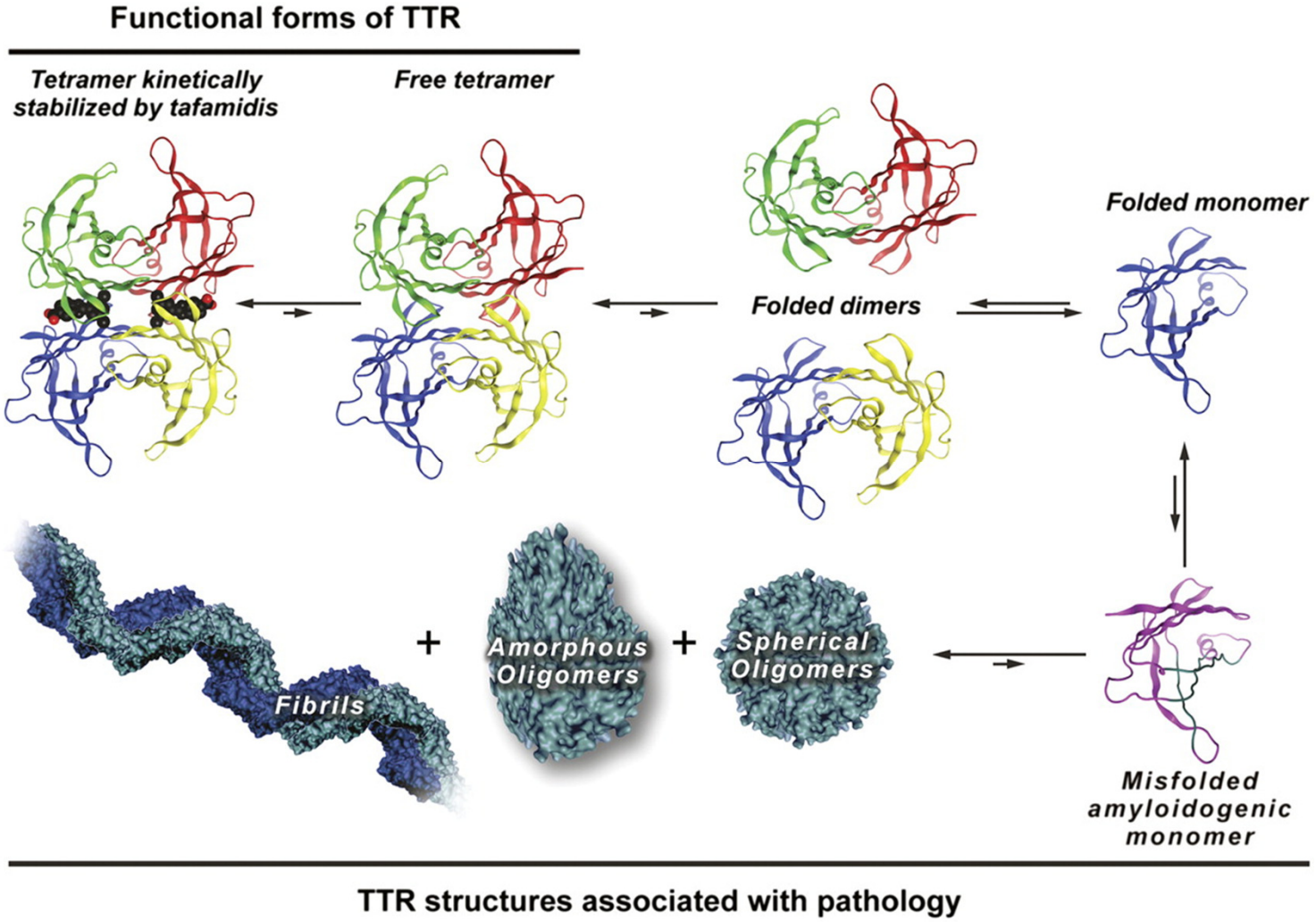
Wachek & Zangemeister-Wittke, Crit Rev Oncol/Hematol 2006;59:65-73

Efficacy of ALN-TTR01 in Patients with Transthyretin Amyloidosis.



Coelho T et al. N Engl J Med 2013;369:819-829.

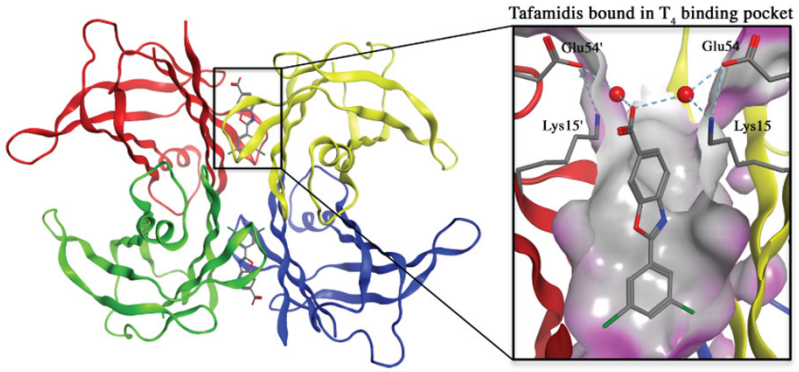
The TTR amyloid cascade.



Bulawa C E et al. PNAS 2012;109:9629-9634

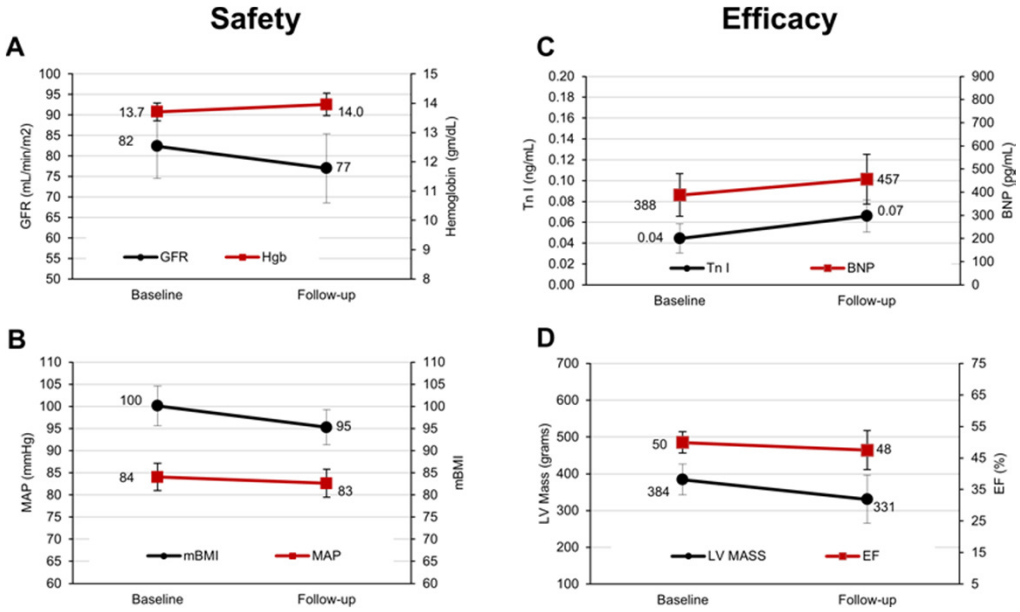
©2012 by National Academy of Sciences

Tafamidis for ATTR amyloidosis



The current *Proceedings of the National Academy of Sciences* study provides new molecular and structural data showing how tafamidis works. (Image courtesy of the Wilson and Kelly labs, The Scripps Research Institute.)

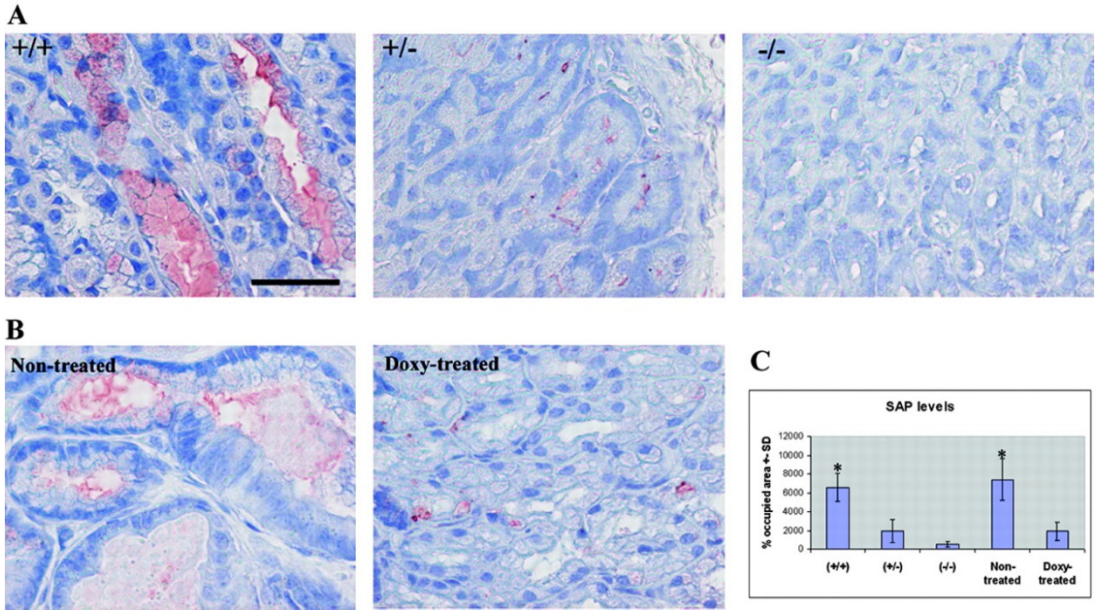
Diflunisal for ATTR cardiac amyloidosis



Castaño A et al
Congest Heart Fail. 2012 Nov-Dec;18(6):315-9.

Protecting and disrupting fibrils in cardiac ATTR and AL – new role for an old drug (Doxycycline)

- Tetracyclines are concentrated in the heart
- Impair fibril formation in ATTR and AL
- Ongoing clinical trials
  - Doxy in AL
  - Doxy + TUDCA in ATTR



Cardoso I , and Saraiva M J FASEB J 2006;20:234-239

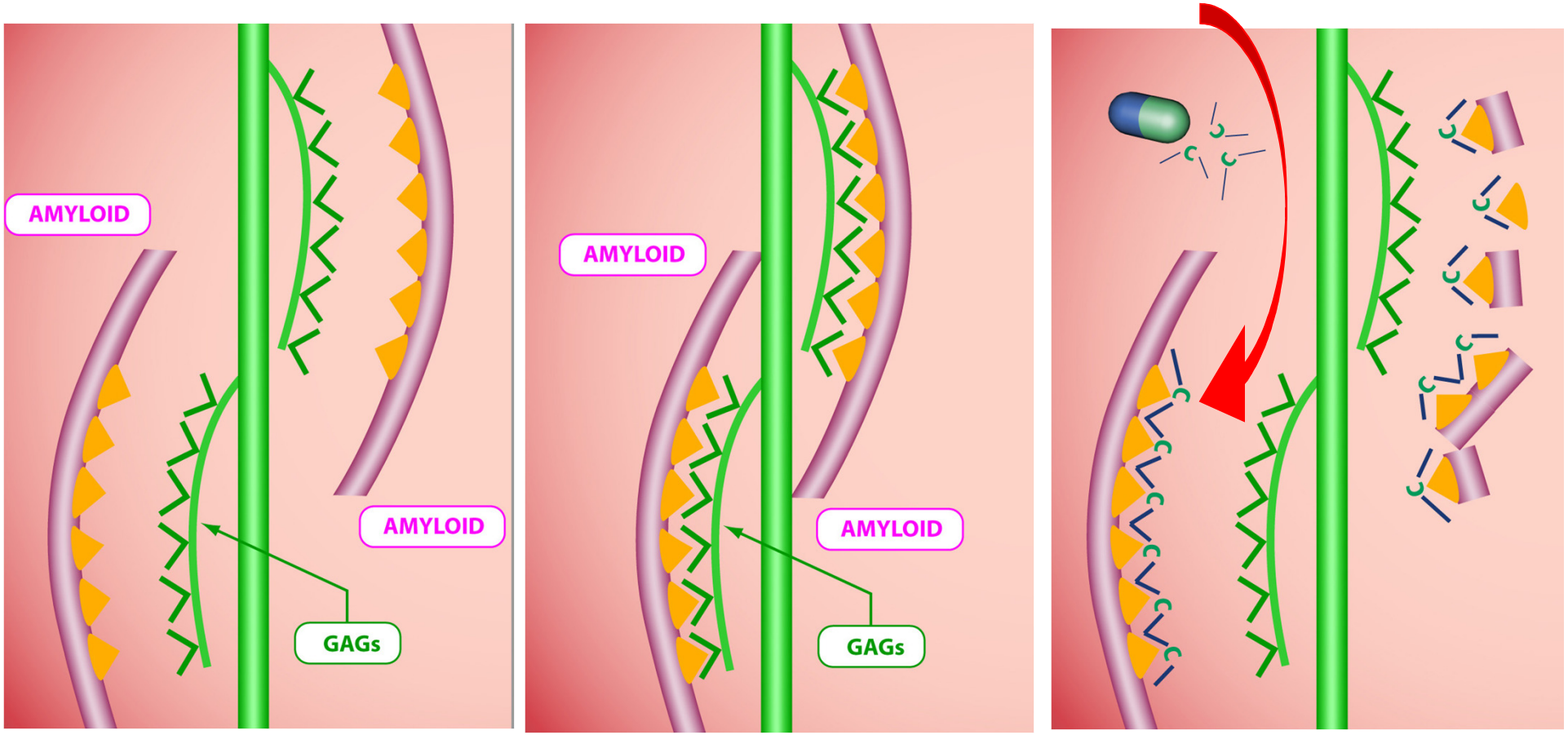
: Doxycycline hyclate

INN (International Nonproprietary Name)	:	-	Type of product	:	Ingredient/substance
Code name	:	-	Type of production	:	Synthetic / extractive chemistry
Chemical name	:	-	Orphan designation	:	Europe
			Orpha number	:	ORPHA35266

Orphan designation - Europe
Diseases list
Dialysis-related amyloidosis | Autosomal dominant beta2-microglobulinic amyloidosis
Detailed information

Additional information
Research on this medical product
> Clinical trials (4)
> Research projects (0)
> Networks (0)

Targeting GAG's - Eprodisate



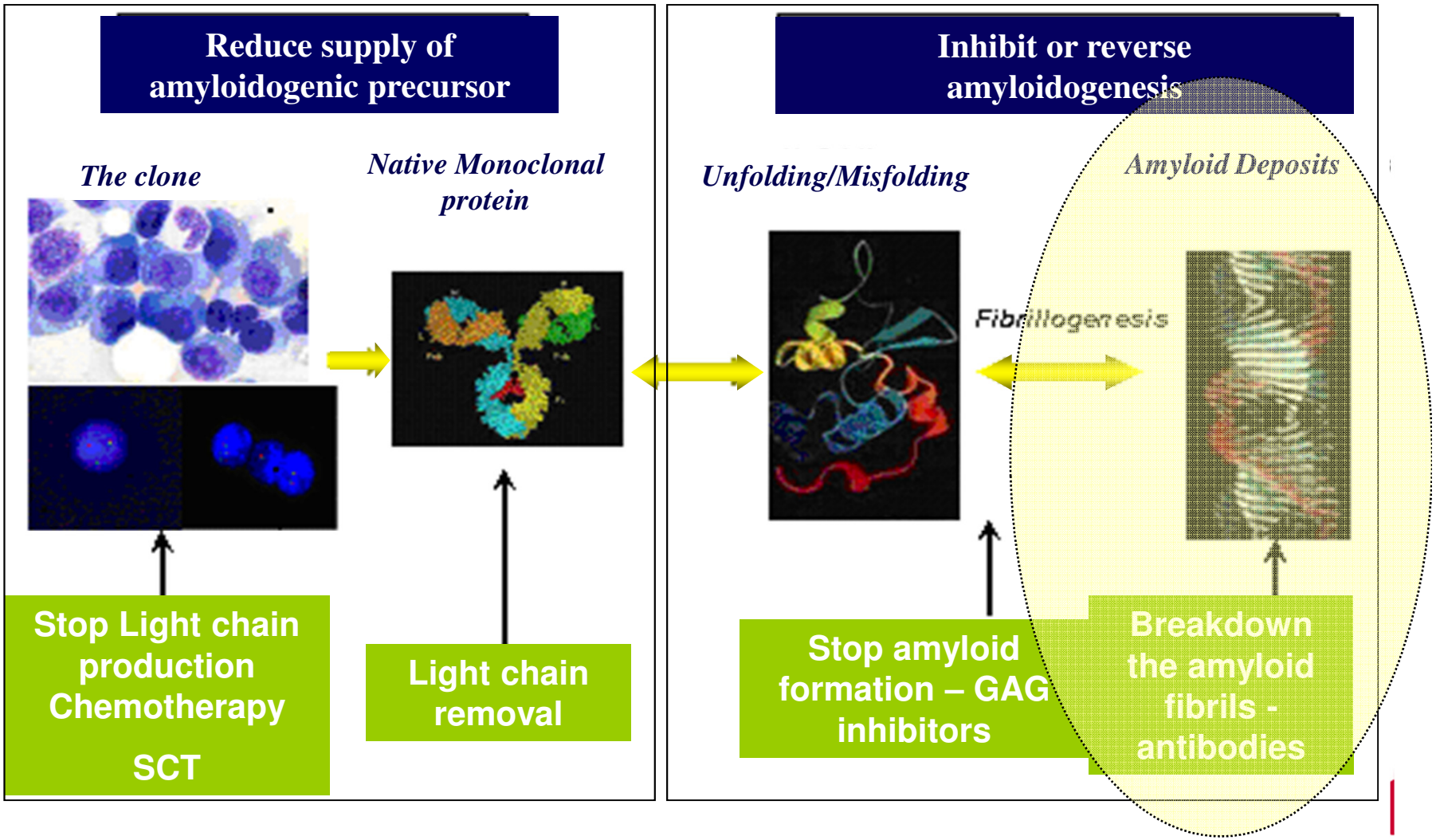
UCL

Amyloid + GAGs:

Amyloid fibril formation leads to progression of disease

Eprodisate should prevent amyloid fibril formation, deposition and associated toxicity in the organs.

Targeting the deposits



Immunotherapy – Anti-SAP antibodies – the Concept

Deplete plasma of SAP using CPHPC

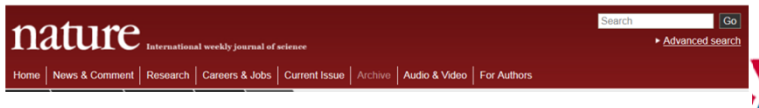
↓

Some SAP still remains on amyloid deposits

↓

Give anti-SAP antibody to target amyloid deposits

UCL



Antibodies to human serum amyloid P component eliminate visceral amyloid deposits

A Study to Evaluate the Safety of GSK2398852 When Co-administered With GSK2315698 in Patients With Systemic Amyloidosis

This study is currently recruiting participants.

Verified February 2014 by GlaxoSmithKline

Sponsor:

ClinicalTrials.gov Identifier:
NCT01777243

First received: January 24, 2013

Prothena is developing NEOD001, a humanized novel monoclonal antibody designed to neutralize and clear soluble and insoluble amyloid aggregates in patients with AL. NEOD001 is being studied in an ongoing Phase 1 study.

The abstract accepted for poster presentation is as follows:

(Abstract #PB-48) Preliminary cardiac biomarker responses demonstrated in an ongoing phase 1 study of NEOD001 in patients with AL amyloidosis and persistent organ dysfunction

- Presenter: Dr. Michaela Liedtke, Stanford Cancer Institute, Stanford, California
- Date: Tuesday, April 29

Acknowledgements

Physicians
Prof Philip Hawkins
Prof Sir Mark Pepys
Dr Julian Gillmore
Dr Helen Lachmann
Dr Carol Whelan
Dr Marianna Fontana
Dr Sajitha Sachichitanatnam
Dr Shameem Mahmood

Nurses
Thirusha Lane
Darren Foard
Lisa Rannigan
Nicola Stewart
Annie Hughes
Eleanor Pyart

Histology
Janet Gilbertson

Echocardiography
Babita Mahadikova

Imaging
David Hutt
Steph McKnight
Dr Anne-Marie Quigley
Danny McCool

Genetics
Dr Alison Bybee
Dorota Rowczenio
Hadija Trojer
Ania Zaremba

Protein Analysis
Dr Nancy Wassef



Thanks' for your kind attention!!!!!!



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