IV Congresso
Novas Fronteiras em Cardiologia

Polineuropatia Amiloidótica Familiar

Valor da Eco e da Cintigrafia de MIBG no Prognóstico

7 a 9 de Fevereiro 2014
Hotel Vila Galé Ericeira

Conceição Azevedo Coutinho
Hospital de Santa Maria

FAMILIAL AMYLOID POLYNEUROPATHY

- **Familial amyloid polyneuropathy** (FAP) is a rare, systemic, disease resulting from autosomally dominant single-point mutations in the transthyretin (TTR) gene.
- The FAP V30M-TTR is characterised by sensory-motor and autonomic neuropathy and amyloid deposits of in various organs and tissues. In typical cases, symptoms develop before the age of 40 years leading to death in 10 to 15 years.
- **Cardiovascular manifestations** in V30M-TTR are due to autonomic neuropathy (blood pressure and heart rate control disturbances) and to amyloid deposits in the heart (infiltrative cardiomyopathy, arrhythmias and conduction defects).
- Because transthyretin is predominantly synthesized in the liver, l**iver transplantation** is used to halt or at least attenuate the disease progression. As symptoms will not regress, the procedure should be performed at an early stage.

^{123}I MIBG IMAGING

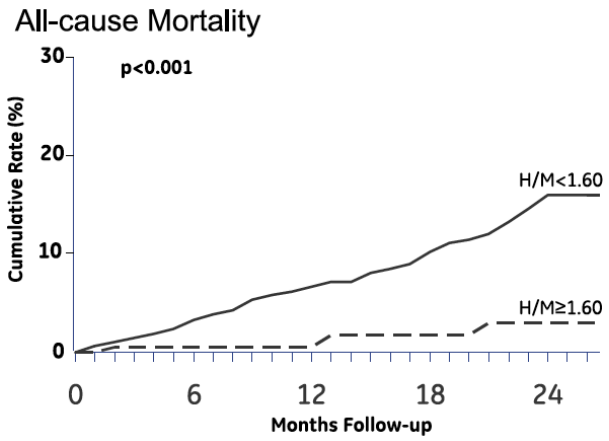
- ^{123}I metaiodobenzylguanidine (MIBG) imaging is a non-invasive tool for assessing myocardial sympathetic innervation.

- Some studies suggested that myocardial sympathetic denervation often precedes the neurological and cardiac manifestations of the FAP V30M-TTR disease.

Tanaka M et al. *JACC* 1997;29:168-74.
Azevedo Coutinho C et al. *Rev Port Cardiol* 2004;23:201-11

- **Late heart-to-mediastinum (H/M) MIBG uptake ratio <1.60** is a strong prognostic predictor in ischemic and non-ischemic cardiomyopathies.

- Prognostic value of MIBG imaging in FAP V30M-TTR was never evaluated.



Jacobson AF et al. (ADMIRE-HF). *JACC* 2010;55:2212-21.

AIMS

- To provide a prospective validation of the long-term prognostic value of myocardial sympathetic denervation assessed by MIBG imaging
- To compare it with other methods for cardiovascular and neurological evaluation in FAP V30M-TTR

Circulation
Cardiovascular Imaging
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Reduced Myocardial 123-Iodine Meta-iodobenzylguanidine Uptake: A Prognostic Marker in Familial Amyloid Polyneuropathy

Maria C. Azevedo Coutinho, Nuno Cortez-Dias, Guilhermina Cantinho, Isabel Conceição, António Oliveira, Armando Bordalo e Sá, Susana Gonçalves, Ana G. Almeida, Mamede de Carvalho and António Nunes Diogo

(*Circ Cardiovasc Imaging. 2013;6:627-636*)

NEUROLOGICAL EVALUATION

1. **Clinical score** (0-100) for quantification of neurological symptoms: motor and sensory function, autonomic symptoms and weight

2. **Neurophysiological (NP) score** (0-100) calculated from standardized nerve conduction studies and needle electromyography.

Neurological involvement was defined by any NP abnormality (i.e., NP score > 0)

- Asymptomatic carriers: NP score = 0
- Mild neurological involvement: NP score < 20
- Moderate-to-severe neurological involvement: NP score ≥ 20

CARDIOVASCULAR EVALUATION

1. **ECG**

2. **Holter recording**

   Holter abnormality: LBBB; AV block ≥2nd degree; pacemaker; PAC or PVC ≥240/24h; supraventricular or ventricular arrhythmias

3. **Ambulatory blood pressure monitoring (ABPM)**

   ABPM abnormality: mean daytime BP ≥140/90 mmHg or nighttime BP ≥125/75 mmHg; nocturnal systolic BP drop <10% or systolic BP higher at night

4. **Conventional echocardiography**

   Echo abnormality: the mean of septal and posterior wall thicknesses ≥12mm and mitral inflow E/A ratios <1.0 or >2.5

5. **^{123}I MIBG imaging**

   MIBG abnormality: late H/M <1.60

STUDY POPULATION

Prospective longitudinal study
September 1998 - December 2010

169 individuals V30M TTR mutation

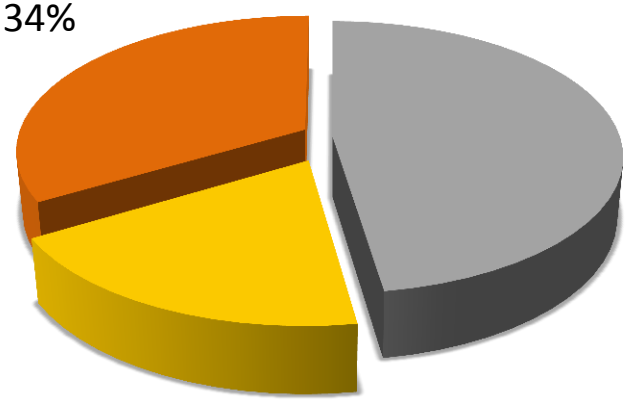
26 individuals did not complete all cardiac exams

143 individuals
42 yrs (19-84); Fem. 55%

Neurological involvement
N=75; 52%

Moderate to severe
N=48; 34%

Mild
N=27; 19%



Asymptomatic carriers
N=68; 48%

Baseline Clinical Characteristics of the Study Population

Characteristic	All study participants (N=143)
Neurological involvement, n (%)	**75 (52.4)**
Neurophysiological score, median (IQR)	2.5 (0-35)
Clinical score, median (IQR)	6 (0-22)
Late onset (age ≥50 years), n (%)	**48 (33.6)**
Cardiovascular symptoms, n (%)	**55 (38.5)**
Dizziness or pre-syncope, n (%)	37 (25.9)
Syncope, n (%)	14 (9.6)
Congestive heart failure, n (%)	3 (2.1)
ECG abnormalities, n (%)	**55 (38.5)**
1st degree AV block, n (%)	15 (10.5)
2nd degree AV block, n (%)	2 (1.4)
Pacemaker rhythm, n (%)	6 (4.2)
Left anterior fascicular block, n (%)	17 (11.9)
Right bundle branch block, n (%)	1 (0.7)
Left bundle branch block, n (%)	1 (0.7)
Poor R wave progression in the precordial leads, n (%)	12 (8.4)
Non-specific left ventricular repolarization abnormalities, n (%)	2 (1.4)
Low QRS voltage, n (%)	1 (0.7)
Sinus bradycardia, n (%)	1 (0.7)
Sinus tachycardia, n (%)	11 (7.7)

Characteristic	All study participants (N=143)
Holter abnormalities, n (%)	**45 (31.5)**
≥2nd degree AV block, n (%)	6 (4.2)
Pacemaker rhythm, n (%)	12 (8.4)
Atrial tachycardia, n (%)	3 (3.5)
Atrial flutter, n (%)	1 (0.7)
Atrial fibrillation, n (%)	1 (0.7)
Non-sustained ventricular tachycardia, n (%)	4 (2.8)
Premature atrial contraction ≥240/24 hour, n (%)	26 (18.2)
Premature ventricular contraction ≥240 / 24 hour, n (%)	11 (7.7)
Ambulatory blood pressure monitoring abnormalities, n (%)	**83 (58.0)**
High BP, n (%)	51 (35.7)
Non-dipper pattern, n (%)	49 (34.3)
Reverse dipper pattern, n (%)	15 (10.5)
Echocardiographic characteristics	
Left ventricular wall thickness ≥12 mm, n (%)	33 (23.1)
Mitral E/A ratio <1.0 or >2.5, n (%)	47 (32.9)
Left ventricular wall thickness ≥12 mm & mitral E/A ratio <1.0 or >2.5, n (%)	19 (13.3)

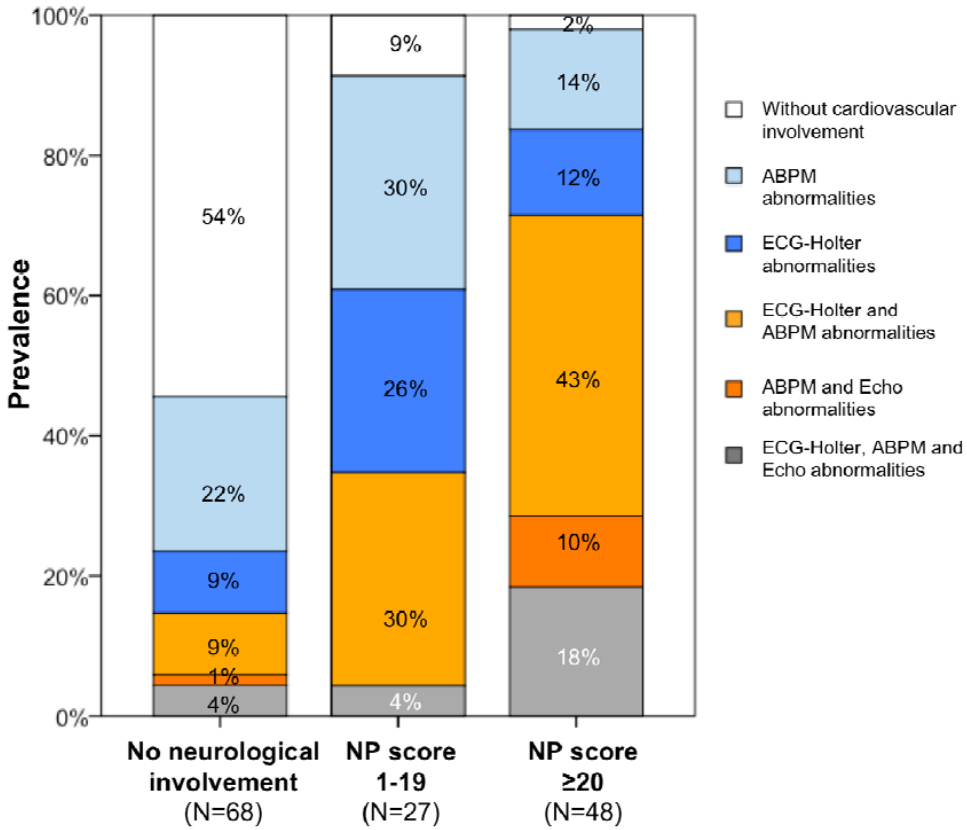
Cardiovascular abnormalities identified by the ECG, Holter, ABPM and echocardiography were present in 102 subjects (71.3%)

RESULTS

- **Characterization of the phenotypic spectrum of V30M-TTR:** neurological *versus* cardiovascular involvement
- **Prognostic stratification:** prediction of long-term mortality
- **MIBG imaging and liver transplantation outcome**

Cardiovascular Findings According to the Severity of Neurological Involvement

Prevalence of Cardiovascular Abnormalities According to Neurological Involvement



- **46% of asymptomatic carriers had already cardiovascular abnormalities.**
- **96% of patients with neurological involvement had cardiovascular abnormalities** and their prevalence increased with the severity of neurological disability.

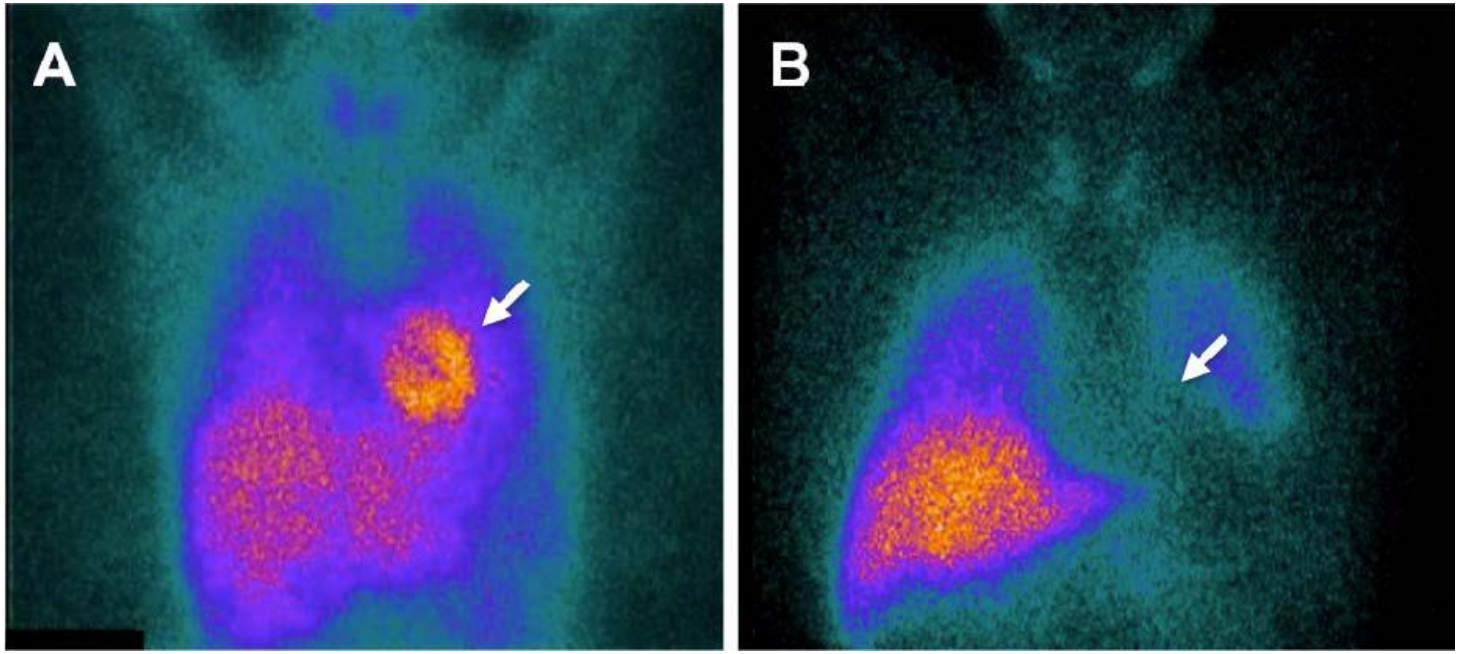
Cardiovascular Findings According to the Severity of Neurological Involvement

Variable	Group I Asymptomatic Carriers (N=68)	Group II NP Score 1-19 (N=27)	Group III NP Score ≥20 (N=48)	p-Value I vs. II-III	p-Value I vs. II vs. III
ECG abnormalities, n (%)	11 (16.2)	13 (48.1)	31 (64.6)	<0.001	<0.001
Holter abnormalities , n (%)	8 (11.8)	9 (33.3)	28 (58.3)	<0.001	<0.001
PAC (number per 24h), median (IQR)	4 (0-19)	14 (3-137)	80 (9-479)	<0.001	<0.001
PVC (number per 24h), median (IQR)	3 (0-10)	18 (4-83)	25 (7-95)	<0.001	<0.001
≥2nd degree AV block/pacemaker, n (%)	3 (4.4)	5 (21.7)	10 (21.7)	0.002	0.011
ABPM abnormalities, n (%)	25 (36.8)	15 (65.2)	42 (85.7)	<0.001	<0.001
Daytime SBP, mean ± SD, mmHg	121 ± 9	122 ± 14	122 ± 15	NS	NS
Daytime DBP, mean ± SD, mmHg	76 ± 6	77 ± 7	75 ± 9	NS	NS
Nighttime SBP, mean ± SD, mmHg	106 ± 10	112 ± 15	114 ± 15	<0.001	0.003
Nighttime DBP, mean ± SD, mmHg	62 ± 7	68 ± 10	67 ± 9	<0.001	<0.001
High BP, n (%)	14 (20.6)	12 (44.4)	26 (54.2)	<0.001	0.001
Nocturnal SBP drop, mean ± SD, %	13 ± 6	8 ± 7	6 ± 7	<0.001	<0.001
Non-dipper pattern, n (%)	14 (20.6)	12 (44.4)	23 (47.9)	<0.001	<0.001
Reverse dipper pattern, n (%)	2 (2.9)	2 (7.4)	11 (22.9)	<0.001	<0.001
Echo characteristics					
LV wall thickness , mean ± SD, mm	9 ± 2	10 ± 1	11 ± 3	<0.001	<0.001
LV wall thickness ≥12 mm, n (%)	6 (8.8)	4 (14.8)	23 (47.9)	<0.001	<0.001
Mitral inflow E/A ratio, median (IQR)	1.40 (1.10-1.76)	1.08 (0.83-1.34)	1.00 (0.77-1.34)	<0.001	0.001
Mitral E/A ratio <1.0 or >2.5, n (%)	12 (17.6)	11 (40.7)	24 (50.0)	0.002	0.001
LV wall thickness ≥12 mm & mitral E/A ratio <1.0 or >2.5, n (%)	4 (5.9)	2 (7.4)	13 (27.1)	0.021	0.001

Student T-test or Mann-Whitney test, according to the variable distribution

Cardiac Enervation Assessed by ^{123}I MIBG Imaging According to the Severity of Neurological Involvement

MIBG Parameters	Group I Asymptomatic Carriers (N=68)	Group II NP Score 1-19 (N=27)	Group III NP Score ≥20 (N=48)	p-Value I vs. II-III	p-Value I vs. II vs. III
Early H/M, mean ± SD	2.04 ± 0.29	1.88 ± 0.36	1.55 ± 0.33	<0.001	<0.001
Late H/M , mean ± SD	2.11 ± 0.31	1.77 ± 0.36	1.49 ± 0.33	<0.001	<0.001
Washout rate, mean ± SD	-3.8 ± 11.6	5.5 ± 10.2	4.1 ± 9.3	<0.001	<0.001
Late H/M <1.60, n (%)	**2 (2.9)**	**9 (33.3)**	**28 (58.3)**	**<0.001**	**<0.001**



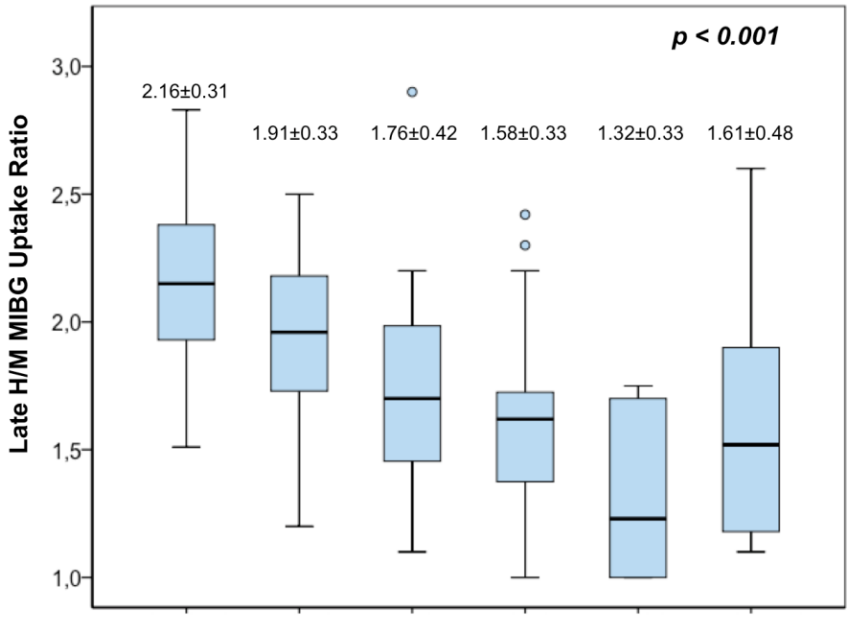
A. Asymptomatic carrier with late H/M=2.5.

B. Patient with neurophysiological score of 55 and late H/M=1.2 who underwent liver transplant 6 months later.

Myocardial Sympathetic Enervation Assessed by ^{123}I MIBG Imaging in FAP V30M-TTR

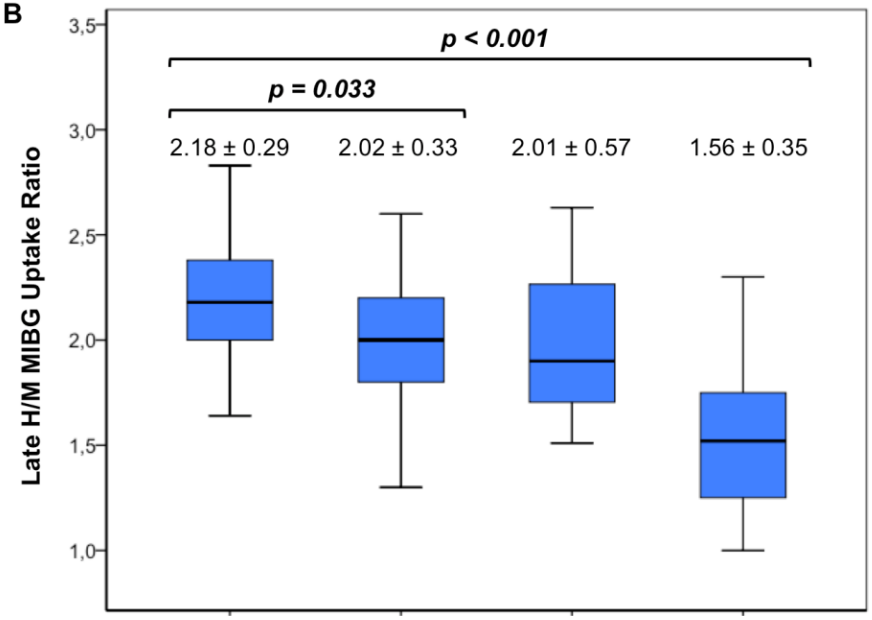
Distribution of the Late H/M MIBG Uptake Ratio According to Cardiovascular and Neurological Involvement

A



ABPM abnormalities	No	Yes	No	Yes	Yes	Yes
ECG-Holter abnormalities	No	No	Yes	Yes	No	Yes
Echo abnormalities	No	No	No	No	Yes	Yes
Number of patients	41	34	19	13	17	7

B



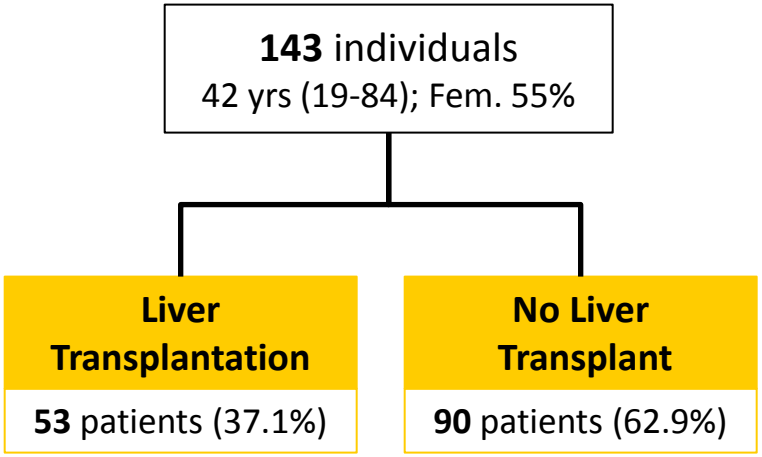
Neurological involvement	No	No	Yes	Yes
Cardiovascular involvement	No	Yes	No	Yes
Number of patients	37	31	4	71

RESULTS

- **Characterization of the phenotypic spectrum of V30M-TTR:** neurological *versus* cardiovascular involvement
- **Prognostic stratification:** prediction of long-term mortality
- **MIBG imaging and liver transplantation outcome**

PROGNOSTIC ANALYSIS

- Median follow-up duration: **5.5 years**
- **53 patients (37.1%) submitted to liver transplantation** after a median of 2.8 years
- **32 patients died (22.4%) –** the cause of death was directly related to V30M-TTR in 91%
- 10 patients submitted to transplant died (6 due to transplant-related complications)

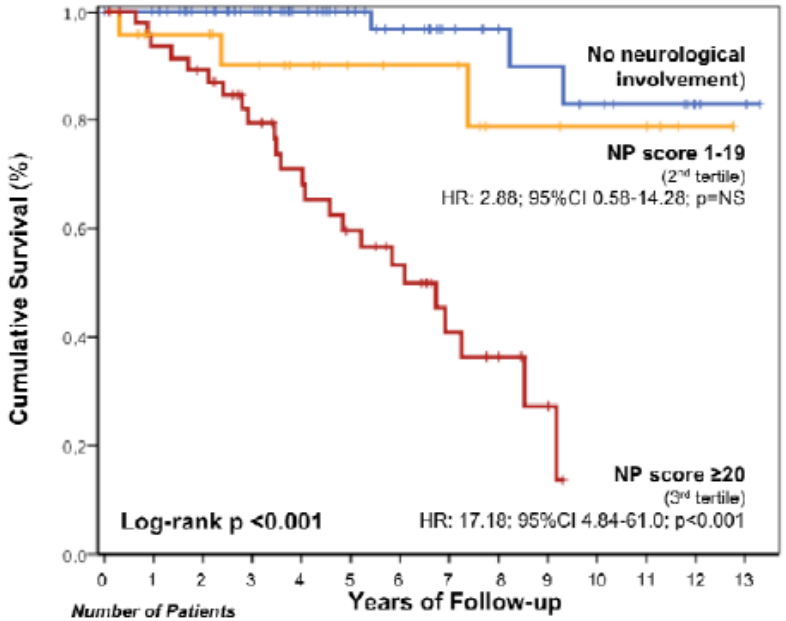


Causes of Death During Follow-Up	Non-transplanted Patients (N=90)	Transplanted Patients (N=53)	Total (N=143)
End-stage cachexia	14	3	17
Surgery-related complications	0	6	6
Late acute liver rejection	0	1	1
Acute infectious diseases	5	0	5
Stroke	1	0	1
Accidental death	1	0	1
Cancer	1	0	1
Total	22	10	32

PROGNOSTIC STRATIFICATION
CLINICAL AND NEUROLOGICAL CHARACTERISTICS

Survival in Relation to the Neurophysiological and Clinical Scores

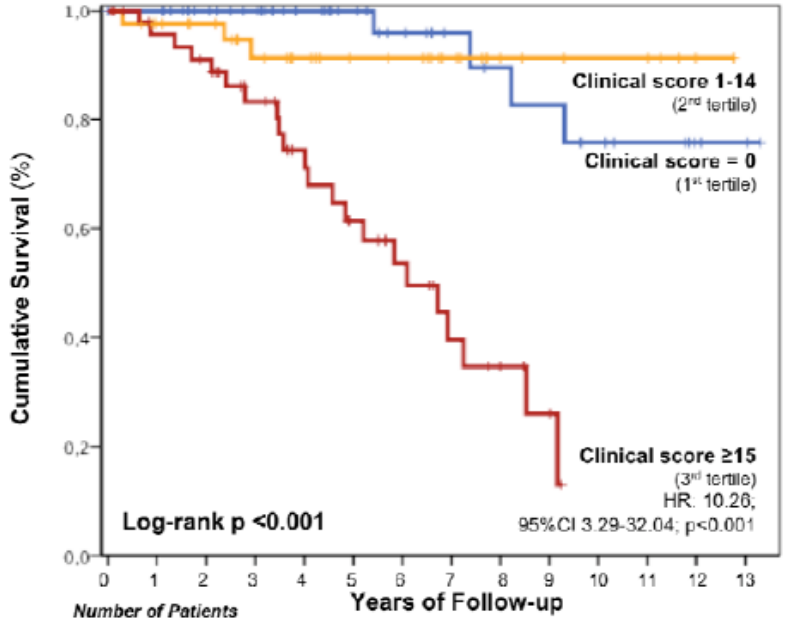
A



Number of Patients

No neurological involvement	68	66	55	47	37	30	27	18	14	13	10	7	3	1
NP score 1-19	27	25	24	19	16	13	9	9	5	5	4	4	1	0
NP score ≥20	48	43	40	31	25	20	16	9	6	3	0	0	0	0
Total	143	134	119	97	78	63	52	36	25	21	14	11	4	1

B



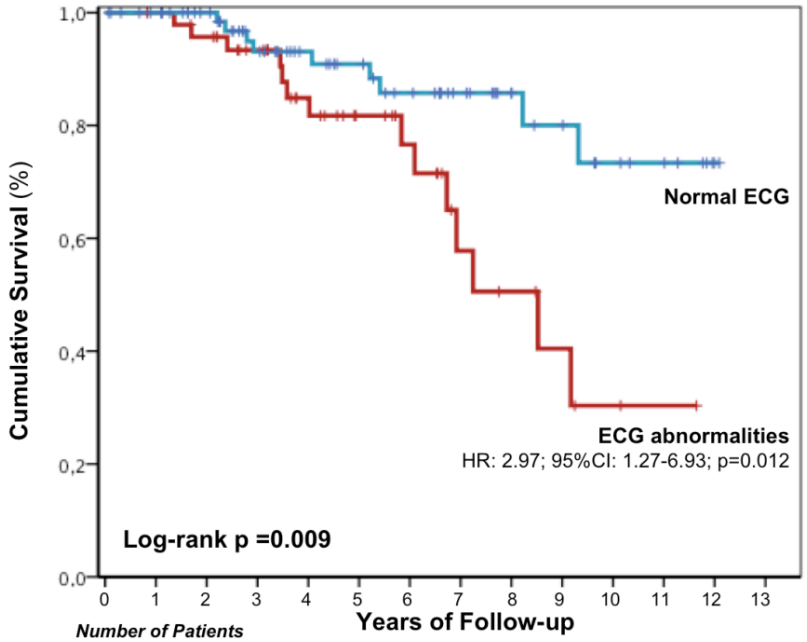
Number of Patients

Clinical score = 0	50	49	40	36	30	26	23	19	14	14	11	9	3	1
Clinical score 1-14	45	43	40	31	25	20	16	9	6	4	3	2	1	0
Clinical score ≥15	48	42	39	30	23	17	13	8	5	3	0	0	0	0
Total	143	134	119	97	78	63	52	36	25	21	14	11	4	1

PROGNOSTIC STRATIFICATION
ECG AND HOLTER CHARACTERISTICS

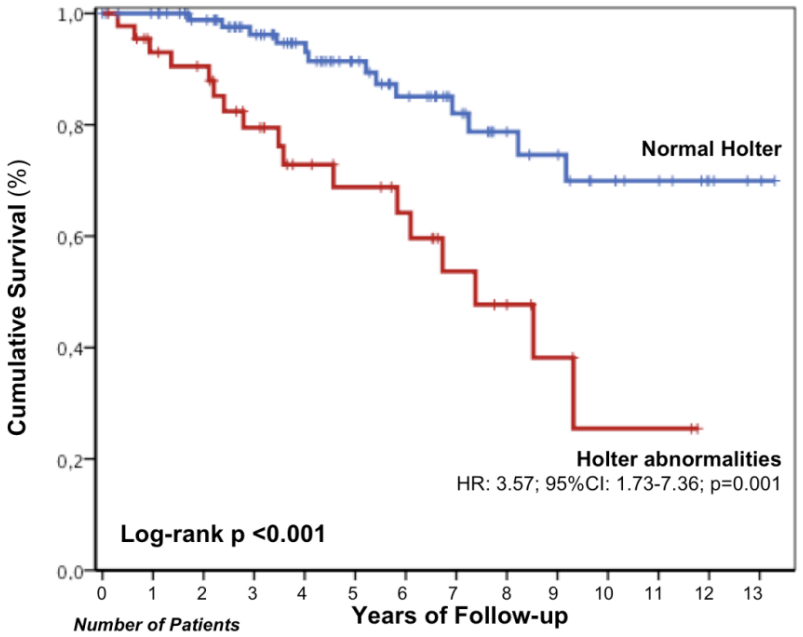
Survival in Relation to the ECG and Holter Characteristics

A



Number of Patients														
Normal ECG	88	85	75	49	45	44	37	28	19	17	12	10	4	1
ECG abnormalities	55	49	44	38	33	19	15	8	6	4	2	1	0	0
Total	143	134	119	97	78	63	52	36	25	21	14	11	4	1

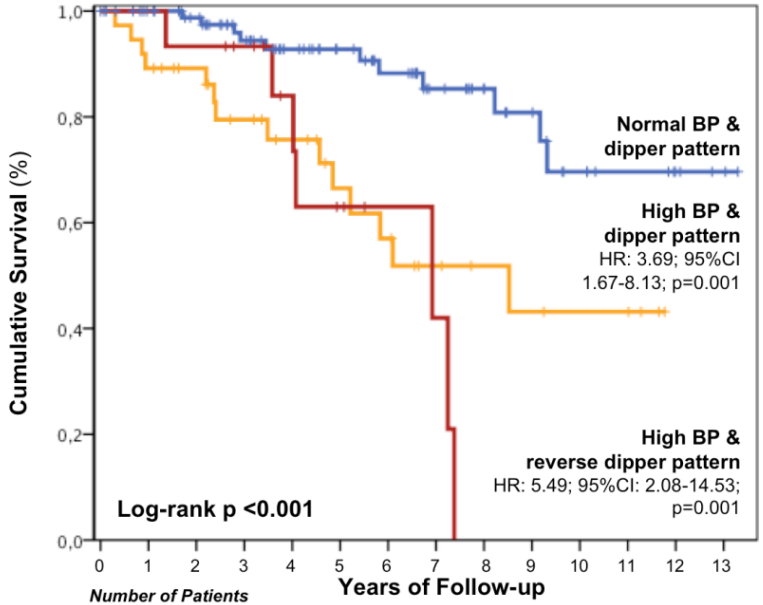
B



Number of Patients														
Normal Holter	98	96	84	70	58	46	38	27	19	17	12	10	4	1
Holter abnormalities	45	38	35	27	20	17	14	9	6	4	2	1	0	0
Total	143	134	119	97	78	63	52	36	25	21	14	11	4	1

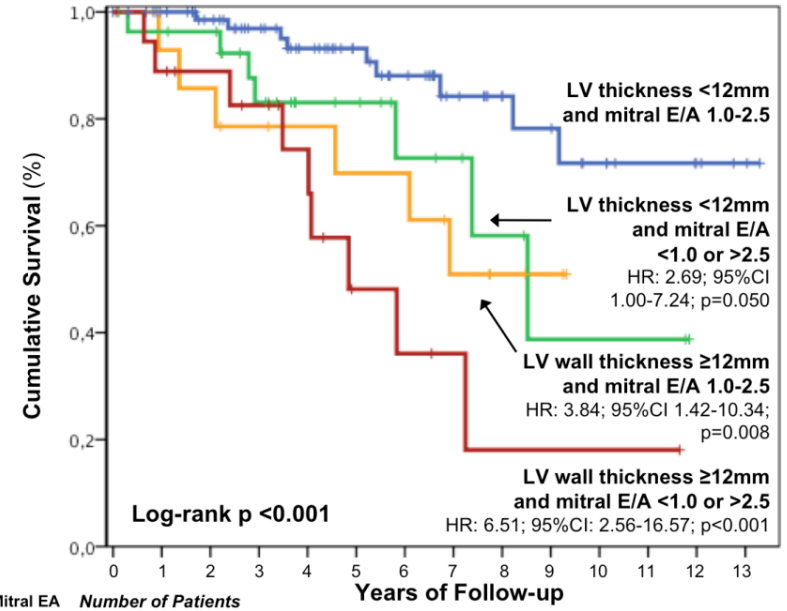
PROGNOSTIC STRATIFICATION
ABPM AND ECHOCARDIOGRAPHIC CHARACTERISTICS

Survival in Relation to ABPM and Echo Characteristics



	Number of Patients													
Normal BP & dipper	92	87	77	62	51	44	37	26	19	16	10	7	4	1
High BP & dipper	36	33	29	23	19	14	12	8	6	5	4	4	0	0
High BP & reverse dipper	15	14	13	12	8	5	3	2	0	0	0	0	0	0
Total	143	134	119	97	78	63	52	36	25	21	14	11	4	1

* All patients with reverse dipping pattern had high BP.

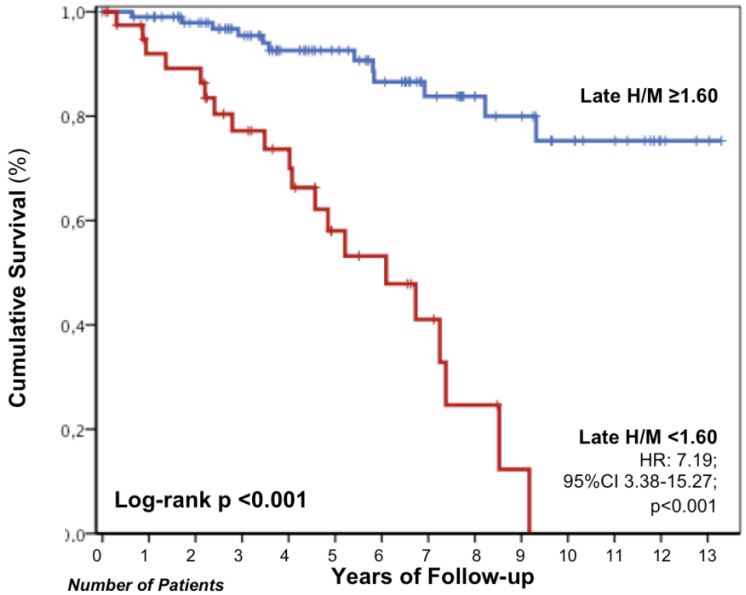


LV thickness	Mitral EA	Number of Patients												
<12mm	1.0-2.5	82	79	68	57	48	40	34	23	17	16	11	8	4	1
<12mm	<1.0 or >2.5	28	26	25	18	12	11	7	6	4	2	2	2	0	0
≥12mm	1.0-2.5	14	13	12	10	9	8	8	5	3	2	0	0	0	0
≥12mm	<1.0 or >2.5	19	16	14	12	9	4	3	2	1	1	1	1	0	0
Total		143	134	119	97	78	63	52	36	25	21	14	11	4	1

Prognostic Stratification
^{123}I MIBG Imaging

MIBG Characteristics	Favourable Outcome (N=111)	All-cause Death (N=32)	p-Value	Univariate Cox Regression Analysis		
				Hazard Ratio	95% CI	p-Value
Early H/M, mean ± SD	1.9±0.4	1.6±0.4	<0.001	0.07	0.02-0.19	<0.001
Late H/M, mean ± SD	1.9±0.4	1.5±0.4	<0.001	0.07	0.03-0.20	<0.001
Washout rate, mean ± SD	0±11	3±11	NS	1.02	0.99-1.05	NS
Late H/M <1.60, n (%)	21 (18.9)	20 (62.5)	<0.001	**7.19**	**3.38-15.27**	**<0.001**

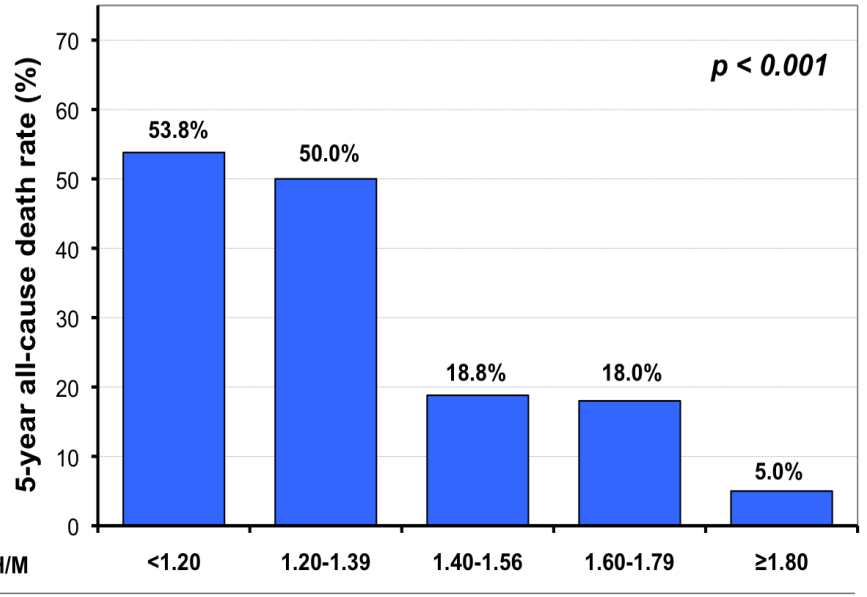
Survival in Relation to Late H/M Uptake Ratio



Number of Patients

H/M ≥1.60	102	101	87	73	58	51	42	30	22	20	14	11	4	1
H/M <1.60	41	33	32	24	20	12	10	6	3	1	0	0	0	0
Total	143	134	119	97	78	63	52	36	25	21	14	11	4	1

5-year Mortality Rates According to Late H/M Uptake Ratio



PROGNOSTIC STRATIFICATION – MULTIVARIATE ANALYSIS

Variable	Univariate Cox Regression Analysis		Multivariate Cox Regression Analysis		
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	p-Value
Age	1.06	1.04-1.09	**1.04**	**1.01-1.06**	**0.010**
Late onset of disease *	2.52	1.25 – 5.01	0.40	0.09-1.91	NS
Neurological involvement †	10.14	3.06 – 33.63	4.37	0.89-21.52	NS
Holter abnormality ‡	3.57	1.73 – 7.36	1.31	0.52-3.34	NS
ABPM characteristics					
High BP §	3.61	1.76 – 7.40	0.64	0.23-1.78	NS
Non-dipper pattern ¶	2.98	1.20 – 7.40	0.34	0.09-1.27	NS
Reverse dipper pattern ¶	0.81	0.36 – 1.84	1.29	0.39-4.20	NS
Echo characteristics ♯					
LV wall <12mm & mitral E/A <1.0 or >2.5	2.69	1.0 – 7.24	1.70	0.59-4.88	NS
LV wall ≥12mm & mitral E/A 1.0 to 2.5	3.84	1.42 – 10.34	1.92	0.63-5.86	NS
LV wall ≥12mm & mitral E/A <1.0 or >2.5	6.51	2.56 – 16.57	--	--	NS
Late H/M	0.07	0.03 – 0.20	**0.18**	**0.06 – 0.57**	**0.003**

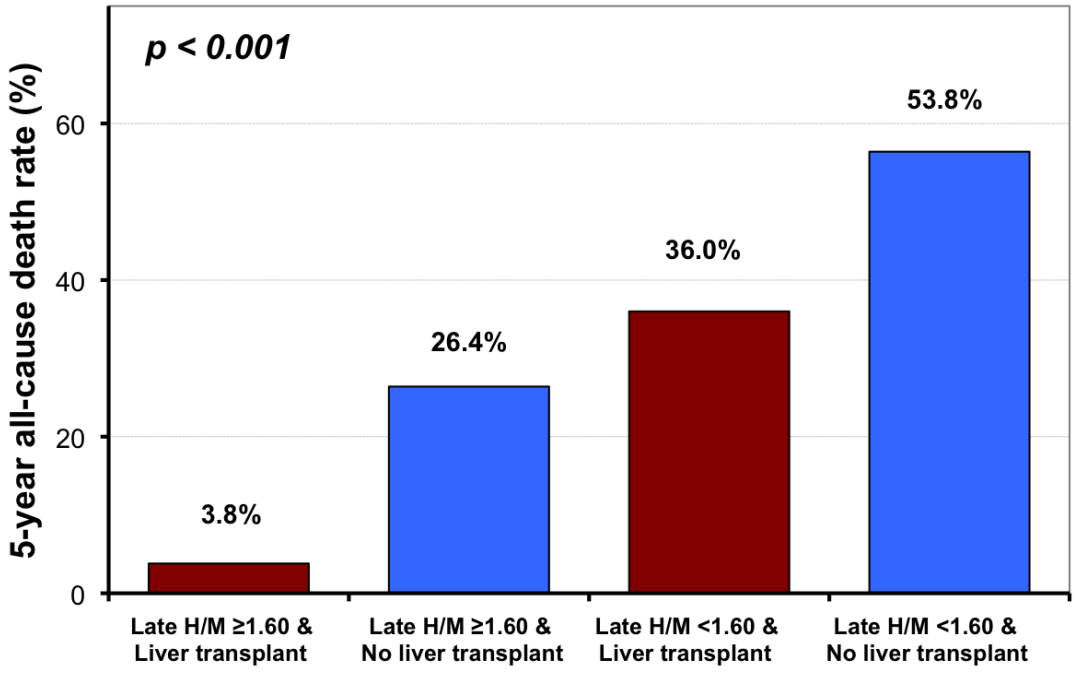
* Reference class: onset of disease <50 years; † Reference class: neurophysiological score=0. ‡ Reference class: without Holter abnormalities; § Reference class: normal BP as defined by mean daytime BP <140/90 mmHg and nighttime BP <125/75 mmHg. ¶ Reference class: normal dipper pattern as defined by nocturnal systolic BP fall ≥10%. ♯ Reference class: LV wall <12mm and mitral E/A 1.0 to 2.5

RESULTS

- **Characterization of the phenotypic spectrum of V30M-TTR:** neurological *versus* cardiovascular involvement
- **Prognostic stratification:** prediction of long-term mortality
- **MIBG imaging and liver transplantation outcome**

^{123}I MIBG Imaging for Prediction of the Outcome after Liver Transplantation

5-Year Mortality According to Liver Transplant and H/M ^{123}I-MIBG Uptake Ratio



Mean survival ± SE (years)	10.1 ± 0.4	8.3 ± 1.3	5.8 ± 0.9	4.4 ± 0.8

- Long-term mortality after liver transplantation differed significantly according to the late H/M assessed before transplantation.
- Patients with late H/M <1.60 were at higher risk of unfavourable outcome, however they still benefited from the procedure.

CONCLUSIONS

1. **Cardiovascular abnormalities antedated the neurological involvement** in a large series of symptomatic and asymptomatic V30M-TTR mutation carriers.

2. Abnormalities in the **ECG, Holter, ABPM** and **echo** are associated with higher long-term mortality but **are not independent prognostic markers.**

3. This study demonstrated, for the first time, that **cardiac sympathetic denervation detected by MIBG imaging is a useful prognostic marker** in V30M-TTR patients.

4. **Patients with late H/M MIBG uptake <1.60 have a 7 times higher risk of death**. However, those who were submitted to liver transplantation seemed to benefit from the procedure.