7e MASTERCLASS AMYLOSES CARDIAQUES
ÉVÉNEMENT HYBRIDE
PRÉSENTIEL & DISTANCIEL
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Comment adapter le traitement de nos patients à la vue d'ATTRIBUTE-CM ?

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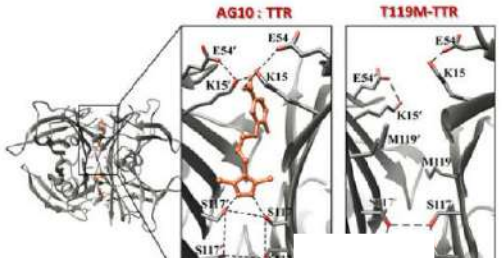
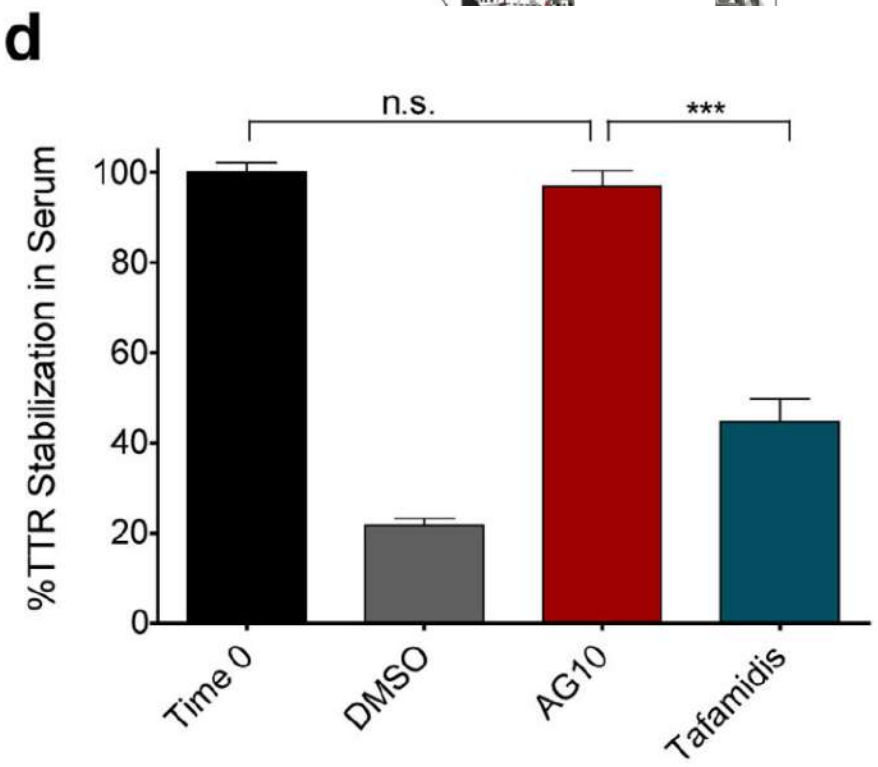
Conflits d'intérêts

- **Pfizer**
- **Alnylam**
- **Astra Zeneca**
- **Bayer**

Les promesses de l'Acoramidis



- La mutation TTR T119M est protectrice, empêche la dissociation du tétramère.
- Acoramidis mime la mutation.
- Stabiliserait mieux le TTR que le Tafamidis



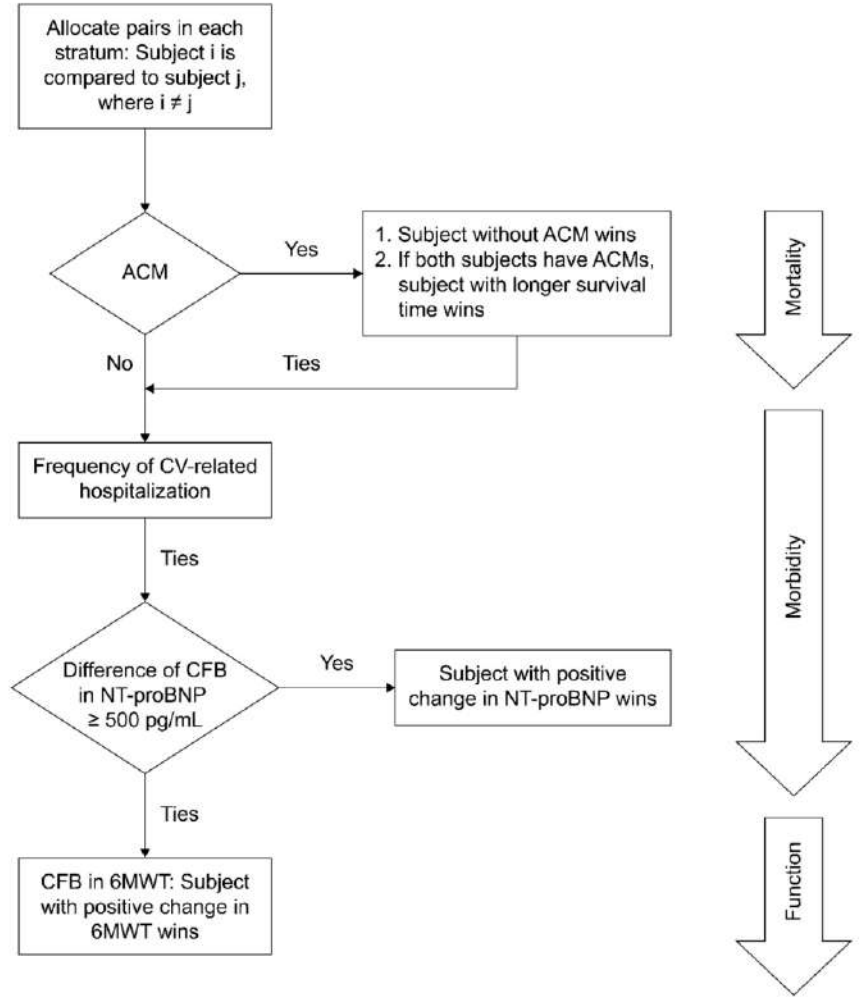
Mark Miller J Med Chem. 2018

Etude ATTRIBUTE-CM

- Etude de phase 3
- Double aveugle
- 2:1
- Acoramidis 800 mg x 2 vs placebo
- Diagnostic posé d'amylose selon les recommandations
- NT pro BNP > 300 mais < 8500 pg/ml
- DFG > 15 ml/min mais seuls les > 30 ml/min sont analysés
- Tafamidis interdit dans les 12 premiers mois de l'étude

Etude ATTRIBUTE-CM

- Evaluation en win ratio
- Décès toute cause
- Fréquence d'hospitalisation pour cause cardiovasculaire
- Différence NT pro BNP
- TM 6



1. Positive change in NT-proBNP can be smaller increase or a larger decrease from baseline in paired comparison.
2. Positive change in 6MWT can be a smaller decrease or a larger increase from baseline in paired comparison.
3. The paired comparison for NT-proBNP and 6MWT will use last available non-missing pair for both subjects.
4. A score will be assigned to the subject i within each pair with the following rules: win (+1), tie (0), loss (−1).

Résultats

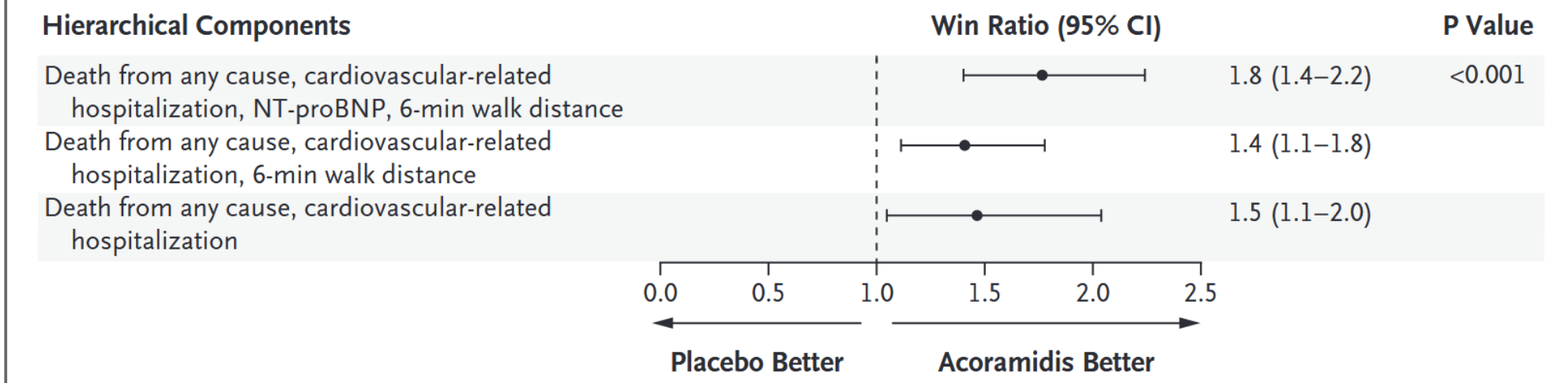


Figure 1. Primary Efficacy Analysis and Prespecified Secondary Analyses.

The four-step primary hierarchical analysis included death from any cause, cardiovascular-related hospitalization, the change from baseline in the level of N-terminal pro–B-type natriuretic peptide (NT-proBNP), and the change from baseline in the 6-minute walk distance. Also shown are the results of prespecified secondary analyses for the three-component hierarchy of death from any cause, cardiovascular-related hospitalization, and 6-minute walk distance and the two-component hierarchy of death from any cause and cardiovascular-related hospitalization. The P value for the win ratio was calculated with the use of the Finkelstein–Schoenfeld method.

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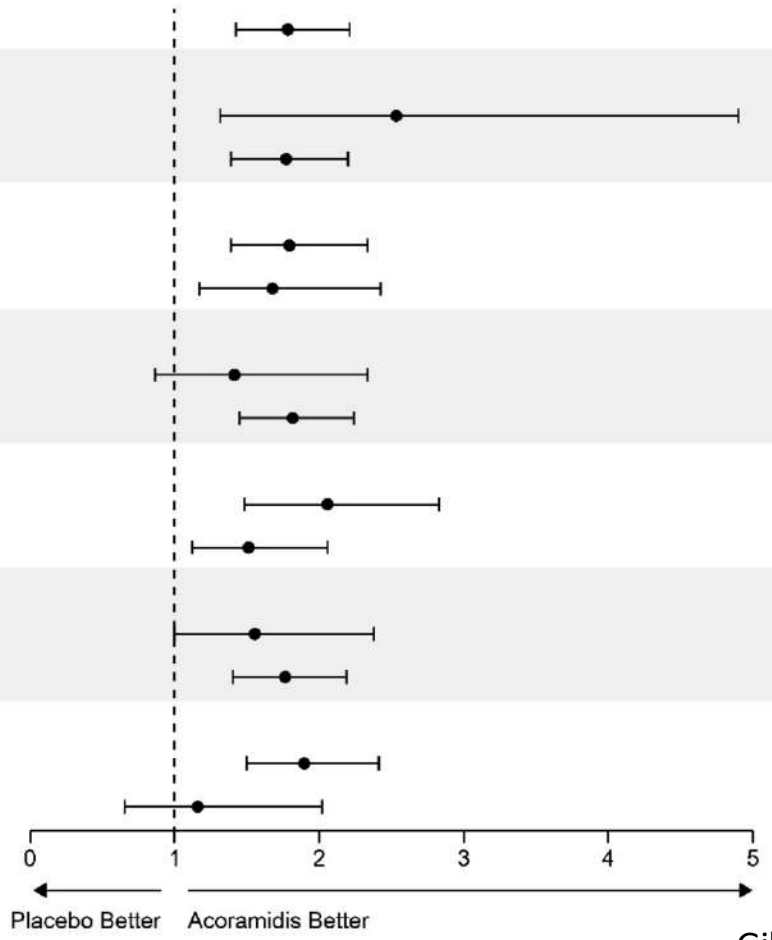
Résultats

Supplementary Figure S3. Forest Plot of Win Ratios for Randomization Strata and Other Important Subgroups.

Subgroup	Number of Patients	Win Ratio [95% CI]
Overall	611 (100.0)	1.772 [1.417, 2.217]
ATTR-CM Genotype		
ATTRv-CM	59 (9.7)	2.529 [1.303, 4.911]
ATTRwt-CM	552 (90.3)	1.756 [1.396, 2.208]
NT-proBNP (pg/mL)		
≤3000	401 (65.6)	1.787 [1.373, 2.325]
>3000	210 (34.4)	1.678 [1.160, 2.426]
eGFR (mL/min/1.73m²)		
<45	94 (15.4)	1.410 [0.849, 2.341]
≥45	517 (84.6)	1.797 [1.452, 2.226]
Age (years)		
<78	299 (48.9)	2.052 [1.489, 2.829]
≥78	312 (51.1)	1.499 [1.098, 2.045]
Country		
United States	119 (19.5)	1.544 [0.999, 2.385]
Rest of World	492 (80.5)	1.759 [1.411, 2.194]
NYHA Class		
I, II	512 (83.8)	1.892 [1.479, 2.419]
III	99 (16.2)	1.150 [0.652, 2.030]



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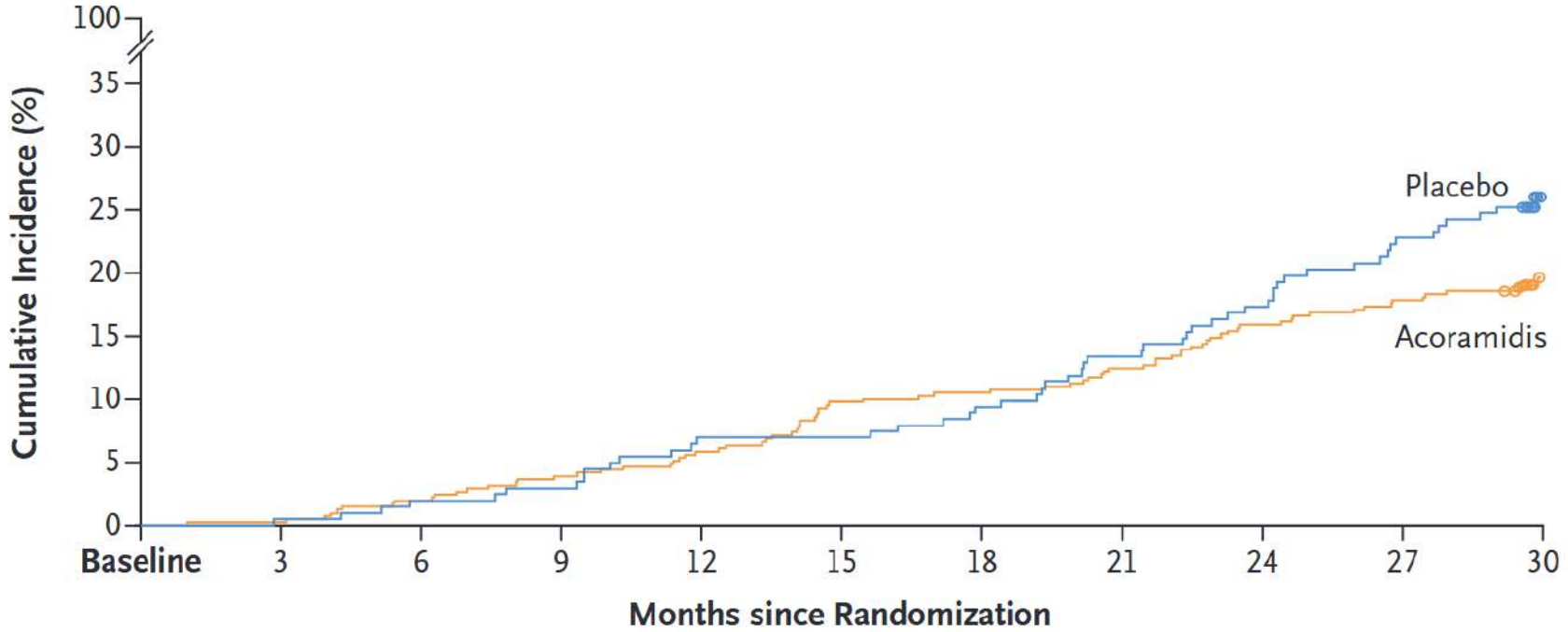
Résultats

E Death from Any Cause



No. at Risk (no. of events)											
Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)

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	ATTR-ACT n=441		ATTRIBUTE-CM n=632	
	Placebo	Tafamidis	Placebo	Acoramidis
N	177	264	211	421
Start/end recrutement	Dec 2013	Aug 2015	Apr 2019	OCt 2020
Age, n(%)	74.1 ± 6.7	74.5 ± 7.2	77.1 ± 6.8	77.4 ± 6.5
Male, n(%)	157 (88.7)	241 (91.3)	186 (88.2)	384(91.2)
NYHA, n(%)				
1	13 (7.3)	24 (9.1)	17 (8.1)	51 (12.1)
2	101 (57.1)	162 (61.4)	162 (76.8)	293 (69.6)
3	63 (35.6)	78 (29.5)	32 (15.2)	77 (18.3)
ATTRwt, n(%)	134 (75.7)	201 (76.1)	191 (90.5)	380 (90.3)
NT-proBNP, ng/l	2995.9 (1751.5-4861.5)	3161.0 (1864.4-4825.0)	2306 (1128-3754)	2326 (1332-4019)
% of death on KM curves at 30Months	42.4%	29.5%	24,6%	18.8%

Emprunté au Pr Damy

Place du Tafamidis dans l'étude

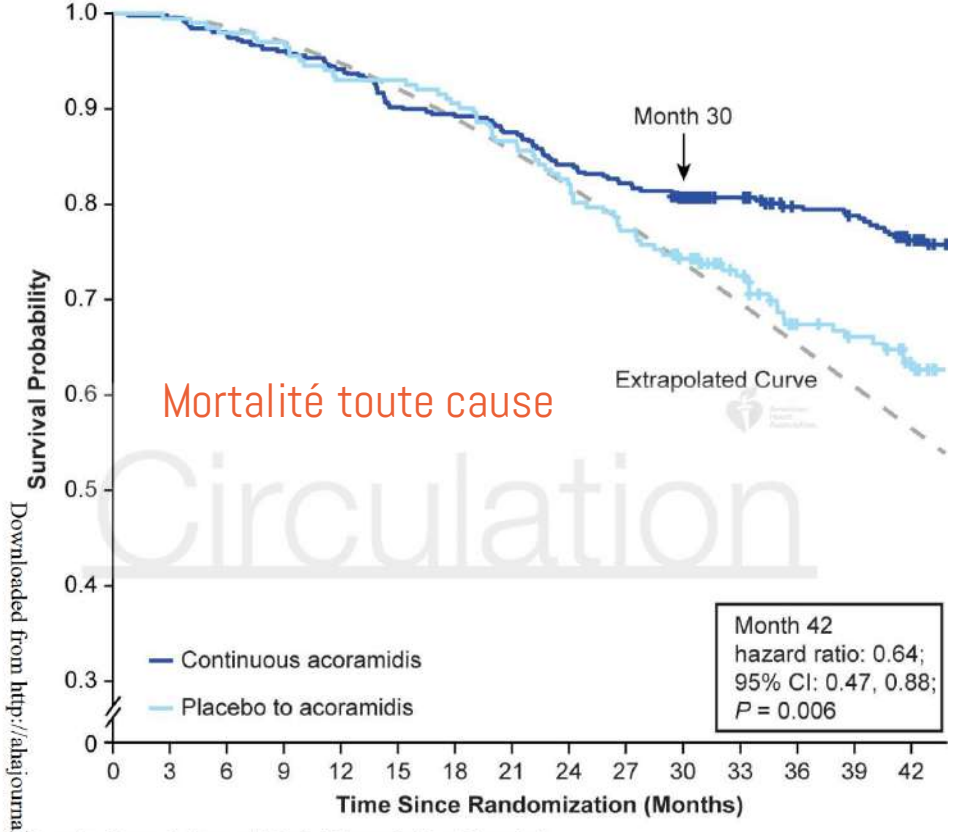
- Pas avant 1 an de traitement :

➔ 107 patients (17%) mis sous Tafamidis

➔ 15 % du groupe Acoramidis / 23% du groupe Placebo

➔ Exposition médiane de 11 mois

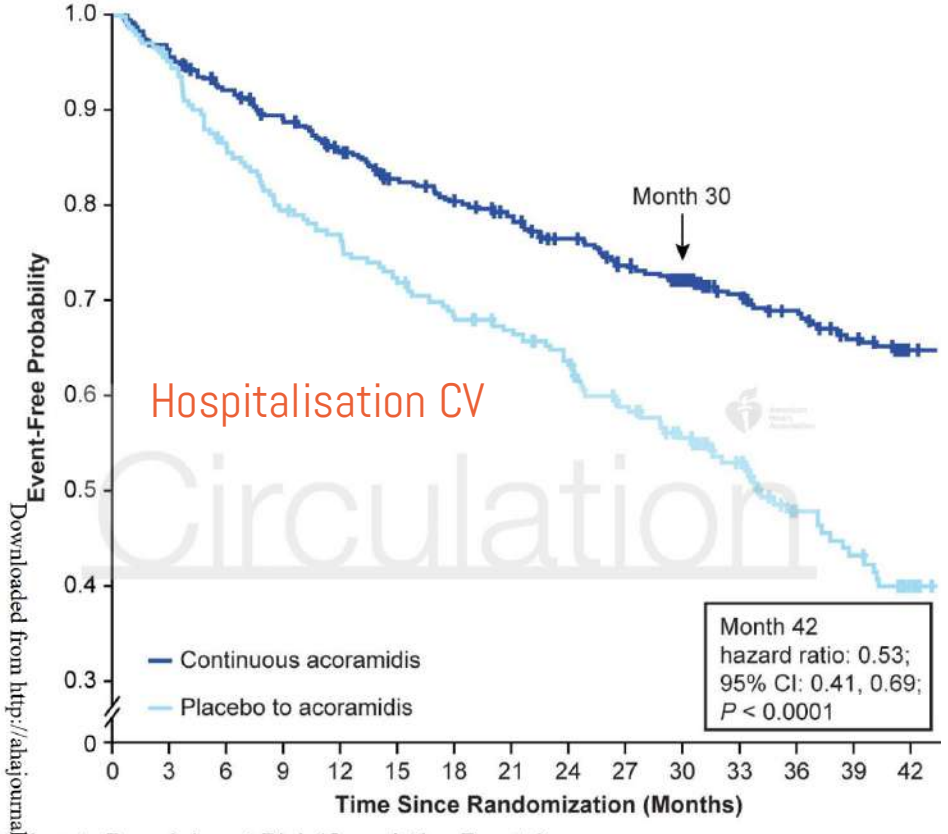
Long-Term Efficacy and Safety of Acoramidis in ATTR-CM: Initial Report From the Open-Label Extension of the ATTRibute-CM Trial



Mortalité toute cause

Participants Remaining at Risk (Cumulative Events)

Continuous acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	297 (79)	260 (79)	247 (82)	243 (85)	216 (93)
Placebo to acoramidis	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	143 (52)	118 (55)	102 (63)	98 (65)	87 (70)



Hospitalisation CV

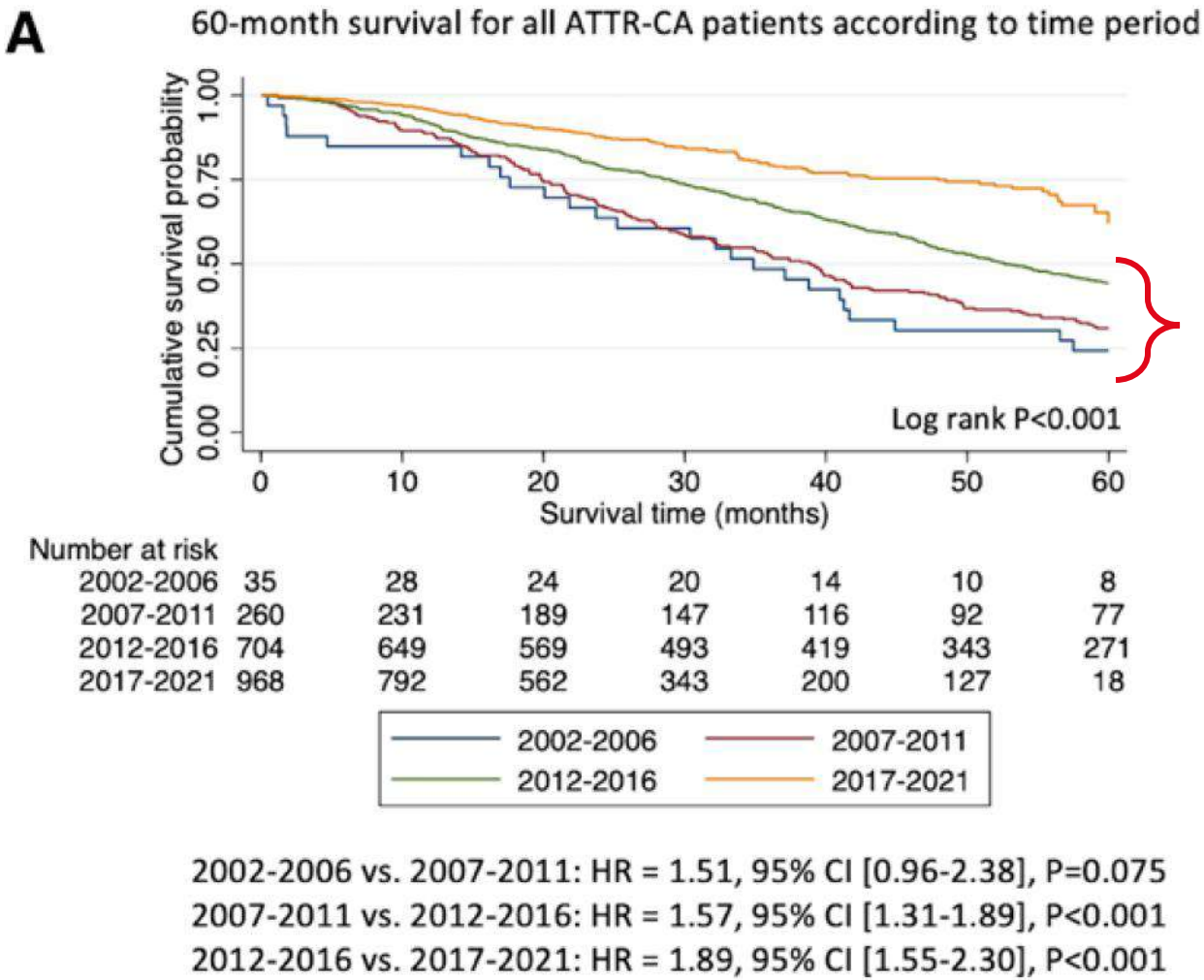
Participants Remaining at Risk (Cumulative Events)

Continuous acoramidis	409 (0)	389 (18)	370 (32)	355 (44)	337 (58)	319 (69)	308 (78)	298 (84)	284 (93)	270 (103)	233 (109)	200 (113)	189 (118)	177 (126)	152 (129)
Placebo to acoramidis	202 (0)	191 (10)	172 (28)	159 (41)	152 (47)	143 (56)	135 (63)	129 (66)	121 (72)	108 (81)	97 (87)	78 (91)	61 (98)	55 (104)	46 (108)

Daniel P. Judge, Circulation 2024

Au total :

- Acoramidis est une molécule d'intérêt sensée mieux stabiliser la TTR
- Etude desservit par les avancées importantes dans la thématique
- + critères de sélections excluant les patients les plus sévères
- Avec interaction du tafamidis

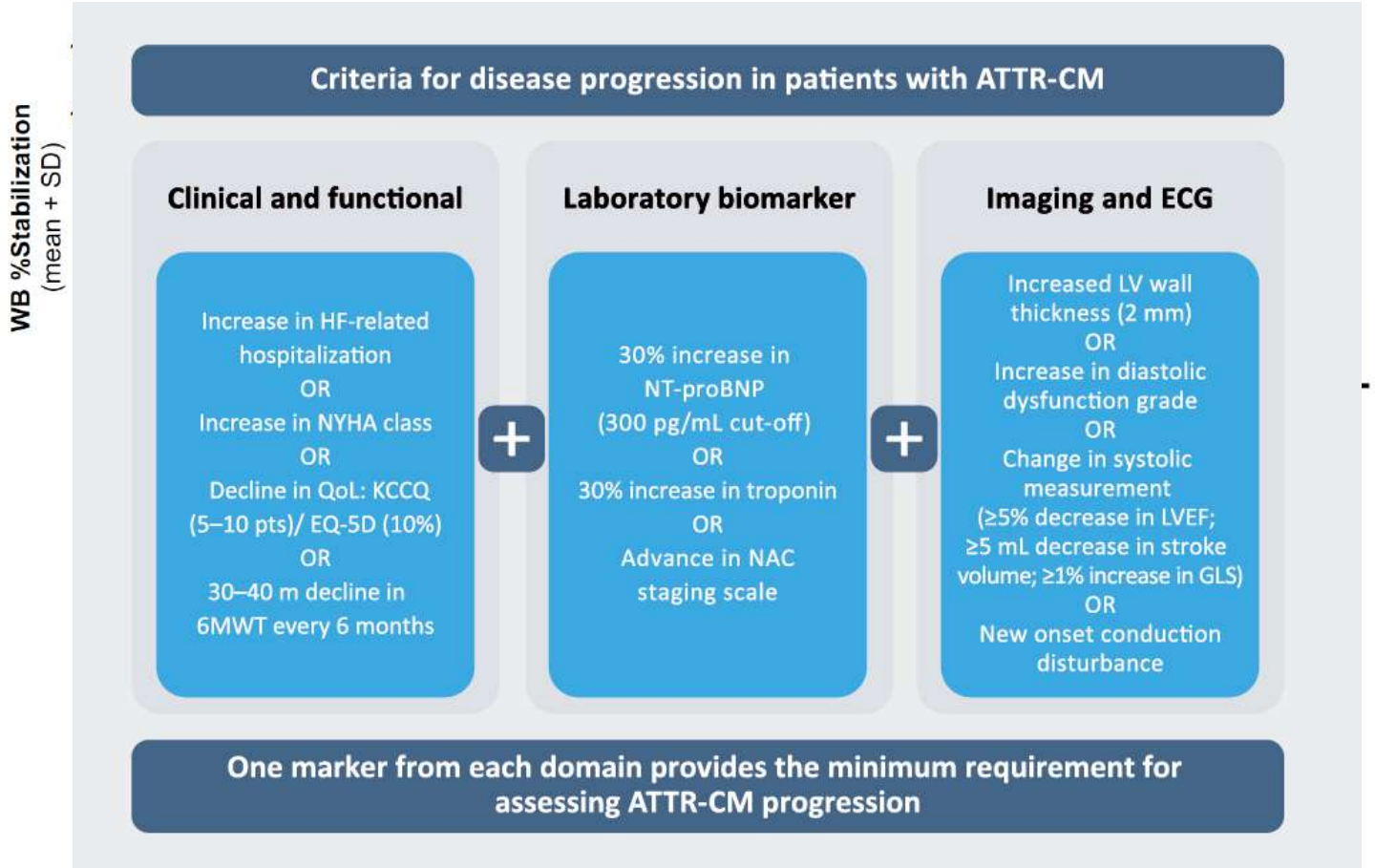


2002-2006 vs. 2007-2011: HR = 1.51, 95% CI [0.96-2.38], P=0.075
2007-2011 vs. 2012-2016: HR = 1.57, 95% CI [1.31-1.89], P<0.001
2012-2016 vs. 2017-2021: HR = 1.89, 95% CI [1.55-2.30], P<0.001

Adam Ioannou Circulation 2022

Comment adapter le traitement de nos patients à la vue d'ATTRIBUTE-CM ?

- Patient intolérant au Tafamidis
- Patient ATTRv ?
- Patient progressant sous Tafamidis ?
- Patient âgé sans espérance de gain de survie ?
- En première intention ?



Merci de votre attention !

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