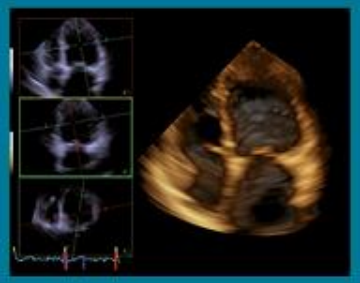


EuroValve

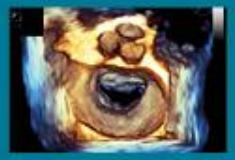
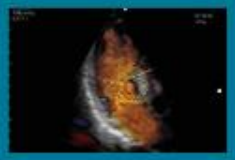
October 24-25, 2014

Emerging biomarkers in valvular heart disease (aortic stenosis)

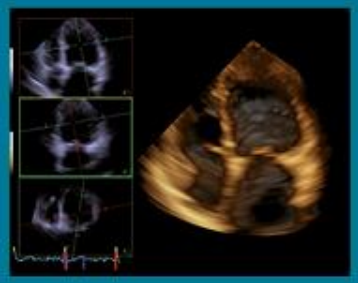
Cécile Oury, PhD

GIGA Cardiovascular Sciences

Université de Liège

www.eurovalvecongress.com



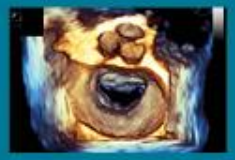
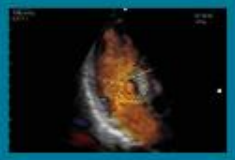
EuroValve

October 24-25, 2014

Faculty disclosure

Cécile OURY

I have **no financial relationships** to disclose

www.eurovalvecongress.com

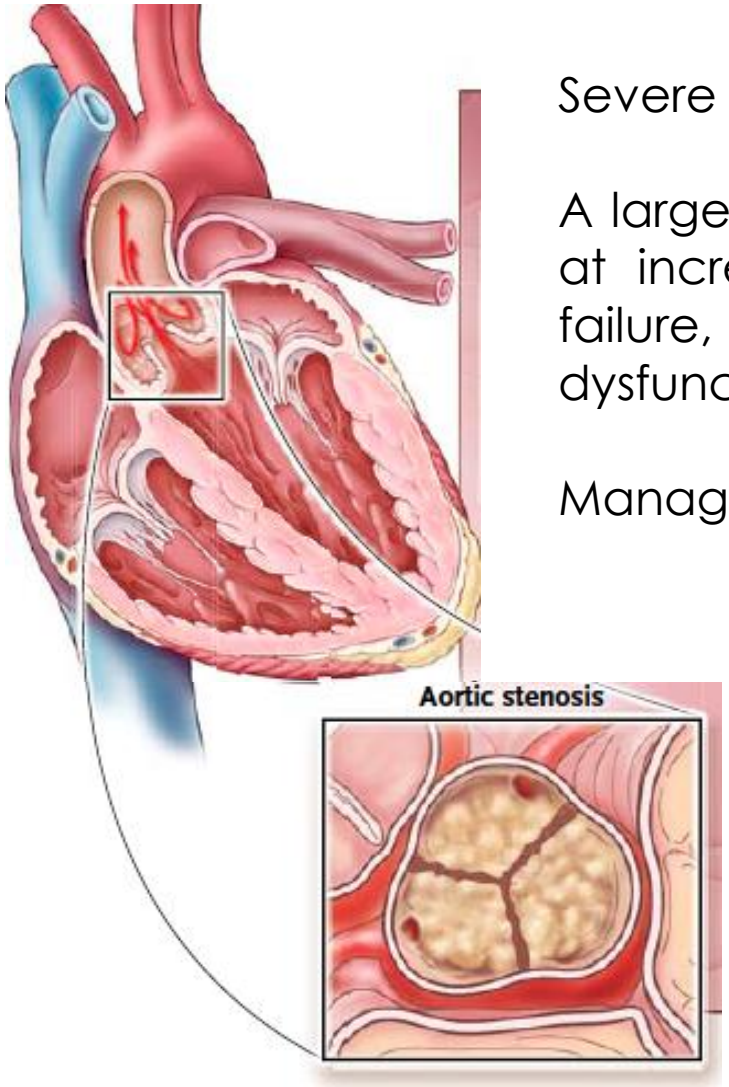
Biomarker: definition

"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention."

Include any representation of a biological process, including circulating molecules, genetic markers, cellular markers, results of imaging, or findings on physical examination

Biomarkers Definitions Working Group. Clin Pharmacol Ther. 2001;69:89–95

Aortic stenosis



Severe AS affects > 3-7 % of patients over 65 years.

A large majority of patients are asymptomatic and are at increased risk for untoward events (death, heart failure, symptomatic deterioration, ventricular dysfunction).

Management : controversial. Risk stratification required.

Diagnosis: imaging techniques, high cost, skill.

- Need for easily accessible blood biomarkers that can provide incremental diagnostic and prognostic information to the existing tests in asymptomatic patients.
  - Severity
  - Progression
  - outcome

Biomarkers

Hypothesis-driven Biomarkers

« omics » Biomarkers

Advanced age, male sex, smoking
Hypertension, diabetes,
High LDL-C, Lp(a) levels,
obesity, overweight,
CKD, congenital AV malformation

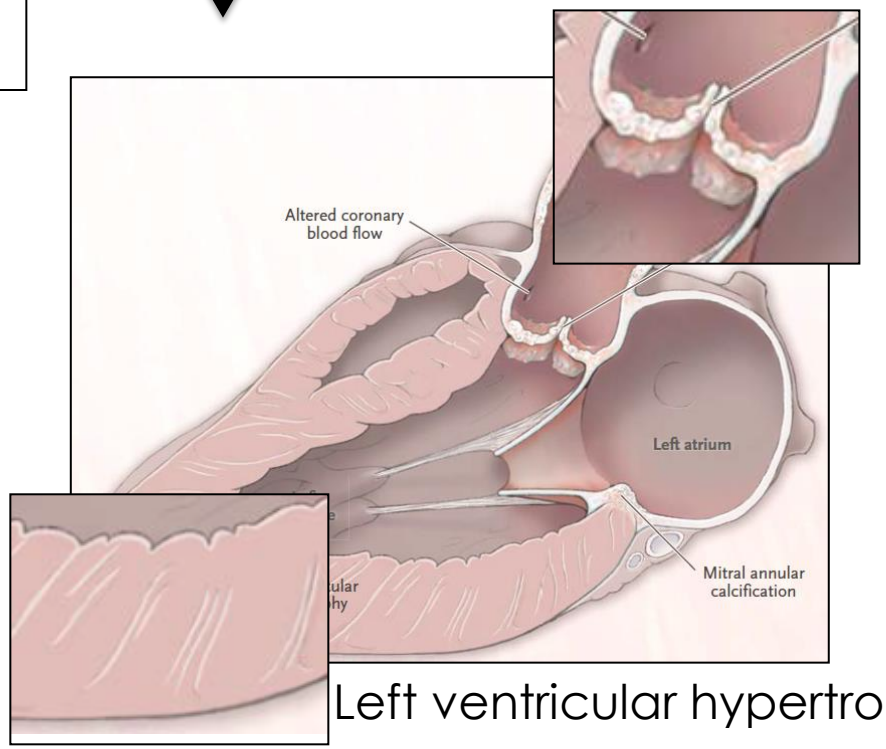
↓

Disease progression

Aortic stenosis

?

Leaflet calcification

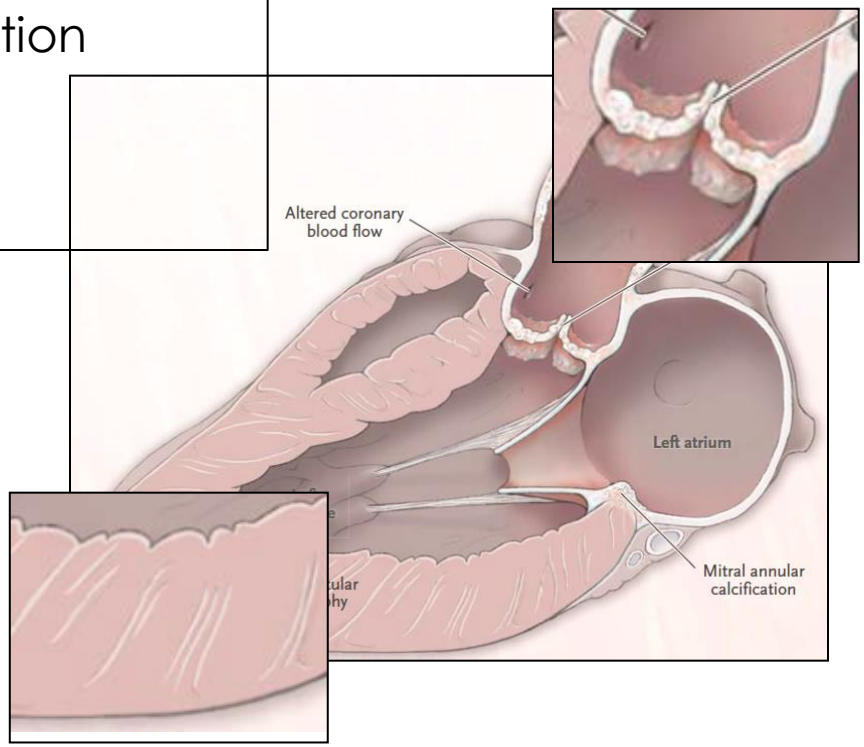


Left ventricular hypertrophy

Mechanisms of disease progression:
Inflammation
Lipid infiltration
Myofibroblast differentiation
Shear stress, platelet activation
Cardiac angiotensin II production
Procalcific stimuli
ECM deposition
Remodeling

Hypothesis-driven Biomarkers

Leaflet calcification

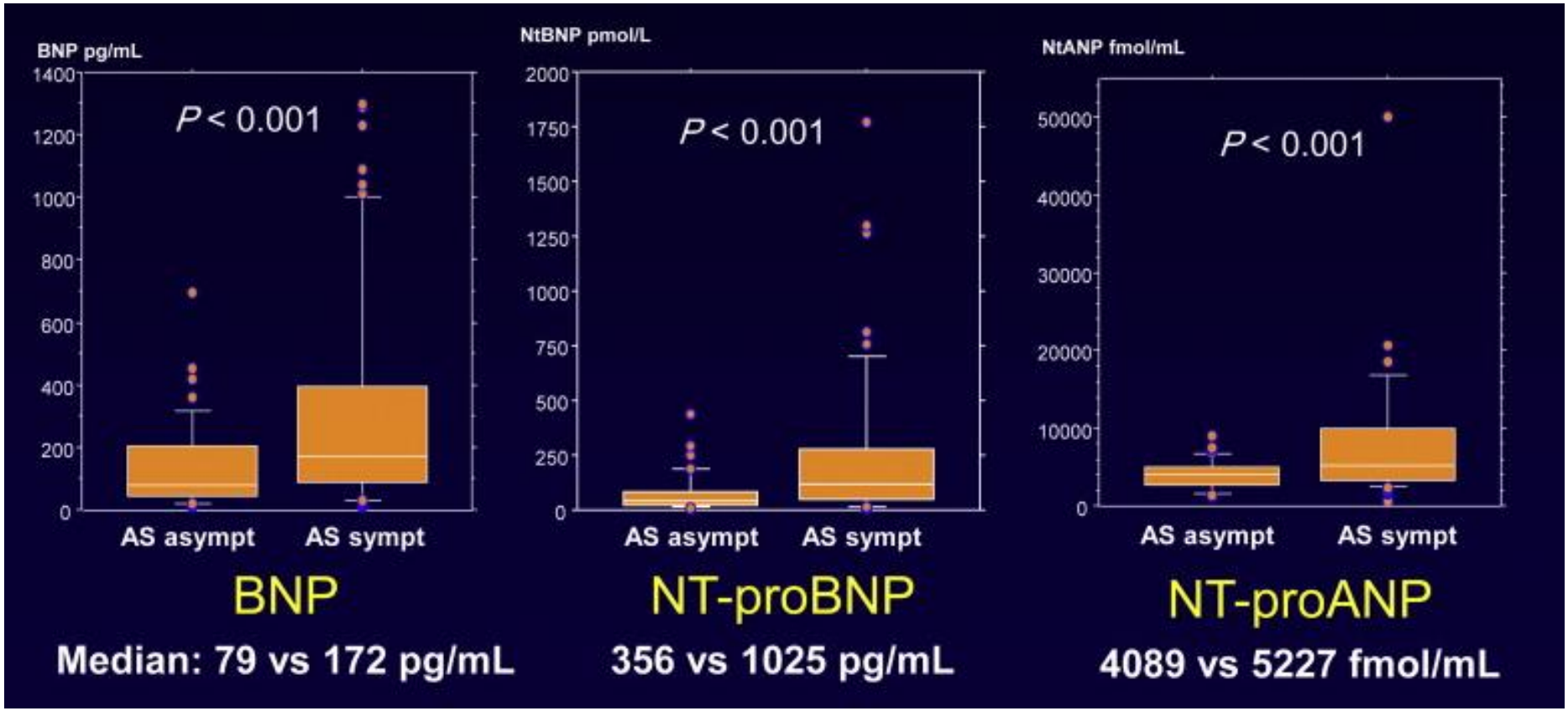


Left ventricular hypertrophy

Natriuretic peptides

Markers of myocardial response to intracardiac pressure increases

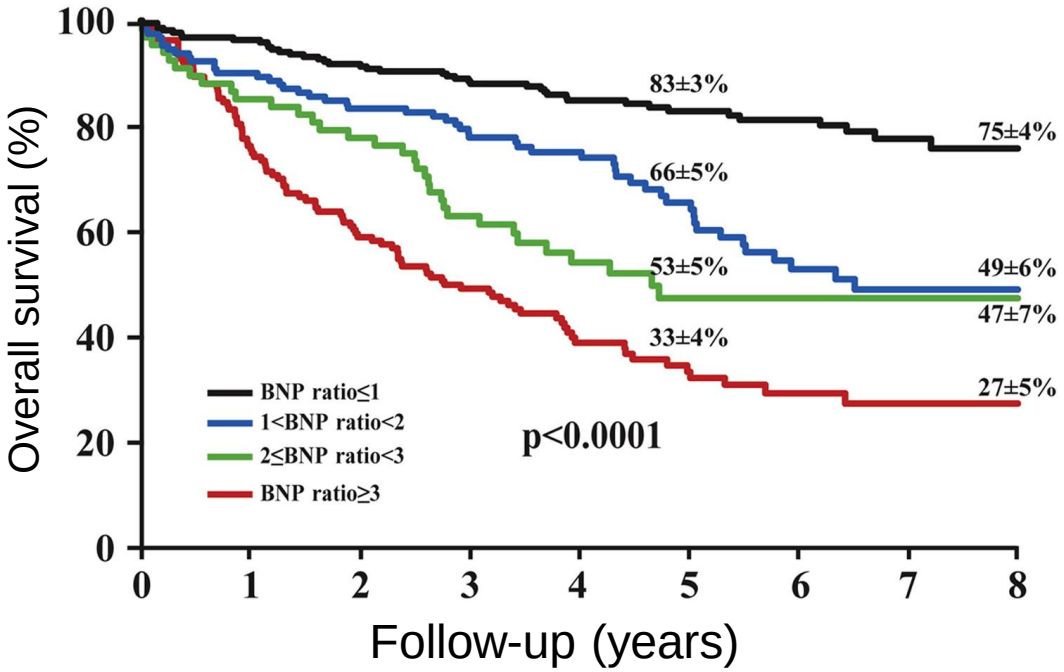
Natriuretic peptides are significantly higher in symptomatic patients compared with asymptomatic patients with severe AS



Bergler-Klein et al. Circulation 2004

Natriuretic peptides

BNP clinical activation is associated with excess long-term mortality incrementally and independently of all baseline characteristics



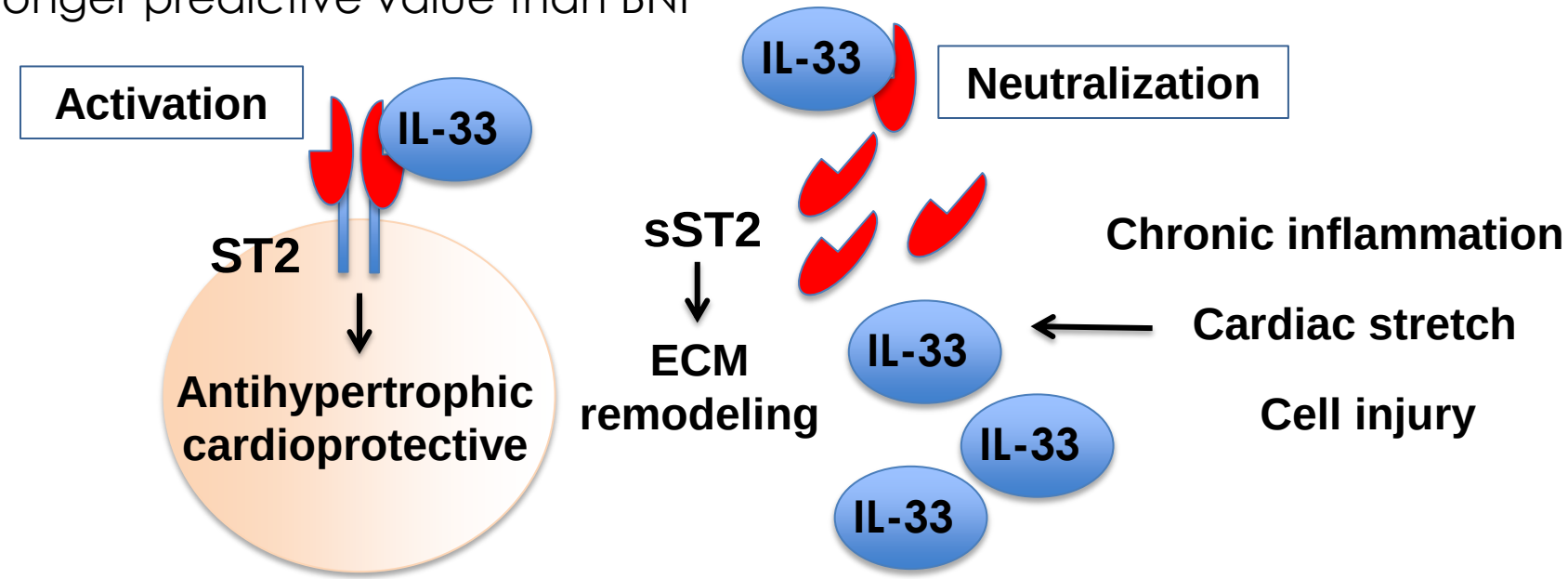
Asymptomatic with normal LVEF AS patients

BNP clinical activation = BNP ratio (measured BNP/maximal normal BNP value specific to age and sex) **>**1

Clavel et al. J Am Coll Cardiol 2014

Soluble ST2

- Member of the IL-1 receptor family.
- Elevated concentrations of sST2: worse prognosis of acute and chronic HF
- Stronger predictive value than BNP

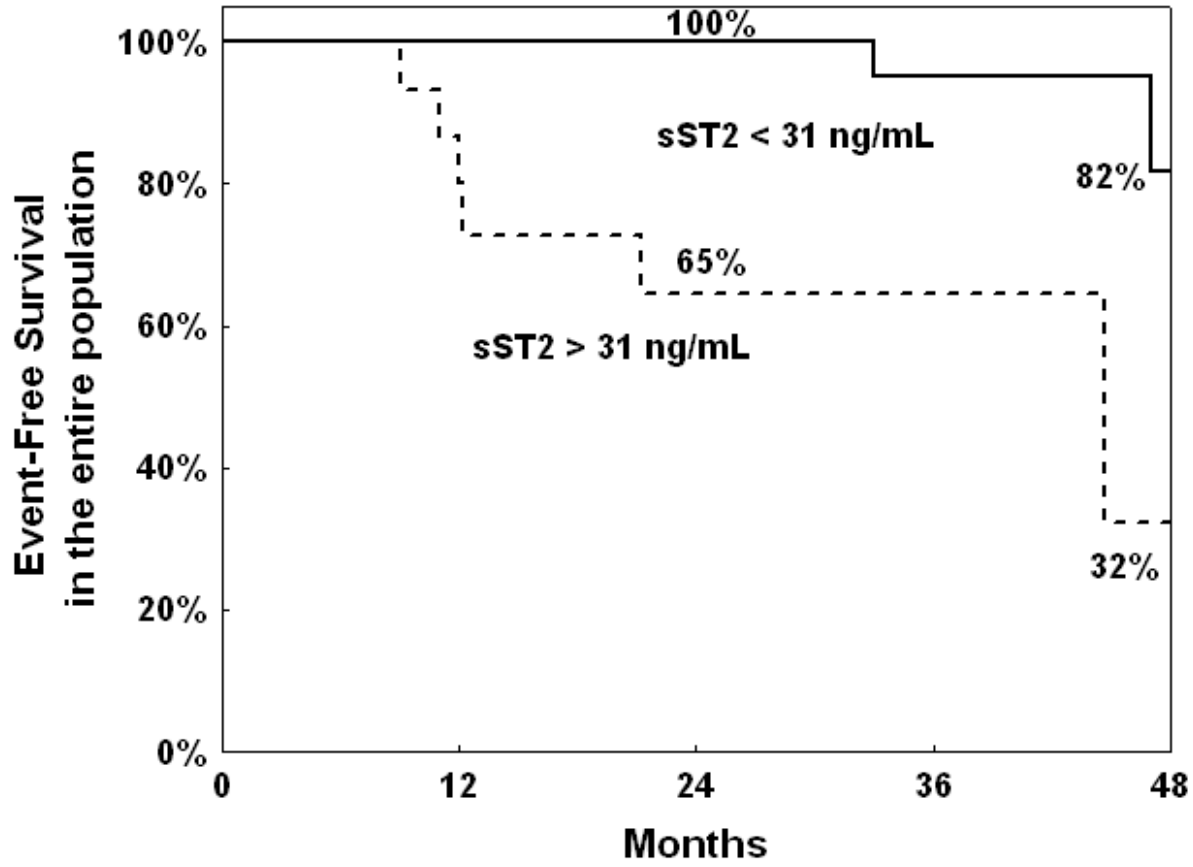


➢ Involved in at least three pathophysiological mechanisms of AS: inflammation/remodeling,fibrosis/cardiac stretch

Bayes-Genis et al JACC 2014; Mueller and Dieplinger Expert Rev Mol Diagn 2014

Soluble ST2

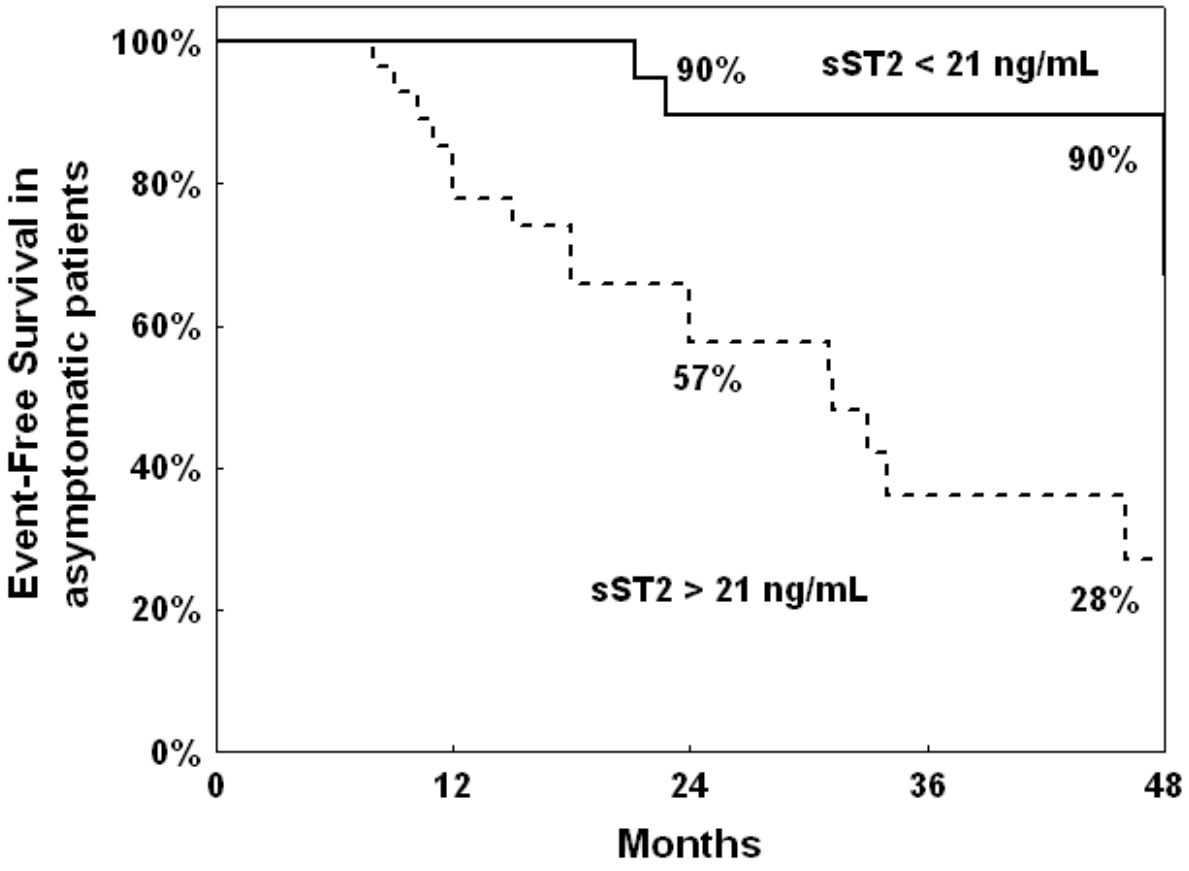
Independently predicts mortality in aortic stenosis



Lancellotti et al. 2014

Soluble ST2

Independently predicts mortality in aortic stenosis in asymptomatic patients



Lancellotti et al. 2014

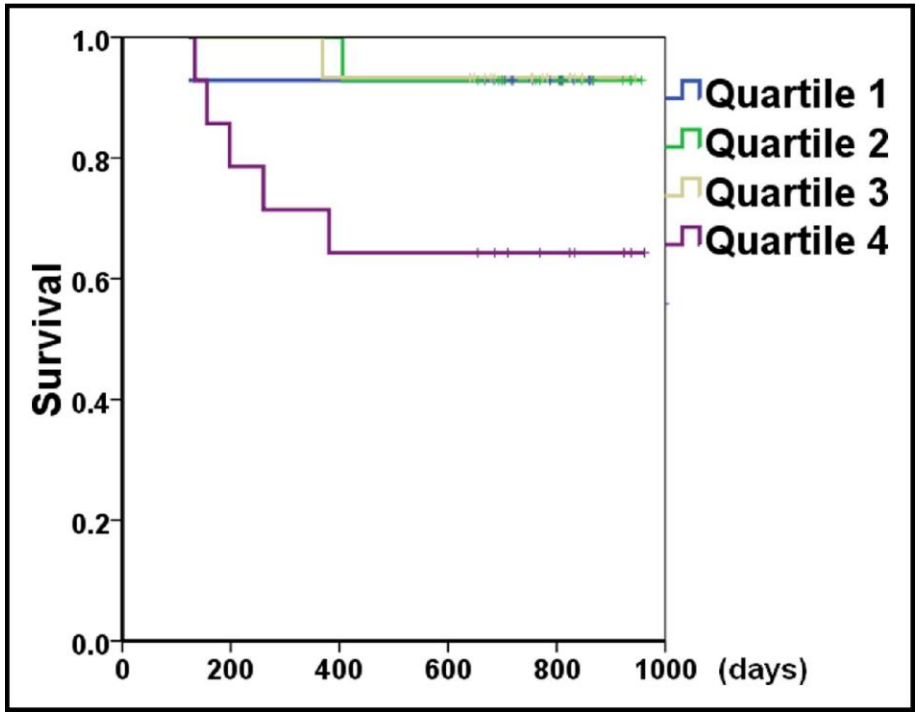
Troponins

High sensitivity assays

cardiac troponins circulate in a variety of acute and chronic cardiac and non-cardiac disease conditions, including acute heart failure and chronic symptomatic and asymptomatic left ventricular dysfunction

Troponins

High hs-TnT levels: worse prognosis in moderate to severe **AS**



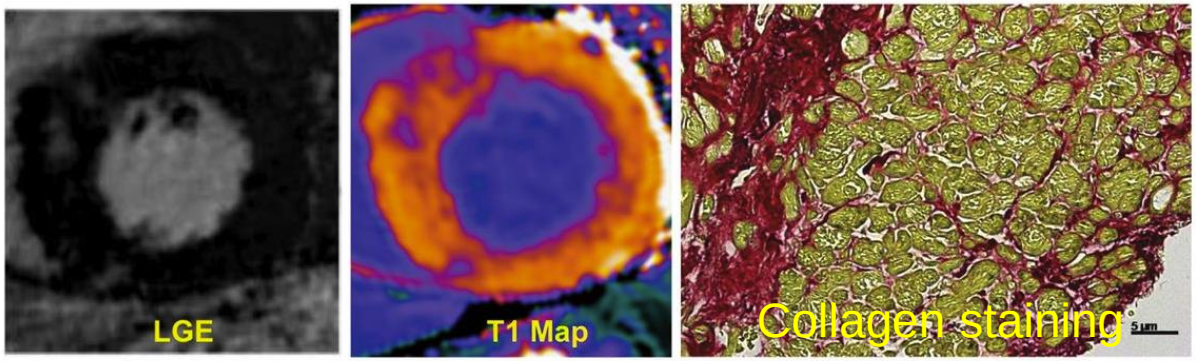
Left ventricular mass is a major determinant of circulating hs-TnT levels

Rosjo et al. Am J Cardiol 2011

Troponins

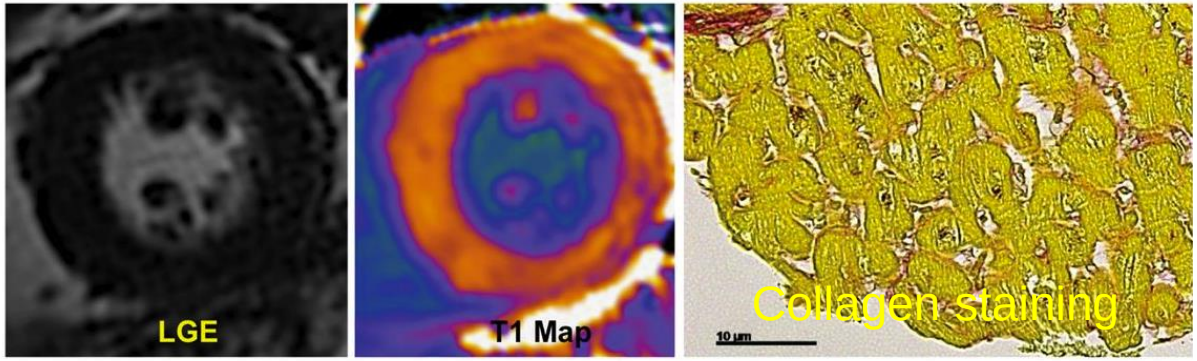
High-sensitivity troponin I concentrations: marker of advanced hypertrophic response and adverse outcomes in AS with normal LVEF

P1



Peak aortic jet velocity: 4.8 m/s
LV mass index: 114 g/m^2
Plasma cTnI: 11.9 ng/L

P2



Peak aortic jet velocity: 5.1 m/s
LV mass index: 81 g/m^2
Plasma cTnI: 2.5 ng/L

- High sensitivity troponins seem to reflect myocardial remodeling and fibrosis

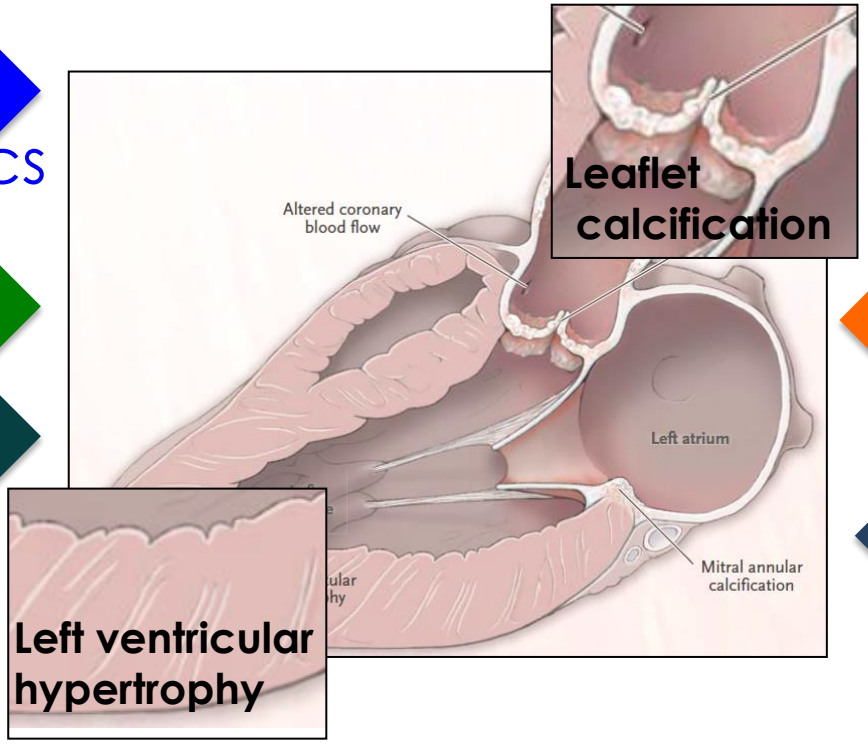
Chin et al. Eur Heart J 2014

« omics » biomarkers

transcriptomics

genomics

epigenomics



proteomics

metabolomics

interactomics

- Analysis of biomolecules on a large scale
- Global integrated view of molecular and cellular processes
- Basis for a highly directed **personalised and predictive medicine**
- Impact on health and disease

Genomics

Genetic Associations with Valvular Calcification and Aortic Stenosis

Genome wide association study (n=6942 patients)

- One SNP in the **lipoprotein(a)** locus (*LPA)* locus reaches genomewide significance for the presence of aortic valve calcification (CT scanning) across multiple ethnic groups
- Correlation of genetically determined Lp(a) levels and aortic valve calcification
- *LPA* genotype is associated with incident clinical aortic stenosis and aortic-valve replacement

Lp(a):

- cholesterol-rich particle (apolipoprotein B100 + apolipoprotein(a))
- risk factor for coronary artery disease
- accumulate in both early-stage and end-stage aortic-valve lesions

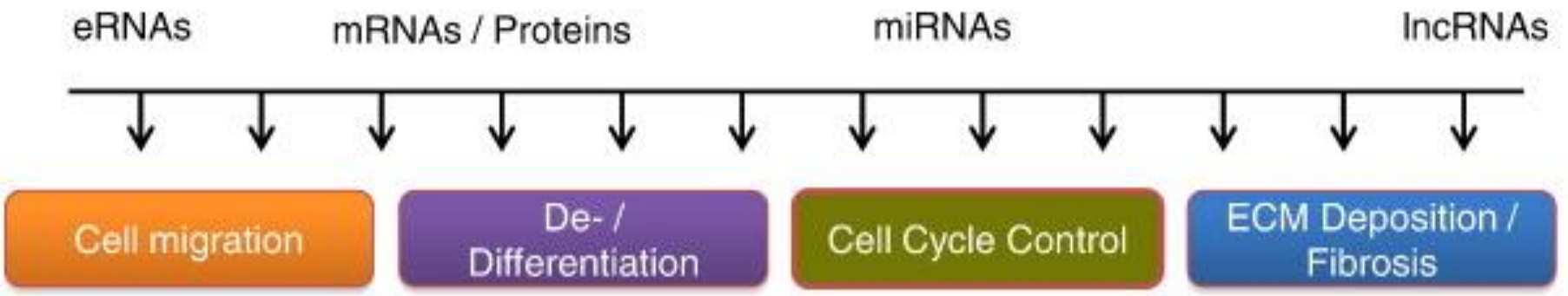
- ➢ Causal relationship Lp(a) / aortic valve disease
- ➢ Lowering Lp(a) levels to slow down disease progression ?

Thanassoulis et al. N Engl J Med 2014

Transcriptomics

Small and long non-coding RNAs in cardiac homeostasis

Gene regulatory networks



Targeted pathways

Ounzain et al BBA 2014

Studies on miRNA in aortic stenosis

Patient cohort	Samples	Observation	References
9 patients (AS versus aortic insufficiency requiring AVR)	Aortic valve leaflets	Decreased expression of miR-26a, miR-30b, and miR-195 in the aortic valves of patients requiring AVR due to AS	Nigam et al. *J Heart Valve Dis* 2010
46 AS patients requiring AVR	LV intraoperative biopsies	**miR-133a** predict regression of **LV hypertrophy** (1 year) after valve replacement	Villar et al. *Heart* 2011
19 biscupid aortic valve versus 17 tricuspid aortic valve patients	aortic valve leaflets	Decreased expression of **miR-141** in bicuspid aortic valves associated with increased BMP-2 and **calcification**	Yanagawa et al. *J Thorac Cardiovasc Surg* 2012
75 AS patients requiring AVR versus 32 surgical controls	LV intraoperative biopsies + plasma	High expression of **miR-21** correlates with mean **transvalvular gradient and LV fibrosis**	Villar et al. *Int J Cardiol* 2013
5 AS patients before TAVI versus healthy controls	LV intraoperative biopsies + plasma	Decreased **miR-1** correlates with increased soluble FABP3 in AS patients upon **LVH**	Varrone et al *J Am Coll Cardiol* 2013

Studies on miRNA in aortic stenosis

Patient cohort	Samples	Observation	References
112 patients with moderate to severe AS versus 40 healthy controls	Plasma	levels of **miR-1, miR-133**, and miR-378 **predict LVH** in patients with AS miR-378 levels correlate with left ventricular mass index	Chen et al. *PLoS One* 2014
57 patients with moderate to severe AS versus 10 healthy controls	Plasma	Increased **miR-210** levels in AS patients comparable to increment in NT-proBNP levels miR-210 levels associate with **higher mortality** (3.5 year follow-up)	Rosjo et al. *PLoS One* 2014
28 patients with moderate to severe AS versus 10 healthy controls	endomyocardial biopsies and necropsies	down-regulation of **miR-122** in severe myocardial fibrosis in AS, through **TGF-β1 up-regulation**	Beaumont et al. *Clin Sci (Lond)* 2014
74 AS patients requiring AVR	LV intraoperative biopsies + plasma	miR-133a as a positive predictor of the hypertrophy reversibility after surgery	Garcia et al. *J Am Heart Assoc* 2013
10 AS patients requiring AVR	LV intraoperative biopsies	**miRNA-30b** regulates aortic **valvular calcification and apoptosis** through direct targeting of Runx2, Smad1, and caspase-3	Varrone et al *J Thorac Cardiovasc Surg* 2013

Studies on miRNA in aortic stenosis

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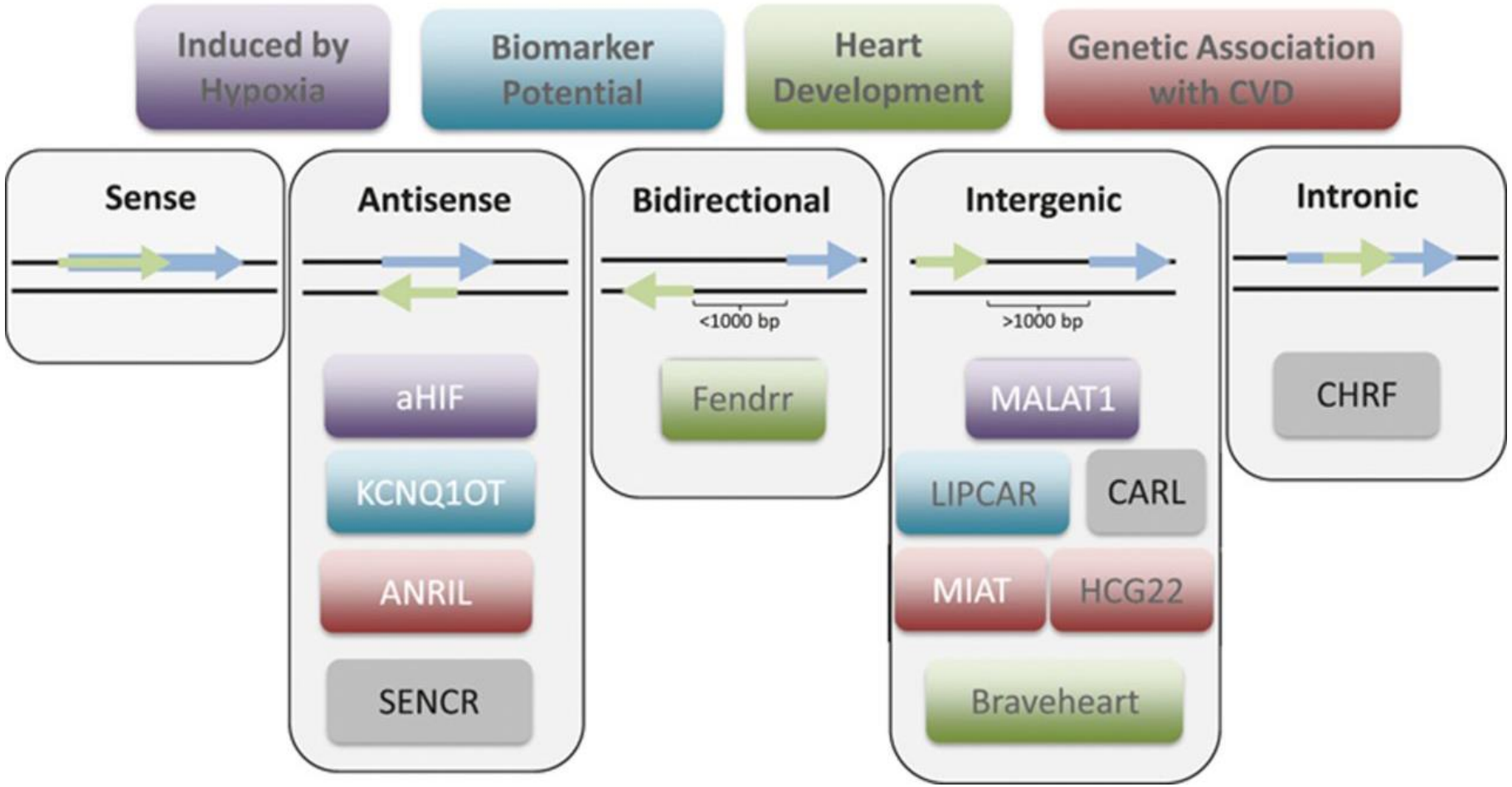
Transcriptomics

- A few miRNA have been involved in LVH or fibrosis
- Circulating miRNA levels reflect myocardial expression
- Plasma levels of miR-210 correlate with BNP levels and increased mortality

Transcriptomics

Long non-coding RNAs: novel attractive biomarkers



Skroblin P , and Mayr M Circ Res. 2014

Transcriptomics

Genome-wide profiling of the cardiac transcriptome after myocardial infarction identifies novel heart-specific long non-coding RNAs

- Mouse model
- heart-specific lncRNAs
- relevant to maladaptive remodelling, cardiac function

lncRNAs in aortic stenosis

Downregulation of Novlnc44
in LV biopsies from AS patients

Ounzain et al Circ 2014

Biomarkers: the future is bright

Biomarkers will be more and more used in patients with VHD

- in the diagnostic work-up
- to characterize the symptomatic status
- to predict the outcome
- to evaluate the impact of treatment

➢ Toward a multi-biomarker approach ?