**Reviewer’s report**

**Title:** Evaluating the Effectiveness of Rosuvastatin in Preventing the Progression of Diastolic Dysfunction in Aortic Stenosis: A Substudy of the Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin (ASTRONOMER) Study

**Version:** 1  **Date:** 17 December 2010

**Reviewer:** Denisa Muraru

**Reviewer’s report:**

General comments:
Jassal DS and coworkers examined the effect of rosuvastatin therapy in 3 subgroups of patients with mild-to-moderate aortic stenosis and they concluded that statin does not attenuate LV diastolic dysfunction progression in comparison with placebo. The study idea is original and in line with preliminary experimental and clinical evidence of the possible beneficial effects of statin therapy on myocardial fibrosis and stiffness (Chang SA Hypertension 2009; Zhang J et al. Can J Physiol Pharmacol 2010) and in diastolic heart failure (Fukuta H et al. Circulation 2005, Tehrani F et al. Clin Cardiol 2010). However, the rationale of this study is unclear, since statin therapy did not prevent the progression of aortic stenosis in several randomized trials (as stated by the Authors) and therefore having an impact on diastolic function in such case is unlikely. In addition, the echo Doppler assessment of diastolic function used in this paper is simplistic and does not comply with current guidelines recently issued by ASE and EAE (Nagueh SF et al. Eur J Echocardiogr 2009).

There are several issues to address:

- Major Compulsory Revisions

1. **Study population**
   1.1. The representativeness of the study cohort (62% of the original sample of ASTRONOMER study, selected on the basis of completeness of echo study) is questionable
   1.2. Since only patients in NYHA class III and IV were excluded, enrolled patients cannot be defined “asymptomatic”
   1.3. No information is provided on the coexisting valvular lesions (significant native mitral or aortic regurgitation or presence of prosthetic mitral valves etc) or other abnormalities (e.g. clinically silent wall motion abnormalities, significant mitral annular calcification) and associated medication (e.g. antihypertensive treatment as diuretics, beta-blockers, calcium channel blockers etc) in statin vs placebo arms. These may affect LV diastolic function evaluation by E/E’ lateral and/or the aortic stenosis severity assessment based on flow velocity and gradients. Additional data should be provided.
1.4. Were patients with rhythm abnormalities (e.g. atrial fibrillation, significant bradycardia etc) or conduction disturbancies (AV block) excluded from the study?

1.5. What was the proportion of the subjects with LV systolic dysfunction (if any), with diastolic dysfunction and estimated increased filling pressures at baseline and at follow-up in statin vs placebo arms?

2. Methods

2.1. I agree with the Authors that the results of this sub-study need to be interpreted cautiously. As acknowledged by Authors, there is a small sample size at enrolment to study treatment effects (168 pts). No preliminary estimation of the sample size needed to reach the statistical power to test the hypothesis that statin treatment would have improved diastolic function in patients with aortic stenosis was done. In addition, the reason for dividing the population by AS peak velocity into 3 subgroups to be studied separately is unclear.

2.2. Categorizing and assessing aortic stenosis severity progression by load-dependent parameters only (peak AS velocities and pressure gradients) is criticable. Calculated aortic valve area and its progression in both arms should be provided as well (as some patients could actually have “paradoxically low-flow, low-gradient” severe AS that could interfere with the study findings). Whether HR and BP recordings were done at the time of echo examination should be also mentioned.

2.3. Since significant differences among different vendors in measuring myocardial velocities using TDI have been reported it is important to know if the machines used to assess E' lat were comparable among placebo and statin groups, and if the same echo scanners have been used for baseline and follow-up studies.

2.4. Evaluation of LV diastolic function by mitral inflow and TDI E' lat as single measures and of LV filling pressures by E/E' lat (instead of E/E’average, as recommended by recent guidelines - Nagueh SF et al. Eur J Echocardiogr 2009) are important limitations of this study that includes AS patients with normal EF. Other parameters would have been needed (indexed LA volume instead of LA antero-posterior diameter, IVRT/TE-E’ etc) before drawing a definite conclusion about the progression of LV diastolic dysfunction. As the patients showed worsening LV diastolic function parameters at follow-up, with mean E/E’ of 15 in Groups II and III, was there any change in their symptomatic status?

3. Discussions

3.1. Comments should be more focused on the interpretation of the study findings (worsening of LV diastolic parameters despite no apparent change in EF, LV mass or LA size etc).

- Minor Essential Revisions

1. Table 3 shows similar values for E’ and E/E’ in Group III, so that the increase in diastolic dysfunction and filling pressures at follow-up seems valid only for Group I and II. The results in the abstract and the discussions and conclusions in
the manuscript should be reformulated accordingly.

- Discretionary Revisions

1. Title: Although the findings of this study are not so surprising in the light of recent negative studies of statin therapy on aortic stenosis progression, the title is however misleading and could be reformulated by excluding the term “…preventing…”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests