



# **AMILOIDOSI CARDIACA SENILE DA TRANSTIRETINA: LE NUOVE EVIDENZE**

Obiettivi, modalità e timing della terapia:  
quale anziano trattare

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**Università di Firenze**



# Amiloidosi cardiaca da transtiretina una patologia dell'anziano

- ✓ Epidemiologia dell'amiloidosi cardiaca negli ultimi 20 anni
- Cardio-Geriatria, fragilità e amiloidosi cardiaca
- Amiloidosi Cardiaca: l'incontro tra cardiologia e geriatria



ORIGINAL RESEARCH ARTICLE



## Impact of Earlier Diagnosis in Cardiac ATTR Amyloidosis Over the Course of 20 Years

Variable	2002–2006 (n=35)	2007–2011 (n=260)	2012–2016 (n=704)	2017–2021 (n=968)	P value
Baseline characteristics					
Age	67.22±6.20*†‡	73.99±7.19§	75.81±7.72	76.03±9.01	<0.001
Male sex, n (%)	26 (74.3%)	224 (86.2%)	613 (87.1%)	834 (86.2%)	0.200
Body surface area	...	1.89±0.20	1.89±0.19	1.91±0.20	0.180
Ischemic heart disease	4 (11.4%)	35 (13.5%)	145 (20.6%)	198 (20.5%)	0.035
Diabetes	1 (2.9%)	23 (8.8%)§	125 (17.8%)	167 (17.3%)	<0.001
Hypertension	5 (14.3%)	39 (15.0%)§	224 (31.8%)¶	396 (40.9%)	<0.001
Stroke/transient ischemic attack	0 (0.0%)	23 (8.8%)	69 (9.8%)	115 (11.9%)	0.067

**1967 pazienti con ATTR-CA diagnosticati in 20 anni**

**Negli ultimi 20 anni:**  
 ↑ Età alla diagnosi  
 mediana italiana 80 anni  
**Comorbosità**  
 ↑ Cardiopatia Ischemica  
 ↑ Diabete mellito  
 ↑ Ipertensione  
**Clinica**  
 ↓ NYHA alla diagnosi  
 ↓ Gravità (NAC score)

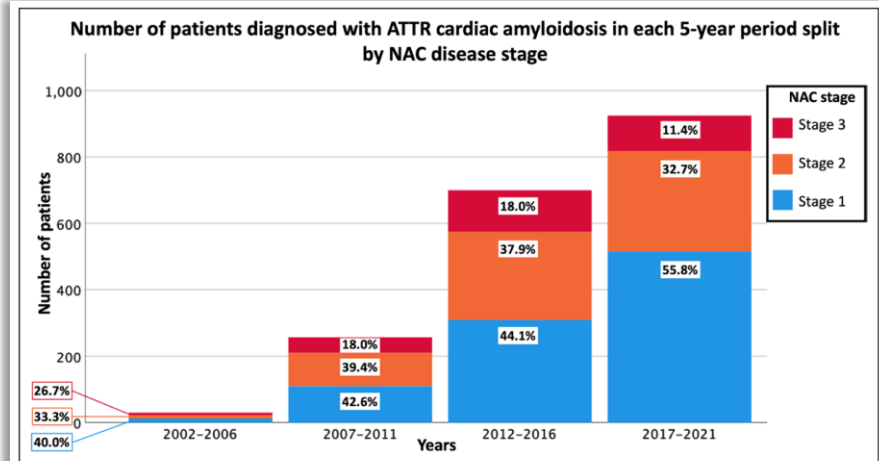


Figure 4. Number of patients diagnosed with transthyretin cardiac amyloidosis between 2002 and 2021, and the proportion of patients with each NAC disease stage for each 5-year period. NAC indicates National Amyloidosis Centre.



## Il ritardo diagnostico e il suo impatto clinico

National Amyloidosis Centre, UK 2002 - 2017

- 711 pazienti diagnosticati con ATTR-CA
- 305 pazienti diagnosticati con V122I-hATTR-CA,
- 118 pazienti diagnosticati con non-V122I-hATTR-CA

**RESULTS:** There was substantial diagnostic delay, with patients using hospital services a median (interquartile range) of 17 (9–27) times during the 3 years before diagnosis, by which time quality of life was poor; diagnosis of wild-type ATTR-CM was delayed >4 years after presentation with cardiac symptoms in 42% of cases. Patients with V122I-hATTR-CM were more impaired functionally ( $P<0.001$ ) and had worse measures of cardiac disease ( $P<0.001$ ) at the time of diagnosis, a greater decline in quality of life, and poorer survival ( $P<0.001$ ) in comparison with the other subgroups.

### ORIGINAL RESEARCH ARTICLE

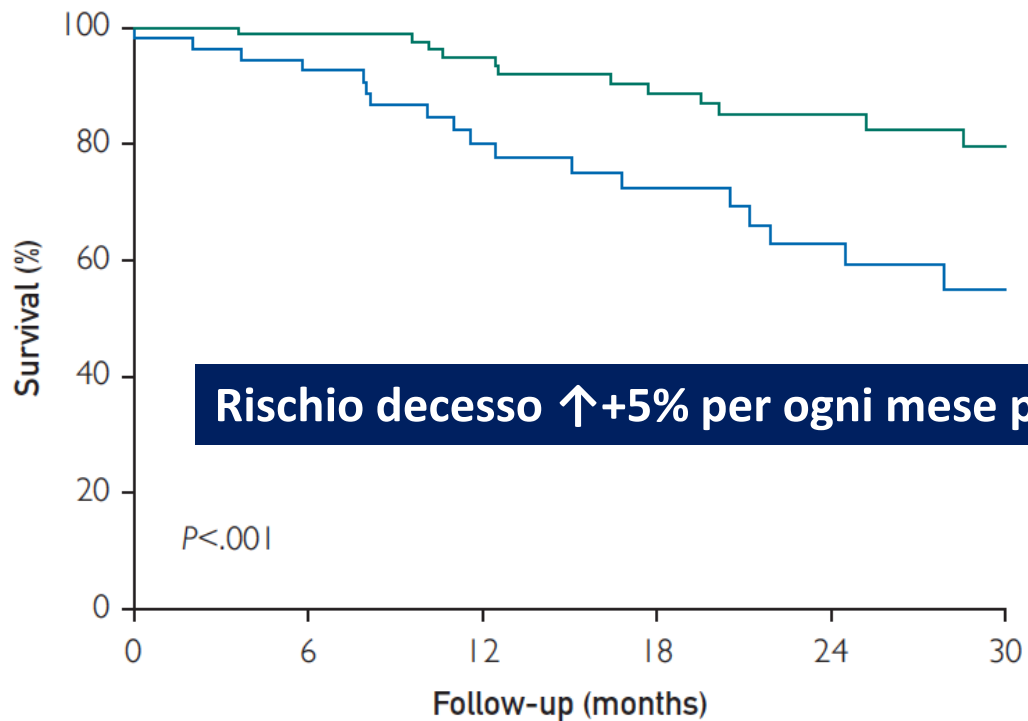


Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis

**17 Visite in 3 anni prima della diagnosi**



## Time is Therapy



	0	6	12	18	24	30
<6 Months	100	86	68	51	37	26
≥6 Months	60	50	34	27	17	10

Diagnostic timing — <6 Months — ≥6 Months



Early Diagnosis and Outcome in Patients With Wild-Type Transthyretin Cardiac Amyloidosis

**Epoca 'Pre-Tafamidis'**  
**N=160 pazienti**

Variable	Hazard ratio (95% CI)	P value
Diagnostic timing (per month increase)	1.049 (1.017-1.083)	.003
Age at diagnosis (per year increase)	1.078 (1.008-1.153)	.004
Coronary artery disease	4.291 (1.678-10.979)	.002
NYHA class (III/IV vs I/II)	4.240 (1.923-9.348)	<.001
Disease stage <sup>b</sup>		
II vs I	2.928 (1.169-7.335)	.022
III vs I	9.951 (3.043-32.543)	<.001
Ejection fraction (per % increase)	0.971 (0.940-1.003)	.149



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## 2022: l'anno della Cardio-Geriatria

### Journal of the American College of Cardiology 2022

#### THE PRESENT AND FUTURE

#### JACC STATE-OF-THE-ART REVIEW

### Interventions for Frailty Among Older Adults With Cardiovascular Disease



JACC State-of-the-Art Review

*[...]Cardiovascular disease and frailty are interdependent and have the same physiological underpinning that predisposes to the progression of both disease processes*

*[...] Contemporary cardiovascular practice should actively identify patients with physical frailty who could benefit from frailty interventions and aim to deliver these therapies in a patient-centered model to optimize quality of life, particularly after cardiovascular interventions.*

### JACC: Advances 2022

#### STATE-OF-THE-ART REVIEW

#### GERIATRIC CARDIOLOGY

### Geriatric Cardiology: Coming of Age

*[...]Multimorbidity, polypharmacy, cognitive changes, and diminished functional capacity, along with changes in the social environment, result in complexity that makes provision of CVD care to older adults challenging. In this review, we first describe the history of geriatric cardiology, an orientation that acknowledges the unique needs of older adults with CVD [...]*

### European Journal of Preventive Cardiology, 2022



European Society of Cardiology  
European Journal of Preventive Cardiology (2022) 29, 216-227  
doi:10.1093/ejpc/zwaa167

CONSENSUS DOCUMENT  
Aging

### Frailty in cardiology: definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for

*[...]Frailty increases cardiovascular (CV) morbidity and mortality both in patients with or without known CV disease. Though the recognition of this additional risk factor has become increasingly clinically relevant in CV diseases, uncertainty remains about operative definitions, screening, assessment, and management of frailty.*



# La fragilità nella amiloidosi cardiaca

## RESEARCH LETTER

### Prevalence and Prognostic Significance of Frailty Among Patients With Transthyretin Amyloidosis Cardiomyopathy

Nowell M. Fine<sup>1</sup>, MD, SM; Jacqueline M. McMillan<sup>2</sup>, MD

- 145 pazienti ATTR-CA dal 2014 al 2019
- Fragilità studiata tramite la Clinical Frailty Scale (CFS)

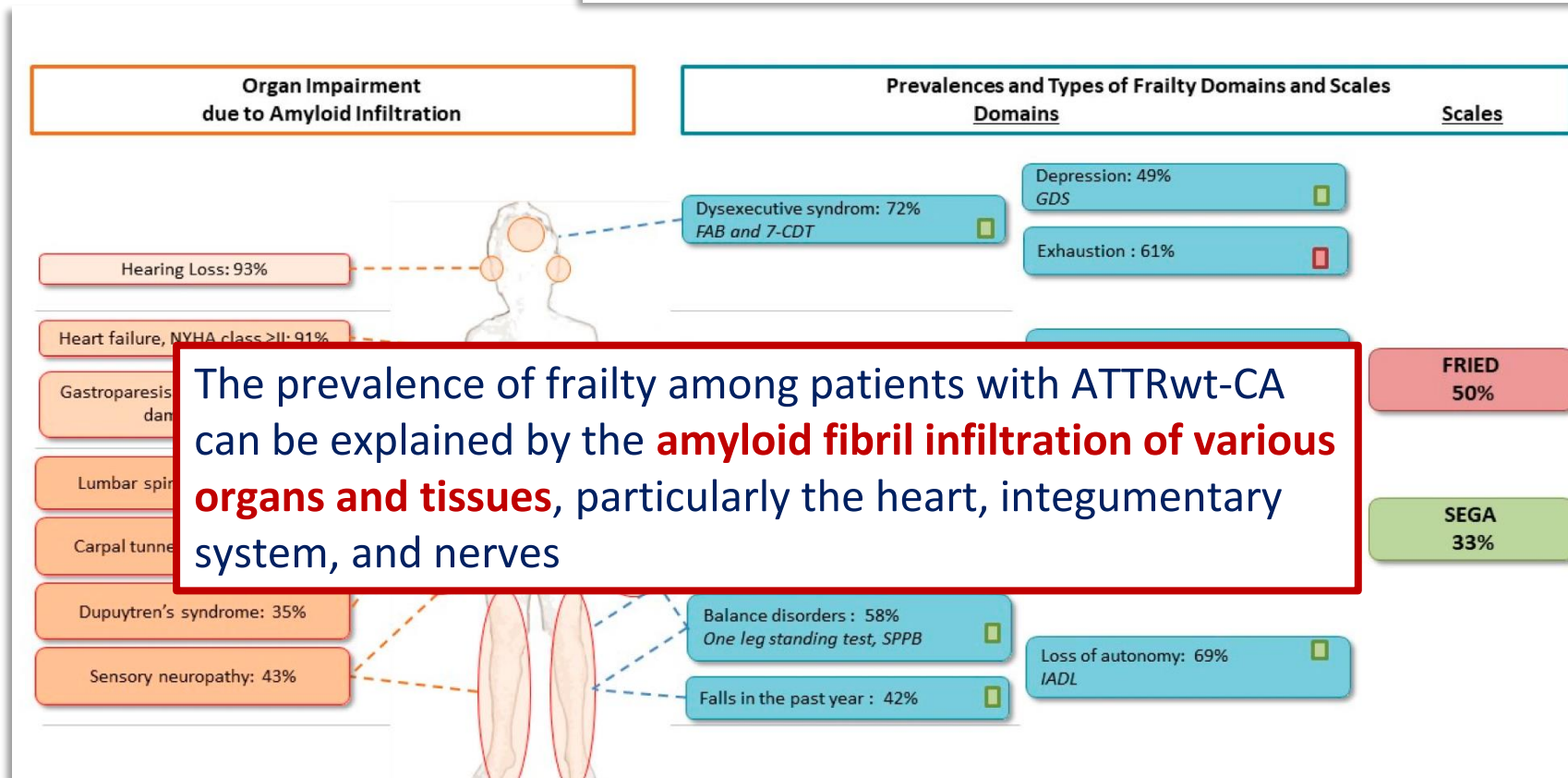
Dopo aggiustamento per classe NYHA e NAC score, i terzili di CFS rimanevano associati alla mortalità al follow up (HR1.49 [95% CI, 1.28–1.83], P<0.001).

Parameter	Study population (N=145)	CFS 1-3 (n=46)	CFS 4-6 (n=76)	CFS 7-9 (n=23)	P value
Demographic and clinical					
Age, y	78 (73-84)	75 (69-83)	78 (71-85)	86 (81-89)	<0.001
Sex (male)	132 (91)	41 (89)	69 (91)	22 (96)	0.67
Body mass index, kg/m <sup>2</sup>	22.9 (19.8-26.1)	24.3 (21.6-27.7)	22.5 (20.6-26.2)	21.1 (18.3-24.1)	0.009
NYHA class III/IV	78 (54)	22 (48)	42 (55)	15 (65)	0.38
Laboratory					
Hemoglobin, g/dl	10.8 (9.3-12.4)	11.5 (10.0-12.9)	10.7 (10.2-12.4)	9.8 (8.5-10.9)	0.011
<p><b>Among patients with ATTR-CM, frailty was highly prevalent and an important risk factor for mortality. As assessed by the CFS, frailty was independently associated with mortality and may be a valuable component of routine clinical assessment.</b></p>					
ATTRwt	136 (94)	42 (91)	72 (95)	22 (96)	
Tafamidis therapy	16 (11)	6 (13)	8 (11)	2 (9)	0.84
ATTR-CM stage*					
Stage I	45 (31)	18 (39)	26 (34)	4 (17)	0.22
Stage II	76 (52)	23 (50)	35 (46)	12 (52)	
Stage III	24 (17)	5 (11)	15 (20)	7 (31)	





- 36 pazienti ATTR-CA dal 2018 al 2019
- Fragilità studiata secondo il modello di Fried e *Short Emergency Geriatric Assessment* (SEGA)





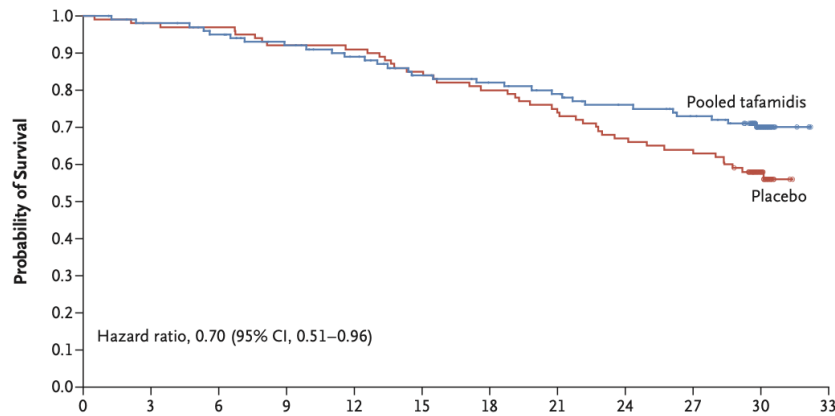
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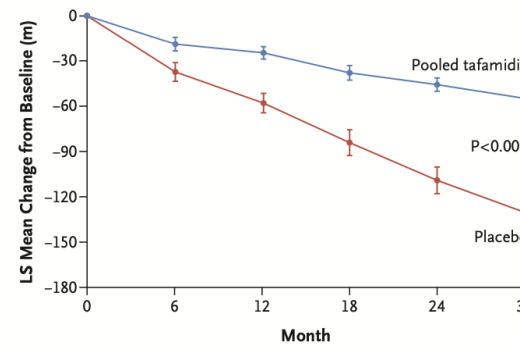
## Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Analysis of All-Cause Mortality



Survival

A Change from Baseline in 6-Minute Walk Test

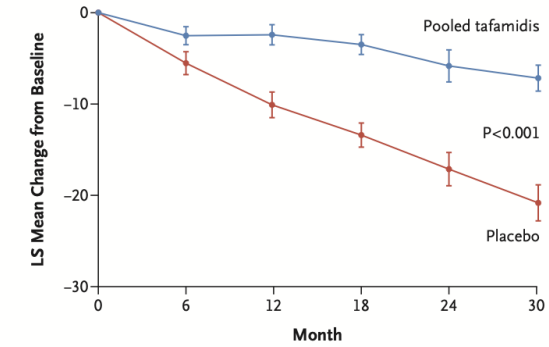


No. of Patients

Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

6MWT

B Change from Baseline in KCCQ-OS



No. of Patients

Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

Quality of life  
(KCCQ)



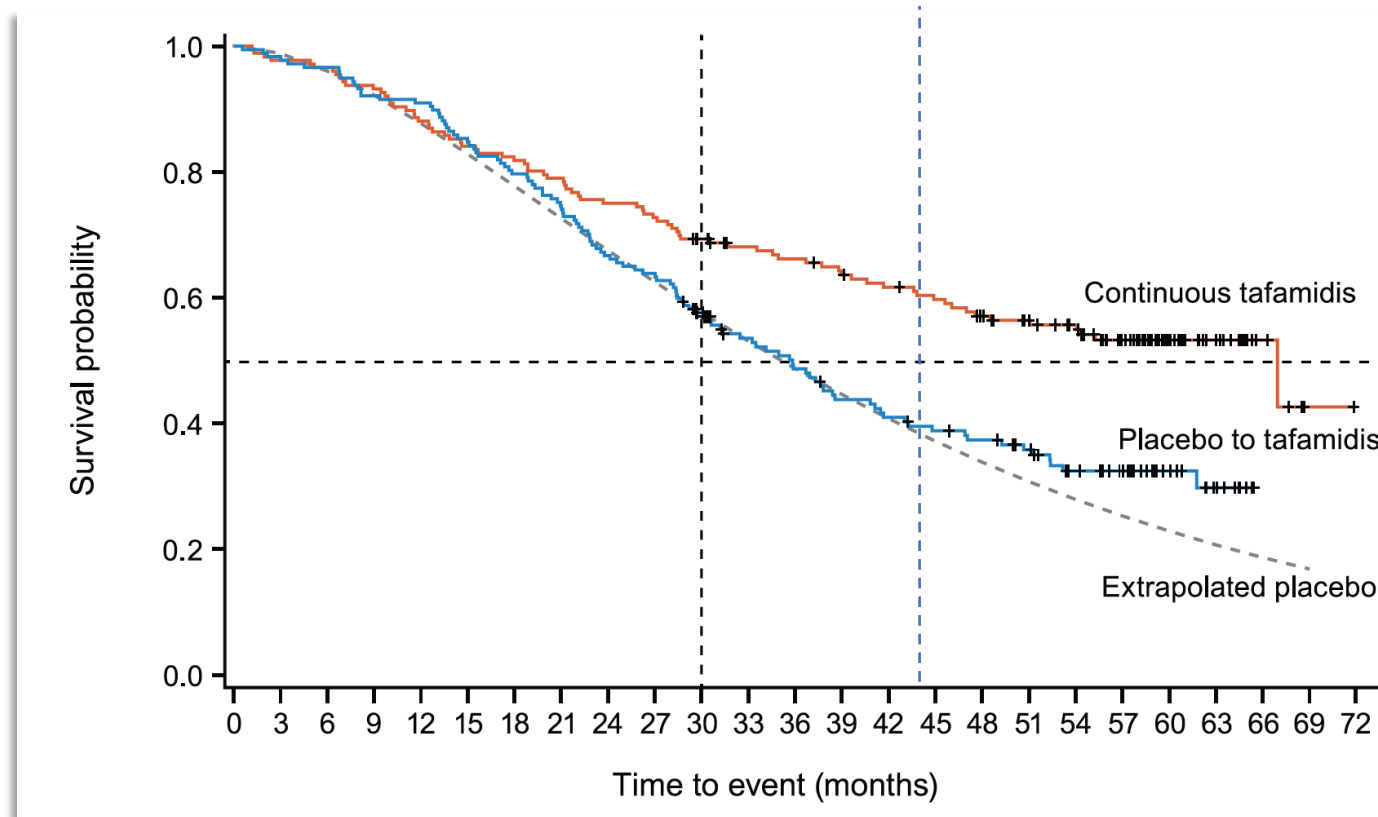
Circulation: Heart Failure

**ORIGINAL ARTICLE**

### Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy

Perry Elliott MD; Brian M. Drachman, MD; Stephen S. Gottlieb MD; James E. Hoffman, MD; Scott L. Hummel MD; Daniel J. Lenihan MD; Ben Ebede, MS, MBA; Balarama Gundapaneni, MS; Benjamin Li, MS; Marla B. Sultan, MD, MBA; Sanjiv J. Shah MD

While the reduction in mortality was similar in patients with ATTRwt and patients with ATTRv ( $\approx 40\%$  in each), there was a greater reduction in patients with NYHA class I or II (44%) than NYHA class III (35%). Together with results from ATTR-ACT,<sup>13,20</sup> these data support the use of tafamidis in all patients with ATTR-CM but emphasize the importance of early diagnosis and treatment.





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- ✓ Cardio-Geriatria, fragilità e amiloidosi cardiaca
- ✓ Amiloidosi Cardiaca: l'incontro tra cardiologia e geriatria
- ✓ Amiloidosi Cardiaca: Come viene selezionato il paziente per la terapia?



ESC

European Society  
of Cardiology

European Heart Journal (2018) 39, 2799–2806  
doi:10.1093/eurheartj/ehx589

FASTTRACK CLINICAL RESEARCH

Heart failure/cardiomyopathy

## A new staging system for cardiac transthyretin amyloidosis

Julian D. Gillmore<sup>1\*</sup>, Thibaud Damy<sup>2</sup>, Marianna Fontana<sup>1</sup>, Matthew Hutchinson<sup>1</sup>, Helen J. Lachmann<sup>1</sup>, Ana Martinez-Naharro<sup>1</sup>, Candida C. Quarta<sup>1</sup>, Tamer Rezk<sup>1</sup>, Carol J. Whelan<sup>1</sup>, Esther Gonzalez-Lopez<sup>1</sup>, Thirusha Lane<sup>1</sup>, Janet A. Gilbertson<sup>1</sup>, Dorota Rowczenio<sup>1</sup>, Aviva Petrie<sup>3</sup>, and Philip N. Hawkins<sup>1</sup>

### Stadio I:

- eGFR  $\geq 45$  ml/min e NTproBNP  $> 3000$  pg/ml

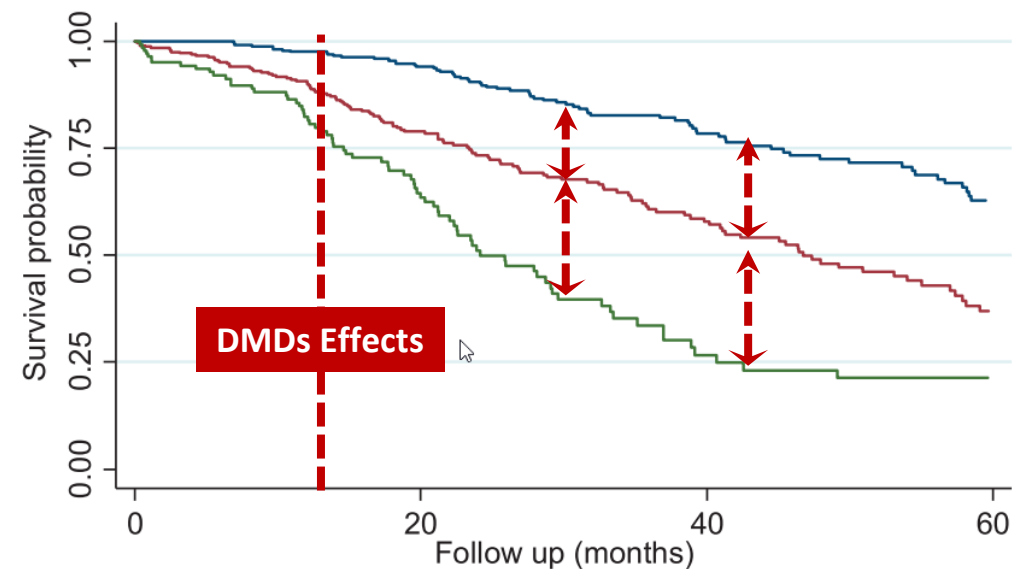
### Stadio II:

- eGFR  $< 45$  ml/min e NTproBNP  $> 3000$  pg/ml
- eGFR  $\geq 45$  ml/min e NTproBNP  $\leq 3000$  pg/ml

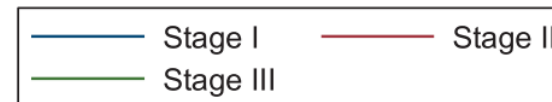
### Stadio III:

- eGFR  $< 45$  ml/min e NTproBNP  $\leq 3000$  pg/ml

Staging of cardiac ATTR amyloidosis at diagnosis using NT-proBNP and eGFR



Number at risk	0	20	40	60
Stage I	393	254	117	58
Stage II	334	181	78	30
Stage III	142	60	15	8





Classe NYHA e NAC sono  
strumenti efficaci a breve termine  
nel paziente anziano?

Quali pazienti dobbiamo trattare?  
Quali pazienti possiamo trattare?



# Disabilità

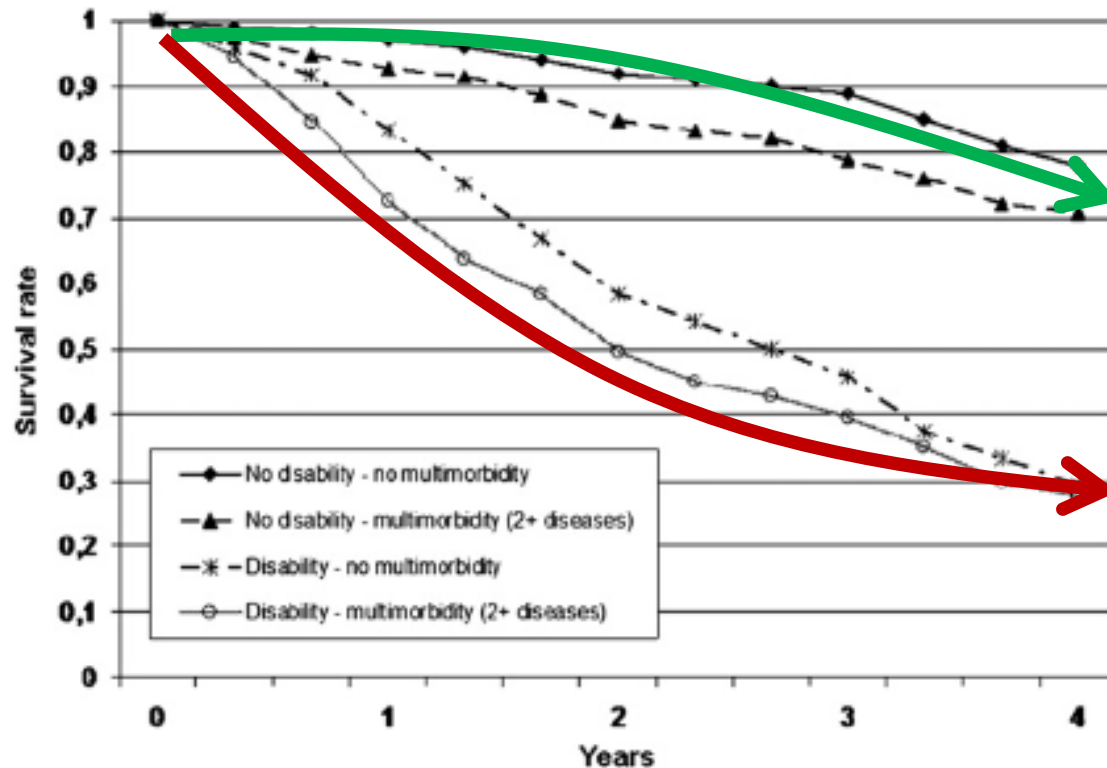


ELSEVIER

Journal of Clinical Epidemiology 63 (2010) 752–759

Journal of  
Clinical  
Epidemiology

Disability, more than multimorbidity, was predictive of mortality among older persons aged 80 years and older



No disability

Disability





## **Consensus SIGG** per la definizione e lo studio della **fragilità** nei pazienti affetto da **amiloidosi** cardiaca da transtiretina

### RESPONSABILI SCIENTIFICI

Prof. Dott. Andrea Ungar, MD, PhD, e Dott. Carlo Fumagalli, MD

### Esperti in Cardio-geriatria:

- Prof. Andrea Ungar, Università degli Studi di Firenze
- Prof. Stefano Fumagalli, Università degli Studi di Firenze
- Dott. Samuele Baldasseorni, Università degli Studi di Firenze
- Prof. Mario Bo, Università degli Studi di Torino
- Prof. Francesco Landi, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore
- Prof. Dario Leosco, Università degli Studi di Napoli – Federico II

### Collaboratori Scientifici, *fellow in training*:

- Dott. Carlo Fumagalli, Università degli Studi di Firenze e Università degli Studi della Campania, L. Vanvitelli
- Dott. Emanuele Monda, Università degli Studi della Campania, L. Vanvitelli
- Dott.ssa Federica Verrillo, Università degli Studi della Campania, L. Vanvitelli
- Dott.ssa Maddalena Gibello, Università degli Studi di Torino

### Esperti nella diagnosi e cura dell'ATTR-CA e delle cardiomiopatie:

- Dott. Francesco Cappelli, Università degli Studi di Firenze
- Prof. Iacopo Olivetto, Università degli Studi di Firenze
- Prof. Claudio Rapezzi, Università degli Studi di Ferrara
- Prof. Giuseppe Limongelli, Università degli Studi della Campania, L. Vanvitelli
- Dott. Giuseppe Palmiero, Università degli Studi della Campania, L. Vanvitelli e AORN Monaldi
- Prof.ssa Beatrice Musumeci, Università Sapienza, Roma
- Dott.ssa Cristina Chimenti, Università Sapienza, Roma
- Prof. Marco Canepa, Università degli Studi di Genova





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PALAZZO DEI CONGRESSI



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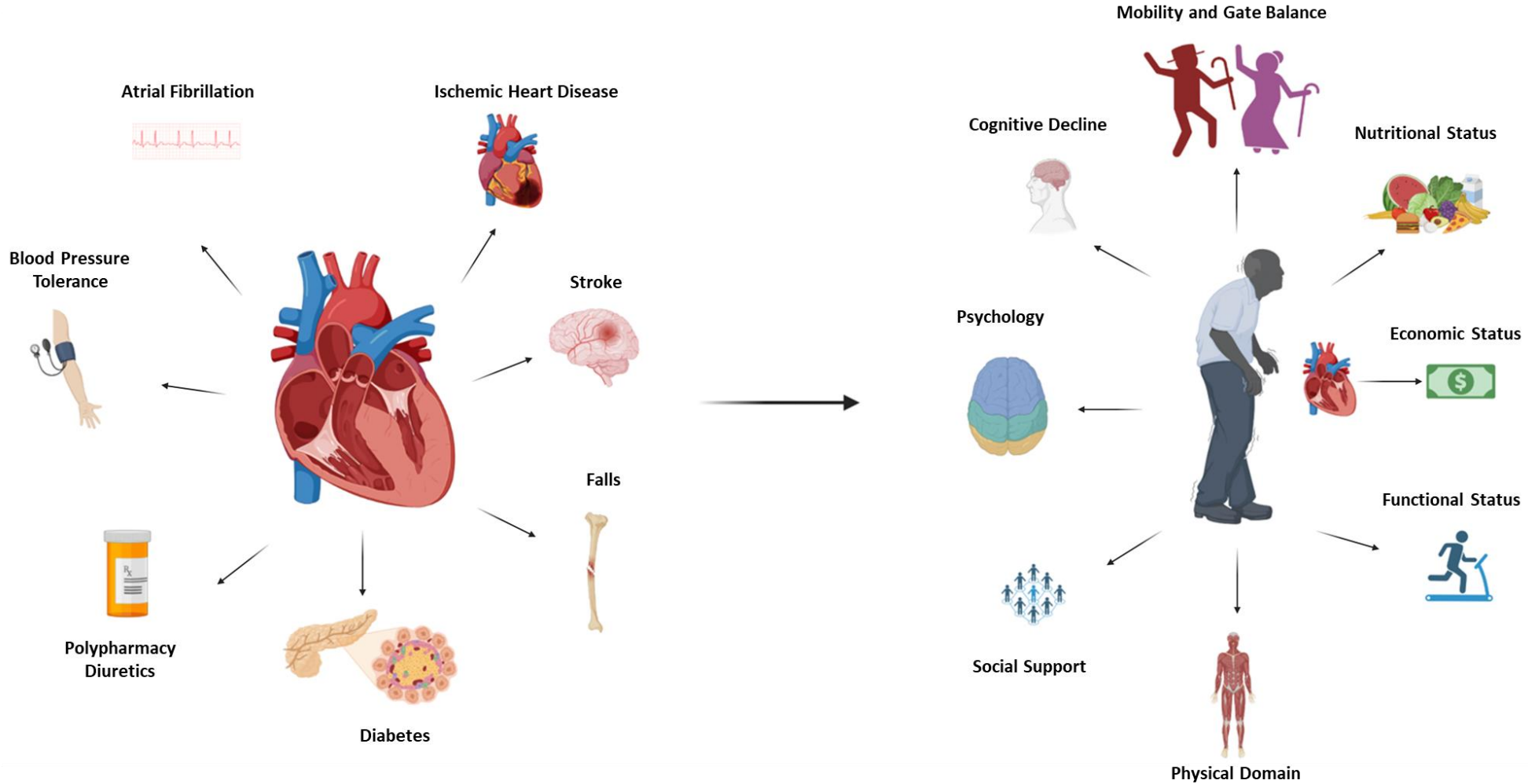
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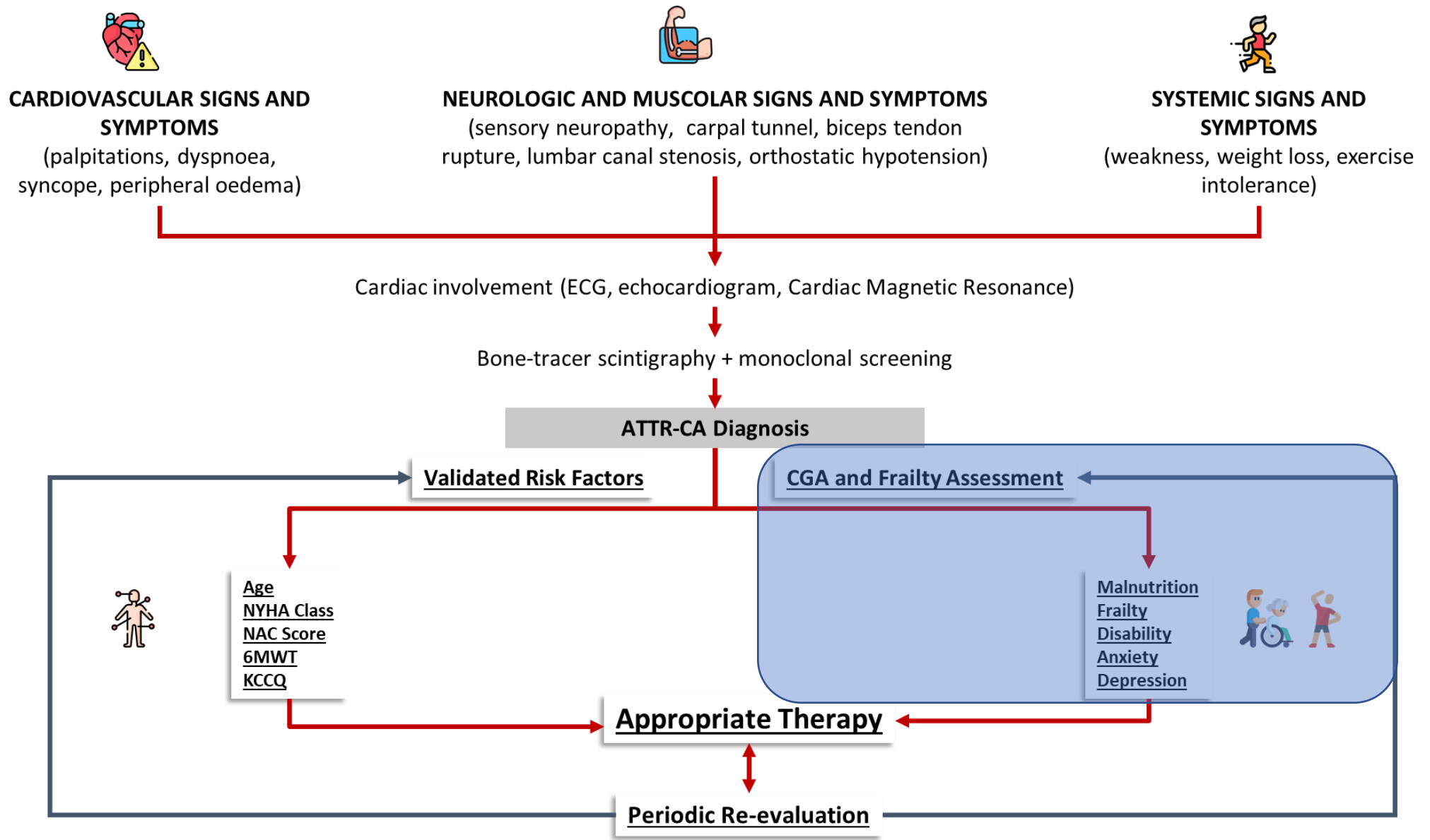


# THE ROLE OF FRAILTY AND THE COMPREHENSIVE GERIATRIC ASSESSMENT IN THE MANAGEMENT OF TRANSTHYRETIN AMYLOIDOSIS CARDIOMYOPATHY IN OLDER PATIENTS – A FOCUS REVIEW



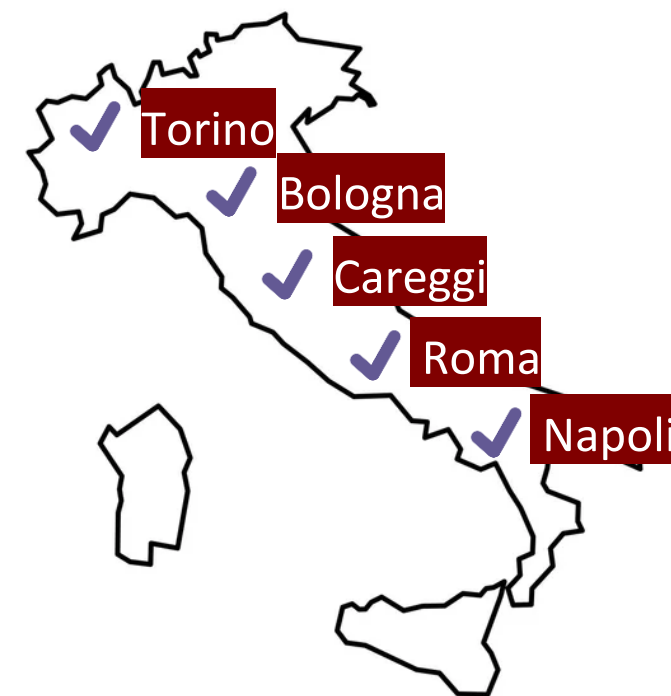
**CARDIAC AMYLOIDOSIS**

**CGA in CARDIAC AMYLOIDOSIS**



## La fragilità nella amiloidosi cardiaca Progetto Pilota Firenze – Roma – Napoli – Bologna - Torino

- **Design:** studio multicentrico prospettico di prevalenza della della fragilità nei pazienti affetti da ATTR-CA
- Pazienti valutati tramite valutazione multidimensionale: **MPI, CFS, SPPB e GDS**
- **137 pazienti** ATTR-CA al 2023 con follow up >6 mesi



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FIRENZE



FLORENCE  
CARDIO  
MYOPATHIES



SAPIENZA  
UNIVERSITÀ DI ROMA



UNIVERSITÀ  
DI TORINO





### Frailty and social status are associated with impaired quality of life in old patients diagnosed with transthyretin cardiac amyloidosis

Carlo Fumagalli, MD<sup>\*,a,b</sup>, Lucia Ponti<sup>\*,c,d</sup>, PsyD, PhD, Martina Smorti, PsyD<sup>e</sup>, Francesca Pozza, MD<sup>f</sup>, Dr. Alessia Argirò, MD<sup>b,e</sup>, Mattia Zampieri, MD<sup>d</sup>, Carlo Di Mario MD, PhD<sup>g</sup>, Raffaele Marfella, MD, PhD<sup>a</sup>, Niccolò Marchionni, MD,<sup>h</sup> Iacopo Olivotto, MD<sup>b,i</sup>, Federico Perfetto, MD, PhD<sup>e,f</sup>, Andrea Ungar, MD, PhD<sup>g</sup>, Francesco Cappelli, MD, PhD<sup>g</sup>

Table 1. Demographic and clinical characteristics of the study population	
	Overall Population N=115
<b>Demographic characteristics</b>	
Age, median [IQR] (years)	79 [75-84]
Men, N (%)	96 (83)
ATTR type	
WT-, N (%)	97 (84)
V-, N (%)	18 (16)
Ile68Leu, N (%)	13/18
Glu74Gln, N (%)	1/18
Phe84Ile, N (%)	1/18
Val122Ile, N (%)	3/18
KCCQ, median [IQR] (score)	66 [50-75]
Disease duration, median [IQR] (months)	23 [50-75]
<6 months, N (%)	11 (10)
NYHA Class III/IV, N (%)	25 (22)
NAC Score	
Class I, N (%)	67 (58)
Class II, N (%)	34 (30)
Class III, N (%)	14 (12)
Modified Frailty Index – 11 items, median [IQR]	0.09 [0-0.36]
≥0.36, N (%)	15 [13]
Ischemic Heart Disease, N (%)	16 (15)
Type 2 Diabetes Mellitus, N (%)	20 (17)
Stroke/TIA, N (%)	11 (10)
Disability, N (%)	8 (7.0)
Widow, N (%)	21 (18)
Living alone, N (%)	23 (20)
Higher Education (College degree or more), N (%)	6 (5.2)
<b>Instrumental Evaluation</b>	
Left Atrial Diameter, median [IQR] (mm)	45 [41-50]
Interventricular septal thickness, median [IQR] (mm)	16 [15-18]
Posterior Wall, median [IQR] (mm)	15 [14-16]
LVEDD, median [IQR] (mm)	44 [40-48]
LVEF, median [IQR] (%)	57 [50-61]
LVEF<50%, N (%)	26 (23)
E/e', median [IQR] (%)	15 [12-19]
Diastolic Dysfunction ≥ grade III, N (%)	22 (19)

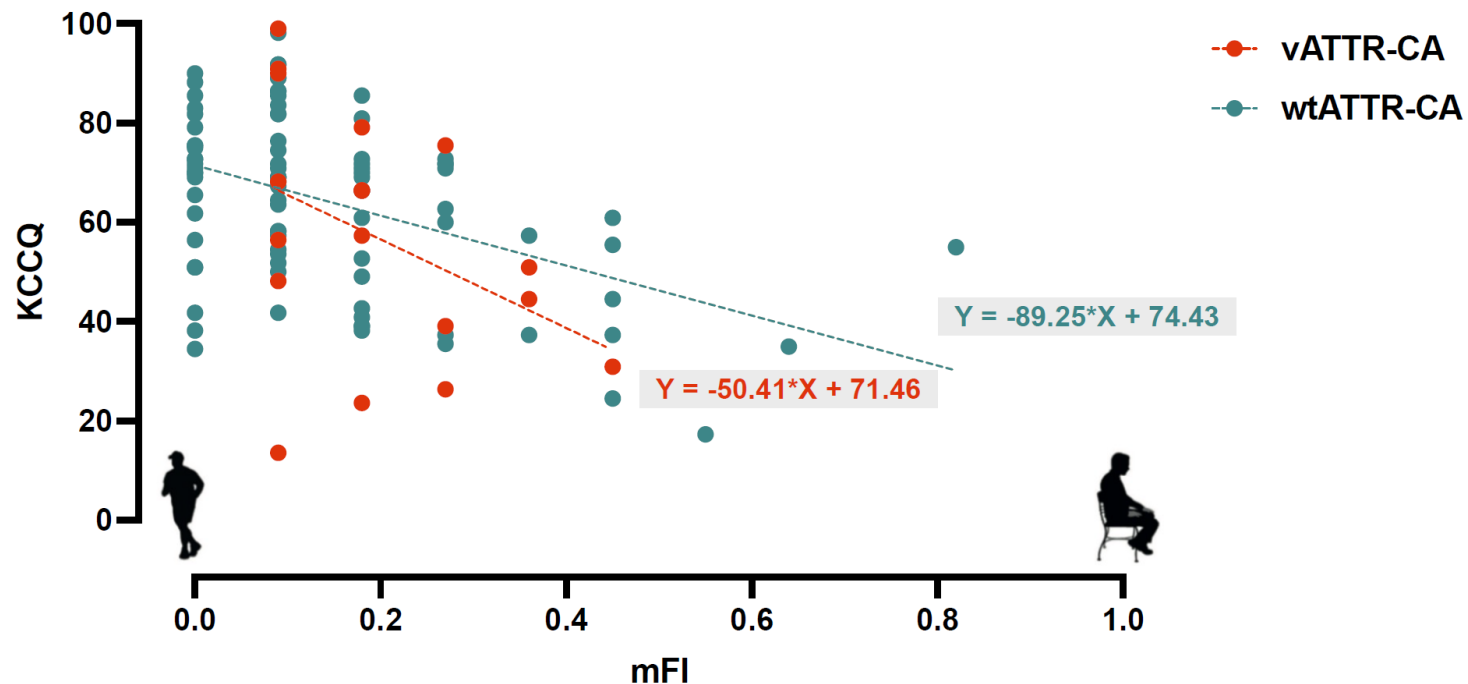


### Frailty and social status are associated with impaired quality of life in old patients diagnosed with transthyretin cardiac amyloidosis

Carlo Fumagalli, MD<sup>\*,a,b</sup>, Lucia Ponti<sup>\*,c,d</sup>, PsyD, PhD, Martina Smorti, PsyD<sup>e</sup>, Francesca Pozz Dr, Alessia Argirò, MD<sup>b,e</sup>, Mattia Zampieri, MD<sup>d</sup>, Carlo Di Mario MD, PhD<sup>e</sup>, Raffaele Marfe PhD<sup>a</sup>, Niccolò Marchionni, MD,<sup>h</sup> Iacopo Olivotto, MD<sup>b,i</sup>, Federico Perfetto, MD, PhD<sup>e,f</sup>, Andre MD, PhD<sup>g,l</sup>, Francesco Cappelli, MD, PhD<sup>g</sup>

inherited genetic variant of TTR (vATTR)  
non-inheritable wild type TTR (wtATTR)

### Distribution of KCCQ Score by mFI





**Frailty and social status are associated with impaired quality of life in old patients diagnosed with transthyretin cardiac amyloidosis**

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In conclusion, in older patients diagnosed with ATTR-CA, **frailty, social status, NYHA Class and disease duration were associated with KCCQ, while pure instrumental variables were not.**

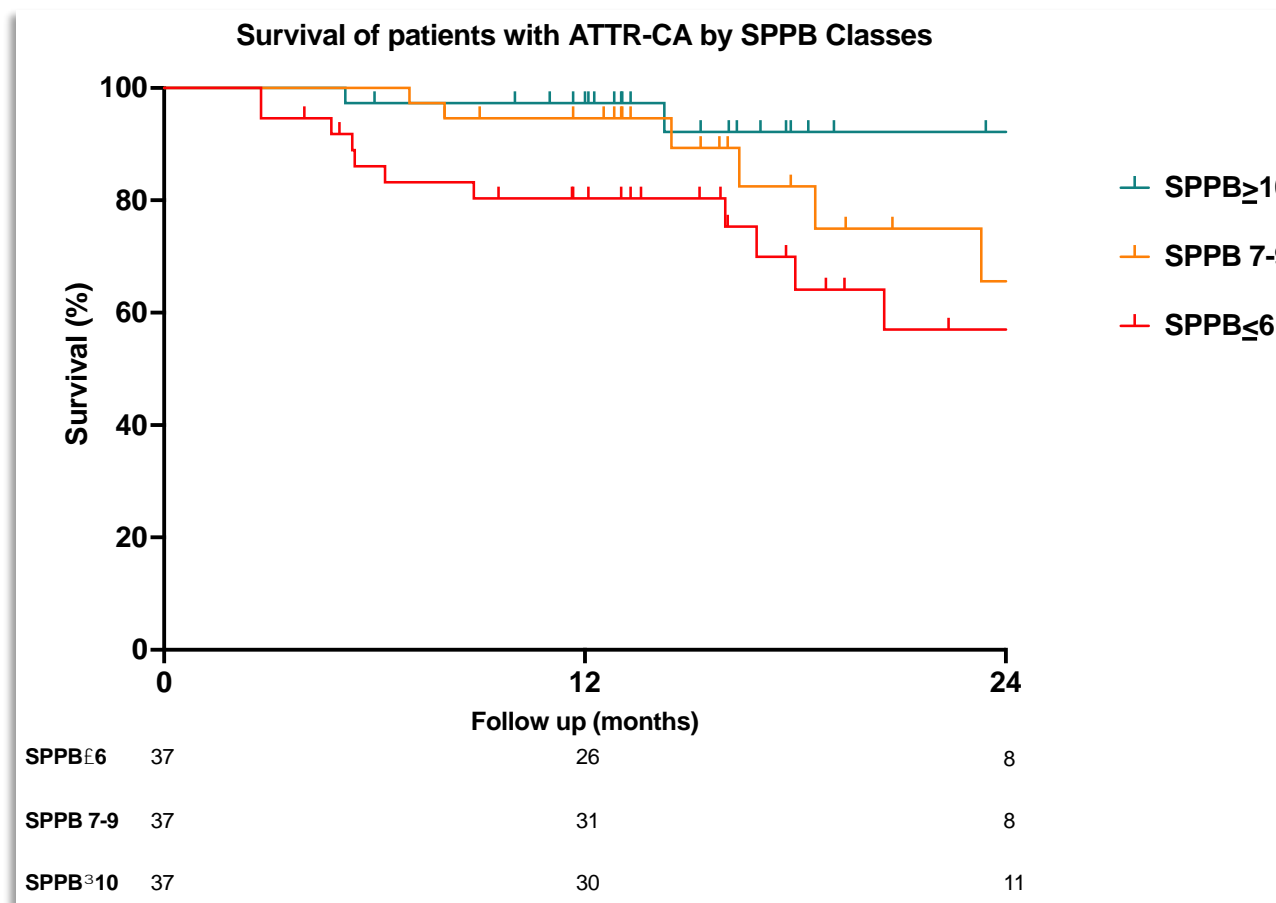
These results **highlight the importance of functional status** in the determining quality of life in older individuals also when diagnosed with ATTR-CA





## Overall Survival of patients diagnosed with ATTR-CA by SPPB

**Preliminary Data**  
**Florence Cohort**  
**N=111 patients**





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**La prevalenza dell'amiloidosi è molto elevata nell'anziano.  
La VMD ci aiuta nella selezione e la scelta dei pazienti da  
trattare**



**Grazie per la  
vostra attenzione**

