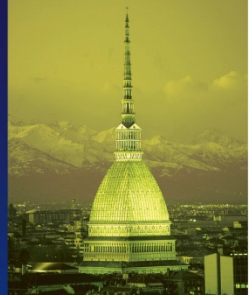
TURIN,
October
25th-27th
2018
Starhotels
Majestic

GIORNATE
CARDIOLOGICHE
TORINESI



UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

NO DISCLOSURE

Dr Giulia Benevolo
Dipartimento di Oncologia ed Ematologia
S.C. Ematologia
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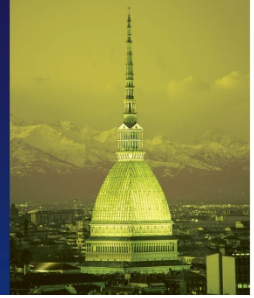

UNIVERSITÁ DEGLI STUDI DI TORINO

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JANUS-FACED: MYELOMA AND AMYLOIDOSIS VARIOUS DISEASES, SAME ORIGIN

Dr Giulia Benevolo
Dipartimento di Oncologia ed Ematologia
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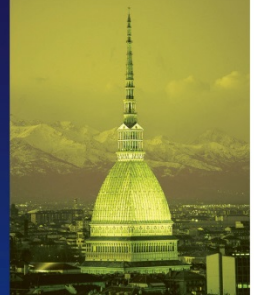


MYELOMA AND AMYLOIDOSIS

Multiple Myeloma → malignant neoplasm characterized by plasma cell proliferation in bone marrow with monoclonal protein in the blood or urine or both.

Patients often present with anemia, renal insufficiency, bone lytic lesions, and hypercalcemia

Amyloidosis → abnormal protein, known as amyloid fibrils, builds up in tissue. There are about 30 different types of amyloidosis, each due to a specific protein misfolding. Some are genetic while others are acquired

AL → clonal population of bone marrow PC that produces a clonal light chain of κ or λ type as either an intact molecule or a fragment

Mathur P et al Expert Review of Cardiovascular Therapy 2017; vol15(12) 933-943

CARDIOVASCULAR COMPLICATIONS IN MM

MM is the third most common type of malignancy associated with cardiovascular disease.

The prevalence of coronary artery diseases **(CADs) increases with age**.

Around **62%** of the patients with MM are **≥65 years** at the time of diagnosis.

Elderly patients with CAD are more susceptible to adverse cardiac events with chemotherapeutic agents.

The mechanisms of cardiac dysfunction in multiple myeloma are varied

Mathur P et al Expert Review of Cardiovascular Therapy 2017; vol15(12) 933-943

AGE-RELATED changes in cardiovasclar system

Table 1. Age-related changes in cardiovascular system predisposing to side effects.

- Atrial dilatation
- Increased sinoatrial nodal disease
- Cardiac muscle loss, disruption of normal atrial musculature, and age-related fibrosis
- Focal deposition of amyloid
- Mitral annular valve calcification
- Cardiac remodeling with increasing left ventricular wall thickness, especially increased concentric remodeling in women and more eccentric remodeling in men

Mathur P et al Expert Review of Cardiovascular Therapy 2017; vol15(12) 933-943

AGE-RELATED changes in cardiovasclar system

MM

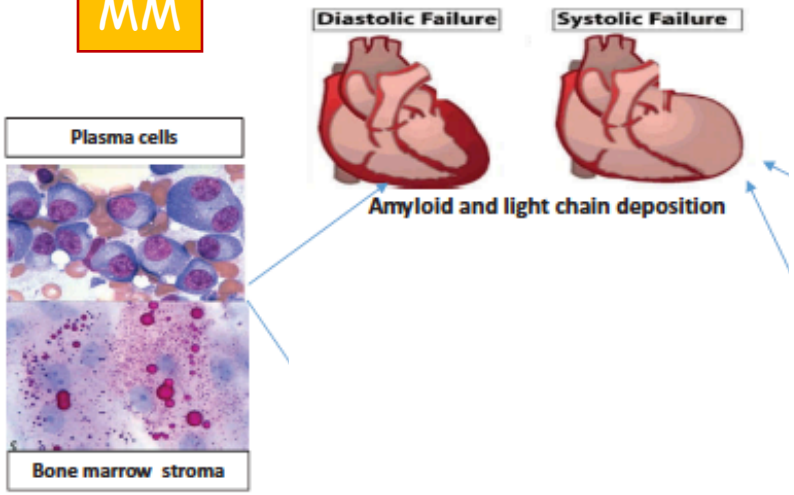


Figure 1. Mechanisms of cardiovascular complications in the elderly patients with multiple myeloma.

Mathur P et al Expert Review of Cardiovascular Therapy 2017; vol15(12) 933-943

AGE-
chan
cardi

Table 3. Risk factors for venous thromboembolic events.

- Obesity (BMI > 30)
- Previous history of venous thromboembolic events
- Cigarette smoking
- Use of immunomodulatory drugs such as thalidomide and lenalidomide
- Combination of immunomodulatory drugs with high-dose dexamethasone/ doxorubicin-based regimen
- High dose of dexamethasone (>480 mg/month)
- History of erythropoietin use
- Hyperviscosity
- Immobilization/Surgery/Use of central venous catheter

Figure 1. Mechanisms of cardiovascular complications in the elderly patients with multiple myeloma.

Mathur P et al Expert Review of Cardiovascular Therapy 2017; vol15(12) 933-943

AGE-RELATED changes in cardiovasclar sy

Table 2. Cardiac side effects of the commonly used chemotherapeutic agents used in patients with multiple myeloma.

Chemotherapeutic agent	Risk factors	Side effects
Melphalan	Age >65 years, higher dose, previous administration of cyclophosphamide	Supraventricular arrhythmias, especially atrial fibrillation [32–35,37,38]
Thalidomide, Lenalidomide Pomalidomide	Concurrent cardiac amyloidosis, age >65 years	Bradycardia [30,31], venous thromboembolism [43–46]
	Bortezomib coadministration decreases thromboe	Arterial thrombosis [46]
Doxorubicin	Decreased d doxorubicin in elderly population	related cardiac dysfunction [11]
Bortezomib Carfilzomib	Age >65 years, concurrent cardiac amyloidosis	Congestive heart failure Endothelial dysfunction with carfilzomib [18,19,47]
Cyclophosphamide	Concurrent doxorubicin, melphalan administration Age >65 years	Congestive heart failure, supraventricular arrhythmias [32–35]

Hypertension: Dr Milan

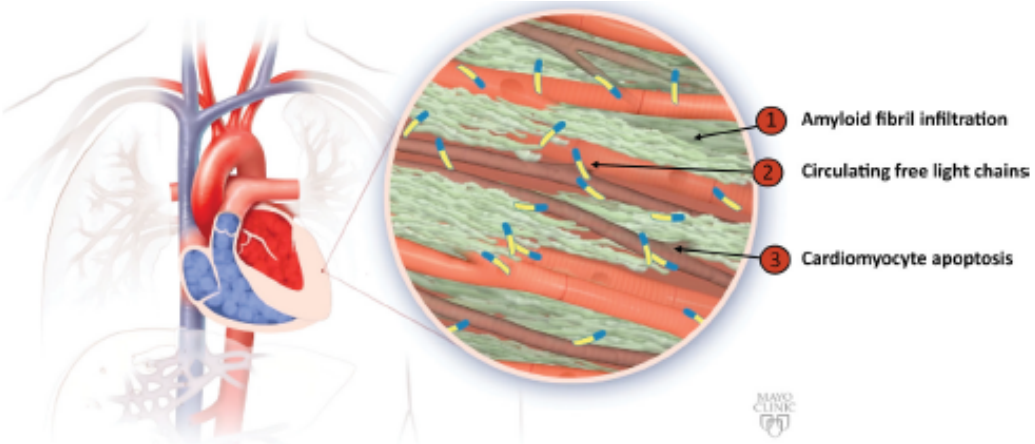
ersible and ROS rsible and ent

Mathur P et al Expert Review of Cardiovascular Therapy 2017; vol15(12) 933-943

CARDIOVASCULAR COMPLICATIONS IN AL

AL amyloidosis may develop in patients with multiple myeloma (10%–15%) or may progress from monoclonal gammopathy of undetermined significance (MGUS) (9%).

Median age 63 years



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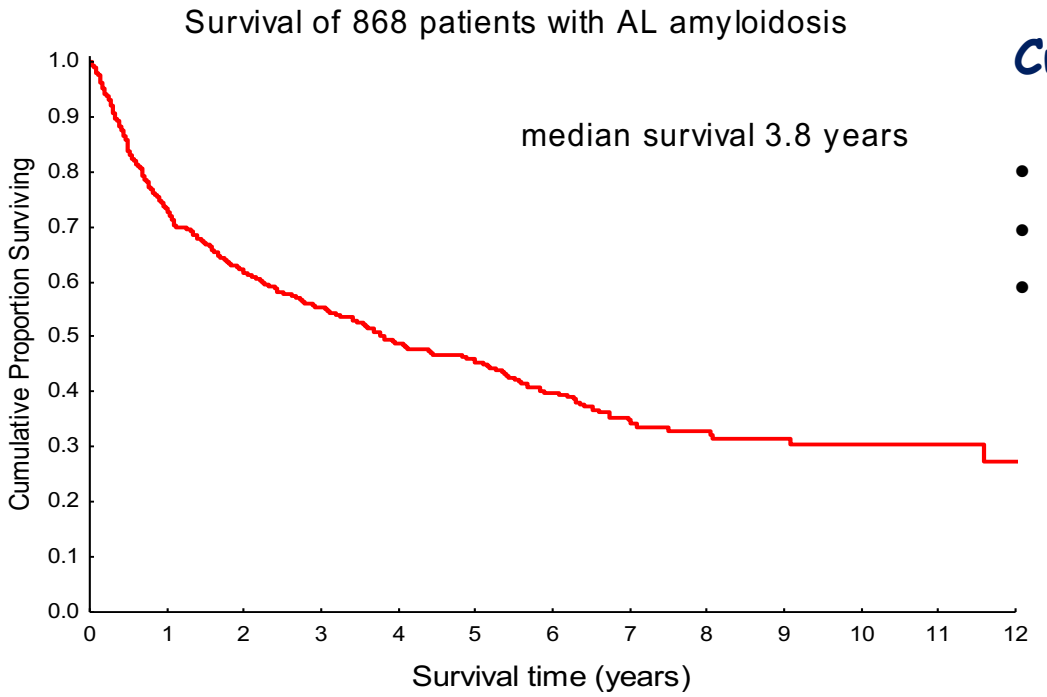
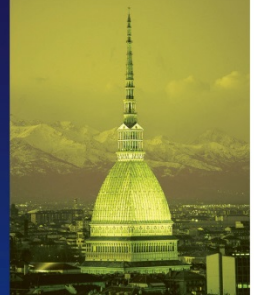
CARDIOVASCULAR COMPLICATIONS IN AL



Cumulative proportion surviving:

- 1 year: 73%
- 5 years: 46%
- 10 years: 31%

Merlini G, et al JCO 2011 (29) 14: 1924-1933



CARDIOVASCULAR COMPLICATIONS IN AL

A clinician should suspect amyloidosis whenever a patient presents with:

-proteinuria >0.5/day with or without renal insufficiency
-congestive heart failure from restrictive cardiomyopathy
-unexplained hepatomegaly, or functional hyposplenism with >ALP
-progressive peripheral neuropathy
-orthostatic hypotension, autonomic neuropathy
-weight loss, edema, fatigue and CM

No single imaging, blood or urine test is diagnostic

Clinical Chemistry 51:5
878–881 (2005)

Hematology

Diagnostic Performance of Quantitative κ and λ Free Light Chain Assays in Clinical Practice

JERRY A. KATZMANN,* ROSHINI S. ABRAHAM, ANGELA DISPENZIERI, JOHN A. LUST, and ROBERT A. KYLE

Diagnostic performance in AL (n = 110)

Assay	% Positive (CI)[a]
FLC κ/λ ratio	91 (84–96)
Serum IFE	69 (60–78)
Urine IFE	83 (74–89)
Serum IFE + urine IFE	95 (90–99)
FLC κ/λ ratio + urine IFE	91 (84–96)
FLC κ/λ ratio + serum IFE	99 (95–100)
All 3 assays	99 (95–100)

[a] CI, confidence interval determined by the exact binomial distribution.

Bone marrow biopsy
Abdominal subcutaneous fat aspiration

NEG → 15% AL LIKELIHOOD
Biopsy of involved organ

CARDIOVASCULAR COMPLICATIONS IN AL

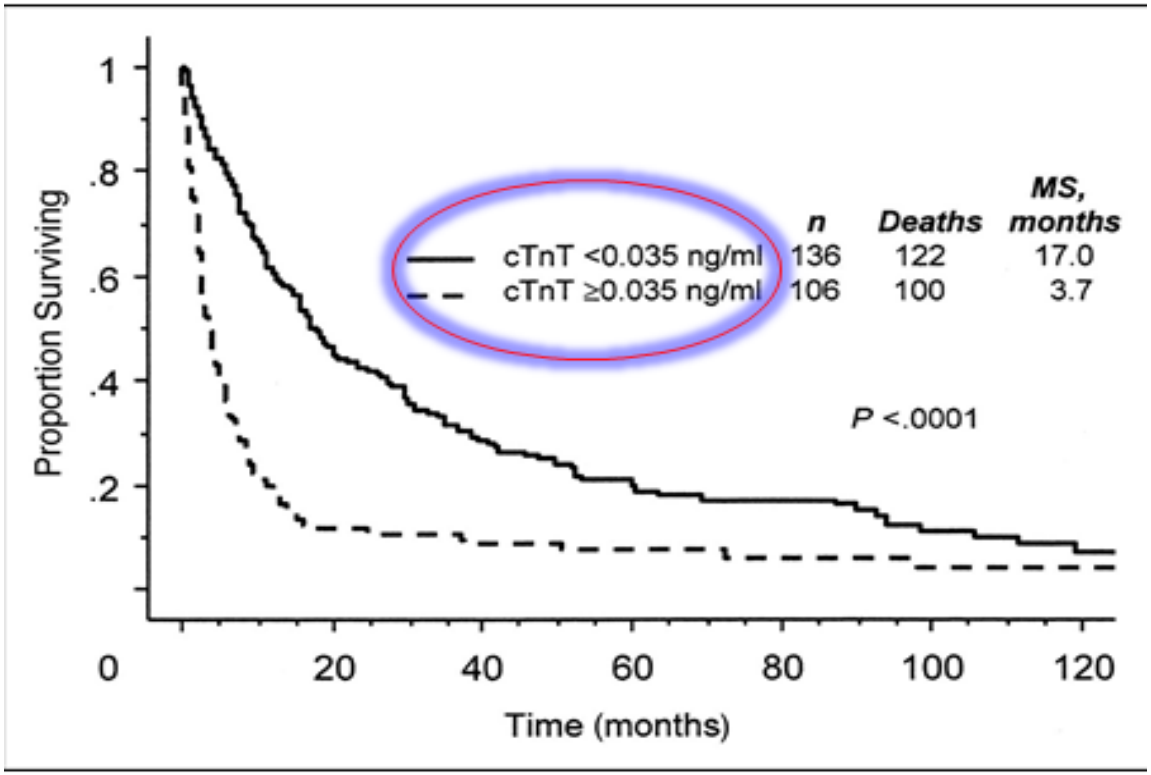
OUTCOME → CARDIAC INVOLVEMENT (75% death)

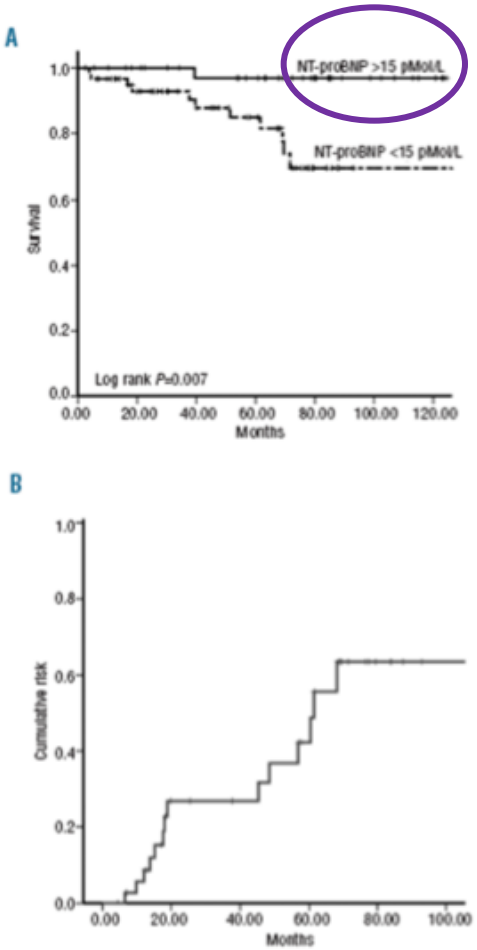
Troponin T <0.035 mcg/L
NT-proBNP <332 pg/mL

3 stages:
Stage I (both low) 33%
Stage II (1 marker high) 37%
Stage III (both high) 30%

DIFFERENT OS

CARDIOVASCULAR COMPLICATIONS IN AL

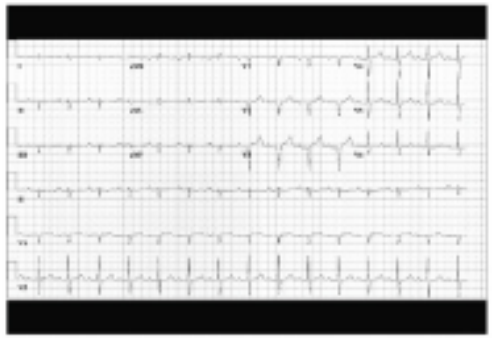




Dispenzieri A et al. JCO 2004;22:3751-3757

CARDIOVASCULAR COMPLICATIONS IN AL

A ECG



ECG → Amiloide= elettricamente inerte

45% bassi voltaggi QRS (derivazioni periferiche <5mm) → early stage, worse prognosis

Onde Q pseudoinfartuali (QS) in almeno 2 derivazioni precordiali consecutive

Blocchi di branca

BAV I-II-III grado

Allungamento QT

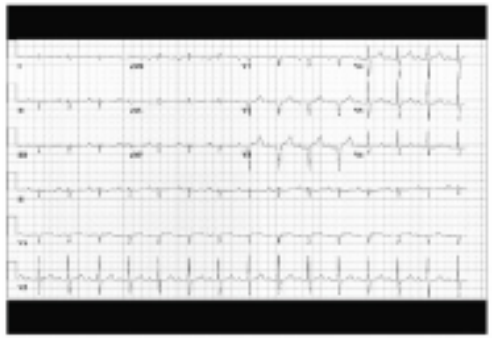
Tachiaritmie

ECG Holter

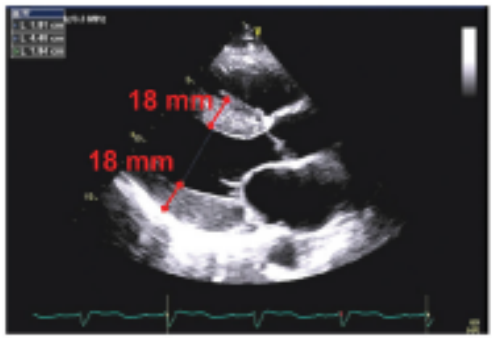
Grogan M et al. Heart 2017

CARDIOVASCULAR COMPLICATIONS IN AL

A ECG



B ECHO



Echo → Aumento spessore parietale del Vsx con distribuzione uniforme dell'ipertrofia e peculiare ecoriflettenza miocardica con aspetto «a vetro smerigliato» (**granular sparkling**)

Disfunzione diastolica di grado II-IV

Aumento dello spessore della parete libera del VDx

Dilatazione biatriale con presenza di trombi intracavitari (35%)

Aumento di spessore del setto interatriale

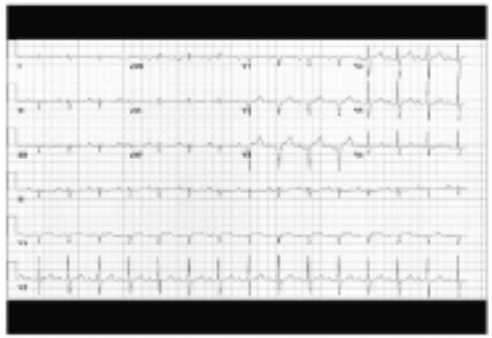
Ispessimento delle valvole atrio-ventricolari

Versamento pericardico e pleurico

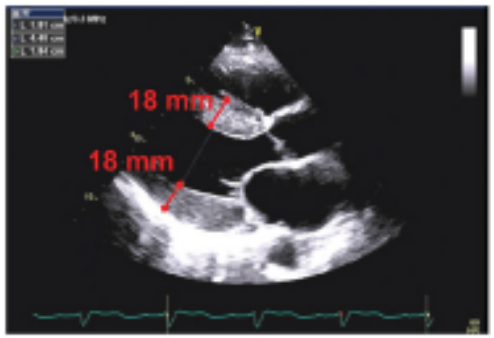
Grogan M et al. Heart 2017

CARDIOVASCULAR COMPLICATIONS IN AL

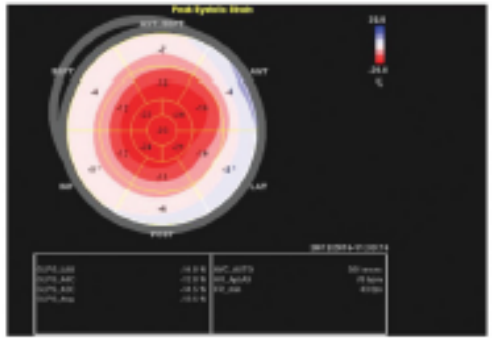
A ECG



B ECHO



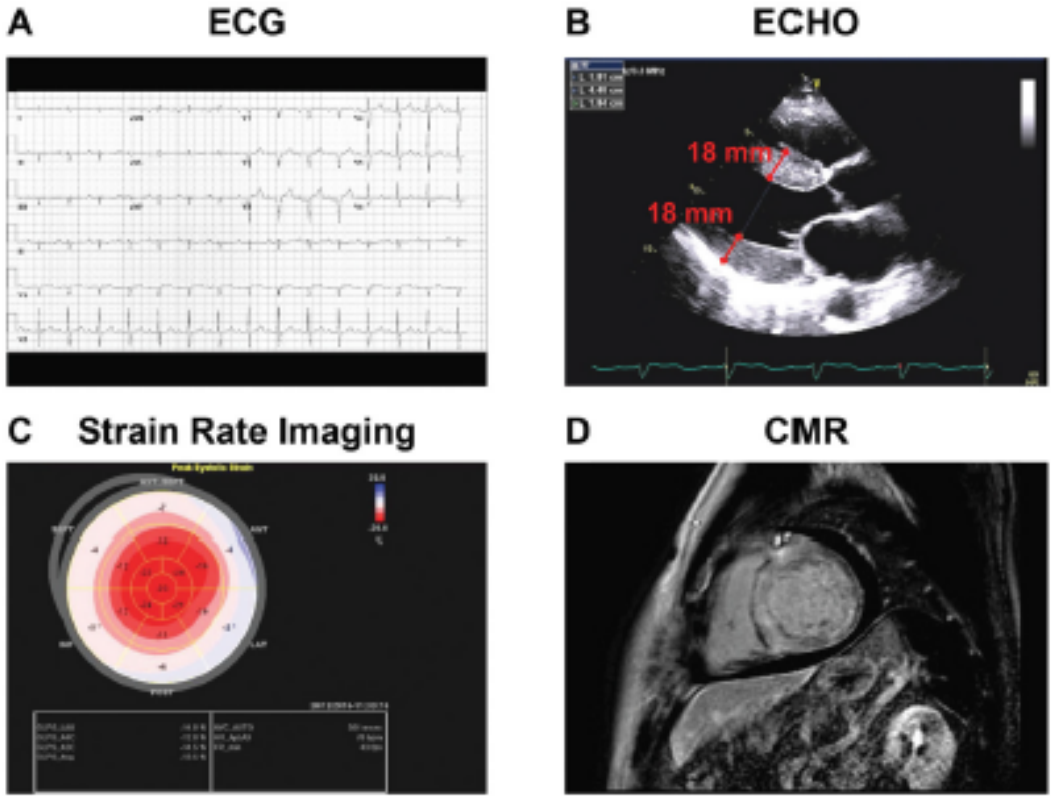
C Strain Rate Imaging



STRAIN → A characteristic LV strain pattern with preservation of the apex **(bull's eye)** is often an indication of the disease
Abnormalities of longitudinal ventricular function demonstrated by strain imaging are independent predictors of survival.
Furthermore, abnormal right ventricular strain may be an early diagnostic clue.
The severity of echocardiographic abnormalities and the rapidity at which they develop may correlate with worse prognosis.

Grogan M et al. Heart 2017

CARDIOVASCULAR COMPLICATIONS IN AL



RMN cardiaca →

aumento globale del volume extracellulare

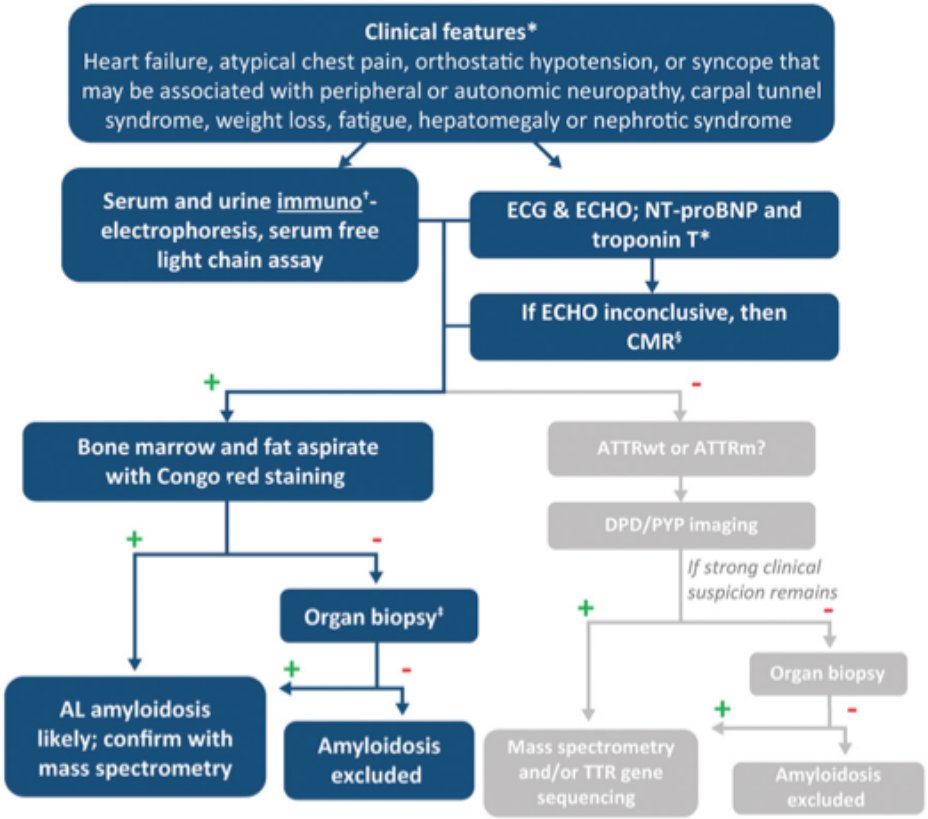
Immagine tipica di «late enhancement» del subendocardio del Vsx e del VDx (aspetto "a zebra" del SIV) ma spesso alterazione a tutto spessore; la misura dell'espansione dell'interstizio potrebbe quantificare l'entità del danno cardiaco

Le alterazioni RMN possono precedere le alterazioni eco e correlano con la prognosi

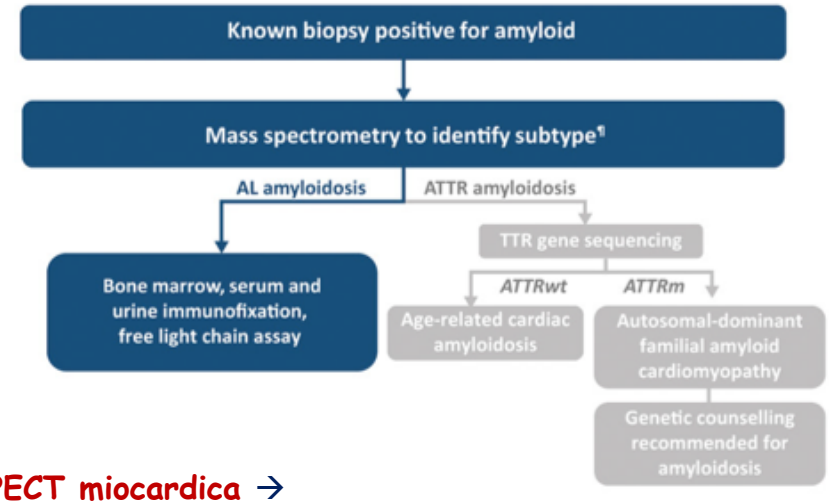
Grogan M et al. Heart 2017

CARDIOVASCULAR COMPLICATIONS IN AL

A Algorithm for diagnosis in patients with suspected cardiac amyloidosis*

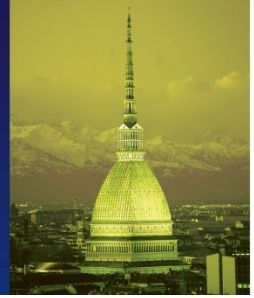


B Algorithm for diagnosis in patients with amyloidosis established by biopsy



SPECT miocardica →
Ac.difosfono-propanodicarbossilico
Si lega ai depositi di amiloide con elevata sensibilità nei pz con **ATTR** nelle fasi molto precoci quando eco, biomarkers e forse persino RMN sono normali.
Il tracciante è captato debolmente in 1/3 di pz con AL. .

Grogan M et al. Heart 2017

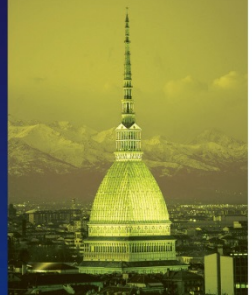


AL AMYLOIDOSIS
A NEW PARADIGM FOR THERAPY

AIM OF THERAPY

OBTAIN HEMATOLOGIC AND ORGAN RESPONSE → hematologist

OBTAIN DURABLE IMPROVEMENT OF ORGAN (HEART) FUNCTION → cardiologist



AL AMYLOIDOSIS
A NEW PARADIGM FOR THERAPY

BASSO RISCHIO
(tutte le condizioni seguenti)

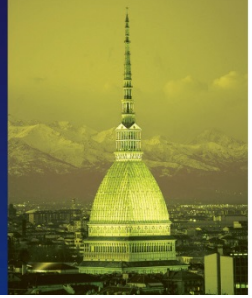
età ≤ 65 anni
cTnT nella norma
FEV>45%
PAO ortostatica >90 mmHg
DLCO>50%
PS ECOG <3
eGFR >50ml/min

ALTO RISCHIO
(una sola delle seguenti condizioni)

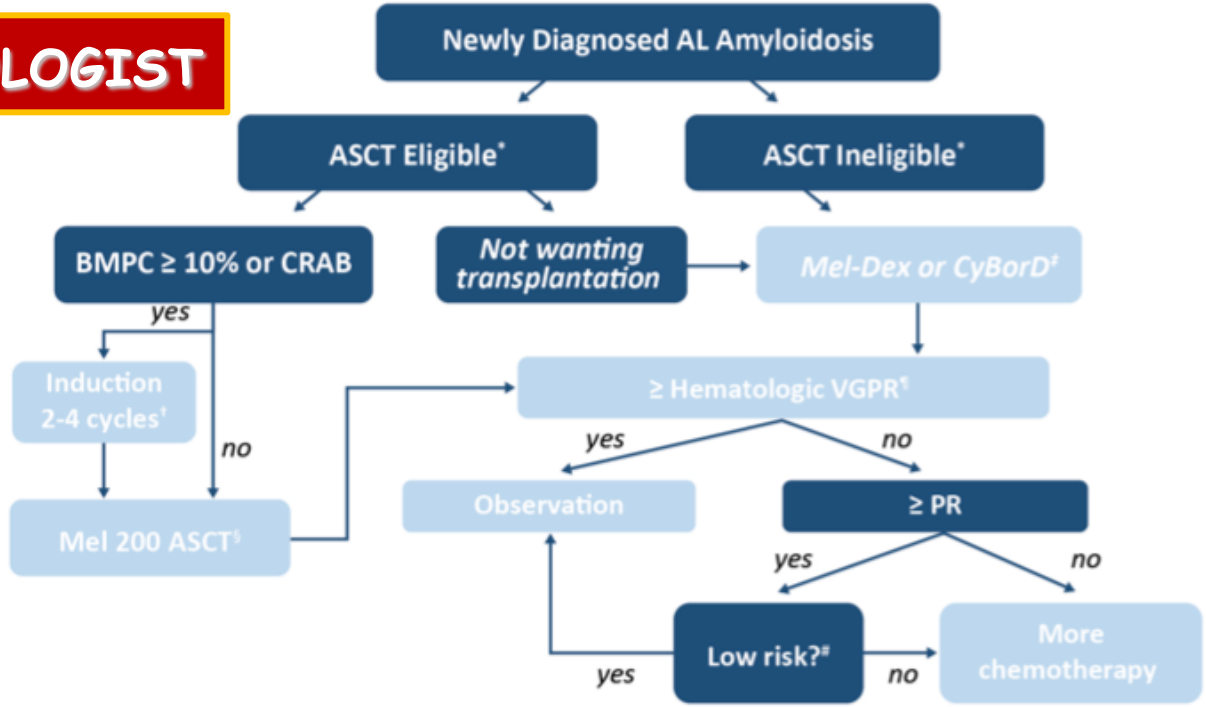
cTnT >0.035
PS ECOG ≥3 (escluso SNP)

RISCHIO INTERMEDIO

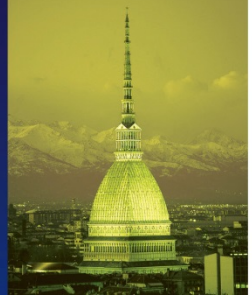
I pazienti non considerati a basso o alto rischio

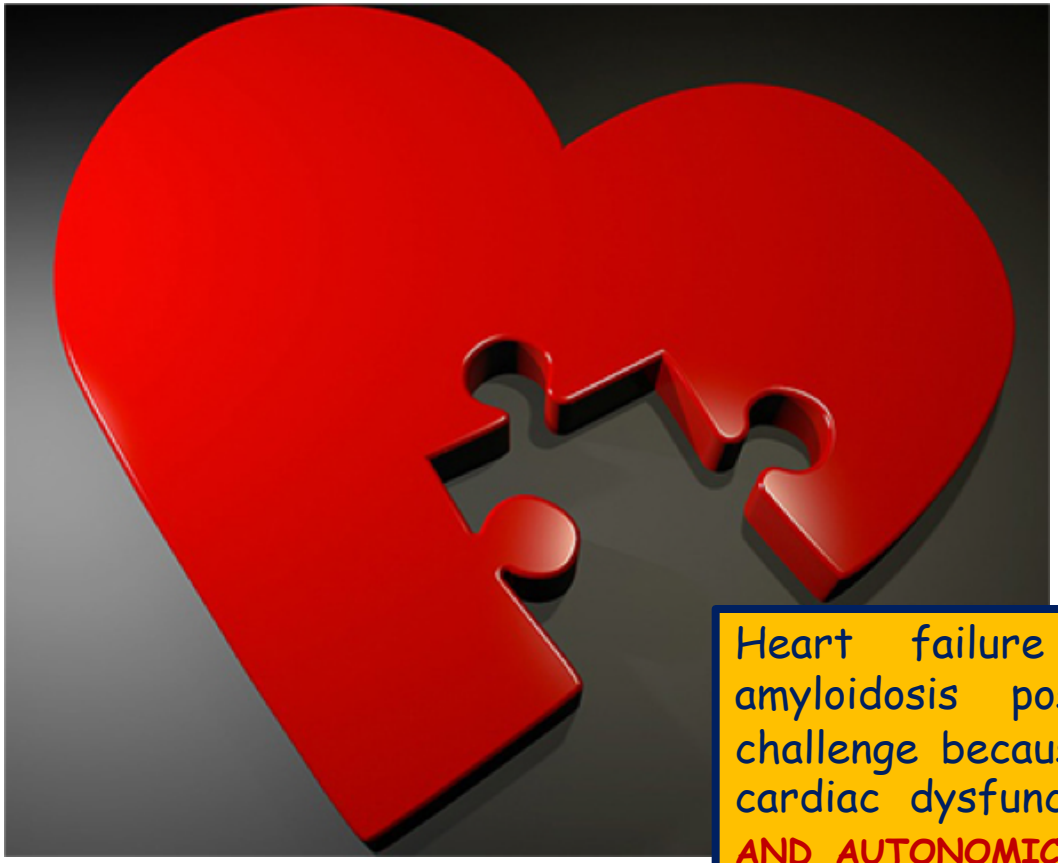


HEMATOLOGIST



*Criteria for ASCT: Troponin T <0.06 and blood pressure ≥90 mmHg
†Induction also used if delay in proceeding to ASCT, or as clinically indicated
‡If < PR at 2 months, consider changing therapy
§For age >70 or creatine clearance <30 mg/mL, use Mel 140 mg/m^2
¶Day 100 ASCT or after 4-6 cycles of chemotherapy
#Mayo 2012 stage I or II





CARDIOLOGIST

Heart failure caused by cardiac AL amyloidosis poses a unique therapeutic challenge because of the complex nature of cardiac dysfunction in patients with **RENAL AND AUTONOMIC COMORBIDITIES** and because typically used supportive measures are contraindicated.

HEART INVOLVEMENT IN AL: THERAPY

Terapia di supporto (terapia delle scompenso cardiaco modificata) →

Mantenere adeguate pressioni di riempimento ventricolare.

Contrastare la ritenzione idrica e la congestione venosa bilanciando con precisione e continui adattamenti la ritenzione idrosalina e la terapia diuretica (educazione del pz e dei caregivers, supporto dietistico)

Attenzione all'assetto proteico (ipoalbuminemia)

Valutazione quotidiana del peso

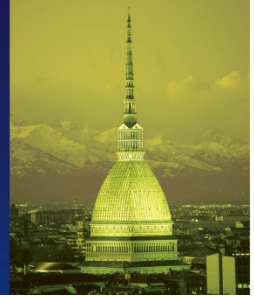
Valutazione settimanale diuresi 24h

Norme igienico-comportamentali per contrastare l'ipotensione ortostatica, postminzionale e da ipertono vagale (sovradistensione gastrica, shave..)

Calze elastiche classe I

Alfa.I agonisti (midodrina): il mantenimento PA adeguata può permettere dosi più alte di diuretico dell'ansa, spt nei pz con neuropatia autonomica.

Linee Guida SIEC 2011



HEART INVOLVEMENT IN AL: THERAPY

ACE-I: possono causare severa ipotensione (la PA dei pz con AL è dipendente dall'angiotensina)

Andrebbero riservati per trattare la proteinuria nei pz con s.nefrosica

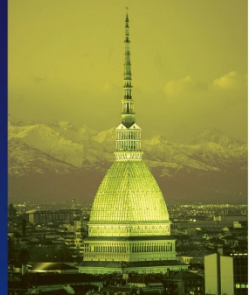
BETA-BLOCCANTI: nelle forme restrittive la GC dipende dalla FC (GC= GSxFC), per cui sono spesso mal tollerati.

Inoltre: beta-bloccante + talidomide (AL): bradicardia spiccata.

CALCIO-ANTAGONISTI (verapamil): abnorme legame con fibrille amiloidi, effetto intropo negativo

DIGITALE: aritmie pericolose anche a livelli di digossinemia apparentemente in range, per legame stretto e selettivo tra farmaco e fibrille. Non correlazione tra digossinemia e tossicità, che si esplica anche a dosaggi bassi.

Linee Guida SIEC 2011



HEART INVOLVEMENT IN AL: THERAPY

TAO: indipendentemente dalla presenza o meno del ritmo sinusale, l'infiltrazione degli atri porta a stasi e trombosi.

Valutare all'eco l'assenza o la spiccata riduzione di onda A.

I pz sono anche a rischio elevato di sanguinamento (alterazioni della coagulazione, fragilità vascolare….) e di traumi da sincope.

Mantenere mobilità ed evitare le cadute (deambulatori).

ATTENZIONE AI CORTICOSTEROIDI!!!

AMIODARONE 200 mg/die x 5 gg/sett se aritmie ventricolari sostenute all'Holter (valutare con attenzione!)

Linee Guida SIEC 2011

HEART INVOLVEMENT IN AL: THERAPY

ICD →

Può non prevenire MCI perché spesso dovuta a dissociazione elettromeccanica.

Soglie elevate, benefici incerti.

PMD: sec guidelines, preferendo i PM bicamerali quando possibile

Trapianto cardiaco

EMERGING TREATMENTS: AMYLOID-DIRECTED THERAPIES →

Antibody-mediated phagocytosis combined with the clearance of amyloid is a promising approach to reverse organ dysfunction.

Three antibodies are in clinical development.

Linee Guida SIEC 2011

AL AMYLOIDOSIS-RESPONSE CRITERIA

Hematologic response:

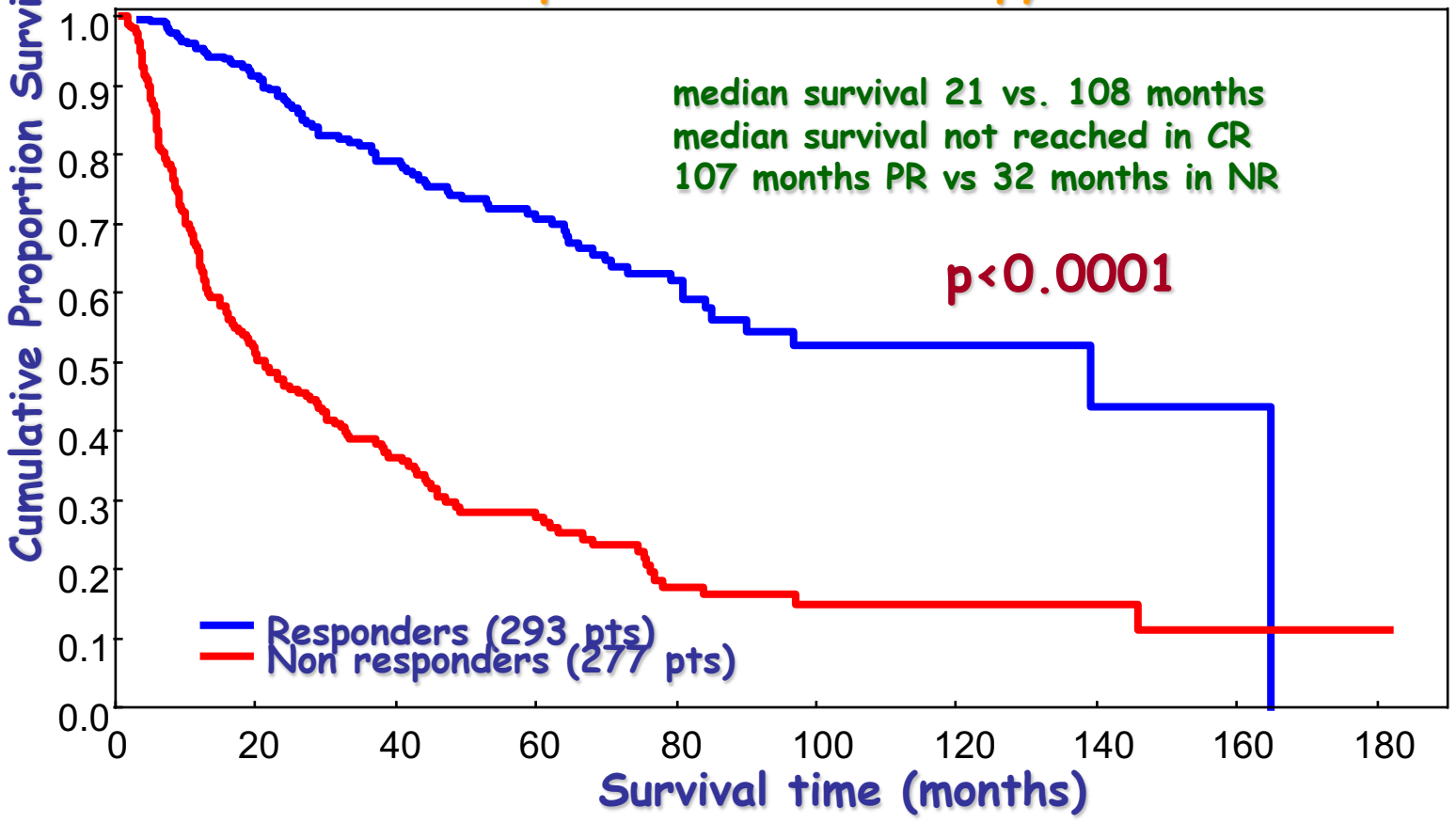
CR → negative serum and urine IF, normal κ:λ
VGPR → dFLC <40 mg/L
PR → dFLC reduction >50%
NR → other

Organ response:

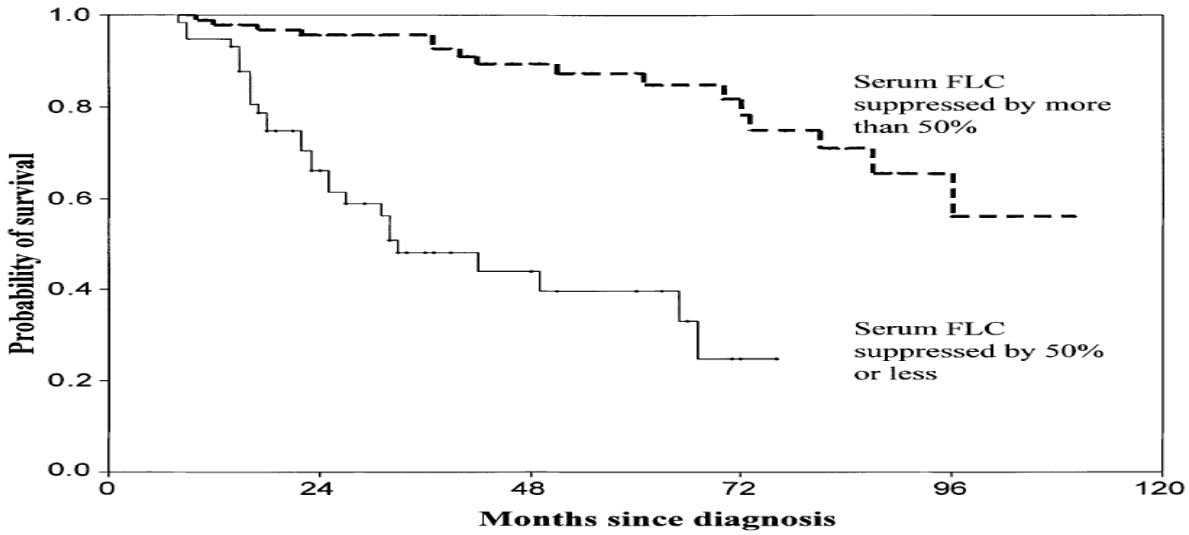
Heart → reduction by 2mm septal, 20% improvement FEV, >NYHA class, reduction NT-proBNP
Kidney → 50% decrease urinary protein excretion
Liver → 50% decrease ALP and decrease liver size >2 cm

Gertz MA, AM J Hematol 2005;79:319-328

Survival of 570 patients with AL amyloidosis according to hematologic response to chemotherapy

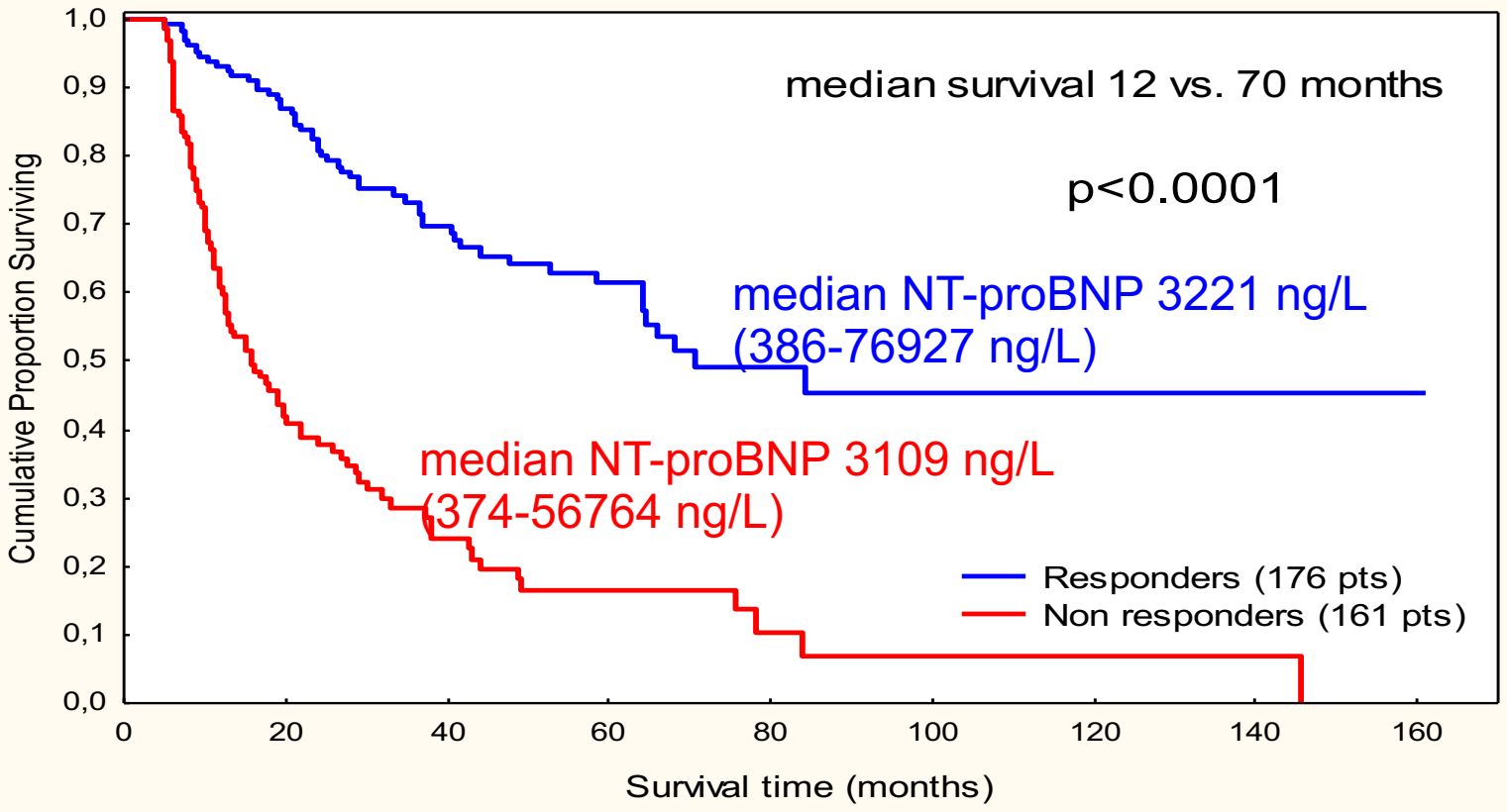


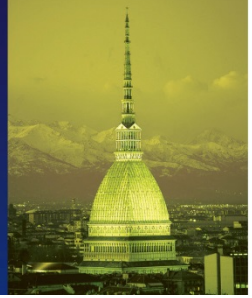
Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy



Lachmann et al, Br J Haematol. 2003;122:78-84.

Survival of 337 patients with cardiac AL amyloidosis according to hematologic response to chemotherapy






COLLABORATION
TOGETHER
SUCCESS
KNOWLEDGE
LEARNING
SECTION
BASED
PRODUCTION
SOURCES
MANAGEMENT
GROUPS
WORK
PROJECT
COLLABORATIVE
LEADERSHIP
CORPORATION
PEOPLE
SOFTWARE
INTERNET
TOOLS
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CITATIONS
ORGANIZATIONS
ORGANIZATION
SOCIAL
COMMUNICATION
INDUSTRY
SKILLS
COMMUNITY
CHALLENGED
TERM
PEER
UNITED
THEORY
GROUP
DEVELOPMENT
COMMUNITIES
PRACTICE
BETWEEN
INCLUDE
RELIABLE
SHARED
MEMBERS
EDUCATION


Together
Everyone
Achieves
More
T
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JANUS-FACED:
MIELOMA AND AMYLOIDOSIS
VARIOUS DISEASES,
SAME ORIGIN

THANK YOU