

# Noves perspectives terapèutiques en Amiloïdosi cardíaca

## Webinar Societat Catalana de Cardiologia



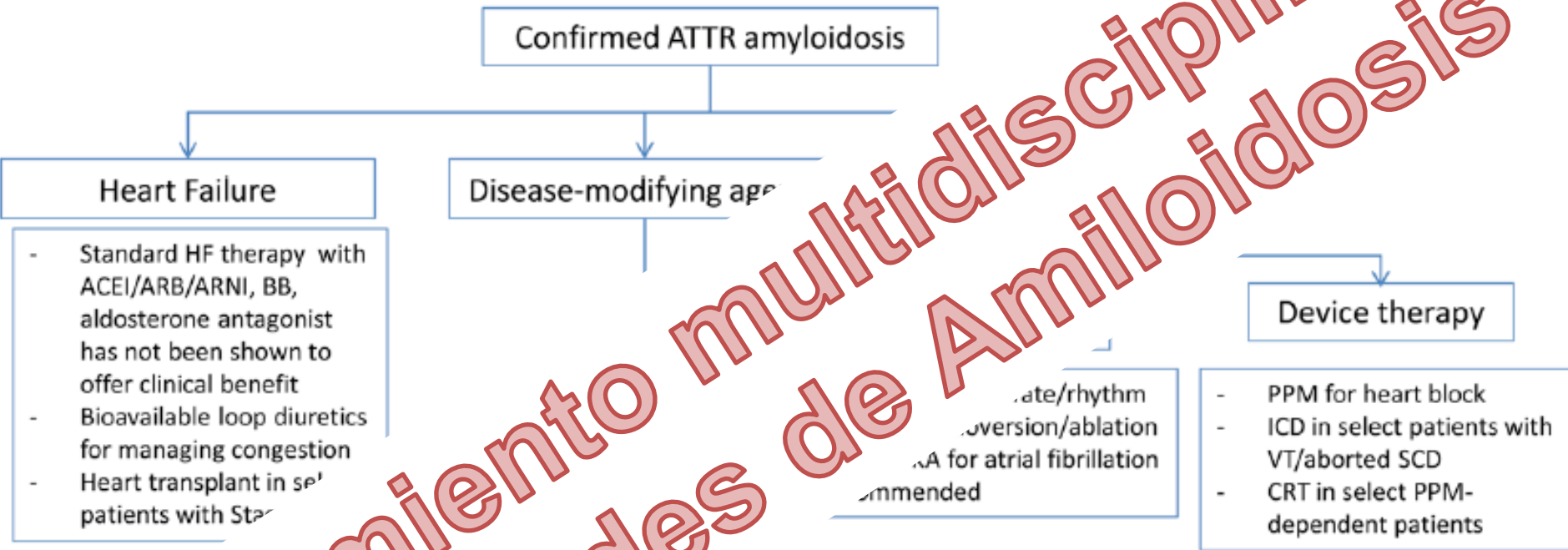
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# Tipos de Amiloidosis

- AL: Enfermedad hematológica por depósito de cadenas ligeras
  - Afectación cardíaca en 50% de casos
  - Supervivencia inferior a 1 año si IC
  - Tto: Tx médula ósea + TCO previo si afectación cardíaca significativa sin afect otros órganos
- ATTR: Depósito de TTR (90% viene del hígado)
  - PAF: Genética
  - Wild-type o senil: Esporádica. 25% en > 80 años
- AA: Inducida por inflamación crónica
  - Afectación cardíaca con IC < 1%

# Tratamiento cardiopatía amiloidótica ATTR

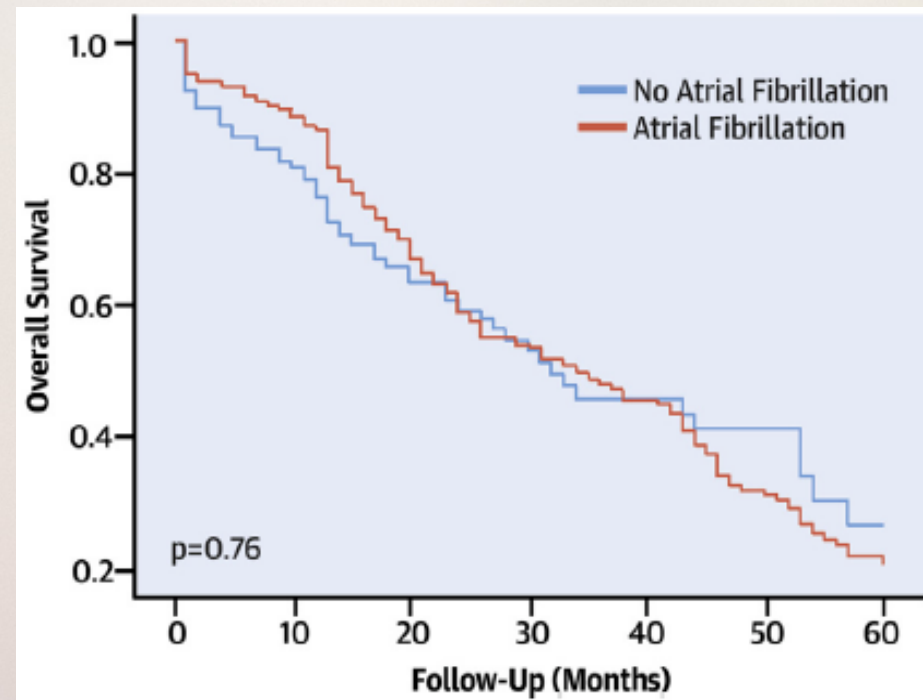
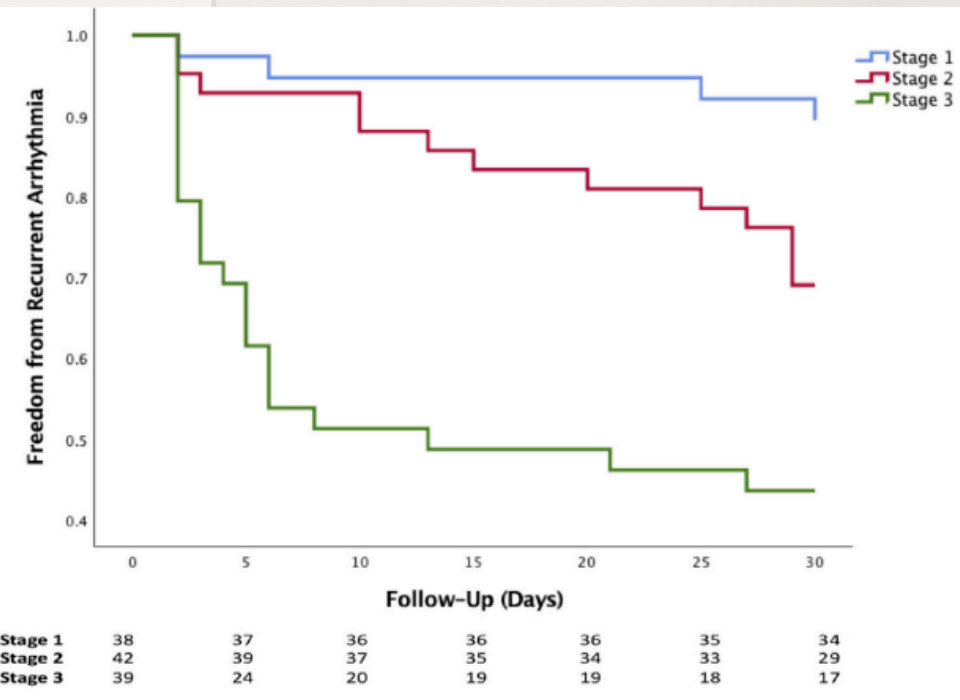
Tratamiento multidisciplinar en Unidades de Amiloidosis



ATTR es una enfermedad sistémica que puede dar lugar a insuficiencia cardíaca, renal, oftálmica, etc..



# Prevalencia FA >50% en CA TTR sobre todo en WT



Se prefiere amiodarona para control del ritmo y OJO con bbloq y digoxina para control de FC

# Predictores de BAV alto grado en CA TTR

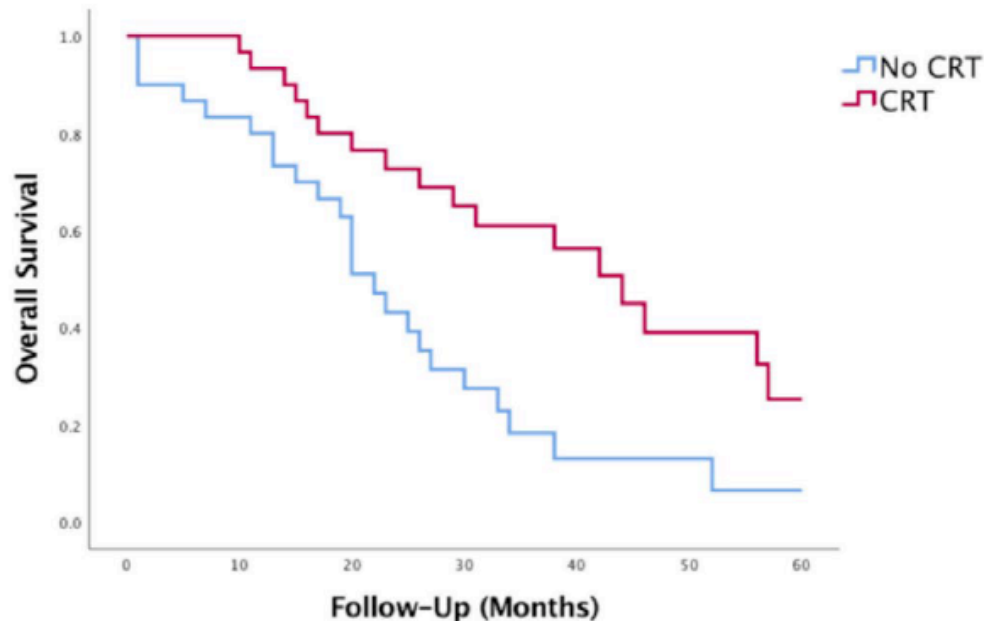
Univariable and multivariable Cox regression analyses for the development of high-grade AV block

Variable	Univariable		Multivariable	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	0.99 (0.96-1.03)	0.61		
ATTR-CA stage	1.18 (0.79-1.77)	0.41		
eGFR	1.01 (0.99-1.04)	0.26		
Obstructive CAD	1.58 (0.82-3.03)	0.17		
Digoxin use	0.28 (0.04-2.02)	0.21		
Beta blocker use	1.26 (0.68-2.34)	0.46		
hATTR-CA	0.81 (0.41-1.61)	0.55		
Diabetes mellitus	1.18 (0.58-2.4)	0.65		
Normal sinus rhythm	0.34 (0.19-0.63)	0.001	0.39 (0.21-0.73)	0.003
Atrial fibrillation	2.27 (0.89-5.8)	0.09	1.97 (0.77-5.05)	0.16
PR interval $\geq$ 200 msec	0.73 (0.28-1.9)	0.52		
QRS duration $\geq$ 120 ms	5.2 (2.2-12.37)	<0.001	4.71 (1.97-11.26)	<0.001
QRS duration <100 msec	0.15 (0.055-0.43)	<0.001	0.17 (0.06-0.49)	0.001
Ejection fraction	0.99 (0.97-1.01)	0.3		
LV mass index	1.0006 (0.997-1.02)	0.2		

BAV avanzado no predijo la supervivencia, sólo el estadio de la Clínica Mayo

# ¿TRC en pacientes con CA TTR?

Variable	No CRT (n=30)	CRT (n=30)	p-value
Age (Years)	76±7	76±7	0.99
Male Sex	27 (90%)	27 (90%)	0.99
Wild-Type ATTR	10 (33%)	10 (33%)	0.99
ATTR-CA Stage	2.2±0.7	2.1±0.6	0.17
NYHA Class	2.6±0.6	2.9±0.7	0.7
Native QRS Duration (msec)	128±36	147±33	0.04
Left Bundle Branch Block	4 (13%)	18 (60%)	<0.001
Atrial Fibrillation	23 (77%)	29 (97%)	0.03
Obstructive CAD	9 (30%)	6 (20%)	0.28
Beta Blocker	10 (33%)	7 (23%)	0.57
ACE/ARB	5 (17%)	1 (3%)	0.2
Aldosterone Antagonist	8 (27%)	10 (33%)	0.78
Tafamidis	1 (3%)	3 (10%)	0.61
NT-proBNP (pg/mL)	6954±8840	9417±13459	0.44
eGFR (ml/min/1.73m <sup>2</sup> )	46±15	44±14	0.59
LV Mass Index (g/m <sup>2</sup> )	163±27	188±48	0.11
Ejection Fraction (%)	34±9	33±15	0.73



At Risk:

No CRT	30	25	13	7	2	2	1
CRT	30	29	22	16	11	6	3

# Tratamiento específico amiloidosis TTR

## Suppression of TTR

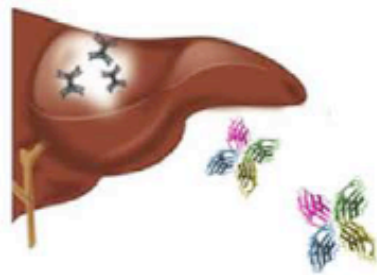
- Liver Transplantation
- TTR Gene silencers (Patisiran/Inotersen)

## TTR Stabilization

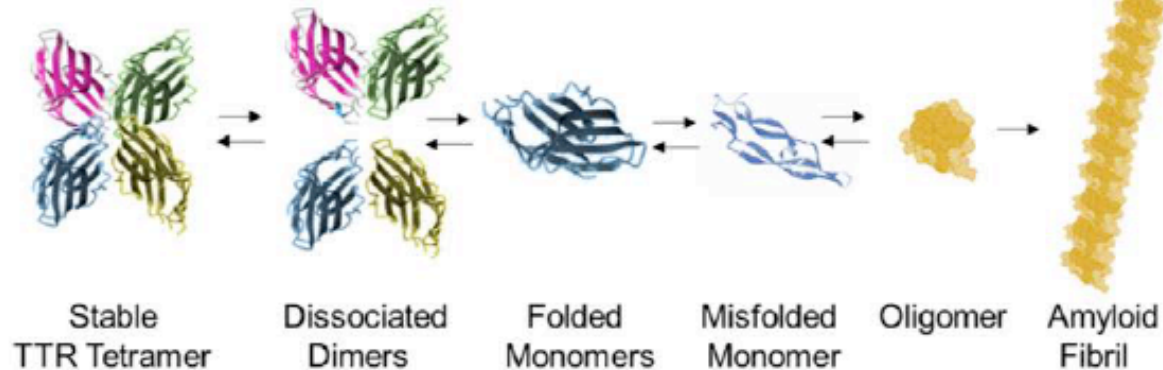
- Tafamidis
- Diflunisal
- Green Tea
- AG10

## TTR disruption/resorption

- Doxycycline/TUDCA
- Monoclonal antibodies

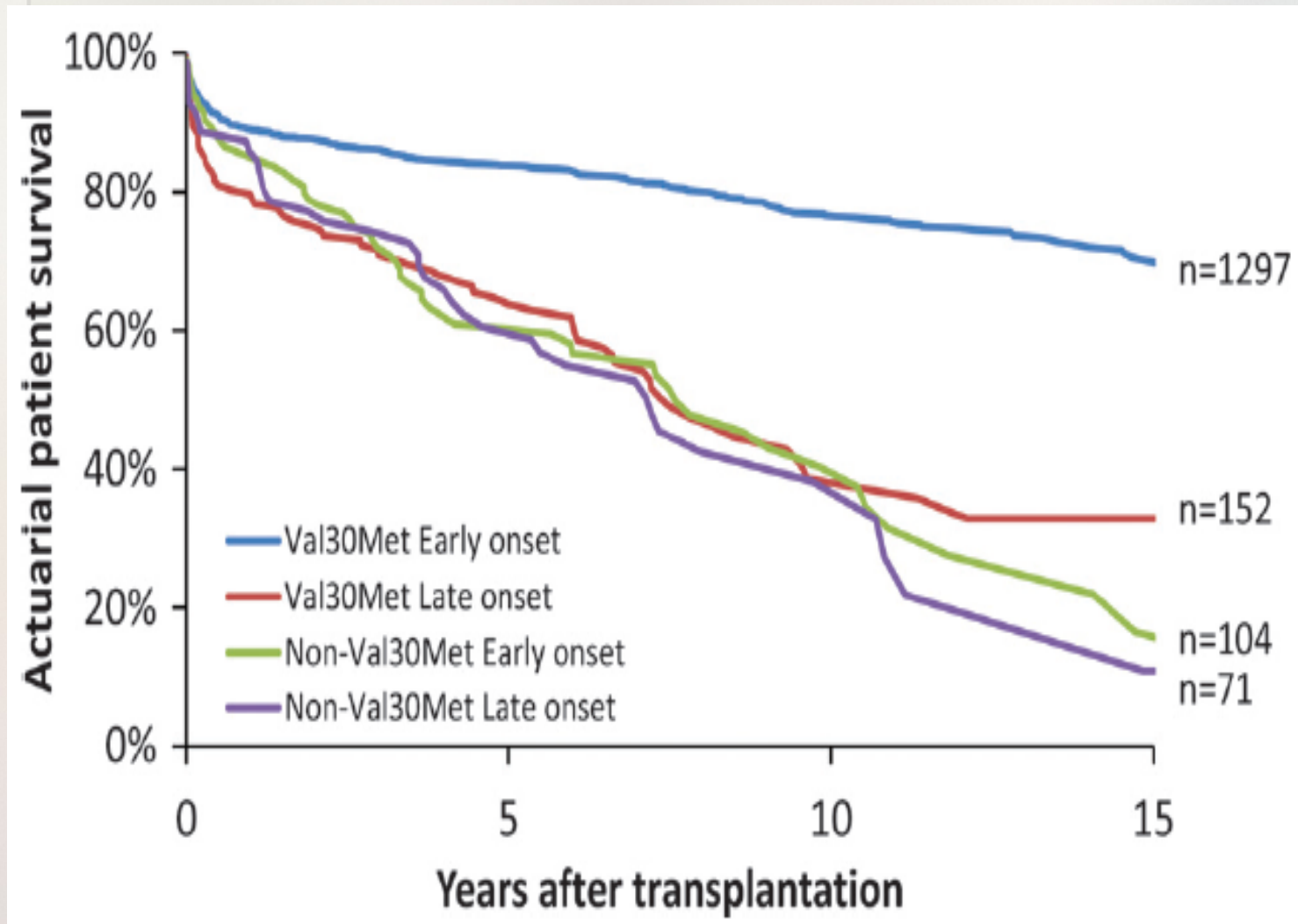


Liver





# Trasplante hepático





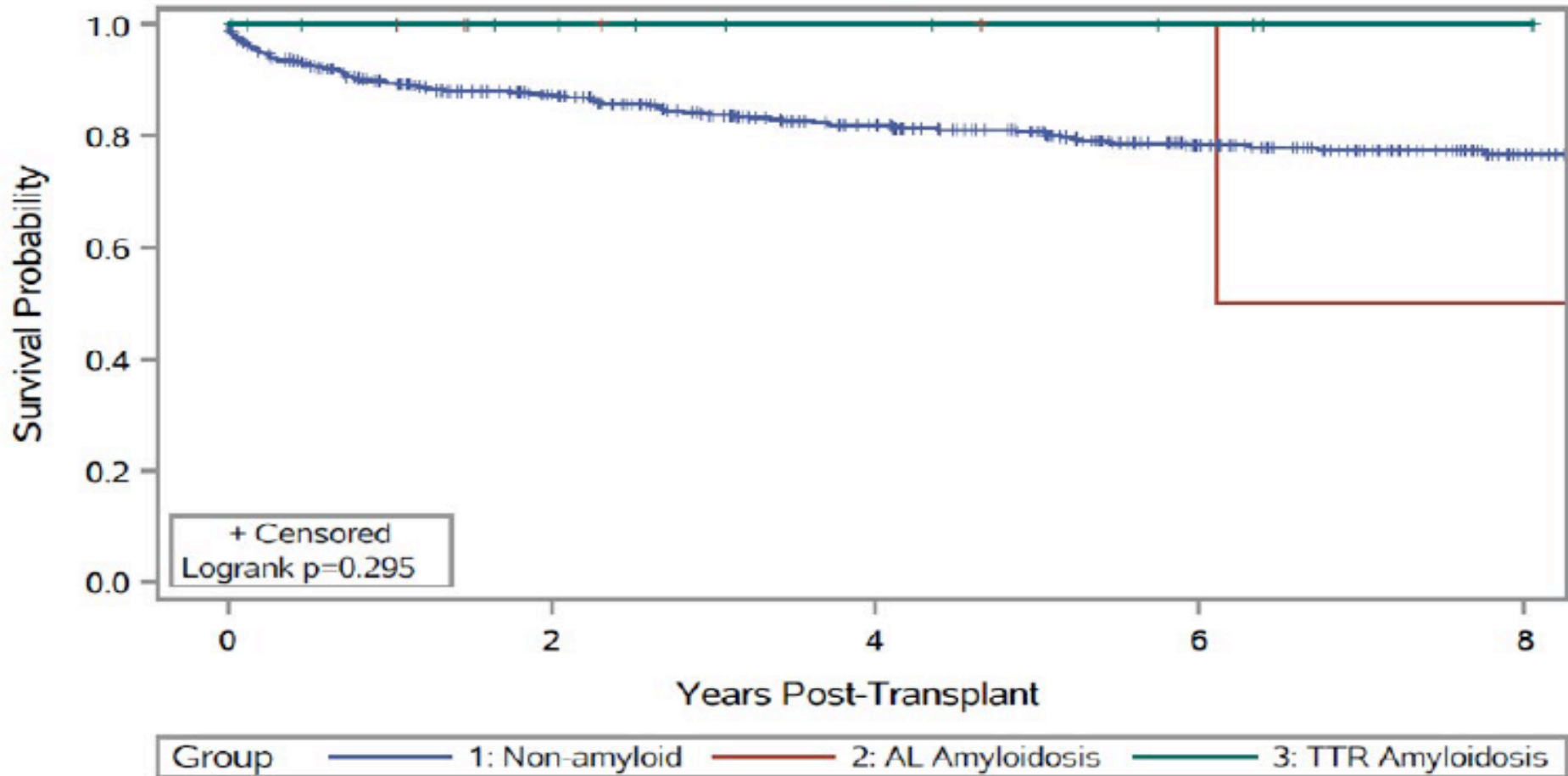
# ¿Trasplante hepático, cardíaco o doble ante cardiomiopatía por ATTR?

- Depende de la mutación y de la afectación extracardíaca

Age (years) /sex	NYHA-FC	Mutation type	Neuropathy	Clr.Creat. mL/min.	Bilirubin mg/dL	HTx year	Organs transplanted	Dead/days follow-up
45/M	IV+IABP	Unknown	No	37	2.0	1990	Heart	Yes/2290
66/M	III	Val122	No	>60	1.8	2001	Heart	No/2553
70/M	III	Val122	No	38	2.0	2003	Heart	No/1860
60/F	III	Unknown	Yes	>60	-	2003	Heart	Yes/510
63/M	III	Met30	Yes	>60	1.3	2005	Heart	Yes/3
37/F	III	Gli47	Yes	>60	0.7	2005	Heart and liver (later)	Yes/730
52/M	III	Glu89	Yes	>60	1.2	2005	Heart and liver (later)	No/875
60/F	III	Glu89	Yes	35	1.5	2005	Heart and liver (combined)	No/1123
62/M	III	Val122	Yes	>60	1.7	2007	Heart and liver (combined)	No/365
50/M	III	Lis89	No	>60	3.5	2008	Heart and liver (combined)	No/180

# TC en ATTR tiene buen pronóstico

Post-Transplant Survival in Era 2 (2008-2018)



Non-amyloid	538	387	297	194	107
AL Amyloidosis	6	4	3	2	1
TTR Amyloidosis	15	9	6	4	2

# Tafamidis en cardiopatía TTRm o wt

## ATTR-ACT

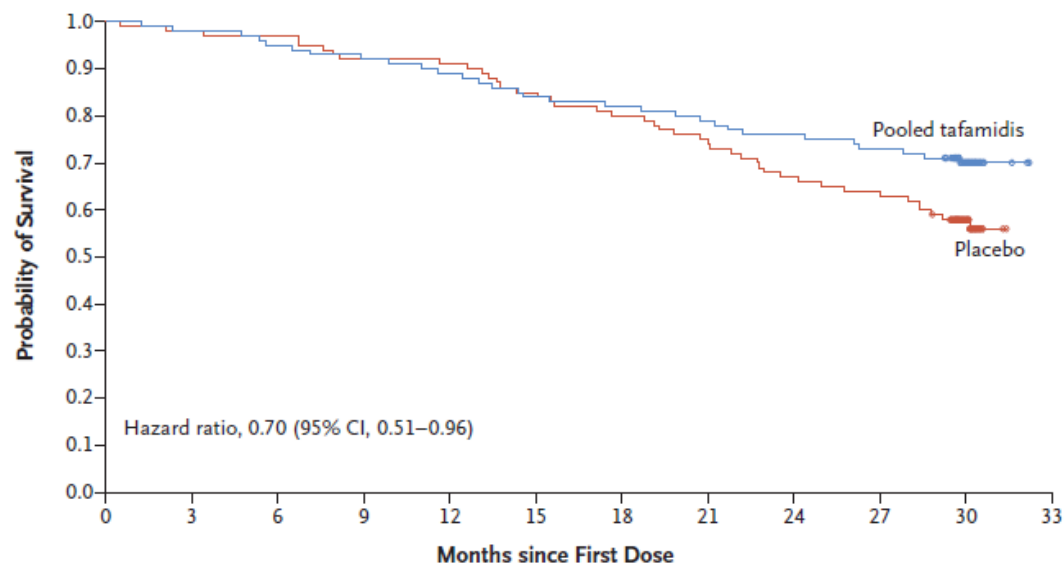
- 441 pacientes con miocardiopatía por ATTR y:
  - SIV > 12 mm
  - IC con hospitalización o necesidad de diurético
  - NTproBNP > 600 pg/ml
  - T6MIN > 100 metros
- Randomizados a Tafamidis 80 mg/día, 20 mg/día o placebo 2:1:2 estratificado por TTRm vs TTRwt y CF NYHA



**A Primary Analysis, with Finkelstein–Schoenfeld Method**

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 <i>no. (%)</i>	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 <i>per patient per yr</i>
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

**B Analysis of All-Cause Mortality**



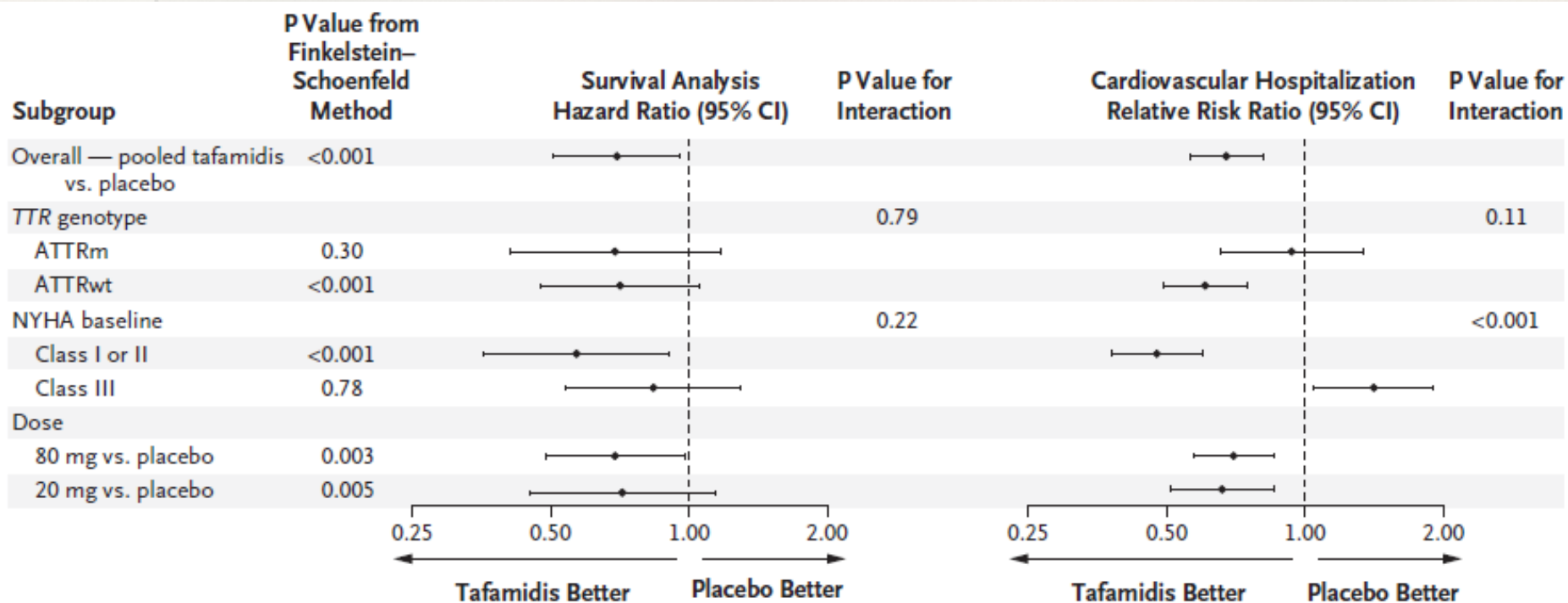
**No. at Risk (cumulative no. of events)**

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

**C Frequency of Cardiovascular-Related Hospitalizations**

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations <i>total no. (%)</i>	Cardiovascular- Related Hospitalizations <i>no. per yr</i>	Pooled Tafamidis vs. Placebo Treatment Difference <i>relative risk ratio (95% CI)</i>
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

# ATTR-ACT



Echocardiography Measure	Pooled Tafamidis (N = 264)	Placebo (N = 177)	Difference (tafamidis – placebo)	
			LS Mean	95% CI
Left ventricular end diastolic interventricular septal wall thickness — mm				
Baseline, mean (SD)	16.7 (3.8)	16.2 (3.5)		
Change from baseline at 30 months, LS mean (SE)	-0.11 (0.24)	0.33 (0.34)	-0.44 (0.34)	-1.11 to 0.23
Left ventricular posterior wall thickness — mm				
Mean (+/- SD) baseline value	17.0 (3.9)	16.7 (4.1)		
Change from baseline at 30 months, LS mean (SE)	0.92 (0.36)	1.19 (0.44)	-0.27 (0.65)	-1.55 to 1.01
Left ventricular ejection fraction — %				
Baseline, mean (SD)	48.4 (10.3)	48.6 (9.5)		
Change from baseline at 30 months, LS mean (SE)	-2.82 (0.85)	-4.34 (1.10)	1.51 (1.06)	-0.57 to 3.60
Left ventricular stroke volume — ml				
Baseline, mean (SD)	45.8 (16.1)	45.1 (16.9)		
Change from baseline at 30 months, LS mean (SE)	-5.38 (0.99)	-11.66 (2.09)	6.28 (2.20)	1.96 to 10.59
Circumferential mid global strain — %				
Baseline, mean (SD)	-16.4 (8.6)	-16.8 (9.6)		
Change from baseline at 30 months, LS mean (SE)	-0.77 (0.65)	1.91 (0.65)	-2.67 (0.78)	-4.20 to -1.15
Radial mid global strain — %				
Baseline, mean (SD)	17.8 (11.0)	17.6 (10.4)		
Change from baseline at 30 months, LS mean (SE)	0.25 (0.77)	-3.28 (1.18)	3.53 (1.29)	1.00 to 6.06
Global longitudinal strain — %				
Baseline, mean (SD)	-9.3 (3.5)	-9.4 (3.6)		
Change from baseline at 30 months, LS mean (SE)	1.46 (0.28)	2.16 (0.33)	-0.70 (0.37)	-1.43 to 0.02

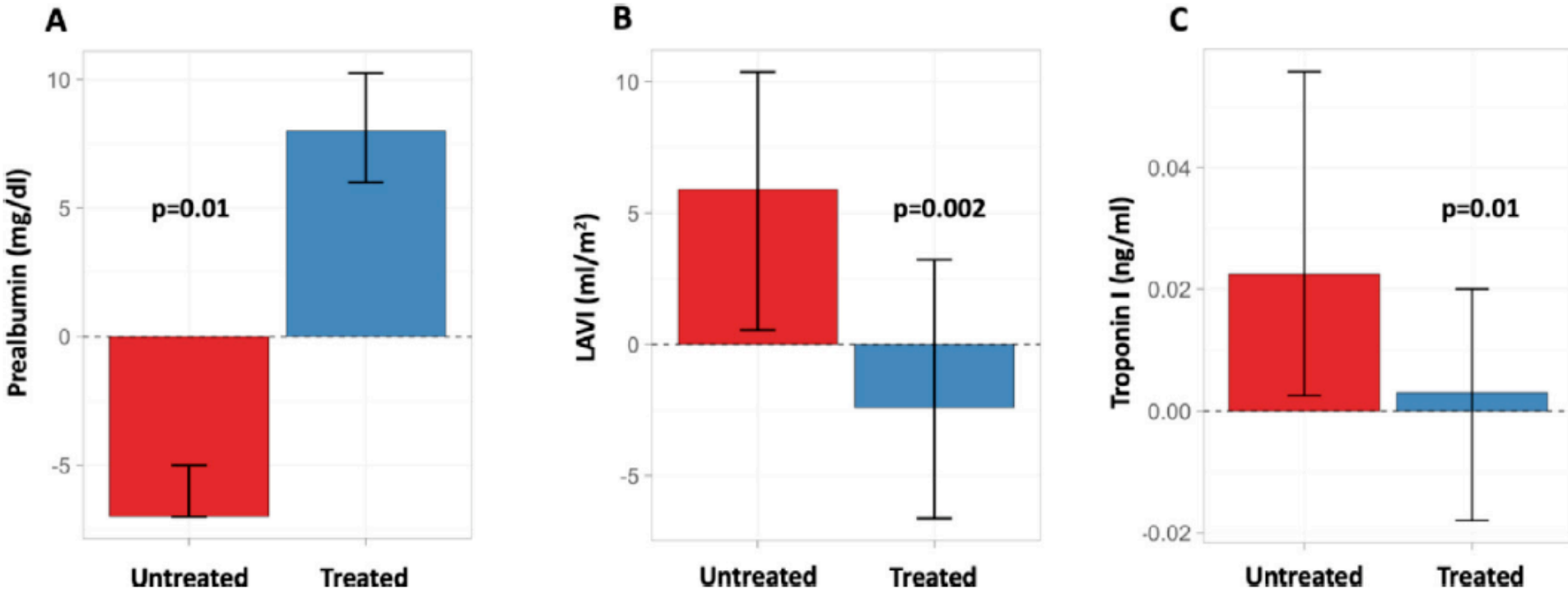


# Coste-eficiencia de Tafamidis

	Usual Care	Tafamidis
Healthcare outcomes		
Survival, life years*	3.46 (2.88–4.25)	5.43 (4.17–6.76)
Survival, life yearst	3.23 (2.73–3.84)	4.83 (3.82–5.79)
Incremental life yearst	Comparator	1.60 (0.48–2.47)
Quality-adjusted survival, quality-adjusted life-yearst	2.19 (1.94–2.56)	3.48 (2.85–4.15)
Incremental quality-adjusted life-yearst	Comparator	1.29 (0.47–1.75)
No. of cardiovascular hospitalizations	2.36 (1.87–3.02)	2.53 (1.78–3.43)
Direct healthcare costs		
Lifetime healthcare costs, 2019 US dollarst	126 000 (105 000–157 000)	1 262 000 (996 000–1 515 000)
Spending on tafamidis	—	1 086 000 (861 000–1 303 000)
Spending on cardiovascular hospitalizations	34 000 (26 000–46 000)	34 000 (23 000–47 000)
Background healthcare costs	92 000 (77 000–113 000)	142 000 (110 000–174 000)
Incremental healthcare costs, 2019 US dollarst	Comparator	\$1 135 000 (872 000–1 377 000)
Incremental cost-effectiveness ratio		
US dollars per life-year gained	Comparator	\$709 000 (547 000–1 943 000)
US dollars per quality-adjusted life-year gained	Comparator	\$880 000 (697 000–1 564 000)

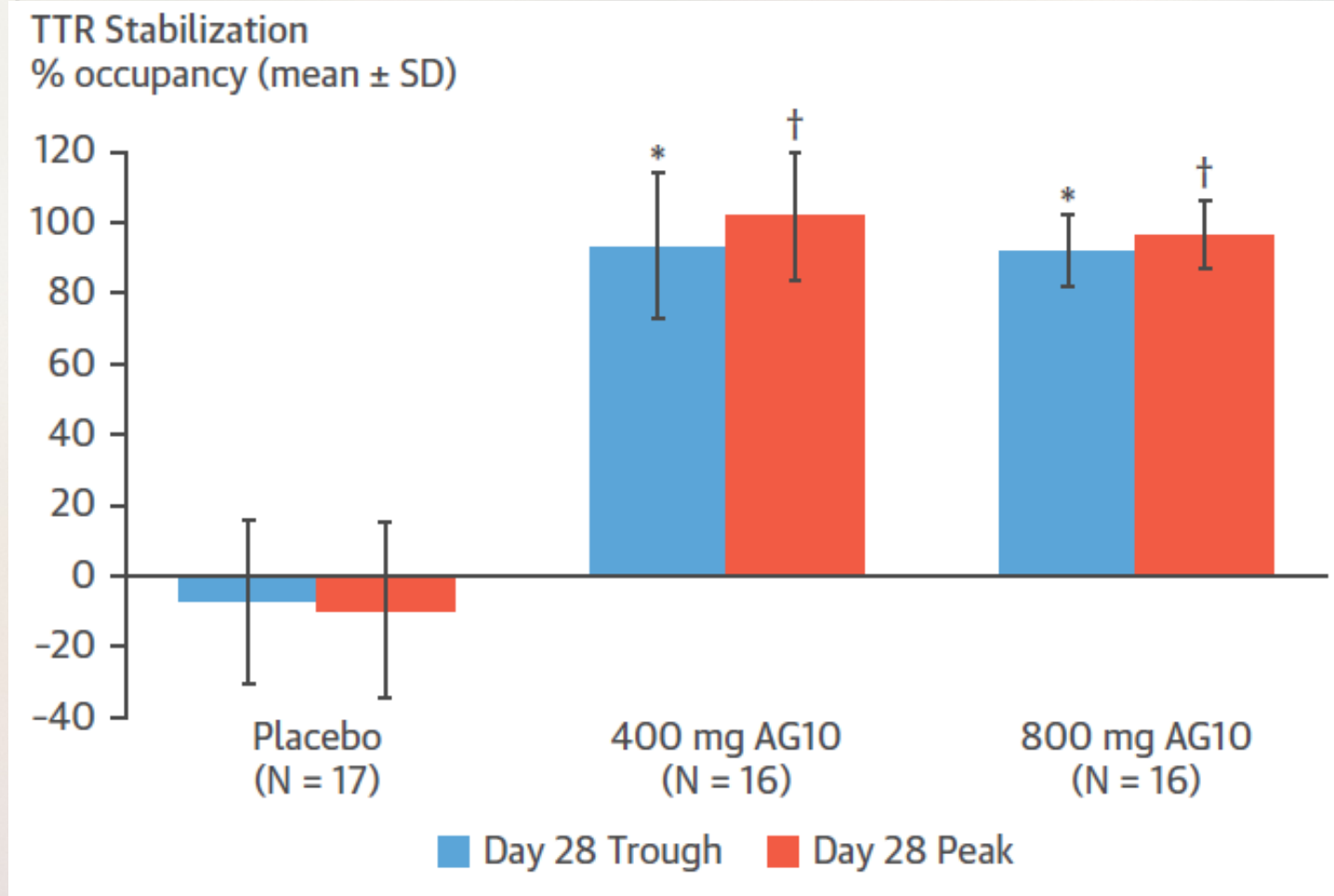
# Diflunisal 250 mg/12 h en CA TTR

## Estudio retrospectivo no randomizado



Efectos secundarios: Trombocitopenia e insuficiencia renal  
Ventaja: Coste 60 Euros/mes

# AG10: Ensayo clínico fase 2



Aumenta los niveles de TTR y la estabilidad de la misma sin eventos adversos significativos



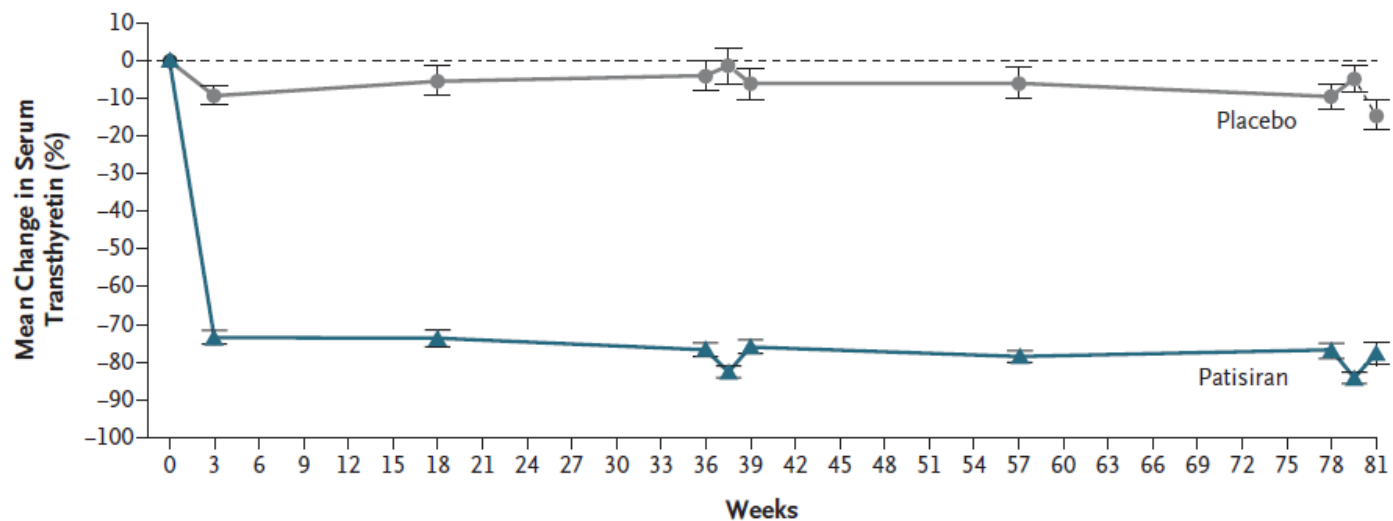
# Patisiran (silenciador RNAm)

## Estudio APOLLO

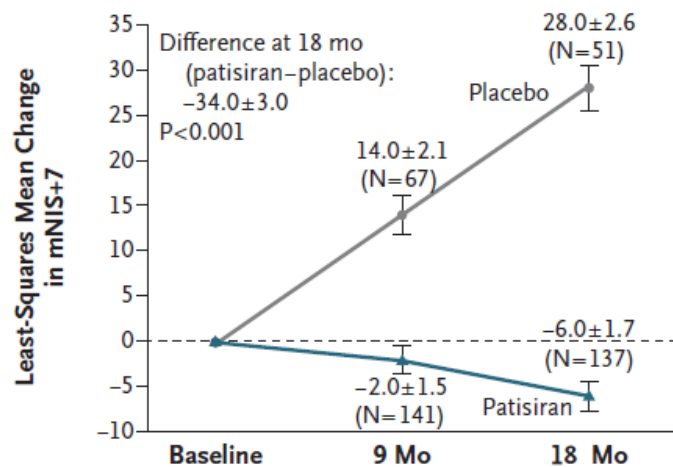
- 225 pacientes con PNP por ATTR randomizados a Patisiran 0.3 mg/kg ev/3 semanas vs placebo 2:1 y estratificada por NIS, Val30Met precoz y uso previo de estabilizadores TTR
- Premedicación: Dexametasona 10 mg, Paracetamol 500 mg, Difenhidramina 50 mg y Ranitidina 50 mg
- Suplementos con Vitamina A
- Subgrupo cardiológico (SIV>13 mm sin causa clara)

# Patisiran en estudio APOLLO

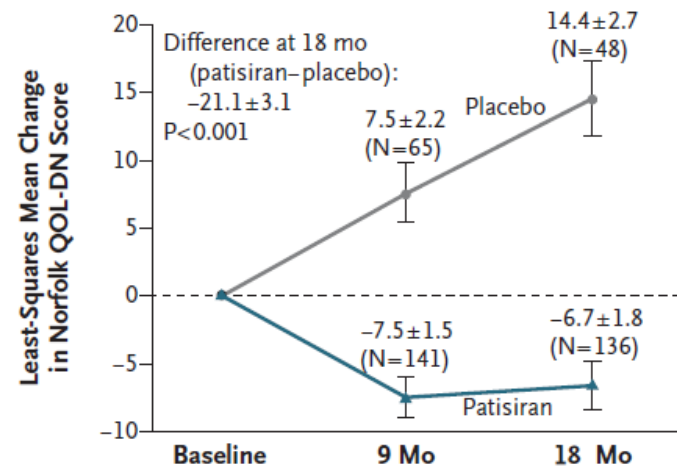
**A Serum Transthyretin**



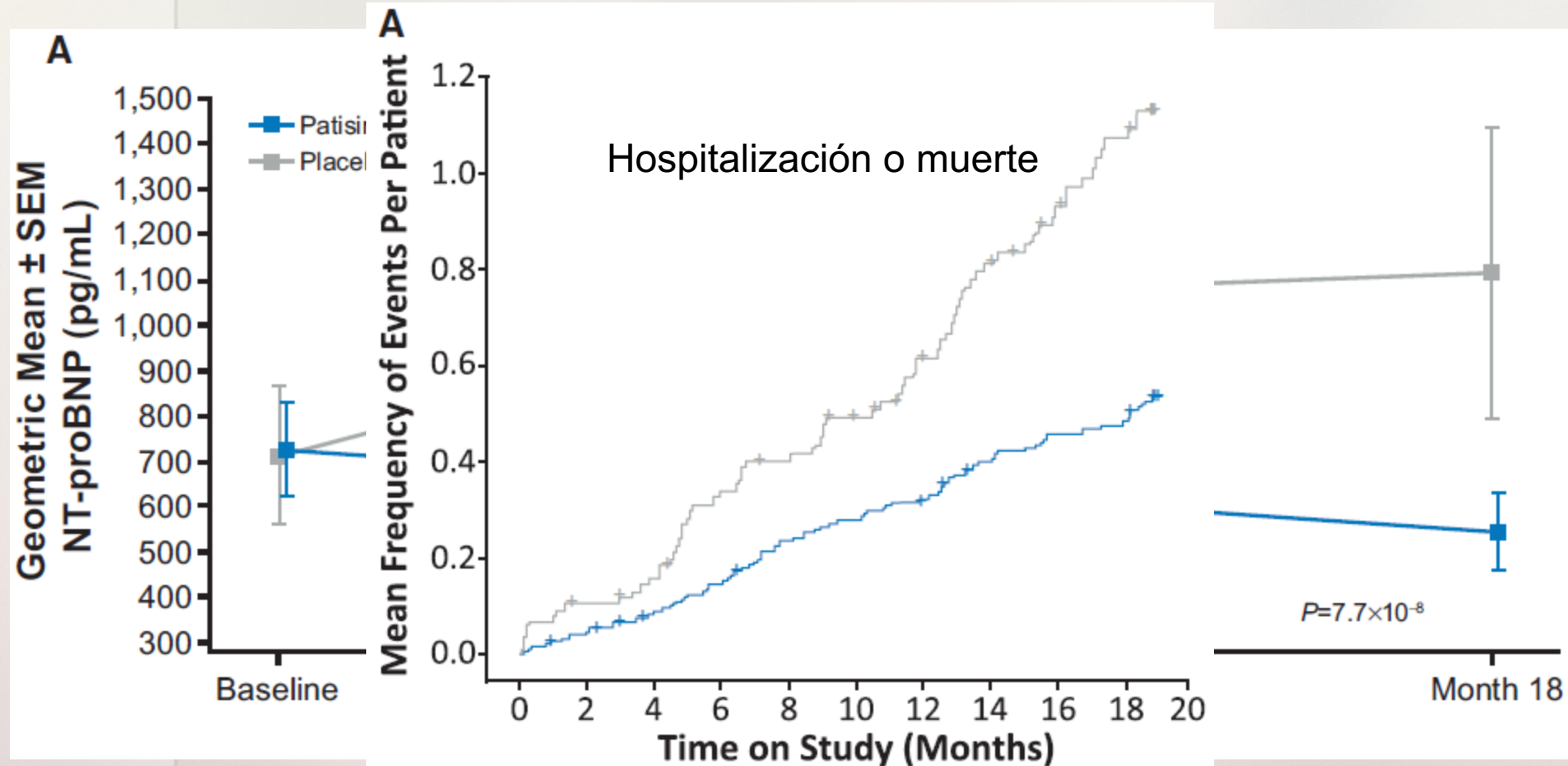
**B mNIS+7**



**C Norfolk QOL-DN Score**



# Subestudio cardiaco APOLLO



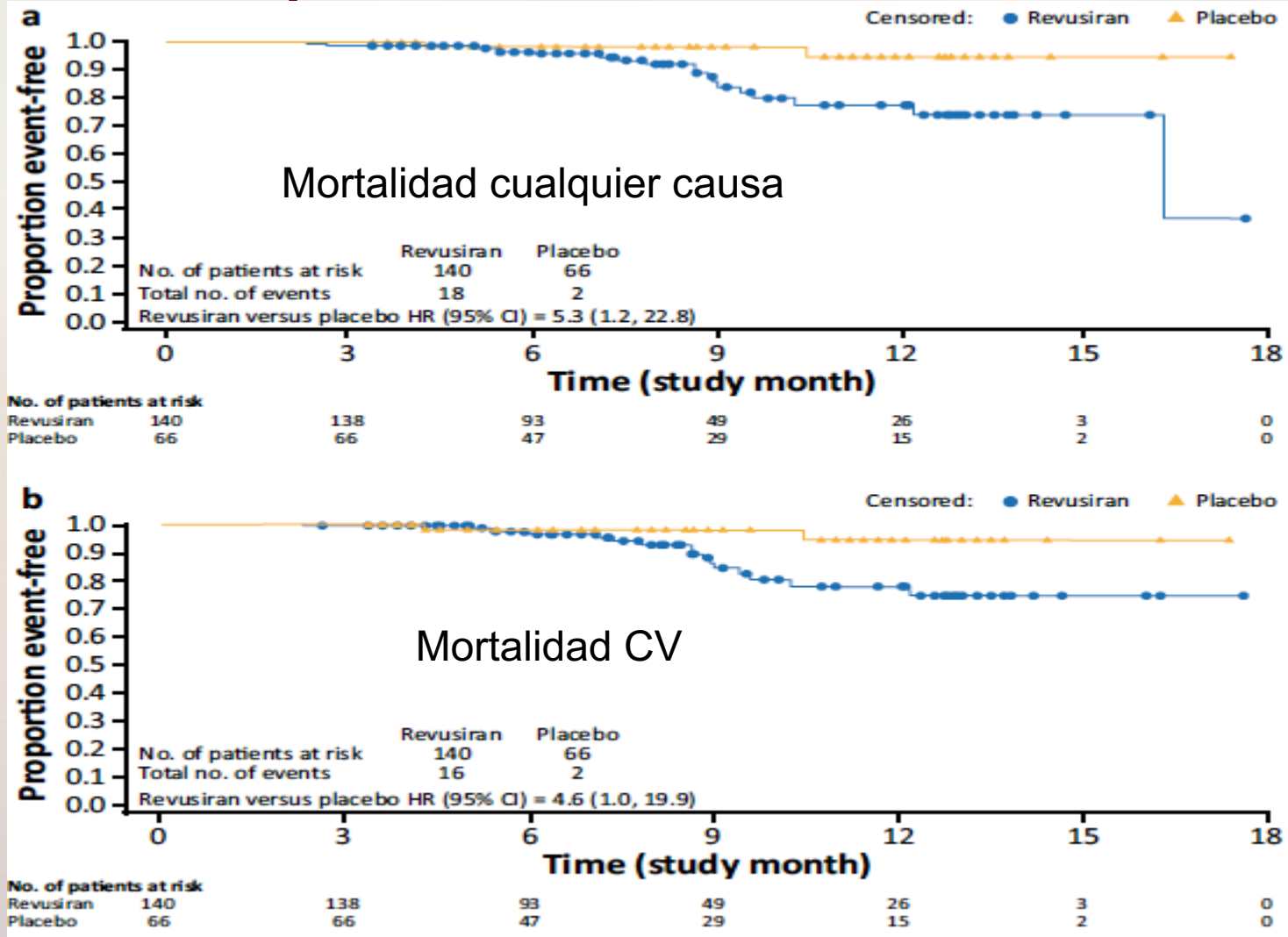


# Causas de muerte en estudio APOLLO

Treatment group	Causes of death
Patisaran (n=7; 4,7%)	
Patient 1	Cardiac arrest, cardiac failure
Patient 2	Sudden cardiac death
Patient 3	Sudden cardiac death
Patient 4	Cardiac failure, acute pulmonary edema
Patient 5	Cardiac arrest
Patient 6	Pulseless electrical activity
Patient 7	Cardiac failure
Placebo (N=6; 7,8%)	
Patient 1	GI hemorrhage
Patient 2	Staphylococcal sepsis
Patient 3	Anemia, GI hemorrhage (complicated by heart failure)
Patient 4	Acute kidney failure, UTI, bacteremia
Patient 5	Colorectal cancer metastatic
Patient 6	Ischemic stroke

**Ojo!!**

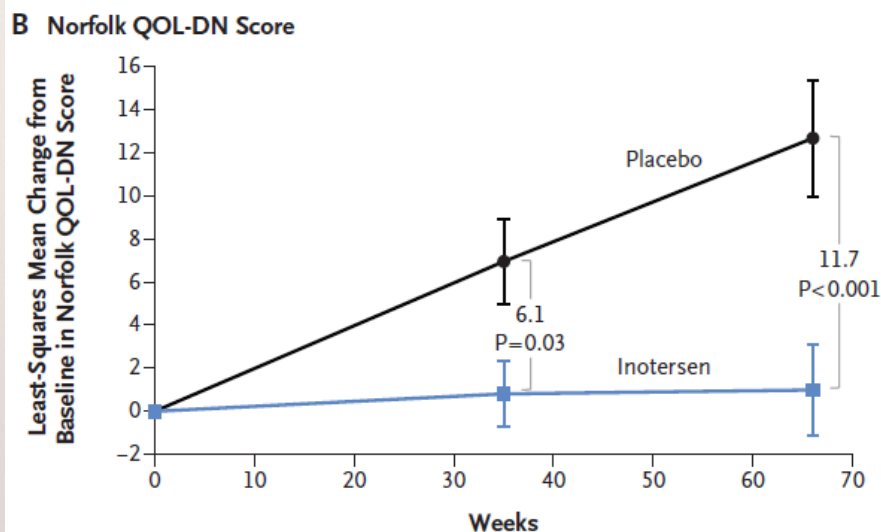
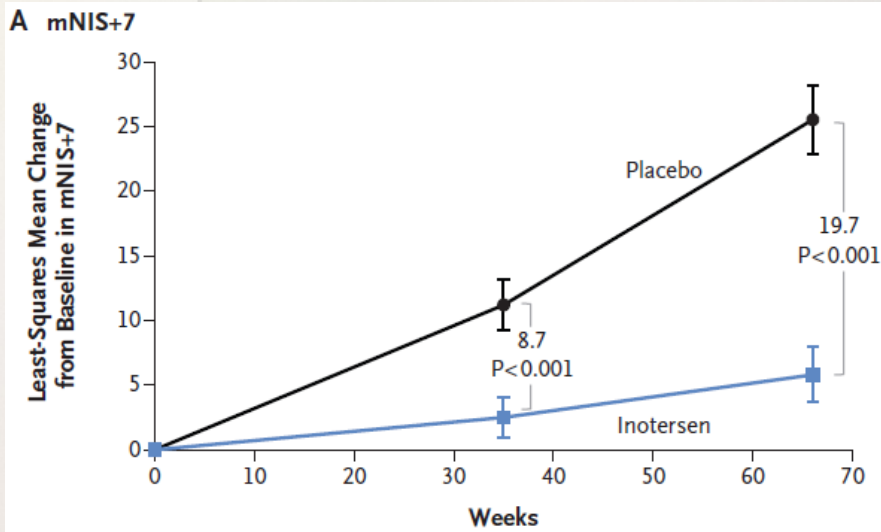
# Revusiran en CA TTR (ENDEAVOUR) parado por exceso mortalidad CV



# Inotersen (oligonucleótido antisentido) NEURO-TTR

- 172 pacientes con PNP por ATTR randomizados a Inotersen 300 mg sc/semana vs placebo 2:1 estratificados por Val30Met, estadio 1 vs 2, tto previo con estabilizadores TTR
- Edad media: 59 años
- Val30Met 52%
- Estadio PAF I: 67%
- Presencia miocardiopatía: 63%

# Inotersen (NEURO-TTR trial)



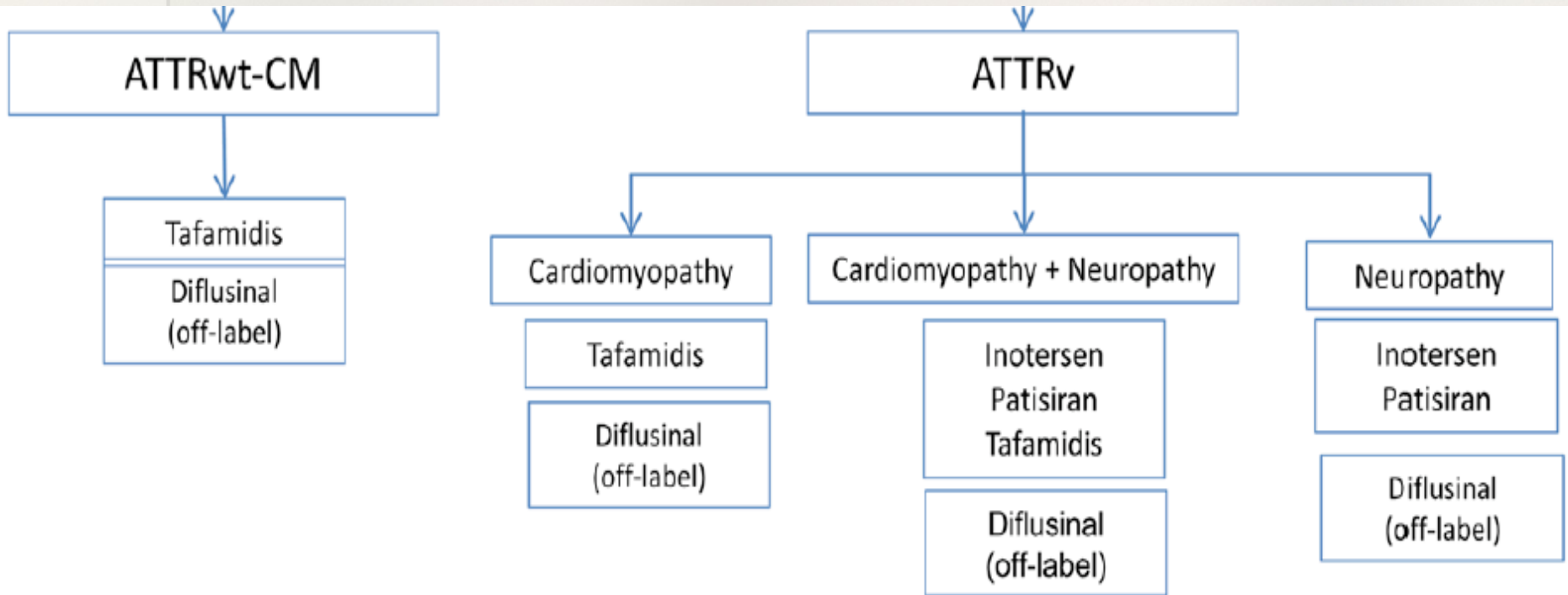
**Table 2. Summary of Adverse Events.\***

Event	Placebo (N = 60)	Inotersen (N = 112)
	<i>no. of patients (%)</i>	
Any adverse event	60 (100)	111 (99)
Event related to trial regimen†	23 (38)	87 (78)
Any serious adverse event	13 (22)	36 (32)
Event related to trial regimen†	1 (2)	8 (7)
Glomerulonephritis	0	3 (3)‡
Thrombocytopenia	0	2 (2)
Deep-vein thrombosis	1 (2)	1 (<1)
Intracranial hemorrhage	0	1 (<1)§
Tubulointerstitial nephritis	0	1 (<1)¶
Pulmonary embolism	0	1 (<1)
Embolic stroke	0	1 (<1)
Myelopathy	0	1 (<1)
Death	0	5 (4)

**Ojo!!**



# Tratamiento específico amiloidosis TTR



# Conclusiones

- Equipo multidisciplinar para el tto de la amiloidosis TTR
- Ajustar el tto medico y de dispositivos
- En pacientes con CA TTR hereditaria y Neuropatía podemos iniciar tto con silenciadores de RNAm o Tafamidis
- Tafamidis pendiente de aprobación en España para CA TTR hereditarian y wild-type
- Ensayos clínicos en marcha con silenciadores y AG10 en CA TTR
- TC +/- hepático en CA TTR avanzada



# Gracias

