

Manuscript NO.: 30814

Column: Minireviews

Title: Assessment of aortic valve disease – a clinician oriented review

Authors: Andrei D Margulescu

Dear Editor,

Thank you very much for your letter dated February 17th, 2017 regarding manuscript no. 30814. I read carefully the helpful comments from the reviewers, and I have modified the article accordingly. Below, I copy-pasted these comments (in Bold font) and provided my answer to each of these questions (in Italics font).

Reviewer 1 (no. 39411)

**That is a very nice review about aortic valve diseases.**

*Thank you for your appreciation.*

Reviewer 2 (no. 2633655).

**The article is interesting for a general practitioner or general cardiologist, but there are some concepts that should be corrected in my point of view.**

*Thank you for your comments, with which I agree. I have modified the article following your suggestions and comments. These modifications are highlighted in red throughout the revised manuscript.*

## **Aortic stenosis**

**1.1 “The natural history of AS is progressive but slow”, I suggest “Aortic stenosis is a slowly progressive disease”**

*Thank you for your suggestion. The manuscript has been corrected accordingly.*

**1.2 and “tarvus et parvus”, it should be “tardus et parvus”**

*Thank you for spotting out this mistake. It has now been corrected.*

**1.2.1 (Echocardiography) DLVOT measurement is performed from the inner anterior edge to the inner posterior edge of the LVOT (“inner-edge to inner-edge”), should be added “in mid-systole”.**

*Thank you for your suggestion. I agree with it and I have modified the manuscript accordingly.*

**1.2.1.1 (“paradoxical” severe AS, where the anatomical AVA is  $>1$  cm<sup>2</sup>). I think it is not correct, “paradoxical severe AS” refers to an severe AS with low flow and normal EF, not to an anatomical AVA  $>1$  cm<sup>2</sup>. The situation the author refers is “pseudo-severe AS”, situation in which there is a non severe AS with area less than 1 cm<sup>2</sup> but because of low EF but not cause by a real AS (this is correctly explained in figure 3 of this manuscript).**

*Thank you for spotting out this mistake. Of course, the condition described is pseudo-severe AS, and not paradoxical severe AS, as written in error. This mistake has now been corrected.*

**1.2.2 “Establishing the presence or absence of symptoms can be difficult because many older patients (the majority of patients with AS) deny the presence of symptoms due to lifestyle adaptations to lower functional needs.” I suggest to add that also older patients refer usually symptoms (“fatigue”) that can be vague, related to AS or to other comorbidities related with advanced age but not caused by AS.**

*Thank you for your suggestion. I agree with it and I have modified the manuscript accordingly.*

**TABLE 2. “Low-flow/low-gradient/Low-LVEF severe AS with proof of contractile reserve presence” AHA/ACC guideline “IIa regardless of the presence of contractile / flow reserve”: I don't think the guideline defines that. It assesses that :”Some patients without contractile reserve may also benefit from AVR, but decisions in these high-risk patients must be individualized because there are no data indicating who will have a better outcome with surgery” (page e78 of the guideline) “- Velocity 4 to 5 m/s or mean gradient 40 to 60 mmHg AND severe valvular calcification AND stress test demonstrating reduced tolerance or drop in blood pressure.” Actually, the guideline says “- Velocity 4 to 4,9 m/s or mean gradient 40 to 59 mmHg AND severe valvular calcification AND stress test demonstrating reduced tolerance or drop in blood pressure.”**

*I agree with the above comments and I have modified the manuscript accordingly.*

**“Truly asymptomatic severe AS (no symptoms during treadmill test, no risk criteria) with preserved LVEF if the surgical risk is deemed low and 1 or more of the following criteria are also satisfied: - severely increased BNP / Nt-ProBNP levels at serial determinations and without an alternative explanation; - increased transaortic pressure gradient at stress echocardiography by >20 mmHg; - excessive LV hypertrophy without an alternative explanation. “**

**I didn't find a IIa indication in AHA/ACC guidelines for this condition.**

*I agree with the above comments and I have modified the manuscript accordingly.*

**“The 1- and 5-year mortality rates for asymptomatic severe AS with preserved LVEF are 7.8% and 26.4%, respectively”. I think there is a mistake, 7,8% is the mortality of the hole cohort, not at 1 year.**

*Thank you. I agree with the above comments and I have corrected the manuscript.*

**“In a recent study, the presence of a resting transaortic pressure gradient of >35 mmHg that increased by >20 mmHg during exercise was encountered in all patients who developed MACE within the following 2 years. In this study, the best prognosis was encountered in patients with a resting transaortic gradient of <35 mmHg that increased by >20 mmHg during exercise (10% MACE at 2 years), whereas patients with an increase in transaortic pressure gradient of <20 mmHg had intermediate prognosis (20% MACE at 2 years in patients with a resting transaortic pressure gradient of <35 mmHg, and 50% MACE at 2 years in patients with a transaortic pressure gradient of >35 mmHg).”**

**I think this paper should be explained better to show the worse prognosis for those with an increase in mean gradiente more than 20 mmHg during exercise test.**

*Thank you for these comments. I have modified this section so it is easier to understand. It now reads:*

*“The response of transaortic pressure gradient to exercise has also been suggested to have prognostic importance. Thus, MACE event rate is highest (100% at 2 years) in patients with high resting transaortic pressure gradient (>35 mmHg) that increases by >20 mmHg during exercise, intermediate in patients where the transaortic pressure gradient increases by <20% during exercise (50% at 2 years for patients with high resting transaortic pressure gradient, and 20% at 2 years for patients with low transaortic pressure gradient), and lowest (10% at 2 years) in patients with low transaortic pressure gradient (≤35 mmHg) that increases by <20% during exercise[44].”*

**1.3. “Currently, the only established treatment for AS is AVR.” I think this opinion is “too strict, taxactive”. As the author discusses later in the manuscript, TAVR is an option in some patients.**

*I agree with the above comments and I have modified the manuscript accordingly. It now reads: “Currently, the most effective treatment for AS is AVR.” The AVR was defined previously in the manuscript as aortic valve replacement, therefore including surgery (surgical AVR, SAVR) and TAVR.*

## **2. Aortic regurgitation**

### **2.1 Table 5.**

**For “Asymptomatic severe AR with normal LVEF (>50%) but with severe LV dilatation “, definitions of “AHA/ACC guidelines: end-diastolic LV diameter >50 mm”, it is wrong, actually it is end-systolic LV diameter >50 mm.**

*Thank you for spotting out this mistake. This mistake has now been corrected.*

### **2.2. Table 6**

**“Leoys-Diets syndrome”. It is “Loeys-Dietz syndrome”**

*Thank you for spotting out this mistake. Table 6 has been simplified and this mistake has now been corrected.*

**2.3. Finally, there is information about BNP and NT-proBNP levels in AR that can be useful in AR stratification. I suggest to add some of this information.**

*I agree with the above comments and I have modified the manuscript accordingly, by adding the following text:*

*“B-type natriuretic peptide (BNP) levels may also play a role in predicting outcomes in patients with severe AR. Pizarro et al. studied 294 patients with severe asymptomatic AR and LVEF >55%, and found that a BNP level >130 pg/ml had 77% sensitivity and 94% specificity for predicting LV dysfunction symptoms or death after 38 +/- 9 months of follow-up. BNP level had additive prognostic value to echocardiographic prognostic indices.[75] Further studies are needed to establish the role of BNP levels for indication of surgery in patients with AR.”*

*In addition to the comments above, I modified Table 6 from the Aortic Regurgitation section to make it more easy to follow.*

*Also, I have updated the Reference list with 3 important articles.*

*All these modifications are highlighted in red throughout the revised manuscript.*

I hope that by answering the reviewer's comments I have improved the article significantly and that it is now acceptable for publication in World Journal of Cardiology.

I look forward for your response.

Yours sincerely,

Andrei-Dumitru Margulescu, MD, PhD

A handwritten signature in black ink, appearing to read 'Andrei', with a long, sweeping horizontal stroke extending to the right.

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