Rational and design of the ROTAS study: a randomized study for the optimal treatment of symptomatic patients with low-gradient severe aortic valve stenosis and preserved left ventricular ejection fraction

Elena Galli1, Florent Le Ven2, Augustin Coisne3, Catherine Sportouch4, Thierry Le Tourneau5, Anne Bernard6, Loic Bière7, Gilbert Habib8, Patrizio Lancellotti9, Mathieu Lederlin10, Christophe Tribouilloy11, Emmanuel Oger12, and Erwan Donal1*

1University of Rennes, CHU Rennes, Inserm, LTSI – UMR 1099, F-35000 Rennes, France; 2Service de cardiologie, hôpital Cavale Blanche, CHRU Brest, 29200 Brest, France; 3Department of Clinical Physiology and Echocardiography, CHU Lille, Heart Valve Center, Univ Lille, U1011 - EGID, Institut Pasteur de Lille, F-59000 Lille, France; 4Clinique du Millénaire, 34000 Montpellier, France; 5Department of Cardiology, Thorax Institute, Centre Hospitalier Universitaire de Nantes, Site Hotel-Dieu-Hme 1, Place Alexis Ricordeau, Nantes, France; 6Cardiology Department, Trousseau Hospital, University of Tours, Tours, France; 7Institut MITOVASC, UMR INSERM U1083 and CNRS 6015, Service de Cardiologie, CHU Angers, Université Angers, Angers, France; 8Aix Marseille Université, IRD, APHM, MEDI, IHU-Méditerranée Infection, France; 9Department of Cardiology, Heart Valve Clinic, University of Liège Hospital, GIGA Cardiovascular Sciences, CHU Sart Tilman, Belgium; 10Image médicale—CHU de Rennes, 35000 Rennes, France; 11Department of Cardiology, Amiens University Hospital; 1 Rue du Professeur Christian Cabrol, Amiens, France; and 12Pharmacologie Clinique et CIC-IP 1414, CHU Rennes et Université Rennes-1, Rennes, France

Received 1 January 2020; editorial decision 10 February 2020; accepted 17 February 2020; online publish-ahead-of-print 18 March 2020

Aims

Fifteen to thirty percentage of patients with severe aortic stenosis (AS) have preserved left ventricular ejection fraction (LVEF) and a discordant AS pattern at Doppler echocardiography, which is characterized by a small (<1 cm²) aortic area and low mean aortic gradient (<40 mmHg). The ‘Randomized study for the Optimal Treatment of symptomatic patients with low-gradient severe Aortic Stenosis and preserved left ventricular ejection fraction’ (ROTAS trial) aims at demonstrating the superiority of aortic valve replacement vs. a ‘watchful waiting strategy’ in symptomatic patients with low-gradient (LS), severe AS, and preserved LVEF, stratified according to indexed stroke volume, in terms of all-cause mortality or cardiovascular-related hospitalization during follow-up (FU).

Methods and results

The ROTAS trial will be a multicentre randomized non-blinded study involving 16 reference centres. AS severity will be confirmed by a multimodality approach (rest and stress echocardiography, calcium scoring, and cardiac magnetic resonance imaging for optimally characterize the population), which could provide important inputs to improve the pathophysiological understanding of this complex disease. Well-characterized patients will be randomized according to the management strategy. The primary endpoint will be the occurrence of all-cause mortality or cardiac related-hospitalizations during 2-year FU. One hundred and eighty subjects per group will be included.

Conclusion

The management of patients with LS severe AS and preserved LVEF is largely debated. ROTAS trial will allow a comprehensive evaluation of this particular pattern of AS and will establish which is the most appropriate management of these patients.

Keywords

low gradient • stroke volume • aortic stenosis • randomized study
Introducțion

Rationale of the study

Aortic stenosis (AS) has become the most frequent valvular heart disease (VHD) in Europe and North America, particularly in adults of advanced age. The reported prevalence in patients older than 65 years is between 2% and maximum 7%.1 Due to the continuing ageing of the population in western countries, the prevalence of AS might double in the next 20 years,2 which means that AS becomes a public health issue with sizable economic impact.

According to current guidelines on the management of VHD,2,3 the diagnosis and management of AS are determined primarily on the haemodynamic assessment of the aortic valve at Doppler echocardiography, the estimation of left ventricular ejection fraction (LVEF), and the presence of symptoms. Aortic valve replacement (AVR) is recommended with a Class I evidence in symptomatic patients with ‘classical’ severe AS and in patients with true severe low-flow (LF)/low-gradient (LG) AS and reduced LVEF, independently from symptomatic status.

Nevertheless, 15–30% of patients with severe AS have preserved LVEF and a discordant AS pattern at Doppler echocardiography, which is characterized by a small (<1 cm²) aortic area and low mean aortic gradient (<40 mmHg).4 This condition raises many questions on the actual severity of AS. A multimodality imaging approach that includes transthoracic echocardiography, dobutamine stress echocardiography (DSE), and aortic calcium score at multidetector computed tomography (MDCT), together with the verification of the accuracy of the Doppler echocardiographic measurements, is necessary for the appropriate quantification of AS.5 Once the severity of LG AS with preserved LVEF is confirmed, further classification in terms of all-cause mortality or cardiovascular-related hospitalization during follow-up (FU). In the ROTAS study, AS severity will be confirmed by a multimodality approach, which could provide important inputs to improve the pathophysiological understanding of this complex disease.

Methods

The ROTAS trial will be a multicentre randomized non-blinded study involving 16 reference centres in France and Belgium. The list of the participating centres is provided in Supplementary data online, Table S1. The centres should be able to recruit consecutive adult patients with symptomatic severe LG AS and preserved LVEF over a period of 3 years. The FU period will last 24 months for the last included patient up to 60 months for the first included patient. For each patient included, symptomatic medical treatment (heart failure with preserved ejection fraction) should be optimized according to the clinical experience and practice of each centre.17 Institutional ethical approval will be requested to each centre and the study will be performed following the principles of the Declaration of Helsinki for research in human subjects.

Study population

Symptomatic patients with preserved LVEF and LG severe AS confirmed at multimodality imaging are eligible for the study.

Inclusion criteria are age >18 years, signature of informed consent, severe LG AS defined by an effective aortic valve area (AVA) ≤1 cm² or ≤0.6 cm²/m² and a mean trans-aortic pressure-gradient <40 mmHg, confirmed at multimodality imaging, LVEF ≥50%, feasibility of AVR (surgical or percutaneous approach) according to the heart team, and signature of the informed consent.

Exclusion criteria are uncontrolled atrial or ventricular arrhythmias; patient having a life expectancy <1 year, independently from their aortic valve pathology; presence of a concomitant valve disease needing surgical treatment; and patients with unsuitable anatomy for surgical or percutaneous AVR according to the advice of the local heart team (Figure 1). Patients diagnosed with a transthyretin amyloidosis can be included.18 Patients having a coronary artery disease that is requiring a revascularization at the time of the randomization can be included. But for all the patients, it is mandatory to identify possible causes of LF (e.g. atrial fibrillation) and to optimize anti-hypertensive medical therapy and re-assess parameters of stenosis before to proceed with inclusion and randomization.

Study protocol

During the screening phase, every patient will undergo clinical evaluation for the assessment of the New York Heart Association (NYHA)
functional class; 6-min walking test (6MWT), quality of life test (QoL) by the EQ-5D questionnaire; dosage of NTproBNP; electrocardiogram (ECG) recording; transthoracic echocardiography (TTE); low-dose DSE (as much as possible); and aortic calcium scoring at computed tomography (CT), and cardiac magnetic resonance (CMR) evaluation of cardiac dimension, mass, and LV fibrosis. During the screening phase, confirmation of AS severity should be obtained by a multimodality approach as described below (Figure 1). The CMR will not impact on the inclusion in ROTAS and in the randomization. It is performed for getting before treatment, the best characterization possible of the included patients.

**Confirmation of AS severity**

AS severity will be confirmed by a multimodality approach including standard TTE, DSE, and aortic calcium score at MDCT (Figure 2). The cut-offs are for the calcium score 1200 in women and 2000 in men. It could be possible to include according to investigators’ experience if calcium scoring and DSE are not both providing convincing results. One of them is enough for including a patient.

**Transthoracic echocardiography**

Screening TTE to confirm the presence of LG severe AS will be performed by an experienced echocardiographer to avoid typical pitfalls in the assessment of AS. Particular attention will be paid to avoid the underestimation of the aortic annulus. Doppler data will be obtained in several views including systematically the right parasternal view as recommended, to avoid the underestimation of aortic velocities and gradients. LV dimensions and function, including global longitudinal strain, will be performed. Left atrial volume and diastolic function parameters, right ventricular size and function will be recorded as indicated in guidelines.

AS severity will be confirmed in case of positive DSE and/or calcium score. In case of doubt or discordant data, the decision to include or not the patient in the study will be taken by the local heart team considering the clinical context, the qualitative analysis of the CT and echocardiography.

**Dobutamine stress echocardiography**

DSE will be performed according to a standardized protocol. Dobutamine dose will be increased of 5 μg/kg/min up to a maximal dose of 20 μg/kg/min and transaortic pressure and gradients will be measured at each step. The presence of severe AS will be confirmed by (i) the increase in the mean aortic pressure-gradient above 40 mmHg and AVA persistently <1 cm² during DSE; or (ii) projected AVA <1 cm² in the case of mean aortic gradient persistently below <40 mmHg and increase in flow rate >15%. In patients with an increase in flow rate <15%, DSE will be considered inconclusive and AS severity should be corroborated by aortic valve calcium score.

Projected AVA will be calculated with the simplified formula as indicated below:
Projected AVA = \frac{AVA_{peak} - AVA_{rest}}{Q_{peak} - Q_{rest}} \times \left(250 - Q_{rest}\right) + AVA_{rest}

where AVA_{rest} and Q_{rest} are AVA and aortic flow rate at rest, and AVA_{peak} and Q_{peak} are AVA and aortic flow rate measured at peak stress echocardiography.

Aortic calcium score
Aortic calcium score will be estimated by MDCT using the modified Agatston method. The presence of a severe AS is suggested by a score >1200 AU in women and >2000 AU in men.21

Cardiac magnetic resonance imaging
CMR will be performed during the screening phase to all patients without specific contraindication using standard magnetic resonance imaging (MRI) scanners (1.5 T and 3 T). The CMR protocol will include standard long-axis views (3-, 2-, and 4-chamber views) followed by a full stack of continuous short-axis cine encompassing the LV/right ventricular (RV) from base to apex using a breath-hold steady-state free precession cine technique. For the assessment of replacement fibrosis, late gadolinium enhancement (LGE)-CMR imaging will be performed in the same short- and long-axis cine orientation 10–15 min after administration of 0.1–0.2 mmol/kg of gadolinium chelate contrast agent. Images will be acquired using an inversion recovery prepared breath-hold gradient-echo technique following a Lock-Locker T1 shout sequence for the identification of the optimal starting T1 value to null the signal in the normal myocardium. The inversion time will be progressively optimized to null normal myocardium (typical values, 250–350 ms). Each slice will be obtained during a breath hold of 10–15 s depending on the patient’s heart rate. The parameters measured will be LV and RV volumes and ejection fraction. LV fibrosis will be measured using the full-width half-maximum method of the tissue characterization module, and expressed both in grams and in percentage of the LV mass, as previously described.22 The presence of mid-wall LGE will be determined both qualitatively and quantitatively by experienced operators, and its distribution recorded. The location and numbers of myocardial segments affected by LGE will be recorded.23 For the assessment of interstitial fibrosis, extracellular volume (ECV) fraction (ECV\%) and indexed ECV (iECV: ECV\% × LV end-diastolic myocardial volume normalized to body surface area) will be calculated using the motion-corrected native and post-contrast T1 maps.22

Feasibility of AVR
After confirmation of AS severity, the feasibility of AVR by the surgical (surgical valve replacement, SAVR) or per-cutaneous approach (trans-aortic valve replacement, TAVR) will be established in each centre by the local heart team. The best choice between SAVR and TAVR will be performed according to valve characteristics and the patient’s clinical status. AVR will be performed 1–3 months after randomization.

Patients’ randomization
Patients accomplishing the inclusion criteria and giving their informed consent will be included in the ROTAS trial and randomized 1:1 between ‘AVR’ or ‘watchful waiting’ strategy. Randomization will be performed on a web interface 0–15 days after inclusion in the protocol. A stratification according to the SV\i at baseline (SV\i ≥35 mL/m\textsuperscript{2} or <35 mL/m\textsuperscript{2}) will be applied.

Endpoints
The primary endpoint will be the occurrence of all-cause mortality or cardiac related-hospitalizations during FU. The secondary endpoints will be (i) a composite of all-cause mortality, cardiac-related hospitalizations,
and cerebrovascular events; (ii) the modification of 6MWT, NT-proBNP plasma levels, and QoL during FU.

Follow-up

The FU period will last 24 months for the last included patient and up to 60 months for the first included patient (Figure 3).

Patients in the AVR arm will benefit from an on-site FU visit 12 and 24 months after randomization. The FU visit will include clinical evaluation (6MWT, QoL, and NT-proBNP dosage), ECG recording, TTE, and collection of major adverse events and cardiovascular events. Moreover, a phone interview with the patient of his/her physician will be scheduled at 6- and 18-month FU to assess the occurrence of events.

In patients in the ‘watchful waiting’ arm, an FU with the same characteristics described above will be performed 6, 12, 18, and 24 months after randomization. In the case of cardiovascular events, the clinical case will be discussed by the heart team in each participating centre and the need for AVR will be established. An independent validation committee will check and validate each switch from the watchful waiting arm to the AVR arm. After 2 years of FU, and up to 5 years for the first included patient, a phone interview will be performed every year to assess the occurrence of events.

Imaging data analysis

TTE, DSE, aortic calcium score at CT, and MRI data collected during the screening visit and TTE data collected at 12-month FU will be stocked by each participating centre. A centralized lecture at the Core Lab of the University Hospital of Rennes (CIC-IT, INSERM 1099, ISO 9001) will be performed for baseline echocardiography and dobutamine echocardiography at baseline and rest echocardiography at 12-month FU in order to obtain homogeneous data analysis. The list of echo data that should be sent to the Echo Core Lab for further analysis is indicated in Table 1.

A centralized lecture at the University Hospital of Rennes will be performed for MRI data.

Statistical analysis

A sample size of 180 subjects per group (for an overall population of 360 patients) will provide 90% power to detect a 35% relative risk reduction for the primary composite endpoint at an \( \alpha = 0.05 \), based on a hypothesis of cumulative percentage of events at 2 years of 0.50, on an accrual time of 3 years and an FU time of 2 years. Demographics, clinical presentation, medical history including cardiovascular risk factors, and other conditions, collected at the time of randomization, will be summarized by the treatment group and compared between patients in the AVR arm and watchful waiting arm. Similar comparison and description will be performed according to the secondary endpoint. After the assessment of the normality distribution, all baseline continuous variables will be compared by the Student’s \( t \)-test or Mann–Whitney test, as appropriate. Categorical variables will be compared using the \( \chi^2 \) or Fisher’s exact test. Efficacy analysis will be carried out according to the intention-to-treat principle including all the efficacy endpoints which will occur between randomization and the end of the study. For each parameter, the estimation of the cumulative hazard will use the Kaplan–Meier method. Comparison of cumulative hazard functions will be based on the log-rank test. The estimates of hazard ratio, under the assumption of proportional hazards and corresponding confidence intervals will be based on a Cox proportional hazards regression analysis. Subgroup analysis evaluating potential influence of the presence of normal or reduced SVi (<35 mL/m² vs. ≥35 mL/m²) will be assessed using the Cox proportional hazards regression. Potential heterogeneity related to the presence of normal or reduced SVi will be assessed through an interaction term in a Cox proportional hazards regression.
**Table 1  Echocardiographic acquisitions that will be mandatory for the Echo Core Lab analysis**

<table>
<thead>
<tr>
<th>Parameters loops</th>
<th>At baseline</th>
<th>12-Month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transthoracic echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasternal long-axis view</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Parasternal long-axis—zoom on the aortic valve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical 4–2–3–ch views</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>showing LV and LA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical 4–2–3–ch views</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>showing LV and LA with colour Doppler in valves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral inflow (E and A wave)</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Mitral annulus TDI (‘e’ septal and lateral assessment)</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>PWD in 3-ch and/or 5-ch view on the LVOT</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CWD in 3-ch and/or 5-ch view on the aortic valve</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Dedicated loops on the RV in 4-ch view</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Lateral tricuspid annulus TDI</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CWD on tricuspid regurgitation</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>DSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>5–10–15–20 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Parasternal long-axis view</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Parasternal long-axis—zoom on the aortic valve</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Apical 4–2–3–ch views</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>showing LV and LA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWD in 3-ch and/or 5-ch view on the LVOT</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CWD in 3-ch and/or 5-ch view on the aortic valve</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Ch, chamber; CWD, continuous-wave Doppler; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; PWD, pulsed wave Doppler; RV, right ventricle; TDI, tissue Doppler imaging.

Discussion

In the last few years, the understanding of the pathophysiology of AS and its different phenotypes has progressively improved. Nevertheless, the diagnosis and management of patients with LS severe AS and preserved LVEF is object of debate. It should be underlined that the majority of the available data on this topic comes from retrospective, observational studies, and only a small post hoc analysis of the prospective PARTNER I trial showed the benefit of AVR in patients with LF/LG AS and preserved LVEF.7

The ROTAS trial is the first prospective randomized trial specifically designed to establish which is the best management for patients with severe LG AS and preserved LVEF, stratified according to the SVA, among AVR and ‘watchful waiting’ strategy. In patients with LG severe AS, a fundamental issue is a confirmation of AS severity. In the ROTAS trial, a multimodality approach including the assessment of aortic calcium score at MDCT and/or DSE will be performed in order to verify and confirm AS severity. DSE has been extensively validated in patients with LF/LG AS and reduced LVEF,5 whereas only few studies were designed to demonstrate the role of DSE in differentiating true-severe from pseudo-severe AS in patients with LG AS.19 Patients with LG AS can have an LF state despite the presence of a preserved LVEF, which can lead to the underestimate of AS severity at baseline. The estimation of projected AVA during DSE, and particularly in patients with persisting LS during stress, allows the assessment of AVA, which is standardized for flow rate, resulting in an improved diagnostic accuracy compared to traditional DSE.20

On the other hand, some patients can have only a modest increase of the LV flow rate under dobutamine, which might be attributable to the extensive LV remodelling and fibrosis which is often observed in the LG AS population. In these patients, the assessment of valvular calcification at MDCT can be of pivotal importance. It should be underscored that aortic calcium scoring can underestimate the entity of AS in patients with dominant fibrosis, as in younger patients, particularly in the presence of a bicuspid aortic valve, and in female subjects.24,25

The assessment of interstitial and replacement fibrosis at MRI might contribute to the characterization of LG severe AS and to disclose the relationship between LV morphology and the LV subclinical functional impairment typical of these patients. The multimodality imaging approach proposed in the ROTAS study for the evaluation of patients with LG AS will provide a comprehensive pathophysiological insight of this kind of AS.

Many patients with severe LG AS and preserved LVEF are elder and have significant comorbidities, which might substantially contribute to their symptomatic status. The role of comorbidities in the natural history of LG AS has not been clearly disclosed. In many of these patients, AS is not a ‘lone disease’ but is often associated and aggravates intrinsic heart failure with preserved ejection fraction. One of the pathophysiological hypothesis in support of the ‘watchful waiting’ strategy might be that the treatment of the comorbidities and risk factors could have a greater symptomatic and prognostic impact than the removal of the increase in afterload linked to the supposed severe AS.53 On the contrary, another potential hypothesis is that the removal of the obstacle to LV ejection can improve symptoms and LV reverse remodelling. The careful clinical, functional, and psychological assessment of patients enrolled in the ROTAS
trial will allow to disclose the role of comorbidities on the symptom- 
atic status and prognosis of patients.

Limitations
In this article, the sub-analyses scheduled on the ROTAS database 
are not provided. Only the main goals of the study are provided.

Conclusion
The management of patients with LG severe AS and preserved 
LVEF is largely debated. The prospective, randomized ROTAS trial 
will allow a comprehensive evaluation of this particular pattern of 
AS and a better understanding of the pathophysiology of LG AS. 
Finally, the result of the ROTAS study will establish which is the 
most appropriate management of these patients with low pressure- 
gradient severe AS and preserved LV ejection fraction.

Supplementary data

Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

Acknowledgements
Direction General de l’offre de soins, commission du PHRC- 
National; Anne Ganivet (project manager), Melanie Glotin, Manon 
Guiguen, Romain Muraz (research assistant of the Direction for re- 
search and innovation of the CHU Rennes); and Isabau Labrousse for 
CIC 1414, Inserm, CHU Rennes.

Funding
This Project was supported by the PHRC-N 2017 (National grant from 
« direction generale de la sante » -ministere de la sante, France).

Conflict of interest: none declared.

References
1. Iung B, Vahanian A. Valvular disease: implications of the new AHA/ACC valvular 
Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of 
RA et al. 2014 AHA/ACC guideline for the management of patients with valvular 
Cardiol 2014;63:2438–89.
4. Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. Eur Heart J 2016;37: 
2645–57.
5. Clavel MA, Burwash IG, Pibarot P. Cardiac imaging for assessing low-gradient se- 
Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: characteristics, outcome, and implications for surgery. J Am Coll Cardiol 
2015;65:55–64.
8. Dayan V, Vignoli G, Magne J, Clavel MA, Mohaty D, Pibarot P. Outcome and 
impact of aortic valve replacement in patients with preserved LVEF and low- 
and impact of surgery in paradoxical low-flow, low-gradient severe aortic sten- 
10. Khadha G, Bobbey Y, Rusinaru D, Marechaux S, Tribouilloy C. Outcome of 
normal-flow low-gradient severe aortic stenosis with preserved left ventricular 
low-gradient, low-flow, severe aortic stenosis with preserved left ventricular 
valve replacement on outcome of symptomatic patients with severe aortic sten- 
13. Rusinaru D, Bobbey Y, Ringle A, Marechaux S, Drouf M, Tribouilloy C. Impact of 
low stroke volume on mortality in patients with severe aortic stenosis and pre- 
14. Chahal NS, Drakopouliou M, Gonzalez-Gonzalez AM, Manivannan R, Khattar R, 
Senior R. Resting aortic valve area at normal transaortic flow rate reflects true 
valve area in suspected low-gradient severe aortic stenosis. JACC Cardiovasc 
long-term survival in patients with moderate aortic stenosis. J Am Coll Cardiol 
2017;74:1851–63.
versus early aortic valve replacement for symptomatic patients with normal flow, 
17. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 
20. Clavel MA, Burwash IG, Mundigler G, Dumesnil JG, Baumgartner H, Bergler- 
Klein J et al. Validation of conventional and simplified methods to calculate pro- 
jected valve area at normal flow rate in patients with low flow, low gradient aor- 
Circulation 2009;120:577–84.
discordance between aortic valve calcification and hemodynamic severity of 
25. Shen M, Tastet L, Capoulade R, Larose E, Bedard E, Arsenault M et al. Effect of 
age and aortic valve anatomy on calcification and haemodynamic severity of 