

# Amyloses cardiaques et biomarqueurs

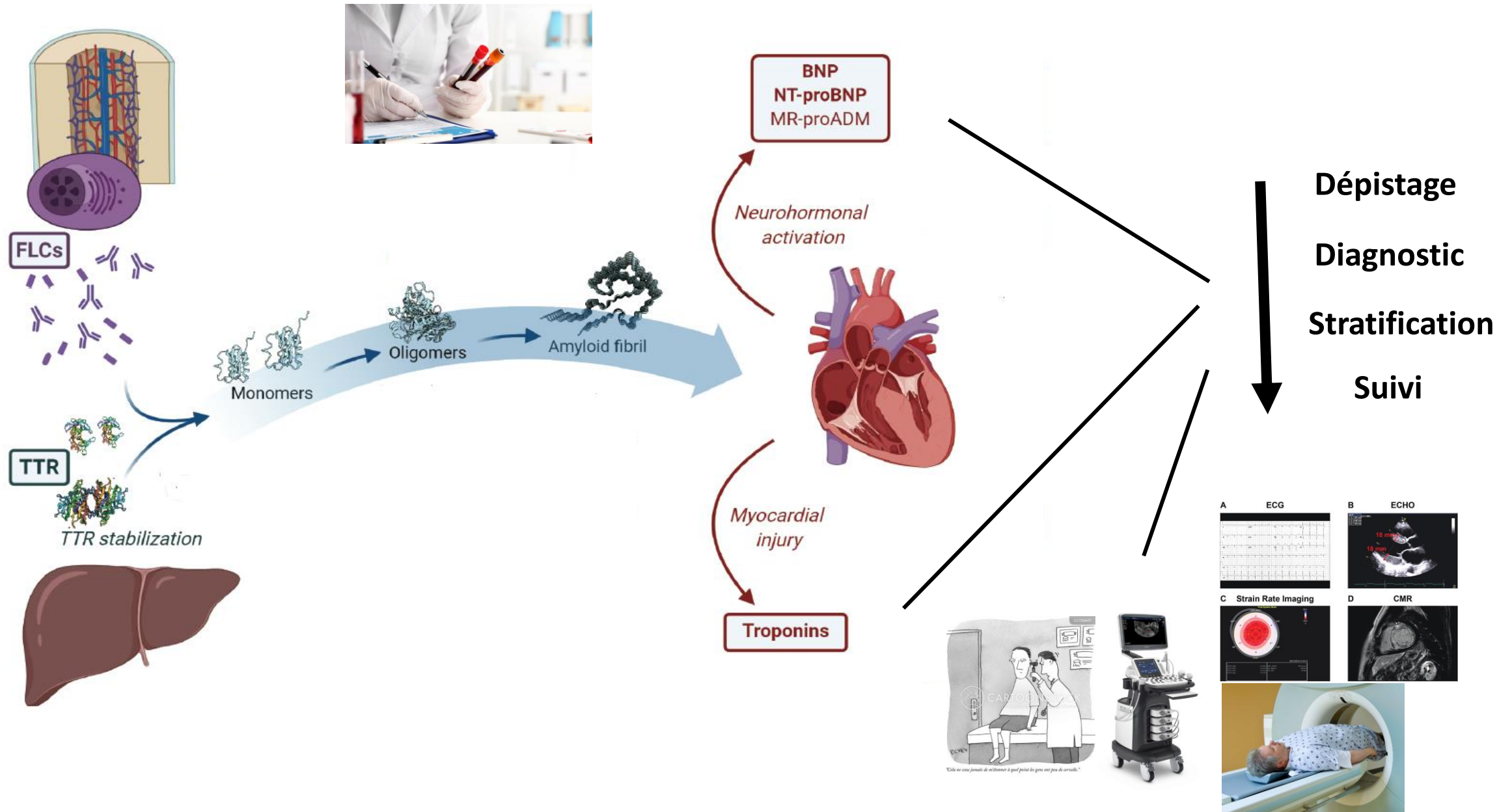
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Hôpital Lariboisière, APHP

Université Paris Cité



# De quels biomarqueurs disposons nous et pourquoi faire?



# Peptides natriurétiques de type B

## Stimuli de synthèse

- Pressions de remplissage
- Contraintes pariétales
- Masse ventriculaire
- Débit cardiaque
- Catécholamines, AgII
- Cytokines

Age  
Insuffisance rénale  
Fibrillation atriale  
Sepsis  
Maladies pulmonaires/HTAP

Obésité

+

-

**NTproBNP**

BNP  
T-proBNP  
R-proADM

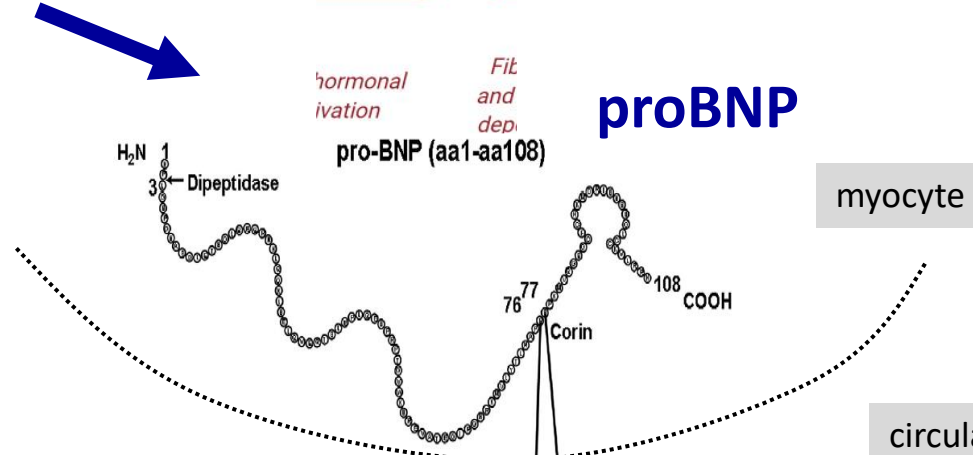
G

hormonal  
ivation

Fit  
and  
dep.

pro-BNP (aa1-aa108)

**proBNP**



myocyte

circulation

H<sub>2</sub>N 1  
3  
Dipeptidase

NTpro-BNP(aa1-aa76)

COOH 76

H<sub>2</sub>N 77

79  
Dipeptidase

COOH 108

COOH 76

H<sub>2</sub>N 77

79  
Dipeptidase

COOH 108

COOH 76

H<sub>2</sub>N 77

79  
Dipeptidase

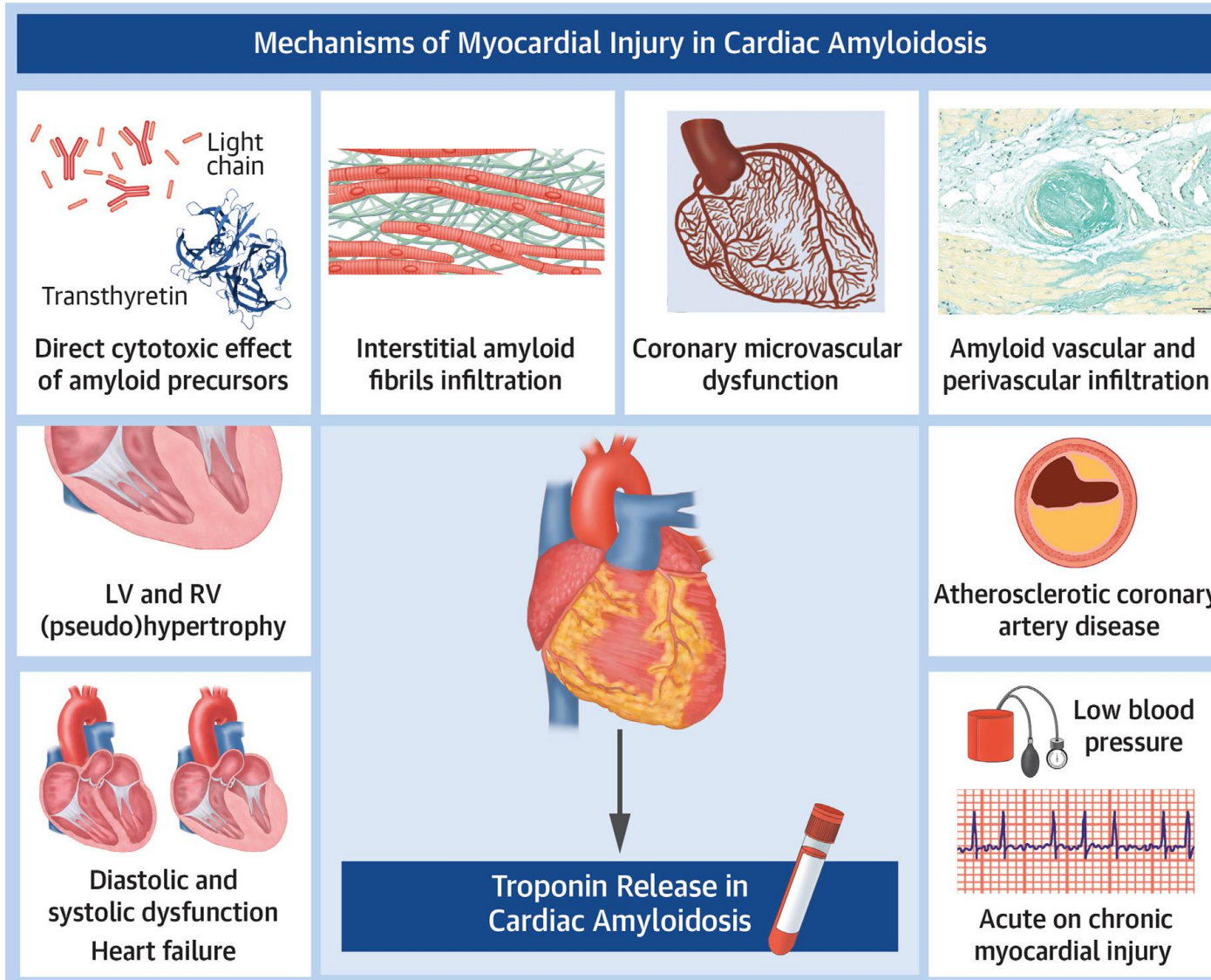
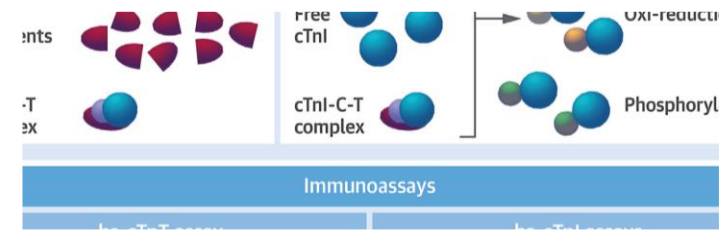
COOH 108

**BNP**

Les taux reflètent  
le degré de dysfonction cardiaque

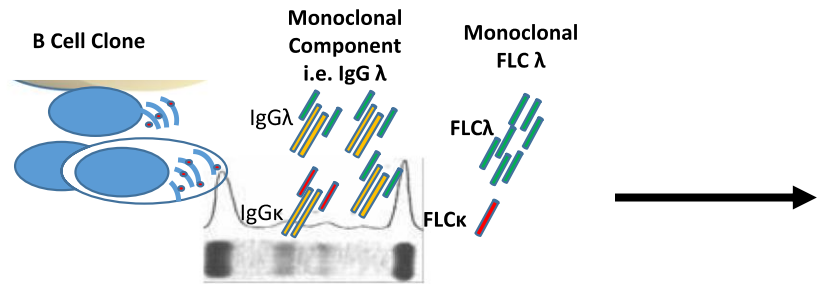
Le marqueur pronostique le plus puissant  
dans l'insuffisance cardiaque

# Troponines cardiaques



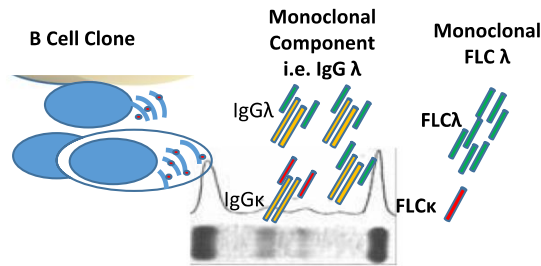
Taux de Tn dans amyloses cardiaques => + faibles que dans un infarctus

# Amyloses AL et diagnostic



- EPP
  - IEP
  - Dosage quantitatif des chaines légères  $\kappa$  et  $\lambda$
  - Purie de Bence Jones
- (ratio  $\kappa/\lambda$  0.26-1.65)

# Amyloses AL et diagnostic



- EPP
- IEP
- Dosage quantitatif des chaines légères κ et λ
- Purie de Bence Jones

BNP  
T-proBNP  
R-proADM

G

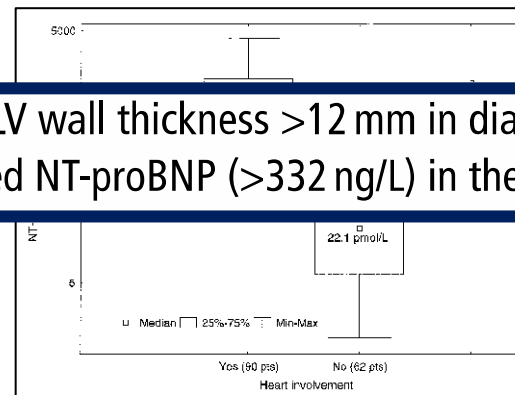
hormonal  
ivation

Fib  
and  
dep

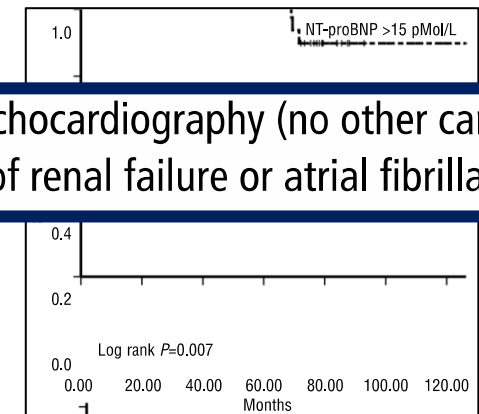
**NTproBNP (330pg/mL) (ou BNP 80pg/mL)**

Consensus  
(Mayo)

Mean LV wall thickness >12 mm in diastole on echocardiography (no other cardiac cause)  
Elevated NT-proBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation

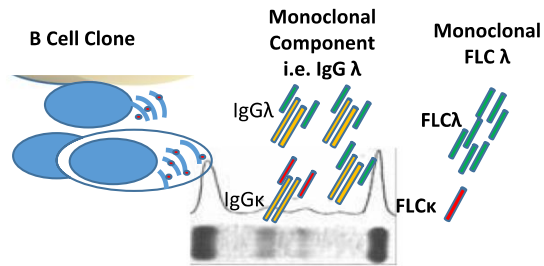


Circulation 2003;107:2440 – 2445



Haematologica | 2011; 96(7)

# Amyloses AL et diagnostic



- EPP
- IEP
- Dosage quantitatif des chaines légères  $\kappa$  et  $\lambda$
- Purie de Bence Jones

BNP  
 T-proBNP  
 R-proADM

G

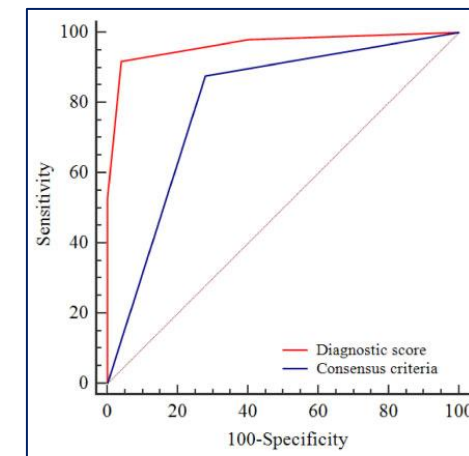
hormonal  
 ivation

Fib  
 and  
 dep

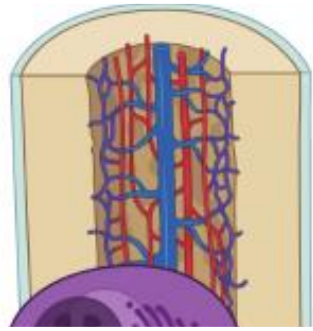
NTproBNP (330pg/mL) (ou BNP 80pg/mL)  
**Troponine cardiaque (hs-TnT 35 ng/L)**

**Table 3** Independent diagnostic variables from the multivariate analysis and diagnostic score

Variables	Log OR	Standard error	P-value	Point in the new score
GLS $\geq$ -17%	4.1	1.27	0.001	1
Apical sparing of GLS $\geq$ 0.90	3.9	1.48	0.009	1
Hs troponin T >35 ng/L	3.9	1.28	0.002	1



# Amyloses TTR et diagnostic

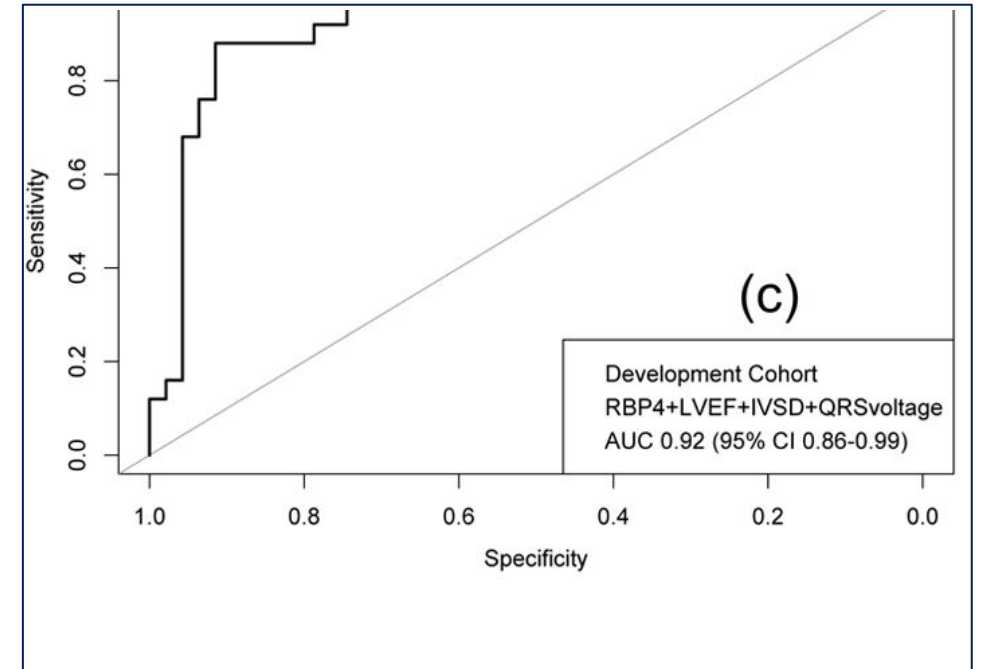
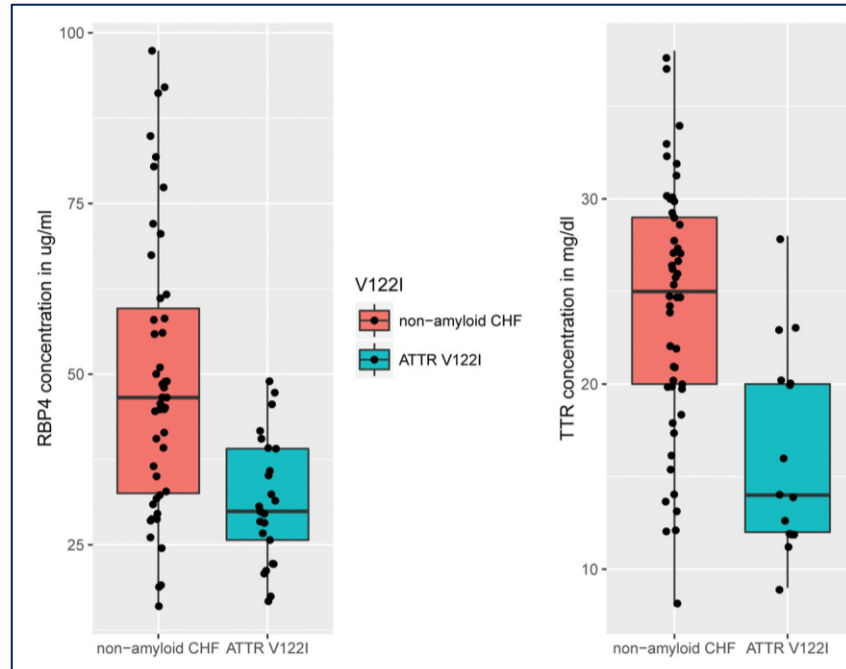


*B*  
*meta*



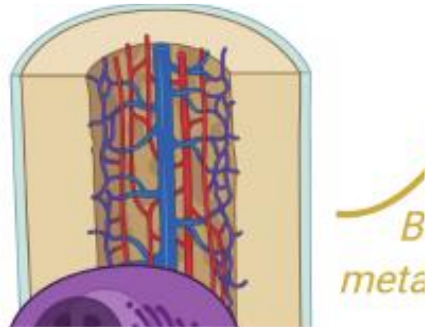
- TTR ?
- RBP4 ?

Identification of V122I (Val122Ile) transthyretin cardiac amyloidosis (ATTR) using serum retinol-binding protein 4 (RBP4) and a clinical prediction model





# Amyloses TTR et diagnostic



- TTR ?
- RBP4 ?

BNP  
Γ-proBNP  
R-proADM

G

hormonal  
ivation

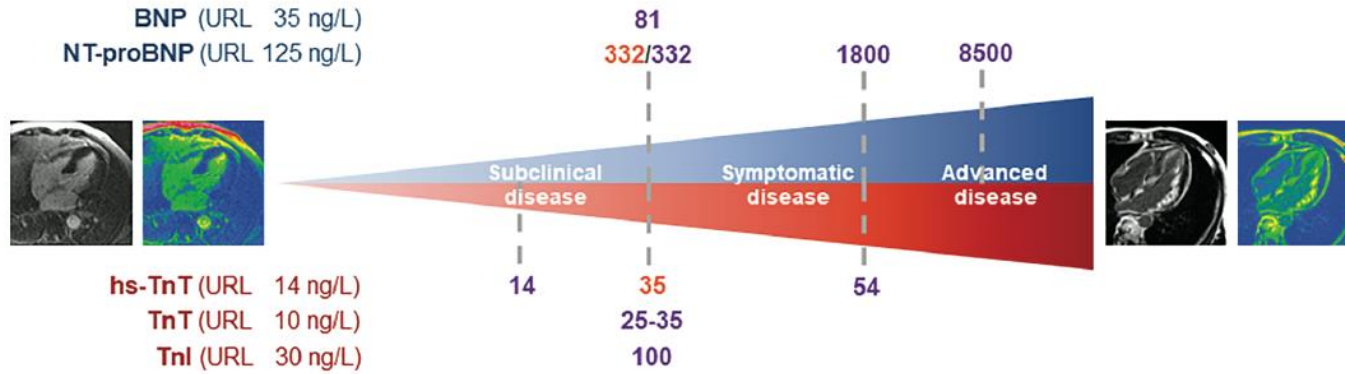
Fib  
and  
depo

**NTproBNP (82pg/mL)**  
Troponine cardiaque (TnT 10 ng/L)

(Taux moindres que amylose AL)

# Amyloses et stratification par les biomarqueurs

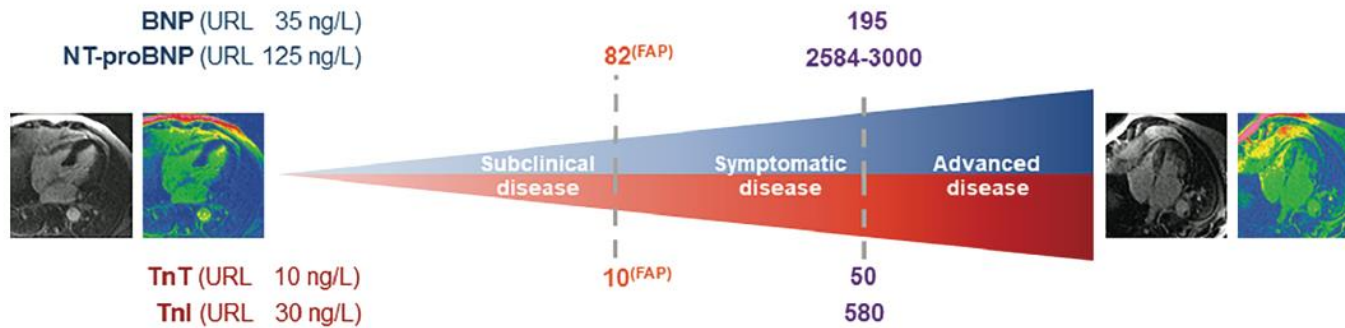
## AL amyloidosis



## Seuils pronostiques

NTproBNP 1800 pg/mL  
Hs-TnT 54 ng/L

## ATTR amyloidosis



NTproBNP 3000 pg/mL  
TnT 50 ng/L

Diagnostic cut-off for cardiac involvement  
Prognostic cut-off

# Amylose AL et stratification, scores pronostiques

Model	Risk factor thresholds			Stages*	Hazard ratio† for death (95%CI)
	cTnT, µg/L	NT-proBNP, ng/L	Other factors		
<b>AL amyloidosis</b>					
Mayo 2004 model	≥0.035‡	≥332	None	1	Reference
				2	2.5 (1.9-3.5)
				3	6.7 (5.0-9.1)
European 2015 modification of Mayo 2004 model	≥0.035‡	≥332	Stage 3 only: NT-proBNP >8500 ng/L	1	Reference
				2	2.6 (1.9-3.5)
				3a	4.9 (3.6-6.8)
				3b	11.1 (8.1-15.4)
Mayo 2012 model	≥0.025	≥1800§	Difference between involved to uninvolved light chain ≥180 mg/L	1	Reference
				2	1.7 (1.2-2.3)
				3	4.1 (3.1-5.5)
				4	6.3 (4.8-8.3)

**Eviter greffe cellules souches si**  
**TnT > 0.06 mg/L (hs-cTnT 75 ng/L)**  
**NTproBNP > 5000 ng/L**

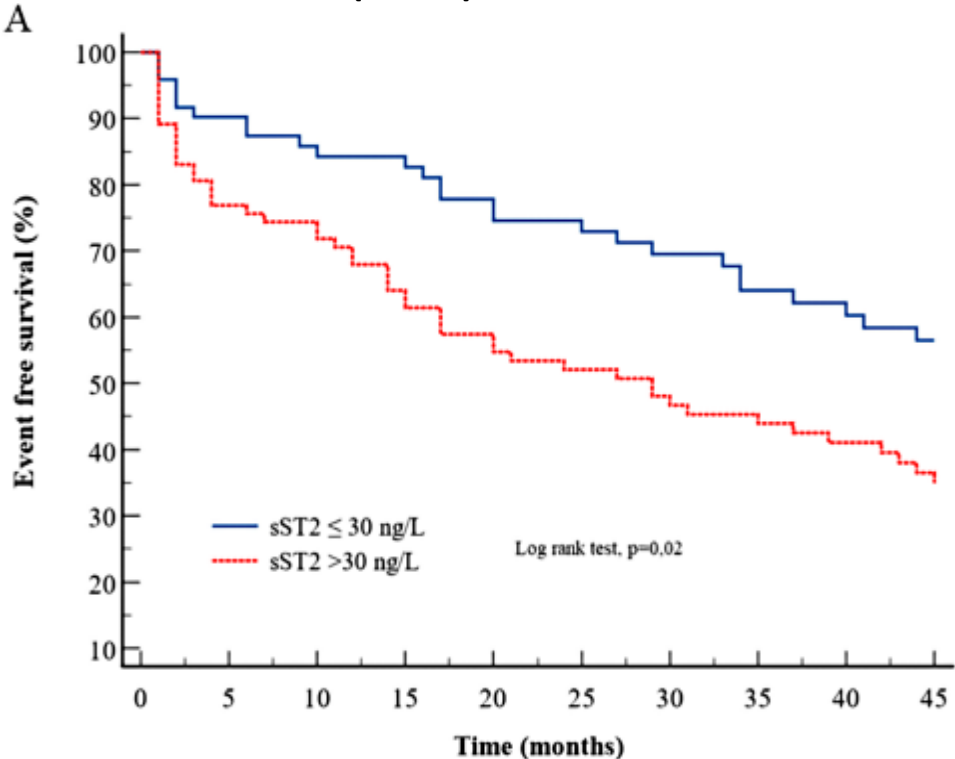
Blood 2019, 133 : 763

# Amylose AL et stratification, scores pronostiques

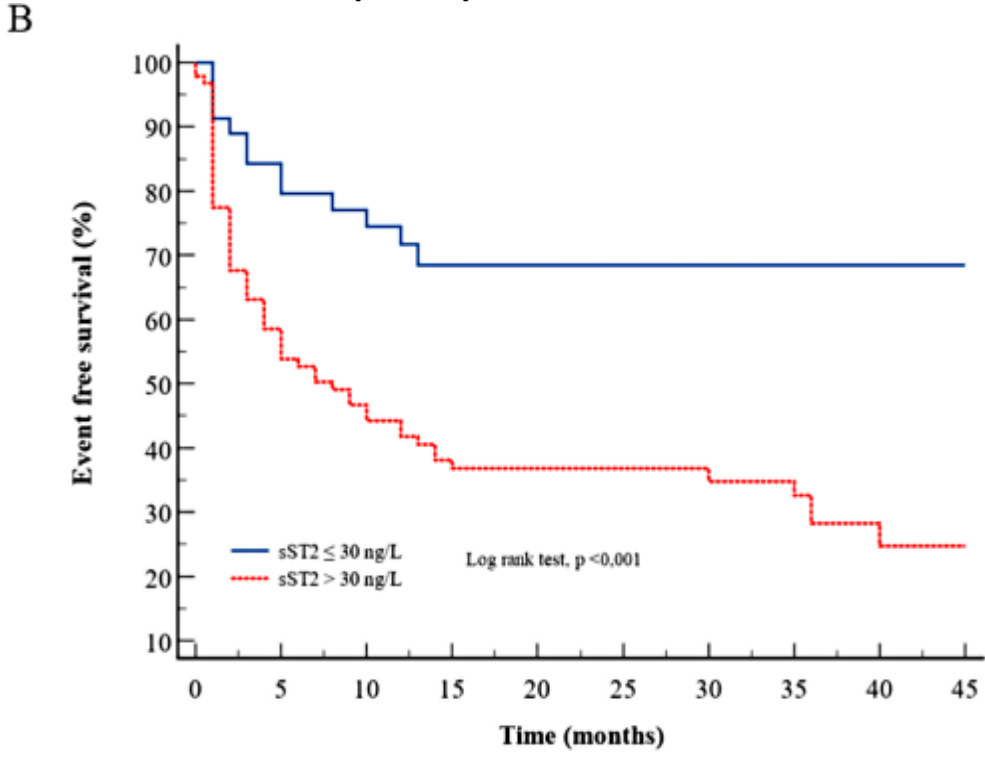
Model	cTnT, µg/L	cTnI, µg/L	Hs-cTnT, ng/L	NT-proBNP, ng/L	BNP, ng/L
<b>AL amyloidosis</b>					
Mayo 2004 model*	≥0.035	≥0.1	≥50†‡	≥332	81 <sup>21</sup>
Euro 2015 modification of Mayo 2004 model§	≥0.035	≥0.1†	≥50†‡	≥332 >8500	81 <sup>21</sup> >700 <sup>21</sup>
Mayo 2012 model	≥0.025	ND	≥41‡ Round >40	≥1800	≥400¶

# Prognostic value of soluble ST2 in AL and TTR cardiac amyloidosis: a multicenter study

**152 TTR amyloidosis**  
73y, 54 NYHA 3-4, LV mass 149,  
NTproBNP 2640, Tn 51, eGFR 55  
**sST2 32 (21-46)**



**133 AL amyloidosis**  
69y, 73 NYHA 3-4, LV mass 135  
NTproBNP 2183, Tn 55, eGFR 52  
**sST2 39 (26-80)**

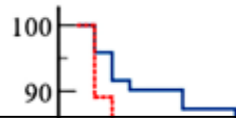


# Prognostic value of soluble ST2 in AL and TTR cardiac amyloidosis: a multicenter study

## 152 TTR amyloidosis

73y, 54 NYHA 3-4, LV mass 149,  
NTproBNP 2640, Tn 51, eGFR 55  
**sST2 32 (21-46)**

A



Covariate without sST2	HR	CI 95%	<i>p</i>
NT-proBNP >3,000 pg/mL	3.46	1.90–6.30	<0.001
Hs cTnT >65 ng/L	1.63	0.97–2.73	0.07
eGFR <45 mL/min	1.01	0.62–1.66	0.96
AUC 0.71 (95% CI: 0.66–0.76)			
Covariate with sST2	HR	CI 95%	<i>p</i>
sST2 >30 ng/L	1.17	0.77–1.89	0.55
NT-proBNP >3,000 pg/mL	4.42	2.48–7.87	<0.001
Hs cTnT >65 ng/L	1.54	0.94–2.50	0.08
eGFR <45 mL/min	1.22	0.70–1.75	0.65
AUC 0.72 (95% CI: 0.68–0.76)			

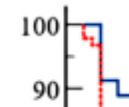
0 5 10 15 20 25 30 35 40 45

Time (months)

## 133 AL amyloidosis

69y, 73 NYHA 3-4, LV mass 135  
NTproBNP 2183, Tn 55, eGFR 52  
**sST2 39 (26-80)**

B



Covariate with sST2	HR	CI 95%	<i>p</i>
NT-proBNP >1,800 pg/mL	1.28	0.69–2.38	0.50
<b>sST2 &gt;30 ng/L</b>	<b>3.92</b>	<b>1.65–9.32</b>	<b>0.002</b>
Hs cTnT >40 ng/L	2.48	1.20–5.12	0.01
DFLC >180	1.68	0.94–3.00	0.07
AUC 0.73 (95% CI: 0.67–0.79)			
Covariate with sST2 in Mayo Clinic staging	HR	CI 95%	<i>p</i>
2012 Mayo Clinic staging 1–2 vs. 3–4	1.76	1.37–2.26	<0.001
<b>sST2 (ng/L) &gt;30</b>	<b>2.16</b>	<b>1.17–3.99</b>	<b>0.01</b>
AUC 0.70 (95% CI: 0.64–0.75)			

0 5 10 15 20 25 30 35 40 45

Time (months)

# Amylose AL et monitoring du traitement/suivi

Table 1. Validated haematologic response criteria for AL amyloidosis.		
Response categories	Original definition	Updated definitions
Complete response	negative serum and urine immunofixation and normal FLC ratio	<ul style="list-style-type: none"> <li>•Both criteria must be met: Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative immunofixation electrophoresis of both serum and urine</li> <li>•Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio</li> </ul>
Very good partial response	dFLC concentration < 40 mg/L	dFLC concentration < 40 mg/L
Partial response	dFLC decrease > 50% compared to baseline	dFLC decrease > 50% compared to baseline
No response	All other patients	All other patients

# Amylose AL et monitoring du traitement/suivi

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## (B) Organ response (OR)

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Organ	Criteria
Heart (NT-proBNP based)	Reduction of NT-proBNP of 30% and 300 pg/mL over the starting value Baseline NT-proBNP has to be $\geq 650$ pg/mL to be measurable
Heart (BNP based)	Reduction of BNP of 30% and 50 ng/L over the starting value Baseline BNP has to be $\geq 150$ pg/mL to be measurable
Kidney	A 30% reduction in 24-h urine protein excretion or a drop of proteinuria below 0.5 g per 24 h in the absence of progressive renal insufficiency (defined as a decrease in eGFR to 25% over baseline)
Liver	A greater than 30% reduction in hepatomegaly on physical exam or a 50% decrease of an elevated alkaline phosphatase level

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Majoration NTproBNP > 30% ou > 300pg/mL ou Tn > 33% ou diminution de FEVG > 10%  
=> aggravation de l'atteinte cardiaque

Chimio immunomodulatrices (Thalidomide, Lenalidomide and Pomalidomide)  
=> cardiotoxiques => majoration biomarqueurs cardiaques



# Amylose TTR et stratification, scores pronostiques

## Grogan et al., 2016 (Mayo)<sup>4</sup> ATTRwt

Staging parameters:

Troponin T >0.05 ng/mL

NT-proBNP >3000 pg/mL

## Gillmore et al., 2018 (NAC)<sup>14</sup> ATTRv and ATTRwt

Staging parameters:

eGFR <45 mL/min

NT-proBNP >3000 pg/mL

## Cheng et al., 2020 (Columbia)<sup>15</sup> ATTRv and ATTRwt

Scoring parameters:

Mayo or NAC score (0 to 2 points)

Daily dose of furosemide or equivalent:

0 mg/kg (0 points), >0–0.5 mg/kg (1 point),

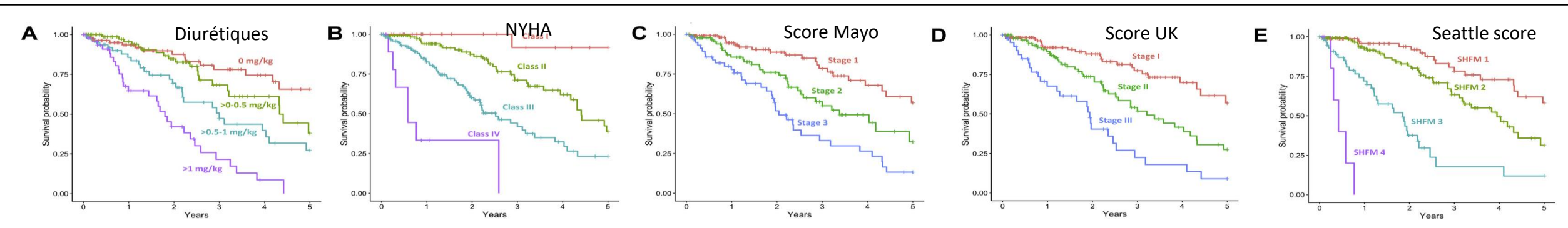
>0.5–1 mg/kg (2 points), and >1 mg/kg (3 points)

NYHA class I–IV (1 to 4 points)

Stage	Median survival	Stage	Median survival	Score	Mean survival
Stage I (0 parameters)	66 months	Stage I (0 parameters)	69.2 months	Score 1–3	78 months
Stage II (1 parameter)	40 months	Stage II (1 parameter)	46.7 months	Score 4–6	48 months (Mayo) 45.6 months (NAC)
Stage III (2 parameters)	20 months	Stage III (2 parameters)	24.1 months	Score 7–9	26.4 months (Mayo) 22.8 months (NAC)

# Amylose TTR et stratification, scores pronostiques

Incremental Benefit of Adding Diuretic Dose and NYHA Class to TTR Amyloidosis Cardiomyopathy Risk Models for All-Cause Mortality

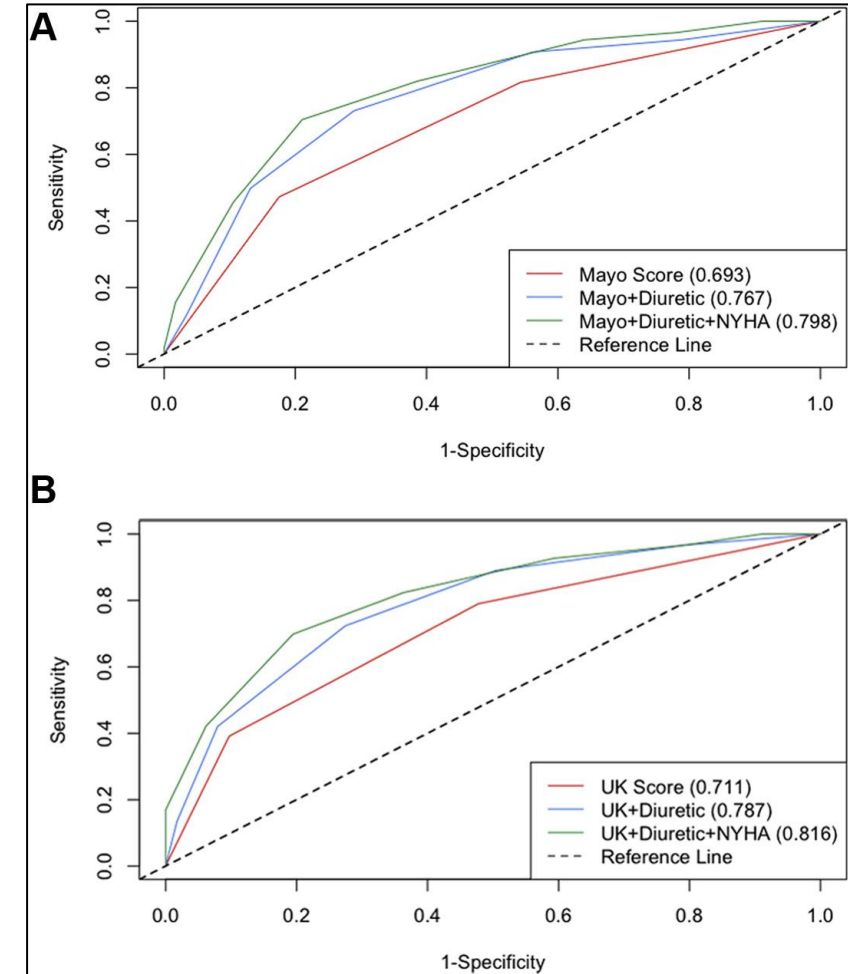
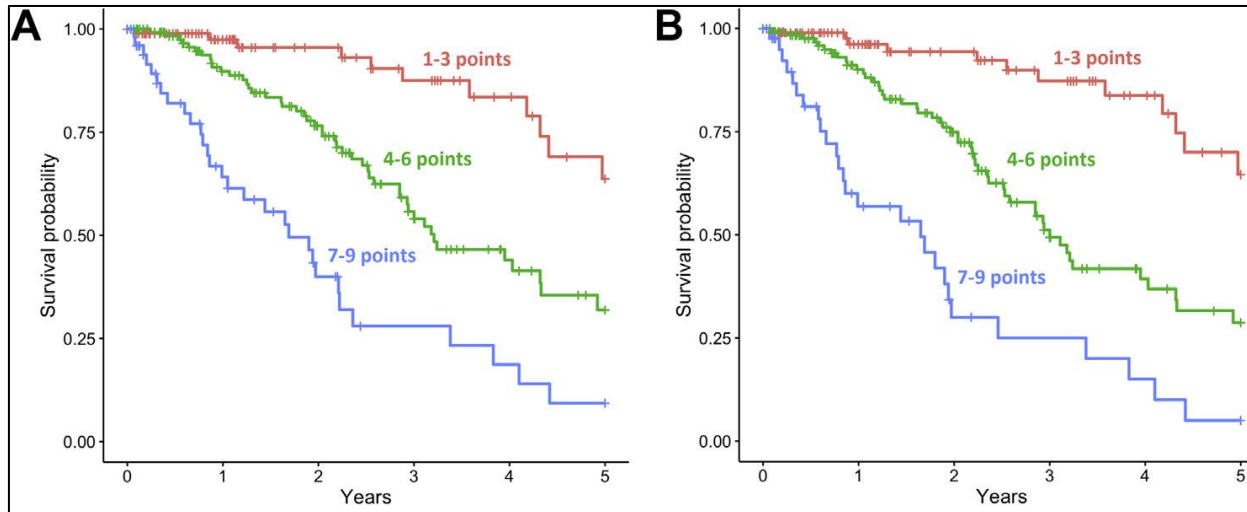
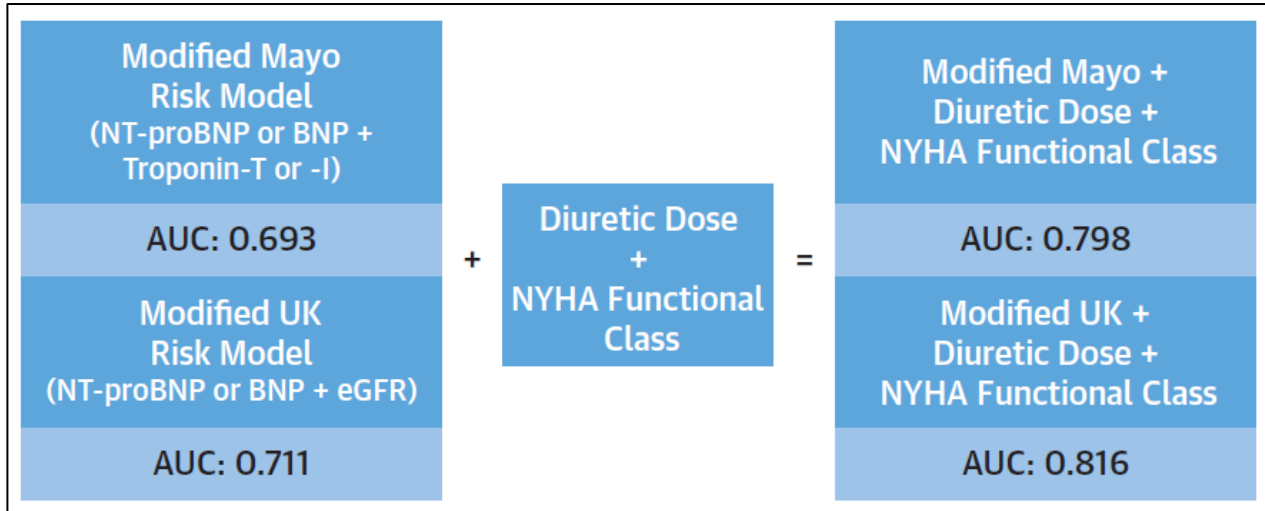


309 patients,  
cohorte monocentrique

	All-Cause Mortality AUC (95% CI)	Gain From Reference	p Value
<b>Mayo model</b>	<b>0.693 (0.609-0.777)</b>	Reference	Reference
Diuretic dose only	0.713 (0.627-0.799)	0.020	0.784
Mayo + diuretic dose	0.767 (0.692-0.843)	0.074	0.046
Mayo + diuretic dose + NYHA functional class	0.798 (0.729-0.868)	0.105	0.006
SHFM	0.820 (0.751-0.889)	0.127	<0.001
<b>UK model</b>	<b>0.711 (0.630-0.792)</b>	Reference	Reference
Diuretic dose only	0.713 (0.627-0.799)	0.002	0.918
UK + diuretic dose	0.787 (0.717-0.856)	0.076	0.059
UK + diuretic dose + NYHA functional class	0.816 (0.749-0.883)	0.105	0.009
SHFM	0.820 (0.751-0.889)	0.109	0.011

# Amylose TTR et stratification, scores pronostiques

Incremental Benefit of Adding Diuretic Dose and NYHA Class to TTR Amyloidosis Cardiomyopathy Risk Models for All-Cause Mortality



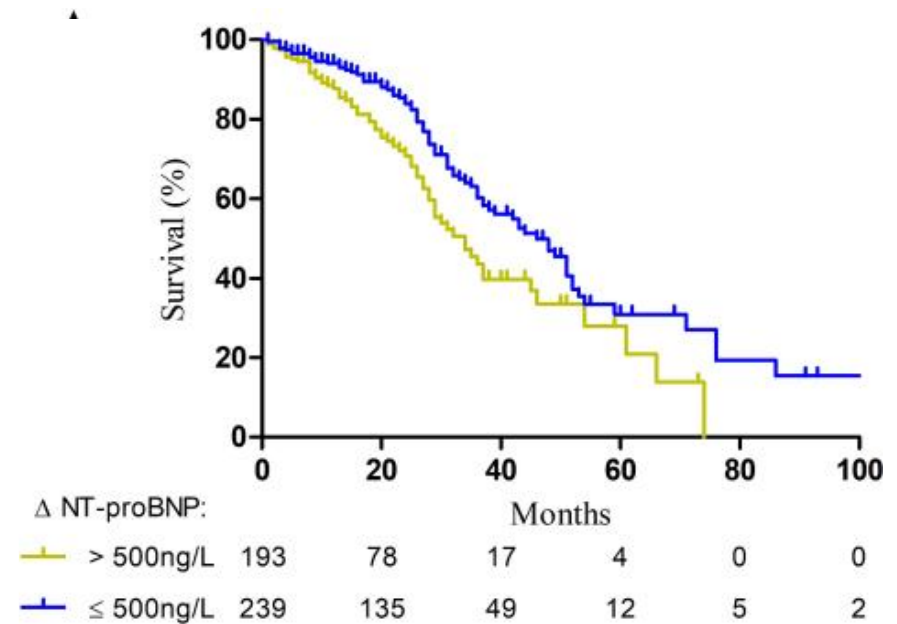
# Amylose TTR et monitoring/suivi

## Majoration du NTproBNP au fil du temps : plus puissant marqueur de gravité

**Table 3** Multivariable analysis including  $\Delta$  NT-proBNP at 12 months and a range of variables and baseline patient characteristics known to affect prognosis

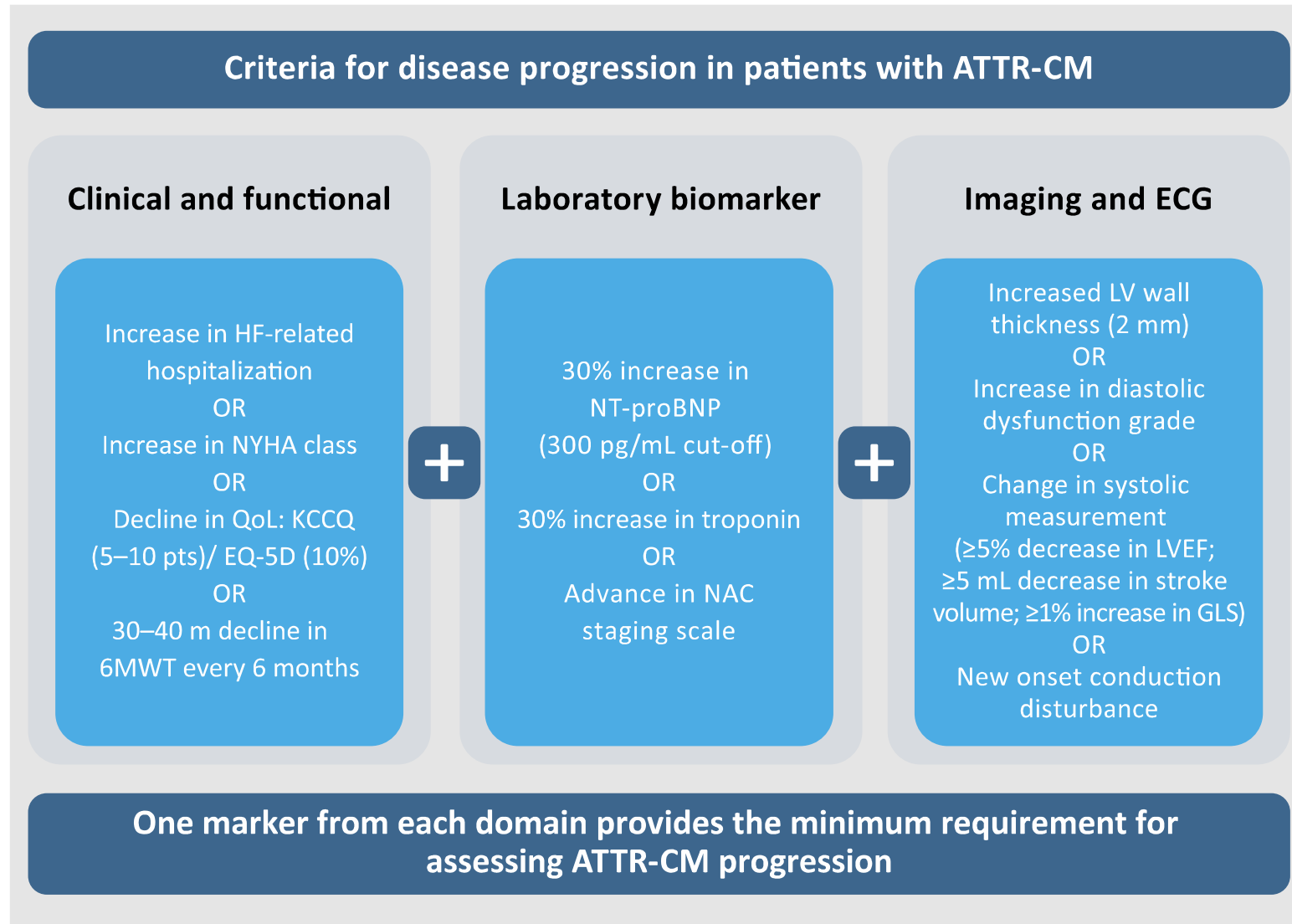
	HR	95% CI	P value
$\Delta$ NT-proBNP at 12 months*	1.07	1.02 to 1.13	<b>0.007</b>
Diagnostic NT-proBNP (ng/L)*	1.07	1.02 to 1.13	<b>0.006</b>
Diagnostic troponin T (ng/L)	1.01	1.00 to 1.02	0.147
Diagnostic eGFR (mL/min/1.73 m <sup>2</sup> )	1.01	0.99 to 1.03	0.377
Age at diagnosis	1.08	1.02 to 1.13	<b>0.004</b>
NYHA class at diagnosis			
I	1		
II	0.74	0.33 to 1.65	0.461
$\geq$ III	0.39	0.14 to 1.15	0.089
IVSd at diagnosis	0.93	0.81 to 1.07	0.321
Body mass index (kg/m <sup>2</sup> )	0.95	0.88 to 1.03	0.244
6 min walk test distance at diagnosis (m) <sup>†</sup>	0.91	0.72 to 1.16	0.457
Atrial fibrillation	0.90	0.50 to 1.63	0.738
Hypertension	1.01	0.54 to 1.89	0.986
Diabetes	2.19	0.99 to 4.86	0.054
Permanent pacemaker in situ	0.73	0.31 to 1.68	0.454
Aortic stenosis <sup>‡</sup>	1.47	0.53 to 4.11	0.459

432 patients avec wtATTR-CM au UK NAC  
Pas de tafamidis



Law S, et al. *Heart* 2022;108:474–478.

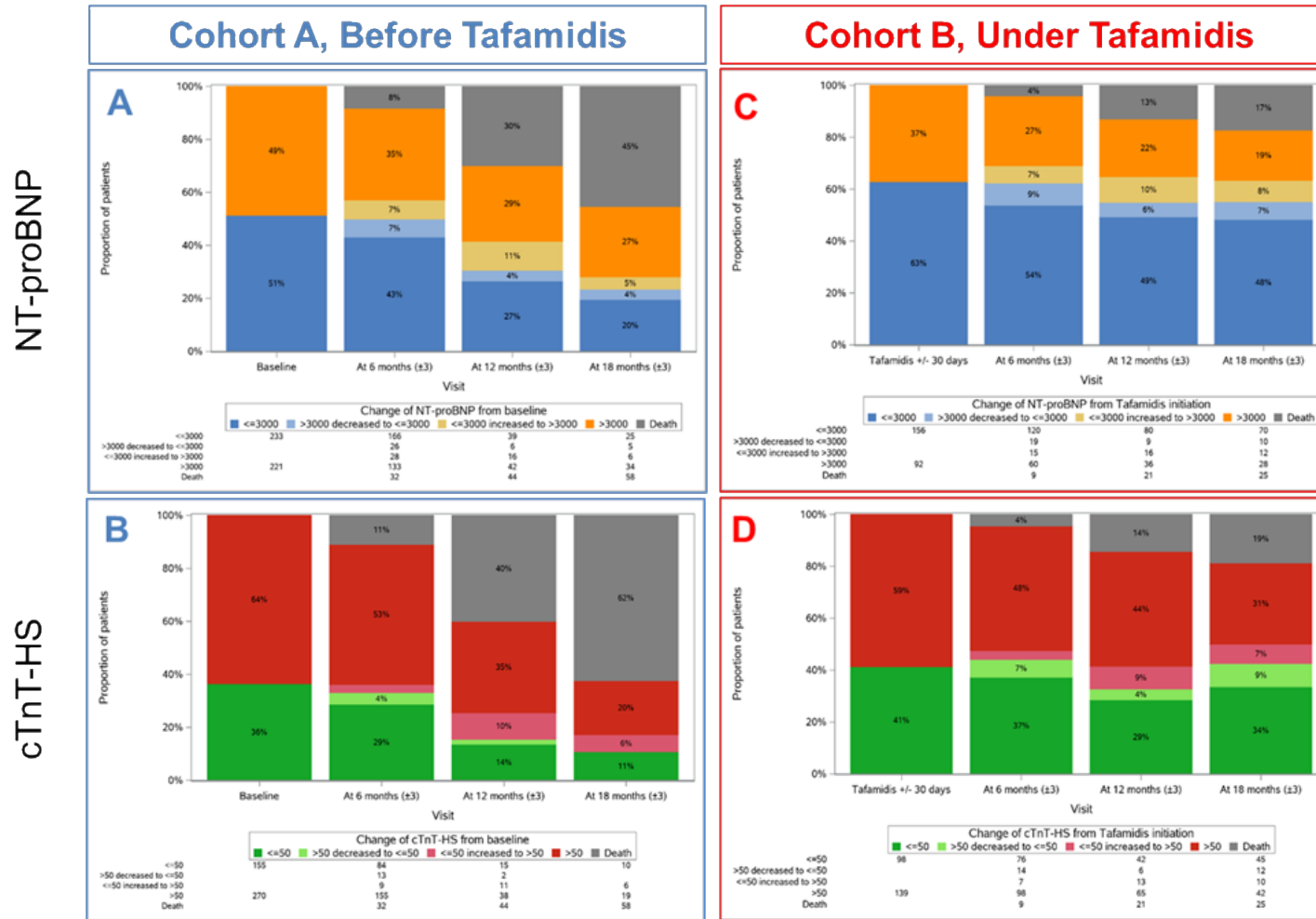
# Amylose TTR et monitoring/suivi



# Amylose TTR et monitoring/suivi

Majoration du NTproBNP au fil du temps : plus puissant marqueur de gravité (> Troponine)

Sous tafamidis : réduction de la majoration de NTproBNP et troponine

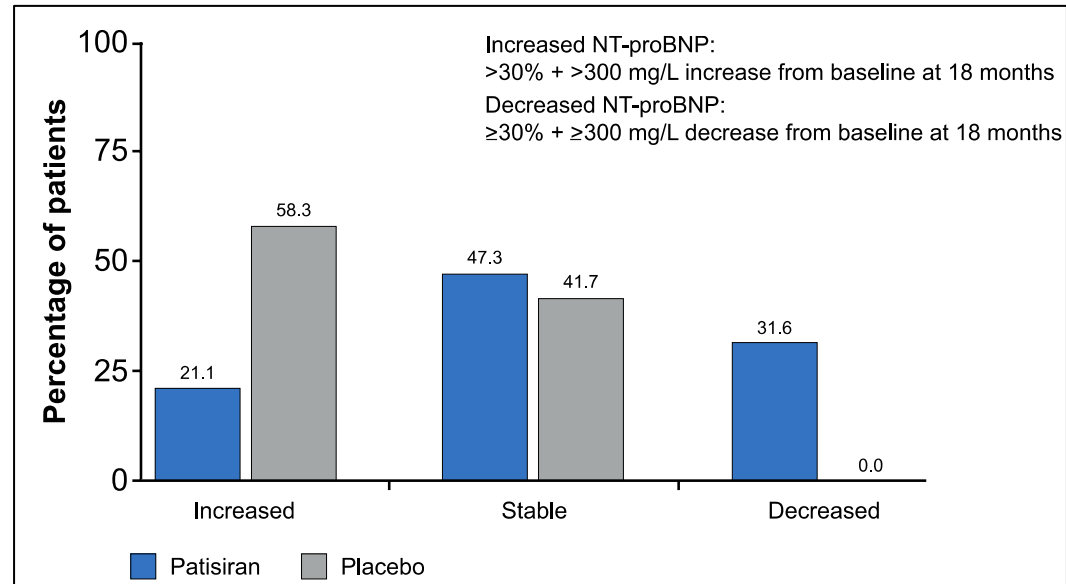
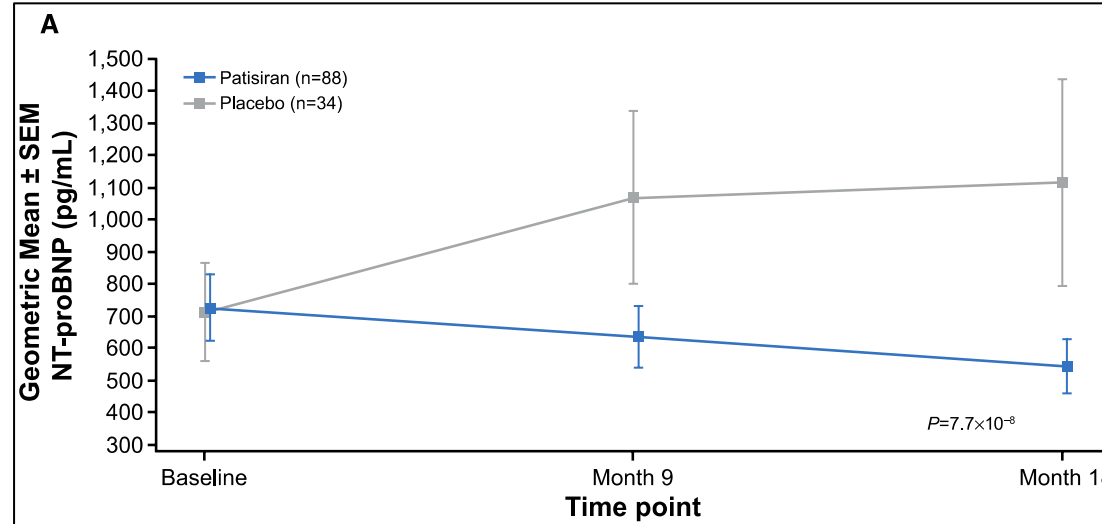
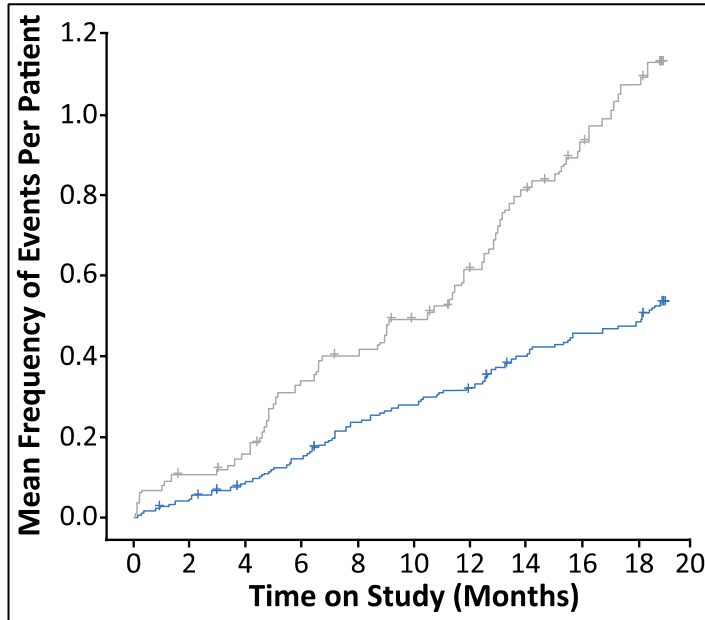


N = 454

N = 248

# Amylose TTR et monitoring/suivi

APOLLO : baisse du NTproBNP sous patisiran (sous population cardiaque , n = 126)



# Conclusions

- Amyloses cardiaques : majoration des taux de BNP/NTproBNP et de troponine.
- Outils diagnostiques et pronostiques très puissants  
=> base des scores recommandés.
- Recommandés (NTproBNP surtout) comme critères de suivi.  
Possibilité de les utiliser comme critères de substitution : à étudier
- Dépistage des populations à risque par biomarqueurs cardiaques => à étudier  
(porteurs de mutations, amyloses sans atteinte cardiaque, MGUS, IC-FE préservée sans cause, RAC)