

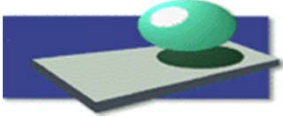


# Nouveautés pour les Biomarqueurs Biologiques de l'Insuffisance Cardiaque

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ACNBH



ODPC N°1495

**3<sup>èmes</sup> Journées Francophones de Biologie médicale**  
**Monaco, 6-8 novembre 2019**



**DECLARATION D'INTERET**  
**DANS LE CADRE DE MISSIONS DE FORMATION**  
**RÉALISÉES POUR L'ACNBH**

**Pr JP CRISTOL**

**Exerçant au CHU de Montpellier**  
**déclare sur l'honneur**

**avoir été orateur à titre d'expert, pour Siemens, Diasys, Sanofi, Novartis**

**mais ne pas avoir d'intérêt, direct ou indirect (financier), avec les entreprises pharmaceutiques, du diagnostic ou d'édition de logiciels susceptible de modifier mon jugement ou mes propos, concernant le sujet et les DMDIV présentés.**

# **Biomarqueurs de l'Insuffisance Cardiaque**

## **I) Les Biomarqueurs en 2019**

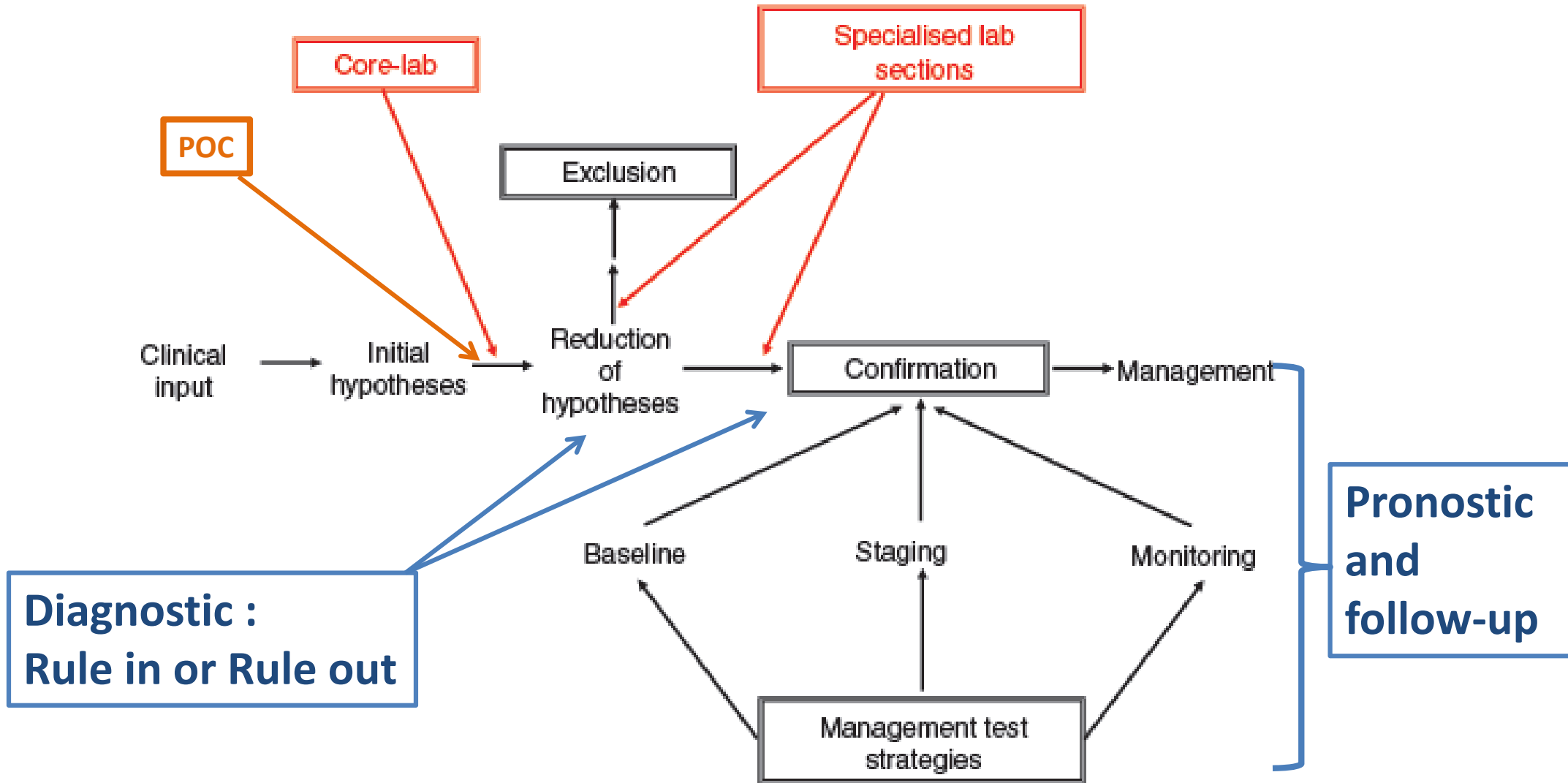
- Qu'attendre d'un Biomarqueur ?**
- Quel critère analytique ou biologique**

## **II) Les peptides natriurétiques : 20 ans après**

## **III) Quelle place pour le Laboratoire en dehors des peptides ?**

## **IV) La voie du ST2 et la stratégie multimarqueur.**

# Quel apport pour la biologie ?



# Un biomarqueur : plus que des critères analytiques, des critères biologiques

- 1) The interindividual (CVG) variance reflects changes between a relevant population of subjects.
- 2) The intraindividual (CVI) variance reflects changes within a subject over time
- 3) The index of individuality :  $CVI / CVG$ 
  - < 0.6 usefull for monitoring : Creatinine II : 0.27
  - > 0.6 usefull for diagnostic : Cystatine II : 1.64
- 4) The reference change value

# Optimal cutoff should be determined according to Reference Change Value observed in healthy subjects

## Reference Change Values (RCV)

- The “reference change value” is the modification in level that would be expected due to inherent sources of variation.
- In order to decide whether a change is due to the patient improving or deteriorating, the observed variation must be greater than the “reference change value” .
- The RCV depend on probability [Z], analytical [CVA] and within-subject biological [CVI] variation, if pre-analytical variation is minimized –

# Pathobiologic processes in HF and biomarkers

## Seven pathobiologic processes operative in HF :

Myocyte injury :

hs-TN

Myocyte stretch :

Natriuretic peptides

Myocardial fibrosis and remodeling :

sST2; Galectine; GDF-15,  
métabolisme du collagène

Inflammation :

hs-CRP, suPAR

Oxidative stress :

?

Neurohormonal activation :

Rénine/aldo –  
chromogranine A

Renal function :

Cardio-renal syndrome

# **Biomarqueurs de l'Insuffisance Cardiaque**

## **I) Les Biomarqueurs en 2019**

- Biomarqueurs de diagnostique et de pronostique**
- Variabilité intra et interindividuelle, RCV**

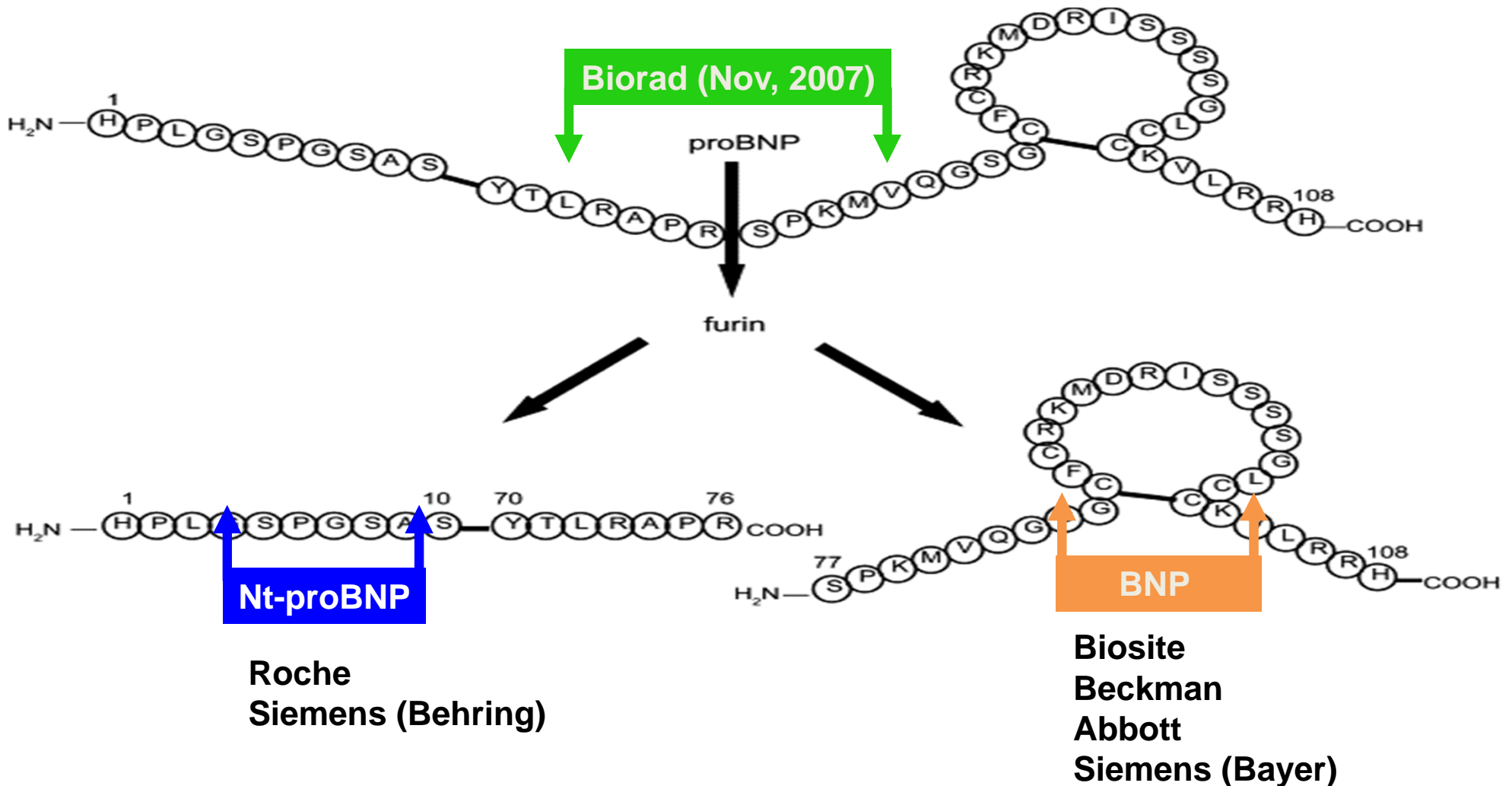
## **II) Les peptides natriurétiques : 20 ans après**

## **III) Quelle place pour le Laboratoire en dehors des peptides ?**

## **IV) La voie du ST2 et la stratégie multimarqueur.**



# Natriuretic Peptides are synthesized in response to a mechanical stress



# Insuffisance cardiaque (IC)

## Diagnostic et évaluation initiale de l'insuffisance cardiaque (IC)

- Penser à l'IC :
  - même devant des signes non spécifiques chez la personne âgée
  - dosage BNP ou NT-proBNP si doute diagnostique
- Prévoir une consultation cardiologique avec ECG et échocardiographie Doppler qui :
  - confirme ou non le diagnostic d'IC
  - distingue IC systolique (ICS) ou IC à fraction d'éjection préservée (ICFEP)
- Définir le stade fonctionnel NYHA
- Rechercher des critères de mauvais pronostic
- Rechercher des causes déclenchantes de décompensation :
  - notamment fibrillation auriculaire (FA), cause pulmonaire
- Évaluer les besoins du patient :
  - avec évaluation gériatrique si nécessaire
- Annoncer le diagnostic

# Natriuretic peptides in the definition of Heart Failure

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

Type of HF	HFrEF	HFmrEF	HFpEF
<b>CRITERIA</b>	<b>1</b>	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>
	<b>2</b>	LVEF <40%	LVEF 40–49%
	<b>3</b>	–	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).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

<sup>a</sup>Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

<sup>b</sup>BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL

# 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

## Biomarkers: Recommendation for Diagnosis

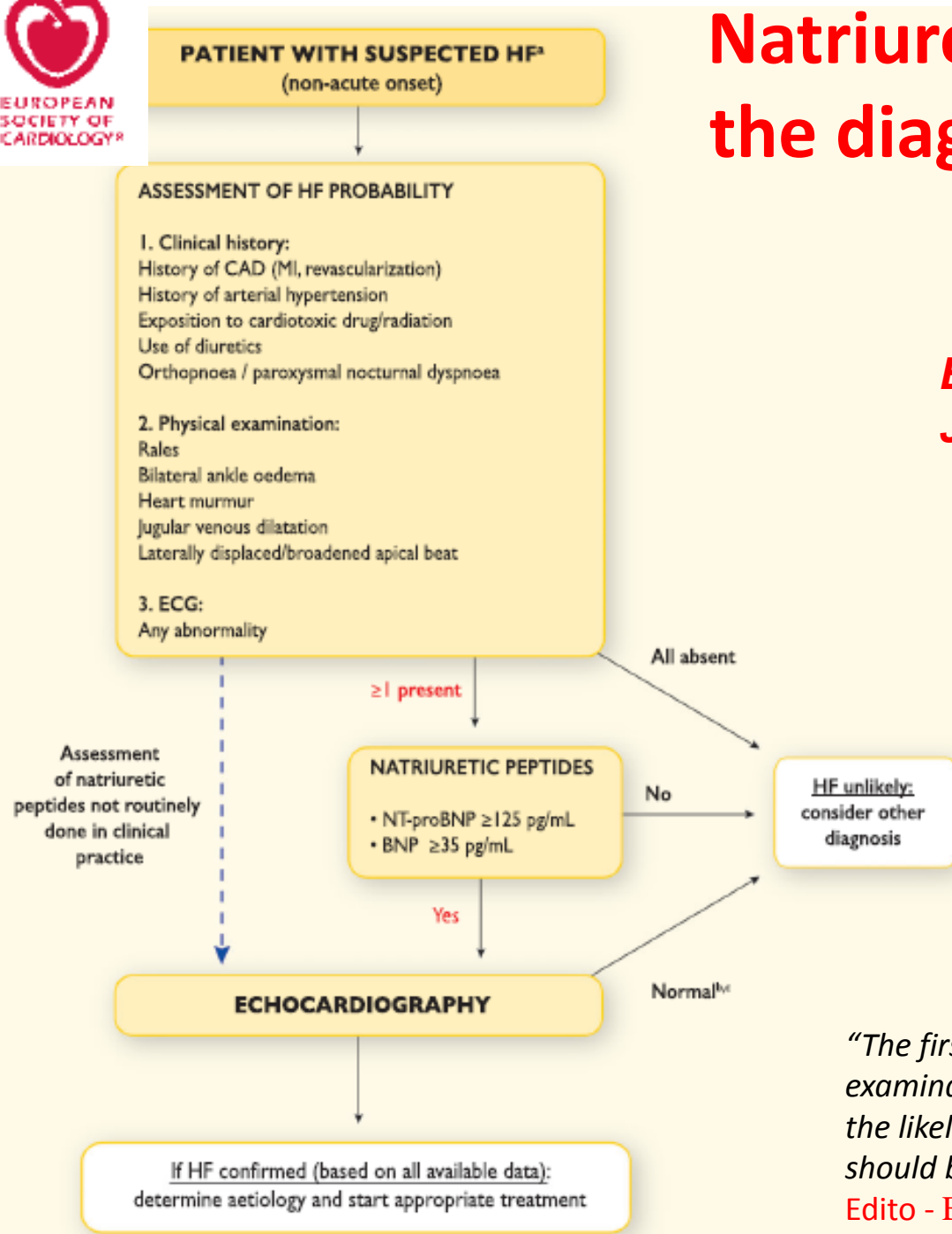
COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a <u>diagnosis or exclusion of HF (15–24,28–30)</u> .	<b>MODIFIED:</b> 2013 acute and chronic recommendations have been combined into a diagnosis section.

See Online Data Supplements A and B.

Natriuretic peptide biomarker testing in the setting of chronic ambulatory HF provides incremental diagnostic value to clinical judgment, especially when the etiology of dyspnea is unclear (15–21). In emergency settings, natriuretic peptide biomarker levels usually have higher sensitivity than specificity and may be more useful for ruling out than ruling in HF (20). Although lower values of natriuretic peptide biomarkers exclude the presence of HF, and higher values have reasonably high positive predictive value to diagnose HF, clinicians should be aware that elevated plasma levels for both natriuretic peptides have been associated with a wide variety of cardiac and noncardiac causes (Table 2) (38–41).

# Natriuretic Peptides : Algorithm for the diagnosis of heart failure in the non-acute setting

*ESC Guidelines – European Heart Journal (2016) 37:2129-2200*



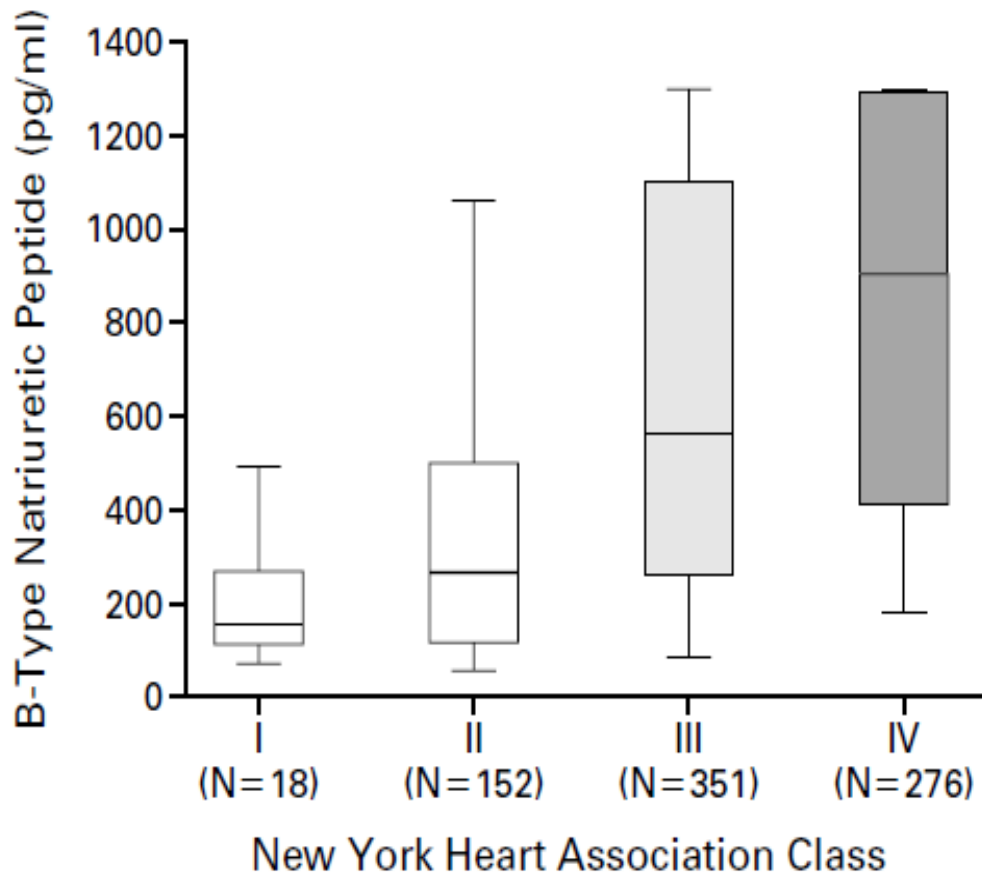
**=> Résultat rapide**



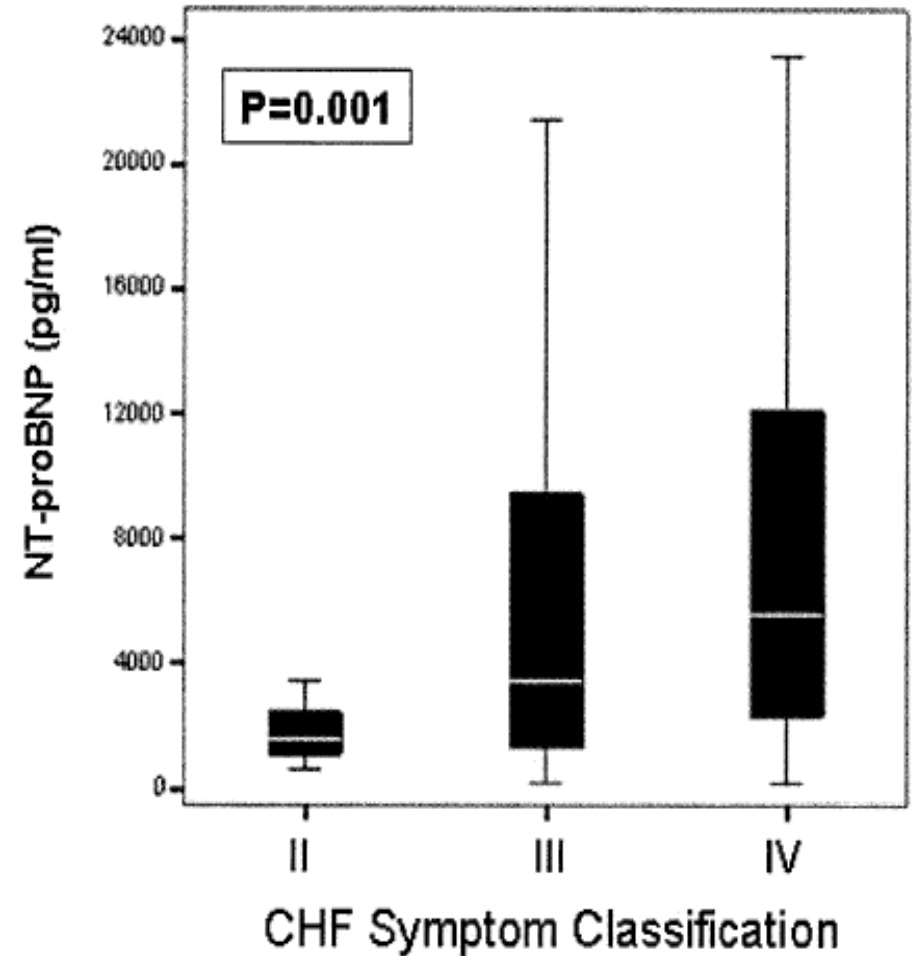
*“The first workup consists of taking the clinical history, physical examination and ECG. If all normal and/or if (NT-pro) BNP is low, the likelihood of HF is very low and other causes of the symptoms should be explored. If abnormal, echocardiography is recommended”.*

*Edito - European Heart Journal (2016) 37, 3121–3129*

# BNP and Nt-Pro-BNP are well recognized as biomarkers for chronic heart failure

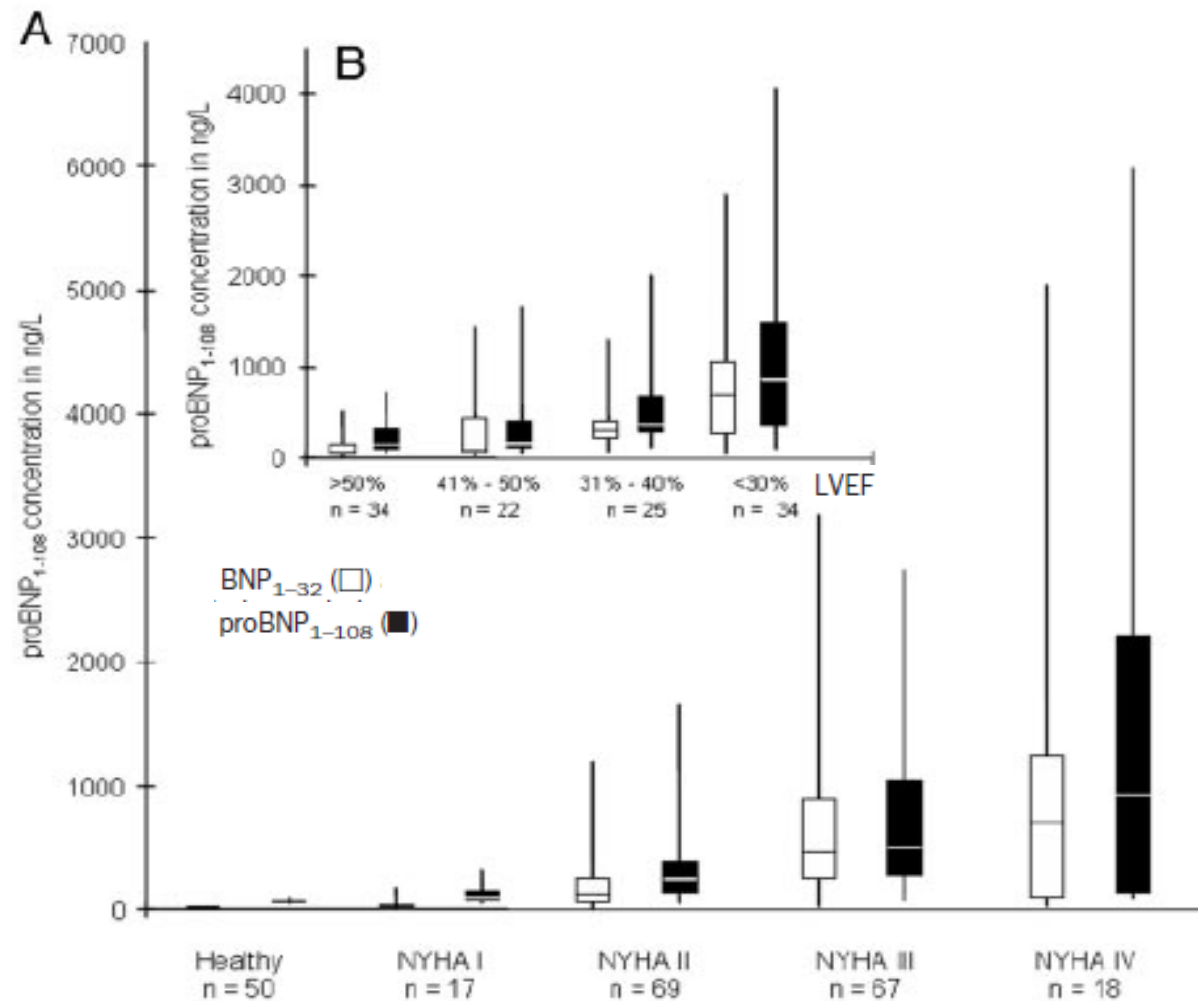


*Maissel A.S. et al., N Engl J Med, Vol. 347, 2002*



*Januzzi JL et al., Am J Cardiol 2005;95:948-954*

# ProBNP is a circulating peptide related to heart failure



# Biological variability of biomarkers for monitoring chronic cardiac disease

Marker	Duration	CV <sub>I</sub>	CV <sub>G</sub>	RCV (up, down*)	Index	Reference
CK	2 mo	30%	30%	82% (+139, -58)	1.00	Wu ,Clin Chim Acta 2009
BNP	2 mo	50%	28%	138% (NA)	1.11	Wu , Am J Cardiol 2003
NT-proBNP	2 mo	33%	36%	92% (NA)	0.91	Wu , Am J Cardiol 2003
hs-cTnI	2 mo	14%	63%	63% (+81, -45)	0.39	Wu , Clin Chem 2009
hs-cTnI	9 mo	28%	71%	73% (+98, -49)	0.45	Wu , Clin Biochem 2012
hs-cTnT	1 mo	31%	32%	87% (+138, -58)	0.97	Frankenstein L, Clin Chem 2011
sST2	1.5 mo	10.5%	46.4%	30% (NA)	0.23	Dieplinger B Clin Chim Acta 2009
sST2	2 mo	11%	46%	30% (+34, -26)	0.25	Wu Am Heart J 2013
Galectin-3	Hourly	16%	16%	39% (+47, -32)	1.00	Wu Am Heart J 2013
Galectin-3	2 mo	20%	23%	61% (+78, -44)	1.01	Wu Am Heart J 2013

CK, cytokeatin; NA, data not available (results were not log transformed); *hs-cTnI*, high-sensitivity cardiac troponin I; *Index*, index of individuality.

\*The RCV is computed from log-transformed data as necessary because of nonparametric distribution. This results in a different limits for serial results that are increasing versus decreasing.

*The natriuretic peptides play an essential role in the diagnosis of acute decompensated heart failure (Index) – and correction of the congestion.*

*However, the biological variation of natriuretic peptides to monitor outpatients have been less certain (RC and Index).*

**Alan H.B. Wu et al., Am Heart J 2013;165:995-9.**



## Suivi en cas d'ICS stable

*L'implication du patient dans sa prise en charge repose sur le médecin traitant et sur tous les soignants en contact avec le patient*

### ■ Acquis à maintenir :

- mesure fréquente du poids, noté, connaissance des signes d'alerte
- activité physique régulière et régime peu salé
- observance des médicaments et du rythme des consultations

### ■ Le suivi de l'efficacité et de la tolérance du traitement est essentiel

- Évaluation de la dyspnée, de la fatigue, des capacités cognitives
- Surveillance clinique, notamment observance du traitement, PA et FC
- Surveillance biologique (ionogramme et DFG)
- Majoration thérapeutique, renforcement temporaire du diurétique si rétention
- Surveillance clinique hebdomadaire par une infirmière (DSI) si besoin

### ■ La coordination des professionnels est parfois complexe

- Au mieux gérée dans le cadre d'un programme d'ETP et d'organisation des soins
- Surveillance spécifique si stimulation biventriculaire
- Il est essentiel de prendre en charge l'ensemble des maladies du patient

## Prévention de la décompensation cardiaque

*Le patient connaît les signes d'alerte devant conduire à une consultation rapide ou urgente*

- Prise de 2-3 kg en quelques jours, dyspnée majorée, FC rapide ou irrégulière

- Dosage du BNP (ou NT-proBNP) en cas de doute sur une décompensation

*Le médecin doit prendre la décision d'hospitalisation au bon moment*

- Dégradation clinique majeure, hypotension mal tolérée, dégradation biologique
- À la sortie, lettre au médecin généraliste avec copie pour le patient



JUIN 2014

# 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

## Biomarkers: Recommendations for Prognosis

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	A	<u>Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (16,87-92).</u>	2013 recommendation remains current.
I	A	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF (27,93-100).	<b>MODIFIED:</b> Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful.

See Online Data Supplements A and B.

Higher levels of natriuretic peptide biomarkers on admission are usually associated with greater risk for clinical outcomes, including all-cause and cardiovascular mortality, morbidity, and composite outcomes, across different time intervals in patients with decompensated HF (20,27,29,93-101). Similarly, abnormal levels of circulating cardiac troponin are commonly found in patients with acute decompensated HF, often without obvious myocardial ischemia or underlying coronary artery disease (CAD), and this is associated with worse clinical outcomes and higher risk of death (95,99,102,103).

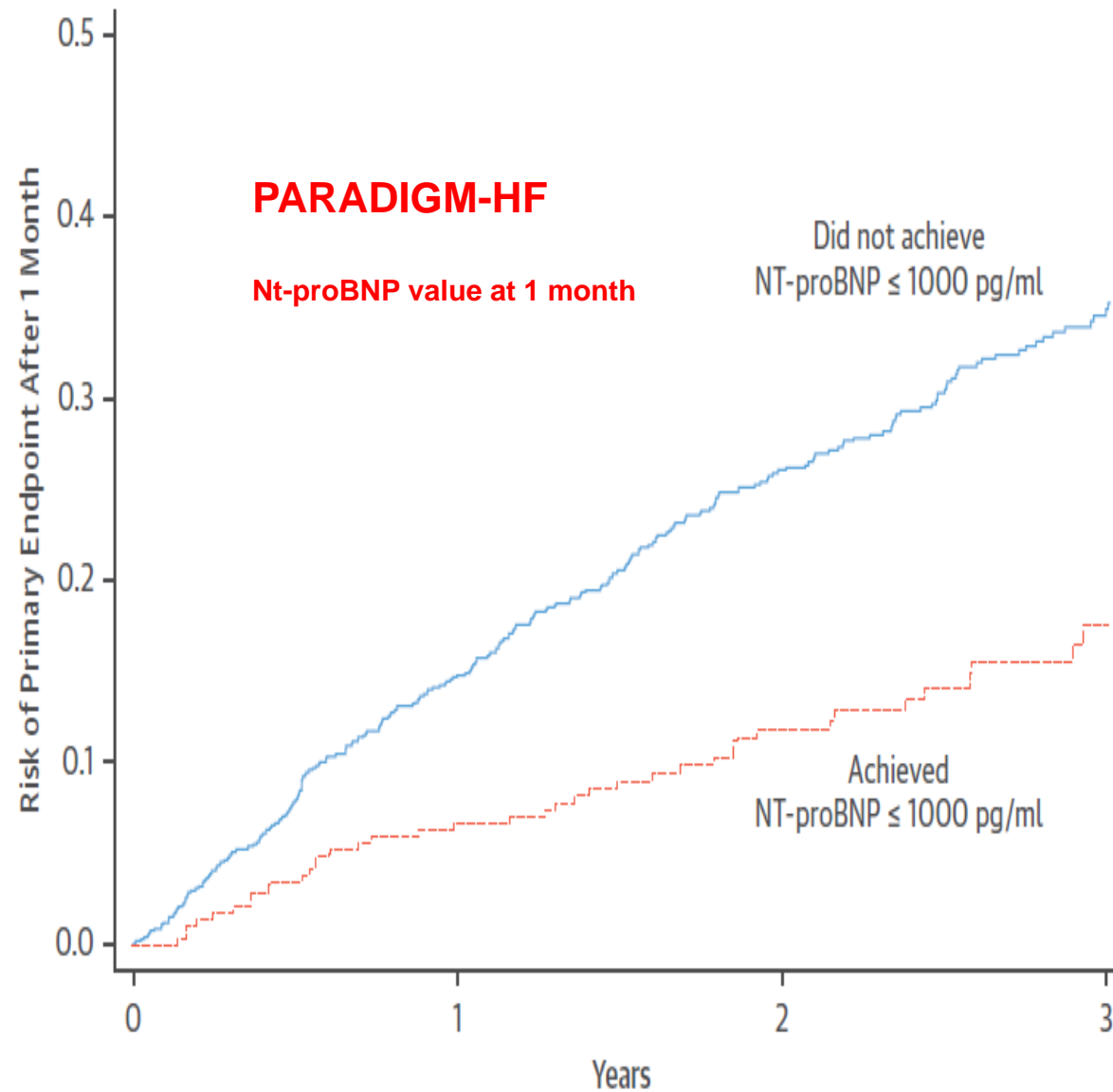
Studies have demonstrated incremental prognostic value of these biomarkers to standard approaches of cardiovascular disease risk assessment (29,95). However, there were differences in the risk prediction models, assay cutpoints, and lengths of follow-up (29). Furthermore, not all patients may need biomarker measurement for prognostication, especially if they already have advanced HF with established poor prognosis or persistently elevated levels of biomarkers in former settings. Therefore, assays of natriuretic peptide biomarkers for incremental prognostication should not preclude good clinical judgment; an individualized approach to each patient is paramount.

IIa	B-NR	<u>During a HF hospitalization, a predischage natriuretic peptide level can be useful to establish a postdischarge prognosis (93,96,104-113).</u>	<b>NEW:</b> Current recommendation reflects new observational studies.
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See Online Data Supplements A and B.

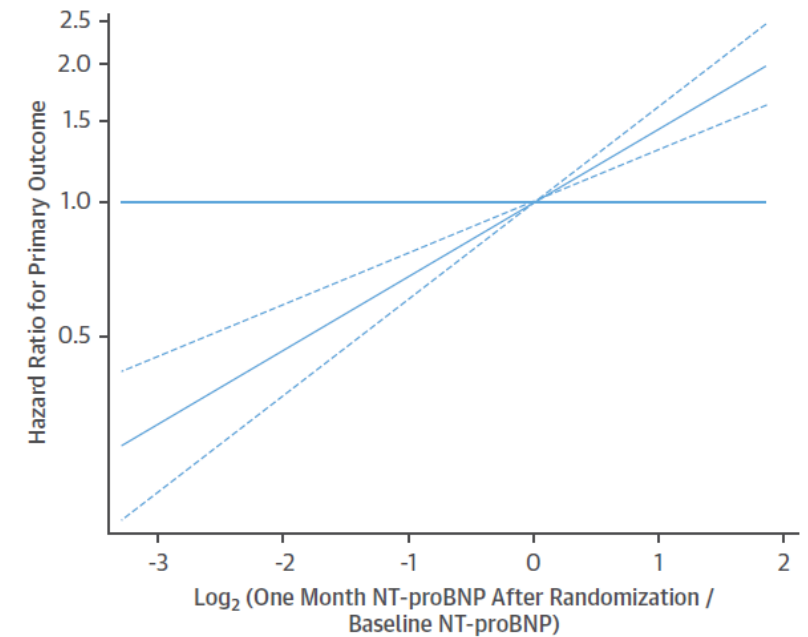
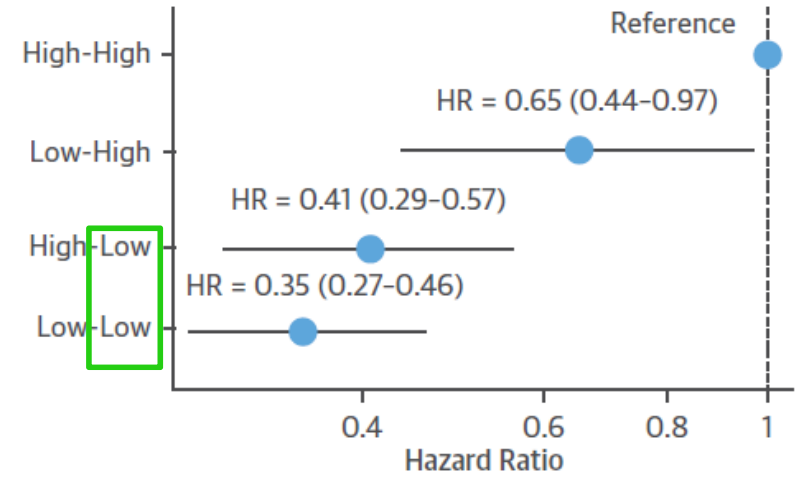
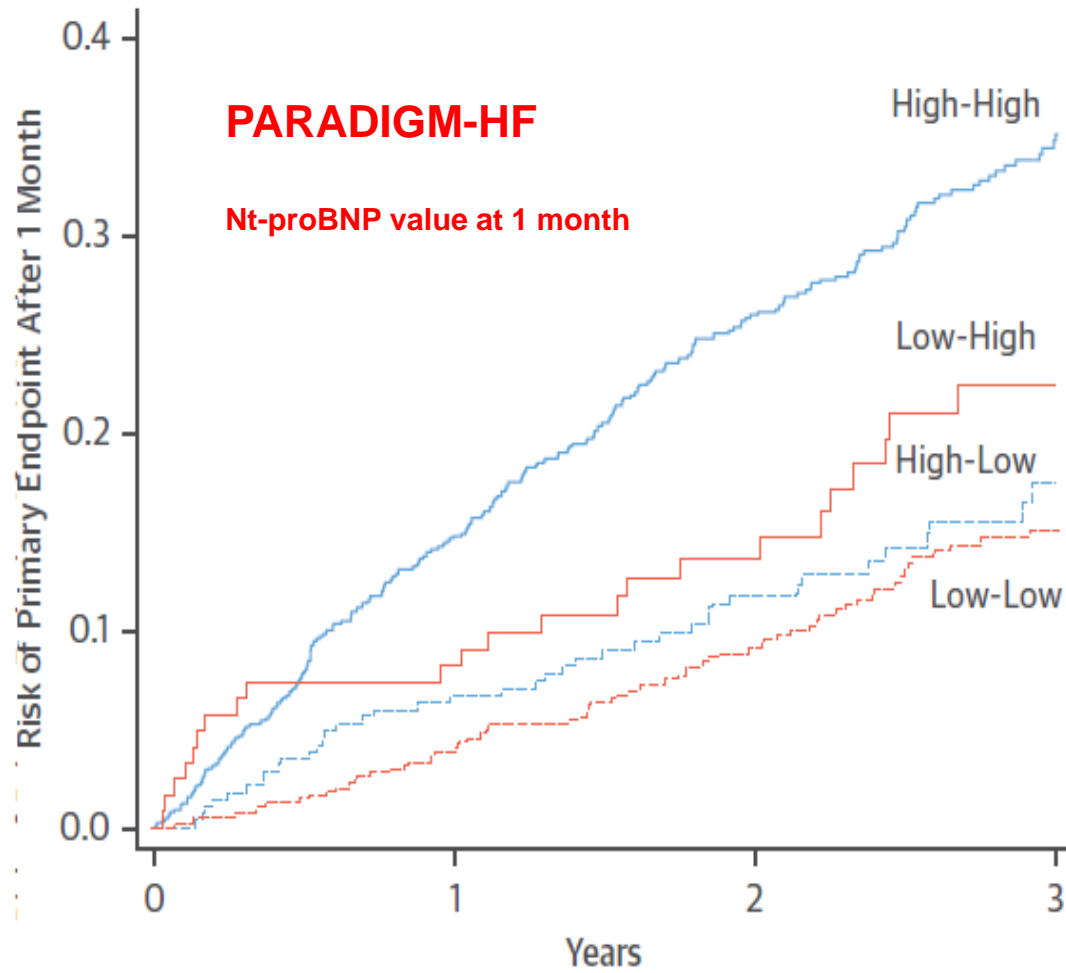
Predischage natriuretic peptide biomarker levels and the relative change in levels during hospital treatment are strong predictors of the risk of death or hospital readmission for HF (93,96,104-113). Several studies have suggested that predischage natriuretic peptide biomarker levels had higher reclassification and discrimination value than clinical variables in predicting outcomes (96,106,108-111). Patients with higher predischage levels and patients who do not have a decrease in natriuretic peptide biomarker levels during hospitalization have worse outcomes (96,106,108-111). Although observational or retrospective studies have suggested that patients with natriuretic peptide biomarker reduction had better outcomes than those without any changes or with a biomarker rise (93,107,112,113), targeting a certain threshold, value, or relative change in these biomarker levels during hospitalization may not be practical or safe for every patient and has not been tested in a prospective large-scale trial. Clinical assessment and adherence to GDMT should be the emphasis, and the prognostic value of a predischage value or relative changes does not imply the necessity for serial and repeated biomarker measurements during hospitalization.

# Nt-proBNP : une vision dynamique



*Michael R. Zile et al. J Am Coll Cardiol 2016;68:2425–36*

# Nt-proBNP : une vision dynamique



*Michael R. Zile et al. J Am Coll Cardiol 2016;68:2425-36*

**Table 12.3 Causes of elevated concentrations of natriuretic peptides**<sup>522 – 524</sup>

<b>Cardiac</b>	<ul style="list-style-type: none"> <li>Heart failure</li> <li>Acute coronary syndromes</li> <li>Pulmonary embolism</li> <li>Myocarditis</li> <li>Left ventricular hypertrophy</li> <li>Hypertrophic or restrictive cardiomyopathy</li> <li>Valvular heart disease</li> <li>Congenital heart disease</li> <li>Atrial and ventricular tachyarrhythmias</li> <li>Heart contusion</li> <li>Cardioversion, ICD shock</li> <li>Surgical procedures involving the heart</li> <li>Pulmonary hypertension</li> </ul>
<b>Non-cardiac</b>	<ul style="list-style-type: none"> <li><u>Advanced age</u></li> <li>Ischaemic stroke</li> <li>Subarachnoid haemorrhage</li> <li><u>Renal dysfunction</u></li> <li>Liver dysfunction (mainly liver cirrhosis with ascites)</li> <li>Paraneoplastic syndrome</li> <li>Chronic obstructive pulmonary disease</li> <li>Severe infections (including pneumonia and sepsis)</li> <li>Severe burns</li> <li>Anaemia</li> <li>Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketosis)</li> </ul>

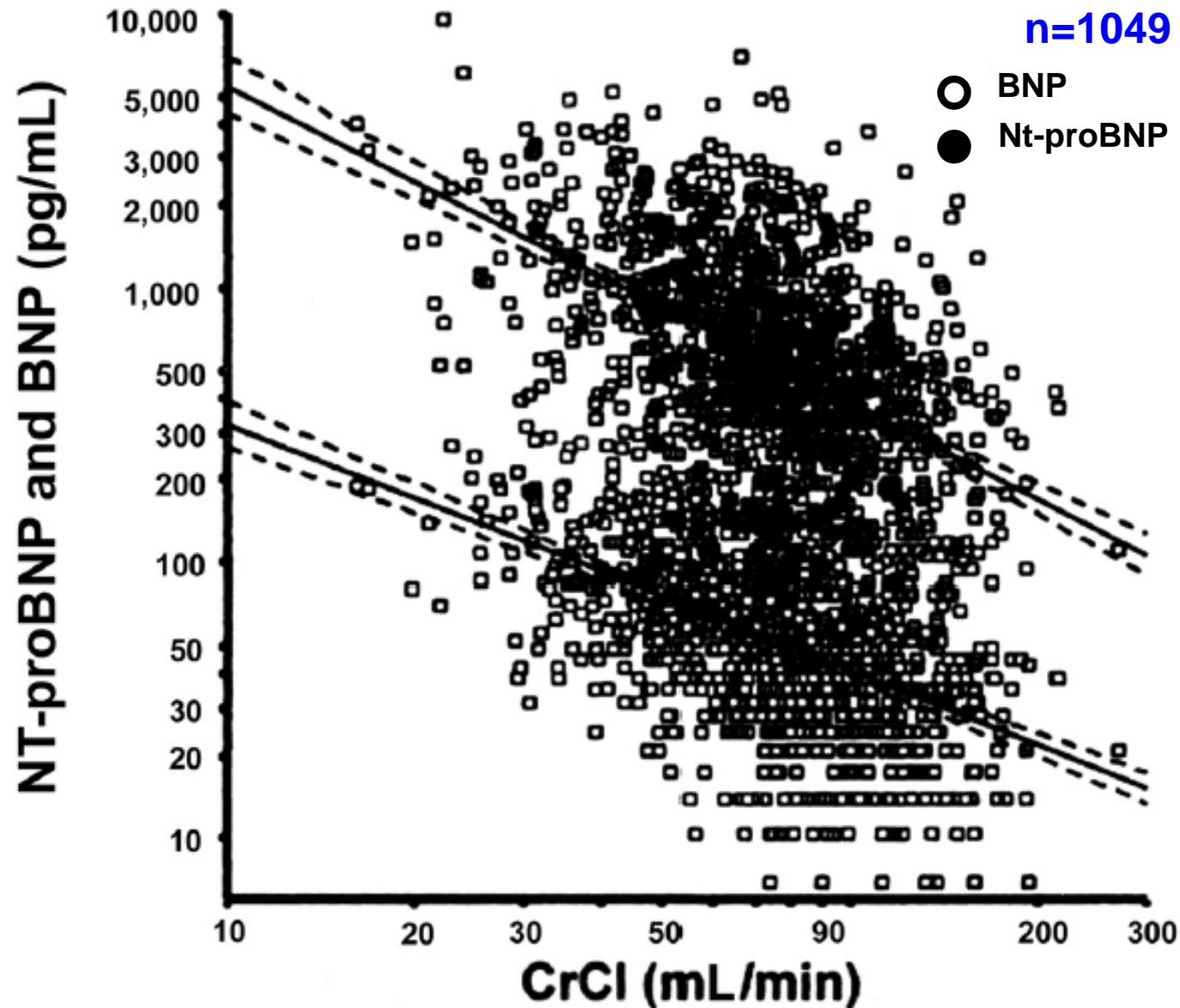
HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator.

## Natriuretic Peptides in acute heart failure : lack of specificity



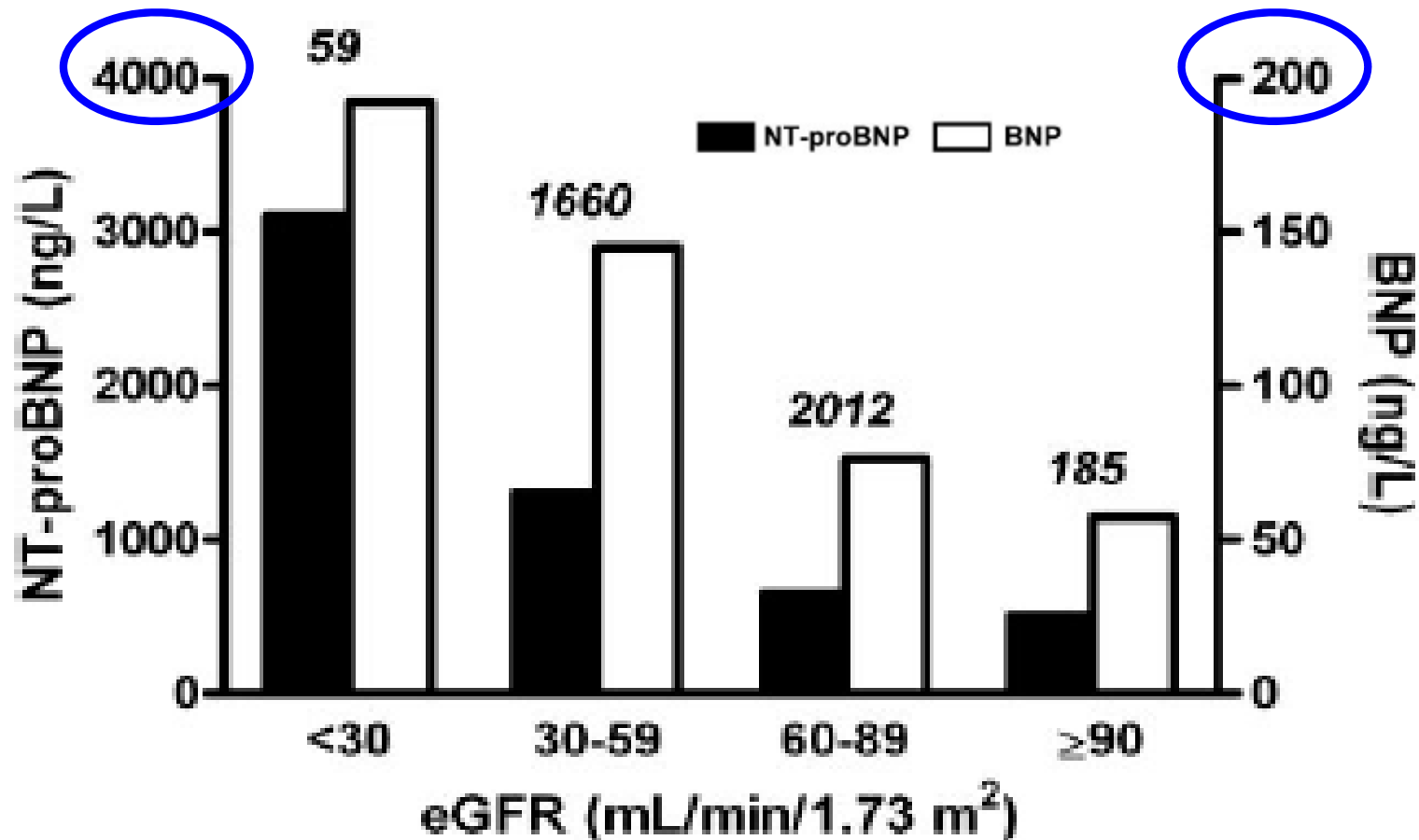
**ESC Guidelines – European Heart Journal (2016) 37:2129-2200**

# Les taux de Nt-proBNP ... et de BNP sont influencés par les fonctions rénales :



# Comparaison BNP et Nt-proBNP en fonction de la fonction rénale

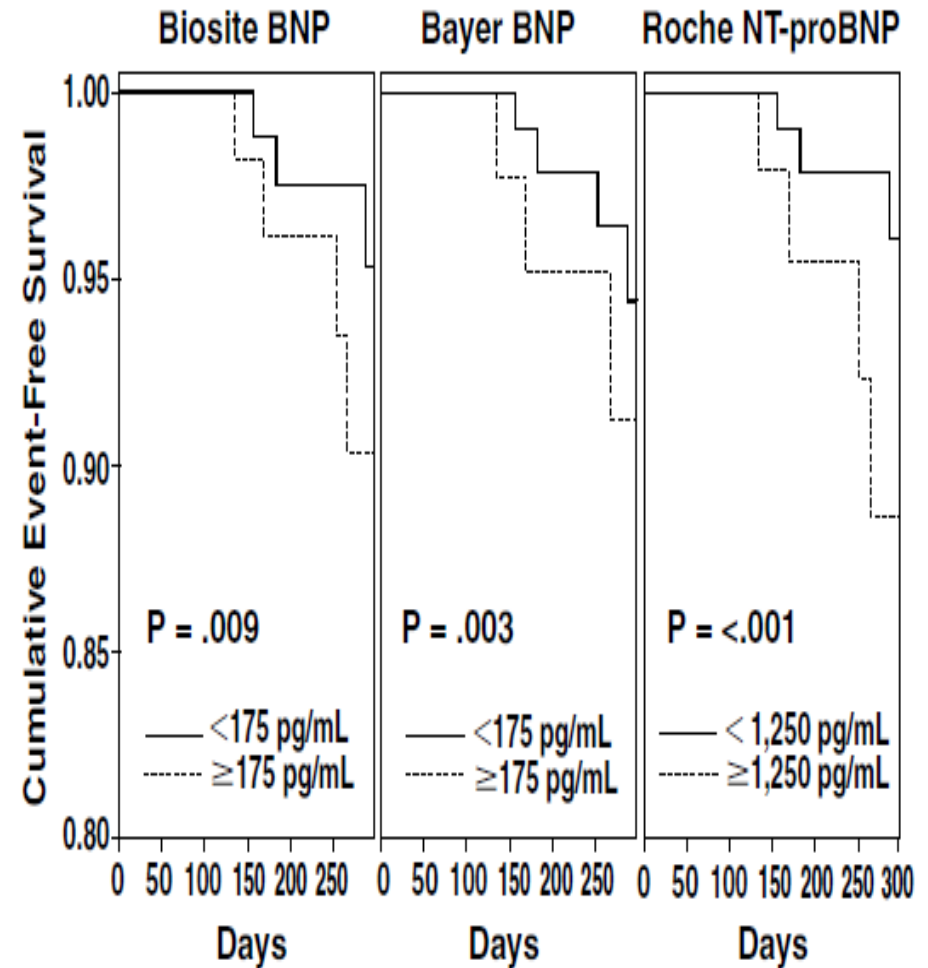
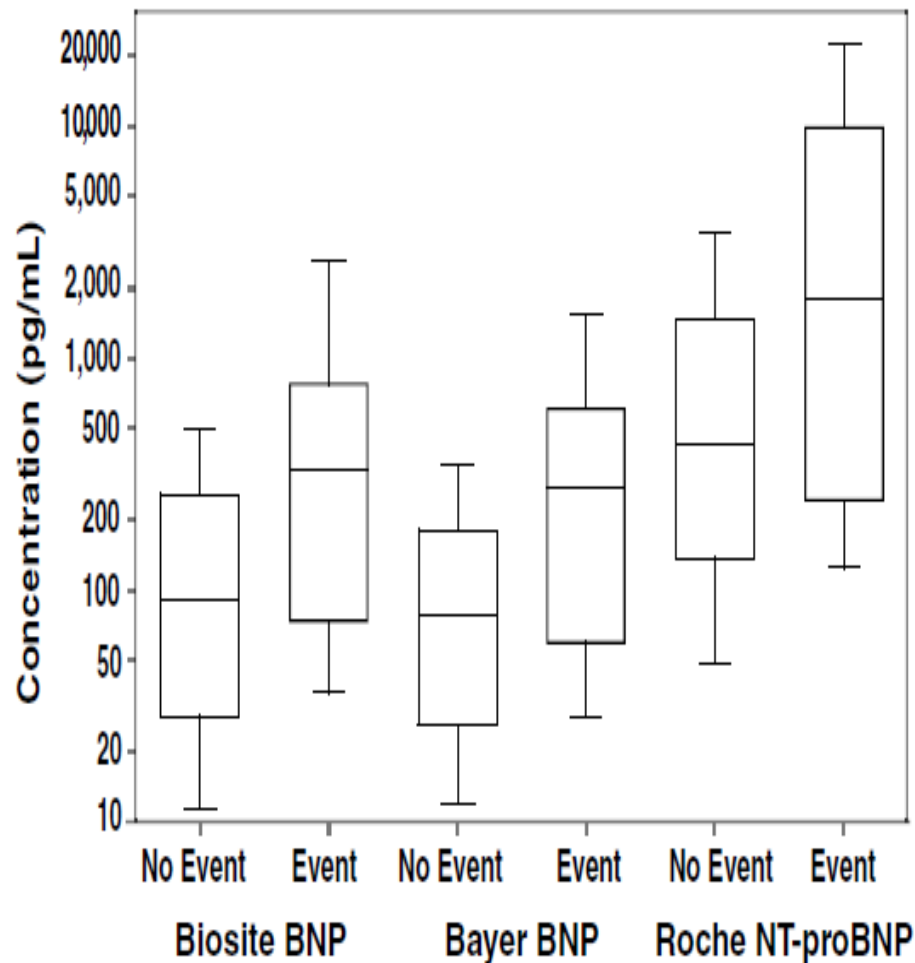
n = 3 916, IC stable, Valsartan Heart Failure Trial



*Masson S et al. Clinical Chemistry 2006.*

# Valeur pronostic du BNP et du Nt-proBNP

N=171 patients de stade 1 à 5

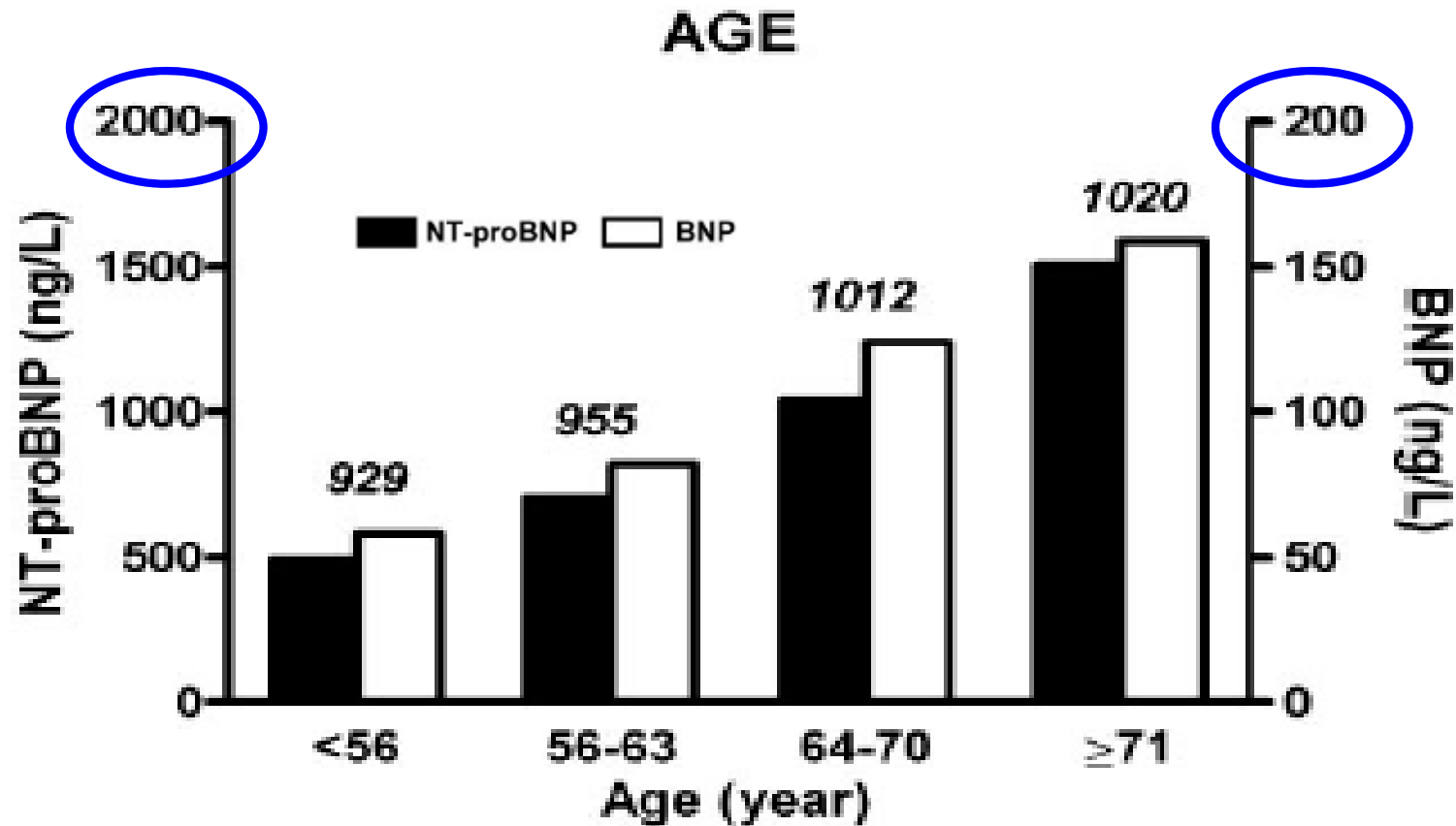


*Austin et al., Am J Clin Pathol 2006;126:506-512*



# Comparaison BNP et Nt-proBNP en fonction de l'âge dans l'insuffisance ventriculaire gauche

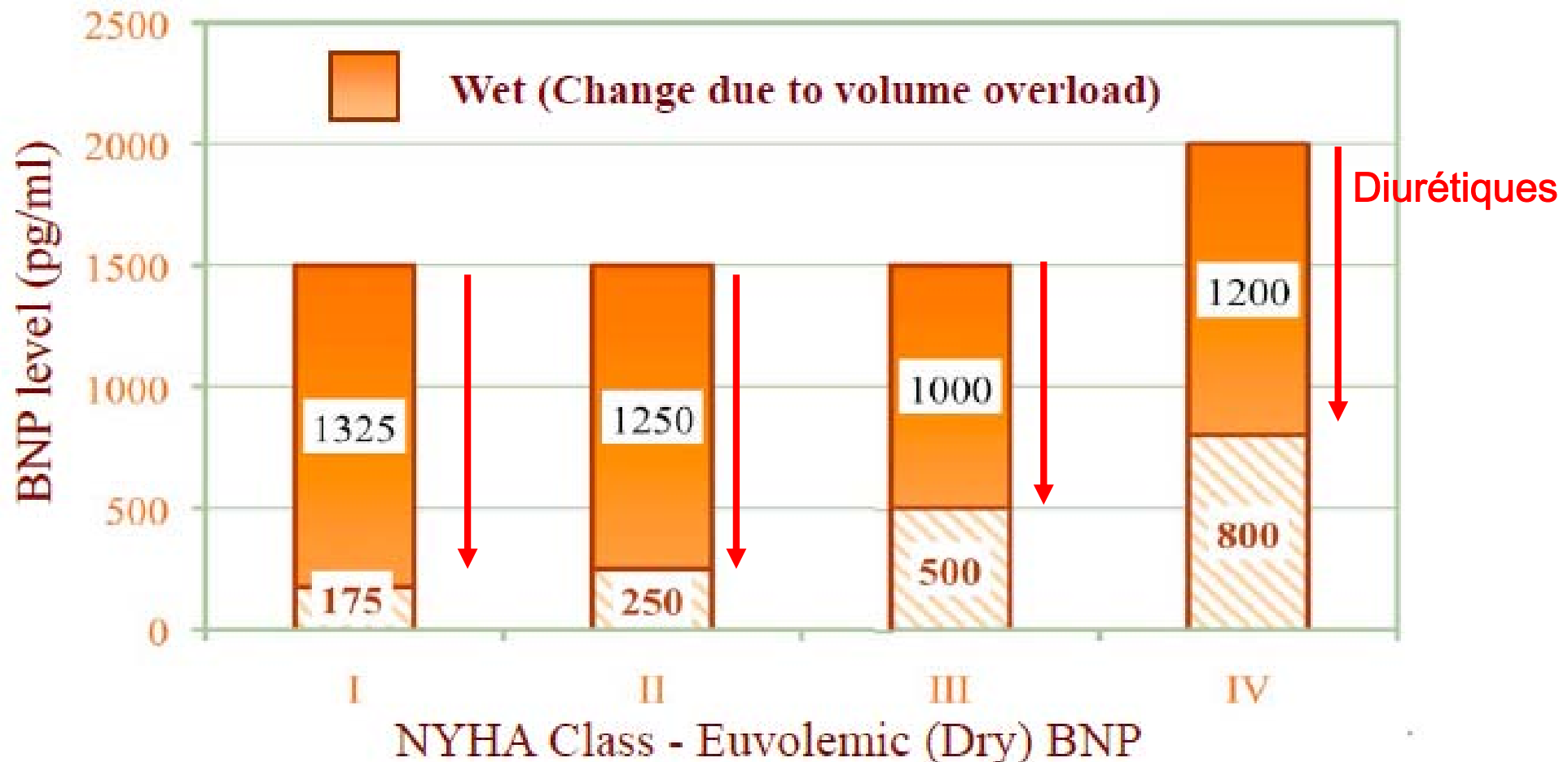
n = 3 916, IC stable, Valsartan Heart Failure Trial



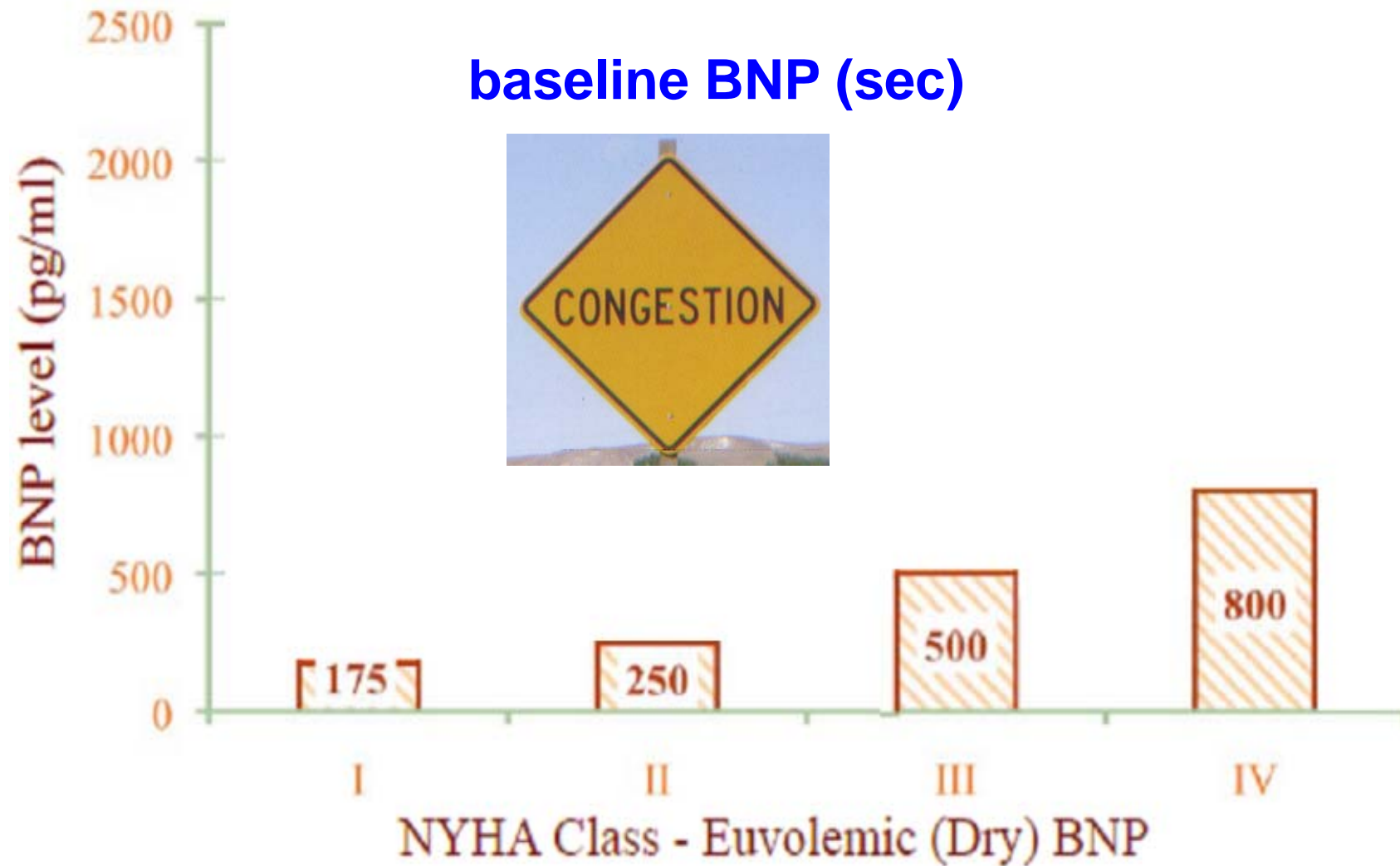
Masson S *et al.* Clinical Chemistry 2006.

# BNP et surcharge volémique au cours de l'Insuffisance cardiaque :

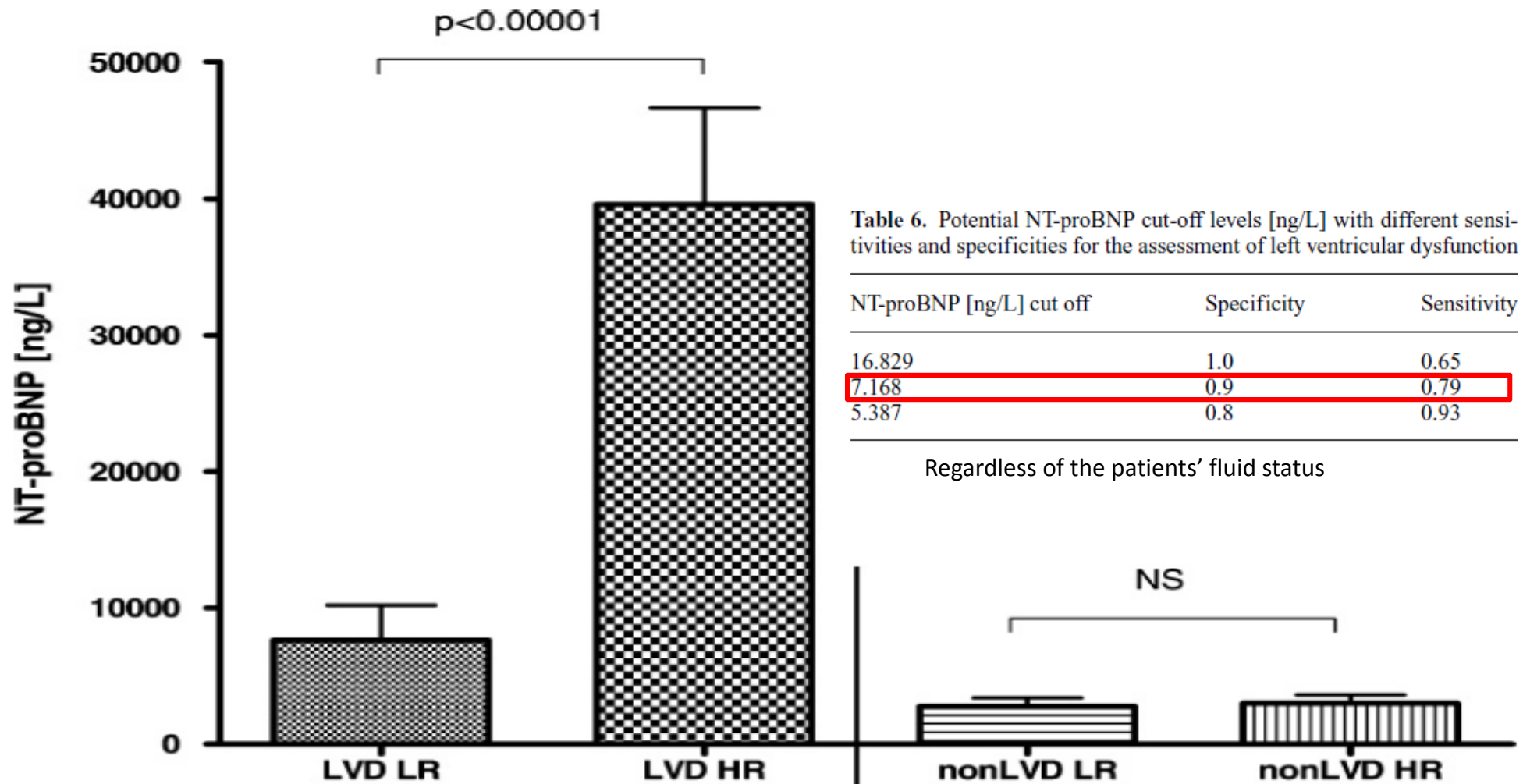
“le taux de BNP = baseline BNP (sec)  
et facteur de surcharge volémique”



# BNP : L'influence de la surcharge volémique



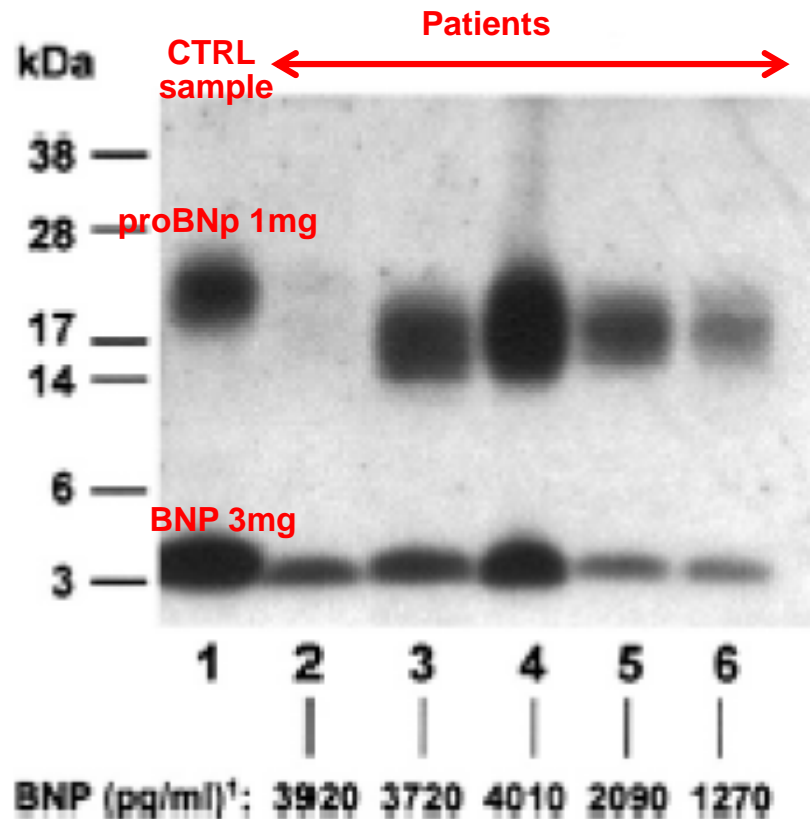
# La surcharge volémique modifie les taux de peptide natriurétique au cours de l'Insuffisance cardiaque



62 stable patients on maintenance Haemodialysis

Hydration status: low range (LR) and high range (HR) subgroups

# Interferences between peptides



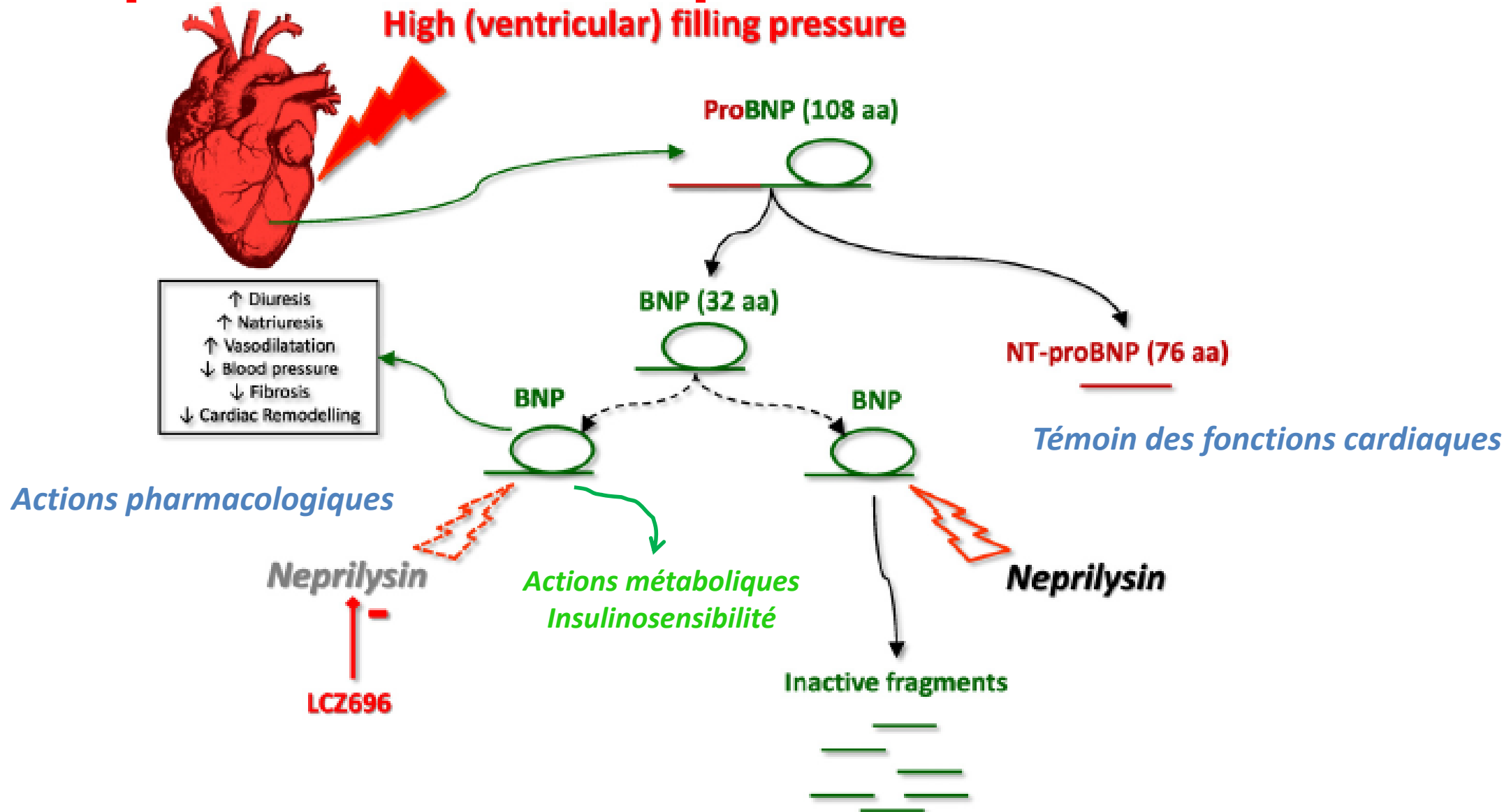
## 180 patients with chronic HF

Values	Before depletion	After depletion	Mean reduction (%)	P value
BNP (pg/ml)	684.3+/-1092	317.9+/-435.3	53%	P<0.0001
NT-proBNP (pg/ml)	6054+/-11539	5760+/-11510	5%	P=0.02
proBNP (pg/ml)	316.8+/-265.9	13.3+/-29.1	96%	P<0.0001

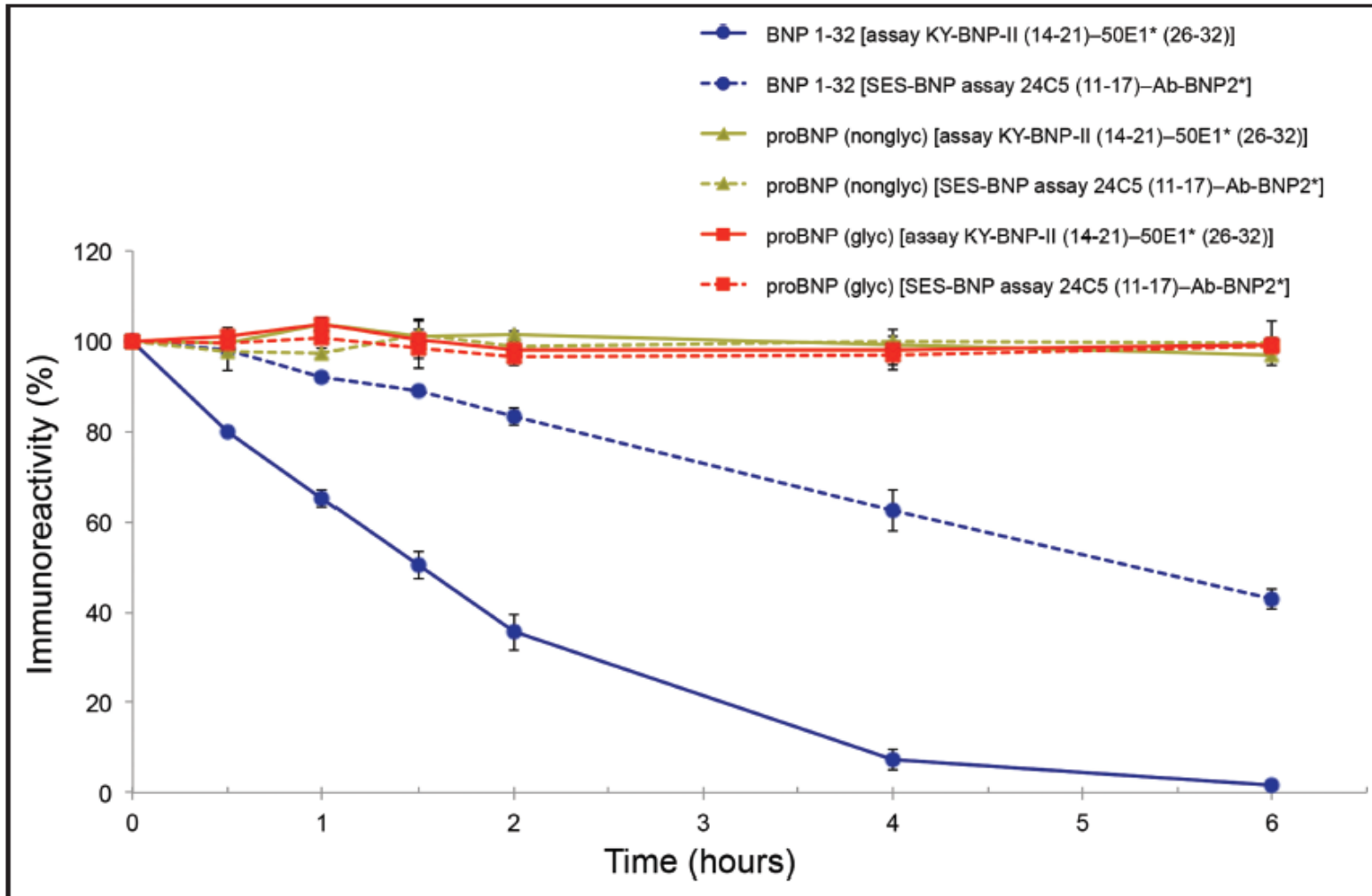
*Liang F et al., J Am Coll Cardiol 2007; 49:1071-8*

*Roubille F et al., Plos One 2013*

# Quelle surveillance chez les patients traités par Entresto : Nt-proBNP et BNP ???



# BNP et pro-BNP : susceptibilité à la Neprilysin



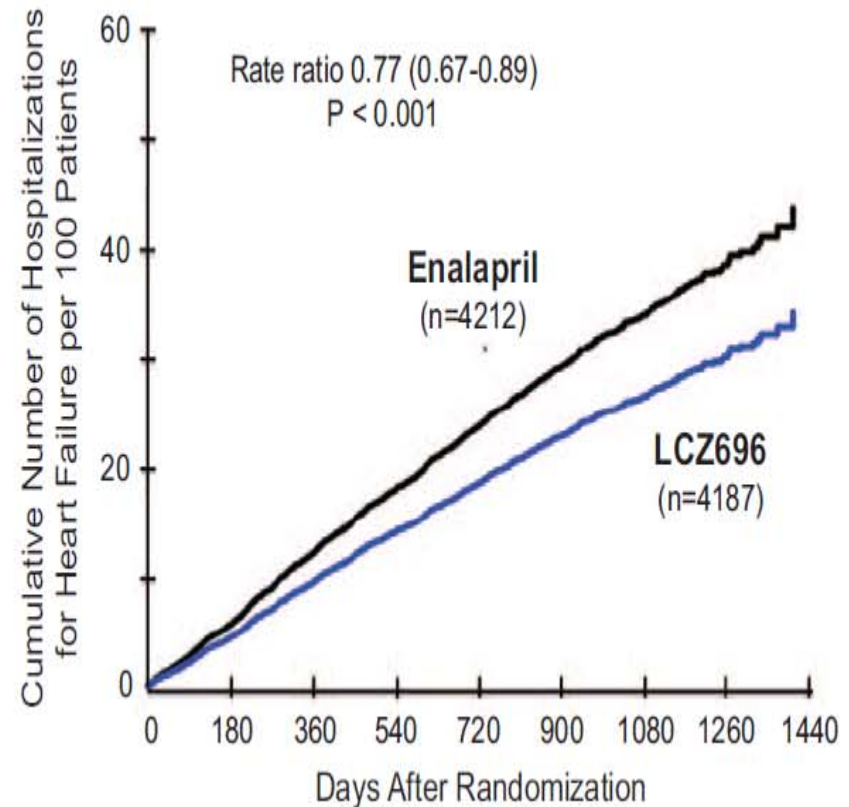
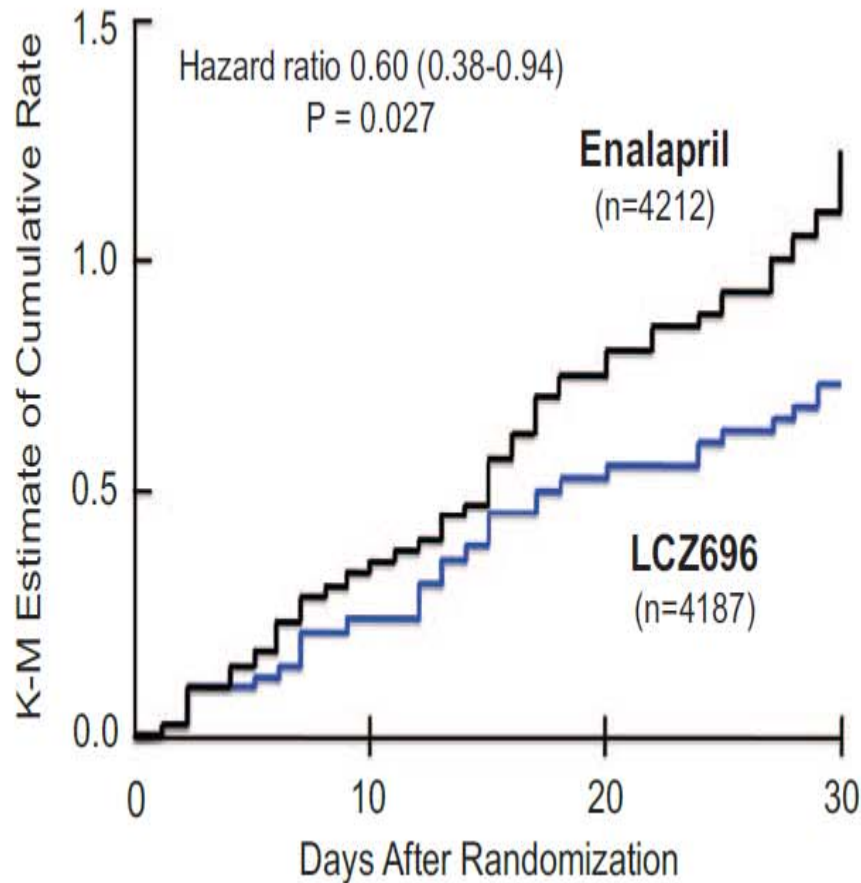
**Modulation of neprilysin activity by specific inhibitors may not greatly influence the circulating concentrations of immunoreactive BNP, mostly represented in HF by proBNP, which is not susceptible to neprilysin.**

**Fig. 1.** Degradation of BNP 1-32, nonglycosylated (expressed in *E. coli*) and glycosylated (expressed in mammalian cells) proBNP 1-108 by the action of neprilysin.

The immunoreactivity of BNP, nonglycosylated and glycosylated proBNP was measured by the KY-BNP-II(14-21)-50E1(26-32) assay and the SES-BNP assay (24C5 (11-17) Ab-BNP2). The immunoreactivity was calculated as (immunoreactivity in neprilysin-treated sample/immunoreactivity in nontreated sample) × 100%. The data are presented as the mean (n = 3)(SD).

# Angiotensin Receptor Neprilysin Inhibition and outcome of Patients With HFrEF

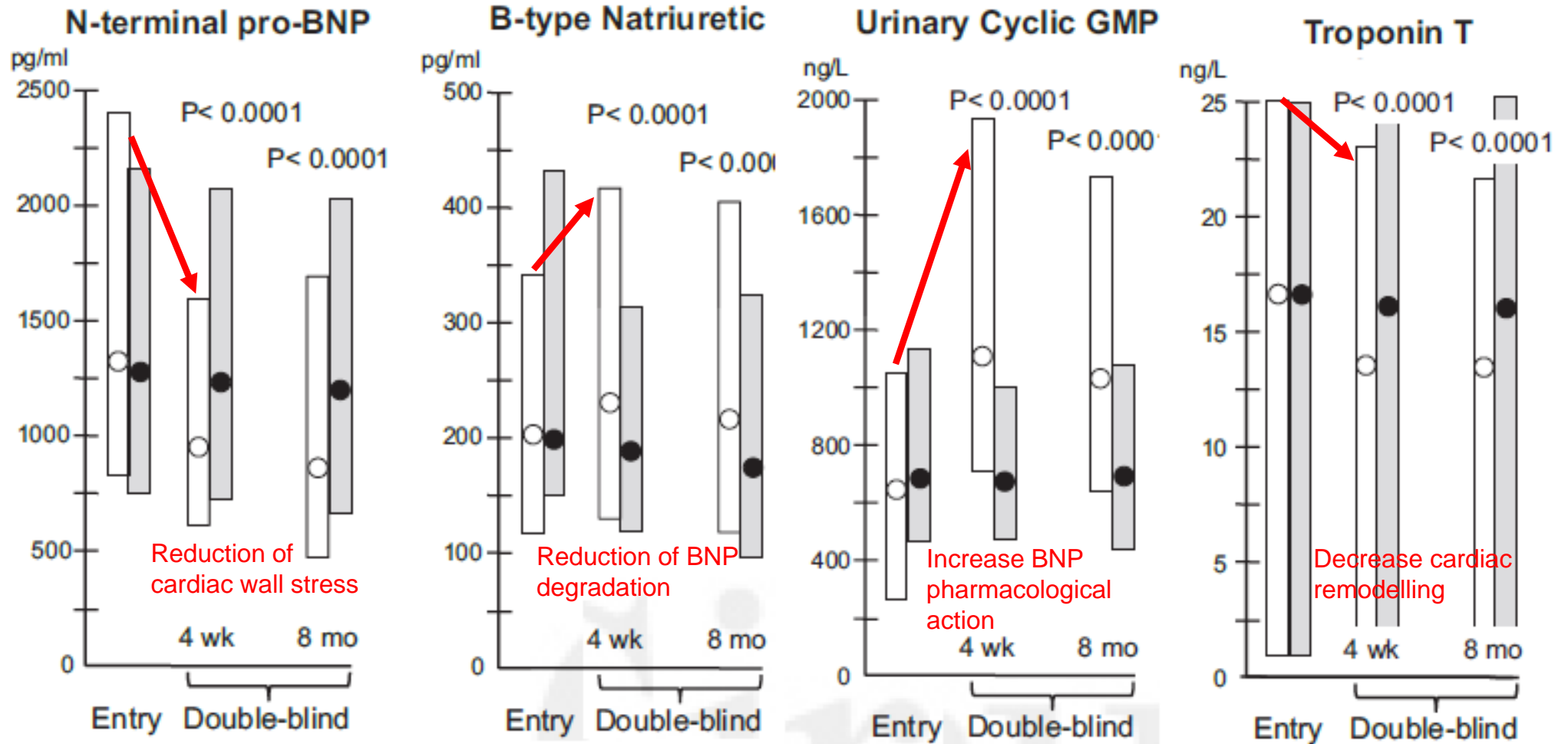
PARADIGM-HF :8399 patients with HFrEF (EF $\leq$ 40%)



Packer M et al. *Circulation*. 2015;131:54-61.



# Angiotensin Receptor Neprilysin Inhibition and natriuretic peptides

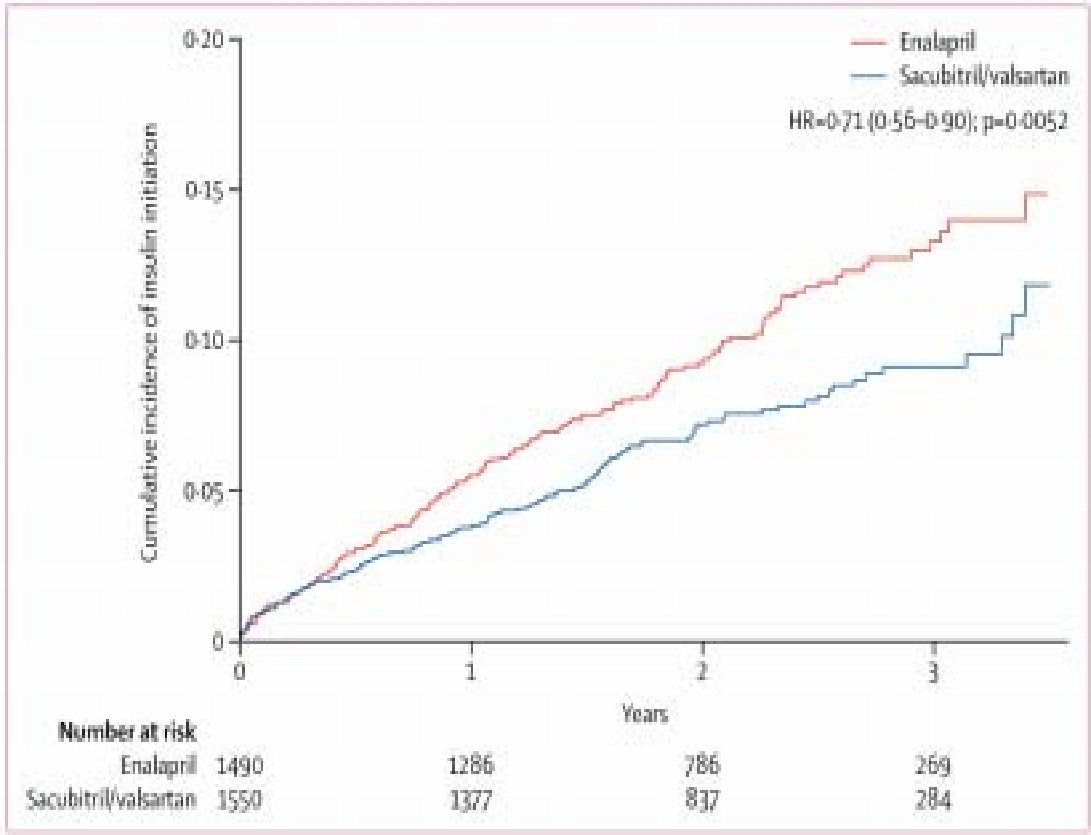
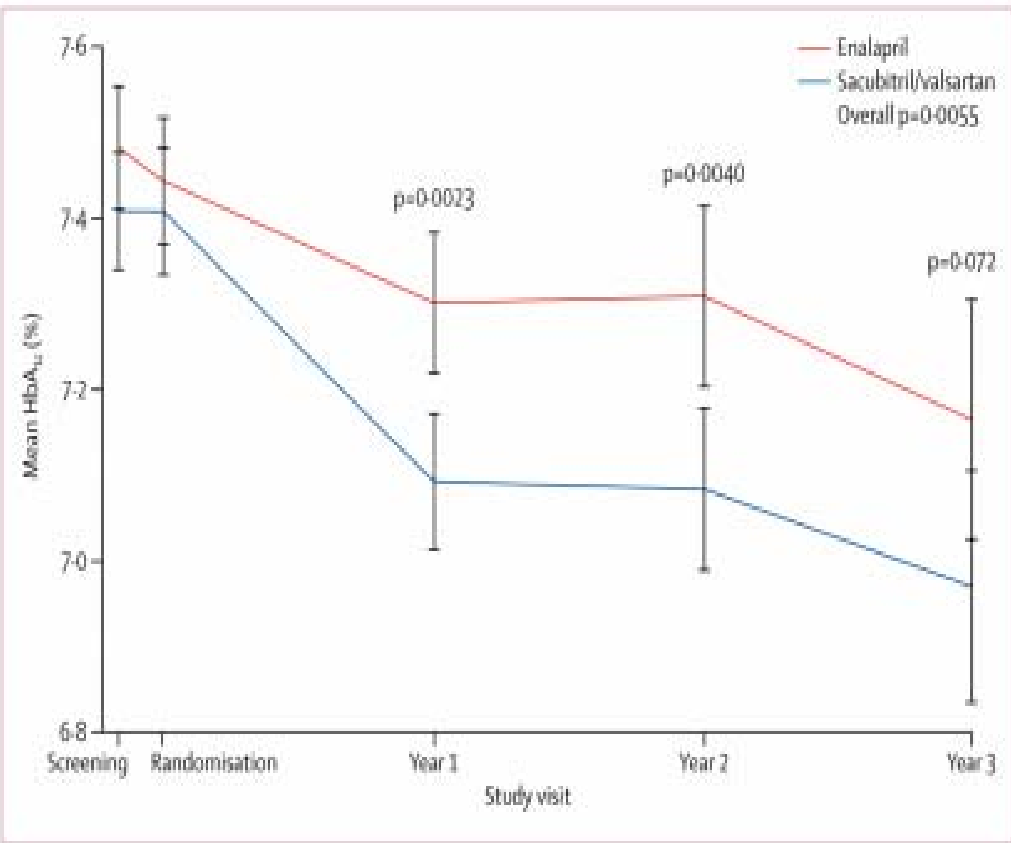


## PARADIGM-HF

- LCZ696
- Enalapril

*Packer M et al. Circulation. 2015;131:54–61.*

# Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial

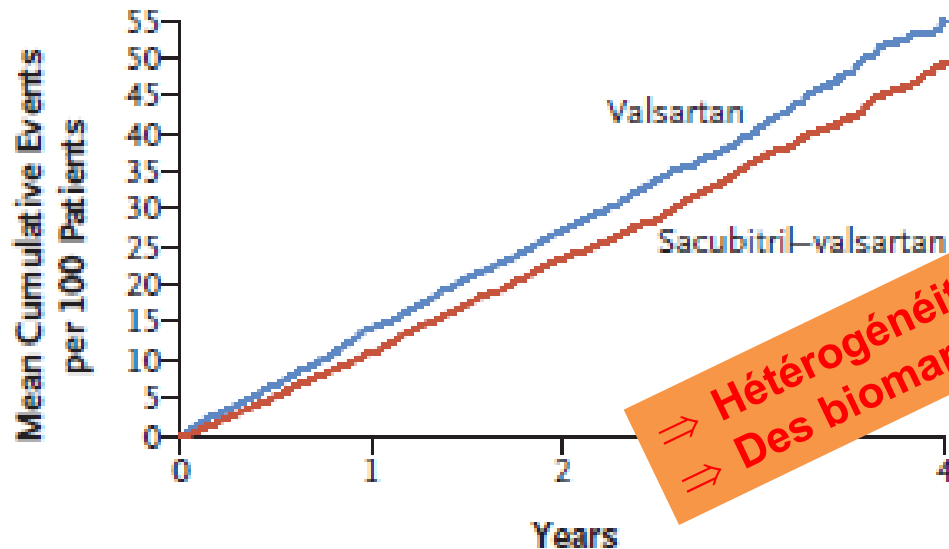


**JP Seferovic et al., Lancet Diabetes Endocrinol. 2017 May ; 5(5): 333–340.**

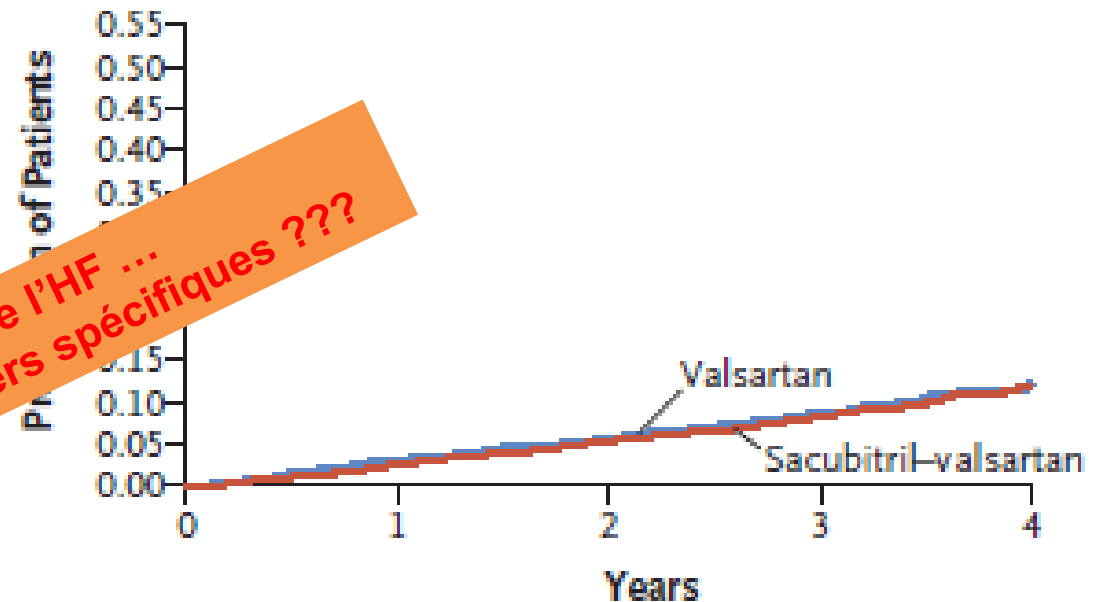
# Angiotensin Receptor Neprilysin Inhibition and outcome of Patients With HFpEF

PARAGON-HF, 4822 pts, EF > 45%

Total Hospitalizations for Heart Failure and Death from Cardiovascular Causes



Death from Cardiovascular Causes



⇒ Hétérogénéité de l'HF ...  
 ⇒ Des biomarqueurs spécifiques ???

Primary Outcome in Prespecified Subgroups

Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75-1.01)
Age		
<75 yr	938/2597	0.82 (0.66-1.02)
≥75 yr	965/2199	0.92 (0.76-1.11)
Sex		
Male	980/2317	1.03 (0.85-1.25)
Female	923/2479	0.73 (0.59-0.90)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64-0.95)
>Median (57%)	855/2301	1.00 (0.81-1.23)

0.4 0.6 0.8 1.0 2.0

Sacubitril-Valsartan Better Valsartan Better

Scott D. Solomon et al. N Engl J Med 2019; 381:1609-1620.

# **Biomarkers of Heart Failure**

## **I) Les Biomarqueurs en 2016**

- Un biomarqueur de diagnostic, d'élimination, de suivi
- Des critères analytiques et biologiques pour l'interprétation

## **II) Les peptides natriurétiques : 20 ans après**

- Une valeur diagnostique plus que pronostique
- Une interprétation cinétique (Entrée – Sortie – Surcharge)
- Des limites analytiques et biologiques
- Un métabolisme complexe

## **III) Quelle place pour le Laboratoire en dehors des peptides ?**

## **IV) La voie du ST2 et la stratégie multimarqueur.**

# Natriuretic Peptides in heart failure

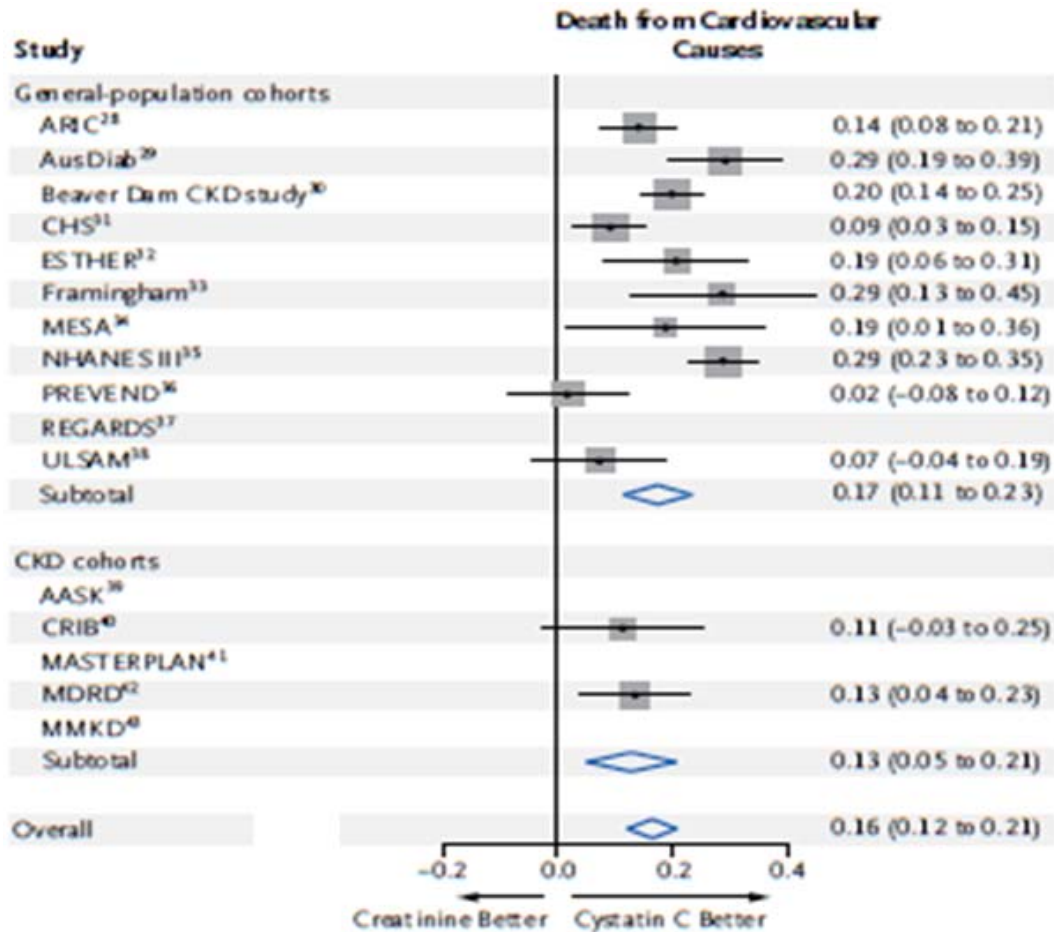
## Recommendations regarding applied diagnostic measurements

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Upon presentation a measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP) is recommended in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea.	I	A	531–534
At admission in all patients presenting with suspected AHF, the following diagnostic tests are recommended:			
a. 12-lead ECG;	I	C	
b. chest X-ray to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms;	I	C	
c. the following laboratory assessments in the blood: cardiac troponins, BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests and TSH.	I	C	
Echocardiography is recommended immediately in haemodynamically unstable AHF patients and within 48 hours when cardiac structure and function are either not known or may have changed since previous studies.	I	C	

NPs have high sensitivity, and normal levels in patients with suspected AHF makes the diagnosis unlikely (thresholds: BNP ,100 pg/mL, NT-proBNP ,300 pg/mL, MR-proANP ,120 pg/mL).<sup>57 – 61,77,78,521</sup> However, elevated levels of NPs do not automatically confirm the diagnosis of AHF, as they may also be associated with a wide variety of cardiac and non-cardiac causes.

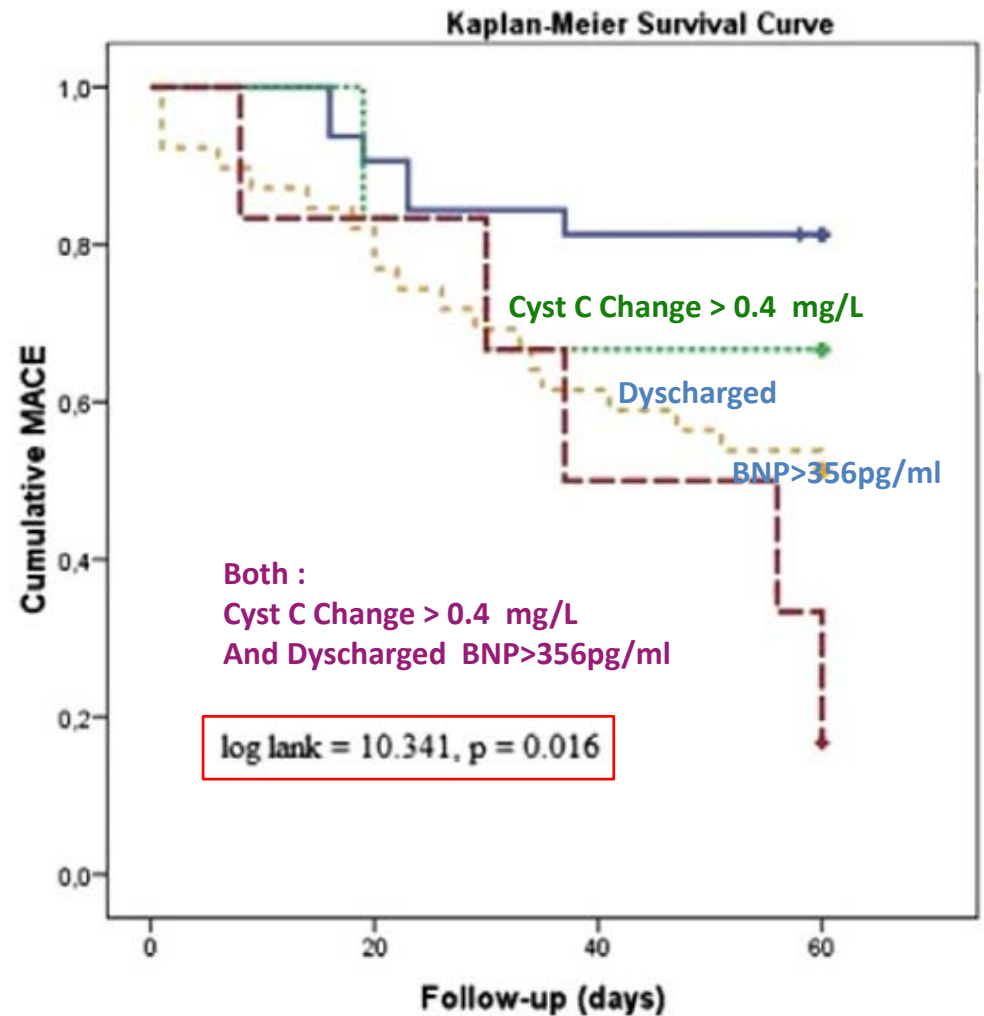
# Cystatin C as a biomarker of cardiorenal syndrome

CRS type IV : Chronic disease



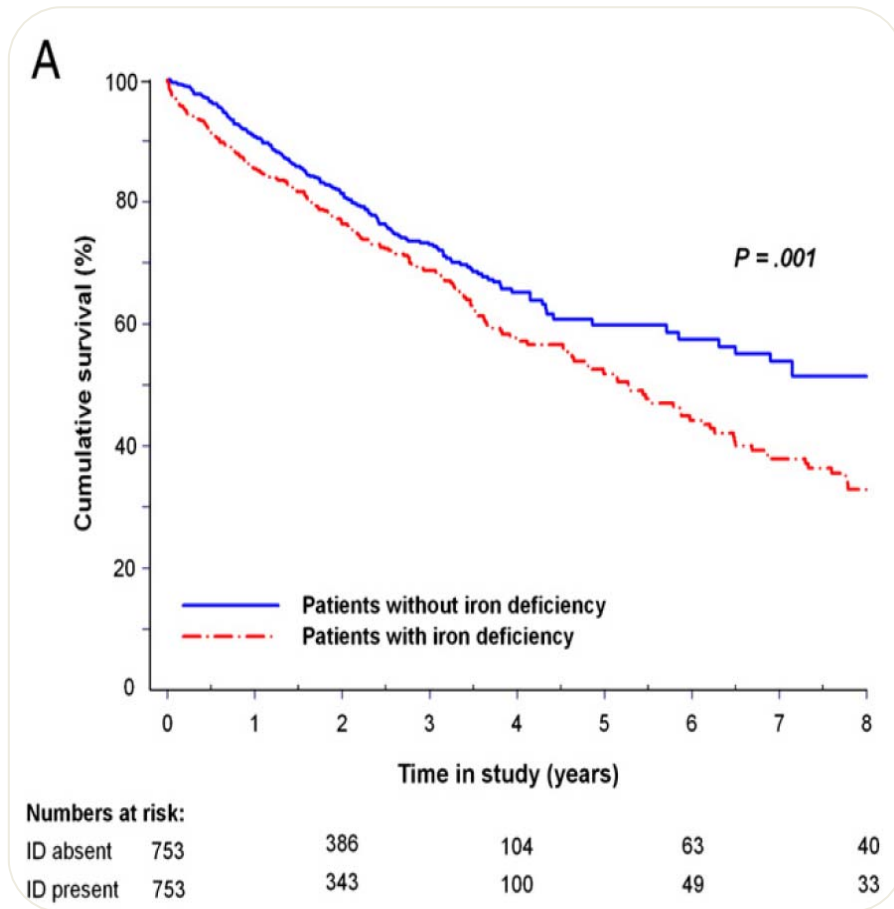
Michael G. Shlipak et al., *N Engl J Med* 2013;369:932-43.

In-hospital change (48h) in cystatin predicts adverse events in acute heart failure (n=96) (CRS type I)



P. Rafouli-Stergiou et al., *International Journal of Cardiology* 182 (2015) 74-76

# La carence martiale aggrave le pronostic de l'ICC : recommandations internationales



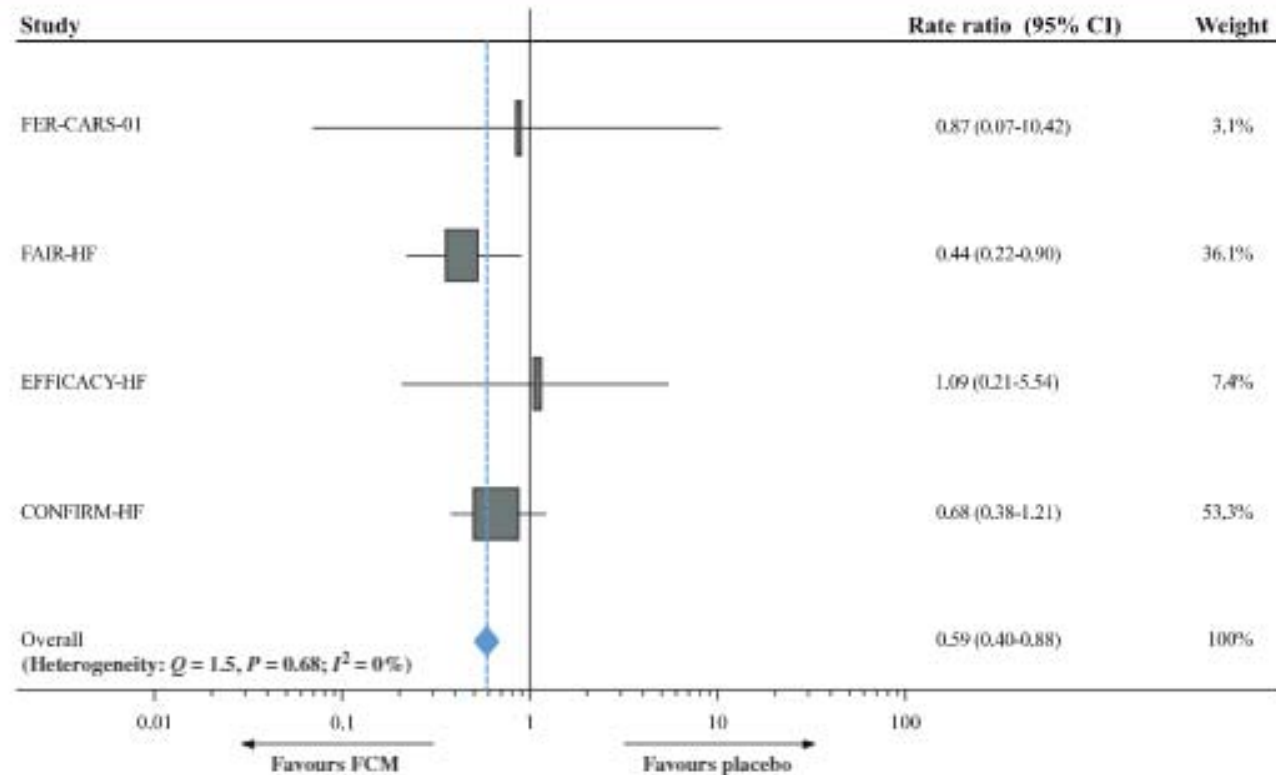
Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Iron deficiency</b>		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	<b>IIa</b>	<b>A</b>



Klip I. et al. Am Heart J. 2013;165(4):575-582

ESC Guidelines – European Heart Journal (2016) 37:2129-2200

# La supplémentation martiale améliore l'IC et prévient la réhospitalisation pour IC



**Figure 2** Rate ratios for cardiovascular hospitalisations and cardiovascular mortality for the individual randomised controlled trials included in this meta-analysis. CI, confidence interval; FCM, ferric carboxymaltose.

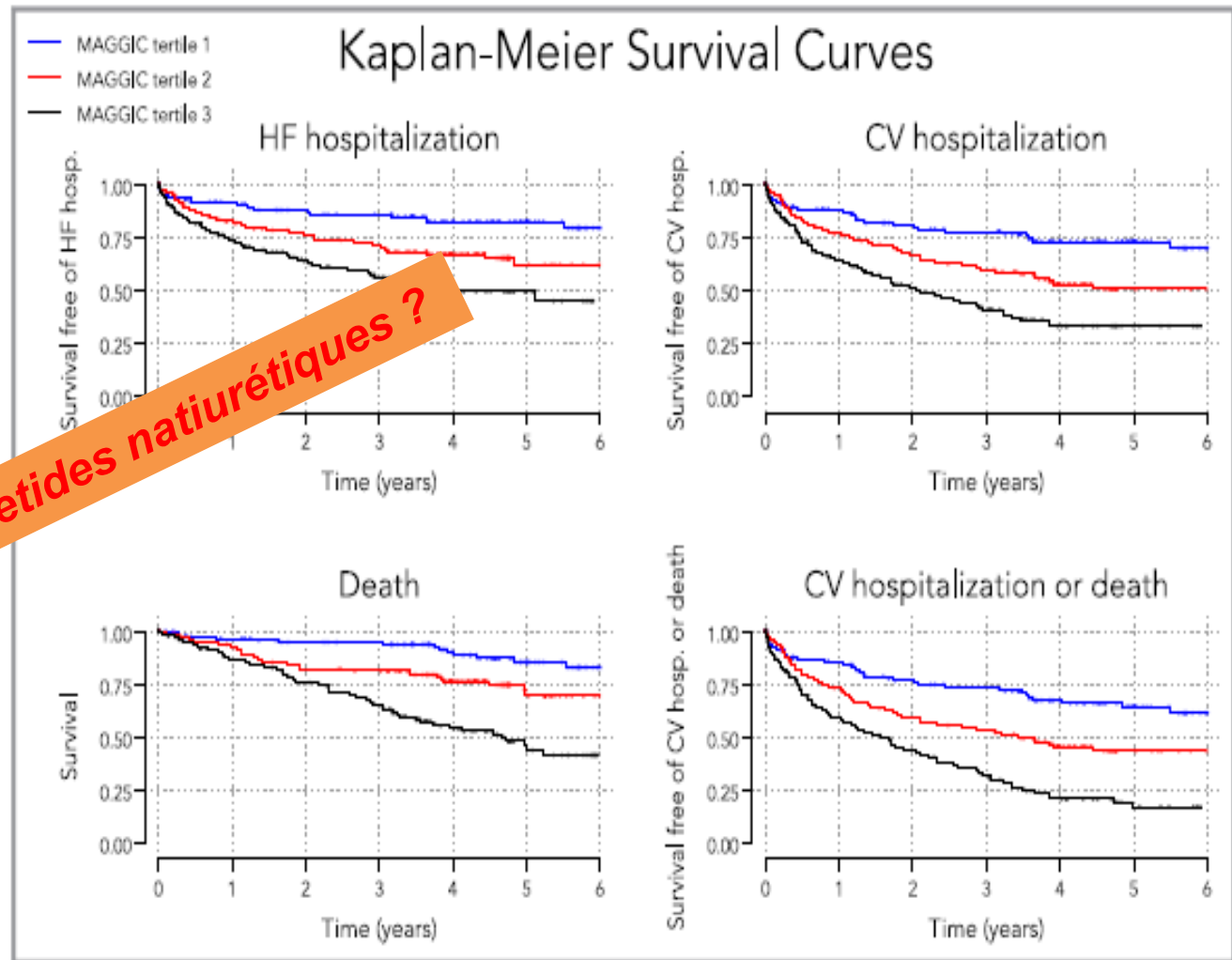
**S.D. Anker et al. European Journal of Heart Failure (2018)20,125–133**



# Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score: a Simple Tool for the Prediction of Morbidity and Mortality in HFpEF

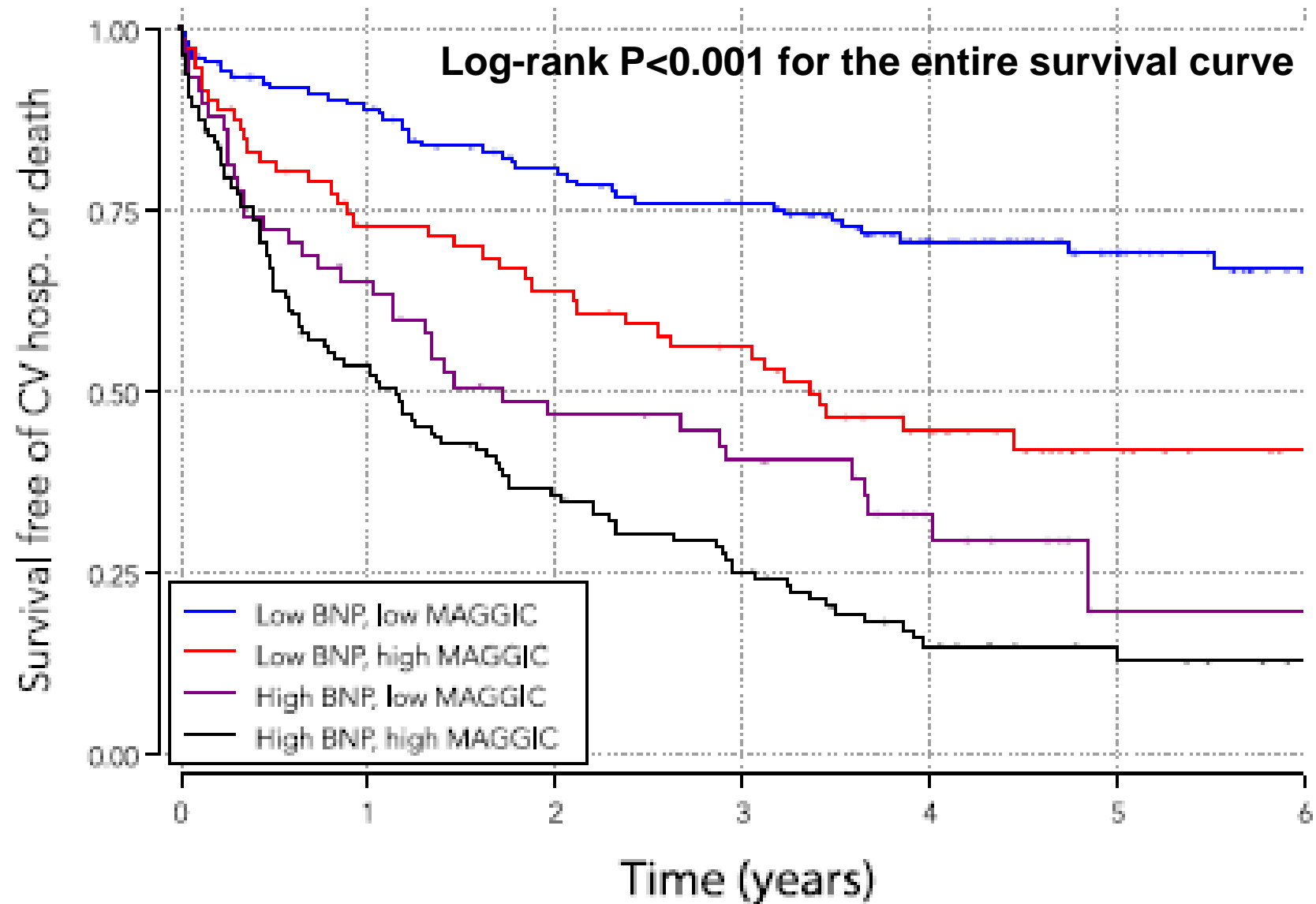
Variable	MAGGIC (13 Variables)	SHFM (20 Variables)
Age	X	X
Male sex	X	X
Diabetes mellitus	X	
COPD	X	
Current smoker	X	
Ischemic cause		X
HF duration <18 mo	X	
NYHA class	X	X
$\beta$ -Blocker use	X	X
ACE-inhibitor/ARB use	X	X
Aldosterone blocker use		X
Allopurinol use		X
Statin use		X
Loop diuretic dose		X
Systolic blood pressure	X	X
Body mass index	X	X
Serum creatinine	X	
Sodium		X
Hemoglobin		X
Total cholesterol		X
Lymphocytes		X
Uric acid		X
Ejection fraction	X	X
Device therapy		X
QRS duration		X

Seattle Heart Failure Model



*JD. Rich, et al., J Am Heart Assoc. 2018;7: e009594*

# MAGGIC score et peptides natriuretiques



# Biomarkers of Heart Failure

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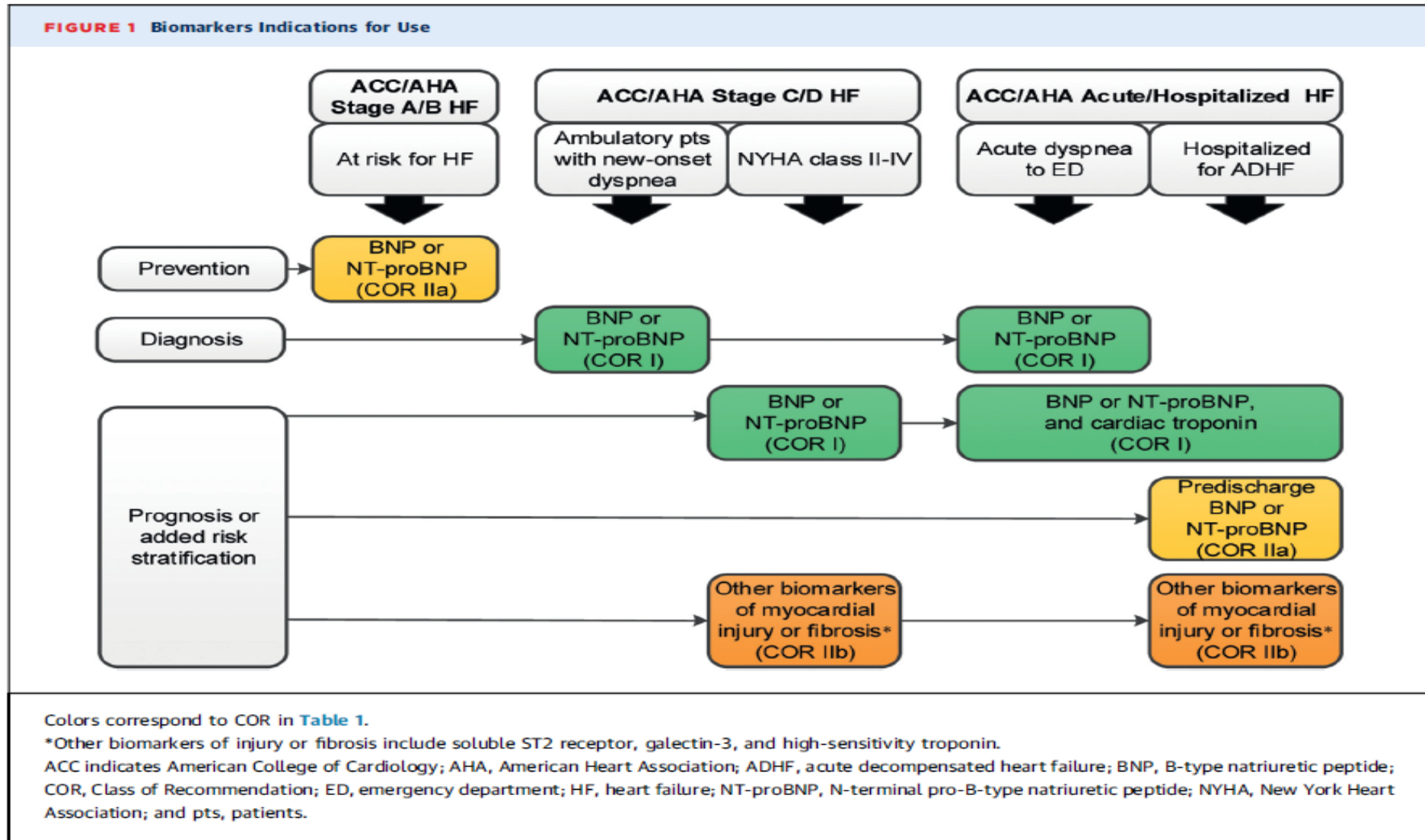
## III) Quelle place pour le Laboratoire en dehors des peptides ?

- Le syndrome cardiorénal ... et les perturbations électrolytiques
- Ne pas oublier le bilan martial

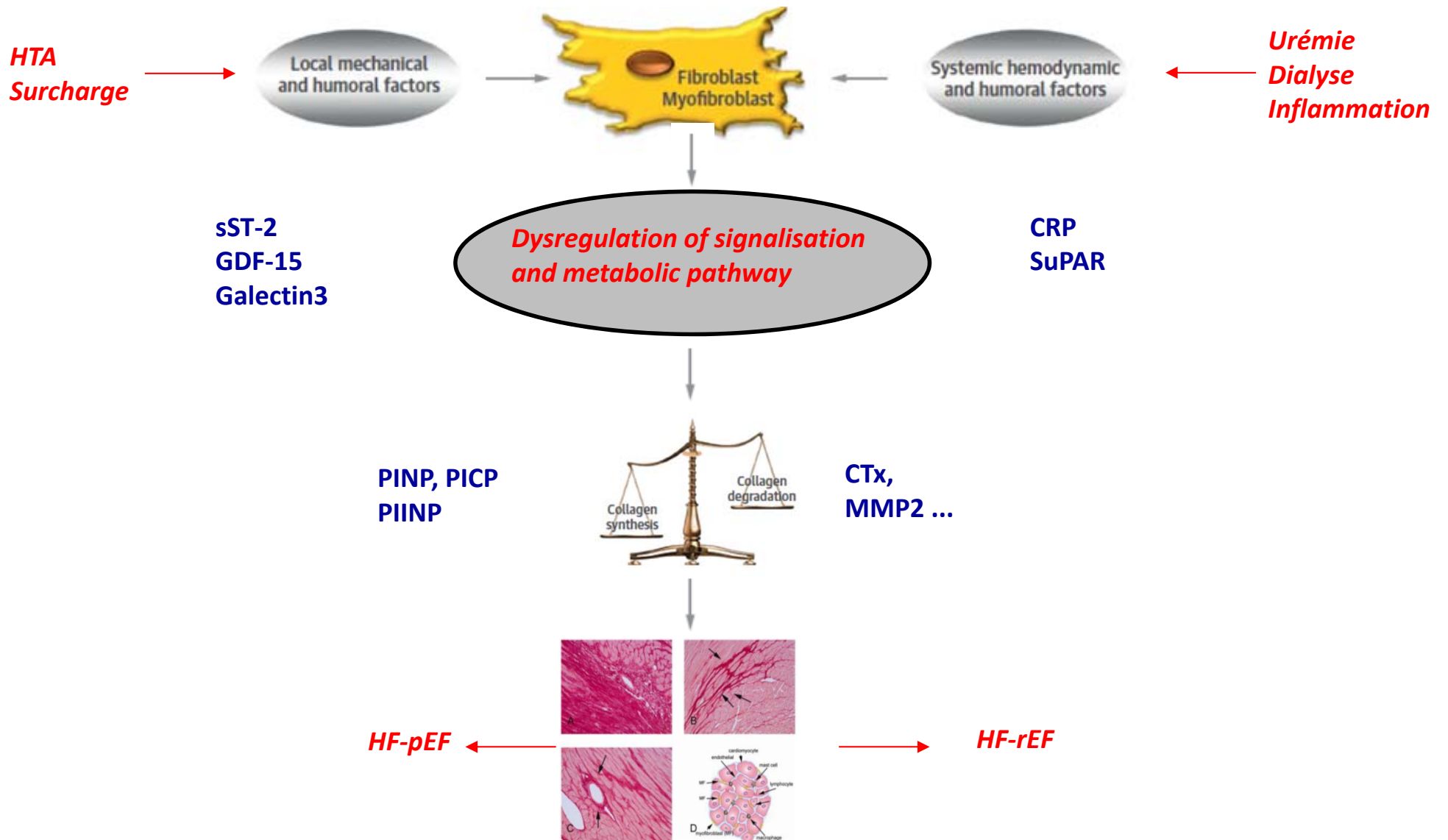
## IV) La voie du ST2 et la stratégie multimarqueur.

# Quelle place pour les nouveaux biomarqueurs dans la stratification du risque ?

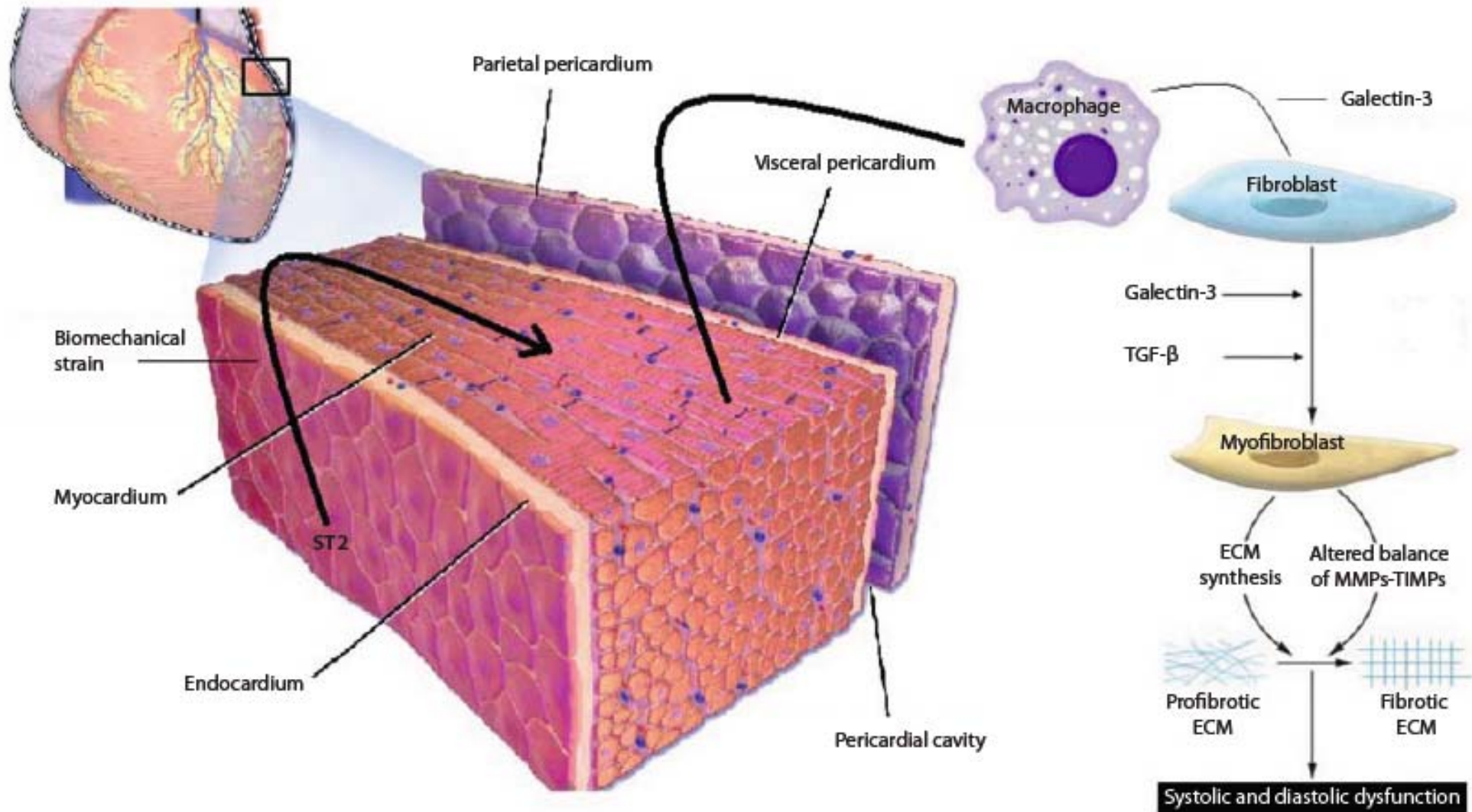
2017 ACC/AHA/HFSA Focused Update of the 2013 Guideline for the Management of HF



# Les marqueurs de fibrose et de remodelage cardiaque

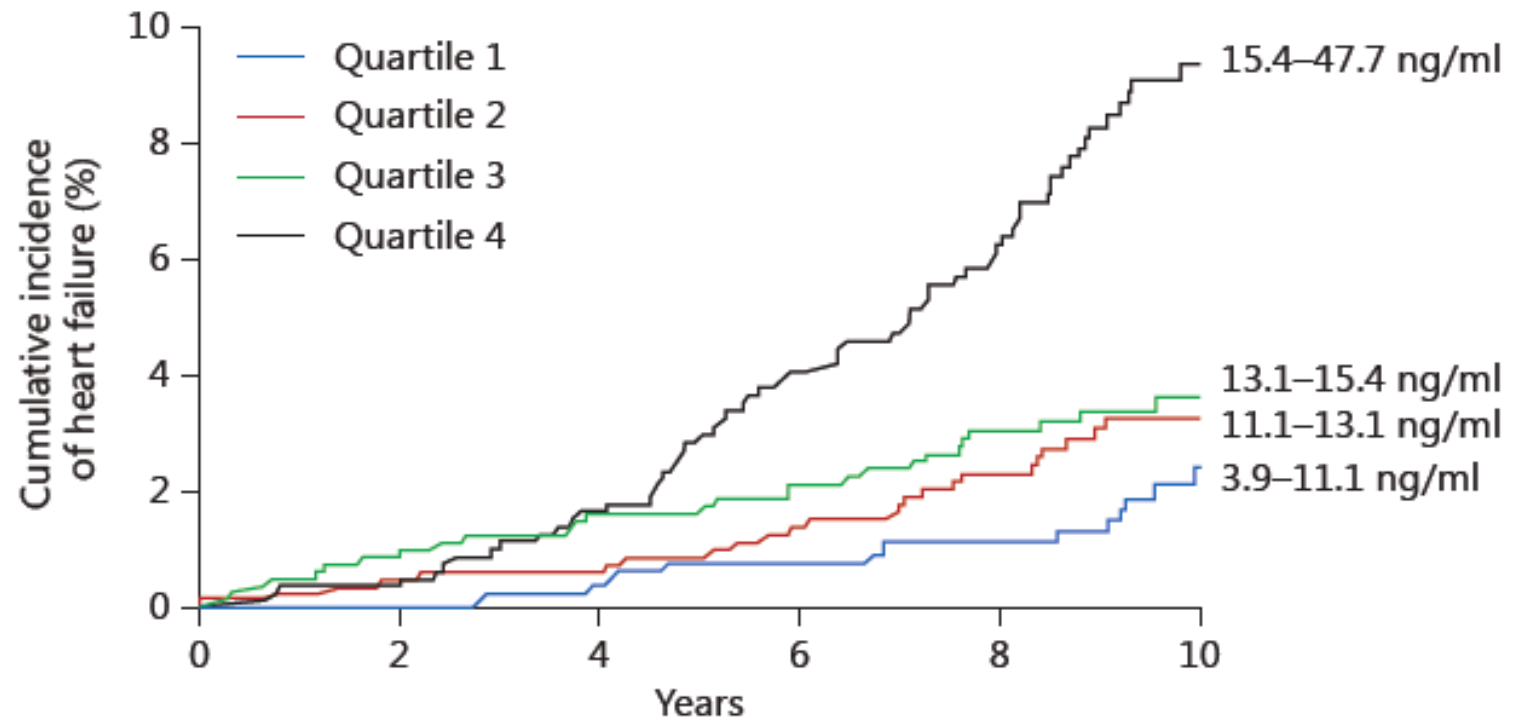


# Roles of ST2 and galectin-3 in pathogenic cardiac fibrosis.



*Aneley Hundae; Peter A. McCullough; Nephron Clin Pract 2014;127:106–112*

# Baseline galectin-3 predicts incident HF in the Framingham Heart Study.



Number at risk	0	2	4	6	8	10
Quartile 1	835	811	760	747	702	278
Quartile 2	842	808	762	736	661	235
Quartile 3	842	801	755	726	647	233
Quartile 4	834	789	712	662	591	228

*HO JE et al. J Am Coll Cardiol 2012; 60: 1249–1256.*

# Biological variability of biomarkers for monitoring chronic cardiac disease

Marker	Duration	CV <sub>I</sub>	CV <sub>G</sub>	RCV (up, down*)	Index	Reference
CK	2 mo	30%	30%	82% (+139, -58)	1.00	Wu ,Clin Chim Acta 2009
BNP	2 mo	50%	28%	138% (NA)	1.11	Wu , Am J Cardiol 2003
NT-proBNP	2 mo	33%	36%	92% (NA)	0.91	Wu , Am J Cardiol 2003
hs-cTnI	2 mo	14%	63%	63% (+81, -45)	0.39	Wu , Clin Chem 2009
hs-cTnI	9 mo	28%	71%	73% (+98, -49)	0.45	Wu , Clin Biochem 2012
hs-cTnT	1 mo	31%	32%	87% (+138, -58)	0.97	Frankenstein L, Clin Chem 2011
sST2	1.5 mo	10.5%	46.4%	30% (NA)	0.23	Dieplinger B Clin Chim Acta 2009
sST2	2 mo	11%	46%	30% (+34, -26)	0.25	Wu Am Heart J 2013
Galectin-3	Hourly	16%	16%	39% (+47, -32)	1.00	Wu Am Heart J 2013
Galectin-3	2 mo	20%	23%	61% (+78, -44)	1.01	Wu Am Heart J 2013

CK, cytokeatin; NA, data not available (results were not log transformed); hs-cTnI, high-sensitivity cardiac troponin I; Index, index of individuality.

\*The RCV is computed from log-transformed data as necessary because of nonparametric distribution. This results in a different limits for serial results that are increasing versus decreasing.

*The biological variation data suggest that a single result for galectin-3 is diagnostic for remodeling, whereas changes in sST2 indicate ongoing disease progression.*

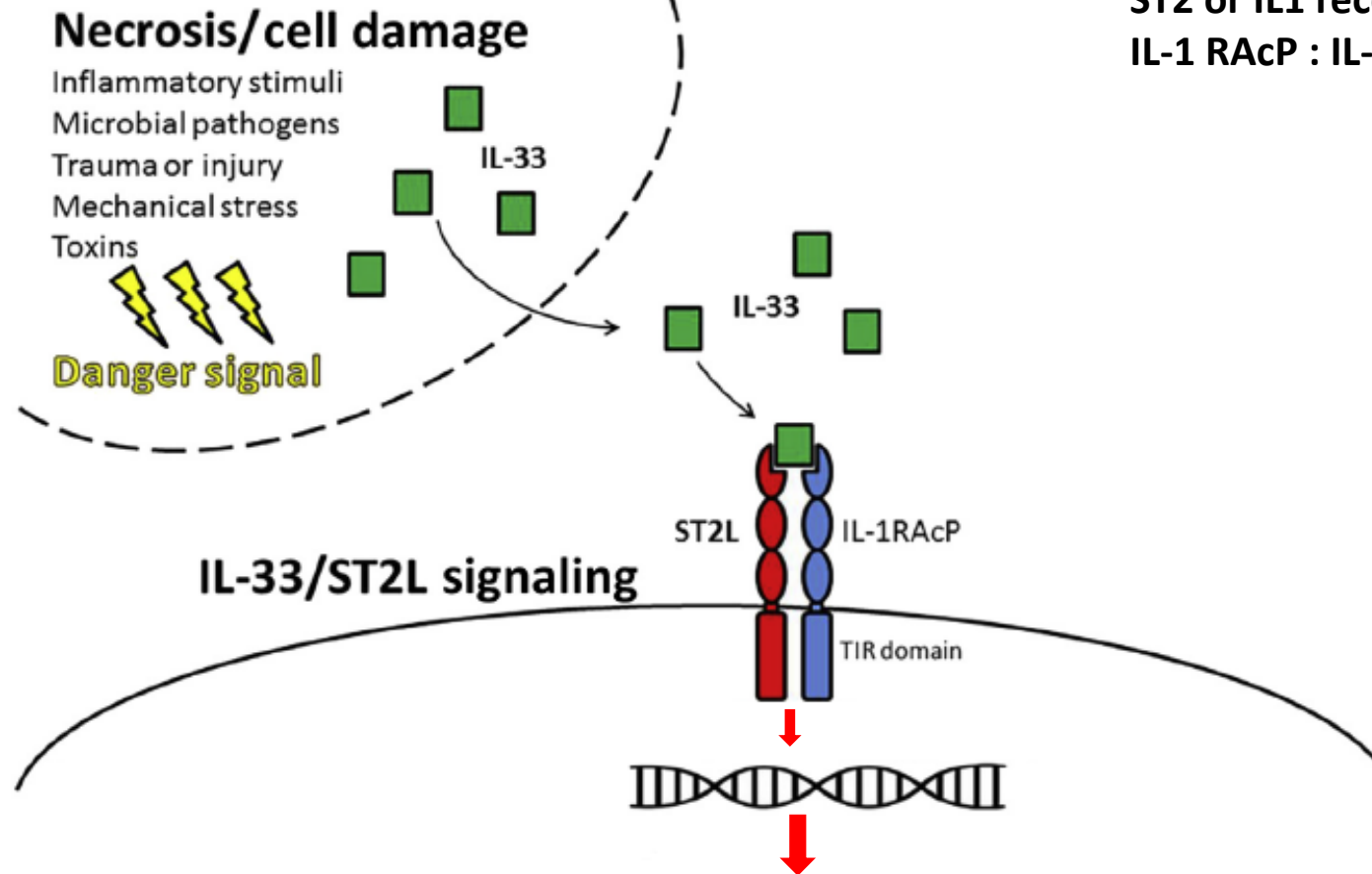
*These results suggest that sST2 and galectin-3 may provide complementary information for patients with chronic heart failure.*

**Alan H.B. Wu et al., Am Heart J 2013;165:995-9.**



# IL-33/ST2L signaling is a mechanically activated, cardioprotective system

Cardiac fibroblasts or cardiomyocytes



ST2 or IL1 receptor – like 1

IL-1 RAcP : IL-1R accessory protein

**Modulation of inflammation**

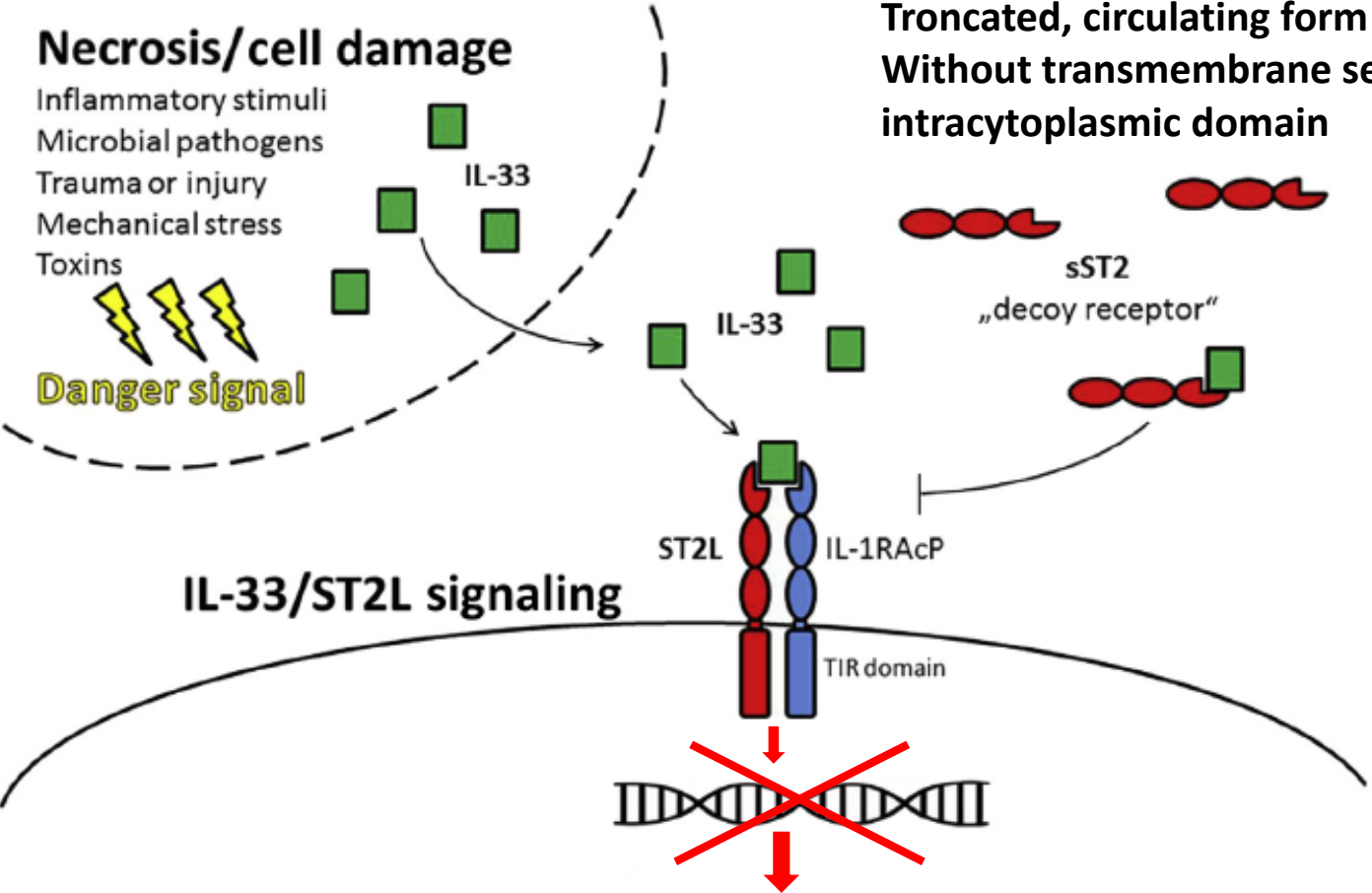
**Cardioprotection : prevents apoptosis, hypertrophy and fibrosis**

*Benjamin Dieplinger, Thomas Mueller. Clinica Chimica Acta xxx (2014) xxx–xxx*

# sST2 acts as a decoy receptor of the IL-33/ST2L signaling pathway

Cardiac fibroblasts or cardiomyocytes

Cardiac fibroblasts or cardiomyocytes



~~Modulation of inflammation~~  
~~Cardioprotection: prevents apoptosis, hypertrophy and fibrosis~~

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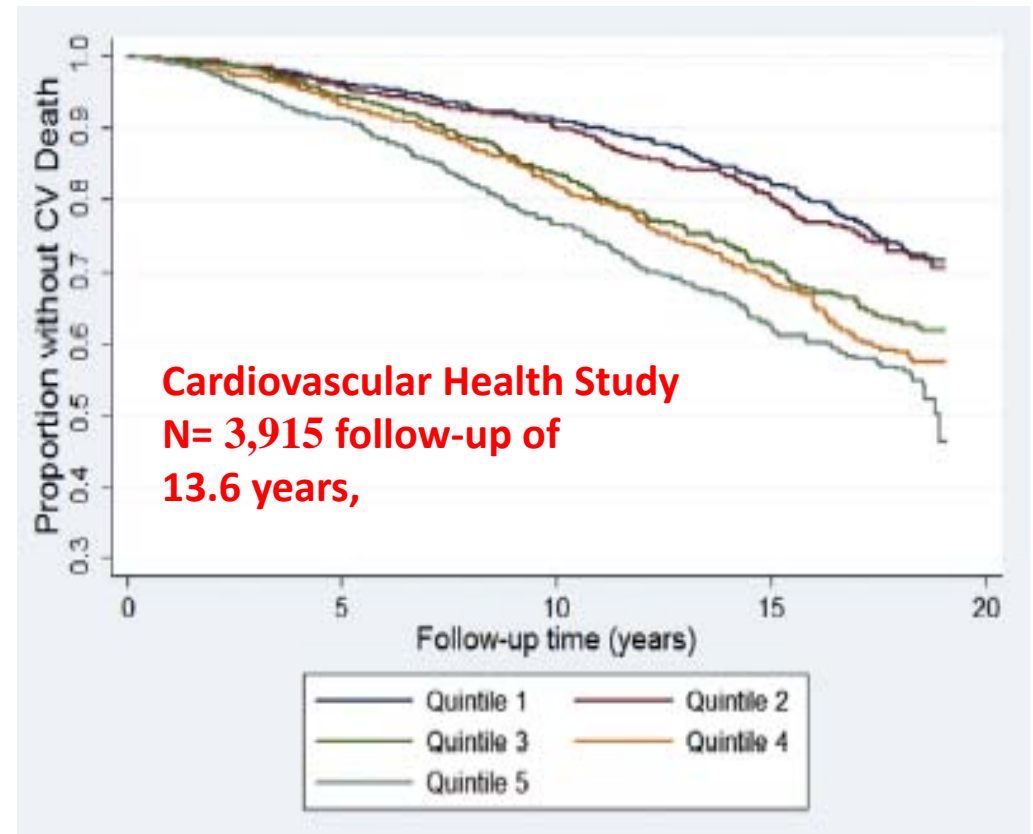
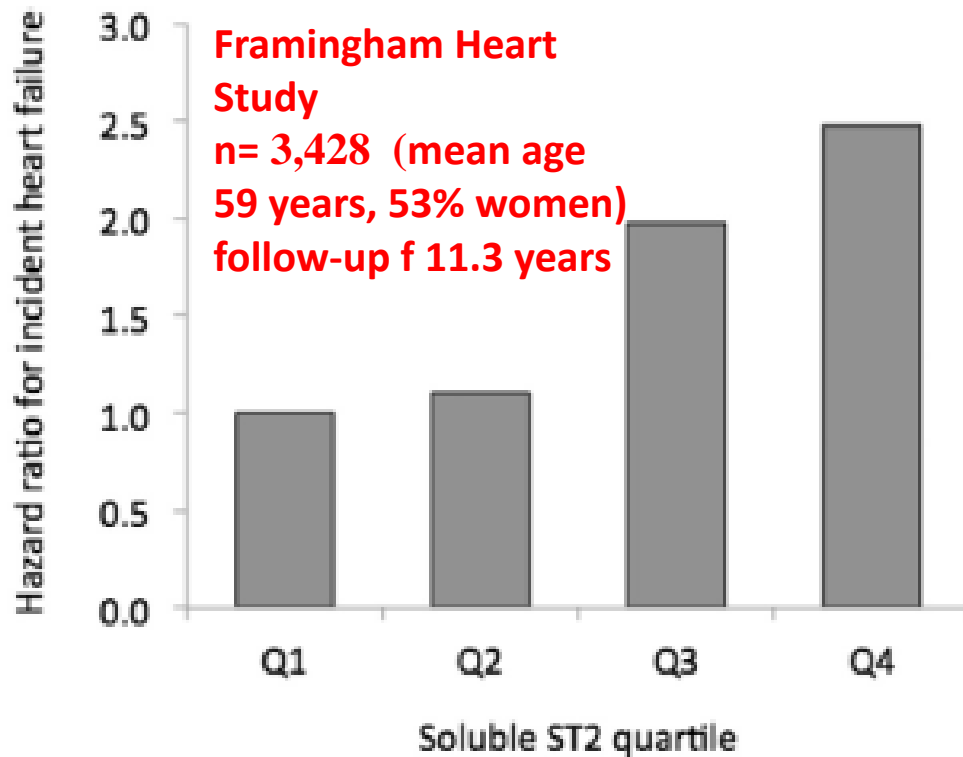
\*The RCV is computed from log-transformed data as necessary because of nonparametric distribution. This results in a different limits for serial results that are increasing versus decreasing.

*sST2 has a low index of individuality, therefore, sST2 is a monitoring biomarker. A change in sST2 results would indicate heart failure disease progression.*

*Serial testing could be required for better interpretation of results.*

**Alan H.B. Wu et al., Am Heart J 2013;165:995-9.**

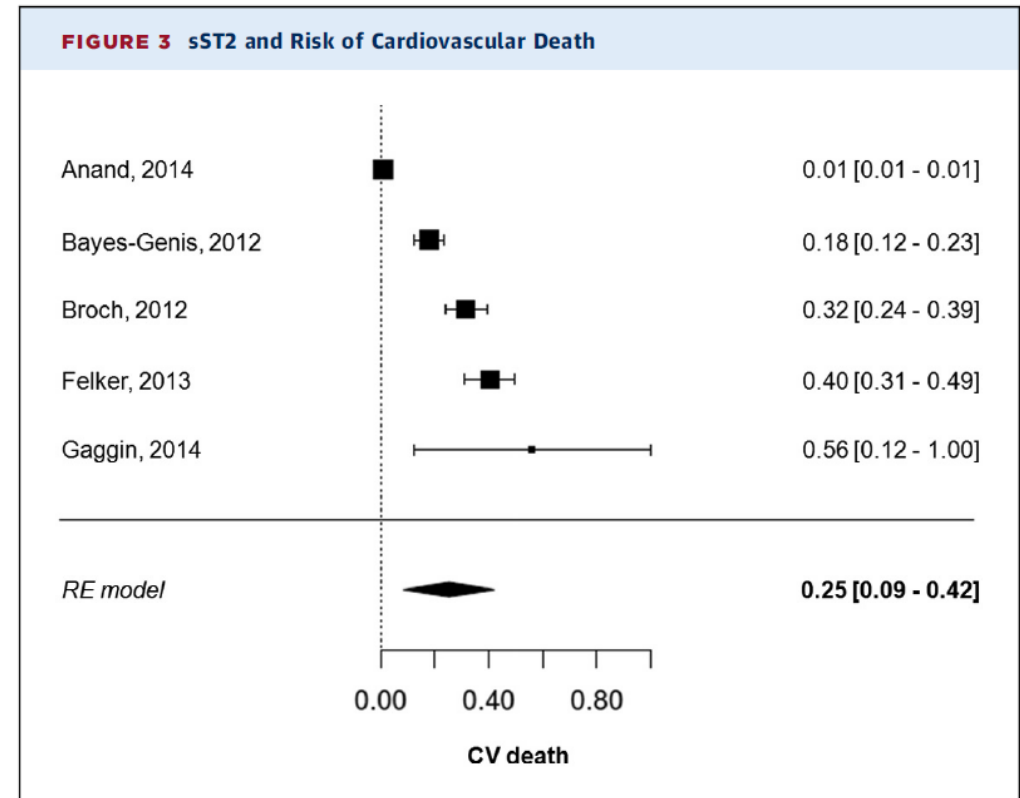
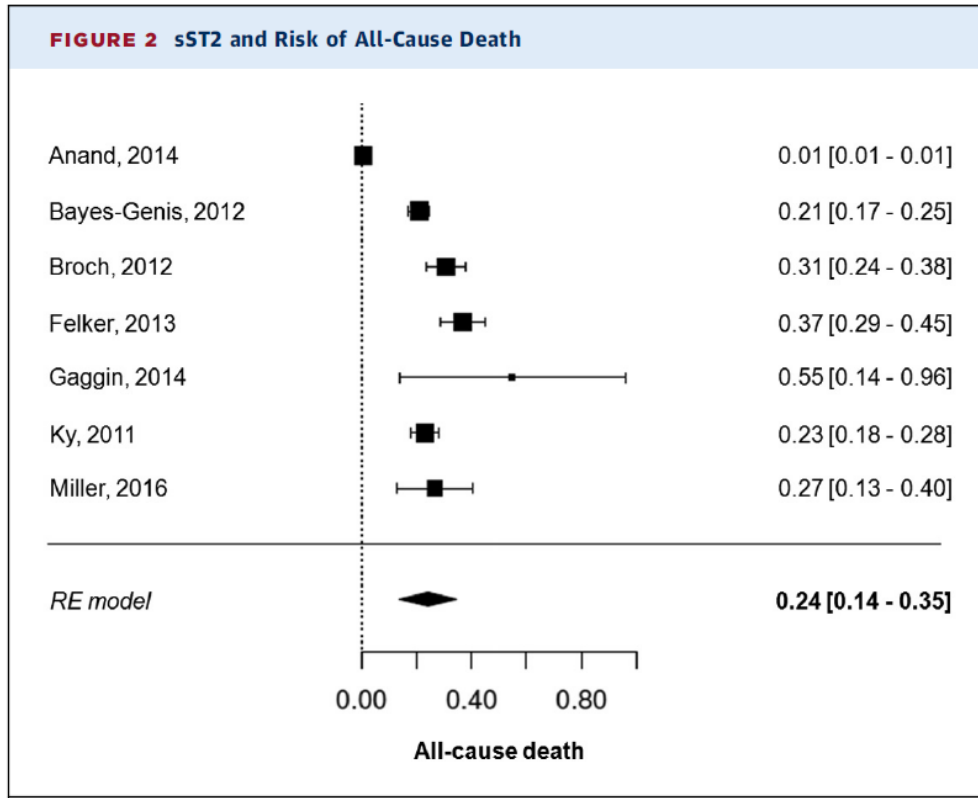
# sST2 as a cardiovascular risk factor in general population



**Wang TJ, et al., Circulation 2012; 126:1596-1604.**

**Ginsberg E et al., J Am Coll Cardiol 2014;63:A768.**

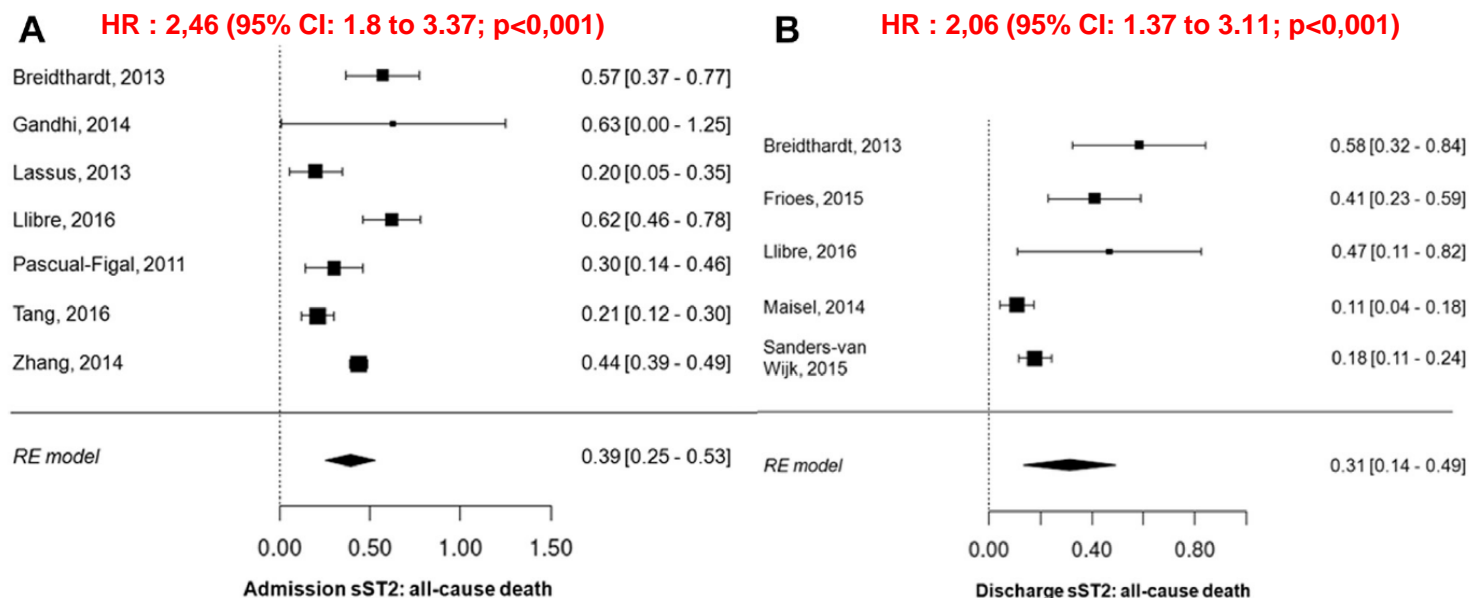
# sST-2 Prognostic Value of Soluble Suppression of Tumorigenicity-2 in Chronic Heart Failure (meta-analysis)



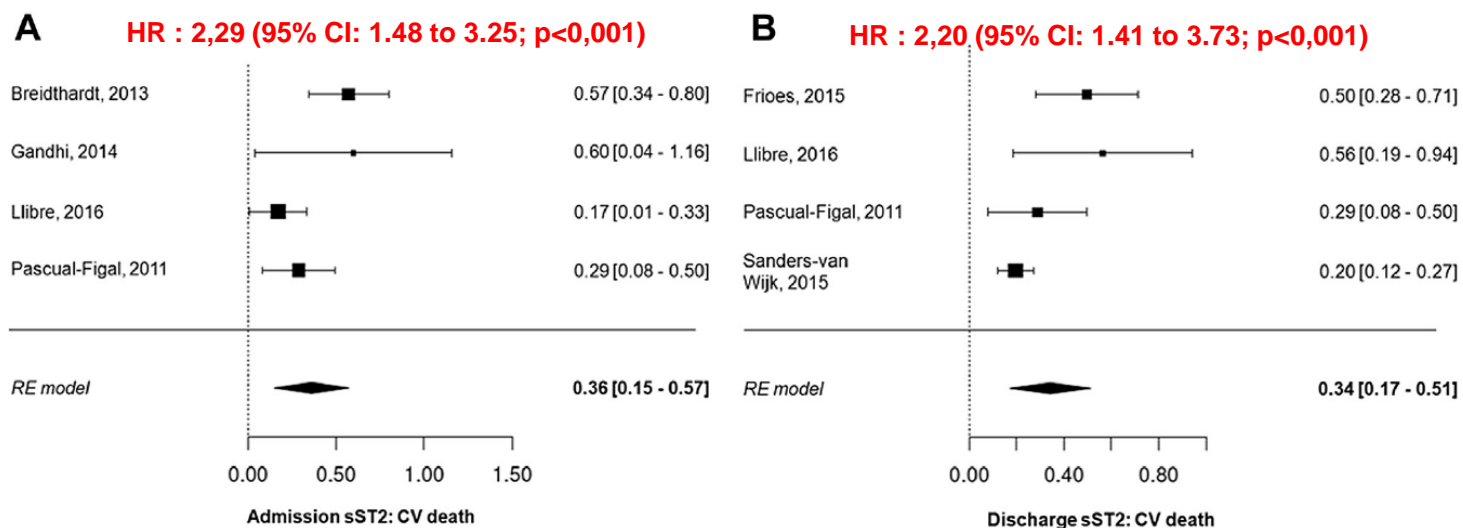
**HR : 1.75 (95% CI: 1.37 to 2.22; p<0,001) (HR : 1.79 (95% CI: 1.22 to 2.65; p<0,001)**

# sST-2 Prognostic Value of Soluble Suppression of Tumorigenicity-2 in Acute Heart Failure

**FIGURE 2 Risk for All-Cause Death**



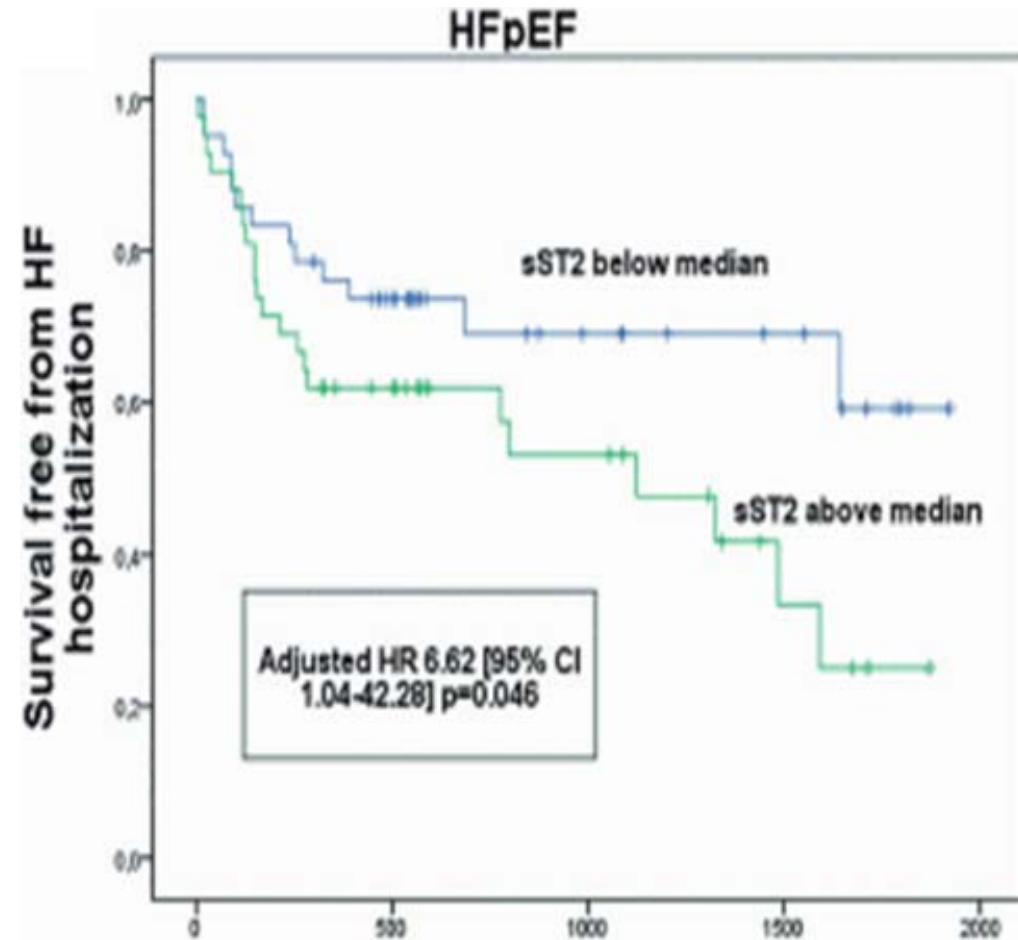
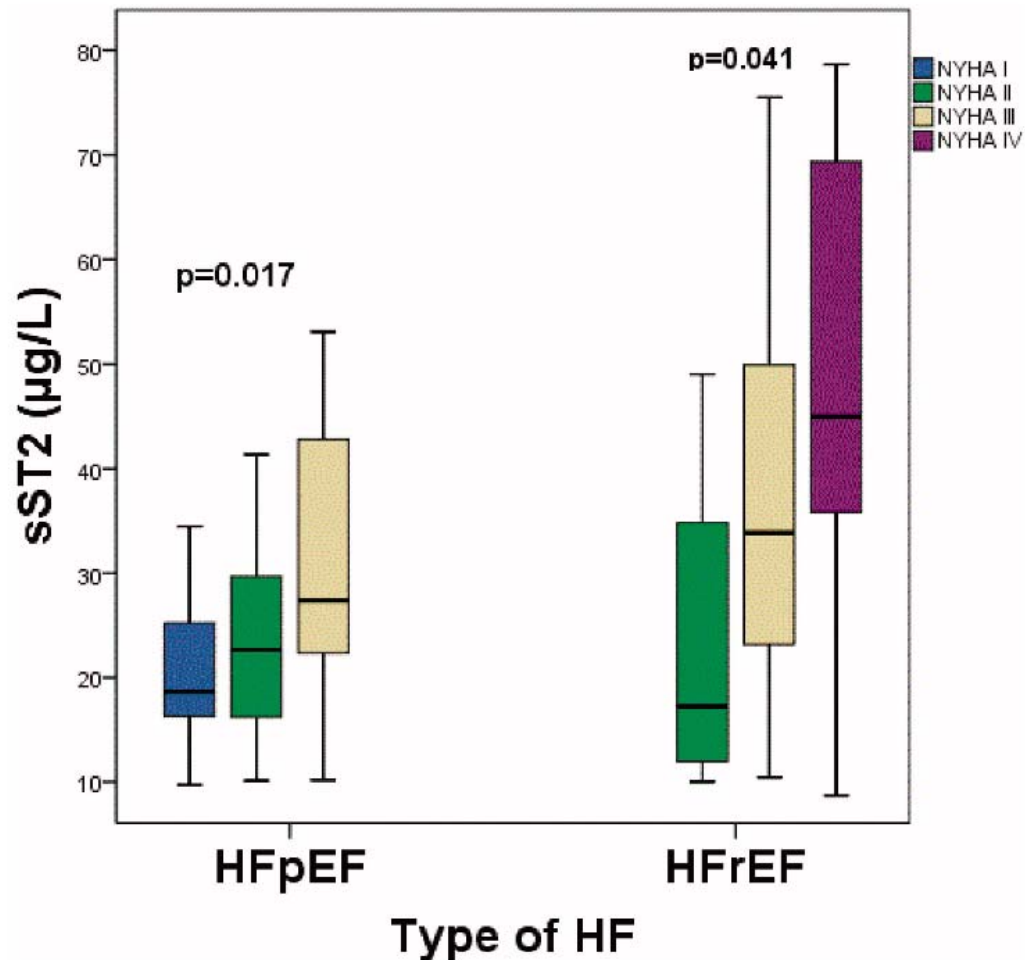
**FIGURE 3 Risk for Cardiovascular Death**



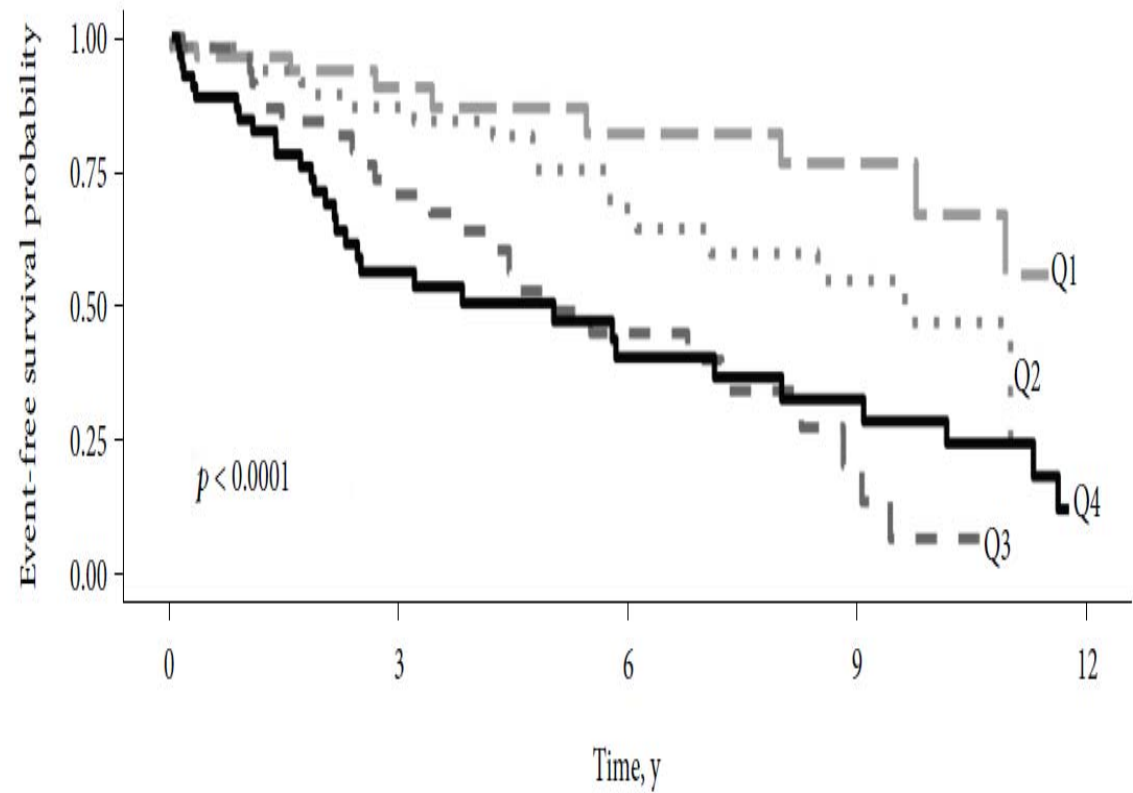
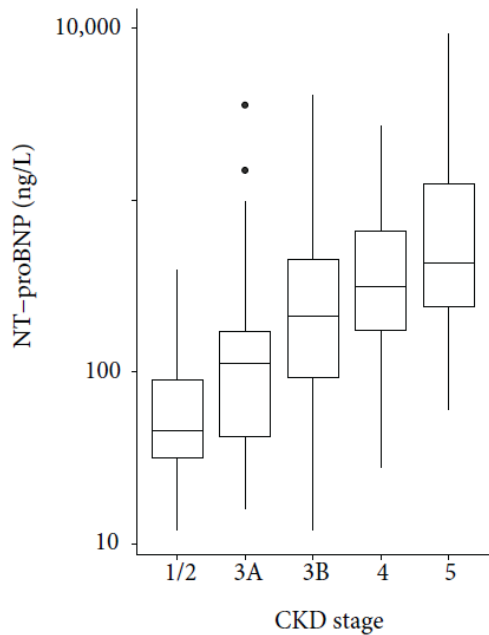
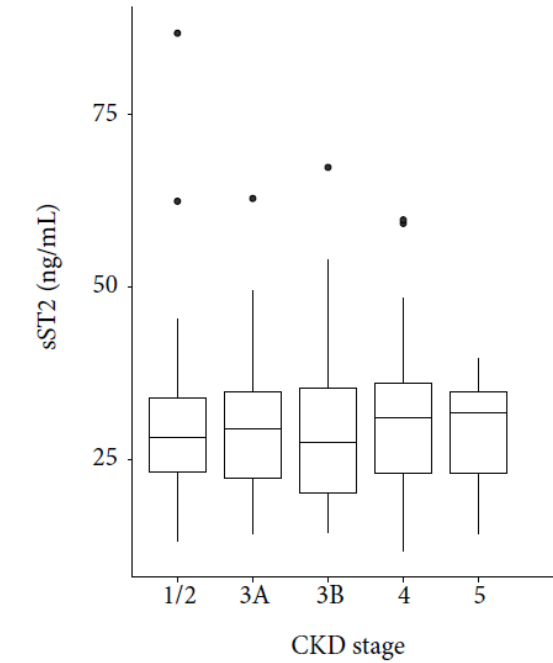
**Alberto Aimo et al.,  
 J Am Coll Cardiol HF  
 2017;5:287-96**

# sST2 in HFrEF and HFpEF

193 subjects, 3 different cohorts



# sST-2 : un marqueur indépendant des fonctions rénales



**Maëlle Plawecki et al., Mediators of Inflammation, 2018.**



# ST2 outperformed NT-proBNP for predicting the risk of all-cause mortality or HF-related rehospitalization in elderly

**Table 3** Cox regression analyses for the 1-year composite endpoint (all-cause death or HF related rehospitalization)

	1-year composite endpoint					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Age	1.04	1.02–1.06	< 0.001	1.03	1.01–1.06	0.003
Female sex	1.28	0.96–1.70	0.09	1.64	1.20–2.23	0.002
NYHA	1.54	1.18–2.01	0.002	–	–	–
Diabetes	1.16	0.98–1.38	0.09	–	–	–
Charlson comorbidity index	1.15	1.08–1.22	< 0.001	1.10	1.03–1.18	0.008
Barthel index	0.99	0.98–0.99	< 0.001	–	–	–
Urea	1.01	1.01–1.01	< 0.001	1.01	1.00–1.01	< 0.001
Creatinine	1.00	1.00–1.01	0.3	–	–	–
Hb	0.90	0.82–0.98	0.01	–	–	–
Na	0.97	0.93–1.00	0.07	–	–	–
NT-proBNP <sup>a</sup>	1.43	1.25–1.65	< 0.001	1.18	1.00–1.38	0.04
ST2 <sup>a</sup>	1.63	1.44–1.85	< 0.001	1.41	1.21–1.63	< 0.001

# sST-2 et marqueurs du collagène : un lien avec la fibrose cardiaque

Variable	Baseline Model		Model 1		Model 2		Model 3		Model 4	
	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
	1.05 [1.01-1.09]	0.004	1.03 [1.00-1.07]	0.03	1.05 [1.01-1.09]	0.003	1.04 [1.01-1.08]	0.009	1.05 [1.01-1.08]	0.007
Age										
NYHA class	1.74 [0.77-3.93]	0.176	1.51 [0.66-3.48]	0.324	0.90 [0.38-2.15]	0.826	0.95 [0.40-2.24]	0.908	0.89 [0.37-2.13]	0.804
LVEF	0.98 [0.95-1.00]	0.192	0.99 [0.96-1.02]	0.83	0.99 [0.96-1.01]	0.5	0.99 [0.96-1.02]	0.596	0.99 [0.96-1.02]	0.742
Hs-cTnT (log 10)			0.89 [0.68-1.16]	0.394						
CRP (log 10)			1.33 [1.04-1.70]	0.021						
NT-proBNP (log 10)			1.56 [1.14-2.14]	0.005			1.28 [0.94-1.74]	0.11	1.22 [0.90-1.67]	0.192
CTx/PIIINP ratio					2.23 [1.14-4.38]	0.019			2.22 [1.17-4.22]	0.014
sST2 (log 10)					1.94 [1.31-2.86]	0.001	1.80 [1.16-2.79]	0.008	1.67 [1.07-2.61]	0.023
Galectin-3 (log 10)					1.11 [0.54-2.28]	0.769				

Model 1: Baseline model adjusted by hs-cTnT, CRP and NT-proBNP.

Model 2: Baseline model adjusted by CTx/PIIINP ratio, sST2 and Galectin-3.

Model 3: Baseline model adjusted by NT-proBNP and sST2.

Model 4: Baseline model adjusted by NT-proBNP, CTx/PIIINP ratio and sST2.

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; hs-cTnT: high-sensitivity cardiac troponin T; CRP: C-reactive protein; sST2: soluble suppression of tumorigenicity 2; PINP: procollagen type I N-terminal propeptide; PIIINP: procollagen type III N-terminal propeptide; CTx: c-terminal telopeptide of collagen type I.

# Development of a Novel HF Risk Tool: The Barcelona Bio-HF Calculator

**BCN BioHF**

**iCor.cat** **IGTP**  **Germans Trias i Pujol Hospital**

**Clinical Variables**

Age, years\*  
68

Sex\*  
 Male  
 Female

NYHA functional class\*  
 I-II  
 III-IV

Ba, mmol/L  
138

eGFR, ml/min/1.73m2  
50

Hb, g/dL  
12.5

LVEF, %  
35

**Treatments**

Loop diuretic, mg/d\*  
Furosemide  
40  
Torsemide

Statin\*  
 Yes  
 No

Beta-blocker\*  
 Yes  
 No

ACEI or ARB\*  
 Yes  
 No

**Biomarkers**

hs-cTnT, ng/L (pg/mL)  
20

ST2, ng/mL  
70

NT-proBNP, ng/L (pg/mL)  
2000

**Calculate**

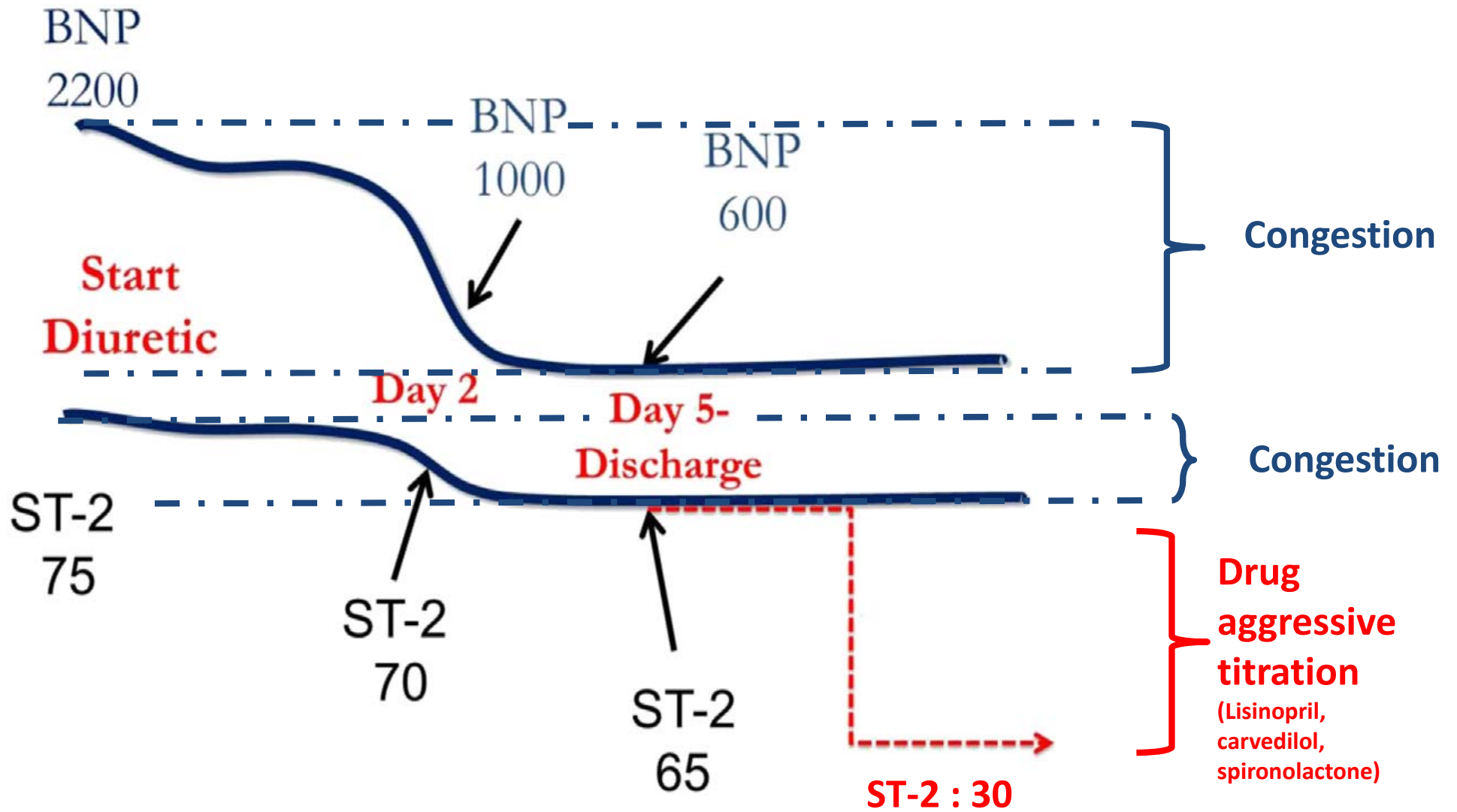
Mortality	Risk at 1 year	Risk at 2 years	Risk at 3 years
Model without biomarkers	9.03%	19.19%	29.7%
+ Combined Biomarkers	13.74%	28.29%	42.3%

— Model without biomarkers — + Combined Biomarkers

Life expectancy	years
Model without biomarkers	6.3
+ Combined Biomarkers	4.6

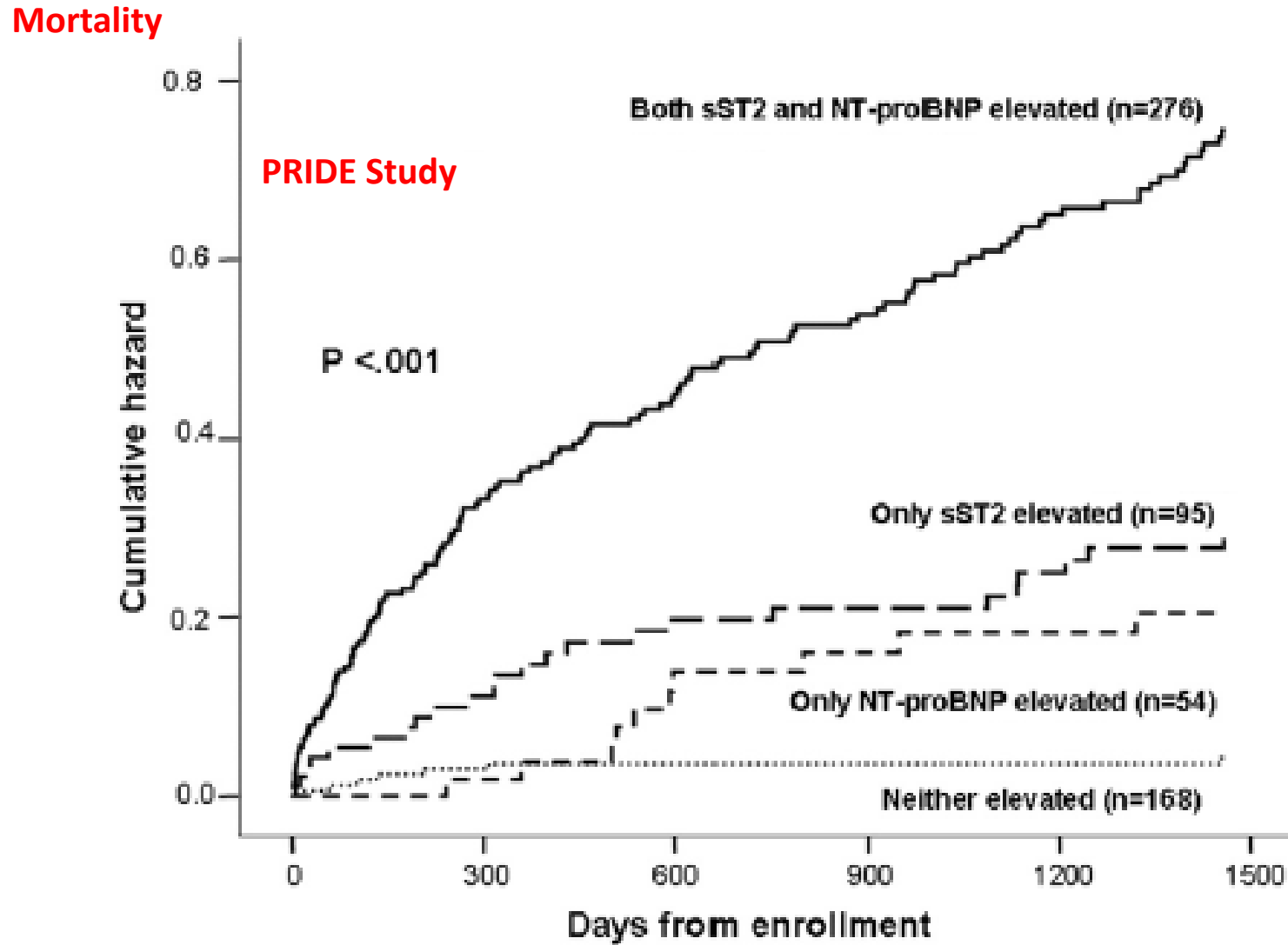
(\*) Required fields.

# sST2 as a therapeutic monitoring tool : Case report



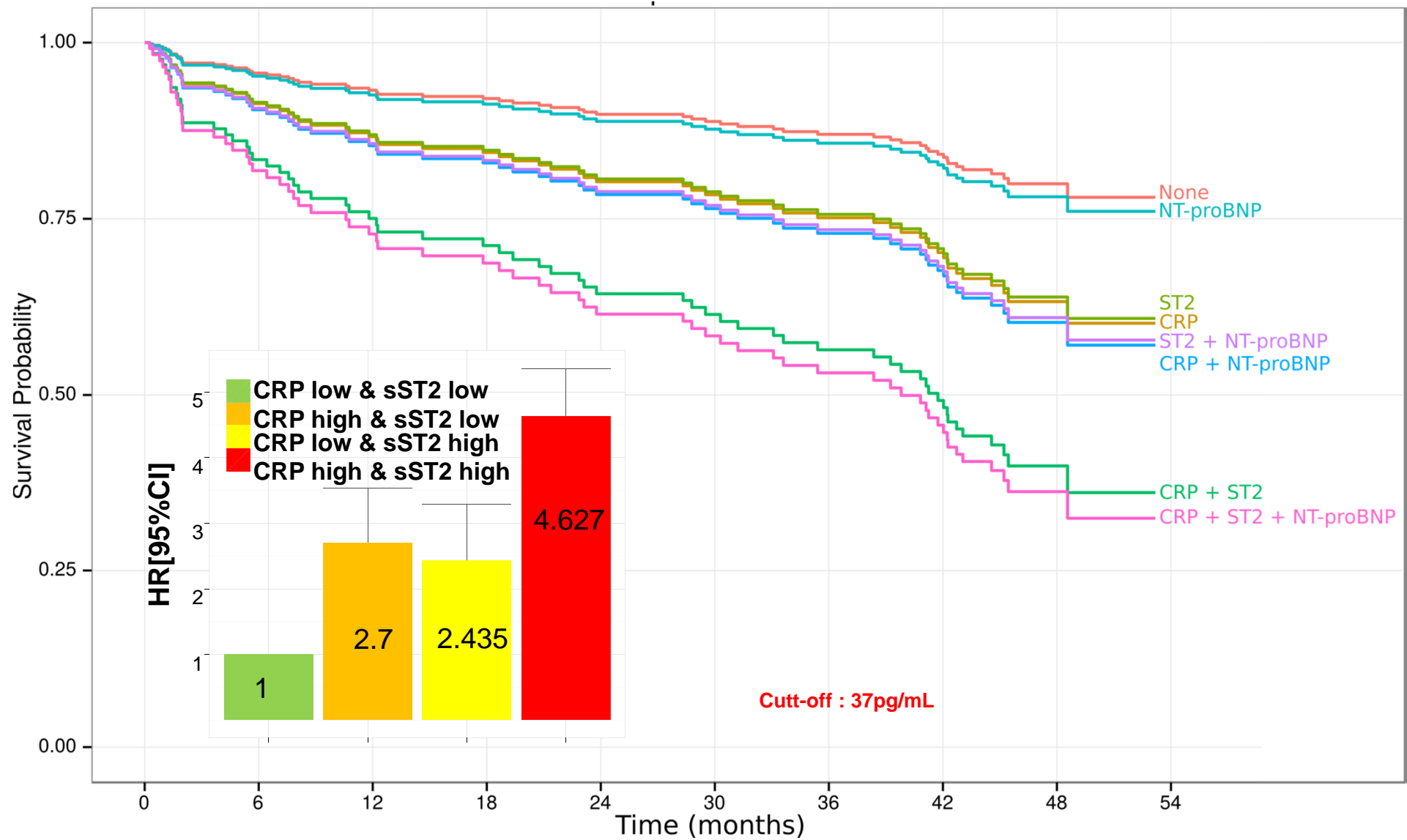
*Maisel A.S. et al., Am. J. Cardiol. 2015; 115 (suppl) 32B-37B.*

# sST2 and Nt-pro-BNP are additive in Acutely Decompensated Heart Failure

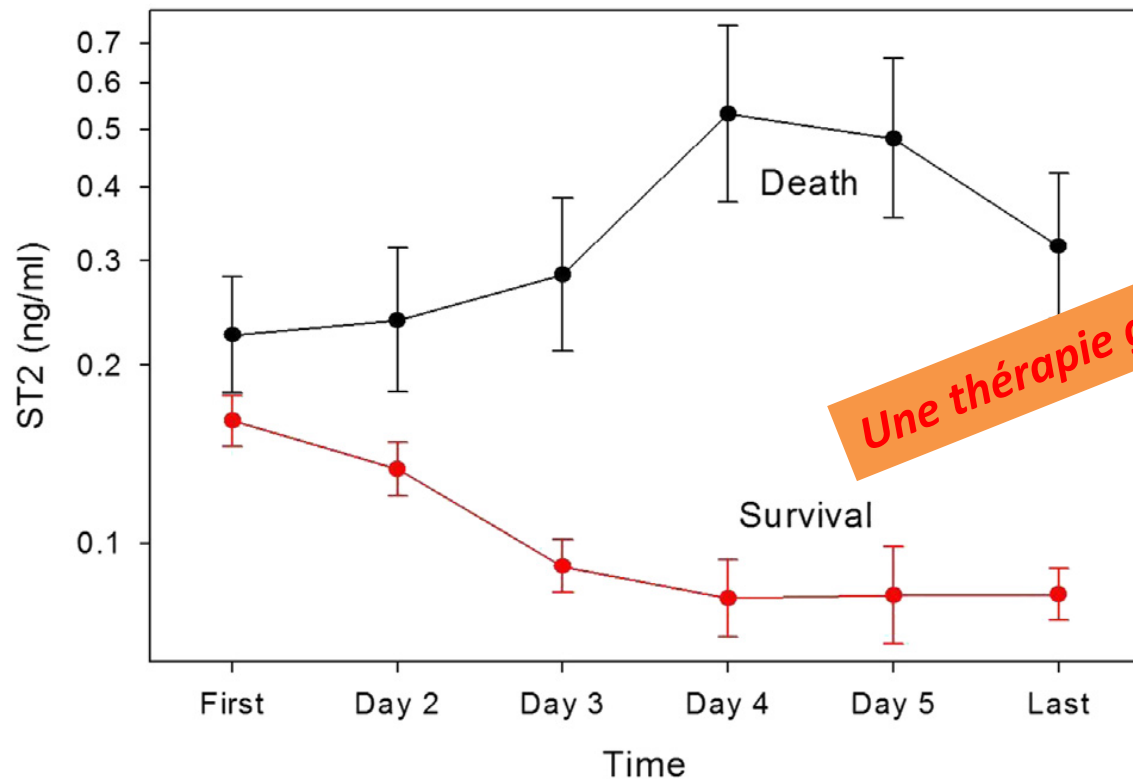


Januzzi JL et al., J Am Coll Cardiol 2007;50:607-613.

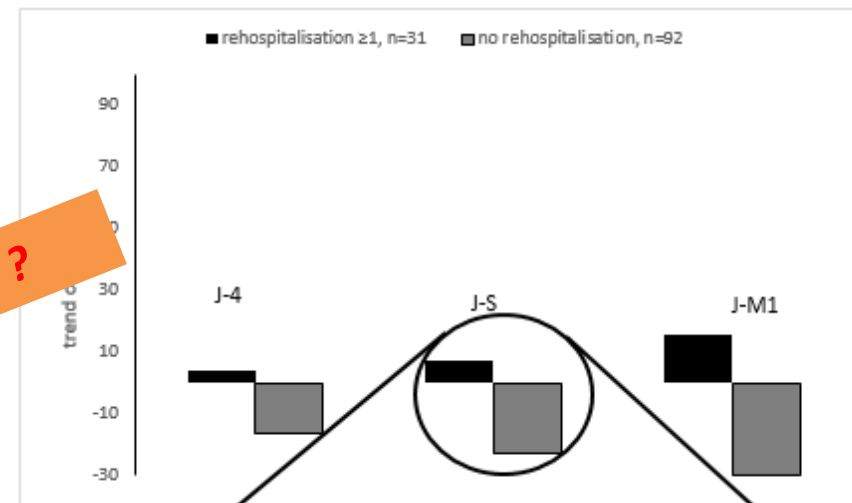
# sST2 : Synergie avec l'inflammation



# sST2 serial testing : predicting outcome and rehospitalization



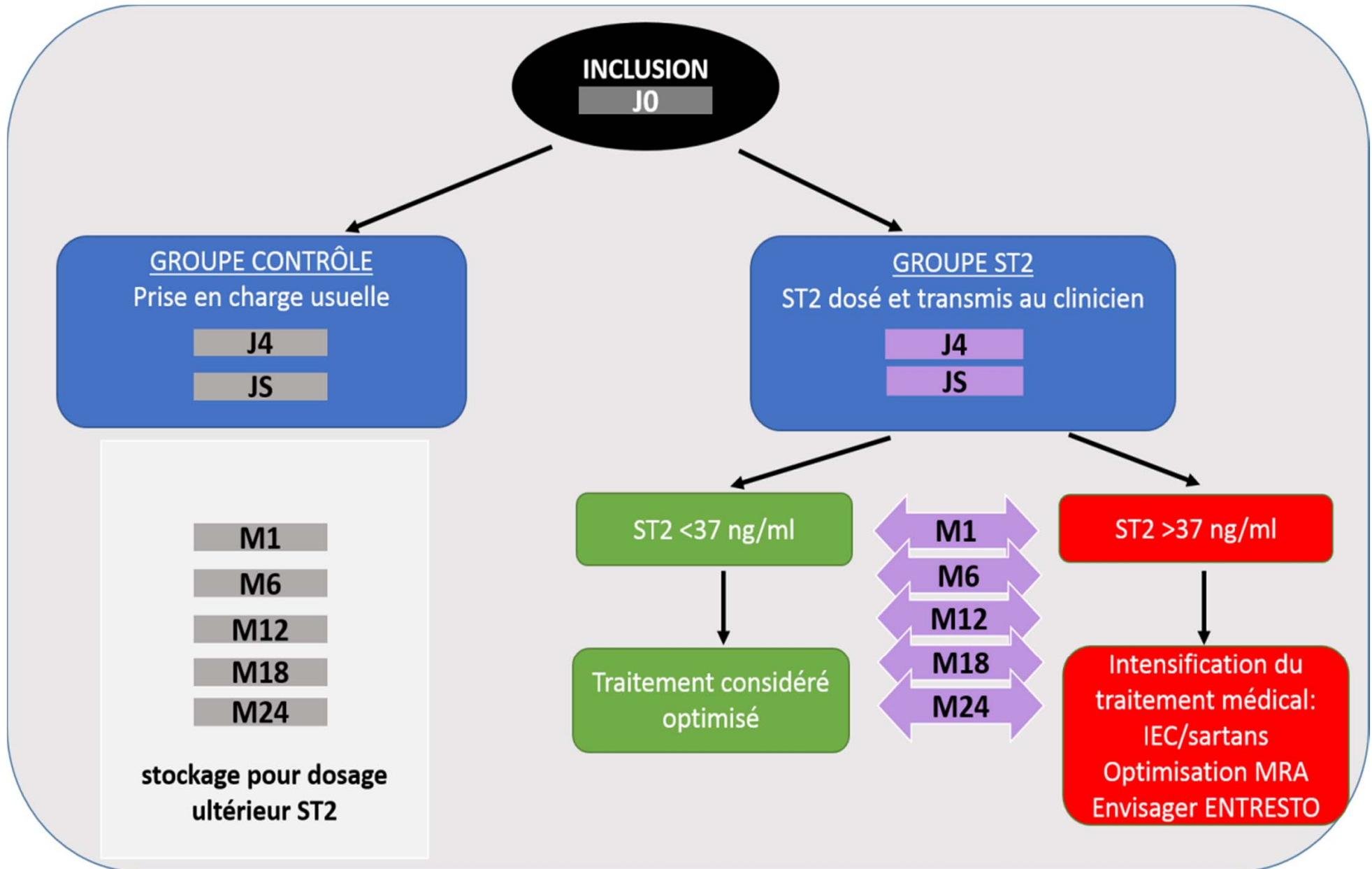
**Une thérapie guidée ?**



		<u>Decrease in ST2 &gt; 18%</u>	<u>Decrease in ST2 &lt; 18%</u>	P (Chi2)
<u>Rehospitalization</u>	No	15 (56%)	53 (85,5%)	0,0022
	Yes	12 (44%)	9 (14,5%)	

***A decreasing value by discharge is desirable, and lower is always better***

# ICAME : un PRME multicentrique (mise en place 2020)





# Biomarkers of Heart Failure

## I) Les Biomarqueurs en 2019

- Un biomarqueur dediagnostic, d'élimination, de suivi
- Des critères analytiques et biologiques pour l'interprétation

## II) Les peptides natriurétiques : 20 ans après

- Une valeur diagnostique plus que pronostique
- Une interprétation cinétique (Entrée – Sortie – Surcharge)
- Des limites analytiques et biologiques
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- Le syndrome cardiorénal ... et les perturbations électrolytiques
- Ne pas oublier le bilan martial

## IV) La voie du ST2 et la stratégie multimarqueur.

- Un marqueur pronostique (HFrEF et HFpEF)
- Témoin du remodelage cardiaque
- Dans une stratégie multimarqueur (NPs, CRP, hs-Tn, CTX/PINP)
- Un guide thérapeutique ?