Oct 30, 2015

Professor Lian-Sheng Ma,
President and Company Editor-in-Chief
Baishideng Publishing Group Inc

Dear Professor Lian-Sheng Ma,

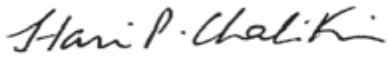
Thank you very much for the opportunity to revise the manuscript entitled, “Diagnosis and Management of Patients with Asymptomatic Severe Aortic Stenosis” (Manuscript No:20986) for publication in the World Journal Cardiology as an invited review article.

We have carefully read reviewer’s comments and revised the manuscript accordingly. The detailed answers to the reviewer’s comments are attached to this cover letter. The revised text is highlighted. We also edited some typographical errors and made minor changes in the manuscript to further improve clarity. We hope the revised manuscript is now acceptable for publication.

The content of the manuscript has not been published or accepted for publication. No part of the manuscript is currently under consideration for publication elsewhere.

Thank you very much for your consideration.

Sincerely,



Hari Chaliki, M.D.
Division of Cardiovascular Diseases, Mayo Clinic
13400 East Shea Boulevard
Scottsdale, AZ 85259
480-301-8000
chaliki.hari@mayo.edu

Response to the reviewers

Thank you very much for your careful reviews and insightful comments to the manuscript. We appreciate all your comments and have revised the manuscripts as stated below. The changes are highlighted.

Response to the reviewer #00227531:

1. **Role of CT in paradoxical low gradient-low flow is insufficiently treated.**

   Thank you for pointing out an important subject. We add sentences as below.

   Page 9, Line 20-28

   When it is difficult to judge the severity of AS due to discordant measurements in echocardiography or a possible paradoxical low-flow/low-gradient AS, CT imaging can help to provide the calcium score, which relates to stenosis severity and prognosis[38, 39]. Due to the recent rapid development of transcatheter aortic valve replacement (TAVR) procedures, the cardiac CT scan has emerged as a key imaging modality not only to assess aortic valve and root calcification, but also for precise measurement of the aortic annulus and peripheral arteries[40-42]. Whether or not three-dimensional LVOT measurements by CT imaging should replace echocardiography in order to resolve the measurement error issue is still uncertain, and warrants further research[43, 44].

2. **ESC guidelines have suggested but not recommended surgery in patients with increase in mean gradients with increases in mean gradients with exercise, as the indication is not even IIa. Also, the differences between American and ESC guidelines are not discussed.**

   Thank you for the comment. We revised the sentence as below.

   Page 12, Line 3-5

   Although ESC guidelines[53] have suggested the use of an increased mean gradient during exercise testing (>20 mm Hg) as an indication for surgery in asymptomatic patients (Class IIb), it was not supported in the more recent ACC/AHA guidelines[16].

   Page 12, Line 15-22

   Indications for AVR in asymptomatic patients are shown in Figure 1, which is based on 2014 AHA/ACC guidelines. Indications for AVR have been consistent between AHA/ACC guidelines and ESC guidelines, though there are slight differences. Asymptomatic patients with severe calcification and a rapid increase in aortic peak transvalvular velocity should be considered for AVR in ESC guidelines with a Class IIa indication, but that is a Class IIb indication according to AHA/ACC guidelines. Patients with elevated BNP levels, an increase in the Doppler mean pressure gradient with exercise, and excessive LVH may be considered for AVR by ESC guidelines (Class IIb), but these are not employed in AHA/ACC guidelines.

3. **The authors do not limit the discussion/recommendations to asymptomatic patients and that the paper is disperse. More information regarding to techniques like dobutamine stress echo, exercise echo, and CT would be pertinent.**

   Thank you for your comments. We felt that all of the methods described in the manuscript will apply to asymptomatic patients. We revised some of the information to clarify this point. Hope the revised manuscript is acceptable for this reviewer.

   Page 8, Line 8-9
   A low-dose dobutamine stress echocardiography is performed to diagnose true or pseudo AS in low-gradient, reduced EF patients (though usually symptomatic, patients rarely present with low LVEF and gradient without any symptom).

   Page 9, Line 7-10
   Further research studies and standardization of analyzing software are necessary to incorporate these measurements into current clinical practice, specifically their role in surgical decision making for patients with asymptomatic severe AS.

Response to the reviewer #02794723:

1. **The manuscript is very long and some shortening is necessary. Most missing point to me is a discussion of risk scores of the patients and a discussion of new replacement methods in critical patients like TAVR for example.**

   Thank you for the comment. As suggested we deleted the section (definition of AS) which is redundant. Given the title of the manuscript being "management of patients with asymptomatic aortic stenosis", we did not feel that discussion of TAVR should be included. Moreover, it will make the manuscript even longer. However, if the editor and this reviewer feel, this section need to be included, we will be happy to do that.

2. **Minor comments: Please add page and line numbers. Can you give more detailed information about grading by BNP level? Here a more clearly statement would be helpful.**

Thank you for the comment. We summarized the information of BNP level in a table so that the readers can get the point easily.

Page 11

Table2. High-risk Patients Predicted From BNP Level.

Source	BNP Cut-off Value	Results	Enrolled Patients
Bergler-Klein et al.[51]	BNP 130 pg/ml	BNP <130 pg/mL (n=25) had better symptom-free survival (*P*<0.001)	Asymptomatic severe AS, EF≥50% (n=43)
Biner et al.[33]	BNP 300 pg/ml	Combined use of BNP >300 pg/mL and E/e' >15 predicted 1-year mortality (relative risk 2.59; 95% CI 1.21-5.55, *P*=0.014)	Severe AS, symptomatic and asymptomatic, any EF included (n=79)
Berger-Klein et al.[54]	BNP 550 pg/mL	BNP ≥550 pg/mL showed poorer survival both in medically and surgically treated groups	Indexed effective orifice area ≤0.6cm^2/m^2 with low-flow/low-gradient AS; symptomatic and asymptomatic EF <40%
Clavel et al.[52]	BNP ratio: Measured BNP/maximal-normal-BNP for age and sex	Higher BNP ratio showed worse mortality in entire group and was asymptomatic with preserved EF (hazard ratio 2.35; 95% CI 1.57-3.56, *P*<0.0001)	Total, moderate or severe AS, any EF (n=1,953) Asymptomatic, with EF>50% (n=565)

Abbreviations: AS, aortic stenosis; BNP, brain natriuretic peptide; CI, confidence interval; EF, ejection fraction.

Responses to the reviewer #00259343:

1. **Are there any genetic factors/variations associated with aortic stenosis in human populations? If so, a short section discussing them would be appropriate to include in this review.**

   Thank you for the comment. Given prior reviewers comments regarding excessive of length of the manuscript, we included the following comments in the manuscript. We hope the revised manuscript is now acceptable to the reviewer.

   Page 3, Line 19
   There is some evidence to suggest that NOTCH 1 genetic mutations and specific lipoprotein polymorphism is associated with congenital aortic stenosis and valve calcification. (Otto et al. N Engl J Med. 2014 Aug 21;371(8):744-56.)

Response to reviewers #02633299 and #00259340:

Thank you very much for your positive comments. The authors could not find any specific comments to answer in the manuscript review page.