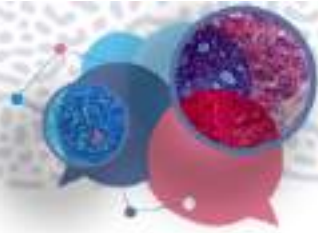


Actualités sur les traitements : de la physiopathologie aux essais: les stabilisateurs

Fabrice BAUER

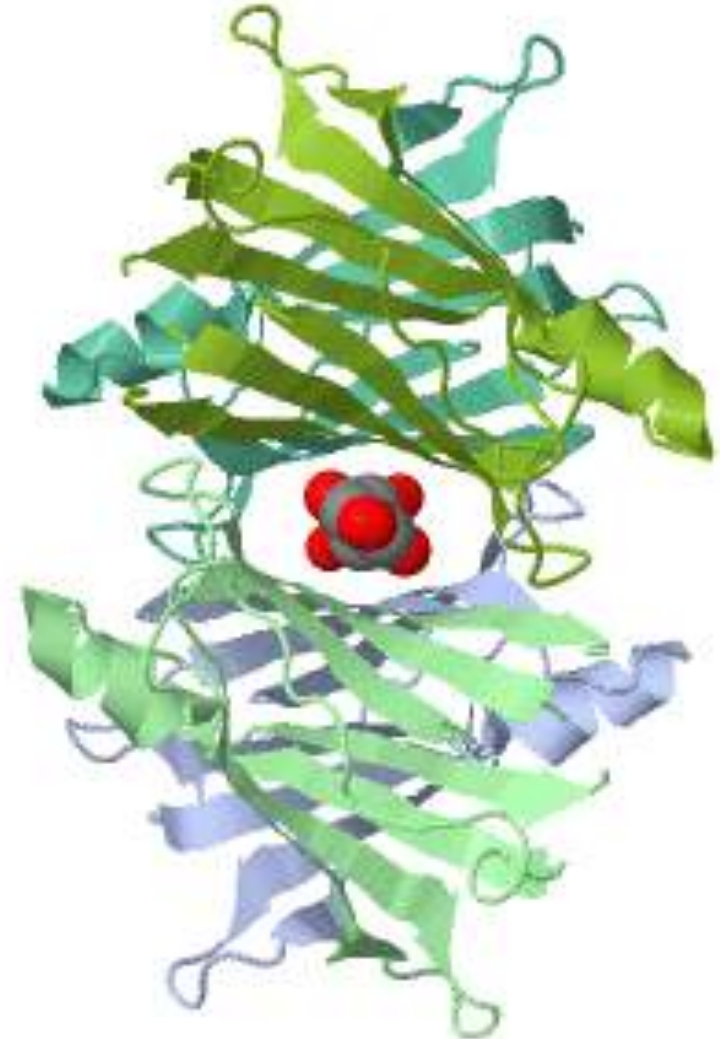
CHU Rouen

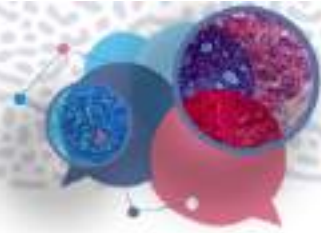
CARDIOGEN



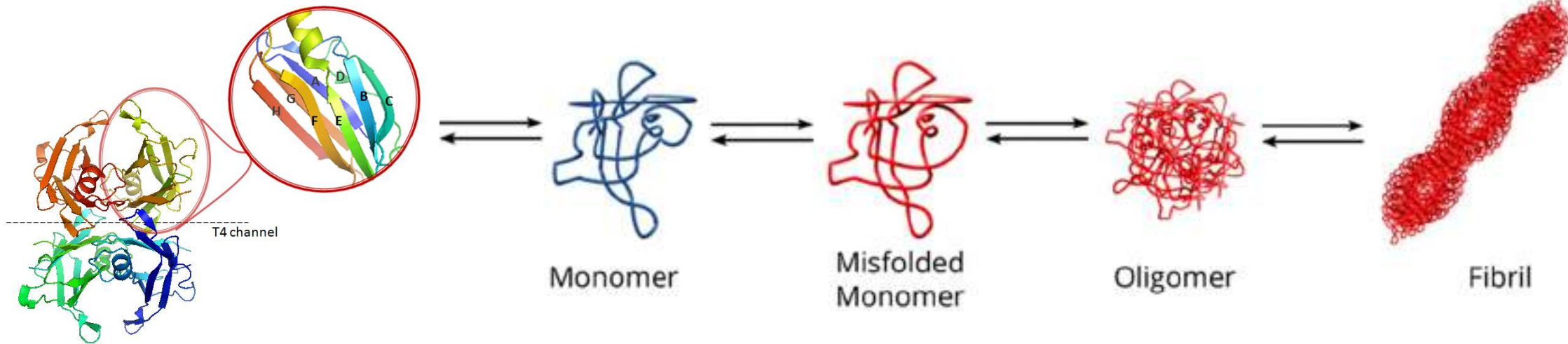
La transthyrétine

- Protéine
- Synthétisée par le foie et le plexus choroïde avec circulation plasmatique et cérébrospinale
- Transport T4 et vitamine A (RBP)
- Structure tétramérique
- Tunnel hydrophobe entre 2 dimères (T4) = site de stabilisation



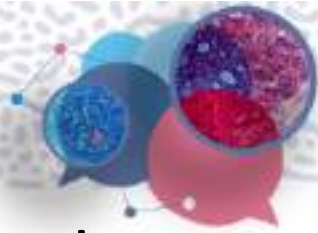


On ne sait pas grand-chose sur la dépolymérisation



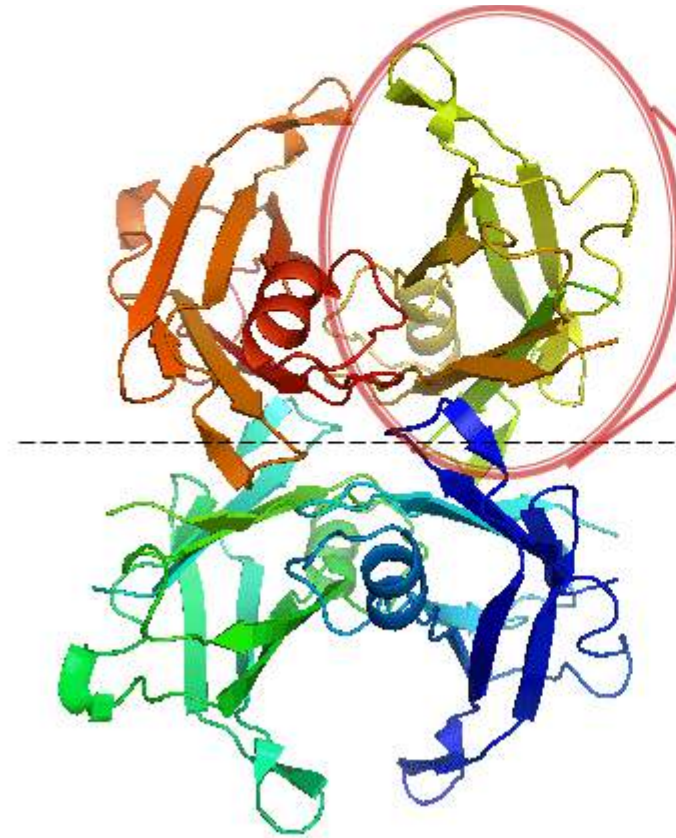
Instabilité de β -strands
(Age et variants)

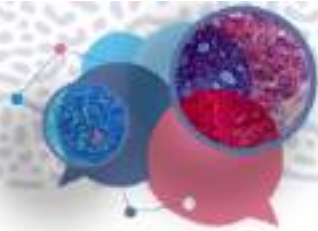
Facteur oxydants
Défaut des protéases
Déstabilisations par mutation



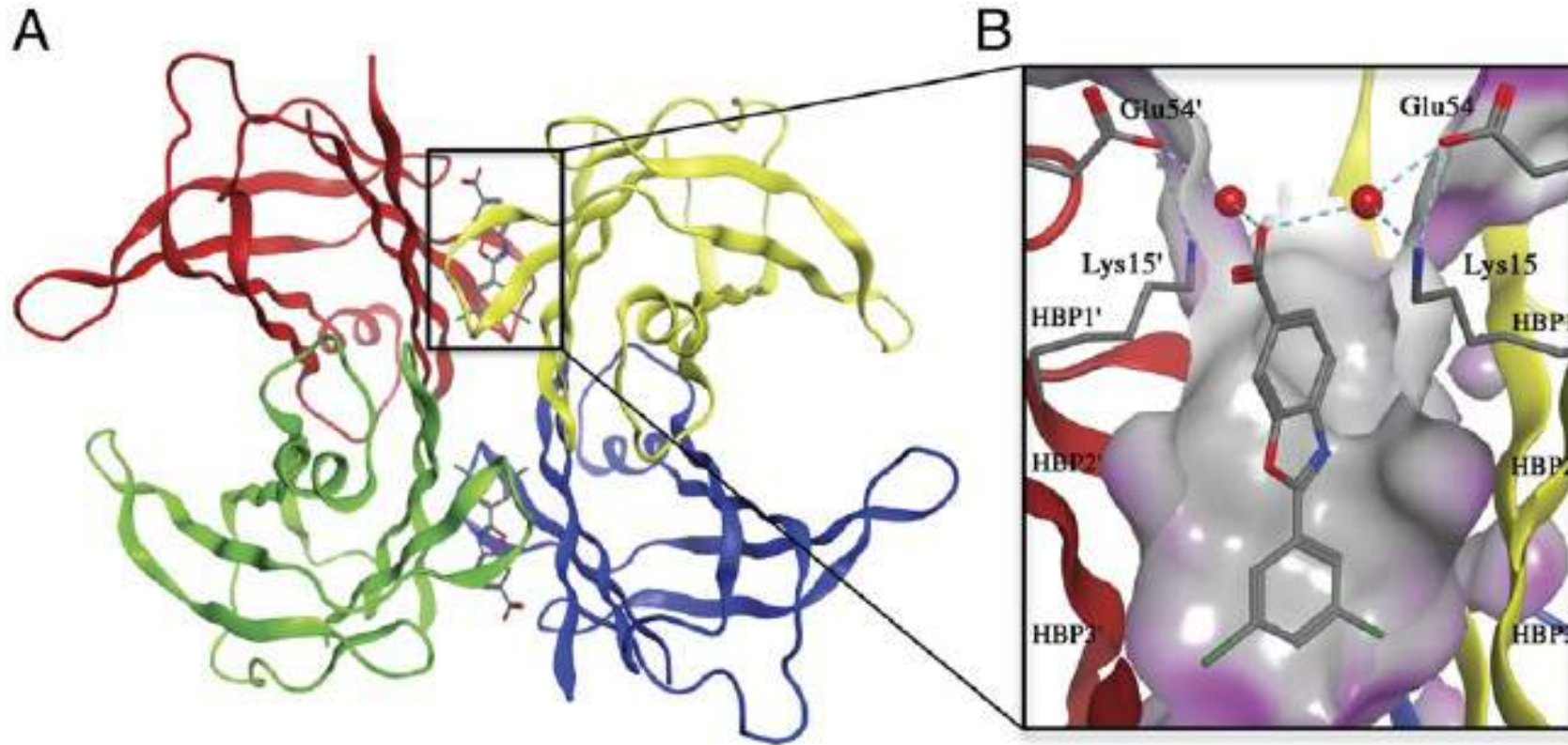
Les stabilisateurs de la transthyrétine

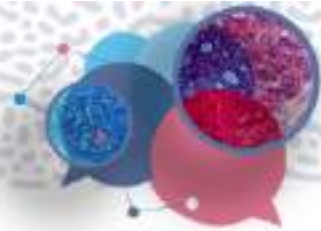
- Tafamidis
- Acoramidis
- Diflunisal et AINS
- Tolcapone et ECGC





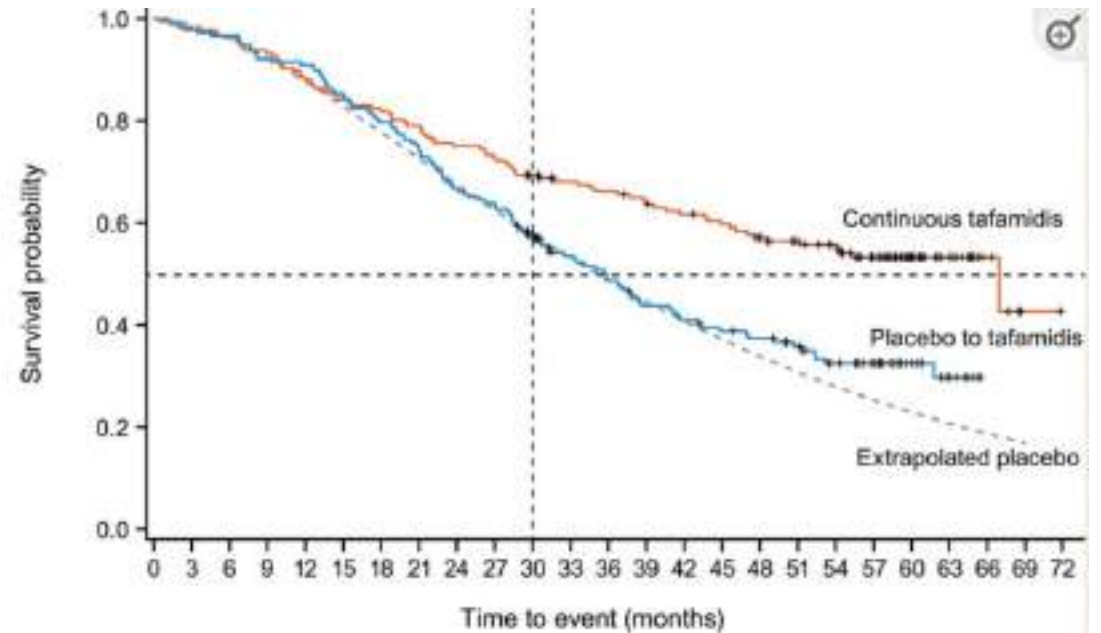
Le TAFAMIDIS





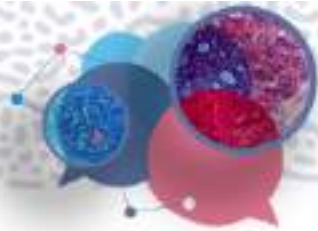
ATTRACT HF LONG TERM EXPOSITION

- Patients with transthyretin amyloid cardiomyopathy who completed ATTR-ACT could enroll in an LTE, continuing with the same tafamidis dose or, if previously treated with placebo, randomized (2:1) to tafamidis meglumine 80 or 20 mg.
- Median follow-up was 58.5 months in the continuous tafamidis group (n=176) and 57.1 months in the placebo to tafamidis group (n=177).
- There were 79 (44.9%) deaths with continuous tafamidis and 111 (62.7%) with placebo to tafamidis (hazard ratio, 0.59 [95% CI, 0.44–0.79]; $P < 0.001$). (variant transthyretin amyloidosis (0.57 [0.33–0.99]; $P = 0.05$) and wild-type transthyretin amyloidosis (0.61 [0.43–0.87]; $P = 0.006$))
- Baseline New York Heart Association class I and II (0.56 [0.38–0.82]; $P = 0.003$) and class III (0.65 [0.41–1.01]; $P = 0.06$).



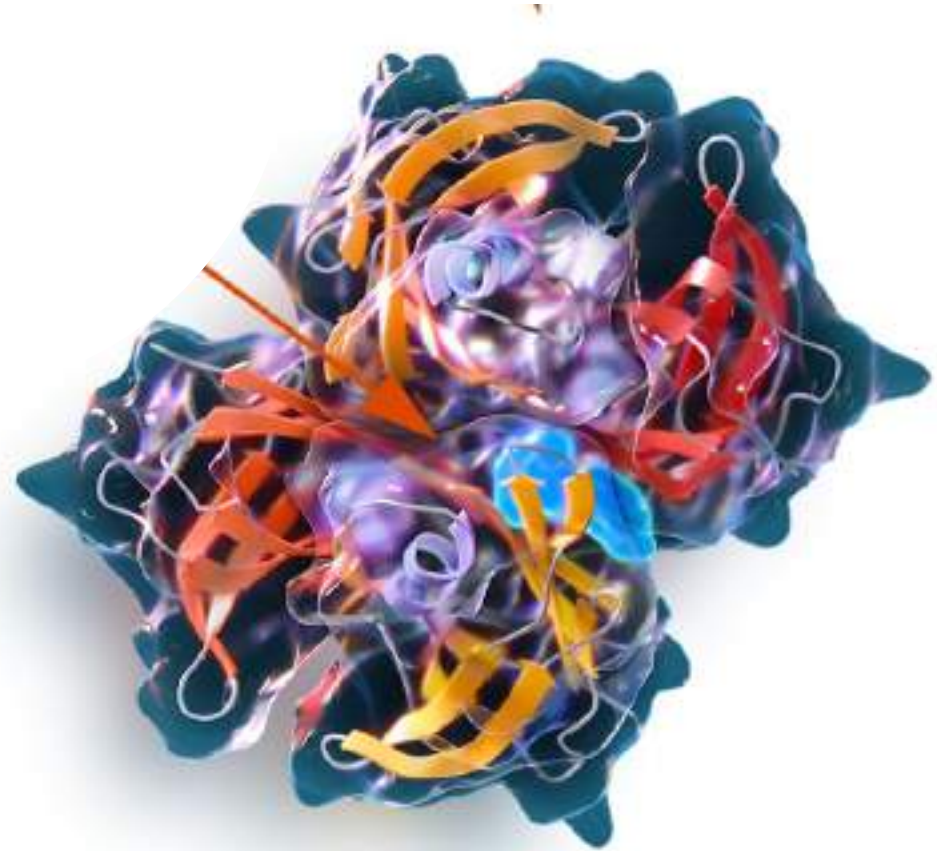
NEJM 2019

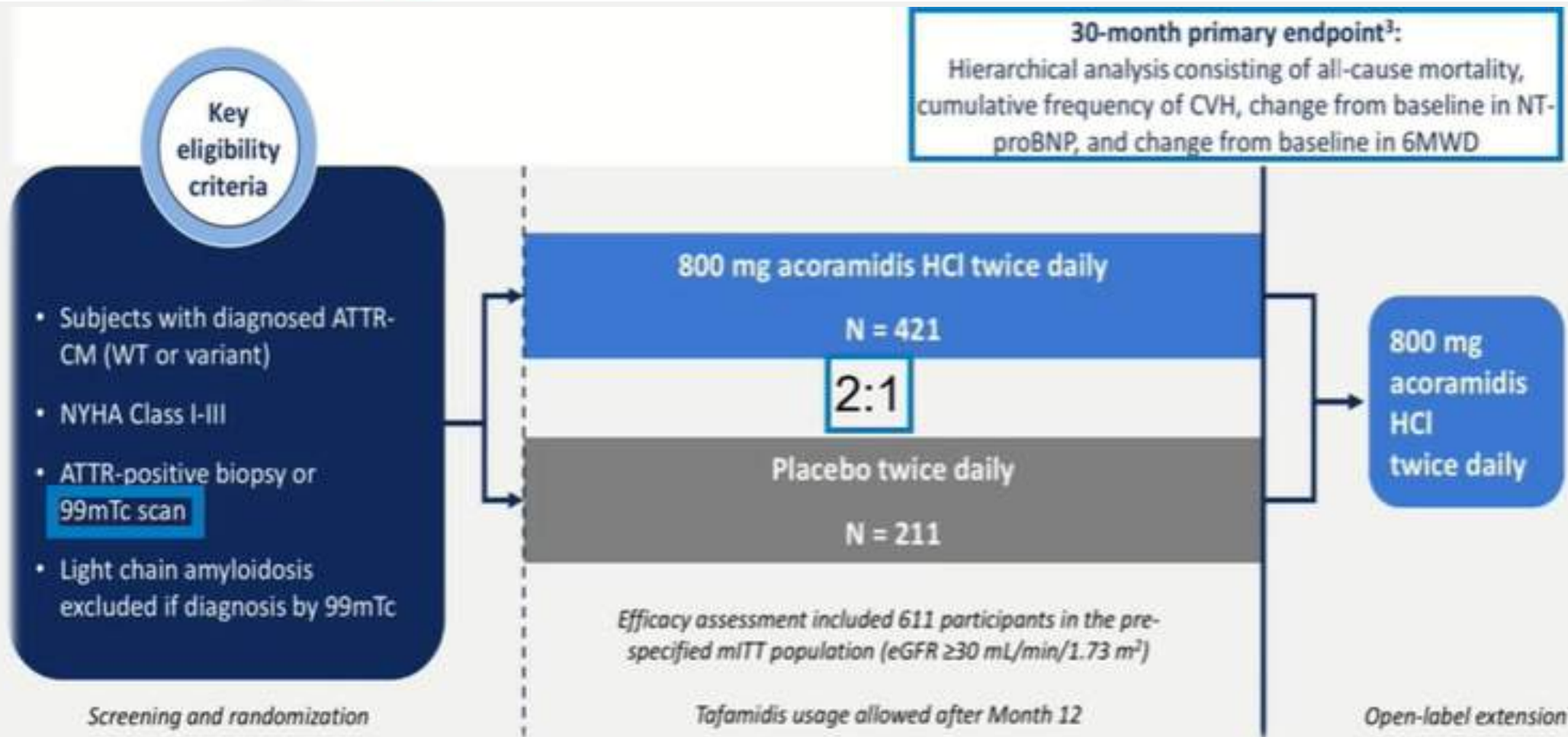
CIRC HF 2022



ACORAMIDIS

- ACORAMIDIS (AG10) est une petite molécule stabilisatrice à biodisponibilité orale.
- AG10 émule la propriété stabilisatrice en créant des liaisons hydrogène entre les résidus de Ser117 des monomères de TTR
- D'après des études in vitro, l'efficacité et la sélectivité de l'acoramidis semblent supérieures à celles du tafamidis et du diflunisal





SECONDARY ENDPOINTS: Cumulative frequency of CVH, change from baseline in 6MWD, change from baseline in KCCQ-OS, change from baseline in serum TTR, change from baseline in NT-proBNP and all cause mortality.

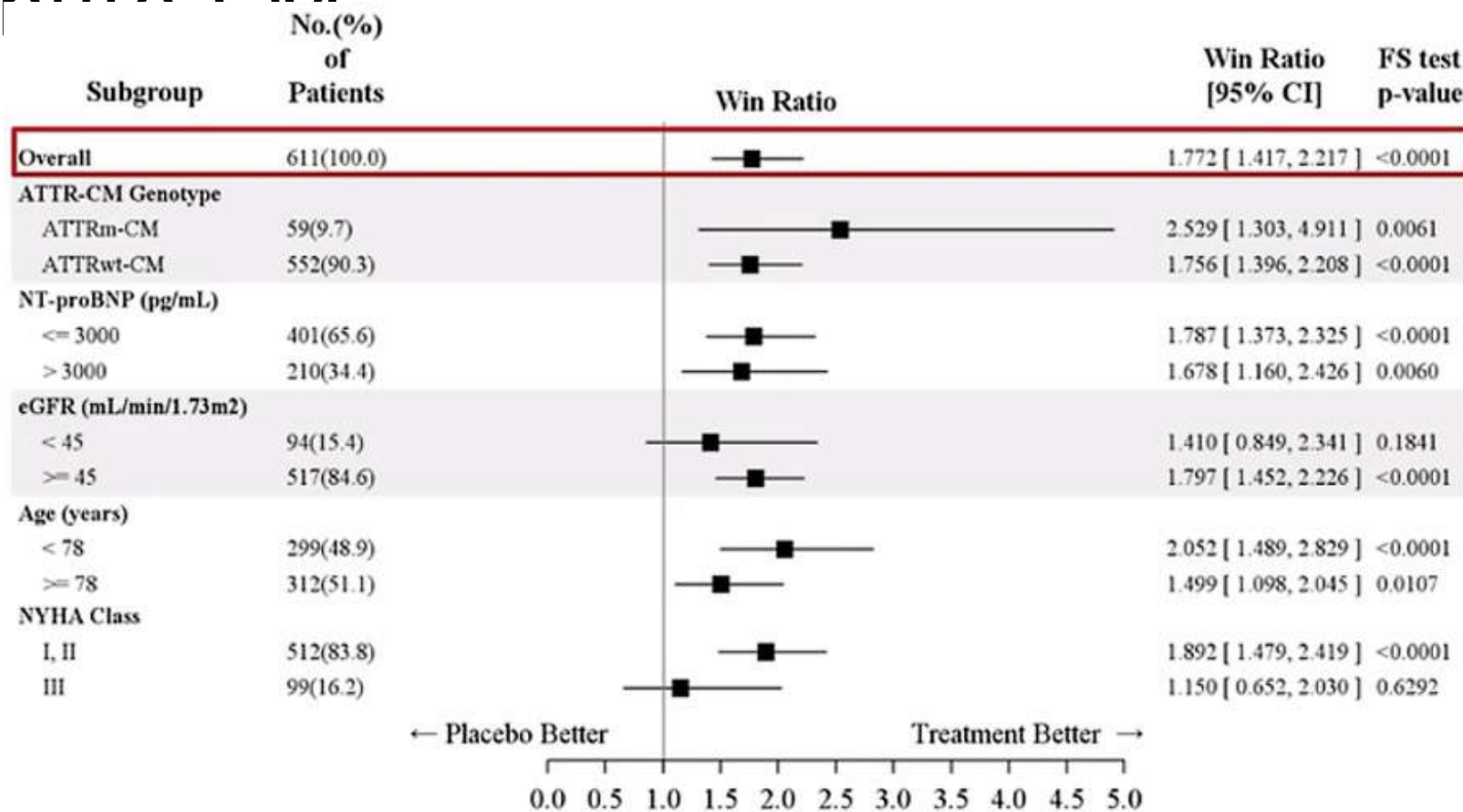


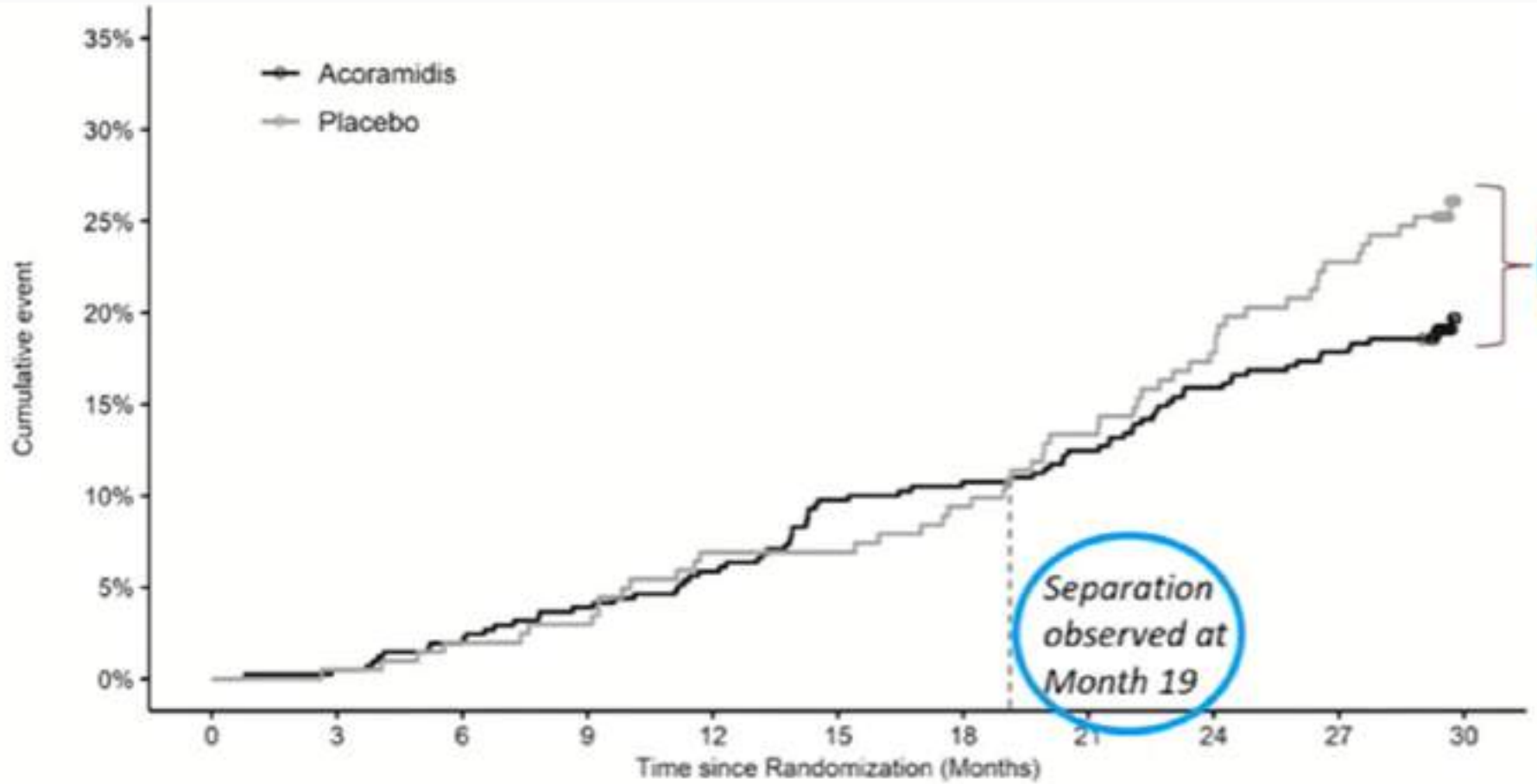
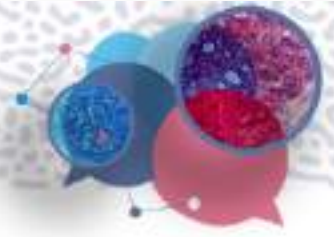
Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy - ATTRibute-CM

- A total of 632 patients with ATTR-CM were randomised.
- The median age was 78 years, 90% of participants were male, and 10% were variant TTR carriers.
- Most participants had either New York Heart Association Class II (72.0%) or Class III (17.2%) symptoms.



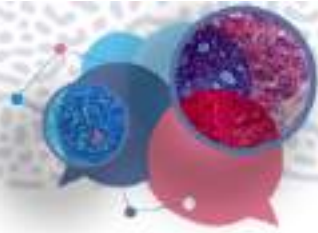
Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy - ATTRi_hto CM





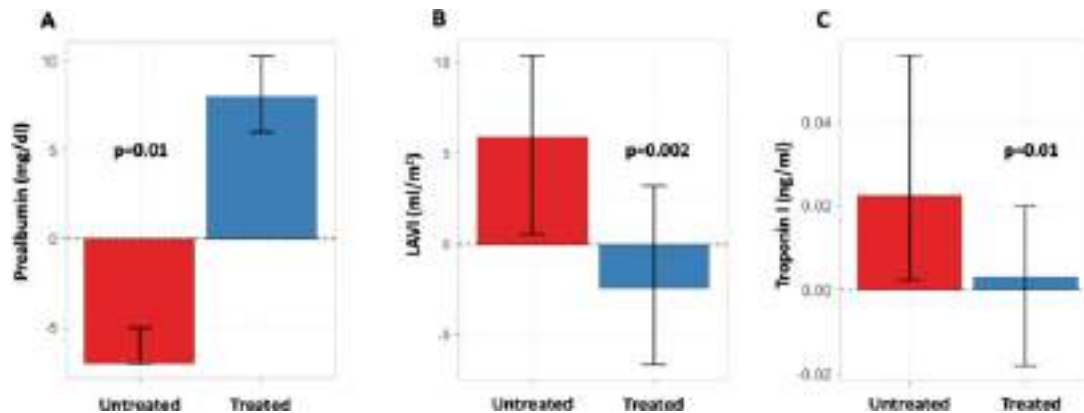
Number at risk (number of events)

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)



DIFLUNISAL et AINS

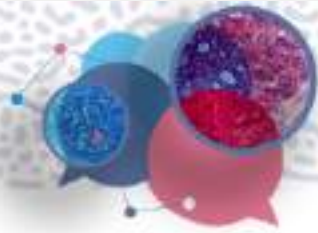
DIFLUNISAL



2D Strain: $p = 0,04$
HVG: $p = 0,2$
BNP: $p = 0,42$

AINS et autres

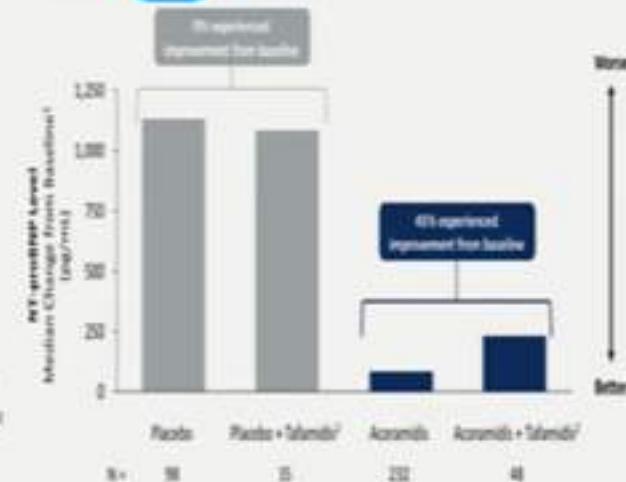
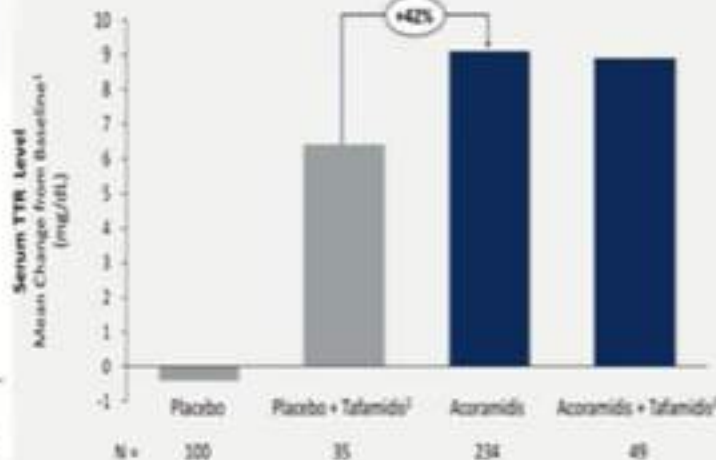
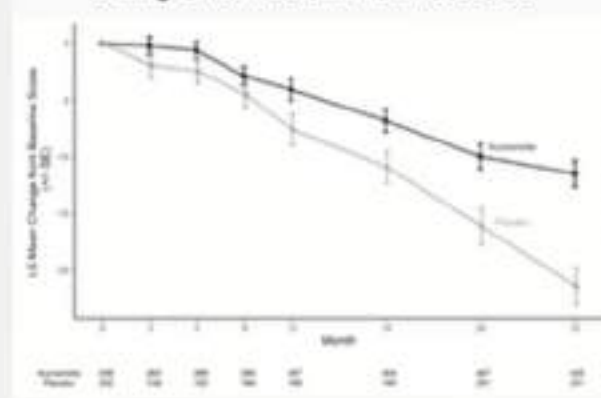
- FLUFENAMIC: aussi efficace que DIFLUNISAL in vitro
- DICLOFENAC: très inférieur au DIFLUNISAL in vitro
- FLURBIPROFEN: Supérieur au DIFLUNISAL in vitro
- RESVERATROL: aussi efficace que DIFLUNISAL chez la souris



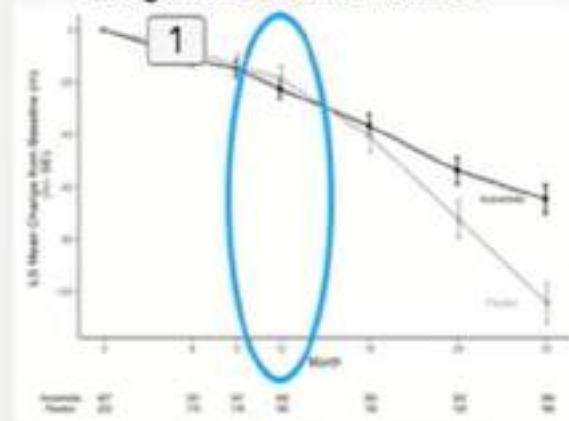
ATTRibute-CM: critères secondaires

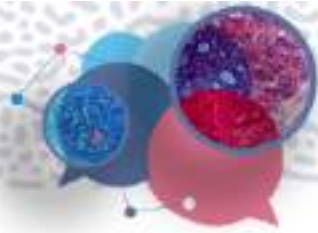
Select secondary endpoints	p-value
Cumulative frequency of CVH ³	p<0.0001
Change from baseline in 6MWD ⁴	p<0.0001
Change from baseline in KCCQ-OS ⁴	p<0.0001
Change from baseline in serum TTR ⁴	p<0.0001
Change from baseline in NT-proBNP ⁵	p<0.0001
All-cause mortality ^{2,6}	p=0.057

Change from Baseline in KCCQ-OS¹



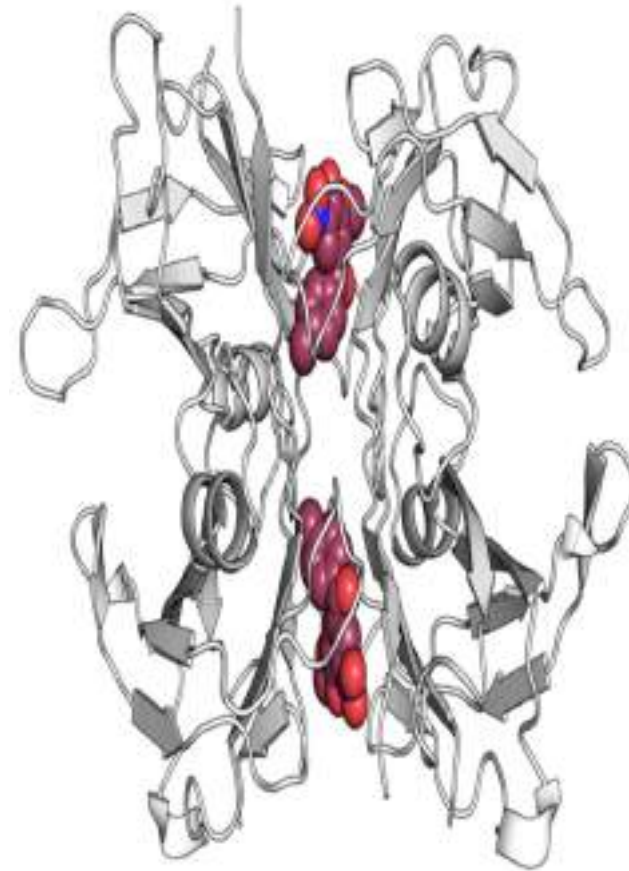
Change from Baseline in 6MWD¹

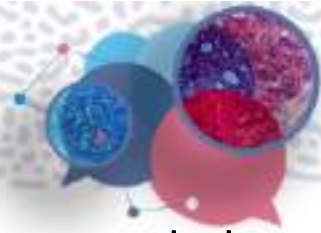




TOLCAPONE

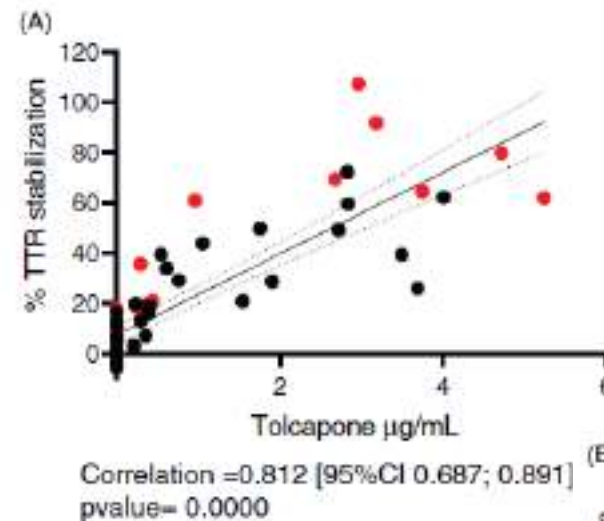
- La tolcapone est un inhibiteur de la catéchol-O-méthyltransférase traditionnellement utilisé pour le traitement de la maladie de Parkinson
- Son action stabilisatrice sur la TTR peut être due à une forte affinité pour le site de liaison T4





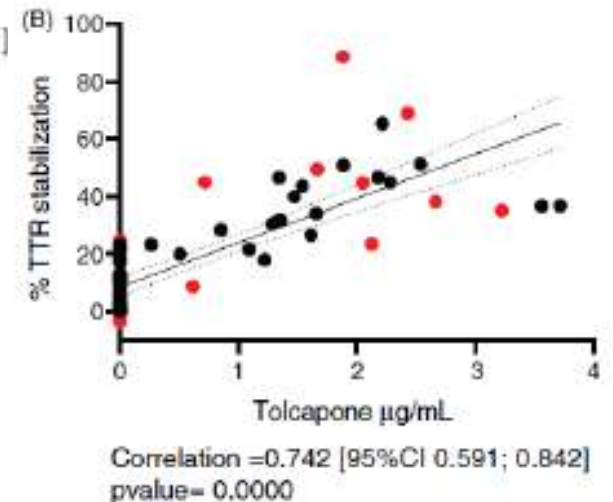
Transthyretin stabilization activity of the catechol-O-methyltransferase inhibitor tolcapone (SOM0226) in hereditary ATTR amyloidosis patients and asymptomatic carriers: Proof-of-concept study

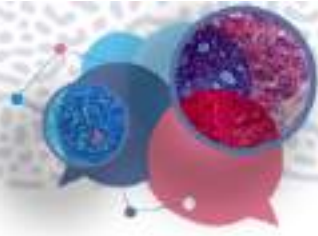
- Etude de preuve de concept
- 17 patients
- wild type, $n = 6$; mutation TTR Val30Met, $n = 11$
- 50% avec phénotype myocardique



200 mg en une seule prise

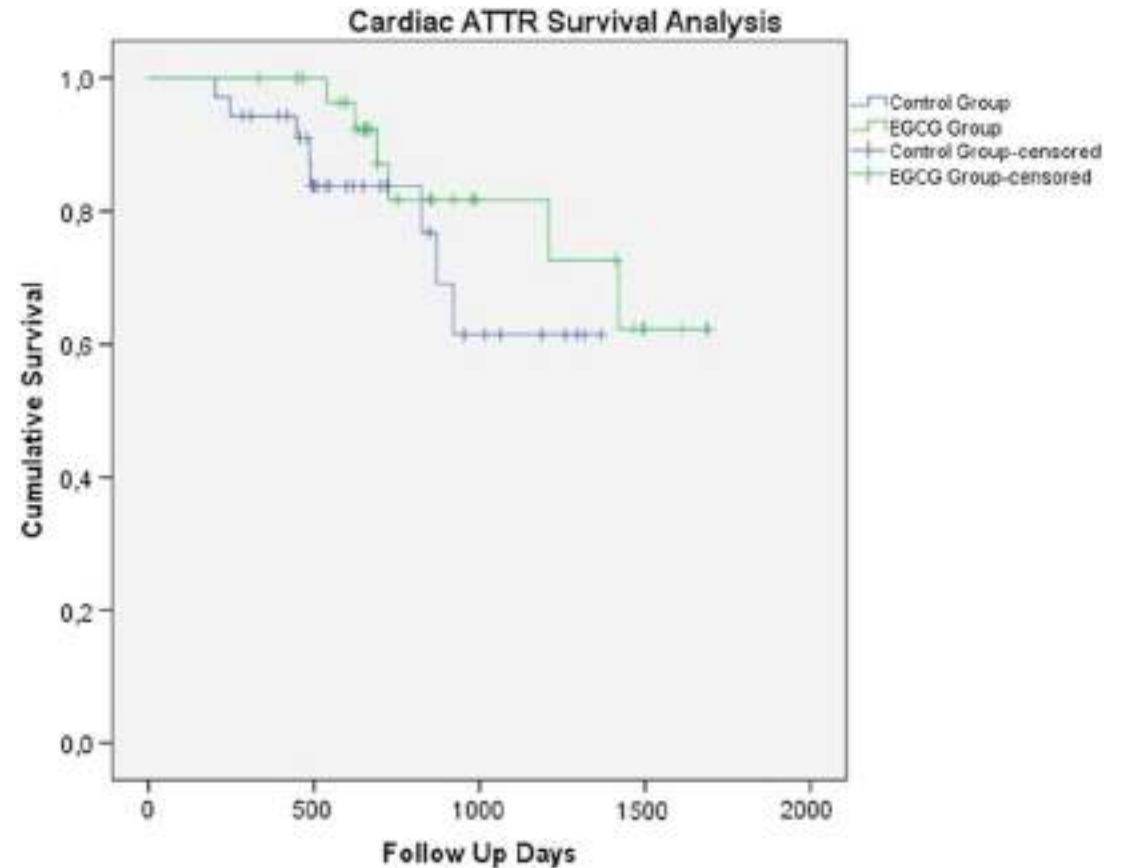
3 x 100 mg toutes les 4h

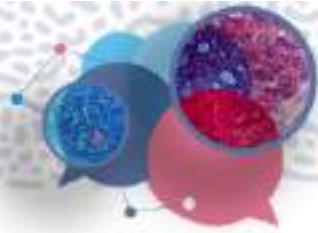




epigallocatechin-3-gallate (EGCG)

	EGCG group (N=25)		Control group (N=23)		p [*]
	Baseline	1-year FU	Baseline	1-year FU	
IVS, mm	17.7 ± 2.3	18.4 ± 3.0	16.8 ± 2.7	17.8 ± 3.5	0.659
PW, mm	16.6 ± 2.8	17.6 ± 3.0	15.7 ± 2.5	16.2 ± 2.8	0.495
LVEDD, mm	45.9 ± 4.7	44.0 ± 4.6	47.6 ± 6.3	45.4 ± 6.7	0.853
LVESD, mm	30 ± 2.8	28 ± 5.5	30.7 ± 3.3	28.0 ± 4.1	0.829
LVEDV, mL	90.2 ± 21.4	80.6 ± 26.8	93.9 ± 20.9	82.0 ± 33.9	0.802
LVESV, mL	44.7 ± 17.2	45.8 ± 27.2	42.7 ± 19.8	41.7 ± 23.8	0.761
EF, %	53.6 ± 9.5	51.5 ± 11.8	52.5 ± 12.9	49.9 ± 12.0	0.878
Left Atrium, cm ²	28.5 ± 7.0	30.0 ± 5.9	27.6 ± 9.1	26.2 ± 6.0	0.325
TAPSE, mm	18.7 ± 4.5	15.8 ± 5.2	17.6 ± 4.6	16.4 ± 5.6	0.110
PASP, mmHg	36.8 ± 10.0	39.3 ± 8.5	39.31 ± 8.8	36.5 ± 5.4	0.119
LV mass, g/m ²	193.6 ± 42.8	192.5 ± 61.9	164.4 ± 5	166.6 ± 48.2	0.849
E/E [*]	16.0 ± 4.4	15.3 ± 6	17.8 ± 6	18.8 ± 8	0.535
NT-proBNP	4612 ± 5758	6436 ± 7207	5264 ± 5441	5854 ± 6393	0.117





Conclusion

- 2 molécules prometteuses
 - TAFAMIDIS
 - ACORAMIDIS
 - (un abandon du DIFLUNISAL un peu rapide?)
- A quand une étude randomisée de combinaison initiale
 - X 2 stabilisateurs
 - 1 stabilisateur + SI RNA/ASO