ORIGINAL ARTICLE

Determinants and prognostic value of Galectin-3 in patients with aortic valve stenosis

Dimitri Arangalage,1,2,3 Virginia Nguyen,1,2,3 Tiphaine Robert,4 Maria Melissopoulou,1 Tiffany Mathieu,7 Candice Estellat,5 Isabelle Codogno,1 Virginie Huart,6 Xavier Duval,7 Claire Cimadevilla,8 Alec Vahanian,1,2,3 Monique Dehoux,4 David Messika-Zeitoun1,2,3

ABSTRACT

Objective Myocardial fibrosis has been proposed as an outcome predictor in asymptomatic patients with severe aortic stenosis (AS) that may lead to consider prophylactic surgery. It can be detected using MRI but its widespread use is limited and development of substitute biomarkers is highly desirable. We analysed the determinants and prognostic value of galectin-3, one promising biomarker linked to myocardial fibrosis.

Methods Patients with at least mild degenerative AS enrolled between 2006 and 2013 in two ongoing studies, COFRASA/GENERAC (COhort Francaise de Rétrécissement Aortique du Sujet Ageé/GENEtique du Rétrécissement Aortique), aiming at assessing the determinants of AS occurrence and progression, constituted our population.

Results We prospectively enrolled 583 patients. The mean galectin-3 value was 14.3±5.6 ng/mL. There was no association between galectin-3 and functional status (p=0.55) or AS severity (p=0.58). Independent determinants of galectin-3 were age (p=0.008), female gender (p=0.04), hypertension (p=0.002), diabetes (p=0.02), reduced left ventricular ejection fraction (p=0.01), diastolic dysfunction (E/e’, p=0.02) and creatinine clearance (p<0.0001). Among 330 asymptomatic patients at baseline, galectin-3 was neither predictive of outcome in univariate analysis (p=0.73), nor after adjustment for age, gender, rhythm, creatinine clearance and AS severity (p=0.66).

Conclusions In a prospective cohort of patients with a wide range of AS severity, galectin-3 was not associated with AS severity or functional status. Main determinants of galectin-3 were age, hypertension and renal function. Galectin-3 did not provide prognostic information on the occurrence of AS-related events. Our results do not support the use of galectin-3 in the decision-making process of asymptomatic patients with AS.

Trial registration number COFRASA NCT00338676 and GENERAC CT00647088

INTRODUCTION

Current guidelines recommend surgery in patients with severe aortic stenosis (AS) and either symptoms or left ventricular (LV) systolic dysfunction because of poor survival under conservative management.1 2 In contrast, the management of asymptomatic patients remains debated due to the risk of sudden death and irreversible myocardial dysfunction without preceding symptoms on one hand and the operative risk and the risk of prosthetic valve complications on the other. Thus, the identification of subsets of asymptomatic patients who may benefit from an early intervention is an important clinical goal.

The increased afterload associated with AS triggers a hypertrophic response in the LV. Although initially adaptive, patients ultimately progress to heart failure and the transition from adaptation to decompensation is related to the occurrence of myocardial fibrosis. Myocardial fibrosis is an independent predictor of cardiovascular morbidity and mortality and can be accurately detected using MRI.3 4 5 However, the widespread use of MRI has been limited by cost, availability and patient suitability and its use remains mainly limited to research purposes underlining the crucial need for the development of methods for assessing myocardial fibrosis that could be easily and widely used in clinical practice.

Galectin-3 is an emerging biomarker that has been linked to myocardial fibrosis, tissue remodelling and heart failure development and has been shown to be associated with heart failure severity.6 11 Despite the numerous publications linking galectin-3 to chronic heart failure (CHF) and myocardial fibrosis, studies focusing on AS have seldom been reported and were mainly carried out following aortic valve replacement.12 13 In this study, we seek to analyse the determinants and prognostic value of galectin-3 in a large prospective cohort of patients with AS.

METHODS

Study population—the COFRASA-GENERAC cohort

Patients with at least mild degenerative AS, either on bicuspid or tricuspid valve leaflets, enrolled between November 2006 and July 2013 in two ongoing prospective clinical studies, COFRASA (COhorte Francaise de Rétrécissement Aortique du Sujet Ageé, clinicalTrial.gov number NCT00338676) and GENERAC (GENEtique du Rétrécissement Aortique, clinicalTrial.gov number NCT00647088), aiming at assessing the determinants of AS occurrence and progression constituted our study population. Exclusion criteria were AS due to rheumatic valve disease or radiotherapy, history of infective endocarditis, more than mild associated valvular disease and severe respiratory or renal insufficiency (creatinine clearance ≤30 mL/min). Clinical,
Valvular heart disease

biological measurements including galectin-3 and echocardiographic evaluations were performed at study entry for all patients. Asymptomatic patients were contacted every 6 months and seen at our research centre every year. The study was approved by our regional ethics committee. All patients provided written informed consent.

Clinical assessment

Medical history and cardiovascular risk factors were prospectively recorded. A physical examination and an ECG were performed at study entry. The body mass index (BMI) was calculated and obesity defined as a BMI >30 kg/m². Coronary artery disease (CAD) was defined as a history of angina, coronary angioplasty, coronary artery bypass or myocardial infarction. Experienced clinicians blinded to galectin-3 values assessed symptomatic status. The severity of dyspnoea was graded according to the New York Heart Association (NYHA) functional classification. Patients were considered asymptomatic based on clinical judgement in the absence of dyspnoea, angina and syncope. Occurrence of sudden death, CHF or new onset of symptoms (dyspnoea, angina or syncope) in patients asymptomatic at study entry was prospectively recorded up to December 2014.

Echocardiography

A comprehensive Doppler echocardiography was performed at study entry. Assessment of AS severity was based on peak velocity (PV), mean pressure gradient (MPG) and the calculation of the aortic valve area (AVA) using the continuity equation. Based on AVA, mild AS was defined by an area between 1.5 and 2 cm², moderate AS by an AVA between 1 and 1.5 cm² and severe AS by an AVA <1 cm². Two-dimensional measurements of LV diameters, wall thickness and left atrial volume were performed according to the American Society of Echocardiography and the American Society of Echocardiography criteria. LV mass was calculated using Devereux’s formula. LV ejection fraction (LVEF) was assessed using the biplane Simpson method or visually and considered abnormal if <50%. LV diastolic function was assessed by measuring mitral peak early filling (E), late diastolic filling (A) and early filling deceleration time using pulsed-wave Doppler. The ratio of mitral peak early filling to early diastolic mitral annulus velocity (E/E) was calculated using Doppler tissue imaging.

Laboratory analysis

All blood samples were collected from a peripheral vein at inclusion and processed under identical conditions, at 08:00 h after 12 h fasting and within 48 h of the echocardiography. Plasma was separated within 30–60 min of collection and aliquots were frozen to −80°C and kept on site without freeze–thaw cycles. Galectin-3 dosages were performed at one core laboratory blinded of any clinical or echocardiographic information using an enzyme-linked fluorescent immunoassay on the VIDAS analyser (bioMérieux, France). Glomerular filtration rate was calculated using the modified diet in renal disease formula.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, median (IQR) or number of patients (percentage). As galectin-3 was not normally distributed a log transformation was used. Comparisons between groups and between quartiles of galectin-3 values were performed using the t-test, one-way analysis of variance, the χ² test, Wilcoxon test or Fisher’s exact test as appropriate. Association between galectin-3 values and clinical and echocardiographic variables was evaluated using linear regression. Univariate and stepwise multiple linear regression analysis was used to identify the determinants of galectin-3.

RESULTS

Patient characteristics

During the study period, 583 patients were prospectively enrolled. Clinical, echocardiographic and biological characteristics of the population are presented in table 1 (left part). Briefly, mean age was 75±10 years and 369 (63%) patients were male. Most patients were in sinus rhythm (89%) and 30 patients (5%) were implanted with a pacemaker. History of CAD was reported in 164 (28%) patients. Mean LVEF was 62±7% and was <50% in 38 patients (7%). Severe AS was diagnosed in 307 (53%) patients. Among these 307 patients, 220 (72%) were asymptomatic. All symptomatic patients had severe AS and by design all patients with mild or moderate AS were asymptomatic. The flow chart of the study is presented in figure 1.

Determinants of galectin-3 level

Mean and median (IQR) Gal-3 values were 14.3±5.6 ng/mL and 13.2 (10.7–16.5) ng/mL, respectively. Characteristics of the population according to quartiles of galectin-3 are presented in table 1 (right part).

Galectin-3 and functional status

Galectin-3 level was significantly higher in severely symptomatic patients (NYHA functional class III/IV II–IV) compared with those who were moderately symptomatic or asymptomatic (NYHA class I–II) (16.4±7.3 vs 13.8±5.0 ng/mL, p<0.0001). However, there was no difference regarding the presence or absence of symptoms (15.1±6.5 vs 13.9±5.0 ng/mL, p=0.08) and across the four quartiles of galectin-3 (p=0.53). Galectin-3 level according to functional status overall and in the subset of severe AS is presented in table 2 and figure 2.

Galectin-3 and AS severity

Table 1 shows that there was no significant association between galectin-3 quartiles and the three parameters of AS severity (p=0.58 for AVA; p=0.53 for MPG and p=0.81 for PV) (table 1). Galectin-3 level according to grades of AS severity is presented in figure 2 and regressions between galectin-3 values and haemodynamic parameters in table 3.

Galectin-3 and LV structure and function

Modest and inconstant associations between LV diameters and LV mass were observed. Patients with reduced LVEF (<50%) tended to present with higher galectin-3 values (p=0.04) and a significant but modest association between galectin-3 and LVEF...
was observed ($r=−0.16$, $p=0.0003$). LV diastolic function parameters significantly associated with galectin-3 values (peak $E$ wave velocity, $r=0.13$, $p=0.02$ and $E/E'_0$ ratio, $r=0.25$, $p<0.0001$) (tables 1 and 3).

Other determinants of galectin-3
As shown in tables 1 and 3, there were significant associations between galectin-3 level and age ($p<0.0001$), hypertension ($p<0.0001$), diabetes mellitus ($p=0.002$) and non-sinus rhythm

---

**Table 1** Clinical, echocardiographic and biological characteristics of the overall population and according to galectin-3 quartiles

<table>
<thead>
<tr>
<th>Galectin-3</th>
<th>Overall population (N=583)</th>
<th>10.7 &lt; galectin-3 &lt; 13.2 ng/mL (N=143)</th>
<th>13.2 &lt; galectin-3 &lt; 16.5 ng/mL (N=148)</th>
<th>Galectin-3 ≥ 16.5 ng/mL (N=148)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75±10</td>
<td>69±11</td>
<td>74±10</td>
<td>77±9</td>
<td>79±7</td>
</tr>
<tr>
<td>Men</td>
<td>369 (63)</td>
<td>104 (72)</td>
<td>104 (73)</td>
<td>84 (57)</td>
<td>77 (52)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28±11</td>
<td>28±5</td>
<td>28±5</td>
<td>28±6</td>
<td>29±6</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>164 (28)</td>
<td>32 (22)</td>
<td>40 (28)</td>
<td>41 (28)</td>
<td>51 (35)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>396 (68)</td>
<td>77 (54)</td>
<td>93 (65)</td>
<td>108 (73)</td>
<td>118 (80)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>149 (26)</td>
<td>35 (24)</td>
<td>22 (15)</td>
<td>41 (28)</td>
<td>51 (34)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>308 (53)</td>
<td>68 (47)</td>
<td>79 (55)</td>
<td>84 (57)</td>
<td>77 (52)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>220 (38)</td>
<td>48 (33)</td>
<td>53 (37)</td>
<td>58 (39)</td>
<td>61 (41)</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>520 (89)</td>
<td>141 (98)</td>
<td>127 (98)</td>
<td>132 (89)</td>
<td>120 (81)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>30 (5)</td>
<td>3 (2)</td>
<td>7 (5)</td>
<td>8 (5)</td>
<td>12 (8)</td>
</tr>
</tbody>
</table>

**AS severity**

| Aortic valve area (cm²) | 1.12±0.42 | 1.14±0.40 | 1.11±0.42 | 1.15±0.46 | 1.10±0.42 | 0.58 |
| Mean gradient (mm Hg)   | 37±21      | 39±21      | 38±21      | 37±23      | 36±20      | 0.53 |
| Peak velocity (m/s)     | 3.72±1.00  | 3.76±1.06  | 3.74±0.99  | 3.68±1.11  | 3.70±1.01  | 0.81 |
| Severe AS               | 307 (53)   | 74 (51)    | 76 (53)    | 76 (51)    | 81 (55)    | 0.93 |

**Left ventricular size and function**

| Left ventricular ejection fraction (%) | 62±7     | 63±5     | 62±7     | 62±8     | 61±10     | 0.29 |
| Left ventricular ejection fraction <50% | 38 (7)   | 3 (2)    | 11 (8)   | 10 (7)   | 14 (10)   | 0.04 |
| Left ventricular end-diastolic diameter (mm/m²) | 27±4     | 27±3     | 27±4     | 27±4     | 27±4      | 0.53 |
| Left ventricular end-systolic diameter (mm/m²) | 17±4     | 16±4     | 17±4     | 17±3     | 17±4      | 0.40 |
| Left ventricular mass (g) | 124±36 | 123±35 | 122±33 | 125±39 | 125±37 | 0.87 |
| Peak $E$ wave velocity (cm/s) | 79±26   | 77±26    | 75±21    | 79±26    | 84±28     | 0.02 |
| $E$ wave deceleration time (ms) | 238±80 | 230±68 | 238±73 | 257±77 | 227±97 | 0.02 |
| $E/A$ wave ratio | 0.95±0.48 | 0.91±0.33 | 0.92±0.42 | 0.92±0.49 | 1.03±0.62 | 0.85 |
| $E/E'_0$ ratio | 15±7 | 14±6 | 14±6 | 15±6 | 18±9 | 0.0004 |
| Creatinine clearance (mL/min) | 75±23 | 89±21 | 80±19 | 73±19 | 57±20 | <0.0001 |

Data are expressed as mean±SD, or number (percentage). AS, aortic stenosis.

---

**Figure 1** Flow chart of the study population. AS, aortic stenosis.
Valvular heart disease

We evaluated the determinants and prognostic value of galectin-3 level in a large prospective cohort of patients with a wide range of AS severity and symptoms. Results can be summarised as follows: (1) galectin-3 level was not associated with AS severity or functional status; (2) independent determinants of galectin-3 level in a population of patients with AS were age, female sex, hypertension, diabetes, LV EF, diastolic function and renal function; and (3) galectin-3 provided no prognostic information in regard to the occurrence of AS-related events in the subset of asymptomatic patients. Our results do not support the use of galectin-3 as a biomarker for the risk stratification and clinical management of asymptomatic patients with AS.

DISCUSSION

We evaluated the determinants and prognostic value of galectin-3 level in a large prospective cohort of patients with a wide range of AS severity and symptoms. Results can be summarised as follows: (1) galectin-3 level was not associated with AS severity or functional status; (2) independent determinants of galectin-3 level in a population of patients with AS were age, female sex, hypertension, diabetes, LV EF, diastolic function and renal function; and (3) galectin-3 provided no prognostic information in regard to the occurrence of AS-related events in the subset of asymptomatic patients. Our results do not support the use of galectin-3 as a biomarker for the risk stratification and clinical management of asymptomatic patients with AS.

Myocardial fibrosis impairs cardiac function and facilitates arrhythmias and ischaemia. MRI has been validated as an accurate method for the assessment of myocardial fibrosis providing important additional prognostic information beyond conventional markers of AS severity.1–5 Presence of myocardial fibrosis as detected using MRI is associated with increased mortality, adverse LV remodelling, incomplete functional recovery and worse outcome after aortic valve replacement.19 However, the widespread use of MRI has been limited by cost, availability and

(p<0.0001), but not with history of CAD (p=0.14) or hypercholesterolaemia (p=0.38). Galectin-3 level was also associated with reduced glomerular filtration rate (p<0.0001).

Multivariable analysis

In multivariable analysis (table 4), independent determinants of galectin-3 were age (p=0.0008), female gender (p=0.04), hypertension (p=0.002), diabetes (p=0.02), reduced LV EF (p=0.01), diastolic dysfunction (E/E', p=0.02) and creatinine clearance (p<0.0001). Galectin-3 level was not influenced by AS severity (p=0.10).

Prognostic value of galectin-3 in asymptomatic patients with AS

Among 363 asymptomatic patients (62%) at baseline, 25 patients underwent a prophylactic surgery immediately after enrolment and eight patients were either lost to follow-up or refused to remain in the study. Thus, 330 patients (mean age 74 ±10 years, 29% female) were considered for this analysis. Ninety-one patients had mild AS (28%), 179 moderate AS (54%) and 60 severe AS (18%). Mean follow-up duration was 3.0±1.7 years. During the study period, 37 patients died (11%) including 14 cardiac deaths (three AS-related deaths). Non-cardiac deaths were mainly related to cancer, strokes and infection. Patients with non-AS-related deaths were censored at the time of death. New onset of symptoms occurred in 85 patients (25%), dyspnoea in 74 patients, angina in nine and syncope in two.

Event-free survival was not different according to galectin-3 above and below the median (13.2 ng/mL) (p=0.95), the proposed 17.8 ng/mL threshold17 18 (p=0.54) or galectin-3 quartiles (p=0.96) (figure 3). Event-free survival according to galectin-3 median value was also not different in the 60 patients with severe AS (p=0.86). Galectin-3 was neither predictive of outcome in univariate analysis (p=0.73), nor after adjustment for age, gender, rhythm, hypertension, creatinine clearance and AS severity (p=0.91).

DISCUSSION

We evaluated the determinants and prognostic value of galectin-3 level in a large prospective cohort of patients with a wide range of AS severity and symptoms. Results can be summarised as follows: (1) galectin-3 level was not associated with AS severity or functional status; (2) independent determinants of galectin-3 level in a population of patients with AS were age, female sex, hypertension, diabetes, LV EF, diastolic function and renal function; and (3) galectin-3 provided no prognostic information in regard to the occurrence of AS-related events in the subset of asymptomatic patients. Our results do not support the use of galectin-3 as a biomarker for the risk stratification and clinical management of asymptomatic patients with AS.

Myocardial fibrosis impairs cardiac function and facilitates arrhythmias and ischaemia. MRI has been validated as an accurate method for the assessment of myocardial fibrosis providing important additional prognostic information beyond conventional markers of AS severity.1–5 Presence of myocardial fibrosis as detected using MRI is associated with increased mortality, adverse LV remodelling, incomplete functional recovery and worse outcome after aortic valve replacement.19 However, the widespread use of MRI has been limited by cost, availability and
been published regarding the prognostic value of fibrosis as assessed using MRI in asymptomatic patients and preliminary data have suggested that T1 mapping may not differentiate asymptomatic patients with moderate-severe AS from age-matched controls without valvular heart disease.\(^2^4\)

High-sensitivity plasma cardiac troponin I concentrations\(^2^2\) and the presence of LV hypertrophy with strain pattern on the ECG\(^2^3\) are both independently associated with myocardial fibrosis on MRI. However, whereas high-sensitivity troponin I is a sensitive marker of myocardial fibrosis, the ECG strain pattern is very specific. Thus, there is a need to further refine risk stratification in patients with AS particularly by focusing on the evaluation and validation of circulating biomarkers tracking myocardial fibrosis.

Galectin-3, a β-galactoside-binding lectin secreted by activated macrophages, is involved in inflammation, fibrosis and tissue remodelling pathways.\(^2^4\) Multiple experimental studies have provided strong proof for the pivotal role of galectin-3 in myocardial fibrosis. Clinical studies have linked galectin-3 plasmatic level to outcome in patients with congestive heart failure with either reduced or preserved EF.\(^2^5\)\(^2^6\) In addition, it has been shown that galectin-3 was a predictor of all-cause mortality in the general population.\(^2^7\) Consequently, the US Food and Drug Administration approved the use of a commercial assay of galectin-3 as a prognostic test for CHF and recently the American College of Cardiology/American Heart Association guidelines for Heart Failure implemented galectin-3 as a class IIb recommendation for prognosis and risk stratification in patients with acute and CHF.\(^2^8\)

In contrast, the relationship between galectin-3 and AS has seldom been studied and the few studies carried out were mainly performed following aortic valve replacement. In a first study, in 101 patients, elevated galectin-3 levels were associated with adverse outcome after TAVI and combining galectin-3 with N-terminal of the prohormone brain natriuretic peptide provided an additional value for risk stratification.\(^1^2\) In a second study evaluating the prognostic value of a combination of biomarkers to predict outcome after both surgical and transcatheter aortic valve replacement, galectin-3 predicted the outcome in univariate analysis but not after adjustment for clinical factors or Society of Thoracic Surgeon (STS) score.\(^1^1\) In our study, main determinants of galectin-3 level were age, female gender, hypertension, diabetes, LVEF, diastolic function and renal function. The absence of association between galectin-3 levels and AS severity parameters, and the absence of prognostic information for galectin-3 in our study may have several explanations. First, galectin-3 level was assessed at a relatively early stage of the disease, possibly before the development of significant LV fibrotic lesions. Therefore, a potential association with galectin-3 may only be observed at a more advanced stage of LV

### Table 4 Determinants of galectin-3 in multivariable analysis

<table>
<thead>
<tr>
<th>p Value</th>
<th>R coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.04</td>
</tr>
<tr>
<td>Rhythm</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.02</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.10</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>0.01</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
remodelling. Previous studies have reported that plasmatic levels of galectin-3 range from 10 to 13 ng/mL in the general population and increase to 15–30 ng/mL in patients with congestive heart failure. In contrast, plasmatic levels measured in our study were relatively low (14.2±5.6 ng/mL) and also lower than those observed in the two studies mentioned above evaluating the prognostic value of galectin-3 after aortic valve replacement.12 13 Second, galectin-3 is not a specific marker of myocardial fibrosis and seems to play a role in fibrosis occurring in many organs (pancreas, lungs, kidneys, liver and also arterial vessels).24 As AS is an ageing process and as fibrosis occurring in other organs also increases with age, it is possible that extracardiac organ fibrosis may have affected galectin-3 plasmatic levels and limited its diagnostic and prognostic value. However, the low galectin-3 level in our study makes this hypothesis unlikely. Similarly, the relationship between hypertension, diabetes, diastolic function, renal function and galectin-3 plasmatic levels may also explain its lack of diagnostic and prognostic value. Nevertheless, these limitations are inherent to AS epidemiology and our results do not support the use of galectin-3 as a risk-stratification biomarker in asymptomatic patients with AS. Additional studies are however warranted to analyse the role of galectin-3 at a later stage of AS and to determine whether galectin-3 provides additional prognostic information on the postoperative outcome of patients with severe symptomatic AS.

Several potential limitations of our study deserve consideration. First, this was a single-centre study. However, it is also worth emphasising that the main strength of our study is the prospective cohort design involving a large study population. Second, a large proportion of our population was composed of patients with non-severe AS. However, we did not observe any association between galectin-3 plasmatic levels and either AS severity parameters or functional status. Furthermore, the absence of prognostic value of galectin-3 plasmatic levels was also sustained in the subset of 60 patients with severe AS and event-free survival curves were very close. Third, myocardial fibrosis is only one among several determinants of the occurrence of symptoms in AS in association with degree of valve calcification, aortic valve reserve, and so on. Fourth, patients were considered asymptomatic based on clinical judgement and no exercise test was performed. Finally, no MRI examinations were performed to quantify myocardial fibrosis and we were not able to non-invasively validate galectin-3 level as a marker of myocardial fibrosis in our population of patients with AS. However,
it must be emphasised that the main objective of our study was to assess the role of galectin-3 as a prognostic biomarker in asymptomatic patients with AS, and not to validate galectin-3 as a marker of myocardial fibrosis.

CONCLUSION
In a large prospective cohort of patients with a wide range of AS severity, galectin-3 level was not associated with AS severity or functional status and the main determinants of galectin-3 level were age, rhythm and renal function. Most importantly, galectin-3 did not provide prognostic information on the occurrence of AS-related events. Consequently, our results do not support the use of this biomarker in the decision-making process for asymptomatic patients with AS. Further studies are however warranted to determine whether galectin-3 provides additional prognostic information on the postoperative outcome of patients with severe symptomatic AS.

Key messages
What is already known on this subject?
Galectin-3 is a biomarker that has been linked to myocardial remodelling, myocardial fibrosis and outcome in patients with congestive heart failure. Literature on its potential value in aortic valve stenosis is scarce.

What might this study add?
In a large prospective cohort of patients with aortic stenosis (AS) we have evaluated the determinants and prognostic value of galectin-3. Main determinants were age, hypertension and renal function. Galectin-3 did not provide prognostic information on the occurrence of AS-related events in asymptomatic patients.

How might this impact on clinical practice?
Our results do not support the use of galectin-3 for the risk stratification and clinical management of asymptomatic patients with aortic valve stenosis.

Acknowledgements
We would like to thank Dr Wim Houdijk from bioMérieux for his support and valuable assistance. We would like to specially thank the team of the Centre d’Investigation Clinique, Christophe Aucan from the DRC and Estelle Marcault from the URC for their help and support during all these years. We would also like to thank Veronique Lecon and all the technicians in the Biochemistry Department of Bichat Hospital involved in this study.

Contributors
Conception and design, or analysis and interpretation of data: all authors. DA and DM-Z: drafting the article or revising it critically for important intellectual content; final approval of the version to be published; contributors as being responsible for the overall content as guarantors.

Funding
The COFARASA and GENERAC studies are supported by grants from French Ministry of Health (PHRC National 2005 and 2010, and PHRC Regional 2007) (ClinicalTrials.gov NCT00338676 and NCT00647088). BioMérieux graciously provided dosage kits of galectin-3.

Competing interests
None declared.

Ethics approval
Regional ethics committee.

Provenance and peer review
Not commissioned; externally peer reviewed.

REFERENCES
15. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
29. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
Determinants and prognostic value of Galectin-3 in patients with aortic valve stenosis

Dimitri Arangalage, Virginia Nguyen, Tiphaine Robert, Maria Melissopoulou, Tiffany Mathieu, Candice Estellat, Isabelle Codogno, Virginie Huart, Xavier Duval, Claire Cimadevilla, Alec Vahanian, Monique Dehoux and David Messika-Zeitoun

Heart published online February 19, 2016

Updated information and services can be found at:
http://heart.bmj.com/content/early/2016/02/18/heartjnl-2015-308873

These include:

References
This article cites 30 articles, 10 of which you can access for free at:
http://heart.bmj.com/content/early/2016/02/18/heartjnl-2015-308873
#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Aortic valve disease (396)
Drugs: cardiovascular system (8570)
Hypertension (2900)
Epidemiology (3599)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/