Emerging biomarkers in valvular heart disease (aortic stenosis)

Cécile Oury, PhD

Cardiovascular Sciences
Faculty disclosure

Cécile OURY

I have no financial relationships to disclose
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
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 are significantly higher in symptomatic patients compared with asymptomatic patients with severe AS.
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

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

- High sensitivity troponins seem to reflect myocardial remodeling and fibrosis

**P1**
- Peak aortic jet velocity: 4.8 m/s
- LV mass index: 114 g/m²
- Plasma cTnl: 11.9 ng/L

**P2**
- Peak aortic jet velocity: 5.1 m/s
- LV mass index: 81 g/m²
- Plasma cTnl: 2.5 ng/L

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?

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

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

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

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

Transcriptomics

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

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

IncRNAs in aortic stenosis
Downregulation of NovInc44 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?