CORATA Belgique

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Galectin-3:

A new kid on the block?

Cliniques universitaires SAINT-LUC UCL BRUXELLES

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Heart Failure

High prevalence

High morbidity and mortality

Economical burden

Vasoconstriction

Decrease of Natriuresis

Cardiac Hypertrophy

Inflammation

Fibrosis

Neurohormonal activation:

-Sympathetic nervous system

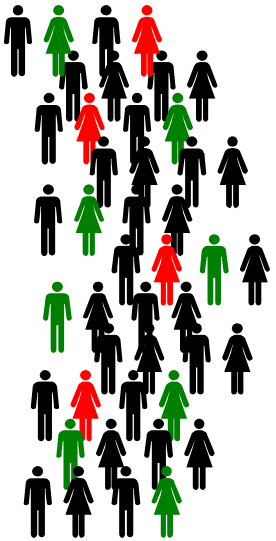
-Endothelin

- Angiotensin II

- Aldosterone

-Natriuretic peptides

HF GENERAL POPULATION

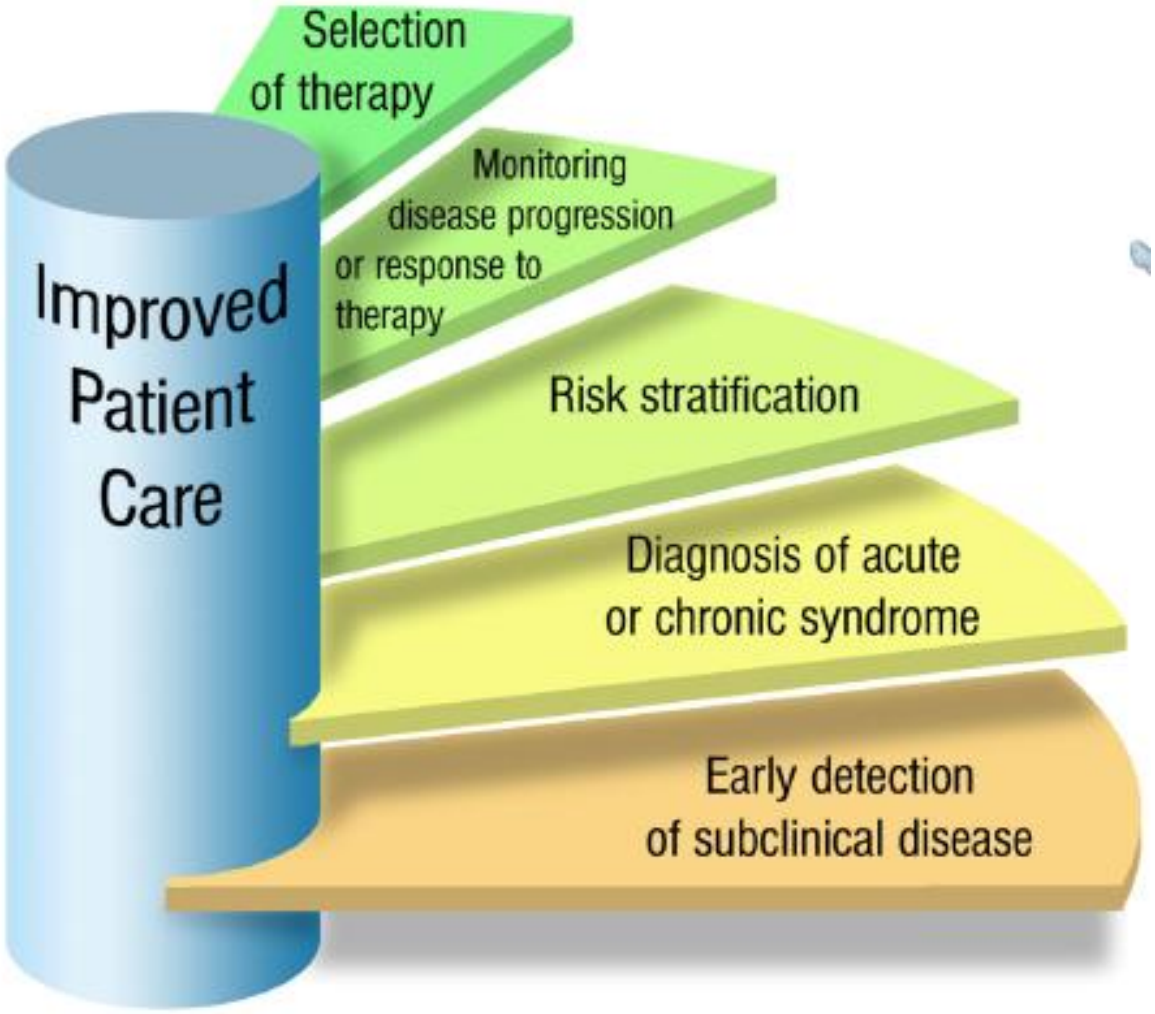


Allocation of resources

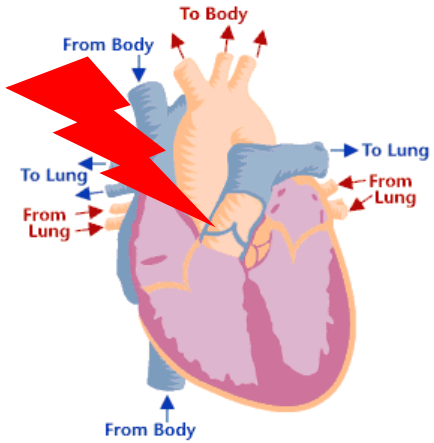
Heart failure (HF) accounts for more than 1 million hospital admissions per year, with an estimated cost exceeding $39 billion annually in the U.S

The mean in-hospital stay for HF was 14.8 days.
The total in-hospital cost of HF as a primary diagnosis was euro 94,113,827, representing 1.8% of the total hospital expenditure.

Why biomarkers ?



Which biomarkers ?



Endothelial Markers
- Endothelin / BigET1
- Urotensin II
- adrenomedullin

→ **Proinflammatory Cytokines**
- IL6
- TNFa
- LpPLA2

→ **Plaque Destabilization**
- MMP9
- MPO
- ICAM

→ **Plaque Rupture**
- sCD40L
- PAPP-A

Ischemia
- IMA
- FFA
- Choline

→ **Necrosis**
- cTnT (hs)
- cTnI (hs)

Stress
- Copeptine
- Urocortine

→ **Myocardial Dysfunction**
- BNP
- Nt-proBNP
- MRproANP

→ **Remodeling**
- Galectin 3
- Myostatin
- Osteopontin
- GDF-15
- ST2

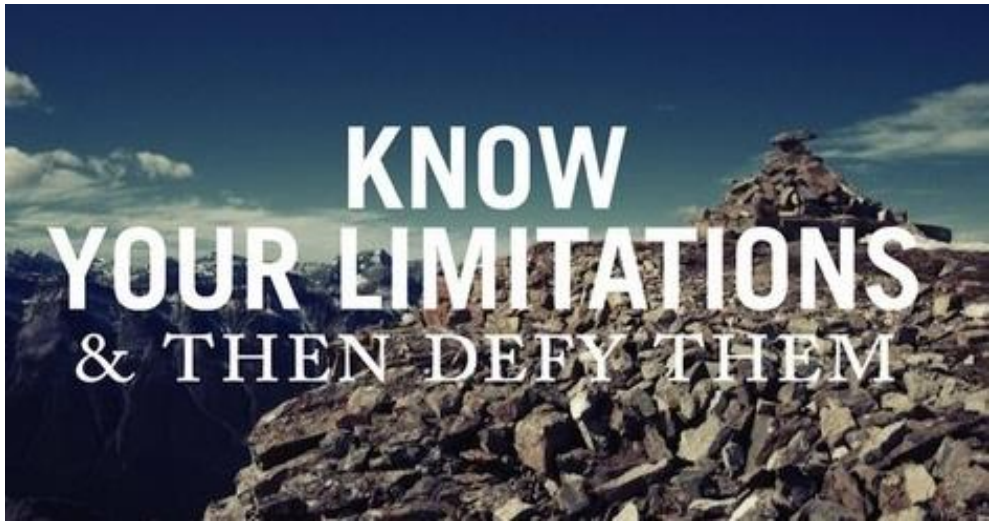
What have we learnt from plasma biomarkers?

- **Impact of translational research**
- **Better understanding of physiopathology**
- **Promises for**
  - **Diagnosis and Triage**
  - **Risk stratification**
  - **Tailored therapy**
- **Identify new therapeutic targets**

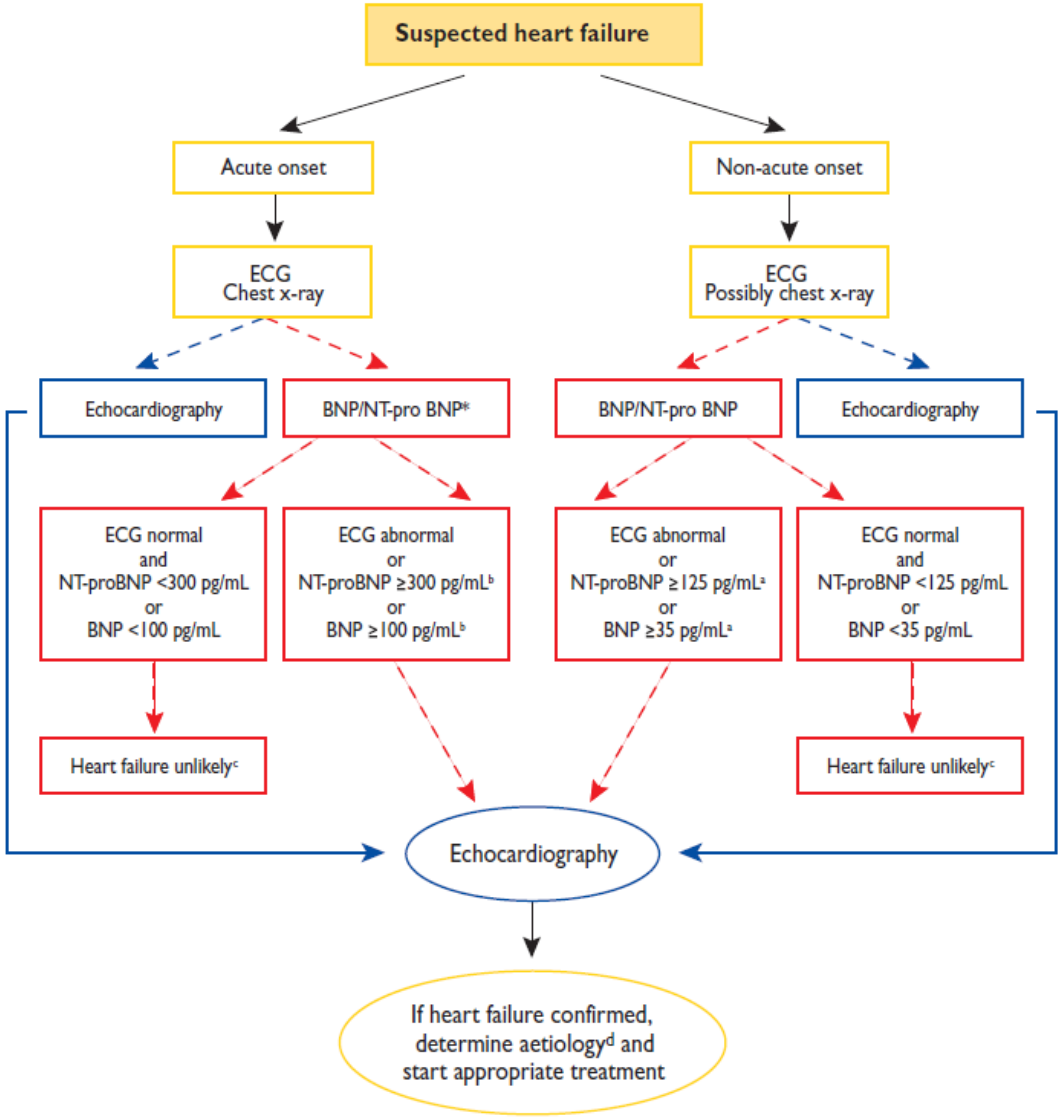
- **New hope from emerging / innovative biomarkers**
- **Work in multidiscilpinary teams / Education**
- **Define quality standards and specifications**

What have we learnt from plasma biomarkers?

- **Not (yet) ideal biomarkers**
  - **Limitations**
  - **Is there any added value / clinical impact?**
  - **MMS**



Heart Failure



2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

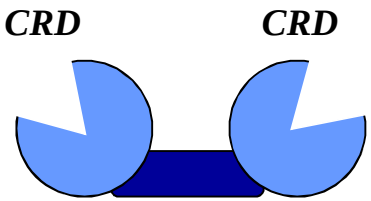
Developed in Collaboration With the Heart Rhythm Society

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

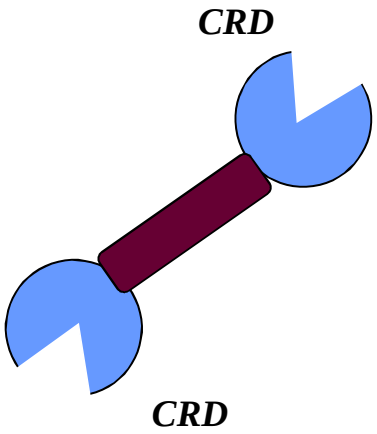
6.3.3. Other Emerging Biomarkers

Besides natriuretic peptides or troponins, multiple other biomarkers, including those reflecting inflammation, oxidative stress, neurohormonal disarray, and myocardial and matrix remodeling, have been widely examined for their prognostic value in HF. Biomarkers of myocardial fibrosis, soluble ST2 and galectin-3 are not only predictive of hospitalization and death in patients with HF but also additive to natriuretic peptide levels in their prognostic value. Markers of renal injury may also offer additional prognostic value because renal function or injury may be involved in the pathogenesis, progression, decompensation, or complications in chronic or acute decompensated HF (242-244, 264, 265, 279). Strategies that combine multiple biomarkers may ultimately prove beneficial in guiding HF therapy in the future.

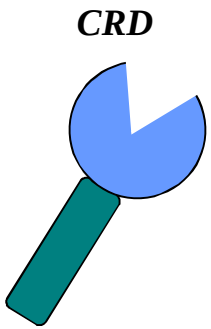
Galectins



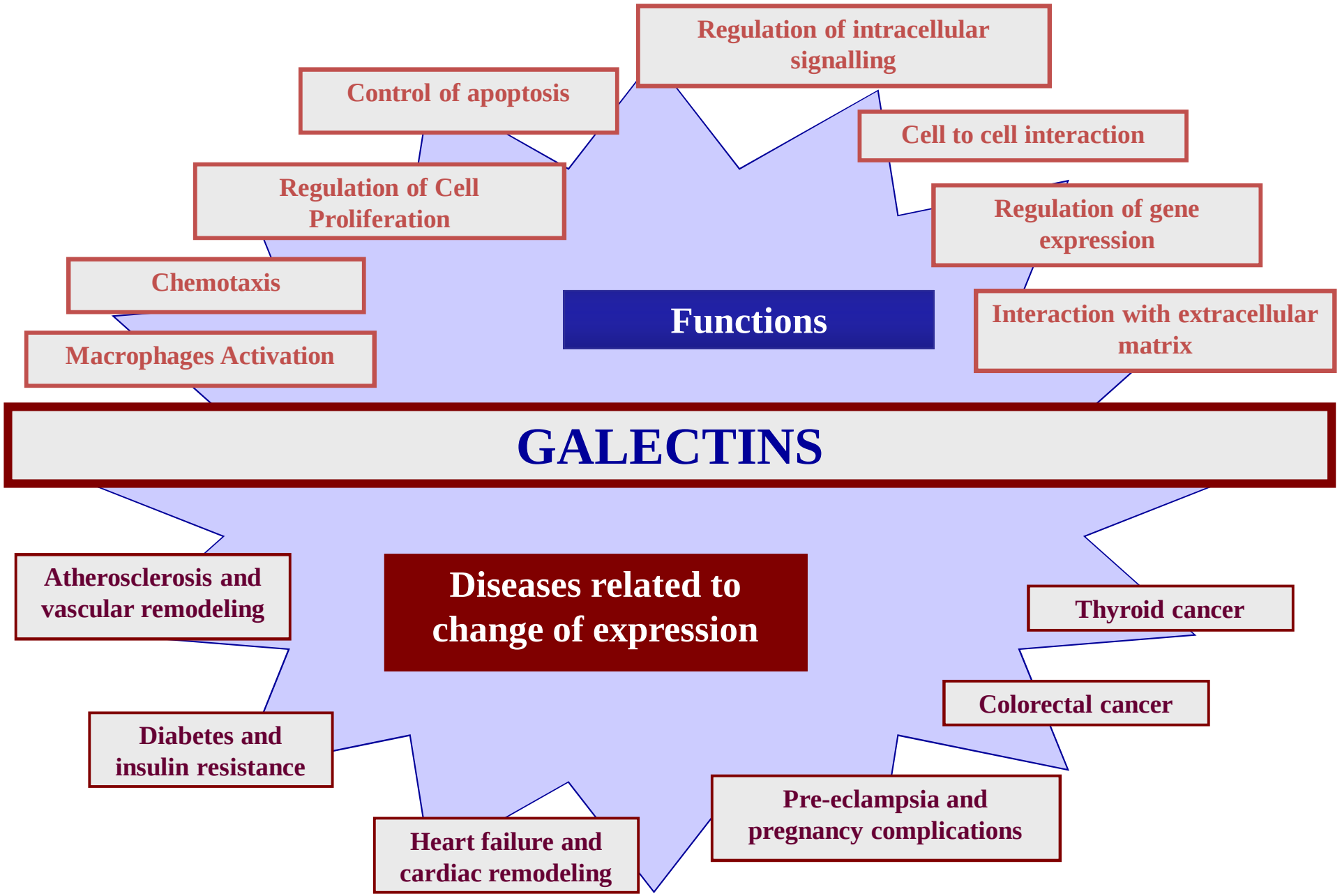
Prototype galectins



Tandem-repeat-type galectins

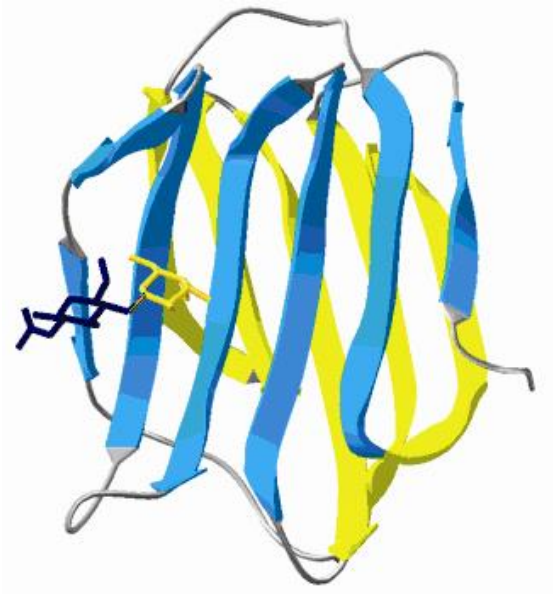


Chimera-type galectin

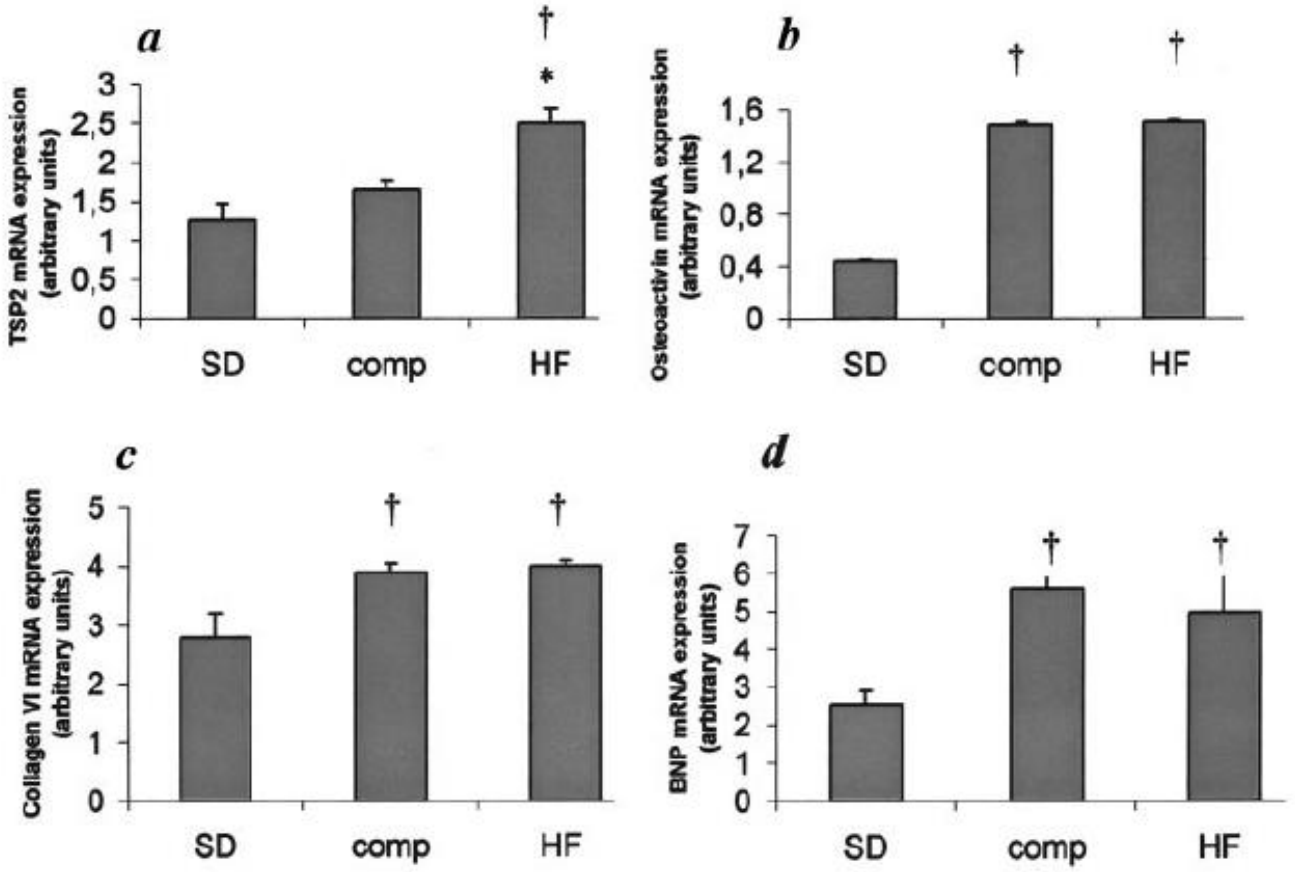

Regulation of intracellular signalling
Control of apoptosis
Cell to cell interaction
Regulation of Cell Proliferation
Regulation of gene expression
Chemotaxis
Functions
Interaction with extracellular matrix
Macrophages Activation
GALECTINS
Atherosclerosis and vascular remodeling
Diseases related to change of expression
Thyroid cancer
Colorectal cancer
Diabetes and insulin resistance
Pre-eclampsia and pregnancy complications
Heart failure and cardiac remodeling

Galectin-3 and Cardiac Remodeling

- β-galactoside-binding lectin found in the nucleus, cytoplasm, cell surface and extracellular matrix
- Associated with biological processes important to the development & progression of HF (i.e., inflammation and fibrosis)
- Secreted by macrophages and promotes collagen synthesis
- Discovered in 2004 to be a mediator in the development and progression of heart failure



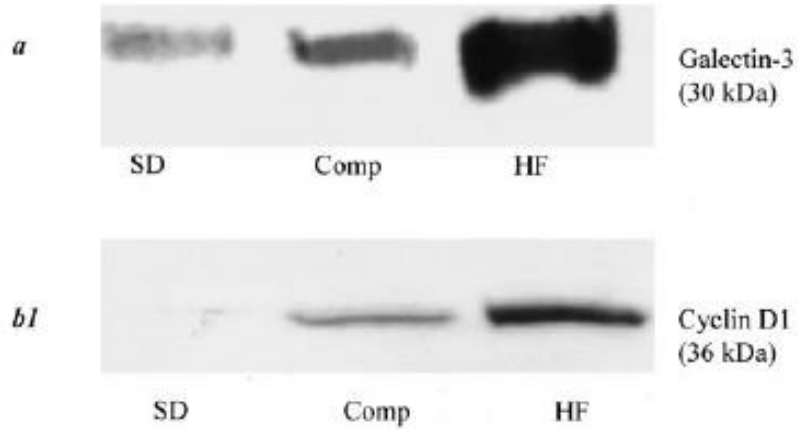
Galectin-3 and Cardiac Remodeling



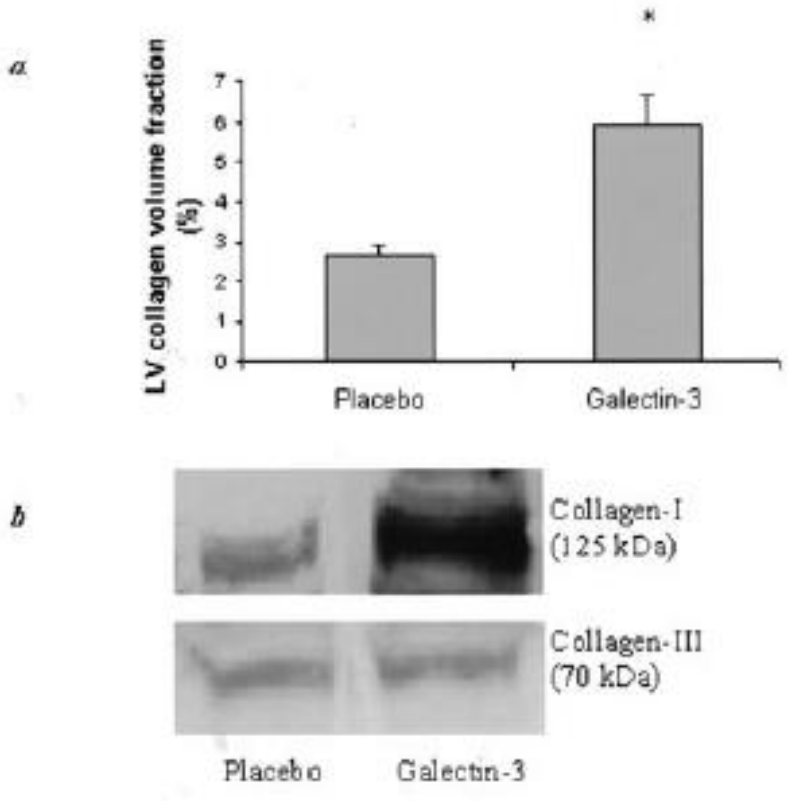
Emerged as the most over-expressed gene in failing versus functionally compensated hearts in animal model of heart failure (TGRmRen2-27 rats)

Schroen et al., 2004

Galectin-3 and Cardiac Remodeling

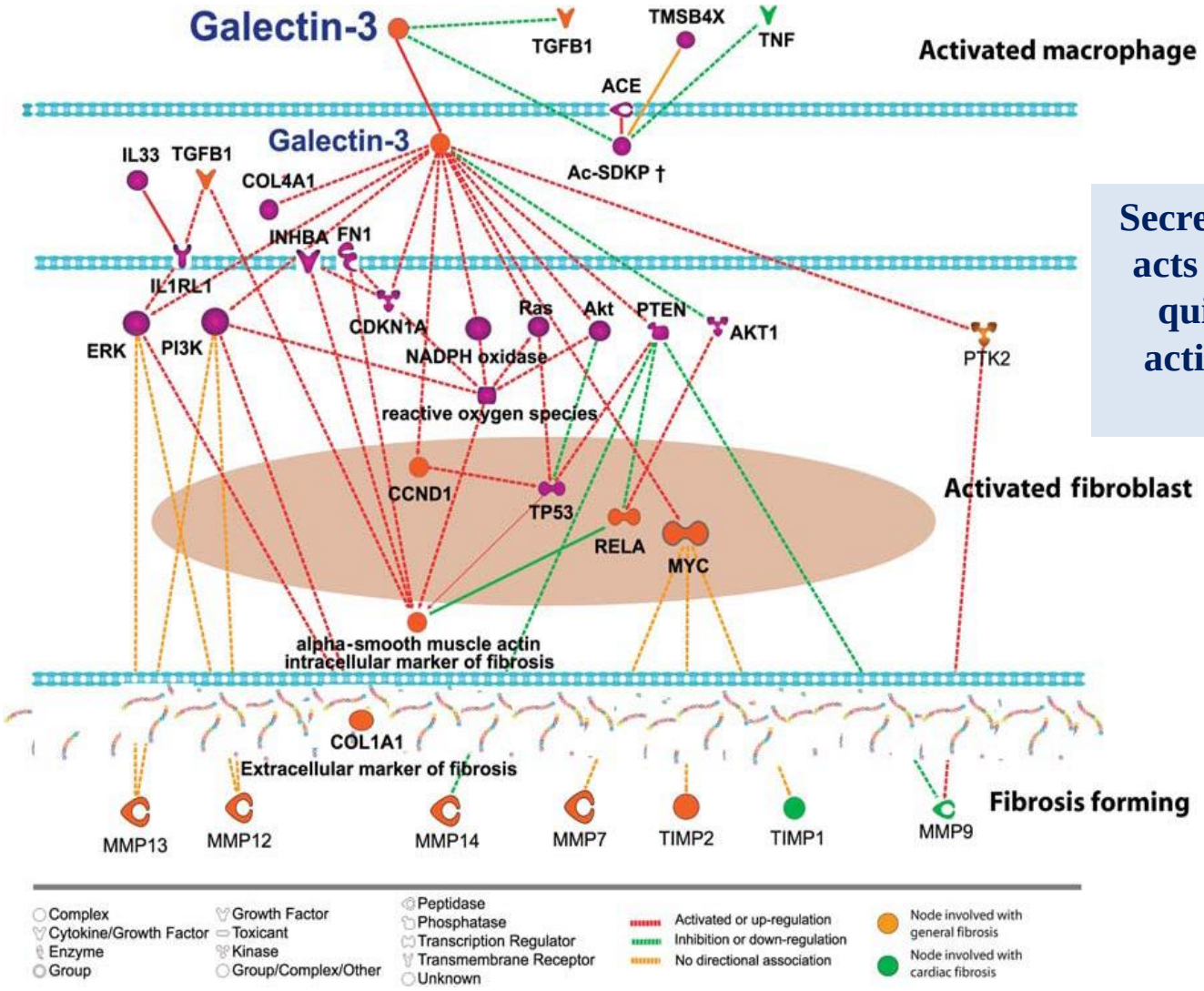


Representative blot for galectin-3 in failing and compensat rat myocardial homogenates and SD controls;



Sharma et al., 2004

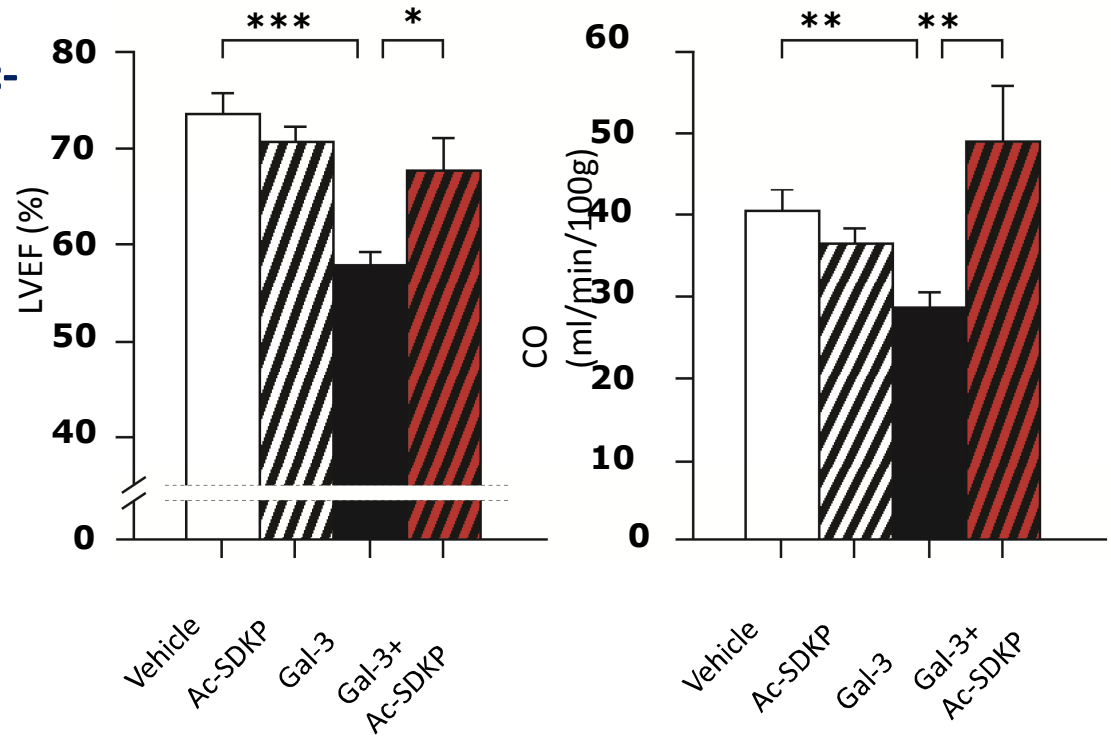
Galectin-3 and Cardiac Remodeling



Secreted by macrophages and acts as a ñswitchò that turns quiescent fibroblasts into activated, matrix-secreting myofibroblasts

Galectin-3 and Cardiac Remodeling

- Galectin-3 inhibition with Ac-SKDP shown to reduce collagen content and hypertrophy
- Galectin-3 inhibition shown to improve cardiac function



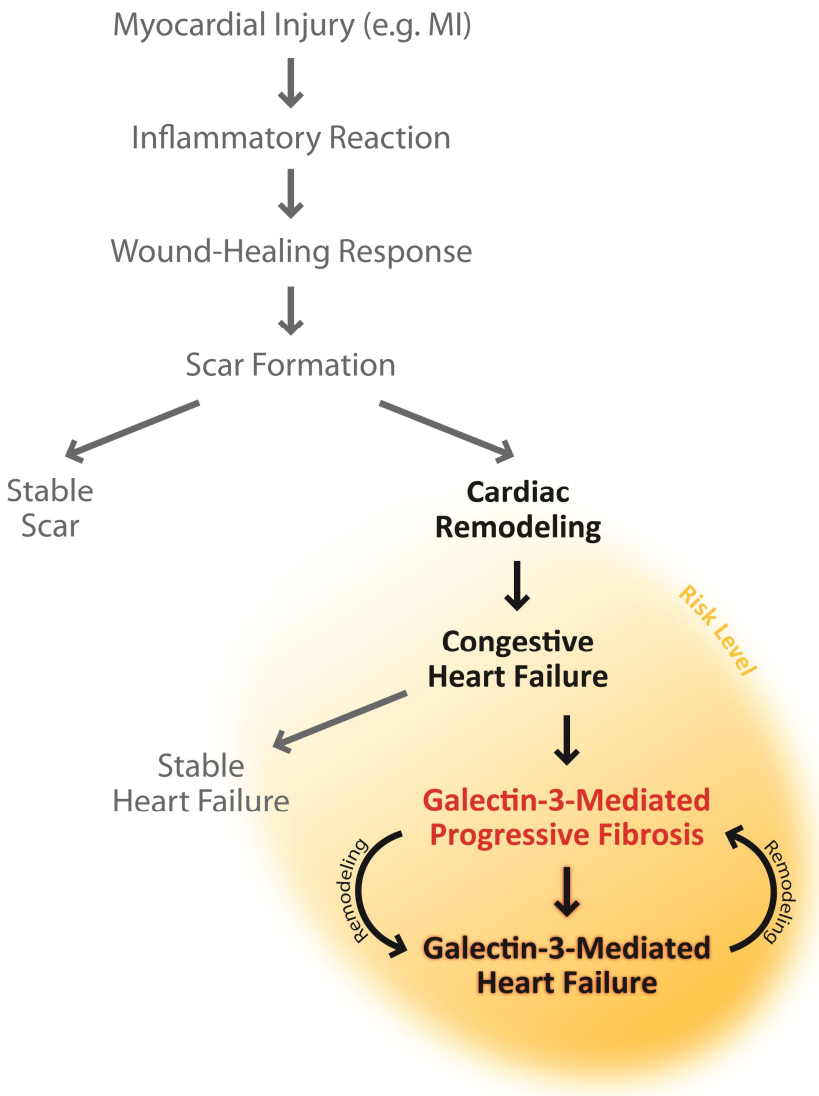
Effect of Ac-SDKP on LVEF (left) and CO (right) in Gal-3-induced cardiac dysfunction. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$

Liu Y-H, et al. *Am J Physiol Heart Circ Physiol* 2009;296:H404-12

Gal-3, Cardiac Remodeling and Risk Stratification

Heart Failure Progression

- HF ranges from near stable to inherently progressive
- Patients with an elevated Galectin-3 have a greater risk for death and hospitalization[1,2]
- Elevated Galectin-3 occurs in ~30-50% of NYHA Class II-IV patients[1,2]



1) Galectin-3 Product Insert (US), BG Medicine, January 2011
2) De Boer R, et al. *Ann Med* 2011;43:60-8

Adapted from Lambert JM, et al. Int J Cardiol 2008;130: 147–58

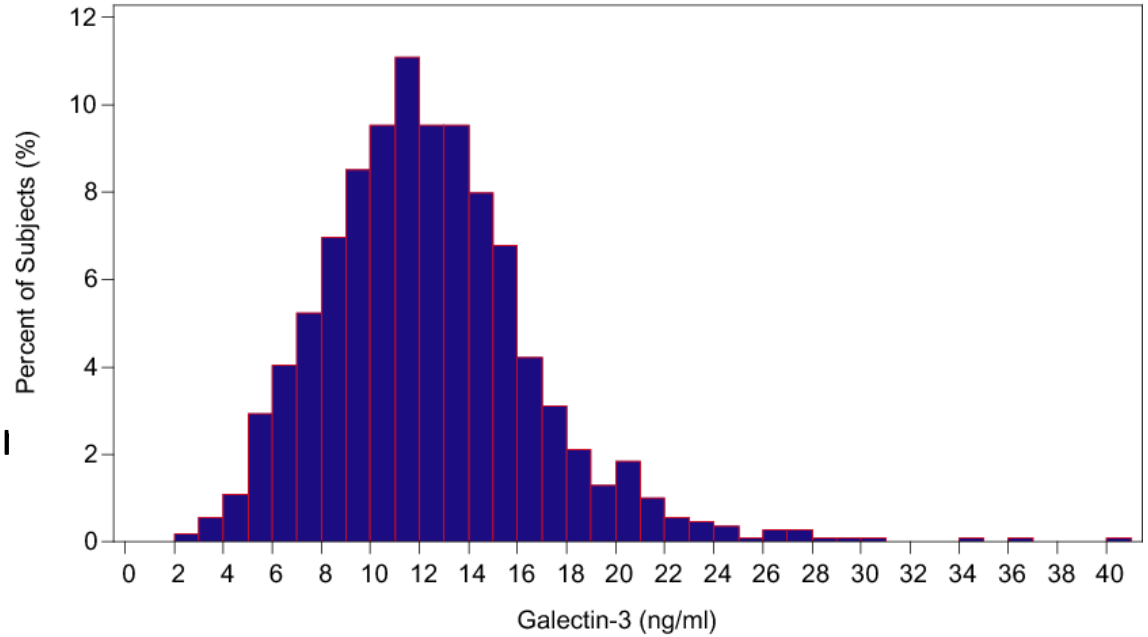
Galectin-3: Normal Population

Identifying Cardiac Remodeling[1,2]

- Galectin-3 is measurable in most healthy individuals
- HF patients with no or minimal remodeling have normal galectin-3 levels
- Galectin-3 is involved in the development of cardiac fibrosis and adverse remodeling, mediating the progression of HF

BioImage Study[1,2]

- Conducted with Humana
- ≥55 years
- Free of CVD
- Ethnic diversity
- Detailed clinical evaluatio
- Normal distribution



1) Muntendam P, et al. *Clin Chem* 2009;55:A73
2) Christenson RH, et al. *Clin Biochem* 2010;43:683-90

Gal-3, Cardiac Remodeling and Risk Stratification

Galectin-3, a Marker of Cardiac Fibrosis, Predicts Incident Heart Failure in the Community

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Framingham and Boston, Massachusetts; and Bethesda, Maryland

Table 1 Baseline Characteristics of 3,353 Participants by Sex-Specific Gal-3 Quartile

Characteristic	Quartile of Gal-3* 1 (n = 835)	2 (n = 842)	3 (n = 842)	4 (n = 834)	p for Trend
Clinical					
Age (yrs)	55 ± 9	58 ± 9	60 ± 9	64 ± 10	<0.0001
Women	454 (54%)	431 (51%)	436 (52%)	461 (55%)	0.98
Systolic blood pressure (mm Hg)	124 ± 18	127 ± 18	130 ± 19	132 ± 20	<0.0001
Diastolic blood pressure (mm Hg)	75 ± 9	76 ± 9	76 ± 9	75 ± 10	0.34
Antihypertensive medication use	134 (16%)	193 (23%)	250 (30%)	355 (43%)	<0.0001
Diabetes mellitus	56 (7%)	66 (8%)	81 (10%)	115 (14%)	<0.0001
Coronary heart disease	32 (4%)	40 (5%)	66 (8%)	106 (13%)	<0.0001
Body mass index (kg/m^2)	26.9 (4.7%)	27.6 (5.1%)	28.5 (5.2%)	28.6 (5.3%)	<0.0001
Smoking	121 (14%)	132 (16%)	149 (18%)	109 (13%)	0.63
Laboratory					
Total cholesterol (mg/dl)	200 ± 36	205 ± 37	209 ± 37	208 ± 42	<0.0001
HDL cholesterol (mg/dl)	54 ± 17	52 ± 16	51 ± 16	48 ± 15	<0.0001
eGFR (ml/min/1.73 m^2)	94 ± 22	90 ± 24	88 ± 25	80 ± 25	<0.0001
BNP (pg/ml)	12.8 ± 15.6	13.7 ± 17.7	14.7 ± 18.3	22.4 ± 30.6	<0.0001
Echocardiography (n = 2,425)*					
Left ventricular mass (g/m^2)	156 ± 42	159 ± 44	163 ± 45	166 ± 45	<0.0001
Fractional shortening (%)	37.1 ± 5.2	37.1 ± 5.7	37.1 ± 5.4	37.3 ± 6.2	0.59
Left atrial dimension (mm)	39.0 ± 5.0	39.3 ± 5.2	39.3 ± 5.1	40.0 ± 5.4	0.001

JACC 2012

Gal-3, Cardiac Remodeling and Risk Stratification

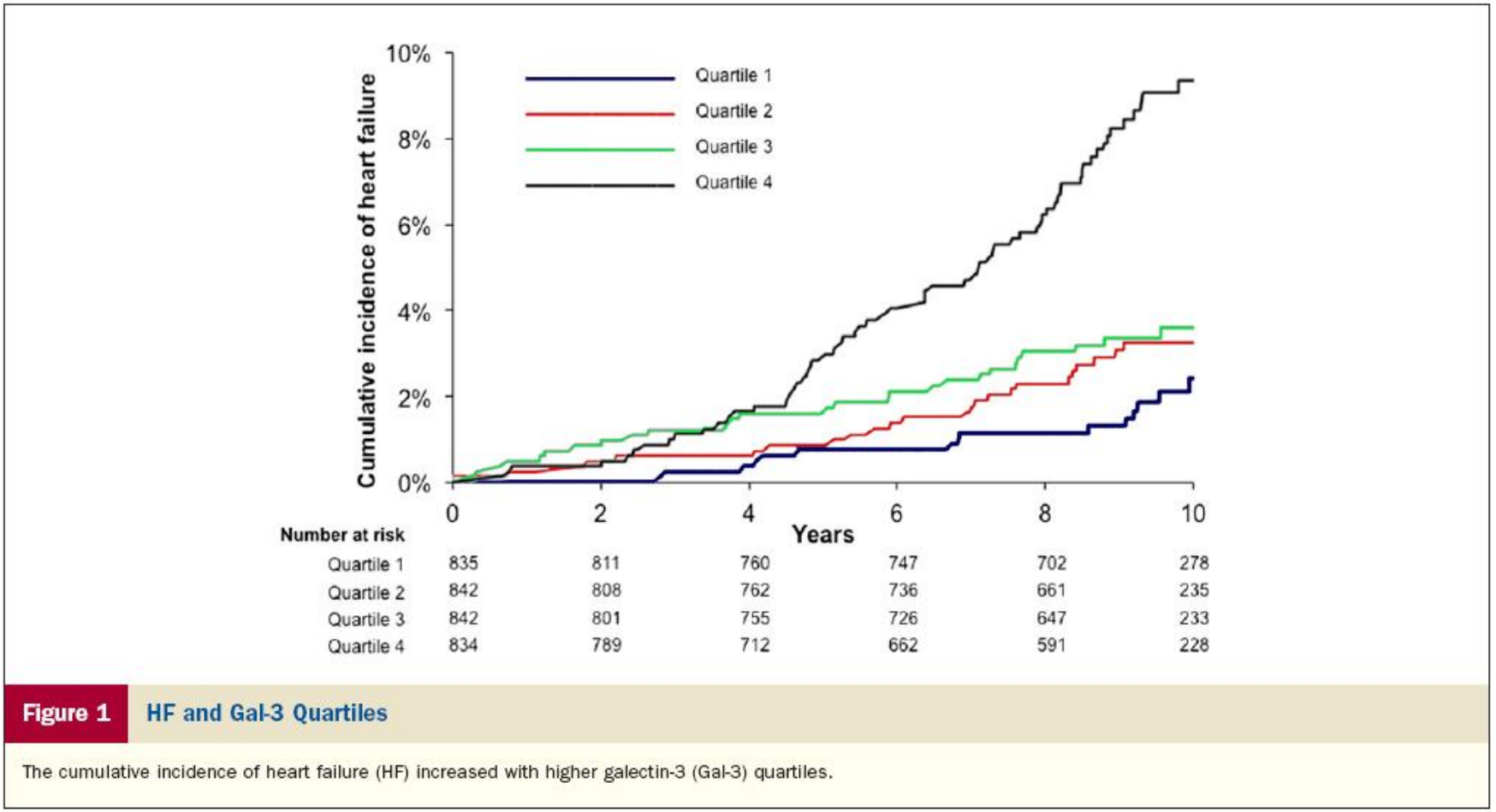


Figure 1 HF and Gal-3 Quartiles

The cumulative incidence of heart failure (HF) increased with higher galectin-3 (Gal-3) quartiles.

ñThe addition of Gal-3 to clinical factors resulted in negligible changes to the C-statistic and minor improvements in net reclassification improvement.ò

JACC 2012

Galectin-3 and the Development of Heart Failure after Acute Coronary Syndrome: Pilot Experience from PROVE IT-TIMI 22

100 cases with a hospitalization for new or worsening HF.
Controls were matched (1:1) for age, sex, ACS type, and randomized treatment.
Serum galectin-3 was measured at baseline (within 7 days post-ACS)

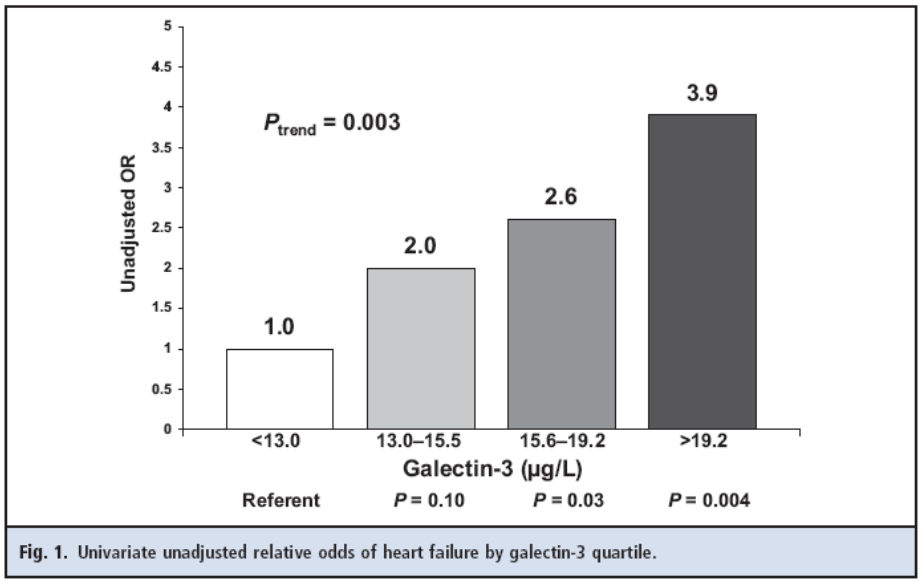
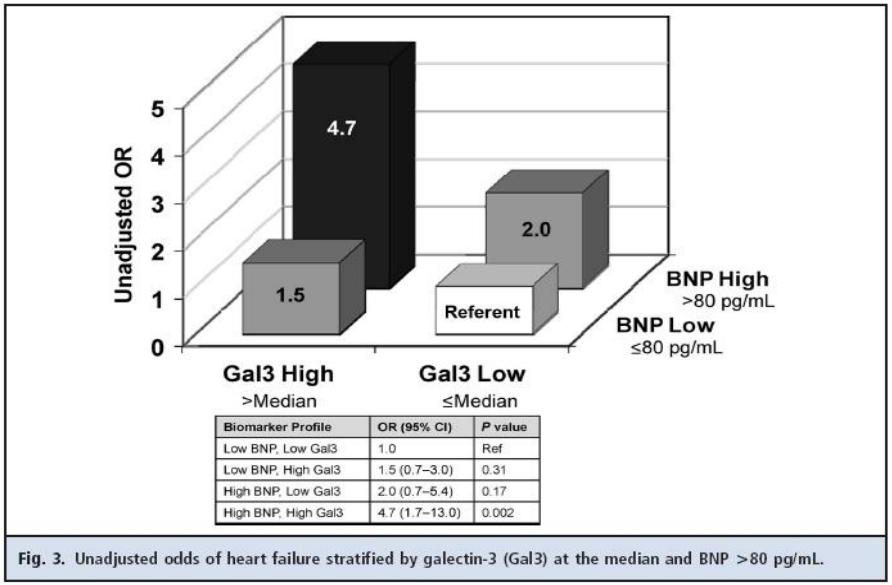


Fig. 1. Univariate unadjusted relative odds of heart failure by galectin-3 quartile.



Biomarker Profile	OR (95% CI)	*P* value
Low BNP, Low Gal3	1.0	Ref
Low BNP, High Gal3	1.5 (0.7–3.0)	0.31
High BNP, Low Gal3	2.0 (0.7–5.4)	0.17
High BNP, High Gal3	4.7 (1.7–13.0)	0.002

Fig. 3. Unadjusted odds of heart failure stratified by galectin-3 (Gal3) at the median and BNP >80 pg/mL.

Patients who developed HF had higher baseline galectin-3 [median 16.7 ε g/L (25th, 75th percentile 14.0, 20.6) vs 14.6 ε g/L (12.0, 17.6), P=0.004]. Patients with baseline galectin-3 above the median had an odds ratio of 2.1 (95% CI 1.2-3.6) for developing HF, P=0.010. Galectin-3 showed a graded relationship with risk of HF.

Cases were more likely to have hypertension, diabetes, prior MI, and prior HF; after adjustment for these factors, this graded relationship with galectin-3 quartile and HF remained significant [adjusted OR 1.4 (95% CI 1.1-1.9), P=0.020]. When BNP was added to the model, the relationship between galectin-3 and HF was attenuated [adjusted OR 1.3 (95% CI: 0.96-1.9), P=0.08]

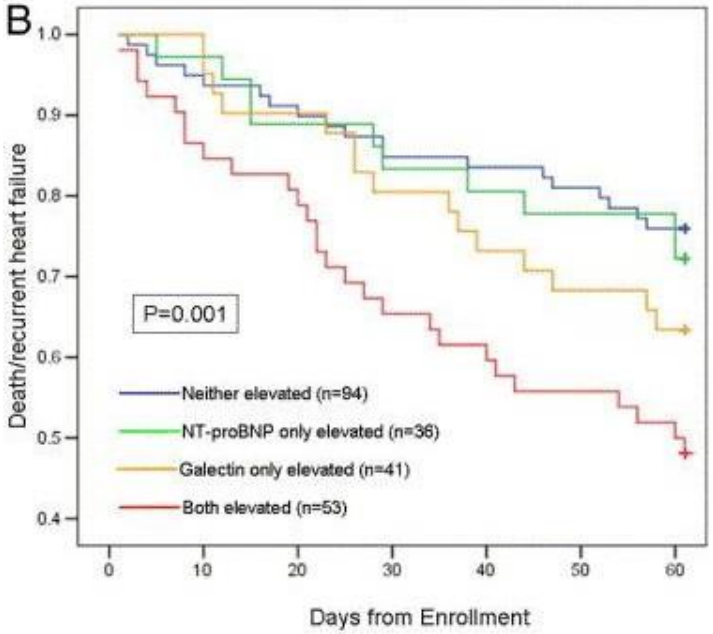
Galectin-3 is associated with the risk of developing HF following ACS

Grandin et al., 2012

Gal-3, Cardiac Remodeling and Risk Stratification

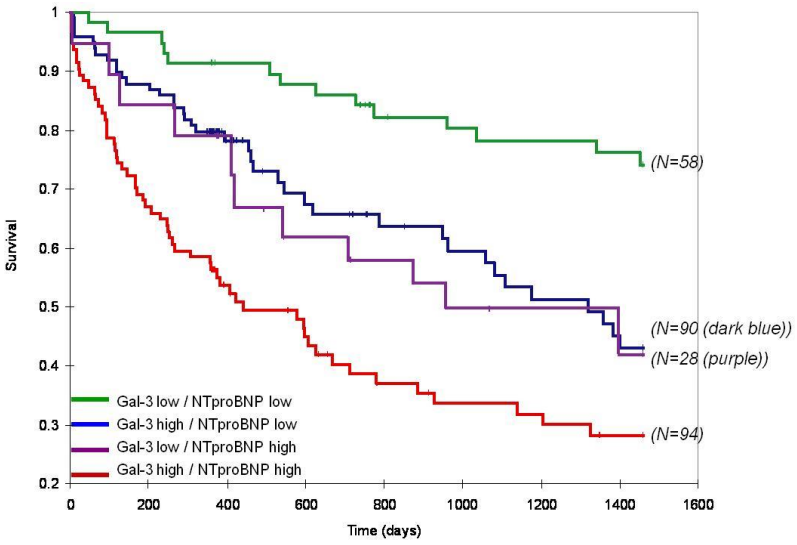
Acute Heart Failure: PRIDE – Investigation of Dyspnea in Emergency Room[1]

- N = 209 (ADHF)
- 60-day mortality: OR = 10.3 (p<0.01)
- 60-day death/recurrent HF: OR = 14.3 (p<0.001)
- Independent of NT-proBNP



Acutely Destabilized Heart Failure[2]

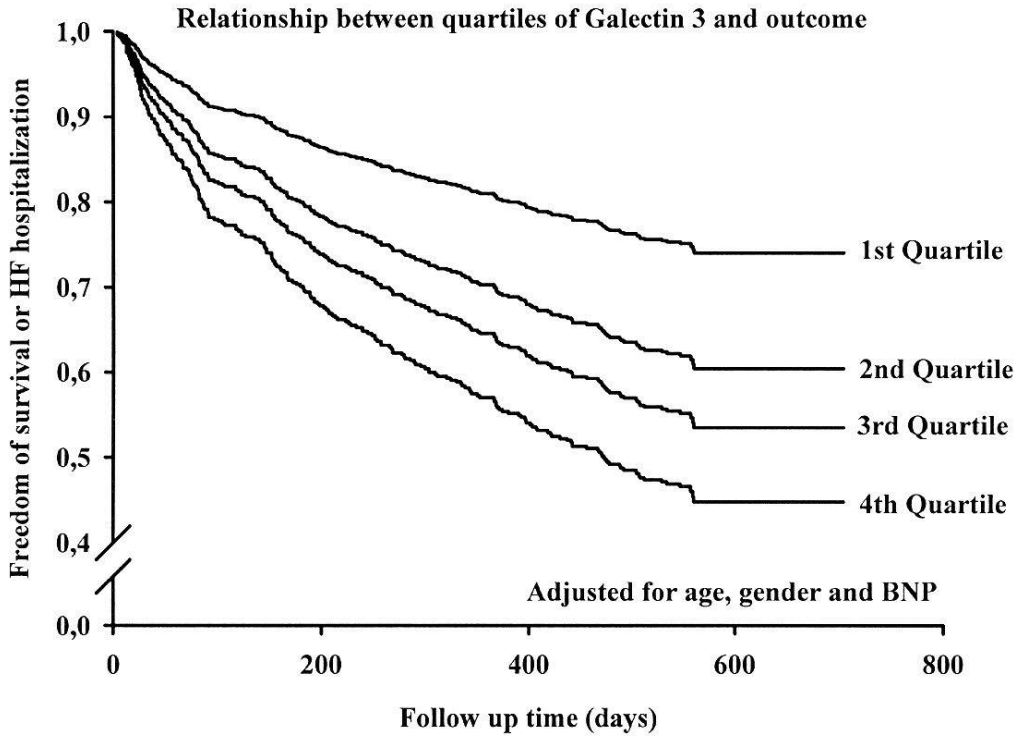
- N = 310 (ADHF)
- Follow-up = 800 days
- HR = 2.19 (p<0.001)
- Independent of age/race/CRP/NT-proBNP



1) van Kimmenade RR, et al. *J Am Coll Cardiol* 2006;48:1217–24
2) DeFilippi C, et al. *J Card Fail* 2009;15:S9

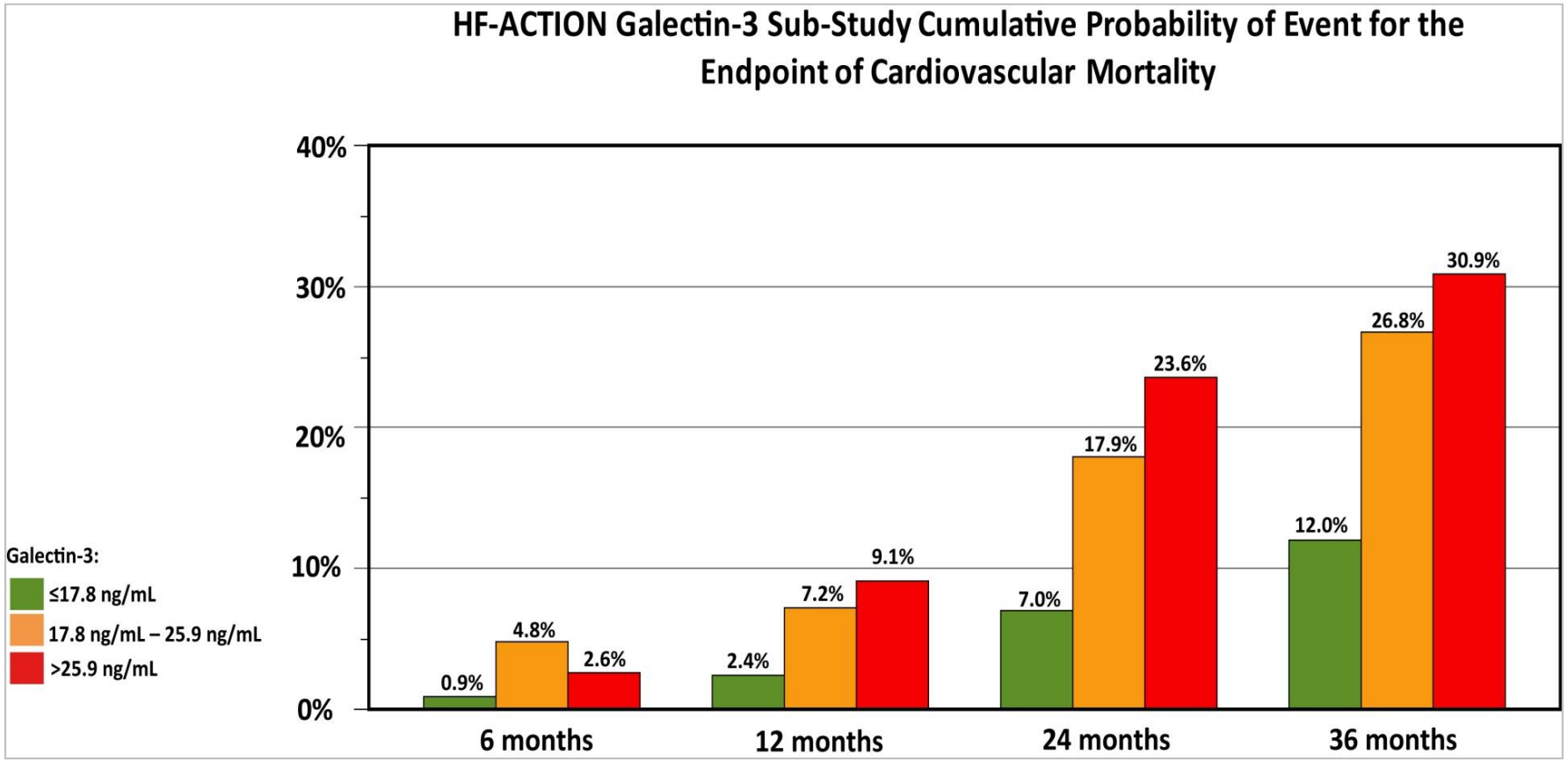
Gal-3, Cardiac Remodeling and Risk Stratification

- **Chronic Heart Failure: COACH – Advising & Counselling in Heart Failure[1]**
  - **N = 592 (NYHA II-IV patients)**
  - **N = 248 (reached primary endpoint)**
  - **HR = 2.67 (1.74 – 4.09); p < 0.00001 (age/gender/BNP adjusted)**



1) van Veldhuisen DJ, et al. *J Card Fail* 2009;15:814

Gal-3, Cardiac Remodeling and Risk Stratification



Cumulative Probability of Event for the Endpoint of Cardiovascular Mortality, at Various Time Points and By Baseline Galectin-3 Level, for HF Subjects in the Clinical Validation Study

Gal-3, Cardiac Remodeling and Risk Stratification

HF-ACTION Hazard Ratios for Cardiovascular Mortality Events

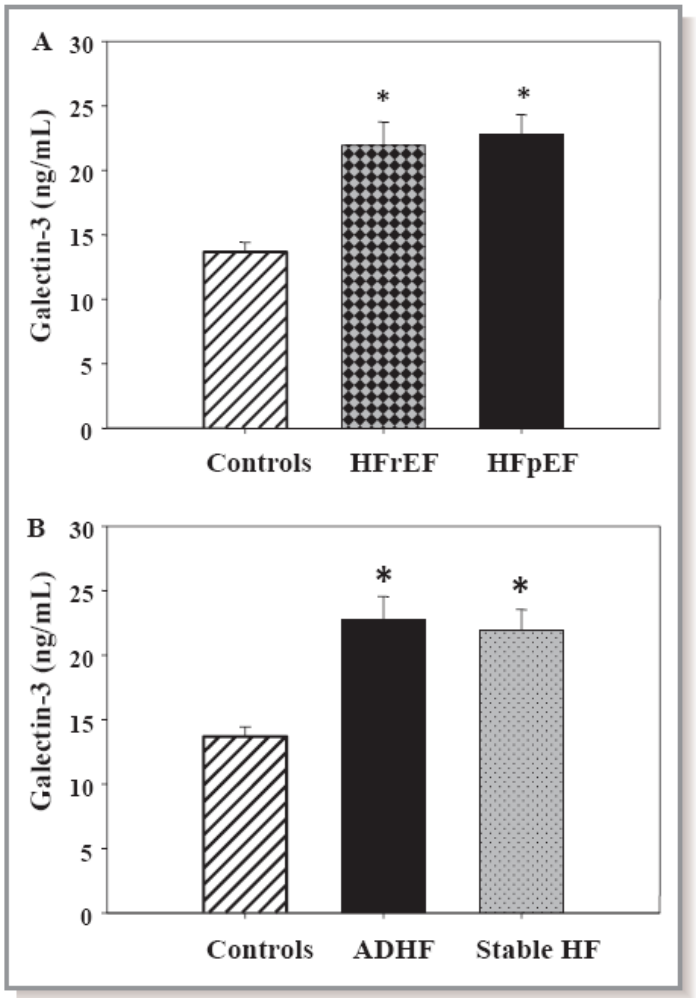
	Hazard Ratio (95% CI, p value)		
Galectin-3 Category	≤17.8 ng/mL	17.8–25.9 ng/mL	> 25.9 ng/mL
Number of Subjects	647	170	78
Galectin-3*	1.0	1.91 (1.28–2.86, p=0.002)	2.33 (1.43–3.80, p<0.001)

* Adjusted for baseline risk factors: age, gender, NYHA functional classification, left ventricular ejection fraction, diabetes status, and smoking status.

Galectin-3 ?

Galectin-3?

Relationship of plasma GAL-3 levels to the type of HF (A) or level of decompensation (B).



*Plasma GAL-3 in 32 controls without HF, 40 patients with HF with reduced LVEF (HFrEF), and 35 patients with HF with preserved LVEF (HFpEF). GAL-3 was elevated to a similar degree in patients with HFrEF vs HFpEF. *P<0.05 vs control*

*Plasma GAL-3 in 32 controls without HF, 37 patients admitted to the hospital with acute decompensated HF (ADHF), and 38 ambulatory patients with chronic stable HF. GAL-3 was elevated to a similardegree in patients with decompensated vs stable HF. *P<0.05 vs control.*

Gopal et al., 2012

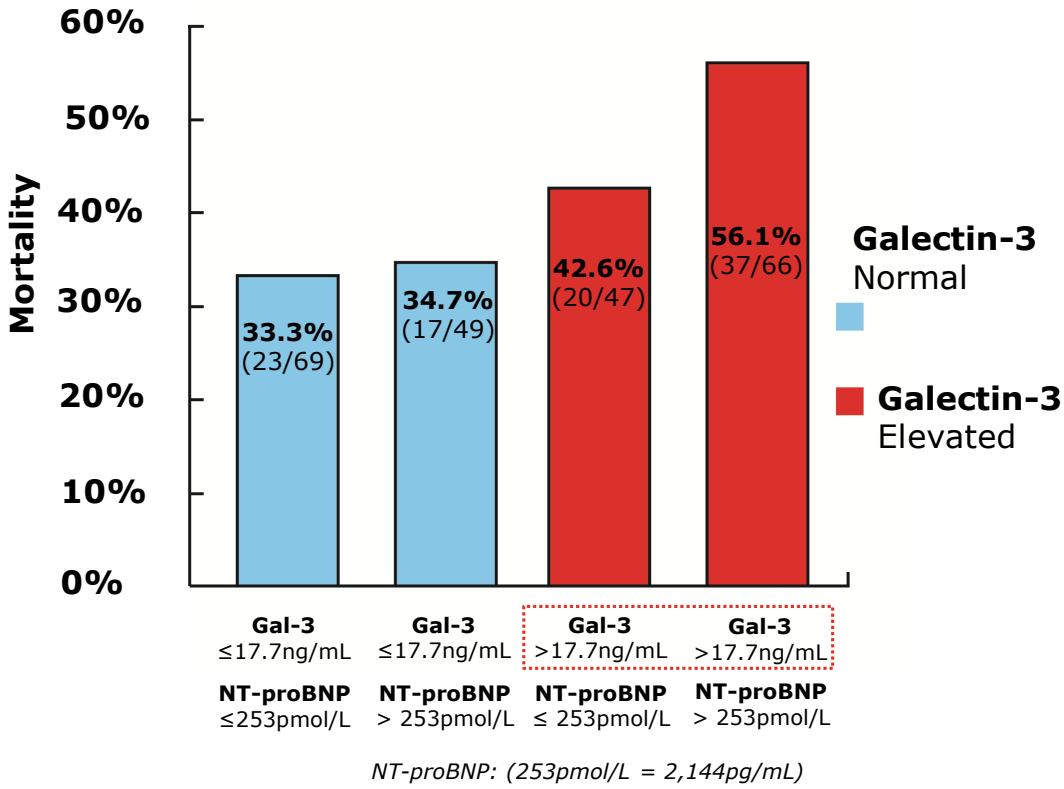
Gal-3, Cardiac Remodeling and Risk Stratification

Chronic Heart Failure[1]

- 232 NYHA III-IV patients
- 6+ year follow-up
- Both high: ~1.5- to 2-fold higher mortality risk; p=0.036 for the trend

Added Value vs. NT-proBNP Alone

- Identified ~21% more patients at the highest risk of mortality
- Identified ~10% more patients at increased risk not captured by a LOW NT-proBNP



Independent and Additive to Natriuretic Peptides

1) Lok, DJA, et al. *Clin Res Cardiol* 2010;99:323-8.

Prognostic Value of Changes in Galectin-3 Levels Over Time in Patients with Heart Failure: Data from CORONA and COACH

Plasma galectin-3 was measured at baseline and at 3 months in patients enrolled in the CORONA trial (n=1,329), and at baseline and at 6 months in patients enrolled in the COACH trial (n=324).

A threshold value of 17.8 ng/mL or 15% change from baseline was used to categorize patients.

Increasing galectin-3 levels over time, from a low to high galectin-3 category, were associated with significantly more HF hospitalization and mortality compared to stable or decreasing galectin-3 levels

HR in CORONA: 1.60 (95% CI: 1.13-2.25, P= 0.007
HR in COACH: 2.38 (95% CI: 1.02-5.55, P=0.046

In addition, patients whose galectin-3 increased by more than 15% between measurements had a 50% higher relative hazard of adverse event than those whose galectin-3 stayed within +/- 15% of the baseline value, independent of age, gender, diabetes, LVEF, renal function, medication (beta-blocker, ACE-i, ARB) and NT-proBNP (HR in CORONA: 1.50 (95% CI: 1.17-1.92, P=0.001)).

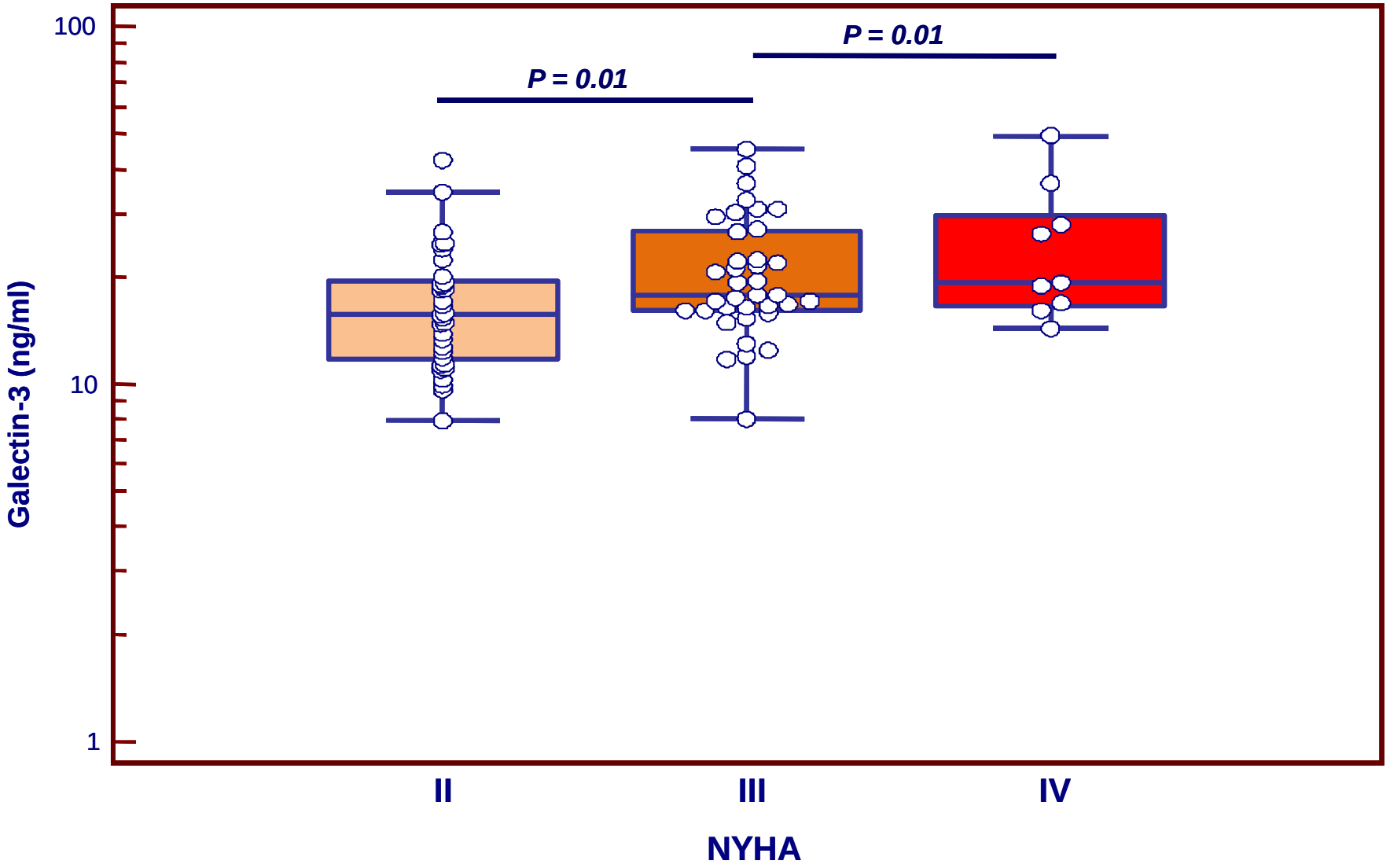
CONCLUSIONS

In two large cohorts of patients with chronic and acute decompensated HF, repeated measurements of galectin-3 level provided important and significant prognostic value in identifying HF patients at elevated risk for subsequent HF morbidity and mortality.

Van der Velde et al., Circ Heart Fail. 2013

Circulating levels of Galectin-3 in HF (I)

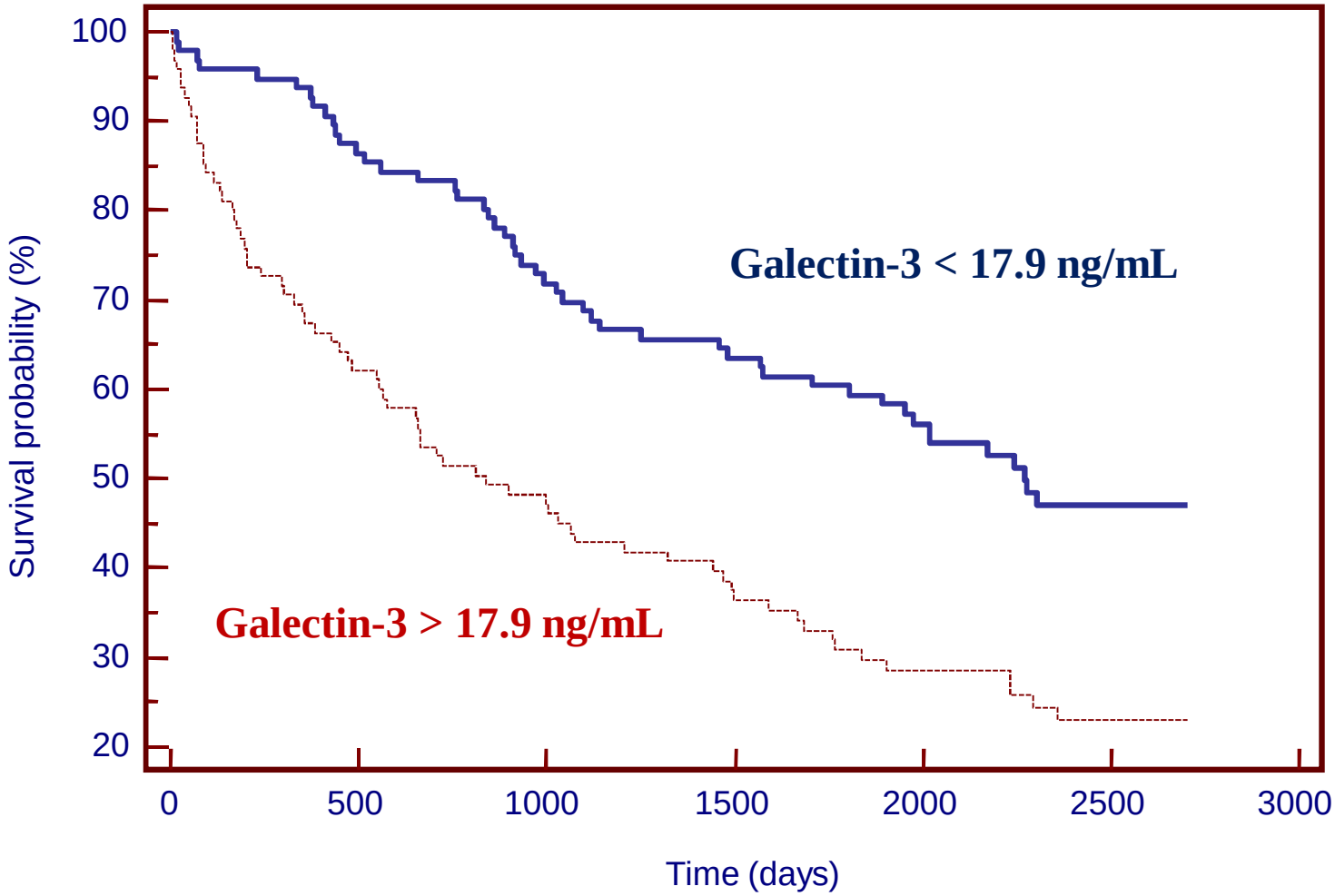
Relation with severity of HF



Gruson et al. AHA 2011

Circulating levels of Galectin-3 in HF (II)

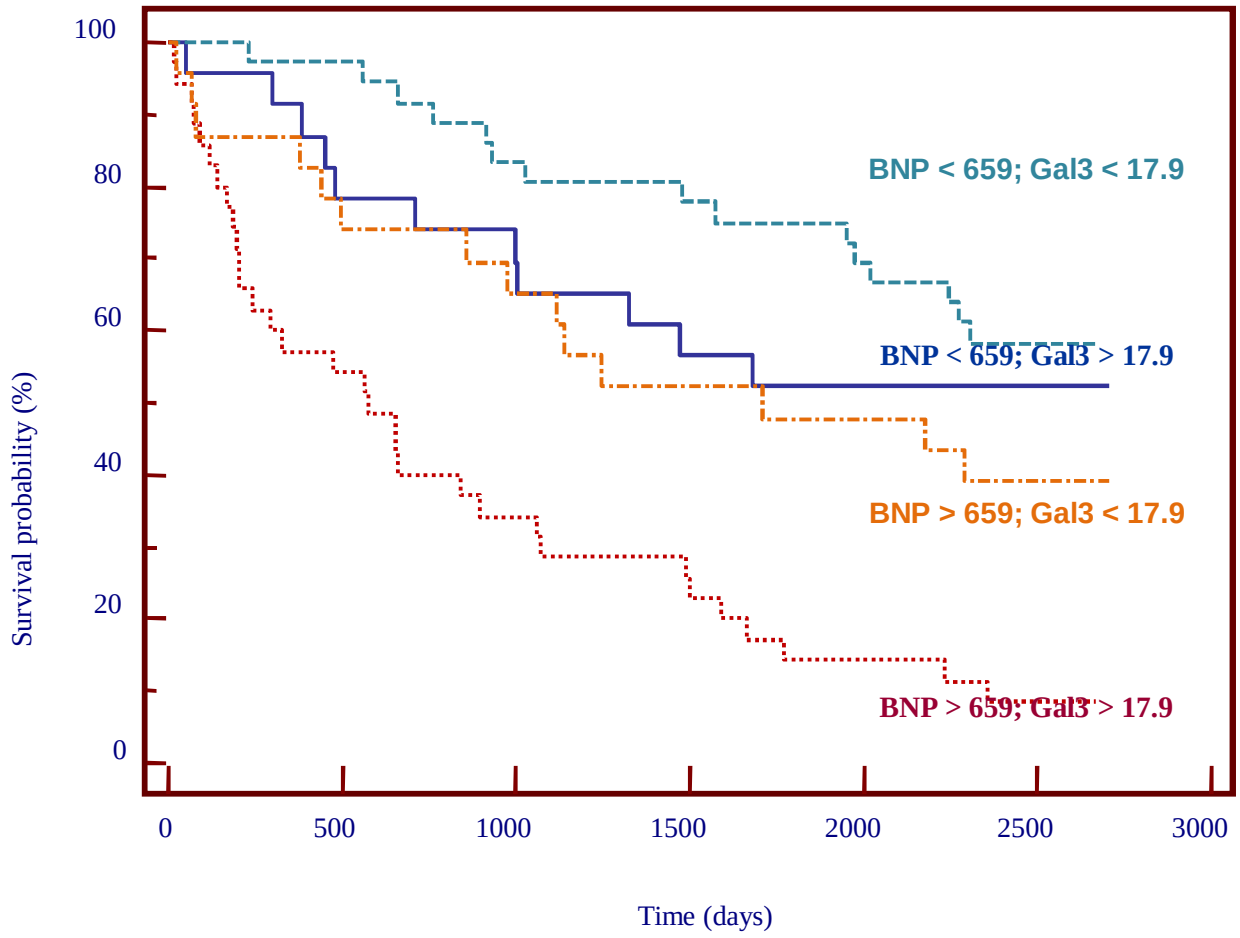
Galectin-3 as a prognostic biomarker in HF (n=193)



Gruson et al. AACC 2013

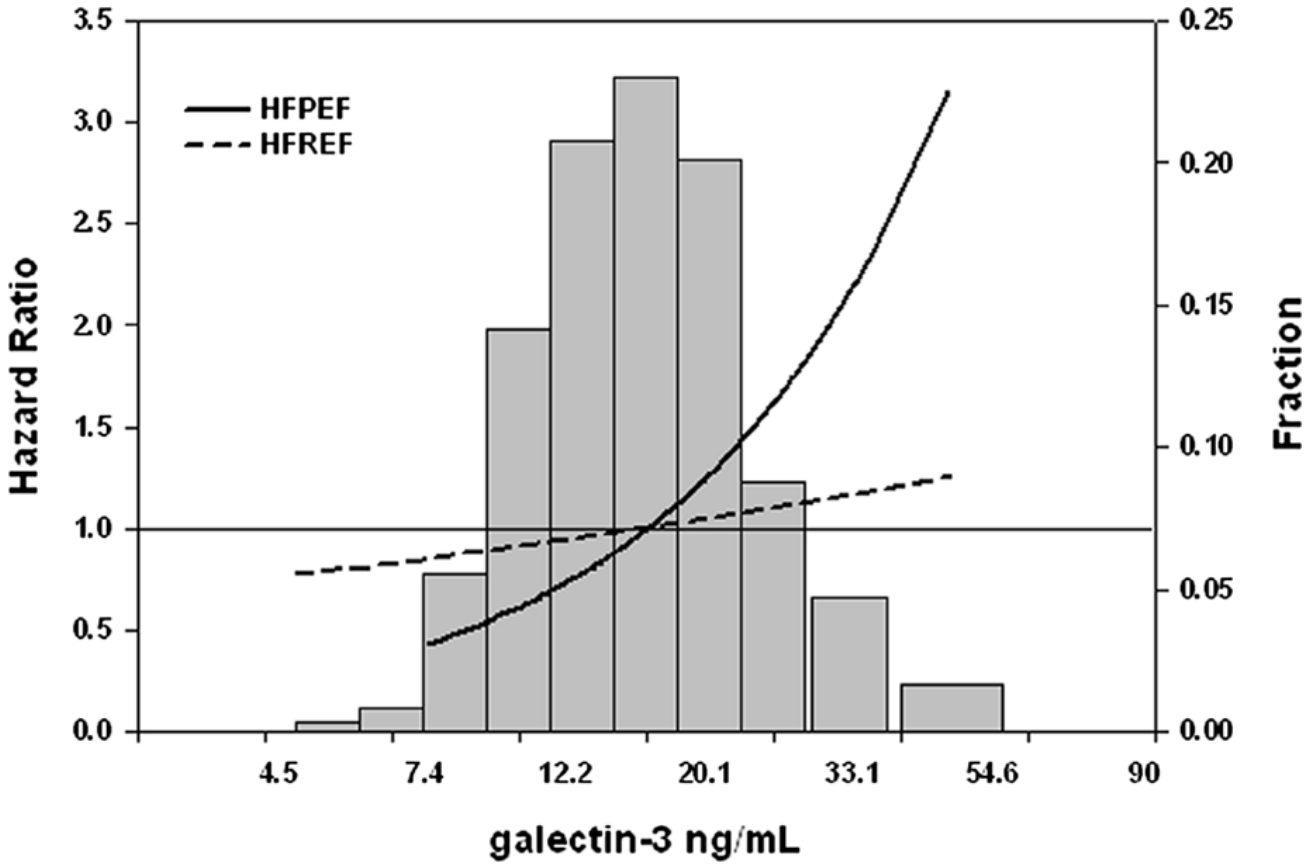
Circulating levels of Galectin-3 in HF (III)

Galectin-3 as a prognostic biomarker in HF (n=193)



Gruson et al. AACC 2013

Circulating levels of Galectin-3 in HF



De Boer et al., 2011

Galectin-3 predicts response to statin therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA).

Patients with ischaemic systolic HF enrolled in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) were randomly assigned to 10 mg/day of rosuvastatin or placebo.
Galectin-3 was measured in plasma.
The primary outcome was cardiovascular death, myocardial infarction, or stroke. Of 1492 patients, 411 had a primary event during a median follow-up of 32.8 months.

Among patients with below the median plasma concentrations of galectin-3 (Ò19.0 ng/mL), those assigned to rosuvastatin had a

-lower primary event rate [hazard ratio (HR) 0.65; 95% confidence interval (CI), 0.46-0.92; P= 0.014],
- lower total mortality (HR 0.70; 95% CI, 0.50-0.98; P= 0.038),
- lower event rate of all-cause mortality and HF hospitalizations (HR 0.72; 95% CI, 0.54-0.98; P= 0.017)

compared with placebo,

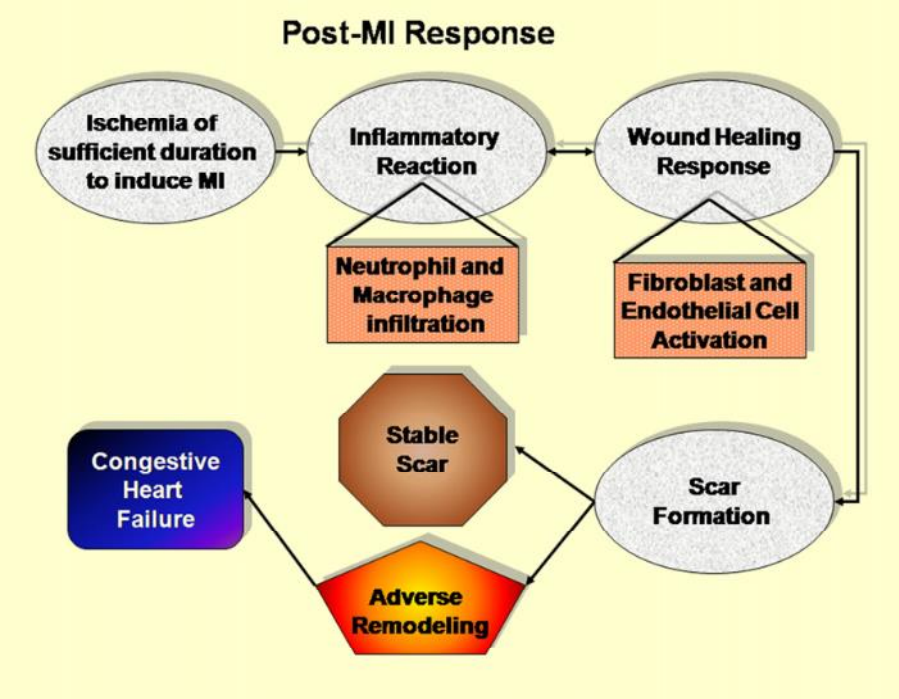
é .but no benefit was observed in patients with higher levels of galectin-3

Patients with systolic HF of ischaemic aetiology who have galectin-3 values <19.0 ng/mL may benefit from rosuvastatin treatmenté

Gullestad et al., 2012

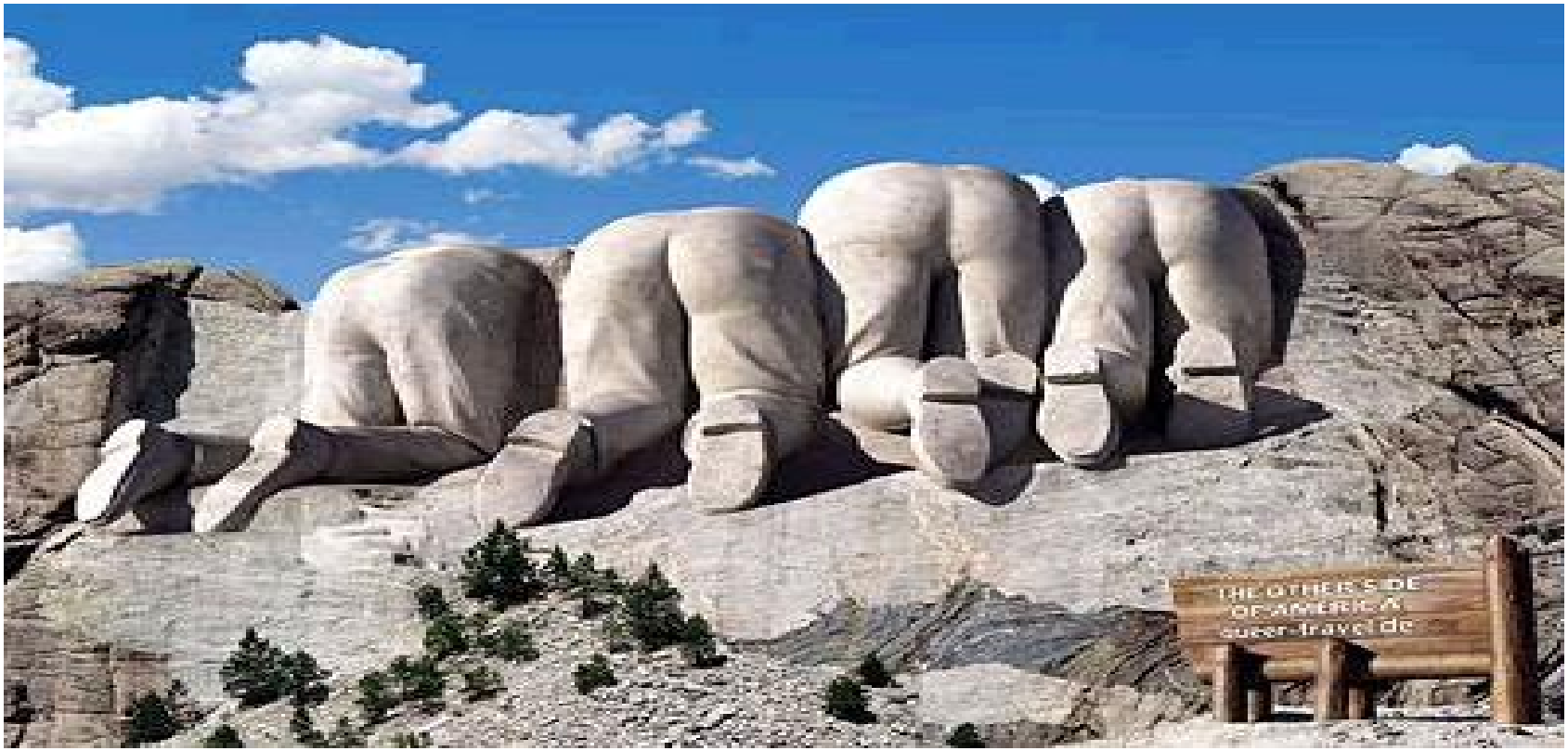
Gal-3, Cardiac Remodeling and Risk Stratification

- **Segmenting Heart Failure (HF):**
  - ***Non-remodeling HF***
    - Relatively good prognosis
    - Focus on cardiac function and underlying stressors
  - ***Remodeling HF***
    - Poor prognosis
    - Specific anti-remodeling agents
      - Eplerenone, spironolactone
      - Novel agents – e.g. aldosterone synthase inhibitor (LCI699)
    - Device therapy
      - Cardiac resynchronization therapy (CRT)
      - HeartNet™ Ventricular Support System



Lambert JM, et al. *Int J Cardiol* 2008;130:147–58

Galectin-3 Testing

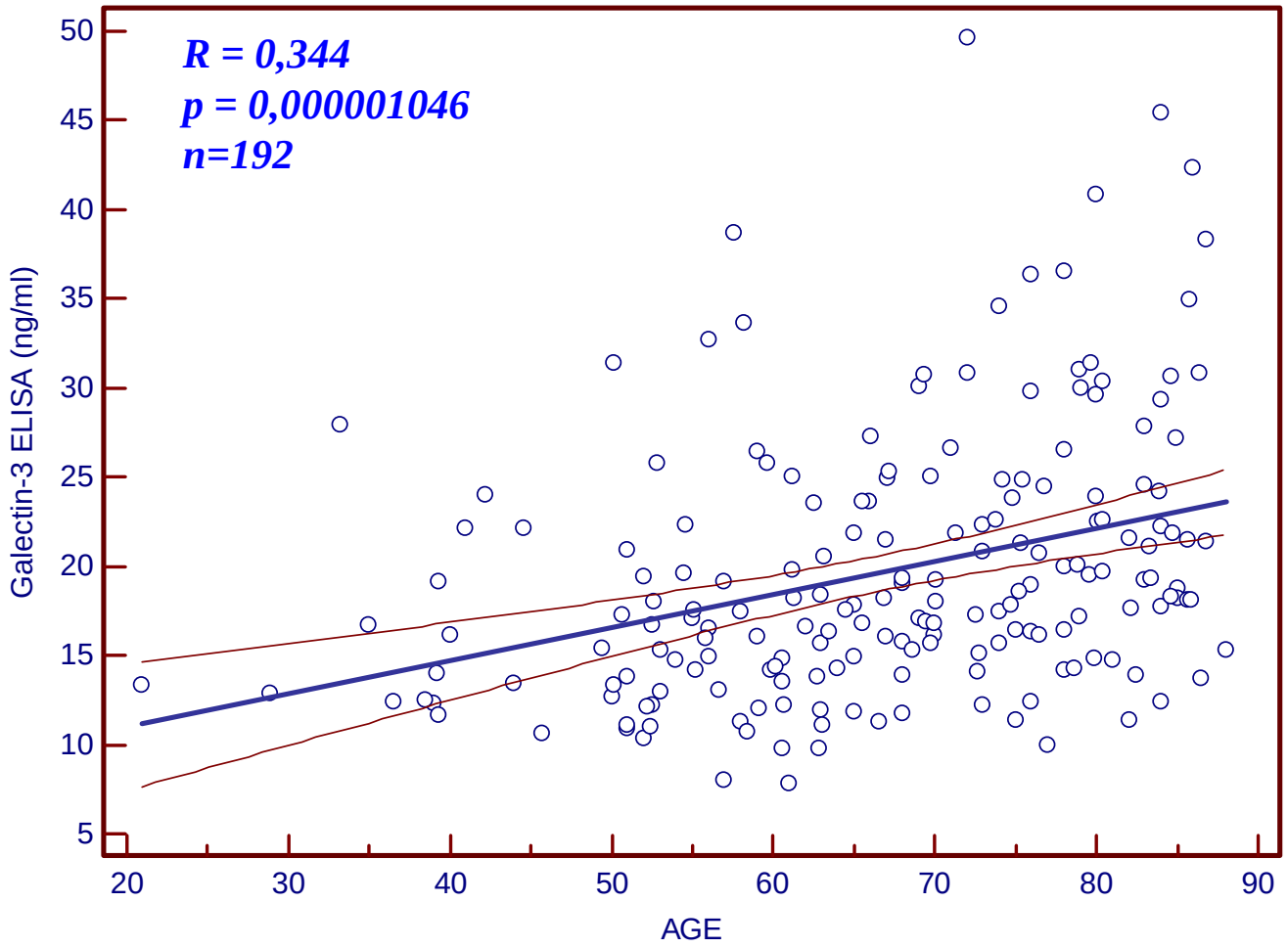


A look Behind the Scenes…

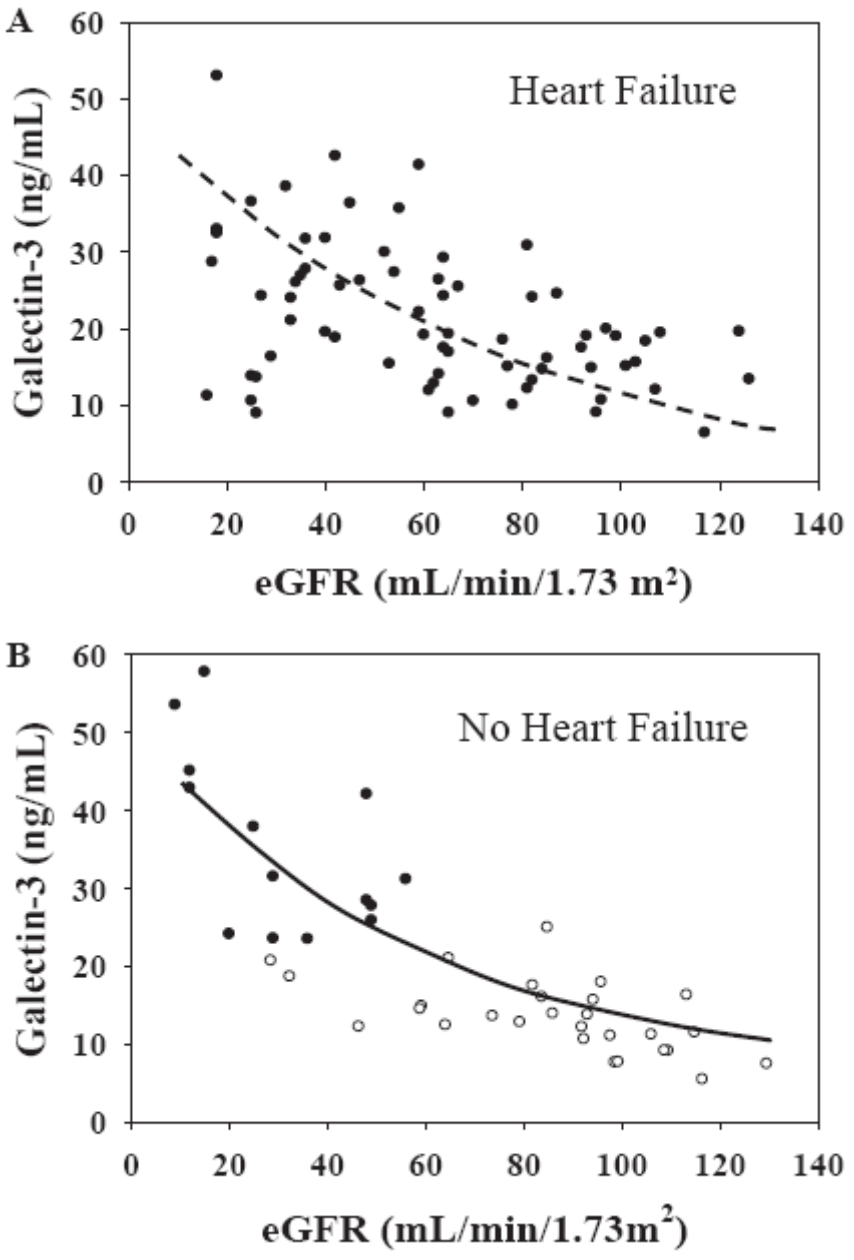
Accessibility?

How to measure Gal-3: Automated assays?

Confounding factors?



Confounding factors?



Cost effectiveness / Financingé

Galectin-3:

-A potential to guide interventions

- A potential to optimise the management of individual patients

- A potential to support the allocation of limited health care resources.

Table 2. End Points.*

End Point	B-Type Natriuretic Peptide Group (N=225)	Control Group (N=227)	P Value
Time to treatment — min			0.03†
Median	63	90	
Interquartile range	16–153	20–205	
Time to discharge — days			0.001†
Median	8.0	11.0	
Interquartile range	1.0–16.0	5.0–18.0	
Hospitalization — no. (%)	169 (75)	193 (85)	0.008
Admission to intensive care — no. (%)	33 (15)	54 (24)	0.01
Cost of intensive care — $			0.07
Median	874	1,516	
95% Confidence interval	423–1,324	989–2,043	
Total treatment cost — $			0.006
Median	5,410	7,264	
95% Confidence interval	4,516–6,304	6,301–8,227	
In-hospital mortality — no. (%)	13 (6)	21 (9)	0.21‡
30-day mortality — no. (%)	22 (10)	28 (12)	0.45‡
30-day readmission rate — no. (%)	26 (12)	23 (10)	0.63

* The time to treatment was defined as the interval from presentation at the emergency department to the initiation of the appropriate therapy according to the final discharge diagnosis.
† The Mann–Whitney U test was used.
‡ Fisher's exact test was used.

Mueller et al. NEJM, 2004

In Belgiumé

In the case of applying NP for diagnostic purposes the model simulates the number of avoided echocardiographies and the number of hospital days avoided (as in the KCE report).

We find an estimated saving per patient of ú859.

In the case of applying NP as monitoring tool,

the savings are obtained by reducing the number of hospital stays due to more adequate monitoring and adapting the patient management timely. It is assumed that 15% reduction in the number of hospitalisations can be achieved.

In that case, more than 4 million EUR can be saved per semester, already taking into account the cost of NP.

The total potential saving, the diagnostic and monitoring indication included,
amounts to 10.3 million EUR in year 1;
10.5 million EUR in year 2
and 10.7 million EUR in year 3

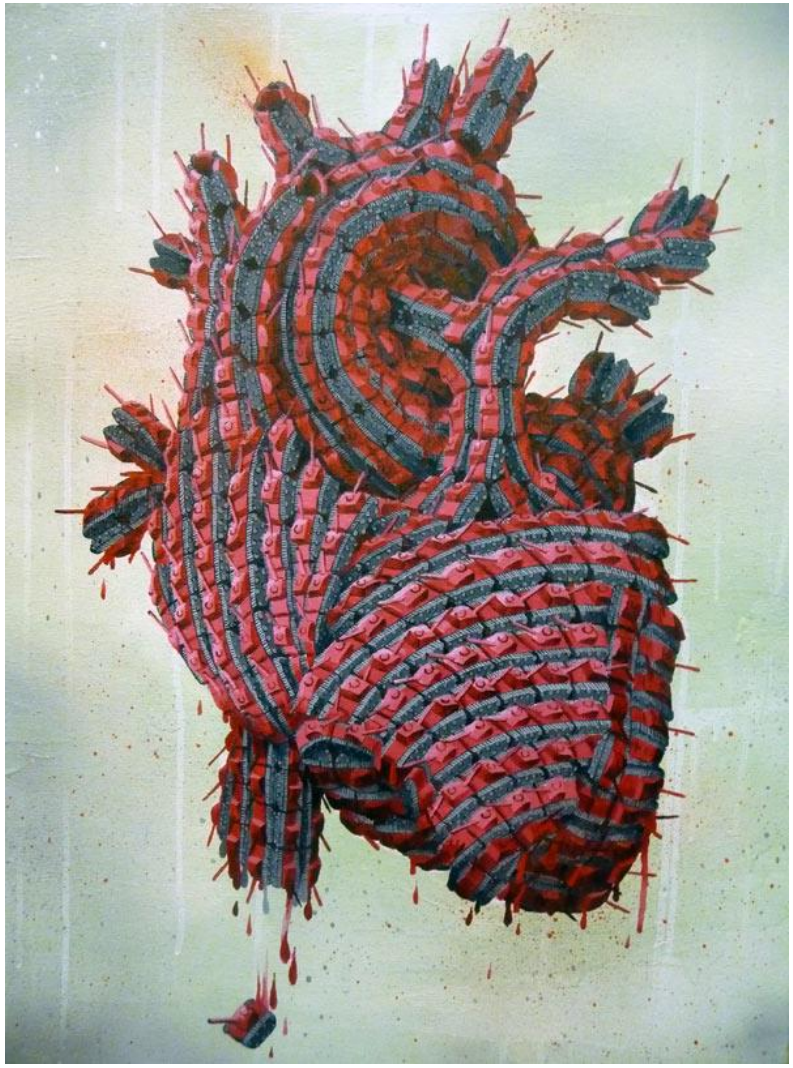
Thanks for your attention !

Il pleure dans mon coeur
Comme il pleut sur la ville ;
Quelle est cette langueur
Qui pénètre mon coeur ?

Ô bruit doux de la pluie
Par terre et sur les toits !
Pour un coeur qui s'ennuie,
Ô le chant de la pluie !

Il pleure sans raison
Dans ce coeur qui s'écoeure.
Quoi ! nulle trahison ?...
Ce deuil est sans raison.

C'est bien la pire peine
De ne savoir pourquoi
Sans amour et sans haine
Mon coeur a tant de peine !



Annual Symposium

Belgische Vereniging voor Klinische Biologie
Koninklijke Belgische Vereniging voor Klinische Chemie
Société Belge de Biologie Clinique
Société Royale Belge de Chimie Clinique

Address:

Auditoires Centraux
Cliniques Universitaires Saint –Luc
Avenue Hippocrate 10
1200 Brussels

By car:

Take E40 exit 20 and follow the signs
"UCL Saint-Luc"
When you enter the site from the Woluwelaan/ Boulevard de la Woluwe, take the first street on your right (Avenue Mounier).
After approximately 1km, you arrive at the parking Mounier. (Free on Saturday).

By public transport:

From Brussels-South train station
- take subway line 2 or 6 direction "Simonis (Elizabeth)"
- change lines at Arts-Loi / Kunst-Wet to line 1 direction "Stockel/Stokkel"
- take the exit "Alma"

Saturday, October 5th 2013

The Changing Landscape of Laboratory Medicine

BVKB - SBBC

B VKC S BCC

Location:

Auditoires Centraux
Cliniques Universitaires Saint-Luc
Avenue Hippocrate 10
1200 Brussels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Special Events
21 IFCC-EFLM
European Congress of Clinical Chemistry
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Palais des Congrès
de Paris
EuroMedLab JIB 2015
Exhibition, 22 - 24 June
EUROMEDLAB - JIB
EXHIBITION
PARIS 2015
DATE TO FOCUS ON
1 February 2015
POSTER ABSTRACT
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30 April 2015
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