Discordant severity criteria in patients with moderate aortic stenosis: prognostic implications

Stephan M Pio,1 Mohammed R Amanullah,2 Steele C Butcher,1,3 Kenny Y Sin,4 Nina Ajmone Marsan,1 Philippe Pibarot,5 Nicolas M Van Mieghem,6 Zee Pin Ding,2 Philippe Généreux,7 Martin B Leon,8 See Hooi Ewe,2 Victoria Delgado,9,1 Jeroen J Bax1

ABSTRACT

Background The criteria to define the grade of aortic stenosis (AS)—aortic valve area (AVA) and mean gradient (MG) or peak jet velocity—do not always coincide into one grade. Although in severe AS, this discrepancy is well characterised, in moderate AS, the phenomenon of discordant grading has not been investigated and its prognostic implications are unknown.

Objectives To investigate the occurrence of discordant grading in patients with moderate AS (defined by an AVA between 1.0 cm² and 1.5 cm² but with an MG <20 mm Hg) and how these patients compare with those with concordant grading moderate AS (AVA between 1.0 cm² and 1.5 cm² and MG ≥20 mm Hg) in terms of clinical outcomes.

Methods From an ongoing registry of patients with AS, patients with moderate AS based on AVA were selected and classified into discordant or concordant grading (MG <20 mm Hg or ≥20 mm Hg, respectively). The clinical endpoint was all-cause mortality.

Results Of 790 patients with moderate AS, 150 (19.0%) had discordant grading, moderate AS. Patients with discordant grading were older, had higher prevalence of previous myocardial infarction and left ventricular (LV) hypertrophy, larger LV end-diastolic and end-systolic volume index, higher LV filling pressure and lower LV ejection fraction and stroke volume index as compared with their counterparts. After a median follow-up of 4.9 years (IQR 3.0–8.2), patients with discordant grading had lower aortic valve replacement rates (26.7% vs 44.1%, p<0.001) and higher mortality rates (60.0% vs 43.1%, p<0.001) as compared with patients with concordant grading. Discordant grading moderate AS, combined with low LV ejection fraction, presented the higher risk of mortality (HR 2.78 (2.00–3.87), p<0.001).

Conclusion Discordant-grading moderate AS is not uncommon and, when combined with low LV ejection fraction, is associated with high risk of mortality.

INTRODUCTION

Grading aortic stenosis (AS) with echocardiography requires accurate assessment of aortic valve morphology and hemodynamics including the measurement of the peak jet velocity and the calculation of the mean transvalvular gradient and aortic valve area (AVA). Among patients with severe AS, one-third can have discordant criteria (AVA <1.0 cm² with low transvalvular gradient (<40 mm Hg) or peak jet velocity (<4 min/s)) posing a diagnostic and therapeutic challenge.3 Low flow status, inaccurate measurement of the left ventricular (LV) outflow tract cross-sectional area and misalignment of the aortic jet with the ultrasound beam are frequent reasons that lead to discordant grading. While in severe AS, the occurrence and clinical implications of discordant grading have been extensively investigated,2,5 in patients with moderate AS, these questions have not been evaluated. Moderate AS has been associated with

Key questions

What is already known about this subject?

► Patients with moderate aortic stenosis (AS) have worse prognosis compared with general population and patients with mild AS.

► Misclassification of AS severity may lead to longer burden of increased afterload to the left heart.

What does this study add?

► Prevalence of discordant severity criteria in patients with moderate AS and predominantly preserved left ventricular ejection fraction (LVEF) is high.

► Discordant grading is associated with poor prognosis, particularly among patients with LVEF <50%.

How might this impact on clinical practice?

► Patients with moderate AS and discordant gradient might benefit from a closer follow-up and multimodality imaging.

► The discrepancy between aortic valve area and mean gradient is to be confirmed in TAVR-UNLOAD trial with a probably higher prevalence due to LV systolic dysfunction.
impaired survival at follow-up.8 9 The ongoing TAVR-
UNLOAD (Transcatheter Aortic Valve Replacement to
UNload the Left Ventricle in Patients With AdVanced
Heart Failure) trial is currently recruiting patients
with symptomatic heart failure and moderate AS who
are randomised to conventional treatment (guideline-
based medical therapy and valve intervention when
AS becomes severe) versus transcatheter aortic valve
implantation.10

The prevalence of discordant grading among patients
with moderate AS (overall and according to LV ejection
fraction), and its prognostic implications have not
been evaluated. Accordingly, the present retrospective
multicentre study aimed at evaluating the prevalence
of discordant-grading moderate AS and investigating its
prognostic implications.

METHODS

Patient population

From the echocardiographic database of two tertiary
centres (Leiden University Medical Center, Leiden,
The Netherlands and the National Heart Centre Singa-
pore, Singapore), patients who were diagnosed with
moderate AS with AVA between 1.0 cm² and 1.5 cm² were
selected. Patients with moderate or severe coexisting
aortic regurgitation, dynamic subaortic obstruction,
unavailable echocardiographic data allowing offline
two-dimensional analysis and active endocarditis were
excluded. Patients included in this analysis were further
dichotomised according to concordant mean gradient
(MG) and AVA for moderate AS (AVA ≥20mm Hg and
AVA between 1.0 cm² and 1.5 cm²) versus discordant
grading (AVA <20 mm Hg and AVA between 1.0 cm² and
1.5 cm²). Demographic and clinical data (cardiovas-
cular risk factors and medication use) as well as clinical
outcomes (all-cause mortality) were collected using the
hospital records and departmental patient information
systems and analysed retrospectively.

This retrospective analysis of clinically acquired data
was approved by the respective institutional review
boards of each participating centre, and the need for
patient written informed consent was waived due to the
retrospective nature of the study.

Echocardiography

Transthoracic echocardiography was performed with
the subjects at rest using commercially available ultra-
sound systems. All images were digitally stored on
hard disks for offline analysis with proprietary soft-
ware. A complete two-dimensional, colour, pulsed
and continuous-wave Doppler echocardiogram was
performed. LV end-diastolic volume and end-systolic
volume were calculated using Simpson’s biplane
method of discs and corrected for body surface area.
Left ventricular ejection fraction (LVEF) was calculated
and expressed as a percentage. LV mass index was
calculated from the formula as recommended by the
American Society of Echocardiography and the Euro-
pean Association of Cardiovascular Imaging.11 The cut-
of values of 95 g/m² for women and 115 g/m² for men
were used to define LV hypertrophy.

Mitrail inflow velocities were recorded using conven-
tional pulsed-wave Doppler echocardiography in the
apical four-chamber view using a 2 mm sample volume.
Transmitral early (E wave) and late (A wave) diastolic
velocities as well as deceleration time were recorded at
the mitral leaflet tips. Tissue Doppler imaging in the
apical four-chamber view with measurement of the peak
differentiation (e’ septal) and lateral (e’ lateral) basal regions were obtained, and the
LV filling pressures were estimated using the E/e’ ratio.
On a zoomed parasternal long-axis view, the LV
outflow tract (LVOT) diameter was measured and
the cross-sectional area was derived. From the apical
LV long-axis or five-chamber views, continuous wave
and pulsed wave Doppler spectral recordings were
obtained through the aortic valve and at the LVOT,
respectively. The peak and mean aortic pressure gradi-
ents were estimated with the modified Bernoulli equa-
tion. The continuity equation was used to calculate the
AVA.12 Severity of AS was categorised based on current
recommendations.13

Follow-up

Patients were followed-up for the occurrence of all-
cause mortality. Survival data were complete for all
subjects and collected from the departmental cardiol-
ogy information system, which is linked to the respec-
tive national governmental death registry database.
In addition, the occurrence and timing of aortic valve
replacement (AVR) during follow-up were noted.

Statistical analysis

Continuous variables are presented as mean±SD and
compared using the Student’s t-test. All categorical
variables are presented as percentages and compared
using χ² analysis or the Fisher exact test. Linear regres-
sion analysis was performed to assess the clinical and
echocardiographic correlates of discordant grading
moderate AS. The OR and 95% CIs were calculated.
Variables with a significant p value in the univariate
analysis (p<0.05) were included in the multivariate anal-
ysis. Cumulative event rates for all-cause mortality were
then estimated using the Kaplan-Meier method and log-rank
tests were used for comparisons between groups. The
Cox proportional hazards models were used to estimate
HRs and 95% CI for the independent predictors of all-
cause mortality. Given that LVEF <50% can account
as a confounding factor in patients with discordant
grading, subjects were categorised according to discordant/concordant grading and LVEF for purposes
of survival analysis: (1) discordant moderate AS with
LVEF <50%, (2) discordant moderate AS with LVEF
≥50%, (3) concordant moderate AS and LVEF ≤50%
and (4) concordant moderate AS and LVEF ≥50%.
The variables included in the univariate Cox regression analysis were those that were significantly different between patients with concordant versus discordant grading. In the multivariate Cox regression analysis, a forward stepwise approach was used. A two-sided p value <0.05 was considered as significant. All statistical analyses were performed using SPSS for Windows V.23 (SPSS, Armonk, New York: IBM).

RESULTS

Study population
Of 790 patients (mean age 71±12 years, 52% men) diagnosed with moderate AS (defined by an AVA between 1.0 cm² and 1.5 cm²) between 30 October 2001 and 5 June 2018, 150 (19.0%) had discordant moderate AS (MG <20 mm Hg) (figure 1). Tables 1 and 2 summarise the clinical and echocardiographic characteristics of the patients. Patients with discordant-grading moderate AS were significantly older, had higher prevalence of previous myocardial infarction and LV hypertrophy, higher LV filling pressure, larger LV end-diastolic and end-systolic volume index, lower LVEF and stroke volume index (SVI) as compared with patients with concordant grading moderate AS (figure 2). Table 3 summarises the clinical and echocardiographic correlates of discordant-grading moderate AS.

Outcomes
During a median follow-up of 4.9 (IQR 3.0–8.2) years, 40 (26.7%) patients in the discordant grading group underwent aortic valve replacement (surgical or transcatheter) compared with 282 (44.1%) patients in the concordant grading group and 90 (60.0%) patients died in the discordant grading group compared with 276 (43.1%) in the concordant grading group.

When assessing the all-cause mortality rates according to concordant/discordant grading and LVEF <50% versus ≥50%, the estimated death rates at 1, 2 and 5-year follow-up were, respectively, 13%, 31.2% and 75.3% for discordant-grading moderate AS with LVEF <50%.
<50%, 8%, 17.4% and 42.4% for discordant-grading moderate AS with LVEF ≥50%, 12.1%, 32.8% and 53.8% for concordant-grading moderate AS with LVEF <50%, and 3.8%, 10.3% and 31.6% for concordant-grading moderate AS with LVEF ≥50% (figure 3).

Table 4 outlines the univariate associates of all-cause mortality in the entire population. Older age, previous myocardial infarction, impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m²), LV hypertrophy, LV end-diastolic volume index, significant (moderate or severe) mitral regurgitation, SVi, TAPSE <1.7 cm and concordant/discordant grading combined with LVEF were independently associated with mortality. On multivariate analysis, age, renal dysfunction, LV hypertrophy, discordant-grading moderate AS with LVEF <50% (HR 2.78 (2.00–3.87), p<0.001) and concordant grading moderate AS with LVEF <50% (HR 1.58 (1.06–2.36), p=0.025) were independently associated with all-cause mortality.

**DISCUSSION**
The main findings of the present study are the relatively high frequency of patients with low gradient (MG

---

**Table 2** Echocardiographic characteristics at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discordant moderate AS (N=150)</th>
<th>Concordant moderate AS (N=640)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVA (cm²)</td>
<td>1.23±0.16</td>
<td>1.18±0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>15.7±3.1</td>
<td>28.5±6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>125±35</td>
<td>120±36</td>
<td>0.093</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>52±7</td>
<td>48±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>115±44</td>
<td>105±37</td>
<td>0.012</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>62±39</td>
<td>42±25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic volume index (mL/m²)</td>
<td>70±29</td>
<td>61±21</td>
<td>0.003</td>
</tr>
<tr>
<td>LV end-systolic volume index (mL/m²)</td>
<td>37±24</td>
<td>25±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>49±16</td>
<td>61±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke volume index (mL/m²)</td>
<td>42±11</td>
<td>55±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke volume index &lt;35 mL/m²</td>
<td>38 (26.6%)</td>
<td>9 (1.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAVI (mL/m²)</td>
<td>42.3±17.9</td>
<td>41.2±25.5</td>
<td>0.661</td>
</tr>
<tr>
<td>E/e’ septal ratio</td>
<td>21±10</td>
<td>17±8</td>
<td>0.002</td>
</tr>
<tr>
<td>LV hypertrophy, n (%)</td>
<td>105 (70.5%)</td>
<td>387 (61.4%)</td>
<td>0.040</td>
</tr>
<tr>
<td>LVEF &lt;50%, n (%)</td>
<td>62 (41.3%)</td>
<td>58 (9.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate/severe MR, n (%)</td>
<td>22 (14.7%)</td>
<td>42 (6.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate/severe TR, n (%)</td>
<td>17 (11.3%)</td>
<td>51 (8.0%)</td>
<td>0.186</td>
</tr>
<tr>
<td>TAPSE &lt;1.7 cm, n (%)</td>
<td>21 (14.2%)</td>
<td>31 (5.0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AVA, aortic valve area; LAI, left atrial volume index; LV, left ventricle; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

---

Figure 2 Echocardiographic differences between patients with discordant vs concordant grading. Patients with discordant grading, moderate AS significantly lower SVi and LVEF values compared with patients with concordant grading moderate AS. AS, aortic stenosis; AVA, aortic valve area; LVEF, left ventricular ejection fraction; SVi, stroke volume index.
Valvular heart disease

<20 mm Hg), but AVA between 1.0 cm² and 1.5 cm² (discordant grading) among patients with moderate AS and its association with poor prognosis, particularly among patients with LVEF <50%.

**Discordant grading in moderate AS**

Discordant grading in moderate AS was detected in 150 (19.0%) patients in the present population, which is slightly lower than the reported prevalence of discordant grading in patients with severe AS (up to 30%).1 4 The most common findings that explain discordant grading in patients with AS are low flow status (low SVi), low LVEF, inaccurate measurement of LVOT cross-sectional area and misalignment of the aortic jet with the ultrasound beam.14 Patients with discordant grading moderate AS showed significantly lower SVi and LVEF values compared with patients with concordant-grading moderate AS. Furthermore, AVA was significantly larger in the discordant-grading moderate AS, which would be expected since the classification is based on MG values, given that larger AVA yields a lower MG value. Conditions associated with low flow status such as coronary artery disease, larger LV volumes, moderate or severe mitral regurgitation and lower TAPSE were also more prevalent in the group with discordant grading.15 16 Although LVOT cross-sectional area is measured as accurate as possible, the limitations of two-dimensional transthoracic echocardiography are well known, and correcting for body surface area should be performed, particularly in children, adolescents and women.11 Previous studies have reported on the frequency of discordant grading in patients with moderate AS.16–18

Tan and colleagues analysed flow and gradient patterns in patients with mild and moderate AS and

**Table 3 Clinical and echocardiographic correlates of discordant grading moderate AS**

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odds ratio (95% CI)</strong></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>1.04 (1.02 to 1.05)</td>
</tr>
<tr>
<td>Male</td>
<td>1.40 (0.98 to 2.01)</td>
</tr>
<tr>
<td>Coronary artery disease (yes/no)</td>
<td>2.94 (2.01 to 4.31)</td>
</tr>
<tr>
<td>Previous MI (yes/no)</td>
<td>3.08 (2.02 to 4.70)</td>
</tr>
<tr>
<td>LV mass index (per unit increase)</td>
<td>1.01 (1.00 to 1.01)</td>
</tr>
<tr>
<td>LVEF (per unit increase)</td>
<td>0.93 (0.92 to 0.94)</td>
</tr>
<tr>
<td>Moderate/severe MR (yes/no)</td>
<td>2.45 (1.41 to 4.24)</td>
</tr>
<tr>
<td>Stroke volume index (per unit increase)</td>
<td>0.88 (0.86 to 0.90)</td>
</tr>
<tr>
<td>Atrial fibrillation (yes/no)</td>
<td>1.64 (1.12 to 2.40)</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation.

**Figure 3** Kaplan-Meier estimates of all-cause mortality according to gradient concordance and LVEF. LVEF, left ventricular ejection fraction.
Table 4  Uni- and multivariate Cox proportional hazard analyses for the identification of independent correlates of all-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P value</td>
<td>Hazard ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>1.05 (1.03 to 1.06)</td>
<td>&lt;0.001</td>
<td>1.04 (1.02 to 1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>1.00 (0.81 to 1.22)</td>
<td>0.973</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI (yes/no)</td>
<td>1.72 (1.33 to 2.22)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m² (yes/no)</td>
<td>2.55 (2.07 to 3.15)</td>
<td>&lt;0.001</td>
<td>2.15 (1.71 to 2.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV hypertrophy (yes/no)</td>
<td>1.75 (1.39 to 2.20)</td>
<td>&lt;0.001</td>
<td>1.67 (1.30 to 2.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV index (per 1 mL/m² increase)</td>
<td>1.007 (1.003 to 1.011)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe MR (yes/no)</td>
<td>1.50 (1.05 to 2.13)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume index (per unit increase)</td>
<td>0.986 (0.977 to 0.996)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAPSE &lt;1.7 cm (yes/no)</td>
<td>1.71 (1.18 to 2.47)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of moderate AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concordant moderate AS +LVEF≥50%</td>
<td>Reference</td>
<td>...</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>Discordant moderate AS +LVEF&lt;50%</td>
<td>3.11 (2.26 to 4.27)</td>
<td>&lt;0.001</td>
<td>2.78 (2.00 to 3.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discordant moderate AS +LVEF≥50%</td>
<td>1.46 (1.06 to 2.01)</td>
<td>0.022</td>
<td>1.01 (0.78 to 1.56)</td>
<td>0.595</td>
</tr>
<tr>
<td>Concordant moderate AS +LVEF&lt;50%</td>
<td>2.12 (1.49 to 3.01)</td>
<td>&lt;0.001</td>
<td>1.58 (1.06 to 2.36)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; MI, myocardial infarction; MR, mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion.

preserved LVEF and demonstrated a 70.3% prevalence of discordant grading in the moderate AS group. van Gils and colleagues analysed patients with moderate AS and reduced LVEF and reported a high rate of discordance MG (81%) versus peak velocity (84%). The demographic and clinical characteristics of the patients included in the later study are similar to those of the present population with high prevalence of comorbidities (hypertension, hyperlipidaemia and coronary artery disease). However, the prespecified criterium of reduced LVEF may explain the higher prevalence of discordant grading in that report as compared with the current results.

Prognostic relevance of discordant grading in moderate AS

In the present study, patients with discordant grading had worse prognosis as compared with patients with concordant grading. Few studies have evaluated the association between discordant grading and prognosis in patients with moderate AS. Delesalle and colleagues observed that among 508 patients with moderate AS and preserved LVEF, patients who were not referred for aortic valve replacement during follow-up had significantly lower MG as compared with patients who were operated (23±8 mm Hg vs 29±11 mm Hg, p<0.001). This suggests that among patients with moderate AS, there were patients with a low gradient that could mask the severity of the disease during follow-up (underdiagnosing severe AS), preventing the treating physician to refer these patients for intervention. In addition, van Gils and colleagues showed that patients with moderate AS and reduced LVEF (81% of them with a MG <20 mm Hg) had a cumulative incidence of the composite of death, aortic valve replacement or heart failure hospitalisation of 61% at 4 years of follow-up. Although stroke volume is associated with poor prognosis in patients with severe AS, recent studies including patients with moderate AS do not confirm that low-flow status is an independent prognostic marker, and this is consistent in the present analysis.

Similarly, to the current study population, patients with calcific moderate AS have high prevalence of comorbidities and increased incidence of cardiovascular events compared with the general population. In the present study, comorbidities such as prior myocardial and impaired renal function were associated with increased mortality. These comorbidities may lead to symptoms that confound the symptoms of moderate AS. Patients in the discordant moderate AS group are usually misclassified by MG values as having mild AS and the symptoms may be attributed to the comorbidities. Since AS does not have a predictable progression pattern, patients may be misclassified as having nonsevere AS and remain unoperated for a long period of time leading also to increased mortality. It has been postulated that the increased afterload imposed by the calcific stenotic aortic valve onto the LV may have a considerable role in the development of symptoms and increased risk of mortality in patients with heart failure with moderate AS. Whether these patients will benefit from early aortic valve intervention will be elucidated by the ongoing trial TAVR-UNLOAD.
CONCLUSIONS
Discordant grading moderate AS is not uncommon and is characterised by a high prevalence of comorbidities. The combination of discordant grading with moderate AS and low LVEF is associated with high risk of mortality.

Author affiliations
1Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
2Department of Cardiology, National Heart Centre, Singapore
3Department of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia
4Department of Cardiothoracic Surgery, National Heart Centre Singapore, Singapore
5Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec Heart and Lung Institute, Laval University, Quebec, Quebec, Canada
6Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands
7 GANGSTON Cardiovascular Institute, Morristown Medical Center, Morristown, New Jersey, USA
8Department of Cardiology, Columbia University Medical Center, New York, New York, USA

Twitter Philippe Pibarat @ppibarat

Contributors
SMP: conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript.
MRA: conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript; KYS: conception and design of the study; collection, analysis and design of the study; drafting of the manuscript; final approval of the manuscript; MMV: conception and design of the study; drafting of the manuscript; final approval of the manuscript; YS: conception and design of the study; drafting of the manuscript; final approval of the manuscript; NAM: conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript; JJB: conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript.

REFERENCES


