



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

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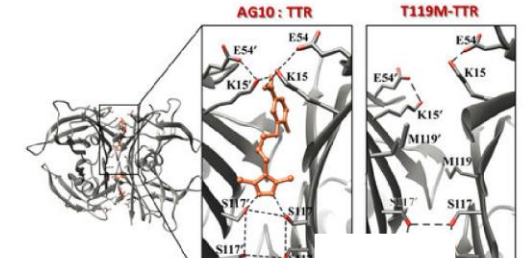


Conflits d'intérêts

- Pfizer
- Alnylam
- Astra Zeneca
- Bayer

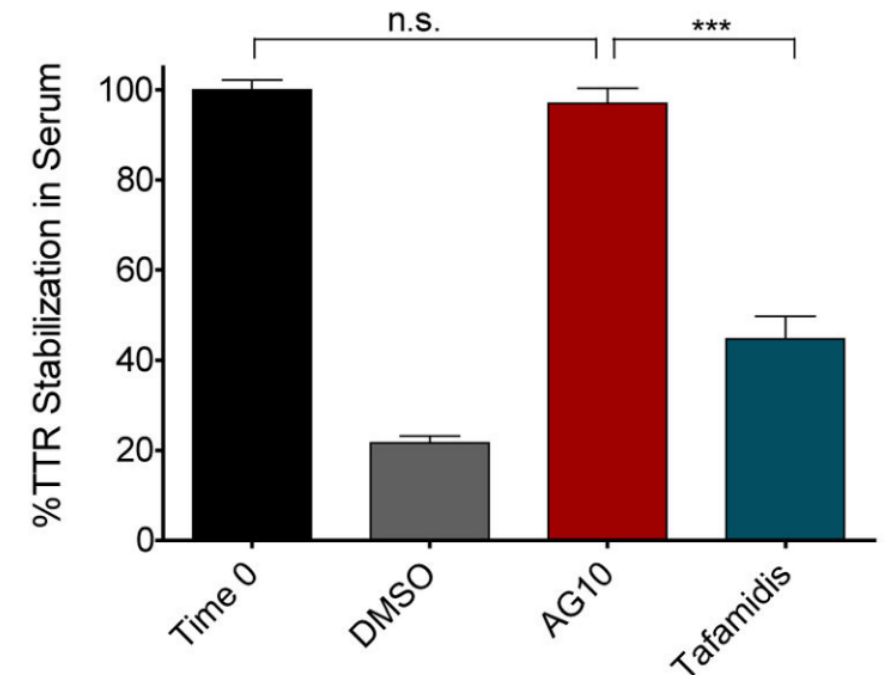


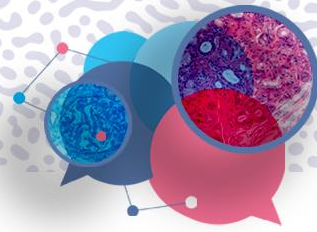
Les promesses de l'Acoramidis



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

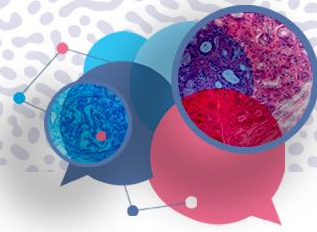
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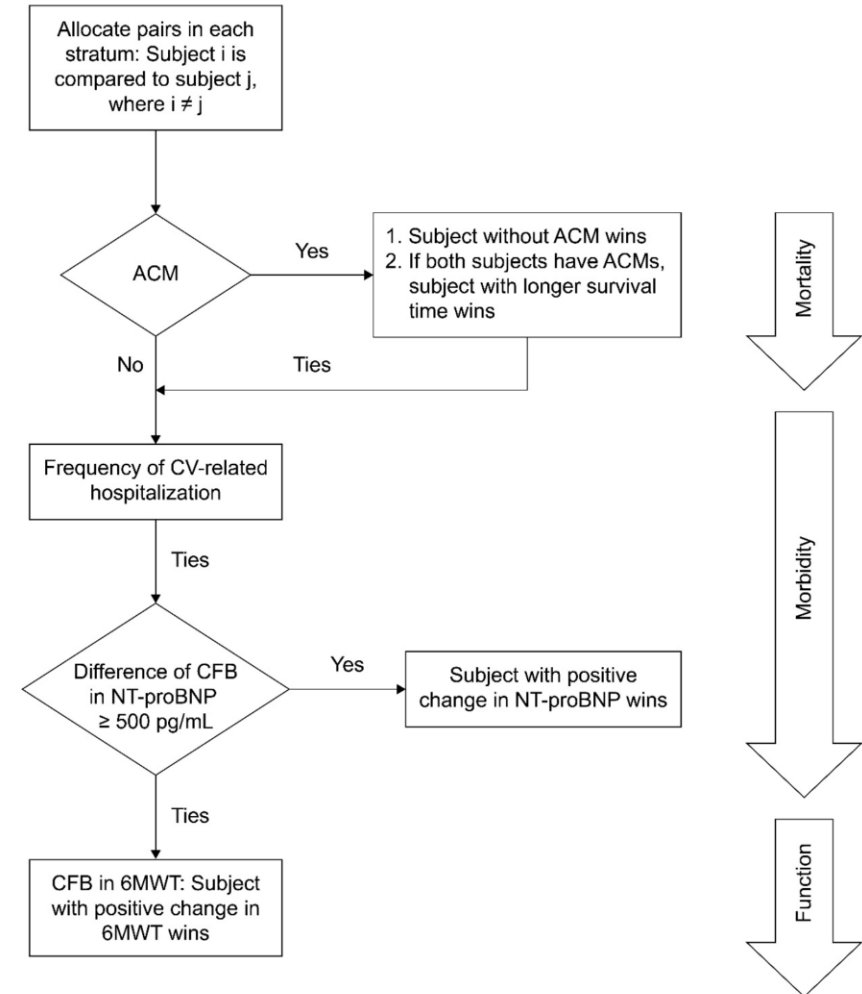
Etude ATTRIBUTE-CM

- 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

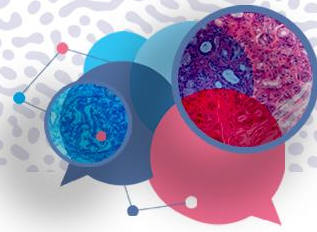


Etude ATTRIBUTE-CM

- 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

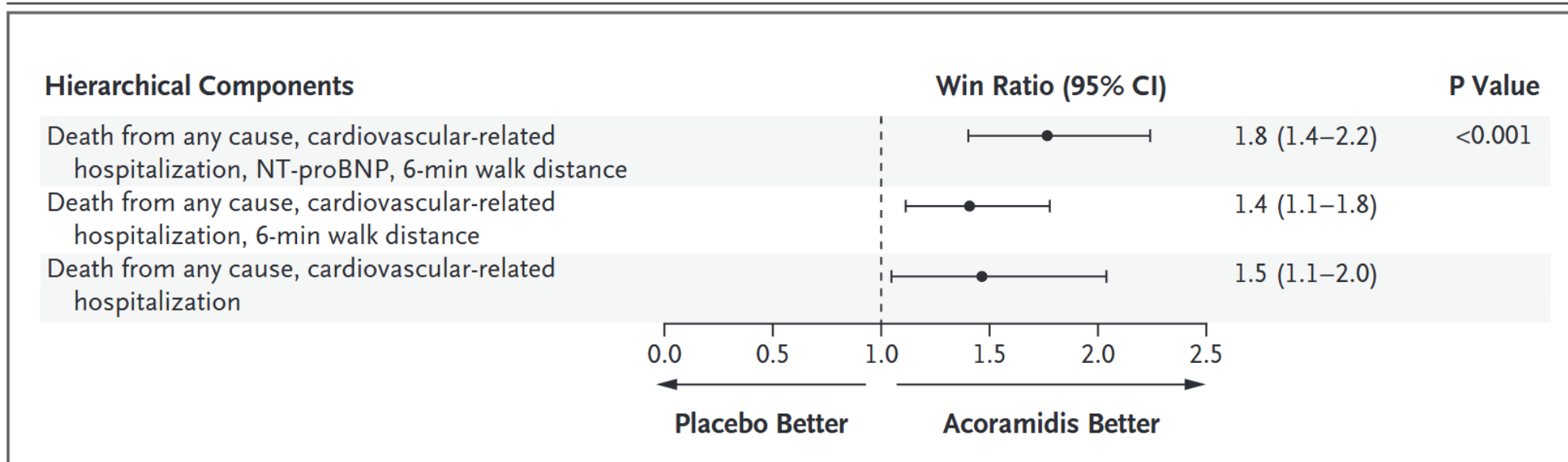
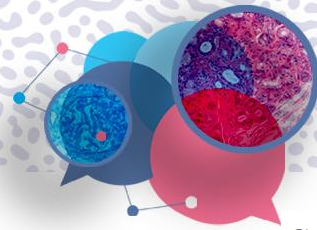


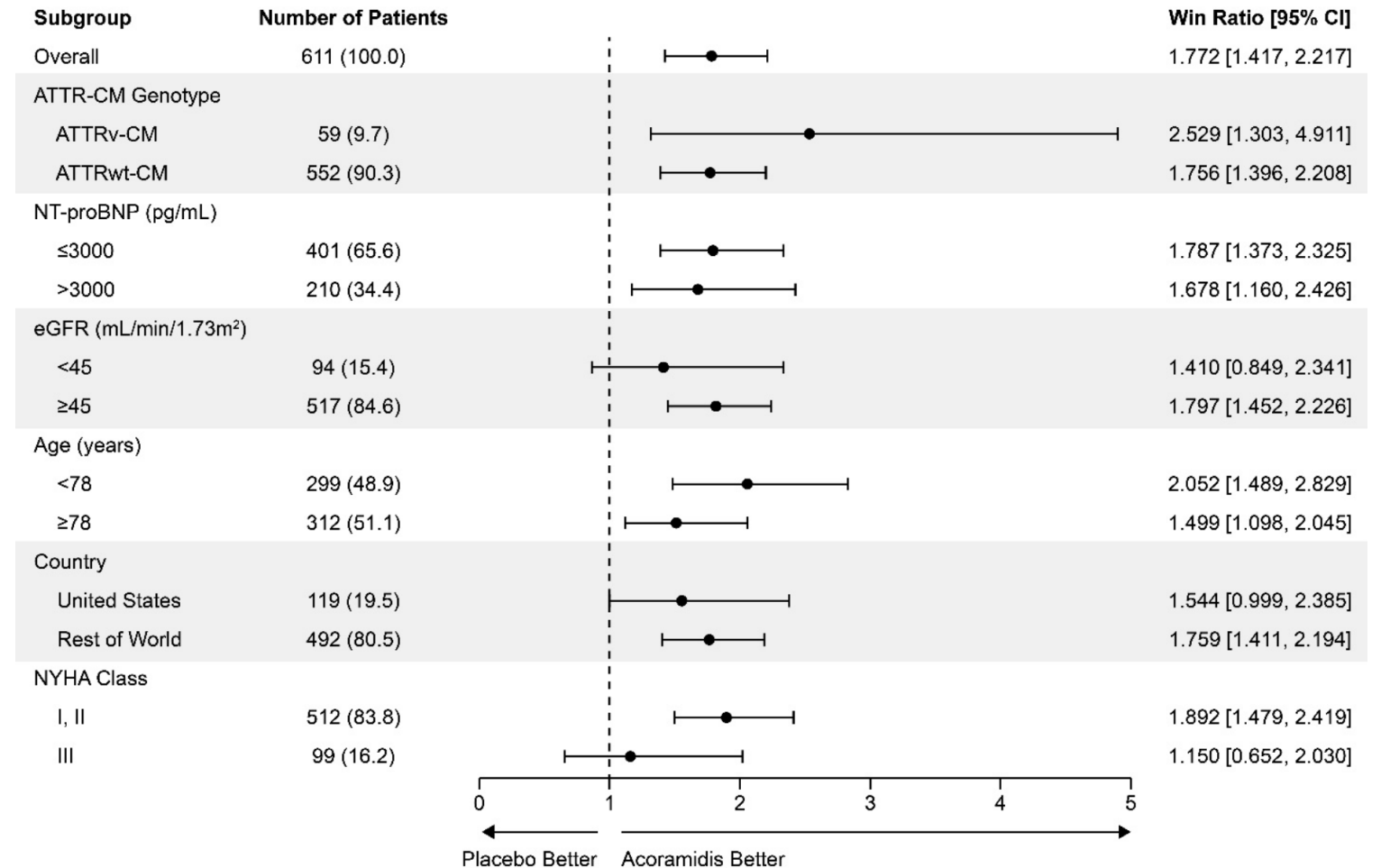
Figure 1. Primary Efficacy Analysis and Prespecified Secondary Analyses.

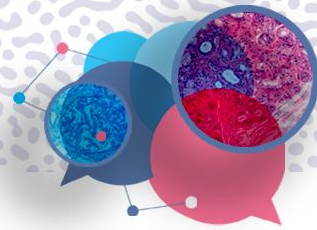
The four-step primary hierarchical analysis included death from any cause, cardiovascular-related hospitalization, the change from baseline in the level of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and the change from baseline in the 6-minute walk distance. Also shown are the results of 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.



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

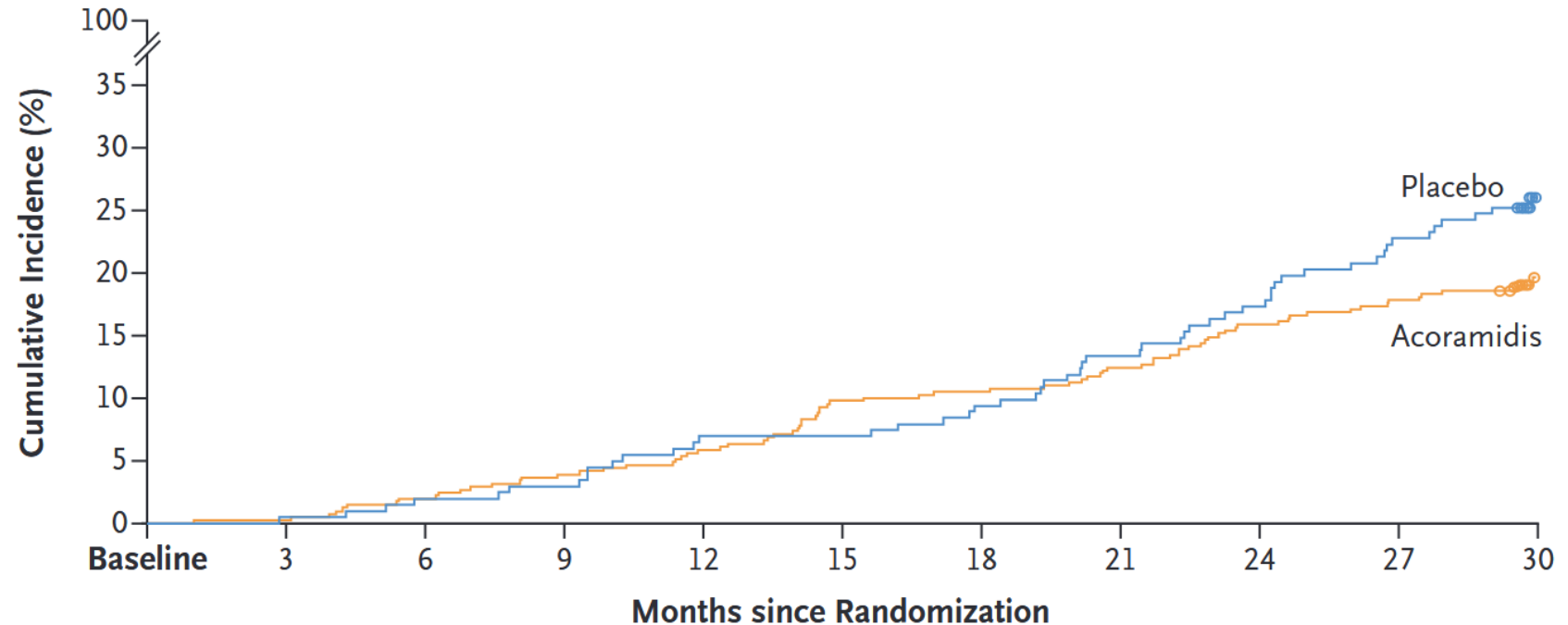
Résultats





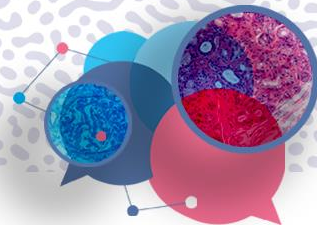
Résultats

E Death from Any Cause



No. at Risk (no. of events)

	Baseline	3	6	9	12	15	18	21	24	27	30
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)

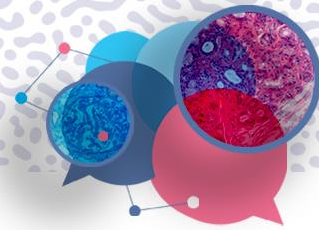


	ATTR-ACT n=441		ATTRIBUTE-CM n=632	
	Placebo	Tafamidis	Placebo	Acoramidis
N	177	264	211	421
Start/end recrutement	Dec 2013	Aug 2015	Apr 2019	Oct 2020
Age, n(%)	74.1 ± 6.7	74.5 ± 7.2	77.1 ± 6.8	77.4 ± 6.5
Male, n(%)	157 (88.7)	241 (91.3)	186 (88.2)	384(91.2)
NYHA, n(%)				
1	13 (7.3)	24 (9.1)	17 (8.1)	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%

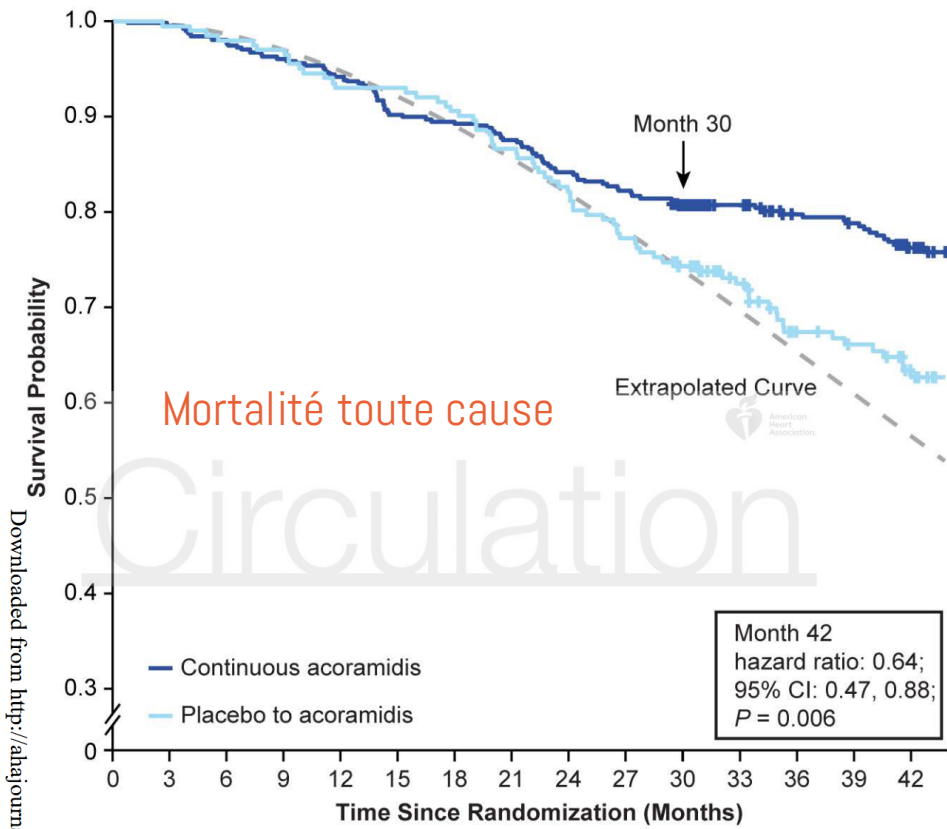


Place du Tafamidis dans l'étude

- 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

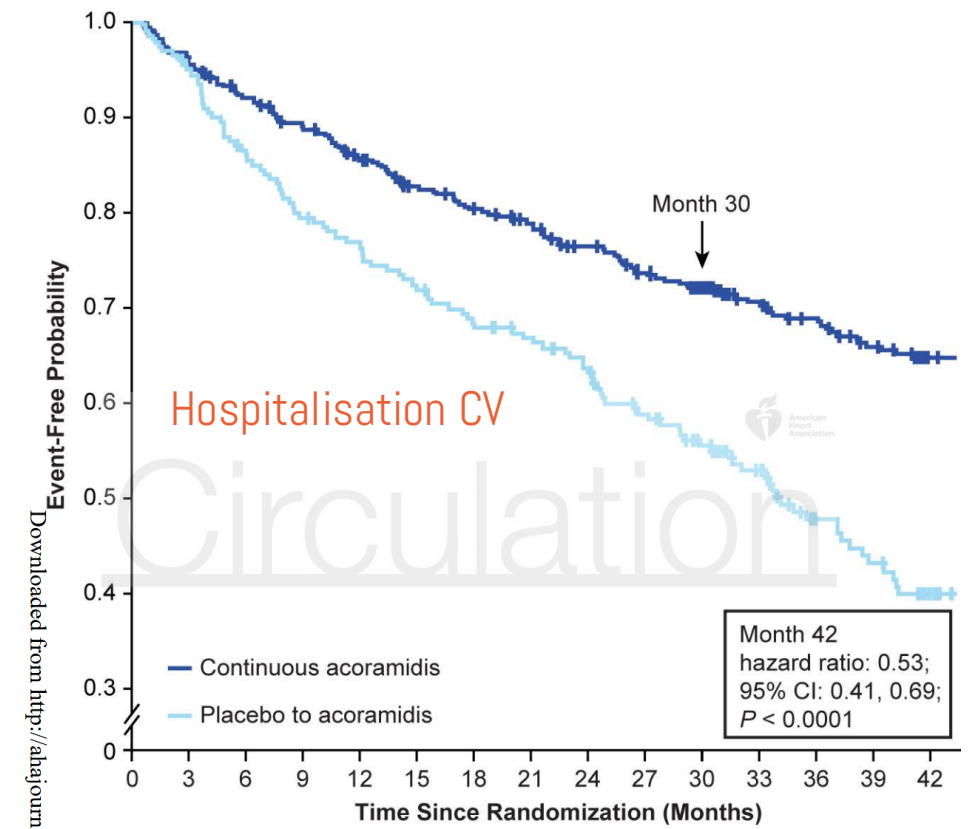


Long-Term Efficacy and Safety of Acoramidis in ATTR-CM: Initial Report From the Open-Label Extension of the ATTRIBUTE-CM Trial



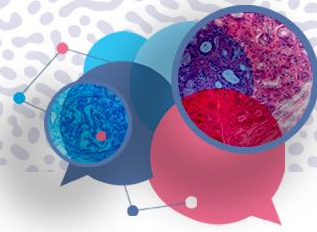
Participants Remaining at Risk (Cumulative Events)

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



Participants Remaining at Risk (Cumulative Events)

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

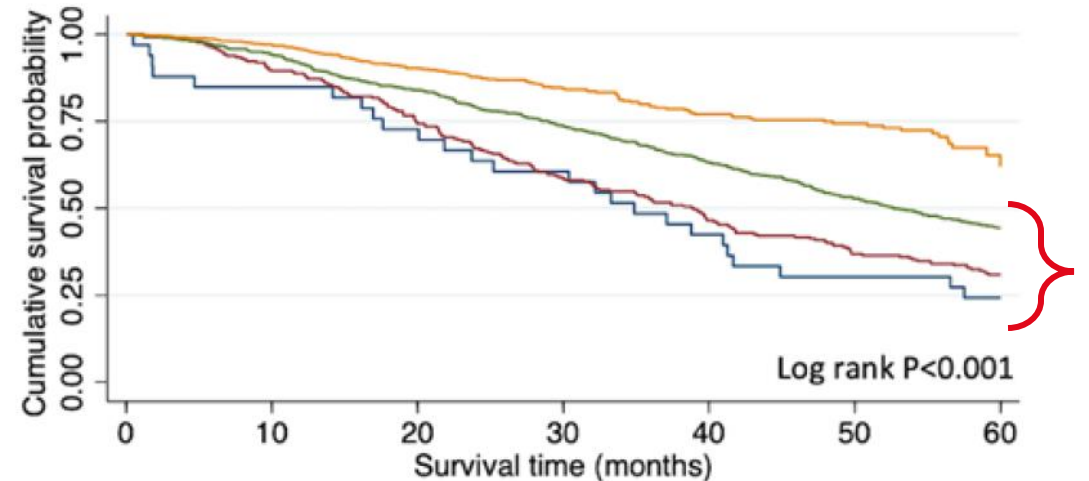


Au total :

- 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

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60-month survival for all ATTR-CA patients according to time period



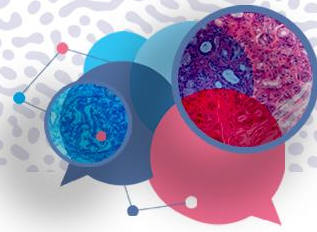
Number at risk	0	10	20	30	40	50	60
2002-2006	35	28	24	20	14	10	8
2007-2011	260	231	189	147	116	92	77
2012-2016	704	649	569	493	419	343	271
2017-2021	968	792	562	343	200	127	18



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

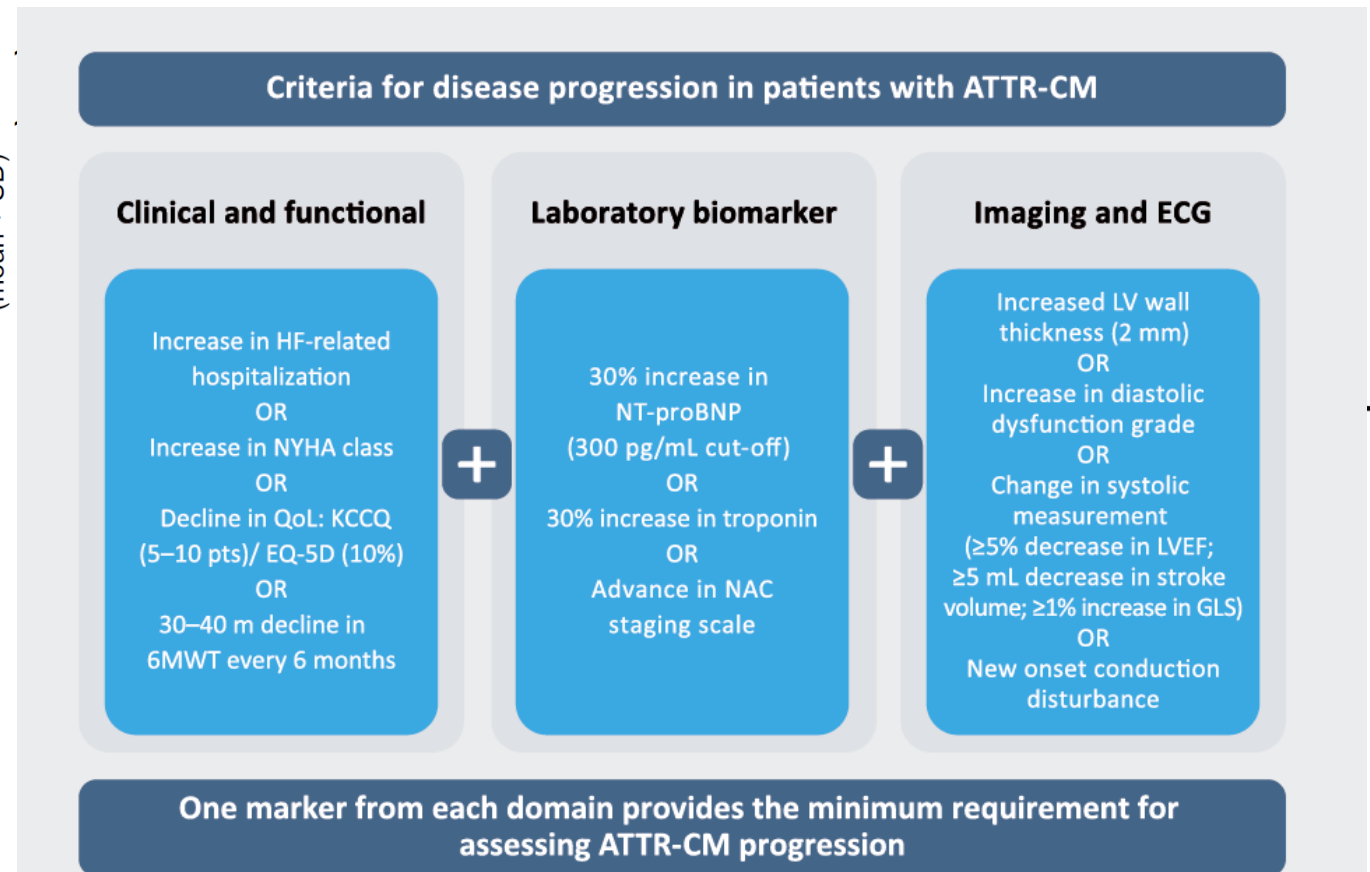
2012-2016 vs. 2017-2021: HR = 1.89, 95% CI [1.55-2.30], P<0.001

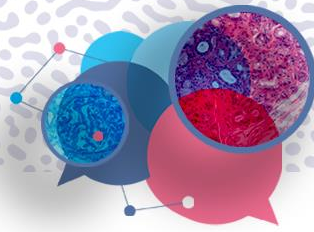


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- Patient intolérant au Tafamidis
- Patient ATTRv ?
- Patient progressant sous Tafamidis ?
- Patient âgé sans espérance de gain de survie ?
- En première intention ?

WB %Stabilization
(mean + SD)





Merci de votre attention !

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