

# ATTR-CM: casuïstiek en behandelopties

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# Disclosures

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## Diagnosis

Heart Failure with Preserved Ejection fraction  
based on **wild-type aTTR amyloidosis**




# Diagnosis HFpEF

**Table 3.1** Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides <sup>b</sup> ; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides <sup>b</sup> ; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).



# Specific etiologies of HFpEF

Genetic testing (e.g. for ATTR amyloidosis and HCM; see also section 5.10.1)
Bence-Jones proteinuria (AL amyloidosis)
99mTc-DPD scintigraphy (wild-type transthyretin amyloidosis) 
Eosinophilia, IL-2 receptor, ACE (sarcoidosis)
Hs troponin, CK, CK-MB (myocarditis)
<i>Borellia burgdorferi</i> IgM (borreliosis)
HIV serology (HIV cardiomyopathy)
<i>Trypanosoma cruzi</i> serology (Chagas disease)
Serum ferritin, genetic testing (haemochromatosis)

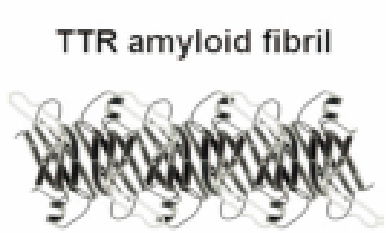
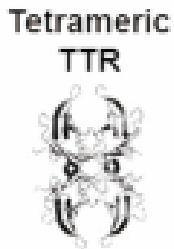
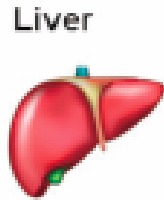
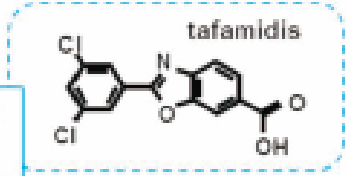


# Behandeling ATTRwt

## Current treatment

Liver transplantation  
(1990 ~)

TTR stabilizer  
(2011 ~)

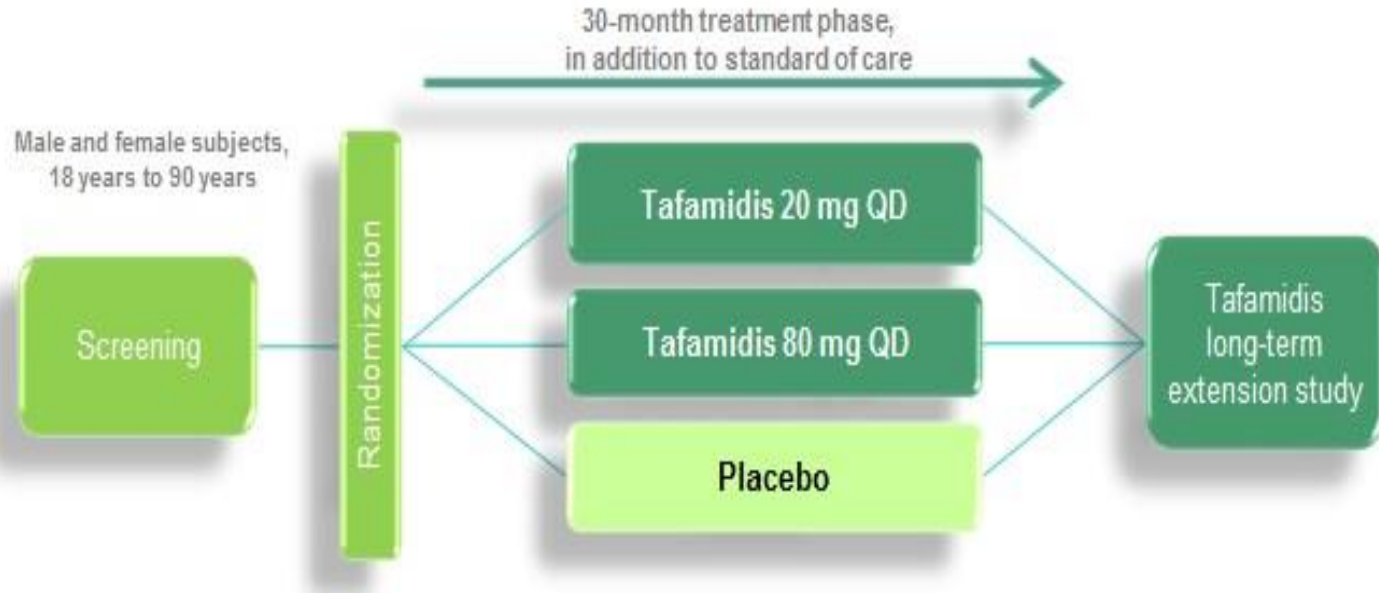


## Future treatment

Oligonucleotide-based therapy  
(in near future)



# ATTR-ACT Study Design



# Inclusion/Exclusion Criteria<sup>1</sup>

## • Key Inclusion Criteria

- Presence of amyloid deposits in biopsy tissue (cardiac or non-cardiac) and TTR precursor protein identification by mass spectrometry, immunohistochemistry or scintigraphy
- Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm
- A medical history of heart failure (HF) with at least 1 prior hospitalization for HF signs or symptoms of congestive HF requiring treatment with a diuretic for improvement
- NT-proBNP  $\geq 600$  pg/mL
- 6-Minute Walk Test distance >100 meters

## • Key Exclusion Criteria

- New York Heart Association (NYHA) class IV
- Glomerular filtration rate (eGFR) of <25 mL/min/1.73 m<sup>2</sup>

<sup>1</sup>Maurer MS, et al. Circ Heart Fail 2017;10.





# Efficacy Outcomes

- Primary efficacy analysis: hierarchical combination of all- cause mortality and frequency of cardiovascular-related hospitalizations comparing **pooled tafamidis data** with placebo
- Key secondary endpoints were change from Baseline to Month 30:
  - 6-minute walk test (6MWT)
  - Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score



# Baseline Demographic Characteristics

Characteristic	Pooled Tafamidis (N=264)	Placebo (N=177)
Age, mean (SD)	74.5 (7.2)	74.1 (6.7)
Male, n (%)	241 (91.3)	157 (88.7)
ATTRm, n (%)	63 (23.9)	43 (24.3)
ATTRwt, n (%)	201 (76.1)	134 (75.7)
Race, n (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)
Other	3 (1.1)	0



# Baseline Clinical Characteristics

Characteristic	Pooled Tafamidis (N=264)	Placebo (N=177)
LV ejection fraction, mean (SD)	48.4 (10.3)	48.6 (9.5)
Interventricular wall thickness, mean (SD)	16.7 (3.8)	16.2 (3.5)
LV posterior wall thickness, mean (SD)	17.0 (3.9)	16.7 (4.1)
LA anterior-posterior diameter size, mean (SD)	43.8 (7.0)	43.7 (6.1)
LV stroke volume mean (SD)	45.8 (16.1)	45.1 (16.9)
Global longitudinal strain, mean (SD)	-9.3 (3.5)	-9.4 (3.6)
NYHA Class, n (%)		
NYHA Class I	24 (9.1)	13 (7.3)
NYHA Class II	162 (61.4)	101 (57.1)
NYHA Class III	78 (29.5)	63 (35.6)
NT-proBNP, median (Q1, Q3)	2995.9 (1751.5, 4861.5)	3161.0 (1864.4, 4825.0)
Troponin I, median (Q1, Q3)	0.14 (0.09, 0.20)	0.14 (0.08, 0.19)

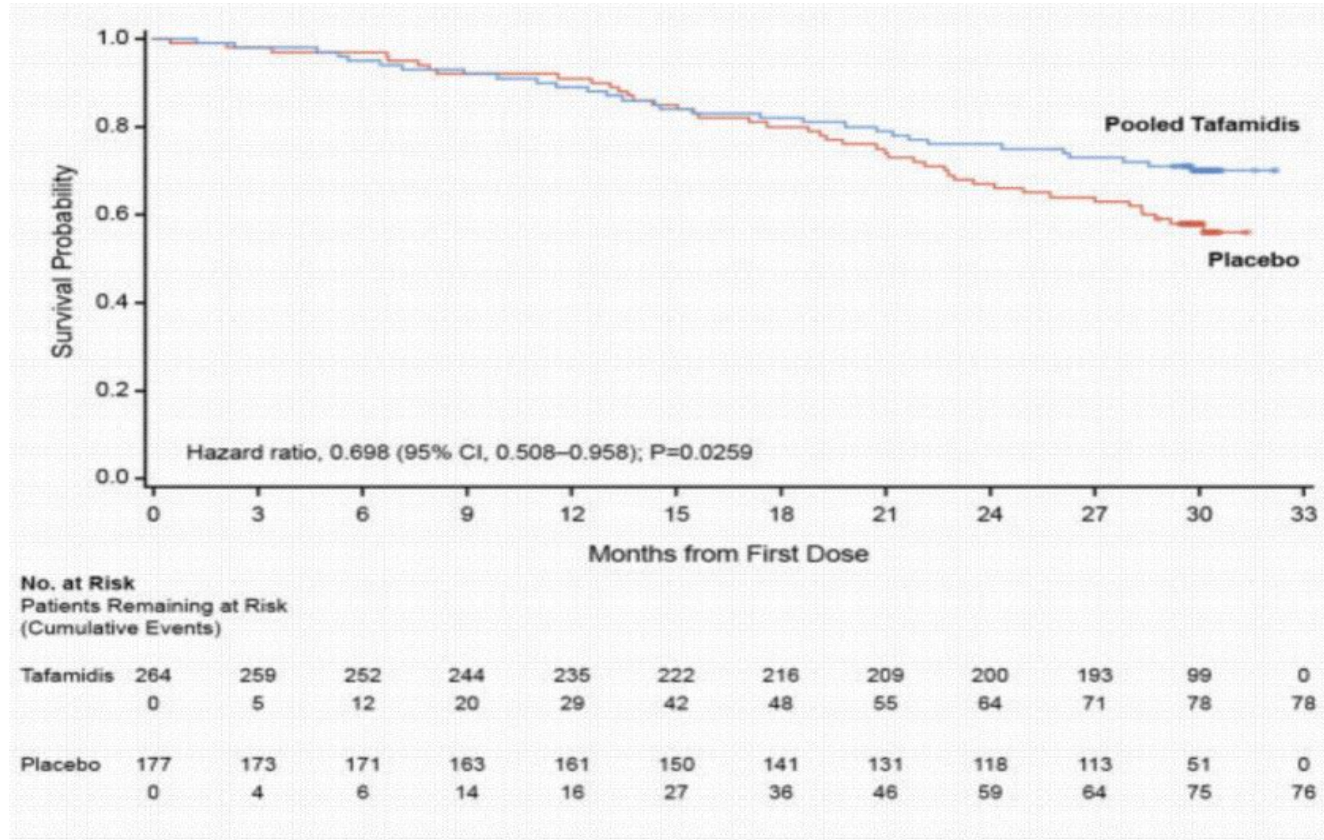


# Primary Analysis

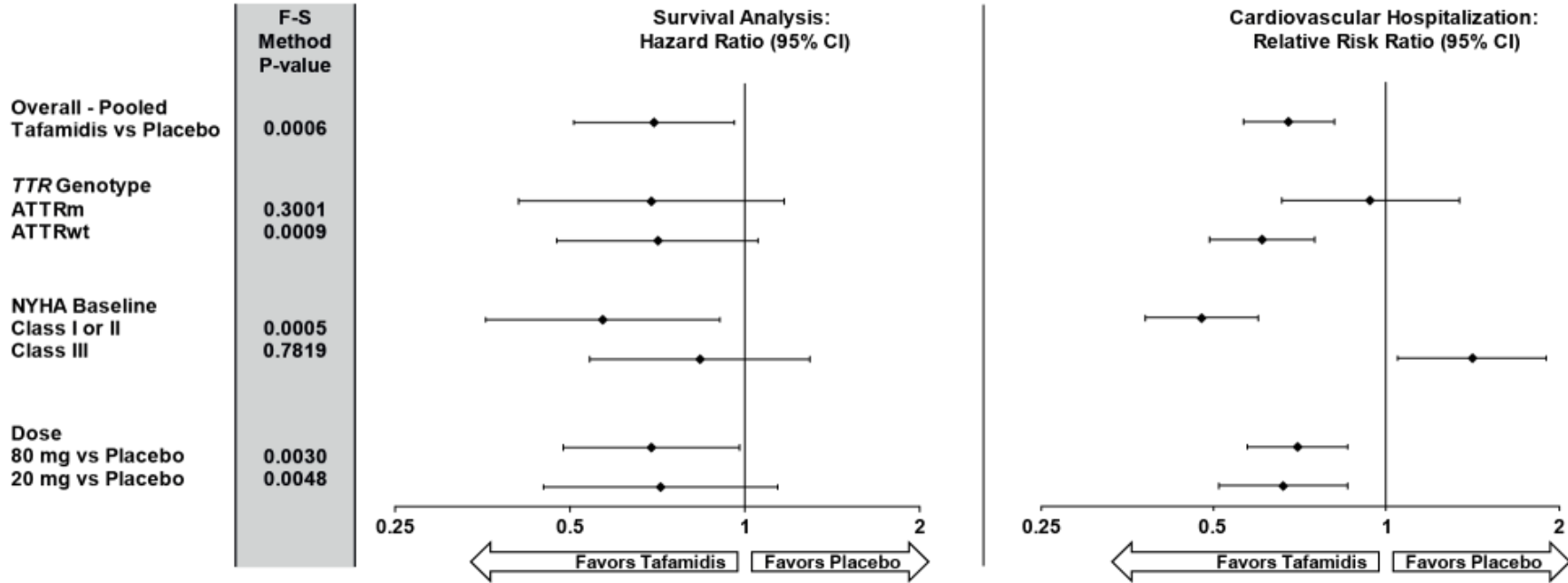
	Pooled Tafamidis n=264	Placebo n=177
<b>P-value from F-S method</b>		<b>0.0006</b>
Patients alive <sup>a</sup> at Month 30, n (%)	186 (70.5)	101 (57.1)
Average cardiovascular-related hospitalizations during 30 mo (per pt per yr) among those alive at Month 30	0.297	0.455



# All-Cause Mortality

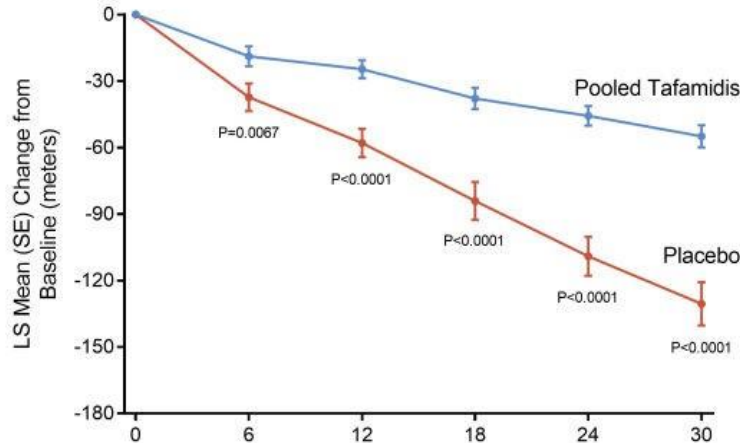


# Pre-specified Subgroup Results: All-cause Mortality, and CV-related Hospitalization



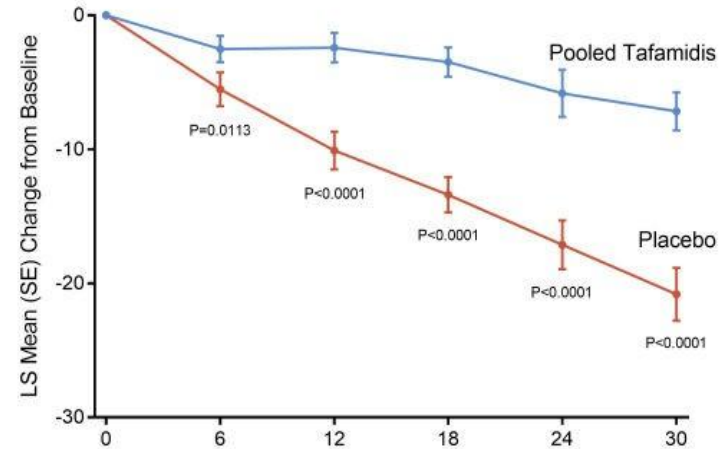
# Key Secondary Endpoints: 6-minute Walk Test and KCCQ-OS

6-Minute Walk Test Change from Baseline



No. of Patients	Month					
Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

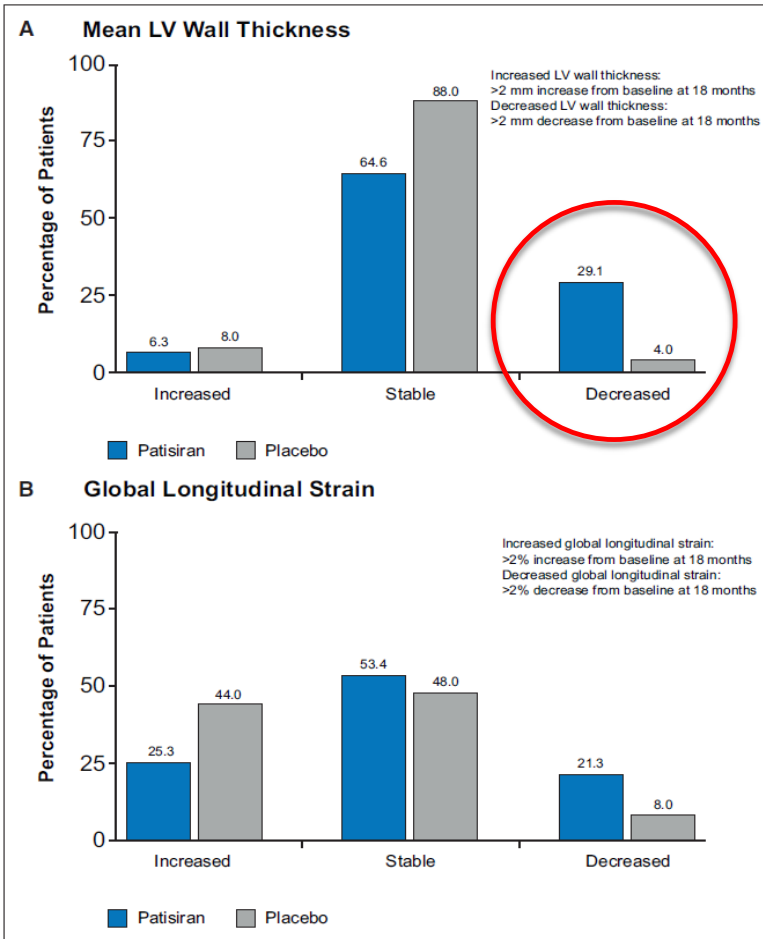
KCCQ-OS Change from Baseline



No. of Patients	Month					
Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84



# APOLLO trial – Patisiran; een RNA interference



Hereditary TTR

Substudy on cardiac effects

Decrease = LVWT < 2mm





# Conclusions

- Search for the etiology of HFpEF (aTTR / Fabry / atypical HCM / etc)
- Bone scintigraphy has a high sensitivity and specificity for aTTR
- AL needs to be excluded
- Genetic testing to exclude hereditary form
- aTTR = first steps in personalized medicine in HFpEF (tafamidis – patisiran)

