Reviewer's report

Title: Global LV load in asymptomatic aortic stenosis: covariates and prognostic implication (the SEAS trial)

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Reviewer: Julien Magne

Reviewer's report:

This study by Rieck et al. aimed to assess the impact of valvulo-arterial impedance (ZVa) on outcome in the SEAS trial. They have included 1 446 patients in whom Zva calculation was available and they reported that patients with high Zva (>median) are characterized by a higher rate of hypertension, female gender, concentric geometry and by older age, higher left ventricular (LV) mass and lower LV ejection fraction. This aspect of the paper is not new and the determinants of high Zva in patients with aortic stenosis (AS) are well known. Nevertheless, the confirmation of these features in a large prospective trial should be acknowledged. The authors also showed an independent relationship between Zva level and major cardiovascular (CV) events. In opposition, they found no relationship with mortality. The paper is well written, the hypothesis is relevant, the data strongly support the conclusion and the authors had a long and robust experience in the field of AS.

Major Compulsory Revisions:

1- The table 1 should provide data regarding LV volumes, LV stroke volume, cardiac output and cardiac index, as well as the rate of patients with low flow (and paradoxical low flow) and low flow/low gradient severe AS.

2- Previous study emphasized the lack of relationship between Zva and operative and long term mortality in patients with low-flow/low gradient AS[1 2]. Although these results are mainly explained by the high flow-dependency of Zva in low flow state (see editorial), these 2 references could be added to the paper and discussed. In addition, separate analysis excluding low flow patients should be added in the paper.

3- The last section of the results and the ROC curve should be deleted. Indeed, the end-point used in this analysis is time dependent. ROC curves analysis does not integrate time and thus, are not appropriate to predict outcome and in this regard, to identify a cut-off value or the superiority of a parameter over another.

4- Various cut-offs value of Zva are recognized in the literature. The authors have chosen to use the median of Zva distribution in their population. Nevertheless, this value is low and suggest that a substantial number of patients classified in “high Zva group” actually only have “mildly or moderately” elevated Zva. In this regard, the relationship between “elevated” Zva and mortality could be missed. The authors could separate the 2 groups according to Zva=4.5 or 5 (depending on the number of patients in each group and the statistical power expected).
5- Did the authors try to include the Zva in all multivariate models as a continuous data and not as categorical? This additional data may help to understand the relationship between Zva and outcome.

6- Even if the studied population is large, the lack of significant relationship in Figure 2 Panel C and D could be explained by the relative small number of events.

Minor Essential Revisions:
1- The impact of Zva in asymptomatic AS was also reported in a paper by Lancellotti et al[3]. This paper could be added in the introduction and discussed.

2- Page 4, the formula used to calculate Zva was not derived from the “method of Briand”. Even if Briand is the first author of this paper, the method rather arises from the group of Philippe Pibarot than from Briand himself. The reference is appropriate but the wording could be modified.

3- All exact p-value could be provided. Avoid “p<0.05”.

4- Figure 1, please report the n and percentage at the top of each bar.

5- Figure 2, please add the number of patients remaining at risk in each panel and for each group. In addition, rate of event-free survival or of mortality could be added in the text at 2- and 4-years (for example).

Reference List


Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

None.