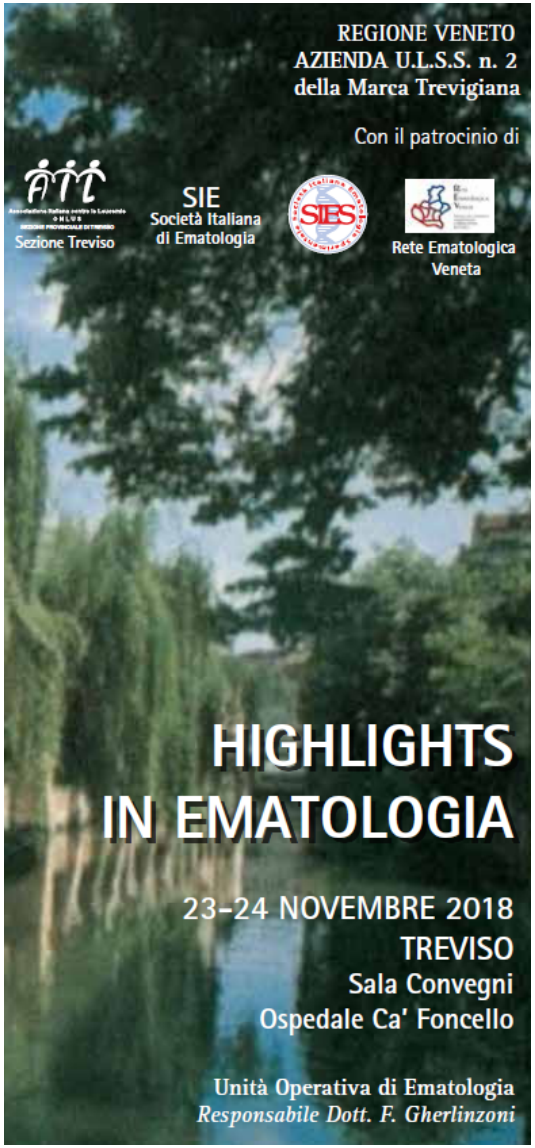


Cardiopatie nel paziente emopatico

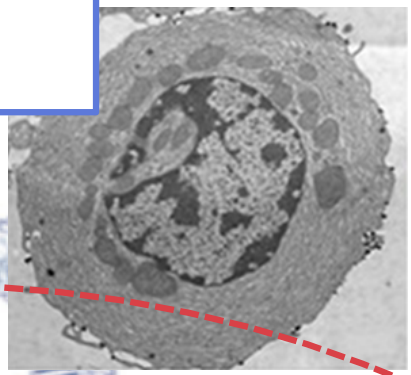
Interessamento cardiaco da depositi di amiloide

Giovanni Palladini

Amyloidosis Research and Treatment Center
Fondazione IRCCS Policlinico San Matteo
and Department of Molecular Medicine
University of Pavia
Pavia, Italy

AL amyloidosis

Dangerous, small clone
Median BMPC infiltrate: 10%

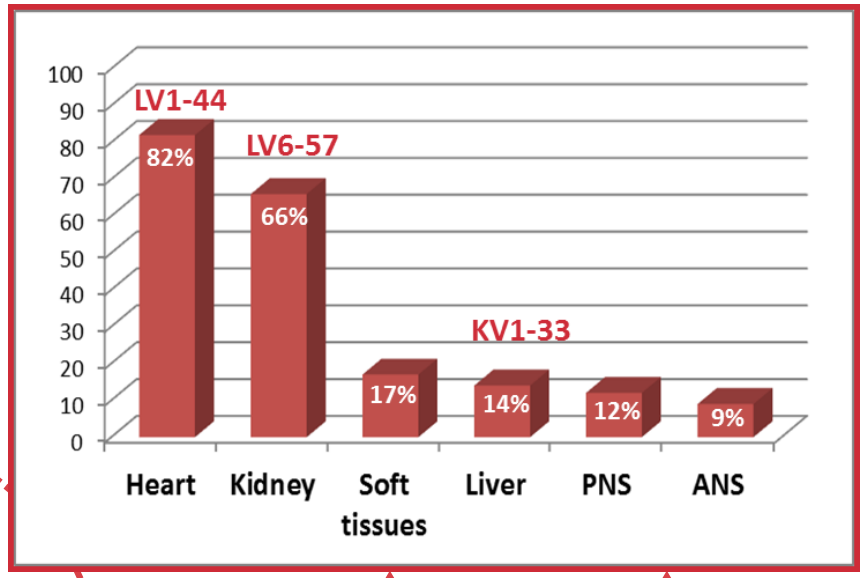


Unstable LCs

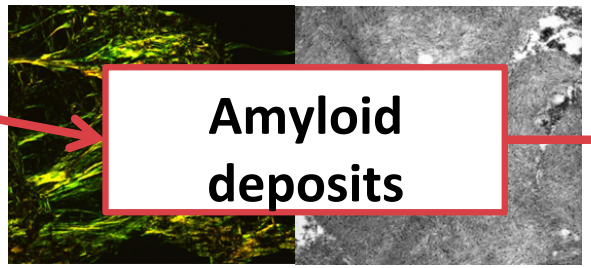
endoproteases, metal ions
shear forces

Oligomers

SAP, GAGs

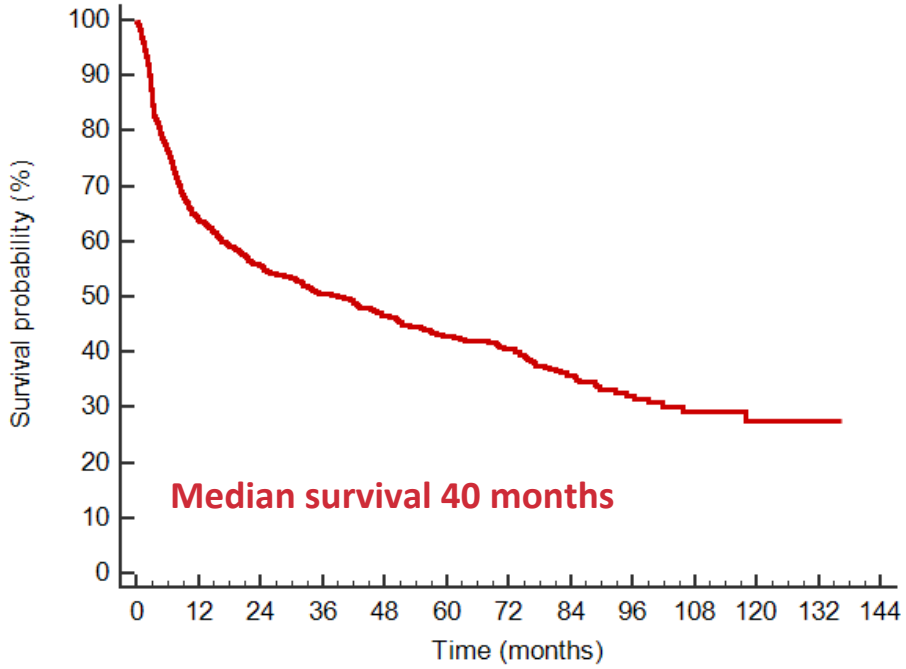


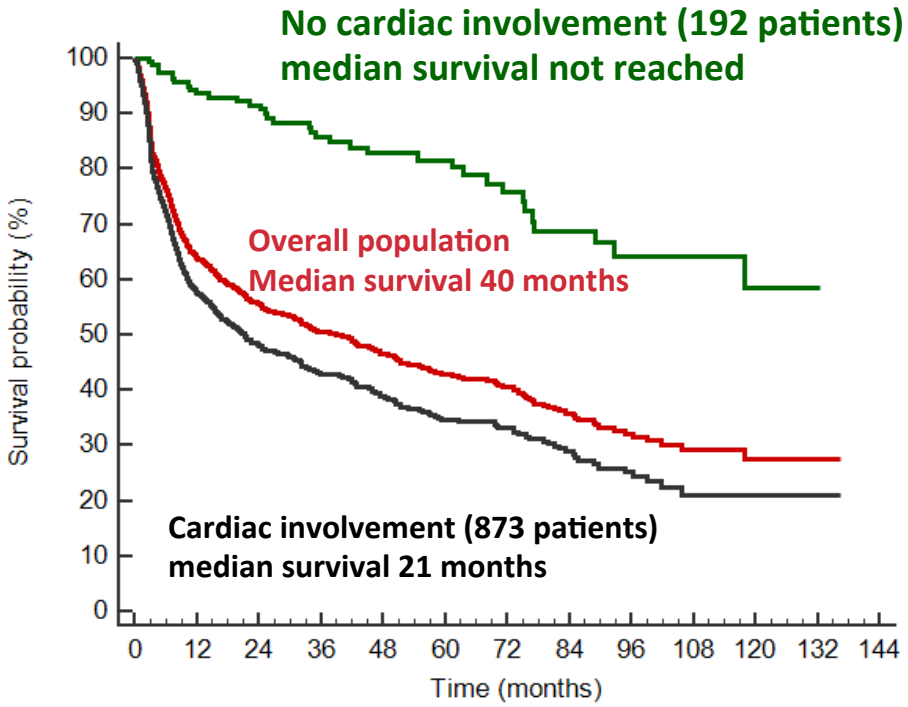
Proteotoxicity



Amyloid deposits

Survival of 1065 patients with AL amyloidosis





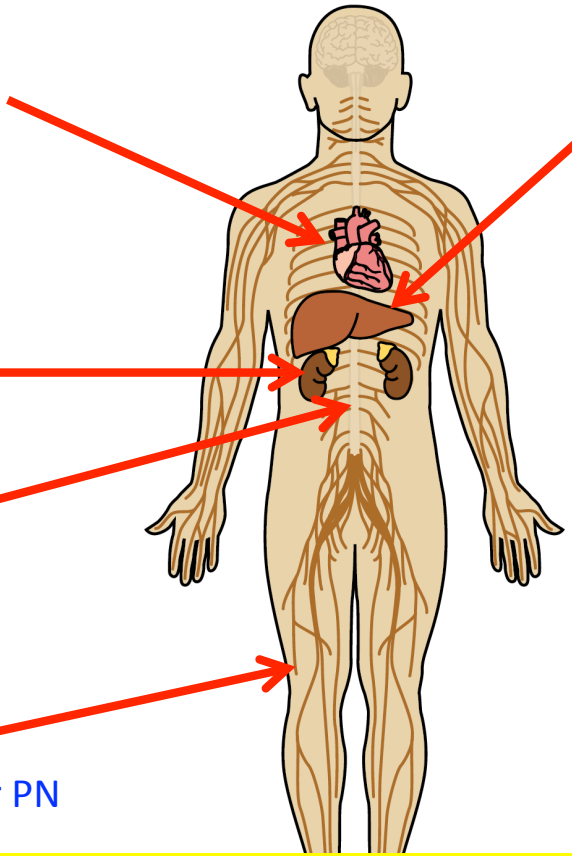
Amyloidosis is a great imitator

Heart
Heart failure with preserved ejection fraction
Thickened ventricular walls, low voltages at ECG
Dyspnea at rest or exertion, fatigue
Hypotension or syncope
Peripheral edema

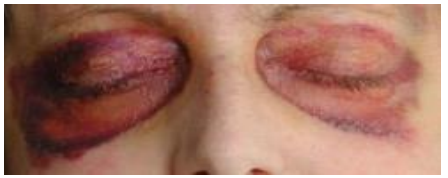
Kidney
Nephrotic range proteinuria
Renal failure
Peripheral edema

GI tract
Malabsorption, weight loss
Bleeding (Factor X def.)

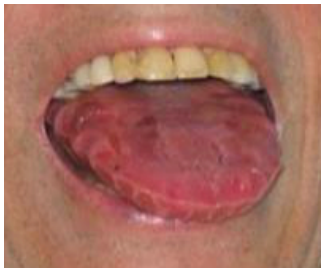
Nervous system
Peripheral: symmetric lower extremity sensorimotor PN
Carpal tunnel syndrome (bilateral)
Autonomic: postural hypotension,
erectile dysfunction (males), GI motility alte



Liver
Increased alkaline phosph
Hepatomegaly



Periorbital purpura 11%



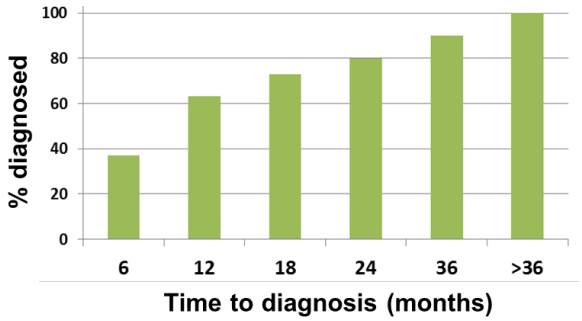
Macroglossia 14%

→ **advanced stage of the disease!**

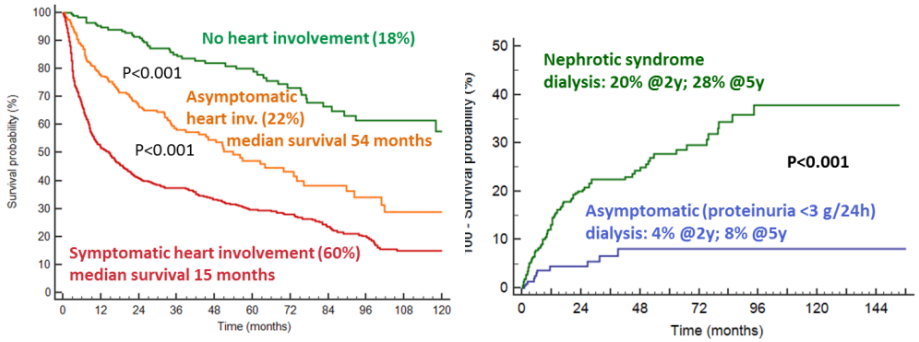
→ **need for more sensitive markers of organ involvement**

Biomarker-based (early) diagnosis

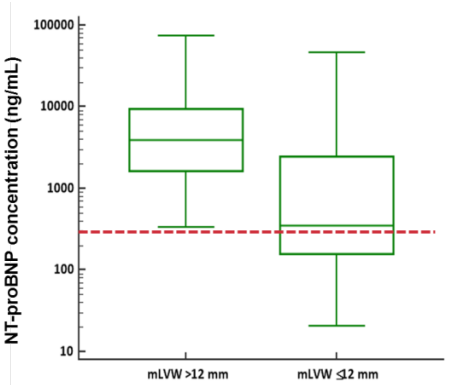
Systemic amyloidosis is diagnosed several months after the onset of symptoms



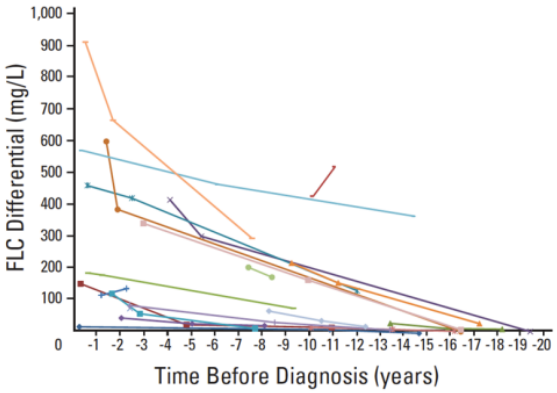
Biomarkers identify pre-symptomatic organ involvement with better outcome



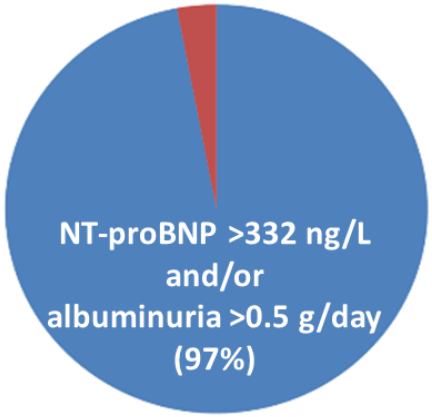
NT-proBNP has 100% sensitivity for cardiac AL



Increased FLC precedes clinical presentation by years



Screening with NT-proBNP and albuminuria of patients with MGUS and abnormal FLC ratio allows diagnosis at a pre-symptomatic stage



13 patients

→VGPR/CR + organ response

Lousada, et al. Adv Ther 2015
Palladini, et al. Circulation 2003
Weiss, et al. JCO 2014
Merlini & Palladini. Hematology 2012
Merlini, et al. Blood 2013
Palladini, et al. ASH 2017 [abstract 1760]

Tissue diagnosis of AL amyloidosis

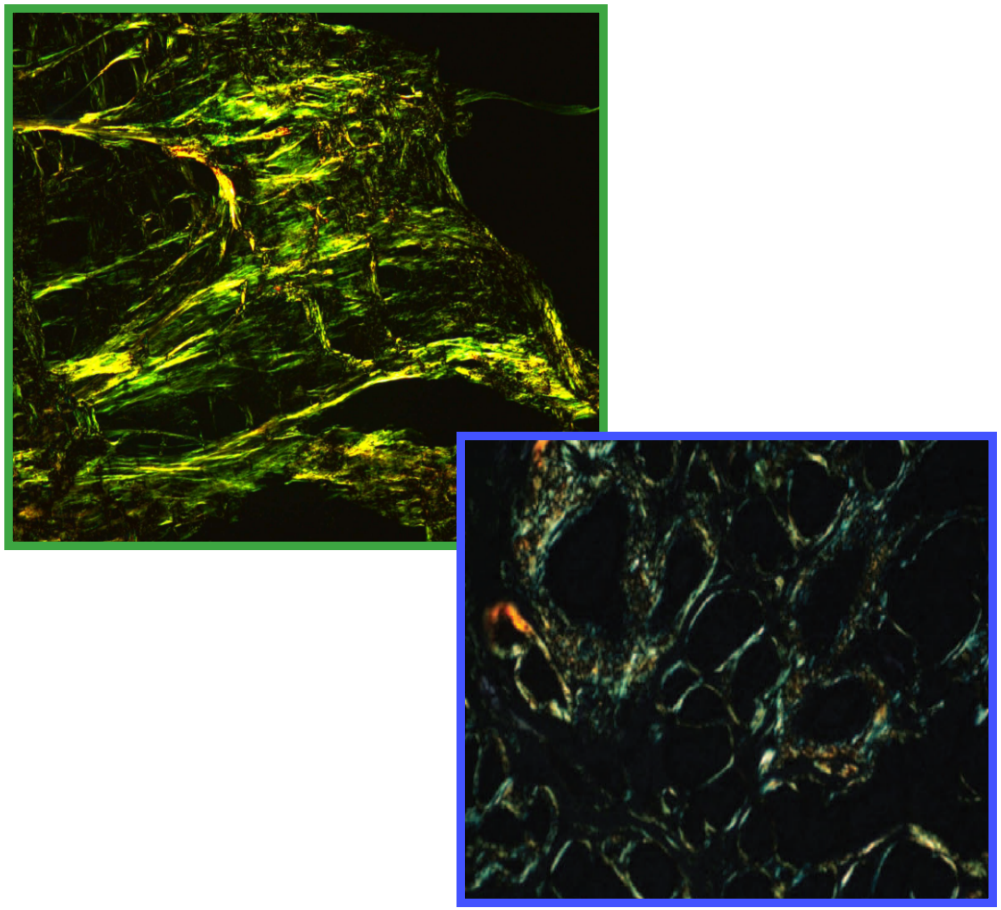
Abdominal fat aspirate
sensitivity 79%

↓

Minor salivary gland biopsy
sensitivity 58% in patients with negative fat aspirate

↓

Biopsy of the organ involved
beware of hemorrhagic risk, transjugular approach preferred for liver biopsy



1. *Fernandez de Larrea, et al. Blood 2015*
2. *Foli, et al. Amyloid 2011*

Substantial overlap of clinical presentation of the most common forms of systemic amyloidosis

Amyloid type	Organ involvement					
	Heart	Kidney	Liver	PNS	ANS	ST
AL amyloidosis (~70%)	++	++	+	+	+	+
Hereditary ATTR amyloidosis	++	±	-	++	+	-
AA (reactive) amyloidosis	±	++	+	-	+	-
Wild-type ATTR amyloidosis (~10%) (Senile systemic amyloidosis)	++	-	-	-	-	-
Hereditary AApoAI amyloidosis	+	+	+	-	-	-
ALECT2 Amyloidosis (Leukocyte chemotactic factor 2)	-	+	+	-	-	-

Unequivocal amyloid typing is vital to avoid catastrophic therapeutic mistakes

Tissue typing

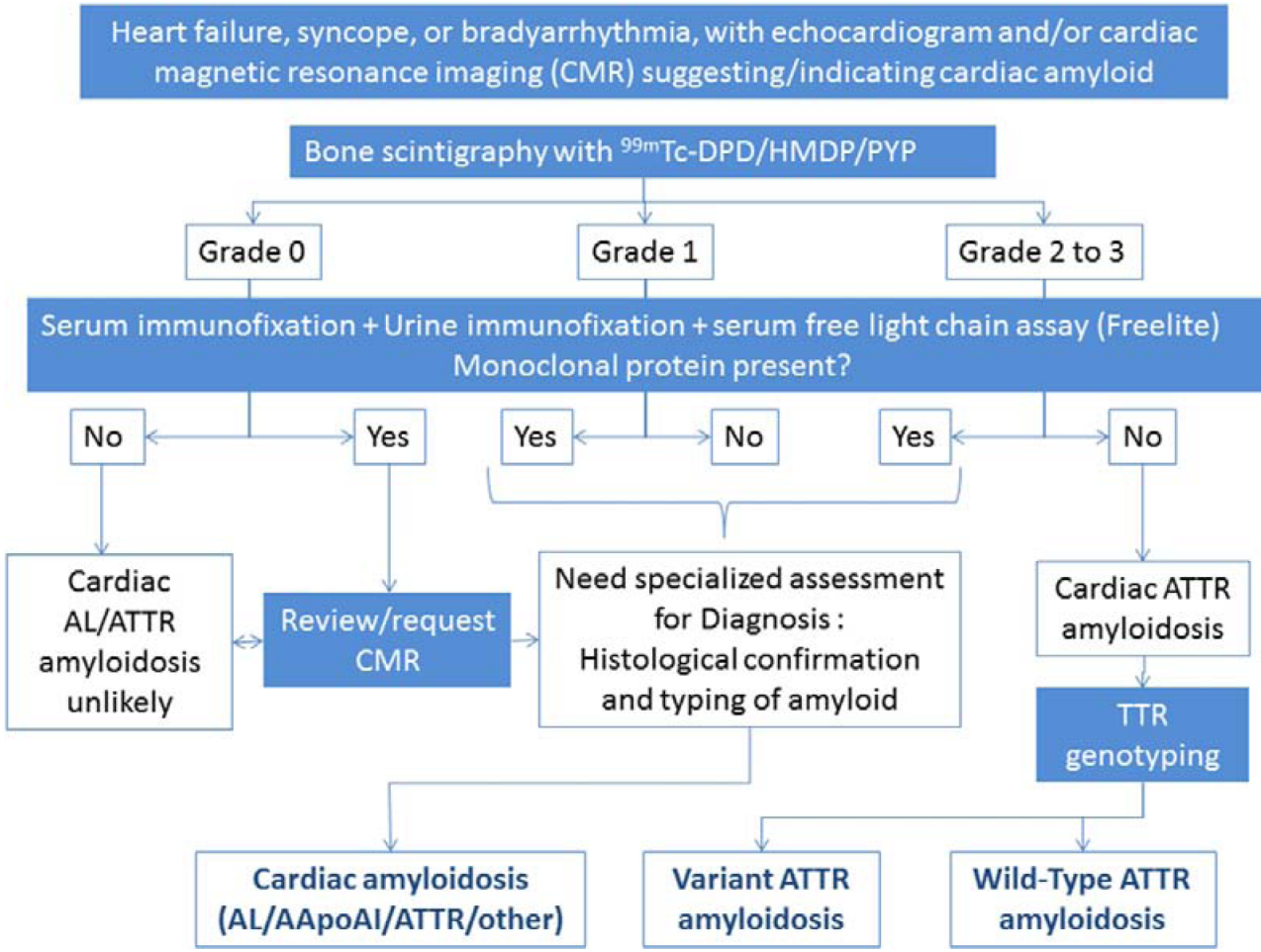
- **Light microscopy immunohistochemistry**
  - reliable in AA amyloidosis with commercial antibodies
  - correctly classifies 94% of patients with custom-made antibodies[1]
- **Immuno-electron microscopy**
  - sensitivity 76%, specificity 100% on abdominal fat
  - correctly classifies >99% of patients with commercial antibodies[2]
- **MS-based proteomics**[3, 4]
  - laser capture microdissection, MudPIT
  - not antibody dependant

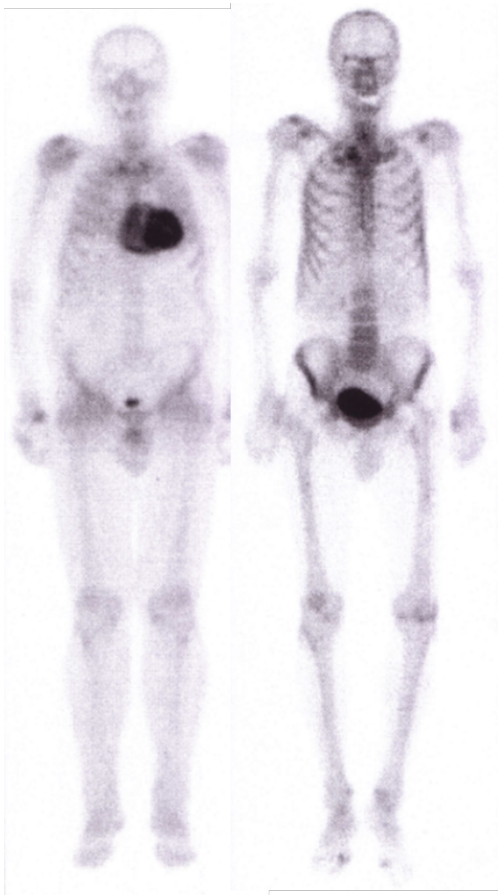
DNA analysis

Cardiac scintigraphy with bone tracers[5, 6] cardiac uptake in ATTR but not in AL amyloidosis

1. *Schönland, et al. Blood 2012*
2. *Férnandez de Larrea, et al. Blood 2014*
3. *Vrana, et al. Blood 2009*
4. *Brambilla, et al. Blood 2012*
5. *Perugini, et al. J Am Coll Cardiol 2005*
6. *Gillmore, et al. Circulation 2017*

Non-biopsy diagnosis of cardiac ATTR amyloidosis

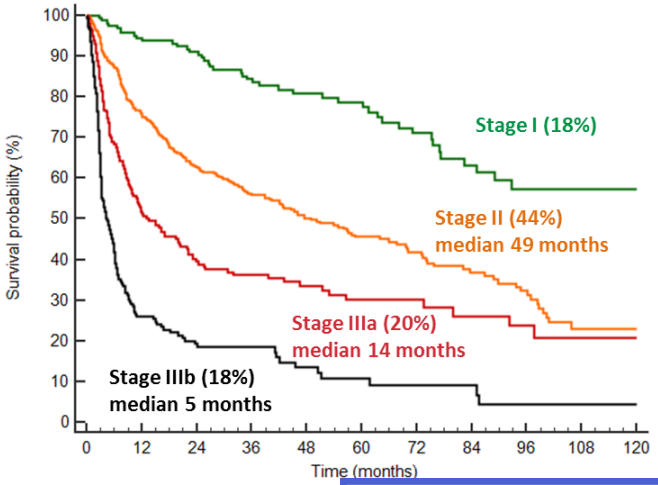




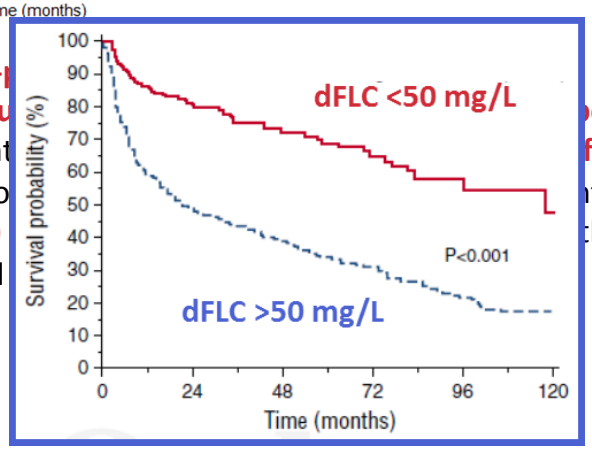
Gillmore, et al. Circulation 2017

Biomarker-based staging

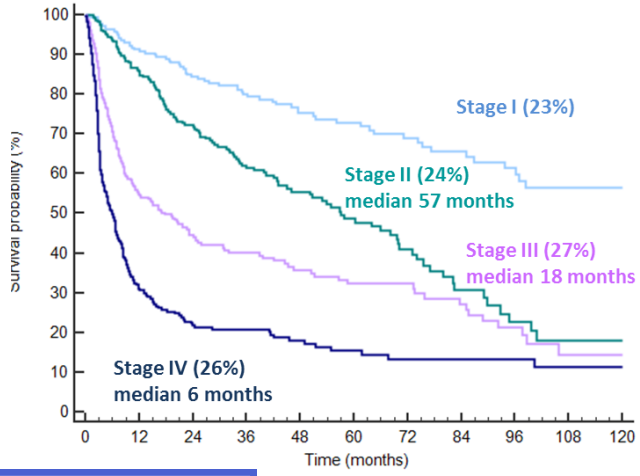
Mayo Clinic / European staging system



Staging is based on **NT-p ng/L)** and **troponin I (cu** stage I, II, and III patient markers above the cuto **Very high (>8500 ng/L)** patients with advanced (Stage IIIb)



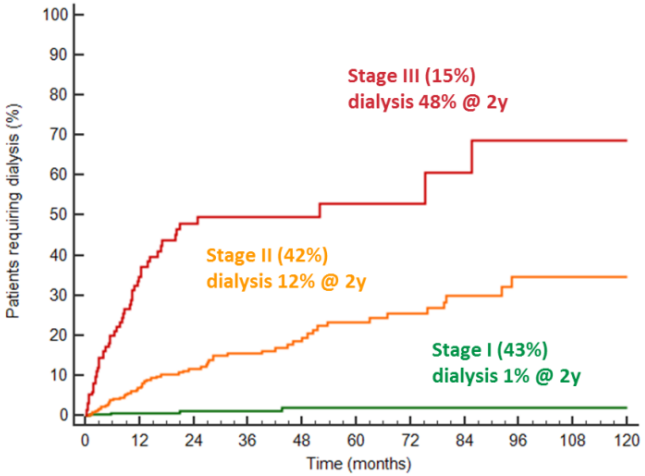
Revised Mayo Clinic staging system



on **NT-proBNP** (cutoff **onin I (cutoff 0.07 ng/mL)**, **f 180 mg/L)**, with stage I, II, nts having 0, 1, 2, or 3 the cutoffs.

Dispenzieri, et al. JCO 2004
Wechalekar, et al. Blood 2013
Kumar, et al. JCO 2012

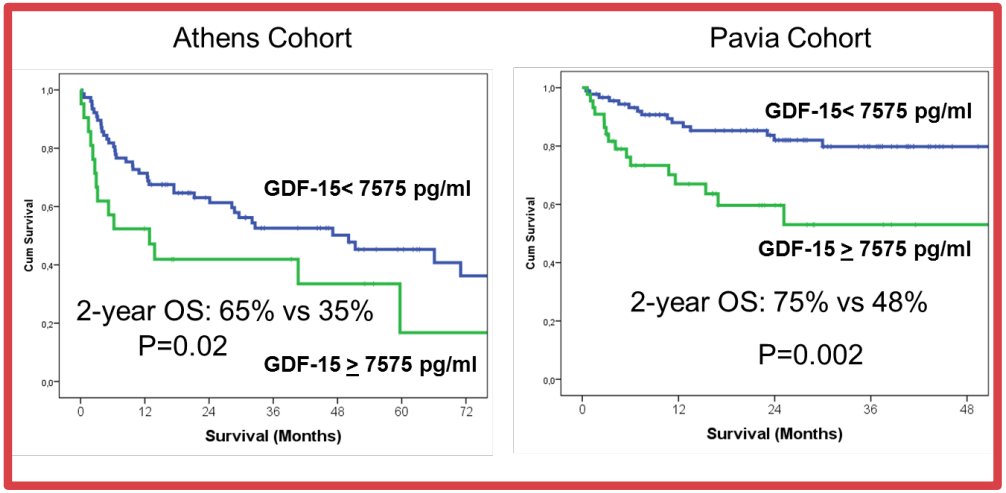
Renal staging system

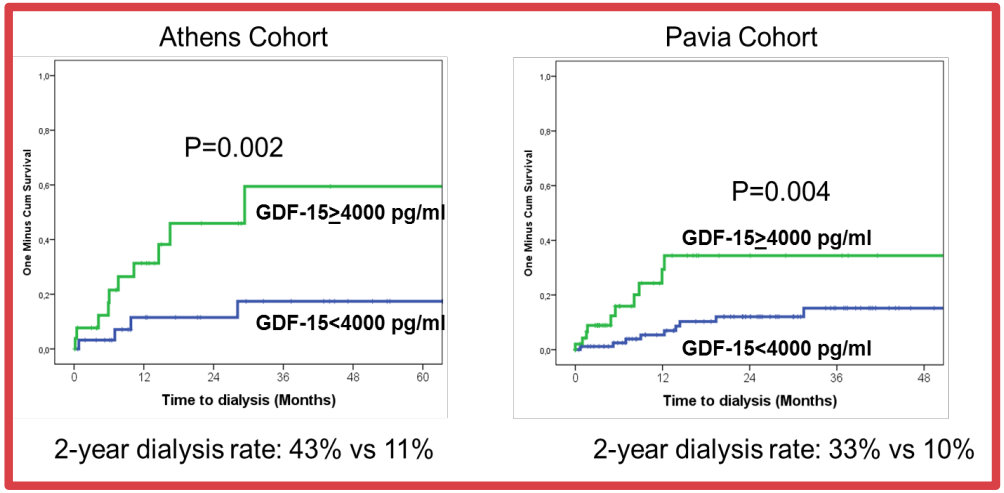


- Stage I: both proteinuria ≤5g/24h and eGFR ≥50 mL/min per 1.73 m^2
- Stage II: either proteinuria >5g/24h or eGFR <50 mL/min per 1.73 m^2
- Stage III: both proteinuria >5g/24h and eGFR <50 mL/min per 1.73 m^2

Palladini, et al. Haematologica 2014
Milani, et al. Blood 2017
Dittrich, et al. Blood 2017
Sidana, et al. Leukemia 2017

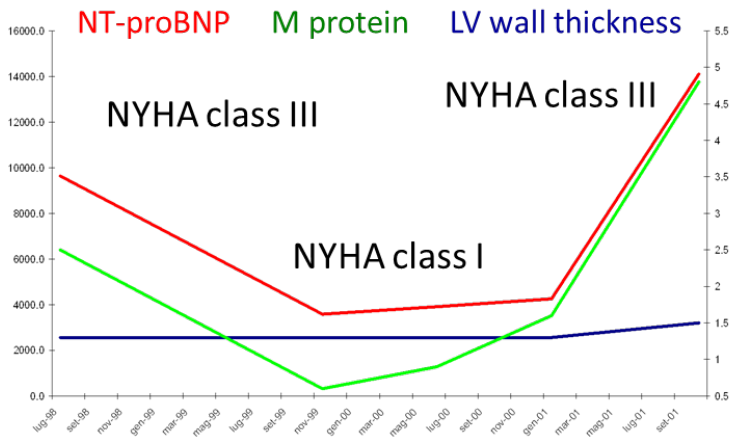
GDF-15 is a new biomarker for survival and renal outcomes in AL amyloidosis



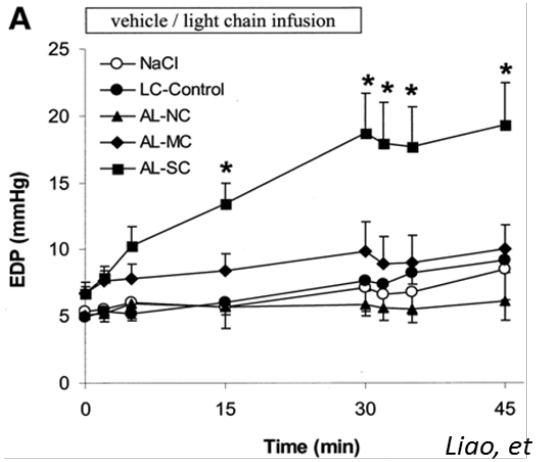


Kastritis, et al. Blood 2018

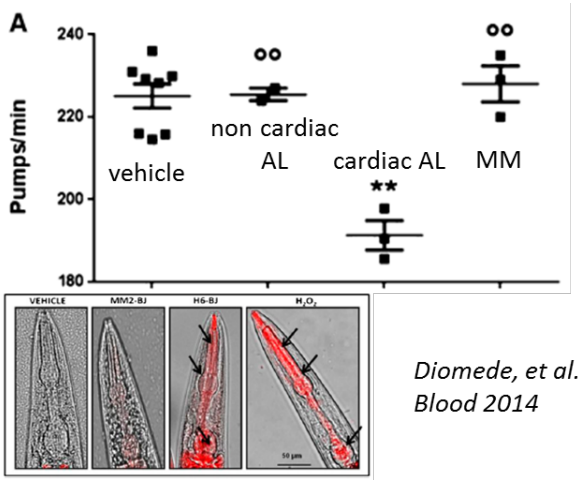
Amyloidogenic light chains are cardiotoxic



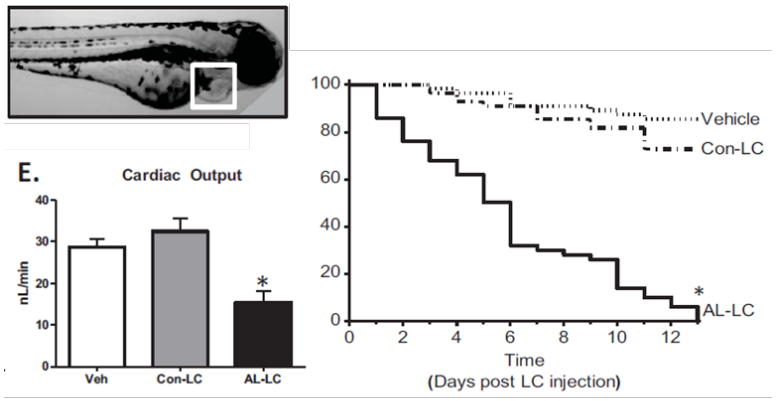
Palladini, et al. Circulation 2003; Palladini, et al. Blood 2006



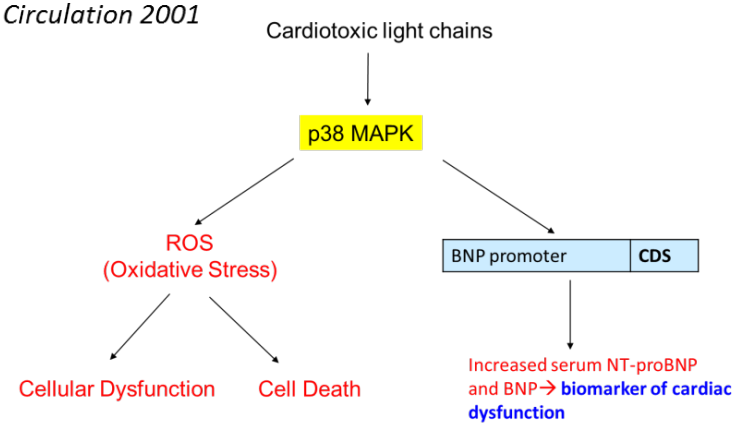
Liao, et al. Circulation 2001



Diomede, et al. Blood 2014



Mishra, et al. Am J Physiol Heart Circ Physiol 2014

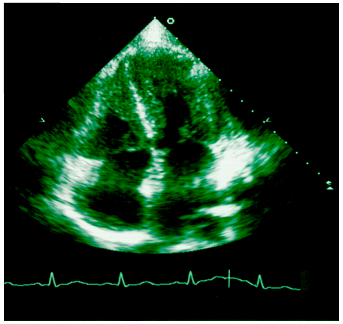


Shi et al, *Proc Natl Acad Sci U S A. 2010*
Guan et al, *Basic Res Cardiol. 2013*

Koivisto et al, *Mol Cell Endocrinol 2011*

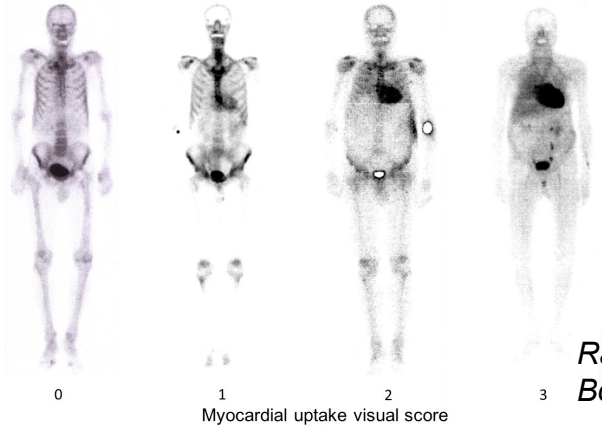
Imaging cardiac ATTR amyloidosis

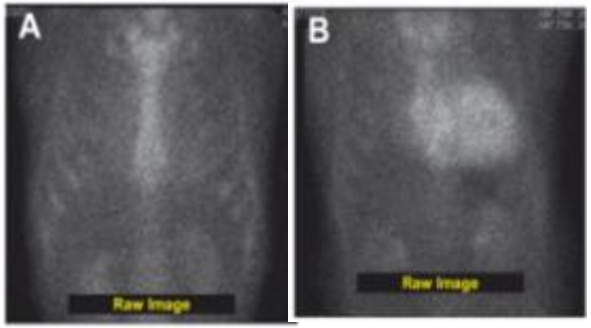
Echo: the cornerstone for diagnosis and management



Strain Doppler imaging
Falk & Quarta, *Heart Fail Rev 2015*

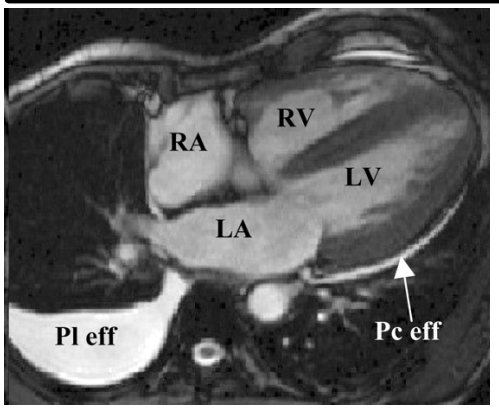
^{99m}TC-DPD/HMDP and ^{99m}Tc-PYP scan





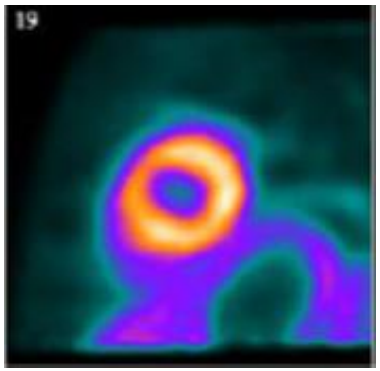
Rapezzi et al, JACC Img 2011
Bokhari et al, Circ Cardiov Img 2013

Cardiac MRI - T1 map - LGE



Maceira et al, *Circulation 2005*
Banypersad et al. *Circ Cardiovasc Img 2013*
Fontana et al. *JACC Cardiovasc Img 2014*
Fontana et al, *Circulation 2015*

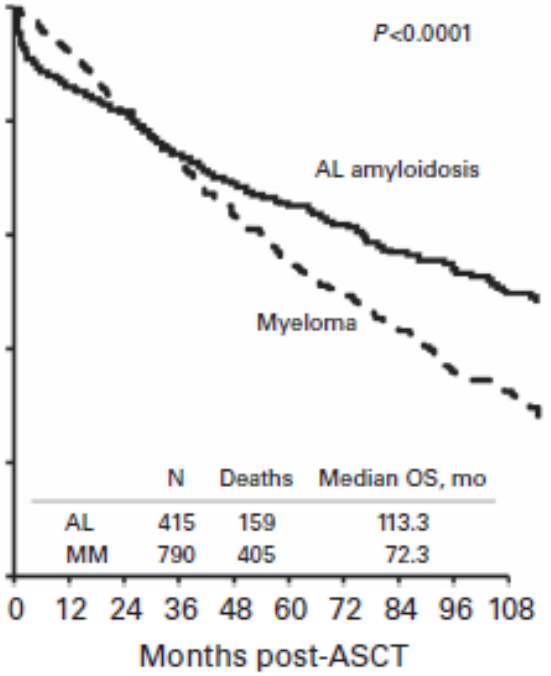
18F-florbetapir imaging

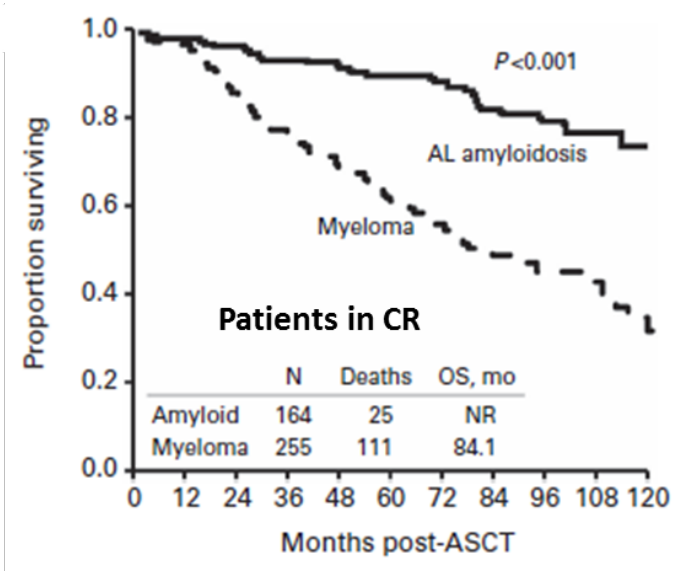


Dorbala et al, *EJNMMI 2014*
Park et al, *Circ Cardiovasc Img. 2015*

Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center.

A Dispenzieri, K Seenithamby, MQ Lacy, SK Kumar, FK Buadi, SR Hayman, D Dingli, MR Litzow, DA Gastineau, DJ Inwards, IN Micallef, SM Ansell, PB Johnston, LF Porrata, MM Patnaik, WJ Hogan and MAA Gertz





Bone Marrow Transplantation (2013), 1–6

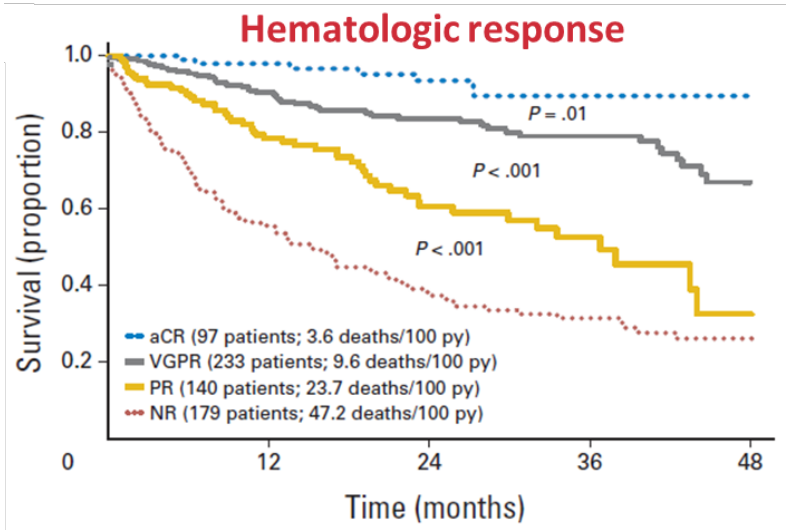
www.nature.com/bmt

Validated criteria for early assessment of response in AL amyloidosis based on biomarkers

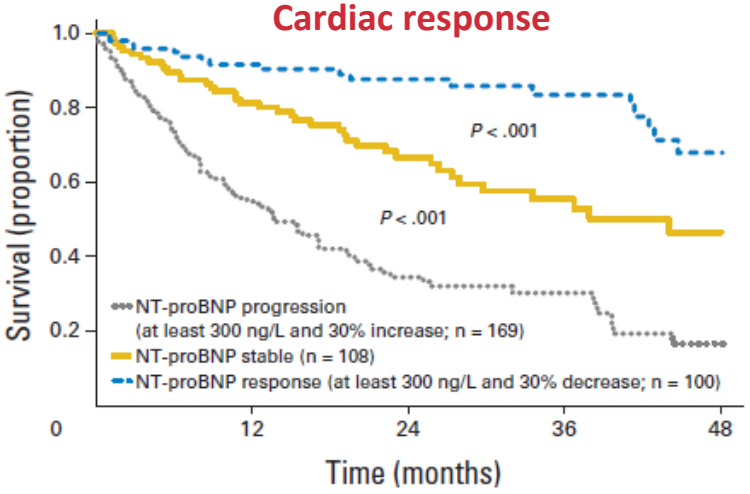
Response	Definition
Hematologic **For dFLC 20-50 mg/L**	**CR:** negative s&u IFE + normal FLCR **VGPR:** dFLC <40 mg/L **PR:** dFLC decrease >50% **Low-dFLC response:** dFLC <10 mg/L
Cardiac	NT-proBNP decrease >30% & >300 ng/L
Renal	Proteinuria decrease >30%

Response criteria were validated at 3 and 6 months after treatment initiation

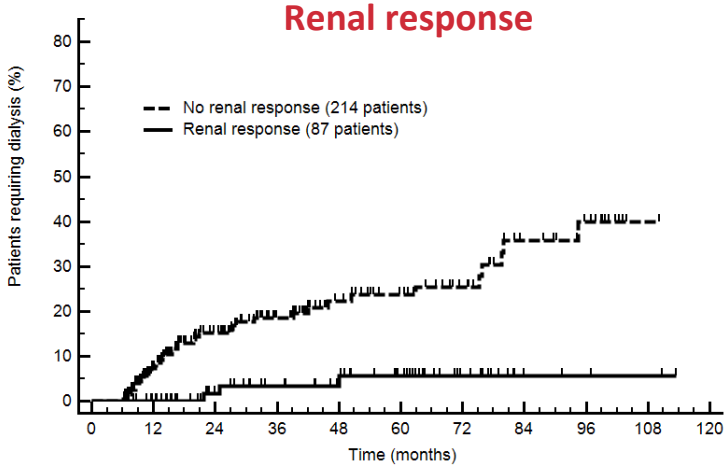
Hematologic response



Cardiac response



Renal response



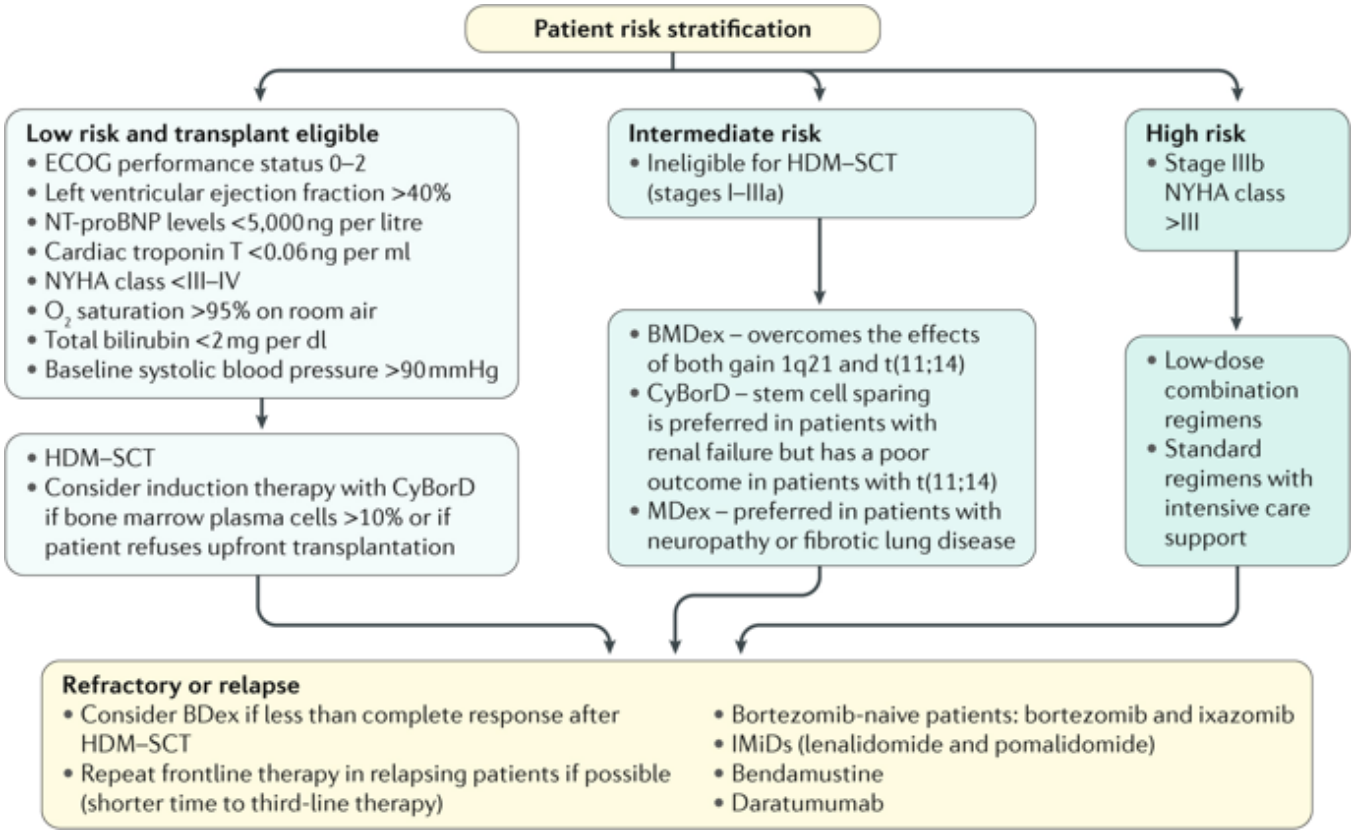
Palladini, et al. JCO 2012
Palladini, et al. Blood 2014
Milani, et al. Blood 2017
Dittrich, et al. Blood 2017
Sidana, et al. Leukemia 2017

Systemic immunoglobulin light chain amyloidosis

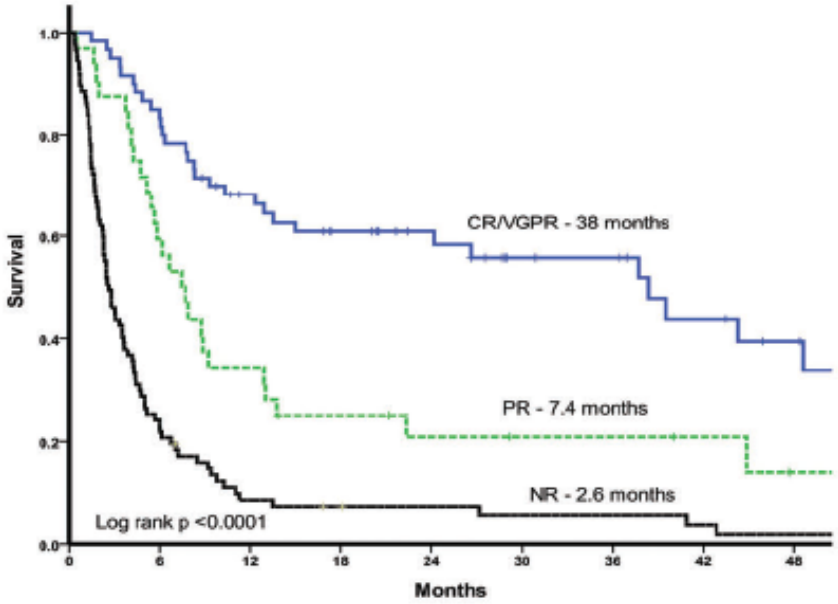
Giampaolo Merlini[1,2], Angela Dispenzieri[3], Vaishali Sanchorawala[4], Stefan O. Schönland[5], Giovanni Palladini[1,2], Philip N. Hawkins[6] and Morie A. Gertz[3]*

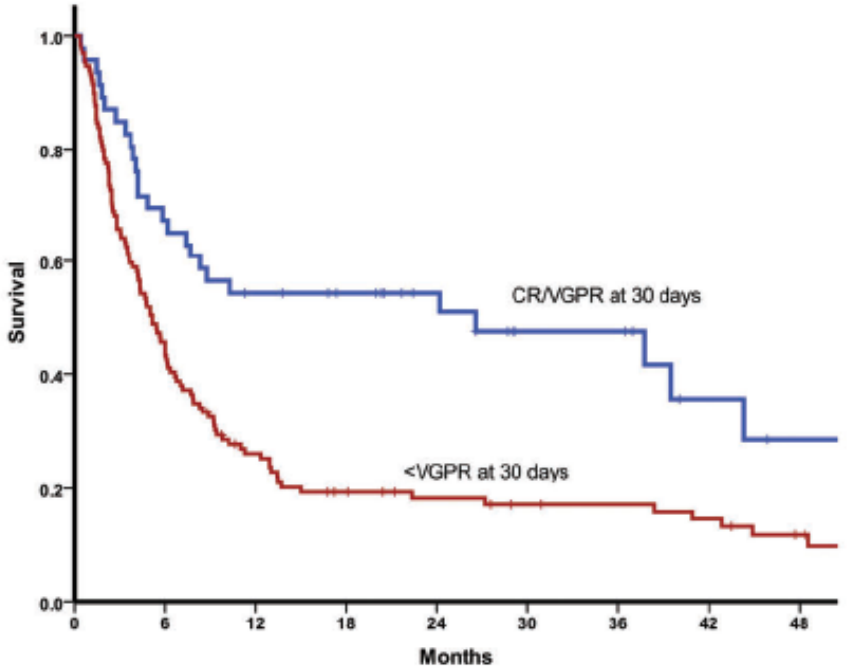
PRIMER

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2018) 4:38



Rapid and deep responses improve outcome of patients with advanced heart involvement





Manwani, et al. Haematologica 2018

AL amyloidosis – where do we stand?

The last decade witnessed impressive advances:

- better understanding of **pathogenesis and mechanisms of organ damage**
- **biomarkers** for early diagnosis, staging, response assessment, and improving the design of clinical trials
- novel **imaging** tools
- **tailored treatment design** based on risk assessment and clonal characteristic
- **novel effective treatments** and improvement of survival
- **networks and international collaboration**

Much is left to do

Now we better understand the disease and we have tools to diagnose early and effectively treat AL amyloidosis, but much is left to do …

- when ad how to re-treat
- placing of newest drugs
- interfering with amyloid organ toxicity
- treatment of patients with advanced cardiac dysfunction

We should promote the collaboration between amyloid centers to quickly reach these goals

Clinical research and routine patient management still need to be combined

… so please refer patients to specialized centers for enrolment in clinical trials and other research programs

info and patient referral at:

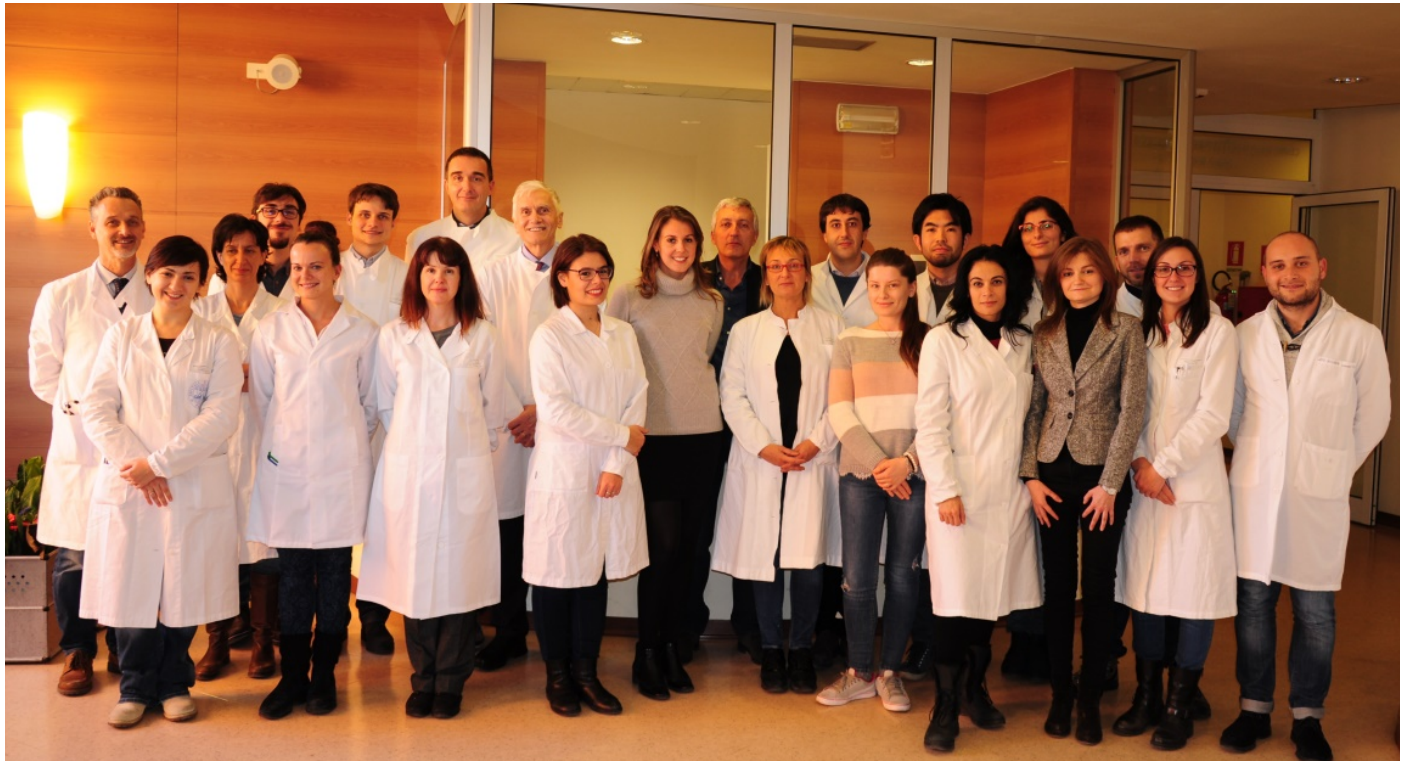
segreteria.amiloidosi@smatteo.pv.it
giovanni.palladini@unipv.it

SIA

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

www.isaamyloidosis.org

Acknowledgements



Giampaolo Merlini
Laura Obici
Andrea Foli
Paolo Milani
Mario Nuvolone
Francesca Lavatelli
Roberta Mussinelli

Marco Basset
Stefano Perlini
Giuseppina Palladini
Margherita Massa
Paola Rognoni
Tasaki Masayoshi
Giovanni Ferraro

Pasquale Cascino
Margherita Bozzola
Claudia Cagnoni
Simona Casarini
Jessica Ripepi
Alice Nevone
Anna Carnevale Baraglia

Caludia Sforzini
Elona Luka
Eleonora Di Buduo
Alberto Bovera
Arianna Pasi