Les biomarqueurs cardiaques: le tour de la question

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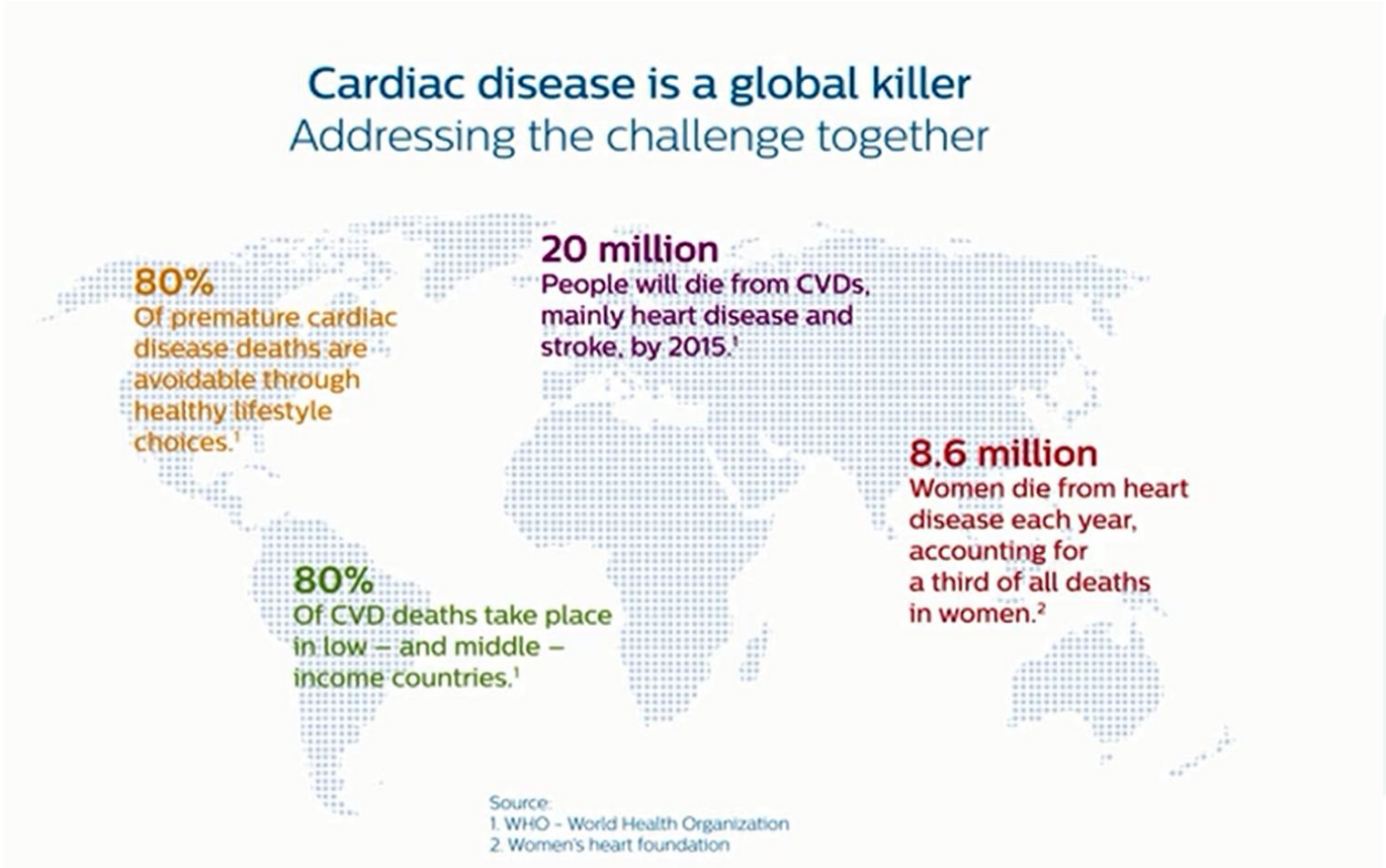
SLBC 08/03/2018

Plan

- Introduction
- Insuffisance cardiaque
- Syndrome coronarien aigu

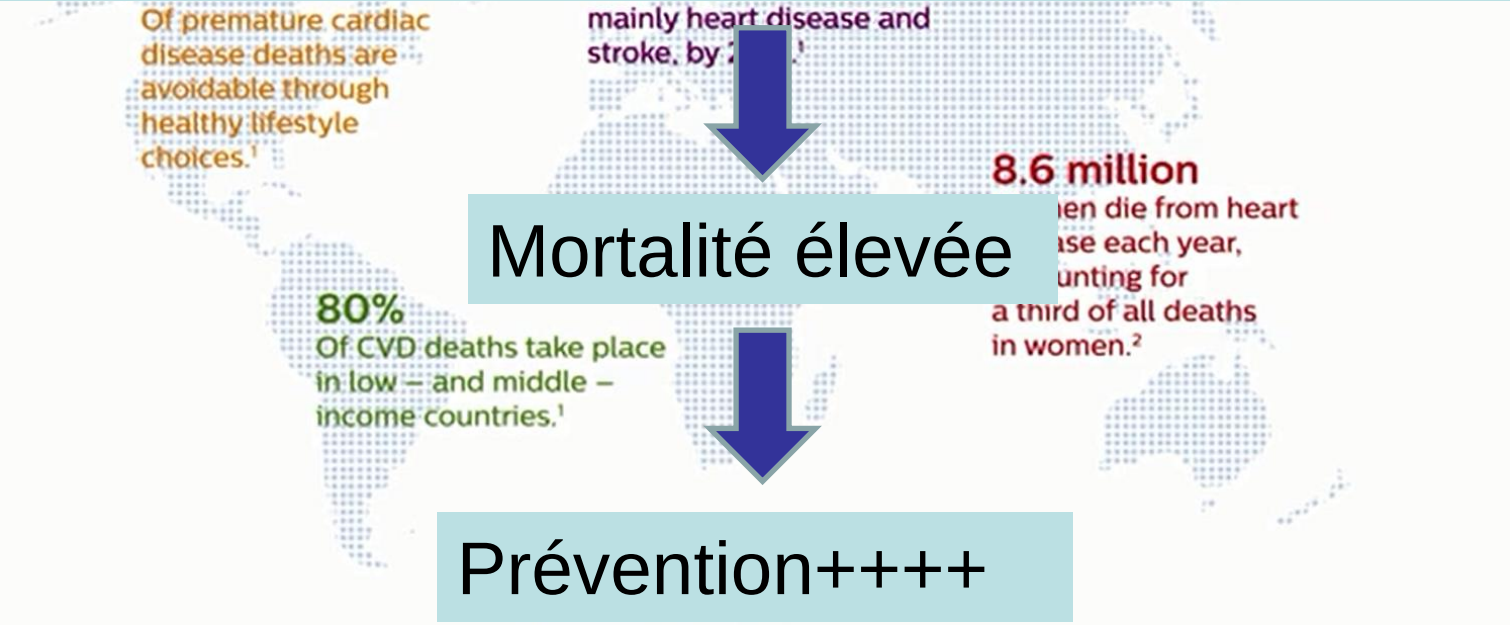
➔ Les marqueurs actuels et les nouveaux

Introduction



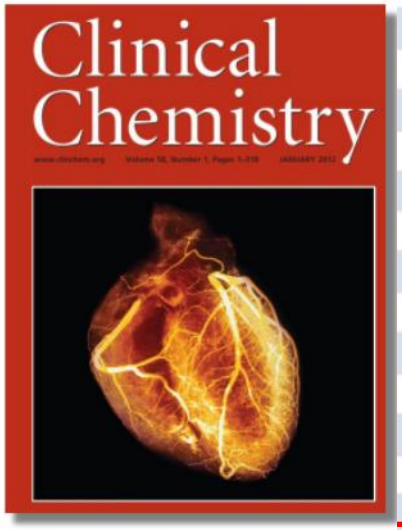
Introduction

En 2018, 29 millions de personnes seront affectées par l'IC avec une prévalence de 42 millions



Mortalité élevée

Prévention++++



Inflammation	Neurohormones
CRP	Norepinephrine
TNF-α	Renin
TWEAK (TNF-like weak inducer of apoptosis)	Angiotensin II
IL-1, −6, −10, and −18	Aldosterone
LP-PLA2 (lipoprotein-associated phospholipase A2)	Arginine vasopressin, copeptin
Soluble TNF receptors 1 and 2	Endothelin-1
YKL-40	Urocortin
IL-1 receptor antagonist	Chromogranin A and B
Midkine	MR-proADM
Leucine-rich 2-glycoprotein	**Myocyte injury and apoptosis**
PTX3	Troponins I and T
CA-125	Myosin light-chain kinase I
S100A8/A9 complex	Heart-type fatty-acid–binding protein
Osteoprotegerin	Creatine kinase MB fraction
Serine protease PR3	sFAS (soluble apoptosis-stimulating fragment)
Soluble endoglin	Heat shock protein 60
Adiponectin	sTRAIL (soluble TNF-related apoptosis-inducing ligand)
Oxidative stress	**Myocyte stress**
Oxidized LDLs	BNP, NT-proBNP, MR-proANP
MPO	sST2
Urinary biopyrrins	GDF-15
Urinary and plasma isoprostanes	**Extracardiac involvement**
Urinary 8-hydroxy-2′-deoxyguanosine	RDW
Plasma malondialdehyde	Cystatin-C, β-trace protein
Extracellular-matrix remodeling	NGAL, NAG [N-acetyl-β-(D)-glucosaminidase], KIM-1 (kidney injury molecule-1)
MMPs (MMP2, MMP3, MMP9)	β2-microglobulin
TIMP1	Urinary albumin-to-creatinine ratio
IL-6	Triiodothyronine
Collagen propeptides	
N-terminal collagen type III peptide	
Myostatin	
Syndecan-4	
Galectin-3	

L'insuffisance cardiaque

- Incapacité mécanique progressive du cœur à assurer les besoins hémodynamiques de l'organisme

→Élévation des pressions d'amont (insuffisance cardiaque congestive) *et/ou*

→Diminution du débit d'aval (insuffisance cardiaque systémique)

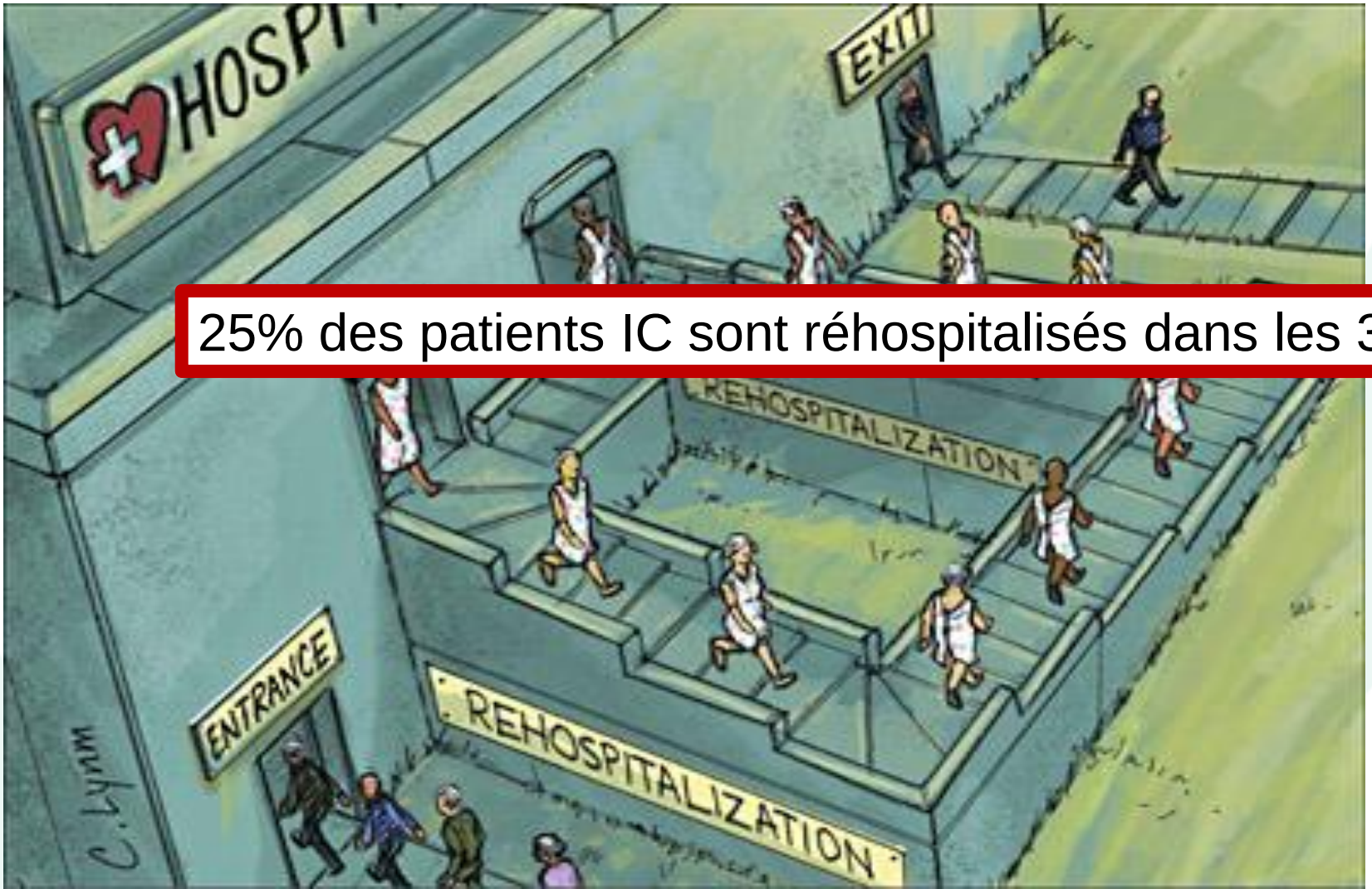
Bien que l'IC soit courante…

Ca peut être un challenge de la reconnaître et la prendre en charge….

- Symptômes variés
- Signes cliniques peuvent être difficiles à identifier lors de l'anamnèse
- Evaluer la sévérité de l'IC et la traiter adéquatement peut être difficile

Problème de réhospitalisation lié à l'IC

Problème de réhospitalisation lié à l'IC



25% des patients IC sont réhospitalisés dans les 30 j

La famille des peptides natriurétiques

- ANP : peptide natriurétique de type A
- BNP : peptide natriurétique de type B
- CNP : peptide natriurétique de type C
- DNP : peptide natriurétique de type D
- VNP : peptide natriurétique de type V (vasonatrine)
- Urodilatine (origine rénale)

Peptides natriurétiques de type B

BNP et NT-proBNP

- Extraite la 1er fois du cerveau de porc
- Indicateur sensible et spécifique de lésions ventriculaires
- Intérêt :
  - Diagnostic de l'IC
  - Estimation du pronostic de l'IC
  - Stratification du risque après IDM
  - Surveillance du traitement et évolution de l'IC

Valeurs décisionnelles

NT-proBNP
<300 pg/ml
BNP
<100 pg/ml

IC très peu probable
VPN=98%

NT-proBNP
<50ans
300-450 pg/ml
50-75 ans
300-900 pg/ml
>75 ans
300-1800 pg/ml
BNP
100-400 pg/ml

Zone grise
IC peu probable
Imagerie

NT-proBNP
<50 ans
>450 pg/ml
50-75 ans
>900 pg/ml
>75 ans
>1800 pg/ml
BNP
>400 pg/ml

IC probable
Confirmation
VPP= 92%

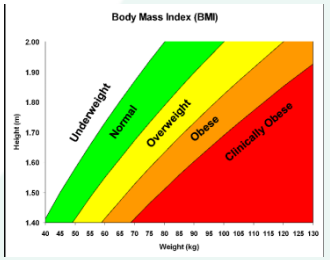
Adapté de Thygesen K et al.(2012). Eur Heart J.33,2001-2006

Facteurs influençant la concentration plasmatique du BNP et du NT-proBNP

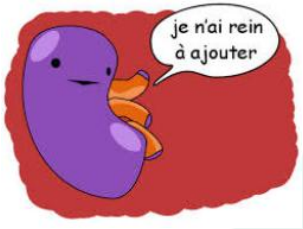
-Sexe : valeurs plus élevées chez la femme

-Age : valeurs plus élevées chez le sujet âgé

-BMI : valeurs inversement corrélées à la surcharge pondérale



- Rein: valeurs plus élevées en fonction GFR



L'âge et l'IR➔adaptation des seuils décisionnels (en particulier seuil de positivité)

Influence du BMI

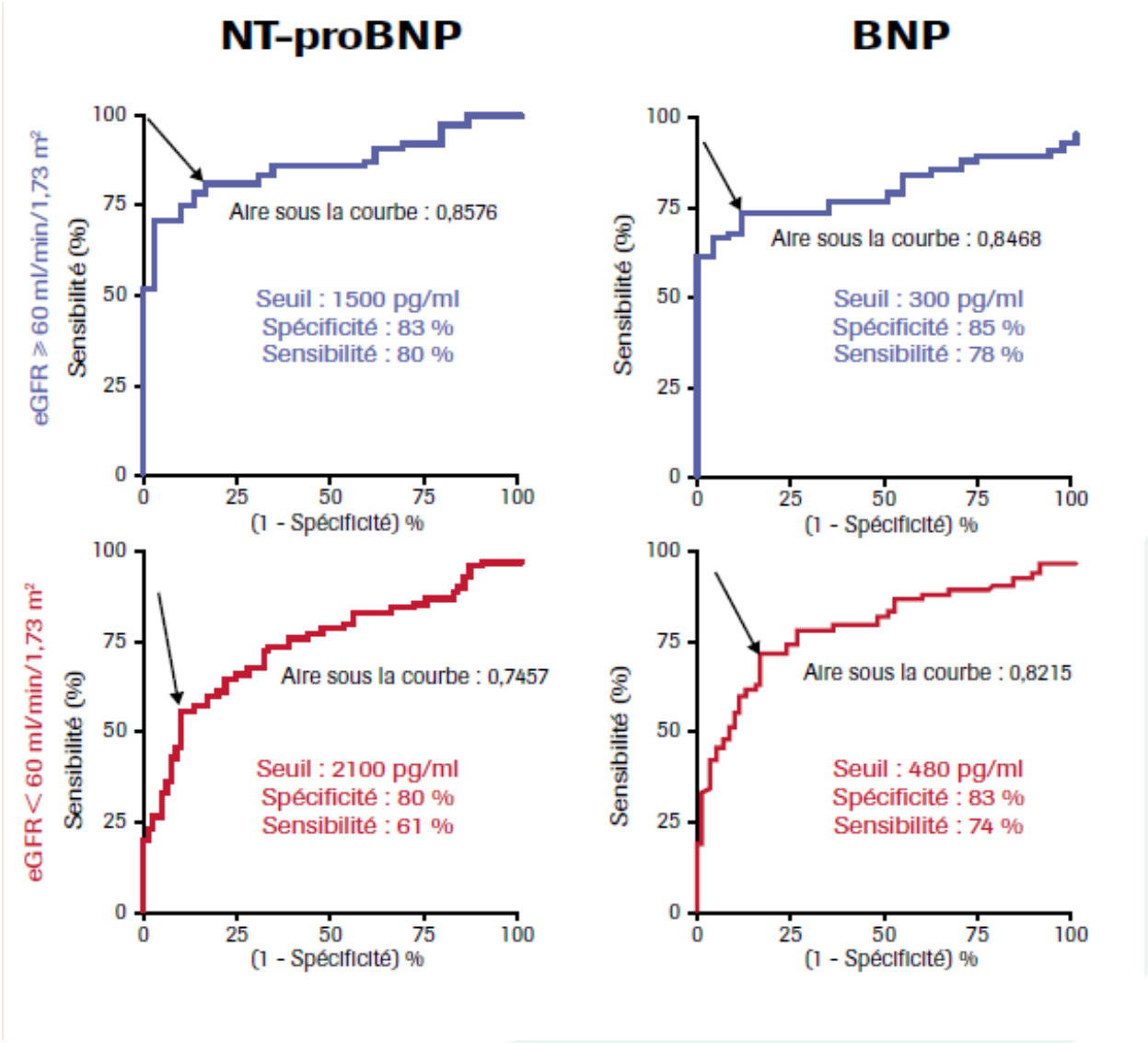
- Inversement proportionnel à l'obésité (IC ou non)

- Plusieurs hypothèses:
  - Diminution de la synthèse au niveau cardiaque
  - Augmentation de l'excrétion
  - Augmentation de la dégradation par hyperexpression du récepteur de clairance au niveau adipocytaire

Influence de la fonction rénale

- Controverse;-)
- Fraction d'extraction glomérulaire est équivalente pour BNP et NT-proBNP

Influence de la fonction rénale



Roche website

Quel biomarqueur choisir?

Méthodes de dosage des peptides natriurétiques

Société	Système	Peptide	Ac Capture	Ac Détection
Abbott	Axsym	BNP	Scios (structure en anneau et probablement la partie d'extension en C terminal)	Shionogi (COOH terminus ; BC 203)
Beckman	Access	BNP	Scios (structure en anneau et probablement la partie d'extension en C terminal)	Biosite (NH2 terminus)
Inverness	Triage	BNP	Scios (structure en anneau et probablement la partie d'extension en C terminal)	Biosite (NH2 terminus)
Siemens	Centaur	BNP	Shionogi (structure en anneau, KYhBNP-II)	Shionogi (COOH terminus)
BioMérieux	Vidas	NT-proBNP	Roche (NH2 terminus ; amino acids 1-21)	Roche (Central molecule ; amino acids 39-50)
OCD	Vitros	NT-proBNP	Roche (NH2 terminus ; amino acids 1-21)	Roche (Central molecule ; amino acids 39-50)
Roche	Modular Elecsys	NT-proBNP	Roche (NH2 terminus ; amino acids 1-21)	Roche (Central molecule ; amino acids 39-50)
Roche	Cobas e601/e411	NT-proBNP	Roche (NH2 terminus ; amino acids 1-21)	Roche (Central molecule ; amino acids 39-50)
Roche	Cardiac Reader/cobas h232	NT-proBNP	Roche (NH2 terminus ; amino acids 1-21)	Roche (Central molecule ; amino acids 39-50)
Siemens	RXL, Immulite Stratus, Vista	NT-proBNP	Roche (NH2 terminus ; amino acids 1-21)	Roche (Central molecule ; amino acids 39-50)

Ann Biol Clin, vol. 67, no 3, mai-juin 2009

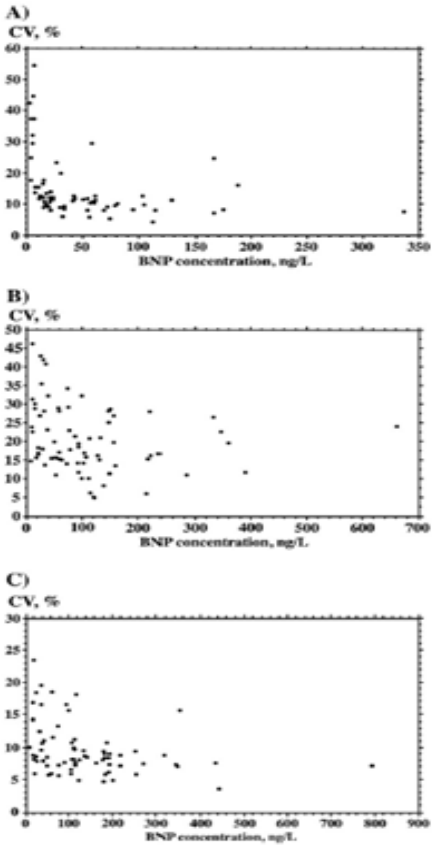
CardioOrmoCheck study

- 7 ans (2005-2011)
- N= 130 laboratoires (85% hopitaux)
  - 75 NT-proBNP
  - 55 BNP
- Echantillons→n= 72 →6706 résultats
  - 3269 BNP
  - 3446 NT-pro
  - BUT= évaluer la différence des performances analytiques et sur les résultats

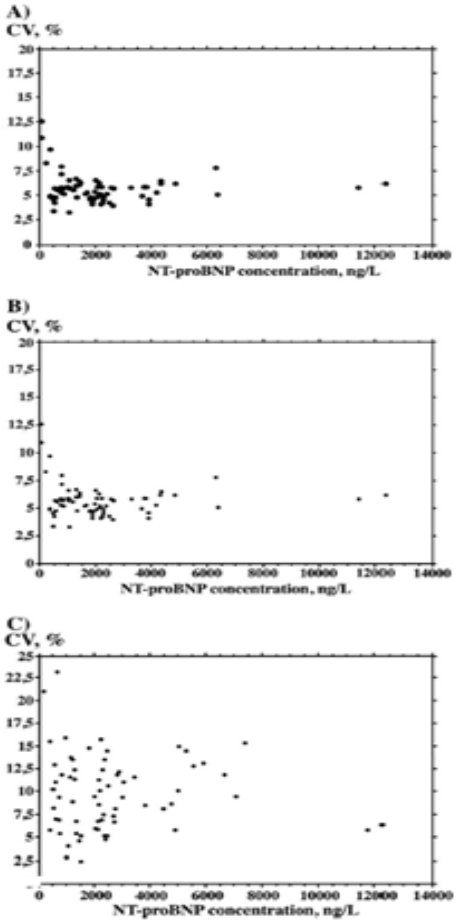
Clerio A. et al., CCA 414(2012),112-119

CardioOrmoCheck study:Résultats

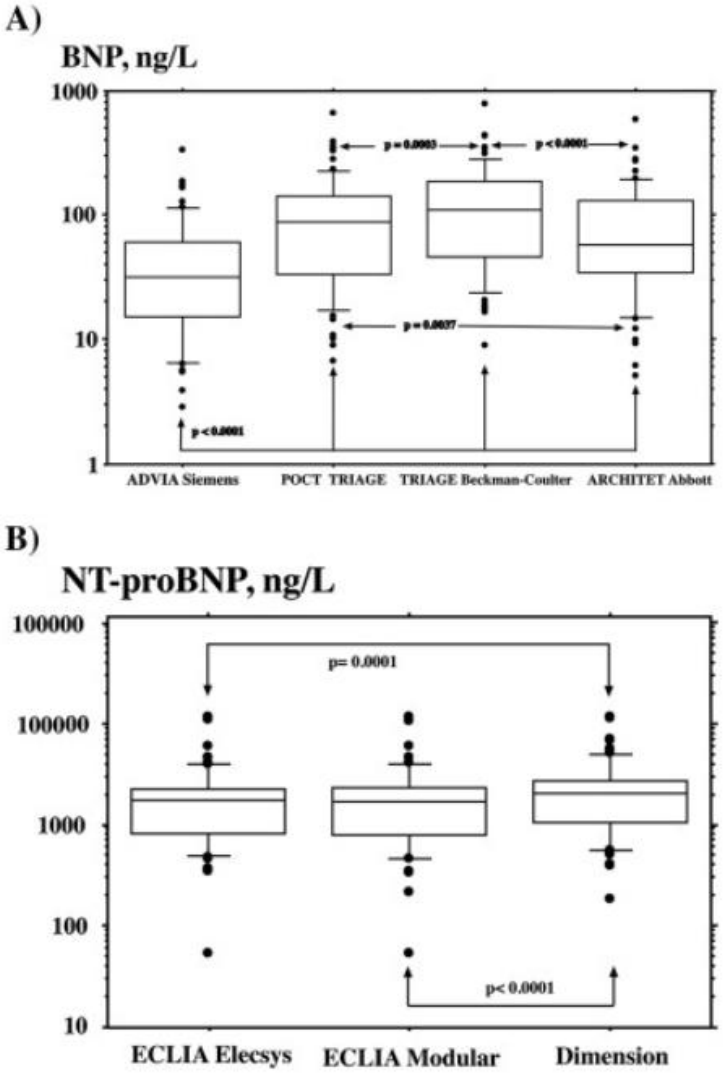
BNP:
A=ADVIA centaur Siemens (32%)
B= TRIAGE POCT Alere (13%)
C= TRIAGE Beckman-Coulter (48%)



NT-proBNP
A= Elecsys Roche (32%)
B= Modular Roche (41%)
C= Dimension Siemens (6%)



CardioOrmoCheck study: Résultats



Un cut-off identique pour le BNP n'est pas recommandé!

Légende: Box (distribution) plot of BNP (Part A) and NT-proBNP (Part B) values measured by the most popular methods of the study. The data are reported as boxes indicating the 10th, 25th, 50th (median), 75th and 90th percentiles of BNP and NT-proBNP values measured in the 72 study samples; the outliners were indicated as separated black circles. The concentrations (Y-axis) are reported as log-scale. The levels of statistical significance (p values) are also indicated in the figure.

Clerico, A. et al. (2012). *Clin Chim Acta,* 414, 112-119.

Standardisation des marqueurs cardiaques

Clinical Chemistry 51:5
000–000 (2005)

Review

Future Biomarkers for Detection of Ischemia and Risk Stratification in Acute Coronary Syndrome

Fred S. Apple,[1*] Alan H.B. Wu,[2] Johannes Mair,[3] Jan Ravkilde,[4] Mauro Panteghini,[5] Jillian Tate,[6] Franca Pagani,[5] Robert H. Christenson,[7] Martin Mockel,[8] Oliver Danne,[9] and Allan S. Jaffe,[10] on behalf of the Committee on Standardization of Markers of Cardiac Damage of the IFCC

Clinical Chemistry 51:3
486–493 (2005)

Special Report

Quality Specifications for B-Type Natriuretic Peptide Assays

Fred S. Apple,[1*] Mauro Panteghini,[2] Jan Ravkilde,[3] Johannes Mair,[4] Alan H.B. Wu,[5] Jillian Tate,[6] Franca Pagani,[2] Robert H. Christenson,[7] and Allan S. Jaffe,[8] on Behalf of the Committee on Standardization of Markers of Cardiac Damage of the IFCC

Stabilité des peptides natriurétiques

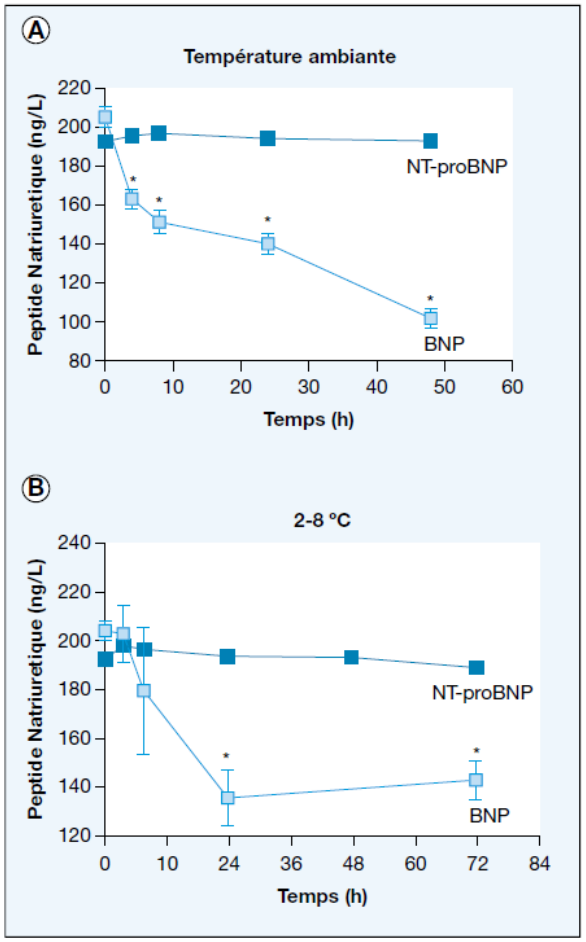


Figure 2. Stabilité comparée du BNP et du NT-proBNP (d'après [25]). **A** : température ambiante ; **B** : entre + 4 et + 8 °C.

Ann Biol Clin, vol. 67, no 3, mai-juin 2009

BNP

- T1/2: 20 min
- 24h RT ou 12h à 30°c
- EDTA stable 1 mois à -20°c (protease inhibiteur aprotinin)

NT-proBNP

- T1/2= 1-2h
- 72h RT ou 4°c
- 1 an à -80°c
- 5 cycles congélations

Clin Chem 51:3, 486-93 2005

CV Intra-individuel et RCV

Review Articles

The Biologic Variability of B-Type Natriuretic Peptide and N-Terminal Pro-B-Type Natriuretic Peptide in Stable Heart Failure Patients

RORY O'HANLON, MB,[1] PAULA O'SHEA, MSC,[2] MARK LEDWIDGE, PhD,[1] CHRISTINA O'LOUGHLIN, DPhil,[1] SOPHIE LANGE, BSC,[1] CARMEL CONLON, BSC,[1] DERMOT PHELAN, MB,[1] SEAN CUNNINGHAM, PhD,[2] AND KEN MCDONALD, MD[1]

Table 1. Baseline Demographics of Study Sample

Demographics	Mean ± Standard Deviation/n (%)
n	45
Age: median (range)	70.4 (38–89)
Gender: male	29 (64%)
New York Heart Association: I	10 (22%)
II	26 (58%)
III	9 (20%)
Weight (kg)	83 ± 18
Body mass index (kg/m^2)	33.5 ± 13.9
Systolic blood pressure/diastolic blood pressure (mm Hg)	133/72 ± 22/15
Heart rate (bpm)	66 ± 10
Ischemic	28 (62%)
Hypertensive	13 (29%)
Systolic dysfunction	38 (84%)
Medications	
Angiotensin-converting enzyme inhibitor/ARB	40 (89%)
β-blocker	38 (84%)
Nitrate	24 (53%)
Statin	28 (62%)
Diuretic	43 (96%)
Digoxin	13 (29%)
Biochemical markers	Median (range)
Creatinine (μmol/L)	118 (51–871)
GFR (mL/min)	52 (5–152)
B-type natriuretic peptide (pg/mL)	158 (5–758)
N-terminal proBNP (pg/mL)	781 (49–10,492)

Table 3. Analytical Variability (CV_A), Biological Variability (CV_I), and Reference Change Values (RCV) for BNP and NT-proBNP

	Within-Hour		Within-Week	
	NT-proBNP	BNP	NT-proBNP	BNP
CV_A %	2.8	13.7	2.8	13.7
Mean CV_I %	6.3	5.0	20.9	24.8
Mean CV_T %	6.9	14.6	21.1	28.4
RCV %	16.1	34.0	49.2	66.2

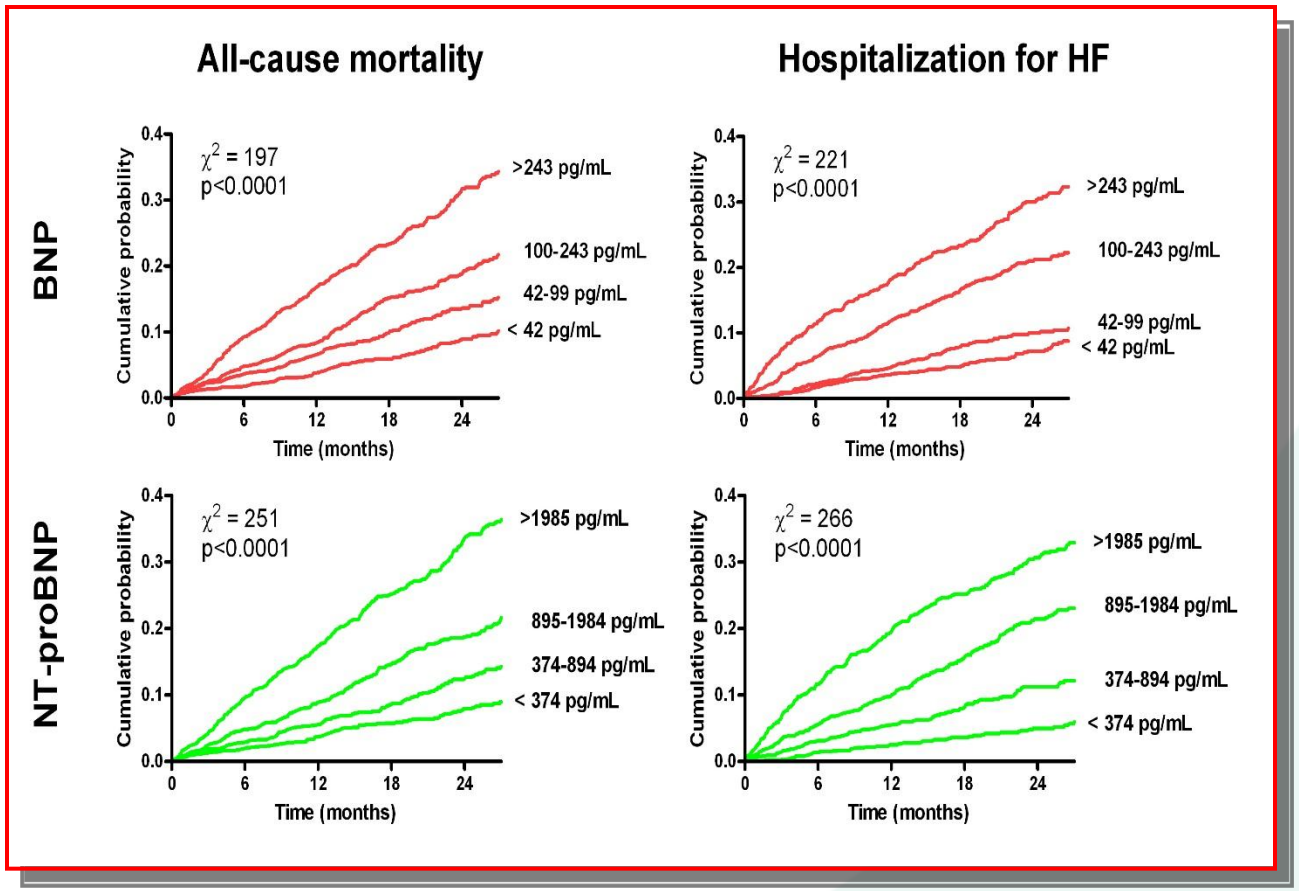
Biological Variation of N-Terminal Pro-Brain Natriuretic Peptide in Healthy Individuals

Table 1.

Mean values; estimated mean analytical (CV_A), intraindividual (CV_I), and interindividual (CV_G) variation; and derived indices for serum NT-proBNP.

Group	Mean, pmol/L	CV_A, %	CV_I, %	CV_G, %	II[1]	Desirable quality specifications			CD, %	No. speci
						Imprecision, %	Bias, %	Total error, %		
All	8.37	2.7	9.1	14	0.64	4.6	4.22	11.72	26.33	3
Men	9.42	1.1	6.5	16	0.41	3.2	4.29	9.65	18.18	2
Women	7.98	3.1	10	14	0.71	5.0	4.32	12.57	29.04	4

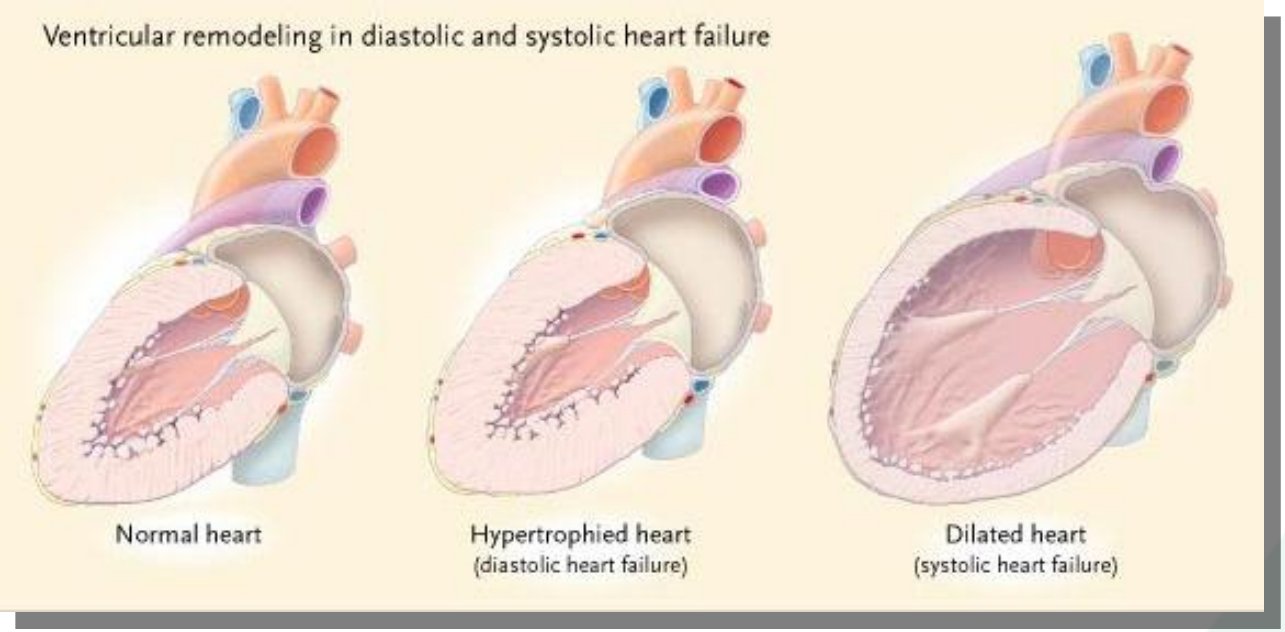
BNP/NT-proBNP- pronostic d'IC



Masson, et al, Clin Chem, 2006

Pourquoi chercher autre chose ?

Remodelage dans le SCA et IC



- Remodelage n'est pas resenti par le patient mais est le résultat d'un stress mycoardique et de fibrose au cours de temps

- Remodelage n'est pas détectable lors de l'examen physique (jusqu'à ce qu'il soit trop tard)

- L'imagerie peut mettre en évidence un remodelage (pas tjs évident)…mais alors il est trop tard

- After HF diagnosis
  - 60% men and 45% women die within 5y.

  (Ho JE et al, J Am Coll Cardiol 2012)

➔Strategies to target patients with cardiac remodeling earlier

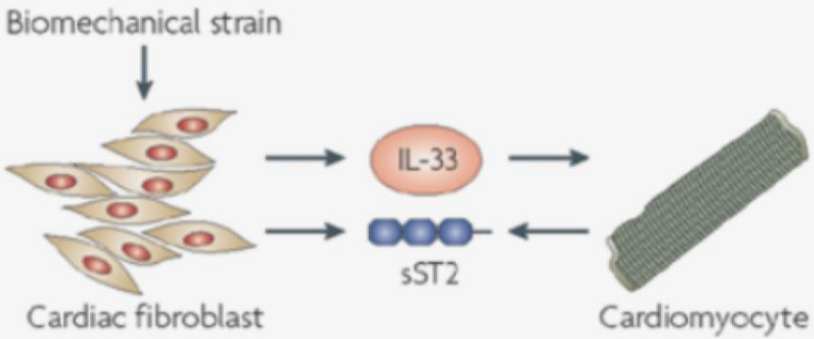
Qu’est ce que le ST2?

- Initialement (1989) étudié dans la prolifération cellulaire, l’inflammation et les maladies auto-immunes.
- En 2002, Richard Lee met en évidence l’expression de ST2 en réponse à un stress et atteinte myocardique.
- Marqueur de fibrose et de remodelage en cas d’infarctus, d’insuffisance cardiaque ou de sténose aortique.

ST2

ST2 and IL-33: Cardioprotective

- ST2: member of the Interleukin-1 receptor family
- Exists in two main isoforms
  - ST2L
  - Circulating sST2
- IL-33 binding to ST2L triggers cardioprotective effects.



** Cardioprotection **

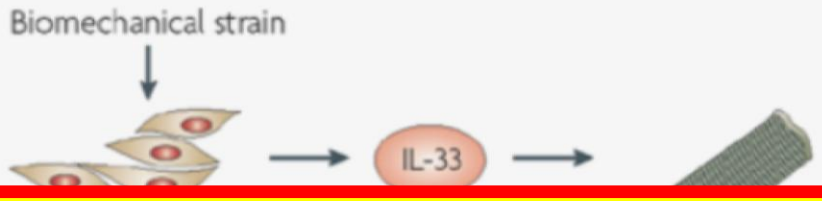
Cardioprotection:
- Reduced fibrosis
- Reduced hypertrophy
- Preserved ventricular function
- Improved survival

Kakkar et al. Nat Rev Drug Discov 2008

ST2

ST2 and IL-33: Cardioprotective

- ST2: member of the Interleukin-1 receptor family



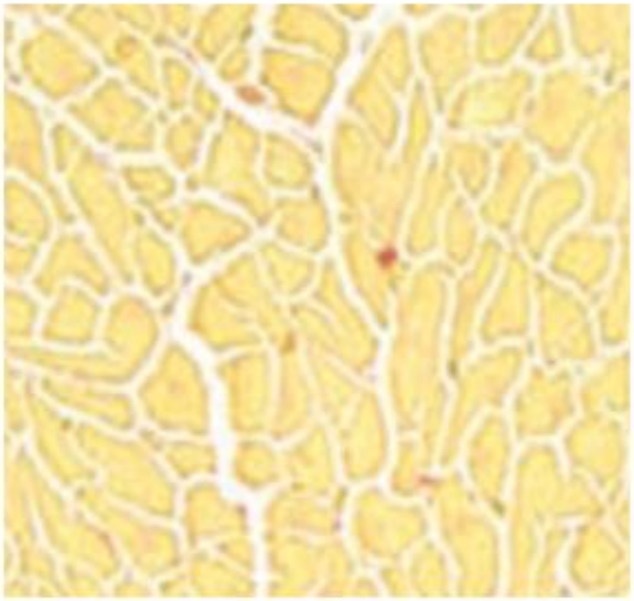
Liaison IL-33/ST2L → action protectrice: inhibition de la fibrose et de l'hypertrophie

Liaison sST2/IL-33 : inhibition de l'action protectrice de l'IL33

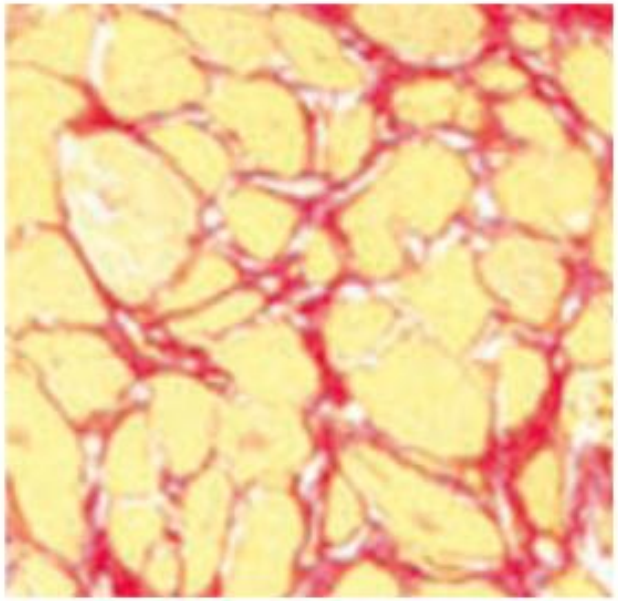
Kakkar et al. Nat Rev Drug Discov 2008

ST2 joue un rôle en réduisant l'hypertrophie des cardiomycoytes et la fibrose

sST2 knock out



Intact sST2



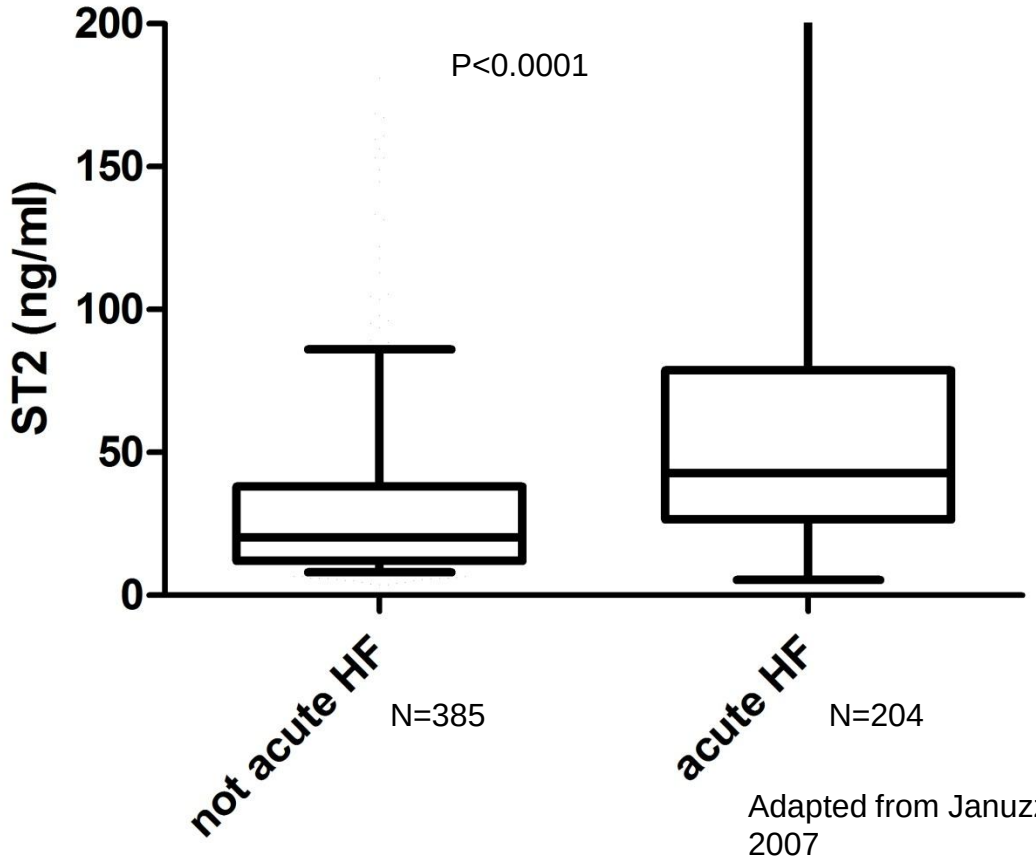
ST2 dans l'IC

ST2

- Inclus dans les recommandations 2013 ACCF/AHA pour la prise en charge des patients IC.

- En avril 2015, l'AJC a publié un panel de publications consensus sur le ST2: 12 chapitres et plus de 80 pg supportant l'utilisation clinique du ST2 à travers les stades d'IC.

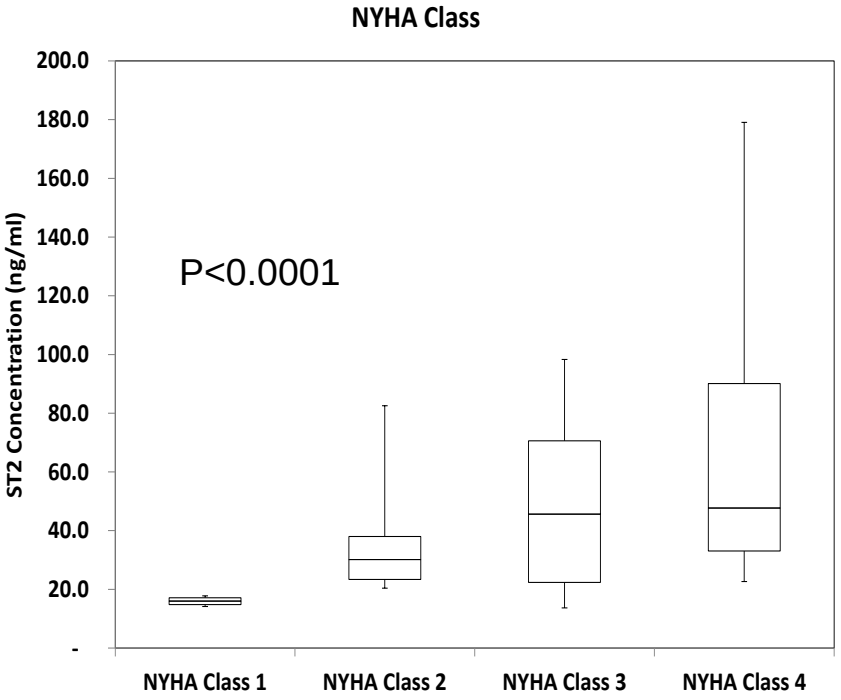
sST2 est plus élevé chez les patients en IC aigue



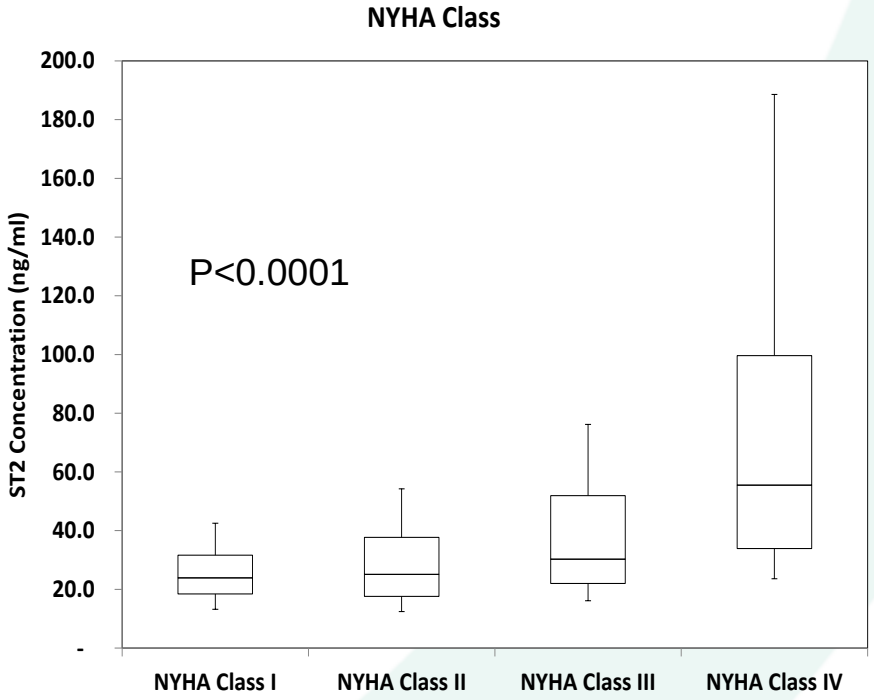
Adapted from Januzzi et al, J Am Coll Cardiol, 2007

sST2 est associé à la sévérité des symptômes

Acute HF (PRIDE)



Chronic HF (PHFS)



sST2
Rôle pronostic

sST2

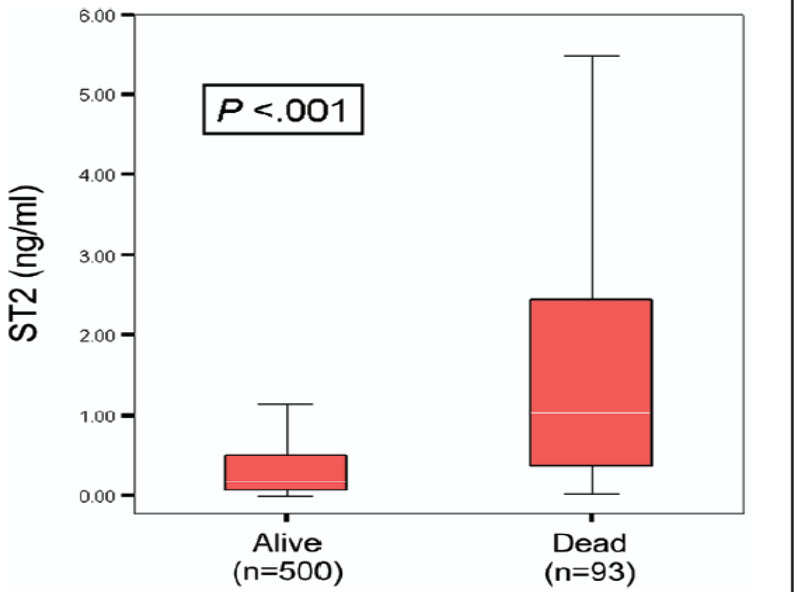


Figure 1 **ST2 Concentrations at Presentation as a Function of Survival at 1 Year**

Medians are depicted; **boxes** represent the 25th and 75th percentile, whereas **whiskers** represent the 5th and 95th percentile.

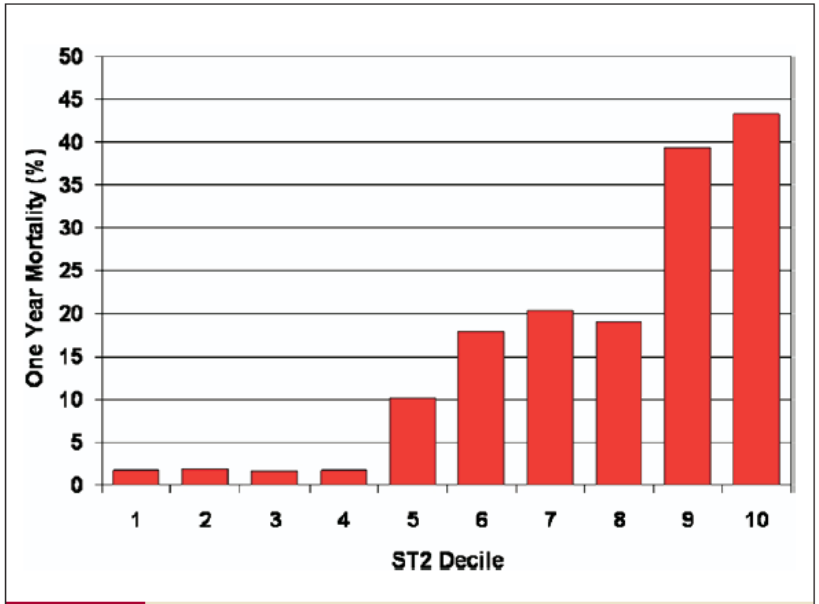


Figure 2 **Rates of Death at 1 Year as a Function of ST2 Decile in Dyspneic Patients**

Rates of death at 1 year as a function of ST2 concentrations in dyspneic patients.

Results From the PRIDE (Pro-Brain Natriuretic Peptide Investigation of **Dyspnea** in the Emergency Department) Study - Januzzi J. et al, JACC 2007

sST2

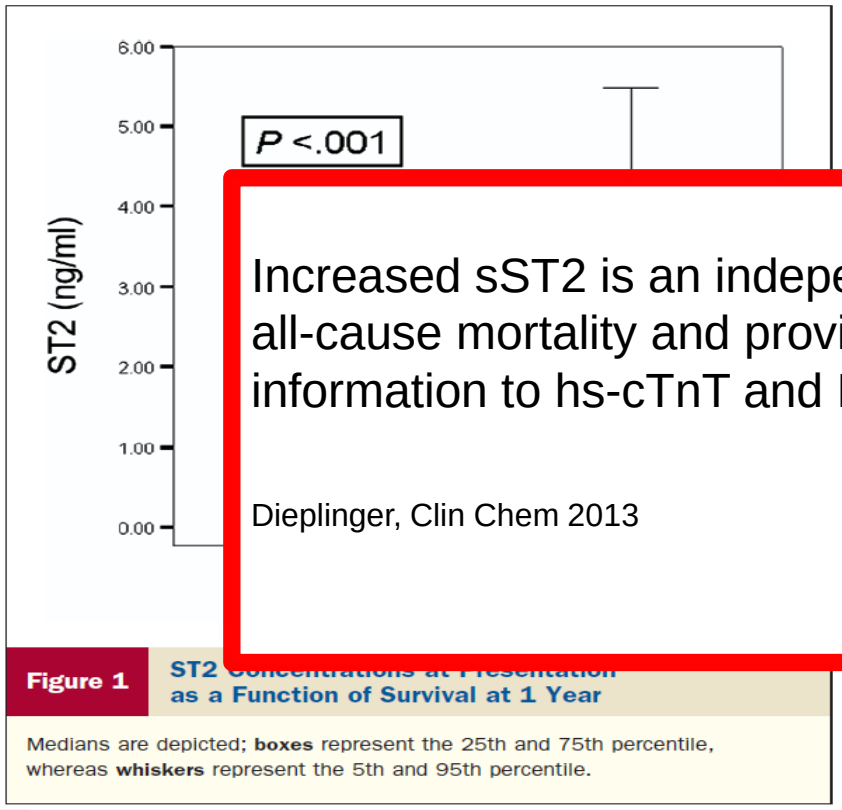
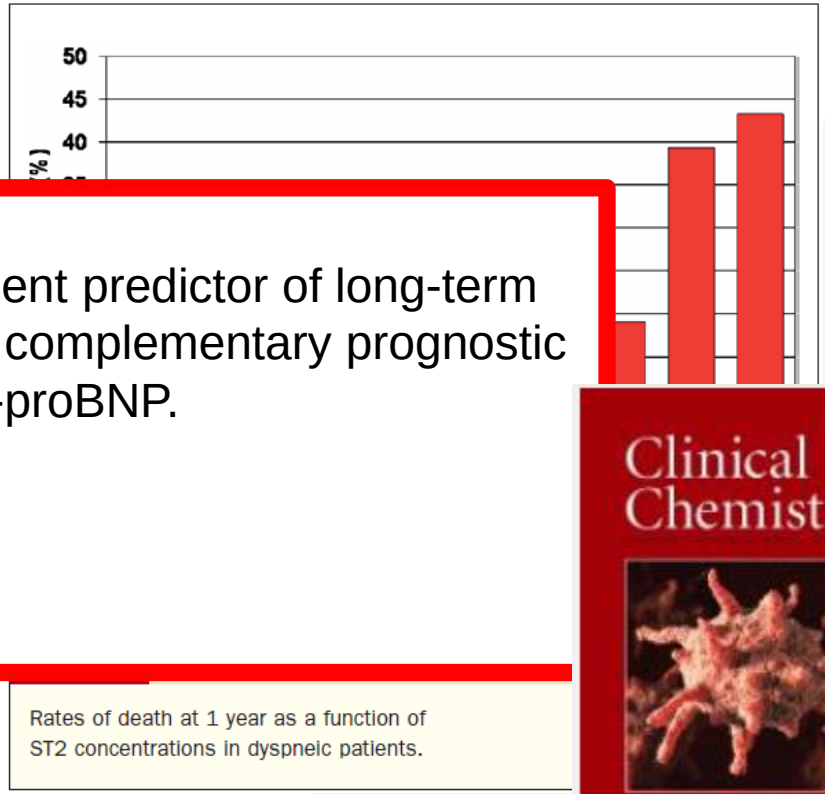


Figure 1 ST2 Concentrations at Presentation as a Function of Survival at 1 Year

Medians are depicted; **boxes** represent the 25th and 75th percentile, whereas **whiskers** represent the 5th and 95th percentile.



Rates of death at 1 year as a function of ST2 concentrations in dyspneic patients.

Increased sST2 is an independent predictor of long-term all-cause mortality and provide complementary prognostic information to hs-cTnT and NT-proBNP.

Dieplinger, Clin Chem 2013

Results From the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) Study - Januzzi J. et al, JACC 2007

Point de vue analytique

Considération analytique

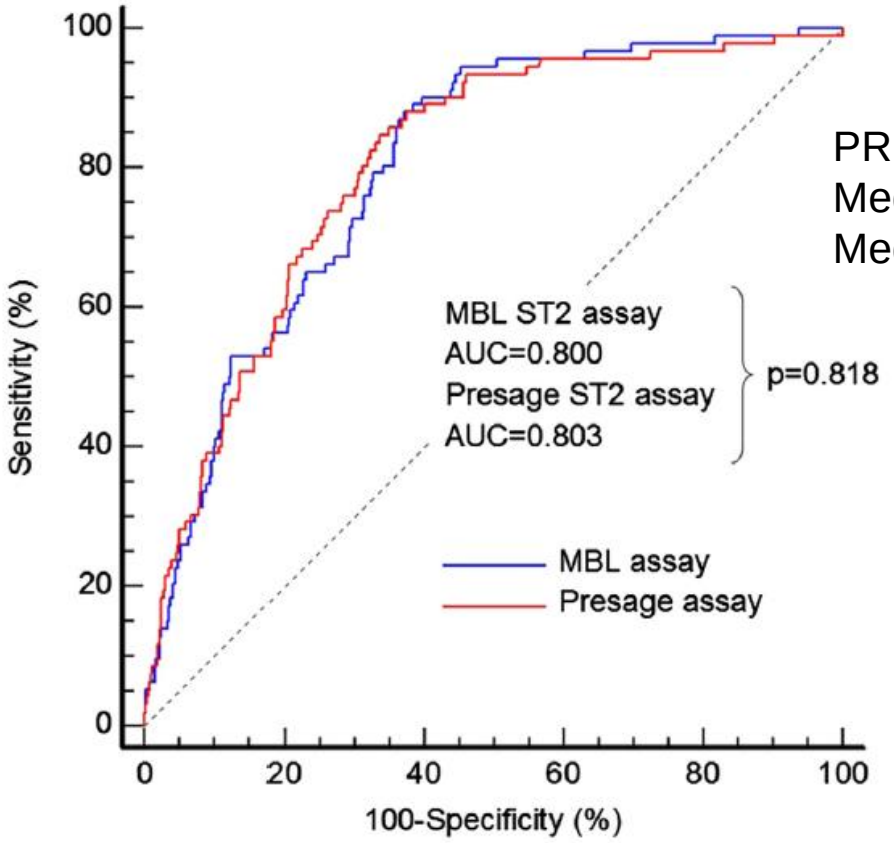
Table 2
Information on selected commercially available ready-to-use assay kits for measurement of sST2 in human serum/plasma*

Manufacturer	Assay/kit	Limit of detection†	Measurement range†	Intra-assay CV†	Inter-assay CV†
Critical Diagnostics (*www.criticaldiagnostics.com*)	Presage ST2 ST2 kit	1.3 ng/mL	up to 200 ng/mL	<7%	<9%
MBL International (*www.mblintl.com*)	Human ST2 ELISA kit	0.032 ng/mL	up to 20 ng/mL	<6%	<6%
RayBiotech (*www.raybiotech.com*)	Human IL-1 R4/ST2 ELISA kit	0.002 ng/mL	up to 1.2 ng/mL	<10%	<12%
R&D Systems (*www.rndsystems.com*)	ST2/IL-1 R4 DuoSet ELISA or Quantikine ELISA	0.005 ng/mL	up to 2.0 ng/mL	<6%	<8%

Considération analytique

Comparaison de méthode:

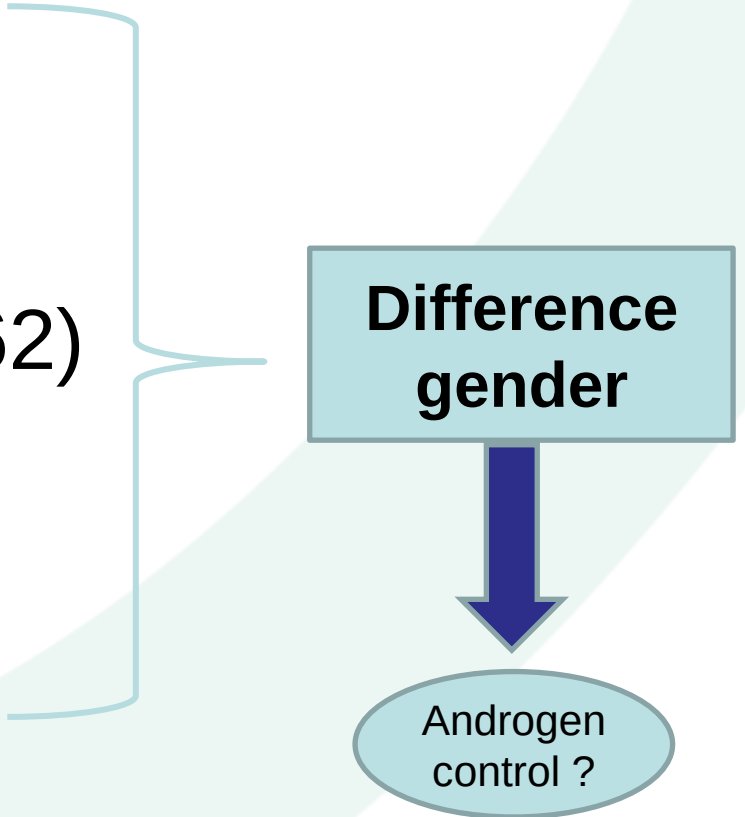
- SEULEMENT 1 publication! Similaire..



PRIDE study(n=599)
Median conc Presage= 27ng/ml
Median conc MBL=0.22 ng/ml

Considération analytique

- Valeurs de référence (Presage kit)
- 528 european healthy blood donors (18-60yo)
  - MALE: 4-31 ng/ml
  - FEMALE: 2-21 ng/ml
- Framingham Study(n=462)
  - MALE:11-45 ng/ml
  - FEMALE: 9-35 ng/ml



Considération analytique

- Echantillons-matrices:

  Sérum, plasma hépariné lithium, plasma-EDTA K3
- Conservation: 2-8°C
- Stabilité analytique in vitro: stable 48 heures à RT, 7 jours à 4°C, 1.5 ans à -20°C et -80°C.
- A jeun ou non: indépendant

Variation biologique

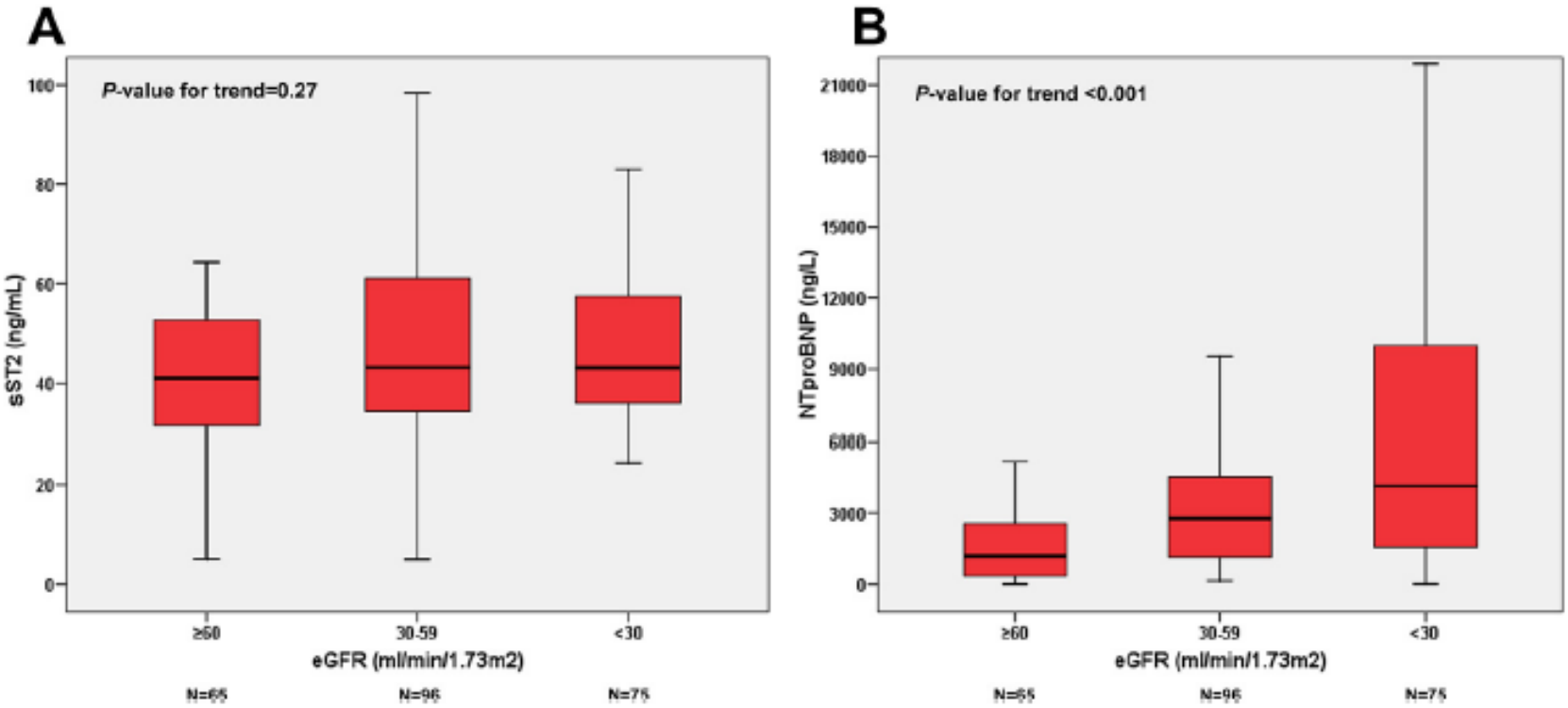
Marker	Duration	CV_I	RCV
CK	2 mths	30%	82%
BNP	2 mths	50%	138%
NT-proBNP	2 mths	33%	92%
hs-cTnI	2 mths	14%	63%
hs-cTnI	9 mths	28%	73%
hs-cTnT	1 mths	31%	87%
Gal-3	2 mths	20%	61%
sST2	1.5 mths	10.5%	30%
sST2	2 mths	11%	30%

sST2 a la plus faible variation intra-individuelle et le plus petit RCV.

Wu, et al, Am Heart Jour, 2013

ST2 et fonction rénale

Pas corrélé à la fonction rénale



In a cohort of 879 heart failure patients ST2 did not show any correlation with renal function whereas NT-proBNP concentrations increased significantly with decreasing renal function.

Bayes-Genis et al. 2013 JCF

ST2 augmente dans d'autres cas…

- Sepsis sévère
- Maladie inflammatoire
- Cancer disséminé
- Fibrose hépatique ou autre organe

ST2: résumé

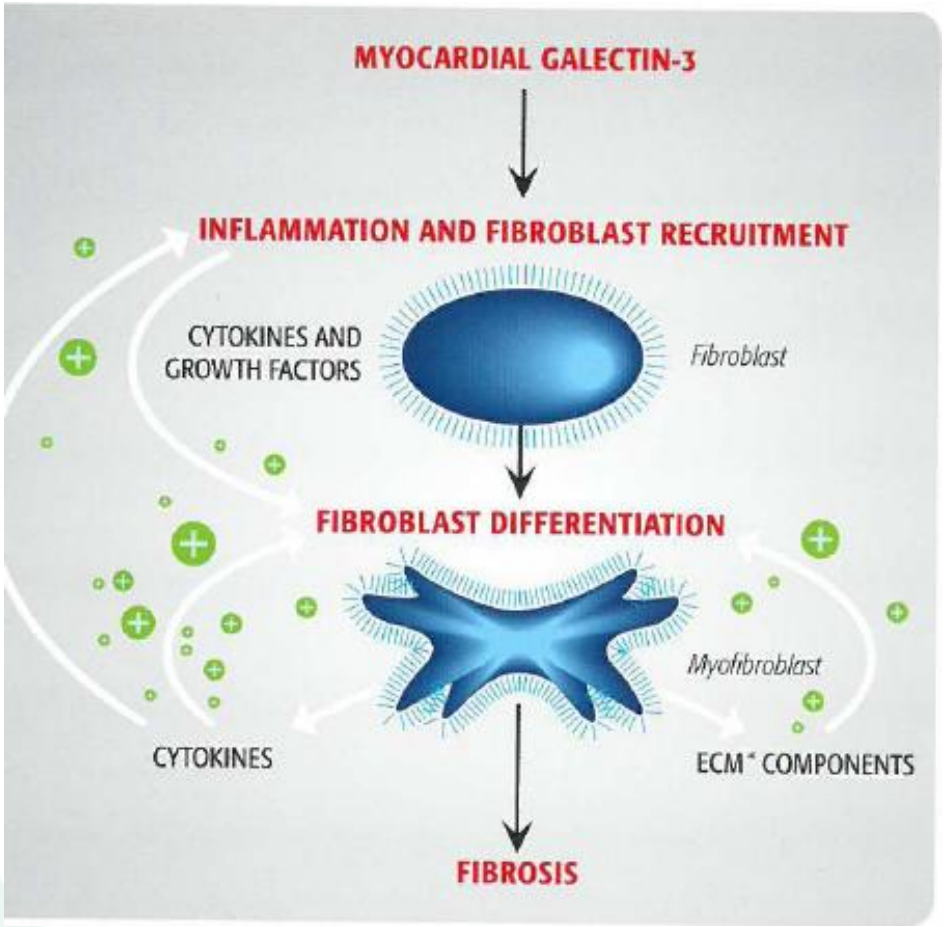
- Point de vue clinique
  - Pas un marqueur de stretch
  - Pas un maqueur inflammatoire
  - EST un marqueur de fibrose et de remodelage cardiaque utile pour le suivi thérapeutique
  - Pas affecté par des facteurs confondants comme l'obésité, le BMI ou l'IR

ST2: résumé

- Point de vue du biologiste
  - 3 ELISA mais 1! FDA
  - Pré-ana: haute stabilité pré-ana
  - Rapide POC
  - RCV:30%
  - Val Ref homme > femme
  - Pas de facteur confondant
  - ST2 augmente ds de nombreuses situations→ manque de spécificité→ diagnostic---
  - Marqueur pronostique puissant!

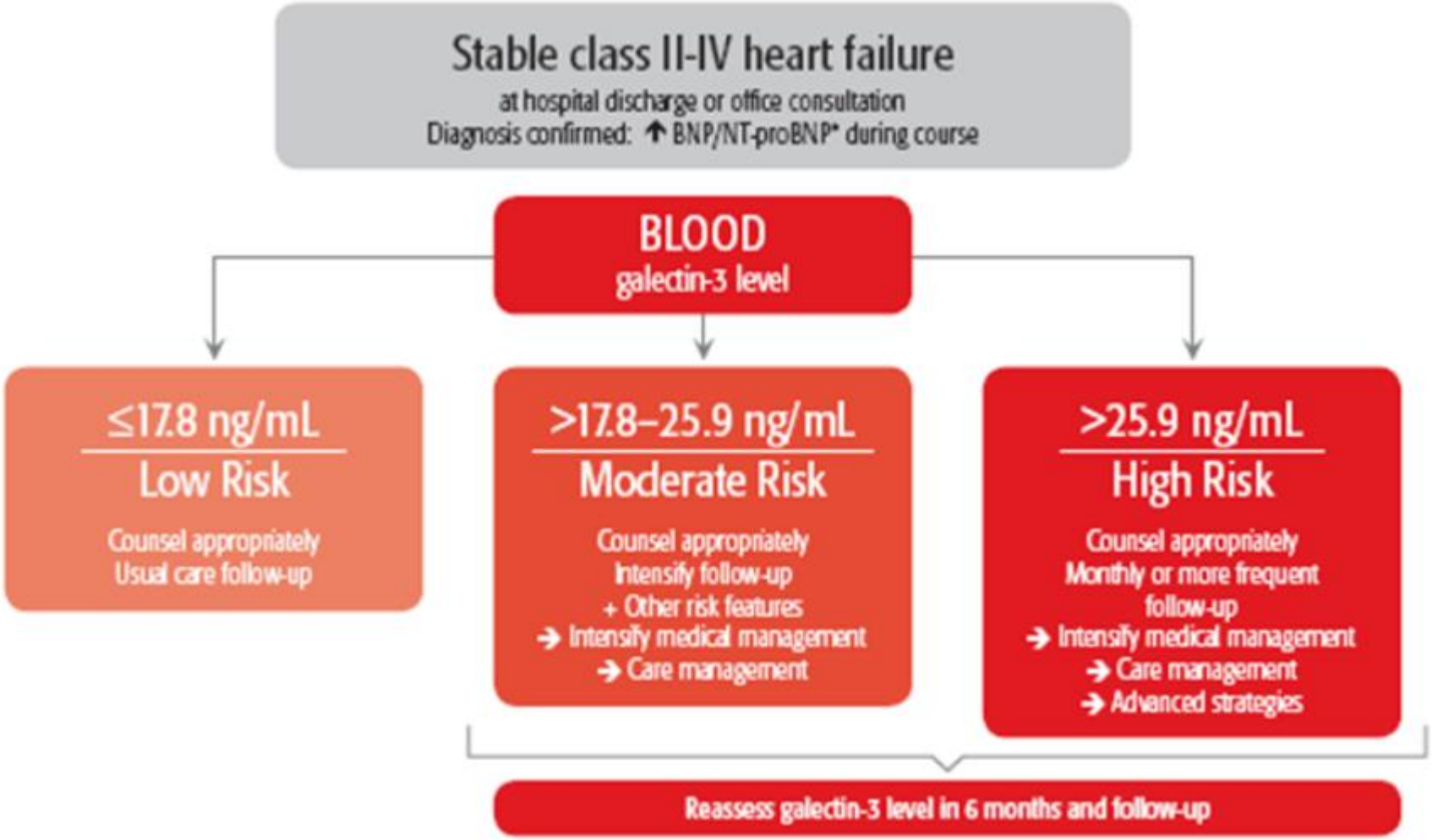
Galectin-3

Galectin-3



Galectin-3 is a beta-galactoside-binding lectin that appears to be a mediator of cardiac fibrosis in a number of recent experimental studies.

Galectin-3


Stable class II-IV heart failure
at hospital discharge or office consultation
Diagnosis confirmed: ↑ BNP/NT-proBNP* during course
BLOOD
galectin-3 level
≤17.8 ng/mL
Low Risk
Counsel appropriately
Usual care follow-up
>17.8–25.9 ng/mL
Moderate Risk
Counsel appropriately
Intensify follow-up
+ Other risk features
→ Intensify medical management
→ Care management
>25.9 ng/mL
High Risk
Counsel appropriately
Monthly or more frequent follow-up
→ Intensify medical management
→ Care management
→ Advanced strategies
Reassess galectin-3 level in 6 months and follow-up

Galectin-3

Clinical studies on the prognostic role

Study	Population	Outcome
HF-ACTION	CHF	Increased risk for all-cause and CV mortality and all-cause and HF-related hospitalization
COACH	CHF	Prognostic utility, stronger for HFpEF patients
DEAL-HF	CHF	Predictor of all-cause mortality, independent of natriuretic peptides
PRIDE	ADHF	Prognostic utility for 60 day mortality and death/recurrent HF
PROVE-IT TIMI 22	ACS	ACS patients with elevated Gal-3 were at higher risk for developing HF
PREVEND	Healthy	Elevated Gal-3 levels were associated with increased risk of long-term mortality
Framingham Offspring	Healthy	Elevated Gal-3 levels were associated with development of HF and long term mortality
CORONA	CHF	Predictive of long-term outcomes. Patients with low Gal-3 benefited more from statin therapy
CARE-HF	CHF	Elevated Gal-3 associated with death of HF hospitalization

Jennifer E. Ho, Galectin-3, a Marker of Cardiac Fibrosis, Predicts Incident Heart Failure in the Community, *Am Coll Cardiol*. October 02, 2012,60(14):1249-1256

Galectin-3

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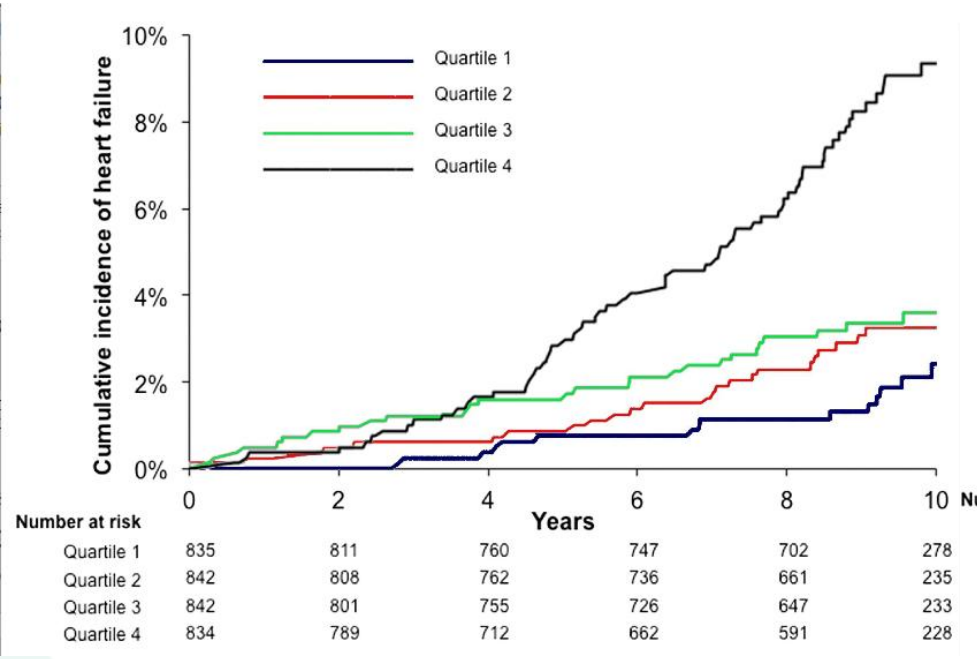
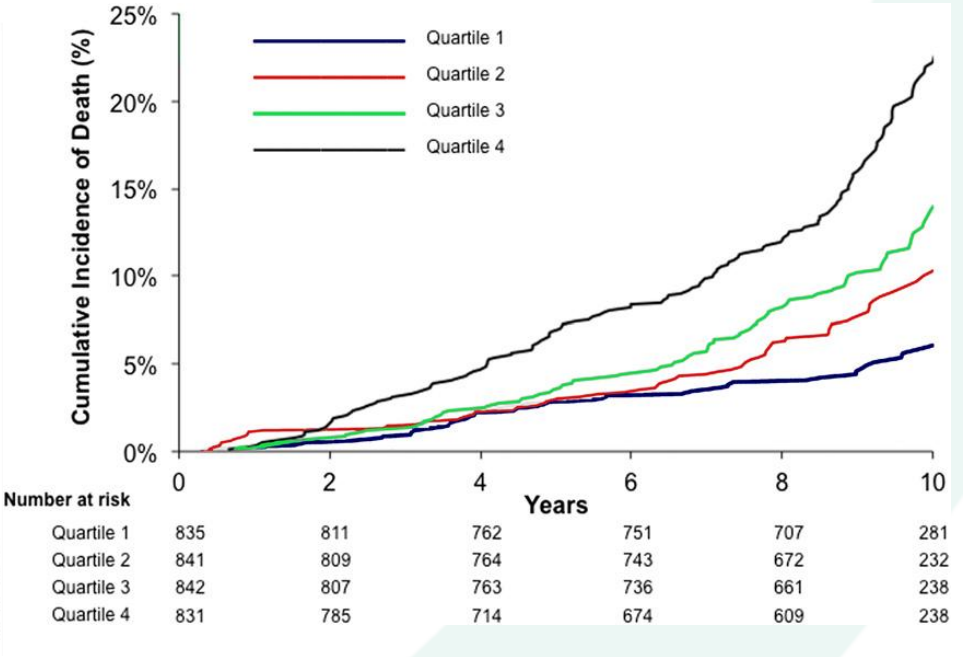
Galectin-3

Framingham Study in 1948, prospective
n=3353



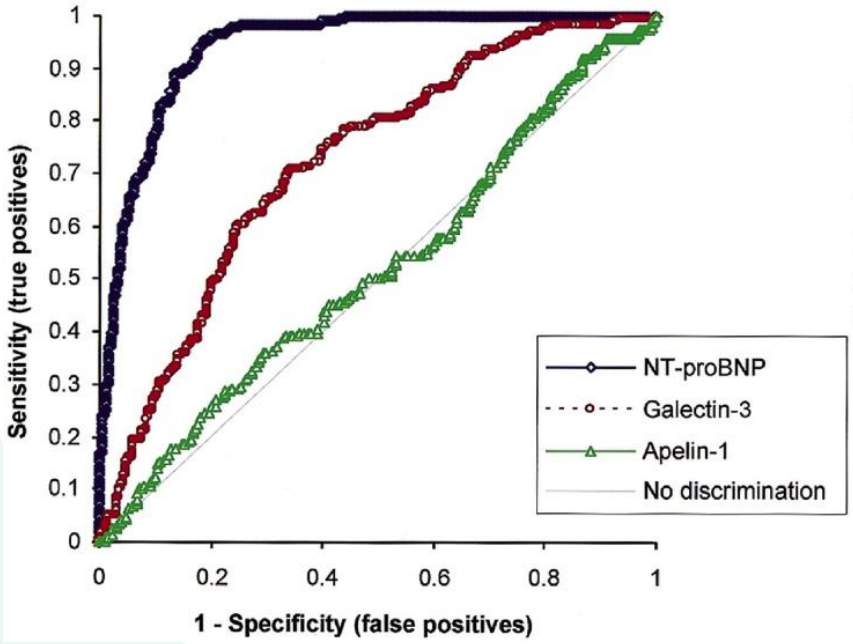


•Gal-3 levels were measured at the sixth examination (1996–1998)

Ho JE et al, J Am Coll Cardiol 2012

Galectin 3

- Inferior to NT-proBNP for diagnosis of HF, but better for evaluation of 60 days mortality



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Published by Elsevier Inc.

Vol. 48, No. 6, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.03.061

Heart Failure

Utility of Amino-Terminal Pro-Brain Natriuretic Peptide, Galectin-3, and Apelin for the Evaluation of Patients With Acute Heart Failure

Roland R. van Kimmenade, MD, PHD,* James L. Januzzi, JR, MD, FACC,†

Copeptin

Copeptin

- Copeptin is the C-terminal fragment of the vasopressin precursor hormone and directly mirrors vasopressin production since it is stoichiometrically co-secreted.
- Released in response to
  - Low blood pressure
  - Cytokines
  - Endogenous stress
  - Hypoxemia
- Short half life in vivo BUT longer half life in the circulation that makes it easier to measure

Copeptin

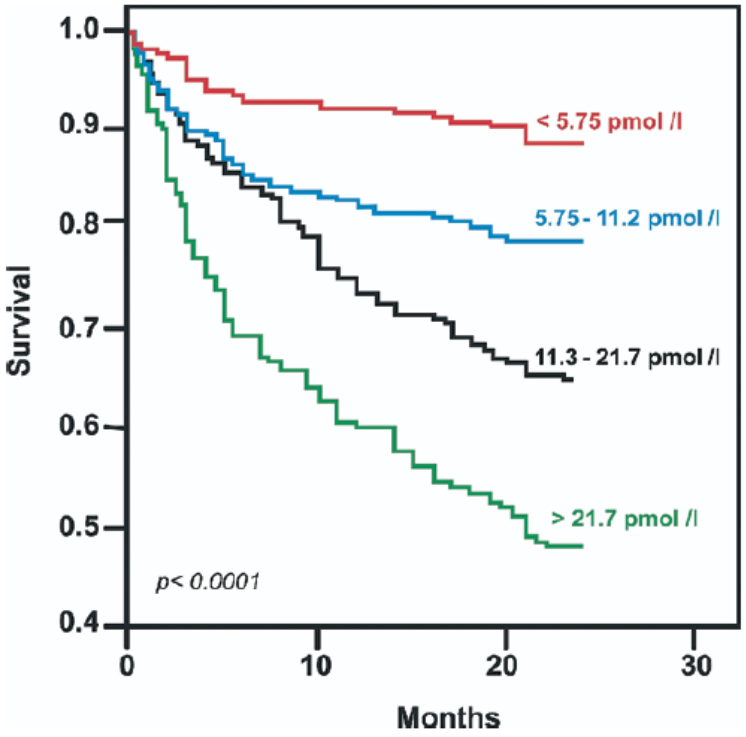


Figure 2 **Quartiles of Copeptin**

Kaplan-Meier plots: survival in patients grouped according to quartiles of plasma copeptin.

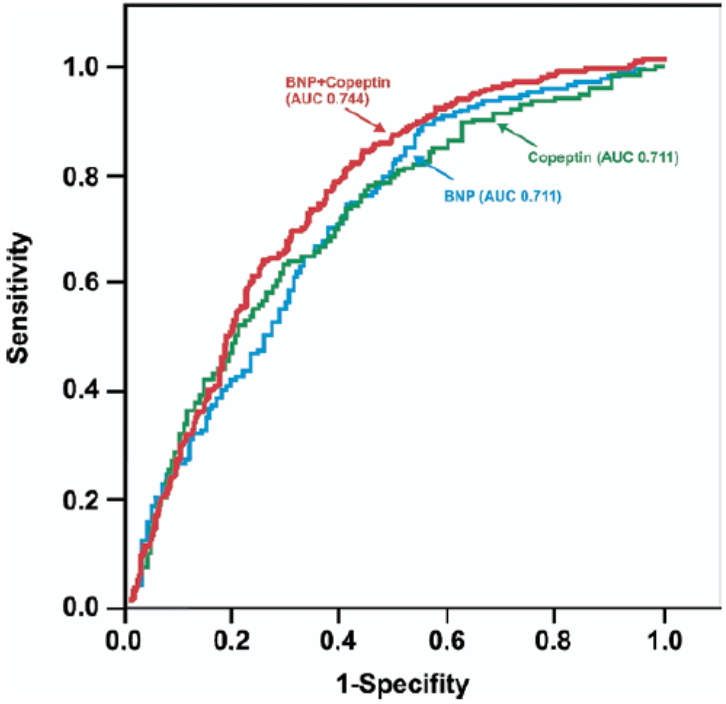


Figure 3 **ROC for 24-Month Survival**

Area under receiver-operator characteristic (ROC) curves for 24-month survival for copeptin, BNP, and copeptin plus BNP. AUC = area under the receiver-operator characteristic curve; other abbreviations as in Figure 1.

Neuhold S et al. JACC2008;52:266

European Heart Journal (2016) **37**, 267–315
doi:10.1093/eurheartj/ehv320

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Among the multitude of additional biomarkers evaluated for the diagnosis of NSTE-ACS, only CK-MB and copeptin seem to have clinical relevance.[2,6,8,10,44–50] CK-MB shows a more rapid decline after MI as compared with cardiac troponin and may provide added value for the timing of myocardial injury and the detection of early reinfarction.[2,6,8,10] Assessment of copeptin, the C-terminal part of the vasopressin prohormone, may quantify the endogenous stress level in multiple medical conditions including MI. As the level of endogenous stress appears to be invariably high at the onset of MI, the added value of copeptin to conventional (less sensitive) cardiac troponin assays is substantial.[44–50] Therefore the routine use of copeptin as an additional biomarker for the early rule-out of MI is recommended whenever sensitive or high-sensitivity cardiac troponin assays are not available. Copeptin may have some added value even over high-sensitivity cardiac troponin in the early rule-out of MI.[44–48]

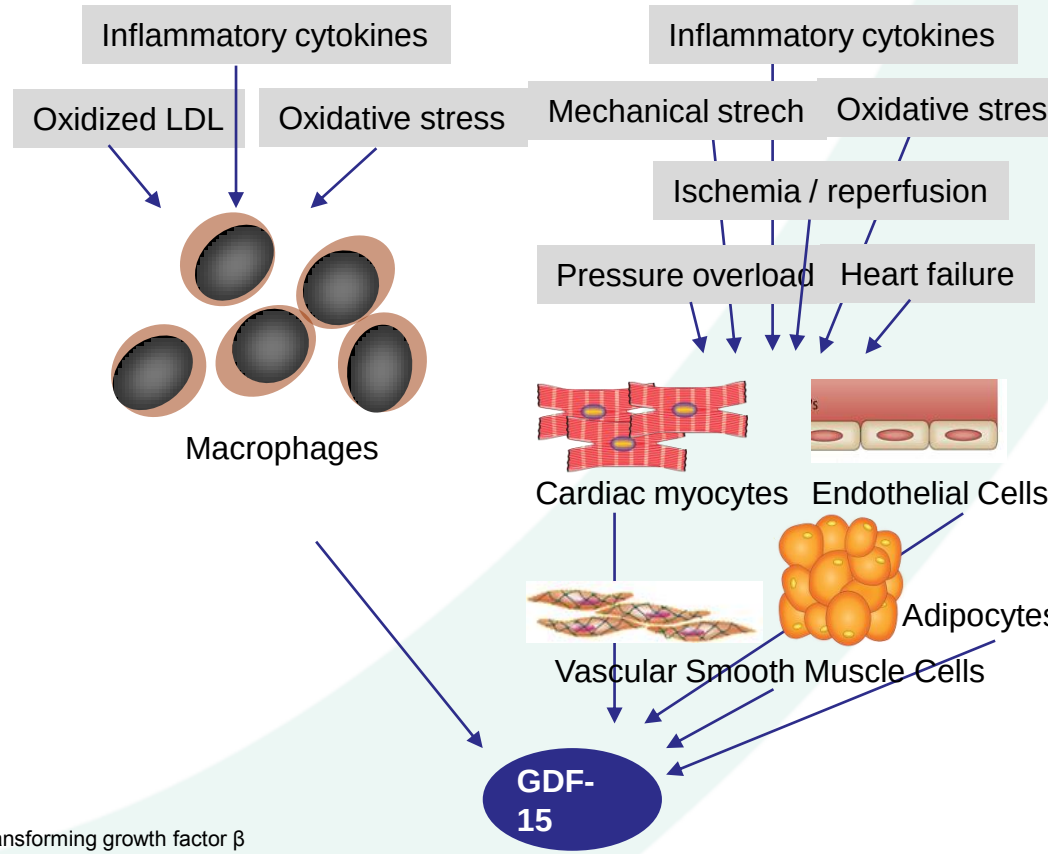
GDF15

GDF15

GDF-15 - member of the TGFβ cytokine superfamily

- GDF-15 is a stress-responsive member of the TGF-β cytokine superfamily and is **weakly expressed under healthy conditions**
  - high levels in the placenta[1]
- Expression increases sharply in response to pathological or environmental **stress signals:**
  - hypoxia
  - oxidative stress
  - inflammation
  - tissue injury
  - remodeling
- Under pathological conditions, GDF-15 can be **produced by many CV and non-CV cell types**
- GDF-15 levels **reflect both acute and chronic cellular stress** associated with aging and disease

several independent pathways
depend on tissue, cellular and signaling contexts[1]



LAD, left anterior descending coronary artery; TGFβ, transforming growth factor β

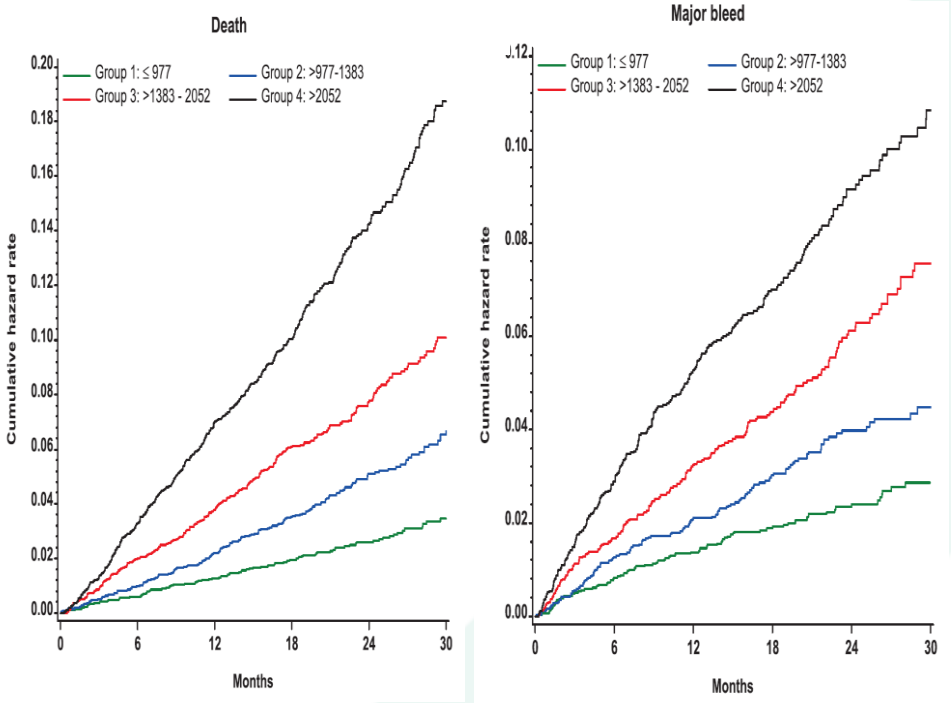
1. Corre J, et al. (2013). Stem Cells Transl Med, 2:946–52; 2. Kempf T, et al. (2006). Circ Res, 98:351–60; 3. Frank D, et al. (2008). Hypertension, 51:309–18.

GDF-15 predicts bleeding and mortality in AF

ARISTOTLE study

- Patients with **baseline GDF-15 in the highest quartile** (vs. the lowest quartile) had **significantly higher rates of:**
  - stroke/systemic embolism (2.03% vs. 0.9%)
  - major bleeding (4.53% vs. 1.22%)
  - mortality (7.19% vs. 1.34%)
  - ($p<0.001$ for all comparisons)

Cumulative hazard rate of death or major bleed according to GDF-15 quartile (*n*=14 798)



ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
Wallentine L, et al. (2014). Circulation, 130:1847–58.

GDF-15

Disease/population/follow-up period	Sample size	Major findings
Acute myocardial infarction [AMI]	1142	GDF-15 is a prognostic marker of death and HF in patients with AMI Multimarker approach with GDF-15 and NT-pro-BNP is more informative than either marker alone and may be useful for risk stratification in AMI patients
Acute coronary syndrome [ACS] (PROVE IT-TIMI 22)	3501	GDF-15 is altered with recurrent events after ACS. GDF-15 may be used as a prognostic marker in ACS
Human model of acute muscle wasting following cardiac surgery	42	GDF-15 is a potential novel factor associated with muscle atrophy, which may become a therapeutic target in patients with ICU acquired paresis and other forms of acute muscle wasting
Non–ST-elevation ACS (FRISC-II) trial (2 years)	2079	GDF-15 is a potential tool for risk stratification and therapeutic decision making in patients with non-ST-elevation acute coronary syndrome
General adult population (Dallas Heart Study) (7.3 years follow up period)	3219	GDF-15 is independently marker for subclinical coronary atherosclerosis and mortality
Framingham Offspring cohort participants (9.5 years follow up period)	2614	Higher circulating GDF-15 was observed with incident renal outcomes and improves risk prediction of incident chronic kidney diseases (CKD)
Hypertensive left ventricular hypertrophy (H-LVH), hypertensive cardiomyopathy (HCM)	149	GDF-15 might be a useful biomarker for discriminating HCM from H-LVH

Ramu A.et al. Journal of Diabetes Research(2015)

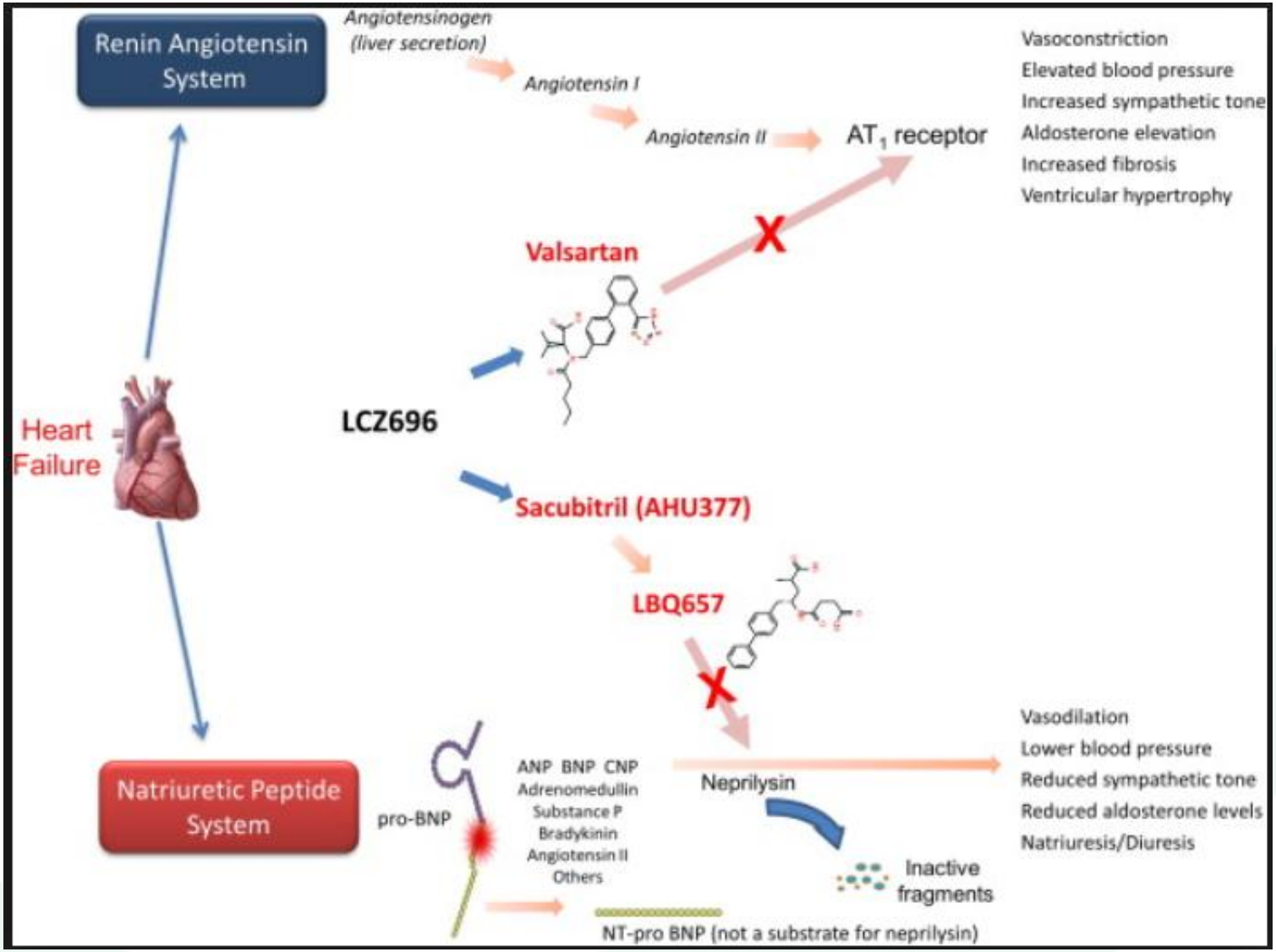
GDF-15

Higher GDF-15 levels

- Higher age
- Current smoking
- Physical activity
- Diabetes
- Acute or chronic inflammation
- Genetic factors
- Renal dysfunction
- Anemia and bleeding
- Vascular disease
- Heart failure
- Atrial fibrillation
- Cancer

Entresto

Entresto


Renin Angiotensin System
Angiotensinogen (liver secretion)
Angiotensin I
Angiotensin II
AT1 receptor
Vasoconstriction
Elevated blood pressure
Increased sympathetic tone
Aldosterone elevation
Increased fibrosis
Ventricular hypertrophy
Valsartan
X
Heart Failure
LCZ696
Sacubitril (AHU377)
LBQ657
X
Natriuretic Peptide System
pro-BNP
ANP BNP CNP
Adrenomedullin
Substance P
Bradykinin
Angiotensin II
Others
Neprilysin
Vasodilation
Lower blood pressure
Reduced sympathetic tone
Reduced aldosterone levels
Natriuresis/Diuresis
Inactive fragments
NT-pro BNP (not a substrate for neprilysin)

BNP???

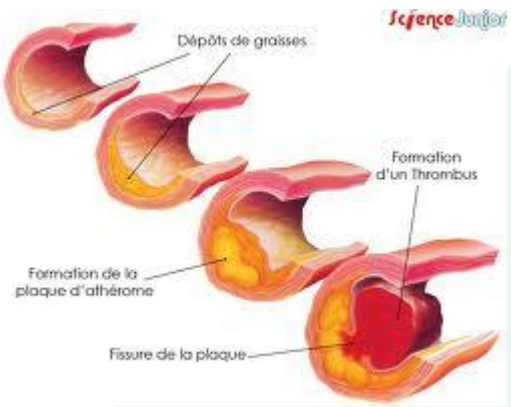
- Protease neprilysin is known to be responsible for the degradation of natriuretic peptides.
- Increase the circulating B-type natriuretic peptide (BNP) concentrations, making the results of BNP measurements diagnostically ambiguous….. (STOP Guide-IT)

Semenov et al., Different Susceptibility of B-Type Natriuretic Peptide (BNP) and BNP Precursor to Cleavage by Neprylisin,Clinical chemistry 2016, 62:4

Les maladies cardiovasculaires

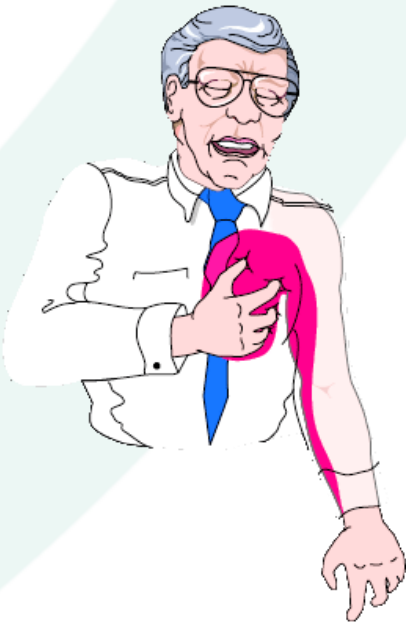
- Maladies coronariennes (SCA)
- Accidents vasculaires cérébraux (AVC)
- Artérite oblitérante des membres inférieurs (AOMI)

- ➔ athérosclérose



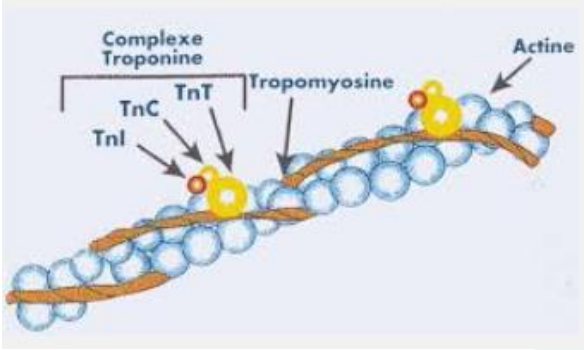
Quelques chifres

- 3% des patients reçus pour une douleur thoracique par le service des urgences
- Parmi ces patients:
  - 7% présentent un infarctus du myocarde
  - 8% présentent un angor instable
  - 6 % présentent un angor stable



Les marqueurs d’ischémie et de nécrose

Les troponines cardiaques



Le complexe troponine est constitué de 3 sous-unités de nature polypeptidique (troponines C, I, T)

Ce complexe est localisé sur les filaments fins des muscles striés et son rôle consiste à réguler la contraction de ces muscles

- Troponine C
  - Fixe le Ca 2+ nécessaire à la contraction : elle n'est pas spécifique au muscle cardiaque.
- Troponine I
  - Présente sous 3 isoformes dont 1 **de spécificité cardiaque très forte**

- Troponine T
  - 1 isoforme **de spécificité cardiaque très forte** et des isoformes squelettiques

Diagnostic précoce de la nécrose myocardique

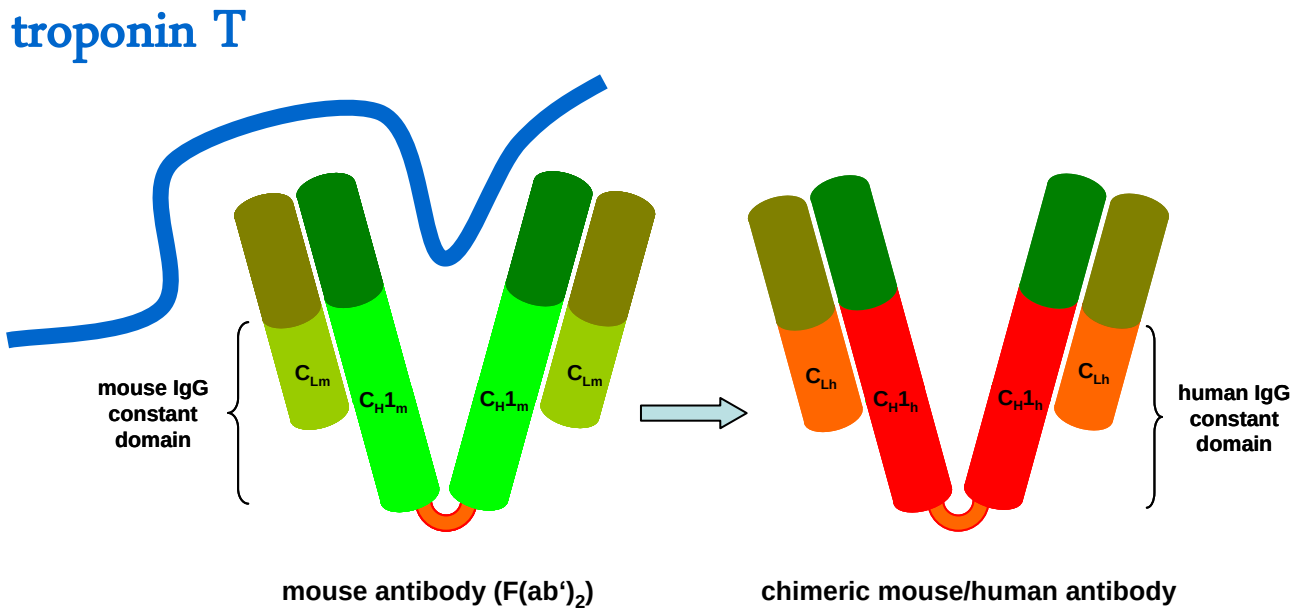
- Le dosage conventionnel de la troponine manque de sensibilité au moment des premiers symptômes de l'IM.

→ Il faut donc plusieurs dosages pour établir une cinétique.

→ Tout retard dans la confirmation du diagnostic d'IM risque d'augmenter les complications et la morbi/mortalité associée.

→ De plus, tout délai pour établir le diagnostic contribue à engorger le service des urgences.

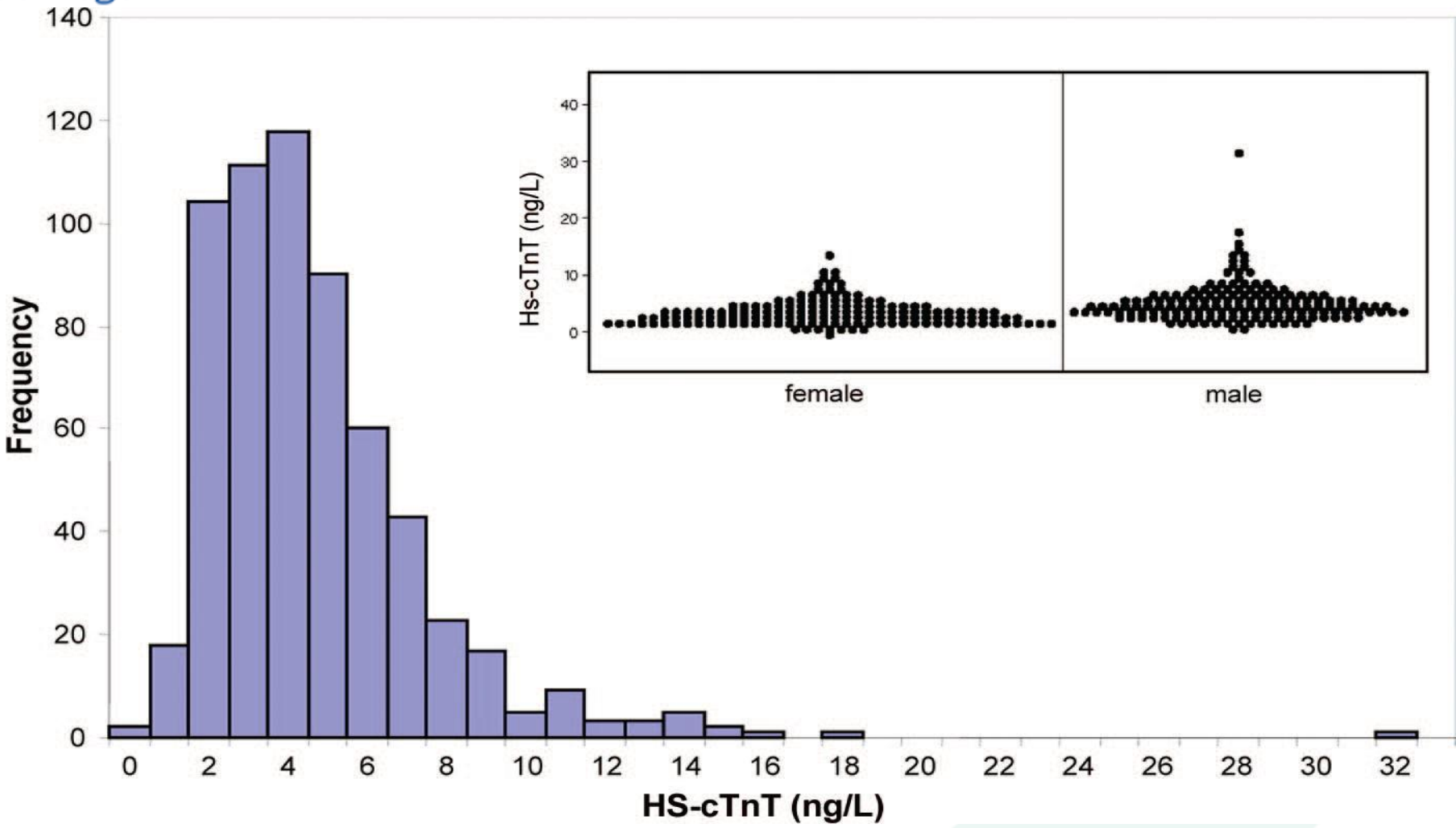
Le dosage…



TnT Gen 4 ab (TnT M7 – IgG) **TnT-hs ab genetically re-engineered**

New concept for minimizing HAMA interference:
cTnT-hs detection antibody genetically re-engineered

Distribution of cTnT values in the reference population



All subjects
99th percentile 13.5 ng/L

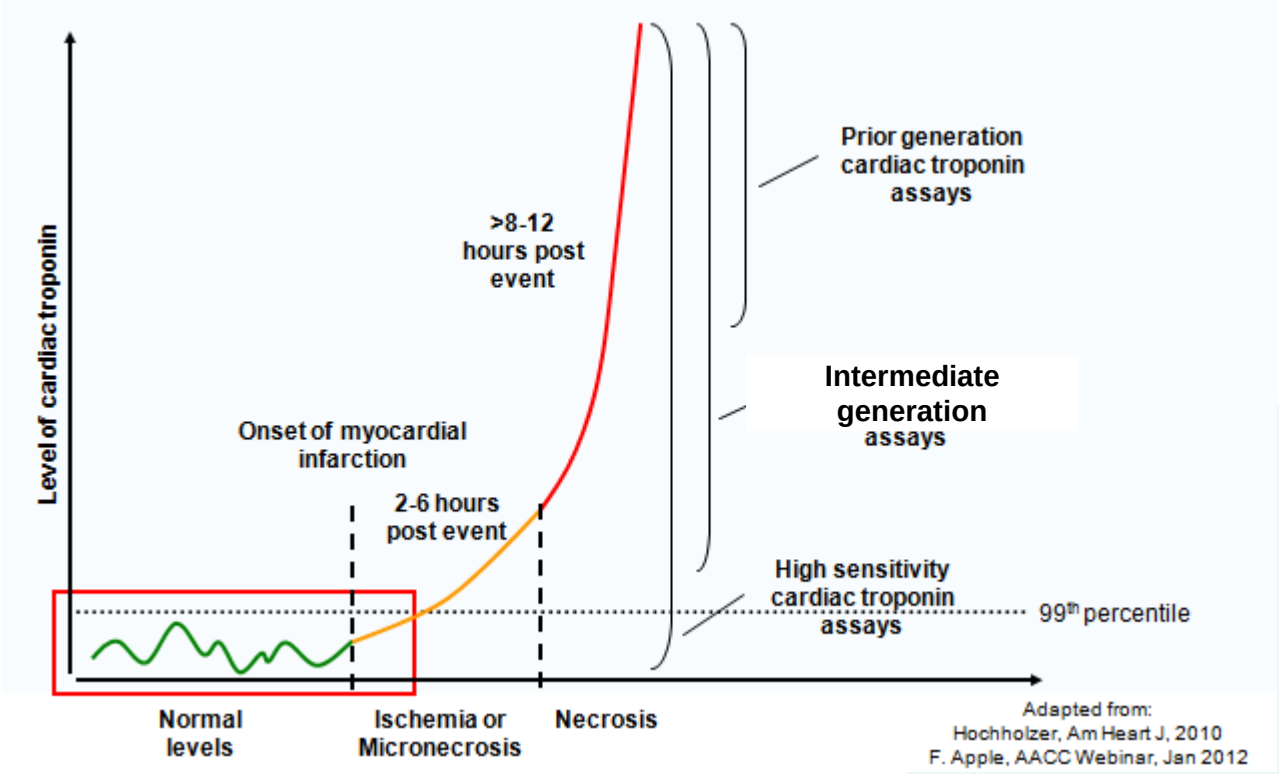
Women
99th percentile 10.0 ng/L

Men
99th percentile 14.5 ng/L

= decision limit for AMI: 99th percentile
→14 ng/L

Giannitsis, Clin Chem 2010, 56 : 254-261

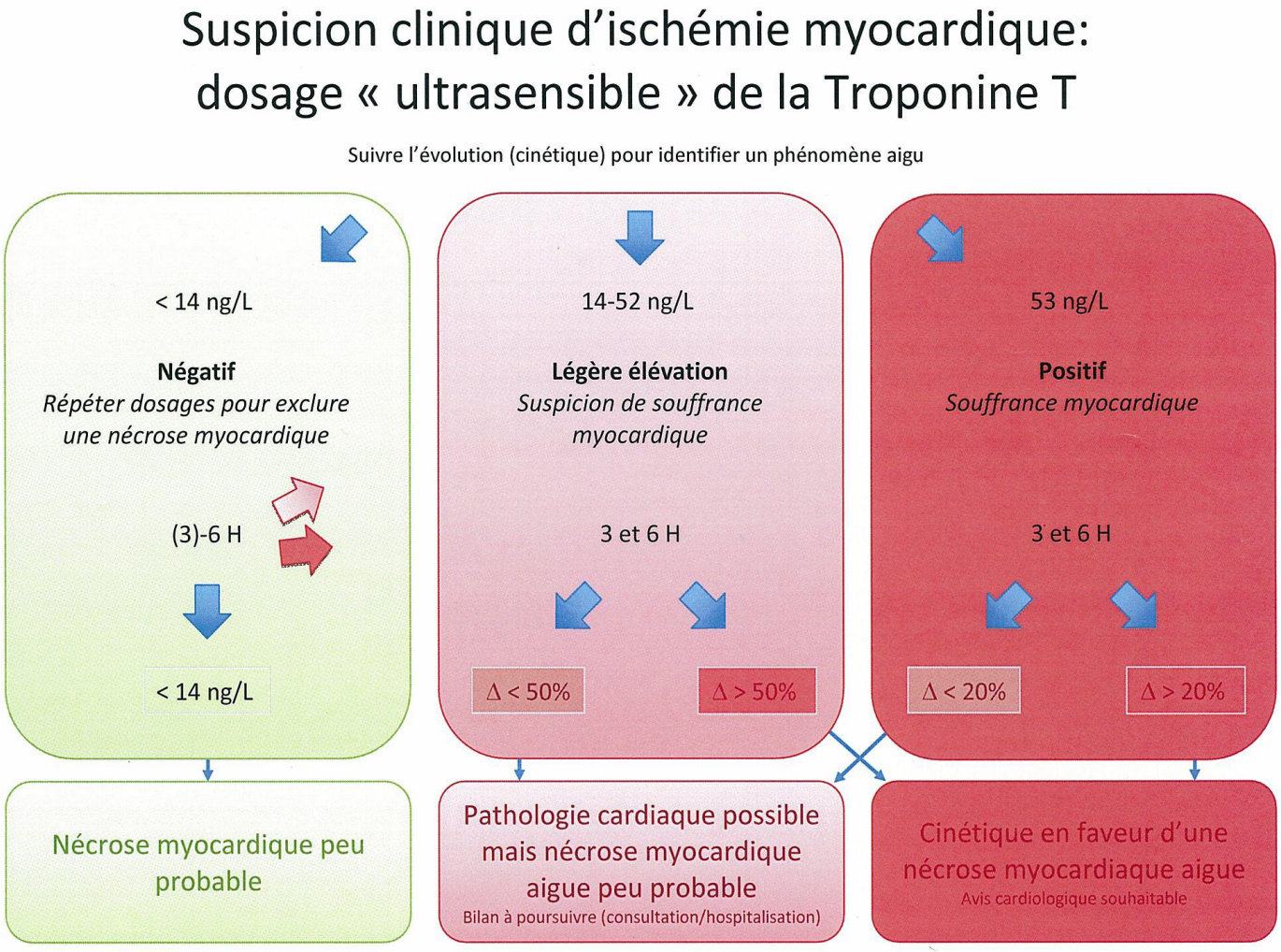
Les troponines



Recommandations ACC/ESC

- Les marqueurs de choix sont les troponines I et T en raison de leur spécificité
- La CK-MB a une spécificité inférieure aux troponines, mais peut être utilisée
- La myoglobine (ou les isoformes de la CK-MB) sont à considérer pour le diagnostic rapide
- CK totale, ASAT (TGO) et LDH sont peu spécifiques et ne sont plus recommandées
- Les dosages de troponines ou CK-MB doivent être réalisés à l'admission, après 1h ou 3h ou 6 à 9 h et après 12 à 24 h.

Algorithme ESC : 0h/+3h



White H. ,Higher sensitivity troponin levels in the community: What do they mean and how will the diagnosis of myocardial infarction be made? [Editorial] Am Heart J 2010; 159(6):933-6.

ESC 2015

Timing for measurements ?

kinase (CK), its MB isoenzyme (CK-MB) and myoglobin.[6] If the clinical presentation is compatible with myocardial ischaemia, then a dy-

na

he

tro i.e. usually within 1 h if using high-sensitivity assays) after symptom onset and remain elevated for a variable period of time (usually several days).[2,6] Advances in technology have led to a

1 heures après la survenue des symptômes

ESC 2015

Timing for measurements ?

1/ TAT

At present, measurements of troponins play a key role in the diagnosis of myocardial infarction. There is a consensus that a turnaround time (TAT) of 1 h or less should be achieved for cardiac marker assays. However, little is known about the real delays between the patient's arrival at the emergency department (ED) and the reporting of the test.

kinase (CK), its MB isoenzyme (CK-MB) and myoglobin.[5] If the clinical presentation is compatible with myocardial ischaemia, then a dy-

1 heures après la survenue des symptômes

says) after symptom onset and remain elevated for a variable period of time (usually

have led to a

2/ Algorithm

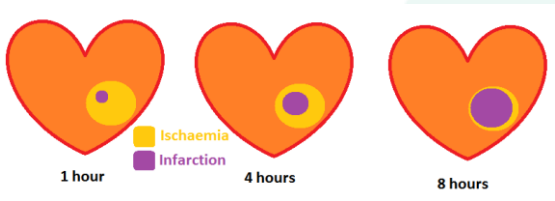
Performance of the 1-h algorithm for rapid AMI diagnosis

Reichlin T. et al., CMAJ. 2015

Les bénéfices de la hs Tn et du 1h-algorithm

1. Bénéfice 1: Valeurs médicales pour le patient
   ➔***Time* is Life**

2. Bénéfice 2: Valeurs médicales pour le clinicien
   ➔**Time is Myocardium**



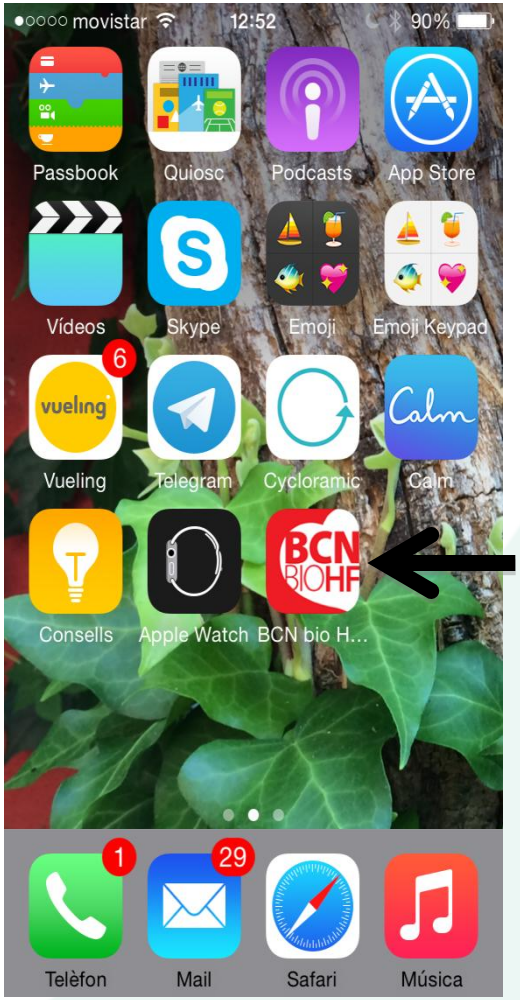
3. Bénéfice 3*: Valeurs* médicales pour les soins de santé
   ➔**Time is Money**

Reichlin et al. (2012). *Arch Intern Med* 172 (16):1211-8.
Reichlin et al. (2015). *CMAJ* May 19;187 (8):E243-52.
De Luca *et al. (2004*). Circulation 109:1223-1225.
Hamm et al (2011).*Eur Heart J* 32:2999–3054.

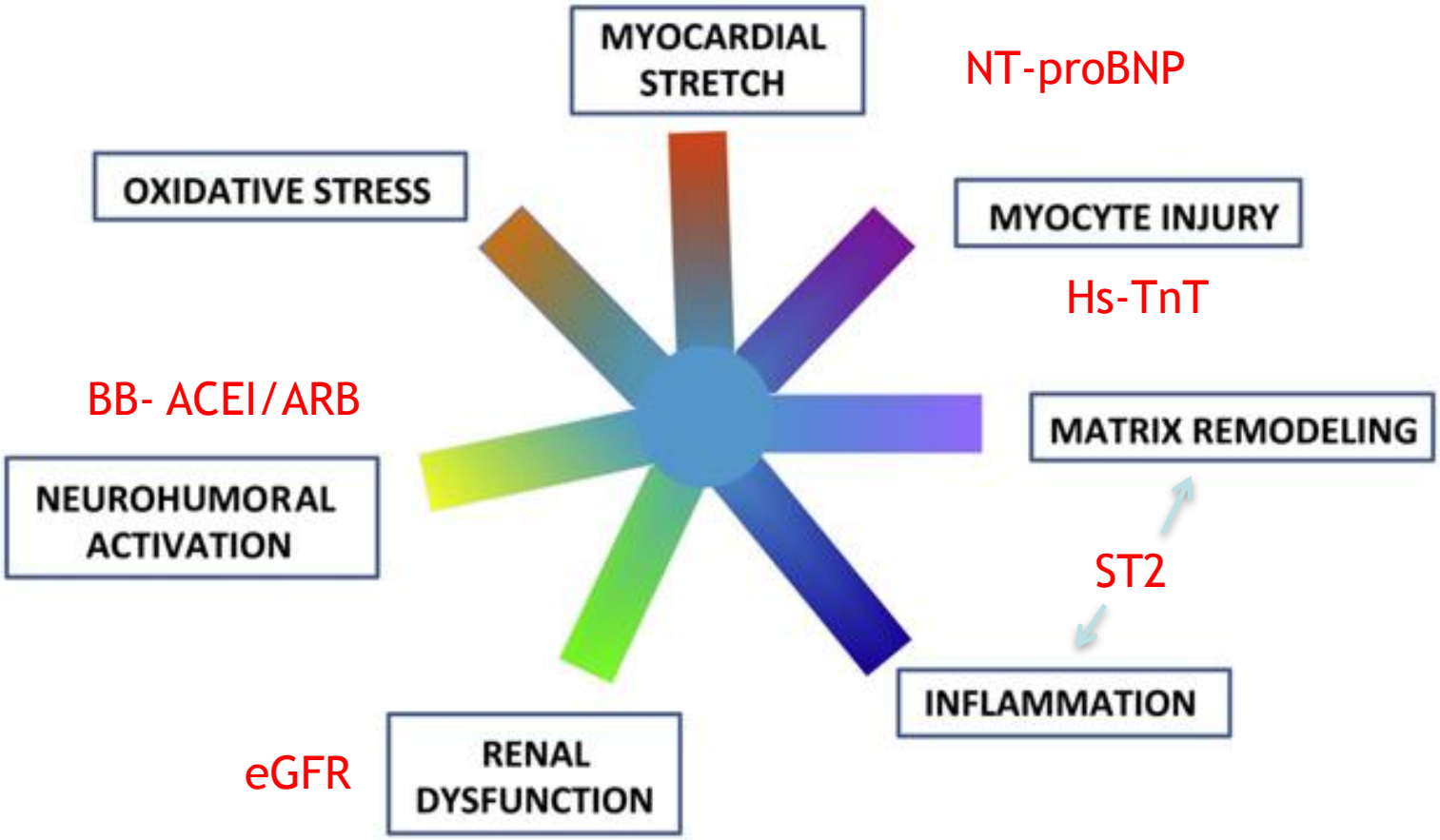
BCN Bio-HF Calculator

www.bcnbiohfcalculator.org

Lupon J et al. Mayo Clin Proc 2013;88:234-43
Lupon J et al. PLoS One 2014;9:854



BCN Bio-HF Calculator



CHU de Liège

Clinical Variables

Age, years*: 44

Sex*: (•) Male ( ) Female

NYHA functional class*: ( ) I-II (•) III-IV

Na, mmol/L: 139

eGFR, ml/min/1.73m2: 33.5

Hb, g/dL:

LVEF, %: 15

Treatments

Loop diuretic, mg/d

Furosemide: 80

Torasemide:

Statin*: ( ) Yes (•) No

Beta-blocker*: (•) Yes ( ) No

ACEI or ARB*: (•) Yes ( ) No

Biomarkers

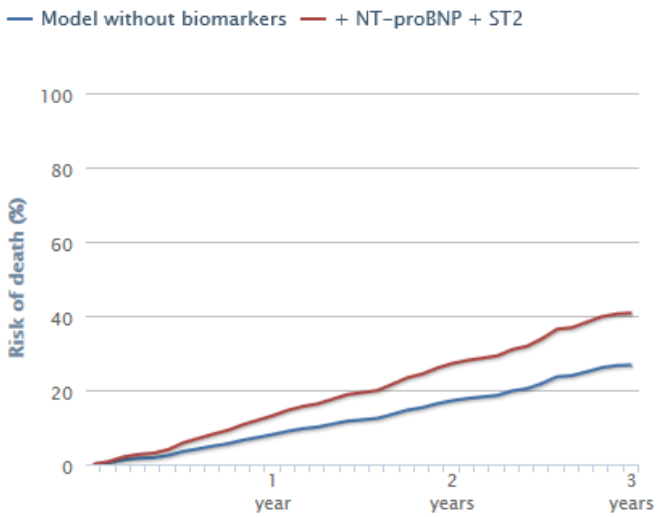
hs-cTnT, ng/L (pg/mL):

ST2, ng/mL: 132

NT-proBNP, ng/L (pg/mL): 3520

Calculate

Mortality	Risk at 1 year	Risk at 2 years	Risk at 3 years
Model without biomarkers	8.04%	17.18%	26.79%
+ NT-proBNP + ST2	13.13%	27.16%	40.79%



Life expectancy	years
Model without biomarkers	7.0
+ NT-proBNP + ST2	4.6

(*) Required fields.

Merci pour votre attention